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Preliminary communication

Sulfate as a blocking group in alkali-catalyzed permethylation: an alternative synthesis of 3,4,6-tri-*O*-methyl-D-glucose

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The presence in relative abundance of a unique and potently antigenic, phenolic glycolipid (PGL) in harvests of *Mycobacterium leprae*[1,2] has stimulated considerable effort toward synthesis of various products that incorporate a 3,6-di-*O*-methyl-D-glucose, as it is this moiety in which the immunological specificity of PGL resides[3]. Such synthetic substances, of potential abundant availability, are sought as substitutes for the relatively rare natural lipid, for use in appropriate, serological tests in man to detect infection, even cryptic, with *M. leprae*[3].

We are currently involved in a similar, albeit modest, program of synthesis of relatively simple, lipid 3,6-di-*O*-methylglycosides, of potential serological utility. We sought, however, to test a 3,4,6-tri-*O*-methyl-D-glucoside in order to determine whether humoral antibody to the PGL was capable of notable cross-reactivity with the tri-*O*-methyl analog, or if, instead, recognition was virtually restricted to the specific di-*O*-methylglycosides. Indeed, the latter was found to be the case.

Prior experience suggested to us that, for synthesis of the desired sugar, a 2-sulfuric ester should be potentially very useful as a blocking group, stable to alkaline conditions of methylation, and subsequently readily removed by facile, gentle solvolysis in slightly moist, acidified ether or 1,4-dioxane[4–6]. Thus, we anticipated that a methyl D-glucoside 2-sulfate should be readily convertible into the 3,4,6-tri-*O*-methyl derivative by such a scheme.

3,4,6-Tri-*O*-methyl-D-glucose had been synthesized from methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside, and by other methods which involved the shielding of O-2 by the presence either of a double bond or an anhydro ring[7]. More recently, it was prepared from 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose[8], from 1,2-*O*-isopropylidene-4,6-di-*O*-methyl-α-D-glucopyranose[9], and from 1,3,4,6-tetra-*O*-acetyl-D-glucopyranose[10].

We have recently described the synthesis of trehalose 2-sulfate from 4,6:4′,6′-di-*O*-

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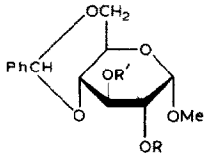
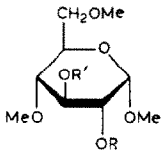
benzylidene-α,α-trehalose[6]. In this synthesis, the selective removal of the benzylidene group was achieved by dilute, aqueous sulfuric acid (conditions under which the sulfuric ester is stable; thus, only a trace of desulfation product could be detected). In the present attempt to develop an alternative synthesis for 3,4,6-tri-*O*-methyl-D-glucose, the sulfate group was successfully employed, as anticipated, as the group to provide selective blocking of OH-2.

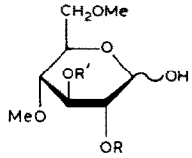


	R	R'
1	H	H
2	SO_3 · pyr	H
3	H	SO_3 · pyr

pyr = C_5H_5N



	R	R'
4	H	Me
5	Me	H
6	Ac	Me
7	Me	Ac



	R	R'
8	H	Me
9	Me	H

Treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[11] (**1**) with pyridine–sulfur trioxide complex in pyridine at room temperature gave a mixture of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2-sulfate (**2**, major) and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 3-sulfate (**3**). A small amount of unchanged starting-material was removed by chromatography on silica gel, but the two isomers (isolated in 69% yield) could not be separated at this stage. Selective removal of the benzylidene group with 1% aqueous sulfuric acid, followed by methylation with methyl iodide and sodium hydride in *N,N*-dimethylformamide, gave a crude mixture of the corresponding, permethylated sulfates. Purification of the mixture was tedious, and so it was desulfated with 2% sulfuric acid in 1,4-dioxane containing a few drops of water, to give a mixture of methyl 3,4,6-tri-*O*-methyl-α-D-glucopyranoside (**4**) and methyl 2,4,6-tri-*O*-methyl-α-D-glucopyranoside (**5**). The mixture was freed of minor impurities by chromatography on silica gel, but the two products (which, in t.l.c., yielded two superimposed spots) were still inseparable (yield: 70%, based on the mixture of the sulfates **2** and **3**).

Acetylation of **4** and **5** gave a mixture of two *O*-acetyl derivatives which were readily separated by chromatography on silica gel, using 1:1 ethyl acetate–hexane as the eluant. The major product, methyl 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (**6**) was obtained in 61% yield; $[\alpha]_D$ +145° (*c* 0.9, chloroform). The ^{1}H-n.m.r. spectra of **6** and **7** confirmed the structures assigned. In the spectrum of **6**, the H-2 signal (partially obscured by the H-1 signal) shifted to lower field (δ 4.90, $J_{2,1}$ 3.2, $J_{2,3}$ 10.0 Hz) as a result of the deshielding effect of the adjacent *O*-acetyl group. In the spectrum of **7**, the H-3 signal appeared at low field (δ 5.42, $J_{3,2} = J_{3,4}$ = 10.0 Hz). Compound **6** was hydrolyzed with 2M hydrochloric acid at 100°, to give homogeneous 3,4,6-tri-*O*-methyl-D-glucose (**8**; a syrup, 81%); $[\alpha]_D$ +76° (*c* 0.7, chloroform–methanol 9:1), lit.[7] $[\alpha]_D$ +77°. Similarly, acid hydrolysis of **7** gave 2,4,6-tri-*O*-methyl-D-glucose (**9**, 85%). It crystallized from chloroform–hexane, to give the α anomer; m.p. 120–122°, $[\alpha]_D$ +86° (*c* 0.69, chloroform–methanol 9:1), lit.[12] m.p. 123–126°, $[\alpha]_D$ +70°.

When methyl 4,6-*O*-benzylidene-β-D-glucopyranoside was used as the starting material, the isomeric 2- and 3-sulfates were obtained in the ratio of 3:2 (as judged by ^{1}H-n.m.r. spectroscopy). Thus, sulfation of the α anomer leads to a more desirable ratio of products when blocking at O-2 is sought.

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