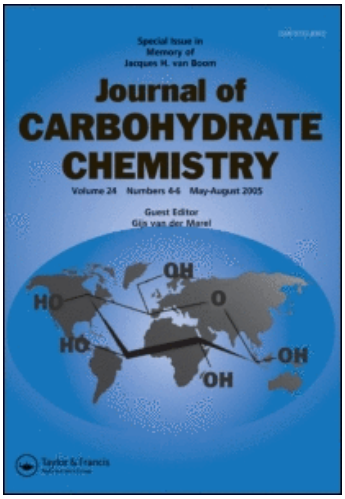

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Synthesis and Thermotropic Behavior of Simple New Glucolipid Amides

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Synthesis and Thermotropic Behavior of Simple New Glucolipid Amides

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The coupling reaction of 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside 2-*O*-lactone **1** (α-CMGL) with two kinds of lipophilic amines, aminosteroids and fatty amines, efficiently yielded, after deprotection, the corresponding free α-glucolipid amides. The latter family of compounds exhibited good thermal stability, allowing the higher homologs having longer linear fatty chains or saturated steroids to possess lamellar smectic A phases.

Keywords Liquid crystals, Steroids, Glycolipids, Carbohydrate, Carboxylmethyl, Glycoside

INTRODUCTION

Glycolipids are biologically very important molecules that are involved in complex mechanisms that are thought to involve membrane subdomains containing liquid-ordered phases, termed lipid rafts.[1] Our current interests lie in the synthesis and study of the thermotropic liquid-crystalline behavior

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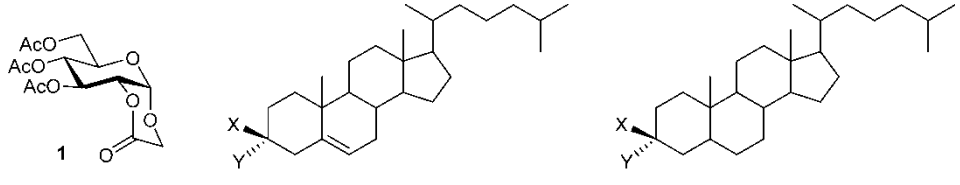
of a variety of synthetic glycolipids.[2–5] Based on a strategy developed recently for anchoring an α-glucosyl moiety on to various amines,[6,7] we present here the synthesis and liquid-crystalline properties of several new simple glucolipids obtained from carboxymethyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside 2-*O*-lactone (**1**, α-CMGL).[8]

RESULTS AND DISCUSSION

Carboxymethyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside 2-*O*-lactone **1** (α-CMGL) was obtained using a two-step procedure starting from the readily available disaccharide isomaltulose.[6,8] It was selected for the initial synthetic step of coupling a glucose unit to four different amino steroids, each of which was obtained by literature routes. Thus, 3α-aminocholesterol (**2**) was prepared using a procedure described by Bittman et al.[9] involving the reduction of 3α-azido-5-cholestene, obtained via reaction of HN_3 with cholesterol under Mitsunobu conditions. 3β-Aminocholesterol (**3**) was prepared using the same strategy with epicholesterol as the starting material (Sch. 1). The amine **4** was synthesized starting from cholestanol and involving the same Mitsunobu reaction conditions to establish the stereochemistry at C-3 of the steroid followed by reduction of the azido group. Prior inversion of stereochemistry at the C-3 position gave access to the amine **5** (Sch. 1).[10]

Reaction of the amino steroid **4** with lactone **1** was performed under anhydrous THF. The acetylated derivative **6** was isolated in 87% yield and was characterized notably by its NMR spectrum, which showed the typical patterns for H-2, H-3, and H-4 at, respectively, 3.82, 5.28, and 5.04 ppm as in all CMG-adducts described in preceding studies.[6–8] Deprotection of **6** was performed under standard Zemplén conditions to furnish **7** in 90% yield. The same conditions were applied to the other aminosteroids **2**, **3,** and **5**. The absence of any coupling reagent or catalyst allowed a short and efficient workup, involving evaporation followed by deprotection of the acetyl groups, to give direct access to **8–10** in 61% to 75% yield (Sch. 2).

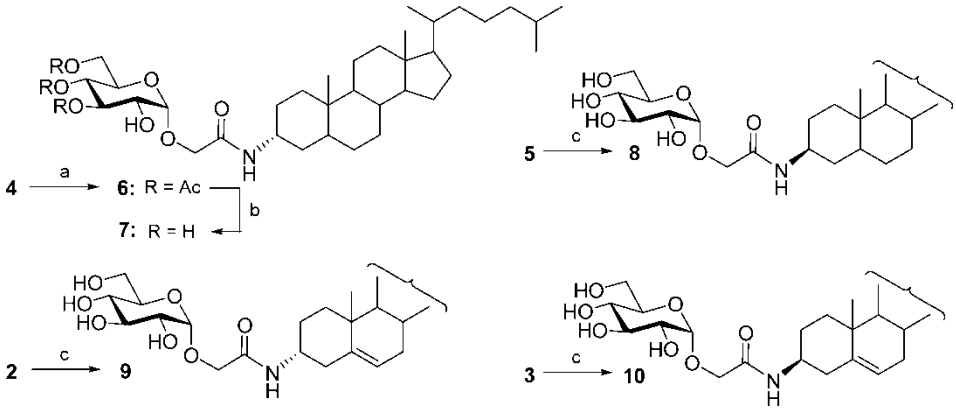
The coupling procedure with α-CMGL (**1**) in THF was then applied to a series of aliphatic amines (C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}). After evaporation, the



2: X = H, Y = NH_2
3: X = NH_2, Y = H

4: X = H, Y = NH_2
5: X = NH_2, Y = H

Scheme 1: Structure of the building blocks.



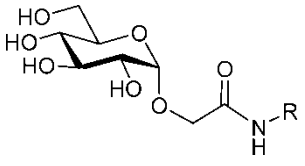
Scheme 2: Synthesis of the glucosteroid analogs: a) **1**, THF, rt; b) MeONa/MeOH, rt; c) **1**, THF, rt, then MeONa/MeOH, rt.

resulting residues were directly deacetylated in methanol using catalytic amounts of sodium methanolate to afford compounds **11**–**13** in 57% to 71% yield. The synthesis of compounds **14**–**16** has already been described (Sch. 3).[6]

The liquid crystal properties of the unprotected sugar-based amides were investigated; the results obtained are summarized in Table 1. All of the liquid crystal phases observed were found to be lamellar (smectic A) upon cooling from the isotropic liquid.

Steroidal glycolipids having direct connection or short spacer (1 to 4 atoms) between the carbohydrate moiety and the steroid backbone often exhibit high melting points and no liquid crystalline phase or of very limited temperature range.[11–16] In the case of compounds **7**–**10**, we could confirm this trend and observed that these steroidal materials had relatively high melting with associated high clearing points. Thus, the compounds tended to decompose at elevated temperatures through caramelization. The photomicrographs shown in Figures 1(a) and (b) for **7** and **8** demonstrate this process with gas bubbles distorting the liquid crystal texture.

The texture shown in Figure 1(a) for compound **7** shows the material contracting away from the surface as decomposition occurs; however, in the remnant texture there are crosses associated with elliptical and hyperbolic lines of optical discontinuity. These defects are associated with focal-conic



11: R = C_6H_{13} **14**: R = $C_{12}H_{25}$
12: R = C_8H_{17} **15**: R = $C_{14}H_{29}$
13: R = $C_{10}H_{21}$ **16**: R = $C_{16}H_{33}$

Scheme 3: Structure of the linear lipophilic amides.

Table 1: Transition temperatures (°C) for compounds **7**–**16**.

Compounds	Melting point (°C)	Clearing point (°C)
7	202	>230 (dec)
8	181	>230 (dec)
9	>200 (dec)	/
10	>200 (dec)	/
11	63	/
12	74	/
13	81	94
14	89	122
15	92	178
16	100	192

domains and are diagnostic for the presence of a smectic A phase. The upper middle part of the texture is optically extinct, demonstrating that the texture is homeotropic and uniaxial, with the molecules arranged with their long axes perpendicular to the glass surfaces of the slide and cover-slip. Figure 1(b) shows the defect texture of compound **8** as the material undergoes caramelization. Here focal-conic domains align on the right-hand and far left-hand sides of the photomicrograph to give a ribbon. To the left of the center of the photograph, ribbons are formed with the molecular layers being parallel to the axis of the ribbon. Again, these defects are typical of the formation of layered smectic A phases. The unsaturated analogs **9** and **10** did not exhibit any liquid crystalline phase as they tend to decompose at lower temperatures compared to the more flexible saturated compounds **7** and **8**. As for the effect of the stereochemistry at C-3 of the steroid, **8** exhibits a wider temperature range of the liquid crystal phase with a lower melting point.

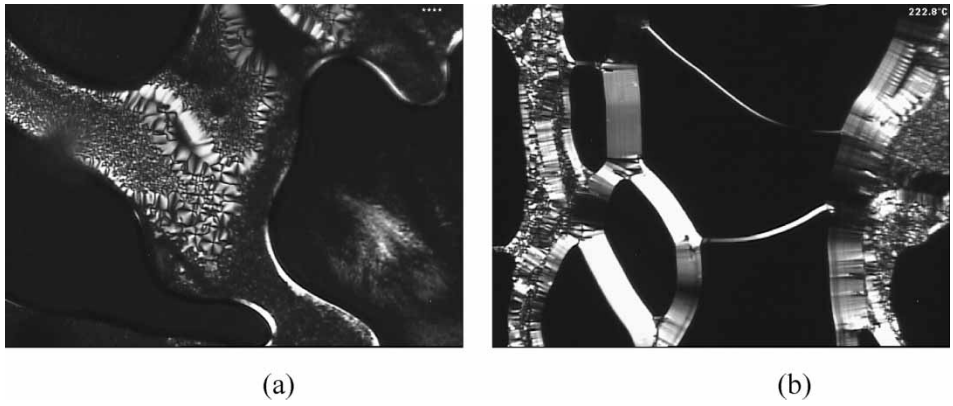


Figure 1: (a) Compound **7** shows elliptical and hyperbolic lines of optical discontinuity (center) (×100). (b) Compound **8** exhibits typical ribbons found for smectic A phases (×100).

Linear derivatives **11**–**16** were then studied. Compounds **11** and **12** did not show any liquid crystal phases, having probably alkyl chains that were too short. Figure 2 (a–d) shows the defect textures found for **13**–**16,** respectively. For **13** the black homeotropic texture is shown in order to demonstrate that the molecules are perpendicular to the glass substrates and thus the mesophase is uniaxial. Around the two air bubbles the layers curve and thus the optic axis is no longer perpendicular to the substrates and the texture becomes birefringent. These two textures together demonstrate that the mesophase is smectic A in type. The defect texture for **14** was selected because focal-conic domains are found with lines of optical discontinuity. Apart from the two air bubbles, the remaining black areas are again homeotropic, demonstrating that the phase is uniaxial. Compounds **15** and **16** exhibit the more typical lamellar textures found for amphiphiles. Here, the flowing edge and focal-conic defects create ribbons that join together to give a myelin-like texture. The black homeotropic area to the bottom left next to the air bubble for **15** again demonstrates that the mesophase is uniaxial and smectic A. For all of the materials the bubbles are due to air exclusion rather than to gases caused

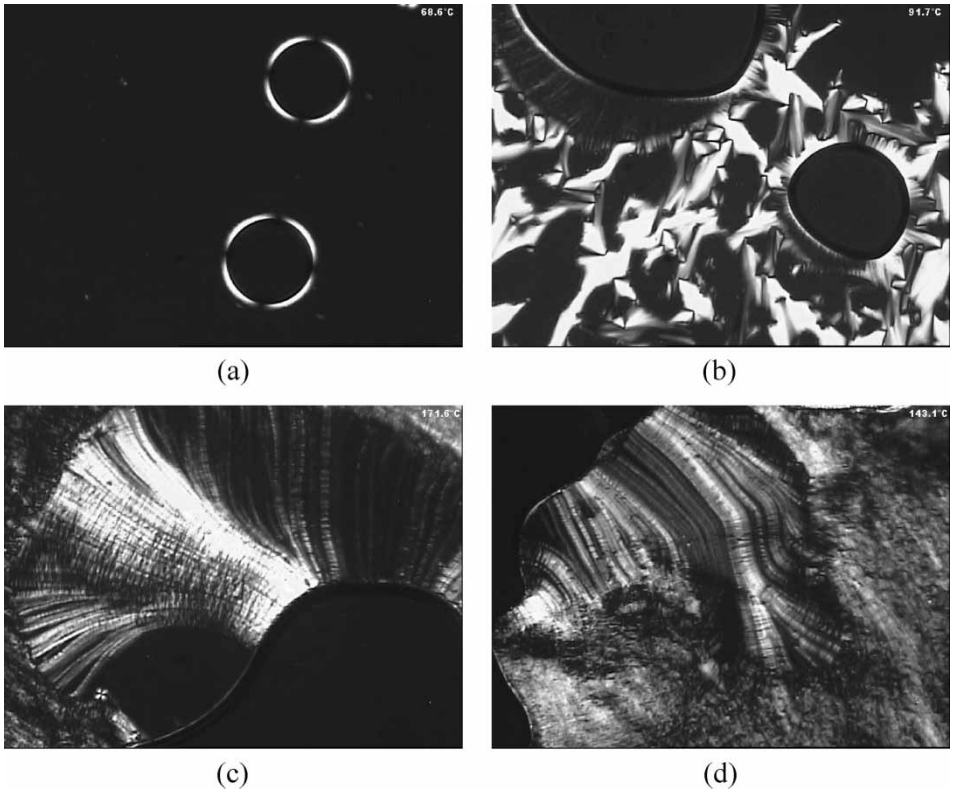


Figure 2: The defect textures exhibited by compounds **13**–**16** (a–d) respectively (×100).

through decomposition. This was confirmed by differential scanning calorimetry, which shows sharp peaks for the clearing points and no violent changes in the baselines before the clearing points are reached.

Thus, the materials are all shown to exhibit smectic A phases, the structure of which is probably where the sugar moieties are arranged toward the exterior of the layers with the aliphatic segments located toward the centers of the layers. The steroid derivatives have the higher transition temperatures possibly because the steroid ring system adds rigidity to the structure, unlike for the other materials, which possess flexible aliphatic chains. With respect to the layers, the molecules will be disordered and free to rotate and translate across and between the layers.

Figure 3 shows a cartoon of the local structure of the layers in steroidal systems. The steroid core units are of cross-sectional area, which is larger than glucosyl head groups, and as a consequence, the steroidal units fill the space within the layers and provide room for overlap of the head groups between the layers. Thus, the layer ordering will be more extensive than that for the aliphatic substituted analogs, where the aliphatic chains will have a higher degree of flexibility within the layers. Thus, the clearing points for the steroids will be higher, and the defect textures better defined as shown in Figure 1(b).

Differential scanning calorimetry results for the products **14**–**16** showed that these materials were much more thermally stable in comparison to the steroidal compounds. This may be because the steroids have much higher clearing points.

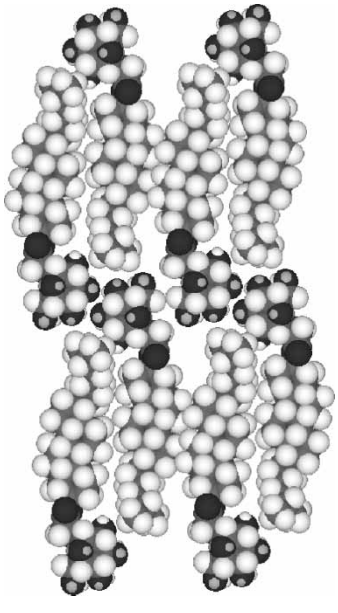


Figure 3: Proposed layer ordering in the smectic A phase of the steroidal compounds.

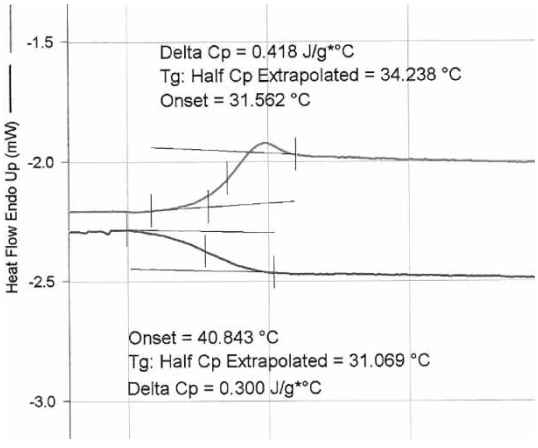


Figure 4: DSC traces of compound **15** upon heating (upper curve) and cooling (lower curve).

Typically for **14**–**16** the first heating cycle showed strong fluctuations in the baseline as the clearing points were approached. Subsequent heating and cooling gave reproducible data with sharp peaks for the clearing points, and in most cases well-defined glass transitions upon cooling (e.g., see Fig. 4 for compound **15**). The fluctuations observed on the first heating cycles were thus thought to be associated with the settling of the materials in the DSC pans.

Summary

The synthesis developed here showed the reasonably good thermal stability of simple α-glucolipid amides, which have been tested for their thermotropic behavior. Lamellar smectic A phases were observed for some of the linear fatty chain derivatives and, although they had too high a melting point, for the saturated aminosteroid derivatives **7** and **8** as well. Further work is in progress using similar strategies toward the study of other glycolipid amides, including sugar/steroid adducts, bearing structural variations on the sugar moiety and/or on the lipid part as well as incorporating longer spacer chains, which might provide increased flexibility and enlarge the liquid crystalline phase temperature domain.[17,18]

EXPERIMENTAL

General Methods

The phase identifications and determination of phase transition temperatures were carried out, concomitantly, by thermal polarized light microscopy

using a Zeiss Universal polarizing transmitted light microscope equipped with a Mettler FP52 microfurnace in conjunction with an FP50 Central Processor. Photomicrographs were obtained using a Zeiss polarizing light microscope equipped with a Nikon AFM camera. Differential scanning calorimetry was used to determine enthalpies of transition and to confirm the phase transition temperatures determined by optical microscopy. Differential scanning thermograms (scan rate 10°C min^{-1}) were obtained using a Perkin Elmer DSC 7 PC system operating on DOS software. The results obtained were standardized to indium (measured onset 156.68°C, ΔH 28.47 Jg^{-1}, lit. value 156.60°C, ΔH 28.45 Jg^{-1}). (CRC Handbook of Physics and Chemistry, Ed R.C. Priest, CRC Press, Boca Raton, 68th Edition, 1988.)

Molecular modeling was performed using Chem Draw Ultra version 6/Chem Draw 3D using a MacIntosh G5 computer OSX.4. The modeling was performed with minisation in the gas phase at absolute zero.

All chemicals were purchased from Aldrich. Organic solutions were dried over anhydrous sodium sulfate. The reactions were monitored by thin-layer chromatography on Silica Gel 60 F254 (Merck); detection was carried out by charring with a 5% H_2SO_4 solution in ethanol. Silica gel (Kieselgel 60, 70–230 mesh ASTM, Merck) was used for flash chromatography. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Bruker ALS300 or DRX300 spectrometer. The signal of the residual protonated solvent was taken as reference. Chemical shift (d) and coupling constants (J) are reported in ppm and Hz, respectively. Elemental analyses were performed by Service Central de Microanalyses du CNRS 69360 Solaize (France).

(*N*-(5-Cholestane-3-α-carbamoyl))methyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (6)

To a solution of carboxymethyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside, 2-*O*-lactone (**1**) (768 mg, 2.22 mmol) in anhydrous THF (15 mL) was added the amine **4** (780 mg, 2.01 mmol). The reaction was stirred under nitrogen at rt for 24 h. THF was then evaporated under reduced pressure and the yellow foam that was obtained was purified by column chromatography over SiO_2 using dichloromethane:ethyl acetate (4:1) as the eluent to give the amide **6** as a colorless solid (1.278 g, 1.74 mmol, 87%): ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, $J = 7.6$ Hz, 1H, NH), 5.28 (t, $J = 9.7$ Hz, 1H, H-3), 5.04 (t, $J = 9.8$ Hz, 1H, H-4), 4.92 (d, $J = 3.7$ Hz, 1H, H-1), 4.27 (dd, $J = 12.6$, J = 4.9 Hz, 1H, H-6a), 4.20 (d, $J = 15.8$ Hz, 1H, H-7a), 4.14 (m, 1-H, OH), 4.09–3.99 (m, 3H, H-5, H-6b, H-7b), 3.82 (dd, $J = 9.9$, $J = 3.7$ Hz, 1H, H-2), 2.09 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.03 (s, 3H, Ac), 1.95 (m, 1H), 1.81–0.63 (m, 46H, steroid H), 0.86 (d, $J = 6.5$ Hz, 3H, CH_3), 0.85 (d, $J = 6.6$ Hz, 3H, CH_3), 0.84 (d, $J = 6.6$ Hz, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.63 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 170.6, 169.5, 167.7, 99.1, 73.7, 70.6, 68.2,

67.6, 67.3, 61.8, 56.4, 56.4, 54.3, 44.7, 42.5, 40.6, 40.0, 39.4, 36.1, 35.9, 35.7, 35.4, 33.0, 32.7, 31.9, 28.5, 28.2, 28.0, 25.9, 21.1, 23.7, 22.8, 22.5, 20.9, 20.8, 20.7, 20.6, 18.6, 12.0, 11.4, $[\alpha]_D^{20}$ +84 (c 1.0, CH_2Cl_2), HRMS (ES) calcd for $[M + Na]^+$ 756.4663; found 756.4668. Anal. calcd for $C_{41}H_{67}NO_{10}\cdot 1H_2O$: C, 65.49; H, 9.25; N, 1.86. Found: C, 65.10; H, 9.00; N, 1.84.

(*N*-(5-Cholestane-3-α-carbamoyl))methyl-α-D-glucopyranoside (7)

To a solution of the amide **6** (500 mg, 0.68 mmol) in anhydrous methanol (10 mL), catalytic amounts (5 drops) of a sodium methanolate solution in methanol (1 M) were added. The reaction was stirred under nitrogen at rt for 2 h. The solution was then neutralized using the minimum amount of an aqueous solution of KH_2PO_4 (10%, three drops), and the solvent was evaporated under reduced pressure. The resulting white solid was purified by column chromatography over SiO_2 using dichloromethane:methanol (9:1) as the eluent to afford unprotected amide **7** as a colorless solid (376 mg, 0.62 mmol, 90%): ^{1}H NMR (300 MHz, $CDCl_3$:MeOD, 2:1): δ 4.80 (d, $J = 3.8$ Hz, 1H, H-1), 4.15 (d, $J = 15.8$ Hz, 1H, H-7a), 4.03 (d, $J = 15.8$ Hz, 1H, H-7b), 4.02 (m, 1H, H-3′), 3.79 (dd, $J = 12.0$, $J = 2.2$ Hz, 1H, H-6a), 3.70 (t, $J = 9.2$ Hz, 1H, H-3), 3.70 (dd, $J = 12.0$, $J = 4.8$ Hz, H-6b), 3.56 (ddd, $J = 9.8$, $J = 4.8$, $J = 2.2$ Hz, 1H, H-5), 3.52 (dd, $J = 9.6$, $J = 3.8$ Hz, 1H, H-2), 3.35 (t, $J = 9.8$ Hz, 1H, H-4), 1.94 (m, 1H), 1.60–0.60 (m, 46H, steroid H), 0.87 (d, $J = 6.5$ Hz, 3H, CH_3), 0.83 (d, $J = 6.6$ Hz, 3H, CH_3), 0.82 (d, $J = 6.6$ Hz, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.62 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$:MeOD, 2:1): δ 170.1, 100.2, 74.1, 73.1, 72.2, 70.6, 67.2, 61.8, 57.0, 56.7, 54.8, 45.9, 43.1, 40.5, 40.0, 37.8, 36.6, 36.2, 36.0, 35.9, 35.2, 32.4, 29.1, 28.7, 28.6, 28.4, 24.6, 24.3, 23.0, 22.8, 21.6, 19.0, 12.4, 12.4, $[\alpha]_D^{20}$ +81 (c 1.0, CH_2Cl_2:MeOH, 1:1), HRMS (ES) calcd for $[M + Na]^+$ 630.4346; found 630.4349. Anal. calcd for $C_{35}H_{61}NO_7 \cdot 1.5H_2O$: C, 66.21; H, 10.16; N, 2.21. Found: C, 66.44; H, 10.42; N, 2.30.

(*N*-(5-Cholestane-3-β-carbamoyl))methyl-α-D-glucopyranoside (8)

The amine **5** (219 mg, 0.56 mmol) was added to a solution of lactone **1** (215 mg, 0.62 mmol) in dry THF (8 mL). The reaction was stirred under nitrogen at rt for 24 h. THF was then evaporated under reduced pressure and the yellow foam that was obtained was dissolved in anhydrous methanol (5 mL) and catalytic amounts (five drops) of a sodium methanolate solution in methanol (1 M) were added. The reaction was stirred under nitrogen at rt for 2 h. The solution was then neutralized using the minimum amount of an aqueous solution of KH_2PO_4 (10%, three drops) and the solvent was removed

by evaporation under reduced pressure. The white solid that was obtained was purified by column chromatography over SiO_2 using dichloromethane:methanol (9:1) as the eluent to afford the deprotected amide **8** as a colorless solid (208 mg, 0.34 mmol, 61%): ^{1}H NMR (300 MHz, $CDCl_3$:MeOD, 2:1): δ 4.74 (d, $J = 3.7$ Hz, 1H, H-1), 4.10 (d, $J = 15.9$ Hz, 1H, H-7a), 3.93 (d, $J = 15.9$ Hz, 1H, H-7b), 3.77 (dd, $J = 12.1$, $J = 2.7$ Hz, 1H, H-6a), 3.75–3.67 (m, 2H, H-3′, H-6b), 3.67 (t, $J = 9.4$ Hz, 1H, H-3), 3.55 (ddd, $J = 9.6$, $J = 4.2$, $J = 3.0$ Hz, 1H, H-5), 3.47 (dd, $J = 9.6$, $J = 3.7$ Hz, 1H, H-2), 3.34 (t, $J = 9.8$ Hz, 1H, H-4), 1.94 (m, 1H), 1.80–0.60 (m, 46H, steroid H), 0.87 (d, $J = 6.4$ Hz, 3H, CH_3), 0.83 (d, $J = 6.6$ Hz, 3H, CH_3), 0.82 (d, $J = 6.6$ Hz, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.62 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$:MeOD, 2:1): δ 170.2, 100.3, 74.2, 73.2, 72.2, 70.7, 67.3, 61.9, 57.1, 56.9, 54.9, 49.5, 46.0, 43.1, 40.6, 40.1, 38.0, 36.7, 36.3, 36.1, 36.0, 35.3, 32.5, 29.2, 28.8, 28.7, 28.5, 24.7, 24.3, 23.1, 22.8, 21.7, 19.0, 12.5, 12.4, $[\alpha]_D^{20}$ +68 (c 0.4, CH_2Cl_2:MeOH, 1:1), HRMS (ES) calcd for $[M + Na]^+$ 630.4346; found 630.43489. Anal. calcd for $C_{35}H_{61}NO_7 \cdot 2H_2O$: C, 65.29; H, 10.18; N, 2.18. Found: C, 65.29; H, 10.08; N, 2.28.

(*N*-(5-Cholestene-3-α-carbamoyl))methyl-α-D-glucopyranoside (9)

Coupling of the amine **2** (770 mg, 2.00 mmol) with α-CMGL (**1**, 760 mg, 2.19 mmol) and direct deprotection of the obtained residue were performed using the same procedure developed for the amide **8**, affording the deprotected compound **9** (918 mg, 1.51 mmol, 75%): ^{1}H NMR (300 MHz, $CDCl_3$:MeOD, 2:1): δ 7.24 (d, $J = 7.0$ Hz, 1H, NH), 5.36 (m, 1H, H-5′), 4.77 (d, $J = 3.7$ Hz, 1H, H-1), 4.11 (d, $J = 15.9$ Hz, 1H, H-7a), 4.06 (m, 1H, H-3′), 4.00 (d, $J = 15.9$ Hz, 1H, H-7b), 3.77 (dd, $J = 12.0$, $J = 2.7$ Hz, 1H, H-6a), 3.72 (dd, $J = 12.0$, $J = 4.6$ Hz, 1H, H-6b), 3.64 (t, $J = 9.5$ Hz, 1H, H-3), 3.55 (m, 1H, H-5), 3.46 (dd, $J = 9.5$, J = 3.7 Hz, 1H, H-2), 3.36 (t, $J = 9.5$ Hz, 1H, H-4), 2.54 (m, 2H), 2.04–0.80 (m, 44H, steroid H), 1.00 (s, 3H, CH_3), 0.89 (d, $J = 6.3$ Hz, 3H, CH_3), 0.83 (d, $J = 6.6$ Hz, 6H, $2CH_3$), 0.66 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$:MeOD, 2:1): δ 170.3, 138.6, 124.3, 99.5, 74.3, 73.2, 72.2, 70.5, 66.5, 61.8, 57.0, 56.7, 50.5, 42.7, 40.1, 40.0, 37.7, 36.9, 36.6, 36.3, 34.2, 32.3, 28.6, 28.4, 26.1, 24.7, 23.0, 22.8, 21.2, 19.2, 19.0, 12.1, $[\alpha]_D^{20}$ +27 (c 1, CH_2Cl_2:MeOH, 1:1), HRMS (ES) calcd for $[M + Na]^+$ 628.4189; found 628.4178. Anal. calcd for $C_{35}H_{59}NO_7 \cdot 0.33H_2O$: C, 68.48; H, 10.13; N, 2.28. Found: C, 68.40; H, 9.76; N, 2.07.

(*N*-(5-Cholestene-3-β-carbamoyl))methyl-α-D-glucopyranoside (10)

Coupling of the amine **3** (334 mg, 0.87 mmol) with α-CMGL (**1**, 360 mg, 1.04 mmol) and direct deprotection of the resulting residue were performed

using the same procedure developed for the amide **8**, affording the deprotected compound **10** (351 mg, 0.58 mmol, 67%): ^{1}H NMR (300 MHz, $CDCl_3$:MeOD, 2:1): δ 5.25 (m, 1H, H-5′), 5.09 (d, $J = 3.9$ Hz, 1H, H-1), 4.41 (d, $J = 14.7$ Hz, 1H, H-7a), 4.15 (d, $J = 14.7$ Hz, 1H, H-7b), 3.87 (t, $J = 9.4$ Hz, 1H, H-3), 3.81 (dd, $J = 9.5$, $J = 2.7$ Hz, 1H, H-6a), 3.76 (dd, $J = 9.5$, $J = 4.2$ Hz, 1H, H-6b), 3.66–3.54 (m, 2H, H-2, H-5), 3.45 (t, $J = 9.5$ Hz, 1H, H-4), 2.19 (m, 2H), 1.98–0.80 (m, 44H, steroid H), 0.94 (s, 3H, CH_3), 0.85 (d, $J = 6.3$ Hz, 3H, CH_3), 0.80 (d, $J = 6.6$ Hz, 3H, CH_3), 0.79 (d, $J = 6.6$ Hz, 3H, CH_3), 0.62 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$:MeOD, 2:1): δ 170.6, 140.4, 122.2, 98.7, 74.7, 72.9, 71.9, 69.6, 66.1, 61.2, 57.9, 57.0, 51.0, 50.4, 41.5, 40.6, 39.7, 38.5, 38.1, 36.8, 36.5, 36.1, 32.1, 28.4, 28.2, 24.5, 24.0, 22.9, 22.6, 21.3, 19.4, 18.9, 12.0, $[\alpha]_D^{20}$ +8 (c 1, CH_2Cl_2:MeOH, 1:1), HRMS (ES) calcd for $[M + Na]^+$ 628.4189; found 628.4189.

General Procedure for the preparation of the Linear Amides 11–16: Synthesis of 11

To a solution of lactone **1** (300 mg, 0.86 mmol) in anhydrous THF (5 mL) was added hexylamine (126 μL, 0.95 mmol). The reaction mixture was stirred under nitrogen at rt for 15 h. THF was then removed by evaporation under reduced pressure, the residue obtained was dissolved in anhydrous methanol (10 mL), and catalytic amounts (five drops) of a sodium methanolate solution in methanol (1 M) were added. The reaction mixture was stirred under nitrogen at rt for 2 h, strongly acidic resin (Dowex 50 × 8) was added, and the mixture was further stirred for 15 min. After filtration and evaporation, the obtained yellow oil was purified by column chromatography over SiO_2 using dichloromethane:methanol (4:1) as eluent to afford **11** as a white solid (176 mg, 0.54 mmol, 63%; 57% for **12**; 71% for **13**; the compounds **14**–**16** have been already described[6]).

(*N*-Hexylcarbamoyl)methyl-α-D-glucopyranoside (11)

^{1}H NMR (300 MHz, MeOD): δ 5.07 (d, $J = 3.8$ Hz, 1H, H-1), 4.42 (d, $J = 15.0$ Hz, 1H, H-7a), 4.21 (d, $J = 15.0$ Hz, 1H, H-7b), 3.86 (dd, $J = 12.0$, $J = 2.2$ Hz, 1H, H-6a), 3.73 (t, $J = 9.0$ Hz, 1H, H-3), 3.76–3.65 (m, 3H, H-2, H-3, H-6b), 3.54 (ddd, $J = 9.8$, $J = 5.5$, $J = 2.2$ Hz, 1H, H-5), 3.36 (dd, $J = 9.8$, $J = 9.0$ Hz, 1H, H-4), 3.29 (t, $J = 7.2$ Hz, 2H, CH_2N), 1.55 (m, 2H, CH_2), 1.31 (m, 6H, $3CH_2$), 0.89 (t, $J = 6.8$ Hz, 3H, CH_3), ^{13}C NMR (75 MHz, MeOD): δ 172.5, 100.2, 75.0, 74.7, 73.2, 70.8, 66.9, 62.2, 40.7, 32.6, 30.0, 27.6, 23.5, 14.3, $[\delta]_D^{20}$ +41 (c 1.0, MeOH), HRMS (ES) calcd for $[M + Na]^+$ 344.1685; found 344.1690.

(*N*-Octylcarbamoyl)methyl-α-D-glucopyranoside (12)

^{1}H NMR (300 MHz, MeOD): δ 5.01 (d, $J = 3.7$ Hz, 1H, H-1), 4.37 (d, $J = 15.1$ Hz, 1H, H-7a), 4.17 (d, $J = 15.1$ Hz, 1H, H-7b), 3.85 (dd, $J = 12.0$, J = 2.0 Hz, 1H, H-6a), 3.74–3.59 (m, 3H, H-2, H-3, H-6b), 3.54 (ddd, $J = 9.1$, $J = 5.5$, $J = 2.0$ Hz, 1H, H-5), 3.34 (t, $J = 9.1$ Hz, 1H, H-4), 3.28 (t, $J = 7.2$ Hz, 2H, CH_2N), 1.55 (m, 2H, CH_2), 1.30 (m, 10H, $5CH_2$), 0.89 (t, $J = 6.7$ Hz, 3H, CH_3), ^{13}C NMR (75 MHz, MeOD): δ 172.4, 100.4, 75.0, 74.8, 73.3, 71.0, 67.1, 62.3, 40.6, 33.0, 30.4, 30.4, 30.2, 28.0, 23.7, 14.4, $[\alpha]_D^{20}$ +51 (c 1.0, MeOH), HRMS (ES) calcd for $[M + Na]^+$ 372.1998; found 372.1997.

(*N*-Decylcarbamoyl)methyl-α-D-glucopyranoside (13)

^{1}H NMR (300 MHz, MeOD): δ 4.81 (d, $J = 3.7$ Hz, 1H, H-1), 4.18 (d, $J = 15.8$ Hz, 1H, H-7a), 4.01 (d, $J = 15.8$ Hz, 1H, H-7b), 3.81 (dd, $J = 11.8$, $J = 2.1$ Hz, 1H, H-6a), 3.68 (t, $J = 9.4$ Hz, 1H, H-3), 3.67 (dd, $J = 11.8$, $J = 5.7$ Hz, 1H, H-6b), 3.56 (ddd, $J = 9.4$, $J = 5.7$, $J = 2.1$ Hz, 1H, H-5), 3.47 (dd, $J = 9.6$, $J = 3.7$ Hz, 1H, H-2), 3.31 (t, $J = 9.4$ Hz, 1H, H-4), 3.24 (t, $J = 6.8$ Hz, 2H, CH_2N), 1.54 (m, 2H, CH_2), 1.30 (m, 14H, $7CH_2$), 0.90 (t, $J = 6.7$ Hz, 3H, CH_3), ^{13}C NMR (75 MHz, MeOD): δ 172.0, 101.1, 74.9, 74.4, 73.2, 71.6, 67.8, 62.5, 40.1, 33.1, 30.7, 30.7, 30.5, 30.5, 30.4, 28.0, 23.8, 14.5, $[\alpha]_D^{20}$ +95 (c 1.0, MeOH), HRMS (ES) calcd for $[M + Na]^+$ 400.2311; found 400.2312.

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