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Synthetic Routes toward Acidic Pentasaccharide Related to the *O*-Antigen of *E. coli* 120 Using One-Pot Sequential Glycosylation Reactions

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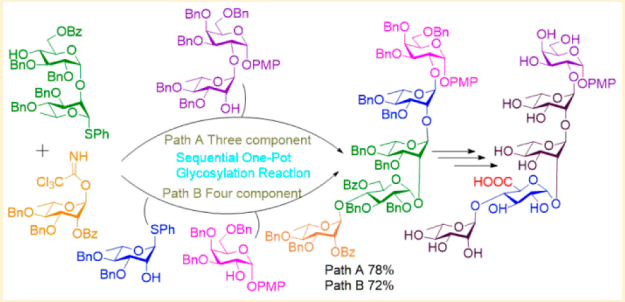
Supporting Information

ABSTRACT: Concise syntheses of the acidic pentasaccharide, related to the *O*-antigenic polysaccharide of *Escherichia coli* 120, as its *p*-methoxyphenyl glycoside, have been achieved using a one-pot sequential glycosylation technique. The glycosylations have been accomplished either by the activation of the thioglycosides using NIS in the presence of $FeCl_3$ or by a preactivation by Ph_2SO, TTBP, Tf_2O, and the activation of the trichloroacetimidates using $FeCl_3$ alone or TMSOTf. Most of the intermediate steps are high yielding, and the stereo outcomes of the glycosylation steps were excellent. The syntheses of the targeted pentasaccharide have been performed with both three- and four-component, one-pot sequential glycosylation reactions, and in both cases, the orthogonal glycosylations are carried out utilizing catalytic activity of $FeCl_3$. A late-stage TEMPO-mediated regioselective oxidation has been performed to achieve the required uronic acid motif.



INTRODUCTION

Being a major component of the cell wall of Gram-negative bacteria, the *O*-antigens often play important roles during host infections, in subsequent immune responses in the host, and in controlling the host's virulence properties. The *O*-antigen is one of the most variable cell constituents and consists of a polysaccharide chain with a number of repeats of an oligosaccharide. *Escherichia coli* is a facultative Gram-negative bacteria present predominantly in the human and animal kingdoms. Identification of *E. coli* clones including the commensal and pathogenic strains are normally done by the combination of their somatic (O), flagellar (H), and occasionally capsular (K) antigens.[1] More than 180 *O*-antigen forms of *E. coli* have been recognized so far.[2] The pathogenic *E. coli* strains in general cause three common infections such as (i) enteric/diarrheal, (ii) septicaemia/meningitis, and (iii) urinary tract.[3] The virulent *E. coli* strains causing diarrhea are classified in six classes as (i) enteropathogenic *E. coli* (EPEC), (ii) enterotoxigenic *E. coli* (ETEC), (iii) enteroinvasive *E. coli* (EIEC), (iv) diffusely adherent *E. coli* (DAEC), (v) enteroaggregative *E. coli* (EAEC), and (vi) enterohemorrhagic *E. coli* (EHEC).[4]

The enterohemorrhagic *E. coli* (EHEC) causes food-borne diseases with life threatening complications like hemorrhagic colitis (HC) and hemolytic−uremic syndrome (HUS) in human and animal kingdoms worldwide.[4] Because of their toxic effect on the cultured Vero cells, these EHEC strains are also called "verotoxigenic *E. coli* (VTEC)". They are also termed as Shiga toxin producing *E. coli* (STEC) as they produce a bacteriophage-mediated Shiga-like toxin.[5] The strains belonging to *E. coli* O120 isolated from their reservoirs like swine feces, cattle, and beef products are identified as STEC.[6,7] Recently, Knirel et al. elucidated the structure of the repeating unit of the *O*-antigen from *E. coli* 120 and found to contain an acidic hexasaccharide repeating unit (Figure 1).[8]

It has been well established that bacterial *O*-antigens regulate immunochemical activity of glycovaccines, which makes them attractive targets to synthetic organic chemists for the development of glycoconjugate vaccine candidates.[9] Recently, a number of reports have appeared for the synthesis of glycoconjugate vaccines and their evaluation against bacterial interactions.[9] Synthesis of an oligosaccharide with a temporary protecting group at the reducing end would be useful for its easy removal whenever necessary as it is often required to attach the oligosaccharide with a carrier protein through a spacer linker toward synthesis of glycoconjugates.[10] In this direction, the synthesis of the oligosaccharide related to the repeating unit of the *O*-antigen from *E. coli* 120 was only reported by Mukhopadhyay et al.,[11] using a conventional stepwise approach. However, introduction of a step-economic multistep, one-pot total synthesis is still necessary and needs refinement of the entire synthetic protocol. The stepwise oligosaccharide syntheses[12] demand extensive protecting group manipulation and purification after each step, making them expensive, time-consuming, and tedious procedures.

In contrast, the one-pot sequential oligosaccharide syntheses are step economic, comparatively environmentally friendly,

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α-L-Rhap-(1
↓
4
→3)-α-D-GlupA-(1→2)-α-L-Rhap-(1→2)-α-L-Rhap-(1→2)-α-D-Galp-(1→3)-β-D-GalNAc-(1.→

Figure 1. Hexasaccharide repeating unit of the *O*-antigen of *E. coli* type 120.

cost-effective, and expeditious. We report herein concise synthesis of the acidic pentasaccharide part of the hexasaccharide repeating unit in the form of its 4-methoxyphenyl glycoside via both three and four component one-pot sequential glycosylation reactions (1, Figure 2). The convergent strategy

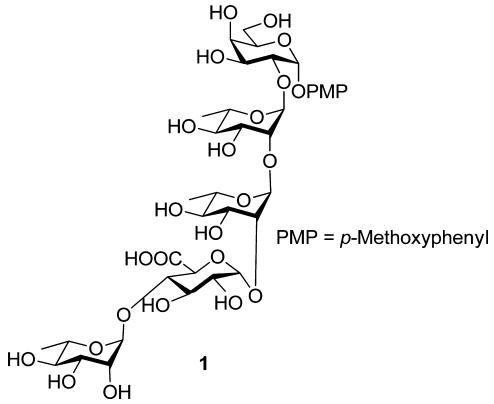

Figure 2. Structure of the target pentasaccharide.

will give the scope for the preparation of this important oligosaccharide structure in the pure form and in a quantity that will pave the way for understanding its role in the pathogenic cycle. Moreover, a selective oxidative removal of the *p*-methoxyphenyl aglycon group of the pentasaccharide derivative using ceric ammonium nitrate (CAN) followed by formation of the corresponding trichloroacetimidate derivative will allow the formation of glycoconjugate with suitable aglycons targeting potential vaccine candidates against this deadly pathogen.

RESULTS AND DISCUSSION

The sequential one-pot glycosylation technique was applied for these total syntheses. Application of this in both three- and four-component one-pot reactions requires different sets of chemically distinct glycosyl donors requiring different activation conditions. For the convergent synthesis of the targeted acidic pentasaccharide **1** two different pathways were contemplated, one of which was a three-component sequential glycosylation. i.e., via a [1 + 2 + 2] approach, and the other one was a four-component sequential glycosylation reaction, i.e., via a [1 + 2 + 1 + 1] approach.

For each pathway, a retrosynthetic analysis of the fully protected pentasaccharide derivative **2** led to two common building blocks, one is a 2-*O*-benzoyl-3,4-di-*O*-benzyl-L-rhamnopyranosyl trichloroacetimidate donor **3** and other is the disaccharide acceptor **5**, which can be prepared from the monomeric units **8** and **9**. Whereas the retrosynthetic analysis for the second approach [1 + 2 + 1 + 1] of the total synthesis guided us for use of the monomeric units **10** and **11**, the first synthetic approach [1 + 2 + 2] led us to work with another disaccharide segment **7** to be prepared from **10** and **11** (Figure 3). The disaccharide building blocks **5** and **7** can be obtained from their corresponding parent disaccharides **4** and **6** via selective removal of acetate protection.

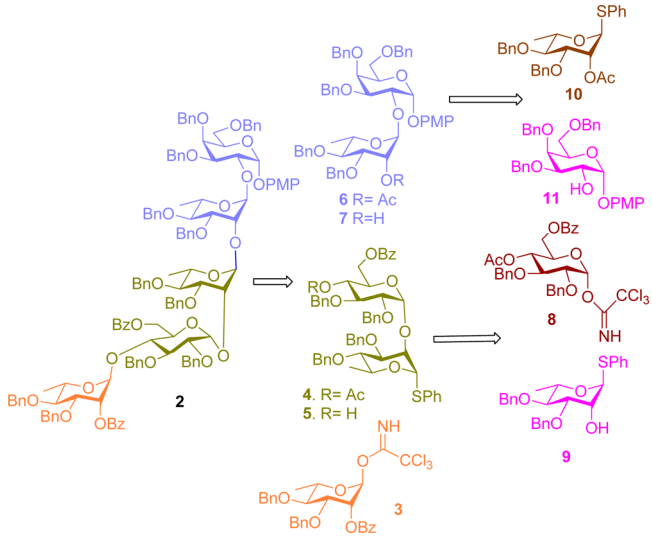

Figure 3. Retrosynthetic analysis of the pentasaccharide derivative **2**.

Dry L-rhamnose was acetylated by acetic anhydride and a catalytic amount of magnesium(II) trifluoromethanesulfonate [$Mg(OTf)_2$][13] under neat conditions; after full consumption of the starting material (checked by TLC) into the same reaction vessel, thiophenol followed by $BF_3{\cdot}Et_2O$ were added to furnish phenyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamanopyranoside **13** in 93% yield over two steps after purification by column chromatography. This phenyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamanopyranoside **13** was converted to phenyl 3,4-di-*O*-benzyl-1-thio-α-L-rhamanopyranoside **9** according to a reported procedure.[14] Compound **9** was acetylated quantitatively using $Mg(OTf)_2$ and acetic anhydride to achieve phenyl 2-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamanopyranoside **10**.[15] On the other hand, benzoylation of **9** produced phenyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamanopyranoside **14**.[14] Thioglycoside hydrolysis of **14** was carried out following the method developed by us using trichloroisocyanuric acid (TCCA)[16] in aqueous acetone to give compound **15**. Reaction of **15** with trichloroacetonitrile and DBU in dry DCM afforded 2-*O*-benzoyl-3,4-di-*O*-benzyl-L-rhamnopyranosyl trichloroacetimidate donor **3** in 90% yield. Thus, L-rhamnose-based monosaccharide units **3**, **9**, and **10** were gathered (Scheme 1).

D-Glucose was used as the preliminary starting material to synthesize the glucose-based monomeric building block **8** (Scheme 2). Dry D-glucose was acetylated using acetic anhydride and catalytic $Mg(OTf)_2$[13] under neat conditions. After completion of the reaction (checked by TLC), into the same reaction vessel was added thiophenol followed by $BF_3{\cdot}Et_2O$ to produce phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **17** in 94% overall yield. Compound **17** was transformed to phenyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside **18**[17] according to the reported procedure. Then

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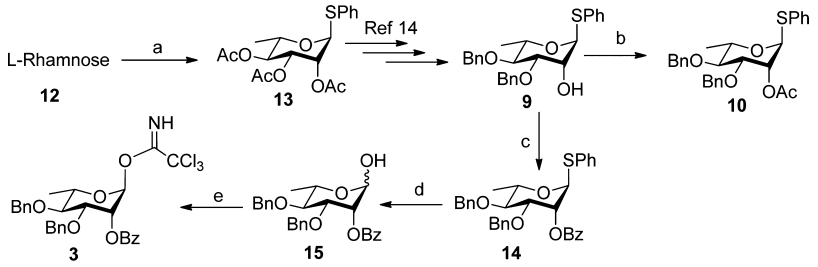
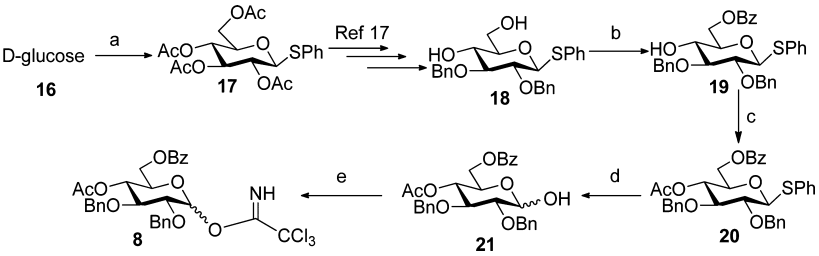
Scheme 1. Synthesis of L-Rhamnose-Based Building Blocks[a]



[a]Reagents and conditions: (a) (i) Ac_2O, $Mg(OTf)_2$, 3 min, (ii) PhSH, $BF_3{\cdot}Et_2O$, 8 h, 93%; (b) Ac_2O, $Mg(OTf)_2$, 30 min, quantitative; (c) BzCl, Py, DCM 1:1, 5 h, 97%; (d) Me_2CO/H_2O, TCCA, 40 min, 97%; (e) CCl_3CN, DBU, 0 °C, 5 h, 90%.

Scheme 2. Synthesis of D-Glucose-Based Donor 8[a]



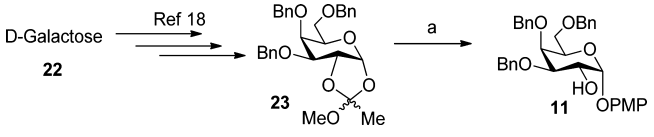
[a]Reagents and conditions: (a) (i) $Mg(OTf)_2$, Ac_2O, 2 min; (ii) PhSH, $BF_3{\cdot}Et_2O$, 8 h, 94% over two steps; (b) DCM, MeCN, NEt_3, −78 °C, BzCN, 2 h, 95%; (c) Ac_2O, $Mg(OTf)_2$, DCM, 30 min, 97%; (d) Me_2CO/H_2O, TCCA, 20 min, 96%; (e) CCl_3CN, DBU, 0 C, 5 h, 91%.

compound **18** was chemoselectively benzoylated using 1:1:0.5 DCM/MeCN/NEt_3 and benzoyl cyanide at −78 °C for 2 h to afford phenyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-*β*-D-glucopyranoside **19** in 95% yield. Quantitative acetylation of **19** with $Mg(OTf)_2$ and acetic anhydride produced phenyl 4-*O*-acetyl-6-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-*β*-D-glucopyranoside **20**. Thioglycoside hydrolysis of **20** with TCCA in wet acetone followed by base-catalyzed formation of trichloroacetimidate furnished the desired glycosyl donor **8** (Scheme 2).

Dry D-galactose was converted to 3,4,6-tri-*O*-benzyl-*α*-D-galactopyanosyl-1,2-(methyl orthoacetate) **23**[18] according to the literature-reported process. Then the reaction of this benzylated orthoester **23** with *p*-methoxyphenol using $BF_3{\cdot}Et_2O$ in dry MeCN and this followed by Zemplén deacetylation[19] gave the acceptor *p*-methoxyphenyl 3,4,6-tri-*O*-benzyl-*α*-D-galactopyanoside **11** in 92% overall yield after two steps (Scheme 3). The *α*-configuration of the glycoside **11** was established from both the ^1H NMR spectrum (δ 5.50, H_1, $J_{1,2}$ = 3.5 Hz) and the ^{13}C spectrum (δ 98.9, J_{C-H} = 169.8 Hz).

Glycosylation of acceptor **9** was first attempted with phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside donor **24**[20] based on a preactivation technique using 1-benzenesulfinylpiperidine (BSP),[20] 2,4,6-tri-*tert*-butylpyrimidine (TTBP), and Tf_2O in dry DCM under standard reaction conditions (entry 1, Table 1). Instead of formation of glycosylated product, decomposition of the glycosyl donor was observed under these conditions. A similar fate was observed when the preactivation-based glycosylation was attempted using diphenyl sulfoxide (Ph_2SO), TTBP, and Tf_2O in dry DCM (entry 2, Table 1).[21] Exchanging the donor **24** with the more reactive 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranosyl trichloroacetimidate **25** was next ventured. Coupling of **25** with rhamnopyranosyl acceptor **9** was explored using TMSOTf[22] as activator at different temperatures such as 0, −30, and −10 °C (entries 3, 4, and 5, Table 1).

Scheme 3. Synthesis of D-Galactose-Based Acceptor 11[a]



[a]Reagents and conditions: (a) (i) *p*-methoxyphenol, MeCN, $BF_3{\cdot}Et_2O$, 0 °C, 30 min; (ii) NaOMe, MeOH, DCM, 2 h, 92% over two steps.

Unfortunately, in all cases either decomposition of the reaction mixture was observed or unreacted starting materials were recovered. Again, another preactivation-based glycosylation technique using BSP, TTBP, and Tf_2O was attempted on phenyl 4-*O*-acetyl-6-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-*β*-D-glucopyranoside **20**, but the result was comparable to the previous results (entry 6, Table 1).

Gratifyingly, when 4-*O*-acetyl-6-*O*-benzoyl-2,3-di-*O*-benzyl-D-glucopyranosyl trichloroacetimidate donor **8** was allowed to couple with **9** using TMSOTf at −10 °C, the desired coupling product was obtained in 58% yield and an α/β = 3:2 ratio (entry 7, Table 1). Pleasingly, proper tuning of the reaction conditions (entry 8, Table 1) allowed the isolation of the coupling product in good yield but with poor steroselectivity. Then the glycosylations were run in a mixture of DCM and Et_2O, the ratio (2:1 to 3:2) of which was optimized (entries 9 and 10, Table 1) to comply with solubility requirements and glycosylation stereoselectivity.

Finally, under the optimized conditions, 4-*O*-acetyl-6-*O*-benzoyl-2,3-di-*O*-benzyl-D-glucopyranosyl trichloroacetimidate **8** and the glycosyl acceptor phenyl 3,4-di-*O*-benzyl-1-thio-*α*-L-rhamanopyranoside **9** were allowed to couple using TMSOTf[22] at 0 °C in 3:2 DCM/Et_2O to produce the desired disaccharide

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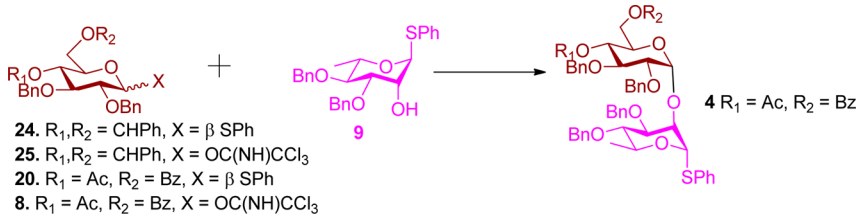
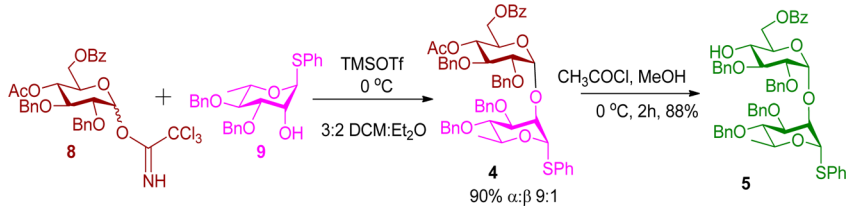
Table 1. Optimization of α-D-Glucosylation on Acceptor 9

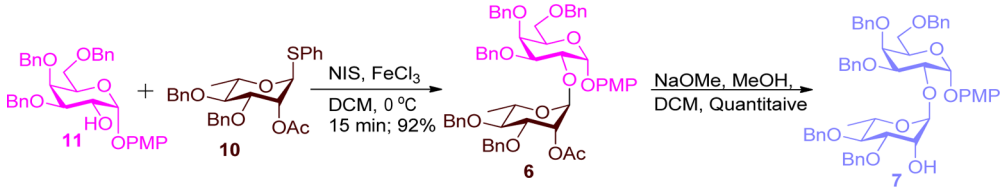


entry	donor (equiv)	promoter	solvent DCM/Et_2O	temp (°C)	yield (α/β)
1	**24** (1.2)	BSP, TTBP, Tf_2O	1:0	−60 to −78 to −40	dec
2	**24** (1.2)	Ph_2SO, TTBP, Tf_2O	1:0	−60 to −78 to rt	dec
3	**25** (1.0)	TMSOTf	1:0	0	dec
4	**25** (1.2)	TMSOTf	1:0	−30	no reaction
5	**25** (1.2)	TMSOTf	1:0	−10	dec
6	**20** (1.2)	BSP, TTBP, Tf_2O	1:0	−60 to −78 to −40	dec
7	**8** (1.0)	TMSOTf	1:0	−10	58% (3:2)
8	**8** (1.2)	TMSOTf	1:0	0	94% (3:2)
9	**8** (1.2)	TMSOTf	2:1	0	90% (5:2)
10	**8** (1.2)	TMSOTf	3:2	0	90% (9:1)

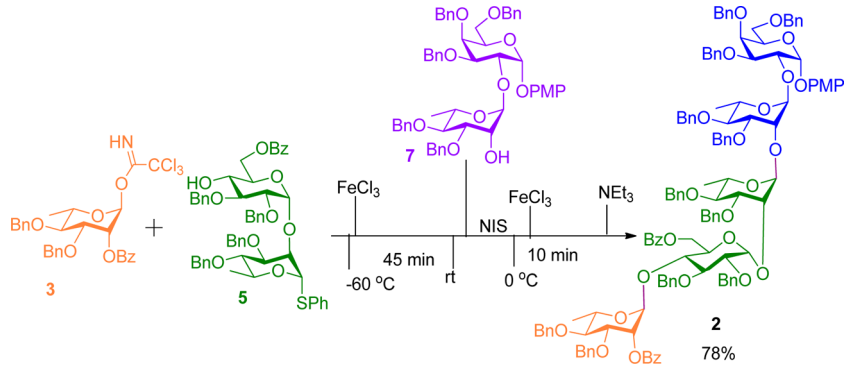
Scheme 4. Synthesis of Disaccharide Acceptor 5



Scheme 5. Synthesis of Disaccharide Acceptor 7



Scheme 6. Synthesis of Pentasaccharide Derivative 2 via a Three-Component, One-Pot Sequential Glycosylation Technique



in 90% yield with 9:1 α/β ratio. The NMR spectra of disaccharide **4** showed signals characteristic of the presence of both donor and acceptor moieties, while an α-configuration of the interglycosidic linkage was confirmed from the ^1H and ^{13}C NMR spectra. A chemoselective deacetylation in the presence of 6-OBz of **4** using acetyl chloride in dry MeOH at 0 °C produced the disaccharide acceptor **5** (Scheme 4) in 88% yield. Compared to the NMR spectra of **4**, the disappearance of one signal of carbonyl carbon from 169.6 ppm in the corresponding ^{13}C spectrum and the sharp singlet signal from 1.99 ppm in the ^1H spectrum in **5** clearly indicated the selective removal of the acetate protecting group in the presence of 6-OBz.

A mixture of thioglycoside donor **10** and glycosyl acceptor *p*-methoxyphenyl 3,4,6-tri-*O*-benzyl-α-D-galactopyanoside **11** in dry DCM at 0 °C was treated with NIS and $FeCl_3$[23] to produce

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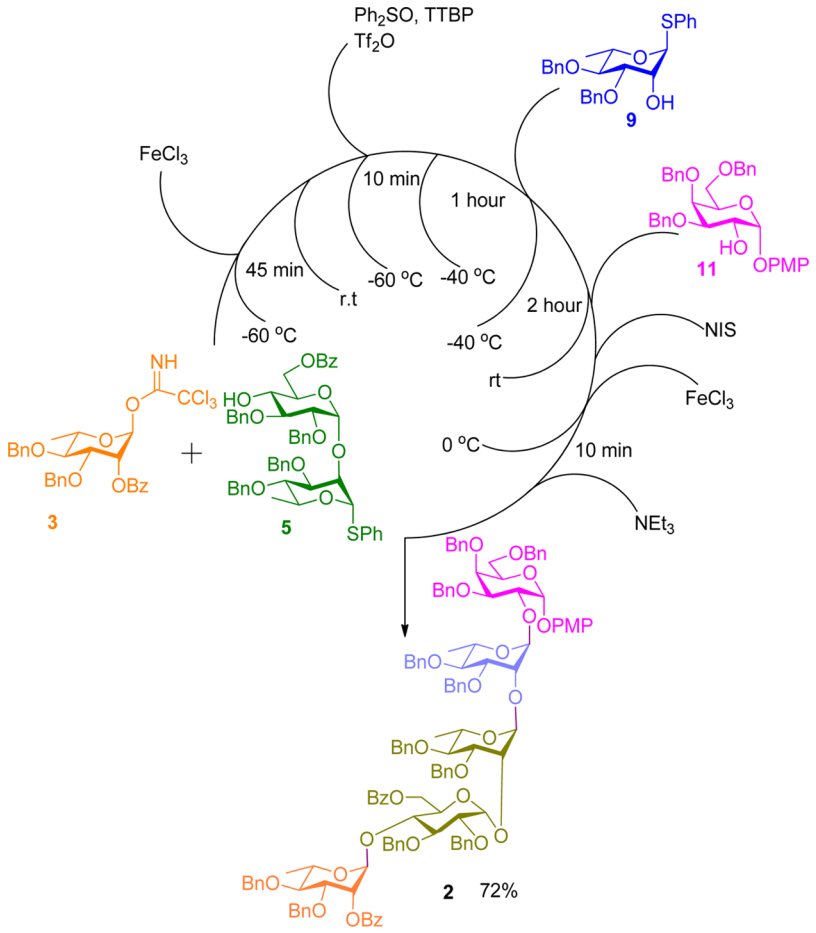
Scheme 7. Synthesis of Pentasaccharide Derivative 2 via a Four-Component, One-Pot Sequential Glycosylation Technique



disaccharide **6** in 92% yield. The NMR spectra of disaccharide **6** showed signals characteristic of the presence of both donor and acceptor moieties, while an α-configuration of the interglycosidic linkage was confirmed from the corresponding ^{1}H (δ 5.01, H_1', $J_{1,2}$ = 0.8 Hz) and ^{13}C NMR (δ 97.8) spectra. Deacetylation of **6** with NaOMe−MeOH and dry DCM furnished quantitatively the disaccharide acceptor **7**, necessary for the one-pot sequential glycosylation via a [1 + 2 + 2] approach (Scheme 5).

With the present set of donors and acceptors in hand, we first attempted the one-pot glycosylation reactions toward targeted pentasaccharide via a [1 + 2 + 2] approach. Disaccharide acceptor **5** was glycosylated with glycosyl donor **3** at −60 °C to room temperature using 10 mol % of $FeCl_3$.[23] After full consumption of the starting materials (checked by TLC), into the same pot second disaccharide acceptor **7** followed by NIS were added. The reaction mixture was cooled to 0 °C, and another 10 mol % of $FeCl_3$ was added; TLC after 10 min showed complete consumption of the starting materials. Thus, the targeted pentasaccharide was prepared via a three-component, one-pot sequential glycosylation technique in 78% yield (Scheme 6). The formation of the pentasaccharide derivative **2** was confirmed by NMR spectroscopic techniques (^{1}H-, ^{13}C-, COSY, HSQC, HMBC, NOESY) and also by HRMS.

The anomeric protons of compound **2** appeared at δ 4.68 (bs, H_1'''), 5.03 (2 bs, H_1' and H_1''), 5.21 (bs, H_1''''), and 5.23 (d, J 3.5 Hz, H_1) ppm and the corresponding carbons at 94.1(C_1'''), 98.2 (C_1'), 101.6 (C_1''), 97.9 (C_1''''), and 98.0 (C_1) ppm, respectively, and the signal of the carbonyl carbons appeared at 165.8 and 166.1 ppm.

After successfully achieving a synthetic route toward pentasaccharide derivative **2** via a three-component, one-pot sequential glycosylation technique, we sought to synthesize the same in a more step-economic way. A four-component, one-pot sequential glycosylation reactions for synthesis of the target **2** were then explored. For this, disaccharide acceptor **5** was first glycosylated with 2-*O*-benzoyl-3,4-di-*O*-benzyl-L-rhamnopyranosyl trichloroacetimidate donor **3** via the previously standardized procedure using 10 mol % of $FeCl_3$ at −60 °C to room temperature.[23] After the reaction showed a clear conversion toward our desired trisaccharide derivative (indicated by TLC), the reaction mixture was again cooled to −60 °C. To this cold mixture were added diphenyl sulfoxide (Ph_2SO), TTBP, and triflic anhydride (Tf_2O), the mixture was kept at that temperature for 10 min, and then the temperature was raised to −40 °C. After 1 h at that temperature, the second glycosyl acceptor **9** in dry DCM was injected into the cold reaction vessel, and the reaction mixture was allowed to attain room temperature. After consumption of both of the starting materials (checked by TLC), the last acceptor **11** and NIS were added into the same reaction vessel. The temperature was lowered to 0 °C, into this mixture $FeCl_3$ was added again, the resulting mixture was kept for 10 min at that temperature, and after complete conversion toward the desired pentasaccharide derivative **2** (indicated by TLC) the reaction was quenched with NEt_3. Thus, the targeted pentasaccharide was prepared via

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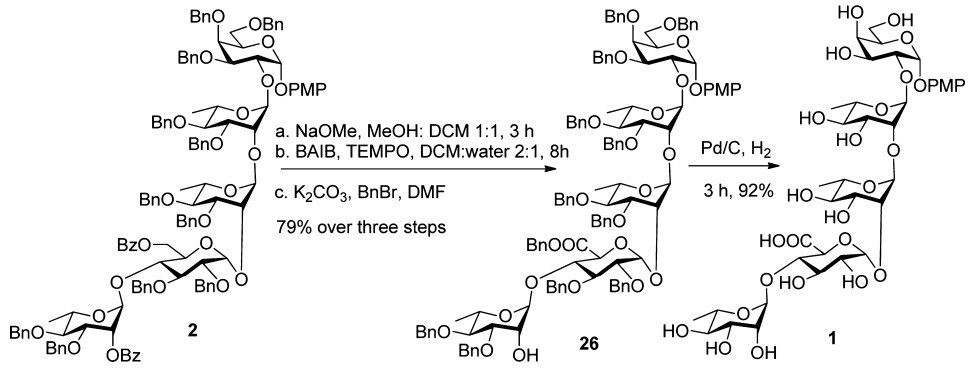
Scheme 8. Conversion of Pentasaccharide Derivative 2 to the Target Pentasaccharide 1



a four-component, one-pot sequential glycosylation technique in 72% yield (Scheme 7).

Finally, debenzoylation under Zemplén conditions followed by regioselective oxidation of the primary hydroxyl group in the presence of a secondary one using TEMPO and bis-acetoxy iodobenzene (BAIB) in DCM water followed by benzylation using K_2CO_3 and benzyl bromide in dry DMF afforded the fully benzylated derivative of the acidic pentasaccharide derivative **26** in 79% yield over three steps (Scheme 8). Finally, a global debenzylation using hydrogen and palladium−charcoal in a mixture of ethyl acetate, water, and methanol ultimately afforded the desired pentasaccharide **1** in 92% yield (Scheme 8). Compound **1** was characterized by NMR spectroscopic techniques (^{1}H-, ^{13}C-, COSY) and also by HRMS.

■ CONCLUSION

In conclusion, we have developed an expeditious strategy for the synthesis of the acidic pentasaccharide, related to the *O*-antigen of *E. coli* 120, in the form of its *p*-methoxyphenyl glycoside (**1**) via one-pot sequential glycosylation techniques. The synthesis of the target compound is achieved through suitable protecting group manipulations on commercially available monosaccharides and stereoselective glycosylations. Protecting group manipulation like per-*O*-acetylation−thioglycosidation was performed in one pot. The glycosylations were achieved either by the activation of the thioglycosides using NIS in the presence of $FeCl_3$ or by a preactivation using Ph_2SO, TTBP, and Tf_2O and the activation of the trichloroacetimidates using $FeCl_3$ alone or TMSOTf. The targeted pentasaccharide syntheses were performed with both three- and four-component, one-pot sequential glycosylation reactions, and in both cases, the orthogonal glycosylations were carried out using the catalytic activity of $FeCl_3$.

■ EXPERIMENTAL SECTION

General Procedure. All reactions were performed in flamed-dried flasks fitted with rubber septa under a positive pressure of argon, unless otherwise stated. DCM was refluxed with P_2O_5, distilled before use, and stored over 4 Å molecular sieves. Traces of water in the starting materials were removed by coevaporation with toluene. Flash column chromatography was performed employing silica gel 60 sorbent (40−63 μm, 230−400 mesh). Thin-layer chromatography (analytical and preparative) was performed using Merck silica gel plates (60-F254) to monitor the reactions and visualized under UV (254 nm) and/or by charring with 5% ethanolic solution of sulfuric acid. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 (300 MHz), a Bruker DPX-400 (400 MHz), a Bruker DPX-500 (500 MHz) spectrometer at ambient temperature in $CDCl_3$ or D_2O and assigned using 2D methods (COSY, HSQC). Optical rotations were measured using a JASCO P-1020 digital polarimeter. High-resolution mass spectra (HRMS) were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface on a Micro (YA-263) mass spectrometer (Manchester, UK).

*2-O-Benzoyl-3,4-di-O-benzyl-α-L-rhamnopyranosyl Trichloroacetimidate (**3**).* To a solution of compound **14** (2 g, 3.7 mmol) in aqueous acetone (4:1) was added TCCA (1.2 g, 3.7 mmol) at 0 °C, and the reaction mixture was stirred for 40 min. Then the white precipitate was filtered, and the bed was washed with DCM (3 × 5 mL). The combined filtrate and washings was evaporated, and the resulting mixture was again dissolved in DCM. This organic part was subsequently washed with saturated $NaHCO_3$ solution (200 mL) and water (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish compound **19**. Column filtration of the crude product furnished pure compound as a white foam (**15**, 1.6 g, 97%). Then to this solution of compound **15** (1 g, 2.23 mmol) and CCl_3CN (0.34 mL, 3.34 mmol) in dry DCM (15 mL) was added DBU (0.1 mL, 0.67 mmol) was added at −5 °C, and the reaction mixture was stirred at that temperature. After 5 h, excess solvent was removed, and the resulting mixture was purified through flash column chromatography (PE/EA, 5:1) to furnish pure compound **3** as colorless syrup (1.18 g, 90%). $[\alpha]^{25}_D$ = 4.2 (*c* 1.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (s, 1H, N*H*), 8.11−8.09 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.64−7.26 (m, 13H, Ar*H*), 6.31 (s, 1H, H_1), 5.72 (s, 1H, H_2), 4.93 (d, *J* = 10.8 Hz, 1H, Bn*H*), 4.80 (d, *J* = 11.4 Hz, 1H, Bn*H*), 4.66 (d, *J* = 11.1 Hz, 1H, Bn*H*), 4.61 (d, *J* = 11.5 Hz, 1H, Bn*H*), 4.11 (dd, *J* = 3.0, 9.4 Hz, 1H, H_3), 4.00 (m, 1H, H_5), 3.65 (app t, *J* = 9.5 Hz, 1H, H_4), 1.39 (d, *J* = 6.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C═O), 160.2 (C═NH), 138.1, 137.6, 133.4, 130.0, 129.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 95.4 (C_1), 90.9, 79.4, 77.4, 75.6, 71.9, 70.8, 68.1, 18.2 (CH_3). HRMS (ESI-TOF): calcd for $C_{29}H_{28}Cl_3NO_6Na$ (M + Na) 614.088, found 614.0882.

*Phenyl 6-O-Benzoyl-2,3-di-O-benzyl-1-thio-β-D-glucopyranoside (**19**).* To a solution of phenyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside **18** (3 g, 6.64 mmol) in a 1:1:0.5 mixture of DCM/MeCN/NEt_3 (10 mL) was added benzoyl cyanide (0.9 mL, 7.3 mmol) diluted in 2 mL of dry DCM at −78 °C, and the reaction mixture was stirred at that temperature for 2 h. The reaction mixture was diluted in DCM and subsequently washed with saturated $NaHCO_3$ solution (200 mL) and water (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish crude product **19**. Purification of **19** by silica gel column chromatography (PE/EA, 3:1) yielded phenyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside as a white solid (**19**, 3.5 g, 95%). Mp (EA/PE): 90−92 °C. $[\alpha]^{25}_D$ = −21.8 (*c* 1.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09−8.06 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.61−7.14 (m, 18H, Ar*H*), 4.95−4.92 (m, 2H), 4.81−4.70 (m, 3H), 4.64 (bs, 1H), 3.52−3.59 (m, 4H), 3.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C═O), 138.3, 137.9, 133.5, 133.3, 132.2, 129.9, 129.8, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 87.5 (C_1), 85.9, 80.4, 77.8, 75.7, 75.4, 70.1, 63.9. HRMS (ESI-TOF): calcd for $C_{33}H_{32}O_6SNa$ (M + Na) 579.1818, found 579.1819.

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*Phenyl 4-O-Acetyl-6-O-benzoyl-2,3-di-O-benzyl-1-thio-β-D-glucopyranoside (**20**).* Acetic anhydride (0.56 mL, 5.94 mmol) and $Mg(OTf)_2$ (9.4 mg, 0.027 mmol) were added to a solution of compound **19** (3 g, 5.39 mmol) in dry DCM (15 mL) at 0 °C, and the resulting mixture was stirred for 30 min. After completion of the reaction (indicated by TLC), excess acetic anhydride was removed using a rotatory evaporator. The resulting syrup was dissolved in DCM and subsequently washed with saturated $NaHCO_3$ solution (200 mL) and water (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product. It was purified by column chromatography on silica gel. Column elution by PE/EA, 4:1 furnished pure compound **20** as white solid (3.13 g, 97%). Mp (EA/PE): 84−86 °C. $[\alpha]^{27}_D$ = −27.8 (*c* 2.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08−8.05 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.60−7.10 (m, 18H, Ar*H*), 4.74−4.64 (m, 3H, H_1, H_6, Bn*H*), 4.54 (d, *J* = 12.1 Hz, 1H, Bn*H*), 5.14 (t, *J* = 9.7 Hz, 1H, H_4), 4.93−4.82 (m, 2H, Bn*H*), 4.32 (m, 1H, H_6), 3.77−3.68 (m, 2H, H_3, H_5), 3.58 (t, *J* = 9.3 Hz, 1H, H_2), 1.93 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 (*C*═O), 166.2 (*C*═O), 138.0, 137.8, 133.2, 133.1, 132.4, 129.9, 129.8, 128.9, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 87.5 (C_1), 83.9, 80.6, 76.0, 75.6, 69.9, 63.2, 20.8 (CH_3CO). HRMS (ESI-TOF): calcd for $C_{35}H_{34}O_7SNa$ (M + Na) 621.1923, found 621.1940.

*4-O-Acetyl-6-O-benzoyl-2,3-di-O-benzyl-D-glucopyranose (**21**).* To a solution of compound **20** (2 g, 3.3 mmol) in aqueous acetone (4:1) was added TCCA (1.2 g, 3.3 mmol) at ambient temperature, and the mixture was stirred for 20 min. Then the white precipitate was filtered, and the bed was washed with DCM (3 × 15 mL). The combined filtrate and washings was evaporated, and the resulting mixture was again dissolved in DCM. This organic part was subsequently washed with saturated $NaHCO_3$ solution (200 mL) and water (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to furnish compound **21**. Column filtration of the crude product furnished white foam of pure compound as mixture of anomers (**21**, 1.62 g, 96%). HRMS (ESI-TOF): calcd for $C_{29}H_{30}O_8Na$ (M + Na) 529.1839, found 529.1840.

*4-O-Acetyl-6-O-benzoyl-2,3-di-O-benzyl-D-glucopyranosyl Trichloroacetimidate (**8**).* To a solution of compound **21** (1.5 g, 2.96 mmol) and CCl_3CN (0.46 mL, 4.44 mmol) in dry DCM (15 mL) was added DBU (0.14 mL, 0.9 mmol) at −5 °C, and the reaction mixture was stirred at that temperature. After 5 h, excess solvent was removed, and the resulting crude product was purified through flash column chromatography (PE/EA, 5:1) to furnish pure compound **8** as a colorless syrup (1.75 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1H, N*H*), 8.02−8.00 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.55−7.25 (m, 13H, Ar*H*), 6.84 (d, *J* = 3.0 Hz, 1H, H_1), 5.21 (t, *J* = 10.0 Hz, 1H, H_4), 4.89 (d, *J* = 11.5 Hz, 1H, Bn*H*), 4.76−4.67 (m, 3H, H_5, Bn*H*), 4.47 (d, *J* = 12.0 Hz, 1H, Bn*H*), 4.27 (dd, *J* = 12.5, 5.0 Hz, 1H, H_6), 4.21 (dd, *J* = 10.5, 4.5 Hz, 1H, H_6), 4.02 (t, *J* = 9.5 Hz, 1H, H_3), 3.83 (dd, *J* = 9.5, 3.5 Hz, 1H, H_2), 1.97 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (*C*═O), 166.2 (*C*═O), 162.3, 160.9, 138.2, 137.7, 133.1, 129.8, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 93.9 (C_1), 91.1, 79.2, 78.4, 75.4, 73.1, 70.5, 69.2, 62.6, 20.8 ($COCH_3$). HRMS (ESI-TOF): calcd for $C_{31}H_{30}NCl_3O_8Na$ (M + Na) 672.0935, found 672.0930.

*p-Methoxyphenyl 3,4,6-Tri-O-benzyl-α-D-galactopyranoside (**11**).* To a solution of 3,4,6-tri-*O*-benzyl-α-D-galactose 1,2-(methyl orthoacetate) **23** (2.50 g, 4.94 mmol) in dry CH_3CN (30 mL) containing 4 Å molecular sieves was added *p*-methoxyphenol (1.23 g, 9.96 mmol) at room temperature. $BF_3{\cdot}Et_2O$ (1.9 mL, 14.94 mmol) was added to this mixture on an ice bath and kept for 30 min. The reaction mixture was filtered through a Celite bed, and the residue was washed with DCM (3 × 15 mL). The combined filtrate and washings was subsequently washed with cold 5% aqueous NaOH (250 mL) followed by water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude residue was used for further reaction. To a solution of this crude material in a mixture of dry DCM (10 mL) and dry MeOH (8 mL) was added 1 M methanolic NaOMe (2 mL) solution, and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was then neutralized with Dowex-50W cation exchange resin (H^+) and filtered. The resin was washed with MeOH, and the combined filtrate and washings was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA, 9:1) to afford **11** as white solid (2.56 g, 92% over two steps). Mp (EA/PE): 96−98 °C. $[\alpha]^{29}_D$ = +100.6 (*c* 2.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.26 (m, 15H, Ar*H*), 7.07−7.04 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.83−6.79 (d, *J* = 8.9 Hz, 2H, Ar*H*), 5.51 (d, *J* = 3.5 Hz, 1H, H_1), 4.76 (d, *J* = 11.3 Hz, 1H, Bn*H*), 4.84−4.75 (ABq, *J* = 11.5 Hz, 2H, Bn*H*), 4.62 (d, *J* = 11.3 Hz, 1H, Bn*H*), 4.51−4.35 (m, 3H, O*H*, Bn*H*), 4.17 (app t, *J* = 6.3, 6.1 Hz, 1H, H_6), 4.10 (bs, 1H, H_4), 3.92 (dd, *J* = 9.9, 2.4 Hz, 1H, H_3), 3.77 (s, 3H, OCH_3), 3.69−3.56 (m, 3H, H_2, H_5, H_6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 150.8, 138.5, 138.2, 137.9, 128.6, 128.4, 128.3, 128.2, 127.8, 127.76, 118.7, 114.6, 98.9 (C_1, J_{C-H} = 169.8), 79.6, 74.8, 74.0, 73.5, 72.6, 70.4, 69.0, 68.8, 55.6 (OCH_3). HRMS (ESI-TOF): calcd for $C_{34}H_{36}O_7Na$ (M + Na) 579.2359, found 579.2379.

*Phenyl 2-O-Acetyl-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranosyl-(1→2)-3,4-di-O-benzyl-1-thio-α-L-rhamnopyranoside (**4**).* To a solution of 2-*O*-acetyl-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-glucopyranosyl trichloroacitimidate **8** (200.0 mg, 0.31 mmol) and phenyl 3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside **9** (120.9 mg, 0.28 mmol) in a 3:2 (v/v) mixture of dry DCM/Et_2O (30 mL) was added activated molecular sieves (4 Å), and the reaction mixture was stirred under argon atmosphere for 45 min. Then the reaction vessel was placed in a 0 °C cold bath, and TMSOTf (10 μL, 0.06 mmol) was added via a microsyringe. After 10 min, complete consumption of both starting materials was observed. The reaction mixture was quenched by Et_3N and filtered through the Celite bed, and the bed was washed with DCM (3 × 15 mL). The combined filtrate and washings was subsequently washed with saturated $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by flash column chromatography (eluent: PE/EA, 3:1) to afford the desired disaccharide derivative **4** as white foam (230.6 mg, 90%). $[\alpha]^{28}_D$ = +11.8 (*c* 3.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.06 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.99−7.18 (m, 28H, Ar*H*), 5.48 (s, 1H, H_1), 5.18 (app t, *J* = 9.6, 10.0 Hz, 1H, H_4'), 5.04−4.89 (m, 3H, H_1', Bn*H*), 4.82−4.61 (m, 5H, Bn*H*), 4.54 (d, *J* = 11.6 Hz, 1H, Bn*H*), 4.38−4.23 (m, 4H, H_2, H_5, H_5', H_6'), 4.06 (t, *J* = 9.6 Hz, 1H, H_3'), 3.97−3.89 (m, 2H, H_3, H_6'), 3.77 (t, *J* = 9.2 Hz, 1H, H_4), 3.76 (dd, 1H, *J* = 9.6, 2.8 Hz, H_2'), 1.99 (s, 3H, $COCH_3$), 1.45 (d, 3H, *J* = 6.0 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (*C*═O), 166.2 (*C*═O), 138.4, 138.6, 138.2, 138.0, 134.6, 133.1, 131.7, 129.9, 129.8, 129.1, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.5, 127.3, 94.6 (C_1), 84.9 (C_1'), 80.4, 79.9, 79.2, 78.7, 75.3, 75.2, 74.5, 73.0, 72.3, 69.7, 69.4, 67.8, 62.5, 20.9 ($COCH_3$), 17.9 (CH_3). HRMS (ESI-TOF): calcd for $C_{55}H_{56}O_{11}SNa$ (M + Na) 947.3441, found 947.3457.

*Phenyl 6-O-Benzoyl-2,3-di-O-benzyl-α-D-glucopyranosyl-(1→2)-3,4-di-O-benzyl-1-thio-α-L-rhamnopyranoside (**5**).* Compound **4** (200 mg, 0.22 mmol) was dissolved in dry MeOH (15 mL), and the solution was cooled to 0 °C on an ice bath. Acetyl chloride (0.16 mL, 2.2 mmol) was added dropwise, with continuous stirring, and the solution was stirred under anhydrous conditions for 2 h. After completion of the reaction (indicated by TLC), excess MeOH and acetyl chloride were removed in vacuo. The resulting syrup was dissolved in DCM (15 mL), and the solution was subsequently washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated. This was purified by column chromatography on silica gel (PE/EA, 4:1) to afford **5** as colorless syrup (168 mg, 88%). $[\alpha]^{25}_D$ = +48.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.05 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.24−7.61 (m, 28H, Ar*H*), 5.51 (s, 1H, H_1), 5.04−4.98 (m, 2H, Bn*H*), 4.96 (d, *J* = 3.4 Hz, 1H, H_1'), 4.87 (d, *J* = 11.2 Hz, 1H, Bn*H*), 4.78−4.63 (m, 5H, Bn*H*), 4.46 (dd, *J* = 12.0, 4.0 Hz, 1H, H_6'), 4.37 (bs, 1H, H_2), 4.26−4.20 (m, 3H, H_5, H_5', H_6'), 3.97 (t, *J* = 9.2 Hz, 1H, H_4'), 3.90 (dd, *J* = 2.6, 9.2 Hz, 1H, H_3), 3.75 (t, *J* = 9.6 Hz, 1H, H_3'), 3.62−3.56 (m, 2H, H_2', H_4), 1.43 (d, *J* = 6.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (*C*═O), 138.7, 138.4, 138.3, 137.9, 133.2, 131.5, 129.8, 129.7, 129.1, 128.54, 128.45, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 95.2 (C_1), 85.1 (C_1'), 80.6, 80.4, 79.7, 79.2, 75.4, 75.1, 72.7, 72.4, 70.0, 69.4, 63.4, 17.9 (CH_3).

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HRMS (ESI-TOF): calcd for $C_{53}H_{54}O_{10}SNa$ (M + Na) 905.3336, found 905.3337.

*p-Methoxyphenyl 2-O-Acetyl-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-galactopyranoside (**6**).* To a mixture of phenyl 2-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside **10** (189.3 mg, 0.39 mmol) and *p*-methoxyphenyl 3,4,6-tri-*O*-benzyl-α-D-galactopyranoside **11** (200 mg, 0.36 mmol) in dry DCM (15 mL) were added flame-activated molecular sieves (4 Å). The mixture was stirred at room temperature under argon atmosphere. After 40 min, the mixture was cooled to 0 °C, and NIS (90 mg, 0.39 mmol) was added. Then $FeCl_3$ (13.0 mg, 0.08 mmol) was added. After 15 min, when the acceptor was consumed completely (checked by TLC), the reaction mixture was filtered through a Celite bed. The filtrate was diluted with DCM and subsequently washed with saturated sodium thiosulfate (100 mL), $NaHCO_3$ solution (100 mL), and water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the glycosylated product. The residue was purified by flash column chromatography (PE/EA, 5:1) to afford the title compound **6** as a colorless syrup (305.8 mg, 92%). $[\alpha]^{25}_D$ = +19.9 (*c* 6.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42−7.21 (m, 25H, Ar*H*), 7.01−6.99 (m, 2H, Ar*H*), 6.78−6.75 (d, *J* = 9.2 Hz, 2H, Ar*H*), 5.58 (dd, *J* = 2.8, 2.0 Hz, 1H, H_2'), 5.50 (d, *J* = 3.6 Hz, 1H, H_1), 5.10 (d, *J* = 0.8 Hz, 1H, H_1'), 4.96 (d, *J* = 11.2 Hz, 1H, Bn*H*), 4.86 (d, *J* = 10.8 Hz, 1H, Bn*H*), 4.79−4.68 (m, 3H), 4.59−4.48 (m, 3H, Bn*H*), 4.43−4.35 (ABq, *J* = 11.6 Hz, 2H, Bn*H*), 4.31 (dd, *J* = 10.0, 3.6 Hz, 1H, H_2), 4.13−4.04 (m, 3H, H_3, H_4, H_6), 3.95 (dd, *J* = 9.6, 3.2 Hz, 1H, H_3'), 3.78 (m, 1H, H_5'), 3.75 (s, 3H, OCH_3), 3.53−3.60 (m, 2H, H_5, H_6), 3.37 (app t, *J* = 9.6, 9.2 Hz, 1H, H_4'), 2.13 (s, 3H, $COCH_3$), 1.00 (d, *J* = 6.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 (*C*═O), 155.0, 151.0, 138.6, 138.4, 138.3, 138.1, 137.9, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 118.1, 114.6, 99.9 (C_1'), 97.9 (C_1), 79.9, 78.3, 77.9, 76.3, 75.1, 75.0, 74.8, 73.4, 73.2, 71.7, 69.9, 68.6, 68.4, 55.6 (OCH_3), 21.1 ($COCH_3$), 17.7 (CH_3). HRMS (ESI-TOF): calcd for $C_{56}H_{60}O_{12}Na$ (M + Na) 947.3983, found 947.4022.

*p-Methoxyphenyl 3,4-Di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-galactopyranoside (**7**).* To a solution of **6** (250 mg, 0.27 mmol) in dry DCM (5 mL) and dry MeOH (5 mL) was added 1 M methanolic NaOMe (0.2 mL) solution, and the reaction mixture was stirred for 3 h at room temperature. The solvent was removed under pressure, the crude mixture was diluted with DCM (10 mL) and subsequently washed with brine solution (100 mL), and washings were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA, 5:1) to give glassy syrupy product **7** (236 mg, 99%). $[\alpha]^{27}_D$ = +21.9 (*c* 3.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.22 (m, 25H, Ar*H*), 7.05−7.02 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.79−6.77 (d, *J* = 9.2 Hz, 2H, Ar*H*), 5.57 (d, *J* = 3.2 Hz, 1H, H_1), 5.13 (s, 1H, H_1'), 4.96 (d, *J* = 11.6 Hz, 1H, Bn*H*), 4.83 (d, *J* = 11.2 Hz, 1H, Bn*H*), 4.85−4.70 (ABq, *J* = 11.6 Hz, 2H, Bn*H*), 4.69−4.62 (ABq, *J* = 11.6 Hz, 2H, Bn*H*), 4.61−4.58 (d, *J* = 11.2 Hz, 2H, Bn*H*), 4.44−4.36 (q, *J* = 11.6 Hz, 2H, Bn*H*), 4.31 (dd, *J* = 10.0, 3.6 Hz, 1H, H_2), 4.13−4.04 (m, 4H, H_3/ H_3' H_4, H_2', H_5'), 3.87 (dd, *J* = 3.0, 9.0 Hz, 1H, H_3/H_3'), 3.80 (dd, *J* = 9.6, 6.4 Hz, 1H, H_5), 3.75 (s, 3H, OCH_3), 3.62 (m, 1H, H_6), 3.54 (dd, *J* = 9.2, 6.0 Hz, 1H, H_6), 3.41 (t, *J* = 9.2 Hz, 1H, H_4'), 0.95 (d, *J* = 6.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 151.0, 138.6, 138.5, 138.4, 138.0, 137.9, 128.6, 128.5, 128.4, 128.32, 128.3, 127.9, 127.82, 127.8, 127.7, 127.4, 118.0, 114.6, 101.8 (C_1'), 97.8 (C_1), 79.9, 79.8, 78.1, 77.4, 75.1, 74.9, 73.4, 73.1, 72.0, 69.9, 68.8, 68.7, 68.0, 55.6 (OCH_3), 17.6 (CH_3). HRMS (ESI-TOF): calcd for $C_{54}H_{58}O_{11}Na$ (M + Na) 905.3877, found 905.3943.

*p-Methoxyphenyl 2-O-Benzoyl-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→4)-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranosyl-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-galactopyranoside (**2**).* A mixture of **3** (73.6 mg, 0.13 mmol), **5** (100.0 mg, 0.113 mmol), and flame-activated 4 Å molecular sieves was stirred in dry DCM (10 mL) for 40 min at room temperature under argon atmosphere. The mixture was cooled to −60 °C, $FeCl_3$ (2.2 mg, 0.013 mmol) was added, and the reaction mixture was allowed to achieve room temperature. After 45 min, complete consumption of both starting materials was observed (checked by TLC). Acceptor **7** (89.7 mg, 0.10 mmol) and NIS (25.4 mg, 0.113 mmol) were then added to the same vessel. After the addition reaction vessel was placed in a 0 °C cold bath, another 10 mol % of $FeCl_3$ (2.2 mg, 0.013 mmol) was added. The second step of the reaction was completed within 10 min (indicated by TLC). The reaction was quenched by Et_3N and then filtered through a Celite bed. The bed was washed with DCM (3 × 15 mL). The combined filtrate and washings was subsequently washed with saturated sodium thiosulfate, aqueous $NaHCO_3$ (2 × 50 mL), and water (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by flash column chromatography (eluent: toluene/Et_2O, 9.5:0.5) to afford the desired fully protected pentasaccharide **2** as white foam (184.5 mg, 78%). $[\alpha]^{27}_D$ = +28.1 (*c* 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06−8.03 (d, *J* = 7.0 Hz, 2H, Ar*H*), 8.01−7.98 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.57−7.48 (m, 2H, Ar*H*), 7.43−7.03 (m, 56H, Ar*H*), 7.01−6.98 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.77−6.74 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.53 (d, *J* = 3.5 Hz, 1H, H_1), 5.46 (t, *J* = 2.5 Hz, 1H, H_2''''), 5.21 (bs, 1H, H_1''''), 5.03 (bs, 2H, H_1', H_1''), 4.97−4.93 (m, 3H, Bn*H*), 4.87−4.75 (m, 5H, Bn*H*), 4.73−4.53 (m, 10H, H_1''', Bn*H*), 4.43 (d, *J* = 12.0 Hz, 1H, Bn*H*), 4.41−4.33 (ABq, *J* = 11.5 Hz, 2H, Bn*H*), 4.32−4.24 (m, 3H, H_2, H_6''', Bn*H*), 4.19−4.12 (m, 4H, H_2', H_2'', H_6''', H_5''''), 4.06 (app t, *J* = 6.5, 6.0 Hz, 1H, H_5'''), 4.04−4.01 (m, 2H, H_4, H_3''''), 3.97−3.86 (m, 5H, H_3, H_3'', H_3''', H_4''', Bn*H*), 3.84−3.78 (m, 1H, H_5'', 1dd, *J* = 10.0, 3.0 Hz, 1H, H_3'), 3.75−3.68 (1s, OCH_3, m, 1H, H_5'), 3.64 (app t, *J* = 7.0 Hz, 1H, H_4''), 3.61−3.49 (m, 4H, H_5, H_6, H_6, H_4'''), 3.40−3.34 (m, 2H, H_4', H_2'''), 1.27 (d, *J* = 6.5 Hz, 3H, CH_3''''), 1.19 (d, *J* = 6.0 Hz, 3H, CH_3''), 0.94 (d, *J* = 6.0 Hz, 3H, CH_3'). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1 (*C*═O), 165.8 (*C*═O), 155.1, 151.2, 138.9, 138.87, 138.8, 138.7, 138.6, 138.5, 138.4, 138.3, 138.2, 133.1, 133.0, 130.3, 130.26, 130.0, 129.9, 128.7, 128.69, 128.64, 128.5, 128.4, 128.31, 128.3, 128.2, 128.1, 127.9, 127.89, 127.86, 127.83, 127.77, 127.7, 127.65, 127.60, 127.5, 127.4, 127.1, 118.2, 114.8, 101.6 (C_1''), 98.2 (C_1'), 98.0 (C_1), 97.9 (C_1''''), 94.1 (C_1'''), 80.62, 80.6, 80.5, 80.1, 79.8, 78.2, 78.1, 78.0, 75.6, 75.5, 75.34, 75.3, 75.2, 75.13, 75.10, 74.3, 73.5, 73.2, 73.1, 72.6, 72.4, 71.9, 71.6, 70.1, 69.8, 69.04, 69.0, 68.8, 68.7, 68.67, 62.9, 55.8 (OCH_3), 18.3 (CH_3), 18.1 (CH_3), 17.9 (CH_3). HRMS (ESI-TOF): calcd for $C_{128}H_{132}O_{26}Na$ (M + Na) 2107.8905, found 2107.8908.

*p-Methoxyphenyl 2-O-Benzoyl-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→4)-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranosyl-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-galactopyranoside (**2**).* A mixture of **3** (73.7 mg, 0.13 mmol), **5** (100.0 mg, 0.0.113 mmol), and flame-activated 4 Å molecular sieves were stirred in dry DCM (10 mL) for 40 min at room temperature under argon atmosphere. The mixture was cooled to −60 °C, $FeCl_3$ (2.2 mg, 0.013 mmol) was added, and the reaction mixture was allowed to achieve room temperature. After 45 min, complete consumption of both starting materials was observed (checked by TLC). The reaction was cooled to −60 °C, and to this Ph_2SO (50.2 mg, 0.25 mmol), TTBP (42.1 mg, 0.17 mmol), and Tf_2O (0.03 mL, 0.14 mmol) were added one by one. Then the reaction mixture was slowly brought to −40 °C and kept at that temperature for another 1 h, at which time phenyl 3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside **9** (44.4 mg, 0.10 mmol) in dry DCM (2 mL) was added. The reaction mixture was slowly warmed to room temperature. After full consumption of starting materials (checked by TLC), acceptor **11** (58.0 mg, 0.10 mmol) and NIS (22.5 mg, 0.10 mmol) were then added to the same vessel. After the addition reaction vessel was placed in a 0 °C cold bath, another 10 mol % of $FeCl_3$ (2.2 mg, 0.0078 mmol) was added. The reaction was completed within 10 min (indicated by TLC). The reaction mixture was quenched by Et_3N and then filtered through a Celite bed. The bed was washed with DCM (3 × 15 mL). The combined filtrate and washings was subsequently washed with saturated sodium thiosulfate (2 × 50 mL), aqueous $NaHCO_3$ (2 × 50 mL), and water (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a syrupy compound. The crude product was purified by flash column chromatography (eluent: toluene/diethyl ether, 9.5:0.5) to afford the desired fully protected pentasaccharide **2** as white foam

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(188.7 mg, 72%). Spectral data match that of the substrate synthesized previously.

*p-Methoxyphenyl 3,4-Di-O-benzyl-α-L-rhamnopyranosyl-(1→4)-benzyl-2,3-di-O-benzyl-α-D-glucopyranosyluronate-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-O-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-galactopyranoside (**26**).* To a solution of **2** (150 mg, 0.075 mmol) in DCM (5 mL) and dry MeOH (5 mL) was added 1 M methanolic NaOMe (0.2 mL) solution, and the reaction mixture was stirred for 3 h at room temperature. The solvent was removed under pressure and coevaporated with toluene, and the crude mixture was diluted with DCM (10 mL) and subsequently washed with brine solution (100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 concentrated under reduced pressure. The crude material was used for the next step without any purification. To this crude debenzoylated pentasaccharide derivative in DCM−H_2O (2:1, 10 mL) was added TEMPO (5.9 mg, 0.038 mmol) followed by BAIB (72.4 mg, 0.23 mmol), and the two-phase reaction mixture was stirred vigorously at room temperature for 8 h until TLC (4:1 toluene/acetone) indicated complete conversion of the starting material to a lower running spot. The mixture was diluted with DCM (10 mL) and subsequently washed with saturated sodium thiosulfate solution (100 mL) and saturated $NaHCO_3$ solution (100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and used for further reaction without any purification. Anhydrous K_2CO_3 (12.4 mg, 0.09 mmol) followed by BnBr (10 μL, 0.09 mmol) was added at 0 °C under argon to a solution of the foregoing material in dry DMF (10 mL), and the mixture was allowed to warm to room temperature. The organic layer was dried, concentrated, and coevaporated with toluene. The crude mixture was diluted with DCM (10 mL) and subsequently washed with brine solution (100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 concentrated under reduced pressure. Purification of this crude mass by silica gel column chromatography (toluene/acetone 9:1) yielded the desired benzyl urinate **26** (124.7 mg, 79% over three steps). $[\alpha]^{25}_D$ = +15.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.18 (m, 60H, Ar*H*), 6.99−6.97 (d, *J* = 9.2 Hz, 2H, Ar*H*), 6.77−6.74 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.51 (d, *J* = 3.2 Hz, 1H), 5.09−4.99 (m, 4H), 4.94−4.74 (m, 9H), 4.69−4.53 (m, 10H), 4.50−4.45 (m, 2H), 4.41−4.23 (m, 5H), 4.11−3.81 (m, 11H), 3.78−3.74 (m, 2H), 3.75 (s, 3H, OCH_3), 3.68 (m, 1H), 3.59−3.49 (m, 4H), 3.37 (m, 1H), 3.26 (app t, *J* = 9.6, 9.2 Hz, 1H), 1.23 (d, *J* = 6.0 Hz, 3H, CH_3), 1.00 (d, *J* = 6.0 Hz, 3H, CH_3), 0.86 (d, *J* = 6.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (C═O), 155.1, 151.2, 139.4, 138.9, 138.8, 138.7, 138.6, 138.5, 138.4, 138.3, 138.2, 138.1, 135.0, 128.7, 128.68, 128.6, 128.5, 128.45, 128.4, 128.35, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.56, 127.52, 127.5, 127.2, 118.1, 114.7, 114.2, 101.4, 99.5, 98.5, 97.9, 95.7, 80.2, 79.9, 78.0, 77.5, 77.4, 75.5, 75.3, 75.2, 75.1, 74.6, 73.5, 73.2, 72.23, 72.2, 72.0, 71.83, 71.8, 70.8, 70.0, 69.0, 68.9, 68.7, 68.3, 68.2, 67.6, 55.8 (OCH_3), 18.1 (CH_3), 18.0 (CH_3), 17.9 (CH_3). HRMS (ESI-TOF): calcd for $C_{121}H_{128}O_{25}K$ (M + K) 2020.8416, found 2020.8438.

*p-Methoxyphenyl α-L-Rhamnopyranosyl (1→4)-α-D-glucopyranosyluronic acid-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-D-galactopyranoside (**1**).* A mixture of protected acidic pentasaccharide **35** (75 mg, 0.038 mmol), the resulting mixtur,e and 10% Pd−C (90 mg) was taken in ethyl acetate (1 mL), methanol (3 mL), and H_2O (1 mL) and stirred under H_2 atmosphere for 3 h. The catalyst was filtered through Celite bed, and the bed was washed with methanol (3 × 5 mL). The combined filtrate and washings were concentrated under reduced pressure and then passed through a 0.45 μm Millipore membrane and lyophilized to afford **1** as a white foam (31.3 mg, 92%). $[\alpha]^{25}_D$ = +45.5 (*c* 0.37, H_2O). ^{1}H NMR (400 MHz, D_2O): δ 7.08−7.01 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.95−6.92 (d, *J* = 9.2 Hz, 2H, Ar*H*), 5.60 (d, *J* = 3.6 Hz, 1H, H_1), 5.09 (s, 1H, H_1'), 5.03 (s, 1H, H_1''), 4.99 (d, *J* = 3.6 Hz, 1H, H_1'''), 4.59 (s, 1H, H_1''''), 4.57 (s, 1H, H_5'''), 4.00 (dd, *J* = 10.4, 3.2 Hz, 1H, H_3), 4.05 (m, 1H, H_2'), 4.02−3.99 (m, 3H, H_4, H_5', H_2''), 3.97−3.91 (m, 2H, H_2, H_5), 3.88 (m, 1H, H_3'), 3.83 and 3.81 (each t, *J* = 3.2 Hz, 1H, H_3'', H_3''''), 3.75 (s, 3H, OCH_3), 3.78−3.68 (m, 3H, H_3, H_5''), 3.66 and 3.64 (bs, 2H, H_3''', H_4'''), 3.62−3.53 (m, 4H, H_4'', H_2''', H_2'''', H_5''''), 3.49−3.43 (t, *J* = 10.0 Hz, 2H, H_4', H_4''''), 3.40−3.35 (m, 2H, H_6, H_6), 1.25 (d, *J* = 6.4 Hz, 3H, CH_3''), 1.18 (d, *J* = 6.4 Hz, 3H, CH_3'), 0.91 (d, *J* = 6.0 Hz, 3H, CH_3''''). ^{13}C NMR (100 MHz, D_2O): δ 173.0 (C═O), 154.6, 150.2, 118.1, 115.2, 101.4, 101.0, 99.9, 97.9, 97.1, 79.2, 78.6, 77.3, 77.0, 71.9, 71.5, 71.34, 71.3, 70.5, 70.3, 70.2, 70.0, 69.6, 69.4, 69.3, 69.1, 68.5, 61.0, 55.9 (OCH_3), 16.6 (CH_3), 16.5 (CH_3), 16.4 (CH_3). HRMS (ESI-TOF): calcd for $C_{37}H_{56}O_{25}Na$ (M + Na) 923.3009, found 923.3005.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00561.

Syntheses of compounds **10**, **13**, **14**, and **17**; ^{1}H and ^{13}C NMR spectra of compounds **1**−**8**, **10**, **11**, **13**, **14**, **17**, **19**, **20**, and **26**; COSY spectra of compounds **1**, **2**, **4**, **6**, and **11**; DEPT, HSQC, HMBC, and NOSEY spectra of compound **2** (PDF)

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Notes

The authors declare no competing financial interest.

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