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Synthesis of *p*-trifluoroacetamidophenyl 6-deoxy-2-*O*-{3-*O*-[2-*O*-methyl-3-*O*-(2-*O*-methyl-α-D-rhamnopyranosyl)-α-L-fucopyranosyl]-α-L-rhamnopyranosyl}-α-L-talopyranoside: a spacer armed tetrasaccharide glycopeptidolipid antigen of *Mycobacterium avium* serovar 20

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ABSTRACT

The synthesis of the title tetrasaccharide glycoside **38** is reported. *p*-Nitrophenyl *endo*-3,4-*O*-benzylidene-6-deoxy-α-L-talopyranoside (**4**), 3-*O*-acetyl-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl trichloroacetimidate (**7**), methyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-1-thio-β-L-fucopyranoside (**15**), 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl bromide (**16**), and ethyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-1-thio-α-D-rhamnopyranoside (**33**) were prepared as intermediates. Compound **4** was glycosylated with imidate **7** as well as with methyl 3-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (**9**), affording the same disaccharide derivative **8**. Deacetylation of **8** gave crystalline **17**. Condensation of **17** with both fucosyl donors **15** and **16** yielded the same trisaccharide derivative **18** stereoselectively. Compound **18** was also prepared by the coupling of **4** with disaccharide glycosyl donor **20**. After deacetylation of **18** (→ **34**), methyl triflate-promoted glycosylation with compound **33** resulted in tetrasaccharide **35**. Conversion of the *p*-nitrophenyl group of **35** into the *p*-trifluoroacetamidophenyl group (→ **36**) and removal of the protecting groups gave the title tetrasaccharide glycoside **38**.

INTRODUCTION

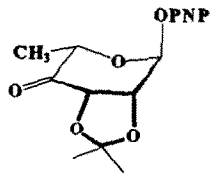
The type-specific surface antigens of the *Mycobacterium avium–M. intracellulare–M. scrofulaceum* (MAIS) serocomplex are glycopeptidolipids (GPLs) in which the outer mono- or oligo-saccharide residues are responsible for the specific immunoreactions[1]. The growing interest in members of the MAIS complex originates mainly from the occurrence of several serovariants as opportunistic pathogens in persons with acquired immunodeficiency syndrome (AIDS)[2]. Recently, a similar observation has also been made in the case of *M. kansasii*[3]. Among the structurally established antigens of the MAIS serogroup, the serovar 20 has one of the most complex structures: 2-*O*-Me-α-D-Rha*p*-(1 → 3)-2-*O*-Me-α-L-Fuc*p*-(1 → 3)-α-L-Rha*p*-(1 → 2)-6d-α-L-Tal*p*-(1 → Tetrapeptide)[4]. The reducing disaccharide unit

[α-L-Rha*p*-(1 → 2)-6d-α-L-Tal*p*-(1 →] is the so-called conservative core-region and its synthesis has been published[5]. We wished to prepare the tetrasaccharide hapten in the form of the glycoside **38** suitable for coupling to proteins. Our strategy was to use benzyl or benzyl-equivalent persistent protecting groups in the synthesis in order to be able to remove them under mild conditions in the last step of the synthetic procedure.

RESULTS AND DISCUSSION

For the synthesis of the title tetrasaccharide glycoside **38**, the following intermediates were chosen to meet our criteria: *p*-nitrophenyl *endo*-3,4-*O*-benzylidene-6-deoxy-α-L-talopyranoside (**4**), 3-*O*-acetyl-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl trichloroacetimidate (**7**), methyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-1-thio-β-L-fucopyranoside (**15**), 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl bromide (**16**), and ethyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-1-thio-α-D-rhamnopyranoside (**33**).

p-Nitrophenyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[6,7] was oxidised by pyridinium dichromate to obtain *p*-nitrophenyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose (**1**) in crystalline form, which was reduced by $NaBH_4$ to *p*-nitrophenyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**2**). The crystalline **2** was hydrolysed and *p*-nitrophenyl 6-deoxy-α-L-talopyranoside (**3**) was isolated. Kinetically controlled benzylidenation[8] of **3** resulted in compound **4** exclusively (δ_H: 5.78; δ_C: 104.30 ppm; acetalic proton[9] and acetalic carbon, respectively). A suitably substituted rhamnosyl donor **7** was prepared from 2,4-di-*O*-benzyl-L-rhamnose[10] by acetylation, giving 1,3-di-*O*-acetyl-2,4-di-*O*-benzyl-α-L-rhamnopyranose (**5**), followed by the removal of the anomeric acetyl group using hydrazine acetate[11], yielding 3-*O*-acetyl-2,4-di-*O*-benzyl-L-rhamnose (**6**), which was converted into **7** by treatment with trichloroacetonitrile in the presence of DBU[12]. The trimethylsilyl triflate-catalysed glycosylation of **4** with the imidate **7** at low temperature (−50°C) resulted in *p*-nitrophenyl 2-*O*-(3-*O*-acetyl-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-*endo*-3,4-*O*-benzylidene-6-deoxy-α-L-talopyranoside (**8**). Under these reaction conditions, no isomerisation of the benzylidene ring occurred (δ_H: 5.80 and δ_C: 104.65 ppm), and only the α-anomeric interglycosidic bond was formed. Compound **8** was also obtained when methyl 3-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside[13] (**9**) was used as glycosyl donor and activated[14] by methyl triflate. The yield of this latter coupling reaction (65–70%) was comparable with the yield of the imidate procedure. Saponification (Zemplén) of compound **8** afforded crystalline *p*-nitrophenyl *endo*-3,4*O*-benzylidene-6-deoxy-2-*O*-(2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-talopyranoside (**17**), the ideal glycosyl acceptor for the synthesis of higher oligosaccharides containing this conservative core-region. The third synthon, compound **15**, was prepared by the following route: methyl 1-thio-β-L-fucopyranoside[15] was converted into the 3,4-*O*-isopropylidene



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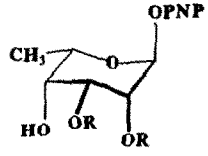
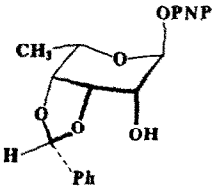


2 R,R = Ip
3 R = H



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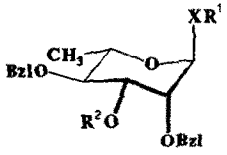
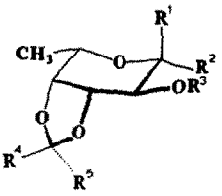
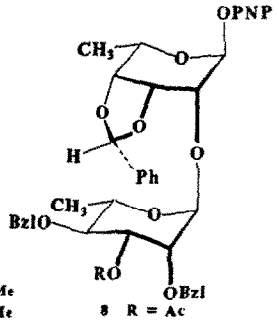


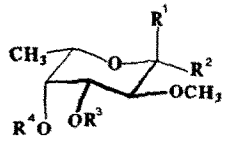
5 $R^1 = R^2 = Ac$; X = O
6 $R^1 = H$; $R^2 = Ac$; X = O
7 $R^1 = HN{=}C{-}CI_3$; $R^2 = Ac$; X = O
9 $R^1 = Me$; $R^2 = Ac$; X = S
19 $R^1 = Me$; $R^2 = H$; X = S



10 $R^1 = R^3 = H$; $R^2 = SMe$; $R^4 = R^5 = Me$
11 $R^1 = H$; $R^2 = SMe$; $R^3 = R^4 = R^5 = Me$
13 $R^1 = R^4 = H$; $R^2 = SMe$; $R^3 = Me$; $R^5 = Ph$

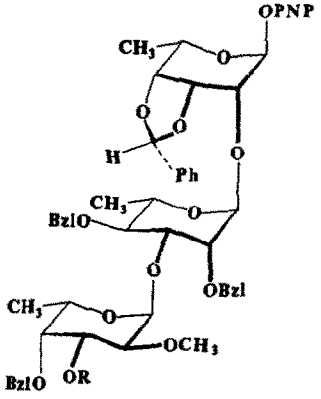


8 R = Ac
17 R = H



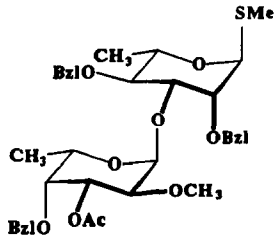
12 $R^1 = R^3 = R^4 = H$; $R^2 = SMe$
14 $R^1 = R^2 = H$ $R^2 = SMe$; $R^4 = Bzl$
15 $R^1 = H$; $R^2 = SMe$; $R^3 = Ac$; $R^4 = Bzl$
16 $R^1 = Br$; $R^2 = H$; $R^3 = Ac$; $R^4 = Bzl$

PNP = *p*-Nitrophenyl



18 R = Ac
34 R = H

derivative[16] (**10**), and the free HO-2 was methylated to obtain methyl 3,4-*O*-isopropylidene-2-*O*-methyl-1-thio-β-L-fucopyranoside (**11**). Acid hydrolysis of the isopropylidene group gave methyl 2-*O*-methyl-1-thio-β-L-fucopyranoside (**12**) which was an excellent derivative for kinetically controlled benzylidenation[8], giving rise to methyl *endo*-3,4-*O*-benzylidene-2-*O*-methyl-1-thio-β-L-fucopyranoside (**13**). Its reductive ring opening[17] resulted in methyl 4-*O*-benzyl-2-*O*-methyl-1-thio-β-L-fucopyranoside (**14**) exclusively. Conventional acetylation of **14** yielded methyl



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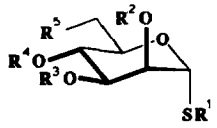
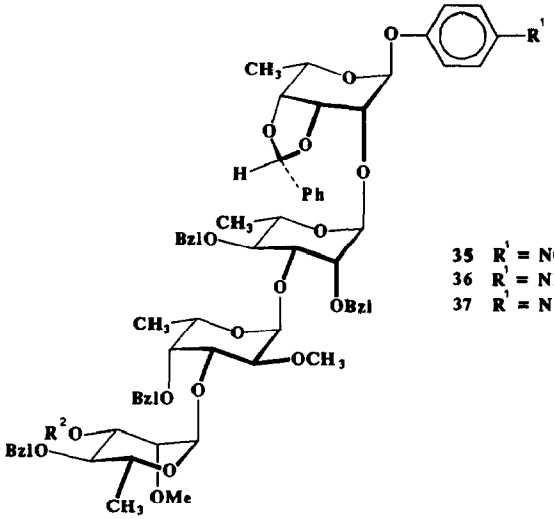


21 R^1 = Ph; R^2 = R^3 = R^4 = H; R^5 = OTs
22 R^1 = Ph; R^2, R^3 = Ip; R^4 = H; R^5 = OTs
23 R^1 = Ph; R^2, R^3 = Ip; R^4 = H; R^5 = H
24 R^1 = Ph; R^2, R^3 = Ip; R^4 = Bzl; R^5 = H
25 R^1 = Ph; R^2 = R^3 = H; R^4 = Bzl; R^5 = H
26 R^1 = Ph; R^2 = Me; R^3 = H; R^4 = Bzl; R^5 = H
27 R^1 = Ph; R^2 = Me; R^3 = Ac; R^4 = Bzl; R^5 = H
28 R^1 = Et; R^2 = R^3 = R^4 = H; R^5 = OTs
29 R^1 = Et; R^2, R^3 = Ip; R^4 = H; R^5 = OTs
30 R^1 = Et; R^2, R^3 = Ip; R^4 = H; R^5 = H
31 R^1 = Et; R^2 = R^3 = H; R^4 = Bzl; R^5 = H
32 R^1 = Et; R^2 = Me; R^3 = H; R^4 = Bzl; R^5 = H
33 R^1 = Et; R^2 = Me; R^3 = Ac; R^4 = Bzl; R^5 = H



35 R^1 = NO_2; R^2 = Ac
36 R^1 = $NHCOCF_3$; R^2 = Ac
37 R^1 = $NHCOCF_3$; R^2 = H

38 2-OMe-α-D-Rha*p*-(1 → 3)-2-OMe-α-L-Fuc*p*-(1 → 3)-α-L-Rha*p*-(1 → 2)-6d-α-L-Tal*p*-(1 → OPTFAAP)
PTFAAP = *p*-Trifluoroacetamidophenyl

3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-1-thio-β-L-fucopyranoside (**15**) which was one of our fucosyl donors. Compound **15** was converted into the bromo sugar derivative (**16**) by bromine[18]. Both glycosyl donors (**15** and **16**) were used for coupling. The reaction of **17** with **15** was promoted by $CuBr_2$–Bu_4NBr[19] to give *p*-nitrophenyl 2-*O*-[3-*O*-(3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl]-*endo*-3,4-*O*-benzylidene-6-deoxy-α-L-talopyranoside (**18**) in a yield of 63%. Condensation of **17** with **16**, using Bu_4NBr as a promoter, resulted in

trisaccharide derivative **18** in a yield of 71%. Under these conditions, no isomerisation of the benzylidene ring occurred and only the 1,2-*cis*-fucopyranoside derivative was formed. The complete assignment of the ^{13}C NMR spectra of the trisaccharide **18** confirmed this finding. Compound **18** was also prepared by block-synthesis. The disaccharide glycosyl donor (**20**) was obtained in the following way: methyl 2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside[13] (**19**) was glycosylated with bromide **16** under the Lemieux[20] conditions to give methyl 3-*O*-(3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-α-L-fucopyranosyl)-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (**20**). The structure of **20** was established by ^{13}C NMR spectroscopy. Condensation of compound **4** with disaccharide donor **20**, with methyl triflate as promoter, afforded trisaccharide derivative **18**. Although the synthesis of 2-*O*-methyl-D-rhamnose was reported[21] to give the suitably protected fourth synthon with glycosyl donor as well as glycosyl acceptor ability, we worked out a new procedure. Phenyl 1-thio-α-D-mannopyranoside[22,23] was converted into phenyl 6-*O*-(*p*-toluenesulfonyl)-1-thio-α-D-mannopyranoside (**21**), which was isopropylidenated with 2,2-dimethoxypropane (→ **22**) and then reduced to phenyl 2,3-*O*-isopropylidene-1-thio-α-D-rhamnopyranoside (**23**). Benzylation of **23** gave phenyl 4-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-D-rhamnopyranoside (**24**). Acid hydrolysis of the isopropylidene group (→ **25**), followed by a phase-transfer mediated methylation of the axial OH group (→ **26**), and conventional acetylation of **26** resulted in phenyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-1-thio-α-D-rhamnopyranoside (**27**). Some pilot experiments showed that glycosylation reactions with **27** proceeded very slowly and yields were low to moderate. To overcome this difficulty, a synthon similar to **27** was prepared, with thioethyl in place of thiophenyl. Ethyl 1-thio-α-D-mannopyranoside[22,24] was selectively tosylated at position 6. The ethyl 6-*O*-(*p*-toluenesulphonyl)-1-thio-α-D-mannopyranoside (**28**) was isopropylidenated (→ **29**), then reduced to the corresponding D-rhamnose derivative **30**. Compound **30** was benzylated at position 4 and the isopropylidene group was hydrolysed to give ethyl 4-*O*-benzyl-1-thio-α-D-rhamnopyranoside (**31**). Methylation under phase-transfer catalysed conditions[25] afforded ethyl 4-*O*-benzyl-2-*O*-methyl-1-thio-α-D-rhamnopyranoside (**32**). Conventional acetylation of **32** gave ethyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-methyl-1-thio-α-D-rhamnopyranoside (**33**), which proved to be a suitable glycosyl donor for the preparation of our target tetrasaccharide derivative. The glycosyl acceptor was obtained by the removal of the temporary acetyl protecting group from compound **18** (→ **34**). Methyl triflate-promoted glycosylation[14] of **34** with **33** gave the fully protected tetrasaccharide **35**. The nitro group in compound **35** was reduced using Adams' catalyst[26] and the resulting amino group was acylated with trifluoroacetic anhydride to obtain the *p*-trifluoroacetamidophenyl derivative (**36**) of the blocked haptenic tetrasaccharide. The acetyl group of **36** was removed (→ **37**) and compound **37** subjected to hydrogenolysis in the presence of 10% Pd-on-carbon catalyst. The smooth removal of the benzyl as well as the benzylidene groups gave the desired target compound **38**. The conjugation of these types of glycosides to proteins is well-documented[27].

EXPERIMENTAL

General methods.—Melting points (uncorrected) were determined on a Kofler apparatus. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker WP-200 SY (^{1}H, 200 MHz) spectrophotometer for solutions in $CDCl_3$ (internal Me_4Si) or in D_2O (internal, 1,4-dioxane). Reactions were monitored by TLC on Kieselgel G F_{254} (Merck) with detection by charring with H_2SO_4 after examination under UV light. Column chromatography was performed on Kieselgel G (Reanal) or Kieselgel 60 (Merck). All solvents were distilled from appropriate drying agents.

p-*Nitrophenyl 6-deoxy-2,3-*O*-isopropylidene-α-*L*-lyxo-hexopyranosid-4-ulose* (**1**).—Pyridinium dichromate (16.6 g, 44 mmol) and molecular sieves (4A, 8 g) were added to a stirred solution of *p*-nitrophenyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[7] (5.0 g, 15.37 mmol) in dry CH_2Cl_2 (60 mL). The reaction mixture was stirred for 1.5 h at room temperature, filtered through a bed of Celite, and evaporated. Column chromatography of the residue resulted in crystalline **1** which was recrystallised from EtOH; **1** (4.03 g, 81%) had mp 101°C; $[\alpha]_D$ −182° (*c* 0.55, $CHCl_3$), R_f 0.73 (95:5 CH_2Cl_2–EtOAc); ν_{max}^{KBr} 1740 cm^{-1} (C=O). NMR data ($CDCl_3$): ^{1}H, δ 8.24 and 7.19 (2 m, each 2 H, aromatic), 5.78 (bs, 1 H, H-1) 4.72–4.58 (m, 2 H, H-2,3), 4.19 (q, 1 H, H-5), 1.56 and 1.43 (2 s, each 3 H, CMe_2), 1.4 (d, 3 H, $J_{5,6}$ 7.0 Hz, H-6). Anal. Calcd for $C_{15}H_{17}NO_7$: C, 55.72; H, 5.30. Found: C, 55.70; H, 5.32.

p-*Nitrophenyl 6-deoxy-2,3-*O*-isopropylidene-α-*L*-talopyranoside* (**2**).—Compound **1** (3.9 g, 12.06 mmol) was dissolved in 1:1 CH_2Cl_2–MeOH (60 mL), and $NaBH_4$ (700 mg, 18.5 mmol) was added. After 5 min of stirring, TLC showed the complete disappearance of **1**. The mixture was diluted with CH_2Cl_2 (150 mL), washed with water (3 × 50 mL), dried (Na_2SO_4), and evaporated to give a crystalline residue. GLC investigation showed that **2** and the corresponding *rhamno* epimer were produced in a ratio of 98:2. Recrystallisation of the crude product from EtOH yielded **2** (3.32 g, 85%); mp 52–53°C; $[\alpha]_D$ −115° (*c* 1.18, $CHCl_3$); R_f 0.64 (9:1 CH_2Cl_2–EtOAc). NMR data ($CDCl_3$): ^{1}H, δ 8.22 and 7.17 (2 m, each 2 H, aromatic), 5.88 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.45-4.29 (m, 2 H, H-2,3), 3.93 (m, 1 H, H-5), 3.71 (m, 1 H, H-4), 2.38 (d, 1 H, OH, disappeared after addition of D_2O), 1.62 and 1.46 (2 s, each 3 H, CMe_2), 1.32 (d, 3 H, H-6). Anal. Calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.89. Found: C, 55.42; H, 5.85.

p-*Nitrophenyl 6-deoxy-α-*L*-talopyranoside* (**3**).—A solution of **2** (3.0 g, 9.22 mmol) in 6:4 acetic acid–water (60 mL) was kept at 60°C for 2 h, then concentrated. Toluene (3 × 10 mL) was evaporated from the residue, which was crystallised from EtOH to give **3** (2.34 g, 89%), mp 144°C; $[\alpha]_D$ −162° (*c* 0.89, MeOH); R_f 0.66 (85:15 CH_2Cl_2–MeOH). NMR data (D_2O): ^{13}C, δ 99.89 (C-1), 17.13 (C*Me*). Anal. Calcd for $C_{12}H_{15}NO_7$: C, 50.53; H, 5.30. Found: C, 50.56; H, 5.32.

p-*Nitrophenyl* endo-*3,4-*O*-benzylidene-6-deoxy-α-*L*-talopyranoside* (**4**).—*p*-Toluenesulfonic acid monohydrate (50 mg) was added to a stirred solution of **3**

(1.71 g, 5.99 mmol) in α,α-dimethoxytoluene (24 mL) and dry DMF (2.4 mL). After 3 h, TLC revealed one main spot. The mixture was diluted with CH_2Cl_2 (200 mL), and the organic layer was washed with aq $NaHCO_3$ and water, dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue yielded **4** (1.74 g, 78%); $[\alpha]_D$ −106° (*c* 0.68, $CHCl_3$); R_f 0.39 (1:1 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 8.12–7.00 (m, 9 H, aromatic), 5.78 (s, 1 H, PhC*H*), 5.51 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.55 (dd, 1 H, $J_{3,4}$ 8.2 Hz, H-3), 4.15 (dd, 1 H, $J_{4,5}$ 2 Hz, H-4), 4.02 (m, 1 H, H-2; after deuteration, dd, 1 H, $J_{2,3}$ 3.6 Hz, H-2), 3.91 (m, 1 H, $J_{5,6}$ 6.6 Hz, H-5), 2.75 (d, 1 H, $J_{H,OH}$ 7.65 Hz, OH; after deuteration disappeared), 1.25 (d, 3 H, H-6). For ^{13}C NMR data, see Table I. Anal. Calcd for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13. Found: C, 61.07; H, 5.10.

3-O-Acetyl-2,4-di-O-benzyl-α-L-rhamnopyranosyl trichloroacetimidate (**7**).—2,4-Di-*O*-benzyl-L-rhamnose[10] (2.87 g, 8.33 mmol) was treated with 1:1 Ac_2O–pyridine (30 mL) overnight. The mixture was concentrated and toluene (3 × 10 mL) was evaporated from the residue to give **5** (3.3 g, 92%); R_f 0.52 (65:35 hexane–EtOAc). Hydrazine acetate (0.78 g, 8.47 mmol) was added to a stirred solution of this crude product (3.3 g, 7.7 mmol) in DMF (5 mL). The temperature was kept at 50°C for 15 min. When TLC showed that the reaction was complete, the mixture was cooled to room temperature, diluted with EtOAc (150 mL), washed with aq 5% NaCl and water, dried (Na_2SO_4), and concentrated to yield derivative **6** (2.26 g, 76%); R_f 0.35 (65:35 hexane–EtOAc). DBU[11] (0.294 mL, 1.96 mmol) was added to a solution of **6** (570 mg, 1.47 mmol) in dry CH_2Cl_2 (6 mL) and trichloroacetonitrile (1.47 mL, 14.7 mmol). The mixture was stirred for 15 min and then concentrated. Column chromatography of the residue gave **7** (0.67 g, 85%); $[\alpha]_D$ −5.9° (*c* 0.75 $CHCl_3$); R_f 0.68 (7:3 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 8.59 (s, 1 H, =NH), 7.40–7.22 (m, 10 H, aromatic), 6.28 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 5.23 (dd, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 4.79–4.56 (m, 4 H, 2 PhCH_2), 4.10 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-2), 4.05–3.92 (m, 1 H, H-5), 3.71 (dd, 1 H, $J_{4,5}$ 9.1 Hz, H-4), 1.98 (s, 3 H, OAc), 1.37 (d, 3 H, $J_{5,6}$ 6 Hz, H-6). Anal. Calcd for $C_{24}H_{26}Cl_3NO_6$: C, 54.30; H, 4.94. Found: C, 54.43; H, 4.86.

p-*Nitrophenyl 2-O-(3-O-acetyl-2,4-di-O-benzyl-α-L-rhamnopyranosyl)*-endo-*3,4-O-benzylidene-6-deoxy-α-L-talopyranoside* (**8**).—*Procedure A.* A solution of **4** (373 mg, 1 mmol) and **7** (531 mg, 1 mmol) in CH_2Cl_2 (8 mL) containing molecular sieves (4A, 1.5 g) was stirred for 30 min under Ar. A solution of trimethylsilyl triflate (90 μL, 0.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise at −40°C, and, after 10 min, pyridine was added. The mixture was filtered through Celite, concentrated, and co-concentrated with toluene (3 × 5 mL). Column chromatography (3:2 hexane–EtOAc) of the residue gave **8** (560 mg, 76%); $[\alpha]_D$ −96° (*c* 0.66, $CHCl_3$); R_f 0.59.

Procedure B. A solution of **4** (1.12 g, 3 mmol) and **9**[13] (1.5 g, 3.6 mmol) in dry CH_2Cl_2 (20 mL) containing molecular sieves (4A, 6 g) was stirred for 30 min under Ar, then methyl triflate (2.35 mL, 21.6 mmol) was added. After 1.5 h, pyridine was injected and the mixture was filtered through Celite, concentrated, and co-con-

TABLE I

^{13}C NMR data of some selected compounds [a]

Carbon	Chemical shifts (ppm)				
	4	**8**	**20**	**18**	**38**
*6-deoxy-α-L-Tal*p					
1	99.68	98.39		98.76	99.61
2	66.65	71.86		72.13	78.65
3	75.00	73.14		73.26	72.60
4	76.40	76.30		76.39	69.19
5	68.10	68.13		68.73	69.19
6	15.60	15.40		15.49	16.74
C_a [b]	104.30	104.65		104.75	
$J_{C\text{-}1,H\text{-}1}$ (Hz)					172.9
*α-L-Rha*p					
1		95.32	82.38	94.76	103.42
2		76.12	76.03	75.91	70.92
3		71.05	78.33	77.91	78.16
4		78.74	79.24	78.38	72.48
5		67.40	68.72	67.51	70.72
6		17.91	17.91	18.12	17.63
$J_{C\text{-}1,H\text{-}1}$ (Hz)					172.2
*α-L-Fuc*p					
1			99.39	98.91	99.08
2			79.24	78.38	77.60
3			71.08	71.16	77.30
4			80.26	79.84	72.18
5			66.16	66.38	66.61
6			16.36	16.41	16.18
OCH_3			59.30	59.30	59.55
$J_{C\text{-}1,H\text{-}1}$ (Hz)					~170
*α-D-Rha*p					
1					99.00
2					81.27
3					71.06
4					73.40
5					67.87
6					17.57
OCH_3					58.80
$J_{C\text{-}1,H\text{-}1}$ (Hz)					171.9

[a] All spectra were recorded in $CDCl_3$ except that of **38** which was measured in D_2O. [b] C_a = acetalic carbon.

centrated with toluene (4 × 15 mL). Column chromatography (3 : 2 hexane–EtOAc) of the residue gave **8** (1.56 g, 70%); $[\alpha]_D$ −97° (*c* 0.46, $CHCl_3$); R_f 0.59. NMR data ($CDCl_3$): ^1H, δ 8.20–7.10 (m, 19 H, aromatic), 5.80 (s, 1 H, PhC*H*), 5.65 (d, 1 H, $J_{1,2}$ 6.5 Hz, H-1), 5.09 (dd, 1 H, $J_{2',3'}$ 4, $J_{3',4'}$ 9 Hz, H-3′), 4.99 (d, 1 H, $J_{1',2'}$ 2 Hz, H-1′), 3.60 (dd, 1 H, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4′), 1.92 (s, 3 H, OAc), 1.34 and 1.28 (2 d, each 3 H, H-6,6′). For ^{13}C NMR data, see Table I. Anal. Calcd for $C_{41}H_{43}NO_{12}$: C, 66.38; H, 5.84. Found: C, 66.27; H, 5.80.

p-*Nitrophenyl* endo-*3,4-O-benzylidene-6-deoxy-2-O-(2,4-di-O-benzyl-α-L-rhamnopyranosyl)-α-L-talopyranoside* (**17**).—Sodium methoxide (catalytic amount) was added to a solution of **8** (1.5 g, 2.02 mmol) in dry MeOH (50 mL) which was then stirred overnight. The solution was neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. The residue was crystallised from EtOAc–hexane to give **17** (1.29 g, 91%); mp 188–190°C; $[\alpha]_D$ −84° (*c* 0.23, $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 8.20–7.10 (m, 19 H, aromatic), 5.80 (s, 1 H, PhC*H*), 5.51 (d, 1 H, H-1), 4.98 (bs, 1 H, H-1'), 2.25 (d, 1 H, OH), 1.38 and 1.29 (2 d, each 3 H, H-6,6'). Anal. Calcd for $C_{39}H_{41}NO_{11}$: C, 66.94; H, 5.91. Found: C, 66.99; H, 5.98.

Methyl 3,4-O-isopropylidene-1-thio-β-L-fucopyranoside (**10**).—*p*-Toluenesulfonic acid monohydrate (100 mg) was added to a solution of methyl 1-thio-β-L-fucopyranoside[15] (5.0 g, 21.3 mmol) in 2,2-dimethoxypropane (50 mL). After 30 min, solid $NaHCO_3$ was added. The mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue (5.68 g, 94%) was crystallised from cyclohexane to give **10**; mp 69°C; $[\alpha]_D$ −44° (*c* 0.86, $CHCl_3$); R_f 0.50 (9:1 CH_2Cl_2–acetone). NMR data ($CDCl_3$): ^1H, δ 4.14 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.07–4.01 (m, 2 H, H-3,4), 3.89 (m, 1 H, H-5), 3,56 (m, 1 H, H-2), 2.63 (bs, 1 H, OH), 2.22 (s, 3 H, SMe), 1.54 and 1.37 (2 s, 6 H, CMe_2). Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74; Found: C, 51.15; H, 7.69.

Methyl 3,4-O-isopropylidene-2-O-methyl-1-thio-β-L-fucopyranoside (**11**).—Powdered KOH (4 g) was added to a solution of **10** (5.5 g, 22.14 mmol) in dry DMF (25 mL) and the mixture was cooled to 0°C. MeI (3.5 mL) was added and the mixture was stirred for 4 h. The mixture was diluted with CH_2Cl_2 (300 mL), the inorganic salts were filtered off, and the organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue (4.98 g, 85%) was crystallised from cyclohexane to yield **11**; mp 95°C; $[\alpha]_D$ −1.5° (*c* 1.5, $CHCl_3$); R_f 0.71 (95:5 CH_2Cl_2–acetone). NMR data ($CDCl_3$): ^1H, δ 4.19 (d, 1 H, $J_{1,2}$ 10 Hz, H-1), 4.11–3.98 (m, 2 H, H-3,4), 3.78 (m, 1 H, H-5), 3.53 (s, 3 H, OMe), 3.18 (dd, 1 H, H-2), 2.20 (s, 3 H, SMe), 1.52 and 1.34 (2 s, each 3 H, CMe_2), 1.38 (d, 3 H, H-6). Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.29; H, 8.08.

Methyl 2-O-methyl-1-thio-β-L-fucopyranoside (**12**).—Compound **11** (2.48 g, 10 mmol) was stirred in 6:4 acetic acid–water (30 mL) for 1 h at 80°C and the mixture was then concentrated and co-concentrated with toluene (4 × 10 mL) and CH_2Cl_2 (4 × 10 mL) to give **12** (1.98 g, 95%); $[\alpha]_D$ +17° (*c* 0.86, $CHCl_3$); R_f 0.30 (3:1 CH_2Cl_2–acetone). NMR data ($CDCl_3$): ^1H, δ 4.18 (d, 1 H, H-1), 3.59 (s, 3 H, OMe), 2.19 (s, 3 H, SMe), 1.27 (d, 3 H, H-6). Anal. Calcd for $C_8H_{16}O_4S$: C, 46.14; H, 7.74. Found: C, 46.22; H, 7.70.

Methyl endo-*3,4-O-benzylidene-2-O-methyl-1-thio-β-L-fucopyranoside* (**13**).—Compound **12** (2.08 g, 10 mmol) was treated with α,α-dimethoxytoluene, as described for the preparation of compound **4**. Purification of the crude product by column chromatography gave **13** (2.25 g, 75.9%); $[\alpha]_D$ +17° (*c* 0.99, $CHCl_3$); R_f 0.74 (9:1 CH_2Cl_2–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.58–7.33 (m, 5 H, aromatic), 5.93 (s, 1 H, PhC*H*), 4.26 (d, 1 H, $J_{1,2}$ 10 Hz, H-1), 4.25 (t, 1 H, $J_{3,4}$ 6

Hz, H-3), 4.13 (dd, 1 H, H-4), 3.90 (m, 1 H, H-5), 3.49 (s, 3 H, OMe), 3.24 (dd, 1 H, $J_{2,3}$ 6 Hz, H-2), 2.20 (s, 3 H, SMe), 1.48 (d, 3 H, H-6). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.86; H, 6.78.

Methyl 4-O-benzyl-2-O-methyl-1-thio-β-L-fucopyranoside (**14**).—Compound **13** (880 mg, 2.97 mmol) was hydrogenolysed in 1:1 ether–CH_2Cl_2 (30 mL) with $LiAlH_4$ (440 mg) and $AlCl_3$ (880 mg) at room temperature for 30 min. The reaction was terminated by the addition of EtOAc (5 mL) and water (2 mL). The organic layer was decanted and the residue washed with ether (2 × 50 mL). The combined solutions were washed with water (3 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was crystallised from cyclohexane to afford **14** (780 mg, 88%); mp 77°C; $[\alpha]_D$ +16° (*c* 0.54, $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 7.45–7.28 (m, 5 H aromatic), 4.80 (s, 2 H, PhCH_2), 4.19 (d, 1 H, H-1), 3.65 (s, 3 H, OMe), 3.28 (m, 1 H, H-5), 2.38 (d, 1 H, OH), 2.22 (s, 3 H, SMe), 1.30 (d, 3 H, H-6). Anal. Calcd for $C_{15}H_{22}O_4S$: C, 60.37; H, 7.43. Found: C, 60.45; H, 7.49.

Methyl 3-O-acetyl-4-O-benzyl-2-O-methyl-1-thio-β-L-fucopyranoside (**15**).—Compound **14** (400 mg, 1.34 mmol) was dissolved in 1:1 pyridine–Ac_2O (12 mL) and left for 3 h. The mixture was concentrated and co-concentrated with toluene. Column chromatography of the residue gave **15** (395 mg, 87%); $[\alpha]_D$ −24° (*c* 1.18, $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 7.39–7.23 (m, 5 H, aromatic), 4.84 (dd, 1 H, $J_{2,3}$ 9.7, $H_{3,4}$ 3 Hz, H-3), 4.65 (2 d, 2 H, PhCH_2), 4.26 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 3.54 (s, 3 H, OMe), 2.23 (s, 3 H, SMe), 2.04 (s, 3 H, OAc), 1.23 (d, 3 H, H-6). Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11. Found: C, 60.07; H, 7.07.

p-*Nitrophenyl 2-O-[3-O-(3-O-acetyl-4-O-benzyl-2-O-methyl-α-L-fucopyranosyl)-2,4-di-O-benzyl-α-L-rhamnopyranosyl]*-endo-*3,4-O-benzylidene-6-deoxy-α-L-talopyranoside* (**18**).—*Procedure A.* A mixture of **17** (160 mg, 0.23 mmol), **15** (117 mg, 0.34 mmol), $CuBr_2$ (144 mg, 0.65 mmol), Bu_4NBr (186 mg, 0.58 mmol), and molecular sieves (4A, 1 g) was stirred in 5:1 CH_2Cl_2–DMF (6 mL) for 24 h under Ar. Then the mixture was diluted with CH_2Cl_2, filtered through Celite, washed with aq $NaHCO_3$ and water, then dried (Na_2SO_4), filtered, and concentrated. Column chromatography (94:6 CH_2Cl_2–EtOAc) yielded **18** (115 mg, 51%).

Procedure B. Bromine (116 μL, 2.26 mmol) was added to a solution of **15** (586 mg, 1.72 mmol) in dry CH_2Cl_2 (8 mL) at 0°C. After stirring the mixture for 10 min at room temperature, the solution was concentrated and co-concentrated with toluene (3 × 5 mL). The residue (**16**) was dissolved in dry CH_2Cl_2 (8 mL) and this solution was added to a stirred mixture of **17** (600 mg, 0.86 mmol), Bu_4NBr (832 mg, 2.58 mmol), and molecular sieves (4A, 2.4 g) in dry DMF (8 mL). The mixture was stirred for 24 h, diluted with CH_2Cl_2, filtered through Celite, washed with aq $NaHCO_3$ and water, then dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue afforded **18** (587 mg, 69%); $[\alpha]_D$ −129° (*c* 0.65, $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 8.20–7.10 (m, 24 H, aromatic), 5.84 (s, 1 H, PhC*H*), 5.63 (d, 1 H, $J_{1,2}$ 6.5 Hz, H-1), 5.22 (dd, 1 H, $J_{2'',3''}$ 10.5, $J_{3'',4''}$ 3 Hz, H-3), 3.19 (s, 3 H, OMe), 2.04 (s, 3 H, OAc), 1.32, 1.28 and 0.97 (3 d, each 3 H, 3CMe). For ^{13}C NMR data, see Table I. Anal. Calcd for $C_{55}H_{61}NO_{16}$: C, 66.59; H, 6.20. Found: C, 66.48; H, 6.19.

Methyl 3-O-(3-O-acetyl-4-O-benzyl-2-O-methyl-α-L-fucopyranosyl)-2,4-di-O-benzyl-1-thio-α-L-rhamnopyranoside (**20**).—Bromine (42 μL, 0.74 mmol) was added to a solution of **15** (210 mg, 0.62 mmol) in dry CH_2Cl_2 (4 mL) at 0°C. After 10 min, the reaction was worked up as described for **18**. The residue (**16**) was dissolved in dry CH_2Cl_2 (4 mL) and this solution was added to a stirred mixture of **19**[13] (210 mg, 0.62 mmol), Bu_4NBr (189 mg, 0.90 mmol), and molecular sieves (4A, 800 mg) in dry DMF (4 mL). The mixture was stirred for 24 h, then worked up as described for **18** (Procedure B). Column chromatography of the residue gave **20** (228 mg, 61%); $[\alpha]_D$ −154° (*c* 0.35, $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 7.48–7.22 (m, 15 H, aromatic), 3.29 (s, 3 H, OMe), 2.12 (s, 3 H, SMe), 2.02 (s, 3 H, OAc), 1.31 and 0.93 (2 d, each 3 H, H-6,6′). For ^{13}C NMR data, see Table I. Anal. Calcd for $C_{37}H_{46}O_9S$: C, 66.64; H, 6.95. Found: C, 66.62; H, 6.89.

p-*Nitrophenyl 2-O-[3-O-(3-O-acetyl-4-O-benzyl-2-O-methyl-α-L-fucopyranosyl)-2,4-di-O-benzyl-α-L-rhamnopyranosyl]*-endo-*3,4-O-benzylidene-6-deoxy-α-L-talopyranoside* (**18**).—*Procedure C.* A solution of **20** (140 mg, 0.21 mmol), and **4** (93 mg, 0.25 mmol) in CH_2Cl_2 (4 mL) containing molecular sieves (4A, 250 mg) was stirred for 30 min under Ar, then methyl triflate (185 μL, 1.68 mmol) was added. After 4 h, pyridine was injected and the mixture was filtered through Celite, concentrated, and co-concentrated with toluene. Column chromatography of the residue gave **18** (121 mg, 58%).

Phenyl 6-O-(p-toluenesulfonyl)-1-thio-α-D-mannopyranoside (**21**).—Phenyl 1-thio-α-D-mannopyranoside[22,23] (9.21 g 33.82 mmol) was treated with *p*-toluenesulfonyl chloride (9.67 g, 50.72 mmol) in dry pyridine (60 mL) at 0°C overnight. The mixture was concentrated, diluted with CH_2Cl_2, washed with aq $NaHCO_3$ and water, then dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue afforded **21** (8.65 g, 60%); $[\alpha]_D$ +147° (*c* 0.40, $CHCl_3$); R_f 0.66 (92:8 CH_2Cl_2–MeOH). Anal. Calcd for $C_{19}H_{22}O_7S_2$: C, 53.50; H, 5.20. Found: C, 53.62; H, 5.15.

Phenyl 2,3-O-isopropylidene-6-O-(p-toluenesulfonyl)-1-thio-α-D-mannopyranoside (**22**).—*p*-Toluenesulfonic acid monohydrate (150 mg) was added to a solution of **21** (8.0 g, 19.30 mmol) in 2,2-dimethoxypropane (30 mL). After 30 min, solid $NaHCO_3$ was added. The mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue gave **22** (8.01 g, 89%); $[\alpha]_D$ +99° (*c* 0.9, $CHCl_3$); R_f 0.51 (6:4 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.75–7.25 (m, 9 H, aromatic), 5.70 (bs, 1 H, H-1), 2.80 (d, 1 H, OH), 2.45 (s, 3 H, ArMe), 1.50 and 1.38 (2 s, each 3 H, CMe_2). Anal. Calcd for $C_{22}H_{26}O_7S_2$: C, 56.63; H, 5.62. Found: C, 56.71; H, 5.60.

Phenyl 2,3-O-isopropylidene-1-thio-α-D-rhamnopyranoside (**23**).—Compound **22** (9.17 g, 19.6 mmol) was dissolved in 1:1 benzene–ether (70 mL) and then $LiAlH_4$ (1.5 g, 39.52 mmol) was added. The mixture was boiled for 10 min under reflux. After cooling, EtOAc was added to decompose the excess of reagent and then water was added to precipitate the aluminium hydroxide. The organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated. Column chro-

matography of the residue gave a crystalline product that was recrystallised from EtOAc–hexane to afford **23** (4.19 g, 72%); mp 82°C; $[\alpha]_D$ +206° (*c* 1.0, $CHCl_3$); R_f 0.71 (6:4 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.51–7.25 (m, 5 H, aromatic), 5.75 (bs, 1 H, H-1), 4.35 (d, 1 H, H-2), 4.20–4.02 (m, 2 H, H-3,5), 3.52–3.40 (m, 1 H, H-4), 2.90 (d, 1 H, OH), 1.54 and 1.37 (2 s, each 3 H, CMe_2), 1.24 (d, 3 H, H-6). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.67; H, 6.73.

Phenyl 4-O-benzyl-2,3-O-isopropylidene-1-thio-α-D-rhamnopyranoside (**24**).—Powdered KOH (3.18 g, 56.67 mmol) and benzyl bromide (4.2 mL) were added to a stirred solution of **23** (4.19 g, 14.1 mmol) in dry DMF (15 mL). After the reaction was complete, MeOH (2 mL) was added to the mixture which was then diluted with CH_2Cl_2. The inorganic salts were filtered off, and the organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated. The crystalline residue was recrystallised from EtOH to yield **24** (3.71 g, 68%); mp 90°C; $[\alpha]_D$ +220° (*c* 0.66, $CHCl_3$); R_f 0.81 (6:4 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.50–7.22 (m, 10 H, aromatic), 5.74 (bs, 1 H, H-1), 4.92 and 4.63 (2 d, each 1 H, PhCH_2), 4.39–4.28 (m, 2 H, H-2,3), 4.14 (m, 1 H, H-5), 3.30 (dd, 1 H, H-4), 1.51 and 1.39 (2 s, each 3 H, CMe_2), 1.23 (d, 3 H, H-6). Anal. Calcd for $C_{22}H_{26}O_4S$: C, 68.36; H, 6.78. Found: C, 68.40; H, 6.70.

Phenyl 4-O-benzyl-1-thio-α-D-rhamnopyranoside (**25**).—Compound **24** (3.71 g, 9.6 mmol) was stirred in 6:4 acetic acid–water (30 mL) for 1 h at 80°C, then concentrated, and co-concentrated with toluene. The crystalline residue was recrystallised from EtOAc–hexane to give **25** (2.69 g, 81%); mp 117°C; $[\alpha]_D$ +232° (*c* 0.90, $CHCl_3$); R_f 0.33 (6:4 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.48–7.25 (m, 10 H, aromatic), 5.47 (d, 1 H, H-1), 4.75 (s, 2 H, PhCH_2), 4.28–4.13 (m, 2 H, H-2,5), 3.98–3.87 (m, 1 H, H-3), 3.42 (dd, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 2.81 (bs, 1 H, OH), 2.56 (d, 1 H, OH), 1.35 (d, 3 H, H-6). Anal. Calcd for $C_{19}H_{22}O_4S$: C, 65.87; H, 6.40. Found: C, 65.97; H, 6.45.

Phenyl 4-O-benzyl-2-O-methyl-1-thio-α-D-rhamnopyranoside (**26**).—A mixture of **25** (2.69 g, 7.7 mmol), Bu_4NBr (620 mg, 1.92 mmol), MeI (2.5 mL, 38.53 mmol), and aq NaOH (1 mL of a 20% solution) in CH_2Cl_2 (20 mL) was stirred at room temperature for 1 day. Then the mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue afforded **26** (1.56 g, 57%); $[\alpha]_D$ +195° (*c* 0.30, $CHCl_3$); R_f 0.71 (93:7 CH_2Cl_2–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.51–7.21 (m, 10 H, aromatic), 5.58 (d, 1 H, $J_{1,2}$ 1.1 Hz, H-1), 4.90 and 4.71 (2 d, each 1 H, PhCH_2), 4.17 (dd, 1 H, $J_{5,6}$ 6 Hz, H-5), 3.95 (dt, 1 H, $J_{3,4}$ 9, $J_{3,OH}$ 8.8 Hz, H-3), 3.75 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-2), 3.47 (s, 3 H, OMe), 3.34 (dd, 1 H, $J_{4,5}$ 9 Hz, H-4), 2.5 (d, 1 H, OH), 1.42 (d, 3 H, $J_{5,6}$ 6 Hz, H-6). Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71. Found: C, 66.56; H, 6.73.

Phenyl 3-O-acetyl-4-O-benzyl-2-O-methyl-1-thio-α-D-rhamnopyranoside (**27**).—Compound **26** (560 mg, 1.55 mmol) was dissolved in 1:1 pyridine–Ac_2O (20 mL) and left for 3 h. Then the mixture was concentrated and co-concentrated with

toluene. Column chromatography of the residue yielded **27** (575 mg, 92%); $[\alpha]_D$ +156° (*c* 0.95, $CHCl_3$); R_f 0.87 (93:7 CH_2Cl_2–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.52–7.23 (m, 10 H, aromatic), 5.52 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 5.19 (dd, 1 H, $J_{3,4}$ 9 Hz, H-3), 4.70 (ABq, 2 H, PhCH_2), 4.24 (m, 1 H, $J_{5,6}$ 6 Hz, H-5), 3.92 (dd, 1 H, $J_{2,3}$ 3 Hz, H-2), 3.63 (dd, 1 H, $J_{4,5}$ 9 Hz, H-4), 3.43 (s, 3 H, OMe), 2.08 (s, 3 H, OAc), 1.33 (d, 3 H, H-6). Anal. Calcd for $C_{22}H_{26}O_5S$: C, 65.65; H, 6.51. Found: C, 65.76; H, 6.60.

Ethyl 6-O-(p-toluenesulfonyl)-1-thio-α-D-mannopyranoside (**28**).—*p*-Toluenesulfonyl chloride (6.25 g, 32.78 mmol) was added to a solution of ethyl 1-thio-α-D-mannopyranoside[22,24] (4.9 g, 21.85 mmol) in dry pyridine (30 mL) and kept at 0°C overnight. The mixture was then concentrated, diluted with CH_2Cl_2 (200 mL), washed with aq $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. Column chromatography of the residue gave **28** (5.04 g, 61%); $[\alpha]_D$ +115° (*c* 0.34, MeOH); R_f 0.31 (92:8 CH_2Cl_2–MeOH). NMR data ($CDCl_3$): ^1H, δ 7.8 and 7.34 (2 d, each 2 H, aromatic), 5.26 (bs, 1 H, $J_{1,2}$ 1 Hz, H-1), 2.52 (m, 2 H, MeCH_2S), 2.42 (s, 3 H, Ar*Me*), 1.21 (t, 3 H, *Me*CH_2S). Anal. Calcd for $C_{15}H_{22}O_7S_2$: C, 47.60; H, 5.86. Found: C, 47.51; H, 5.81.

Ethyl 2,3-O-isopropylidene-6-O-(p-toluenesulfonyl)-1-thio-α-D-mannopyranoside (**29**).—*p*-Toluenesulfonic acid monohydrate (100 mg) was added to a solution of **28** (2.6 g, 6.87 mmol) in 2,2-dimethoxypropane (15 mL). After 25 min, solid $NaHCO_3$ was added. The mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue afforded **29** (2.56 g, 89%); $[\alpha]_D$ +86° (*c* 0.20, $CHCl_3$), R_f 0.49 (6:4 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.79 and 7.34 (2 d, each 2 H, aromatic), 5.49 (bs, 1 H, H-1), 2.51 (m, 2 H, MeCH_2S), 2.44 (s, 3 H, Ar*Me*), 1.49 and 1.33 (2 s, each 3 H, CMe_2), 1.25 (t, 3 H, *Me*CH_2S). Anal. Calcd for $C_{18}H_{26}O_7S_2$: C, 51.65; H, 6.26. Found: C, 51.69; H, 6.19.

Ethyl 2,3-O-isopropylidene-1-thio-α-D-rhamnopyranoside (**30**).—Compound **29** (2.4 g, 5.73 mmol) was dissolved in 1:1 benzene–ether (20 mL), and then $LiALH_4$ (435 mg, 11.46 mmol) was added. The mixture was boiled for 10 min under reflux. After cooling, EtOAc was added to decompose the excess of reagent and then water was added to precipitate the aluminium hydroxide. The organic layer was decanted, then washed with water, dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue yielded **30** (1.16 g, 81%); $[\alpha]_D$ +178° (*c* 1.2, $CHCl_3$); R_f 0.52 (6:4 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 5.52 (bs, 1 H, H-1), 4.18 (d, 1 H, H-2), 4.09–3.90 (m, 2 H, H-3,5), 3.43 (m, 1 H, H-4; after addition of D_2O, dd), 2.61 (m, 2 H, MeCH_2S), 1.55 and 1.35 (2 s, each 3 H, CMe_2), 1.31 (t, 3 H, *Me*CH_2S), 1.29 (d, 3 H, H-6). Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.11; H, 8.13.

Ethyl 4-O-benzyl-1-thio-α-D-rhamnopyranoside (**31**).—A solution of **30** (1.04 g, 4.19 mmol) and benzyl bromide (0.75 mL, 6.29 mmol) in dry DMF (10 mL) was added dropwise to NaH (201 mg, 8.38 mmol) and the mixture was stirred for 10 min. Then MeOH was added to decompose the excess of hydride, and the mixture

was diluted with CH_2Cl_2 (150 mL), washed with water, dried (Na_2SO_4), and concentrated. The crude product (R_f 0.87 in 6:4 hexane–EtOAc) was stirred in 6:4 acetic acid–water (20 mL) for 1 h at 80°C, then concentrated, and co-concentrated with toluene (4 × 10 mL). The residue was crystallised from hexane–EtOAc to afford **31** (910 mg, 73%); mp 94–95°C; $[\alpha]_D$ +185° (*c* 0.60, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_4S$: C, 60.37; H, 7.43. Found: C, 60.43; H, 7.50.

*Ethyl 4-O-benzyl-2-O-methyl-1-thio-α-*D*-rhamnopyranoside* (**32**).—A mixture of **31** (800 mg, 2.68 mmol), Bu_4NBr (216 mg, 0.67 mmol), MeI (0.83 mL, 13.4 mmol), and aq NaOH (0.3 mL of a 20% solution) in CH_2Cl_2 (6 mL) was stirred for 24 h, then MeI (0.33 mL, 5.3 mmol) was added to the mixture which was stirred for another 24 h. The mixture was diluted with CH_2Cl_2 (60 mL), washed with water (4 × 10 mL), dried (Na_2SO_4), and concentrated. Column chromatography of the residue gave **32** (461 mg, 55%); $[\alpha]_D$ +126° (*c* 0.40, $CHCl_3$); R_f 0.58 (9:1 CH_2Cl_2–EtOAc). NMR data ($CDCl_3$): ^1H, δ 7.40–7.25 (m, 5 H, aromatic, 5.39 (bs, 1 H, $J_{1,2}$ 1 Hz, H-1), 4.91 and 4.67 (2 d, each 1 H, PhCH_2), 4.04 (m, 1 H, H-5), 3.90 (m, 1 H; after addition of D_2O, dd, $J_{3,4}$ 9.5 Hz; H-3), 3.59 (dd, 1 H, $J_{2,3}$ 4 Hz, H-2), 3.49 (s, 3 H, OMe), 3.29 (dd, 1 H, $J_{4,5} \sim J_{3,4}$ 9.5 Hz, H-4), 2.62 (m, 2 H, MeCH_2S), 1.32 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6), 1.30 (t, 3 H, *Me*CH_2S). Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74. Found: C, 61.61; H, 7.68.

*Ethyl 3-O-acetyl-4-O-benzyl-2-O-methyl-1-thio-α-*D*-rhamnopyranoside* (**33**).—Compound **32** (400 mg, 1.28 mmol) was dissolved in 1:1 pyridine–Ac_2O (12 mL) and left for 3 h. The mixture was concentrated using toluene (5 × 5 mL) to give **33** (440 mg, 97%); $[\alpha]_D$ +125° (*c* 0.67, $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 7.37–7.25 (m, 5 H, aromatic), 5.31 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.16 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 4.68 (q, 2 H, PhCH_2), 4.13 (m, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 3.75 (dd, 1 H, $J_{2,3}$ 3 Hz, H-2), 3.57 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.45 (s, 3 H, OMe), 2.63 (m, 2 H, MeCH_2S), 2.06 (s, 3 H, OAc), 1.32 (d, 3 H, H-6), 1.30 (t, 3 H, *Me*CH_2S). Anal. Calcd for $C_{18}H_{26}O_5S$: C, 60.99; H, 7.39. Found: C, 61.10; H, 7.35.

p-*Nitrophenyl* endo-*3,4-O-benzylidene-6-deoxy-2-O-[2,4-di-O-benzyl-3-O-(4-O-benzyl-2-O-methyl-α-*L*-fucopyranosyl)-α-*L*-rhamnopyranosyl]-α-*L*-talopyranoside* (**34**).—Sodium methoxide (catalytic amount) was added to a solution of **18** (280 mg, 0.28 mmol) in dry MeOH (8 mL) and stirred overnight. Then the mixture was neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated to give **34** (257 mg, 96%); $[\alpha]_D$ −125° (*c* 0.32, $CHCl_3$). Anal. Calcd for $C_{53}H_{59}NO_{15}$: C, 67.00; H, 6.26. Found: C, 67.11; H, 6.31.

p-*Nitrophenyl* 2-O-{3-O-[3-O-(3-O-*acetyl-4-O-benzyl-2-O-methyl-α-*D*-rhamnopyranosyl)-4-O-benzyl-2-O-methyl-α-*L*-fucopyranosyl]-2,4-di-O-benzyl-α-*L*-rhamnopyranosyl}*-endo-*3,4-O-benzylidene-6-deoxy-α-*L*-talopyranoside* (**35**).—A solution of **34** (190 mg, 0.2 mmol) and **33** (92 mg, 0.26 mmol) in dry CH_2Cl_2 (6 mL) containing molecular sieves (4A, 600 mg) was stirred for 30 min under Ar, then methyl triflate (227 μL, 2.08 mmol) was added. After 2 h, pyridine was injected, and the mixture was filtered through Celite, concentrated, and co-concentrated with toluene. Column chromatography of the residue yielded **35** (220 mg, 89%); $[\alpha]_D$ −78° (*c*

0.39, $CHCl_3$); R_f 0.55 (55:45 hexane–EtOAc). NMR data ($CDCl_3$): ^1H, δ 8.20–7.10 (m, 29 H, aromatic), 5.82 (s, 1 H, PhC*H*), 5.63 (d, 1 H, H-1), 5.29 (dd, 1 H, H-3‴), 3.40 and 3.13 (2 s, each 3 H, 2 × OMe), 2.05 (s, 3 H, OAc), 1.39–1.20 (m, 9 H, 3 × CMe), 1.01 (d, 3 H, CMe); ^{13}C, δ 104.72 (Ph*C*H), 98.84, 98.61, 98.35 and 94.44 (anomeric carbons), 58.78 and 58.49 (2 × OMe), 21.07 (*Me*CO), 18.13, 18.11, 16.72, and 15.45 (4 × C*Me*). Anal. Calcd for $C_{69}H_{79}NO_{20}$: C, 66.71; H, 6.41. Found: C, 66.59; H, 6.33.

p-*Trifluoroacetamidophenyl 2-O-{3-O-[3-O-(3-O-acetyl-4-O-benzyl-2-O-methyl-α-D-rhamnopyranosyl)-4-O-benzyl-2-O-methyl-α-L-fucopyranosyl]-2,4-di-O-benzyl-α-L-rhamnopyranosyl}*-endo-*3,4-O-benzylidene-6-deoxy-α-L-talopyranoside* (**36**).—A solution of **35** (110 mg, 0.09 mmol) in EtOAc (4 mL) was hydrogenated over Adams' catalyst (60 mg) at atmospheric pressure for 1 h. Pyridine (1 mL) and trifluoroacetic anhydride (0.4 mL) were added and the reaction mixture was stirred for 20 min, then filtered, and concentrated. Column chromatography of the residue afforded **36** (83 mg, 72%); $[\alpha]_D$ −59° (*c* 0.28, $CHCl_3$); R_f 0.52 (55:45 hexane–EtOAc).

p-*Trifluoroacetamidophenyl* endo-*3,4-O-benzylidene-6-deoxy-2-O-{2,4-di-O-benzyl-3-O-[4-O-benzyl-3-O-(4-O-benzyl-2-O-methyl-α-D-rhamnopyranosyl)-2-O-methyl-α-L-fucopyranosyl]-α-L-rhamnopyranosyl}-α-L-talopyranoside* (**37**).—Sodium methoxide (catalytic amount) was added to a solution of **36** (70 mg, 0.054 mmol) in dry MeOH (4 mL) and stirred overnight. Then the mixture was neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Column chromatography of the residue gave **37** (64 mg, 94%); $[\alpha]_D$ −74° (*c* 0.19, $CHCl_3$); R_f 0.35 (55:45 hexane–EtOAc).

p-*Trifluoroacetamidophenyl 6-deoxy-2-O-{3-O-[2-O-methyl-3-O-(2-O-methyl-α-D-rhamnopyranosyl)-α-L-fucopyranosyl]-α-L-rhamnopyranosyl}-α-L-talopyranoside* (**38**).—A solution of **37** (50 mg, 0.04 mmol) in acetic acid (8 mL) was hydrogenated at room temperature over 10% Pd–C (20 mg). When TLC (2:1:1 1-butanol–MeOH–water) showed complete reaction, the mixture was filtered and concentrated to give **38** as a white glass (29 mg, 90%); $[\alpha]_D$ −21° (*c* 0.21, MeOH). NMR data (D_2O): ^1H, δ 7.50 and 7.18 (2 d, each 2 H, aromatic), 5.68, 5.16, and 5.08 (3 bs, each 1 H) and 5.43 (d, 1 H), anomeric protons, 3.52 and 3.48 (2 s, each 3H, 2 × OMe), 1.32–1.20 (m, 12 H, 4 × CMe). For ^{13}C NMR data, see Table I.

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