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Synthesis of Methyl 3-O-[3-O-(2,3,4-tri-O-Methyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl]-α-L-rhamnopyranoside : The Outer Trisaccharide Unit of a Unique Mycobacterium xenopi Glycopeptidolipid

Mukund K Gurjar* and Anupama S Mainkar
Indian Institute of Chemical Technology, Hyderabad 500 007, India

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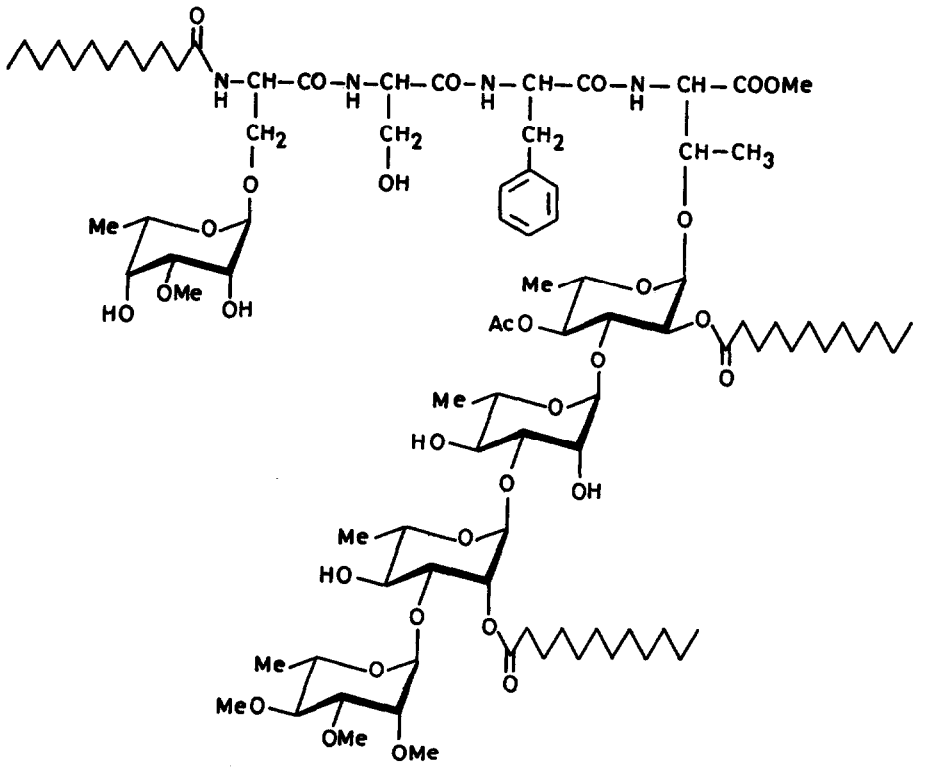
Abstract

The combination of sugars present in Mycobacterium xenopi glycopeptidolipid (GPL X-1) has been characterised as O-(2,3,4-tri-O-methyl-α-L-rhamnopyranosyl)-(1-3)-O-(α-L-rhamnopyranosyl)-(1-3)-O-(α-L-rhamnopyranosyl)-(1-3)-6-deoxy-L-glucose. Two synthetic routes (A and B) towards the outer trisaccharide segment (**2**) have been designed. Route A involved the condensation of the aglycone (**7**) with 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide (**13**) to afford **8** which was sequentially deacetylated, methylated, deallylated and reacetylated to afford **12**. Condensation of **12** with **16** in the presence of borontrifluoride etherate was unsuccessful. In route B, the disaccharide **21** was synthesised by the coupling reaction between **16** and **18** in the presence of borontrifluoride-etherate followed by deallylation. Alternatively, the disaccharide triacetate (**22**) was first prepared and routine modifications on it led to the formation of **21**. Final condensation of **21** with the trichloroacetimidate (**29**) followed by sequential deacetylation, methylation and debenzylation afforded the trisaccharide (**2**).

Introduction

The observed changes in the epidemiology of mycobacterial diseases have led to a significant increase in activity[1]. The carbohydrates that accumulate on the surface of the bacteria, are the recognised immunodominating factors. They hold tremendous promise: in developing the immunodiagnostic tool for detecting the infection at a very early stage, in improving drug chemotherapy of the disease; and in arresting the infection from spreading further. Mycobacterium (M.) xenopi is associated with pulmonary infection and recently reported as a causal agent of tuberculosis in immunocompromised patients[2].

The structure (1) of the M. xenopi glucopeptidolipid (GPL X-1) has been elucidated by chemical and spectroscopic studies[3]. The structure (1) was unique as it contained serine-serine residues in its molecular framework, while the characteristic[4] D-alanine-L-alanilol terminal core common to C-mycoside glycopeptidolipid, was absent. In addition, 6-deoxy-3-O-methyl-L-talose moiety was attached to the serine residue, an unknown feature in the mycobacterial genus. Moreover the typical[5] distal disaccharide : L-RhaP-(α 1-3)-6-deoxy-L-talP present in C-mycoside, was absent in M. xenopi. The oligosaccharide was attached to allo threonine methyl ester which now occupied the terminal position of the peptide backbone. This unique structure of GPL X-1 could find greater usefulness for species-specific recognition



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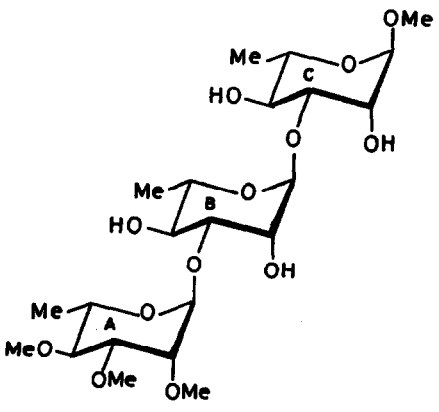
of M. xenopi. In this report we describe the stereoselective synthesis of the outer trisaccharide segment (2) as its methyl glycoside.

Results and Discussion

For the synthesis of the terminal trisaccharide : methyl 3-O-[3-O-(2,3,4-tri-O-methyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl]-α-L-rhamnopyranoside (2), we have attempted to

Scheme - 1



Route - A*

A + B → AB + C → ABC

Route - B*

B + C → BC + A → ABC

* underlined alphabets represent glycosylating moieties

2

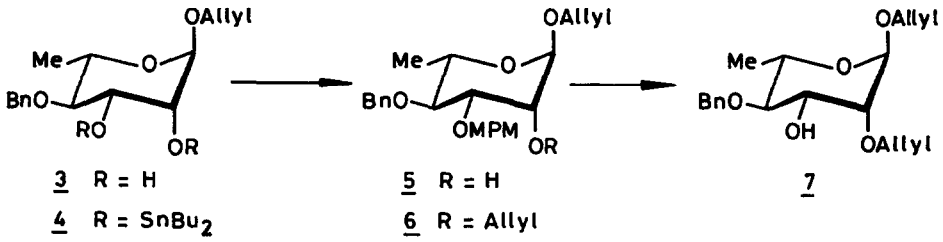
devise two synthetic routes (A and B) which mainly differ from one another by the sequence of monosaccharide assemblage (Scheme 1).

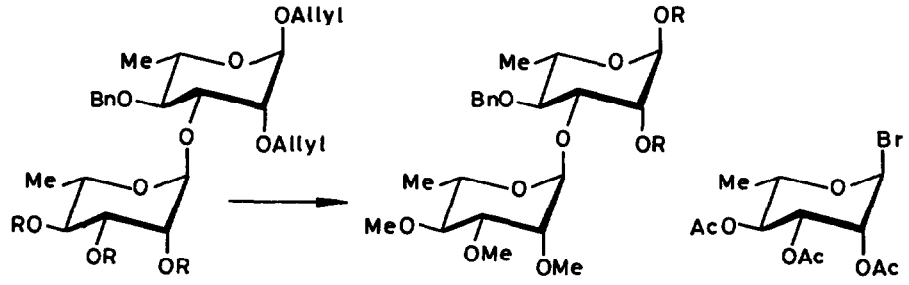
Route A

The known[6] starting material allyl 4-O-benzyl-α-L-rhamnopyranoside (**3**) was converted into the dibutylstannane acetal (**4**) with di-n-butyltin oxide in refluxing toluene with azeotropic removal of water. **4** was treated with 1.2 equivalents of p-methoxybenzyl bromide in the same solvent to provide the 3-O-p-methoxybenzylate derivative (**5**) together with traces of starting material[7]. The remaining free hydroxyl group in **5** was blocked as the allyl ether (**6**) by using sodium hydride-allyl bromide. The characteristic resonance pattern of the p-methoxybenzyl and allyl groups were seen in the ^{1}H-n.m.r. spectrum of **6**. Removal of the p-methoxybenzyl group from **6** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone provided the aglycone (**7**) (Scheme 2).

Condensation[8] of **7** with 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide (**13**) in the presence of mecuric cyanide-mercuric bromide in methylene chloride gave the disaccharide

Scheme - 2





(**8**). The partially decoupled ^{13}C-N.m.r. spectrum of **8** revealed large coupling constants (165 Hz) for both the anomeric carbons, thus confirming the α-configurations at both these centers[9]. Zemplen deacetylation of **8** with methanolic sodium methoxide gave **9** which on usual methylation with sodium hydride-methyl iodide furnished **10**. The allyl groups present in **10** were removed[10] by first refluxing with tris(triphenylphosphine)-rhodium (I) chloride

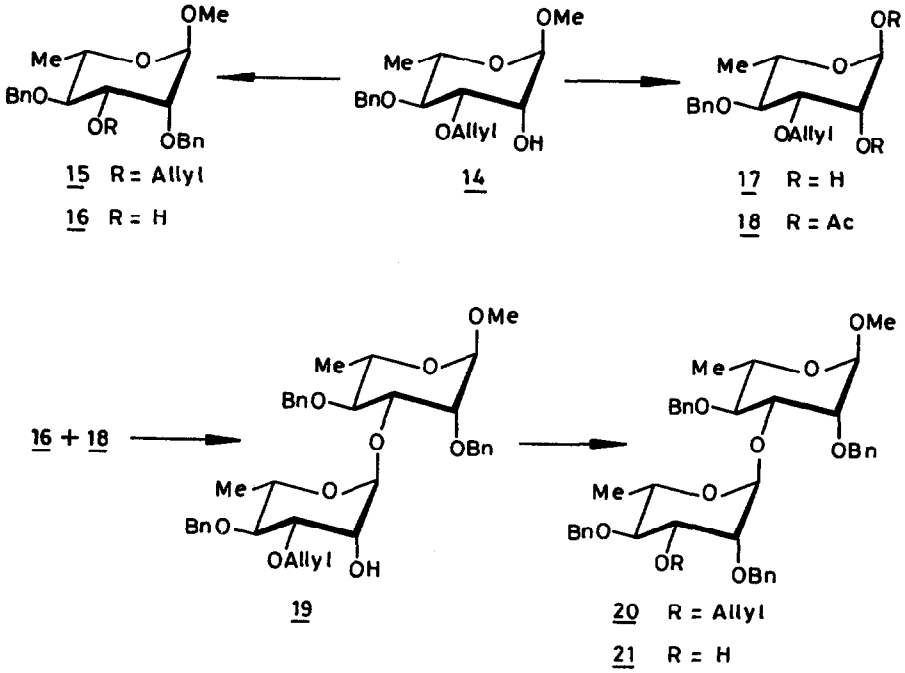
(Wilkinson's catalyst) and then by stirring with mercuric oxide-mercuric chloride in a 1:1 mixture of acetone-water to give the diol (**11**) which was acetylated to obtain **12**.

In order to prepare the aglycone **16**, methyl 3-O-allyl-4-O-benzyl-α-L-rhamnopyranoside[11] (**14**) was benzylated with sodium hydride-benzyl bromide to give **15** which was deallylated as described above to provide **16**. Condensation of **12** with **16** was carried out in the presence of borontrifluoride-etherate[12] in methylene chloride at 0°C but, as judged by t.l.c., a number of products had formed, which were not analysed. This failure was attributed to the decomposition of **12** under acidic conditions, however, it led us to device an alternate route B for the trisaccharide (**2**) synthesis.

Route B

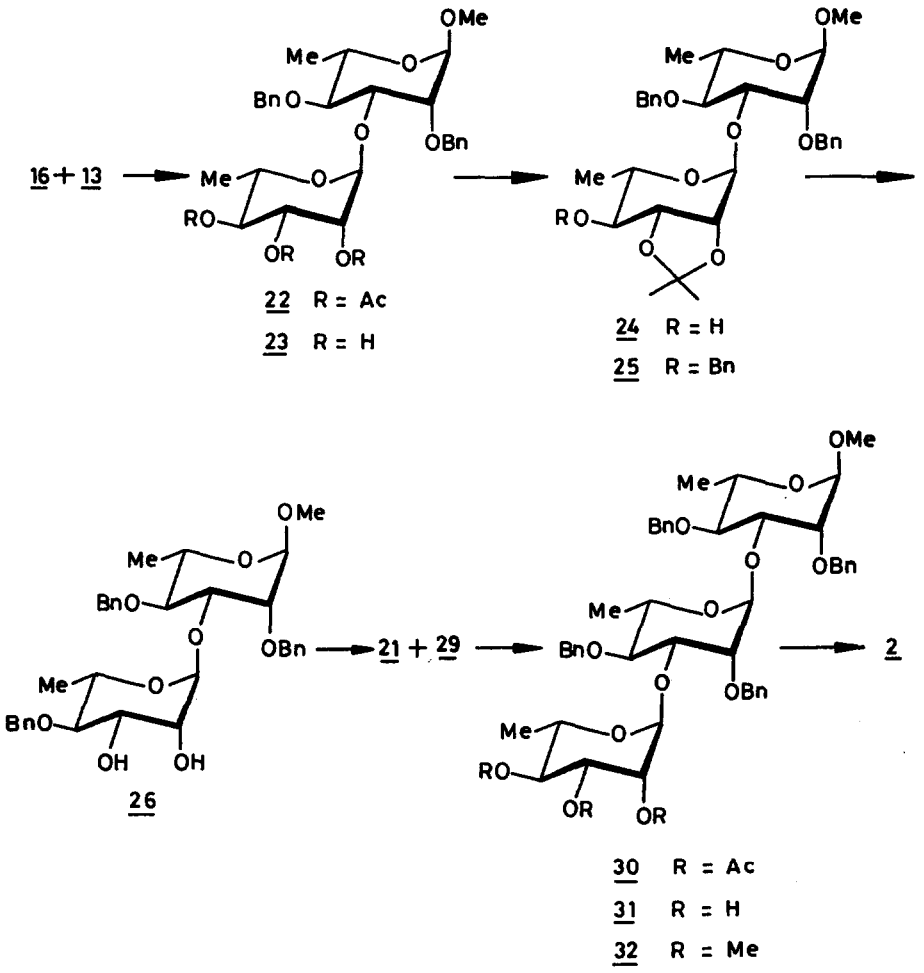
Compound **14** was hydrolysed (Scheme 3) with dilute sulfuric acid at 80°C and then acetylated to give the diacetate **18**. The coupling reaction of **18** with **16** in methylene chloride and a catalytic amount of borontrifluoride-etherate at 0°C followed by deacetylation gave the disaccharide (**19**). The α-configurations at anomeric centers were confirmed by ^{13}C-N.m.r. spectrum ($J_{C\text{-}1,H\text{-}1}$ = 167 Hz). Compound **19** was benzylated in an usual manner to give **20** which was then deallylated to provide **21**.

Scheme - 3



We have also devised an alternate pathway (Scheme 4) for compound **21** in which **16** was first coupled with **13** in the presence of mercuric cyanide in acetonitrile at ambient temperature to give **22**. The anomeric configuration of **22** was confirmed by ^{13}C-N.m.r. spec-

Scheme - 4

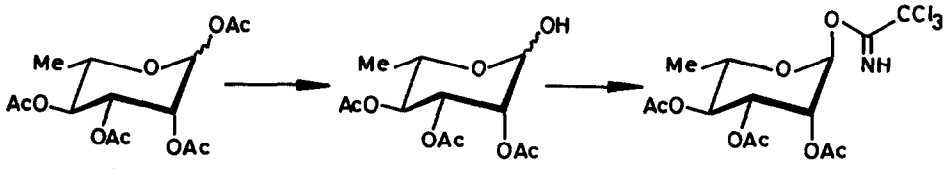


trum. Removal of the three acetyl groups with methanolic sodium methoxide gave the triol **23** which was treated with 2,2-dimethoxypropane and p-toluenesulfonic acid in methylene chloride to give **24**. The ^{1}H-N.m.r. spectrum of **24** revealed two methyl singlets of the isopropylidene group at 1.31 and 1.51 ppm. The free hydroxyl group at O-4 in **24** was protected as a benzyl ether (**25**) and then the isopropylidene group was removed by using aqueous acetic acid to afford the diol **26**. Selective benzylation of **26** was conveniently achieved by employing[13] tetra-n-butylammonium bromide and 1.2 equivalents of benzyl bromide in a mixture of 5% aqueous sodium hydroxide and methylene chloride at ambient temperature to afford **21** which was found identical with the product described above.

For the final condensation[14] reaction, we utilised 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyltrichloroacetimidate (**29**) as a glycosylating agent. The synthesis of **29** was achieved by first removing[15] the acetyl group at the anomeric carbon of α-L-rhamnopyranosyl tetraacetate

(27) with tri-n-butyltin ethoxide in ethylene dichloride under reflux followed by treatment[16] with trichloroacetonitrile and a catalytic amount of 1,8-diazabicyclo-[5.4.0]-undec-7-ene at ambient temperature for 15 min (Scheme 5). Condensation of **29** with **21** in the presence of borontrifluoride-etherate at 0°-room temperature gave **30**. The structure of **30** was unambiguously assigned by ^{1}H and ^{13}C-N.m.r. spectra. Sequential deacetylation of **30** with sodium methoxide (to **31**), methylation with sodium hydride-methyl iodide (to **32**) and debenzylation by hydrogenolysis over palladised carbon at normal pressure and temperature gave **2** in whose ^{1}H-N.m.r. spectrum (CD_3COCD_3) the anomeric protons were located at 4.54, 5.00, 5.08 ppm.

Scheme - 5



27 28 29

Experimental

Allyl 2-O-allyl-4-O-benzyl-3-O-p-methoxybenzyl-α-L-rhamnopyranoside (**6**). A solution of **3**[6] (3.4 g, 11.56 mmol) and dibutyltin oxide (4.1 g, 16.5 mmol) in dry toluene (50 mL) was heated under reflux for 3 h with azeotropic removal of water. The solution was concentrated and the residue was taken in dry N,N-dimethylformamide (40 mL) and then p-methoxybenzyl bromide (3.46 g, 17.2 mmol) was added, and heated at 90° for 3 h. It was cooled to room temperature and partitioned between ether and water, the ether layer dried and concentrated. The residue was purified on silica gel with ethyl acetate-light petroleum (1:9) as eluent to give **5** (4.0 g, 83%), as a syrup, $[\alpha]_D$ -22° (c 1.0, chloroform). ^{1}H-N.m.r. data ($CDCl_3$) : δ 1.27 (d, 3 H, J 6.5 Hz, H-6,6',6''), 2.50 (bs, 1 H, OH), 3.40 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 3.6-4.2 (m, 5 H), 3.74 (s, 3 H, OMe), 4.62, 4.87 (ABq, 2 H, $ArCH_2$), 4.60 (s, 2 H, $PhCH_2$), 4.78 (s, 1 H, H-1), 5.1-5.3 (m, 2 H, CH_2=), 5.85 (m, 1 H, HC=), 6.83, 7.23 (A_2B_2q, 4 H, Ar), 7.29 (s, 5 H, Ph).

To the solution of **5** (4.0 g, 9.66 mmol), in dry tetrahydrofuran (30 mL) was added sodium hydride (0.93 g, 80% suspension in oil). After 2 h, allyl bromide (1.0 mL, 11.5 mmol) was introduced and the solution stirred for 18 h. Methanol was added to decompose excess of sodium hydride and then concentrated. The residue was partitioned between water and ethyl acetate. The ethyl acetate layer was dried, concentrated and the residue chromatographed on silica gel with ethyl acetate-light petroleum (1:20) to give **6** (4.1 g, 93%), as a syrup, $[\alpha]_D$ -33.4° (c 5.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$) : δ 1.30 (d, 3 H, J 6.5 Hz, H-6,6',6''), 3.50 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 3.6-4.3 (m, 10 H), 4.60, 4.91 (ABq, 2 H, $ArCH_2$), 4.60 (s, 2 H, $PhCH_2$), 4.76 (s, 1 H, H-1), 5.2 (m, 4 H, 2 x CH_2=), 5.9 (m, 2 H, 2 x HC=), 6.83, 7.24 (A_2B_2q, 4 H, Ar), 7.30 (s, 5 H, Ph).

6 (4.1 g, 9.0 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.1 g) in methylene chloride were stirred at room temperature for 30 min. The solution was filtered, washed with sodium dithionate solution, sodium bicarbonate solution, water and dried. Solvent was removed and the residue chromatographed on silica gel by eluting with ethyl acetate-light petroleum (1:20) to give **7** (2.5 g, 83%), as a syrup, $[\alpha]_D$ -36.6° (c 0.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$) : δ 1.32 (d, 3 H, J 6.5 Hz, H-6,6',6''), 3.0-4.3 (m, 8 H), 4.86 (ABq, 2 H, $PhCH_2$), 4.94 (s, 1 H, H-1), 5.3 (m, 4 H, 2 x CH_2=), 5.9 (m, 2 H, 2 x HC=), 7.44 (s, 5 H, Ph). Anal. Calc. for $C_{19}H_{26}O_5$; C, 68.3; H, 7.8. Found: C, 68.1; H, 7.7.

Allyl 2-O-allyl-4-O-benzyl-3-O-(2,3,4-tri-O-methyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**10**). To a stirred solution of **7** (1.0 g, 2.99 mmol), mercuric cyanide (0.68 g), mercuric bromide (0.18 g) and 4A° molecular sieves (2 g) was added **13** (1.2 g, 3.3 mmol). The reaction mixture was stirred at room temperature overnight, filtered, washed with water, dried and concentrated. The residue was chromatographed on silica gel with ethyl acetate-light petroleum (1:5) to give **8** (1.2 g, 66%), as a syrup, $[\alpha]_D$ -58.5° (c 0.9, chloroform). N.m.r. data ($CDCl_3$) ^{1}H : δ 1.20, 1.28 (2d, 6 H, J 6.0 Hz, CH_3-5, CH_3-5'), 1.97, 2.04, 2.06 (3s, 9 H, 3 x OAc), 3.6 (m, 3 H), 3.8-4.3 (m, 6 H), 4.60, 4.80 (ABq, 2 H, $PhCH_2$), 4.77 (s, 1H, H-1), 4.9-5.5 (m, 8 H), 5.9 (m, 2 H, 2 x CH=), 7.36 (m, 5 H, Ph). ^{13}C : δ 96.4 (C-1, $J_{C-1,H-1}$ 168 Hz), 98.9 (C-1', $J_{C-1',H-1'}$ 174 Hz).

To a solution of **8** (1.2 g, 1.98 mmol) in methanol (15 mL) was added sodium (20 mg). After 3 h, the reaction mixture was neutralised with Amberlite IR 120 (H) resin, filtered and concentrated. The residue **9** was codistilled with benzene, and diluted with N,N-dimethylformamide (10 mL). Sodium hydride (0.4 g, 80% suspension in oil) was added followed after 2 h, by methyl iodide (1 mL). After 18 h the reaction mixture was worked-up in an usual fashion and the residue was chromatographed on silica gel with ethyl acetate-light petroleum (1:6) to give **10** (0.75 g, 72%).

A solution of **10** (0.75 g, 1.43 mmol), Wilkinson's catalyst (45 mg), 1,4-diazabicyclo[2.2.2]-octane (60 mg) in ethanol-benzene-water (7:3:1, 15 mL) was heated under reflux for 20 h, filtered, concentrated and partitioned between chloroform-water and the chloroform layer concentrated. The residue was dissolved in aqueous acetone (1:1, 20 mL) and then mercuric chloride (0.18 g) and mercuric oxide (50 mg) were added. After stirring for 1 h, the solution was filtered, concentrated and dissolved in chloroform, which was washed with water, dried and concentrated. The residue (0.38 g, 60%) was acetylated with acetic anhydride (3 mL) and pyridine (5 mL). After usual work-up, the residue was purified by column chromatography on silica gel by using ethyl acetate-light petroleum (1:3) to give **12** (0.4 g, 90%), as a syrup. ^{1}H-N.m.r. data ($CDCl_3$) : δ 1.23, 1.34 (2 d, 6 H, J 6.5 Hz, 5-CH_3, 5'-CH_3), 2.13, 2.20 (2s, 6 H, 2 x OAc), 3.10 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz, H-4), 3.27, 3.45, 3.53 (3s, 9 H, 3 x OMe), 4.79 (ABq, 2 H, $PhCH_2$), 5.06 (d, 1 H, J 1.3 Hz, H-1), 5.13 (m, 1 H, H-2), 6.00 (d, 1 H, J 1.5 Hz, H-1'), 7.36 (s, 5 H, Ph). Anal. Calc. for $C_{26}H_{38}O_{11}$: C, 59.3; H, 7.2. Found: C, 59.0; H, 7.15.

1,2-Di-O-acetyl-3-O-allyl-4-O-benzyl-α-L-rhamnopyranose (**18**). Methyl 3-O-allyl-4-O-benzyl-α-L-rhamnopyranoside (**14**) (5.0 g, 16.2 mmol) and 3 N sulfuric acid (25 mL) in dioxane (40 mL) were heated under reflux for 20 h, cooled and neutralised with barium carbonate. Solid was filtered, the filtrate concentrated and codistilled with toluene to remove traces of moisture. The residue (3.57 g) was acetylated with acetic anhydride (10 mL) and pyridine (15 mL). After usual work up, the residue was purified by column chromatography on silica gel by using ethyl acetate-light petroleum (1:4) to give **18** (4.3 g, 94%), as a syrup, $[\alpha]_D$ -38.5° (c 0.8, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.32 (d, 3 H, J 6.0 Hz, H-6,6',6''), 2.08, 2.17 (2s, 6 H, 2xOAc), 4.90 (ABq, 2 H, $PhCH_2$), 5.22 (m, 2 H, CH_2=), 5.9 (m, 1 H, HC=), 5.95 (d, 1 H, J 2.0 Hz, H-1), 7.28 (s, 5 H, Ph).

Methyl 2,4-di-O-benzyl-3-O-(2,4-di-O-benzyl-α-L-rhamnopyrnaosyl)-α-L-rhamnopyranoside (**21**). To a mixture of **16** (0.80 g, 2.23 mmol), **18** (1.01 g, 2.67 mmol) and 4A° molecular sieves (2 g) in methylene chloride (20 mL) at 0°C was added borontrifluoride-etherate (50 μ L). After 1 h at room temperature, potassium carbonate was added, filtered and washed with water. The organic layer was dried, concentrated and the residue was chromatographed on silica gel by eluting with ethyl acetate-light petroleum (1:10) to give a residue (0.35 g, 23%) which was stirred with methanol (10 mL) and sodium (20 mg) for 1 h, and then the reaction mixture was neutralised with Amberlite IR 120 (H) resin, filtered and concentrated. The residue purified by silica gel column chromatography with ethyl acetate-light petroleum (1:4) as eluent to give **19** (0.31 g, 96%), as a syrup, $[\alpha]_D$ -39° (c 0.5, chloroform), ^{1}H-N.m.r. data ($CDCl_3$): δ 1.23, 1.29 (2d, 6 H, J 6.0 Hz, 5-CH_3, 5'-CH_3), 3.29 (s, 3 H, OMe), 5.08 (s, 1 H, H-1), 5.2 (m, 2 H, CH_2=), 5.9 (m, 1 H, CH=), 7.3 (m, 15 H, 3xPh).

To **19** (0.31 g, 0.50 mmol) in dry tetrahydrofuran (10 mL) was added sodium hydride (0.2 g, 80% dispersion in oil) followed after 2 h by benzyl bromide (0.15 mL). After usual work up, the residue was purified by column chromatography on silica gel by eluting with

ethyl acetate-light petroleum (1:12) to give **20** (0.34, 94%), as a syrup, $[\alpha]_D$ - 39° (c 0.3, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.30 (2d, 6 H, J 6.5 Hz, 5-CH_3,5'-CH_3), 3.30 (s, 3H, OMe), 3.40-3.85 (m, 7 H), 4.0 (m, 3 H), 4.40 (s, 2 H, PhCH_2), 4.58 (s, 1 H, H-1), 4.90 (d, 1 H, 1/2 PhCH_2), 5.00-5.35 (m, 2 H, CH_2=), 5.10 (s, 1 H, H-1'), 5.9 (m, 1 H, CH=), 7.1-7.5 (m, 20 H, 4xPh).

20 (0.34 g, 0.48 mmol) was deallylated according to the procedure described earlier to afford **21** (0.21 g, 65%), as a syrup, $[\alpha]_D$ -17.2° (c 1.0, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.25, 1.28 (2d, 6 H, J 6.0 Hz, 5-CH_3, 5'-CH_3), 3.27 (t, 1 H, $J_{3,4}$=$J_{4,5}$=10.0 Hz, H-4), 3.31 (s, 3 H, OMe), 4.67 (s, 1 H, H-1), 5.11 (s, 1 H, H-1'), 7.3 (m, 20 H, 4xPh). Anal. Calc. for $C_{41}H_{48}O_9$: C, 71.9; H, 7.0. Found: C, 72.0; H, 7.05.

Methyl 2,4-di-O-benzyl-3-O-(2,4-di-O-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**21**). To a stirred solution of **16** (0.70 g, 1.95 mmol) and **13** (1.1 g, 3.14 mmol) and 4A° molecular sieves (2 g) in dry acetonitrile (50 mL) was added mercuric cyanide (1.0 g). The reaction mixture was stirred at room temperature for 3 h, filtered, washed with water, dried and concentrated. The residue was chromatographed on silica gel with ethyl acetate-light petroleum (1:4) to give **22** (0.80 g, 65%), as a syrup. ^{13}C-N.m.r. data ($CDCl_3$): δ 97.9 ($J_{C-1,H-1}$ 167 Hz), 99.8 ($J_{C-1',H-1'}$ 171 Hz).

To a solution of **22** (0.80 g, 1.27 mmol) in methanol (10 mL) was added sodium (20 mg). After 2 h, the reaction mixture was neutralised with Amberlite IR 120 (H) resin, filtered and concentrated. The residue was chromatographed on silica gel with methanol-chloroform (1:20) to give **23** (0.60 g, 94%), as a syrup, $[\alpha]_D$ -32° (c 0.6, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.19, 1.29 (2d, 6 H, J 6.5 Hz, 5-CH_3, 5'-CH_3), 2.40 (bs, OH), 3.31 (s, 3 H, OCH_3), 3.20-3.85 (m, 10 H), 3.97 (dd, 1 H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 4.61 (s, 1 H, H-1), 4.63 (ABq, 2 H, PhCH_2), 4.66 (s, 2 H, PhCH_2), 5.00 (s, 1 H, H-1), 7.35 (m, 10 H, 2 Ph).

To a solution of **23** (0.60 g, 1.2 mmol) in dry dichloromethane (15 mL) was added 2,2-dimethoxypropane (0.5 mL) and p-toluenesulphonic acid (20 mg). After 3 h, the reaction mixture was neutralised with triethylamine (0.5 mL), concentrated and chromatographed on silica gel with ethyl acetate-light petroleum (1:5) to give **24** (0.56 g, 85%), as a syurp, $[\alpha]_D$ -11° (c 1.4, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.19, 1.30 (2d, 6 H, J 6.0 Hz, 5-CH_3, 5'-CH_3), 1.31, 1.51 (2s, 6 H, Me_2C), 3.34 (s, 3 H, OMe), 3.6 (m, 4 H), 4.1 (m, 3H), 4.59 (s, 1H, H-1), 4.61, 4.76 (ABq, 2H, PhCH_2), 4.65 (ABq, 2 H, PhCH_2), 5.21 (s, 1 H, H-1), 7.3 (m, 10 H, 2 Ph).

Compound **24** (0.56 g, 1.02 mmol) was taken in dry tetrahydrofuran (40 mL) and sodium hydride (0.15 g, 80% suspension in oil) was added followed after 2 h, by benzyl bromide (0.2 mL). After 18 h, the reaction mixture was worked in an usual fashion and the residue chromatographed on silica gel with ethyl acetate-light petroleum (1:10) to give **25** (0.60 g, 92%), as a syrup, $[\alpha]_D$ -23° (c 0.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.17, 1.28 (2d, 6 H, J 6.5 Hz, 5-CH_3, 5'-CH_3), 1.38, 1.46 (2s, 6 H, Me_2C), 3.13 (dd, 1 H, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.65 (m, 4 H), 4.08 (dd, 1H, J 3.0 Hz, 10.0 Hz, H-3'), 4.58, 4.73, 4.79, 4.99 (2ABq, 4 H, PhCH_2), 4.59 (s, 1H, H-1), 4.62 (s, 2H, PhCH_2), 5.23 (s, 1H, H-1'), 7.3 (m, 15 H, 3xPh).

Compound **25** (0.60 g, 0.90 mmol) was taken in aqueous acetic acid (60%, 10 mL) and heated at 70° for 18 h. The reaction mixture was diluted with water, neutralised with sodium bicarbonate and then extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated, and the residue chromatographed on silica gel with methanol-chloroform (1:50) to give **26** (0.40 g, 70%), as a syrup, $[\alpha]_D$ -30.5° (c 0.4, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.24, 1.31 (2d, 6 H, J 6.5 Hz, 5-CH_3, 5'-CH_3), 3.29 (t, 1 H, $J_{3,4}$=$J_{4,5}$= 10.0 Hz, H-4), 3.30 (s, 3 H, OMe), 3.45-3.89 (m, 6 H), 3.47 (dd, 1 H, $J_{2,3}$ = 3.5, $J_{3,4}$ = 9.0 Hz, H-3), 4.63 (d, 1 H, J 1.5 Hz, H-1), 4.71, 4.75 (2s, 4 H, 2xPhCH_2), 4.73 (ABq, 2 H, PhCH_2), 5.00 (s, 1 H, H-1'), 7.32 (m, 15 H, 3xPh).

A solution of **26** (0.40 g, 0.66 mmol) in dichloromethane (10 mL), sodium hydroxide solution (4 mL, 5%), tetra-n-butylammoniumbromide (50 mg) and benzyl bromide (0.2 mL, 1.54 mmol) was vigorously stirred for 48 h. The organic layer was separated and aqueous layer extracted with dichloromethane. The combined organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel by eluting with ethyl

acetate-light petroleum (1:10) to give **21** (0.27 g, 60%), as a syrup, $[\alpha]_D$ -19° (c 1.0, chloroform). The sample was identical with the compound reported above.

2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**29**): A solution of 1,2,3,4-tetra-O-acetyl-α-L-rhamnopyranose (**27**) (1.0 g, 3.01 mmol), tri-n-butyltin ethoxide (1.2 mL) in dichloroethane (15 mL) was heated under reflux for 3 h and then concentrated. The residue was purified by column chromatography on silica gel by eluting with ethyl acetate- light petroleum (1:5) to give **28** (0.80 g, 92%), m.p. 107°C. ^{1}H-N.m.r. data ($CDCl_3$) (α-anomer): δ 1.21 (d, 3 H, J 6.5 Hz, H-6,6',6"), 2.00, 2.06, 2.18 (3s, 9 H, 3xOAc), 2.92 (d, 1 H, OH), 4.15 (m, 1 H, H-5), 5.02 (t, 1 H, $J_{3,4}=J_{4,5}$=10.0 Hz, H-4), 5.10 (bs, 1 H, H-1), 5.25 (m, 1 H, H-2), 5.33 (dd, 1 H, $J_{2,3}$ = 3.0, $J_{3,4}$=10.0 Hz, H-3).

A mixture of **28** (0.20 g, 0.69 mmol), 1,8-diazabicyclo[5.4.0]- undec-7-ene (0.1 mL) and trichloroacetonitrile (0.5 mL) in methylene chloride (10 mL) was stirred for 30 min and then poured over dry silica gel column. Eluting with methylene chloride gave **29** (0.28 g, 94%) as a syrup which was used for the next reaction with delay.

Methyl 3-O-[3-O-(2,3,4-tri-O-methyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl]-α-L-rhamnopyranoside (**2**): To a solution of **21** (0.27 g, 0.4 mmol), **29** (0.28 g, 0.64 mmol) and 4A° molecular sieves (1 g) in dichloromethane at 0°C was added borontrifluoride-etherate (50 L). After 3 h at room temperature, the reaction mixture was decomposed by adding potassium carbonate, filtered and concentrated. The residue was chromatographed on silica gel by using ethyl acetate-light petroleum (1:10) as eluent to get **30** (0.30 g, 67%) as a syrup, $[\alpha]_D$ -30° (c 1.0, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.26, 1.30 (2d, 9 H, J 6.0 Hz, 5-CH_3, 5'-CH_3, 5"-CH_3), 1.96 (s, 6 H, 2xOAc)), 2.06 (s, 3 H, OAc), 3.30 (s, 3 H, OMe), 3.65 (m, 7 H), 4.05 (m, 2 H), 4.16, 4.40 (ABq, 2 H, $PhCH_2$), 4.60 (s, 1 H, H-1), 4.66 (m, 4 H, $PhCH_2$), 4.70, 4.82 (ABq, 2 H, $PhCH_2$), 5.00 (s, 1 H, H-1'), 5.13 (s, 1 H, H-1"), 5.3 (m, 3 H, H-2",3",4"), 7.35 (m, 20 H, 4xPh).

To the above product **30** (0.30 g, 0.31 mmol) in methanol (10 mL) was added sodium (20 mg). After 2 h, the reaction mixture was deionised with Amberlite IR 120 (H) resin, filtered and concentrated. The residue (**31**) was codistilled with benzene and diluted with N,N-dimethylformamide (10 mL). Sodium hydride (0.2 g, 80% dispersion in oil) was added followed by after 2 h by methyl iodide (0.5 mL). After 18 h, the reaction mixture was worked-up as usual and the residue was chromatographed on silica gel by using ethyl acetate- light petroleum (1:50) to give **32** (0.19 g, 75%), as a syrup, $[\alpha]_D$ -30.5° (c 1.0, chloroform). N.m.r. data ($CDCl_3$) ^{1}H: δ 1.18, 1.24, 1.28 (3d, 9 H, J 6.0 Hz, 5-CH_3, 5'-CH_3, 5"-CH_3), 3.09 (t, 1 H, $J_{3,4}=J_{4,5}$=9.0 Hz, H-4"), 3.16, 3.31, 3.42, 3.50 (4s, 12 H, 4xOMe), 3.7 (m, 7 H), 4.08 (dd, 1 H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 4.18 (dd, 1 H, $J_{2',3'}$= 3.0, $J_{3',4'}$=9.0 Hz, H-3'), 4.34 (ABq, 2 H, $PhCH_2$), 4.5-4.9 (m, 7 H, 3x$PhCH_2$+H-1), 5.13 (s, 2 H, H-1', H-1"), 7.35 (m, 20 H, 4xPh), ^{13}C: δ 98.4 (C-1, $J_{C-1,H-1}$ 166 Hz), 98.6 (C-1', $J_{C-1',H-1'}$ 166 Hz), 99.3 (C-1", $J_{C-1",H-1"}$ 170 Hz).

A solution of **32** (70 mg, 0.08 mmol), 10% Pd-C (40 mg) in ethanol (2 mL) was hydrogenated at normal pressure and temperature for 96 h, filtered and concentrated. The residue was chromatographed on silica gel by using methanol-chloroform (1:50) as eluent to give **2** (25 mg, 61%), as a syrup, $[\alpha]_D$ -120° (c 0.4, methanol). N.m.r. data (CD_3COCD_3) ^{1}H: δ 1.17, 1.21, 1.22 (3d, 9 H, J 6.0 Hz, 5-CH_3, 5'-CH_3, 5"-CH_3), 3.28 (t, 1 H, $J_{3,4}=J_{4,5}$=10.0 Hz, H-4), 3.32, 3.37, 3.40, 3.45 (4s, 12 H, 4xOMe), 3.5-4.3 (m, 12 H), 4.54 (s, 1 H, H-1), 5.00 (d, 1 H, J 1.1 Hz, H-1'), 5.08 (d, 1 H, J 1.1 Hz, H-1"); ^{13}C: δ 100.24 (C-1), 101.95 (C-1'), 103.41 (C-1"). Anal. Calcd. for $C_{22}H_{40}O_{13}$: C, 51.5; H, 7.8. Found: C, 51.15; H, 7.7.

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