An Expeditious and Stereocontrolled Preparation of 2-Azido-2-deoxy-β-D-glucopyranose Derivatives from D-Glucal

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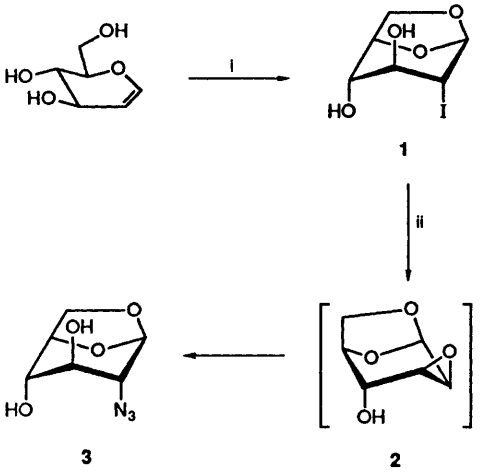
1,6-Anhydro-2-azido-2-deoxy-β-D-glucopyranose has been prepared by a two-step procedure from D-glucal and transformed into precursors useful in the synthesis of oligosaccharides.

Selectively blocked 2-azido-2-deoxy-D-glucopyranose derivatives, precursors extensively used[1–3] in the preparation of D-glucosamine-containing oligosaccharides, are commonly prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (tri-*O*-acetyl-D-glucal) by azidonitration[4] or azidochloration,[5] and from 1,6-anhydro-D-gluco-[6] or D-mannopyranose[7–10] by adapted regio- and stereo-selective reactions. These units are also available from either D-glucosamine by diazo transfer from trifluoromethanesulfonyl azide,[11] or from the corresponding *N*-benzyl derivative by a nitrosation procedure.[12]

We now report a configurationally controlled access to 2-azido-2-deoxy-D-glucose derivatives by a high-yielding two-step procedure from D-glucal.

The recently described[13] 1,6-iodocyclization of D-glucal was slightly modified as follows. *O*-Stannylated D-glucal, obtained by heating D-glucal under reflux in acetonitrile with bis(tributylstannyl) oxide (0.8 equiv.), was treated with iodine (1.2 equiv.) to give 1,6-anhydro-2-deoxy-2-iodo-β-D-glucopyranose **1** in 84% yield† (Scheme 1). When treated with sodium azide in



Scheme 1 *Reagents and conditions:* i, $(Bu_3Sn)_2O$ (0.8 equiv.), MS 3 Å, MeCN, reflux, 3 h then I_2 (1.2 equiv.), room temp., 1.5 h, 84%; ii, NaN_3, DMF–water (9:1, v/v), 120 °C, 3 h, 81%

DMF–water (9:1, v/v) at 120 °C, the iodide **1** gave crystalline 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose **3** as the only isolable product in 81% yield. This stereoselective transformation occurring with retention of configuration is obviously explained by the transient formation of the epoxide **2** opened in a *trans*-diaxial fashion by the azide ion.‡ This high-yielding process is noteworthy because the *manno* epoxide **2** is known to isomerize readily to 1,6:3,4-dianhydro-β-D-altropyranose in an alkaline medium.[14] The diol **3** was easily transformed into either glycosyl acceptors or donors in a straightforward manner. Thus, benzylation followed by a $TiCl_4$-mediated debenzylation at position 4[9] furnished 1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (Scheme 2), a useful acceptor in the preparation of a number of bioactive oligosaccharides incorporating *N*-acyl-D-glucosamine glycosylated at position 4.

Moreover, a variety of D-glucosaminyl donors are now available stereoselectively in a limited number of steps as exemplified by the transformation of compounds **4** and **5**. Azide reduction of compound **4**, protection by the benzyloxycarbonyl group, acetolysis with acetic anhydride containing trifluoroacetic acid, selective de-*O*-acetylation at the anomeric centre,[15] and trichloroacetimidate formation provided the α-imidate **6**,§ $[\alpha]_D$ +81 (*c* 1, chloroform), in an overall yield of 75%, selectively protected at position 6 (Scheme 2). The utility of this β-selective[16] glycosyl donor was substantiated by the synthesis in 91% yield of the β(1→4) linked disaccharide **8**.

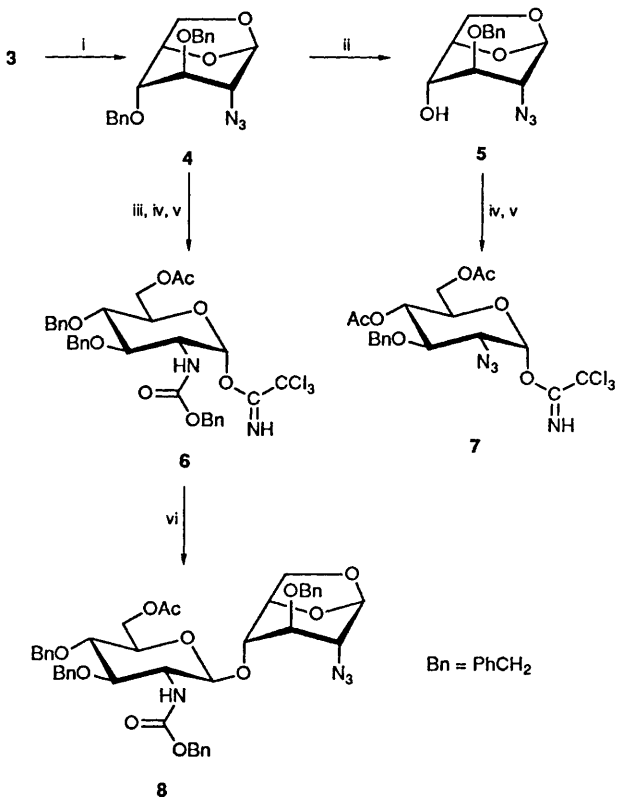
Similarly, the azide **5** was transformed in 73% overall yield into the α-imidate **7**,§ $[\alpha]_D$ +47 (*c* 1, chloroform), an α- or β-selective[2] D-glucosaminyl donor. The use of these easily accessible building blocks is currently being evaluated in the preparation of the signal molecules produced by *Rhizobium* bacteria and responsible for the host-specific interaction between the bacterium and the leguminous plant.[17]

Experimental

1,6-*Anhydro*-2-*azido*-2-*deoxy*-β-D-*glucopyranose* **3**.—A mixture of 1,6-anhydro-2-deoxy-2-iodo-β-D-glucopyranose **1** (46 g, 169.1 mmol) and sodium azide (33 g, 507.3 mmol) in *N*,*N*-dimethylformamide (300 cm^3) and water (38 cm^3) was stirred at 120 °C for 2 h. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in 95% ethanol (135 cm^3) and water (15 cm^3) and treated with charcoal (1 g) under reflux. After 0.5 h the mixture was filtered through Celite, concentrated and the residue was washed through a silica gel column (25 g), with toluene–methanol (5:2) as eluent. Solvents

† This procedure avoids the concomitant formation of the D-*manno* isomer, as described in the original report.[13]

‡ The preparation of the epoxide **2** from the iodide **1** was possible but needed strictly controlled conditions [MeONa (1 mol dm^{-3}; 1 equiv.), room temp., 45 min] in order to minimize the formation of the *altro* isomer (*manno*:*altro* isomeric ratio of 90–95:10–5 as judged by NMR).
§ Selected ^1H NMR data (300 MHz): **6**: δ($CDCl_3$) 4.19 (m, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3} \sim J_{2,NH} \sim$ 9.5 Hz, 2-H), 4.45 (br d, 1 H, $J_{2,NH}$ 9.5 Hz, NHZ), 6.28 (d, 1 H, $J_{1,2}$ 3.8 Hz, 1-H) and 8.68 (s, 1 H, C=NH); **7**: δ($CDCl_3$) 3.77 (dd, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.2 Hz, 2-H), 6.45 (d, 1 H, $J_{1,2}$ 3.8 Hz, 1-H) and 8.80 (s, 1 H, C=NH).



Scheme 1 Reagents and conditions: i, $PhCH_2Br$, $Ba(OH)_2$, DMF, room temp., 97%; ii, $TiCl_4$ (1.1 equiv.), CH_2Cl_2, room temp., 45 min, 82%; iii, $NaBH_4$, $NiCl_2$, EtOH, room temp. then $PhCH_2OCOCl$, $NaHCO_3$, room temp., 87%; iv, Ac_2O–CF_3CO_2H (9:1, v/v), room temp., 16 h, 97%; v, $PhCH_2NH_2$ (10 equiv.), Et_2O, room temp. then CCl_3CN, DBU, CH_2Cl_2, room temp., 88%; vi, **5** (1.4 equiv.), BF_3·Et_2O (0.1 equiv.), $PhCH_3$, −78 to −20 °C, 20 min, 91% (5% of the α-linked disaccharide was also isolated)

were removed under reduced pressure and the resulting solid, dissolved in water, was continuously extracted with ethyl acetate for 18 h. Concentration of the extract provided the azide **3** (25.6 g, 81%) as crystals, m.p. 114 °C (from ethyl acetate) (lit.,[6] 115–117 °C); $[\alpha]_D$ −30 (*c* 1, EtOH) {lit.,[6] $[\alpha]_D$ −33 (*c* 1, EtOH)}; δ_H(300 MHz; [$^2H_6$]-DMSO) 2.92 (1 H, t, $J_{1,2}$ 1.5, $J_{2,3}$ 3, 2-H), 3.31 (1 H, m, 4-H), 3.44 (1 H, dd, $J_{5,6a}$ 6, $J_{6a,6b}$ 7, 6a-H), 3.45 (1 H, br s, 3-H), 3.83 (1 H, dd, $J_{5,6b}$ 1, $J_{6a,6b}$ 7, 6b-H), 4.33 (1 H, m, $J_{4,5}$ 1.2, $J_{5,6a}$ 6, $J_{5,6b}$ 1, 5-H), 5.18 (1 H, d, *J* 4, OH), 5.27 (1 H, br s, 1-H) and 5.31 (1 H, d, *J* 4, OH).

4-O-(6-O-*Acetyl*-2-*benzyloxycarbonylamino*-2-*deoxy*-3,4-*di*-O-*benzyl*-β-D-*glucopyranosyl*)-1,6-*anhydro*-2-*azido*-3-O-*benzyl*-2-*deoxy*-β-D-*glucopyranose* **8**.—A mixture of the imidate **6** (3 g, 4.41 mmol), the alcohol **5** (1.71 g, 6.17 mmol) and activated powdered 4 Å molecular sieves (3 g) in dry toluene (30 cm^3) was stirred at room temperature under argon and then cooled to −78 °C. BF_3·Et_2O in toluene (1 mol dm^{-3}; 0.44 cm^3, 10 mol%) was added to the mixture which was then stirred until the temperature reached −20 °C (1 h). To simplify the purification of the products, excess of the alcohol **5** was silylated by addition of pyridine (1.1 cm^3) and trimethylsilyl chloride (1.6 cm^3). After being stirred at room temperature for 0.5 h, the mixture was diluted with dichloromethane (150 cm^3) and filtered. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (150 g), with hexane–ethyl acetate (2:1, containing 0.2% of triethylamine) as eluent to give the disaccharide **8** (3.2 g, 91%), m.p. 131 °C (from 95% ethanol); $[\alpha]_D$ +66 (*c* 1, $CHCl_3$); δ_H(300 MHz, [$^2H_6$]-DMSO) 1.93 (3 H, s, Ac), 3.34 (1 H, br s, 2-H), 3.45 (1 H, dd, $J_{1',2'}$ 8.5, $J_{2',3'}$ 9.5, 2′-H), 3.61 (1 H, t, $J_{5,6a}$ 7, $J_{6a,6b}$ 7, 6a-H), 3.66 (1 H, br s, 4-H), 3.83 (1 H, br s, 3-H), 3.93 (1 H, dd, $J_{5,6b}$ 1.5, $J_{6a,6b}$ 7, 6b-H), 4.11 (1 H, dd, $J_{5',6'a}$ 4.5, $J_{6'a,6'b}$ 12, 6′a-H), 4.24 (1 H, dd, $J_{5',6'b}$ 1.5, $J_{6'a,6'b}$ 12, 6′b-H), 4.7 (1 H, $J_{1',2'}$ 8.5, 1′-H), 5.04 (2 H, $COOCH_2Ph$), 5.42 (1 H, br s, 1-H) and 7.55 (1 H, d, $J_{2',NH}$ 9, NH) (Found: C, 64.5; H, 6.0; N, 7.0. $C_{43}H_{46}N_4O_{11}$ requires C, 65.0; H, 5.8; N, 7.0%).

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