Stereoselective Syntheses of Functionalized Precursors of the CDEF and CDE 2,6-Dideoxy-Tetra- and Trisaccharide Units of Durhamycins A and B

Supporting Information

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General Methods: All reaction solvents were purified before use. Tetrahydrofuran, dichloromethane, and toluene were purified by passage through a solvent column¹ composed of activated A-1 alumina. Unless otherwise indicated, all commercial reagents were used as received without further purification.

Physical Properties and Spectroscopic Measurements: Proton nuclear magnetic resonance (¹H NMR) spectra and carbon-13 (¹³C) NMR spectra were recorded on a Varian VXR-400 spectrometer at 400 MHz and 100 MHz respectively, or on a Varian Inova-500 spectrometer at 500 MHz and 125 respectively. The proton signal of residual, non-deuterated solvent (δ 7.26 ppm for CHCl₃; δ 7.16 ppm for C₆D₅H) or tetramethylsilane (δ 0 ppm, CDCl₃) was used as an internal reference for ¹H spectra. For ¹³C spectra, chemical shifts are reported relative to the δ 77.23 ppm resonance of CDCl₃ or the δ 128.39 ppm resonance of C₆D₆. Coupling constants are reported in Hz. Infrared (IR) spectra were recorded as thin films on a Perkin-Elmer Spectrum 1000 FTIR. Optical rotations were measured on a Rudolph Autopol III polarimeter using a quartz cell with 1 mL capacity and a 10 cm path length. Mass spectra were recorded on a VG 70-250-S spectrometer manufactured by Micromass Corp. (Manchester UK).

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F₂₅₄ glass plates precoated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with Hanessian stain (a mixture of ceric sulfate and ammonium molybdate in aqueous sulfuric acid), KMnO₄, or *p*-anisaldehyde solutions. Column chromatography was generally performed using Kieselgel 60 (230-400 mesh) silica gel. Unless noted otherwise, all compounds isolated by chromatography were sufficiently pure by ¹H NMR analysis for use in subsequent reactions.

HPLC purifications were performed by using a HPLC system composed of two Rainin HPXL pumps connected to various Dynamax[®] axial compression columns packed with Rainin 60 Å irregular silica gel. Samples were loaded into the system with a 2 mL Rheodyne 7125 injector and were detected using either a Rainin Dynamax[®] UV-C detector or a Rainin Dynamax[®] RI-1 detector. Integration of the various signals was performed using the reprocessing program within the Dynamax[®] HPLC Method Manager.

Experimental:

4-Acetyl-6-bromo-3-(triethylsilyl)-D-glucal. Tosylate **9** (8.44 g, 20.3 mmol),² NaBr (29.0 g, 282 mmol), and sodium bicarbonate (4.4 g, 52 mmol) were suspended in dry DMF (130 mL) under a nitrogen atmosphere. The resulting mixture was heated to 65 °C and stirred vigorously for 10 h. The mixture was cooled to 23 °C and diluted with EtOAc. The resulting solution was washed with water (x 4) followed by saturated NaCl solution, dried over Na₂SO₄, filtered, and concentrated to give a clear oil (6.3 g, 95%).

The bromide was then dissolved in dry CH₂Cl₂ (200 mL) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and DMAP (134 mg, 1.09 mmol), Et₃N (4.2 mL, 30 mmol), and Ac₂O (2.8 mL, 30 mmol) were

successively added. After 30 min, the reaction mixture was warmed to 23 °C and stirred for 10 h. The mixture was diluted with EtOAc. The resulting solution was washed with water, saturated sodium bicarbonate solution, and saturated NaCl solution, dried over Na₂SO₄, filtered, and concentrated to give an oil which was purified by flash chromatography (20 : 1 hexanes/EtOAc) to give the title compound as a clear oil (6.09 g, 82%): $[\alpha]_D^{27^\circ} = -35.4^\circ$ (c = 1.0, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.39 (d, *J* = 1.00, 6.50 Hz, 1H), 5.11 (td, *J* = 1.00, 4.00 Hz, 1H), 4.81 (ddd, *J* = 1.00, 4.00, 6.50 Hz, 1H), 4.27 (dddd, *J* = 1.00, 5.00, 5.00, 8.00 Hz, 1H), 4.13 (tt, *J* = 1.00, 4.00, 5.00 Hz, 1H), 3.66 (dd, *J* = 5.50, 11.00 Hz, 1H), 3.62 (dd, *J* = 8.00, 11.00 Hz, 1H), 2.11 (s, 3H), 0.96 (t, 8.00 Hz, 9H), 0.62 (q, *J* = 8.00 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 169.81, 142.97, 102.75, 75.51, 71.57, 64.01, 30.06, 21.14, 6.85, 4.87; IR (thin film) 1743 cm⁻¹; HRMS (ES) calcd for C₁₄H₂₅O₄BrSiNa (M+Na)⁺ 387.0603, found 387.0600 *m/z*.

4-Acetyl-6-deoxy-3-(triethylsilyl)-D-glucal (10). Bromide **10** (1.02 g, 2.80 mmol) and AIBN (257 mg, 1.57 mmol) were dissolved in dry benzene (30 mL) under a nitrogen atmosphere. To the resulting solution was added Bu₃SnH (0.80 mL, 3.0 mmol) and the mixture was heated to reflux. After 5 h, the reaction was cooled to 23 °C and was stirred vigorously with 20% KF solution (20 mL) for 10 min. The resulting mixture was transferred to a separatory funnel and diluted with EtOAc (100 mL). The aqueous layer was discarded and the organic phase was washed with 20% KF solution (x 4), saturated NaCl solution, dried over Na₂SO₄, filtered, and concentrated to give an oil which was purified by flash chromatography (long column, 50 : 1 hexanes/EtOAc) to provide the title compound as a clear oil (725 mg, 90%): $[\alpha]_D^{27^\circ} = -42.7^\circ$ (c = 0.3, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.31 (dd, *J* = 6.00, 1.50 Hz, 1H), 4.92 (dd, *J* = 6.00, 8.00 Hz, 1H), 4.69 (dd, *J* = 3.00, 6.00 Hz, 1H), 4.55 (m, 1H), 4.02 (m, 1H), 2.10 (s, 3H), 1.29 (d, *J* = 6.50 Hz, 1H), 0.96 (t, *J* = 8.00 Hz, 9H), 0.60 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 170.10, 143.77, 103.50, 75.23, 72.86, 66.77, 21.27, 16.92, 6.91, 5.02; IR (thin film) 1750 cm⁻¹; HRMS (ES) calcd for C₁₄H₂₆O₄SiNa (M+Na)⁺ 309.1498, found 309.1509 *m/z*.

Acetyl 4-O-acetyl-6-deoxy-2-deoxy-2-iodo- α -D-mannopyranoside (11) and α,β -Acetyl 4-O-acetyl-6-deoxy-2-deoxy-2-iodo-D-glucopyranoside (8). Galactal **10** (1.28 g, 4.46 mmol) was dissolved in dry toluene (50 mL) under nitrogen in a round-bottom flask equipped with a reflux condensor. To the resulting solution was added AcOH (1.00 mL, 17.5 mmol) followed by *N*-iodosuccinimide (3.03 g, 13.5 mmol). The flask was then immediately plunged into a preheated (>150 °C) oil bath. The reaction mixture was allowed to reflux for 15 min and then removed from the bath and cooled to 23 °C. The reaction was quenched by the addition of 10% Na₂S₂O₃ and the resulting mixture was stirred vigorously until it had become colorless. The mixture was then diluted with EtOAc, transferred to a separatory funnel, and the aqueous layer was discarded. The organic phase was washed with 10 % Na₂S₂O₃ (x 3), saturated NaCl solution, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (4 : 1 hex/EtOAc) to provide the title compounds (2.01 g, 95%) as yellow oil. The 39 : 47 : 14 mixture of α -manno/ β -gluco/ α -gluco mixture of iodoacetate diastereomers was inseparable by flash chromatography and HPLC.

The mixture of carbohydrate derivatives (1.72 g, 3.65 mmol) was dissolved in dry CH₃CN (35 mL) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and Et₃N•3HF (1.4 mL, 8.6 mmol) was added dropwise. The reaction was stirred for 5.5 h, then warmed to 23 °C and diluted with EtOAc (150 mL). The solution was washed with saturated sodium bicarbonate solution (x 3), brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (7 : 1 then 4 : 1 hex/EtOAc, glucoside **8** elutes first) to provide glucoside **8** (720 mg, 55%, 80:20 β/α) and mannoside **11** (464 mg, 36%) as white solids. The mixture of glucoside anomers was then recrystallized from diethyl ether/hexanes to give 606 mg of a white crystalline solid (88 : 12 β/α , if the recrystallization is stopped earlier, the ratio can be increased up to 98 : 2): Data for mannoside **11**: $[\alpha]_D^{27^\circ} = -29.5^\circ$ (c = 0.2, CH₂Cl₂); mp = 124 °C (d); ¹H NMR (500 MHz, CDCl₃) δ 6.35 (as, 1H), 4.93 (at, *J* = 9.50 Hz, 1H), 4.49 (dd, *J* = 1.50, 4.00 Hz, 1H), 4.00 (dddd, *J* = 6.50, 6.50, 6.50, 9.50 Hz), 3.22 (td, *J* = 4.00, 9.00 Hz, 1H), 2.80 (d, *J* = 8.50 Hz, 1H), 2.15 (s, 3H), 2.14 (s, 3H), 1.25 (d, *J* = 6.50 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 171.34, 168.68, 94.85, 76.09, 69.53, 67.73, 36.43, 21.03, 20.98, 17.63; IR (thin film) 3474 (b), 1745 cm⁻¹; HRMS (ES) calcd for C₁₀H₁₅O₆INa (M+Na)⁺ 380.9811, found 380.9813 *m/z*.

Data for β -**8**: $[\alpha]_D^{27^\circ} = -11.7^\circ$ (c = 1.5, CH₂Cl₂); mp = 124 °C (d); mp = 148-150 °C (d); ¹H NMR (500 MHz, CDCl₃) δ 5.83 (d, *J* = 9.50 Hz, 1H), 4.67 (dd, *J* = 9.00, 9.50 Hz, 1H), 3.93 (dd, *J* = 9.25, 10.75, 1H), 3.86 (ddd, *J* =

4.00, 9.00, 10.50, 1H), 2.65 (m, 1H), 2.17 (s, 3H), 2.14 (s, 3H), 1.25 (d, $J = 6.50$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.94, 169.11, 93.86, 76.44, 75.52, 71.40, 33.60, 21.12, 21.00, 17.47; IR (thin film) 3480, 1749, 1731 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{10}\text{H}_{15}\text{O}_6\text{INa}$ ($\text{M}+\text{Na}$) $^+$ 380.9811, found 380.9816 m/z .

Conversion of mannoside 11 to glucal derivative 10. Mannoside **11** (101 mg, 0.282 mmol) and imidazole (44 mg, 0.64 mmol) were dissolved in dry DMF (1 mL) under a nitrogen atmosphere. To the resulting solution was added TESCOI (57 μL , 0.34 mmol). The mixture was stirred overnight and then diluted with EtOAc. The solution was washed with saturated sodium bicarbonate solution (x 2), brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was dried under vacuum and then dissolved in dry THF under a nitrogen atmosphere. The flask was covered with foil and LiI (366 mg, 2.74 mmol) was added. Upon complete consumption of the starting material (20 h), the mixture was diluted with EtOAc. The solution was washed with 10% $\text{Na}_2\text{S}_2\text{O}_4$ solution (until colorless), brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (7 : 1 hexanes/EtOAc) to give glucal derivative **10** (43 mg, 53%) as a clear oil.

Acetyl 4-*O*-Acetyl-3-*O*-(3,4-di-*O*-(carbonyl)-2,6-dideoxy-2-bromo- β -D-galactopyranosyl)-(1 $\rightarrow$ 3)-D-glucopyranoside (β -12). Glucoside **8** (301 mg, 0.840 mmol) and donor **7**³ (498 mg, 1.25 mmol) were dissolved in dry CH_2Cl_2 (4.2 mL) under argon and the resulting solution cooled to -78°C . To this solution was added TBSOTf (19.0 μL , 0.0825 mmol) and the resulting mixture was stirred for 10 h during which time a white precipitate formed. After this time, TLC analysis indicated all of acceptor **8** had been consumed. The reaction was quenched with neat Et_3N and warmed to 23°C . The resulting solution was diluted with EtOAc and washed with saturated NaHCO_3 solution followed by saturated NaCl. The solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (4 : 1 then 2 : 1 hexanes/EtOAc) to give disaccharide **12** (469 mg, 94%). An analytical sample of β,β -**12** was obtained by carrying out the reaction with β -**8** (98 : 2 β/α , obtained through recrystallization as described above). Data for β,β -**12**: $[\alpha]_{\text{D}}^{27^\circ\text{C}} = +61.0^\circ$ ($c = 0.2$, CH_2Cl_2); mp = 124°C (d); ^1H NMR (400 MHz, CDCl_3) δ 5.81 (d, $J = 9.00$ Hz, 1H), 5.25 (d, $J = 6.00$ Hz, 1H), 5.07 (dd, $J = 7.50, 6.00$ Hz, 1H), 4.73 (at, $J = 9.00$ Hz, 1H), 4.59 (dd, $J = 7.50, 2.00$ Hz, 1H), 4.16 (dq, $J = 6.50, 2.00$ Hz, 1H), 3.97-4.05 (m, 3H), 3.60 (m, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 1.44 (d, $J = 7.00$ Hz, 1H), 1.22 (d, $J = 6.50$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.65, 169.13, 153.15, 101.09, 93.92, 82.98, 78.68, 76.16, 73.97, 71.29, 67.76, 45.18, 29.27, 21.22, 20.95, 17.52, 16.67; IR (thin film) 1818, 1754 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{22}\text{H}_{22}\text{BrFIO}_{10}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 614.9339, found 614.9337 m/z .

4-*O*-Acetyl-3-*O*-(3,4-di-*O*-(carbonyl)-2,6-dideoxy-2-bromo- β -D-galactopyranosyl)-(1 $\rightarrow$ 3)- α -D-glucopyranosyl Fluoride (13**).** Acetate **12** (100 mg, 0.169 mmol) was dissolved in dry CH_2Cl_2 (3.6 mL) under nitrogen and the resulting solution was cooled to 0°C . HF•Pyridine (65-70%, 270 μL) was added and the resulting mixture stirred for 75 min. The reaction was diluted with CH_2Cl_2 and washed with NaHCO_3 solution (x 2) followed by saturated NaCl. The solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (2 : 1 hexanes/EtOAc) to give fluoride **13** (82 mg, 88%) as a clear oil: $[\alpha]_{\text{D}}^{25^\circ\text{C}} = +232^\circ$ ($c = 0.3$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 5.67 (dd, $J = 50.74, 2.25$ Hz, 1H), 5.19 (d, $J = 6.00$ Hz, 1H), 5.06 (dd, $J = 5.50, 7.50$ Hz, 1H), 4.79 (at, $J = 9.25$ Hz, 1H), 4.57 (dd, $J = 7.25, 1.75$ Hz, 1H), 3.98-4.16 (m, 5H), 2.08 (s, 3H), 1.44 (d, $J = 6.50$ Hz, 3H), 1.22 (d, $J = 6.00$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.62, 153.14, 107.40 (d $J = 224$ Hz), 101.15, 79.49, 78.75, 76.16, 73.51, 68.78 (d, $J = 4.5$ Hz), 67.80, 45.14, 25.82 (d, $J = 29$ Hz), 21.18, 17.51, 16.63; IR (thin film) 1818, 1757, 1739 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{15}\text{H}_{19}\text{BrFIO}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 574.9190, found 574.9189 m/z .

4-*O*-Acetyl-3-*O*-(2,6-dideoxy-2-bromo- β -D-galactopyranosyl)-(1 $\rightarrow$ 3)- α -D-glucopyranosyl Fluoride (6a**).**

Carbonate **13** (170 mg, 0.307 mmol) was dissolved in freshly distilled MeOH (6.5 mL) and the resulting solution was cooled to 0 °C. To this solution was added anhydrous potassium carbonate (28 mg, 0.20 mmol) and the resulting mixture was stirred vigorously. The reaction progress was followed closely by TLC analysis. Upon complete consumption of carbonate **13**, the reaction mixture was added directly to a silica gel column which had been packed with hexanes. The column was washed with 1.5 column lengths of hexanes followed by 2 : 1 hexanes/EtOAc until diol **6a** had been completely eluted, thereby providing the title compound (151 mg, 93%) as a white solid: $[\alpha]_D^{25^\circ} = +221^\circ$ ($c = 0.6$, CH₂Cl₂); mp = 124 °C (d); mp = 150 °C (d); ¹H NMR (500 MHz, CDCl₃) δ 5.67 (dd, $J = 2.25$, 50.74 Hz, 1H), 4.97, (d, $J = 7.50$ Hz, 1H), 4.75 (at, $J = 9.50$ Hz, 1H), 4.23 (dd, $J = 9.00$, 11.00 Hz, 1H), 4.12 (dddd, $J = 6.00$, 6.00, 6.00, 10.00 Hz, 1H), 4.05 (ddd, $J = 2.25$, 11.0, 28.87 Hz, 1H), 3.73-3.83 (m, 3H), 3.66 (aq, $J = 6.50$ Hz, 1H), 2.81 (bs, 1H), 2.38 (bs, 1H), 2.12 (s, 3H), 1.37 (d, $J = 6.50$ Hz, 3H), 1.23 (d, $J = 6.50$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.42, 107.66 (d, $J = 224$ Hz), 100.45, 76.78, 75.16, 73.74, 71.40, 70.86, 68.67 (d, $J = 4.6$ Hz), 54.48, 25.33 (d, $J = 29.0$ Hz), 21.33, 17.56, 16.40; IR (thin film) 3459, 1732(b) cm⁻¹; HRMS (ES) calcd for C₁₄H₂₁BrFIO₇Na (M+Na)⁺ 548.9397, found 548.9392 m/z .

Acetyl 3,4-di-*O*-acetyl-6-deoxy-2-deoxy-2-iodo- α -D-mannoside (15**) and α,β - Acetyl 3,4-di-*O*-acetyl-6-deoxy-2-deoxy-2-iodo-D-glucopyranoside (α,β -**16**).** Carbohydrate derivatives **15** and **16** were prepared from 6-deoxy glucal derivative **14**⁴ according to the haloacetoxylation procedure described for the preparation of compounds **11** and **8**. The title compounds were isolated by flash chromatography (7:1 hexanes/EtOAc, gluco compound **16** eluted first) as yellow oils. Data for mannoside **15**: $[\alpha]_D^{25^\circ} = +30.1^\circ$ ($c = 0.8$, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.34 (as, 1H), 5.20 (m, 1H), 4.53 (m, 2H), 4.02 (dddd, $J = 6.00$, 6.00, 6.00, 10.00 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 1.25 (d, $J = 6.50$ Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 170.22, 169.80, 168.66, 94.95, 72.19, 69.68, 68.94, 28.20, 21.19, 21.12, 20.95, 17.79; IR (thin film) 1749 cm⁻¹; HRMS (ES) calcd for C₁₂H₁₇IO₇Na (M+Na)⁺ 422.9917, found 422.9915 m/z .

Purification of glucosides α,β -**16** by preparative HPLC (85% hexanes/EtOAc) provided an analytical sample of β -**16**: $[\alpha]_D^{25^\circ} = +110^\circ$ ($c = 1.2$, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 5.85 (d, $J = 9.50$ Hz, 1H), 5.30 (dd, $J = 9.00$, 11.00 Hz, 1H), 4.74 (at, $J = 9.25$ Hz, 1H), 3.96 (dd, $J = 9.50$, 11.00 Hz, 1H), 3.76 (dddd, $J = 6.50$, 6.50, 6.50, 9.50 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.24 (d, $J = 6.00$ Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 169.97, 169.76, 169.89, 93.98, 75.36, 73.90, 71.36, 26.65, 20.97, 20.94, 20.88, 17.43; IR (thin film) 1755 cm⁻¹; HRMS (ES) calcd for C₁₂H₁₇IO₇Na (M+Na)⁺ 422.9917, found 422.9922 m/z .

α,β -3,4-Di-*O*-acetyl-6-deoxy-2-deoxy-2-iodo-D-glucosyl Trichloroacetimidate (α,β -5b**).** Glucoside **16** (461 mg, 1.15 mmol) was dissolved in 1 : 1 MeOH/Et₂O (11 mL) and the resulting solution was cooled to 0 °C. Aqueous hydrazine solution (180 μ L, 35% wt.) was added. The progress of the reaction was monitored closely by TLC analysis. Upon complete consumption of acetate **16** (40 min), the reaction was filtered through a pad of silica (2 : 1 hexanes/EtOAc) and the filtrate was concentrated to yield the hemiacetal (414 mg). The hemiacetal was dissolved in CH₂Cl₂ (6.5 mL) under nitrogen and the resulting solution was cooled to 0 °C. To the cold solution was added Cl₃CCN (6.5 mL). After several minutes, DBU (54 μ L, 0.36 mmol) was added and the solution became orange. After 2 h, the solution was concentrated on the rotary evaporator and the residue was chromatographed on DavisilTM silica (pH = 7.0, 7 : 1 hexanes EtOAc) to give the title compound (white solid, 460 mg, 80%) as a 1 : 1 mixture of anomers. Partial data for the 1:1 mixture of imidates: ¹H NMR (500 MHz, C₆D₆) δ 8.67 (s, 1H), 8.66 (s, 1H), 6.49 (d, $J = 3.50$ Hz, 1H), 6.04 (d, $J = 9.50$ Hz, 1H), 5.76 (dd, $J = 9.50$, 11.00 Hz, 1H), 5.33 (dd, $J = 9.00$, 11.00 Hz, 1H), 4.86 (at, $J = 9.50$ Hz, 1H), 4.71 (at, $J = 9.50$ Hz, 1H), 4.23 (dddd, $J = 6.00$, 6.00, 6.00, 11.00 Hz, 1H), 3.82 (dd, $J =$

9.50, 11.00 Hz, 1H), 3.73 (dd, $J = 3.50, 11.50$ Hz, 1H), 3.26 (dddd, $J = 6.00, 6.00, 6.00, 11.00$ Hz, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.07 (d, $J = 6.00$ Hz, 1H), 0.99 (d, $J = 6.00$ Hz, 1H).

α,β -Acetyl 4-*O*-Acetyl-3-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo- β -D-glucopyranosyl)-(1 $\rightarrow$ 3)-D-glucopyranoside (β -17). Alcohol **8** (145 mg, 0.405 mmol, 88:12 β/α) and imidate **5b** (317 mg, 0.631 mmol) were dissolved in dry CH₂Cl₂ (1.65 mL) under argon and the resulting solution cooled to -78 °C. To this solution was added TBSOTf (4.7 μ L, 0.0022 mmol) and the resulting mixture was stirred for 5.5 h. After this time, TLC analysis indicated all of acceptor **8** had been consumed and the reaction was quenched with neat Et₃N and warmed to 23 °C. The resulting solution was diluted with EtOAc and washed with saturated NaHCO₃ solution followed by saturated NaCl. The solution was dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was then dissolved in dry CH₂Cl₂ (1.6 mL) under nitrogen and Et₃N (220 μ L, 1.58 mmol), acetic anhydride (120 μ L, 1.26 mmol), and DMAP (2-3 crystals) and the resulting solution was stirred at 23 °C for 10.5 h (this step eases the subsequent purification step by converting the reaction by-products to higher R_f materials). The resulting solution was diluted with EtOAc and washed with saturated NaHCO₃ solution followed by saturated NaCl solution. The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (2 : 1 hexanes/EtOAc) to give disaccharide β -**17** (267 mg, 94%) as a 80:20 mixture of β/α acetates: An analytical sample of β,β -**17** was obtained by HPLC purification of this mixture using the same solvent system: $[\alpha]_D^{25^\circ\text{C}} = +145^\circ$ ($c = 0.7$, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 5.82 (d, $J = 9.60$ Hz, 1H), 5.29 (dd, $J = 9.00, 11.00$ Hz, 1H), 5.24 (d, $J = 8.80$ Hz, 1H), 5.24 (at, $J = 8.80$ Hz, 2H), 4.07 (m, 2H), 3.75 (dd, $J = 9.00, 11.40$ Hz, 1H), 3.68 (m, 1H), 3.63 (dddd, $J = 6.40, 6.40, 6.40, 8.80$ Hz, 1H), 2.16 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.26 (d, $J = 6.40$ Hz, 3H), 1.22 (d, $J = 6.40$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 170.06, 169.99, 169.75, 169.18, 100.52, 94.08, 80.90, 75.54, 74.48, 74.15, 71.19, 70.34, 28.34, 27.43, 21.34, 21.03, 20.96, 20.91, 17.77, 17.60; IR (thin film) 1749(b) cm⁻¹; HRMS (ES) calcd for C₂₀H₂₈I₂O₁₁Na (M+Na)⁺ 720.9619, found 720.9622 m/z .

α,β -Acetyl 4-*O*-Acetyl-3-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo- β -D-glucopyranosyl)-(1 $\rightarrow$ 3)-D-glucopyranosyl Trichloroacetimidate (α,β -5a). β -Disaccharide **17** (100 mg, 0.143 mmol) was dissolved in 1 : 1 MeOH/CH₂Cl₂ (2 mL). Aqueous hydrazine solution (32 μ L, 35% wt.) was added. After 2 h, the reaction was filtered through a pad of silica (1 : 1 hexanes/EtOAc) and the filtrate was concentrated to yield the hemiacetal (91 mg). The hemiacetal was dissolved in CH₂Cl₂ (0.7 mL) under nitrogen and the resulting solution was cooled to 0 °C. To the cold solution was added Cl₃CCN (0.7 mL). After several minutes, DBU (5 μ L, 0.36 mmol) was added and the solution became orange. After 1.5 h, the solution was concentrated on the rotary evaporator and the residue was filtered through a short DavisilTM silica column (pH = 7.0, 2 : 1 hexanes EtOAc) to give, upon concentration of the fractions, the title compound (white solid, 108 mg, 94% overall) as a ~60 : 40 mixture of anomers: ¹H NMR analysis of the mixture of imidates revealed characteristic peaks which could be integrated to allow determination of the anomeric composition: ¹H NMR (500 MHz, C₆D₆) δ 8.63 (s, 1H, β), 8.61 (s, 1H, α), 6.44 (d, $J = 3.00$ Hz, 1H, α), 6.04 (d, $J = 9.50$ Hz, 1H, β).

4-*O*-Acetyl-3-*O*-(3-*O*-(3,4-di-*O*-acetyl-6-deoxy-2-deoxy-2-iodo- β -D-glucosyl)-(1 $\rightarrow$ 3))-2,6-dideoxy-2-bromo- β -D-galactopyranosyl)-(1 $\rightarrow$ 3)- α -D-glucopyranosyl Fluoride (18**).** Diol **6a** (22 mg, 0.042 mmol) and imidate **5b**

(32 mg, 0.064 mmol) were dissolved in dry CH_2Cl_2 (400 μL) under argon and the resulting solution cooled to -78°C . To this solution was added TBSOTf (0.5 μL , 0.0022 mmol) and the resulting mixture was stirred for 5.5 h. The reaction was quenched with neat Et_3N and warmed to 23°C . The resulting solution was diluted with EtOAc and washed with saturated NaHCO_3 solution followed by saturated NaCl. The solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (4 : 1 then 2 : 1 hexanes/EtOAc) to give 35 mg of aclear oil (~2:1 mixture of mono:bis glycosidation products). Purification of this material by preparative HPLC (66% hexanes/EtOAc) provided the title compound (24 mg, 67 %) as a clear oil: $[\alpha]_{\text{D}}^{25^\circ\text{C}} = +63.2^\circ$ ($c = 2.4$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 5.67 (dd, $J = 2.25$, 50.74 Hz, 1H), 5.26 (dd, $J = 9.00$, 11.00 Hz, 1H), 4.99 (d, $J = 8.00$ Hz, 1H), 4.93 (d, $J = 9.00$ Hz, 1H), 4.75 (at, $J = 11.00$ Hz, 1H), 4.72 (at, $J = 10.50$ Hz, 1H), 4.26 (dd, $J = 9.00$, 11.00 Hz, 1H), 4.12 (m, 1H), 4.06 (dd, $J = 2.00$, 11.00, 29.00 Hz, 1H), 3.82-3.91 (m, 3H), 3.72 (m, 1H), 3.60-3.66 (m, 2H), 2.44 (m, 1H), 2.13 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.37 (d, $J = 6.50$ Hz, 1H), 1.23 (d, $J = 6.50$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.37, 169.94, 107.73 (d, $J = 224$ Hz), 103.08, 100.57, 83.52, 76.24, 75.42, 74.07, 73.66, 71.64, 70.59, 70.23, 68.76 (d, $J = 4.7$ Hz), 50.09, 27.05, 25.39 (d, $J = 29.0$ Hz), 21.24, 21.02, 20.89, 17.64, 17.55, 16.46; IR (thin film) 3540, 1750 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{24}\text{H}_{34}\text{BrFIO}_{12}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 888.9205, found 888.9207 m/z .

4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-3-*O*-(3,4-di-*O*-acetyl-6-deoxy-2-deoxy-2-iodo- β -D-glucosyl-(1 $\rightarrow$ 3))-2,6-dideoxy-2-bromo- β -D-galactopyranosyl)-(1 $\rightarrow$ 3)- α -D-glucopyranosyl Fluoride (4). Diol **18** (33 mg, 0.038 mmol) was dissolved in dry CH_2Cl_2 (1.0 μL) under a nitrogen atmosphere and DMAP (10 mg, 0.082 mmol), Et_3N (28 μL , 0.20 mmol), and Ac_2O (14 μL , 0.15 mmol) were added successively. The resulting mixture was stirred for 24 h and then diluted with EtOAc and washed with saturated NaHCO_3 solution followed by saturated NaCl. The solution was dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (2 : 1 hexanes/EtOAc) to give the title compound (35 mg, quantitative) as glass: $[\alpha]_{\text{D}}^{25^\circ\text{C}} = 139^\circ$ ($c = 0.3$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 5.67 (dd, $J = 2.00$, 50.49 Hz, 1H), 5.23 (dd, $J = 9.00$, 11.00 Hz, 1H), 5.18 (dd, $J = 3.25$, 0.75 Hz, 1H), 5.04 (d, $J = 8.00$ Hz, 1H), 4.95 (d, $J = 9.00$ Hz, 1H), 4.77 (at, $J = 10.00$ Hz, 1H), 4.70 (at, $J = 9.25$ Hz, 1H), 4.25 (dd, $J = 8.75$, 10.75, 1H), 4.11 (m, 1H), 4.07 (ddd, $J = 2.25$, 11.00, 28.49 Hz, 1H), 3.96 (dd, $J = 3.25$, 10.75 Hz, 1H), 3.91 (dd, $J = 8.25$, 10.75 Hz, 1H), 3.75 (dd, $J = 9.00$, 11.00 Hz, 1H), 3.58 (dddd, $J = 6.00$, 6.00, 6.00, 9.50 Hz, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.23 (d, $J = 6.50$ Hz, 3H), 1.23 (d, $J = 6.50$ Hz, 3H), 1.20 (d, $J = 6.00$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.18, 169.96, 169.94, 169.84, 107.72 (d, $J = 224$ Hz), 102.56, 100.59, 79.37, 76.44, 75.50, 74.23, 73.73, 72.96, 70.49, 69.83, 68.73, 50.41, 31.80, 27.46, 25.11 (d, $J = 29.0$ Hz), 22.87, 21.11, 21.02, 21.00, 20.90, 17.53, 17.42, 16.56, 14.34; IR (thin film) 1749 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{26}\text{H}_{36}\text{BrFI}_2\text{O}_{13}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 930.9311, found 930.9333 m/z .

4-*O*-Acetyl-3-*O*-(4-*O*-acetyl-2,6-dideoxy-2-bromo- β -D-galactopyranosyl)-(1 $\rightarrow$ 3)- α -D-glucopyranosyl Fluoride (6b). Diol **6a** (86 mg, 0.16 mmol) was dissolved in dry CH_2Cl_2 (1.6 μL) under nitrogen and cooled to 0°C . Trimethylorthoacetate (32 μL , 0.250 mmol) was added to the reaction by syringe followed by the addition of $\text{TsOH}\cdot\text{H}_2\text{O}$ (4 mg, 0.02 mmol).⁵ After 30 min, water (50 μL) was added and the reaction was stirred vigorously for 15 min. The reaction was quenched with saturated sodium bicarbonate solution and then diluted with EtOAc. The aqueous layer was discarded and the organics washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (2 : 1 hexanes/EtOAc) to give the title compound (85 mg, 91%) as a white solid: $[\alpha]_{\text{D}}^{25^\circ\text{C}} = +150^\circ$ ($c = 0.2$, CH_2Cl_2); mp = 150°C (d); ^1H NMR (400 MHz, CDCl_3) δ 5.66 (dd, $J = 2.20$, 50.80 Hz, 1H), 5.15 (ad, $J = 3.20$ Hz, 1H), 5.01 (d, $J = 8.00$ Hz, 1H), 4.75 (at, $J = 9.60$ Hz, 1H), 4.21 (dd, $J = 9.00$, 10.60 Hz, 1H), 3.99-4.13 (m, 2H), 3.90 (dt, $J = 3.70$, 10.67 Hz, 1H), 3.73-3.80 (m, 2H), 2.69 (d, $J = 4.00$ Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 1.21 (d, $J = 6.40$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.06, 169.90, 107.63 (d, $J = 224$ Hz), 100.44, 76.59, 73.71, 73.54, 72.30, 69.74, 68.65, 53.87, 25.05 (d, $J = 29.8$ Hz), 21.10, 20.87, 17.50, 16.42; IR (thin film) 3479, 1742 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{16}\text{H}_{23}\text{BrFIO}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 590.9503, found 590.9517 m/z .

Synthesis of Trisaccharide 4 from Acetate 6b. Acetate **6b** (26 mg, 0.046 mmol) and imidate **5b** (38 mg, 0.076 mmol) were dissolved in dry CH_2Cl_2 (250 μL) under argon and the resulting solution cooled to -78°C . To this solution was added TBSOTf (0.5 μL , 0.0022 mmol) and the resulting mixture was stirred for 1 h. The reaction was quenched with neat Et_3N and warmed to 23°C . The resulting solution was diluted with EtOAc and washed with saturated NaHCO_3 solution followed by saturated NaCl solution. The organic phase was dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (2 : 1 hexanes/ EtOAc) to give trisaccharide **4** (36 mg, 86%) as a glass.

4-O-Acetyl-3-O-(4-O-acetyl-3-O-(3,4-di-O-acetyl-6-deoxy-2-deoxy-2-iodo-β-D-glucosyl-(1→3)-4-O-acetyl-6-deoxy-2-deoxy-2-iodo-β-D-glucosyl-(1→3))-2,6-dideoxy-2-bromo-β-D-galactopyranosyl)-(1→3)-α-D-glucopyranosyl Fluoride (3). Acetate **6b** (18 mg, 0.032 mmol) and imidate **5a** (83 mg, 0.10 mmol) were dissolved in dry CH_2Cl_2 (200 μL) under argon and the resulting solution cooled to 0°C . To this solution was added TBSOTf (0.3 μL , 0.0013 mmol) and the resulting mixture was stirred for 75 min. The reaction was quenched with neat Et_3N and warmed to 23°C . The resulting solution was diluted with EtOAc and washed with saturated NaHCO_3 solution followed by saturated NaCl solution. The organic phase was dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (7 : 1 then 4 : 1 hexanes/ EtOAc) to give tetrasaccharide **3** (28 mg, 86%) as a white solid: $[\alpha]_{\text{D}}^{25^\circ\text{C}} = +230^\circ$ ($c = 0.1$, CH_2Cl_2); mp = 147°C (d); ^1H NMR (500 MHz, CDCl_3) δ 5.67 (dd, $J = 2.25, 50.74$ Hz, 1H), 5.28 (dd, $J = 9.00, 11.00$ Hz, 1H), 5.28 (d, $J = 9.00$ Hz, 1H), 5.17 (dd, $J = 0.75, 3.25$ Hz, 1H), 5.04 (d, $J = 8.00$ Hz, 1H), 4.91 (d, $J = 9.00$ Hz, 1H), 4.77 (at, $J = 9.50$ Hz, 1H), 4.64 (at, $J = 9.25$ Hz, 1H), 4.63 (at, $J = 9.25$ Hz, 1H), 4.91 (dd, $J = 9.00, 11.00$ Hz, 1H), 4.01-4.14 (m, 3H), 3.90-3.96 (m, 2H), 3.86 (dd, $J = 9.00, 10.50$ Hz, 1H), 3.73 (dd, $J = 9.00, 11.50$ Hz, 1H), 3.72 (dd, $J = 1.00, 11.50$ Hz, 1H), 3.60 (dddd, $J = 6.00, 6.00, 6.00, 10.0$ Hz, 1H), 3.50 (dddd, $J = 6.00, 6.00, 6.00, 10.00$ Hz, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.24 (d, $J = 6.50$ Hz, 3H), 1.23 (d, $J = 6.50$ Hz, 3H), 1.21 (d, $J = 6.00$ Hz, 3H), 1.20 (d, $J = 6.00$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.16, 170.06, 169.99, 169.87, 169.71, 107.70 (d, $J = 224$ Hz), 102.56, 100.61, 100.50, 80.80, 79.23, 76.41, 75.61, 74.57, 73.73, 72.97, 70.29, 69.90, 68.73 (d, $J = 3.1$ Hz), 50.65, 28.98, 27.34, 25.19 (d, $J = 29.0$ Hz), 21.39, 21.12, 21.02(b), 20.93, 17.76, 17.61, 17.53, 16.56; IR (thin film) 1750 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{34}\text{H}_{47}\text{BrFI}_3\text{O}_{17}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1228.9013, found 1228.9036 m/z .

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