Synthesis of methyl 3-amino-3,6-dideoxy-\(\alpha\)-D-galactopyranoside carrying different amide substituents†

Hani Mobarak, Olof Engström and Göran Widmalm*

Bacterial polysaccharides may contain rare sugars of different stereochemistry and diverse functional groups; the repertoire can be further extended by varying the exocyclic substituents. Synthesis of four monosaccharides is described utilizing a suitably protected key intermediate obtained by regioselective acetal ring-opening reduction, deoxygenation at C6, alcohol oxidation at C3 followed by formation of an oxime, which was stereoselectively reduced by samarium diiodide to give a 3-amino-derivative having the desired galacto-configuration. Subsequent functionalization was performed resulting in one to four carbon atoms in the amide substituent.

Introduction

Lipopolysaccharides (LPS) cover a large portion of the outer membrane of Gram-negative bacteria where they play important roles in interactions with host cells. The LPS consists of three parts, namely, the lipid A which anchors it in the membrane, a core region which is the outer part in rough bacteria and the O-antigen polysaccharide which contains the outer part in smooth type bacteria. Whereas many of the biological effects are the consequences of the interactions of lipid A with the immune system of the host, the O-antigen plays important roles in colonization of the host and resistance to its immune system.

The lipid A and the core region of different bacteria are relatively conserved within a species and usually only a few variants are observed. The O-antigen polysaccharide, on the other hand, shows large variability both with respect to the polymer synthesized and the sugar components being part of it, where to date several hundred different sugar residues have been identified as constituents. Branched sugars with carbon chains extending from the cyclic ring of the monosaccharide are rare and many sugars are uncommon only being found in nature in a few instances. The monosaccharide \(\nu\)-Fucp3N (3-amino-3,6-dideoxy-\(\alpha\)-galactopyranose) has been found \(\alpha\)-linked as a side-chain to the backbone polymer in the O-antigen polysaccharide of *Providencia alcalifaciens* O21 (ref. 6) in which it was previously shown for an \(\alpha\)-D-mannopyranoside derivative by *Aneurinibacillus thermoacidophilus* L420-91T. In the core part of *Proteus penneri* strain 16 LPS the terminal Fuc3N residue carries an \(R\)-3-hydroxybutyryl group and in the O-antigen from *Pseudoalteromonas nigrifaciens* strain KMM 161 the substituent is a 4-hydroxybutyryl group. In the O-antigens of *Escherichia coli* O74 and *Proteus vulgaris* O45 the \(\nu\)-Fucp3NAc residues are \(\beta\)-linked. Herein, we describe the synthesis of methyl 3-amino-3,6-dideoxy-\(\alpha\)-D-galactopyranoside having the above four amide-linked groups as substituents.

Results and discussion

The synthesis is described from the monobenzylated 4,6-O-benzylidene acetal \(5\) which previously has been reported in the literature. Benzoylation of the hydroxyl group in position 3 gave the fully protected compound \(6\) (Scheme 1). The \(\text{BH}_3\cdot\text{THF}\) complex together with \(\text{CoCl}_2\) (ref. 15) was used to reductively open the benzylidene acetal in a regioselective fashion to obtain the 6-hydroxy derivative \(7\). The use of this reagent was previously shown to result in high selectivity toward producing the 6-hydroxy derivatives in several hexopyranosides and the reaction was also successfully carried out with compound \(5\) or its 3-O-acetyl derivative, but the highest yield (92%) was achieved with the benzoyl derivative \(6\).

The deoxygenative reduction of a 6-hydroxy group was previously shown for an \(\alpha\)-o-mannopyranose derivative by tosylation followed by reduction with sodium borohydride in DMF, but for compound \(7\) the procedure resulted in the bicyclic 3,6-anhydro product. Instead, bromination with \(\text{CBr}_4\) and \(\text{Pb}_3\text{P}^\text{tBu}_1\) to give the 6-bromo derivative \(8\), followed by reduction with tributyltin hydride in the presence of \(\text{AIBN}\) was successfully used to obtain the 6-deoxy sugar \(9\).
Deprotection with sodium methoxide in MeOH furnished compound 10 has been reported using 2-iodoxybenzoic acid (IBX) or pyridinium dichromate. The use of IBX gave the highest yield (92%) and was thus employed to oxidize 10 to the keto derivative 11. This was followed by reaction with hydroxylamine hydrochloride to give the oxime 12.

The key step in the synthesis is the reduction of oxime 12 to the amine derivative 13 having the desired galacto-configuration. Different reducing reagents were reported earlier by Hsu et al. for the corresponding L-enantiomer,21 where, for example, Red-Al® favored the gulo-configuration, but the highest stereoselectivity for the desired product was achieved by using samarium diiodide as a single-electron donor reducing agent (the ratio between galacto- and gulo-configurations being >19 : 1). This reagent was used to reduce oxime 12 to obtain compound 13 in an isolated yield of 54%. It can be noted that for ethyl 2,4-di-O-benzyl-6-deoxy-1-thio-β-D-xylo-hexopyranosid-3-ulose (E)-oxime reduction with Red-Al® worked well and the amino derivative having the galacto-configuration was isolated in 80% yield,28 highlighting the stereochemical effects of the anomeric configuration on the reduction of the oxime at position 3 of these derivatives.

The target compounds were obtained via amide coupling of 13 with activated formic acid and acetic anhydride, respectively, to form compounds 14 and 15, which were deprotected by catalytic hydrogenolysis over Pd/C to give 1 and 2 (Scheme 2). The acids 16 and 19 were prepared according to Torizuka et al.23 and Brewer et al.24 respectively, and were coupled with 13 by using DCC as the coupling reagent to obtain compounds 17 and 18, respectively. The subsequent deprotection of the silyl ethers was performed with tetra-n-butylammonium fluoride (TBAF) in THF to give 18 and 21, respectively. In the last deprotection step catalytic hydrogenolysis over Pd/C afforded compounds 3 and 4.

The monosaccharide 3-amino-3,6-dideoxy-α-L-galactopyranose is an unusual component in O-antigen polysaccharides and together with a specific substituent the structure can form a characteristic antigenic determinant, being different (or the same) for the various serogroups in bacteria of diverse origin. The substituents are readily identified by the different 1H chemical shifts (Fig. 1) where the N-formyl group in 1 shows two resonances at 8.05 and 8.17 ppm (Fig. 1a) due to two conformations in slow exchange at the amide linkage, a phenomenon observed also for other N-formylated sugars.25,26 The 1H resonance of the N-acetyl group in 2 is observed at 2.06 ppm (Fig. 1b). In compound 3 the 1H resonances of the N-3-(R)-hydroxybutyramid group are present at 1.27, 2.51 and 4.25 ppm (Fig. 1c) whereas in compound 4 having an N-4-hydroxybutyramid group they are instead found at 1.86, 2.39 and 3.62 ppm (Fig. 1d), clearly differing between the compounds.

Conclusions
The synthesis has produced four variants with differently attached amide substituents on methyl 3-amino-3,6-dideoxy-α-L-galactopyranoside. The synthesis methodology applied herein will be of use in formation of larger oligosaccharides containing 3-amino-3,6-dideoxy-α-L-galactopyranoside as a component and the 1H and 13C NMR data obtained can be utilized to improve the NMR chemical shift predictions of oligo- and polysaccharides.27,28

Experimental section
General experimental methods
All reagents were used as delivered. Column chromatography was performed manually on silica gel with a pore size of 60 Å or by using a Biotage Isolera flash purification system with KP-Sil snap chromatography cartridges. TLC was carried out on silica gel 60 F254 (20 x 20 cm, 0.2 mm thickness), and monitored with either UV light 254 nm, sulfuric acid 8%, Ce(IV) molybdate or KMnO4. NMR spectra were recorded at 25 °C, except for compounds 1–4 which were recorded at 15 °C, on spectrometers operating at a 1H

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The target compounds were obtained via amide coupling of 13 with activated formic acid and acetic anhydride, respectively, to form compounds 14 and 15, which were deprotected by catalytic hydrogenolysis over Pd/C to give 1 and 2 (Scheme 2). The acids 16 and 19 were prepared according to Torizuka et al.23 and Brewer et al.24 respectively, and were coupled with 13 by using DCC as the coupling reagent to obtain compounds 17 and 18, respectively. The subsequent deprotection of the silyl ethers was performed with tetra-n-butylammonium fluoride (TBAF) in THF to give 18 and 21, respectively. In the last deprotection step catalytic hydrogenolysis over Pd/C afforded compounds 3 and 4.

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frequency of 400 or 500 MHz. The NMR chemical shifts are reported in ppm and for $^1$H referenced to TMS, sodium 3-tri-
methylsilyl-(2,2,3,3-$^2$H$_4$)-propanoate (TSP), both set to 0 ppm, or
the residual CHCl$_3$ solvent peak at 7.26 ppm as an internal
standard; for $^{13}$C the chemical shifts were referenced to 1,4-
dioxane in D$_2$O, 67.40 ppm, using an external standard or
internally to the CDCl$_3$ solvent signal at 77.16 ppm. For
compounds 1–4 $^1$H chemical shifts and $^1$H coupling constants
were re-
defined from 1D $^1$H NMR spectra using NMR spin simula-
tion methodology.

Methyl 3-O-benzoyl-2-O-benzyl-4,6-O-benzylidene-$\alpha$-D-
galactopyranoside (6). Compound 5 (4.01 g, 10.80 mmol) was dis-
solved in pyridine whereafter BzCl (1.38 mL, 11.87 mmol) was
added at 0 °C and the solution was stirred for 40 min. The
pyridine was evaporated under reduced pressure and the crude
material was filtered through a silica gel plug to obtain the
product as a white solid (4.80 g, 10.07 mmol, 93%). $^1$H NMR
(CDCl$_3$): $d$ 3.44 (s, 3 H, OMe), 3.80 (m, 1H, H-5), 4.08 (dd,
$^1$H$_5$-$^1$H$_6a$ 1.70 Hz, $^1$H$_6$-$^1$H$_{gem}$ 12.53, 1H, H-6a), 4.25 (dd, $^1$H$_{11}$-$^1$H$_{12}$ 3.49 Hz, $^1$H$_{12}$-$^1$H$_{13}$
10.49 Hz, 1 H, H-2), 4.27 (dd, $^1$H$_{15}$-$^1$H$_{16a}$ 1.70 Hz, $^1$H$_{16}$-$^1$H$_{gem}$ 12.53 Hz, 1H,
H-6b), 4.58 (dd, $^1$H$_{13}$-$^1$H$_{14}$ 3.57 Hz, $^1$H$_{14}$-$^1$H$_{15}$ 13.2 Hz, 1H, H-4), 4.65 (d,
$^1$H$_{gem}$ 12.22 Hz, 1H, PhCH$_2$), 4.76 (d, $^1$H$_{gem}$ 12.22 Hz, 1H, PhCH$_2$),
4.87 (d, $^1$H$_{11}$-$^1$H$_{12}$ 3.49 Hz, 1H, H-1), 5.51 (s, 1H, PhCH), 5.57 (dd,
$^1$H$_{12}$-$^1$H$_{13}$ 10.49 Hz, $^1$H$_{13}$-$^1$H$_{14}$ 3.57 Hz, 1H, H-3), 7.23–8.07 (m, 15 H, H-
Ar). $^{13}$C NMR (CDCl$_3$): $\delta$ 55.8 (OMe), 62.3 (C-5), 69.4 (C-6), 71.4
(C-3), 73.6 (PhCH$_2$), 73.8 (C-2), 74.5 (C-4), 99.4 (C-1), 100.6
(PhCH$_2$), 126.2–133.2 (16 C-Ar), 137.9, 138.2 (2 $\times$ C-ipso), 166.3
(CO). ESIMS: [M + Na]$^+$ m/z calcd for C$_{28}$H$_{28}$O$_7$Na 499.1727,
found 499.1730.
The solvent was evaporated and the crude mixture was chromatographed over silica gel (toluene–EtOAc 1 : 1) to afford the product as a colorless syrup (3.52 g, 7.35 mmol, 92%). 1H NMR (CDCl3): δ 1.63 (distorted m, 1H, OH), 3.41 (s, 3H, OMe), 3.55 (distorted m, 1H, H-6a), 3.78 (dd, Jgem 11.35 Hz, 1H, H-6b), 3.95 (m, 1H, H-5), 4.14 (dd, Jgem 3.10 Hz, JH1,4.14, 1.43 Hz, 1H, H-4), 4.20 (dd, JH1,14, 3.61 Hz, JH2,14, 10.54 Hz, 1H, H-2), 4.46 (dd, Jgem 11.80 Hz, 1H, PhCH2), 4.66 (dd, Jgem 12.35 Hz, 1H, PhCH2), 4.72 (d, Jgem 11.80 Hz, 1H, PhCH2), 4.82 (dd, JH1,14, 3.61 Hz, 1H, H-1), 5.56 (dd, JH1,14, 10.54 Hz, JH3,14, 3.10 Hz, 1H, H-3), 7.20–8.04 (m, 15H, H-Ar). 13C NMR (CDCl3): δ 55.6 (OMe), 62.3 (C-6), 70.1 (C-5), 73.3 (C-3), 73.3 (PhCH3), 74.2 (C-2), 75.1 (PhCH2), 75.5 (C-4), 98.7 (C-1), 128.0–133.4 (16 C-Ar), 137.6, 138.2 (2 × C-ipso), 166.0 (CO). ESIMS: [M + Na]+ m/z calcld for C28H30O7Na 501.1884, found 501.1880.

**Methyl 3-O-benzoyl-2,4-di-O-benzyl-6-bromo-α-D-galactopyranoside (8).** To a solution of compound 7 (0.89 g, 1.70 mmol) in pyridine, PPh3 (0.89 g, 3.40 mmol) and CBr4 (0.62 g, 1.87 mmol) were added and stirred at 65 °C for 40 min. The mixture was cooled, diluted with MeOH and stirred for 5 min, whereafter it was concentrated and purified by column chromatography (pentane–EtOAc 5 : 1) to give the product as white crystals (0.93 g, 1.69 mmol, 99%). 1H NMR (CDCl3): δ 3.33 (dd, JH1,6a 6.90 Hz, Jgem 10.20 Hz, 1H, H-6a), 3.41 (dd, JH1,6b 6.90 Hz, Jgem 10.20 Hz, 1H, H-6b), 3.44 (s, 3H, OMe), 4.08 (m, 1H, H-5), 4.17 (dd, JH1,14 3.60 Hz, JH3,14 10.53 Hz, 1H, H-2), 4.27 (dd, JH1,14 3.10 Hz, JH4,14 1.42 Hz, 1H, H-4), 4.52 (d, Jgem 11.30 Hz, 1H, PhCH2), 4.64 (d, Jgem 12.31 Hz, 1H, PhCH2), 4.71 (d, Jgem 12.31 Hz, 1H, PhCH2), 4.75 (d, Jgem 11.30 Hz, 1H, PhCH2), 4.77 (d, JH1,14 3.60 Hz, 1H, H-1), 5.58 (dd, JH1,14 10.53 Hz, JH3,14 3.10 Hz, 1H, H-3), 7.22–8.04 (m, 15H, H-Ar). 13C NMR (CDCl3): δ 30.1 (C-6), 55.8 (OMe), 70.5 (C-5), 73.2 (C-3), 73.4 (PhCH3), 73.9 (C-2), 75.6 (PhCH3), 75.6 (C-4), 98.8 (C-1), 128.0–133.4 (16 C-Ar), 137.7, 138.1 (2 × C-ipso), 165.9 (CO). ESIMS: [M + Na]+ m/z calcld for C28H30BrO7Na 563.1040, found 563.1028.

**Methyl 3-O-benzoyl-2,4-di-O-benzyl-6-deoxy-α-D-galactopyranoside (9).** Bu3SnH (9.84 mL, 36.60 mmol) and compound 8 (3.30 g, 6.10 mmol) were dissolved in toluene, stirred for 5 min at 95 °C, followed by the addition of AIBN (0.36 g, 2.20 mmol) and the stirring continued for 40 min at the same temperature. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography over silica gel (pentane–EtOAc 5 : 1) to obtain the product as a colorless syrup (2.29 g, 4.95 mmol, 81%). 1H NMR (CDCl3): δ 1.17 (d, JH1,4 6.56 Hz, 3H, Me-6), 3.40 (s, 3H, OMe), 3.90 (dd, JH1,14 3.13 Hz, JH1,15 1.31 Hz, 1H, H-4), 4.05 (m, 1H, H-5), 4.17 (dd, JH1,14 10.53 Hz, JH1,15 3.64 Hz, 1H, H-2), 4.51 (d, Jgem 11.47 Hz, 1H, PhCH2), 4.65 (d, Jgem 12.35 Hz, 1H, PhCH2), 4.68 (d, Jgem 11.47 Hz, 1H, PhCH2), 4.70 (d, Jgem 12.35 Hz, 1H, PhCH2), 4.76 (d, JH1,15 3.64 Hz, 1H, H-1), 5.54 (dd, JH1,15 10.53 Hz, JH1,14 3.13 Hz, 1H, H-3), 7.21–8.02 (m, 15H, H-Ar). 13C NMR (CDCl3): δ 16.5 (C-6), 55.5 (OMe), 65.9 (C-5), 73.3 (C-3), 73.7 (PhCH2), 74.0 (C-2), 75.6 (PhCH3), 78.3 (C-4), 98.7 (C-1), 127.7–133.3 (16 C-Ar), 138.0, 138.3 (2 × C-ipso), 166.1 (CO). ESIMS: [M + Na]+ m/z calcld for C28H30ONa 485.1935, found 485.1922.
NaOMe in MeOH was added dropwise until pH 8 and stirred for 4 h. The reaction was quenched with Dowex 50 H⁺, filtered and chromatographed over silica gel (pentane-EtOAc 1 : 1) to obtain 9 as a pale yellow syrup (0.10 g, 0.29 mmol, 54%). ¹H NMR (CDCl₃): δ 1.22 (d, J₁H,₁H 6.66 Hz, 3H, Me-6), 3.12 (dd, J₁H,₁H 10.40 Hz, J₁H,₂H 3.15 Hz, 1H, H-3), 3.35 (s, 3H, OMe), 3.49 (dd, J₁H,₁H 10.40 Hz, J₁H,₂H 3.42 Hz, 1H, H-2), 3.61 (dd, J₁H,₂H 3.15 Hz, 1H, H-4), 3.94 (m, 1H, H-5), 4.56 (d, J₉₈,₁H 11.82 Hz, 1H, PhCH₂), 4.64 (d, J₉₈,₁H 11.82 Hz, 1H, PhCH₂), 4.67 (d, J₉₈,₁H 11.30 Hz, 1H, PhCH₂), 4.69 (d, J₉₈,₁H 13.42 Hz, 1H, H-1), 4.72 (d, J₉₈,₁H 11.30 Hz, 1H, PhCH₂), 7.28–7.35 (m, 10H, H-Ar). ¹³C NMR (CDCl₃): δ 6.16 (C-6), 51.8 (C-3), 55.4 (OMe), 66.9 (C-5), 72.7 (PhCH₂), 76.4 (PhCH₂), 78.7 (C-2), 81.6 (C-4), 97.6 (C-1), 127.9–128.6 (10 C-Ar), 138.3, 138.4 (2 × C-ipsO). ESIMS: [M + Na⁺] m/z calculated for C₂₁H₂₃NO₄Na 380.1832, found 380.1820.

Methyl 2,4-di-O-benzyl-3-formamido-3,6-dideoxy-α-D-galactopyranoside (14). Acetic anhydride (10 mL) and formic acid (4.70 mL) were heated at 60 °C for 4 h, then 2 mL were added to compound 13 (30 mg, 0.08 mmol) and the mixture was stirred at r.t. for 24 h. The solvent was evaporated and the crude was purified by column chromatography (pentane-acetone 3 : 1) to obtain the product as white solid (32 mg, 0.08 mmol, 99%). 

Major ¹H NMR (CDCl₃): δ 1.21 (d, J₁H,₁H 6.62 Hz, 1H, 1H-Me), 3.38 (s, 1.8H, OMe), 3.70 (dd, J₁H,₁H 3.63 Hz, J₁H,₂H 11.20 Hz, 0.6H-H-2), 4.41 (d, J₉₈,₁H 11.90 Hz, 0.6H, PhCH₂), 4.42 (m, 0.6H, H-3), 4.47 (d, J₁H,₁H 12.15 Hz, 0.6H, PhCH₂), 4.65 (d, J₁H,₂H 12.15 Hz, 0.6H, PhCH₂), 4.73 (d, J₉₈,₁H 11.90 Hz, 0.6H, PhCH₂), 4.77 (d, J₁H,₁H 3.62 Hz, 0.6H-H-1), 5.10 (d, J₁H,₁H 7.30 Hz, 0.6H, NH), 7.24–7.41 (m, 6H, 10 H-Ar), 7.75 (dd, J₀₉,₁H 0.93 Hz, 1.70 Hz, 0.6H, HCO). ¹³C NMR (CDCl₃): δ 16.6 (C-6), 48.6 (C-3), 55.4 (OMe), 65.9 (C-5), 72.2 (PhCH₂), 73.8 (C-2), 76.2 (PhCH₂), 79.6 (C-4), 97.5 (C-1), 128.0–128.9 (5 C-Ar), 138.0, 138.2 (2 × C-ipsO), 161.0 (CO). Minor ¹H NMR (CDCl₃): δ 1.27 (d, J₁H,₁H 6.70 Hz, 1H, 1H-Me), 3.37 (s, 1.2H, OMe), 3.54 (dd, J₁H,₁H 10.41 Hz, J₁H,₁H 2.50 Hz, 0.4H-H-2), 3.59 (dd, J₁H,₁H 3.40 Hz, J₁H,₂H 1.24 Hz, 0.4H-H-4), 3.74 (dd, J₁H,₁H 3.22 Hz, J₁H,₂H 1.23 Hz, 0.6H-H-4), 3.80 (dd, J₁H,₁H 10.41 Hz, J₁H,₁H 10.72 Hz, J₁H,₁H 3.40 Hz, 0.4H-H-3), 3.98 (m, 1H, H-5, H-5), 4.51 (d, J₉₈,₁H 11.90 Hz, 0.4H, PhCH₂), 4.53 (d, J₉₈,₁H 11.33 Hz, 0.4H, PhCH₂), 4.61 (d, J₉₈,₁H 11.90 Hz, 0.4H, PhCH₂), 4.65 (d, J₁H,₂H 3.50 Hz, 0.4H-H-1), 4.76 (d, J₁H,₁H 11.33 Hz, 0.4H-HCO), 4.81 (dd, J₁H,₁H 11.24 Hz, J₁H,₂H 3.40 Hz, 0.4H-H, 4.81 (dd, J₁H,₁H 11.24 Hz, J₁H,₂H 3.40 Hz, 0.4H-H, 4.81 (dd, J₁H,₁H 11.24 Hz, J₁H,₂H 3.40 Hz, 0.4H-H). ¹³C NMR (CDCl₃): δ 16.9 (C-6), 52.4 (C-3), 55.5 (OMe), 66.1 (C-5), 72.5 (PhCH₂), 78.9 (C-1), 85.3 (C-1), 127.9–128.6 (10 C-Ar), 137.7, 137.8 (2 × C-ipsO), 152.9 (C-3). ESIMS: [M + Na⁺] m/z calculated for C₂₁H₂₃NO₄Na 408.1781, found 408.1777.

Methyl 3-formamido-3,6-dideoxy-α-D-galactopyranoside (1). Compound 14 (32 mg, 0.08 mmol) was dissolved in 4 mL EtOAc–EtOH 1 : 1, a catalytic amount of 20% Pd/C was added and 14 was hydrogenolyzed at 100 psi for 4 h. The reaction mixture was filtered through Celite and the solvent was evaporated to afford the product as a white solid (15 mg, 0.07 mmol, 88%). Major ¹H NMR (D₂O): δ 1.22 (d, J₁H,₁H 6.58 Hz, 2H-H-2), 3.45 (2H-H, OMe), 3.76 (dd, J₁H,₁H 3.15 Hz, J₁H,₁H 1.34 Hz, 0.8H-H-2), 3.84 (dd, J₁H,₁H 11.08 Hz, J₁H,₁H 3.80 Hz, 0.8H-H-2), 4.12 (dd, J₁H,₁H 13.40 Hz, J₁H,₁H 6.58 Hz, 0.8H-H-2), 4.26 (dd, J₁H,₁H 11.08 Hz, J₁H,₁H 6.58 Hz, 0.8H-H-2),
Compound 13 (23 mg, 0.064 mmol) was dissolved in EtOAc (2 mL), acetic anhydride (7.5 mg, 0.073 mmol) and pyridine (0.05 mmol) was added and the mixture was stirred at room temperature. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to give the product as a white solid (21 mg, 0.053 mmol, 82%).

1H NMR (CDCl3): δ 1.22 (d, J = 6.5 Hz, H-6J, Me-6), 2.05 (s, 3H, NAc), 3.44 (s, 3H, OMe), 3.73 (ddd, J = 13.0 Hz, H-3J, Me-3, 1.9 Hz, H-3), 4.35 (ddd, J = 12.0, 1.7 Hz, H, PhCH2), 4.44 (ddd, J = 12.3, 1.7 Hz, H, PhCH2), 4.68 (d, J = 12.3 Hz, 1H, PhCH2), 4.73 (d, J = 12.0 Hz, 1H, PhCH2), 4.80 (d, J = 3.1 Hz, 1H, H-1), 4.96 (d, J = 7.4 Hz, 1H, NH), 7.21-7.36 (m, 10H, H-Ar). 13C NMR (CDCl3): δ 16.7 (C-6), 23.2 (NAC), 49.8 (C-3), 55.4 (OMe), 66.0 (C-5), 72.2 (PhCH2), 73.8 (C-7), 76.4 (PhCH2), 80.1 (C-4), 97.6 (C-1), 128.1-128.7 (10 C-Ar), 138.3, 138.5 (2 × C-IPSO), 170.0 (CO). ESIMS: [M + Na]^+ m/z calculated for C24H21NO6Na 422.1938, found 422.1932.

**Methyl 3-acetamido-2,4-di-O-benzyl-3,6-dideoxy-α-D-galactopyranoside (2).** Compound 15 (21 mg, 0.053 mmol) was dissolved in 4 mL EtOAc–EtOH 1:1, and deprotected as for compound 14 to obtain the product as a white solid (8.7 mg, 0.039 mmol, 75%).

1H NMR (CDCl3): δ 1.22 (d, J = 6.5 Hz, JH2,JH4 = 3.6 Hz, 3H, Me-6), 2.05 (s, 3H, NAc), 3.44 (s, 3H, OMe), 3.73 (ddd, J = 13.0 Hz, H-3J, Me-3, 1.9 Hz, H-3), 4.35 (ddd, J = 12.0, 1.7 Hz, H, PhCH2), 4.44 (ddd, J = 12.3, 1.7 Hz, H, PhCH2), 4.68 (d, J = 12.3 Hz, 1H, PhCH2), 4.73 (d, J = 12.0 Hz, 1H, PhCH2), 4.80 (d, J = 3.1 Hz, 1H, H-1), 4.96 (d, J = 7.4 Hz, 1H, NH), 7.21-7.36 (m, 10H, H-Ar). 13C NMR (CDCl3): δ 16.7 (C-6), 23.2 (NAC), 49.8 (C-3), 55.4 (OMe), 66.0 (C-5), 72.2 (PhCH2), 73.8 (C-7), 76.4 (PhCH2), 80.1 (C-4), 97.6 (C-1), 128.1-128.7 (10 C-Ar), 138.3, 138.5 (2 × C-IPSO), 170.0 (CO). ESIMS: [M + Na]^+ m/z calculated for C24H21NO6Na 422.1938, found 422.1932.

**Methyl 3-acetamido-2,4-di-O-benzyl-3,6-dideoxy-α-D-galactopyranoside (15).** Compound 13 (23 mg, 0.064 mmol) was dissolved in EtOAc (2 mL), acetic anhydride (7.5 mg, 0.073 mmol) was added and the mixture was stirred at room temperature. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to give the product as a white solid (21 mg, 0.053 mmol, 82%).

1H NMR (CDCl3): δ 1.22 (d, J = 6.5 Hz, JH2,JH4 = 3.6 Hz, 3H, Me-6), 2.05 (s, 3H, NAc), 3.44 (s, 3H, OMe), 3.73 (ddd, J = 13.0 Hz, H-3J, Me-3, 1.9 Hz, H-3), 4.35 (ddd, J = 12.0, 1.7 Hz, H, PhCH2), 4.44 (ddd, J = 12.3, 1.7 Hz, H, PhCH2), 4.68 (d, J = 12.3 Hz, 1H, PhCH2), 4.73 (d, J = 12.0 Hz, 1H, PhCH2), 4.80 (d, J = 3.1 Hz, 1H, H-1), 4.96 (d, J = 7.4 Hz, 1H, NH), 7.21-7.36 (m, 10H, H-Ar). 13C NMR (CDCl3): δ 16.7 (C-6), 23.2 (NAC), 49.8 (C-3), 55.4 (OMe), 66.0 (C-5), 72.2 (PhCH2), 73.8 (C-7), 76.4 (PhCH2), 80.1 (C-4), 97.6 (C-1), 128.1-128.7 (10 C-Ar), 138.3, 138.5 (2 × C-IPSO), 170.0 (CO). ESIMS: [M + Na]^+ m/z calculated for C24H21NO6Na 422.1938, found 422.1932.

**Methyl 3-(3-R)-hydroxybutyramido)-2,4-di-O-benzyl-3,6-dideoxy-α-D-galactopyranoside (18).** Compound 17 (31 mg, 0.055 mmol) was dissolved in THF (3 mL), TBAF (35 mg, 0.11 mmol) was added and the mixture stirred for 30 min. The solvent was evaporated under reduced pressure and the crude material was purified by column chromatography (pentane-EtOAc 1:1) to obtain the product as a white solid (24 mg, 0.054 mmol, 97%).

1H NMR (CDCl3): δ 1.11, 1.22 (2 × d, J = 6.3 Hz, 1.7 Hz, 2 × 3H, Me-6, Me-4), 1.82 (s, 2H, CH2), 3.40 (s, 3H, OMe), 3.59 (d, J = 8.3 Hz, 1H, OH), 3.71 (dd, J = 11.2 Hz, 1H, H-1), 3.72 (m, 1H, H-4), 3.99 (m, 2H, H-5, H-3'), 4.38 (d, J = 11.0 Hz, 1H, PhCH2), 4.39 (m, 1H, H-3), 4.44 (d, J = 12.0 Hz, 1H, PhCH2), 4.67 (d, J = 12.0 Hz, 1H, PhCH2), 4.74 (d, J = 11.0 Hz, 1H, PhCH2), 4.79 (d, J = 3.1 Hz, 1H, H-1), 5.24 (d, J = 7.4 Hz, 1H, NH), 7.23-7.35 (m, 10H, H-Ar). 13C NMR (CDCl3): δ 16.7, 22.8 (C-6, C-4'), 43.6 (C-2), 49.6 (C-3), 55.4 (OMe), 64.8, 66.1 (C-5, C-3'), 72.3 (PhCH2), 74.1 (C-2), 76.4 (PhCH2), 80.2 (C-4), 97.6 (C-1), 128.1-128.8 (10 C-Ar), 138.3, 138.5 (2 × C-IPSO), 172.5 (CO). ESIMS: [M + Na]^+ m/z calculated for C25H23NO6Na 466.2200, found 466.2207.
CH$_2$-3'), 1.89 (m, 2H, CH$_2$-2'), 3.38 (s, 3H, OMe), 3.56 (ddd, J = 1.4, 6.29, 7.52 Hz, 2H, CH$_2$-4'), 3.72 (dd, J$_{H1,H3}$ = 10.90 Hz, J$_{H1,H2}$ = 3.30 Hz, 1H, H-2), 3.80 (dd, J$_{H3,H4}$ = 3.15 Hz, J$_{H1,H5}$ = 1.12 Hz, 1H, H-1), 3.99 (m, 1H, H-5), 4.35 (ddd, J$_{H1,H3}$ = 10.90 Hz, J$_{H1,H2}$ = 7.15 Hz, J$_{H3,H4}$ = 3.15 Hz, 1H, H-3), 4.40 (d, J$_{gem}$ = 11.90 Hz, 1H, PhCH$_3$), 4.46 (d, J$_{gem}$ = 12.30 Hz, 1H, PhCH$_3$), 4.66 (d, J$_{gem}$ = 11.90 Hz, 1H, PhCH$_3$), 4.78 (d, J$_{H1,H2}$ = 3.30 Hz, 1H, H-1), 5.11 (d, J$_{H3,H4}$ = 7.15 Hz, 1H, NH), 7.21–7.35 (m, 10H, H-5, Ar). $^1$H NMR (CDCl$_3$): δ = 5.2 (2 × Me-Si), 16.7 (C-6), 18.4 (t-C), 26.1 (t-Cu), 28.7 (C-3'), 33.0 (C-2'), 49.9 (C-3), 55.3 (OMe), 62.4 (C-4'), 66.0 (C-6), 72.0 (PhCH$_3$), 73.7 (C-2), 76.2 (PhCH$_3$), 79.8 (C-4), 97.6 (C-1), 128.0–128.7 (10 C- Ar), 138.2, 138.4 (2 × C-ipso), 172.9 (CO). ESIMS: [M + Na]$^+$ m/z calced for C$_{41}$H$_{34}$NO$_7$Na $580.0365$, found 580.0352.

**Methyl 3-(4-hydroxybutyramido)-2,4-di-O-benzyl-3,6-dideoxy-$\alpha$-galactopyranoside (4)**. Compound 20 (45 mg, 0.081 mmol) was dissolved in THF (5 mL), TBAF (51 mg, 0.16 mmol) was added and the mixture was stirred for 1 h. The solvent was evaporated under reduced pressure and the crude material was purified by column chromatography (pentane–EtOAc 1:4) to obtain the product as a white solid (25 mg, 0.056 mmol, 70%). $^1$H NMR (CDCl$_3$): δ 1.62 (d, J$_{H5,H6}$ = 6.63 Hz, 3H, Me-6), 1.67 (m, 2H, CH$_2$-3'), 1.83 (m, 1H, H-2'a), 1.95 (m, 1H, H-2'b), 2.75 (n.r., 1H, OH), 3.40 (s, 3H, OMe), 3.56 (m, 2H, CH$_2$-4'), 3.71 (dd, J$_{H3,H4}$ = 11.8 Hz, J$_{H1,H3}$ = 3.40 Hz, 1H, H-2), 3.75 (dd, J$_{H3,H4}$ = 11.8 Hz, J$_{H1,H3}$ = 3.30 Hz, 1H, H-1), 3.85 (m, 2H, CH$_2$-4'), 3.97 (d, J$_{H2,H3}$ = 11.29 Hz, J$_{H3,H4}$ = 11.90 Hz, 1H, PhCH$_3$), 4.44 (d, J$_{H2,H3}$ = 12.14 Hz, 1H, PhCH$_3$), 4.74 (d, J$_{H2,H3}$ = 11.90 Hz, 1H, PhCH$_3$), 4.80 (d, J$_{H1,H2}$ = 3.40 Hz, 1H, H-1), 5.19 (d, J$_{H3,H4}$ = 7.37 Hz, 1H, NH), 7.22–7.36 (m, 10H, H-5, Ar). $^1$C NMR (CDCl$_3$): δ 16.7 (C-6), 27.9 (C-3'), 34.0 (C-2'), 49.9 (C-3), 55.4 (OMe), 62.5 (C-4'), 66.1 (C-5), 72.1 (PhCH$_3$), 73.9 (C-2), 76.3 (PhCH$_3$), 80.1 (C-4), 97.6 (C-1), 128.0–128.8 (10 C- Ar), 138.2, 138.5 (2 × C-ipso), 173.5 (CO). ESIMS: [M + Na]$^+$ m/z calced for C$_{32}$H$_{33}$NO$_7$Na $466.2200$, found 466.2201.

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