

Rigid Spacer-Mediated Synthesis of Bis-Spiroketal Ring Systems: Stereoselective Synthesis of Nonsymmetrical Spiro Disaccharides

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Supporting Information

General Methods. All solvents and reagents were purchased from commercial sources and used without further purification, except for dichloromethane, which was distilled under Ar stream over CaH₂. 1,2-*O*-Isopropylidene- β -D-fructofuranose (**5**) was prepared according to described procedures (see ref. 9 in the manuscript). Optical rotations were measured at 20 °C in 1-cm or 1-dm tubes on a Perkin-Elmer 141 MC polarimeter. ¹H (and ¹³C NMR) spectra were recorded at 500 (125.7) MHz with a Bruker 500 DRX instrument, respectively. 2D COSY, 1D TOCSY, HMQC and HSQC experiments were used to assist on NMR assignments. Thin-layer chromatography (TLC) was carried out on aluminium sheets coated with Kieselgel 60 F254 (E. Merck), with visualisation by UV light and by charring with 10% H₂SO₄. Column chromatography was carried out on Silica Gel 60 (E. Merck, 230-400 mesh). FAB mass spectra were obtained with a Kratos MS-80 RFA instrument. The operating conditions were the following: the primary beam consisted of Xe atoms with a maximum energy of 8 keV; the samples were dissolved in thioglycerol, and the positive ions were separated and accelerated over a potential of 7 keV; NaI was added as cationizing agent. Elemental analyses were performed at the Instituto de Investigaciones Químicas (Sevilla, Spain).

3-*O*-(2-Bromomethylbenzyl)-1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose (7**).** To a solution of 1,2-dibromomethylbenzene **6** (1.99 g, 7.56 mmol) in dry DMF (50 mL), NaH (60% in mineral oil, 378 mg, 9.45 mmol) was added and the suspension was stirred at room temperature for 15 min. 1,2:4,5-Di-*O*-isopropylidene- β -D-fructopyranose **5** (1.0 g, 3.78 mmol) was then added and the reaction mixture was further stirred for 24 h. Et₂O (15 mL) and water (15 mL) were added, the organic layer was separated, washed with water (5 \times 10 mL), dried (MgSO₄), filtered, and

concentrated. The resulting residue was purified by column chromatography (1:8 EtOAc-petroleum ether) to yield **7** (628 mg, 73%); $R_f = 0.73$ (2:5 EtOAc-petroleum ether); $[\alpha]_D = -38.6$ (c 0.8, CHCl_3); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.28\text{--}7.24$ (m, 4 H, Ph), 5.08, 4.76 (2 d, 2 H, $^2J_{\text{H,H}} = 12.0$ Hz, CHPh), 4.73, 4.58 (2 d, 2 H, $^2J_{\text{H,H}} = 10.2$ Hz, CHBr), 4.36 (dd, 1 H, $J_{3,4} = 7.2$ Hz, $J_{4,5} = 5.6$ Hz, H-4), 4.21 (dd, 1 H, $J_{5,6a} = 2.5$ Hz, H-5), 3.96 (dd, 1 H, $J_{6a,6b} = 13.4$ Hz, H-6a), 3.99 (d, 1 H, H-6b), 3.96 (d, 1 H, $J_{1a,1b} = 8.8$ Hz, H-1a), 3.88 (d, 1 H, H-1b), 3.53 (d, 1 H, H-3), 1.60, 1.55, 1.37, 1.36 (4 s, 12 H, CMe_2); ^{13}C NMR (125.7 MHz, CDCl_3): $\delta = 136.8\text{--}128.5$ (Ph), 112.1, 109.1 (CMe_2), 104.3 (C-2), 77.5 (C-4), 76.8 (C-3), 73.8 (C-5), 72.2 (C-1), 70.8 (CH_2Ph), 60.4 (C-6), 31.1 (CH_2Br), 28.2, 26.6, 26.3, 26.2 (CMe_2); FABMS: m/z 465, 467 (80%, $[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{BrO}_6$: C 54.18, H 6.14. Found: C 54.08, H 6.30.

3-*O*-(2-Bromomethylbenzyl)-1,2-*O*-isopropylidene- β -D-fructopyranose (8**)** Compound **7** (628 mg, 1.41 mmol) was dissolved in 60% aqueous acetic acid (3.5 mL) and stirred at 45 °C for 2 h. The reaction mixture was then diluted with water (5 mL) and extracted with EtOAc (4 \times 4 mL). The combined organic phase was washed with saturated aqueous NaHCO_3 (6 mL), dried (MgSO_4), filtered, and concentrated. The resulting residue was purified by column chromatography (2:3 \rightarrow 1:1 EtOAc-petroleum ether) to give **8** (400 mg, 70%); $R_f = 0.47$ (3:1 EtOAc-petroleum ether); $[\alpha]_D = -60.3$ (c 0.8 in CHCl_3); ^1H NMR (500 MHz, CD_3OD): $\delta = 7.37\text{--}7.26$ (m, 4 H, Ph), 5.15, 4.75 (2 d, 2 H, $^2J_{\text{H,H}} = 11.6$ Hz, CHPh), 4.90, 4.66 (2 d, 2 H, $^2J_{\text{H,H}} = 10.2$ Hz, CHBr), 3.93 (dd, 1 H, $J_{3,4} = 9.8$ Hz, $J_{4,5} = 3.5$ Hz, H-4), 3.89 (dd, 1 H, $J_{6a,6b} = 12.4$ Hz, $J_{5,6a} = 1.4$ Hz, H-6a), 3.85 (d, 1 H, $J_{1a,1b} = 8.6$ Hz, H-1a), 3.84 (m, 1 H, H-5), 3.80 (d, 1 H, H-1b), 3.69 (d, 1 H, H-3), 3.62 (d, 1 H, $J_{5,6b} = 1.9$ Hz, H-6b), 1.39, 1.30 (2 s, 6 H, CMe_2); ^{13}C NMR (125.7 MHz, CD_3OD): $\delta = 137.1\text{--}128.1$ (Ph), 111.5 (CMe_2), 105.8 (C-2), 75.8 (C-3), 71.8 (CH_2Ph), 71.7 (C-1), 71.5 (C-4), 70.1 (C-5), 64.3 (C-6), 30.5 (CH_2Br), 25.7, 25.2 (CMe_2); FABMS: m/z 425, 427 (70%, $[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{BrO}_6$: C 50.63, H 5.75. Found: C 50.23, H 5.79.

3-*O*-(2-Chloromethylbenzyl)-1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose (9**).** To a solution of the bromomethylbenzyl derivative **7** (200 mg, 0.34 mmol) in DMF (30 mL), saturated aqueous NaCl (4.0 mL) was added and the mixture was stirred at 60 °C for 16 h. Water (25 mL) was added and the resulting solution was extracted with Et_2O (5 \times 10 mL). The combined organic layer was dried (MgSO_4), filtered, and concentrated to yield **9** (170 mg, 95%); $R_f = 0.73$ (2:5 EtOAc-petroleum ether); $[\alpha]_D = -58.8$ (c 0.9, CHCl_3); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.39\text{--}7.26$ (m, 4 H, Ph), 5.11, 4.76 (d, 1 H, $^2J_{\text{H,H}} = 12.0$ Hz, CHPh), 4.84, 4.70 (d, 1 H, $^2J_{\text{H,H}} = 11.6$ Hz, CHCl), 4.38 (dd, 1 H, $J_{3,4} = 7.3$ Hz, $J_{4,5} = 5.4$ Hz, H-4), 4.22 (dd, 1 H, $J_{5,6a} = 2.3$ Hz, H-5), 4.14 (dd, 1 H, $J_{6a,6b} = 13.4$ Hz, H-6a), 4.01 (d, 1 H, H-6b), 3.97 (d, 1 H, $J_{1a,1b} = 8.6$ Hz, H-1a), 3.89 (d, 1 H, H-1b),

3.53 (d, 1 H, H-3), 1.58, 1.54, 1.39, 1.38 (4 s, 12 H, CMe₂); ¹³C NMR (125.7 MHz, CDCl₃): δ = 136.6-128.4 (Ph), 112.1, 109.1 (CMe₂), 104.0 (C-2), 77.5 (C-4), 76.7 (C-3), 73.8 (C-5), 72.2 (C-1), 70.8 (CH₂Ph), 60.4 (C-6), 43.7 (CH₂Cl), 28.2, 26.6, 26.3, 26.2 (CMe₂); FABMS: *m/z* 421, 423 (50%, [M+Na]⁺); elemental analysis calcd. (%) for C₂₀H₂₇ClO₆: C 60.22, H 6.82; found: C 60.28, H 6.56.

3-*O*-(2-Cloromethylbenzyl)-1,2-*O*-isopropylidene-β-D-fructopyranose (10). Treatment of **9** (150 mg, 0.37 mmol) with 60% aqueous AcOH, following the procedure above described for the preparation of **8**, and purification by column chromatography (2:3→1:1 EtOAc-petroleum ether) yielded **10** (120 mg, 88%); *R_f* = 0.47 (3:1 EtOAc/petroleum ether); [α]_D = -79.8 (*c* 1.6, CHCl₃); ¹H NMR (500 MHz, CD₃OD): δ = 7.38-7.28 (m, 4 H, Ph), 5.16, 4.74 (d, 1 H, ²*J*_{H,H} = 11.6 Hz, CHPh), 4.88, 4.86 (d, 1 H, ²*J*_{H,H} = 11.8 Hz, CHCl), 3.92 (dd, 1 H, *J*_{3,4} = 9.8 Hz, *J*_{4,5} = 3.4 Hz, H-4), 3.89 (dd, 1 H, *J*_{6a,6b} = 12.4 Hz, *J*_{5,6a} = 1.4 Hz, H-6a), 3.83 (d, 1 H, *J*_{1a,1b} = 8.6 Hz, H-1a), 3.82 (m, 1 H, H-5), 3.79 (d, 1 H, H-1b), 3.68 (d, 1 H, H-3), 3.62 (d, 1 H, *J*_{5,6b} = 1.9 Hz, H-6b), 1.39, 1.30 (2 s, 6 H, CMe₂); ¹³C NMR (125.7 MHz, CD₃OD): δ = 129.8-128.0 (Ph), 111.5 (CMe₂), 105.8 (C-2), 75.8 (C-3), 71.9 (CH₂Ph), 71.7 (C-1), 71.5 (C-4), 70.1 (C-5), 64.3 (C-6), 43.1 (CH₂Cl), 25.7, 25.2 (CMe₂); FABMS: *m/z* 381 (60%, [M+Na]⁺). Anal. Calcd for C₁₇H₂₃ClO₆: C 56.90, H 6.46. Found: C 56.58, H 6.33.

4,5-Di-*O*-Benzyl-3-*O*-(2-bromomethylbenzyl)-1,2-*O*-isopropylidene-β-D-fructopyranose (11). To an suspension of NaH (60% in mineral oil, 66 mg, 1.6 mmol) and benzyl bromide (794 μL, 6.68 mmol) in DMF (7 mL), a solution of **10** (120 mg, 0.33 mmol) in dry DMF (3 mL) was dropwise added. The reaction mixture was stirred for 2 h at 50 °C, then quenched with H₂O (2 mL), extracted with Et₂O (5 × 5 mL), the combined organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by column chromatography (1:5 EtOAc-petroleum ether) to give **11** (122 mg, 70%); *R_f* = 0.78 (1:4 EtOAc-petroleum ether); [α]_D = -37.1 (*c* 3.8 in CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = 7.39-7.24 (m, 14 H, Ph), 5.16, 4.81 (2d, 2 H, ²*J*_{H,H} = 12.0 Hz, CHPh), 4.75, 4.68 (2 d, 2 H, ²*J*_{H,H} = 12.5 Hz, CHPh), 4.62, 4.59 (2 d, 2 H, ²*J*_{H,H} = 11.5 Hz, CHPh), 4.59 (s, 2 H, CH₂Br), 3.96 (d, 1 H, *J*_{3,4} = 9.8 Hz, H-3), 3.93 (d, 1 H, *J*_{1a,1b} = 8.6 Hz, H-1a), 3.91 (dd, 1 H, *J*_{4,5} = 3.4 Hz, H-4), 3.90 (d, 1 H, H-1b), 3.81 (dd, 1 H, *J*_{6a,6b} = 13.0 Hz, *J*_{5,6a} = 2.0 Hz, H-6a), 3.80 (m, 1 H, H-5), 3.76 (dd, 1 H, *J*_{5,6b} = 1.5 Hz, H-6b), 1.45, 1.41 (2 s, 6 H, CMe₂); ¹³C NMR (125.7 MHz, CD₃OD): δ = 137.2-127.6 (Ph), 111.7 (CMe₂), 105.8 (C-2), 80.1 (C-4), 75.4 (C-3), 73.3 (C-5), 72.3 (CH₂Ph), 72.2 (C-1), 71.8, 71.6 (CH₂Ph), 61.5 (C-6), 31.2 (CH₂Br), 26.7, 26.4 (CMe₂); FABMS: *m/z* 607, 605 (20%, [M+Na]⁺). Anal. Calcd for C₃₁H₃₅BrO₆: C 63.81, H 6.05. Found: C 63.74, H 5.79.

4,5-Di-*O*-Benzyl-1,2-*O*-isopropylidene- β -D-fructopyranose 1,2:4,5-Di-*O*-isopropylidene- β -D-fructopyranose 3,3'-*O*-(*o*-Xylenylene) (12): To a solution of **5** (59 mg, 0.23 mmol) in dry DMF (2 mL), an oily suspension of NaH (60%, 19 mg, 0.46 mmol, 2.5 eq) was added and the reaction mixture was stirred at room temperature for 15 min. A solution of **11** (100 mg, 0.186 mmol) in DMF (3 mL) was then added and the reaction mixture was further stirred at room temperature for 1 h. The reaction was quenched by addition of MeOH (2 mL) and water (4 mL), and extracted with Et₂O (2 \times 8 mL). The combined organic layer was washed with water (5 \times 5 mL), dried (MgSO₄), concentrated and purified by column chromatography (1:6 EtOAc-petroleum ether) to yield **12** (83 mg, 70%); R_f = 0.44 (1:3 EtOAc/petroleum ether); $[\alpha]_D = -65.3$ (c 0.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = 7.31-7.24 (m, 14 H, Ph), 5.15, 4.78 (2 d, 2 H, ² $J_{H,H}$ = 12.5 Hz, CHPh), 4.96, 4.73 (2 d, 2 H, ² $J_{H,H}$ = 12.4 Hz, CHPh), 4.67, 4.59 (2 d, 2 H, ² $J_{H,H}$ = 12.5 Hz, CHPh), 4.33 (dd, $J_{3,4}$ = 7.2 Hz, $J_{4,5}$ = 5.7 Hz, 1 H, H-4), 4.18 (dd, 1 H, $J_{5,6a}$ = 1.8 Hz, H-5), 4.10 (dd, 1 H, $J_{6a,6b}$ = 13.4 Hz, H-6a), 3.96 (d, 1 H, H-6b), 3.94 (d, 1 H, $J_{3',4'}$ = 9.8 Hz, H-3'), 3.90 (dd, 1 H, $J_{4',5'}$ = 10.0 Hz, $J_{5',6a'}$ = 2.9 Hz, H-4'), 3.88 (d, 1 H, $J_{1a',1b'}$ = 8.7 Hz, H-1a'), 3.85 (d, 2 H, $J_{1a,1b}$ = 8.5 Hz, H-1b', H-1a), 3.79 (d, 1 H, ² $J_{H,H}$ = 8.6 Hz, H-1b), 3.77 (m, 2 H, H-5', H-6a'), 3.74 (dd, 1 H, $J_{5',6b'}$ = 1.4 Hz, H-6b'), 3.44 (d, 1 H, H-3), 1.51, 1.45, 1.44, 1.41, 1.37, 1.33 (6 s, 18 H, CMe₂); ¹³C NMR (125.7 MHz, CDCl₃): δ = 138.4-127.3 (Ph), 112.1, 111.7, 109.0 (CMe₂), 105.9 (C-2'), 104.4 (C-2), 80.2 (C-4'), 77.7 (C-4), 76.4 (C-3), 75.1 (C-3'), 73.8 (C-5), 73.5 (C-5'), 72.2, 72.1 (CH₂Ph), 71.9 (C-1, C-1'), 71.6, 70.5 (CH₂Ph), 61.5 (C-6'), 60.3 (C-6), 28.2, 26.9, 26.7, 26.4, 26.2 (CMe₂); FABMS: m/z 785 (100%, [M+Na]⁺). Anal. Calcd for C₄₃H₅₄O₁₂: C 67.70, H 7.13. Found: C 67.45, H 6.87.

β -D-Fructofuranose 4,5-di-*O*-Benzyl- β -D-fructopyranose 1,2':2,1'-Dianhydride 3,3'-*O*-(*o*-Xylylene) (13). To a solution of **12** (124 mg, 0.162 mmol) in CH₂Cl₂ (36 mL) at -78 °C under Ar, trifluoromethanesulfonic acid (22 μ L) was added. The reaction mixture was allowed to reach room temperature and stirred for 1 h. Et₃N (1 mL) was then added, the reaction mixture was concentrated and the resulting residue was purified column chromatography using 3:1 EtOAc-petroleum ether to give **13** (40 mg (41%); R_f = 0.40 (4:1 EtOAc-petroleum ether); $[\alpha]_D = -122.9$ (c 1.15 in CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = 7.40-7.12 (m, 14 H, Ph), 5.69, 5.58 (2 d, 2 H, ² $J_{H,H}$ = 8.1 Hz, CHPh), 4.78, 4.72 (2 d, 2 H, ² $J_{H,H}$ = 12.7 Hz, CHPh), 4.55, 4.50 (2 d, 2 H, ² $J_{H,H}$ = 12.1 Hz, CHPh), 4.46, 4.34 (2 d, 2 H, ² $J_{H,H}$ = 8.1 Hz, CHPh), 4.40 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 7.8 Hz, H-4), 4.16 (d, 1 H, $J_{1a,1b}$ = 12.8 Hz, H-1a), 3.95 (d, 1 H, $J_{1a,1b}$ = 12.9 Hz, H-1a), 3.91 (d, 1 H, H-1b), 3.90 (d, 1 H, $J_{3',4'}$ = 9.5 Hz, H-3'), 3.85 (dd, 1 H, $J_{5,6b}$ = 5.6 Hz, H-5), 3.87 (d, 1 H, H-3), 3.82 (d, 1 H, H-1b), 3.75 (dd, 1 H, $J_{6a',6b'}$ = 12.5 Hz, $J_{5',6a'}$ = 2.1 Hz, H-6a'), 3.74 (m, 1 H, H-5'), 3.69 (m, 1 H, H-

6a), 3.66 (d, 1 H, H-6b), 3.61 (dd, 1 H, $J_{4',5'} = 3.2$ Hz, H-4'), 3.59 (m, 1 H, H-6b); ^{13}C NMR (125.7 MHz, CDCl_3): $\delta = 138.6$ -127.3 (Ph), 101.3 (C-2), 97.5 (C-2'), 89.6 (C-3), 80.3 (C-5), 80.0 (C-3'), 77.9 (C-4'), 74.7 (C-4), 73.1 (CH_2Ph), 72.9 (C-5'), 71.6, 71.4 (CH_2Ph), 66.4 (C-1), 62.9 (C-1), 62.5 (C-6), 61.0 (C-6'); FABMS: m/z 629 (65%, $[\text{M}+\text{Na}]^+$). Anal. Calcd for $\text{C}_{34}\text{H}_{38}\text{O}_{10}$: C 67.31, H 6.31. Found: C, 67.51, H 6.25.

β -D-Fructofuranose β -D-Fructopyranose 1,2':2,1'-Dianhydride (1). Conventional catalytic hydrogenation of **13** (30 mg, 0.092 mmol) with 10% Pd-C in 1:1 EtOAc-MeOH containing 10% HCOOH (1 mL) at 1 atm overnight, afforded the fully unprotected bis-spiro fructodisaccharide **1** having physicochemical and spectroscopic properties identical to those reported ($[\alpha]_{\text{D}} = -181$ (c 1.2 in H_2O); Lit. $[\alpha]_{\text{D}} = -179$ and -183 (c 3.6 and 1.8 in H_2O , respectively); see refs. 1 and 11 in the manuscript). The identity of **1** was additionally confirmed by GC after transformation into the corresponding hexa-*O*-trimethylsilyl derivative, following the protocol previously reported (see ref. 5 in the manuscript).