A Versatile and Stereocontrolled Route to Pyranose and Furanose C-Glycosides

Joanne E. Harvey,* Steven A. Raw, Richard J. K. Taylor*

Supporting Information

Experimental Section

All new compounds were fully characterized spectroscopically and by HRMS or elemental analysis.

a) Preparation of Z-alkene Z-1: To a solution of 2,3-anhydromannose **5** (0.300 g, 1.20 mmol) and triethylamine (0.20 mL, 1.44 mmol) in dry MeOH (12 mL) at r.t. under N₂ was added (ethoxycarbonylmethylene)triphenylphosphorane (0.501 g, 1.44 mmol) in one portion. After 30 min, t.l.c. showed no starting material remaining and the mixture was concentrated under reduced pressure to give a yellow oil. This was purified by column chromatography (SiO₂, 1:9 EtOAc/CH₂Cl₂) to give **Z-1** (0.271 g, 71%) as a colorless oil: *R*_f (1:4 EtOAc/CH₂Cl₂) = 0.48. $[\alpha]_D^{20}$ -331.71 (*c* 0.78, CHCl₃). Found: 338.1607; C₁₇H₂₄NO₆ (MNH₄⁺) requires: 338.1604 (0.9 ppm error). ¹H NMR (270 MHz, CDCl₃, 25 °C) 7.46-7.57 (m, 2H), 7.32-7.42 (m, 3H), 6.28 (dd, ³*J*_(H,H) 11.4, 5.8 Hz, 1H), 6.09 (dd, ³*J*_(H,H) 11.4 Hz, ⁴*J*_(H,H) 1.2 Hz, 1H), 5.47 (s, 1H), 4.27-4.35 (complex m, 2H), 4.23 (q, ³*J*_(H,H) 7.3 Hz, 2H), 3.86-3.98 (m, 1H), 3.59 (dd (app. t), ²*J*_(H,H) 10.4 Hz, ³*J*_(H,H) 10.4 Hz, 1H), 3.40-3.50 (complex m, 2H), 3.04 (d, ³*J*_(H,H) 2.8 Hz, 1H), 1.31 (t, ³*J*_(H,H) 7.3 Hz, 3H). ¹³C NMR (68 MHz, CDCl₃, 25 °C) 167.6 (C), 144.7 (CH), 137.1 (C), 129.0 (CH), 128.2 (CH), 126.2 (CH), 124.0 (CH), 100.7 (CH), 81.1 (CH), 70.0 (CH₂), 63.3 (CH), 61.3 (CH₂), 59.0 (CH), 54.1 (CH), 14.1 (CH₃). IR (KBr): 3431 (br), 2931, 2868, 1720, 1454, 1396, 1309, 1267, 1078, 1028, 737, 700 cm⁻¹. MS (CI⁺) *m/z*: 338 (32%, MNH₄⁺), 321 (99%, MH⁺), 113 (100%), followed by **E-1** (0.065 g, 17%) as a colorless oil: *R*_f (1:4 EtOAc/CH₂Cl₂) = 0.33. $[\alpha]_D^{22}$ -112.8 (*c* 2.32, CHCl₃). Found: 338.1606; C₁₇H₂₄NO₆ (MNH₄⁺) requires: 338.1604 (0.8 ppm error). ¹H NMR (270 MHz, CDCl₃, 25 °C) 7.46-7.56 (m, 2H), 7.33-7.42 (m, 3H), 6.92 (dd, ³*J*_(H,H) 15.8, 6.8 Hz, 1H), 6.21 (dd, ³*J*_(H,H) 15.8 Hz, ⁴*J*_(H,H) 1.0 Hz, 1H), 5.50 (s, 1H), 4.32 (dd, ²*J*_(H,H) 10.7 Hz, ³*J*_(H,H) 5.3 Hz, 1H), 4.22 (q, ³*J*_(H,H) 7.0 Hz, 2H), 3.87 (dddd, ³*J*_(H,H) 10.2, 9.2, 6.3, 5.3 Hz, 1H), 3.71 (ddd, ³*J*_(H,H) 6.8, 4.6 Hz, ⁴*J*_(H,H) 1.0 Hz, 1H), 3.61 (dd, ²*J*_(H,H) 10.7 Hz, ³*J*_(H,H) 10.2 Hz, 1H), 3.57 (dd, ³*J*_(H,H) 9.2, 7.8 Hz, 1H), 3.43 (dd, ³*J*_(H,H) 7.8, 4.6 Hz, 1H), 1.94 (d, ³*J*_(H,H) 6.3 Hz, 1H), 1.29 (t, ³*J*_(H,H) 7.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) 166.2 (C), 142.5 (CH), 137.2 (C), 129.2 (CH), 128.4 (CH), 126.3 (CH), 125.0 (CH), 100.9 (CH), 80.0 (CH), 70.8 (CH₂), 63.3 (CH), 61.0 (CH₂), 59.0 (CH), 55.1 (CH), 14.2 (CH₃). IR (KBr): 3465, 2983, 2906, 1745. MS (CI): *m/z* 338 (85%, M+NH₄⁺), 321 (59%, MH⁺), 215 (100%, MH⁺-PhCHO).

b) Preparation of *E*-alkene *E*-1: A solution of triethyl phosphonoacetate (0.060 mL, 0.30 mmol) in THF (1.0 mL) under N₂ was cooled to −78 °C and treated, dropwise over 10 min, with a solution of KHMDS in toluene (0.5 M, 0.64 mL, 0.32 mmol). After 15 min, a solution of the hemiacetal **5** (50 mg, 0.20 mmol) in THF (1.5 mL) was added dropwise over 10 min. The reaction mixture was stirred at −78 °C for 2 h, before being quenched with saturated aqueous NH₄Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated to afford a yellow oil. Subjection of this material to flash chromatography (SiO₂, 1:4 EtOAc/CH₂Cl₂) provided *E*-1 (51 mg, 80%) as a colorless oil: *R*_f (1:4 EtOAc/CH₂Cl₂) = 0.33. The spectroscopic and spectrometric data matched those described above.

c) Preparation of β-*C*-furanoside **6:** A brown suspension of Pd(OAc)₂ (1.3 mg, 0.0058 mmol) in CH₂Cl₂ (1.0 mL) was treated with PPh₃ (7.6 mg, 0.029 mmol) and the resulting yellow reaction mixture was stirred in the dark under N₂ for 2 h. A solution of *Z*-1 (30 mg, 0.094 mmol) in CH₂Cl₂ (1.5 mL) was added and stirring continued for 2.5 h. The resulting orange reaction mixture was quenched with water (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated to afford a yellow oil. Subjection of this material to flash chromatography (SiO₂, 1:9 EtOAc/CH₂Cl₂) provided the β-*C*-furanoside **6** (21 mg, 70%) as a white solid: *R*_f (1:9 EtOAc/CH₂Cl₂) = 0.22. Recrystallization from Et₂O gave white needles, m.p. = 121-124 °C. [α]_D²² −80.0 (*c* 1.13, CHCl₃). Found: 321.1339; C₁₇H₂₁O₆ (MH⁺) requires: 321.1338 (0.2 ppm error). ¹H NMR (400 MHz, CDCl₃, 25 °C) 7.50 (m, 2H), 7.40-7.37 (complex m, 3H), 7.01 (dd, ³*J*_(H,H) 15.7, 5.0 Hz, 1H), 6.13 (dd, ³*J*_(H,H) 15.7 Hz, ⁴*J*_(H,H) 1.7 Hz, 1H), 5.52 (s, 1H), 4.78 (ddd, ³*J*_(H,H) 8.2, 5.0 Hz, ⁴*J*_(H,H) 1.7 Hz, 1H), 4.65 (ddd, ³*J*_(H,H) 8.2, 8.2, 4.9 Hz, 1H), 4.53 (dd, ²*J*_(H,H) 9.5 Hz, ³*J*_(H,H) 4.0 Hz, 1H), 4.22 (q, ³*J*_(H,H) 7.0 Hz, 2H), 3.92 (dd, ³*J*_(H,H) 9.8 Hz, ²*J*_(H,H) 9.5 Hz, 1H), 3.66-3.59 (complex m, 2H), 2.49 (d, ³*J*_(H,H) 4.9 Hz, 1H), 1.30 (t, ³*J*_(H,H) 7.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25 °C) 166.2 (C), 143.5 (CH), 136.8 (C), 129.5 (CH), 128.5 (CH), 126.4 (CH), 123.1 (CH), 102.6 (CH), 85.6 (CH), 78.3 (CH), 74.0 (CH), 71.3 (CH₂), 69.7 (CH), 60.8 (CH₂), 14.4 (CH₃). IR (KBr): 3441, 2987, 2875, 1714, 1660 cm^{−1}. MS (CI⁺): *m/z* 321 (100%, MH⁺).

d) Preparation of α-*C*-furanoside **7:** A brown suspension of Pd(OAc)₂ (2 mg, 0.009 mmol) in CH₂Cl₂ (1.0 mL) was treated with PPh₃ (11 mg, 0.042 mmol) and the resulting yellow reaction mixture was stirred in the dark under N₂ for 2 h. A solution of *E*-1 (43 mg, 0.13 mmol) in CH₂Cl₂ (1.0 mL) was added and stirring continued for 2 h. The resulting orange reaction mixture was quenched with water (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The

combined organic fractions were dried (MgSO_4), filtered and concentrated to afford a yellow oil. Subjection of this material to flash chromatography (SiO_2 , 1:9 EtOAc/ CH_2Cl_2) provided the α -C-furanoside **7** (33 mg, 77%) as a white solid: R_f (1:9 EtOAc/ CH_2Cl_2) = 0.22. Recrystallization from hot MeOH gave a white fluffy solid, m. p. = 112-113 °C. $[\alpha]_D^{22} +39.5$ (c 1.59, CHCl_3). Found: C 63.71, H 6.15; $\text{C}_{17}\text{H}_{20}\text{O}_6$ requires: C 63.74, H 6.29. ^1H NMR (400 MHz, CDCl_3 , 25 °C) 7.48 (m, 2 H), 7.38 (m, 3 H), 7.06 (dd, $^3J_{(\text{H,H})}$ 15.6, 4.9 Hz, 1 H), 6.16 (dd, $^3J_{(\text{H,H})}$ 15.6 Hz, $^4J_{(\text{H,H})}$ 1.7 Hz, 1 H), 5.53 (s, 1 H), 4.52 (concealed m, 1 H), 4.51 (dd, $^2J_{(\text{H,H})}$ 9.8 Hz, $^3J_{(\text{H,H})}$ 4.6 Hz, 1 H), 4.33 (ddd, $^3J_{(\text{H,H})}$ 8.1, 6.7, 4.3 Hz, 1 H), 4.23 (q, $^3J_{(\text{H,H})}$ 7.0 Hz, 2 H), 3.93 (dd, $^3J_{(\text{H,H})}$ 9.8 Hz, $^2J_{(\text{H,H})}$ 9.8 Hz, 1 H), 3.82 (dd, $^3J_{(\text{H,H})}$ 9.8, 8.1 Hz, 1 H), 3.75 (ddd, $^3J_{(\text{H,H})}$ 9.8, 9.8, 4.6 Hz, 1 H), 2.52 (d, $^3J_{(\text{H,H})}$ 4.3 Hz, 1 H), 1.31 (t, $^3J_{(\text{H,H})}$ 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, CDCl_3 , 25 °C) 166.6 (C), 145.4 (CH), 136.7 (C), 129.5 (CH), 128.5 (CH), 126.4 (CH), 120.7 (CH), 102.5 (CH), 85.3 (CH), 81.8 (CH), 76.8 (CH), 71.2 (CH_2), 70.7 (CH), 60.9 (CH_2), 14.3 (CH_3). IR (KBr): 3462, 2981, 2925, 2880, 1723, 1663, 1466 cm^{-1} . MS (CI^+): m/z 321 (100%, MH^+).

e) Preparation of β -C-pyranoside 8: To a solution of α,β -unsaturated ester **Z-1** (0.013 g, 0.041 mmol) in dry DMF (1.2 mL) at r.t. under N_2 was added NaH (60% (w/w) suspension in mineral oil) (0.002 g, 0.05 mmol) causing vigorous effervescence. After 15 min, t.l.c. showing no starting material, the mixture was poured into saturated NH_4Cl solution (15 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were dried over MgSO_4 , filtered and concentrated under reduced pressure to a colourless oil. ^1H NMR spectroscopy of the crude mixture showed only the desired product and residual mineral oil. Column chromatography (SiO_2 , 1:4 EtOAc/petroleum ether) gave compound **8** (0.012 g, 92%) as a colorless oil: R_f (1:4 EtOAc/petroleum ether) = 0.32. $[\alpha]_D^{20} +30.2$ (c 2.41, CHCl_3). Found: 321.1340; $\text{C}_{17}\text{H}_{21}\text{O}_6$ (MH^+) requires: 321.1338 (0.7 ppm error). ^1H NMR (400 MHz, CDCl_3 , 25 °C) 7.50 (m, 2H), 7.41-7.34 (complex m, 3H), 5.56 (s, 1H), 4.43 (ddd, $^3J_{(\text{H,H})}$ 7.0, 6.7, 0.9 Hz, 1H), 4.27 (dd, $^2J_{(\text{H,H})}$ 10.4 Hz, $^3J_{(\text{H,H})}$ 4.9 Hz, 1H), 4.19 (q, J 7.0 Hz, 2H), 3.69 (dd, $^2J_{(\text{H,H})}$ 10.4 Hz, $^3J_{(\text{H,H})}$ 10.2 Hz, 1H), 3.64 (d, $^3J_{(\text{H,H})}$ 9.7 Hz, 1H), 3.53 (d, $^3J_{(\text{H,H})}$ 3.9 Hz, 1H), 3.31 (dd, $^3J_{(\text{H,H})}$ 3.9, 0.9 Hz, 1H), 3.27 (ddd, $^3J_{(\text{H,H})}$ 10.2, 9.7, 4.9 Hz, 1H), 2.74 (dd, $^3J_{(\text{H,H})}$ 16.2, 6.7 Hz, 1H), 2.96 (dd, $^3J_{(\text{H,H})}$ 16.2, 7.0 Hz, 1H), 1.28 (t, $^3J_{(\text{H,H})}$ 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3 , 25 °C) 170.5 (C), 137.2 (C), 129.3 (CH), 128.5 (CH), 126.2 (CH), 102.4 (CH), 75.1 (CH), 71.5 (CH), 69.8 (CH), 69.5 (CH_2), 61.0 (CH_2), 54.8 (CH), 52.1 (CH), 37.0 (CH_2), 14.3 (CH_3). IR (KBr): 2927, 2866, 1732, 1645, 1456, 1388, 1286, 1186, 1109, 1001, 758, 700 cm^{-1} . MS (CI): m/z 321 (100%, MH^+).

f) Preparation of α -C-pyranoside 9: A suspension of NaH (washed with petroleum ether and dried under reduced pressure) (4.3 mg, 0.18 mmol) in THF (1.0 mL) at $-40\text{ }^{\circ}\text{C}$ under N_2 was treated, dropwise over 5 min, with a solution of the *E*-alkene *E*-1 (45 mg, 0.14 mmol) in THF (1.5 mL). The resulting grey-white suspension was maintained at $-40\text{ }^{\circ}\text{C}$ for 15 h before being quenched with EtOH (0.5 mL) and saturated aqueous ammonium chloride solution (10 mL), warmed to room temperature and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated to a pale yellow oil. Subjection of this material to flash chromatography (SiO_2 , 1:4 EtOAc/petroleum ether ($40\text{--}60\text{ }^{\circ}\text{C}$)) provided a mixture of α - and β -C-pyranosides **8** and **9**: R_f (1:4 EtOAc/petroleum ether) = 0.32 and 0.28. Crystallization from hot MeOH provided compound **9** (25 mg, 56%) as white needles, m.p. = $112\text{--}113\text{ }^{\circ}\text{C}$. $[\alpha]_D^{22} +48.0$ (c 1.03, CHCl_3). Found: C 63.72, H 6.50; $\text{C}_{17}\text{H}_{20}\text{O}_6$ requires: C 63.74, H 6.29. ^1H NMR (500 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$) 7.50 (m, 2H), 7.41–7.35 (complex m, 3H), 5.58 (s, 1H), 4.67 (dd, $^3J_{(\text{H,H})}$ 8.7, 6.3 Hz, 1H), 4.23–4.17 (complex m, 3H), 3.68 (dd, $^3J_{(\text{H,H})}$ 10.3 Hz, $^2J_{(\text{H,H})}$ 10.3 Hz, 1H), 3.67 (d, $^3J_{(\text{H,H})}$ 9.5 Hz, 1H), 3.52 (d, $^3J_{(\text{H,H})}$ 3.7 Hz, 1H), 3.35 (ddd, $^3J_{(\text{H,H})}$ 10.3, 9.5, 4.7 Hz, 1H), 3.15 (d, $^3J_{(\text{H,H})}$ 3.7 Hz, 1H), 2.86 (dd, $^3J_{(\text{H,H})}$ 15.0, 8.7 Hz, 1H), 2.68 (dd, $^3J_{(\text{H,H})}$ 15.0, 6.3 Hz, 1H), 1.29 (t, $^3J_{(\text{H,H})}$ 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$) 170.0 (C), 137.1 (C), 129.4 (CH), 128.5 (CH), 126.2 (CH), 102.4 (CH), 75.4 (CH), 69.8 (CH), 69.7 (CH_2), 63.8 (CH), 61.1 (CH_2), 54.1 (CH), 51.9 (CH), 39.0 (CH_2), 14.4 (CH_3). IR (KBr): 2983, 2910, 1722 cm^{-1} . MS (CI^+): m/z 321 (100%, MH^+).