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Efficient Synthesis of the Pentasaccharide Repeating Unit of the *O*-Antigenic Polysaccharide of *Escherichia coli* O166 Strain

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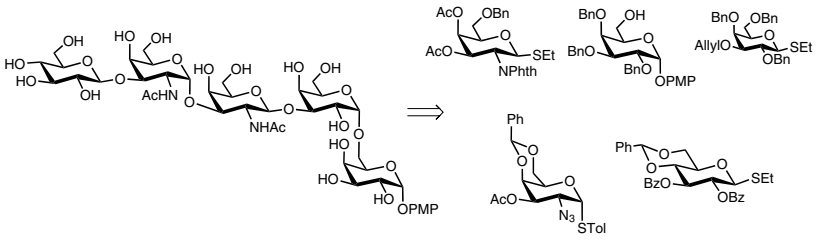


Received: 20.06.2014
Accepted after revision: 06.10.2014
Published online: 10.11.2014
DOI: 10.1055/s-0034-1378911; Art ID: ss-2014-n0384-op

Abstract An efficient strategy has been developed for the synthesis of the pentasaccharide repeating unit of the cell-wall polysaccharide of *Escherichia coli* O166 strain through sequential stereoselective glycosylations of monosaccharide intermediates. All the glycosylation steps were high-yielding with high stereoselectivities.

Key words carbohydrates, glycosylations, glycosides, stereoselectivity, oligosaccharides

Diarrheal outbreaks and gastrointestinal complications are important health problems in developing countries.[1] In general, intake of contaminated food and water and a lack of adequate sanitation are the leading causes of enteric disorders.[2] Recently, gastrointestinal infections have also become significant health hazards in developed countries.[3] Among the several enteropathogenic microbes that are responsible for the diarrheal infections, pathogenic strains of *Escherichia coli* merit particular attention. These are associated with several gastrointestinal infections, particularly 'travelers' diarrhea' and they can be classified into several pathotypes, such as enteropathogenic, enterohemorrhagic, enterotoxigenic, enteroinvasive, enteroaggregative, or diffusely adherent.[4] The O166 strain of *E. coli* is generally classed as belonging to the enteroaggregative pathotype and causes diarrhea in human by producing a heat-stable enterotoxin.[5] *E. coli* O166 has also been isolated from the environment and from cattle, and has also been classified as an enterohemorrhagic strain.[6] In 1996, *E. coli* O166 was identified as the cause of an outbreak of diarrhea in Japan.[7]

Cell-wall polysaccharides of virulent strains of bacteria play crucial roles in the initial stages of bacterial infections in hosts. As result, researchers have focused attention on the characterization of cell-wall *O*-antigenic polysaccharides from several bacterial strains. Recently, the structure of the pentasaccharide repeating unit of the *O*-antigenic polysaccharide of *E. coli* O166 was reported by Ali et al.[8] This pentasaccharide contains D-glucose, D-galactose, and *N*-acetyl-D-galactosamine moieties. As the result of the acceleration in the failure of antibiotics to act on multidrug-resistant strains of bacteria, the development of alternative approaches to the control of bacterial infections is currently a major area in drug-discovery research.[9] It is therefore relevant to develop therapeutics based on glycoconjugate derivatives related to cell-wall polysaccharide *O*-antigens, because of their involvement in the process of bacterial infection. Sufficient quantities of oligosaccharides free of biological impurities are required for biological studies, and these cannot readily be isolated from natural sources. Therefore, the development of efficient strategies for chemical synthesis of these oligosaccharides would be extremely useful in providing access to significant quantities of pure oligosaccharides with appropriate structures. In this context, an efficient synthesis of the pentasaccharide repeating unit of the *O*-antigenic polysaccharide of *E. coli* O166 has been developed.

The target pentasaccharide **1** was synthesized as its 4-methoxyphenyl glycoside by a series of stereoselective sequential glycosylation reactions of suitably functionalized monosaccharide intermediates. For this purpose, the monosaccharide intermediates **2**, **3**,[10] **4**,[11] **5**,[12] and **6**[13] were prepared by following the methods previously reported (Figure 1).

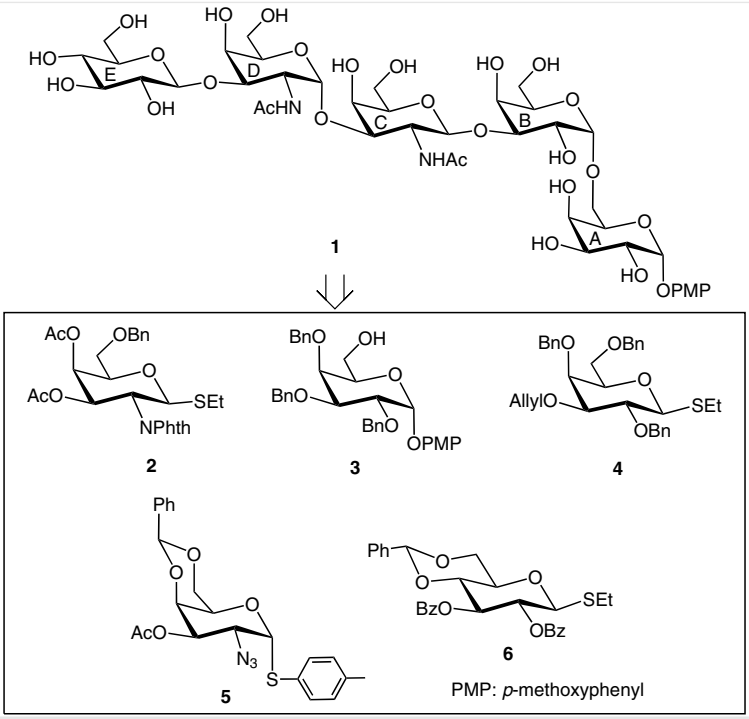
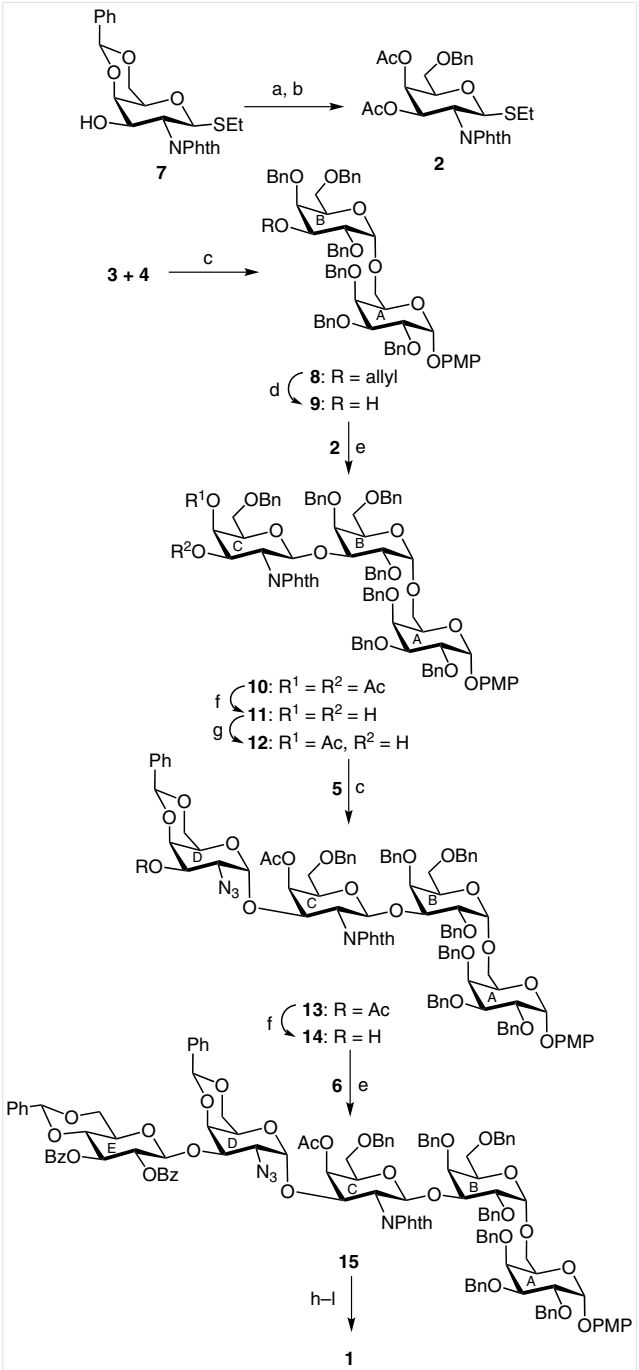


Figure 1 Structures of the synthesized pentasaccharide repeating unit of the *O*-antigenic polysaccharide of *E. coli* O166 (**1**) and various monosaccharide intermediates (**2**–**6**)

Treatment of the known ethyl 4,6-*O*-benzylidene-2-deoxy-2-(*N*-phthalimido)-1-thio-β-D-galactopyranoside (**7**)[14] with triethylsilane in the presence of molecular iodine,[15] followed by acetylation with acetic anhydride and pyridine[16] gave ethyl 3,4-di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(*N*-phthalimido)-1-thio-β-D-galactopyranoside (**2**) in 75% overall yield (Scheme 1).

Stereoselective 1,2-*cis* glycosylation of the D-galactosyl donor **3**[10] with the D-galactosyl acceptor **4**[11] in the presence of *N*-iodosuccinimide and trimethylsilyl trifluoromethanesulfonate[17,18] in dichloromethane–diethyl ether gave the disaccharide derivative **8** in 72% yield, together with a minor quantity (~8%) of another isomer. Disaccharide **8** was purified by column chromatography and its stereoselective formation was confirmed by spectroscopic analysis. Removal of the allyl ether group from disaccharide **8** by using palladium(II) chloride[19] gave the partially deprotected disaccharide **9** in 75% yield. Stereoselective 1,2-*trans* glycosylation of disaccharide **9** with the D-galactosamine donor **2** in the presence of *N*-iodosuccinimide and trimethylsilyl trifluoromethanesulfonate[17,18] gave the trisaccharide derivative **10** in 74% yield. The exclusive formation of compound **10** was confirmed by NMR spectroscopy. De-O-acetylation of compound **10** with sodium methoxide[20] gave the trisaccharide diol derivative **11**, which was selectively 4-O-acetylated through the formation of an ortho ester[21] and subsequent acidic hydrolysis to give trisaccharides **12** in 86% overall yield. Stereoselective 1,2-*cis* glycosylation of trisaccharide **12** with the D-galactosamine derivative **5**[12] as a glycosyl donor in the presence of *N*-iodosuccinimide and trimethylsilyl trifluoromethanesulfonate[17,18] in dichloromethane–diethyl ether gave the tetrasaccharide derivative **13** in 68% yield, together with a minor quantity of the *trans*-glycosylation product (~10%), which was separated by column chromatography. Stereoselective formation of the tetrasaccharide derivative **13** was confirmed by spectroscopic analysis. Selective removal[22] of the 3-*O*-acetyl group from compound **13** by using sodium methoxide left the internally located 4-*O*-acetyl group unaffected and gave the tetrasaccharide acceptor **14** in 95% yield. *N*-Iodosuccinimide–trimethylsilyl trifluoromethanesulfonate-mediated 1,2-*trans*-glycosylation of tetrasaccharide **14** with the D-glucose thioglycoside derivative **6**[13] in dichloromethane gave the pentasaccharide derivative **15** in 72% yield. NMR spectroscopic analysis of compound **15** confirmed that it was formed exclusively. Finally, pentasaccharide **15** was subjected to a series of reactions to remove the protecting groups completely. These reactions included (a) removal of the *N*-phthaloyl group by treatment with hydrazine monohydrate,[23] followed by acetylation of the resulting amine using acetic anhydride and pyridine; (b) removal of the benzyl ethers and benzylidene acetals and reduction of the azido group by hydrogenolysis over palladium(II) hydroxide/carbon,[24] followed by *N*-acetylation with acetic anhydride in methanol; and (c) removal of the acetyl and benzoyl groups by treatment with sodium methoxide to give the target penta-



Scheme 1 *Reagents and conditions*: (a) Et_3SiH, MeCN, I_2, 0–5 °C; (b) Ac_2O, py, r.t., 2 h, 75% (two steps); (c) NIS, TMSOTf, CH_2Cl_2–Et_2O (1:3), 0 °C, MS-4Å, 45 min, 72% for compound **8**, 68% for compound **13**; (d) $PdCl_2$, MeOH, r.t., 3 h, 75%; (e) NIS, TMSOTf, CH_2Cl_2, MS-4Å, –20 °C, 30 min, 74% for compound **10**, 72% for compound **15**; (f) 0.1 M NaOMe, MeOH, r.t., 1.5 h, quant for compound **11**, 95% for compound **14**; (g) $(EtO)_3CMe$, TsOH, DMF, r.t., 2 h then H_2O, r.t., 30 min, 86%; (h) $NH_2NH_2{\cdot}H_2O$, EtOH, 80 °C, 10 h; (i) Ac_2O, py, r.t., 1 h; (j) H_2, 20% $Pd(OH)_2/C$, MeOH, r.t., 15 h; (k) Ac_2O, MeOH, r.t., 1 h; (l) 0.1 M NaOMe, MeOH, r.t., 1.5 h, 54% (overall).

saccharide **1** in 54% overall yield. The formation of compound **1** was unambiguously confirmed by spectroscopic analysis.

In summary, a straightforward strategy has been developed for the synthesis of the pentasaccharide repeating unit of the *O*-antigen of *Escherichia coli* O166 by a series of sequential stereoselective glycosylations of monosaccharide intermediates. The glycosylation steps were high-yielding and gave an excellent stereochemical outcome. Similar reaction conditions were used in each of the glycosylation reactions.

All reactions were monitored by TLC on silica gel coated plates. TLC spots were visualized by spraying the plates with ceric sulfate [2% $Ce(SO_4)_2$ in 2 N H_2SO_4] and warming the sprayed TLC plates on a hotplate. Silica gel (230–400 mesh) was used for column chromatography. NMR spectra were recorded on Bruker Avance 500 MHz spectrometer with $CDCl_3$ as solvent and TMS as the internal reference, unless stated otherwise. Chemical shifts (δ =) are expressed in ppm. Complete assignment of the ^1H and ^{13}C NMR spectra was carried out by means of a standard set of NMR experiments, e.g. ^1H NMR, ^{13}C NMR, ^{13}C DEPT 135, 2D COSY, and 2D HSQC. MALDI mass spectra were recorded on a Bruker mass spectrometer. Optical rotations were recorded in a JASCO P-2000 polarimeter. Commercially available grades of organic solvents of adequate purity were used in all reactions.

Ethyl 3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(*N*-phthalimido)-1-thio-β-D-galactopyranoside (2)

Et_3SiH (1.8 mL, 11.27 mmol) and I_2 (250 mg, 0.98 mmol) were added sequentially to a solution of monosaccharide derivative **7** (2 g, 4.53 mmol) in MeCN (10 mL) at 0–5 °C, and the mixture was stirred at 0–5 °C for 40 min. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed successively with 5% aq $Na_2S_2O_3$ (50 mL) and H_2O (100 mL), then dried (Na_2SO_4) and concentrated. A solution of the crude product in Ac_2O (5 mL) and pyridine (5 mL) was kept at r.t. for 2 h. The reagents were removed under reduced pressure and the crude product was purified by chromatography [silica gel, hexane–EtOAc (3:1)] to give a yellow oil; yield: 1.8 g (75%); $[\alpha]_D^{23}$ +43 (*c* 1.0, $CHCl_3$).

IR (neat): 3024, 1736, 1515, 1372, 1216, 1096, 766 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.83–7.21 (m, 9 H, Ar-H), 5.79 (dd, *J* =11.0, 3.0 Hz, 1 H, H-3), 5.55 (d, *J* =2.0 Hz, 1 H, H-4), 5.44 (d, *J* = 10.5 Hz, 1 H, H-1), 4.57 (d, *J*= 12.0 Hz, 1 H, $PhCH_2$), 4.53 (t, *J*= 10.5 Hz, 1 H, H-2), 4.43 (d, *J*= 12.0 Hz, 1 H, $PhCH_2$), 4.07–4.04 (m, 1 H, H-5), 3.59–3.56 (m, 1 H, H-6_a), 3.50–3.46 (m, 1 H, H-6_b), 2.71–2.63 (m, 2 H, SCH_2CH_3), 2.08–1.82 (2 s, 6 H, 2 $COCH_3$), 1.26 (t, *J* = 7.4 Hz, 3 H, SCH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 169.5 (2 $COCH_3$), 167.8, 167.3 (Phth*C*O), 137.6–123.6 (m, Ar-C), 81.5 (C-1), 75.9 (C-3), 73.5 ($PhCH_2$), 69.0 (C-4), 67.6 (C-6), 67.4 (C-5), 50.3 (C-2), 24.4 (SCH_2CH_3), 20.7, 20.5 (2 $COCH_3$), 14.9 (SCH_2CH_3).

ESI-MS: 550.1 $[M + Na]^+$.

Anal. Calcd for $C_{27}H_{29}NO_8S$ (527.16): C, 61.47; H, 5.54. Found: C, 61.30; H, 5.70.

4-Methoxyphenyl (3-*O*-Allyl-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (8)

MS-4Å (3 g) were added to a solution of compound **3** (1.5 g, 2.69 mmol) and compound **4** (1.6 g, 3.0 mmol) in anhyd 1:3 CH_2Cl_2–Et_2O (20 mL), and the mixture was cooled to 0 °C under argon. The cooled mixture was treated with NIS (0.7 g, 3.11 mmol) and TMSOTf (15 μL) then stirred at 0 °C for 45 min. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed successively with 5% aq $Na_2S_2O_3$ (50 mL), sat. aq $NaHCO_3$ (100 mL), and H_2O (100 mL). The organic phase was then dried (Na_2SO_4) and concentrated under reduced pressure to give a crude product that was purified by chromatography [silica gel, hexane–EtOAc (4:1)] to give a colorless oil; yield: 2 g (72%); $[\alpha]_D^{23}$ +60 (*c* 1.0, $CHCl_3$).

IR (neat): 3025, 2363, 1719, 1509, 1387, 1216, 1097, 758 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.20 (m, 30 H, Ar-H), 6.98 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.74 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.96–5.86 (m, 1 H, C*H*=CH$_2$), 5.37 (d, *J* = 2.5 Hz, 1 H, H-1$_A$), 5.32–5.28 (m, 1 H, CH=C*H*$_2$), 5.15–5.13 (m, 1 H, CH=C*H*$_2$), 4.95–4.67 (7 d, *J* = 11.0 Hz each, 7 H, PhC*H*$_2$), 4.65 (d, *J* = 3.5 Hz, 1 H, H-1$_B$), 4.58–4.34 (5 d, *J* =11.0 Hz each, 5 H, PhC*H*$_2$), 4.14–4.11 (m, 5 H, H-2$_A$, H-5$_A$, H-5$_B$, OC*H*$_2$=CH), 3.94 (br s, 1 H, H-4$_A$), 3.90–3.88 (m, 2 H, H-2$_B$, H-3$_A$), 3.85 (br s, 1 H, H-4$_B$), 3.71–3.65 (m, 1 H, H-6$_{aA}$), 3.67 (s, 2 H, OC*H*$_3$), 3.58–3.53 (m, 2 H, H-3$_B$, H-6$_{aB}$), 3.49–3.46 (dd, *J* = 12.0, 5.5 Hz, 1 H, H-6$_{bB}$), 3.41–3.39 (dd, *J* = 12.0, 4.5 Hz, 1 H, H-6$_{bA}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8–114.4 (m, Ar-C, *C*H$_2$=*C*H), 98.0 (C-1$_B$), 96.9 (C-1$_A$), 78.9 (C-5$_A$), 78.7 (C-5$_B$), 76.4 (C-3$_B$), 76.1 (C-3$_A$), 75.4 (C-4$_B$), 74.7 (2 C, 2 PhCH$_2$), 74.6 (C-4$_A$), 73.6 (PhCH$_2$), 73.4 (PhCH$_2$), 73.3 (2 C, 2 PhCH$_2$), 71.4 (OCH$_2$), 70.3 (C-2$_A$), 69.1 (C-2$_B$), 68.6 (C-6$_B$), 67.4 (C-6$_A$), 55.3 (OCH$_3$).

MALDI-MS: 1051.4 $[M + Na]^+$.

Anal. Calcd for $C_{64}H_{68}O_{12}$ (1028.47): C, 74.69; H, 6.66. Found: C, 74.54; H, 6.80.

4-Methoxyphenyl (2,4,6-Tri-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (9)

$PdCl_2$ (125 mg, 0.70 mmol) was added to a solution of compound **8** (1.8 g, 1.75 mmol) in anhyd MeOH (25 mL), and the mixture was stirred at r.t. for 3 h. The mixture was then concentrated under reduced pressure and purified by chromatography [silica gel, hexane–EtOAc (4:1)] to give a colorless oil; yield: 1.3 g (75%); $[\alpha]_D^{23}$ +95 (*c* 1.0, $CHCl_3$).

IR (neat): 3020, 2362, 1722, 1599, 1513, 1426, 1217, 1046, 927, 761 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 30 H, Ar-H), 6.97 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.72 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.33 (d, *J* = 2.5 Hz, 1 H, H-1$_A$), 4.96–4.70 (6 d, *J* = 11.0 Hz each, 6 H, PhC*H*$_2$), 4.67 (d, *J* = 2.5 Hz, 1 H, H-1$_B$), 4.60–4.34 (6 d, *J* = 11.0 Hz each, 6 H, PhC*H*$_2$), 4.13–4.10 (m, 3 H, H-2$_A$, H-5$_A$, H-5$_B$), 3.92 (br s, 1 H, H-4$_A$), 3.89–3.83 (m, 2 H, H-2$_B$, H-3$_A$), 3.79 (br s, 1 H, H-4$_B$), 3.70 (s, 3 H, OC*H*$_3$), 3.68–3.66 (m, 2 H, H-3$_B$, H-6$_{aA}$), 3.52–3.48 (m, 2 H, H-6$_{abB}$), 3.35–3.32 (m, 1 H, H-6$_{bA}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1–114.4 (m, Ar-C), 97.5 (C-1$_B$), 97.1 (C-1$_A$), 78.9 (C-5$_A$), 77.3 (C-5$_B$), 76.7 (C-4$_B$), 76.4 (C-3$_A$), 75.4 (C-4$_A$), 75.1 (PhCH$_2$), 74.6 (PhCH$_2$), 73.4 (2 C, 2 PhCH$_2$), 73.3 (PhCH$_2$), 72.7 (PhCH$_2$), 70.2 (C-3$_B$), 69.9 (C-2$_A$), 68.9 (C-2$_B$), 68.6 (C-6$_B$), 67.3 (C-6$_A$), 55.4 (OCH$_3$).

MALDI-MS: 1011.4 $[M + Na]^+$.

Anal. Calcd for $C_{61}H_{64}O_{12}$ (988.44): C, 74.07; H, 6.52. Found: C, 73.87; H, 6.70.

4-Methoxyphenyl [3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(*N*-phthalimido)-β-D-galactopyranosyl]-(1→3)-(2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (10)

MS-4Å (1 g) were added to a solution of compound **9** (1.2 g, 1.21 mmol) and compound **2** (960 mg, 1.82 mmol) in anhyd CH_2Cl_2 (10 mL), and the mixture was cooled to –20 °C under argon. NIS (560 mg, 2.49 mmol) and TMSOTf (10 μL) were added, and the cooled mixture was stirred at –20 °C for 30 min. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed successively with 5% aq $Na_2S_2O_3$ (50 mL), sat. aq $NaHCO_3$ (100 mL), and H_2O (100 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude product that was purified by chromatography [silica gel, hexane–EtOAc (4:1)] to give white solid; yield: 1.3 g (74%); mp 74–75 °C (EtOH); $[\alpha]_D^{23}$ +33 (*c* 1.0, $CHCl_3$).

IR (KBr): 3020, 2362, 1719, 1610, 1511, 1216, 1098, 1400, 761 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.48–6.77 (m, 43 H, Ar-H), 5.87 (dd, *J* = 11.0, 3.5 Hz, 1 H, H-3$_C$), 5.58 (d, *J* = 3.0 Hz, 1 H, H-4$_C$), 5.55 (d, *J*= 8.0 Hz, 1 H, H-1$_C$), 5.28 (d, *J* = 2.5 Hz, 1 H, H-1$_A$), 4.95–4.58 (7d, *J* = 11.5 Hz each, 7 H, PhC*H*$_2$), 4.56 (t, *J* = 8.5 Hz each, 1 H, H-2$_C$), 4.51 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.38–4.35 (m, 3 H, PhC*H*$_2$), 4.33 (br s, 1 H, H-1$_B$), 4.26–4.16 (m, 3 H, PhC*H*$_2$), 4.09–3.99 (m, 4 H, H-2$_A$, H-3$_B$, H-5$_A$, H-5$_B$), 3.98–3.92 (m, 2 H, H-3$_A$, H-4$_A$), 3.87–3.82 (m, 2 H, H-4$_B$, H-5$_C$), 3.75 (s, 3 H, OC*H*$_3$), 3.65 (dd, *J* = 10.0, 3.5 Hz, 1 H, H-2$_B$), 3.56–3.51 (m, 3 H, H-6$_{aA}$, H-6$_{abc}$), 3.42–3.28 (m, 2 H, H-6$_{abB}$), 3.24 (dd, *J* = 12.0, 5.5 Hz, 1 H, H-6$_{bA}$), 2.02, 1.84 (2 s, 6 H, 2 COC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 169.4 (2 *C*OCH$_3$), 167.7, 167.4 (PhthCO), 155.0–114.4 (m, Ar-C), 99.7 (C-1$_C$), 97.7 (C-1$_A$), 97.6 (C-1$_B$), 78.8 (2 C, C-5$_A$, C-5$_B$), 76.7 (C-3$_A$), 76.3 (C-2$_B$), 75.5 (C-3$_B$), 75.2 (C-2$_A$), 74.5 (PhCH$_2$), 74.4 (PhCH$_2$), 73.4 (PhCH$_2$), 73.3 (PhCH$_2$), 73.2 (PhCH$_2$), 73.1 (PhCH$_2$), 72.6 (PhCH$_2$), 71.6 (C-4$_B$), 69.9 (C-5$_C$), 69.0 (2 C, C-4$_A$, C-6$_B$), 67.9 (C-3$_C$), 67.4 (C-4$_C$), 67.2 (C-6$_A$), 67.1 (C-6$_C$), 55.5 (OCH$_3$), 51.9 (C-2$_C$), 20.6, 20.5 (2 COCH$_3$).

MALDI-MS: 1476.5 $[M + Na]^+$.

Anal. Calcd for $C_{86}H_{87}NO_{20}$ (1453.58): C, 71.01; H, 6.03. Found: C, 70.84; H, 5.85.

4-Methoxyphenyl [4-*O*-Acetyl-6-*O*-benzyl-2-deoxy-2-(*N*-phthalimido)-β-D-galactopyranosyl]-(1→3)-(2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (12)

A solution of compound **10** (1.2 g, 0.82 mmol) in 0.1 M methanolic NaOMe (20 mL) was stirred at r.t. for 1.5 h, then neutralized with Dowex 50W X8 (H^+) resin, filtered, and concentrated under reduced pressure. A solution of the crude product **11**in DMF (5 mL) was treated with MeC(OEt)$_3$ (0.6 mL, 3.27 mmol) and TsOH (100 mg) and then stirred at r.t. for 2 h. H_2O (2 mL) was added and the mixture was stirred at r.t. for a further 30 min. The mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was washed successively with sat. aq $NaHCO_3$ (100 mL) and H_2O (100 mL), then dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography [silica gel, hexane–EtOAc (4:1)] to give a colorless oil; yield: 1 g (86%, two steps); $[\alpha]_D^{23}$ +35 (*c* 1.0, $CHCl_3$).

IR (neat): 2929, 2365, 1719, 1629, 1386, 1227, 1099, 768 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46–6.75 (m, 43 H, Ar-H), 5.48 (d, *J* = 8.5 Hz, 1 H, H-1$_C$), 5.44 (d, *J* = 3.0 Hz, 1 H, H-4$_C$), 5.27 (d, *J* = 2.0 Hz, 1 H, H-1$_A$), 4.93–4.49 (10 d, *J* = 11.5 Hz each, 10 H, PhC*H*$_2$), 4.41 (d, *J* = 2.5 Hz, 1 H, H-1$_B$), 4.36–4.32 (m, 4 H, H-2$_C$, PhC*H*$_2$), 4.22 (d, *J*= 11.5 Hz, 1 H, PhC*H*$_2$), 4.09–4.01 (m, 4 H, H-2$_A$, H-3$_B$, H-5$_A$, H-5$_B$), 3.98 (dd, *J* = 10.5, 3.0 Hz, 1 H, H-3$_C$), 3.96–3.87 (m, 3 H, H-3$_A$, H-4$_A$, H-4$_B$), 3.82–

3.80 (m, 1 H, H-5_C), 3.72 (s, 3 H, OCH_3), 3.67 (dd, *J* = 10.5, 3.0 Hz, 1 H, H-2_B), 3.58–3.51 (m, 3 H, H-6_{abc}, H-6_{aA}), 3.42–3.35 (m, 1 H, H-6_{aB}), 3.34–3.26 (m, 2 H, H-6_{bA}, H-6_{bB}), 2.05 (s, 3 H, COCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5 (*C*OCH$_3$), 167.7, 167.4 (PhthCO), 155.0–114.4 (m, Ar-C), 99.9 (C-1_C), 97.8 (C-1_B), 97.7 (C-1_A), 78.8 (C-5_A), 78.7 (C-5_B), 76.7 (C-3_A), 76.3 (C-2_B), 75.6 (C-3_B), 75.2 (C-2_A), 74.6 (PhCH$_2$), 74.4 (PhCH$_2$), 73.5 (PhCH$_2$), 73.3 (PhCH$_2$), 73.2 (PhCH$_2$), 73.1 (PhCH$_2$), 72.8 (PhCH$_2$), 71.8 (C-4_B), 70.2 (C-4_A), 69.9 (C-3_C), 69.1 (C-4_C), 69.0 (C-6_B), 67.8 (C-6_A), 67.2 (C-5_C), 67.1 (C-6_C), 55.5 (OCH$_3$), 54.8 (C-2_C), 20.8 (COCH$_3$).

MALDI-MS: 1434.5 [M + Na]$^+$.

Anal. Calcd for $C_{84}H_{85}NO_{19}$ (1411.57): C, 71.42; H, 6.07. Found: C, 71.25; H, 6.27.

4-Methoxyphenyl (3-*O*-Acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl)-(1→3)-[4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(*N*-phthalimido)-β-D-galactopyranosyl]-(1→3)-(2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (13)

MS-4Å (2 g) were added to a solution of compound **12** (900 mg, 0.64 mmol) and compound **5** (700 mg, 1.58 mmol) in anhyd 1:3 CH_2Cl_2–Et_2O (15 mL), and reaction mixture was cooled to 0 °C under argon. The cooled mixture was treated with NIS (360 g, 1.6 mmol) and TMSOTf (5 μL) then stirred at 0 °C for 45 min. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed successively with 5% aq $Na_2S_2O_3$ (50 mL), sat. aq $NaHCO_3$ (100 mL), and H_2O (100 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by chromatography [silica gel, hexane–EtOAc (4:1)] to a white solid; yield: 750 mg (68%); mp 93–94 °C (EtOH); $[\alpha]_D^{23}$ +101 (*c* 1.0, $CHCl_3$).

IR (KBr): 2937, 1749, 1510, 1371, 1229, 1088, 1050, 827, 759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–6.76 (m, 48 H, Ar-H), 5.66 (d, *J* = 3.0 Hz, 1 H, H-4_C), 5.49 (d, *J* = 8.0 Hz, 1 H, H-1_C), 5.28 (d, *J* = 2.0 Hz, 1 H, H-1_A), 5.23 (s, 1 H, PhC*H*), 5.11 (d, *J* = 3.5 Hz, 1 H, H-1_D), 4.96 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.86 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.82 (dd, *J* = 10.0, 3.0 Hz, 1 H, H-3_D), 4.81–4.70 (m, 4 H, PhC*H*$_2$), 4.69–4.58 (m, 3 H, H-2_C, PhC*H*$_2$), 4.48 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.41 (d, *J* = 3.0 Hz, 1 H, H-1_B), 4.40–4.23 (5 d, *J* = 11.5 Hz each, 5 H, PhC*H*$_2$), 4.09–4.04 (m, 5 H, H-2_A, H-3_B, H-4_D, H-5_A, H-5_B), 3.99–3.90 (m, 4 H, H-2_D, H-3_A, H-3_C, H-4_A), 3.87 (br s, 1 H, H-4_B), 3.82–3.80 (m, 1 H, H-5_C), 3.73 (s, 3 H, OCH_3), 3.70 (dd, *J* = 10.0, 3.0 Hz, 1 H, H-2_B), 3.60–3.50 (m, 4 H, H-6_{abc}, H-6_{abD}), 3.47–3.37 (m, 2 H, H-6_{aA}, H-6_{aB}), 3.18–3.17 (m, 1 H, H-5_D), 2.11, 2.06 (2 s, 6 H, 2 COCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 169.9 (2 *C*OCH$_3$), 167.7, 167.4 (PhthCO), 155.0–114.5 (m, Ar-C), 100.6 (PhCH), 99.8 (C-1_C), 97.8 (2 C, C-1_A, C-1_B), 97.0 (C-1_D), 78.8 (2 C, C-5_A, C-5_B), 76.4 (C-3_A), 76.3 (C-2_B), 75.5 (C-2_A), 75.2 (C-3_B), 74.5 (2 C, 2 PhCH$_2$), 73.6 (PhCH$_2$), 73.5 (PhCH$_2$), 73.3 (2 C, PhCH$_2$), 73.1 (C-4_A), 73.0 (C-4_D), 72.9 (PhCH$_2$), 72.6 (C-4_B), 69.8 (C-3_D), 69.7 (C-3_C), 69.2 (C-4_C), 69.1 (C-6_D), 68.3 (2 C, C-6_A, C-6_B), 67.0 (C-6_C), 66.4 (C-5_C), 62.9 (C-5_D), 57.2 (C-2_D), 55.5 (OCH$_3$), 53.4 (C-2_C), 20.9, 20.7 (2 COCH$_3$).

MALDI-MS: 1751.6 [M + Na]$^+$.

Anal. Calcd for $C_{99}H_{100}N_4O_{24}$ (1728.67): C, 68.74; H, 5.83. Found: C, 68.60; H, 6.00.

4-Methoxyphenyl (2-Azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl)-(1→3)-[4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(*N*-phthalimido)-β-D-galactopyranosyl]-(1→3)-(2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (14)

A solution of compound **10** (700 mg, 0.40 mmol) in 0.1 M methanolic NaOMe (20 mL) was stirred at r.t. for 1.5 h. The mixture was then neutralized with Dowex 50W X8 (H^+), filtered, and concentrated under reduced pressure. The crude product was passed through a short pad of silica gel with elution by hexane–EtOAc (2:1) to give a white solid; yield: 650 mg (95%); mp 95–96 °C (EtOH); $[\alpha]_D^{23}$ +61 (*c* 1.0, $CHCl_3$).

IR (KBr): 2927, 1746, 1508, 1456, 1369, 1233, 1109, 1055, 987, 826, 739 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–6.76 (m, 48 H, Ar-H), 5.66 (d, *J* = 3.0 Hz, 1 H, H-4_C), 5.47 (d, *J* = 8.5 Hz, 1 H, H-1_C), 5.27 (s, 1 H, PhC*H*), 5.26 (d, *J* = 2.5 Hz, 1 H, H-1_A), 5.09 (d, *J* = 3.0 Hz, 1 H, H-1_D), 4.95–4.69 (6 d, *J* = 11.5 Hz each, 6 H, PhC*H*$_2$), 4.65–4.58 (m, 4 H, H-2_C, PhC*H*$_2$), 4.45 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.40 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.38 (d, *J* = 3.0 Hz, 1 H, H-1_B), 4.35–4.22 (3 d, *J* = 11.5 Hz each, 3 H, PhC*H*$_2$), 4.07–4.00 (m, 4 H, H-2_A, H-3_B, H-5_A, H-5_B), 3.99–3.95 (m, 2 H, H-3_C, H-4_D), 3.92–3.84 (m, 2 H, H-3_A, H-3_D), 3.82–3.75 (m, 3 H, H-4_A, H-4_B, H-5_C), 3.73 (s, 3 H, OCH_3), 3.66 (d, *J* = 10.0, 3.0 Hz, 1 H, H-2_B), 3.62–3.60 (m, 1 H, H-6_{aD}), 3.58–3.48 (m, 4 H, H-2_D, H-6_{abc}, H-6_{bD}), 3.43–3.35 (m, 2 H, H-6_{aA}, H-6_{aB}), 3.32–3.25 (m, 2 H, H-6_{bA}, H-6_{bB}), 3.12–3.11 (m, 1 H, H-5_D), 2.10 (s, 3 H, COCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2 (*C*OCH$_3$), 167.7, 167.4 (PhthCO), 155.2–114.5 (m, Ar-C), 101.1 (PhCH), 99.8 (C-1_C), 97.7 (2 C, C-1_A, C-1_B), 96.6 (C-1_D), 78.8 (2 C, C-5_A, C-5_B), 76.7 (C-5_C), 76.3 (C-3_A), 75.5 (C-2_B), 75.1 (C-2_A), 74.9 (C-3_B), 74.5 (2 C, 2 PhCH$_2$), 73.6 (PhCH$_2$), 73.3 (PhCH$_2$), 73.1 (2 C, 2 PhCH$_2$), 72.5 (PhCH$_2$), 72.4 (C-4_A), 72.3 (C-4_D), 69.8 (C-4_B), 69.1 (C-3_D), 69.0 (C-6_D), 68.5 (C-6_A), 68.3 (C-6_B), 67.6 (C-3_C), 67.0 (C-6_C), 66.0 (C-4_C), 63.1 (C-5_D), 60.7 (C-2_D), 55.5 (OCH$_3$), 53.3 (C-2_C), 20.7 (COCH$_3$).

MALDI-MS: 1709.6 [M + Na]$^+$.

Anal. Calcd for $C_{97}H_{98}N_4O_{23}$ (1686.66): C, 69.03; H, 5.85. Found: C, 68.84; H, 6.00.

4-Methoxyphenyl (2,3-*O*-Benzoyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-(1→3)-(2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranosyl)-(1→3)-[4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(*N*-phthalimido)-β-D-galactopyranosyl]-(1→3)-(2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (15)

MS-4Å (500 mg) were added to a solution of compound **14** (600 mg, 0.36 mmol) and compound **6** (225 mg, 0.43 mmol) in anhyd CH_2Cl_2 (5 mL), and the mixture was cooled to – 20 °C under argon. NIS (100 mg, 0.44 mmol) and TMSOTf (3 μL) were added and the mixture was stirred at –20 °C for 30 min. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed successively with 5% aq $Na_2S_2O_3$ (25 mL), sat. aq $NaHCO_3$ (50 mL), and H_2O (50 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude product that was purified by chromatography [silica gel, hexane–EtOAc (4:1)] to give a white solid; yield: 550 mg (72%); mp 162–163 °C (EtOH); $[\alpha]_D^{23}$ +72 (*c* 1.0, $CHCl_3$).

IR (KBr): 2932, 1776, 1748, 1720, 1509, 1388, 1229, 1107, 1081, 1052, 1029, 998, 827, 738, 722 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89–6.70 (m, 63 H, Ar-H), 5.64 (t, *J* = 8.5 Hz, 1 H, H-2_E), 5.56 (d, *J* = 3.0 Hz, 1 H, H-4_C), 5.44 (d, *J* = 8.5 Hz, 1 H, H-1_C), 5.40 (t, *J* = 9.0 Hz, 1 H, H-3_E), 5.37 (s, 1 H, PhC*H*), 5.21 (d, *J* = 2.5 Hz, 1 H, H-1_A), 5.19 (s, 1 H, PhC*H*), 4.97 (d, *J* = 3.0 Hz, 1 H, H-1_D), 4.95

(d, J = 8.5 Hz, 1 H, H-1_E), 4.91–4.52 (8 d, J= 11.5 Hz each, 8 H, PhCH_2), 4.51 (t, J = 8.5 Hz, 1 H, H-2_C), 4.41 (d, J=11.5 Hz, 1 H, PhCH_2), 4.34 (d, J=3.0 Hz, 1 H, H-1_B), 4.32–4.27 (m, 4 H, PhCH_2), 4.26–4.21 (m, 1 H, H-6_{aE}), 4.17 (d, J = 11.5 Hz, 1 H, PhCH_2), 4.02–3.96 (m, 5 H, H-2_A, H-3_B, H-5_A, H-5_B, H-5_E), 3.92–3.89 (m, 3 H, H-3_A, H-3_C, H-4_D), 3.85–3.80 (m, 2 H, H-3_D, H-4_A), 3.78–3.62 (m, 6 H, H-2_B, H-2_D, H-4_B, H-4_E, H-5_C, H-6_{bE}), 3.72 (s, 3 H, OCH_3), 3.55–3.46 (m, 4 H, H-6_{aA}, H-6_{abc}, H-6_{aD}), 3.43–3.40 (m, 1 H, H-6_{bD}), 3.38–3.32 (m, 1 H, H-6_{aB}), 3.30–3.20 (m, 2 H, H-6_{bA}, H-6_{bB}), 3.06–3.05 (m, 1 H, H-5_D), 1.95 (s, 3 H, COCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0 (*C*OCH$_3$), 167.7, 167.4 (PhthCO), 165.7, 165.3 (2 PhCO), 155.1–114.5 (m, Ar-C), 102.1 (C-1_E), 101.6 (PhCH), 100.4 (PhCH), 99.7 (C-1_C), 97.7 (C-1_A), 97.6 (C-1_B), 97.2 (C-1_D), 78.8 (2 C, C-5_A, C-5_B), 78.4 (C-5_E), 76.7 (C-5_C), 76.3 (C-3_A), 75.4 (2 C, C-2_A, C-2_B), 75.2 (C-3_B), 74.9 (C-3_E), 74.5 (2 C, 2 PhCH_2), 73.6 (PhCH_2), 73.3 (PhCH_2), 73.1 (2 C, 2 PhCH_2), 72.7 (C-2_E), 72.5 (PhCH_2), 72.3 (2 C, C-4_A, C-4_E), 72.2 (C-4_D), 69.8 (C-4_B), 69.1 (C-3_D), 69.0 (C-6_D), 68.6 (C-6_E), 68.2 (C-6_A), 68.0 (C-6_B), 67.0 (C-6_C), 66.4 (2 C, C-3_C, C-4_C), 63.5 (C-5_D), 59.2 (C-2_D), 55.5 (OCH$_3$), 53.5 (C-2_C), 20.7 (COCH_3).

MALDI-MS: 2167.7 [M + Na]$^+$.

Anal. Calcd for $C_{124}H_{120}N_4O_{30}$ (2144.80): C, 69.39; H, 5.64. Found: C, 69.23; H, 5.85.

4-Methoxyphenyl (β-D-glucopyranosyl)-(1→3)-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-(1→3)-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→3)-(α-D-galactopyranosyl)-(1→6)-α-D-galactopyranoside (1)

$NH_2NH_2{\cdot}H_2O$ (0.3 mL) was added to a solution of compound **15** (500 mg, 0.23 mmol) in EtOH (15 mL), and the mixture was stirred at 80 °C for 10 h. The solvents were removed under reduced pressure, the crude product was dissolved in Ac_2O (2 mL) and pyridine (2 mL), and the solution was kept at r.t. for 1 h. The solvents were removed under reduced pressure to give an acetylated product that was passed through a short pad of silica gel with EtOAc (50 mL) as eluent. A solution of the purified acetylated in MeOH (10 mL) was treated with 20% $Pd(OH)_2$/C (100 mg) under a positive pressure of H_2 with stirring at r.t. for 15 h. The mixture was then filtered through a bed of Celite that was washed MeOH (30 mL), and the filtrate was concentrated to half of its original volume. Ac_2O (1 mL) was added and the mixture was stirred at r.t. for 1 h. The solvents were removed under reduced pressure and a solution of the crude product in 0.1 M methanolic NaOMe (10 mL) was stirred at r.t. for 1.5 h. The mixture was neutralized with Dowex 50W X8 (H^+), filtered, and concentrated to give the crude product that was purified by chromatography [Sephadex LH-20 gel, MeOH–H_2O (3:1)] to give **1** as a white powder; 125 mg (54%); $[\alpha]_D^{23}$ +99 (*c* 1.0, H_2O).

IR (KBr): 3020, 2928, 1744, 1377, 1220, 1069, 764 cm^{-1}.

^{1}H NMR (500 MHz, D_2O): δ = 7.02, 6.86 (2 d, J = 9.0 Hz each, 4 H, Ar-H), 5.45 (d, J = 4.0 Hz, 1 H, H-1_A), 4.95 (d, J = 3.5 Hz, 1 H, H-1_D), 4.70 (d, J = 3.5 Hz, 1 H, H-1_B), 4.51 (d, J = 8.0 Hz, 1 H, H-1_C), 4.37 (d, J = 7.5 Hz, 1 H, H-1_E), 4.28–4.24 (m, 1 H, H-2_D), 4.16–4.09 (m, 2 H, H-3_A, H-4_B), 4.02 (br s, 1 H, H-4_C), 3.98–3.90 (m, 5 H, H-2_A, H-2_C, H-3_C, H-4_A, H-4_D), 3.86–3.81 (m, 1 H, H-3_D), 3.77–3.56 (m, 13 H, H-2_B, H-3_B, H-3_E, H-5_B, H-6_{abA}, H-6_{abB}, H-6_{abC}, H-6_{abD}, H-6_{aE}), 3.68 (s, 3 H, OCH_3), 3.55–3.47 (m, 3 H, H-5_A, H-5_C, H-6_{bE}), 3.35 (t, J = 8.5 Hz, 1 H, H-4_E), 3.31–3.27 (m, 2 H, H-5_D, H-5_E), 3.14 (t, J = 9.0 Hz, 1 H, H-2_E), 1.90, 1.89 (2 s, 6 H, 2 CO-CH_3).

^{13}C NMR (125 MHz, D_2O): δ = 174.8, 174.6 (2 *C*OCH$_3$), 154.7–115.0 (m, Ar-C), 104.3 (C-1_E), 102.6 (C-1_C), 98.2 (2 C, C-1_A, C-1_B), 93.8 (C-1_D), 79.5 (C-5_A), 77.4 (C-5_B), 75.8 (2 C, C-5_C, C-5_E), 75.6 (2 C, C-3_D, C-4_E), 74.7 (2 C, C-3_B, C-3_E), 72.9 (2 C, C-2_E, C-5_D), 71.1 (C-4_D), 70.0 (2 C, C-3_C, C-4_B), 69.0 (C-3_A), 68.6 (C-4_A), 68.0 (C-2_B), 67.5 (C-2_A), 67.1 (C-6_A), 63.5 (C-4_C), 61.0 (C-6_D), 60.7 (2 C, C-6_B, C-6_C), 60.5 (C-6_E), 56.1 (OCH$_3$), 51.0 (C-2_C), 48.1 (C-2_D), 22.5, 22.3 (2 COCH_3).

ESI-MS: 1039.3 [M + Na]$^+$.

Anal. Calcd for $C_{41}H_{64}N_2O_{27}$ (1016.37): C, 48.42; H, 6.34. Found: C, 48.24; H, 6.50.

Acknowledgments

A.S. thanks CSIR, India, for providing a Junior Research Fellowship. This work was supported by CSIR, New Delhi, [Project no. 02(0038)/11/EMR-II] and the Bose Institute, Kolkata.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378911.

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