# Facile Preparation of 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose and Its 4-*O*-Substituted Derivatives

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**Synopsis.** Treatment of 1,6-anhydro-2,3-*O*-*endo*-benzylidene-β-D-mannopyranose derivatives with trimethylamine–borane (1/1)–aluminium chloride resulted in highly regioselective fission of the cyclic acetals to give the corresponding 2-*O*-unprotected-3-*O*-benzyl derivatives. Trifluoromethanesulfonylation of these, followed by nucleophilic substitution, afforded 2-azido-2-deoxy derivatives in good yields.

1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose derivatives are versatile intermediates for the synthesis of D-glucosamine-containing complex oligosaccharides,[1] and have been commonly prepared by nucleophilic ring opening of "Cerny epoxide" derived from 1,6-anhydro-β-D-glucopyranose.[2] Recently, a short-step preparation of these compounds has been developed employing D-mannopyranose as the starting material.[3] However, this procedure is sometimes inapplicable to substrates bearing such labile protecting groups as acetyl or *p*-methoxybenzyl groups because of substantial removal of the protecting groups during reductive ring opening of the 2,3-*O*-benzylidene intermediates with lithium aluminium hydride–aluminium chloride or sodium cyanoborohydride–hydrogen chloride. We now report a modified procedure for the preparation of D-glucosamine precursors by use of trimethylamine–borane (1/1)–aluminium chloride as the reducing agent.

Starting materials, 4-*O*-acetyl (**2**), 4-*O*-*p*-methoxybenzyl (**3**), and 4-*O*-benzyl derivatives (**4**) were derived from crystalline 1,6-anhydro-2,3-*O*-*endo*-benzylidene-β-D-mannopyranose (**1**)[3] by conventional ways. Compound **2** was prepared in 90% yield by acetylation of **1** with $Ac_2O$–pyridine, while **3** and **4** were prepared in 87 and 91% yields by alkylation of **1** with NaH-*p*-methoxybenzyl chloride–sodium iodide and NaH–benzyl bromide, respectively (Scheme 1). We employed **2** as the model compound to examine the reductive cleavage of the benzylidene group. The reaction with trimethylamine–borane (1/1) and aluminium chloride[4] was found to proceed regioselectively without any affection to the 4-*O*-acetyl group. Thus, treatment of **2** with an excess amount (5.8 mol equiv) of the reagent in tetrahydrofuran (THF) at room temperature for 5 h gave the 3-*O*-benzyl derivative (**5**) in 87% yield. In a similar way, the hydrogenolytic ring cleavage of the 4-*O*-*p*-methoxybenzyl and 4-*O*-benzyl derivative (**3** and **4**) afforded the 4-*O*-(*p*-methoxybenzyl)-3-*O*-benzyl (**6**) and 3,4-di-*O*-benzyl derivative (**7**) as the sole products (80 and 89% yields, respectively).

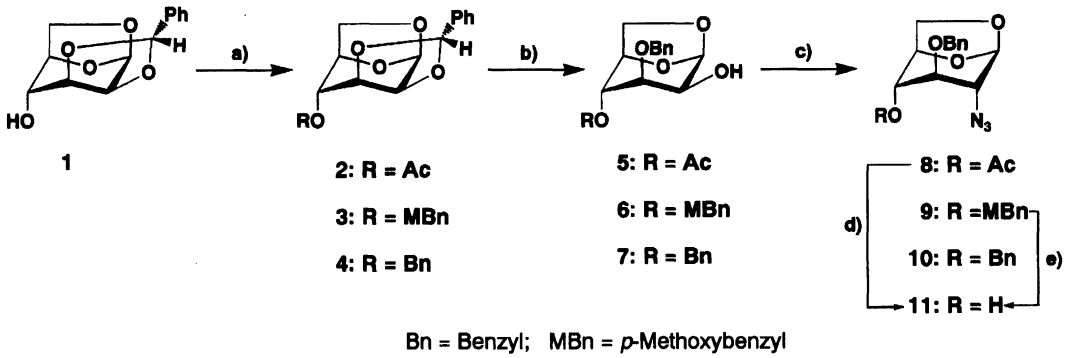
The next conversions of the 2-*O*-unprotected D-mannose derivatives into 2-azido-2-deoxy-D-glucose derivatives were carried out in a two-step manner: trifluoromethanesulfonylation and subsequent nucleophilic substitution.[3,5,6] Thus, **5** and **6** were treated with trifluoromethanesulfonic anhydride in pyridine–dichloromethane to give the corresponding 2-triflates, which were subjected to $S_N2$ reaction with lithium azide in *N*,*N*-dimethylformamide (DMF) at room temperature, giving the 2-azido-2-deoxy-β-D-glucopyranose derivatives (**8** and **9**) in 73 and 81% overall yields, respectively. Compound **7** was also converted into the 2-azido-2-deoxy derivative (**10**) in almost quantitative yield according to Dasgupta and Geregg.[6] The 2-azido-2-deoxy derivatives thus obtained were readily converted into both glucosamine acceptors and donors. Either Zemplen deacetylation of **8** or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of **9** afforded known 4-hydroxy derivative (**11**) in almost quantitative yield. Furthermore, **9** was converted into the corresponding thioglycoside and glycosyl trichloroacetimidate, which were used as key intermediates for the synthesis of 2-amino-2-deoxy-β-cyclodextrin.[11]

In conclusion, D-glucosamine precursors having acid- or base-sensitive protecting groups at *O*-4 position were prepared from D-mannose in good overall yields, employing reductive ring opening of 2,3-*O*-benzylidene group with trimethylamine–borane (1/1)–aluminium chloride as the key reaction.

## Experimental

**General Procedures.** Melting points were determined in a capillary with an Ishii melting-point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241MC polarimeter. $^1$H NMR spectra were recorded at 270 MHz or 500 MHz with JEOL JNM-EX 270 or JEOL JNM-GX 500 spectrometers, using tetramethylsilane as the internal standard. Reactions were monitored by TLC on a precoated plate of silica gel $60F_{254}$ (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany). Column chromatography was performed on silica gel 60 (70—230 or 230—400 mesh; E. Merck, Darmstadt, Germany). Molecular sieves 4A was activated at 180—200 °C under reduced pressure on diphosphorus pentaoxide prior to use.

**4-*O*-Acetyl-1,6-anhydro-2,3-*O*-*endo*-benzylidene-β-D-mannopyranose (2).** A solution of 1,6-anhydro-2,3-*O*-*endo*-benzylidene-β-D-mannopyranose (**1**)[3] (5.0 g, 20 mmol) in pyridine (50 $cm^3$) and acetic anhydride (20 $cm^3$) was stirred at room temperature for 1 d, evaporated under reduced pressure, and coevaporated with toluene sev-




Scheme 1. Reagents and conditions. a) **1**→**2**: $Ac_2O$–pyridine, r.t.; **1**→**3**: *p*-methoxybenzyl chloride–NaH–NaI, DMF, r.t.; **1**→**4**: benzyl bromide–NaH, DMF, r.t. b) $BH_3$·$Me_3N$–$AlCl_3$, THF, r.t. c) **5**→**8**, **6**→**9**, **7**→**10**: $Tf_2O$, pyridine–$CH_2Cl_2$ then $LiN_3$, DMF, r.t. d) MeONa, MeOH. e) DDQ, aq $CH_2Cl_2$, r.t.

eral times. Crystallization of the residual syrup with diethyl ether gave 5.3 g (90%) of the 4-acetate (**2**): Mp 190—191 °C (lit, 190—192 °C);[7] $[\alpha]_D^{23}$ −88° (*c* 0.20, $CHCl_3$) (lit, $[\alpha]_D^{20}$ −92° (*c* 0.7, $CHCl_3$))[7] Found: C, 61.37; H, 5.53%. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52%.

**1,6-Anhydro-2,3-*O*-*endo*-benzylidene-4-*O*-(*p*-methoxybenzyl)-β-D-mannopyranose (3).** To an ice-cold solution of **1** (60 g, 0.24 mol) and sodium iodide (10 g) in DMF (400 $cm^3$) was added 60% sodium hydride oil dispersion (25 g, 0.63 mol): Then the mixture was stirred at 0 °C for 2 h. *p*-Methoxybenzyl chloride (50 g, 0.32 mol) was added dropwise to the resulting mixture at 0 °C. The suspension was stirred at room temperature for 2 d, quenched by careful addition of MeOH, poured into ice cold aqueous ammonia (0.4 mol $dm^{-3}$, 2 $dm^3$), and allowed to stand overnight. The precipitates were collected by filtration, and washed with water and EtOH. Recrystallization from EtOH gave 77 g (87%) of the 4-*p*-methoxybenzyl ether (**3**): Mp 105—106 °C; $[\alpha]_D^{27}$ −49° (*c* 0.21, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=3.76 (1H, s, H-4), 3.79—3.83 (4H, m, H-6a, OMe), 3.94 (1H, d, $J_{6a,6b}$=7.3 Hz, H-6a), 4.24 (1H, dd, $J_{1,2}$=2.9 and $J_{2,3}$=7.0 Hz, H-2), 4.28 (1H, d, H-3), 4.60 (1H, d, $J_{gem}$=11.9 Hz, 1/2×C$H_2$Ar), 4.64 (1H, d, $J_{5,6}$=6.7 Hz, H-5), 4.68 (1H, d, 1/2×C$H_2$Ar), 5.52 (1H, br.s, H-1), and 5.76 (1H, s, C*H*Ph). Found: C, 67.99; H, 5.98%. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99%.

**1,6-Anhydro-4-*O*-benzyl-2,3-*O*-*endo*-benzylidene-β-D-mannopyranose (4).** Treatment of **1** (45 g, 0.18 mmol) with 60% sodium hydride oil dispersion (15 g, 0.38 mol) and benzyl bromide (65 g, 0.38 mmol) in DMF (300 $cm^3$) as described for the preparation of **3**, followed by crystallization from EtOH, gave 55.7 g (91%) of the 4-*O*-benzyl derivative (**4**): Mp 126.5—127 °C (lit, mp 127—128 °C);[8] $[\alpha]_D^{20}$ −51° (*c* 1.0, $CHCl_3$) (lit, $[\alpha]_D^{25}$ −49.7° (*c* 1, $CHCl_3$));[8] $^1$H NMR ($CDCl_3$) $\delta$=3.78 (1H, br.s, H-4), 3.82 (1H, dd, $J_{5,6}$=6.3 and $J_{6exo,6endo}$=7.3 Hz, H-6), 3.95 (1H, dd, $J_{5,6}$=1.0 Hz, H-6), 4.25 (1H, dd, $J_{1,2}$=2.9 and $J_{2,3}$=6.9 Hz, H-2), 4.31 (1H, br.d, H-3), 4.67, 4.75 (1H, 2×d, $J_{gem}$=12.2 Hz, C$H_2$Ph), 4.66—4.68 (1H, m, H-5), 5.53 (1H, d, H-1), and 5.76 (1H, s, C*H*Ph).

**4-*O*-Acetyl-1,6-anhydro-3-*O*-benzyl-β-D-mannopyranose (5).** To a suspension of **2** (5.0 g, 17 mmol), powdered molecular sieves 4A (5 g), and trimethylamine–borane (1/1) (7.3 g, 0.10 mmol) in THF (100 $cm^3$) was added aluminium chloride (13.3 g, 0.10 mmol) by portions. The mixture was stirred at room temperature for 5 h, filtered through a Celite pad, and washed with chloroform. The combined filtrate and washings were washed successively with 6% hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and concentrated. Chromatographic purification on a silica gel column with toluene–EtOAc (3:1 v/v) gave 4.3 g (85%) of the 2-hydroxy derivative (**5**): $[\alpha]_D^{20}$ −61° (*c* 0.32, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=2.13 (3H, s, OAc), 3.03 (1H, d, $J_{2,OH}$=11.6 Hz, OH), 3.63—3.71 (2H, m, H-2,3), 3.75 (1H, dd, $J_{5,6a}$=6.1 and $J_{6a,6b}$=7.6 Hz, H-6a), 4.17 (1H, dd, $J_{5,6b}$=1.0 Hz, H-6b), 4.52 (1H, dd, H-5), 4.58, 4.81 (1H, 2×d, $J_{gem}$=11.9 Hz, C$H_2$Ph), 4.97 (1H, s, H-4), and 5.36 (1H, br.s, H-1). Found: C, 61.10; H, 6.19%. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.17%.

**1,6-Anhydro-3-*O*-benzyl-4-*O*-(*p*-methoxybenzyl)-β-D-mannopyranose (6).** To a suspension of **3** (2.0 g, 5.4 mmol), powdered molecular sieves 4A (5 g), and trimethylamine–borane (1/1) (2.9 g, 40 mmol) in THF (50 $cm^3$) was added aluminium chloride (5.3 g, 40 mmol) by portions. The mixture was stirred at room temperature for 5 h, filtered through a Celite pad, and washed with chloroform. The combined filtrate and washings were washed successively with 10% hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and concentrated. Column chromatography of the residue with benzene–EtOAc (19:1, v/v) as the eluant gave 1.6 g (80%) of the 2-hydroxy derivative (**6**): $[\alpha]_D^{27}$ −48° (*c* 0.60, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=3.74 (1H, s, H-4), 3.80 (1H, dd, $J_{6a,6b}$=10.1 and $J_{5,6a}$=6.0 Hz, H-6a), 3.85 (3H, s, OMe), 3.94 (1H, d, H-6b), 4.29 (1H, m, H-2), 4.55—4.70 (5H, m, 2×ArC$H_2$, H-5), and 5.58 (1H, br.s, H-1). Found: C, 67.63; H, 6.56%. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50%.

**1,6-Anhydro-3,4-di-*O*-benzyl-β-D-mannopyranose (7).** Treatment of **4** (0.30 g, 0.88 mmol) with trimethylamine–borane (1/1) (0.37 g, 5.1 mmol), aluminium chloride (0.68 mg, 5.1 mmol), and powdered molecular sieves 4A (0.6 g) in a similar way as described for the preparation of **6** afforded 0.27 g (89%) of the 3,4-di-*O*-benzyl derivative (**7**): $[\alpha]_D^{20}$ −57° (*c* 1.0, $CHCl_3$) (lit, $[\alpha]_D^{23}$ −58.5° (*c* 0.76, $CHCl_3$));[6] $^1$H NMR ($CDCl_3$) $\delta$=3.01 (1H, d, $J_{2,OH}$=11.0 Hz, OH), 3.50 (1H, br.s, H-2), 3.68—3.79 (3H, m, H-3,4, 6*exo*), 4.07 (1H, br.d, $J_{6exo,6endo}$=6.8 Hz, H-6*exo*), 4.47—4.70 (5H, m, 2×C$H_2$Ph, H-5), and 5.36 (1H, br.s, H-1).

**4-*O*-Acetyl-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (8).** To a solution of trifluoromethanesulfonic anhydride (3.4 $cm^3$, 20 mmol) and pyridine (2.2 $cm^3$, 27 mmol) in $CH_2Cl_2$ (100 $cm^3$) was added a solution of **5** (4.0 g, 14 mmol) in $CH_2Cl_2$ (20 $cm^3$) at −10 °C. The mixture was stirred for 1 h at 0 °C, quenched with MeOH (1 $cm^3$), poured into ice-water, and extracted with $CH_2Cl_2$. The organic layer was successively washed with 10% hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and concentrated. To a solution of the residual syrup in DMF (100 $cm^3$) was added $LiN_3$ (6.6 g, 0.14 mol). The solution was stirred for 30 min at room temperature, diluted with water (50 $cm^3$), and extracted with diethyl ether (3×100 $cm^3$). The combined extracts were successively washed with water (2×100 $cm^3$) and brine (2×100 $cm^3$), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on a silica-gel column with toluene–EtOAc (4 : 1, v/v) to give 3.2 g (73%) of the 2-azido-2-deoxy derivative (**8**): $[\alpha]_D^{20}$ +71° (*c* 0.26, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=2.14 (3H, s, OAc), 3.23 (1H, br.s, H-2), 3.56 (1H, m, H-3), 3.77 (1H, dd, $J_{5,6a}$=6.0 and $J_{6a,6b}$=7.6 Hz H-6a), 4.19 (1H, dd, $J_{5,6}$=1.0 Hz, H-6b), 4.62 (1H, br.d, H-5), 4.69 (2H, ABq, $CH_2Ph$), 4.77 (1H, br.s, H-4), and 5.52 (1H, br.s, H-1). Found: C, 56.34; H, 5.37; N, 13.15%. Calcd for $C_{15}H_{17}O_5N_3$: C, 56.42; H, 5.37; N, 13.16%.

**1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(*p*-methoxybenzyl)-β-D-glucopyranose (9).** To a solution of **6** (3.90 g, 10.5 mmol) in 8 : 1 $CH_2Cl_2$–pyridine (45 $cm^3$) was dropwise added trifluoromethanesulfonic anhydride (3.8 $cm^3$, 23 mmol) with stirring at −18 °C. The solution was stirred at −18 °C for 40 more min, then quenched with water (20 $cm^3$), and extracted with with $CH_2Cl_2$. The organic layer was successively washed with 10% hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and concentrated. A solution of the residual syrup (5.1 g) and $LiN_3$ (2 g, 41 mmol) in DMF (20 $cm^3$) was stirred at room temperature overnight, diluted with water, and extracted with diethyl ether. The extract was washed with brine, dried, and concentrated. Column chromatography with benzene–EtOAc (24 : 1, v/v) as the eluant gave 3.4 g (81%) of the 2-azido-2-deoxy derivative (**9**): $[\alpha]_D^{23}$ +45° (*c* 0.40, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=3.27 (1H, br.s, H-2), 3.63 (1H, br.s, H-3), 3.71 (1H, t, $J_{5,6a}=J_{6a,6b}$=6.1 Hz, H-6a), 3.80 (3H, s, OMe), 4.00 (1H, d, H-6b), 4.45—4.58 (5H, m, 2×Ar$CH_2$, H-5), and 5.48 (1H, br.s, H-1). Found: C, 63.61; H, 5.85, N, 10.35%. Calcd for $C_{21}H_{23}O_5N_3$: C, 63.47; H, 5.38; N, 10.57%.

**1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (11). Method A:** To a solution of **8** (0.32 g, 1.0 mmol) in MeOH (10 $cm^3$) was added 1 mol $dm^3$ methanolic sodium methoxide (0.1 $cm^3$). The mixture was stirred at room temperature overnight, then neutralized with Dowex 50W-X8 ($H^+$ form), and evaporated. The residue was chromatographed on a column of silica gel with $CHCl_3$–MeOH (97 : 3, v/v) as the eluant to give 0.27 g (96%) of the 2-hydroxy derivative (**11**): $[\alpha]_D^{21}$ −6.2° (*c* 0.34, $CHCl_3$) (lit, $[\alpha]_D^{22}$ −5° (*c* 1, $CHCl_3$)).[10]

**Method B.** To a solution of **9** (37 g, 94 mmol) in $CH_2Cl_2$ (650 $cm^3$) was added water (6 $cm^3$) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (33 g, 145 mmol): then the mixture was stirred at room temperature for 2 h. Aqueous sodium thiosulfate was added to the orange-colored suspension, the precipitate was filtered off and washed with $CH_2Cl_2$. The combined filtrate and washings were washed with aqueous sodium thiosulfate three times, dried, and evaporated. The residue was purified by column chromatography with $CHCl_3$–MeOH (97 : 3, v/v) as the eluant to give 24.2 g (93%) of the 2-hydroxy derivative (**11**).

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