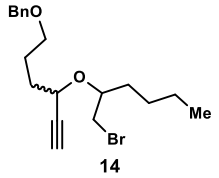
II. Experimental Procedures and Characterization Data

[({4-[(1-Bromohexan-2-yl)oxy]hex-5-yn-1-yl}oxy)methyl]benzene (**14**): To a stirred solution of alkyne

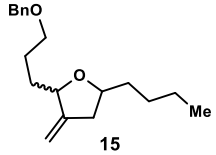


14

13[1] (500 mg, 2.45 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 23 °C was added a $Co_2(CO)_8$ (1.00 g, 2.94 mmol, 1.2 equiv) in one portion. After 20 min, a solution of **11**[2] (887 mg, 4.89 mmol, 2.0 equiv) in CH_2Cl_2 (6 mL) was added. The resulting mixture was cooled to 0 °C, and $BF_3{\cdot}Et_2O$ (604 µL, 4.89 mmol, 2.0 equiv) was added dropwise. After 0.5 h, the reaction mixture was carefully quenched by the addition of saturated aqueous $NaHCO_3$ solution (30 mL), and allowed to warm to 23 °C. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

To a stirred solution of the so-obtained crude residue in acetone (30 mL) was added portion wise diammonium cerium(IV) nitrate (CAN) (6.71 g, 12.2 mmol, 5.0 equiv) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 0.5 h before it was quenched by the addition of water (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 5 → 20% ethyl acetate in hexanes) to afford a mixture of diastereomers **14** (1:1 *dr*, 566 mg, 1.54 mmol, 63% yield overall) as colorless oil. **14**: R_f = 0.40 (SiO_2, hexanes/EtOAc 5:1, *v*/*v*); FT-IR (film) ν_{max} = 3293, 2931, 2859, 1495, 1454, 1361, 1091, 735 cm^{-1}; ^1H NMR (mixture of isomers, 600 MHz, $CDCl_3$) δ = 7.36–7.33 (m, 4 H), 7.31–7.26 (m, 1 H), 4.51 (s, 2 H), 4.26 (dt, *J* = 6.2, 2.8 Hz, 0.53 H), 4.16 (dt, *J* = 6.2, 3.1 Hz, 0.45 H), 3.81 (dq, *J* = 7.5, 4.9 Hz, 0.51 H), 3.73 (tt, *J* = 6.6, 4.9 Hz, 0.46 H), 3.58 (dd, *J* = 10.3, 4.3 Hz, 0.48 H), 3.51 (td, *J* = 5.9, 3.2 Hz, 2 H), 3.46–3.36 (m, 1.6 H), 2.47–2.43 (m, 0.42 H), 2.41 (dd, *J* = 2.1, 0.8 Hz, 0.49 H), 1.88–1.77 (m, 4.0 H), 1.72–1.54 (m, 2.0 H), 1.46–1.23 (m, 4 H), 0.91 (t, *J* = 6.9 Hz, 3 H) ppm; ^{13}C NMR (mixture of isomers, 151 MHz, $CDCl_3$) δ = 138.7, 138.6, 128.5, 127.8, 127.7, 127.67, 127.65, 83.4, 83.0, 78.0, 76.2, 74.0, 73.9, 73.0, 70.0, 69.9, 68.8, 67.7, 35.4, 34.9, 33.5, 33.0, 32.9, 32.3, 27.4, 27.1, 25.63, 25.62, 22.8, 22.7, 14.14, 14.12 ppm; HRMS (ESI-TOF) calcd for $C_{19}H_{27}BrO_2Na^+$ $[M+Na]^+$ 389.1087; Found 389.1089.

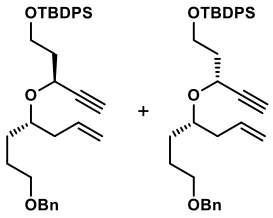
2-[3-(Benzyloxy)propyl]-5-butyl-3-methylidenetetrahydrofuran (15): To a stirred solution of bromide **14** (0.10 g, 0.27 mmol, 1.0 equiv) in toluene (20 mL) was added *n*-Bu_3SnH (0.11 mL, 0.41 mmol, 1.5 equiv) followed by AIBN (4.5 mg, 0.027 mmol, 0.1 equiv) in one portion, and the resulting mixture was heated to 90 °C. After 0.5 h, the reaction mixture was allowed to cool to 23 °C and the solvent was removed under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 2 → 10% EtOAc in hexanes) to afford a mixture of diastereomers of tetrahydrofuran derivative **15** (3:2 *dr*, 64 mg, 0.22 mmol, 82% yield) as a colorless foam.



15

15: R_f = 0.20 (SiO_2, hexanes/EtOAc 20:1, *v*/*v*); FT-IR (film) ν_{max} = 3030, 2929, 2857, 1496, 1454, 1361, 1204, 1098, 883, 734 cm^{-1}; ^1H NMR (mixture of isomers, 600 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 4.4 Hz, 4 H), 7.29–7.26 (m, 1 H), 4.97 (q, *J* = 2.2 Hz, 0.6 H), 4.94 (td, *J* = 2.5, 1.6 Hz, 0.4 H), 4.84 (q, *J* = 2.2 Hz, 0.6 H), 4.81 (dt, *J* = 3.4, 1.9 Hz, 0.4 H), 4.51 (s, 2 H), 4.39 (dq, *J* = 6.2, 2.2 Hz, 0.6 H), 4.30–4.24 (m, 0.4 H), 3.98 (p, *J* = 6.6 Hz, 0.6 H), 3.80 (dtd, *J* = 9.9, 6.4, 5.5 Hz, 0.4 H), 3.56–3.47 (m, 2 H), 2.65 (ddq, *J* = 15.5, 6.1, 2.0 Hz, 0.6 H), 2.59 (ddq, *J* = 15.4, 5.4, 1.5 Hz, 0.4 H), 2.24 (ddtd, *J* = 15.5, 7.0, 2.4, 0.9 Hz, 0.6 H), 2.16 (ddq, *J* = 15.2, 10.0, 2.6 Hz, 0.4 H), 1.85–1.64 (m, 3.6 H), 1.62–1.54 (m, 1.4 H), 1.54–1.44 (m, 0.4 H), 1.45–1.37 (m, 1 H), 1.37–1.23 (m, 3.6 H), 0.90 (td, *J* = 7.1, 2.1 Hz, 3 H) ppm; ^{13}C NMR (mixture of isomers, 151 MHz, $CDCl_3$) δ = 152.3, 152.1, 138.8, 138.8, 128.5, 127.8, 127.60, 127.59, 104.7, 104.2, 80.5, 79.6, 78.5, 77.4, 73.0, 72.9, 70.6, 70.5, 39.7, 39.0, 35.3, 35.1, 32.1, 31.9, 28.3, 28.3, 26.0, 25.6, 23.0, 22.9, 14.21, 14.19 ppm; HRMS (ESI-TOF) calcd for $C_{19}H_{28}O_2Na^+$ $[M+Na]^+$ 311.1982; Found 311.1981.

(6*S*,8*S*)-8-Ethynyl-13,13-dimethyl-1,12,12-triphenyl-6-(prop-2-en-1-yl)-2,7,11-trioxa-12-silatetradecane (18a) and (6*S*,8*R*)-8-ethynyl-13,13-dimethyl-1,12,12-triphenyl-6-(prop-2-en-1-yl)-2,7,11-trioxa-12-silatetradecane (18b): To a stirred solution of alkyne **17**[3] (3.00 g, 8.86 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 25 °C was added $Co_2(CO)_8$ (3.63 g, 10.6 mmol, 1.2 equiv) in one portion. After 20 min, a solution of olefin **16**[4] (3.90 g, 17.7 mmol, 2.0 equiv) in CH_2Cl_2 (8 mL) was added. The reaction mixture was cooled to 0 °C, and $BF_3{\cdot}Et_2O$ (2.19 mL, 17.7 mmol, 2.0 equiv) was added dropwise. After 0.5 h, the reaction mixture was carefully quenched by the addition of saturated aqueous



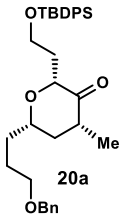
18a 18b

$NaHCO_3$ solution (50 mL), and allowed to warm to 23 °C. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

To a stirred solution of the so-obtained crude residue in acetone (30 mL) was added portion wise diammonium cerium(IV) nitrate (CAN) (24.3 g, 44.3 mmol, 5.0 equiv) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 1 h before it was quenched by the addition of water (60 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 1 → 5% ethyl acetate in hexanes) to afford *cis*-isomer **18b** (2.01 g, 3.72 mmol, 42% yield overall) and *trans*-isomer **18a** (1.68 g, 3.10 mmol, 35% yield overall) as colorless oils. **18b** (*cis*-isomer): R_f = 0.50 (SiO_2, hexanes/EtOAc 20:1, *v*/*v*); $[\alpha]_D^{23}$ = +6.65 (*c* = 2.0, CH_2Cl_2); FT-IR (film) ν_{max} = 3289, 2999, 2857, 2150, 1472, 1427, 1173, 1093, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.67 (dt, *J* = 8.0, 1.6 Hz, 4 H), 7.41 (tdd, *J* = 6.1, 3.8, 2.2 Hz, 2 H), 7.37–7.32 (m, 4 H), 7.33 (d, *J* = 6.3 Hz, 4 H), 7.28 (td, *J* = 6.0, 2.6 Hz, 1 H), 5.87 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1 H), 5.14–5.00 (m, 2 H), 4.48 (d, *J* = 2.6 Hz, 2 H), 4.45–4.41 (m, 1 H), 3.88–3.74 (m, 2 H), 3.66 (p, *J* = 5.8 Hz, 1 H), 3.44 (td, *J* = 6.4, 2.2 Hz, 2 H), 2.44–2.30 (m, 3 H), 2.00 (dtd, *J* = 13.4, 7.0, 5.2 Hz, 1 H), 1.90 (dtd, *J* = 13.2, 6.7, 5.4 Hz, 1 H), 1.70 (ddt, *J* = 11.9, 8.1, 6.1 Hz, 1 H), 1.65–1.52 (m, 3 H), 1.05 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.7, 135.70, 135.66, 135.2, 133.9, 133.8, 129.8, 128.5, 127.79, 127.77, 127.75, 127.6, 116.9, 84.1, 78.0, 73.2, 73.0, 70.6, 64.8, 60.0, 39.4, 39.1, 30.0, 27.0, 25.5, 19.3 ppm; HRMS (ESI-TOF) calcd for $C_{35}H_{44}O_3SiNa^+$ $[M+Na]^+$ 563.2952; Found 563.2957. **18a** (*trans*-isomer): R_f = 0.48 (SiO_2, hexanes/EtOAc 20:1, *v*/*v*); $[\alpha]_D^{23}$ = −26.6 (*c* = 1.5, CH_2Cl_2); FT-IR (film) ν_{max} = 3303, 3030, 2857, 2188, 1640, 1589, 1428, 1361, 1104, 1089, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.69–7.64 (m, 4 H), 7.45–7.40 (m, 2 H), 7.40–7.36 (m, 4 H), 7.34 (d, *J* = 4.4 Hz, 4 H), 7.30–7.26 (m, 1 H), 5.80 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1 H), 5.13–4.97 (m, 2 H), 4.52–4.46 (m, 3 H), 3.85–3.76 (m, 2 H), 3.69 (ddt, *J* = 8.6, 6.4, 4.6 Hz, 1 H), 3.55–3.42 (m, 2 H), 2.31 (d, *J* = 2.0 Hz, 1 H), 2.30–2.23 (m, 2 H), 1.98 (dddd, *J* = 13.7, 7.6, 6.3, 5.0 Hz, 1 H), 1.90 (dddd, *J* = 13.4, 7.0, 6.1, 5.3 Hz, 1 H), 1.80 (dddd, *J* = 13.1, 9.7, 6.6, 5.0 Hz, 1 H), 1.73–1.59 (m, 2 H), 1.55–1.47 (m, 1 H), 1.05 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.9, 135.7, 135.6, 134.7, 133.9, 133.8, 129.7, 128.5, 127.8, 127.7, 127.5,

117.4, 84.0, 76.8, 73.1, 72.9, 70.5, 64.2, 60.0, 39.3, 38.1, 31.0, 27.0, 25.9, 19.3 ppm; HRMS (ESI-TOF) calcd for $C_{35}H_{44}O_3SiNa^+$ $[M+Na]^+$ 563.2952; Found 563.2952.

(2*R*,4*R*,6*S*)-6-[3-(Benzyloxy)propyl]-2-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-4-methyldihydro-2*H*-pyran-3(4*H*)-one (20a): To a stirred solution of a mixture of alkynes **18b** and **18a** [2.00 g (**18b**:**18a** = 1.2:1), 3.70 mmol, 1.0 equiv] in Et_2O (600 mL) at −78 °C was added Ti(O*i*-Pr)$_4$ (1.64 g, 5.55 mmol, 1.5 equiv), followed by diisoproyl magnesium chloride (2 M solution in THF, 5.55 mL, 11.1 mmol, 3.0 equiv). After 5 min of stirring, the reaction mixture was allowed to warm to 0 °C over 1 h and then quenched by the addition of 0.5 M aqueous HCl (100 mL). The layers were separated, the aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was passed through pad of silica gel to obtain a mixture of compounds **19a–c** (1.80 g, 3.33 mmol, 90% yield) that was used for the next step without further purification.

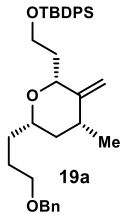


A stirred solution of the crude residue obtained above in CH_2Cl_2 (80 mL) was cooled to −78 °C. Freshly generated ozone was bubbled through this solution until the color of the mixture changed to light blue (ca. 15 min). The reaction mixture was quenched by the addition of dimethyl sulfide (2.72 mL, 37.0 mmol, 10.0 equiv), and allowed to warm to 23 °C. After stirring for 10 h, the solvent was removed under reduced pressure, and the obtained residue was purified by flash column chromatography (SiO_2, 5 → 20% ethyl acetate in hexanes) to afford a mixture of three diastereomers **20** (1.57 g, 2.89 mmol, 87% yield overall) as a colorless oil. The mixture of diastereomers was subjected to isomerization under basic conditions without further purification.

To a stirred solution of the above mixture of diastereomers **20** (1.50 g, 2.75 mmol, 1.0 equiv) in MeOH (30 mL) was added K_2CO_3 (571 mg, 4.13 mmol, 1.5 equiv) and the resulting mixture was heated to 70 °C. After 4 h, the reaction mixture was allowed to cool to 23 °C and quenched by the addition of saturated aqueous NH_4Cl solution (40 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 5 → 20% ethyl acetate

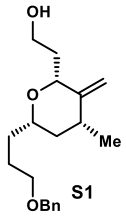
in hexanes) to afford the required isomer **20a** (899 mg, 1.65 mmol, 60% yield) as a colorless oil. **20a**: R_f = 0.45 (SiO_2, hexanes/Et_2O 5:1, *v*/*v*); $[\alpha]_D^{23}$ = +4.75 (*c* = 2.8, CH_2Cl_2); FT-IR (film) ν_{max} = 3070, 2957, 2856, 1721, 1472, 1427, 1361, 1260, 1107, 1091, 822, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.75–7.73 (m, 1 H), 7.69–7.64 (m, 4 H), 7.46–7.34 (m, 9 H), 7.32–7.28 (m, 1 H), 4.51 (AB quart, *J* = 11.2 Hz, 2 H), 4.14–4.04 (m, 1 H), 3.85 (tdd, *J* = 9.3, 4.7, 1.5 Hz, 1 H), 3.82–3.75 (m, 2 H), 3.56–3.43 (m, 2 H), 2.55 (dp, *J* = 12.9, 6.5 Hz, 1 H), 2.27–2.20 (m, 1 H), 2.19–2.15 (m, 1 H), 1.79 (ddt, *J* = 12.6, 9.8, 5.9 Hz, 1 H), 1.73–1.65 (m, 2 H), 1.64–1.52 (m, 3 H), 1.09 (d, *J* = 6.5 Hz, 3 H), 1.06 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 209.6, 138.7, 135.6, 135.3, 134.9, 129.7, 128.5, 127.8, 127.78, 127.75, 78.4, 76.8, 73.0, 70.2, 59.9, 42.8, 42.6, 32.24, 32.17, 27.0, 26.7, 19.4, 14.5 ppm; HRMS (ESI-TOF) calcd for $C_{34}H_{44}O_4SiNa^+$ $[M+Na]^+$ 567.2901; Found 567.2900.

(2-{(2*R*,4*R*,6*S*)-6-[3-(Benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}ethoxy)-(*tert*-butyl)diphenylsilane (19a): To a stirred solution of methyl triphenyl phosphonium bromide (2.62 g, 7.34 mmol, 5.0 equiv) in THF (40 mL) at −78 °C was added dropwise *n*-butyl lithium (1.6 M in hexanes, 4.13 mL, 6.62 mmol, 4.5 equiv), and the reaction mixture was warmed to 0 °C. After 0.5 h, a solution of ketone **20a** (800 mg, 1.47 mmol, 1.0 equiv) in THF (15 mL) was added to the preformed ylide solution and the resulting mixture was allowed to warm to 23 °C. After 1 h, the reaction mixture was carefully quenched by the addition of saturated aqueous NH_4Cl solution (80 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 2 → 10% EtOAc in hexanes) to afford pure olefin **19a** (734 mg, 1.35 mmol, 92% yield) as a colorless foam. **19a**: R_f = 0.55 (SiO_2, hexanes/EtOAc 5:1, *v*/*v*); $[\alpha]_D^{23}$ = +6.60 (*c* = 2.0, CH_2Cl_2); FT-IR (film) ν_{max} = 2956, 2929, 2855, 1649, 1472, 1361, 1261, 1105, 1084, 822, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.72–7.65 (m, 4 H), 7.43–7.35 (m, 6 H), 7.35–7.32 (m, 4 H), 7.28 (tt, *J* = 6.9, 2.4 Hz, 1 H), 4.85 (d, *J* = 1.8 Hz, 1 H), 4.79 (d, *J* = 1.8 Hz, 1 H), 4.48 (AB quart, *J* = 11.5 Hz, 2 H), 3.96–3.89 (m, 2 H), 3.83 (ddd, *J* = 10.1, 6.5, 4.0 Hz, 1 H), 3.55–3.40 (m, 3 H), 2.28 (dqd, *J* = 12.2, 6.2, 3.1 Hz, 1 H), 2.13–2.04 (m, 1 H), 1.89–1.68 (m, 3 H), 1.67–1.59 (m, 1 H), 1.55–1.48 (m, 2 H), 1.10–1.08 (m,



4 H), 1.06 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.9, 138.8, 135.7, 135.6, 134.2, 129.6, 128.4, 127.8, 127.7, 127.6, 104.3, 77.4, 74.9, 72.9, 70.5, 60.8, 43.4, 36.0, 34.7, 32.8, 27.0, 26.2, 19.4, 18.2 ppm; HRMS (ESI-TOF) calcd for $C_{35}H_{46}O_3SiNa^+$ $[M+Na]^+$ 565.3108; Found 565.3111.

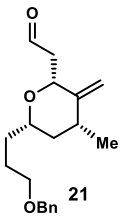
2-{(2*R*,4*R*,6*S*)-6-[3-(Benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}ethanol (S1): To a stirred solution of olefin derivative **19a** (500 mg, 0.921 mmol, 1.0 equiv) in THF (20 mL) at 0 °C



S1

was added dropwise tetra-*n*-butylammonium fluoride (1 M in THF, 0.920 mL, 0.920 mmol, 1.0 equiv), and the reaction mixture was allowed to warm to 23 °C. After 2.5 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 10 → 40% EtOAc in hexanes) to afford pure alcohol **S1** (264 mg, 0.866 mmol, 94% yield) as a colorless oil. **S1**: R_f = 0.40 (SiO_2, hexanes/EtOAc 3:2, *v*/*v*); $[\alpha]_D^{23}$ = +8.10 (*c* = 2.0, CH_2Cl_2); FT-IR (film) ν_{max} = 3431, 2954, 2850, 1650, 1454, 1364, 1312, 1091, 1058, 903, 736 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.36–7.32 (m, 4 H), 7.30–7.26 (m, 1 H), 4.87 (d, *J* = 1.6 Hz, 1 H), 4.82 (d, *J* = 1.6 Hz, 1 H), 4.49 (s, 2 H), 3.95–3.89 (m, 1 H), 3.84 (dd, *J* = 6.0, 4.9 Hz, 2 H), 3.66–3.57 (m, 1 H), 3.53–3.41 (m, 2 H), 2.31–2.23 (m, 1 H), 2.02–1.91 (m, 2 H), 1.81–1.61 (m, 3 H), 1.56 (td, *J* = 7.6, 6.1 Hz, 2 H), 1.13–1.06 (m, 4 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 150.9, 138.7, 128.5, 127.8, 127.6, 105.0, 79.4, 77.7, 73.0, 70.3, 61.8, 42.6, 35.6, 33.5, 32.8, 26.1, 18.1 ppm; HRMS (ESI-TOF) calcd for $C_{19}H_{28}O_3Na^+$ $[M+Na]^+$ 327.1931; Found 327.1930.

{(2*R*,4*R*,6*S*)-6-[3-(Benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}acetaldehyde (21): To a stirred solution of alcohol **S1** (200 mg, 0.657 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at

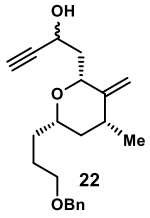


21

23 °C was added DMP (418 mg, 0.985 mmol, 1.5 equiv) portion wise. After 0.5 h, the reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (20 mL) and the obtained suspension was further stirred for 2 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$

solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 10→30% EtOAc in hexanes) to afford pure aldehyde **21** (179 mg, 0.591 mmol, 90% yield) as a colorless foam. **21**: R_f = 0.80 (SiO_2, hexanes/EtOAc 3:2, *v*/*v*); $[\alpha]_D^{23}$ = +17.0 (*c* = 2.0, CH_2Cl_2); FT-IR (film) ν_{max} = 3004, 2848, 2725, 1725, 1650, 1454, 1363, 1087, 1028, 904, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 9.81 (dd, *J* = 2.7, 2.0 Hz, 1 H), 7.36–7.32 (m, 4 H), 7.30–7.26 (m, 1 H), 4.84 (dd, *J* = 1.9, 0.6 Hz, 1 H), 4.75 (d, *J* = 1.9 Hz, 1 H), 4.49 (s, 2 H), 4.29–4.22 (m, 1 H), 3.62–3.54 (m, 1 H), 3.47 (ddt, *J* = 26.7, 9.3, 6.5 Hz, 2 H), 2.79–2.65 (m, 2 H), 2.36–2.28 (m, 1 H), 1.84–1.68 (m, 2 H), 1.67–1.59 (m, 1 H), 1.57–1.47 (m, 2 H), 1.14–1.07 (m, 4 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 201.9, 150.2, 138.7, 128.4, 127.8, 127.6, 105.4, 77.7, 74.4, 72.9, 70.3, 45.7, 42.6, 35.6, 32.5, 26.0, 18.0 ppm; HRMS (ESI-TOF) calcd for $C_{19}H_{26}O_3Na^+$ $[M+Na]^+$ 325.1774; Found 325.1771.

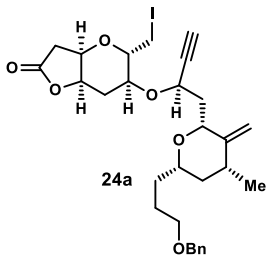
1-{(2*R*,4*R*,6*S*)-6-[3-(Benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}but-3-yn-2-ol (22): To a stirred solution of aldehyde **21** (600 mg, 1.98 mmol, 1.0 equiv) in THF (15 mL) at −78 °C

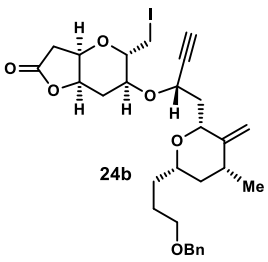


was added ethynylmagnesium bromide (0.5 M in THF, 9.92 mL, 4.96 mmol, 2.5 equiv), and the reaction mixture was warmed to −10 °C. After 15 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 5→20% EtOAc in hexanes) to afford alcohol **22** (mixture of diastereomers, 1.5:1 *dr*, 520 mg, 1.58 mmol, 80% yield) as a colorless foam. **22**: R_f = 0.35 (SiO_2, hexanes/EtOAc 5:1, *v*/*v*); $[\alpha]_D^{23}$ = +21.3 (*c* = 3.0, CH_2Cl_2); FT-IR (film) ν_{max} = 3415, 3297, 2956, 2850, 1650, 1454, 1365, 1312, 1206, 1089, 1062, 903, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.36–7.31 (m, 4 H), 7.29–7.26 (m, 1 H), 4.87 (d, *J* = 1.5 Hz, 0.6 H), 4.84 (d, *J* = 1.6 Hz, 0.4 H), 4.83 (d, *J* = 1.6 Hz, 1 H), 4.67 (tdt, *J* = 7.3, 5.2, 2.4 Hz, 1 H), 4.51–4.47 (m, 2 H), 4.34–4.28 (m, 0.4 H), 3.98–3.93 (m, 0.6 H), 3.66 (dddd, *J* = 11.2, 7.3, 5.5, 2.1 Hz, 0.4 H), 3.62–3.57 (m, 0.6 H), 3.54–3.43 (m, 2 H), 2.46 (d, *J* = 2.1 Hz, 1 H), 2.45 (d, *J* = 2.1 Hz, 1 H), 2.35–2.23 (m, 1 H), 2.21–2.09 (m, 1.6 H), 2.05 (ddd, *J* = 14.4, 5.9, 2.7 Hz, 0.4 H), 1.83–1.61 (m, 3 H), 1.59–1.50 (m, 2 H), 1.15–1.08 (m, 4 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 150.5, 150.3, 138.7, 138.6,

128.5, 127.8, 127.7, 127.6, 127.5, 105.3, 105.1, 84.8, 84.6, 78.5, 77.8, 77.7, 76.7, 73.0, 72.9, 72.6, 70.2, 70.1, 62.0, 60.9, 42.5, 39.2, 37.3, 35.6, 35.5, 32.7, 32.6, 26.1, 26.0, 18.1, 18.0 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{28}O_3Na^+$ $[M+Na]^+$ 351.1931; Found 351.1935.

(3a*R*,5*S*,6*S*,7a*R*)-6-{[(2*R*)-1-{(2*R*,4*R*,6*S*)-6-[3-(Benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}but-3-yn-2-yl]oxy}-5-(iodomethyl)hexahydro-2*H*-furo[3,2-*b*]pyran-2-one (24a) and (3a*R*,5*S*,6*S*,7a*R*)-6-{[(2*S*)-1-{(2*R*,4*R*,6*S*)-6-[3-(benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}but-3-yn-2-yl]oxy}-5-(iodomethyl)hexahydro-2*H*-furo[3,2-*b*]pyran-2-one (24b):



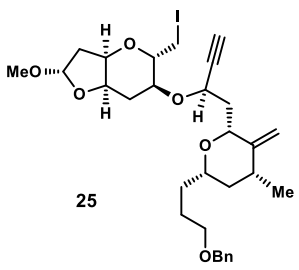


To a stirred solution of alkyne **22** (200 mg, 0.609 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 23 °C was added $Co_2(CO)_8$ (250 mg, 0.731 mmol, 1.2 equiv) in one portion. After 20 min, a solution of iodide **23**[5] (363 mg, 1.22 mmol, 2.0 equiv) in CH_2Cl_2 (8 mL) was added. The reaction mixture was cooled to 0 °C, and $BF_3{\cdot}Et_2O$ (151 µL, 1.22 mmol, 2.0 equiv) was added dropwise. After 0.5 h, the reaction mixture was carefully quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL), and allowed to warm to 23 °C. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

To a stirred solution of the so-obtained crude residue in acetone (20 mL) was added portion wise diammonium cerium(IV) nitrate (CAN) (1.67 g, 3.04 mmol, 5.0 equiv) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 1 h before it was quenched by the addition of water (60 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 10 → 40% ethyl acetate in hexanes) to afford pure *cis*-isomer **24a** (185 mg, 0.304 mmol, 50% yield overall) and *trans*-isomer **2b** (59.0 mg, 0.097 mmol, 16% yield overall) as colorless oils (3:1 *dr*). **24a** (*cis*-isomer): R_f = 0.50 (SiO_2, 40% EtOAc in hexanes); $[\alpha]_D^{23}$ = +108.3 (*c* = 0.6, CH_2Cl_2); FT-IR (film) ν_{max} = 3283, 3030, 2929, 2854, 1781, 1454, 1365, 1095, 1050, 904, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.36–7.31 (m, 4H), 7.30–7.26 (m, 1H), 4.80 (d, *J* = 1.5 Hz, 1H), 4.77 (d,

J = 1.5 Hz, 1 H), 4.56–4.45 (m, 5 H), 3.97 (dt, J = 11.0, 1.6 Hz, 1 H), 3.83 (dt, J = 6.4, 4.8 Hz, 1 H), 3.74 (dddd, J = 11.2, 7.4, 5.3, 2.1 Hz, 1 H), 3.59 (ddd, J = 7.7, 6.3, 3.9 Hz, 1 H), 3.53–3.43 (m, 3 H), 3.28 (dd, J = 10.8, 7.8 Hz, 1 H), 2.76 (dd, J = 18.5, 6.3 Hz, 1 H), 2.67 (dd, J = 18.4, 1.6 Hz, 1 H), 2.42 (d, J = 2.0 Hz, 1 H), 2.39–2.30 (m, 1 H), 2.21–2.10 (m, 2 H), 2.06 (dt, J = 14.9, 4.9 Hz, 1 H), 1.96 (ddd, J = 14.2, 11.1, 2.2 Hz, 1 H), 1.86–1.74 (m, 2 H), 1.73–1.65 (m, 1 H), 1.59–1.49 (m, 2 H), 1.08–1.01 (m, 4 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.0, 151.5, 138.8, 128.5, 127.8, 127.7, 104.2, 83.4, 76.7, 76.0, 74.5, 73.5, 73.1, 72.9, 70.6, 69.4, 63.3, 53.6, 43.3, 38.3, 35.7, 35.6, 32.8, 26.6, 26.4, 18.1, 5.5 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{37}O_6INa^+$ $[M+Na]^+$ 631.1527; Found 631.1528. **24b** (*trans*-isomer): R_f = 0.4 (SiO_2, hexanes/EtOAc 3:2, *v*/*v*); $[\alpha]_D^{23}$ = +22.6 (*c* = 0.50, CH_2Cl_2); FT-IR (film) ν_{max} = 3285, 2929, 2852, 1781, 1454, 1364, 1194, 1092, 1049, 904, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.36–7.31 (m, 4 H), 7.30–7.27 (m, 1 H), 4.85 (brs, 1 H), 4.81 (d, J = 1.9 Hz, 1 H), 4.63–4.55 (m, 2 H), 4.51 (AB quart, J = 11.5 Hz, 2 H), 4.46 (ddd, J = 10.3, 4.9, 2.1 Hz, 1 H), 3.90 (dd, J = 10.6, 3.0 Hz, 1 H), 3.73–3.64 (m, 1 H), 3.56 (td, J = 6.7, 4.0 Hz, 1 H), 3.49 (dddd, J = 15.8, 13.2, 9.0, 6.5 Hz, 3 H), 3.36 (dd, J = 10.9, 4.0 Hz, 1 H), 3.30 (dd, J = 10.9, 6.7 Hz, 1 H), 2.79–2.63 (m, 2 H), 2.56 (ddd, J = 14.4, 6.1, 4.7 Hz, 1 H), 2.48 (d, J = 2.0 Hz, 1 H), 2.35–2.23 (m, 1 H), 2.19–2.09 (m, 2 H), 2.04 (ddd, J = 13.2, 10.3, 3.1 Hz, 1 H), 1.79 (dddd, J = 17.2, 9.2, 6.8, 4.3 Hz, 2 H), 1.71–1.61 (m, 1 H), 1.55–1.48 (m, 2 H), 1.11–1.05 (m, 4 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.7, 150.7, 138.7, 128.5, 127.8, 127.7, 104.8, 82.8, 77.5, 76.2, 75.2, 74.9, 74.0, 73.1, 73.0, 70.4, 69.2, 67.9, 43.2, 37.9, 35.8, 34.7, 32.5, 30.3, 26.2, 18.1, 6.0 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{37}O_6INa^+$ $[M+Na]^+$ 631.1527; Found 631.1528.

Methyl 3,7-anhydro-6-*O*-[(2*R*)-1-{(2*R*,4*R*,6*S*)-6-[3-(benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}but-3-yn-2-yl]-2,5,8-trideoxy-8-iodo-α-D-*altro*-octofuranoside (25): To a stirred solution of lactone **24b** (200 mg, 0.329 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise DIBAL-H (1.0 M in toluene, 395 µL, 0.395 mmol, 1.2 equiv). The resulting mixture was warmed to −20 °C and stirred for 1 h before it was diluted with ethyl acetate (20 mL) and quenched by the addition of saturated aqueous solution of Rochelle salt solution (40 mL), allowed to

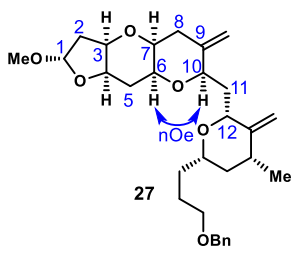


25

warm to 23 °C, and stirred for 2 h until the reaction mixture became a clear solution. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

The so-obtained crude residue was dissolved in MeOH (8 mL) and *p*-TsOH·H_2O (11.2 mg, 0.0658 mmol, 0.2 equiv) was added at 23 °C. After 0.5 h, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (6 mL) and diluted with water (6 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, 5 → 20% EtOAc in hexanes) to afford pure acetal **25** (154 mg, 0.247 mmol, 75% yield overall) as a colorless oil. **25**: R_f = 0.60 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +86.2 (*c* = 1.5, CH_2Cl_2); FT-IR (film) ν_{max} = 3286, 2927, 2853, 1454, 1366, 1211, 1114, 1093, 1057, 904, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.36–7.31 (m, 4 H), 7.30–7.27 (m, 1 H), 5.13 (dd, *J* = 4.3, 3.1 Hz, 1 H), 4.83 (d, *J* = 1.8 Hz, 1 H), 4.79 (d, *J* = 1.8 Hz, 1 H), 4.50 (s, 2 H), 4.48 (q, *J* = 5.2 Hz, 1 H), 4.44 (dt, *J* = 11.0, 2.2 Hz, 1 H), 4.13 (q, *J* = 4.5 Hz, 1 H), 4.02–3.96 (m, 1 H), 3.71–3.60 (m, 2 H), 3.55–3.42 (m, 4 H), 3.29 (s, 3 H), 3.22 (dd, *J* = 10.5, 8.1 Hz, 1 H), 2.39 (d, *J* = 2.0 Hz, 1 H), 2.30–2.21 (m, 3 H), 2.14 (ddd, *J* = 14.1, 11.1, 2.1 Hz, 1 H), 2.06–1.90 (m, 3 H), 1.87–1.79 (m, 1 H), 1.77 (ddd, *J* = 12.8, 4.6, 2.1 Hz, 1 H), 1.68 (ddq, *J* = 12.8, 9.5, 6.7 Hz, 1 H), 1.55 (ddd, *J* = 8.8, 7.3, 4.3 Hz, 2 H), 1.11–1.05 (m, 4 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.1, 138.6, 128.5, 127.7, 127.6, 104.5, 104.1, 83.8, 74.4, 73.2, 73.1, 73.0, 72.9, 72.6, 63.1, 54.9, 43.3, 40.0, 38.3, 35.9, 33.0, 27.3, 26.4, 18.1, 7.9 ppm; HRMS (ESI-TOF) calcd for $C_{30}H_{41}O_6INa^+$ $[M+Na]^+$ 647.1840; Found 647.1842.

(2*S*,3a*R*,4a*S*,7*R*,8a*S*,9a*R*)-7-({(2*R*,4*R*,6*S*)-6-[3-(Benzyloxy)propyl]-4-methyl-3-methylidenetetrahydro-2*H*-pyran-2-yl}methyl)-2-methoxy-6-methylidenedecahydrofuro[3,2-*b*]pyrano[2,3-*e*]pyran (27):



To a stirred solution of **25** (108 mg, 0.173 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was added KO*t*-Bu (38.8 mg, 0.346 mmol, 2.0 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 10 min before it was diluted with hexanes (30 mL) and EtOAc (15 mL) and filtered through a pad of SiO_2. The filtrate was concentrated under reduced pressure to give crude

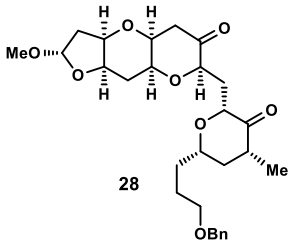
exocyclic olefin **26** (90.2 mg, 0.173 mmol, quantitative yield), which was used in the next step without further purification.

To a stirred solution of the obtained exocyclic olefin **26** (90.2 mg, 0.173 mmol, 1.0 equiv) in toluene (10 mL) at 23 °C were added *n*-Bu_3SnH (100 µL, 0.346 mmol, 2.0 equiv) and AIBN (14.2 mg, 0.0865 mmol, 0.5 equiv). The resulting mixture was transferred and submerged into a preheated oil bath (90 °C) and stirred for 2 h before it was allowed to cool to 23 °C. The resulting mixture was concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 20:1, *v*/*v* → 2:1, *v*/*v*) of the residue afforded the corresponding organotin intermediate (80.1 mg, 0.102 mmol, 58% yield) as a colorless oil.

To a stirred solution of the residue obtained above (mixture of isomers, 80.1 mg, 0.102 mmol, 1.0 equiv) in MeOH (4 mL) at 23 °C was added *p*-TsOH·H_2O (17.5 mg, 0.102 mmol, 1.0 equiv). The resulting mixture was stirred for 45 min and then diluted with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, 5 → 20% EtOAc in hexanes) of the residue afforded **27** (40.7 mg, 0.0816 mmol, 80% yield) as a colorless oil. NOE studies indicate the *cis*-relation between H6 and H10. **27**: R_f = 0.20 (SiO_2, hexanes/EtOAc 5:1, *v*/*v*); $[\alpha]_D^{23}$ = +67.8 (*c* = 2.0, CH_2Cl_2); FT-IR (film) ν_{max} = 2953, 2850, 1651, 1454, 1364, 1194, 1094, 1028, 897, 697 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 7.33 (dd, *J* = 7.4, 1.5 Hz, 2 H), 7.19 (td, *J* = 7.6, 1.8 Hz, 2 H), 7.11 (td, *J* = 7.2, 1.4 Hz, 1 H), 5.02 (dd, *J* = 5.7, 2.8 Hz, 1 H), 4.87 (brs, 1 H), 4.84 (brs, 1 H), 4.82 (brs, 1 H), 4.73 (d, *J* = 1.9 Hz, 1 H), 4.37 (s, 2 H), 4.34 (d, *J* = 10.5 Hz, 1 H), 4.28–4.23 (m, 1 H), 3.73 (dt, *J* = 5.4, 3.3 Hz, 1 H), 3.66 (ddd, *J* = 5.7, 3.2, 1.8 Hz, 1 H), 3.40 (dddd, *J* = 15.4, 9.0, 6.4, 2.8 Hz, 3 H), 3.31 (ddd, *J* = 5.5, 3.6, 2.1 Hz, 1 H), 3.15 (s, 3 H), 2.95 (td, *J* = 4.4, 2.0 Hz, 1 H), 2.54 (dd, *J* = 14.0, 4.1 Hz, 1 H), 2.36 (dt, *J* = 15.0, 3.6 Hz, 1 H), 2.31–2.23 (m, 3 H), 2.13 (ddd, *J* = 13.5, 10.7, 2.4 Hz, 1 H), 2.06 (ddd, *J* = 14.1, 6.1, 2.8 Hz, 1 H), 1.99 (ddt, *J* = 12.6, 6.3, 3.3 Hz, 1 H), 1.90 (dddd, *J* = 15.9, 8.5, 4.6, 1.7 Hz, 1 H), 1.77 (dtd, *J* = 13.3, 6.6, 3.0 Hz, 1 H), 1.69 (dt, *J* = 14.9, 5.4 Hz, 1 H), 1.61 (dtt, *J* = 13.9, 9.2, 4.0 Hz, 1 H), 1.49 (dddd, *J* = 13.7, 10.1, 6.3, 4.2 Hz, 1 H), 1.40 (ddd, *J* = 12.5, 4.6, 2.1 Hz, 1 H), 1.05–0.99 (m, 1 H), 0.96 (d, *J* = 6.5 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 152.6, 144.8, 139.5, 128.6, 128.4, 127.7, 108.9, 104.7,

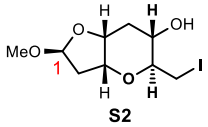
104.0, 77.1, 77.0, 74.9, 74.4, 73.4, 73.0, 72.3, 70.8, 70.6, 55.1, 43.4, 41.4, 38.3, 36.0, 35.2, 33.0, 30.6, 26.7, 18.2 ppm; HRMS (ESI-TOF) calcd for $C_{30}H_{42}O_6Na^+$ $[M+Na]^+$ 521.2874; Found 521.2874.

Methyl (16*S*)-3,7:6,10:12,16-trianhydro-16-[3-(benzyloxy)propyl]-2,5,8,11,14,15-hexadeoxy-14-methyl-D-*xylo*-β-L-galactadecofuranoside-9,13-diulose (28): Through a stirred solution of olefin **27** (30.0 mg, 0.0602 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at −78 °C was bubbled freshly generated ozone. After the color of the reaction mixture changed to light blue (ca. 5 min), the resulting mixture was quenched by the addition of dimethyl sulfide (44.0 µL, 0.602 mmol, 10.0 equiv), and allowed to warm to 23 °C. After stirring for 10 h, the solvent was removed under reduced pressure, and the obtained residue was purified by flash column chromatography (SiO_2, 20 → 40% ethyl acetate in hexanes) to afford pure diketone **28** (28.4 mg, 0.0566 µmol, 94% yield) as a colorless oil. **3**: R_f = 0.40 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +74.2 (*c* = 0.60, CH_2Cl_2); FT-IR (film) ν_{max} = 2928, 2854, 1724, 1454, 1362, 1262, 1094, 1046, 740 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.17–6.98 (m, 4 H), 6.95–6.79 (m, 1 H), 4.75 (dd, *J* = 5.6, 2.9 Hz, 1 H), 4.18 (s, 2 H), 3.85 (ddd, *J* = 9.9, 3.8, 1.0 Hz, 1 H), 3.77 (dd, *J* = 9.5, 3.9 Hz, 1 H), 3.48 (dt, *J* = 5.3, 3.8 Hz, 1 H), 3.32 (dddt, *J* = 11.2, 8.9, 5.0, 2.9 Hz, 1 H), 3.21–3.13 (m, 3 H), 2.96 (dt, *J* = 5.0, 2.5 Hz, 1 H), 2.94 (s, 3 H), 2.76 (td, *J* = 4.9, 2.3 Hz, 1 H), 2.39 (dd, *J* = 15.5, 4.4 Hz, 1 H), 2.35–2.28 (m, 2 H), 2.04 (dt, *J* = 14.6, 4.3 Hz, 1 H), 1.96–1.89 (m, 2 H), 1.81 (ddd, *J* = 14.2, 6.2, 2.9 Hz, 1 H), 1.64–1.53 (m, 2 H), 1.47–1.38 (m, 2 H), 1.37–1.31 (m, 1 H), 1.26 (ddd, *J* = 13.1, 6.2, 1.9 Hz, 1 H), 1.24–1.21 (m, 1 H), 0.98 (td, *J* = 12.9, 11.0 Hz, 1 H), 0.74 (d, *J* = 6.6 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ 207.4, 205.8, 139.4, 129.9, 128.7, 127.8, 104.7, 79.0, 77.7, 77.1, 76.6, 73.7, 73.1, 72.2, 70.32, 70.26, 55.2, 43.4, 42.39, 42.37, 41.1, 32.3, 30.4, 30.1, 26.6, 14.6 ppm; HRMS (ESI-TOF) calcd for $C_{28}H_{38}O_8Na^+$ $[M+Na]^+$ 525.2459; Found 525.2462.



28

Methyl 3,7-anhydro-2,5,8-trideoxy-8-iodo-α-D-*altro*-octofuranoside (S2): To a stirred solution of **23** (10.2 g, 34.2 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) at −78 °C was added dropwise DIBAL-H (1.0 M in toluene, 85.5 mL, 85.5 mmol, 2.5 equiv). The resulting mixture was



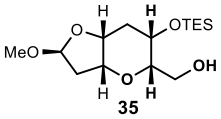
S2

allowed to slowly warm to −20 °C and stirred for 1 h. The mixture was acidified by addition of HCl (3 M in MeOH, 150 mL, 450 mmol, 13.2 equiv), the resulting mixture was allowed to warm to 23 °C and stirred for 8 h before it was diluted with H_2O (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with $NaHCO_3$ solution (100 mL, sat. aq.), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 1:2, *v*/*v*) of the residue afforded **S2** (7.63 g, 24.3 mmol, 71% yield) and C1-*epi*-**S2** (1.51 g, 4.79 mmol, 14% yield) as colorless oils, respectively. The configurations of the newly generated stereocenters were confirmed by nOe studies (see spectrum part). **S2:** R_f = 0.40 (SiO_2, hexanes/EtOAc 1:1, *v*/*v*); $[\alpha]_D^{23}$ = +97.1 (*c* = 1.0, $CHCl_3$); FTIR (film): ν_{max} 3504, 2926, 2831, 1430, 1368, 1345, 1248, 1212, 1184, 1140, 1096, 1055, 1038, 1018, 993, 969, 950, 916, 890, 846, 800 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 4.74 (dd, *J* = 6.0, 3.5 Hz, 1 H), 3.82 (dddd, *J* = 9.4, 5.4, 2.8, 1.1 Hz, 1 H), 3.59–3.48 (m, 3 H), 3.44–3.32 (m, 1 H), 3.09 (s, 3 H), 2.66 (dd, *J* = 10.7, 9.6 Hz, 1 H), 2.54 (dd, *J* = 10.7, 5.3 Hz, 1 H), 2.15 (ddd, *J* = 14.6, 6.0, 0.8 Hz, 1 H), 1.91 (ddt, *J* = 15.3, 2.5, 1.1 Hz, 1 H), 1.83 (ddd, *J* = 14.6, 5.2, 3.5 Hz, 1 H), 1.20 (dt, *J* = 15.6, 3.7 Hz, 1H). ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 104.5, 78.0, 73.7, 70.4, 65.3, 55.5, 41.4, 26.9, 3.6 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_9H_{15}IO_4Na^+$ 336.9907; Found 336.9903.

Methyl 3,7-anhydro-2,5,8-trideoxy-8-iodo-6-*O*-(triethylsilyl)-α-D-*altro*-octofuranoside (34): To a stirred solution of **S2** (7.60 g, 24.3 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at 0 °C was added imidazole (3.31 g, 48.6 mmol, 2.0 equiv) and TESCl (4.00 mL, 31.6 mmol, 1.3 equiv). The resulting mixture was allowed to slowly warm to 23 °C and stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 20:1, *v*/*v* → 2:1, *v*/*v*) of the residue afforded **34** (10.4 g, 24.3 mmol, quant. yield) as colorless oil. **34:** R_f = 0.70 (SiO_2, hexanes/EtOAc 5:1, *v*/*v*); $[\alpha]_D^{23}$ = +93.5 (*c* = 1.0, $CHCl_3$); FTIR (film): ν_{max} 2954, 2911, 2877, 1458, 1369, 1343, 1212, 1177, 1118, 1100, 1043, 1018, 1002, 918, 878, 805, 744, 728 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.10 (dd, *J* = 5.6, 1.7 Hz, 1 H), 4.52 (dt, *J* = 7.3, 4.7 Hz,

1 H), 4.15 (q, *J* = 6.0 Hz, 1 H), 3.63 (td, *J* = 7.8, 5.7 Hz, 1 H), 3.42 (dd, *J* = 10.4, 3.0 Hz, 1 H), 3.35 (ddd, *J* = 7.9, 6.7, 3.0 Hz, 1 H), 3.31 (s, 3 H), 3.24 (dd, *J* = 10.4, 6.7 Hz, 1 H), 2.29–2.20 (m, 2 H), 2.17 (ddd, *J* = 14.4, 7.3, 1.7 Hz, 1 H), 1.82 (ddd, *J* = 13.8, 7.7, 6.2 Hz, 1 H), 0.96 (t, *J* = 8.0 Hz, 9 H), 0.62 (qd, *J* = 7.9, 1.4 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 104.1, 75.3, 74.0, 73.6, 68.2, 55.0, 39.1, 34.2, 8.7, 7.0, 5.1 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{15}H_{29}IO_4SiNa^+$ 451.0772; Found 451.0774.

Methyl 3,7-anhydro-2,5-dideoxy-6-*O*-(triethylsilyl)-β-L-*galacto*-octofuranoside (35): To a stirred solution of **34** (9.30 g, 21.7 mmol, 1.0 equiv) in THF (60 mL) at 0 °C was added KO*t*-Bu (3.65 g, 32.6 mmol, 1.5 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 5 min before it was diluted with hexanes (100 mL) and EtOAc (30 mL), and filtered through a pad of SiO_2. The filtrate was concentrated under reduced pressure to give crude exocyclic olefin **26** (6.50 g, 21.7 mmol, quantitative yield), which was used in the next step without further purification.

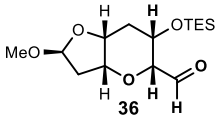


35

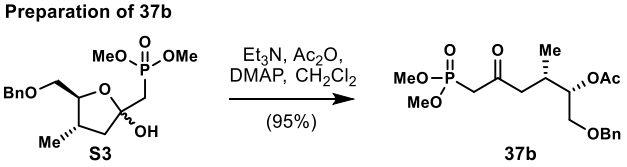
To a stirred solution of the above obtained olefin intermediate (6.50 g, 21.7 mmol, 1.0 equiv) in THF (100 mL) at 0 °C were added BH_3·Me_2S (2.0 M in THF; 12.0 mL, 23.9 mmol, 1.1 equiv), the resulting mixture was allowed to warm to 23 °C and stirred for 0.5 h before it was quenched by the addition of H_2O (150 mL). To this mixture was added $NaBO_3$ (9.46 g, 95.6 mmol, 4.4 equiv) and the resulting mixture was further stirred for 6 h. The reaction mixture was then extracted with EtOAc (3 × 100 mL), the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 1:2, *v*/*v*) afforded **35** (5.32 g, 16.7 mmol, 77% yield for the two steps) as a colorless oil. **35**: R_f = 0.40 (SiO_2, hexanes/EtOAc 1:1, *v*/*v*); $[\alpha]_D^{23}$ = +75.3 (*c* = 1.0, EtOAc); FT-IR (film): ν_{max} 3473, 2953, 2911, 2877, 1459, 1419, 1374, 1238, 1181, 1143, 1097, 1022, 926, 867, 783, 741, 726 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6): δ 5.15 (dd, *J* = 5.8, 3.7 Hz, 1 H), 3.86 (dd, *J* = 11.1, 7.2 Hz, 1 H), 3.72 (dt, *J* = 5.1, 2.6 Hz, 1 H), 3.66–3.56 (m, 2 H), 3.51–3.40 (m, 1 H), 3.25 (s, 3 H), 3.03 (ddd, *J* = 7.2, 4.6, 1.8 Hz, 1 H), 2.26 (ddt, *J* = 14.3, 5.8, 0.8 Hz, 1 H), 2.07 (dt, *J* = 15.1, 2.9 Hz, 1 H), 2.01 (ddd, *J* = 14.3, 5.6, 3.7 Hz, 1 H), 1.82 (d, *J* = 6.8 Hz, 1 H), 1.34 (ddd, *J* = 15.1, 4.8, 4.1 Hz, 1 H), 1.02 (t, *J* = 7.9 Hz, 9 H), 0.59 (qd, *J* = 7.9, 5.9 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 105.1, 78.7, 77.2, 73.1, 64.4, 63.6, 55.2, 41.7, 32.9, 7.1, 5.4 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{15}H_{30}O_5SiNa^+$

341.1755; Found 341.1760.

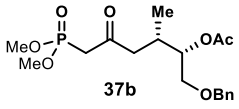
Methyl (8*S*)-2,6-anhydro-4,7-dideoxy-3-*O*-(triethylsilyl)-D-*galacto*-octodialdo-8,5-furanoside (36): To



a stirred solution of alcohol **35** (4.70 g, 14.7 mmol, 1.0 equiv) in dry CH_2Cl_2 (50 mL) at 0 °C was added Dess–Martin periodinane (9.37 g, 22.1 mmol, 1.5 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (30 mL) and a sat. aq. $Na_2S_2O_3$ solution (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 1:1, *v*/*v*) afforded aldehyde **10** (3.86 g, 12.2 mmol, 83% yield) as a colorless oil. **36:** R_f = 0.70 (SiO_2, hexanes/EtOAc 1:1, *v*/*v*); $[\alpha]_D^{23}$ = +130.0 (*c* = 1.0, EtOAc); FT-IR (film): ν_{max} 2954, 2912, 2878, 1740, 1461, 1411, 1370, 1296, 1182, 1142, 1123, 1099, 1021, 985, 886, 862, 785, 728 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 9.68 (brs, 1 H), 5.16 (dd, *J* = 5.8, 3.8 Hz, 1 H), 3.93 (dt, *J* = 4.2, 2.2 Hz, 1 H), 3.63 (dt, *J* = 4.7, 2.3 Hz, 1 H), 3.45 (dd, *J* = 5.4, 2.5 Hz, 1 H), 3.24 (s, 3 H), 3.07 (dd, *J* = 1.9, 0.9 Hz, 1 H), 2.32 (ddt, *J* = 14.4, 5.9, 0.8 Hz, 1 H), 2.05–1.89 (m, 2 H), 1.22–1.12 (m, 1 H), 1.02 (t, *J* = 7.9 Hz, 9 H), 0.60 (qd, *J* = 7.9, 2.3 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 202.1, 105.0, 82.5, 76.9, 72.5, 65.2, 55.3, 41.5, 32.3, 7.0, 5.3 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{15}H_{28}O_5SiNa^+$ 339.1597; Found 339.1598.



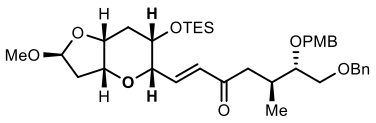
(2*S*,3*S*)-1-(Benzyloxy)-6-(dimethoxyphosphoryl)-3-methyl-5-oxohexan-2-yl acetate (37b): To a stirred



solution of ketal **S3**[5] (6.30 g, 18.3 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) were added Et_3N (5.10 mL, 36.6 mmol, 2.0 equiv), Ac_2O (2.59 mL, 27.4 mmol, 1.5 equiv) and *N*,*N*-dimethylpyridin-4-amine (DMAP, 220 mg, 1.83 mmol, 0.1 equiv) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 15 h before it was quenched by the addition of MeOH (2 mL) and

a sat. aq. $NaHCO_3$ solution (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 1:3, *v*/*v*) of the residue afforded phosphonate **37b** (8.07 g, 17.4 mmol, 95% yield) as a colorless oil. **37b:** R_f = 0.40 (SiO_2, 100% EtOAc); $[\alpha]_D^{23}$ = −6.1 (*c* = 0.87, $CHCl_3$); FT-IR (film): ν_{max} 3643, 2957, 2856, 1716, 1454, 1402, 1372, 1236, 1158, 1104, 1023, 808, 740, 699 cm^{-1}; ^1H NMR (600 MHz, CD_3CN): δ 7.41–7.23 (m, 5 H), 4.86 (ddd, *J* = 6.7, 5.5, 4.0 Hz, 1 H), 4.59–4.34 (m, 2 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.58–3.51 (m, 2 H), 3.18–2.99 (m, 2 H), 2.69 (dd, *J* = 17.7, 4.2 Hz, 1 H), 2.52–2.44 (m, 1 H), 2.43–2.33 (m, 1 H), 2.00 (s, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_3CN): δ 202.23 (d, *J* = 6.1 Hz), 171.3, 139.5, 129.3, 128.6, 128.5, 76.2, 73.6, 70.3, 53.49 (d, *J* = 6.5 Hz), 47.43 (d, *J* = 1.9 Hz), 47.42, 42.1, 41.3, 30.6, 21.3, 16.7 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{18}H_{27}O_7PNa^+$ 409.1387; Found 409.1390.

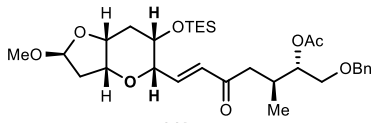
Methyl (8*E*)-3,7-anhydro-14-*O*-benzyl-2,5,8,9,11,12-hexadeoxy-13-*O*-(4-methoxybenzyl)-12-methyl-6-*O*-(triethylsilyl)-D-*threo*-β-L-*galacto*-tetradec-8-enofuranosid-10-ulose (38a): To a stirred solution of aldehyde **36** (1.10 g, 3.47 mmol, 1.0 equiv) and phosphonate **37a** (2.09 g, 4.51 mmol, 1.3 equiv) in MeCN (30 mL) at 0 °C was added LiCl (441 mg, 10.4 mmol, 3.0 equiv) and Et_3N (2.42 mL, 17.3 mmol, 5.0 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 1.5 h before it was quenched by the addition of sat. aq. NH_4Cl solution (20mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 2:1, *v*/*v*) of the residue afforded enone **38a** (1.93 g, 2.95 mmol, 85% yield) as a colorless oil. **38a:** R_f = 0.70 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +30.7 (*c* = 0.40, EtOAc); FT-IR (film): ν_{max} 2954, 2910, 2876, 1696, 1637, 1613, 1513, 1455, 1368, 1301, 1247, 1180, 1140, 1097, 1054, 1028, 983, 889, 820, 740, 699 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 7.34–7.17 (m, 5 H), 7.13–7.00 (m, 2 H), 6.86 (d, *J* = 4.6 Hz, 1 H), 6.84–6.78 (m, 2 H), 6.50 (dd, *J* = 16.0, 1.5 Hz, 1 H), 5.18 (dd, *J* = 5.8, 3.8 Hz, 1 H), 4.66 (d, *J* = 11.3 Hz, 1 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 4.33 (s, 2 H), 3.75–3.69 (m, 1 H), 3.59 (dd, *J* = 5.5, 2.6 Hz, 1 H), 3.53–3.44



38a

(m, 3 H), 3.43–3.37 (m, 2 H), 3.32 (s, 3 H), 3.26 (s, 3 H), 2.82 (dd, *J* = 16.6, 4.3 Hz, 1 H), 2.75–2.64 (m, 1 H), 2.47 (dd, *J* = 16.6, 8.8 Hz, 1 H), 2.33 (dd, *J* = 14.3, 5.8 Hz, 1 H), 2.09 (d, *J* = 15.1 Hz, 1 H), 2.04 (ddd, *J* = 14.3, 5.5, 3.8 Hz, 1 H), 1.34 (dt, *J* = 15.2, 4.4 Hz, 1 H), 1.09–0.85 (m, 12 H), 0.62–0.55 (m, 6H).ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 198.5, 159.6, 143.5, 139.2, 131.8, 130.5, 129.6, 128.6, 127.79, 127.78, 127.69, 114.0, 105.1, 81.7, 77.7, 77.1, 73.4, 72.5, 72.5, 71.8, 66.1, 55.3, 54.8, 43.7, 41.7, 33.0, 31.8, 17.1, 7.1, 5.4 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{37}H_{54}O_8SiNa^+$ 677.3480; Found 677.3479.

Methyl (8*E*)-13-*O*-acetyl-3,7-anhydro-14-*O*-benzyl-2,5,8,9,11,12-hexadeoxy-12-methyl-6-*O*-(triethylsilyl)-D-*threo*-β-L-*galacto*-tetradec-8-enofuranosid-10-ulose (38b): To a stirred solution of the aldehyde

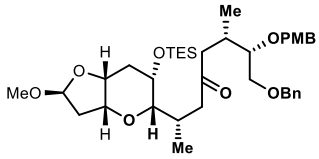


38b

36 (3.10 g, 9.80 mmol, 1.0 equiv) and phosphonate **37b** (4.92 g, 12.7 mmol, 1.3 equiv) in MeCN (50 mL) at 0 °C were added LiCl (1.25 g, 29.4 mmol, 3.0 equiv) and Et_3N (6.83 mL, 49.0 mmol, 5.0 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 1.5 h before it was quenched by the addition of sat. aq. NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 2:1, *v*/*v*) of the residue afforded enone **38b** (5.03 g, 8.72 mmol, 89% yield) as a colorless oil. **38b:** R_f = 0.60 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +30.3 (*c* = 2.0, EtOAc); FT-IR (film): ν_{max} 2953, 2910, 2876, 1740, 1697, 1675, 1637, 1455, 1415, 1371, 1238, 1181, 1139, 1127, 1097, 1053 1023, 982, 887, 739, 699 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6): δ 7.35–7.27 (m, 4 H), 7.23–7.13 (m, 1 H), 6.76 (dd, *J* = 16.0, 5.0 Hz, 1 H), 6.31 (dd, *J* = 16.0, 1.6 Hz, 1 H), 5.19 (dd, *J* = 5.7, 3.9 Hz, 1 H), 4.95 (ddd, *J* = 6.4, 5.4, 4.4 Hz, 1 H), 4.61–4.37 (m, 2 H), 4.09 (dd, *J* = 5.4, 2.7 Hz, 1 H), 3.99–3.96 (m, 1 H), 3.94 (dt, *J* = 5.1, 1.9 Hz, 1 H), 3.84 (td, *J* = 3.6, 2.0 Hz, 1 H), 3.58–3.49 (m, 2 H), 3.36 (s, 3 H), 2.66 (dd, *J* = 16.6, 3.7 Hz, 1 H), 2.55 (ddq, *J* = 13.2, 6.6, 3.6 Hz, 1 H), 2.42 (dd, *J* = 16.6, 9.5 Hz, 1 H), 2.38 (dd, *J* = 14.5, 5.8 Hz, 1 H), 2.24 (dt, *J* = 15.1, 3.0 Hz, 1 H), 2.09–2.03 (m, 4 H), 1.93 (dt, *J* = 15.1, 4.4 Hz, 1 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.59–0.55 (m, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 198.8, 170.8, 143.9, 138.1, 130.2, 128.5, 127.8, 127.7, 104.8, 77.8, 77.1, 75.8, 73.2, 72.6, 69.5, 66.0, 55.6, 43.0, 41.2, 32.9, 30.1, 21.2, 16.7, 6.9, 5.0 ppm;

HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{31}H_{48}O_8SiNa^+$ 599.3011; Found 599.3009.

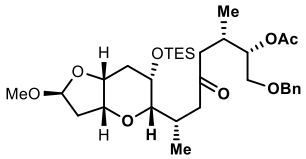
Methyl 3,7-anhydro-14-*O*-benzyl-2,5,8,9,11,12-hexadeoxy-13-*O*-(4-methoxybenzyl)-8,12-dimethyl-6-*O*-(triethylsilyl)-D-*arabino*-β-L-*galacto*-tetradecofuranosid-10-ulose (39a): To a stirred solution of



39a

CuCN (349 mg, 3.90 mmol, 3.0 equiv) in THF (50 mL) was added MeLi (1.6 M in Et_2O, 4.87 mL, 7.80 mmol, 6.0 equiv) at −78 °C. The resulting mixture was stirred at −40 °C for 10 min and then cooled to −78 °C. Then, TMSCl (990 µL, 7.80 mmol, 6.0 equiv) and **38a** (850 mg, 1.30 mmol, 1.0 equiv) in THF (10 mL) were added. The resulting mixture was allowed to warm to −40 °C and stirred for additional 0.5 h before it was quenched by the addition of sat. aq. NH_4Cl solution (30 mL). The mixture was allowed to warm to 23 °C and vigorously stirred for 3 h. The layers were separated and filtered through a pad of celite, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with aq. HCl (0.05 M, 30 mL), $NaHCO_3$ (30 mL, sat. aq.), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 2:1, *v*/*v*) of the residue afforded ketone **39a** (706 mg, 1.05 mmol, 81% yield) as a colorless oil. **39a:** R_f = 0.80 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +14.8 (*c* = 0.50, EtOAc); FT-IR (film): ν_{max} 2953, 2910, 2876, 1709, 1613, 1514, 1456, 1414, 1369, 1302, 1248, 1183, 1139, 1098, 1029, 972, 943, 824, 738 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 7.36–7.18 (m, 5 H), 7.13–6.97 (m, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 5.18 (dd, *J* = 5.8, 3.9 Hz, 1 H), 4.68 (d, *J* = 11.3 Hz, 1 H), 4.47 (d, *J* = 11.3 Hz, 1 H), 4.35 (d, *J* = 1.7 Hz, 2 H), 3.73 (dt, *J* = 4.6, 2.0 Hz, 1 H), 3.63 (brs, 1 H), 3.58 (dd, *J* = 5.4, 2.5 Hz, 1 H), 3.53–3.46 (m, 2 H), 3.45 (td, *J* = 5.3, 4.0 Hz, 1 H), 3.32 (s, 3 H), 3.27 (s, 3 H), 2.74 (dd, *J* = 16.1, 4.0 Hz, 1 H), 2.68–2.52 (m, 4 H), 2.33–2.12 (m, 4 H), 2.02 (ddd, *J* = 14.2, 5.4, 3.8 Hz, 1 H), 1.31 (dt, *J* = 15.3, 4.4 Hz, 1 H), 1.09 (t, *J* = 7.9 Hz, 9 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.75–0.60 (m, 6H).ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 209.0, 159.7, 139.2, 131.8, 129.7, 128.6, 127.8, 127.7, 114.0, 105.1, 81.9, 81.8, 77.6, 73.4, 72.9, 72.5, 71.8, 63.5, 55.2, 54.8, 47.1, 46.1, 41.8, 33.4, 31.6, 30.7, 17.1, 16.5, 7.3, 5.7 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{38}H_{58}O_8SiNa^+$ 693.3793; Found 693.3794.

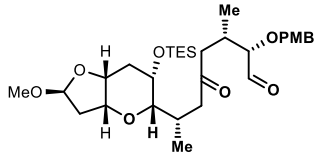
Methyl 13-*O*-acetyl-3,7-anhydro-14-*O*-benzyl-2,5,8,9,11,12-hexadeoxy-8,12-dimethyl-6-*O*-(triethylsilyl)-D-*arabino*-β-L-*galacto*-tetradecofuranosid-10-ulose (39b): To a stirred solution of CuCN (605 mg, 6.75 mmol, 3.0 equiv) in THF (60 mL) was added MeLi (1.6 M in Et_2O, 8.44 mL, 13.5 mmol, 6.0 equiv) at −78 °C. The reaction mixture was stirred at −40 °C for 10 min and then cooled to −78 °C. Then, TMSCl (1.71 mL, 13.5 mmol, 6.0 equiv) and **38a** (1.30 g, 2.25 mmol, 1.0 equiv) in THF (15 mL) were added. The resulting mixture was allowed to warm to −40 °C and stirred for additional 0.5 h before it was quenched by the addition of sat. aq. NH_4Cl solution (40 mL). The mixture was allowed to warm to 23 °C and vigorously stirred for 3 h. The layers were separated and filtered through a pad of celite, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with aq. HCl (0.05 M, 30 mL), $NaHCO_3$ (30 mL, sat. aq.), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 2:1, *v*/*v*) of the residue afforded ketone **39b** (1.11 g, 1.87 mmol, 83% yield) as a colorless oil.



39b

39b: R_f = 0.60 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +27.5 (*c* = 0.50, EtOAc); FT-IR (film): ν_{max} 2954, 2912, 2877, 1740, 1712, 1455, 1415, 1372, 1311, 1238, 1185, 1139, 1099, 1060, 1027, 972, 943, 880, 789, 737, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.27 (m, 5 H), 5.16–5.12 (m, 1 H), 4.92 (q, *J* = 5.4 Hz, 1 H), 4.58–4.45 (m, 2 H), 3.91 (ddd, *J* = 10.6, 5.1, 2.5 Hz, 2 H), 3.84 (s, 1 H), 3.57–3.50 (m, 2 H), 3.34 (s, 3 H), 2.81 (d, *J* = 9.5 Hz, 1 H), 2.71 (dd, *J* = 15.9, 4.5 Hz, 1 H), 2.54–2.43 (m, 2 H), 2.41–2.33 (m, 1 H), 2.31–2.17 (m, 4 H), 2.06 (s, 3 H), 1.95 (dt, *J* = 14.3, 4.7 Hz, 1 H), 1.78 (dt, *J* = 15.4, 4.4 Hz, 1 H), 0.98 (t, *J* = 7.9 Hz, 9 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.67–0.60 (m, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 209.8, 170.8, 138.1, 128.5, 127.8, 127.7, 104.8, 82.2, 77.7, 75.9, 73.2, 72.8, 69.6, 63.1, 55.5, 47.3, 45.6, 41.2, 33.4, 30.5, 30.0, 21.3, 16.7, 16.3, 7.0, 5.3 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{32}H_{52}O_8SiNa^+$ 615.3324; Found 615.3332.

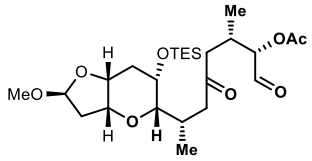
Methyl (14*S*)-8,12-anhydro-3,4,6,7,10,13-hexadeoxy-2-*O*-(4-methoxybenzyl)-3,7-dimethyl-9-*O*-(triethylsilyl)-D-*lyxo*-D-*manno*-tetradecodialdo-14,11-furanosid-5-ulose (32a): A solution of benzyl ether **12** (30.7 mg, 0.0457 mmol, 1.0 equiv) and excess Raney Ni (~ 200 mg) in EtOH (3 mL) was stirred under a hydrogen atmosphere (1 bar) at 23 °C for 12 h. The resulting mixture was filtrated through a pad of Celite and the filtrate was concentrated under reduced pressure to give the crude alcohol. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 5:1, *v*/*v*) of the residue afforded the corresponding alcohol intermediate (14.1 mg, 0.0242 mmol, 53% yield), which was used for the next step without further characterization (Note: the yield of the reaction was 39% at 350 mg scale).



32a: fragment A

To a stirred solution of the above alcohol (14.1 mg, 0.0242 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) were added $NaHCO_3$ (14.2 mg, 0.169 mmol, 7.0 equiv) and Dess–Martin periodinane (30.8 mg, 0.0726 mmol, 3.0 equiv) at 0 °C. The reaction mixture was stirred for 1 h at 23 °C before it was quenched by the addition of sat. aq. $Na_2S_2O_3$ solution (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 1:1, *v*/*v*) of the residue afforded aldehyde fragment *A* (**A**) (11.3 mg, 0.0196 mmol, 81% yield) as a colorless oil. **32a:** R_f = 0.50 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +3.3 (*c* = 0.20, $CHCl_3$); FT-IR (film): ν_{max} 2954, 1877, 1731, 1711, 1613, 1514, 1463, 1373, 1303, 1249, 1183, 1249, 1141, 1098, 1029, 973, 742, 726 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 9.43 (d, *J* = 2.0 Hz, 1 H), 7.15 (d, *J* = 8.6 Hz, 2H, one proton merged in solvent peak), 6.78 (d, *J* = 8.6 Hz, 2 H), 5.19 (dd, *J* = 5.8, 3.9 Hz, 1 H), 4.43 (d, *J* = 11.4 Hz, 1 H), 4.18 (d, *J* = 11.4 Hz, 1 H), 3.72 (dt, *J* = 4.7, 2.3 Hz, 1 H), 3.61 (s, 1 H), 3.59 (dd, *J* = 5.4, 2.5 Hz, 1 H), 3.36 (dd, *J* = 4.9, 2.1 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 2.66–2.49 (m, 5 H), 2.29 (dd, *J* = 14.2, 5.8 Hz, 1 H), 2.18–2.07 (m, 3 H), 2.03 (ddd, *J* = 14.2, 5.5, 3.9 Hz, 1 H), 1.31 (dt, *J* = 15.3, 4.4 Hz, 1 H), 1.08 (t, *J* = 7.9 Hz, 9 H), 0.90 (d, *J* = 6.7 Hz, 6 H), 0.74–0.60 (m, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 208.3, 202.6, 160.0, 130.2, 130.0, 114.2, 105.1, 86.6, 81.8, 77.6, 72.9, 72.5, 63.4, 55.2, 54.8, 47.1, 44.8, 41.8, 33.3, 30.6, 30.2, 16.82, 16.45, 7.2, 5.7 ppm; HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{31}H_{50}O_8SiNa^+$ 601.3167; Found 601.3162.

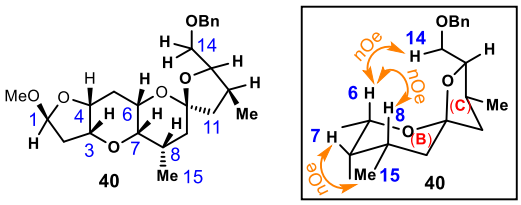
Methyl (14*S*)-2-*O*-acetyl-8,12-anhydro-3,4,6,7,10,13-hexadeoxy-3,7-dimethyl-9-*O*-(triethylsilyl)-D-*lyxo*-D-*manno*-tetradecodialdo-14,11-furanosid-5-ulose (32b): A solution of benzyl ether **39b** (2.30 g, 3.88 mmol, 1.0 equiv) and Pd/C (30 wt% Pd/C, 20% loading of **39b**, 460 mg) in THF (50 mL) was stirred under a hydrogen atmosphere (1 bar) at 23 °C for 1.5 h. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give the crude alcohol which was used for the next step without further purification.



32b: fragment A'

To a stirred solution of the above alcohol in CH_2Cl_2 (50 mL) were added $NaHCO_3$ (2.28 g, 27.2 mmol, 7.0 equiv) and Dess–Martin periodinane (4.11 g, 9.70 mmol, 2.5 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (30 mL) and sat. aq. $Na_2S_2O_3$ solution (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 1:1, *v*/*v*) afforded fragment *A'* (**32b**; 1.26 g, 2.52 mmol, 65% yield for the two steps) as a colorless oil. **32b:** R_f = 0.50 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +19.5 (*c* = 0.62, EtOAc); FT-IR (film): ν_{max} 2954, 2912, 2878, 1738, 1712, 1459, 1416, 1371, 1312, 1231, 1185, 1141, 1098, 1059, 1028, 973, 943, 881, 789, 741, 726 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 9.16 (s, 1 H), 5.20 (dd, *J* = 5.8, 3.8 Hz, 1 H), 4.77 (d, *J* = 3.8 Hz, 1 H), 3.73 (dd, *J* = 4.9, 2.5 Hz, 1 H), 3.60 (dd, *J* = 5.5, 2.5 Hz, 2 H), 3.28 (s, 3 H), 2.69–2.58 (m, 2 H), 2.57–2.45 (m, 2 H), 2.36 (dd, *J* = 17.7, 5.5 Hz, 1 H), 2.28 (dd, *J* = 14.2, 5.8 Hz, 1 H), 2.14 (dd, *J* = 15.3, 2.4 Hz, 1 H), 2.10–1.99 (m, 3 H), 1.69 (s, 3 H), 1.30 (dt, *J* = 15.3, 4.3 Hz, 1 H), 1.08 (t, *J* = 7.9 Hz, 9 H), 0.87 (d, *J* = 6.4 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 0.68–0.62 (m, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 207.6, 197.1, 169.7, 128.6, 105.1, 81.9, 81.5, 77.6, 72.8, 63.4, 55.3, 47.1, 44.2, 41.8, 33.2, 30.6, 28.7, 20.0, 17.0, 16.4, 7.2, 5.6 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{25}H_{44}O_8SiNa^+$ 523.2698; Found 523.2703.

(2*R*,2′*S*,3a′*R*,4*S*,4a′*S*,5′*S*,8a′*S*,9a′*R*)-5-[(Benzyloxy)methyl]-2′-methoxy-4,5′-dimethyldecahydro-2′*H*,3*H*-spiro[furan-2,7′-furo[3,2-*b*]pyrano[2,3-*e*]pyran] (40): To a stirred solution of **39b** (35.7 mg, 0.0602 mmol, 1.0 equiv) in MeCN (1 mL) at 0 °C was added HF·py (70% HF, 200 µL, excess). The resulting mixture was stirred for 0.5 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude alcohol without further purification.

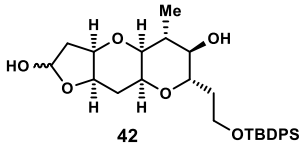


To the aboved obtained alcohol in MeOH (2 mL) at 0 °C was added K_2CO_3 (41.5 mg, 0.301 mmol, 5.0 equiv). The resulting mixture was stirred for 2.5 h before it was quenched by the addition of sat. aq. NH_4Cl solution (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude alcohol without further purification.

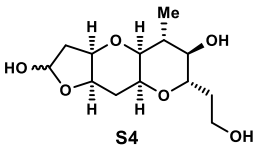
To the aboved obtained alcohol in CH_2Cl_2 (2 mL) at 23 °C was added *p*-TsOH·H_2O (11.4 mg, 0.0602 mmol, 1.0 equiv). The resulting mixture was stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 3:1, *v*/*v*) of the residue afforded **40** (15.9 mg, 0.0379 mmol, 63% yield) as a colorless oil. **40:** R_f = 0.60 (SiO_2, hexanes/EtOAc 2:1, *v*/*v*); $[\alpha]_D^{23}$ = +12.3 (*c* = 0.30, EtOAc); FT-IR (film): ν_{max} 2954, 2926, 2873, 1497, 1454, 1370, 1333, 1311, 1259, 1196, 1123, 1096, 1032, 1016, 1004, 968, 910, 897, 845, 738, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.31 (m, 4 H), 7.29–7.27 (m, 1 H), 5.13 (dd, *J* = 5.8, 3.7 Hz, 1 H), 4.65–4.47 (m, 2 H), 3.94 (dd, *J* = 5.5, 2.4 Hz, 1 H), 3.85 (dt, *J* = 3.8, 1.9 Hz, 1 H), 3.80 (td, *J* = 7.8, 3.7 Hz, 1 H), 3.68 (d, *J* = 4.4 Hz, 1 H), 3.54–3.40 (m, 2 H), 3.37 (s, 3 H), 3.01 (d, *J* = 2.8 Hz, 1 H), 2.35 (dq, *J* = 11.2, 7.0 Hz, 1 H), 2.26 (dd, *J* = 14.4, 5.8 Hz, 1 H), 2.19–2.09 (m, 2 H), 2.07–1.98 (m, 2 H), 1.81 (dt, *J* = 16.1, 5.0 Hz, 1 H), 1.70 (t, *J* = 12.9 Hz, 1 H), 1.40–1.31 (m, 2 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz,

3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$,): δ 138.6, 128.5, 128.4, 128.0, 127.9, 127.6, 106.6, 104.9, 85.8, 76.7, 74.0, 73.6, 73.3, 72.3, 63.7, 55.7, 46.7, 41.8, 36.0, 34.8, 30.4, 30.2, 17.9, 17.4 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{24}H_{34}O_6Na^+$ 441.2248; Found 441.2251.

3,7:6,10-Dianhydro-12-*O*-[*tert*-butyl(diphenyl)silyl]-2,5,8,11-tetradeoxy-8-methyl-L-*arabino*-L-*galacto*-dodecofuranose (42) and 3,7:6,10-dianhydro-2,5,8,11-tetradeoxy-8-methyl-L-*arabino*-L-*galacto*-dodecofuranose (S4): To a stirred solution of ketone **41**[5] (1.35 g, 2.57 mmol, 1.0 equiv) in THF



and tautomer **43**

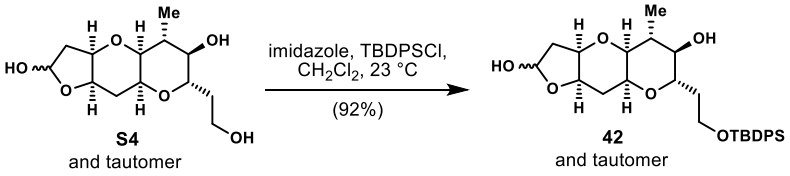


and tautomer

(20 mL) at −78 °C was added dropwise $LiAlH_4$ (1.0 M in THF, 2.83 mL, 2.83 mmol, 1.1 equiv). The resulting mixture was stirred for 10 min and then carefully quenched by dropwise addition of a mixture of AcOH/H_2O (AcOH, 20 mL; H_2O, 10 mL), and the resulting mixture was warmed to 50 °C and stirred for 1 h. The resulting mixture was allowed to cool to 23 °C and concentrated under reduced pressure to give crude **42**. Flash column chromatography (SiO_2, hexanes/EtOAc 2:1, *v*/*v* → 1:2, *v*/*v*) of the residue afforded **42/43** (mixture of tautomers, 948 mg, 1.85 mmol, 72% yield) and desilyl product **S4** (148 mg, 0.540 mmol, 21% yield) as colorless oils. **42/43** (mixture of tautomers): R_f = 0.30 (SiO_2, hexanes/EtOAc 1:1, *v*/*v*); $[\alpha]_D^{23}$ = −14.0 (*c* = 0.38, EtOAc, mixture of tautomers); FT-IR (film, mixture of tautomers): ν_{max} 3412, 2929, 2891, 2858, 1724, 1471, 1428, 1361, 1111, 1086, 1028, 1008, 823, 739, 703 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6, mixture of tautomers): δ 9.37 (s, 0.18 H), 7.95–7.64 (m, 4 H), 7.36–7.21 (m, 6 H), 5.46 (dd, *J* = 5.3, 3.0 Hz, 0.31 H), 5.42 (d, *J* = 5.1 Hz, 0.41 H), 4.32–4.24 (m, 0.26 H), 4.01 (dt, *J* = 9.8, 4.0 Hz, 0.45 H), 3.97 (td, *J* = 6.1, 3.7 Hz, 0.32 H), 3.86 (dtd, *J* = 9.6, 6.4, 5.8, 3.0 Hz, 1.24 H), 3.83–3.79 (m, 0.99 H), 3.68–3.63 (m, 0.44 H), 3.61 (dq, *J* = 6.3, 3.0 Hz, 0.32 H), 3.50–3.44 (m, 0.75 H), 3.41 (t, *J* = 3.9 Hz, 0.58 H), 3.37 (dt, *J* = 8.5, 4.4 Hz, 0.36 H), 3.32 (brs, 0.28 H), 3.27–3.22 (m, 0.49 H), 3.17 (s, 0.29 H), 3.10 (t, *J* = 4.1 Hz, 0.65 H), 3.05 (t, *J* = 6.8 Hz, 0.33 H), 2.88 (dd, *J* = 6.2, 4.4 Hz, 0.35 H), 2.78 (dd, *J* = 4.2, 2.6 Hz, 0.57 H), 2.73 (brs, 0.32 H), 2.54–2.37 (m, 0.48 H), 2.19 (ddd, *J* = 14.6, 5.6, 3.4 Hz, 0.51 H), 2.15–2.06 (m, 0.61 H), 2.06–1.95 (m, 1.96 H), 1.93–1.84 (m, 0.61 H), 1.79 (tdd, *J* = 10.2, 8.5, 5.2 Hz, 0.83 H), 1.75–1.58 (m, 1.14 H), 1.51 (dt, *J* = 13.7, 4.9 Hz, 0.48 H), 1.45 (dddd, *J* = 14.2, 8.2, 7.0, 3.8 Hz, 0.24 H), 1.38 (ddd, *J* = 14.5, 5.9, 4.0 Hz, 0.52 H), 1.21–1.13 (m, 9 H), 1.03 (d, *J* = 7.0 Hz, 0.95 H),

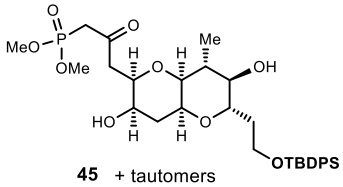
0.81 (d, J=7.5 Hz, 1.40 H), 0.59 (d, J=7.9 Hz, 0.58 H) ppm; ^{13}C NMR (151 MHz, C_6D_6, mixture of tautomers): δ 199.3, 136.2, 136.10, 136.08, 136.07, 136.0, 134.4, 134.23, 134.21, 134.1, 134.0, 133.8, 130.12, 130.06, 130.02, 129.98, 99.6, 98.1, 78.3, 77.3, 76.9, 76.3, 76.2, 75.82, 75.81, 75.6, 75.4, 74.80, 74.75, 73.6, 72.5, 71.9, 66.1, 64.3, 61.7, 61.7, 61.6, 61.5, 61.1, 46.3, 42.1, 41.7, 39.6, 39.3, 38.4, 35.0, 34.5, 33.8, 32.7, 31.3, 29.5, 27.15, 27.12, 27.1, 19.44, 19.41, 15.69, 15.65, 15.6 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{29}H_{40}O_6SiNa^+$ 535.2486; Found 535.2491.

preparation of **42** from **S4**:



3,7:6,10-Dianhydro-12-*O*-[*tert*-butyl(diphenyl)silyl]-2,5,8,11-tetradeoxy-8-methyl-L-*arabino*-L-*galacto*-dodecofuranose (42): To a stirred solution of **S4** (mixture of tautomers, 148 mg, 0.540 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C were added imidazole (73.5 mg, 1.08 mmol, 2.0 equiv) and TBDPSCl (178 mg, 0.648 mmol, 1.2 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 3 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 1:1, *v*/*v*) of the residue afforded **42/43** (mixture of tautomers, 255 mg, 0.497 mmol, 92% yield) as a colorless oil.

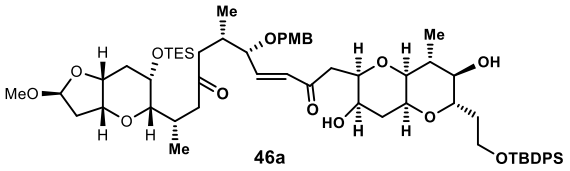
4,8:7,11-Dianhydro-13-*O*-[*tert*-butyl(diphenyl)silyl]-1,3,6,9,12-pentadeoxy-1-(dimethoxyphosphoryl)-9-methyl-L-*arabino*-L-*galacto*-tridec-2-ulose (45): To a stirred solution of **42/43** (mixture of tautomers, 1.28 g, 2.50 mmol, 1.0 equiv) and dimethyl diazomethylphosphonate **44** (1.87 g, 12.5 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C were added $SnCl_2$ (1.18 g, 6.24 mmol, 2.5 equiv). The resulting mixture was warmed to 23 °C and stirred for 3 h before it was diluted with CH_2Cl_2 (30 mL) and quenched



45 + tautomers

by the addition of H_2O (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 2:1, *v*/*v* → 1:2, *v*/*v*; then EtOAc/ MeOH 20:1, *v*/*v* → 5:1, *v*/*v*) afforded phosphonate **45** (mixture of tautomers, 1.16 g, 1.83 mmol, 73% yield) as a colorless oil. **45** (mixture of tautomers)**:** R_f = 0.70 (SiO_2, EtOAc/MeOH 5:1, *v*/*v*); $[\alpha]_D^{23}$ = −13.3 (*c* = 0.20, $CHCl_3$); FT-IR (film): ν_{max} 3504, 2957, 2930, 2857, 1716, 1472, 1462, 1428, 1391, 1362, 1254, 1187, 1110, 1083, 1030, 823, 741, 704, 688 cm^{-1}; ^1H NMR (600 MHz, CD_3CN, major isomer): δ 7.72 (ddt, *J* = 7.9, 3.8, 1.5 Hz, 4 H), 7.52–7.42 (m, 6 H), 4.12–4.06 (m, 1 H), 3.86–3.80 (m, 2 H), 3.77–3.70 (m, 7 H), 3.69–3.63 (m, 1 H), 3.59 (d, *J* = 10.7 Hz, 1 H), 3.51–3.43 (m, 1 H), 3.40–3.37 (m, 1 H), 3.29–3.12 (m, 3 H), 3.02 (dd, *J* = 17.0, 8.0 Hz, 1 H), 2.76 (dd, *J* = 17.1, 4.6 Hz, 1 H), 2.03–1.98 (m, 1 H), 1.92 (dddd, *J* = 14.7, 10.0, 5.5, 4.2 Hz, 1 H), 1.83 (dt, *J* = 14.9, 3.2 Hz, 1 H), 1.77 (dddd, *J* = 14.2, 8.7, 6.9, 3.4 Hz, 1 H), 1.12–1.02 (m, 12 H) ppm; ^{13}C NMR (151 MHz, CD_3CN, major isomer): δ 201.1 (d, *J* = 6.1 Hz), 136.0, 136.0, 134.3, 134.2, 130.39, 130.36, 128.38, 128.35, 78.8, 76.9, 72.2, 66.5, 62.4, 61.3, 53.12 (t, *J* = 5.8 Hz, 2 C), 46.74 (d, *J* = 1.9 Hz), 42.1, 41.2, 39.3, 34.6, 33.1, 19.3, 15.7 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{32}H_{47}PO_9SiNa^+$ 657.2619; Found 657.2620.

Methyl (14*E*)-3,7:18,22:21,25-trianhydro-27-*O*-[*tert*-butyl(diphenyl)silyl]-2,5,8,9,11,12,14,15,17,20,23,26-dodecadeoxy-13-*O*-(4-methoxybenzyl)-8,12,23-trimethyl-6-*O*-(triethylsilyl)-L-*erythro*-D-*gulo*-L-*galacto*-α-D-*gluco*-heptacos-14-enofuranoside-10,16-diulose (46a): To a stirred solution of phosphonate

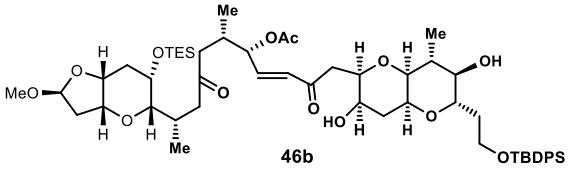


46a

45 (57 mg, 0.090 mmol, 1.0 equiv) and **32a** (52 mg, 0.090 mmol, 1.0 equiv) in THF (2 mL) at 23 °C were added LiBr (24 mg, 0.27 mmol, 3.0 equiv) and Et_3N (75 µL, 0.54 mmol, 6.0 equiv). The resulting mixture was stirred for 5 h before it was quenched by the addition of sat. aq. NH_4Cl solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 1:1, *v*/*v*) of the residue afforded enone **46a** (54 mg, 0.0050 mmol, 55% yield) as a colorless oil.

46a: R_f = 0.70 (SiO_2, hexanes/EtOAc 1:1, *v*/*v*); $[\alpha]_D^{23}$ = −10.6 (*c* = 0.45, $CHCl_3$); FT-IR (film): ν_{max} 3511, 2955, 2877, 1708, 1461, 1428, 1248, 1182, 1098, 1029, 823, 741 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 7.98–7.68 (m, 4H), 7.36–7.29 (m, 2H), 7.29–7.19 (m, 6H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.69 (dd, *J* = 16.1, 6.4 Hz, 1H), 6.34 (dd, *J* = 16.1, 1.2 Hz, 1H), 5.20 (dd, *J* = 5.8, 3.9 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 10.6 Hz, 1H), 4.15 (d, *J* = 11.4 Hz, 1H), 4.07 (d, *J* = 10.3 Hz, 1H), 3.97 (d, *J* = 10.7 Hz, 1H), 3.91–3.87 (m, 1H), 3.74 (dt, *J* = 4.6, 2.2 Hz, 1H), 3.70–3.62 (m, 3H), 3.62–3.56 (m, 3H), 3.33 (s, 3H), 3.29 (s, 3H), 3.23–3.18 (m, 1H), 3.14–3.09 (m, 1H), 3.05–2.92 (m, 2H), 2.83 (brs, 1H), 2.73 (dd, *J* = 16.1, 3.8 Hz, 1H), 2.63–2.53 (m, 3H), 2.51–2.44 (m, 1H), 2.31 (dd, *J* = 14.2, 5.8 Hz, 1H), 2.22–2.10 (m, 4H), 2.04 (ddd, *J* = 14.2, 5.4, 3.9 Hz, 1H), 1.93 (dt, *J* = 14.6, 2.9 Hz, 1H), 1.62 (dq, *J* = 10.1, 4.9 Hz, 1H), 1.49–1.40 (m, 1H), 1.33 (dt, *J* = 15.3, 4.3 Hz, 1H), 1.17 (s, 9H), 1.10 (t, *J* = 7.9 Hz, 9H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.76–0.62 (m, 6H), 0.58 (d, *J* = 7.9 Hz, 3H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 208.6, 197.3, 159.8, 145.5, 136.1, 136.0, 134.3, 133.9, 132.6, 130.8, 130.1, 130.0, 129.8, 128.6, 114.2, 105.1, 82.0, 81.9, 78.2, 78.1, 77.6, 77.4, 72.9, 71.9, 71.3, 66.1, 63.5, 61.6, 61.1, 55.2, 54.8, 47.2, 45.7, 42.4, 41.8, 38.4, 34.7, 33.7, 33.4, 32.6, 30.7, 27.1, 19.4, 16.7, 16.5, 15.5, 7.3, 7.3, 5.75, 5.70 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{61}H_{90}O_{13}Si_2Na^+$ 1109.5812; Found 1109.5799.

Methyl (14*E*)-13-*O*-acetyl-3,7:18,22:21,25-trianhydro-27-*O*-[*tert*-butyl(diphenyl)silyl]-2,5,8,9,11,12,14,15,17,20,23,26-dodecadeoxy-8,12,23-trimethyl-6-*O*-(triethylsilyl)-L-*erythro*-D-*gulo*-L-*galacto*-α-D-*gluco*-heptacos-14-enofuranoside-10,16-diulose (46b): To a stirred solution of phosphonate



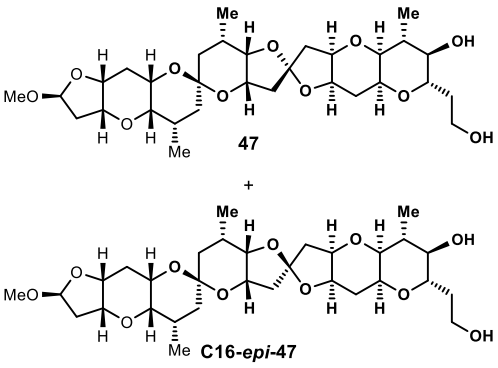
46b

45 (857 mg, 1.35 mmol, 1.0 equiv) and **32b** (676 mg, 1.35 mmol, 1.0 equiv) in THF (5 mL) at 23 °C were added LiBr (352 mg, 4.05 mmol, 3.0 equiv) and Et_3N (1.13 mL, 8.10 mmol, 6.0 equiv). The resulting mixture was stirred for 5 h before it was quenched by the addition of sat. aq. NH_4Cl solution (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 5:1, *v*/*v* → 1:1, *v*/*v*) of the residue afforded enone **46b** (722 mg, 0.716 mmol, 53% yield) as a colorless oil.

18: R_f = 0.60 (SiO_2, hexanes/EtOAc 1:1, *v*/*v*); $[\alpha]_D^{23}$ = −2.4 (*c* = 0.50, EtOAc); FT-IR (film): ν_{max} 3508, 2954,

2877, 1744, 1709, 1674, 1457, 1428, 1371, 1233, 1139, 1098, 1060, 1026, 986, 941, 823, 741, 705 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 7.87–7.68 (m, 4 H), 7.34–7.30 (m, 2 H), 7.30–7.21 (m, 4 H), 6.67 (dd, *J* = 16.0, 5.2 Hz, 1 H), 6.29 (dd, *J* = 16.0, 1.6 Hz, 1 H), 5.37 (td, *J* = 5.2, 1.6 Hz, 1 H), 5.21 (dd, *J* = 5.8, 3.9 Hz, 1 H), 4.33 (dt, *J* = 10.4, 2.9 Hz, 1 H), 3.99 (d, *J* = 10.2 Hz, 1 H), 3.92 (d, *J* = 10.7 Hz, 1 H), 3.80 (td, *J* = 6.3, 1.1 Hz, 1 H), 3.75 (dt, *J* = 4.7, 2.3 Hz, 1 H), 3.69–3.60 (m, 4 H), 3.54–3.50 (m, 1 H), 3.29 (s, 3 H), 3.19 (dt, *J* = 10.2, 2.6 Hz, 1 H), 3.11 (s, 1 H), 2.91 (dd, *J* = 6.3, 1.9 Hz, 2 H), 2.81 (s, 1 H), 2.70 (dd, *J* = 15.9, 3.4 Hz, 1 H), 2.62–2.54 (m, 2 H), 2.53–2.45 (m, 1 H), 2.39–2.26 (m, 2 H), 2.20–2.00 (m, 6 H), 1.91 (dt, *J* = 14.7, 2.9 Hz, 1 H), 1.67 (s, 3 H), 1.66–1.57 (m, 1 H), 1.50–1.41 (m, 1 H), 1.33 (dt, *J* = 15.4, 4.4 Hz, 1 H), 1.17 (s, 9 H), 1.10 (t, *J* = 8.0 Hz, 9 H), 0.91 (d, *J* = 6.1 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.74–0.63 (m, 6 H), 0.59 (d, *J* = 8.0 Hz, 2 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 207.7, 197.1, 169.3, 142.4, 136.1, 136.0, 134.3, 133.9, 131.5, 130.1, 130.0, 128.6, 105.1, 81.9, 78.2, 77.9, 77.7, 77.3, 76.0, 72.9, 71.9, 66.0, 63.5, 61.6, 61.1, 55.2, 47.3, 45.1, 42.7, 41.8, 38.4, 34.7, 33.3, 32.8, 32.6, 30.7, 27.1, 20.4, 19.4, 16.5, 16.3, 15.5, 7.25, 7.22, 5.69, 5.66 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{55}H_{84}O_{13}Si_2Na^+$ 1031.5343; Found 1031.5330.

(2*S*,2″*S*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-7-(2-Hydroxyethyl)-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-6-ol (47) and (2*R*,2″*S*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-7-(2-hydroxyethyl)-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-6-ol (C16-*epi*-47): procedure 1, from 46a: To a stirred solution of enone **46a** (30 mg, 0.028 mmol, 1.0 equiv) in THF (2 mL) at 23 °C were added a premixed solution of TBAF/HOAc (TBAF, 1.0 M in THF, 0.42 mL, 0.17 mmol, 15.0 equiv; HOAc, 8.0 µL, 0.14 mmol, 5.0 equiv). The resulting mixture was stirred for 15 h before it was diluted with hexanes (1 mL). The mixture was passed through a pad of SiO_2 (hexanes/EtOAc 1:1, *v*/*v*; then EtOAc/MeOH 20:1, *v*/*v* → 5:1, *v*/*v*) to afford the

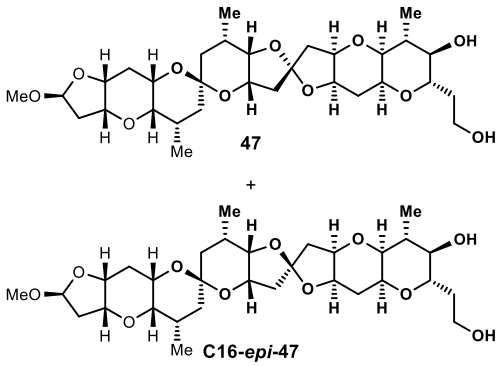


corresponding crude triol intermediate (about 15 mg), which was used in the next step without further purification.

To a stirred solution of the above obtained triol intermediate (15 mg, 0.021 mmol, 1.0 equiv) in THF/MeOH (3 mL, 10:1, *v*/*v*) at 23 °C was added 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (48 mg, 0.21 mmol, 10.0 equiv). The resulting mixture was vigorously stirred for 3 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (RP-C18, MeCN/H_2O 1:2, *v*/*v* → 1:1, *v*/*v*) of the residue afforded **47** (1.7 mg, 0.0028 mmol, 10% yield for the two steps) and C16-*epi*-**47** (4.8 mg, 0.0081 mmol, 29% yield for the two steps) as colorless oils, respectively. **47:** R_f = 0.60 (SiO_2, EtOAc /MeOH 10:1, *v*/*v*); $[\alpha]_D^{23}$ = −31.5 (*c* = 0.13, EtOAc); FT-IR (film): ν_{max} 3465, 2924, 2875, 1452, 1433, 1371, 1265, 1185, 1123, 1090, 1070, 1022, 1005, 972, 809 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 5.17 (dd, *J* = 5.9, 3.5 Hz, 1 H), 3.90 (td, *J* = 5.8, 3.7 Hz, 1 H), 3.83 (ddd, *J* = 9.1, 6.9, 3.7 Hz, 1 H), 3.80–3.74 (m, 2 H), 3.74–3.63 (m, 2 H), 3.59 (dt, *J* = 6.1, 2.7 Hz, 2 H), 3.42 (t, *J* = 3.0 Hz, 1 H), 3.37 (dt, *J* = 5.0, 1.4 Hz, 1 H), 3.34 (dt, *J* = 7.3, 4.4 Hz, 1 H), 3.20 (s, 3 H), 2.98 (t, *J* = 6.8 Hz, 1 H), 2.87 (dd, *J* = 5.7, 4.2 Hz, 1 H), 2.74–2.70 (m, 1 H), 2.54 (d, *J* = 14.0 Hz, 1 H), 2.43 (ddt, *J* = 12.7, 7.3, 3.8 Hz, 1 H), 2.34–2.26 (m, 4 H), 2.12–2.02 (m, 2 H), 1.99–1.91 (m, 2 H), 1.89 (dd, *J* = 14.1, 4.6 Hz, 1 H), 1.79–1.72 (m, 1 H), 1.71–1.64 (m, 3 H), 1.64–1.51 (m, 4 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 4.3 Hz, 3 H), 0.99 (d, *J* = 4.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 113.4, 104.9, 97.2, 79.9, 77.3, 76.9, 76.1, 75.8, 75.4, 74.1, 74.0, 72.4, 71.7, 64.4, 63.9, 60.0, 55.3, 46.4, 44.5, 42.1, 40.1, 37.6, 37.2, 35.2, 30.4, 29.8, 29.1, 26.3, 18.0, 17.5, 15.8 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{31}H_{48}O_{11}Na^+$ 619.3089; Found 619.3090. C16-*epi*-**47:** R_f = 0.55 (SiO_2, EtOAc /MeOH 10:1, *v*/*v*); $[\alpha]_D^{23}$ = −55.0 (*c* = 0.10, EtOAc); FT-IR (film): ν_{max} 3454, 2951, 2923, 2874, 1431, 1371, 1322, 1264, 1209, 1196, 1118, 1096, 1049, 1025, 1006, 972, 821, 786 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 5.16 (dd, *J* = 5.9, 3.6 Hz, 1 H), 4.09 (ddd, *J* = 9.3, 6.7, 3.7 Hz, 1 H), 3.94 (t, *J* = 2.5 Hz, 1 H), 3.81–3.73 (m, 3 H), 3.70 (ddd, *J* = 10.7, 6.3, 4.1 Hz, 1 H), 3.61–3.49 (m, 2 H), 3.45–3.37 (m, 2 H), 3.32 (dt, *J* = 4.9, 1.5 Hz, 1 H), 3.20 (s, 3 H), 3.10 (dd, *J* = 6.8, 5.0 Hz, 1 H), 2.96 (t, *J* = 4.8 Hz, 1 H), 2.69 (d, *J* = 2.8 Hz, 1 H), 2.44–2.37 (m, 2 H), 2.38–2.26 (m, 4 H), 2.20–2.10 (m, 2 H), 2.09–2.01 (m,

2 H), 1.95 (dd, *J* = 14.2, 5.9 Hz, 1 H), 1.81 (ddt, *J* = 14.2, 7.8, 3.9 Hz, 1 H), 1.75–1.67 (m, 1 H), 1.65–1.55 (m, 2 H), 1.52 (dt, *J* = 15.6, 5.1 Hz, 1 H), 1.49–1.38 (m, 2 H), 1.29 (dd, *J* = 13.0, 4.3 Hz, 1 H), 1.10 (d, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 115.0, 104.9, 97.0, 80.0, 77.3, 76.6, 76.4, 76.05, 76.02, 74.5, 73.9, 72.3, 72.1, 64.5, 63.8, 60.8, 55.4, 46.5 (2 C), 42.1, 40.0, 37.7, 37.1, 35.7, 30.9, 30.2, 29.2, 26.2, 18.0, 17.5, 15.8 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{31}H_{48}O_{11}Na^+$ 619.3089; Found 619.3092.

(2*S*,2″*S*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-7-(2-Hydroxyethyl)-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-6-ol (47) and (2*R*,2″*S*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-7-(2-hydroxyethyl)-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-6-ol (C16-*epi*-47): procedure 2, from 46b: To a stirred solution of enone



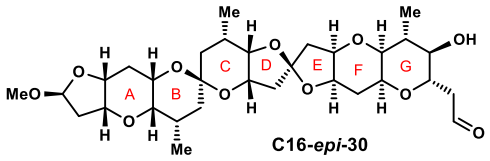
46b (0.10 g, 0.099 mmol, 1.0 equiv) in THF (2.5 mL) at 23 °C were added a premixed solution of TBAF/HOAc (TBAF, 1.0 M in THF, 0.5 mL, 0.5 mmol, 5.1 equiv; HOAc, 10 µL, 0.17 mmol, 1.7 equiv). The resulting mixture was stirred for 20 h before K_2CO_3 (0.14 g, 0.10 mmol, 10.0 equiv) and MeOH (15 mL) were added. The mixture was further stirred for 15 h before it was quenched by the addition of sat. aq. NH_4Cl solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 20mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was passed through a pad of SiO_2 (hexanes/EtOAc 1:1, *v*/*v*; then EtOAc/MeOH 20:1, *v*/*v* → 5:1, *v*/*v*) to afford the corresponding crude triol intermediate (~49 mg, 0.079 mmol, 80% yield), which was divided into three portion used in the next step without further purification.

PPTS-facilitated cyclization: To a stirred solution of the above obtained triol intermediate (16 mg, 0.026 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at 23 °C was added PPTS (6.5 mg, 0.027 mmol, 1.0 equiv). The

resulting mixture was stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (RP-C18, MeCN/H_2O 1:2, *v*/*v* → 1:1, *v*/*v*) of the residue afforded **47** (6.1 mg, 0.010 mmol, 33% yield for the two steps) and C16-*epi*-**47** (5.6 mg, 0.0093 mmol, 30% yield for the two steps) as colorless oils.

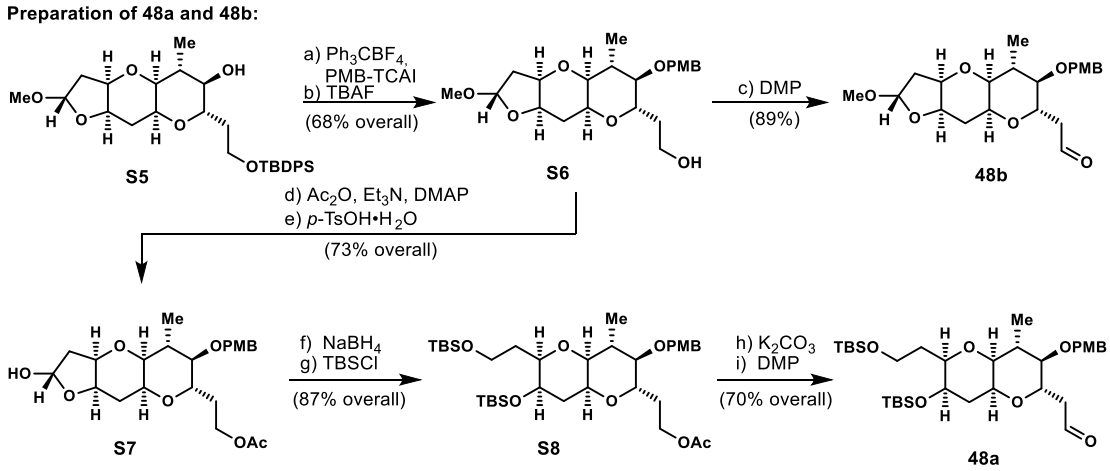
(±)-CSA-facilitated cyclization: To a stirred solution of the above obtained triol intermediate (16 mg, 0.026 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at 23 °C was added (±)-CSA (6.1 mg, 0.027 mmol, 1.0 equiv). The resulting mixture was stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (RP-C18, MeCN/H_2O 1:2, *v*/*v* → 1:1, *v*/*v*) of the residue afforded **47** (3.5 mg, 0.0060 mmol, 18% yield for the two steps) and C16-*epi*-**47** (8.7 mg, 0.015mmol, 45% yield for the two steps) as colorless oils.

[(2*R*,2″*S*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-6-Hydroxy-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-7-yl]acetaldehyde (C16-*epi*-30): To a stirred solution of alcohol **47** (30 mg, 0.050 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 23 °C was added (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (3.9 mg, 0.025 mmol, 0.5 equiv) and bis(acetoxy)iodobenzene (32 mg, 0.10 mmol, 2.0 equiv). The resulting mixture was stirred for 5 h before it was quenched by the addition of sat. aq. $Na_2S_2O_3$ solution (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 1:2, *v*/*v*) affording aldehyde **30** (23 mg, 0.038 mmol, 77% yield) as a colorless oil. **30:** R_f = 0.50 (SiO_2, 100% EtOA); $[\alpha]_D^{23}$ = −36.6 (*c* = 0.16, EtOAc); FT-IR

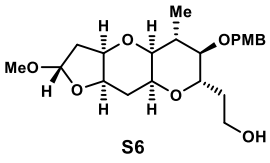


C16-*epi*-30

(film): ν_{max} 3468, 2926, 2874, 1724 1433, 1370, 1321, 1263, 1196, 1100, 1051, 1025, 1006, 973, 845 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 9.55 (dd, *J* = 3.5, 1.5 Hz, 1 H), 5.16 (dd, *J* = 5.9, 3.5 Hz, 1 H), 4.30 (ddd, *J* = 9.9, 6.5, 4.0 Hz, 1 H), 3.83 (t, *J* = 2.5 Hz, 1 H), 3.77 (dd, *J* = 4.8, 2.0 Hz, 2 H), 3.59–3.55 (m, 2 H), 3.40 (dd, *J* = 5.8, 4.0 Hz, 1 H), 3.35 (dt, *J* = 7.1, 4.5 Hz, 1 H), 3.32 (d, *J* = 4.8 Hz, 1 H), 3.20 (s, 3 H), 2.92–2.89 (m, 2 H), 2.69 (d, *J* = 2.9 Hz, 1 H), 2.44–2.38 (m, 2 H), 2.37–2.24 (m, 6 H), 2.21–2.10 (m, 2 H), 2.11–2.01 (m, 3 H), 1.92 (dd, *J* = 14.2, 5.9 Hz, 1 H), 1.62–1.49 (m, 3 H), 1.50–1.40 (m, 2 H), 1.30 (dd, *J* = 12.9, 4.3 Hz, 1 H), 1.07 (d, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 200.5, 114.8, 104.9, 97.0, 79.9, 77.4, 76.4, 76.2, 76.1, 73.8, 73.6, 72.5, 72.3, 72.1, 64.8, 63.8, 55.4, 46.7, 46.4, 46.2, 42.1, 39.9, 37.7, 37.1, 30.5, 30.3, 29.2, 26.2, 18.1, 17.5, 15.6 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{31}H_{46}O_{11}Na^+$ 617.2932; Found 617.2933.



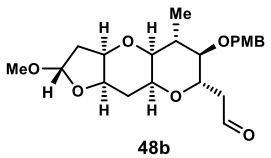
Methyl 3,7:6,10-dianhydro-2,5,8,11-tetradeoxy-9-*O*-(4-methoxybenzyl)-8-methyl-L-*arabino*-β-L-*galacto*-dodecofuranoside (S6): To a stirred solution of **S5**[5] (378 mg, 0.718 mmol, 1.0 equiv) in Et_2O (60 mL) at 0 °C was added 4-methoxybenzyl-2,2,2-trichloroacetimidate (PMB-TCAI; 305 mg, 1.08 mmol, 1.5 equiv) and triphenylcarbenium tetrafluoroborate (47.5 mg, 0.144 mmol, 0.2 equiv). The resulting mixture was warmed to 23 °C and stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were



washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 2:1, *v*/*v* → 1:1, *v*/*v*) of the residue afforded the corresponding PMB-protected alcohol derivative, which was used for the next step without further purification.

To a stirred solution of the above obtained PMB-protected alcohol in THF (30 mL) was added TBAF (1.0 M in THF; 1.08 mL, 1.08 mmol, 1.5 equiv) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 1 h. The resulting mixture was quenched by the addition of sat. aq. NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 1:5, *v*/*v*) of the residue afforded diol **S6** (199 mg, 0.488 mmol, 68% yield for the two steps) as a white foam. **S6:** R_f = 0.60 (SiO_2, 100% EtOAc); $[\alpha]_D^{23}$ = −8.5 (*c* = 0.50, $CHCl_3$); FT-IR (film): ν_{max} 3486, 2908, 2837, 1612, 1513, 1463, 1351, 1302, 1248, 1175, 1098, 1037, 990 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 5.15 (dd, *J* = 5.7, 3.2 Hz, 1 H), 4.58–4.42 (m, 2 H), 4.04 (ddd, *J* = 10.4, 9.2, 2.7 Hz, 1 H), 4.01–3.96 (m, 2 H), 3.83 (ddd, *J* = 11.6, 8.0, 3.7 Hz, 1 H), 3.81–3.78 (m, 4 H), 3.70 (ddd, *J* = 10.9, 6.1, 4.4 Hz, 1 H), 3.37–3.34 (m, 4 H), 2.94 (dd, *J* = 9.2, 6.0 Hz, 1 H), 2.25 (ddd, *J* = 14.2, 5.8, 1.7 Hz, 1 H), 2.23–2.17 (m, 1 H), 2.08–1.98 (m, 3 H), 1.92 (dt, *J* = 14.5, 4.8 Hz, 1 H), 1.49 (dddd, *J* = 14.1, 10.1, 6.1, 3.7 Hz, 1 H), 1.10 (d, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.4, 130.5, 129.7, 114.0, 105.0, 82.4, 77.1, 75.6, 73.7, 72.3, 72.1, 64.3, 60.8, 55.7, 55.5, 41.1, 39.2, 34.9, 30.1, 17.7 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{22}H_{32}O_7Na^+$ 431.2040; Found 431.2046.

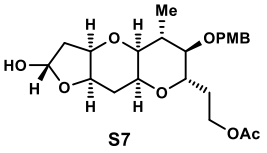
Methyl 3,7:6,10-dianhydro-2,5,8,11-tetradeoxy-9-*O*-(4-methoxybenzyl)-8-methyl-L-*arabino*-β-L-*galacto*-dodecodialdo-1,4-furanoside (48b): To a stirred solution of alcohol **S6** (77.6 mg, 0.190 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C was added Dess–Martin periodinane (121 mg, 0.285 mmol, 1.5 equiv). The resulting mixture was warmed to 23 °C and stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (10 mL) and sat. aq. $Na_2S_2O_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and



48b

concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 2:1, *v*/*v*) afforded aldehyde **48b** (68.7 mg, 0.169 mmol, 89% yield) as a colorless oil. **48b:** R_f = 0.80 (SiO_2, 100% EtOAc); $[\alpha]_D^{23}$ = +5.6 (*c* = 0.80, $CHCl_3$); FT-IR (film): ν_{max} 2884, 1721, 1613, 1514, 1463, 1353, 1303, 1251, 1222, 1186, 1130, 1101, 1065, 1055, 1037, 987, 821 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.63 (dd, *J* = 3.3, 2.0 Hz, 1 H), 7.16 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 5.05 (dd, *J* = 5.4, 2.7 Hz, 1 H), 4.41 (AB quart, *J* = 10.9 Hz, 2 H), 4.16 (td, *J* = 8.9, 4.1 Hz, 1 H), 3.99–3.88 (m, 2 H), 3.76–3.73 (m, 1 H), 3.73 (s, 3 H), 3.32 (dd, *J* = 6.2, 4.9 Hz, 1 H), 3.27 (s, 3 H), 2.88 (dd, *J* = 9.1, 7.6 Hz, 1 H), 2.58 (ddd, *J* = 15.7, 4.1, 2.0 Hz, 1 H), 2.34 (ddd, *J* = 15.7, 8.8, 3.3 Hz, 1 H), 2.14–2.00 (m, 3 H), 2.00–1.94 (m, 1 H), 1.93–1.86 (m, 1 H), 1.09 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 201.6, 159.6, 130.0, 129.8, 114.0, 104.7, 81.4, 76.9, 75.3, 74.4, 72.9, 69.6, 66.1, 55.4, 55.3, 47.0, 40.7, 39.2, 29.0, 16.9 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{22}H_{30}O_7Na^+$ 429.1884; Found 429.1884.

12-*O*-Acetyl-3,7:6,10-dianhydro-2,5,8,11-tetradeoxy-9-*O*-(4-methoxybenzyl)-8-methyl-L-*arabino*-β-L-*galacto*-dodecofuranose (S7): To a stirred solution of **S6** (130 mg, 0.318 mmol, 1.0 equiv) in dry CH_2Cl_2



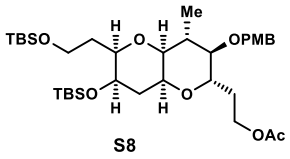
S7

(10 mL) at 0 °C were added Et_3N (89.0 µL, 0.636 mmol, 2.0 equiv), Ac_2O (45.0 µL, 0.477 mmol, 1.5 equiv) and *N*,*N*-dimethylpyridin-4-amine (DMAP, 19.4 mg, 0.159 mmol, 0.5 equiv) at 0 °C. The resulting mixture was allowed to warm to 23 °C and stirred for 5 h before it was quenched by the addition of MeOH (1 mL) and sat. aq. $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 2:1, *v*/*v*) to afford aldehyde **Ac-S6** (129 mg, 0.286 mmol, 90% yield) as a colorless oil, which was used without further purification.

To a stirred solution of **Ac-S6** (129 mg, 0.286 mmol, 1.0 equiv) in acetone/H_2O (6 mL, 3:1, *v*/*v*) at 23 °C were added *p*-TsOH·H_2O (54.5 mg, 0.286 mmol, 1.0 equiv). The resulting mixture was warmed to 45 °C and stirred for 5 h before it was diluted with sat. aq. $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over

Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1, *v*/*v* → 1:5, *v*/*v*) of the residue afforded **S7** (mixture of tautomers, 101 mg, 0.232 mmol, 81% yield). **S7** (mixture of tautomers): R_f = 0.60 (SiO_2, 100% EtOAc); $[\alpha]_D^{23} = -33.3$ (*c* = 0.58, $CHCl_3$); FT-IR (film): ν_{max} 3458, 2924, 1736, 1612, 1514, 1462, 1366, 1302, 1247, 1174, 1123, 1029, 822 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 5.31 (d, *J* = 5.2 Hz, 1 H), 4.50–4.35 (m, 2 H), 4.14–4.09 (m, 2 H), 4.02 (ddd, *J* = 11.1, 8.0, 6.4 Hz, 1 H), 3.97 (t, *J* = 3.1 Hz, 1 H), 3.81 (dt, *J* = 4.7, 2.4 Hz, 1 H), 3.73 (s, 4 H), 3.15 (t, *J* = 2.0 Hz, 1 H), 2.92 (t, *J* = 2.0 Hz, 1 H), 2.40 (dt, *J* = 15.6, 2.8 Hz, 1 H), 2.24 (qd, *J* = 8.0, 4.5 Hz, 1 H), 2.20–1.99 (m, 3 H), 1.98–1.94 (m, 4 H), 1.84 (dt, *J* = 15.5, 4.5 Hz, 1 H), 1.57 (dddd, *J* = 14.3, 8.1, 7.2, 4.0 Hz, 1 H), 1.02 (d, *J* = 8.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.2, 159.2, 123.0, 129.6, 113.9, 99.6, 75.6, 74.6, 74.2, 72.6, 70.4, 62.0, 59.4, 55.4, 42.0, 35.6, 31.1, 28.9, 21.2, 16.6 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{23}H_{32}O_8Na^+$ 459.1989; Found 459.1994.

12-*O*-Acetyl-3,7:6,10-dianhydro-1,4-bis-*O*-[*tert*-butyl(dimethyl)silyl]-2,5,8,11-tetradeoxy-9-*O*-(4-methoxybenzyl)-8-methyl-L-*arabino*-L-*galacto*-dodecitol (S8): To a stirred solution of **S7** (78.1 mg, 0.179 mmol, 1.0 equiv) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (13.5 mg, 0.358 mmol, 2.0 equiv). The resulting mixture was stirred for 0.5 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude diol without further purification.

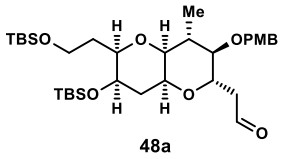


S8

To a stirred solution of the above obtained diol in CH_2Cl_2 (5 mL) at 0 °C were added imidazole (122 mg, 1.79 mmol, 10.0 equiv) and TBSCl (135 mg, 0.895 mmol, 5.0 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 15 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 5:1, *v*/*v*) of the residue afforded **S8** (104 mg, 0.156 mmol, 87% yield for the two steps) as a colorless oil. **S8:** R_f = 0.60 (SiO_2,

hexanes/EtOAc 5:1, *v*/*v*); $[\alpha]_D^{23} = -45.0$ (*c* = 0.40, $CHCl_3$); FT-IR (film): ν_{max} 2955, 2928, 2856, 1740, 1613, 1514, 1471, 1463, 1302, 1249, 1173, 1093, 1038, 835, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 7.9 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.56–4.40 (m, 2 H), 4.21–4.09 (m, 2 H), 3.85 (td, *J* = 8.7, 3.6 Hz, 1 H), 3.80 (s, 3 H), 3.80–3.75 (m, 2 H), 3.73 (td, *J* = 5.2, 2.8 Hz, 1 H), 3.69 (ddd, *J* = 9.8, 5.6, 4.0 Hz, 1 H), 3.53 (dt, *J* = 9.8, 3.1 Hz, 1 H), 3.38 (dd, *J* = 6.2, 4.4 Hz, 1 H), 2.94 (dd, *J* = 9.2, 8.0 Hz, 1 H), 2.07–1.98 (m, 6 H), 1.84–1.69 (m, 3 H), 1.65–1.55 (m, 1 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 4.0 Hz, 18 H), 0.06–0.03 (m, 12 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.3, 159.4, 130.5, 129.6, 113.9, 82.0, 78.5, 73.9, 72.9, 70.4, 68.1, 66.2, 61.6, 59.7, 55.4, 39.4, 34.5, 34.4, 31.7, 26.15, 26.06, 21.2, 18.5, 18.4, 17.2, −4.1, −4.7, −5.1, −5.2 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{35}H_{62}O_8Si_2Na^+$ 689.3875; Found 689.3877.

3,7:6,10-Dianhydro-9,12-bis-*O*-[*tert*-butyl(dimethyl)silyl]-2,5,8,11-tetradeoxy-4-*O*-(4-methoxybenzyl)-5-methyl-D-*lyxo*-D-*gulo*-dodecose (48a): To a stirred solution of **S8** (63.1 mg, 0.0944 mmol, 1.0 equiv) in MeOH (3 mL) at 0 °C was added K_2CO_3 (13.0 mg, 0.0944 mmol, 1.0 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 2 h. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl solution (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude primary alcohol (~60 mg), which was used in the next step without further purification.

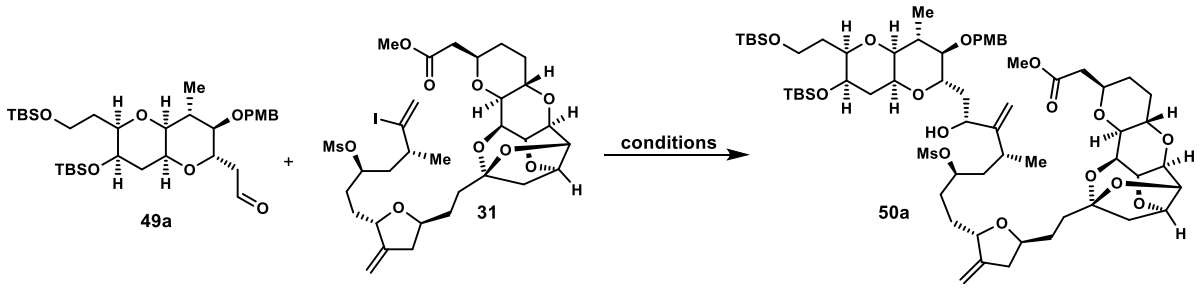


48a

To a stirred solution of the above obtained crude primary alcohol in CH_2Cl_2 (5 mL) at 0 °C was added Dess–Martin periodinane (80.0 mg, 0.189 mmol, 2.0 equiv). The resulting mixture was allowed to warm to 23 °C and stirred for 1 h before it was quenched by the addition of sat. aq. $NaHCO_3$ solution (5 mL) and sat. aq. $Na_2S_2O_3$ solution (5 mL), the resulting mixture was further vigorously stirred for 2 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 10:1, *v*/*v* → 2:1, *v*/*v*) afforded **48a** (41.2 mg, 0.0661 mmol, 70% yield for the two steps) as a colorless oil. **48a:** $R_f = 0.35$ (SiO_2, hexanes/EtOAc 5:1, *v*/*v*); $[\alpha]_D^{23} = -28.5$

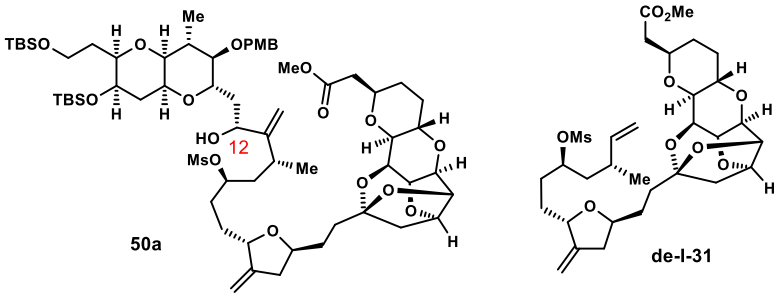
(c = 0.50, $CHCl_3$); FTIR (film): ν_{max} 2955, 2928, 2856, 1725, 1611, 1514, 1463, 1387, 1361, 1250, 1093, 1037, 835, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.64 (s, 1 H), 7.18 (d, J = 8.2 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 2 H), 4.54 (dt, J = 9.4, 6.2 Hz, 1 H), 4.40 (dd, J = 68.9, 10.9 Hz, 2 H), 3.81–3.72 (m, 5 H), 3.69–3.59 (m, 2 H), 3.44 (dd, J = 9.8, 2.6 Hz, 1 H), 3.32 (t, J = 3.2 Hz, 1 H), 2.96 (dd, J = 9.6, 5.6 Hz, 1 H), 2.48 (dd, J = 6.6, 2.9 Hz, 2 H), 2.08 (dt, J = 13.6, 3.6 Hz, 2 H), 1.81 (ddt, J = 14.0, 9.1, 4.1 Hz, 1 H), 1.69 (dt, J = 14.5, 4.4 Hz, 1 H), 1.55–1.46 (m, 1 H), 1.06 (d, J = 7.3 Hz, 3 H), 0.85 (brs, 18 H), 0.03–−0.01 (m, 12 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 201.6, 159.5, 130.3, 129.8, 114.0, 82.8, 79.3, 75.2, 72.1, 68.4, 67.3, 65.5, 59.6, 55.4, 48.3, 39.4, 36.1, 35.2, 26.15, 26.13, 18.6, 18.5, 18.3, −3.9, −4.8, −5.1, −5.2 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{33}H_{58}O_7Si_2Na^+$ 645.3613; Found 645.3610.

NHK reaction toward 50a:



Condition 1:

Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{(3*R*,5*R*,7*R*)-8-{(2*S*,3*R*,4*R*,4a*S*,6*R*,7*R*,8a*S*)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-6-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-3-[(4-methoxybenzyl)-oxy]-4-methyloctahydropyrano[3,2-*b*]pyran-2-yl}-7-hydroxy-5-methyl-6-methylidene-3-[(methyl-sulfonyl)oxy]octyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo-[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]heptadec-4-yl]acetate (50a): In a glove box, to a stirred solution of **48a** (37.9 mg, 0.0608 mmol, 2.0 equiv) and **31** (22.9 mg, 0.0304 mmol, 1.0 equiv) in THF/DMF (1.0 mL, 4:1, *v*/*v*) at 23 °C



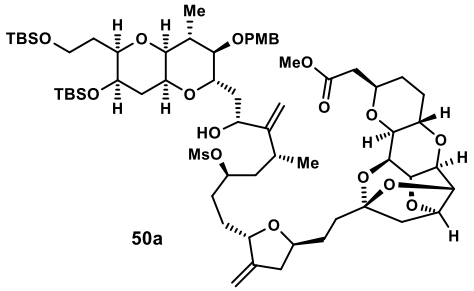
was added 2.0% $NiCl_2/CrCl_2$ (37.4 mg, 0.3604 mmol, 10.0 equiv). The resulting mixture was vigorously stirred for 24 h before it was quenched by the addition of H_2O (10 mL). The layers

were separated, and the aqueous layer was extracted with EtOAc (4 × 30 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc hexanes/EtOAc 3:1, *v*/*v* → 1:3, *v*/*v*) of the residue afforded alcohol **50a** (8.70 mg, 0.00700 mmol, 23% yield, 3:1 *dr* at C12) as a colorless oil, methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-4-methylidene-5-{(3*R*,5*R*)-5-methyl-3-[(methylsulfonyl)oxy]hept-6-en-1-yl}tetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.$0^{2,7}$.$0^{9,16}$.$0^{10,14}$]heptadec-4-yl]acetate (**de-I-31**; 14.9 mg, 0.0238 mmol, 70% yield) as a colorless oil, and recovered aldehyde **48a** (26.5 mg, 0.0426 mmol, 70%) as a white foam. **50a**: R_f = 0.75 (SiO_2, hexanes/EtOAc 1:3, *v*/*v*); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 5.14 (s, 1 H), 5.00 (d, *J* = 3.0 Hz, 1 H), 4.87–4.82 (m, 2 H), 4.77 (td, *J* = 13.1, 12.2, 6.8 Hz, 1 H), 4.68 (t, *J* = 4.8 Hz, 1 H), 4.60 (t, *J* = 4.5 Hz, 1 H), 4.58–4.45 (m, 2 H), 4.42 (dd, *J* = 3.9, 1.9 Hz, 1 H), 4.36 (d, *J* = 8.2 Hz, 1 H), 4.31–4.24 (m, 2 H), 4.20 (dd, *J* = 6.6, 4.6 Hz, 1 H), 4.06 (dd, *J* = 6.6, 4.0 Hz, 2 H), 3.94 (dt, *J* = 10.5, 5.2 Hz, 1 H), 3.85–3.75 (m, 6 H), 3.74–3.68 (m, 3 H), 3.67 (s, 3 H), 3.52 (dt, *J* = 9.8, 2.9 Hz, 1 H), 3.37 (dd, *J* = 6.4, 4.0 Hz, 1 H), 3.00 (s, 3 H), 2.92 (dd, *J* = 9.6, 1.9 Hz, 1 H), 2.72–2.59 (m, 2 H), 2.38 (dd, *J* = 15.8, 5.9 Hz, 1 H), 2.36–2.30 (m, 1 H), 2.30–2.25 (m, 1 H), 2.16–2.08 (m, 3 H), 2.08–1.99 (m, 3 H), 1.99–1.94 (m, 2 H), 1.93–1.88 (m, 2 H), 1.87–1.80 (m, 3 H), 1.81–1.74 (m, 4 H), 1.73–1.64 (m, 5 H), 1.43–1.38 (m, 1 H), 1.17 (d, *J* = 6.7 Hz, 3 H), 1.10–1.06 (m, 3 H), 0.89 (s, 9 H), 0.89 (s, 9 H), 0.09 – −0.02 (m, 12 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7, 159.4, 156.0, 151.4, 130.4, 129.7, 129.0, 114.0, 110.5, 105.3, 83.0, 82.2, 82.0, 81.1, 79.1, 78.5, 78.1, 76.7, 75.6, 74.6, 74.5, 74.1, 73.9, 73.9, 73.2, 68.4, 67.7, 66.1, 59.7, 55.4, 51.8, 47.2, 41.4, 40.6, 39.1, 39.1, 38.8, 38.8, 35.0, 34.7, 34.6, 34.5, 32.5, 31.1, 30.7, 30.3, 30.1, 29.8, 29.7, 26.2, 26.1, 22.1, 18.5, 18.4, 16.9, −3.9, −4.8, −5.1, −5.2 ppm; **De-I-31**: R_f = 0.80 (SiO_2, 100% EtOAc); $[\alpha]_D^{23}$ = −68.0 (*c* = 0.15, EtOAc); FT-IR (film): ν_{max} 2936, 2868, 1738, 1438, 1336, 1290, 1263, 1211, 1172, 1133, 1077, 1013, 830, 790 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6): 5.54 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1 H), 5.15 (ddd, *J* = 17.2, 1.8, 1.0 Hz, 1 H), 5.00 (ddd, *J* = 10.3, 1.8, 0.7 Hz, 1 H), 4.91 (dtd, *J* = 9.5, 5.8, 3.7 Hz, 2 H), 4.80 (d, *J* = 2.2 Hz, 1 H), 4.55–4.46 (m, 1 H), 4.41 (dd, *J* = 4.0, 1.9 Hz, 1 H), 4.37–4.30 (m, 1 H), 4.14 (dt, *J* = 33.3, 4.6 Hz, 2 H), 4.01–3.94 (m, 1 H), 3.94–3.89 (m, 1 H), 3.76 (dddd, *J* = 10.8, 7.3, 5.2, 2.1 Hz, 1 H), 3.67 (dd, *J* = 6.6, 3.9 Hz, 1 H), 3.32 (s, 3 H), 2.62–2.53 (m, 2 H), 2.48–2.41 (m, 1 H), 2.41–2.36 (m, 1 H), 2.33 (s, 3 H), 2.18 (dd, *J* = 15.7, 5.3 Hz, 1 H), 2.16–2.02 (m, 3 H), 2.02–1.97

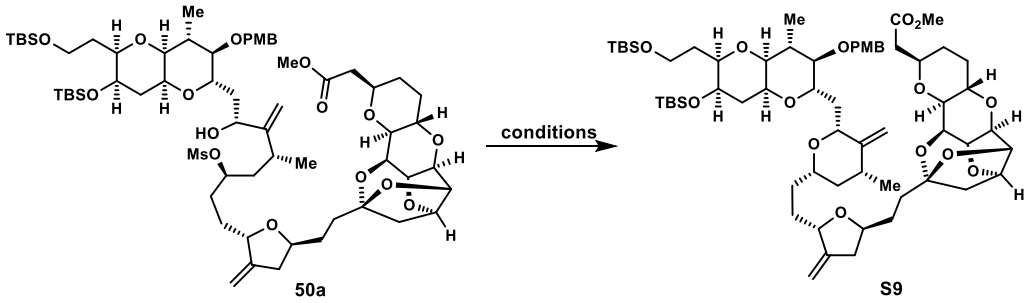
(m, 1 H), 1.95–1.91 (m, 1 H), 1.78–1.66 (m, 4 H), 1.64–1.57 (m, 2 H), 1.47 (dd, J = 13.1, 5.1 Hz, 1 H), 1.44–1.39 (m, 1 H), 1.35–1.21 (m, 4 H), 0.89 (d, J = 6.8 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 171.1, 152.3, 143.2, 114.7, 110.4, 104.9, 82.4, 81.7, 80.9, 79.0, 78.6, 77.4, 77.0, 74.9, 74.7, 74.3, 68.5, 51.1, 47.4, 41.7, 40.8, 39.1, 38.5, 35.9, 34.5, 31.7, 30.9, 30.8, 30.7, 30.3, 21.0 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{31}H_{46}O_{11}SNa^+$ 649.2653; Found 649.2663

Condition 4:

Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{(3*R*,5*R*,7*R*)-8-{(2*S*,3*R*,4*R*,4a*S*,6*R*,7*R*,8a*S*)-7-{[*tert*-butyl(dimethyl)silyl]oxy}-6-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-3-[(4-methoxybenzyl)-oxy]-4-methyloctahydropyrano[3,2-*b*]pyran-2-yl}-7-hydroxy-5-methyl-6-methylidene-3-[(methyl-sulfonyl)oxy]octyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo-[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]heptadec-4-yl]acetate (50a): In a glove box, to a stirred solution of **48a** (21 mg, 0.033 mmol, 1.1 equiv), **31** (23 mg, 0.030 mmol, 1.0 equiv), Et_3N (21 µL, 0.15 mmol, 5.0 equiv) and $CrCl_2$ (11mg, 0.099 mmol, 3.0 equiv) in THF (0.5 mL) at 23 °C was added a premixed solution of ligand **49** (23 mg, 0.075 mmol, 2.5 equiv) and $NiCl_2$ (1.0 mg, 0.0075 mmol, 0.25 equiv) in THF (0.5 mL). The resulting mixture was stirred for 6 h before it was quenched by the addition of H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 30 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 1:3, *v*/*v*) of the residue afforded **50a** (24mg, 0.019 mmol, 63% yield) as a colorless oil.



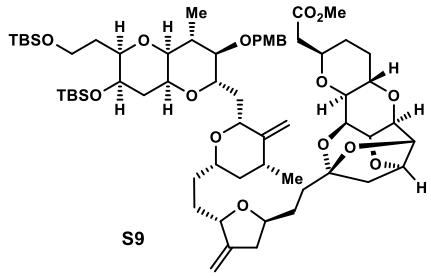
Cyclization Toward Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{2-[(2*R*,4*R*,6*S*)-6-({(2*R*,3*R*,4*R*,4a*R*,6*S*,7*R*,8a*R*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethyl)-3-[(4-methoxybenzyl)oxy]-4-methyloctahydropyrano[3,2-*b*]pyran-2-yl}methyl)-4-methyl-5-methylidenetetrahydro-2*H*-pyran-2-yl]ethyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.$0^{2,7}$.$0^{9,16}$.$0^{10,14}$]heptadec-4-yl]acetate (S9):



entry	base	solvent	ϑ / °C	time / h	yield
A	KO*t*-Bu (5 equiv)	THF/MeOAc	0 to 23	1	53%
B	K_2CO_3/18-crown-6 (3 equiv)	toluene:MeOH 10:1	60	0.5	61%
C	DBU (50 equiv)	toluene	100	1.5	33%

Note: NaH, KH, KHMDS, KO*t*-Bu, in THF, –78 to 0 °C, SM decomposed

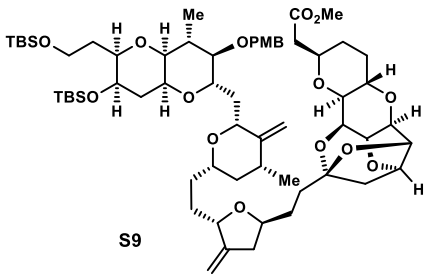
Condition A:



To a stirred solution of **50a** (5.0 mg, 0.0040 mmol, 1.0 equiv) in THF/MeOAc (2 mL, 5:1, *v*/*v*) at 0 °C were added KO*t*-Bu (4.5 mg, 0.040 mmol, 10.0 equiv). The resulting mixture was warmed to 23 °C and stirred for 15 min before it was quenched by the addition of sat. aq. NH_4Cl solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 1:1, *v*/*v*) of the residue afforded **S9** (2.4 mg, 0.0021 mmol, 53% yield) as a colorless oil. **S9:** R_f = 0.70 (SiO_2, hexanes/EtOAc 1:1, *v*/*v*); $[\alpha]_D^{23} = -33.4$ (*c* = 0.53, $CHCl_3$); FT-IR (film): ν_{max} 2954, 2927, 2855, 1741, 1613, 1514, 1462, 1437, 1361, 1250, 1189, 1134, 1079, 1039, 1008, 902, 834, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.27 (s, 1 H), 7.25 (s, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 4.96 (d, *J* = 2.1 Hz, 1 H), 4.93 (s, 1 H), 4.83 (d, *J* = 2.1 Hz, 1 H), 4.79 (d, *J* = 1.8 Hz, 1 H), 4.68 (t, *J* = 4.7 Hz, 1 H), 4.63–4.56 (m, 2 H), 4.50 (d, *J* = 10.5 Hz, 1 H), 4.42 (dd, *J* = 4.0, 1.9 Hz, 1 H), 4.38 (s, 1 H),

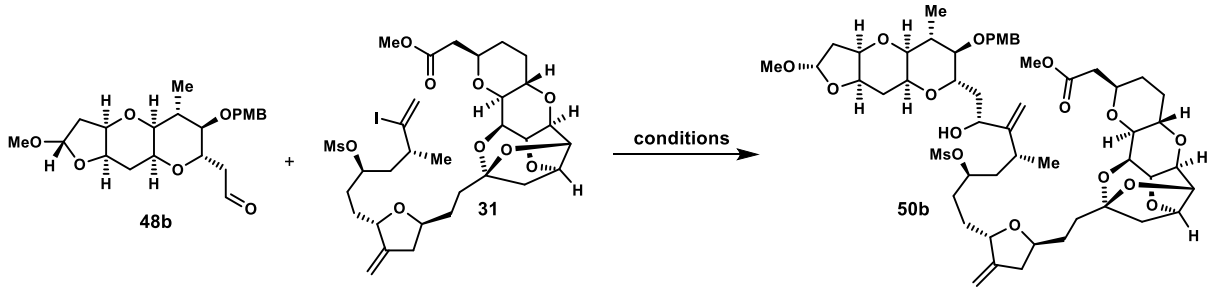
4.30–4.26 (m, 1 H), 4.19 (dd, *J* = 6.6, 4.6 Hz, 1 H), 4.06 (dd, *J* = 6.7, 4.0 Hz, 2 H), 3.95 (t, *J* = 6.5 Hz, 1 H), 3.86–3.80 (m, 1 H), 3.79 (s, 4 H), 3.78–3.73 (m, 3 H), 3.69 (dd, *J* = 5.6, 4.3 Hz, 1 H), 3.66 (s, 3 H), 3.55 (dt, *J* = 9.8, 3.4 Hz, 2 H), 3.36 (dd, *J* = 7.5, 4.8 Hz, 1 H), 3.09 (t, *J* = 9.2 Hz, 1 H), 2.92 (dd, *J* = 9.6, 1.9 Hz, 1 H), 2.68–2.60 (m, 2 H), 2.38 (dd, *J* = 15.9, 6.0 Hz, 1 H), 2.29–2.21 (m, 3 H), 2.18–2.08 (m, 2 H), 2.08–2.06 (m, 1 H), 2.03–1.92 (m, 3 H), 1.90–1.82 (m, 2 H), 1.82–1.75 (m, 4 H), 1.74–1.57 (m, 6 H), 1.53–1.45 (m, 1 H), 1.42–1.34 (m, 2 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 1.07 (d, *J* = 6.4 Hz, 3 H), 1.05–1.02 (m, 1 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.08—0.08 (m, 12 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7, 159.3, 151.8, 151.2, 130.8, 129.60, 129.57, 113.9, 110.5, 104.9, 104.7, 82.5, 82.2, 81.1, 79.4, 78.6, 78.1, 77.7, 76.7, 75.5, 74.6, 74.5, 74.1, 73.7, 73.5, 72.2, 68.4, 68.3, 66.6, 59.9, 55.4, 51.8, 47.1, 43.5, 40.6, 40.5, 39.7, 39.0, 36.2, 35.0, 34.7, 34.3, 33.7, 31.7, 30.7, 30.1, 29.85, 29.80, 26.1, 26.0, 18.5, 18.4, 18.2, 16.6, −4.2, −4.7, −5.1, −5.2 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{63}H_{100}O_{15}Si_2Na^+$ 1175.6493; Found 1175.6481. The data is in accordance with Phillips' intermediate.[6]

Condition B:



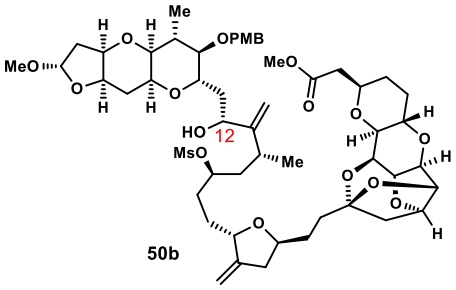
To a stirred solution of **50a** (5.0 mg, 0.0040 mmol, 1.0 equiv) in toluene/MeOH (1.5 mL, 10:1, *v*/*v*) at 23 °C were added a premixed solution of K_2CO_3/18-crown-6 (K_2CO_3: 1.7 mg, 0.012 mmol, 3.0 equiv; 18-crown-6: 3.2 mg, 0.012 mmol, 3.0 equiv) in toluene/MeOH (0.1 mL, 10:1, *v*/*v*). The resulting mixture was allowed to warm to 60 °C and stirred for 0.5 h before it was cooled to 0 °C and quenched by the addition of sat. aq. NH_4Cl solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 1:1, *v*/*v*) of the residue afforded **S9** (2.8 mg, 0.0024 mmol, 61% yield) as a colorless oil.

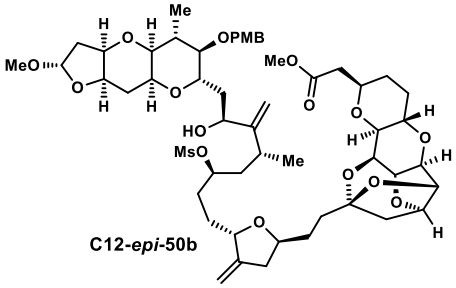
NHK Reaction Toward 50b:



Condition 1:

Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{(3*R*,5*R*,7*R*)-7-hydroxy-8-{(2*S*,3a*R*,4a*S*,5*R*,6*R*,7*S*,8a*S*,9a*R*)-2-methoxy-6-[(4-methoxybenzyl)oxy]-5-methyldecahydrofuro[3,2-*b*]pyrano[2,3-*e*]pyran-7-yl}-5-methyl-6-methylidene-3-[(methylsulfonyl)oxy]octyl}-4-methylidene-tetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]heptadec-4-yl]acetate (50b) and methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{(3*R*,5*R*,7*S*)-7-hydroxy-8-{(2*S*,3a*R*,4a*S*,5*R*,6*R*,7*S*,8a*S*,9a*R*)-2-methoxy-6-[(4-methoxybenzyl)oxy]-5-methyldeca-hydrofuro[3,2-*b*]pyrano[2,3-*e*]pyran-7-yl}-5-methyl-6-methylidene-3-[(methylsulfonyl)oxy]octyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]hepta-dec-4-yl]acetate (C12-*epi*-50b): In a glove box, to a stirred solution of **48b** (24.7 mg, 0.0608 mmol, 2.0 equiv) and **31** (22.9 mg, 0.0304 mmol, 1.0 equiv) in THF/DMF (1.0 mL, 4:1, *v*/*v*) at 23 °C was added 2.0% $NiCl_2/CrCl_2$ (37.4 mg, 0.304 mmol, 10.0 equiv). The resulting mixture was vigorously stirred for 24 h before it was quenched by the addition of H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 30 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc hexanes/EtOAc 3:1, *v*/*v* → 1:3, *v*/*v*) of the residue afforded alcohol **50b** (13.5 mg, 0.0131 mmol, 43% yield, 1:1 *dr* at C12) as a colorless oil, **de-I-31** (10.0 mg, 0.0152 mmol, 50%) as a colorless oil, and recovered



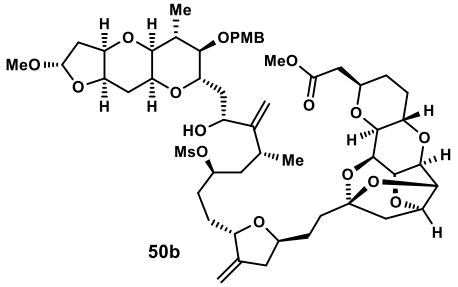


aldehyde **48a** (13.6 mg, 0.0334 mmol, 55%) as a white foam. Analytical samples were obtained by preparative TLC. **50b** (desired isomer): R_f = 0.60 (SiO_2, hexanes/EtOAc 1:4, *v*/*v*); $[\alpha]_D^{23}$ = −38.7 (*c* = 0.41, $CHCl_3$); FT-IR (film): ν_{max} 3477, 2936, 2878, 1737, 1613, 1514, 1438, 1336, 1301, 1249, 1211, 1171, 1133, 1074, 1039, 903, 828, 758 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 7.29 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 5.44 (d, *J* = 1.3 Hz, 1 H), 5.08 (dd, *J* = 5.4, 2.7 Hz, 1 H), 5.03–4.96 (m, 1 H), 4.91 (s, 2 H), 4.83 (d, *J* = 2.2 Hz, 1 H), 4.60 (dd, *J* = 9.5, 2.7 Hz, 1 H), 4.55–4.44 (m, 3 H), 4.41 (dd, *J* = 4.0, 1.9 Hz, 1 H), 4.34 (d, *J* = 7.8 Hz, 1 H), 4.20–4.15 (m, 2 H), 4.13 (t, *J* = 4.7 Hz, 1 H), 3.99–3.93 (m, 1 H), 3.91 (dd, *J* = 6.5, 4.5 Hz, 1 H), 3.78–3.74 (m, 2 H), 3.68 (dd, *J* = 6.6, 3.9 Hz, 1 H), 3.63 (dt, *J* = 6.5, 3.1 Hz, 1 H), 3.51–3.44 (m, 1 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.29 (s, 3 H), 3.00–2.87 (m, 2 H), 2.66–2.62 (m, 1 H), 2.62–2.55 (m, 2 H), 2.45 (s, 3 H), 2.27–2.16 (m, 4 H), 2.15–2.03 (m, 7 H), 2.01–1.94 (m, 2 H), 1.92 (dt, *J* = 14.2, 9.8 Hz, 1 H), 1.87–1.73 (m, 4 H), 1.70 (ddt, *J* = 17.2, 10.4, 3.1 Hz, 2 H), 1.65–1.60 (m, 2 H), 1.49 (dd, *J* = 13.2, 5.1 Hz, 1 H), 1.44–1.41 (m, 1 H), 1.34–1.23 (m, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.07 (d, *J* = 7.0 Hz, 3 H) ppm; ^1H NMR (151 MHz, C_6D_6): δ 171.1, 159.9, 157.0, 152.3, 131.2, 129.8, 114.2, 110.4, 108.6, 105.01, 104.96, 82.5, 82.44, 82.38, 81.0, 79.1, 78.6, 77.43, 77.35, 77.0, 75.9, 75.7, 75.5, 75.0, 74.7, 74.33, 74.30, 73.1, 68.5, 65.4, 55.1, 54.9, 51.2, 47.4, 42.0, 40.9, 40.8, 39.34, 39.09, 39.06, 38. 8, 35.8, 32.5, 31.6, 30.9, 30.7, 30.6, 30.3, 29.7, 22.8, 16.9 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{53}H_{76}O_{18}SNa^+$ 1055.4645; Found 1055.4635. C12-*epi*-**50b** (undesired isomer): R_f = 0.60 (SiO_2, hexanes/EtOAc 1:4, *v*/*v*); ^1H NMR (600 MHz, C_6D_6): δ 7.29 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 5.40 (s, 1 H), 5.17 (dd, *J* = 5.7, 3.1 Hz, 1 H), 5.10–5.05 (m, 1 H), 4.95–4.88 (m, 2 H), 4.83 (d, *J* = 2.1 Hz, 1 H), 4.78 (d, *J* = 10.8 Hz, 1 H), 4.57–4.45 (m, 3 H), 4.44–4.38 (m, 2 H), 4.36 (d, *J* = 7.2 Hz, 1 H), 4.18 (t, *J* = 4.5 Hz, 1 H), 4.13 (t, *J* = 4.7 Hz, 1 H), 4.01–3.94 (m, 1 H), 3.94–3.85 (m, 1 H), 3.77 (ddq, *J* = 6.7, 3.8, 2.1 Hz, 2 H), 3.68 (dd, *J* = 6.6, 3.9 Hz, 1 H), 3.61 (d, *J* = 3.9 Hz, 1 H), 3.52 (td, *J* = 4.6, 1.7 Hz, 2 H), 3.35–3.29 (m, 9 H), 3.03 (dd, *J* = 9.0, 5.8 Hz, 1 H), 3.00 (t, *J* = 4.2 Hz, 1 H), 2.68 (dt, *J* = 9.3, 6.3 Hz, 1 H), 2.63–2.55 (m, 2 H), 2.45 (s, 3 H), 2.31–2.15 (m, 6 H), 2.09–2.03 (m, 3 H), 2.02–1.94 (m, 4 H), 1.88–1.81 (m, 3 H), 1.80–1.76 (m, 2 H), 1.75–1.71 (m, 2 H), 1.71–1.66 (m, 2 H), 1.56 (dt, *J* = 14.3, 4.9 Hz, 2 H), 1.49 (dd, *J* = 13.1, 5.0 Hz, 2 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.02 (d, *J* = 7.3 Hz, 3 H) ppm; ^{13}H NMR (151 MHz, C_6D_6): δ 171.2, 159.8, 157.2, 152.3, 131.4, 129.8, 114.1, 110.5, 108.9, 105.2, 105.0, 83.2, 82.8, 82.4, 81.0, 79.1, 78.6, 77.3, 77.2, 77.0, 75.7, 74.9, 74.7, 74.3, 73.9, 72.3,

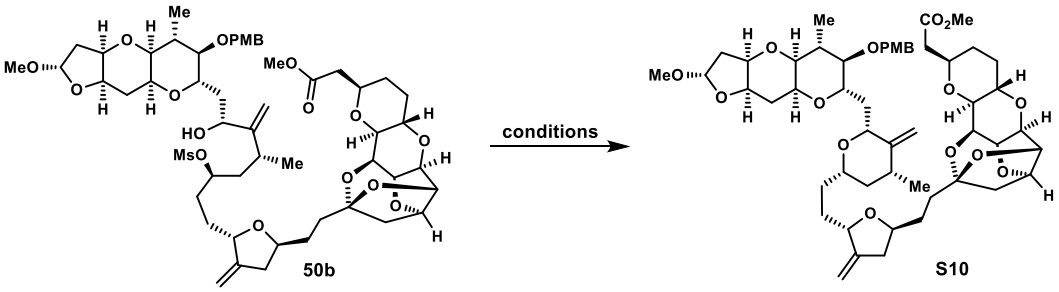
70.1, 69.8, 68.5, 64.3, 55.5, 54.8, 51.2, 47.4, 41.5, 41.4, 40.8, 40.7, 39.3, 39.1, 38.7, 35.8, 32.7, 31.7, 30.9, 30.7, 30.6, 30.3, 30.1, 22.8, 17.7 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{53}H_{76}O_{18}SNa^+$ 1055.4645; Found 1055.4633.

Condition 4:

Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{(3*R*,5*R*,7*R*)-7-hydroxy-8-{(2*S*,3a*R*,4a*S*,5*R*,6*R*,7*S*,8a*S*,9a*R*)-2-methoxy-6-[(4-methoxybenzyl)oxy]-5-methyldecahydrofuro[3,2-*b*]pyrano[2,3-*e*]pyran-7-yl}-5-methyl-6-methylidene-3-[(methylsulfonyl)oxy]octyl}-4-methylidene-tetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]heptadec-4-yl]-acetate (50b): In a glove box, to a stirred solution of **48b** (15 mg, 0.036 mmol, 1.2 equiv), **31** (23 mg, 0.031 mmol, 1.0 equiv), Et_3N (21 μL, 0.15 mmol, 5.0 equiv) and $CrCl_2$ (11 mg, 0.090 mmol, 3.0 equiv) in THF (0.5 mL) at 23 °C was added a premixed solution of ligand **49** (45 mg, 0.15 mmol, 2.5 equiv) and $NiCl_2$ (1.0 mg, 0.0075 mmol, 0.25 equiv) in THF (0.5 mL). The resulting mixture was stirred for 6 h before it was quenched by the addition of H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 30 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc hexanes/EtOAc 3:1, *v*/*v* → 1:3, *v*/*v*) of the residue afforded **50b** (19 mg, 0.019 mmol, 62% yield, *dr* > 5: 1) as a colorless oil.

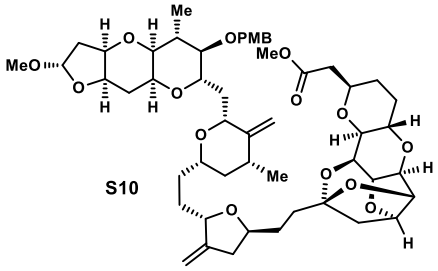


Cyclization Toward Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{2-[(2*S*,4*R*,6*R*)-6-({(2*S*,3a*R*,4a*S*,5*R*,6*R*,7*S*,8a*S*,9a*R*)-2-Methoxy-6-[(4-methoxybenzyl)oxy]-5-methyldecahydrofuro-[3,2-*b*]pyrano[2,3-*e*]pyran-7-yl}methyl)-4-methyl-5-methylidenetetrahydro-2*H*-pyran-2-yl]ethyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.$0^{2,7}$.$0^{9,16}$.$0^{10,14}$]-heptadec-4-yl]acetate (S10):



entry	base	solvent	ϑ / °C	time / h	yield
A	KO*t*-Bu (5 equiv)	THF/MeOAc	0 to 23	1	55%
B	K_2CO_3/18-crown-6 (3 equiv)	toluene:MeOH 10:1	60	0.5	63%
C	DBU (50 equiv)	toluene	100	1.5	35%
D	DBU (100 equiv)	toluene	110	1.5	70%

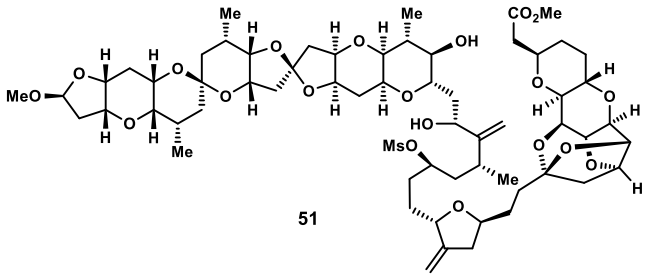
Condition D:



To a stirred solution of **50b** (10 mg, 0.0097 mmol, 1.0 equiv) in toluene (2 mL) at 23 °C were added DBU (0.15 mL, 0.97 mmol, 1.0 equiv). The resulting mixture was warmed to 110 °C and stirred for 1.5 h before it was allowed to cool to 23 °C and quenched by the addition of sat. aq. NH_4Cl solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 1:2, *v*/*v*) of the residue afforded **S10** (6.3 mg, 0.0068 mmol, 70% yield) as a colorless oil. **S10:** R_f = 0.80 (SiO_2, 100% EtOAc); $[\alpha]_D^{23}$ = −32.6 (*c* = 0.60, EtOAc); FT-IR (film): ν_{max} 2928, 2870, 1738, 1612, 1514, 1438, 1354, 1301, 1248, 1210, 1188, 1154, 1133, 1076, 1039, 997, 907, 824, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 5.05 (dd, *J* = 5.4, 2.0 Hz, 1 H), 4.97 (d, *J* = 2.1 Hz, 1 H), 4.93 (s, 1 H), 4.84 (d, *J* = 2.1 Hz, 1 H), 4.80 (d, *J* = 1.9 Hz, 1 H), 4.68 (t, *J* = 4.7 Hz, 1 H), 4.60 (t, *J* = 4.6 Hz, 1 H), 4.58–4.48 (m, 2 H), 4.43 (dd, *J* = 4.0,

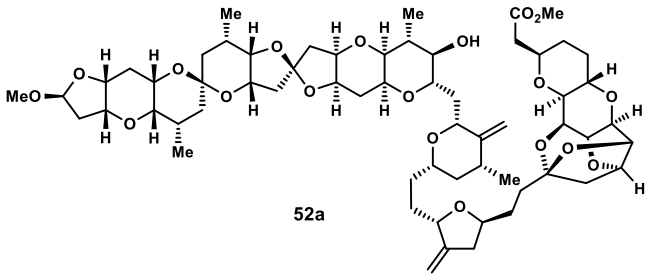
1.9 Hz, 1 H), 4.39 (s, 1 H), 4.28 (td, *J* = 10.1, 4.4 Hz, 1 H), 4.20 (dd, *J* = 6.6, 4.6 Hz, 1 H), 4.09–4.03 (m, 2 H), 4.05–3.98 (m, 2 H), 3.91 (dd, *J* = 8.3, 4.8 Hz, 1 H), 3.84–3.78 (m, 5 H), 3.78–3.74 (m, 1 H), 3.67 (s, 3 H), 3.62–3.55 (m, 1 H), 3.32–3.30 (m, 4 H), 2.99 (t, *J* = 8.4 Hz, 1 H), 2.92 (dd, *J* = 9.5, 1.9 Hz, 1 H), 2.65 (dd, *J* = 15.9, 6.8 Hz, 2 H), 2.39 (dd, *J* = 15.9, 6.0 Hz, 1 H), 2.31–2.21 (m, 3 H), 2.17–2.05 (m, 5 H), 1.97 (tt, *J* = 14.8, 7.1 Hz, 4 H), 1.87–1.75 (m, 4 H), 1.74–1.60 (m, 6 H), 1.51–1.47 (m, 1 H), 1.42–1.33 (m, 2 H), 1.14 (d, *J* = 6.8 Hz, 3 H), 1.07 (d, *J* = 6.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7, 159.4, 151.9, 151.14, 130.6, 129.6, 114.0, 110.5, 104.9, 104.8, 104.6, 82.5, 82.2, 81.2, 79.5, 78.2, 77.8, 77.5, 76.8, 75.6, 75.2, 74.9, 74.59, 74.55, 74.1, 73.3, 72.3, 68.4, 66.0, 55.4, 55.0, 51.8, 47.1, 43.6, 40.6, 40.4, 39.0, 38.8, 36.2, 35.1, 35.0, 31.72, 31.67, 30.7, 30.1, 29.8, 29.0, 18.2, 16.4 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{52}H_{72}O_{15}Na^+$ 959.4763; Found 959.4757.

Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{(3*R*,5*R*,7*R*)-7-hydroxy-8-[(2*R*,2″*R*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-6-hydroxy-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-7-yl]-5-methyl-6-methylidene-3-[(methylsulfonyl)oxy]octyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]heptadec-4-yl]acetate (51): In a glove box, to a stirred solution of C16-*epi*-**30** (20 mg, 0.034 mmol, 1.0 equiv), **31** (31 mg, 0.041 mmol, 1.2 equiv), Et_3N (29 µL, 0.20 mmol, 6.0 equiv), and $CrCl_2$ (15 mg, 0.12 mmol, 3.6 equiv) in THF (0.2 mL) at 23 °C was added a premixed solution of ligand **49** (31 mg, 0.10 mmol, 3.0 equiv) and $NiCl_2$ (1.1 mg, 0.0082 mmol, 0.2 equiv) in THF (0.5 mL). The resulting mixture was stirred for 6 h before it was quenched by the addition of H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 30 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 3:1, *v*/*v* → 1:3, *v*/*v*) of the residue afforded **51** (27 mg, 0.022 mmol, 65% yield) as a light



green oil. **51**: R_f = 0.40 (SiO_2, 100% EtOAc); $[\alpha]_D^{23}$ = −36.0 (*c* = 0.10, EtOAc); FT-IR (film): ν_{max} 3477, 2926, 2872, 1736, 1555, 1436, 1333, 1264, 1194, 1171, 1076, 1019, 973, 904, 846 cm^{-1}; ^1H NMR (151 MHz, C_6D_6): δ 5.33 (s, 1 H), 5.15 (dd, *J* = 5.8, 3.7 Hz, 1 H), 4.99–4.93 (m, 1 H), 4.93 (d, *J* = 2.2 Hz, 1 H), 4.88 (s, 1 H), 4.83 (d, *J* = 2.2 Hz, 1 H), 4.58–4.45 (m, 1 H), 4.41 (dd, *J* = 4.0, 1.9 Hz, 1 H), 4.39–4.32 (m, 1 H), 4.19 (t, *J* = 4.5 Hz, 1 H), 4.14 (t, *J* = 4.7 Hz, 1 H), 4.06–4.00 (m, 1 H), 4.01–3.95 (m, 1 H), 3.93–3.90 (m, 1 H), 3.90–3.87 (m, 1 H), 3.82 (dd, *J* = 4.7, 2.2 Hz, 1 H), 3.78–3.72 (m, 4 H), 3.68 (dd, *J* = 6.6, 3.9 Hz, 1 H), 3.58 (dd, *J* = 5.5, 2.4 Hz, 1 H), 3.55–3.51 (m, 1 H), 3.35 (s, 3 H), 3.34–3.31 (m, 1 H), 3.20 (s, 3 H), 3.10–3.04 (m, 1 H), 3.02 (dd, *J* = 6.7, 5.2 Hz, 1 H), 2.69 (d, *J* = 2.8 Hz, 1 H), 2.63–2.56 (m, 3 H), 2.47–2.43 (m, 2 H), 2.43 (s, 3 H), 2.40–2.33 (m, 1 H), 2.33–2.25 (m, 3 H), 2.20 (dd, *J* = 15.7, 5.3 Hz, 1 H), 2.18–2.12 (m, 4 H), 2.08–2.02 (m, 4 H), 2.02–1.93 (m, 5 H), 1.82–1.67 (m, 7 H), 1.54–1.48 (m, 2 H), 1.48–1.40 (m, 4 H), 1.35–1.26 (m, 5 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 1.06 (d, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H) ppm; ^1H NMR (151 MHz, C_6D_6): δ 171.2, 156.8, 152.3, 114.8, 110. 5, 109.0, 105.0, 104.9, 97.0, 82.6, 82.4, 81.0, 79.5, 79.0, 78.6, 77.6, 77.41, 77.36, 77.33, 77.2, 77.00, 76.9, 76.4, 75.0, 74.8, 74.7, 74.3, 74.0, 73.9, 72.3, 72.01 71.5, 68.5, 66.3, 63.8, 55.3, 51.2, 47.4, 42.1, 41.8, 40.8, 39.6, 39.1, 38.9, 38.7, 37.7, 37.2, 35.8, 32.4, 31.5, 30.9, 30.7, 30.6, 30.5, 30.3, 29.2, 26.1, 22.8, 18.1, 17.5, 16.7, 15.7 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{62}H_{92}O_{22}SNa^+$ 1243.5693; Found 1243.5697.

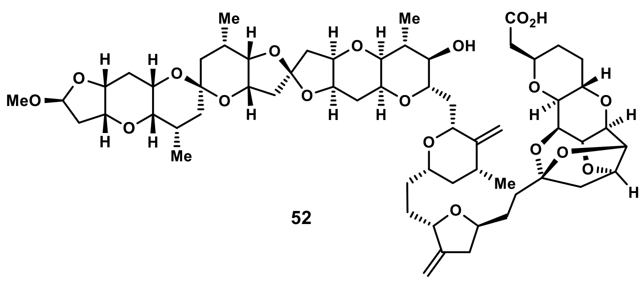
Methyl [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{2-[(2*S*,4*R*,6*R*)-6-{[(2*R*,2″*R*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-6-hydroxy-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo-[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-7-yl]methyl}-4-methyl-5-methylidenetetrahydro-2*H*-pyran-2-yl]ethyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo-[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]heptadec-4-yl]acetate (52a): To a stirred solution of **51** (10 mg, 0.0082 mmol, 1.0 equiv) in toluene (1.5 mL) at 23 °C was added DBU (0.13 mL, 0.82 mmol, 100 equiv). The



52a

resulting mixture was warmed to 110 °C and stirred for 1 h before it was allowed to cool to 23 °C and quenched by the addition of sat. aq. NH_4Cl solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 2:1, *v*/*v* → 1:5, *v*/*v*) of the residue afforded **52a** (6.5 mg, 0.0057 mmol, 70% yield) as a colorless oil. **52a:** R_f = 0.60 (SiO_2, 100% EtOAc); $[\alpha]_D^{23} = -36.7$ (*c* = 0.10, EtOAc); FT-IR (film): ν_{max} 3493, 2925, 2870, 1739, 1553, 1457, 1330, 1261, 1193, 1078, 1021, 900,802 cm^{-1}. ^1H NMR (600 MHz, C_6D_6): δ 5.16 (dd, *J* = 5.9, 3.6 Hz, 1 H), 4.99–4.91 (m, 3 H), 4.79 (d, *J* = 1.8 Hz, 1 H), 4.56–4.50 (m, 2 H), 4.43 (dd, *J* = 3.9, 1.9 Hz, 1 H), 4.17 (t, *J* = 4.6 Hz, 1 H), 4.11 (t, *J* = 4.8 Hz, 1 H), 4.08 (t, *J* = 5.7 Hz, 1 H), 4.03 (t, *J* = 6.7 Hz, 1 H), 3.91 (ddd, *J* = 13.1, 6.9, 4.7 Hz, 3 H), 3.87 (t, *J* = 2.6 Hz, 1 H), 3.81 (dd, *J* = 4.8, 2.0 Hz, 1 H), 3.76 (dd, *J* = 5.1, 2.4 Hz, 2 H), 3.72–3.67 (m, 2 H), 3.66–3.61 (m, 1 H), 3.57 (dd, *J* = 5.5, 2.3 Hz, 1 H), 3.48–3.37 (m, 1 H), 3.39–3.30 (m, 6 H), 3.25–3.18 (m, 4 H), 2.69 (d, *J* = 2.8 Hz, 1 H), 2.62–2.53 (m, 3 H), 2.53–2.42 (m, 3 H), 2.38–2.28 (m, 3 H), 2.26–2.10 (m, 8 H), 2.10–2.02 (m, 3 H), 2.02–1.92 (m, 4 H), 1.90–1.83 (m, 1 H), 1.82–1.73 (m, 4 H), 1.71–1.66 (m, 1 H), 1.55–1.45 (m, 5 H), 1.40 (d, *J* = 12.5 Hz, 3 H), 1.35–1.27 (m, 4 H), 1.10–1.08 (m, 1 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 171.2, 152.8, 151.4, 127.6, 114.7, 110.5, 104.9, 104.8, 97.0, 82.3, 81.0, 79.4, 79.2, 78.7, 78.5, 77.9, 77.3, 77.0, 76.9, 76.1, 75.7, 75.0, 74.7, 74.42, 74.36, 73.9, 73.1, 72.3, 72.1, 68.5, 67.7, 63.8, 55.3, 51.1, 47.3, 45.6, 45.4, 43.1, 42.1, 40.7, 40.0, 39.3, 37.7, 37.2, 36.2, 35.9, 34.2, 32.1, 31.9, 30.9, 30.7, 30.6, 30.5, 30.3, 30.1, 29.2, 26.1, 18.2, 18.0, 17.5, 15.8 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{61}H_{88}O_{19}Na^+$ 1147.5812; Found 1147.5796.

[(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{2-[(2*S*,4*R*,6*R*)-6-{[(2*R*,2″*R*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-6-Hydroxy-2″-methoxy-5,5″,7′-trimethyl-icosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-7-yl]methyl}-4-methyl-5-methylidenetetrahydro-2*H*-pyran-2-yl]ethyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo[10.4.1.0^{2,7}.0^{9,16}.0^{10,14}]-heptadec-4-yl]acetic acid (52): To a stirred solution of **52a** (6.5 mg, 0.0057 mmol, 1.0 equiv) in THF/H_2O (1 mL, 2:1, *v*/*v*) at 23 °C was added LiOH (2.5 mg, 0.11 mmol, 20.0 equiv). The resulting mixture was stirred for 2 h before it was quenched by the addition of aq. HCl (0.1 M, 2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, EtOAc:MeOH 100:1, *v*/*v* → 3:1, *v*/*v*) of the residue afforded carboxylic acid **52** (6.3 mg, 0.0057 mmol, quant. yield) as a colorless oil. **52**: R_f = 0.60 (SiO_2, EtOAc/MeOH 5:1, *v*/*v*); $[\alpha]_D^{23}$ = −43.3 (*c* = 0.15, $CHCl_3$); FTIR (film): ν_{max} 3430, 2927, 2870, 1732, 1556, 1457, 1370, 1262, 1191, 1131, 1072, 1050, 1021, 972, 895, 828 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6): δ 5.16 (dd, *J* = 5.8, 3.6 Hz, 1 H), 5.00 (s, 1 H), 4.97 (d, *J* = 2.3 Hz, 1 H), 4.95 (s, 1 H), 4.80–4.76 (m, 1 H), 4.57 (s, 1 H), 4.50 (td, *J* = 10.4, 4.1 Hz, 1 H), 4.39 (s, 1 H), 4.18 (t, *J* = 4.4 Hz, 1 H), 4.12 (t, *J* = 4.7 Hz, 2 H), 4.06 (t, *J* = 6.0 Hz, 1 H), 4.01 (q, *J* = 5.7 Hz, 1 H), 3.95–3.88 (m, 2 H), 3.88 (d, *J* = 5.0 Hz, 1 H), 3.85–3.79 (m, 1 H), 3.76 (d, *J* = 4.2 Hz, 1 H), 3.72–3.69 (m, 2 H), 3.62 (t, *J* = 5.7 Hz, 1 H), 3.60–3.53 (m, 2 H), 3.51–3.44 (m, 1 H), 3.36 (t, *J* = 7.8 Hz, 1 H), 3.34–3.30 (m, 1 H), 3.22 (s, 3 H), 3.22–3.19 (m, 1 H), 2.68 (d, *J* = 2.9 Hz, 1 H), 2.59–2.44 (m, 6 H), 2.44–2.34 (m, 2 H), 2.34–2.22 (m, 4 H), 2.21–2.08 (m, 7 H), 2.07–1.99 (m, 4 H), 1.98–1.85 (m, 3 H), 1.84–1.68 (m, 5 H), 1.61–1.53 (m, 2 H), 1.53–1.42 (m, 7 H), 1.36 (t, *J* = 3.0 Hz, 1 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 152.4, 151.5, 114.8, 110.2, 105.1, 104.8, 104.8, 97.0, 82.6, 81.0, 79.4, 79.2, 78.3, 78.2, 77.7, 77.6, 77.3, 77.0, 76.9, 76.2, 75.8, 74.6, 74.5, 74.1, 73.9, 73.1, 72.3, 72.1, 68.7, 63.7, 55.7, 55.4, 47.7, 45.7, 45.5, 43.1, 42.0, 39.9, 39.0, 37.7, 37.1, 36.2, 35.7, 34.3, 32.1, 31.8, 30.7, 30.5, 30.3, 30.24,

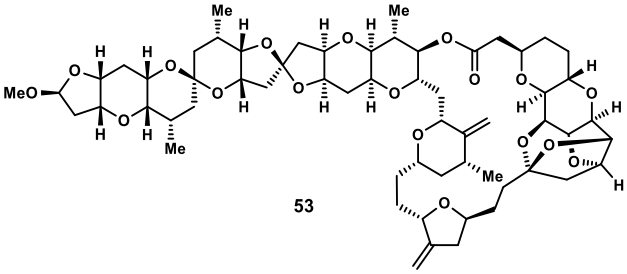


52

30.22, 30.18, 29.8, 29.2, 26.1, 18.2, 18.1, 17.5, 15.8 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{60}H_{86}O_{19}Na^+$ 1133.5656; Found 1133.5634.

One-Pot Procedure Toward [(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*,12*S*,14*R*,16*R*)-12-{2-[(2*S*,5*S*)-5-{2-[(2*S*,4*R*,6*R*)-6-{[(2*R*,2″*R*,3a*R*,3a′*S*,3a″*R*,4a*S*,4a″*S*,5*R*,5′*R*,5″*S*,6*R*,7*S*,7′*S*,7a′*S*,8a*S*,8a″*S*,9a*R*,9a″*R*)-6-Hydroxy-2″-methoxy-5,5″,7′-trimethylicosahydro-2″*H*,3*H*,3′*H*-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-2,2′-furo-[3,2-*b*]pyran-5′,7″-furo[3,2-*b*]pyrano[2,3-*e*]pyran]-7-yl]methyl}-4-methyl-5-methylidenetetrahydro-2*H*-pyran-2-yl]ethyl}-4-methylidenetetrahydrofuran-2-yl]ethyl}-3,8,11,15,17-pentaoxapentacyclo-[10.4.1.$0^{2,7}$.$0^{9,16}$.$0^{10,14}$]heptadec-4-yl]acetic acid (52): To a stirred solution of **51** (10 mg, 0.0082 mmol, 1.0 equiv) in toluene (1.5 mL) at 23 °C was added DBU (0.13 mL, 0.82 mmol, 100 equiv). The resulting mixture was warmed to 110 °C and stirred for 1 h before it was allowed to cool to 23 °C. Then, a LiOH solution in THF/H_2O [2 mL, 0.5 M in THF:H_2O (1:1, *v*/*v*)] was added. The resulting mixture was stirred for 3.5 h before it was quenched by the addition of aq. HCl (0.3 M, 10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were washed with aq. HCl (0.1 M, 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, EtOAc:MeOH 100:1, *v*/*v* → 3:1, *v*/*v*) of the residue afforded carboxylic acid **52** (6.0 mg, 0.0055 mmol, 67% yield) as a colorless oil.

[1″*R*-[1″*S*,2″*R*,3″a*R*,3″b*S*,5″*S*,8″*S*,11″*S*,14″*S*,16″*R*,18″*R*,19″a*S*,20″a*S*,21″a*R*,23″*R*[3′a*S*,5′*R*(2*S*,3a*R*,4a*S*,5*S*,8a*S*,9a*R*),7′*S*,7′a*S*],24″a*R*,25″a*S*,26″*S*,26″a*R*,30″*R*,31″a*S*,32″*S*,33″a*R*]]-dotetracontahydro-2-methoxy-5,7′,16″,26″-tetramethyl-10″,17″-bis(methylene)-dispiro[furo[3,2-*b*]pyrano[2,3-*e*]pyran-7(2*H*),5′-[5*H*]furo[3,2-*b*]pyran-2′(3′*H*),23″(6″*H*)-[1,5:8,11:14,18]triepoxy[30,32]ethano[2,5]methano-[2*H*,5*H*,28*H*]furo[2′,3′:5,6]pyrano[4,3-*b*]furo[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-*i*][1,4,8]trioxa-cyclopentacosin]-28″-one (53): To a stirred solution of 2-methyl-6-nitrobenzoic anhydride (8.8 mg, 0.026 mmol, 5.0 equiv.) and *N*,*N*-dimethylpyridin-4-amine (6.2 mg, 0.051 mmol, 10.0 equiv) in toluene (1.5 mL) at 70 °C was added a solution of **52** (5.7 mg, 0.0051 mmol, 1.0 equiv) and *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (5.0 µL, 0.026 mmol, 5.0 equiv.) in toluene (1 mL) via a syringe pump over 12 h. After completion of the addition, the syringe was rinsed with toluene (0.3 mL). After being stirred for additional 0.5 h, the reaction mixture was allowed to cool to 23 °C and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 2:1, *v*/*v* → 1:2, *v*/*v*) of the residue afforded macrolide **53** (3.9 mg, 0.0036 mmol, 70% yield) as a colorless oil.

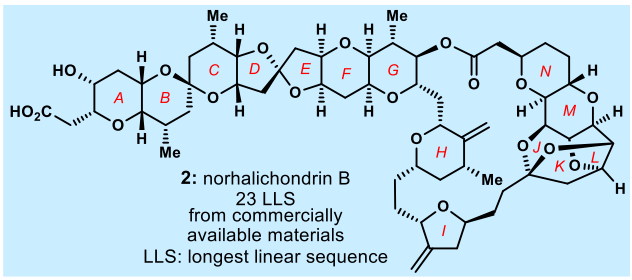


53

53: R_f = 0.80 (SiO_2, 100% EtOA); $[\alpha]_D^{23}$ = −35.0 (*c* = 0.10, EtOAc); FTIR (film): ν_{max} 2925, 2853, 1735, 1263, 1187, 1076, 1023, 898, 798, 731 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 5.15 (dd, *J* = 5.8, 3.7 Hz, 1 H), 5.01 (d, *J* = 2.5 Hz, 1 H), 4.96 (s, 2 H), 4.93 (dd, *J* = 10.6, 6.4 Hz, 1 H), 4.84 (d, *J* = 1.8 Hz, 1 H), 4.65–4.56 (m, 2 H), 4.55–4.48 (m, 1 H), 4.30–4.27 (m, 1 H), 4.15 (t, *J* = 4.6 Hz, 1 H), 4.10–4.03 (m, 2 H), 3.99 (dt, *J* = 12.1, 6.2 Hz, 1 H), 3.95–3.86 (m, 3 H), 3.84–3.79 (m, 3 H), 3.80–3.72 (m, 2 H), 3.63 (dd, *J* = 6.6, 4.1 Hz, 1 H), 3.58 (dd, *J* = 5.5, 2.4 Hz, 1 H), 3.42 (dt, *J* = 11.7, 6.0 Hz, 1 H), 3.33 (d, *J* = 4.5 Hz, 1 H), 3.21 (s, 3 H), 2.73–2.67 (m, 3 H), 2.66–2.61 (m, 2 H), 2.58 (dd, *J* = 12.8, 5.8 Hz, 2 H), 2.46 (dd, *J* = 14.1, 4.8 Hz, 1 H), 2.39–2.27 (m, 7 H), 2.26–2.21 (m, 3 H), 2.19–2.10 (m, 6 H), 2.05 (ddd, *J* = 14.1, 5.7, 3.7 Hz, 2 H), 2.01–1.91 (m, 2 H), 1.87 (td, *J* = 9.0, 4.4 Hz, 1 H), 1.73–1.65 (m, 2 H), 1.63–1.56 (m, 1 H), 1.54–1.48 (m, 2 H), 1.48–1.42 (m, 5 H), 1.32–1.29 (m, 4 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.05 (d, *J* = 6.4 Hz, 3 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 7.0 Hz, 3H). ppm; ^{13}C NMR (151 MHz, C_6D_6): δ 171.1, 152.9, 152.5, 114.3, 110.2, 104.9, 104.4, 104.0, 97.0, 82.5, 81.0, 79.0, 78.5, 78.4, 78.2, 77.4, 77.33, 77.31, 76.9, 75.4, 75.3, 75.1, 75.0, 74.2, 74.1,

73.9, 73.8, 72.4, 72.3, 71.9, 68.4, 67.3, 63.8, 55.4, 48.7, 45.3, 44.8, 44.0, 42.1, 40.6, 39.2, 37.7, 37.5, 37.2, 36.7, 36.5, 35.1, 32.8, 31.0, 30.9, 30.6, 30.3, 29.6, 29.2, 28.7, 25.9, 18.2, 18.0, 17.6, 15.1 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{60}H_{84}O_{18}Na^+$ 1115.5550; Found 1115.5531

(1″*S*,2*R*,2′*R*,2″*R*,3′a*S*,3″a*R*,3″b*S*,4*S*,4a*S*,5″*S*,6*R*,7*R*,7′*S*,7′a*S*,8″*S*,8a*S*,11″*S*,14″*S*,16″*R*,18″*R*,19″a*S*,20″a*S*,21″a*R*,24″a*R*,25″a*S*,26″*S*,26″a*R*,30″*R*,31″a*S*,32″*S*,33″a*R*)-Tetracontahydro-7-hydroxy-4,7′,16″,26″-tetramethyl-10″,17″-bis(methylene)-28″-oxo-dispiro[pyrano[3,2-*b*]pyran-2(3*H*),5′-[5*H*]furo[3,2-*b*]pyran-2′(3′*H*),23″(6″*H*)-[1,5:8,11:14,18]triepoxy[30,32]ethano[2,5]methano[2*H*,5*H*,28*H*]furo[2′,3′:5,6]pyrano[4,3-*b*]furo[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-*i*][1,4,8]trioxacyclopentacosin]-6-acetic acid (2): A solution of **53** (2.7 mg, 0.0025 mmol, 1.0 equiv) in AcOH/H_2O (0.6 mL, 2:1, *v*/*v*) at 50 °C was stirred 1 h before it was concentrated under reduced pressure to the give the crude corresponding hemiacetal and its tautomer.



To a stirred solution of the above obtained hemiacetal and tautomer in *t*-BuOH/THF (1.0 mL, 4:1, *v*/*v*) at 23 °C was added 2-methylbut-2-ene (13 µL, 0.25 mmol, 25.0 equiv), followed by a solution of $NaClO_2$ (2.2 mg, 0.025 mmol, 10.0 equiv) and $NaH_2PO_4 \cdot H_2O$ (8.0 mg, 4.5 mmol, 20 equiv) in H_2O (0.15 mL). The resulting mixture was stirred for 0.5 h before it was diluted with aq. HCl (0.05 M, 3 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, EtOAc:MeOH 50:1, *v*/*v* → 4:1, *v*/*v*) of the residue afforded norhalichondrin B (**2**; 1.8 mg, 0.0017 mmol, 68% for the two steps) as a colorless oil. **2**: R_f = 0.50 (SiO_2, EtOAc/MeOH 5:1, *v*/*v*); $[\alpha]_D^{23}$ = −55.4 (*c* = 0.10, MeOH); FTIR (film): ν_{max} 3446, 2928, 2872, 1735, 1649, 1572, 1407, 1338, 1268, 1190, 1134, 1071, 1045, 1019, 995 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ 5.06 (d, *J* = 1.5 Hz, 1 H), 5.02 (brs, 1 H), 4.88 (s, 1H, from HSQC), 4.81 (s, 1 H), 4.70 (t, *J* = 4.6 Hz, 1 H), 4.64–4.57 (m, 2 H), 4.45 (d, *J* = 11.0 Hz, 1 H), 4.33 (dt, *J* = 10.4, 5.1 Hz, 1 H), 4.31–4.28 (m, 1 H), 4.27–4.21 (m, 1 H), 4.18 (dd, *J* = 6.6, 4.5 Hz, 1 H), 4.13–4.09 (m, 3 H), 4.10–4.04 (m, 1 H), 3.98 (d,

J = 2.6 Hz, 1 H), 3.92–3.84 (m, 2 H), 3.82–3.75 (m, 2 H), 3.74–3.67 (m, 2 H), 3.63–3.58 (m, 2 H), 3.31 (m, 1H, from HSQC), 3.21 (dd, *J* = 6.5, 4.6 Hz, 1 H), 2.98 (dd, *J* = 9.5, 2.1 Hz, 1 H), 2.83–2.77 (m, 1 H), 2.56 (dd, *J* = 17.5, 9.7 Hz, 1 H), 2.48 (d, *J* = 6.7 Hz, 2 H), 2.45 (dd, *J* = 17.8, 2.3 Hz, 1 H), 2.39 (dd, *J* = 13.2, 5.8 Hz, 1 H), 2.33 (d, *J* = 2.9 Hz, 2 H), 2.31–2.23 (m, 4 H), 2.22–2.13 (m, 3 H), 2.11–2.03 (m, 5 H), 2.03–1.92 (m, 4 H), 1.87–1.79 (m, 2 H), 1.76–1.66 (m, 3 H), 1.60 (td, *J* = 12.7, 6.2 Hz, 1 H), 1.55–1.47 (m, 3 H), 1.46–1.28 (m, 6 H), 1.10 (d, *J* = 6.5 Hz, 3 H), 1.06 (d, *J* = 7.1 Hz, 3 H), 1.02 (d, *J* = 11.8 Hz, 1 H), 0.98 (d, *J* = 7.4 Hz, 3 H), 0.96 (d, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_3OD): δ 179.8, 172.8, 153.3, 153.2, 114.8, 111.3, 105.7, 104.8, 98.5, 83.8, 82.4, 80.7, 79.10, 79.08, 78.98, 77.95, 77.9, 77.32, 77.30, 77.2, 76.3, 76.1, 75.8, 75.3, 75.0, 74.9, 73.8, 72.6, 69.6, 68.2, 68.1, 65.6, 45.5, 44.9, 41.5, 41.2, 39.7, 38.3, 38.1, 37.8, 37.4, 37.2, 35.8, 35.7, 33.0, 31.8, 31.3, 31.1, 30.9, 30.1, 29.4, 27.3, 18.4, 18.1, 17.4, 15.8 ppm; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{59}H_{82}O_{19}Na^+$ 1117.5343; Found 1117.5330.