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Note

Synthesis of 1D-1,2-anhydro-*myo*-inositol

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Glycosidase inhibitors are of major interest for the study of glycosidase activity and in the control of disorders of carbohydrate metabolism[1]. Naturally occurring[2] and mechanism-based inhibitors[3] have been reported. Conduritol B epoxide (**5**, 1,2-anhydro-*myo*-inositol), the first reported site-directed irreversible inhibitor, is still considered to be one of the most suitable glucosidase inhibitors[1a]. Racemic **5** reacts with several β-D-glucosidases by nucleophilic attack of a carboxylate anion of the active site on the protonated epoxide to give an ester of (+)-*chiro*-inositol[4a], which indicates that only D-**5** had reacted.

As a part of a project on the synthesis of derivatives of glycosylphosphatidylinositol which might be implicated in a second-messenger mechanism for the signal transduction of insulin[5], we have found that 2,4/3-tribenzyloxycyclohex-5-enone[6] (**1**) can be reduced stereoselectively and then epoxidised to give 1D-1,2-anhydro-*myo*-inositol (**5**) in good yield.

Racemic **5** has been synthesised[3a,7] from *myo*-inositol and from benzene, and the L form has been prepared[8] from an optically active *chiro*-inositol derivative but, apparently, no synthesis of the D form has been reported.

Reduction of **1** with lithium aluminum hydride or di-isobutylaluminum hydride gave[9] a 6:4 mixture of the epimeric alcohols **2** and **3**. In our hands, the reduction of **1** with lithium aluminum hydride gave a 1:1 mixture and the use of sodium borohydride at −75° gave a 1:3 mixture.

The presence of cerium chloride[10] in borohydride reductions changes the stereoselectivity when applied[11] to cyclohexenones related to **1**. Thus, similar reduction of **1** at −75° afforded a 14:1 mixture of **2** and **3**, from which the desired isomer **2** was isolated in a yield of 90%. The nature of protecting groups affects the stereoselectivity, since our results are in sharp contrast with those[12c] obtained when *tert*-butyldimethylsilyl ethers were used.

Epoxidation of **2** with *m*-chloroperoxybenzoic acid yielded 84% of **4**, debenzylation of which afforded 1D-1,2-anhydro-*myo*-inositol (**5**, 81%), $[\alpha]_D$ +66° (*cf.* −70° for the L enantiomer[8]). The ^1H- and ^{13}C-n.m.r. spectra and analytical data of the tetra-acetate (**6**) of **5** accorded with the structure proposed.

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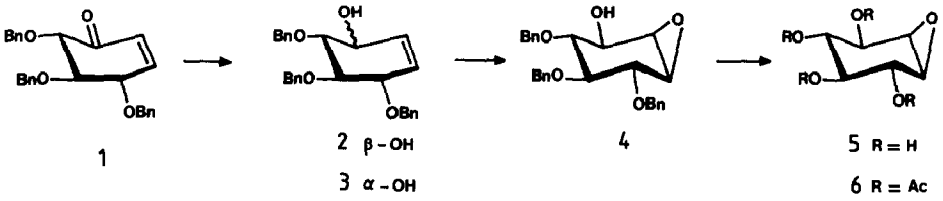

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. T.l.c. was performed on Silica Gel GF_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Silica Gel (Merck 70–230). ^{1}H-N.m.r. spectra were recorded with a Varian XL-300 (300 MHz) or Bruker AM-200 (200 MHz) spectrometer, and ^{13}C-n.m.r. spectra with a Bruker AM-200 (50 MHz) spectrometer. Optical rotations were determined with a Perkin–Elmer 141 polarimeter.

1D-1,2,3-Tri-O-benzyl-(1,3/2,4)-5-cyclohexene-1,2,3,4-tetrol (**2**, *1,2,3-tri-O-benzylconduritol B*). — A stirred mixture of **1** (ref. 6) (565 mg, 1.36 mmol), methanol (70 mL), and $CeCl_3 \cdot 7H_2O$ (490 mg, 0.97 equiv.) at −75° was treated with sodium borohydride (76 mg, 5.88 equiv.) for 5 h. Water (40 mL) was then added, volatile solvents were evaporated under vacuum, the aqueous phase was extracted with dichloromethane (2 × 50 mL), and the combined extracts were dried (Na_2SO_4) and concentrated. Column chromatography (1:3 ethyl acetate–hexane) of the residue afforded **2** (515 mg, 91%), m.p. 116–119°, $[\alpha]_D$ +117° (*c* 0.9, chloroform); lit.[11] $[\alpha]_D$ +114.6°. N.m.r. data: ^{1}H (200 MHz, C_6D_6), δ 7.40–7.20 (m, 15 H, 3 Ph), 5.23 (m, 2 H, H-1,2), 4.67 (d, 1 H, PhC*H*), 4.58 (s, 2 H, PhCH_2), 4.38 (d, 1 H, PhC*H*), 4.19 (s, 2 H, PhCH_2), 3.92 (m, 1 H, H-6), 3.83 (m, 1 H, H-3), 3.47 (dd, 1 H, $J_{3,4}$ 7.5, $J_{4,5}$ 10.3 Hz, H-4), 3.17 (dd, 1 H, $J_{5,6}$ 7.7, $J_{4,5}$ 10.3 Hz, H-5), 1.44 (d, 1 H, *J* 4.4 Hz, HO-6); ^{13}C ($CDCl_3$), 138.6 (C-ipso), 129.4 [C-1 (or 2)], 128.6, 128.4, 127.9, 127.8, 127.7, 127.6 (aromatic), 127.0 [C-2 (or 1)], 84.3, 83.3, 80.5, 75.3, 72.2, 71.9, and 71.8 p.p.m.

Anal. Calc. for $C_{27}H_{28}O_4$: C, 77.87; H, 6.78. Found: C, 77.60; H, 6.70.

*1D-1,2-Anhydro-4,5,6-tri-O-benzyl-*myo*-inositol* (**4**). — A solution of **2** (100 mg, 0.24 mmol) in dichloromethane (5 mL) was treated with 55% *m*-chloroperoxybenzoic acid (121 mg, 1.60 equiv.) at room temperature for 2 days. Aqueous 10% $Na_2S_2O_3$ (5 mL) and dichloromethane (5 mL) were then added, and the organic phase was dried (Na_2SO_4) and concentrated. Column chromatography (1:2 ethyl acetate–hexane) of the residue gave **4** (87 mg, 84%), m.p. 147–150°, $[\alpha]_D$ +78° (*c* 0.4, chloroform). N.m.r. data ($CDCl_3$): ^{1}H (300 MHz), δ 7.40–7.30 (m, 15 H, 3 Ph), 4.94 (d, 1 H, PhC*H*), 4.82 (s, 2 H, PhCH_2), 4.78 (d, 1 H, PhC*H*), 4.71 (d, 1 H, PhC*H*), 4.63 (d, 1 H, PhC*H*), 4.02 (dd, 1 H, $J_{1,6}$ 1.7, $J_{5,6}$ 8.1 Hz, H-6), 3.93 (d, 1 H, $J_{3,4}$ 7.4 Hz, H-3), 3.48 (m, 2 H, H-4,5), 3.41 (m, 1 H, H-1), 3.23 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-2); ^{13}C, 138.3, 138.2, and 137.4 (C-ipso), 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6 (aromatic), 83.3, 79.5, 79.3, 75.6, 75.2, 73.2, 71.9, 56.2 and 53.6 p.p.m. (oxirane).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.52. Found: C, 75.10; H, 6.86.

1D-1,2-Anhydro-myo-*inositol* (**5**). — A solution of **4** (427 mg, 0.99 mmol) in methanol (50 mL) and ethyl acetate (10 mL) was treated with hydrogen in the presence of 10% Pd–C at room temperature overnight, then filtered, and concentrated. Column chromatography (1:3 methanol–chloroform) of the residue afforded **5** (129 mg, 81%), m.p. 158–160°, lit.[8,9] 160°; $[\alpha]_D$ +66° (*c* 0.6, D_2O); ^{13}C-N.m.r. data (D_2O): δ 76.0, 72.6, 71.9, 71.7, 58.6 and 57.9 p.p.m. (oxirane).

Anal. Calc. for $C_6H_{10}O_5$: C, 44.45; H, 6.22. Found: C, 44.29; H, 6.35.

The tetra-acetate (**6**) of **5** had m.p. 108–111°, $[\alpha]_D$ +80° (*c* 0.5, chloroform). N.m.r. data (C_6D_6): ^{1}H (300 MHz), δ 5.53 (dd, 1 H, $J_{5,6}$ 9.0, $J_{4,5}$ 10.6 Hz, H-5), 5.33 (dd, 1 H, $J_{1,6}$ 1.7, $J_{5,6}$ 9.0 Hz, H-6), 5.30 (dd, 1 H, $J_{3,4}$ 8.0, $J_{4,5}$ 10.6 Hz, H-4), 5.20 (d, 1 H, $J_{3,4}$ 8.0 Hz, H-3), 3.11 (dd, 1 H, $J_{1,6}$ 1.7, $J_{1,2}$ 3.7 Hz, H-1), 2.76 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 1.71, 1.67, 1.67, and 1.66 (4 s, 3 H each, 4 Ac); ^{13}C, 169.9, 169.5, 169.3, 169.0, 71.6, 71.4, 70.9, 68.1, 54.5 and 53.9 (oxirane), 20.2, 20.1, and 20.0 p.p.m. (2 C).

Anal. Calc. for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49. Found: C, 51.15; H, 5.67.

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