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# Synthesis of a unique trisaccharide having an acetal linkage between open-chain and cyclic sugar found in the cell wall of *Proteus* ☆

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ABSTRACT

The first stereoselective synthesis of a unique trisaccharide containing an open-chain glycosyl cyclic acetal moiety found in the cell wall of *Proteus* has been successfully achieved. Most of the intermediate steps are high yielding and highly reproducible. The acetal linkage of the open-chain D-galactosamine moiety with an (*S*)-configuration was formed exclusively.



## 1. Introduction

*Proteus mirabilis* is one of the most common gram-negative pathogens encountered in clinical specimens belonging to 'Enterobacteriaceae' and can cause a variety of community or hospital-acquired illnesses, including urinary tract, wound, and bloodstream infections (BSI).[1] *Proteus mirabilis* is a common cause of urinary tract infection (UTI) in catheterized patients and those with urinary tract abnormalities and occurs with significant frequency in hospitals.[2] It shows a preference for the upper urinary tract where it can cause serious kidney damage, acute pyelonephritis, bladder or renal stones, fever, and bacteriemia.[3] The mechanism of pathogenesis is unclear, but several virulence properties have been cited in the literature,[4] which include uroepithelial cell adhesin, fimbriae, hemolysin production, the ability to invade kidney epithelium, and the production of urease.

In 1999, for the first time, Vinogardov and Bock[5] discovered a trisaccharide found in the core lipopolysaccharide (LPS) of the cell wall of two serotypes of *Proteus*, in which an open-chain monosaccharide moiety is linked to a cyclic monosaccharide through an acetal linkage (Fig. 1). Afterwards, a number of oligosaccharides of similar structures have been found in other strains of Gram-negative bacteria.[6] Generally, in the naturally occurring glycosides, monosaccharide units exist in the cyclic form (pyranose or furanose) and are joined together through *O*-glycosidic and sometimes through *C*-glycosidic bonds. Several biosynthetic pathways for the formation of naturally occurring glycoconjugates have been demonstrated by considering the involvement of several glycosyltransferase enzymes in their biosynthesis.[7] According to the generally

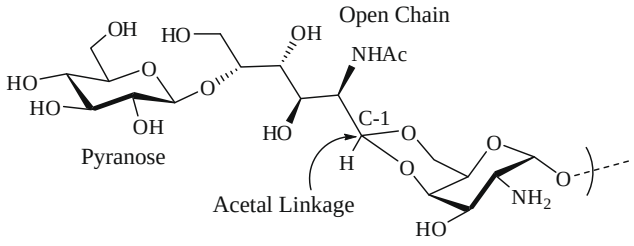


**Figure 1.** A unique trisaccharide found in the core lipopolysaccharide of the cell wall of *Proteus mirabilis* O27.

accepted and well-supported mechanism for the biosynthesis of polysaccharides, it is believed that a glycosyltransferase enzyme stereospecifically joins a cyclic pyranose or furanose sugar to another sugar residue using required cyclic sugar nucleotides.[8] In contrast to the generally accepted knowledge, the formation of such types of glycosidic linkage found in the cell wall lipopolysaccharide of *Proteus* probably takes place via a new, yet unknown, biosynthetic pathway.[9] After the discovery of such a new type of glycosylidine glycoside in the cell wall of *Proteus*, it is essential to establish whether this type of glycosides has any role in important biological function or can function as a cellwall antigen or act as a virulence factor. The existence of this new type of glycoside certainly indicated the existence of a new class of enzymes for their biosynthesis, which are different from the existing glycosyltransferases as they use cyclic sugar nucleotides as substrates. For a detailed study on the biological role of this unique trisaccharide, it is essential to synthesize it chemically, as the natural source cannot provide it in large quantity. Due to the unique structural features of this trisaccharide, it poses some extra challenges to the synthetic chemist.

In the present scenario, the preparation of carbohydrate-derived molecules of biological importance becomes an important area in medicinal chemistry. Herein, we report a concise chemical

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synthesis of the unique trisaccharide found in the core lipopolysaccharide of *Proteus mirabilis* O27 (Fig. 2). A number of reports[10] have already appeared in the literature for the syntheses and isolations of oligosaccharides containing acetal linkages between two cyclic monosaccharides. Recently, the formation of glycosylidene acetals and their selective reduction toward the formation of 6,6′-ether-linked disaccharide natural product, coyolosa has been reported.[11] Very recently, Yu et al.[12] also reported the synthesis of a natural product containing such a type of acyclic glycosylidene linkage.

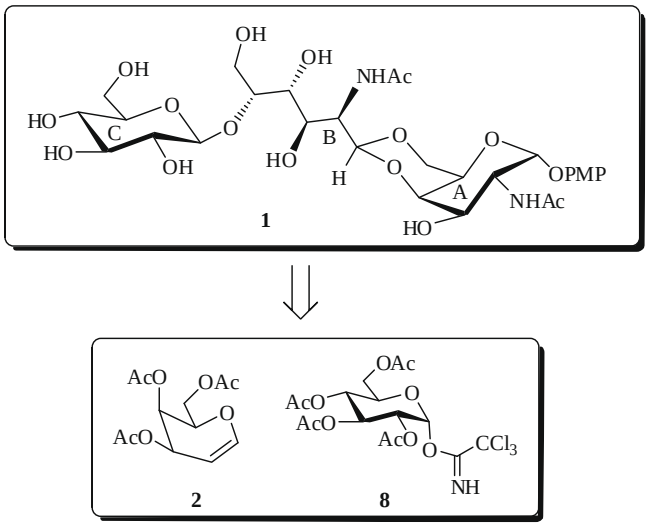
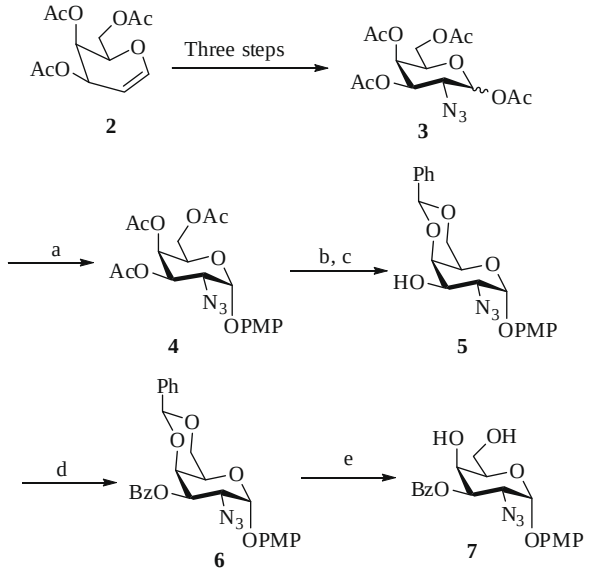



**Figure 2.** Structure of the synthesized trisaccharide as its 4-methoxyphenyl glycoside and its precursors.

## 2. Results and discussion

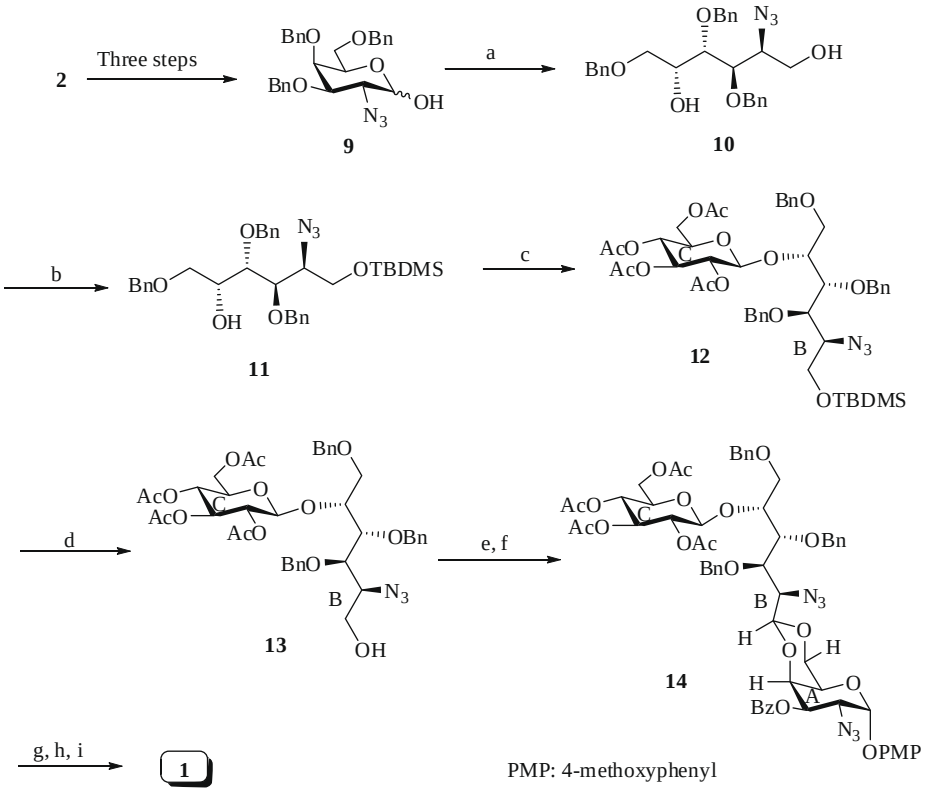
The synthesis of the target trisaccharide **1** as its 4-methoxyphenyl glycoside has been achieved from D-galactal-derived intermediates in a minimum number of steps. 1,3,4,6-Tetra-*O*-acetyl-2-azido-2-deoxy-α,β-D-galactopyranose **3**[13] was prepared from 3,4,6-tri-*O*-acetyl-D-galactal **2** under azido-nitration condition reported earlier. Compound **3** was reacted with 4-methoxyphenol in the presence of borontrifluoride[14] to give compound **4** in 70% yield. Deacetylation followed by benzylidenation of compound **4** furnished compound **5** in 88% overall yield. Conventional benzoylation of compound **5** followed by removal of the benzylidene acetal using perchloric acid supported over silica gel ($HClO_4$–$SiO_2$)[15] furnished compound **7** in excellent yield (Scheme 1).

Initially, it was planned to use an acyclic glycosyl dithioacetal derivative as the precursor of acyclic galactosamine moiety to form glycosylidene acetal using our earlier reported reaction condition.[16] For this purpose, treatment of the 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-galactosamine derivative with ethanethiol in the presence of conc. HCl furnished only ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranoside instead of giving dithioacetal derivative. Alternatively, the reaction of the 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranose derivative with ethanethiol in the presence of borontrifluoride also did not furnish the required dithioacetal derivative. We presumed that the azido group may be reduced in the presence of ethanethiol and borontrifluoride diethyletherate leading to the formation of an uncharacterized product. Prompted by a recent report,[12] in which a suitably protected acyclic glycosyl aldehyde has been used for the preparation of glycosylidene derivative, the synthetic strategy has been modified to use protected acyclic 2-amino-2-deoxy-galactitol derivative for the preparation of the target trisaccharide derivative.




**Scheme 1.** Reagents and conditions: (a) 4-Methoxy phenol, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 0 °C→15 °C, 3 h, 70%; (b) $CH_3ONa$, $CH_3OH$, room temperature, 3 h; (c) benzaldehyde dimethylacetal, *p*-TsOH, $CH_3CN$, room temperature, 2 h, 88% over two steps; (d) benzoyl chloride, pyridine, room temperature, 2 h, 95%; (e) $HClO_4$–$SiO_2$, $CH_3CN$–$H_2O$ (20:1, v/v) 20 min, room temperature, 85%.

Using 3,4,6-tri-*O*-acetyl-D-galactal **2** as a starting material, 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α,β-D-galactopyranose **9**[17] was prepared in three steps following literature-reported reaction conditions. Compound **9** was converted to linear galactitol derivative **10** via sodium borohydride reduction[18] in 86% yield. Selective protection of the primary hydroxy group[19] of compound **10** using *tert*-butyldimethylchlorosilane furnished the linear galactitol acceptor **11** in 90% yield. Glycosylation of compound **11** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **8**[20] in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[21] afforded disaccharide derivative **12** in 82% yield. Signals at δ 99.3 (C-$1_C$) and 71.5 (C-$1_B$) in the $^{13}C$ NMR spectra supported the formation of compound **12**. Removal of the silyl protection of compound **12** under acidic conditions[22] gave compound **13** in 86% yield. Oxidation of the primary hydroxy group of compound **13** using the Dess–Martin periodinane followed by acetal formation[12] with compound **7** in the presence of TMSOTf furnished trisaccharide derivative **14** in 69% overall yield. Signals at $\delta$ 5.69 (d, $J$ = 3.3 Hz, H-$1_A$), 5.39 (d, $J$ = 5.4 Hz, H-$1_B$), 4.88 (d, $J$ = 8.1 Hz, H-$1_C$) in the $^1H$ NMR and at $\delta$ 99.6 (C-$1_C$), 97.5 (C-$1_A$), 95.9 (C-$1_B$) in the $^{13}C$ NMR spectra supported the formation of compound **14**. Compound **14** has a new stereogenic center which is C-$1_B$ of acyclic D-galactosamine moiety. It is noteworthy that compound **14** was formed only as a single stereoisomer, which was confirmed from its 2D NOESY NMR spectrum. In the NOESY spectrum of compound **14** cross peaks appeared between the H-$1_B$ and H-$4_A$ and H-$6_A$, which is possible only if H-$1_B$ is present in an axial orientation having (*S*)-configuration. Reduction of the azido group and removal of benzyl protection under a recently reported reduction conditions[23] using triethylsilane over 10% Pd–C followed by N-acetylation furnished the target trisaccharide **1** as its 4-methoxyphenyl glycoside in 82% overall yield. Signals at $\delta$ 5.48 (d, $J$ = 3.4 Hz, H-$1_A$), 5.12 (d, $J$ = 5.7 Hz, H-$1_B$), 4.54 (d, $J$ = 7.7 Hz, H-$1_C$) in the $^1H$ NMR and at $\delta$ 103.4 (C-$1_C$), 98.9 (C-$1_A$), 96.6 (C-$1_B$) in the $^{13}C$ NMR spectra confirmed the structure of compound **1** (Scheme 2).




**Scheme 2.** Reagents and conditions: (a) Sodium borohydride, $CH_3OH$, room temperature, 2 h, 86%; (b) *tert*-butyldimethylchlorosilane, pyridine, DMF, room temperature, 5 h, 90%; (c) **8**, TMSOTf, $CH_2Cl_2$, −20 °C, 1 h, 82%; (d) 80% aq AcOH, 60 °C, 2 h, 86%; (e) Dess–Martin periodinane, $CH_2Cl_2$, room temperature, 2 h; (f) **7**, TMSOTf, $CH_2Cl_2$, −20 °C, 1 h, 69% in two steps; (g) 10% Pd-C, $Et_3SiH$, $CH_3OH$–$CHCl_3$ (5:1), room temperature, 6 h; (h) acetic anhydride, pyridine, room temperature, 12 h; (i) $CH_3ONa$, $CH_3OH$, room temperature, 12 h, 82% in three steps.

## 3. Conclusion

In conclusion, an expedient approach for the synthesis of a unique trisaccharide containing open-chain cyclic acetal linkage has been developed. The stereoselective formation of the acetal linkage of the acyclic D-galactosamine moiety has been achieved for the first time leading to the synthesis of uncommon trisaccharide present in *Proteus mirabilis* O27. This will certainly open up an avenue for the large-scale preparation of this class of compounds for their potential use in the preparation of therapeutics.

## 4. Experimental

### 4.1. General methods

All the reactions were monitored by thin layer chromatography over silica gel-coated TLC plates. The spots on TLC were visualized by warming ceric sulfate (2% $Ce(SO_4)_2$ in 2 N $H_2SO_4$)-sprayed plates in hot plate. Silica gel 230–400 mesh was used for column chromatography. $^1H$ and $^{13}C$ NMR, 2D COSY, HSQC, and NOESY spectra were recorded on Brucker Advance DPX 300 MHz using $CDCl_3$ and $D_2O$ as solvents and TMS as internal reference unless stated otherwise. Chemical shift values are expressed in $\delta$ ppm. ESI-MS were recorded on a MICROMASS QUTTRO II triple quadrupole mass spectrometer. Elementary analysis was carried out on Carlo ERBA-1108 analyzer. Optical rotations were measured at 25 °C on a Rudolf Autopol III polarimeter. Commercially available grades of organic solvents of adequate purity are used in many reactions.

### 4.2. 4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranoside 4

To a solution of compound **3** (570 mg, 1.53 mmol) and 4-methoxyphenol (230 mg, 1.83 mmol) in dry $CH_2Cl_2$ (8 mL) was added $BF_3{\cdot}OEt_2$ (390 μl, 3.06 mmol) at 0 °C and stirred at 15 °C for 3 h. The reaction mixture was diluted with $CH_2Cl_2$ (15 mL), and the organic layer was washed in succession with water (2 × 10 mL) and satd. $NaHCO_3$ solution (2 × 10 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified over $SiO_2$ using hexane–EtOAc (3:1) as eluant to give pure compound **4** (470 mg, 70%) as a colorless oil; $[\alpha]_D^{25} = +146$ (*c* 1.0, $CHCl_3$); IR (neat): 3021, 2360, 2112, 1750, 1216, 761, 670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 7.04 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.83 (d, *J* = 9.1 Hz, 2H, Ar-H), 5.55 (dd, *J* = 11.1, 3.2 Hz, 1H, H-3), 5.50 (d, *J* = 3.2 Hz, 1H, H-1), 5.50 (br s, 1H, H-4), 4.43–4.37 (m, 1H, H-5), 4.16–4.03 (m, 2H, $H\text{-}6_{ab}$), 3.78 (s, 3 H, $OCH_3$), 3.74 (dd, *J* = 11.3, 3.6 Hz, 1H, H-2), 2.17, 2.09, 1.99 (3s, 9 H, 3 $COCH_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 170.0, 169.7, 169.5 (3C, 3 $COCH_3$), 155.6 (Ar-C), 150.2 (Ar-C), 118.2 (2C, Ar-C), 114.6 (2C, Ar-C), 98.0 (C-1), 68.1 (C-4), 67.4 (C-6), 67.3 (C-3), 61.3 (C-5), 57.3 ($OCH_3$), 55.5 (C-2), 20.6 (3C, 3 $COCH_3$); ESI-MS: *m/z* 460.3 $[M+Na]^+$; Anal. Calcd for $C_{19}H_{23}N_3O_9$ (437.1): C, 52.17; H, 5.30. Found: C, 52.0; H, 5.50.

### 4.3. 4-Methoxyphenyl 2-azido-4,6-*O*-benzylidine-2-deoxy-α-D-galactopyranoside 5

To a solution of compound **4** (430 mg, 0.98 mmol) in anhyd MeOH (10 mL) was added solid sodium methoxide until the pH of the solution reached to ~10. The reaction mixture was allowed

to stir at room temperature for 3 h, neutralized with Dowex-50W X-8 ($H^+$), filtered, and evaporated to dryness. To a solution of the deacetylated product in dry acetonitrile (6 mL) were added benzaldehyde dimethylacetal (220 μl, 1.47 mmol) and *p*-TsOH (50 mg), and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was quenched with triethylamine (0.1 mL), and the solvents were removed under reduced pressure. The residue was diluted with $CH_2Cl_2$ (15 mL) and the organic layer was washed with water (2 × 8 mL) and satd $NaHCO_3$ (2 × 8 mL) successively. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified over $SiO_2$ using hexane–EtOAc (7:2) as eluant to give pure compound **5** (345 mg, 88%) as a white solid; mp 73 °C; $[\alpha]_D^{25} = -22$ (*c* 1.0, $CHCl_3$); IR (KBr): 2935, 2362, 2104, 1508, 1452, 1249, 1218, 1103, 1041, 999, 827, 796, 755, 701 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.50–7.45 (m, 2H, Ar-H), 7.38–7.34 (m, 3 H, Ar-H), 7.0 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.80 (d, *J* = 9.1 Hz, 2H, Ar-H), 5.54 (s, 1H, PhC*H*), 5.51 (d, *J* = 3.2 Hz, 1H, H-1), 4.38–4.27 (m, 2H, H-3 and H-5), 4.22 (dd, *J* = 12.7, 1.1 Hz, 1H, H-$6_a$), 4.00 (dd, *J* = 12.5, 1.4 Hz, 1H, H-$6_b$), 3.82 (br s, 1H, H-4), 3.75 (s, 3H, O$CH_3$), 3.62 (dd, *J* = 10.3, 3.2 Hz, 1H, H-2), 2.66 (d, *J* = 10.4 Hz, 1H, O*H*); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 155.3–114.7 (12C, Ar-C), 101.2 (Ph*C*H), 98.3 (C-1), 75.4 (C-4), 69.1 (C-6), 67.3 (C-3), 63.4 (C-5), 60.4 (C-2), 55.5 (O$CH_3$); ESI-MS: *m/z* 422.4 $[M+Na]^+$; Anal. Calcd for $C_{20}H_{21}N_3O_6$ (399.1): C, 60.14; H, 5.30. Found: C, 59.93; H, 5.52.

### 4.4. 4-Methoxyphenyl 2-azido-3-*O*-benzoyl-4,6-*O*-benzylidine-2-deoxy-α-D-galactopyranoside 6

To a solution of compound **5** (300 mg, 0.75 mmol) in dry pyridine (5 mL) was added benzoyl chloride (130 μl, 1.12 mmol), and the reaction mixture was stirred at room temperature for 2 h. The solvents were removed under reduced pressure, and the crude material was purified over $SiO_2$ using hexane–EtOAc (6:1) as eluant to give pure compound **6** (360 mg, 95%) as a white solid; mp 70 °C; $[\alpha]_D^{25} = +117$ (*c* 1.0, $CHCl_3$); IR (KBr): 3021, 2359, 2113, 1723, 1596, 1216, 1039, 760, 671 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 8.14–8.07 (m, 2H, Ar-H), 7.59–7.54 (m, 1H, Ar-H), 7.47–7.41 (m, 4H, Ar-H), 7.35–7.30 (m, 3H, Ar-H), 7.05 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.81 (d, *J* = 9.1 Hz, 2H, Ar-H), 5.76 (dd, *J* = 11.1, 3.4 Hz, 1H, H-3), 5.67 (d, *J* = 3.2 Hz, 1H, H-1), 5.52 (s, 1H, PhC*H*), 4.65 (d, *J* = 3.1 Hz, 1H, H-4), 4.28–4.22 (m, 1H, H-$6_a$), 4.19 (dd, *J* = 11.1, 3.3 Hz, 1H, H-2), 4.06–4.01 (m, 1H, H-$6_b$), 3.95 (br s, 1H, H-5), 3.75 (s, 3H, O$CH_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 165.8–114.7 (18C, Ar-C), 100.6 (Ph*C*H), 98.1 (C-1), 73.5 (C-4), 69.8 (C-3), 69.0 (C-6), 63.2 (C-5), 57.5 (C-2), 55.5 (O$CH_3$); ESI-MS: *m/z* 526.3 $[M+Na]^+$; Anal. Calcd for $C_{27}H_{25}N_3O_7$ (503.2): C, 64.41; H, 5.00. Found: C, 64.22; H, 5.25.

### 4.5. 4-Methoxyphenyl 2-azido-3-*O*-benzoyl-2-deoxy-α-D-galactopyranoside 7

To a solution of compound **6** (315 mg, 0.63 mmol) in $CH_3CN$–$H_2O$ (8 mL, 20:1, v/v) was added $HClO_4$–$SiO_2$ (100 mg), and the reaction mixture was allowed to stir at room temperature for 20 min. The reaction mixture was filtered through a Celite® bed and was washed with $CH_2Cl_2$ (20 mL). Solvents were evaporated and co-evaporated with toluene (3 × 5 mL), and the crude product was purified over $SiO_2$ using hexane–EtOAc (1:1) as eluant to give pure compound **7** (220 mg, 85%) as a white solid. Mp 145 °C; $[\alpha]_D^{25} = +205$ (*c* 1.0, $CH_3CN$); IR (KBr): 3021, 2928, 2359, 2112, 1724, 1597, 1430, 1216, 760, 671 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 8.14–8.10 (m, 2H, Ar-H), 7.64–7.58 (m, 1H, Ar-H), 7.50–7.44 (m, 2H, Ar-H), 7.06 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.84 (d, *J* = 9.1 Hz, 2H, Ar-H), 5.68 (dd, *J* = 11.0, 2.9 Hz, 1H, H-3), 5.60 (d, *J* = 3.5 Hz, 1H, H-1), 4.52 (d, *J* = 2.3 Hz, 1H, H-4), 4.16–4.11 (m, 1H, H-5), 4.08 (dd, *J* = 11.0, 3.5 Hz, 1H, H-2), 3.98–3.86 (m, 2H, H-$6_{ab}$), 3.78 (s, 3H, O$CH_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 165.9–114.6 (12C, Ar-C), 98.2 (C-1), 71.5 (C-4), 70.2 (C-6), 67.8 (C-5), 61.9 (C-3), 57.5 (C-2), 55.5 (O$CH_3$); ESI-MS: *m/z* 438.4 $[M+Na]^+$; Anal. Calcd for $C_{20}H_{21}N_3O_7$ (415.1): C, 57.83; H, 5.10. Found: C, 57.66; H, 5.30.

### 4.6. 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactitol 10

To a solution of compound **9** (465 mg, 0.98 mmol) in dry methanol (8 mL) was added $NaBH_4$ (75 mg, 1.96 mmol) at 0 °C under argon. The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was cooled to 0 °C and was quenched by the addition of glacial AcOH (2 mL). After removal of the solvents under reduced pressure, the crude product was dissolved in $CH_2Cl_2$ (15 mL) and the organic layer was washed with water (2 × 8 mL) and brine (2 × 8 mL) successively. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified over $SiO_2$ using hexane–EtOAc (1:1) as eluant to give pure compound **10** (400 mg, 86%) as a white solid; mp 55 °C; $[\alpha]_D^{25} = -245$ (*c* 1.0, $CHCl_3$); IR (KBr): 3020, 2360, 2110, 1216, 1100, 928, 760, 670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.32–7.21 (m, 15 H, Ar-H), 4.72 (d, *J* = 11.4 Hz, 1H, PhC$H_2$), 4.63 (d, *J* = 11.1 Hz, 1H, PhC$H_2$), 4.58 (d, *J* = 11.4 Hz, 1H, PhC$H_2$), 4.50 (d, *J* = 10.8 Hz, 1H, PhC$H_2$), 4.44 (d, *J* = 11.9 Hz, 1H, PhC$H_2$), 4.40 (d, *J* = 11.0 Hz, 1H, PhC$H_2$), 4.01–3.97 (m, 1H, H-5), 3.86 (dd, *J* = 7.4, 3.0 Hz, 1H, H-$1_a$), 3.78 (dd, *J* = 7.4, 1.4 Hz, 1H, H-$1_b$), 3.73 (dd, *J* = 8.0, 3.6 Hz, 1H, H-$6_a$), 3.64 (dd, *J* = 11.1, 5.8 Hz, 1H, H-$6_b$), 3.55–3.43 (m, 3H, H-2, H-3 and H-4); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 137.6–127.9 (18C, Ar-C), 77.9 (C-4), 77.6 (C-3), 74.5 (2C, Ph$CH_2$), 73.4 (Ph$CH_2$), 71.1 (C-1), 69.2 (C-5), 62.8 (C-2), 61.8 (C-6); ESI-MS: *m/z* 500.3 $[M+Na]^+$; Anal. Calcd for $C_{27}H_{31}N_3O_5$ (477.2): C, 67.91; H, 6.54. Found: C, 67.74; H, 6.75.

### 4.7. 2-Azido-3,4,6-tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-galactitol 11

To a solution of compound **10** (370 mg, 0.77 mmol) in dry DMF (2 mL) was added pyridine (1 mL) followed by *tert*-butyldimethylchlorosilane (130 mg, 0.85 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 5 h. After removal of the solvents under reduced pressure, the crude material was purified over $SiO_2$ using hexane–EtOAc (4:1) as eluant to afford pure compound **11** (410 mg, 90%) as a colorless oil; $[\alpha]_D^{25} = -2$ (*c* 1.0, $CHCl_3$); IR (neat): 3020, 2360, 2105, 1596, 1216, 1107, 840, 761, 670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.40–7.22 (m, 15 H, Ar-H), 4.73 (d, *J* = 11.4 Hz, 1H, PhC$H_2$), 4.64 (d, *J* = 11.1 Hz, 1H, PhC$H_2$), 4.58 (d, *J* = 11.5 Hz, 1H, PhC$H_2$), 4.53 (d, *J* = 11.8 Hz, 1H, PhC$H_2$), 4.51 (d, *J* = 11.3 Hz, 1H, PhC$H_2$), 4.46 (d, *J* = 11.9 Hz, 1H, PhC$H_2$), 4.08–3.97 (m, 1H, H-5), 3.89–3.76 (m, 3H, H-3, H-4 and H-$6_a$), 3.67 (dd, *J* = 10.3, 5.5 Hz, 1H, H-$6_b$), 3.61–3.45 (m, 3H, H-2 and H-$6_{ab}$), 2.40 (d, *J* = 7.4 Hz, 1H, O*H*), 0.90 (s, 9H, C($CH_3$)$_3$), 0.04, 0.03 (2s, 6H, 2$CH_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 137.8–127.8 (18C, Ar-C), 77.9 (C-4), 77.2 (C-3), 74.6 (2C, 2 Ph$CH_2$), 73.4 (Ph$CH_2$), 71.3 (C-1), 69.1 (C-5), 63.2 (C-6), 63.0 (C-2), 25.9 (3C, C($CH_3$)$_3$), 18.2 (*C*($CH_3$)$_3$), −5.4 (2C, 2$CH_3$); ESI-MS: *m/z* 615.2 $[M+Na]^+$; Anal. Calcd for $C_{33}H_{45}N_3O_5Si$ (591.3): C, 66.97; H, 7.66. Found: C, 66.80; H, 7.85.

### 4.8. 2-Azido-5-*O*-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)]-3,4,6-tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-galactitol 12

To a solution of compound **11** (370 mg, 0.63 mmol) and compound **8** (370 mg, 0.75 mmol) in dry $CH_2Cl_2$ (8 mL) was added activated MS 4 Å (200 mg), and the reaction mixture was allowed to

stir under argon at room temperature for 1 h. After cooling the reaction mixture to −20 °C, TMSOTf (5 μl) was added to it and the reaction mixture was allowed to stir at −20 °C for 1 h. The reaction mixture was filtered through a Celite® bed and washed with $CH_2Cl_2$ (3 × 10 mL). The organic layer was washed successively with water (2 × 10 mL) and satd. aq. $NaHCO_3$ (2 × 10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The crude material was purified over $SiO_2$ using hexane–EtOAc (3:1) as eluant to afford pure compound **12** (475 mg, 82%) as colorless oil; $[\alpha]_D^{25} = -12$ (*c* 1.0, $CHCl_3$); IR (neat): 3021, 2931, 2360, 2105, 1751, 1371, 1216, 1040, 761, 670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.45–7.21 (m, 15H, Ar-H), 5.22–5.09 (m, 1H, H-$3_C$), 5.07–4.91 (m, 3H, H-$1_C$, H-$2_C$ and H-$4_C$), 4.81 (d, *J* = 11.6 Hz, 1H, PhC$H_2$), 4.68 (d, *J* = 11.6 Hz, 1H, PhC$H_2$), 4.54 (d, *J* = 10.7 Hz, 1H, PhC$H_2$), 4.51 (d, *J* = 10.9 Hz, 1H, PhC$H_2$), 4.43 (br s, 1H, PhC$H_2$), 4.39–4.31 (m, 1H, H-$5_B$), 4.10 (dd, *J* = 12.3, 3.7 Hz, 1H, H-$6_{aC}$), 3.98–3.88 (m, 2H, H-$3_B$ and H-$6_{bC}$), 3.86–3.63 (m, 5H, H-$1_{abB}$, H-$4_B$ and H-$6_{abB}$), 3.62–3.49 (m, 2H, H-$2_B$ and H-$5_C$), 2.02, 1.88, 1.85 (3s, 12H, 4COC$H_3$), 0.9 (s, 9H, C(C$H_3$)$_3$), 0.04, 0.04 (2s, 6H, 2C$H_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 170.2, 170.0, 169.2, 169.0 (4C, 4C$OCH_3$), 138.3–127.2 (18C, Ar-C), 99.3 (C-$1_C$), 79.0 (C-$4_B$), 77.1 (C-$3_B$), 76.0 (C-$5_B$), 74.3 (PhC$H_2$), 73.7 (PhC$H_2$), 73.5 (PhC$H_2$), 72.8 (C-$3_C$), 71.9 (C-$5_C$), 71.5 (2C, C-$2_C$ and C-$1_B$), 68.4 (C-$4_C$), 63.5 (C-$6_B$), 63.4 (C-$2_B$), 61.7 (C-$6_C$), 25.9 (3C, C(C$H_3$)$_3$), 20.6, 20.5, 20.4 (4C, 4COC$H_3$), 18.2 (C(CH$_3$)$_3$), −5.4 (2C, 2C$H_3$); ESI-MS: *m/z* 938.9 $[M+NH_4]^+$; Anal. Calcd for $C_{47}H_{63}N_3O_{14}Si$ (921.4): C, 61.22; H, 6.89. Found: C, 61.05; H, 7.10.

### 4.9. 5-[*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)]-2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactose 13

A solution of **12** (440 mg, 0.48 mmol) in 80% aq AcOH (12 mL) was allowed to stir at 60 °C for 2 h, and the solvents were removed under reduced pressure. The crude product was purified over $SiO_2$ using hexane–EtOAc (3:2) as eluant to give pure compound **13** (330 mg, 86%) as colorless oil; $[\alpha]_D^{25} = -14$ (*c* 1.0, $CHCl_3$); IR (neat): 3021, 2917, 2361, 2108, 1751, 1631, 1428, 1372, 1216, 1040, 762, 670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.40–7.22 (m, 15H, Ar-H), 5.15 (t, *J* = 9.1 Hz, 1H, H-$3_C$), 5.02 (t, *J* = 9.6 Hz, 1H, H-$4_C$), 4.97–4.87 (m, 2H, H-$1_C$ and H-$2_C$), 4.78 (d, *J* = 11.1 Hz, 1H, PhC$H_2$), 4.68 (d, *J* = 11.7 Hz, 1H, PhC$H_2$), 4.59 (d, *J* = 10.9 Hz, 1H, PhC$H_2$), 4.56 (d, *J* = 11.6 Hz, 1H, PhC$H_2$), 4.42 (br s, 2H, PhC$H_2$), 4.30–4.22 (m, 1H, H-$5_B$), 4.11 (dd, *J* = 12.4, 4.3 Hz, 1H, H-$6_{aC}$), 4.02 (dd, *J* = 12.3, 2.1 Hz, 1H, H-$6_{bC}$), 3.88–3.78 (m, 2H, H-$3_B$ and H-$4_B$), 3.77–3.67 (m, 4H, H-$1_{abB}$ and H-$6_{abB}$), 3.66–3.60 (m, 1H, H-$2_B$), 3.59–3.51 (m, 1H, H-$5_C$), 2.02, 2.01, 1.98, 1.97 (4s, 12H, 4COC$H_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 170.4, 170.0, 169.3, 169.2 (4C, 4C$OCH_3$), 138.1–127.5 (18C, Ar-C), 99.6 (C-$1_C$), 78.7 (C-$4_B$), 78.6 (C-$5_B$), 77.0 (C-$3_B$), 74.6 (PhC$H_2$), 73.5 (2PhC$H_2$), 72.6 (C-$3_C$), 71.9 (C-$5_C$), 71.4 (2C, C-$1_B$ and C-$2_C$), 68.3 (C-$4_C$), 64.2 (C-$6_B$), 62.3 (C-$2_B$), 61.5 (C-$6_C$), 20.5 (4C, 4COC$H_3$); ESI-MS: *m/z* 830.2 $[M+Na]^+$; Anal. Calcd for $C_{41}H_{49}N_3O_{14}$ (807.3): C, 60.96; H, 6.11. Found: C, 60.78; H, 6.30.

### 4.10. 4-Methoxyphenyl 2-azido-3-*O*-benzoyl-2-deoxy-4,6-*O*-(1*S*)-[5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-azido-3,4,6-tri-*O*-benzyl-2-deoxy]-D-galactosylidene–D-galactopyranoside 14

To a solution of compound **13** (305 mg, 0.38 mmol) in dry $CH_2Cl_2$ (5 mL) was added Dess–Martin periodinane (240 mg, 0.57 mmol), and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with $CH_2Cl_2$ (5 mL) and the organic layer was washed with 10% aq $Na_2S_2O_3$ (3 mL) and satd $NaHCO_3$ (3 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde as a colorless oil, which was used in the next step without further purification. To a solution of crude aldehyde (285 mg, 0.35 mmol) and compound **7** (165 mg, 0.39 mmol) in anhyd $CH_2Cl_2$–$CH_3CN$ (6 mL, 5:1, v/v) was added activated MS 4 Å (150 mg), and the reaction mixture was allowed to stir under argon at room temperature for 1 h. After cooling the reaction mixture to −40 °C, TMSOTf (60 μL, 0.35 mmol) was added to it and the reaction mixture was allowed to stir at −20 °C for 1 h. The reaction mixture was quenched with triethylamine (0.1 mL), filtered through a Celite® bed, and washed with $CH_2Cl_2$ (3 × 10 mL). The organic layer was washed successively with water (2 × 10 mL) and brine (2 × 10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The crude product was purified over $SiO_2$ using toluene–EtOAc (7:2) as eluant to afford the title compound **14** (315 mg, 69%) as a colorless oil; $[\alpha]_D^{25} = +96$ (*c* 1.0, $CHCl_3$); IR (neat): 3020, 2361, 2338, 2112, 1755, 1507, 1368, 1216, 1041, 760, 669 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): δ 8.18 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.63 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.47 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.39–7.22 (m, 15H, Ar-H), 7.07 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.86 (d, *J* = 9.1 Hz, 2H, Ar-H), 5.77 (dd, *J* = 7.9, 3.0 Hz, 1H, H-$3_A$), 5.69 (d, *J* = 3.3 Hz, 1H, H-$1_A$), 5.39 (d, *J* = 5.4 Hz, 1H, H-$1_B$), 5.15 (t, *J* = 9.4 Hz, 1H, H-$3_C$), 5.00–4.92 (m, 2H, H-$2_C$ and H-$4_C$), 4.88 (d, *J* = 8.1 Hz, 1H, H-$1_C$), 4.78–4.60 (m, 4H, H-$6_{abC}$ and PhC$H_2$), 4.59–4.38 (m, 5H, H-$4_A$ and 2 PhC$H_2$), 4.32–4.27 (m, 1H, H-$5_B$), 4.26–4.01 (m, 4H, H-$2_A$, H-$6_{aA}$, H-$4_B$ and H-$6_{aB}$), 3.98–3.88 (m, 2H, H-$6_{bA}$ and H-$2_B$), 3.78 (s, 3H, OC$H_3$), 3.85–3.70 (m, 3H, H-$5_A$, H-$3_B$ and H-$6_{bB}$), 3.58–3.50 (m, 1H, H-$5_C$), 2.03, 2.02, 1.98, 1.97 (4s, 12H, 4COC$H_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 170.1, 170.0, 169.4, 168.8 (4C, 4C$OCH_3$), 165.6 (COPh), 155.3–114.7 (30C, Ar-C), 99.6 (C-$1_C$), 97.5 (C-$1_A$), 95.9 (C-$1_B$), 78.6 (C-$3_B$), 77.4 (C-$5_A$), 76.8 (C-$5_B$), 74.8 (PhC$H_2$), 73.4 (PhC$H_2$), 72.9 (2C, C-$3_C$ and PhC$H_2$), 71.8 (C-$5_C$), 71.5 (C-$6_C$), 71.3 (C-$4_C$), 69.2 (C-$3_A$), 68.3 (C-$2_C$), 66.9 (C-$4_A$), 65.8 (C-$6_B$), 64.4 (C-$4_B$), 62.1 (C-$2_B$), 61.9 (C-$6_A$), 57.5 (C-$2_A$), 55.6 (OC$H_3$), 20.5 (4C, 4COC$H_3$); ESI-MS: *m/z* 1219.9 $[M+NH_4]^+$; Anal. Calcd for $C_{61}H_{66}N_6O_{20}$ (1202.4): C, 60.89; H, 5.53. Found: C, 60.71; H, 5.75.

### 4.11. 4-Methoxyphenyl 2-acetamido-2-deoxy-4,6-*O*-(1*S*)-[5-*O*-(β-D-glucopyranosyl)-2-acetamido-2-deoxy]-D-galactosylidene-α-D-galactopyranoside 1

To a solution of compound **14** (280 mg, 0.23 mmol) in $CH_3OH$–$CHCl_3$ (6 mL, 5:1, v/v) was added 10% Pd-C (100 mg) and $Et_3SiH$ (560 μL, 3.5 mmol) under argon, and the reaction mixture was stirred at room temperature for 2 h. Another portion of $Et_3SiH$ (250 μL) was added to the reaction mixture and it was allowed to stir at room temperature for 4 h. The reaction mixture was filtered through a Celite® bed and washed with $CH_3OH$ (3 × 10 mL). The solvents were removed under reduced pressure, and a solution of the crude mass in pyridine and acetic anhydride (5 mL, 3:2, v/v) was kept at room temperature for 12 h. The reaction mixture was evaporated to dryness and co-evaporated with toluene (3 × 5 mL). A solution of the crude product in 0.1 M $CH_3ONa$ in $CH_3OH$ (5 mL) was allowed to stir at room temperature for 12 h and was neutralized with Dowex-50W X8 ($H^+$). The reaction mixture was filtered and evaporated to dryness to give pure compound **1** (130 mg, 82%) as a white powder; $[\alpha]_D^{25} = +91$ (*c* 1.0, $H_2O$); IR (KBr): 3020, 2362, 1653, 1367, 1216, 763, 669 $cm^{-1}$; $^1H$ NMR ($D_2O$, 300 MHz): δ 7.01 (d, *J* = 9.2 Hz, 2H, Ar-H), 6.88 (d, *J* = 9.2 Hz, 2H, Ar-H), 5.48 (d, *J* = 3.4 Hz, 1H, H-$1_A$), 5.12 (d, *J* = 5.7 Hz, 1H, H-$1_B$), 5.03 (br s, 1H, H-$2_B$), 4.54 (d, *J* = 7.7 Hz, 1H, H-$1_C$), 4.37 (dd, *J* = 11.0, 3.4 Hz, 1H, H-$2_A$), 4.30 (d, *J* = 2.8 Hz, 1H, H-$4_A$), 4.22–4.12 (m, 2H, H-$3_A$ and H-$6_{aB}$), 4.11–4.00 (m, 2H, H-$5_A$ and H-$4_C$), 3.95 (br s, 1H, H-$4_B$), 3.73 (s, 3H, $OCH_3$), 3.88–3.64 (m, 5H, H-$6_{abA}$, H-$6_{bB}$ and H-$6_{abC}$), 3.47–3.21 (m, 5H, H-$3_B$, H-$5_B$, H-$2_C$, H-$3_C$ and H-$5_C$), 1.98 (s, 6H, 2NHCOC$H_3$); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 173.9 (2C, 2NHC$OCH_3$), 155.9 (Ar-C),

151.8 (Ar-C), 119.9 (2C, Ar-C), 116.0 (2C, Ar-C), 103.4 (C-$1_C$), 98.9 (C-$1_A$), 96.6 (C-$1_B$), 78.6 (C-$5_A$), 77.1 (C-$4_B$), 76.9 (C-$5_C$), 74.4 (C-$5_B$), 71.0 (C-$2_C$), 70.1 (C-$3_C$), 68.4 (C-$4_C$), 68.3 (C-$4_A$), 66.6 (C-$3_A$), 64.6 (C-$3_B$), 63.7 (C-$6_B$), 62.3 (C-$6_C$), 62.0 (C-$6_A$), 56.7 ($OCH_3$), 50.4 (C-$2_A$), 46.2 (C-$2_B$), 23.4 (2C, $2NHCOCH_3$); ESI-MS: *m/z* 715.3 $[M+Na]^+$; Anal. Calcd for $C_{29}H_{44}N_2O_{17}$ (692.3): C, 50.29; H, 6.40. Found: C, 50.10; H, 6.65.

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