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# Novel sugar bola-amphiphiles with a pseudo macrocyclic structure

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**Abstract**

Novel bola-amphiphilic compounds have been synthesised with D-glucose or D-galactose moieties as polar head groups. The sugar groups are coupled to the hydrophobic bridge, a chain of ten or twelve methylene groups, by an amide function at the C-2 site (2-alkylamido-2-deoxy-D-glucose derivative) or a glycuronamido function at the C-6 site. The former series is glycosylated with a cinnamyl group and the latter with octyl or decyl groups to afford pseudo macrocyclic compounds. © 1997 Elsevier Science Ltd.

*Keywords:* Bola-amphiphiles; Glucose head groups; 2-Alkylamido-2-deoxy-D-glucose; D-Glycofuranuronamide

## 1. Introduction

Bolaform amphiphilic compounds exhibit diverse interesting properties [1–3]. Bola-amphiphiles are molecules with two polar head groups separated by one or more hydrophobic spacer groups; three general types can be identified (Fig. 1). The polar groups include glycerol and related polyols and are connected to the hydrophobic chain through ether, acetal, ester, and amide links [4]. Compounds of Type I can form micelles or monolayer lipid vesicles for a range of variants in the structure, but more complex behaviour has been observed for bis(azacrown ether) bola-amphiphiles (micelle or multilamellar vesicle formation depending on the length of the spacer group) [5]. Compounds with polyhydroxy head groups act as gelling agents in water by forming fibre-like aggregates [6]; similar rods and tubules are formed by self-assembly of bola-amphiphiles with amino acid and ammonium functionalities as the head groups [7].

One interesting property of many bola-amphiphiles is their capacity to become incorporated into lipid membranes. Depending on its structure, the bola-amphiphile can act either as a membrane disrupting agent [8] or as a membrane stabiliser [9,10]. Most studies of bola-amphiphiles which interact with membranes involve either macrocyclic Type II, or pseudo macrocyclic Type III structures (Fig. 1). These are analogs of the lipid constituents of the highly stable membranes from archaebacteria. These bacterial membranes are made up of macrocyclic lipids (Type II) with two polyisoprenoid spacer groups attached to glycerol head groups by ether linkages [3]. Synthetic

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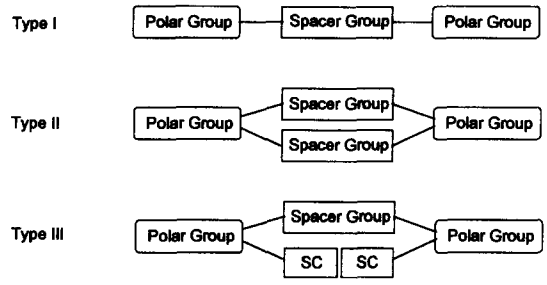


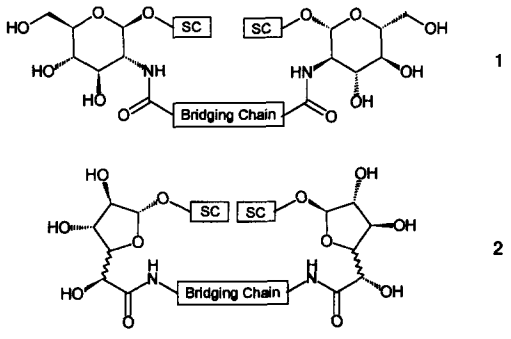

Fig. 1. Basic structure elements in a bola-amphiphile.

macrocyclic bola-amphiphiles include Type II compounds with polymethylene chains attached to glycerol [11] and similar Type III compounds with the two short chains (SC) having a combined length equal to that of the bridging chain [9]. Pseudo macrocyclic compounds are the more interesting type since they have the potential to be incorporated into membranes by bridging a monolayer or a bilayer or by forming a U-shape insert into one layer of a bilayer.

Although many amphiphilic compounds are known in which the polar group is a sugar or related derivative, only a few bola-amphiphiles display such a structural feature [12]. The use of sugar moieties as polar head groups can offer greater potential for interaction at cell surfaces by molecular recognition with the surface glycoproteins of a viral particle. The potential for useful application is diversified. We now report the synthesis of several examples of pseudo macrocyclic bola-amphiphiles with an unprotected carbohydrate moiety as the polar group but with two different modes of attaching the bridging chain and the short chain (SC).

## 2. Results and discussion

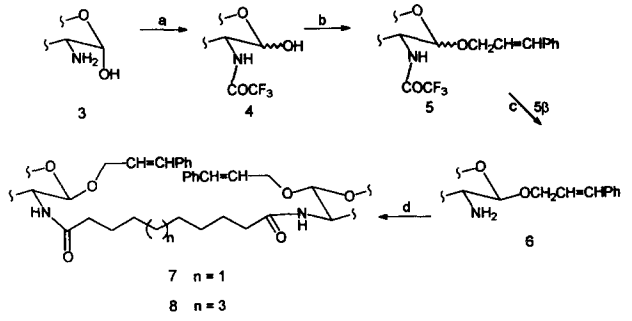
The basic architecture of the polar group is shown in structures **1** and **2**. Type **1** is based on 2-amino-2-deoxy-D-glucose and has the two types of chain attached to vicinal sites on a pyranose sugar in an arrangement which is closely analogous to the juxtaposition of the vicinally disposed chains in natural lipids based on glycerol head groups. Type **2** is based on glycuronic acids and has the chains attached to a furanose ring in a 1,3 orientation. In both cases, the short chains are attached by glycosidic links at the anomeric site, but a further variant was introduced by using a $C_8$ alkyl chain in Type **2** and a cinnamyl group [(*E*)-3-phenylprop-2-enyl] in Type **1**. Although an amide link is used to attach the bridging chain in both cases, notably two alternative modes of bonding are used with the chain attached through nitrogen in **1** and through the carbonyl group in **2**.



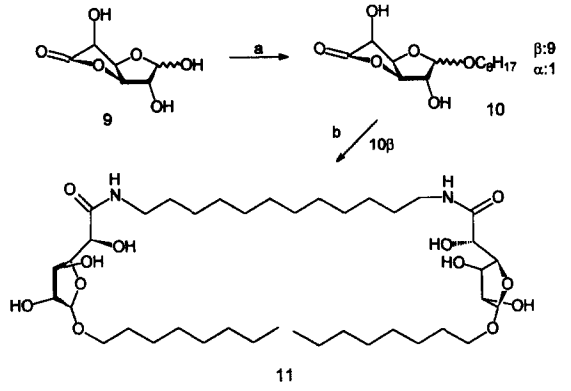

Determining the best route to a bola-amphiphile of Type **1** starting from 2-amino-2-deoxy-D-glucose needs consideration of: i) the balance of the relative ease of glycosidation and *N*-acylation; ii) the relative stability of the derivative at one site during the second step; iii) the need to control the anomeric ratio; iv) the need to avoid reaction at the other hydroxyl groups, i.e. if possible a protection/deprotection strategy is to be avoided. Most strategies for glycosylation such as the Koenigs–Knorr reaction or the oxazoline, or phthalimido methods require the sugar to be fully protected [13]. Recently, we reported [14] an improvement of the Fischer methodology using a Lewis acid as promoter, and obtained excellent yields of long-chain alkyl glycosides from glucose with significant selectivity for the $\beta$ anomer ($\alpha,\beta$ ratio 1:7–1:19). Unfortunately 2-acetamido-2-deoxy-D-glucose behaved atypically and the glycosylation gave a low yield, mainly of the $\alpha$ anomer.

2-Amino-2-deoxy-D-glucose can be *N*-acylated directly with or without protection of the hydroxy groups but protection is necessary for stereoselectivity [15]. We have found mild conditions which can give effective selectivity for the $\beta$ anomer during *N*-acylation with $CF_3COCl$ without prior *O*-protection. The complete reaction scheme for the preparation of bola-amphiphiles from 2-amino-2-deoxy-D-glucose is shown in Scheme 1.

The amino group of 2-amino-2-deoxy-D-glucose (**3**) was first protected (68% yield) with the trifluoroacetyl group since this protecting group is easier to remove than acetyl. This protecting group is also more deactivating than acetyl resulting in an enhanced rate of formation of the cinnamyl glucoside **5** which was best achieved by the method of Schmidt and coworkers [16] with sodium hydride as base



Scheme 1. *Reagents and conditions:* (a) $(CF_3CO)_2O$, $Et_3N$, DMF, 0–20 °C; (b) NaH, PhHCH=CHCH$_2$Br, DMF, 0–20 °C; (c) $K_2CO_3$ in aq MeOH, reflux 2 h; (d) $ClOC(CH_2)_nCOCl$, 0–20 °C, 15 h.



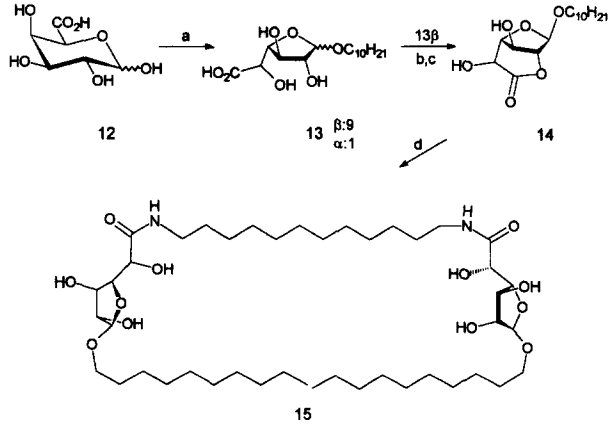
Scheme 2. *Reagents and conditions:* (a) *n*-octanol, THF, $BF_3 \cdot OEt$, 66 °C, 1 h; (b) 1,12-diaminododecane, MeOH, 25 °C, 15 h.

using dimethylformamide as solvent [1]. The glucoside **5** had an $\alpha,\beta$ ratio 1:3 and the two anomers were readily separated by simple chromatography. Using the $\beta$ anomer, the quantitative removal of the amino protecting group was achieved efficiently with potassium carbonate as the base and the amino sugar **6**$\beta$ was then reacted with the acid chloride from decanedioic acid to give the bola-amphiphile **7**$\beta$ in 52% yield.

The corresponding compound, with a 12-carbon bridge **8**$\beta$, was obtained in 86% yield. For comparison, the same reaction was carried out with the corresponding $\alpha$ anomer of **5**. Compound **8**$\alpha$ was obtained as a crude material only, in poor yield.

The second approach to a glucose bola-amphiphile, i.e. system **2**, started from the readily available compound, D-glucofuranurono-6,3-lactone **9**. This was converted to a D-glucofuranoside by the method we reported recently [14], using boron trifluoride etherate (Scheme 2) to give the octyl D-glucofuranosidurono-6,3-lactone **10** in excellent yield with good selectivity for the $\beta$ anomer ($\alpha,\beta$ ratio 1:9). The pure $\beta$ anomer was readily obtained by chromatography. Treatment of this lactone, with 1,12-diaminododecane at room temperature gave the required bis(amide) **11** in 80% yield after chromatography. Thus, a new pseudo macrocyclic bola-amphiphile is available in two steps from a commercially available starting material.

Since the tendency for pseudo macrocyclic bola-amphiphiles to undergo self-assembly is intimately related to the stereochemistry of the polar head groups, we synthesised for comparison the analog of the bis(amide) **11** with the opposite configuration at C-4 of the sugar moieties, i.e. the corresponding galacturonic system **15** (Scheme 3). We have shown previously [14] that Lewis acid-promoted conversion of D-galactopyranuronic acid to a glycoside in the presence of calcium chloride leads exclusively to the corresponding D-galactofuranoside, and the decyl derivative **13** was obtained by this method. In the D-galacturonic series, the stereochemistry is less favourable for five-membered lactone formation since the OH-3 and carboxyl groups are in a *trans*-relationship. However, lactonisation to the 2-position was



Scheme 3. *Reagents and conditions:* (a) decanol, $FeCl_3$, $CaCl_2$, THF, 25 °C, 4 d; (b) triphosgene, pyridine, $CH_2Cl_2$, −15 °C; (c) $Et_3N$, 25 °C, 20 h; (d) 1,12-diaminododecane, MeOH, 25 °C, 15 h.

[1] We found that dimethylformamide is a better solvent for the formation of glycosides of unprotected sugars than *N,N'*-dimethyl-*per*hydropyrimidin-2-one [16]. It leads to greater stereoselectivity, and using a substrate–alkylating agent–base ratio 1:1.5:1.3 we have obtained glucosides with an $\alpha,\beta$ ratio 1:10 or better. 2-Acylamino-2-deoxyglucopyranosides were obtained with an $\alpha,\beta$ ratio 1:2 or better (P. Letellier, D.F. Ewing, J.W. Goodby, J. Haley, S.M. Kelly, and G. Mackenzie, in preparation).

successfully achieved by conversion to the acid chloride with triphosgene at low temperature and then treatment with triethylamine at room temperature (Scheme 3) giving compound **14** in 75% yield after chromatography. The structure of this novel lactone was confirmed by NMR spectroscopy. Relative to the precursor acid, low frequency shifts are observed for C-1 (3.4 ppm), C-3 (7.6 ppm), and C-4 (5.5 ppm), and a high frequency shift for C-2 (1.5 ppm) in agreement with the general trend observed in similar systems [17]. Treatment of lactone **14** with 1,12-diaminododecane in MeOH at room temperature afforded the bola-amphiphile **15** in 80% yield.

## 3. Experimental

*General procedures.*—NMR spectra were recorded with Bruker ARX400 or JEOL GX270 spectrometers using standard conditions with a data point resolution of ~0.1 Hz. $^1$H Chemical shifts were measured relative to $Me_4Si$ and $^{13}$C chemical shifts relative to $CDCl_3$ ($\delta$ 77.05) or $(CD_3)_2SO$ ($\delta$ 39.5). Coupling constants are given in Hz. Assignments of the $^1$H spectra were made by detailed analysis using decoupling or correlation techniques where appropriate. Assignments to the cinnamyl group [(*E*)-3-phenylprop-2-enyl] are indicated as 'cin'. Generally chemical shifts are not given for phenyl groups or alkyl chains. For anomeric mixtures the $\alpha,\beta$ ratio was determined from the integration of suitable peaks. Column chromatography was performed on silica gel (230–400 mesh; Aldrich) and TLC on Silica Gel $60F_{254}$ (E. Merck) with detection by UV absorbance or ethanolic $H_2SO_4$. Rotations were obtained using an ETL-NPL automatic polarimeter and $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$.

*2-Deoxy-2-trifluoracetamido-*D*-glucopyranose* (**4**).—Trifluoracetic anhydride (3.6 mL, 25.5 mmol) in anhyd $Me_2NCHO$ (DMF) (5 mL) was added at 0 °C to 2-amino-2-deoxy-D-glucose (as the hydrochloride salt), **3** (5.0 g, 23.2 mmol), and $Et_3N$ (7.0 mL, 69.6 mmol) in anhyd DMF (45 mL), and the mixture was stirred overnight. Water (10 mL) was added, and the mixture was taken to dryness by rotary evaporation. The residue was triturated with hot EtOAc and filtered. The extract was concd and chromatographed (9:1 EtOAc–MeOH) and the solid recrystallised (EtOAc–hexanes) to give **4** in 68% yield, $\alpha,\beta$ ratio 1:3 ($^1$H NMR): mp 179–181 °C; $R_f$ 0.38 (8:2 EtOAc–MeOH); $^1$H NMR [$(CD_3)_2SO$]: $\delta$ 9.12 (d, 1 H, $J_{2,NH}$ 7.6 Hz, NH$\alpha$), 9.30 (d, 1 H, $J_{2,NH}$ 6.8 Hz, NH$\beta$), 6.81 (d, 1 H, OH-1$\alpha$), 6.65 (d, 1 H, OH-1$\beta$); $^{13}$C NMR [$(CD_3)_2SO$]: $\delta$ 55.6, 57.6 (C-2$\alpha$, C-2$\beta$), 89.77 (C-1$\alpha$), 94.4 (C-1$\beta$), 116.0, 116.2 ($CF_3$), 156.3, 156.5 (CO). Anal. Calcd for $C_8H_{12}F_3NO_6$: C, 34.92; H, 4.40; N, 5.09. Found: C, 34.82; H, 4.35; N, 5.00.

*Cinnamyl 2-deoxy-2-trifluoracetamido-*D*-glucopyranoside* (**5**).—Sodium hydride (0.33 g, 13.8 mmol) was added portionwise with stirring at 0 °C to a soln of amide **4** (2.0 g, 7.3 mmol) and cinnamyl bromide (2.15 g, 11.9 mmol) in anhyd DMF (30 mL). This mixture was stirred for a further 2 h at 20 °C and then MeOH (10 mL) was added to destroy excess NaH. The soln was taken to dryness and the residue extracted with water and EtOAc. This extract was worked up and the $\alpha,\beta$ mixture chromatographed (9:1 $CHCl_3$–MeOH) to separate the anomers of compound **5**. The first eluted species was the $\alpha$ anomer **5$\alpha$** (0.29g, 18% from $CHCl_3$): mp 176–178 °C; $[\alpha]_D^{23}$ +149° (*c* 2.18, MeOH); $R_f$ 0.43 (8:2 EtOAc–EtOH); $\lambda_{max}$ 252 nm (MeOH); $^1$H NMR [$(CD_3)_2SO$]: $\delta$ 4.85 (d, 1 H, $J_{1,2}$ < 1 Hz, H-1), 4.59 (t, 1 H, OH-6), 4.93 (d, 1 H, OH), 5.13 (d, 1 H, OH), 4.13 (m, 1 H, cin $CH_2$), 4.28 (1 H, cin $CH_2$), 6.32 (dt, 1 H, cin CH=), 6.65 (d, 1 H, cin CH=), 9.50 (d, 1 H, NH); $^{13}$C NMR [$(CD_3)_2SO$]: $\delta$ 95.2 (C-1), 54.9 (C-2), 69.6, 70.7, 73.1 (C-3, C-4, C-5), 60.7 (C-6), 66.9 (cin $CH_2$), 116.1 ($CF_3$), 156.6 (CO). Anal. Calcd for $C_{17}H_{20}F_3NO_6$: C, 52.18; H, 5.15; N, 3.58. Found: C, 52.32; H, 5.19; N, 3.51.

The second eluted species was the $\beta$ anomer **5$\beta$** (1.0 g, 34% from $CHCl_3$): mp 203–204 °C; $[\alpha]_D^{23}$ −21° (*c* 1.46, MeOH); $R_f$ 0.30 (8:2 EtOAc–EtOH); $\lambda_{max}$ 252 nm (MeOH); $^1$H NMR [$(CD_3)_2SO$]: $\delta$ 4.47 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 4.62 (t, 1 H, OH-6), 5.14 (d, 1 H, OH), 5.23 (d, 1 H, OH), 4.20 (m, 1 H, *J* 5.8, 13.9 Hz, cin $CH_2$), 4.39 (1 H, *J* 4.8 Hz, cin $CH_2$), 6.27 (dt, 1 H, cin CH=), 6.55 (d, 1 H, cin CH=), 9.50 (d, 1 H, $J_{2,NH}$ 7.6 Hz, NH); $^{13}$C NMR [$(CD_3)_2SO$]: $\delta$ 99.4 (C-1), 56.2 (C-2), 70.5, 73.2, 77.2 (C-3, C-4, C-5), 60.9 (C-6), 68.3 (cin $CH_2$), 116.1 ($CF_3$), 156.3 (CO). Anal. Calcd for $C_{17}H_{20}F_3NO_6 \cdot 0.5H_2O$: C, 51.00; H, 5.29; N, 3.50. Found: C, 51.38; H, 5.33; N, 3.44.

*N,N′-Bis(cinnamyl 2-deoxy-β-*D*-glucopyranosid-2-yl)decan-1,10-diamide* (**7β**).—A mixture of the cinnamyl glucoside **5$\beta$** (1.0 g, 2.6 mmol) in MeOH (20 mL) and $K_2CO_3$ (1.06 g, 7.7 mmol) in water (1.2 mL) was stirred under reflux for 2 h and then cooled, diluted, and extracted with BuOH. This extract was dried and reduced to dryness to give the crude cinnamyl glucoside **6**. This material was used directly

for the next step. 1,10-Decanedioyl chloride (0.4 eq) was added slowly at 0 °C to the cinnamyl glucoside **6** (0.5 g, 1.51 mmol) in anhyd DMF (10 mL) containing $Et_3N$ (0.92 g, 9.04 mmol). This mixture was stirred for 15 h at 20 °C and then taken to dryness. The residue was partitioned between water and BuOH. The water phase was filtered and the solid combined with the butanol phase and the solvent removed in vacuo. The crude material was purified by precipitation from hot DMF with water to give the diamide **7** in 52% yield: mp 202–203 °C; $[\alpha]_D^{23}$ −36.9° (*c* 0.91, $Me_2SO$); $R_f$ 0.2 (8:2 $CHCl_3$–MeOH); $^1H$ NMR [$(CD_3)_2SO$]: δ 1.42 (m, 2 H, β-methylene), 2.02 (t, 2 H, α-methylene), 4.37 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 4.56 (t, 1 H, OH-6), 4.86 (d, 1 H, OH), 4.97 (d, 1 H, OH), 4.14 (m, 1 H, *J* 5.8 Hz, 13.9, cin $CH_2$), 4.39 (1 H, cin $CH_2$), 6.27 (dt, 1 H, cin CH=), 6.55 (d, 1 H, cin CH=), 7.62 (d, 1 H, $J_{2,NH}$ 9.0 Hz, NH); $^{13}C$ [$(CD_3)_2SO$]: δ 25.4, 28.7, 28.8, 36.0 (methylene chain), 100.5 (C-1), 55.2(C-2), 70.7, 74.2, 77.1 (C-3, C-4, C-5), 61.1 (C-6), 68.1 (cin $CH_2$), 172.1 (CO). Anal. Calcd for $C_{40}H_{56}N_2O_{12} \cdot 2H_2O$: C, 60.59; H, 7.63; N, 3.53. Found: C, 60.23; H, 7.60; N, 3.58.

N,N′-*Bis(cinnamyl 2-deoxy-β-*D-*glucopyranosid-2-yl)dodecan-1,10-diamide* (**8β**).—Using the same method as described above with 1,12-dodecandioyl chloride gave **8β** in 86% yield: mp 192–194 °C; $[\alpha]_D^{23}$ −36.9 (*c* 0.91, $Me_2SO$); $R_f$ 0.2 (8:2 $CHCl_3$–MeOH); $^1H$ and $^{13}C$ NMR [$(CD_3)_2SO$] data identical to that for **7β** except for extra methylenes. Anal. Calcd for $C_{42}H_{60}N_2O_{12} \cdot 2H_2O$: C, 61.45; H, 7.86; N, 3.41. Found: C, 61.54, H 7.78; N, 3.32.

N,N′-*Bis(cinnamyl 2-deoxy-α-*D-*glucopyranosid-2-yl)dodecan-1,10-diamide* (**8α**).—Starting from the α anomer **5α** this compound was obtained in the same way as the corresponding β anomer, but in much lower yield (12%) and was not purified further.

*1,12-Bis(*n*-octyl β-*D-*glucofuranosiduronamido)-dodecane* (**11**).—1,12-Diaminododecane (1.05 g, 5.2 mmol) was added to lactone **10** [14] (3.17 g, 11 mmol) in MeOH (40 mL), and the mixture was stirred at room temperature for 15 h. The solvent was removed under vacuum and the solid residue chromatographed (9:1 EtOAc–MeOH) to give the bis(amide) **11**, 3.3 g (80%): mp 83–84 °C (from EtOAc); $[\alpha]_D^{23}$ −51.9° (*c* 0.90, MeOH); $^1H$ NMR [$(CD_3)_2SO$]: δ 4.67 (s, 2 H, $J_{1,2}$ 0 Hz, H-1), 7.86 (t, 2 H, NH); $^{13}C$ NMR [$(CD_3)_2SO$]: δ 108.4 (C-1), 80.4 (C-2), 75.5 (C-3), 82.8 (C-4), 70.2 (C-5), 60.9 (C-6), 67.2 ($OCH_2$), 38.8 ($NCH_2$), 171.8 (CO); *m/z* (CI, $NH_3$) 778 (36%, $[M + H]^+$), 490 (50, $[M - C_{14}H_{24}O_6]^+$), 307 (100, $[M - C_{26}H_{49}O_6 + H]^+$). Anal. Calcd for $C_{40}H_{76}N_2O_{12}$: C, 61.83; H, 9.86; N, 3.60. Found: C, 61.86, H, 9.99; N, 3.64.

*Decyl β-*D-*galactofuranosidurono-6,2-lactone* (**14**).—The galactofuranosiduronic acid **13** [14] (2.50 g, 7.5 mmol) and pyridine (0.6 mL, 7.5 mmol) in THF–$CH_2Cl_2$ (2:3, 20 mL) was added with stirring at −15 °C to triphosgene (0.74 g, 2.5 mmol) in $CH_2Cl_2$ (25 mL). The temperature was allowed to rise to −5 °C when $Et_3N$ (1.1 mL, 8.2 mmol) in $CH_2Cl_2$ (20 mL) was added. The mixture was stirred for 20 h at room temperature and then taken to dryness. The residue was chromatographed to give lactone **14** (1.77 g, 75%): mp 96–97 °C (from $Et_2O$–*n*-hexane); $[\alpha]_D^{23}$ −91.6° (*c* 1.1, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): δ 5.19 (s, 1 H, H-1), 4.63 (t, 1 H, $J_{2,3} = J_{2,4} = 1.2$ Hz, H-2), 4.42 (m, 1 H, $J_{3,4}$ 1.3 Hz, H-3), 4.51 (dd, 1 H, $J_{4,5}$ 3.3 Hz, H-4), 4.26 (d, 1 H, H-5); $^{13}C$ NMR ($CDCl_3$): δ 105.2 (C-1), 80.3 (C-2), 70.5 (C-3), 81.8 (C-4), 71.8 (C-5), 170.2 (C-6), 69.6 ($OCH_2$); *m/z* (CI, $NH_3$) 316 (2%, $[M]^+$), 324 (100, $[M + NH_4]^+$). Anal. Calcd for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92. Found: C, 60.73; H, 8.92.

*1,12-Bis(decyl β-*D-*galactofuranosiduronamido)-dodecane* (**15**).—Lactone **14** (1.0 g, 3.2 mmol) was reacted with 1,12-diaminododecane (0.32 g, 1.6 mmol) as described above. The crude product was chromatographed (9:1 EtOAc–MeOH) to give the bis(amide) **15**, 1.1 g (78%): mp 117–119 °C; $[\alpha]_D^{20}$ −79.1° (*c* 0.66, THF); $^{13}C$ NMR ($CD_3OD$): δ 110.1 (C-1), 83.8 (C-2), 79.1 (C-3), 85.6 (C-4), 72.6 (C-5), 175.2 (C-6), 69.8 ($OCH_2$). Anal. Calcd for $C_{44}H_{84}N_2O_{12}$: C, 63.43; H, 10.16; N, 3.36). Found: C, 63.25; H, 10.31; N, 3.35.

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