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Cascade In Situ Phosphorylation and One-Pot Glycosylation for Rapid Synthesis of Heptose-Containing Oligosaccharides

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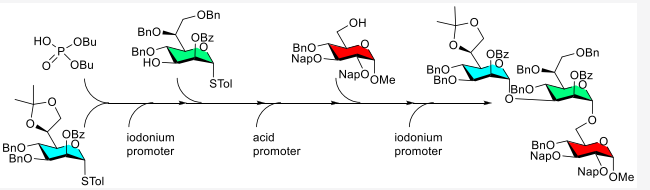
ABSTRACT: We report a one-pot glycosylation strategy for achieving rapid syntheses of heptose (Hep)-containing oligosaccharides. The reported procedure was designed to incorporate an in situ phosphorylation step into an orthogonal one-pot glycosylation. Hep-containing oligosaccharides were assembled directly from building blocks with minimal effort expended on manipulation of protecting and aglycone leaving groups. The utility of our one-pot procedure was illustrated by synthesizing partial core oligosaccharide structure present in the lipopolysaccharide of *Ralstonia solanacearum*.



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INTRODUCTION

A unique feature of bacterial inner core oligosaccharides is the presence of higher carbon sugars.[1,2] Typical examples include L-/D-*glycero*-D-*manno*-heptopyranoses (L,D- or D,D-Hep), 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo), and D-*glycero*-D-*talo*-oct-2-ulosonic acid (Ko).[3] Because the higher carbon sugars are absent in mammalian glycans, the bacterial inner core oligosaccharides and related structures are potential antigen candidates for development of vaccines and diagnostic agents.[4−7] Structurally defined core oligosaccharide samples are required for immunological studies, and an efficient glycosylation method for higher carbon sugars is therefore highly desired.

Despite the advances in glycosylation methods for synthesis of mammalian glycans, synthesizing a bacterial inner core oligosaccharide target remains a nontrivial and challenging task.[8−14] A major challenge in the synthesis is the unavailability of Hep sugars, which have to be prepared from monosaccharide precursors[15,16] or by de novo synthesis from achiral compounds.[17] In most cases, the acquired Hep sugars have to be further modified prior to glycosylation. Such lengthy processes constitute a barrier for development of new glycosylation methods. As a consequence, the bacterial inner core oligosaccharides are still prepared by the less effective stepwise glycosylation.[5,18−23]

Because of the biological relevance and potential utility of inner-core oligosaccharides, a straightforward one-pot glycosylation method that involves (i) minimal protecting group modification, (ii) a single type of glycosylation building block, and (iii) no iterative adjustments of the reaction temperature is needed. However, such prerequisites are difficult to achieve with classical reactivity-based,[24−28] orthogonal glycosylation,[29−33] and preactivation one-pot glycosylation methods.[34−36]

In the syntheses of heparin-based idraparinux[32] and SSEA-4 hexasaccharide,[33] glycosyl phosphates have been used as donors for glycosylation of thioglycosyl acceptors (Figure 1a). Such phosphate donors have to be prepared from thioglycoside precursors in separate reactions. We realized that if the conditions for phosphorylation are compatible with those for phosphate activation, these reaction steps could, in theory, be merged to give a cascade one-pot procedure (Figure 1b). Such a protocol would enable the coupling of two thioglycosyl building blocks with no concern regarding differences between their reactivities and no need to prepare the phosphate building block in a separate reaction.

RESULTS AND DISCUSSION

At first, the feasibility of the proposed cascade one-pot reaction was investigated by performing a model study with thiomannosyl building blocks **1** and **2** and methyl mannoside acceptor **3** (Scheme 1a). Building block **2** was derived from a known thiomannoside via standard protecting group manipulation, while building blocks **1** and **3** were known compounds.[37,38]

In the model cascade one-pot reaction, thiomannoside **1** (1.2 equiv) was phosphorylated by treatment with dibutyl phosphate (1.3 equiv), *N*-iodosuccinimide (NIS; 1.2 equiv),

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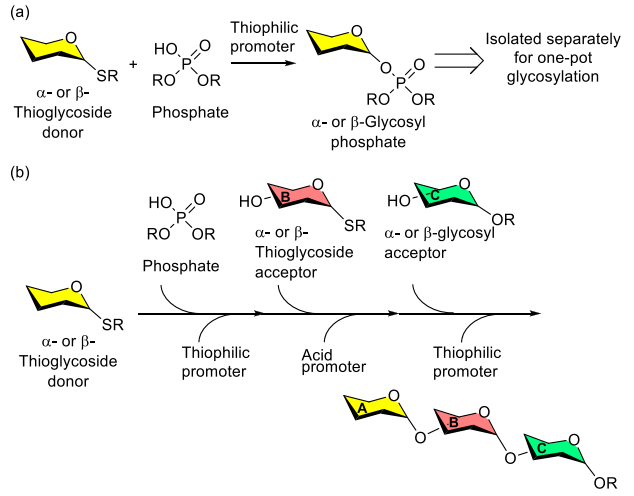
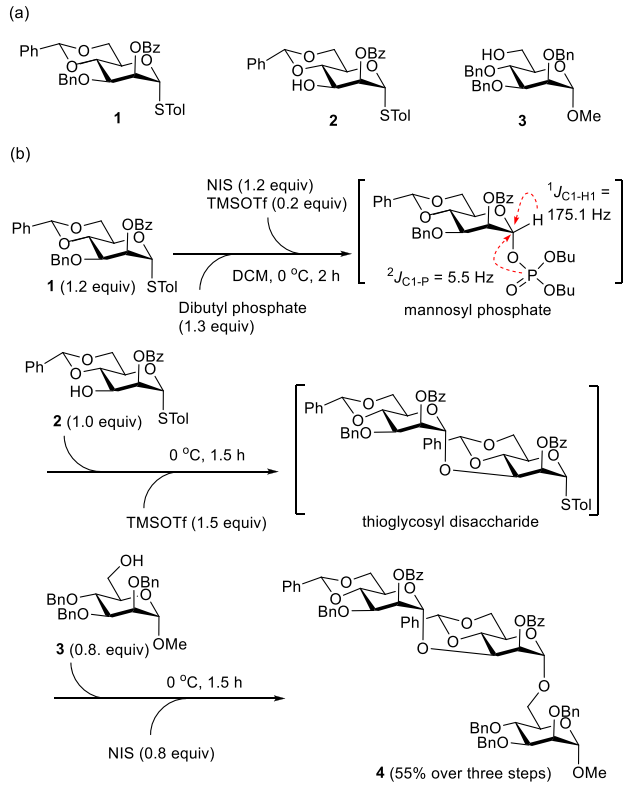


Figure 1. (a) Preparation of phosphate donor for one-pot reaction. (b) Cascade in situ phosphorylation and one-pot glycosylation procedure.

Scheme 1. (a) Mannosyl Building Blocks 1−3. (b) Validation of the Cascade Phosphorylation and One-Pot Glycosylation Procedure



and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf; 0.2 equiv) according to the procedure reported in the literature (Scheme 1b).[32,33,39] The phosphorylation worked well at 0 °C to give a phosphate adduct, which was detected by TLC. Next, thiomannoside acceptor **2** (1 equiv) and TMSOTf (1.5 equiv) were added to the reaction mixture to trigger the first glycosylation. Glycosylation of **2** with the phosphate adduct was complete within 1.5 h, and a disaccharide thioglycoside was obtained cleanly. Without isolation, the thioglycoside was subjected to a second glycosylation by iterative treatment with reducing-end acceptor **3** (0.8 equiv) and a supplementary dose of NIS (0.8 equiv). The acid byproduct produced in the first glycosylation also participated in activation of the NIS promoter; therefore, no supplementary dose of TMSOTf was required in the second glycosylation. After glycosylation for an additional 1.5 h, the desired trisaccharide **4** was obtained in 55% yield over one phosphorylation and two glycosylation steps.

After validation of the cascade one-pot procedure, its applicability to Hep building blocks was examined. In this regard, the non-natural trisaccharide **5** was employed as the synthetic target, which could be assembled from L,D-Hep thioglycoside donor **6**, L,D-Hep thioglycoside acceptor **7**, and reducing-end glucosyl acceptor **8** (Scheme 2a). Acceptor **8** is a known compound and is derived from methyl *α*-glucoside.[40]

L,D-Hep thioglycoside **6** was synthesized from a known thiomannoside **9** (Scheme 2b).[41] Dibutyltin oxide (Bu_2SnO) mediated benzylation of **9** afforded a 3-*O*-Bn-protected thiomannoside, which was subsequently alkylated with 2-naphthylmetyhyl bromide to give 2-*O*-Nap-3-*O*-Bn-protected thiomannoside **10**. The structure of **10** was confirmed by 1D and 2D NMR spectroscopy with the anomeric proton and carbon signals found at 5.43 and 87.8 ppm, respectively (see 2D NMR spectra in the SI). Reductive cleavage of **10** with borane (BH_3)−THF and TMSOTf afforded thiomannoside intermediate **11**.[42] Iodoxybenzoic acid (IBx) oxidation of **11** followed by methoxymethyl (MOM) Wittig olefination and acid hydrolysis furnished the 1,7-dialdo substrate **12**. L-Proline (L-Pro)-catalyzed aminoxylation of **12** allowed the procurement of the key 6-(anilinyl)oxy-L,D-Hep substrate with nearly perfect L-*glycero* selectivity.[16] Cleavage of the N−O bond at the 6-(anilinyl)oxy-substituted substrate was performed with nitrosobenzene (PhNO) as the cleaving agent;[43] this was found to be more effective than the commonly used $CuSO_4$.[16,44] As such, L,D-Hep diol **13** was obtained from **12** in 40% overall yield over three steps. The structure of diol **13** was supported by the 2D NMR spectroscopy; whereas, the correlation signals between the hydroxyl protons and the protons at C6 and C7 positions were clearly identified in the COSY spectrum (SI). Further elaboration of diol **13** gave the designated L,D-Hep building block **6** over three steps, which included the (i) acetonide protection at the C6 and C7 hydroxyls, (ii) cleavage of the Nap protecting group at C2, and (iii) reprotection of the C2 hydroxyl with benzoyl chloride (BzCl).

The L,D-Hep building block **7** was prepared from Hep thioglycoside **15** (Scheme 2c).[16] Benzylation of the C6 and C7 hydroxyls of **15** and subsequent removal of the isopropylidene group afforded Hep 2,3-diol **16**. Conversion of diol **16** to the designated building block **7** involved orthogonal ester formation and acid hydrolysis. The structure of building block **7** was characterized with 1D and 2D NMR spectroscopy. The proton signals at C6 and C7 positions were clearly identified at 4.20, 3.74, and 3.53 ppm in the COSY and HSQC spectra (SI).

With building blocks **6**−**8** in hand, we tackled the synthesis of trisaccharide **5** (Scheme 3). The L,D-Hep donor **6** was phosphorylated at −20 °C under NIS-promoted conditions to give a phosphate intermediate. Subsequent treatment of the adduct with L,D-Hep acceptor **7** and a stoichiometric amount of TMSOTf initiated the first glycosylation, which proceeded well at −20 °C to give an L,D-Hep disaccharide intermediate. After completion of the first glycosylation (ca. 3 h), the

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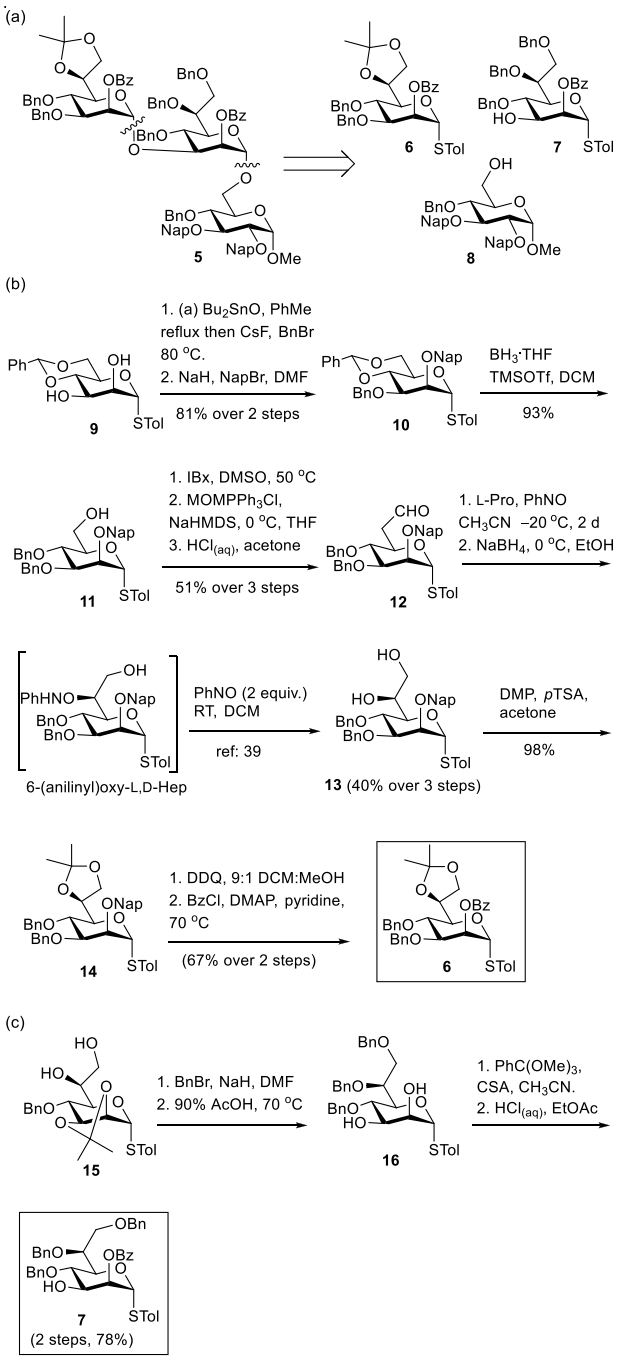
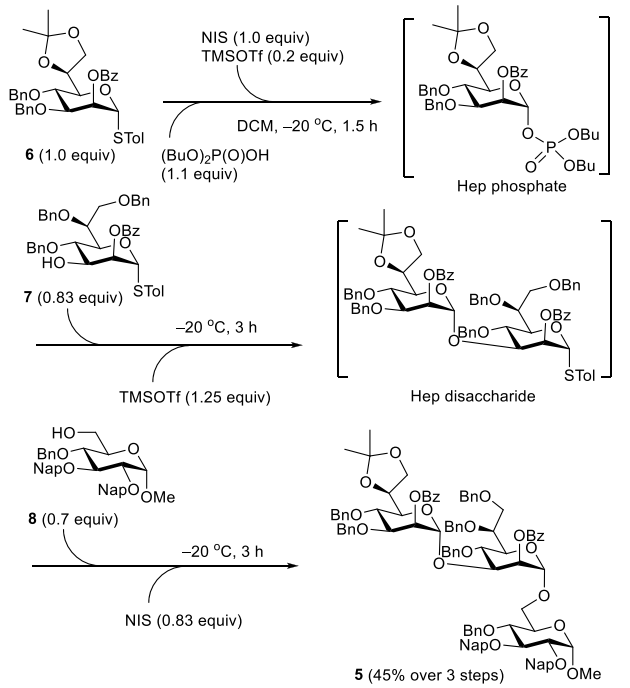
Scheme 2. (a) L,D-Hep-Containing Trisaccharide 5 and Its Constituent Building Blocks 6–8. (b) Preparation of L,D-Hep Building Block 6. (c) Preparation of L,D-Hep Building Block 7



Scheme 3. One-Pot Synthesis of L,D-Hep-Containing Trisaccharide 5 Using the Cascade in Situ Phosphorylation and One-Pot Glycosylation



reducing-end acceptor **8** and a supplementary dose of NIS were added to the mixture. As was the case in the cascade one-pot reaction shown in Scheme 1, no supplementary dose of TMSOTf was needed to initiate the second glycosylation. The target trisaccharide **5** was obtained in 45% yield over three steps.

The key to the cascade phosphorylation and one-pot glycosylation method is the in situ preparation of a phosphate intermediate. To confirm the presence of the intermediate, the mannosyl phosphate in Scheme 1 was isolated for NMR characterization. The presence of the phosphate leaving group was clearly indicated by the heteronuclear $^{2}J_{C1-P}$ coupling constant of 5.5 Hz. The α-anomeric configuration of the phosphate group was supported by the $^{1}J_{C1-H1}$ coupling constant of 175.1 Hz. The exclusive formation of the α-anomer is attributed to the Bz group at C2 position, which directs the formation of 1,2-*trans* glycosidic bond. As the Hep phosphate in Scheme 3 has the same stereodirecting group at C2, it is presumably an α-anomer without the need for NMR characterization.

Furthermore, one may question if the phosphate leaving group generated from the first glycosylation would engage with the oxacarbenium ion in the second glycosylation to form a phosphate intermediate. In practice, but no such a phosphate intermediate was observed in the one-pot reactions of Schemes 1 and 3. However, we do not exclude the possibility because the phosphate intermediate when formed might be immediately activated by an acid byproduct, which is also produced in the glycosylation. To ensure the complete activation of a possible phosphate intermediate, we applied a stoichiometric amount of TMSOTf and NIS in subsequent cascade one-pot reaction (see Scheme 4b).

The rapid synthesis of trisaccharide **5** motivated us to apply the cascade one-pot procedure for procurement of a bacterial inner core oligosaccharide. To this aim, the branched tetrasaccharide **17** was chosen as the synthetic target, which is the partial structure of the inner-core structure of the lipopolysaccharide (LPS) of *Ralstonia solanacearum* Toudk-2 (Figure 2).[45] Tetrasaccharide **17** consists of two L-rhamnose (Rha) units, which are attached to the 2- and 3-hydroxyls of a branching Hep residue and which is in turn connected to a reducing-end Hep at the C3 position. All the glycosidic bonds in the target have a 1,2-*trans* α-configuration.

Disconnection of target **17** gives known thiorhamnosyl donor **18**,[46] L,D-Hep thioglycosyl acceptor **16**, and reducing-end L,D-Hep acceptor **19**. The L,D-Hep thioglycosyl acceptor

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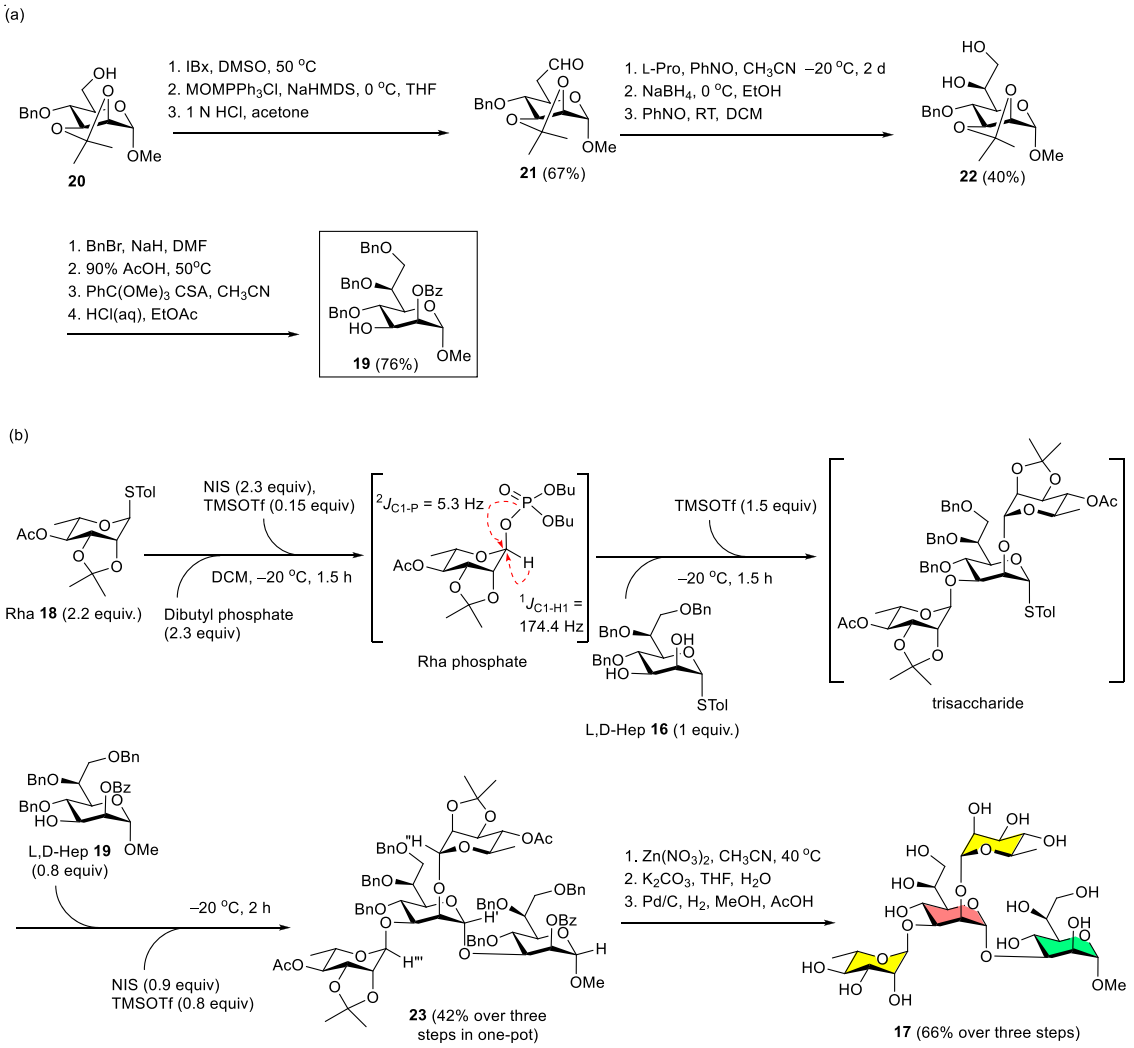
Scheme 4. (a) Preparation of L,D-Hep Building Block 19 from Methyl Mannoside 20. (b) One-Pot Synthesis of Partial Core Tetrasaccharide 17 of *R. solanacearum* LPS via the Cascade Phosphorylation and One-Pot Glycosylation Method



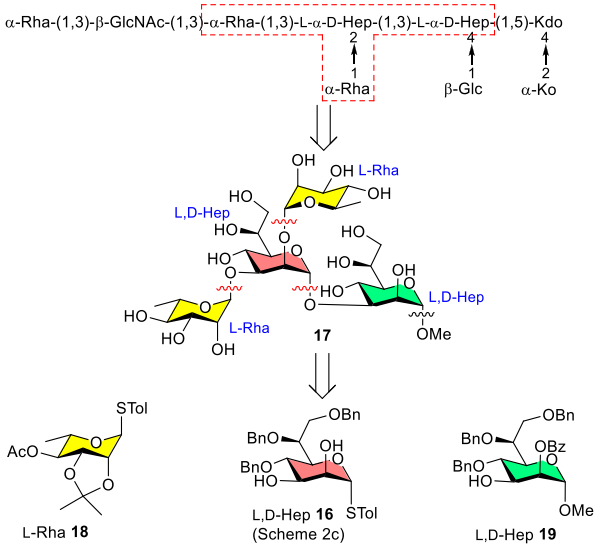


Figure 2. Inner core oligosaccharide of *R. solanacearum* LPS, partial core tetrasaccharide structure **17**, and building blocks **16**, **18**, and **19**.

16 was an advanced intermediate and was prepared as shown in Scheme 2c. The L,D-Hep acceptor **19** was derived from available methyl α-mannoside **20**.[47] Thus, IBx oxidation of **20** followed by MOM-Wittig olefination and acid hydrolysis obtained the Hep-1,7-dialdo intermediate **21** (Scheme 4a). Subsequent L-Pro-catalyzed aminoxylation of **21** followed by reduction and N−O bond cleavage furnished Hep-1,7-diol **22**.[48] Conversion of **22** to the desired Hep acceptor **19** was achieved by (i) benzylation of the C6 and C7 hydroxyls, (ii) deprotection of the isopropylidene acetal at C2 and C3, and (iii) orthoester formation and then acid hydrolysis. Similar to Hep building block **7** in Scheme 2c, Hep building block **19** was characterized with 1D and 2D NMR spectroscopy. From the COSY NMR spectrum, the correlation signal between the C3 hydroxyl and the proton at C3 position of the Hep scaffold was clearly identified in the COSY spectrum (see the SI).

Having prepared building blocks **16**, **18**, and **19**, we investigated the one-pot synthesis of tetrasaccharide **17** (Scheme 4b). First, thiorhamnoside **18** (2.2 equiv) was phosphorylated under NIS-promoted conditions to give a Rha phosphate intermediate. The Rha phosphate was in α-anomeric configuration as indicated by the $^{1}J_{C1-H1}$ coupling constant of 174.4 Hz and $^{2}J_{C1-P}$ coupling constant of 5.3 Hz

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(SI). Next, the branching Hep building block **16** (1 equiv) and a supplementary dose of TMSOTf (1.5 equiv) were added to trigger the first glycosylation, whereas two glycosidic bonds would be formed at the C2 and C3 hydroxyls of **16**. Despite the close proximity of these hydroxyl groups, the double glycosylation took place swiftly to give the desired trisaccharide product. Gladly, no undesired anomer or monoglycosylated product was detected in the reaction mixture. After completion of the first glycosylation (ca. 1.5 h), the reducing-end Hep acceptor **19** (0.8 equiv), a supplementary dose of NIS (0.9 equiv), and TMSOTf (0.8 equiv) were added to initiate the second glycosylation. With no adjustment of the reaction temperature, the glycosylation worked well to give the desired tetrasaccharide **23** as a single isomer in 42% yield over three steps.

The α-configurations of the glycosidic bonds in tetrasaccharide **23** are supported by the $^{2}J_{C-H}$ coupling constants (167.0−171.2 ppm) at the anomeric centers (Figure 3).[49] The

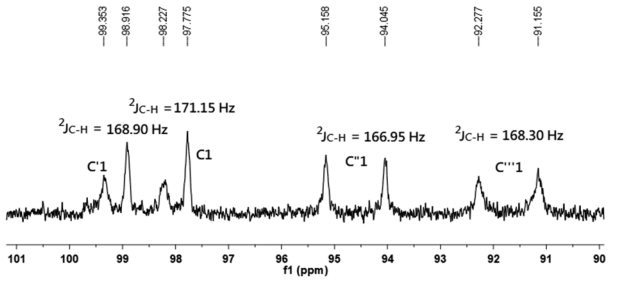

Figure 3. Partial nondecoupling ^{13}C NMR spectrum of protected tetrasaccharide **23**.

α-selectivity of isopropylidene-protected L-Rha donor **18** is attributed to the conformation restrained isopropylidene group at C2 and C3 positions. This has been reported in various glycosylation settings.[50,51] The α-selectivity of the trisaccharide intermediate is likely related to the presence of two Rha residues, which shield the β-face of the heptose from attack of the acceptor. Global deprotection of **23** was accomplished by (i) hydrolytic removal of the acetal and ester protecting groups and (ii) Pd-catalyzed hydrogenolysis. As such, inner core tetrasaccharide **17** was obtained from known mannoside building block **20** in 6.4% yield over 14 linear steps. To the best of our knowledge, this is the first example of a one-pot synthesis of a Hep-containing inner core oligosaccharide.

Tetrasaccharide **17** was characterized with 1D and 2D NMR spectroscopy. The anomeric proton and carbon signals of the sugar residues could be clearly assigned on the base of the COSY, HSQC, and HMBC correlation studies (see 2D spectra in the SI). A unique feature of the ^{1}H NMR spectrum of **17** is the relative downfield shift of H2′ (at 4.13 ppm) and H3′ (at ~3.92 ppm) proton signals of the branching Hep unit (SI). This should be attributed to the substitution of the rhamnose at the C2′ and C3′ positions. The glycosidic linkages between the rhamnose and the Hep were confirmed by the HMBC correlation signals between the anomeric protons of the rhamnose substituents (H1′′ and H1′′′) and the C2′ and C3′ carbons of the Hep residue (Figure 4).

CONCLUSION

In summary, we have developed a cascade phosphorylation and one-pot glycosylation procedure for the synthesis of heptose-containing oligosaccharides The cascade procedure combines

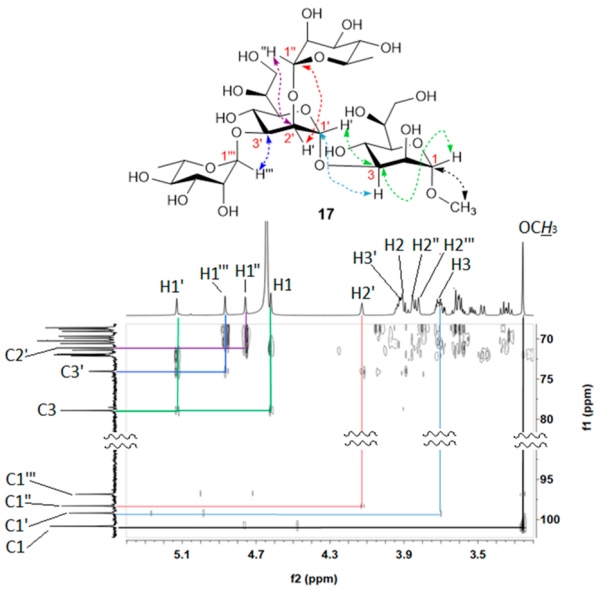

Figure 4. Partial HMBC correlation spectrum of inner core tetrasaccharide **17**.

an in situ phosphorylation step with an orthogonal one-pot reaction. The new procedure streamlines the classical orthogonal one-pot glycosylation and also avoids loss of the phosphate intermediate during purification. The utility of the method was shown by a one-pot synthesis of mannosyl trisaccharide **4**, Hep-containing trisaccharide **5**, and the protected inner-core tetrasaccharide structure **23** from the LPS of *Ralstonia solanacearum*. We believe that this new one-pot glycosylation procedure provides a valuable tool for rapid synthesis of heptose-containing oligosaccharides.

EXPERIMENTAL SECTION

General Experimental Procedures. All reagents were of commercial grade and used as received. All moisture-sensitive reactions were performed under nitrogen atmosphere. DCM used in the glycosylation reactions was predried with an aluminum oxide-based solvent drying system before used. Progress of the reaction was monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with an acidified solution of *p*-anisaldehyde in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ in 10% sulfuric acid (aq) followed by charring with a hot gun. The heat source for reactions requiring heating is an oil bath, and the temperature reported is the oil bath temperature. Column chromatography was carried out using silica gel (0.040−0.063 or 0.063−0.200 mm) from Silicycle. ^{1}H and ^{13}C spectra were recorded on a Varian 400 or 600 MHz in $CDCl_3$ or D_2O. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane as internal standard or the residual signal of the deuterated solvent. Coupling constants (J) are measured in hertz. NMR peak assignments were made using COSY and HSQC experiments, where applicable.

Preparation of Building Blocks 1−3. *Preparation of Tolyl 2-O-Benzoyl-3-O-benzyl-4,6-O-benzylidene-1-thio-α-D-mannopyranoside 1.* Thiomannopyranoside **1** is a known compound prepared as a colorless glassy solid (12.3 g, 39% over six steps) from D-mannose (10.0 g, 55 mmol) following the literature procedures.[37]

Preparation of Tolyl 2-O-Benzoyl-4,6-O-benzylidene-1-thio-α-D-mannopyranoside 2. To a mixture of known thiomannoside **9** (4.0 g, 10.7 mmol)[37] in CH_3CN (36 mL) were added CSA (0.25 g, 1.1 mmol) and $PhC(OMe)_3$ (2.9 mL, 16.1 mmol). The reaction mixture was stirred at rt for 1 h, and then the reaction was quenched with Et_3N. The solvent was removed by a rotary evaporator, and the resulting syrup was absorbed in 40 mL of EtOAc to which was added 2 N $HCl_{(aq)}$ (8.0 mL). The EtOAc/$HCl_{(aq)}$ mixture was stirred

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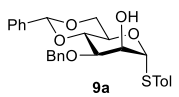
vigorously at rt for 10 min, and then the mixture was diluted with EtOAc (40 mL). The combined EtOAc solution was washed with satd $NaHCO_3$ (40 mL) and brine (40 mL), dried (over $MgSO_4$), and filtered, and the filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 6:1) to give thiomannoside **2** as a colorless glassy solid (4.4 g, 86% over two steps). Analytical data for **2**: R_f = 0.34 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ = +113.48 (*c* 0.022 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.3 Hz, 2H, ArH), 7.60−7.52 (m, 3H, ArH), 7.45 (t, *J* = 7.7 Hz, 2H, ArH), 7.38 (d, *J* = 7.3 Hz, 5H, ArH), 7.12 (d, *J* = 7.9 Hz, 2H, ArH), 5.69 (d, *J* = 2.5 Hz, 1H, H-2), 5.65 (s, 1H, benzylidene-CH), 5.53 (s, 1H, H-1), 4.47−4.40 (m, 1H, H-5), 4.35−4.30 (m, 1H, H-3), 4.27 (dd, *J* = 10.4, 4.9 Hz, 1H, H-6b), 4.10 (t, *J* = 9.6 Hz, 1H, H-4), 3.87 (t, *J* = 10.3 Hz, 1H, H-6a), 2.71 (d, *J* = 4.0 Hz, 1H, OH), 2.32 (s, 3H, SCH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8 (C═O), 138.3, 137.0, 133.4, 132.7, 130.0, 129.9, 129.8, 129.4, 129.3, 129.2, 128.4, 128.3, 126.3, 102.2 (benzylidene-CH), 87.3 (C-1), 79.5, 74.1 (C-2), 68.5, 67.9, 64.5, 21.1 (SCH_3); HRMS (ESI-TOF) (*m*/*z*) [M + H]$^+$ calcd for $C_{27}H_{27}O_6S$ 479.1523, found 479.1521.

Preparation of Methyl 2,3,4-Tri-O-benzyl-α-D-mannopyranoside ***3***. Methyl mannopyranoside **3** is a known compound prepared as a white amorphous solid (5.4 g, 58% over three steps) from methyl α-D-mannoside (4 g, 20 mmol) following the literature procedures.[38]

One-Pot Synthesis of Methyl 3-O-Benzyl-4,6-O-benzylidene-2-O-benzoyl-α-D-mannopyranosyl-(1,3)-4,6-O-benzylidene-2-O-benzoyl-α-D-mannopyranosyl-(1,6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside ***4***. To a mixture of thiomannoside **1** (130 mg, 0.23 mmol), activated 4 Å MS (0.43 g), and dibutylphosphate (49.6 μL, 0.25 mmol) in DCM (4.6 mL) were added NIS (51.7 mg, 0.23 mmol) and TMSOTf (8.33 μL, 0.046 mmol) at −20 °C. After the mixture was stirred at −20 °C for 2 h, thiomannoside acceptor **2** (91 mg, 0.19 mmol) and TMSOTf (52.5 μL, 0.29 mmol) were added, and the resulting mixture was stirred at 0 °C for 1.5 h. Then the reducing-end acceptor **3** (71 mg, 0.152 mmol) and NIS (34.2 mg, 0.152 mmol) were added. The mixture was stirred at 0 °C for an additional 1.5 h. The reaction was quenched with Et_3N (50 μL) and MS was removed by filtration. The filtrate was diluted with DCM (12 mL) and then washed with satd $Na_2S_2O_3$ (15 mL), satd $NaHCO_3$ (15 mL), and brine (15 mL). The organic phase was dried (over $MgSO_4$), filtered, and concentrated for column chromatography purification (elution: hexanes/EtOAc, 4:1) to give **4** as a light-yellow oily liquid (95 mg, 55% over three steps). Analytical data for **4**: R_f = 0.26 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ = −35.4 (*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.5 Hz, 2H, ArH), 8.05 (d, *J* = 7.5 Hz, 2H, ArH), 7.63−7.52 (m, 3H, ArH), 7.46 (dd, *J* = 15.8, 7.2 Hz, 9H, ArH), 7.35 (d, *J* = 7.6 Hz, 3H, ArH), 7.32 (s, 5H, ArH), 7.30 (d, *J* = 3.2 Hz, 5H, ArH), 7.28 (s, 2H, ArH), 7.24 (s, 4H, ArH), 7.16 (d, *J* = 3.3 Hz, 2H, ArH), 7.10 (d, *J* = 1.9 Hz, 3H, ArH), 5.70 (s, 1H, H-2″), 5.64 (s, 1H, H-2), 5.59 (s, 2H, H-1″, H-2′), 5.37 (s, 1H, H-1), 5.05 (s, 1H, H-1′), 4.97 (d, *J* = 11.1 Hz, 1H), 4.73 (s, 2H), 4.70 (s, 1H), 4.62−453 (m, 4H), 4.49−4.44 (m, 2H), 4.32−4.21 (m, 3H), 4.11 (t, *J* = 10 Hz, 1H), 4.04 (dd, *J* = 9.6, 4.5 Hz, 2H), 3.97 (dd, *J* = 9.6, 2.9 Hz, 1H), 3.91−3.86 (m, 3H), 3.84−3.77 (m, 5H), 3.32 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.4 (C═O), 165.3 (C═O), 138.31, 138.26, 138.2, 137.9, 137.5, 137.1, 133.3, 133.1, 129.8, 129.7, 129.6, 128.70, 128.66, 128.5, 128.32, 128.28, 128.2, 128.1, 128.04, 128.03, 127.95, 127.91, 127.85, 127.77, 127.61, 127.56, 127.5, 127.4, 127.35, 126.3, 125.9, 101.6 (C-1″), 101.2, 99.6 (C-1), 98.8, 98.3 (C-1′), 80.2, 79.3, 78.4, 74.9, 74.7, 74.1, 73.9, 72.6, 71.9, 71.6, 70.8, 70.0, 68.7, 68.6, 67.1, 64.5, 63.6, 54.7 (OCH_3); HRMS (ESI−TOF) (*m*/*z*) [M + Na]$^+$ calcd for $C_{75}H_{74}O_{18}Na$, 1285.4767, found, 1285.4717.

Preparation of Building Block 6. *Preparation of Tolyl 3-O-Benzyl-4,6-O-benzylidene-1-thio-α-D-mannopyranoside* ***9a***.



9a

To a solution of thiomannoside **9** (12.0 g, 32.1 mmol)[37] in toluene (236 mL) was added Bu_2SnO (8.1 g, 32.7 mmol). The reaction mixture was stirred under reflux with a Dean−Stark apparatus. After ca. 4 h, the mixture was cooled to rt followed by addition of CsF (5.0 g, 32.7 mmol), BnBr (4.0 mL, 33.7 mmol), and Bu_4NBr (11.0 g, 34.0 mmol). The reaction mixture was stirred at 100 °C for an additional 3 h then cooled to rt. The mixture was filtered over Celite to remove the salts, and the filtrate was concentrated by a rotary evaporator to give an oily syrup, which was absorbed in 150 mL of DCM. The DCM solution was washed with H_2O (100 mL) and brine (100 mL), dried (over $MgSO_4$), filtered, and concentrated for column chromatography purification (elution: hexanes/EtOAc, 4:1) to obtain thiomannoside **9a** (13.2 g, 92%) as a white glassy substance. Analytical data for thiomannoside **9a**: R_f = 0.38 (hexanes/EtOAc, 2:1); $[\alpha]_D^{25}$ = +195.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H, ArH), 7.40−7.29 (m, 10H, ArH), 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 5.60 (s, 1H), 5.50 (s, 1H, H-1), 4.87 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.34 (td, *J* = 9.6, 4.8 Hz, 1H, H-5), 4.24−4.23 (m, 1H, H-2), 4.22−4.14 (m, 2H, H-4, H-6a), 3.95 (dd, *J* = 9.6, 3.2 Hz, 1H, H-3), 3.83 (t, *J* = 10.2 Hz, 1H, H-6b), 2.95−2.94 (m, 1H), 2.31 (s, 3H, SCH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.2, 137.9, 137.6, 132.5, 130.1, 129.6, 129.1, 128.7, 128.4, 128.2, 128.1, 126.3, 101.8 (CHPh), 88.4 (CH, C-1), 79.2 (CH, C-4), 75.9 (CH, C-3), 73.4 (CH_2Ar), 71.5 (CH, C-2), 68.7 (CH_2, C-6), 64.7 (CH, C-5), 21.3 (SCH_3); HRMS (ESI-TOF) (*m*/*z*) [M + Na]$^+$ calcd for $C_{27}H_{28}O_5SNa$ 487.1550, found 487.1565.

Preparation of Tolyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside ***10***. To a solution of thiomannoside **9a** and NapBr in DMF (112 mL) was added NaH (1.7 g, 42.2 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was stirred at rt for an additional 2.5 h. The reaction was quenched by addition of satd NH_4Cl (10 mL) then diluted with DCM (120 mL). The DCM solution was washed with H_2O (90 mL) and brine (100 mL), dried (over $MgSO_4$), filtered, and concentrated for column chromatography purification (elution: hexanes/EtOAc, 6:1) to give thiomannoside **10** as an oily syrup (15.8 g, 81% over two steps). Analytical data for thiomannoside **10**: R_f = 0.48 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ = +66.7 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.75 (m, 4H, ArH), 7.53−7.46 (m, 5H, ArH), 7.41−7.27 (m, 8H, ArH), 7.21−7.18 (m, 2H, ArH), 7.01 (d, *J* = 8.0 Hz, 2H, ArH), 5.66 (s, 1H), 5.43 (d, *J* = 1.6 Hz, 1H, H-1), 4.86−4.82 (m, 3H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.38−4.28 (m, 2H, H-4,H-5), 4.27−4.21 (m, 1H, H-6a), 4.07 (s, 1H, H-2), 4.01−3.98 (m, 1H, H-3), 3.89 (t, *J* = 9.8 Hz, 1H, H-6b), 2.29 (s, 3H, SCH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.6, 138.1, 137.8, 135.3, 133.4, 133.3, 132.5, 130.1, 130.0, 129.0, 128.53, 128.45, 128.4, 128.1, 127.9, 127.8, 127.2, 126.31, 126.28, 126.2, 101.7 (benzylidene-CH), 87.8 (C-1), 79.4 (C-4), 78.1 (CH, C-2), 76.4 (C-3), 73.4 (CH_2Ar), 73.3 (CH_2Ar), 68.7 (C-6), 65.7 (C-5), 21.3 (SCH_3); HRMS (ESI-TOF) (*m*/*z*) [M + Na]$^+$ calcd for $C_{38}H_{36}O_5SNa$ 627.2176, found 627.2190.

Preparation of Tolyl 3,4-Di-O-benzyl-2-O-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside ***11***. To a solution of the foregoing thiomannoside **10** (14.6 g, 24.1 mmol) in DCM (80 mL) were added BH_3·THF (1 M in THF, 120.5 mL, 120.5 mmol) and TMSOTf (0.66 mL, 3.6 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, the reaction temperature was raised to rt and the stirring was continued for additional 3 h. The reaction was then quenched with Et_3N (1 mL) followed by cautious addition of methanol (20 mL) to quench the excess borane reagent. The mixture was concentrated by a rotary evaporator, and the crude product was purified by column chromatography (elution: hexanes/EtOAc, 4:1) to give thiomannoside **11** (13.6 g, 93%) as an amorphous substance. Analytical data for thiomannoside **11**: R_f = 0.25 (hexane/EtOAc, 4:1); $[\alpha]_D^{25}$ = +48.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.80 (m, 1H, ArH), 7.78−7.74 (m, 3H, ArH), 7.50−7.45 (m, 3H, ArH), 7.36−7.23 (m, 10H, ArH), 7.21 (d, *J* = 8.4 Hz, 2H, ArH), 7.03 (d, *J* = 8.0 Hz, 2H, ArH), 5.43 (d, *J* = 1.2 Hz, 1H, H-1), 4.97 (d, *J* = 10.8 Hz, 1H), 4.83 (s, 2H), 4.69−4.60 (m, 3H), 4.15−4.11 (m, 1H, H-5), 4.07 (d, *J* = 9.2 Hz, 1H, H-4), 4.03−4.02 (m, 1H, H-2), 3.90 (dd, *J* = 9.2, 3.2 Hz, 1H, H-3), 3.82 (s, 2H, H-6a, H-6b), 2.30 (s, 3H, SCH_3), 1.88 (br, 1H, OH); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.5, 138.3, 138.2, 135.5, 133.4, 133.3, 132.70, 131.7, 130.2, 130.1, 128.73, 128.65, 128.5, 128.4, 128.3, 128.1, 128.01, 127.99, 127.94, 127.91, 127.8, 127.0,

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126.4, 126.21, 126.18, 86.7 (CH, C-1), 80.3 (CH, C-3), 76.5 (CH, C-2), 75.5 (CH_2Ar), 75.1 (CH, H-4), 73.4 (CH, C-5), 72.7 (CH_2Ar), 72.5 (CH_2Ar), 62.5 (CH_2, C-6), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{38}H_{38}O_5SNa$ 629.2332, found 629.2326.

Preparation of Tolyl 3,4-Di-O-benzyl-6-deoxy-2-O-(2-naphthylmethyl)-1-thio-α-D-manno-hept-1,7-dialdo-pyranoside ***12***. To a solution of thiomannoside **11** (13.7 g, 22.6 mmol) in DMSO (113 mL) was added IBx (9.5 g, 33.9 mmol). The reaction mixture was stirred at 60 °C for 4 h. After the oxidation was complete, the mixture was cooled to rt followed by addition of a brine solution (60 mL). The resulting heterogeneous mixture was filtered to remove the insoluble IBx byproduct. The filtrate was then diluted with DCM (120 mL) and washed with brine (2 × 50 mL). The organic phase was dried (over $MgSO_4$), filtered, and concentrated by a rotary evaporator to give the crude aldehyde product for the Wittig olefination.

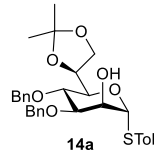
To a suspension of $CH_3OCH_2PPh_3Cl$ salt (23.2 g, 67.8 mmol) in THF (63 mL) was added NaHMDS (2 M in THF, 31.7 mL, 63.3 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. Meanwhile, the foregoing aldehyde was absorbed in 50 mL of THF and the solution was transferred to the ylide solution by a syringe. The resulting mixture was stirred at 0 °C overnight and then diluted with EtOAc (100 mL), which was washed with H_2O (80 mL) and brine (100 mL). The organic phase was dried (over $MgSO_4$) and filtered. The filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 6:1) to give an enol ether as a pair of *cis*- and *trans*-isomers (8.2 g, 57% over two steps) (R_f = 0.38 and 0.43 for hexanes/EtOAc, 4:1). To the foregoing enol ether isomers (8.2 g, 12.9 mmol) in acetone (129 mL) was added 2 N $HCl_{(aq)}$ (3.2 mL) at rt. After the mixture was stirred at rt for 30 min, satd Na_2CO_3 (15 mL) was added to neutralize the solution. Then the mixture was diluted with EtOAc (100 mL) then washed with H_2O (60 mL) and brine (80 mL). After drying over $MgSO_4$, the EtOAc solution was filtered and subsequently concentrated for column chromatography purification (elution: hexanes/EtOAc, 4:1) to give Hep-1,7-dialdo substrate **12** (5.1 g, 51% from **11** over three steps) as a colorless glassy substance. Analytical data for **12**: R_f = 0.48 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ = +44.8 (*c* 0.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (t, *J* = 2.4 Hz, 1H, CHO), 7.82−7.73 (m, 4H, ArH), 7.49−7.45 (m, 3H, ArH), 7.32−7.26 (m, 10H, ArH), 7.20 (d, *J* = 8.0 Hz, 2H, ArH), 7.03 (d, *J* = 8.0 Hz, 2H, ArH), 5.42 (d, *J* = 1.6 Hz, 1H, H-1), 4.97 (d, *J* = 10.8 Hz, 1H), 4.84 (d, *J* = 12.4 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.61−4.56 (m, 4H, H-5), 4.05 (dd, *J* = 2.8, 2.0 Hz, 1H, H-2), 3.89 (dd, *J* = 9.2, 2.8 Hz, 1H, H-3), 3.82 (t, *J* = 9.4 Hz, 1H, H-4), 2.77 (ddd, *J* = 16.0, 4.0, 2.0 Hz, 1H, H-6a), 2.59 (ddd, *J* = 16.4, 8.4, 2.8 Hz, 1H, H-6b), 2.29 (s, 3H, SCH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.5 (CHO), 138.13, 138.09, 138.02, 135.3, 133.4, 133.3, 132.2, 130.2, 130.1, 128.7, 128.5, 128.4, 128.14, 128.08, 128.07, 128.02, 128.00, 127.9, 127.1, 126.4, 126.21, 126.15, 86.5 (CH, C-1), 80.3 (CH, C-3), 78.0 (CH, C-4), 76.3 (CH, C-2), 75.4 (CH_2Ar), 72.5 (CH_2Ar), 72.3 (CH_2Ar), 68.5 (CH, C-5), 46.0 (CH_2, C-6), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{39}H_{38}O_5SNa$ 641.2332, found 641.2329.

Preparation of Tolyl 3,4-Di-O-benzyl-2-O-(2-naphthylmethyl)-L-glycero-1-thio-α-D-manno-heptopyranoside ***13***. To a solution of L,D-Hep 1,7-dialdo substrate **12** (5.8 g, 9.4 mmol) in CH_3CN (31 mL) were added L-proline (0.32 g, 2.8 mmol) and PhNO (3.0 g, 28.2 mmol). The reaction mixture was stirred at −20 °C for 2 d. Then $NaBH_4$ (0.78 g, 20.7 mmol) in ethanol (10 mL) was added, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd NH_4Cl (5 mL). The heterogeneous mixture was diluted with EtOAc (50 mL), which was then washed with H_2O (40 mL) and brine (40 mL), dried over $MgSO_4$, and filtered. And the filtrate was concentrated to give the crude 6-(anilinyl)oxy-L,D-Hep intermediate, which was directly used as a substrate in the next reaction.

To a solution of crude 6-(anilinyl)oxy-L,D-Hep intermediate in DCM (31 mL) was added PhNO (2.0 g, 18.8 mmol). The reaction mixture was stirred at rt for 1 d then concentrated for column chromatography purification (elution: hexanes/EtOAc, 2:1) to give L,D-Hep diol **13** as a light-brown syrup (2.3 g, 40% over three steps). Analytical data for **13**: R_f = 0.25 (hexanes/EtOAc, 1:1); $[\alpha]_D^{25}$ = +56.3 (*c* 0.71, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.81 (m, 1H, ArH), 7.79−7.75 (m, 3H, ArH), 7.50−7.47 (m, 3H, ArH), 7.33−7.27 (m, 10H, ArH), 7.17 (d, *J* = 8.0 Hz, 2H, ArH), 7.05 (d, *J* = 8.0 Hz, 2H, ArH), 5.45 (d, *J* = 1.2 Hz, 1H, H-1), 4.98 (d, *J* = 10.8 Hz, 1H), 4.84 (s, 2H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.24 (t, *J* = 9.4 Hz, 1H, H-4), 4.04 (d, *J* = 10.0 Hz, 1H, H-5), 4.01−4.00 (m,1H, H-2), 3.97 (br, 1H, H-6), 3.89 (dd, *J* = 9.2, 3.2 Hz, 1H, H-3), 3.57−3.52 (m, 2H, H-7a, H-7b), 2.43 (d, *J* = 9.6 Hz, 1H, OH), 2.30 (s, 3H, SCH_3), 1.91 (d, *J* = 6.0 Hz, 1H, OH); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 138.3, 135.4, 133.4, 133.3, 132.5, 130.2, 129.6, 128.7, 128.5, 128.3, 128.1, 128.01, 127.99, 127.96, 127.91, 127.0, 126.4, 126.2, 126.1, 86.6 (C-1), 80.2 (C-3), 76.2 (C-2), 75.6 (CH_2Ar), 74.6 (C-4), 74.0 (C-5), 72.8 (CH_2Ar), 72.53 (CH_2Ar), 69.4 (CH, C-6), 65.2 (CH_2, C-7), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{39}H_{40}O_6SNa$ 659.2438, found 659.2429.

Preparation of Tolyl 3,4-Di-O-benzyl-6,7-O-isopropylidene-2-O-(2-naphthylmethyl)-L-glycero-1-thio-α-D-manno-heptopyranoside ***14***. To a solution of L,D-Hep diol **13** (1.5 g, 2.4 mmol) in acetone (24 mL) were added 2,2- dimethoxypropane (0.6 mL, 4.8 mmol) and *p*TSA (5 mg, 0.24 mmol). The reaction mixture was stirred at rt for 4 h. The reaction was quenched by addition of Et_3N (35 μL), and the acetone was removed by a rotary evaporator. The concentrated residue was absorbed in 30 mL of EtOAc solution, which was washed with H_2O (20 mL) and brine (20 mL), dried (over $MgSO_4$), and filtered. The filtrate was concentrated for chromatography purification (elution: hexanes/EtOAc, 6:1) to obtain L,D-Hep **14** (1.6 g, 98%). Analytical data for **14**: R_f = 0.58 (hexanes/EtOAc, 1:1); $[\alpha]_D^{25}$ = +48.7 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz $CDCl_3$) δ 7.81−7.79 (m, 1H, ArH), 7.76−7.72 (m, 3H, ArH), 7.49−7.43 (m, 3H, ArH), 7.32−7.28 (m, 10H, ArH), 7.25 (d, *J* = 8.4 Hz, 2H, ArH), 7.03 (d, *J* = 8.0 Hz, 2H, ArH), 5.59 (s, 1H, H-1), 4.99 (d, *J* = 10.8 Hz, 1H), 4.83 (d, *J* = 12.4 Hz, 1H), 4.76 (d, *J* = 12.4 Hz, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.62 (s, 2H), 4.49−4.48 (m, 1H, H-6), 4.15 (t, *J* = 9.6 Hz, 1H, H-4), 4.04−4.01 (m, 2H, H-2, H-5), 3.93−3.89 (m, 2H, H-3, H-7a), 3.81 (t, *J* = 7.6 Hz, 1H, H-7b), 2.29 (s, 3H, SCH_3), 1.44 (s, 3H), 1.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.6, 138.4, 137.9, 135.6, 133.4, 133.2, 132.5, 130.2, 123.0, 128.6, 128.3, 128.1, 128.0, 127.9, 127.84, 127.83, 126.7, 126.2, 126.1, 126.0, 109.2, 86.1 (CH, C-1), 80.3 (CH, C-3), 76.3 (CH, C-2), 76.2 (CH, C-4), 75.5 (CH_2Ar), 74.9 (CH, C-6), 72.3 (CH, C-5), 72.2 (CH_2Ar), 72.0 (CH_2Ar), 65.8 (CH_2, C-7), 26.5 (CH_3), 26.1 (CH_3), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{42}H_{44}O_6SNa$ 699.2751, found 699.2753.

Preparation of Tolyl 3,4-Di-*O*-benzyl-6,7-*O*-isopropylidene-L-*glycero*-1-thio-α-D-*manno*-heptopyranoside 14a.



To a solution of L,D-Hep thioglycoside **14** (1.5 g, 2.2 mmol) in DCM (19.4 mL) and MeOH (2.2 mL) was added DDQ (0.98 g, 4.4 mmol) in three equal portions over 1.5 h. The reaction mixture was stirred at rt for 2 h and then quenched with satd $Na_2S_2O_3$ (6 mL). The mixture was diluted with DCM (12 mL) followed by washing with H_2O (10 mL) and brine (20 mL), dried (over $MgSO_4$), and filtered. The filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 4:1) to give L,D-Hep thioglycoside **14a** (0.87 g, 74%). Analytical data for **14a**: R_f = 0.40 (hexanes/EtOAc, 2:1); $[\alpha]_D^{25}$ = +169.0 (*c* 0.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 12H, ArH), 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 5.59 (s, 1H, H-1), 4.91 (d, *J* = 10.8 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.44 (td, *J* = 7.2, 2.4 Hz, 1H, H-6), 4.23−4.22 (m, 1H, H-2), 4.02 (dd, *J* = 9.6, 2.8 Hz, 1H, H-5), 3.98 (t, *J* = 9.0 Hz, 1H, H-4), 3.89 (dd, *J* = 8.4, 3.2 Hz, 1H, H-3), 3.81 (dd, *J* = 7.86, 7.0 Hz, 1H, H-7a), 3.63 (t, *J* = 7.6 Hz, 1H, H-7b), 2.73−2.69 (m, 1H, OH), 2.31 (s, 3H, SCH_3), 1.38 (s, 3H), 1.35

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(s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.4, 138.0, 137.8, 132.3, 130.1, 129.6, 128.8, 128.6, 128.22, 128.18, 128.10, 128.0, 109.3, 87.5 (CH, C-1), 80.4 (CH, C-3), 75.7 (CH, C-4), 75.6 (CH_2Ar), 74.2 (CH, C-6), 72.2 (CH_2Ar), 71.0 (CH, C-5), 69.8 (CH, C-2), 65.3 (CH_2, C-7), 26.4 (CH_3), 26.0 (CH_3), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{31}H_{36}O_6SNa$ 559.2125, found 559.2138.

Preparation of Tolyl 2-O-Benzoyl-3,4-di-O-benzyl-6,7-O-isopropylidene-L-glycero-1-thio-α-D-manno-heptopyranoside ***6***. To a solution of L,D-Hep thioglycoside **14a** in pyridine (8.6 mL) were added BzCl (0.2 mL, 1.7 mmol) and DMAP (50 mg, 0.43 mmol). The reaction mixture was stirred at 70 °C overnight then diluted with EtOAc (20 mL) and washed with 1 N $HCl_{(aq)}$ (3 × 15 mL) and brine (15 mL), dried (over $MgSO_4$), and filtered. The filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 6:1) to yield L,D-Hep building block **6** (0.5 g, 91%). Analytical data for **6**: R_f = 0.45 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ = +92.5 (*c* 0.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.2 Hz, 2H, ArH), 7.57 (t, *J* = 7.4 Hz, 1H, ArH), 7.44 (t, *J* = 7.8 Hz, 2H, ArH), 7.35−7.23 (m, 12H, ArH), 7.10 (d, *J* = 8.4 Hz, 2H, ArH), 5.84−5.83 (m, 1H, H-2), 5.59 (d, *J* = 1.6 Hz, 1H, H-1), 4.95 (d, *J* = 10.8 Hz, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.69 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.54 (td, *J* = 6.8, 2.8 Hz, 1H, H-6), 4.18−4.10 (m, 2H, H-4, H-5), 4.06 (dd, *J* = 8.6, 3.0 Hz, 1H, H-3), 3.94 (t, *J* = 7.6 Hz, 1H, H-7a), 3.81 (t, *J* = 7.2 Hz, 1H, H-7b), 2.31 (s, 3H, SCH_3), 1.42 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7(C═O), 138.5, 138.3, 137.9, 133.4, 132.7, 130.2, 130.11, 130.07, 129.6, 128.59, 128.56, 128.54, 128.3, 128.2, 127.9, 109.3, 86.6 (CH, C-1), 78.7 (CH, C-3), 75.9 (CH, C-5), 75.7 (CH_2Ar), 74.5 (CH, C-6), 71.9 (CH, C-4), 71.8 (CH_2Ar), 70.6 (CH, C-2), 65.5 (CH_2, C-7), 26.4 (CH_3), 25.9 (CH_3), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{38}H_{40}O_7SNa$ 663.2387, found 663.2393.

Preparation of Building Block 7. *Preparation of Tolyl 4-O-Benzyl-2,3-O-isopropylidene-L-glycero-1-thio-α-D-heptopyranoside* ***15***. Thioheptopyranoside **15** is a known compound prepared as a colorless glassy solid (1.67 g, 6.8% over nine steps) from D-mannose (10 g, 55 mmol) following the literature procedures.[16]

Preparation of Tolyl 4,6,7-Tri-O-benzyl-L-glycero-1-thio-α-D-manno-heptopyranoside ***16***. To a solution of L,D-Hep thioglycoside **15** (2.7 g, 5.9 mmol) and BnBr (1.9 mL, 16.5 mmol) in DMF (20 mL) was added NaH (0.4 g, 16.5 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, the reaction temperature was raised to rt and the stirring was continued for additional 2 h. Then the reaction was quenched with satd NH_4Cl (10 mL). The reaction mixture was diluted with DCM (40 mL), which was washed with H_2O (30 mL) and brine (30 mL), dried (over $MgSO_4$), and filtered. The DCM filtrate was concentrated to give a crude product for subsequent reaction.

The crude benzylation product above was absorbed in 90% AcOH (30 mL) solution and the reaction mixture was stirred at 70 °C for 4 h. After the hydrolysis of the acetal group was complete, the solvent was reduced by a rotary evaporator. The resulting residue was absorbed in 40 mL of EtOAc, which was washed with satd $NaHCO_3$ (30 mL), brine (30 mL), dried (over $MgSO_4$), and filtered. The EtOAc filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 1:1) to give L,D-Hep diol **16** (2.3 g, 77% over two steps). Analytical data for **16**: R_f = 0.20 (hexanes/EtOAc, 1:1); $[\alpha]_D^{25}$ = +182.3 (*c* 0.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 17H, ArH), 7.03 (d, *J* = 7.6 Hz, 2H, ArH), 5.57 (s, 1H, H-1), 4.82−4.76 (m, 2H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 9.6 Hz, 1H, H-5), 4.10 (t, *J* = 5.2 Hz, 1H, H-6), 3.98 (br, 1H, H-2), 3.91 (td, *J* = 8.0, 3.2 Hz, 1H, H-3), 3.82 (t, *J* = 9.0 Hz, 1H, H-4), 3.63 (dd, *J* = 10.0, 6.4 Hz, 1H, H-7a), 3.41 (dd, *J* = 10.0, 4.8 Hz, 1H, H-7b), 3.16 (m, 1H, OH), 2.53 (dd, *J* = 7.24, 0.8 Hz, 1H, OH), 2.31 (s, 3H, SCH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.6, 138.29, 138.27, 137.4, 131.4, 130.3, 130.0, 128.7, 128.64, 128.56, 128.50, 128.1, 128.0, 127.81, 127.76, 87.7 (C-1), 75.9 (C-4), 75.7 (C-6), 74.5 (CH_2Ar), 73.5 (CH_2Ar), 73.3 (CH_2Ar), 73.0 (C-3), 72.5 (C-2), 72.4 (C-5), 71.4 (C-7), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{35}H_{38}O_6SNa$ 609.2281, found 609.2286.

Preparation of Tolyl 2-O-Benzoyl-4,6,7-tri-O-benzyl-L-glycero-1-thio-α-D-manno-heptopyranoside ***7***. To a solution of L,D-Hep diol **16** (0.32 g, 0.55 mmol) in CH_3CN (5.5 mL) were added CSA (26 mg, 0.11 mmol) and $PhC(OMe)_3$ (0.28 mL, 1.6 mmol). The reaction mixture was stirred at rt for 1 h, and then the reaction was quenched with addition of Et_3N. The solvent was removed by a rotary evaporator. The residue was absorbed in an EtOAc solution (3 mL), which was mixed with 2 N $HCl_{(aq)}$ (2.7 mL). The resulting mixture was stirred vigorously at rt for 30 min and then diluted with EtOAc (10 mL). The EtOAc solution was washed with satd $NaHCO_3$ (10 mL) and brine (10 mL), dried (over $MgSO_4$), and filtered. The filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 4:1) to give L,D-Hep building block **7** (0.3 g, 78%). Analytical data for **7**: R_f = 0.45 (hexanes/EtOAc, 2:1); $[\alpha]_D^{25}$ = +100.0 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.4, 1.2 Hz, 2H, ArH), 7.55 (t, *J* = 7.4 Hz, 1H, ArH), 7.40−7.26 (m, 19H, ArH), 7.04 (d, *J* = 8.0 Hz, 2H, ArH), 5.67 (d, *J* = 1.6 Hz, 1H, H-1), 5.60 (dd, *J* = 3.2, 1.6 Hz, 1H, H-2), 4.94 (d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 14.0 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.30−4.23 (m, 2H, H-5, H-3), 4.20 (t, *J* = 5.2 Hz, 1H, H-6), 4.14 (t, *J* = 9.4 Hz, 1H, H-4), 3.74 (dd, *J* = 10.0, 6.8 Hz, 1H, H-7a), 3.53 (dd, *J* = 10.0, 4.8 Hz, 1H H-7b), 2.30 (s, 3H, SCH_3), 2.23−2.22 (m, 1H, OH); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3 (C═O), 139.0, 138.4, 138.3, 137.8, 133.5, 132.0, 130.1, 129.96, 129.76, 128.7, 128.62, 128.58, 128.56, 128.1, 128.0, 127.8, 127.7, 86.1 (C-1), 76.0 (C-4), 75.7 (C-6), 74.9 (CH_2Ar), 74.5 (C-2), 73.6 (CH_2Ar), 73.0 (CH_2Ar), 72.8 (C-5), 71.8 (C-3), 71.2 (C-7), 21.3 (SCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{42}H_{42}O_7SNa$ 713.2543, found 713.2551.

One-Pot Synthesis of Methyl 2-O-Benzoyl-3,4-di-O-benzyl-6,7-O-isopropylidene-L-glycero-α-D-manno-heptopyranosyl-(1,3)-2-O-benzoyl-4,6,7-tri-O-benzyl-L-glycero-1-thio-α-D-manno-heptopyranosyl-(1,7)-4-O-benzyl-2,3-di(2-naphthylmethyl)-α-D-glucopyranoside ***5***. To a mixture of L,D-Hep thioglycoside **6** (0.14 g, 0.218 mmol), dibutyl phosphate (46 μL, 0.234 mmol), and activated 4 Å molecular sieves (0.4 g) in dried DCM (4.4 mL) were added NIS (49 mg, 0.218 mmol) and TMSOTf (8 μL, 0.044 mmol) at −20 °C. After the mixture was stirred at −20 °C for 1.5 h, L,D-Hep thioglycoside acceptor **7** (0.126 g, 0.182 mmol) and TMSOTf (49 μL, 0.273 mmol) were added, and the resulting mixture was stirred at −20 °C for 3 h. Then reducing-end L,D-Hep acceptor **8** (82.4 mg, 0.146 mmol) and NIS (41 mg, 0.182 mmol) were added followed by stirring at −20 °C for additional 3 h. The reaction was quenched by addition of Et_3N (45 μL) and MS was removed by filtration over Celite. The filtrate was diluted with DCM (8 mL) then washed with satd $Na_2S_2O_3$ (10 mL) and brine (10 mL). The organic phase was dried (over $MgSO_4$), filtered, and concentrated for chromatography purification (elution: hexanes/EtOAc, 4:1) to give trisaccharide **5** as a light yellow glassy solid (0.13 g, 45%). Analytical data for **5**: R_f = 0.20 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ = +12.0 (c 0.5, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.05−8.02 (m, 4H, ArH), 7.79−7.68 (m, 8H, ArH), 7.56−7.54 (m, 2H, ArH), 7.48−7.18 (m, 35H, ArH), 7.13−7.12 (m, 5H, ArH), 5.55 (s, 1H, H-2), 5.35 (s, 1H, H-2′), 5.26 (s, 1H, H-1), 5.15 (d, *J* = 11.4 Hz, 1H), 5.03 (s, 1H, H-1′), 4.97 (d, *J* = 10.8 Hz, 2H), 4.95−4.89 (m, 2H), 4.85 (d, *J* = 10.8 Hz, 2H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.67−4.65 (m, 2H, including H-1″), 4.60 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.45−4.40 (m, 2H), 4.37−4.32 (m, 4H), 4.21 (s, 1H), 4.09−4.05 (m, 4H), 3.99 (s, 1H), 3.92−3.90 (m, 1H), 3.86−3.83 (m, 2H), 3.81−3.80 (m, 1H), 3.76−3.74 (m, 2H), 3.67−3.66 (m, 1H), 3.61−3.58 (m, 2H), 3.49−3.46 (m, 1H), 3.39 (s, 3H, OCH_3), 1.41 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 165.7 (C═O), 165.5 (C═O), 138.98, 138.95, 138.4, 138.20, 138.17, 138.0, 136.6, 135.9, 133.5, 133.44, 133.41, 133.3, 133.2, 133.1, 130.2, 130.1, 129.9, 128.7, 128.59, 128.55, 128.50, 128.38, 128.36, 128.30, 128.14, 128.05, 127.9, 127.82, 127.78, 127.71, 127.6, 127.5, 126.9, 126.5, 126.23, 126.18, 126.12, 126.05, 125.8, 100.0 (C-1), 97.9 (C-1″), 97.8 (C-1′), 82.4, 80.6, 78.0, 77.80,

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75.8, 75.4, 75.1, 75.0, 74.2, 73.61, 73.56, 72.8, 72.2, 71.9, 71.5, 71.0, 69.8, 69.4, 66.4, 65.3, 55.4 (OCH_3), 26.4 (CH_3), 26.1 (CH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{102}H_{102}O_{20}Na$ 1669.6857, found 1669.6888.

Preparation of Tolyl 4-O-Benzyl-2,3-O-isopropylidene-1-thio-α-L-rhamnopyranoside ***18***. Thio-L-rhamnopyranoside **18** is a known compound prepared as a white amorphous solid (1.9 g, 45% over five steps) from L-rhamnose (2.0 g, 12 mmol) following the literature procedures.[46]

Preparation of Building Block 19 via Intermediates 21 and 22. *Preparation of Methyl 4-O-Benzyl-6-deoxy-2,3-O-isopropylidene-α-D-manno-hept-1,7-dialdopyranoside* ***21***. To a solution of methyl α-mannoside **20**[47] (6.9 g, 21.27 mmol) in DMSO (106 mL) was added IBx (11.92 g, 42.54 mmol). The reaction mixture was stirred at 50 °C for 3 h. Then the reaction mixture was cooled to rt followed by addition of brine (60 mL). The resulting mixture was filtered, and the filtrate was diluted with DCM (120 mL) and then washed with brine (2 × 50 mL), dried (over $MgSO_4$), and filtered. The DCM filtrate was concentrated to give the crude 1,7-dialdo substrate **21** for the Wittig olefination.[16]

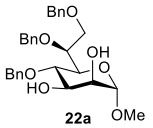
To a solution of $CH_3OCH_2PPh_3Cl$ salt (21.8 g, 63.6 mmol) in THF (60 mL) was added NaHMDS (2 M in THF, 30 mL, 59.4 mmol) at 0 °C. After the mixture was stirred for 1 h, the 1,7-dialdo substrate **21** in 46 mL of THF was transferred to the mixture. The resulting mixture was stirred at 0 °C overnight, and the reaction mixture was diluted with EtOAc (100 mL). The EtOAc solution was washed with H_2O (80 mL), brine (100 mL), dried (over $MgSO_4$), and filtered. The EtOAc filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 6:1) to give a *cis/trans* mixture of enol ether isomers (5.37 g, 72% over two steps) (R_f = 0.43 and 0.49 for *cis*- and *trans*-isomers, hexanes/EtOAc, 4:1).

To a mixture of the foregoing enol ether isomers (5.37 g, 15.3 mmol) in acetone (150 mL) was added 2 N $HCl_{(aq)}$ (3.8 mL). The mixture was stirred vigorously at rt for 30 min, and a solution of satd Na_2CO_3 (15 mL) was added to quench the reaction. The mixture was diluted with EtOAc (100 mL) and then washed with H_2O (60 mL) and brine (80 mL), dried (over $MgSO_4$), and filtered. The EtOAc filtrate was concentrated for column chromatography purification (elution: hexanes/EtOAc, 4:1) to give the known L,D-Hep 1,7-dialdo substrate **21** (4.8 g, 67% from **20** over three steps).[16] Spectroscopic data for **21**: R_f = 0.39 (hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 7.35−7.30 (m, 5H, ArH), 4.90 (d, J = 11.6 Hz, 1H), 4.85 (s, 1H, H-1), 4.58 (d, J = 11.5 Hz, 1H), 4.30 (t, J = 6.3 Hz, 1H), 4.15 (d, J = 5.4 Hz, 1H), 3.40 (s, 3H, OCH_3), 3.35−3.26 (m, 2H), 2.85 (dd, J = 16.6, 2.0 Hz, 1H, H-6a), 2.55 (ddd, J = 16.4, 8.6, 2.8 Hz, 1H, H-6b), 1.52 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.1 (CHO), 137.8, 128.4, 128.1, 127.8, 109.4, 98.2 (C-1), 78.5, 78.3, 75.8, 72.6, 63.5, 55.4, 45.9, 28.0 (CH_3), 26.2 (CH_3).

Preparation of Methyl 4-O-Benzyl-2,3-O-isopropylidene-L-glycero-α-D-heptopyranoside ***22***. To a solution of the foregoing L,D-Hep 1,7-dialdo substrate **21** (3.6 g, 10.7 mmol) in CH_3CN (210 mL) were added L-Pro (0.62 g, 5.35 mmol) and PhNO (3.44 g, 32.1 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 2 d. Then $NaBH_4$ (1.21 g, 32.1 mmol) in ethanol (10 mL) was added, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was then quenched with satd NH_4Cl (5 mL). The mixture was diluted with EtOAc (50 mL) and washed with H_2O (40 mL) and brine (40 mL), dried (over $MgSO_4$), and filtered. The EtOAc filtrate was concentrated with a rotary evaporator to give the crude 6-(anilinyl)oxy-L,D-Hep intermediate.

To a solution of the crude 6-(anilinyl)oxy-L,D-Hep intermediate in DCM (35 mL) was added PhNO (2.3 g, 21.4 mmol). The reaction was stirred at rt for 1 d. Then the reaction mixture was concentrated for column chromatography purification (elution: hexanes/EtOAc, 3:1) to give the known L,D-Hep diol **22** as a light-yellow oily substance (1.52 g, 40% from **21** over three steps).[16] NMR spectroscopic data for **22**: R_f = 0.16 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H, ArH), 4.93 (s, 1H, H-1), 4.92 (d, J = 11.5 Hz, 1H, CH_2Ar), 4.65 (d, J = 11.5 Hz, 1H, CH_2Ar), 4.32 (t, J = 6.3 Hz, 1H, H-3), 4.13 (d, J = 5.7 Hz, 1H), 3.99 (m, 1H, H-6), 3.80 (dd, J = 10.8, 6.6 Hz, 1H), 3.75−3.66 (m, 2H), 3.62 (d, J = 10.1 Hz, 1H), 3.37 (s, 3H, OCH_3), 2.29 (d, J = 8.9 Hz, 1H, H-7a), 2.19−2.08 (m, 1H, H-7b), 1.53 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.0, 128.4, 128.1, 127.8, 109.5, 98.5 (C-1), 78.6, 75.4, 75.2, 73.1, 69.4, 68.9, 64.8, 55.2, 28.0 (CH_3), 26.3 (CH_3).

Preparation of Methyl 4,6,7-Tri-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside 22a.



22a

To a mixture of L,D-Hep diol **22** (3.0 g, 8.6 mmol) and BnBr (2.9 mL, 24.1 mmol) in DMF (28 mL) was added NaH (0.58 g, 24.1 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, the reaction temperature was raised to rt and the stirring was continued for 2 h. The reaction was quenched with satd NH_4Cl (10 mL) and then diluted with DCM (40 mL). The DCM solution was washed with H_2O (30 mL) and brine (30 mL), dried (over $MgSO_4$), and filtered. The DCM solution was concentrated to give the crude benzylation product; which was directly subjected to acetal deprotection by acetic acid (AcOH).

The foregoing crude benzylation product was absorbed in 30 mL of 90% AcOH and the mixture was stirred at 50 °C for 4 h. After the cleavage of the isopropylidene acetal group was complete, the solvent was removed by a rotary evaporator to give a light-yellow syrup. The syrup was absorbed in 40 mL of EtOAc, which was washed with satd $NaHCO_3$ (30 mL), brine (30 mL), dried (over $MgSO_4$), and filtered. The EtOAc filtrate was subsequently concentrated for column chromatography purification (elution: hexanes/EtOAc, 1:1) to give L,D-Hep 2,3-diol **22a** as a colorless glassy substance (3.1 g, 75% over 2 steps). NMR spectroscopic data for **22a**: R_f = 0.15 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.22 (m, 15H, ArH), 4.80 (d, J = 12.0 Hz, 1H), 4.77 (d, J = 11.2 Hz, 1H), 4.72 (s, 1H, H-1), 4.54 (m, 2H), 4.51 (d, J = 11.6 Hz, 1H), 4.43 (d, J = 11.4 Hz, 1H), 4.10 (t, J = 6.0 Hz, 1H), 3.92 (m, 1H), 3.86−3.79 (m, 2H), 3.79−3.72 (m, 3H), 3.28 (s, 3H, OCH_3), 2.59 (m, 1H, OH), 2.42 (d, J = 7.3 Hz, 1H, OH); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.6, 138.2, 137.9, 128.5, 128.4, 128.2, 127.8, 127.7, 100.6 (C-1), 75.7, 75.1, 74.1, 73.5, 73.0, 72.3, 71.0, 70.3, 70.1, 55.0 (OCH_3). Noted **22a** was employed for preparation of building block **19**. Its optical rotation and HRMS data were not acquired.

Preparation of Methyl 2-O-Benzoyl-4,6,7-tri-O-benzyl-L-glycero-α-D-manno-heptopyranoside ***19***. To a solution of the L,D-Hep 2,3-diol **22a** (3.1 g, 6.4 mmol) in CH_3CN (31 mL) were added CSA (148 mg, 0.64 mmol) and $PhC(OMe)_3$ (1.6 mL, 9.6 mmol). The reaction mixture was stirred at rt for 1 h. After completion of the *ortho*-ester formation, the reaction was quenched with Et_3N then CH_3CN was removed by a rotary evaporator. The crude ortho-ester was absorbed in EtOAc (20 mL), which was treated with 1 N $HCl_{(aq)}$ (5.0 mL). The resulting mixture was stirred vigorously for 10 min. After completion of the benzoyl ester formation, the mixture was diluted with EtOAc (20 mL), which was washed with satd $NaHCO_3$ (20 mL) and brine (20 mL), dried (over $MgSO_4$), and filtered. The EtOAc filtrate was subsequently concentrated for column chromatography purification (elution: hexanes/EtOAc, 6:1) to give reducing-end L,D-Hep acceptor **19** (2.9 g, 76%). Analytical data for **19**: R_f = 0.18 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ = −8.0 (c 0.013, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.1 Hz, 2H, ArH), 7.56 (t, J = 7.4 Hz, 1H, ArH), 7.42−7.24 (m, 17H, ArH), 5.33 (dd, J = 2.8, 1.6 Hz, 1H, H-2), 4.93 (d, J = 11.7 Hz, 1H), 4.85 (s, 1H, H-1), 4.80 (d, J = 11.3 Hz, 1H), 4.57 (m, 2H), 4.55 (d, J = 12.0 Hz), 4.48 (d, J = 11.6 Hz, 1H), 4.31−4.24 (m, 1H, H-3), 4.19 (t, J = 6.2 Hz, 1H), 4.08 (t, J = 9.5 Hz, 1H), 3.91 (dd, J = 9.5, 6.3 Hz, 1H), 3.86 (d, J = 9.7 Hz, 1H), 3.81 (dd, J = 9.5, 6.3 Hz, 1H), 3.31 (s, 3H, OCH_3), 2.16−2.18 (m, 1H, OH); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2 (C═O), 138.7, 138.4, 138.0, 133.2, 129.9, 129.6, 128.4, 127.7, 127.61, 127.58, 127.51, 98.4 (C-1), 75.6, 75.2, 74.5 (C-4), 73.5, 72.8, 71.0, 70.8, 70.1,

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54.9 (OCH_3); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{36}H_{38}O_8Na$ 621.2459, found 621.2453.

One-Pot Synthesis of Methyl 4-O-Acetyl-2,3-O-isopropylidene-α-L-rhamnopyranosyl-(1,2)-[4-O-acetyl-2,3-O-isopropylidene-α-L-rhamno-pyranosyl-(1,3)]-4,6,7-tri-O-benzyl-L-glycero-α-D-manno-heptopyranosyl-(1,3)-2-O-benzoyl-4,6,7-tri-O-benzyl-L-glycero-α-D-manno-heptopyranoside ***23***. To a solution of thiorhamnoside **18** (273 mg, 0.776 mmol) and dibutyl phosphate (161 μL, 0.812 mmol) in dried DCM (7.0 mL) with activated 4 Å molecular sieves (0.7 g) were added NIS (182 mg, 0.812 mmol) and TMSOTf (9.0 μL, 0.053 mmol) at −20 °C. After the mixture was stirred for 1.5 h, L,D-Hep thioglycoside acceptor **16** (207 mg, 0.353 mmol) and TMSOTf (95 μL, 0.53 mmol) were added at −20 °C. The mixture was stirred at −20 °C for 1.5 h, and then reducing-end L,D-Hep acceptor **9** (170 mg, 0.283 mmol), NIS (71 mg, 0.318 mmol) and TMSOTf (51 μL, 0.283 mmol) were added. After reaction at −20 °C for additional 2 h, the reaction was quenched by Et_3N (0.15 mL). The MS was removed by filtration and the filtrate was diluted with DCM (12 mL) then washed with satd $Na_2S_2O_3$ (15 mL × 2) and brine (15 mL). The organic phase was separated, dried (over $MgSO_4$), filtered, and concentrated for column chromatography purification (elution: hexanes/DCM/EtOAc, 6:1:1) to give tetrasaccharide **23** (185 mg, 42%) as a white amorphous substance. Analytical data for **23**: R_f = 0.23 (hexanes/DCM/EtOAc, 6:1:1); $[\alpha]_D^{25}$ = −25.5 (*c* 0.022, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.52 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.41−7.36 (m, 26H, Ar*H*), 7.19 (d, *J* = 7.1 Hz, 2H, Ar*H*), 5.37 (s, 1H, H-2), 5.23 (s, 1H, H′-1), 5.03 (s, 1H, H‴-1), 4.96 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 11.6 Hz, 1H), 4.81 (dd, *J* = 9.8, 8.5 Hz, 1H, H″-4), 4.75 (s, 1H, H″-1), 4.73 (s, 1H, H-1), 4.69−4.63 (m, 4H), 4.56 (s, 3H), 4.51−4.43 (m, 2H), 4.44 (br, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.33 (dd, *J* = 9.5, 2.6 Hz, 1H, H-3), 4.25−4.20 (m, 1H), 4.20−4.16 (m, 1H, H″-3), 4.16−4.09 (m, 4H), 4.07 (d, *J* = 5.2 Hz, 1H), 4.04 (d, *J* = 9.5 Hz, 1H), 4.02−3.95 (m, 3H), 3.92 (d, *J* = 9.0 Hz, 1H), 3.91 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.86 (s, 1H), 3.85 (s, 1H), 3.80 (dd, *J* = 9.7, 6.2 Hz, 2H), 3.60 (dt, *J* = 11.8, 5.9 Hz, 1H, H‴-5), 3.25 (s, 3H, OC*H*$_3$), 2.08 (s, 3H, C═OC*H*$_3$), 1.93 (s, 3H, C = OC*H*$_3$), 1.53 (s, 3H, C*H*$_3$), 1.49 (s, 3H, C*H*$_3$), 1.27 (s, 3H, C*H*$_3$), 1.24 (s, 3H, C*H*$_3$), 1.07 (d, *J* = 6.2 Hz, 3H, H‴-6), 0.60 (d, *J* = 4.8 Hz, 3H, H″-6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 170.2 (C═O), 170.1 (C═O), 139.2, 138.7, 138.6, 138.4, 138.1, 137.8, 133.3, 133.0, 129.8, 128.8, 128.59, 128.58, 128.56, 128.46, 128.3, 128.2, 128.0, 127.89, 127.87, 127.77, 127.70, 127.6, 127.5, 127.4, 127.24, 127.19, 127.1, 109.88, 109.86, 99.0 (C′-1, $^1J_{CH}$ = 167.0 Hz), 98.5 (C-1, $^1J_{CH}$ = 168.3 Hz), 94.8 (C″-1, $^1J_{CH}$ = 171.1 Hz), 91.9 (C‴-1, $^1J_{CH}$ = 168.9 Hz), 76.04, 76.02, 75.8, 75.6, 75.1, 74.9, 74.7, 74.5, 74.2, 73.7, 73.5, 73.4, 72.8, 72.6, 71.8, 71.77, 71.74, 71.66, 70.0, 64.5 (C‴-5), 63.7 (C″-5), 55.0, 27.9, 27.8, 26.6, 21.2, 21.1, 17.4, 16.4. HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calcd for $C_{86}H_{100}O_{24}Na$ 1539.6359, found 1539.6357.

*Inner Core Structure from LPS of Ralstonia solanacearum Toudk-2 (***17***).* To a solution of **23** (185 mg, 0.12 mmol) in CH_3CN (1.2 mL) was added zinc nitrate hexahydrate $[Zn(NO_3)_2{\cdot}6H_2O]$ (68 mg, 0.36 mmol). The reaction mixture was stirred at 40 °C for 16 h and was then quenched with satd NH_4Cl (3 mL). The mixture was diluted with EtOAc (15 mL), which was washed with H_2O (8 mL × 2) and brine (12 mL). The organic layer was dried over $MgSO_4$ and concentrated for column chromatography purification (elution: hexanes/EtOAc, 3:1) to give a deisopropylidene intermediate (149 mg, 87%) with R_f = 0.33 (hexanes/EtOAc, 3:1). To a solution of deisopropylidene tetrasaccharide in THF (1.5 mL) and methanol (0.5 mL) was added K_2CO_3 (35 mg, 0.6 mmol). The reaction mixture was stirred at 50 °C for 2 h. After the deprotection was complete, the mixture was neutralized with 1 N HCl (3 mL), then diluted with DCM (15 mL) and washed with H_2O (8 mL) and brine (12 mL). The DCM organic phasewas dried over $MgSO_4$, filtered, and concentrated for column chromatography purification (elution: DCM/MeOH, 8:1) to give a debenzoyl tetrasaccharide intermediate (110 mg, 85%) with R_f = 0.25 (DCM/MeOH, 8:1).

To a solution of the debenzoyl tetrasaccharide (110 mg, 0.09 mmol) in MeOH (4.0 mL) and a trace amount of acetic acid (0.2 mL) was added 10% Pd/C (75 mg). The resulting suspension was stirred at rt under H_2 atmosphere for 18 h. Then the Pd catalyst was removed by filtration (over a Celite pad), and the filtrate was concentrated for purification, which was carried out byy FPLC (elution: 1:1 MeOH/$NH_4HCO_{3(aq)}$, flow rate 0.5 mL/min) to give **17** (57 mg, 90%). Analytical data for **17**: R_f = 0.40 ($NH_{3(aq)}$/IPA, 1:1); $[\alpha]_D^{25}$ = +6.15 (*c* 0.005, H_2O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.13 (s, 1H, H′-1), 4.87 (s, 1H, H‴-1), 4.76 (s, 1H, H″-1), 4.62 (s, 1H, H-1), 4.13 (t, *J* = 1.8 Hz, 1H, H′-2), 3.94−3.91 (broad m, 5H, including H3′ and H2), 3.85 (broad m, 2H, including H″-2), 3.84 (broad m, 1H), 3.82 (s, 1H, H‴-2), 3.75−3.67 (m, 4H) 3.64−3.57 (m, 4H), 3.53 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.47 (d, *J* = 10.0 Hz, 1H), 3.35 (dt, *J* = 16.2, 9.7 Hz, 1H), 3.26 (s, 3H, OCH_3), 1.19 (d, *J* = 6.3 Hz, 3H, Rha-H6), 1.16 (d, *J* = 6.2 Hz, 3H, Rha-H6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 100.8 (C-1), 99.2 (C′-1), 98.3 (C″-1), 96.8 (C‴-1), 78.9, 74.0, 72.1, 72.0, 71.9. 71.4, 71.1, 70.6, 70.3, 69.9, 69.7, 69.0, 68.8, 68.61, 68.59, 65.3, 64.4, 62.8, 62.6, 54.7, 17.0 (Rha-C6), 16.5 (Rha-C6); HRMS (ESI-TOF) (m/z) $[M + H]^+$ calcd for $C_{27}H_{49}O_{21}$ 709.2761, found 709.2763.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01828.

^{1}H, ^{13}C, COSY-, and HSQC-NMR spectra and HRMS data of the compounds synthesized in the present study (PDF)

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Notes

The authors declare no competing financial interest.

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