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Preliminary communication

Synthesis of α-D-mannopyranosyl α-D-mannopyranoside from α,α-trehalose: a route to cord factor analogs

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For some years, our laboratory has been interested in the synthesis of cord factor (6,6′-di-*O*-mycoloyl-α,α-trehalose) and cord factor analogs, and several syntheses of this type of biologically important compound have been described[1–5]. In these syntheses, divers linkages between the disaccharide and the lipid moieties were investigated. In continuation of this study, and in order to probe stereochemical requirements for expression of various biological activities, we have synthesized a part of a cord-factor analog in which the natural sugar (α,α-trehalose) is replaced by the corresponding D-*manno* disaccharide[6].

Although a per-*O*-benzylated D-*manno* analog of α,α-trehalose has been synthesized from suitable tetra-*O*-benzyl-D-mannopyranosyl derivatives[7,8], the methods reported did not provide the selective blocking of O-6 and O-6′ necessary for subsequent introduction of the ester groups thereat. In the present work, we describe the synthesis of α-D-mannopyranosyl α-D-mannopyranoside from α,α-trehalose.

Treatment of 4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose[9] (**1**) with 2 Mol equivalents of trifluoromethanesulfonyl chloride in pyridine for 1 h gave a mixture of two components, namely, 4,6:4′,6′-di-*O*-benzylidene-2,2′-di-*O*-triflyl-α,α-trehalose (**2**), (23%), $[\alpha]_D^{22}$ +75° (*c* 1.0, chloroform), and 4,6:4′,6′-di-*O*-benzylidene-2-*O*-triflyl-α,α-trehalose (**3**), (57%), $[\alpha]_D^{22}$ +76° (*c* 1.0, 3:1 chloroform–methanol). The desired ditriflate **2** could be obtained as the sole product (yield, >70%) when the reaction was conducted for 24 h with a slight excess of the chloride. The structure of **2** was confirmed by converting it into the known α-D-mannopyranosyl α-D-mannopyranoside[10], and also by the n.m.r. spectrum of the corresponding 3,3′-di-*O*-acetyl derivative **4**: the signal of H-3, H-3′ shifted to a lower field (δ 5.72, $J_{3,2} = J_{3,4} = 9.5$ Hz), owing to the deshielding effect of the adjacent *O*-acetyl group.

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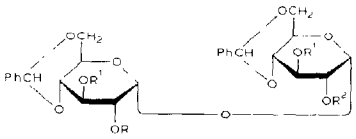
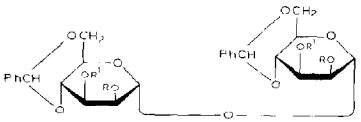
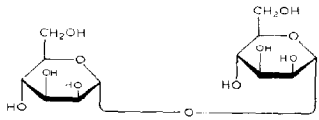
Before solvolyzing the triflate groups in **2**, we found it necessary to block OH-3 by a nonparticipating group, in order to avoid complicating side-reactions (with **2** alone, as many as seven products were obtained on attempted benzoate displacement). The tetrahydropyran-2-yl group[11] was found satisfactory for this purpose, and the corresponding 3,3'-di(tetrahydropyran-2-yl) ether **5** was obtained in 88% yield by treatment of **2** with dihydropyran in dichloromethane at room temperature in the presence of *p*-toluenesulfonic acid (pyridinium salt); **5** had $[\alpha]_D^{22}$ +56° (*c* 0.9, chloroform).



1 R = R^1 = R^2 = H
2 R = R^2 = SO_2CF_3, R^1 = H
3 R = SO_2CF_3, R^1 = R^2 = H
4 R = R^2 = SO_2CF_3, R^1 = Ac

5 R = R^2 = SO_2CF_3, R^1 =





6 R = Bz, R^1 =

7

Solvolysis of **5** with sodium benzoate in hexamethylphosphoric triamide was performed for 72 h at 115°, and the α-D-mannopyranosyl α-D-mannopyranoside derivative **6** was isolated in 61% yield following column chromatography on silica gel; **6** had $[\alpha]_D^{22}$ +12° (*c* 0.5, chloroform). Debenzoylation of **6** with sodium methoxide in methanol, followed by hydrolysis with 80% acetic acid to remove the blocking groups, gave the known α-D-mannopyranosyl α-D-mannopyranoside **7**: (yield, 50%); m.p. 230–235°, $[\alpha]_D^{22}$ +123° (*c* 0.65, methanol); (lit.[10] m.p. 240–243°, $[\alpha]_D$ +124°).

While this manuscript was in preparation, a similar conversion of a D-*gluco* triflate derivative into the corresponding D-*manno* analog was reported[12]; in this method, OH-3 was blocked by an acetyl group. However, in our experience, blocking by an ester group leads to undesired side-reaction in the subsequent solvolysis.

Microanalysis and n.m.r. data confirmed the structural assignments given compounds **2**–**6**.

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