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SYNTHESIS OF A TRISACCHARIDE COMPONENT OF THE CAPSULAR POLYSACCHARIDE OF *Streptococcus pneumoniae* TYPE 19F

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ABSTRACT

2-*O*-[4-*O*-(2-Acetamido-2-deoxy-β-D-mannopyranosyl)-α-D-glucopyranosyl]-α,β-L-rhamnopyranose, a structural component of the capsular polysaccharide of *Streptococcus pneumoniae* type 19F, has been synthesized by sequential glycosylation reactions using the glycosyl acceptor 2,2,2-trichloroethyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (prepared from the known 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride), and the glycosyl donors 4-*O*-acetyl-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride and 4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-D-mannopyranosyl bromide (prepared in seven steps from the known methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside). The corresponding 8-(methoxycarbonyl)octyl glycoside has also been synthesized, by coupling of 8-(methoxycarbonyl)octyl trifluoromethanesulfonate and the sodium salt of 2-*O*-[4-*O*-(2-acetamido-4,6-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]-3,4-di-*O*-benzyl-α,β-L-rhamnopyranose.

INTRODUCTION

The pneumococcal polysaccharides have recently been attracting attention because of their use in a multivalent vaccine against pneumococcal infections[1]. Group 19 of *S. pneumoniae* is serologically classified into four types, 19A, 19B, 19C, and 19F, of which the type 19F polysaccharide has been used in the vaccine, based on surveys of the types of pneumococcal disease from which it has been isolated[2]. The structure of type 19F polysaccharide was independently elucidated in 1980 by Jennings *et al.*[3] and Miyazaki *et al.*[4] as being →4)-β-D-Man*p*NAc-(1→4)-α-D-Glc*p*-(1→2)-α-L-Rha*p*-(1-PO_4^-)→.

As part of a project on the synthesis of physiologically active carbohydrates, we describe here the synthesis of the trisaccharide **19** and the corresponding 8-(methoxycarbonyl)octyl glycoside (**22**) of **19** by sequential glycosylation reactions.

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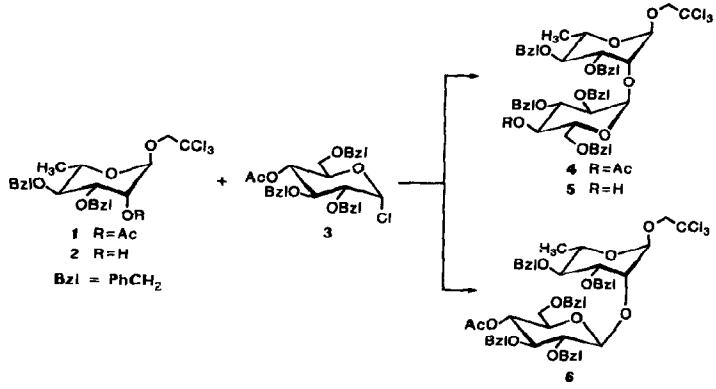
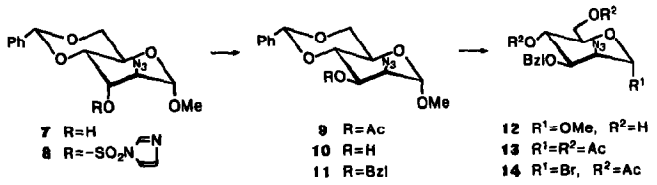
RESULTS AND DISCUSSION

In the stepwise synthesis of the trisaccharide **19**, we first synthesized the disaccharide acceptor **5** (which carries a free 4′-hydroxyl group) by coupling of the glycosyl acceptor **2** with the known[5] glycosyl donor **3**, and then coupled **5** with the glycosyl donor **14** to obtain the trisaccharide.



Reaction of 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride, which was prepared by the method reported by Bundle and Josephson[6], with 2,2,2-trichloroethanol in the presence of silver triflate and 1,1,3,3-tetramethylurea in dichloromethane gave 2,2,2-trichloroethyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**1**) in 94% yield. Deacetylation of **1** with sodium methoxide in methanol gave crystalline 2,2,2-trichloroethyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**2**) in 76.6% yield. Coupling of 4-*O*-acetyl-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride (**3**), which was prepared by a slight modification of the method reported by Ogawa *et al.*[5], with **2** in the presence of silver perchlorate and *sym*-collidine for 1 h at 0°, and chromatography of the product on a Lobar column, gave the disaccharide **4** and its β anomer (**6**) in 28.4 and 15.8% yields, respectively. The ^{13}C-n.m.r. data for **4** and **6** revealed two anomeric carbon atoms, C-1 and C-1′, at δ 98.0 ($^1J_{CH}$ 168 Hz) and δ 96.5 ($^1J_{CH}$ 166 Hz) in **4**, and at δ 100.3 ($^1J_{CH}$ 175 Hz) and δ 104.7 ($^1J_{CH}$ 164 Hz) in **6**, respectively. These $^1J_{CH}$ values indicated[7] the newly formed glycosidic bond to be α in **4** and β in **6**, respectively. The low selectivity of the glycosylation reaction was presumably due to the poor reactivity of the 2-hydroxyl group in **2**, because the 2,2,2-trichloroethyl group at the anomeric position decreased the reactivity of the hydroxyl groups in the rhamnoside[8]. When coupling of **2** with **3** was conducted in the presence of silver triflate and 1,1,3,3-tetramethylurea, or tetrabutylammonium bromide and diisopropylethylamine, no condensation products were obtained. Deacetylation of **4** with sodium methoxide in methanol gave 2,2,2-trichloroethyl 3,4-di-*O*-benzyl-2-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-α-L-rhamnopyranoside (**5**) in 85.3% yield.

Having prepared the disaccharide acceptor (**5**), we then synthesized the glycosyl donor **14** in which the 3-hydroxyl group had been protected with a benzyl group so that the phosphoric acid moiety might be introduced at the 4″-hydroxyl group in **19**. Treatment of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[9] (**7**) with sodium hydride in *N,N*-dimethylformamide for 30 min at 0°, followed by *N,N*-sulfuryldiimidazole[10] for 20 min at −40°, and chromatography of the product on silica gel, gave, in 96% yield, methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(*N*-imidazolylsulfonyl)-α-D-altropyranoside (**8**), which showed in the ^{1}H-n.m.r. spectrum a deshielded signal for H-3 at δ 4.77, with $J_{2,3} = J_{3,4} = 3$ Hz. Displacement of the 3-*O*-(*N*-imidazolylsulfonyl) group of **8** with tetrabutylammonium acetate in boiling toluene for 2 h, and chromatography of the product on a Lobar column, gave methyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside[10] (**9**) in 63.1% yield. The structure of **9** was assigned from the ^{1}H-n.m.r. spectrum, which contained a doublet of doublets for H-3 at δ 5.40, with $J_{2,3}$ 4.5 and $J_{3,4}$ 9 Hz. Deacetylation of **9** with sodium methoxide in methanol, and benzylation of the product with benzyl bromide and sodium hydride in *N,N*-dimethylformamide gave methyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (**11**) in 99% yield. Acid hydrolysis of the benzylidene group of **11** with hot hydrochloric acid in aq. acetone gave methyl 2-azido-3-*O*-benzyl-2-deoxy-α-D-mannopyranoside (**12**) in 91% yield. Treatment of **12** with acetic anhydride in the presence of conc. sulfuric acid for 17 h at −20°, and chromatography of the product on silica gel, gave 1,4,6-tri-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-D-mannopyranose (**13**) in 84.2% yield. Treatment of **13** with titanium tetrabromide in dichloromethane–ethyl acetate, and chromatography of the product on silica gel, gave 4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-D-mannopyranosyl bromide (**14**) in 56% yield.



Coupling of **5** with **14** in the presence of silver silicate[11] and powdered molecular sieves 4 A in dichloromethane–benzene overnight at room temperature, and chromatography of the product on a Lobar column, gave the desired trisaccharide **15** and its α anomer (**16**) in 32.7 and 5.2% yields, respectively. The ^{1}H-n.m.r. spectra of **15** and **16** contained three anomeric protons, for H-1, H-1′, and H-1″, at δ 4.97 with $J_{1,2}$ 2, at δ 4.86 with $J_{1',2'}$ 4, and at δ 4.52 with $J_{1'',2''}$ 1 Hz for **15**, and at δ 5.17 with $J_{1,2}$ 2, δ 4.97 with $J_{1',2'}$ 3.5, and δ 5.01 with $J_{1'',2''}$ 2 Hz for **16**, respectively. The ^{13}C-n.m.r. data for **15** and **16** also revealed three anomeric carbon atoms, C-1, C-1′, C-1″, at δ 98.6 ($^1J_{CH}$ 168 Hz), δ 97.2 ($^1J_{CH}$ 165.5 Hz), and δ 100.1 ($^1J_{CH}$ 158.5

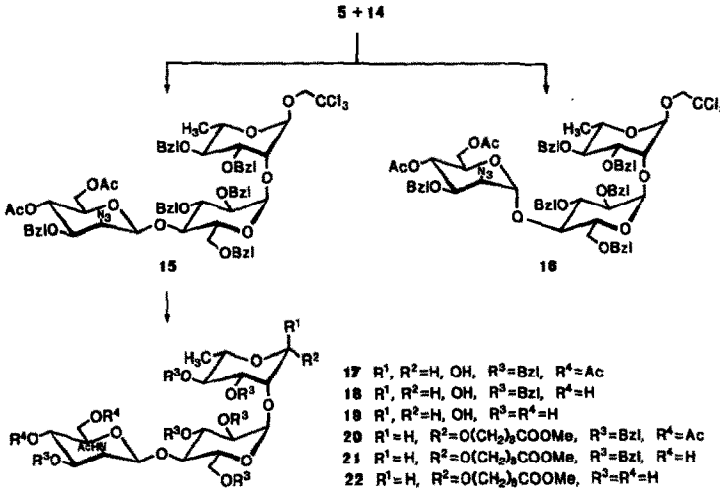
Hz) in **15**, and at δ 97.9 ($^1J_{CH}$ 169 Hz), δ 95.3 ($^1J_{CH}$ 165 Hz), and δ 100.5 ($^1J_{CH}$ 175 Hz) in **16**, respectively. These $^1J_{CH}$ values indicated the newly formed glycosidic bond to be β in **15** and α in **16**, respectively. When coupling of **5** with **14** was carried out with silver perchlorate and *sym*-collidine in ether–benzene for 2 h at 0°, **15** and **16** were obtained in 5.7 and 17% yields, respectively. Removal of the 2,2,2-trichloroethyl group and simultaneous reduction of the azido group to the amino group in **15** with a zinc–copper couple[12] in the presence of 2,4-pentanedione in *N*,*N*-dimethylformamide for 1 h at 60°, and acid hydrolysis of the resulting enaminoketone derivative with M hydrochloric acid in tetrahydrofuran, followed by *N*-acetylation of the hydrolysis product with acetic anhydride–methanol, gave the partially deblocked trisaccharide **17** in 65.5% yield. The structure of **17** was assigned from the ^{1}H-n.m.r. and secondary-ion mass spectra, which contained two singlets at δ 1.73 and 1.97 for *N*- and two *O*-acetyl groups, respectively, and a peak at *m/z* 1259 for $[MH + DEA]^+$, respectively. Deacetylation of **17** with sodium methoxide in methanol gave the *O*-deacetylated trisaccharide **18** in 86% yield. Catalytic hydrogenolysis of the benzyl groups in **18** over 10% palladium-on-charcoal in aq. methanol for 13.5 h at room temperature, and lyophilization of the product, gave the title trisaccharide **19**, which had $[\alpha]_D^{22.5}$ +52.5° (water), and a peak at *m/z* 530 for $[M + H]^+$ in the secondary-ion mass spectrum. As shown in Table I, the ^{13}C-n.m.r. data for **19** were identical with those for the phosphomonoesterase-treated B-unit reported by Miyazaki *et al.*[4].

To provide the linker arm necessary for attachment of the sugar sequence to the carrier proteins, we next synthesized the 8-(methoxycarbonyl)octyl glycoside of **19**. Compound **17** was treated with an equimolar amount of sodium hydride in tetrahydrofuran for 1 h at 0°, and the resulting glycosyl anion was treated with 8-(methoxycarbonyl)octyl triflate that had been freshly prepared from trifluoromethanesulfonic anhydride and 8-(methoxycarbonyl)octanol[13] in the presence of triethylamine in tetrahydrofuran for 1 h at 0°. Chromatography of the product on a Lobar column gave, in 64.5% yield, the 8-(methoxycarbonyl)octyl trisaccharide

TABLE I

^{13}C-N.M.R. DATA FOR SYNTHETIC AND NATURAL[4] POLYSACCHARIDES

Monosaccharide unit			*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*NAc*
Rha*p*	synthetic	α-form	92.4	78.2	70.1	72.0	69.4	17.5	
		β-form	94.6	81.8	73.0	72.3	71.4	17.5	
	natural	α-form	92.7	78.4	70.3	72.9	69.5	17.7	
		β-form	94.8	81.9	72.9	72.4	72.9	17.7	
Glc*p*	synthetic		98.5	72.0	72.1	79.5	71.1	61.2	
	natural		98.7	72.2	72.2	79.6	71.2	61.3	
Man*p*NAc	synthetic		100.1	54.1	72.8	67.4	77.3	60.6	22.9, 176.2
	natural		100.2	54.3	72.9	67.5	77.4	60.7	23.0, 176.3



(**20**), which had a peak at *m/z* 1429 for $[MH + DEA]^+$ in the secondary-ion mass spectrum. The ^{1}H-n.m.r. spectrum of **20** had a singlet at δ 3.62 and a triplet at δ 2.23 for methoxyl and $-CH_2CO-$ groups, respectively. The stereochemistry of the newly formed glycosidic bond was assigned from the ^{13}C-n.m.r. data, which had δ 101.6 ($^1J_{CH}$ 151 Hz), δ 96.0 ($^1J_{CH}$ 172 Hz), and δ 99.9 ($^1J_{CH}$ 160 Hz) for C-1, C-1′, and C-1″, respectively. Deacetylation of **20** with sodium methoxide in methanol, followed by catalytic hydrogenolysis of the benzyl groups over 10% palladium-on-charcoal under conditions similar to those used for **17**, gave 8-(methoxycarbonyl)-octyl 2-*O*-[4-*O*-(2-acetamido-2-deoxy-β-D-mannopyranosyl)-α-D-glucopyranosyl]-β-L-rhamnopyranoside (**22**), which had a peak at *m/z* 688 for $[M + H]^+$ in the secondary-ion mass spectrum. The ^{1}H-n.m.r. spectrum of **22** contained three anomeric protons, at δ 4.72 as a singlet, δ 4.80 with $J_{1',2'}$ 4, and δ 5.14 with $J_{1'',2''}$ 2 Hz, for H-1, H-1′, and H-1″, respectively, in accord with the stereochemistry assigned.

EXPERIMENTAL

General methods. — Melting points were measured with a Yanagimoto micro melting-point apparatus and were not corrected. Evaporations were conducted under diminished pressure. Optical rotations were measured in chloroform with a Perkin–Elmer Model 141 polarimeter, unless otherwise stated. Column chromatography was performed on columns of silica gel Merck (70–230 mesh; E. Merck, Darmstadt, Germany) or prepacked LiChroprep Si 60 Merck (40–63 μm; E. Merck, Darmstadt, Germany). ^{1}H-N.m.r. spectra were recorded with a Varian EM 390, XL-200, or XL-400 n.m.r. spectrometer, using tetramethylsilane as the internal standard. ^{13}C-N.m.r. spectra were recorded with a Varian XL-100-12A FT n.m.r. spectrometer operated at 25.16 MHz. The values of δ_H and δ_C are expressed

in p.p.m. downwards from the internal standard for the solutions in deuteriochloroform, unless otherwise stated. secondary-ion mass spectra (s.i.m.s.) were measured with a Hitachi M-68 mass spectrometer, with Xe as the primary ion gas, using glycerol, diethanolamine (DEA), or triethanolamine (TEA) as the matrix.

2,2,2-Trichloroethyl 2-O-acetyl-3,4-di-O-benzyl-α-L-rhamnopyranoside (**1**). — Silver triflate (3.53 g), 1,1,3,3-tetramethylurea (6.7 mL), and 2,2,2-trichloroethanol (1.45 mL) were dissolved in dichloromethane (50 mL), and 10 mL of the solvent was distilled off in an atmosphere of nitrogen. After being cooled to −78° in a Dry Ice–acetone bath, a solution of 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride[6] (5 g) in dichloromethane (10 mL) was added dropwise with stirring. The cooling bath was removed, and the temperature was allowed to rise gradually to room temperature. After stirring for 18 h, the mixture was filtered through Celite. The filtrate was successively washed with aqueous sodium hydrogencarbonate and water, dried (magnesium sulfate), and evaporated. The residue was purified on a Lobar column with 3:1 hexane–ethyl acetate, to give 6.09 g (94%) of **1** as a syrup; $[\alpha]_D^{23}$ −31.7° (*c* 1.060); n.m.r. data: δ_H 1.32 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.12 (s, 3 H, OAc), 3.43 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 4.97 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.43 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), and 7.30 (10 H, benzyl); δ_C 98.4 (C-1), 68.9 (C-2), 79.6 (C-3), 77.6 (C-4), 68.5 (C-5), 17.9 (C-6), 79.2 (CH_2CCl_3), 96.1 (CCl_3), 71.9 and 75.4 (2 CH_2Ph), and 21.0 and 170.1 (OAc).

Anal. Calc. for $C_{24}H_{24}Cl_3O_6$: C, 55.65; H, 5.25; Cl, 20.53. Found: C, 55.37; H, 5.13; Cl, 20.51.

2,2,2-Trichloroethyl 3,4-di-O-benzyl-α-L-rhamnopyranoside (**2**). — A solution of **1** (1.55 g) in methanol (20 mL) containing 0.35 mL of M sodium methoxide in methanol was kept for 4 h at room temperature, made neutral with Amberlite IR-120B (H^+) resin, and the resin filtered off and washed with methanol. The filtrate and washings were combined and evaporated. The residue was purified on a Lobar column with 3:1 hexane–ethyl acetate, and the product crystallized from ether–petroleum ether, to give 1.09 g (76.6%) of **2** as colorless prisms; m.p. 66.5–68°, $[\alpha]_D^{22.5}$ −58.1° (*c* 1.027); n.m.r. data: δ_H 1.30 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.63 (br.s., 1 H, OH), and 5.03 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1); δ_C 100.0 (C-1), 68.5 (C-2), 79.6 (C-3), 79.7 (C-4), 68.2 (C-5), 17.8 (C-6), 79.2 (CH_2CCl_3), 96.5 (CCl_3), and 72.3 and 75.4 (2 CH_2Ph).

Anal. Calc. for $C_{22}H_{22}Cl_3O_5$: C, 54.49; H, 5.40; Cl, 21.93. Found: C, 55.41; H, 5.22; Cl, 22.49.

2,2,2-Trichloroethyl 2-O-(4-O-acetyl-2,3,6-tri-O-benzyl-α-D-glucopyranosyl)-3,4-di-O-benzyl-α-L-rhamnopyranoside (**4**) *and its β anomer* (**6**). — To an ice-cooled solution of **2** (136 mg), 126 mg of 4-*O*-acetyl-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride[5] (**3**), and 0.042 mL of *sym*-collidine in a mixture of anhydrous benzene (4.6 mL) and anhydrous ether (0.55 mL) was added 9.1 mL of 0.035M etheral silver perchlorate, with stirring, in an atmosphere of argon. Stirring was continued for 1 h, and the resulting precipitate was removed by filtration and

washed with ether. The combined filtrate and washings were successively washed with aqueous sodium hydrogen carbonate and water, dried (magnesium sulfate), and evaporated. The residue was purified on a Lobar column with 2:1 hexane–ether. Each fraction was 12 mL. Fractions 23–27 crystallized from methanol, to give 40 mg (15.8%) of **6** as colorless prisms; m.p. 95–96°, $[\alpha]_D^{24}$ −18.9° (*c* 1.00); n.m.r. data: δ_H 1.27 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 1.80 (s, 3 H, OAc), and 7.0–7.5 (25 H, benzyl); δ_C 100.3 ($^1J_{CH}$ 175 Hz, C-1), 104.7 ($^1J_{CH}$ 164 Hz, C-1'), 18.0 (C-6), 79.2 (CH_2CCl_3), 96.5 (CCl_3), and 20.8 and 169.7 (OAc).

Anal. Calc. for $C_{51}H_{55}Cl_3O_{11}$: C, 64.45; H, 5.83; Cl, 11.19. Found: C, 64.59; H, 5.89; Cl, 11.40.

Fractions 31–35 gave 72 mg (28.4%) of **4** as a syrup; $[\alpha]_D^{24}$ +30.7° (*c* 1.059); n.m.r. data: δ_H 1.33 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 1.83 (s, 3 H, OAc), and 7.1–7.4 (25 H, benzyl); δ_C 98.0 ($^1J_{CH}$ 168 Hz, C-1), 96.5 ($^1J_{CH}$ 166 Hz, C-1'), 18.0 (C-6), 79.1 (CH_2CCl_3), and 20.8 and 169.4 (OAc).

Anal. Calc. for $C_{51}H_{55}Cl_3O_{11}$: C, 64.45; H, 5.83; Cl, 11.19. Found: C, 64.02; H, 6.00; Cl, 11.76.

*2,2,2-Trichloroethyl 3,4-di-*O*-benzyl-2-*O*-(2,3,6-tri-*O*-benzyl-α-*D*-glucopyranosyl)-α-*L*-rhamnopyranoside* (**5**). — Compound **4** (465 mg) was deacetylated with sodium methoxide in methanol as described for the preparation of **2**, and the product was chromatographed on a Lobar column with 1:1 hexane–ether, to give 379 mg (85.3%) of **5** as a syrup; $[\alpha]_D^{23}$ +23.1° (*c* 0.108); n.m.r. data: δ_H 1.32 (d, 3 H, $J_{5,6}$ 6 Hz, H-6) and 7.1–7.5 (25 H, benzyl); δ_C 98.3 (C-1), 96.7 (C-1), 18.1 (C-6), 79.1 (CH_2CCl_3), and 96.6 (CCl_3).

Anal. Calc. for $C_{49}H_{53}Cl_3O_{10}$: C, 64.79; H, 5.88; Cl, 11.71. Found: C, 65.07; H, 5.89; Cl, 11.81.

*Methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(N-imidazolylsulfonyl)-α-*D*-altropyranoside* (**8**). — Sodium hydride (918 mg, 50% dispersion in oil) was added with stirring to an ice-cooled solution of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[9] (**7**) (4.9 g) in *N,N*-dimethylformamide (98 mL) in an atmosphere of nitrogen, and the mixture was stirred for 30 min. After being cooled to −40° in a Dry Ice–acetone bath, *N,N'*-sulfuryldiimidazole (6.32 g) was added, and stirring was continued for 2 min. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (magnesium sulfate), and evaporated. The residue was purified by column chromatography on silica gel, and the product crystallized from ethyl acetate–hexane, to give 6.7 g of **8** as colorless prisms; m.p. 111–112°, $[\alpha]_D^{22.5}$ +50.2° (*c* 1.011); n.m.r. data: δ_H 3.43 (s, 3 H, OMe), 4.73 (s, 1 H, H-1), 4.77 (t, 1 H, $J_{2,3} = J_{3,4} = 3$ Hz, H-3), 5.51 (s, 1 H, benzylidene), and 6.87, 7.20, and 7.93 (each 1 H, imidazolyl); δ_C 98.5 (C-1), 58.4 (C-2), 72.5 (C-3), 78.0 (C-4), 60.3 (C-5), 68.8 (C-6), 55.8 (OMe), 102.2 (benzylidene), 118.3, 131.0, and 136.9 (imidazolyl), and 126.2, 128.2, 129.3, and 136.4 (benzylidene).

Anal. Calc. for $C_{17}H_{19}N_5O_7S$: C, 46.68; H, 4.38; N, 16.01; S, 7.33. Found: C, 46.96; H, 4.46; N, 15.87; S, 7.33.

Methyl 3-O-acetyl-2-azido-4,6-O-benzylidene-2-deoxy-α-D-mannopyranoside (**9**). — A solution of **8** (3.95 g) and tetrabutylammonium acetate (15.3 g) in anhydrous toluene (350 mL) was boiled under reflux for 2 h. After being cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (magnesium sulfate), and evaporated. The residue was purified on a Lobar column with 3:1 hexane–ethyl acetate, to give 1.99 g (63.1%) of **9** as a syrup; $[\alpha]_D^{25.5}$ +39.1° (*c* 1.005); n.m.r. data: δ_H 2.10 (s, 3 H, OAc), 3.37 (s, 3 H, OMe), 4.65 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.40 (dd, 1 H, $J_{2,3}$ 4.5, $J_{3,4}$ 9 Hz, H-3), 5.53 (s, 1 H, benzylidene), and 7.2–7.6 (m, 5 H, benzylidene); δ_C 99.9 (C-1), 62.1 (C-2), 70.3 (C-3), 75.8 (C-4), 63.8 (C-5), 68.7 (C-6), 55.1 (OMe), 102.0 (benzylidene), 126.1, 128.3, 129.1, and 137.1 (benzylidene), and 20.7 and 170.0 (OAc).

Anal. Calc. for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 55.07; H, 5.57; N, 11.94.

Methyl 2-azido-4,6-O-benzylidene-2-deoxy-α-D-mannopyranoside (**10**). — Compound **9** (1.9 g) was deacetylated with sodium methoxide in methanol as described for the preparation of **2**, to give 1.55 g (93%) of **10** as a syrup; $[\alpha]_D^{25}$ +69.5° (*c* 1.059); n.m.r. data: δ_H 2.97 (br.s., 1 H, OH), 3.12 (s, 3 H, OMe), 4.60 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.50 (s, 1 H, benzylidene), and 7.3–7.6 (m, 5 H, benzylidene); δ_C 100.1 (C-1), 63.4 (C-2), 69.0 (C-3), 79.0 (C-4), 63.7 (C-5), 68.7 (C-6), 55.2 (OMe), 102.3 (benzylidene), and 126.3, 128.4, 129.3, and 137.1 (benzylidene).

Anal. Calc. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.68. Found: C, 54.77; H, 5.60; N, 13.74.

Methyl 2-azido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-α-D-mannopyranoside (**11**). — Sodium hydride (34 mg, 50% dispersion in oil) was added to an ice-cooled solution of **10** (180 mg) in *N,N*-dimethylformamide (3 mL) in an atmosphere of nitrogen, with stirring. The mixture was stirred for 20 min, and benzyl bromide (0.08 mL) was added. After stirring for 1 h, the mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (magnesium sulfate), and evaporated. The residue was purified on a Lobar column with 4:1 hexane–ethyl acetate, to give 230 mg (99%) of **11** as a syrup; $[\alpha]_D^{23.5}$ +47.8° (*c* 1.056); n.m.r. data: δ_H 3.28 (s, 3 H, OMe), 4.58 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.64 and 4.82 (ABq, 2 H, J_{AB} 12 Hz, benzyl), 5.55 (s, 1 H, benzylidene), and 7.1–7.6 (m, 10 H, benzyl and benzylidene); δ_C 100.2 (C-1), 62.7 (C-2), 79.1 (C-3), 75.6 (C-4), 63.7 (C-5), 68.7 (C-6), 55.0 (OMe), 73.2 (benzyl), 101.6 (benzylidene), and 126.0, 127.5, 127.7, 128.4, 128.9, 137.5, and 138.1 (benzyl and benzylidene).

Anal. Calc. for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.46; H, 5.85; N, 10.60.

Methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannopyranoside (**12**). — A turbid solution of **11** (1.4 g) in a mixture of 2M hydrochloric acid (6 mL) and acetone (20 mL) was heated under reflux for 1 h. The acid was neutralized with solid barium carbonate, and the resulting precipitate was removed by filtration and washed with acetone. The filtrate and washings were combined, and evaporated. The residue

was purified by column chromatography on silica gel (ethyl acetate), to give 1.119 g (91.3%) of **12** as a syrup; $[\alpha]_D^{23.5}$ +32.9° (*c* 1.055); n.m.r. data: δ_H 3.35 (s, 3 H, OMe), 4.67 (s, 1 H, H-1), 4.63 and 4.67 (ABq, 2 H, J_{AB} 12 Hz, benzyl), and 7.38 (s, 5 H, benzyl); δ_C 99.4 (C-1), 60.5 (C-2), 79.4 (C-3), 66.9 (C-4), 72.2 (C-5), 62.3 (C-6), 55.0 (OMe), 72.5 (benzyl), and 128.0, 128.1, 128.6, and 137.6 (benzyl).

Anal. Calc. for $C_{14}H_{19}N_3O_5$: C, 54.36; H, 6.19; N, 13.58. Found: C, 54.57; H, 6.06; N, 13.52.

*1,4,6-Tri-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-*D*-mannopyranose* (**13**). — A solution of **12** (2.33 g) in 187mM sulfuric acid in acetic anhydride (142 mL) was kept for 17 h at −20°. The mixture was partitioned between ethyl acetate and water. The organic phase was successsively washed with aqueous sodium hydrogencarbonate and water, dried (magnesium sulfate), and evaporated. The residue was purified by column chromatography on silica gel with 2:1 hexane–ethyl acetate, to give 2.1 g of **13** as a syrup; $[\alpha]_D^{21}$ +41.8° (*c* 1.032); n.m.r. data: δ_H 2.00, 2.03, and 2.07 (3 s, 9 H, 3 OAc), 4.57 and 4.72 (ABq, 2 H, J_{AB} 12 Hz, benzyl), 5.33 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 6.03 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), and 7.35 (s, 5 H, benzyl); δ_C 91.8 (C-1), 60.1 (C-2), 76.1 (C-3), 67.0 (C-4), 71.2 (C-5), 62.2 (C-6), 72.6 (benzyl), and 20.7, 20.8, 168.2, 169.4, and 170.7 (3 OAc).

Anal. Calc. for $C_{19}H_{23}N_3O_8$: C, 54.15; H, 5.50; N, 9.97. Found: C, 54.17; H, 5.55; N, 10.02.

*4,6-Di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-*D*-mannopyranosyl bromide* (**14**). — A solution of **13** (130 mg) and titanium tetrabromide (125 mg) in a mixture of dichloromethane (4 mL) and ethyl acetate (0.8 mL) was kept for 50 h at room temperature. The solution was diluted with acetonitrile (2 mL) and sodium acetate (500 mg) was added with stirring. Stirring was continued until the color of the mixture had disappeared. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by column chromatography on silica gel, to give 76 mg of **15** as a syrup; $[\alpha]_D^{23}$ +146.4° (*c* 0.845); n.m.r. data: δ_H 2.0 and 2.05 (2 s, 6 H, 2 OAc), 4.65 (s, 2 H, benzyl), 5.35 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 6.33 (s, 1 H, H-1), and 7.37 (s, 5 H, benzyl), which was used in the glycosylation reaction immediately after preparation.

*2,2,2-Trichloroethyl 2-*O*-[2,3,6-tri-*O*-benzyl-4-*O*-(4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-β-*D*-mannopyranosyl)-α-*D*-glucopyranosyl]-3,4-di-*O*-benzyl-α-*L*-rhamnopyranoside* (**15**) *and its β anomer* (**16**). — (*A*) Compounds **14** (445 mg) and **5** (640 mg) were dissolved in anhydrous benzene (30 mL), and 15 mL of the solvent was removed by distillation in an atmosphere of nitrogen. After being cooled to room temperature dichloromethane (15 mL) and powdered molecular sieves 4 A (900 mg) were added. The mixture was stirred for 1 h, silver silicate[11] (900 mg) was added, and stirring was continued overnight. The mixture was filtered through Celite, and the filtrate was evaporated. The residue was purified on a Lobar column with 3:1 hexane–ethyl acetate. Each fraction was 16 mL. Fractions 25–30 gave 47 mg (5.2%) of **16** as a syrup; $[\alpha]_D^{23}$ +30.1° (*c* 0.339), n.m.r. data: δ_H (400 MHz): 1.40 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6), 1.99 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 4.04 (d, 1

H, J_{AB} 10.5 Hz, CH_2CCl_3), 4.20 (d, 1 H, CH_2CCl_3), 4.97 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1'), 5.01 (d, 1 H, $J_{1'',2''}$ 2 Hz, H-1''), 5.17 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 5.25 (t, 1 H, $J_{3'',4''} = J_{4'',5''} = 10$ Hz, H-4''), and 7.18–7.40 (m, 30 H, benzyl); δ_C 97.9 ($^1J_{CH}$ 169 Hz, C-1), 95.3 ($^1J_{CH}$ 165 Hz, C-1'), 100.5 ($^1J_{CH}$ 175 Hz, C-1''), 18.0 (C-6), 96.5 (CCl_3), and 20.7, 20.8, 169.2, and 170.6 (2 OAc).

Anal. Calc. for $C_{66}H_{72}Cl_3N_3O_{16}$: C, 62.43; H, 5.72; Cl, 8.38; N, 3.31. Found: C, 62.43; H, 5.63; Cl, 8.38; N, 3.36.

Fractions 52–92 gave 293 mg (32.7%) of **15** as a syrup; $[\alpha]_D^{24.5}$ +4.9° (*c* 0.486); n.m.r. data: δ_H (400 MHz): 1.37 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6), 1.95 (s, 3 H, OAc), 1.97 (s, 3 H, OAc), 3.12 (ddd, 1 H, $J_{4',5'}$ 10, $J_{5',6'a}$ 2.3, $J_{5',6'b}$ 4.9 Hz), 3.52 (dd, 1 H, $J_{2,3}$ 4, $J_{3,4}$ 9.5 Hz, H-3), 3.59 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.72 (dd, $J_{1'',2''}$ 2, $J_{2'',3''}$ 3.5 Hz, H-2''), 4.11 (dd, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 4 Hz, H-2), 4.02 (d, 1 H, J_{AB} 11.5 Hz, CH_2CCl_3), 4.17 (d, 1 H, CH_2CCl_3), 4.52 (d, 1 H, $J_{1'',2''}$ 1 Hz, H-1''), 4.86 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), 4.97 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 5.15 (t, 1 H, $J_{3'',4''} = J_{4'',5''} = 10$ Hz, H-4''), and 7.18–7.40 (m, 30 H, benzyl); δ_C 98.6 ($^1J_{CH}$ 168 Hz, C-1), 97.2 ($^1J_{CH}$ 165.5 Hz, C-1'), 100.1 ($^1J_{CH}$ 158.5 Hz, C-1''), 18.0 (C-6), 96.6 (CCl_3), and 20.7, 20.8, 169.3, and 170.8 (2 OAc).

Anal. Calc. for $C_{66}H_{72}Cl_3O_{16}$: C, 62.43; H, 5.72; Cl, 8.38; N, 3.31. Found: C, 62.39; H, 5.63; Cl, 8.39; N, 3.52.

(*B*) Compounds **5** (112 mg) and **14** (54 mg) were dissolved in anhydrous benzene (6 mL) and 3 mL of the solvent was removed by distillation in an atmosphere of argon. After being cooled to 0°, anhydrous ether (2 mL) and *sym*-collidine (0.02 mL) were added, followed by 76mM ethereal silver perchlorate (2.02 mL) and the mixture was stirred for 2 h. The resulting precipitate was filtered off. The filtrate was successively washed with aqueous sodium hydrogencarbonate and water, dried (magnesium sulfate), and evaporated. The residue was purified by column chromatography on silica gel as already described, to give 26 mg (17%) of **16** and 9 mg (5.7%) of **15**.

2-O-[4-O-(2-Acetamido-4,6-di-O-acetyl-3-O-benzyl-2-deoxy-β-D-mannopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl]-3,4-di-O-benzyl-α,β-L-rhamnopyranose (**17**). — A mixture of **15** (800 mg), 2,4-pentanedione (1.6 mL) and zinc–copper couple[12] (2.01 g) in *N,N*-dimethylformamide (14 mL) was stirred for 1 h at 60°. After being cooled to room temperature, the mixture was filtered through Celite. The filtrate was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (magnesium sulfate), and evaporated. The residue was dissolved in tetrahydrofuran (30 mL), and M hydrochloric acid (3.8 mL) was added. The solution was kept for 1 h at room temperature, and then evaporated. The residue was dissolved in methanol containing acetic anhydride (0.32 mL) and triethylamine (0.088 mL) was added dropwise, with stirring. The mixture was stirred for 1 h and then evaporated. The residue was purified on a Lobar column with 1:1 hexane–ethyl acetate, to give 470 mg (65.5%) of **17** as a colorless powder; $[\alpha]_D^{26}$ +17.9° (*c* 0.312); s.i.m.s. (diethanolamine): *m/z* 1259 $[MH + DEA]^+$; n.m.r. data: δ_H 1.30 and 1.38 (2 d, 3 H, H-6), 1.73 and 1.97 (2 s, 9 H, OAc and NAc), and 7.1–7.7 (m, 30 H, benzyl).

Anal. Calc. for $C_{66}H_{75}NO_{17} \cdot 0.5\ H_2O$: C, 68.14; H, 6.59; N, 1.20. Found: C, 68.13; H, 6.55; N, 1.19.

2-O-[4-O-(2-Acetamido-3-O-benzyl-2-deoxy-β-D-mannopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl]-3,4-di-O-benzyl-α,β-L-rhamnopyranose (**18**). — Compound **17** (93 mg) was deacetylated with sodium methoxide in methanol as described for the preparation of **2**, and the product was purified on a Lobar column with 3:1 ethyl acetate–hexane, to give 83 mg (86%) of **18** as a colorless powder; $[\alpha]_D^{23}$ +16.8° (*c* 0.427); s.i.m.s. (glycerol): 1070 $[M + H]^+$; n.m.r. data: δ_H (CD_3OD): 1.25 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 1.93 (s, 3 H, NAc), and 7.1–7.7 (m, 30 H, benzyl).

Anal. Calc. for $C_{62}H_{71}NO_{15}$: C, 69.58; H, 6.69; N, 1.31. Found: C, 69.31; H, 6.60; N, 1.41.

2-O-[4-O-(2-Acetamido-2-deoxy-β-D-mannopyranosyl)-α-D-glucopyranosyl]-α,β-L-rhamnopyranose (**19**). — A solution of **18** (45 mg) in a mixture of methanol (19 mL) and water (3 mL) was hydrogenolyzed over 10% palladium-on-charcoal (33 mg) for 13.5 h at room temperature. After removal of the catalyst by filtration, the filtrate was evaporated. The residue was dissolved in water, and the solution was lyophilized, to give **19** (45 mg) as a colorless powder; $[\alpha]_D^{22.5}$ +52.5° (*c* 0.408); s.i.m.s. (glycerol): *m/z* 530 $[M + H]^+$; n.m.r. data: δ_H (D_2O): 1.77 (d, 3 H, $J_{5,6}$ 6 Hz, H-6) and 2.05 (s, 3 H, NAc).

Anal. Calc. for $C_{20}H_{35}NO_5 \cdot 3\ H_2O$: C, 41.16; H, 7.08; N, 2.40. Found: C, 41.39; H, 6.84; N, 2.54.

8-(Methoxycarbonyl)octyl 2-O-[2-acetamido-4,6-di-O-acetyl-3-O-benzyl-2-deoxy-β-D-mannopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl]-3,4-di-O-benzyl-β-L-rhamnopyranoside (**20**). — (*A*) Trifluoromethanesulfonic anhydride (0.28 mL) was added to an ice-cooled solution of 8-(methoxycarbonyl)octanol[13] (320 mg) and triethylamine (0.28 mL) in anhydrous benzene (5 mL) in an atmosphere of nitrogen. After being stirred for 30 min, the mixture was diluted with benzene (5 mL), adsorbed onto a column of silica gel (10 g) and eluted with benzene (100 mL), to give 376 mg (69.1%) of 8-(methoxycarbonyl)octyl trifluoromethanesulfonate as a syrup, n.m.r. data: δ_H 1.2–2.1 (m, 12 H, $-(CH_2)_6-$), 2.32 (t, 2 H, *J* 7.5 Hz, $-CH_2CO-$), 3.70 (s, 3 H, OMe), and 4.55 (t, 2 H, *J* 6 Hz, $-CH_2OSO_2CF_3$).

(*B*) Sodium hydride (10 mg, 50% dispersion in oil) was added to an ice-cooled solution of **17** (166 mg) in anhydrous tetrahydrofuran (10 mL) in an atmosphere of nitrogen. After stirring for 1 h, a solution of 8-(methoxycarbonyl)octyl trifluoromethanesulfonate (68 mg) in tetrahydrofuran (1.5 mL) was added, and stirring was continued for 1 h. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (magnesium sulfate), and evaporated. The residue was purified on a Lobar column with 2:1 hexane–ethyl acetate, to give 122 mg (64.5%) of **20** as a colorless powder; $[\alpha]_D^{23.5}$ +50.2° (*c* 0.209); s.i.m.s. (diethanolamine); *m/z* 1429 $[MH + DEA]^+$; n.m.r. data: δ_H 1.1–1.7 (m, 12 H, 6-CH_2–), 1.37 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 1.77 and 1.95 (2 s, 9 H, OAc and NAc), 2.23 (t, 2 H, *J* 7.5 Hz, $-CH_2CO-$), 3.62 (s, 3 H, OMe), and 7.1–7.7 (m,

30 H, benzyl); δ_C 101.6 ($^1J_{CH}$ 151 Hz, C-1), 96.0 ($^1J_{CH}$ 172 Hz, C-1'), 99.9 ($^1J_{CH}$ 160 Hz, C-1''), 18.0 (C-6), 51.4 (OMe), 20.8, 23.3, 169.5, and 170.5 (2 OAc and NAc), and 174.2 (CO).

Anal. Calc. for $C_{76}H_{93}NO_{19} \cdot 0.5\ H_2O$: C, 68.45; H, 7.11; N, 1.05. Found: C, 68.54; H, 7.10; N, 1.14.

8-(Methoxycarbonyl)octyl 2-O-[4-O-(2-acetamido-3-O-benzyl-2-deoxy-β-D-mannopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl]-3,4-di-O-benzyl-β-L-rhamnopyranoside (**21**). — Compound **20** (87 mg) was deacetylated with sodium methoxide in methanol as described for the preparation of **2**, to give 75 mg (92.6%) of **21** as a colorless powder; $[\alpha]_D^{21}$ +45° (*c* 0.324); s.i.m.s. (triethanolamine): *m/z* 1390 [MH + TEA]$^+$; n.m.r. data: δ_H 1.1–1.8 (m, 12 H, 6–CH_2–), 1.38 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 1.80 (s, 3 H, NAc), 2.25 (t, 2 H, *J* 7.5 Hz, –CH_2CO–), 3.62 (s, 3 H, OMe), and 7.1–7.6 (m, 30 H, benzyl).

Anal. Calc. $C_{72}H_{89}NO_{17} \cdot 0.6\ H_2O$: C, 68.61; H, 7.21; N, 1.11. Found: C, 68.85; H, 7.23; N, 1.13.

8-(Methoxycarbonyl)octyl 2-O-[4-O-(2-acetamido-2-deoxy-β-D-mannopyranosyl)-α-D-glucopyranosyl]-β-L-rhamnopyranoside (**22**). — A solution of **21** (69 mg) in aq. methanol was hydrogenolyzed over 10% palladium-on-charcoal as described for the preparation of **19**, the product dissolved in water, and the solution lyophilized, to give 29 mg of **22** as a colorless powder; $[\alpha]_D^{20.5}$ +30.4° (*c* 0.286, water); s.i.m.s. (glycerol): *m/z* 688 [M + H]$^+$; n.m.r. data: δ_H (200 MHz, D_2O): 1.29 (m, 11 H, 4 –CH_2– and H-6), 1.32 (m, 4 H, 2 –CH_2–), 2.06 (s, 3 H, NAc), 2.38 (t, 2 H, *J* 6 Hz, –CH_2CO–), 3.68 (s, 3 H, OMe), 4.72 (s, 1 H, H-1), 4.88 (d, 1 H, $J_{1'',2''}$ 2 Hz, H-1''), and 5.14 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1').

Anal. Calc. for $C_{29}H_{53}NO_{17} \cdot 2\ H_2O$: C, 48.12; H, 7.94; N, 1.94. Found: C, 48.40; H, 7.83; N, 1.85.

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