Published in final edited form as:

J Org Chem. 2008 September 19; 73(18): 7003–7010. doi:10.1021/jo801414c.

Block Synthesis of Tetra- and Hexasaccharides (β -D-glycero-D-manno-Hepp-(1 $\rightarrow$ 4)-[α -L-Rhap-(1 $\rightarrow$ 3)- β -D-glycero-D-manno-Hepp-(1 $\rightarrow$ 4)]_n- α -L-Rhap-OMe (n = 1 and 2) Corresponding to Multiple Repeat Units of the Glycan from the Surface-Layer Glycoprotein from *Bacillus thermoaerophilus*

David Crich* and Ming Li

Chemistry Department, Wayne State University, 5101 Cass Avenue, Detroit, MI 48202

Abstract

n = 1 and 2

A fully stereocontrolled block synthesis of the title tetra- and hexasaccharides has been achieved taking advantage of the ability of the 4,6-*O*-benzylidene acetal to control the stereochemistry of the β -D-glycero-D-mannoheptopyranoside unit, and of a 2,3-*O*-diphenylmethylene acetal to install the α -L-rhamnopyranosidic linkages. Comparison of the spectral data for the hexasaccharide with that of the natural confirms the structure of this very unusual and structurally challenging glycan.

Introduction

In 1995 Kosma and coworkers described the characterization of the surface-layer glycoprotein from *Bacillus thermoaerophilus*, and proposed the very unusual disaccharide motif $\rightarrow$ 4)-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 3)- β -D-glycero-D-mannoheptopyranosyl-(1 $\rightarrow$ as the repeating unit of the glycan chain, with the stereochemistry of the β -D-glycero-D-manno-heptopyranoside assigned on the basis of comparison of spectral data with synthetic methyl β -L-glycero-D-manno-heptopyranoside.¹ Having recently described the first stereocontrolled route to β -D-glycero-D-manno-heptopyranosides and their 6-deoxy analogs,² and applied this chemistry to a linear synthesis of methyl α -L-rhamnopyranosyl-(1 $\rightarrow$ 3)- β -D-glycero-D-mannoheptopyranosyl-(1 $\rightarrow$ 3)-6-deoxy- β -glycero-D-manno-heptopyranosyl-(1 $\rightarrow$ 4)- α -L-rhamnopyranoside, a tetrasaccharide subunit from the *Plesimonas shigelloides* lipopolysaccharide,³ we selected this oligomer as a proving ground for a block synthesis approach to glycans containing the unusual β -D-glycero-D-manno-heptoside structure.^{4,5}

dcrich@chem.wayne.edu.

Supporting Information Available: Comparison of spectral data of glycan **25** with that of the natural isolate, and copies of spectra of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Results and Discussion

Although our previous approach to the synthesis of the key *D*-glycero-*D*-manno-thioheptopyranoside donor was successful, and has subsequently been adopted by others,⁶ it suffered from a low yield at the level of the homologation step in which a six-carbon thiomannopyranoside was extended to a seven carbon system by Swern oxidation and Wittig olefination owing to competing elimination of a benzyloxy group from the 4-position in the course of the Wittig reaction.^{2,3} We began, therefore, by seeking to improve the homologation step and were attracted to the use of the Ley-bisacetal function⁷ for protection of the 3,4-diol functionality on the grounds that elimination would be retarded by the confinement of the putative alkoxide leaving group within the a fused bicyclic ring system. Thus, treatment of the bisacetal **1**⁸ with sodium hydride and benzyl bromide in DMF from -40 to 10 °C, according to the method described by Ley and others,⁹ afforded the 2-*O*-benzyl derivative **2** with good selectivity alongside a minor amount of the 2,6-di-*O*-benzyl system **3**.¹⁰ Swern oxidation followed by standard Wittig homologation then afforded alkene **4** in 84% yield along with a minor amount of a methylthioalkene **5**.¹¹ representing a distinct improvement over the earlier protocol (Scheme 1).

Catalytic osmylation of **4** took place with excellent yield but poor selectivity for the formation of **6** and **8**,¹² whatever the conditions employed, in keeping with our previous observations³ and those of other workers¹³ with closely related compounds (Table 1). Some minor over-oxidation to the corresponding sulfones **7** and **9** was also observed in these reactions.¹⁴

Selective monobenylation with dibutyltin oxide and benzyl bromide¹⁵ of **6** and **8** afforded the corresponding 7-*O*-benzyl-6-ols **10** and **11** in excellent yield. Attempted inversion of the unwanted *L*,*D*-alcohol **11** to the desired *D*,*D*-isomer **10** by the Mitsunobu protocol¹⁶ was stymied by poor yields but the desired effect was achieved by recourse to displacement of the 6-*O*-triflate with potassium nitrite with in situ hydrolysis of the corresponding nitroso ester.¹⁷ Hydrolysis of the biacetal function in **10** to give a triol was followed by selective benzyldiene acetal formation across the 1,3-diol functionality and introduction of a naphthylmethyl ether¹⁸ onto the remaining alcohol, thereby providing the known glycosyl donor **13** and, incidentally, confirming the *D*,*D*-stereochemistry of **6** (Scheme 2).

Two *L*-rhamnopyranosyl acceptors **16** and **17** were prepared by protection of the corresponding triols as the benzophenone acetals¹⁹ in moderate yield (Scheme 3). Somewhat better yields of **16** and **17** have been reported in the literature for alkylation of **14** and **15** with dichlorodiphenylmethane in pyridine.^{19a}

A first glycosidic bond forming reaction involved activation of donor with 4-nitrophenylsulfenyl chloride and silver triflate in dichloromethane at -78 °C to give the corresponding glycosyl triflate followed by addition of the acceptor **16**, when disaccharide **18** was obtained in 81% yield and exquisite β -selectivity in keeping with our previous observations in the benzyldiene protected *D*-glycero-*D*-manno-heptoside series. The 4-nitrophenylsulfenyl chloride/silver triflate protocol²⁰ is a convenient variant on benzenesulfenyl triflate activation protocol²¹ that employs a commercial, stable sulfenyl chloride. The anomeric stereochemistry of the newly assigned glycosidic bond is readily assigned on the basis of the shield, upfield nature of the heptoside H5 resonance (δ 2.63), something that is highly characteristic of 4,6-*O*-benzyldiene protected β -mannosides and which carries over to corresponding benzyldiene acetals of the β -*D*-glycero-*D*-manno-heptosides. Confirmation of this anomeric stereochemistry derives from the anomeric 159.7 Hz $^1J_{H1,C1}$ coupling constant.²² Removal of the naphthylmethyl ether with dichlorodicyanoquinone in wet dichloromethane gave the glycosyl acceptor **19** in good yield (Scheme 4).

An analogous protocol was then applied to the coupling of donor **13** with the thioglycoside-containing acceptor **17** to give the thiodisaccharide **20**, again with exquisite β -selectivity (for the heptopyranoside: δ_{H5} 2.63, $^1J_{\text{H1,C1}}$ 159.0 Hz). Unfortunately, yield were lower with acceptor **17** than with the corresponding methyl glycoside **16**, maximizing at 54% when 1.2 eq of the sulfonyl chloride was employed. However, the 1-benzenesulfinyl piperidine (BSP)/trifluoromethanesulfonic anhydride protocol proved superior when the activation was conducted in the presence of 1-octene as a sacrificial olefin, resulting in a 73% yield of the desired disaccharide (Scheme 5).

The tetrasaccharide **21**, comprising two iterations of the *Bacillus thermoaerophilus* glycan repeating unit was then assembled by coupling of the disaccharide acceptor with the disaccharide donor **20** on activation with *N*-iodosuccinimide and silver triflate in excellent yield and α -selectivity. The 4-nitrophenylsulfenyl chloride/silver triflate protocol was also attempted but only gave the target compound in 26% yield. In addition to the two anomeric resonances characterizing the pre-installed β -mannoheptoside linkages, the ^{13}C NMR spectrum of the tetrasaccharide contained resonances at δ 93.9 and 98.1 with $^1J_{\text{CH}}$ of 168.7 and 172.3 Hz indicative of the α -nature for the two rhamnoside linkages. Finally, global deprotection of **21** was achieved cleanly by hydrogenolysis over palladium on charcoal leading to the isolation of the target tetrasaccharide **22** in 85% yield (Scheme 6).

The synthesis of the hexasaccharide **25** began with removal of the naphthylmethyl protecting group from tetrasaccharide **21** to give the acceptor **23**, and was followed by NIS/AgOTf mediated coupling with the disaccharide donor **20** to give the hexasaccharide **24** in 64% yield as a single anomer. The α -nature of the rhamnopyranosidic linkage formed in this glycosylation again rested on the one bond CH coupling constant at the anomeric center of the newly formed glycosidic bond (167 Hz). Global deprotection was again achieved by hydrogenolysis, affording the target hexasaccharide in 60% yield (Scheme 7).

The spectral data for the central residues in hexasaccharide **25** were compared to those reported for the natural isolate and found to show a very high degree of concordance (supporting information), thereby confirming the structure proposed by Kosma and coworkers.

Conclusion

A block synthesis of the target hexasaccharide has been achieved and confirms the very rare β -D-glycero-D-mannoheptospyranoside linkage at the heart of this glycan.

Experimental Section

General Experimental

Peak assignments in the NMR spectra were made in the usual manner with the assistance of phase sensitive COSY-45 and phase sensitive NOESY experiments.

Phenyl 2-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-thia- α -D-mannopyranoside (2) and Phenyl 2,6-di-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-thia- α -D-mannopyranoside (3)—To a cooled (-40°C) solution of diol **1**⁸ (12.24 g, 31.67 mmol) in dry DMF (140 mL) was added benzyl bromide (4.20 mL, 35.4 mmol) followed by 60% NaH in mineral oil (2.57 g, 64.3 mmol). The resultant mixture was stirred for 1 h at -40°C , then for 16 h at -10°C . The reaction mixture was poured into water and extracted with CH_2Cl_2 . The collected organic phase was further washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel chromatography ($\text{AcOEt}/\text{hexane} = 1/4$ to $1/3$, then $\text{AcOEt}/\text{CH}_2\text{Cl}_2 = 3/1$ to $2/1$) to afford the monobenzylated ether **2** (12.21 g, 25.6 mmol, 81%). $[\alpha]_{\text{D}}^{24} = +221.3$ (c 1.2, CHCl_3); ^1H NMR

(500 MHz, CDCl₃) δ 7.43–7.41 (m, 4 H), 7.35–7.26 (m, 6 H), 5.48 (s, 1 H), 4.93 (d, 1 H, J = 11.5 Hz), 4.68 (d, 1 H, J = 11.5 Hz), 4.29 (t, 1 H, J = 10.0 Hz), 4.25–4.22 (m, 1 H), 4.08 (dd, 1 H, J = 2.5, 9.5 Hz), 3.99 (br. s, 1 H), 3.85–3.77 (m, 2 H), 3.33 (s, 3 H), 3.30 (s, 3 H), 1.90 (br. s, 1 H), 1.37 (s, 3 H), 1.34 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 134.2, 132.0, 129.3, 128.5, 128.2, 127.8, 100.3, 99.9, 87.8, 77.7, 73.4, 72.2, 69.6, 64.1, 61.7, 48.3, 48.1, 18.0; HRMS m/z : calcd for C₂₅H₃₂O₇NaS, 499.1766 [M+Na⁺]; Found C₂₅H₃₂O₇NaS, 499.1761; and **3**⁸ (1.51 g, 3.90 mmol, 12%). $[\alpha]_D^{23}$ = +172.2 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.51–7.46 (m, 4 H), 7.36–7.24 (m, 11 H), 5.59 (s, 1 H), 4.94 (d, 1 H, J = 12.5 Hz), 4.74 (d, 1 H, J = 12.0 Hz), 4.66 (d, 1 H, J = 11.5 Hz), 4.55 (d, 1 H, J = 11.5 Hz), 4.50–4.48 (m, 1 H), 4.36–4.32 (m, 1 H), 4.13–4.10 (m, 1 H), 4.03 (s, 1 H), 3.88–3.84 (m, 2 H), 3.58 (s, 3 H), 3.25 (s, 3 H), 1.40 (s, 3 H), 1.36 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.83, 138.81, 134.6, 132.0, 129.2, 128.5, 128.4, 128.0, 127.74, 127.71, 127.67, 127.5, 100.3, 99.9, 87.6, 77.9, 73.6, 73.0, 72.0, 69.8, 69.0, 64.2, 48.3, 48.2, 18.12, 18.09; HRMS m/z : calcd for C₃₂H₄₂NO₇NaS, 584.2682 [M+NH₄⁺]; C₃₂H₄₂NO₇NaS, 584.2674; calcd for C₃₂H₃₈O₇NaS, 589.2236 [M+Na⁺], Found C₃₂H₃₈O₇NaS, 589.2238.

Phenyl 2-O-benzyl-6,7-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-thia- α -D-manno-hepto-6-enopyranoside (4) and Phenyl 2-O-benzyl-6,7-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-thia- α -D-manno-hepto-(E)-7-methylthio-6-enopyranoside (5)—To a cooled (–75 °C) solution of oxalyl chloride (1.07 mL, 12.46 mmol) in dry CH₂Cl₂ (30 mL) was added a solution of DMSO (1.80 mL, 25.34 mmol) in dry CH₂Cl₂ (3 mL). After stirring for 10 min. at –75 °C, a solution of alcohol **2** (2.95 g, 6.19 mmol) in CH₂Cl₂ (10 mL + 1 mL rinse) was added dropwise. The mixture was stirred for 15 min. at –75 °C, then for 45 min at –60 °C, and then for 45 min at –45 °C. At this stage Et₃N (6.80 mL, 48.92 mmol) was added dropwise, after which stirring was continued for 45 min. at –45 °C, before the reaction mixture was allowed to warm to –0 °C over 2 h. The reaction mixture was diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered, and concentrated, and the residue was dried for 12 hours at –20 °C in vacuum before it was taken up in THF (9 mL + 2 mL rinse) and added to a –40 °C stirred solution of the Wittig reagent formed by addition of *n*-BuLi in hexane (1.80 M, 7.5 mL, 13.50 mmol) at 0 °C to a suspension of Ph₃PCH₃Br (5.00 g, 14.00 mmol) in THF (30 mL) and cooling to –40 °C. The resulting mixture was stirred for 1.5 h at –40 °C, then warmed to 10 °C over 2.5 h before it was poured into water and extracted with CH₂Cl₂. The collected organic phase was further washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel chromatography (AcOEt/hexane = 1/15) to furnish alkene **4** (2.45 g, 5.17 mmol, 84%). $[\alpha]_D^{24}$ = +251.7 (c 1.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.41 (m, 4 H), 7.35–7.25 (m, 6 H), 6.02–5.95 (m, 1 H), 5.52 (s, 1 H), 5.45–5.42 (m, 1 H), 5.27–5.24 (m, 1 H), 4.91 (d, 1 H, J = 12.0 Hz), 4.71 (d, 1 H, J = 12.0 Hz), 4.63 (t, 1 H, J = 7.50 Hz), 4.09–4.03 (m, 2 H), 3.99 (m, 1 H), 3.33 (s, 3 H), 3.26 (s, 3 H), 1.38 (s, 3 H), 1.34 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 134.8, 134.0, 131.6, 129.2, 128.5, 128.2, 127.8, 127.6, 118.1, 100.2, 100.0, 87.6, 77.8, 73.2, 72.3, 69.8, 67.8, 48.2, 48.1, 18.1, 18.0; HR-ESI m/z : calcd for C₂₆H₃₂O₆NaS, 495.1817 [M+Na⁺], Found C₂₆H₃₂O₆NaS, 495.1826; and alkene **5** (58.1 mg, 112 μ mol, 1.8%). $[\alpha]_D^{23}$ = +218.3 (c 0.97, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.43–7.38 (m, 4 H), 7.34–7.24 (m, 6 H), 6.45 (dd, 1 H, J = 1.0, 15.0 Hz), 5.47 (s, 1 H), 5.45 (dd, 1 H, J = 6.5, 15.5 Hz), 4.89 (d, 1 H, J = 12.5 Hz), 4.70 (d, 1 H, J = 12.0 Hz), 4.65 (t, 1 H, J = 7.5 Hz), 4.05–4.00 (m, 2 H), 3.96 (m, 1 H), 3.32 (s, 3 H), 3.25 (s, 3 H), 2.24 (s, 3 H), 1.36 (s, 3 H), 1.33 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 134.8, 131.6, 129.8, 129.3, 128.5, 128.2, 127.8, 127.6, 120.4, 100.2, 100.0, 87.7, 77.8, 73.3, 72.4, 69.7, 68.0, 48.2, 48.0, 18.1, 18.0, 14.6; HR-ESI m/z : calcd for C₂₇H₃₄O₆NaS₂, 541.1695 [M+Na⁺], Found C₂₇H₃₄O₆NaS, 541.1675.

Phenyl 2-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)- α -D-manno-heptopyranoside (6), Phenyl 2-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)- α -D-glycero-1-sulfonyl- α -D-manno-heptopyranoside (7), Phenyl 2-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-L-glycero-1-thia- α -D-manno-heptopyranoside (8), and Phenyl 2-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-L-glycero-1-sulfonyl- α -D-manno-heptopyranoside (9)

Method 1: To a solution of alkene **4** (345 mg, 730 μ mol) in 8/1 acetone/H₂O (9 mL), chilled in an ice-water bath, was added NMO (139 mg, 1.2 mmol) and OsO₄ (13.0 mg, 5 μ mol). After stirring for 7 h, the reaction was quenched with a solution of sodium sulfite and extracted with AcOEt. The collected organic phase was further washed with brine, dried over Na₂SO₄, and concentrated. The residue was subjected to silica gel chromatography (AcOEt/CH₂Cl₂ = 1/4, then AcOEt/hexane = 1/1 and AcOEt/CH₂Cl₂ = 2/5) to afford **6** (219.3 mg, 433 μ mol, 59%), [α]_D²⁴ = + 240.3 (c 0.94, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.40 (m, 4 H), 7.35-7.26 (m, 6 H), 5.43 (s, 1 H), 4.91 (d, 1 H, *J* = 12.0 Hz), 4.67 (d, 1 H, *J* = 12.0 Hz), 4.37 (t, 1 H, *J* = 10.0 Hz), 4.26 (dd, 1 H, *J* = 6.0, 10.0 Hz), 4.07 (dd, 1 H, *J* = 3.0, 10.0 Hz), 3.96-3.93 (m, 2 H), 3.70-3.63 (m, 2 H), 3.33 (s, 3 H), 3.31 (s, 3 H), 3.16 (d, 1 H, OH, *J* = 3.0 Hz), 2.20 (t, 1 H, OH, *J* = 6.5 Hz), 1.36 (s, 3 H), 1.33 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.5, 133.7, 132.2, 129.4, 128.5, 128.2, 128.1, 127.9, 100.3, 100.2, 87.8, 77.5, 73.5, 73.4, 71.2, 69.4, 67.1, 63.2, 48.6, 48.3, 18.1, 18.0; HR-ESI *m/z*: calcd for C₂₆H₃₄O₈NaS, 529.1872 [M+Na⁺], Found C₂₆H₃₄O₈NaS, 529.1859; **7** (18.3 mg, 34 μ mol, 4.6%), [α]_D²³ = + 148.7 (c 0.78, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, 2 H, *J* = 7.5 Hz), 7.69 (t, 1 H, *J* = 7.5 Hz), 7.58 (t, 2 H, *J* = 7.5 Hz), 7.44 (d, 2 H, *J* = 7.0 Hz), 7.37-7.31 (m, 3 H), 5.00 (d, 1 H, *J* = 11.5 Hz), 4.72 (s, 1 H), 4.67 (d, 1 H, *J* = 11.0 Hz), 4.61 (d, 1 H, *J* = 3.0 Hz), 4.52-4.49 (m, 2 H), 4.35 (t, 1 H, *J* = 9.0 Hz), 3.79-3.75 (m, 1 H), 3.57-3.52 (m, 2 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 3.27 (br s, 1 H, OH), 2.23 (br s, 1 H, OH), 1.37 (s, 3 H), 1.35 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.1, 136.7, 134.6, 129.5, 129.3, 128.6, 128.4, 128.1, 100.3, 100.1, 93.0, 74.7, 74.1, 73.9, 71.9, 69.1, 66.1, 62.4, 48.6, 48.4, 18.0, 17.9; HR-ESI *m/z*: calcd for C₂₆H₃₄O₁₀NaS, 561.1770 [M+Na⁺], Found C₂₆H₃₄O₁₀NaS, 561.1748; **8** (101.0 mg, 199 μ mol, 27%), [α]_D²⁴ = + 232.2 (c 1.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, 1 H, *J* = 7.5 Hz), 7.38-7.28 (m, 8 H), 5.52 (s, 1 H), 4.95 (d, 1 H, *J* = 12.0 Hz), 4.67 (d, 1 H, *J* = 11.5 Hz), 4.42 (t, 1 H, *J* = 10.0 Hz), 4.14 (dd, 1 H, *J* = 2.0, 10.0 Hz), 4.08 (dd, 1 H, *J* = 3.0, 10.0 Hz), 3.97-3.95 (m, 1 H), 3.94-3.90 (m, 1 H), 3.50 (br s, 2 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 2.66 (d, 1 H, OH, *J* = 6.0 Hz), 1.85 (br s, 1 H, OH), 1.36 (s, 3 H), 1.33 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.5, 133.3, 132.1, 129.5, 128.6, 128.2, 127.9, 100.3, 100.0, 87.6, 77.3, 73.5, 72.9, 69.7, 68.8, 65.1, 63.4, 48.3, 18.1, 18.0; HR-ESI *m/z*: calcd for C₂₆H₃₄O₈NaS, 529.1872 [M+Na⁺], Found C₂₆H₃₄O₁₀NaS, 529.1874; **9** (15.1 mg, 28 μ mol, 3.8%), [α]_D²³ = + 135.8 (c 0.67, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, 2 H, *J* = 8.0 Hz), 7.70 (t, 1 H, *J* = 7.5 Hz), 7.59 (t, 2 H, *J* = 8.0 Hz), 7.44 (d, 2 H, *J* = 7.0 Hz), 7.37-7.30 (m, 3 H), 5.03 (d, 1 H, *J* = 11.0 Hz), 4.81 (s, 1 H), 4.67 (d, 1 H, *J* = 11.0 Hz), 4.60 (d, 1 H, *J* = 3.0 Hz), 4.49-4.45 (m, 1 H), 4.41-4.37 (m, 2 H), 3.89 (m, 1 H), 3.51-3.44 (m, 2 H), 3.35 (s, 3 H), 3.32 (s, 3 H), 2.10 (br s, 1 H, OH), 1.72 (br s, 1 H, OH), 1.37 (s, 3 H), 1.33 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.1, 136.9, 134.7, 129.6, 128.9, 128.6, 128.5, 128.1, 100.1, 100.0, 93.2, 76.8, 74.7, 71.9, 69.2, 68.9, 64.6, 62.0, 48.4, 48.3, 17.9; HR-ESI *m/z*: calcd for C₂₆H₃₄O₁₀NaS, 561.1770 [M+Na⁺], Found C₂₆H₃₄O₁₀NaS, 561.1746.

Method 2: To a mixture of alkene **4** (1.52 g, 3.2 mmol) in 1/1 *t*-BuOH/H₂O (32 mL) was added toluene (2.5 mL), K₂CO₃ (1.31 g, 9.7 mmol), and K₃Fe(CN)₆ (3.29 g, 10.0 mmol). After stirring for 10 min, the mixture was cooled to 0 °C followed by addition of (DHQ)₂Pry (29.1 mg, 0.033 mmol), and a solution of OsO₄ in *t*-BuOH (2.5 wt%, 161 μ L). After the mixture was stirred for 24 h, additional *t*-BuOH/H₂O (8 mL, 1/1), K₂CO₃ (344 mg, 2.5 mmol), and K₃Fe(CN)₆ (832 mg, 2.5 mmol) were added. Stirring was continued for another 24 h before the reaction mixture was diluted with CH₂Cl₂, washed with sat. aqueous NaSO₃ and brine. The organic

phase was dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography (AcOEt/CH₂Cl₂ = 1/4) to give **6** (1.12 g, 2.2 mmol, 68%) and **8** (455 mg, 0.9 mmol, 28%).

Phenyl 2,7-di-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-glycero-1-thia- α -D-manno-heptopyranoside (10)—To a solution of diol **6** (1.69 g, 3.33 mmol) in anhydrous toluene (80 mL) was added Bu₂SnO (957 mg, 3.84 mmol) after which the reaction mixture was heated to reflux in a Dean-Stark apparatus. After 2 h, the resulting clear solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in DMF (30 mL) under N₂, and benzyl bromide (0.48 mL, 4.04 mmol) and CsF (1.07 g, 7.06 mmol) were added. The resulting mixture was stirred for 16 h at room temperature under N₂, then was diluted with CH₂Cl₂, washed with aqueous KF and brine. The organic phase was collected, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (AcOEt/Hexane = 1/6) to yield ether **10** (1.90 g, 3.19 mmol, 96%). [α]_D²⁴ = +186.5 (*c* 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.41-7.36 (m, 4 H), 7.34-7.23 (m, 11 H), 5.47 (s, 1 H), 4.89 (d, 1 H, *J* = 12.5 Hz), 4.67 (d, 1 H, *J* = 12.0 Hz), 4.53 (d, 1 H, *J* = 12.0 Hz), 4.48 (d, 1 H, *J* = 12.5 Hz), 4.36 (t, 1 H, *J* = 10.0 Hz), 4.20 (dd, 1 H, *J* = 5.0, 10.0 Hz), 4.13-4.10 (m, 1 H), 4.03 (dd, 1 H, *J* = 3.0, 10.5 Hz), 3.93-3.92 (m, 1 H), 3.57 (d, 2 H, *J* = 5.0 Hz), 3.30 (s, 3 H), 3.23 (s, 3 H), 2.84 (d, 1 H, OH, *J* = 2.5 Hz), 1.33 (s, 3 H), 1.28 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 138.5, 134.3, 131.6, 129.3, 128.6, 128.2, 128.1, 127.9, 127.8, 127.7, 100.3, 100.0, 87.5, 77.5, 73.6, 73.3, 72.8, 71.0, 69.6, 65.9, 48.5, 48.3, 18.1, 18.0; HR-ESI *m/z*: calcd for C₃₃H₄₀O₈NaS, 619.2342 [M+Na⁺], Found C₃₃H₄₀O₈NaS, 619.2323.

Phenyl 2,7-di-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-L-glycero-1-thia- α -D-manno-heptopyranoside (11)—Following the protocol for **10**, diol **8** (1.16 g, 2.29 mmol) gave rise to ether **11** (1.24 g, 2.08 mmol, 91%). [α]_D²⁴ = +198.7 (*c* 0.97, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, 2 H, *J* = 7.5 Hz), 7.36-7.22 (m, 13 H), 5.56 (s, 1 H), 4.92 (d, 1 H, *J* = 12.0 Hz), 4.69 (d, 1 H, *J* = 11.5 Hz), 4.48-4.40 (m, 3 H), 4.15-4.13 (m, 2 H), 4.06 (dd, 1 H, *J* = 2.5, 10.0 Hz), 3.95 (br. s, 1 H), 3.38 (t, 1 H, *J* = 10.5 Hz), 3.31-3.29 (m, 7 H), 2.15 (br s, 1 H, OH), 1.36 (s, 3 H), 1.31 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 138.3, 134.1, 131.5, 129.2, 128.6, 128.5, 128.2, 127.9, 127.8, 127.6, 100.3, 99.9, 87.3, 77.3, 73.5, 73.3, 71.8, 71.3, 69.9, 67.6, 63.1, 48.2, 18.0; HR-ESI *m/z*: calcd for C₃₃H₄₀O₈NaS, 619.2342 [M+Na⁺], Found C₃₃H₄₀O₈NaS, 619.2333.

Formation of Phenyl 2,7-di-O-benzyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-glycero-1-thia- α -D-manno-heptopyranoside (10) by Stereochemical Inversion of **11**

Method 1: To a solution of alcohol **11** (267.9 mg, 450 μ mol), 4-nitrobenzoic acid (155 mg, 924 μ mol), and triphenylphosphine (238 mg, 910 μ mol), cooled at 0 °C, in THF (125 mL) was added diisopropyl azodicarboxylate (177 μ L, 899 μ mol). The reaction mixture was allowed to ambient temperature and was stirred for 12 h before it was diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃ and brine. The residue was subjected to silica gel chromatography to give ester (73.1 mg, 98 μ mol, 22%), which was treated with K₂CO₃ (45.8 mg, 331 μ mol) in 2/1 MeOH/THF (3 mL). The resulting mixture was stirred for 16 h at ambient temperature under N₂, then concentrated under reduced pressure. The solid was diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, filtered, concentrated, and purified by silica gel chromatography (AcOEt/hexane = 1/5) to afford **10** (55.4 mg, 93 μ mol, 95%).

Method 2: To a chilled (−40 °C) solution of alcohol **11** (478.7 mg, 802 μ mol) in CH₂Cl₂ (12 mL) was added anhydrous pyridine (163 μ L, 2.0 mmol) and Tf₂O (240 μ L, 1.45 mmol, 1.8

eq) after which the reaction mixture was stirred for 10 min at $-40\text{ }^{\circ}\text{C}$, then warmed to $-5\text{ }^{\circ}\text{C}$ over 80 min, then was poured into cold 0.2 N HCl and extracted with CH_2Cl_2 . The collected organic phase was further washed with cold aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The resulting residue was dissolved in dry DMF (10 mL), 18-C-6 (57 mg, 0.22 mmol) and KNO_2 (460 mg, 5.4 mmol) were added. After stirring for 13 hours, more 18-c-6 (256.3 mg, 0.97 mmol) and KNO_2 (324 mg, 3.8 mmol) were added. Stirring was continued for 71 h before the reaction mixture was poured into 1 N aqueous K_2CO_3 , and stirred for 2 h, and extracted with CH_2Cl_2 . The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography ($\text{AcOEt}/\text{hexane} = 1/5$) to afford alcohol **10** (331 mg, 556 μmol , 69%).

Phenyl 2,7-di-O-benzyl-4,6-O-benzylidene- β -glycero-1-thia- α -manno-heptopyranoside (12)—To a solution of 1,2-diacetal **10** (2.21 g, 3.7 mmol) in CH_2Cl_2 (30 mL) was added a 10/1 mixture of TFA/ H_2O (15 mL). The resulting mixture was stirred for 40 min at ambient temperature under N_2 before the volatiles were removed under reduced pressure and residue purified by silica gel chromatography ($\text{AcOEt}/\text{CH}_2\text{Cl}_2 = 1/1$ to $3/2$) to give triol (1.600 g, 3.3 mmol, 89%), which was dissolved in dry CH_2Cl_2 (36 mL) and treated with camphorsulfonic acid (52.2 mg, 0.23 mmol) and benzaldehyde dimethyl acetal (2.4 mL, 16 mmol). After stirring for 14 h at room temperature under N_2 , the mixture was diluted with CH_2Cl_2 , washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue was subjected to flash chromatography on silica gel to afford benzylidene **12** (1.641 g, 2.9 mmol, 87%). $[\alpha]_{\text{D}}^{23} = +144.3$ (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.54-7.53 (m, 2 H), 7.41-7.24 (m, 18 H), 5.68 (s, 1 H), 5.62 (s, 1 H), 4.77 (d, 1 H, $J = 11.5$ Hz), 4.66 (d, 1 H, $J = 11.5$ Hz), 4.53 (d, 1 H, $J = 12.5$ Hz), 4.48 (d, 1 H, $J = 12.0$ Hz), 4.14-4.01 (m, 5 H), 3.58-3.51 (m, 2 H), 2.44 (d, 1 H, OH , $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.4, 137.5, 137.4, 133.7, 131.9, 129.3, 128.9, 128.5, 128.4, 128.3, 127.8, 127.7, 126.7, 101.9, 86.0, 79.9, 78.8, 78.7, 73.7, 73.5, 69.4, 65.7; HRMS m/z : calcd for $\text{C}_{34}\text{H}_{34}\text{O}_6\text{NaS}$, 593.1974 $[\text{M}+\text{Na}^+]$; Found $\text{C}_{34}\text{H}_{34}\text{O}_6\text{NaS}$, 593.1962.

Phenyl 2,7-di-O-benzyl-4,6-O-benzylidene-3-O-(2-naphthalenylmethyl)- β -glycero-1-thia- α -manno-heptopyranoside (13)—To a solution of alcohol **12** (1.60 g, 2.8 mmol) in dry DMF (24 mL), cooled in an ice-water bath, was added 60% NaH in mineral oil (230 mg, 5.8 mmol). After stirring for 20 min, tetrabutylammonium iodide (106 mg, 0.29 mmol) and 2-(bromomethyl)naphthalylene (843 mg, 3.7 mmol) were added and the resulting mixture was stirred for 12.5 h in the dark at room temperature under N_2 . At this point MeOH (2.0 mL) was added, followed by neutralization with acidic resin to pH 6.0. The solid was filtered off and the filtrate was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 , and washed with aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel chromatography ($\text{AcOEt}/\text{hexane} = 1/8$ to $1/6$) to yield ether **13**³ (1.941 g, 2.7 mmol, 97%). $[\alpha]_{\text{D}}^{24} = +110.0$ (c 0.80, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.82 (m, 3 H), 7.76-7.74 (m, 1 H), 7.62-7.60 (m, 2 H), 7.49-7.46 (m, 3 H), 7.44-7.22 (m, 18 H), 5.80 (s, 1 H), 5.60 (s, 1 H), 4.98 (d, 1 H, $J = 12.0$ Hz), 4.84 (d, 1 H, $J = 12.5$ Hz), 4.80 (d, 1 H, $J = 12.5$ Hz), 4.76 (d, 1 H, $J = 12.5$ Hz), 4.57 (d, 1 H, $J = 12.5$ Hz), 4.51 (d, 1 H, $J = 13.0$ Hz), 4.42 (t, 1 H, $J = 8.5$ Hz), 4.19-4.12 (m, 2 H), 4.09-4.04 (m, 2 H), 3.63 (d, 1 H, $J = 11.0$ Hz), 3.57 (dd, 1 H, $J = 5.5, 12.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 137.9, 136.1, 133.8, 133.6, 133.2, 131.8, 129.3, 129.1, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 126.6, 126.3, 126.1, 125.9, 101.4, 86.8, 78.8, 78.4, 77.9, 76.7, 73.7, 73.4, 73.3, 69.5, 66.4; HR-ESI m/z : calcd for $\text{C}_{45}\text{H}_{42}\text{O}_6\text{NaS}$, 733.2600 $[\text{M}+\text{Na}^+]$; Found $\text{C}_{45}\text{H}_{42}\text{O}_6\text{NaS}$, 733.2561.

Methyl 2,3-O-diphenylmethylene- α -L-rhamnopyranoside (16)—Triol **14**²³ (1.426 g, 8.0 mmol), benzophenone dimethyl acetal²⁴ (3.649 g, 16.0 mmol), and camphorsulfonic acid

(308.4 mg, 1.39 mmol) were dissolved in dry DMF (20 mL). The mixture was stirred in a 50 °C water bath in a rotary evaporator for 8 h under the reduced pressure (27 mm Hg), to remove methanol formed during the reaction, then was poured into a saturated solution of NaHCO₃ in H₂O, and extracted with AcOEt. The organic phase was washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/hexane = 1/5 to 1/4) to afford **16**^{19a} (1.29 g, 3.8 mmol, 47%). [α]_D²⁴ = −71.6 (*c* 0.65, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.53–7.51 (m, 4 H), 7.34–7.27 (m, 6 H), 5.02 (s, 1 H), 4.28 (t, 1 H, *J* = 6.5 Hz), 4.06 (d, 1 H, *J* = 5.5 Hz), 3.71–3.66 (m, 1 H), 3.42–3.39 (m, 1 H), 3.38 (s, 3 H), 2.28 (br s, 1 H, *OH*), 1.27 (d, 3 H, *J* = 6.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 143.1, 142.7, 128.4, 128.3, 126.3, 126.2, 109.8, 98.3, 79.1, 76.1, 74.1, 66.2, 55.2, 17.3; HR-ESI *m/z*: calcd for C₂₀H₂₂O₅Na, 365.1365 [M+Na⁺]; Found C₂₀H₂₂O₅Na, 365.1353.

Phenyl 2,3-O-diphenylmethylene-1-thia- α -L-rhamnopyranoside (17)—Following the protocol for **16**, treatment of thioglycoside **15**²⁵ (1.60 g, 6.2 mmol) with benzophenone dimethyl acetal²⁴ (2.84 g, 12.5 mmol) and camphorsulfonic acid (81 mg, 0.35 mmol) furnished alcohol **17**^{19a} (1.03 g, 2.4 mmol, 39%). [α]_D²⁴ = −191.0 (*c* 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.54–7.47 (m, 6 H), 7.46–7.25 (m, 9 H), 5.91 (s, 1 H), 4.34 (dd, 1 H, *J* = 5.5, 7.0 Hz), 4.29 (d, 1 H, *J* = 6.0 Hz), 4.14–4.09 (m, 1 H), 3.45–3.40 (m, 1 H), 2.14 (br s, 1 H), 1.19 (d, 3 H, *J* = 6.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 143.2, 142.9, 133.6, 132.3, 129.3, 128.5, 128.4, 127.9, 126.2, 126.0, 109.8, 83.8, 79.3, 77.1, 74.9, 67.2, 17.3; HR-ESI *m/z*: calcd for C₂₅H₂₄O₄NaS, 443.1293 [M+Na⁺]; Found C₂₅H₂₄O₄NaS, 443.1277.

Methyl 2,7-di-O-benzyl-4,6-O-benzylidene-3-O-(2-naphthalenylmethyl)- β -D-glycero- β -D-manno-heptopyranosyl-(1 $\rightarrow$ 4)-2,3-O-(diphenylmethylene)- α -L-rhamnopyranoside (18)—A flask, charged with thioheptoside **13** (206.4 mg, 290 μ mol), TTBP (240.1 mg, 967 μ mol), silver triflate (232 mg, 903 μ mol) and 4 Å molecular sieves (500 mg), was dried under vacuum for 1 h with the exclusion of light. Then dry CH₂Cl₂ (7 mL) was added, and the resulting mixture was stirred for 0.5 h at −78 °C before 4-nitrobenzenesulfonyl chloride (112.0 mg, 591 μ mol) was added in one portion as a solid. After stirring for 10 min at −78 °C, the mixture was warmed to −45 °C, and stirring continued for 15 min before the reaction mixture was recooled to −78 °C. A solution of methyl rhamnoside **16** (130 mg, 380 μ mol) in CH₂Cl₂ (1 mL + 0.5 mL rinse) then was added dropwise. The reaction mixture was stirred for 30 min at −78 °C, then warmed to −45 °C and stirring continued for 3 h. Saturated aqueous NaHCO₃ was added, and after filtration of the solid, the filtrate was further washed with aqueous NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/PhCH₃ = 1/40 to 1/30) to afford disaccharide **18** (221.1 mg, 234 μ mol, 81%) as a white foam. [α]_D²⁴ = −59.5 (*c* 0.63, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.80–7.78 (m, 3 H), 7.68–7.56 (m, 1 H), 7.52–7.27 (m, 25 H), 7.07–7.05 (m, 3 H), 5.71 (s, 1 H), 5.02 (s, 1 H), 4.97 (d, 1 H, *J* = 12.5 Hz), 4.88 (d, 1 H, *J* = 12.0 Hz), 4.85 (d, 1 H, *J* = 13.0 Hz), 4.78 (d, 1 H, *J* = 13.0 Hz), 4.54 (d, 1 H, *J* = 12.5 Hz), 4.50 (d, 1 H, *J* = 12.0 Hz), 4.38 (s, 1 H), 4.23 (dd, 1 H, *J* = 6.0, 7.5 Hz), 4.18 (t, 1 H, *J* = 9.5 Hz), 4.10 (t, 1 H, *J* = 8.0 Hz), 4.03–4.02 (m, 2 H), 3.65–3.60 (m, 1 H), 3.53–3.50 (m, 2 H), 3.39 (s, 3 H), 3.34 (dd, 1 H, *J* = 7.5, 11.5 Hz), 3.27 (dd, 1 H, *J* = 7.5, 10.0 Hz), 2.63 (t, 1 H, *J* = 9.5 Hz), 1.19 (d, 3 H, *J* = 6.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 143.2, 143.1, 138.8, 138.5, 137.9, 133.5, 133.2, 129.0, 128.9, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 126.6, 126.4, 126.3, 126.2, 126.1, 125.8, 109.4, 102.3 (*J*_{C1–H1} = 159.7 Hz), 101.2, 98.0 (*J*_{C1–H1} = 174.6 Hz), 80.8, 79.1, 78.9, 78.0, 77.8, 76.5, 76.2, 75.0, 73.6, 72.5, 69.5, 68.7, 64.6, 55.2, 17.8; HR-ESI *m/z*: calcd for C₅₉H₅₈O₁₁Na, 965.3877 [M+Na⁺]; Found C₅₉H₅₈O₁₁Na, 965.3904.

Methyl 2,7-di-O-benzyl-4,6-O-benzylidene- β -D-glycero- β -D-manno-heptopyranosyl-(1 $\rightarrow$ 4)-2,3-O-(diphenylmethylene)- α -L-rhamnopyranoside (19)

—To a heterogeneous mixture of **18** (252.2 mg, 267 μ mol) in 9/1 CH₂Cl₂/H₂O (6.6 mL) was

added DDQ (96.0 mg, 423 μmol). The reaction mixture was stirred for 3 h at ambient temperature under N_2 , then was diluted with CH_2Cl_2 , washed with aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 , and concentrated. The residue was purified by flash chromatography on silica gel ($\text{AcOEt}/\text{hexane} = 1/4$ to $1/3$) to furnish alcohol **19** (185.2 mg, 231 μmol , 86%) as a white foam. $[\alpha]_{\text{D}}^{24} = -88.1$ (c 0.1.1, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.48 (m, 6 H), 7.41-7.22 (m, 18 H), 7.15 (t, 1 H, $J = 7.5$ Hz), 5.60 (s, 1 H), 5.05 (s, 1 H), 5.02 (d, 1 H, $J = 11.5$ Hz), 4.68 (d, 1 H, $J = 12.0$ Hz), 4.58 (s, 1 H), 4.55 (d, 1 H, $J = 12.5$ Hz), 4.52 (d, 1 H, $J = 12.5$ Hz), 4.35 (dd, 1 H, $J = 6.0, 7.5$ Hz), 4.06-3.99 (m, 3 H), 3.77 (t, 1 H, $J = 9.5$ Hz), 3.68-3.62 (m, 2 H), 3.49 (dd, 1 H, $J = 1.5, 11.5$ Hz), 3.39 (s, 3 H), 3.72-3.32 (m, 2 H), 2.60 (t, 1 H, $J = 9.0$ Hz), 2.37 (br. s, 1 H, OH), 1.21 (d, 3 H, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 143.2, 138.5, 138.4, 137.5, 129.2, 128.7, 128.6, 128.5, 128.4, 128.2, 127.9, 126.6, 126.2, 126.1, 125.9, 109.5, 102.1, 101.6, 98.0, 80.6, 79.2, 79.0, 78.6, 78.5, 76.5, 75.8, 73.6, 71.1, 69.5, 68.3, 64.5, 55.2, 17.9; HR-ESI m/z : calcd for $\text{C}_{48}\text{H}_{50}\text{O}_{11}\text{Na}$, 825.3251 $[\text{M}+\text{Na}^+]$; Found $\text{C}_{48}\text{H}_{50}\text{O}_{11}\text{Na}$, 825.3207.

Phenyl 2,7-di-O-benzyl-4,6-O-benzylindene-3-O-(2-naphthalenylmethyl)- β -glycero- β -manno-heptopyranosyl-(1 $\rightarrow$ 4)-2,3-O-diphenylmethylene-1-thia- α -L-rhamnopyranoside (20)

Method 1: A mixture of thioheptoside **13** (90.1 mg, 127 μmol), TTBP (70.9 mg, 285 μmol), and AgOTf (81.6 mg, 318 μmol) in CH_2Cl_2 (3 mL) in the presence of 4 Å molecular sieves (290 mg) was stirred for 0.5 h at -78°C before 4-nitrobenzenesulfonyl chloride (29.6 mg, 156 μmol) was added as a solid. After stirring for 10 min, the reaction mixture was warmed to -45°C , and stirred for 10 min before it was recooled to -78°C followed by the addition of a solution of thiorhamnoside **17** (64.8 mg, 154 μmol) in CH_2Cl_2 (1 mL + 0.5 mL rinse). The resulting mixture was stirred for 4 h at -78°C and then saturated aqueous NaHCO_3 was added to quench the reaction, and the solid was filtered off. The filtrate was washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel chromatography ($\text{AcOEt}/\text{PhCH}_3 = 1/40$) to afford disaccharide **20** (70.1 mg, 69 μmol , 54%). $[\alpha]_{\text{D}}^{23} = -115.5$ (c 0.74, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.80 (m, 3 H), 7.73-7.70 (m, 1 H), 7.54-7.28 (m, 30 H), 7.06-7.04 (m, 3 H), 5.89 (s, 1 H), 5.72 (s, 1 H), 4.99 (d, 1 H, $J = 12.5$ Hz), 4.94 (d, 1 H, $J = 12.5$ Hz), 4.90 (d, 1 H, $J = 13.0$ Hz), 4.83 (d, 1 H, $J = 12.5$ Hz), 4.54 (d, 1 H, $J = 12.0$ Hz), 4.50 (d, 1 H, $J = 12.5$ Hz), 4.31 (s, 1 H), 4.26 (d, 1 H, $J = 5.5$ Hz), 4.22-4.18 (m, 2 H), 4.11-4.04 (m, 2 H), 4.04 (d, 1 H, $J = 2.5$ Hz), 3.52 (dd, 1 H, $J = 3.0, 10.0$ Hz), 3.49 (d, 1 H, $J = 10.0$ Hz), 3.59-3.29 (m, 2 H), 2.60 (t, 1 H, $J = 10.0$ Hz), 1.14 (d, 3 H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 143.12, 143.07, 138.8, 138.5, 137.9, 136.1, 133.5, 133.2, 132.3, 129.4, 129.1, 128.6, 128.5, 128.4, 128.13, 128.07, 127.96, 127.90, 127.86, 126.6, 126.5, 126.4, 126.1, 125.8, 125.6, 109.4, 102.3 ($J_{\text{C1-H1}} = 159.0$ Hz), 101.2, 83.9 ($J_{\text{C1-H1}} = 167.2$ Hz), 81.2, 78.9, 78.8, 78.0, 77.9, 77.0, 76.1, 75.0, 73.6, 72.6, 69.5, 68.6, 66.3, 17.6; HR-ESI m/z : calcd for $\text{C}_{64}\text{H}_{60}\text{O}_{10}\text{NaS}$, 1043.3805 $[\text{M}+\text{Na}^+]$; Found $\text{C}_{64}\text{H}_{60}\text{O}_{10}\text{NaS}$, 1043.3755.

Method 2: A mixture of thioheptoside **13** (535.6 mg, 753 μmol), TTBP (298.1 mg, 1.2 mmol), and BSP (168.5 mg, 805 μmol) in CH_2Cl_2 (15 mL) in the presence of 4 Å molecular sieves (500 mg) was stirred for 0.5 h at ambient temperature. Then the mixture was cooled to -60°C , and Ti_2O (156 μL , 940 μmol) was added dropwise. After stirring for 6 min at -78°C , 1-octene (2.0 mL, 12.7 mmol) was added, and stirring continued for 5 min. The reaction mixture was cooled to -78°C followed by the addition of a solution of thiorhamnoside **17** (480.0 mg, 1.1 mmol) in CH_2Cl_2 (3 mL + 0.5 mL rinse). The resulting mixture was stirred for 1 h at -78°C before saturated aqueous NaHCO_3 was added to quench the reaction, and the solid was filtered off. The filtrate was washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel chromatography ($\text{AcOEt}/\text{PhCH}_3 = 1/50$) to afford disaccharide **20** (561.0 mg, 549 μmol , 73%).

Methyl 2,7-di-O-benzyl-4,6-O-benzylidene-3-O-(2-naphthalenylmethyl)-D-glycero-β-D-manno-heptopyranosyl-(1→4)-2,3-O-(diphenylmethylene)-α-L-rhamnopyranosyl-(1→3)-2,7-di-O-benzyl-4,6-O-benzylidene-D-glycero-β-D-manno-heptopyranosyl-(1→4)-2,3-O-(diphenylmethylene)-α-L-rhamnopyranoside (21)—A mixture of alcohol **19** (90.0 mg, 112 μmol), and thioheptoside **20** (135.3 mg, 132 μmol) in CH₂Cl₂ (6 mL) in the presence of 4 Å molecular sieves (320 mg) was stirred for 50 min at ambient temperature under N₂ atmosphere. Then the mixture was cooled to −15 °C, and NIS (38.4 mg, 170 μmol) and AgOTf (16.9 mg, 66 μmol) was subsequently added. The reaction mixture was stirred for 2.5 h while the reaction temperature was increased to 5 °C. The solids were filtered off, and the filtrate was washed with saturated aqueous Na₂S₂O₃ containing NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/PhCH₃ = 1/20 to 1/15) to afford tetrasaccharide **21** (164.2 mg, 96 μmol, 85%). [α]_D²³ = −86.6 (*c* 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.80–7.76 (m, 3 H), 7.68–7.66 (m, 1 H), 7.57–7.19 (m, 46 H), 7.15–7.01 (m, 7 H), 5.70 (s, 1 H), 5.60 (s, 1 H), 5.07 (s, 1 H), 5.01 (s, 1 H), 4.85 (d, 1 H, *J* = 12.0 Hz), 4.83 (d, 1 H, *J* = 12.0 Hz), 4.77–4.64 (m, 4 H), 4.56–4.48 (m, 5 H), 4.34 (dd, 1 H, *J* = 5.5, 7.0 Hz), 4.30 (t, 2 H, *J* = 6.5 Hz), 4.14 (t, 1 H, *J* = 9.5 Hz), 4.11–4.04 (m, 3 H), 4.02–3.92 (m, 3 H), 3.91–3.86 (m, 1 H), 3.83 (dd, 1 H, *J* = 6.0, 9.5 Hz), 3.70–3.66 (m, 1 H), 3.52 (d, 1 H, *J* = 9.5 Hz), 3.47 (d, 1 H, *J* = 10.0 Hz), 3.43–3.41 (m, 4 H), 3.37–3.33 (m, 1 H), 3.28 (dd, 1 H, *J* = 7.5, 11.0 Hz), 3.23 (dd, 1 H, *J* = 7.5, 10.0 Hz), 2.67 (t, 1 H, *J* = 9.5 Hz), 2.46 (t, 1 H, *J* = 9.5 Hz), 1.23 (d, 1 H, *J* = 6.5 Hz), 1.03 (d, 1 H, *J* = 6.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 143.19, 143.15, 143.11, 143.04, 143.07, 138.5, 138.4, 138.1, 138.0, 137.6, 136.1, 133.5, 133.1, 129.2, 129.0, 128.66, 128.63, 128.6, 128.5, 128.45, 128.41, 128.39, 128.35, 128.2, 128.12, 128.09, 127.98, 127.90, 127.8, 126.6, 126.44, 126.38, 126.3, 126.0, 125.9, 125.82, 125.77, 109.6, 109.3, 102.5 (*J*_{C1–H1} = 161.8 Hz), 102.4 (*J*_{C1–H1} = 160.5 Hz), 101.6, 101.1, 98.1 (*J*_{C1–H1} = 172.3 Hz), 93.9 (*J*_{C1–H1} = 168.7 Hz) 81.0, 80.3, 79.2, 79.1, 78.96, 78.92, 77.9, 77.7, 76.5, 76.4, 75.6, 75.1, 74.9, 74.5, 74.0, 73.9, 73.5, 72.2, 69.6, 69.4, 69.1, 68.7, 65.0, 64.6, 55.2, 17.9, 17.5; ESI-HRMS *m/z*: calcd for C₁₀₆H₁₀₄O₂₁Na, 1735.6968 [M+Na⁺]; Found 1735.7017.

Methyl D-glycero-β-D-manno-heptopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-D-glycero-β-D-manno-heptopyranosyl-(1→4)-α-L-rhamnopyranoside (22)—To a solution of tetrasaccharide **21** (37.5 mg, 22 μmol) in 4/4/1 MeOH/THF/H₂O (4.5 mL) was added AcOH (13.0 μL, 227 μmol) and 10% Pd/C (84.6 mg). The mixture was purged with H₂ six times and stirred for 84 h at ambient temperature under 1 atmosphere of H₂. The catalyst was filtered off, and the filtrate was concentrated. The residue was dissolved in H₂O, and washed with AcOEt. The aqueous layer was concentrated to give tetrasaccharide **22** (13.2 mg, 19 μmol, 85%). [α]_D²³ = −104.0 (*c* 0.45, MeOH); ¹H NMR (500 MHz, D₂O) δ 4.83 (d, 1 H, *J* = 1.5 Hz), 4.72 (s, 1 H), 4.71 (s, 1 H), 4.55 (d, 1 H, *J* = 1.5 Hz), 4.13 (d, 1 H, *J* = 1.8 Hz), 3.94–3.83 (m, 5 H), 3.78 (dd, 1 H, *J* = 2.0, 4.0 Hz), 3.71–3.47 (m, 13 H), 3.30 (dd, 1 H, *J* = 3.0, 9.5 Hz), 3.26–3.24 (m, 4 H), 1.22 (d, 3 H, *J* = 6.0 Hz), 1.18 (d, 3 H, *J* = 6.0 Hz); ¹³C NMR (125 MHz, D₂O) δ 100.98 (*J*_{C1–H1} = 172.1 Hz), 100.86 (*J*_{C1–H1} = 161.5 Hz), 100.78 (*J*_{C1–H1} = 161.3 Hz), 96.3 (*J*_{C1–H1} = 173.0 Hz), 79.5, 79.2, 77.1, 76.2, 76.1, 73.4, 72.5, 70.8, 70.6, 70.5, 70.4, 68.3, 67.7, 67.3, 66.4, 66.2, 62.2, 54.9, 17.1; ESI-HRMS *m/z*: calcd for C₂₇H₄₈O₂₁Na, 731.2586 [M+Na⁺]; Found C₂₇H₄₈O₂₁Na, 731.2585.

Methyl 2,7-di-O-benzyl-4,6-O-benzylidene-D-glycero-β-D-manno-heptopyranosyl-(1→4)-2,3-O-(diphenylmethylene)-α-L-rhamnopyranosyl-(1→3)-2,7-di-O-benzyl-4,6-O-benzylidene-D-glycero-β-D-manno-heptopyranosyl-(1→4)-2,3-O-(diphenylmethylene)-α-L-rhamnopyranoside (23)—To a mixture of tetrasaccharide **21** (180.1 mg, 106 μmol) in 15/3/5 CH₂Cl₂/H₂O/phosphate buffer (pH = 7.4) (15/3/5) (9.2 mL) was added DDQ (38.6 mg, 170 μmol). The mixture was

stirred for 2.5 h at ambient temperature under N₂, before another portion of DDQ (34.5 mg, 152 μmol) was added. After the mixture was stirred for another 2 h, it was diluted with CH₂Cl₂, and washed with saturated aqueous NaHCO₃ and brine. The collected organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography to furnish alcohol **23** (123.6 mg, 79 μmol, 74%) as white foam. $[\alpha]_D^{23} = -96.5$ (*c* 0.71, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.53-7.45 (m, 10 H), 7.40-7.02 (m, 40 H), 5.59 (s, 1 H), 5.58 (s, 1 H), 5.07 (s, 1 H), 5.02 (s, 1 H), 4.85 (d, 1 H, *J* = 12.0 Hz), 4.84 (d, 1 H, *J* = 12.0 Hz), 4.68 (d, 1 H, *J* = 12.0 Hz), 4.53-4.44 (m, 7 H), 4.41 (dd, 1 H, *J* = 5.5, 7.5 Hz), 4.35 (dd, 1 H, *J* = 5.5, 7.0 Hz), 4.09-3.99 (m, 5 H), 3.95 (t, 1 H, *J* = 10.0 Hz), 3.92-3.88 (m, 2 H), 3.83 (dd, 1 H, *J* = 3.5, 10.5 Hz), 3.81-3.64 (m, 4 H), 3.60-3.56 (m, 2 H), 3.52 (d, 1 H, *J* = 9.0), 3.44 (dd, 1 H, *J* = 1.5, 11.0 Hz), 3.41 (s, 3 H), 3.37-3.26 (m, 4 H), 2.67 (t, 1 H, *J* = 9.5 Hz), 2.44 (t, 1 H, 9.5 Hz), 2.30 (d, 1 H, *J* = 9.0 Hz, *OH*), 1.23 (d, 1 H, *J* = 6.5 Hz), 1.03 (d, 1 H, *J* = 6.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 143.23, 143.19, 143.15, 143.13, 138.5, 138.4, 138.3, 138.1, 137.6, 129.2, 129.1, 128.8, 128.7, 128.62, 128.59, 128.56, 128.52, 128.49, 128.45, 128.41, 128.2, 128.1, 128.0, 127.94, 27.89, 126.7, 126.5, 126.4, 126.3, 126.0, 109.6, 109.4, 102.6, 102.2, 101.6, 98.1, 93.9, 81.1, 80.2, 79.2, 79.1, 79.03, 78.96, 78.6, 78.0, 76.6, 76.4, 75.6, 75.3, 74.9, 73.9, 73.8, 73.64, 73.60, 71.0, 69.7, 69.4, 69.1, 68.4, 64.9, 64.6, 55.3, 17.9, 17.6; ESI-HRMS *m/z*: calcd for C₉₅H₉₆O₂₁Na, 1595.6342 [M+Na⁺]; Found 1595.6427.

Methyl 2,7-di-O-benzyl-4,6-O-benzylindene-3-O-naphthalenylmethyl)-D-glycero-β-D-manno-heptopyranosyl-(1→4)-2,3-O-(diphenylmethylene)-α-L-rhamnopyranosyl-(1→3)-2,7-di-O-benzyl-4,6-O-benzylindene-D-glycero-β-D-manno-heptopyranosyl-(1→4)-2,3-O-(diphenylmethylene)-α-L-rhamnopyranosyl-(1→3)-2,7-di-O-benzyl-4,6-O-benzylindene-D-glycero-β-D-manno-heptopyranosyl-(1→4)-2,3-O-(diphenylmethylene)-α-L-rhamnopyranoside (24)—A solution of thioglycoside **20** (106.2 mg, 104 μmol) and alcohol **23** (121.6 mg, 77 μmol) in CH₂Cl₂ (8 mL) was stirred for 30 min in the presence of 4 Å molecular sieves at ambient temperature under N₂ before it was cooled to -15 °C, and treated with NIS (29.9 mg, 133 μmol) and AgOTf (27.4 mg, 106 μmol). The resulting mixture was stirred for 1.5 h while the temperature was increased to 10 °C. The solid was filtered off, and the filtrate was washed with saturated aqueous Na₂S₂O₃ containing NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/PhCH₃ = 1/18) to afford hexasaccharide **24** (124.2 mg, 50 μmol, 64%). $[\alpha]_D^{23} = -92.0$ (*c* 0.44, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.80-7.75 (m, 3 H), 7.68-7.66 (m, 1 H), 7.57-7.09 (m, 76 H), 6.93 (t, 2 H, *J* = 8.0 Hz), 5.69 (s, 1 H), 5.58 (s, 1 H), 5.07 (s, 1 H), 5.01 (s, 1 H), 4.88-4.81 (m, 3 H), 4.76-4.62 (m, 5 H), 4.55-4.42 (m, 8 H), 4.38-4.34 (m, 3 H), 4.30-4.26 (m, 3 H), 4.15-4.01 (m, 7 H), 3.98-3.82 (m, 8 H), 3.74-3.65 (m, 2 H), 3.51-3.33 (m, 9 H), 3.30-3.25 (m, 3 H), 3.18 (dd, 1 H, *J* = 7.5, 10.0 Hz), 2.67 (t, 1 H, *J* = 9.5 Hz), 2.48 (t, 1 H, *J* = 9.0 Hz), 2.42 (t, 1 H, *J* = 9.5 Hz), 1.23 (d, 3 H, *J* = 6.5 Hz), 1.04 (d, 3 H, *J* = 6.5 Hz), 1.00 (d, 3 H, *J* = 6.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 143.22, 143.18, 143.12, 143.08, 138.6, 138.5, 138.4, 138.06, 137.98, 137.8, 137.63, 137.60, 136.1, 133.5, 133.2, 129.2, 129.1, 129.0, 128.7, 128.65, 128.60, 128.53, 128.5, 128.45, 128.41, 128.4, 128.33, 128.30, 128.27, 128.2, 128.1, 128.0, 127.9, 127.86, 127.84, 126.6, 126.5, 126.4, 126.3, 126.04, 125.98, 125.83, 125.79, 109.6, 109.5, 109.3, 102.6, 102.5, 102.4, 101.7, 101.6, 101.1, 98.1 (*J*_{C1-H1} = 169.5 Hz), 93.86 (*J*_{C1-H1} = 168.5 Hz), 93.79 (*J*_{C1-H1} = 167.0 Hz), 81.2, 80.5, 80.3, 79.2, 79.1, 79.0, 78.9, 77.9, 77.7, 76.6, 76.5, 76.4, 75.6, 75.1, 74.9, 74.5, 74.3, 73.9, 73.8, 73.7, 73.65, 73.62, 73.55, 72.9, 72.2, 69.7, 69.6, 69.4, 69.2, 69.1, 68.8, 64.9, 64.6, 55.3, 17.9, 17.5; ESI-HRMS *m/z*: calcd for C₁₅₃H₁₅₀O₃₁Na, 2506.0059 [M+Na⁺]; Found 2506.0273.

Methyl D-glycero-β-D-manno-heptopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-D-glycero-β-D-manno-heptopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-D-glycero-β-D-manno-heptopyranosyl-(1→4)-α-L-rhamnopyranoside (25)

—To a solution of hexasaccharide **24** (58.3 mg, 23 μ mol) in 3/1 MeOH/THF (6 mL) was added AcOH (100 μ L, 1.7 mmol) and 10% Pd/C (100 mg). The mixture was purged with H₂ six times, and stirred for 24 h under H₂ at 50 psi. The solid was filtered off, and the filtrate was concentrated to dryness. The resulting residue was dissolved in water, and washed with CHCl₃ (5 mL $\times$ 3). The aqueous phase was concentrated under reduced pressure, and dried under vacuum to afford hexamer **25** (14.9 mg, 14 μ mol, 60%). $[\alpha]_D^{23} = -84.6$ (*c* 0.71, H₂O); ¹H NMR (500 MHz, D₂O, 330 K, referenced to an external standard sodium 3-trimethylsilyl-(2,2,3,3-²H) propionate (δ = 0.00) in D₂O) δ 4.96 (s, 2 H), 4.84 (s, 2 H), 4.83 (s, 1 H), 4.68 (s, 1 H), 4.24 (br. s, 2 H), 4.05-3.96 (m, 8 H), 3.92-3.90 (m, 1 H), 3.83-3.60 (m, 19 H), 3.44-3.41 (m, 2 H), 3.38-3.35 (m, 4 H), 1.33 (d, 3 H, *J* = 6.5 Hz), 1.31 (d, 6 H, *J* = 6.5 Hz); ¹³C NMR (125 MHz, D₂O, 330 K, referenced to an external standard 1,4-dioxane (δ = 67.40) in D₂O) δ 101.63 (*J*_{C1-H1} = 174.5 Hz), 101.48 (*J*_{C1-H1} = 160.5 Hz), 101.36 (*J*_{C1-H1} = 161.4 Hz), 97.09 (*J*_{C1-H1} = 170.2 Hz), 80.27, 80.10, 77.99, 76.84, 76.71, 74.08, 73.29, 73.25, 71.52, 71.28, 71.17, 69.10, 68.34, 67.92, 67.29, 67.14, 63.03, 62.98, 55.59, 17.78; ESI-HRMS *m/z*: calcd for C₄₀H₇₀O₃₁Na, 1069.3799 [M+Na⁺]; Found 1069.3762; calcd for C₄₀H₇₀O₃₁Na₂, 546.1848 [M+2Na²⁺], Found, 546.1837.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the NIH (GM57335) for support of this work.

References

1. (a) Kosma P, Wugeditsch T, Christian R, Zayni S, Messner P. *Glycobiology* 1995;5:791–796. [PubMed: 8720077] (b) Kosma P, Wugeditsch T, Christian R, Zayni S, Messner P. *Glycobiology* 1996;6:5–5.
2. Crich D, Banerjee A. *Org. Lett* 2005;7:1935–1938. [PubMed: 15876023]
3. Crich D, Banerjee A. *J. Am. Chem. Soc* 2006;128:8078–8086. [PubMed: 16771524]
4. For reviews expounding the difficulties of β -mannoside synthesis and presenting classical and indirect solutions to the problem see (a) Barresi, F.; Hindsgaul, O. *Modern Methods in Carbohydrate Synthesis*. Khan, SH.; O'Neill, RA., editors. Amsterdam: Harwood Academic Publishers; 1996. p. 251-276. (b) Demchenko AV. *Synlett* 2003:1225–1240. (c) Pozsgay, V. *Carbohydrates in Chemistry and Biology*. Ernst, B.; Hart, GW.; Sinaý, P., editors. Vol. 1. Weinheim: Wiley-VCH; 2000. p. 319-343. (d) Gridley JJ, Osborn HMI. *J. Chem. Soc., Perkin Trans.1* 2000:1471–1491. (e) Ito, Y.; Ohnishi, Y. *Glycoscience: Chemistry and Chemical Biology*. Fraser-Reid, B.; Tatsuta, K.; Thiem, J., editors. Vol. 2. Springer; 2001. p. 1589-1619.
5. For the direct approach to β -mannopyranoside synthesis and its mechanism see (a) Crich D, Sun S. *J. Org. Chem* 1997;62:1198–1199. (b) Crich D, Sun S. *Tetrahedron* 1998;54:8321–8348. (c) Crich D, Smith M. *J. Am. Chem. Soc* 2001;123:9015–9020. [PubMed: 11552809] (d) Crich D, Banerjee A, Li W, Yao Q. *J. Carbohydr. Chem.* 2005 24:415–424. (e) Crich D, Sun S. *J. Am. Chem. Soc* 1997;119:11217–11223. (f) Crich D, Chandrasekera NS. *Angew. Chem. Int. Ed* 2004;43:5386–5389. (g) Jensen HH, Nordstrom M, Bols M. *J. Am. Chem. Soc* 2004;126:9205–9213. [PubMed: 15281809]
6. Jaipuri FA, Collet BYM, Pohl NL. *Angew Chem. Int. Ed* 2008;47:1707–1710.
7. Ley SV, Baeschlin DK, Dixon DJ, Foster AC, Ince SJ, Priepke HWM, Reynolds DJ. *Chem. Rev* 2001;101:53–80. [PubMed: 11712194]
8. Crich D, Cai W, Dai Z. *J. Org. Chem* 2000;65:1291–1297. [PubMed: 10814088]
9. Regioselective monobenzoylation of the 2-methoxyphenyl thioglycoside analog of Ley SV, Humphries AC, Eick H, Downham R, Ross AR, Boyce RJ, Pavey JBJ, Pietruszka J. *J. Chem. Soc., Perkin Trans 1* 1998:3907–3912.

10. The regioselectivity of the benzylation reaction was assigned according to the work of Ley with a direct analog,⁹ and was confirmed by the subsequent reaction sequence
11. Shi M, Shen Y-MJ. *J. Chem. Res. (S)* 2002:422–427.
12. The stereochemistry of diols **6** and **8** can be determined based on comparison of the double doublet representing H5 with literature values. Thus, the *L,D*-series (**8**) has a the smaller $^3J_{5,6}$ of 2.0 Hz when compared to the $^3J_{5,6}$ coupling of 6.0 Hz observed in the *D,D*-series (**6**). In addition the 6- and 7-OH signals for **6** resonate downfield (δ 3.16 and 2.20, respectively) relative to those for **8** (δ 2.66 and 1.85, respectively) Read JA, Ahmed RA, Tanner ME. *Org. Lett* 2005;7:2457–2460. [PubMed: 15932222]
13. (a) Denmark SE, Cottell JJ. *J. Org. Chem* 2001;66:4276–4284. [PubMed: 11397164] (b) Guzlek H, Graziani A, Kosma P. *Carbohydr. Res* 2005;340:2808–2811. [PubMed: 16263101] (c) Dong L, Roosenberg JM, Miller MJ. *J. Am. Chem. Soc* 2002;124:15001–15005. [PubMed: 12475343] (d) Gurjar MK, Talukdar A. *Tetrahedron* 2004;60:3267–3271.
14. (a) Kaldor SW, Hammond M. *Tetrahedron Lett* 1991;32:5043–5046. (b) Aucagne V, Tatibouet A, Rollin P. *Tetrahedron* 2004;60:1817–1826.
15. (a) David S, Hanessian S. *Tetrahedron* 1985;41:643–663. (b) David, S. *Preparative Carbohydrate Chemistry*. Hanessian, S., editor. New York: Dekker; 1997. p. 69–86.
16. (a) Mitsunobu O. *Synthesis* 1981:1–28. (b) Hughes DL. *Org. React* 1992;42:335–656. (c) Martin SF, Dodge JA. *Tetrahedron Lett* 1991;32:3017–3020.
17. Adapted from (a) Crich D, Vinogradova O. *J. Am. Chem. Soc* 2007;129:11756–11765. [PubMed: 17725351] (b) Lattrell R, Lohaus G. *Liebigs Ann. Chem* 1974:901–920. (c) Moriarty RM, Zhuang H, Penmasta R, Liu K, Awasthi AK, Tuladhar SM, Rao MSC, Singh VK. *Tetrahedron Lett* 1993;34:8029–8032. (d) Binkley RWJ. *Org. Chem* 1991;56:3892–3896. (e) Binkley RWJ. *Carbohydr. Chem* 1994;13:111–123. (f) Dong H, Pei Z, Ramstroem O. *J. Org. Chem* 2006;71:3306–3309. [PubMed: 16599637] (g) Albert R, Dax K, Link RW, Stuetz AE. *Carbohydr. Res* 1983;118:C5–C6.
18. (a) Xia J, Abbas SA, Locke RD, Piskorz CF, L AJ, Matta KL. *Tetrahedron Lett* 2000;41:169–173. (b) Liao W, D LR, Matta KL. *Chem. Commun* 2000:369–370. (c) Csávas, M.; Szabó, ZB.; Borbás, A.; Lipták, A. *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis*. Crich, D., editor. Chichester: Wiley; 2005. p. 459–460.
19. (a) Borbás A, Hajkó J, Kajtár-Peredy M, Lipták A, Lipták A. *J. Carbohydr. Chem* 1993;12:191–200. (b) Borbás A. *Carbohydr. Res* 1993;241:99. [PubMed: 8472263] 116 (c) Hajkó J, Borbás A, Szabovik G, Kajtár-Peredy M, Lipták A. *J. Carbohydr. Chem* 1997;16:1123–1144.
20. Crich D, Cai F, Yang F. *Carbohydr. Res* 2008;343:1858–1862. [PubMed: 18374318]
21. Crich D, Sun S. *J. Am. Chem. Soc* 1998;120:435–436.
22. (a) Bock K, Pedersen C. *J. Chem. Soc., Perkin Trans. 2* 1974:293–297. (b) Tvaroska I, Taravel FR. *Adv. Carbohydr. Chem. Biochem* 1995;51:15–61. [PubMed: 7484362] (c) Duus JO, Godfredsen CH, Bock K. *Chem. Rev* 2000;100:4589–4614. [PubMed: 11749359]
23. Tatsuta K, Akimoto K, Annaka M, Ohno Y, Kinoshita M. *Bull. Chem. Soc. Jpn* 1985;58:1699–1706.
24. Iurre J, Alonso-Alija C. *Tetrahedron: Asymmetry* 1992;3:1591–1596.
25. Groneberg RD, Miyazaki T, Stylianides NA, Schulze TJ, Stahl W, Schreiner EP, Suzuki T, Iwabuchi Y, Smith AL, Nicolaou KC. *J. Am. Chem. Soc* 1993;117:7593–7611.

Scheme 1.
Improved homologation procedure

Scheme 2.
 Synthesis of Heptosyl Donor **13**

Scheme 3.
Rhamnosyl Acceptor Preparation

Scheme 4.
Upstream Disaccharide Synthesis

Scheme 5.
Disaccharide Donor Synthesis.

Scheme 6.
Tetrasaccharide Synthesis

21: R = Nap
23: R = H, 74%
DDQ, CH₂Cl₂, pH 7.4 buffer

Scheme 7.
Hexasaccharide Synthesis

Table 1

Osmoylation of Alkene 4

Entry	Oxidant/ligand	Solvent	T/ $^{\circ}$ C	6/8 (yield)	7/9 (yield)
1	OsO ₄ /NMO	Acetone/H ₂ O	22	2.2/1 (86%)	1.2/1 (8.4%)
2	AD- β -mix	<i>t</i> -BuOH/H ₂ O	22	1/1.2 (97%)	not detected
3	AD- α -mix	<i>t</i> -BuOH/H ₂ O	0	1.2/1 (93%)	not detected
4	K ₃ Fe(CN) ₆ /OsO ₄ /(DHQD) ₂ Pry	<i>t</i> -BuOH/H ₂ O	22	1.5/1 (96%)	not detected
5	K ₃ Fe(CN) ₆ /OsO ₄ /(DHQD) ₂ Pry	<i>t</i> -BuOH/H ₂ O/PhCH ₃	0	2.5/1 (96%)	not detected