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Carbohydrate Research 336 (2001) 181–194

CARBOHYDRATE RESEARCH

Syntheses and interfacial behaviour of neoglycolipid analogues of glycosyl ceramides

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Received 20 July 2001; accepted 18 September 2001

Abstract

Four glycosyl ceramides analogues having D-galactose or 2-acetamido-2-deoxy-D-glucose moieties linked to enantiomeric lipids have been synthesised to study their interfacial behaviour at the air | water interface. The lipid chains were prepared in two steps by opening 1,2-epoxyhexadecane using Jacobsen kinetic hydrolytic resolution (KHR) followed by an azidosilylation reaction of the diol so obtained. Glycosylation reactions were realised either with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate or 1,3,4,6-tetra-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy-β-D-glucopyranose as donors and (2*R*)- or (2*S*)-2-azidohexadecanol derivatives as acceptors. Transformation of the azido glycosides into *N*-acylated products was done by a modified Staudinger reaction in the presence of fatty acyl chlorides. The four neoglycolipids are able to form a condensed monolayer at the air | water interface; their π-A isotherm diagrams are similar to that described for the natural glycosyl ceramides. The detailed analysis of the isotherms, taking into account the chirality of the lipid chains, allowed to determine the contribution of the different parts of the molecule under the monolayer packing.

Keywords: Neoglycosyl ceramides; Kinetic hydrolytic resolution; Glycosylation; Imidate; Staudinger reaction; Monolayers; Interfacial behaviour; 2D compressibility

1. Introduction

Glycosphingolipids or glycosyl ceramides are constituents of animal cell membranes consisting of various oligosaccharides bound to ceramides by a glycosidic bound. They serve as identifying markers and regulate cellular recognition, growth, and development.[1] The chemistry of glycosphingolipids-carbohydrate molecules of biological significance has been reviewed recently.[2] The biosynthesis of glycosyl ceramides results of biochemical events leading to complex structures in which the lipid moiety is a sphingosine amidified by a fatty acid. The above structures are embedded at the surface of cells by non-covalent interactions between phospholipids and the ceramide part of the glycolipids. The carbohydrate is endowed of recognition properties, modulated by the nature of the lipid moiety responsible of the self-assembling properties of the whole. Other lipid structures, more easily accessible by chemical syntheses than the natural ceramides, could afford the same type of assemblies or different assemblies giv-

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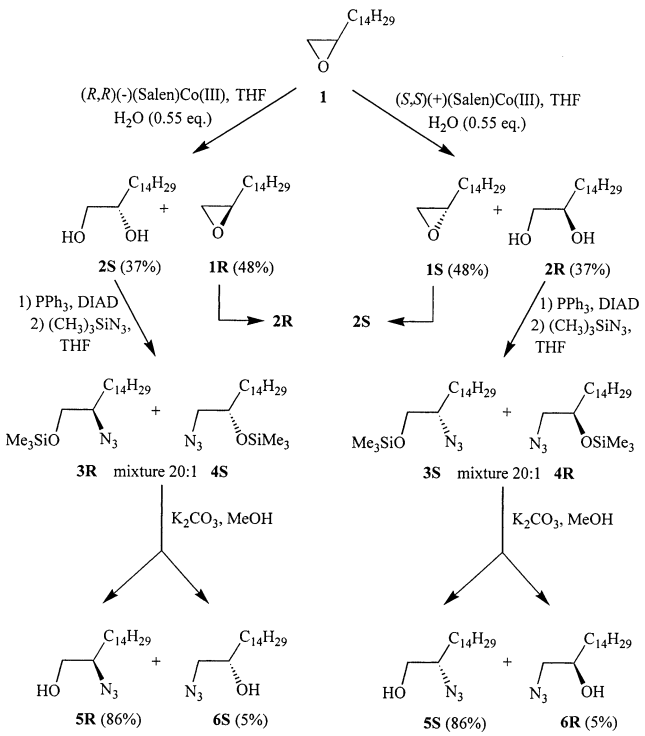
0008-6215/01/$ - see front matter
PII: S0008-6215(01)00255-5

ing rise to different biochemical properties. With this purpose in mind, we have already prepared fucopyranosyl and 2-acetamido-2-deoxy-D-glucopyranosyl neoglycolipids and studied their self associations at the air | water interface, their self organisations with phospholipids and the recognition of their molecular assemblies by specific lectins.[3–5] This paper deals with a short synthesis of new glycosyl ceramide analogues having the (*R*) or (*S*) configuration at the β-position of the aglycone, and preliminary studies of their self organisation at the air | water interface. The β-D-galactopyranosyl head group was chosen because of its widespread occurrence at both the reducing and non-reducing ends of natural glycosyl ceramides. The 2-acetamido-2-deoxy-D-glucopyranosyl head group, uncommon in glycosyl ceramides, was chosen for comparison with other neoglycolipids in their molecular associations and molecular recognition by lectins.[3–5] The Langmuir monolayers of chiral molecules is a unique system to analyse, under defined conditions, both the interfacial properties and the importance of chirality-dependent interactions and may help to elucidate some structural functions.



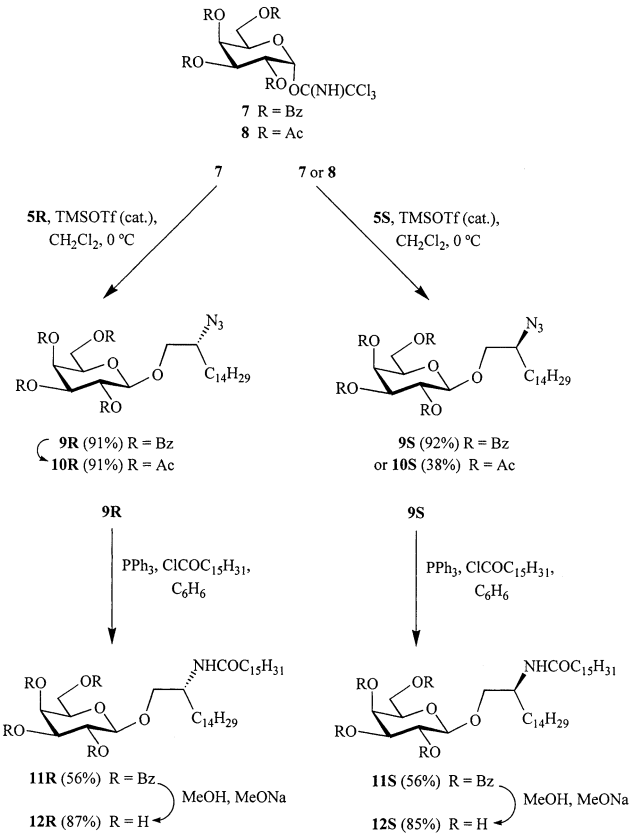
Scheme 1.

2. Results and discussion

Synthesis.—In the glycosphingolipids, the ceramide portion consists of a sphingosine moiety amidified with a fatty acid (usually C_{16}–C_{24}). The variation in fatty acids, sphingosines and carbohydrates results in a great variety of distinct glycosphingolipids.[6] In the present paper, we describe a short synthesis of neoglycosyl ceramides with D-galactose and 2-acetamido-2-deoxy-D-glucose as the carbohydrate moieties and (2*R*)- or (2*S*)-2-*N*-acylaminohexadecane as the lipidic part.

In order to obtain enantiomerically pure derivatives, we decided to use the asymmetric catalysis of epoxide ring opening, described for smaller alkyl chains by Jacobsen and coworkers.[7,8] Thus, treatment of 1,2-epoxyhexadecane (**1**) with water (0.55 equiv) in THF in the presence of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert* - butylsalicylidene) - 1,2 - cyclohexanediaminocobalt(III) acetate afforded the expected (2*S*)-hexadecane-1,2-diol (**2S**) and (2*R*)-1,2-epoxyhexadecane (**1R**) in 37 and 48% yields, respectively. The high enantioselectivity of the reaction (ee > 95%) was confirmed by comparison of the optical rotation of these two products with that of the literature.[9,10] (2*R*)-Hexadecane-1,2-diol (**2R**) was similarly obtained in the presence of (*S*,*S*)-(+)-*N*,*N*′-bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) acetate and a slight excess of water (10%) either from racemic 1,2-epoxyhexadecane (**1**) or from (2*R*)-1,2-epoxyhexadecane (**1R**) in 37 and 78% yields, respectively (Scheme 1).

Treatment of diol **2S** with triphenylphosphine, diisopropylazodicaboxylate (DIAD) and azidotrimethylsilane afforded a 20:1 unseparable mixture of (2*R*)-2-azido-1-trimethylsilyloxyhexadecane (**3R**) and (2*S*)-1-azido-2-trimethylsilyloxyhexadecane (**4S**) in high yield. The azidosilylation proceeded via a cyclic dioxaphospholane intermediate with inversion of configuration at C-2.[11,12] Desilylation of the mixture **3R**/**4S** was realised in the presence of an excess of potassium carbonate in dry methanol affording **5R** (86%) and **6S** (5%), that could be separated by column chromatography. The same sequence, applied to diol **2R**, afforded a mixture of **3S** and **4R**

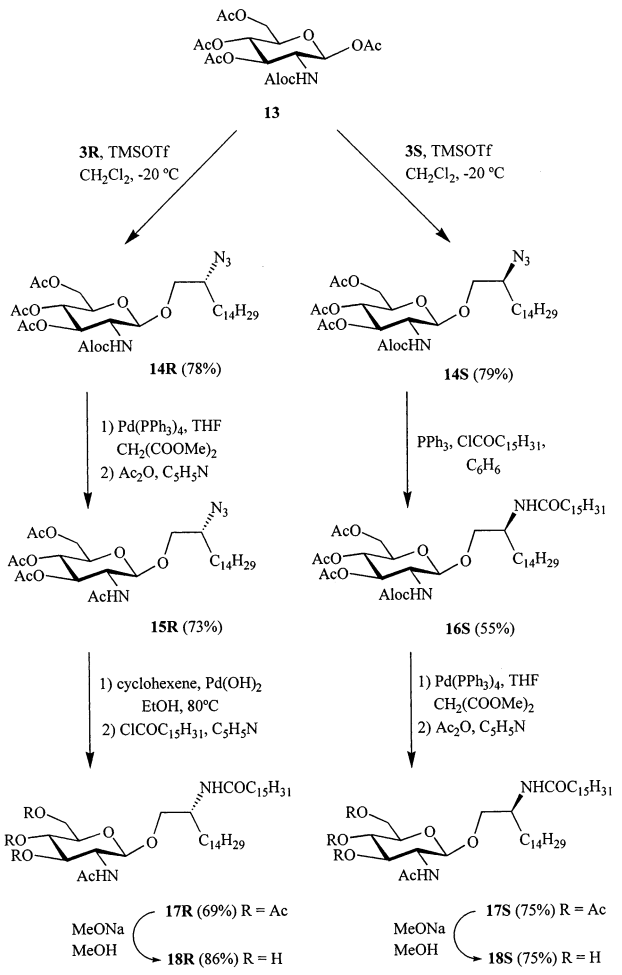


Scheme 2.

whose desilylation afforded **5S** and **6R** with similar yields. The high regio- and stereoselectivity of the introduction of the azido group at the secondary position has also been reported recently by Bittman and co-workers[13] on 1,2- and 1,3-diols under similar conditions (Mitsunobu reaction). Nevertheless, it should be noted that the above regioselectivity was not observed previously in the case of partly protected carbohydrates having a primary and a secondary free hydroxyl group.[14]

Galactosylation was carried out with the azidoalcohol acceptors **5R** and **5S** and 2,3,4, 6-tetra-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate (**7**) as the donor (Scheme 2). Preparation of **7** was achieved in three steps starting from penta-*O*-benzoyl-α-D-galactopyranose.[15] 1-*O*-Debenzoylation with hydrazine acetate was followed by reaction with trichloroacetonitrile and DBU in CH_2Cl_2 to afford the known imidate **7**.[16,17] Glycosylation of the acceptors **5R** and **5S** with the donor **7** in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate at 0 °C afforded the desired glycosides **9R** and **9S** in 91 and 92% yields, respectively. The ^{13}C NMR spectra for each epimers showed a single signal for C-1[δ C-1(R) 101.59 ppm or δ C-1(S) 101.92 ppm], C-1′ [δ C-1′(R) 71.46 ppm or δ C-1′(S) 72.78 ppm] and C-2′ [δ C-2′ (R) 61.34 ppm or δ C-2′(S) 62.00 ppm]. 2,3,4, 6-Tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (**8**)[18,19] was previously tried as the glycosylation donor with the alcohol **5S**, but a lower yield was obtained (38%). For identification purposes, glycosides **10R** and **10S** were also prepared by de-*O*-benzoylation and re-*O*-acetylation of **9R** and **9S**. Transformation of the azidoderivatives **9R** and **9S** into the *N*-acyl derivatives **11R** and **11S** was effected via a modification of the Staudinger reaction involving hexadecanoyl chloride and triphenylphosphine in dry benzene.[20] Derivatives **11R** and **11S** were then de-*O*-acylated by the Zemplén procedure to give products **12R** and **12S**, respectively, in high yields.

2-Acetamido-2-deoxy-D-glucopyranosides were obtained with 1,3,4,6-tetra-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy-β-D-glucopyranose (**13**)[21,22] as the donor, the silylated mixture **3R**/**4S** or **3S**/**4R** as the acceptor and trimethylsilyl trifluoromethanesulfonate as the promotor (Scheme 3). The β-glycosides **14R** or **14S** were obtained in a pure form in 78 or 79% yields, respectively (after removal of the minor glycosylation product of **4S** or **4R** by column chromatography). The ^{1}H and ^{13}C NMR spectra of the two glycosides confirmed the presence of one epimer only. Two different routes were tested for the transformation of **14R** and **14S** to **17R** and **17S**, respectively. The glycoside **14R** was first subjected to *N*-deallyloxycarbonylation followed by *N*-acetylation to afford product **15R** in 73% overall yield. The azido function of the latter was reduced by hydrogen transfer and *N*-acylated with hexadecanoyl chloride in pyridine to give the peracetylated glycosyl ceramide analogue **17R** in 69% overall yield. On the other hand, the glycoside **14S** was transformed into the *N*-hexadecanoyl derivative **16S** (55% yield) via the modified Staudinger reaction already mentioned.[20] *N*-Deallyloxycarbonylation and re-*N*-acetylation gave the product **17S** in 75% yield. Derivatives **17R** and **17S** were then *O*-



Scheme 3.

deacylated by the Zemplén procedure to give products **18R** and **18S**, respectively, in high yields.

Interfacial behaviour.—The four neoglycosyl ceramides (**12R**, **12S**, **18R** and **18S**) were spread at the air | water interface from 2:1 chloroform–methanol solutions. The π-A isotherms (Fig. 1) did not exhibit any two-dimensional phase transition and are characteristic of monolayers in a liquid-condensed phase with a high chain order. The isotherm shapes at 20 °C are comparable with that previously reported for natural cerebrosides,[23] glucosyl cerebrosides[24,25] and galactosyl ceramides[26–29] at temperatures ranging from 20 to 24 °C. The characteristic magnitudes reflecting the monolayer properties, are given in Table 1. Whatever the glycolipid, the limiting molecular area extrapolated at zero surface pressure is close to 40 Å^2/molecule representative of the cross-sectional area of two hydrocarbon chains in a tightly packed arrangement. The polar groups orientated themselves in such a way that they do not significantly increase the cross-sectional area over that of the hydrocarbon chains. This apparently low influence of the polar group is in accordance with the limiting molecular area (41.5 Å^2/molecule), determined by X-ray diffraction at grazing angles incidence, recently reported for a D-erythro C_{18} ceramide.[30] The value of the minimal two-dimensional compressibility[31] (C_s, Table 1), determined at the highest-surface pressure just before collapse, confirmed the liquid-condensed behavior of the neoglycosyl ceramides at the air | water

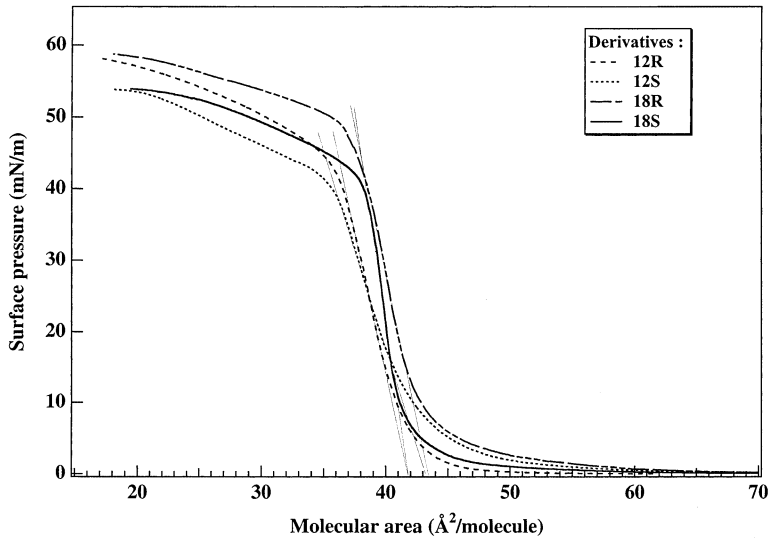


Fig. 1. Pressure–area (π-A) isotherms for the analogues of glycosyl ceramides at 20 °C.

Table 1
Characteristic magnitudes of the glycosyl-ceramide analogue monolayers

Glycosylceramide analogue	Limiting molecular area [a] A_0 (Å^2/molecule)	Apparent collapse pressure π_c (mN/m)	Minimal compressibility C_s ($\times 10^{-2}$) (m/mN)
12R	41.90	~41	0.41
12S	43.30	~38	0.53
18R	43.40	~47	0.46
18S	41.90	~40	0.30

[a] Extrapolated area at zero surface pressure.

interface; this could be related to the high transition temperature of the gel to liquid crystalline phase already reported for saturated galactosyl cerebrosides.[32] The values of the apparent collapse-surface pressure, determined for the neoglycosyl ceramide monolayers, are lower than those reported for natural galactosyl ceramides.[26–29] However, it could be noted that the galactocerebroside isotherms[33] and the collapse surface pressures for monolayers of natural galactosyl ceramides[26] are highly dependent on the compression rate. The common feature with natural glycosyl ceramides is the poorly defined collapse pressure[26] and the possibility to compress the film to very low molecular areas (below 40 Å^2/molecule).[34] The increase of pressure at areas too small to be compatible with that of a single monolayer argues against a true collapse and about a loss of order of the film. In a detailed study performed with natural galactocerebrosides of similar behavior, Johnston and Chapman[34] suggested the formation of a bilayer at smallest areas. Like these authors, we observed that at very small areas, the molecules formed a film so rigid that it was able to physically move the Wilhelmy plate and eject it from the interface. It is noteworthy that a recent AFM study on galactocerebrosides reported the formation of nanotubes at the air | water interface from the beginning of the compression.[33]

A detailed analysis of the isotherms of the neoglycosyl ceramides (**12R**, **12S**, **18R** and **18S**) allows to distinguish three regions in the diagram which could be tentatively explained taking into account the 'chiral' structure of each glycolipid molecules. The first part (less condensed monolayer), in which compounds **12R** and **18S** on one hand, and **12S** and **18R** on the other hand behave similarly—until 43 Å^2/molecule for **12S** and **18R** and 41 Å^2/molecule for **12R** and **18S**—could be related to the limiting molecular areas of the neoglycosyl ceramides extrapolated at zero surface pressure. A_0 are identical for **12R** and **18S** (42 Å^2/molecule) and **12S** and **18R** (43.3 Å^2/molecule), respectively (Table 1). This value, corresponding to the smallest area that a molecule can occupy at the air | water interface, is correlated to the molecular cross-section area (which can be determined by X-ray scattering). An over-simple explanation could be a compensation of the higher cross section of the 2-acetamido-2-deoxy-D-glucose head group over that of D-galactose (displayed in the second part of the isotherm) by the higher cross section of the (*R*)-lipid moiety over that of the (*S*)-lipid (displayed in the third part of the isotherm). The difference in the packing effect of the headgroups seems to be partially compensated by the chiral position of the *N*-acyl chain. Therefore, it appears that in the monolayer weakly compressed, the spatial configuration of the whole molecule controls the self-ability of the neoglycosyl ceramides to pack closely. In the second part (liquid condensed phase, from 41 Å^2/molecule to the beginning of the collapse), the isotherms of **12R** and **12S** on one hand and of **18R** and **18S** on the other hand, are close together, each group being separated by 2 Å^2/molecule. The differences can be attributed to the contribution of the polar group. The packing with a 2-acetamido-2-deoxy-D-glucose headgroup (**18R** and **18S**) is less condensed than that with a galactose one (**12R** and **12S**). The smaller, less hydrated headgroup of galactosyl ceramide would allow a closer intermolecular approach than is possible with the larger,

more hydrated glucosamine headgroup.[28] In the third part, occurring for molecular areas lower than 37 $Å^2$/molecule (apparent collapse phase), the isotherms of **12R** and **18R** on one hand and of **12S** and **18S** on the other hand, join at the same surface pressure for molecular areas lower than 20 $Å^2$/molecule. This could be interpreted as interdigitation of the alkyl chains solely dependent on their chirality and a possible change in molecular arrangements independent on the nature of the polar group. The isotherms of **12R** and **18R** and of **12S** and **18S** join respectively at the same surface pressure value which is higher for the (*R*)-configuration than for the (*S*)-one. It is noteworthy that for a same *N*-acyl chain position, the apparent collapse surface pressure is lower with a galactose headgroup than with a 2-acetamido-2-deoxy-D-glucose one. This fact can be related to the more condensed state obtained with a galactose headgroup during the monolayer compression.

3. Conclusion

Four different neoglycolipids have been synthesized with a β-D-galactose or a 2-acetamido-2-deoxy-D-glucose head group and a 2-hexadecanoylaminohexadecyl aglycone of (*R*) or (*S*) configuration. Their interfacial behavior has been studied by the Langmuir monolayer technique. Compared with the natural glycosyl ceramides, these analogues are also able to form condensed monolayer at the air | water interface. The simplified structure of the analogue derivatives (with the absence of both the hydroxyl group at C-3 and the unsaturation at C-4 of the sphingosine main chain) allowed us to determine the contribution of the different parts of the glycosphingolipid-like molecule (carbohydrate head and *N*-acyl chain) on the packing of the monolayer. Differences arise from the nature of the carbohydrate and the stereochemistry of the *N*-acyl linkage; a more precise study on the influence of the chirality on the molecular packing through Langmuir monolayer technique is now under investigation. The molecular packing of mixtures of glycolipids and phospholipids could also be affected by the chirality of the lipid moiety and this investigation seems of interest in the study of biological membranes.

4. Experimental

General methods.—Pyridine was dried by boiling with CaH_2 prior to distillation. Dichloromethane was washed twice with water, dried with $CaCl_2$ and distilled from CaH_2. Methanol was distilled from magnesium. Tetrahydrofurane was distilled from Na–benzophenone. Pyridine, THF and CH_2Cl_2 were stored over 4 Å molecular sieves and MeOH over 3 Å molecular sieves. Melting points were determined on a Büchi apparatus and were uncorrected. Thin-layer chromatography was performed on aluminium sheets coated with Silica Gel 60 F_{254} (E. Merck). Compounds were visualised by spraying the TLC plates with dilute 15% aq H_2SO_4, followed by charring at 150 °C for a few min. Column chromatography was performed on Silica-Gel 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 the internal standard. Elemental analyses were performed by the 'Laboratoire Central d'Analyses du CNRS' (Vernaison, France).

Langmuir monolayer experiments were performed using a computerized KSV 3000 Langmuir–Blodgett trough (Finland) enclosed in a filtered air dry flow cabinet to avoid dust deposition. The surface pressure was measured using a platinum Wilhelmy plate attached to a sensitive balance with an accuracy of ± 0.3 mN/m. The trough was filled with Milli-Q ultrapure water (resistivity = 18.2 MΩ/cm) produced by a four-cartridge purification system (Millipore, France). The whole trough was temperature-controlled with a commercially available heating–cooling system.

Monolayer experiments.—The water subphase was cleaned by suction with a capillary connected to a water vacuum jet pump. The cleanliness was checked at surface pressure

lower than 0.05 mN/m after reducing the trough area to the minimum. The subphase was maintained at 20 °C. The spreading solutions were prepared by dissolving each glycolipid into a mixture of analytical grade 2:1 $CHCl_3$–MeOH at a precise concentration comprised between $5 \times 10^{-4}$and 6×10^{-4} M. Each solution was stored at 4 °C. The monolayer was prepared by spreading an aliquot (200 μL) of the glycolipid solution at the air | water interface, using a 200 μL SGE microsyringe. After allowing 10 min for a complete solvent evaporation, the monolayer was symmetrically compressed by two mobile barriers at the rate of 15 cm^2/min. The compression was continuously achieved in a single step. The interfacial parameters, collapse surface pressure (π_c), two-dimensional compressibility of the monolayer (C_s) and limiting molecular area extrapolated at zero surface pressure (A_0) were determined from the isotherm. The accuracy of the molecular area measurements was calculated to be lower than ± 0.8 Å^2/molecule on the whole range of pressure. C_s was directly calculated from the π-A isotherm data by the KSV's software according to the following equation:

$$C_s = -1/A_\pi(\partial A_\pi/\partial\pi)_T$$

where A_π is the area per molecule at the indicated surface pressure and π is the corresponding surface pressure.

*(2*R*)-1,2-Epoxyhexadecane* (**1R**) *and (2*S*)-1,2-hexadecanediol* (**2S**).—To a solution of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) acetate prepared from the commercially available precursor (*R*,*R*)-(salen)Co(II) complex (25.3 mg, 0.042 mmol) according to Jacobsen et al.,[7,8] and racemic 1,2-epoxyhexadecane **1** (1.0 g, 4.16 mmol) in dry THF (1 mL) was added at 0 °C over 1 h a mixture of THF (0.5 mL) and water (41.5 μL, 2.30 mmol, 0.55 equiv). The mixture was stirred for 6 h at 0 °C, then allowed to reach rt and stirring was maintained overnight. After concentration, the residue was purified by column chromatography. Elution with 1:5 EtOAc–petroleum ether afforded **1R** as an oil (0.480 g, 48% yield): $[\alpha]_D$ +4.7° (*c* 2.0, $CHCl_3$), lit.[10] $[\alpha]_D$ +4.84° (*c* 2.8, $CHCl_3$); R_f 0.75 (1:10 EtOAc–petroleum ether). Further elution with 2:1 EtOAc–petroleum ether as the eluent afforded the expected derivative **2S** which was crystallised from petroleum ether (0.400 g, 37% yield): mp 83 °C; $[\alpha]_D$ −8.9° (*c* 1.3, EtOH), lit.[9] $[\alpha]_D$ −9.0° (*c* 0.9, EtOH); R_f 0.48 (2:1 EtOAc–petroleum ether); ^{1}H and ^{13}C NMR data were in accordance with the literature.[9]

*(2*R*)-1,2-Hexadecanediol* (**2R**).—Compound **2R** was obtained in 37% yield from racemic 1,2-epoxyhexadecane **1** and the (*S*,*S*)-(salen)Co(III) complex as described for **2S**. Compound **2R** was also prepared in 78% yield from the (2*R*)-1,2-epoxyhexadecane (**1R**) as previously described, using a slight excess of water (1.1 equiv.): mp 83 °C, lit.[35] mp 84–84.4 °C; $[\alpha]_D$ +9.2° (*c* 1.0, EtOH).

*(2*R*)-2-Azido-1-trimethylsilyloxy hexadecane* (**3R**) *and (2*S*)-1-azido-2-trimethylsilyloxy hexadecane* (**4S**).—Diisopropylazodicarboxylate (0.720 mL, 3.73 mmol) and PPh_3 (0.929 g, 3.54 mmol) were successively added under an argon atmosphere to a suspension of (2*S*)-1,2-hexadecanediol (**2S**) (0.832 g, 3.22 mmol) in dry THF (7 mL). The mixture became homogeneous after a few seconds and was stirred for 1 h before cooling to 0 °C. After addition of Me_3SiN_3 (1.06 mL, 8.06 mmol), the mixture was allowed to reach rt and stirred overnight. Excess of Me_3SiN_3 was destroyed by stirring with cold satd aq $NaHCO_3$ (30 mL) and the product was extracted with CH_2Cl_2 (2 × 30 mL). The organic phase was dried (Na_2SO_4) and concentrated to afford the crude product which was purified by column chromatography (1:25 EtOAc–petroleum ether). Product **3R** and a small amount of (2*S*)-1-azido-2-trimethylsilyloxy hexadecane (**4S**) (6% of the total amount) were recovered as an oil: (0.882 g, 89% yield). Compounds **3R** and **4S** could not be separated, they were identified by ^{1}H and ^{13}C NMR and directly used in further reactions.

Product **3R**: R_f 0.90 (1:25 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 3.70 (dd, 1 H, $J_{1a,2}$ 4.0, $J_{1a,1b}$ 10.5 Hz, H-1a), 3.57 (dd, 1 H, $J_{1b,2}$ 6.9 Hz, H-1b), 3.36 (m, 1 H, H-2), 1.40–1.26 (m, 26 H, 13 CH_2 alkyl chain), (0.88, t, 3 H, *J* 6.6 Hz, CH_3 alkyl chain); ^{13}C NMR ($CDCl_3$): δ 65.62 (C-1), 63.57 (C-2), 31.80, 30.27, 29.53–29.21, 26.15,

22.73 (13 C, CH_2 alkyl chain), 14.12 (CH_3 alkyl chain).

Product **4S**: ^{13}C NMR ($CDCl_3$): δ 71.95 (C-2), 56.63 (C-1).

(2S)-2-Azido-1-trimethylsilyloxy hexadecane (**3S**) *and (2R)-1-azido-2-trimethylsilyloxy hexadecane* (**4R**).—Obtained as a mixture as described above from (2*R*)-1,2-hexadecanediol **2R** in 88% yield.

(2R)-2-Azidohexadecan-1-ol (**5R**) *and (2S)-1-azidohexadecan-2-ol* (**6S**).—Potassium carbonate (0.500 g, 3.62 mmol) was added to a mixture of **3R**/**4S** (0.850 g, 2.39 mmol) solubilised in MeOH (30 mL) and the suspension was stirred overnight. After concentration, the residue was partitioned between $CHCl_3$ (50 mL) and water (50 mL). The aqueous phase was extracted twice with $CHCl_3$ (2 × 30 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated; the residue was purified by column chromatography (1:4 EtOAc–petroleum ether) affording first the pure product **6S** (0.034 g, 5%), then the desired compound **5R** (0.583 g, 86%).

5R: white solid, mp 46 °C; $[\alpha]_D$ −9.5° (*c* 1.0, $CHCl_3$); R_f 0.72; ^1H NMR ($CDCl_3$ + D_2O): δ 3.71 (dd, 1 H, $J_{1a,2}$ 7.2, $J_{1a,1b}$ 11.5 Hz, H-1a), 3.59 (dd, 1 H, $J_{1b,2}$ 3.5 Hz, H-1b), 3.45 (m, 1 H, H-2), 1.55–1.26 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, *J* 6.6 Hz, CH_3 alkyl chain); ^{13}C NMR ($CDCl_3$): δ 65.17 (C-1), 64.51 (C-2), 31.99, 30.62, 29.71-29.48, 26.06, 22.71 (13 C, CH_2 alkyl chain), 14.09 (CH_3 alkyl chain). Anal. Calcd for $C_{16}H_{33}N_3O$ (283.45): C, 67.79; H, 11.74; N, 14.82. Found; C, 67.66; H, 11.73; N, 14.79.

6S: white solid, mp 45 °C; $[\alpha]_D$ +3.1° (*c* 1.0, $CHCl_3$); R_f 0.80; ^1H NMR ($CDCl_3$): δ 3.76 (m, 1 H, H-2), 3.39 (dd, 1 H, $J_{1a,2}$ 3.3, $J_{1a,1b}$ 12.3 Hz, H-1a), 3.25 (dd, 1 H, $J_{1b,2}$ 7.3 Hz, H-1b), 1.92 (m, 1H, O*H*), 1.50–1.21 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, *J* 6.6 Hz, CH_3 alkyl chain).

(2S)-2-Azidohexadecan-1-ol (**5S**) *and (2R)-1-azidohexadecan-2-ol* (**6R**).—These product were obtained in 86 and 5%, respectively, as described above from the mixture **3S**/**4R**.

5S: white solid, mp 46 °C, lit.[13] mp 45–45.5 °C; $[\alpha]_D$ +9.7° (*c* 1.0, $CHCl_3$), lit.[13] $[\alpha]_D$ +9.9° (*c* 1.2, $CHCl_3$).

6R: white solid, mp 44 °C, lit.[13] mp 45.8-46.1 °C; $[\alpha]_D$ -3.4° (*c* 1.0, $CHCl_3$), lit.[13] $[\alpha]_D$ −3.3° (*c* 1.2, $CHCl_3$).

2,3,4,6-Tetra-O-benzoyl-α-D-galactopyranosyl trichloroacetimidate (**7**).—Hydrazine acetate (0.945 g, 10.26 mmol) was added to a solution of 1,2,3,4,6-penta-*O*-benzoyl-α-D-galactopyranose[15] (6.00 g, 8.56 mmol) in dry DMF (50 mL) and the mixture was stirred for 16 h before a new addition of hydrazine acetate (0.630 g, 6.86 mmol) and stirring was maintained for 24 h. The mixture was poured into EtOAc (300 mL), washed with brine (50 mL), then with water (50 mL) and dried (Na_2SO_4). After concentration, the crude product was purified by column chromatography (2:3 EtOAc–petroleum ether) to afford the 1-*O*-debenzoylated derivative as an oily mixture of anomers (4.10 g, 80% yield). R_f 0.65–0.58; ^1H NMR ($CDCl_3$ + water): δ 5.88 (d, 0.73 H, $J_{1,2}$ 3.5 Hz, H-1α), 5.09 (d, 0.27 H, $J_{1,2}$ 7.4 Hz, H-1β); ^{13}C NMR ($CDCl_3$): δ 96.32 (C-1β), 91.18 (C-1α).

Trichloroacetonitrile (4.3 mL, 42.9 mmol) and DBU (1.0 mL, 6.69 mmol) were successively added to a cooled solution (0 °C) of the above derivative (4.10 g) in dry CH_2Cl_2 (24 mL). The mixture was allowed to reach rt and stirred for 4 h. After concentration, the residue was purified by column chromatography (2:5 EtOAc–petroleum ether containing 0.5% NEt_3) to afford the pure product **7** which was obtained as an amorphous solid (4.07 g, 80% yield). $[\alpha]_D$ +138° (*c* 1.0, $CHCl_3$), lit.[16] $[\alpha]_D$ +113° (*c* 1.0, $CHCl_3$), lit.[17] $[\alpha]_D$ +141° (*c* 1.0, $CHCl_3$); R_f 0.70 (2:5 EtOAc–petroleum ether);^1H NMR ($CDCl_3$): δ 8.12–7.25 (m, 20 H, 4 C$_6H_5$), 6.61 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.57 (bd, 1 H, $J_{3,4}$ 2.8, $J_{4,5}$ 0.5 Hz, H-4), 5.44 (dd, 1 H, $J_{2,3}$ 10.8 Hz, H-3), 5.37 (dd, 1 H, H-2), 4.45 (bdd, 1 H, $J_{5,6a}$ 6.4, $J_{5,6b}$ 6.8 Hz, H-5), 4.18 (dd, 1 H, $J_{6a,6b}$ 11.3 Hz, H-6a), 4.09 (dd, 1 H, H-6b).

(2R)-2-Azidohexadecyl 2,3,4,6-tetra-O-benzoyl-β-D-galactoyranoside (**9R**).—2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl trichloroacetimidate (**7**) (0.741 g, 1.00 mmol), (2*R*)-2-azidohexadecanol (**5R**) (0.272 g, 0.96 mmol) and activated 4 Å molecular sieves (0.5 g) were added to alcohol-free CH_2Cl_2 (4 mL). The reaction mixture was flushed with argon

while cooling to 0 °C. A solution of TMSOTf (0.015 mL, 0.07 mmol) in CH_2Cl_2 (0.5 mL) was introduced through a syringe over a 1 h period. The mixture was stirred overnight at 0 °C before filtration over Celite and dilution with CH_2Cl_2 (50 mL). The organic phase was washed with satd aq $NaHCO_3$ and dried (Na_2SO_4). Concentration of the solution gave a residue which was purified by column chromatography (1:3 EtOAc–petroleum ether) to afford pure derivative **9R** as an oil (0.753 g, 91% yield): $[\alpha]_D$ +72.0° (*c* 1.0, $CHCl_3$); R_f 0.77; ^{1}H NMR ($CDCl_3$): δ 8.13–7.21 (m, 20 H, 4 C_6H_5), 6.02 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 0.5 Hz, H-4), 5.83 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 10.4 Hz, H-2), 5.63 (dd, 1 H, H-3), 4.91 (d, 1 H, H-1), 4.72 (dd, 1 H, $J_{5,6a}$ 6.1 Hz, $J_{6a,6b}$ 10.6 Hz, H-6a), 4.45 (dd, 1 H, $J_{5,6b}$ 6.5 Hz, H-6b), 4.36 (bdd, 1 H, H-5), 4.02 (dd, 1 H, $J_{1'a,2'}$ 5.9, $J_{1'a,1'b}$ 10.3 Hz, H-1′a), 3.66 (dd, 1 H, $J_{1'b,2'}$ 5.0 Hz, H-1′b), 3.48 (m, 1 H, H-2′), 1.50–1.20 (m, 26 H, 13 CH_2 alkyl chain), 0.89 (t, 3 H, *J* 6.3 Hz, CH_3 alkyl chain). ^{13}C NMR ($CDCl_3$): δ 166.05, 165.65, 165.62, 165.30 (4 C, 4 C_6H_5CO), 101.59 (C-1), 71.85, 71.54 (2 C, C-3,5), 71.46 (C-1′), 69.86 (C-2), 68.31 (C-4), 62.17 (C-6), 61.34 (C-2′), 32.02, 30.75, 30.64, 29.77–29.36, 25.87, 22.79 (CH_2 alkyl chain), 14.24 (CH_3 alkyl chain). Anal. Calcd for $C_{50}H_{59}N_3O_{10}$ (861.99): C, 69.66; H, 6.90; N, 4.87. Found; C, 69.50; H, 7.17; N, 5.23.

*(2*S*)-2-Azidohexadecyl 2,3,4,6-tetra*-O-*benzoyl-β*-D-*galactoyranoside* (**9S**).—Obtained as described above from trichoroacetimidate **7** (0.741 g, 1.00 mmol) and (2*S*)-2-azidohexadecanol (**5S**) (0.272 g, 0.96 mmol). Compound **9S** was obtained as an oil (0.761 g, 92% yield): $[\alpha]_D$ +57.5° (*c* 1.0, $CHCl_3$); R_f 0.77; ^{1}H NMR ($CDCl_3$): δ 8.12–7.22 (m, 20 H, 4 C_6H_5), 6.01 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 0.5 Hz, H-4), 5.85 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.5 Hz, H-2), 5.63 (dd, 1 H, H-3), 4.90 (d, 1 H, H-1), 4.72 (dd, 1 H, $J_{5,6a}$ 5.8, $J_{6a,6b}$ 10.5 Hz, H-6a), 4.44 (dd, 1 H, $J_{5,6b}$ 6.5 Hz, H-6b), 4.37 (ddd, 1 H, H-5), 4.05 (m, 1 H, H-1′a), 3.65-3.55 (m, 2 H, H-1′b,2′), 1.39–1.27 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, *J* 6.3 Hz, CH_3 alkyl chain). ^{13}C NMR ($CDCl_3$): δ 166.08, 165.64, 165.64, 165.30 (4 C, 4 C_6H_5CO), 101.92 (C-1), 72.78 (C-1′), 71.79, 71.49 (2 C, C-3,5), 69.73 (C-2), 68.16 (C-4), 62.09 (C-6), 62.00 (C-2′), 31.99, 30.91, 30.64, 29.76-29.39, 25.98, 22.77 (CH_2 alkyl chain), 14.22 (CH_3 alkyl chain). Anal. Calcd for $C_{50}H_{59}N_3O_{10}$ (861.99): C, 69.66; H, 6.90; N, 4.87. Found; C, 69.88; H, 6.86; N, 4.90.

*(2*R*)-2-Azidohexadecyl 2,3,4,6-tetra*-O-*acetyl-β*-D-*galactoyranoside* (**10R**).—Compound **10R** was prepared by *O*-debenzoylation of **9R** (0.259 g, 0.30 mmol) in MeOH containing a catalytic amount of sodium. After 16 h, the solution was concentrated and the residue was acetylated overnight in a 2:1 pyridine–Ac_2O mixture (10 mL). After concentration and purification by column chromatography (eluent 2:1 EtOAc–petroleum ether), the product **10R** (164 mg, 91% yield) was obtained as an oil: $[\alpha]_D$ −7.6° (*c* 1.0, $CHCl_3$); R_f 0.42 (5:2 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 5.40 (dd, 1 H, $J_{3,4}$ 3.3, $J_{4,5}$ 0.5 Hz, H-4), 5.25 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.4 Hz, H-2), 5.03 (dd, 1 H, H-3), 4.54 (d, 1 H, H-1), 4.21 (dd, 1 H, $J_{5,6a}$ 6.9, $J_{6a,6b}$ 11.2 Hz, H-6a), 4.13 (dd, 1 H, $J_{5,6b}$ 6.8 Hz, H-6b), 3.92 (bdd, 1 H, H-5), 3.91 (dd, 1 H, $J_{1'a,2'}$ 5.6, $J_{1'a,1'b}$ 10.4 Hz, H-1′a), 3.60 (dd, 1 H, $J_{1'b,2'}$ 6.4 Hz, H-1′b), 3.41 (m, 1 H, H-2′), 2.17, 2.07, 2.06, 1.99 (4s, 12 H, 4 CH_3COO), 1.52–1.26 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, *J* 6.3 Hz, CH_3 alkyl chain). ^{13}C NMR ($CDCl_3$): δ 170.33, 170.22, 170.09, 169.34 (4 C, 4 CH_3COO), 101.10 (C-1), 71.25 (C-1′), 70.91 (C-3), 70.81 (C-5), 68.59 (C-2), 67.04 (C-4), 61.24 (C-6), 61.20 (C-2′), 31.91, 30.50, 29.64-29.35, 25.96, 22.68 (CH_2 alkyl chain), 20.74, 20.63, 20.63, 20.54 (4 C, 4 CH_3COO), 14.10 (CH_3 alkyl chain). Anal. Calcd for $C_{30}H_{51}N_3O_{10}$ (613.73): C, 58.71; H, 8.38; N, 6.85. Found; C, 58.41; H, 8.58; N, 6.74.

*(2*S*)-2-Azidohexadecyl 2,3,4,6-tetra*-O-*acetyl-β*-D-*galactoyranoside* (**10S**).—2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl trichoroacetimidate (**8**)[18,19] (0.616 g, 1.25 mmol) and (2*S*)-2-azidohexadecanol (**5S**) (0.283 g, 1.00 mmol) were treated as described for compounds **9R** and **9S**. After purification by column chromatography (2:1 EtOAc–petroleum ether), ^{1}H NMR of the product showed the presence of trichloroacetamide which was eliminated after a new chromatography using 20:1 $CHCl_3$–MeOH as the eluent. Product **10S** was obtained as an oil (0.233 g, 38% yield): $[\alpha]_D$ −18.6° (*c* 1.0, $CHCl_3$); R_f

0.42 (5:2 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 5.41 (dd, 1 H, $J_{3,4}$ 3.3, $J_{4,5}$ 0.5 Hz, H-4), 5.26 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.4 Hz, H-2), 5.03 (dd, 1 H, H-3), 4.56 (d, 1 H, H-1), 4.21 (dd, 1 H, $J_{5,6a}$ 6.8 Hz, $J_{6a,6b}$ 11.3 Hz, H-6a), 4.13 (dd, 1 H, $J_{5,6b}$ 6.4 Hz, H-6b), 3.99 (dd, 1 H, $J_{1'a,2'}$ 2.4, $J_{1'a,1'b}$ 9.5 Hz, H-1′a), 3.92 (dd, 1 H, H-5), 3.54 (m, 1 H, H-2′), 3.44 (dd, 1 H, $J_{1'b,2'}$ 8.8 Hz, H-1′b), 2.17, 2.07, 2.06, 1.99 (4s, 12 H, 4 CH_3COO), 1.39–1.26 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, J 6.5 Hz, CH_3 alkyl chain). ^{13}C NMR ($CDCl_3$): δ 170.37, 170.27, 170.16, 169.48 (4 C, 4 CH_3COO), 101.29 (C-1), 72.68 (C-1′), 70.95 (C-3), 70.65 (C-5), 68.65 (C-2), 67.08 (C-4), 62.08 (C-2′), 61.25 (C-6), 31.89, 30.86, 29.62-29.36, 25.88, 22.67 (CH_2 alkyl chain), 20.75, 20.63, 20.63, 20.54 (4 C, 4 CH_3COO), 14.22 (CH_3 alkyl chain). Anal. Calcd for $C_{30}H_{51}N_3O_{10}$ (613.73): C, 58.71; H, 8.38; N, 6.85. Found; C, 58.67; H, 8.37; N, 6.68.

Compound **10S** was also prepared from **9S** in 92% yield, following the same procedure as that used for **10R** from **9R**.

*(2*R*)-2-Hexadecanoylaminohexadecyl 2,3,4,6-tetra*-O-*benzoyl-β*-D-*galactoyranoside* (**11R**). —A solution of PPh_3 (0.262 g, 1.00 mmol) in deoxygenated C_6H_6 (1 mL) was added dropwise over 1 h under an argon atmosphere to a mixture of glycoside **9R** (0.560 g, 0.65 mmol), hexadecanoyl chloride (0.330 mL, 1.09 mmol) and crushed 4 Å molecular sieves (0.5 g) in dry C_6H_6. The mixture was stirred for 24 h, and after filtration over Celite and concentration of the solution, the product was purified by two successive column chromatographs first with 1:3 EtOAc–petroleum ether as the eluent, then with 24:1 $CHCl_3$–EtOH. Compound **11R** was obtained as an oil (0.391 g, 56% yield): $[\alpha]_D$ +63.8° (*c* 1.0, $CHCl_3$); R_f 0.27 (1:3 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 8.12–7.25 (m, 20 H, 4 C_6H_5), 6.01 (dd, 1 H, $J_{3,4}$ 3.3, $J_{4,5}$ 0.5 Hz, H-4), 5.78 (dd, 1 H, $J_{1,2}$ 7.5, $J_{2,3}$ 10.4 Hz, H-2), 5.66 (dd, 1 H, H-3), 5.34 (d, 1 H, $J_{2',NH}$ 8.8 Hz, NH), 4.79 (d, 1 H, H-1), 4.68 (dd, 1 H, $J_{5,6a}$ 6.5, $J_{6a,6b}$ 10.9 Hz, H-6a), 4.43 (dd, 1 H, $J_{5,6b}$ 6.4 Hz, H-6b), 4.34 (bdd, 1 H, H-5), 4.04 (m, 1 H, H-2′), 3.95 (dd, 1 H, $J_{1'a,2'}$ 1.5 Hz, $J_{1'a,1'b}$ 9.2 Hz, H-1′a), 3.62 (dd, 1 H, $J_{1'b,2'}$ 3.2 Hz, H-1′b), 1.71 (t, 2 H, J 7.5 Hz, CH_2CO), 1.58–1.26 (m, 52 H, 26 CH_2 alkyl chains), 0.89 (t, 6 H, J 6.3 Hz, 2 CH_3 alkyl chains). ^{13}C NMR ($CDCl_3$): δ 172.56 (NHCOO), 165.98, 165.55, 165.50, 165.41 (4 C, 4 C_6H_5CO), 133.62, 133.55–133.32, 130.04–128.32 (24 C, 4 C_6H_5), 101.81 (C-1), 71.56 (3 C, C-1′,3,5), 70.25 (C-2), 68.26 (C-4), 62.14 (C-6), 48.49 (C-2′), 36.52, 31.97, 31.78, 29.76-29.25, 26.06, 25.67, 22.74 (CH_2 alkyl chains), 14.17 (CH_3 alkyl chains). Anal. Calcd for $C_{66}H_{91}NO_{11}$ (1074.40): C, 73.78; H, 8.54; N, 1.30. Found; C, 73.87; H, 8.63 N, 1.44.

*(2*S*)-2-Hexadecanoylaminohexadecyl 2,3,4,6-tetra*-O-*benzoyl-β*-D-*galactoyranoside* (**11S**). —Obtained from **9S** in 55% yield as described for **11R**. Compound **11S** was obtained as an amorphous solid: $[\alpha]_D$ +36.7° (*c* 1.0, $CHCl_3$); R_f 0.27 (1:3 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 8.12–7.25 (m, 20 H, 4 C_6H_5), 6.02 (dd, 1 H, $J_{3,4}$ 3.3, $J_{4,5}$ 0.5 Hz, H-4), 5.81 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.5 Hz, H-2), 5.74 (d, 1 H, $J_{2',NH}$ 9.0 Hz, NH), 5.66 (dd, 1 H, H-3), 4.82 (d, 1 H, H-1), 4.67 (dd, 1 H, $J_{5,6a}$ 6.4, $J_{6a,6b}$ 11.0 Hz, H-6a), 4.46 (dd, 1 H, $J_{5,6b}$ 6.4 Hz, H-6b), 4.34 (bdd, 1 H, H-5), 4.01-3.97 (m, 2 H, H-1′a,2′), 3.62 (bd, 1 H, H-1′b), 2.16 (m, 2 H, CH_2CO), 1.60–1.26 (m, 52 H, 26 CH_2 alkyl chains), 0.89 (t, 6 H, J 6.3 Hz, 2 CH_3 alkyl chains). ^{13}C NMR ($CDCl_3$): δ 172.74 (NHCOO), 165.71, 165.55, 165.43, 165.37 (4 C, 4 C_6H_5CO), 133.57, 133.25, 129.97–128.27 (24 C, 4 C_6H_5), 102.06 (C-1), 71.92 (C-1′), 71.53 (2 C, C-3,5), 70.05 (C-2), 68.37 (C-4), 62.10 (C-6), 48.62 (C-2′), 36.79, 31.95, 31.57, 29.74-29.40, 26.17, 25.82, 22.72 (CH_2 alkyl chains), 14.15 (CH_3 alkyl chains). Anal. Calcd for $C_{66}H_{91}NO_{11}$ (1074.40): C, 73.78; H, 8.54; N, 1.30. Found; C, 73.38; H, 8.51; N, 1.43.

*(2*R*)-2-Hexadecanoylaminohexadecyl β*-D-*galactopyranoside* (**12R**). —The benzoylated product **11R** (0.600 g, 0.558 mmol) was added to a mixture of MeOH (20 mL) containing a catalytic amount of MeONa and CH_2Cl_2 (5 mL). Dissolution occurred after a few minutes, then the product started to crystallise. Stirring was maintained for 16 h and CH_2Cl_2 was vaporised. The product was recovered by filtration and washed twice with MeOH (2 × 5 mL) (0.317 g, 87% yield): mp 143 °C (MeOH). $[\alpha]_D$ −6.0° (*c* 1.0, 1:1 $CHCl_3$–MeOH); ^{1}H

NMR (C_5D_5N): δ 8.23 (d, 1 H, $J_{2',NH}$ 7.9 Hz, N*H*), 7.21, 6.82, 6.55 and 6.44 (4 m, 4 H, 4 O*H*), 4.87 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.58–3.86 (m, 9 H, H-2,3,4,5,6a,6b,1′a,1′b,2′), 2.41 (t, 2 H, *J* 7.0 Hz, COCH_2), 1.79, 1.60–1.10 (m, 52 H, 26 CH_2 alkyl chains), 0.87 (m, 6 H, 2 CH_3 alkyl chains). Anal. Calcd for $C_{38}H_{75}NO_7$ (657.99): C, 69.36; H, 11.49; N, 2.13. Found; C, 69.13; H, 11.80; N, 2.12.

(2S)-2-Hexadecanoylaminohexadecyl β-D-galactopyranoside (**12S**).—Product **12S** was prepared in 85% yield from **11S** as described above for **12R**: mp 150 °C (MeOH). $[\alpha]_D$ + 15.8° (*c* 1.0, 1:1 $CHCl_3$–MeOH); ^{1}H NMR (C_5D_5N): δ 8.25 (d, 1 H, $J_{2',NH}$ 8.5 Hz, N*H*), 7.12, 6.82, 6.59 and 6.43 (4 m, 4 H, 4 O*H*), 4.82 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 4.54–4.08 (m, 9 H, H-2,3,4,5,6a,6b,1′a,1′b,2′), 2.45 (t, 2 H, *J* 7.0 Hz, COCH_2), 1.79, 1.60–1.10 (m, 52 H, 26 CH_2 alkyl chains), 0.87 (m, 6 H, 2 CH_3 alkyl chains). Anal. Calcd for $C_{38}H_{75}NO_7 \cdot H_2O$ (676.00): C, 67.51; H, 11.48; N, 2.07. Found; C, 67.59; H, 11.47; N, 2.13.

(2R)-2-Azidohexadecyl 3,4,6-tri-O-acetyl-2-allyloxycarbonylamino-2-deoxy-β-D-glucopyranoside (**14R**).—Tetra-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy-β-D-glucopyranose (**13**)[21] (1.048 g, 2.43 mmol) and the silylated mixture **3R**/**4S** (0.850 g, 2.39 mmol) were added to alcohol-free CH_2Cl_2. The reaction mixture was flushed with argon while cooling to −20 °C. Trimethylsilyl trifluoromethanesulfonate (0.470 mL, 2.43 mmol) was introduced through a syringe and the argon flush maintained for 0.5 h. The mixture was stirred overnight at −20 °C, then poured into satd aq $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 50 mL). After drying (Na_2SO_4), concentration of the solution gave a residue which was purified by column chromatography (2:3 EtOAc–petroleum ether) to afford the pure derivative **14R** as a solid (1.24 g, 78% yield): mp 81–82 °C (EtOH); $[\alpha]_D$ + 5.9° (*c* 1.0, $CHCl_3$); R_f 0.61; ^{1}H NMR (CD_3COCD_3): δ 6.49 (d, 1 H, $J_{2,NH}$ 7.8 Hz, N*H*), 5.92 (ddd, 1 H, C*H*=), 5.26 (bd, 1 H, 0.5 CH_2=), 5.24 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.5 Hz, H-3), 5.13 (dd, 1 H, 0.5 CH_2=), 5.00 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 4.87 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 4.57–4.40 (m, 2 H, allyl CH_2), 4.27 (dd, 1 H, $J_{5,6a}$ 4.9, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.13 (dd, 1 H, $J_{5,6b}$ 2.5 Hz, H-6b), 3.89 (dd, 1 H, $J_{1'a,2'}$ 6.3, $J_{1'a,1'b}$ 10.4 Hz, H-1′a), 3.85 (ddd, 1 H, H-5), 3.69 (ddd, 1 H, H-2), 3.68 (dd, 1 H, $J_{1'b,2'}$ 4.3 Hz, H-1′b), 3.62 (m, 1 H, H-2′), 2.03, 1.99, 1.95 (3 s, 9 H, 3 CH_3COO), 1.59–1.29 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, *J* 6.7 Hz, CH_3 alkyl chain). ^{13}C NMR ($CDCl_3$): δ 170.67, 170.59, 169.45 (3 C, CH_3COO), 155.67 (NH*C*OO), 132.68 (*C*H=), 117.57 (*C*H_2=), 100.83 (C-1), 72.13 (C-3), 71.82 (C-5), 71.49 (C-1′), 68.85 (C-4), 65.80 (allyl *C*H_2), 62.13 (C-6), 61.45 (C-2′), 55.99 (C-2), 31.89, 30.59, 29.67-29.34, 25.99, 22.67 (*C*H_2 alkyl chain), 20.72, 20.66, 20.61 (3 C, 3 *C*H_3COO), 14.11 (*C*H_3 alkyl chain). Anal. Calcd for $C_{32}H_{54}N_4O_{10}$ (654.78): C, 58.69; H, 8.31; N, 8.56. Found; C, 58.54; H, 8.27; N, 8.30.

(2S)-2-Azidohexadecyl 3,4,6-tri-O-acetyl-2-allyloxycarbonylamino-2-deoxy-β-D-glucopyranoside (**14S**).—Obtained as described above from **13** (0.897 g, 2.08 mmol) and the silylated mixture **3S**/**4R** (0.729 g, 2.05 mmol). Compound **14S** (1.060 g, 79% yield) was obtained as a white solid: mp 119–120 °C (EtOH); $[\alpha]_D$ −1.4° (*c* 1.0, $CHCl_3$); R_f 0.61; ^{1}H NMR (CD_3COCD_3): δ 6.50 (d, 1 H, $J_{2,NH}$ 6.3 Hz, N*H*), 5.92 (ddd, 1 H, C*H*=), 5.26 (bd, 1 H, 0.5 CH_2=), 5.22 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.4 Hz, H-3), 5.13 (dd, 1 H, 0.5 CH_2=), 5.00 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 4.87 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 4.60–4.40 (m, 2 H, allyl CH_2), 4.26 (dd, 1 H, $J_{5,6a}$ 4.9, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.13 (dd, 1 H, $J_{5,6b}$ 2.6 Hz, H-6b), 3.96 (d, 1 H, $J_{1'a,1'b}$ 6.9 Hz, H-1′a), 3.85 (ddd, 1 H, H-5), 3.69 (ddd, 1 H, H-2), 3.62 (1 H, H-2′), 3.57 (dd, 1 H, $J_{1'b,2}$ 7.2 Hz, H-1′b), 2.03, 1.99, 1.95 (3 s, 9 H, 3 CH_3COO), 1.55–1.29 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, *J* 6.7 Hz, CH_3 alkyl chain). ^{13}C NMR ($CDCl_3$): δ 170.62, 170.55, 169.46 (3 C, CH_3COO), 155.67 (NH*C*OO), 132.73 (*C*H=), 117.46 (*C*H_2=), 100.16 (C-1), 72.76 (C-1′), 72.16 (C-3), 71.75 (C-5), 68.89 (C-4), 65.74 (allyl *C*H_2), 62.11 (2 C, C-6,2′), 56.02 (C-2), 31.89, 30.83, 29.64-29.32, 25.91, 22.65 (*C*H_2 alkyl chain), 20.72, 20.64, 20.59 (3 C, 3 *C*H_3COO), 14.11 (*C*H_3 alkyl chain). Anal. Calcd for $C_{32}H_{54}N_4O_{10}$ (654.78): C, 58.69; H, 8.31; N, 8.56. Found; C, 59.08; H, 8.39; N, 8.14.

(2R)-2-Azidohexadecyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (**15R**).—A solution of palladium tetrakis(triphenylphosphine)—prepared under argon from tris(dibenzylideneacetone)dipalladium(0) (0.015 g, 0.013 mmol) and PPh_3 (0.038 g, 0.144 mmol) in dry THF (1.5 mL)—was added to a solution of compound **14R** (0.753 g, 1.15 mmol) and dimethylmalonate (1.1 mL) in THF (4 mL). The mixture was stirred for 16 h, then concentrated and the products were purified on a short column of silica-gel (1:1 EtOAc–petroleum ether, followed by pure EtOAc) to afford the NH_2-free derivative which was *N*-reacetylated in a 2:1 pyridine–Ac_2O mixture (15 mL). After concentration, the residue was purified by column chromatography (3:1 EtOAc–petroleum ether); pure product **15R** was obtained as a white solid (0.515 g, 73% yield): mp 91–92 °C; $[\alpha]_D$ −6.7° (*c* 1.0, $CHCl_3$); R_f 0.69 (1:3 petroleum ether–EtOAc); ^1H NMR ($CDCl_3$): δ 5.67 (d, 1 H, $J_{2,NH}$ 8.5 Hz, N*H*), 5.35 (dd, 1 H, $J_{2,3}$ 10.1, $J_{3,4}$ 9.7 Hz, H-3), 5.07 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.82 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.26 (dd, 1 H, $J_{5,6a}$ 4.6, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.14 (dd, 1 H, $J_{5,6b}$ 2.2 Hz, H-6b), 3.88 (dd, 1 H, $J_{1'a,2}$ 6.0, $J_{1'a,1'b}$ 10.3 Hz, H-1′a), 3.81 (ddd, 1 H, H-2), 3.75 (ddd, 1 H, H-5), 3.64 (dd, 1 H, $J_{1'b,2'}$ 3.7 Hz, H-1′b), 3.38 (m, 1 H, H-2′), 2.08, 2.03, 2.02, 1.94 (4 s, 12 H, 4 C*H*$_3$CO), 1.50–1.25 (m, 26 H, 13 C*H*$_2$ alkyl chain), 0.88 (t, 3 H, *J* 6.7 Hz, C*H*$_3$ alkyl chain). ^{13}C NMR ($CDCl_3$): δ 170.63, 170.63, 170.63, 169.37 (4 C, 3 CH_3COO, CH_3CON), 100.24 (C-1), 72.29 (C-3), 71.76 (C-5), 71.21 (C-1′), 68.92 (C-4), 62.17 (C-6), 61.38 (C-2′), 54.56 (C-2), 31.88, 30.49, 29.63–29.31, 26.01, 22.64 (*C*H$_2$ alkyl chain), 23.20 (*C*H$_3$CON), 20.68, 20.65, 20.57 (3 C, 3 *C*H$_3$COO), 14.08 (*C*H$_3$ alkyl chain). Anal. Calcd for $C_{30}H_{52}N_4O_9$ (612.74): C, 58.80; H, 8.55; N, 9.14. Found; C, 58.94; H, 8.66; N, 9.09.

(2S)-2-Hexadecanoylaminohexadecyl 3,4,6-tri-O-acetyl-2-allyloxycarbonylamino-2-deoxy-β-D-glucopyranoside (**16S**).—Triphenylphosphine (0.315 g, 1.20 mmol) in deoxygenated C_6H_6 (0.50 mL) was added dropwise over 1 h to a solution of the glycoside **14S** (0.524 g, 0.80 mmol) and hexadecanoyl chloride (0.390 mL, 1.29 mmol) in deoxygenated C_6H_6 (3 mL) under argon. The mixture was stirred for 16 h, before a new addition of PPh_3 (0.105 g, 0.40 mmol) in C_6H_6 (0.4 mL). Stirring was maintained for 24 h, then the solution was concentrated and the residue was purified by column chromatography (1:1 EtOAc–petroleum ether) to afford the pure product **16S** (0.354 g, 51% yield): mp 139–140 °C; $[\alpha]_D$ −21.5° (*c* 1.0, $CHCl_3$); R_f 0.50 (4:5 EtOAc–petroleum ether); ^1H NMR ($CDCl_3$): δ 5.89 (ddd, 1 H, C*H*=), 5.78 (d, 1 H, $J_{2,NH}$ 8.0 Hz, N*H*), 5.32–5.11 (m, 3 H, H-3, C*H*$_2$=), 5.06 (dd, 1 H, $J_{3,4}$ 8.8, $J_{4,5}$ 9.9 Hz, H-4), 4.88 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 4.55 (m, 2 H, allyl C*H*$_2$), 4.48 (d, 1 H, $J_{2',NH}$ 8.2 Hz, N*H*), 4.28 (dd, 1 H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.11 (dd, 1 H, $J_{5,6b}$ 2.0 Hz, H-6b), 4.04 (m, 1 H, H-2′), 3.87 (dd, 1 H, $J_{1'a,2'}$ 3.3, $J_{1'a,1'b}$ 9.8 Hz, H-1′a), 3.77-3.62 (m, 2 H, H-2,5), 3.56 (dd, 1 H, $J_{1'b,2}$ 2.2 Hz, H-1′b), 2.16 (m, 2 H, C*H*$_2$CO), 2.09, 2.05, 2.03 (3 s, 9 H, 3 C*H*$_3$COO), 1.70–1.56 (m, 52 H, 26 C*H*$_2$ alkyl chains), 0.88 (t, 6 H, *J* 6.7 Hz, 2 C*H*$_3$ alkyl chains). ^{13}C NMR ($CDCl_3$): δ 172.85 (NH*C*OCH$_2$), 170.79, 170.59, 169.41 (3 C, CH_3COO), 155.88 (NH*C*OO), 132.59 (*C*H=), 117.66 (*C*H$_2$=), 102.06 (C-1), 72.29 (C-3), 71.83 (2 C, C-5,C-1′), 68.66 (C-4), 65.77 (allyl *C*H$_2$), 62.06 (C-6), 56.02 (C-2), 48.61 (C-2′), 36.87, 31.91–29.35, 26.17, 25.83, 22.67 (*C*H$_2$ alkyl chains), 20.70, 20.66, 20.55 (3 C, 3 *C*H$_3$COO), 14.09 (2 C, 2 *C*H$_3$ alkyl chains). Anal. Calcd for $C_{48}H_{86}N_2O_{11}$ (867.18): C, 66.48; H, 10.00; N, 3.23. Found; C, 66.28; H, 10.06; N, 3.28.

(2R)-2-Hexadecanoylaminohexadecyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (**17R**).—$Pd(OH)_2C$ (0.150 g) was added to a solution of the azido derivative **15R** (0.490 g, 0.80 mmol) and freshly distilled cyclohexene (5 mL) in abs EtOH (12 mL). The suspension was refluxed for 4 h with stirring, then cooled to rt and the N*H*$_2$-free product was recovered as an amorphous solid by filtration over Celite and concentration of the solution: R_f 0.50 (1:3 petroleum ether–EtOAc); ^1H NMR ($CDCl_3$): δ 6.00 (d, 1 H, $J_{2,NH}$ 8.5 Hz, N*H*), 5.26 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 9.5 Hz, H-3), 5.08 (dd, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 4.70 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.30–4.10 (m, 3 H, H-6a,6b,1′a), 3.93 (ddd, 1 H, H-2), 3.70–3.61 (m, 2 H, H-5,2′), 3.57 (dd, 1 H, $J_{1'b,2'}$ 3.8,

$J_{1'a,1'b}$ 10.2 Hz, H-1′b), 2.09, 2.04, 2.03, 1.96 (4 s, 12 H, 4 CH_3CO), 1.50–1.26 (m, 26 H, 13 CH_2 alkyl chain), 0.88 (t, 3 H, J 6.7 Hz, CH_3 alkyl chain). ^{13}C NMR ($CDCl_3$): δ 170.86, 170.58, 170.54, 169.37 (4 C, 3 CH_3COO, CH_3CON), 100.79 (C-1), 73.81 (C-1′), 72.64 (C-3), 71.61 (C-5), 68.84 (C-4), 62.20 (C-6), 54.35 (C-2), 50.82 (C-2′), 33.44, 31.84, 29.62-29.28, 25.99 (CH_2 alkyl chain), 23.22 (CH_3CON), 20.67, 20.67, 20.56 (3 C, 3 CH_3COO), 14.05 (CH_3 alkyl chain).

Hexadecanoyl chloride (0.380 mL, 1.25 mmol) was added dropwise at 0 °C to a solution of the NH_2-free derivative in dry pyridine. The mixture was allowed to reach rt and stirring was maintained for 16 h before a new addition of hexadecanoyl chloride (0.100 mL, 0.33 mmol). After 12 h, the reaction mixture was cooled to 0 °C and water (0.5 mL) was added dropwise over 1 h. The solution was poured into ice-water and extracted with CH_2Cl_2 (2 × 30 mL); the organic phase was washed with 10% aq HCl, then with satd aq $NaHCO_3$, dried and concentrated to afford a residue which was purified by column chromatography using 12:1 $CHCl_3$–MeOH as the eluent. Pure product **17R** was recovered as a solid (0.455 g, 69% yield): mp 168–169 °C (EtOH); $[\alpha]_D$ −16.0° (*c* 1.0, $CHCl_3$); R_f 0.80 (12:1 $CHCl_3$–MeOH); ^{1}H NMR ($CDCl_3$): δ 5.93 (d, 1 H, J 8.5 Hz, NH), 5.67 (d, 1 H, J 8.9 Hz, NH), 5.16 (dd, 1 H, $J_{2,3}$ 9.2, $J_{3,4}$ 9.9 Hz, H-3), 5.08 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.63 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.28 (dd, 1 H, $J_{5,6a}$ 4.7, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.13 (dd, 1 H, $J_{5,6b}$ 2.2 Hz, H-6b), 4.10 (m, 1 H, H-2′), 3.96 (dd, 1 H, H-2), 3.66 (m, 3 H, H-5,1′a,1′b), 2.16 (t, 2 H, J 7.5 Hz, COCH_2), 2.09, 2.04, 2.03, 1.95 (4 s, 12 H, 4 CH_3CO), 1.63–1.25 (m, 52 H, 26 CH_2 alkyl chains), 0.88 (t, 6 H, J 6.7 Hz, 2 CH_3 alkyl chains). ^{13}C NMR ($CDCl_3$): δ 173.40, 170.85, 170.61, 170.58, 169.36 (5 C, 3 CH_3COO, CH_3CON, CH_2CON), 100.10 (C-1), 72.97 (C-3), 71.91 (C-5), 70.63 (C-1′), 68.62 (C-4), 62.19 (C-6), 54.19 (C-2), 47.78 (C-2′), 36.91, 31.91, 31.56, 29.70-29.35, 26.02, 25.95, 22.68 (CH_2 alkyl chains), 23.29 (CH_3CON), 20.72, 20.72, 20.60 (3 C, 3 CH_3COO), 14.11 (2 C, 2 CH_3 alkyl chains). Anal. Calcd for $C_{46}H_{84}N_2O_{10}$ (825.15): C, 66.95; H, 10.26; N, 3.39. Found; C, 66.88; H, 10.19; N, 3.29.

(2S)-2-Hexadecanoylaminohexadecyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (**17S**).—Obtained as described above for the preparation of **15R** from **14R** starting from compound **16S** (0.512 g, 0.59 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.012 g, 0.0104 mmol). The crude product was purified by column chromatography (1:10 $CHCl_3$–EtOAc) affording **17S** as a white solid (0.365 g, 75% yield): mp 157–158 °C (from EtOAc–petroleum ether); $[\alpha]_D$ −30.5° (*c* 1.0, $CHCl_3$); R_f 0.63 (EtOAc); ^{1}H NMR ($CDCl_3$): δ 5.76 and 5.68 (2 d, 2 H, $J_{2,NH}$ 8.9 Hz, 2 NH), 5.16 (dd, 1 H, $J_{2,3}$ 8.8, $J_{3,4}$ 9.5 Hz, H-3), 5.08 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.50 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.27 (dd, 1 H, $J_{5,6a}$ 4.6 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.14 (dd, 1 H, $J_{5,6b}$ 2.3 Hz, H-6b), 4.07–4.00 (m, 2 H, H-2,2′), 3.88 (dd, 1 H, $J_{1'a,2}$ 3.5, $J_{1'a,1'b}$ 9.7 Hz, H-1′a), 3.67 (ddd, 1 H, H-5), 3.53 (dd, 1 H, $J_{1'b,2'}$ 3.7 Hz, H-1′b), 2.16 (2 H, COCH_2), 2.08, 2.04, 2.03, 1.95 (4 s, 12 H, 4 CH_3CO), 1.62–1.25 (m, 52 H, 26 CH_2 alkyl chains), 0.88 (t, 6 H, J 6.7 Hz, 2 CH_3 alkyl chains). ^{13}C NMR ($CDCl_3$): δ 172.96, 170.96, 170.58, 170.28, 169.36 (5 C, 3 CH_3COO, CH_3CON, CH_2CON), 100.66 (C-1), 72.53 (C-3), 71.82 (C-5), 71.75 (C-1′), 68.63 (C-4), 62.06 (C-6), 54.21 (C-2), 48.71 (C-2′), 36.87, 31.91, 31.56, 29.69-29.35, 26.15, 25.88, 22.66 (CH_2 alkyl chains), 23.20 (CH_3CON), 20.70, 20.70, 20.58 (3 C, 3 CH_3COO), 14.02 (2 C, 2 CH_3 alkyl chains). Anal. Calcd for $C_{46}H_{84}N_2O_{10}$ (825.15): C, 66.95; H, 10.26; N, 3.39. Found; C, 66.93; H, 10.25; N, 3.46.

(2R)-2-Hexadecanoylaminohexadecyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**18R**).—Product **18R** was prepared in 86% yield from **17R** as described above for **12R**. Mp 220 °C (MeOH). Anal. Calcd for $C_{40}H_{78}N_2O_7 \cdot 0.5\ H_2O$ (708.05): C, 67.85; H, 11.25; N, 3.94. Found; C, 67.83; H, 11.24; N, 4.24.

(2S)-2-Hexadecanoylaminohexadecyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**18S**).—Obtained in 89% yield from **17S** as described above for **12S**. Mp 214 °C (MeOH). Anal. Calcd for $C_{40}H_{78}N_2O_7 \cdot 0.5\ H_2O$ (708.05): C, 67.85; H, 11.25; N, 3.94. Found; C, 67.82; H, 11.44; N, 4.03.

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