Supporting Information

Total Synthesis and Evaluation of Cytostatin, its C10–C11 Diastereomers, and Key Analogues: Impact on PP2A Inhibition

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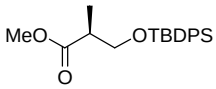
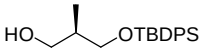
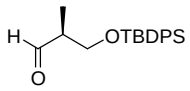


methyl (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate (8). A solution of methyl (*S*)-3-hydroxy-2-methylpropionate (**7**, 50.0 g, 424 mmol) in 500 mL of DMF was treated with imidazole (63.5 g, 932 mmol) and TBDPSCl (125 g, 455 mmol). After stirring at 25 °C for 2 h, the reaction mixture was poured into H_2O (500 mL) and extracted with Et_2O (500 mL). The organic extract was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl before being dried (Na_2SO_4) and concentrated under reduced pressure to provide **7** (150 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +17 (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65–7.63 (m, 4H), 7.44–7.36 (m, 6H), 3.82 (dd, 1H, *J* = 7.0, 9.7 Hz), 3.71 (dd, 1H, *J* = 5.9, 9.7 Hz), 3.67 (s, 3H), 2.71 (m, 1H), 1.14 (d, 3H, *J* = 7.0 Hz), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.8, 136.0, 133.9, 133.8, 130.1, 128.1, 66.3, 52.0, 42.8, 27.1, 19.7, 13.9; IR (film) ν_{max} 2932, 2857, 1741, 1428, 1199, 1112, 792 cm^{-1}; MALDIFTMS (DHB) *m/z* 379.1708 ($C_{21}H_{28}O_3Si$ + Na^+ requires 379.1700). Data for (*R*)-**8**: $[\alpha]^{25}_D$ –15 (*c* 3.4, $CHCl_3$).

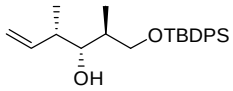


(*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol. A solution of **8** (75 g, 210 mmol) in 300 mL of toluene at –78 °C was treated with DIBAL-H (308 mL of a 1.5 M

solution in toluene, 463 mmol) and stirred for 1 h. The reaction mixture was treated with 1 M aqueous sodium potassium tartrate (600 mL) and after stirring vigorously at 25 °C for 14 h, the mixture was extracted with Et_2O (5 × 400 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol as a colorless oil (55.5 g, 87%): $[\alpha]^{25}_D$ +5.3 (*c* 8.9, $CHCl_3$, lit.[1] $[\alpha]^{25}_D$ +6.3 (*c* 1.0, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.70 (m, 4H), 7.69–7.39 (m, 6H), 3.74 (dd, 1H, *J* = 4.4, 9.9 Hz), 3.68 (m, 2H), 3.61 (dd, 1H, *J* = 7.7, 9.9 Hz), 2.00 (m, 1H), 0.85 (s, 9H), 0.84 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ136.03, 136.01, 133.61, 133.59, 130.2, 128.2, 69.1, 68.0, 37.8, 27.3, 19.6, 13.6; IR (film) ν_{max} 3358, 2930, 1472, 1428, 1112, 1040, 701 cm^{-1}; MALDIFTMS (DHB) *m/z* 351.1755 ($C_{20}H_{28}O_2Si$ + Na^+ requires 351.1751). Data for (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol: $[\alpha]^{25}_D$ –5.5 (*c* 3.8, $CHCl_3$).



(*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal (9). A solution of (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol (20.0 g, 61.0 mmol) in 100 mL of CH_2Cl_2 was treated with powdered 4 Å molecular sieves (10 g), NMO (10.7 g, 91.3 mmol), and TPAP (1.00 g, 2.85 mmol) and stirred at 0 °C for 30 min. The reaction mixture was filtered through SiO_2 (50% EtOAc–hexanes wash) and concentrated under reduced pressure to provide **9** as a colorless oil (19.0 g, 95%) that was used immediately in the subsequent reaction: ^{1}H NMR ($CDCl_3$, 400 MHz) δ9.69 (d, 1H, *J* = 1.6 Hz), 7.56 (m, 4H), 7.32 (m, 6H), 3.80 (m, 2H), 2.50 (m, 1H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.97 (s, 9H).



(2*S*,3*R*,4*S*)-1-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhex-5-en-3-ol (10).
cis-2-butene (23 mL) was condensed and transferred to a solution of *t*-BuOK (8.74 g, 80 mmol) in 140 mL of THF at –78 °C. *n*-BuLi (32 mL of a 2.5 M solution in hexanes, 80 mmol) was added and the solution was warmed to –50 °C for 10 min. Upon recooling to

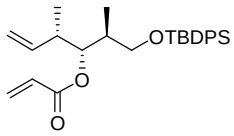
–78 °C, the mixture was treated with a solution of (+)-*B*-methoxydiisopinocampheylborane (30.0 g, 95.1 mmol) in 60 mL of Et_2O and stirred for 45 min before being treated with BF_3–Et_2O (15.4 mL, 122 mmol). A solution of **9** (19.0 g, 58.0 mmol) in 60 mL of Et_2O was added dropwise via cannula, and the reaction mixture was stirred for 16 h at –78 °C before being warmed to 25 °C. The mixture was then treated with 3 M aqueous NaOH (117 mL), heated at reflux (70 °C) and 30% aqueous H_2O_2 (41 mL) was added dropwise over 5 h. The mixture was then diluted with saturated aqueous Na_2SO_3 and saturated aqueous NaCl and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 10% EtOAc–hexane) to provide **10** as a colorless oil (12.0 g, 56%) and its (2*R*,3*R*,4*S*)- isomer as a colorless oil (1.50 g, 7%). Data for **10**: $[\alpha]^{25}_D$ +4.7 (*c* 2.0, $CHCl_3$, lit.[2] $[\alpha]^{20}_D$ +2.3 (*c* 2.5, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.66 (m, 4H), 7.47–7.37 (m, 6H), 5.87 (m, 1H), 5.00 (m, 2H), 3.82 (dd, 1H, *J* = 3.8, 10.0 Hz), 3.65 (dd, 1H, *J* = 6.2, 10.3 Hz), 3.49 (dd, 1H, *J* = 5.0, 7.0 Hz), 2.34 (m, 1H), 1.84 (m, 1H), 1.06 (d, 3H, *J* = 7.9 Hz), 1.05 (s, 9H), 0.91 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.4, 135.6, 132.9, 132.8, 129.8, 127.8, 114.0, 79.1, 68.4, 41.0, 37.0, 26.8, 19.1, 14.1, 13.2; IR (film) ν_{max} 3508, 2960, 2930, 2858, 1472, 1428, 1113, 1072, 998, 823, 702 cm^{-1}; MALDIFTMS (DHB) *m/z* 405.2222 ($C_{24}H_{34}O_2Si + Na^+$ requires 405.2220).

Data for (2*R*,3*R*,4*S*)-**10**: $[\alpha]^{25}_D$ –2.3 (*c* 1.7, $CHCl_3$, lit.[2] $[\alpha]^{20}_D$ +2.4 (*c* 1.0, $CHCl_3$) for *ent*-(2*S*,3*S*,4*R*)-**9**); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (m, 4H), 7.40 (m, 6H), 5.60 (m, 1H), 5.06–4.95 (m, 2H), 3.76 (dd, 1H, *J* = 3.5, 10.0 Hz), 3.67–3.62 (m, 2H), 2.79 (s, 1H), 2.31 (m, 1H), 1.81 (m, 1H), 1.11 (d, 3H, *J* = 6.5 Hz), 1.07 (s, 9H), 0.96 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.3, 135.7, 135.6, 132.9, 129.8, 127.7, 114.5, 78.9, 69.4, 42.1, 36.7, 26.9, 19.2, 17.1, 9.5; IR (film) ν_{max} 3500, 2960, 2933, 2858, 1472, 1112, 1072, 702 cm^{-1}; ESI MS *m/z* 405.3 ($C_{24}H_{34}O_2Si + Na^+$ requires 405.2).

Data for (2*R*,3*R*,4*R*)-**10** (from *trans*-2-butene and (*R*)-**9**): $[\alpha]^{25}_D$ –5.2 (*c* 2.9, $CHCl_3$, lit.[2] $[\alpha]^{20}_D$ +4.9 (c 2.8, $CHCl_3$) for *ent*-(2*S*,3*S*,4*S*)-**10**); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.64 (m, 4H), 7.45–7.37 (m, 6H), 5.83 (ddd, 1H, *J* = 8.5, 10.6, 16.7 Hz), 5.09 (m, 2H), 3.72 (d, 2H, *J* = 5.0 Hz), 3.59 (dd, 1H, *J* = 2.6, 8.5 Hz), 2.28 (m, 1H), 1.83 (m, 1H), 0.96 (s, 9H), 0.95 (d, 6H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.9, 135.7, 135.6, 133.4, 133.3, 129.7,

127.9, 127.8, 127.7, 115.4, 76.1, 68.4, 41.8, 36.7, 26.9, 19.2, 16.8, 9.6; IR (film) ν_{max} 3506, 2944, 2862, 1426, 1088, 703 cm^{-1}; MALDIFTMS (DHB) *m/z* 405.2222 ($C_{24}H_{34}O_2Si + Na^+$ requires 405.2220).

Data for (2*S*,3*R*,4*R*)-**10** (from *trans*-2-butene and (*S*)-**9**): $[\alpha]^{25}_D$ +16 (*c* 2.1, $CHCl_3$, lit.[2] $[\alpha]^{20}_D$ +26.2 (c 0.8, $CHCl_3$)); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.67 (m, 4H), 7.46–7.39 (m, 6H), 5.95 (ddd, 1H, *J* = 8.5, 10.7, 17.3 Hz), 5.07 (m, 2H), 3.73 (dd, 1H, *J* = 4.4, 10.3 Hz), 3.69 (dd, 1H, *J* = 7.3, 10.3 Hz), 3.44 (dd, 1H, *J* = 3.7, 8.1 Hz), 2.37 (m, 1H), 1.83 (m, 1H), 1.11 (d, 3H, *J* = 7.0 Hz), 1.06 (s, 9H), 0.81 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.3, 136.0, 133.4, 133.3, 130.3, 128.2, 115.6, 80.2, 69.4, 41.6, 38.3, 27.3, 19.5, 18.2, 14.0; IR (film) ν_{max} 3498, 2960, 2931, 1472, 1428, 1113, 701 cm^{-1}; MALDIFTMS (DHB) *m/z* 405.2231 ($C_{24}H_{34}O_2Si + Na^+$ requires 405.2220).

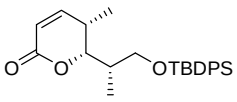


(2*S*,3*R*,4*S*)-3-acryloxy-1-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhex-5-ene (11). A solution of **9** (14.5 g, 38.0 mmol) in 140 mL of CH_2Cl_2 at 0 °C was treated with *i*-Pr_2NEt (13.4 mL, 77.0 mmol), acryloyl chloride (4.74 mL, 57.6 mmol), and allowed to warm to 25 °C over 2 h. The reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$ (200 mL) and was extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 5% EtOAc–hexane) to provide **11** (15.0 g, 91%) as a colorless oil: $[\alpha]^{25}_D$ +1.7 (*c* 4.6, EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.63 (m, 4H), 7.43–7.34 (m, 6H), 6.29 (dd, 1H, *J* = 1.5, 17.3 Hz), 6.02 (dd, 1H, *J* = 10.3, 17.3 Hz), 5.75 (dd, 1H, *J* = 1.5, 10.3 Hz), 5.69 (m, 1H), 4.94 (m, 3H), 3.70 (dd, 1H, *J* = 4.7, 10.0 Hz), 3.46 (dd, 1H, *J* = 7.6, 10.0 Hz), 2.53 (m, 1H), 2.08 (m, 1H), 1.04 (s, 9H), 1.01 (d, 3H, *J* = 7.0 Hz), 0.94 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 140.3, 135.6, 133.7, 133.6, 130.5, 129.5, 128.5, 127.6, 115.0, 78.0, 64.6, 39.3, 37.5, 26.8, 19.2, 14.7, 14.5; IR (film) ν_{max} 2963, 2932, 2858, 1728, 1193, 1113, 702 cm^{-1}; MALDIFTMS (DHB) *m/z* 459.2331 ($C_{27}H_{36}O_3Si + Na^+$ requires 459.2326).

Data for (2*R*,3*R*,4*S*)-**11** (from (2*R*,3*R*,4*S*)-**10**): $[\alpha]^{25}_{D}$ −3.0 (*c* 4.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 4H), 7.39 (m, 6H), 6.37 (dd, 1H, *J* = 1.5, 17.0 Hz), 6.10 (dd, 1H, *J* = 10.0, 17.0 Hz), 5.80 (dd, 1H, *J* = 1.5, 10.5 Hz), 5.67 (m, 1H), 5.16 (dd, 1H, *J* = 3.5, 8.0 Hz), 5.06 (d, 1H, *J* = 17.0 Hz), 5.01 (dd, 1H, *J* = 1.5, 10.5 Hz), 3.51 (dd, 1H, *J* = 7.0, 10.0 Hz), 3.41 (dd, 1H, *J* = 6.5, 10.0 Hz), 2.53 (m, 1H), 2.05 (m, 1H), 1.05 (s, 9H), 0.98 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 140.4, 135.7, 135.6, 133.7, 133.6, 130.3, 129.5, 128.7, 127.6, 115.0, 78.0, 66.0, 40.2, 37.4, 26.8, 19.2, 16.1, 10.9; IR (film) ν_{max} 3070, 2964, 2857, 1726, 1472, 1267, 1193, 1112, 1043 cm^{-1}; ESI-MS *m/z* 459.3 ($C_{27}H_{36}O_3Si + Na^+$ requires 459.2).

Data for (2*R*,3*R*,4*R*)-**11** (from (2*R*,3*R*,4*R*)-**10**): $[\alpha]^{25}_{D}$ −14 (*c* 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (m, 4H), 7.40 (m, 6H), 6.34 (dd, 1H, *J* = 1.5, 17.3 Hz), 6.08 (dd, 1H, *J* = 10.7, 17.6 Hz), 5.78 (dd, 1H, *J* = 1.5, 10.3 Hz), 5.70 (ddd, 1H, *J* = 8.8, 10.3, 17.3 Hz), 5.09 (dd, 1H, *J* = 5.9, 5.9 Hz), 4.92 (dd, 1H, *J* = 1.9, 10.3 Hz), 4.87 (dd, 1H, *J* = 1.1, 17.3 Hz), 3.54 (dd, 1H, *J* = 5.9, 9.9 Hz), 3.46 (dd, 1H, *J* = 5.9, 9.9 Hz), 2.40 (m, 1H), 1.95 (m, 1H), 1.05 (s, 9H), 0.95 (d, 3H, *J* = 6.6 Hz), 0.82 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 139.9, 135.7, 135.6, 133.7, 133.6, 130.2, 129.6, 129.5, 128.8, 127.6, 115.3, 76.8, 65.7, 40.5, 37.3, 26.8, 19.2, 17.4, 11.9; IR (film) ν_{max} 2917, 1726, 1404, 1267, 1194, 1112, 702 cm^{-1}; MALDIFTMS (DHB) *m/z* 459.2328 ($C_{27}H_{36}O_3Si + Na^+$ requires 459.2326).

Data for (2*S*,3*R*,4*R*)-**11** (from (2*S*,3*R*,4*R*)-**10**): $[\alpha]^{25}_{D}$ −12 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (m, 4H), 7.40 (m, 6H), 6.31 (dd, 1H, *J* = 1.5, 17.3 Hz), 6.01 (dd, 1H, *J* = 10.6, 17.3 Hz), 5.75 (dd, 1H, *J* = 1.4, 10.2 Hz), 5.71 (ddd, 1H, *J* = 8.7, 10.7, 16.7 Hz), 4.98 (m, 2H), 4.92 (dd, 1H, *J* = 5.3, 7.3 Hz), 3.62 (dd, 1H, *J* = 4.4, 10.0 Hz), 3.47 (dd, 1H, *J* = 6.7, 10.0 Hz), 2.55 (m, 1H), 2.00 (m, 1H), 1.04 (s, 9H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 139.4, 135.6, 135.5, 133.7, 133.6, 130.4, 129.6, 129.5, 128.5, 127.6, 115.4, 78.1, 64.9, 40.1, 37.5, 26.8, 19.2, 17.6, 14.2; IR (film) ν_{max} 2963, 2930, 2857, 1727, 1192, 1112, 702 cm^{-1}; MALDIFTMS (DHB) *m/z* 459.2330 ($C_{27}H_{36}O_3Si + Na^+$ requires 459.2326).



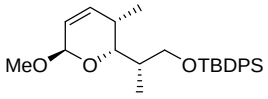
(5*S*,6*S*)-6-[(1*S*)-2-(*tert*-butyldiphenylsilyloxy)-1-methylethyl]-5-methyl-5,6-dihydro-2*H*-pyran-2-one (12). A solution of **11** (8.10 g, 18.5 mmol) in 800 mL of degassed CH_2Cl_2 was treated with Grubbs' I catalyst (2.6 g, 3.2 mmol) and stirred at 40 °C for 12 h. The reaction was quenched by bubbling air through the mixture for 15 min before being concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 20% EtOAc–hexane) to provide **12** as a colorless oil (6.90 g, 89%): $[\alpha]^{25}_D$ +97 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66–7.65 (m, 4H), 7.43–7.36 (m, 6H), 6.99 (dd, 1H, *J* = 6.3, 9.6 Hz), 5.96 (d, 1H, *J* = 9.6 Hz), 4.39 (dd, 1H, *J* = 3.0, 10.7 Hz), 4.00 (dd, 1H, *J* = 4.4, 10.0 Hz), 3.73 (dd, 1H, *J* = 3.0, 9.9 Hz), 2.43 (m, 1H), 1.97 (m, 1H), 1.04 (d, 3H, *J* = 5.2 Hz), 1.03 (s, 9H), 1.01 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 152.2, 136.0, 134.1, 133.9, 130.1, 130.0, 128.1, 128.0, 120.5, 80.3, 64.6, 36.7, 30.5, 27.3, 19.8, 13.3, 11.2; IR (film) ν_{max} 2964, 2932, 2857, 1738, 1732, 1716, 1113, 1428, 1252, 702 cm^{-1}; MALDIFTMS (DHB) *m/z* 431.2024 ($C_{25}H_{32}O_3Si + Na^+$ requires 431.2013).

Data for **13** (from (2*R*,3*R*,4*S*)-**11**): $[\alpha]^{25}_D$ +17 (*c* 3.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (m, 4H), 7.40 (m, 6H), 6.89 (dd, 1H, *J* = 6.5, 9.5 Hz), 5.94 (d, 1H, *J* = 9.5 Hz), 4.28 (dd, 1H, *J* = 3.0, 9.5 Hz), 3.60 (m, 2H), 2.33 (m, 1H), 2.03 (m, 1H), 1.20 (d, 3H, *J* = 7.0 Hz), 1.06 (s, 9H), 0.93 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 152.0, 135.6, 135.5, 133.1, 129.8, 127.8, 127.7, 119.9, 82.2, 65.2, 36.5, 30.9, 26.9, 19.3, 13.9, 11.5; IR (film) ν_{max} 3048, 2961, 2931, 2857, 1727, 1472, 1427, 1245, 1112, 989 cm^{-1}; ESI-MS *m/z* 431.2 ($C_{25}H_{32}O_3Si + Na^+$ requires 431.2).

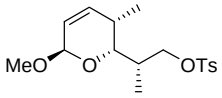
Data for **14** (from (2*R*,3*R*,4*R*)-**11**): $[\alpha]^{25}_D$ –24 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (m, 4H), 7.40 (m, 6H), 6.65 (d, 1H, *J* = 10.1 Hz), 5.94 (dd, 1H, *J* = 2.2, 9.7 Hz), 4.39 (d, 1H, *J* = 10.9 Hz), 3.80 (dd, 1H, *J* = 9.2, 9.7 Hz), 3.58 (dd, 1H, *J* = 5.5, 9.9 Hz), 2.63 (m, 1H), 1.98 (m, 1H), 1.08 (d, 3H, *J* = 7.0 Hz), 1.03 (s, 9H), 0.87 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8, 152.5, 136.0, 135.9, 134.1, 133.9, 130.1, 128.2, 128.1, 120.6, 82.8, 65.4, 37.3, 30.9, 27.3, 19.7, 16.5, 10.3; IR (film) ν_{max} 2930, 2857, 1728, 1238, 1113, 702 cm^{-1}; MALDIFTMS (DHB) *m/z* 431.2015 ($C_{25}H_{32}O_3Si + Na^+$ requires 431.2013).

Data for **15** (from (2*S*,3*R*,4*R*)-**11**): $[\alpha]^{25}_D$ +12 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (m, 4H), 7.40 (m, 6H), 6.62 (dd, 1H, *J* = 2.7, 9.8 Hz), 5.92 (dd, 1H, *J* = 2.4, 9.8 Hz), 4.06 (dd, 1H, *J* = 3.3, 9.5 Hz), 3.87 (dd, 1H, *J* = 6.8, 10.5 Hz), 3.59 (dd, 1H, *J* = 5.9, 10.7

Hz), 2.89 (m, 1H), 2.13 (m, 1H), 1.10 (d, 3H, J = 7.3 Hz), 1.04 (s, 9H), 1.03 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.7, 152.6, 136.0, 133.8, 130.2, 128.2, 120.3, 86.5, 64.7, 37.4, 31.5, 27.2, 19.6, 17.1, 15.4; IR (film) ν_{max} 2959, 2931, 2857, 1728, 1112, 702 cm^{-1}; MALDIFTMS (DHB) *m/z* 431.2017 ($C_{25}H_{32}O_3Si$ + Na^+ requires 431.2013).

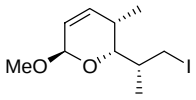


(2*R*,5*S*,6*S*)-6-[(1*S*)-2-(*tert*-butyldiphenylsilyloxy)-1-methylethyl]-5-methyl-2-methoxy-5,6-dihydro-2*H*-pyran (19). A solution of **12** (10.0 g, 23.2 mmol) in 200 mL of CH_2Cl_2 at –78 °C was treated with DIBAL-H (20.0 mL of 1.5 M in toluene, 30.0 mmol). After 1 h, 500 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (5 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 10.0 g of a colorless oil which was used immediately in the subsequent reaction. The product was dissolved in 200 mL of MeOH and PPTS (0.64 g, 2.54 mmol) was added. The reaction mixture was stirred at 25 °C for 10 min before being quenched by addition of 7 mL of Et_3N. The mixture was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 10% EtOAc–hexane) to provide **19**as a colorless oil (8.50 g, 82% for two steps): $[\alpha]^{25}_D$ +50 (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67–7.64 (m, 4H), 7.40–7.34 (m, 6H), 6.04 (dd, 1H, J = 6.0, 9.5 Hz), 5.62 (dd, 1H, J = 2.0, 10.0 Hz), 4.70 (d, 1H, J = 3.0 Hz), 3.95 (dd, 1H, J = 3.0, 9.5 Hz), 3.68 (dd, 1H, J = 3.0, 10.5 Hz), 3.63 (dd, 1H, J = 7.0, 9.5 Hz), 3.14 (s, 3H), 2.05 (m, 1H), 1.85 (m, 1H), 1.10 (s, 9H), 0.96 (d, 3H, J = 6.5 Hz), 0.90 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.9 135.8, 135.7, 129.4, 127.5, 124.0, 96.0, 70.3, 66.1, 55.1, 37.0, 30.0, 27.0, 19.4, 13.2, 11.8; IR (film) ν_{max} 2964, 2923, 2851, 1428, 1112, 1048, 701 cm^{-1}; MALDIFTMS (DHB) *m/z* 447.2333 ($C_{26}H_{36}O_3Si$ + Na^+ requires 447.2326).



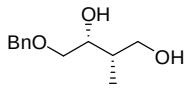
(2*R*,5*S*,6*S*)-6-[(1*S*)-2-(*p*-toluenesulfonyl)-1-methylethyl]-5-methyl-2-methoxy-5,6-dihydro-2*H*-pyran (21). A solution of **19** (8.50 g, 20.0 mmol) in 45 mL of THF was treated with

Bu_4NF (22.2 mL of 1.0 M in THF, 22.2 mmol) and stirred at 25 °C for 12 h. The reaction was quenched with the addition of saturated aqueous NH_4Cl (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure to provide **20**, which was used immediately in the subsequent reaction. Crude **20** was dissolved in benzene (60 mL) and treated with NaH (8.0 g of 60% dispersion in oil, 208 mmol). After 45 min, *p*-TsCl (8.3 g, 43 mmol) was added and the mixture was stirred for 3 h at 25 °C. The reaction was quenched with the addition of saturated aqueous NH_4Cl (200 mL), and the mixture was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with saturated aqueous NaCl (500 mL), dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 20% EtOAc–hexane) to provide **21** as a colorless oil (5.50 g, 81% for two steps): $[\alpha]^{25}_D$ +42 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 6.01 (dd, 1H, *J* = 5.8, 9.9 Hz), 5.62 (dd, 1H, *J* = 2.8, 9.8 Hz), 4.74 (d, 1H, *J* = 2.0 Hz), 4.29 (dd, 1H, *J* = 3.1, 9.0 Hz), 4.10 (dd, 1H, *J* = 6.8, 9.2 Hz), 3.66 (dd, 1H, *J* = 2.7, 10.6 Hz), 3.30 (s, 3H), 2.44 (s, 3H), 2.02 (m, 1H), 1.95 (m, 1H), 0.90 (d, 3H, *J* = 6.8 Hz), 0.87 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 135.2, 133.0, 129.7, 127.8, 123.9, 96.0, 72.4, 69.5, 55.3, 34.3, 29.6, 21.6, 12.7, 11.5; IR (film) ν_{max} 2970, 1455, 1360, 1190, 1176, 1050, 967, 667 cm^{-1}; MALDIFTMS (DHB) *m/z* 363.1244 ($C_{17}H_{24}O_5S$ + Na^+ requires 363.1237).

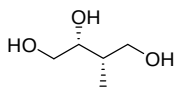


(2*R*,5*S*,6*S*)-6-[(1*S*)-2-iodo-1-methylethyl]-5-methyl-2-methoxy-5,6-dihydro-2*H*-pyran (16). A solution of **21** (1.83 g, 5.40 mmol) in 70 mL of acetone was treated with NaI (3.0 g, 20 mmol) and warmed to 56 °C. After 12 h, the mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed sequentially with water (50 mL) and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 5% EtOAc–hexane) to provide **16** as a colorless oil (1.40 g, 90%): $[\alpha]^{25}_D$ +4.6 (*c* 0.5, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.03 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.66 (dd, 1H, *J* = 2.4, 10.0 Hz),

4.80 (d, 1H, J = 2.4 Hz), 3.61 (dd, 1H, J = 2.8, 10.4 Hz), 3.54 (dd, 1H, J = 2.8, 9.2 Hz), 3.47 (s, 3H), 3.45 (m, 1H), 2.08 (m, 1H), 1.50 (m, 1H), 0.96 (d, 3H, J = 6.4 Hz), 0.93 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.4, 124.0, 96.3, 72.3, 56.0, 35.2, 29.9, 17.0, 15.6, 12.2; IR (film) ν_{max} 2964, 2930, 1454, 1192, 1051, 961, 803, 736 cm^{-1}; ESI-TOF HRMS *m/z* 319.0170 ($C_{10}H_{17}IO_2$ + Na^+ requires 319.0165).

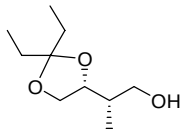


(2*S*,3*R*)-4-(benzyloxy)-2-methylbutane-1,3-diol (23). A suspension of CuI (0.89 g, 4.65 mmol) in 200 mL of 6:1 Et_2O–THF at 0 °C was treated with MeMgI (15.5 mL of 3 M in Et_2O, 46.5 mmol). The mixture was cooled to –40 °C and a solution of **22**[3] (3.00 g, 15.5 mmol) in 15 mL of Et_2O was added dropwise. The mixture was stirred at –40 °C for 3 h before being quenched with the addition of saturated aqueous NH_4Cl/NH_4OH (pH 8, 200 mL) and extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 67% EtOAc–hexane) to provide **23** and its regioisomer (1,2-diol) as a colorless oil (2.50 g, 69%). This material was dissolved in Et_2O (80 mL) and treated with a solution of $NaIO_4$ (1.25 g, 5.90 mmol) in 40 mL of H_2O. After stirring for 1.5 h at 25 °C, the mixture was extracted with Et_2O (5 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 67% EtOAc–hexane) to provide **23**[4] as a colorless oil (1.80 g, 91%): $[\alpha]^{25}_D$ +5.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (m, 5H), 4.54 (d, 2H, J = 5.2 Hz), 4.00 (m, 1H), 3.59 (d, 2H, J = 6.0 Hz), 3.49 (d, 2H, J = 5.2 Hz), 3.21 (br s, 2H), 1.83 (m, 1H), 0.90 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 128.3, 127.7, 73.3, 72.5, 71.9, 65.8, 37.2, 10.8; IR (film) ν_{max} 3396, 2877, 1454, 1366, 1099, 1028 cm^{-1}; ESI-TOF HRMS *m/z* 233.1146 ($C_{12}H_{18}O_3$ + Na^+ requires 233.1148).

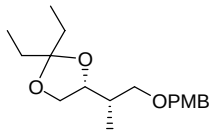


(2*R*,3*S*)-3-methylbutane-1,2,4-triol (24). A solution of **23** (8.80 g, 37.8 mmol) in 400 mL

of MeOH was treated with 10% Pd/C (1.6 g) and the mixture was stirred for 2 h at 25 °C under H_2. The mixture was then filtered through Celite and concentrated under reduced pressure to provide **24**[5] as a colorless oil (5.00 g, 99%): $[\alpha]^{25}_D$ +6.8 (*c* 1.9, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (m, 1H), 3.70 (dd, 1H, *J* = 4.0, 10.8 Hz), 3.63–3.57 (m, 3H), 2.01 (br s, 3H), 1.84 (m, 1H), 0.90 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 74.5, 65.8, 64.2, 37.6, 11.7; IR (film) ν_{max} 3324, 2934, 2861, 1460, 1379, 1026 cm^{-1}; ESI-TOF HRMS *m/z* 121.0509 ($C_5H_{12}O_3$ + Na^+ requires 121.0859).

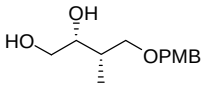


(*S*)-2-[(*R*)-2,2-diethyl-1,3-dioxolan-4-yl]propan-1-ol (25). A solution of **24** (2.50 g, 21.0 mmol) in 20 mL of DMF at 25 °C was treated with 3,3-dimethoxypentane[6] (10.0 g, 76.0 mmol) and *p*-TsOH–H_2O (0.20 g, 1.0 mmol) and the mixture was stirred for 12 h. The mixture was diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and saturated aqueous NaCl (100 mL), dried ($MgSO_4$), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexane) to provide **25**[5b] as a colorless oil (2.70 g, 68%): $[\alpha]^{25}_D$ –3.0 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.11 (m, 1H), 4.01 (dd, 1H, *J* = 6.0, 8.0 Hz), 3.67 (t, 1H, *J* = 8.4 Hz), 3.60 (m, 2H), 2.11 (br s, 1H), 1.95 (m, 1H), 1.68–1.58 (m, 4H), 0.97 (d, 3H, *J* = 6.8 Hz), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.4, 78.7, 67.4, 65.7, 37.5, 29.6, 29.1, 12.2, 8.3, 8.0; IR (film) ν_{max} 3426, 2972, 2940, 2881, 1463, 1172, 1079, 1038, 921 cm^{-1}.

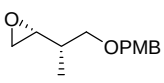


(*R*)-2,2-diethyl-4-[(*S*)-1-(4-methoxybenzyloxy)propan-2-yl]-1,3-dioxolane (26). A solution of **25** (6.50 g, 34.6 mmol) in 150 mL of THF at 0 °C was treated with NaH (2.0 g of 60% dispersion in oil, 50.7 mmol), PMBCl (5.0 mL, 37.9 mmol), and Bu_4NI (1.28 g, 3.46 mmol) and the mixture was stirred and allowed to warm to 25 °C over 20 h. The mixture

was then diluted with Et_2O (400 mL), washed sequentially with H_2O (300 mL) and saturated aqueous NaCl (300 mL), dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 10% EtOAc–hexane) to provide **26** as a colorless oil (8.50 g, 80%): $[\alpha]^{25}_D$ +5.0 (*c* 1.9, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.23 (d, 2H, *J* = 7.0 Hz), 6.87 (d, 2H, *J* = 7.0 Hz), 4.41 (s, 2H), 4.01 (dd, 1H, *J* = 4.8, 6.0 Hz), 3.94 (m, 1H), 3.81 (s, 3H), 3.63 (t, 1H, *J* = 6.4 Hz), 3.33 (m, 2H), 1.92 (m, 1H) 1.62 (m, 4H), 1.03 (d, 3H, *J* = 5.2 Hz), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ159.1, 130.5, 129.1, 113.7, 111.8, 78.7, 72.8, 72.7, 68.8, 55.2, 37.1, 29.8, 29.5, 13.5, 8.3, 8.0 ; IR (film) ν_{max} 2970, 2937, 2679, 1513, 1248, 1077, 1037 cm^{-1}; ESI-TOF HRMS *m/z* 331.1879 ($C_{18}H_{28}O_4$ + Na^+ requires 331.1880).

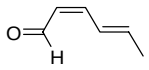


(2*R*,3*S*)-4-(4-methoxybenzyloxy)-3-methylbutane-1,2-diol (27). A solution of **26** (8.50 g, 27.6 mmol) in 2.5 L of MeOH at 25 °C was treated with *p*-TsOH–H_2O (1.0 g, 5.3 mmol) and stirred for 7 h. Et_3N (5 mL) was added and the mixture was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 67% EtOAc–hexanes) to provide **27** (4.90 g, 75%) and **26** (1.90 g, 22%). Recovered **26** was resubjected to this procedure once again to provide additional **27** as a colorless oil (5.80 g total, 89% overall): $[\alpha]^{25}_D$ +2.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.23 (d, 2H, *J* = 7.0 Hz), 6.85 (d, 2H, *J* = 7.0 Hz), 4.45 (d, 1H, *J* = 9.2 Hz), 4.42 (d, 1H, *J* = 9.2 Hz), 3.80 (s, 3H), 3.71 (m, 1H), 3.64–3.56 (m, 2H), 3.50 (dd, 1H, *J* = 3.2, 7.2 Hz), 3.41 (dd, 1H, *J* = 5.6, 7.2 Hz), 2.55 (br s, 2H), 1.97 (m, 1H), 0.95 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ159.3, 129.7, 129.4, 113.8, 74.7, 73.1, 64.3, 55.2, 36.2, 12.4; IR (film) ν_{max} 3388, 2933, 2872, 1613, 1514, 1248, 1035, 820 cm^{-1}; ESI-TOF HRMS *m/z* 263.1246 ($C_{13}H_{20}O_4$ + Na^+ requires 263.1254).

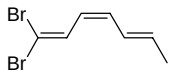


(*R*)-2-[(*S*)-1-(4-methoxybenzyloxy)propan-2-yl]oxirane (17). A solution of **27** (5.80 g, 24.2 mmol) in 300 mL of THF at 0 °C was treated with NaH (2.34 g of 60% dispersion in oil,

59.0 mmol). After 1 h, the mixture was cooled to −78 °C, 1-(*p*-toluenesulfonyl)imidazole (5.73 g, 25.8 mmol) was added, and the mixture was stirred and allowed to warm to 25 °C over 4 h. After recooling to 0 °C, saturated aqueous NH_4Cl (100 mL) was added and the mixture was diluted with Et_2O (500 mL), washed sequentially with H_2O (300 mL) and saturated aqueous NaCl (300 mL), dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 14% EtOAc–hexane) to provide **17** as a colorless liquid (4.41 g, 82%): $[\alpha]^{25}_D$ +5.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, 2H, *J* = 8.8 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 4.41 (s, 2H), 3.78 (s, 3H), 3.37 (m, 2H), 2.83 (m, 1H), 2.73 (dd, 1H, *J* = 4.0, 4.8 Hz), 2.57 (dd, 1H, *J* = 2.8, 4.8 Hz), 1.67 (m, 1H), 0.98 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 130.4, 129.1, 113.7, 72.8, 72.5, 55.3, 54.9, 46.6, 36.5, 13.4; IR (film) ν_{max} 2962, 2856, 1612, 1513, 1248, 1095, 1035, 820 cm^{-1}; ESI-TOF HRMS *m/z* 245.1060 ($C_{19}H_{36}O_5$ + Na^+ requires 245.1148).

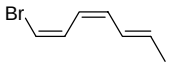


(2*Z*,4*E*)-hexa-2,4-dienal (28). A suspension of pyrylium tetrafluoroborate[7] (1.20 g, 7.15 mmol) in 50 mL of THF at –78 °C was treated with MeLi (6.7 mL of 1.6 M in Et_2O, 10.7 mmol). After stirring at –78 °C for 3 h, 50 mL of saturated aqueous NH_4Cl was added and the mixture was warmed to 25 °C, extracted with Et_2O (3 × 100 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 15% EtOAc–hexane) to provide **28**[8] (337 mg, 66%) as a yellow liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.17 (d, 1H, *J* = 8.0 Hz), 7.06 (dd, 1H, *J* = 12.0, 14.0 Hz), 6.92 (dd, 1H, *J* = 10.8, 12.0 Hz), 6.21 (dq, 1H, *J* = 7.0, 14.0 Hz), 5.78 (dd, 1H, *J* = 8.6, 10.8 Hz), 1.92 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 189.2, 146.5, 140.4, 126.1, 125.9, 18.2; IR (film) ν_{max} 1663, 1635, 1580, 1225, 1156, 1119, 1023 cm^{-1}; ESI-TOF HRMS *m/z* 97.0648 (C_6H_8O + H^+ requires 97.0653).

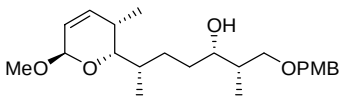


(3*Z*,5*E*)-1,1-dibromohepta-1,3,5-triene (29). A solution of Ph_3P (8.30 g, 31.6 mmol) in 15

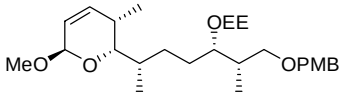
mL of CH_2Cl_2 was added at once to a solution of CBr_4 (5.26 g, 15.9 mmol) in 15 mL of CH_2Cl_2 at 0 °C. After 5 min, Et_3N (11 mL) was added followed by a solution of **28** (0.55 g, 5.7 mmol) in 2 mL of CH_2Cl_2. After 10 min, 100 mL of H_2O was added and the mixture was extracted with CH_2Cl_2 (2×200 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was extensively extracted with 2% Et_3N–hexane and the extracts filtered through a short column of silica gel (2% Et_3N–hexane wash) to provide **29** (1.30 g, 97%) as a yellow oil: ^{1}H NMR (C_6D_6, 500 MHz) δ 7.21 (d, 1H, J = 9.7 Hz), 5.99–5.94 (m, 1H), 5.84 (m, 2H), 5.47 (m, 1H), 1.43 (d, 1H, J = 6.7 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 134.5, 133.7, 133.4, 127.7, 123.3, 92.4, 18.7; IR (film) ν_{max} 3021, 2929, 1631, 1548, 1446, 1364, 1262, 1235, 1032 cm^{-1}; MALDIFTMS (DHB) *m/z* 249.8987 ($C_7H_8Br_2^+$ requires 249.8992).



(1*Z*,3*Z*,5*E*)-1-bromohepta-1,3,5-triene (18). A solution of **29** (0.50 g, 2.0 mmol) in 5 mL of Et_2O at 0 °C was treated with $Pd(PPh_3)_4$ (0.50 g, 0.44 mmol) and Bu_3SnH (0.98 mL, 3.6 mmol). After 20 min, the mixture was carefully concentrated under reduced pressure (50 mm Hg) and the residue was purified by flash chromatography (SiO_2, pentane). Et_3N (1 mL) was added to the chromatography fractions containing **18** prior to careful concentration under reduced pressure (50 mm Hg) to provide **18** (0.25 g, 73%) as a 2:1:1 mixture with pentane–Et_3N that was used immediately for the subsequent reaction or diluted with Et_2O and stored at 4 °C. Data for **18**: ^{1}H NMR (C_6D_6, 400 MHz) δ 6.65 (ddd, 1H, J = 1.2, 7.2, 11.2 Hz), 6.31 (dd, 1H, J = 10.8, 11.2 Hz), 6.19 (dd, 1H, J = 11.2, 14.8 Hz), 5.96 (dd, 1H, J = 10.8, 10.8 Hz), 5.81 (d, 1H, J = 7.2 Hz), 5.46 (dq, 1H, J = 6.8, 14.8), 1.49 (d, 3H, J = 6.8 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 133.9, 133.5, 128.4, 127.9, 122.7, 109.2, 18.7; IR (film) ν_{max} 2927, 1684, 1636, 1559, 1457, 1374, 1297, 1071 cm^{-1}; GCMS *m/z* 172 ($C_7H_9Br^+$ requires 172).

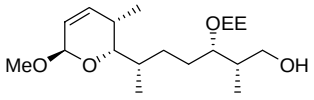


(2*S*,3*S*,6*S*)-6-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl)-1-(4-methoxybenzyloxy)]-2-methylheptan-3-ol (29). A solution of **16** (1.30 g, 4.50 mmol) in 20 mL of Et_2O at –78 °C was treated with *t*-BuLi (5.2 mL of 1.7 M in pentane, 8.84 mmol) dropwise over 2 min. After 5 min, freshly prepared (2-Th)CuCNLi[9] (14 mL of 0.4 M in THF, 5.6 mmol) was added and the mixture was immediately warmed to 0 °C. After 5 min, a solution of **17** (0.76 g, 3.4 mmol) in 20 mL of Et_2O was added dropwise over 5 min, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with the addition of saturated aqueous NH_4Cl/NH_4OH (pH 8, 200 mL) and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 25% EtOAc–hexane) to provide **30** as a colorless oil (1.16 g, 84%): $[\alpha]^{25}_D$ +47 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 6.04 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.65 (dd, 1H, *J* = 3.0, 10.0 Hz), 4.82 (d, 1H, *J* = 3.0 Hz), 4.45 (d, 1H, *J* = 11.5 Hz), 4.41 (d, 1H, *J* = 11.5 Hz), 3.80 (s, 3H), 3.73 (d, 1H, *J* = 9.0 Hz), 3.54 (dd, 1H, *J* = 3.0, 10.5 Hz), 3.49 (dd, 2H, *J* = 5.0, 6.5), 3.43 (s, 3H), 2.58 (br s, 1H), 2.08 (m, 1H), 1.90–1.85 (m, 2H), 1.65–1.55 (m, 2H), 1.33 (m, 2H), 0.92 (d, 3H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 7.5 Hz), 0.85 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 159.2, 136.1, 130.2, 129.2, 123.9, 113.8, 96.4, 74.4, 74.3, 73.5, 73.0, 55.5, 55.2, 38.1, 33.9, 30.9, 30.2, 29.7, 15.2, 11.8, 11.0; IR (film) ν_{max} 3484, 2962, 2931, 2857, 1613, 1513, 1247, 1040, 820 cm^{-1}; ESI-TOF HRMS *m/z* 415.2342 ($C_{23}H_{36}O_5$ + Na^+ requires 415.2455).



(2*S*,3*S*,6*R*)-2-[(2*S*,5*S*,6*S*)-5-(1-ethoxyethyloxy)-7-(4-methoxybenzyloxy)-6-methylheptan-2-yl]-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran (31). A solution of **30** (103 mg, 0.29 mmol) in 12 mL of CH_2Cl_2 was treated with ethyl vinyl ether (0.46 mL, 4.76 mmol) and PPTS (20 mg, 0.08 mmol) and stirred for 1 h at 25 °C. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 15% EtOAc–hexane) to provide **31** as a 1.2:1

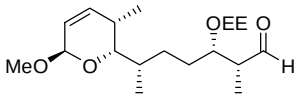
mixture of diastereomers, as a colorless oil (110 mg, 90%): $[\alpha]^{25}_{D}$ +37 (*c* 3.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.24 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 6.05 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.64 (dd, 1H, *J* = 1.6, 10.0 Hz), 4.81 (d, 1H, *J* = 2.8 Hz), 4.67 (m, 1H), 4.42 (m, 2H), 3.80 (s, 3H), 3.75–3.70 (m, 1H), 3.64–3.44 (m, 4H), 3.43 (s, 1H), 3.42 (s, 2H), 3.30–3.10 (m, 1H), 2.21 (d, 1H, *J* = 2.0 Hz), 2.10–1.70 (m, 3H), 1.66–1.50 (m, 3H), 1.29–1.14 (m, 7H), 0.96–0.82 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ159.0, 136.1, 130.8, 130.2, 129.2, 129.1, 123.9, 113.8, 113.7, 99.6, 96.4, 74.5, 74.4, 73.5, 73.4, 73.0, 72.6, 72.5, 60.7, 55.5, 55.4, 55.3, 38.0, 37.2, 34.1, 33.9, 31.0, 30.9, 30.2, 29.7, 29.3, 28.4, 28.1, 20.7, 15.4, 15.3, 15.0, 12.5, 11.8, 9.8; IR (film) ν_{max} 2959, 2932, 1613, 1513, 1455, 1247, 1080, 1042 cm^{-1}; ESI-TOF HRMS *m/z* 487.3018 ($C_{27}H_{44}O_6$ + Na^+ requires 487.3030).



(2*S*,3*S*,6*S*)-3-(1-ethoxyethyloxy)-6-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-2-methylheptan-1-ol (32). A solution of **31** (153 mg, 0.33 mmol) in 10 mL of CH_2Cl_2 was treated with H_2O (0.5 mL) and DDQ (112 mg, 0.50 mmol) and stirred at 25 °C for 30 min. The mixture was diluted with 40 mL of CH_2Cl_2 and 40 mL of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexane) to provide **32a** (47 mg, 46%) as a colorless oil and its diastereomer **32b** (39 mg, 39%) as a colorless oil. Data for **32a**: $[\alpha]^{25}_{D}$ +80 (*c* 2.1, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ5.79 (ddd, 1H, *J* = 1.2, 6.0, 10.0 Hz), 5.66 (ddd, 1H, *J* = 1.2, 3.6, 10.0 Hz), 4.76 (d, 1H, *J* = 2.4 Hz), 4.64 (q, 1H, *J* = 5.2 Hz), 3.94–3.82 (m, 2H), 3.67–3.61 (m, 2H), 3.35 (s, 3H), 3.21 (m, 2H), 1.92–1.60 (m, 5H), 1.40–1.30 (m, 2H), 1.21 (d, 3H, *J* = 5.2 Hz), 1.07 (t, 3H, *J* = 7.0 Hz), 0.87 (d, 3H, *J* = 7.2 Hz), 0.85 (d, 3H, *J* = 6.8 Hz), 0.66 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ135.5, 125.0, 100.7, 97.0, 77.0, 73.2, 65.3, 61.4, 55.4, 39.2, 34.0, 30.5, 29.5, 29.0, 20.4, 15.3, 15.1, 11.9, 10.4; IR (film) ν_{max} 3480, 2969, 2932, 2807, 1456, 1398, 1379, 1185, 1076, 1043, 961 cm^{-1}; ESI-TOF HRMS *m/z* 367.2445 ($C_{19}H_{36}O_5$ + Na^+ requires 367.2455).

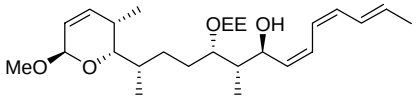
Data for **32b**: $[\alpha]^{25}_{D}$ +31 (*c* 1.8, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ5.79 (ddd, 1H, *J* =

0.8, 6.0, 10.0 Hz), 5.67 (ddd, 1H, *J* = 0.8, 2.8, 10.0 Hz), 4.78 (d, 1H, *J* = 2.8 Hz), 4.72 (q, 1H, *J* = 5.2 Hz), 3.65–3.60 (m, 3H), 3.53 (dd, 1H, *J* = 7.2, 9.2 Hz), 3.45–3.35 (m, 2H), 3.40 (s, 3H), 2.00–1.60 (m, 3H), 1.46 (m, 2H), 1.26 (d, 3H, *J* = 5.2 Hz), 1.13 (t, 3H, *J* = 7.2 Hz), 0.85 (d, 3H, *J* = 6.8 Hz), 0.79 (d, 3H, *J* = 6.8 Hz), 0.71 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ135.5, 125.1, 99.3, 96.9, 78.9, 73.4, 65.4, 60.3, 55.4. 38.1, 34.4, 30.6, 29.9, 28.2, 20.6, 15.7, 15.2, 12.0; IR (film) ν_{max} 3450, 2970, 2932, 2807, 1456, 1379, 1105, 1043, 961 cm^{-1}; ESI-TOF HRMS *m/z* 367.2452 ($C_{19}H_{36}O_5$ + Na^+ requires 367.2455).



(2*R*,3*S*,6*S*)-3-(1-ethoxyethyloxy)-6-[(2*S*,3S,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-2-methylheptanal (33). A solution of **32a** (43 mg, 0.13 mmol) in 7 mL of CH_2Cl_2 was treated with Dess–Martin periodinane (78 mg, 0.18 mmol) at 25 °C. After 15 min, 3 mL of saturated aqueous $NaHCO_3$ and 3 mL of 10% aqueous $Na_2S_2O_3$ were added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and the residue was filtered through a short SiO_2 column (10% EtOAc–hexane wash) to provide **33a** as a colorless oil (39 mg, 91%): $[\alpha]^{25}_D$ +28 (*c* 0.4, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ9.77 (d, 1H, *J* = 0.8 Hz), 5.78 (ddd, 1H, *J* = 0.8, 5.6, 10.0 Hz), 5.65 (ddd, 1H, *J* = 0.8, 2.8, 10.0 Hz), 4.75 (d, 1H, *J* = 2.0 Hz), 4.66 (q, 1H, *J* = 5.2 Hz), 3.89 (m, 1H), 3.59 (dd, 1H, *J* = 2.8, 10.4 Hz), 3.35 (s, 3H), 3.34–3.24 (m, 2H), 2.26 (m, 1H), 1.85–1.55 (m, 4H), 1.28 (m, 2H), 1.20 (d, 3H, *J* = 5.2 Hz), 1.10 (m, 6H), 0.84 (d, 3H, *J* = 6.8 Hz), 0.61 (d, 3H, *J* = 6.8 Hz); IR (film) ν_{max} 2972, 2932, 2870, 1733, 1456, 1380, 1185, 1104, 1078, 1044, 961 cm^{-1}; ESI-TOF HRMS *m/z* 365.2284 ($C_{19}H_{34}O_5$ + Na^+ requires 365.2284).

Data for **33b** (from **32b**): $[\alpha]^{25}_D$ +18 (*c* 0.10, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ9.67 (d, 1H, *J* = 0.8 Hz), 5.78 (ddd, 1H, *J* = 0.8, 6.0, 9.2 Hz), 5.66 (dd, 1H, *J* = 1.6, 9.2 Hz), 4.77 (d, 1H, *J* = 2.8 Hz), 4.59 (q, 1H, *J* = 5.2 Hz), 3.88 (m, 1H), 3.60 (dd, 1H, *J* = 2.8, 10.0 Hz), 3.47–3.28 (m, 2H), 3.37 (s, 3H), 2.20 (m, 1H), 1.92–1.55 (m, 4H), 1.36 (m, 2H), 1.17 (d, 3H, *J* = 5.2 Hz), 1.10 (t, 3H, *J* = 7.0 Hz), 1.00 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 7.2 Hz), 0.64 (d, 3H, *J* = 6.4 Hz); IR (film) ν_{max} 2972, 2931, 1725, 1456, 1378, 1185, 1105, 1078, 1045, 961.



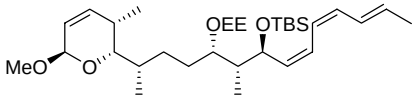
(2*S*,5*S*,6*S*,7*S*,8*Z*,10*Z*,12*E*)-5-(1-ethoxyethyloxy)-2-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-6-methyltetradeca-8,10,12-trien-7-ol (34). A solution of **18** (70 mg, 0.40 mmol) in 2.5 mL of Et_2O at –78 °C was treated with *t*-BuLi (0.50 mL of 1.5 M in pentane, 0.75 mmol) and stirred for 1.5 h at –78 °C before a solution of CuI–PBu_3[10] (60 mg, 0.16 mmol) in 1 mL of Et_2O was added. After 10 min, a solution of **33a** (27 mg, 0.079 mmol) in 2 mL of Et_2O was added dropwise over 5 min. The mixture was stirred for 1 h at –78 °C before being quenched with the addition of saturated aqueous NH_4Cl/NH_4OH (pH 8, 10 mL). The mixture was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 13% EtOAc–hexane) to provide *anti*-**34a** (23 mg, 67%) as a colorless oil and *syn*-**34a** (3 mg, 9%) as a colorless oil. Data for *anti*-**34a**: $[\alpha]^{25}_D$ +21 (*c* 2.1, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ6.63 (dd, 1H, *J* = 11.5, 11.5 Hz), 6.51 (dd, 1H, *J* = 11.5, 14.0 Hz), 6.41 (dd, 1H, *J* = 11.5, 11.5 Hz), 5.95 (dd, 1H, *J* = 11.0, 11.0 Hz), 5.79 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.75 (dd, 1H, *J* = 11.0, 11.0 Hz), 5.65 (dd, 1H, *J* = 3.0, 10.0 Hz), 5.51 (dq, 1H, *J* = 7.0, 14.0 Hz), 4.90 (ddd, 1H, *J* = 4.0, 9.0, 9.5 Hz), 4.76 (d, 1H, *J* = 2.5 Hz), 4.70 (q, 1H, *J* = 5.0 Hz), 4.25 (d, 1H, *J* = 4.0 Hz), 4.19 (m, 1H), 3.63 (dd, 1H, *J* = 2.5, 10.0 Hz), 3.36 (s, 3H), 3.24 (m, 2H), 1.90 (m, 2H), 1.78 (m, 2H), 1.67 (m, 1H), 1.55 (d, 3H, *J* = 7.0 Hz), 1.43 (m, 1H), 1.33 (m, 1H), 1.23 (d, 3H, *J* = 5.0 Hz), 1.08 (t, 3H, *J* = 7.0 Hz), 1.03 (d, 3H, *J* = 7.0 Hz), 0.85 (d, 3H, *J* = 6.5 Hz), 0.68 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (C_6D_6, 150 MHz) δ135.5, 134.8, 131.0, 130.8, 127.5, 125.1, 125.0, 123.1, 100.7, 97.0, 76.6, 69.1, 68.0, 61.8, 55.4, 43.6, 34.0, 30.5, 29.6, 29.2, 20.4, 18.4, 15.3, 15.1, 11.9, 10.4; IR (film) ν_{max} 3449, 2969, 2944, 2886, 1375, 1096, 1082, 1044 cm^{-1}; ESI-TOF HRMS *m/z* 459.3081 ($C_{26}H_{44}O_5$ + Na^+ requires 459.3081).

Data for *syn*-**34a**: $[\alpha]^{25}_D$ +87 (*c* 1.1, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ6.54–6.40 (m, 3H), 6.01 (dd, 1H, *J* = 10.8, 10.8 Hz), 5.91 (dd, 1H, *J* = 7.2, 10.8 Hz), 5.78 (dd, 1H, *J* = 6.0, 9.6 Hz), 5.65 (dd, 1H, *J* = 2.8, 10.8 Hz), 5.55 (dq, 1H, *J* = 7.2, 14.8 Hz), 5.11 (ddd, 1H, *J* = 2.0, 3.6, 7.8), 4.75 (d, 1H, *J* = 2.4 Hz), 4.66 (q, 1H, *J* = 5.2 Hz), 3.89 (dt, 1H, *J* = 2.0, 6.4 Hz), 3.61

(dd, 1H, *J* = 2.4, 10.4 Hz), 3.59 (d, 1H, *J* = 2.0 Hz), 3.37 (s, 3H), 3.28 (m, 2H), 1.95–1.70 (m, 4H), 1.60 (m, 1H), 1.56 (d, 3H, *J* = 5.6 Hz), 1.35 (m, 1H), 1.27 (d, 3H, *J* = 7.2 Hz), 1.21 (d, 3H, *J* = 5.2 Hz), 1.07 (t, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.8 Hz), 0.66 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 135.5, 135.4, 131.3, 130.6, 127.4, 125.1, 123.6, 122.8, 100.2, 97.0, 81.7, 73.3, 72.7, 61.7, 55.3, 43.1, 34.1, 30.5, 29.7, 29.4, 20.8, 18.4, 15.5, 15.1, 11.9, 7.2; IR (film) ν_{max} 3450, 2969, 2945, 2886, 1375, 1096, 1082, 1045 cm^{-1}; ESI-MS *m/z* 459.3 ($C_{26}H_{44}O_5$ + Na^+ requires 459.3).

Data for *anti*-**34b** (from **33b**): $[\alpha]^{25}_D$ –20 (*c* 1.5, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ 6.57 (dd, 1H, *J* = 11.5, 11.5 Hz), 6.51 (dd, 1H, *J* = 11.5, 14.5 Hz), 6.34 (dd, 1H, *J* = 11.5, 11.5 Hz), 6.00 (dd, 1H, *J* = 11.0, 10.5 Hz), 5.79 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.66 (dd, *J* = 3.0, 9.5 Hz), 5.54 (dq, 1H, *J* = 7.0, 14.5 Hz), 5.52 (dd, 1H, *J* = 10.0, 10.5 Hz), 4.85 (q, 1H, *J* = 5.5 Hz), 4.78 (d, 1H, *J* = 2.5 Hz), 4.73 (dd, 1H, *J* = 9.0, 9.5 Hz), 4.01 (m, 1H), 3.67 (dd, 1H, *J* = 3.0, 10.5 Hz), 3.59 (dd, 1H, *J* = 7.0, 9.5 Hz), 3.46–3.38 (m, 2H), 3.41 (s, 3H), 2.79 (br s, 1H), 2.01 (m, 2H), 1.84 (m, 1H), 1.78 (m, 1H), 1.67 (m, 2H), 1.57 (d, 3H, *J* = 5.5 Hz), 1.50 (m, 1H), 1.33 (d, 3H, *J* = 5.5 Hz), 1.15 (t, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 3H, *J* = 7.0 Hz), 0.73 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 135.5, 134.4, 131.6, 131.3, 127.3, 125.5, 125.1, 122.5, 99.5, 96.9, 78.5, 73.5, 69.4, 60.5, 55.4, 41.7, 34.4, 30.6, 30.1, 28.7, 20.7, 18.4, 15.7, 15.2, 12.0, 11.6; IR (film) ν_{max} 3450, 2970, 2945, 2885, 1375, 1096, 1045 cm^{-1}; ESI-MS *m/z* 459.2 ($C_{26}H_{44}O_5$ + Na^+ requires 459.3).

Data for *syn*-**34b** (from **33b**): $[\alpha]^{25}_D$ +40 (*c* 0.74, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 6.49 (dd, 1H, *J* = 11.6, 14.8 Hz), 6.48 (dd, 1H, *J* = 11.2, 11.6 Hz), 6.29 (dd, 1H, *J* = 10.8, 11.6 Hz), 6.01 (dd, 1H, *J* = 10.8, 10.8 Hz), 5.79 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.66 (m, 2H), 5.55 (dq, 1H, *J* = 6.8, 14.8 Hz), 4.82 (m, 1H), 4.79 (d, 1H, *J* = 2.0 Hz), 4.68 (q, 1H, *J* = 5.2 Hz), 3.65 (m, 2H), 3.51 (dd, 1H, *J* = 6.8, 8.8 Hz), 3.44–3.32 (m, 2H), 3.39 (s, 3H), 2.10–1.95 (m, 3H), 1.89 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.57 (d, 3H, *J* = 6.4 Hz), 1.29 (d, 3H, *J* = 5.2 Hz), 1.21 (d, 3H, *J* = 6.8 Hz), 1.13 (t, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.8 Hz), 0.74 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ 135.5, 134.9, 131.7, 131.2, 128.6, 127.3, 125.1, 124.5, 122.3, 100.0, 96.9, 81.4, 73.5, 70.3, 60.0, 55.4, 42.3, 34.5, 30.6, 29.5, 20.7, 18.4, 15.7, 15.2, 12.0, 8.4; IR (film) ν_{max} 3454, 2969, 2929, 1677, 1378, 1104, 1044, 962 cm^{-1}; ESI-MS *m/z* 459.3 ($C_{26}H_{44}O_5$ + Na^+ requires 459.3).



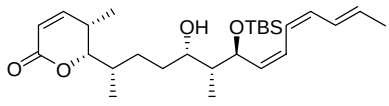
(2*S*,5*S*,6*R*,7*S*,8*Z*,10*Z*,12*E*)-7-(*tert*-butyldimethylsilyloxy)-5-(1-ethoxyethyloxy)-2-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-6-methyltetradeca-8,10,12-triene (35). A solution of *anti*-**34a** (5 mg, 0.012 mmol) and imidazole (13 mg, 0.19 mmol) in 0.10 mL of DMF was treated with TBSCl (10 mg, 0.068 mmol) and stirred at 25 °C. After 2 h, H_2O (1 mL) was added and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 4% EtOAc−hexane) to provide **35a** as a colorless oil (6 mg, 95%): $[\alpha]^{25}_D$ –26 (*c* 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ 6.52 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.48 (dd, 1H, *J* = 10.2, 14.0 Hz), 6.43 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.01 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.79 (dd, 1H, *J* = 6.0, 9.6 Hz), 5.67 (dd, 1H, *J* = 2.4, 9.6 Hz), 5.52 (dq, 1H, *J* = 7.2, 14.0 Hz), 5.47 (dd, 1H, *J* = 10.2, 10.2 Hz), 4.99 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.90 (q, 1H, *J* = 5.4 Hz), 4.79 (d, 1H, *J* = 2.4 Hz), 4.16 (dt, 1H, *J* = 2.4, 6.6 Hz), 3.67 (m, 2H), 3.51 (m, 1H), 3.45 (s, 3H), 2.13 (m, 1H), 1.96–1.86 (m, 2H), 1.79 (m, 1H), 1.72 (m, 1H), 1.55 (d, 3H, *J* = 6.6 Hz), 1.51 (m, 1H), 1.41 (d, 3H, *J* = 5.4 Hz), 1.36 (m, 1H), 1.23 (t, 3H, *J* = 7.2 Hz), 1.10 (d, 3H, *J* = 7.2 Hz), 1.04 (s, 9H), 0.87 (d, 3H, *J* = 7.2 Hz), 0.74 (d, 3H, *J* = 6.6 Hz), 0.25 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ 135.4, 134.4, 131.6, 131.4, 127.4, 125.1, 124.8, 122.4, 99.6, 96.9, 76.3, 73.5, 70.0, 60.3, 55.4, 44.8, 34.2, 30.6, 30.3, 29.6, 26.3, 21.1, 18.5, 18.4, 15.9, 15.2, 12.0, 10.4, –2.9, –4.3; IR (film) ν_{max} 2971, 2933, 2857, 1389, 1248, 1040, 964 cm^{-1}; ESI-TOF HRMS *m/z* 573.3936 ($C_{32}H_{58}O_5Si$ + Na^+ requires 573.3945).

Data for **35b** (from *anti*-**34b**): $[\alpha]^{25}_D$ +6.0 (*c* 0.77, $CHCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ 6.47 (m, 2H), 6.34 (dd, 1H, *J* = 10.8, 12.0 Hz), 5.99 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.79 (dd, 1H, *J* = 7.2, 10.2 Hz), 5.67 (dd, 1H, *J* = 2.4, 9.6 Hz), 5.53 (dq, 1H, *J* = 7.2, 14.4 Hz), 5.44 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.98 (q, 1H, *J* = 5.4 Hz), 4.81 (m, 2H), 4.14 (m, 1H), 3.71 (dd, 1H, *J* = 3.0, 10.8 Hz), 3.63–3.52 (m, 2H), 3.48 (s, 3H), 2.12 (m, 2H), 1.87 (m, 1H), 1.80 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.55 (d, 3H, *J* = 7.2 Hz), 1.43 (m, 1H), 1.42 (d, 3H, *J* = 4.8 Hz), 1.21 (t, 3H, *J* = 7.2 Hz), 1.06 (d, 3H, *J* = 7.2 Hz), 1.02 (s, 9H), 0.87 (d, 3H, *J* = 7.2 Hz), 0.78 (d, 3H, *J* = 6.6 Hz), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ 135.5, 134.4, 131.8, 131.6,

127.3, 125.1, 124.8, 122.0, 100.2, 96.9, 77.8, 73.5, 70.0, 59.2, 55.4, 44.1, 34.5, 30.8, 30.6, 29.8, 26.3, 26.2, 20.8, 18.4, 15.8, 15.3, 12.0, 9.9, 1.4, –2.9, –4.5; IR (film) ν_{max} 2980, 2933, 2857, 1461, 1389, 1249, 1047, 964 cm^{-1}; ESI-MS *m/z* 573.3 ($C_{32}H_{58}O_5Si + Na^+$ requires 573.4).

Data for **45a** (from *syn*-**34a**): $[\alpha]^{25}_D$ +76 (*c* 0.82, $CHCl_3$); ^1H NMR (C_6D_6, 600 MHz) δ 6.48 (m, 3H), 6.06 (dd, 1H, *J* = 10.2, 10.8 Hz), 5.78 (dd, 1H, *J* = 5.4, 9.6 Hz), 5.71 (dd, 1H, *J* = 9.0, 10.8 Hz), 5.66 (dd, 1H, *J* = 3.0, 10.2 Hz), 5.53 (dq, 1H, *J* = 7.2, 14.4 Hz), 5.00 (dd, 1H, *J* = 5.4, 9.0 Hz), 4.81 (q, 1H, *J* = 5.4 Hz), 4.77 (d, 1H, *J* = 3.0 Hz), 3.83 (dd, 1H, *J* = 6.0, 10.2 Hz), 3.65 (dd, 1H, *J* = 3.0, 10.8 Hz), 3.58 (m, 1H), 3.44 (m, 1H), 3.39 (s, 3H), 2.13 (m, 1H), 2.01 (m, 1H), 1.93 (m, 1H), 1.79 (m, 1H), 1.69–1.59 (m, 2H), 1.55 (d, 3H, *J* = 7.2 Hz), 1.35 (d, 3H, *J* = 4.8 Hz), 1.31 (m, 1H), 1.29 (d, 3H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.2 Hz), 1.03 (s, 9H), 0.87 (d, 3H, *J* = 7.2 Hz), 0.77 (d, 3H, *J* = 6.6 Hz), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ135.4, 135.2, 131.4, 131.0, 128.3, 128.2, 127.3, 125.2, 99.3, 96.9, 77.5, 73.7, 69.8, 60.7, 55.3, 44.4, 34.6, 30.6, 29.3, 29.2, 26.3, 26.2, 20.9, 18.5, 18.4, 15.8, 15.3, 12.0, 10.7, –3.4, –4.5; IR (film) ν_{max} 2958, 2930, 2857, 1640, 1462, 1377, 1250, 1077, 1049, 960, 835 cm^{-1}; ESI-MS *m/z* 573.3 ($C_{32}H_{58}O_5Si + Na^+$ requires 573.4).

Data for **45b** (from *syn*-**34b**): $[\alpha]^{25}_D$ +44 (*c* 0.26, $CHCl_3$); ^1H NMR (C_6D_6, 500 MHz) δ 6.45 (m, 2H), 6.35 (dd, 1H, *J* = 11.0, 11.5 Hz) 6.04 (dd, 1H, *J* = 10.5, 11.5 Hz), 5.79 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.66 (dd, 1H, *J* = 3.0, 10.0 Hz), 5.60 (dd, 1H, *J* = 9.2, 10.0 Hz), 5.55 (dq, 1H, *J* = 7.0, 15.0 Hz), 4.91 (dd, 1H, *J* = 6.0, 9.5 Hz), 4.80 (dd, 1H, *J* = 2.5, 9.0 Hz), 4.77 (q, 1H, *J* = 5.0 Hz), 3.74–3.68 (m, 2H), 3.60–3.45 (m, 2H), 3.58 (m, 1H), 3.42 (s, 3H), 2.16–2.10 (m, 2H), 1.95 (m, 1H), 1.82–1.68 (m, 3H), 1.55 (d, 3H, *J* = 6.5 Hz), 1.40 (m, 1H), 1.35 (d, 3H, *J* = 5.0 Hz), 1.23 (d, 3H, *J* = 6.8 Hz), 1.16 (t, 3H, *J* = 7.2 Hz), 1.03 (s, 9H), 0.86 (d, 3H, *J* = 6.8 Hz), 0.81 (d, 3H, *J* = 6.8 Hz), 0.19 (s, 3H), 0.16 (s, 3H); IR (film) ν_{max} 2960, 2928, 2858, 1462, 1377, 1257, 1077, 1048, 836 cm^{-1}; ESI-MS *m/z* 573.3936 ($C_{32}H_{58}O_5Si + Na^+$ requires 573.3945).

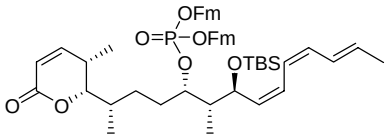


(5*S*,6*S*)-6-[(2*S*,5*S*,6*R*,7*S*,8*Z*,10*Z*,12*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-6-methy

ltetradeca-8,10,12-trien-2-yl]-5-methyl-5,6-dihydropyran-2-one (37). A solution of **35a** (3.5 mg, 0.0064 mmol) in 2.7 mL of acetone at 25 °C was treated with aqueous HCl (0.14 mL of 0.5 M, 0.070 mmol). After 10 min, saturated aqueous $NaHCO_3$ (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 20% EtOAc–hexane) to provide **36** as a colorless oil (2.5 mg, 85%) that was immediately used in the subsequent reaction. A solution of **36** (2.5 mg, 0.0054 mmol) in 0.5 mL of benzene at 80 °C was treated with 50% Ag_2CO_3–Celite (200 mg, 0.36 mmol) in 4 portions added over the course of 1 h. After the final addition, the mixture was stirred for 30 min, then cooled and filtered through Celite (EtOAc wash). The filtrate was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 25% EtOAc–hexane) to provide **37** as a colorless oil (2.0 mg, 80%): $[\alpha]^{25}_D$ +41 (*c* 0.17, $CHCl_3$); ^{1}H NMR (CD_3CN, 400 MHz) δ7.06 (dd, 1H, *J* = 6.0, 9.6 Hz), 6.58 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.51 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.13 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.05 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.87 (d, 1H, *J* = 9.6 Hz), 5.84 (dq, 1H, *J* = 7.2, 15.0 Hz), 5.47 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.64 (dd, 1H, *J* = 6.6, 9.6 Hz), 4.03 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.89 (m, 1H), 2.84 (d, 1H, *J* = 4.8 Hz), 2.52 (dt, 1H, *J* = 3.0, 7.0 Hz), 1.84–1.74 (m, 2H), 1.79 (d, 3H, *J* = 6.6 Hz), 1.58 (m, 1H), 1.49 (m, 1H), 1.32–1.25 (m, 2H), 0.96 (d, 3H, *J* = 7.2 Hz), 0.87 (m, 12H), 0.82 (d, 3H, *J* = 6.6 Hz), 0.076 (s, 3H), 0.017 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ163.5, 150.6, 134.3, 132.1, 131.8, 128.4, 127.2, 124.0, 121.6, 120.4, 83.5, 73.7, 71.2, 44.4, 34.3, 32.7, 30.3, 29.8, 26.0, 18.4, 18.3, 14.6, 10.8, 10.6, –3.9, –5.0; IR (film) ν_{max} 3502, 2966, 2923, 2855, 1716, 1462, 1377, 1251, 1068, 836 cm^{-1}; ESI-TOF HRMS *m/z* 485.3044 ($C_{27}H_{46}O_4Si$ + Na^+ requires 485.3057).

Data for **47** (from **45**): $[\alpha]^{25}_D$ +72 (*c* 0.09, $CHCl_3$); ^{1}H NMR (CD_3CN, 500 MHz) δ7.06 (dd, 1H, *J* = 6.5, 9.5 Hz), 6.58 (dd, 1H, *J* = 11.5, 14.5 Hz), 6.49 (dd, 1H, *J* = 11.5, 11.5 Hz), 6.17 (dd, 1H, *J* = 11.5, 11.5 Hz), 6.03 (dd, 1H, *J* = 11.0, 11.5 Hz), 5.87 (d, 1H, *J* = 10.0 Hz), 5.83 (dq, 1H, *J* = 7.0, 14.5 Hz), 5.44 (dd, 1H, *J* = 9.5, 10.5 Hz), 4.70 (dd, 1H, *J* = 6.0, 9.0 Hz), 4.03 (dd, 1H, *J* = 3.0, 10.5 Hz), 3.60 (m, 1H), 2.52 (d, 1H, *J* = 5.0 Hz), 2.51 (m, 1H), 1.79 (d, 3H, *J* = 7.0 Hz), 1.70 (m, 1H), 1.55 (m, 1H), 1.47 (m, 1H), 1.34 (m, 1H), 1.27 (m, 2H), 0.96 (d, 3H, *J* = 7.0 Hz), 0.93 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 6.5 Hz), 0.88 (s, 9H), 0.055 (s, 3H), 0.007 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ163.5, 150.7, 134.3, 131.9, 131.7, 127.3,

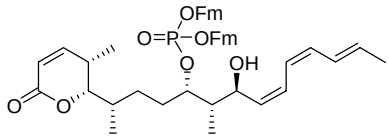
123.9, 121.9, 120.3, 83.3, 73.8, 73.3, 45.0, 34.2, 33.0, 30.3, 29.5, 26.1, 18.4, 18.3, 14.7, 10.5, 7.8, –3.6, –4.7; IR (film) ν_{max} 3476, 2926, 2854, 1721, 1462, 1377, 1257, 1068, 853 cm^{-1}; ESI- MS *m/z* 485.3 ($C_{27}H_{46}O_4Si$ + Na^+ requires 485.3).



bis[(9*H*-fluoren-9-yl)methyl] (2*S*,5*S*,6*S*,7*S*,8*Z*,10*Z*,12*E*)-7-(*tert*-butyldimethylsilyloxy)-6-methyl-2-((2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)tetradeca-8,10,12-trien-5-yl phosphate (38). A solution of **37** (2.0 mg, 0.0044 mmol) and tetrazole (0.92 mg, 0.013 mmol) in 0.10 mL of CH_3CN at 25 °C was treated with a solution of *i*-$Pr_2NP(OFm)_2$[11] (9.2 mg, 0.018 mmol) in 0.13 mL CH_2Cl_2 and stirred for 30 min before 30% aqueous H_2O_2 (0.027 mL, 0.18 mmol) was added. After 10 min, 1 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexane) to provide **38** as a colorless oil (3.2 mg, 82%): $[\alpha]^{25}_D$ +12 (*c* 0.32, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.85–7.70 (m, 4H), 7.50 (m, 4H), 7.37 (m, 4H), 7.28 (m, 4H), 7.07 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.53 (dd, 1H, *J* = 11.4, 14.4 Hz), 6.47 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.95 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.86 (d, 1H, *J* = 6.6 Hz), 5.83 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.78 (dq, 1H, *J* = 7.2, 14.4 Hz), 5.26 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.52 (dd, 1H, *J* = 8.4, 9.0 Hz), 4.42 (m, 1H), 4.31–4.25 (m, 2H), 4.12 (m, 4H), 3.92 (dd, 1H, *J* = 3.0, 10.2 Hz), 2.48 (dq, 1H, *J* = 3.0, 6.6 Hz), 1.78 (d, 3H, *J* = 6.0 Hz), 1.78–1.60 (m, 3H), 1.44–1.20 (m, 2H), 1.12 (m, 1H), 0.95 (d, 3H, *J* = 7.2 Hz), 0.84 (d, 3H, *J* = 7.0 Hz), 0.83 (s, 9H), 0.00 (s, 3H), –0.05 (s, 3H); ^{13}C NMR (CD_3CN, 150 MHz) δ165.2, 153.7, 144.4, 144.3, 142.2, 133.5, 133.2, 132.1, 128.7, 128.6, 128.1, 128.0, 127.4, 126.0, 125.9, 125.8, 125.4, 122.4, 120.9, 120.8, 120.0, 84.1, 80.9, 69.4, 69.3, 69.0, 48.7, 48.6, 44.3, 34.3, 31.0, 28.5, 26.3, 18.5, 14.7, 11.0, 10.1, –3.6, –4.4; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.20; IR (film) ν_{max} 2966, 2923, 2854, 1721, 1450, 1377, 1251, 1077, 1007 cm^{-1}; ESI-TOF HRMS *m/z* 921.4278 ($C_{55}H_{67}O_7PSi$ + Na^+ requires 921.4286).

Data for **48** (from **47**): $[\alpha]^{25}_D$ +50 (*c* 0.30, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ

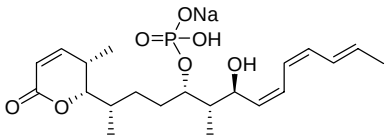
7.81–7.75 (m, 4H), 7.53–7.47 (m, 4H), 7.41–7.32 (m, 4H), 7.30–7.24 (m, 4H), 7.06 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.47 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.36 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.07 (dd, 1H, *J* = 11.4, 12.0 Hz), 5.87 (dd, 1H, *J* = 12.0, 12.0 Hz), 5.86 (d, 1H, *J* = 9.6 Hz), 5.75 (dq, 1H, *J* = 7.2, 14.4 Hz), 5.37 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.61 (dd, 1H, *J* = 4.2, 9.0 Hz), 4.27–4.19 (m, 2H), 4.17–4.08 (m, 5H), 3.90 (dd, 1H, *J* = 3.0, 10.2 Hz), 2.47 (m, 1H), 1.76 (d, 3H, *J* = 6.6 Hz), 1.67 (m, 3H), 1.59 (m, 1H), 1.46 (m, 1H), 1.09 (m, 1H), 0.93 (d, 3H, *J* = 7.2 Hz), 0.85 (s, 9H), 0.83 (d, 3H, *J* = 6.6 Hz), –0.014 (s, 3H), –0.051 (s, 3H); ^{13}C NMR (CD_3CN, 150 MHz) δ165.2, 153.7, 144.5, 144.4, 144.3, 142.3, 142.2, 134.2, 133.0, 131.9, 128.7, 128.1, 128.0, 127.4, 126.0, 125.9, 125.8, 124.4, 122.5, 121.0, 120.9, 120.8, 120.0, 84.1, 82.2, 69.3, 69.1, 69.0, 48.7, 48.6, 44.4, 37.2, 30.9, 28.5, 26.2, 18.6, 14.8, 11.0, 10.6, –3.7, –4.6; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.45; IR (film) ν_{max} 2953, 2913, 2851, 1718, 1451, 1262, 1021 cm^{-1}; ESI-TOF HRMS *m/z* 921.3 ($C_{55}H_{67}O_7PSi$ + Na^+ requires 921.4).



bis[(9*H*-fluoren-9-yl)methyl] (2*S*,5*S*,6*S*,7*S*,8*Z*,10*Z*,12*E*)-7-hydroxy-6-methyl-2-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]tetradeca-8,10,12-trien-5-yl phosphate (39). A solution of **38** (2.4 mg, 0.0027 mmol) in 0.10 mL of THF and 0.020 mL of pyridine at 0 °C was treated with a solution of HF–pyr (0.050 mL) in 0.10 mL of THF and the mixture was allowed to stand at 25 °C for 4 h. The reaction mixture was carefully transferred to a mixture of saturated aqueous $NaHCO_3$ (3 mL) and EtOAc (1 mL) and the resulting mixture was extracted with EtOAc (3 × 2 mL). The organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 60% EtOAc–hexane) to provide **39** as a colorless oil (1.7 mg, 85%): $[\alpha]^{25}_D$ +43 (*c* 0.13, $CHCl_3$, lit.[11a] $[\alpha]^{20}_D$ +49 (*c* 0.24, $CHCl_3$)); ^{1}H NMR (CD_3CN, 600 MHz) δ 7.84–7.74 (m, 4H), 7.55–7.50 (m, 4H), 7.42–7.33 (m, 4H), 7.31–7.25 (m, 4H), 7.06 (dd, 1H, *J* = 6.0, 9.0 Hz), 6.56 (dd, 1H, *J* = 10.8, 15.0 Hz), 6.52 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.94 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.89 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.85 (d, 1H, *J* = 10.2 Hz), 5.82 (dq, 1H, *J* = 6.6, 15.0 Hz), 5.32 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.58 (m, 1H), 4.33 (m, 1H), 4.30–4.20 (m, 4H), 4.14 (m,

2H), 3.91 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.76 (d, 1H, *J* = 4.8 Hz), 2.47 (m, 1H), 1.79 (d, 3H, *J* = 6.6 Hz), 1.75–1.64 (m, 2H), 1.62–1.48 (m, 2H), 1.40 (m, 1H), 1.11 (m, 1H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.77 (d, 3H, *J* = 6.6 Hz), 0.66 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ165.2, 153.7, 144.4, 142.3, 142.2, 133.8, 133.0, 131.8, 128.8, 128.7, 128.1, 127.5, 125.9, 125.8, 122.6, 121.0, 120.9, 120.0, 84.1, 80.2, 69.6, 69.3, 67.8, 48.7, 44.4, 43.9, 34.4, 30.9, 29.0, 18.5, 14.8, 11.0, 9.2; ^{31}P NMR (CD_3CN, 160 MHz) δ 0.37; IR (film) ν_{max} 3415, 2966, 2922, 2851, 1721, 1449, 1267, 1020 cm^{-1}; ESI-TOF HRMS *m/z* 807.3416 ($C_{49}H_{53}O_7P + Na^+$ requires 807.3421).

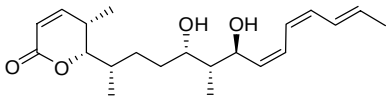
Data for **49** (from **48**): $[\alpha]^{25}_D$ +70 (*c* 0.22, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ 7.81–7.76 (m, 4H), 7.54–7.48 (m, 4H), 7.41–7.33 (m, 4H), 7.31–7.25 (m, 4H), 7.06 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.49 (dd, 1H, *J* = 11.4, 14.4 Hz), 6.39 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.05 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.87 (dd, 1H, *J* = 11.4, 12.0 Hz), 5.86 (d, 1H, *J* = 9.6 Hz), 5.75 (dq, 1H, *J* = 6.6, 15.0 Hz), 5.39 (dd, 1H, *J* = 9.6, 10.2 Hz), 4.48 (m, 1H), 4.28 (m, 1H), 4.22–4.14 (m, 3H), 4.11 (m, 3H), 3.91 (dd, 1H, *J* = 3.0, 10.2 Hz), 2.93 (d, 1H, *J* = 4.8 Hz), 2.47 (m, 1H), 1.76 (d, 3H, *J* = 6.6 Hz), 1.70–1.55 (m, 3H), 1.43 (m, 1H), 1.30 (m, 1H), 1.06 (m, 1H), 0.93 (d, 3H, *J* = 7.2 Hz), 0.84 (d, 3H, *J* = 6.6 Hz), 0.75 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ165.2, 153.7, 144.5, 144.4, 142.3, 142.2, 134.2, 132.8, 131.7, 128.6, 128.1, 128.0, 127.5, 126.0, 125.9, 125.8, 124.9, 122.7, 120.9, 120.8, 120.0, 84.2, 83.0, 82.9, 69.2, 69.0, 68.3, 48.7, 48.6, 43.7, 34.6, 30.9, 28.6, 18.5, 14.7, 11.0, 9.6; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.19; IR (film) ν_{max} 3416, 2970, 2851, 1721, 1450, 1267, 1077 cm^{-1}; ESI-TOF HRMS *m/z* 807.3 ($C_{49}H_{53}O_7P + Na^+$ requires 807.3).



Cytostatin (1). A solution of **39** (1.7 mg, 0.0022 mmol) in 0.40 mL of CH_3CN at 0 °C was treated with 0.10 mL of Et_3N and the mixture was allowed to stand at 25 °C for 17 h before 0.50 mL of toluene was added and the solution was concentrated under reduced pressure. The residue was dissolved in 1 mL of H_2O, washed with Et_2O (5 × 1 mL), and the aqueous layer was concentrated under reduced pressure. The residue was dissolved in 0.5 mL of 1:1

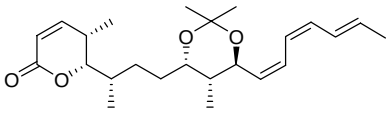
MeOH–H_2O and passed through a short column of Dowex-Na^+ (0.8 × 2 cm, 1:1 MeOH–H_2O wash) to provide **1** as a white solid (1.0 mg, 99%): $[\alpha]^{25}_D$ +45 (*c* 0.07, MeOH, lit.[11a] $[\alpha]^{20}_D$ +46 (*c* 0.29, MeOH)); ^{1}H NMR (CD_3OD, 600 MHz) δ7.15 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.59 (dd, 1H, *J* = 10.2, 11.4 Hz), 6.58 (dd, 1H, *J* = 11.4, 14.4 Hz), 6.25 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.00 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.93 (d, 1H, *J* = 9.6 Hz), 5.76 (dq, 1H, *J* = 6.6, 14.4 Hz), 5.41 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.59 (dd, 1H, *J* = 9.0, 9.6 Hz), 4.53 (m, 1H), 4.10 (dd, 1H, *J* = 3.0, 10.2 Hz), 2.58 (ddq, 1H, *J* = 3.0, 6.6, 7.2 Hz), 2.06 (m, 1H), 1.85–1.75 (m, 2H), 1.80 (d, 3H, *J* = 6.6 Hz), 1.63–1.47 (m, 2H), 1.25 (m, 1H), 1.00 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 0.80 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, 150 MHz) δ 167.4, 155.1, 134.0, 132.2, 131.7, 128.2, 126.5, 123.6, 120.1, 85.6, 75.3, 68.8, 44.2, 35.5, 31.7, 31.6, 29.5, 18.6, 14.9, 11.0, 9.1; ^{31}P NMR (CD_3OD, 160 MHz) δ 3.60; IR (film) ν_{max} 3406, 2966, 2924, 1710, 1449, 1374, 1260, 963 cm^{-1}; ESI-TOF HRMS *m/z* 427.1884 ($C_{21}H_{33}O_7 - H^+$ requires 427.1891).

Data for **42** (from **49**): $[\alpha]^{25}_D$ +89 (*c* 0.11, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.15 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.56 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.47 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.21 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.01 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.92 (d, 1H, *J* = 9.6 Hz), 5.76 (dq, 1H, *J* = 7.2, 15.0 Hz), 5.64 (dd, 1H, *J* = 9.6, 10.2 Hz), 4.83 (dd, 1H, *J* = 1.8, 9.6 Hz), 4.30 (m, 1H), 4.10 (dd, 1H, *J* = 3.0 10.2 Hz), 2.58 (m, 1H), 1.94–1.82 (m, 2H), 1.80 (d, 3H, *J* = 6.6 Hz), 1.77 (m, 1H), 1.57 (m, 1H), 1.31 (m, 2H), 1.00 (d, 6H, *J* = 7.2 Hz), 0.96 (d, 3H, *J* = 7.2 Hz); ^{31}P NMR (CD_3OD, 160 MHz) δ 2.34; IR (film) ν_{max} 3400, 2970, 2923, 1715, 1445, 1260, 960 cm^{-1}; ESI-TOF HRMS *m/z* 451.1852 ($C_{21}H_{33}O_7 + Na^+$ requires 451.1856).



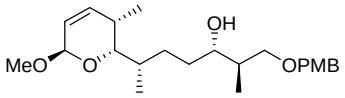
Dephosphocytostatin (40). A solution of **37** (2.0 mg, 0.0043 mmol) in 0.10 mL of THF and 0.020 mL of pyridine at 0 °C was treated with a solution of HF–pyr (0.050 mL) in 0.10 mL of THF and the mixture was allowed to stand at 25 °C for 2 h. The reaction mixture was carefully transferred to a mixture of saturated aqueous $NaHCO_3$ (3 mL) and EtOAc (1 mL) and the resulting mixture was extracted with EtOAc (3 × 2 mL). The organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 60% EtOAc–hexane) to provide **40** as a colorless oil (1.5 mg, 99%): $[\alpha]^{25}_D$ +40 (*c* 0.13,

$CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.07 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.59 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.53 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.17 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.03 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.87 (d, 1H, *J* = 9.6 Hz), 5.82 (dq, 1H, *J* = 7.2, 15.0 Hz), 5.47 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.52 (ddd, 1H, *J* = 4.8, 8.4, 9.6 Hz), 4.05 (dd, 1H, *J* = 3.0, 9.6 Hz), 3.84 (m, 1H), 3.29 (d, 1H, *J* = 4.2 Hz), 2.95 (d, 1H, *J* = 5.4 Hz), 2.52 (m, 1H), 1.80 (d, 3H, *J* = 6.6 Hz), 1.77–1.73 (m, 2H), 1.63–1.54 (m, 2H), 1.38–1.29 (m, 2H), 0.97 (d, 3H, *J* = 7.2 Hz), 0.89 (d, 3H, *J* = 7.2 Hz), 0.80 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ165.4, 153.8, 135.0, 132.8, 131.6, 127.5, 125.0, 122.7, 120.0, 84.5, 73.3, 72.4, 44.2, 34.5, 31.5, 31.0, 18.5, 14.7, 11.0, 10.8; IR (film) ν_{max} 3406, 2962, 2923, 2844, 1712, 1453, 1376, 1260, 1110 cm^{-1}; ESI-TOF HRMS *m/z* 371.2193 ($C_{21}H_{32}O_4$ + Na^+ requires 371.2193).

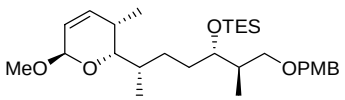


(5*S*,6*S*)-6-[(*S*)-4-(4*S*,5*R*,6*S*)-6-[(1*Z*,3*Z*,5*E*)-hepta-1,3,5-trienyl]-2,2,5-trimethyl-1,3-dioxan-4-yl)butan-2-yl]-5-methyl-5,6-dihydropyran-2-one (41). A solution of **40** (1.5 mg, 0.0043 mmol) in 1 mL of THF was treated with 2,2-dimethoxypropane (0.030 mL, 0.24 mmol) and anhydrous p-TsOH (0.2 mg, 0.0012 mmol) and stirred at 25 °C for 1 h before Et_3N (3 drops) was added. The mixture was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 40% EtOAc–hexane) to provide **41** as a colorless oil (1.7 mg, 99%): $[\alpha]^{25}_D$ +63 (*c* 0.17, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.07 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.60 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.59 (dd, 1H, *J* = 10.8, 12.0 Hz), 6.22 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.05 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.87 (d, 1H, *J* = 9.6 Hz), 5.84 (dq, 1H, *J* = 6.6, 15.0 Hz), 5.44 (dd, 1H, *J* = 9.6, 10.2 Hz), 4.27 (dd, 1H, *J* = 8.4, 9.6 Hz), 4.03 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.89 (ddd, 1H, *J* = 3.0, 4.8, 9.6 Hz), 2.52 (m, 1H), 1.83 (m, 1H), 1.80 (d, 3H, *J* = 7.2 Hz), 1.74 (m, 2H), 1.52 (m, 1H), 1.35–1.26 (m, 2H), 1.33 (s, 3H), 1.30 (s, 3H), 0.97 (d, 3H, *J* = 6.6 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 0.80 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ165.4, 153.8, 133.1, 132.2, 131.8, 127.5, 126.4, 122.6, 120.0, 101.2, 84.4, 71.2, 70.0, 41.5, 34.4, 31.0, 29.4, 28.0, 25.1, 24.6, 18.5, 14.7, 11.5, 10.9; IR (film) ν_{max} 2974, 2923, 2844, 1723, 1456, 1369, 1251, 815 cm^{-1}; ESI-TOF HRMS *m/z* 411.2510 ($C_{24}H_{36}O_4$ + Na^+ requires

411.2506).

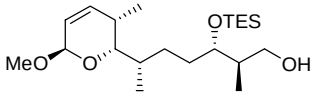


(2*R*,3*S*,6*S*)-6-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl)-1-(4-metho xybenzyloxy)]-2-methylheptan-3-ol (51). A solution of **16** (1.28 g, 4.4 mmol) in 20 mL of Et_2O at –78 °C was treated with *t*-BuLi (5.2 mL of 1.6 M in pentane, 8.3 mmol) dropwise over 2 min. After 5 min, freshly prepared (2-Th)CuCNLi[9] (14 mL of 0.4 M in THF, 5.6 mmol) was added and the mixture was immediately warmed to 0 °C. After 5 min, a solution of **50**[12] (0.72 g, 3.2 mmol) in 20 mL of Et_2O was added dropwise over 5 min, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with the addition of saturated aqueous NH_4Cl/NH_4OH (pH 8, 200 mL) and the mixture was extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 25% EtOAc–hexane) to provide **51** as a colorless oil (0.91 g, 72%): $[\alpha]^{25}_D$ +35 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 6.05 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.65 (dd, 1H, *J* = 3.0, 10.0 Hz), 4.83 (d, 1H, *J* = 2.5 Hz), 4.44 (s, 2H), 3.80 (s, 3H), 3.58 (dd, 1H, *J* = 4.0, 9.0 Hz), 3.56–3.41 (m, 3H), 3.45 (s, 3H), 3.26 (m, 1H), 2.09 (m, 1H), 1.91 (m, 1H), 1.83 (m, 1H), 1.63–1.45 (m, 3H), 1.35 (m, 1H), 0.91 (d, 6H, *J* = 7.0 Hz), 0.85 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ159.1, 136.0, 129.2, 129.1, 123.8, 113.5, 96.3, 76.1, 74.5, 73.5, 72.9, 55.4, 55.1, 38.5, 33.8, 32.0, 29.9, 28.8, 15.0, 14.0, 11.7; IR (film) ν_{max} 3484, 2958, 1614, 1512, 1457, 1244, 1038, 814 cm^{-1}; ESI-TOF HRMS *m/z* 415.2450 ($C_{23}H_{36}O_5 + Na^+$ requires 415.2455).

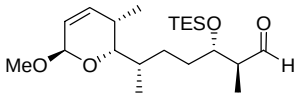


(2*S*,3*S*,6*R*)-2-[(2*S*,5*S*,6*R*)-5-triethylsilyloxy-7-(4-methoxybenzyloxy)-6-methylheptan-2-yl]-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran (52). A solution of **51** (0.883 g, 2.20 mmol) in 2 mL of DMF was treated with imidazole (0.913 g, 13.4 mmol) and TESCl (0.75 mL, 4.5 mmol) and stirred at 25 °C for 1 h before being quenched with the addition of H_2O

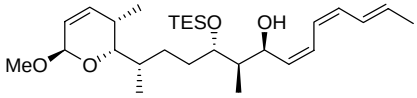
(50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 5% EtOAc–hexane) to provide **52** as a colorless oil (0.98 g, 87%): $[\alpha]^{25}_D$ +33 (*c* 1.3, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ7.24 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 5.79 (ddd, 1H, *J* = 1.0, 6.0, 10.0 Hz), 5.67 (ddd, 1H, *J* = 1.0, 3.0, 10.0 Hz), 4.80 (d, 1H, 3.0 Hz), 4.39 (d, 1H, *J* = 12.0 Hz), 4.31 (d, 1H, *J* = 12.0 Hz), 3.98 (m, 1H), 3.65 (dd, 1H, *J* = 3.0, 10.5 Hz), 3.44 (s, 3H), 3.42 (m, 1H), 3.35–3.30 (m, 1H), 3.31 (s, 3H), 2.18 (m, 1H), 2.17 (m, 1H), 1.79 (m, 1H), 1.66 (m, 2H), 1.41 (m, 2H), 1.06 (m, 12 H), 0.87 (d, 3H, *J* = 7.0 Hz), 0.71 (m, 9H) ; ^{13}C NMR (C_6D_6, 125 MHz) δ159.7, 135.4, 131.4, 129.2, 125.2, 114.1, 96.9, 74.3, 73.6, 73.0, 72.7, 55.4, 54.8, 40.1, 34.4, 30.6, 29.8, 29.5, 15.2, 12.8, 12.0, 7.4, 5.7; IR (film) ν_{max} 2951, 2873, 1614, 1510, 1451, 1377, 1244, 1077, 1038, 959 cm^{-1}; ESI-TOF HRMS *m/z* 529.3310 ($C_{29}H_{50}O_5Si$ + Na^+ requires 529.3320).



(2*R*,3*S*,6*S*)-6-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-2-methyl-3-(triethylsilyloxy)heptan-1-ol (53). A solution of **52** (76.0 mg, 0.15 mmol) in 4 mL of CH_2Cl_2 was treated with H_2O (0.2 mL) and DDQ (51.0 mg, 0.22 mmol) and stirred at 25 °C for 15 min. The reaction mixture was diluted with 10 mL of CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 15% EtOAc–hexane) to provide **53** as a colorless oil (42 mg, 72%): $[\alpha]^{25}_D$ +39 (*c* 0.9, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ 5.79 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.66 (dd, 1H, *J* = 2.5, 10.0 Hz), 4.78 (d, 1H, *J* = 3.0 Hz), 3.76 (m, 1H), 3.63 (dd, 2H, *J* = 2.5, 10.0 Hz), 3.50 (m, 1H), 3.41 (s, 3H), 2.07 (m, 1H), 1.77 (m, 2H), 1.74–1.62 (m, 2H), 1.41 (m, 1H), 1.26 (m, 1H), 1.02 (t, 9H, *J* = 8.0 Hz), 0.96 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 3H, *J* = 7.0 Hz), 0.70 (d, 3H, *J* = 6.5 Hz), 0.65 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (C_6D_6, 125 MHz) δ135.4, 125.1, 97.0, 76.7, 73.6, 65.4, 55.4, 40.4, 34.5, 31.5, 30.6, 28.9, 15.1, 12.0, 11.0, 7.2, 5.6; IR (neat) ν_{max} 3494, 2944, 2871, 1458, 1413, 1379, 1239, 1184, 1105, 1074, 1044, 1005, 961, 740 cm^{-1}; ESI-TOF HRMS *m/z* 409.2735 ($C_{21}H_{42}O_4Si$ + Na^+ requires 409.2744).



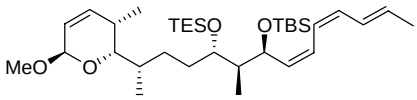
(2*S*,3*S*,6*S*)-6-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-2-methyl-3-(triethylsilyloxy)heptanal (54). A solution of **53** (100 mg, 0.24 mmol) in 5 mL of CH_2Cl_2 was treated with Dess-Martin periodinane (155 mg, 0.36 mmol) and stirred at 25 °C. After 10 min, 2 mL of saturated aqueous $NaHCO_3$ and 2 mL of 10% aqueous $Na_2S_2O_3$ were added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and the residue was filtered through a short SiO_2 column (10% EtOAc–hexane wash) to provide **54** as a colorless oil (90.0 mg, 90%): $[\alpha]^{25}_D$ +52 (*c* 0.6, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ 9.64 (d, 1H, *J* = 2.0 Hz), 5.78 (dd, 1H, *J* = 6.0, 10.0 Hz), 5.66 (dd, 1H, *J* = 2.5, 10.0 Hz), 4.77 (d, 1H, *J* = 2.5 Hz), 3.91 (m, 1H), 3.59 (dd, 1H, *J* = 3.0 10.0 Hz), 3.41 (s, 3H), 2.34 (m, 1H), 2.01 (m, 1H), 1.76 (m, 1H), 1.67–1.54 (m, 3H), 0.98 (m, 12H), 0.84 (d, 3H, *J* = 7.0 Hz), 0.65 (d, 3H, *J* = 6.5 Hz), 0.60 (q, 6H, *J* = 8.0 Hz); IR (neat) ν_{max} 2956, 2875, 1724, 1683, 1456, 1373, 1239, 1184, 1105, 1074, 1045, 1006, 962, 825, 741 cm^{-1}; ESI-TOF HRMS *m/z* 407.2585 ($C_{21}H_{40}O_4Si + Na^+$ requires 407.2588).



(2*S*,5*S*,6*R*,7*S*,8*Z*,10*Z*,12*E*)-2-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-6-methyl-5-(triethylsilyloxy)tetradeca-8,10,12-trien-7-ol (55). A solution of **18** (160 mg, 0.92 mmol) in 10 mL of Et_2O at –78 °C was treated with *t*-BuLi (0.80 mL of 1.6 M in pentane, 1.28 mmol), and stirred for 1.5 h at –78 °C before a solution of **54** (90.0 mg, 0.23 mmol) in 2 mL of Et_2O was added dropwise over 5 min. The mixture was stirred for 1 h at –78 °C before being quenched with the addition of saturated aqueous NH_4Cl (20 mL). The mixture was then extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 6% EtOAc–hexane) to provide *syn*-**55** (52 mg, 47%) as a colorless oil and *anti*-**55** (26 mg, 23%) as a colorless oil. Data for *syn*-**55**: $[\alpha]^{25}_D$ +20 (*c* 1.1, $CHCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ 6.51 (dd, 1H, *J* = 11.4, 14.8 Hz), 6.49 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.06 (dd, 1H, *J* =

10.8, 11.4 Hz), 5.79 (dd, 1H, *J* = 6.0, 10.2 Hz), 5.74 (dd, 1H, *J* = 9.6, 9.6 Hz), 5.67 (dd, 1H, *J* = 2.4, 10.2 Hz), 5.54 (dq, 1H, *J* = 6.6, 14.8 Hz), 5.13 (d, 1H, *J* = 7.8 Hz), 4.81 (d, 1H, *J* = 3.0 Hz), 3.79 (m, 1H), 3.61 (dd, 1H, *J* = 2.4, 10.2 Hz), 3.40 (s, 3H), 2.76 (s, 1H), 2.08 (m, 1H), 1.84–1.78 (m, 4H), 1.60–1.50 (m, 2H), 1.56 (d, 3H, *J* = 6.6 Hz), 1.18 (d, 3H, *J* = 6.6 Hz), 1.02 (t, 9H, *J* = 7.8 Hz), 0.85 (d, 3H, *J* = 6.6 Hz), 0.70 (d, 3H, *J* = 6.6 Hz), 0.65 (q, 6H, *J* = 7.8 Hz); ^{13}C NMR (C_6D_6, 150 MHz) δ 135.4, 134.9, 131.4, 131.1, 127.4, 125.1, 124.0, 122.5, 97.0, 77.6, 73.5, 68.1, 55.5, 43.2, 34.5, 31.9, 30.6, 29.0, 18.4, 15.1, 12.0, 11.4, 7.2, 5.5; IR (neat) ν_{max} 3498, 2959, 2874, 1653, 1559, 1457, 1370, 1183, 1042, 965 cm^{-1}; ESI-TOF HRMS *m/z* 501.3368 ($C_{28}H_{50}O_4Si$ + Na^+ requires 501.3370).

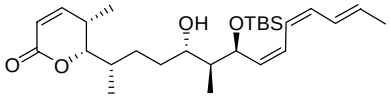
Data for *anti*-**55**: $[\alpha]^{25}_D$ +52 (*c* 0.6, $CHCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ 6.49 (m, 2H), 6.23 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.00 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.80 (dd, 1H, *J* = 6.0, 9.6 Hz), 5.69 (dd, 1H, *J* = 3.0, 9.6 Hz), 5.56 (dq, 1H, *J* = 7.2, 15.0 Hz), 5.42 (dd, 1H, *J* = 9.0, 10.8 Hz), 4.82 (d, 1H, *J* = 2.4 Hz), 4.45 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.29 (m, 1H), 3.70 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.47 (s, 3H), 2.18 (m, 1H), 1.96 (m, 1H), 1.84–1.70 (m, 3H), 1.58 (d, 3H, *J* = 7.2 Hz), 1.56 (m, 2H), 1.08 (t, 9H, *J* = 7.8 Hz), 0.98 (d, 3H, *J* = 7.2 Hz), 0.89 (d, 3H, *J* = 7.2 Hz), 0.77 (d, 3H, *J* = 7.2 Hz), 0.73 (q, 6H, *J* = 7.8 Hz); ^{13}C NMR (C_6D_6, 150 MHz) δ 135.4, 134.0, 131.8, 131.5, 127.3, 125.5, 125.2, 122.2, 96.9, 74.1, 73.6, 70.0, 55.4, 45.6, 34.3, 31.9, 30.6, 29.2, 18.4, 15.2, 12.1, 11.2, 7.3, 5.7; IR (neat) ν_{max} 3498, 2959, 2874, 1653, 1559, 1457, 1370, 1183, 1042, 965 cm^{-1}; ESI-MS *m/z* 501.3 ($C_{28}H_{50}O_4Si$ + Na^+ requires 501.3).



(2*S*,5*S*,6*S*,7*S*,8*Z*,10*Z*,12*E*)-7-(*tert*-butyldimethylsilyloxy)-5-(triethylsilyloxy)-2-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyl-3,6-dihydro-2*H*-pyran-2-yl]-6-methyltetradeca-8,10,12-triene (56). A solution of *syn*-**55** (38.0 mg, 0.082 mmol) and imidazole (49.0 mg, 0.72 mmol) in 0.20 mL of DMF was treated with TBSCl (38.0 mg, 0.25 mmol) and stirred at 25 °C. After 1 h, H_2O (2 mL) was added and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 3% EtOAc–hexane) to provide **56** as a colorless oil (33.0 mg, 71%): $[\alpha]^{25}_D$ –17 (*c* 0.7, $CHCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ 6.44 (dd, 1H, *J* =

11.4, 11.4 Hz), 6.43 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.25 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.05 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.79 (dd, 1H, *J* = 5.4, 9.6 Hz), 5.68 (dd, 1H, *J* = 3.0, 9.6 Hz), 5.59 (dd, 1H, *J* = 10.2, 10.2 Hz), 5.54 (dq, 1H, *J* = 7.2, 15.0 Hz), 4.81 (d, 1H, *J* = 2.4 Hz), 4.65 (dd, 1H, *J* = 7.8, 8.4 Hz), 3.92 (m, 1H), 3.67 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.48 (s, 3H), 2.02 (m, 2H), 1.80–1.72 (m, 2H), 1.68 (m, 1H), 1.37 (m, 1H), 1.27 (d, 3H, *J* = 7.2 Hz), 1.03 (t, 9H, *J* = 7.8 Hz), 1.03 (s, 9H), 0.86 (d, 3H, *J* = 6.6 Hz), 0.75 (d, 3H, *J* = 6.6 Hz), 0.70 (q, 6H, *J* = 7.8 Hz), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ135.5, 134.8, 131.8, 131.6, 127.3, 125.2, 123.9, 121.9, 96.9, 73.9, 73.2, 70.7, 55.4, 47.9, 34.3, 30.5, 29.6, 29.2, 26.2, 18.5, 18.4, 15.2, 12.0, 10.5, 7.4, 5.8, –3.5, –4.1; IR (film) ν_{max} 2911, 2851, 1464, 1376, 1254, 1044, 992, 829, 735 cm^{-1}; ESI-TOF HRMS *m/z* 615.4230 ($C_{34}H_{64}O_4Si_2$ + Na^+ requires 615.4235).

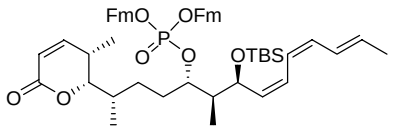
Data for **61** (from *anti*-**55**): $[\alpha]^{25}_D$ +55 (*c* 0.2, $CHCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ6.46 (m, 2H), 6.23 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.00 (dd, 1H, *J* = 10.8, 10.8 Hz), 5.80 (dd, 1H, *J* = 6.0, 10.2 Hz), 5.69 (dd, 1H, *J* = 3.0, 10.2 Hz), 5.54 (dq, 1H, *J* = 7.2, 15.0 Hz), 5.43 (dd, 1H, *J* = 9.6, 10.2 Hz), 4.84 (d, 1H, *J* = 2.4 Hz), 4.57 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.40 (m, 1H), 3.73 (dd, 1H, *J* = 2.4, 9.6 Hz), 3.56 (s, 3H), 2.04 (m, 2H), 1.79 (m, 3H), 1.56 (d, 1H, *J* = 6.6 Hz), 1.48 (m, 1H), 1.36–1.26 (m, 1H), 1.11 (t, 9H, *J* = 7.8 Hz), 1.06 (d, 3H, *J* = 7.2 Hz), 1.04 (s, 9H), 0.89 (d, 3H, *J* = 7.2 Hz), 0.81 (d, 3H, *J* = 6.6 Hz), 0.76 (q, 6H, *J* = 7.8 Hz), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ136.1, 135.3, 132.5, 132.2, 127.9, 125.9, 125.1, 122.7, 97.6, 73.7, 71.8, 68.6, 56.2, 47.8, 35.1, 31.2, 30.9, 27.9, 26.8, 19.0, 15.9, 12.6, 10.6, 8.1, 6.4, –2.8, –4.1; IR (film) ν_{max} 2911, 2851, 1464, 1376, 1254, 1044, 992, 829, 735 cm^{-1}; ESI-MS *m/z* 615.3 ($C_{34}H_{64}O_4Si_2$ + Na^+ requires 615.4).



(5*S*,6*S*)-6-[(2*S*,5*S*,6*S*,7*S*,8*Z*,10*Z*,12*E*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-6-methyltetradeca-8,10,12-trien-2-yl]-5-methyl-5,6-dihydropyran-2-one (58). A solution of **56** (20.0 mg, 0.033 mmol) in 10 mL of acetone at 25 °C was treated with aqueous HCl (0.50 mL of 0.5 M, 0.25 mmol). After 10 min, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography

(SiO_2, 20% EtOAc–hexane) to provide **57** as a colorless oil (9.5 mg, 61%) that was immediately used in the subsequent reaction. A solution of **57** (9.5 mg, 0.020 mmol) in 2.5 mL of benzene at 80 °C was treated with 50% Ag_2CO_3–Celite (150 mg, 0.27 mmol) and stirred for 30 min, then cooled and filtered through Celite (EtOAc wash). The filtrate was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 20% EtOAc–hexane) to provide **58** as a colorless oil (6.3 mg, 66%): $[\alpha]^{25}_D$ +37 (*c* 0.4, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.06 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.58 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.48 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.12 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.04 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.87 (d, 1H, *J* = 9.6 Hz), 5.82 (dq, 1H, *J* = 7.2, 15.0 Hz), 5.55 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.95 (dd, 1H, *J* = 3.0, 9.6 Hz), 4.02 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.50 (m, 1H), 3.27 (d, 1H, *J* = 4.8 Hz), 2.51 (dt, 1H, *J* = 3.0, 7.0 Hz), 1.84–1.74 (m, 2H), 1.79 (d, 3H, *J* = 7.2 Hz), 1.56 (m, 1H), 1.47–1.37 (m, 2H), 1.27 (m, 1H), 0.95 (d, 3H, *J* = 7.2 Hz), 0.87 (s, 9H), 0.86 (d, 3H, *J* = 7.2 Hz), 0.80 (d, 3H, *J* = 6.6 Hz), 0.063 (s, 3H), 0.040 (s, 3H); ^{13}C NMR (CD_3CN, 150 MHz) δ165.4, 153.8, 134.5, 133.0, 131.7, 127.5, 124.0, 122.5, 120.0, 84.6, 73.0, 70.9, 46.4, 34.5, 31.7, 31.0, 28.4, 26.1, 18.5, 14.6, 11.2, 11.0, –4.1, –4.8; IR (film) ν_{max} 3500, 2966, 2923, 2856, 1716, 1463, 1377, 1250, 836 cm^{-1}; ESI-TOF HRMS *m/z* 485.3055 ($C_{27}H_{46}O_4Si + Na^+$ requires 485.3057).

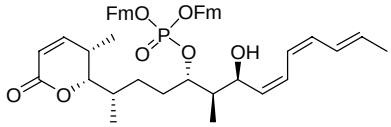
Data for **63** (from **61**): $[\alpha]^{25}_D$ +127 (*c* 0.6, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.06 (dd, 1H, *J* = 6.0, 9.6 Hz), 6.58 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.52 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.21 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.03 (dd, 1H, *J* = 10.8, 10.8 Hz), 5.87 (d, 1H, *J* = 9.6 Hz), 5.82 (dq, 1H, *J* = 6.6, 15.0 Hz), 5.38 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.74 (dd, 1H, *J* = 7.2, 9.6 Hz), 4.03 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.51 (m, 1H), 2.96 (d, 1H, *J* = 4.8 Hz), 2.52 (dt, 1H, *J* = 3.0, 7.2 Hz), 1.83–1.75 (m, 2H), 1.79 (d, 3H, *J* = 6.6 Hz), 1.48–1.38 (m, 2H), 1.35–1.25 (m, 2H), 0.96 (d, 3H, *J* = 6.6 Hz), 0.88 (m, 12H), 0.76 (d, 3H, *J* = 7.2 Hz), 0.057 (s, 3H), 0.012 (s, 3H); ^{13}C NMR (CD_3CN, 150 MHz) δ165.4, 153.8, 134.0, 132.8, 131.6, 127.5, 124.8, 123.0, 120.0, 118.2, 84.5, 73.1, 71.8, 46.8, 34.7, 31.0, 30.6, 28.8, 26.1, 18.6, 18.5, 14.7, 10.9, –3.8, –4.7; IR (film) ν_{max} 3399, 2970, 2933, 2860, 1718, 1470, 1265, 1113, 823 cm^{-1}; ESI-MS *m/z* 485.3 ($C_{27}H_{46}O_4Si + Na^+$ requires 485.3).



bis[(9*H*-fluoren-9-yl)methyl] (2*S*,5*S*,6*R*,7*S*,8*Z*,10*Z*,12*E*)-7-(*tert*-butyldimethylsilyloxy)-6-methyl-2-((2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)tetradeca-8,10,12-trien-5-yl phosphate (59). A solution of **58** (4.1 mg, 0.0089 mmol) and tetrazole (1.90 mg, 0.027 mmol) in 0.20 mL of CH_3CN at 25 °C was treated with a solution of *i*-$Pr_2NP(OFm)_2$[11] (18.4 mg, 0.035 mmol) in 0.26 mL CH_2Cl_2 and stirred for 5 min before 30% aqueous H_2O_2 (0.050 mL, 0.33 mmol) was added. After 5 min, 2 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexane) to provide **59** as a colorless oil (6.3 mg, 79%): $[\alpha]^{25}_D$ +11 (*c* 0.27, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.80–7.73 (m, 4H), 7.56–7.45 (m, 4H), 7.40–7.31 (m, 4H), 7.29–7.25 (m, 4H), 7.05 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.52 (dd, 1H, *J* = 11.4, 14.4 Hz), 6.41 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.02–5.92 (m, 2H), 5.86 (d, 1H, *J* = 9.6 Hz), 5.78 (dq, 1H, *J* = 7.2, 14.4 Hz), 5.29 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.46 (dd, 1H, *J* = 6.6, 9.6 Hz), 4.32–4.18 (m, 3H), 4.16–4.04 (m, 4H), 3.91 (dd, 1H, *J* = 3.0, 10.2 Hz), 2.45 (m, 1H), 1.76 (d, 3H, *J* = 7.2 Hz), 1.67 (m, 1H), 1.51 (m, 2H), 1.37–1.27 (m, 2H), 1.13 (m, 1H), 0.95 (d, 3H, *J* = 7.2 Hz), 0.90 (d, 3H, *J* = 6.6 Hz), 0.87 (s, 9H), 0.84 (d, 3H, *J* = 6.6 Hz), 0.73 (d, 3H, *J* = 7.2 Hz), –0.025 (s, 3H), –0.036 (s, 3H); ^{13}C NMR (CD_3CN, 150 MHz) δ165.9, 154.4, 145.6, 145.2, 145.1, 145.0, 142.9, 135.2, 134.0, 133.0, 129.4, 129.3, 129.2, 129.1, 128.8, 128.7, 128.1, 126.7, 126.6, 126.5, 126.4, 125.1, 122.8, 121.6, 121.5, 120.7, 84.4, 70.5, 69.8, 69.3, 67.9, 49.6, 49.3, 46.3, 46.2, 35.1, 31.6, 29.2, 26.9, 23.3, 19.3, 19.2, 15.4, 11.7, 10.6, –3.6, –4.5; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.48; IR (film) ν_{max} 2967, 2920, 2850, 1720, 1450, 1377, 1250, 1007 cm^{-1}; ESI-TOF HRMS *m/z* 899.4461 ($C_{55}H_{67}O_7PSi + H^+$ requires 899.4466).

Data for **64** (from **63**): $[\alpha]^{25}_D$ +65 (*c* 0.46, $CHCl_3$); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.89–7.85 (m, 4H), 7.66–7.55 (m, 4H), 7.48–7.42 (m, 4H), 7.39–7.34 (m, 4H), 7.15 (dd, 1H, *J* = 6.65 9.5 Hz), 6.63 (dd, 1H, *J* = 11.5, 14.5 Hz), 6.57 (dd, 1H, *J* = 11.5, 11.5 Hz), 6.19 (dd, 1H, *J* = 11.5, 11.5 Hz), 6.07 (dd, 1H, *J* = 11.0, 11.0 Hz), 5.96 (d, 1H, *J* = 9.5 Hz), 5.88 (dq, 1H,

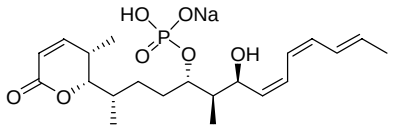
J = 7.0, 15.0 Hz), 5.30 (dd, 1H, *J* = 9.5, 10.5 Hz), 4.68 (m, 1H), 4.46 (dd, 1H, *J* = 8.5, 9.0 Hz), 4.31 (m, 2H), 4.25–4.15 (m, 4H), 2.57 (m, 1H), 1.96 (m, 1H), 1.87 (d, 3H, *J* = 7.0 Hz), 1.82 (m, 1H), 1.76 (m, 2H), 1.68–1.59 (m, 2H), 1.58–1.36 (m, 1H), 1.05 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.90 (d, 3H, *J* = 7.0 Hz), 0.74 (d, 3H, *J* = 7.0 Hz), 0.090 (s, 3H), 0.030 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ164.7, 153.1, 143.9, 141.8, 141.7, 133.7, 132.7, 131.5, 128.2, 127.6, 127.5, 126.9, 125.4, 124.7, 122.1, 120.4, 120.3, 119.6, 83.5, 70.4, 68.6, 68.5, 48.3, 48.2, 44.5, 34.1, 30.5, 29.1, 26.3, 25.7, 18.1, 18.0, 14.2, 10.5, 9.6, –4.1, –5.3; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.38; IR (film) ν_{max} 3049, 2931, 2860, 1721, 1450, 1252, 1011, 837 cm^{-1}; ESI-TOF HRMS *m/z* 921.4279 ($C_{55}H_{67}O_7PSi$ + Na^+ requires 921.4286).



bis[(9*H*-fluoren-9-yl)methyl] (2*S*,5*S*,6*R*,7*S*,8*Z*,10*Z*,12*E*)-7-hydroxy-6-methyl-2-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]tetradeca-8,10,12-trien-5-yl phosphate (60). A solution of **59** (9.0 mg, 0.010 mmol) in 0.40 mL of THF and 0.080 mL of pyridine at 0 °C was treated with a solution of HF–pyr (0.200 mL) in 0.40 mL of THF and the mixture was allowed to stand at 25 °C for 3 h. The reaction mixture was carefully transferred to a mixture of saturated aqueous $NaHCO_3$ (3 mL) and EtOAc (1 mL) and the resulting mixture was extracted with EtOAc (3 × 2 mL). The organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 65% EtOAc–hexane) to provide **59** as a colorless oil (5.5 mg, 70%): $[\alpha]^{25}_D$ +26 (*c* 0.11, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.81–7.75 (m, 4H), 7.57–7.49 (m, 4H), 7.41–7.32 (m, 4H), 7.31–7.25 (m, 4H), 7.06 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.54 (dd, 1H, *J* = 10.8, 15.0 Hz), 6.42 (dd, 1H, *J* = 10.8, 10.8 Hz), 5.93 (m, 2H), 5.86 (d, 1H, *J* = 9.6 Hz), 5.79 (dq, 1H, *J* = 6.6, 14.4 Hz), 4.54 (m, 1H), 4.44 (m, 1H), 4.29 (m, 1H), 4.23–4.12 (m, 4H), 3.93 (m, 1H), 3.87 (dd, 1H, *J* = 3.0, 10.8 Hz), 3.28 (d, 1H, *J* = 4.8 Hz), 2.45 (m, 1H), 1.78 (d, 3H, *J* = 6.6 Hz), 1.65–1.47 (m, 4H), 1.42 (m, 1H), 1.10 (m, 1H), 0.90 (d, 3H, *J* = 7.2 Hz), 0.75 (d, 3H, *J* = 6.6 Hz), 0.68 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ165.2, 153.7, 144.5, 144.4, 142.3, 142.2,

134.2, 131.8, 128.7, 128.6, 128.1, 128.0, 126.2, 126.0, 125.9, 125.8, 124.2, 122.4, 121.0, 120.9, 120.0, 83.9, 69.5, 69.1, 67.1, 60.9, 48.8, 48.6, 43.7, 34.4, 30.9, 28.5, 26.9, 14.5, 11.0, 9.4; ^{31}P NMR (CD_3CN, 160 MHz) δ 0.30; IR (film) ν_{max} 3423, 2968, 2850, 1720, 1450, 1267, 1077 cm^{-1}; ESI-TOF HRMS *m/z* 785.3597 ($C_{49}H_{53}O_7P + H^+$ requires 785.3601).

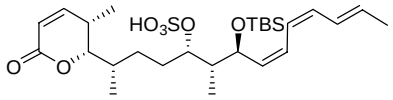
Data for **65** (from **64**): $[\alpha]^{25}_D$ +50 (*c* 0.28, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ 7.80–7.76 (m, 4H), 7.55–7.47 (m, 4H), 7.41–7.34 (m, 4H), 7.31–7.26 (m, 4H), 7.07 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.56 (dd, 1H, *J* = 10.8, 15.0 Hz), 6.50 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.12 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.98 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.88 (d, 1H, *J* = 9.6 Hz), 5.80 (dq, 1H, *J* = 6.6, 15.0 Hz), 5.27 (dd, 1H, *J* = 9.6, 10.2 Hz), 4.51 (m, 1H), 4.29–4.19 (m, 3H), 4.09 (dd, 1H, *J* = 5.4, 6.6 Hz), 3.95 (dd, 1H, *J* = 3.0, 10.8 Hz), 2.89 (d, 1H, *J* = 4.2 Hz), 2.49 (m, 1H), 1.82 (m, 1H), 1.80 (d, 3H, *J* = 7.2 Hz) 1.74 (m, 1H), 1.68 (m, 1H), 1.51 (m, 2H), 1.20 (m, 1H), 0.94 (d, 3H, *J* = 7.2 Hz), 0.79 (d, 3H, *J* = 7.2 Hz), 0.62 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ166.0, 154.5, 145.2, 145.1, 143.0, 142.9, 136.2, 134.7, 133.6, 132.5, 129.3, 128.8, 128.7, 128.2, 126.6, 126.4, 123.4, 121.6, 121.5, 120.7, 85.0, 82.5, 69.7, 69.6, 49.5 49.4, 49.3, 44.7, 35.1, 31.6, 30.0, 27.6, 19.2, 15.2, 11.7, 11.0; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.27; IR (film) ν_{max} 3400, 2954, 2930, 1713, 1448, 1255, 1008 cm^{-1}; ESI-MS *m/z* 807.3 ($C_{49}H_{53}O_7P + Na^+$ requires 807.3).



***epi*-(10*R*)-Cytostatin (43).** A solution of **60** (2.3 mg, 0.0029 mmol) in 0.54 mL of CH_3CN at 0 °C was treated with 0.14 mL of Et_3N and the mixture was allowed to stand at 25 °C for 13 h before 0.50 mL of toluene was added and the solution was concentrated under reduced pressure. The residue was dissolved in 1 mL of H_2O, washed with Et_2O (5 × 1 mL), and the aqueous layer was concentrated under reduced pressure. The residue was dissolved in 0.5 mL of 1:1 MeOH–H_2O and passed through a short column of Dowex-Na^+ (0.8 × 2 cm, 1:1 MeOH–H_2O wash) to provide **43** as a white solid (1.2 mg, 92%): $[\alpha]^{25}_D$ +25 (*c* 0.12, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.14 (dd, 1H, *J* = 6.0, 9.6 Hz), 6.56 (dd, 1H, *J* = 11.4, 14.4 Hz), 6.46 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.21 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.98 (dd, 1H, *J* = 10.8,

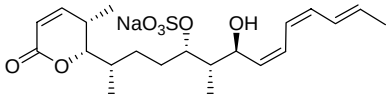
11.4 Hz), 5.91 (d, 1H, *J* = 9.6 Hz), 5.75 (dq, 1H, *J* = 6.6, 14.4 Hz), 5.56 (dd, 1H, *J* = 9.6, 9.6 Hz), 5.11 (dd, 1H, *J* = 1.8, 8.4 Hz), 4.12 (m, 1H), 4.10 (dd, 1H, *J* = 3.0, 10.8 Hz), 2.57 (m, 1H), 1.99 (m, 1H), 1.85 (m, 1H), 1.80 (d, 3H, *J* = 6.6 Hz), 1.79–1.64 (m, 2H), 1.40–1.33 (m, 2H), 1.00 (d, 3H, *J* = 7.2 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 3H, *J* = 6.6 Hz); ^{31}P NMR (CD_3OD, 160 MHz) δ 3.64; IR (film) ν_{max} 3400, 2970, 2920, 1715, 1450, 1260, 963 cm^{-1}; ESI-TOF HRMS *m/z* 451.1859 ($C_{21}H_{33}O_7 + Na^+$ requires 451.1856).

Data for **44** (from **65**): $[\alpha]^{25}_D$ +109 (*c* 0.15, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.15 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.57 (dd, 1H, *J* = 10.8, 14.4 Hz), 6.54 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.19 (dd, 1H, *J* = 10.8, 12.0 Hz), 6.00 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.92 (d, 1H, *J* = 9.6 Hz), 5.76 (dq, 1H, *J* = 6.6, 14.4 Hz), 5.49 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.47 (m, 1H), 4.37 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.11 (dd, 1H, *J* = 3.0, 10.2 Hz) 2.59 (m, 1H), 2.17 (m, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 1.80 (d, 3H, *J* = 6.6 Hz), 1.63 (m, 2H), 1.51 (m, 1H), 1.01 (d, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.85 (d, 3H, *J* = 6.6 Hz); ^{31}P NMR (CD_3OD, 160 MHz) δ 0.54; IR (film) ν_{max} 3400, 2970, 2920, 1712, 1454, 1250, 1007 cm^{-1}; ESI-TOF HRMS *m/z* 451.1836 ($C_{21}H_{33}O_7 + Na^+$ requires 451.1856).

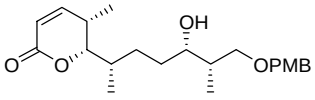


(2*S*,5*S*,6*S*,7*S*,8*Z*,10*Z*,12*E*)-7-(*tert*-butyldimethylsilyloxy)-6-methyl-2-((2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)-tetradeca-8,10,12-trien-5-yl sulfate (66). A solution of **37** (2.3 mg, 0.0050 mmol) in 0.2 mL of THF was treated with SO_3–pyr (1.6 mg, 0.100 mmol) and stirred at 25 °C for 30 min before being filtered through a short column of silica gel (15% MeOH–CH_2Cl_2 wash) to provide **66** as a colorless oil (1.9 mg, 71%): $[\alpha]^{25}_D$ +8.4 (*c* 0.19, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.15 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.57 (dd, 1H, *J* = 10.8, 14.4 Hz), 6.53 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.23 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.00 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.93 (d, 1H, *J* = 9.6 Hz), 5.77 (dq, 1H, *J* = 6.6, 14.4 Hz), 5.36 (dd, 1H, *J* = 9.6, 10.8 Hz), 4.80 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.65 (m, 1H), 4.08 (dd, 1H, *J* = 3.0, 10.2 Hz), 2.58 (m, 1H), 2.02 (m, 1H), 1.90 (m, 1H), 1.83 (m, 1H), 1.80 (d, 3H, *J* = 6.6 Hz), 1.77 (m, 1H), 1.64 (m, 1H), 1.29 (m, 1H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.89 (s, 9H), 0.86 (d, 3H, *J* = 7.2 Hz), 0.14 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (CD_3OD, 150 MHz)

δ155.1, 134.5, 132.4, 131.9, 128.1, 125.5, 123.4, 120.1, 85.6, 80.9, 70.2, 44.4, 35.3, 31.7, 30.7, 29.1, 26.7, 19.1, 18.6, 15.0, 11.1, 10.3, –3.5, –4.3; IR (film) ν_{max} 3476, 2933, 2840, 1712, 1466, 1379, 1256, 1056 cm^{-1}; ESI-TOF HRMS *m/z* 541.2670 ($C_{27}H_{46}O_7SSi - H^+$ requires 541.2661).

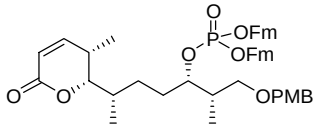


Sulfocytostatin (67). A solution of **66** (1.5 mg, 0.00277 mmol) in 0.1 mL of THF and 0.025 mL of pyridine was treated with HF–pyr (0.050 mL) in 0.1 mL of THF and allowed to stand at 25 °C for 1.5 h. The reaction mixture was carefully transferred to a mixture of saturated aqueous $NaHCO_3$ (3 mL) and EtOAc (2 mL) and the resulting mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2,15% MeOH–CH_2Cl_2) to provide **67** as a white solid (1.0 mg, 83%): $[\alpha]^{25}_D$ +30 (*c* 0.10, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.16 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.61 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.58 (dd, 1H, *J* = 11.4, 14.4 Hz), 6.21 (dd, 1H, *J* = 10.8, 12.0 Hz), 6.02 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.93 (d, 1H, *J* = 9.6 Hz), 5.78 (dq, 1H, *J* = 6.6, 14.4 Hz), 5.41 (dd, 1H, *J* = 9.6, 10.2 Hz), 4.72 (m, 1H), 4.62 (dd, 1H, *J* = 9.0, 9.6 Hz), 4.10 (dd, 1H, *J* = 3.0, 10.2 Hz), 2.59 (m, 1H), 2.10 (m, 1H) 1.86 (m, 1H), 1.81 (d, 3H, *J* = 7.2 Hz), 1.69 (m, 1H), 1.62 (m, 1H), 1.34–1.22 (m, 2H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 0.83 (d, 3H, *J* = 6.6 Hz); IR (film) ν_{max} 3450, 2932, 1712, 1466, 1380, 1256, 1011 cm^{-1}; ESI-TOF HRMS *m/z* 427.1799 ($C_{21}H_{32}O_7S - H^+$ requires 427.1796).



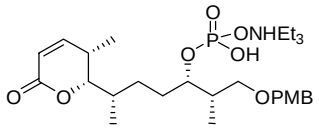
(5*S*,6*S*)-6-[(2*S*,5*S*,6*S*)-5-hydroxy-7-(4-methoxybenzyloxy)-6-methylheptan-2-yl]-5-methyl-5,6-dihydropyran-2-one (68). A solution of **30** (30.0 mg, 0.094 mmol) in 25 mL of acetone at 25 °C was treated with aqueous HCl (1.3 mL of 0.5 M, 0.065 mmol). After 10 min, saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated

under reduced pressure, and subjected to flash chromatography (SiO_2, 50% EtOAc–hexane) to provide the lactol as a colorless oil (22.0 mg, 99%) that was immediately used in the subsequent reaction. A solution of the lactol (22.0 mg, 0.094 mmol) in 8 mL of benzene at 80 °C was treated with 50% Ag_2CO_3–Celite (800 mg, 1.44 mmol) and stirred for 1 h before being cooled and filtered through Celite (EtOAc wash). The filtrate was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 50% EtOAc–hexane) to provide **68** as a colorless oil (21.0 mg, 96%): $[\alpha]^{25}_D$ +99 (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3CN, 400 MHz) δ7.26 (dd, 2H, *J* = 8.8 Hz), 7.07 (dd, 1H, *J* = 6.4, 9.6 Hz), 6.90 (d, 2H, *J* = 8.8 Hz), 5.87 (dd, 1H, *J* = 0.8, 9.6 Hz), 4.39 (s, 2H), 4.03 (dd, 1H, *J* = 2.8, 10.0 Hz), 3.77 (s, 3H), 3.58 (m, 1H), 3.45 (dd, 1H, *J* = 6.4, 9.2 Hz), 3.35 (dd, 1H, *J* = 6.4, 9.2 Hz), 2.62 (d, 1H, *J* = 5.6 Hz), 2.52 (m, 1H), 1.77 (m, 3H), 1.51 (m, 1H), 1.32 (m, 2H), 0.96 (d, 3H, *J* = 7.2 Hz), 0.87 (d, 3H, *J* = 6.8 Hz), 0.86 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (CD_3CN, 125 MHz) δ165.4, 160.1, 153.8, 131.9, 130.2, 120.0, 114.5, 84.6, 74.2, 55.8, 39.4, 34.5, 31.7, 31.0, 29.7, 14.7, 11.6, 11.0; IR (film) ν_{max} 3481, 2967, 2932, 2882, 1716, 1513, 1249, 1109, 1071, 824 cm^{-1}; ESI-TOF HRMS *m/z* 399.2135 ($C_{22}H_{32}O_5$ + Na^+ requires 399.2142).

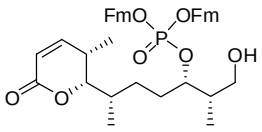


bis[(*9H*-fluoren-9-yl)methyl](2*S*,3*S*,6*S*)-1-(4-methoxybenzyloxy)-2-methyl-6-((2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)heptan-3-yl phosphate (69). A solution of **68** (7.0 mg, 0.019 mmol) and tetrazole (3.0 mg, 0.043 mmol) in 0.30 mL of CH_3CN at 25 °C was treated with a solution of *i*-$Pr_2NP(OFm)_2$[11] (30.0 mg, 0.056 mmol) in 0.40 mL CH_2Cl_2 and stirred for 1.5 h before 30% aqueous H_2O_2 (0.10 mL, 0.66 mmol) was added. After 10 min, 3 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexane) to provide **69** as a colorless oil (13.0 mg, 88%): $[\alpha]^{25}_D$ +38 (*c* 0.56, $CHCl_3$); ^{1}H NMR (CD_3CN, 400 MHz) δ7.77 (m, 4H), 7.55–7.44 (m, 4H), 7.40–7.32 (m, 4H), 7.30–7.24 (m, 4H), 7.17 (d, 2H, *J* = 8.8 Hz), 7.05 (dd, 1H, *J* = 6.4, 9.6 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 5.85 (dd,

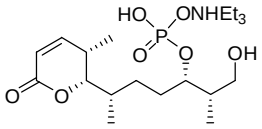
1H, *J* = 0.4, 9.6 Hz), 4.23 (m, 3H), 4.16–4.00 (m, 6H), 3.89 (dd, 1H, *J* = 3.2, 10.4 Hz), 3.72 (s, 3H), 3.24–3.13 (m, 2H), 2.45 (m, 1H), 1.80 (m, 1H), 1.72–1.52 (m, 2H), 1.42–1.25 (m, 2H), 1.05 (m, 1H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.75 (d, 3H, *J* = 6.8 Hz), 0.71 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (CD_3CN, 125 MHz) δ165.2, 160.0, 153.7, 144.5, 144.4, 142.3, 142.2, 131.8, 130.2, 128.6, 128.0, 125.9, 125.8, 120.9, 120.0, 114.5, 84.2, 82.0, 73.0, 72.3, 69.0, 68.9, 55.8, 48.7, 31.5, 30.9, 29.8, 28.5, 14.6, 12.0, 11.0; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.22; IR (film) ν_{max} 3056, 2967, 1716, 1441, 1250, 1105, 989, 741 cm^{-1}; ESI-TOF HRMS *m/z* 813.3551 ($C_{50}H_{53}O_8P + H^+$ requires 813.3554).



(2*S*,3*S*,6*S*)-1-(4-methoxybenzyloxy)-2-methyl-6-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl]heptan-3-yl hydrogenphosphate, triethylamine salt (70). A solution of **69** (2.0 mg, 0.0025 mmol) in 0.40 mL of CH_3CN at 0 °C was treated with 0.10 mL of Et_3N and the mixture was allowed to stand at 25 °C for 20 h before 0.50 mL of toluene was added and the solution was concentrated under reduced pressure. The residue was dissolved in 1 mL of H_2O, washed with Et_2O (4 × 1 mL), and the aqueous layer was concentrated under reduced pressure to provide **70** as a white solid (1.2 mg, 88%): $[\alpha]^{25}_D$ +66 (*c* 0.25, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.27 (d, 2H, *J* = 8.4 Hz), 7.14 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 5.92 (d, 1H, *J* = 9.6 Hz), 4.49 (d, 1H, *J* = 11.4 Hz), 4.39 (d, 1H, *J* = 11.4 Hz), 4.20 (m, 1H), 4.08 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.78 (s, 3H), 3.63 (dd, 1H, *J* = 5.4, 9.0 Hz), 3.42 (dd, 1H, *J* = 1.8, 7.2 Hz), 3.15 (q, 6H, *J* = 7.8 Hz), 2.56 (m, 1H), 2.06 (m, 1H), 1.85 (dd, 1H, *J* = 3.0, 9.0 Hz), 1.80 (m, 2H), 1.59 (m, 1H), 1.30 (m, 1H), 1.29 (t, 9H, *J* = 7.2 Hz), 1.00 (d, 3H, *J* = 7.2 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, 150 MHz) δ167.4, 160.7, 155.0, 132.2, 130.6, 122.1, 120.1, 114.7, 85.6, 78.3, 74.1, 73.8, 55.2, 47.0, 38.1, 35.5, 31.7, 29.1, 14.9, 12.3, 11.0, 9.3; ^{31}P NMR (CD_3OD, 160 MHz) δ 1.64; IR (film) ν_{max} 3415, 2964, 2933, 1708, 1538, 1513, 1246, 1169 cm^{-1}; ESI-TOF HRMS *m/z* 457.1980 ($C_{22}H_{33}O_8P + H^+$ requires 457.1986).

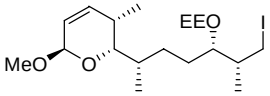


bis[(*9H*-fluoren-9-yl)methyl](2*S*,3*S*,6*S*)-2-methyl-6-((2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)heptan-3-yl phosphate (71). A solution of **69** (11.4 mg, 0.014 mmol) in 0.4 mL of CH_2Cl_2 was treated with H_2O (0.020 mL) and DDQ (5.0 mg, 0.022 mmol) and stirred at 25 °C for 30 min before saturated aqueous $NaHCO_3$ (2 mL) was added the mixture was extracted with CH_2Cl_2 (3×2 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 80% EtOAc–hexane) to provide **71** as a colorless oil (6.8 mg, 70%): $[\alpha]^{25}_D$ +52 (*c* 0.67, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ7.79 (m, 4H), 7.52 (m, 4H), 7.40–7.34 (m, 4H), 7.30 (m, 4H), 7.06 (dd, 1H, *J* = 6.0, 9.6 Hz), 5.85 (d, 1H, *J* = 9.6 Hz), 4.28–4.18 (m, 5H), 4.12 (m, 2H), 3.90 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.27–3.20 (m, 2H), 2.47 (m, 1H), 1.68 (m, 1H), 1.61–1.55 (m, 2H), 1.39 (m, 1H), 1.11–1.05 (m, 1H), 0.93 (d, 3H, *J* = 7.2 Hz), 0.75 (d, 3H, *J* = 7.2 Hz), 0.71 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ165.2, 153.7, 144.5, 144.4, 142.3, 142.2, 128.7, 128.6, 128.1, 128.0, 125.9, 125.8, 120.9, 120.0, 84.2, 81.1, 81.0, 69.2, 69.1, 64.0, 48.7, 48.6, 40.2, 34.5, 30.9, 30.2, 28.9, 14.7, 11.0, 10.3; ^{31}P NMR (CD_3CN, 160 MHz) δ 0.032; IR (film) ν_{max} 3444, 2966, 2872, 1716, 1652, 1450, 1254, 990, 741 cm^{-1}; ESI-TOF HRMS *m/z* 693.2977 ($C_{42}H_{45}O_7P$ + H^+ requires 693.2976).

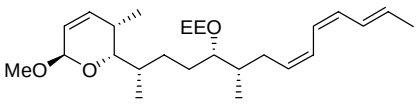


(2*S*,3*S*,6*S*)-2-methyl-6-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl]heptan-3-yl hydrogenphosphate, triethylamine salt (72). A solution of **71** (4.7 mg, 0.0084 mmol) in 1.0 mL of CH_3CN was treated with 0.3 mL of Et_3N and allowed to stand at 25 °C for 17 h before 0.50 mL of toluene was added and the solution was concentrated under reduced pressure. The residue was dissolved in 1 mL of H_2O, washed with Et_2O (4×1 mL), and the aqueous layer was concentrated under reduced pressure to provide **72** as a colorless oil (2.3 mg, 99%): $[\alpha]^{25}_D$ +61 (*c* 0.23, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.14 (dd, 1H, *J* = 6.6,

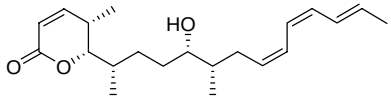
9.6 Hz), 5.91 (d, 1H, *J* = 9.6 Hz), 4.32 (m, 1H), 4.09 (dd, 1H, *J* = 3.0, 10.8 Hz), 3.64 (dd, 1H, *J* = 9.6, 11.4 Hz), 3.39 (dd, 1H, *J* = 6.0, 11.4 Hz), 3.12 (q, 6H, *J* = 7.2 Hz), 2.57 (m, 1H), 1.95–1.86 (m, 4H), 1.52 (m, 1H), 1.29 (m, 1H), 1.27 (t, 9H, *J* = 7.2 Hz), 1.00 (d, 3H, *J* = 7.2 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.83 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, 150 MHz) δ 167.4, 155.1, 120.1, 85.6, 75.9, 65.2, 47.8, 39.8, 35.5, 31.7, 31.4, 29.6, 15.0, 11.0, 9.7, 9.5; ^{31}P NMR (CD_3OD, 160 MHz) δ 1.52; ESI-TOF HRMS *m/z* 359.1230 ($C_{14}H_{25}O_7P + Na^+$ requires 359.1230).



(2*S*,3*S*,6*R*)-2-[(2*S*,5*S*,6*R*)-5-(1-ethoxyethyloxy)-7-iodo-6-methylheptan-2-yl]-3,6-dihydro-6-methoxy-3-methyl-*2H*-pyran (73). A solution of NIS (525 mg, 2.33 mmol) in 8 mL of THF was treated with PPh_3 (600 mg, 2.29 mmol) and stirred at 25 °C for 2 min before imidazole (225 mg, 3.30 mmol) was added. After 1 min, a solution of **32b** (100 mg, 0.27 mmol) in 2 mL of THF was added and the mixture was stirred at 25 °C for 5 min before being quenched with the addition of H_2O (40 mL) and extracted with Et_2O (2 × 40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 5% EtOAc–hexane) to provide **73** as a colorless oil (93 mg, 74%): $[\alpha]^{25}_D$ +38 (*c* 0.46, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 5.79 (ddd, 1H, *J* = 1.2, 6.0, 9.6 Hz), 5.66 (ddd, 1H, *J* = 1.2, 2.8, 9.6 Hz), 4.77 (d, 1H, *J* = 2.8 Hz), 4.59 (q, 1H, *J* = 5.2 Hz), 3.62 (dd, 1H, *J* = 2.8, 10.4 Hz), 3.56–3.47 (m, 2H), 3.39 (s, 3H), 3.38–3.32 (m, 1H), 3.24 (dd, 1H, *J* = 6.0, 9.6 Hz), 2.79 (dd, 1H, *J* = 7.6, 9.6 Hz), 1.90 (m, 2H), 1.77 (m, 1H), 1.71–1.54 (m, 2H), 1.40–1.26 (m, 2H), 1.21 (d, 3H, *J* = 5.2 Hz), 1.13 (t, 3H, *J* = 7.2 Hz), 0.89 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.8 Hz), 0.68 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (C_6D_6, 100 MHz) δ 135.4, 125.1, 99.9, 96.9, 79.5, 73.4, 60.4, 55.4, 40.1, 34.3, 30.5, 29.4, 28.4, 20.8, 15.7, 15.5, 15.1, 12.0; IR (film) ν_{max} 2970, 2931, 1455, 1378, 1335, 1185, 1105, 1046, 961 cm^{-1}; ESI-TOF HRMS *m/z* 477.1467 ($C_{19}H_{35}IO_4 + Na^+$ requires 477.1472).

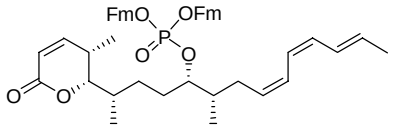


(2*S*,3*S*,6*R*)-2-[(2*S*,5*S*,6*S*,8*Z*,10*Z*,12*E*)-5-(1-ethoxyethyloxy)-6-methyltetradeca-8,10,12-trien-2-yl]-3,6-dihydro-6-methoxy-3-methyl-*2H*-pyran (74). A solution of **18** (130 mg, 0.75 mmol) in 1.5 mL of Et_2O at –78 °C was treated with *t*-BuLi (0.71 mL of 1.5 M in pentane, 1.07 mmol) and stirred for 1 h at –78 °C before a solution of CuI–PBu_3[10] (100 mg, 0.26 mmol) in 0.5 mL of Et_2O was added. After 10 min, a solution of **73** (67 mg, 0.15 mmol) in 0.5 mL of Et_2O was added and the mixture was warmed to 0 °C and stirred for 1 h before being quenched with the addition of saturated aqueous NH_4Cl/NH_4OH (pH 8, 10 mL). The mixture was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 5% EtOAc–hexane) to provide **74** as a colorless oil (38 mg, 63%): $[\alpha]^{25}_D$ +19 (*c* 0.83, $CHCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ6.62 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.58 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.32 (dd, 1H, *J* = 11.4, 11.4 Hz), 6.03 (dd, 1H, *J* = 10.8, 10.8 Hz), 5.79 (dd, 1H, *J* = 6.0, 9.6 Hz), 5.67 (dd, 1H, *J* = 2.4, 9.6 Hz), 5.55 (dq, 1H, *J* = 7.2, 15.0 Hz), 5.54 (m, 1H), 4.79 (d, 1H, *J* = 2.4 Hz), 4.72 (q, 1H, *J* = 4.8 Hz), 3.68 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.59–3.51 (m, 2H), 3.47–3.39 (m, 1H), 3.42 (s, 3H), 2.52 (m, 1H), 2.14–2.04 (m, 2H), 1.81 (m, 3H), 1.69 (m, 1H), 1.58 (d, 3H, *J* = 6.6 Hz), 1.49 (m, 2H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.16 (t, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.87 (d, 3H, *J* = 6.6 Hz), 0.74 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (C_6D_6, 150 MHz) δ135.5, 131.7, 130.1, 129.9, 128.6, 127.7, 125.2, 122.7, 99.4, 96.9, 80.7, 73.6, 59.9, 55.4, 37.1, 34.5, 30.6, 29.9, 28.4, 20.9, 18.4, 15.7, 15.2, 15.1, 12.0; IR (film) ν_{max} 2968, 2931, 2851, 1456, 1384, 1339, 1107, 1041, 964 cm^{-1}; ESI-TOF HRMS *m/z* 443.3126 ($C_{26}H_{44}O_4$ + Na^+ requires 443.3132).



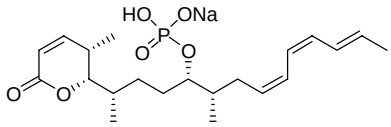
(5*S*,6*S*)-5,6-dihydro-6-[(2*S*,5*S*,6*S*,8*Z*,10*Z*,12*E*)-5-hydroxy-6-methyltetradeca-8,10,12-trien-2-yl]-5-methylpyran-2-one (76). A solution of **74** (29 mg, 0.069 mmol) in 30 mL of acetone at 25 °C was treated with aqueous HCl (2.0 mL of 0.5 M, 1.0 mmol) before being quenched with the addition of saturated aqueous $NaHCO_3$ (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 35%

EtOAc–hexane) to provide **75** as a colorless oil (17 mg, 77%) that was immediately used in the subsequent reaction. A solution of **75** (17 mg, 0.051 mmol) in 7 mL of benzene at 80 °C was treated with 50% Ag_2CO_3–Celite (500 mg, 0.9 mmol) and stirred for 30 min before being cooled and filtered through Celite (EtOAc wash). The filtrate was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 35% EtOAc–hexane) to provide **76** as a colorless oil (13 mg, 76%): $[\alpha]^{25}_D$ +96 (*c* 0.25, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ 7.07 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.57 (dd, 1H, *J* = 10.8, 14.4 Hz), 6.51 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.17 (dd, 1H, *J* = 11.4, 12.0 Hz), 5.97 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.87 (d, 1H, *J* = 9.6 Hz), 5.78 (dq, 1H, *J* = 6.6, 14.4 Hz), 5.53 (m, 1H), 4.03 (dd, 1H, *J* = 3.0, 10.2), 3.42 (m, 3H), 2.52 (m, 1H), 2.44 (d, 2H, *J* = 5.4 Hz), 2.28 (m, 1H), 2.08 (m, 1H), 1.83–1.74 (m, 2H), 1.79 (d, 3H, *J* = 6.6 Hz), 1.57–1.48 (m, 2H), 1.38 (m, 1H), 1.30 (m, 1H), 0.97 (d, 3H, *J* = 7.2 Hz), 0.88 (d, 3H, *J* = 6.6 Hz), 0.86 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ 165.4, 153.8, 132.4, 131.8, 130.1, 127.9, 125.3, 123.2, 120.0, 84.6, 74.8, 40.0, 34.6, 32.0, 31.7, 31.0, 29.7, 18.4, 14.7, 14.1, 11.0; IR (film) ν_{max} 3444, 2974, 2932, 2861, 1716, 1456, 1375, 1254, 1109, 989, 824 cm^{-1}; ESI-TOF HRMS *m/z* 333.2422 ($C_{21}H_{32}O_3$ + H^+ requires 333.2424).



bis[(*9H*-fluoren-9-yl)methyl]-(2*S*,5*S*,6*S*,8*Z*,10*Z*,12*E*)-6-methyl-2-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl]tetradeca-8,10,12-trien-5-yl phosphate (77). A solution of **76** (5.0 mg, 0.015 mmol) and tetrazole (3.2 mg, 0.045 mmol) in 0.34 mL of CH_3CN was treated with a solution of *i*-$Pr_2NP(OFm)_2$[11] (31.4 mg, 0.060 mmol) in 0.44 mL of CH_2Cl_2 and stirred for 30 min before 30% aqueous H_2O_2 (0.085 mL, 0.57 mmol) was added. After 5 min, 2 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 40% EtOAc–hexane) to provide **77** as a colorless oil (7.5 mg, 65%): $[\alpha]^{25}_D$ +70 (*c* 0.70, $CHCl_3$); ^{1}H NMR (CD_3CN, 600 MHz) δ 7.78 (m, 4H), 7.53–7.45 (m, 4H), 7.41–7.34 (m, 4H), 7.31–7.25 (m, 4H), 7.06

(dd, 1H, *J* = 6.6, 9.6 Hz), 6.53 (dd, 1H, *J* = 12.0, 14.4 Hz), 6.44 (dd, 1H, *J* = 10.8, 11.4 Hz), 5.99 (dd, 1H, *J* = 11.4, 11.4 Hz), 5.88 (m, 1H), 5.86 (d, 1H, *J* = 9.6 Hz), 5.76 (dq, 1H, *J* = 6.6, 15.0 Hz), 5.30 (m, 1H), 4.26–4.18 (m, 4H), 4.11 (m, 2H), 3.91 (dd, 1H, *J* = 3.0, 10.2 Hz), 3.87 (m, 1H), 2.47 (m, 1H), 2.05 (m, 1H), 1.78 (d, 3H, *J* = 6.6 Hz), 1.74 (m, 1H), 1.67 (m, 1H), 1.57 (m, 2H), 1.35–1.26 (m, 2H), 1.08 (m, 1H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.74 (d, 3H, *J* = 6.6 Hz), 0.69 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ165.9, 154.4, 145.2, 145.1, 142.9, 132.7, 131.9, 131.1, 129.3, 128.8, 128.7, 128.5, 126.5, 126.2, 123.6, 121.6, 120.7, 85.2, 84.9, 69.6, 61.6, 49.4, 38.7, 35.2, 31.6, 29.3, 19.2, 15.4, 15.1, 11.7; ^{31}P NMR (CD_3CN, 160 MHz) δ –1.41; IR (film) ν_{max} 3039, 2965, 2933, 1716, 1450, 1252, 990, 740 cm^{-1}; ESI-TOF HRMS *m/z* 769.3649 ($C_{49}H_{53}O_6P$ + H^+ requires 769.3652).



11-deshydroxycytostatin (78). A solution of **77** (6.0 mg, 0.0078 mmol) in 1.4 mL of CH_3CN at 0 °C was treated with 0.35 mL of Et_3N and the mixture was allowed to stand at 25 °C for 17 h before 0.50 mL of toluene was added and the solution was concentrated under reduced pressure. The residue was dissolved in 1 mL of H_2O, washed with Et_2O (5 × 1 mL), and the aqueous layer was concentrated under reduced pressure. The residue was dissolved in 0.5 mL of 1:1 MeOH–H_2O and passed through a short column of Dowex-Na^+ (0.8 × 2 cm, 1:1 MeOH–H_2O wash) to provide **78** as a colorless oil (2.7 mg, 79%): $[\alpha]^{25}_D$ +75 (*c* 0.16, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ7.15 (dd, 1H, *J* = 6.6, 9.6 Hz), 6.54 (dd, 1H, *J* = 11.4, 15.0 Hz), 6.48 (dd, 1H, *J* = 11.4, 12.0 Hz), 6.19 (dd, 1H, *J* = 10.8, 12.0 Hz), 5.92 (d, 1H, *J* = 9.6 Hz), 5.91 (m, 1H), 5.71 (dq, 1H, *J* = 6.6, 15.0 Hz), 5.56 (m, 1H), 4.11 (m, 2H), 2.58 (m, 1H), 2.37–2.24 (m, 1H), 1.86–1.74 (m, 4H), 1.79 (d, 3H, *J* = 6.6 Hz), 1.57 (m, 1H), 1.37–1.29 (m, 2H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD, 150 MHz) δ167.5, 155.1, 132.7, 131.1, 130.1, 128.5, 125.5, 123.7, 120.1, 85.7, 80.8, 38.4, 35.5, 31.7, 31.6, 29.4, 18.5, 14.9, 14.5, 11.0; ^{31}P NMR (CD_3OD, 160 MHz) δ 1.80; IR (film) ν_{max} 3417, 2964, 2913, 1713, 1451, 1390, 1256, 1072, 826 cm^{-1}; ESI-TOF HRMS *m/z* 435.1901 ($C_{21}H_{33}O_6P$ + Na^+ requires 435.1907).

Computational Methods. Docking models were generated on a Silicon Graphics Octane2/V6 dual graphics workstation using Insight *II* version 2000 software developed by Molecular Simulations, Inc. of Accelrys, Inc., San Diego, CA. Minimizations and dynamics calculations were performed using the Discover_3 module with the CF991 forcefield. The cytostatin–PP2A model was generated by superimposing cytostatin on the fostriecin–PP2A homology model[13] followed by energy minimization of the cytostatin backbone. Minimization calculations were performed over 20,000 steps using the steepest descents method followed by the conjugate gradients method to reach a final convergence of 0.01 kcal/mol Å. Dynamics simulations were run at an initial temperature of 300, 400, and 600 K with a direct velocity scaling control method over 5000 fs (with a timestep of 1 fs) and each simulation provided 100 structures. The five lowest energy systems from each of the dynamics simulations were re-minimized and the final lowest energy minimum was determined by comparisons of the fifteen final minimized structures.

Supplemental Table 1. ^{1}H NMR comparison for natural cytostatin, **1**, and **42**–**44**.

	δ, ppm (multiplicity, *J*, Hz)				
Position	natural cytostatin	**1**	**42**	**43**	**44**
1	--	--	--	--	--
2	5.93 (d 9.5)	5.93 (d 9.6)	5.92 (d 9.6)	5.91 (d 9.6)	5.92 (d 9.6)
3	7.15 (dd 6.5, 9.5)	7.15 (dd 6.6, 9.6)	7.15 (dd 6.6, 9.6)	7.14 (dd 6.0 9.6)	7.15 (dd 6.6, 9.6)
4	2.58 (ddd 3.0, 6.6, 7.2)	2.58 (ddd 3.0, 6.6, 7.2)	2.58 (m)	2.57 (m)	2.59 (m)
5	4.10 (dd 3.0, 10.0)	4.10 (dd 3.0, 10.2)	4.10 (dd 3.0, 10.2)	4.10 (dd 3.0 10.8)	4.11 (dd 3.0, 10.2)
6	1.79 (m)	1.79 (m)	1.79 (m)	1.79 (m)	1.85 (m)
7	1.25, 1.79 (m)	1.25, 1.79 (m)	1.25, 1.79 (m)	1.39, 1.73 (m)	1.63 (m)
8	1.50, 2.06 (m)	1.50, 2.06 (m)	1.58, 1.91 (m)	1.67, 1.99 (m)	1.51, 2.17 (m)
9	4.52 (m)	4.53 (m)	4.30 (m)	4.12 (m)	4.47 (m)
10	1.53 (m)	1.53 (m)	1.87 (m)	1.86 (m)	1.97 (m)
11	4.60 (dd 9.0, 9.5)	4.59 (dd 9.0, 9.6)	4.83 (dd 1.8, 9.6)	5.11 (dd 1.8, 8.4)	4.37 (dd 9.0, 9.0)
12	5.41 (dd 9.5, 11.0)	5.41 (dd 9.6, 10.8)	5.64 (dd 9.6, 10.2)	5.56 (dd 9.6, 9.6)	5.49 (dd 9.6, 10.8)
13	6.59 (dd 11.0, 11.5)	6.59 (dd 10.2, 11.4)	6.47 (dd 11.4, 11.4)	6.46 (dd 11.4, 12.0)	6.54 (dd 11.4, 11.4)
14	6.26 (dd 10.5, 11.5)	6.25 (dd 11.4, 11.4)	6.21 (dd 11.4, 12.0)	6.21 (dd 11.4, 11.4)	6.19 (dd 10.8, 12.0)
15	5.99 (dd 11.0, 11.5)	6.00 (dd 11.4, 11.4)	6.01 (dd 10.8, 11.4)	5.98 (dd 10.8, 11.4)	6.00 (dd 10.8, 11.4)
16	6.58 (dd 11.5, 14.5)	6.58 (dd 11.4, 14.4)	6.56 (dd 11.4, 15.0)	6.56 (dd 11.4, 14.4)	6.57 (dd 10.8, 14.4)
17	5.76 (dq 7.0, 14.5)	5.76 (dq 6.6, 14.4)	5.76 (dq 7.2, 15.0)	5.75 (dq 6.6, 14.4)	5.76 (dq 6.6, 14.4)
18	1.80 (d 7.0)	1.80 (d 6.6)	1.80 (d 6.6)	1.80 (d 6.6)	1.80 (d 6.6)
19	1.00 (d 7.0)	1.00 (d 6.6)	1.00 (d 7.2)	1.00 (d 7.2)	1.01 (d 7.2)
20	0.97 (d 7.0)	0.97 (d 6.6)	0.96 (d 7.2)	0.94 (d 6.6)	0.95 (d 6.6)
21	0.80 (d 7.0)	0.80 (d 7.2)	1.00 (d 7.2)	0.90 (d 6.6)	0.85 (d 6.6)

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