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Synthesis of iminoalditol analogues of galactofuranosides and their activities against glycosidases

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Dedicated to Professor Yongzheng Hui on the occasion of his 70th birthday

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ABSTRACT

Iminoalditol analogues of galactofuranosides were synthesized from 1-*C*-(2′-oxo-propyl)-1,4-dideoxy-1,4-imino-D-galactosides and different amines by reductive amination, followed by removal of protecting groups. The activity of these compounds against galactosidases and other glycosidases was investigated. The best inhibitor against β-galactosidase (bovine liver) is a diastereomeric mixture of an iminoalditol (**10h**), which contains a hydrophobic hexadecyl aglycon ($R = C_{16}H_{33}$), whereas no significant inhibitory activity was observed with compounds having a hydrophilic aglycon. Surprisingly, activation of α-galactosidase (coffee bean) by **10h** was also observed. Because these results were obtained from a mixture of iminoalditols, the inhibition and activation of glycosidases could result from different diastereomers.

1. Introduction

Iminosugars as potent glyco-processing enzyme inhibitors have been clinically applied to the treatment of diabetes and glycosidase-deficient diseases.[1] For example, Miglitol (*N*-hydroxyethyldeoxynojirimycin), a α-glucosidase inhibitor, is used for blood glucose control. Miglustat (*N*-butyldeoxynojirimycin), a glucosylceramide synthase inhibitor, is one of the therapeutics for type 1 Gaucher disease. The therapeutic applications of iminosugars could be expanded if better inhibition specificity against α- or β-glycosidases can be obtained. There have been examples suggesting that homoiminosugars and 1-*C*-alkyl iminosugars are more selective inhibitors, particularly against α-glycosidases.[2] The improved selectivity was attributed to the defined anomeric configuration and additional interaction between the aglycon and the lipophilic domain of glycosidases.[3]

In addition, iminosugars can also be utilized at subinhibitory concentrations as chemical chaperons that resurrect misfolded enzymes in the ER/Golgi from degradation and facilitate the transportation to lysosome, where lower pH stabilizes the enzyme.[4] This chemical chaperon approach has been explored for the treatment of both Gaucher[5] and Fabry[6] diseases with lysosomal β-glucocerebrosidase and α-galactosidase A deficiency. Other glycosidase deficiency diseases, such as GM1-gangliosidosis and Morquio B disease, have also been investigated in the animal model using glycosidase inhibitors as chemical chaperons.[7]

Previously, we have synthesized various 2-keto-iminoalditols with the aim of using them for diversity-oriented synthesis.[8] For example, by conjugation with various amines by reductive amination we will be able to obtain an array of diverse iminoalditols that can be tested against glycosidases. In this report, we describe the synthesis of various iminoalditol analogues of galactofuranosides and their activities against glycosidases, particularly, α- and β-galactosidases.

2. Results and discussion

Five-membered iminosugar derivatives, containing a pyrrolidine core, demonstrated inhibitory potency against various glycosidases because of their ability to mimic transition states.[9] The core structure of this study is an iminoalditol analogue of the galactofuranoside ring, which was derivatized through the 2-keto group via reductive amination with different amines. We first synthesized **5** as a key intermediate following a procedure similar to that used for the synthesis of similar iminosugar analogues of pyranosides,[8,10] which is illustrated in Scheme 1. Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**1**)[11] was used as the starting material

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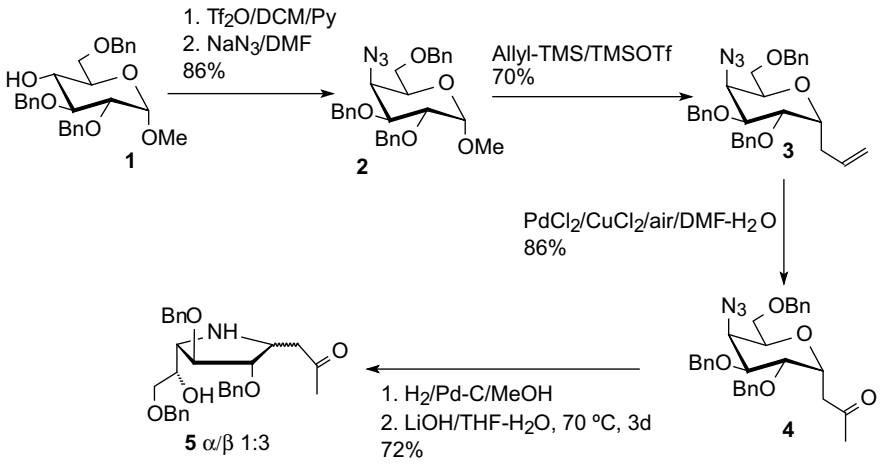
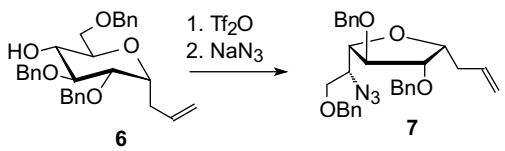


Scheme 1. Synthesis of 2-keto-iminoalditol **5**.

and was converted to the 4-azido derivative **2** by a standard method, which was followed by 1-C-allylation to give compound **3**. This reaction sequence was necessary to avoid a ring contraction reaction that occurred during azide substitution of the 4-OH of allyl C-glycoside **6**, leading to the formation of 5-azido-*C*-galactofuranoside **7** (Scheme 2).[8a]

Introduction of the ketone functionality was achieved by treatment of **3** with either $Hg(OAc)_2$–Jones reagent[12] or $PdCl_2$–$CuCl_2$.[13] A better chemical yield of **4** was obtained by the latter method. The reduction of the 4-azido group by catalytic hydrogenation of **4** under balloon pressure afforded the 4-amino-derivative completely as indicated by TLC analysis. Without further purification, the amine was treated with LiOH in THF–H_2O at 70 °C for three days to obtain keto-iminoalditol **5** as a mixture of anomers (α/β 1:3). Apparently, the tandem β-elimination and Michael addition of the 2-keto-*C*-glycopyranosides such as **4** requires stronger conditions than respective C-furanosides,[8,10] which underwent the same intramolecular rearrangement at room temperature using 1–4% NaOMe.

Iminoalditol derivatives **10a–i** were then prepared from **5** and respective amines by reductive amination followed by catalytic hydrogenation (Scheme 3). The reductive amination using sodium cyanoborohydride led, in most cases, to amine **9**; however, a significant amount of unreduced imine intermediate **8** was also obtained when 1-(2-aminoethyl)-piperazine and 1-(2-aminoethyl)-morpholine were used (**8a** and **8b**), as indicated by the presence of a singlet of 3′-Me resonance in the ^{1}H NMR spectrum. Fortunately, the catalytic hydrogenation in the next step converted both to desired products (**10a** and **10b**). In this study, we included heterocycles (**10a** and **10b**), α- and β- amino acids (**10c**, **10d**, and **10f**), alkylamines (**10g** and **10h**), and a uridine derivative (**10i**) as part of the aglycon to evaluate their roles in the interaction with glycosidases. Under catalytic hydrogenation, the iminoalditol containing the uridine group[14] (**9i**) underwent not only de-O-benzylation but also reduction of the double bond of nucleotide, which consequently afforded **10i**. Compound **11** with only the core structure was obtained by direct catalytic removal of *O*-benzyl groups from **5**. It should be noted that all those compounds obtained from reductive amination are mixtures of four diastereomers as indicated by ^{1}H NMR.



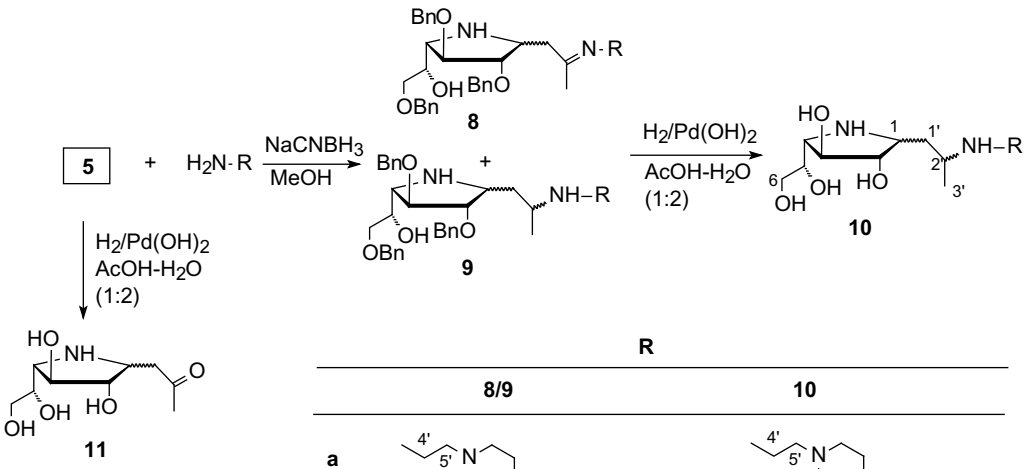
Scheme 2. Ring contraction of C-glycopyranoside.

The reductive amination between **5** and hexylamine to produce **9g** was very sluggish and resulted in a poor yield of the target. An alternative method to improve the chemical yield of the reductive amination involved protection of both amino and 5-hydroxyl groups of **5** (Scheme 4). Thus, compound **5** was treated with benzyl bromide/K_2CO_3 (to **12**), followed by acetic anhydride to furnish **13**. The reductive amination of **13** with hexylamine afforded iminoalditol **14** in 66% yield, which, after catalytic removal of *O*-benzyl groups, produced **10g**.

With these compounds, we performed inhibition assays against a range of glycosidases. None of these compounds showed significant inhibitory activity against α-glucosidase, (*B.* yeast), β-glucosidase (almond), α-mannosidase (jack bean), β-mannosidase (snail), and α-fucosidase (bovine kidney) at 100 μM concentrations. When screened against galactosidases, only **10h** and **11** were found to be active. The diastereomeric mixture **10h** was particularly potent against bovine liver β-galactosidase, with an IC_{50} = 2.74 μM (81% at 100 μM). On the other hand, compound **11** was shown to be a moderate inhibitor of α-galactosidase from coffee bean (58% at 100 μM). The results provide another example that the hydrophobic aglycon is critical to the binding affinity to a particular enzyme, which have been repeatedly observed previously, for example, hydrophobicity of α-1-*C*-alkyl-deoxynojirimycin derivatives played a critical secondary binding to enzyme in the inhibition against isomaltase.[3] However, one cannot exclude the possibility that the hydrophobic binding could be the initial interaction prior to the more specific binding of iminosugar motif to the enzyme, which may explain why **10h** and **11** showed completely different specificities. In addition, an inhibition kinetic study using a Lineweaver–Burk plot showed that the inhibition was not entirely competitive.

Because a diastereomeric mixture was used for the inhibition assay, it is possible that not all the isomers contributed equally to the activities observed. There have been examples indicating that six-membered (piperidine) β-homoiminosugars are often weaker inhibitors than α-anomers as had been observed by Fleet et al.[15] in homonojirimycin and Martin et al. in homogalactonojirimycin[16] and α-1-C-substituted fagomines.[2c] Both α-homonojirimycin and α-homogalactonojirimycin showed excellent specificity toward α-glycosidases but not β-galactosidases.

The non-activity of **10a–c**, **10f**, **10g**, and **10i** against galactosidases was not a surprise as the serendipitous hydrophobic interaction, observed for **10h**, is now absent or depleted with these



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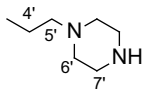
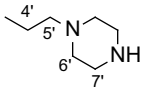
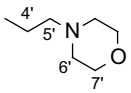
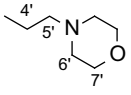
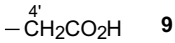
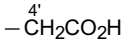
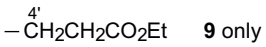
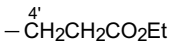
a		
b		
c	 **9** only	
d	 **9** only	
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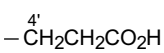
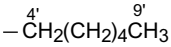
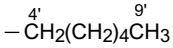
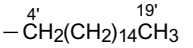
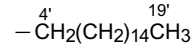
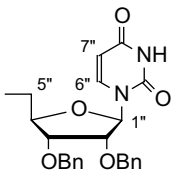
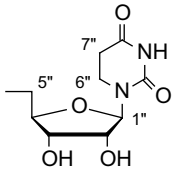
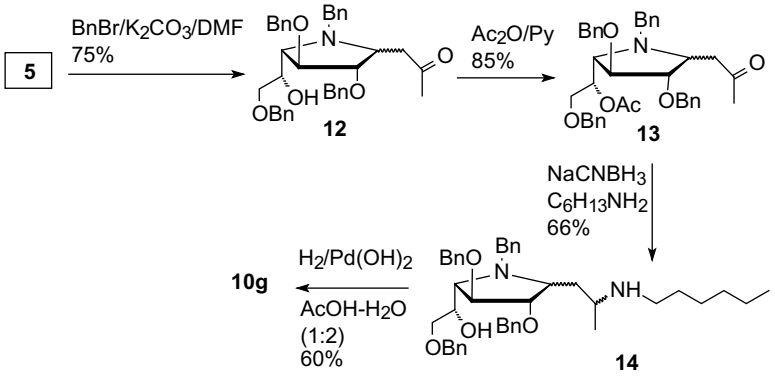
f		
g		
h	 **9** only	
i	 **9** only	

Scheme 3. Reductive amination of 2-keto-iminoalditol **5**.

hydrophilic aglycons. What surprised us was the observation of activation of α-galactosidase from coffee bean by **10h** with AC_{50} = 47 μM (62% activation at 100 μM). Because there are four diastereomers in **10h**, we are not sure at this moment if the same molecule played dual roles as inhibitor for one enzyme and activator for another, or the different activities were contributed individually from different molecules in the mixture. To the best of our knowledge, this is the first example of activating a galactosidase by a small molecule, but examples of enzyme activation by proteins are well known.[17] Although the enzyme activated is α-galactosidase from coffee bean, the importance of this observation should not be undermined, because it provides the possibility that an activator for human glycosidases could be found and used for the treatment of glycolipid storage diseases in conjunction with enzyme replacement therapies.

In summary, we have synthesized an array of iminoalditol analogues of galactofuranosides that contain entities of hydrophobic and hydrophilic nature through reductive amination from 2′-carbonyl iminosugar and different amines. The inhibition assay revealed that a diastereomeric mixture of **10h** specifically inhibited



Scheme 4. Synthesis of **10g** by an indirect route.

β-galactosidase from bovine liver and, unexpectedly, activated α-galactosidase from coffee bean. Currently, we are investigating the function of each diastereomer of **10h**, and the results will be reported in due course.

3. Experimental

3.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, with a Varian instrument at 293 K. Chemical shifts were given in ppm downfield to the signal of internal TMS, and were assigned on the basis of 2D ^{1}H–^{1}H COSY and ^{1}H–^{13}C chemical-shift-correlated experiments. For high resolution mass spectroscopic analysis, samples in CH_2Cl_2–MeOH 1:1 were mixed with Agilent ES tuning mix for internal mass calibration and infused into an AB/MDS-Sciex (Concord, ON) QSTAR mass spectrometer at a flow-rate of 4 μL/min. All glycosidases were purchased from Sigma and all chemicals were purchased from Aldrich Co. without further purification.

3.2. General method for reductive amination

To the solution of ketone **5** (1 mmol) in anhydrous MeOH (20 mL) was added amine (2 mmol), followed by sodium cyanoborohydride (1.5 mmol) at room temperature. The reaction mixture was stirred for 2 days and concentrated. The residue was dissolved in CH_2Cl_2 and washed with satd aq $NaHCO_3$. The organic layer was further washed with water followed by brine, dried over sodium sulfate and concentrated to an oily residue, which was purified by flash chromatography.

3.3. General method for debenzylation

The product from the reductive amination (0.13 mmol) was dissolved in acetic acid (3 mL) and water (4 mL). 20% $Pd(OH)_2$ (0.05 g) was added, and the reaction mixture was subjected to hydrogenation at 45 psi for 12 to 24 h. The reaction mixture was filtered from $Pd(OH)_2$, rinsed with water, and lyophilized. The final products were thus ammonium acetates.

3.4. Inhibition assay

The inhibition assay was performed following a procedure previously reported in the literature.[18] Briefly, the enzyme and the inhibitor were pre-incubated at room temperature for 5 min before the addition of an appropriate nitrophenyl glycoside as substrate at the optimum pH of each enzyme. The microtiter plate was incubated at 37 °C for 10 min, and the reaction was terminated by addition of 0.5 M Na_2CO_3. The released nitrophenol was measured spectrometrically at 400 nm using a microtiter plate reader. IC_{50} and AC_{50} were estimated from inhibition-concentration plot at different inhibitor concentrations.

3.5. Methyl 4-azido-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-galactopyranoside (2)

To a solution of **1** (1.57 g, 3.38 mmol) in a mixture of anhydrous pyridine (1.36 mL, 16.9 mmol) and CH_2Cl_2 (40 mL) was added trifluoromethanesulfonic anhydride (0.76 mL, 4.52 mmol) over 5 min at 0 °C. Gradually, warming to room temperature over 3 h led to near quantitative conversion. The reaction mixture was diluted with CH_2Cl_2 (50 mL), and washed with equal amount of ice-cold water, dried, filtered, and concentrated to a brown syrup. Without further purification, the intermediate was dissolved in DMF (15 mL) and sodium azide (0.439 g, 6.75 mmol) was added. After stirring overnight, water (25 mL) was added and the aqueous layer was extracted with diethyl ether. The combined organic layer was further washed with satd NaCl (25 mL), dried, filtered, and concentrated. Purification by column chromatography (20:1→3:1 hexane–EtOAc) gave **2** (1.42 g, 86%) as a syrup. $[\alpha]_D$ +4.0 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.26 (m, 15H, 3 × Ph), 4.83 and 4.64 (2d, 2H, CH_2Ph, *J* = 12.0 Hz), 4.81 and 4.74 (2d, 2H, CH_2Ph, *J* = 11.7 Hz), 4.58 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 4.57 and 4.51 (2d, 2H, CH_2Ph, *J* = 11.8 Hz), 4.02 (dd, 1H, H-3, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 3.7 Hz), 3.99 (dd, 1H, H-4, $J_{4,5}$ = 1.3 Hz), 3.93 (m, 1H, H-5), 3.83 (dd, 1H, H-2), 3.55 (m, 2H, H-6a, H-6b), 3.34 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.3, 137.9, 128.7, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9, 98.9 (C-1), 77.9 (C-3), 76.3 (C-2), 74.0 (CH_2Ph), 73.9 (CH_2Ph), 73.4 (CH_2Ph), 69.2 (C-6), 67.3 (C-5), 61.7 (C-4), 55.7 (Me); HRMS calcd for $C_{28}H_{32}N_3O_5$ $[M+H]^+$ 490.2342, found 490.2325.

3.6. 3-*C*-(4-Azido-2,3,6-tri-*O*-benzyl-1,4-dideoxy-α-D-galactopyranosyl)-propene (3)

To a solution of **2** (5.28 g, 10.8 mmol) and allyl trimethylsilane (8.56 mL, 53.9 mmol) in anhydrous acetonitrile (100 mL) was added TMSOTf (2.92 mL, 16.2 mmol) over a period of 15 min at 0 °C under a nitrogen atmosphere. The solution was stirred for 20 h and diluted with CH_2Cl_2 (100 mL). Usual work-up and column chromatography (20:1→3:1 hexane–EtOAc) gave **3** (3.78 g, 70%) as a white solid. $[\alpha]_D$ +41.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.23 (m, 15H, 3 Ph), 5.75 (m, 1H, CH_2–CH=CH_2), 5.13–5.01 (m, 2H, CH_2–CH=CH_2), 4.79–4.70 (m, 3H, CH_2Ph), 4.63–4.48 (m,

3H, CH_2Ph), 4.11–4.02 (m, 2H, H-1, H-4), 3.96 (dd, 1H, H-2, $J_{1,2}$ = 5.9 Hz, $J_{2,3}$ = 9.1 Hz), 3.84–3.76 (m, 2H, H-3, 5), 3.61–3.52 (m, 2H, H-6a, 6b), 2.49–2.30 (m, 2H, CH_2–CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.1, 138.0, 134.9, 128.7, 128.6, 128.6, 128.1, 128.0, 127.9, 117.2, 78.0 (C-3), 76.3 (C-2), 74.2 (C-1), 73.9 (CH_2Ph), 73.8 (CH_2Ph), 72.9 (CH_2Ph), 68.9 (C-6), 68.8 (C-5), 61.1 (C-4), 30.2 (C-1′); HRMS calcd for $C_{30}H_{34}N_3O_4$ $[M+H]^+$ 500.2549, found 500.2547.

3.7. 1-*C*-(4-Azido-2,3,6-tri-*O*-benzyl-1,4-dideoxy-α-D-galactopyranosyl)-acetone (4)

To a mixture of **3** (3.78 g, 7.57 mmol), $PdCl_2$ (0.635 g, 3.56 mmol), and $CuCl_2·2H_2O$ (3.22 g, 18.93 mmol) in DMF–water (10:1, 100 mL) was bubbled with air for 2 h. The reaction mixture was then stirred for 5 days under constant pressure of air. The mixture was diluted by the addition of water and extracted with Et_2O. Usual work-up and column chromatography (20:1→6:1 hexanes–EtOAc) afforded **4** (3.34 g, 86%) as a white solid. $[\alpha]_D$ +31.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.24 (m, 15H, 3 × Ph), 4.75 and 4.71 (2d, 2H, CH_2Ph, *J* = 11.7 Hz), 4.70 and 4.55 (2d, 2H, CH_2Ph, *J* = 11.1 Hz), 4.61 (ddd, 1H, H-1, $J_{1,2}$ = 5.7 Hz, $J_{1,1'a}$ = 5.7 Hz, $J_{1,1'b}$ = 8.4 Hz), 4.54 and 4.50 (2d, 2H, CH_2Ph, *J* = 11.6 Hz), 4.04 (dd, 1H, H-4, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 2.1 Hz), 3.97 (dd, 1H, H-2, $J_{2,3}$ = 9.0 Hz), 3.78 (dd, 1H, H-5, $J_{5,6}$ = 6.4 Hz), 3.71 (dd, 1H, H-3), 3.55 (d, 2H, H-6a, 6b), 2.77 (dd, 1H, H-1′a, $J_{1'a,1'b}$ = 15.6 Hz), 2.60 (dd, 1H, H-1′b), 2.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 138.1, 137.9, 137.9, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 77.8 (C-3), 75.7 (C-2), 74.2 (CH_2Ph), 73.8 (CH_2Ph), 72.8 (CH_2Ph), 71.0 (C-1), 70.0 (C-5), 68.7 (C-6), 60.6 (C-4), 41.5 (C-1′), 30.5 (C-3′); HRMS calcd for $C_{30}H_{34}N_3O_5$ $[M+H]^+$ 516.2498, found 516.2490.

3.8. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-acetone (5)

A mixture of **4** (2.25 g, 4.36 mmol) and 10% palladium on charcoal (0.67 g) in MeOH (40 mL) was stirred under H_2 atmosphere (balloon pressure) for 2 h. The reaction mixture was filtered and the filtrate was concentrated to obtain 2.1 g of amine. To a solution of above amine in THF–H_2O (80 mL, 1:1) was added LiOH (2.16 g, 51.47 mmol), and the mixture was stirred at 70 °C for 3 days. The reaction mixture was allowed to cool and separated into two layers. The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL). Usual work-up and purification by chromatography using a linear gradient from hexane to EtOAc (0–100% EtOAc) gave **5** (1.54 g, 72%), a mixture of two anomers (α/β = 1:3), as a syrup.

For the β-anomer (pure compound): ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 15H, 3 × Ph), 4.60–4.45 (m, 5H, CH_2Ph), 4.32 (d, 1H, CH_2Ph, *J* = 11.2 Hz), 3.90 (dd, 1H, H-3, *J* = 3.6, 1.2 Hz), 3.82 (dd, 1H, H-2, *J* = 4.8, 1.2 Hz), 3.76 (m, 2H, H-1, H-5), 3.50–3.40 (m, 2H, H-6a, 6b), 3.30 (dd, 1H, H-4, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 3.6 Hz), 2.72 (d, 2H, H-1′a, 1′b, *J* = 6.8 Hz), 2.08 (s, 3H, 3′-Me); ^{13}C NMR ($CDCl_3$): δ 208.0 (CO), 138.1, 137.9, 137.8, 128.5, 128.4, 127.8, 127.7, 127.6, 84.5 (C-3), 82.9 (C-2), 73.4 (CH_2Ph), 72.8 (C-6), 71.8 (CH_2Ph), 71.5 (CH_2Ph), 69.7 (C-5), 64.5 (C-4), 56.0 (C-1), 44.2 (C-1′), 30.5 (C-3′); HRMS calcd for $C_{30}H_{36}NO_5$ $[M+H]^+$ 490.2593, found 490.2579.

For the α-anomer (data extracted from the spectrum of a mixture): ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 15H, 3 × Ph), 4.60–4.34 (m, 6H, 3 × CH_2Ph), 3.90 (m, 1H, H-3), 3.76 (m, 1H, H-5), 3.70 (m, 1H, H-2), 3.64 (m, 1H, H-1), 3.54–3.50 (m, 2H, H-6a, 6b), 3.28 (dd, 1H, H-4, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 3.5 Hz), 2.71–2.66 (m, 2H, H-1′a, 1′b), 2.10 (s, 3H, 3′-Me); ^{13}C NMR ($CDCl_3$): δ 207.0 (CO), 87.7 (C-2), 86.6 (C-3), 73.7 (CH_2Ph), 73.0 (C-6), 72.0 (CH_2Ph), 71.7 (CH_2Ph), 69.8 (C-5), 64.1 (C-4), 58.3 (C-1), 47.3 (C-1′), 30.7 (C-3′).

3.9. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-(1-piperazineethyl)-2-propylideneamine (8a) and 1-*C*-(2,3,6-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-(1-piperazineethyl)-2-propylamine (9a)

Reductive amination of **5** (0.24 g, 0.50 mmol) with 1-(2-aminoethyl)-piperazine (0.13 g, 1.00 mmol) gave, after purification by flash chromatography using a linear gradient from CH_2Cl_2 to 10% NH_4OH–MeOH (30%), a mixture of imine **8a** and amine **9a** (0.15 g, 52%) as a syrup. Small amounts of the pure compounds were collected for NMR analysis.

For **8a–α**: ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 15H, 3 × Ph), 4.73 (d, 1H, CH_2Ph, *J* = 11.6 Hz), 4.58–4.46 (m, 5H, CH_2Ph), 4.27 (dd, 1H, H-3, *J* = 6.0, 6.0 Hz), 3.94–3.82 (m, 3H, H-4, 1, 5), 3.72–3.61 (m, 2H, H-2, 6a), 3.56–3.50 (dd, 1H, H-6b, *J* = 12.4, 4.8 Hz), 2.85 (t, 4H, 2 × 7′-CH_2, *J* = 4.8 Hz), 2.59 (t, 2H, 4′-CH_2, *J* = 5.2 Hz), 2.44 (t, 2H, 5′-CH_2, *J* = 5.2 Hz), 2.40–2.26 (m, 3H, 2 × 6′-CH_2, H-1′a), 1.82 (dd, 1H, H-1′b, *J* = 13.2, 7.6 Hz), 1.30 (s, 3H, 3′-Me); ^{13}C NMR ($CDCl_3$): δ 173.1 (C=N), 138.4, 138.2, 137.5, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 89.5 (C-2), 86.3 (C-3), 74.5 (C-5), 73.6 (CH_2Ph), 72.7 (CH_2Ph), 72.5 (C-6), 72.4 (CH_2Ph), 64.2 (C-4), 62.3 (C-1), 57.8 (C-5′), 54.3 (C-6′), 46.4 (C-7′), 43.0 (C-1′) 39.7 (C-4′), 24.6 (C-3′).

For **8a–β**: ^{1}H NMR ($CDCl_3$): δ 7.80–7.40 (m, 15H, 3 × Ph), 4.70 (d, 1H, CH_2Ph, *J* = 11.6 Hz), 4.58–4.46 (m, 5H, CH_2Ph), 4.31 (dd, 1H, H-3, *J* = 5.6, 5.6 Hz), 4.04–3.96 (m, 1H, H-4), 3.96–3.88 (m, 1H, H-5), 3.86–3.78 (m, 1H, H-1), 3.76–3.68 (m, 2H, H-2, 6a), 3.62–3.54 (m, 1H, H-6b), 2.81 (t, 4H, 2 × 7′-CH_2, *J* = 4.8 Hz), 2.58–2.50 (m, 2H, 4′-CH_2), 2.46–2.28 (m, 6H, 5′-CH_2, 2 × 6′-CH_2), 2.02–1.94 (m, 2H, H-1′a, 1′b), 1.03 (s, 3H, 3′-Me); ^{13}C NMR ($CDCl_3$): δ 173.4 (C=N), 138.5, 138.1, 137.5, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 89.0 (C-2), 85.2 (C-3), 73.5 (CH_2Ph), 72.6 (C-5), 72.4 (CH_2Ph), 73.3 (C-6), 64.9 (C-4), 61.7 (C-1), 58.8 (C-5′), 54.9 (C-6′), 46.3 (C-7′), 40.1 (C-1′) 39.7 (C-4′), 26.0 (C-3′).

For **9a**: ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 15H, 3 × Ph), 4.62–4.28 (m, 6H, 6 × CH_2Ph), 3.94–3.88 (m, 1H, H-3), 3.87–3.64 (m, 2H, H-2, 5), 3.60–3.44 (m, 2H, H-6a, 6b), 3.42–3.14 (m, 2H, H-1, 4), 2.88–2.78 (m, 4H, 2 × 7′-CH_2), 2.64–2.50 (m, 3H, 5′-CH_2, H-2′), 2.48–2.30 (m, 4H, 2 × 6′-CH_2), 1.78–1.48 (m, 2H, 1′-CH_2), 1.12–1.02 (m, 3H, 3′-Me); ^{13}C NMR ($CDCl_3$): δ 138.4, 138.3, 138.2, 128.8, 128.6, 128.5, 127.9, 127.7, 90.8 (C-2), 90.2 (C-2), 86.4 (C-3), 86.3 (C-3), 85.4 (C-3), 85.2 (C-3), 83.7 (C-2), 83.5 (C-2), 73.7 (CH_2Ph), 73.6 (CH_2Ph), 73.2 (CH_2Ph), 73.1 (CH_2Ph), 72.6 (CH_2Ph), 72.5 (CH_2Ph), 72.2 (CH_2Ph), 72.1 (CH_2Ph), 72.0 (CH_2Ph), 71.5 (CH_2Ph), 70.4 (C-5), 70.3 (C-5), 68.6 (C-5), 68.4 (C-5), 65.3 (C-4), 65.2 (C-4), 64.1 (C-4), 64.0 (C-4), 60.8 (C-1), 59.9 (C-1), 59.1 (C-5′), 58.9 (C-5′), 58.7 (C-1), 54.8 (C-6′), 54.7 (C-6′), 52.4 (C-2′), 52.3 (C-2′), 51.4 (C-2′), 51.2 (C-2′), 46.4 (C-7′), 46.3 (C-7′), 43.8 (C-4′), 41.9 (C-1′), 41.2 (C-1′), 37.1 (C-1′), 36.7 (C-1′), 21.3 (C-3′), 21.1 (C-3′), 20.9 (C-3′), 20.7 (C-3′); HRMS calcd for $C_{36}H_{51}N_4O_4$ $[M+H]^+$ 603.3910, found 603.3840.

3.10. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-(1-piperazineethyl)-2-propylamine (10a)

Catalytic hydrogenation of **8a** and **9a** (0.04 g, 0.06 mmol) afforded **10a** (0.02 g, 80%) as pale yellow solid. Selected data: ^{1}H NMR (D_2O): δ 4.30–4.15 (m, 2H, H-1, 3), 4.10–3.60 (m, 5H, H-5, 2, 4, 6a, 6b), 3.40–3.10 (m, 5H, 2 × 7′-CH_2, H-2′), 3.05–2.65 (m, 8H, 2 × 6′-CH_2, 4′-CH_2, 5′-CH_2), 2.65–2.35 (m, 1H, H-1′a), 2.35–2.10 (m, 1H, H-1′b), 1.70–1.25 (m, 3H, 3′-Me); ^{13}C NMR (D_2O): δ 80.2, 80.1, 79.1, 78.8, 72.3, 68.9, 68.4, 65.8, 64.8, 64.6, 64.5, 61.7, 56.9,

56.2, 52.8, 49.2, 49.1, 43.2, 42.7, 42.4, 40.5, 22.2; HRMS calcd for $C_{15}H_{33}N_4O_4$ $[M+H]^+$ 333.2501, found 333.2509.

3.11. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-(1-morpholineethyl)-2-propylideneamine (8b) and 1-*C*-(2,3,6-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-(1-morpholineethyl)-2-propylamine (9b)

Reductive amination of **5** (0.17 g, 0.36 mmol) with 1-(2-aminoethyl)-morpholine (0.09 g, 0.72 mmol) afforded, after purification by flash chromatography using a linear gradient with CH_2Cl_2 and 0.1% Et_3N–MeOH (0–10%), a mixture of **8b** and **9b** (4:1, 0.14 g, 63%) as a syrup. Selected data: ^{1}H NMR ($CDCl_3$): δ 7.39–7.20 (m, 30H, 6 × Ph), 4.72–4.38 (m, 12H, 6 × CH_2Ph), 4.29 (dd, 1H, H-3_{8b}, J = 5.4, 5.4 Hz), 3.96–3.80 (m, 4H, H-1_{8b}, 4_{8b}, 3_{9b}, 5_{8b}), 3.80–3.72 (m, 2H, H-5_{9b}, 2_{9b}), 3.71–3.60 (m, 11H, 4 × 7′-CH_2, H-6_{9b}, 6_{8b}, 2_{8b}), 3.59–3.43 (m, 2H, H-6_{9b}, 6_{8b}), 3.42–3.14 (m, 3H, H-4_{9b}, 4_{8b}, 1_{9b}), 2.78–2.50 (m, 5H, H-$2'_{9b}$, $4'_{9a}$-CH_2, $4'_{8b}$-CH_2), 2.50–2.26 (m, 13H, $5'_{9b}$-CH_2, $5'_{8b}$-CH_2, 2 × $6'_{9b}$-CH_2, 2 × $6'_{8b}$-CH_2, H-$1'_{8b}$), 1.88–1.50 (m, 3H, $1'_{9b}$-CH_2, H-$1'_{8b}$), 1.32 (s, 3H, $3'_{8b}$-Me), 1.10–1.01 (m, 3H, $3'_{9b}$-Me); ^{13}C NMR ($CDCl_3$): δ 172.9 (C=N), 138.4, 138.3, 138.2, 138.1, 137.5, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 90.8 (C-2_{9b}), 90.0 (C-2_{8b}), 89.4 (C-2_{9b}), 86.3 (C-3_{8b}), 86.2 (C-3_{9b}), 85.3 (C-3_{9b}), 85.2 (C-3_{9b}), 83.7 (C-2_{9b}), 83.5 (C-2_{9b}), 73.9 (C-5_{8b}), 73.6 73.5, 73.2, 73.1, 72.7, 72.5, 72.4, 72.2, 71.9, 71.4 (6 × CH_2Ph and 2 × C-6), 70.3 (C-5_{9b}), 70.2 (C-5_{9b}), 68.5 (C-5_{9b}), 68.4 (C-5_{9b}), 67.2 (C-7′), 67.1 (C-7′), 65.5, 65.3, 65.2, 64.5, 64.2, 64.1, 62.7, 60.8, 59.9, 59.1, 58.6, 58.5, 58.2, 57.7 (C-1, C-4, and C-5′), 53.8 (C-6′), 53.5 (C-6′), 52.4 (C-2′), 52.3 (C-2′), 51.4 (C-2′), 51.2 (C-2′), 43.6 (C-4′), 43.4 (C-4′), 42.6 (C-$1'_{8b}$), 41.6, 40.8, 39.6, 37.1 (C-$1'_{9b}$), 36.5, 24.8 (C-$3'_{8b}$), 21.2 (C-$3'_{9b}$), 21.0 (C-$3'_{9b}$), 20.8 (C-$3'_{9b}$), 20.7 (C-$3'_{9b}$); HRMS calcd for $C_{36}H_{50}N_3O_5$ $[M+H]^+$ 604.3750, found 604.3718.

3.12. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-(1-morpholineethyl)-2-propylamine (10b)

Catalytic hydrogenation of **8b/9b** (0.11 g, 0.19 mmol) afforded solid **10b** (0.07 g, 78%) as a mixture of diastereomers. Selected data: ^{1}H NMR (D_2O): δ 4.28–4.14 (m, 4H), 4.10–3.60 (m, 28H), 3.50–3.34 (m, 6H), 3.33–3.06 (m, 12H), 2.98–2.74 (m, 6H), 2.70–2.60 (m, 8H), 2.55 (dd, 1H, J = 14.4, 7.6 Hz), 2.22 (dd, 1H, J = 14.4, 7.2 Hz), 2.16–1.98 (m, 4H), 1.56 (s, 3H), 1.44–1.25 (m, 12H); ^{13}C NMR (D_2O): δ 80.1, 79.7, 79.2, 77.4, 76.8, 76.5, 76.2, 74.7, 72.4, 70.2, 69.9, 69.3, 68.3, 67.5, 66.7, 66.1, 65.8, 64.6, 64.4, 63.2, 63.1, 63.0, 62.2, 61.8, 58.4, 58.3, 58.1, 56.5, 53.7, 53.6, 53.5, 52.7, 52.6, 52.3, 52.1, 51.6, 46.8, 40.1, 37.7, 34.9, 30.1, 29.1, 15.9; HRMS calcd for $C_{15}H_{32}N_3O_5$ $[M+H]^+$ 334.2341, found 334.2333.

3.13. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-carboxymethyl-2-propylamine (9c)

Reductive amination of **5** (0.30 g, 0.61 mmol) with glycine gave, after purification by flash chromatography using a linear gradient with EtOAc and 0.1% Et_3N–MeOH (0–30%), **9c** (0.20 g, 72%) as a syrup. Selected data: ^{1}H NMR ($CDCl_3$): δ 7.38–7.14 (m, 60H), 4.60–4.24 (m, 28H), 4.22–3.72 (m, 12H), 3.68–2.99 (m, 28H), 2.81 (d, 1H, J = 14.4 Hz), 2.29 (dd, 2H, J = 13.6, 6.8 Hz), 1.94–1.66 (m, 4H), 1.58–1.42 (m, 4H), 1.19 (d, 6H, J = 6.8 Hz), 1.14 (d, 6H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ 177.0, 173.2, 171.5, 171.4, 170.9, 170.7, 138.7, 138.6, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 137.7, 137.6, 137.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 89.8, 88.5, 86.2, 86.1, 84.7, 83.2, 82.9, 73.5, 73.4, 73.2, 72.9, 72.6, 72.4, 72.3, 72.2, 72.1, 72.0, 71.8, 70.9, 70.8, 70.1, 69.7, 68.5, 66.2, 65.9, 65.1, 64.6, 64.1, 61.5, 58.1, 57.0, 55.3, 54.7, 54.2, 48.5, 48.1, 47.7, 47.4, 41.4, 35.1, 33.2, 32.8, 25.2, 22.8, 18.2, 18.0; HRMS calcd for $C_{32}H_{41}N_2O_6$ $[M+H]^+$ 549.2964, found 549.2978.

3.14. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-carboxymethyl-2-propylamine (10c)

Catalytic hydrogenation of **9c** (0.08 g, 0.15 mmol) gave, after purification on a Biogel P2 column eluted by water, **10c** (0.03 g, 80%) as a solid. Selected data: ^{1}H NMR (D_2O): δ 4.20–4.06 (m, 2H, H-2, H-3), 4.02–3.92 (m, 1H, H-3), 3.92–3.78 (m, 3H, 2 × H-5, 2), 3.78–3.50 (m, 9H, H-6, H-4′, H-1), 3.50–3.40 (m, 2H, 2 × H-2′), 3.30–3.20 (m, 2H, H-4, H-1), 3.14–3.06 (m, 1H, H-4), 2.04–1.93 (m, 4H, 2 × H-1′), 1.39 and 1.35 (d and d, 6H each, J = 6.4 Hz, 3′-CH_3); ^{13}C NMR (D_2O): δ 171.9 (COOH), 81.1 (C-2), 77.3 (C-3), 77.2 (C-3), 76.9 (C-2), 70.9 (C-5), 70.1 (C-5), 65.4 (C-5), 63.3 (C-6), 63.2 (C-6), 61.9 (C-4), 58.7 (C-7), 57.8 (C-1), 53.5 (C-2′), 53.2 (C-2′), 46.6 (C-4′), 35.4 (C-1′), 16.1 (C-3′), 15.9 (C-3′); HRMS calcd for $C_{11}H_{23}N_2O_6$ $[M+H]^+$ 279.1556, found 279.1565.

3.15. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-ethoxycarbonylethyl-2-propylamine (9d)

To the solution of ketone **5** (0.26 g, 0.53 mmol) in anhydrous MeOH (20 mL) was added β-alanine ethyl ester (0.16 g, 1.00 mmol), followed by sodium cyanoborohydride (0.66 g, 1.00 mmol) and anhydrous $ZnCl_2$ (0.03 g, 0.27 mmol) at room temperature. The reaction mixture was stirred for 2 days and concentrated. Usual work-up and purification by flash chromatography using a linear gradient with CH_2Cl_2 and 0.1% Et_3N–MeOH (0–20%) gave **9d** (0.16 g, 52%) as a syrup. Selected data: ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 30H, Ph), 4.64–4.36 (m, 12H, CH_2Ph), 4.18–4.06 (m, 4H, 2 × 6′-CH_2), 3.96–3.88 (m, 2H, 2 × H-3), 3.88–3.80 (m, 1H, H-5), 3.80–3.72 (m, 2H, H-5, 2), 3.70–3.62 (m, 1H, H-2), 3.60–3.44 (m, 4H, 2 × 6-CH_2), 3.38–3.14 (m, 4H, 2 × H-4, 1), 2.88–2.84 (m, 2H, 2 × H-4′), 2.80–2.60 (m, 4H, 2 × H-4′, 2′), 2.50–2.38 (m, 4H, 2 × 5′-CH_2), 1.74–1.48 (m, 4H, 2 × H-1′), 1.30–1.20 (m, 6H, 2 × 7′-Me), 1.10–1.02 (m, 6H, 2 × 3′-Me); ^{13}C NMR ($CDCl_3$): δ 173.0 (CO), 138.4, 138.3, 138.2, 138.1, 128.7, 128.6, 128.0, 127.9, 127.8, 90.7 (C-2), 90.0 (C-2), 86.4 (C-3), 86.2 (C-3), 85.3 (C-3), 85.2 (C-3), 83.6 (C-2), 83.5 (C-2), 73.6 (CH_2Ph), 73.1 (CH_2Ph), 73.0 (CH_2Ph), 72.6 (CH_2Ph), 72.5 (CH_2Ph), 72.2 (CH_2Ph), 72.1 (CH_2Ph), 72.0 (CH_2Ph), 71.9 (CH_2Ph), 71.4 (CH_2Ph), 70.3 (C-5), 70.2 (C-5), 68.7 (C-5), 68.6 (C-5), 65.2 (C-4), 64.9 (C-4), 64.1 (C-4), 64.0 (C-4), 61.1 (C-1), 60.6 (C-6′), 60.5 (C-6′), 59.8 (C-1), 59.3 (C-1), 57.9 (C-1), 52.4 (C-2′), 52.1 (C-2′), 51.0 (C-2′), 50.9 (C-2′), 42.5 (C-4′), 41.6 (C-1′), 40.8 (C-1′), 37.1 (C-1′), 36.6 (C-1′), 35.2 (C-5′), 35.1 (C-5′), 21.1 (C-3′), 20.9 (C-3′), 20.8 (C-3′), 20.7 (C-3′), 14.4 (C-7′); HRMS calcd for $C_{35}H_{47}$ N_2O_6 $[M+H]^+$ 591.3434, found 591.3434.

3.16. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-ethoxycarbonylethyl-2-propylamine (10d)

Catalytic hydrogenation of **9d** afforded **10d** (0.03 g, 91%) as a solid. Selected data: ^{1}H NMR (D_2O): δ 4.18 (q, 4H, 2 × 6′-CH_2, J = 6.8 Hz), 4.16–3.78 (m, 6H, 2 × H-2, 3, 5), 3.78–3.52 (m, 5H, 2 × H-6, H-1), 3.52–3.08 (m, 9H, 2 × H-4′, 2′, 4, H-1), 2.90–2.70 (m, 4H, 2 × 5′-CH_2), 2.40–2.28 (m, 1H, H-1′), 2.10–1.88 (m, 3H, H-1′, 1′-CH_2), 1.46–1.30 (m, 6H, 2 × 3′-Me), 1.30–1.18 (t, 6H, 2 × 7′-Me, J = 6.8 Hz); ^{13}C NMR (D_2O): δ 172.6 (CO_2Et), 80.1 (C-2 or C-3), 77.5 (C-2 or C-3), 76.9 (C-2 or C-3), 76.6 (C-2 or C-3), 74.8 (C-2 or C-3), 70.2 (C-5), 70.0 (C-5), 69.6 (C-5), 67.2 (C-4), 66.2 (C-4), 64.9 (C-4), 63.2 (C-6), 63.0 (C-6), 62.5 (C-6′), 62.0 (C-4), 58.1 (C-1), 57.5 (C-1), 57.3 (C-1), 53.3 (C-2′), 52.1 (C-2′), 52.0 (C-2′), 40.3 (C-4′), 40.2 (C-4′), 35.1 (C-1′), 34.9 (C-1′), 30.7 (C-5′),

30.6 (C-5′), 29.1 (C-1′), 15.8 (C-3′), 15.7 (C-3′), 13.3 (C-7′); HRMS calcd for $C_{14}H_{29}N_2O_6$ $[M+H]^+$ 321.2025, found 321.2020.

3.17. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-methoxycarbonylethyl-2-propylamine (9e)

Reductive amination of **5** (0.15 g, 0.30 mmol) with β-alanine ethyl ester (0.09 g, 0.60 mmol) in MeOH gave a mixture of methyl and ethyl esters. Purification by flash chromatography using a linear gradient with CH_2Cl_2 and 0.1% Et_3N–MeOH (0–20%) gave ethyl ester **9d** (0.03 g, 20%) and methyl ester **9e** (0.09 g, 54%) as a syrup and as a mixture of diastereomers. Selected data for **9e**: ^{1}H NMR ($CDCl_3$): δ 7.40–7.18 (m, 30H, 6 × Ph), 4.60–4.34 (m, 12H, 6 × CH_2Ph), 3.96–3.88 (m, 2H, H-3, 2), 3.88–3.70 (m, 2H, 2 × H-5), 3.70–3.60 (m, 8H, 2 × 6′-Me, H-3, 2), 3.60–3.44 (m, 4H, 2 × 6-CH_2), 3.44–3.04 (m, 4H, 2 × H-1, 4), 3.00–2.82 (m, 2H, 2 × H-4′), 2.82–2.62 (m, 4H, 2 × H-4′, 2′), 2.54–2.40 (m, 4H, 2 × 5′-CH_2), 1.78–1.50 (m, 4H, 2 × 1′-CH_2), 1.10–1.02 (m, 6H, 2 × 3′-Me); ^{13}C NMR ($CDCl_3$): δ 173.4 (CO), 173.3 (CO), 173.2 (CO), 138.4, 138.3, 138.2, 138.1, 138.0, 128.7, 128.6, 128.0, 127.9, 127.8, 90.5 (C-2 or C-3), 89.5 (C-2 or C-3), 86.1 (C-2 or C-3), 84.7 (C-2 or C-3), 83.7 (C-2 or C-3), 83.6 (C-2 or C-3), 73.7 (*C*H_2Ph), 73.6 (*C*H_2Ph), 73.1 (C-6), 73.0 (C-6), 72.5 (C-6), 72.1 (*C*H_2Ph), 72.0 (*C*H_2Ph), 71.9 (*C*H_2Ph), 71.6 (*C*H_2Ph), 71.5 (*C*H_2Ph), 70.2 (C-5), 70.1 (C-5), 68.8 (C-5), 68.5 (C-5), 65.2 (C-4), 65.0 (C-4), 64.2 (C-4), 64.1 (C-4), 61.4 (C-1), 59.8 (C-1), 59.2 (C-1), 57.8 (C-1), 52.9 (C-2′), 52.7 (C-2′), 51.9 (C-6′), 51.8 (C-6′), 51.2 (C-2′), 51.0 (C-2′), 42.3 (C-4′), 42.2 (C-4′), 42.1 (C-4′), 36.4 (C-1′), 36.0 (C-1′), 34.6 (C-5′), 34.5 (C-5′), 34.4 (C-5′), 20.7 (C-3′), 20.6 (C-3′), 20.3 (C-3′); HRMS calcd for $C_{34}H_{45}N_2O_6$ $[M+H]^+$ 577.3277, found 577.3267.

3.18. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-carboxyethyl-2-propylamine (10f)

Hydrogenation of **9e** (0.09 g, 0.16 mmol) in HOAc–H_2O led to the hydrolysis of methyl ester to carboxylic acid. Purification on Biogel P2 column eluted with water gave a mixture of **10f** (0.04 g, 91%) as a white solid. Selected data for two sets of diastereomers (A and B): ^{1}H NMR (D_2O): δ 4.34–3.96 (m, 6H), 3.96–3.56 (m, 10H), 3.56–3.44 (m, 2H, 2 × H-2′), 3.42–3.18 (m, 6H), 3.18–3.08 (m, 1H), 2.90–2.70 (m, 2H, $4'_B$-CH_2), 2.70–2.50 (m, 5H, $5'_A$-CH_2, $1'_A$-CH_2, H-$1'_B$), 2.46–2.30 (m, 2H, $5'_B$-CH_2), 2.30–2.14 (m, 1H, H-$1'_B$), 2.10–1.95 (m, 2H, 2 × H-$1'_A$), 1.50–1.30 (m, 6H, 3′-Me); ^{13}C NMR (D_2O): δ 180.5, 178.2, 80.9, 80.2, 79.0, 77.3, 77.1, 76.9, 76.8, 75.4, 72.5, 70.6, 70.4, 70.2, 68.4, 65.7, 64.7, 63.3, 63.2, 61.9, 61.8, 58.3, 57.7, 57.1, 53.2, 53.1, 51.9, 51.7, 41.8, 41.7, 41.6, 40.1, 37.7, 37.1, 35.5, 35.3, 32.8, 32.7, 32.5, 32.6, 16.0, 15.9, 15.8; HRMS calcd for $C_{12}H_{25}N_2O_6$ $[M+H]^+$ 293.1712, found 293.1700.

3.19. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-hexyl-2-propylideneamine (8g) and 1-*C*-(2,3,6-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-hexyl-2-propylamine (9g)

Reductive amination of **5** (0.09 g, 0.19 mmol) with hexylamine (0.07 g, 0.76 mmol) gave, after flash chromatography using a linear gradient with EtOAc and 0.1% Et_3N–MeOH (0–30%), a mixture of **8g** and **9g** (0.04 g, 22%) as a syrup. Selected data: ^{1}H NMR ($CDCl_3$): δ 7.39–7.19 (m, Ph), 4.60–4.32 (m, CH_2Ph, H-5, 3), 4.03–3.81 (m, H-1, 4), 3.78–3.63 (m, H-2, 6), 3.60–3.51 (m, H-6), 3.40–-3.28 (m, H-1), 2.96–2.84 (m, H-4′), 2.72–2.64 (m, H-4′), 2.48–2.36 (m, H-2′, 4′), 2.24–2.06 (m, H-4′, H-1′), 2.04–2.03 (m, H-1′), 1.95 (s, 3′-Me), 1.90–1.64 (m, H-1′), 1.38 (m, 3′-Me), 1.33–1.14 (m, 5′,6′,7′,8′-CH_2–), 0.88 (m, 9′-Me); ^{13}C NMR ($CDCl_3$): δ 172.1 (C═N), 138.3, 138.2, 138.0, 137.9, 137.6, 137.3, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 88.2, 87.7, 85.3, 84.0, 73.7 (*C*H_2Ph), 72.9, 72.4 (C-6), 72.3 (*C*H_2Ph), 72.2 (*C*H_2Ph), 72.1 (*C*H_2Ph), 71.8 (*C*H_2Ph), 68.8, 68.4, 68.2, 67.6, 65.0, 64.4, 43.3, 38.6, 32.0, 31.7, 28.6, 25.2, 24.6, 22.8, 22.7, 14.2; HRMS calcd for $C_{36}H_{51}N_2O_4$ $[M+H]^+$ 575.3848, found 575.3820.

3.20. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-hexadecyl-2-propylamine (9h)

Reductive amination of **5** (0.17 g, 0.35 mmol) with hexadecyl amine (0.17 g, 0.71 mmol) gave, after purification by flash chromatography using a linear gradient with CH_2Cl_2 and 0.1% Et_3N–MeOH (0–10%), **9h** (0.19 g, 78%) as a syrup. Selected data for two major diastereomers (A and B): ^{1}H NMR ($CDCl_3$): δ 7.38–7.18 (m, 30H, 6 × Ph), 4.78–4.35 (m, 12H, 6 × CH_2Ph), 4.30–4.25 (m, 1H, H-3_B), 3.95–3.88 (m, 2H, H-3_A, H-1_B), 3.88–3.70 (m, 3H, H-5_A, H-5_B, H-4_B), 3.70–3.59 (m, 4H, H-6_A, H-6_B, H-2_A, H-2_B), 3.58–3.43 (m, 2H, H-$6'_A$, H-6_B), 3.33–3.22 (m, 3H, H-1_A, 2 × H-4_A), 3.21–3.14 (m, 1H, H-1_A), 2.76–2.67 (m, 1H, H-$2'_A$), 2.66–2.52 (m, 2H, H-$2'_A$, H-$4'_A$), 2.50–2.37 (m, 2H, H-$4'_A$, H-$4'_B$), 2.30–2.24 (m, 1H, H-$1'_B$), 1.82–1.74 (m, 1H, H-$1'_B$), 1.62–1.48 (m, 2H, H-$1'_A$), 1.48–1.32 (m, 2H, H-$5'_A$, H-$5'_B$), 1.32–1.14 (m, 58H, $3'_B$-Me, 6′–18′ –CH_2–), 1.04 (d, 3H, $3'_A$-Me, J = 6.4 Hz), 0.80–0.90 (2d, 6H, 2 × 19′-Me, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 138.3, 138.2, 137.7, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.7, 90.6 (C-2_A), 89.6 (C-2_B), 86.3 (C-3_A), 86.2 (C-3_B), 83.8 (C-2_A), 73.7 (*C*H_2Ph), 73.6 (*C*H_2Ph), 73.1 (C-6), 72.7 (*C*H_2Ph), 72.6 (C-6), 72.5 (C-6), 72.1 (*C*H_2Ph), 72.0 (*C*H_2Ph), 71.5 (*C*H_2Ph), 70.2 (C-5_A), 68.6 (C-5_A), 65.3 (C-4_A), 65.2 (C-4_B), 64.4 (C-4_A), 63.9 (C-5_B), 61.2 (C-1_A), 59.3 (C-1_A), 52.6 (C-$2'_A$), 52.5 (C-$2'_A$, 47.5 (C-$4'_A$), 43.9 (C-$4'_B$), 42.5 (C-$1'_B$), 41.5 (C-$1'_A$), 32.1 (C-6′–18′), 30.8 (C-$5'_A$), 35.6 (C-$5'_A$), 29.9 (C-6′–18′), 29.8 (C-6′–18′), 28.5 (C-6′–18′), 27.7 (C-6′–18′), 27.5 (C-6′–18′), 22.9 (C-6′–18′), 20.6 (C-$3'_A$), 14.3 (C-19′); HRMS calcd for $C_{46}H_{71}N_2O_4$ $[M+H]^+$ 715.5414, found 715.3376.

3.21. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-hexadecyl-2-propylamine (10h)

Hydrogenation of **9h** (0.09 g, 0.13 mmol) and purification on a Biogel P2 column eluted with water yielded **10h** (0.05 g, 92%) as a white solid. Selected data (NMR spectra were very complicated due to presence of diastereomers): ^{1}H NMR (CD_3OD): δ 4.30–4.22 (m, 1 H), 4.07–3.35 (m, 12H), 3.24–3.09 (m, 2H), 3.04–2.74 (m, 5H), 2.66–2.38 (m, 3H), 2.34–2.21 (m, 2H), 2.07–1.99 (m, 1H), 1.83–1.52 (m, 5H), 1.41–1.20 (m, 58H), 0.80–0.90 (2d, 6H, 19′-Me, J = 6.8 Hz); ^{13}C NMR (CD_3OD): δ 179.3, 172.9, 172.2, 82.9, 81.4, 81.3, 80.6, 79.4, 79.2, 78.6, 78.3, 78.2, 77.9, 77.6, 77.3, 77.1, 71.6, 71.3, 70.7, 70.6, 70.2, 70.1, 68.9, 68.3, 66.8, 66.1, 65.6, 65.5, 64.5, 64.3, 64.2, 63.5, 63.1, 62.9, 62.0, 59.8, 57.9, 57.1, 54.8, 54.7, 53.1, 52.6, 45.2, 44.9, 43.6, 43.2, 38.0, 37.2, 35.7, 32.8, 32.4, 31.9, 29.7, 29.6, 29.4, 29.3, 29.2, 27.5, 27.3, 27.0, 26.9, 24.8, 23.4, 22.6, 16.9, 16.8, 13.6; HRMS calcd for $C_{25}H_{53}N_2O_4$ $[M+H]^+$ 445.4005, found 445.4048.

3.22. 1-*C*-(2,3,6-Tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-(2′,3′-di-*O*-benzyl-5′-deoxyuridine-5′)-2-propylamine (9i)

Reductive amination of **5** (0.15 g, 0.30 mmol) with 5′-amino-2′,3′-di-*O*-benzyl-5′-deoxyuridine[14] (0.15 g, 0.36 mmol) gave, after flash chromatography using a linear gradient with EtOAc–10% NH_4OH–MeOH (0–30%), **9i** (0.15 g, 55%) as a syrup. Selected data: ^{1}H NMR ($CDCl_3$): δ 7.40–7.10 (m, 26H, Ph, H-6″), 5.62 (d, 1H, H-7″, J = 8.0 Hz), 5.53 (d, 1H, H-1″, J = 3.6 Hz), 4.70–4.35 (m, 11H, 5 × CH_2Ph, H-4″), 4.28–4.21 (m, 1H, H-2″), 3.96–3.87 (m, 2H, H-3, 3″), 3.87–3.74 (m, 2H, H-5, 1), 3.72–3.60 (m, 2H, H-2, 4), 3.60–3.44 (m, 2H, H-6a,b), 3.26–3.04 (m, 3H, H-2′, H-5″a,b), 2.0–1.84

(m, 1H, H-1′a), 1.42 (d, 1H, H-1′b, J = 15.2 Hz), 1.17 (d, 3H, H-3′, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 163.8 (CO-Ur), 149.8 (CO-Ur), 142.8 (C-6$_B$), 137.9, 137.4, 137.3, 137.1, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 102.6 (C-7″), 93.2 (C-1″), 86.8 (C-2), 84.8 (C-3″), 78.6 (C-4″), 78.2 (C-2″), 77.7 (C-3), 73.5 (CH_2Ph), 72.8 (CH_2Ph), 72.5 (CH_2Ph), 72.0 (C-6), 71.7 (CH_2Ph), 69.5 (C-5), 64.4 (C-4), 62.9 (C-1), 53.7 (C-2′), 46.5 (C-5″), 33.4 (C-1′), 18.8 (C-3′); HRMS calcd for $C_{53}H_{61}N_4O_9$ $[M+H]^+$ 897.4420, found 897.4422.

3.23. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-(5′-deoxy-C5,C6-tetrahydro-uridine-5′)-2-propylamine (10i)

Hydrogenation of **9i** (0.11 g, 0.12 mmol) and purification on a Biogel P2 eluted with water yielded **10i** (0.07 g, 92%) as a syrup. Selected data for two major diastereomers: ^{1}H NMR (D_2O): δ 5.82–5.55 (m, 2H, 2 × H-1″), 4.48–3.84 (m, 12H, 2 × H-2″, 3″, 4″, 2, 3, 5), 3.82–3.02 (m, 18H, 2 × H-1, 4, 6-CH_2, 2′, 5″, 6″-CH_2), 2.95–2.50 (m, 4H, 2 × 7″-CH_2), 2.22–1.58 (m, 4H, 2 × 1′-CH_2), 1.50–1.15 (m, 6H, 2 × 3′-Me); ^{13}C NMR (D_2O): δ 154.4 (CO-Ur), 154.3 (CO-Ur), 90.3 (C-1$_C$), 89.8 (C-1$_C$), 79.7, 78.6, 78.2, 77.9, 76.6, 76.5, 76.3, 71.4, 71.3, 71.1, 70.7, 70.6, 70.0, 69.1, 63.2 (C-6), 62.1, 58.4 (C-1), 58.3 (C-1), 52.9 (C-2′), 47.0 (C-5″), 46.8 (C-5″), 41.6, 38.1 (C-6″), 37.8 (C-6″), 34.8 (C-1′), 30.2, 16.1 (C-3′), 15.7 (C-3′); HRMS calcd for $C_{18}H_{33}N_4O_9$ $[M+H]^+$ 449.2247, found 449.2246.

3.24. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-acetone (11)

Hydrogenation of **5** (0.12 g, 0.39 mmol) gave, after purification on Biogel P2 column eluted with water, **11** (0.06 g, 70%), an anomeric mixture as a syrup. ^{1}H NMR (D_2O): δ 4.30–3.82 (m, 7H, H-1, 2 × H-2, 5, 3), 3.82–3.58 (m, 5H, H-1, 2 × 6-CH_2), 3.58–3.40 (m, 2H, 2 × H-4), 3.28–3.00 (m, 4H, 2 × H-1′), 1.80 (s, 6H, 2 × 3′-Me); ^{13}C NMR (D_2O): δ 210.9 (CO), 77.7 (C-2), 76.6 (C-3), 75.8 (C-3), 75.1 (C-2), 69.6 (C-5), 68.8 (C-5), 67.3 (C-4), 63.0 (C-6), 62.5 (C-4), 67.4 (C-1), 56.6 (C-1), 43.2 (C-1′), 43.0 (C-1′), 23.4 (C-3′); HRMS calcd for $C_9H_{18}NO_5$ $[M+H]^+$ 220.1184, found 220.1176.

3.25. 1-*C*-(*N*-Benzyl-2,3,6-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-acetone (12)

To a suspension of iminosugar **5** (0.61 g, 1.24 mmol) in DMF (10 mL) was added benzyl bromide (0.37 mL, 3.11 mmol) followed by K_2CO_3 (0.38 g, 2.73 mmol). The mixture was stirred at 50 °C overnight. Usual work-up and purification by chromatography (0–50%, hexanes–EtOAc) gave **12** (0.93 mg, 75%) as a syrup. Selected data for major anomer: ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 20H, 4 × Ph), 4.60–4.40 (m, 5H, CH_2Ph), 4.30 (d, 1H, CH_2Ph, J = 12.0 Hz), 4.10 (d, 1 H, H-2, J = 5.2 Hz), 4.00–3.90 (m, 2H, H-3, NCH_2Ph), 3.80–3.60 (m, 3H, H-1, H-5, NCH_2Ph), 3.45 (m, 2H, H-6a, 6b), 3.30 (d, 1H, H-4, J = 4.4 Hz), 2.70 (dd, 1H, H-1′a, J = 17.2, 8.0 Hz), 2.20 (dd, 1H, H-1′b, J = 5.2 Hz), 1.80 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 208.0 (CO), 139.4, 138.3, 138.2, 137.7, 129.3, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 83.4 (C-3), 83.3 (C-2), 73.5 (CH_2Ph), 72.6 (CH_2Ph), 72.3 (C-6), 71.5 (CH_2Ph), 71.1 (C-4), 69.8 (C-5), 63.5 (C-1), 62.2 (NCH_2Ph), 44.4 (C-1′), 30.4 (C-3′); HRMS calcd for $C_{37}H_{42}NO_5$ $[M+H]^+$ 580.3062, found 580.3057.

3.26. 1-*C*-(*N*-Benzyl-5-*O*-acetyl-2,3,6-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-acetone (13)

A solution of **12** (0.85 g, 1.46 mmol) in pyridine (9 mL) and Ac_2O (6 mL) was stirred at room temperature for 12 h. Usual work-up and chromatography (0–20%, hexanes–EtOAc) gave **13** (0.78 g, 85%) as a syrup. Selected data for major anomer: ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 20H, 4 × Ph), 5.05 (ddd, 1H, H-5, J = 2.8, 6.8, 6.8 Hz), 4.60–4.30 (m, 5H, CH_2Ph), 4.25 (d, 1H, CH_2Ph, J = 11.6 Hz), 4.0 (d, 1H, H-2, J = 5.2 Hz), 3.95 (d, 1H, NCH_2Ph, J = 14.4 Hz), 3.88 (br s, 1H, H-3), 3.76 (d, 1H, NCH_2Ph, J = 14.4 Hz), 3.70 (dd, 1H, H-6a, J = 11.2, 2.8 Hz), 3.52–3.59 (m, 1H, H-1), 3.44 (dd, 1H, H-6b, J = 11.2, 6.8 Hz), 3.22 (dd, 1H, H-4, J = 6.8, 2.4 Hz), 2.7 (dd, 1H, H-1′a, J = 17.6, 9.2 Hz), 2.3 (dd, 1H, H-1′b, J = 17.6, 4.8 Hz), 1.94 (s, 3H, OAc), 1.86 (s, 3H, 3′-Me); ^{13}C NMR ($CDCl_3$): δ 208.3 (CO), 170.6 (Ac), 139.9, 138.3, 138.0, 128.8, 128.6, 128.5, 128.0, 127.9, 127.8, 127.7, 127.2, 83.0 (C-2), 81.5 (C-3), 73.9 (C-5), 74.0 (CH_2Ph), 73.0 (CH_2Ph), 72.3 (CH_2Ph), 71.2 (CH_2Ph), 70.8 (C-4), 69.6 (C-6), 63.2 (C-1), 60.5 (NCH_2Ph), 44.1 (C′-1), 30.7 (C-3′), 21.4 (Ac); HRMS calcd for $C_{39}H_{44}NO_6$ $[M+H]^+$ 622.3168, found 622.3169.

3.27. 1-*C*-(*N*-Benzyl-2,3,6-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-galactosyl)-2-*N*-hexyl-2-propylamine (14)

Reductive amination of **13** (0.11 g, 0.18 mmol) with hexylamine (0.05 g, 0.55 mmol) gave, after purification by flash chromatography using a linear gradient with CH_2Cl_2 and 0.1% Et_3N–MeOH (0–10%), **14** (0.08 g, 66%) as a syrup. Selected data: ^{1}H NMR ($CDCl_3$): δ 7.40–7.14 (m, 40H, 8 × Ph), 5.02–4.96 (m, 1H, H-5), 4.58–4.20 (m, 12H, 6 × CH_2Ph), 3.99–3.65 (m, 10H), 3.46–3.14 (m, 9H), 2.54–2.18 (m, 6H), 1.82–1.73 (m, 2H), 1.60–1.15 (m, 16H, 8 × –CH_2–), 0.93–0.78 (m, 12H, 2 × 9′-Me, 3′-Me); ^{13}C NMR ($CDCl_3$): δ 136.7, 135.9, 135.4, 127.0, 126.0, 125.9, 125.4, 125.3, 125.2, 124.9, 81.0, 80.3, 75.0, 74.7, 74.4, 70.9, 69.9, 69.5, 68.9, 67.5, 67.4, 60.8, 58.4, 48.6, 44.9, 33.7, 29.5, 28.2, 24.8, 20.3, 17.8, 11.7; HRMS calcd for $C_{43}H_{57}N_2O_4$ $[M+H]^+$ 665.4318, found 665.4343.

3.28. 1-*C*-(1,4-Dideoxy-1,4-imino-D-galactosyl)-2-*N*-hexyl-2-propylamine (10g)

Hydrogenation of **14** (0.07 g, 0.11 mmol) gave, after purification on a Biogel P2 column eluted with water, **10g** (0.02 g, 60%) as a solid. Selected data: ^{1}H NMR (D_2O): δ 4.23–4.16 (m, 4H, 2 × H-2, 3), 4.00–3.93 (m, 2H, 2 × H-5), 3.88–3.74 (m, 4H, 2 × H-1, 6a), 3.68 and 3.65 (2d, 1H each, 2 × H-6b, J = 4.91 Hz), 3.57–3.48 (m, 2H, 2 × H-4), 3.48–3.36 (m, 2H, 2 × H-2′), 3.16–3.0 (m, 4H, 2 × 4′-CH_2), 2.50–2.41 (m, 1H, H-1′), 2.40–2.25 (m, 1H, H-1′), 2.16–2.06 (m, 1H, H-1′), 2.03–1.92 (m, 1H, H-1′), 1.63–1.59 (m, 4H, 2 × 5′-CH_2), 1.48–1.21 (m, 18H, 2 × 3′-Me, 6 × –CH_2–), 0.92–0.81 (m, 6H, 2 × 9′-Me); ^{13}C NMR (D_2O): δ 77.1 (C-2 or C-3), 76.6 (C-2 or C-3), 76.2 (C-2 or C-3), 74.3 (C-2 or C-3), 69.9 (C-5) 69.8 (C-5), 68.0 (C-4), 67.8 (C-4), 62.8 (C-6), 58.7 (C-1), 58.6 (C-1), 51.8 (C-2′), 51.2 (C-2′), 45.1 (C-5′), 45.0 (C-5′), 30.5 1 (C-7′), 29.2 (C-1′), 28.6 (C-1′), 25.8 (C-5′) 25.7 (C-5′), 25.5 (C-6′), 21.8 (C-8′), 15.7 (C-3′), 15.6 (C-3′), 13.3 (C-9′); HRMS calcd for $C_{15}H_{33}N_2O_4$ $[M+H]^+$ 305.2440, found 305.2433.

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