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Synthesis of methyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside and methyl 2,4-di-*O*-methyl-3-*O*-[2-*O*-methyl-3-*O*-(2-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl]-α-L-rhamnopyranoside: di- and tri-saccharide segments of a phenolic glycolipid of *Mycobacterium kansasii*

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ABSTRACT

Syntheses of the title glycosides are described. The critical *O*-glycosylations were carried out in the presence of boron trifluoride etherate with a high degree of α-selectivity.

INTRODUCTION

Since the isolation[1] of the phenolic glycolipid of *Mycobacterium kansasii*, different structures have been proposed for the oligosaccharide moiety[2]. Brennan and coworkers[3] proposed the trisaccharide structure 2,4-di-*O*-Me-L-Rha*p*-(1→4)-2-*O*-Me-L-Fuc*p*-(1→4)-2-*O*-Me-L-Rha*p*-1-lipid. However, Fournie *et al.*[4] produced evidence for the tetrasaccharide structure 2,6-dideoxy-4-*O*-Me-*arabino*-Hex*p*-(1→3)-4-*O*-Ac-2-*O*-Me-α-L-Fuc*p*-(1→3)-2-*O*-Me-α-L-Rha*p*-(1→3)-2,4-di-*O*-Me-α-L-Rh*p*-1-lipid (**1**). The novel terminal sugar has been identified[5] as 2,6-dideoxy-4-*O*-methyl-D-*arabino*-hexopyranose and unambiguous syntheses have been reported[6,7]. We now report stereoselective syntheses of the di- (**9**) and tri-saccharide (**2**) methyl glycosides which represent the inner core of the oligosaccharide of the phenolic glycolipid*.

RESULTS AND DISCUSSION

For the synthesis of **2**, the disaccharide derivative **8** with HO-3′ unsubstituted was synthesised first. Thus, methyl 3-*O*-allyl-4-*O*-benzyl-α-L-rhamnopyranoside[8] (**3**) was methylated at O-2 with sodium hydride–methyl iodide to obtain **4** (95%). Acid hydrolysis of **4** followed by treatment with acetic anhydride–pyridine produced the 1-acetate **5**.

* A recent report [G. T. Valainis, L. M. Cardona, and D. L. Greer, *J. Acquired Immune Defic. Syndr.*, 4 (1991) 516–520] revealed that *Mycobacterium kansasii* is being observed increasingly in patients with positive HIV-I. It ranks second behind *Mycobacterium avium-intracellulare* complex and accounts for 2.9% of nontuberculous infections in patients suffering from AIDS.

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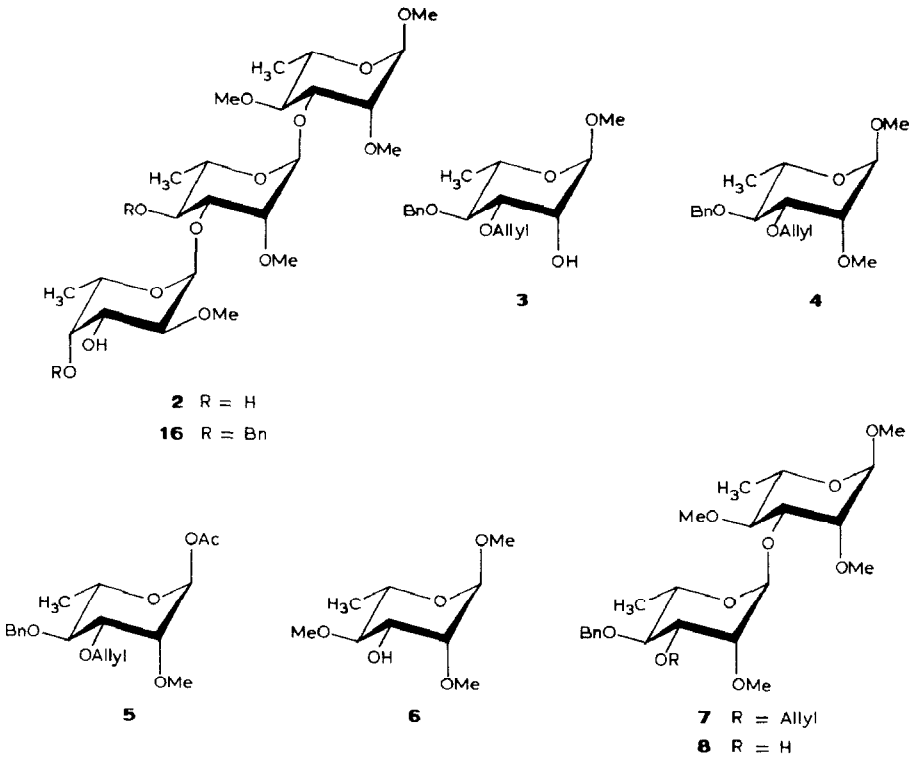
2, 6-dideoxy-4-*O*-Me-α-D-*arabino*-Hex*p*-(1→3)-4-*O*-Ac-2-*O*-Me-α-L-Fuc*p*-(1→3)-
-2-*O*-Me-α-L-Rha*p*-(1→3)-2, 4-di-*O*-Me-α-L-Rha*p*-phenoldimycocerosyl

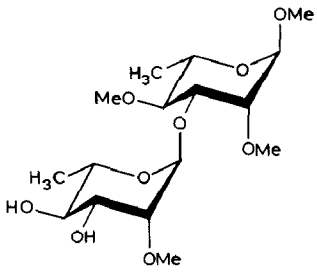
1



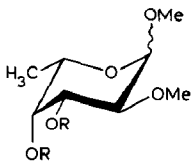
Acetylated L sugars can be used as facile glycosylation agents with high degrees of α-selectivity in the presence of boron trifluoride etherate at low temperature. Thus, **5** was reacted with methyl 2,4-di-*O*-methyl-α-L-rhamnopyranoside[11] (**6**) in the presence of boron trifluoride etherate at 0°. The allyl group in the product **7** (55%) was isomerised with tris(triphenylphosphine)rhodium(I) chloride[12] (Wilkinson's catalyst) and 1,4-diazabicyclo[2.2.2]octane followed by cleavage with mercuric chloride–mercuric oxide to afford **8**, the structure of which was confirmed by the ^{1}H- and ^{13}C-n.m.r. data. The $J_{C\text{-}1,H\text{-}1}$ and $J_{C\text{-}1',H\text{-}1'}$ values of 167 Hz indicated both the sugar moieties to be α. Debenzylation of **8** by hydrogenolysis (Pd/C) then gave the disaccharide methyl glycoside **9**.

1-*O*-Acetyl-3-*O*-allyl-4-*O*-benzyl-2-*O*-methyl-L-fucopyranose (**14**) was then synthesised starting from methyl 2-*O*-methyl-L-fucopyranoside[13] (**10**). In order to selectively protect position 3, **10** was converted into the dibutylstannyl derivative **11**, reaction of which with allyl bromide (1.5 equiv.) gave **12** (91%). Benzylation of HO-3 then gave **13**, acid hydrolysis of which followed by acetylation gave **14**.

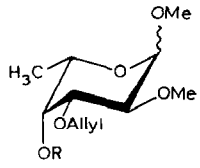
Glycosylation of **8** with **14** in the presence of boron trifluoride etherate afforded the trisaccharide derivative **15** (55%). Although the ^{1}H-n.m.r. spectrum of **15** showed the presence (10%) of **8**, purification was not necessary because, after deallylation, the



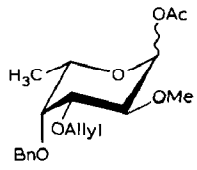
9



10 R = H
11 R = $SnBu_2$



12 R = H
13 R = Bn



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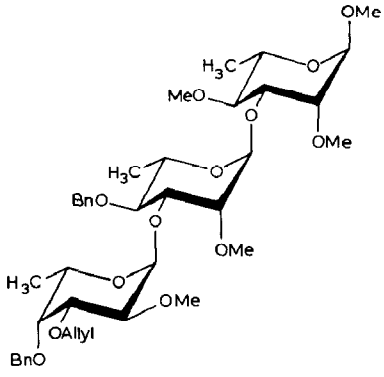

15

product **16** (65%) could be separated from **8** by chromatography. The ^{1}H-n.m.r. spectrum of **16** was in agreement with the structure depicted. Compound **16** having HO-3″ unsubstituted is suitable for a glycosylation reaction leading to the tetrasaccharide component of the phenolic glycolipid **1**.

Hydrogenolysis (Pd/C) of the benzyl ether groups in **16** completed the synthesis of **2**, the ^{1}H-n.m.r. spectrum of which contained a signal at δ 5.08 (d, $J_{1,2}$ 4 Hz) for H-1 of the fucose residue, which indicated the newly formed linkage to be α.

EXPERIMENTAL

General. — The ^{1}H and ^{13}C-n.m.r. spectra were recorded with a Varian Gemini spectrometer on solutions in $CDCl_3$ (internal Me_4Si). Optical rotations were measured at 24° with a JASCO DIP 360 polarimeter. All solvents were distilled before use. Dichloromethane was dried over calcium hydride. Silica gel (Merck, 70–230 mesh) was used for column chromatography. Reactions were monitored by t.l.c. on Silica Gel 60 F_{254} (Merck) and detection with α-naphthol.

1-O-Acetyl-3-O-allyl-4-O-benzyl-2-O-methyl-α-L-rhamnopyranose (**5**). — To a stirred solution of **3**[8] (2.3 g, 7.46 mmol) in dry tetrahydrofuran (40 mL) was added sodium hydride (0.716 g, 60% dispersion in oil). After 30 min, methyl iodide (0.55 mL,

8.94 mmol) was introduced followed, after 3 h, by methanol to decompose the excess of sodium hydride. The mixture was concentrated, the residue was partitioned between water and ethyl acetate, and the ethyl acetate layer was concentrated. Column chromatography (ethyl acetate–light petroleum, 1:9) of the residue gave methyl 3-*O*-allyl-4-*O*-benzyl-2-*O*-methyl-α-L-rhamnopyranoside (**4**; 2.30 g, 95%), isolated as a syrup, $[\alpha]_D$ −68° (*c* 1.4, chloroform). ^{1}H-N.m.r. data: δ 1.35 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6,6,6), 3.21, 3.40 (2, s, each 3 H, 2 OMe), 3.42 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.66 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 10.0 Hz, H-3), 4.14 (m, 2 H, CH_2O), 4.58, 4.90 (ABq, 2 H, PhCH_2), 4.68 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 5.12–5.34 (m, 2 H, CH_2=), 5.94 (m, 1 H, HC=), 7.3 (m, 5 H, Ph).

A mixture of **4** (1.95 g, 6.05 mmol), 1,4-dioxane (10 mL), and 1.5M sulfuric acid (10 mL) was heated at 100° for 3 h. After the usual work-up, the product (1.3 g) was treated with acetic anhydride (3 mL) and pyridine (10 mL) containing 4-dimethylaminopyridine (20 mg) for 18 h, and the mixture was then processed in the usual manner. Column chromatography (ethyl acetate–light petroleum, 1:4) of the product gave **5** (1.33 g, 63%), isolated as a syrup, $[\alpha]_D$ −54° (*c* 1.6, chloroform). ^{1}H-N.m.r. data: δ 1.30 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6,6,6), 2.05 (s, 3 H, AcO), 3.53 (s, 3 H, OMe), 4.18 (bd, 2 H, OCH_2), 4.59, 4.92 (ABq, 2 H, PhCH_2), 5.07–5.44 (m, 2 H, CH_2=), 5.89 (m, 1 H, HC=), 6.10 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 7.30 (s, 5 H, Ph).

Anal. Calc. for $C_{19}H_{26}O_6$: C, 65.1; H, 7.4. Found: C, 65.0; H, 7.25.

*Methyl 3-*O*-(4-*O*-benzyl-2-*O*-methyl-α-*L*-rhamnopyranosyl)-2,4-di-*O*-methyl-α-*L*-rhamnopyranoside* (**8**). — To a stirred mixture of **5** (0.30 g, 0.85 mmol), **6**[11] (0.15 g, 0.72 mmol), powdered molecular sieves 4A (1.5 g), and dichloromethane (15 mL) at 0° was added freshly distilled boron trifluoride etherate (20 μL). After 30 min, triethylamine (30 μL) was added, and the mixture was washed with water, dried, and concentrated. Column chromatography (ethyl acetate–light petroleum, 1:4) of the residue gave methyl 3-*O*-(3-*O*-allyl-4-*O*-benzyl-2-*O*-methyl-α-L-rhamnopyranosyl)-2,4-di-*O*-methyl-α-L-rhamnopyranoside (**7**; 0.20 g, 55%), isolated as a syrup, $[\alpha]_D$ −81° (*c* 0.7, chloroform). ^{1}H-N.m.r. data: δ 1.32, 1.34 (2 d, each 3 H, Me-5,5′), 3.16 (t, 1 H, $J_{3',4'} = J_{4',5'}$ = 10.5 Hz, H-4′), 3.35, 3.46, 3.55 (3 s, 12 H, 4 OMe), 3.85 (m, 3 H), 4.20 (m, 2 H, CH_2O), 4.62, 4.94 (ABq, 2 H, PhCH_2), 4.67 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.10 (d, 1 H, $J_{1',2'}$ 1.5 Hz, H-1′), 5.1–5.4 (m, 2 H, CH_2=), 5.97 (m, 1 H, CH=), 7.3 (m, 5 H, Ph). C.i.-mass spectrum: *m/z* 497 ($M^+ + 1$).

A mixture of **7** (0.20 g, 0.40 mmol), Wilkinson's catalyst[12] (31 mg), and 1,4-diazabicyclo[2.2.2]octane (DABCO, 69 mg) in ethanol–benzene–water (7:3:1, 11 mL) was boiled under reflux for 8 h, then concentrated. A solution of the residue in dichloromethane was washed with 0.1M hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and concentrated. A solution of the residue in water–acetone (1:4, 10 mL) was stirred with mercury(II) chloride (300 mg) at room temperature for 5 h and then filtered, the solids were washed with acetone, and the combined filtrate and washings were concentrated. Column chromatography (ethyl acetate–light petroleum, 1:1) of the residue gave **8** (0.14 g, 77%), isolated as a syrup, $[\alpha]_D$ −69° (*c* 0.8, chloroform). N.m.r. data: ^{1}H, δ 1.29, 1.34 (2 d, each 3 H, $J_{5,6} = J_{5',6'}$ = 6.5 Hz, Me-5,5′), 2.21 (bs, 1 H, OH), 3.17 (t, 1 H, $J_{3',4'} = J_{4',5'}$ = 10.5 Hz, H-4′), 3.27 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.5

Hz, H-4), 3.36, 3.46, 3.51, 3.55 (4 s, each 3 H, 4 OMe), 3.9 (m, 4 H), 4.66 (s, 1 H, H-1), 4.68, 4.91 (ABq, 2 H, PhCH_2), 5.15 (s, 1 H, $J_{1',2'} < 1.0$ Hz, H-1'), 7.3 (m, 5 H, Ph); ^{13}C, δ 97.98 (C-1), 98.22 (C-1'). C.i.-mass spectrum: *m/z* 457 ($M^+ + 1$).

Anal. Calc. for $C_{23}H_{36}O_9$: C, 60.5; H, 7.9. Found: C, 60.2; H, 7.85.

*Methyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-α-*L*-rhamnopyranosyl)-α-*L*-rhamnopyranoside* (**9**). — A solution of **8** (0.14 g, 0.308 mmol) in ethyl acetate (10 mL) was hydrogenolysed at normal temperature and pressure for 20 h in the presence of 10% Pd/C (30 mg), then filtered, and concentrated. Column chromatography (ethyl acetate–light petroleum, 4:1) of the residue gave **9** (0.11 g, 96%), isolated as a syrup, $[\alpha]_D$ −77° (*c* 1.8, chloroform). N.m.r. data: ^1H, δ 1.23, 1.28 (2 d, each 3 H, $J_{5,6}$ 6.0 Hz, Me-5,5'), 3.10 (t, 1 H, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4'), 3.28, 3.41, 3.48 (3 s, 12 H, 4 OMe), 3.70 (m, 2 H), 3.84 (dd, 1 H, $J_{3,4}$ 4.0 Hz, H-3 or H-3'), 4.60 (d, 1 H, $J_{1,2} < 1.0$ Hz, H-1), 5.10 (s, 1 H, $J_{1',2'} < 1.0$ Hz, H-1'); ^{13}C, δ 97.98 (C-1), 98.41 (C-1').

Anal. Calc. for $C_{16}H_{30}O_9$: C, 52.45; H, 8.2. Found: C, 52.0; H, 8.1.

*1-*O*-Acetyl-3-*O*-allyl-4-*O*-benzyl-2-*O*-methyl-α,β-*L*-fucose* (**14**). — The dibutylstannyl derivative **11** was prepared from **10**[13] (1.5 g, 7.8 mmol) and dibutyltin oxide (2.25 g, 9.0 mmol) in benzene (80 mL) at reflux temperature for 5 h. To this solution were added allyl bromide (1.5 mL, 17.3 mmol) and tetrabutylammonium iodide (1 g), and boiling under reflux was continued for 5 h. After the usual work-up, column chromatography (ethyl acetate–light petroleum, 1:1) of the product gave **12** (1.65 g, 91%).

Compound **12** (1.65 g, 7.1 mmol) was treated with sodium hydride (0.48 g, 60% dispersion in oil, 9.95 mmol) and benzyl bromide (1.28 g, 7.47 mmol) in dry tetrahydrofuran for 18 h at room temperature to give **13** (2.0 g, 90%), which was purified by column chromatography (ethyl acetate–light petroleum, 1:3). ^1H-N.m.r. data: δ 1.23 (t, 3 H, H-6,6,6), 3.46, 3.58, 3.60, 3.67 (4 s, 6 H, 2 OMe), 4.2 (m, 2 H, OCH_2), 4.71, 4.74, 5.03, 5.05 (4 d, 2 H, PhCH_2), 5.2–5.5 (m, 2 H, CH_2 =), 6.05 (m, 1 H, HC =), 7.4 (m, 5 H, Ph).

A mixture of **13** (2.0 g, 6.21 mmol), 1,4-dioxane (20 mL), and 1.5M sulfuric acid (20 mL) was heated at 100° for 4 h, then neutralised with barium carbonate, filtered, and concentrated. Toluene was distilled from the residue which was treated with acetic anhydride (5 mL), pyridine (10 mL), and 4-dimethylaminopyridine (20 mg) in dichloromethane (10 mL) to give **14** (1.5 g, 69%).

Anal. Calc. for $C_{19}H_{26}O_6$: C, 65.1; H, 7.42. Found: C, 64.9; H, 7.35.

*Methyl 3-*O*-[3-*O*-(3-*O*-allyl-4-*O*-benzyl-2-*O*-methyl-α-*L*-fucopyranosyl)-4-*O*-benzyl-2-*O*-methyl-α-*L*-rhamnopyranosyl]-2,4-di-*O*-methyl-α-*L*-rhamnopyranoside* (**15**). — To a stirred mixture of **14** (0.12 g, 0.34 mmol), **8** (0.080 g, 0.17 mmol), and molecular sieves 4A (0.5 g) in dichloromethane (5 mL) at −10° was added boron trifluoride ethereate (6 μL). After 30 min, triethylamine was added, and the mixture was worked-up in the usual way. Column chromatography (ethyl acetate–light petroleum, 1:3) of the product gave **15** (0.065 g, 50%), the ^1H-n.m.r. spectrum of which indicated contamination with 10% of **8**.

*Methyl 2,4-di-*O*-methyl-3-*O*-[2-*O*-methyl-3-*O*-(2-*O*-methyl-α-*L*-fucopyranosyl)-α-*L*-rhamnopyranosyl]-α-*L*-rhamnopyranoside* (**2**). — Impure **15** (0.065 g) was deallylated in the presence of Wilkinson's catalyst[12] (7 mg) and DABCO (13 mg) in ethanol–

benzene–water (5 mL, 7:3:1) for 8 h followed by treatment with mercuric chloride and mercuric oxide as described above to afford methyl 3-*O*-[4-*O*-benzyl-3-*O*-(4-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl)-2-*O*-methyl-α-L-rhamnopyranosyl]-2,4-di-*O*-methyl-α-L-rhamnopyranoside (**16**; 0.039 g, 65%). N.m.r. data: ^{1}H, δ 1.18, 1.27, 1.30, (3 d, each 3 H, $J_{5,6}$ 6.0 Hz, Me-5,5′,5″), 2.35 (d, 1 H, OH), 3.12 (t, 1 H, $J_{3',4'} = J_{4',5'} = 9.0$ Hz, H-4′), 4.56, 5.09 (ABq, 2 H, PhCH_2), 4.70, 4.90 (ABq, 2 H, PhCH_2), 4.64 (s, 1 H, $J_{1,2} < 1.0$ Hz, H-1), 5.05 (s, 1 H, $J_{1',2'} < 1.0$ Hz, H-1′), 5.17 (d, 1 H, $J_{1'',2''}$ 3.5 Hz, H-1″), 7.3 (m, 10 H, 2 Ph); ^{13}C, δ 97.6 (C-1), 98.6 (C-1′), 98.9 (C-1″).

A solution of **16** in ethyl acetate was hydrogenolysed in the presence of 10% Pd/C (15 mg) at room temperature and pressure for 20 h, then filtered. The solids were washed with ethyl acetate, and the combined filtrate and washings were concentrated. Column chromatography (ethyl acetate) of the residue gave **2** (0.026 g, 90%), isolated as a syrup, $[\alpha]_D$ − 78° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 1.27, 1.30, 1.32 (3 d, each 3 H, $J_{5,6}$ 6.0 Hz, Me-5,5′,5″), 3.12 (t, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4′), 3.32, 3.42, 3.46, 3.51 (4 s, each 3 H, 4 OMe), 4.64 (s, 1 H, $J_{1,2} < 1.0$ Hz, H-1), 5.05 (s, 1 H, $J_{1',2'} < 1.0$ Hz, H-1′), 5.08 (d, 1 H, $J_{1'',2''}$ 4.0 Hz, H-1″).

Anal. Calc. for $C_{23}H_{42}O_{13}$: C, 52.5; H, 8.0. Found: C, 52.55; H, 8.05.

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