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Supporting Information

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Total Synthesis of Dinophysistoxin-2 and 2-*epi*-Dinophysistoxin-2 and Their PPase Inhibition**

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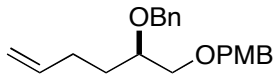
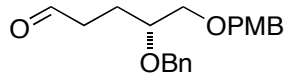
Total Synthesis of DTX2



(*R*)-1-(((2-(Benzyloxy)hex-5-en-1-yl)oxy)methyl)-4-methoxybenzene.

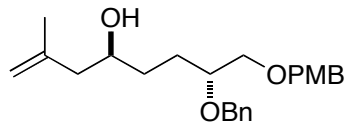
To a mixture of CuI (1.10 g, 5.78 mmol.) and diethyl ether (100 mL) at -20 °C was added 1.0 M solution of allylmagnesium bromide in diethyl ether (31 mL, 31 mmol) dropwise. After stirring for 30 min, a solution of (*R*)-2-(((4-methoxybenzyl)oxy)methyl)oxirane (5.62 g, 28.9 mmol) in 20 mL of diethyl ether was added to the reaction mixture. After another 1 h of stirring, 30 mL of saturated ammonium chloride solution was added to the reaction mixture and it was warmed to 25 °C. After the aqueous phase turned dark blue, the organic phase was separated and the aqueous phase was extracted with 100 mL of diethyl ether three times. The organic extracts were combined, dried over sodium sulfate, and filtered. Evaporation of the filtrate gave a light yellow oil which was then dissolved in 80 mL of THF. The solution was cooled to 0 °C and 2.2 g of a 60% suspension of NaH in mineral oil was added. The mixture was warmed to 25 °C and stirred for 1 h. After the reaction mixture was re-cooled to 0 °C, tetra-*n*-butylammonium bromide (0.50 g, 1.3 mmol) and benzyl bromide (4.2 mL, 35 mmol) were added and the reaction mixture was warmed to 25 °C. After stirred for 16 h, 2 mL of methanol followed by 20 mL of saturated aqueous ammonium chloride solution were added. After the mixture was warmed to room temperature, THF was evaporated and the aqueous mixture was extracted with 120 mL of diethyl ether four times. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexanes: EtOAc, 15:1, v/v) to give a colorless oil (7.80 g, 23.9 mmol, 84%, two steps): R_f 0.60 (hexanes-ethyl acetate, 8:1, v/v); $[\alpha]_D^{20}$ +10.1 (*c* 0.50, $CHCl_3$); IR (neat): 3024, 2927, 2860, 1719, 1510, 1454, 1246, 1089, 1039, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.79 (m, 1H), 5.00 (d, *J* = 12 Hz, 1H), 4.95 (d, *J* = 10 Hz, 1H), 4.68 (d, *J* = 12 Hz, 1H), 4.55 (d, *J* = 12 Hz, 1H), 4.49 (s, 2H), 3.81 (s, 3H), 3.60 (m, 1H), 3.55 (dd, *J* = 10, 4.5 Hz, 1H), 3.50 (dd, *J* = 10, 4.5 Hz, 1H), 2.15 (m, 2H), 1.66 (m, 2H)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 138.9, 138.5, 130.5, 129.2, 128.3, 127.8, 127.5, 114.7, 113.8, 77.6, 73.0, 72.5, 72.0, 55.3, 31.3, 29.7; HRMS calcd for $C_{21}H_{26}O_3Na$ $[M + Na]^+$: 349.1780; found : 349.1776.



(*R*)-4-(Benzyloxy)-5-((4-methoxybenzyl)oxy)pentanal (**13**)

To a mixture of (*R*)-1-(((2-(Benzyloxy)hex-5-en-1-yl)oxy)methyl)-4-methoxybenzene (6.80 g, 20.8 mmol), CH_2Cl_2 (120 mL) and methanol (60 mL) at -78 °C was treated with ozone until a light blue color persisted. The excess ozone was then displaced with argon and triphenylphosphine (5.47 g, 20.8 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 2 h more. The solvent was then evaporated and the residue was purified by chromatography (hexanes: ethyl acetate, 6:1, v/v) to provide **13** (5.70 g 17.3 mmol, 83%) as a colorless oil:

R_f 0.46 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ +23.2 (*c* 0.44, $CHCl_3$); IR (neat): 3024, 2927, 2860, 1719, 1510, 1454, 1246, 1089, 1039, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.71 (t, *J* = 1.5 Hz, 1H), 7.33 (m, 5H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.47 (s, 2H), 3.81 (s, 3H), 3.60 (m, 1H), 3.55 (dd, *J* = 10, 4.5 Hz, 1H), 3.48 (dd, *J* = 10, 4.5 Hz, 1H), 2.49 (m, 2H), 1.91(m, 2H);); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 159.3, 138.4, 130.2, 129.3, 128.4, 127.9, 127.7, 113.8, 76.8, 73.1, 72.0, 71.9, 55.3, 40.0, 24.8; HRMS calcd for $C_{21}H_{28}O_5Na$ [M + Na+CH_3OH]$^+$: 383.1834, found: 383.1832.

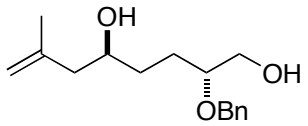


(4*S*,7*R*)-7-(Benzyloxy)-8-((4-methoxybenzyl)oxy)-2-methyloct-1-en-4-ol (**14**)

A mixture of (*R*)-(+)-1,1'-bi-2-naphthol (0.430 g, 1.50 mmol), Ti(O*i*-Pr)$_4$ (0.44 mL, 1.50 mmol) and oven-dried powdered 4Å molecular sieves (7.2 g) in CH_2Cl_2 (20 mL) was heated at reflux for 1 h. The red-brown mixture was cooled to room temperature and a solution of **13** (4.25 g, 12.9 mmol) in CH_2Cl_2 (10 mL) was added. After being stirred for 10 min, the contents were cooled to -78 °C, and 2-methyl-allyl tri-n-butylstannane (6.00 g, 17.4 mmol) was added. The reaction was stirred for 10 min then placed in a -20 °C freezer for 72 h. A solution of saturated $NaHCO_3$ (4 mL) was added and the mixture was stirred for 1 h. Na_2SO_4 (6.0 g, 42.2 mmol) was then added and the mixture was filtered through a plug of Celite and

concentrated. The residue was purified by flash chromatography (hexanes-EtOAt, 4:1, v/v) to give **14** as a light yellow oil (4.98 g, 12.9 mmol, quant.):

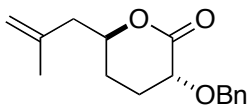
R_f 0.32 (hexanes-ethyl acetate, 4:1, v/v); IR (neat): 3444, 3067, 3022, 2918, 2856, 1644, 1614, 1586, 1454, 1302, 1247, 1173, 1089, 891, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32 (m, 5H), 7.27 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.49 (s, 2H), 3.81(s, 3H), 3.70 (m, 1H), 3.63 (m, 1H), 3.57 (dd, J = 10, 5 Hz, 1H), 3.52 (dd, J = 10, 5 Hz, 1H), 2.14 (m, 2H), 1.99 (brs, 1H), 1.77 (m,1H), 1.76 (s, 3H), 1.64 (m, 2H), 1.47 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 142.9 138.8, 130.5, 129.3, 128.3, 127.9, 127.5, 113.8, 113.3, 78.3, 77.3, 73.1, 72.4, 72.0, 68.9, 55.3, 46.2, 33.0, 28.4, 22.4; HRMS calcd for $C_{24}H_{32}O_4Na$ $[M + Na]^+$: 407.2198, found: 407.2231.



(2*R*,5*S*)-2-(Benzyloxy)-7-methyloct-7-ene-1,5-diol (**15**)

To a mixture of **14** (2.00g, 5.20 mmol), *tert*-butanol (1.0 mL), pH = 7 buffer (4.0 mL) and CH_2Cl_2 (40 ml) at 25 °C was added 2,3-dichloro-5,6-dicyanobenzoquinone (1.77 g, 7.80 mmol). The mixture was stirred for 2 hours before a saturated $NaHCO_3$ solution (80 mL) was added. The mixture was then diluted with 100 mL of diethyl ether and the organic phase was separated. The aqueous phase was further extracted with diethyl ether (5×50 mL) and the combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (hexanes-EtOAc, 1:1, v/v) to give **15** (1.09 g, 4.16 mmol, 80%) as a light pink oil.

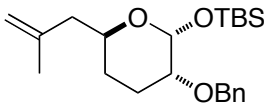
R_f 0.25 (hexanes-ethyl acetate, 1:1, v/v); IR (neat): 3390, 3070, 3031, 2930, 2872, 1645, 1454, 1381, 1346, 1207, 1067, 890, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36 (d, J = 4.5 Hz, 4H), 7.30 (m, 1H), 4.89 (t, J = 1.5 Hz, 1H), 4.79 (d, J = 1 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 3.71 (m, 2H), 3.57 (m, 2H), 2.18 (dd, J = 13, 3.5 Hz, 1H), 2.11 (dd, J = 13, 9 Hz, 1H), 1.95 (brs, 1H), 1.87 (brs, 1H), 1.75 (s, 3H), 1.73 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.6, 138.4, 128.5, 127.9, 127.8, 113.6, 79.7, 71.6, 68.7, 64.2, 46.2, 32.7, 27.1, 22.4; HRMS calcd for $C_{16}H_{24}O_3Na$ $[M + Na]^+$: 283.1623, found: 283.1629.



(3*R*,6*S*)-3-(Benzyloxy)-6-(2-methylallyl)tetrahydro-2*H*-pyran-2-one (16)

To a solution of **15** (0.90 g, 3.40 mmol) in CH_2Cl_2 (30 mL) was added iodobenzene diacetate (2.74 g, 8.51 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (0.0265 g, 0.170 mmol). The reaction mixture was stirred for 12 h before saturated $Na_2S_2O_3$ solution (10 mL) was added. Diethyl ether (60 mL) was then added to the mixture and the organic phase was separated. The aqueous phase was then extracted with diethyl ether (3 × 20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to give compound **16** (0.75 g, 4.61 mmol, 83%) as a colorless oil.

R_f 0.36 (hexanes-ethyl acetate, 8:1, v/v); $[\alpha]_D^{20}$ +96.0 (*c* 0.31, $CHCl_3$); IR (neat): 3074, 3031, 2936, 2860, 1747, 1650, 1454, 1378, 1312, 1249, 1192, 1129, 1057, 895, 738, 700 cm^{-1} ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37 (m, 5H), 4.91 (d, *J* = 12 Hz, 1H), 4.86 (s, 1H), 4.78 (s, 1H), 4.71-464 (m, 1H), 4.67 (d, *J* = 12 Hz, 1H), 3.96 (dd, *J* = 7, 5 Hz, 1H), 2.47 (dd, *J* = 12, 8 Hz, 1H), 2.24 (dd, *J* = 12, 6 Hz, 1H), 2.16 (m, 1H), 2.00 (m, 2H), 1.96 (s, 3H), 1.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 140.4, 137.4, 128.5, 128.1, 128.0, 114.0, 78.4, 73.9, 72.7, 44.0, 26.9, 26.5, 22.7. HRMS calcd for $C_{16}H_{20}O_3Na$ $[M + Na]^+$: 283.1310; found: 283.1310.

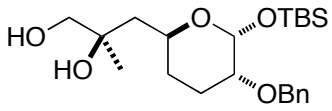


(((2*R*,3*R*,6*S*)-3-(Benzyloxy)-6-(2-methylallyl)tetrahydro-2*H*-pyran-2-yl)oxy)(*tert*-butyl)dimethylsilane (17)

To a solution of **16** (0.68 g, 2.61 mmol) in CH_2Cl_2 (22 mL) at -78 °C was added diisopropylaluminum hydride (1 M in toluene, 3.13 mL 3.13 mmol) dropwise. The solution was gradually warmed to -40 °C and was stirried at this temperature for 1 h. Methanol (1 mL), saturated sodium potassium tartrate solution (20 mL) and diethyl ether (30 mL) was added to the reaction mixture in sequence. The mixture was warmed to 25 °C and was stirred for 12 h. The organic phase was separated and the aqueous phase was extracted with

diethyl ether (4 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The colorless residue was then dissolved in 14 mL of dry dichloromethane. Imidazole (0.444g, 6.53 mmol), 4-dimethylaminopyridine (0.032 g, 0.261 mmol) and tert-butyldimethylchlorosilane (0.473g, 3.13 mmol) were also added to the solution in sequence. The mixture was stirred for 3 h before saturated NH_4Cl solution (10 mL) and diethyl ether (20 mL) were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 30:1, v/v) to give **17** as a colorless oil (0.980 g, 2.60 mmol, 99%, two steps):

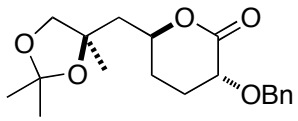
R_f 0.50 (hexanes-ethyl acetate, 20:1, v/v); $[\alpha]_D^{25}$ = -4.8 (*c* 1.25, $CHCl_3$); IR (neat): 3074, 3030, 2929, 2888, 2856, 1452, 1391, 1292, 1250, 1167, 1099, 1068, 1005, 892, 836, 733, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 4.82 (d, *J* = 12 Hz, 1H), 4.77 (s, 1H), 4.73 (s, 1H), 4.65 (d, *J* = 12 Hz, 1H), 4.56 (d, *J* = 7 Hz, 1H), 3.54 (m, 1H), 3.16 (ddd, *J* = 12, 7, 5 Hz, 1H), 2.28 (dd, *J* = 14, 8 Hz, 1H), 2.12 (dd, *J* = 14, 5 Hz, 1H), 2.02 (m, 1H), 1.74 (s, 3H), 1.62 (m, 1H), 1.48 (m, 1H), 1.32 (m, 1H), 0.94 (s, 9H), 0.14 (d, *J* = 3.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.2, 139.1, 128.3, 127.7, 127.4, 112.6, 100.2, 78.2, 74.0, 72.7, 74.0, 72.7, 43.9, 30.7, 29.2, 25.8, 22.7, 18.1, -4.0, -5.1; HRMS calcd for $C_{22}H_{36}O_3SiNa$ $[M + Na]^+$: 399.2331; found: 399.2333.



(*R*)-3-((2*S*,5*R*,6*R*)-5-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-2-methylpropane-1,2-diol (**18**)

To a mixture of **17** (0.940 g, 2.50 mmol), *tert*-butanol (12.5 mL) and water (12.5 mL) at 0 °C was added AD-mix-α (3.5 g). The mixture was stirred vigorously for 48 h then sodium sulfite (4.0 g) was added. The mixture was stirred at 25 °C for 1 h before 20 mL diethyl ether was added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1 to 1:1, v/v) to give **18** (0.701 g, 1.71 mmol, 68%) and **18a** (0.236 g, 0.575 mmol, 23%) as colorless oils. Data for **18**:

R_f 0.20 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{25}$ +6.7 (*c* 0.34, $CHCl_3$); IR (neat): 3415, 2929, 2857, 1650, 1454, 1392, 1252, 1170, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 4.73 (d, *J* = 12 Hz, 1H), 4.62 (d, *J* = 12 Hz, 1H), 4.59 (d, *J* = 7 Hz, 1H), 3.76 (m, 1H), 3.57 (dd, *J* = 11, 5 Hz, 1H), 3.43 (dd, *J* = 11, 8 Hz, 1H), 3.41 (s, 1H), 3.14 (ddd, *J* = 12, 7, 4.5 Hz, 1H), 2.29 (m, 1H), 2.04 (m, 1H), 1.81 (dd, *J* = 14, 8.5 Hz, 1H), 1.69 (dd, *J* = 14, 4 Hz, 1H), 1.59 (m, 1H), 1.51-1.36(m, 2H), 1.18 (s, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7, 128.3, 127.7, 127.5, 99.3, 78.0, 73.7, 72.5, 72.3, 69.3, 43.6, 31.7, 28.8, 25.7, 25.6, 25.2, 17.9, -4.5, -4.9; HRMS calcd for $C_{22}H_{38}O_5SiNa$ $[M + Na]^+$: 433.2386; found: 433. 2377.

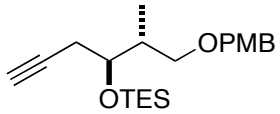


(3R,6S)-3-(Benzyloxy)-6-(((R)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)tetrahydro-2H-pyran-2-one (10)

To a solution of **18** (0.560 g, 1.36 mmol) in CH_2Cl_2 (10 mL) was added 2,2-dimethoxypropane (1.01 mL, 0.852 g, 8.18 mmol) followed by pyridinium *p*-toluenesulfonate (18.3 mg, 0.068 mmol). The reaction mixture was stirred for 2.5 h before 0.5 mL of triethylamine was added. The solvent was evaporated and the residue was filtered through a pad of silica gel with hexanes-ethyl acetate (4:1, v/v). The obtained solution was concentrated and the residue was dissolved in THF (10 mL) and was treated with tetra-*n*-butylammonium fluoride solution (1.0 M in THF, 1.43 mL, 1.43 mmol) dropwise within 1 h. The mixture was stirred for another 0.5 h before saturated ammonium chloride solution (5 mL) was added. THF was removed from the mixture and diethyl ether (20 mL) was added. The mixture was stirred for 10 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was filtered through a pad of silica gel with hexanes-ethyl acetate (2:1, v/v) and the obtained solution was concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) followed by addition of $NaHCO_3$ (0.40 g, 4.82 mmol), iodobenzene diacetate (0.526 g, 1.63 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (12.0 mg, 0.077 mmol). The reaction was stirred for 12 h before saturated $Na_2S_2O_3$ solution (3.0 mL) was added. Diethyl ether (20 mL) was added to the mixture and organic phase was separated. The aqueous phase was then

extracted with diethyl ether (3 × 15 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (hexanes: ethyl acetate, 4:1, v/v) to give compound **10** (0.370 g, 1.11 mmol, 82%, three steps) as a colorless oil.

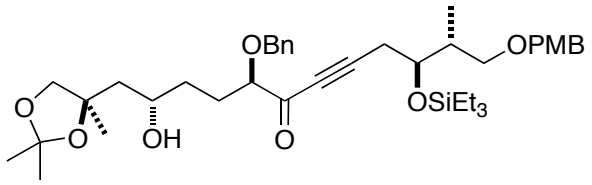
R_f 0.34 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +80.0 (*c* 0.40, $CHCl_3$); IR (neat): 3058, 3028, 2928, 2930, 2868, 1745, 1454, 1379, 1246, 1209, 1118, 1058, 806, 739, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36 (m, 5H), 4.89 (d, J = 12 Hz, 1H), 4.73 (m, 1H), 4.66 (d, *J* = 12 Hz, 1H), 3.95 (dd, *J* = 7.5, 5 Hz, 1H), 3.86 (d, *J* = 9 Hz, 1H), 3.80 (d, *J* = 9 Hz, 1H), 2.12 (m, 1H), 2.02 (m, 2H), 1.92 (dd, *J* = 14, 8.5 Hz, 1H), 1.84 (dd, *J* = 14, 4 Hz, 1H), 1.38(s, 3H), 1.35(s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 137.4, 128.5, 128.1, 128.0, 109.0, 79.6, 77.3, 46.0, 28.3, 27.2, 27.1, 26.6, 24.2; HRMS calcd for $C_{19}H_{26}O_5Na$ $[M + Na]^+$: 357.1678; found: 357.1672.



Triethyl(((2*R*,3*S*)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-yn-3-yl)oxy)silane (**20**)

To a solution of **19**[1] (0.885 g, 3.56 mmol), imidazole (0.389 g, 5.70 mmol) and 4-dimethylaminopyridine (0.0435 g, 0.356 mmol) in CH_2Cl_2 (15 mL) was added chlorotriethylsilane (0.590 g, 0.66 mL, 3.92 mmol). The mixture was stirred for 30 min before saturated NH_4Cl solution (6 mL) and diethyl ether (20 mL) were added. The organic phase was separated and the aqueous phase was extracted by diethyl ether (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes: ethyl acetate, 16:1, v/v) to give **20** (1.290 g, quantitative) as a colorless oil.

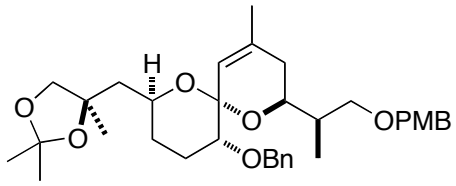
R_f 0.66 (hexanes-ethyl acetate, 8:1, v/v); $[\alpha]_D^{25}$ +19.0 (*c* 0.64, $CHCl_3$); IR (neat): 3310, 2955, 2910, 2876, 2119, 1613, 1514, 1462, 1247, 1085, 1007, 822, 742; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (m, 2H), 6.87 (m, 2H), 4.44 (d, *J* = 6.5 Hz, 1H), 4.40 (d, *J* = 6.5 Hz, 1H), 3.84 (q, *J* = 5.5 Hz, 1H), 3.81 (s, 3H), 3.51 (dd, *J* = 9, 5.5 Hz, 1H), 3.33(dd, *J* = 9, 6 Hz, 1H), 2.42 (ddd, *J* = 17, 6, 3 Hz, 1H), 2.33 (ddd, *J* = 17, 6, 3 Hz, 1H), 2.11 (m, 1H), 1.96 (t, *J* = 3 Hz, 1H), 0.96 (t, *J* = 8 Hz, 1H), 0.61 (q, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 130.9, 129.1, 113.7, 81.9, 72.6, 72.5, 71.7, 69.8, 55.3, 38.5, 24.8, 13.8, 6.9, 5.1; HRMS calcd for $C_{21}H_{34}O_3Na$ $[M + Na]^+$: 385.2175; found: 385.2187.



(2*S*,5*R*,10*S*,11*R*)-5-(Benzyloxy)-2-hydroxy-12-((4-methoxybenzyl)oxy)-11-methyl-10-((triethylsilyl)oxy)-1-((*R*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)dodec-7-yn-6-one (**21**)

To a stirred -78 °C solution of **20** (0.976 g, 2.69 mmol) in THF (15 mL) was added *n*-butyllithium (1.0 mL of a 2.5 M solution in hexanes, 2.5 mmol). After the mixture was stirred for 40 min, a solution of **10** (0.360 g, 1.07 mmol) in THF (5 mL) was added via cannula. After one hour, saturated aqueous NH_4Cl solution (15 mL) was added and the mixture was warmed to room temperature. The mixture was extracted with diethyl ether (3×50 mL) and the combined organic extracts were washed with water and saturated aqueous NaCl. The combined organic fraction was dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel (hexanes-ethyl acetate, 5:1, v/v) to give **21** (0.725 g, 1.05 mmol, 99%) as colorless oil.

R_f 0.42 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +42.9 (*c* 0.55, $CHCl_3$); IR (neat): 3438, 3059, 3034, 2953, 2875, 2209, 1672, 1613, 1513, 1371, 1247, 1082, 822, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 7.23 (d, *J* = 7 Hz, 2H), 6.86 (d, *J* = 7 Hz, 2H), 4.73 (d, *J* = 12 Hz, 1H), 4.42 (d, *J* = 12 Hz, 1H), 4.37 (d, *J* = 12 Hz, 2H), 3.91 (m, 2H), 3.82 (d, *J* = 8.5 Hz, 1H), 3.79 (s, 3H), 3.71 (d, *J* = 8.5 Hz, 1H), 3.45 (dd, *J* = 9, 6 Hz, 1H), 3.32 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.10 (d, *J* = 2 Hz, 1H), 2.65 (dd, *J* = 17, 6 Hz, 1H), 2.53 (dd, *J* = 17, 6 Hz, 1H), 2.08 (m, 1H), 1.99 (m, 1H), 1.72-1.45 (m, 6H), 1.43 (s, 3H), 1.40 (m, 1H), 1.37 (s, 3H), 1.32 (m, 2H), 1.29 (s, 3H), 0.94 (m, 12H), 0.60 (q, *J* = 8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 189.0, 159.1, 137.4, 130.6, 129.1, 128.5, 128.1, 127.9, 127.7, 113.7, 109.2, 95.6, 84.9, 81.3, 80.5, 73.5, 72.7, 72.3, 71.9, 71.4, 68.1, 55.3, 45.3, 38.8, 33.6, 28.3, 27.6, 26.8, 26.7, 25.6, 13.6, 6.9, 5.0; HRMS calcd for $C_{40}H_{60}O_8Na$ $[M + Na]^+$: 719.3955; found: 719.3958



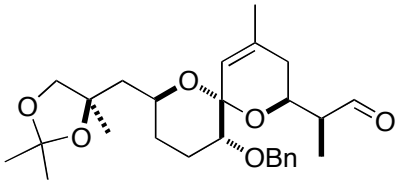
(2*S*,6*R*,8*S*,11*R*)-11-(Benzyloxy)-2-((*R*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-8-(((*R*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-ene (**23**)

To a solution of **21** (0.60 g, 0.861 mmol) in CH_2Cl_2 (16 mL) at 0 °C was added triethylamine (0.47 mL, 3.35 mmol), followed by chlorotrimethylsilane (0.15 mL, 1.18 mmol) and 4-dimethylaminopyridine (6 mg, 0.050 mmol). After stirring for 50 min, saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with water and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was directly used for next step without further purification.

To a -78 °C suspension of CuI (0.984 g, 5.17 mmol) in diethyl ether (4 mL) under argon was added methyllithium (6.9 mL of a 1.5 M solution in diethyl ether, 10.3 mmol). The mixture was allowed to warm slowly to -30 °C until a clear and colorless solution formed. The solution was cooled to -78 °C, and a solution of crude TMS-protected **21** in diethyl ether (4 mL) was added via cannula. After 1.0 h, saturated aqueous NH_4Cl (10 mL) was added and the mixture was warmed to room temperature and stirred until the aqueous became bright blue. The solution was extracted the diethyl ether (3 × 25 mL) and the combined organic phases were washed with water and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated to give a crude enone product which was then dissolved in the mixture of dichloromethane (16 mL) and methanol (7 mL), and pyridinium *p*-toluenesulfonate (11.6 mg, 0.0431 mmol). After the solution was stirred at 25 °C for 2 h, triethylamine (0.50 mL) was added. After the mixture was stirred for 10 min, the solvent was removed and the residue was purified via chromatography (hexanes-ethyl acetate, 8:1 to 6:1, v/v) to give **23** (0.185 g, 0.319 mmol, 37% based on **21**) as colorless oil.

R_f 0.42 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +11.8 (*c* 0.70, $CDCl_3$); IR (neat): 3058, 3026, 2931, 2862, 1609, 1521, 1250, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.26 (m, 7H), 6.86 (d, *J* = 7 Hz, 2H), 5.15 (s, 1H), 4.61(d, *J* = 12 Hz, 1H), 4.48 (d, *J* = 12 Hz, 1H), 4.43 (d, *J* = 4 Hz, 1H), 3.78(m, 2H), 3.78(s, 3H), 3.72 (m, 1H), 3.65 (m, 2H), 3.35 (dd, *J* = 9, 8 Hz, 1 H), 3.24 (dd, *J* = 11.5, 8.5, 1H), 2.08 (m, 1H), 2.01(m, 1H),

1.92 (qd, J = 12.5, 3 Hz, 1H), 1.80 (m, 2H), 1.73 (s, 3H), 1.66(m, 2H), 1.36 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.00 (d, J = 7, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 139.0, 136.9, 130.9, 129.2, 128.1, 127.8, 127.4, 123.0, 113.7, 108.2, 95.9, 80.4, 78.8, 77.2, 75.0, 72.7, 72.2, 71.3, 69.8, 66.2, 55.3, 46.2, 38.5, 32.8, 32.4, 27.5, 27.0, 24.4, 24.3, 23.0, 13.8; HRMS calcd for $C_{35}H_{48}O_7Na$ $[M + Na]^+$: 603.3298; found: 603.3290.

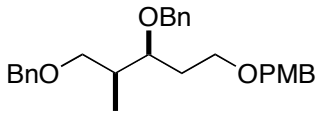


(*S*)-2-((2*S*,6*R*,8*S*,11*R*)-11-(Benzyloxy)-4-methyl-8-(((*R*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)propanal (5)

To a mixture of **23** (30 mg, 51 μmol), CH_2Cl_2 (5.0 mL), an aqueous NaH_2PO_4 buffer (pH = 7, 1.0 mL), and *tert*-butyl alcohol (0.30 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (70 mg, 0.31 mmol). The reaction flask was placed in an aqueous bath and sonicated for 5 min. The mixture was diluted with diethyl ether (8 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous phase was extracted with diethyl ether (3 × 2 mL) and the combined organic phases were washed with saturated aqueous NaCl (1.5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 5:1 to 3:2, v/v) to give a colorless oil which was then dissolved in CH_2Cl_2 (3.0 mL). The solution was added $NaHCO_3$ (150 mg, 1.8 mmol) followed by the Dess−Martin periodinane reagent (80 mg, 0.19 mmol). The mixture was stirred for 30 min before diethyl ether (4.0 mL) and 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (1.0 mL ea.) were added. The mixture was stirred until the organic phase became clear and colorless. The separated aqueous phase was extracted with diethyl ether (3 × 2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (1 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 5:1, v/v) of the residue gave **5** (22 mg, 45 μmol, 90%) as a white crystalline solid.

R_f 0.31 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +29.2 (*c* 0.42, $CDCl_3$); IR (neat): 3080, 3061, 3030, 2972, 2928, 2864, 1726, 1453, 1378, 1244, 1206, 1174, 1092, 1053, 1002, 977, 926, 856, 805, 735, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.98 (d, J = 2 Hz, 1H), 7.33-7.24 (m, 5H), 5.17 (s, 1H), 4.61 (d, J = 12.5 Hz, 1H), 4.47 (d, J = 12.5 Hz, 1H), 4.03 (ddd, J = 11.5, 8.5, 3 Hz, 1H), 3.85-3.79 (m, 2H), 3.67 (d, J = 8.5 Hz,

1H), 3.24 (dd, J = 11.5, 5 Hz, 1H), 2.70 (m, 1H), 2.10 (m, 1H), 1.92-1.81 (m, 3H), 1.75 (s, 3H), 1.72-1.61 (m, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.11 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.5, 138.7, 136.1, 128.2, 127.8, 127.5, 123.3, 108.4, 96.1, 80.3, 78.5, 75.2, 71.4, 69.7, 66.7, 50.5, 45.8, 33.3, 32.1, 27.4, 27.1, 24.5, 24.2, 22.9, 10.5; HRMS calcd for $C_{27}H_{38}O_6Na$ $[M + Na]^+$: 481.2566; found: 481.2566.

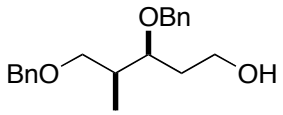


(3*S*,4*S*)-3,5-bis(Benzyloxy)-4-methylpentan-1-oxyl 4-methoxybenzyl ether (27)

To a 0 °C solution of **26**[2] (5.61 g, 13.1 mmol) in THF (120 mL) was added $NaBH_4$ (2.48 g, 65.7 mmol) followed by water (15 mL). The mixture was stirred for 14 h before saturated NH_4Cl solution (30 mL) was added. The mixture was stirred for another 1 h before THF was removed via rotary evaporation. The aqueous phase was extracted with diethyl ether (4 × 50 mL) and the combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in THF (110 mL). After the solution was cooled to 0 °C, NaH (60% in mineral oil, 2.78 g, 69.4 mmol) was added. The reaction mixture was warmed to room temperature and was stirred for 1 h. After the reaction mixture was cooled to 0 °C, benzyl bromide (9.97 g, 6.9 mL, 57.8 mmol) and tetra-*n*-butylammonium iodide (4.27 g, 11.6 mmol) were added. The mixture was warmed to room temperature and stirred for 72 h before methanol (3 mL) was added. The mixture was stirred for another 1 h before saturated NH_4Cl solution (20 mL) was added. THF was removed by rotary evaporation and the aqueous phase was extracted with diethyl ether (4 × 50 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave products **27** (3.79 g, 8.73 mmol, 67%) and **26** (1.74 g, 31%). Data for **27**:

R_f 0.39 (hexanes-ethyl acetate, 8:1, v/v); $[\alpha]_D^{25}$ -17.0 (*c* 0.70, $CHCl_3$); IR (neat): 3080, 3057, 3027, 2921, 2856, 1613, 1513, 1454, 1362, 1302, 1248, 1092, 820, 736, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.21 (m, 12H), 6.86 (m, 2H), 4.47 (m, 4H), 4.42 (d, J = 12 Hz, 1H), 4.38 (d, J = 12 Hz, 1H), 3.80 (s, 3H), 3.73 (m, 1H), 3.53 (m, 3H), 3.34 (dd, J = 9, 7 Hz, 1H), 2.03 (m, 1H), 1.82 (m, 2H), 0.97 (d, J = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.2, 139.1, 138.7, 130.7, 129.3, 128.3, 128.3, 127.7, 127.6, 127.5, 127.4,

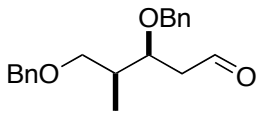
113.8, 77.2, 73.0, 72.7, 72.6, 72.5, 67.0, 55.3, 37.2, 32.1, 12.1; HRMS calcd for $C_{28}H_{34}O_4Na$ $[M + Na]^+$: 457.2355; found: 457.2360.



(3*S*,4*S*)-3,5-bis(Benzyloxy)-4-methylpentan-1-ol

To a mixture of **27** (2.64 g, 6.07 mmol), 1.0 mL *tert*-butanol, 5.0 mL pH = 7 buffer and dichloromethane (50 mL) at 25 °C was added 2,3-dichloro-5,6-dicyanobenzoquinone (3.18 g, 14.0 mmol). The mixture was stirred for 2 h before saturated $NaHCO_3$ (50 mL) solution was added. The mixture was then diluted with diethyl ether (100 mL) and the organic phase was separated. The aqueous phase was further extracted with diethyl ether (3 × 50 mL) before the combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 1:1, v/v) to give the product (1.80 g, 5.72 mmol, 94%) as a light yellow oil.

R_f 0.16 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ -20.0 (*c* 0.64, $CHCl_3$); IR (neat): 3407, 3084, 3056, 3029, 2921, 2874, 1496, 1454, 1362, 1206, 1066, 1028, 736, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.27 (m, 10H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.49 (s, 2H), 3.74 (m, 3H), 3.56 (dd, *J* = 9, 6 Hz, 1H), 3.36 (dd, *J* = 9, 6.5 Hz, 1H), 2.12 (m, 1H), 2.05 (brs, 1H), 1.77 (m, 2H), 1.01 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.6, 138.5, 128.4, 128.4, 127.9, 127.7, 127.7, 127.6, 79.2, 73.2, 72.3, 60.9, 36.8, 33.8, 12.8; HRMS calcd for $C_{20}H_{26}O_3Na$ $[M + Na]^+$: 337.1780; found: 337.1778.

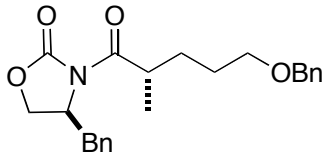


(3*S*, 4S)-3,5-Bis(benzyloxy)-4-methylpentanal (28)

To a 0 °C solution of (3*S*,4*S*)-3,5-bis(benzyloxy)-4-methylpentan-1-ol (1.80 g, 5.72 mmol) in dichloromethane (30 mL) was added DMSO (2.5 mL), diisopropylethylamine (6.0 mL) and sulfur trioxide pyridine complex (2.00 g, 12.6 mmol). The solution was stirred for 1 h at 0 °C before saturated NH_4Cl solution (8 mL) and diethyl ether (60 mL) were added. The mixture was stirred for 5 min before the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined

organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave product **28** (1.67 g, 5.34 mmol, 93%).

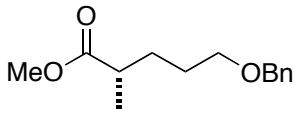
R_f 0.61 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ -2.2 (*c* 0.67, $CHCl_3$); IR (neat): 3082, 3062, 3029, 2963, 2910, 2856, 2726, 1723, 1487, 1454, 1369, 1204, 1091, 736, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.77 (dd, *J* = 1.5, 1 Hz, 1H), 7.37-7.27 (m, 10H), 4.56 (d, *J* = 12 Hz, 1H), 4.52 (d, *J* = 12 Hz, 1H), 4.49 (d, *J* = 12 Hz, 1H), 4.46 (d, *J* = 12 Hz, 1H), 4.14 (m, 1H), 3.52 (m, 1H), 3.40 (m, 1H), 2.74 (m, 1H), 2.58 (m, 1H), 2.07 (m, 1H), 1.00 (d, *J* = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.5, 138.4, 128.4, 128.4, 127.7, 127.7, 127.6, 75.1, 73.1, 72.4, 72.0, 46.6, 37.7, 12.4; HRMS calcd for $C_{20}H_{24}O_3Na$ $[M + Na]^+$: 335.1623; found: 335.1620.



(*S*)-4-Benzyl-3-((*S*)-5-(benzyloxy)-2-methylpentanoyl)oxazolidin-2-one (24)[3]

Procedure Reference: Altmann, K. H.; Bold, G.; Caravatti, G.; Denni, D.; Florsheimer, A.; Schmidt, A.; Rihs, G.; Wartmann, M. " The total synthesis and biological assessment of trans-epothilone A" *Helv. Chim. Act.* **2002**, *85*, 4086.

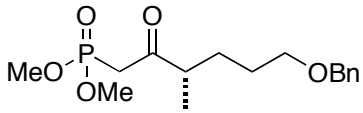
R_f 0.38 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +56.4 (*c* 0.75, $CHCl_3$); IR (neat): 3021, 2930, 2857, 1779, 1696, 1454, 1385, 1210, 1100, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.26 (m, 8H), 7.20 (d, *J* = 7.5 Hz, 1H), 4.64 (m, 1H), 4.49 (s, 2H), 4.12 (m, 2H), 3.75 (tq, *J* = 7, 7 Hz, 1H), 3.47 (m, 2H), 3.26 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.76 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.84 (m, 2H), 1.67 (m, 1H), 1.24 (d, *J* = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.0, 153.0, 138.6, 135.4, 129.5, 128.9, 128.4, 127.6, 127.5, 127.3, 77.2, 72.9, 70.3, 66.0, 55.3, 37.9, 37.5, 30.1, 27.4, 17.5; HRMS calcd for $C_{23}H_{27}O_4Na$ $[M + Na]^+$: 404.1838; found: 404.1837.



(*S*)-Methyl 5-(benzyloxy)-2-methylpentanoate

To methanol (70 mL) at 0 °C was added methylmagnesium bromide (1 M in diethyl ether, 18.9 mL, 18.9 mmol) dropwise. After stirring for 15 min, **24** (5.40 g, 14.2 mmol) in methanol (20 mL) was cannulated into the flask and the reaction was stirred for 2 h before saturated NH_4Cl solution (20 mL) was added. Methanol in the reaction mixture was removed under vacuum and diethyl ether (100 mL) was added. The mixture was stirred for another 10 min and the organic phase was separated. The aqueous phase was extracted with diethyl ether (2 × 30 mL) before the combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (hexanes-EtOAc, 15:1, v/v) to give (*S*)-methyl 5-(benzyloxy)-2-methylpentanoate (2.82 g, 11.9 mmol, 84%) as light yellow oil.

R_f 0.21 (hexanes-ethyl acetate, 20:1, v/v); $[\alpha]_D^{25}$ +14.7 (*c* 0.82, $CHCl_3$); IR (neat): 3084, 3056, 3028, 2947, 2857, 1736, 1454, 1360, 1169, 1101, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.27 (m, 5H), 4.49 (s, 2H), 3.66 (s, 3H), 3.46 (m, 2H), 2.46 (tq, *J* = 7, 7 Hz, 1H), 1.71 (m, 1H), 1.61 (m, 2H), 1.55 (m, 1H), 1.16 (d, *J* = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.1, 138.6, 128.4, 127.6, 127.5, 72.9, 70.1, 51.5, 39.3, 30.4, 27.5, 17.1; HRMS calcd for $C_{14}H_{20}O_3Na$ $[M + Na]^+$: 259.1310; found: 259.1305.

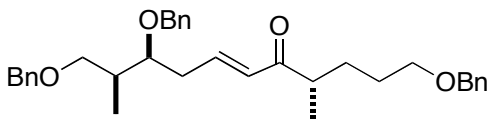


(*S*)-Dimethyl (6-(benzyloxy)-3-methyl-2-oxohexyl)phosphonate (25)

To a -78 °C solution of dimethyl methylphosphonate (1.53 g, 12.4 mmol) in THF (50 mL) was added *n*-butyllithium (2.5 M in hexanes, 5 mL, 12.5 mmol). The solution was stirred at -78 °C for 1 h before (*S*)-methyl 5-(benzyloxy)-2-methylpentanoate (2.24 g, 9.5 mmol) in THF (20 mL) was cannulated into the reaction flask. The reaction mixture was stirred for one more hour before saturated NH_4Cl solution (20 mL) was added. The mixture was warmed to room temperature and was stirred for 15 min. After removal of THF from the mixture on vacuum, the residue was extracted with diethyl ether (4 × 60 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography

(hexanes-ethyl acetate, 1:1 to 1:4, v/v) of the residue gave product **25** (3.68 g, 11.2 mmol, 91%) as a clear colorless oil.

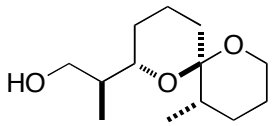
R_f 0.56 (hexanes-ethyl acetate, 1:5, v/v); $[\alpha]_D^{25}$ +7.9 (*c* 0.58, $CHCl_3$); IR (neat): 3083, 3058, 3022, 2953, 2919, 2854, 1713, 1454, 1366, 1258, 1179, 1100, 1030, 876, 810, 740, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.27 (m, 5H), 4.48 (s, 2H), 3.77 (dd, *J* = 11.5, 2 Hz, 6H), 3.46 (m, 2H), 3.11 (d, *J* = 22.5 Hz, 2H), 2.76 (tq, *J* = 7 Hz, 1H), 1.77 (m, 1H), 1.60 (m, 2H), 1.45 (m, 1H), 1.11 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.5, 138.5, 128.4, 127.6, 127.6, 72.9, 70.0, 53.0, 46.9, 40.2, 39.1, 29.1, 27.2, 16.0; HRMS calcd for $C_{16}H_{25}O_5PNa$ $[M + Na]^+$: 351.1337; found: 351.1333.



(4*S*,9*S*,10*S*,*E*)-1,9,11-tris(Benzyloxy)-4,10-dimethylundec-6-en-5-one (29)

To a 25 °C solution of **25** (1.89 g, 5.76 mmol) in CH_3CN (20 mL) was added LiCl (0.285 g, 6.72 mmol) followed by diisopropylethylamine (1.2 mL, 6.72 mmol). The mixture was stirred for 15 min before **28** (1.60 g, 5.12 mmol) in 10 mL CH_3CN was cannulated into the reaction. The mixture was stirred for another 16 h before saturated NH_4Cl solution (5 mL) was added. CH_3CN was removed from the mixture under vacuum and the residue was extracted with diethyl ether (4 × 60 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 10:1, v/v) of the residue gave product **29** (2.55 g, 4.95 mmol, 97%) as a colorless oil.

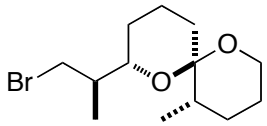
R_f 0.68 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ -0.8 (*c* 0.75, $CHCl_3$); IR (neat): 3081, 3051, 3021, 2962, 2909, 2855, 1693, 1667, 1632, 1620, 1538, 1454, 1360, 1099 cm-1; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.26 (m, 15H), 6.87 (dt, *J* = 15.5, 7.5 Hz, 1H), 6.20 (d, *J* = 15.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.74-4.45 (m, 5H), 3.71 (m, 1H), 3.49 (dd, *J* = 9, 7 Hz, 1H), 3.44 (t, *J* = 6 Hz, 2H), 3.36 (dd, *J* = 9, 6 Hz, 1H), 2.72 (tq, *J* = 7, 7 Hz, 1H), 2.50 (m, 1H), 2.43 (m, 1H), 1.99 (m, 1H), 1.74 (m, 1H), 1.58 (m, 2H), 1.45 (m, 1H), 1.08 (d, *J* = 7 Hz, 3H), 0.98 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.4, 143.9, 138.6, 138.5, 130.7, 128.4, 128.3, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 78.6, 73.1, 72.9, 72.5, 72.4, 70.2, 43.6, 37.4, 35.3, 29.7, 27.5, 16.7, 11.7; HRMS calcd for $C_{34}H_{42}O_4Na$ $[M + Na]^+$: 537.2981; found: 537.3015.



(*S*)-2-((2*S*,6*R*,11*S*)-11-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl)propan-1-ol (30)

A mixture of **29** (2.50 g, 4.86 mmol) and 20% $Pd(OH)_2$ on carbon (0.30 g, 0.5 mmol) in absolute ethanol (50 mL) was stirred vigorously under 1 atm of H_2 for 15 h. The mixture was filtered through Celite with ethyl acetate. The filtrate was concentrated and the residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 5:1, v/v) to give **30** (1.03 g, 4.52 mmol, 93%) as a clear, colorless oil.

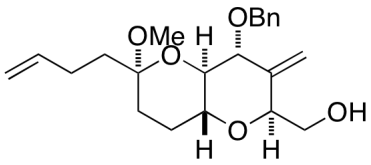
R_f 0.43 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +63.6 (*c* 0.68, $CHCl_3$); IR (neat): 3404, 2930, 2877, 1452, 1378, 1272, 1227, 1071, 1027, 990, 967, 947, 915, 865, 851, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.82 (ddd, *J* = 14.5, 5, 2.5 Hz, 1H), 3.75-3.56 (m, 4H), 2.82 (brt, *J* = 5 Hz, 1H), 2.06 (m, 1H), 1.90 (m, 1H), 1.74 (m, 3H), 1.63 (m, 2H), 1.47 (m, 1H), 1.39 (td, *J* = 12.5, 4 Hz, 1H), 1.31 (m, 2H), 1.21 (td, *J* = 13.5, 4.5 Hz, 1H), 0.99 (d, *J* = 7 Hz, 3H), 0.93 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 98.4, 73.2, 66.4, 60.6, 39.0, 35.9, 32.2, 25.9, 25.8, 19.9, 18.7, 14.5, 11.9; HRMS calcd for $C_{13}H_{24}O_3Na$ $[M + Na]^+$: 251.1623; found: 251.1622.



(2*S*,6*R*,11*S*)-2-((*R*)-1-Bromopropan-2-yl)-11-methyl-1,7-dioxaspiro[5.5]undecane (8)

To a solution of **30** (0.851 g, 3.73 mmol), triphenylphosphine (1.23 g, 4.68 mmol) and triethylamine (1.1 mL, 7.80 mmol) in dichloromethane (20 mL) was added carbon tetrabromide (1.68 g, 5.07 mmol). The solution was stirred for 16 h before saturated NH_4Cl solution (5 mL) and diethyl ether (30 mL) were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 30:1, v/v) of the residue gave product **8** (1.029 g, 3.54 mmol, 95%) as a colorless oil:

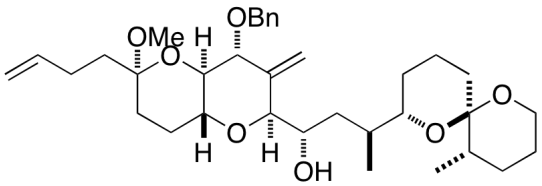
R_f 0.50 (hexanes-ethyl acetate, 20:1, v/v); $[\alpha]_D^{25}$ +67.2 (*c* 0.75, $CHCl_3$); IR (neat): 2942, 2873, 1462, 1378, 1270, 1239, 1211, 1194, 1171, 1107, 1067, 1027, 968, 948, 915, 866, 852, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.68 (m, 2H), 3.58 (dd, *J* = 10, 5 Hz, 1H), 3.57 (m, 1H), 3.37 (dd, *J* = 10, 7 Hz, 1H), 2.13 (m, 1H), 1.87 (m, 1H), 1.77 (m, 2H), 1.70 (m, 1H), 1.62 (m, 2H), 1.52 (m, 1H), 1.32-1.25 (m, 3H), 1.15 (td, *J* = 13.5, 4.5 Hz, 1H), 1.11 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 97.9, 70.4, 60.5, 40.8, 38.2, 35.9, 32.3, 27.6, 25.7, 19.8, 18.8, 14.4, 14.2; HRMS calcd for $C_{13}H_{23}O_2BrNa$ $[M + Na]^+$: 313.0779, 315.0759; found: 313.0771, 313.0745.



((2*S*,4*R*,4a*R*,6*R*,8a*R*)-4-(Benzyloxy)-6-(but-3-en-1-yl)-6-methoxy-3-methyleneoctahydropyrano-[3,2-*b*]pyran-2-yl)methanol (37)

To the solution of **31**[4] (0.890 g, 1.82 mmol) in THF (15 mL) was added tetrabutylammonium fluoride (1 M in THF, 2.2 mL, 2.2mmol). The mixture was stirred for 2 h before saturated NH_4Cl solution (10 mL) and diethyl ether (20 mL) were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (20 mL) three more times. The organic extracts were combined and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified through column chromatography to give **37** (0.681 g, 1.82 mmol, quant.) as a white solid:

R_f 0.10 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ -31.1 (*c* 0.32, $CHCl_3$); IR (neat): 3453, 3083, 3032, 2956, 2873, 1643, 1453, 1354, 1130, 1100, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 5.86 (ddt, *J* = 17, 10, 6.5 Hz, 1H), 5.47 (t, *J* = 1.5 Hz, 1H), 5.13 (s, 1H), 5.05 (dq, *J* = 17, 1.5 Hz, 1H), 5.00 (dq, *J* = 10, 1.5 Hz, 1H), 4.92 (d, *J* = 12 Hz, 1H), 4.78 (d, *J* = 12 Hz, 1H), 4.04 (dt, *J* = 9.5, 1.5 Hz, 1H), 3.95 (t, *J* = 10.5 Hz, 1H), 3.50 (m, 3H), 3.22 (s, 3H), 2.08 (m, 2H), 1.96-1.76 (m, 5H), 1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.1, 138.7, 138.2, 128.3, 127.5, 127.5, 114.6, 113.0, 99.2, 80.3, 77.5, 76.7, 74.1, 69.5, 61.4, 47.5, 34.8, 32.3, 27.9, 25.5; HRMS calcd for $C_{22}H_{30}O_5Na$ $[M + Na]^+$: 397.1991; found: 397.2007.



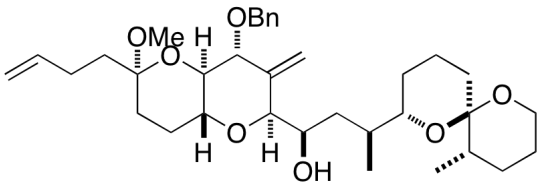
(1*S*,3*S*)-1-((2*S*,4*R*,4a*R*,6*R*,8a*R*)-4-(Benzyloxy)-6-(but-3-en-1-yl)-6-methoxy-3-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butan-1-ol (32)

To a 0 °C solution of alcohol **37** (120 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (1.00 g, 11.9 mmol) followed by Dess-Martin periodinane (0.50 g, 1.18 mmol). The reaction was stirred for 1 h before the addition of saturated NaS_2O_3 solution (1 mL) followed by diethyl ether (10 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was passed through a pad of silica gel with a mixture of hexanes and ethyl acetate (3:1, v/v) and the filtrate was concentrated. The residue was used for next step without further purification.

To a -78 °C solution of **8** (374 mg, 1.28 mmol) in diethyl ether (8 mL) was added *t*-butyllithium (1.7 M in pentane, 1.4 mL, 2.4 mmol) dropwise. The reaction was stirred at -78 °C before warmed to room temperature. After stirred at room temperature for 30 min, the mixture was re-cooled to -78 °C before a solution of **7** (crude, 0.32 mmol theor) in diethyl ether (2 mL) was added via cannula. After 30 min, saturated NH_4Cl solution (2 mL) was added before the mixture was warmed up to room temperature. The organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 3 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 8:1 to 2:1, v/v) of the residue gave **32** (39 mg, 0.0667 mmol) and **32a** (51 mg, 0.0873 mmol, 48% combined yield) as colorless oil. Data for **32**:

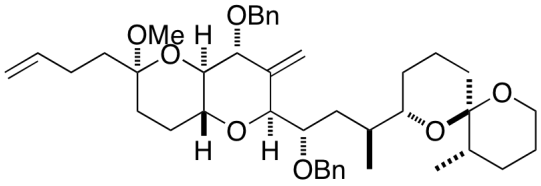
R_f 0.18 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ +3.1 (*c* 0.54, $CHCl_3$); IR (neat): 3425, 3068, 3028, 2942, 2863, 1644, 1556, 1454, 1368, 1209, 1074, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 5.87 (ddt, *J* = 17, 10, 6.5 Hz, 1H), 5.47 (t, *J* = 2 Hz, 1H), 5.07 (s, 1H), 5.06 (dd, *J* = 17, 1.5 Hz, 1H), 4.99 (dd, *J* = 10, 1.5 Hz, 1H), 4.90 (d, *J* = 12 Hz, 1H), 4.81 (d, *J* = 12 Hz, 1H), 3.94 (m, 3H), 3.67-3.55 (m, 3H), 3.44 (m, 2H), 3.23 (s, 3H), 2.88 (brs, 1H), 2.19-2.04 (m, 3H), 1.95-1.55 (m, 13H), 1.47 (d, *J* = 12.5 Hz, 1H), 1.32-1.08 (m, 5H), 1.00 (d, *J* = 7 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.4,

138.7, 138.2, 128.3, 127.5, 127.5, 114.6, 113.3, 99.2, 98.0, 85.1, 77.3, 73.7, 73.3, 70.2, 65.9, 60.4, 47.5, 36.8, 35.9, 34.8, 34.5, 32.4, 27.9, 26.9, 25.7, 25.6, 20.0, 19.0, 15.0, 14.4; HRMS calcd for $C_{35}H_{52}O_7Na$ [M + Na]$^+$: 607.3611; found: 607.3615



(1*R*,3*S*)-1-((2*S*,4*R*,4a*R*,6*R*,8a*R*)-4-(Benzyloxy)-6-(but-3-en-1-yl)-6-methoxy-3-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butan-1-ol (32a). Data for **32a:**

R_f 0.34 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ -4.1 (*c* 0.36, $CHCl_3$); IR (neat): 3456, 3068, 3028, 2942, 2870, 1643, 1454, 1358, 1213, 1094, 1044, 948, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.30 (m, 5H), 5.85 (ddt, *J* = 17, 10, 6.5 Hz, 1H), 5.52 (t, *J* = 2 Hz, 1H), 5.10 (t, *J* = 1.5 Hz, 1H), 5.05 (dd, *J* = 17, 1.5 Hz, 1H), 4.98 (dd, *J* = 10, 1.5 Hz, 1H), 4.91 (d, *J* = 12 Hz, 1H), 4.80 (d, *J* = 12 Hz, 1H), 4.18 (d, *J* =10 Hz, 1H), 4.12 (m, 1H), 4.01 (d, *J* = 8 Hz, 1H), 3.67-3.48 (m, 5H), 3.42 (t, *J* = 9.5 Hz, 1H), 3.22 (s, 3H), 2.90 (brs, 1H), 2.11-2.04 (m, 3H), 1.95-1.45 (m, 14H), 1.40-1.12 (m, 5H), 0.99 (d, *J* = 7 Hz, 3H), 0.98 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.7, 139.0, 138.2, 128.3, 127.5,127.4, 114.5, 113.2, 99.1, 98.6, 83.0, 78.0, 77.2, 73.9, 73.3, 71.0, 68.4, 60.7, 47.5, 36.2, 36.1, 34.8, 33.2, 32.4, 31.9, 27.9, 26.1, 25.8, 24.5, 20.2, 18.7, 18.2, 14.6; HRMS calcd for $C_{35}H_{52}O_7Na$ [M + Na]$^+$: 607.3611; found: 607.3616.

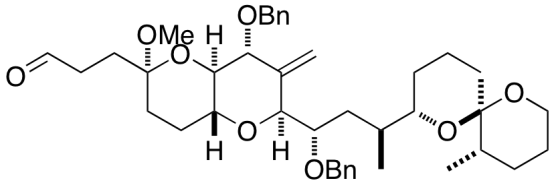


(2*R*,4a*R*,6*S*,8*R*,8a*R*)-8-(benzyloxy)-6-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-(but-3-en-1-yl)-2-methoxy-7-methyleneoctahydropyrano[3,2-*b*]pyran (33)

To a stirred 0 °C solution of **32** (39 mg, 0.0667 mmol) in THF (1.5 mL) was added 60% NaH (25 mg). The solution was stirred for 1 h before the addition of benzyl bromide (50 μL, 0.422 mmol) followed by

tetra-*n*-butylammonium iodide (5.0 mg, 0.0152 mmol). This mixture was allowed to warm to room temperature and stirred for 16 h. Diethyl ether (10 mL) and saturated aqueous NH_4Cl (1 mL) were added, and the separated organic phase was washed with water (1 × 3 mL) and saturated aqueous NaCl solution (2 × 3 mL). The aqueous phases were extracted with diethyl ether, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 8:1, v/v) of the residue gave **33** (42 mg, 0.0623 mmol, 93%) as colorless oil:

R_f 0.63 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +11.4 (*c* 0.67, $CHCl_3$); IR (neat): 3073, 3028, 2938, 2873, 1598, 1454, 1350, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 10H), 5.86 (ddt, *J* = 17, 10, 6.5 Hz, 1H), 5.47 (t, *J* = 1.5 Hz, 1H), 5.07 (dd, *J* = 18, 1.5 Hz, 1H), 5.05 (d, *J* = 1.5 Hz, 1H), 4.99 (dd, *J* = 10, 1.5 Hz, 1H), 4.86 (d, *J* = 12 Hz, 1H), 4.78 (d, *J* = 12 Hz, 1H), 4.65 (d, *J* = 11 Hz, 1H), 4.53 (d, *J* = 11 Hz, 1H), 4.36 (d, *J* = 7 Hz, 1H), 4.07 (d, *J* = 9.5 Hz, 1H), 3.92 (m, 1H), 3.69 (td, *J* = 10, 5 Hz, 1H), 3.62 (m, 1H), 3.53 (dd, *J* = 11, 5, Hz, 1H), 3.44 (t, *J* = 10 Hz, 1H), 3.40 (m, 1H), 3.24 (s, 3H), 2.19-2.02 (m, 3H), 1.95-1.55 (m, 13H), 1.47 (d, *J* = 12.5 Hz, 1H), 1.32-1.08 (m, 5H), 0.99 (d, *J* = 7 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.1, 138.9, 138.8, 138.3, 128.3, 128.3, 127.8, 127.6, 127.5, 127.5, 114.5, 112.0, 99.1, 97.9, 83.9, 77.8, 75.9, 73.6, 73.4, 72.3, 70.8, 60.4, 47.4, 36.0, 35.5, 34.9, 34.0, 32.4, 28.0, 26.8, 25.8, 25.6, 20.0, 19.0, 15.3, 14.4; HRMS calcd for $C_{42}H_{58}O_7Na$ $[M + Na]^+$: 697.4080; found: 697.4065.

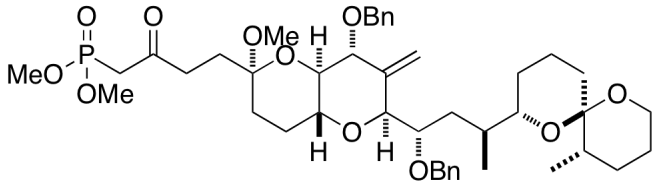


3-((2*S*,4a*R*,6*S*,8*R*,8a*R*)-8-(Benzyloxy)-6-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)propanal (34)

To a stirred solution of **33** (39 mg, 0.578 mmol) in THF (1.5 mL) and H_2O (0.5 mL) was added sodium periodate (40 mg, 0.173 mmol), pyridine (1 μL) and OsO_4 (50 μL, 4% in water). The mixture was stirred for 2 h before 2 mL of 20% $Na_2S_2O_3$ solution was added. The mixture was stirred for another 15 min and 10 mL diethyl ether was added. The organic phase was separated and the aqueous phase was extracted with

diethyl ether (3 × 5 mL). The combined organic phase was dried over Na_2SO_4 filtered, and concentrated. Silica gel column chromatography (hexanes-ethyl acetate, 4:1, v/v) of the residue gave **34** (30 mg, 0.0443 mmol, 77%) as a colorless oil.

R_f 0.18 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ +10.8 (*c* 0.50, $CHCl_3$); IR (neat): 3080, 3037, 3027, 2937, 2861, 2711, 1728, 1454, 1386, 1363, 1273, 1213, 1092, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.80 (s, 1H), 7.33 (m, 10H), 5.43 (t, *J* = 1.5 Hz, 1H), 5.05 (s, 1H), 4.81 (d, *J* = 12 Hz, 1H), 4.74 (d, *J* = 12 Hz, 1H), 4.63 (d, *J* = 11 Hz, 1H), 4.53 (d, *J* = 11 Hz, 1H), 4.36 (d, *J* = 7 Hz, 1H), 4.07 (d, *J* = 9.5 Hz, 1H), 3.91 (m, 1H), 3.70-3.60 (m, 2H), 3.53 (dd, *J* = 11, 5 Hz, 1H), 3.41 (t, *J* = 9.5 Hz, 1H), 3.40 (m, 1H), 3.22 (s, 3H), 2.48 (dd, *J* = 8, 7 Hz, 1H), 2.14 (tt, *J* = 12, 5 Hz,1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.86-1.51 (m, 13H), 1.47 (d, *J* = 12.5 Hz, 1H), 1.31-1.09 (m, 5H), 0.99 (d, *J* = 7.5 Hz, 1H), 0.88 (d, *J* = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.3, 144.0, 138.8, 138.7, 128.3, 127.8, 127.6, 127.5, 112.0, 98.7, 97.9, 83.6, 77.8, 76.3, 73.7, 73.4, 72.3, 70.6, 60.4, 47.5, 38.7, 36.0, 35.4, 34.0, 32.3, 32.2, 27.7, 26.7, 25.8, 25.5, 20.0, 19.0, 15.5, 14.4; HRMS calcd for $C_{41}H_{56}O_8Na$ $[M + Na]^+$: 699.3873; found: 699.3867.



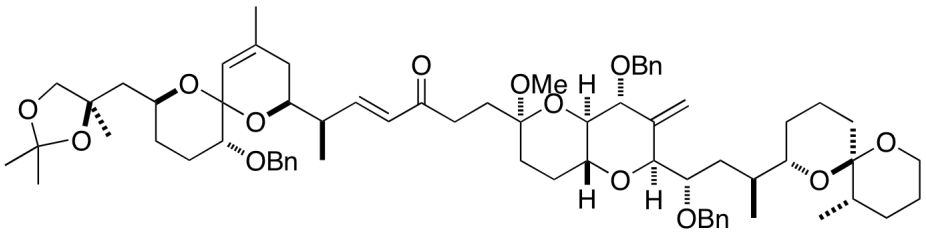
Dimethyl (4-((2*S*,4a*R*,6*S*,8*R*,8a*R*)-8-(benzyloxy)-6-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)-2-oxobutyl)phosphonate (6)

To a stirred −78 °C solution of dimethyl methylphosphonate (40 μL, 0.37 mmol) in THF (1.5 mL) under argon was added *tert*-butyllithium (180 μL of a 1.7 M solution in pentane, 280 μmol) dropwise. The solution was stirred for 45 min before a solution of **34** (26 mg, 39 μmol) in THF (1 mL) was added slowly via cannula. The resultant pale yellow solution was stirred for an additional 45 min, at which time TLC showed no remaining **34**. Saturated aqueous NaCl (1 mL) was added, and the mixture was allowed to warm to room temperature. THF was removed by rotary evaporation and the aqueous residue was extracted with diethyl ether (15 mL). The separated organic phase was washed with H_2O (2 × 3 mL) and saturated aqueous NaCl (2 × 3 mL). The combined aqueous phases were extracted with ethyl acetate, and the

combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was filtered through silica gel with hexanes−ethyl acetate−triethylamine (1:5:0.3, v/v) and the filtrate concentrated to yield crude β-hydroxy phosphonate as oil, which was used without further purification.

To a stirred room temperature solution of β-hydroxy phosphonate (39 μmol theor.) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (120 mg, 1.4 mmol) and Dess−Martin periodinane reagent (60 mg, 0.14 mmol). The resultant mixture was stirred for 45 min, at which time TLC showed no remaining β-hydroxy phosphonate. Diethyl ether (15 mL), saturated aqueous $NaHCO_3$ (1 mL), and 10% aqueous $Na_2S_2O_3$ (1 mL) were added, and the mixture was stirred vigorously until the organic layer became clear. The separated organic phase was washed with H_2O (2 × 3 mL) and saturated aqueous NaCl (2 × 3 mL). The aqueous phases were extracted with diethyl ether, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 1:2−1:5, v/v) to give **6** (21.4 mg, 27 μmol, 70% from **34**) as a pale oil:

R_f 0.36 (hexanes-ethyl acetate, 1:5, v/v); $[\alpha]_D^{25}$ +12.8 (*c* 0.33, $CHCl_3$); IR (neat): 3080, 3060, 2925, 2850, 1713, 1591, 1454, 1123, 1089, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 10H), 5.43 (s, 1H), 5.04 (s, 1H), 4.83 (d, J = 12.5 Hz, 1H), 4.75 (d, J = 12.5 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 4.52 (d, J = 12 Hz, 1H), 4.35 (d, J = 7 Hz, 1H), 4.06 (d, J = 9.5 Hz, 1H), 3.92 (m, 1H), 3.78 (d, $J_{P\text{-}H}$ = 11.5 Hz, 1H), 3.70-3.59 (m, 2H), 3.53 (m, 1H), 3.41 (m, 2H), 3.22 (s, 3H), 3.11 (d, $J_{P\text{-}H}$ = 22.5 Hz, 6H), 2.65 (t, J = 8 Hz, 2H), 2.17-2.05 (m, 2H), 1.77-1.90 (m, 7H), 1.47-1.68 (m, 8H), 1.35-1.45 (m, 3H), 0.99 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.1, 144.0, 138.8, 138.7, 128.3, 127.9, 127.6, 127.5, 127.5, 112.0, 98.7, 97.9, 83.8, 77.8, 76.1, 73.6, 73.4, 72.3, 70.6, 60.4, 53.1, 53.1, 47.5, 42.1, 41.0, 38.7, 36.0, 35.5, 34.0, 32.4, 32.2, 29.7, 29.0, 26.8, 25.8, 25.5, 20.0, 19.9, 15.4, 14.4; HRMS calcd for $C_{44}H_{63}O_{11}PNa$ $[M + Na]^+$: 821.4006; found: 821.3983.

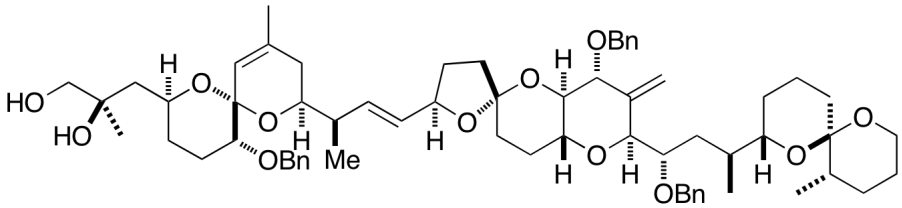


(6*R*,*E*)-6-((2*S*,8*S*,11*R*)-11-(Benzyloxy)-4-methyl-8-(((*R*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)-1-((2*S*,4a*R*,6*S*,8*R*,8a*R*)-8-(benzyloxy)-6-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)hept-4-en-3-one (4)

To a stirred solution of **6** (20 mg, 25 μmol) in CH_3CN (0.6 mL) was added LiCl (5 mg, 0.12 mmol) followed by diisopropylethylamine (7 μL, 0.035 mmol). After stirring for 10 min, a solution of **5** (10.5 mg, 23 μmol) in CH_3CN (0.8 mL) was added. The resulting mixture became turbid after 10 min and was stirred for an additional 20 h. The mixture was diluted with diethyl ether (5 mL), washed with H_2O and saturated aqueous NaCl (0.5 mL ea), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 5:1, v/v) of the residue gave **4** (25.2 mg, 22 μmol, 93%) as a clear, colorless oil:

R_f 0.24 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ +10.5 (*c* 0.29, $CHCl_3$); IR (neat): 3082, 3064, 3025, 2931, 2844, 1674, 1629, 1454, 1378, 1239, 1208, 1090, 1026, 983, 912, 855, 813, 734, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.26 (m, 15H), 7.08 (dd, *J* = 16, 7.5 Hz, 1H), 6.19 (d, *J* = 16 Hz, 1H), 5.43 (s, 1H), 5.16 (s, 1H), 5.04 (s, 1H), 4.85 (d, *J* = 12.5 Hz, 1H), 4.76 (d, *J* = 12 Hz, 1H), 4.64 (d, *J* = 11 Hz, 1H), 4.59 (d, *J* = 12.5 Hz), 4.52 (d, *J* = 11 Hz, 1H), 4.46 (d, *J* = 12.5 Hz, 1H), 4.35 (d, *J* = 7 Hz, 1H), 4.05 (d, *J* = 10 Hz, 1H), 3.91 (m, 1H), 3.80 (d, *J* = 8.5 Hz), 3.80 (m, 1H), 3.66 (d, *J* = 8.5 Hz, 1H), 3.71- 3.59 (m, 3H), 3.54 (m, 1H), 3.40 (t, *J* = 10 Hz, 1H), 3.39 (m, 1H), 3.24 (dd, *J* = 12, 4 Hz, 1H), 3.19 (s, 3H), 2.56 (m, 3H), 2.14 (m, 2H), 2.03 (t, *J* = 11 Hz, 1H), 1.94 (td, *J* = 13, 3 Hz, 1H), 1.82-1.76 (m, 9H), 1.73 (s, 3H), 1.72-1.48 (m, 11H), 1.39 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.16 (d, *J* = 7 Hz, 3H), 0.99 (d, *J* = 7 Hz, 1H), 0.86 (d, *J* = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 199.2, 149.2, 144.0, 138.9, 138.8, 138.7, 136.5, 130.1, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.5, 127.4, 123.1, 112.1, 108.3, 98.9, 97.9, 96.0, 83.9, 80.3, 79.0, 78.6, 78.2, 77.6, 77.4, 75.8, 75.1, 73.7, 73.4, 72.3, 71.3, 70.6, 66.5, 60.4, 47.5, 46.1, 41.3, 36.0, 35.5,

34.5, 34.0, 33.4, 32.4, 32.3, 32.3, 29.3, 27.5, 27.0, 26.8, 25.8, 25.5, 24.4, 24.3, 22.9, 20.0, 19.0, 15.5, 15.4, 14.4; HRMS calcd for $C_{69}H_{94}O_{13}Na$ $[M + Na]^+$: 1153.6592; found: 1153.6580.

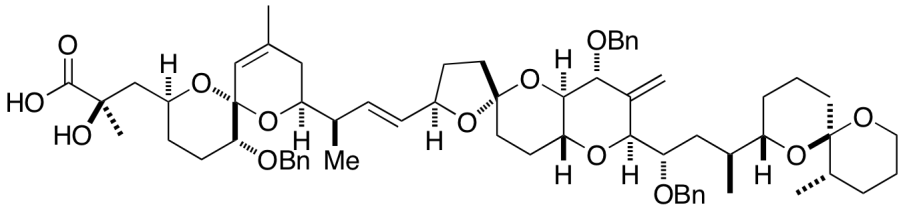


(2*R*)-3-((2*S*,6*R*,8*S*)-5-(Benzyloxy)-8-((*R*,*E*)-4-((2*R*,4a'*R*,5*R*,6'*S*,8'*R*,8a'*R*)-8'-(benzyloxy)-6'-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3*H*,3'*H*-spiro[furan-2,2'-pyrano[3,2-*b*]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropane-1,2-diol (35)

To a stirred solution of (*S*)-2-methyl-CBS-oxazaborolidine (200 μL of a 1.0 M solution in toluene, 0.20 mmol) in THF (0.6 mL) at 0 °C and under N_2 was added borane-tetrahydrofuran complex (140 μL of a 1 M solution in THF, 140 μmol) followed by a solution of **4** (12.0 mg, 10.6 μmol) in THF (0.35 mL). After 7 min, H_2O (200 μL) was added and the mixture was allowed to warm to room temperature. Diethyl ether (2 mL) was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was extracted with diethyl ether (2 × 0.5 mL), and the combined organic phases were washed with H_2O and saturated aqueous NaCl (0.5 mL ea), dried over Na_2SO_4, filtered, and concentrated. The crude allylic alcohol (R_f 0.40; hexanes−ethyl aceatate, 2:1, v/v) was filtered through silica gel with ethyl acetate, the filtrate was concentrated and then diluted with a mixture of THF (0.65 mL), acetic acid (0.50 mL) and H_2O (0.26 mL) in a 10 mL vial. The vial was then capped and the reaction was heated at 55^o C for 40 h before being cooled to room temperature. The solvent was removed by vacuum and the residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1) to give **35** (9.0 mg, 8.5 μmol, 80%) as white solid.

R_f 0.31 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{20}$ +30.5 (*c* 0.20, $CHCl_3$); IR (neat): 3399, 2920, 2852, 1644 1378, 1180, 1078, 1027, 964, 734, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.25 (m, 15H), 5.83 (dd, J = 15.5, 7.5 Hz, 1H), 5.60 (dd, J = 15.5, 7 Hz, 1H), 5.39 (t, J = 1.5 Hz, 1H), 5.15 (s, 1H), 5.02 (s, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 12.5 Hz, 1H), 4.58 (m, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 12.5 Hz, 1H), 4.30 (d, J = 7 Hz, 1H), 4.11 (brt, J = 11 Hz, 1H),

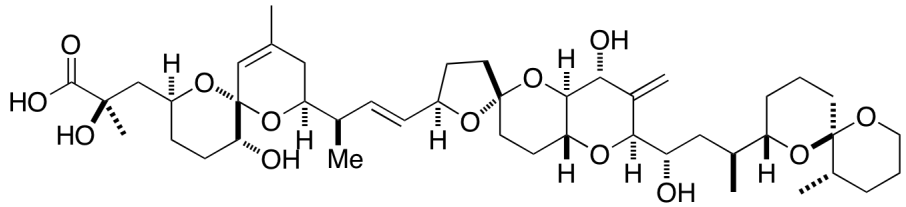
4.01 (d, J = 9.5 Hz, 1H), 3.90 (m, 1H), 3.69-3.58 (m, 4H), 3.53 (m, 2H), 3.46-3.35 (m, 3H), 3.24 (dd, J = 12, 4 Hz, 1H), 2.65 (brs, 1H), 2.43 (tq, J = 7.5, 7.5 Hz, 1H), 2.22-1.93 (m, 6H), 1.88−1.77 (m, 10H), 1.73 (s, 3H), 1.69−1.30 (m, 14H), 1.12 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.5 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 143.9, 138.8, 138.7, 137.9, 130.9, 128.3, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 127.5, 122.5, 112.1, 105.6, 97.9, 96.4, 84.2, 79.0, 78.6, 77.6, 75.3, 73.4, 73.3, 72.7, 72.4, 72.2, 71.4, 70.6, 69.1, 67.4, 60.4, 43.9, 40.9, 37.2, 36.0, 35.7, 34.0, 33.4, 33.0, 32.5, 32.3, 30.7, 27.0, 26.7, 25.8, 25.2, 23.9, 23.0, 20.0, 19.0, 15.6, 15.0, 14.4; HRMS calcd for $C_{69}H_{94}O_{13}Na$ $[M + Na]^+$: 1083.6173; found: 1083.6155.



(2*R*)-3-((2*S*,6*R*,8*S*)-5-(Benzyloxy)-8-((*R*,*E*)-4-((2*R*,4a'*R*,5*R*,6'*S*,8'*R*,8a'*R*)-8'-(benzyloxy)-6'-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3*H*,3'*H*-spiro[furan-2,2'-pyrano[3,2-*b*]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-hydroxy-2-methylpropanoic acid (36)

To a stirred solution of **35** (3.9 mg, 3.7 μmol), DMSO (0.05 mL) and diisopropylethylamine (0.10 mL) in CH_2Cl_2 (0.10 mL) was added sulfur trioxide pyridine complex (5.0 mg, 31.4 μmol). The mixture was stirred for 2 h before saturated NH_4Cl solution (1 mL) and diethyl ether (2 mL) was added. After stirring for another 15 min, the organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 1 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude product was then dissolved in a mixture of *t*-butanol (0.25 mL) and water (0.05 mL) before $NaH_2PO_4{\cdot}2H_2O$ (7 mg, 44.9 μmol), 2-methyl-2-butene (0.2 mL) and $NaClO_2$ (4 mg, 44.2 μmol) were added in sequence. The mixture was stirred for 1 h before saturated $Na_2S_2O_3$ solution (1 mL) was added. The mixture was stirred for another 20 min before the solution was acidified to pH = 2 with 1 M HCl. The mixuture was then extracted with diethyl ether (6 × 1 mL) and the combined organic extract was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (dichloromethane−methanol, 20:1, v/v) of the residue gave **36** (3.5 mg, 3.3 μmol, 89%) as a clear, colorless oil:

R_f 0.48 (dichloromethane-methanol, 19:1, v/v); $[\alpha]_D^{25}$ +42.9 (*c* 0.22, $CHCl_3$); IR (neat): 3067, 3020, 2925, 2851, 1730, 1713, 1462, 1378, 1075, 1028, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.74 (dd, *J* = 15, 8 Hz, 1H), 5.61 (dd, *J* = 15.5, 7.5 Hz, 1H), 5.43 (s, 1H), 5.13 (s, 1H), 5.04 (s, 1H), 4.88 (d, *J* = 12.5 Hz, 1H), 4.78 (d, *J* = 12.5 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.62 (m, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 11 Hz, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 4.32 (d, *J* = 7.5 Hz, 1H), 4.05 (m, 1H), 3.90 (m, 1H), 3.69-3.52 (m, 5H), 3.37 (ddd, *J* = 11.5, 5, 2 Hz, 1H), 3.25 (dd, *J* = 12, 4 Hz, 1H), 2.42 (tq, *J* = 7.5, 7.5 Hz, 1H), 2.22-1.93 (m, 6H), 1.88−1.77 (m, 10H), 1.72 (s, 3H), 1.69−1.30 (m, 14H), 1.35 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.5 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 176.4, 143.8, 139.0, 138.8, 138.7, 135.0, 131.3, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 122.2, 112.2, 105.8, 98.0, 96.6, 84.3, 79.3, 78.5, 77.9, 75.7, 75.6, 74.5, 73.5, 73.4, 72.5, 71.6, 71.3, 70.8, 68.4, 60.5, 43.8, 41.6, 37.4, 36.2, 35.8, 34.1, 32.9, 32.8, 32.5, 32.3, 32.1, 30.4, 29.5, 29.4, 27.5, 27.1, 26.9, 26.7, 25.9, 23.7, 23.2, 22.9, 22.8, 20.1, 19.2, 17.9, 16.0, 15.3, 14.5; HRMS calcd for $C_{65}H_{86}O_{13}Na$ $[M + Na]^+$: 1097.5966; found: 1097.5958.



(2*R*)-2-Hydroxy-3-((2*S*,6*R*,8*S*)-5-hydroxy-8-((*R*,*E*)-4-((2*R*,4a'*R*,5*R*,6'*S*,8'*R*,8a'*S*)-8'-hydroxy-6'-((1*S*,3*S*)-1-hydroxy-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3*H*,3'*H*-spiro[furan-2,2'-pyrano[3,2-*b*]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropanoic acid (3)

To a stirred −78 °C solution of **36** (2.1 mg, 1.9 μmol) in THF (0.2 mL) under argon was added a solution of lithium di-*tert*-butylbiphenylide (0.5 mL of 0.13 M solution in THF, 0.06 mmol). After stirring for 30 min, H_2O (0.2 mL) was added to the deep blue-green solution and the resulting colorless mixture was allowed to warm to room temperature. The THF was removed under a stream of argon, and the residue was diluted with H_2O (0.2 mL) and washed with hexanes (3 × 1 mL). The aqueous phase was cooled to 0 °C and was acidified to pH 2 with 0.5 M aqueous HCl, and extracted with diethyl ether (4 × 1 mL). The combined ether extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (dichloromethane-methanol, 18:1, v/v) to give **3** (1.0 mg, 1.3 μmol,

69%) as a colorless solid. This material matched the data reported for the natural product by NMR spectroscopy, sign of optical rotation, hplc retention time, and HRMS.

R_f 0.24 (dichloromethane-methanol, 19:1, v/v); $[\alpha]_D^{25}$ +12.0 (*c* 0.075, $CHCl_3$); ^1H NMR (CD_3OD, 500 MHz): δ 5.84 (dd, J = 15.5, 8.5 Hz, 1H), 5.52 (dd, J = 15.5, 8 Hz, 1H), 5.36 (s, 1H), 5.29 (s, 1H), 4.62 (q, J = 7 Hz, 1H), 4.10 (m, 1H), 4.07 (m, 1H), 3.97 (d, J = 9 Hz, 1H), 3.75-3.62 (m, 3H), 3.51 (dd, J = 11, 5 Hz, 1H), 3.45-3.35 (m, 3H), 2.34 (q, J = 1.75 Hz, 1H), 2.20-2.15 (m, 2H), 2.00-1.95 (m, 3H), 1.90-1.16 (m, 23H), 1.75 (s, 3H), 1.34 (s, 3H), 1.07 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 147.5, 140.0, 137.5, 132.4, 123.1, 112.1, 107.1, 99.3, 97.7, 86.4, 80.5, 78.1, 76.3, 75.0, 73.1, 72.2, 72.0, 71.4, 69.5, 67.1, 61.4, 45.6, 43.4, 38.6, 38.1, 37.4, 35.3, 34.1, 34.1, 33.4, 31.6, 28.6, 27.7, 27.6, 26.7, 23.1, 21.0, 20.1, 16.7, 14.7, 14.4; HRMS calcd for $C_{44}H_{68}O_{13}Na$ $[M + Na]^+$: 827.4558; found: 827.4527.

References:

[1] S. F. Sabes, R. A. Urbanek, C. J. Forsyth, *J. Am. Chem. Soc.* **1998**, *120*, 2534-2542.

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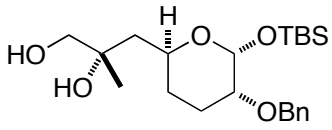
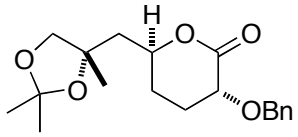
Total Synthesis of 2-epi-DTX2



(*S*)-3-((2*S*,5*R*,6*R*)-5-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl)-2-methylpropane-1,2-diol (18a)

To a mixture of **17** (1.542 g, 4.10 mmol), *tert*-butanol (20 mL) and water (20 mL) at 0 °C was added AD-mix-α (5.74 g). The mixture was stirred vigorously for 24 h then sodium sulfite (6.2 g) was added. The mixture was stirred at 25 °C for 1 h before diethyl ether (20 mL) was added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 20 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1 to 1:1, v/v) to give **18** (0.156 g, 0.381 mmol, 9.3%) and **18a** (1.391g, 3.39 mmol, 83%) as colorless oils. Data for **18**a:

R_f 0.30 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{25}$ = +11.8 (*c* 2.40, $CDCl_3$); IR (neat): 3416, 2929, 2858, 1648, 1456, 1396, 1252, 1170, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33 (m, 5H), 4.74 (d, *J* = 12 Hz, 2H), 4.63 (m, 2H), 3.86 (t, *J* = 11 Hz, 1H), 3.74 (s, 1H), 3.42 (dd, *J* = 11, 5 Hz, 1H), 3.32 (dd, *J* = 11, 8 Hz), 3.16 (m, 1H), 2.31 (dd, *J* = 8, 5.5 Hz), 2.06 (m, 1H), 1.98 (dd, *J* = 14.5, 9.5 Hz, 1H), 1.60-1.41 (m, 4H), 1.22 (s, 3H), 0.95 (s, 9H), 0.17(m, 6H). ^{13}C NMR ($CDCl_3$, 125MHz) δ 138.6, 128.3, 127.3, 99.4, 78.0, 73.5, 72.6, 72.3, 70.9, 42.1, 31.5, 28.8, 25.6, 23.9, 17.9, -4.5, -4.9. HRMS calcd for $C_{22}H_{38}O_5SiNa$ $[M + Na]^+$: 433.2386; found: 433. 2378.

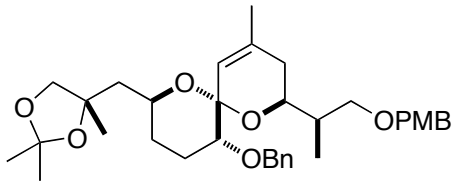


(3*R*,6*S*)-3-(Benzyloxy)-6-(((*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)tetrahydro-2*H*-pyran-2-one (10a)

To a solution of **18a** (1.560g, 3.80 mmol) in CH_2Cl_2 (20 mL) was added 2,2-dimethoxypropane (3.0 mL, 24.4 mmol) followed by pyridinium *p*-toluenesulfonate (37 mg, 0.14 mmol). The reaction mixture was stirred for 2.5 h then triethylamine (0.5 mL) was added. The solvent was evaporated and the residue was

filtered through a pad of silica gel with hexanes-ethyl acetate (4:1, v/v). The filtrate was concentrated and the residue was dissolved in THF (20 mL). A solution of tetra-*n*-butylammonium fluoride (1.0 M in THF, 3.90 mL, 3.90 mmol) was added dropwise over 1 h. The mixture was stirred for another 0.5 h and saturated ammonium chloride solution (5 mL) was added. THF was removed from the mixture and diethyl ether (20 mL) was added. The mixture was stirred for 10 min before the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was filtered through a pad of silica gel with hexanes-ethyl acetate (2:1, v/v) and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and $NaHCO_3$ (1.03 g, 12.3 mmol), iodobenzene diacetate (1.69 g, 5.25 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (54 mg, 0.35 mmol) were added. The mixture was stirred for 12 h before saturated $Na_2S_2O_3$ solution (3.0 mL) was added. Diethyl ether (30 mL) was added and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (hexanes: ethyl acetate, 4:1, v/v) to give compound **10a** (0.956 g, 2.86 mmol, 75%, three steps) as a colorless oil.

R_f 0.34 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ = +35.0 (*c* 0.34, $CDCl_3$); IR (neat): 3058, 3027, 2928, 2930, 2868, 1745, 1454, 1379, 1246, 1209, 1118, 1058, 807, 738, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36 (m, 5H), 4.86 (d, *J* = 12 Hz, 1H), 4.82 (m, 1H), 4.06 (d, *J* = 8.5 Hz, 1H), 3.97 (t, *J* = 6 Hz, 1H), 3.72 (d, *J* =8.5 Hz, 1H), 2.17-1.94 (m, 4H), 1.82 (dd, *J* = 15, 3.5 Hz, 1H), 1.69 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 125MHz) δ 170.6, 137.3, 128.5, 128.1, 128.0, 109.2, 79.7, 76.5, 73.8, 72.8, 72.6, 44.8, 28.3, 27.2, 27.1, 26.8, 26.3. HRMS calcd for $C_{19}H_{26}O_5Na$ $[M + Na]^+$: 357.1678; found: 357.1670.



(2*S*,6*R*,8*S*,11*R*)-11-(Benzyloxy)-2-((*R*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-8-(((*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-ene (23a)

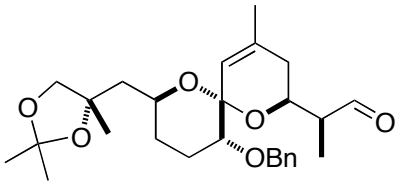
To a stirred -78 °C solution of **20** (2.154 g, 5.94 mmol) in THF (20 mL) was added *n*-butyllithium (1.0 mL of a 2.5 M solution in hexanes, 2.5 mmol). After the mixture was stirred for 40 min, a solution of **10a** (0.903 g, 2.70 mmol) in THF (5 mL) was added via cannula. After 1 h, saturated aqueous NH_4Cl solution (15 mL) was added and the mixture was warmed to room temperature. The mixture was extracted with diethyl ether (3×50 mL) and the combined organic extracts were washed with water and saturated aqueous NaCl. The combined organic fraction was dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel (hexanes-ethyl acetate, 5:1, v/v) to give **21a** (1.50 g, 2.23 mmol, 83%) as colorless oil.

To a solution of **21a** (1.27 g, 1.90 mmol) in CH_2Cl_2 (16 mL) at 0 °C was added imidazole (0.260 g, 3.80 mmol), followed by chlorotrimethylsilane (0.36 mL, 2.85 mmol) and 4-dimethylaminopyridine (23 mg, 0.190 mmol). After stirring for 50 min, saturated aqueous NH_4Cl solution (10 mL) was added. The mixture was extracted with diethyl ether (3 × 35 mL) and the combined organic phases were washed with water and saturated aqueous NaCl (16 mL), dried over Na_2SO_4, filtered, and concentrated. The residue of crude TMS-protected **21a** was directly used for next step without further purification.

To a -78 °C suspension of CuI (1.49 g, 7.80 mmol) in diethyl ether (6 mL) under argon was added methyllithium (9.7 mL of a 1.6 M solution in diethyl ether, 15.6 mmol). The mixture was allowed to warm slowly to -30 °C until a clear and colorless solution formed. The solution was cooled to -78 °C, and the solution of crude TMS-protected **21a** in diethyl ether (5 mL) was added via cannula. After 1.0 h, saturated aqueous NH_4Cl (10 mL) was added and the mixture was warmed to room temperature and stir until the aqueous phase became bright blue. The solution was extracted with diethyl ether (3 × 30 mL) and the combined organic phases were washed with water and saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated to give a crude enone product. This was dissolved in a mixture of

dichloromethane (20 mL), methanol (8 mL), and pyridinium *p*-toluenesulfonate (16 mg, 0.059 mmol). After the solution was stirred at 25 °C for 2 h, triethylamine (0.50 mL) was added. After the mixture was stirred for 10 min, the solvent was removed and the residue was purified via chromatography (hexanes-ethyl acetate, 8:1 to 6:1, v/v) to give **23a** (0.371 g, 0.64 mmol, 34% based on **21a**) as colorless oil.

R_f 0.43 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ = +24.2 (*c* 1.1, $CDCl_3$); IR (neat): 3058, 3026, 2930, 2861, 1611, 1512, 1247, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.24 (m, 7H), 6.86 (m, 2H), 5.18 (s, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 4.49 (d, *J* = 12.5 Hz, 1H), 4.44 (d, *J* = 2 Hz, 2H), 3.80-3.67 (m, 6H), 3.64 (d, *J* = 8 Hz, 1H), 3.34 (t, *J* = 8.5 Hz, 1H), 3.26 (dd, *J* = 12, 4.5 Hz, 1H), 2.11 (m, 1H), 2.04 (dd, *J* = 16.5, 11.5 Hz, 1H), 1.92 (qd, *J* = 12.5, 4 Hz, 1H), 1.83-1.76 (m, 3H), 1.73 (s, 3H), 1.62 (dd, *J* = 13, 6 Hz, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H), 1.03 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 159.1, 139.0, 137.2, 130.9, 129.2, 128.1, 127.7, 127.4, 123.0, 113.7, 108.8, 96.2, 80.5, 78.7, 73.6, 72.7, 72.4, 71.3, 69.7, 66.4, 55.3, 45.9, 38.4, 32.8, 32.7, 27.3, 27.2, 26.3, 24.4, 23.0, 13.8; HRMS calcd for $C_{35}H_{48}O_7Na$ $[M + Na]^+$: 603.3298; found: 603.3292.

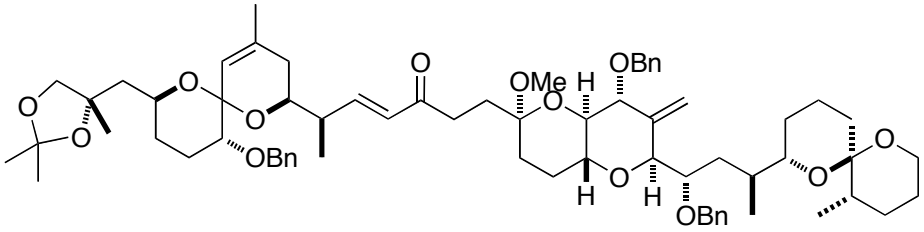


(*S*)-2-((2*S*,6*R*,8*S*,11*R*)-11-(Benzyloxy)-4-methyl-8-(((*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)propanal (5a)

To a mixture of **23a** (30 mg, 51 μmol), CH_2Cl_2 (5.0 mL), an aqueous NaH_2PO_4 buffer (pH = 7, 1.0 mL), and *tert*-butyl alcohol (0.30 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (70 mg, 0.31 mmol). The reaction flask was placed in an aqueous bath and sonicated for 5 min. The mixture was diluted with diethyl ether (8 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous phase was extracted with diethyl ether (3 × 2 mL) and the combined organic phases were washed with saturated aqueous NaCl (1.5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 5:1 to 3:2, v/v) to give a colorless oil which was then dissolved in CH_2Cl_2 (3.0 mL). $NaHCO_3$ (150 mg, 1.8 mmol) followed by the Dess−Martin periodinane (80 mg, 0.19 mmol) were added to the solution. The mixture was stirred for 30 min before diethyl ether

(4.0 mL) and 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (1.0 mL ea.) were added. The mixture was stirred until the organic phase became clear and colorless. The separated aqueous phase was extracted with diethyl ether (3 × 2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (1 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 5:1, v/v) of the residue gave **5a** (17 mg, 35 μmol, 69%, two steps) as a white crystalline solid.

R_f 0.70 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{25}$ = +16.1 (*c* 0.18, $CDCl_3$); IR (neat): 3066, 3035, 2924, 2852, 1727, 1604, 1454, 1378, 1245, 1209, 1089, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.92 (d, *J* = 2.5 Hz, 1H), 7.32-7.24 (m, 5H), 5.20 (s, 1H), 4.61 (d, *J* = 12 Hz, 1H), 4.47 (d, *J* = 12 Hz, 1H), 4.10 (m, 1H), 3.89 (d, *J* = 8.5 Hz, 1H), 3.80 (m, 1H), 3.71 (d, *J* = 8.5 Hz, 1H), 3.26 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.71 (m, 1H), 2.09 (dd, *J* = 14, 11.5 Hz, 1H), 1.90-1.71 (m, 4H), 1.71 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H), 1.11 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 204.3, 138.8, 136.4, 128.2, 127.8, 127.5, 123.3, 108.9, 96.3, 80.3, 78.5, 73.6, 71.4, 69.2, 66.7, 50.5, 46.0, 33.1, 32.7, 27.2, 27.1, 26.4, 24.3, 23.0, 10.4; HRMS calcd for $C_{27}H_{38}O_6Na$ $[M + Na]^+$: 481.2566; found: 481.2575.

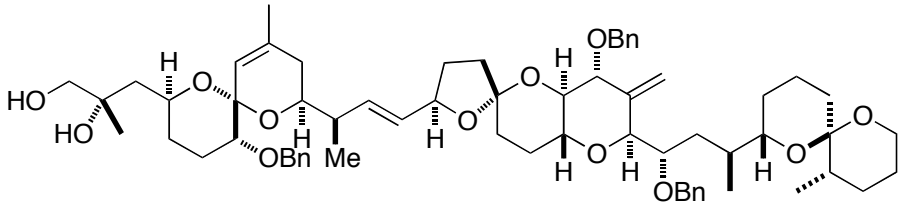


(6*R*,*E*)-6-((2*S*,8*S*,11*R*)-11-(Benzyloxy)-4-methyl-8-(((*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)-1-((2*S*,4a*R*,6*S*,8*R*,8a*R*)-8-(benzyloxy)-6-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-2-methoxy-7-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)hept-4-en-3-one (4a)

To a stirred solution of **6** (15 mg, 18 μmol) in CH_3CN (0.6 mL) was added LiCl (5 mg, 0.12 mmol) followed by diisopropylethylamine (7 μL, 0.035 mmol). After stirring for 10 min, a solution of **5** (8.6 mg, 18 μmol) in CH_3CN (0.8 mL) was added. The resulting mixture became turbid after 10 min and was stirred for an additional 20 h. The mixture was diluted with diethyl ether (5 mL), washed with H_2O and saturated aqueous NaCl (0.5 mL ea), dried over Na_2SO_4, filtered, and concentrated. Silica gel column

chromatography (hexanes−ethyl acetate, 5:1, v/v) of the residue gave **4a** (18.2 mg, 16 μmol, 89%) as a clear, colorless oil:

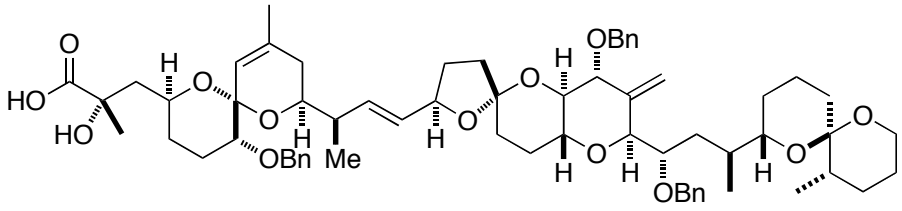
R_f 0.18 (hexanes-ethyl acetate, 4:1, v/v); $[\alpha]_D^{20}$ = +13.3 (*c* 0.33, $CDCl_3$); IR (neat): 3082, 3060, 3025, 2931, 2852, 1674, 1629, 1454, 1378, 1239, 1208, 1090, 1026, 983, 912, 856, 734, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.24 (m, 15H), 7.07 (dd, *J* = 16, 7.5 Hz, 1H), 6.21 (d, *J* = 16 Hz, 1H), 5.43 (s, 1H), 5.20 (s, 1H), 5.04 (s, 1H), 4.86 (d, *J* = 12.5 Hz, 1H), 4.76 (d, *J* = 12 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 12.5 Hz), 4.52 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 12.5 Hz, 1H), 4.35 (d, *J* = 7 Hz, 1H), 4.06 (d, *J* = 9.5 Hz, 1H), 3.91 (m, 1H), 3.81 (m, 3H), 3.66 (m, 2H), 3.64 (m, 1H), 3.55 (m, 1H), 3.41 (m, 2H), 3.26 (m, 1H), 3.19 (s, 3H), 2.59 (m, 3H), 2.14 (m, 1H), 2.08-1.90 (m, 2H), 1.82-1.48 (m, 20H), 1.73 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H), 1.18 (d, *J* = 7 Hz, 3H), 0.99 (d, *J* = 7 Hz, 3H), 0.86 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 199.2, 149.1, 144.01, 139.0, 138.8, 136.7, 130.1, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 127.4, 123.1, 112.0, 108.8, 99.0, 97.9, 96.2, 83.9, 80.4, 78.6, 78.5, 75.9, 73.7, 73.4, 72.3, 71.2, 70.9, 70.6, 68.0, 66.5, 60.4, 47.5, 46.0, 41.4, 36.0, 35.5, 34.7, 34.0, 33.1, 32.8, 32.4, 29.4, 27.3, 27.2, 26.8, 26.2, 25.8, 25.5, 24.4, 23.0, 20.0, 19.0, 15.5, 15.4, 14.4; HRMS calcd for $C_{69}H_{94}O_{13}Na$ [M + Na]$^+$: 1153.6592; found: 1153.6581.



(2*S*)-3-((2*S*,6*R*,8*S*)-5-(Benzyloxy)-8-((*R*,*E*)-4-((2*R*,4a'*R*,5*R*,6'*S*,8'*R*,8a'*R*)-8'-(benzyloxy)-6'-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3*H*,3'*H*-spiro[furan-2,2'-pyrano[3,2-*b*]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropane-1,2-diol (35a)

To a stirred solution of (*S*)-2-methyl-CBS-oxazaborolidine (180 μL of a 1.0 M solution in toluene, 0.18 mmol) in THF (0.6 mL) at 0 °C and under N_2 was added borane-tetrahydrofuran complex (140 μL of a 1 M solution in THF, 140 μmol) followed by a solution of **4a** (16.5 mg, 14.6 μmol) in THF (0.35 mL). After 7 min, H_2O (200 μL) was added and the mixture was allowed to warm to room temperature. Diethyl ether (2 mL) was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was extracted with

diethyl ether (2 × 0.5 mL), and the combined organic phases were washed with H_2O and saturated aqueous NaCl (0.5 mL ea), dried over Na_2SO_4, filtered, and concentrated. The crude allylic alcohol (R_f 0.40; hexanes−ethyl aceatate, 2:1, v/v) was filtered through silica gel with ethyl acetate, the filtrate was concentrated and then diluted with a mixture of THF (0.65 mL), acetic acid (0.50 mL) and H_2O (0.26 mL) in a 10 mL vial. The vial was then capped and the reaction was heated at 55^{o}C for 40 h before cooled to room temperature. The solvent was removed under vacuum and the residue was purified through column chromatography (hexanes-ethyl acetate, 4:1 to 2:1) to give **35a** (11.6 mg, 10.8 μmol, 74%) as a white solid. R_f 0.31 (hexanes-ethyl acetate, 2:1, v/v); $[\alpha]_D^{20}$ = +28.4 (*c* 0.25, $CHCl_3$); IR (neat): 3387, 3087, 3061, 3023, 2953, 2925, 2864, 2854, 1491, 1455, 1379, 1250, 1206, 1078, 1026, 964, 913, 735, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.24 (m, 15H), 5.83 (dd, *J* = 15.5, 7.5 Hz, 1H), 5.59 (dd, *J* = 15.5, 7 Hz, 1H), 5.39 (t, *J* = 1.5 Hz, 1H), 5.15 (s, 1H), 5.02 (s, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.75 (d, *J* = 12.5 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 4.58 (m, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 4.30 (d, *J* = 7 Hz, 1H), 4.11 (s, 1H), 4.02 (d, *J* = 9.5 Hz, 1H), 3.91 (m, 1H), 3.69-3.53 (m, 6H), 3.37 (m, 2H), 3.24 (m, 2H), 2.54 (m, 1H), 2.44 (q, *J* = 7.5 Hz, 1H), 2.22-1.93 (m, 6H), 1.88−1.77 (m, 10H), 1.73 (s, 3H), 1.69−1.30 (m, 14H), 1.16 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 144.1, 138.8, 138.7, 138.1, 134.8, 130.9, 128.3, 128.2, 128.2, 127.9, 127.9, 127.6, 127.5, 127.5, 122.4, 112.0, 105.5, 97.9, 96.4, 84.1, 79.0, 78.6, 77.7, 75.3, 73.4, 73.3, 72.5, 72.4, 72.2, 71.3, 70.6, 70.4, 67.4, 60.4, 42.7, 41.0, 37.4, 36.0, 35.7, 34.0, 33.4, 33.1, 32.4, 32.3, 31.9, 30.8, 27.0, 26.7, 25.8, 24.9, 24.7, 23.8, 23.0, 20.0, 19.0, 15.7, 15.1, 14.4; HRMS calcd for $C_{69}H_{94}O_{13}Na$ $[M + Na]^+$: 1083.6173; found: 1083.6158.

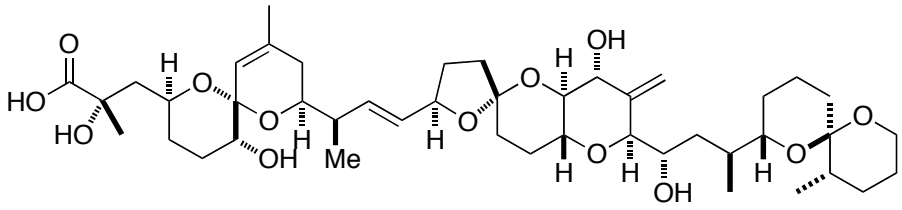


(2*S*)-3-((2*S*,6*R*,8*S*)-5-(Benzyloxy)-8-((*R*,*E*)-4-((2*R*,4a'*R*,5*R*,6'*S*,8'*R*,8a'*R*)-8'-(benzyloxy)-6'-((1*S*,3*S*)-1-(benzyloxy)-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3*H*,3'*H*-spiro[furan-2,2'-pyrano[3,2-*b*]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-hydroxy-2-methylpropanoic acid (36a)

To a stirred solution of **35a** (4.5 mg, 4.2 μmol), DMSO (0.05 mL) and diisopropylethylamine (0.10 mL) in CH_2Cl_2 (0.10 mL) was added sulfur trioxide pyridine complex (5.0 mg, 31.4 μmol). The mixture was stirred for 2 h before saturated NH_4Cl solution (1 mL) and diethyl ether (2 mL) was added. After stirring for another 15 min, the organic phase was separated and the aqueous phase was extracted with diethyl ether (4 × 1 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude product was dissolved in a mixture of *t*-butanol (0.25 mL) and water (0.05 mL) before $NaH_2PO_4 \cdot 2H_2O$ (7 mg, 44.9 μmol), 2-methyl-2-butene (0.2 mL) and $NaClO_2$ (4 mg, 44.2 μmol) were added sequentially. The mixture was stirred for 1 h before saturated $Na_2S_2O_3$ solution (1 mL) was added. The mixture was stirred for another 20 min before the solution was acidified to pH = 2 with 1 M HCl. The mixuture was then extracted with diethyl ether (6 × 1 mL) and the combined organic extract was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (dichloromethane−methanol, 20:1, v/v) of the residue gave **36a** (3.5 mg, 3.3 μmol, 78%) as a clear, colorless oil:

R_f 0.22 (dichloromethane-methanol, 19:1, v/v); $[\alpha]_D^{25}$ = +19.2 (*c* 0.33, $CHCl_3$); IR (neat): 3066, 3021, 2924, 2853, 1738, 1713, 1462, 1378, 1180, 1078, 1027, 964, 734, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.24 (m, 15H), 5.81 (dd, *J* = 15.5, 7.5 Hz, 1H), 5.59 (dd, *J* = 15.5, 7 Hz, 1H), 5.44 (s, 1H), 5.14 (s, 1H), 5.04 (s,1H), 4.79 (m, 2H), 4.67 (d, *J* = 11 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 4.57-4.51 (m, 2H), 4.46 (d, *J* = 12.5 Hz, 1H), 4.32 (d, *J* = 7.5 Hz, 1H), 4.23 (brt, *J* = 10 Hz, 1H), 4.03 (d, *J* = 9.5 Hz, 1H), 3.92 (m, 1H), 3.68-3.52 (m, 5H), 3.38 (dd, *J* = 11.5, 3 Hz, 1H), 3.23 (dd, *J* = 12, 4 Hz, 1H), 2.44 (dd, *J* = 14.5, 9.5 Hz, 1H), 2.33 (q, *J* = 7.5 Hz, 1H), 1.73 (s, 3H), 1.39 (s, 3H), 1.07 (d, *J* = 7 Hz, 3H), 0.99 (d, *J* = 7 Hz, 3H), 0.83 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 175.6, 143.7, 138.8, 138.7, 138.3, 130.9, 128.3,

128.2, 128.2, 127.9, 127.8, 127.6, 127.5, 122.2, 112.4, 105.6, 97.9, 96.4, 84.2, 78.8, 78.4, 77.9, 75.3, 73.4, 73.2, 72.4, 71.9, 71.3, 70.6, 66.9, 60.4, 42.7, 41.1, 37.2, 36.0, 35.6, 34.0, 33.2, 32.9, 32.3, 31.9, 30.6, 29.6, 29.5, 29.4, 29.3, 29.1, 27.2, 27.0, 26.8, 25.8, 24.9, 24.8, 23.7, 23.0, 22.7, 20.0, 19.0, 15.8, 15.1, 14.4, 14.1; HRMS calcd for $C_{65}H_{86}O_{13}Na$ $[M + Na]^+$: 1097.5966; found: 1097.5960.



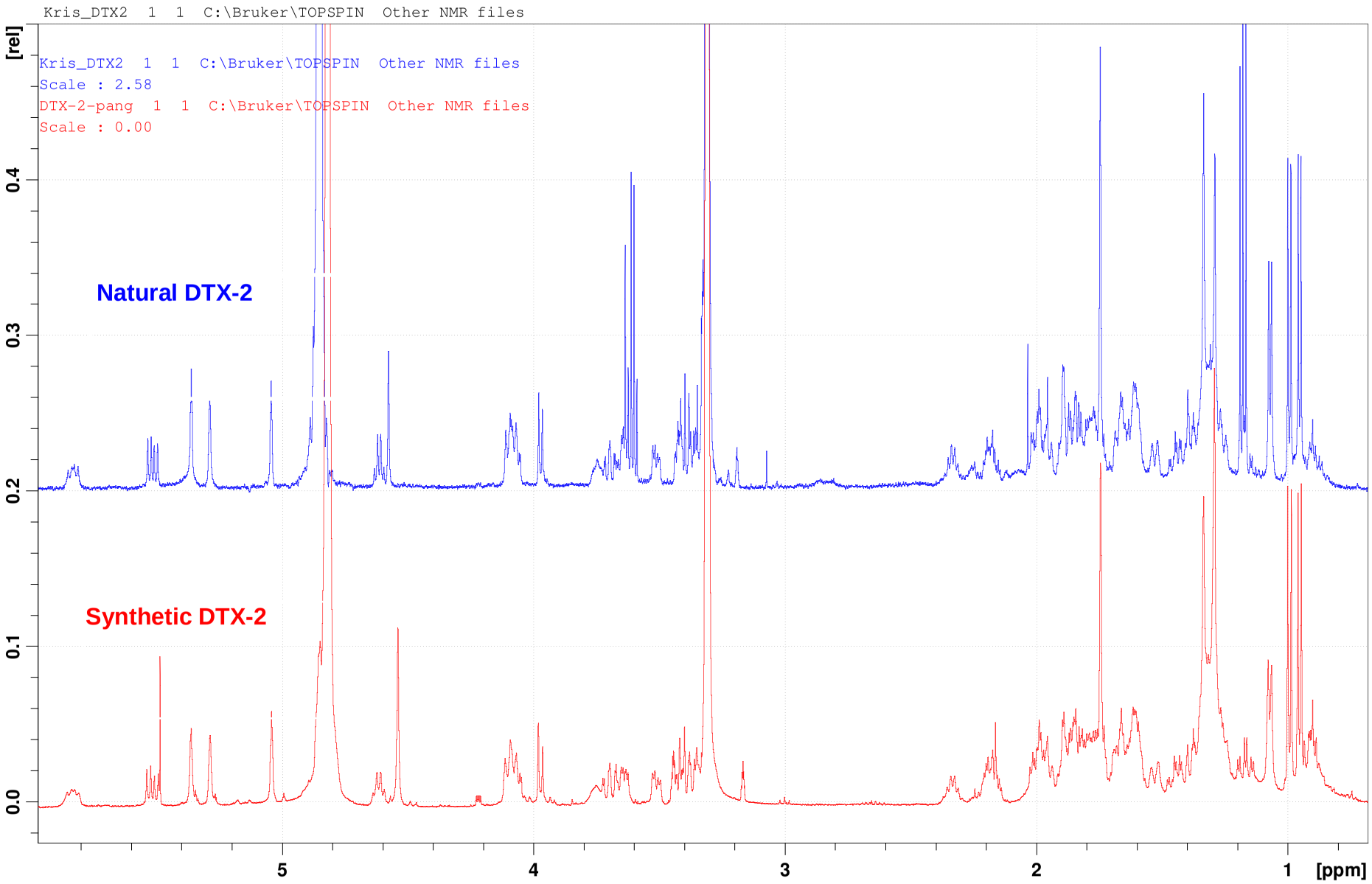
(2*S*)-2-Hydroxy-3-((2*S*,6*R*,8*S*)-5-hydroxy-8-((*R*,*E*)-4-((2*R*,4a'*R*,5*R*,6'*S*,8'*R*,8a'*S*)-8'-hydroxy-6'-((1*S*,3*S*)-1-hydroxy-3-((2*S*,6*R*,11*S*)-11-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)butyl)-7'-methyleneoctahydro-3*H*,3'*H*-spiro[furan-2,2'-pyrano[3,2-*b*]pyran]-5-yl)but-3-en-2-yl)-10-methyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl)-2-methylpropanoic acid (2-epi-dinophysistoxin-2) (3a, 2-epi-DTX-2)

To a stirred −78 °C solution of **36a** (1.5 mg, 1.3 μmol) in THF (0.2 mL) under argon was added a solution of lithium di-*tert*-butylbiphenylide (0.4 mL of 0.13 M solution in THF, 0.05 mmol). After stirring for 30 min, H_2O (0.2 mL) was added to the deep blue-green solution and the resulting colorless mixture was allowed to warm to room temperature. The THF was removed under a stream of argon, and the residue was diluted with H_2O (0.2 mL) and washed with hexanes (3 × 1 mL). The aqueous phase was cooled to 0 °C and was acidified to pH 2 with 0.5 M aqueous HCl, and extracted with diethyl ether (4 × 1 mL). The combined ether extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (dichloromethane-methanol, 18:1, v/v) to give **3** (0.7 mg, 0.9 μmol, 67%) as a colorless solid.

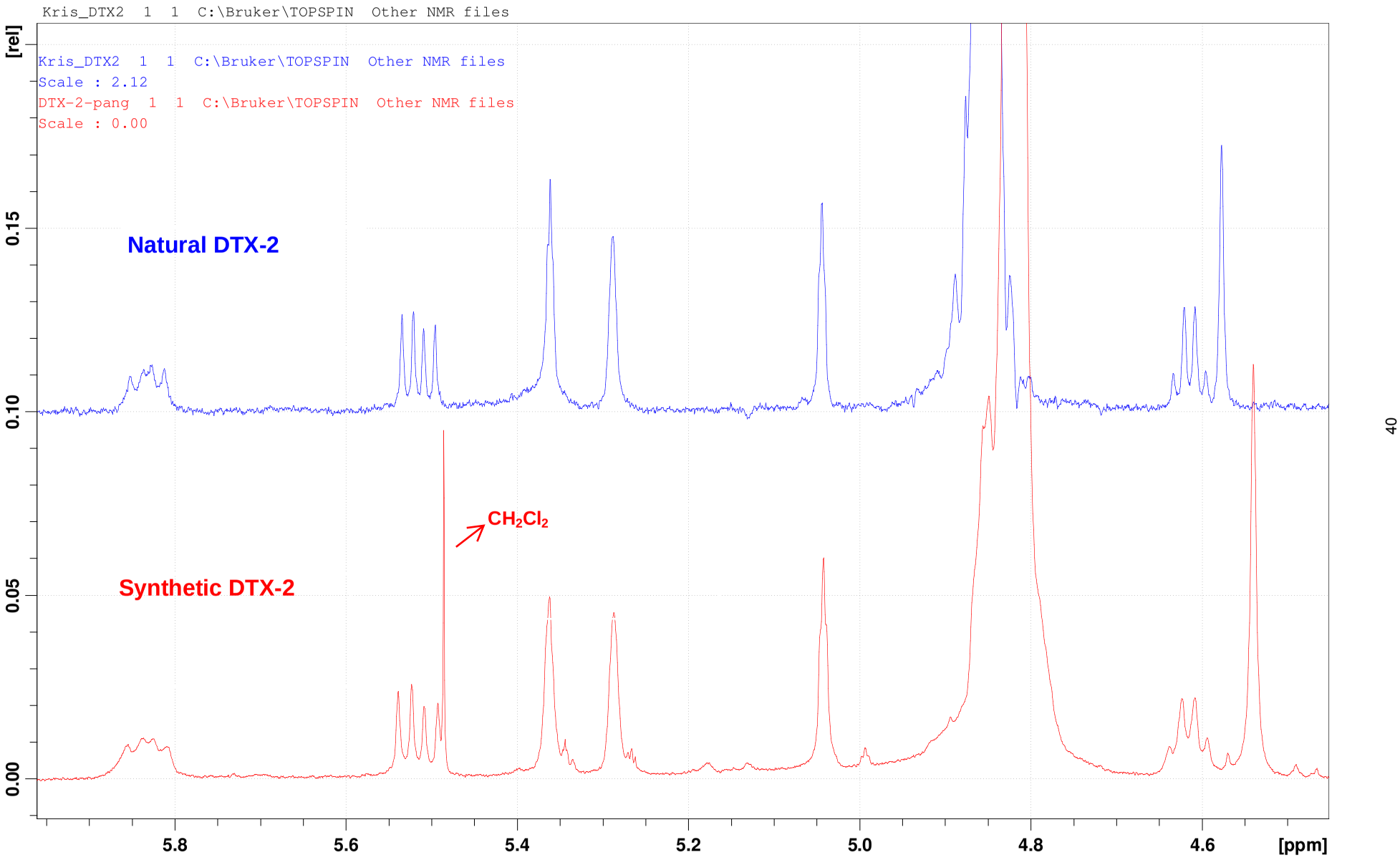
R_f 0.09 (dichloromethane-methanol, 19:1, v/v); $[\alpha]_D^{25}$ = +10.8 (*c* 0.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.78 (dd, *J* = 15, 8 Hz, 1H), 5.54 (dd, *J* = 15, 8 Hz, 1H), 5.44 (s, 1H), 5.32 (s, 1H), 5.14 (s, 1H), 4.49 (q, *J* = 7 Hz, 1H), 4.21 (d, *J* = 10 Hz, 1H), 4.00 (m, 1H), 3.65 (m, 2H), 3.55 (m, 1H), 3.45 (dd, *J* = 7.5 Hz, 1H), 3.42 (t, *J* = 10 Hz, 1H), 3.40 (m, 1H), 2.33 (q, *J* = 7 Hz, 1H), 2.23-1.30 (m, 20H), 1.77 (s, 3H), 1.48 (s, 3H), 1.07 (d, *J* = 7 Hz, 3H), 0.99 (d, *J* = 7.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (CD_3OD, 125MHz) δ 147.4, 137.8, 132.0, 123.7, 112.2, 107.1, 99.3, 97.7, 86.4, 80.7, 79.5, 75.0, 73.3, 72.1, 71.4,

67.0, 61.4, 38.6, 38.1, 37.4, 35.3, 34.3, 34.2, 33.3, 31.6, 28.6, 27.7, 26.7, 25.3, 23.2, 21.0, 20.1, 16.8, 14.7, 14.4; HRMS calcd for $C_{44}H_{68}O_{13}Na$ $[M + Na]^+$: 827.4558; found: 827.4545.

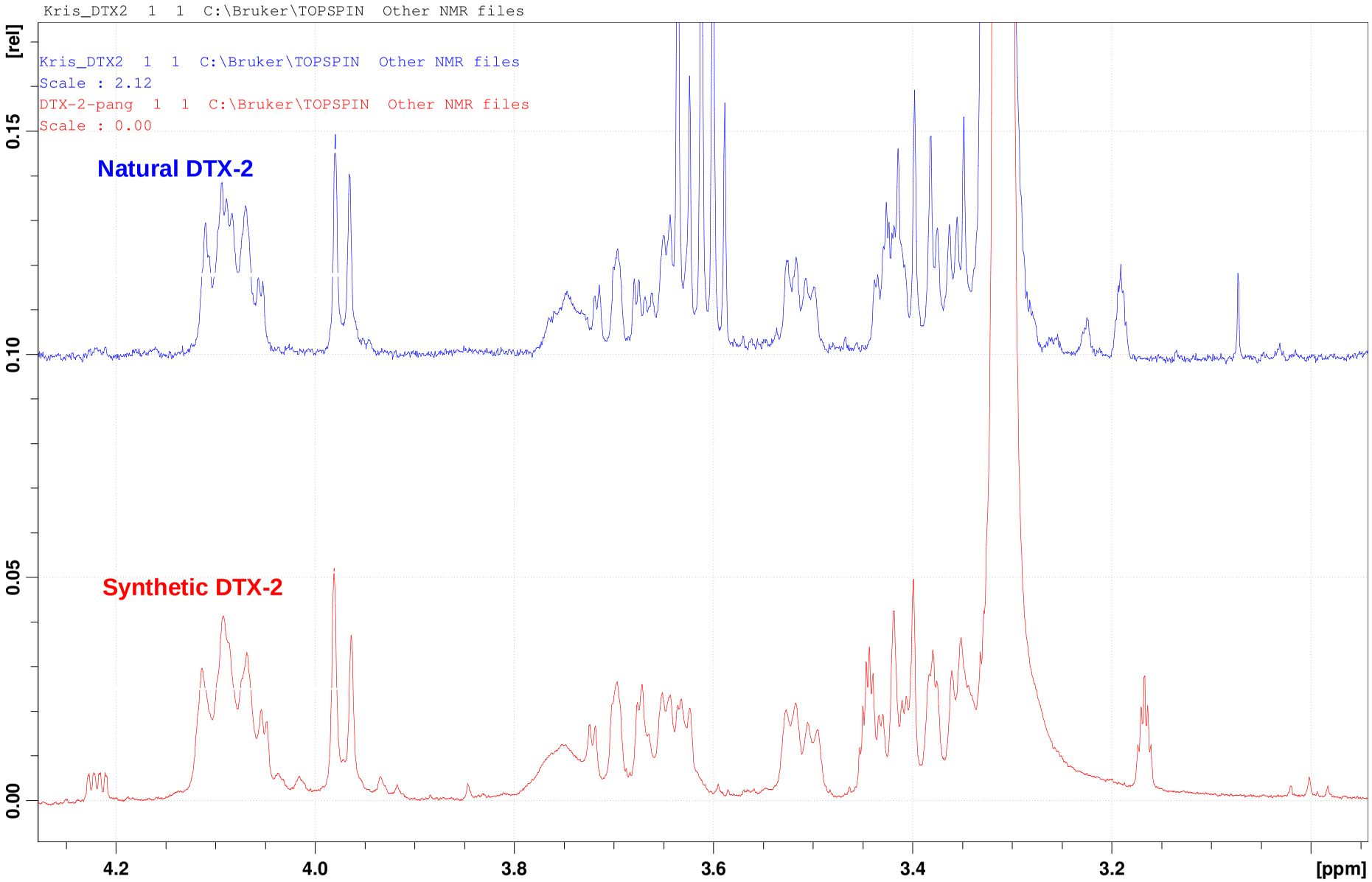
^{1}H NMR of Natural and Syntheic DTX-2



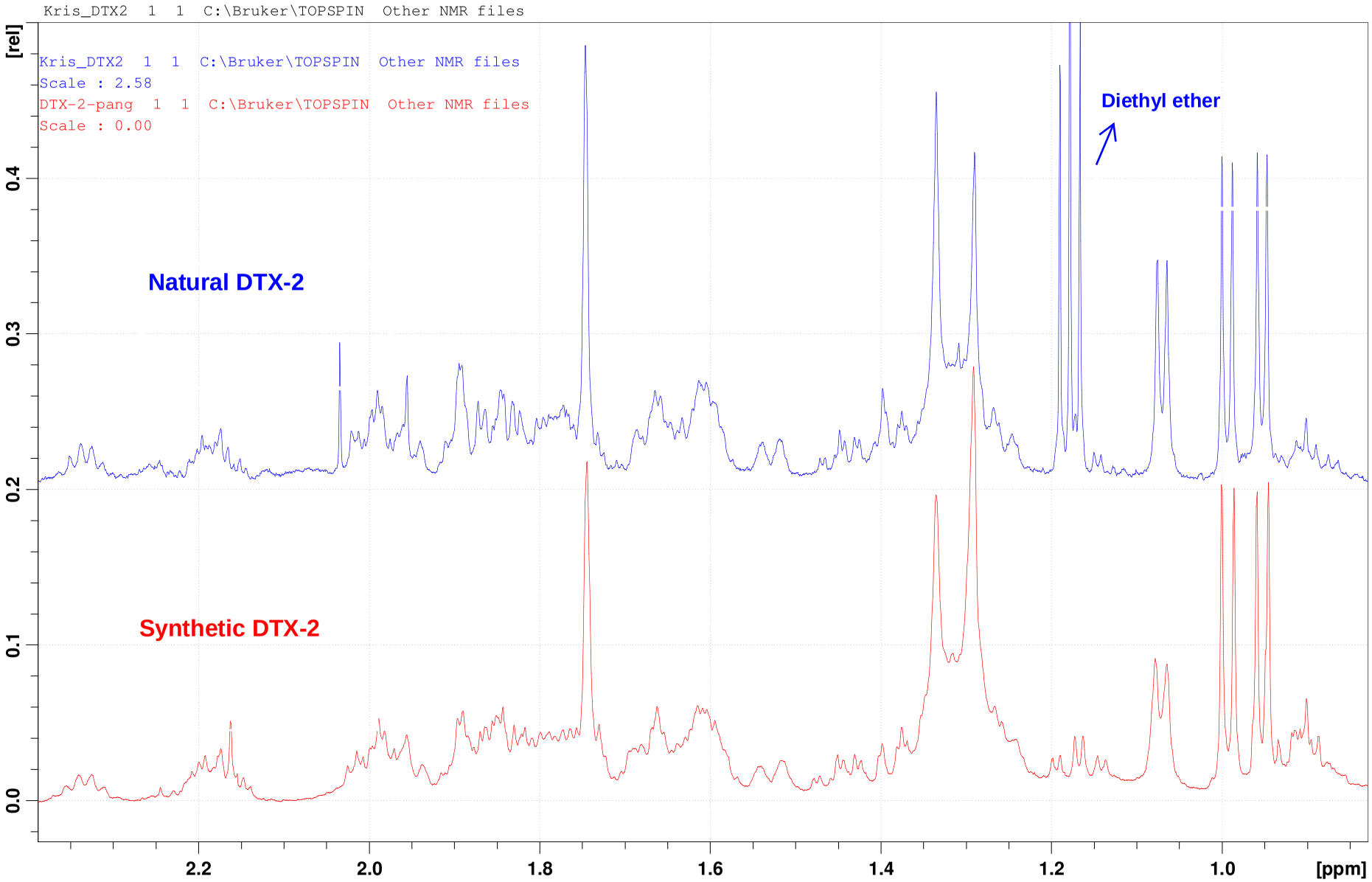
^{1}H NMR of Natural and Svntheic DTX-2

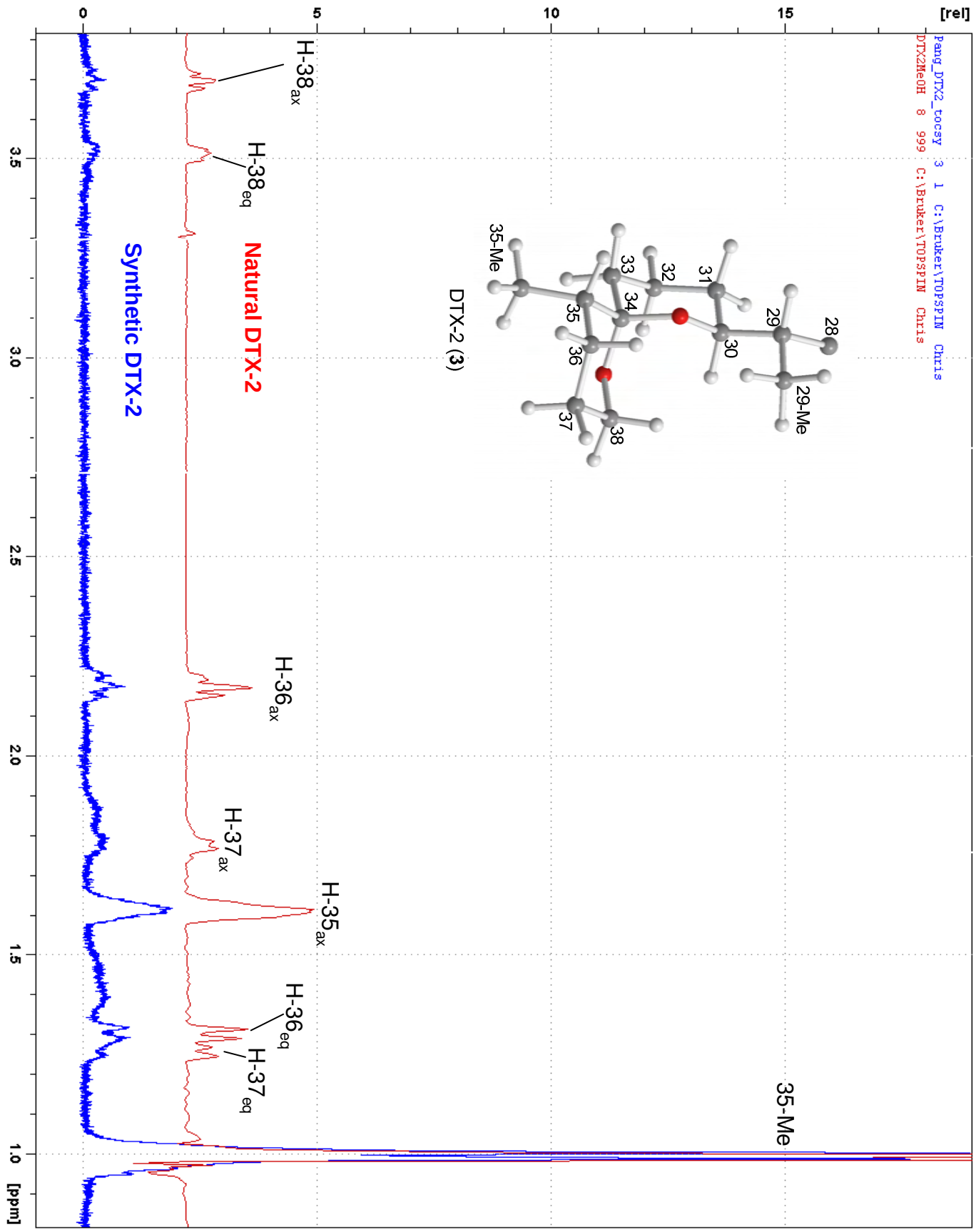


^{1}H NMR of Natural and Svntheic DTX-2



^{1}H NMR of Natural and Svntheic DTX-2





1D Selective TOCSY at δ = 0.99 ppm (35-Me)

Table 1. Calculated IC_{50} values and relative potencies for natural OA (**1**), natural DTX-2 (Nat. **3**), synthetic DTX-2 (Syn. **3**), and synthetic 2-*epi*-DTX-2 (2-*epi*-**3**) based on PP2A and PP1 inhibition.

Inhibitor	PP2A			PP1		
	IC_{50} (nM)	95% Conf. Intervals	Rel. Potency	IC_{50} (nM)	95% Conf. Intervals	Rel. Potency
Nat. **1**	0.47	0.40–0.54	1.000	25	18–35	1.000
Nat. **3**	0.99	0.84–1.2	0.47	76.4	58–100	0.330
Syn. **3**	1.4	1.1–1.6	0.35	82.6	55–120	0.305
2-*epi*-**3**	140	110–180	0.003	3100	2100–4700	0.008