Supporting information

Stereoselective Synthesis of the α-Glycoside of a KDO "*C*"-Disaccharide.

Mamoru Koketsu, Balagurunathan Kuberan and Robert J. Linhardt*

Department of Chemistry, Medicinal and Natural Products Chemistry Chemical and Biochemical Engineering, University of Iowa, Iowa City, Iowa 52242

1,2:3,4-Di-*O*-isopropylidene-6-deoxy-6-iodogalactopyranose 2

1,2:3,4-di-*O*-isopropylidene-D-galactopylanose (3 g; 12.3 mmol) was dissolved in dry toluene (20 mL) and acetonitrile (10 mL). To the solution, imidazole (3.7 g; 5.4 mmol), triphenylphosphine (7.0 g; 26.9 mmol) and iodine (6.1 g; 4.8 mmol) were added. The mixture was stirred at 90°C for 24 h. The reaction was cooled in an ice bath and filtered. The mixture was extracted with chloroform and washed with saturated sodium bicarbonate solution. The extracts were dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (10/1) to give 4.53 g (99.4%) as a white powder; mp 54.5-55 °C; $[\alpha]_D^{25}$ -40.0 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, s), 1.35 (3H, s), 1.44 (3H, s), 1.54 (3H, s), 3.20 (1H, dd, *J* = 7.5, 10.0 Hz), 3.31 (1H, dd, *J* = 7.5, 10.0 Hz), 3.94 (1H, t, *J* = 7.5 Hz), 4.30 (1H, dd, *J* = 2.5, 4.5 Hz), 4.40 (1H, dd, *J* = 1.0, 7.5 Hz), 4.61 (1H, dd, *J* = 2.5, 7.5 Hz), 5.54 (1H, d, *J* = 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 24.3, 24.8, 25.8, 25.9, 68.8, 70.4, 71.0, 71.4, 96.5, 108.7, 109.3; MS (ES): calcd. for $C_{12}H_{19}O_5I$: 370.18, found *m*/*z* = 370.9 $(M+H)^+$.

1,2:3,4-Di-*O*-isopropylidene-6-deoxy-6-galactopyranosiduronitrile 3

2 (490 mg; 1.32 mmol) was dissolved in dry DMF (50 mL) and to the solution, NaCN (130 mg; 2.64 mmol) was added. The mixture was stirred at 80 °C for 24 h, cooled in an ice bath and filtered. The filtrate was extracted with ethyl acetate and washed with water. The extracts were dried over sodium sulfate and evaporated to dryness. The combined residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (5/1) to give 224 mg (63%) as a white powder; mp 62.7-63 °C; $[\alpha]_D^{25}$ -36.0 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, s), 1.36 (3H, s), 1.45 (3H, s), 1.54 (3H, s), 2.68 (2H, dd, *J* = 5.0, 7.0 Hz), 4.05 (1H, t, *J* = 7.0 Hz), 4.24 (1H, dd, *J* = 1.5, 8.0 Hz), 4.34 (1H, dd, *J* = 2.5, 5.0 Hz), 4.66 (1H, dd, *J* = 2.5, 7.5 Hz), 5.50 (1H, d, *J* = 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 24.3, 24.6, 25.7, 25.8, 64.1, 70.0, 70.6, 71.0, 96.2, 108.8, 109.6; MS (ES):

calcd. for $C_{13}H_{19}O_5N$: 269.30, found m/z = 270.1 $(M+H)^+$.

1,2:3,4-Di-*O*-isopropylidene-6-deoxy-6-formyl-D-galactopyranosylanose 4

3 (200 mg; 0.74 mmol) was dissolved in dry dichloromethane (5 mL) at -78 °C. DIBAL-H (0.74 mL; 0.74 mmol) was added to the solution. The mixture was stirred at -78 °C for 1 h, warmed to 0°C and stirred for 1 h. Methanol (1 mL) and water (1 mL) were added to the reaction. The mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with toluene/ethyl ether (10/1) to give 118 mg (59%) as a colorless syrup; $[\alpha]_D^{25}$ -72.9 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.34 (6H, s), 1.43 (3H, s), 1.54 (3H, s), 2.67 (1H, dd, *J* = 5.4, 17.4 Hz, H6b), 2.77 (1H, dd, *J* = 6.8 17.4 Hz, H6a), 4.21 (1H, d, *J* = 7.8 Hz, H4), 4.30 (1H, d, *J* = 5.4 Hz, H5), 4.32 (1H, m, H2), 4.62 (1H, dd, *J* = 2.0, 7.8 Hz, H3), 5.50 (1H, d, *J* = 5.0 Hz, H1), 9.79 (1H, s, CHO) ^{13}C NMR ($CDCl_3$) δ 24.3, 24.8, 25.8, 25.8, 63.2, 70.1, 70.6, 72.2, 96.2, 108.6, 109.2, 200.2; MS (ES): calcd. for $C_{13}H_{20}O_6$: 272.30, found m/z = 273.4 $(M+H)^+$.

***t*-Butyl (4,5,7,8-tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosyl chloride)onate 7**

Ammonium KDO **5** (1 g; 3.92 mmol) was added to acetyl chloride (24 mL) at 0 °C. Acetate (1.2 mL) was added to the solution and the mixture was stirred at room temperature for 15 h. The reaction mixture was evaporated completely to dryness to yield **6**. Compound **6** was dissolved in dry dichloromethane (5 mL) and *t*-butyl trichloroacetimidate (1 mL) in cyclohexane (3 mL) and a catalytic amount of BF_3 were added. The mixture was stirred at room temperature for 15 h. The mixture was extracted with chloroform and washed with water. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with toluene/ethyl ether (4/1) to give **7** in 91% yield (2 steps overall) as a colorless syrup; $[\alpha]_D^{25}$ +98.1 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.54 (9H, s, ^{t}Bu), 2.01 (3H, s, CH_3), 2.03 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.35 (1H, t, *J* = 13.5 Hz, H3ax), 2.49 (1H, dd, *J* = 4.9, 13.5 Hz, H3eq), 4.19 (1H, dd, *J* = 4.4, 12.2 Hz, H8b), 4.43 (1H, dd, *J* = 2.0, 12.2 Hz, H8a), 4.47 (1H, dd, *J* = 1.2, 9.8 Hz, H6), 5.24 (1H, ddd, *J* = 2.0, 4.4, 9.8 Hz, H7), 5.42 (1H, d, *J* = 3.2 Hz, H5), 5.47 (1H, ddd, *J* = 3.2, 4.9, 13.5 Hz, H4); ^{13}C NMR ($CDCl_3$) δ 20.52, 20.57, 20.60, 20.63 (4 x CH_3), 27.6 (^{t}Bu), 35.1 (C3), 62.1 (C8), 63.8 (C5), 66.6 (C4), 67.0 (C7), 71.0 (C6), 84.1 (C of ^{t}Bu), 96.9 (C2), 163.9 (C1),

169.6, 169.8, 170.2, 170.5 (4 x C=O); MS (FAB): calcd. for $C_{20}H_{29}O_{11}Cl$: 480.90, found m/z = 481.2 $(M+H)^+$; HRMS (FAB): calcd. for $C_{20}H_{29}O_{11}Cl$: 481.1477, found m/z = 481.1495 $(M+H)^+$.

6-*C*-[*t*-Butyl (4,5,7,8-tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosyl)onate]-6-*C*-hydroxy-1,2:3,4-di-*O*-isopropylidene-6-deoxy-6-formyl-D-galactopyranose 8

A solution of compounds **7** (50 mg; 0.10 mmol) and **4** (20 mg; 0.07 mmol) in $CHCl_3$ (3 mL) was evaporated to dryness and the resulting residue dried for 15 h under high vacuum. The dried residue was placed under nitrogen and a solution of freshly prepared SmI_2 (0.1 M, 5 mL) was added. The reaction mixture was stirred at room temperature for 30 min. The mixture was evaporated to dryness. The residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (5/1) affording **8** in 77% yield as a colorless syrup; $[\alpha]_D^{25}$ -16.1 (*c* 1, $CHCl_3$). **8(*R*)**: ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.50 (9H, s, ^{t}Bu), 1.51 (1H, m, H6b of Gal), 1.52 (6H, s, CH_3), 1.78 (1H, m, H6a of Gal), 1.98 (3H, s, CH_3), 2.01 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.09 (1H, t, J = 13.5 Hz, H3ax of KDO), 2.10 (3H, s, CH_3), 2.21 (1H, dd, J = 4.9, 13.5 Hz, H3eq), 2.42 (1H, t, J = 6.4 Hz, OH of bridge carbon), 3.95 (1H, m, bridge proton), 4.09 (1H, d, J = 8.6 Hz, H5 of Gal), 4.24 (1H, m, H3 of Gal), 4.25 (1H, dd, J = 2.2, 9.5 Hz, H6 of KDO), 4.29 (1H, dd, J = 2.4, 7.3 Hz, H8b of KDO), 4.30 (1H, d, J = 4.9 Hz, H2 of Gal), 4.38 (1H, dd, J = 2.9, 7.3 Hz, H8a of KDO), 4.60 (1H, dd, J = 2.4, 7.6 Hz, H4 of Gal), 4.89 (1H, m, H4 of KDO), 5.10 (1H, m, H7 of KDO), 5.28 (1H, s, H5 of KDO), 5.51 (1H, d, J = 4.9 Hz, H1 of Gal); ^{13}C NMR ($CDCl_3$) δ 20.7, 20.8, 20.9 (4 x CH_3 of Ac of KDO), 24.4, 25.0, 26.0 (4 x CH_3 of Gal), 27.9 (^{t}Bu), 28.8 (C3 of KDO), 32.1 (C6 of Gal), 62.8 (C8 of KDO), 64.1 (C5 of Gal), 64.6 (C5 of KDO), 67.6 (C4 of KDO), 68.2 (C7 of KDO), 70.7 (C6 of KDO), 70.9 (C2 of Gal), 71.10 (C3 of Gal), 71.12 (C4 of Gal), 72.3 (Bridge carbon), 73.6 (C5 of Gal), 83.0 (C of ^{t}Bu), 83.4 (C2 of KDO), 96.5 (C1 of Gal), 108.7, 109.0 (2 x C of isopropylidene of Gal), 168.8 (C1 of KDO), 169.8, 170.0, 170.5, 171.0 (4 x C=O); MS (FAB): calcd. for $C_{33}H_{50}O_{17}$: 718.75, found m/z = 719.2 $(M+H)^+$; HRMS (FAB): calcd. for $C_{33}H_{50}O_{17}Na$: 741.2946, found m/z = 741.2992 $(M+H)^+$; Anal. calcd. for $C_{33}H_{50}O_{17}$: C 55.15, H 7.01, found C 54.91, H 6.85.