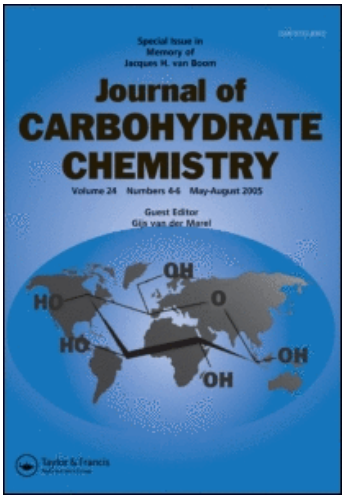

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N. C. R. van Straten[a]; N. M. A. J. Kriek[a]; C. M. Timmers[a]; S. C. M. Wigchert[a]; G. A. van der Marel[a]; J. H. van Boom[a]

[a] Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, Leiden, RA, The Netherlands

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SYNTHESIS OF A TRISACCHARIDE FRAGMENT CORRESPONDING TO THE LIPOPOLYSACCHARIDE REGION OF *VIBRIO PARAHAEMOLYTICUS*

N.C.R. van Straten, N.M.A.J. Kriek, C.M. Timmers, S.C.M. Wigchert, G.A. van der Marel and J.H. van Boom*

Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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ABSTRACT

Vicinal *syn*-dihydroxylation of D-*manno*-hept-6-enopyranosides **4** and **10** with OsO_4 afforded D-*glycero*-α-D-*manno*-heptopyranosides **5** and **11**, respectively, in good yield and with a high degree of stereoselectivity. Compound **5** was converted into DD-Hep*p* acceptor **8**. Glycosylation of acceptor **8** under the agency of *N*-iodosuccinimide and triflic acid with ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-7-deoxy-7-(phenyldimethyl)silane-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (**22**), obtained after hydroxymethylation of aldehyde **17** with (phenyldimethylsilyl)methyl magnesium chloride, followed by protective group manipulations, gave α-linked dimer **23**. Oxidative removal of the $PhMe_2Si$ moiety in dimer **23**, protective group manipulations (→ **26**), and condensation with ethyl 1-thio-β-D-glucopyranosyl donor **27** furnished trisaccharide **28**. Oxidation of the C-6 in **29** and hydrogenolysis yielded target trisaccharide **2**, a fragment of the inner-core lipopolysaccharide region of *Vibrio parahaemolyticus*, serotype O2.

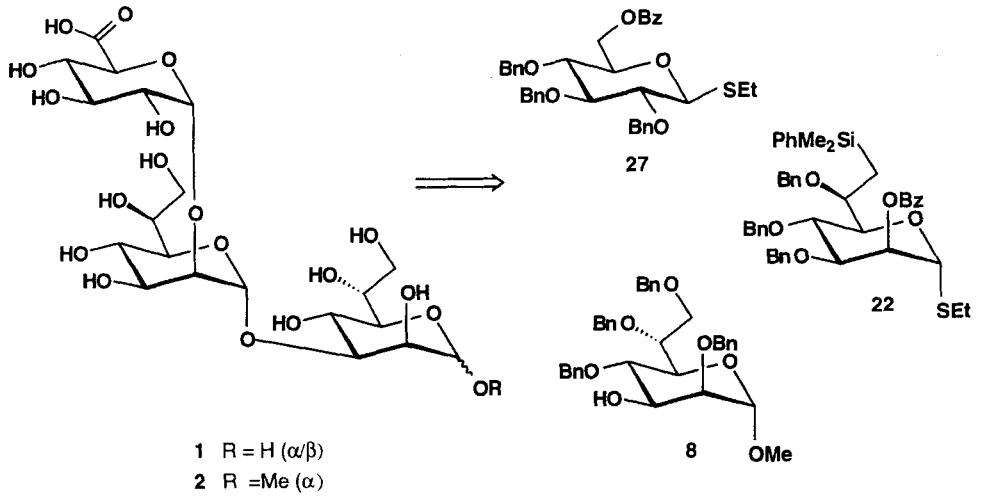
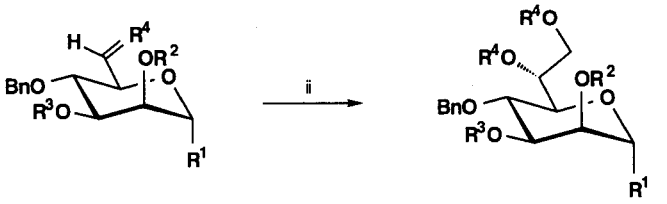


Figure 1

INTRODUCTION

Recently, Kondo *et al.*[1] showed that the uncommon seven-carbon sugar D-*glycero*-D-*manno*-heptopyranose (DD-Hep*p*) is a constituent of the trimeric sequence α-D-GlcA-(1→2)-L-α-D-Hep*p*-(1→3)-DD-Hep*p* (**1**, Fig. 1) from the inner-core lipopolysaccharide (LPS) region of *Vibrio parahaemolyticus* serotype O2, a halophilic marine vibrio responsible for food poisoning. Earlier studies from this laboratory revealed that the C-6 epimer of DD-Hep*p* (*i.e.*, L-*glycero*-D-*manno*-heptopyranose, LD-Hep*p*) can be prepared in a highly stereoselective manner by reaction of D-*manno*-hexodialdo-1,5-pyranosides with the Grignard reagent (phenyldimethylsilyl)methyl magnesium chloride, followed by oxidative removal of the $PhMe_2Si$ moiety in the addition product. The usefulness of the latter hydroxymethylation approach was demonstrated in the successful synthesis of immunologically interesting LD-Hep*p*-containing oligomeric fragments of the LPS from the Gram-negative bacterium *Neisseria meningitidis*.[2]

We here present an expeditious route to methyl 2,4,6,7-tetra-*O*-benzyl-D-*glycero*-α-D-*manno*-heptopyranoside (**8**) and its use in the synthesis of α-D-GlcA-(1→2)-L-α-D-Hep*p*-(1→3)-D-α-D-Hep*p*-OMe (**2**).



i → **3** R^1 = OMe, R^2 : R^3 = CMe_2, R^4 = O
i → **4** R^1 = OMe, R^2 : R^3 = CMe_2, R^4 = CH_2
i → **9** R^1 = SEt, R^2 = R^3 = Bn, R^4 = O
i → **10** R^1 = SEt, R^2 = R^3 = Bn, R^4 = CH_2

iii → **5** R^1 = OMe, R^2 : R^3 = CMe_2, R^4 = H
iv → **6** R^1 = OMe, R^2 : R^3 = CMe_2, R^4 = Bn
v → **7** R^1 = OMe, R^2 = R^3 = H, R^4 = Bn
8 R^1 = OMe, R^2 = R^4 = Bn, R^3 = H
11 R^1 = SEt, R^2 = R^3 = Bn, R^4 = H

Reagents and conditions: (i) CH_3PPh_3Br, *n*-BuLi, 30 min, **4**: 71%, **10**: 83% (2 steps); (ii) $K_2OsO_2(OH)_4/K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 1/1, 0 °C, 16 h, **5**: DD-Hep*p*: 79%, LD-Hep*p*: 11%, **11**: DD-Hep*p*: 64%, LD-Hep*p*: 9%; (iii) BnBr, NaH, DMF, 5 h, 91%; (iv) AcOH/H_2O, 9/1, v/v, 16 h; (v) BnBr, NaOH (4 N), TBAI, CH_2Cl_2, 16 h, 76% (2 steps).

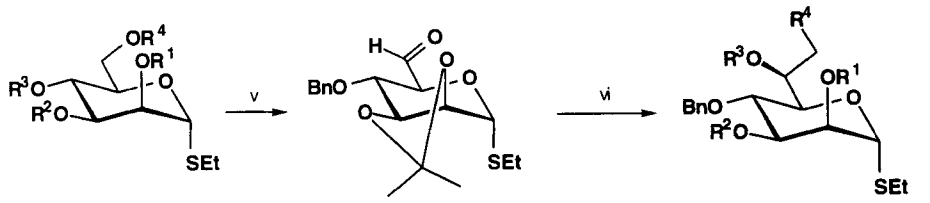
Scheme 1

RESULTS AND DISCUSSION

Retrosynthetic analysis (Fig. 1) reveals that methyl D-*glycero*-α-D-*manno*-heptopyranoside **8**, ethyl 1-thio-L-*glycero*-α-D-*manno*-heptopyranoside **22** and ethyl 1-thio-β-D-glucopyranoside **27** are suitable building blocks for the introduction of the interglycosidic linkages in trisaccharide **2**. Stereoselective introduction of the 1,2-*trans* linkage in **2** can be accomplished by condensation of DD-Hep*p* acceptor **8** with the disarmed LD-Hep*p* donor **22**. On the other hand, it may be expected[3] that glycosylation of the 2'-OH of the dimer, resulting from reaction of **8** with **22**, with the armed donor **27** will proceed with a high degree of stereoselectivity to give the 1,2-*cis* glycosidic linkage. Furthermore, saponification of the benzoyl protective group in glucosyl donor **27** allows the conversion of the C-6-OH into the corresponding carboxylic acid. Apart from this, it is evident that a straightforward and stereoselective route to DD-Hep*p* **8** is a crucial element in the construction of **2**. The routes thus far devised for the preparation of DD-Hep*p* are not completely satisfactory.[4] It occurred to us that *syn*-dihydroxylation of methyl 4-*O*-benzyl-6,7-dideoxy-2,3-*O*-isopropylidene-α-D-*manno*-hept-6-enopyranoside (**4**, Scheme 1) would proceed with a high degree of stereoselectivity[5] to give methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-D-*glycero*-α-D-*manno*-heptopyranoside (**5**), which in turn can be transformed into the requisite glycosyl acceptor **8**.

Syn-dihydroxylation of olefin **4**, prepared by Swern oxidation[6] of the corresponding alcohol[7] followed by Wittig-olefination of aldehyde **3** resulted in the isolation of the individual diastereoisomers of **5** in a yield of 79% and 11%, respectively. The configuration at C-6 of the minor isomer was assigned the L-*glycero*-D-*manno* configuration by executing the following sequence of reactions: acetonation of the 6,7-diol function in **5** and hydrogenolysis yielded a partially protected product, which was in all aspects identical with earlier prepared[8] methyl 2,3:6,7-di-*O*-isopropylidene-L-*glycero*-α-D-*manno*-heptopyranoside. Benzylation of the diol function in DD-Hep*p* **5** and subsequent deacetonation of **6** gave, after regioselective benzylation under phase-transfer conditions of diol **7**, acceptor **8**. In this respect, it is of interest to note that the presence of an anomeric ethyl 1-thio group is compatible with the OsO_4-mediated *syn*-dihydroxylation. For example, osmylation of ethyl 1-thio-α-D-mannopyranoside **10**, obtained by Wittig-olefination of the corresponding aldehyde **9**, furnished ethyl 1-thio-D-*glycero*-α-D-*manno*-heptopyranoside **11** and its C-6 epimer as a mixture of diastereoisomers (DD-Hep*p*:LD-Hep*p* 7:1[9]). Interestingly, Sharpless asymmetric dihydroxylation[10] of **4** with AD-mix α or β did not improve the diastereochemical outcome. Thus, osmylation of **4** in the presence of AD-mix α gave a less favourable DD-Hep*p*/LD-Hep*p* mixture (DD-Hep*p*:LD-Hep*p* = 2.1:1). Similarly, AD-mix β resulted in the isolation of a DD-Hep*p*:LD-Hep*p* mixture in a ratio of 4.5:1.[11]

The assembly of trisaccharide **2** commences with the glycosylation of acceptor **8** with ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-7-deoxy-7-(phenyldimethyl)silane-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside[12] (**22**, Scheme 2). Donor **22** could be readily prepared by hydroxymethylation of ethyl 4-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-D-*manno*-hexodialdo-1,5-pyranoside (**17**) with the Grignard reagent (phenyldimethylsilyl)methyl magnesium chloride. To this end, alcohol **16** was synthesized from known[13] ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside by deacetylation (→ **12**), followed by regioselective protection of the 6-OH with a trityl (Tr) group to give **13**. Introduction of the 2,3-acetonide function in **13** followed by benzylation of compound **14** and detritylation of **15**, furnished alcohol **16**. Hydroxymethylation[14] of aldehyde **17**, obtained after Swern oxidation of **16**, with (phenyldimethylsilyl)methyl magnesium chloride gave LD-Hep*p* derivative **18** in excellent diastereoselectivity (> 95%). Protective group manipulations on **18** comprising benzylation (→ **19**), deacetonation (→ **20**), regioselective benzylation (→ **21**), and benzoylation of the 2-OH in **21**, afforded ethyl 1-thio-L-*glycero*-α-D-*manno*-heptopyranosyl donor **22**. Condensation of donor **22** with acceptor **8** (Scheme 3) under the agency of *N*-iodosuccinimide (NIS) and catalytic trifluoromethanesulfonic acid (TfOH) afforded the α-linked heptosyl disaccharide **23** in 76%. Oxidative removal[15] of

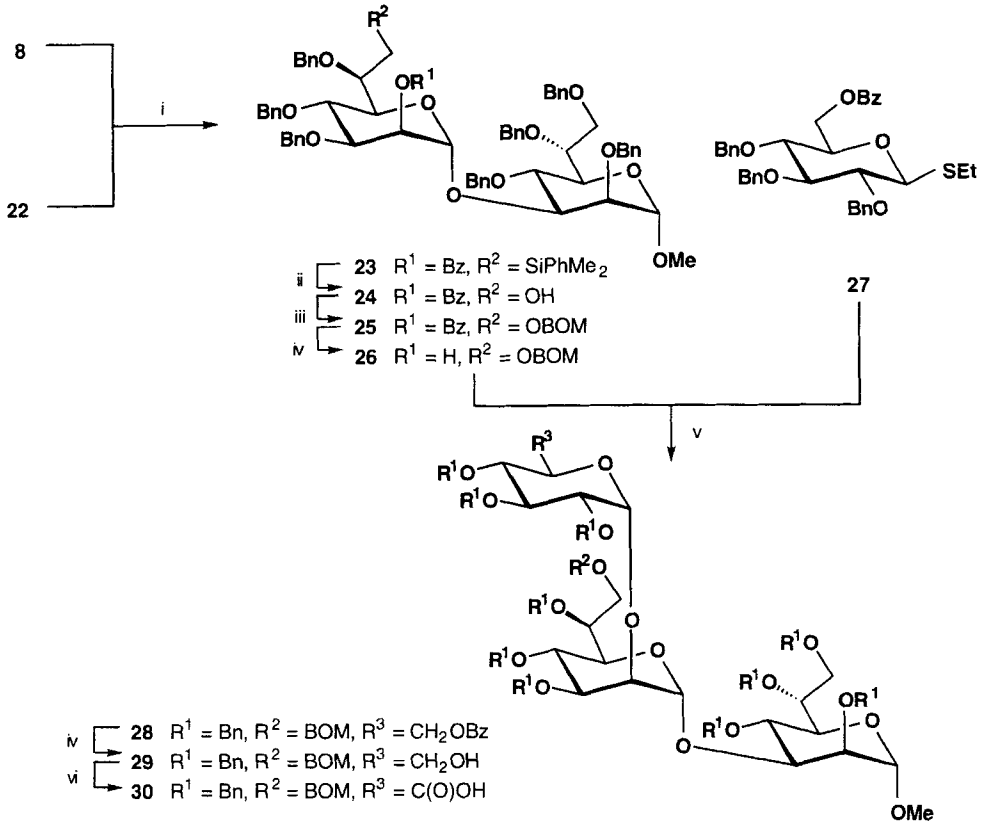


Reagents and conditions: (i) TrCl, pyr, 5 h, 82%; (ii) 2,2-DMP, CSA, 16 h, 70%; (iii) BnBr, NaH, DMF, 5 h, **15**: 76%, **19**: 82%; (iv) pyrrole/TFA, CH_2Cl_2, 10 min, 78%; (v) ClC(O)C(O)Cl, DMSO, CH_2Cl_2, -60 °C, then DIPEA, rt, 30 min; (vi) $PhMe_2SiCH_2MgCl$, Et_2O, 0 °C, 1 h, 94%; (vii) AcOH/H_2O, 9/1, v/v, 50 °C, 16 h; (viii) a. Bu_2SnO, MeOH, reflux, 1 h; b. BnBr, CsF, NaI, DMF, 16 h, 64% (2 steps); (ix) BzCl, pyr, 1 h, 89%.

Scheme 2

the phenyldimethylsilane in dimer **23** gave **24**. Subsequent protection of the primary hydroxyl in **24** with a benzyloxymethyl (BOM) group and debenzoylation of **25** afforded disaccharide **26**.

The last stage in the assembly of **2** entails 1,2-*cis* glucuronylation of the 2'-OH in dimer **26**. Recently, it was reported[16] that the introduction of 1,2-*cis* linkages, using ethyl 1-thio-β-D-(glucopyranosid)uronates as donors, proceeded with a moderate degree of stereoselectivity. For this reason, a similar two-step approach as described by Zegelaar-Jaarsveld *et al.*[17] was followed. Thus, iodonium dicollidine triflate (IDCT)-mediated condensation of acceptor **26** with ethyl 1-thio-β-D-glucopyranosyl donor **27**, prepared by benzoylation of known[18] ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside afforded α-linked trisaccharide **28** as the sole trimeric product in a yield of 73%. Zemplén-type debenzoylation of **28** yielded partially protected **29**. Swern oxidation of **29** and treatment of the resulting aldehyde under buffered conditions with sodium chlorite in the presence of 2-methyl-2-butene[19] gave α-D-glucuronic acid-containing trimer **30**. Finally, hydrogenolysis of the benzyl and benzyloxymethyl groups over Pd/C resulted in the isolation of target trisaccharide **2**, the ^1H, ^{13}C NMR and ESI-mass spectroscopic data of which were in good accordance with the assigned structure.



Reagents and conditions: (i) NIS/TfOH (*cat.*), 1,2-dichloroethane, 0 °C, 15 min, 76%; (ii) KBr, AcOOH, NaOAc, AcOH, 3 h, 85%; (iii) BOMCl, DIPEA, CH_3CN, 16 h, 84%; (iv) KO*t*-Bu, MeOH, 1 h, **26**: 67%, **29**: 67%; (v) IDCT, 1,2-dichloroethane/Et_2O, 1/5, v/v, 2 h, 73%; (vii) a. ClC(O)C(O)Cl, DMSO, -60 °C, then DIPEA, rt, 30 min; b. $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O, 1/1, v/v, 16 h.

Scheme 3

CONCLUSION

In summary, the results presented in this paper clearly demonstrate the versatility of OsO_4-mediated *syn*-dihydroxylation of 6,7-dideoxy-α-D-*manno*-hept-6-enopyranoses to afford DD-Hep*p* donors and acceptors with a high degree of stereoselectivity. Moreover, the successful assembly of DD-Hep*p*-containing trisaccharide **2** may be of great value for the design and synthesis of immunologically interesting DD-Hep*p*- and LD-Hep*p*-protein conjugates.

EXPERIMENTAL

General methods and materials

Diethyl ether, toluene, dichloromethane and pyridine were refluxed for 2 h in the presence of CaH_2 (5 g L^{-1}) and subsequently distilled and stored over molecular sieves 4Å. *N,N*-diisopropylethylamine and triethylamine were refluxed for 2 h in the presence of CaH_2 (5 g L^{-1}) and subsequently distilled. *N,N*-dimethylformamide, acetonitrile, 1,4-dioxane, 1,2-dichloroethane, dimethyl sulfoxide, and tetrahydrofuran were stored over molecular sieves 4Å and used as received. Acetic acid and *t*-butyl alcohol were used as received. Solvents used for column chromatography were of technical grade and distilled before use. Reactions were followed by TLC analysis conducted at Schleicher and Schüll DC Fertigfolien (F 1500 LS 254). The following eluents were used: diethyl ether/light petroleum, 3/1, v/v (System A), 1/1, v/v (System B), 1/3, v/v (System C), ethyl acetate/light petroleum, 1/9, v/v (System D), 1/1, v/v (System E), methanol/diethyl ether, 15/85, v/v (System F). Compounds were visualized by UV light and by spraying with 20% sulfuric acid in methanol followed by charring at 140°C. Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). Gel filtration was performed on Sephadex LH-20 (Pharmacia). Optical rotations were measured with a Propol polarimeter for solutions in chloroform (p.a. Baker) unless stated otherwise (20 °C). NMR spectra were recorded with a Jeol JNM-FX-200 (^1H and ^{13}C at 200 and 50.1 MHz, respectively) and a Bruker WM-300 spectrometer equipped with an Aspect 2000 computer (^1H and ^{13}C at 300 and 75 MHz, respectively). Chemical shifts are given in ppm (δ) relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT TSQ-70 equipped with a custom-made Electrospray Interface (ESI).

Methyl 4-*O* -benzyl-6,7-dideoxy-2,3-*O*-isopropylidene-α-D-*manno*-hept-6-enopyranoside (4). To a cooled (-60 °C) solution of oxalyl chloride (1.0 mL, 10.7 mmol) in dichloromethane (20 mL) under a nitrogen atmosphere was added dropwise a mixture of dimethyl sulfoxide (1.2 mL) in dichloromethane (10 mL). After stirring for 5 min at -60 °C known[7] methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (2.4 g, 7.3 mmol) in dichloromethane (10 mL) was added dropwise and the reaction mixture was stirred at -60 °C for 30 min. Subsequently, *N,N*-diisopropylethylamine (12.7 mL) was added and the solution was allowed to warm to room temperature. The mixture was diluted with dichloromethane (25 mL) and washed with water (2x 15 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Crude aldehyde **3** was used without further purification. Methyltriphenylphosphonium bromide (3.9 g, 10.9 mmol) in THF (25 mL) was treated at 0 °C under a nitrogen atmosphere with *n*-butyllithium (6.5 mL,

1.6 M in hexanes), allowed to warm to room temperature and stirred for an additional 30 min. To the resulting yellow suspension a solution of crude aldehyde **3** (7.3 mmol) in THF (20 mL) was added dropwise. TLC analysis (System D) after stirring for 30 min showed conversion of the starting aldehyde into a more lipophilic product. The reaction mixture was quenched with acetone (10 mL), diluted with diethyl ether (50 mL) and twice washed with water (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting yellow oil was applied on a silica gel column. Elution was effected with ethyl acetate/light petroleum (1/9, v/v). Concentration of the appropriate fractions furnished olefin **4** as a colorless oil (1.7 g, 5.2 mmol, 71%); Rf 0.48; ^1H NMR ($CDCl_3$): δ 7.34-7.24 (m 5H, CH arom), 5.96 (ddd, 1H, H-6, $J_{5,6}$ = 6.5 Hz, $J_{6,7trans}$ = 17.0 Hz, $J_{6,7cis}$ = 10.5 Hz), 5.48-5.23 (2x dd, 2H, H-7a, H-7b, $J_{7a,7b}$ = 1.6 Hz), 4.92 (s, 1H, H-1), 4.87-4.59 (AB, 2H, CH_2 Bn), 4.29 (t, 1H, H-3, $J_{2,3} = J_{3,4}$ = 6.2 Hz), 4.14 (d, 1H, H-2), 3.99 (dd, 1H, H-5, $J_{4,5}$ = 10.1 Hz), 3.37 (s, 3H, OCH_3), 3.29 (dd, 1H, H-4), 1.48, 1.37 (2x s, 6H, 2x CH_3 isoprop); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.9 (Cq Bn), 134.8 (C-6), 127.8-127.2 (CH arom), 116.7 (C-7), 108.8 (Cq isoprop), 97.7 (C-1), 79.1, 78.4, 75.4, 68.4 (C-2, C-3, C-4, C-5), 72.5 (CH_2 Bn), 54.4 (OCH_3), 27.6, 26.0 (2x CH_3 isoprop).

Anal. Calcd for $C_{18}H_{24}O_5$ (320.16): C, 67.48; H, 7.55. Found: C, 67.52; H, 7.59.

Methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-D-*glycero*-α-D-*manno*-heptopyranoside (5). To a stirred mixture of *t*-butyl alcohol (25 mL) and water (25 mL) was added $K_2OsO_2(OH)_4$ (45 mg, 0.12 mmol), $K_3Fe(CN)_6$ (4.8 g, 14.5 mmol), and K_2CO_3 (2.2 g, 16.0 mmol). The resulting suspension was cooled (0 °C), a solution of olefin **4** (1.7 g, 5.2 mmol) in toluene (10 mL) was added and the mixture was stirred for 16 h at 0 °C after which TLC analysis (acetone/dichloromethane, 3/97, v/v) showed complete conversion of starting material into two products. To the reaction mixture Na_2SO_3 (8.0 g) was added and the solution was stirred at room temperature for 1 h. The product was extracted with ethyl acetate (3x 50 mL) and washed with aq KOH (1 M, 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Separation of the two diastereoisomers was accomplished by silica gel column chromatography (eluent: methanol/dichloromethane, 0/1 to 2/98, v/v). Subsequent concentration of the appropriate fractions gave DD-Hep*p* derivative **5** (1.4 g, 4.1 mmol, 79%); Rf 0.69; $[\alpha]_D$ +8.2° (*c* 1.0); ^1H NMR ($CDCl_3$): δ 7.34-7.26 (m, 5H, CH arom), 5.00-4.60 (AB, 2H, CH_2 Bn), 4.89 (s, 1H, H-1), 4.33 (t, 1H, H-3, $J_{2,3} = J_{3,4}$ = 5.8 Hz), 4.14 (d, 1H, H-2), 3.84-3.61 (m, 5H, H-4, H-5, H-6, H-7a, H-7b), 3.40 (s, 3H, OCH_3), 1.52, 1.37 (2x s, 6H, 2x CH_3 isoprop); $^{13}C\{^1H\}$ NMR: δ 137.0 (Cq Bn), 128.3-127.7 (CH arom), 109.0 (Cq isoprop), 97.8 (C-1), 78.3, 77.9, 75.5, 75.3, 72.8 (C-2, C-3, C-4, C-5, C-6), 72.2 (CH_2 Bn), 62.3 (C-7), 54.8 (OCH_3), 27.6, 25.9 (2x CH_3 isoprop).

Anal. Calcd for $C_{18}H_{26}O_7$ (351.17): C, 61.00; H, 7.39. Found: C, 61.05; H, 7.35.

Methyl 4,6,7-tri-*O*-benzyl-2,3-*O*-isopropylidene-D-*glycero*-α-D-*manno*-hepto-pyranoside (6). To a cooled (0 °C) solution of diol **5** (1.4 g, 4.1 mmol) in DMF (25 mL) was added sodium hydride (0.42 g, 10.6 mmol, 60% in oil) and the mixture was stirred for 30 min. Subsequently, benzyl bromide (1.2 mL, 9.8 mmol) and a catalytic amount of tetrabutylammonium iodide were added and the mixture was stirred for 5 h after which TLC analysis (System D) indicated complete conversion of starting material into a more lipophilic product. Excess sodium hydride was destroyed with methanol (15 mL) and the mixture was concentrated. The residual oil was taken up in diethyl ether (50 mL) and washed with aq $NaHCO_3$ (10%, 25 mL) and water (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification of the crude product by silica gel column chromatography (eluent: ethyl acetate/light petroleum, 0/1 to 1/3, v/v) furnished fully protected heptose **6** (2.0 g, 3.7 mmol, 91%); Rf 0.31; ^{1}H NMR ($CDCl_3$): δ 7.39-7.24 (m, 15H, CH arom), 4.89-4.46 (m, 6H, 3x CH_2 Bn, s, 1H, H-1), 4.31 (t, 1H, H-3, $J_{2,3}$ = $J_{3,4}$ = 6.1 Hz), 4.14-3.56 (m, 6H, H-2, H-4, H-5, H-6, H-7a, H-7b), 3.37 (s, 3H, OCH_3), 1.36, 1.26 (2x s, 6H, 2x CH_3 isoprop); ^{13}C{^{1}H} NMR: δ 139.1, 138.8, 138.6 (3x Cq Bn), 128.5-127.8 (CH arom), 109.5 (Cq isoprop), 98.3 (C-1), 79.5, 78.2, 76.0, 75.9, 69.1 (C-2, C-3, C-4, C-5, C-6), 73.4, 72.9, 72.7 (3x CH_2 Bn), 70.8 (C-7), 54.9 (OCH_3), 28.2, 26.7 (2x CH_3 isoprop).

Anal. Calcd for $C_{32}H_{38}O_7$ (534.26): C, 71.89; H, 7.16. Found: C, 71.84; H, 7.14.

Methyl 2,4,6,7-tetra-*O*-benzyl-D-*glycero*-α-D-*manno*-heptopyranoside (8). Fully protected D-*glycero*-α-D-*manno*-heptopyranoside **6** (2.0 g, 3.7 mmol) was dissolved in acetic acid/water (9/1, v/v, 50 mL) and the mixture was stirred at 50 °C for 16 h after which TLC analysis (System E) showed conversion of starting material into a lower-running product (Rf 0.15). The solution was concentrated and the residue was repeatedly diluted with toluene (25 mL) and concentrated again. Crude diol **7** was dissolved in dichloromethane (40 mL) and aq NaOH (4 N, 9 mL) was added together with benzyl bromide (0.59 mL, 5.0 mmol), and a catalytic amount of tetrabutylammonium iodide. The mixture was stirred vigorously for 16 h after which TLC analysis (System E) showed almost complete disappearance of starting diol. The solution was diluted with dichloromethane, washed with water (25 mL) and the layers were separated. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The oily residue was purified by silica gel column chromatography (eluent: ethyl acetate/light petroleum, 1/9 to 1/3, v/v) to afford **8** as an oil (1.6 g, 2.8 mmol, 76%); $[\alpha]_D$ +56.5° (*c* 1.0); Rf 0.80; ESI-MS: $[M+H]^+$ 585; ^{1}H NMR ($CDCl_3$, 300 MHz, HH-COSY): δ 7.38–7.23 (m, 20H, CH arom), 4.85-4.47 (m, 8H, 4x CH_2 Bn), 4.78 (d, 1H, H-1, $J_{1,2}$ = 1.6 Hz), 4.03 (ddd, 1H, H-6, $J_{5,6}$ = 1.2 Hz, $J_{6,7a}$ = 4.7 Hz, $J_{6,7b}$ = 6.3 Hz), 3.86 (dd, 1H, H-5, $J_{4,5}$ =

9.9 Hz), 3.79 (dd, 1H, H-3, $J_{2,3}$ = 4.6 Hz, $J_{3,4}$ = 10.5 Hz), 3.78-3.71 (m, 3H, H-4, H-7a, H-7b), 3.45 (dd, 1H, H-2), 3.33 (s, 3H, OCH_3), 2.36 (bs, 1H, OH); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.9, 138.8, 138.4, 138.2 (4x Cq Bn), 128.4-127.5 (CH arom), 98.0 (C-1), 78.6, 78.4, 76.4, 72.2, 71.7 (C-2, C-3, C-4, C-5, C-6), 74.3, 73.0, 72.6, 72.4 (4x CH_2 Bn), 70.8 (C-7), 54.5 (OCH_3).

Anal. Calcd for $C_{36}H_{40}O_7$ (584.28): C, 73.95; H, 6.90. Found: C, 73.98; H, 6.91.

Ethyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-1-thio-α-D-*manno*-hept-6-enopyranoside (10). Olefin **10** was prepared from ethyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (0.46 g, 1.3 mmol) as described for compound **4**. Purification of the crude product by silica gel column chromatography (eluent: ethyl acetate/light petroleum, 5/95, v/v) furnished pure **10** (0.52 g, 1.1 mmol, 83%); ^1H NMR ($CDCl_3$): δ 7.40-7.24 (m, 15H, CH arom), 6.03 (ddd, 1H, H-6, $J_{5,6}$ = 6.4 Hz, $J_{6,7trans}$ = 17.1 Hz, $J_{6,7cis}$ = 10.5 Hz), 5.51-5.28 (2x dd, 2H, H-7a, H-7b), 4.87-4.59 (AB, 6H, 3x CH_2 Bn, s, 1H, H-1), 4.42 (m, 1H, H-5), 3.83-3.78 (m, 3H, H-2, H-3, H-4), 2.55 (m, 2H, CH_2 SEt), 1.22 (t, 3H, CH_3 SEt); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.5, 138.4, 138.3 (3x Cq Bn), 135.4 (C-6), 128.4-127.7 (CH arom), 118.1 (C-7), 82.0 (C-1), 80.0, 79.0, 76.6, 73.1 (C-2, C-3, C-4, C-5), 75.2, 72.3, 72.2 (3x CH_2 Bn), 25.4 (CH_2 SEt), 15.2 (CH_3 SEt).

Anal. Calcd for $C_{30}H_{34}O_4S$ (490.22): C, 73.44; H, 6.98; S, 6.53. Found: C, 73.48; H, 7.01; S, 6.54.

Ethyl 2,3,4-tri-*O*-benzyl-1-thio-D-*glycero*-α-D-*manno*-heptopyranoside (11). DD-Hep*p* derivative **11** was synthesized from olefin **10** (0.15 g, 0.30 mmol) as described for DD-Hep*p* **5**. Purification was accomplished by silica gel column chromatography. Elution with dichloromethane and subsequent concentration of the appropriate fractions afforded pure **11** as a mixture of diastereoisomers (73%, DD-Hep*p*:LD-Hep*p* 7:1); ^{13}C NMR ($CDCl_3$): δ 137.7, 137.6 (3x Cq Bn), 128.4-126.5 (CH arom), 81.7 (C-1), 80.4, 76.7, 76.1, 72.5, 71.6 (C-2, C-3, C-4, C-5, C-6), 74.9, 72.3, 71.8 (3x CH_2 Bn), 63.0 (C-7), 25.0 (CH_2 SEt), 14.6 (CH_3 SEt).

Anal. Calcd for $C_{30}H_{36}O_6S$ (524.67): C, 68.68; H, 6.92. Found: C, 68.64; H, 6.94.

Ethyl 4-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-D-mannopyranoside (16). Known[13] ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (15.0 g, 38.2 mmol) was dissolved in methanol (200 mL) and potassium *tert*-butoxide (1.5 g, 13.7 mmol) was added. The mixture was stirred for 1 h, after which complete disappearance of starting material into a more polar product was indicated by TLC analysis (System F). The reaction mixture was neutralized with Dowex 50Wx4 (H^+-form), filtered and concentrated. To a suspension of crude **12** (9.4 g, 24 mmol) in pyridine (100 mL) was added triphenylmethyl chloride (8.7 g, 31 mmol). The mixture was stirred for 5 h after which TLC analysis (System F) showed the reaction to be complete. The reaction

mixture was quenched with methanol (10 mL) and concentrated. The residual oil was dissolved in ethyl acetate (200 mL), washed with aq $NaHCO_3$ (10%, 100 mL) and water (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (eluent: diethyl ether/light petroleum, 3/1 to 1/0, v/v) furnished ethyl 1-thio-6-*O*-trityl-α-D-mannopyranoside (**13**) as a yellow oil (9.2 g, 19.7 mmol, 82%); Rf 0.66; $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.3 (Cq arom), 128.3-126.7 (CH arom), 85.5 (Cq Tr), 83.2 (C-1), 72.0, 71.7, 71.3, 67.9 (C-2, C-3, C-4, C-5), 63.5 (C-6), 23.4 (CH_2 SEt), 13.8 (CH_3 SEt). A mixture of 2,2-dimethoxypropane (15 mL), camphorsulphonic acid (pH 5) and ethyl 1-thio-α-D-mannopyranoside **13** (9.2 g, 19.7 mmol) in acetone (40 mL) was stirred for 16 h, until TLC analysis (System A) indicated complete reaction. The mixture was neutralized with triethylamine and the solvents were evaporated. The residue was applied onto a column of silica gel. Elution with diethyl ether/light petroleum (1/3 to 1/1, v/v) and concentration of the appropriate fractions furnished ethyl 2,3-*O*-isopropylidene-1-thio-6-*O*-trityl-α-D-mannopyranoside (**14**, 6.8 g, 13.8 mmol, 70%); Rf 0.77; ^1H NMR ($CDCl_3$): δ 7.48-7.22 (m, 15H, CH arom), 5.58 (s, 1H, H-1), 5.15 (d, 1H, H-2, $J_{2,3}$ = 5.6 Hz), 4.04 (t, 1H, H-3, $J_{3,4}$ = 6.5 Hz), 3.72 (dd, 1H, H-4, $J_{4,5}$ = 10.6 Hz), 3.68 (m, 1H, H-5), 3.41 (dd, 1H, H-6a, $J_{5,6}$ = 4.1 Hz, $J_{6a,6b}$ = 11.0 Hz), 3.34 (dd, 1H, H-6b, $J_{5,6b}$ = 5.5 Hz), 3.64 (m, 2H, CH_2 SEt), 1.51, 1.34 (2x s, 6H, 2x CH_3 isoprop), 1.27 (t, 3H, CH_3 SEt); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.7 (Cq arom), 128.5-127.0 (CH arom), 109.4 (Cq isoprop), 86.8 (Cq Tr), 79.0 (C-1), 77.6, 76.2, 71.0, 69.0 (C-2, C-3, C-4, C-5), 63.7 (C-6), 28.0, 26.2 (2x CH_3 isoprop), 23.9 (CH_2 SEt), 14.3 (CH_3 SEt). Mannose derivative **14** (6.8 g, 13.8 mmol) was benzylated as described for DD-Hep*p* derivative **5** (→ **6**). Purification of the crude product by silica gel column chromatography (eluent: diethyl ether/light petroleum, 0/1 to 1/3, v/v) furnished ethyl 4-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-6-*O*-trityl-α-D-mannopyranoside (**15**, 6.8 g, 10.1 mmol, 76%); Rf 0.79 (System C); ^1H NMR ($CDCl_3$): δ 7.50-7.01 (m, 20H, CH arom), 5.68 (s, 1H, H-1), 4.94-4.51 (AB, 2H, CH_2 Bn), 4.27-3.65 (m, 2H, H-2, H-3), 3.64 (dd, 1H, H-6a, $J_{5,6a}$ = 7.3 Hz, $J_{6a,6b}$ = 10.5 Hz), 3.53-3.42 (m, 2H, H-5, H-6b), 3.64 (dd, 1H, H-4, $J_{3,4}$ = 5.5 Hz, $J_{4,5}$ = 10.1 Hz), 2.65 (m, 2H, CH_2 SEt), 1.54, 1.38 (2x s, 6H, 2x CH_3 isoprop), 1.24 (t, 3H, CH_3 SEt); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.9 (Cq arom, Tr), 137.9 (Cq Bn), 128.7-126.8 (CH arom), 109.1 (Cq isoprop), 86.3 (Cq Tr), 78.8, 78.5, 76.5, 76.3, 69.0 (C-1, C-2, C-3, C-4, C-5), 72.8 (CH_2 Bn), 63.0 (C-6), 27.9, 26.4 (2x CH_3 isoprop), 23.8 (CH_2 SEt), 14.1 (CH_3 SEt). To a cooled (0 °C) solution of **15** (6.8 g, 10.1 mmol) in dichloromethane (25 mL) were subsequently added pyrrole (4.1 mL, 58.7 mmol) and trifluoroacetic acid (1.5 mL, 19.6 mmol). After stirring for 10 min, the reaction mixture was poured in aq $NaHCO_3$ (10%, 15 mL). The layers were

separated and the organic layer was washed with water (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was applied onto a silica gel column. Elution with diethyl ether/light petroleum (1/3 to 1/1, v/v) and concentration of the appropriate fractions yielded pure **16** (2.7 g, 7.9 mmol, 78%); Rf 0.44 (System B); $[\alpha]_D$ +2.4° (*c* 1.0); ^1H NMR ($CDCl_3$): δ 7.34-7.26 (m, 5H, CH arom), 5.57 (s, 1H, H-1), 4.96-4.55 (AB, 2H, CH_2 Bn), 4.31 (t, 1H, H-3, $J_{2,3} = J_{3,4} = 5.8$ Hz), 4.18 (d, 1H, H-2), 4.03 (ddd, 1H, H-5, $J_{4,5} = 10.0$ Hz, $J_{5,6a} = 8.1$ Hz, $J_{5,6b} = 3.6$ Hz), 3.85-3.74 (m, 2H, H-6a, H-6b), 3.63 (dd, 1H, H-4), 2.61 (m, 2H, CH_2 SEt), 1.89 (t, 1H, OH), 1.51, 1.37 (2x s, 6H, 2x CH_3 isoprop), 1.29 (t, 3H, CH_3 SEt); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.8 (Cq Bn), 128.9-127.3 (CH arom), 108.9 (Cq isoprop), 79.2, 78.1, 76.3, 75.7, 69.0 (C-1, C-2, C-3, C-4, C-5), 72.8 (CH_2 Bn), 61.6 (C-6), 27.7, 26.1 (2x s, CH_3 isoprop), 23.8 (CH_2 SEt), 14.1 (CH_3 SEt).

Anal. Calcd for $C_{18}H_{26}O_5S$ (354.15): C, 60.99; H, 7.39; S, 9.04. Found: C, 61.02; H, 7.42; S, 9.05.

Ethyl 4-*O*-benzyl-2,3-*O*-isopropylidene-7-deoxy-7-(phenyldimethyl)silane-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (18). Aldehyde **17** was prepared from alcohol **16** (1.8 g, 5 mmol) as described earlier for the conversion of methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannopyranoside into aldehyde **3**. Crude aldehyde **17** was used without further purification. To a solution of dry magnesium turnings (0.49 g, 20.0 mmol) in diethyl ether (5 mL) was added a small amount of (phenyldimethylsilyl)methyl chloride (3.8 mL, 20.0 mmol) in diethyl ether (15 mL). The mixture was heated until reflux and the reaction was initiated by the addition of a small quantity of 1,2-dibromoethane (0.1 mL). The remaining chloride was added at such a rate that a gentle reflux was maintained. The Grignard reagent thus obtained was added dropwise to a cooled (0°C) solution of aldehyde **17** in diethyl ether (25 mL). After stirring for 1 h, TLC analysis (System B) indicated complete conversion of **17**. The reaction mixture was diluted with diethyl ether (25 mL) and poured into aq NH_4Cl (20%, 25 mL). After separation of the layers, the organic phase was washed with water (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the crude heptose by silica gel column chromatography (eluent: diethyl ether/light petroleum, 0/1 to 1/3, v/v) furnished L-*glycero*-α-D-*manno*-heptopyranosyl derivative **18** as an oil (2.4 g, 4.7 mmol, 94%); Rf 0.78; ESI-MS: $[M+Na]^+$ 525; $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.9 (2x Cq Bn, Ph), 133.6-127.5 (CH arom), 109.0 (Cq isoprop), 79.5 (C-1), 78.5, 76.3, 72.7 (C-2, C-3, C-4, C-5), 73.0 (CH_2 Bn), 67.0 (C-6), 27.8, 26.3 (2x CH_3 isoprop), 24.0 (CH_2 SEt), 21.4 (C-7), 14.3 (CH_3 SEt), -2.3, -2.5 (2x CH_3Si).

Anal. Calcd for $C_{27}H_{38}O_5SSi$ (502.22): C, 64.51; H, 7.62; S, 6.38; Si, 5.59. Found: C, 64.47; H, 7.64; S, 6.41; Si, 5.54.

Ethyl 4,6-di-*O*-benzyl-2,3-*O*-isopropylidene-7-deoxy-7-(phenyldimethyl)silane-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (19). L-*Glycero*-α-D-*manno*-heptopyranoside **18** (1.7 g, 3.4 mmol) was benzylated as described for DD-Hep*p* derivative **5** (→ **6**). Purification of the crude benzylated L D-Hep*p* was accomplished by silica gel chromatography (eluent: ethyl acetate/light petroleum, 1/9 to 1/3, v/v). Yield: 1.7 g, 2.8 mmol, 82%; Rf 0.39 (System D); ^{1}H NMR ($CDCl_3$): δ 7.53-7.06 (m, 15H, CH arom), 5.59 (d, 1H, H-1, $J_{1,2}$ = 1.3 Hz), 4.79-4.43 (AB, 2H, CH_2 Bn), 4.25-3.99 (m, 4H, H-2, H-5, CH_2 Bn), 3.95 (t, 1H, H-3, $J_{2,3} = J_{3,4}$ = 5.9 Hz), 3.78-3.64 (m, 2H, H-4, H-6), 2.63 (m, 2H, CH_2 SEt), 1.52, 1.35 (2x s, 6H, 2x CH_3 isoprop), 1.29-1.21 (m, 5H, CH_3 SEt, H-7a, H-7b), 0.33, 0.32 (2x s, 6H, 2x CH_3Si); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.3, 138.0 (3x Cq Bn, Ph), 133.3-127.0 (CH arom), 109.0 (Cq isoprop), 80.0, 78.7, 76.2, 75.8, 72.9, 72.1 (C-1, C-2, C-3, C-4, C-5, C-6), 71.7, 70.4 (2x CH_2 Bn), 27.6, 26.1 (2x CH_3 isoprop), 24.4 (CH_2 SEt), 17.4 (C-7), 14.3 (CH_3 SEt), -2.3, -2.8 (2x CH_3Si).

Anal. Calcd for $C_{33}H_{41}O_5SSi$ (577.24): C, 68.60; H, 7.15; S, 5.55; Si, 4.86. Found: C, 68.57; H, 7.16; S, 5.53; Si, 4.70.

Ethyl 3,4,6-tri-*O*-benzyl-7-deoxy-7-(phenyldimethyl)silane-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (21). Removal of the 2,3-*O*-isopropylidene moiety in **19** (1.7 g, 2.8 mmol) was achieved as described for DD-Hep*p* derivative **6**. Crude diol **20** (Rf 0.34, System E) was dissolved in methanol (15 mL) and dibutyl tin oxide (0.81 g, 3.1 mmol) was added. The mixture was stirred under reflux until the solution became clear, concentrated and the residue was dissolved in DMF (15 mL). Subsequently, benzyl bromide (0.3 mL, 3.4 mmol), sodium iodide (0.16 g, 1.1 mmol) and cesium fluoride (0.86 g, 5.4 mmol) were added and the mixture was vigorously stirred for 16 h. TLC analysis (System E) indicated almost complete conversion of starting material into a more lipophilic product. The reaction mixture was quenched with methanol (5 mL), diluted with ethyl acetate (25 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was applied onto a column of silica gel. Elution with ethyl acetate/light petroleum (1/9 to 1/3, v/v) and concentration of the appropriate fractions yielded **21** as an oil (1.1 g, 1.8 mmol, 64%); Rf 0.65; ^{1}H NMR ($CDCl_3$): δ 7.52-7.06 (m, 20H, CH arom), 5.40 (d, 1H, H-1, $J_{1,2}$ = 1.7 Hz), 4.71-4.51 (m, 4H, CH_2 Bn), 4.15-3.76 (m, 7H, H-2, H-3, H-4, H-5, H-6, CH_2 Bn), 2.60 (m, 2H, CH_2 SEt), 1.41-1.36 (m, 2H, H-7a, H-7b), 1.28 (t, 3H, CH_3 SEt), 0.35, 0.33 (2x s, 3H, CH_3Si); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.3-137.4 (4x Cq Bn, Ph), 133.1-126.7 (CH arom), 83.9 (C-1), 80.5, 73.9, 73.5, 72.0, 69.0 (C-2, C-3, C-4, C-5, C-6), 73.7, 70.8, 69.2 (3x CH_2 Bn), 24.8 (CH_2 SEt), 16.4 (C-7), 14.3 (CH_3 SEt), -2.4, -3.1 (2x CH_3Si).

Anal. Calcd for $C_{38}H_{46}O_5SSi$ (642.28): C, 70.99; H, 7.21; S, 4.99; Si, 4.37. Found: C, 70.96; H, 7.23; S, 5.03; Si, 4.38.

Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-7-deoxy-7-(phenyldimethyl)silane-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (22). To a solution of **21** (1.1 g, 1.8 mmol) in pyridine (10 mL) was added benzoyl chloride (0.27 mL, 2.3 mmol) and the mixture was stirred for 1 h. TLC analysis (System D) indicated the reaction to be complete and methanol (5 mL) was added. After removal of the solvents, the residue was dissolved in ethyl acetate (25 mL) and washed with aq $NaHCO_3$ (10%, 10 mL) and water (10 mL). The organic phase was dried ($MgSO_4$), concentrated and applied onto a silica gel column. Elution with ethyl acetate/light petroleum (1/9 to 1/3, v/v) and concentration of the appropriate fractions afforded **22** as a colorless oil (1.2 g, 1.6 mmol, 89%); Rf 0.24; $[\alpha]_D$ +34.4° (*c* 0.9); ESI-MS: $[M+NH_4]^+$ 764; ^1H NMR ($CDCl_3$, 300 MHz, HH-COSY): δ 8.14-7.08 (m, 25H, CH arom), 5.72 (dd, 1H, H-2, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 2.9 Hz), 5.48 (d, 1H, H-1), 4.76 (t, 2H, CH_2 Bn), 4.66-4.48 (AB, 2H, CH_2 Bn), 4.21-4.10 (AB, 2H, CH_2 Bn), 4.12 (t, 1H, H-4, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz), 4.10 (m, 1H, H-5), 3.94 (dd, 1H, H-3), 3.89 (m, 1H, H-6), 2.63 (m, 2H, CH_2 SEt), 1.44 (m, 2H, H-7a, H-7b), 1.29 (t, 3H, CH_3 SEt), 0.38, 0.35 (2x s, 6H, 2x CH_3Si); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 165.7 (C(O) Bz), 138.9, 138.6, 138.2, 137.9 (4x Cq Bn, Ph), 133.8-127.6 (CH arom), 130.1 (Cq Bz), 83.0 (C-1), 79.5, 75.0, 73.2, 70.9 (C-2, C-3, C-4, C-5, C-6), 71.7, 70.3 (3x CH_2 Bn), 26.0 (CH_2 SEt), 17.1 (C-7), 15.0 (CH_3 SEt), -1.6, -2.3 (2x CH_3Si).

Anal. Calcd for $C_{45}H_{50}O_6SSi$ (746.31): C, 72.35; H, 6.75; S, 4.29; Si, 3.76. Found: C, 72.35; H, 6.78; S, 4.26; Si, 3.78.

Methyl 3-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-7-deoxy-7-(phenyldimethyl)silane-L-*glycero*-α-D-*manno*-heptopyranosyl)-2,4,6,7-tetra-*O*-benzyl-D-*glycero*-α-D-*manno*-heptopyranoside (23). A solution of LD-Hep*p* donor **22** (0.19 g, 0.25 mmol) and DD-Hep*p* acceptor **8** (0.12 g, 0.21 mmol) in 1,2-dichloroethane (2 mL) was stirred for 30 min under a blanket of nitrogen in the presence of activated molecular sieves (4Å). The mixture was cooled (0 °C) and a solution of NIS (57 mg, 0.25 mmol) in THF (2 mL) and TfOH (4 mg, 25 μmol) were subsequently added. After stirring for 15 min, the reaction mixture was quenched with triethylamine (0.5 mL), filtered and diluted with dichloromethane (10 mL). The solution was washed with aq $Na_2S_2O_3$ (20%, 5 mL), and aq $NaHCO_3$ (10%, 5 mL), dried ($MgSO_4$), filtered and concentrated. The residual oil was extensively purified by silica gel column chromatography (eluent: ethyl acetate/light petroleum, 1/9, v/v) and gel filtration (LH-20: eluent: methanol/dichloromethane, 1/2, v/v) to furnish pure α-linked heptosyl disaccharide **23** (0.20 g, 0.16 mmol, 76%); Rf 0.45 (System D); $[\alpha]_D$ +21.3° (*c* 1.0); ESI-MS: $[M+NH_4]^+$ 1288; ^1H NMR ($CDCl_3$, 300 MHz, HH-COSY): δ 7.95-7.04 (m, 45H, CH arom), 5.78 (t, 1H, H-2' $J_{1,2}$ = $J_{2,3}$ = 2.1 Hz), 4.45 (d, 1H, H-1'), 4.86-4.45 (m, 12H, 6x CH_2 Bn), 4.69 (d, 1H, H-1, $J_{1,2}$ = 1.9 Hz), 4.35-4.17

(AB, 2H, CH_2 Bn, dd, 1H, H-3, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 10.3 Hz), 4.14-4.04 (m, 4H, H-4, H-3', H-4', H-6'), 3.98 (ddd, 1H, H-6, $J_{5,6}$ = 4.2 Hz, $J_{6,7a}$ = 7.8 Hz), 4.82 (dd, 1H, H-5, $J_{4,5}$ = 10.3 Hz, m, 1H, H-7a), 3.73 (dd, 1H, H-7b, $J_{6,7b}$ = 6.7 Hz, $J_{7a,7b}$ = 10.4 Hz), 3.62 (dd, 1H, H-2), 3.56 (bd, 1H, H-5'), 3.48 (s, 3H, OCH_3), 1.53 (dd, 1H, H-7a', $J_{6,7a}$ = 7.2 Hz, $J_{7a,7b}$ = 15.4 Hz), 1.10 (dd, 1H, H-7b', $J_{6,7b}$ = 6.1 Hz), 0.27, 0.23 (2x s, 6H, 2x CH_3Si); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 165.2 (C(O) Bz), 138.7-138.3 (8x Cq Bn, Ph), 129.6 (Cq Bz), 133.6-127.0 (CH arom), 98.6, 98.5 (C-1, C-1', $J_{C\text{-}1',H\text{-}1'}$ = 175.8 Hz), 78.3, 77.9, 76.9, 75.7, 75.5, 74.7, 72.5, 68.4 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6'), 77.6, 77.1, 75.0, 73.6, 72.7, 70.6 (7x CH_2 Bn), 69.6 (C-7), 54.5 (OCH_3), 17.4 (C-7'), -2.5, -2.7 (2x CH_3Si).

Anal. Calcd for $C_{79}H_{84}O_{13}Si$ (1268.57): C, 74.74; H, 6.67; Si, 2.21. Found: C, 74.72; H, 6.69; Si, 2.25.

Methyl 3-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-2,4,6,7-tetra-*O*-benzyl-D-*glycero*-α-D-*manno*-heptopyranoside (24). A mixture of NaOAc (0.52 g, 6.3 mmol) and acetic acid was heated until all NaOAc was dissolved. The solution was added to phenylsilane containing disaccharide **23** (0.67 g, 0.53 mmol), KBr (75 μg, 0.64 mmol) was added and the mixture was cooled to 10 °C. Subsequently, peracetic acid (2.6 mL, 30% in acetic acid) was added dropwise under the exclusion of light, during which addition, gas was liberated. After stirring for 3 h at room temperature, TLC analysis (System E) showed complete conversion of compound **24** in a more polar product. The mixture was diluted with ethyl acetate (10 mL) and poured into a cooled (0 °C) solution of $Na_2S_2O_3$ (5 mL, 15%). After separation of the layers, the organic phase was washed with aq $NaHCO_3$ (10%, 10 mL) and water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was applied onto a silica gel column. Elution was effected with ethyl acetate/light petroleum (1/3 to 1/1, v/v). Concentration of the appropriate fractions afforded dimer **24** as a colorless oil (0.50 g, 0.44 mmol, 85%); Rf 0.37; ESI-MS: $[M+Na]^+$ 1174; ^1H NMR ($CDCl_3$): δ 8.02-7.06 (m, 40H, H arom), 5.31 (t, 1H, H-2', $J_{1,2} = J_{2,3}$ = 2.0 Hz), 5.39 (d, 1H, H-1'), 4.96-4.41 (m, 14H, 7x AB CH_2 Bn, s, 1H, H-1), 4.18-3.73 (m, 13H, H-2, H-3, H-4, H-5, H-6, H-7a, H-7b, H-3', H-4', H-5', H-6', H-7a', H-7b'), 3.34 (s, 3H, OCH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 165.3 (C(O) Bz), 138.7-137.5 (7x Cq Bn), 129.7 (Cq Bz), 133.0-127.5 (CH arom), 98.8 (C-1, C-1'), 78.6, 78.0, 77.3, 76.1, 75.7, 74.8, 73.9, 73.2, 71.0, 68.5 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6'), 77.1, 74.8, 74.6, 73.3, 72.8, 72.4, 71.5 (7x CH_2 Bn), 70.5 (C-7), 60.0 (C-7'), 54.8 (OCH_3).

Anal. Calcd for $C_{71}H_{74}O_{14}$ (1150.36): C, 74.07; H, 6.48. Found: C, 74.12; H, 6.46.

Methyl 3-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-7-*O*-benzyloxymethyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-2,4,6,7-tetra-*O*-benzyl-D-*glycero*-α-D-*manno*-heptopyra-

noside (25). To a solution of disaccharide **24** (0.69 g, 0.61 mmol) in acetonitrile (5 mL) was added *N,N*-diisopropylethylamine (0.4 mL, 2.3 mmol). Benzyloxymethyl chloride (0.16 mL, 0.76 mmol) was added dropwise and the mixture was stirred for 16 h, after which TLC analysis (System A) showed almost complete consumption of starting material. The reaction mixture was quenched with methanol (1 mL) and concentrated *in vacuo*. The residual oil was diluted with diethyl ether (15 mL), washed with aq KH_2PO_4 (1 M, 3x 10 mL) and aq $NaHCO_3$ (10%, 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification was accomplished by silica gel column chromatography (eluent: ethyl acetate/light petroleum, 1/9 to 1/1, v/v) and gel-filtration (eluent: methanol/dichloromethane, 1/2, v/v) to yield pure **25** as a colorless oil (0.63 g, 0.50 mmol, 84%); Rf 0.76; ESI-MS: $[M+Na]^+$ 1294; ^1H NMR ($CDCl_3$): δ 8.00-7.06 (m, 45H, CH arom), 5.79 (t, 1H, H-2', $J_{1,2} = J_{2,3} = 1.8$ Hz), 5.39 (bs, 1H, H-1'), 4.97-4.33 (m, 19H, 7x CH_2 Bn, CH_2 BOM, OCH_2O BOM, H-1), 4.13-3.68 (m, 13H, H-2, H-3, H-4, H-5, H-6, H-7a, H-7b, H-3', H-4', H-5', H-6', H-7a', H-7b'), 3.22 (s, 3H, OCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 165.4 (C(O) Bz), 139.0-137.8 (8x Cq Bn, BOM), 130.0 (Cq Bz), 133.2-127.7 (CH arom), 99.5, 99.0 (C-1, C-1'), 95.1 (OCH_2O BOM), 78.6, 78.3, 77.3, 76.9, 76.0, 75.2, 74.1, 71.9, 68.8 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6'), 77.5, 74.8, 73.4, 72.8, 72.5, 71.6, 70.8, 69.6 (7x CH_2 Bn, CH_2 BOM, C-7), 66.7 (C-7'), 54.6 (OCH_3).

Anal. Calcd for $C_{79}H_{82}O_{15}$ (1270.56): C, 74.63; H, 6.50. Found: C, 74.67; H, 6.46.

Methyl 3-*O*-(3,4,6-tri-*O*-benzyl-7-*O*-benzyloxymethyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-2,4,6,7-tetra-*O*-benzyl-D-*glycero*-α-D-*manno*-heptopyranoside (26). Fully protected disaccharide **25** (0.63 g, 0.50 mmol) was debenzoylated in the same way as described for the deacetylation of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (→ **12**). The crude product was purified by silica gel column chromatography (eluent: ethyl acetate/light petroleum, 1/9, v/v) to afford **26** as an oil (0.54 g, 0.47 mmol, 94%); Rf 0.22 (System A); ESI-MS: $[M+Na]^+$ 1190; ^1H NMR ($CDCl_3$, 300 MHz, HH-COSY): δ 7.35-7.14 (m, 40H, CH arom), 5.32 (d, 1H, H-1', $J_{1,2}$ = 1.8 Hz), 4.89-4.30 (m, 18H, 7x CH_2 Bn, CH_2 BOM, OCH_2O BOM), 4.66 (d, 1H, H-1, $J_{1,2}$ = 1.2 Hz), 4.13 (dd, 1H, H-3, $J_{2,3}$ = 2.8 Hz, $J_{3,4}$ = 9.4 Hz), 4.05 (t, 1H, H-4, $J_{4,5}$ = 8.7 Hz), 3.99-3.89 (m, 5H, H-5, H-7a, H-2', H-4', H-7a'), 3.87-3.79 (m, 3H, H-5, H-7b, H-6'), 3.76-3.73 (m, 3H, H-2, H-6, H-7b'), 3.64 (m, 1H, H-3'), 3.23 (s, 3H, OCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 139.3-138.0 (8x Cq Bn, BOM), 101.3 (C-1'), 99.1 (C-1), 95.1 (OCH_2O BOM), 80.6, 78.6, 77.5, 77.1, 76.2, 75.1, 73.9, 71.7, 68.5 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6'), 74.9, 74.6, 73.6, 73.5, 72.9, 72.7, 72.6, 71.9, 71.0, 69.9, 69.6 (7x CH_2 Bn, CH_2 BOM), 66.8, 66.0 (C-7, C-7'), 54.8 (OCH_3).

Anal. Calcd for $C_{72}H_{78}O_{14}$ (1166.54): C, 74.08; H, 6.73. Found: C, 74.05; H, 6.78.

Ethyl 6-*O*-benzoyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (27). Benzoylation of known[18] ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (8.5 g, 15.3 mmol) was accomplished as described for LD-Hep*p* derivative **21**. Purification by silica gel column chromatography (eluent: diethyl ether/light petroleum, 1/3, v/v) and concentration of the appropriate fractions yielded ethyl 1-thio-β-D-glucopyranoside **27** (8.3 g, 13.8 mmol, 90%); Rf 0.79 (System B); $[\alpha]_D$ -26.8° (*c* 1.0); ^{1}H NMR ($CDCl_3$): δ 8.05-7.25 (m, 20H, CH arom), 4.99-4.44 (m, 7H, 3x CH_2 Bn, H-6a), 4.86 (d, 1H, H-1, $J_{1,2}$ = 5.8 Hz), 4.41 (dd, 1H, H-6b, $J_{5,6b}$ = 3.6 Hz, $J_{6a,6b}$ = 10.9 Hz), 3.78-3.63 (m, 3H, H-2, H-4, H-5), 3.44 (dd, 1H, H-3, $J_{2,3}$ = 8.4 Hz, $J_{3,4}$ = 10.0 Hz), 2.67 (m, 2H, CH_2 SEt), 1.24 (t, 3H, CH_3 SEt); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 165.8 (C(O) Bz), 137.5, 137.4, 137.2 (3x Cq Bn), 132.7-127.5 (CH arom), 86.3 (C-1), 84.7, 81.4, 77.5, 76.7 (C-2, C-3, C-4, C-5), 75.6, 75.3, 74.8 (3x CH_2 Bn), 63.5 (C-6), 24.7 (CH_2 SEt), 14.8 (CH_3 SEt).

Anal. Calcd. for $C_{71}H_{74}O_{14}$ (1268.57): C, 74.07; H, 6.48. Found: C, 74.03; H, 6.52.

Methyl 3 -*O*-(2-*O*-{6-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl}-3,4,6-tri-*O*-benzyl-7-*O*-benzyloxymethyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-2,4,6,7-tetra-*O*-benzyl-D-*glycero*-α-D-*manno*-heptopyranoside (28). To a stirred mixture of ethyl 1-thio-β-D-glucoside donor **27** (72 mg, 0.12 mmol), heptose disaccharide acceptor **26** (0.12 g, 0.10 mmol), and activated molecular sieves (4Å) in 1,2-dichlorethane/diethyl ether (1/5, v/v, 2 mL) was added IDCT (0.11 g, 0.22 mmol). After stirring for 2 h under a blanket of nitrogen, TLC analysis showed almost complete consumption of both donor and acceptor. The reaction mixture was filtered, diluted with dichloromethane (10 mL), washed with aq $Na_2S_2O_3$ (20%, 5 mL), and aq $NaHCO_3$ (10%, 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by silica gel column chromatography (eluent: diethyl ether/light petroleum, 1/2 to 1/1, v/v) followed by gel filtration (eluent: methanol/dichloromethane, 2/1, v/v) afforded pure α-linked trisaccharide **28** (0.12 g, 73 μmol, 73%) as the only product; Rf 0.70 (System A); $[\alpha]_D$ +11.9° (*c* 0.5); ESI-MS: $[M+Na]^+$ 1728; $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 165.8 (C(O) Bz), 139.0-137.5 (11x Cq Bn, BOM), 130.0 (Cq Bz), 132.7-125.3 (CH arom), 100.3 (C-1'), 98.6 (C-1), 96.7 (C-1", $J_{C\text{-}1",H\text{-}1"}$ = 168.5 Hz), 94.6 (OCH_2O BOM), 81.2, 80.0, 78.3, 77.9, 77.3, 77.1, 75.4, 74.7, 74.2, 72.3, 69.1 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5"), 75.5, 74.8, 74.1, 73.0, 72.4, 72.1, 71.9, 71.7, 70.6 (11x CH_2 Bn, BOM), 69.2 (C-7), 66.4 (C-7'), 62.8 (C-6"), 54.4 (OCH_3).

Anal. Calcd for $C_{106}H_{110}O_{20}$ (1702.76): C, 74.72 H, 6.51. Found: C, 74.76; H, 6.52.

Methyl 3-*O*-(2-*O*-{2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl}-3,4,6-tri-*O*-benzyl-7-*O*-benzyloxymethyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-2,4,6,7-tetra-*O*-benzyl-D-

***glycero*-α-D-*manno*-heptopyranoside (29).** Trimer **28** (0.24 g, 0.14 mmol) was debenzoylated as described for the deacetylation of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (→ **12**). Purification of the crude product by silica gel column chromatography (eluent: diethyl ether/light petroleum, 1/1, v/v) gave trisaccharide **29** as an oil (0.15 g, 93 mmol, 67%); Rf 0.19 (System A); ESI-MS: $[M+Na]^+$ 1623; ^{13}C NMR ($CDCl_3$): δ 139.0-137.1 (11x Cq Bn, BOM), 128.2-126.5 (CH arom), 100.3 (C-1'), 98.7 (C-1), 96.9 (C-1"), 94.6 (OCH_2O BOM), 81.2, 80.0, 79.9, 78.2, 77.4, 75.4, 74.5, 74.4, 74.2, 72.2, 71.3 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5"), 75.3, 74.8, 74.1, 73.9, 73.1, 72.4, 72.2, 71.7, 71.6, 70.7 (11x CH_2 Bn, BOM), 69.3 (C-7), 66.2 (C-7'), 61.4 (C-6"), 54.5 (OCH_3).

Anal. Calcd for $C_{99}H_{106}O_{19}$ (1598.73): C, 74.32 H, 6.68. Found: C, 74.34; H, 6.64.

Methyl 3 -*O*-(2-*O*-{α-D-glucopyranosyluronic acid}-L-*glycero*-α-D-*manno*-heptopyranosyl)-D-*glycero*-α-D-*manno*-heptopyranoside (2). Swern oxidation of trisaccharide **29** (73 mg, 45 μmol) was performed as described for the oxidation of methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (→ **3**). To a suspension of the crude aldehyde in *t*-butyl alcohol (0.75 mL) was added water (0.75 mL), NaH_2PO_4 (38 mg), 2-methyl-2-butene (0.1 mL), and $NaClO_2$ (38 mg, 0.32 mmol). After stirring for 16 h, the mixture was diluted with ethyl acetate (5 mL). The organic phase was washed with water (3x 3 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residual oil was diluted with ethanol (5 mL) and dichloromethane (5 mL) and concentrated again to yield uronic acid-containing trisaccharide **30**. Crude uronic acid-containing trimer **30** was dissolved in *t*-butyl alcohol/H_2O (1/1, v/v) and acetic acid (2 drops) was added. Subsequently, palladium on charcoal (0.3 g, 10%) was added, the solution was degassed and hydrogen gas was bubbled through. After stirring for 4 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Extensive purification of crude deblocked target trimer **2** was accomplished by gel filtration using Fractogel HW-40 (S, Omnilabo, eluent: 0.15 M triethylammonium carbonate/10% methanol in H_2O). Ion-exchange (Dowex 50Wx4, Na^+-form) and lyophilization afforded pure target trisaccharide **2** (18 mg, 30 μmol) as a white fluffy solid; $[\alpha]_D$ +23.1° (H_2O, *c* 0.3); ESI-MS: $[M + Na]^+$ 615; ^1H NMR (D_2O, 300 MHz, HH-COSY): δ 5.39 (d, 1H, H-1', $J_{1,2}$ = 1.6 Hz), 5.13 (d, 1H, H-1", $J_{1,2}$ = 3.8 Hz), 4.71 (d, 1H, H-1, $J_{1,2}$ = 1.8 Hz), 4.12 (d, 1H, H-5", $J_{4,5}$ = 10.2 Hz), 4.09-3.97 (m, 6H, H-2, H-3, H-4, H-2', H-3', H-4'), 3.76 (t, 1H, H-3"), 3.85-3.62 (m, 8H, H-5, H-6, H-7a, H-7b, H-5', H-6', H-7a', H-7b'), 3.58 (dd, 1H, H-2", $J_{2,3}$ = 9.8 Hz), 3.47 (dd, 1H, H-4", $J_{3,4}$ = 9.1 Hz), 3.40 (s, 3H, OCH_3); $^{13}C\{^1H\}$ NMR (D_2O, 75 MHz, CH-COSY): δ 177.4 (C(O) GlcA), 101.5 (C-1), 101.4 (C-1'), 101.1 (C-1"), 73.7 (C-3"), 73.6 (C-5"), 72.8 (C-4"), 72.4 (C-2"), 80.1, 78.9, 73.5, 72.5, 72.3,

71.3, 70.2, 69.8, 67.5, 67.1 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-6'), 63.4, 62.4 (C-7, C-7'), 55.5 (OCH_3).

Anal. Calcd for $C_{21}H_{36}O_{19}$ (592.19): C, 42.57; H, 6.12. Found: C, 42.54; H, 6.15.

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