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Total Synthesis of the Polyene Macrolide Roflamycoin

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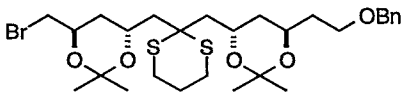
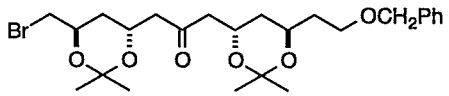
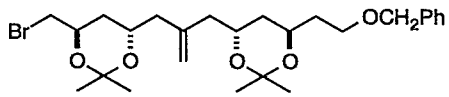


(3*R*,5*S*,9*R*,11*R*)-12-Bromo-7-(1,3-dithiane-2,2'-yl)-3,5:9,11-bis-*O*-(1-methylethyledene)-1-*O*-(phenylmethyl)-dodecane-1,3,5,9,11-pentol (5): To a solution of dithiane (obtained after protection of diol 3 as an acetonide) (0.80 g, 1.19 mmol, 1.00 equiv) in 3 mL of THF under Ar at –40 °C was added dropwise a 2.50 M solution of butyllithium (0.48 mL, 1.21 mmol, 1.01 equiv). After stirring for 1 h, a solution of dibromide 4 (0.69 g, 2.30 mmol, 1.93 equiv) in 1.5 mL of THF was added dropwise followed by addition of DMPU (2 mL, 16.5 mmol, 14 equiv). The reaction mixture was then warmed up to –10 °C. After stirring overnight (16 h) at –10 °C, the reaction was quenched by addition of 3 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (SiO_2, 5% ethyl acetate/hexanes) gave the product (430 mg, 60%) as a colorless oil: $[\alpha]^{24}_D = +4.79°$ (*c* 1.79, CH_2Cl_2); IR (neat) 2985, 2937, 2857, 1454, 1441, 1421, 1379, 1223, 1170, 1125, 1102, 1038, 1027, 993, 907, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.35 (m, 5 H), 4.47 (s, 2 H), 4.06-4.12 (m, 2 H), 3.93-3.97 (m, 2 H), 3.51-3.55 (m, 2 H), 3.33-3.36 (m, 2 H), 2.72-2.78 (m, 4 H), 1.58-1.65 (m, 2 H), 1.28-1.37 (m, 12 H); ^{13}NMR (75 MHz, $CDCl_3$, DEPT) : δ *C* 138.55, 101.17, 100.59; *C*H 128.43 (2), 127.75 (2), 127.62, 66.94, 64.05, 63.89, 63.83; *C*H_2 73.18, 66.71,

43.86, 43.72, 39.67, 38.07, 36.06, 35.38, 26.30, 26.21, 25.28; *C*H_3 24.84 (2), 24.79, 24.63. Anal. Calcd. for $C_{28}H_{43}O_5S_2$: C, 55.71; H, 7.18. Found: C, 55.81; H, 6.97.

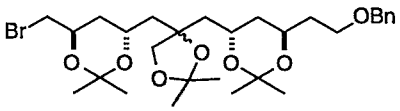


(3*R*,5*S*,9*R*,11*R*)-12-Bromo-7-oxo-3,5:9,11-bis-*O*-(1-methylethyledene)-1-*O*-(phenylmethyl)-dodecane-1,3,5,9,11-pentol: To a solution of dithiane **5** (92 mg, 0.15 mmol, 1 equiv) and $CaCO_3$ (270 mg, 2.69 mmol, 18 equiv) in THF (7 mL) and H_2O (1.5 mL) was added dropwise a 2.0 M aqueous solution of $Hg(ClO_4)_2$ (170 μL, 0.34 mmol, 2.26 equiv). After stirring for 30 min at 23 °C, the reaction mixture was diluted with Et_2O and filtered through a plug of neutral alumina. The organic layer was separated, dried (Na_2SO_4), and concentrated to give product (66 mg, 85%) as a colorless oil: $[\alpha]^{24}_D$ = +8.61° (*c* 1.3, CH_2Cl_2); IR (neat) 2986, 2937, 2858, 1716, 1454, 1380, 1223, 1117, 1098, 738, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 5 H), 4.47 (s, 2 H), 4.20-4.36 (m, 2 H), 3.28-3.36 (m, 2 H), 2.65-2.76 (m, 2 H), 2.42-2.52 (m, 2 H), 1.62-1.84 (m, 6 H), 1.36 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ *C* 206.22, 138.33, 100.96, 100.40; *C*H 128.26 (2), 127.59 (2), 127.46, 66.55, 62.85 (2), 62.79; *C*H_2 73.00, 66.39, 49.30, 48.98, 38.01, 36.54, 35. 76, 34.98; *C*H_3 24.61, 24.59, 24.49, 24.41. Anal. Calcd. for $C_{25}H_{37}BrO_6$: C, 58.48; H 7.26. Found C, 58.33; H 7.43.



(3*R*,5*R*,9*S*,11*R*)-12-Bromo-7-methylene-3,5:9,11-bis-*O*-(1-methylethyledene)-1-*O*-(phenylmethyl)-dodecane-1,3,5,9,11-pentol: To a solution of ketone obtained from previous step (92 mg, 0.163 mmol, 1 equiv) in THF (3 mL) was added 0.5 M solution of Cp_2TiMe_2 in toluene (1.31 mL, 4 equiv) under nitrogen

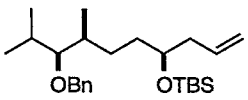
in dark and the reaction mixture was heated at 75 °C. After stirring for 48 h at this temperature, the reaction mixture was gradually cooled to 0 °C and was diluted with hexanes. The resulting yellow-orange precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 8% ethyl acetate/hexanes) gave 77 mg (85%) of the product as a colorless oil: $[\alpha]^{24}_D$ = +4.36° (*c* 1.1, CH_2Cl_2); IR (neat) 3068, 3029, 2985, 2931, 2854, 1644, 1495, 1443, 1454, 1379, 1223, 1125, 1100, 903, 735, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.36 (m, 5 H), 4.85 (s, 2 H), 4.82 (s, 2 H), 3.93-4.05 (m, 4 H), 3.52-3.59 (m, 2 H), 3.35 (d, *J* = 5.77 Hz, 2 H), 2.23-2.32 (m, 2 H), 2.09-2.18 (m, 2 H), 1.57-1.79 (m, 6 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 1.25 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 138.65, 101.07, 100.49; *C*H 128.54 (2), 127.86 (2), 127.74, 66.97, 65.37 (2), 63.89; *C*H_2 113.97, 73.29, 66.82, 42.73, 42.63, 38.59, 36.97, 36.17, 35.60; *C*H_3 25.11, 24.98, 24.93, 24.80. Anal. Calcd. for $C_{26}H_{39}BrO_5$: C, 61.05; H 7.68. Found C, 60.89; H 7.53.



(3*R*,5*S*,9*R*,11*R*)-12-Bromo-7-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-3,5:9,11-bis-*O*-(1-methylethyledene)-1-*O*-(phenylmethyl)-dodecane-1,3,5,9,11-pentol (6): To a stirred solution of alkene obtained from previous step (64 mg, 0.12 mmol, 1 equiv) and *N*-methylmorpholine-*N*-oxide hydrate (28 mg, 0.24 mmol, 2 equiv) in 2 mL of acetone:water (9:1) was added 0.025 mL (0.0025 mmol, 2%) of OsO_4 solution (2.5% in *t*-BuOH). After 40 h at 25 °C the reaction was quenched by addition of Celite and 0.2 mL of 0.5 M $Na_2S_2O_4$ solution. The mixture was filtered through Celite after 1 h and concentrated under reduced pressure to give the crude diol as a colorless oil. It was then dissolved in 6 mL of acetone and 2 mL of 2,2-dimethoxypropane with 5 mg of CSA and stirred for 14 h. The crude product was purified by chromatography on silica

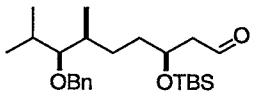
gel, eluting with 8% ethyl acetate/hexanes to give major diastereomer of 6 (41 mg, 0.075 mmol, 62%): IR (neat) 2984, 2937, 2859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.38 (m, 5 H), 4.47 (s, 2 H), 3.91-3.99 (m, 4 H), 3.87 (s, 2 H), 3.51-3.59 (m, 2 H), 3.34 (d, J = 5.58 Hz, 2 H), 1.87-1.97 (m, 2 H), 1.53-1.78 (m, 8 H), 1.38 (s, 9 H), 1.33 (s, 6H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 138.50, 108.65, 100.79, 100.25; *C*H 128.38 (2), 127.69 (2), 127.57, 66.82, 63.70, 63.32, 63.23; *C*H_2 73.12, 70.84, 66.62, 44.69, 44.44, 40.06, 38.42, 35.99, 35.34; *C*H_3 27.19, 27.09, 24.91, 24.85 (2), 24.76.

In addition to the major diastereomer, 20 mg (0.036 mmol, 31%) of the minor diastereomer was also isolated. IR (neat) 2985, 2937, 2857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.39 (m, 5 H), 4.47 (s, 2 H), 3.92-4.10 (m, 4 H), 3.72 (s, 2 H), 3.43-3.58 (m, 2 H), 3.35 (d, J = 5.80, 2 H), 1.76-1.93 (m, 2 H), 1.53-1.78 (m, 8 H), 1.35 (s, 9 H), 1.33 (s, 6 H), 1.30 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 138.49, 107.90, 100.67, 100.12; *C*H 128.38 (2), 127.70 (2), 127.57, 66.82, 62.72 (2), 63.42, 63.24; *C*H_2 75.34, 73.10, 66.64, 42.59, 42.39, 39.21, 37.53, 35.98, 35.37; *C*H_3 27.34 (2), 24.97, 24.83 (2), 24.68. Anal. Calcd. for $C_{29}H_{45}BrO_7$: C, 59.48; H 7.75. Found C, 59.54; H 7.76.

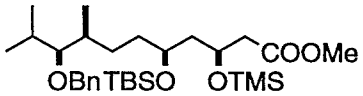


(3*S*,4*S*,7*S*)-3-*O*-(Phenylmethyl)-7-*O*-((1,1-dimethylethyl)dimethylsilyl)-2,4-dimethyl-9-decene-3,7-diol: To a salt-free solution of B-allyldiisopinocampheylborane (14.5 mmol, 2 equiv, prepared from (–)-α-pinene) in 10 mL of ether, a pre-cooled (–78 °C) solution of aldehyde **8** (1.8 g, 7.25 mmol, 1 equiv) in 2 mL of ether was added dropwise at –100 °C. The reaction mixture was stirred for 1 h and quenched with 0.5 mL of methanol and was then allowed to warm to 23 °C. The reaction mixture was cooled to 0 °C and oxidized with NaOH (9 mL, 3 N) and 30% H_2O_2 (7 mL). After stirring for 12 h, the reaction mixture was diluted with water, extracted with ether (3 x 15 mL), washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (5% ethyl acetate/hexanes) to give product which was contaminated by isopinocampheol. The contaminated product was then dissolved in 50 mL of CH_2Cl_2 under N_2, and the solution was cooled to 0 °C. 2,6-Lutidine (1.35 mL, 11.58 mmol, 1.5 equiv) was added to the solution followed by TBSOTf (2.13 mL, 9.26 mmol, 1.2 equiv). After stirring at 0 °C for 30 min , the reaction mixture was allowed to warm to 23 °C and stirred overnight. The reaction was then quenched by addition of 15 mL of saturated $NaHCO_3$ solution. The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 x 15 mL), washed (brine), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 2.12 g, (75% for two steps) of the product as a colorless oil: $[\alpha]^{24}_D$ = – 8.15° (*c* 1.52, CH_2Cl_2); IR (neat) : 2957, 2930, 2857, 1471, 1463, 1455, 1254, 1095, 1068, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.45 (m, 5 H), 5.86-5.90 (m, 1 H), 5.09-5.13 (m, 2 H), 4.67 (s, 2 H), 3.74 (t, *J* = 10.74 Hz, 1 H), 3.03 (dd, *J* = 6.76, 4.37 Hz, 1 H), 2.24-2.33 (m, 2 H), 1.95-2.01 (m, 1 H), 1.76 (br s, 1 H), 1.44-1.56 (m, 4 H), 1.08 (d, *J* = 6.76 Hz, 3 H), 0.97-1.05 (m, 15 H), 0.13 (s, 3 H), 0.12 (s, 3 H). ^{13}C

NMR (125 MHz, $CDCl_3$, DEPT) : δ *C* 139.38, 18.14; *C*H 135.34, 128.24 (2), 127.56, 127.42, 127.27, 89.39, 72.85, 36.53, 31.62; *C*H_2 116.70, 75.16, 42.00, 34.66, 30.25; *C*H_3 25.93 (3), 20.25, 18.18, 14.41, –4.3, –4.45. Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.20; H, 10.96. Found: C, 74.39; H, 10.72.



(3*S*,4*S*,7*S*)-3-*O*-((1,1-Dimethylethyl)dimethylsilyl)-7-*O*-(phenylmethyl)-6,8-dimethyl-3,7-dihydroxy-1-decanal (9) : To a stirred solution of alkene obtained from previous step (0.824 g, 2.03 mmol, 1 equiv) and *N*-methylmorpholine-*N*-oxide hydrate (0.405 g, 3.45 mmol, 1.7 equiv) in 10 mL of acetone : water (8 : 2) was added 0.6 mL (0.06 mmol, 3%) of OsO_4 solution (2.5% in *t*-BuOH). After 12 h at 25 °C, the mixture was diluted with water, extracted with Et_2O (2 x 15 mL), washed (Na_2SO_3, brine) and concentrated. The crude product was purified by chromatography on silica gel eluting with 10% ethyl acetate/hexanes to give 0.642 g (78%) of the product as colorless oil: IR (neat) : 2957, 2932, 2859, 1726, 1463, 1383, 1363, 1255, 1101, 1067, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : δ 9.80 (s, 1 H), 7.31-7.37 (m, 5 H), 4.54-4.63 (m, 2 H), 4.11-4.17 (m, 1 H), 2.90-2.96 (m, 1 H), 1.86-1.96 (m, 2 H), 1.57-1.71 (m, 3 H), 1.31-1.46 (m, 2 H), 1.22-1.35 (m, 1 H), 0.99-1.02 (m, 3 H), 0.90-0.95 (m, 6 H), 0.87 (s, 9 H), 0.066 (s, 3 H), 0.051 (s, 3 H). This sensitive aldehyde was used in the next step without further purification.

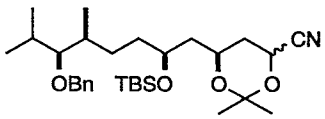


Methy [3*S*,4*S*,7*S*,9*S*]-3-*O*-(phenylmethyl)-7-*O*-((1,1-dimethylethyl)-dimethylsilyl)-9-*O*-(trimethylsilyl)-2-4-dimethyl-3,7,9-

trihydroxyundecanoate (10): Schiff Base (Catalyst) Formation: A solution of (*R*)-(+)-2-amino-2'-hydroxy-1,1'-binapthyl (25 mg, 0.087 mmol) and 3-bromo-5-*tert*-butyl-salicylaldehyde (27 mg, 0.105 mmol) in 1 mL of absolute ethanol was heated at reflux for 24 h. After removal of the volatiles, the product was purified on silica gel column (15% ethyl acetate/hexanes). The orange product was dissolved in 5 mL of CH_2Cl_2 and washed with 5 mL of 5% aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), solvent was evaporated and the resulting powder (28 mg) was dried over vacuum (0.1 mm) overnight.

Aldol Reaction : To the solution of Schiff base (28 mg) in toluene (22 mL) was added Ti(*i*-PrO)$_4$ (0.24 mmol, 6.9 mg, 7.3 μL) under N_2. The orange solution was stirred for 1 h at 23 °C and 3,5-di-*tert*-butyl salicylic acid (0.029 mmol, 6.9 mg) was added in 1 mL of toluene. Stirring was continued for additional 1 h. The solvent was removed under vacuum and the solid orange residue was dissolved in ether (5 mL). The solution was cooled to –78 °C, and 2,6-lutidine (0.098 mmol, 10.54 mg, 12 μL) was added, followed by aldehyde **9** (0.492 mmol, 196 mg) in ether (2 mL) and excess of ketene silyl acetal (150 μL). The reaction was stirred at –10 °C for 3 d, and quenched with 5% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The pure product was obtained (0.907 mg, 84%) by flash chromatography (SiO_2, 10% ethyl acetate/hexanes): IR (neat) 2956, 2930, 2858, 1742, 1471, 1463, 1382, 1362, 1251, 1098, 1069, 838, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5 H); 4.61 (s, 2 H); 4.24-4.60 (m, 1 H); 3.67 (s, 3 H); 2.94-2.97 (m, 1 H); 2.49-2.52 (m, 2 H); 2.39-2.44 (m, 2 H); 1.89-1.91 (m, 1 H); 1.67-1.71 (m, 3 H); 1.44-1.63 (m, 4 H), 0.99 9 (d, J = 6.3 Hz, 3 H); 0.93-0.97 (m, 6 H); 0.89 (s, 9 H); 0.06 (d, J = 7.9 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.95, 139.23, 128.26, 128.12, 127.55, 127.38, 127.23, 90.36, 89.12, 75.11, 69.62, 66.92, 51.39, 45.20, 42.82, 36.01, 34.96, 30.88, 29.98, 25.83, 20.19, 18.59, 17.96, 14.38,

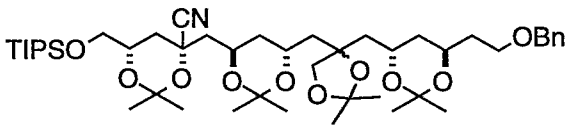
0.33, 0.22, –4.35, –4.52. Anal. Calcd for $C_{30}H_{56}O_5$: C, 65.17; H, 10.21. Found: C, 65.29; H, 10.24.



(3*S*,4*S*,7*S*,9*R*,11*R*)-and(3*S*,4*S*,9*R*,11*S*)-3-*O*-(Phenylmethyl)-7-*O*-((1,1-dimethylethyl)dimethylsilyl)-9,11-*O*-(1-methyethyledene)-3,7,9,11-tetrahydroxyundecanenitrile (11): To a solution of **10** (0.823 g, 1.57 mmol, 1 equiv) in Et_2O at –78 °C was added dropwise a 1.0 M solution of DIBAL-H (1.73 mL, 1.73 mmol, 1.1 equiv) under N_2 and the reaction was stirred for 90 min. The reaction was quenched with 0.8 mL of ethyl formate followed by 10 mL of 10% aqueous AcOH solution and the reaction mixture was warmed to 0 °C. The layers were separated and the aqueous fraction was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The product was quickly purified by flash column chromatography (SiO_2, 10 % ethyl acetate/hexanes) to obtain the aldehyde (0.634 g, 82%).

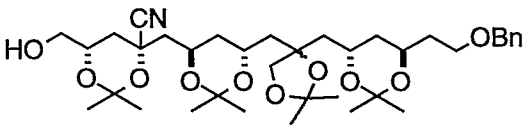
The aldehyde was cooled to 0 °C, and trimethylsilyl cyanide (180 μL, 1.34 mmol, 1.1 equiv) was added followed by 1 mg KCN/18-crown-6 complex. After stirring for 6 h at 23 °C, 70 mg CSA and 30 mL of acetone/2,2-dimethoxypropane (3:2) were added. After stirring for 16 h, 1 mL of Et_3N was added and the reaction mixture was concentrated under reduced pressure. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave (280 mg, 47%) of the desired product as a colorless oil. $[\alpha]^{24}_D = -6.5°$ (*c* 0.4, CH_2Cl_2); IR (neat) : 2956, 2931, 2858, 1472, 1383, 1362, 1256, 1205, 1162, 1068, 1029, 1004, 983, 836, 809, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.38(m, 5 H), 4.82-4.84 (m, 0.5 H), 4.71-4.73 (m, 0.5 H), 4.56-4.62 (m, 2 H), 4.31-4.33 (m, 0.5 H), 4.01-4.02 (m, 0.5 H), 3.76-3.81 (m, 1 H), 2.93-2.97 (m, 1 H), 1.60-1.82 (m, 4 H), 1.56 (s, 3 H),

1.32-1.47 (m, 4 H), 1.31 (s, 3 H), 1.26 (s, 3 H), 0.88 (d, J = 6.76, 3 H), 0.76-0.86 (m, 15 H), 0.07-0.09 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ *C* 139.23, 119.88, 117.80, 100.69, 99.85, 18.66; *C*H 128.84, 128.79, 127.94, 127.91, 127.86, 1217.83, 89.74, 89.66, 69.23, 69.20, 65.61, 63.29, 59.67, 59.36, 36.40, 36.37, 31.49, 26.39; *C*H_2 75.71, 75.69, 43.54, 43.44, 35.29, 35.26, 34.10, 29.91; *C*H_3 30.99, 26.38 (3), 22.24, 20.78, 20.76, 19.58, 19.32, 19.24, 14.93, 14.83, –3.74, –3.92. Anal. Calcd for $C_{30}H_{51}NO_4Si$: C, 69.59; H, 9.93. Found: C, 69.83; H, 10.05.



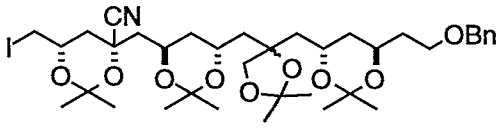
(2*S*,4*S*,6*R*,8*R*,12*S*,14*R*)-4-Cyano-10-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-2,4:6,8:12,14-tris-*O*-(1-methylethylidine)-16-*O*-phenylmethyl-1-*O*-(tri(1-methylethyl))silyl-hexadecane-1,2,4,6,8,12,14,16-octanol: To a solution of $LiNEt_2$ (0.51 mmol, 3.0 equiv) in 5 mL THF under Ar at –78 °C was added nitrile **12** (138 mg, 0.42 mmol, 2.5 equiv) in 0.6 mL THF via cannula. After stirring for 1 h, DMPU (80 μL, 0.67 mmol, 4.0 equiv) was added, followed by a solution of bromide **6** (100 mg, 0.17 mmol, 1.0 equiv) dissolved in 0.5 mL of THF. The reaction mixture was allowed to warm up to 23 °C slowly in an ice-methanol bath. The reaction was then quenched with 5 mL of saturated $NaHCO_3$ solution and 5 mL of H_2O. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave the product (120 mg, 85%) as a colorless syrup. $[\alpha]^{24}_D$ = +15.3° (*c* 4.45, $CHCl_3$); IR (neat) 2986, 2941, 2867, 1462, 1380, 1224, 1175, 1124, 1054, 992, 942, 910, 883, 803, 772, 738, 688, 661 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (m, 5 H), 4.34 (m, 2 H), 4.26 (AB, J = 4.0 Hz, 2 H), 3.98 (m, 3 H), 3.83 (dd, J = 17.2, 1.9 Hz, 2 H), 3.64 (dd, J = 10.0, 4.7 Hz, 1 H), 3.50 (dd, J = 10.3, 5.6 Hz, 1 H), 3.45 (ddd, J = 8.6, 8.5, 5.6 Hz, 1 H), 3.36 (ddd, J = 9.4,

5.6, 5.5 Hz, 1 H), 2.10 (m, 1 H), 1.90 (m, 2 H), 1.84-1.50 (m, 7 H), 1.66 (s, 3 H), 1.42 (s, 3 H), 1.38 (s, 6 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 1.27 (s, 3 H), 1.40-1.30 (m, 7 H), 1.01 (s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ *C* 138.4, 121.4, 108.5, 100.8, 100.5, 100.2, 81.9, 68.7; *C*H 128.3 (2), 127.6 (2), 126.5, 67.0, 63.6, 63.15, 63.10, 62.3, 11.8 (3); *C*H_2 73.0, 70.7, 66.5, 66.1, 47.8, 44.6, 44.4, 40.2, 40.0, 38.1, 35.9; *C*H_3 30.8, 27.1, 27.0, 24.8, 24.7, 24.5, 24.4, 21.6, 17.9 (6). HRMS (FAB) Calcd for $C_{46}H_{78}NO_{10}Si$ 832.5395, Found 832.5385 $[M + H]^+$.



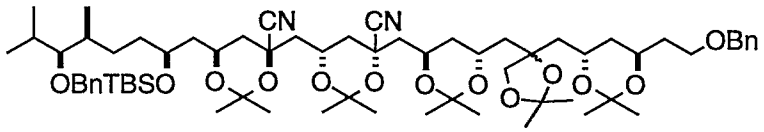
(2*S*,4*S*,6*R*,8*R*,12*S*,14*R*)-4-Cyano-10-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-2,4:6,8:12,14-tris-*O*-(1-methylethylidine)-16-*O*-phenylmethyl-hexadecane -1,2,4,6,8,12,14,16-nonol: To a solution of compound obtained from previous step (120 mg, 0.144 mmol, 1.0 equiv) and 5 mL dry THF at 0 °C was added TBAF (1.0 M solution in THF, 0.58 mL, 0.58 mmol, 4.0 equiv) dropwise and stirred for 2 h at 0 °C. The reaction was quenched with saturated NH_4Cl. THF was removed by rotovap. The residue was extracted by (3 × 10 mL) of CH_2Cl_2. Combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated under reduced pressure. Chromatography (SiO_2, 45% ethyl acetate/hexanes) gave a colorless heavy oil (88 mg, 89%) as the desired product: $[\alpha]^{24}_D$ = +19.2° (*c* 1.56, $CHCl_3$); IR (neat) 3466, 2986, 2939, 2868,2244, 1455, 1381, 1225, 1174, 1122, 1053, 994, 972, 940, 911, 881, 843, 816, 735, 699, 647 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 5 H), 4.45 (s, 2 H), 4.23 (m, 2 H), 3.95 (m, 3 H), 3.86 (s, 2 H), 3.68 (m, 1 H), 3.50 (m, 3 H), 2.15 (s, br, 1 H), 1.98–1.83 (m, 6 H), 1.76 (m, 2 H), 1.72 (s, 3 H), 1.69–1.59 (m, 6 H), 1.39 (s, 3 H), 1.38 (s, 6 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ *C* 138.4, 121.2, 108.5, 101.0, 100.5, 100.2, 81.9, 68.1;

*C*H 128.3 (2), 127.6 (2), 127.5, 66.8, 63.6 (2), 63.1, 62.1; *C*H_2 73.0, 70.9, 66.5, 65.1, 47.6, 44.6, 44.4, 40.2, 40.0, 36.5, 35.9; *C*H_3 30.8, 27.1, 27.0, 24.8, 24.7, 24.5, 24.4, 21.6. HRMS (FAB) Calcd for $C_{37}H_{58}NO_{10}$ 676.4060, Found 676.4061 $[M + H]^+$.



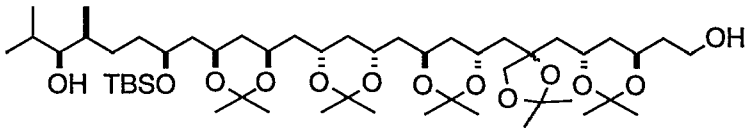
(2*S*,4*S*,6*R*,8*R*,12*S*,14*R*)-4-Cyano-1-iodo-10-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-2,4:6,8:12,14-trikis-*O*-(1-methylethylidine)-16-*O*-phenylmethyl-hexadecane-2,4,6,8,12,14,16-heptol (13): Alcohol made at previous step (138 mg, 0.2 mmol, 1.0 equiv), Ph_3P (185 mg, 0.7 mmol, 3.5 equiv) and imidazole (54 mg, 0.8 mmol, 4.0 equiv) were dissolved in 15 mL PhH/Et_2O (1 : 2). At 0 °C, iodine (152 mg, 0.6 mmol, 3.0 equiv) was added quickly, resulting a yellowish suspension. After stirring at 0 °C for 2.5 h, reaction mixture was diluted with 25 mL of Et_2O, washed with 0.5 M $Na_2S_2O_3$ (yellow color faded) and brine, dried with $MgSO_4$. Filtered and concentrated under reduced pressure. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave the desired product as a colorless oil (144 mg, 92%) : $[\alpha]^{24}_D$ = +18.3° (*c* 1.69, $CHCl_3$); IR (neat) 2988, 2940, 2861,2280, 2268, 1455, 1378, 1290, 1127, 990, 955, 908, 884, 813, 737, 699, 614, 600 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.22 (m, 5 H), 4.29–4.20 (m, 1 H), 4.26 (AB, *J* = 4 Hz, 2 H), 4.00 (m, 3 H), 3.83 (s, 2 H), 3.80 (m, 1 H), 3.43 (ddd, *J* = 9.5, 8.0, 5.5 Hz, 1 H), 3.35 (dt, *J* = 9.5, 5.5 Hz, 1 H), 2.64 (dd, *J* = 10.0, 6.0 Hz, 1 H), 2.58 (dd, *J* = 10.5, 5.0 Hz, 1 H), 1.98 (m, 2 H), 1.83 (dd, *J* = 13.5, 2.0 Hz, 1 H), 1.73–1.56 (m, 5 H), 1.54 (s, 3 H), 1.43–1.30 (m, 4 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H), 1.13 (dd, *J* = 14.0, 11.5 Hz, 2 H); ^{13}C NMR (125 MHz, C_6D_6, DEPT) δ *C* 138.9, 120.9, 108.3, 101.3, 100.2, 99.9, 81.7, 68.3; *C*H 128.1 (2), 127.3 (2), 127.2, 65.8, 63.4, 63.1 (2), 62.1; *C*H_2 72.7, 70.9, 66.3, 47.4, 44.7, 44.5, 40.6, 40.0 (2), 36.2, 7.7; *C*H_3 30.5, 27.1, 27.0,

24.7, 24.6, 24.44, 24.41, 21.3. HRMS (FAB) Calcd for $C_{37}H_{57}NO_9I$ 786.3080, Found 786.3082 $[M + H]^+$.



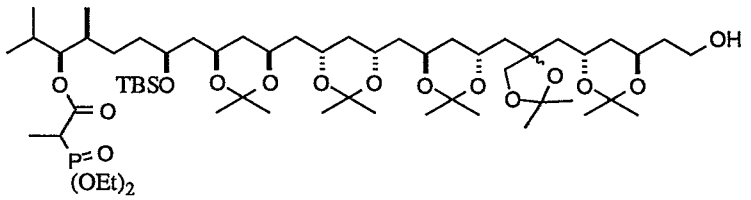
(3*R*,5*S*,9*R*,11*R*,13*S*,15*S*,17*S*,19*S*,21*S*,24*S*,25*S*)-13,17-Di-cyano-1,25-di-*O*-phenylmethyl-21-*O*-((1,1-dimethylethyl)dimethylsilyl)-3,5:9,11:13,15:17,19-tetrakis-*O*-(1-methylethylidine)-7-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-24,26-dimethyl-heptacosane-1,3,5,9,11,13,15,17,19,21,25-undecol (14): To a solution of $LiNEt_2$ (0.54 mmol, 3.0 equiv) in 5 mL THF under Ar at –78 °C, was added nitrile **11** (228 mg, 0.44 mmol, 2.4 equiv) in 0.6 mL THF via cannula. After stirring for 1 h, DMPU (87 µl, 0.72 mmol, 4.0 equiv) was added, followed by a solution of iodide **13** (142 mg, 0.18 mmol, 1.0 equiv) dissolved in 0.5 mL of THF. The reaction mixture was allowed to warm up to 23 °C slowly in an ice-methanol bath. The reaction was then quenched with 5 mL of saturated $NaHCO_3$ solution and 5 mL of H_2O. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography (SiO_2, 25% ethyl acetate/hexanes) gave a mixture of the product and unreacted iodide which upon MPLC separation gave recovered iodide **13** (27 mg, 19%) and the product (148 mg, 70%) as a colorless syrup: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.22 (m, 10 H), 4.61 (m, 1 H), 4.59 (s, 2 H), 4.48 (AB, J = 3.0 Hz, 2 H), 4.32 (m, 1 H), 4.22 (m, 1 H), 4.00 (m, 3 H), 3.88 (s, 2 H), 3.78 (m, 1 H), 3.53 (m, 2 H), 2.95 (dd, J = 7.0, 4.5 Hz, 1 H), 2.01–1.84 (m, 10 H), 1.77–1.60 (m, 8 H), 1.75 (s, 3 H), 1.70 (s, 3 H), 1.57–1.45 (m, 8 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 6 H). 1.30 (s, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ *C* 139.2, 138.4, 121.0,

120.9, 108.5, 101.0 (2), 100.5, 100.2, 81.8, 68.5, 67.8, 17.9; *C*H 128.3 (2), 128.2 (2), 127.6 (2), 127.5, 127.3 (2), 127.2, 89.0, 68.6, 63.6, 63.1 (2), 63.2, 62.3, 62.2, 35.8, 30.9; *C*H_2 75.1, 73.0,70.7, 66.5, 60.3, 47.8, 44.6, 44.4, 43.0, 41.1, 40.8, 40.2, 40.0, 35.9, 34.7, 29.9; *C*H_3 31.0, 30.8, 27.1, 25.8 (3), 24.8, 24.7, 24.6, 24.5, 21.5, 21.3, 20.2, 18.9, 14.4, –4.3, –4.5. HRMS (FAB) Calcd for $C_{67}H_{107}N_2O_{13}Si$ 1175.7542, Found 1175.7603 $[M + H]^+$.



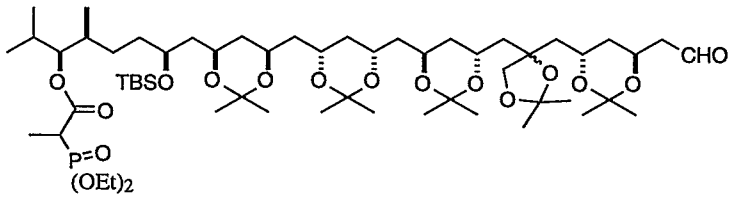
(3*R*,5*S*,9*R*,11*S*,13*R*,15*R*,17*S*,19*S*,21*S*,24*S*,25*S*)-7-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-21-O-[(1,1-dimethylethyl)dimethylsilyl]-3:5,9:11,13:15,17:19-tetrakis-*O*-(1-methylethylidine)-24,26-dimethylheptacosane-1,3,5,9,11,13,15,17,19,21,25-undecol (15): Lithium metal (80 mg, 11.5 mmol, 150 equiv) was dissolved in 15 mL of ammonia at –78 °C to give a bright blue solution. To this solution, then compound **14** (90 mg, 0.057 mmol, 1 equiv) in 5 mL of dry THF was added *via* cannula. After stirring for 1 h, the reaction was warmed to reflux and allowed to stir for an additional 30 min. The reaction was then quenched with 1 g of solid NH_4Cl and warmed to room temperature and the ammonia was allowed to evaporate. The resulting residue was dissolved in 20 mL of CH_2Cl_2 and H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were washed with water, brine, and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography (SiO_2, 40% ethyl acetate/hexanes) gave the product (48 mg, 69%) as a colorless syrup. IR (neat) 3550, 2983, 2935, 1379, 1223, 1166, 1133, 1053, 938, 835, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.14-4.07 (m, 8 H), 3.86 (m, 2 H), 3.77-3.73 (s, 4 H), 1.96-1.90 (m, 2 H), 1.80-1.62 (m, 12 H), 1.62-1.54 (m, 9 H), 1.54-1.42 (m, 14 H), 1.42-1.32 (m, 16 H), 1.32-1.28 (m, 6 H),

0.96 (d, J = 6.5 Hz, 3 H), 0.89-0.88 (m, 2 H), 0.87 (s, 9 H), 0.86 (s, 2 H), 0.85 (s, 1 H), 0.03 (d, J = 2.14 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl3, DEPT) *C* 108.60, 100.37, 100.27, 98.47, .98.32, 81.93; *C*H 80.03, 69.06, 66.85, 66.17, 65.31, 65.14, 63.36, 63.27, 62.42, 35.18, 30.78; *C*H$_2$ 70.84, 61.17, 44.78, 44.63, 43.56, 43.24, 42.31, 40.36, 39.77, 37.99 (2), 37.69, 34.27, 29.30; *C*H$_3$ 30.36, 30.30, 27.15, 27.09, 25.89, 24.91, 24.73, 24.60, 19.85, 19.76, 19.44, 18.39, 18.05, 13.16 (3), -4.35, -4.44. HRMS (FAB) Calcd for $C_{50}H_{93}O_{13}Si$ $(M–CH_3)^+$ 929.6385, Found 929.6392.

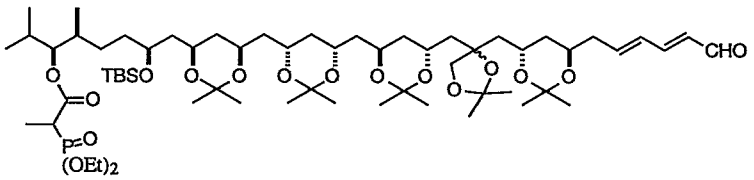


(3*R*,5*S*,9*R*,11*S*,13*R*,15*R*,17*S*,19*S*,21*S*,24*S*,25*S*)-7-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-21-*O*-[(1,1-dimethylethyl)dimethylsilyl]-25-*O*-(2-diethylphosphono)propionyl-3:5,9:11,13:15,17:19-tetrakis-*O*-(1-methylethylidine)-24,26-dimethylheptacosane-1,3,5,9,11,13,15,17,19,21,25,-undecol. A solution of 54 mg (0.25 mmol, 5.0 equiv) of the diethylphosphonopropionic acid in 2 mL of CH_2Cl_2 was added dropwise to a solution of a diol **13** (4.7 mg, 0.051 mmol, 1.0 equiv), DMAP (35 mg, 0.282 mmol, 5.5 equiv), and BOP (91 mg, 0.205 mmol, 4.0 equiv) at 23 °C. The mixture was stirred at 23 °C for 2 d and diluted with EtOAc, washed with NH_4Cl and $NaHCO_3$ solutions, dried (Na_2SO_4) and concentrated under reduced pressure. The crude bis-ester was then treated with 10 mL of NH_3 saturated MeOH for 4 d at 23 °C. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (60% ethyl acetate/hexanes) to give 43 mg (74%) of the product as a colorless syrup. Starting diol (8 mg, 17%) was also recovered. IR (neat) : 2984, 2936, 1734, 1379, 1311, 1167, 1052, 1025, 969, 940, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.1-4.2 (m, 4 H); 3.96-

4.08 (m, 5 H); 3.91-3.98 (m, 2 H); 3.88 (s, 2 H); 3.70-3.80 (br S, 4 H); 2.95-3.10 (m, 1 H); 1.88-1.98 (m, 3 H), 1.56-1.78 (m, 9 H); 1.24-1.52 (m, 52 H); 0.82-0.96 (m, 21 H), 0.02 (s, 6 H). HRMS (FAB) Calcd for $C_{58}H_{109}O_{17}PSi$ 1159.7069, Found 1159.7073 [M + Na]$^+$.



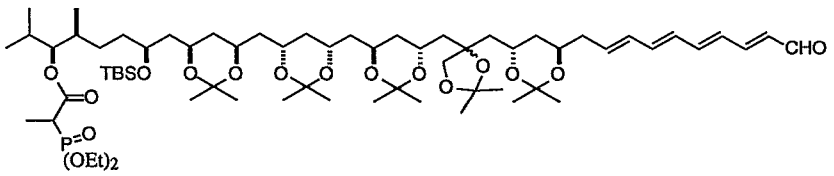
(3*R*,5*S*,9*R*,11*S*,13*R*,15*R*,17*S*,19*S*,21*S*,24*S*,25*S*)-7-(1,3-Dioxalan-2,2-dimethyl-4,4'-yl)-21-*O*-[(1,1-dimethylethyl)dimethylsilyl]-25-*O*-(2-diethylphosphono)propionyl-1-oxo-3:5,9:11,13:15,17:19-tetrakis-*O*-(1-methylethylidine)-24,26-dimethylheptacosane-3,5,9,11,13,15,17,19,21,25-decol-1-al (16): A solution of alcohol from the previous step (30 mg, 0.026 mmol. 1 equiv) in 3 mL of CH_2Cl_2 was treated with solid $NaHCO_3$ (56 mg, 0.06 mmol, 25 equiv) and Dess-Martin reagent (23 mg, 0.052 mmol, 2 equiv). After 4 h the reaction mixture was diluted with EtOAc, and quenched with saturated aqueous $NaHCO_3$ (5 mL) and 0.5 M $Na_2S_2O_3$ (5 mL). The organic portion was then washed with $NaHCO_3$, water, brine, dried (Na_2SO_4) and concentrated under reduced pressure to give 26.7 mg (89%) of the aldehyde as a colorless oil : IR (neat) 2986, 2940, 2863, 1729, 1459, 1376, 1234, 1172, 1131, 1053, 1033, 945, 832 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1 H), 4.95-4.97 (m, 1 H), 4.07-4.17(m,2 H), 3.89-4.11 (m, 9 H), 3.87 (s, 2 H), 3.81-3.85 (m, 2 H), 2.95-3.10 (m, 1 H), 2.12-1.8 (m, 1 H),1.95-2.12 (m, 2 H), 1.76-1.92 (m, 3 H), 1.62-1.66 (m, 2 H), 1.6 (s, 3 H), 1.35-1.54 (m, 31 H), 1.3 (s, 6 H), 1.22 (s, 6 H), 1.00-1.18 (m, 10 H), 0.98 (s, 9 H), 0.90-0.94 (m, 2 H), 0.75-0.88 (m, 9 H), 0.2 (s, 6 H).



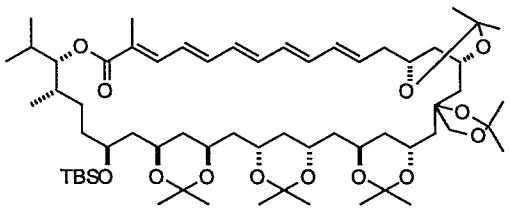
(6*R*,8*S*,12*R*,14*S*,16*R*,18*R*,20*S*,22*S*,24*S*,27*S*,28*S*)-10-(1,3-Dioxalan-2,2-dimethyl-4,4'-yl)-24-*O*-[(1,1-dimethylethyl)dimethylsilyl]-28-*O*-(2-diethylphosphono)propionyl-6:8,12:14,16:18,20:22-tetrakis-*O*-(1-methylethylidine)-27,29-dimethyl-1,3-dienal-triacontane-1-al-6,8,12,14,16,18,20,22,24,26-decol: The Grignard reagent was prepared by combining 1-(4-ethoxybutadienyl)tributylstannane (57 μL, 0.16 mmol, 7.02 equiv) and butyllithium (2.26 M in hexanes, 66 μL, 0.0148 mmol, 6.5 equiv) in 1 mL of THF at –78 °C followed by the addition of a 0.22 M solution of $MgBr_2$ in THF (0.4 mL, 0.0087 mmol, 3.8 equiv). A solution of aldehyde **16** (26 mg, 0.0023 mmol, 1 equiv) in 0.5 mL of THF was added to the Grignard solution at – 78 °C by cannula, and the flask was rinsed with another 0.5 mL of THF. After 1 h the reaction was warmed slowly to 0 °C and then quenched with pH 7 phosphate buffer. The mixture was stirred for 10 min and diluted with CH_2Cl_2 . The aqueous layer was extracted (2 x 5 mL) with CH_2Cl_2. The organic layers were dried with Na_2SO_4 and concentrated under reduced pressure.

The crude adduct was dissolved in 1 mL of CH_2Cl_2, cooled to –40 °C, and treated with Et_3N (70 μL, 20 equiv) followed by MsCl (22 μL, 10 equiv). After 30 min the reaction was quenched with pH 7 phosphate buffer. The mixture was stirred for 15 min, diluted with 15 mL of CH_2Cl_2, and then extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 50% ethyl acetate/hexanes) gave 20.7 mg (76%) of the dienal as a light yellow oil. IR (neat) 2986, 2940, 2863, 2355, 1727, 1684, 1641, 1464, 1377, 1248, 1224, 1167, 1109, 1042, 1028, 937, 893, 826, 774 cm^{-1}. ^1H NMR (500 MHz, C_6D_6) δ 9.31 (d, J = 7.75, 1 H), 6.31-6.36(m, 1 H), 5.83-5.88 (m, 1 H), 5.76-5.78 (m, 2 H), 4.98 (quintet, J = 9.2 Hz, 1

H), 3.88-4.19 (m, 14 H), 3.66 (d, J = 1.8 Hz, 1 H), 3.00-3.02 (m, 1 H), 2.05-2.11 (m, 3 H), 1.75-1.95 (m, 3 H), 1.68-1.73 (m, 2 H), 1.30-1.65 (m, 33 H), 1.28 (s, 6 H), 1.13-1.26 (m, 3 H), 0.81-0.96 (m, 28 H), 0.63 (br s, 4 H), 0.17 (s, 6 H).

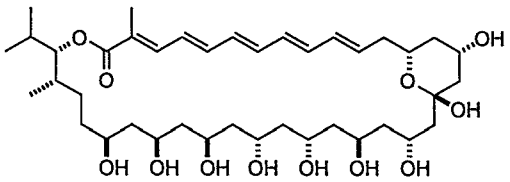


(10*R*,12*S*,16*R*,18*S*,20*R*,22*R*,24*S*,26*S*,31*S*,32*S*)-14-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-28-*O*-[(1,1-dimethylethyl)dimethylsilyl]-32-*O*-(2-diethylphosphono)propionyl-10:12,16:18,20:22,24:26-tetrakis-*O*-(1-methylethylidine)-31,33-dimethyl-1,3,5,7-tetraene-tetratriacontane-1-al-10,12,16,18,20,22,24,26,28,32-decol (17): The same procedure was repeated using the 20 mg (16.8 μmol, 1 equiv) of dienal and 64 μmol of the Grignard reagent to give 13.3 mg (10.5 μmol, 64%) of tetraenal **17**: ^{1}H NMR (500 MHz, C_6D_6) δ 9.38 (d, J = 7.78 Hz, 1 H), 6.45 (m, 1 H), 5.98-6.19 (m, 3 H), 5.78-5.95 (m, 4 H), 5.02 (m, 1 H), 3.82-4.22 (m, 14 H), 3.66 (m, 1 H), 2.96-3.05 (m, 1 H), 2.02-2.14 (m, 3 H), 1.81-1.98 (m, 3 H), 1.63-1.78 (m, 2 H), 1.29-1.56 (m, 33 H), 1.23-1.26 (m, 6 H), 1.12-1.19 (m, 3 H), 0.85-1.10 (m, 28 H), 0.55 (br s, 4 H), 0.12 (s, 6 H).



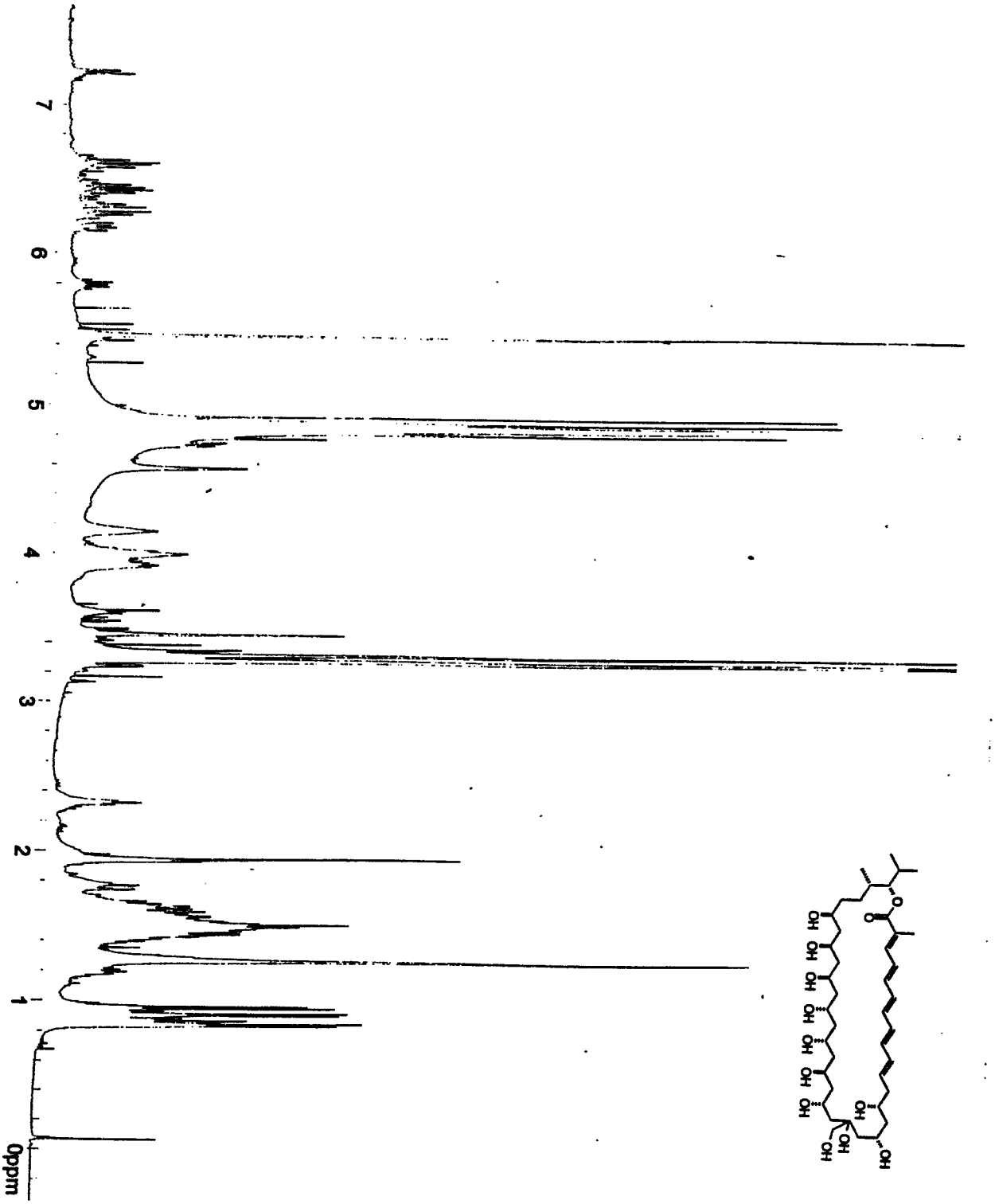
(13*R*,15*S*,19*R*,21*S*,23*S*,25*S*,27*R*,29*R*,31*R*,33*S*,35*S*)-17-(1,3-dioxalan-2,2-dimethyl-4,4'-yl)-13:15,19:21,23:25,27:29-pentakis-O-(1-methylethylidine)-31-O-((1,1-dimethylethyl)dimethylsilyl)roflamycoin (18):

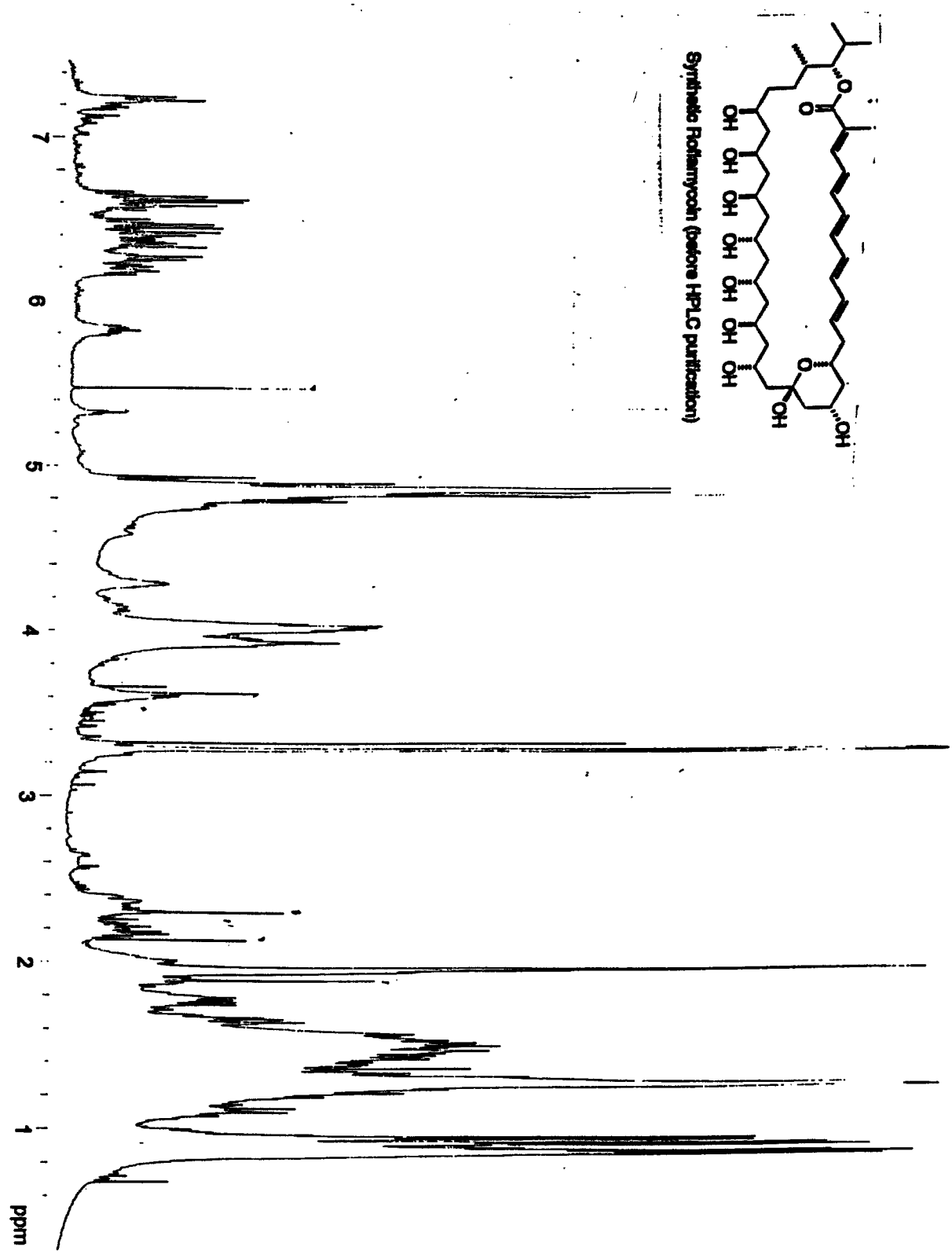
LiCl (9.0 mg, 0.21mmol, 21 equiv) was dried under high vacuum with heat gun and to it under N_2 was added tetraenal **17** (13 mg, 0.010 mmol, 1 equiv) in 8 mL of dry CH_3CN. The reaction mixture was stirred for 30 min at room temperature, followed by addition of 24 μL (0.16 mmol, 16 equiv) of DBU. The reaction mixture was stirred for 16 h, and then diluted with pH 7 phosphate buffer and extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 15% ethyl acetate/hexanes) gave 5 mg (44%) of the macrocyclic lactone : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.63 (d, J = 11.6 Hz, 1 H), 6.33-6.46 (m, 2 H), 6.19-6.25 (dd, J = 10.4, 14.6 Hz, 1 H), 5.98-6.15 (m, 4 H), 5.88-5.96 (m, 1 H), 5.08-5.10 (m, 1 H), 4.28-4.36 (m, 1 H), 4.08-4.24 (m, 2 H), 3.86-4.06 (m, 6 H), 3.66-3.76 (m, 2 H), 2.48-2.56 (m, 1 H), 2.19-2.25 (m, 1 H), 2.08-2.16 (m, 1 H), 1.90-1.97 (m, 3 H), 1.70-1.80 (m, 2 H), 1.56 (s, 3 H), 1.55 (s, 3 H), 1.52 (s, 6 H), 1.44-1.50 (m, 6 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.02-1.03 (d, J = 1.5 Hz, 1 H), 1.00 (s, 9 H), 0.98 (s, 3 H), 0.90-0.92 (m, 2 H), 0.70-0.90 (m, 9 H), 0.34 9s, 6 H), 0.15 (s, 3 H), 0.13 (s, 3 H); HRMS (FAB) Calcd for $C_{62}H_{104}O_{13}Si$ 1083.7171, Found 1083.7179 $(M - H)^+$.

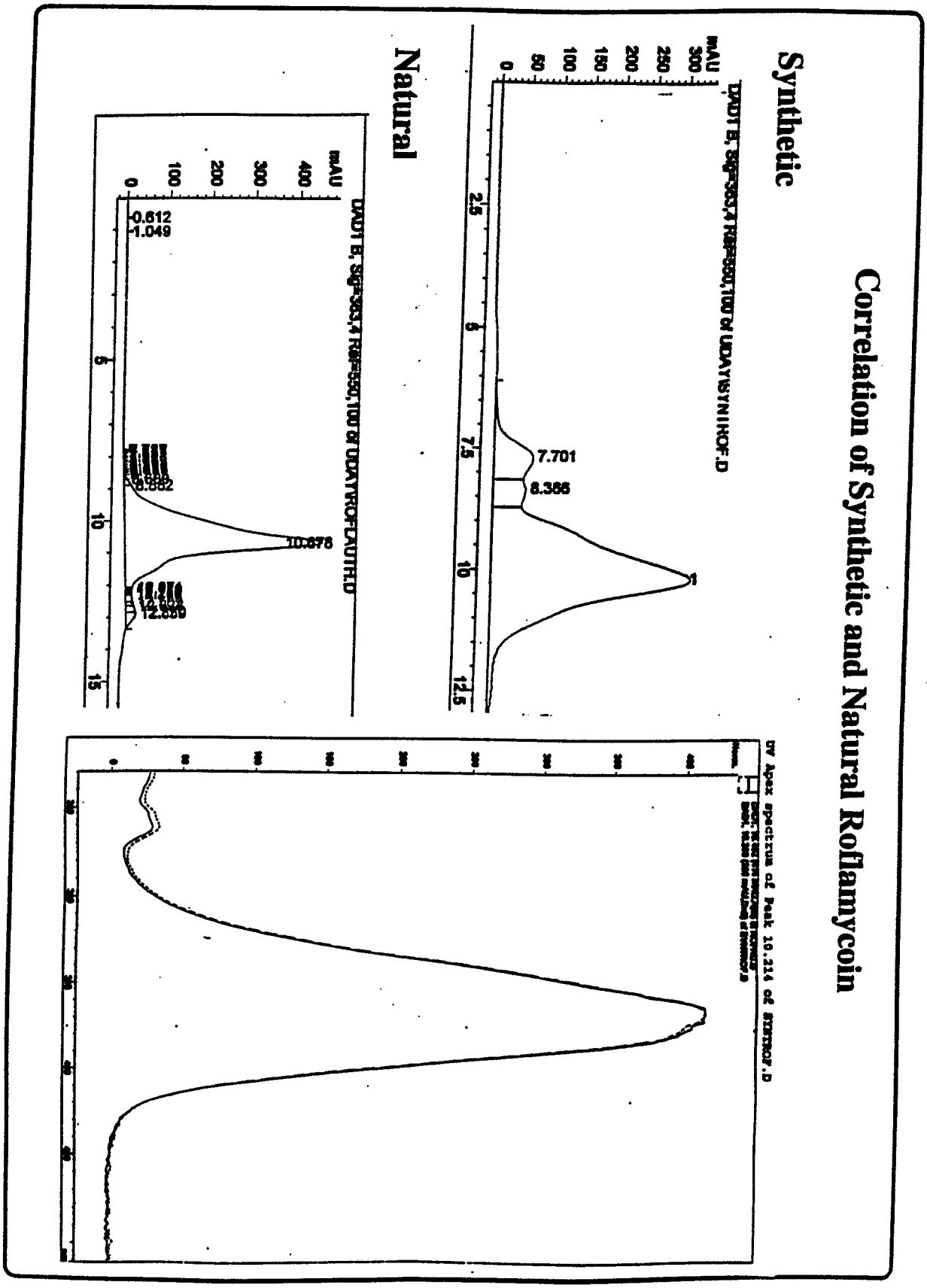


Roflamycoin: A solution of 5.0 mg (4.6 μmol) of protected roflamycoin **18** in 1 mL of MeOH was treated with 10 mg of Dowex 50 W-X1 acidic resin in the dark under N_2. After stirring for 10 h the reaction mixture was filtered and concentrated under reduced pressure. Column chromatography (SiO_2, 20% MeOH/ethyl acetate) gave 2.0 mg (2.5 μmol, 57%) of polyol **19**. This compound was dissolved in 600 μL of MeOH and to it in dark was added $NaIO_4$ (2 mg, 9.3 μmol, 3.74 equiv) dissolved in H_2O (200 μL). After 1.5 h, the

reaction mixture was directly loaded onto a flash column (SiO_2, 20% MeOH/ethyl acetate) to give Roflamycoin (1.8 mg, 2.4 μmol, 94%). It was further purified by reverse phase HPLC conditions, eluting with 80:20 MeOH/ H_2O to give 1.0 mg of Roflamycoin as a yellow solid which was found to be identical with natural roflamycoin by TLC mobility, ^1H NMR, UV, and reverse-phase HPLC analysis. HRMS (FAB) Calcd for $C_{40}H_{66}O_{12}Na$ 761.4451, Found 761.4454 $[M + Na]^+$.




Synthetic Roflamycoin (before HPLC purification)
OH
O
ppm
7
6
5
4
3
2
1


Correlation of Synthetic and Natural Roflamycoin
Synthetic
mAU
7.701
8.386
Natural
mAU
0.612
1.049
8.382
10.678
12.350