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# Synthesis of 2-(4-aminophenyl)ethyl 3-deoxy-5-*O*-(3,4,6-tri-*O*-β-D-glucopyranosyl-α-D-glucopyranosyl)-α-D-*manno*-oct-2-ulopyranosidonic acid, a highly branched pentasaccharide corresponding to structures found in lipopolysaccharides from *Moraxella catarrhalis*

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**Abstract**

Syntheses of the pentasaccharide 2-(4-aminophenyl)ethyl 3-deoxy-5-*O*-(3,4,6-tri-*O*-β-D-glucopyranosyl-α-D-glucopyranosyl)-α-D-*manno*-oct-2-ulopyranosidonic acid and of the tetrasaccharide 3,4,6-tri-*O*-β-D-glucopyranosyl-α-D-glucopyranoside, both as its methyl and 2-(4-trifluoroacetamidophenyl)ethyl glycoside, are described. These oligosaccharides correspond to structures found in the lipopolysaccharide of *Moraxella catarrhalis* and were needed for biological experiments aimed at producing antibodies against the bacteria. The best way to introduce the glucopyranosyl groups into the 3-, 4-, and 6-positions of the branched target compounds was found to be a one-step reaction using a 3,4,6-triol as acceptor and 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl bromide as donor in a silver trifluoromethanesulfonate-promoted coupling. The spacer arm, necessary for the formation of immunoactive glycoconjugates, was introduced into the glucose moiety via a dimethyl(methylthio)sulfonium trifluoromethanesulfonate-promoted reaction using the ethyl thioglucoside as donor, whereas for Kdo, the acetylated glycal derivative, methyl 4,5,7,8-tetra-*O*-acetyl-2,6-anhydro-3-deoxy-D-*manno*-oct-2-enonate, was used as donor and phenylselenyl trifluoromethanesulfonate as a stereocontrolling promoter.

*Keywords:* Carbohydrates; Oligosaccharide synthesis; Bacterial antigens; Kdo; Glycoconjugates

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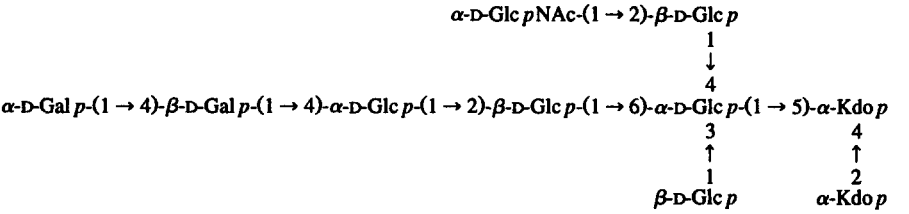
## 1. Introduction

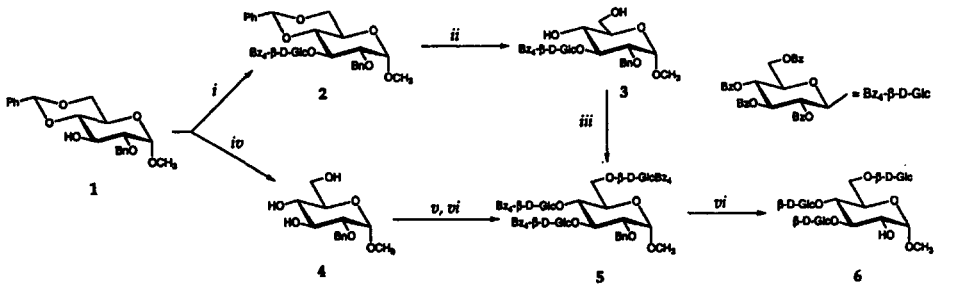
*Moraxella catarrhalis* has been increasingly recognized as a major pathogen in a number of respiratory diseases, especially in children [1]. The structure of the cell-surface lipopolysaccharide (LPS) produced by *M. catarrhalis* serotype A has recently been determined [2,3]. It lacks the extended polymeric O-antigenic side chains and the structure without the lipid A part is shown below.



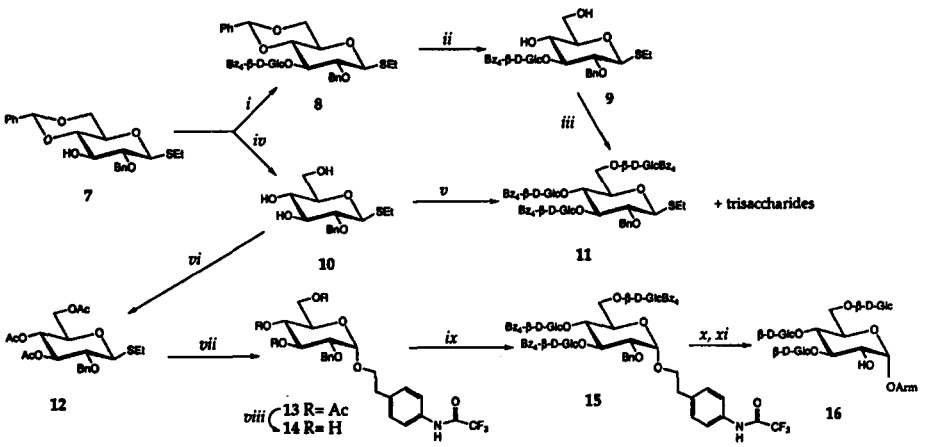

To investigate whether parts of the LPS structure can induce production of antibodies that will protect against disease and accordingly function as a vaccine, synthesis of partial structures of the LPS was of interest. As a primary target, structures containing the glucose branching point, which also is known to be part of the LPS from serogroup C [4], were selected. Thus, the title pentasaccharide and the integral tetrasaccharide 3,4,6-tri-*O*-β-D-glucopyranosyl-α-D-glucopyranose, lacking the Kdo-moiety, have been synthesized, both as their spacer glycosides, which will enable the formation of immunoactive neo-glycoconjugates.

## 2. Results and discussion

One of the main points that has to be considered in the synthesis of the target compounds is the best way to introduce the three substituents into the branched central glucosyl residue. To find out if this is best performed via a one-step reaction or a consecutive introduction of the substituents, methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-




Scheme 1. (*i*) 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide ($Bz_4GlcBr$), AgOTf; (*ii*) 70% HOAc (aq); (*iii*) $Bz_4GlcBr$, AgOTf; (*iv*) 70% HOAc (aq); (*v*) $Bz_4GlcBr$, AgOTf; (*vi*) $MeO^-$; (*vii*) $H_2$, Pd–C.

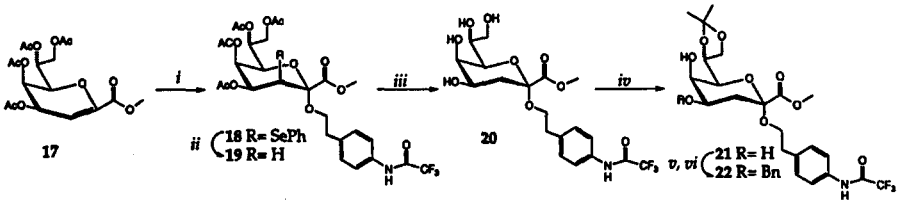



Scheme 2. (*i*) $Bz_4GlcBr$, AgOTf; (*ii*) 70% HOAc (aq); (*iii*) $Bz_4GlcBr$, AgOTf; (*iv*) 70% HOAc (aq); (*v*) $Bz_4GlcBr$, AgOTf; (*vi*) $Ac_2O$, pyridine; (*vii*) 2-(4-trifluoroacetamidophenyl)ethanol, DMTST; (*viii*) $MeO^-$; (*ix*) $Bz_4GlcBr$, AgOTf; (*x*) $MeO^-$; (*xi*) $H_2$, Pd–C.

glucopyranoside (**1**) [5] was chosen as a model starting material and manipulated in two different ways (Scheme 1). A silver trifluoromethanesulfonate (silver triflate)-promoted coupling reaction with **1** as acceptor and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (benzobromoglucose) [6] as donor gave the (1 → 3)-β-linked disaccharide **2** (82%), which was debenzylidenated (→ 4,6-diol **3**, 77%) and then once more coupled with benzobromoglucose, using silver triflate as promoter, to give the protected target tetrasaccharide **5** in 72% yield (45% overall yield from **1**). On the other hand, **1** was directly debenzylidenated (→ 3,4,6-triol **4**, 95%), and then the three glucosyl groups were introduced all at the same time in a coupling reaction using the same donor and promoter as above to yield 81% of **5** (77% overall yield from **1**). Compound **5** was then deprotected using standard conditions, i.e., Zemplén deacylation and catalytic hydrogenolysis, to give **6** (65%), which can be used for NMR studies and inhibition experiments.

So, according to these model studies the three substituents could be introduced either way; the first pathway, although giving lower overall yield, has the advantage of giving intermediates that can be used in the synthesis of other structures of the lipopolysaccharide with different substituents at the branching points.

The same synthetic pathways were tested using the corresponding ethyl 1-thio-β-D-glucopyranoside **7** [7] as starting material (Scheme 2). Once more, coupling with benzobromoglucose, using silver triflate as promoter, gave a high yield (86%) of the (1 → 3)-β-linked disaccharide **8**, which was debenzylidenated to yield the 4,6-diol **9**. The direct removal of the benzylidene acetal from **7** (→ **10**, 92%) was also without problem, but when the glucosylation of diol **9** or triol **10** with benzobromoglucose was attempted, a large quantity of a trisaccharide (probably 3,6-linked) was obtained in a mixture with the wanted tetrasaccharide **11**, which was difficult to separate. Whether this lower yield of the tetrasaccharide was due to the thio function or the different

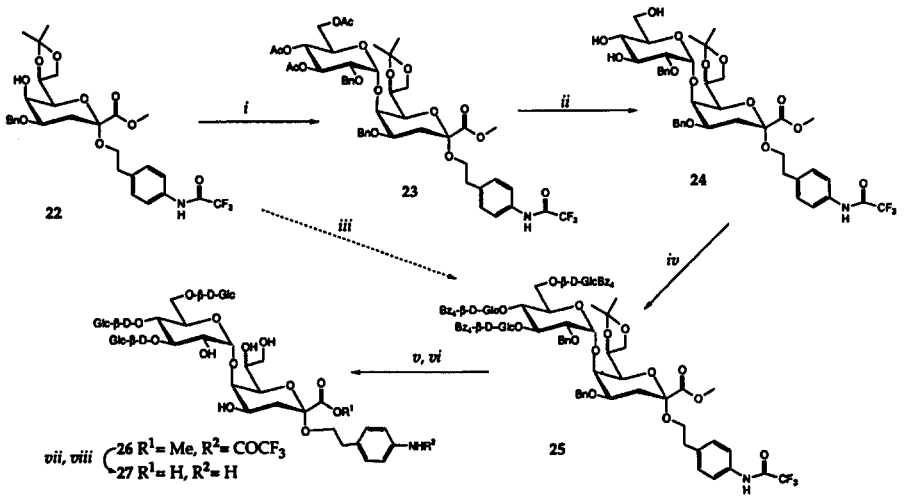


Scheme 3. (*i*) 2-(4-Trifluoroacetamidophenyl)ethanol, PhSeCl, AgOTf, TMSOTf; (*ii*) $Bu_3SnH$; (*iii*) $MeO^-$; (*iv*) $Me_2C(OMe)_2$, *p*-TsOH; (*v*) $Bu_2SnO$; (*vi*) BnBr, $Et_4NBr$.

anomeric configuration (compared to **3** and **4** above) was not investigated. When **10** was converted into the $\alpha$-*O*-linked spacer glycoside **14** via acetylation (→ **12**, 93%), coupling with the spacer 2-(4-trifluoroacetamidophenyl)ethanol using dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) [8] as promoter (→ **13**, 92%), and finally deacetylation (→ **14**, 96%), this derivative in the same type of glycosylation reaction once more produced a good yield (71%) of the tetrasaccharide **15**. Deacylation with sodium methoxide in methanol and then debenzylation using catalytic hydrogenolysis of **15** gave the target spacer tetrasaccharide **16** (50%) ready for attachment to carriers and formation of neo-glycoconjugates.

In the synthesis of the title pentasaccharide another issue is the introduction of the spacer arm into the Kdo moiety. Several acetylated methyl ester Kdo donors were tried, including the glycosyl bromide, the ethyl 2-thio-$\beta$-glycoside, and the 2,3-glycal derivative (**17**) [9]. The ethyl 2-thio-$\beta$-glycoside promoted by DMTST gave a high yield of spacer glycoside (82%) [9], but, as observed earlier by van Boom and co-workers [10], mainly the $\beta$ configuration was obtained. Since the naturally occurring $\alpha$ configuration was desired, the method described by Achiwa and co-workers [11], using the glycal **17** [12] as donor and phenylselenyl triflate prepared in situ as promoter, was used instead (Scheme 3). Compound **18** was obtained and subsequent reduction of the phenylselenium group using triphenyltin hydride gave the $\alpha$-linked spacer Kdo-derivative **19** in an overall yield of 93%. The following manipulations to obtain a suitably protected Kdo acceptor followed the protocol used by Hasegawa and co-workers [13]. Deacetylation (→ **20**), regioselective isopropylidenation (→ **21**), and finally regioselective benzylation using tin activation gave **22**, with a free OH-5 ready for glycosidation.

The one-step introduction of the three branching substituents was chosen in the synthesis of the title pentasaccharide (Scheme 4). Thus, coupling of **22** with donor **12** using DMTST as promoter gave the (1 → 5)-$\alpha$-linked disaccharide **23** (84%), which was deacetylated to yield the triol **24** (83%). The coupling between **24** and benzobromoglucose with silver triflate as promoter gave the fully glycosylated pentasaccharide in a complex mixture with different tetrasaccharides. Fortunately these compounds could be separated by HPLC to give pure **25** in 38% yield. Attempts to use the corresponding ethyl thioglycoside as donor in a DMTST-promoted reaction resulted in a lower yield of the pentasaccharide **25**. Another approach was also tried, in which the tetrasaccharide donor **11** made earlier was used in a DMTST-promoted coupling with **22** as acceptor, but this reaction gave almost no yield of **25** (according to TLC). Deprotection of **25** by



Scheme 4. (*i*) **12**, DMTST; (*ii*) $MeO^-$; (*iii*) **11**, DMST; (*iv*) $Bz_4GlcBr$, AgOTf; (*v*) $MeO^-$; (*vi*) $H_2$, Pd–C; (*vii*) NaOH (aq); (*viii*) HCl (aq).

acid hydrolysis followed by Zemplén deacylation and catalytic hydrogenolysis gave the methyl ester derivative **26** (70%), which after saponification gave the title compound **27**.

## 3. Experimental

*General methods.*—These were as previously described [14]. NMR spectra in $D_2O$ were recorded at 25°C (unless otherwise stated) using acetone ($\delta = 31.0$, $^{13}C$) or sodium 3-trimethylsilyl[$^2H_4$]propanoate (TSP) ($\delta = 0.00$, $^1H$) as references.

*Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-benzoyl-β-D-gluco-pyranosyl)-α-D-glucopyranoside* (**2**).—Silver triflate was added at −30°C to a stirred solution of **1** [5] (200 mg, 0.54 mmol) and benzobromoglucose [6] (540 mg, 0.82 mmol) in $CH_2Cl_2$ (25 mL) containing molecular sieves (4 Å). After 30 min triethylamine (1 mL) was added and the stirring was continued for 20 min. The mixture was diluted with $CH_2Cl_2$, filtered through Celite, concentrated, and purified by silica gel chromatography (10:1 toluene–EtOAc) to give **2** (420 mg, 82%); mp 180–182°C (from EtOAc–hexane); $[\alpha]_D$ −21° (*c* 1.0, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 55.2 (OMe), 62.2, 63.2, 68.9, 69.8, 71.9, 72.3, 73.3, 74.1, 77.7, 79.4, 79.7 (C-2–6, C-2′–6′, $OCH_2Ph$), 98.9, 101.1, 101.3 (C-1, C-1′, PhCH), 125.3–138.1 (Ph), 165.1, 165.3, 165.8, 166.1 (PhCO). Anal. Calcd for $C_{55}H_{50}O_{15}$: C, 69.5; H, 5.3. Found: C, 69.3; 5.4.

*Methyl 2-O-benzyl-α-D-glucopyranoside* (**4**).—Glycoside **1** [5] (400 mg, 1.07 mmol) was dissolved in AcOH (70% aq, 40 mL) and stirred at 70°C. After 30 min the solution was concentrated and the residue purified by silica gel chromatography (11:1 $CHCl_3$–MeOH) to give **4** (290 mg, 95%); mp 120–122°C (from EtOAc–hexane), $[\alpha]_D$ +80° (*c* 1.0, MeOH); NMR data ($CD_3OD$): $^{13}C$, δ 55.4 (OMe), 62.5, 71.7, 73.2, 74.0, 74.2, 80.9

(C-2–6, O*C*$H_2$Ph), 99.2 (C-1), 128.8–139.8 (Ph). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.1; H, 7.1. Found: C, 59.1; H, 7.1.

*Methyl 2-O-benzyl-3,4,6-tri-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside* (**5**).—*Route 1.* Silver triflate (410 mg, 1.6 mmol) was added at −20°C to a stirred solution of **4** (76 mg, 0.27 mmol) and benzobromoglucose [6] (790 mg, 1.2 mmol) in $CH_2Cl_2$ containing molecular sieves (4 Å). After 1 h, triethylamine (1 mL) was added, and the stirring was continued for 20 min. The mixture was diluted with $CH_2Cl_2$, filtered through Celite, concentrated, and purified by silica gel chromatography (8:1 toluene–EtOAc) to give **5** (437 mg, 81%); $[\alpha]_D$ +25° (*c* 0.8, $CHCl_3$); NMR data ($CDCl_3$): $^{13}$C, δ 54.8 (OMe), 62.8, 63.3, 63.8, 68.6, 69.1, 69.6, 70.2, 71.8, 71.9, 72.1, 72.6, 72.7, 73.2, 73.4, 73.8, 75.7, 77.2, 81.2 (C-2–6, C-2′–6′, C-2″–6″, C-2‴–6‴, O*C*$H_2$Ph), 97.0, 99.0, 100.2, 101.5 (C-1–1‴), 127.9–137.7 (Ph), 164.6–166.0 (Ph*C*O). Anal. Calcd for $C_{116}H_{98}O_{33}$: C, 69.0; H, 4.9. Found: C, 68.5; H, 4.9.

*Route 2.* Disaccharide **2** (186 mg, 0.20 mmol) was dissolved in aq 70% AcOH (20 mL) and stirred at 70°C. After 1 h the solution was concentrated and the product purified by silica gel chromatography (1:1 toluene–EtOAc) to give methyl 2-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**3**, 130 mg, 77%); NMR data ($CDCl_3$): $^{13}$C, δ 55.0 (OMe), 62.8, 69.4, 69.6, 70.7, 71.7, 72.6, 72.8, 73.7, 78.0, 83.9 (C-2–6, C-2′–6′, O*C*$H_2$Ph), 98.0 (C-1), 101.7 (C-1′), 127.7–138.0 (Ph), 165.1, 165.2, 165.7, 166.1 (Ph*C*O). Silver triflate was added at −20°C to a stirred solution of **3** (195 mg, 0.23 mmol) and benzobromoglucose (450 mg, 0.68 mmol) in $CH_2Cl_2$ (5 mL) containing molecular sieves (4 Å). The mixture was stirred for 2 h and the temperature was slowly increased to −5°C. Triethylamine (1 mL) was added and the stirring was continued for 20 min. The mixture was diluted with $CH_2Cl_2$, filtered through Celite, concentrated, and purified by silica gel chromatography (8:1 toluene–EtOAc) to give **5** (330 mg, 72%), which was identical to the material obtained via Route 1 above.

*Methyl 3,4,6-tri-O-β-D-glucopyranosyl-α-D-glucopyranoside* (**6**).—A solution of **5** (340 mg, 0.17 mmol) in dry MeOH (20 mL) was treated with a catalytic amount of 1 M methanolic NaOMe at room temperature. After 1 h the solution was neutralized with Dowex-50 ($H^+$) ion-exchange resin, filtered, and hydrogenolyzed over 10% Pd–C (50 mg) at 400 kPa for 20 h. The mixture was filtered, concentrated, dissolved in $H_2O$, and washed with diethyl ether. The water phase was concentrated and the residue was purified by reversed-phase HPLC (95:5 $H_2O$–MeOH) to give, after lyophilization, **6** (75 mg, 65%); $[\alpha]_D$ +52° (*c* 1.0, $H_2O$); NMR data ($D_2O$): $^{13}$C, δ 55.9 (OMe), 61.3, 61.5, 68.1, 70.1, 70.2, 70.3, 70.4, 72.3, 73.7, 73.8 (2 C), 74.4, 76.3, 76.4, 76.5, 76.6, 76.8, 77.1 (C-2–6, C-2′–6′, C-2″–6″, C-2‴–6‴), 99.8 ($J_{C\text{-}1,H\text{-}1}$ 172 Hz, C-1), 101.8 ($J_{C\text{-}1,H\text{-}1}$ 163 Hz), 102.1 ($J_{C\text{-}1,H\text{-}1}$ 165 Hz), 103.0 ($J_{C\text{-}1,H\text{-}1}$ 167 Hz) (C-1′–1‴); $^1$H (70°C), δ 4.50 (d, $J_{1,2}$ 7.7 Hz), 4.69 (d, $J_{1,2}$ 8.1 Hz), 4.81 (d, $J_{1,2}$ 4.0 Hz), 4.89 (d, $J_{1,2}$ 8.1 Hz, H-1–1‴). Anal. Calcd for $C_{25}H_{44}O_{21} \cdot 1.5\ H_2O$: C, 42.4; H, 6.7. Found: C, 42.4; H, 6.4.

*Ethyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside* (**8**).—Silver triflate was added at −30°C to a stirred mixture of ethyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside [7] (**7**, 200 mg, 0.50 mmol) and benzobromoglucose [6] (500 mg, 0.76 mmol) in $CH_2Cl_2$ (5 mL) containing molecular sieves (4 Å). The mixture was left to attain −5°C over 1.5 h.

Triethylamine (1 mL) was added and the stirring was continued for 20 min. The mixture was diluted with $CH_2Cl_2$, filtered through Celite, concentrated, and purified by silica gel chromatography (30:1 toluene–EtOAc) to give **8** (420 mg, 86%); $[\alpha]_D$ +2.5° (*c* 1.0, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 15.0 (*Me*$CH_2$), 25.0 (S*C*$H_2$Me), 63.0, 68.6, 69.7, 70.4, 71.9, 72.3, 73.2, 75.4, 79.2, 80.9, 81.8, (C-2–6, C-2′–6′, O*C*$H_2$Ph), 85.5 (C-1), 100.4, 101.3 (C-1′, Ph*C*H), 125.2–137.7 (Ph), 165.1, 165.2, 165.7, 166.0 (Ph*C*O). Anal. Calcd for $C_{56}H_{52}O_{14}S$: C, 68.56; H, 5.34. Found: C, 68.49; H, 5.45.

*Ethyl 2-O-benzyl-3-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside* (**9**).—Disaccharide **8** (147 mg, 0.15 mmol) dissolved in aq 70% HOAc (20 mL) was stirred at 70°C. After 6 h the solution was evaporated and the residue was purified by silica gel chromatography (3:1 toluene–EtOAc) to give **9** (125 mg, 93%).

*Ethyl 2-O-benzyl-1-thio-β-D-glucopyranoside* (**10**).—Thioglycoside **7** [7] (1.22 g, 3.03 mmol) was dissolved in AcOH (70% aq, 50 mL) and stirred at 70°C. After 1 h the solvent was evaporated and the product was purified by silica gel chromatography (20:1 $CHCl_3$–MeOH) to give **10** (880 mg, 92%); mp 99–100°C (from EtOAc–hexane); $[\alpha]_D$ −25° (*c* 1.2, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 15.0 (*Me*$CH_2$), 25.1 (S*C*$H_2$Me), 61.5, 69.5, 75.1, 77.8, 79.2, 81.0, (C-2–6, O*C*$H_2$Ph), 84.8 (C-1), 127.9–138.0 (Ph). Anal. Calcd for $C_{15}H_{22}O_5S$: C, 57.3; H, 7.1. Found: C, 57.3; H, 6.9.

*Ethyl 2-O-benzyl-3,4,6-tri-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside* (**11**).—Silver triflate was added at −20°C to a stirred mixture of **10** (50 mg, 0.16 mmol) and benzobromoglucose (470 mg, 0.71 mmol) in $CH_2Cl_2$ (2 mL) containing molecular sieves (4 Å). After 1 h triethylamine (1 mL) was added and the stirring was continued for 20 min. The mixture was diluted with $CH_2Cl_2$, filtered through Celite, and concentrated. Purification by silica gel chromatography (16:1 → 10:1 toluene–EtOAc) gave one pure fraction containing a trisaccharide and one mixed fraction. The mixed fraction was purified again by silica gel chromatography [3:1 light petroleum (bp 40–60°C)–EtOAc] which gave one pure fraction of the tetrasaccharide **11** and one mixed fraction. NMR data ($CDCl_3$) of **11**: $^{13}C$, δ 14.8 (*Me*$CH_2$), 24.8 (S*C*$H_2$Me), 63.1, 63.4, 63.7, 69.3, 69.5, 70.0, 71.9, 72.0, 72.2, 72.6, 73.0, 73.1, 74.3, 75.7, 77.6, 78.2, 82.3 (C-2–6, C-2′–6′, C-2″–6″, C-2‴–6‴, O*C*$H_2$Ph), 84.1 (C-1), 99.1, 99.4, 101.5 (C-1′–1‴), 128.2–137.7 (Ph), 164.8, 164.9, 165.1, 165.2, 165.8, 166.0 (Ph*C*O).

NMR data of the trisaccharide ($CDCl_3$): $^{13}C$, δ 14.8 (*Me*$CH_2$), 24.5 (S*C*$H_2$Me), 62.7, 63.0, 68.2, 69.1, 69.5, 69.8, 71.8, 71.9, 72.1, 72.6, 72.8, 73.0, 74.7, 79.3, 79.6, 84.5 (C-2–6, C-2′–6′, C-2″–6″, O*C*$H_2$Ph), 87.3 (C-1), 101.3, 101.6 (C-1′, C-1″), 125.3–137.6 (Ph), 165.0, 165.2, 165.7, 165.8, 166.0, 166.1 (Ph*C*O).

*Ethyl 3,4,6-tri-O-acetyl-2-O-benzyl-1-thio-β-D-glucopyranoside* (**12**).—A solution of **10** (0.83 g, 2.64 mmol) in pyridine (10 mL) and $Ac_2O$ (5 mL) was stirred at room temperature. After 2 h the solution was concentrated and the residue was purified by silica gel chromatography (4:1 toluene–EtOAc) to give **12** (1.08 g, 93%); mp 83–84°C (from EtOAc–hexane); $[\alpha]_D$ +24° (*c* 1.0, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 14.9 (*Me*$CH_2$), 20.6 (*Me*CO), 25.3 (S*C*$H_2$Me), 62.3, 68.6, 75.2, 75.5, 78.9, 79.0 (C-2–6, O*C*$H_2$Ph), 85.2 (C-1), 127.9–137.5 (Ph), 169.6, 170.0, 170.5 (Me*C*O). Anal. Calcd for $C_{21}H_{28}O_8S$: C, 57.3; H, 6.4. Found: C, 57.3; H 6.3.

*2-(4-Trifluoroacetamidophenyl)ethyl 3,4,6-tri-O-acetyl-2-O-benzyl-α-D-glucopyranoside* (**13**).—DMTST (0.92 g, 3.57 mmol) was added at 0°C to a solution of **12** (0.40 g, 0.91 mmol) and 2-(4-trifluoroacetamidophenyl)ethanol (0.28 g, 1.18 mmol) in dry diethyl ether (100 mL) containing molecular sieves (4 Å). The mixture was left to attain room temperature. After 18 h triethylamine (1 mL) was added and the stirring was continued for 20 min. The mixture was filtered and concentrated, and the residue was purified by silica gel chromatography (2:1 toluene–EtOAc) to give **13** (0.51 g, 92%); $[\alpha]_D$ +68° (*c* 1.4, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 20.4, 20.5, 20.7 (*Me*CO), 35.2 (Ar*C*$H_2$*C*$H_2$O), 61.8, 67.1, 68.5, 68.8, 71.7, 72.7, 76.8 (C-2–6, O*C*$H_2$*C*$H_2$Ar, O*C*$H_2$Ph), 96.5 (C-1), 120.6–137.7 (Ar), 154.4 (NHCO), 169.7, 170.2, 170.6 (Me*C*O); $^1H$, δ 4.76 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1). Anal. Calcd for $C_{29}H_{32}F_3NO_{10}$: C, 56.9; H, 5.3; N, 2.3. Found: C, 56.6; H, 5.2; N, 2.2.

*2-(4-Trifluoroacetamidophenyl)ethyl 2-O-benzyl-α-D-glucopyranoside* (**14**).—A solution of **13** (510 mg, 0.83 mmol) in dry MeOH (25 mL) was treated with a catalytic amount of 1 M methanolic NaOMe at room temperature. After 2 h the solution was neutralized with Dowex-50 ($H^+$) resin, filtered, and concentrated. The residue was purified by silica gel chromatography (10:1 $CHCl_3$–MeOH) to give **14** (390 mg, 96%); mp 148–150°C (from EtOAc–hexane); $[\alpha]_D$ +76° (*c* 1.0, MeOH); NMR data ($CDCl_3$): $^{13}C$, δ 36.4 (Ar*C*$H_2$*C*$H_2$O), 62.5, 69.5, 71.7, 73.4, 73.7, 74.2, 81.1 (C-2–6, O*C*$H_2$*C*$H_2$Ar, O*C*$H_2$Ph), 98.0 (C-1), 122.2–139.9 (Ar), 156.4, 156.9 (NHCO). Anal. Calcd for $C_{23}H_{26}F_3NO_7$: C, 56.9; H, 5.4; N, 2.9. Found: C, 56.8; H, 5.4; N, 2.7.

*2-(4-Trifluoroacetamidophenyl)ethyl 2-O-benzyl-3,4,6-tri-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside* (**15**).—Silver triflate was added at −20°C to a stirred mixture of **14** (110 mg, 0.23 mmol) and benzobromoglucose [6] (670 mg, 1.02 mmol) in $CH_2Cl_2$ (10 mL) containing molecular sieves (4 Å). After 1 h triethylamine (1 mL) was added and the stirring was continued for 20 min. The mixture was diluted with $CH_2Cl_2$, filtered through Celite, concentrated, and purified by silica gel chromatography (8:1 toluene–EtOAc) to give **15** (356 mg, 71%); $[\alpha]_D$ +33° (*c* 0.7, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 34.9 (Ar*C*$H_2$*C*$H_2$O), 63.1, 63.3, 63.6, 67.7, 67.9, 69.1, 69.7, 69.9, 70.3, 71.7, 72.0, 72.1, 72.7, 72.9, 73.3, 73.4, 74.4, 77.2, 81.1 (C-2–6, C-2′–6′, C-2″–6″, C-2‴–6‴, O*C*$H_2$*C*$H_2$Ar, O*C*$H_2$Ph), 95.5, 100.1 (2 C), 101.3 (C-1–1‴), 121.0–137.9 (Ar), 164.8, 164.9, 165.0, 165.2, 165.8, 165.9, 166.0 (Ph*C*O). Anal. Calcd for $C_{125}H_{104}F_3NO_{34}$: C, 67.6; H, 4.7; N, 0.63. Found: C, 67.6; H, 4.9; N, 0.58.

*2-(4-Trifluoroacetamidophenyl)ethyl 3,4,6-tri-O-β-D-glucopyranosyl-α-D-glucopyranoside* (**16**).—A solution of **15** (310 mg, 0.14 mmol) in dry MeOH (5 mL) was treated with a catalytic amount of 1 M methanolic NaOMe at room temperature. After 1 h the solution was neutralized with Dowex-50 ($H^+$) resin, filtered, and hydrogenolyzed over 10% Pd–C (50 mg) at 400 kPa for 20 h. The solution was filtered, concentrated, dissolved in $H_2O$, and washed with diethyl ether. The water phase was concentrated and the residue was purified by reversed-phase HPLC (65:35 $H_2O$–MeOH) to give, after lyophilization, **16** (61 mg, 50%); $[\alpha]_D$ +50° (*c* 0.9, $H_2O$); NMR data ($D_2O$): $^{13}C$, δ 35.4 (Ar*C*$H_2$*C*$H_2$O), 61.5, 67.6, 69.7, 70.2, 70.4, 72.4, 73.7, 73.8, 74.3, 76.4, 76.5, 76.9, 77.2 (C-2–6, C-2′–6′, C-2″–6″, C-2‴–6‴, O*C*$H_2$*C*$H_2$Ar), 98.5 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz, C-1), 101.8 ($J_{C\text{-}1,H\text{-}1}$ 165 Hz), 102.1 ($J_{C\text{-}1,H\text{-}1}$ 167 Hz), 102.9 ($J_{C\text{-}1,H\text{-}1}$ 163 Hz) (C-1′–1‴), 122.7, 130.6, 134.0, 138.7 (Ar), 157.2 (NH*C*O); $^1H$, δ 4.46 (d, 1 H, $J_{1,2}$ 8.1

Hz), 4.62 (d, 1 H, $J_{1,2}$ 7.7 Hz), 4.92–4.95 (2 d, 2 H) (H-1–H-1‴). Anal. Calcd for $C_{34}H_{50}F_3NO_{22} \cdot 3H_2O$: C, 43.6; H, 6.0; N, 1.5. Found: C, 43.6; H, 5.5; N, 1.5.

*Methyl [2-(4-trifluoroacetamidophenyl)ethyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-α-*D*-manno-oct-2-ulopyranosid]onate* (**19**).—Silver triflate (380 mg, 1.48 mmol) and $Me_3Si$ triflate (24 μL, 0.12 mmol) were added at 0°C to a stirred solution of phenylselenyl chloride (480 mg, 2.48 mmol) in $CH_2Cl_2$. After 30 min a solution of methyl 4,5,7,8-tetra-*O*-acetyl-2,6-anhydro-3-deoxy-D-*manno*-oct-2-enonate [12] (**17**, 500 mg, 1.24 mmol) and 2-(4-trifluoroacetamidophenyl)ethanol (350 mg, 1.50 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise. The solution was stirred for 2 h, then diluted with $CH_2Cl_2$, extracted with aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography (4:1 toluene–EtOAc). The resulting syrup (**18**) was dissolved in toluene, triphenyltin hydride (840 mg, 2.40 mmol) and azobisisobutyronitrile (AIBN) (90 mg, 0.55 mmol) were added, the solution was refluxed for 30 min and then concentrated, and the residue was purified by silica gel chromatography (4:1 toluene–EtOAc) to give **19** (735 mg, 93%); $[\alpha]_D$ +93° (*c* 1.1, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 20.5, 20.7 (2 C), 20.8 (*Me*CO), 32.0 (C-3), 35.3 (Ar*C*$H_2$C$H_2$O), 52.8 (OMe), 62.4, 64.2, 64.5, 66.4, 67.4, 68.4 (C-4–8, O*C*$H_2$C$H_2$Ar), 98.7 (C-2), 113.7, 118.0 ($CF_3$), 120.9, 129.8, 134.2, 136.5 (Ar), 154.7, 155.2 (NH*C*O), 167.6 (C-1) 169.8, 170.2, 170.6, 170.7 (Me*C*O). Anal. Calcd for $C_{27}H_{32}F_3NO_{13}$: C, 51.0; H, 5.1; N, 2.2. Found: C, 50.9; H, 5.1; N, 2.2.

*Methyl [2-(4-trifluoroacetamidophenyl)ethyl 3-deoxy-7,8-*O*-isopropylidene-α-*D*-manno-oct-2-ulopyranosid]onate* (**21**).—A solution of **19** (826 mg, 1.3 mmol) in dry MeOH (25 mL) was treated with a catalytic amount of 1 M methanolic NaOMe at room temperature. After 2 h the solution was neutralized with Dowex-50 ($H^+$) resin, filtered, and concentrated. The residue was purified on a silica gel column (10:1 $CHCl_3$–MeOH). The resulting syrup (**20**, 577 mg) was dissolved in DMF (10 mL) and treated with dimethoxypropane (360 μL, 3.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid. After 20 h the solution was neutralized with $NaHCO_3$, filtered, and concentrated. The residue was purified by silica gel chromatography (1:2 toluene–EtOAc) to give **21** (330 mg, 50%); $[\alpha]_D$ +4.6° (*c* 1.0, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, δ 25.1, 26.8 (C*M*$e_2$), 34.9, 35.5 (C-3, Ar*C*$H_2$C$H_2$O), 52.7 (OMe), 64.1, 65.7, 66.5, 67.1, 72.8, 73.5 (C-4–8, O*C*$H_2$C$H_2$Ar), 98.8 (C-2), 109.4 (*C*$Me_2$), 120.7, 129.9, 133.7, 137.0 (Ar), 155.1 (NH*C*O), 168.8 (C-1); $^1H$, δ 1.84 (dd, 1 H, $J_{gem}$ 12.5, $J_{3ax,4}$ 12.1 Hz, H-3ax), 2.09 (dd, 1 H, $J_{3eq,4}$ 4.8 Hz, H-3eq). Anal. Calcd for $C_{22}H_{28}F_3NO_9$: C, 52.1; H, 5.6; N, 2.8. Found: C, 51.3; H, 5.3; N, 2.7.

Further elution with a more polar eluent (9:1 EtOAc–MeOH) afforded 200 mg (35%) of **20**.

*Methyl [2-(4-trifluoroacetamidophenyl)ethyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-*D*-manno-oct-2-ulopyranosid]onate* (**22**).—A solution of **21** (659 mg, 1.3 mmol) and dibutyltin oxide (388 mg, 1.6 mmol) was refluxed in dry MeOH (5 mL). After 2.5 h the solution was concentrated and coevaporated twice with toluene. The residue was dissolved in DMF (5 mL), benzyl bromide (540 mL, 4.5 mmol) and tetrabutylammonium iodide (575 mg, 1.8 mmol) were added, and the mixture was stirred at 60°C for 20 h. The mixture was diluted with $CH_2Cl_2$, washed with $H_2O$, dried ($MgSO_4$), and concentrated. The obtained oil was coevaporated twice with toluene, dissolved in dry

MeOH, and treated with a catalytic amount of 1 M methanolic NaOMe. After 18 h the solution was neutralized with Dowex-50 ($H^+$) resin, filtered, and concentrated. The residue was purified by silica gel chromatography [1:1 light petroleum (bp 40–60°C)–EtOAc] to give **22** (500 mg, 64%); $[\alpha]_D$ +57° (*c* 1.4, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, $\delta$ 25.0, 26.6 ($CMe_2$), 32.0 (C-3), 35.3 ($ArCH_2CH_2O$), 52.5 (OMe), 63.9, 64.0, 66.9, 69.8, 72.1, 72.6, 73.3 (C-4–8, $OCH_2CH_2Ar$, $OCH_2Ph$), 98.7 (C-2), 109.1 ($CMe_2$), 120.6–137.6 (Ar), 154.5, 155.0 (NHCO), 168.5 (C-1). Anal. Calcd for $C_{29}H_{34}F_3NO_9$: C, 58.3; H, 5.7; N, 2.3. Found: C, 57.5; H, 5.7; N, 2.4.

*Methyl [2-(4-trifluoroacetamidophenyl)ethyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-5-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-*D*-glucopyranosyl)-α-*D*-manno-oct-2-ulopyranosid]onate* (**23**).—DMTST (940 mg, 3.6 mmol) was added at 0°C to a solution of **12** (800 mg, 1.8 mmol) and **22** (453 mg, 0.76 mmol) in $CH_2Cl_2$ (25 mL) containing molecular sieves (4 Å). The mixture was left to attain room temperature and the stirring was continued for 18 h, whereupon triethylamine (1 mL) was added, and the mixture stirred for another 20 min and then concentrated. The residue was purified on a silica gel column (4:1 toluene–EtOAc) to give **23** (620 mg, 84%); $[\alpha]_D$ +145° (*c* 1.1, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, $\delta$ 20.7, 20.9 (*Me*CO), 25.2, 27.0 ($CMe_2$), 32.7 (C-3), 35.5 ($ArCH_2CH_2O$), 52.5 (OMe), 61.3, 63.9, 67.0, 67.3, 68.6, 70.2, 71.9, 72.0, 72.3, 73.0, 74.1, 77.0 (C-4–8, C-2′–6′, $OCH_2CH_2Ar$, $OCH_2Ph$), 97.8 (C-1′, $J_{C\text{-}1',H\text{-}1'}$ 176.0 Hz), 98.6 (C-2), 109.1 ($CMe_2$), 120.4–137.9 (Ar), 154.8 (NHCO), 168.1 (C-1), 169.9, 170.2, 170.7 (MeCO). Anal. Calcd for $C_{48}H_{56}F_3NO_{17}$: C, 59.1; H, 5.8; N, 1.4. Found: C, 58.8; H, 5.7; N, 1.4.

*Methyl [2-(4-trifluoroacetamidophenyl)ethyl 4-*O*-benzyl-5-*O*-(2-*O*-benzyl-α-*D*-glucopyranosyl)-3-deoxy-7,8-*O*-isopropylidene-α-*D*-manno-oct-2-ulopyranosid]onate* (**24**).—A solution of **23** (117 mg, 0.12 mmol) in dry MeOH (10 mL) was treated with a catalytic amount of 1 M methanolic NaOMe at room temperature. After 7 h the solution was neutralized with Dowex-50 ($H^+$) resin, filtered, and evaporated. The residue was purified by silica gel chromatography (20:1 $CHCl_3$–MeOH) to give **24** (85 mg, 83%); $[\alpha]_D$ +91° (*c* 0.9, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, $\delta$ 25.2, 27.1 ($CMe_2$), 32.9 (C-3), 35.4 ($ArCH_2CH_2O$), 52.6 (OMe), 61.9, 64.0, 67.2, 70.0, 70.7, 71.1, 72.1, 72.4, 72.9, 74.1, 79.6 (C-4–8, C-2′–6′, $OCH_2CH_2Ar$, $2\times OCH_2Ph$), 98.1 (C-1′), 98.6 (C-2), 109.1 ($CMe_2$), 120.5–138.0 (Ar), 154.3 (NHCO), 168.4 (C-1). Anal. Calcd for $C_{42}H_{50}F_3NO_{14}$: C, 59.4; H, 5.9; N, 1.6. Found: C, 57.7; H, 5.8; N, 1.6.

*Methyl [2-(4-trifluoroacetamidophenyl)ethyl 4-*O*-benzyl-5-*O*-[2-*O*-benzyl-3,4,6-tri-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-*D*-glucopyranosyl)-α-*D*-glucopyranosyl]-3-deoxy-7,8-*O*-isopropylidene-α-*D*-manno-oct-2-ulopyranosid]onate* (**25**).—Silver triflate (280 mg, 1.1 mmol) was added at −20°C to a stirred mixture of **24** (156 mg, 0.18 mmol) and benzobromoglucose (544 mg, 0.83 mmol) in $CH_2Cl_2$ (5 mL) containing molecular sieves (4 Å). After 3 h triethylamine (1 mL) was added and stirring was continued for 20 min. The mixture was diluted with $CH_2Cl_2$, filtered through Celite, and concentrated. Purification on a silica gel column (9:1 toluene–EtOAc) gave a mixture of the pentasaccharide **25** and tetrasaccharides. Separation on HPLC (55:45 hexane–EtOAc) gave one fraction of tetrasaccharides (98 mg, 22%) and one fraction of **25** (178 mg, 38%); $[\alpha]_D$ +57° (*c* 0.9, $CHCl_3$); NMR data ($CDCl_3$): $^{13}C$, $\delta$ 25.3, 27.2 ($CMe_2$), 33.1 (C-3), 35.4 ($ArCH_2CH_2O$), 52.5 (OMe), 63.2, 63.6, 63.9, 66.7, 67.0, 69.7, 69.8, 70.0,

70.2, 71.6, 71.8, 72.0, 72.2, 72.5, 72.9, 73.0, 73.5, 73.6, 73.8, 74.6, 75.6, 81.5 (C-4–8, C-2′–6′, C-2″–6″, C-2‴–6‴, C-2⁗–6⁗, $OCH_2CH_2Ar$, $OCH_2Ph$), 97.2, 98.6, 100.1, 100.6, 100.8 (C-2, C-1′–1⁗), 109.0 ($CMe_2$), 120.3–138.3 (Ar), 154.3 (NH*C*O), 164.8, 164.9, 165.1, 165.2, 165.7, 166.0, 166.2 (Ph*C*O), 168.1 (C-1). Anal. Calcd for $C_{144}H_{128}F_3NO_{41}$: C, 66.9; H, 5.0; N, 0.5. Found: C, 66.7; H, 5.0; N, 0.5.

*Methyl [2-(4-trifluoroacetamidophenyl)ethyl 3-deoxy-5-*O*-(3,4,6-tri-*O*-β-*D*-glucopyranosyl-α-*D*-glucopyranosyl)-α-*D*-*manno*-oct-2-ulopyranosid]onate* (**26**).—Aq 90% $CF_3CO_2H$ was added dropwise to a solution of **25** (122 mg, 0.05 mmol) in $CH_2Cl_2$ (2 mL) until pH 2. The solution was stirred at room temperature for 30 min and then evaporated. The residue was dissolved in dry MeOH (4 mL) and treated with a catalytic amount of 1 M methanolic NaOMe. After 1 h the solution was neutralized with Dowex-50 ($H^+$) resin, filtered, evaporated, dissolved in 1:1 MeOH–AcOH (4 mL), and hydrogenolyzed over 10% Pd–C (50 mg) at 400 kPa for 20 h. The mixture was filtered, concentrated, dissolved in water, and washed with diethyl ether. The water phase was lyophilized and purified by HPLC (1:1 $H_2O$–MeOH) to give, after lyophilization, the ester derivative **26** (37 mg, 70%); $[\alpha]_D$ +46° (*c* 1.1, MeOH); NMR data ($D_2O$): $^{13}C$, δ 35.1, 35.3 (C-3, $ArCH_2CH_2O$), 54.2 (OMe), 61.5, 63.7, 65.2, 65.9, 68.1, 69.1, 70.2, 70.3, 70.5, 70.9, 72.6, 73.1, 73.8, 73.9, 74.0, 74.6, 76.2, 76.4, 76.5, 76.6, 76.8 (C-4–8, C-2′–6′, C-2″–6″, C-2‴–6‴, C-2⁗–6⁗, $OCH_2CH_2Ar$), 99.4, 100.5, 101.9, 102.1, 103.0 (C-2, C-1′–1⁗), 123.0, 130.8, 134.0, 138.5 (Ar), 157.9 (NH*C*O), 170.9 (C-1).

*2-(4-Aminophenyl)ethyl 3-deoxy-5-*O*-(3,4,6-tri-*O*-β-*D*-glucopyranosyl-α-*D*-glucopyranosyl)-α-*D*-*manno*-oct-2-ulopyranosidonic acid* (**27**).—0.1 M Sodium hydroxide was added dropwise to a solution of **26** (10 mg, 0.009 mmol) in 1:1 water–MeOH (1 mL) until pH 11, whereupon the solution was stirred at room temperature. After 44 h, when TLC (3:2:1:1 EtOAc–HOAc–EtOH–$H_2O$) indicated full conversion of the ester and amide into the acid and amine (TLC developed by spraying with ninhydrin), the solution was acidified (pH 5) by addition of 0.1 M hydrochloric acid and lyophilized to give **27** (6 mg, 67%); $[\alpha]_D$ +69° (*c* 0.6, $H_2O$); NMR data ($D_2O$): $^1H$, δ 7.15 (d, 2 H, *J* 8.4 Hz, Ar), 6.82 (d, 2 H, *J* 8.1 Hz, Ar), 5.07 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1′), 4.92 (d, 1 H, *J* 8.1 Hz), 4.68 (d, 1 H, *J* 7.7 Hz), 4.49 (d, 1 H, *J* 7.7 Hz, H-1″–1⁗), 4.35 (d, 1 H, *J* 9.9 Hz), 4.21 (q, 2 H, *J* 9 Hz), 4.02–3.87 (m, 8 H), 3.82–3.70 (m, 5 H), 3.56–3.25 (m, 15 H), 2.85 (d, 1 H, *J* 8.8 Hz, $OCH_2CH_2Ar$), 2.77 (t, 2 H, *J* 5.5 Hz, $OCH_2CH_2Ar$), 2.03 (dd, 1 H, $J_{gem}$ 12.8 Hz, $J_{3eq,4}$ 4.4 Hz, H-3eq), 1.82 (dd, 1 H, $J_{3ax,4}$ 12.5 Hz, H-3ax). FAB-MS: *m*/*z* 1004.38 [M − 1]. Calcd for $C_{40}H_{62}NO_{28}$: *m*/*z* 1004.35.

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