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2-Deoxy-disaccharide approach to natural and unnatural glycosphingolipids synthesis

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Abstract

2-Deoxy-disaccharides were easily converted into glycosylphytosphingosines, as new and efficient precursors of natural and unnatural glycosphingolipids.

1. Introduction

Recently, the development of the synthetic strategies of naturally occurring glycosphingolipids, such as α-galactosylceramide **1** (Fig. 1), have received great attention, due to their interesting biological properties.[1] Glycosphingolipids are amphipathic compounds, consisting of sugar and ceramide moieties. Structurally, the ceramide is formed from two units: a sphingoid base, which is an amino alcohol such as (2*S*,3*S*,4*R*)-2-amino-hexadecane-1,3,4-triol **2** and a long chain fatty acid, such as (*R*)-2-hydroxy-tetracosanoic acid **3** (Fig. 1).

Usually, the last step in the total syntheses of these molecules is the coupling of a ceramide with a given sugar, and several protocols have been developed for this purpose.[1–6] However, classical regio- and stereospecific glycosylation procedures have involved multiple step sequences, which include the protection and deprotection strategies of the sugar moiety, its activation as glycosyl donor and the use of a reaction promoter for the coupling, generally a Lewis acid. The yields are variable from poor to good.[7–10]

Glycosphingolipids are essential both in inter- and intramolecular communications. Simultaneously, they play key-roles in the regulation of cell growth and differentiation and antibody interactions.[11–19] Owing to their recognised importance, efficient methods for their preparation are continuously requested.

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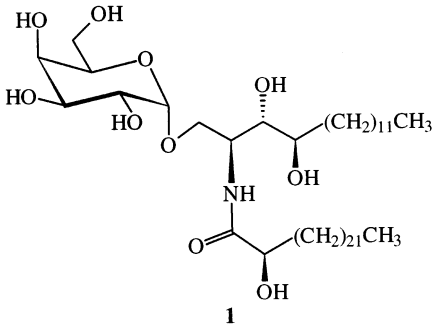
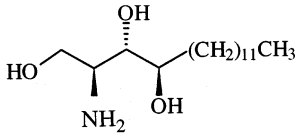


1



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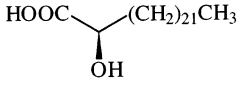

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Figure 1.

A recent achievement of our group was a simple and efficient synthesis of 2-deoxy-sugars: protected glycals, derived from mono-, di- and trisaccharides were easily converted in very excellent yields into the corresponding 2-deoxy-sugars, by reaction with aqueous mercuric(II) acetate/sodium borohydride.[20]

The reaction shows a wide generality and makes 2-deoxy-sugars from more complex compounds easily available in one reaction flask and in large amounts, such as the perbenzylated derivatives of D-melibial [3,4-di-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol], D-lactal [3,6-di-*O*-benzyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol] and D-cellobial [3,6-di-*O*-benzyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol], prepared from the corresponding naturally occurring disaccharides.[20]

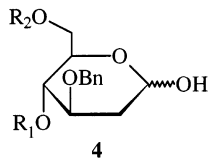
Stimulated by the above, we considered the exploitation of the reactivity and the synthetic utility of 2-deoxy-disaccharides to be of interest, particularly with the aim of finding new and efficient strategies for the preparation of complex biologically active natural compounds. Now we report a practical and enantioselective route, which makes easily available glycosyl-phytosphingosines, such as **6a**–**c** and **17**, as new and efficient precursors of both natural and unnatural glycosphingolipids. In fact, the strategy of the present syntheses focuses on the construction of the fragment which contains a sugar and a sphingoid base, starting from suitable 2-deoxy-disaccharides. The last step of this procedure is the easy formation of the amide linkage, thus avoiding lengthy protocols for the glycosylation combination.

Then, this new strategy shows high flexibility, allowing relatively inaccessible unnatural glycolipids from suitable 2-deoxy-disaccharides to be prepared, which can be studied in biomedical research.

Although the literature provides several important laboratory processes for the utilisation of carbohydrates as the source of chirality for preparing the sphingoid bases,[1,21–24] the direct use of disaccharide derivatives in this synthetic field, though very attractive, is completely unrealised.

2. Results and discussion

First, we explored the synthetic utility in this field of 2-deoxy-sugars **4a–c** (Fig. 2) derived from naturally occurring disaccharides melibiose, lactose and cellobiose, and easily available from the corresponding glycosyl-glycals according to our previously described protocol, in a large amount as well.[20]



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a: 2-deoxy-melibiose: R_1=Bn; R_2=2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl
b: 2-deoxy-lactose: R_1=2',3',4',6'-tetra-*O*-benzyl-β-D-galactopyranosyl; R_2=Bn
c: 2-deoxy-cellobiose: R_1=2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl; R_2=Bn

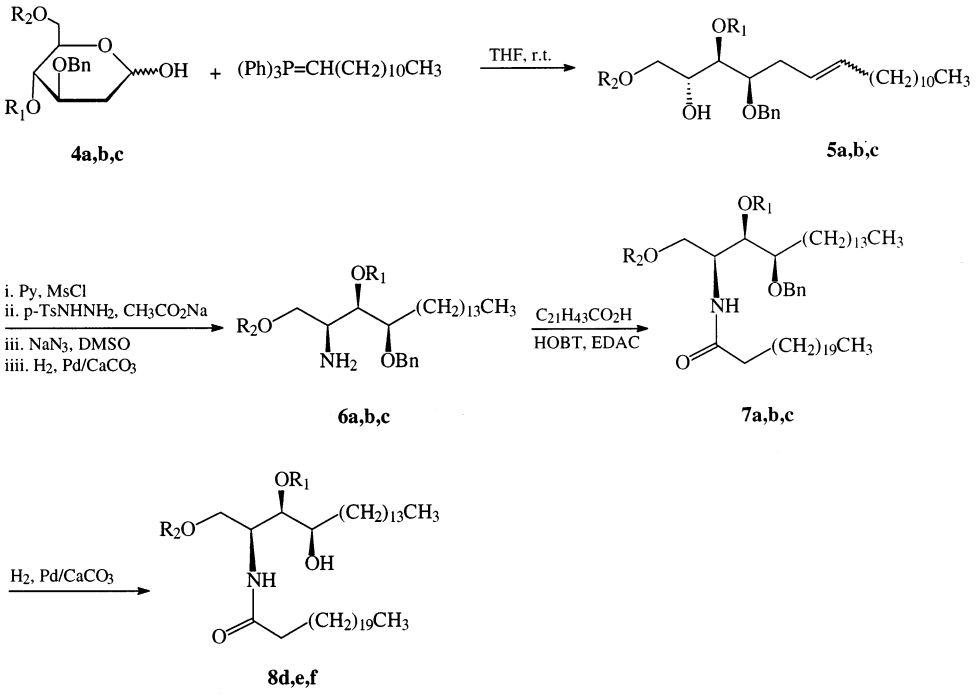
Figure 2.

However, the 2-deoxy-glucose moiety of **4a–c** does not possess the D-*arabino* configuration required for the natural phytosphingosine synthesis.[6] Thus, their D-*lyxo* configuration will give rise to the formation of both unnatural phytosphingosines and glycosphingolipids. Scheme 1 outlines the synthetic sequence leading to the new glycosyl-phytosphingosines **6a–c**. For the chain extension, the Wittig reaction was utilised; when *n*-dodecyltriphenylphosphonium bromide was treated with *n*-butyllithium to generate the Wittig reagent, the expected (2*R*,3*R*,4*R*)-1-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-3,4-di-*O*-benzyl-6-octadecen-2-ol **5a** (90:10 *E*/*Z* mixture) was obtained starting from **4a**. Using the same protocol, the intermediates **5b**,**c** were obtained from **4b**,**c** (see Section 4).

It is worth noting that all the intermediates **5a–c** derived from **4a–c** have the carbon skeleton of the chain with the protected required functionality and the free hydroxyl group for the introduction of the amino group in the same position as in the natural sphingoid bases.

The generation of the amino group from **5a–c** proceeded smoothly following a previous protocol of four steps sequence:[24] (i) 2-*O*-mesylation of **5a–c** with methanesulfonyl chloride in pyridine, (ii) then a high yield chemoselective hydrogenation of the double bond with diimine (prepared in situ from tosylhydrazide) as reducing agent, (iii) treatment with sodium azide in DMSO at 100°C and (iv) reduction of the azido group with hydrogen and $Pd/CaCO_3$ with the formation of 2-amino derivatives **6a–c**. The remaining steps of the synthesis involved the amide formation **7a–c**, which was easily carried out from **6a–c** with docosanoic acid in presence of HOBT and EDAC.[25] After removing the benzyl groups, the unnatural glycosphingolipids **8d–f** were obtained in ~25% total yield from the starting disaccharides.

Stemming from the above results, we wanted to explore the flexibility and the utility of our strategy for preparing naturally occurring glycosphingolipids, whose synthesis had not been described before. The α-galactosyl-ceramide **1**, Agelasphin AGL-7a, isolated from the marine sponge *Agelas mauritianus*,[26,27] is the synthetic target of choice. The examined biological activity showed that **1** possesses a stronger antitumour activity against B16-bearing mice and stimulatory effects of lymphocyte proliferation on allergenic mixed lymphocyte reaction (MRL) than β-glucosyl-ceramide.[28] To our knowledge, the total synthesis of **1** has not been reported to date.

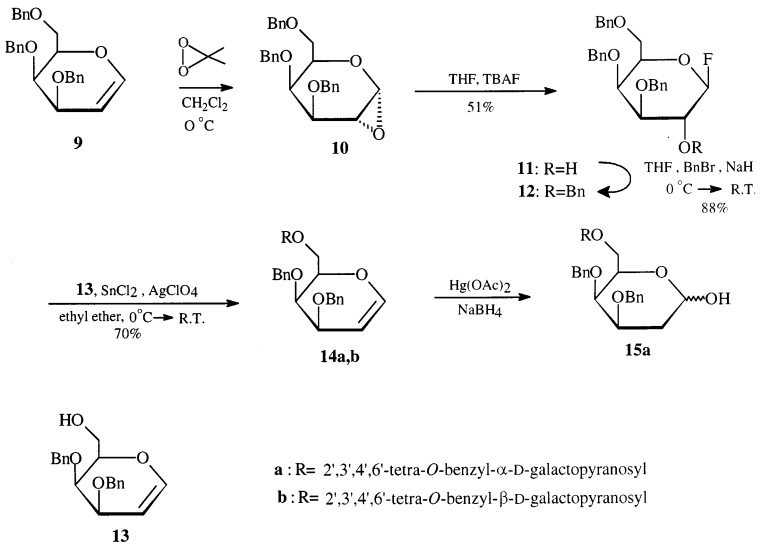


a: R_1=Bn; R_2=2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl
b: R_1=2',3',4',6'-tetra-*O*-benzyl-β-D-galactopyranosyl; R_2=Bn
c: R_1=2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl; R_2=Bn
d: R_1=H; R_2=α-D-galactopyranosyl
e: R_1=β-D-galactopyranosyl; R_2=H
f: R_1=β-D-glucopyranosyl; R_2=H

Scheme 1.

The retrosynthetic analysis shows that the 3,4-di-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-deoxy-D-galactose **15a** can be considered a suitable starting material, possessing already the D-*arabino* configuration required for the natural phytosphingosine synthesis (Scheme 2).[21–24] However, being not naturally available the corresponding disaccharide as precursor, the perbenzylated 6-*O*-(α-D-galactopyranosyl)-D-galactal [3,4-di-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol] **14a** was prepared in a stepwise manner utilising a conventional approach, the condensation of an activated galactosyl donor and an unactivated galactosyl acceptor.

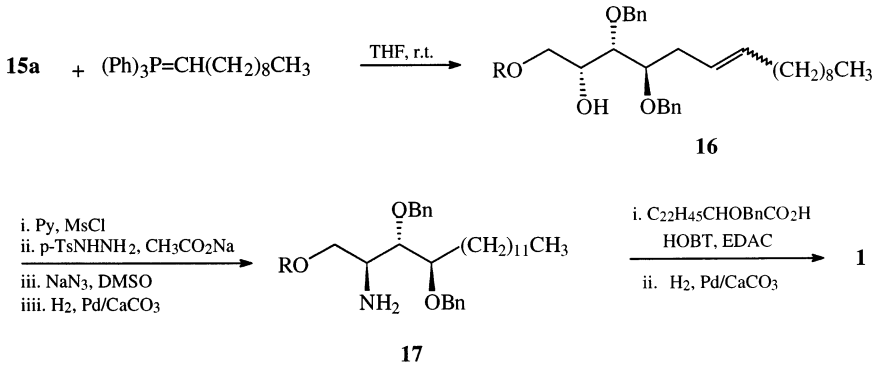
The details for the synthesis of 2-deoxy-sugar progenitor **15a** are shown in Scheme 2. Thus, 3,4,6-tri-*O*-benzyl-D-galactal (3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol) **9** reacted smoothly with 2,2-dimethyldioxirane to afford stereoselectively the epoxide **10** from the α-face, which immediately reacted with dry TBAF to generate 3,4,6-tri-*O*-benzyl-D-galactopyranosyl fluoride **11**.[29]



Scheme 2.

The subsequent coupling of the benzyl derivative **12** with 3,4-di-*O*-benzyl-D-galactal **13** under Mukaiyama's conditions[30] led to the formation of the protected D-galactosyl-D-galactals **14a**,**b** as an anomeric epimers mixture (4:1 α/β ratio). The previously described mercuration–demercuration strategy,[20] carried out on **14a**, gave rise to the formation of the corresponding 2-deoxy-sugar **15a**, never described before.

The synthesis of **1** is described in Scheme 3 and follows the same above strategy. The Wittig reaction, carried out with *n*-decyltriphenylsphophonium bromide, gave the expected (2*R*,3*S*,4*R*)-3,4-di-*O*-benzyl-1-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-6-hexadecen-2-ol **16** (90:10 *E*/*Z* mixture). The intermediate **16** derived from **15a** has the carbon skeleton of the chain with the protected required functionality and the free hydroxyl group with the right configuration for introducing the amino group with the same configuration (2*S*) as in the natural sphingoid bases.



Scheme 3.

The generation of the amino group from **16** proceeded smoothly following the previous utilised protocol of a four step sequence, as outlined in Scheme 3. The remaining steps of the synthesis first involved the amide formation, which was easily carried out by reaction of **17** with (*R*)-2-*O*-benzyl-tetracosanoic acid in presence of HOBT and EDAC.[25] The subsequent removal of the benzyl groups led to the synthetic **1**, which showed physical data identical with the natural compound ($[\alpha]_D^{20}$ +54, *c* 0.6 Pyr; mp 192–194.5°C; lit. $[\alpha]_D^{24}$ +52.3, *c* 1.0 Pyr; mp 193.5–195°C).[26]

The described straightforward synthesis of **1** demonstrates the power of the developed 2-deoxy-disaccharide strategy for the preparation of complex molecules, and renders the glycosphingolipids readily available in pure form for further biological investigations.

3. Conclusions

The utilisation of the readily available 2-deoxy-disaccharides, such as **4a**–**c**, renders them the most attractive starting materials for the construction of structurally modified glycolipids, which should be biologically important. Thus, the route described here is much shorter than was possible by classical glycosylation. The latter required extensive manipulations in each synthesis to expose the glycosyl donor. We think that the interfacing of 2-deoxy-disaccharide chemistry with enzymatically driven processes in the molecule holds considerable promise for a remarkable simplification in the field of glycolipids synthesis.

However, this strategy avoids the need for a multistep installation of the glycosyl framework only if the correct disaccharide exists already as a readily available starting material.

Further extension of this strategy to the synthesis of more complex glycolipids from 2-deoxy-trisaccharides is currently in progress.

4. Experimental

Solvents were purified and dried by standard procedures before use. Analytical TLC was performed using silica gel 60 F_{254} plates (Merck) and detected by treatment with a solution of 2N H_2SO_4. Column chromatography was performed using silica gel 60 (0.063–0.200 nm) (Merck) and flash chromatography using silica gel 60 (0.040–0.063) (Merck). Optical rotations were measured using sodium D line on DIP-370 JASCO digital polarimeter. Melting points were determined on a Mettler FP 800 melting point apparatus. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) were recorded in $CDCl_3$ and NC_5D_5. IR spectra were recorded in $CHCl_3$ solution and KBr, using a Shimadzu IR spectrometer 470 and are reported in wavenumbers (cm^{-1}). Mass spectra were obtained on an API 356 mass spectrometer.

*4.1. (2*R,*3*R,*4*R*)-3,4-Di*-O-*benzyl-1*-O-*(2′,3′,4′,6′-tetra*-O-*benzyl-α-D-galactopyranosyl)-6-octadecen-2-ol* ***5a***

To a solution of *n*-dodecyltriphenylphosphonium bromide (1.2 g, 2.4 mmol) in dry tetrahydrofuran (10 mL) was added, under N_2, *n*-butyllithium 1.6 M in hexane (1.5 mL, 2.4 mmol), furnishing a dark orange solution. The mixture was stirred for 15 min; thereafter a solution of

2-deoxy-sugar **4a** (415 mg, 0.48 mmol) in dry tetrahydrofuran (8 mL) was added dropwise. The reaction was complete within 5 min; subsequently acetone (4 mL) was added and the reaction mixture was treated with 1N hydrochloric acid until pH ~ 7 and concentrated in vacuo. After dilution with ethyl acetate, the organic phase was washed with water, then brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography over silica gel with hexane/diethyl ether (8:2) to give **5a** (390 mg, 80%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.6–5.3 (m, 2H, H6–H7); 5.1–4.4 (fs, 14H); 4.18–3.87 (fs, 7H); 3.7–3.5 (fs, 3H); 2.5–2.4 (fs, 2H, H5); 2.15–2.0 (fs, 3H, H8, OH); 1.35 (bs, 18H, H9–H17); 0.97 (t, 3H, J = 3.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.17–138.44 (CquatCH$_2$–Ph); 134.87, 125.61 (C6, C7 *Z* isomer); 132.73, 125.96 (C6, C7 *E* isomer); 128.89–127.97 (Ph–CH$_2$); 99.39 (C1′); 80.10, 79.82, 79.52, 77.01, 75.38, 70.78, 70.16 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.30, 74.39, 74.10, 73.96, 73.36, 73.14 (CH$_2$–Ph); 71.20, 69.38 (C1, C6′); 32.46 (C5); 30.38–23.23 (C8–C17); 14.67 (C18). ($C_{66}H_{82}O_9$ requires: C, 77.7%; H, 8.1%. Found: C, 77.3%; H, 8.3%).

4.2. (2S,3R,4R)-2-Amino-3,4-di-O-benzyl-1-O-(2′,3′,4′,6′-tetra-O-benzyl-α-D-galacto-pyranosyl)octadecane **6a**

(i) Methanesulfonyl chloride (0.03 mL, 0.4 mmol) was added to **5a** (390 mg, 0.38 mmol) in dry pyridine (4 mL) at 0°C. After stirring at room temperature for 3 h, the reaction mixture was worked up at 0°C by adding methanol (1 mL) and diluted with ethyl acetate. After cold-ice treatment with 6N hydrochloric acid (10 mL) and saturated $NaHCO_3$, the mixture was washed with water, then brine and dried over Na_2SO_4. The organic phase was concentrated and purified by silica gel chromatography (hexane/diethyl ether 8:2) yielding the corresponding mesyl derivative (383 mg, 92%) as colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.5–5.35 (m, 2H, H6–H7); 5.12–4.41 (fs, 14H); 4.2–3.87 (fs, 7H); 3.7–3.5 (fs, 3H); 2.84 (s, 3H, CH_3SO_2); 2.5–2.4 (fs, 2H, H5); 2.15–2.0 (fs, 2H, H8); 1.35 (bs, 18H, H9–H17); 0.97 (t, 3H, J = 3.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.13–138.40 (CquatCH$_2$–Ph); 134.72, 125.63 (C6, C7 *Z* isomer); 133.46, 125.03 (C6, C7 *E* isomer); 128.96–128.09 (Ph–CH$_2$); 98.14 (C1′); 83.52, 81.49, 79.84, 78.73, 76.79, 75.04, 70.18 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.38, 75.18, 74.01, 72.87, 72.78, 72.75 (CH$_2$–Ph); 69.30 (C6′); 66.68 (C1); 38.79 (CH_3SO_2); 32.50 (C5); 30.27–23.28 (C8–C17); 14.74 (C18).

(ii) Tosylhydrazide (651 mg, 3.5 mmol) was added to a solution of the mesyl derivative (383 mg, 0.35 mmol) in absolute ethanol (15 mL). The reaction mixture was refluxed for 5 h and during this time a solution of sodium acetate (574 mg, 7 mmol) in water (8 mL) was added. After dilution with ethyl acetate, organic phases were washed with water, brine, dried over Na_2SO_4 and concentrated. The purification of the residue by column chromatography over silica gel with hexane/diethyl ether (8:2) furnished the intermediate with the reduced double bond C(6)–C(7) (365 mg, 95%) as colourless oil. $[\alpha]_D^{20}$ +57.8 (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.13–4.45 (fs, 14H); 4.2–3.87 (fs, 7H); 3.7–3.5 (fs, 3H); 2.87 (s, 3H, CH_3SO_2); 1.72–1.55 (m, 2H, H5); 1.35 (bs, 24H, H6–H17); 0.97 (t, 3H, J = 3.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.16–138.42 (CquatCH$_2$–Ph); 128.94–128.12 (Ph–CH$_2$); 98.19 (C1′); 83.71, 81.35, 79.81, 78.77, 76.84, 75.10, 71.25 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.41, 75.04, 74.04, 72.96, 72.80 (CH$_2$–Ph); 69.38 (C6′); 66.72 (C1); 38.77 (CH_3SO_2); 32.53 (C5); 30.88–23.31 (C6–C17); 14.78 (C18).

(iii) The above dihydro intermediate (365 mg, 0.33 mmol) and sodium azide (858 mg, 13.2 mmol) in dry dimethylsulfoxid (20 mL) were stirred under N_2 for 36 h at 100°C. The reaction mixture was diluted with ethyl acetate, washed with water, brine and then dried over Na_2SO_4. The organic phase was concentrated and the purification of the residue by column chromatography over silica gel with hexane/diethyl ether (9:1) gave the azido derivative (289 mg, 84%) as a colourless oil. $[\alpha]_D^{20}$ +26 (*c* 1.4, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2870, 2100, 1648, 1513, 1453, 1363, 1247, 1100, 735; ^1H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.13–4.45 (fs, 14H); 4.1–3.5 (fs, 10H); 1.72–1.55 (m, 2H, H5); 1.35 (bs, 24H, H6–H17); 0.92 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.71–137.87 (CquatCH$_2$–Ph); 128.28–127.42 (Ph–CH$_2$); 98.66 (C1′); 79.82, 79.46, 78.70, 76.32, 74.92, 69.66 (C3, C4, C2′, C3′, C4′, C5′); 74.69, 74.34, 73.35, 73.14, 73.06, 72.71 (CH$_2$–Ph); 69.66, 68.41 (C1, C6′); 61.64 (C2) 31.88 (C5); 29.66–22.66 (C6–C17); 14.10 (C18). [$C_{66}H_{83}N_3O_8$ requires: C, 75.7%; H, 8.0%. Found: C, 75.8%; H, 8.2%; MS: m/z 1017 (M^+-N_2)].

(iv) The azido derivative (289 mg, 0.27 mmol) in ethyl acetate/ethanol 95% mixture (18 mL, 1:2) was hydrogenated under atmospheric pressure over Pd/$CaCO_3$ (50 mg, 5%) for 12 h. The reaction mixture was subsequently filtered over Celite, the filtrate concentrated and the residue purified by silica gel (treated with 1 M NaOH) chromatography (hexane/ethyl acetate 9:1) to yield **6a** (224 mg, 80%) as an amorphous white solid. ^1H NMR ($CDCl_3$) δ 7.42 (fm, 30H, Ph); 4.97–4.32 (fs, 12H); 4.18–3.88 (fs, 8H); 3.78–3.06 (fs, 4H); 1.69 (bs, 2H, NH_2); 1.24 (bs, 26H, H5–H17); 0.89 (t, $J=4$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.29–138.40 (CquatCH$_2$–Ph); 128.81–127.92 (Ph–CH$_2$); 99.33 (C1′); 81.85, 80.81, 79.49, 77.19, 75.42, 75.26, (C3, C4, C2′, C3′, C4′, C5′); 73.95, 73.82, 73.47, 73.18, 72.85 (CH$_2$–Ph); 70.03, 69.36 (C1, C6′); 52.57 (C2); 32.43 (C5); 31.48–23.20 (C6–C17); 14.63 (C18).

*4.3. (2*S,*3*R,*4*R*)-3,4-Di*-O-*benzyl-1*-O-*(2′,3′,4′,6′-tetra*-O-*benzyl-α-D-galactopyranosyl)-2*-N-*docosanoil-octadecane* **7a**

A solution of docosanoyl acid (75 mg, 0.22 mmol), EDAC [*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride] (50 mg, 0.26 mmol), HOBT [1-hydroxybenzotriazole] (35 mg, 0.26 mmol) in *N*,*N*-dimethylformamide/dichloromethane (2 mL, 1:2.5) was stirred under N_2 for 30 min at 0°C. Then **6a** (224 mg, 0.22 mmol) and diisopropylethylamine (0.092 mL, 0.53 mmol) in dry dichloromethane (7 mL) were added and the reaction mixture was stirred at room temperature for 3 h. Diluted with ethyl acetate/diethyl ether (50 mL, 8:2) mixture, the organics were treated with saturated Na_2CO_3, then 1N hydrochloric acid and subsequently washed with water, brine and dried over Na_2SO_4. The organic phase was concentrated and the residue was purified by column chromatography over silica gel with hexane/ethyl acetate (95:5) to give **7a** (254 mg, 90%) as an amorphous white solid. $[\alpha]_D^{20}$ +18.4 (*c* 1.4, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2900, 2850, 1735, 1645, 1513, 1248, 1103, 1056, 735; ^1H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.13–3.4 (fs, 24H); 2.33 (t, 2H, $J=6.5$ Hz, H2″); 1.5–1.1 (bs, 64H, H5–H17/H3″–H21″); 0.97 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.69 (HN–C=O); 138.74–137.90 (CquatCH$_2$–Ph); 128.31–127.42 (Ph–CH$_2$); 98.56 (C1′); 80.55, 79.23, 78.67, 76.51, 74.97, 69.84 (C3, C4, C2′, C3′, C4′, C5′); 74.83, 74.69, 73.41, 73.03, (CH$_2$–Ph); 69.02, 68.36 (C1, C6′); 48.63 (C2); 36.78 (C2″); 32.71 (C5); 31.91–22.69 (C6–C17, C3″–C21″); 14.12 (C18, C22″). ($C_{88}H_{127}NO_9$ requires: C, 78.7%; H, 9.5%. Found: C, 78.8%; H, 9.7%).

4.4. (2S,3R,4R)-2-N-Docosanoil-1-O-α-D-galactopyranosyl-octadecane-3,4-diol **8d**

A solution of **7a** (254 mg, 0.19 mmol) in ethyl acetate/ethanol 95% mixture (9 mL, 1:2) was hydrogenated under atmospheric pressure over Pd/C (50 mg, 10%) for 24 h. The reaction mixture was subsequently filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (chloroform/methanol 95:5) to yield **8d** (144 mg, 95%) as a white solid; mp 180–182.3°C (methanol); $[\alpha]_D^{20}$ +12.1 (*c* 1.1, NC_5D_5); IR cm^{-1} (KBr): 3356, 2920, 2851, 1734, 1652, 1547, 1466, 1372, 1260, 1075, 1042; ^1H NMR (NC_5D_5) δ 8.48 (d, 1H, $J=9.2$ Hz, NH); 6.68 (bs, OH); 6.48 (bs, OH); 5.6–4.1 (fs, 12H); 2.35 (t, 2H, $J=6.2$ Hz, H2″); 2.28–1.62 (m, 4H); 1.5–1.1 (bs, 60H); 0.89 (t, 3H, $J=6.5$ Hz, CH_3); ^{13}C NMR (NC_5D_5) δ 173.80 (HN–C=O); 101.59 (C1′); 74.23, 73.28, 72.60, 71.32, 70.74, 70.22 (C3, C4, C2′, C3′, C4′, C5′); 69.85 (C1); 63.05 (C6′); 51.18 (C2); 37.04 (C2″); 35.18–19.39 (C5–C17, C3″–C21″); 14.55 (C18, C22″). ($C_{46}H_{91}NO_9$ requires: C, 68.8%; H, 11.4%. Found: C, 68.6%; H, 11.6%).

4.5. (2R,3R,4R)-1,4-Di-O-benzyl-3-O-(2′,3′,4′,6′-tetra-O-benzyl-β-D-galactopyranosyl)-6-octadecen-2-ol **5b**

Compound **5b** (318 mg, 68%; however, the yields can vary between 60 and 80%) was obtained as an inseparable *E*/*Z* mixture (ratio 9:1) from **4b**, [406 mg, 0.46 mmol in dry tetrahydrofuran (8 mL), *n*-dodecyltriphenylphosphonium bromide (1.2 g, 2.4 mmol) in dry tetrahydrofuran (10 mL), *n*-butyllithium 1.6 M in hexane (1.5 mL, 2.4 mmol)], following the procedure described for **5a**.

^1H NMR ($CDCl_3$) δ 7.53–7.33 (fm, 30H, Ph); 5.62–5.29 (m, 2H, H6–H7); 5.11–4.42 (fs, 14H); 4.18–3.87 (fs, 7H); 3.7–3.5 (fs, 3H); 2.5–2.4 (fs, 2H, H5); 2.15–2.0 (fs, 2H, H8); 1.35 (bs, 18H, H9–H17); 0.96 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.28–138.40 (CquatCH_2–Ph); 134.90, 127.01 (C6, C7 *Z* isomer); 132.49, 126.54 (C6, C7 *E* isomer); 128.96–128.02 (Ph–CH_2); 104.38 (C1′); 82.96, 81.07, 79.90, 77.49, 74.23, 73.78, 71.52* (C2, C3, C4, C2′, C3′, C4′, C5′); 75.71, 75.08, 74.00, 73.68, 73.44, 73.08 (CH_2–Ph); 71.52*, 69.30 (C1, C6′); 32.46 (C5); 30.20–23.23 (C8–C17); 14.67 (C18). ($C_{66}H_{82}O_9$ requires: C, 77.7%; H, 8.1%. Found: C, 77.3%; H, 8.3%).

4.6. (2S,3R,4R)-2-Amino-1,4-di-O-benzyl-3-O-(2′,3′,4′,6′-tetra-O-benzyl-β-D-galacto-pyranosyl)octadecane **6b**

Compound **6b** (183 mg, 58%) was obtained from **5b** (318 mg, 0.31 mmol) following the procedures (i), (ii), (iii) and (iv) described for **6a**.

(i) [318 mg, 0.31 mmol of *E*/*Z* mixture (ratio 9:1) in dry pyridine (4 mL), methanesulfonyl chloride (0.026 mL, 0.33 mmol)]: ^1H NMR ($CDCl_3$) δ 7.52–7.28 (fm, 30H, Ph); 5.51–5.35 (m, 2H, H6–H7); 5.12–4.41 (fs, 14H); 4.2–3.87 (fs, 7H); 3.7–3.5 (fs, 3H); 2.82 (s, 3H, CH_3SO_2); 2.5–2.4 (fs, 2H, H5); 2.15–2.0 (fs, 2H, H8); 1.35 (bs, 18H, H9–H17); 0.97 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.38–138.33 (CquatCH_2–Ph); 134.07, 126.62 (C6, C7 *Z* isomer); 132.81, 125.99 (C6, C7 *E* isomer); 128.95–128.08 (Ph–CH_2); 103.36 (C1′); 84.00, 82.90, 79.96, 79.86, 78.69, 77.79, 74.23, 73.81 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.54, 75.13, 74.22, 74.00, 73.81, 73.40, 73.36, 72.60 (CH_2–Ph); 69.37, 69.06 (C1, C6′); 38.97 (CH_3SO_2); 32.47 (C5); 30.27–23.23 (C8–C17); 14.68 (C18).

(ii) [Mesyl derivative (312 mg, 0.285 mmol) in absolute ethanol (15 mL), tosyl hydrazide (530 mg, 2.85 mmol), sodium acetate (467 mg, 5.7 mmol) in water (6 mL)]: $[\alpha]_D^{20}$ +6.0 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.52–7.28 (fm, 30H, Ph); 5.15–4.45 (fs, 14H); 4.19–3.87 (fs, 7H); 3.71–3.48 (fs, 3H); 2.88 (s, 3H, CH_3SO_2); 1.72–1.55 (m, 2H, H5); 1.35 (bs, 24H, H6–H17); 0.97 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.78–137.75 (CquatCH$_2$–Ph); 128.36–127.53 (Ph–CH$_2$); 102.93 (C1′); 83.58, 82.27, 79.36, 79.21, 78.21, 73.56, 73.12 (C2, C3, C4, C2′, C3′, C4′, C5′); 74.92, 74.58, 73.41, 72.78, 71.97 (CH$_2$–Ph); 69.37, 68.32 (C1, C6′); 38.34 (CH_3SO_2); 31.87 (C5); 29.70–22.64 (C6–C17); 14.09 (C18).

(iii) [Dihydro derivative (294 mg, 0.268 mmol), sodium azide (715 mg, 11 mmol) in dry dimethylsulfoxide (20 mL)]: $[\alpha]_D^{20}$ +1.4 (*c* 1.2, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2870, 2100, 1645, 1520, 1453, 1363, 1250, 1097, 735; ^1H NMR ($CDCl_3$) δ 7.48–7.28 (fm, 30H, Ph); 5.13–4.45 (fs, 14H); 4.11–3.48 (fs, 10H); 1.72–1.55 (m, 2H, H5); 1.35 (bs, 24H, H6–H17); 0.95 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.85–137.79 (CquatCH$_2$–Ph); 128.40–127.35 (Ph–CH$_2$); 104.54 (C1′); 82.43, 79.98, 79.30, 77.47, 73.70, 73.23 (C3, C4, C2′, C3′, C4′, C5′); 75.05, 74.52, 73.48, 73.01, 72.32 (CH$_2$–Ph); 69.99, 68.82 (C1, C6′); 61.93 (C2); 31.91 (C5); 29.73–22.68 (C6–C17); 14.12 (C18). [$C_{66}H_{83}N_3O_8$ requires: C, 75.7%; H, 8.0%. Found: C, 75.6%; H, 8.0%; MS: *m*/*z* 1017 (M^+-N_2)].

(iv) [Azido derivative (236 mg, 0.226 mmol) in ethyl acetate/ethanol 95% mixture (18 mL, 1:2), Pd/$CaCO_3$ (50 mg, 5%)]. **6b**: ^1H NMR ($CDCl_3$) δ 7.42 (fm, 30H, Ph); 5.0–4.33 (fs, 14H); 3.92–3.25 (fs, 10H); 1.74 (bs, 2H, NH_2); 1.25 (bs, 26H, H5–H17), 0.9 (t, $J=4$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.83–137.76 (CquatCH$_2$–Ph); 128.26–127.50 (Ph–CH$_2$); 104.87 (C1′); 82.71, 80.72, 79.49, 73.55, 73.14 (C3, C4, C2′, C3′, C4′, C5′); 75.39, 74.56, 73.41, 73.72, 71.84, 71.74 (CH$_2$–Ph); 71.70, 68.64 (C1, C6′); 52.18 (C2); 31.90 (C5); 29.72–22.67 (C6–C17); 14.12 (C18).

*4.7. (2*S,*3*R,*4*R*)-1,4-Di*-O-*benzyl-3*-O-*(2′,3′,4′,6′-tetra*-O-*benzyl-β-*D*-galactopyranosyl)-2*-N-*docosanoyl-octadecane* **7b**

Compound **7b** (217 mg, 90%) was obtained from **6b** [183 mg, 0.18 mmol in dry dichloromethane (7 mL), diisopropylethylamine (0.075 mL, 0.43 mmol), docosanoyl acid (61 mg, 0.18 mmol), EDAC (39 mg, 0.20 mmol), HOBT (27 mg, 0.20 mmol) in *N*,*N*-dimethylformamide/dichloromethane (2 mL, 1:2.5)], following the procedure described for **7a**.

$[\alpha]_D^{20}$ +6.3 (*c* 1.5, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2898, 2850, 1740, 1645, 1515, 1248, 1100, 1048, 735; ^1H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.13–3.4 (fs, 24H); 2.33 (t, 2H, $J=6.5$ Hz, H2″); 1.53–1.11 (bs, 64H, H5–H17/H3″–H21″); 0.97 (t, 3H, $J=3.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 172.89 (HN–C=O); 139.36–138.33 (CquatCH$_2$–Ph); 128.94–127.54 (Ph–CH$_2$); 104.08 (C1′); 83.39, 80.89, 79.78, 77.74, 74.01, 73.91 (C3, C4, C2′, C3′, C4′, C5′); 75.47, 75.19, 73.77, 73.20, 73.11 72.77 (CH$_2$–Ph); 70.07, 69.01 (C1, C6′); 48.04 (C2); 37.13 (C2″); 32.44 (C5); 30.24–23.21 (C6–C17, C3″–C21″); 14.64 (C18, C22″). ($C_{88}H_{127}NO_9$ requires: C, 78.7%; H, 9.5%. Found: C, 78.9%; H, 9.6%).

*4.8. (2*S,*3*R,*4*R*)-2*-N-*Docosanoyl-3*-O-*β-*D*-galactopyranosyl-octadecane-1,4-diol* **8e**

Compound **8e** (123 mg, 95%) was obtained from **7b** [217 mg, 0.16 mmol in ethyl acetate/ethanol 95% mixture (9 mL, 1:2), Pd/C (50 mg, 10%)], following the procedure described for **8d**; mp

154–155.5°C (methanol); $[\alpha]_D^{20}$ +5.7 (*c* 1.2, NC_5D_5); IR cm^{-1} (KBr): 3356, 2920, 2850, 1735, 1650, 1547, 1466, 1370, 1260, 1080, 1040; ^1H NMR (NC_5D_5) δ 7.85 (d, 1H, $J=9.5$ Hz, NH); 6.62 (bs, OH); 5.59–4.08 (fs, 12H); 2.32 (t, 2H, $J=5.1$ Hz, H2″); 2.21–1.65 (m, 4H); 1.5–1.1 (bs, 60H); 0.88 (t, 3H, $J=6.5$ Hz, CH_3); ^{13}C NMR (NC_5D_5) δ 173.26 (HN–C=O); 106.23 (C1′); 85.27, 77.49, 75.62, 73.22, 71.67, 70.27 (C3, C4, C2′, C3′, C4′, C5′); 62.40, 62.23 (C1, C6′); 58.09 (C2); 36.89 (C2″); 32.30–23.29 (C5–C17, C3″–C21″); 14.64 (C18, C22″). ($C_{46}H_{91}NO_9$ requires: C, 68.8%; H, 11.4%. Found: C, 68.8%; H, 11.5%).

*4.9. (2*R,*3*R,*4*R*)-1,4-Di*-O-*benzyl-3*-O-*(2′,3′,4′,6′-tetra*-O-*benzyl-β-*D*-glucopyranosyl)-6-octadecen-2-ol* **5c**

Compound **5c** (305 mg, 65%; however, the yields can vary between 60–80%) was obtained as an inseparable *E*/*Z* mixture (ratio 9:1) from **4c** [398 mg, 0.4 mmol in dry tetrahydrofuran (8 mL), *n*-dodecyltriphenylphosphonium bromide (1.2 g, 2.4 mmol) in dry tetrahydrofuran (10 mL), *n*-butyllithium 1.6 M in hexane (1.5 mL, 2.4 mmol)], following the procedure described for **5a**.

^1H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.58–5.28 (m, 2H, H6–H7); 5.03–4.38 (fs, 14H); 4.16–3.88 (fs, 7H); 3.7–3.52 (fs, 3H); 2.5–2.4 (fs, 2H, H5); 2.15–2.0 (fs, 2H, H8); 1.35 (bs, 18H, H9–H17); 0.95 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.15–138.73 (CquatCH_2–Ph); 133.87, 127.47 (C6, C7 *Z* isomer); 132.56, 126.55 (C6, C7 *E* isomer); 129.06–128.08 (Ph–CH_2); 103.80 (C1′); 85.29, 82.71, 81.24, 78.40, 77.23, 75.31, 71.37 (C2, C3, C4, C2′, C3′, C4′, C5′); 76.14, 75.46, 75.39, 74.02, 73.80, 71.37* (CH_2–Ph); 71.37*, 69.61 (C1, C6′); 32.45 (C5); 30.22–23.22 (C8–C17); 14.66 (C18). ($C_{66}H_{82}O_9$ requires: C, 77.7%; H, 8.1%. Found: C, 77.3%; H, 8.3%).

*4.10. (2*S,*3*R,*4*R*)-2-Amino-1,4-di*-O-*benzyl-3*-O-*(2′,3′,4′,6′-tetra*-O-*benzyl-β-*D*-gluco-pyranosyl)octadecane* **6c**

Compound **6c** (197 mg, 60%) was obtained from **5c** (305 mg, 0.3 mmol) following the procedures (i), (ii), (iii) and (iv) described for **6a**.

(i) [305 mg, 0.3 mmol of *E*/*Z* mixture (ratio 9:1) in dry pyridine (4 mL), methanesulfonyl chloride (0.025 mL, 0.32 mmol)]: ^1H NMR ($CDCl_3$) δ 7.49–7.31 (fm, 30H, Ph); 5.48–5.35 (m, 2H, H6–H7); 5.14–4.41 (fs, 14H); 4.21–3.87 (fs, 7H); 3.7–3.5 (fs, 3H); 2.84 (s, 3H, CH_3SO_2); 2.5–2.4 (fs, 2H, H5); 2.15–2.0 (fs, 2H, H8); 1.35 (bs, 18H, H9–H17); 0.97 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.56–137.67 (CquatCH_2–Ph); 133.65, 126.09 (C6, C7 *Z* isomer); 132.44, 125.29 (C6, C7 *E* isomer); 128.37–127.64 (Ph–CH_2); 102.38 (C1′); 84.78, 83.26, 82.25, 79.34, 77.80, 77.77, 74.74 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.68, 74.90, 73.51, 72.91, 72.09 (CH_2–Ph); 69.17, 68.88 (C1, C6′); 38.51 (CH_3SO_2); 31.94 (C5); 29.67–22.71 (C8–C17); 14.16 (C18).

(ii) [Mesyl derivative (312 mg, 0.285 mmol) in absolute ethanol (15 mL), tosyl hydrazide (530 mg, 2.85 mmol), sodium acetate (467 mg, 5.7 mmol) in water (6 mL)]: $[\alpha]_D^{20}$ +0.6 (*c* 1.6, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.5–7.32 (fm, 30H, Ph); 5.11–4.43 (fs, 14H); 4.22–3.86 (fs, 7H); 3.72–3.51 (fs, 3H); 2.87 (s, 3H, CH_3SO_2); 1.72–1.56 (m, 2H, H5); 1.35 (bs, 24H, H6–H17); 0.96 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.09–138.21 (CquatCH_2–Ph); 128.88–128.06 (Ph–CH_2); 103.13 (C1′); 85.32, 83.90, 82.78, 79.78, 78.60, 78.29, 75.72* (C2, C3, C4, C2′, C3′, C4′, C5′); 76.20, 75.72*, 75.24, 74.05, 73.44, 72.54 (CH_2–Ph); 69.81, 69.41 (C1, C6′); 38.99 (CH_3SO_2); 32.46 (C5); 30.27–23.23 (C6–C17); 14.68 (C18).

(iii) [Dihydro derivative (300 mg, 0.274 mmol), sodium azide (715 mg, 11 mmol) in dry dimethylsulfoxide (20 mL)]: $[\alpha]_D^{20}$ +1.6 (*c* 1.2, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2870, 2100, 1650, 1513, 1460, 1366, 1245, 1100, 735; ^1H NMR ($CDCl_3$) δ 7.53–7.32 (fm, 30H, Ph); 5.13–4.45 (fs, 14H); 4.1–3.51 (fs, 10H); 1.72–1.54 (m, 2H, H5); 1.35 (bs, 24H, H6–H17); 0.95 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.16–138.31 (CquatCH$_2$–Ph); 128.84–128.02 (Ph–CH$_2$); 104.74 (C1′); 85.25, 82.58, 80.62, 78.33, 77.66, 75.24 (C3, C4, C2′, C3′, C4′, C5′); 76.13, 75.47, 74.04, 73.60, 72.72, 72.20 (CH_2–Ph); 70.54, 69.69 (C1, C6′); 62.36 (C2); 32.42 (C5); 30.24–23.19 (C6–C17); 14.62 (C18). [$C_{66}H_{83}N_3O_8$ requires: C, 75.7%; H, 8.0%. Found: C, 75.8%; H, 8.1%; MS: m/z 1017 (M^+-N_2)].

(iv) [Azido derivative (243 mg, 0.233 mmol) in ethyl acetate/ethanol 95% mixture (18 mL, 1:2), Pd/$CaCO_3$ (50 mg, 5%)]. **6c**: ^1H NMR ($CDCl_3$) δ 7.38 (fm, 30H, Ph); 4.92 (AB, 4H, $J=12$ Hz, 2CH_2Ph); 4.6–4.38 (fs, 12H); 3.78–3.22 (fs, 8H); 1.62 (bs, 2H, NH_2); 1.21 (bs, 26H, H5–H17); 0.88 (t, $J=4$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.35–138.62 (CquatCH$_2$–Ph); 128.97–127.90 (Ph–CH$_2$); 104.96 (C1′); 85.50, 82.87, 81.32, 81.19, 78.41, 75.25 (C3, C4, C2′, C3′, C4′, C5′); 76.09, 75.71, 75.46, 73.50, 73.13, 71.88* (CH_2–Ph); 71.73*, 68.97 (C1, C6′) 52.14 (C2); 31.92 (C5); 29.72–22.68 (C6–C17); 14.11 (C18).

4.11. (2S,3R,4R)-1,4-Di-O-benzyl-3-O-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)-2-N-docosanoyl-octadecane **7c**

Compound **7c** (221 mg, 92%) was obtained from **6c** [197 mg, 0.193 mmol in dry dichloromethane (7 mL), diisopropylethylamine (0.080 mL, 0.46 mmol), docosanoyl acid (66 mg, 0.194 mmol), EDAC (44 mg, 0.227 mmol), HOBT (31 mg, 0.229 mmol) in *N*,*N*-dimethylformamide/dichloromethane (2 mL, 1:2.5)], following the procedure described for **7a**. $[\alpha]_D^{20}$ +7.1 (*c* 1.2, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2900, 2852, 1738, 1649, 1513, 1247, 1103, 1054, 735; ^1H NMR ($CDCl_3$) δ 7.5–7.23 (fm, 30H, Ph); 5.13–3.41 (fs, 24H); 2.33 (t, 2H, $J=6.5$ Hz, H2″); 1.47–1.07 (bs, 64H, H5–H17/H3″–H21″); 0.97 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.31 (HN–C=O); 138.78–138.00 (CquatCH$_2$–Ph); 128.00–126.95 (Ph–CH$_2$); 103.3 (C1′); 84.90, 82.10, 80.47, 77.80, 76.08, 74.81 (C3, C4, C2′, C3′, C4′, C5′); 75.53, 74.81, 74.65, 73.48, 72.79, 72.02 (CH_2–Ph); 69.64, 68.73 (C1, C6′); 47.63 (C2); 36.58 (C2″); 33.71 (C5); 31.87–22.64 (C6–C17, C3″–C21″); 14.07 (C18, C22″). ($C_{88}H_{127}NO_9$ requires: C, 78.7%; H, 9.5%. Found: C, 78.6%; H, 9.4%).

4.12. (2S,3R,4R)-2-N-Docosanoyl-3-O-β-D-glucopyranosyl-octadecane-1,4-diol **8f**

Compound **8f** (125 mg, 95%) was obtained from **7c** [221 mg, 0.165 mmol in ethyl acetate/ethanol 95% mixture (9 mL, 1:2), Pd/C (50 mg, 10%)], following the procedure described for **8d**; mp 161–163°C (methanol); $[\alpha]_D^{20}$ +6.0 (*c* 1.0, NC_5D_5); IR cm^{-1} (KBr): 3358, 2925, 2850, 1738, 1655, 1549, 1466, 1372, 1265, 1075, 1038; ^1H NMR (NC_5D_5) δ 7.86 (d, 1H, $J=9.6$ Hz, NH); 6.68 (bs, OH); 6.5 (bs, OH); 5.62–3.92 (fs, 12H); 2.38 (t, 2H, $J=6.5$ Hz, H2″); 2.28–1.52 (m, 4H); 1.5–1.1 (fs, 60H); 0.89 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR (NC_5D_5) δ 173.28 (HN–C=O); 105.52 (C1′); 85.06, 78.94, 78.77, 75.66, 71.75 (C3, C4, C2′, C3′, C4′, C5′); 62.68, 62.46 (C1, C6′); 52.04 (C2); 36.92 (C2″); 33.32–23.23 (C5– C17, C3″–C21″); 14.57 (C18, C22″). ($C_{46}H_{91}NO_9$ requires: C, 68.8%; H, 11.4%. Found: C, 68.6%; H, 11.5%).

4.13. 2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl fluoride **12**

Compound **9** (3,4,6-tri-*O*-benzyl-D-galactal; 500 mg, 1.2 mmol) in dry dichloromethane (21 mL) under N_2 at 0°C was treated with dimethyldioxirane (21 mL, ~1.7 mmol). The reaction mixture was stirred for 30 min until all the galactal was consumed (TLC hexane/diethyl ether 6:4) and the solvent was evaporated using a dry N_2 steam to give **10**, which had been azeotropically dried using benzene. The residue was dissolved in dry tetrahydrofuran (8 mL) under N_2 at 0°C, treated with TBAF [tetrabutylammonium fluoride] (11 mL, ~11 mmol; stored over molecular sieves) and then stirred at rt for 30 h. The dark brown solution was diluted with ethyl acetate, washed with water, brine, dried over Na_2SO_4 and concentrated to dryness. Flash column chromatography of residue using dichloromethane/ethyl acetate (95:5) as eluent gave **11** (277 mg, 51%) as an amorphous colourless solid. The compound was dissolved in dry *N*,*N*-dimethylformamide (5 mL) under N_2 at 0°C, treated with benzyl bromide (0.20 mL, 1.7 mmol), NaH (40 mg, 1.7 mmol) and stirred for 30 min at 0°C and 30 min at rt. The reaction was quenched by pouring the mixture into ice. Finally the mixture was diluted with ethyl acetate and washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography of residue using hexane/diethyl ether (75:25) as eluent gave **12** (292 mg, 88%) as an amorphous colourless solid.

$[\alpha]_D^{20}$ +16.1 (*c* 0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.48–7.35 (fs, 20H, Ph–CH_2); 5.25 (dd, 1H, $J=52.7$, $J=7.2$ Hz, H-1); 5.02 (d, 1H, $J=11.6$ Hz); 4.92–4.85 (AB q, 2H, $J=11.0$ Hz); 4.81 (t, 2H, $J=11.4$ Hz); 4.69 (d, 1H, $J=11.6$ Hz); 4.58–4.49 (AB q, 2H, $J=11.8$ Hz); 4.12–3.90 (mfs, 2H, H-2, H-5); 3.76 (fs, 3H, H-3, 2H-6); 3.62 (dd, 1H, $J=10.1$, $J=2.3$ Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 138.50–137.80 (CquatCH$_2$–Ph); 128.52–127.88 (Ph–CH_2); 110.42 (d, $J=212$ Hz, C1); 81.17 (d, $J=12.2$ Hz, C3); 79.21 (d, $J=19.8$ Hz, C2); 75.14, 74.78, 73.75, 73.24 (CH_2–Ph); 73.77 (d, $J=4.6$ Hz, C4); 73.18 (C5); 68.50 (C6).

4.14. 3,4-Di-O-benzyl-6-O-(2′,3′,4′,6′-tetra-O-benzyl-α-D-galactopyranosyl)-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol **14a**

Galactal derivative **13** (117 mg, 0.36 mmol) and fluoro sugar **12** (292 mg, 0.54 mmol) were combined in diethyl ether, concentrated, dried in vacuo for 2 h and then treated with 6-methyl-2,4-di-*tert*-butylpyridine[29] (110 mg, 0.54 mmol) in a glovebag and dissolved in dry diethyl ether (8 mL) under argon. Silver perchlorate (112 mg, 0.54 mmol), stannous chloride (102 mg, 0.54 mmol) and 4 Å molecular sieves were placed in a separate flask and the system was flushed with argon. The salt mixture was placed in a water–ice bath, and the sugar solution was introduced via a double-tipped needle. The reaction flask was wrapped with aluminium foil and stirred at room temperature for 30 h. The reaction mixture was quenched by addition of saturated $NaHCO_3$, washed with water, then brine and dried over Na_2SO_4. The organics were concentrated and purified by silica gel chromatography (hexane/diethyl ether 85:15) to afford the desired α-product **14a** (257 mg, 80%) and 64 mg (20%) of β-product **14b**, both as amorphous colourless solids.

14a: $[\alpha]_D^{20}$ +13.1 (*c* 0.5, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2868, 1645, 1613, 1513, 1092, 735; ^{1}H NMR ($CDCl_3$) δ 7.41–7.11 (fm, 30H, Ph); 6.24 (dd, 1H, $J=6.2$, $J=1.1$ Hz, H1); 4.96–3.88 (fs, 22H); 3.68 (dd, 1H, $J=2.5$, $J=8.5$ Hz); 3.48 (t, 2H, $J=6.5$ Hz, H6′); ^{13}C NMR ($CDCl_3$) δ

144.08 (C1); 138.83–137.99 (CquatCH$_2$–Ph); 128.33–127.37 (Ph–CH$_2$); 99.68 (C2); 97.74 (C1′); 79.08, 74.95, 71.78, 70.11, 69.15 (C3, C4, C5, C2′, C3′, C4′, C5′); 74.73, 73.41, 72.96, 70.74 (CH$_2$–Ph); 68.73 (C6′); 66.28 (C6). (C$_{54}$H$_{56}$O$_9$ requires: C, 76.4%; H, 6.6%. Found: C, 76.5%; H, 6.6%).

14b: $[\alpha]_D^{20}$ −20 (*c* 0.5, CH$_2$Cl$_2$); IR cm^{-1} (CHCl$_3$): 2868, 1645, 1620, 1511, 1210, 1092, 735; ^{1}H NMR (CDCl$_3$) δ 7.52–7.18 (fm, 30H, Ph); 6.38 (dd, 1H, $J=5.5$, $J=1.1$ Hz, H1); 5.08–3.80 (fs, 22H); 3.72–3.48 (fm, 3H); ^{13}C NMR (CDCl$_3$) δ 144.10 (C1); 138.81–137.83 (CquatCH$_2$–Ph); 128.36–127.47 (Ph–CH$_2$); 104.29 (C1′); 99.72 (C2); 82.02, 79.43, 75.52, 73.39, 73.12, 71.61, 70.16 (C3, C4, C5, C2′, C3′, C4′, C5′); 74.91, 74.50, 73.43, 72.98, 72.89, 70.87 (CH$_2$–Ph); 68.40, 68.23 (C6, C6′). (C$_{54}$H$_{56}$O$_9$ requires: C, 76.4%; H, 6.6%. Found: C, 76.4%; H, 6.5%).

*4.15. 3,4-Di-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-deoxy-D-galactose* ***15a***

The protected α-galactosyl-galactal **14a** (257 mg, 0.3 mmol) in dry tetrahydrofuran (20 mL) was cooled to 0°C, treated with a solution of mercuric acetate (382 mg, 1.2 mmol) in water (2 mL) and stirred until all glycal was consumed. The reaction mixture was diluted with water (80 mL, water/tetrahydrofuran 4:1), then at 0°C was added sodium borohydride (182 mg, 4.8 mmol). After 1 min the mixture was treated with bubbling carbon dioxide until pH ~7. The suspension was extracted with diethyl ether (3×50 mL). The combined organic phases were washed with water, brine, dried over Na$_2$SO$_4$ and concentrated. The silica gel column chromatography of the crude product, using hexane/diethyl ether (6:4) as eluent, furnished **15a** (217 mg, 84%) as a colourless oil. IR cm^{-1} (CHCl$_3$): 3360, 2868, 1613, 1513, 1092, 735; ^{1}H NMR (CDCl$_3$) δ 5.30 (fm, 1H, H1); 4.90–4.30 (fs, 18H); 4.18 (m, 1H, H4); 4.01 (m, 1H, H3); 3.75 (m, 2H, H6); 3.53 (fs, 1H, H5); 2.35–1.95 (m, 2H, H2); ^{13}C NMR (CDCl$_3$) δ 138.74–137.20 (CquatCH$_2$–Ph); 128.45–127.30 (Ph–CH$_2$); 98.35, 98.25 (C1′); 95.32, 92.15 (C1); 79.14, 79.08, 78.69, 74.97, 74.88, 74.69, 74.46, 73.87, 73.83, 73.64, 73.57, 73.49, 73.01, 70.92, 70.76, 70.53, 69.76, 69.50, 69.22, 69.15 (C3, C4, C5, C6, C2′, C3′, C4′, C5′, C6′, CH$_2$–Ph); 31.11, 29.68 (C2). (C$_{54}$H$_{58}$O$_{10}$ requires: C, 74.8%; H, 6.7%. Found: C, 74.7%; H, 6.8%).

*4.16. (2*R*,3*S*,4*R*)-3,4-Di-*O*-benzyl-1-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-6-hexadecen-2-ol* ***16***

Compound **16** (203 mg, 82%; however, the yields can vary between 75 and 85%) was obtained as an inseparable *E*/*Z* mixture (ratio 9:1) from **15a** [217 mg, 0.25 mmol in dry tetrahydrofuran (4 mL), *n*-decyltriphenylphosphonium bromide (661 mg, 1.3 mmol) in dry tetrahydrofuran (10 mL), *n*-butyllithium 1.6 M in hexane (1.5 mL, 2.4 mmol)], following the procedure described for **5a**.

^{1}H NMR (CDCl$_3$) δ 7.48–7.32 (fm, 30H, Ph); 5.62–5.28 (m, 2H, H6–H7); 5.08–4.41 (fs, 14H); 4.18–3.87 (fs, 7H); 3.72–3.48 (fs, 3H); 2.5–2.4 (fs, 2H, H5); 2.15–2.0 (fs, 2H, H8); 1.35 (bs, 14H, H9–H15); 0.98 (t, 3H, $J=3.5$ Hz, CH$_3$); ^{13}C NMR (CDCl$_3$) δ 139.17–138.52 (CquatCH$_2$–Ph); 134.84, 125.96, (C6, C7 *Z* isomer) 132.76, 124.98 (C6, C7 *E* isomer); 128.89–127.97 (Ph–CH$_2$); 125.96 (C7); 99.39 (C1′); 82.10, 79.82, 79.52, 77.01, 75.38, 70.78, 70.16 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.30, 74.39, 74.10, 73.96, 73.36, 73.14 (CH$_2$–Ph); 71.20 (C6′); 69.38 (C1); 32.46 (C5); 30.38–23.23 (C8–C15); 14.67 (C16). (C$_{64}$H$_{78}$O$_9$ requires: C, 77.5%; H, 7.9%. Found: C, 77.4%; H, 8.0%).

4.17. (2S,3S,4R)-2-Amino-3,4-di-O-benzyl-1-O-(2′,3′,4′,6′-tetra-O-benzyl-α-D-galacto-pyranosyl)hexadecane **17**

Compound **17** (114 mg, 59%) was obtained from **16** (203 mg, 0.2 mmol) following the procedures (i), (ii), (iii) and (iv) described for **6a**.

(i) [203 mg, 0.2 mmol of *E*/*Z* mixture (ratio 9:1) in dry pyridine (2 mL), methanesulfonyl chloride (0.017 mL, 0.22 mmol)]: ^{1}H NMR ($CDCl_3$) δ 7.5–7.31 (fm, 30H, Ph); 5.52–5.35 (m, 2H, H6–H7); 5.1–4.41 (fs, 14H); 4.22–3.85 (fs, 7H); 3.72–3.52 (fs, 3H); 2.82 (s, 3H, CH_3SO_2); 2.49–2.41 (fs, 2H, H5); 2.15–2.0 (m, 2H, H8); 1.35 (bs, 14H, H9–H15); 0.97 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.14–138.42 (CquatCH$_2$–Ph); 134.73, 125.64 (C6, C7 *Z* isomer); 133.45, 125.04 (C6, C7 *E* isomer); 128.97–128.10 (Ph–CH$_2$); 99.15 (C1′); 83.52, 81.49, 79.84, 78.73, 76.79, 75.04, 70.18 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.38, 75.18, 74.01, 72.87, 72.78, 72.75 (CH$_2$–Ph); 69.30 (C6′); 66.68 (C1); 38.79 (CH_3SO_2); 32.51 (C5); 30.24–23.29 (C8–C15); 14.75 (C16).

(ii) [Mesyl derivative (196 mg, 0.184 mmol) in absolute ethanol (7 mL), tosyl hydrazide (342 mg, 1.84 mmol), sodium acetate (304 mg, 3.7 mmol) in water (4 mL)]: $[\alpha]_D^{20}$ +27 (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.13–4.45 (fs, 14H); 4.21–3.85 (fs, 7H); 3.68–3.49 (fs, 3H); 2.84 (s, 3H, CH_3SO_2); 1.72–1.55 (m, 2H, H5); 1.35 (bs, 20H, H6–H15); 0.98 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.16–138.42 (CquatCH$_2$–Ph); 128.94–128.12 (Ph–CH$_2$); 99.19 (C1′); 83.72, 81.35, 79.81, 78.77, 76.84, 75.10, 70.25 (C2, C3, C4, C2′, C3′, C4′, C5′); 75.41, 75.05, 74.05, 72.96, 72.80 (CH$_2$–Ph); 69.38 (C6′), 66.73 (C1); 38.77 (CH_3SO_2); 32.54 (C5); 30.88–23.32 (C6–C15); 14.78 (C16).

(iii) [Dihydro derivative (187 mg, 0.175 mmol), sodium azide (455 mg, 7 mmol) in dry dimethylsulfoxide (12 mL)]: $[\alpha]_D^{20}$ +19.2 (*c* 1.5, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2870, 2100, 1648, 1510, 1460, 1366, 1248, 1100, 735; ^{1}H NMR ($CDCl_3$) δ 7.5–7.3 (fm, 30H, Ph); 5.13–4.45 (fs, 14H); 4.12–3.52 (fs, 10H); 1.72–1.55 (m, 2H, H5); 1.35 (bs, 20H, H6–H15); 0.93 (t, 3H, $J=3.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.73–137.88 (CquatCH$_2$–Ph); 128.28–127.41 (Ph–CH$_2$); 96.66 (C1′); 79.82, 79.46, 78.70, 76.32, 74.92, 69.68 (C3, C4, C2′, C3′, C4′, C5′); 74.69, 74.34, 73.14, 73.06, 72.71 (CH$_2$–Ph); 69.66 (C6′), 68.41 (C1); 61.64 (C2); 31.87 (C5); 29.66–22.64 (C6–C15); 14.09 (C16). [$C_{64}H_{79}N_3O_8$ requires: C, 75.5%; H, 7.8%. Found: C, 75.6%; H, 7.9%; MS: *m*/*z* 989 (M^+-N_2)].

(iv) [Azido derivative (151 mg, 0.148 mmol) in ethyl acetate/ethanol 95% mixture (18 mL, 1:2), Pd/$CaCO_3$ (50 mg, 5%)]. **17**: ^{1}H NMR ($CDCl_3$) δ 7.43–7.22 (fm, 30H, Ph); 4.98–4.33 (fs, 14H); 3.92–3.25 (fs, 10H); 1.74 (bs, 2H, NH_2); 1.25 (bs, 22H, H5–H15), 0.9 (t, $J=4$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.29–138.40 (CquatCH$_2$–Ph); 128.81–127.92 (Ph–CH$_2$); 99.33 (C1′); 81.85, 80.81, 79.49, 75.42, 75.26, 75.08 (C3, C4, C2′, C3′, C4′, C5′); 73.95, 73.82, 73.47, 73.18, 72.85 (CH$_2$–Ph); 70.03, 69.36 (C1, C6′); 52.57 (C2); 32.43 (C5); 31.48–23.20 (C6–C15); 14.63 (C16).

4.18. (2S,3S,4R,2″R)-1-O-α-D-Galactopyranosyl-2-N-(2″-hydroxy-tetracosanoyl)hexadecane-3,4-diol **1**

A solution of (*R*)-2-*O*-benzyl-tetracosanoic acid (52.2 mg, 0.11 mmol), EDAC [*N*-(3-dimethyl-aminopropyl)-*N*′-ethylcarbodiimide hydrochloride] (26 mg, 0.13 mmol), HOBT [1-hydroxyben-zotriazole] (18 mg, 0.13 mmol) in *N*,*N*-dimethylformamide/dichloromethane (2 mL, 1:1) was stirred under N_2 for 30 min at 0°C. Then **17** (114 mg, 0.11 mmol) and diisopropylethylamine (0.005 mL, 0.3 mmol) in dry dichloromethane (7 mL) were added and the reaction mixture was

stirred for 3 h at room temperature. Diluted with ethyl acetate/diethyl ether (50 mL, 8:2) mixture, the organics were treated with saturated Na_2CO_3, then 1N hydrochloric acid and subsequently washed with water, brine and dried over Na_2SO_4. The organic phase was concentrated and the residue was purified by column chromatography over silica gel with hexane/ethyl acetate (95:5) to give amide derivative (146 mg, 90%) as an amorphous white solid. $[\alpha]_D^{20}$ +58.2 (*c* 1.4, CH_2Cl_2); IR cm^{-1} ($CHCl_3$): 2900, 2858, 1740, 1645, 1515, 1247, 1100, 1054, 735; ^1H NMR ($CDCl_3$) δ 7.52–7.33 (fm, 35H, Ph); 5.13–3.42 (fs, 27H); 2.33 (t, 2H, $J=6.5$ Hz, H2″); 1.49–1.12 (m, 64H, H5–H15/H3″–H23″); 0.97 (t, 3H, $J=6.5$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.89 (HN–C=O); 139.36–138.67 (CquatCH$_2$–Ph); 128.94–127.54 (Ph–CH$_2$); 104.08 (C1′); 83.99, 83.40, 80.89, 79.78, 74.01, 73.91, 73.77 (C3, C4, C2′, C3′, C4′, C5′, C2″); 75.47, 75.19, 73.20, 73.11, 72.77, (CH$_2$–Ph); 70.07, 69.01 (C1, C6′); 48.03 (C2); 37.13–23.21 (C5–C15, C3″–C23″); 14.65 (C16, C24″). ($C_{95}H_{133}NO_{10}$ requires: C, 78.7%; H, 9.2%. Found: C, 78.9%; H, 9.4%). A solution of amide derivative (146 mg, 0.1 mmol) in ethyl acetate/ethanol 95% mixture (2.5 mL, 1:2) was hydrogenated under atmospheric pressure over Pd/C (10 mg, 10%) for 24 h. The reaction mixture was subsequently filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (chloroform/methanol 95:5) to yield **1**[26] (79 mg, 95%) as a white solid; mp 192–194.5°C (methanol); $[\alpha]_D^{20}$ +54 (*c* 0.6, NC_5D_5); IR cm^{-1} (KBr): 3358, 2925, 2850, 1738, 1655, 1550, 1465, 1372, 1268, 1070, 1038; ^1H NMR (NC_5D_5) δ 8.50 (d, 1H, $J=9.2$ Hz, NH); 6.71 (bs, OH); 6.68 (bs, OH); 5.58–4.25 (fs, 13H); 2.28–1.62 (m, 4H); 1.5–1.1 (fs, 62H); 0.89 (t, 3H, $J=6.5$ Hz, CH_3); ^{13}C NMR (NC_5D_5) δ 173.80 (HN–C=O); 101.59 (C1′); 75.73, 75.39, 74.56, 73.28, 72.60, 71.32, 70.74, 68.82 (C1, C3, C4, C2′, C3′, C4′, C5′, C2″); 63.05 (C6′); 51.81 (C2); 37.04–19.39 (C5–C15, C3″–C23″); 14.55 (C16, C24″). ($C_{46}H_{91}NO_{10}$ requires: C, 67.5%, H, 11.2%. Found: C, 67.7%, H, 11.2%).

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