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Improved Synthesis of 3,4,6-Tri-*O*-benzyl-α-D-mannopyranosides

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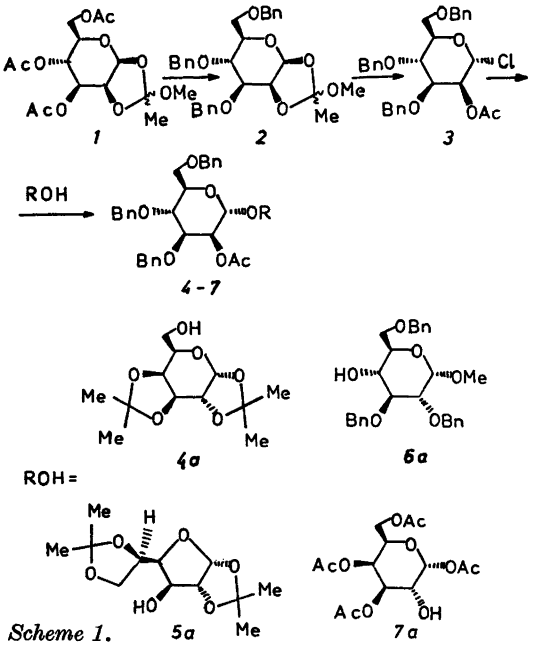
2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosides, which are useful intermediates for the synthesis of α-D-glucopyranosides, have been prepared in good yields from 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride and various monosaccharide aglycones.

A method for the synthesis of β-D-mannopyranosides [1,2] and α-D-glucopyranosides [2] has previously been communicated from this Laboratory. β-D-Glucopyranosides and α-D-mannopyranosides protected with benzyl groups in the 3,4,6-positions are made and the configuration at C-2 is inverted by means of oxidation and reduction producing α-D-mannopyranosides and β-D-glucopyranosides, respectively. The method has been used successfully in disaccharide syntheses.[3–5] A convenient route to the required β-D-glucopyranosides and α-D-mannopyranosides is to start from a 3,4,6-tri-*O*-benzyl-1,2-orthoester using the orthoester synthesis developed by Kochetkov and co-workers.[6] The yields are, however, not always good, and the stereoselectivity which generally is high, diminishes when glycosides of particularly unreactive alcohols are prepared.[7] For these reasons, Shaban and Jeanloz [5] used 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl bromide as starting material, in mercury(II) cyanide-promoted Koenigs Knorr syntheses of disaccharides with terminal β-D-mannopyranosyl groups. The glucosyl bromide was prepared by the treatment of the corresponding orthoester with hydrogen bromide in acetic acid, a method previously described by Kochetkov and co-workers.[8]

We have now used a similar method for the synthesis of 3,4,6-tri-*O*-benzyl-α-D-mannopyranosides. Treatment of 3,4,6-tri-*O*-benzyl-1,2-(methoxyethylidene)-α-D-mannopyranose (*2*) with hydrogen bromide in acetic acid yielded 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl bromide, which, however, was too unstable to be useful. The corresponding α-D-mannosyl chloride *3* was therefore prepared by treatment of the orthoester *2* with hydrogen chloride in diethyl ether, and used in glycosylation reactions, promoted either by mercury(II) cyanide/mercury(II) bromide or silver triflate [9] (Scheme 1). Four aglycones were investigated,



Scheme 1.

namely 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose,[10] 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose,[10] methyl 2,3,6-tri-*O*-benzyl-α-D-glu-

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copyranoside[11] and 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose.[12] The yields of the corresponding disaccharide derivatives *4*–*7* were 58–78 %. Attempts to optimize the yields of the oxidation-reduction of deacetylated *4*–*6*, leading to α-D-glucopyranosides, are under way. A modified preparation of *2* [2,14] is given in the experimental part. After the completion of this work, Ogawa and co-workers have given a preliminary account of the preparation of the mannosyl chloride *3* by a different method and of its use in the synthesis of 1,2-linked oligosaccharides.[13]

EXPERIMENTAL

General methods. Melting points are corrected. Concentrations were performed at reduced pressure at temperatures not exceeding 40 °C. TLC was performed on silica gel F^{254} plates (Merck). For visualization of the compounds, UV-light or spraying with sulfuric acid followed by heating at 120 °C was used. Column chromatography was performed on silica gel (0.040–0.063 mm) columns (Merck). The following solvent systems were used: A (toluene–ethyl acetate, 3:1), B (toluene–ethyl acetate, 2:1, Optical rotations were recorded at room temperature (20–23 °C; chloroform *c* 0.5–1.0) using a Perkin-Elmer 241 instrument. NMR spectra were recorded on a JEOL JNM-FX-100 instrument, in deuteriochloroform, using TMS as internal standard.

*3,4,6-Tri-*O*-benzyl-1,2-*O*-(methoxyethylidene)-β-*D*-mannopyranose* (2).[2,14] *1* (6.0 g) was deacetylated in methanol (50 ml) by the addition of ammonia-saturated methanol (10 ml) at room temperature overnight. The solution was concentrated to a chromatographically pure syrup, (4.4 g). The product (3.3 g) was dissolved in dimethylformamide (80 ml), sodium hydride (3.6 g) was added and the reaction mixture was stirred for 0.5 h. Benzyl bromide (10 ml) was dropped into the reaction mixture during a period of 0.5 h at 15 °C and the stirring was continued for 5 h. Water (260 ml) was added and the mixture was extracted with chloroform, washed with water, 1 M solution of tartaric acid and water. The extract was dried, concentrated and the residue was purified by crystallization from hexane to yield pure *2* (6.0 g, 85 %), m.p. 76–77 °C, $[\alpha]_D$ +29° (lit.[2,14] m.p. 75–77 °C, $[\alpha]_D$ +29°), R_F 0.51 (solvent system A). NMR: δ 7.24–7.35 (15 H, m, aromatics), 3.27 (3 H, s, OCH_3), 1.73 (3 H, s, CH_3).

*6-*O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (4). *Method A.* *2* (2.0 g) was stirred in HCl-saturated diethyl ether (15 ml) at 5–10 °C for 2 h. The solution was concentrated to a syrup and evaporated twice with diethyl ether. Purification gave *3* (1.6 g, 78 %) as a syrup $[\alpha]_D$ +73°, R_F 0.68 (solvent system A). A solution of *4a* [10] (0.86 g) mercury(II) cyanide (1.0 g) and mercury(II) bromide (1.0 g) in 1:1 (v/v) toluene-nitromethane (200 ml) was distilled at atmospheric pressure until the volume was 150 ml, and cooled to room temperature. The chloride *3*, obtained from *2* (2.0 g) without purification was added. After stirring for 48 h additional mercury(II) cyanide (500 mg) was added and the stirring was continued overnight. Chloroform (250 ml) was added, followed by successive washings with water, saturated aqueous sodium hydrogen carbonate, saturated aqueous potassium iodide and water. After drying, the solution was concentrated to give a syrup that was chromatographed on a column of silica gel (solvent system A) to yield *4* (1.8 g, 78 %),[2] $[\alpha]_D$ −6°, R_F 0.57 (solvent system A). NMR: δ 7.20–7.32 (15 H, m, aromatics), 2.14 (3 H, s, $OCOCH_3$), 1.30–1.50 (12 H, 3 s, isopropylidenes).

Method B. *2* (1.0 g) was dissolved in HCl-saturated diethyl ether (10 ml) at 5–10 °C and stirred for 2 h. The solution was concentrated and evaporated twice with diethyl ether. The resulting syrup was dissolved in dry dichloromethane (30 ml) and successively treated at 0 °C with *4a* (0.43 g), 1,1,3,3-tetramethylurea (0.5 ml) and silver trifluoromethanesulfonate (1.2 g) under anhydrous conditions. The suspension was stirred in the dark overnight at 0 °C, and then filtered through a bed of Celite. The filtrate was washed with water, saturated aqueous sodium hydrogen carbonate and water. After drying, the solution was concentrated and the resulting syrup chromatographed on a column of silica gel (solvent system A) to give *4* (0.8 g, 68 %). All physical data were in agreement with an authentic sample of *4*.[2]

*3-*O*-(2-*O*-Acetyl-3,4,6,tri-*O*-benzyl-α-*D*-mannopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (5). *Method A.* The glycosylation of *5a* [10] (0.83 g) with *3* (0.9 g) in the presence of mercury(II) cyanide (0.75 g) and mercury(II) bromide (0.5 g) under similar conditions as those for *4a*, yielded a syrup (0.8 g, 68 %) $[\alpha]_D$ +14°, R_F 0.48 (solvent system A). Anal. $C_{41}H_{50}O_{12}$: C, H. NMR: δ 7.25–7.32 (15 H, m, aromatics), 2.14 (3 H, s, $OCOCH_3$), 1.22–1.47 (12 H, 4 s, isopropylidenes). *Method B.* Similar glycosylation of *5a* [10] (0.83 g), under the same conditions as those for *4a*, yielded a syrup (0.81 g, 70 %). All physical data were in agreement with those of *5*, prepared by method A.

*Methyl 4-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-*D*-glucopyranoside* (6). *Method A.* The glycosylation of *6a* [11] (1.4 g) with *3* (0.9 g) under the same conditions as for *4a* yielded a syrup (0.95 g, 58 %), $[\alpha]_D$ +28° R_F 0.62 (solvent system B).

Anal. $C_{57}H_{62}O_{12}$: C, H. NMR: δ 7.20–7.26 (30 H, m, aromatics), 3.37 (3 H, s, OCH_3), 1.97 (3 H, s, $OCOCH_3$). *Method B.* The glycosylation of *6a* [11] (1.4 g) with *3* (0.9 g), under the same conditions as those for *4a* gave a syrup (0.97 g, 59 %). All physical data were in agreement with those of *6*, prepared by method A.

2-O-(2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-1,3,4,6-tetra-O-acetyl-α-D-galactopyranose (7). *Method A.* The glycosylation of *7a* [12] (1.1 g) with *3* (0.9 g) in the presence of mercury(II) cyanide (0.75 g) and mercury(II) bromide (0.5 g) under similar conditions as those for *4a*, gave a foam (0.85 g, 59 %) $[\alpha]_D$ +66°. R_F 0.40 (solvent system B). Anal. $C_{43}H_{50}O_{16}$: C, H. NMR: δ 7.23–7.31 (15 H, m, aromatics), 1.93–2.17 (15 H, 5 s, $OCOCH_3$). *Method B.* The glycosylation of *7a* [12] (1.1 g) with *3* (0.9 g), under the same conditions as those for *4a* gave a foam (0.90 g, 62 %). All physical data were in agreement with those of *7*, prepared by method A.

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