Preparation of 2,3-Anhydroallopynanosides Functionalised in the 6-Position

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Treatment of methyl 2,3-anhydro-6-bromo-6-deoxy-α-D-allopyranoside with sodium phenylsulfinate, decanethiol, and 2-furylmethanethiol gave sugar epoxides carrying sulfone or sulhide functionalities in the 6-position. Oxidation of the sulfides gave the corresponding sulfones.

Ring-contraction of sugar epoxides to yield furanosidic α,β-unsaturated aldehydes (Fig. 1) was the key reaction in our total syntheses of enantiomERICALLY pure botryodiplodin and several lignans. We now report the preparation, from methyl α-D-glucopyranoside, of the novel sugar epoxides 2–10, functionalised in the 6-position. These epoxides have the potential for ring-contraction, which would furnish several new enantiomERICALLY pure furanosidic building blocks.

Treatment of methyl α-D-glucopyranoside with benzaldehyde and zinc chloride gave crude methyl 4,6-O-benzylidene-α-D-glucopyranoside5, which was treated with p-toluenesulfonyl chloride in pyridine to give methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulfonyl-α-D-glucopyranoside6,7 in 78% overall yield on a 250 g scale. The latter compound was treated with sodium hydroxide–potassium carbonate–tetrabutylammonium hydrogensulfate to give, in 91% yield, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside8, which was treated with N-bromosuccinimide–barium carbonate9 to furnish methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-allopyranoside (I) in 98% yield. Debenzyolization of I (Scheme 1) gave crystalline 2 (98%, 68% overall yield from methyl α-D-glucopyranoside).

Displacement of bromide from 1 or 2, using various base–thiol combinations5 (Scheme 1), proceeded in good yields without opening of the epoxide ring (Scheme 1), although thiol-mediated epoxide opening in anhydro sugars has been reported.8 The recently published10 use of potassium carbonate in dimethyl formamide (DMF) as promoter was superior compared with cesium carbonate–DMF or –acetoneitrile. It is especially rewarding that compound 2 underwent the desired substitution reactions in high yields, since this gives directly the functionalised epoxy alcohols needed for ring-contraction to furanosidic aldehydes.

Treatment of I with sodium phenylsulfinate in DMF for 16 h at room temperature and 30 h at 60°C, gave the sulfone epoxide 3 (61%). The yield decreased both when the reaction was performed only at room temperature or only at 60°C. In the latter case, NMR spectral analysis indicated that the epoxide ring had been opened. Treatment of 2 under similar conditions was unsuccessful.

Treatment of 1 with decanethiol in DMF–cesium carbonate at room temperature, followed by oxidation with m-chloroperbenzoic acid, gave the sulfone epoxide 4 (73%). It was found that formation of by-products in the substitution step was significantly reduced if the DMF was kept at ~15 mmHg for a few min before use. Presumably, volatile contaminants (e.g. dimethylamine and carbon monoxide) were removed from the DMF by the evacuation. In a similar reaction, 2 was transformed, using cesium carbonate in acetonitrile, into the sulfide epoxide 7 (77%).

Treatment of 1 or 2 with 2-furylmethanethiol in DMF–potassium carbonate gave the sulfide epoxides 5 (93%) and 6 (93%), respectively. Compound 5 was transformed into 6 (91%) by debenzyolation.

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The sulfone epoxides 3 and 4 were debenzylated to give the sulfone epoxy alcohols 8 (93%) and 9 (92%), respectively. Oxidation of 6 gave the sulfone epoxy alcohol 10 (87%).

The most characteristic feature of the epoxide sugars is the NMR signals for H-2 and H-3. However, with deuteriochloroform solutions, the H-4,5,6-signals often obscure the spectrum, where the chemical shifts of H-2–H-6 were found in the region 3.5–3.9 ppm. In deuteriobenzene solution the signals were separated over a larger region (2.8–3.8 ppm). The coupling constants for H-2 and H-3 were of similar magnitude in all the compounds.

In summary, nine new epoxy saccharides (2–10), functionalized in the 6-position, have been prepared from the known precursor 1, which in turn was prepared in 68% yield over four steps (all intermediates were crystalline) from commercially available methyl α-D-glucopyranoside.

It should be pointed out that all compounds, except 3 and 5, shown in Scheme 1 are crystalline, which greatly facilitates their large-scale preparation. Ring-contraction to furanosidic α,β-unsaturated aldehydes will be reported in due course.

Experimental

NMR spectra were recorded at 23°C with a Varian XL-300 spectrometer operating at 300 MHz proton frequency using CDCl₃ as the solvent and CHCl₃ as an internal standard (δ 7.26 from Me₂Si). Optical rotations were measured with a Perkin-Elmer 141 polarimeter. For TLC analysis Merck SiO₂, 60 F₂₅₄ precoated aluminium sheets were used and the spots were visualised with UV light, I₂ in SiO₂, or by charring with 5% anisaldehyde in sulfuric acid and ethanol. Liquid chromatography was performed on Matrex SiO₂ 60 (35–70 μm) silica gel.

Methyl 2,3-anhydro-6-bromo-6-deoxy-2,6-d-allopyranoside (2). To a stirred solution of 1 (7.44 g, 21.7 mmol) in dry methanol (250 ml) was added sodium methoxide in methanol (5.0 ml, 0.5 M). After 3 h, SiO₂ (5 g) was added and the stirring was continued until the mixture was neutral. Filtration (Celite), concentration, and drying in vacuo gave a solid (7.23 g), which gave 2 (5.11 g, 98%) after recrystallisation from toluene. M.p. 108–109°C; [α]D + 27°C (c 1.4, CHCl₃). Anal. C₂₊H₁₆BrO₅; C, H NMR (C₅D₅): δ 4.36 (d, 1 H, J 2.9 Hz, H-1), 3.74 (dd, 1 H, J 2.2, 6.9, 9.2 Hz, H-5), 3.48 (dd, 1 H, J 2.2, 11.0 Hz, H-6), 3.40 (br d, 1 H, J 9.3 Hz, H-4), 3.25 (dd, 1 H, J 6.8, 11.0 Hz, H-6), 3.24 (s, 3 H, OMe), 2.88 (dd, 1 H, J 2.9, 4.2 Hz, H-2), 2.84 (dd, 1 H, J 1.7, 4.2 Hz, H-3). ¹³C NMR (CDCl₃): δ 94.6, 68.6, 68.1, 56.0, 55.9, 54.1, 33.5.

Methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-6-phenylsulfonyl-2,6-d-allopyranoside (3). To a stirred solution of 1 (301 mg, 0.88 mmol) in DMF (5.0 ml) was added sodium benzenesulfinate (361 mg, 2.20 mmol). The mixture was kept for 16 h at 22°C and at 60°C for 30 h. After concentration at 50°C, the residue was dissolved in water (75 ml) and the solution was extracted with diethyl ether (3 x 25 ml), then dried (Na₂SO₄), filtered, and concentrated and the residue was chromatographed (heptane-EtOAc 2:1) to give 3 (217 mg, 61%) as an oil; [α]D + 170° (c 4.8, CDCl₃); ¹³C NMR (CDCl₃): δ 7.89 (m, 4 H, Ph), 7.51–7.67 (m, 5 H, Ph), 7.43 (t, 1 H, J 7.8 Hz, Ph), 5.10 (dd, 1 H, J 1.3, 9.5 Hz, H-4), 4.93 (d, 1 H, J 3.1 Hz, H-1), 4.58 (dd, 1 H, J 2.8, 6.4, 9.9 Hz, H-5), 3.62 (dd, 1 H, J 1.6, 4.2 Hz, H-3), 3.58 (m, 1 H, J 3.0 Hz, H-2), 3.57 (s, 3 H, OMe), 3.34 (m, 2 H, H-6). ¹³C NMR (CDCl₃): δ 165.7, 139.8, 133.8, 133.7, 129.9, 129.4, 128.7, 128.6, 127.9, 94.8, 70.1, 61.9, 57.7, 56.6, 54.5, 50.8.
Methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-6-furfurylthio-2-O-p-allylpanoside (5). To a stirred solution of 1 (1.00 g, 2.92 mmol) in dry, degassed DMF (12 ml) was added 2-furfurylmethanethiol (0.36 ml, 3.20 mmol) and K₂CO₃ (602 mg, 4.36 mmol). After 2.5 h, the mixture was poured into water (60 ml) and the mixture was extracted with diethyl ether (4 × 20 ml). The extract was dried (Na₂SO₄) and concentrated. Residual DMF was removed in vacuo.

The residue was chromatographed (heptane-toluene-EtOAc 3:1:1) to give 5 (356 mg, 93%). [α]D₂⁰ + 194° (c 1.1, CHCl₃); Anal. C₉H₁₂O₅S·C₂H₅OH: C, H, N MMR (CDCl₃): δ 4.90 (d, 1 H, J 3.2 Hz, H-1), 3.85 (d, 1 H, J 1.7, 9.2, 9.5 Hz, H-4), 3.73 (d, 1 H, J 3.2, 7.5, 9.2 Hz, H-5), 3.58 (d, 1 H, J 3.2, 4.2 Hz, H-2), 3.50 (s, 3 H, OMe), 3.46 (d, 1 H, J 1.7, 4.1 Hz, H-3), 2.95 (dd, 1 H, J 3.2, 13.9 Hz, H-6), 2.57 (t, 2 H, J 7.6 Hz, SO₂CH₂CH₂), 1.98 (s, 1 H, J 9.5 Hz, OH), 1.58 (quintet, 2 H, J 7.3 Hz, SO₂CH₂CH₂), 1.40-1.20 [m, 14 H, (CH₂)₄], 0.88 (t, 3 H, J 6.8 Hz, CH₂CH₂). ¹³C NMR (CDCl₃): δ 154.9, 69.0, 68.8, 55.9, 55.8, 54.0, 33.1, 29.1.

Methyl 2,3-anhydro-6-deoxy-6-furfurylthio-2-O-p-allylpanoside (6). To a stirred solution of 2 (1.50 g, 6.27 mmol) in dry, degassed DMF (28 ml) was added 2-furfurylmethanethiol (0.97 ml, 9.56 mmol) and K₂CO₃ (1.31 g, 9.41 mmol). After 15 h, the mixture was poured into water (170 ml) and the mixture was extracted with CH₂Cl₂ (5 × 35 ml). The organic extract was dried (Na₂SO₄) and concentrated. Residual DMF was removed in vacuo overnight. The residue was dissolved in diethyl ether, and ligroin (b.p. 80–110°C) was added. The mixture was left for 15 h, which gave crystalline 6 (610 g, 93%). M.p. 69–71°C; [α]D₂⁰ + 123° (c 0.8, CHCl₃). Anal. C₇H₁₀O₄S·C₂H₅OH: C, H, N MMR (CDCl₃): δ 7.36 (dd, 1 H, J 0.6, 2.0 Hz, fur-H-5), 6.30 (dd, 1 H, J 2.0, 3.1 Hz, fur-H-4), 6.18 (dd, 1 H, J 0.6, 3.2 Hz, fur-H-3), 4.89 (d, 1 H, J 3.2 Hz, H-1), 3.83 (br d, 1 H, J 9.9 Hz, H-4), 3.79 (s, 2 H, CH₂-fur), 3.72 (dd, 1 H, J 2.8, 7.6, 9.2 Hz, H-5), 3.57 (dd, 1 H, J 3.2, 4.1 Hz, H-2), 3.50 (s, 3 H, OMe), 3.46 (dd, 1 H, J 1.7, 4.1 Hz, H-3), 2.94 (dd, 1 H, J 2.9, 14.2 Hz, H-6), 2.64 (dd, 1 H, J 7.6, 14.2 Hz, H-6), 2.01 (br s, 1 H, OH). ¹³C NMR (CDCl₃): δ 151.4, 142.3, 110.4, 107.8, 94.5, 69.0, 68.8, 55.9, 55.8, 54.0, 33.1, 29.1.
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9.1 Hz, H-5), 3.71 (m, 1 H, H-4), 3.62 (dd, 1 H, J 2.0, 14.6 Hz, H-6), 3.57 (dd, 1 H, J 3.1, 4.1 Hz, H-2), 3.50 (s, 3 H, OMe), 3.46 (dd, 1 H, J 1.6, 4.0 Hz, H-3), 2.92 (dd, 1 H, J 8.6, 14.6 Hz, H-6), 1.96 (br d, 1 H, J 9.5 Hz, OH). 13C NMR (CDCl3): δ 139.8, 133.8, 129.4, 127.9, 94.6, 68.4, 64.3, 57.8, 56.4, 55.6, 53.3.

Methyl 2,3-anhydro-6-decylsulfonyl-6-deoxy-α-D-allopyranoside (9). To a stirred solution of 4 (250 mg, 0.53 mmol) in dry MeOH (15 ml) was added MeONa–MeOH (0.1 ml, 0.5 M). After 22 h, SiO2 (1.3 g) was added and the mixture was stirred until it was neutral. The mixture was filtered (Celite) and concentrated, and the residue was chromatographed (heptane–EtOAc 1:2) to give 9 (180 mg, 92%), which crystallized upon standing. M.p. 95–96°C, [α]D20 + 83° (c 2.6, CDCl3). Anal. C17H20O7S·2CH3·H2O. 1H NMR (CDCl3): δ 8.88 (d, 1 H, J 3.0 Hz, H-1), 4.20 (dt, 1 H, J 1.8, 9.3 Hz, H-5), 3.79 (br dd, 1 H, J 1.2, 1.7 Hz, H-4), 3.59 (dd, 1 H, J 3.1, 4.2 Hz, H-2), 3.51 (m, 4 H, OMe, H-3), 3.48 (dd, 1 H, J 1.0, 15.0 Hz, H-6), 3.16 (dd, 1 H, J 9.1, 15.0 Hz, H-6), 3.05 (dd, 2 H, J 5.6, 8.0 Hz, SO2CH2CH3), 2.60 (br d, 1 H, J 7.4 Hz, OH), 1.82 (m, 2 H, SO2CH2CH3), 1.40–1.20 [m, 14 H, (CH2)14], 0.87 (t, 3 H, J 7.0 Hz, CH3CH2). 13C NMR (CDCl3): δ 94.9, 68.2, 64.9, 56.4, 55.4, 54.7, 54.2, 53.4, 31.8, 29.5, 29.2, 29.1, 28.5, 22.6, 21.8, 21.8, 14.1.

Methyl 2,3-anhydro-6-deoxy-6-(furfurylsulfonyl)-α-D-allopyranoside (10). To a stirred solution of 6 (302 mg, 1.85 mmol) in EtOAc (100 ml) was added dry m-chloro-phenylbenzoic acid (Fluka 55%, 1.289 g, 11.4 mmol). After 4.5 h, the solution was filtered through basic Al2O3 (activity grade III) and concentrated. The residue was chromatographed (heptane–EtOAc 1:3) to give 10 (490 mg, 87%), which crystallized upon standing. M.p. 94–97°C, [α]D20 + 87° (c 0.5, CHCl3). Anal. C12H16O4·3CH3·SO2. 1H NMR (CDCl3): δ 7.47 (dd, 1 H, J 0.9, 1.9 Hz, f-H-5), 6.52 (d, 1 H, J 3.2 Hz, fur-H-4), 6.43 (dd, 1 H, J 1.9, 3.2 Hz, fur-H-3), 4.94 (d, 1 H, J 3.2 Hz, H-1), 4.49, 4.39 (AB system, 2 H, J 14.9 Hz, CH2-fur), 4.24 (dt, 1 H, J 2.4, 9.3 Hz, H-5), 3.81 (br t, 1 H, J 9.3 Hz, H-4), 3.62 (dd, 1 H, J 3.2, 4.2 Hz, H-2), 3.57 (s, 3 H, OMe), 3.51 (dd, 1 H, J 1.8, 4.2 Hz, H-3), 3.45 (dd, 1 H, J 1.6, 15.1 Hz, H-6), 3.21 (dd, 1 H, J 9.2, 15.1 Hz, H-6), 2.15 (d, 1 H, J 10.4 Hz, OH). 13C NMR (CDCl3): δ 144.0, 142.4, 112.5, 111.4, 94.9, 68.1, 64.9, 56.5, 55.5, 54.3, 53.5, 53.0.

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References


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