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Syntheses of α-D-galactosamine neoglycolipids

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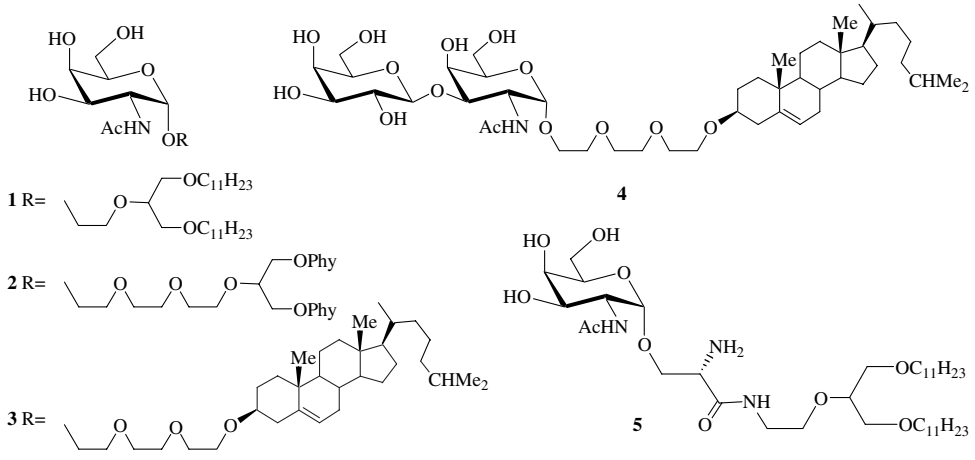
Abstract—Several *N*-acetyl-α-D-galactosamine neoglycolipids, as well as hydrophobized T and T_N antigen analogues, were prepared for embedment onto liposomes. Three different lipidic structures were used for the anchoring, that is cholesterol, 1,3-bis(undecyloxy)propan-2-ol and 1,3-bis(3,7,11,15-tetramethylhexadecyloxy)propan-2-ol. Oligoethyleneglycol spacers were used to link the carbohydrate and the hydrophobic moieties; their lengths were varied in order to obtain model compounds for the selective recognition by sialyl transferases involved in cancer processes. Glycosylation reactions were optimized to sluggish amphiphilic acceptor alcohols, in order to reach good 1,2-cis-stereoselectivities and acceptable yields. This aim was achieved by using 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate as the donor, trimethylsilyl trifluoromethanesulfonate as the promoter and diethyl ether or mixtures of diethyl ether and dichloromethane as solvents.

Keywords: Neoglycolipids; *N*-Acetyl-α-D-galactosamine; Glycosylation; Hydrophobic anchor

1. Introduction

Mucins are transmembrane *O*-glycoproteins found in mucus.[1,2] The biosynthesis of epithelial mucins is initiated by the linkage of *N*-acetyl-α-D-galactosamine to serine or threonine (T_N antigens: α-D-GalNAc-Ser or α-D-GalNAc-Thr). Further galactosylation at C-3 affords the *core 1* saccharidic structures (T antigens: β-D-Gal-(1→3)-α-D-GalNAc-Ser (or Thr)). At this stage, the C-6 position of D-galactose can be glycosylated by means of a β-(1→6)-D-GlcNAc transferase. After chain extension with poly-*N*-acetyllactosamine,



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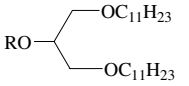
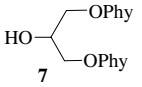
the chain growth is ended by attachment of sialic acid, L-fucose or D-galactose. In tumour cells, the biosynthesis of complex glycans is inhibited by the underexpression of several glycosyltransferases and the overexpression of sialyl transferases. As a consequence, the high levels of short oligosaccharides (such as T_N and T antigens), acting as substrates for sialyl transferases, result in the accumulation of ST_N, α-2,3 ST or α-2,6 ST antigens.[1,3]

Antitumour vaccines were prepared by covalent coupling of the synthetic aforementioned antigens to immunogenic proteins.[4–6] In the same perspective, the aim of this work was the preparation of *N*-acetyl-α-D-galactosamine neoglycolipids **1**–**4** and that of a T_N antigen analogue **5** suitable for embedment onto liposomes. The resulting vesicles could constitute targets for the sialyl transferases involved in cancer processes.

For that purpose, we intended the synthesis of three families of neoglycolipids built on distinct lipid structures: 1,3-bis(undecyloxy)propan-2-ol (**6**), 1,3-bis(3,7,11,15-tetramethylhexadecyloxy)propan-2-ol (**7**) and cholesterol. The oligoethyleneglycol spacer between the lipid and saccharide moieties was set to bring a favourable hydrophilic–hydrophobic balance on the molecule for a good embedment onto liposomes. The length of the latter was chosen with regard to our preceding results,[7] that is monoethyleneglycol for the less hydrophobic structure (**8**) and triethyleneglycol for the more hydrophobic ones (**9** and **10**).



6 R=H
8 R=CH_2CH_2OH
11 R=CH_2CN
12 R=$CH_2CH_2NH_2$



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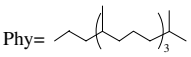
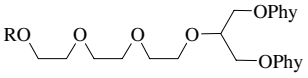
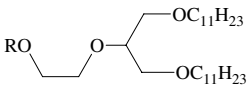
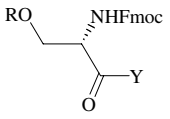




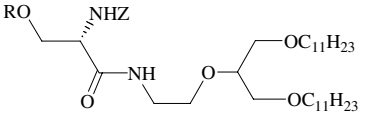
9 R=H
13 R=THP
17a R=Ra
17b R=Rb
2 R=Rc



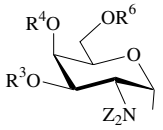
8 R=H
16a R=Ra
16b R=Rb
1 R=Rc



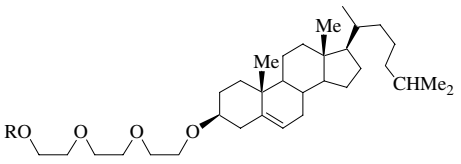
14 R=H, Y=OH
20a R=Ra, Y=OBn
20b R=Rb, Y=OBn
21b R=Rb, Y=OH



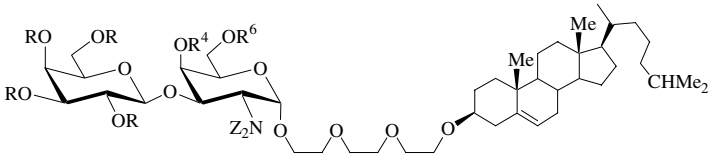
15 R=H, Z=Fmoc
19a R=Ra, Z=Fmoc
19b R=Rb, Z=Fmoc
22b R=Rb, Z=H
5 R=Rc, Z=H



Ra. $NZ_2=N_3$, $R^3=R^4=R^6$=Ac
Rb. NZ_2=NHAc, $R^3=R^4=R^6$=Ac
Rc. NZ_2=NHAc, $R^3=R^4=R^6$=H
Rd. $NZ_2=N_3$, R^3=H, R^4-R^6=PhCH<



10 R=H
18a R=Ra
18b R=Rb
18d R=Rd
3 R=Rc



23 $NZ_2=N_3$, R=Ac, R^4-R^6=PhCH<
24 $NZ_2=N_3$, R=Ac, $R^4=R^6$=H
25 NZ_2=NHAc, $R=R^4=R^6$=Ac
4 NZ_2=NHAc, $R=R^4=R^6$=H

2. Results and discussion

To our knowledge, there were no preparations of neoglycolipids of *N*-acetyl-D-galactosamine reported in the literature. However, several long chain aglycons (e.g., 9-hydroxynonanoic acid methyl ester) were glycosylated with 2-azido-2-deoxy-D-galactopyranosyl chlorides or bromides and various promoters favouring the α-stereoselectivity.[8–10] The most challenging concern in such reactions is the selection of a donor/promoter system able to react with sluggish acceptors and to induce the formation of 1,2-*cis*-glycosides in high yields and with a high stereoselectivity. Latest advancements in the field have been reviewed recently.[11,12] In the D-galactosamine series, the 1,2-cis-stereoselectivity is usually obtained with a donor bearing a non-participating azido group at C-2 and an anomeric leaving group such as β-chloride,[13,14] α-bromide[15,16] or β-imidate.[17–19] Other methods, starting from 2-acetamido-2-deoxy-α-D-galactopyranosyl imidate[20] or 2-nitro-D-galactal[21,22] have also been reported recently.

1,3-Bis(undecyloxy)propan-2-ol (**6**) was prepared in a different way than that already reported.[23] Racemic 1,2-*O*-isopropylidene glycerol was reacted at the OH-free position with undecyl bromide, before hydrolysis of the acetal function in acidic conditions. The diol, thus obtained, was regioselectively alkylated at the primary position with undecyl bromide and dibutyltin oxide[24] to afford the expected derivative **6**[23] in 75% overall yield. This three-step synthesis is more time consuming than the reaction of undecyl alcohol with epichlorohydrin,[23] but it affords a much more better yield. Alcohol **6** was then converted to compound **8** (58%) by reaction with 2-tetrahydropyranyloxyethyl chloride in phase transfer conditions, followed by hydrolysis of the tetrahydropyranyl group in acidic medium. The amino compound **12** (70%) was obtained from alcohol **6**, by reaction with bromoacetonitrile and sodium hydride, followed by reduction of the nitrile intermediate **11** by hydrogenation (10% Pd/C).

1,3-Bis(3,7,11,15-tetramethylhexadecyl)propan-2-ol (**7**) was prepared in 32% overall yield by reaction of phytol (3,7,11,15-tetramethyl-2-hexadecen-1-ol) with epichlorohydrin and sodium hydride in THF, followed by hydrogenation of the crude intermediate in the presence of platinum oxide. Reaction of **7** with tetrahydropyranyl triethyleneglycol monotosylate[25] and NaH in refluxing THF afforded the intermediate **13**, further converted into alcohol **9** by removal of the tetrahydropyranyl group in mild acidic conditions.

Fmoc-L-serine **14**[26] was reacted with the amino intermediate **12** in usual conditions (DCC, HOBt in DMF) to afford the *C*-lipidic aminoacid **15** in 59% yield.

For glycosylation reactions, 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate[27] (1:4, α/β mixture) was used as the donor, diethyl ether or mixtures of diethyl ether and dichloromethane were used as the solvent (diethyl ether is known to favour the formation of α-glycosides and dichloromethane was often necessary to enhance solubility at low temperature), catalytic amounts of trimethylsilyl trifluoromethanesulfonate were used as the promoter. Acceptor alcohol **8** was thus reacted with an excess of donor (1.5 equiv) to afford **16a** (62%) as an inseparable 3:1 α/β-anomeric mixture. After reduction of the azido function (nickel chloride–sodium borohydride) and N-acetylation, pure α isomer **16b** could be separated in 64% yield. Fully deprotected **1** was quantitatively obtained by Zemplén O-deacetylation of **16b**.

Similarly, glycosylation of alcohol **9** afforded **17a** (4:1, α/β mixture, 91%) from which it was possible to separate a small amount of pure α-isomer for analytical purposes. When reduction of the azido function and N-acetylation, in the same conditions as above, was applied to **17a** (α/β mixture), compound **17b** was obtained as an α/β mixture (84%) from which the α anomer could be separated in 51% yield. Finally, **17b** was de-O-acetylated to afford the fully deprotected derivative **2**.

With the monocholesteryl triethyleneglycol acceptor **10**,[7] the results were very similar: the glycosylation led to **18a** (4:1, α/β mixture, 89%), reduction and N-acetylation afforded **18b** from which the pure α-isomer could be separated in 56% yield. O-Deacetylation gave quantitatively the expected neoglycolipid **3**.

Glycosylation of lipopeptide **15** in similar conditions was less efficient. Compound **19a** was obtained in 35% yield only, and the reaction required a stoichiometric amount of promoter (TMSOTf). Furthermore, the stereoselectivity in favour of the α isomer was lower (2:1). The reverse procedure reported by Schmidt and Toepfer[28] did not afford any improvement. Therefore, glycosylation of a protected serine, before condensation of the lipid moiety, was considered as another route to **19b**. Thus, glycosylation of benzyl *N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-L-serinate[24] with 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate afforded the known glycoside **20a**[29] (α-anomer, 72%). The azido function was then converted to acetamide as described previously (**20b**). The benzyl ester was removed by hydrogenolysis to afford **21b**; then, reaction of the latter with the amine **12** in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) afforded **19b** in 43% yield. Compound **19b** could also be obtained in 47% yield by reduction-acetylation of **19a**. The Fmoc group was removed by treatment of **19b** with morpholine to afford **22b** (76%), which was fully O-deacetylated to **5** in Zemplén conditions.

In order to synthesize a neoglycolipid bearing the same disaccharidic determinant as T antigens, the azido derivative **18a** was O-deacetylated and reacted with benzaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid to afford the 4,6-*O*-benzylidene derivative **18d**

(69%). Glycosylation of the latter with 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl trichloroacetimidate[30] and a catalytic amount of trimethylsilyl trifluoromethanesulfonate in dichloromethane at −20 °C afforded the disaccharidic neoglycolipid **23** (71%). Removal of the benzylidene group (borontrifluoride etherate/ethanethiol) afforded compound **24**, which was then O-acetylated. After reduction of the azido function (hydrogenation, 10% Pd/C) and N-acetylation, compound **25** (70%) was quantitatively O-deacetylated in Zemplén conditions to afford the expected compound **4**.

As a conclusion, it can be mentioned that glycosylation reactions with highly hydrophobic acceptor alcohols do not result in yields and stereoselectivities as high as those reported in the literature. Nevertheless, five neoglycolipids (**1**–**5**) in which the hydrophilic moieties are building blocks of T and T_N antigens have been prepared by chemical synthesis in quite acceptable yields. They will be used as substrates of sialyl transferases, specific to the OH-6 position of *N*-acetyl-α-D-galactosamine (ST6GalNAc transferases). The amphiphilic character of these neoglycolipids will allow them to be embedded onto liposomes or adsorbed on immunotitration plates, for enzymatic measurements. The roles of the hydrophobic anchors in the adsorption process and the shifts in specificities of the enzymes towards the different haptens at an interface are expected to give further insights into the biochemistry of some cancer cell surfaces.

3. Experimental

3.1. General methods

Pyridine was dried by refluxing with CaH_2 prior to distillation. Dichloromethane was washed twice with water, dried with $CaCl_2$ and distilled from CaH_2. Tetrahydrofuran was distilled from sodium-benzophenone. Acetonitrile was distilled from CaH_2. Methanol was distilled from magnesium. Pyridine, THF and CH_2Cl_2 were stored over 4 Å molecular sieves; CH_3CN and MeOH over 3 Å molecular sieves. Melting points were determined on a Büchi apparatus and are uncorrected. Thin layer chromatography was performed on aluminium sheets coated with Silica Gel 60 F_{254} (E. Merck). Compounds were visualized by spraying the TLC plates with dilute 15% aq H_2SO_4, followed by charring at 150 °C for a few minutes. Column chromatography was performed on Silicagel Geduran Si 60 (E. Merck). Optical rotations were recorded on a Perkin Elmer 241 polarimeter in a 1 dm cell at 21 °C. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-200 spectrometer working at 200 and 50 MHz, respectively, with Me_4Si as internal standard. Elemental analyses were performed by the 'Laboratoire Central d'Analyses du CNRS' (Vernaison, France).

3.2. 2-*O*-[2-(2-Acetamido-2-deoxy-α-D-galactopyranosyloxy)ethyl]-1,3-bis(undecyloxy)propan-2-ol (1)

A soln of compound **16b** (0.441 g, 0.57 mmol) in MeOH (28 mL) containing a chip of sodium was stirred overnight at rt. After neutralization with Amberlyst IR 120 (H^+) and filtration, the solvent was evaporated under diminished pressure to afford **1** (0.367 g, 94%) as an amorphous solid; $[\alpha]_D$ +30.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.63 (d, 1H, $J_{2,NH}$ 9.7 Hz, N*H*), 4.91 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.72 (s, 1H, O*H*), 4.62 (ddd, 1H, $J_{2,3}$ 11.4 Hz, H-2), 4.00 (dd, 1H, $J_{3,4}$ 2.7, $J_{4,5}$ 1.0 Hz, H-4), 3.87 (dd, 1H, H-3), 3.89–3.76 (m, 6H, H-6a, H-6b, OCH_2CH_2O), 3.68–3.62 (m, 2H, H-5, $CH(CH_2O-C_{11}H_{23})_2$), 3.55–3.39 (m, 8H, $2CH_2OCH_2C_{10}H_{21}$), 2.96 (s, 1H, O*H*), 2.05 (s, 3H, CH_3CON), 1.60–1.48 (m, 4H, $2OCH_2CH_2C_9H_{19}$), 1.35–1.15 (m, 32H, $16CH_2$ alkyl chains), 0.89 (t, 6H, *J* 6.5 Hz, $2CH_3$ alkyl chains); ^{13}C NMR ($CDCl_3$): δ 172.7 (CH_3CO), 97.9 (C-1), 78.2 ($CH(CH_2OC_{11}H_{23})_2$), 71.7, 70.8 ($CH(CH_2OCH_2-C_{10}H_{21})_2$), 70.4, 70.1, 69.5 (C-3, C-4, C-5), 69.0, 67.7 (OCH_2CH_2O), 62.4 (C-6), 50.6 (C-2), 31.9, 29.7, 29.6, 29.5, 29.4, 26.1, 22.7 (CH_2 alkyl chains), 23.1 (CH_3CON), 14.1 (CH_3 alkyl chains). Anal. Calcd for $C_{35}H_{69}NO_9 \cdot 0.5H_2O$ (656.95): C, 63.99; H, 10.74; N, 2.13. Found: C, 63.74; H, 10.69; N, 2.19.

3.3. 15,19,23,27-Tetramethyl-10-(3,7,11,15-tetramethylhexadecyloxymethyl)-3,6,9,12-tetraoxaoctacosyl 2-acetamido-2-deoxy-α-D-galactopyranoside (2)

Prepared from **17b** (0.369 g, 0.33 mmol), as described for **1**, to afford **2** (0.318 g, 97%) as a colourless oil; $[\alpha]_D$ +25.8 (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 172.8 (CH_3CO), 97.9 (C-1), 78.5 ($CH(CH_2OPhy)_2$), 70.9, 70.8, 70.6, 70.4, 70.0, 69.7, 67.3 (($OCH_2CH_2)_3$, $CH(CH_2OCH_2C_{19}H_{39})_2$), 71.0, 70.4, 69.6 (C-3, C-4, C-5), 62.6 (C-6), 50.8 (C-2), 39.4, 37.6, 37.5, 37.4, 37.3, 36.8, 36.7, 32.8, 30.0, 28.0, 25.3, 24.8, 24.5, 23.3, 22.8, 22.7, 19.8, 19.7, 19.7 (CH, CH_2, CH_3 phytyl chains, CH_3CON). Anal. Calcd for $C_{57}H_{113}NO_{11} \cdot 0.5H_2O$ (997.49): C, 68.63; H, 11.52; N, 1.40. Found: C, 68.31; H, 11.10; N, 1.42.

3.4. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 2-acetamido-2-deoxy-α-D-galactopyranoside (3)

Prepared from **18b** (0.705 g, 0.83 mmol), as described for **1**, to afford **3** (0.609 g, 98%) as a colourless oil; $[\alpha]_D$ +10.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.79 (d, 1H, $J_{2,NH}$ 7.7 Hz, NHAc), 5.36–5.34 (m, 1H, H-6_{chol}), 4.90 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1), 4.31–4.27 (m, 1H, H-2), 4.04–4.02 (m, 1H, H-4), 3.87–3.83 (m, 4H, H-3, H-5, H-6a, H-6b), 3.67–3.63 (m, 12H, ($OCH_2-CH_2)_3$), 3.20–3.18 (m, 1H, H-3_{chol}), 2.34–0.68 (m, 43H, cholesterol), 2.06 (s, 3H, CH_3CON); ^{13}C NMR ($CDCl_3$):

δ 172.8 (CH_3CO), 140.8 (C-5_{chol}), 121.7 (C-6_{chol}), 97.9 (C-1), 79.6 (C-3_{chol}), 70.9, 70.5, 69.9, 67.2 ((OCH_2-$CH_2)_3$), 70.0, 69.9, 69.4 (C-3, C-4, C-5), 61.9 (C-6), 56.8 (C-14_{chol}), 56.2 (C-17_{chol}), 50.5 (C-9_{chol}), 50.2 (C-2), 42.4 (C-13_{chol}), 39.8 (C-12_{chol}), 39.5 (C-24_{chol}), 39.0 (C-4_{chol}), 37.2 (C-1_{chol}), 36.9 (C-10_{chol}), 36.2 (C-22_{chol}), 35.8 (C-20_{chol}), 32.0 (C-7_{chol}), 31.9 (C-8_{chol}), 28.4 (C-2_{chol}), 28.3 (C-16_{chol}), 28.0 (C-25_{chol}), 24.3 (C-15_{chol}), 23.9 (C-23_{chol}), 23.2 (C-27_{chol}), 22.8 (C-26_{chol}), 22.6 (CH_3CON), 21.1 (C-11_{chol}), 19.4 (C-19_{chol}), 18.8 (C-21_{chol}), 11.9 (C-18_{chol}). Anal. Calcd for $C_{41}H_{71}NO_9 \cdot 1.5H_2O$ (749.01): C, 65.74; H, 9.89; N, 1.87. Found: C, 65.64; H, 9.79; N, 1.87.

3.5. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 2-acetamido-2-deoxy-3-*O*-β-D-galactopyranosyl-α-D-galactopyranoside (4)

Prepared from **25** (0.273 g, 0.23 mmol), as described for **1**, to afford **4** (0.199 g, 96%) as a white solid; mp 213–214 °C; $[\alpha]_D$ +24.2 (*c* 1.1, 3:1 $CHCl_3$–MeOH); ^1H NMR ($CDCl_3$): δ 5.17–5.15 (m, 1H, 6_{chol}), 4.65 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.28 (dd, 1H, $J_{2,3}$ 10.7 Hz, H-2), 4.11 (d, 1H, $J_{1',2'}$ 7.3 Hz, H-1′), 4.08–4.06 (m, 1H, H-4), 3.97–3.95 (m, 1H, H-4′), 3.68–3.30 (m, 21H, H-3, H-5, H-6a, H-6b, H-2′, H-3′, H-5′, H-6′a, H-6′b, ($OCH_2CH_2)_3$), 3.21–3.19 (m, 1H, H-3_{chol}), 2.30–0.65 (m, 43H, H cholesterol), 1.79 (s, 3H, CH_3CON); ^{13}C NMR ($CDCl_3$): δ 172.8 (CH_3CO), 140.5 (C-5_{chol}), 121.6 (C-6_{chol}), 105.0 (C-1′), 97.7 (C-1), 79.5 (C-3_{chol}), 78.4 (C-3), 74.9 (C-5′), 73.1 (C-3′), 70.9 (C-2′, C-5), 70.6, 70.2, 70.1, 70.0, 67.0, 66.4 (($OCH_2CH_2)_3$), 68.8, 68.6 (C-4, C-4′), 61.3 (C-6, C-6′), 56.6 (C-14_{chol}), 56.0 (C-17_{chol}), 50.1 (C-9_{chol}), 48.2 (C-2), 42.2 (C-13_{chol}), 39.6 (C-12_{chol}), 39.4 (C-24_{chol}), 38.8 (C-4_{chol}), 37.0 (C-1_{chol}), 36.7 (C-10_{chol}), 36.0 (C-22_{chol}), 35.6 (C-20_{chol}), 31.7 (C-7_{chol}), 31.7 (C-8_{chol}), 28.1 (C-2_{chol}), 28.0 (C-16_{chol}), 27.8 (C-25_{chol}), 24.1 (C-15_{chol}), 23.6 (C-23_{chol}), 22.5 (CH_3CON), 22.5 (C-27_{chol}), 22.3 (C-26_{chol}), 20.9 (C-11_{chol}), 19.1 (C-19_{chol}), 18.5 (C-21_{chol}), 11.6 (C-18_{chol}). Anal. Calcd for $C_{47}H_{81}NO_{14} \cdot H_2O$ (902.141): C, 62.57; H, 9.28; N, 1.55. Found: C, 62.67; H, 9.28; N, 1.43.

3.6. 4-Undecyloxymethyl-3,6-dioxaheptadecyl *O*-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-L-serinamide (5)

Prepared from **22b** (0.034 g, 0.040 mmol), as described for **1**, to afford **5** (0.028 g, 95%) as a colourless oil; $[\alpha]_D$ +36.5 (*c* 1.0, $CHCl_3$); ^{13}C NMR (1:1 $CDCl_3$–CD_3OD): δ 172.7 (CH_3CO), 170.8 ($CONH_{Ser}$), 98.5 (C-1), 78.1 ($CH(CH_2OC_{11}H_{23})_2$), 71.7, 70.6, 69.2, 68.7, 68.9 ($CH(CH_2OCH_2C_{10}H_{21})_2$, β-$CH_{2Ser}$, $NHCH_2CH_2O$, C-3, C-4, C-5), 60.8 (C-6), 55.4 (α-CH_{Ser}), 50.4 (C-2), 39.5 ($NHCH_2CH_2O$), 32.1, 29.9, 29.7, 29.6, 26.9, 22.8 (CH_2 alkyl chains), 22.8 (CH_3CON), 14.1 (CH_3 alkyl chains). MS FAB $(M+H)^+$: calcd 734.5531; found, 734.5531.

3.7. 1,3-Bis(undecyloxy)propan-2-ol (6)

Racemic 1,2-*O*-isopropylidene glycerol (3.30 g, 25 mmol) was added to freshly prepared 50% aq NaOH (50 mL) and the mixture was stirred for 1 h at 80 °C. Undecyl bromide (15.0 mL) and Bu_4NBr (1.30 g, 4.0 mmol) were successively added and heating was maintained for 7 h. After cooling to rt, the mixture was poured into water (150 mL) and extracted with CH_2Cl_2 (3 × 50 mL). Then, the combined organic extracts were washed with water (2 × 25 mL), dried (Na_2SO_4) and concentrated. The crude product was dissolved in a mixture of EtOH (20 mL) and 2 N aq HCl (30 mL) and refluxed for 1 h. After evaporation of EtOH, the aq phase was neutralized with satd aq $NaHCO_3$ and extracted with $CHCl_3$. The organic extract was dried and concentrated before purification by column chromatography (3:1 EtOAc–petroleum ether) to afford pure 1-*O*-undecyl glycerol (5.31 g, 86%). A mixture of the latter (2.74 g, 11.12 mmol) and dibutyltin oxide (3.33 g, 13.38 mmol) was refluxed in dry toluene for 5 h; water was removed by azeotropic distillation. The solvent was removed under diminished pressure and the residue was carefully dried. The product was dissolved in DMF (90 mL), undecyl bromide (3.45 mL, 15.40 mmol) and CsF (4.56 g, 30.00 mmol) were added and the mixture was stirred for 24 h at rt. Then, EtOAc (60 mL) and water (1.5 mL) were added and the mixture was stirred for 1 h, before filtration and concentration. The residue was redissolved in CH_2Cl_2 (100 mL), washed with water (2 × 25 mL) and concentrated before purification by column chromatography (1:8 EtOAc–petroleum ether) to afford product **6** (3.87 g, 87%) as a solid; mp 35 °C (lit.[23] mp 38 °C); ^1H NMR ($CDCl_3$): δ 4.02–3.91 (m, 1H, CHOH), 3.55–3.40 (m, 8H, $2CH_2OCH_2C_{10}H_{21}$), 2.59 (d, 1H, *J* 3.9 Hz, OH), 1.64–1.50 (m, 4H, $2OCH_2CH_2C_9H_{19}$), 1.40–1.20 (m, 32H, $16CH_2$ alkyl chains), 0.87 (t, 6H, *J* 6.7 Hz, $2CH_3$ alkyl chains); ^{13}C NMR ($CDCl_3$): δ 71.9, 71.7 ($CH(CH_2OCH_2C_{10}H_{21})_2$), 69.5 (CHOH), 31.9, 29.7, 29.5, 29.4, 26.1, 22.7 (CH_2 alkyl chains), 14.1 (CH_3 alkyl chains).

3.8. 1,3-Bis(3,7,11,15-tetramethylhexadecyloxy)propan-2-ol (7)

A soln of phytol (20.0 mL, 57.32 mmol) in THF (32 mL) was added dropwise (80 min) at rt to a mixture of 60% NaH in oil (5.00 g, 125 mmol), THF (40 mL) and HMPA (3.2 mL). The mixture was refluxed for 1 h, then cooled to 0 °C, before dropwise addition of epichlorohydrin (2.2 mL, 27.8 mmol) in THF (16 mL) for 40 min. The mixture was refluxed for 16 h, then cooled to rt and poured into satd aq NH_4Cl and extracted with EtOAc (3 × 75 mL). The organic phase was dried (Na_2SO_4) and concentrated under diminished pressure.

After filtration on a short column of silica-gel (1:10 EtOAc–petroleum ether), the product was dissolved in EtOAc (50 mL) and the soln was hydrogenated (4 atm) in the presence of PtO_2 (0.400 g) for 6 h at rt. After filtration on Celite, and concentration under diminished pressure, the residue was purified by column chromatography (1:1 EtOAc–petroleum ether) to afford the expected compound **7** (5.85 g, 32%) as an oily material; R_f 0.53; ^{1}H NMR ($CDCl_3$): δ 3.98–3.90 (m, 1H, HOC*H*), 3.53–3.39 (m, 8H, 4OCH_2), 2.46 (d, 1H, *J* 4.1 Hz, O*H*), 1.56–1.08 (m, 48H, 20CH_2, 8C*H* phytyl chains), 0.89–0.84 (m, 30H, 10CH_3 phytyl chains); ^{13}C NMR ($CDCl_3$): δ 72.0, 70.0 (CH(*C*H_2O*C*H_2C$_{19}$H$_{39}$)$_2$), 69.5 (*C*HOH), 39.4, 37.4, 37.3, 36.7, 36.6, 32.8, 29.9, 28.0, 25.4, 24.9, 24.5, 24.4, 22.8, 22.7, 19.8, 19.7 (*C*H_2, *C*H, *C*H_3 phytyl chains). Anal. Calcd for $C_{43}H_{88}O_3$ (653.16): C, 79.07; H, 13.58. Found: C, 79.31; H, 13.65.

3.9. 2-*O*-(2-Hydroxyethyl)-1,3-bis(undecyloxy)propan-2-ol (8)

Freshly prepared 50% aq NaOH (4 mL) was added dropwise with stirring to a soln of alcohol **6** (1.00 g, 2.50 mmol), 2-(2-chloroethoxy)tetrahydro-2*H*-pyran (1.10 mL, 7.50 mmol) and Bu_4NHSO_4 (0.085 g, 0.25 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at 65 °C for 5 days. After dilution with CH_2Cl_2 (40 mL), the organic extract was washed with water (3×10 mL), dried and concentrated under diminished pressure, before purification by column chromatography (1:6 EtOAc–petroleum ether, 0.5% NEt_3) to afford the expected tetrahydropyranyl derivative. The latter was dissolved in a 1:1 MeOH–CH_2Cl_2 mixture (20 mL) and treated during 2 h with 12 N aq HCl (0.2 mL). After neutralization with $NaHCO_3$ (0.730 g), the mixture was evaporated to dryness before addition of EtOAc. After filtration and concentration, the residue was purified by column chromatography (1:3 EtOAc–petroleum ether) to afford **8** (0.645 g, 58%) as an oily material; R_f 0.58; ^{1}H NMR ($CDCl_3$): δ 3.82–3.70 (m, 5H, C*H*OH, OCH_2CH_2OH), 3.58–3.44 (m, 8H, 2CH_2OCH_2C$_{10}$H$_{21}$), 1.64–1.50 (m, 4H, 2OCH$_2$CH_2C$_9$H$_{19}$), 1.38–1.18 (m, 32H, 16CH_2 alkyl chains), 0.87 (t, 6H, *J* 6.7 Hz, 2CH_3 alkyl chains); ^{13}C NMR ($CDCl_3$): δ 78.6 (O*C*H), 72.3 (O*C*H$_2$CH$_2$OH), 71.8, 71.3 (CH(*C*H$_2$O*C*H$_2$C$_{10}$H$_{21}$)$_2$), 62.1 (OCH$_2$*C*H$_2$OH), 31.9, 29.6, 29.5, 29.4, 26.1, 22.7 (*C*H_2 alkyl chains), 14.1 (*C*H_3 alkyl chains). Anal. Calcd for $C_{27}H_{56}O_4$ (444.73): C, 72.92; H, 12.69. Found: C, 72.85; H, 12.87.

3.10. 15,19,23,27–Tetramethyl-10-(3,7,11,15-tetramethylhexadecyloxymethyl)-3,6,9,12-tetraoxaoctacosan-1-ol (9)

Product **13** (0.800 g, 0.920 mmol) was dissolved in 0.3:10:10 12 N aq HCl–MeOH–CH_2Cl_2 (9 mL) and the soln was stirred at rt for 45 min. Then, $NaHCO_3$ (0.300 g, 3.57 mmol) was added to the mixture, before addition of EtOAc (50 mL). The organic extract was washed with water, dried ($MgSO_4$), concentrated and purified by column chromatography (1:2 EtOAc–petroleum ether) to afford product **9** (0.588 g, 81%) as a colourless oil; R_f 0.43; ^{1}H NMR ($CDCl_3$): δ 3.80–3.73 (m, 1H, C*H*(CH$_2$OPhy)$_2$), 3.70–3.59 (m, 12H, (CH_2-CH_2O)$_3$), 3.51–3.44 (m, 8H, 2CH_2OCH_2C$_{19}$H$_{39}$), 1.56–1.08 (m, 48H, 20CH_2, 8C*H* phytyl chains), 0.89–0.85 (m, 30H, 10CH_3 phytyl chains); ^{13}C NMR ($CDCl_3$): δ 78.4 (*C*H(CH$_2$OPhy)$_2$), 72.7, 70.9, 70.6, 70.4, 70.0, 69.7 (CH(*C*H_2O*C*H_2C$_{19}$H$_{39}$)$_2$, (*C*H_2*C*H_2O)$_2$, O*C*H_2CH$_2$OH), 61.7 (*C*H_2OH), 39.4, 37.5, 37.4, 37.3, 36.7, 36.6, 32.8, 29.9, 28.0, 24.8, 24.5, 24.4, 24.1, 22.7, 22.6, 19.8, 19.7 (*C*H_2, *C*H, *C*H_3 phytyl chains). Anal. Calcd for $C_{49}H_{100}O_6$ (785.31): C, 74.94; H, 12.83. Found: C, 74.93; H, 13.09.

3.11. 4-Undecyloxymethyl-3,6-dioxaheptanenitrile (11)

Sodium hydride (600 mg, 15 mmol, 60% in oil) was slowly added under Ar to a soln of the alcohol **6** (1.20 g, 3.00 mmol) in CH_3CN (7 mL). After stirring for 2 h, the mixture was cooled to −20 °C and bromoacetonitrile (1.56 mL, 24.00 mmol) was added slowly. Stirring was maintained overnight at −20 °C, then the reaction mixture was allowed to reach rt and concentrated. After addition of CH_2Cl_2 (50 mL), the salts were removed by centrifugation and filtration. After evaporation of the solvent and purification by column chromatography (1:6 EtOAc–petroleum ether), compound **11** (1.015 g, 77%) was obtained as a colourless oil; R_f 0.75; ^{1}H NMR ($CDCl_3$): δ 4.50 (s, 2H, OCH_2CN), 3.92–3.82 (m, 1H, O*C*H), 3.55 (d, 4H, *J* 4.8 Hz, 2CH_2OC$_{11}$H$_{23}$), 3.44 (t, 4H, *J* 6.6 Hz, 2OCH_2C$_{10}$H$_{21}$), 1.65–1.50 (m, 4H, 2OCH$_2$CH_2C$_9$H$_{19}$), 1.37–1.17 (m, 32H, 16CH_2 alkyl chains), 0.88 (t, 6H, *J* 6.3 Hz, 2CH_3 alkyl chains); ^{13}C NMR ($CDCl_3$): δ 116.7 (*C*N), 78.8 (O*C*H), 71.8, 71.2 (CH(*C*H$_2$O*C*H$_2$C$_{10}$H$_{21}$)$_2$), 56.1 (*C*H$_2$CN), 31.9, 29.7, 29.6, 29.5, 29.4, 26.1, 22.7 (*C*H_2 alkyl chains), 14.1 (*C*H_3 alkyl chains). Anal. Calcd for $C_{27}H_{53}NO_3$ (439.40): C, 73.75; H, 12.15; N, 3.19. Found: C, 73.72; H, 12.08; N, 3.22.

3.12. 2-*O*-(2-Aminoethyl)-1,3-bis(undecyloxy)propan-2-ol (12)

A mixture of compound **11** (0.900 g, 2.05 mmol) in EtOH (25 mL) and 12 N aq HCl (1 mL) containing 10% Pd/C (108 mg) was stirred under hydrogen (10 atm) for 4 h before neutralization with NEt_3 (15 mL). After filtration and evaporation, petroleum ether was added to the mixture. Triethylammonium chloride was filtered off and the organic phase was washed with water (2×5 mL), dried (Na_2SO_4) and con-

centrated to dryness. After purification by column chromatography (10:1 $CHCl_3$–MeOH), product **12** (0.758 g, 83%) was obtained as a colourless oil; R_f 0.50; ^{1}H NMR ($CDCl_3$): δ 3.65–3.60 (m, 3H, OC*H*, $OCH_2CH_2NH_2$), 3.51–3.40 (m, 8H, $2CH_2OCH_2C_{10}H_{21}$), 2.85 (t, 2H, *J* 4.9 Hz, CH_2NH_2), 1.70 (s, 2H, NH_2), 1.65–1.50 (m, 4H, $2OCH_2CH_2C_9H_{19}$), 1.43–1.23 (m, 32H, $16CH_2$ alkyl chains), 0.88 (t, 6H, *J* 6.4 Hz, $2CH_3$ alkyl chains); ^{13}C NMR ($CDCl_3$): δ 78.1 (O*C*H), 72.4 ($OCH_2CH_2NH_2$), 71.6, 70.8 ($CH(CH_2OCH_2C_{10}H_{21})_2$), 42.1 ($OCH_2CH_2NH_2$), 31.9, 29.6, 29.5, 29.3, 26.1, 22.7 (CH_2 alkyl chains), 14.1 (CH_3 alkyl chains). Anal. Calcd for $C_{27}H_{57}NO_3$ (443.75): C, 73.08; H, 12.95; N, 3.16. Found: C, 72.74; H, 12.93; N, 3.14.

3.13. 15,19,23,27-Tetramethyl-10-(3,7,11,15-tetramethylhexadecyloxymethyl)-1-tetrahydropyranyloxy-3,6,9,12-tetraoxaoctacosane (13)

A mixture of alcohol **7** (1.30 g, 0.200 mmol) and NaH (60% in oil, 0.400 g, 10 mmol, washed with pentane) in THF was refluxed for 2 h and then cooled to rt. A soln of 1-tetrahydropyranyloxy-8-tosyloxy-3,6-dioxaoctane[25] (3.90 g, 10 mmol) in THF (70 mL) was added dropwise over 2 h and the mixture was refluxed for 22 h. After cooling to rt and addition of water (50 mL), THF was removed under diminished pressure and the mixture was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with water, dried (Na_2SO_4), concentrated and purified by column chromatography (1:5 EtOAc–petroleum ether) to afford product **13** (1.06 g, 60%) as an amorphous solid; R_f 0.52; ^{1}H NMR ($CDCl_3$): δ 4.64–4.62 (m, 1H, C*H* THP), 3.92–3.84 (m, 1H, $CH(CH_2OPhy)_2$), 3.82–3.74 (m, 2H, OCH_2 THP), 3.71–3.61 (m, 12H, $(CH_2CH_2O)_3$), 3.54–3.42 (m, 8H, $2CH_2OCH_2C_{19}H_{39}$), 1.71–1.08 (m, 54H, $3CH_2$ THP, $20CH_2$, 8C*H* phytyl chains), 0.89–0.85 (m, 30H, $10CH_3$ phytyl chains); ^{13}C NMR ($CDCl_3$): δ 98.9 (*C*H THP), 78.5 ($CH(CH_2OPhy)_2$), 78.5, 70.9, 70.8, 70.6, 70.0, 69.8, 69.4, 67.3, 66.7, 62.2 ($CH(CH_2OCH_2C_{19}H_{39})_2$, $(CH_2CH_2O)_3$, CH_2O THP), 39.4, 37.5, 37.4, 37.3, 36.8, 36.7, 32.8, 30.6, 29.9, 28.0, 25.5, 24.8, 24.5, 24.4, 24.0, 22.8, 22.7, 19.8, 19.7 (CH_2 THP, CH_2, *C*H, CH_3 phytyl chains). Anal. Calcd for $C_{54}H_{108}O_7$ (869.43): C, 74.60; H, 12.52. Found: C, 74.63; H, 12.66.

3.14. 4-Undecyloxymethyl-3,6-dioxaheptadecyl *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-serinamide (15)

A mixture of amine **12** (0.406 g, 0.910 mmol), *N*-(9*H*-fluoren-9-ylmethoxycarbonyl)-L-serine[24] **14** (0.310 g, 0.940 mmol) and 1-hydroxybenzotriazole (0.141 g, 1.04 mmol) in dry DMF (4 mL) was cooled to 0 °C. A soln of dicyclohexylcarbodiimide (0.203 g, 0.980 mmol) in DMF (5 mL) was added dropwise and the mixture was stirred for 10 min at 0 °C, then allowed to reach rt and stirred for 6 h. After dilution with CH_2Cl_2 and filtration on Celite, the organic extract was washed with 0.1 N HCl, then with satd aq $NaHCO_3$ and water. After drying (Na_2SO_4) and concentration, the crude product was purified by column chromatography (2:1 EtOAc–petroleum ether) to afford **15** (0.404 g, 59%) as an amorphous solid; $[\alpha]_D$ +2.4 (*c* 1.0, $CHCl_3$); R_f 0.60; ^{13}C NMR (1:1 $CDCl_3$–CD_3OD): δ 170.8 (*C*ONH), 156.4 ($NHCOO_{Fmoc}$), 143.3, 140.8 (aromatic C_{Fmoc}), 127.1, 126.5, 124.5, 119.3 (aromatic CH_{Fmoc}), 77.5 ($OCH(CH_2OC_{11}H_{23})_2$), 71.1, 69.9, 68.0, 66.6 ($CH(CH_2OCH_2C_{10}H_{21})_2$, OCH_2CH_2NH,CH_{2Fmoc}), 61.8 (β-CH_{2Ser}), 56.5 (α-CH_{Ser}), 46.6 (C-9_{Fmoc}), 39.2 (OCH_2CH_2NH), 33.1, 31.4, 29.0, 28.9, 28.8, 25.5, 25.0, 24.4, 22.1 (CH_2 alkyl chains), 13.2 (CH_3 alkyl chains). Anal. Calcd for $C_{45}H_{72}N_2O_7$ (753.06): C, 71.77; H, 9.64; N, 3.72. Found: C, 71.50; H, 9.55; N, 3.86.

3.15. 2-*O*-[2-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyloxy)ethyl]-1,3-bis(undecyloxy)propan-2-ol (16a)

Trimethylsilyltrifluoromethane sulfonate (64 μL, 0.331 mmol) in Et_2O (0.5 mL) was added dropwise (30 min) to a cooled (−30 °C) soln of **8** (0.650 g, 1.46 mmol) and 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate (1:4 α/β-anomeric mixture, 1.037 g, 2.18 mmol) in 3:1 Et_2O–CH_2Cl_2 (15 mL), containing crushed activated 4 Å molecular sieves. After 2 h at −30 °C, the mixture was allowed to reach rt and stirring was maintained for 18 h. The mixture was then neutralized by addition of NEt_3 (100 μL), diluted with CH_2Cl_2 (50 mL), washed with satd aq $NaHCO_3$ (2×10 mL), dried (Na_2SO_4) and concentrated under diminished pressure. After purification by column chromatography (1:3 EtOAc–petroleum), compound **16a** (0.686 g, 62%) was obtained as a 3:1 α/β-anomeric mixture. A small amount of the α anomer was isolated in a pure form as a colourless oil; $[\alpha]_D$ +83.4 (*c* 1.0, $CHCl_3$); R_f 0.58; ^{1}H NMR ($CDCl_3$): δ 5.45–5.44 (m, 1H, H-4), 5.39 (dd, 1H, $J_{2,3}$ 10.9 Hz, $J_{3,4}$ 3.2 Hz, H-3), 5.11 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.31 (br t, 1H, $J_{5,6a}$, $J_{5,6b}$ 6.7 Hz, H-5), 4.13 (dd, 1H, $J_{6a,6b}$ 11.1 Hz, H-6a), 4.06 (dd, 1H, H-6b), 3.88–3.77 (m, 4H, OCH_2CH_2O), 3.75–3.72 (m, 1H, $CH(CH_2OC_{11}H_{23})_2$), 3.62 (dd, 1H, H-2), 3.51–3.40 (m, 8H, $2CH_2OCH_2C_{10}H_{21}$), 2.14, 2.05, 2.04 (3s, 9H, $3CH_3CO$), 1.64–1.50 (m, 4H, $2OCH_2CH_2C_9H_{19}$), 1.35–1.18 (m, 32H, $16CH_2$ alkyl chains), 0.88 (t, 6H, *J* 6.3 Hz, $2CH_3$ alkyl chains); ^{13}C NMR ($CDCl_3$): δ 170.2, 170.0, 169.7 ($3CH_3CO$), 98.1 (C-1), 78.5 ($CH(CH_2OC_{11}H_{23})_2$), 71.6, 70.9 ($CH(CH_2OCH_2C_{10}H_{21})_2$), 69.3, 67.8 ($OCH_2CH_2O$), 70.9, 68.1, 67.8 (C-3, C-4, C-5), 61.5 (C-6), 57.4 (C-2), 31.9, 29.6, 29.5, 29.3, 26.1, 22.7 (CH_2 alkyl chains), 20.7, 20.6 (CH_3COO), 14.1 (CH_3 alkyl chains). Anal. Calcd for

$C_{39}H_{71}N_3O_{11}$ (757.99): C, 61.80; H, 9.44; N, 5.54. Found: C, 61.78; H, 9.46; N, 5.57.

3.16. 2-*O*-[2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyloxy)ethyl]-1,3-bis(undecyloxy)propan-2-ol (16b)

A soln of $NaBH_4$ in EtOH (0.300 mol/L) was added dropwise to a stirred soln of $NiCl_2{\cdot}6H_2O$ (2.371 g, 10.00 mmol), $B(OH)_3$ (0.927 g, 15.00 mmol) and azido-glycoside **16a** (0.758 g, 1.00 mmol) in EtOH (50 mL), until persistency of the dark colour. After 1.5 h, the mixture was concentrated under diminished pressure and the residue was dissolved in a 3:1 pyr–Ac_2O mixture (10 mL). After stirring for 18 h at rt, the mixture was concentrated under diminished pressure before addition of CH_2Cl_2, washing with 3% aq $KHSO_4$ (10 mL), then water (10 mL). After drying (Na_2SO_4) and concentration, the residue was purified by column chromatography (2:1 EtOAc–petroleum ether) to afford the α-product **16b** (0.495 g, 64%) as an amorphous solid; $[\alpha]_D$ +44.7 (*c* 1.0, $CHCl_3$); R_f 0.50; ^{1}H NMR ($CDCl_3$): δ 6.13 (d, 1H, $J_{2,NH}$ 9.7 Hz, N*H*), 5.38 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 1.0 Hz, H-4), 5.16 (dd, 1H, $J_{3,4}$ 11.2 Hz, H-3), 4.89 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.62 (ddd, 1H, H-2), 4.25 (br t, 1H, $J_{5,6a}$, $J_{5,6b}$ 6.5 Hz, H-5), 4.15–4.05 (m, 2H, H-6a, H-6b), 3.88–3.73 (m, 4H, OCH_2CH_2O), 3.70–3.61 (m, 1H, C*H*($CH_2OC_{11}H_{23}$)$_2$), 3.50–3.40 (m, 8H, 2$CH_2OCH_2C_{10}H_{21}$), 2.16, 2.05, 1.98, 1.96 (4s, 12H, 3CH_3COO, 1CH_3CON), 1.62–1.47 (m, 4H, 2$OCH_2CH_2C_9H_{19}$), 1.40–1.15 (m, 32H, 16CH_2 alkyl chains), 0.88 (t, 6H, *J* 6.3 Hz, 2CH_3 alkyl chains); ^{13}C NMR ($CDCl_3$): δ 170.7, 170.4, 170.2 (4CH_3CO), 98.1 (C-1), 78.3 (*C*H($CH_2OC_{11}H_{23}$)$_2$), 71.7, 70.8 (CH(*C*H_2O-*C*$H_2C_{10}H_{21}$)$_2$), 69.8, 68.1 (O*C*H_2*C*H_2O), 68.7, 67.4, 66.8 (C-3, C-4, C-5), 61.9 (C-6), 47.5 (C-2), 31.9, 29.6, 29.5, 29.3, 26.1, 22.7 (*C*H_2 alkyl chains), 23.1 (*C*H_3CON), 20.7, 20.6 (3*C*H_3COO), 14.1 (*C*H_3 alkyl chains). Anal. Calcd for $C_{41}H_{75}NO_{12}$ (774.03): C, 63.62; H, 9.77; N; 1.81. Found: C, 63.11; H, 9.82; N, 1.94.

3.17. 15,19,23,27-Tetramethyl-10-(3,7,11,15-tetramethylhexadecyloxymethyl)-3,6,9,12-tetraoxaoctacosyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranoside (17a)

Trimethylsilyl trifluoromethanesulfonate (12 μL, 0.062 mmol) was added to a cooled (−30 °C) mixture of alcohol **9** (0.660 g, 0.840 mmol) and 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate (1:5 α/β-anomeric mixture, 0.520 g, 1.09 mmol) in dry Et_2O (7 mL). The mixture was then allowed to reach rt and after 40 min, it was neutralized by addition of *i*-Pr_2NEt (15 μL). After evaporation, the residue was dissolved in CH_2Cl_2 (50 mL), washed with 0.1 N aq HCl (3 × 5 mL), then water (2 × 5 mL), dried ($MgSO_4$) and concentrated under diminished pressure. After purification by column chromatography (1:2 EtOAc–petroleum ether), compound **17a** (4:1 α,β-anomeric mixture, 0.840 g, 91%) was obtained as a colourless oil. A small amount (0.200 g) of pure α-isomer was recovered as an amorphous solid, after a second chromatography; $[\alpha]_D$ +53.0 (*c* 1.0, $CHCl_3$); R_f 0.76 (0.70 for β-isomer); ^{1}H NMR ($CDCl_3$): δ 5.46 (dd, 1H, $J_{3,4}$ 3.3 Hz, $J_{4,5}$ 1.0 Hz, H-4), 5.39 (dd, 1H, $J_{2,3}$ 10.9 Hz, H-3), 5.09 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.30 (br dd, 1H, $J_{5,6a}$ 6.5 Hz, $J_{5,6b}$ 7.0 Hz, H-5), 4.14 (dd, 1H, $J_{6a,6b}$ 11.0 Hz H-6a), 4.06 (dd, 1H, H-6b), 3.88–3.39 (m, 22H, H-2, O*C*H-(CH_2OPhy)$_2$, (OCH_2CH_2)$_3$, 2$CH_2OCH_2C_{19}H_{39}$), 2.15, 2.06, 2.05 (3s, 9H, 3CH_3COO), 1.60–1.08 (m, 48H, 20CH_2, 8C*H* alkyl chains), 0.89–0.85 (m, 30H, 10CH_3 phytyl chains); ^{13}C NMR ($CDCl_3$): δ 170.3, 170.0, 169.8 (3CH_3CO), 98.3 (C-1), 78.4 (*C*H(CH_2OPhy)$_2$), 70.9, 70.8, 70.7, 70.6, 70.1, 69.9, 69.7, 67.8 ((O*C*H_2-*C*H_2)$_3$, CH(*C*H_2O*C*$H_2C_{19}H_{39}$)$_2$), 68.2, 67.6, 66.6 (C-3, C-4, C-5), 61.6 (C-6), 57.4 (C-2), 39.4, 37.5, 37.4, 37.3, 36.8, 36.7, 32.8, 29.9, 28.0, 25.3, 24.8, 24.5, 24.4, 22.8, 22.7, 19.8, 19.7 (*C*H, *C*H_2, *C*H_3 phytyl chains), 20.7, 20.6 (3*C*H_3COO). Anal. Calcd for $C_{61}H_{115}N_3O_{13}$ (1098.58): C, 66.69; H, 10.55; N, 3.82. Found: C, 67.04; H, 10.66; N, 4.02.

3.18. 15,19,23,27-Tetramethyl-10-(3,7,11,15-tetramethylhexadecyloxymethyl)-3,6,9,12-tetraoxaoctacosyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranoside (17b)

Prepared as described for **16b** from the α/β-anomeric mixture **17a** (0.840 g, 0.765 mmol). Purification by column chromatography with EtOAc afforded **17b** as a α/β-anomeric mixture (0.715 g, 84%). This mixture was chromatographed again (2:1 petroleum ether–acetone) to afford the pure α-anomer (0.435 g, 51%) as a colourless oil; $[\alpha]_D$ +29.1 (*c* 1.0, $CHCl_3$); R_f 0.42; ^{1}H NMR ($CDCl_3$): δ 6.25 (d, 1H, $J_{2,NH}$ 7.7 Hz, NHAc), 5.39 (dd, 1H, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 1.0 Hz, H-4), 5.19 (dd, 1H, $J_{3,2}$ 11.3 Hz, H-3), 4.90 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.61 (ddd, 1H, H-2), 4.24 (br dd, 1H, $J_{5,6a}$ 6.0 Hz, $J_{5,6b}$ 7.1 Hz, H-5), 4.14 (dd, 1H, $J_{6a,6b}$ 11.0 Hz H-6a), 4.06 (dd, 1H, H-6b), 3.85–3.43 (m, 21H, O*C*H(CH_2OPhy)$_2$, (OCH_2CH_2)$_3$, 2$CH_2OCH_2C_{19}H_{39}$), 2.17, 2.05, 1.99, 1.97 (4s, 12H, 3CH_3COO, CH_3CON), 1.63–1.08 (m, 48H, 20CH_2, 8C*H* phytyl chains), 0.89–0.85 (m, 30H, 10CH_3 phytyl chains); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.4, 170.3, 170.2 (4CH_3CO), 98.3 (C-1), 78.5 (*C*H(CH_2OPhy)$_2$), 70.9, 70.8, 70.7, 69.9, 69.7, 67.8 ((O*C*H_2*C*H_2)$_3$, CH(*C*H_2O*C*$H_2C_{19}H_{39}$)$_2$), 68.6, 67.5, 66.8 (C-3, C-4, C-5), 61.9 (C-6), 47.6 (C-2), 39.4, 37.5, 37.4, 37.3, 36.8, 36.7, 32.8, 30.0, 28.0, 24.8, 24.5, 24.4, 24.0, 22.8, 22.6, 19.8, 19.7 (*C*H, *C*H_2, *C*H_3 phytyl chains), 23.2 (*C*H_3CON), 20.8, 20.7 (3*C*H_3COO). Anal. Calcd for $C_{63}H_{119}NO_{14}$ (1114.62): C, 67.89; H, 10.76; N, 1.26. Found: C, 67.32; H, 10.70; N, 1.33.

3.19. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranoside (18a)

Trimethylsilyl trifluoromethanesulfonate (18 μL, 0.093 mmol) was added to a cooled (−30 °C) mixture of 8-(cholest-5-en-3β-yloxy)-3,6-dioxa-1-octanol **10**[7] (1.32 g, 2.52 mmol) and 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate (1:5 α/β-anomeric mixture, 0.930 g, 1.95 mmol), in dry Et_2O (18 mL). The mixture was allowed to reach rt and, after 30 min, it was neutralized by addition of *i*-Pr_2NEt (100 μL). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (50 mL) and the soln was washed with 0.1 N aq HCl (3 × 5 mL), then water (2 × 5 mL), dried ($MgSO_4$) and concentrated under diminished pressure, before purification by column chromatography (2:3 EtOAc–petroleum ether), to afford **18a** (1.45 g, 89%) as an inseparable 4:1 α/β-anomeric mixture; R_f 0.46; ^{1}H NMR ($CDCl_3$): selected values δ 5.10 (d, 0.8H, $J_{1,2}$ 3.5 Hz, H-1α), 4.77 (dd, 0.2H, $J_{2,3}$ 10.9 Hz, $J_{3,4}$ 3.2 Hz, H-3β), 4.50 (d, 0.2H, $J_{1,2}$ 8.0 Hz, H-1β); ^{13}C NMR ($CDCl_3$): δ 170.4, 170.1, 169.9 ($3CH_3CO$), 141.0 (C-5_{chol}), 121.6 (C-6_{chol}), 102.5 (C-1β), 98.3 (C-1α), 79.5 (C-3_{chol}).

3.20. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranoside (18b)

Prepared as described for **16b** from the α/β-anomeric mixture **18a** (1.45 g, 1.74 mmol). Purification by column chromatography (2:1 petroleum ether–acetone) afforded an unseparated 1:1 α/β-mixture (0.269 g, 18%) and the pure α-derivative **18b** (0.808 g, 56%) as a colourless oil; $[\alpha]_D$ +13.0 (*c* 1.0, $CHCl_3$); R_f 0.57; ^{1}H NMR ($CDCl_3$): δ 6.18 (d, 1H, $J_{2,NH}$ 9.8 Hz, NHAc), 5.39–5.35 (m, 2H, H-4, H-6_{chol}), 5.19 (dd, 1H, $J_{2,3}$ 11.3 Hz, $J_{3,4}$ 3.1 Hz, H-3), 4.90 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.61 (ddd, 1H, H-2), 4.24–4.20 (m, 1H, H-5), 4.13–4.07 (m, 2H, H-6a, H-6b), 3.86–3.63 (m, 12H, $(OCH_2CH_2)_3$), 3.18 (m, 1H, H-3_{chol}), 2.17, 2.05, 1.99, 1.98 (4s, 12H, $3CH_3COO$, $1CH_3CON$), 2.39–0.67 (m, 43H, H cholesterol); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.4, 170.2 ($4CH_3CO$), 140.9 (C-5_{chol}), 121.6 (C-6_{chol}), 98.1 (C-1), 79.6 (C-3_{chol}), 70.9, 70.6, 69.9, 67.5, 67.3 ($(OCH_2CH_2)_3$), 68.6, 67.4, 66.8 (C-3, C-4, C-5), 61.9 (C-6), 56.8 (C-14_{chol}), 56.2 (C-17_{chol}), 50.2 (C-9_{chol}), 47.6 (C-2), 42.3 (C-13_{chol}), 39.8 (C-12_{chol}), 39.5 (C-24_{chol}), 39.1 (C-4_{chol}), 37.2 (C-1_{chol}), 36.9 (C-10_{chol}), 36.2 (C-22_{chol}), 35.8 (C-20_{chol}), 31.9 (C–7_{chol}), 30.9 (C-8_{chol}), 28.3 (C-2_{chol}), 28.2 (C-16_{chol}), 28.0 (C-25_{chol}), 24.3 (C-15_{chol}), 23.8 (C-23_{chol}), 23.3 (C-27_{chol}), 22.8 (C-26_{chol}), 22.6 (CH_3CON), 21.1 (C-11_{chol}), 20.8, 20.7 ($3CH_3COO$), 19.4 (C-19_{chol}), 18.7 (C-21_{chol}), 11.9 (C-18_{chol}). Anal. Calcd for $C_{47}H_{77}NO_{12}$ (848.11): C, 66.56; H, 9.15; N, 1.65. Found: C, 65.91; H, 9.32; N, 1.72.

3.21. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (18d)

The α/β-anomeric mixture **18b** (0.705 g, 0.847 mmol) obtained from **18a** was quantitatively O-deacetylated with catalytic MeONa in MeOH (20 mL). After neutralization with Amberlyst IR 120 (H^+) and evaporation, the crude product was treated for 4 h at 40 °C with benzaldehyde dimethyl acetal (250 μL, 1.46 mmol) in MeCN (4.1 mL) in the presence of *p*-TsOH (0.005 g). After neutralization with satd aq $NaHCO_3$ (0.5 mL), concentration and coevaporation from toluene, the residue was directly purified by column chromatography (1:4 EtOAc–petroleum ether) to afford the pure α-anomer **18d** (0.488 g, 69%) as an oily material; $[\alpha]_D$ +53.2 (*c* 1.0, $CHCl_3$); R_f 0.57; ^{1}H NMR ($CDCl_3$): δ 7.49–7.38 (m, 5H, C_6H_5), 5.59 (s, 1H, C*H*Ph), 5.39–5.35 (m, 1H, H-6_{chol}), 5.06 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.33–4.29 (m, 1H, H-4), 4.28 (dd, 1H, $J_{5,6a}$ 1.3 Hz, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.25–4.21 (m, 1H, H-3), 4.10 (dd, 1H, $J_{5,6b}$ 1.9 Hz, H-6b), 3.88–3.62 (m, 13H, H-5, $(OCH_2CH_2)_3$), 3.59 (dd, 1H, $J_{2,3}$ 10.3 Hz, H-2), 3.19 (m, 1H, H-3_{chol}), 2.41–0.67 (m, 43H, H cholesterol); ^{13}C NMR ($CDCl_3$): δ 141.0 (C-5_{chol}), 137.5, 129.3, 128.4, 126.3 (C_6H_5), 121.6 (C-6_{chol}), 101.3 (CHC_6H_5), 98.8 (C-1), 79.6 (C-3_{chol}), 75.62 (C-4), 71.0, 70.8, 70.7, 70.2, 67.7, 67.4 ($(OCH_2CH_2)_3$), 69.4 (C-6), 67.5 (C-3), 62.8 (C-5), 60.8 (C-2), 56.8 (C-14_{chol}), 56.2 (C-17_{chol}), 50.2 (C-9_{chol}), 42.4 (C-13_{chol}), 39.8 (C-12_{chol}), 39.6 (C-24_{chol}), 39.2 (C-4_{chol}), 37.2 (C-1_{chol}), 36.9 (C-10_{chol}), 36.2 (C-22_{chol}), 35.8 (C-20_{chol}), 32.0 (C-7_{chol}), 31.9 (C-8_{chol}), 28.4 (C-2_{chol}), 28.3 (C-16_{chol}), 28.0 (C-25_{chol}), 24.3 (C-15_{chol}), 23.9 (C-23_{chol}), 22.9 (C-27_{chol}), 22.6 (C-26_{chol}), 21.1 (C-11_{chol}), 19.4 (C-19_{chol}), 18.8 (C-21_{chol}), 11.9 (C-18_{chol}). Anal. Calcd for $C_{46}H_{71}N_3O_8 \cdot H_2O$ (812.06): C, 68.03; H, 9.06; N, 5.17. Found: C, 67.69; H, 8.82; N, 5.36.

3.22. 4-Undecyloxymethyl-3,6-dioxaheptadecyl *O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl)-*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-serinamide (19a)

A mixture of the serine derivative **15** (0.376 g, 0.499 mmol), 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate (0.356 g, 0.749 mmol) and activated 4 Å molecular sieves in 2:1 Et_2O–CH_2Cl_2 (6.5 mL) was cooled to −18 °C. A soln of TMSOTf (30 μL, 0.155 mmol) in Et_2O (0.1 mL) was added slowly and stirring was continued for 2 h at −18 °C, then 18 h at rt. After neutralization with NEt_3 (30 μL), filtration, concentration and purification by column chromatography (200:1 $CHCl_3$–MeOH) product **19a** (0.177 g, 35%) was obtained as an unseparable 2:1 α/β-anomeric mixture. A fraction containing the α-derivative only, together with some trichloroacetamide, was separated for NMR. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 2H, *J* 7.5 Hz, aromatic H_{Fmoc}), 7.62 (d, 2H, *J* 7.3 Hz, aromatic

H_{Fmoc}), 7.41 (t, 2H, *J* 7.3 Hz, aromatic H_{Fmoc}), 7.33 (t, 2H, *J* 7.5 Hz, aromatic H_{Fmoc}), 7.08–7.04 (m, 1H, N*H*CO), 5.86 (br d, 1H, N*H*COO_{Fmoc}), 5.43 (br d, 1H, $J_{3,4}$ 3.0 Hz, H-4), 5.31 (dd, 1H, $J_{2,3}$ 10.3, H-3), 5.07 (d, 1H, H-1), 4.40–3.40 (m, 23H, H-2, H-5, H-6a, H-6b, H-9_{Fmoc}, α-CH_{Ser}, β-CH_{2Ser} CH($CH_2OC_{11}H_{23}$)$_2$, 2CH_2OC$H_2C_{10}H_{21}$, CH_{2Fmoc}, OCH_2CH_2N), 2.15, 2.06, 2.01 (3s, 9H, 3CH_3COO), 1.62–1.50 (m, 4H, 2OCH_2CH_2), 1.36–1.16 (m, 32H, 16CH_2 alkyl chains), 0.88 (t, 6H, 2CH_3 alkyl chains); ^{13}C NMR ($CDCl_3$): δ 170.4, 170.0, 169.7, 168.9 (3CH_3*C*OO, 1CH_2*C*ON), 156.0 (NH*C*OO_{Fmoc}), 143.8, 141.3 (aromatic C_{Fmoc}), 127.8, 127.1, 125.1, 120.0 (aromatic *C*H_{Fmoc}), 98.5 (C-1), 78.4 (O*C*H($CH_2OC_{11}H_{23}$)$_2$), 71.7, 70.9, 68.9, 68.3, 67.3 (CH(*C*H_2O*C*$H_2C_{10}H_{21}$)$_2$, O*C*H_2CH$_2$NH, β-*C*H_{2Ser}, *C*H_{2Fmoc}) 68.4, 67.4, 67.1 (C-3, C-4, C-5), 61.6 (C-6), 57.7 (C-2), 54.5 (α-*C*H_{Ser}), 47.1 (C-9_{Fmoc}), 40.0 (OCH_2*C*H_2NH), 30.0, 29.9, 29.7, 29.6, 26.4, 22.7 (*C*H_2 alkyl chains), 21.0, 20.9, 20.7 (3*C*H_3COO), 14.1 (*C*H_3 alkyl chains).

3.23. 4-Undecyloxymethyl-3,6-dioxaheptadecyl *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-serinamide (19b)

3.23.1. Method a. Compound **19b** was prepared from **19a** (0.177 g, 0.166 mmol), as described above for **16b** from **16a**. After purification by column chromatography (3:1 EtOAc–petroleum ether), **19b** (0.085 g, 47%) was obtained as an amorphous solid; $[\alpha]_D$ +41.4 (*c* 1.0, $CHCl_3$); R_f 0.30; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, 2H, *J* 7.5 Hz, aromatic H_{Fmoc}), 7.62 (d, 2H, *J* 7.3 Hz, aromatic H_{Fmoc}), 7.41 (t, 2H, *J* 7.3 Hz, aromatic H_{Fmoc}), 7.33 (t, 2H, *J* 7.5 Hz, aromatic H_{Fmoc}), 7.18 (t, 1H, *J* 5.4 Hz, CON*H*), 6.24 (d, 1H, $J_{NH,2}$ 9.6 Hz, N*H*$COCH_3$), 6.00 (d, 1H, *J* 7.4 Hz, N*H*COO_{Fmoc}), 5.36 (br d, 1H, $J_{3,4}$ 3.3, $J_{4,5}$ <1 Hz, H-4), 5.10 (dd, 1H, $J_{2,3}$ 11.0 Hz, H-3), 4.83 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.58 (ddd, 1H, H-2), 4.41 (m, 3H, α-CH_{Ser}, NHCH_2CH_2O), 4.23 (t, 1H, J 6.9 Hz, H-9_{Fmoc}), 4.13 (br t, 1H, $J_{5,6a}$, $J_{5,6b}$ 6.6 Hz, H-5), 4.08 (dd, 1H, $J_{6a,6b}$ 11.0 Hz, H-6a), 4.02 (dd, 1H, H-6b), 3.95 (dd, 1H, *J* 3.5 Hz, *J* 10.1 Hz, β-CH_{Ser}), 3.78 (dd, 1H, β-CH_{Ser}), 3.72–3.66 (m, 2H, CH_{2Fmoc}), 3.64 (quint, 1H, *J* 5.4 Hz, CH($CH_2OC_{11}H_{23}$)), 3.55–3.49 (m, 2H, NHCH_2CH_2O), 3.43 (m, 8H, 2CH_2O-C$H_2C_{10}H_{21}$), 2.15, 2.04, 2.02, 1.96 (4s, 12H, 3CH_3COO, 1CH_3CON), 1.62–1.48 (m, 4H, 2OCH_2C$H_2C_9H_{19}$), 1.34–1.18 (m, 32H, 16CH_2 alkyl chains), 0.87 (t, 6H, *J* 6.9 Hz, 2CH_3 alkyl chains); ^{13}C NMR ($CDCl_3$): δ 171.1, 170.8, 170.7, 169.4 (4CH_3*C*O, CH_2*C*ON), 156.3 (NH*C*OO_{Fmoc}), 144.1, 141.7 (aromatic C_{Fmoc}), 128.2, 127.5, 125.4, 120.5 (aromatic *C*H_{Fmoc}), 99.5 (C-1), 78.8 (*C*H($CH_2OC_{11}H_{23}$)$_2$), 72.2, 71.3 (CH(*C*H_2O*C*H_2C_{10}-H_{21})$_2$), 69.9 (β-*C*H_{2Ser}), 69.1 (*C*H_{2Fmoc}, C-3), 67.7, 67.6 (C-4, C-5) 67.6 (NHCH_2*C*H_2O), 62.2 (C-6), 55.0 (α-*C*H_{Ser}), 47.8 (C-2, C-9_{Fmoc}), 40.1 (NH*C*H_2CH$_2$O), 32.3, 30.0, 29.9, 29.7, 29.6, 26.4, 23.1 (*C*H_2 alkyl chains), 23.5 (*C*H_3CON), 21.1, 21.0 (3*C*H_3COO), 14.5 (*C*H_3 alkyl chains). Anal. Calcd for $C_{59}H_{91}N_3O_{15}$ (1082.37): C, 65.47; H, 8.47; N, 3.88. Found: C, 65.19; H, 8.50; N, 3.82.

3.23.2. Method b. A soln of **20b** (0.106 g, 0.142 mmol) in EtOAc (8 mL) was stirred for 18 h under hydrogen (4 atm) in the presence of 10% Pd/C (58 mg). After filtration and concentration, the intermediate **21b** thus obtained, was used directly in the next step. A soln of EEDQ (0.023 g, 0.093 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C to a soln of **21b** (0.056 g, 0.085 mmol) and **12** (0.045 g, 0.101 mmol) in CH_2Cl_2 (5 mL). Stirring was maintained for 2 h at 0 °C and then for 18 h at rt. The mixture was diluted with CH_2Cl_2, washed with 5% aq NaCl, dried ($MgSO_4$), concentrated and purified by column chromatography (3:1 EtOAc–petroleum ether) to afford product **19b** (0.040 g, 43%) as an amorphous solid.

3.24. Benzyl *O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl)-*N*-[(9*H*-fluoren-9-ylmethoxy)-carbonyl]-L-serinate (20a)

A mixture of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl trichloroacetimidate (0.254 g, 0.530 mmol), benzyl *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-serinate[26] (0.492 g, 1.18 mmol) and crushed activated 4 Å molecular sieves (0.800 g) in 1:1 Et_2O–CH_2Cl_2 (12 mL) was stirred under Ar and cooled to −30 °C. A soln of TMSOTf (38 μL, 0.197 mmol) in CH_2Cl_2 (0.1 mL) was added dropwise through a syringe and the mixture was stirred for 30 min at −30 °C. After addition of *i*-Pr_2NEt (75 μL), the mixture was allowed to reach rt. After dilution with CH_2Cl_2 (50 mL), filtration over Celite, washing three times with 0.1 N aq HCl (3 × 5 mL), then with water (5 mL), the organic phase was dried (Na_2SO_4) and concentrated under diminished pressure. After purification by column chromatography (2:3 EtOAc–petroleum ether), product **20a** (0.281 g, 72%) was obtained as an amorphous solid; $[\alpha]_D$ +84 (*c* 1.0, $CHCl_3$) [lit.[29] $[\alpha]_D$ +86.5 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$): selected values: δ 7.72 and 7.63 (2d, 4H, *J* 7.5 Hz, aromatic H_{Fmoc}), 7.45–7.30 (m, 9H, 4 aromatic H_{Fmoc}, 5 aromatic H_{Bn}), 6.02 (d, 1H, *J* 8.1 Hz, N*H*COO_{Fmoc}), 5.41–5.39 (m, 1H, H-4), 5.27 (s, 2H, CH_2Ph), 4.88 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1), 3.60 (dd, 1H, $J_{2,3}$ 11.1 Hz, H-2), 2.16, 2.08, 1.97 (3s, 9H, 3CH_3COO); ^{13}C NMR ($CDCl_3$): δ 170.5, 170.0, 169.8 (3CH_3*C*O), 163.6 (*C*OOBn), 156.0 (NH*C*OO_{Fmoc}), 143.8, 141.3 (aromatic C_{Fmoc}), 135.0 (aromatic C_{Bn}), 128.7, 128.6, 127.8, 127.2, 125.2, 120.1 (aromatic *C*H_{Fmoc}, *C*H_{Bn}), 99.4 (C-1), 70.0, 67.9, 67.4 (*C*H_{2Fmoc}, *C*H_2Ph, β-*C*H_{2Ser}), 68.0, 67.6, 67.3 (C-3, C-4, C-5), 61.8 (C-6), 57.5 (C-2), 54.6 (α-*C*H_{Ser}), 47.1 (C-9_{Fmoc}), 20.7, 20.6 (3CH_3COO).

3.25. Benzyl *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-*N*-[(9*H*-fluoren-9-ylmethoxy)-carbonyl]-L-serinate (20b)

Prepared from **20a** (0.146 g, 0.20 mmol) as described above for **16b**. After purification by column chromatography (5:1 EtOAc–petroleum ether), **20b** (0.106 g, 71%) was obtained as an amorphous solid; $[\alpha]_D$ +47.5 (*c* 1.0, $CHCl_3$) [lit.[29] $[\alpha]_D$ +60.0 (*c* 1.0, $CHCl_3$)]; R_f 0.50; ^{1}H NMR ($CDCl_3$): selected values: δ 7.65 (d, 2H, *J* 7.5 Hz, aromatic H_{Fmoc}), 7.61 (d, 2H, *J* 6.8 Hz, aromatic H_{Fmoc}), 7.51–7.30 (m, 9H, 4 aromatic H_{Fmoc}, 5 aromatic H_{Bn}), 6.01 (d, 1H, $J_{NH,2}$ 8.4 Hz, N*H*COCH$_3$), 5.80 (d, 1H, *J* 9.0 Hz, N*H*COO$_{Fmoc}$), 5.33 (dd, 1H, $J_{3,4}$ 2.3, $J_{4,5}$ <1 Hz, H-4), 5.20 (s, 2H, CH_2Ph), 5.07 (dd, 1H, $J_{2,3}$ 11.4 Hz, H-3), 4.78 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 170.9, 170.4, 170.3, 170.3, 170.0 (4CH$_3$*C*O, *C*OOBn), 155.9 (NH*C*OO$_{Fmoc}$), 143.7, 141.4 (aromatic C_{Fmoc}), 135.0 (aromatic C_{Bn}), 128.9, 128.4, 127.9, 127.2, 125.0, 120.1 (aromatic *C*H$_{Fmoc}$), 99.1 (C-1), 69.8, 67.7, 67.3 (*C*H$_{2Fmoc}$, *C*H$_2$Ph, β-*C*H$_{2Ser}$), 68.2, 67.3, 67.2 (C-3, C-4, C-5), 62.0 (C-6), 54.6 (α-*C*H$_{Ser}$), 47.6, 47.1 (C-2, C-9$_{Fmoc}$), 23.2 (*C*H$_3$CON), 20.7, 20.6 (3*C*H$_3$COO).

3.26. 4-Undecyloxymethyl-3,6-dioxaheptadecyl *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-L-serinamide (22b)

Compound **19b** (0.060 g, 0.055 mmol) was reacted for 45 min with freshly distilled morpholine (0.8 mL). After evaporation and coevaporation from Et_2O, the residue was diluted with CH_2Cl_2 and the organic layer was washed with brine, before drying (Na_2SO_4). After concentration under diminished pressure and purification by column chromatography (20:1 $CHCl_3$–MeOH), product **22b** (0.036 g, 76%) was recovered as an amorphous solid; $[\alpha]_D$ +47.6 (*c* 1.0, $CHCl_3$); R_f 0.35; ^{1}H NMR ($CDCl_3$): δ 7.75–7.71 (m, 1H, N*H*CO), 6.35 (d, 1H, $J_{NH,2}$ 9.6 Hz, N*H*), 5.37 (dd, 1H, $J_{3,4}$ 2.5, $J_{4,5}$ <1 Hz, H-4), 5.09 (dd, 1H, $J_{2,3}$ 11.3 Hz, H-3), 4.88 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.61 (ddd, 1H, H-2), 4.25–4.20 (m, 1H, α-C*H*$_{Ser}$), 4.15–4.08 (m, 2H, OCH_2CH$_2$N), 3.93–3.40 (m, 16H, H-5, H-6a, H-6b, β-CH_{2Ser}, C*H*(CH$_2$OC$_{11}$H$_{23}$)$_2$, NHCH_2CH$_2$O, 2CH_2OCH_2-C$_{10}$H$_{21}$), 2.16, 2.06, 2.05, 1.98 (4s, 12H, 3CH_3COO, CH_3CON), 1.84 (2s, 2H, NH_2), 1.60–1.48 (m, 4H, 2OCH$_2$CH_2C$_9$H$_{19}$), 1.35–1.18 (m, 32H, 16CH_2 alkyl chains), 0.88 (t, 6H, *J* 6.0 Hz, 2CH_3 alkyl chains); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.5, 170.4 (4CH$_3$*C*O, NH*C*O-$_{Ser}$), 98.9 (C-1), 78.2 (*C*H(CH$_2$OC$_{11}$H$_{23}$)$_2$), 71.9, 71.8, 70.9, 68.9 (CH(*C*H$_2$O*C*H$_2$C$_{10}$H$_{21}$)$_2$, NHCH$_2$*C*H$_2$O, β-*C*H$_{2Ser}$), 68.6, 67.3, 67.2 (C-3, C-4, C-5), 61.6 (C-6), 55.0 (α-*C*H$_{Ser}$), 47.7 (C-2), 39.4 (NH*C*H$_2$CH$_2$O), 32.3, 30.0, 29.9, 29.7, 29.6, 26.4, 22.7 (*C*H$_2$ alkyl chains), 23.1 (*C*H$_3$CON), 20.8 (3*C*H$_3$COO), 14.1 (*C*H$_3$ alkyl chains).

3.27. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (23)

A suspension of glycoside **18d** (0.396 g, 0.500 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate[30] (0.542 g, 1.10 mmol) in CH_2Cl_2 (8.0 mL) was stirred for 1 h at rt in the presence of crushed activated 4 Å molecular sieves (0.370 g). After cooling to −25 °C, TMSOTf (23 μL, 0.119 mmol) was added; stirring was maintained for 0.5 h at −25 °C and the mixture was then allowed to reach rt. After 1 h stirring at rt, the mixture was neutralized by addition of *i*-Pr$_2$NEt (25 μL), filtrated, concentrated and purified by two successive column chromatographies (1:1 EtOAc–petroleum ether, then 2:1 EtOAc–petroleum ether) to afford compound **23** (0.356 g, 71%) as a colourless oil; $[\alpha]_D$ +50.3 (*c* 1.0, $CHCl_3$); R_f 0.38 (2:1 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 7.56–7.35 (m, 5H, C$_6H_5$), 5.57 (s, 1H, C*H*Ph), 5.43 (br d, 1H, $J_{3',4'}$ 3.5, $J_{4',5'}$ 1.3 Hz, H-4′), 5.37–5.35 (m, 1H, H-6$_{chol}$), 5.31 (dd, 1H, $J_{1',2'}$ 7.9, $J_{2',3'}$ 10.4 Hz, H-2′), 5.11 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 5.05 (dd, 1H, H-3′), 4.81 (d, 1H, H-1′), 4.39 (dd, 1H, $J_{3,4}$ 3.1, $J_{4,5}$ 0.5 Hz, H-4), 4.27 (dd, 1H, $J_{5,6a}$ 1.6 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.22 (dd, 1H, $J_{5',6'a}$ 6.7 Hz, $J_{6'a,6'b}$ 10.9 Hz, H-6′a), 4.18 (dd, 1H, $J_{2,3}$ 10.8 Hz, H-3), 4.17 (dd, 1H, $J_{5',6'b}$ 6.7 Hz, H-6′b), 4.07 (dd, 1H, $J_{5,6b}$ 1.6 Hz, H-6b), 3.97 (ddd, 1H, H-5′), 3.89 (ddd, 1H, 1/2 CH_2OC-1), 3.85 (m, 1H, H-5), 3.84 (dd, 1H, H-2), 3.78 (ddd, 1H, 1/2 CH_2OC-1), 3.76–3.68 (m, 10H, 5OCH_2), 3.23–3.19 (m, 1H, H-3$_{chol}$), 2.17, 2.07, 2.06, 1.99 (4s, 12H, 4CH_3COO), 2.41–0.67 (m, 43H, H cholesterol); ^{13}C NMR ($CDCl_3$): δ 170.3, 170.2, 170.0, 169.4 (4CH$_3$*C*O), 140.8 (C-5$_{chol}$), 137.8, 128.8, 128.1, 126.2 (C_6H_5), 121.6 (C-6$_{chol}$), 102.4 (C-1′), 100.6 (*C*HC$_6$H$_5$), 98.9 (C-1), 79.5 (C-3$_{chol}$), 76.2 (C-3, C-4), 71.5 (C-3′), 71.2 (C-5′), 71.4, 71.1, 71.0, 70.7 (O*C*H$_2$), 69.4 (C-6), 68.0 (*C*H$_2$OC-1), 67.7 (*C*H$_2$O-Chol), 69.1 (C-2′), 67.4 (C-4′), 63.5 (C-5) 61.8 (C-6′), 59.30 (C-2), 56.8 (C-14$_{chol}$), 56.1 (C-17$_{chol}$), 50.2 (C-9$_{chol}$), 42.4 (C-13$_{chol}$), 39.8 (C-12$_{chol}$), 39.1 (C-24$_{chol}$), 39.1 (C-4$_{chol}$), 37.2 (C-1$_{chol}$), 36.9 (C-10$_{chol}$), 36.2 (C-22$_{chol}$), 35.8 (C-20$_{chol}$), 32.0 (C-7$_{chol}$), 31.9 (C-8$_{chol}$), 28.4 (C-2$_{chol}$), 28.3 (C-16$_{chol}$), 28.0 (C-25$_{chol}$), 24.3 (C-15$_{chol}$), 23.9 (C-23$_{chol}$), 22.9 (C-27$_{chol}$), 22.6 (C-26$_{chol}$), 21.1 (C-11$_{chol}$), 20.7, 20.5 (4*C*H$_3$COO), 19.4 (C-19$_{chol}$), 18.7 (C-21$_{chol}$), 11.9 (C-18$_{chol}$). Anal. Calcd for $C_{60}H_{89}N_3O_{17}\cdot 1.5H_2O$ (1151.354): C, 62.58; H, 8.05; N, 3.64. Found: C, 62.42; H, 7.72; N, 3.30.

3.28. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-azido-2-deoxy-α-D-galactopyranoside (24)

Ethanethiol (0.72 mL, 3.63 mmol) and borontrifluoride etherate (17 μL, 0.134 mmol) were successively added

at 0 °C to a soln of disaccharide **23** (0.400 g, 0.356 mmol) in dry CH_2Cl_2 (5.6 mL). The mixture was stirred for 3 h at 0 °C and neutralized by addition of satd aq $NaHCO_3$ (0.1 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was then purified by column chromatography (EtOAc) to afford diol **24** (0.274 g, 74%) as a colourless oil; $[\alpha]_D$ +33.8 (*c* 1.0, $CHCl_3$); R_f 0.37 (5:1 EtOAc–petroleum ether); ^1H NMR ($CDCl_3$): δ 5.41 (br d, 1H, $J_{3',4'}$ 3.2, $J_{4',5'}$ 0.6 Hz, H-4′), 5.35–5.33 (m, 1H, H-6_{chol}), 5.30 (dd, 1H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 10.4 Hz, H-2′), 5.04 (dd, 1H, H-3′), 5.02 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1), 4.74 (d, 1H, H-1′), 4.18–3.64 (m, 21H, H-2, H-3, H-4, H-5, H-6a, H-6b, H-5′, H-6′a, H-6′b, (OCH_2CH_2)$_3$), 3.20–3.18 (m, 1H, H-3_{chol}), 2.17, 2.09, 2.07, 2.00 (4s, 12H, 4CH_3COO), 2.41–0.67 (m, 43H, H cholesterol); ^{13}C NMR ($CDCl_3$): δ 170.4, 170.1, 170.0, 169.60 (4CH_3CO), 140.8 (C-5_{chol}), 121.6 (C-6_{chol}), 101.9 (C-1′), 98.9 (C-1), 79.5 (C-3_{chol}), 78.5 (C-3), 71.2, 70.7 (C-3′, C-5′), 70.8, 70.7, 70.4, 67.4, 67.2 ((OCH_2CH_2)$_3$), 69.7, 68.9, 68.5 (C-4, C-5, C-2′), 67.0 (C-4′), 62.2 (C-6), 61.5 (C-6′), 58.7 (C-2), 56.8 (C-14_{chol}), 56.2 (C-17_{chol}), 50.2 (C-9_{chol}), 42.3 (C-13_{chol}), 39.8 (C-12_{chol}), 39.5 (C-24_{chol}), 39.0 (C-4_{chol}), 37.2 (C-1_{chol}), 36.9 (C-10_{chol}), 36.2 (C-22_{chol}), 35.8 (C-20_{chol}), 31.9 (C-7_{chol}), 31.9 (C-8_{chol}), 28.3 (C-2_{chol}), 28.2 (C-16_{chol}), 28.0 (C-25_{chol}), 24.3 (C-15_{chol}), 23.8 (C-23_{chol}), 22.8 (C-27_{chol}), 22.6 (C-26_{chol}), 21.1 (C-11_{chol}), 20.6, 20.5 (4CH_3COO), 19.4 (C-19_{chol}), 18.7 (C-21_{chol}), 11.9 (C-18_{chol}). Anal. Calcd for $C_{53}H_{85}N_3O_{17}\cdot1.5H_2O$ (1063.255): C, 59.87; H, 8.34; N, 3.96. Found: C, 59.92; H, 8.23; N, 3.76.

3.29. 8-(Cholest-5-en-3β-yloxy)-3,6-dioxaoctyl 2-acetamido-4,6-di-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-α-D-galactopyranoside (25)

Compound **24** (0.390 g, 0.376 mmol) was acetylated overnight in 2:1 pyridine–Ac_2O (10 mL), concentrated under diminished pressure and coevaporated from toluene (2 × 20 mL). After dissolution in absolute EtOH (25 mL), $NiCl_2\cdot6H_2O$ (0.896 g, 3.76 mmol) and $B(OH)_3$ (0.349 g, 5.64 mmol) were added, before dropwise addition of a soln of $NaBH_4$ (0.218 g, 5.76 mmol) in EtOH (25 mL), until persistency of a dark colour. After 4 h at rt, the mixture was concentrated under diminished pressure and the residue was treated overnight in a 2:1 pyridine–Ac_2O mixture (10 mL). After evaporation and coevaporation three times from toluene (3 × 20 mL), the crude product was dissolved in CH_2Cl_2 (60 mL), the organic phase was washed with 3% aq $KHSO_4$ and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified twice by column chromatography (1:10 EtOH-EtOAc) to afford product **25** (0.300 g, 70%) as a colourless oil; $[\alpha]_D$ +25.7 (*c* 1.0, $CHCl_3$); R_f 0.57; ^1H NMR ($CDCl_3$): δ 6.87 (d, 1H, $J_{2,NH}$ 9.7 Hz, N*H*), 5.37 (br d, 1H, $J_{3,4}$ 3.1, $J_{4,5}$ <1.0 Hz, H-4), 5.35 (br d, 1H, $J_{3',4'}$ 3.2, $J_{4',5'}$ 0.9 Hz, H-4′), 5.345–5.33 (m, 1H, H-6_{chol}), 5.10 (dd, 1H, $J_{1',2'}$ 7.9, $J_{2',3'}$ 10.4 Hz, H-2′), 4.92 (dd, 1H, H-3′), 4.85 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.59 (d, 1H, H-1′), 4.57 (ddd, 1H, $J_{2,3}$ 10.6 Hz, H-2), 4.17 (dd, 1H, $J_{5',6'a}$ 6.0, $J_{6'a,6'b}$ 11.0 Hz, H-6′a), 4.16–4.13 (m, 2H, H-6a,6′b), 4.11 (br dd, 1H, $J_{5,6a}$ 6.0, $J_{5,6b}$ 6.5 Hz, H-5), 4.00 (dd, 1H, $J_{6a,6b}$ 9.8 Hz, H-6b), 3.98 (dd, 1H, H-3), 3.87 (br dd, 1H, $J_{5',6'b}$ 6.5 Hz, H-5′), 3.81–3.77 (m, 1H, 1/2 CH_2OC-1), 3.70–3.61 (m, 11H, 1/2 CH_2OC-1, OCH_2-$CH_2(OCH_2CH_2)_2$), 3.21–3.19 (m, 1H, H-3_{chol}), 2.16, 2.13, 2.05, 2.04, 1.99, 1.96, 1.95 (7s, 21H, 6CH_3COO, CH_3CON), 2.42–0.67 (m, 43H, H cholesterol); ^{13}C NMR ($CDCl_3$): δ 170.6, 170.3, 170.2, 170.0, 169.6 (7CH_3CO), 140.6 (C-5_{chol}), 121.9 (C-6_{chol}), 101.5 (C-1′), 98.4 (C-1), 79.6 (C-3_{chol}), 72.9 (C-3), 70.8 (C-3′), 70.6 (C-5′), 70.7, 70.5, 70.4, 70.1, 67.1, 66.8 ((OCH_2CH_2)$_3$), 69.2 (C-4), 68.7 (C-2′), 67.5 (C-5), 67.1 (C-4′), 62.9 (C-6), 61.0 (C-6′), 56.8 (C-14_{chol}), 56.2 (C-17_{chol}), 50.2 (C-9_{chol}), 48.7 (C-2), 42.4 (C-13_{chol}), 39.8 (C-12_{chol}), 39.5 (C-24_{chol}), 39.0 (C-4_{chol}), 37.2 (C-1_{chol}), 36.9 (C-10_{chol}), 36.2 (C-22_{chol}), 35.8 (C-20_{chol}), 31.9 (C-7_{chol}), 31.8 (C-8_{chol}), 28.4 (C-2_{chol}), 28.2 (C-16_{chol}), 28.0 (C-25_{chol}), 24.3 (C-15_{chol}), 23.8 (C-23_{chol}), 23.2 (CH_3CON), 22.8 (C-27_{chol}), 22.6 (C-26_{chol}), 21.1 (C-11_{chol}), 20.8, 20.7, 20.5 (6CH_3COO), 19.4 (C-19_{chol}), 18.7 (C-21_{chol}), 11.9 (C-18_{chol}). Anal. Calcd for $C_{59}H_{93}NO_{20}\cdot1.5H_2O$ (1163.364): C, 60.91; H, 8.32; N, 1.19. Found: C, 60.77; H, 8.32; N, 1.10.

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