Carbohydrate Research, 150 (1986) C1–C4
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

Synthesis of some D-mannosyl-disaccharides containing D-mannose 6-phosphate residues*

KHUSHI L. MATTA, MANJIT S. CHOWDHARY†, RAKESH K. JAIN, and SAEED A. ABBAS

Department of Gynecologic Oncology, Roswell Park Memorial Institute, New York State Department of Health, 666 Elm Street, Buffalo, New York 14263 (U.S.A.)

(Received April 4th, 1986; accepted for publication April 23rd, 1986)

Our growing interest in the study of lysosomal-enzyme targeting prompted us to embark on a project for the synthesis of some D-mannosyl oligosaccharides containing D-mannose 6-phosphate residues. D-Mannose 6-phosphate is considered to be an essential part of a recognition marker involved in the targeting of the newly-synthesized lysosomal enzymes to lysosomes[2].

As part of this project and in order to produce some D-mannosyl disaccharides containing such D-mannose 6-phosphate residues, two synthetic procedures appeared to be equally feasible. It was envisaged, for example, that a D-mannosyl donor already bearing a primary phosphoric ester group could be allowed to react with a suitably protected D-mannose derivative to give the desired disaccharide. Alternatively, a suitably protected disaccharide derivative could firstly be prepared, and then selectively phosphorylated at its primary hydroxyl group(s).

In an initial attempt to explore the utility of the first of these synthetic procedures, 2,3,4-tri-*O*-acetyl-6-*O*-(diphenoxyphosphoryl)-α-D-mannopyranosyl bromide (**1**) was prepared by the action of gaseous hydrogen bromide on 1,2,3,4-tetra-*O*-acetyl-6-*O*-(diphenoxyphosphoryl)-β-D-mannopyranose[3] in dichloromethane at 0°. Analytically pure **1** was obtained in 91% yield as an amorphous solid, $[\alpha]_D$ +91.3° (chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.99–2.10 (s, 3 × 3 H, OAc), 6.20 (br.s, 1 H, H-1), and 7.02–7.40 (m, 10 H, arom). It was allowed to react for 4 h at room temperature with 1,2,3,4-tetra-*O*-acetyl-β-D-mannopyranose (**2**; 0.35 g) in freshly distilled acetonitrile (5 mL), in the presence of $HgBr_2$ (0.45 g), $Hg(CN)_2$ (0.31 g), and molecular sieves 4A (1 g). More of bromide **1** was added, and the stirring continued overnight. Processing in the usual manner, followed by crystallization of the resulting, syrupy product mixture from dry ether afforded, in 76% yield, analytically pure 1,2,3,4-tetra-*O*-acetyl-6-*O*-[6-*O*-(diphenoxyphosphoryl)-α-D-mannopyranosyl]-β-D-mannopyranose (**10**), m.p. 142–143°, $[\alpha]_D$ +29.6° (chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 2.0–2.2 (cluster of singlets, 21 H, OAc),

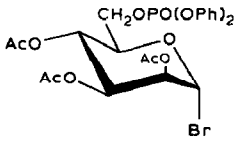
*Synthetic Studies in Carbohydrates, Part XLVI. For Part XVL, see ref. 1, A-112.

This investigation was supported by Grant No. GM-31425 from the National Institute of General Medical Sciences, National Institute of Health.

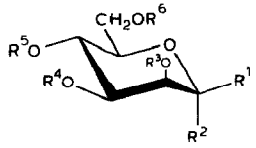
†Present address: Lederle Labs, Bldg. 65A, Rm. 205, Pearl River, NY 10965, U. S. A.

0008-6215/86/$03.50

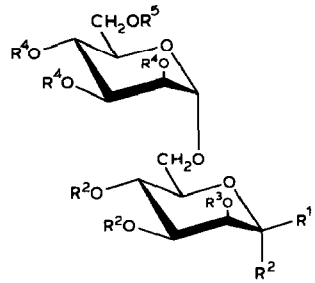
5.8 (br.s, 1 H, H-2), and 7.0–7.4 (m, 10 H, arom). Similar condensation of methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**5**) with bromide **1** gave, in 33.3% yield, methyl 2,4,6-tri-*O*-benzyl-3-*O*-[2,3,4-tri-*O*-acetyl-6-*O*-(diphenoxyphosphoryl)-α-D-mannopyranosyl]-α-D-mannopyranoside (**12**), $[\alpha]_D$ +35.4° (chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.76–1.98 (m, 9 H, OAc), 3.30 (s, 3 H, OMe), and 7.00–7.35 (m, 25 H, arom). A similar condensation of **1** with methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**6**) afforded, in 38.6% yield, methyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4-tri-*O*-acetyl-6-*O*-(diphenoxyphosphoryl)-α-D-mannopyranosyl]-α-D-mannopyranoside (**11**), $[\alpha]_D$ +52.5° (chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.76–1.96 (m, 9 H, OAc), 3.27 (s, 3 H, OMe), and 7.00–7.43 (m, 25 H, arom.).



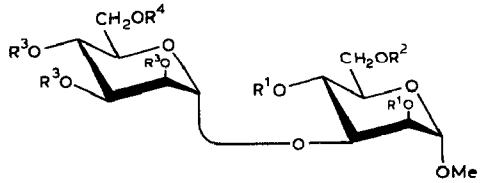
1



2 R^1 = OAc, R^2 = R^6 = H, R^3 = R^4 = R^5 = Ac
3 R^1 = H, R^2 = OMe, R^3 = H, R^4 = R^5 = R^6 = Bn
4 R^1 = OAc, R^2 = R^3 = H, R^4 = R^5 = R^6 = Ac
5 R^1 = R^4 = H, R^2 = OMe, R^3 = R^5 = R^6 = Bn
6 R^1 = R^6 = H, R^2 = OMe, R^3 = R^4 = R^5 = Bn
7 R^1 = R^3 = R^4 = R^5 = R^6 = H, R^2 = OMe
8 R^1 = R^3 = R^4 = R^5 = H, R^2 = OMe, R^6 = $PO(OPh)_2$
9 R^1 = R^3 = R^4 = R^5 = H, R^2 = OMe, R^6 = PO(ONa)



10 R^1 = R^3 = R^4 = Ac, R^2 = H, R^5 = $PO(OPh)_2$
11 R^1 = H, R^2 = OMe, R^3 = Bn, R^4 = Ac, R^5 = $PO(OPh)_2$



12 R^1 = R^2 = Bn, R^3 = Ac, R^4 = $PO(OPh)_2$
13 R^1 = R^2 = R^3 = R^4 = H
14 R^1 = R^3 = H, R^2 = R^4 = $PO(OPh)_2$

Attempted condensation of bromide **1** with methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**3**) or 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose (**4**) were not successful.

During these investigations, Srivastava and Hindsgaul[4] described the phosphorylation of some partially protected mannobiosides with diphenyl phosphorochloridate. This procedure was particularly attractive in so far that it allowed phosphorylation at either the O-6 or -6′, or both, of the *manno*-disaccharides. However, it would yet be more

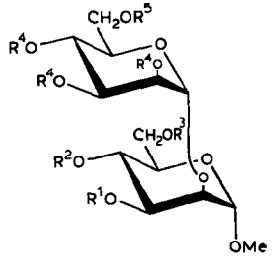
appealing should it be possible to achieve phosphorylation at the primary positions without prior protection of some, or all, of the secondary hydroxyl groups. Interestingly, this was the case in our hands, and selective phosphorylation of either O-6 or -6′, or both, was readily accomplished, despite the presence of free, secondary hydroxyl groups.

TABLE I

PHOSPHORYLATION OF SOME DISACCHARIDES WITH DIPHENYLPHOSPHORO-CHLORIDATE IN PYRIDINE AT 0°

Compound	*Product* [a] *and yield (%)*	$[\alpha]_D^b$ *(degrees)*	*Partial* ^{1}*H-n.m.r. data (δ)*
7	8 (68)	+44.1 [c]	3.20 (s, 3 H, OMe), and 7.00–7.41 (m, 10 H, arom.)
13	14 (57.5)	+42.5 [c]	3.10 (s, 3 H, OMe), and 6.90–7.30 (m, 20 H, arom.)
15	20 (55.5)	+31.8 [c]	3.20 (s, 3 H, OMe), and 7.09–7.41 (m, 25 H, arom.)
16	21 (82)	+43.4 [c]	1.91–2.14 (s, 4 × 3 H, OAc), 3.20 (s, 3 H, OMe), and 7.00–7.41 (m, 10 H, arom.)
17	22 (93)	+22 [d]	3.20 (s, 3 H, OMe), 5.50 (s, 1 H, PhC*H*), and 7.11–7.50 (m, 20 H, arom.)
18	23 (93)	+30.6 [d]	1.86–2.16 (cluster of singlets, 12 H, OAc) 3.30 (s, 3 H, OMe), and 7.10–7.36 (m, 15 H, arom.)
19	24 (58.6)	+33.3 [d]	3.16 (s, 3 H, OMe), and 7.10–7.35 (m, 20 H, arom.)

[a] All products listed gave satisfactory elemental analysis. [b] At ~25°. [c] For a solution in chloroform. [d] For a solution in methanol.



15 $R^1 = R^2 = R^3 = Bn, R^4 = R^5 = H$
16 $R^1 = R^2 = R^3 = H, R^4 = R^5 = Ac$
17 $R^1 = Bn, R^2, R^3 = PhCH, R^4 = R^5 = H$
18 $R^1 = Bn, R^2 = R^3 = H, R^4 = R^5 = Ac$
19 $R^1 = R^2 = R^3 = R^4 = R^5 = H$
20 $R^1 = R^2 = R^3 = Bn, R^4 = H, R^5 = PO(OPh)_2$
21 $R^1 = R^2 = H, R^3 = PO(OPh)_2, R^4 = R^5 = Ac$
22 $R^1 = Bn, R^2, R^3 = PhCH, R^4 = H, R^5 = PO(OPh)_2$
23 $R^1 = Bn, R^2 = H, R^3 = PO(OPh)_2, R^4 = R^5 = Ac$
24 $R^1 = R^2 = R^4 = H, R^3 = R^5 = PO(OPh)_2$

Thus, when methyl α-D-mannopyranoside (**7**) was treated with two molar equivalents of diphenyl phosphorochloridate in dry pyridine, at 0°, methyl 6-*O*-(diphenoxyphosphoryl)-α-D-mannopyranoside (**8**) was obtained in good yield, after column-chromatographic purification. Similar condensation of compounds **15**, **16**, **17**, or **18** with the same reagent afforded the monophosphorylated derivatives **20**, **24**, **22**, and **23** in fair to excellent yields (see Table I).

In order to achieve diphosphorylation at the primary positions of compound **13** or **19**, four molar equivalents of diphenylphosphorochloridate were employed, and the 6,6′-di-*O*-phosphoryl derivatives **14** and **24** were obtained in satisfactory yields (see Table I).

REFERENCES

1 S. S. Rana and K. L. Matta, *Carbohydr. Res.*, A-112.
2 A. Varki and S. Kornfeld, *J. Biol. Chem.*, 255 (1980) 10 847–10 858.
3 T. Posternak and J. P. Rosselet, *Helv. Chim. Acta*, 35 (1953) 1614–1623.
4 O. P. Srivastava and O. Hindsgaul, *Proc. Int. Symp. Glycoconjugates*, H *VIIIth*, 1985, p. 182.