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PII: S0040-4020(19)31074-9

DOI: https://doi.org/10.1016/j.tet.2019.130697

Reference: TET 130697

To appear in: *Tetrahedron*

Received Date: 18 September 2019

Revised Date: 14 October 2019

Accepted Date: 15 October 2019

Please cite this article as: Shit P, Gucchait A, Misra AK, Straightforward sequential and one-pot synthesis of a pentasaccharide repeating unit corresponding to the cell wall *O*-antigen of *Shigella boydii* type 18, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.130697.

Graphical Abstract

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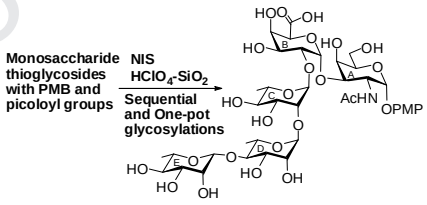

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Straightforward sequential and one-pot synthesis of a pentasaccharide repeating unit corresponding to the cell wall *O*-antigen of *Shigella boydii* type 18

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Abstract— Synthesis of a pentasaccharide repeating unit corresponding to the cell of wall *O*-antigen *Shigella boydii* type 18 has been achieved by sequential as well as iterative glycosylations in one-pot. Use of *p*-methoxybenzyl group (PMB) as an *in situ* removable protecting group allowed obtaining the desired pentasaccharide derivative in a generalized glycosylation condition and in one-pot condition. Synthesis of a beta-L-rhamnosidic linkage present in the molecule has been successfully achieved using L-rhamnosyl thioglycoside donor having a picoloyl group at remote C-3 position influencing beta selectivity in the glycosylation. A combination of *N*-iodosuccinimide (NIS) and perchloric acid supported over silica ($HClO_4$-SiO_2) has been used as thiophilic glycosylation promoter in all glycosylation reactions. TEMPO mediated selective oxidation of the primary hydroxyl group has been carried out at the late stage of the synthetic strategy.

Keywords: Pentasaccharide; one-pot; iterative glycosylation; TEMPO oxidation; *Shigella boydii* type 18.
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1. Introduction

Diarrhoeal epidemics with life threatening incidences are worldwide health concern, which are the result of the consumption of contaminated food and water.[1] Particularly, enteric infections are common in the developing countries where adequate sanitation is absent.[2] In most of the cases, the gastrointestinal disorders are caused by the infection of are *Shigella*, *Salmonella* and *E. coli* bacteria.[3,4,5] One of the long known well studied bacterial infections leading to devastating Diarrhoea is Shigellosis,[6] which is caused by the infection of different species of *Shigella* bacilli, such as *Shigella boydii (S. boydii)*, *Shigella dysenteriae (S. dysenteriae)*, *Shigella flexneri* (S. flexneri) and *Shigella sonnei (S. sonnei)*, which are also classified as *Shigella* subgroups A, B, C, and D, respectively.[7] The majority of *Shigella* infections are caused by *S. boydii*, *S. dysenteriae*, *S. flexneri*. The virulence properties of Shigella strains appeared from the structure of their cell wall *O*-antigens, which are polysaccharide fragments containing some acidic constituents such as uronic acid, pseudaminic acid, lactic acid, pyruvic acid etc.[7] The structure of the cell wall *O*-antigen of *Shigella boydii* type 18 was reported by Feng et al.[8] It is a pentasaccharide repeating unit, acidic in nature consisting of one α-D-galactouronic acid, one β-L-rhamnose, two α-L-rhamnose and one α-D-galactose. Bacterial cell wall polysaccharide derived glycoprotein conjugate vaccines are used in the clinics for several years to control bacterial infections, such as pneumonia,[9,10] *Haemophilia influenza* type b (Hib) infection,[11] meningitides,[12] cholera,[13] hemorrhagic diarrhoeal infections,[14] urinary tract infections to name a few.[9-15] However, use of polysaccharides from the natural sources using bacterial fermentations suffer from several drawbacks, which include handling of live bacterial strains; lack of homogeneity, batch to batch variation; difficulties associated with the removal of biological impurities etc. Therefore, it is quite pertinent to identify alternative approaches to obtain significant quantity of oligosaccharide fragments corresponding to the natural polysaccharides with precise structures and adequate purity. Developments of chemical synthetic strategies for the synthesis of oligosaccharides are the best choice to address this issue.

Emergence of multidrug resistant bacterial strains is a serious concern for controlling of infectious diseases. In spite of development of various therapeutic measures against diarrhoeal infections caused by different strains of Shigella, there is a demand of alternative approaches for the controlling Shigellosis. Since, cell wall polysaccharides are found to be immunogenic in nature, development of glycoconjugate derivatives using oligosaccharides corresponding to the cell wall of Shigella could be useful as potential glycoconjugate vaccine lead against Shigellosis. A significant number of reports appeared in the past for the development of anti-shigellosis agents using glycoconjugate derivatives.[16-20] However, it is essential to have a significant quantity of oligosaccharides to carry out a wide variety of biological studies. Hence, a concise, multistep synthetic strategy for the synthesis of a pentasaccharide repeating unit corresponding to the cell wall polysaccharide of *Shigella boydii* type 18 is presented herein. The synthetic strategy has been designed to carry out stereoselective glycosylations of suitably functionalized monosaccharide units with *in situ* removable temporary protecting groups to achieve the pentasaccharide moiety in step-economic approach avoiding lengthy protection-deprotection steps. In addition to the sequential glycosylation strategy, a one-pot approach for the synthesis of the pentasaccharide derivative has also been developed applying iterative glycosylations of monosaccharide intermediates protected with PMB groups.

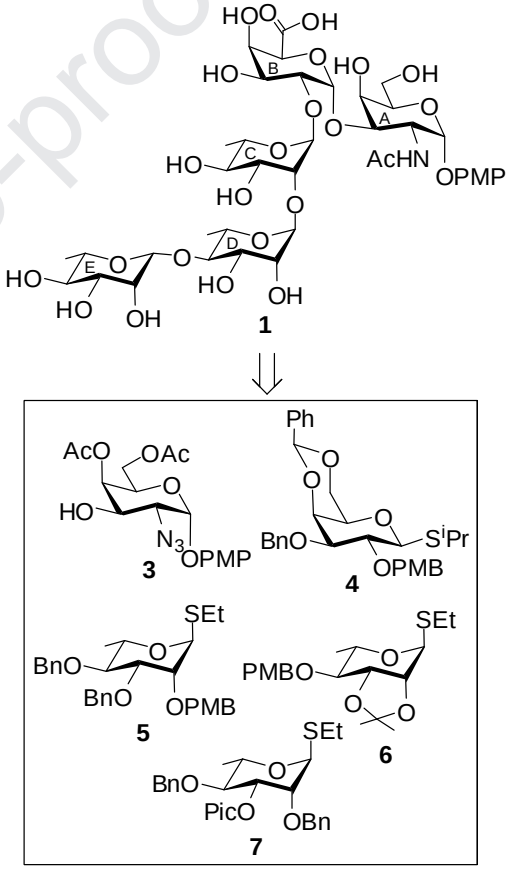


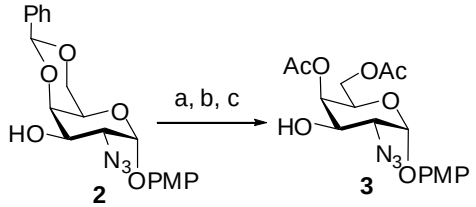
Figure 1: Structure of the synthesized pentasaccharide and its synthetic intermediates.

2. Results and discussion

In order to synthesize the target pentasaccharide **1**, it was decided to apply a generalized reaction condition for the stereoselective glycosylation of monosaccharide units. For this purpose, a set of monosaccharide thioglycoside derivatives **3**, **4**,[21] **5**,[22] **6**[23] containing *p*-methoxybenzyl (PMB) group in suitable positions and **7**[24] having a picoloyl group at C-3 position were prepared following earlier reported reaction conditions

(Figure 1). The monosaccharide derivatives were judiciously functionalized to achieve the best outcome of the stereoselective glycosylations. The PMB groups were installed in the monosaccharide intermediates as an *in situ* removable temporary protecting group.[25] The 3-*O*-picoloylated L-rhamnosyl thioglycoside (**7**) was employed for the synthesis of β-rhamnosidic linkage exploiting the influence of the remotely positioned picoloyl group in β-glycosylation as described earlier by Demchenko *et al.* and Kulkarni *et al.*[26] All stereoselective glycosylation reactions were carried out using a combination[27] of *N*-iodosuccinimide (NIS) and perchloric acid supported over silica ($HClO_4$-SiO_2)[28,29] as thiophilic activator. $HClO_4$-SiO_2 was used as a solid protonic acid avoiding the use of corrosive and moisture sensitive TMSOTf or TfOH. Besides, this solid acid is cheap and can be prepared in the laboratory easily. Since $HClO_4$-SiO_2 is a solid acid, it can be removed from the reaction mixture by simple filtration. Presence of *in situ* removable *p*-methoxybenzyl group[25] in the glycosyl donors allowed completing the reaction sequence in significantly minimum number of steps. Selection of *in situ* removal PMB protecting groups also allowed carrying out the synthesis of the protected pentasaccharide derivative **11** in a one-pot manner using iterative glycosylations of monosaccharide intermediates. The selective oxidation of primary hydroxyl group in the D-galactose moiety keeping the secondary hydroxyl groups unaffected was achieved using TEMPO mediated BAIB oxidation[30] in a late stage of the synthetic sequence.

p-Methoxyphenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (**2**)[31] was subjected to a three step reaction sequence involving (a) allylation using allyl bromide and sodium hydroxide;[32] (b) treatment of the allylated product with acetic anhydride in the presence of $HClO_4$-SiO_2[33] and (c) removal of allyl ether using palladium chloride[34] to give *p*-methoxyphenyl 4,6-di-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside (**3**) in 85% over all yield (Scheme 1).



Scheme 1: (a) Allyl bromide, NaOH, TBAB, DMF, room temperature, 2 h, 95%; (b) acetic anhydride, $HClO_4$-SiO_2, room temperature, 10 min; (c) $PdCl_2$, CH_3OH, room temperature, 30 min, 86% in three steps.

Stereoselective 1,2-*cis* glycosylation of compound **3** with D-galactosyl thioglycoside donor **4** in the presence of a combination[27] of NIS and $HClO_4$-SiO_2 and *in situ* removal[25] of the PMB group by tuning the reaction condition resulted in the formation of disaccharide derivative **8** in 76% yield in which 2-hydroxy group in the D-galactose moiety was available for next step glycosylation. A minor quantity (~5%) of 1,2-*trans* glycosylation product was also formed, which was separated by column chromatography. The presence of signals at δ 5.49 (d, J = 3.5 Hz, H-1_A), 5.42 (s, PhC*H*), 5.26 (d, J = 3.5 Hz, H-1_B) in the ^{1}H NMR spectrum and at δ 100.9 (PhC*H*), 98.1 (C-1_A), 97.5 (C-1_B) in the ^{13}C NMR spectrum confirmed the formation of compound **8**. Stereoselective 1,2-*trans* glycosylation of L-rhamnosyl thioglycoside **5** with disaccharide acceptor **8** in the presence of a combination[27] of NIS and $HClO_4$-SiO_2 and *in situ* removal[25] of the PMB group furnished trisaccharide derivative **9** in 72% yield in which 2-hydroxy group in the L-rhamnose moiety can be used for next step glycosylation. The presence of signals at δ 5.45 (d, J = 3.5 Hz, H-1_A), 5.43 (s, PhC*H*), 5.24 (d, J = 1.5 Hz, H-1_C), 5.21 (d, J = 3.0 Hz, H-1_B) in the ^{1}H NMR spectrum and at δ 100.8 (C-1_C), 100.7 (PhC*H*), 98.1 (C-1_A), 97.7 (C-1_B) in the ^{13}C NMR spectrum confirmed the formation of compound **9**. Stereoselective 1,2-*trans* glycosylation of L-rhamnosyl thioglycoside **6** with trisaccharide acceptor **9** promoted by a combination[27] of NIS and $HClO_4$-SiO_2 and *in situ* removal[25] of the PMB group furnished tetrasaccharide derivative **10** in 74% yield in which 4-hydroxy group in the L-rhamnose moiety was available for next step glycosylation. The presence of signals at δ 5.44 (d, J = 3.0 Hz, H-1_A), 5.35 (s, PhC*H*), 5.24 (d, J = 2.0 Hz, H-1_C), 5.21 (d, J = 3.5 Hz, H-1_B), 5.11 (s, 1 H, PhC*H*) in the ^{1}H NMR spectrum and at δ 100.7 (C-1_C), 100.6 (PhCH), 98.3 (C-1_A), 98.0 (C-1_D), 97.0 (C-1_B) in the ^{13}C NMR spectrum confirmed the formation of compound **10**. At this stage, incorporation of the L-rhamnosyl moiety to the tetrasaccharide acceptor **10** in a β-glycosidic linkage was quite challenging since only a few reports were available to date for the β-glycosylation of L-rhamnosyl moiety. Initially Demchenko *et. al.*[26a] and recently Kulkarni and co-workers[26b] have successfully carried out β-L-rhamnosylation using the L-rhamnosyl thioglycoside donor equipped with a picolinoyl group at the C-3 position exploiting the picolinoyl group mediated hydrogen bond aglycon delivery for β-L-rhamnosylation. With this information, stereoselective 1,2-*cis* glycosylation of 3-*O*-picolinoylated L-rhamnosyl thioglycoside **7** with tetrasaccharide acceptor **10** was attempted using NIS and $HClO_4$-SiO_2 as glycosylation promoter.[27] Most gratifyingly β-L-rhamnose incorporated pentasaccharide derivative **11** was obtained in 72% yield. A minor amount (~5%) of other isomeric product has also been formed as observed in TLC, which was separated by column chromatography. The presence of signals at δ 5.44 (d, J = 3.5 Hz, H-1_A), 5.32 (s, PhC*H*), 5.22 (d, J = 1.5 Hz,

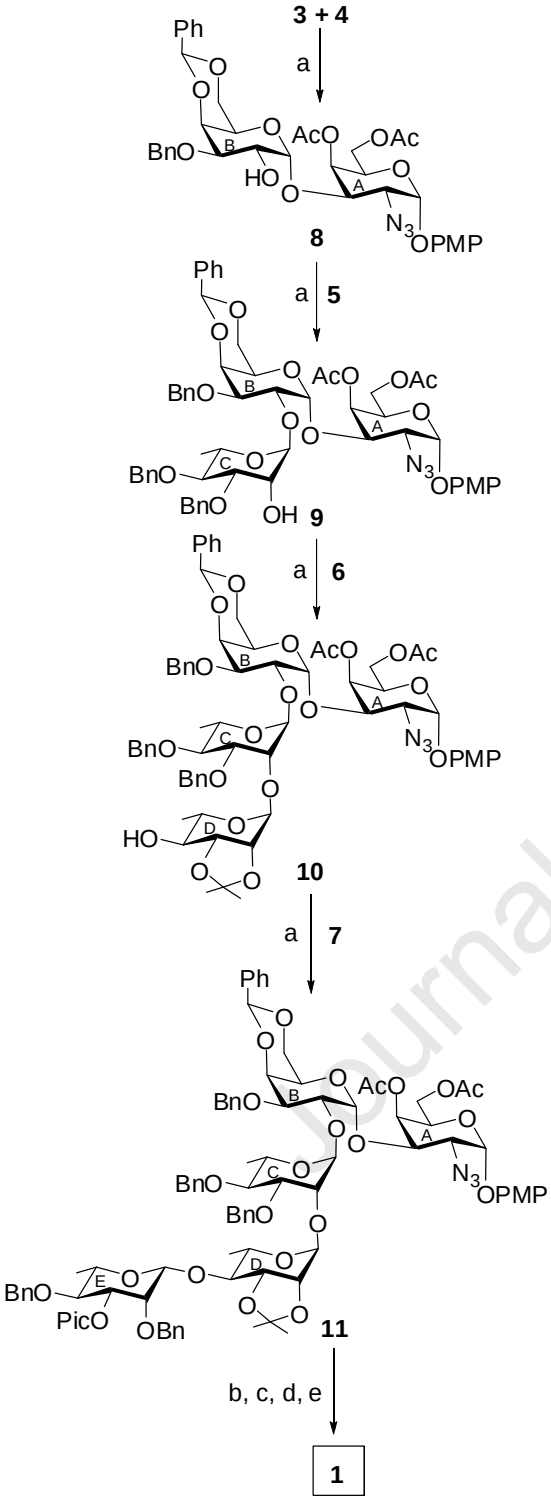
H-1_C), 5.18 (d, J = 3.5 Hz, H-1_B), 5.05 (br s, H-1_D), 4.71 (br s, 1 H, H-1_E) in the ^{1}H NMR spectrum and at δ 100.9 (C-1_E), 100.8 (PhC*H*), 100.6 (C-1_C), 98.1 (2 C, C-1_A, C-1_B), 97.1 (C-1_D) in the ^{13}C NMR spectrum confirmed the formation of compound **11** (Scheme 2).

In order to simplify the synthetic strategy, it was decided to explore the possibility of carrying out multiple numbers of glycosylation steps in a one-pot iterative manner considering the fact that PMB protecting group can be removed *in situ* after each glycosylation steps by simple tuning the reaction conditions. For this purpose, the monosaccharide acceptor **3** was allowed to react with the D-galactosyl thioglycoside donor **4** containing a C-2 PMB group in the presence of a combination of NIS and $HClO_4$-SiO_2 at –30 °C for 45 min and then at 0 °C for 30 min. After consumption of the starting materials and formation of a new major spot in the TLC plate, the reaction mixture was cooled to –30 °C and glycosyl donor **5** was added to the reaction mixture followed by NIS. The same sequence was repeated another two times using glycosyl donors **6** and **7** and finally the pentasaccharide derivative **11** was obtained in 48% over all yield. It is worth mentioning that the stereo chemical outcome of each glycosylation steps and overall yield of the final pentasaccharide derivative **11** in the one-pot iterative sequence was quite satisfactory, which was confirmed from the NMR spectroscopic analysis of compound **11** (Scheme 3). It is worth mentioning that in the one-pot iterative reaction sequence no trace of formation of PMB glycosides with the glycosyl donors was observed although PMB-alcohol might have been generated during the removal of PMB ether. The PMB-alcohol generated *in situ* could have been converted into quinonoid form during the course of reaction resulting it's non-availability for the glycosylation with glycosyl donors.

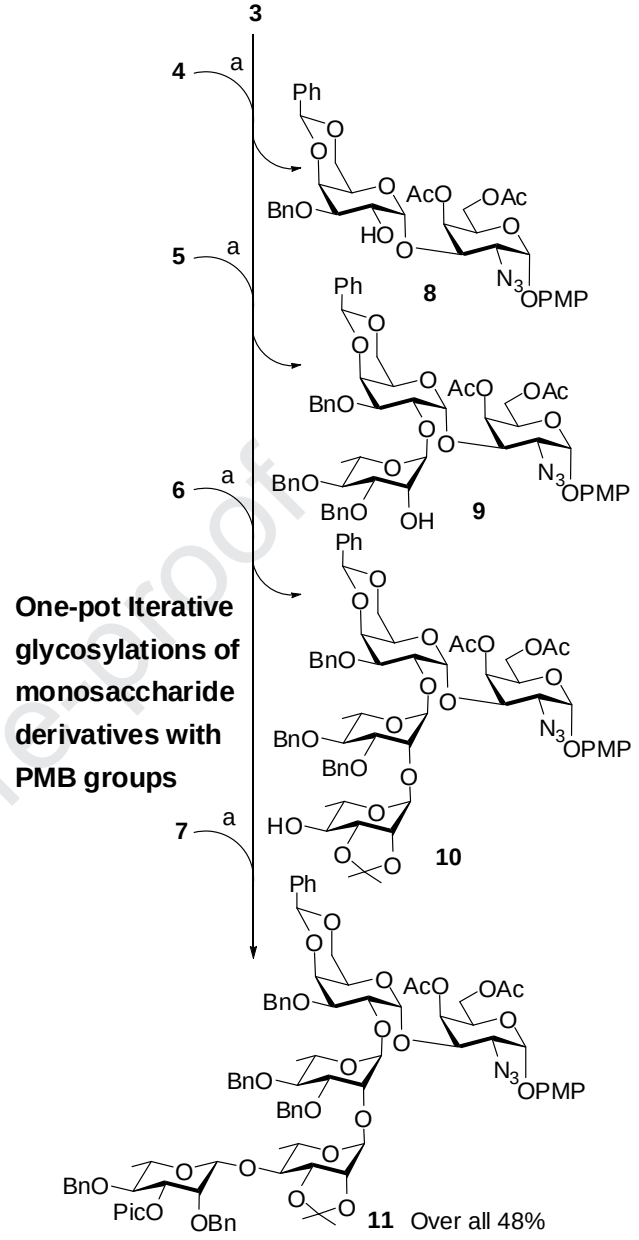
Finally, compound **11** was subjected to a set of reactions consisting of (a) hydrolytic removal of benzylidene and isopropylidene acetals using 80% aq. acetic acid; (b) TEMPO mediated selective oxidation of primary hydroxyl group to carboxylic acid without affecting the secondary hydroxyl groups;[30] (c) hydrogenolysis of benzyl ethers and azido group using hydrogen over Pearlman catalyst;[35] (d) acetylation of amino group using acetic anhydride in methanol and (e) de-*O*-acetylation using moist sodium methoxide to give pentasaccharide **1** as *p*-methoxyphenyl glycoside in 62% over all yield. The presence of signals at δ 5.53 (d, J = 3.5 Hz, H-1_A), 5.32 (br s, H-1_C), 5.23 (d, J = 2.0 Hz, H-1_B), 5.00 (br s, H-1_D), 4.74 (br s, H-1_E) in the ^{1}H NMR spectrum and at δ 101.9 (C-1_D), 100.4 (C-1_E), 99.7 (C-1_C), 97.2 (C-1_B), 95.1 (C-1_A) in the ^{13}C NMR spectrum unambiguously confirmed the formation of compound **1** (Scheme 2).

3. Conclusions

In summary, a straight forward synthetic strategy has been developed for the synthesis of the pentasaccharide repeating unit corresponding to the cell wall O-antigen of *Shigella boydii* type 18 in excellent yield. A generalized reaction condition has been used in all stereoselective glycosylation steps using a combination of NIS and $HClO_4$-SiO_2 as glycosylation activator. Presence of the *in situ* removable PMB groups in the thioglycoside intermediates allowed achieving the pentasaccharide derivative **11** in minimum number of steps. A one-pot reaction sequence applying iterative glycosylation steps has also been developed for the synthesis of pentasaccharide derivative **11** in satisfactory yield. Finally late stage selective oxidation of primary hydroxyl group into a carboxylic acid followed by de-protection of functional groups furnished desired pentasaccharide **1**.



Scheme 2: (a) NIS, $HClO_4$-SiO_2, CH_2Cl_2, MS 4Å, –30 °C, 45 min, then 0 °C for 30 min, 75% for compound **8**, 71% for compound **9**, 75% for compound **10**, 74% for compound **11**; (b) 80% aq. AcOH, 80 °C, 1 h; (c) TEMPO, BAIB, CH_3CN-H_2O (1:1), room temperature, 3 h; (d) H_2, 20% $Pd(OH)_2$-C, CH_3OH, room temperature, 24 h; (e) acetic anhydride, CH_3OH, room temperature, 1 h; (f) 0.1 M $NaOCH_3$, CH_3OH, room temperature, 3 h, 58% yield in five steps.



Scheme 3: (a) NIS, $HClO_4$-SiO_2, CH_2Cl_2, MS 4Å, –30 °C, 45 min, then 0 °C for 30 min, over all 48%.

4. Experimental

General methods: All reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulphate (2% $Ce(SO_4)_2$ in 2N H_2SO_4) sprayed plates in hot plate. Silica gel 230-400 mesh was used for column chromatography. NMR spectra were recorded on Bruker Avance 500 MHz using $CDCl_3$ as solvent and TMS as internal reference unless stated otherwise. Chemical shift value is expressed in δ ppm. The complete assignment of proton and carbon spectra was carried out by using a standard set of NMR experiments, e.g. ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT 135,

2D COSY and 2D HSQC etc. MALDI-MS were recorded on a Bruker mass spectrometer. Optical rotations were recorded in a Jasco P-2000 spectrometer. Commercially available grades of organic solvents of adequate purity are used in all reactions. $HClO_4$-SiO_2 was prepared following the reported method.[28, 29]

***p*-Methoxyphenyl 4,6-di-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyraside (3)**: To a solution of compound **2** (4 g, 10.0 mol) in DMF (10 mL) were added allyl bromide (1.3 mL, 15.0 mmol), powdered NaOH (1.6 g, 40.0 mmol) and TBAB (100 mg) and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was passed through a short pad of SiO_2. To a solution of the allylated product in acetic anhydride (10 mL) was added $HClO_4$-SiO_2 (150 mg) and the reaction mixture was stirred at room temperature for 10 min. The reaction mixture was filtered and concentrated under reduced pressure. To a solution of the acetylated product in CH_3OH (15 mL) was added $PdCl_2$ (350 mg, 1.97 mmol) and the reaction mixture was stirred at room temp. The reaction mixture was filtered and concentrated. The crude product was purified over SiO_2 using hexane-EtOAc (3:1) as eluant to give pure compound **3** (3.4 g, 86% in three steps); Colourless syrup; $[\alpha]_D$ −25 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 9.0 Hz, 2 H, Ar-H), 8.83 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.48 (d, *J* = 3.5 Hz, 1 H, H-1), 5.42 (d, *J* = 3.0 Hz, 1 H, H-4), 4.48-4.44 (dd, *J* = 9.0, 3.0 Hz, 1 H, H-3), 4.36-4.33 (m, 1 H, H-5), 4.17 (d, *J* = 12.5, 3.0 Hz, 1 H, H-6_a), 4.09 (d, *J* = 12.5, 5.0 Hz, 1 H, H-6_b), 3.77 (s, 3 H, OCH_3), 3.62 (dd, *J* = 9.0 Hz, 3.0 Hz, 1 H, H-2) 2.19 (s, 3 H, COCH_3), 2.00 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3 (*C*OCH$_3$), 170.5 (*C*OCH$_3$), 155.6-114.6 (Ar-C), 98.1 (C-1), 70.0 (C-3), 67.6 (C-4), 67.1 (C-5), 62.0 (C-6), 60.0 (C-2), 55.6 (O*C*H$_3$), 20.8 (CO*C*H$_3$), 20.6 (CO*C*H$_3$); HRMS $[M+Na]^+$: Calcd. 418.1227; found, 418.1220.

***p*-Methoxyphenyl (3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl)-(1→3)-4,6-di-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside (8)**: To a solution of compound **3** (3 g, 7.58 mmol) and compound **4** (4.47 g, 8.33 mmol) in anhydrous CH_2Cl_2 (25 mL) was added MS 4Å (5 g) and the reaction mixture was cooled to −30 °C under argon. To the cooled reaction mixture was added NIS (2 g, 8.88 mmol) followed by $HClO_4$-SiO_2 (150 mg) and the reaction mixture was allowed to stir at same temperature for 45 min. The temperature of the reaction was raised to room temperature and stirred for another 30 min. The reaction mixture was filtered and washed with CH_2Cl_2 (100 mL). The combined organic layer was successively washed with 5% aq. $Na_2S_2O_3$ (50 mL), satd. $NaHCO_3$ (50 mL) and H_2O (50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using hexane-EtOAc (5:1) as eluant to give pure compound **8** (4.2 g, 75%); Colourless syrup; $[\alpha]_D$ +42 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.18 (m, 10 H, Ar-H), 7.02 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.81 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.57 (d, *J* = 3.0 Hz, 1 H, H-4_A), 5.49 (d, *J* = 3.5 Hz, 1 H, H-1_A), 5.42 (s, 1 H, PhC*H*), 5.26 (d, *J* = 3.5 Hz, 1 H, H-1_B), 4.74 (dd, *J* = 11.5 Hz, each, 2 H, 2 PhC*H*), 4.42 (dd, *J* = 9.5, 3.5 Hz, 1 H, H-3_A), 4.35-4.30 (m, 2 H, H-3_B, H-5_A), 4.27-4.22 (m, 1 H, H-5_B), 4.18 (d, *J* = 2.5 Hz, 1 H, H-4_B), 4.11 (dd, *J* = 12.5, 5.0 Hz, 1 H, H-6_{aA}), 4.09-4.08 (m, 2 H, H-2_B, H-6_{bA}), 3.86-3.80 (m, 2 H, H-6_{abB}), 3.78 (s, 3 H, OCH_3), 3.69 (dd, *J* = 9.5, 3.0 Hz, 1 H, H-2_A), 2.12 (s, 3 H, COCH_3), 1.98 (s, 3 H,COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8 (*C*OCH$_3$), 170.0 (*C*OCH$_3$), 155.7-114.7 (Ar-C), 100.9 (PhC*H*), 98.1 (C-1_A), 97.5 (C-1_B), 76.0 (C-3 $_B$), 73.8 (C-4 $_A$), 71.7 (C-2_B), 71.5 (PhCH_2), 69.5 (C-6_B), 67.6 (C-3_B), 67.4 (C-5_A), 66.1 (C-4_B), 63.8 (C-5_B), 61.5 (C-6_A), 59.0 (C-2_A), 55.5 (O*C*H$_3$), 20.8 (CO*C*H$_3$), 20.6 (CO*C*H$_3$); HRMS $[M+Na]^+$: Calcd. 758.2537; found, 758.2545.

***p*-Methoxyphenyl (3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl)-(1→3)-4,6-di-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside (9)**: Glycosylation of compound **8** (3.5 g, 4.76 mmol) and compound **5** (1.9 g, 3.73 mmol) was carried out in the presence of NIS (880 mg, 3.91 mmol) and $HClO_4$-SiO_2 (50 mg) following the similar reaction condition as mentioned in the preparation of compound **8**. The crude product was purified over SiO_2 using hexane-EtOAc (4:1) as eluant to give pure compound **9** (3.6 g, 71%); Colourless syrup; $[\alpha]_D$ −17 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.24 (m, 20 H, Ar-H), 7.00 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.78 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.53 (d, *J* = 3.0 Hz, 1 H, H-4_A), 5.45 (d, *J* = 3.5 Hz, 1 H, H-1_A), 5.43 (s, 1 H, PhC*H*), 5.24 (d, *J* = 1.5 Hz, 1 H, H-1_C), 5.21 (d, *J* = 3.0 Hz, 1 H, H-1_B), 4.81 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.68-4.59 (m, 5 H, 5 PhC*H*), 4.36 (dd, *J* = 10.5 Hz, 3.0 Hz, 1 H, H-2_B), 4.30-4.25 (m, 3 H, H-3_A, H-5_A, H-6_{Aa}), 4.19 (d, *J* = 3.5 Hz, 1 H, H-4_B), 4.50-3.95 (m, 5 H, H-2_C, H-3_B, H-6_{abB}, H-6_{aA}), 3.85 (dd, *J* = 10.5 Hz, 3.5 Hz, 1 H, H-3_C), 3.80 (br s, 1 H, H-5_B), 3.77 (dd, *J* = 10.5 Hz, 3.0 Hz, 1 H, H-2_A), 3.76-3.74 (m, 1 H, H-5_C), 3.73 (s, 3 H, OCH_3), 3.40 (t, *J* = 9.5 Hz, each, 1 H, H-4 $_C$), 2.00 (s, 3 H, COCH_3), 1.88 (s, 3 H, COCH_3), 1.30 (d, *J* = 6.5 Hz, 3 H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (*C*OCH$_3$) 169.4 (*C*OCH$_3$), 155.7-114.6 (Ar-C), 100.8 (C-1_C), 100.7 (PhC*H*), 98.1 (C-1_A), 97.7 (C-1_B), 80.0 (C-4_C), 79.8 (C-3_C), 76.2 (C-3_B), 75.1 (PhCH_2), 73.7 (C-4_B), 72.0 (C-3_A), 71.7 (PhCH_2), 71.5 (PhCH_2), 71.4 (C-2_B), 69.3 (C-6_B), 68.3 (C-2_C), 68.1 (C-5_A), 67.9 (C-5_C), 66.6 (C-4_A), 63.7 (C-5_B), 61.8 (C-6_A), 59.3 (C-2_A), 55.5 (O*C*H$_3$), 20.6 (CO*C*H$_3$), 20.5 (CO*C*H$_3$), 18.0 (C*C*H$_3$); HRMS $[M+Na]^+$: Calcd. 1084.4055; found, 1084.4064.

***p*-Methoxyphenyl (2,3-*O*-isopropylidene-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl)-(1→3)-4,6-di-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside (10)**: Glycosylation of compound **9** (2.5 g, 2.35 mmol) and compound **6** (950 mg, 2.58 mmol) was carried out in the presence of NIS (610 mg, 2.71 mmol) and $HClO_4$-SiO_2 (30 mg) following the similar reaction condition as mentioned in the preparation of compound **8**. The crude product was purified over SiO_2 using hexane-EtOAc (4:1) as eluant to give pure compound **10** (2.2 g, 75%); Colourless syrup; $[\alpha]_D$ +80 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.24 (m, 20 H, Ar-H), 6.97 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.78 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.55 (d, *J* = 3.0 Hz, 1 H, H-4_A), 5.44 (d, *J* = 3.0 Hz, 1 H, H-1_A), 5.35 (s, 1 H, PhC*H*), 5.24 (d, *J* = 2.0 Hz, 1 H, H-1_C), 5.21 (d, *J* = 3.5 Hz, 1 H, H-1_B), 5.11 (s, 1 H, PhC*H*), 4.81-4.57 (m, 6 H, 6 PhC*H*), 4.36 (dd, *J* = 9.5 Hz, 3.0 Hz, 1 H, H-2_B), 4.28-4.22 (m, 3 H, H-3_A, H-5_A, H-6_{aA}), 4.15 (dd, *J* = 9.0 Hz, 2.5 Hz, 1 H, H-3_B), 4.11 (br s, 1 H, H-2_D), 4.05 (d, *J* = 2.5 Hz, 1 H, H-4_B), 4.02-3.92 (m, 5 H, H-2_C, H-3_B, H-6_{bA}, H-6_{abB}), 3.83 (dd, *J* = 9.0 Hz, 3.0 Hz, 1 H, H-3_C), 3.79-3.76 (m, 2 H, H-2_A, H-5_B), 3.75 (s, 3 H, OCH_3), 3.74-3.70 (m, 2 H, H-5_C, H-5_D), 3.43 (t, *J* = 9.5 Hz, 1 H, H-4_C), 3.35 (t, *J* = 9.5 Hz, 1 H, H-4_D), 1.99 (s, 3 H, COCH_3), 1.90 (s, 3 H, COCH_3), 1.49 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.26 (d, *J* = 6.5 Hz, 3 H, CCH_3), 1.21 (d, *J* = 6.5 Hz, 3 H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9 (*C*OCH_3), 169.5 (*C*OCH_3), 155.7-114.6 (Ar-C), 109.1 *C*$(CH_3)_2$, 100.7 (C-1_C), 100.6 (PhC*H*), 98.3 (C-1_A), 98.0 (C-1_D), 97.0 (C-1_B), 80.7 (C-4_C), 78.1 (C-3_C), 76.2 (C-3_B), 75.7 (C-3_D), 74.4 (C-2_D), 74.3 (C-2_C, C-4_D, C-5_D), 73.8 (C-4_B), 71.9 (2 C, 2 Ph*C*H_2), 71.8 (C-3_A), 71.3 (Ph*C*H_2), 70.9 (C-2_B), 69.2 (C-6_B), 68.2 (C-2_C), 68.1 (C-5_A), 66.5 (C-5_C), 66.1 (C-4_A), 63.6 (C-5_B), 61.8 (C-6_A), 59.4 (C-2_A), 55.5 (O*C*H_3), 28.0 (*C*H_3), 26.3 (*C*H_3), 20.6 (CO*C*H_3), 20.5 (CO*C*H_3), 18.3 (C*C*H_3), 17.2 (C*C*H_3); HRMS $[M+Na]^+$: Calcd. 1270.4948; found, 1270.4940.

***p*-Methoxyphenyl (2,4-di-*O*-benzyl-3-*O*-picoloyl-β-L-rhamnopyranosyl)-(1→4)-(2,3-*O*-isopropylidene-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl)-(1→3)-4,6-di-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside (11)**: Glycosylation of compound **10** (1.5 g, 1.2 mmol) and compound **7** (625 mg, 1.26 mmol) was carried out in the presence of NIS (300 mg, 1.33 mmol) and $HClO_4$-SiO_2 (25 mg) following the similar reaction condition as mentioned in the preparation of compound **8**. The crude product was purified over SiO_2 using hexane-EtOAc (3:1) as eluant to give pure compound **11** (1.5 g, 74%); Colourless syrup; $[\alpha]_D$ −110 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80-8.78 (m, 1 H, Ar-H), 7.96-6.75 (m, 37 H, Ar-H), 5.55 (d, *J* = 2.5 Hz, 1 H, H-4_A), 5.44 (d, *J* = 3.5 Hz, 1 H, H-1_A), 5.32 (s, 1 H, PhC*H*), 5.22 (d, *J* = 1.5 Hz, 1 H, H-1_C), 5.18 (d, *J* = 3.5 Hz, 1 H, H-1_B), 5.05 (br s, 1 H, H-1_D), 5.03 (dd, *J* = 9.5 Hz, 3.0 Hz, 1 H, H-3_E), 4.88-4.78 (m, 4 H, 4 PhC*H*), 4.71 (br s, 1 H, H-1_E), 4.68-4.53 (m, 6 H, 6 PhC*H*), 4.35-4.32 (m, 2 H, H-2_B, H-3_A), 4.28-4.24 (m, 3 H, H-5_A, H-5_E, H-6_{aA}), 4.16-4.14 (m, 1 H, H-3_D), 4.12-4.06 (m, 3 H, H-2_D, H-2_E, H-4_B), 4.00-3.93 (m, 5 H, H-2_C, H-3_B, H-6_{bA}, H-6_{abB}), 3.85-3.84 (m, 3 H, H-2_A, H-5_B, H-5_D), 3.77 (s, 3 H, OCH_3), 3.76-3.70 (m, 2 H, H-3_C, H-5_C), 3.45-3.36 (m, 3 H, H-4_C, H-4_D, H-4_E), 1.98 (s, 3 H, COCH_3), 1.90 (s, 3 H, COCH_3), 1.50 (s, 3 H, CH_3), 1.40 (d, *J* = 6.5 Hz, 3 H, CCH_3), 1.33 (s, 3 H, CH_3), 1.31 (d, *J* = 6.0 Hz, 3 H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9 (*C*OCH_3), 169.5 (*C*OCH_3), 164.0 (*C*Opic), 155.7-114.6 (Ar-C), 108.6 *C*$(CH_3)_2$ 100.9 (C-1_E), 100.8 (PhC*H*), 100.6 (C-1_C), 98.1 (2 C, C-1_A, C-1_B), 97.1 (C-1_D), 82.9 (C-4_C), 80.7 (C-4_D), 78.5 (2 C, C-5_B, C-5_D), 77.4 (C-3_E), 76.6 (C-3_A), 76.2 (C-3_D), 75.9 (2 C, C-2_D, C-3_C), 75.6 (C-4_B), 75.5 (C-2_E), 75.2 (2 C, 2 Ph*C*H_2), 74.6 (Ph*C*H_2), 73.9 (C-3_B), 71.9 (C-4_E), 71.8 (Ph*C*H_2), 71.5 (Ph*C*H_2), 69.2 (C-6_B), 68.1 (2 C, C-5_A, C-5_E), 66.1 (C-4_A), 64.6 (2 C, C-2_B, C-2_C), 63.6 (C-5_C), 61.8 (C-6_A), 59.4 (C-2_A), 55.5 (O*C*H_3), 28.2 (*C*H_3), 26.4 (*C*H_3), 20.6 (CO*C*H_3), 20.5 (CO*C*H_3), 18.0 (C*C*H_3), 17.8 (C*C*H_3); HRMS $[M+Na]^+$: Calcd.1701.6680; found, 1701.6690.

One-pot iterative reaction condition for the synthesis of compound 11: To a solution of compound **3** (500 mg, 1.26 mmol) and compound **4** (680 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (10 mL) was added MS 4Å (1 g) and the reaction mixture was cooled to −30 °C under argon. To the cooled reaction mixture was added NIS (290 mg, 1.28 mmol) followed by $HClO_4$-SiO_2 (50 mg) and the reaction mixture was allowed to stir at same temperature for 45 min. The temperature of the reaction was raised to 0 °C and stirred for another 30 min. After consumption of the starting materials and formation of a new major spot in TLC (hexane-EtOAc 2:1), the reaction mixture was cooled to −30 °C and compound **5** (640 mg, 1.25 mmol) followed by NIS (270 mg, 1.20 mmol) were added to it and allowed to stir for 45 min at same temperature. The temperature of the reaction mixture was raised to 0 °C and stirred for 30 min. After checking the TLC (hexane-EtOAc 2:1), the reaction mixture was cooled to −30 °C and compound **6** (440 mg, 1.19 mmol) followed by NIS (270 mg, 1.20 mmol) were added to it and allowed to stir for 45 min at same temperature. The temperature of the reaction mixture was raised to 0 °C and stirred for 30 min. Again, after checking the TLC (hexane-EtOAc 1:1), the reaction mixture was cooled to −30 °C and compound **7** (540 mg, 1.09 mmol) followed by NIS (250 mg, 1.11 mmol) were added to it and allowed to stir for 45 min at same temperature. The temperature of the reaction mixture was raised to 0 °C and stirred for 30 min. The reaction mixture was filtered and washed with CH_2Cl_2 (50 mL). The combined organic layer was successively washed with 5% aq. $Na_2S_2O_3$ (50 mL), satd. $NaHCO_3$ (50 mL) and H_2O (50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 using

hexane-EtOAc (5:1) as eluant to give pure compound **11** (1 g, 48%).

***p*-Methoxyphenyl (β-L-rhamnopyranosyl)-(1→4)-(α-L-rhamnopyranosyl)-(1→2)-(α-L-rhamnopyranosyl)-(1→2)-(α-D-galactopyranosyl uronic acid)-(1→3)-2-acetamido-2-deoxy-α-D-galactopyranoside (1)**: A solution of compound **11** (1 g, 0.59 mmol) in 80% aq. AcOH (25 mL) was allowed to stir at 80 °C for 1 h. The solvents were removed under reduced pressure and the product was dissolved in CH_3CN-H_2O (10 mL; 1:1). To the reaction mixture was added TEMPO (200 mg, 1.28 mmol) followed by BAIB (500 mg, 1.55 mmol) and the reaction mixture was allowed to stir for 3 h. The reaction mixture was concentrated under reduced pressure to give the oxidized product, which was passed through a short pad of SiO_2. To a solution of the oxidized product in CH_3OH (10 mL) was added 20% $Pd(OH)_2$-C (100 mg) and the reaction mixture was stirred under a positive pressure of hydrogen for 24 h. The reaction mixture was filtered through a Celite bed and acetic anhydride (2 mL) was added to it. The solvents were removed under reduced pressure and a solution of the hydrogenolized product in 0.1 M $NaOCH_3$ (10 mL) was stirred at room temperature for 3 h. The reaction mixture was neutralized with Dowex 50W X8 (H^+) resin and concentrated to a solid mass, which was passed through a column of Sephadex LH-20 column using methanol-H_2O (4:1) as eluant to give pure compound **1** (320 mg, 58% in five steps). White powder; $[\alpha]_D$ –20 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 7.15 (d, *J* = 9.0 Hz, 2 H, Ar-H), 7.01 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.53 (d, *J* = 3.5 Hz, 1 H, H-1_A), 5.32 (br s, 1 H, H-1_C), 5.23 (d, *J* = 2.0 Hz, 1 H, H-1_B), 5.00 (br s, 1 H, H-1_D), 4.74 (br s, 1 H, H-1_E), 4.56 (dd, *J* = 10.0 Hz, 3.5 Hz, 1 H, H-2_A), 4.27-4.24 (m, 2 H, H-3_A, H-4_B), 4.16 (br s, H, H-2_D), 4.13-4.11 (m, 1 H, H-5_B), 4.10 (d, *J* = 3.0 Hz, 1 H, H-4_A), 4.09 (br s, 1 H, H-2_C), 4.08 (br s, 1 H, H-2_E), 4.07-4.06 (m, 2 H, H-2_B, H-5_A), 3.97-3.94 (m, 1 H, H-3_D), 3.93-3.90 (m, 2 H, H-3_B, H-3_C), 3.82 (s, 3 H, OC*H*$_3$), 3.80-3.76 (m, 3 H, H-5_D, H-6_{abA}), 3.74-3.69 (m, 1 H, H-5_C), 3.63-3.61 (m, 2 H, H-3_E, H-4_C), 3.55-3.50 (m, 1 H, H-4_E), 3.48-3.44 (m, 1 H, H-5_E), 3.42 (t, *J* = 9.5 Hz, 1 H, H-4_D), 2.09 (s, 3 H, COC*H*$_3$), 1.35-1.30 (m, 9 H, 3 CC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.4 (*C*OCH$_3$), 174.2 (*C*OOH), 154.6-115.0 (Ar-C), 101.9 (C-1_D), 100.4 (C-1_E), 99.7 (C-1_C), 97.2 (C-1_B), 95.1 (C-1_A), 82.5 (C-4_D), 78.1 (C-2_C), 73.2 (C-3_E), 72.7 (C-2_B), 72.5 (2 C, C-4_C, C-5_E), 72.2 (C-5_B), 71.9 (C-3_A), 71.8 (C-4_B), 71.4 (C-4_E), 71.3 (C-5_A), 70.5 (C-3_C), 69.8 (C-3_B), 69.6 (C-2_D), 69.5 (C-5_C), 69.3 (C-3_D), 68.8 (C-5_D), 67.6 (C-2_E), 65.3 (C-4_A), 61.0 (C-6_A), 55.7 (OC*H*$_3$), 47.9 (C-2 $_A$), 22.2 (COC*H*$_3$), 17.0 (C*H*$_3$), 16.9 (CC*H*$_3$), 16.8 (CC*H*$_3$); HRMS $[M+Na]^+$: Calcd. 964.3274; found, 964.3285.

Acknowledgements

P.S. thanks CSIR, New Delhi for providing Senior Research Fellowship. The work is supported by SERB, New Delhi (Project No. EMR/2015/000282 dated 17.09.2015) and Bose Institute.

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Research Highlights

- Pentasaccharide of the O-antigen of *Shigella boydii* type 18 A was synthesized.
- A combination of NIS and $HClO_4$-SiO_2 as glycosylation activator.
- *p*-Methoxybenzyl (PMB) was used as *in situ* removable protecting groups.
- A one-pot reaction sequence applying iterative glycosylation steps has been developed.
- $HClO_4$-SiO_2 has been used as a solid acid catalyst.

Conflicts of Interest

There are no conflicts to declare.