Organic Letters

Supporting Information to Accompany:

Facile Synthetic Access to and Biological Evaluation of the Macrocyclic Core of Apoptolidin

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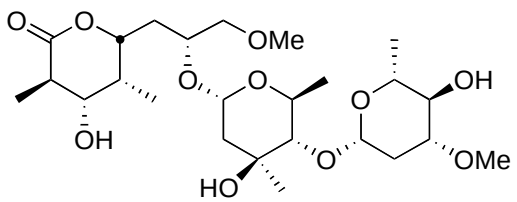
Materials and Methods. General Procedures. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum BX FT-IR spectrometer. The values are reported in cm^{-1} for thin films on NaCl plates. Optical rotations were determined using a Jasco DIP-1000 polarimeter at ambient temperature and are reported as follows: $[a]_D$, concentration (*c* = g/100 mL), solvent. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on the following instrument: 600 MHz Varian UNITY Inova (^1H at 600 MHz) or 500 MHz Varian UNITY Inova (^1H at 500 MHz; ^{13}C at 125 MHz) or 400 MHz Varian XL-400 (^{13}C 100 MHz). Chemical shifts are reported as d values in parts per million relative to the residual solvent resonance (**H**CCl_3: d = 7.26 ppm for ^1H; d = 77.0 ppm for ^{13}C, C**H**D_2OD: d = 3.30 ppm for ^1H; d = 49.0 ppm for ^{13}C, C_6**D**$_6$: d = 7.15 ppm for ^1H; d = 128 ppm for ^{13}C). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, or dddd = doublet of doublet of doublet of doublets), coupling constant (Hz), and integration. ES-MS data were collected at the Stanford Chemistry PAN Facility. Thin-layer chromatography (TLC) was conducted on silica gel 60 F_{254} TLC plates purchased from Merck. All TLC experiments were developed by dipping in a solution of *p*-anisaldehyde in ethanol followed by heating over a hot plate. Preparative column (flash) chromatography was performed using a forced flow of solvent on silica gel 60 (260-400 mesh) purchased from EM Science. When necessary, solvents and reagents were dried prior to use. Dichloromethane was distilled under nitrogen from CaH_2. Tetrahydrofuran (THF) was distilled under nitrogen from sodium-benzophenone ketyl. Toluene was dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Amines were distilled from calcium hydride immediately prior to use. All air and water sensitive reactions were performed in oven-dried glassware under a positive flow of nitrogen. Reaction temperature refers to the temperature of a bath in which the reaction flask was submerged and allowed to equilibrate (dry ice and acetone bath for –78 ^oC; water and ice bath for 0^oC).



4

d-lactone 4. To an equilibrium mixture of apoptolidin (**1**) and isoapoptolidin (77 mg, 0.068 mmol, approximately 2:1 in favor of apoptolidin) and sodium periodate (58.4 mg, 0.27 mmol) was added 50:50 H_2O:MeOH (2 ml). The reaction mixture was stirred at r.t. under an atmosphere of nitrogen for 48 h. The reaction mixture was then diluted with 10 ml of ethylacetate and washed with brine. The organic phase was collected, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (silica gel, 15:85 methanol:chloroform) gave lactone **4** (31 mg 87%) as a white amorphous solid which was pure by TLC.

^{1}H NMR (500 MHz, CD_3OD) d 4.91 (d, J = 3.1 Hz, 1H), 4.82 (dd, J_1 = 1.8 Hz, J_2 = 9.8 Hz, 1H), 4.46 (dt, J_1 = 3.1 Hz, J_2 = 9.5 Hz, 1H), 3.86 – 3.77 (m, 2H), 3.74 – 3.68 (m, 1H), 3.49 – 3.40 (m, 1H), 3.42 (s, 3H), 3.34 (s, 3H), 3.22 – 3.13 (m, 3H), 2.96 (t, J = 9.0 Hz, 1H), 2.45 – 2.37 (m, 2H), 2.10 – 2.06 (m, 1H), 1.95 – 1.87 (m, 2H), 1.79 (dd, J_1 = 4.0 Hz, J_2 = 13.6 Hz, 1H), 1.71 (ddd, J_1 = 2.9 Hz, J_2 = 9.6 Hz, J_3 = 14.5 Hz, 1H), 1.34 (d, J = 7.3 Hz, 3H), 1.33 (s, 3H), 1.29 – 1.25 (m, 2H), 1.27 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H) ppm;

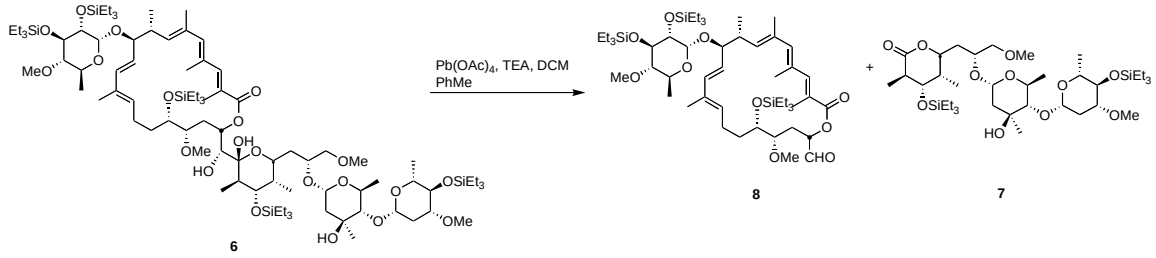
^{13}C NMR (125 MHz $CDCl_3$) d 173.23, 99.87, 98.34, 84.09, 80.75, 76.29, 75.47, 75.24, 74.33, 73.74, 71.78, 71.67, 66.47, 59.18, 56.43, 43.61, 39.71, 37.82, 35.53, 34.55, 23.34, 18.41, 17.81, 14.23, 5.02 ppm;

IR (NaCl Thin Film) n = 3435, 2975, 2933, 1715, 1455, 1375, 1200, 1164, 1099, 1077, 1007, 914, 841, 732 cm^{-1};

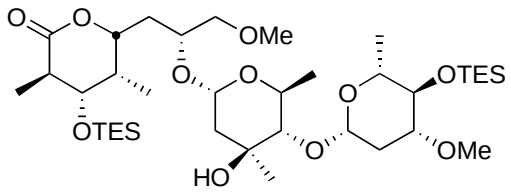
MS (+ESMS) *m/z* = 543.5 (543.2 calcd for $C_{25}H_{44}O_{11}$ + Na);

[a]$_D$ = -21.3 (c = 1.23, MeOH);

R_f = 0.28 (15% MeOH/$HCCl_3$);



Oxidative cleavage of protected apoptolidin (6) to produce fragments 7 and 8: To a solution of penta(triethylsilyl)apoptolidin **6** (29.4 mg, 17.3 µmol) in toluene (5 mL) and triethylamine (34.9 mg, 346 µmol) at 0 ˚C was added lead tetraacetate (11.5 mg, 25.9 µmol) as a solution in methylene chloride (250 µL). The solution was stirred at 0˚C for 1 hour, then quenched with saturated sodium thiosulfate solution (1 ml) and saturated sodium bicarbonate solution (1 ml). The mixture was allowed to warm to room temperature, then extracted with chloroform (3 x 2 ml). The organic layers were collected, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was then purified by column chromatography eluting with ethylacetate:methylene chloride (5:95 then 30:70) to provide **8** (14.6 mg, 89%) as a colorless amorphous solid, and the **7** (11.3 mg, 87%) as a colorless amorphous solid which were pure by TLC analysis.



7

Data for C21-C28 Lactone Fragment 7.

^{1}H NMR (500 MHz, $CDCl_3$) d 4.95 (d, J = 3.6 Hz, 1H), 4.76 (dd, J_1 = 10 Hz, J_2 = 1.7 Hz, 1H), 4.31 (dt, J_1 = 10 Hz, J_2 2.5 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.78 – 3.72 (m, 2H), 3.52 – 3.48 (m, 1H), 3.43 – 3.37 (m, 2H), 3.33 (s, 3H), 3.32 (s, 3H), 3.29 – 3.24 (m, 1H), 3.14 – 3.07 (m, 2H), 2.60 (s, 1H), 2.44 (m, 1H), 2.32 (m, 1H), 1.97 – 1.91 (m, 3H), 1.89 – 1.84 (m, 3H), 1.71 (ddd, J_1 = 12.3 Hz, J_2 = 4.6 Hz, J_3 = 1.9 Hz, 1H), 1.48 (m, 1H), 1.37 (s, 3H), 1.33 (d, J = 7 Hz, 3H), 1.27 (t, J = 5.8 Hz, 3H), 0.99 – 0.92 (m, 21H), 0.65 – 0.59 (m, 12H) ppm;

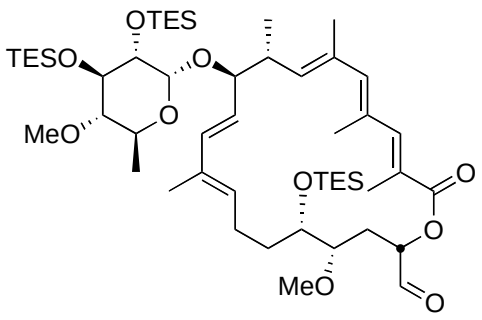
IR (NaCl Thin Film) n = 3468, 2955, 2878, 1731, 1458, 1380, 1116, 1006, 741 cm^{-1};

^{13}C NMR (100 MHz, $CDCl_3$) d 173.77, 99.62, 98.27, 83.84, 81.05, 76.40, 76.04, 75.27, 74.43, 74.29, 72.96, 71.44, 66.51, 59.17, 56.13, 43.43, 40.32, 38.53, 35.66, 34.81, 23.37, 18.42, 18.11, 14.40, 6.89, 6.79, 5.18, 5.10, 4.89 ppm;

MS (ESMS) *m/z* 771.5 (770.44 calcd for $C_{37}H_{71}O_{11}Si_2$+ Na);

$[a]_D$ = -3.27 (c = 0.78 $HCCl_3$);

R_f = 0.25 (10:90 EtOAc:DCM);



8

Data for C1-C20 Aldehyde Fragment 8.

^{1}H NMR (500 MHz, C_6D_6) d 9.29 (s, 1H), 7.48 (s, 1H), 6.24 (d, J = 15.7 Hz, 1H), 6.12 (s, 1H), 5.15 (dd, J_1 = 9.6 Hz, J_2 = 6.8 Hz, 1H), 5.41 – 5.34 (m, 2H), 5.12 (d, J = 3.5 Hz, 1H), 5.07 (d, J = 9.7 Hz, 1H), 4.29 (t, J = 8.7 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.75 (dd, J_1 = 9.5 Hz, J_2 = 3.3 Hz, 1H), 3.49 (m, 1H), 3.41 – 3.37 (m, 2H), 3.37 (s, 3H), 3.25 (s, 3H), 3.08 (m, 1H), 2.77 – 2.69 (m, 2H), 2.56 – 2.48 (m, 1H), 2.06 (s, 3H), 1.92 – 1.86 (m, 2H), 1.80 (s, 3H), 1.77 (s, 3H), 1.53 (s, 3H), 1.41 (d, J = 6 Hz, 3H), 1.23 (d, J = 6 Hz, 3H), 1.18 (t, J = 7.5 Hz, 9H), 1.09 – 1.01 (m, 21H), 0.94 – 0.89 (m, 6H), 0.75 – 0.63 (m, 14 H) ppm;

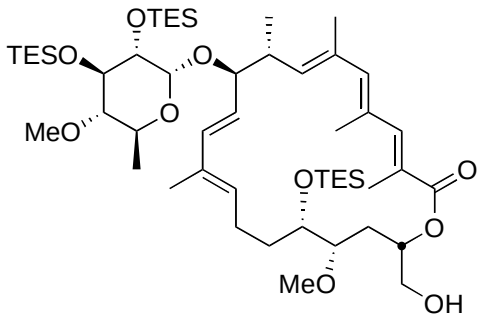
^{13}C NMR (100 MHz, C_6D_6) d 197.51, 168.32, 146.51, 145.71, 140.53, 140.17, 133.34, 132.72, 132.31, 132.16, 125.89, 123.20, 96.03, 87.86, 82.96, 81.28, 76.61, 75.42, 74.77, 74.69, 67.99, 61.07, 60.23, 38.29, 35.51, 32.59, 24.94, 18.67, 18.29, 16.93, 16.18, 13.88, 11.93, 7.44, 7.28, 7.28, 5.85, 5.59, 5.52 ppm;

IR (NaCl Thin Film) n = 2953, 2876, 1741, 1704, 1458, 1242, 1139, 1107, 1008, 743 cm^{-1};

MS (ESMS) *m/z* 1003.6 (1003.62 calcd for $C_{51}H_{92}O_{10}Si_3$ + MeOH + Na);

$[a]_D$ = +2.84 (c = 0.58 C_6H_6);

R_f = 0.55 (10:90 EtOAc:DCM);



9

Primary Alcohol 9. To a cooled solution (0 ˚C) of macrolide **8** (34.1 mg, 0.036 mmol) in 6 mL of THF was added $NaBH_4$ (6.0 mg, 0.16 mmol). The reaction was stirred for 50 min and quenched with saturated NH_4Cl (precooled to 0˚C) dropwise. The reaction was warmed to 24˚C and stirred for 10 min. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, decanted, and concentrated *in vacuo*. Quick purification by flash chromatography afforded 34.0 mg of olefin **9** (99%) as a colorless amorphous solid which was pure by TLC.

^{1}H NMR (500 MHz, $CDCl_3$) d d 7.18 (s, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 6.09 (s, 1H), 5.49 (t, *J* = 7.0 Hz, 1H), 5.15-5.10 (m, 3H), 4.76 (d, *J* = 3.5 Hz, 1H), 3.88 (t, *J* = 9.0 Hz, 1H), 3.81 (ddd, *J* = 12.0, 5.5, 3.0 Hz, 1H), 3.75 (t, *J* = 9.0 Hz, 1H), 3.69 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.64 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.56 (ddd, *J* = 9.0, 6.6, 3.5 Hz, 1H), 3.51 (s, 3H), 3.51-3.48 (m, 1H), 3.41 (s, 3H), 2.90 (dd, *J* = 8.5, 6.5 Hz, 1H), 2.65-2.60 (m, 1H), 2.64 (t, *J* = 9.0 Hz, 1H), 2.44-2.36 (m, 1H), 2.17 (t, *J* = 6.0 Hz, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.10-2.04 (m, 1H), 1.99-1.92 (m, 1H), 1.85 (d, *J* = 1.0 Hz, 3H), 1.81-1.76 (m, 1H), 1.71-1.66 (m, 1H), 1.55 (d, *J* = 0.5 Hz, 3H), 1.39-1.31 (m, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.99 (t, *J* = 7.5 Hz, 9H), 0.97 (t, *J* = 8.0 Hz, 9H), 072-0.66 (m, 12H), 0.61 (dq, *J* = 8.0, 1.5 Hz, 6H) ppm;

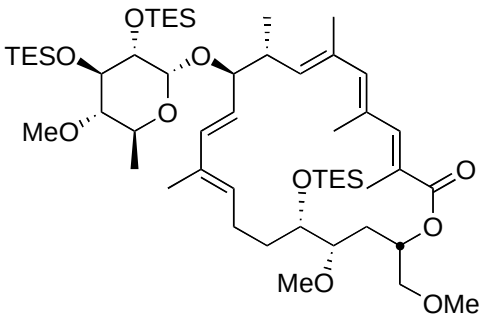
^{13}C NMR (125 MHz $CDCl_3$) d 169.7, 146.1, 145.5, 140.8, 139.8, 133.3, 131.83, 131.81, 128.3, 125.1, 123.0, 95.3, 87.3, 82.3, 81.3, 75.3, 74.0, 74.0, 73.6, 67.2, 65.9, 61.2, 61.0, 37.8, 35.5, 35.3, 24.4, 18.2, 18.0, 17.2, 16.3, 13.7, 11.8, 7.074, 7.068, 6.971, 5.28, 5.27, 5.05 ppm;

IR (NaCl Thin Film) n = 3468, 2954, 2877, 1699, 1459, 1415, 1381, 1241, 1108, 1017, 743 cm^{-1};

MS (+ESMS) *m/z* = 973.5 (973.6 calcd for $C_{51}H_{94}O_{10}Si_3$ + Na);

[a]$_D$ = -26.9 (c = 2.53, THF);

$\mathbf{R_f}$ = 0.20 (20% EtOAc/petroleum ether);



10

Protected Methyl Ether 10. To a cooled solution (0 ˚C) of olefin **9** (5.7 mg, 6.0 µmol) in 1.5 mL CH_2Cl_2 were added 2,6-di-*tert*-butyl-4-methylpyridine (13.5 mg, 66 µmol), and trimethyloxonium tetrafluoroborate (6.0 mg, 41 µmol). The reaction was warmed to 25˚C and stirred for 10 h. The reaction was quenched with 0.5 M HCl. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, decanted, and concentrated *in vacuo*. Purification by flash chromatography afforded 2.4 mg of ether **10** (41%) as a colorless amorphous solid which was pure by TLC.

^{1}H NMR (500 MHz, $CDCl_3$) d 7.16 (s, 1H), 6.09 (d, *J* = 14.0 Hz, 1H), 6.07 (s, 1H), 5.48 (t, *J* = 5.4 Hz, 1H), 5.20-5.16 (m, 1H), 5.11 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 3.5 Hz, 1H), 3.88 (t, *J* = 9.0 Hz, 1H), 3.75 (t, *J* = 9.5 Hz, 1H), 3.71-3.68 (m, 1H), 3.57 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.55-3.52 (m, 1H), 3.51 (s, 3H), 3.49 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.48 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 2.84 (dd, *J* = 9.6, 7.6 Hz, 1H), 2.66-2.59 (m, 2H), 2.44-2.36 (m, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 1.96-1.90 (m, 1H), 1.86-1.80 (m, 1H), 1.84 (d, *J* = 1.0 Hz, 3H), 1.70-1.64 (m, 2H), 1.61 (s, 3H), 1.59-1.51 (m, 1H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.02-0.95 (m, 27H), 0.72-0.60 (m, 18H); ppm;

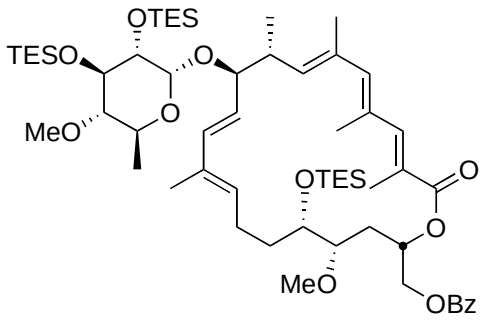
^{13}C NMR (125 MHz, $CDCl_3$) d 168.71, 145.53, 145.12, 140.47, 139.84, 133.11, 131.94, 131.89, 131.81, 125.02, 123.19, 95.33, 87.26, 82.32, 81.45, 75.52, 74.35, 74.02, 73.96, 70.49, 67.20, 61.22, 61.15, 59.28, 37.79, 35.63, 35.43, 24.52, 18.21, 18.05, 17.28, 16.37, 13.76, 11.75, 7.08(2C), 6.97, 5.28, 5.24, 5.04 ppm;

IR (NaCl Thin Film) n = 2953, 2914, 2876, 1703, 1461, 1380, 1242, 1108, 1017, 743 cm^{-1};

MS (ESMS) *m/z* 987.5 (987.6 calcd for $C_{52}H_{96}O_{10}Si_3$ + Na);

[a]$_D$ = -24.5 (*c* = 0.22, $CHCl_3$);

R_f = 0.18 (8:92 EtOAc:petroleum ether);



11

Protected Benzoate 11. To a cooled solution (0 ˚C) of olefin **9** (5.9 mg, 6.2 µmol) in 1.1 mL of CH_2Cl_2 were added Et_3N (0.01 mL, 137 µmol) dropwise, Bz_2O (3.3 mg, 15 µmol), and 4-(dimethylamino)pyridine (0.01 mL of a 0.12 M solution in CH_2Cl_2, 1.2 µmol). The reaction was warmed to 25˚C and stirred for 2 h. To the reaction mixture was added more 4-(dimethylamino)pyridine (0.01 mL of a 0.12 M solution in CH_2Cl_2, 1.2 µmol). The reaction was stirred for another 18 h. Bz_2O (3.4 mg, 15 µmol) and Et_3N (0.01 mL, 137 µmol) were then added. The reaction mixture was stirred for another 10 h. The reaction was quenched with 0.5 M HCl. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. Purification by flash chromatography afforded 4.8 mg of ester **11** (73%) as a colorless amorphous solid which was pure by TLC.

^{1}H NMR (500 MHz, $CDCl_3$) d d 8.06-8.02 (m, 2H), 7.58-7.55 (m, 1H), 7.46-7.42 (m, 2H), 7.14 (t, *J* = 1.0 Hz, 1H), 6.11 (d, *J* = 16.0 Hz, 1H), 6.05 (s, 1H), 5.48 (t, *J* = 7.5 Hz, 1H), 5.45-5.40 (m, 1H), 5.12 (dd, *J* = 13.0, 2.5 Hz, 1H), 5.10 (d, *J* = 15.5 Hz, 1H), 4.76 (d, *J* = 3.0 Hz, 1H), 4.49 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.38 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.88 (t, *J* = 9.0 Hz, 1H), 3.76 (t, *J* = 9.0 Hz, 1H), 3.69 (dddd, *J* = 9.5, 6.0, 6.0, 6.0 Hz, 1H), 3.60-3.56 (m, 1H), 3.51 (s, 3H), 3.49 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.42 (s, 3H), 2.93 (ddd, *J* = 8.7, 6.2, 1.5 Hz, 1H), 2.63 (t, *J* = 9.4 Hz, 1H), 2.66-2.60 (m, 1H), 2.42-2.33 (m, 1H), 2.12 (s, 3H), 2.08 (d, *J* = 1Hz, 3H), 2.04-1.94 (m, 2H), 1.86 (d, *J* = 1.0 Hz, 3H), 1.86-1.76 (m, 2H), 1.62 (s, 3H), 1.60-1.52 (m, 1H), 1.44-1.38 (m, 1H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.02-0.94 (m, 27H), 0.72-0.58 (m, 18H) ppm;

^{13}C NMR (125 MHz $CDCl_3$) d 168.4, 166.2, 145.8, 145.3, 141.1, 139.8, 133.3, 133.0, 131.9, 131.8, 131.7, 129.9, 129.8, 128.4, 125.1, 123.0, 95.3, 87.3, 82.2, 80.9, 75.2, 74.02, 73.97, 69.2, 67.2, 66.0, 61.2, 60.9, 37.7, 35.5, 35.3, 24.3, 18.2, 18.1, 17.3, 16.3, 13.8, 11.8, 7.1,

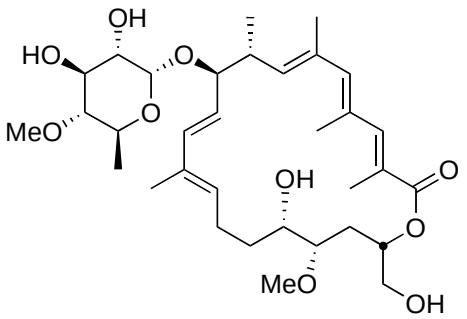
7.0, 5.3, 5.0 ppm;

IR (NaCl Thin Film) n = 2953, 2915, 2876, 1727, 1704, 1454, 1275, 1239, 1107, 1017, 745 cm^{-1};

MS (+ESMS) *m/z* = 1077.6 (1077.6 calcd for $C_{58}H_{98}O_{11}Si_3$ + Na);

[a]$_D$ = +11.9 (*c* = 0.33, CHCl3);

R_f = 0.48 (8:92 EtOAc:Pentane);



12

Macrolide 12. In a Nalgene vial containing olefin **9** (7.4 mg, 0.0078 mmol) in 1.0 mL of THF was added 0.35 mL of buffered pyridinium hydrofluoride (stock solution prepared fresh from 0.5 g of pyridinium hydrofluoride, 1.0 mL of pyridine, and 4 mL of THF, exothermic reaction). After 7 h, the reaction mixture was cooled to 0 ˚C and quenched with saturated $NaHCO_3$ (precooled to 0 ˚C) carefully. The reaction was warmed to 24 ˚C and the aqueous layer was extracted six times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. Purification by flash chromatography afforded 4.7 mg of tetrol **12** (100%) as a colorless amorphous solid which was pure by TLC.

^{1}H NMR (600 MHz, C_6D_6) d 7.48 (s, 1H), 6.11 (s, 1H), 6.04 (d, J = 15.9 Hz, 1H), 5.52 (dd, J_1 = 6.9 Hz, J_2 = 9.9 Hz, 1H), 5.30 – 5.27 (m, 1H), 5.09 – 5.03 (m, 2H), 4.97 (d, J = 10.6 Hz, 1H), 3.99 – 3.94 (m, 1H), 3.90 (t, J = 8.9 Hz, 1H), 3.51 (s, 3H), 3.55 – 3.35 (m, 4H), 3.19 (s, 3H), 2.98 (t, J = 6.7 Hz, 1H), 2.76 (t, J = 9.4 Hz, 1H), 2.57 – 2.51 (m, 2H), 2.12 (s, 3H), 2.06 – 2.00 (m, 2H), 1.84 (s, 3H), 1.85 – 1.80 (m, 1H), 1.66 (s, 3H), 1.75 – 1.58 (m, 3H), 1.51 (s, 3H), 1.39 (d, J = 6.0 Hz, 3H), 1.41 – 1.32 (m, 4H), 1.13 (d, J = 6.6 Hz, 3H) ppm;

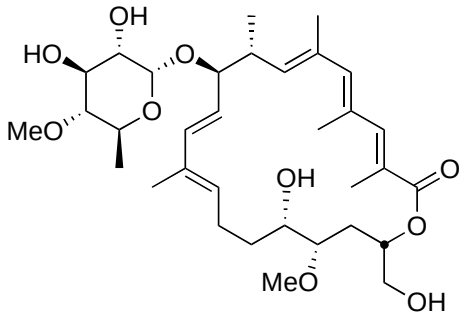
^{13}C NMR (125 MHz, C_6D_6) d 169.37, 145.97, 145.13, 140.75, 140.26, 133.57, 133.45, 132.35, 132.29, 124.74, 123.96, 94.75, 85.39, 83.25, 82.42, 75.84, 74.10, 73.73, 73.29, 67.71, 65.39, 60.59, 59.93, 38.17, 35.36, 34.99, 24.79, 18.23, 18.18, 17.17, 16.26, 13.99, 11.85 ppm;

IR (NaCl Thin Film) n = 3412, 2930, 1694, 1385, 1246, 1084, 732 cm^{-1};

MS (ESMS) *m/z* 631.4 (631.4 calcd for $C_{33}H_{52}O_{10}$ + Na);

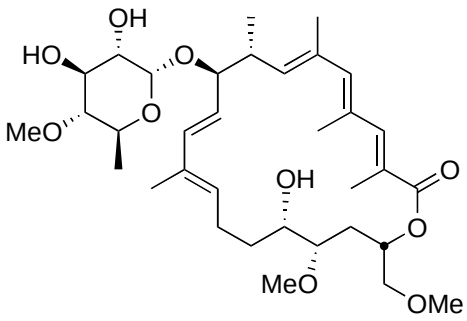
$[a]_D$ = -67 (*c* = 0.16, C_6H_6);

R_f = 0.59 (10:90 MeOH:DCM);



12

! no.	! dH	Compound **12** in C_6D_6 20˚C dC	600 MHz (^{1}H) 125 MHz (^{13}C) no.	! dH	! dC
1	-	169.37	2-Me	2.12	13.99
2	-	124.74	4-Me	1.84	17.17
3	7.48	145.97	6-Me	1.66	16.26
4	-	132.29	8-Me	1.13	18.23
5	6.11	145.13	12-Me	1.51	11.85
6	-	133.45	17-OMe	3.19	59.93
7	4.97	140.26	1′	5.05	94.75
8	2.53	38.17	2′	3.47	73.29
9	3.89	83.17	3′	3.90	75.84
10	5.05	123.96	4′	2.76	85.39
11	6.04	140.75	5′	3.97	67.71
12	-	133.57	6′	1.39	18.18
13	5.52	132.35	4′-OMe	3.51	60.59
14a	2.02	24.79			
14b	2.55	-			
15a	1.33	34.99			
15b	1.37	-			
16	3.38	73.73			
17	2.98	82.42			
18a	1.82	35.36			
18b	1.67	-			
19	5.29	74.10			
20a	3.45	65.39			
20b	3.51	-			



13

Macrolide Methyl Ether 13. In a Nalgene vial containing ether **10** (6.2 mg, 6.4 µmol) in 1.2 mL of THF was added 0.29 mL of buffered pyridinium hydrofluoride (stock solution prepared fresh from 0.5 g of pyridinium hydrofluoride, 1.0 mL of pyridine, and 4 mL of THF, exothermic reaction). After 12 h, the reaction mixture was cooled to 0˚C, and quenched dropwise with saturated $NaHCO_3$ (4 mL). The aqueous layer was extracted with EtOAc (80 mL). The organic layer was washed twice with 1 M HCl (5 mL), saturated $NaHCO_3$, and brine, dried over Na_2SO_4, decanted, and concentrated in vacuo. Purification by flash chromatography and then reverse phase HPLC afforded triol **13** (1.1 mg, 27%) as a colorless amorphous solid which was pure by TLC.

^{1}H NMR (500 MHz, CD_3OD) d 7.22 (s, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 6.11 (s, 1H), 5.69 (dd, *J* = 9.6, 6.5 Hz, 1H), 5.24-5.19 (m, 2H), 5.17-5.12 (m, 1H), 4.80 (d, *J* = 4.0 Hz, 1H), 3.83 (t, *J* = 9.5 Hz, 1H), 3.76-3.69 (m, 2H), 3.57 (s, 3H), 3.52-3.47 (m, 2H), 3.38 (s, 3H), 3.35 (s, 3H), 3.44-3.35 (m, 2H), 2.82-2.79 (m, 1H), 2.75-2.69 (m, 2H), 2.51-2.44 (m, 1H), 2.15 (s, 3H), 2.06 (d, *J* = 1.0 Hz, 3H), 2.08-2.01 (m, 1H), 1.90 (d, *J* = 1.0 Hz, 3H), 1.81-1.79 (m, 2H), 1.68 (s, 3H), 1.53-1.40 (m, 2H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H);

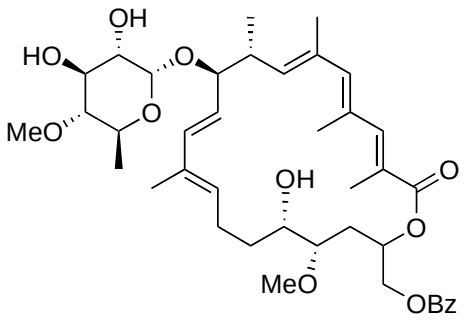
^{13}C NMR (125 MHz, CD_3OD) d 170.26, 147.36, 146.55, 142.21, 141.30, 134.81, 133.37, 133.34, 133.03, 126.40, 124.09, 96.10, 87.51, 84.27, 83.52, 75.36, 74.93, 74.69, 73.62, 71.96, 68.19, 61.09, 61.01, 59.39, 38.82, 36.73, 36.22, 24.71, 18.34, 18.25, 17.53, 16.48, 13.81, 12.02 ppm;

IR (NaCl Thin Film) n = 3400, 2930, 1697, 1245, 1110, 1015 cm^{-1};

MS (ESMS) *m/z* 645.2 (645.36 calcd for $C_{34}H_{54}O_{10}$ + Na);

$[a]_D$ = -71 (*c* = 0.11, MeOH);

R_f = 0.29 (EtOAc);



14

Benzoate 14. In a Nalgene vial containing ester **11** (6.6 mg, 6.3 µmol) in 1 mL of THF was added 0.28 mL of buffered pyridinium hydrofluoride (stock solution prepared fresh from 0.5 g of pyridinium hydrofluoride, 1.0 mL of pyridine, and 4 mL of THF, exothermic reaction). After 7 h, the reaction mixture was cooled to 0˚C, and quenched dropwise with saturated $NaHCO_3$ (4 mL). The aqueous layer was extracted with EtOAc (80 mL). The organic layer was washed twice with 1 M HCl (5 mL), saturated $NaHCO_3$, and brine, dried over Na_2SO_4, decanted, and concentrated *in vacuo*. Purification by flash chromatography and then reverse phase HPLC afforded triol **14** (1.0 mg, 21 %) as a colorless amorphous solid which was pure by TLC.

^{1}H NMR (500 MHz, CD_3OD) d 8.01 – 7.99 (m, 2H), 7.62 – 7.59 (m, 1H), 7.49 – 7.46 (m, 2H), 7.21 (s, 1H), 6.17 (d, J = 15.7 Hz, 1H), 6.06 (s, 1H), 5.69 – 5.66 (m, 1H), 5.39 – 5.34 (m, 1H), 5.21 (dd, J_1 = 9.2 Hz, J_2 = 15.7 Hz, 1H), 5.17 (d, J = 10.5 Hz, 1H), 4.80 (d, J = 3.8 Hz, 1H), 4.57 (dd, J_1 = 3.7 Hz, J_2 = 11.7 Hz, 1H), 4.31 (dd, J_1 = 6.1 Hz, J_2 = 11.8 Hz, 1H), 3.82 (t, J = 9.2 Hz, 1H), 3.75 – 3.68 (m, 2H), 3.56 (s, 3H), 3.47 – 3.44 (m, 1H), 3.40 (s, 3H), 3.38 (dd, J_1 = 4.2 Hz, J_2 = 10.1 Hz, 1H), 2.89 – 2.86 (m, 1H), 2.74 – 2.69 (m, 2H), 2.50 – 2.44 (m, 1H), 2.14 (s, 3H), 2.10 – 2.02 (m, 1H), 2.04 (s, 3H), 1.92 – 1.89 (m, 2H), 1.89 (s, 3H), 1.67 (s, 3H), 1.58 – 1.42 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.12 (d, J = 6.6 Hz, 3H) ppm;

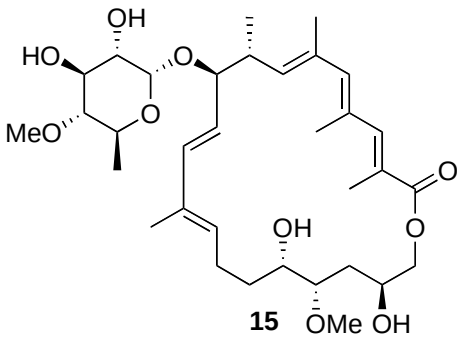
^{13}C NMR (125 MHz, CD_3OD) d 170.12, 167.63, 147.63, 146.79, 124.43, 141.28, 134.87, 134.40, 133.36, 133.32, 132.98, 131.18, 130.66, 129.63, 126.42, 123.87, 96.10, 87.52, 84.27, 83.33, 74.93, 74.56, 73.62, 71.13, 68.20, 67.11, 61.17, 61.02, 38.80, 36.54, 36.22, 24.63, 18.33, 18.25, 17.46, 16.42, 13.80, 12.03 ppm;

IR (NaCl Thin Film) n = 3400, 2929, 1704, 1276, 1236, 1108, 1026 cm^{-1};

MS (ESMS) *m/z* 735.3 (735.37 calcd $C_{40}H_{56}O_{11}$ + Na);

$[a]_D$ = -17 (*c* = 0.1, MeOH);

R_f = 0.48 (EtOAc);



15

Macrolide 15. To an NMR tube containing macrolide **12** (1.6mg, 2.63 µmole) in CD_3OD (800 µL) was added triethylamine (2 µL, 27 µmole). The mixture was allowed to sit at ambient temperature while conversion of **12** to **15** was monitored periodically by proton NMR. After 72h, no **12** could be detected by NMR. The solvent was removed under a stream of nitrogen followed by high vacuum to produce a colorless amorphous solid which was pure by TLC. The sample was redissolved in C_6D_6 for spectral comparison with **12**.

^{1}H NMR (600 MHz, C_6D_6) d 7.35 (s, 1H), 6.07 (d, J = 15.8 Hz, 1H), 6.00 (s, 1H), 5.42 (t, J = 7.9 Hz, 1H), 5.15 (dd, J_1 = 7.9 Hz, J_2 = 15.8 Hz, 1H), 5.04 (d, J = 3.8 Hz, J = 3.8 Hz, 1H), 5.02 (d, J = 9.9 Hz, 1H), 4.17 (dd, J_1 = 5.6 Hz, J_2 = 11.2 Hz, 1H), 4.09 (dd, J_1 = 2.87 Hz, J_2 = 11.2 Hz, 1H), 3.99 – 3.83 (m, 4H), 3.50 (s, 3H), 3.53 – 3.45 (m, 3H), 3.22 – 3.19 (m, 1H), 3.15 (s, 3H), 2.75 (t, J = 9.2 Hz, 1H), 2.63 – 2.58 (m, 1H), 2.45 – 2.38 (m, 1H), 2.23 (s, 1H), 2.17 – 2.09 (m, 1H), 2.11 (s, 3H), 2.00 (d, J = 4.5 Hz, 1H), 1.93 (d, J = 4.8 Hz, 1H), 1.86 (s, 3H), 1.88 – 1.63 (m, 1H), 1.59 (s, 6H), 1.61 – 1.51 (m, 1H), 1.38 (d, J = 6.2 Hz, 3H), 1.39 – 1.27 (m, 2H), 1.10 (d, J = 6.6 Hz, 3H) ppm;

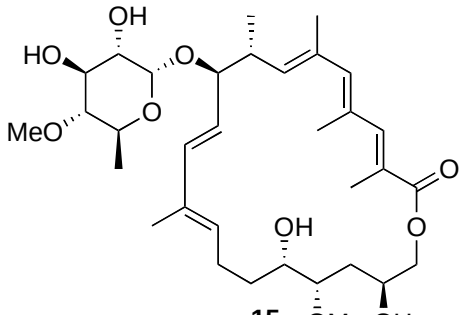
^{13}C NMR (125 MHz, C_6D_6) d 168.73, 145.10, 143.35, 140.12, 136.45, 135.79, 133.61, 133.22, 132.05, 124.75, 123.59, 95.08, 85.43, 82.58, 82.29, 75.83, 73.38, 73.02, 67.77, 67.71, 66.91, 60.55, 59.14, 38.51, 34.63, 33.16, 32.29, 18.18, 18.02, 17.08, 17.03, 13.99, 11.92 ppm;

IR (NaCl Thin Film) n = 3400, 2928, 1694, 1446, 1380, 1249, 1112, 1082, 1058, 1029 cm^{-1};

MS (ESMS) *m/z* 631.3 (631.34 calcd $C_{33}H_{52}O_{10}$ + Na);

$[a]_D$ = -58 (*c* = 0.08, CD_3OD);

R_f = 0.59 (10:90 MeOH:DCM);



15

!		Compound **15** in C_6D_6 20˚C	600 MHz (^{1}H) 125 MHz (^{13}C)		!
no.	! dH	dC	no.	dH	dC
1	-	168.73	2-Me	2.12	13.99
2	-	124.75	4-Me	1.86	17.03
3	7.35	145.10	6-Me	1.59	17.08
4	-	132.05	8-Me	1.11	18.02
5	6.00	143.35	12-Me	1.59	11.92
6	-	135.79	17-OMe	3.15	59.14
7	5.03	136.45	1′	5.04	95.08
8	2.60	38.51	2′	3.47	73.02
9	3.94	82.29	3′	3.89	75.83
10	5.15	123.59	4′	2.74	85.43
11	6.07	140.12	5′	3.97	67.71
12	-	133.61	6′	1.38	18.18
13	5.42	133.22	4′-OMe	3.50	60.55
14a	2.14	33.16			
14b	2.41	-			
15a	1.32	32.29			
15b	1.32	-			
16	3.47	73.38			
17	3.19	82.58			
18a	1.72	34.63			
18b	1.54	-			
19	3.84	66.91			
20a	4.17	67.77			
20b	4.09	-			