Carbohydrate Research, 149 (1986) C13–C16
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

A facile synthesis of 3,6-di-*O*-methyl-D-glucose†

AVRAHAM LIAV

Department of Molecular and Cellular Biology, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206 (U.S.A.)

and MAYER B. GOREN*

Department of Molecular and Cellular Biology, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206 (U.S.A.), and Department of Microbiology and Immunology, University of Colorado Health Sciences Center, Denver, Colorado (U.S.A.)

(Received March 10th, 1986; accepted for publication April 16th, 1986)

The recent recognition[1,2], isolation, purification[3,4], and structural characterization[4,5] of a phenolic glycolipid (PGL-I) from *Mycobacterium leprae* already ranks as a major milestone in leprosy research. PGL-I contains a diacylated phthiocerylphenyl group that is the structural feature commonly shared by various "mycosides" from several mycobacterial species (Scheme 1) (for reviews, see ref. 6). However, PGL-I is singularly distinguished from the other compounds in that the phenolic hydroxyl group is glycosidically linked to a unique trisaccharide (Scheme 1) that confers a highly specific antigenic and serological activity to the almost inert lipid component. The versatility of the glycolipid as a serologic diagnostic-test reagent for recognizing leprosy infection or disease is already well established[7].

The haptenic di- and tri-saccharide components have been synthesized by several investigators[8,9], and glycoconjugates of the synthetic di- or tri-saccharides with bovine serum albumin have been shown to hold great potential as "synthetic" antigens for use in enzyme-linked immunosorbent assays (ELISA) for detecting the specific humoral antibody to the glycolipid[9]. The principal specificity is known to reside in the nonreducing, terminal 3,6-di-*O*-methyl-D-glucopyranosyl group. And, thus, interest in the synthesis of 3,6-di-*O*-methyl-D-glucose (**9**) has recently been revived in several laboratories. This sugar has been used for preparing the di- and tri-saccharides as well as other derivatives. According to Gigg *et al.*[8], this compound is the most difficult to obtain of the three sugars in the oligosaccharide.

3,6-Di-*O*-methyl-D-glucose (**9**) or intermediate compounds have been prepared in the past by several methods: (a) Treatment of 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose with sodium methoxide[10]; (b) methylation of 1,2-*O*-isopropylidene-α-D-glucofuranose 5-nitrate[10]; and (c) methylation of 5-*O*-benzyl-1,2-*O*-iso-

† This investigation was supported by Grant AI-08401 from the U.S.-Japan Cooperative Medical Science Program, administered by the National Institute of Allergy and Infectious Diseases.

*To whom correspondence should be addressed.

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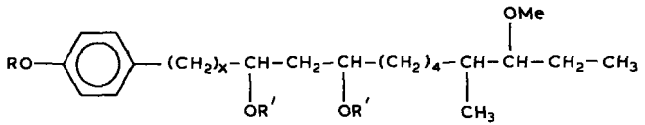


Mycoside A : R = *O*-(2,4-Di-*O*-methylrhamnopyranosyl)→ *O*-(2-*O*-methylfucopyranosyl)→ 2-*O*-methylrhamnopyranoside
x = 16, 17, 18*, 19, and 20

Mycoside B : R = 2-*O*-Methylrhamnopyranoside
x = 14, 15, 16*, 17, and 18

A.I. Lipid : R = Me
x = 16* and 18

PGL-I : R = *O*-(3,6-Di-*O*-methyl-D-glucopyranosyl-(1→4)-*O*-(2,3-Di-*O*-methylrhamnopyranosyl)-(1→2)-3-*O*-methylrhamnopyranoside

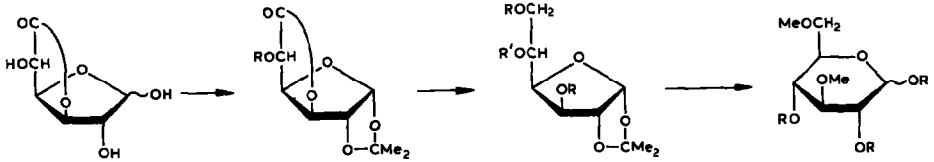
R' = acyl groups: palmitic acid and/or mycocerosic acids ($C_{20}H_{41}$–CH(CH$_3$)–CH$_2$–CH(CH$_3$)–CH$_2$–CH(CH$_3$)–CO$_2$H)

* Major component

Scheme 1. Structures of mycobacterial lipids containing a phthiocerylphenyl group.

propylidene-α-D-glucofuranose[11]. More recently, **9** has been synthesized from 5-*O*-allyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose; **9** was, in fact, obtained in seven steps from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[8].

In an effort to facilitate the synthesis of this biologically important compound, we sought alternative routes. In our experience, the readily available D-glucurono-6,3-lactone (**1**) was found to be a most practical starting material for obtaining **9**. This lactone (Pfanstiehl) was converted into the crystalline 1,2-*O*-isopropylidene derivative **2** as already described[12]. Blocking of OH-5 in **2** by treatment with either 2,3-dihydro-γ-pyran or methyl vinyl ether in dichloromethane in the presence of pyridinium *p*-toluenesulfonate (room temperature, 1 h) gave, after a short chromatography on silica gel, **3** in 95% yield, $[\alpha]_D^{24}$ +52° (*c* 1.0, chloroform), and **4** in 87% yield, $[\alpha]_D^{24}$ +64° (*c* 1.0, chloroform). The 5-*O*-(oxan-2-yl) derivative **3** was reduced with $LiAlH_4$ in ether (boiling under reflux, 1 h) to give **5** which appeared, in t.l.c., as a mixture of two compounds. Separation (by chromatography on silica gel) was feasible but not necessary, as both compounds gave **9** as described below. It appears that these two compounds are diastereoisomers at C-2 of the oxanyl group. This mixture was obtained in 86% yield after a short purification on silica gel (elution with 3:2 ethyl acetate–hexane), $[\alpha]_D^{24}$ −14° (*c* 1.0, chloroform). The 5-*O*-(1-methoxyethyl) derivative **6** also appeared, in t.l.c., as a mixture of two compounds, and was isolated in 84% yield as the diastereoisomeric mixture, $[\alpha]_D^{24}$ −15° (*c* 1.0, chloroform). Treatment of **5** (mixture) with methyl iodide and NaH (oil dispersion) in *N,N*-dimethylformamide (DMF) (room temperature, 30 min) gave the 3,6-di-*O*-methyl derivative **7** which appeared as one spot in t.l.c. A short chromatography on silica gel (3:2 hexane–ethyl acetate) removed the residual oil and syrupy **7** was isolated in 89% yield, $[\alpha]_D^{24}$ −16.5° (*c* 1.1, chloroform). In a similar manner, **6** was converted into the syrupy 3,6-di-*O*-methyl derivative **8** in 87% yield, $[\alpha]_D^{24}$ −45° (*c* 0.5, chloroform). Acid hydrolysis (1% H_2SO_4, 1 h, 85°) of **7**, followed by neutralization with $BaCO_3$ gave **9** as the sole product. Chromatography on silica gel (9:1 chloroform-methanol) gave pure **9** in 92% yield (homogeneous syrup); it crystallized from ethyl acetate, m.p. 118–120°, $[\alpha]_D^{24}$ +93 (5 min) → +63° (water, at equilibrium); lit.[10] m.p. 113–115°, $[\alpha]_D^{20}$ +61.5° (water, equilibrium); lit.[8], m.p. 114–116°, $[\alpha]_D^{24}$ +60° (final value). Compound **9** had the same mobility in t.l.c. (3:1 benzene–methanol) as an authentic sample of 3,6-di-*O*-methyl-D-glucose prepared by a previously published procedure[10]. G.l.c. of the per-*O*-(trimethylsilyl) derivative showed **9** to be identical with 3,6-di-*O*-methyl-D-glucose. The per-*O*-(trimethylsilyl) derivative of the crystalline (m.p. 118–120°) compound just described gave a minor peak (4.3 min) and a single major peak (4.7 min) in g.l.c. (2 mm



1

2 R = H
3 R = oxan-2-yl
4 R = CHMe(OMe)

5 R = H; R′ = oxan-2-yl
6 R = H; R′ = CHMe(OMe)
7 R = Me; R′ = oxan-2-yl
8 R = Me; R′ = CHMe(OMe)

9 R = H
10 R = Ac

diam. × 1.8 m column of SE 30, 150°, N_2 carrier gas, 30 mL/min). Per-*O*-(trimethylsylyl)ation of the mother liquor crystallization gave a product exhibiting two minor peaks (3.1 and 4.2 min) and two substantially equal major peaks at 4.8 and 5.5 min. When the crystalline product was briefly equilibrated in aqueous solution with a trace of pyridine, evaporated to dryness, and per-*O*-(trimethylsilyl)ated, all four peaks seen in the g.l.c. of the mother liquor product were observed at 3.2, 4.1 (both minor), and 4.8 and 5.5 min (very large and equally intense). It is suggested that the minor peaks correspond to the α- and β-furanose forms, and the major peaks to the anomeric pyranose forms. In a similar manner, **8** was converted, in 92% yield, into **9** (having the same physical properties as those described above). Acetylation of **9** gave the 1,3,4-tri-*O*-acetyl derivative **10**, the ^{1}H-n.m.r. spectrum of which was identical with that of an authentic sample of 1,2,4tri-*O*-acetyl-3,6-di-*O*- methyl-D-glucose.

A similar synthetic approach, based on the $LiAlH_4$ reduction of D-glucurono-6,3-lactone, was earlier used by Jones for the synthesis of 5-*O*-methyl-D-glucose[13].

ACKNOWLEDGMENTS

The authors thank Nadia de Stackelburg and Ethel Goren for illustrations and Shirley Downs for careful preparation of the manuscript. MBG is Margaret Regan Investigator in Chemical Pathology, National Jewish Center for Immunology and Respiratory Medicine.

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