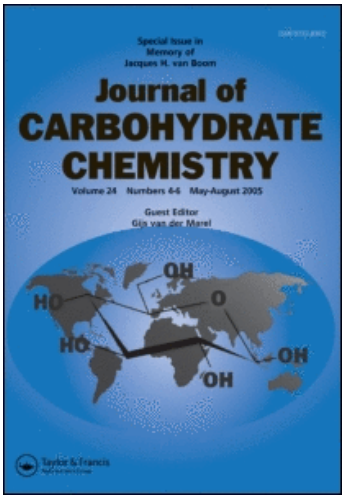

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Methyl 2,6-Dideoxy-4-α-Methyl-α-D-*Arabino*-Hexopyranoside

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METHYL 2,6-DIDEOXY-4-O-METHYL-α-D-ARABINO-HEXOPYRANOSIDE

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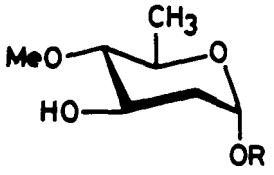
ABSTRACT

Synthesis of methyl 2,6-dideoxy-4-O-methyl-α-D-arabino-hexopyranoside (2) has been accomplished starting from readily available methyl 2-deoxy-α-D-arabino-hexopyranoside (3). The derived 4,6-dimesylate derivative 7 was simultaneously deoxygenated and hydrolysed at C-6 and C-4 with lithium aluminium hydride in refluxing tetrahydrofuran. Subsequent methylation and debenzylation of 8 gave the title product.

INTRODUCTION

2,6-Dideoxy-4-O-methyl-D-arabino-hexopyranose (1) is a unique carbohydrate segment present in the major phenolic glycolipid antigen from Mycobacterium kansasii.[1,2] Its presence as a terminal sugar component is important[2] in antigen-antibody interactions. This communication describes the synthesis of methyl 2,6-dideoxy-4-O-methyl-α-D-arabino-hexopyranoside (2) starting from easily accessible[3] methyl 2-deoxy-α-D-arabino-hexopyranoside (3).



1 R= H

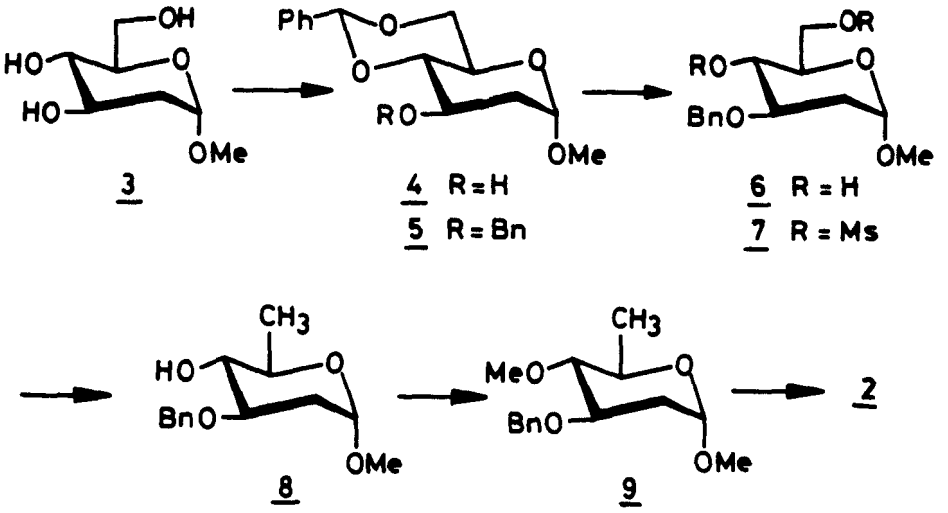
2 R= Me

RRL-H Communication No.2158

RESULTS AND DISCUSSION

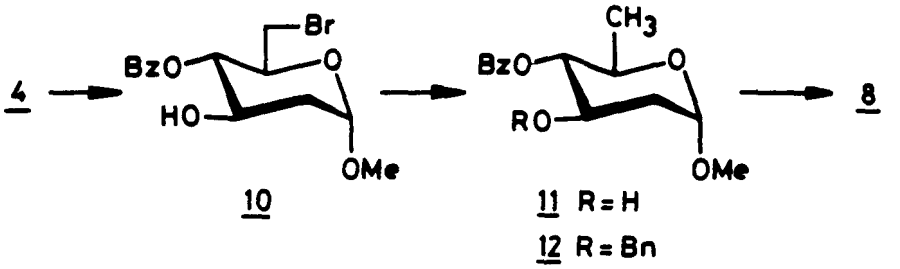
Treatment of **3** *(Scheme 1) with* α,α*-dimethoxytoluene in acetonitrile containing a catalytic amount of* p*-toluene-sulfonic acid at room temperature for 24 h gave*[4] *the 4,6-*O*-benzylidene derivative* **4** *in 87% yield. The free hydroxyl group in* **4** *was protected as the benzyl ether* **5** *by using benzyl bromide-sodium hydride in tetrahydrofuran. After the hydrolysis of the benzylidene group with sulfuric acid in aqueous tetrahydrofuran at room temperature, the resulting diol* **6** *was treated with methanesulfonyl chloride-pyridine to afford the 4,6-dimesylate* **7**. *The* ^1H *NMR spectrum of* **7** *was compatible*

Scheme 1



with the assigned structure. Exhaustive reduction of **7** *with excess of lithium aluminium hydride in refluxing tetrahydrofuran for 7 h effected two transformations. The deoxygenation at C-6 and the hydrolysis of the mesyl group at C-4 occurred simultaneously to give* **8** *in 87% yield. In the* ^1H *NMR spectrum of* **8**, *the characteristic doublet at* $\delta 1.20$ *(J=6 Hz) was observed for H-6,6',6". Treatment of* **8** *with sodium hydride-methyl iodide in tetrahydrofuran afforded the 4-*O*-methyl derivative* **9** *whose hydrogenolysis with lithium in liquid ammonia gave* **2** *(mp 77 °C,* $[\alpha]_D$ *+ 136° (chloroform), lit.*[5] *values for* L*-isomer, mp 70-72 °C,* $[\alpha]_D$ *- 132.7° (chloroform).*

Scheme 2



Alternatively, compound **8** *was also prepared by a different approach. For instance,* **4** *was subjected to the treatment of* N*-bromosuccinimide*[6] *in refluxing carbon tetrachloride to afford* **10** *which was reduced with Raney nickel in refluxing ethanol to produce* **11**. *The free hydroxyl group in* **11** *was protected as the benzyl ether* **12** *by using benzyl bromide-silver oxide in benzene. Usual debenzoylation of* **12** *afforded* **8**, *identical in all respects with the sample prepared above.*

EXPERIMENTAL

General Procedures. *Melting points were determined on a Buchi melting point apparatus.* ^1H *NMR spectra were recorded on a Varian FT-80A or on a Jeol PMX-90 spectrometers using TMS as internal standard. Mass spectra were recorded on a Finnigan Mat 1210 spectrometer. All the solvents were distilled before use, and petroleum ether refers to fraction, bp 60-80 °C. Evaporation of solvent was carried out on a rotary evaporator < 50 °C. Silica gel (60-120 mesh) was purchased from Acme Chemical Company.*

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-α-D-arabino-hexopyranoside (5). *To compound* **4**[4] *(6.0 g, 22.5 mmol) in dry tetrahydrofuran (40 mL) was added sodium hydride (3.0 g, 50% dispersion in oil). After stirring at room temperature for 1 h, benzyl bromide (5.1 g, 30 mmol) was added and stirred for an additional 18 h. Methanol (5 mL) was carefully introduced to decompose the excess sodium hydride, and the mixture was concentrated. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was dried, concentrated, and then purified on a column of silica gel with ethyl acetate-light petroleum (1:9) to afford* **5** *(5.9 g, 73%):*

$[\alpha]_D$ + 38° (c 1, chloroform); ^1H NMR ($CDCl_3$): δ 2.0 (m, 2H, H-2,2'), 3.34 (s, 3H, OMe), 4.65 (m, 3H, H-1, $PhCH_2$), 5.56 (s, 1H, PhCH), 7.0-8.0 (m, 10H, 2xPh). Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: C, 70.7; H, 6.5.

Methyl 3-O-benzyl-2-deoxy-4,6-di-O-mesyl-α-D-arabino-hexopyranoside (7). *Compound* **5** *(5.9 g, 16.6 mmol) was dissolved in 10% aqueous tetrahydrofuran (50 mL), and concentrated sulfuric acid (1 mL) was added. After 24 h, the reaction mixture was neutralised with barium carbonate, filtered, and concentrated. Traces of water were removed by codistillation with toluene to afford* **6** *(4.4 g, 99%).*

Compound **6** *(4.4 g, 16.4 mmol) was dissolved in pyridine (20 mL) and cooled to 0 °C. Methanesulfonyl chloride (5 mL) was added. After 3 h of stirring at room temperature, the reaction mixture was worked up in the usual fashion to give* **7** *(5.27 g, 76%): $[\alpha]_D$ + 54° (c 4, chloroform); ^1H NMR ($CDCl_3$): δ 1.35-2.55 (m, 2H, H-2,2'), 2.90, 3.05 (2s, 6H, 2xMs), 3.32 (s, 3H, OMe), 3.7-4.9 (m, 8H), 7.30 (s, 5H, Ph). Anal. Calcd. for $C_{16}H_{24}O_9S_2$: C, 45.3; H, 5.7. Found: C, 45.3; H, 5.65.*

Methyl 3-O-benzyl-2,6-dideoxy-α-D-arabino-hexopyranoside (8). *To compound* **7** *(5.27 g, 12.4 mmol) in dry tetrahydrofuran (40 mL) was added lithium aluminium hydride (3 g, 78.9 mmol) in small portions. After refluxing for 7 h, the reaction mixture was decomposed with water-saturated sodium sulfate and filtered. The precipitate was vigorously extracted with boiling tetrahydrofuran. The combined filtrates were concentrated, and the residue was purified by column chromatography on silica gel with ethyl acetate-light petroleum (1:4) to afford* **7** *(2.73 g, 87%): $[\alpha]_D$ + 42° (c 0.5, chloroform); ^1H NMR ($CDCl_3$): δ 1.20 (d, 3H, J=6 Hz, H-6,6',6''), 1.4-2.7 (m, 2H, H-2,2'), 3.15 (t, 1H, J=9 Hz, H-4), 3.30 (s, 3H, OMe), 3.6 (m, 2H, H-3,5), 4.48 (ABq, 2H, $PhCH_2$), 4.67 (bs, 1H, H-1), 7.4 (s, 5H, Ph), MS m/z 252 (M^+), 221 (M^+-OMe). Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.7; H, 7.9. Found: C, 66.4; H, 7.8.*

Methyl 2,6-dideoxy-4-O-methyl-α-D-arabino-hexopyranoside (2). *To compound* **8** *(1.7 g, 6.74 mmol) in dry tetrahydrofuran (10 mL) was added sodium hydride (0.8 g, 50% dispersion in oil). After 1 h, methyl iodide (2 mL) was introduced, and the mixture was stirred overnight. After usual work-up, the resulting crude product was purified by column chromatography on silica gel by using ethyl acetate-light petroleum (1:9) to afford* **9** *(1.6 g, 89%).*

To liquid ammonia (100 mL) was added compound **9** *(1.6 g, 6 mmol) in tetrahydrofuran (10 mL), followed by lithium metal (63 mg, 9 mmol) in small portions. After 2 h, ammonium chloride was added to the mixture and the ammonia allowed to evaporate. The reaction mixture was concentrated and partitioned between water and ethyl acetate. The ethyl acetate layer was dried, concentrated, and purified by column chromatography on silica gel with ethyl acetate-light petroleum to give* **2** *(0.9 g, 90%), crystallised from ethyl acetate-light petroleum: mp 77 °C; $[\alpha]_D$ + 136° (c 1.1, chloroform); lit.[5] values for the L-isomer: mp 70-72 °C; $[\alpha]_D$ - 132.7° (chloroform); ^1H NMR ($CDCl_3$): δ 1.31 (d, 3H, J=6 Hz, H-6,6',6''), 1.4-2.5 (m, 2H, H-2,2'), 2.71 (t, 1H, J=9 Hz, H-4), 3.34, 3.59 (2s, 6H, 2xOMe), 4.0 (m, 2H, H-3,5), 4.71 (d, 1H, J=3 Hz, H-1).*

Methyl 4-O-benzoyl-2,6-dideoxy-α-D-arabino-hexopyranoside (11): *The bromide[6]* **10** *(0.9 g, 2.6 mmol), Raney nickel (2 g), hydrazine hydrate (1 mL) in ethanol (10 mL) were heated under reflux for 8 h, filtered, and concentrated to afford* **11** *(0.65 g, 94%): $[\alpha]_D$ + 121° (c 1.7, chloroform); lit.[6] $[\alpha]_D$ + 128° (chloroform).*

Methyl 3-O-benzyl-2,6-dideoxy-α-D-arabino-hexopyranoside (8): *A mixture of compound* **11** *(0.65 g, 2.44 mmol), silver oxide (2 g), and benzyl bromide (0.41 g, 3 mmol) in dry benzene was stirred in the dark overnight. The reaction mixture was filtered through Celite and concentrated. The residue was dissolved in dry methanol, and sodium (15 mg) was added. After 3 h, the reaction mixture was deionised with Amberlite IR-120 [H^+] resin, filtered, and concentrated. The residue was purified by column chromatography on silica gel to afford* **8** *(0.32 g, 52%) identical with compound prepared above.*

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