Facile Preparation of 3,4-Di-*O*-acetyl-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose and Some Derivatives Thereof: Useful Precursors for Oligosaccharide Synthesis

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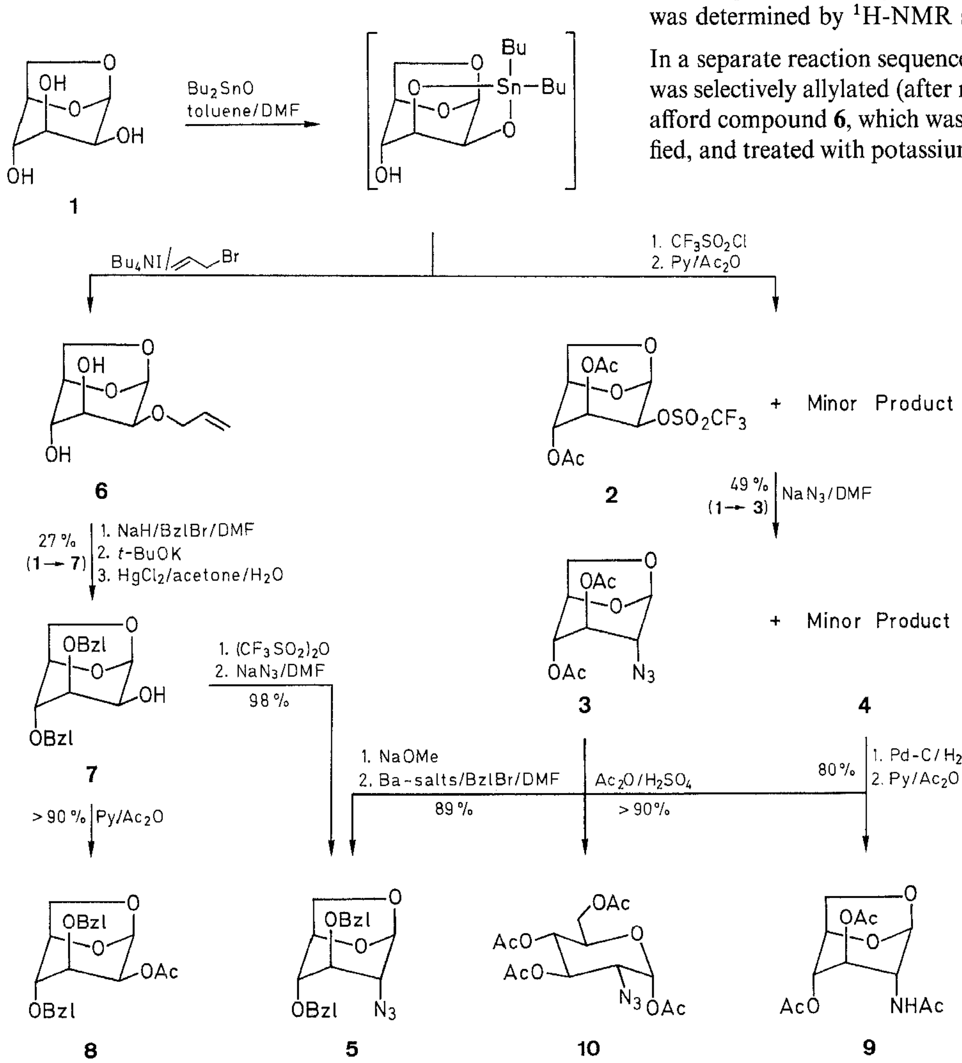
A facile, virtually one-pot synthesis of the title compound and also some of its derivatives is based on regioselective 2-substitutions of 1,6-anhydro-β-D-mannopyranose using stannylidene activation. The compounds thus prepared are useful precursors in the synthesis of glycoprotein-type oligosaccharides.

2-Azido-2-deoxyhexoses, which have been extensively used during the synthesis of complex oligosaccharides,[1] are prepared by (a) azidonitration[2,3] or chloroazidation[4] of commercially available 3,4,6-tri-*O*-acetyl-D-*arabino*-hex-1-enitol, and (b) by stereo- and regio-selective ring opening of the 2,3-epoxide in 1,6:2,3-dianhydro-β-D-mannopyranose (Černý epoxide[5]) with sodium azide.[6]

Although the second method (b) is more direct, the steps involved are sluggish and therefore time consuming. Recently, syntheses of a number of selectively blocked 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose derivatives were reported.[7] However, this method too required several reaction and purification steps. Thus, a short and efficient method for the synthesis of 2-azido-2-deoxy-D-hexoses is still of interest. We report here the synthesis of 3,4-di-*O*-acetyl-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose (**3**) by an almost one-pot procedure, starting from the easily available 1,6-anhydro-β-D-mannopyranose (**1**).[7,8]

In our reaction sequence (Scheme), use is made of the fact that the equatorial hydroxy function, in a 1,2-cis-dihydroxy hexacyclic system, can be selectively alkylated or acylated following activation with dibutyltin oxide.[9,10] Thus, when 1,6-anhydro-β-D-mannopyranose (**1**) having suitably oriented hydroxy groups at C-2 and C-3 was treated first with dibutyltin oxide and then with an equimolar amount of trifluoromethylsulfonyl chloride, reaction took place regioselectively at C-2. Subsequent acetylation and displacement of the triflate group with azide at room temperature (30 min) afforded compound **3** as the major product (> 40% after purification). Compound **3** (R_f 0.28, solvent *C*) could be easily separated from the only side product **4** (R_f 0.11, solvent *C*). The ^{1}H- and ^{13}C-NMR spectra of **3** corroborated the expected structure which was further confirmed by homonuclear decoupling experiments. The ^{1}H- and ^{13}C-NMR spectra of the side product **4** indicated it to be a monoacetylated compound having the acetate function at C-4 of the 1,6-anhydro ring. Hydrogenation of **4** in the presence of acetic anhydride, followed by acetylation with pyridine/acetic anhydride gave 3,4-di-*O*-acetyl-2-acetylamino-1,6-anhydro-2-deoxy-β-D-glucopyranose (**9**) which was also the product when compound **3** was similarly treated. Acetolysis of **3** with acetic anhydride containing 1% concentrated sulfuric acid, at room temperature (8 h),[6] gave the acetolyzed product **10** together with a small quantity of the β-anomer. The identity of the product(s) was determined by ^{1}H-NMR spectrometry.

In a separate reaction sequence, the hydroxy group on C-2 of **1** was selectively allylated (after reaction with dibutyltin oxide) to afford compound **6**, which was immediately benzylated,[11] purified, and treated with potassium *tert*-butoxide in toluene.[12] The



1-propenyl group thus generated at C-2, was hydrolyzed with mercury(II) chloride in aqueous acetone[13] to give 1,6-anhydro-3,4-di-*O*-benzyl-β-D-mannopyranose (**7**) as a syrup. Compound **7**, which was chromatographically (TLC, multiple elution) and spectrometrically pure, was used as such for the preparation of 1,6-anhydro-2-azido-2-deoxy-3,4-di-*O*-benzyl-β-D-glucopyranose (**5**; > 90–95% yield). This was achieved by trifluoromethylsulfonylation followed by reaction with sodium azide in dimethylformamide. Compound **7** could also be converted into its 2-*O*-acetyl derivative **8**. The structure of **8** (hence that of **7**) was unequivocally confirmed by decoupling experiments. Compound **5** prepared from **3** by a deacetylation-benzylation sequence, and compound **5** prepared from **7** (Scheme) matched completely in their physical constants and NMR data.

The merit of the method presented here is its simplicity, the almost complete regioselectivity, and ready accessibility of the final products **3** and **5**.

Melting points are corrected. Optical rotations were measured in $CHCl_3$ solutions using a Perkin-Elmer polarimeter model 141. ^1H- and ^{13}C-NMR spectra were recorded on a JEOL GSX270 FTNMR spectrometer.

All reactions were carried out under N_2. Chromatographic purifications were performed on dry silica gel columns. One or more of the solvent systems (v/v) toluene/acetone (*A*-*E*) and toluene/acetone/methanol (*F*, *G*) were used for chromatography purposes: *A*, 4:1; *B*, 8:1; *C*, 15:1; *D*, 20:1; *E*, 25:1; *F*, 3:1:1; *G*, 40:1:1.

3,4-Di-*O*-acetyl-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose (3):

Dimethylformamide (5 mL) and toluene (40 mL) are added to 1,6-anhydro-β-D-mannopyranose (**1**; 290 mg, 1.79 mmol) in a flask, fitted with a Dean-Stark apparatus. Toluene (10 mL) is distilled off, and dibutyltin oxide (490 mg, 1.97 mmol) is added to the flask. More toluene (25 mL) is then distilled off. The contents of the flask are cooled (– 10 °C) and a cold (0 °C) solution of trifluoromethylsulfonyl chloride (0.21 mL, 1.97 mmol) in CH_2Cl_2 (0.5 mL) is slowly injected through a rubber septum into the stirred mixture. Complete conversion is observed within 1.5 h (TLC, solvent *F*). Pyridine/Ac_2O (2:1, v/v, 4.0 mL) is injected dropwise into the mixture at ~ – 10 °C and the temperature of the bath is allowed to rise to 0 °C. The reaction is complete within 1.5 h as indicated by TLC (solvent *B*; R_f 0.45, major product; R_f 0.33, minor product). Then, CH_2Cl_2 (5 mL) is introduced into the flask, and the mixture is filtered through Celite. The flask and the residue are washed with more CH_2Cl_2 (2 × 3 mL) and the total organic layer is washed successively with cold 10% $NaHCO_3$ solution (20 mL) and with H_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated. Pyridine and Ac_2O are removed by repeated coevaporation with toluene. The syrup so obtained is dissolved in dry DMF (3–5 mL), NaN_3 (170 mg, 2.68 mmol) is added, and the mixture is stirred at room temperature (2 h) to give the azide **3** as the major product along with **4**, the only minor product [R_f 0.28 (major); R_f 0.11 (minor); solvent *C*]. The solvent is evaporated to give a syrup which is dissolved in CH_2Cl_2 (7 mL) and this solution is washed, dried, and evaporated as before. The product is purified by column (50 g) chromatography [eluent, solvent *C* (50 mL) then solvent *E*], to afford pure **3**; yield: 240 mg (49.5%); mp 97–98 °C (CH_2Cl_2/hexane); $[\alpha]_D^{23}$ + 36.8° ($CHCl_3$, *c* = 2).

$C_{10}H_{13}N_3O_6$	calc.	C 44.2	H 4.82	N 15.5
(271.2)	found	43.9	4.80	15.8

^1H-NMR ($CDCl_3$/TMS): δ = 2.13, 2.18 (2 s, 6 H_{acetyl}); 3.18 (s, 1 H, H-2); 3.82 (dd, 1 H, $J_{5,6}$ = 5.7 Hz, $J_{6,6'}$ = 7.7 Hz, H-6_{exo}); 4.13 (dd, 1 H, $J_{5,6}$ = 1 Hz, $J_{6,6'}$ = 7.7 Hz, H-6_{endo}); 4.66 (d, with fine splittings, 1 H, H-5); 4.68 (m, 1 H, H-4); 4.92 (m, 1 H, H-3); 5.52 (s, 1 H, H-1).

^{13}C-NMR ($CDCl_3$/TMS): δ = 20.79, 20.83 ($CO\underline{C}H_3$); 58.7 (C-2); 65.1 (C-6); 69.4, 70.0, 73.6 (C-3, C-4, C-5); 100.3 (C-1); 169.1, 169.8 ($\underline{C}OCH_3$).

1,6-Anhydro-3,4-di-*O*-benzyl-β-D-mannopyranose (7):

Benzene (100 mL) is added to a flask containing 1,6-anhydro-β-D-mannopyranose (**1**; 700 mg, 4.3 mmol) and part of the solvent (30 mL) is distilled off. Dibutyltin oxide (1.18 g, 4.7 mmol) is added and more benzene (50 55 mL) is removed by distillation. The mixture is refluxed (2 h) and allyl bromide (0.75 mL, 8.7 mmol), followed by tetrabutylammonium iodide (1.59 g, 4.3 mmol) are added. The allylation is carried out under reflux until TLC (toluene/acetone/MeOH, 8:2:1) indicates essentially complete conversion (4–6 h). The mixture is concentrated and the remaining syrupy material **6** is purified by column (100 g) chromatography using solvent *A*; yield: 700 mg. This material is immediately benzylated[11] by reaction with benzyl bromide (0.9 mL, 7.56 mmol) and NaH (182 mg) in DMF (5 mL). The crude product (1.18 g) is immediately treated with *t*-BuOK (470 mg, 4.2 mmol) in toluene (50 mL) under reflux (4–6 h). The solution is washed with H_2O (3 × 40 mL), dried ($MgSO_4$), and evaporated to a syrup. This material is dissolved in 10% aqueous acetone (8 mL) and allowed to react with $HgCl_2$ (1.28 g, 4.73 mmol) at room temperature (2–3 h). Solvent is evaporated and the syrupy material is purified by column (80 g) chromatography [solvent *B* (80 mL) then solvent *D*] to give pure **7** as a syrup; yield: 370 mg (27%); $[\alpha]_D^{23}$ – 52° ($CHCl_3$, *c* = 3.4).

^1H-NMR ($CDCl_3$/TMS): δ = 3.05 (d, 1 H, OH); 3.49 (s, 1 H, H-2); 3.66–3.76 (m, 3 H, H-3,4,6_{exo}); 4.05 (dd, 1 H, H-6_{endo}); 4.4–4.7 (m, 5 H, H-5, $C\underline{H}_2C_6H_5$); 5.35 (s, 1 H, H-1); 7.25–7.36 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$/TMS): δ = 64.7, 66.5, 71.4, 73.8, 75.6, 76.1 (C-2, C-3, C-4, C-5, C-6, $\underline{C}H_2C_6H_5$); 101.8 (C-1); 127.8, 127.9, 128.1, 128.2, 128.67, 137.2, 137.5 (C_{arom}).

2-*O*-Acetyl-1,6-anhydro-3,4-di-*O*-benzyl-β-D-mannopyranose (8):

Compound **7** (55 mg) is acetylated with pyridine/Ac_2O (2:1, 2.5 mL) at room temperature. After 4 h, the reagents are evaporated by repeated codistillation with toluene. The product is purified by column (50 g) chromatography using solvent *E*; yield: 60 mg (92%); $[\alpha]_D^{23}$ – 24.7° ($CHCl_3$, *c* = 4.99).

$C_{22}H_{24}O_6$	calc.	C 68.74	H 6.29
(384.35)	found	68.8	6.5

^1H-NMR ($CDCl_3$/TMS): δ = 2.12 (s, 3 H_{acetyl}); 3.45 (s, 1 H, H-4); 3.75 (dd, 1 H, H-6_{exo}); 4.03 (m, 1 H, H-3); 4.22 (dd, 1 H, H-6_{endo}); 4.5 (m, 3 H, H-5, $C\underline{H}_2C_6H_5$); 4.83 (dd, 1 H, $J_{1,2}$ ≈ 2 Hz, $J_{2,3}$ ≈ 5.6 Hz, H-2); 5.44 (bt, 1 H, H-1); 7.26–7.38 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$/TMS): δ = 20.9 ($CO\underline{C}H_3$); 65.0, 69.7, 71.3, 73.7, 74.3, 74.4, 76.5 (C-2, C-3, C-4, C-5, C-6, $\underline{C}H_2C_6H_5$); 99.4 (C-1); 127.7, 128.0, 128.2, 128.5, 137.5 (C_{arom}); 170.3 ($\underline{C}OCH_3$).

1,6-Anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose (5):

Method A: Compound **7** (159 mg, 0.46 mmol) is dissolved in CH_2Cl_2 (2 mL) containing pyridine (84 µL, 1.04 mmol). A cold (0 °C) solution of trifluoromethylsulfonic anhydride (167 µL, 0.99 mmol) in dry CH_2Cl_2 (0.5 mL) is slowly injected into the above solution which is stirred at – 10 °C. The temperature of the mixture is slowly raised to 0 °C. TLC (solvent *D*) indicates 100% conversion after 50 min (R_f 0.51). Cold 10% $NaHCO_3$ solution (5 mL) is added and stirring continued for 15 min. The organic layer is separated, washed with H_2O (2 × 5 mL), dried ($MgSO_4$), filtered, and repeatedly coevaporated with toluene. The syrupy product is dissolved in DMF (2 mL) and allowed to react with NaN_3 (100 mg, 1.54 mmol). Ater 15 min, the solvent is evaporated, the syrup dissolved in CH_2Cl_2 (5 mL), and the resulting solution is washed and dried as before. Column (40 g) chromatography (eluent toluene/acetone 40:1) affords pure **5**; yield: 170 mg (98%); $[\alpha]_D^{23}$ + 38.5° ($CHCl_3$, *c* = 1.99).

$C_{20}H_{21}N_3O_4$	calc.	C 65.38	H 5.76	N 11.44
(367.35)	found	65.2	5.7	11.4

^1H-NMR ($CDCl_3$/TMS): δ = 3.27 (s, 1 H, H-2); 3.37 (s, 1 H, H-4); 3.68 (m, 1 H, H-3); 3.71 (dd, 1 H, H-6_{exo}); 4.0 (dd, 1 H, H-6_{endo}); 4.5–4.6 (m, 3 H, H-5, $C\underline{H}_2C_6H_5$); 5.48 (s, 1 H, H-1); 7.1–7.5 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$/TMS): δ = 59.87 (C-2); 65.3 (C-6); 71.3, 72.3, 74.4, 75.9, 76.2 (C-3, C-4, C-5, $\underline{C}H_2C_6H_5$); 100.5 (C-1); 127.8, 127.9, 128.0, 128.1, 128.6, 137.25, 137.4 (C_{arom}).

Method B: Compound **3** (50 mg, 0.18 mmol) is dissolved in dry MeOH (3 mL) and deacetylated by stirring with sodium methoxide (10 mg) at room temperature. The solution is evaporated and the syrup so obtained is dissolved in DMF (3 mL) and benzylated using benzyl bromide (55 µl) in the presence of BaO (0.14 g, 0.52 mmol) and $Ba(OH)_2$ (0.58 g, 1.84 mmol) at room temperature.[6] The crude material is purified by column (40 g) chromatography to give **5** as a syrup; yield: 60 mg (89%); $[\alpha]_D^{23}$ + 37.7° ($CHCl_3$, *c* = 2.1).

3,4-Di-*O*-acetyl-2-acetylamino-1,6-anhydro-2-deoxy-β-D-glucopyranose (9):

Method A: The minor product **4** (30 mg) is dissolved in CH_2Cl_2 (3 mL) and hydrogenated (6 h) in the presence of 10% Pd–C (40 mg).

When starting material can no more be detected (TLC, solvent *C*), the product is acetylated with pyridine/Ac_2O (2:1, 0.6 mL) until TLC indicates the presence of only one product (R_f 0.29, solvent *G*). The mixture is filtered through Celite, the residue washed with more CH_2Cl_2 (5 mL), and the total organic layer evaporated to a syrup. Pyridine and Ac_2O are distilled off azeotropically with toluene and the syrup is purified by column (50 g) chromatography using solvent *G* to give **9** as a solid; yield: 32.6 mg; mp 140–141 °C (CH_2Cl_2/hexane); $[\alpha]_D^{23}$ $-76.3°$ ($CHCl_3$, $c = 2.0$).

$C_{12}H_{17}NO_7$	calc.	C 50.18	H 5.97	N 4.87
(287.2)	found	49.98	6.13	4.74

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.02, 2.12, 2.18$ (3 s, 9 H_{acetyl}); 3.83 (dd, 1 H, H-6_{exo}); 4.1 (complex d, 1 H, H-2); 4.16 (dd, 1 H, H-6_{endo}); 4.6 (complex d, 1 H, H-5); 4.64 (m, 1 H, H-4); 4.72 (m, 1 H, H-3); 5.37 (s, 1 H, H-1); 5.92 (d, 1 H, NH).

Method B: Hydrogenation followed by acetylation of the compound **3** (22.1 mg), in the same manner as above, gives **9** having the same mp, mixed mp, and ^{1}H-NMR spectrum as **9** obtained by Method A; yield: 18.7 mg (80%).

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