Carbohydrate Research, 88 (1981) C20–C23
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Preliminary communication

Syntheses of 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl bromide and other key intermediates for oligosaccharide synthesis*

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(Received October 30th, 1980; accepted for publication, November 14th, 1980)

In most glycoproteins having a carbohydrate moiety *N*-glycosylically linked to asparagine, a D-mannosyl residue is generally β-D-linked at O-4′ of 2-acetamido-2-deoxy-D-glucose residue. A typical structure of branched-chain D-mannosyl residues in such molecules may be represented by the following formula.

α-Man-(1→6)-β-Man-(1→4)-β-GlcNAc-(1→4)-GlcNAc-Asp
3
↑
1
Man

In order to develop a systematic approach to the synthesis of the complex saccharides that can occur as a part of glycoproteins, investigators have centered their studies on the synthesis of various glycosylating reagents that may be effectively used for the sequential synthesis of higher saccharides[2–4]. Use of both temporary and persistent protecting-groups in such glycosylating reagents is recommended. According to Wulff and Wichelhauss[5], condensation of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl bromide with an aglycon hydroxide in diethyl ether in the presence of silver salicylate gives the corresponding β-D-mannopyranosyl derivative. Based upon such observations, we decided that, reaction of the title sugar halide 3 with an aglycon hydroxide, particularly one having *O*-benzyl and *O*-allyl protecting-groups, followed by removal of the 3-*O*-acetyl group from the resulting product, would provide the O-3 site of a β-D-mannopyranosyl residue for attachment of a D-mannosyl group.

For facile preparation of compound 3 and related compounds described herein, methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside[6] (1) was chosen as a suitable starting-material. On reaction with M HCl in 83:17 1,4-dioxane–water for 12 h at 130°, methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (2), prepared from compound 1 *via* phase-transfer catalysis[6], gave diol 6 in 70% yield; m.p. 72–73°, $[\alpha]_D^{24}$ +2.6° (*c* 1, chloroform);

*Synthetic Studies in Carbohydrates, Part XV. For Part XIV, see ref. 1.
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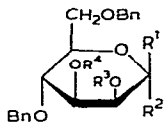
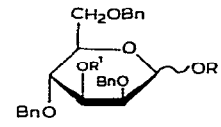
p.m.r. data ($CDCl_3$): δ 5.3 (1 H, H-1) and 7.2–7.5 (m, 15 H, 3 Ph). Acetylation of 6 with acetic anhydride–pyridine gave, in almost quantitative yield, syrupy 7, $[\alpha]_D^{24}$ +8.8° (*c* 1, chloroform); p.m.r. data ($CDCl_3$): δ 1.94–2.36 (6 H, 2 Ac), 5.24 (dd, 1 H, $J_{3,4}$ 9, $J_{3,2}$ 3 Hz, H-3), 6.24 (d, 1 H, *J* 2.5 Hz, H-1), and 7.1–7.5 (m, 15 H, aromatic).

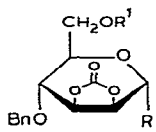


1 $R^1 = R^3 = R^4 = H, R^2 = OMe$
2 $R^1 = R^4 = H, R^2 = OMe, R^3 = Bn$
3 $R^1 = H, R^2 = Br, R^3 = Bn, R^4 = Ac$
4 $R^1 = OMe, R^2 = H, R^3 = Bn, R^4 = Ac$
5 $R^1 = OMe, R^2 = R^4 = H, R^3 = Bn$

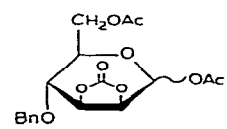
Bn = $PhCH_2$



6 R = $R^1 = H$
7 R = $R^1 = Ac$



8 R = OMe, R^1 = Bn
9 R = Br, R^1 = Ac



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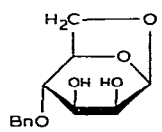

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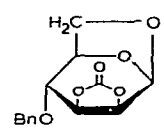

12

For the preparation of compound 3, in a typical experiment, a solution of 7 in anhydrous dichloromethane was added to a stirred, saturated solution of hydrogen bromide in dichloromethane at 0°. After 30 min, the mixture was processed as usual, to afford bromide 3 in 81% yield; $[\alpha]_D^{24}$ +72.9° (*c* 1, $CHCl_3$); p.m.r. data ($CDCl_3$): δ 1.96 (s, 3 H, Ac), 5.60 (dd, 1 H, $J_{3,4}$ 9, $J_{3,2}$ 3 Hz, H-3), 6.46 (d, 1 H, *J* 1.5 Hz, H-1), and 7.2–7.5 (m, 15 H, 3 Ph).

It has been reported that treatment of 2,3,4,6-tetra-*O*-benzyl-α-D-manno-pyranosyl bromide with an excess of methanol gives methyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranoside[5]. Under similar reaction-conditions, bromide 3 gave methyl 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-β-D-mannopyranoside (4), $[\alpha]_D^{24}$ −61.4° (*c* 1, $CHCl_3$); n.m.r. data

($CDCl_3$): δ 1.86 (s, 3 H, Ac), 3.58 (s, 3 H, OMe), 5.26 (dd, 1 H, $J_{3,4}$ 9, $J_{3,2}$ 3 Hz, H-3), and 7.2–7.5 (m, 15 H, aromatic). A singlet at δ 3.58 (OMe) clearly supported the β configuration for compound **4**. Conventional deacetylation of **4**, followed by purification by chromatography in a column of silica gel, produced methyl 2,4,6-tri-*O*-benzyl-β-D-mannopyranoside in an overall yield of 73%; $[\alpha]_D^{24}$ −59.6° (*c* 0.5, $CHCl_3$); n.m.r. data ($CDCl_3$): δ 3.58 (s, 3 H, OMe), 4.42 (d, 1 H, *J* 0.8 Hz, H-1), and 7.2–7.5 (m, 15 H, 3 Ph).

According to Gorin and Perlin[7], β-D-mannopyranosides can be prepared by the Koenigs–Knorr reaction by using 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannopyranosyl bromide. However, formation of β-D-mannopyranosyl compounds seems to depend upon the aglycon hydroxide, the solvent, and the nature of the catalyst[8,9]. 4,6-Di-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannopyranosyl bromide is generally prepared by treatment of 1,4,6-tri-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannose with hydrogen bromide in acetic acid.

We aimed at the preparation of bromide **9**, having an *O*-benzyl group. The reaction of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside (**1**) with ethyl chloroformate in the presence of triethylamine gave compound **8** in 92% yield; $[\alpha]_D^{24}$ +31.4° (*c* 2.0, chloroform); t.l.c. (2:1 ethyl ether–toluene) R_F 0.70; ν_{max}^{film} 1820 cm^{-1} (cyclic carbonate); n.m.r. data ($CDCl_3$): δ 3.41 (s, 3 H, OMe), 5.04 (s, 1 H, H-1), and 7.20–7.42 (m, 10 H, aromatic).

In another approach, 1,6-anhydro-4-*O*-benzyl-β-D-mannopyranose (**11**) under similar conditions gave **12** in 91% yield, m.p. 91° (ether), $[\alpha]_D^{24}$ −58.5° (*c* 1, chloroform); ν_{max}^{KBr} 1790 cm^{-1} (carbonate); n.m.r. data ($CDCl_3$): δ 5.54 (d, 1 H, *J* 2.5 Hz, H-1), and 7.38 (s, 5 H, aromatic).

In a typical experiment, to a solution of **8** (0.75 g) in acetic anhydride (3 mL), was added 1:99 (v/v) concentrated sulfuric acid–acetic anhydride (6 mL), and the solution was stirred for 2 h at room temperature. The mixture was then diluted with chloroform (100 mL), washed successively with ice–water (2 × 10 mL), saturated sodium hydrogencarbonate solution (2 × 10 mL), and water (2 × 10 mL), and evaporated to dryness; a trace of acetic anhydride remaining was removed by addition and evaporation of ethanol, to give **10** in 75% yield; $[\alpha]_D^{24}$ +32.8° (*c* 1, chloroform). T.l.c. of the acetolysis product showed absence of the starting material, and the presence of a major product, R_F 0.50 (2:1 ethyl ether–toluene) which was clearly distinguishable from 1,4,6-tri-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannopyranose, showing thereby that both of the *O*-benzyl groups in **8** were not removed during the acetolysis. The n.m.r. spectrum of compound **10** clearly supported the presence of one *O*-benzyl group and two *O*-acetyl groups, suggesting that, during the acetolysis, one of the *O*-benzyl groups had been replaced by an *O*-acetyl group.

The acetolysis of *O*-benzyl derivatives of certain saccharides has been studied in detail[10,11]. It has been well established that an *O*-benzyl group substituting a primary hydroxyl group in carbohydrates is cleaved during acetolysis[10,11]. Ponpipom[11] reported the acetolysis of 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranose, and suggested that cleavage of benzyl ethers by acetolysis appears to be in the order: 6-*O*-benzyl > 4-*O*-benzyl > 3-*O*-benzyl. Based on these observations, we assigned structure

10 for the product obtained by the acetolysis of **8**. Moreover, acetolysis of 1,6-anhydro-4-*O*-benzyl-2,3-*O*-carbonyl-β-D-mannose (**12**) under similar conditions gave a product found to be identical with **10** on the basis of t.l.c. The optical rotation of this product, $[\alpha]_D^{24}$ +49.5° (*c* 1, $CHCl_3$), showed that the 1-acetate having the α-D configuration preponderated. This observation was further supported by the n.m.r. data, which indicated the presence of α:β-acetate in **10** (from **12**) in the ratio of 4:1, whereas, in **10** from **8**, the ratio was 2:1. Nevertheless, it was clear that the 4-*O*-benzyl group was not removed from **8** and **12** during acetolysis.

Use of HBr–acetic acid for the preparation of bromide **9** was not encouraging. However, use of bromotrimethylsilane in benzene[12] for the preparation of the bromide may be successful. According to preliminary studies, compound **10** under these conditions gave product **9***, having $[\alpha]_D^{24}$ +68.2° (*c* 1, dichloromethane), and the n.m.r. spectrum showed the presence of an *O*-benzyl group, and a singlet for the anomeric proton at δ 6.64.

ACKNOWLEDGMENTS

We thank Conrad F. Piskorz for his excellent technical assistance, and Onda D. Simmons for recording the n.m.r. spectra. The n.m.r. studies were supported by National Cancer Institute Core Grant CA-16056. This investigation was supported by Grant No. IR01-GM-24392-01, awarded by the National Institutes of Health.

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*Together with some starting-material.