Supplementary information

The *o*-xylylene protecting group as an element of conformational control on remote stereochemistry in the synthesis of spiroketals

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General: 1,2-*O*-isopropylidene-6-*O*-*tert*-butyldimethylsilyl-β-D-fructofuranose (**9**) and 1,2-*O*-isopropylidene-β-D-fructopyranose (**14**) were obtained according to literature procedures (see refs. 7c and 14 in the manuscript, respectively). Reagents and solvents were purchased from commercial sources and used without further purification, with the following exceptions: DMF was distilled form BaO and dichloromethane was distilled under Ar stream over CaH_2, Optical rotations were measured at 20 ºC in 1-cm or 1-dm tubes on a Perkin-Elmer 141 MC polarimeter. IR spectra were recorded on a Bomem Michelson MB-120 FTIR spectrometer. ^{1}H (and ^{13}C NMR) spectra were recorded at 500 (125.7) and 300 (75.5) MHz with, respectively, Bruker 500 DRX spectrometers and 300 AMX spectrometers. 2D COSY and HMQC experiments were used to assist on NMR assignments. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with Kieselgel 30 F245 (E. Merck), with visualization by UV light and by charring with 10% H_2SO_4. 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).

6-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranose (10): To a solution of **9** (135 mg, 0.4 mmol) in DMF (2.5 ml) was added a suspension of NaH (60% in mineral oil, 80 mg, 2 mmol) and the suspension was stirred at room temperature for 20 min. 1,2-Bis(bromomethylbenzene) (264 mg, 1 mmol) was then added, the reaction mixture was further stirred for 1 h, quenched by addition of H_2O (0.5 mL) and concentrated. The residue was purified by column chromatography using 1:10 EtOAc-petroleum ether containing 0.5% Et_3N to give **10** (136 mg, 78%); R_f 0.31 (1:6 EtOAc-petroleum ether); $[\alpha]_D$ −5.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.32 (m, 4 H, Ph), 5.07 (d, H, $^2J_{H,H}$ = 12.6 Hz, C*H*Ph), 4.80 (m, 3 H, CH_2), 4.18 (dd, 1 H, $J_{3,4}$ = 6.3 Hz, $J_{4,5}$ = 4.6 Hz, H-4), 3.96 (d, 1 H, $J_{1a,1b}$ = 8.9 Hz, H-1a), 3.89 (ddd, 1 H, $J_{5,6b}$ = 6.9 Hz, H-5), 3.86 (d, 1 H, H-1b), 3.84 (d, 1 H, H-3), 3.72 (dd, 1 H, $J_{6a,6b}$ = 10.3 Hz, H-6a), 3.67 (dd, 1 H, H-6b), 1.45, 1.40 (2 s, each 3 H, CMe_2), 0.88 (s, 9H, $SiCMe_3$), 0.02 (s, 6H, $SiMe_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.1-129.4 (Ph), 111.7 (*C*Me_2), 110.5 (C-2), 83.1 (C-4), 82.9 (C-5), 81.2 (C-3), 71.0 (C-1), 69.6, 69.4 (CH_2), 64.9 (C-6), 27.1, 26.0 (C*Me*$_2$), 25.9 (SiC*Me*$_3$), 18.3 (Si*C*Me_3); FABMS: *m/z* 459 (100%, $[M + Na]^+$); $C_{23}H_{36}O_6Si$: C, 63.30; H, 8.30; Found: C, 63.36; H, 8.30.

1,2-*O*-Isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranose (11): To a stirred solution of **10** (478 mg, 1.09 mmol) in THF (25 mL), under Ar, was added TBAF (1 M in THF, 1.21 mL) at 0 °C. The reaction mixture was stirred for 4 h until disappearance of the starting material (TLC), then diluted with Et_2O (15 mL), washed with water (2 x 8 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the residue by column chromatography (1:1 EtOAc-petroleum ether) gave **11** (326 mg, 93%); R_f 0.58 (2:1 EtOAc-petroleum ether); $[\alpha]_D$ +11.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.24 (m, 4 H, Ph), 5.10, 4.76 (2 d, 2 H, $^2J_{H,H}$ = 13.0 Hz, CH_2), 4.81, 4.78 (2 d, 2 H, $^2J_{H,H}$ = 8.7 Hz, CH_2), 4.50 (dd, 1 H, $J_{3,4}$ = 6.6 Hz, $J_{4,5}$ = 5.5 Hz, H-4), 4.01 (ddd, 1 H, $J_{5,6b}$ = 3.4 Hz, $J_{5,6a}$ = 2.6 Hz, H-5), 3.98 (d, 1 H, $J_{1a,1b}$ = 9.2 Hz, H-1a), 3.91 (d, 1 H, H-1b), 3.84 (d, 1 H, H-3), 3.74 (dt, 1 H, $J_{6a,6b}$ = 12.1 Hz, $J_{OH,6a}$ = 2.3 Hz, H-6a), 3.63 (ddd, 1 H, $J_{OH,6b}$ = 9.7 Hz, H-6b), 2.72 (bs, 1 H, OH), 1.50, 1.41 (2 s, each 3 H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.2-129.5 (Ph), 112.1 (*C*Me_2), 110.2 (C-2), 83.8 (C-5), 81.0 (C-3), 80.7 (C-4), 70.9 (C-1), 69.9, 69.0 (CH_2), 63.0 (C-6), 27.1, 25.5 (C*Me*$_2$);

FABMS: *m/z* 345 (98%, $[M + Na]^+$); $C_{17}H_{22}O_6$: C, 63.34; H, 6.88; Found: C, 63.00; H, 6.92.

6-*O*-Benzyl-1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranose (12): To a solution of **11** (55 mg, 0.17 mmol) in dry DMF (2 mL) was added a suspension of NaH (60% in mineral oil, 17 mg, 0.43 mmol) and benzyl bromide (21 μL, 0.17 mmol). The reaction mixture was stirred for 3 h at room temperature, then saturated aqueous NH_4Cl (2 mL) was added and the solvents were evaporated. The resulting residue was extracted with Et_2O (5 mL), washed with water (3 mL), dried ($MgSO_4$), concentrated and purified by column chromatography (1:4 EtOAc-petroleum ether) to yield **12** (57 mg, 80%); R_f 0.59 (1:2 EtOAc-petroleum ether); $[\alpha]_D$ +4.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.24 (m, 9 H, Ph), 5.08, 4.81 (2 d, 2 H, $^2J_{H,H}$ = 12.6 Hz, CH_2), 4.82, 4.78 (2 d, 2 H, $^2J_{H,H}$ = 12.9 Hz, CH_2), 4.56 (s, 2 H, CH_2), 4.18 (dd, 1 H, $J_{3,4}$ = 6.5 Hz, $J_{4,5}$ = 4.8 Hz, H-4), 4.09 (ddd, 1 H, $J_{5,6a}$ = 7.5 Hz, $J_{5,6b}$ = 5.4 Hz, H-5), 3.99 (d, 1 H, $J_{1a,1b}$ = 8.9 Hz, H-1a), 3.88 (d, 1 H, H-1b), 3.87 (d, 1 H, H-3), 3.65 (dd, 1 H, $J_{6a,6b}$ = 9.9 Hz, H-6a), 3.56 (dd, 1 H, H-6b), 1.45, 1.40 (2 s, each 3 H, CMe_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.2-127.6 (Ph), 111.8 (*C*Me_2), 110.6 (C-2), 83.2 (C-4), 81.4 (C-5), 80.9 (C-3), 72.2 (C-6), 71.0 (C-1), 69.6, 69.4 (CH_2), 27.1, 26.0 (C*Me*$_2$); FABMS: *m/z* 435 (35%, $[M + Na]^+$); $C_{24}H_{28}O_6$: C, 69.88; H, 6.84; Found: C, 69.85; H, 6.70.

6-*O*-Benzyl-3,4-*O*-(*o*-xylenylene)-α-D-fructofuranose 6-*O*-benzyl-3,4-*O*-(*o*-xylenylene)-β-D-fructofuranose 1,2':2,1'-dianhydride (13): To a solution of **12** (90 mg, 0.218 mmol) in CH_2Cl_2 (6 mL) at −78 ºC, trifluoromethanesulfonic acid (28 μL, 0.328 mmol) was added. The reaction mixture was allowed to reach room temperature and stirred for 10 min. Then, Et_3N (1.6 mL) was added, the solvent was eliminated under reduced pressure and the residue was purified by column chromatography using 1:4→1:3 EtOAc-petroleum ether as eluent to give **13** (54 mg, 70%); R_f 0.48 (1:2 EtOAc-petroleum ether); $[\alpha]_D$ +47.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.23 (m, 18 H, Ph), 5.02, 4.76 (2 d, 2 H, $^2J_{H,H}$ = 12.5 Hz, CH_2), 4.86, 4.63 (2 d, 2 H, $^2J_{H,H}$ = 12.7 Hz, CH_2), 4.79, 4.75 (2 d, 2 H, $^2J_{H,H}$ = 13.0 Hz, CH_2), 4.78, 4.70 (2 d, 2 H, $^2J_{H,H}$ = 13.0 Hz, CH_2), 4.62, 4.59 (2 d, 2 H, $^2J_{H,H}$ = 12.0 Hz, CH_2), 4.58, 4.55 (2 d, 2 H, $^2J_{H,H}$ = 12.5 Hz, CH_2), 4.22 (dd, 1 H, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$= 4.5 Hz, H-4β), 4.14 (td, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, H-5β), 4.07 (d, 1 H, $J_{1a,1b}$ = 11.5 Hz, H-1aβ), 4.06 (d, 1 H, $J_{1a,1b}$ =

12.3 Hz, H-1aα), 4.02 (ddd, 1 H, $J_{4,5}$= 9.0 Hz, $J_{5,6b}$ = 6.0 Hz, $J_{5,6a}$ = 2.5 Hz, H-5α), 3.89 (d, 1 H, $J_{3,4}$ = 4.5 Hz, H-3α), 3.83 (dd, 1 H, H-4α), 3.72 (dd, 1 H, $J_{6a,6b}$ = 11.4 Hz, H-6aα), 3.64 (dd, 1 H, $J_{6a,6b}$ = 9.5 Hz, H-6aβ), 3.61 (dd, 1 H, H-6bα), 3.58 (d, 1 H, H-3β), 3.54 (dd, 1 H, H-6bβ), 3.53 (d, 1 H, H-1bα), 3.24 (d, 1 H, H-1bβ); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.5-127.7 (Ph), 102.0 (C-2α), 101.6 (C-2β), 87.4 (C-3α), 83.9 (C-4β), 82.9 (C-3β), 82.8 (C-4α), 81.6 (C-5β), 78.5 (C-5α), 73.4, 73.1, 70.4, 69.5, 69.3, 68.1 (CH_2), 71.9 (C-6β), 69.7 (C-6α), 63.3 (C-1α), 62.8 (C-1β); FABMS: *m/z* 731 (98%, $[M + Na]^+$); $C_{42}H_{44}O_{10}$: C, 71.17; H, 6.26; Found: C, 70.99; H, 6.16.

a-D-Fructofuranose b-D-Fructofuranose 1,2':2,1'-Dianhydride (1): Conventional catalytic hydrogenation of **13** (50 mg, 0.07 mmol) with 10% Pd-C in 1:1 EtOAc-MeOH containing 10% HCOOH (1.5 mL) at 1 atm overnight, afforded the fully unprotected bis-spiro fructodisaccharide **1** (23 mg, 100%) having physicochemical and spectroscopic properties identical to those reported (see ref. 4a in the manuscript). The identity of **2** was additionally confirmed by GC after transformation into the corresponding hexa-*O*-trimethylsilyl derivative, following the protocol previously reported (see ref. 9 in the manuscript).

1,2-*O*-Isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructopyranose (15): To a solution of **14** (250 mg, 1.46 mmol) in DMF (18 mL), NaH (60% in mineral oil, 55 mg, 2.9 mmol) was added and the suspension was stirred at room temperature for 16 h. A solution of 1,2-bis(bromomethylbenzene) (302 mg, 1.46 mmol) in DMF (3 mL) was then added dropwise, the reaction mixture was further stirred for 3 h, quenched by addition of H_2O (0.5 mL) and concentrated. The residue was purified by column chromatography (1:2→1:1 EtOAc-petroleum ether) to give **15** (132 mg, 37%), having physicochemical and spectroscopic properties identical to those previously reported (see ref. 8 in the manuscript), together with unreacted **14** (125 mg, 50%).

5-O-Benzyl-1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructopiranose (16): To a solution of **15** (168 mg, 0.522 mmol) in DMF (7 mL) was added NaH (60% in mineral oil, 52 mg, 1.3 mmol) and the suspension was stirred at room temperature for 15 min. Benzyl bromide (130 μL, 10.4 mmol) was added and the mixture was stirred for 30 min at room temperature. MeOH (4 mL), Et_2O (16 mL) and H_2O (8 mL) were

addded, the organic phase was decanted, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (1:8 EtOAc-petroleum ether) to give **16** (161 mg, 75%); $[\alpha]_D$ −158.9 (*c* 0.8, $CHCl_3$); R_f 0.33 (1:6 EtOAc-petroleum ether); ^{1}H RMN (500 MHz, $CDCl_3$) δ 7.22-7.08 (m, 9 H, Ph), 5.11, 4.75 (2 d, 2 H, $^2J_{H,H}$ = 13.5 Hz, C*H*Ph), 4.96, 4.67 (2 d, 2 H, $^2J_{H,H}$ = 12.3 Hz, C*H*Ph), 4.18 (d, 1 H, $J_{1a,1b}$ = 8.5 Hz, H-1a), 4.04 (d, 1 H, H-1b), 3.96 (m, 2 H, H-3, H-4), 3.84 (m, 1 H, H-5), 3.82 (dd, 1 H, $J_{6a,6b}$ = 11.7 Hz, $J_{5,6a}$ = 1.1 Hz, H-6a), 3.74 (dd, 1 H, $J_{5,6b}$ = 2.0 Hz, H-6b), 1.47, 1.41 (2 s, 6 H, CMe_2); ^{13}C RMN (125.7 MHz, $CDCl_3$) δ 137.2-127.4 (Ph), 111.8 (*C*Me_2), 105.9 (C-2), 79.6 (C-4), 77.2 (C-3), 76.1 (C-5), 72.5, 72.0 (*C*H_2Ph), 71.8 (C-1), 62.8 (C-6), 27.1, 26.1 (C*Me*$_2$). FABMS: *m/z* 435 (30%, $[M+Na]^+$); $C_{24}H_{28}O_6$: C, 69.88; H, 6.84; Found: C, 69.77; H, 6.78.

5,5'-Di-*O*-benzyl-3,4,3',4'-di-*O*-(*o*-xylylene)-di-β-D-fructopyranose 1,2':2,1'-dianhydride (17) and 5-*O*-benzyl-3,4-*O*-(*o*-xylylene)-α-D-fructopyranose 5-*O*-benzyl-3,4-*O*-(*o*-xylylene)-β-D-fructopyranose 1,2':2,1'-dianhydride (18): To a solution of **16** (160 mg, 0.387 mmol) in CH_2Cl_2 (8 mL) at -78 ºC, trifluoromethanesulfonic acid (50 μL, 0.580 mmol) was added. The mixture reaction was allowed to reach room temperature and further stirred for 1 h. Et_3N (5 drops) was then added, the solvent was eliminated under reduced pressure and the residue was purified by column chromatography 1:3→1:2 EtOAc-petroleum ether to give 17 (84 mg, 61%) and 18 (27 mg, 20%).

Data for **17**: $[\alpha]_D$ −72.4 (*c* 1.3, $CHCl_3$); R_f 0.54 (1:1 EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.02 (m, 18 H, Ph), 5.22-4.62 (12 d, 12 H, C*H*$_2$Ph), 4.43 (d, 1 H, $J_{1a,1b}$ = 11.1 Hz, H-1a), 4.16 (d, 1 H, $J_{1a,1b}$ = 12.2 Hz, H-1'a), 3.98 (dd, 1 H, $J_{3,4}$ = 9.6, $J_{4,5}$ = 3.0 Hz, H-4α), 3.95 (bd, 1 H, $J_{6a,6b}$ = 13.1 Hz, H-6aβ), 3.94 (d, 1 H, $J_{3,4}$ = 10.3, H-3β), 3.83 (m, 1 H, $J_{6a,6b}$ = 12.2 Hz, $J_{5,6a}$ = 1.8 Hz, H-6aα), 3.81-3.82 (m, 2 H, H-5α, H-5β), 3.68 (d, 1 H, $J_{3,4}$ = 9.6, H-3α), 3.64 (dd, 1 H, H-6bβ), 3.64 (dd, 1 H, H-6bα), 3.64 (d, 1 H, H-1'b), 3.55 (d, 1 H, H-1b), 3.51 (dd, 1 H, $J_{4,5}$ = 3.3 Hz, H-4β); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.7-127.35 (Ph), 96.8 (C-2α), 95.9 (C-2β), 81.7 (C-3β), 79.5 (C-4β), 78.9 (C-3α), 77.6 (C-4α), 76.0 (C-5β), 75.1 (CH_2), 74.6 (CH_2), 74.3 (C-5α), 73.0, 72.6, 72.3 (CH_2), 64.1 (C-6β), 62.5 (C-1), 61.7 (C-6α), 56.1 (C-1'); FABMS: *m/z* 731 (10%, $[M + Na]^+$); $C_{42}H_{44}O_{10}$: C, 71.17; H, 6.26; Found: C, 71.33; H, 6.46.

Data for **18**: R_f 0.74 (1:1 EtOAc-petroleum ether); $[\alpha]_D$ −173.5 (*c* 0.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.05 (m, 18 H, Ph), 5.10, 4,96 (2 d, 4 H, $^2J_{H,H}$ = 14.3 Hz, CH_2), 5.05 (1 bs, 4 H), 4.74, 4.69 (2 d, 4 H, $^2J_{H,H}$ = 12.4 Hz, CH_2), 4.12 (dd, 2 H, $J_{3,4}$= 10 Hz, $J_{4,5}$ = 3.21 Hz, H-4), 4.06 (d, 1 H, $J_{1a,1b}$ = 11.8 Hz, H-1a), 3.92 (d, 1 H, H-3), 3.83 (m, 2 H, H-5), 3.74 (s, 4 H, H-6a, H-6b), 3.65 (d, 2 H, H-1b); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.7-127.4 (Ph), 96.6 (C-2), 80.5 (C-3), 78.8 (C-4), 75.9 (C-5), 73.9 (CH_2), 73.0 (CH_2), 72.4 (CH_2), 62.7 (C-6), 64.6 (C-1); FABMS: *m/z* 731 (15%, $[M + Na]^+$); $C_{42}H_{44}O_{10}$: C, 71.17; H, 6.26; Found: C, 71.35; H, 6.61.

Di-β-D-fructopyranose 1,2':2,1'-dianhydride (2): Conventional catalytic hydrogenation of **18** (100 mg, 0.141 mmol) with 10% Pd-C in 1:1 EtOAc-MeOH containing 10% HCOOH (3 mL) at 1 atm overnight, afforded the fully unprotected bis-spiro fructodisaccharide **2** (45 mg, 100%) having physicochemical and spectroscopic properties identical to those reported (see ref. 4a in the manuscript). The identity of **2** was additionally confirmed by GC after transformation into the corresponding hexa-*O*-trimethylsilyl derivative, following the protocol previously reported (see ref. 9 in the manuscript).

