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Note

A general radical-mediated stereoselective route for the construction of chiral furo[2,3-*b*]furans from D-xylose*

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Fused cyclic acetals such as furo[2,3-*b*]furans are present in many natural products (*e.g.*, clerodin[1], aflatoxin[2], and astaltoxin[3]), and several strategies have been devised[4] for their construction. We now describe a highly stereoselective synthesis of the chiral furo[2,3-*b*]furan derivative **1** from 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylose[5] (**2**), which utilises a radical-mediated intramolecular cyclisation as the key step.

Reaction of **2** with propargyl alcohol in the presence of Amberlite IR-120 (H^+) resin afforded propargyl 3,5-di-*O*-benzyl-α- (α-**3**) and -β-D-xylofuranoside (β-**3**) (α,β-ratio 3:2), which were isolated by column chromatography. Each of these anomers, which can be prepared stereoselectively by known methods[6], was characterised on the basis of ^{1}H-n.m.r. data (200 MHz). Thus, the signals for H-1 appeared at δ 5.3 (d, $J_{1,2}$ 4.5 Hz) and 5.12 (d, $J_{1,2}$ 2.1 Hz) for α-**3** and β-**3**, respectively. Reaction of α-**3** and β-**3** with sodium hydride, carbon disulfide, and methyl iodide[7] gave the xanthates α-**4** and β-**4**, respectively. The crucial radical-mediated cyclisation[8] was effected by exposure of α-**4** and β-**4** to tributyltin hydride in the presence of α,α-azobisisobutyronitrile in benzene to give the thermodynamically stable[9] *cis*-fused furans **1a** and **1b**, respectively. The structures of **1a** and **1b** were indicated by the ^{1}H-n.m.r. data, *i.e.*, by the disappearance of triplets at δ 2.45, 5.8 (for **1a**), and 5.95 (for **1b**) for the acetylenic proton and H-2, respectively, and the appearance of signals for vinylic protons at δ 5.0 and 5.1 (2 d) for **1a** and 5.1 (br. s) for **1b**. The H-1 signals appeared at δ 6.0 (d, $J_{1,5}$ 4.8 Hz) and 5.7 (d, $J_{1,5}$ 5.34 Hz) for **1a** and **1b**, respectively. Thus, the stereochemistry of **1a** and **1b** was determined by the configuration at the anomeric centre[10].

Treatment of **1a** and **1b** with 3-chloroperoxybenzoic acid in dichloromethane furnished the respective epoxides **5a** and **5b**, the structures of which were based[9c] on the expected direction of attack, *i.e.*, from the less-hindered side.

The above route to **1a** and **1b** yields enantiomerically pure products and should be applicable to other readily available carbohydrate derivatives with various stereochemical arrangements[11].

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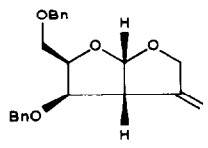
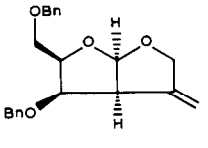
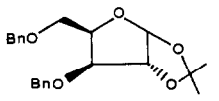


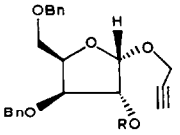
1a



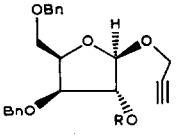
1b



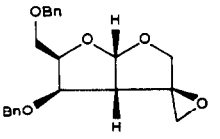
2



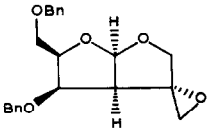
α-3 R = H
α-4 R = CSSCH$_3$



β-3 R = H
β-4 R = CSSCH$_3$



5a



5b

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_3Si) with Jeol PMX-FT and Varian 200-Gemini spectrometers. Optical rotations were measured with a JASCO DIP 360 or 370 polarimeter. Silica gel (60–120 mesh, Acme) was used for column chromatography. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) with detection using a solution of 2% of phosphomolybdic acid and 1% of $Ce_2SO_4 \cdot 4H_2O$ in aqueous 20% H_2SO_4 at 130°. All of the reactions were carried out in dry solvents under anhydrous conditions unless otherwise stated.

Propargyl 3,5-di-O-benzyl-α- (α-3) and -β-D-xylofuranoside (β-3). — A solution of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-D-xylose[5] (**2**; 1 g, 2.7 mmol) in propargyl alcohol (5 mL) containing Amberlite IR-120 (H^+) resin (0.5 g) was boiled under reflux for 3 h, then cooled to room temperature, and filtered, and the solvent was evaporated. Column chromatography (light petroleum–ethyl acetate, 5:1) of the residue gave, first, α-**3** (0.503 g, 50.9%), $[\alpha]_D$ + 74° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 2.5 (t, 1 H, $J_{1',3'}$ 2.2 Hz, $CH_2C{\equiv}CH$), 2.75 (d, 1 H, $J_{2,OH}$ 6.5 Hz, OH), 3.6–3.8 (m, 2 H, H-5a,5b), 4.05 (dd, 1 H, $J_{1,2}$ 4.5, $J_{2,3}$ 6.3 Hz, H-2), 4.25–4.8 (m, 7 H, H-1',3,4 and 2 CH_2Ph), 5.3 (d, 1 H, H-1), 7.2–7.5 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.62; H; 6.45.

Eluted second was β-**3** (0.362 g, 36.4%), $[\alpha]_D$ − 46° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 2.4 (t, 1 H, $J_{1',3'}$ 2.2 Hz, $C{\equiv}CH$), 2.7 (d, 1 H, $J_{2,OH}$ 6.2 Hz, OH), 3.6–3.85 (m, 2 H, H-5a,5b), 4.0 (dd, 1 H, $J_{1,2}$ 2.2, $J_{2,3}$ 6.4 Hz, H-2), 4.2–4.7 (m, 7 H, H-1',3,4 and 2 CH_2Ph), 5.12 (d, 1 H, H-1), 7.2–7.5 (m, 10 H, 2 Ph).

Anal. Found: C, 71.59; H, 6.51.

Propargyl 3,5-di-O-benzyl-2-O-[(S-methylthio)thiocarbonyl]-α- (α-4) and -β-D-xylofuranoside (β-4). — To a solutoin of α-**3** (0.5 g, 1.35 mmol) in dry tetrahydrofuran (5 mL) under N_2 was added sodium hydride (0.068 g, 1.4 mmol; 50% dispersion in oil). After 2 h, dry carbon disulfide (0.106 g, 1.4 mmol) was added, followed, after 20 min, by methyl iodide (0.198 g, 1.4 mmol). After 1 h, the reaction was quenched with water, the

mixture was extracted with ether, the extract was washed with brine and dried (Na_2SO_4), and the solvent was evaporated. Column chromatography (light petroleum–ethyl acetate, 8:1) of the residue afforded **α-4** (0.535 g, 86%), $[\alpha]_D$ + 104° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 2.45 (t, 1 H, $J_{1',3'}$ 2.2 Hz, C≡C*H*), 2.55 (s, 3 H, SMe), 3.65–3.8 (m, 2 H, H-5a,5b), 4.25 (d, 2 H, CH_2≡CH), 4.4–4.7 (m, 6 H, H-3,4 and 2 CH_2Ph), 5.6 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1), 5.8 (t, 1 H, $J_{2,3}$ 4.6 Hz, H-2), 7.2–7.5 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{24}H_{26}O_5S_2$: C, 73.07; H, 6.64; S, 20.28. Found: C, 72.93; H, 6.60; S, 20.21.

Using the above conditions, **β-3** (0.3 g, 0.81 mmol) was converted into **β-4** (0.328 g, 88%), $[\alpha]_D$ − 102° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 2.45 (t, 1 H, $J_{1',3'}$ 2.2 Hz, C≡C*H*), 2.6 (s, 3 H, SMe), 3.7–3.82 (m, 2 H, H-5a,5b), 4.12 (d, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 4.3 (d, 2 H, CH_2C≡CH), 4.45–4.9 (m, 5 H, H-4 and 2 CH_2Ph), 5.4 (s, 1 H, H-1), 5.95 (s, 1 H, H-2), 7.2–7.5 (m, 10 H, 2 Ph).

Anal. Found: C, 72.89; H, 6.58; S, 20.08.

(1S,3R,4R,5R)-4-Benzyloxy-3-benzyloxymethyl-6-methylene-2,8-dioxabicyclo-[3.3.0]octane (**1a**) *and (1R,3R,4R,5S)-4-benzyloxy-3-benzyloxymethyl-6-methylene-2,8-dioxabicyclo[3.3.0]octane* (**1b**). — A stirred solution of **α-4** (0.2 g, 0.436 mmol) in deaerated thiophene-free benzene (5 mL) containing a catalytic amount of α,α′-azobisisobutyronitrile was boiled under reflux under N_2 and treated dropwise with Bu_3SnH (0.132 g, 0.46 mmol). After 1 h, the benzene was evaporated. Column chromatography (light petroleum–ethyl acetate, 10:1) of the residue gave **1a** (0.133 g, 87%), $[\alpha]_D$ − 56° (*c* 1.2, chloroform). ^{1}H-N.m.r. data: δ 3.45 (dd, 1 H, $J_{1,5}$ 4.8, $J_{5,8}$ 3.8 Hz, H-5), 3.7–3.85 (m, 2 H, CH_2OCH_2Ph), 3.95 (d, 1 H, $J_{3,4}$ 3 Hz, H-4), 4.2 (dt, 1 H, J_{3,CH_2} 3 and 6 Hz, H-3), 4.4–4.75 (m, 6 H, H-7a,7b and 2 CH_2Ph), 5.0 (dd, 1 H, $J_{9,9}$ 5.5, $J_{7,9}$ 2.0 Hz, C=C*H*), 5.1 (dd, 1 H, C=C*H*), 6.0 (d, 1 H, H-1), 7.2–7.4 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 74.86; H, 6.69.

Treatment of **β-4** (0.2 g, 0.436 mmol), as described above, gave **1b** (0.128 g, 84%), $[\alpha]_D$ + 52° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 3.44 (dd, 1 H, $J_{1,5}$ 5.3, $J_{4,5}$ 4.3 Hz, H-5), 3.6–3.82 (m, 2 H, CH_2OCH_2Ph), 4.1–4.7 (m, 8 H, H-3,4,7a,7b and 2 CH_2Ph), 5.1 (br. s, 2 H, C=CH_2), 5.7 (d, 1 H, H-1), 7.2–7.4 (m, 10 H, 2 Ph).

Anal. Found: C, 74.84; H, 6.81.

(1S,3R,4R,5S,2′R)-4-Benzyloxy-3-benzyloxymethyl-2,8-dioxabicyclo[3.3.0]octane-6-spiro-2′-oxirane (**5a**) *and (1R,3R,4R,5R,2′S)-4-benzyloxy-3-benzyloxymethyl-2,8-dioxabicyclo[3.3.0]octane-6-spiro-2′-oxirane* (**5b**). A solution of **1a** (0.1 g, 0.284 mmol) in dry dichloromethane (2 mL) at − 10° was treated with 3-chloroperoxybenzoic acid (0.058 g, 0.34 mmol) and stirred at room temperature for 2 h. The reaction was quenched with aqueous sodium metabisulphite and, after 30 min, extracted with dichloromethane. The extract was washed with aqueous sodium hydrogen carbonate and brine, then dried (Na_2SO_4), and the solvent was evaporated. Column chromatography (light petroleum–ethyl acetate, 4:1) of the residue afforded **5a** (0.077 g, 74%), $[\alpha]_D$ + 17° (*c* 0.6, chloroform). ^{1}H-N.m.r. data: δ 2.75 (dd, 1 H, $J_{1,5}$ 5.4, $J_{4,5}$ 6.2 Hz, H-5), 2.85 (ABq, 2 H, *J* 3 Hz, epoxide CH_2), 3.5–4.1 and 4.3–4.7 (m, 9 H, H-3,7a,7b, CH_2OCH_2Ph, and 2 CH_2Ph), 4.15 (dd, 1 H, $J_{3,4}$ 3.8 Hz, H-4), 5.88 (d, 1 H, H-1), 7.2–7.5 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.63; H, 6.49.

Treatment of **1b** (0.1 g, 0.284 mmol), as described above, gave **5b** (0.080 g, 77%), $[\alpha]_D$ −21° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 2.8 (dd, 1 H, $J_{1,5}$ 5.4, $J_{4,5}$ 6.4 Hz, H-5), 2.86 (s, 2 H, epoxide CH_2), 3.6–4.7 (m, 10 H, H-3,4,7a,7b, CH_2OCH_2Ph, and 2 CH_2Ph), 6.08 (d, 1 H, H-1), 7.2–7.4 (m, 10 H, 2 Ph).

Anal. Found: C, 71.61; H, 6.47.

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