RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2020, **10**, 4942

Synthesis of the pentasaccharide repeating unit of the O-antigen from *Enterobacter cloacae* C4115 containing the rare α-D-FucNAc†

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Received 23rd November 2019
Accepted 9th January 2020

DOI: 10.1039/c9ra09807k

rsc.li/rsc-advances

Total synthesis of the pentasaccharide repeating unit associated with the O-antigen of *Enterobacter cloacae* C4115 is reported. The synthesis of the said oligosaccharide was accomplished through rational protecting group manipulations on commercially available monosaccharides followed by stereoselective glycosylations either by activation of thioglycosides or glycosyl trichloroacetimidates and was found to be productive. Towards the synthesis of the rare sugar unit, α-D-FucNAc in this case, it was established that the methoxymethyl (MOM) group is advantageous over the earlier reported tetrahydro pyran (THP) protection. The effect of MOM-protection was successfully tested for the synthesis of a rare sugar synthon which can serve as a precursor to the rare D-fucosamine residue.

Introduction

Enterobacter cloacae belong to the genus Enterobacter and are Gram negative anaerobic bacteria of the Enterobacteriaceae family. These bacterial strains have been recognized as nosocomial pathogens affecting immune-compromised patients.[1] The cell surface polysaccharide profile of disease causing bacteria is deeply implicated in their pathogenicity.[2] The *E. cloacae* are known for their resistance towards various classes of antibiotics like β-lactam, fluoroquinolones, aminoglycosides and tigecyclin.[3] Recently, Knirel *et al.* have reported the structure of the O-antigen of *Enterobacter cloacae* C4115 as illustrated below (Fig. 1).[4] Considering the growing need for robust and practical strategies to deal with the synthesis of bacterial cell surface oligosaccharides bearing rare amino deoxy sugar residues[5] we took up the challenge of developing a concise strategy for the synthesis of this pentasaccharide. Taking a cue from the recent reports directed towards synthesis of rare sugar derivatives,[6,7] herein we report the first total synthesis of the aforesaid pentasaccharide in the form of its *p*-methoxyphenyl glycoside (**1**, Fig. 1).

Results and discussion

The challenging aspect associated with the synthesis of this target pentasaccharide is the terminal α-D-fucosamine residue at the reducing end. The α-(1→2) linked L-rhamnose motif is a fairly common oligosaccharide architecture which has been synthesised by our group previously.[8,9] This was selected as the first point of retrosynthetic disconnection in contemplation of a (3+1+1) convergent strategy for oligosaccharide assembly.

For the non-reducing end α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→2)-α-L-Rha*p* trisaccharide, iterative glycosylation of the same rhamnosyl trichloroacetimidate donor twice with the rhamnose thioglycoside acceptor was planned. On the other hand, the galactosyl thioglycoside donor bearing non-participating naphthyl protection at *O*-2 position and remotely participating 6-*O*-benzoyl protection was envisioned to give the 1,2-*cis* glycosidic linkage with the D-fucosamine equivalent at its *O*-3 position. But prior to this, an efficient protocol had to be developed for the synthesis of the D-fucosamine equivalent.

Synthesis of the trisaccharide fragment (Fig. 2) was commenced with the glycosylation of known rhamnosyl donor

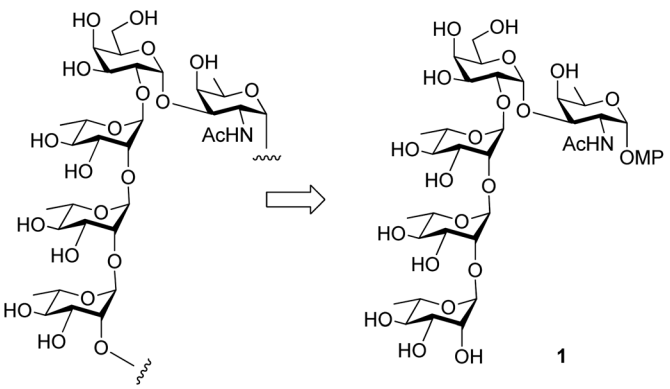

Fig. 1 Pentasaccharide repeating unit associated with the O-antigen of *Enterobacter cloacae* C4115 and the synthetic target (**1**).

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† Electronic supplementary information (ESI) available: Copies of the ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c9ra09807k

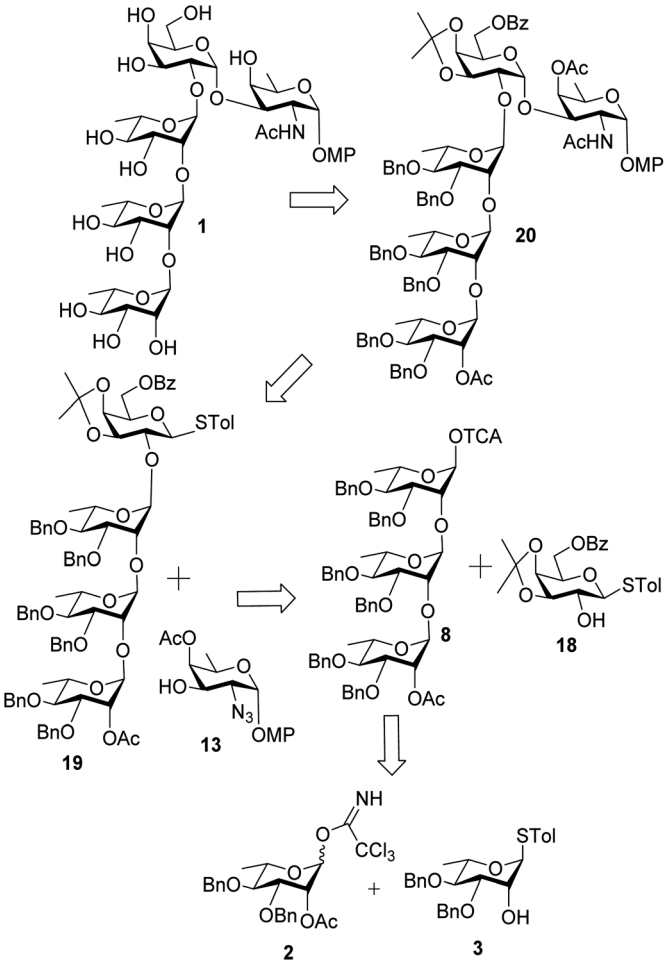
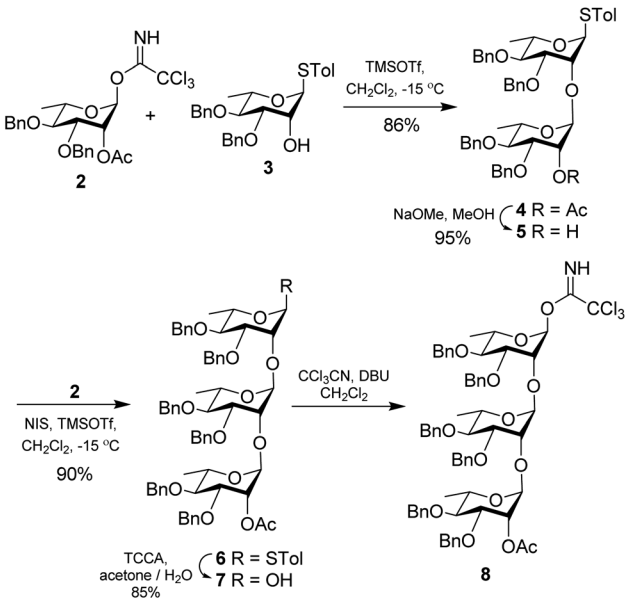


Fig. 2 Retrosynthetic analysis of the total synthesis.

2 [10] and acceptor **3** [11] in the presence of TMSOTf to give the disaccharide **4** in 86% yield. De-*O*-acetylation of **4** under Zemplén conditions[12] led to the disaccharide acceptor **5** in 95% yield. Further it was coupled with the donor **2** once again to give the trisaccharide fragment **6** in 90% yield. The α-stereochemistry of the three L-rhamnoside residues were confirmed by their corresponding J_{C1-H1} coupling constants which were measured at 172.08 Hz, 170.32 Hz and 167.00 Hz respectively.[13] Trisaccharide **6** was converted to its corresponding hemi-acetal derivative **7** using trichloroisocyanuric acid (TCCA) in acetone/H_2O[14] in 85% yield. It was subsequently converted to the corresponding glycosyl trichloroacemidate **8** in 95% yield by treatment with trichloroacetonitrile in the presence of DBU[15] (Scheme 1).

Synthesis of the reducing end residue (Fig. 2) required the development of the D-fucosamine equivalent and we have adopted the method reported by Ghosh *et al.*[16] The synthesis began with di-*tert*-butylperoxide (DTBP) and triisopropylsilanethiol (TIPST) mediated deoxygenation[17] leading to the *C*-6 deoxygenated derivative **9**.[16] Hereafter, we deviated from the aforesaid protocol as we found the methoxymethyl (MOM) protecting group as a suitable alternative for the tetrahydropyranyl (THP) protection used previously for *O*-3

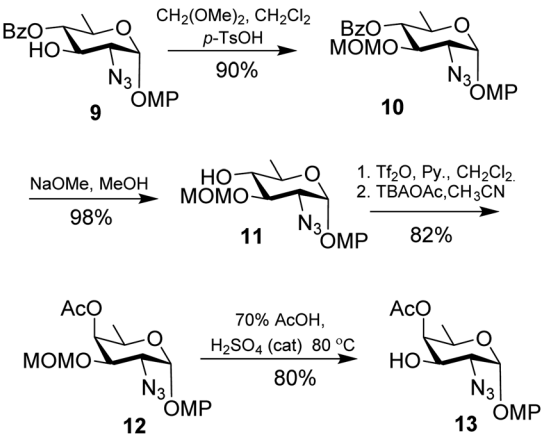


Scheme 1 Synthesis of the trisaccharide trichloroacetimidate **8**.

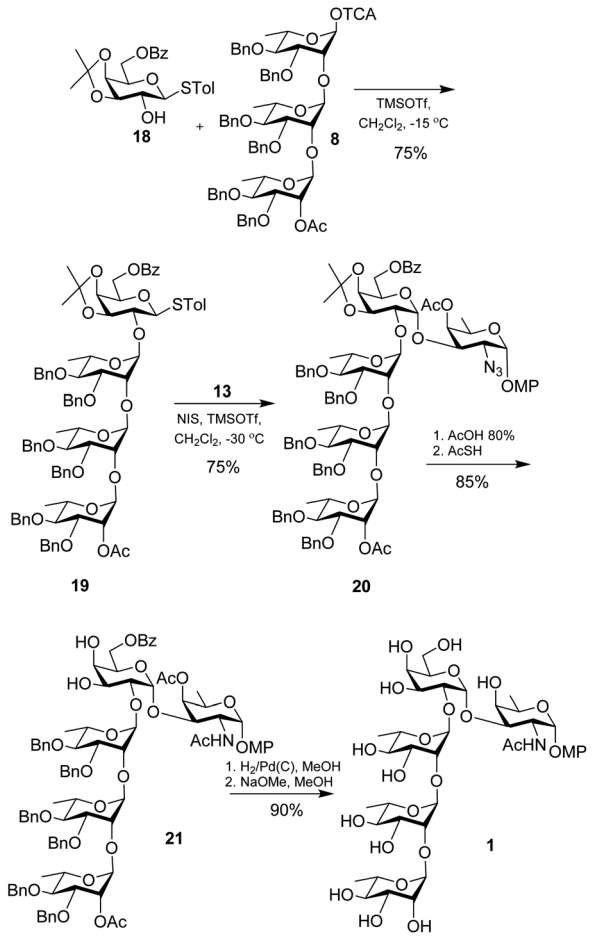
protection. Accordingly, compound **9** was converted to **10** in 90% yield using dimethoxymethane in the presence of *p*-TsOH.[18] Subsequent de-benzoylation at *O*-4 led to intermediate **11** from which epimerisation *via* Lattrell–Dax inversion[19,20] led to the rare sugar derivative **12** in 82% yield over two steps. Deprotection of the methoxymethyl group using 70% (aq.) acetic acid in the presence of catalytic conc. H_2SO_4 at 80 °C [21] gave the desired acceptor **13** in 80% yield (Scheme 2).

In their report, Ghosh *et al.*[16] have used the THP group for orthogonal protection of the *O*-3 position of the glucosamine derivative. However, substantial acid lability of THP protection[22] limits its application in glycosylation reaction. Moreover, introduction of THP inevitably leads to the creation of an added asymmetric centre at the C-1 position of the THP group that in turn can make the spectral characterization cumbersome.[23]

To overcome these issues, we have used MOM protection in place of THP and found that it has little effect on the yield but makes the protocol operationally simpler.



Scheme 2 Preparation of D-fucosaminyl acceptor **13**.



Scheme 3 Synthesis of the target pentasaccharide.

Having the D-fucosamine acceptor **13** in hand we turned our attention towards the galactosyl donor. For the required 1,2-*cis* glycosylation a non-participating temporary protection at 2-position was desired. However, non-orthogonality with the azido group ruled out the option of a benzyl protection. Therefore, known galactose derivative **14** [24] was subjected to a phase transfer reaction with (2-bromomethyl)naphthalene (NapBr) in the presence of Bu_4NBr and 10% aq. NaOH to afford the 2-*O*-napthylmethyl galactoside **15** which was further acetylated using Ac_2O in pyridine to furnish the desired galactosyl donor **16**. Unfortunately, glycosylation between galactosyl donor **16** and acceptor **13** through activation of thioglycoside using NIS in the presence TMSOTf failed to provide the disaccharide. Instead, it led to an undesired derivative **17** formed *via* intra-molecular *C*-glycosidation[25–27] (see Scheme S1 in ESI†).

In resort, the known galactoside **18** [28] was glycosylated with trisaccharide trichloroacetimidate donor **8** using TMSOTf giving the tetrasaccharide **19** in 75% yield. Further glycosylation of the tetrasaccharide **19** through activation of thioglycoside using NIS in the presence of TMSOTf furnished the protected pentasaccharide derivative **20** in 75% yield. It is worth noting that in either of the two aforesaid glycosylation reactions we were unable to detect the corresponding β-isomer. Hydrolysis of the isopropylidene group from the pentasaccharide **20** using 80% AcOH at 80 °C [29] followed by reaction with thioacetic acid to convert the azide group to desired acetamido[30] led to compound **21** in 85% yield over 2 steps. Finally, catalytic hydrogenolysis using H_2 in the presence of 10% Pd–C[31] followed by de-*O*-acylation under Zemplén conditions[12] furnished the target pentasaccharide **1** in 90% yield (Scheme 3).

Conclusions

In conclusion, total synthesis of the pentasaccharide repeating unit of the O-antigen from *E. cloacae* C4115 is accomplished through a bidirectional glycosylation strategy. Synthetic equivalent of the challenging rare sugar D-FucNAc was derived through improved strategy. The MOM protecting group was shown to be a practical alternative to the previously reported THP protection which was crucial for the efficient synthesis the derivative **13** has been utilized successfully in this particular total synthesis.

Experimental section

General

All solvents and reagents were dried prior to use according to literature methods.[32] The commercially purchased reagents were used without any further purification unless mentioned otherwise. Dichloromethane was dried and distilled over P_2O_5 to make it anhydrous and moisture-free. All reactions were monitored by Thin Layer Chromatography (TLC) on silica-gel 60-F254 with detection *via* fluorescence and by charring after immersion in 10% ethanolic solution of sulphuric acid. Flash chromatography was performed with silica gel 230–400 mesh. Optical rotations were measured on sodium D-line at ambient temperature. ^{1}H and ^{13}C NMR were recorded on Bruker Avance 500 MHz spectrometer at 500 MHz and 125 MHz respectively.

p-Tolyl 2-*O*-acetyl-3′,4′-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside [4]

Trichloroacetimidate donor **2** (430 mg, 0.81 mmol) and acceptor **3** (280 mg, 0.81 mmol) were dissolved in CH_2Cl_2 (15 mL) and stirred with 4 Å MS (1.5 g) for 15 minutes under N_2 atmosphere. Thereafter the temperature was lowered to −15 °C and TMSOTf (0.03 mL, 0.16 mmol) was added and the reaction was allowed to continue for 30 minutes. TLC (4 : 1 *n*-hexane/EtOAc, $R_f = 0.6$) at this point showed the reaction to be complete. The MS was filtered out and the filtrate was washed successively with $NaHCO_3$ aq. (100 mL) and brine (100 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue which was purified by column chromatography (6 : 1 *n*-hexane/EtOAc) to give the disaccharide product **4** (570 mg, 86%) as colourless foam.

$[\alpha]_D^{25}$ +28 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.37–7.08 (m, 24H, Ar*H*), 5.51 (s, 1H, H-2′), 5.34 (s, 1H, H-1), 4.94 (s, 1H, H-1′), 4.89 (t, 2H, J = 10.5 Hz, Ph-CH_2), 4.74–4.53 (m, 6H, Ph-CH_2), 4.16 (s, 1H, H-2), 4.12–4.08 (m, 1H, H-5), 3.93 (dd, 1H, J = 2.5 Hz 9.5 Hz, H-3′),

3.85 (dd, 1H, J = 2.0 Hz 9.0 Hz, H-3), 3.80–3.77 (m, 1H, H-5′) 3.47 (t, 1H, J = 9.0 Hz, H-4), 3.40 (t, 1H, J = 9.5 Hz, H-4′), 2.31 (s, 3H, Ar-CH_3), 2.13 (s, 3H, COCH_3), 1.28 (d, 3H, J = 6.0 Hz, H-6), 1.22 (d, 3H, J = 6.0 Hz, H-6′).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.1 (*C*O), 138.4, 138.1, 138.0, 137.5, 131.9, 129.8, 128.5, 128.4, 128.3 (Ar-*C*), 99.5 (C-1′), 87.6 (C-1), 80.2 (C-4), 80.0 (C-4′), 79.9 (C-3), 77.6 (C-3′), 76.6 (C-2), 75.4 (Ph-*C*H_2) 72.2 (Ph-*C*H_2), 71.8 (Ph-*C*H_2), 69.3 (C-5), 68.9 (C-2′), 68.4 (C-5′), 21.1 (Ar-*C*H_3), 21.0 (CO*C*H_3), 17.9 (C-6), 17.8 (C-6′).

HRMS calculated for $C_{49}H_{54}O_9SNa$ (M + Na)$^+$: 841.3386, found: 841.3378.

p-Tolyl 3′,4′-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside [5]

Disaccharide **4** (570 mg, 0.7 mmol) was stirred in NaOMe/MeOH (20 mL, 0.05 M) at room temperature for 2 hours. TLC (5 : 1 *n*-hexane/EtOAc, R_f = 0.35) at this point showed the reaction to be complete and the reaction mixture was quenched with DOWEX 50W resin. The resin was filtered out and the filtrate was evaporated to dryness under reduced pressure to give the crude residue which was purified by column chromatography (5 : 1 *n*-hexane/EtOAc) to give the disaccharide acceptor **5** (540 mg) in 95% yield.

$[\alpha]_D^{25}$ +57 (*c* 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.41–7.30 (m, 22H, Ar-*H*), 7.12 (d, 1H, J = 7.5 Hz, Ar-*H*), 5.41 (d, 1H, J = 1.5 Hz, H-1′), 5.07 (d, 1H, J = 1.5 Hz, H-1), 4.94–4.64 (m, 8H, PhCH_2), 4.2–4.23 (m, 1H, H-2′), 4.17–4.14 (m, 2H, H-2, H-5), 3.89 (dd, 1H, J = 3.0 Hz, 10.0 Hz, H-3′, H-3), 3.82 (m, 1H, H-5′), 3.49 (m, 2H, H-4, H-4′), 2.34 (s, 3H, ArCH_3), 1.34 (d, 3H, J = 6.0 Hz, H-6), 1.25 (d, 3H, J = 6.5 Hz, H-6′).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 138.4, 138.3, 137.9, 137.9, 137.4, 131.8, 130.6, 129.8, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.6, 127.6 (Ar*C*), 100.9 (C-1′), 87.7 (C-1), 80.4 (C-4), 79.9 (C-4′), 79.9 (C-3), 79.5 (C-3′), 76.6 (C-2′), 75.3 (Ph*C*H_2), 75.2 (Ph*C*H_2), 72.3 (Ph*C*H_2), 72.1 (Ph*C*H_2), 69.2 (C-2), 68.7 (C-5), 68.0 (C-5′), 21.0 (Ar*C*H_3), 17.9 (C-6), 17.7 (C-6′).

HRMS calculated for $C_{47}H_{52}O_8SNa$ (M + Na)$^+$: 799.3281, found: 799.3274.

p-Tolyl 2″-*O*-acetyl-3″,4″-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3′,4′-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside [6]

Trichloroacetimidate donor **2** (600 mg, 0.94 mmol) and disaccharide acceptor **5** (540 mg, 0.69 mmol) were dissolved in CH_2Cl_2 (20 mL) and stirred with 4 Å MS (2 g) for 15 minutes under N_2 atmosphere. Thereafter the temperature was lowered to −15 °C and TMSOTf (0.04 mL, 0.18 mmol) was added and the reaction was allowed to continue for 1 hour. TLC (5 : 1 *n*-hexane/EtOAc, R_f = 0.5) at this point showed the reaction to be complete. The MS was filtered out and the filtrate was washed successively with $NaHCO_3$ aq. (100 mL) and brine (100 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue which was purified by column chromatography (6 : 1 *n*-hexane/EtOAc) to give the trisaccharide product **6** (800 mg, 90%) as white foam.

$[\alpha]_D^{25}$ +44 (*c* 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.40–7.26 (m, 32H, Ar*H*), 7.13–7.11 (m, 2H, Ar*H*), 5.58 (s, 1H, H-2″), 5.36 (s, 1H, H-1), 5.07 (s, 1H, H-1′), 5.05 (s, 1H, H-1″), 4.95–4.89 (m, 3H, PhCH_2), 4.79–4.56 (m, 9H, *PhCH*$_2$), 4.17–4.10 (m, 3H, H-2, H-5, H-2′), 4.16 (dd, 1H, J = 9.0 Hz, 3.0 Hz, H-3″), 3.91–3.85 (m, 3H, H-3, H-3′, H-5′), 3.77–3.74 (m, 1H, H-5″), 3.49–3.43 (m, 3H, H-4, H-4′, H-4″), 2.34 (s, 3H, Ar*CH*$_3$), 2.17 (s, 3H, CO*C*H$_3$), 1.31 (d, 3H, J = 6.0 Hz, H-6), 1.29 (d, 3H, J = 6.0 Hz, H-6′), 1.22 (d, 3H, J = 6.0 Hz, H-6″).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.0 (*CO*), 138.5–127.5 (*Ar-C*), 100.6 (C-1′), 99.0 (C-1″), 87.7 (C-1), 80.4 (C-4), 80.0 (C-4′, C-4″), 79.6 (C-3), 79.0 (C-3′), 77.7 (C-3″), 76.4 (C-2), 75.4 (Ph*C*H_2), 75.3 (Ph*C*H_2), 75.2 (Ph*C*H_2), 74.5 (C-5), 72.2 (Ph*C*H_2), 72.1 (Ph*C*H_2), 71.8 (Ph*C*H_2), 69.3 (C-2′), 68.9 (C-2″), 68.6 (C-5″), 68.3 (C-5′), 21.1 (Ar-*C*H_3), 21.0 (CO*C*H_3), 17.9 (C-6 × 2), 17.8 (C-6).

HRMS calculated for $C_{69}H_{76}O_{13}SNa$ (M + Na)$^+$: 1167.4904, found: 1167.4899.

p-Methoxyphenyl 2-azido-4-*O*-benzoyl-2,6-dideoxy-3-*O*-methoxymethyl-α-D-glucopyranoside [10]

To a solution of the substrate **9** (400 mg, 1.04 mmol) dissolved in CH_2Cl_2 (20 mL), dimethoxymethane (0.16 mL, 2.1 mmol) and *p*-TSA (40 mg, 0.2 mmol) were added and the reaction mixture was refluxed for 12 hours. The reaction mixture was quenched with Et_3N (0.1 mL) and the solvent was concentrated under reduced pressure. The crude product was purified by column chromatography (4 : 1 *n*-hexane/EtOAc, R_f = 0.4) to give the pure product **10** (412 mg) in 90% yield as a light yellow oil.

$[\alpha]_D^{25}$ +104 (*c* 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09–6.85 (m, 9H, Ar*H*), 5.47 (d, 1H, J = 3.5 Hz, H-1), 5.15 (t, 1H, J = 9.5 Hz, H-4), 4.79 (d, 1H, J = 7.0 Hz, MOM-CH_2), 4.75 (d, 1H, J = 7.0 Hz, MOM-CH_2), 4.38 (t, 1H, J = 9.5 Hz, H-3), 4.18–4.13 (m, 1H, H-5), 3.78 (s, 3H, Ar-OCH_3), 3.44 (dd, 1H, J = 10.5 Hz, 3.5 Hz, H-2), 3.26 (s, 3H, MOM-OCH_3), 1.22 (d, 3H, J = 6.5 Hz, H-6).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 165.4 (*C*O), 155.3, 150.4, 133.3, 129.7, 129.4, 128.4, 117.8, 114.6 (Ar*C*), 97.8 (C-1), 97.6 (MOM-*C*H_2), 75.5 (C-3), 75.4 (C-4), 66.5 (C-5), 62.7 (C-2), 55.8 (Ar-O*C*H_3), 55.6 (MOM-O*C*H_3), 17.3 (C-6).

HRMS calculated for $C_{22}H_{25}N_3O_7Na$ (M + Na)$^+$: 466.1590, found: 466.1584.

p-Methoxyphenyl 2-azido-2,6-dideoxy-3-*O*-methoxymethyl-α-D-glucopyranoside [11]

The substrate **10** (412 mg, 1.0 mmol) was treated with NaOMe (0.05 M) in methanol (20 mL) and the reaction mixture was stirred at room temperature for 8 hours. The reaction was complete by this time as shown by TLC (2 : 1 *n*-hexane/EtOAc, R_f = 0.4) and it was then quenched with DOWEX 50W H^+ resin. The reaction mixture was filtered and the methanol was evaporated to dryness under vacuum. The crude residue was purified by column chromatography to give the product as a white foam **11** (305 mg) which was purified by column chromatography (3 : 1 *n*-hexane/EtOAc) and obtained in 98% yield.

$[\alpha]_D^{25}$ +97 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.03 (d, 2H, J = 9.0 Hz, Ar*H*), 6.83 (d, 2H, J = 9.0 Hz, Ar*H*), 5.35 (d, 1H, J = 3.5 Hz, H-1), 4.90 (d, 1H, J = 7.0 Hz, MOM-CH_2), 4.86 (d, 1H, J = 7.0 Hz, MOM-CH_2), 4.42 (s, 1H, 4-O*H*), 3.93–3.87 (m, 2H, H-3, H-5), 3.77 (s, 3H, OMP-OCH_3), 3.52 (s, 3H, MOM-OCH_3), 3.42 (dd, 1H, J = 3.5 Hz, 10.5 Hz, H-2), 3.25 (d, 1H, J = 9.0 Hz, H-4), 1.30 (d, 3H, J = 6.0 Hz, H-6).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.3, 150.5, 118.1, 114.6, 98.3 (MOM-CH_2), 97.4 (C-1), 83.2 (C-3), 74.9 (C-4), 68.3 (C-5), 61.8 (C-2), 56.1 (OMP-OCH_3), 55.6 (MOM-OCH_3), 17.7 (C-6).

HRMS calculated for $C_{15}H_{21}N_3O_6Na$ (M + Na)$^+$: 362.1328, found: 362.1327.

p-Methoxyphenyl 4-*O*-acetyl-2-azido-2,6-dideoxy-3-*O*-methoxymethyl-α-D-glucopyranoside [12]

To a solution of the substrate **11** (305 mg, 0.94 mmol) dissolved in CH_2Cl_2 (15 mL) and pyridine (7.5 mmol) was added. The temperature was lowered to 0 °C. Triflic anhydride (0.5 mL, 3.0 mmol) was added and then the temperature was raised. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and the combined organic layer was washed with ice-cold HCl (5% aq., 100 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude triflate which was carried forward to the next step without further purification.

The crude triflate was dissolved in CH_3CN (15 mL) and TBAOAc (427 mg, 1.4 mmol) was added and the reaction mixture was stirred at room temperature for 2.5 hours when TLC (2 : 1 *n*-hexane/EtOAc, R_f = 0.7) showed complete conversion. Thereafter the solvent was concentrated under reduced pressure and the crude residue was dissolved in CH_2Cl_2 (30 mL) and washed with water (100 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the product **12** (285 mg) and was purified by column chromatography (3 : 1 *n*-hexane/EtOAc) and obtained in 82% yield over 2 steps as a white foam.

$[\alpha]_D^{25}$ +112 (*c* 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.03 (d, 2H, J = 8.5 Hz, Ar*H*), 6.83 (d, 2H, J = 8.5 Hz, Ar*H*), 5.47 (d, 1H, J = 3.5 Hz, H-1), 5.36 (d, 1H, J = 2.5 Hz, H-4), 4.85 (d, 1H, J = 7.0 Hz, MOM-CH_2), 4.65 (d, 1H, J = 7.0 Hz, MOM-CH_2), 4.39 (dd, 1H, J = 3.0 Hz, 11.5 Hz, H-3), 4.22 (m, 1H, H-5), 3.77 (s, 3H, OMP-OCH_3), 3.66 (dd, 1H, J = 3.5 Hz 11.0 Hz, H-2), 3.48 (s, 3H, MOM-*OCH*$_3$), 2.18 (s, 3H, CH_3), 1.13 (d, 3H, J = 6.5 Hz, H-6).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.5 (*C*O), 155.3, 150.5, 117.8, 114.6, 97.9 (C-1), 94.9 (MOM-*C*H$_2$), 70.7 (C-3), 70.3 (C-4), 65.7 (C-5), 58.8 (C-2), 56.1 (MOM-O*C*H$_3$), 55.6 (OMP-O*C*H$_3$), 20.7 (*C*H$_3$), 16.1 (C-6).

HRMS calculated for $C_{17}H_{23}N_3O_7Na$ (M + Na)$^+$: 404.1434, found: 404.1429.

p-Methoxyphenyl 4-*O*-acetyl-2-azido-2,6-dideoxy-α-D-glucopyranoside [13]

Compound **12** (230 mg, 0.60 mmol) was suspended in 70% aq. AcOH (20 mL) and H_2SO_4 (conc.) was added in catalytic amount. The reaction mixture was heated at 80 °C for 8 hours when TLC (2 : 1 *n*-hexane/EtOAc, R_f = 0.5) showed complete conversion. The acetic acid was removed under reduced pressure and the crude residue was purified by column chromatography (2.5 : 1 *n*-hexane/EtOAc) to obtain compound **13** (168 mg, 80%) as a white foam.

$[\alpha]_D^{25}$ +76 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.03 (d, 2H, J = 8.5 Hz, Ar*H*), 6.84 (d, 2H, J = 8.5 Hz, Ar*H*), 5.45 (d, 1H, J = 3.5 Hz, H-1), 5.27 (m, 1H, H-4), 4.48 (dd, 1H, J = 3.0 Hz, 11.5 Hz, H-3), 4.28–4.24 (m, 1H, H-5), 3.77 (s, 3H, CH_3), 3.66 (dd, 1H, J = 3.5 Hz 10.5 Hz, H-2), 2.21 (s, 3H, CH_3), 1.13 (d, 3H, J = 6.5 Hz, H-6).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.5 (*C*O), 155.4, 150.7, 117.9, 114.7, 98.0 (C-1), 73.1 (C-4), 67.3 (C-3), 65.7 (C-5), 60.0 (C-2), 55.6 (OMP-O*C*H$_3$), 20.8 (CO*C*H$_3$), 16.1 (C-6).

HRMS calculated for $C_{15}H_{19}N_3O_6Na$ (M + Na)$^+$: 360.1172, found: 360.1166.

p-Tolyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-6-*O*-benzoyl-3,4-di-*O*-isopropylidene-1-thio-α-D-galactopyranoside [19]

Trisaccharide **6** (800 mg, 0.68 mmol) was dissolved in acetone/H_2O (6 : 1, 35 mL) and trichloroisocyanuric acid (175 mg, 0.68 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. TLC (5 : 1 *n*-hexane/EtOAc, R_f = 0.15) at this point showed the reaction to be complete. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (40 mL). The solution was washed with $NaHCO_3$ aq. (100 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue which was purified by column chromatography (3 : 2 *n*-hexane/EtOAc) to give the trisaccharide hemi-acetal **7** (615 mg) in 85% yield. The hemi-acetal derivative was taken forward to the next step without further characterisation.

A part of the hemi-acetal derivative **7** (250 mg, 0.24 mmol) was dissolved in freshly dried CH_2Cl_2 (15 mL) and then it was treated with DBU (0.1 mL, 1.2 mmol) followed by trichloroacetonitrile (0.14 mL, 1.2 mmol). The reaction mixture was stirred at room temperature for 4 hours. TLC (5 : 1 *n*-hexane/EtOAc) at this point showed the reaction to be complete. The solvent was removed under reduced pressure and the residue was purified by column chromatography (2.5 : 1 *n*-hexane/EtOAc) to give the trichloroacetimidate **8** (290 mg) in 95% yield. The trichloroacetimidate derivative was taken forward to the next step without further characterisation.

The trichloroacetimidate donor **8** (290 mg, 0.24 mmol) and galactosyl acceptor **18** (110 mg, 0.26 mmol) were dissolved in CH_2Cl_2 (15 mL) and stirred with 4 Å MS (1.5 g) for 15 minutes under N_2 atmosphere. Thereafter the temperature was lowered to −15 °C and TMSOTf (0.01 mL, 0.06 mmol) was added and the reaction was allowed to continue for 45 minutes. TLC (3 : 1 *n*-hexane/EtOAc, R_f = 0.5) at this point showed the reaction to be complete. The MS was filtered out and the filtrate was washed successively with $NaHCO_3$ aq. (100 mL) and brine (100

mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue which was purified by column chromatography (3 : 1 *n*-hexane/EtOAc) to give the tetrasaccharide **19** (280 mg) in 75% yield.

$[\alpha]_D^{25}$ +109 (*c* 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.07–6.87 (m, 39H, Ar*H*), 5.60 (s, 1H, H-2‴), 5.29 (s, 1H, H-1′), 5.12 (s, 1H, H-1″), 5.06 (s, 1H, H-1‴), 4.96–4.57 (m, 14H, PhCH_2, H6a, H6b), 4.50 (d, 1H, *J* = 10.0 Hz, H-1), 4.24–4.17 (m, 3H, H-2″, H-3, H-4′), 4.09–4.01 (m, 4H, H-2′, H-3‴, H-5, H-5′), 4.24–4.17 (dd, 1H, *J* = 3.0 Hz, 9.0 Hz, H-3″), 3.92–3.81 (m, 4H, H-2, H-3′, H-5″, H-5‴), 3.51 (t, 1H, *J* = 9.5 Hz), 3.47 (t, 1H, *J* = 9.5 Hz), 3.46 (t, 2H, *J* = 9.5 Hz, H-4″, H-4‴), 2.25 (s, 3H, ArCH_3), 2.17 (s, 3H, COCH_3), 1.52 (s, 3H, CH_3), 1.35–1.31 (m, 6H, H-6′, H-6‴), 1.26 (d, 3H, *J* = 6.5 Hz, H-6″).

^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 170.1 (*C*O), 166.4 (*C*O), 155.3, 150.7, 138.7, 138.6, 138.5, 138.0, 132.9, 129.6, 128.15, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3 (Ar-*C*), 110.7 (O_2CMe_2), 100.4 (C-1″), 99.1 (C-1‴), 98.2 (C-1′), 86.2 (C-1), 80.2 (C-4′), 80.1 (C-4″, C-4‴), 79.9 (C-3), 79.2 (C-3″), 79.0 (C-3′), 77.8 (C-3‴), 75.4 (Ph*C*H_2), 75.3 (Ph*C*H_2), 75.0 (C-2), 74.9 (Ph*C*H_2), 74.8 (Ph*C*H_2), 74.6 (C-5), 74.3 (C-5′), 73.7 (C-2″), 72.2 (Ph*C*H_2), 71.8 (Ph*C*H_2), 69.0 (C-2‴), 68.9 (C-2′), 68.5 (C-5″), 68.3 (C-5‴), 64.2 (C-6), 27.8, 26.3 (2 × *C*H_3), 21.1 (Ar-*C*H_3), 21.0 (CO*C*H_3), 17.9 (C-6″), 17.9 (C-6‴), 17.8 (C-6″).

HRMS calculated for $C_{85}H_{94}O_{19}S$ $(M + Na)^+$: 1473.6008, found: 1473.6001.

p-Methoxyphenyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-6-*O*-benzoyl-3,4-di-*O*-isopropylidene-α-D-galactopyranosyl-(1→3)-4-*O*-acetyl-2-azido-2,6-dideoxy-α-D-glucopyranoside [20]

Tetrasaccharide donor **19** (280 mg, 0.19 mmol) and acceptor **13** (70 mg, 0.21 mmol) were dissolved in CH_2Cl_2 (15 mL) and stirred with 4 Å MS (1.5 g) and NIS (56 mg, 0.23 mmol) for 15 minutes under N_2 atmosphere. Thereafter the temperature was lowered to −30 °C and TMSOTf (7 μL, 0.03 mmol) was added and the reaction was allowed to continue for 1 hour. TLC (3 : 1 *n*-hexane/EtOAc, $R_{f=}$0.45) at this point showed the reaction to be complete. The MS was filtered out and the filtrate was washed successively with $NaHCO_3$ aq. (50 mL), $Na_2S_2O_3$ (50 mL) and brine (50 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue which was purified by column chromatography (2.5 : 1 *n*-hexane/EtOAc) to give the fully protected pentasaccharide **20** (240 mg, 75%) as colourless syrup.

$[\alpha]_D^{25}$ +57 (*c* 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.09 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.48–7.22 (m, 33H, Ar*H*), 6.90 (d, 2H, *J* = 9.0 Hz, Ar*H*), 6.78 (d, 2H, *J* = 9.0 Hz, Ar*H*), 5.55 (d, 1H, *J* = 1.5 Hz, H-2‴′), 5.39 (d, 1H, *J* = 8.5 Hz, H-1), 5.36 (d, 1H, *J* = 3.0 Hz, H-4), 5.21 (d, 1H, *J* = 1.0 Hz, H-1″), 5.10 (d, 1H, *J* = 2.5 Hz, H-1′), 5.07 (s, 1H, H-1‴), 5.00 (s, 1H, H-1‴′), 4.92–4.86 (m, 3H, PhCH_2), 4.76–4.54 (m, 11H, PhCH_2, H-6a, H-6b), 4.41–4.38 (m, 2H, H-3′, H-3), 4.31 (dd, 1H, *J* = 3.0 Hz 5.5 Hz, H-3‴), 4.10 (m, 3H, H-2″, H-2‴, H-5), 3.99 (dd, 1H, *J* = 3.0 Hz 9.0 Hz, H-3‴′), 3.93–3.89 (m, 2H, H-2′, H-5′), 3.86–3.78 (m, 8H, H-5″, H-5‴, H-3″, H-2, H-4′, CH_3), 3.74–3.71 (m, 1H, H-5‴′), 3.47 (t, 1H, *J* = 9.5 Hz), 3.42 (t, 1H, *J* = 9.5 Hz), 3.37 (t, 1H, *J* = 9.5 Hz, H-4″, H-4‴, H-4‴′), 2.15 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3), 1.52 (s, 3H, CH_3), 1.32–1.27 (m, 12H, *C*H_3, H-6 × 3), 1.22 (d, 3H, *J* = 6.5 Hz, H-6).

^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 170.1 (*C*O), 170.0 (*C*O), 166.4 (*C*O), 155.3, 150.7, 138.7, 138.6, 138.5, 138.4, 138.0, 118.3, 114.6 (*C*O), 109.8 (O_2CMe_2), 100.4 (C-1‴), 99.1 (C-1‴′), 98.9 (C-1″), 98.0 (C-1), 94.8 (C-1′), 80.2, 80.1, 80.1 (H-4″, H-4‴, H-4‴′), 79.2 (C-5), 78.9 (C-5′), 77.7 (C-3‴′), 75.7 (C-3′), 75.3 (Ph*C*H_2), 75.2 (Ph*C*H_2), 74.8, 74.5 (C-2″, C-2‴), 73.5 (C-3‴), 72.8 (C-2′), 72.1 (Ph*C*H_2), 71.7 (Ph*C*H_2), 71.7 (C-6), 71.2 (C-3), 68.9 (C-2‴′), 68.6 (C-4), 68.4, 68.2 (C-5″, C-2, C-3″), 68.1 (C-5‴), 67.2 (Ph*C*H_2), 65.9 (C-5‴′), 64.3 (Ph*C*H_2), 58.9 (C-4′), 55.6 (*C*H_3), 27.9, 26.2 (2 × *C*H_3), 21.1 (CO*C*H_3), 20.6 (CO*C*H_3), 18.0 (C-6), 17.9 (C-6), 16.1 (C-6).

HRMS calculated for $C_{93}H_{105}N_3O_{25}Na$ $(M + Na)^+$: 1686.6935, found: 1686.6929.

p-Methoxyphenyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-6-*O*-benzoyl-α-D-galactopyranosyl-(1→3)-4-*O*-acetyl-2-*N*-acetimido-2,6-dideoxy-α-D-glucopyranoside [21]

The protected pentasaccharide **20** (140 mg, 0.08 mmol) was suspended in 80% acetic acid (10 mL) at 80 °C for 4 hours. The acetic acid was removed under reduced and the residue was treated with thioacetic acid (10 mL). The reaction mixture was kept standing at room temperature for 7 days. Thereafter the thioacetic acid was removed under reduced pressure and the crude residue which was purified by column chromatography (1 : 3 *n*-hexane/EtOAc) to give the partially deprotected pentasaccharide derivative **21** (120 mg) in 85% yield.

$[\alpha]_D^{25}$ +84 (*c* 0.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.03–8.01 (m, 2H, Ar*H*), 7.56–7.16 (m, 33H, Ar*H*), 6.87 (d, 2H, *J* = 9.0 Hz, Ar*H*), 6.78 (d, 2H, *J* = 9.0 Hz, Ar*H*), 6.22 (d, 1H, *J* = 10.0 Hz, N*H*Ac), 5.52 (m, 1H, H-2′), 5.36 (s, 1H, H-4), 5.30 (d, 1H, *J* = 3.5 Hz, H-1), 5.11 (d, 1H, *J* = 2.5 Hz, H-1‴), 5.06 (d, 1H, *J* = 2.5 Hz, H-1′), 5.00 (s, 1H, H-1″), 4.96 (s, 1H, H-1‴′), 4.88 (dd, 2H, *J* = 5.0 Hz 11.0 Hz, PhCH_2), 4.74–4.53 (m, 13H, H-2, H-6a, H-6b, PhCH_2), 4.30 (t, 1H, *J* = 7.0 Hz, H-5′), 4.15–4.07 (m, 3H, H-3, H-2‴, H-5″), 4.02–3.84 (m, 7H, H-2″, H-2′, H-5‴, H-5‴′, H-3″, H-3‴′, H-3′), 3.80–3.75 (m, 6H, H-4′, CH_3, H-5), 3.45–3.37 (m, 2H), 3.32 (t, 1H, *J* = 9.0 Hz, H-4″, H-4‴, H-4‴′), 2.13 (s, 3H, COCH_3), 2.02 (s, 3H, COCH_3), 1.86 (s, 3H, COCH_3), 1.30–1.20 (m, 9H, H-6 × 3), 1.02 (d, 3H, *J* = 6.5 Hz, H-6).

^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 170.6 (*C*O), 170.0 (*C*O), 169.9 (*C*O), 167.6 (*C*O), 155.2, 150.5, 138.6, 138.4, 138.4, 138.3, 138.2, 138.0, 133.5, 129.7, 129.2, 128.5, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 118.0, 114.6 (Ar-*C*), 100.7 (C-1‴), 99.2 (C-1″), 99.0 (C-1‴′), 98.0 (C-1), 95.5 (C-1′), 80.4, 80.2, 80.0 (H-4″, H-4‴, H-4‴′), 79.0 (C-3‴′), 78.3 (C-5‴′), 77.6 (C-5″, C-5‴), 75.4 (Ph*C*H_2), 75.3 (C-6′), 74.3 (C-2″), 74.2 (Ph*C*H_2), 73.7 (C-2‴), 73.4 (C-2′), 72.0 (Ph*C*H_2), 71.9 (Ph*C*H_2), 71.7 (Ph*C*H_2), 70.5 (C-3), 69.5 (C-4′), 69.2 (C-

3″), 69.0 (C-2‴′), 68.3 (C-3‴), 68.2 (C-3′), 68.0 (C-4), 67.0 (C-5′), 66.0 (C-5), 63.3 (Ph*C*H$_2$), 55.6 (*C*H$_3$), 47.9 (C-2), 23.1 (CO*C*H$_3$), 21.0 (CO*C*H$_3$), 20.5 (CO*C*H$_3$), 18.3 (C-6 × 2), 17.8 (C-6), 16.2 (C-6).

HRMS calculated for $C_{92}H_{105}O_{26}NNa$ $(M + Na)^+$: 1662.6823 found: 1662.6819.

p-Methoxyphenyl α-L-rhamnopyranosyl-(1 → 2)-α-L-rhamnopyranosyl-(1 → 2)-α-L-rhamnopyranosyl-(1 → 2)-α-D-galactopyranosyl-(1 → 3)-2 *N*-acetamido-2,6-dideoxy-α-D-glucopyranoside [1]

The pentasaccharide derivative **26** (105 mg, 0.06 mmol) was dissolved in methanol (10 mL) and 10% Pd–C (100 mg) was added. The reaction mixture was kept stirring under a hydrogen atmosphere at room temperature and pressure for 36 hours. Thereafter the reaction mixture was filtered out and the filtrate was evaporated to dryness under reduced pressure. The crude residue was dissolved in freshly dried methanol (10 mL) and NaOMe (20 mg) was added. The reaction mixture was stirred at room temperature for 24 hours. Thereafter the reaction mixture was quenched with DOWEX 50W resin. The reaction mixture was filtered and the methanol was evaporated to dryness under vacuum to give the deprotected target **1** (55 mg, 90%) as off white amorphous mass.

$[\alpha]_D^{25}$ +41 (*c* 0.6, MeOH).

^{1}H NMR (CD_3OD, 500 MHz) *δ*: 7.00 (d, 2H, *J* = 9.0 Hz, Ar*H*), 6.83 (d, 2H, *J* = 9.0 Hz, Ar*H*), 5.32 (s, 1H, H-1), 5.30 (d, 1H, *J* = 3.0 Hz, H-1‴), 5.11 (s, 1H, H-1′), 5.06 (d, 1H, *J* = 3.5 Hz, H-1″) 4.92 (s, 1H, H-1‴′), 4.53 (dd, 1H, *J* = 3.0 Hz, 10.5 Hz), 4.17–4.11 (m, 2H), 4.03–4.00 (m, 2H), 3.96–3.93 (m, 4H), 3.87–3.84 (m, 2H), 3.82–3.76 (m, 2H), 3.73 (s, 3H, OC*H*$_3$), 3.71–3.60 (m, 4H), 3.39–3.30 (m, 5H), 2.05 (s, 3H, NHCOC*H*$_3$), 1.28–1.24 (m, 12H, 4 × H-6).

^{13}C NMR (CD_3OD, 125 MHz) *δ*: 155.3, 150.9, 117.9, 114.2 (Ar*C*), 102.4 (C-1‴′), 100.9 (C-1′), 100.1 (C-1), 97.5 (C-1‴), 96.5 (C-1″), 78.4, 77.7, 74.6, 72.9, 72.8, 72.6, 72.5, 71.7, 70.8, 70.6, 70.5, 70.4, 69.8, 69.0, 68.9, 68.8, 68.1, 66.4, 61.6, 54.6, 21.2 (NH*C*OCH$_3$), 16.8, 16.6, 16.4, 15.3 (C-6 × 4).

HRMS calculated for $C_{39}H_{61}O_{23}NNa$ $(M + Na)^+$: 934.3532, found: 934.3532.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

AC is thankful to Science and Engineering Research Board (SERB), New Delhi for National Postdoctoral Fellowship (PDF/2017/000919). The work is supported by the research grant EMR/2017/003043 from SERB, New Delhi to BM.

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