Synthesis of a Branched Heptose- and Kdo-Containing Common Tetrasaccharide Core Structure of *Haemophilus influenzae* Lipopolysaccharides via a 1,6-Anhydro-L-*glycero*-*β*-D-*manno*-heptopyranose Intermediate

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The synthesis of a common tetrasaccharide core structure of *Haemophilus influenzae* lipopolysaccharides, *β*-D-glucopyranosyl-(1→4)-[L-*glycero*-α-D-*manno*-heptopyranosyl-(1→3)]-L-*glycero*-α-D-*manno*-heptopyranosyl-(1→5)-3-deoxy-α-D-*manno*-octulopyranoside, and the trisaccharide *β*-D-glucopyranosyl-(1→4)-[L-*glycero*-α-D-*manno*-heptopyranosyl-(1→3)]-L-*glycero*-α-D-*manno*-heptopyranoside is described. The oligosaccharides are synthesized as glycosides of a bifunctional spacer, 2-(4-aminophenyl)ethanol, to allow the subsequent formation of immunogenic glycoconjugates, which will be evaluated as well-defined glycoconjugate vaccine candidates. The syntheses of the 3,4-branched structures were accomplished using a 1,6-anhydro-L-*glycero*-*β*-D-*manno*-heptopyranose intermediate to diminish the steric crowding between the 3- and 4-substituent. This intermediate was effectively synthesized from a mannose precursor via a stereoselective one-carbon elongation using a Barbier reaction (which was found to be more convenient than a Grignard reaction) and anhydro bridge formation through an internal glycosylation of a 6-*O*-trimethylsilylated ethyl thioheptoside using NIS/TfOH as a promoter. The 3- and 4-substituent were readily introduced into the 1,6-anhydro intermediate by glycosylation reactions using thioglycosides as donors and NIS/TfOH as a promoter, a task which has not been possible using acceptors with equatorial 3,4-substituents. Acetolysis of the anhydro bridge followed by conversion into the ethyl thioglycoside afforded a trisaccharide donor, which, in NIS/TfOH-promoted couplings to the spacer and to a Kdo acceptor followed by deprotection, efficiently gave the two target compounds.

Introduction

Haemophilus influenzae is a Gram-negative bacterium that causes, for example, acute otitis, pneumoniae, and meningitis.[1] The bacteria is normally surrounded by a capsular polysaccharide (CPS), which is an important virulence factor. Six different serotypes are known (types a−f), all corresponding to a specific CPS structure.[2] Of these, type b is the cause of more than 90% of the severe infections. The introduction of glycoconjugate vaccines (PRP-vaccines) based on native type b CPS, which is partially hydrolyzed and conjugated to a protein, has dramatically decreased the occurrence of these invasive infections.[3] Recently, PRP-vaccine candidates based on synthetic type b structures conjugated to a protein and even fully synthetic versions where the oligosaccharide is coupled to a synthetic peptide sequence have been reported.[4,5] These vaccines, however, do not protect against noncapsulated *Haemophilus influenzae* bacteria (NTHi: nontypable *H. influenzae*), which are a major cause of frequent acute otitis, especially in small children. Since these bacteria lack the CPS, they are not affected by antibodies against this structure, and vaccines against NTHi have to be based on other immunogenic surface structures. Since *H. influenzae* is a Gram-negative bacterium, the outer membrane of the bacterium contains another polysaccharide structure, a lipopolysaccharide (LPS). The LPS of *H. influenzae* is devoid of the polymeric O-antigen generally found in LPS structures, and this, in combination with a severe microheterogeneity, has made it difficult to elucidate LPS structures. By using mutants showing less heterogeneity and by the development of better analytical methods, it has recently been possible to determine various *H. influenzae* LPS structures (Figure 1).[6−10]

Attempts to construct glycoconjugate vaccines based on native LPS have been performed.[11] Two problems encountered in this approach are the necessity to detoxify the LPS (since the lipid A part is known to be an endotoxin) and the structural heterogeneity, resulting in different antibody responses for different LPS preparations. Glycoconjugates containing synthetic LPS structures are therefore interesting as well-defined, nontoxic

(1) Turk, D. C. *J. Med. Microbiol.* **1984**, *18*, 1.
(2) Lindberg, B.; Kenne, L. In *The Polysaccharides*; Aspinall, G. O., Ed.; Academic Press Inc.: New York, 1983; Vol. 2, p 287.
(3) Lindberg, A. A.; Pillai, S. In *Developments in Biological Standardization*; Brown, F., Ed.; 1996; Vol. 87, p 59.
(4) Chong, P.; Chan, N.; Kandil, A. A.; Tripet, B.; James, O.; Yang, Y.-P.; Shi S.-P.; Klein, M. *Infect. Immun.* **1997**, *65*, 4918.
(5) Kandil, A. A.; Chan, N.; Klein, M.; Chong, P. *Glycoconjugate J.* **1997**, *14*, 13.
(6) Phillips, N. J.; Apicella, M. A.; McLeod Griffiss, J.; Gibson, B. W. *Biochemistry* **1992**, *31*, 4515.
(7) Phillips, N. J.; Apicella, M. A.; McLeod Griffiss, J.; Gibson, B. W. *Biochemistry* **1993**, *32*, 2003.
(8) Schweda, E. K. H.; Hegedus, O. E.; Borelli, S.; Lindberg, A. A.; Weiser, J. N.; Maskell, D. J.; Moxon, E. R. *Carbohydr. Res.* **1993**, *246*, 319.
(9) Schweda, E. K. H.; Jansson, P.-E.; Moxon, E. R.; Lindberg, A. A. *Carbohydr. Res.* **1995**, *272*, 213.
(10) Phillips, N. J.; McLaughlin, R.; Miller, T. J.; Apicella, M. A.; Gibson, B. W. *Biochemistry* **1996**, *35*, 5937.
(11) Gu, X.-X.; Tsai, C.-M.; Ueyama, T.; Barenkamp, S. J.; Robbins, J. B.; Lim, D. J. *J. Bacteriol. Infect. Immun.* **1996**, *645*, 4047.

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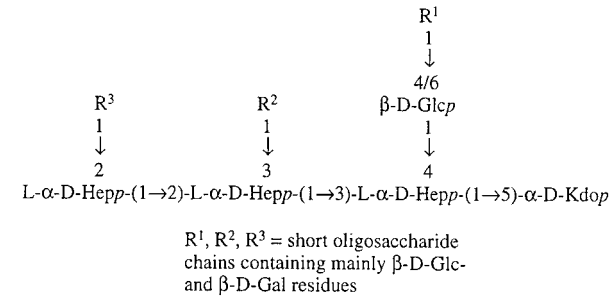


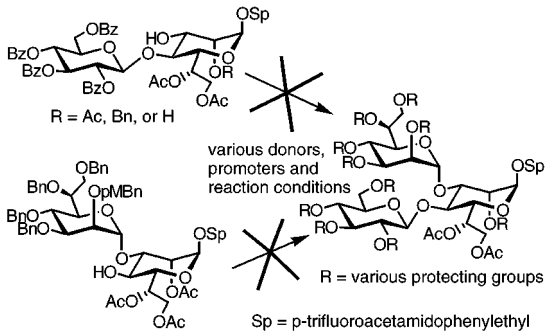
Figure 1. Generalized Structure of the Dephosphorylated LPS of *H. influenzae* Without the Lipid A Moiety.

vaccine candidates. In this article, we describe the synthesis of the common branched tetrasaccharide *β*-D-glucopyranosyl-(1→4)-[L-*glycero*-α-D-*manno*-heptopyranosyl-(1→3)]-(L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→5)-3-deoxy-α-D-*manno*-octulopyranoside and the trisaccharide *β*-D-glucopyranosyl-(1→4)-[L-*glycero*-α-D-*manno*-heptopyranosyl-(1→3)]-L-*glycero*-α-D-*manno*-heptopyranoside, which has been found, so far, in all *H. influenzae* LPS. The oligosaccharides are synthesized as glycosides of a bifunctional spacer to allow convenient subsequent conjugation to a protein. The same common core tri- and tetrasaccharide are found also in *Haemophilus ducreyi* and *Neisseria meningitidis* LPSs,[12,13] and the conjugates will also be evaluated as potential vaccines against these bacteria.

Results and Discussion

Earlier syntheses of linear core structures of the *Haemophilus* and *Salmonella* LPS were designed to provide derivatives suitable as precursors in the synthesis of the 3,4-branched structure.[14,15] Thus, the two disaccharides 2-(4-trifluoroacetamidophenyl)ethyl (2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)-6,7-di-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranoside[14] and 2-(4-trifluoroacetamidophenyl)ethyl (3,4,6,7-tetra-*O*-benzyl-2-*O*-*p*-methoxybenzyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-2,6,7-tri-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranoside[15] were processed to give suitable 3-OH and 4-OH acceptors, respectively. However, when couplings were attempted, no branched products were obtained regardless of the donor, promoter, and conditions used (Scheme 1).[16] Problems in preparing similar branched trisacharides with an α-D-linked moiety at an equatorial O-3 and a *β*-D-moiety at an equatorial O-4 have earlier been found in our laboratory.[17] These problems can usually be solved by changing the order of introduction of the sugar substituents, but such an approach was not feasible in this case. Another solution to this problem of steric crowding is to change completely the conformation of the hexose ring by forming a 1,6-anhydro bridge.[18,19] This will force the ring from a $^4C_1$ to a $^1C_4$ conformation,

Scheme 1. Attempted Syntheses of 3,4-Branched Structures



and consequently the equatorial O-3 and O-4 will become axial with possible steric release between 3- and 4-substituents. This approach was tried using the known 1,6-anhydro-*β*-D-mannose[20,21] as a precursor and model compound but also with the intention to make the target heptose saccharide by a one-carbon elongation at a later stage. The desired 3,4-branched structures could conveniently be prepared using this strategy, but when the elongation was attempted, problems were encountered already in the acetolysis of the anhydro bridge due to the protection group pattern used.[22,23] We therefore decided to try the same strategy but to start from a heptose derivative, thereby avoiding the later elongation.

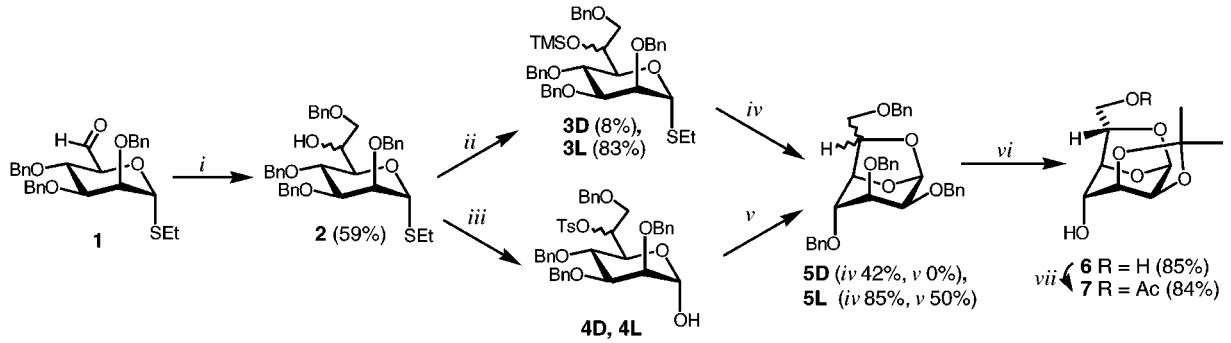
With a heptopyranose, two similar anhydro compounds are possible, containing either a 1,6- or a 1,7-anhydro bridge. According to the literature, the 1,6-anhydro derivative is more stable,[24] and since it also conformationally more resembles the successful model mannose compound, the 1,6-anhydro derivative was chosen as the precursor.

Initially, attempts were made to synthesize the 1,6-anhydroheptose using the same procedure as was used for the 1,6-anhydromannose, i.e., via a S_N2 displacement of a 6-tosylate by the anomeric oxygen aided by a base (DBU).[21] Since the 6 position is chiral, this means that the synthesis has to start from a D-*glycero*-D-*manno*-heptose to give the desired 1,6-anhydro-L-*glycero*-D-*manno*-heptose (acetolysis of the anhydro bridge takes place with retention of C-6 chirality). Most syntheses published, however, give the L-form in large excess, although the ratio is dependent on the precursor and method used.[22] Using a literature procedure[25] utilizing benzyloxymethyllithium and **1**, a 3:2 mixture of the L- and the D-form of **2** could be obtained, separated, and processed to give the perbenzylated 1,6-anhydroheptose **5** (Scheme 2), albeit in a very low overall yield. Interestingly, with this approach the D,D-anhydro derivative could not be synthesized from **4L**, possibly due to unfavorable steric interaction between the 7-CH_2OBn group and the 3-OBn group in the formation of the S_N2 transition state.

Hence, another strategy for the anhydro formation was tried in which the leaving group was in the anomeric

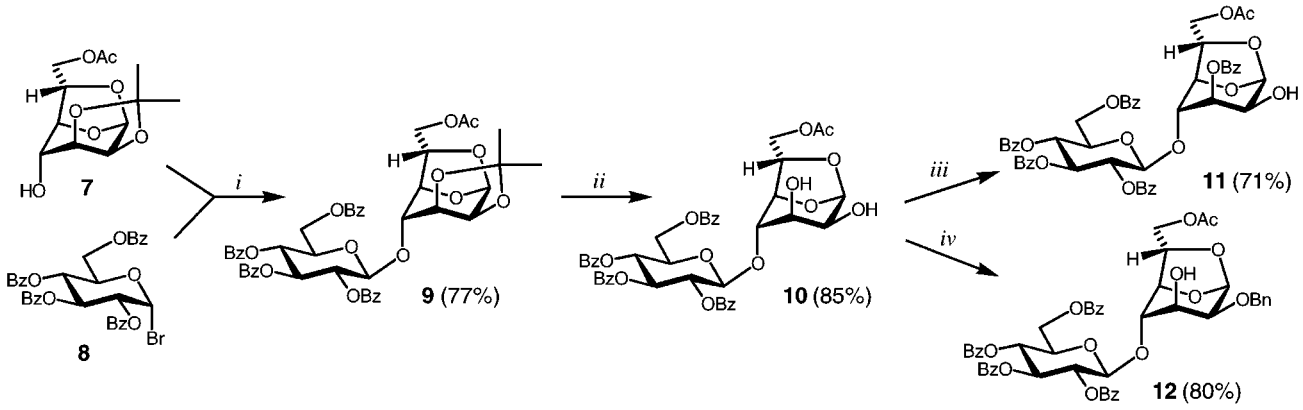
(12) Schweda, E. K. H.; Jonasson, J. A.; Jansson, P.-E. *J. Bacteriol.* **1995**, *177*, 5316.
(13) Di fabio, J. L.; Michon, F.; Brisson, J. R.; Jennings, H. J. *Can. J. Chem.* **1990**, *68*, 1029.
(14) Garegg, P. J.; Oscarson, S.; Ritzén, H.; Szönyi, M. *Carbohydr. Res.* **1992**, *228*, 121.
(15) Bernlind, C.; Oscarson, S. *Carbohydr. Res.* **1997**, *297*, 251.
(16) Bernlind, C. Licentiate Thesis, Stockholm University, 1996.
(17) Söderman, P.; Jansson, P. E.; Widmalm, G. *J. Chem. Soc., Perkin Trans. 2*, in press.
(18) Shapiro, D.; Rabinsohn, Y.; Diver-Haber, A. *Biochem. Biophys. Res. Commun.* **1969**, *37*, 28.
(19) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180.
(20) Lafont, D.; Boullanger, P.; Banoub, J.; Descotes, G. *Can. J. Chem.* **1990**, *68*, 828.
(21) Lafont, D.; Boullanger, P.; Cadas, O.; Descotes, G. *Synthesis* **1989**, 191.
(22) Oscarson, S. *Top. Curr. Chem.* **1997**, *186*, 171.
(23) Bernlind, C. Doctoral Dissertation, Stockholm University, 1998.
(24) Angyal, S. J.; Beveridge, R. J. *Carbohydr. Res.* **1978**, *65*, 229.
(25) Boons, G. J. P. H. Doctoral Dissertation, Leiden University, 1991.

Scheme 2. Synthesis of 1,6-Anhydro-L- and 1,6-Anhydro-D-*glycero*-D-*manno*-heptopyranoside Derivatives[a]



[a] Key: (i) $BnOCH_2Cl$, Mg; (ii) TMS-Cl, pyridine; (iii) (a) Tos-Cl, pyridine, (b) DMTST, H_2O; (iv) NIS, TfOH; (v) DBU; (vi) (a) H_2, Pd-C, (b) $(Me)_2C(OMe)_2$, pTsOH; (vii) AcCl, collidine, −78 °C.

Scheme 3. Synthesis of Selectively Protected 1,6-Anhydrodisaccharides[a]



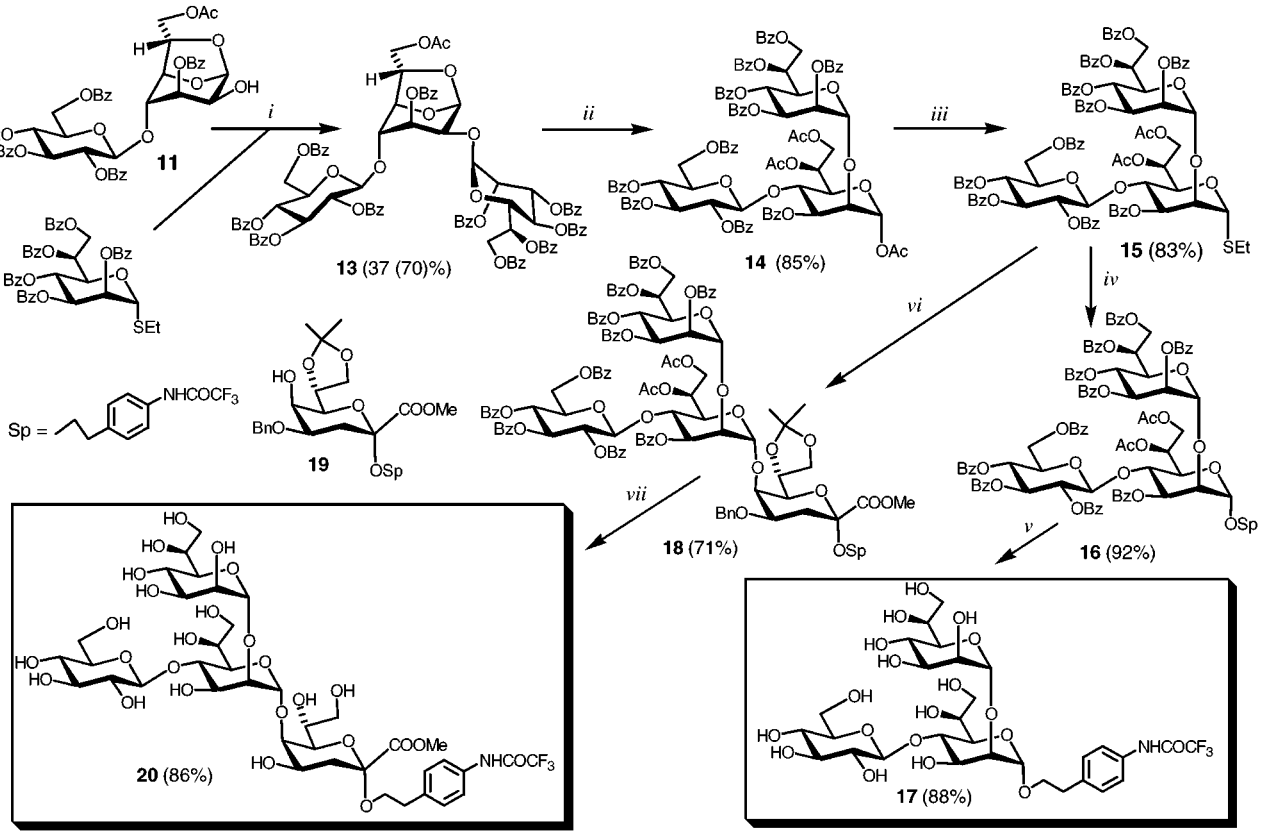
[a] Key: (i) AgOTf; (ii) HOAc (80% aq); (iii) (a) Bu_2SnO, (b) PhCOCl; (iv) (a) Bu_2SnO, (b) BnBr, Bu_4NI.

position and was displaced by the 6-oxygen to give the anhydro bridge in an internal glycosidation reaction. Since the chirality of C-6 is not interfered with in this approach, the more easily available L-*glycero* derivatives could be used as precursors. The reaction between the organomagnesium complex of benzyloxymethyl chloride and **1** gave **2** (59%) as an inseparable 6-L,D-mixture. The benzyl glycoside of **2** had earlier been synthesized by Zamojski et al.[26] using Grignard conditions, and we have also used this method with success, but the reaction is sensitive to the reaction conditions, due to the lability of alkoxymethylmagnesium halides,[27] and reproducibility can be a problem. Therefore, Barbier conditions (simultaneous addition of halide and carbonyl compound to the magnesium turnings), known to be preferable with allyl and benzyl bromide as halides,[28] were tried. The yield and L,D-ratio were very similar to those of the Grignard reaction, but a much smaller excess of the toxic halide (2 equiv instead of 6 equiv) could be used, which simplified the purification procedure considerably. The Barbier reaction was, furthermore, found to be less sensitive to the conditions and thus more reliable. Activation of the obtained L,D-mixture (**2**) with various thiophilic promoters produced mainly hydrolysis of the thioglycoside and no anhydro formation. The 6-position of **2** was therefore trimethylsilylated, which also made the separation of the L-glycero and the D-glycero isomers, **3L** and **3D**, possible. By slow addition of **3L** to a solution of NIS/TfOH in CH_2Cl_2 at this point, an efficient formation of the 1,6-anhydro derivative **5L** (85%) took place. By using the same conditions but starting from **3D**, the D,D-anhydro analogue of **5** could also be obtained this time, albeit in a lower yield (42%).

Compound **5L** was then processed to give a suitable acceptor for the continuing synthesis. Catalytic hydrogenolysis followed by isopropylidenation gave the diol **6** (85%), which was selectively acetylated at the primary position with acetyl chloride/collidine in CH_2Cl_2 at low temperature[29] to yield the 4-OH acceptor **7** (84%) (Scheme 2). Coupling of **7** with benzobromoglucose[30] (**8**) gave stereospecifically the (1→4)-β-linked disaccharide **9** (77%) (Scheme 3). Removal of the isopropylidene acetal then afforded the 2,3-diol **10** (85%), which was to be protected in the 2-position to give a 3-OH acceptor. A benzoate was chosen, since this would be stable toward the conditions to be used in the later acetolysis of the anhydro bridge and also would participate to ensure α-selectivity in coupling reactions. Tin activation[31] of **10** followed by benzoylation gave a major product **11** (71%). As a result of the long-range couplings between the protons in the anhydro ring it was not possible to, unambiguously, establish the substitution pattern by NMR; however, through glycosylation and subsequent methylation analysis of the obtained trisaccharide, the assignment of the benzoyl at the 3-position was proven. Thus, during the

(26) Dziewiszek, K.; Zamojski, A. *Carbohydr. Res.* **1986**, *150*, 163.
(27) Castro, B. *Bull. Soc. Chim. Fr.* **1986**, 1533.
(28) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.
(29) Ishihara, K.; Hideki, K.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791.
(30) Ness, R. K.; Fletcher, H. G., Jr.; Hudson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 2200.
(31) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.

Scheme 4. Synthesis of 2,4-Branched Oligosaccharides[a]



[a] Key: (i) DMTST, NIS; (ii) Ac_2O, H_2SO_4, (iii) EtSH, BF_3 etherate; (iv) *p*-$CF_3CONHPhCH_2CH_2OH$, NIS, TfOH; (v) NaOMe; (vi) **19**, NIS, TfOH; (vii) (a) HOAc (80% aq). (b) NaOMe; (c) H_2, Pd−C.

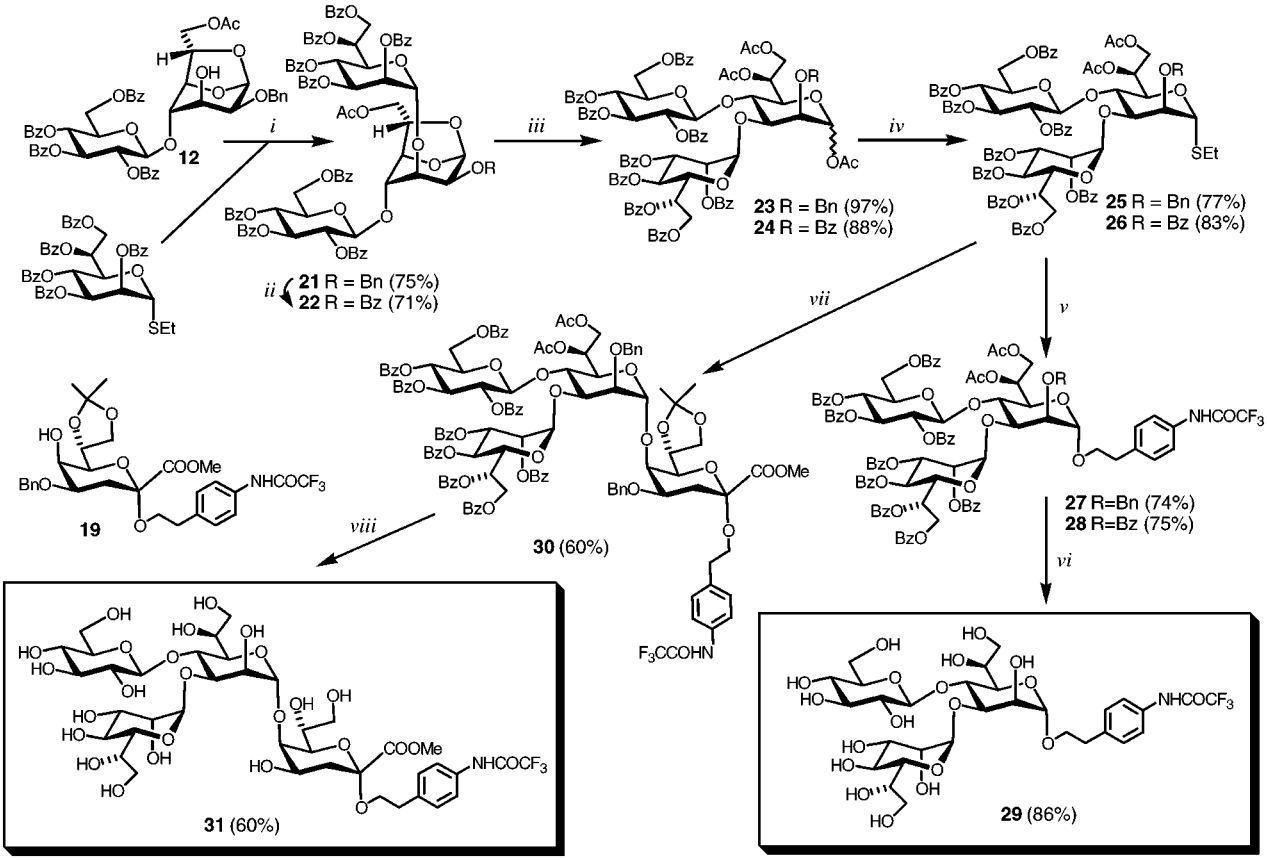
tin-activated benzoylation (and as was also found during glycosylation using the minor 2-*O*-benzoylated product as an acceptor) an O-2 → O-3 benzoyl migration takes place to give the 3-*O*-benzoate **11** as the major product. **11** was coupled with perbenzoylated heptose donors. The bromide[14] promoted by silver triflate gave a lot of transacylation, whereas the thioglycoside promoted by dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST)[32]/NIS[33] in a sluggish reaction yielded the branched α-linked trisaccharide **13** [37% (70% calculated on consumed acceptor)], acetolysis of which gave **14** (85%) as exclusively the α-acetate (Scheme 4). Transformation into the thioglycoside **15** (83%) and subsequent NIS-promoted coupling with the spacer *p*-trifluoroacetamidophenylethanol gave an excellent yield of the α-linked spacer trisaccharide **16** (92%). Deprotection then gave **17** (88%) in one step. To establish the substitution pattern of this trisaccharide, **17** was submitted to methylation analysis,[34] which proved it to be 2,4-branched. The trisaccharide **15** was also coupled in an NIS-promoted reaction to the 5-position of the known Kdo acceptor **19**.[35] Although this position is known to be unreactive, a high yield was obtained of the tetrasaccharide **18** (71%), which was deprotected in a three-step sequence to yield **20** (86%).

To obtain the native 3,4-branched structures, an alternative protection of diol **10** utilizing a protecting group not prone to migration had to be used. Hence, benzylation was performed after tin activation to afford the monobenzylated derivative **12**, with a supposedly free 3-OH (Scheme 3). Coupling of **12** with perbenzoylated heptose donors gave once more a lot of transacylated product when the bromide was used as donor, whereas the ethyl thioglycoside promoted by NIS/TfOH gave smoothly the α-linked trisaccharide **21** (75%) (Scheme 5). The 2-*O*-benzyl group was changed into a benzoyl group to give **22**, which was found to be not identical to **13**, suggesting a 3,4-branched structure. Both **21** and **22** were then treated as **13** was before. Acetolysis gave **23** (97%, α/β 9:1, showing the 2-*O*-benzyl group to be stable under these conditions) and **24** (88%). Methylation analysis of deprotected **23** now gave reliable evidence of a 3,4-branched structure. Transformation into ethyl thioglycosides gave **25** (77%) and **26** (83%), which were coupled to the spacer to yield the spacer trisaccharides **27** (75%) and **28** (74%), respectively. Both couplings afforded exclusively the α-linked spacer glycoside, proving that in these couplings a 2-*O*-participating group is not necessary to ensure stereospecificity. Deprotection of **27** then gave the target 3,4-branched trisaccharide **29** (86%).

Donors **25** and **26** were also tried in couplings to the Kdo acceptor **19**. Earlier experiences in the coupling of a heptose donor to this acceptor have shown low stereoselectivity, making it advantageous to use a 2-*O*-participating group.[36] However, in these reactions, donor **26** turned out to be totally inert to coupling with **19**, whereas **25** in a NIS/TfOH promoted reaction stereospecifically

(32) Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, c9.
(33) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.
(34) Björndal, H.; Hellerqvist, C. G.; Lindberg, B.; Svensson, S. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 610.
(35) Ekelöf, K.; Oscarson, S. *Carbohydr. Res.* **1995**, *278*, 289.

Scheme 5. Synthesis of the Common Core Tri- and Tetrasaccharide[a]



[a] Key: (i) NIS, TfOH; (ii) H_2, Pd−C then PhCOCl, pyridine; (iii) Ac_2O, H_2SO_4; (iv) EtSH, BF_3 etherate; (v) *p*-$CF_3CONHPhCH_2CH_2OH$, NIS, TfOH; (vi) (a) NaOMe, (b) H_2, Pd-C; (vii) **19**, NIS, TfOH; (vii) (a) HOAc (80% aq), (b) NaOMe, (c) H_2, Pd−C.

gave **30** in a good yield (60%). Deprotection in three steps then yielded the target spacer derivative **31**, corresponding to the common core tetrasaccharide of *Haemophilus influenzae*.

In conclusion, Barbier reaction conditions were found to be advantageous in terms of reproducibility and purification simplicity as compared to Grignard conditions in the one-carbon elongation using alkoxymethyl chlorides as reagents to obtain heptose derivatives. 1,6-Anhydro-L- and 1,6-anhydro-D-*glycero*-*β*-D-*manno*-heptopyranose were conveniently prepared from 6-*O*-trimethylsilylated ethyl thioglycosides through activation by NIS/TfOH. The L,D-anhydroheptose was shown to be a good precursor for the synthesis of sterically crowded 3,4-branched oligosaccharide structures. The anhydro bridge could then be readily cleaved by acetolysis and transformed into an ethyl thioglycoside trisaccharide, which could be used as an efficient building block in the construction of spacer glycosides of complex structures from the common core of the lipopolysaccharide from *Haemophilus influenzae* and *ducreyi* and *Neisseria meningitidis*.

Experimental Section

General Remarks. Melting points are corrected. Organic solutions were dried over $MgSO_4$ before concentration, which was performed under reduced pressure at <40 °C (bath temperature). NMR spectra were recorded at 25 °C and 270 MHz (^1H) or 67.5 MHz (^{13}C) in $CDCl_3$ with Me_4Si as the internal standard ($\delta = 0$ ppm), unless otherwise stated. TLC was performed on silica gel F_{254} (E. Merck) with detection by UV light and/or charring with 8% sulfuric acid. Silica gel (0.040−0.063 mm, Amicon) was used for column chromatography. Reversed-phase TLC was performed on silanilized silica gel, 60 silanisiert (E. Merck). Benzyloxymethyl chloride was synthesized according to the literature,[37] dried over $CaCl_2$, and stored without a drying agent in a sealed container at −18 °C. Catalytic hydrogenolyses at elevated pressures were performed using a Parr apparatus.

Ethyl 2,3,4,7-Tetra-*O*-benzyl-1-thio-6-*O*-trimethylsilyl-D-*glycero*-α-D-*manno*-heptopyranoside (3D) and Ethyl 2,3,4,7-Tetra-*O*-benzyl-1-thio-6-*O*-trimethylsilyl-L-*glycero*-α-D-*manno*-heptopyranoside (3L). To a flame-dried flask equipped with an internal thermometer, an efficient stirrer, and two dropping funnels were added freshly activated magnesium turnings (2.22 g, 91.3 mmol) and 132 mg (0.37 mmol) of sublimed $HgBr_2$ under an argon atmosphere. Benzyloxymethyl chloride (6.3 mL, 45.5 mmol) was dissolved in THF (30 mL), and a portion of this solution (approximately 5 mL) was added to the magnesium at room temperature via one of the dropping funnels. Once the exothermic reaction had started (as monitored by the temperature), the flask was partially immersed into an ice bath (0 °C) and ethyl 2,3,4-tri-O-benzyl-1,6-dialdo-1-thio-α-D-*manno*-pyranoside (**1**, 7.52 g, 15.3 mmol) in THF (30 mL) and the alkyl halide solution were added simultaneously through the dropping funnels at such a rate that the internal temperature was kept between 20 and 24 °C (approximate rate: 2 mL/min of each solution). During the addition, the degree of immersion into the ice bath was also used to tune the reaction temperature. After being stirred

(36) Ekelöf, K. Doctoral dissertation, Stockholm University, 1996.

(37) Connor, D. S.; Klein, G. W.; Taylor, G. N. *Org. Synth.* **1972**, *52*, 16.

overnight, the mixture was diluted with diethyl ether (200 mL) and cold NH_4Cl (aq, sat., 250 mL) was added. The mixture was stirred for 2 h. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated. Silica gel column chromatography (toluene/EtOAc 6:1) rendered pure ethyl 2,3,4,7-tetra-*O*-benzyl-1-thio-L,D-*glycero*-α-D-*manno*-heptopyranoside[25] (**2D** and **2L**) as an inseparable diastereomeric mixture (5.51 g, 9.40 mmol, 59%). The above mixture of D- and L-isomers (5.183 g, 8.43 mmol) was dissolved in dry pyridine (50 mL), whereafter trimethylsilyl chloride (1.9 mL, 15.0 mmol) was added at room temperature and the solution was stirred for 90 min, and then concentrated. The residue was dissolved in toluene (150 mL), washed twice with water, dried (Na_2SO_4), and concentrated. Silica gel chromatography (light petroleum (bp 60−70 °C)/EtOAc 9:1 containing 1% pyridine) yielded 438 mg (0.638 mmol, 8%) of **3D** followed by 4.78 g (6.96 mmol, 83%) of **3L**. **3D**: $[\alpha]_D$ +56 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 0.4, 15.0, 25.1, 71.9, 72.2, 72.5, 73.3, 74.3, 74.8, 75.2, 76.6, 80.9, 81.6, 127.4−138.9. **3L**: $[\alpha]_D$ +47 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 1.0, 14.9, 25.1, 69.7, 72.0, 72.6, 73.4, 74.3, 74.4, 76.1, 81.0, 82.0, 127.4−139.0.

1,6-Anhydro-2,3,4,7-tetra-*O*-benzyl-L-*glycero*-β-D-*manno*-heptopyranose (5L). To a solution of NIS (1.65 g, 7.3 mmol) and TfOH (317 μL, 3.6 mmol) in CH_2Cl_2/Et_2O (1:1, 120 mL) was added a solution of **3L** (3.32 g, 4.8 mmol) in CH_2Cl_2 (15 mL) during a period of 45 min. After being stirred for an additional 25 min, the solution was diluted with Et_2O, washed with $NaHCO_3$ (aq, sat., 25 mL) and $Na_2S_2O_3$ (10% aq, 25 mL), dried ($MgSO_4$), and concentrated. Silica gel column chromatography (two columns: toluene/EtOAc 6:1 and light petroleum (bp 40−65 °C(.EtOAc 3:1) yielded **5L** (2.27 g, 85%): $[\alpha]_D$ −18 (*c* 1.0, $CHCl_3$); ^1H NMR (assorted peaks) δ 3.33 (dd), 3.48 (d), 3.52 (dd), 3.55 (dd), 3.81 (dd), 4.40 (s), 4.54, 5.43 (s); ^{13}C NMR (assorted peaks) δ 70.8, 71.3, 73.1, 73.5, 73.6, 74.0, 74.2, 76.2, 100.5 (C-1, $J_{C,H}$ = 174 Hz), 127.7−138.0. Anal. Calcd for $C_{35}H_{36}O_6$: C, 76.1; H, 6.6. Found: C, 75.8; H, 6.4.

1,6-Anhydro-2,3-*O*-isopropylidene-L-*glycero*-β-D-*manno*-heptopyranose (6). Compound **5** (412 mg, 0.75 mmol) was dissolved in absolute ethanol (10 mL) and stirred with activated charcoal for 1 h. The mixture was filtered through Celite, which was then washed with additional ethanol (15 mL). To the solution was added palladium on activated carbon (10%, 50 mg) and 20 droplets of H_2O. Hydrogenation at 8 atm for 16 h followed by filtration, as above, and concentration yielded crude 1,6-anhydro-L-*glycero*-β-D-*manno*-heptopyranose. This residue was dissolved in DMF and treated with 2,2-dimethoxypropane (360 μL, 3.0 mmol). The solution was adjusted to pH 2 by addition of *p*-toluenesulfonic acid and stirred for 15 min at room temperature. Neutralization with triethylamine, concentration, and coevaporation twice from toluene followed by silica gel column chromatography (EtOAc) gave **6** (148 mg, 0.68 mmol, 85% from **4**): mp 119−20 °C (corr.); $[\alpha]_D$ −36 (*c* 1.0, $CHCl_3$); ^1H NMR (D_2O) δ 1.41, 1.56, 3.58, 3.64, 4.11, 4.25, 4.31, 4.37, 4.43, 5.49; NMR (D_2O) ^{13}C δ 25.4, 25.8, 63.4, 68.7, 71.6, 76.0, 76.2, 77.9, 99.8, 111.2. Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9. Found: C, 52.4; H, 6.7.

7-*O*-Acetyl-1,6-anhydro-2,3-*O*-isopropylidene-L-*glycero*-β-D-*manno*-heptopyranose (7). A solution of **6** (526 mg, 2.26 mmol) in CH_2Cl_2/DMF (25:1, 26 mL) was cooled to −78 °C. *sym*-Collidine (603 μL, 4.56 mmol) and acetyl chloride (178 μL, 2.51 mmol) were added. The solution was stirred overnight, and then it was slowly brought to room temperature. The reaction mixture was then concentrated in vacuo and coevaporated twice from toluene. Silica gel chromatography (toluene/EtOAc 1:1 + 10% HOAc) afforded **7** (522 mg, 1.90 mmol, 84%): $[\alpha]_D$ −35 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.8, 25.8, 25.9, 64.7, 68.8, 71.6, 72.5, 76.0, 78.0, 100.2, 110.3, 170.8. Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.6; H, 6.6. Found: C, 52.4; H, 6.6.

(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-7-*O*-acetyl-1,6-anhydro-2,3-*O*-isopropylidene-L-*glycero*-β-D-*manno*-heptopyranose (9). 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[30] (**8**, 1.38 g, 2.09 mmol) and **7** (379 mg, 1.38 mmol) were dissolved in dry CH_2Cl_2 (25 mL), and powdered molecular sieves (4 Å) were added. After being stirred at room temperature for 1.5 h, the mixture was cooled to 0 °C and a solution of silver triflate (544 mg, 2.18 mmol) in dry toluene (6 mL) was added. Stirring was continued for 30 min at 0 °C, when triethylamine (0.3 mL) was added. The mixture was filtered through Celite and directly purified on a silica gel column (toluene/EtOAc 6:1), which rendered 906 mg (1.06 mmol, 77%) of **9**: $[\alpha]_D$ +3 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.7, 25.6, 25.9, 62.9, 64.7, 69.5, 71.5, 71.7, 72.7, 74.6, 75.7, 76.1, 99.9 (C-1, $J_{C,H}$ = 175 Hz), 100.5 (C-1′, $J_{C,H}$ = 161 Hz), 109.9, 128.3−133.5, 165.0, 165.2, 165.8, 166.1, 170.5. Anal. Calcd for $C_{46}H_{44}O_{16}$: C, 64.8; H, 5.2. Found: C, 64.8; H, 5.2.

(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-7-*O*-acetyl-1,6-anhydro-L-*glycero*-β-D-*manno*-heptopyranose (10). HOAc (80% aq, 10 mL) was added to **9** (266 mg, 312 μmol). The mixture was heated to 80 °C, stirred for 4 h, and then concentrated and coevaporated once from toluene. Flash chromatography (toluene/EtOAc 1:2) yielded 215 mg (265 μmol, 85%) of **10**: $[\alpha]_D$ −6 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.8, 62.7, 65.0, 65.9, 69.5, 71.9, 72.7, 72.9, 75.8, 78.7, 100.5, 102.4, 128.3−133.6, 165.3, 165.9, 166.5, 170.8. Anal. Calcd for $C_{43}H_{40}O_{16}$: C, 63.5; H, 5.0. Found: C, 62.4; H, 5.0.

(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-7-*O*-acetyl-1,6-anhydro-3-*O*-benzoyl-L-*glycero*-β-D-*manno*-heptopyranose (11). Dibutyltin oxide (195 mg, 783 μmol) was added to a solution of **10** (575 mg, 707 μmol) in dry toluene (15 mL). The flask was fitted to a reflux condenser with its lower part containing molecular sieve pellets (4 Å). The opalescent mixture was refluxed for 1.5 h, over which time the mixture became clear. The solution was cooled to 0 °C, benzoyl chloride (100 μL, 861 μmol) was added, and the solution was stirred for 4 h at 0 °C and then at ambient temperature overnight. Toluene was added, and the mixture was washed with H_2O, dried ($MgSO_4$), and concentrated. Silica gel chromatography (toluene/EtOAc 2:1) gave 463 mg (505 μmol, 71%) of 3-*O*-benzoate **11** followed by 126 mg (137 μmol, 19%) of the isomeric 2-*O*-benzoate [(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-7-*O*-acetyl-1,6-anhydro-2-*O*-benzoyl-L-*glycero*-β-D-*manno*-heptopyranose]. **11**: $[\alpha]_D$ −25 (*c* 0.16, CH_2Cl_2); ^{13}C NMR δ 20.6 63.0, 64.3, 65.4, 69.5, 70.2, 72.0, 72.9, 73.1, 76.1, 79.3, 102.2, 102.3, 128.2−133.8, 164.9, 165.3, 165.7, 165.8, 166.1, 170.3. Anal. Calcd for $C_{50}H_{44}O_{17}$: C, 65.5; H, 4.8. Found: C, 65.3; H, 4.6. 2-*O*-benzoate: ^{13}C NMR δ 20.7, 62.9, 64.7, 69.0, 69.3, 69.5, 71.8, 72.6, 72.7, 73.4, 76.4, 79.1, 100.4, 100.9, 128.3−133.5, 164.9, 165.0, 165.1, 165.8, 166.1, 170.5.

(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-7-*O*-acetyl-1,6-anhydro-2-*O*-benzyl-L-*glycero*-β-D-*manno*-heptopyranose (12). A round-bottomed flask with 701 mg (0.862 mmol) of **10** in dry benzene (25 mL) was equipped with a reflux condenser with its lower part loosely packed with molecular sieve pellets (4 Å). Dibutyltin oxide (260 mg, 1.04 mmol) was added, and the mixture was heated to reflux. After 1 h, benzyl bromide (205 μL, 1.72 mmol) and tetra-*n*-butylammonium iodide (387 mg, 1.05 mmol) were added, and the solution was refluxed for another 12 h. The mixture was concentrated and purified on a silica gel column (toluene/EtOAc 2:1) to yield **12** (625 mg, 0.692 mmol, 80%) followed by 42 mg (52 μmol, 6%) of unreacted diol **10**. **12**: $[\alpha]_D$ −11 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.7, 62.9, 64.7, 67.8, 69.4, 71.3, 71.9, 72.6, 72.7, 72.9, 76.1, 78.9, 100.8, 101.2, 128.0−137.0, 165.0, 165.2, 165.8, 166.1, 170.5. Anal. Calcd for $C_{50}H_{46}O_{16}$: C, 66.5; H, 5.1. Found: C, 66.3; H, 5.0.

(2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)]-7-*O*-acetyl-1,6-anhydro-3-*O*-benzoyl-L-*glycero*-β-D-*manno*-heptopyranose (13). a. Procedure A (Br). A mixture of 2,3,4,6,7-penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl bromide[14] (500 mg, 630 μmol), **11** (290 mg, 316 μmol), and powdered molecular sieves (4A) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 20 min, whereafter the mixture was cooled (0 °C) and silver triflate (210 mg, 817 μmol) dissolved in dry toluene (2 mL) was added. After the mixture was stirred for 30 min, Et_3N (0.1 mL) was added. Filtration through Celite followed by concentration in vacuo yielded a crude mixture of mainly two products, which were separated and purified on two consecutive silica gel columns (toluene/EtOAc 4:1 and light petroleum (bp 40−65 °C)/EtOAc

3:2) to give **13** (174 mg, 107 μmol, 34%) and 126 mg (123 μmol, 39%) of the transacylated acceptor, (2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-7-*O*-acetyl-1,6-anhydro-2,3-di-*O*-benzoyl-L-*glycero*-β-D-*manno*-heptopyranose.

b. Procedure B (SEt). Ethyl 2,3,4,6,7-penta-*O*-benzoyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (180 mg, 232 μmol) and **11** (157 mg, 171 μmol) were stirred under argon with powdered molecular sieves (4A) in CH_2Cl_2/Et_2O (1:2, 6 mL) at room temperature for 45 min. DMTST (195 mg, 755 μmol) was added, and the mixture was stirred overnight, when an additional 90 mg (348 μmol) of DMTST was added. After the mixture was further stirred overnight, more donor (170 mg, 219 μmol) and NIS (64 mg, 284 μmol) were added. The mixture was left another night, whereafter it was diluted with toluene and washed with $Na_2S_2O_3$. Drying and filtration of the organic phase followed by concentration gave a crude product that was purified by silica gel chromatography (two columns: toluene/EtOAc 4:1 and light petroleum (bp 40−65 °C)/EtOAc 3:2) to give 104 mg (63.8 μmol, 37%) of **13**, 61 mg (83.5 μmol) of hydrolyzed donor, 2,3,4,6,7-penta-*O*-benzoyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranose, and 73 mg (79.6 μmol, 47%) of unreacted **11**. **13**: $[\alpha]_D$ −37 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.7, 62.5, 63.0, 64.4, 65.6, 68.2, 68.7, 69.3, 69.6, 69.9, 70.1, 72.0, 72.8, 73.0, 73.4, 76.2, 78.5, 97.5, 101.0, 101.6, 128.1−133.5, 164.7−166.0, 170.4.

(2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)]-1,6,7-tri-*O*-acetyl-3-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranose (14). To a solution of **13** (180 mg, 110 μmol) in acetic anhydride (10 mL) was added concentrated sulfuric acid (50 μL) at room temperature. The mixture was stirred for 20 min, at which time NaOAc (150 mg) was added. The mixture was stirred for another 10 min, diluted with toluene, and washed with $NaHCO_3$ (10 mL, aq, sat.) and water. The organic phase was dried ($MgSO_4$) and concentrated. Silica gel chromatography (toluene/EtOAc 4:1) of the residue afforded **14** (161 mg, 93 μmol, 85%): $[\alpha]_D$ −27 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.3, 20.9, 21.0, 61.2, 62.4, 63.7, 65.1, 67.1, 68.2, 69.3, 69.8, 70.1, 70.4, 71.0, 71.8, 71.9, 72.1, 73.3, 73.8, 75.5, 91.4 ($J_{C,H}$ = 178 Hz), 99.0 ($J_{C,H}$ = 172 Hz), 101.6 ($J_{C,H}$ = 161 Hz), 127.9−133.5, 164.9−166.0, 168.4, 169.8, 170.7. Anal. Calcd for $C_{96}H_{82}O_{31}$: C, 66.6; H, 4.8. Found: C, 66.4; H, 4.7.

Ethyl (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)]-6,7-di-*O*-acetyl-3-*O*-benzoyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranose (15). Ethanethiol (42 μL, 0.57 mmol) was added to a solution of **14** (139 mg, 80 μmol) in CH_2Cl_2 (4 mL) containing powdered molecular sieves (4 Å), and the mixture was stirred for 10 min at room temperature under argon. Freshly distilled BF_3 etherate (230 μL, 1.87 mmol) was added, and the mixture was stirred overnight. $NaHCO_3$ (aq, sat., 3 mL) was added, and the mixture stirred for another 1 h, whereafter the organic phase was separated, dried ($MgSO_4$), and concentrated. Silica gel chromatography (toluene/EtOAc 4:1) of the residue afforded unreacted **14** (18 mg, 13%) and **15** (115 mg, 66 μmol, 83%): $[\alpha]_D$ −15 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 14.9, 20.3, 21.1, 25.5, 60.7, 62.4, 63.7, 65.2, 67.5, 68.4, 69.4, 69.7, 69.9, 70.6, 70.7, 71.0, 71.8, 72.1, 73.4, 74.3, 79.0, 83.4, 99.0, 101.6, 127.9−133.5, 164.8−166.0, 169.8, 170.5. Anal. Calcd for $C_{96}H_{84}O_{29}S$: C, 66.5; H, 4.9. Found: C, 63.3; H, 4.7.

2-(4-Trifluoroacetamidophenyl)ethyl (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)]-6,7-di-*O*-acetyl-2-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranoside (16). 2-(4-Trifluoroacetamido)phenylethanol (20 mg, 92 μmol) was added to a solution of **15** (67 mg, 39 μmol) in CH_2Cl_2/Et_2O (1:1, 3 mL) containing powdered molecular sieves (4 Å). After being stirred for 30 min, the mixture was cooled (0 °C) and NIS (20 mg, 89 μmol) and triflic acid (1.4 μL, 16 μmol) were added. The ice bath was removed, and the coupling was allowed to continue for 20 min, whereafter the mixture was diluted (CH_2Cl_2) and filtered through Celite. The filtrate was washed with $Na_2S_2O_3$ (10% aq) and water, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography (toluene/EtOAc 4:1) to yield **16** (68 mg, 36 μmol, 92%): ^{13}C NMR δ 20.2, 21.1, 35.2, 61.2, 62.2, 63.4, 65.2, 67.2, 67.7, 68.3, 69.2, 69.6, 69.8, 70.3, 70.5, 70.6, 71.9, 72.4, 73.5, 74.5, 97.5, ($J_{C,H}$ = 172 Hz), 99.1 ($J_{C,H}$ = 173 Hz), 101.5 ($J_{C,H}$ = 163 Hz), 121.8−137.0, 164.9−166.1, 169.7, 170.7.

2-(4-Trifluoroacetamidophenyl)ethyl L-*glycero*-α-D-*manno*-heptopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-L-*glycero*-α-D-*manno*-heptopyranose (17). Compound **16** (64 mg, 34 μmol) was dissolved in MeOH (4 mL). The pH was adjusted to 11 by addition of sodium methoxide (1 M in MeOH), and the mixture was stirred for 5 h. Dowex H^+ ion-exchange resin was added to neutralize the solution. Filtration and concentration gave crude **17**, which was dissolved in H_2O, washed with Et_2O, and purified by size-exclusion chromatography on a Biogel P2 column (eluent H_2O containing 1% *n*-BuOH). Freeze-drying the product-containing fractions yielded pure **17** (23 mg, 29 μmol, 88%): $[\alpha]_D$ +32 (*c* 1.0, H_2O); ^{13}C NMR (D_2O) δ 35.5, 61.5, 63.5, 63.6, 66.8, 68.9, 69.0, 69.6, 70.0, 70.3, 70.7, 70.9, 71.2, 72.4, 74.0, 76.3, 76.7, 77.0, 78.1, 98.6 ($J_{C,H}$ = 172 Hz), 102.7 ($J_{C,H}$ = 172 Hz), 103.3 ($J_{C,H}$ = 161 Hz), 123.1, 130.7, 133.9, 138.9; ^1H NMR (assorted peaks) δ 4.49 ($J_{1,2}$ = 8 Hz), 4.90, 4.98. HRMS calcd for $C_{30}H_{43}F_3NO_{19}$ $[M-H]^-$ 778.2381, found 778.2438.

Methyl [2-(4-Trifluoroacetamidophenyl)ethyl (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)]-(6,7-di-*O*-acetyl-3-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→5)-4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-*manno*-oct-2-ulopyranosid]onate (18). A mixture of **15** (79 mg, 45.6 μmol) and methyl [2-(4-trifluoroacetamidophenyl)ethyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-*manno*-oct-2-ulopyranosid]onate[35] (**19**, 42 mg, 70.3 μmol) in dry CH_2Cl_2 containing powdered molecular sieves (4 Å) was stirred under argon at room temperature for 1 h. The solution was cooled to −25 °C, NIS (16 mg, 71.1 μmol) and triflic acid (1.5 μL, 17.0 μmol) were added, and the mixture was stirred for 1 h, during which it was allowed to reach a temperature of +5 °C. The reaction was quenched with the addition of $NaHCO_3$ (aq, sat., 1.5 mL) and $Na_2S_2O_3$ (10% aq, 1.5 mL), stirred for 10 min, and filtered through Celite. The organic phase was separated and concentrated in vacuo. Coevaporation of the residue from toluene followed by silica gel chromatography (toluene/EtOAc 3:1) gave **18**: (73 mg, 32.2 μmol, 71%). Further elution (toluene/EtOAc 1:1) rendered 12 mg of unreacted **19**. **18** $[\alpha]_D$ −2.2 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.6, 21.4, 24.4, 26.3, 31.8, 35.4, 52.6 (OCH3), 62.5, 63.6, 63.8, 65.0, 65.2, 68.0, 68.4, 68.6, 69.5, 69.8, 70.3, 70.5, 70.9, 71.9, 72.0, 72.7, 73.3, 74.3, 74.4, 74.6, 98.4, 98.6 ($J_{C,H}$ = 174 Hz), 99.2 ($J_{C,H}$ = 171 Hz), 101.5 ($J_{C,H}$ = 165 Hz), 109.3, 120.8−137.8, 164.8−168.0, 170.1, 170.7. Anal. Calcd for $C_{123}H_{112}F_3NO_{38}$: C, 65.1; H, 5.0. Found: C, 65.0; H, 5.0.

Methyl [2-(4-Trifluoroacetamidophenyl)ethyl L-*glycero*-α-D-*manno*-Heptopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-L-*glycero*-α-D-*manno*-heptopyranosyl-(1→5)-3-deoxy-α-D-*manno*-oct-2-ulopyranosid]onate (20). Compound **18** (64 mg, 28 μmol) dissolved in aqueous acetic acid (80%, 3 mL) was heated at 70 °C for 3 h. The solution was concentrated, coevaporated from toluene (3 × 1.5 mL), and then dissolved in MeOH (3 mL). The pH was adjusted to 12 by treatment with a 1 M NaOMe solution in MeOH. The mixture was stirred at room temperature for 3 h, neutralized with Dowex 50 H^+ ion-exchange resin, filtered, and concentrated. The residue was dissolved in H_2O, washed with diethyl ether, and desalted on a Bio-Gel P2 column (eluted with distilled H_2O containing 1% of *n*-BuOH). The product-containing fractions were freeze-dried, and the residue was dissolved in absolute ethanol (3 mL). To the solution was added HOAc (200 μL, aq, 60% v/v) and palladium on activated carbon (10%, 13 mg). The mixture was hydrogenolyzed at 9 atm for 16 h, filtered, and concentrated in vacuo. The residue was once again purified by size-exclusion chromatography as above to give **20** (25 mg, 24.3 mmol, 86%): $[\alpha]_D$ +41 (*c* 1.0, H_2O); ^{13}C NMR (D_2O) δ 35.0, 35.2, 54.1, 61.4, 63.5, 63.6, 63.8, 65.0, 65.8, 66.9, 69.0, 69.4, 69.5, 69.9, 70.3, 70.8, 71.1, 71.4, 72.3, 72.5, 74.0, 75.9, 76.2, 76.7, 77.3, 79.5, 99.3, 100.2 ($J_{C,H}$ = 172 Hz), 102.8 ($J_{C,H}$ = 169

Hz), 103.4 ($J_{C,H}$ = 159 Hz),123.0, 130.8, 133.9, 138.5, 170.1; ^{1}H NMR (assorted peaks) δ 4.53 ($J_{1,2}$ = 8 Hz), 5.04, 5.24. HRMS calcd for $C_{39}H_{57}F_3NO_{26}$ [M−H]$^-$ 1012.3121, found 1012.3178.

(2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-7-*O*-acetyl-1,6-anhydro-2-*O*-benzyl-L-*glycero*-*β*-D-*manno*-heptopyranose (21). a. Procedure A (Br). 12 (326 mg, 0.361 mmol) and 2,3,4,6,7-penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl bromide[14] (426 mg, 0.537 mmol) were dissolved in dry CH_2Cl_2 (20 mL) and stirred under argon with powdered molecular sieves (4 Å) for 1.5 h. After the mixture cooled (−25 °C), a solution of silver triflate (140 mg, 0.545 mmol) in dry toluene (1.5 mL) was added. The solution was stirred for 30 min (temperature 0 °C), at which time triethylamine (350 μL) was added. The mixture was filtered through Celite and concentrated. Purification (two silica gel columns: toluene/EtOAc 4:1 and light petroleum (bp 60−70 °C)/EtOAc 3:2) gave **21** (208 mg, 0.129 mmol, 36%) and the transacylated acceptor.

b. Procedure B (SEt). 12 (299 mg, 0.331 mmol) and ethyl 2,3,4,6,7-penta-*O*-benzoyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (1026 mg, 1.324 mmol) were dissolved in dry CH_2Cl_2 (25 mL) and stirred under argon with powdered molecular sieves for 80 min. After the mixture cooled (−35 °C), NIS (329 mg, 1.462 mmol) and TfOH (20 μL, 0.227 mmol) were added. The solution was stirred for 40 min (temperature of −5 °C), at which time triethylamine (100 μL) was added. The mixture was filtered through Celite, diluted (CH_2Cl_2), washed with $Na_2S_2O_3$ (aq, sat.), dried ($MgSO_4$), and concentrated. Purification (two silica gel columns: light petroleum (bp 60−70 °C)/EtOAc 3:2 and toluene/EtOAc 4:1) gave **21** (401 mg, 0.129 mmol, 75%): $[\alpha]_D$ −28 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.9, 62.2, 64.7, 65.0, 68.2, 69.3, 70.2, 70.5, 71.0, 71.6, 72.0, 72.8, 73.8, 73.9, 75.9, 76.2, 96.8, 99.8, 100.7, 127.8−137.3, 165.0−166.0, 170.8. Anal. Calcd for $C_{92}H_{78}O_{27}$: C, 68.4; H, 4.9. Found: C, 68.3; H, 4.9.

(2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-7-*O*-acetyl-1,6-anhydro-2-*O*-benzoyl-L-*glycero*-*β*-D-*manno*-heptopyranose (22). An amount of 195 mg (0.121 mmol) of **21** was dissolved in EtOAc/EtOH (1:1, 15 mL). Palladium on activated carbon and 60% HOAc (aq, 0.5 mL) were added, and the mixture was hydrogenolyzed at 8 atm for 2 days. The mixture was filtered (Celite), evaporated, and coevaporated twice from pyridine. The residue was dissolved in pyridine (3 mL). Benzoyl chloride (112 μL, 0.965 mmol) and a catalytic amount of 4-(dimethylamino)pyridine were added, and the solution was stirred at 45 °C for 2 h. Evaporation of the solvent and coevaporation twice from toluene yielded a crude mixture of **22**, which was purified on a silica gel column (toluene/EtOAc 3:1) (139 mg, 0.085 mmol, 71%): $[\alpha]_D$ −43 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.9, 62.4, 63.6, 64.9, 68.0, 68.7, 69.5, 70.3, 70.6, 70.8, 71.7, 72.7, 72.8, 73.9, 74.2, 76.2, 96.6, 100.2, 100.8, 128.2−133.5, 165.0−165.9, 170.8. Anal. Calcd for $C_{92}H_{76}O_{28}$: C 67.8, H 4.7. Found: C, 67.8; H, 4.6.

(2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-1,6,7-tri-*O*-acetyl-2-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranose (23α) and (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-1,6,7-tri-*O*-acetyl-2-*O*-benzyl-L-*glycero*-*β*-D-*manno*-heptopyranose (23*β*). A solution of **21** (226 mg, 0.140 mmol) in acetic anhydride (9 mL) was cooled to −30 °C. Concentrated sulfuric acid (45 μL) was added, and the mixture was stirred for 5 min, at which time anhydrous sodium acetate (210 mg) was added. The solution was stirred for another 15 min at −30 °C, whereafter toluene (10 mL) and water (5 mL) were added. After the mixture was stirred at room temperature for 30 min, the organic phase was separated, washed with H_2O (10 mL), concentrated, and purified on a silica gel column (toluene/EtOAc 4:1). Elution and concentration of appropriate fractions yielded 210 mg (0.122 mmol, 87%) of **23**α followed by 23 mg (0.013 mmol, 10%) of **23***β*. **23**α: $[\alpha]_D$ −10 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.2, 20.8, 61.3, 63.1, 63.3, 65.9, 67.7, 68.0, 69.8, 70.7, 71.9, 72.1, 72.2, 73.0, 73.8, 75.0, 75.4, 90.6 ($J_{C,H}$ = 176 Hz), 99.4 ($J_{C,H}$ = 181 Hz), 100.6 ($J_{C,H}$ = 165 Hz), 127.7−137.4, 165.0, 165.1, 165.36, 165.42, 165.5, 165.7, 166.0, 168.7, 169.8, 170.7. **23***β*: $[\alpha]_D$ −12 (*c* 1.0, $CHCl_3$); ^{13}C NMR (ref $CDCl_3$, 77.17) δ 20.5, 21.0, 21.1, 61.2, 62.8, 63.6, 66.2, 68.0, 68.4, 69.8, 70.2, 70.7, 72.3, 73.2, 73.7, 73.8, 75.1, 77.9, 92.7, 99.5, 100.1, 127.9−137.9, 165.1, 165.3, 165.49, 165.54, 165.7, 166.2, 168.4, 170.2, 170.9.

(2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-1,6,7-tri-*O*-acetyl-2-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranose (24). A solution of **22** (113 mg, 69.3 μmol) in Ac_2O (8 mL) was cooled to 0 °C. Sulfuric acid (40 μL) was added, and the reaction was allowed to continue for 15 min. Sodium acetate (anhydrous, 200 mg, 2.4 mmol) was then added, and the mixture was stirred for another 5 min, whereafter dilution with toluene, washing with water, and concentration followed by silica gel chromatography (toluene/EtOAc 3:1) gave only the α-anomer **24** (106 mg, 61.2 μmol, 88%): $[\alpha]_D$ −58 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.3, 20.6, 20.8, 61.3, 62.6, 63.6, 65.7, 67.9, 68.1, 69.7, 69.8, 70.1, 70.4, 70.7, 71.4, 72.3, 72.6, 72.7, 73.2, 73.6, 90.3 ($J_{C,H}$ = 178 Hz), 99.2 ($J_{C,H}$ = 179 Hz), 100.6 ($J_{C,H}$ = 163 Hz), 127.8−133.6, 164.8−165.9, 167.9, 169.8, 170.6.

The 3,4-disubstitution was confirmed by methylation analysis[34] where the branched heptose gave fragmentations at *m*/*z* 117 and *m*/*z* 89.

Ethyl (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-6,7-di-*O*-acetyl-2-*O*-benzyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranose (25). A mixture of **23**α (163 mg, 94.9 μmol) and ethanethiol (60 μL, 0.81 mmol) in freshly distilled CH_2Cl_2 containing powdered molecular sieves (4 Å) was stirred at room temperature for 10 min. BF_3 etherate (0.27 mL, 2.15 mmol) was added, and the mixture was stirred for 52 h, at which time it was concentrated and directly put on a silica gel column. Elution (toluene/EtOAc 4:1) gave pure **25** (126 mg, 73.3 μmol, 77%): $[\alpha]_D$ 0 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 14.6, 20.2, 20.8, 25.4, 60.9, 63.5, 65.9, 68.0, 68.1, 69.9, 70.0, 70.7, 71.8, 72.2, 72.9, 73.6, 73.8, 75.6, 78.1, 82.5, 99.3, 100.7, 127.7−137.7, 164.9−166.0, 169.9, 170.7. Anal. Calcd for $C_{96}H_{86}O_{28}S$: C, 67.0; H, 5.0. Found: C, 66.9; H, 4.9.

Ethyl (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-6,7-di-*O*-acetyl-2-*O*-benzoyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranose (26). A mixture of **24** (105 mg, 60.6 μmol), ethanethiol (50 μL, 0.68 mmol), BF_3 etherate (230 μL, 1.83 mmol), and powdered molecular sieves (4A) in dry CH_2Cl_2 (4 mL) was stirred at room temperature for 2 days, filtered through Celite, and washed with $NaHCO_3$ (aq, sat.). The organic phase was separated, concentrated in vacuo, and coevaporated twice from toluene. Purification of the residue (silica gel column, $CHCl_3$/Me_2CO, 24:1) gave **26** (67 mg, 38.6 μmol, 64%) followed by unreacted **24** (8 mg, 8%): $[\alpha]_D$ −31 (*c* 1.0, $CHCl_3$). **26**: ^{13}C NMR δ 14.5, 20.3, 20.8 25.8 61.1, 62.8, 63.6, 65.7, 68.2, 69.9, 70.2, 70.3, 72.3, 72.6, 73.5, 73.6, 73.8, 73.9, 82.8, 99.3, 100.7, 127.8−133.5, 164.9−165.8, 170.0, 170.5. Anal. Calcd for $C_{96}H_{84}O_{29}S$: C, 66.5; H, 4.9. Found: C, 66.9; H, 4.6.

2-(4-Trifluoroacetamidophenyl)ethyl (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-6,7-di-*O*-acetyl-2-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranose) (27). A solution of **25** (100 mg, 58.1 μmol) and 2-(4-trifluoroacetamido)phenylethanol (27 mg, 116 μmol) in Et_2O (4 mL) containing powdered molecular sieves (4A) was stirred for 100 min under argon, whereafter the mixture was cooled (−38 °C) and NIS (25 mg, 111 μmol) and TfOH (2 μL, 23 μmol) were added. The mixture was stirred for 3 h (the last hour without cooling bath). The mixture was filtered through Celite and diluted with Et_2O. The organic phase was washed with $Na_2S_2O_3$ (10% aq, 3 mL) and dried ($MgSO_4$). Concentration followed by silica gel chromatography (toluene/EtOAc 4:1) gave 81 mg (42.8 μmol, 74%) of **27**: $[\alpha]_D$ +3.9 (*c*

1.0, $CHCl_3$); ^{13}C NMR δ 20.3, 20.8, 34.8, 61.3, 63.3, 65.9, 67.4, 67.8, 68.0, 69.7, 69.8, 69.9, 70.0, 70.7, 72.3, 72.6, 72.8, 73.9, 75.5, 76.4, 97.2, 99.6, 100.7, 121.2−137.9, 165.1−165.9, 169.9, 170.7. Anal. Calcd for $C_{104}H_{90}F_3NO_{30}$: C, 66.1; H, 4.8. Found: C, 65.9; H, 4.7.

2-(4-Trifluoroacetamidophenyl)ethyl (2,3,4,6,7-Penta-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-6,7-di-*O*-acetyl-2-*O*-benzoyl-L-*glycero*-α-D-*manno*-heptopyranose (28). A solution of **26** (50 mg, 28.8 μmol) and 2-(4-trifluoroacetamidophenyl)ethanol (15 mg, 64.3 μmol) in CH_2Cl_2/Et_2O (1:1, 3 mL) was stirred with powdered molecular sieves (4 Å) for 1.5 h at room temperature. NIS (16 mg, 71.1 μmol) and TfOH (1.5 μL, 17 μmol) were added at ambient temperature, and the mixture was stirred for another 20 min. Dilution (CH_2Cl_2) and washing of the organic phase ($Na_2S_2O_3$, 10% aq, 3 mL) followed by drying ($MgSO_4$) and concentration gave a residue, which was purified on a silica gel column (toluene/EtOAc 3:1) to yield **28** (41 mg, 21.5 μmol, 75%): ^{13}C NMR δ 20.3, 20.8, 34.7, 61.4, 62.5, 63.4, 65.8, 67.4, 67.8, 68.1, 69.5, 69.8, 69.9, 70.4, 71.7, 72.5, 72.8, 73.7, 73.8, 74.0, 96.5 ($J_{C,H}$ = 172 Hz), 99.6 ($J_{C,H}$ = 178 Hz), 100.8 ($J_{C,H}$ = 165 Hz), 121.3−136.9, 164.9−165.9, 169.9, 170.5.

2-(4-Trifluoroacetamidophenyl)ethyl L-*glycero*-α-D-*manno*-Heptopyranosyl-(1→3)-[*β*-D-glucopyranosyl-(1→4)]-L-*glycero*-α-D-*manno*-heptopyranoside (29). **27** (54 mg, 28.6 μmol) was dissolved in distilled MeOH (6 mL), and the pH was raised to 11 by the addition of 1 M sodium methoxide (in MeOH). The mixture was stirred for 3 h, then neutralized with Dowex 50 (H^+), filtered, and concentrated. The residue was dissolved in absolute EtOH (10 mL). Palladium on carbon and acetic acid (60% aq, 0.5 mL) were added, and the mixture was hydrogenolyzed at 8 atm overnight. The mixture was centrifuged, and the pellets were washed once with MeOH. The supernatants were combined and concentrated. The pellets were washed with water and centrifuged, and the supernatants were used to dissolve the residue of crude **29**. Washing of the aqueous phase with Et_2O followed by desalting on a Biogel P2 column (eluent: H_2O + 1% *n*-BuOH) gave, after freeze-drying of appropriate fractions, pure **29** (19 mg, 24.4 μmol, 85%): $[\alpha]_D$ +55 (*c* 0.5, H_2O); ^{13}C NMR (D_2O) δ 35.5, 62.3, 63.8, 64.1, 66.9, 68.5, 68.8, 69.7, 70.5, 70.7, 71.0, 71.4, 71.7, 72.6, 74.1, 74.6, 75.2, 76.4, 77.0, 100.0 ($J_{C,H}$ = 170 Hz), 102.4 ($J_{C,H}$ = 176 Hz), 103.2 ($J_{C,H}$ = 164 Hz), 123.1, 130.6, 139.2; ^1H NMR (40 °C, assorted peaks) δ 4.52 (d, $J_{1,2}$ = 7.7 Hz), 4.79 (s), 5.24 (s). HRMS calcd for $C_{30}H_{43}F_3NO_{19}$ $[M-H]^-$ 778.2381, found 778.2426.

Methyl [2-(4-Trifluoroacetamidophenyl)ethyl 2,3,4,6,7-Penta-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranosyl-(1→3)-[(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-(1→4)]-(6,7-di-*O*-acetyl-2-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→5)-4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-*manno*-oct-2-ulopyranosid]onate (30). A solution of **25** (140 mg, 81.4 μmol) and **19**[35] (81 mg, 136 μmol) in dry Et_2O (5 mL) was stirred with powdered molecular sieves in an argon atmosphere for 100 min. The mixture was cooled to −32 °C, and NIS (27 mg, 120 μmol) and triflic acid (3 μL, 33.9 μmol) were added. After 80 min (temperature of the cooling bath was +10 °C), the mixture was filtered through Celite, diluted with Et_2O, and washed with $Na_2S_2O_3$ (10% aq). The organic phase was dried ($MgSO_4$) and concentrated. Purification on a silica gel column (toluene/EtOAc 3:1) rendered 111 mg (49.2 μmol, 60%) of **30**: $[\alpha]_D$ +5.5 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 20.8, 20.9, 25.3, 26.8, 31.5, 35.3, 52.3, 63.4, 63.5, 65.1, 66.0, 67.8, 68.6, 69.3, 69.9, 70.0, 70.9, 71.1, 71.8, 72.3, 72.7, 72.8, 73.7, 74.1, 76.0, 97.0, 98.5, 99.9, 100.5, 109.3, 120.1−137.9, 165.0−168.1, 170.6, 171.1. Anal. Calcd for $C_{123}H_{114}F_3NO_{37}$: C, 65.5; H, 5.1. Found: C, 65.2; H, 5.0.

Methyl [2-(4-Trifluoroacetamidophenyl)ethyl L-*glycero*-α-D-*manno*-heptopyranosyl-(1→3)-[*β*-D-glucopyranosyl-(1→4)]-L-*glycero*-α-D-*manno*-heptopyranosyl-(1→5)-3-deoxy-α-D-*manno*-oct-2-ulopyranosid]onate (31). Totetrasaccharide **30** (111 mg) was added acetic acid (80% aq, 6 mL) and MeCN (0.5 mL). The mixture was heated and stirred at 80 °C for 2h, at which time it was cooled and concentrated on a rotavapor. The residue was coevaporated from toluene twice and dried on a vacuum pump for 1 h. The residue was then dissolved in freshly distilled MeOH (6 mL), and a 1 M solution of sodium methoxide in MeOH (0.5 mL) was added. The solution was stirred for 4 h, neutralized using Dowex 50 H^+ ion-exchange resin, filtered, and concentrated. To the dry residue was added absolute EtOH (10 mL) and 0.5 mL of HOAc (60% aq). The solution was hydrogenolyzed at 8 atm overnight, filtered through Celite, and washed with MeOH, and the combined organic phases were evaporated. The Celite residue was suspended in H_2O (doubly distilled) and centrifuged. The residue of crude **31** was taken up in the aqueous supernatant, washed with Et_2O, separated, and slightly concentrated under reduced pressure. Desalting was then performed on a Biogel P2 column (eluent H_2O + 1% n-BuOH). Freeze-drying of appropriate fractions yielded pure **31** (30 mg, 60%): $[\alpha]_D$ +73 (*c* 1.0, H_2O); ^{13}C NMR (D_2O) δ 34.9, 35.3, 54.1, 62.2, 63.7, 63.9, 64.1, 65.0, 65.7, 66.8, 68.9, 69.3, 69.5, 70.5, 70.7, 70.9, 71.4, 72.0, 72.5, 74.3, 74.47, 74.55, 74.9, 76.3, 77.1, 99.2, 101.5 ($J_{C,H}$ = 171 Hz), 102.2 ($J_{C,H}$ = 176 Hz), 103.2 ($J_{C,H}$ = 161 Hz), 123.0, 130.8, 133.9, 138.6, 170.7; ^1H NMR δ 4.56 ($J_{1',2'}$ = 8 Hz), 5.03, 5.28. HRMS calcd for $C_{39}H_{57}F_3NO_{26}$ $[M-H]^-$ 1012.3121, found 1012.3167.

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Supporting Information Available: Figures showing 67.5 MHz ^{13}C NMR spectra of compounds **3D, 3L, 6**, **7**, **11**, **12**, **16**−**18**, **20**, **and 27**−**31** together with 270 MHz ^1H NMR spectra of compounds **17**, **19**, **29**, and **31** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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