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Synthesis of New Sugar-Based Surfactants and Evaluation of Their Hemolytic Activities

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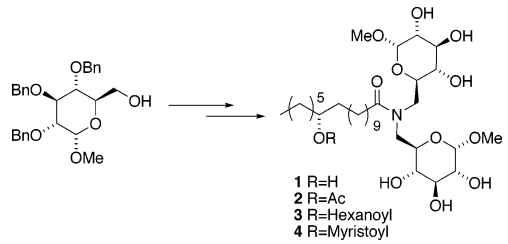
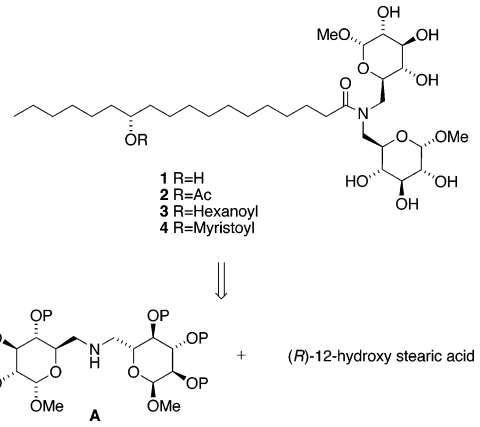


The synthesis of four sugar-based surfactants derived from glucose and (*R*)-12-hydroxystearic acid is described. The surfactants have a hydroxy group in the hydrophobic part, which is either free or acylated using acetyl chloride, hexanoyl chloride, or myristoyl chloride. Three of the synthesized surfactants are water-soluble and are evaluated with respect to their CMCs and hemolytic activities. The fourth surfactant has limited water solubility and is not further included in the study. The investigated surfactants are all hemolytic close to their respective CMC indicating that their use in parenteral formulations may be limited. Nevertheless, surfactants having the proposed structure appear as promising alternatives to existing solubilizing agents for pharmaceutical applications.

Many drug candidates suffer from low water solubility; therefore, one of the major uses of surfactants is as solubilizers in pharmaceutical formulations. Especially at the stage of pharmacological evaluation, the use of surfactants as solubilizers has great advantages compared to chemical modifications of the drug candidate.[1] Nonionic surfactants are most commonly employed in these applications due to their generally lower toxicity compared to anionic and cationic surfactants.[1−5] Yet, existing poly(ethylene oxide)-based surfactants for drug delivery often suffer from other major drawbacks. Available products consist of complex mixtures of many different components giving rise to large batch-to-batch variations, complicated chemical analyses, and product specification issues. Although some of them possess low hemolytic activities,[6,7] they may cause severe side effects, among which histamine release might be the most acute.[1] Therefore, there is a need for new, nontoxic surfactants of well-defined composition to be used in pharmaceutical formulations. In this paper, we wish to report the synthesis of a new class of dicephalic[8] surfactants, as well as an investigation of the hemolytic properties of these surfactants.

SCHEME 1. Retrosynthetic outline



Recent studies of poly(ethylene oxide) surfactants of acylated (*R*)-12-hydroxystearic acid have revealed exceptional properties of these surfactants: good solubilization capacity combined with low cell damaging activity toward erythrocytes and Caco-2 cell monolayers.[7] The surfactants **1**−**4** (Scheme 1) were suggested because they have the hydrophobic part in common with this group of surfactants and also some commercially available surfactants intended for pharmaceutical use.[9] Furthermore, the recent interest within the pharmaceutical industry to replace the poly(ethylene oxide) group with other hydrophilic groups, preferably from renewable sources, led us to choose a sugar group as the hydrophilic part.

We and others have previously reported that glucamide-type surfactants might have limited water solubility.[10−13] We reasoned that the solubility might be increased if the tendency of the surfactants to crystallize could be decreased.[14] Another possible reason for poor solubility in water is an imbalance between the hydrophobic and the hydrophilic part of the surfactant. A large hydrophobic group needs to be balanced by a sufficiently large water-soluble head group. To meet both of

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(1) Attwood, D.; Florence, A. T. *Surfactant Systems: Their chemistry, pharmacy and biology*; Chapman and Hall: London, 1983.

(2) von Rybinski, W.; Hill, K. In *Novel Surfactants. Preparation, Applications, and Biodegradability*, 2nd ed.; Holmberg, K., Ed.; Marcel Dekker: New York, 2003; Vol. 114, pp 35−93.

(3) Lawrence, M. J. *Chem. Soc. Rev.* **1994**, *23*, 417−424.

(4) Macián, M.; Seguer, J.; Infante, M. R.; Selve, C.; Vinardell, M. P. *Toxicology* **1996**, *106*, 1−9.

(5) Bevinakatti, H. S.; Mishra, B. K. *Annu. Surf. Rev.* **1999**, *2*, 1−50.

(6) Söderlind, E. PCT Int. Appl. WO 03039511, 2003.

(7) von Corswant, C.; Hult, K.; Söderlind, E.; Viklund, F. PCT Int. Appl. WO 2004089869, 2004.

(8) Sommerdijk, N. A. J. M.; Hoeks, T. L.; Booy, K. J.; Feiters, M. C.; Nolte, R. J. M.; Zwanenburg, B. *Chem. Commun.* **1998**, 743−744.

(9) Both Solutol HS15 and Cremophor EL contain mainly ethoxylated 12-hydroxystearic acid.

(10) Neimert-Andersson, K.; Blomberg, E.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3746−3752.

(11) Burczyk, B. In *Novel Surfactants. Preparation, Applications, and Biodegradability*, 2 ed.; Holmberg, K., Ed.; Marcel Dekker: New York, 2003; Vol. 114, pp 129−192.

(12) Syper, L.; Wilk, K. A.; Sokolowski, A.; Burczyk, B. *Prog. Colloid Polym. Sci.* **1832**, *110*, 199−203.

(13) Zhang, T.; Marchant, R. E. *J. Colloid Interface Sci.* **1996**, *177*, 419−426.

(14) Söderman, O.; Johansson, I. *Curr. Opin. Coll. Interface Sci.* **2000**, *4*, 391−401.

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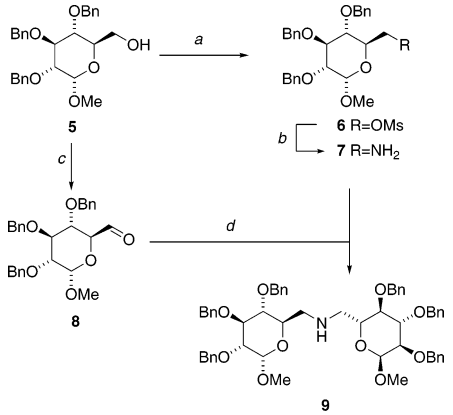
SCHEME 2. Preparation of the Surfactant Head Group[a]



[a] Reaction conditions: (a) MsCl, pyridine, 0 °C → rt, CH_2Cl_2, 98%; (b) aq NH_4OH, THF, 100 °C, 86%; (c) $(COCl)_2$, DMSO, Et_3N, −78 °C, 78%; (d) $Ti(O^iPr)_4$, $NaBH_3CN$, MeOH, 88% over two steps.

these requirements, dicephalic surfactants with a sugar-based head group were suggested. We planned to synthesize the hydrophilic head group **A** from two suitably protected monosaccharides and then couple **A** with (*R*)-12-hydroxystearic acid.[15] Acylation of the 12-hydroxy group and a global deprotection would then complete the synthesis.

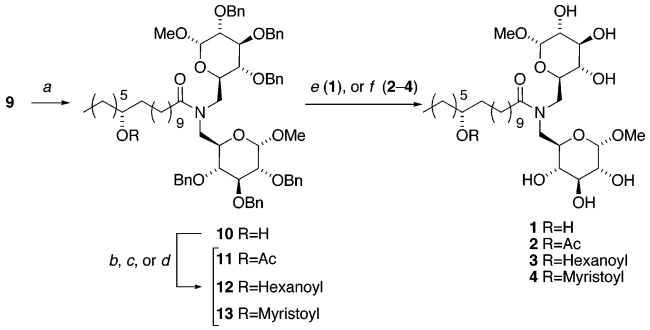
Synthesis of the Surfactant Head Group. Glucoside **5**[16] was transformed, via mesylate **6**,[17] into the corresponding amine **7** (Scheme 2). Reductive amination between aldehyde **8**, available from **5**, with amine **7** then gave the desired amine **9** in 88% yield.

Coupling between Head Group and Tail Group. With a short and efficient procedure for the preparation of dimer **9**, we focused on the coupling between this head group and the hydrophobic tail group (*R*)-12-hydroxy stearic acid. Although there are several coupling reagents available for this transformation,[18] our previous experiences from surfactant synthesis had shown the importance of avoiding tedious purification steps. Thus, the coupling reaction between **9** and fatty acid with EDC[19] provided surfactant precursor **10** in good yield (Scheme 3). The 12-hydroxy group was further derivatized employing selected acid chlorides (acetyl chloride, hexanoyl chloride, and myristoyl chloride) to yield derivatives **11**−**13**, respectively. Global deprotection of **10**−**13** was accomplished using catalytic hydrogenolysis to give surfactants **1**−**4** in nearly quantitative yields.

Surface Chemical Evaluation. Determination of CMC. The CMCs of surfactants **1**−**3** were determined using a colored probe (Eosin Y) according to a previously published procedure.[20] The aqueous solubility of surfactant **4** was limited and was, therefore, excluded from the measurements.

Figure 1 shows how the CMC of surfactant **1** dissolved in saline was extracted from the data points. The CMC is defined as the intersection between the two dashed lines in Figure 1, representing the absorbance in the absence of surfactant and

SCHEME 3. Synthesis of Surfactants 1−4[a]



[a] Reaction conditions: (a) (*R*)-12-hydroxy stearic acid, EDC, CH_2Cl_2, 64%; (b) acetyl chloride, pyridine, CH_2Cl_2, 93%; (c) hexanoyl chloride, pyridine, CH_2Cl_2, 94%; (d) myristoyl chloride, pyridine, CH_2Cl_2, 93%; (e) H_2, Pd/C, MeOH, 98%; (f) H_2, Pd/C, HOAc, MeOH, 100%.

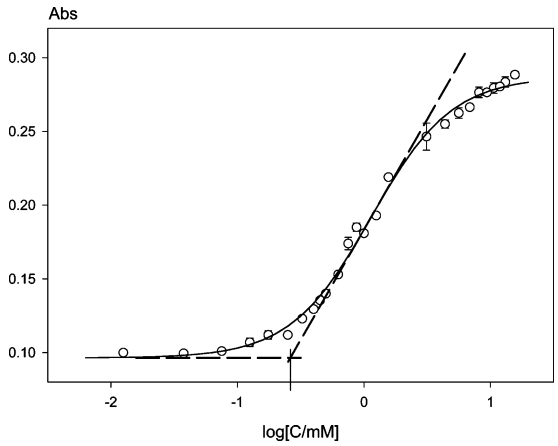


FIGURE 1. Absorbance curve for surfactant **1**, measured in saline.

TABLE 1. CMC for Surfactants 1−3

entry	surfactant	CMC saline[a] (error limits) (mM)
1	**1**	0.26 (0.17−0.35)
2	**2**	0.16 (0.12−0.4)
3	**3**	0.20 (0.15−0.28)

[a] NaCl 9 g/L.

the tangent at the inflection point, respectively. The CMC was obtained by fitting a sigmoidal function, represented by the solid line, to the data and calculating the intersection from the fitted function parameters. The same procedure was carried out for surfactants **2** and **3** (not presented), and the resulting CMCs for surfactants **1**−**3** are given in Table 1 together with the corresponding estimated error limits.[21] The CMC was determined in saline (NaCl 9 g/L) to provide a CMC value under physiologically relevant conditions for the comparison with the concentrations at which hemolysis occurs. The CMC obtained in the presence of electrolytes is generally lower than in pure H_2O, although this effect is only minor for sugar-based surfactants.[22] Preliminary tests using pure aqueous solutions confirmed that the electrolyte effect on the CMCs for the present surfactants is marginal.

The CMC values obtained here are in the same range as previously reported CMCs for dicephalic surfactants with sugar-based head groups: 0.02−0.84 mM.[11,23] Other surfactants with the same number of glucose residues such as alkyl-β-D-mal-

(15) The enantiomeric purity of 12-hydroxy stearic acid was determined to be >95% in analogy with the method described in: Sonnet, P. E.; Hayes, D. *J. Am. Oil Chem. Soc.* **1995**, *72*, 1069−1071.

(16) Ishikawa, T.; Shimizu, Y.; Kudoh, T.; Saito, S. *Org. Lett.* **2003**, *5*, 3879−3882.

(17) Kobertz, W. R.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 1894−1897.

(18) Klausner, Y. S.; Bodansky, M. *Synthesis* **1972**, 453−463.

(19) 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

(20) Patist, A.; Bhagwat, S. S.; Penfield, K. W.; Aikens, P.; Shah, D. O. *J. Surfact. Deterg.* **2000**, *3*, 53−58.

(21) The limiting values were determined by setting the correlation coefficient >0.99.

tosides (C_nG_2, $n = 10-14$) have a wider range of CMC values spanning the CMCs reported here.[24] However, those CMCs depend strongly on the surfactant hydrocarbon chain length.

Commonly, the CMC drops dramatically with increased hydrocarbon chain length (typically a factor of 3 for each added methylene carbon for nonionic surfactants); thus, it is expected that surfactant **3** has the lowest CMC and surfactant **1** the highest.[25] However, when the number of carbon atoms in the hydrophobic chain exceeds 16 this effect is not necessarily very pronounced.[26] Furthermore, previous studies of surfactants derived from acylated 12-hydroxystearic acid have shown that the CMC depends only slightly on the chain length of the acyl group.[27] Hence, it is reasonable to assume that the CMCs for the three surfactants are within the same order of magnitude.

Although the CMCs obtained for surfactants **1**−**3** are in the same range as other sugar-based dicephalic surfactants, they are surprisingly high in comparison to the CMCs for poly(ethylene oxide)-based surfactants with the same hydrophobic part (approximately 1−5 μM).[27] The CMC for a sugar-based surfactant is expected to be somewhat larger than for the poly(ethylene oxide) counterpart, but here the difference is unexpectedly large. The reason for this unexpected property is presently unknown and requires further studies. It has previously been shown that the size of the sugar head group does not influence the CMC;[14] thus, the bulky head group is expected to have a minor effect on the aggregation behavior.

Hemolytic Activity. The haemolytic activity was assessed as previously described.[24] Hemolysis is believed to occur through partitioning of the surfactant into the outer cell membrane, followed by formation of surfactant−lipid mixed micelles and lysis, with cell leakage as a result.[28−30] Surfactant structure is therefore believed to play an important role for the hemolytic activity. It is commonly reported that the hemolytic activity increases as the CMC of the surfactant decreases, the increased hydrophobic character of the surfactant being the reason. Others have reported that bulkier surfactants display lower hemolytic activities compared to less bulkier ones.[31] The hemolysis curves for surfactants **1**−**3** are presented in Figure 2. The relative hemolytic activity of each surfactant is characterized by the CH50 value, i.e., the surfactant concentration that causes 50% hemolysis. Surfactants **1** and **2** have similar hemolytic activity with CH50 values of 0.8 and 0.7 mM, respectively. Surfactant **3** appears slightly less hemolytic, CH50 = 1.2 mM. It was previously demonstrated that the hemolytic activity for poly(ethylene oxide) 12-acyloxystearates decreases when the number of carbon atoms in the acyloxy group increases and is diminished when the number of carbon atoms exceeds 12.[27] Yet, in the present case this trend is not easily seen. To our knowledge, there are only a few previous studies in the literature describing hemolytic activities of sugar surfactants.[32−35] Comparing the concentrations at which compounds **1**−**3** cause severe hemolysis (0.6−0.7 mM) to the hemolytic concentrations for the previously reported sugar surfactants with similar CMCs (1−1.5 mM),[32] it is obvious that surfactants **1**−**3** are only slightly more hemolytic at lower concentrations. Yet, a prerequisite for solubilization is that micelles are present in the solution. It is therefore illustrative to compare the CMC with the concentration at which hemolysis becomes substantial for each surfactant. Previously studied sugar surfactants with C8 or C10 alkyl groups are hemolytic already at premicellar concentrations, which makes them less suited as solubilizers for drug formulations. Similarly to known sugar surfactants with C12 alkyl groups, surfactants **1**−**3**, having CMCs in the range of 0.12−0.4 in saline (Table 1), are hemolytic at concentrations close to their respective CMC. Although the CMCs from Table 1 are recorded at a slightly lower temperature (24 °C) than the hemolysis measurements (37 °C) the effect of temperature on CMC is regarded to be of minor importance.[36]

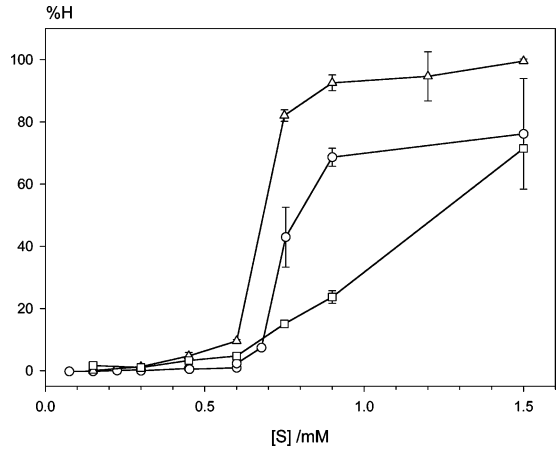


FIGURE 2. Hemolysis curves for surfactants **1**−**3**. Percent hemolysis curves for surfactants **1** (○), **2** (△), and **3** (□).

To assess the usefulness of these surfactants as solubilizers in pharmaceutical formulations, it is also important to consider the capacity to solubilize poorly soluble substances. It was outside the scope of the present study to investigate the solubilization capacity. However, it has been shown in several studies that the hydrocarbon chain length is the surfactant property that has the strongest impact on the capacity to solubilize substances.[32,37] Having considerably larger hydrophobic groups than the previously studied sugar surfactants, this class of surfactants is expected to have a higher solubilization capacity. In solubilization studies using surfactants with the same hydrophobic group there are strong indications that the solubilization capacity of the present surfactants should be in the same range as for commonly used surfactants such as Solutol,

(22) Jin, X.; Zhang, S.; Yang, J.; Lu, R. *Tenside Surf. Det.* **2004**, *41*, 126−129.
(23) Griffiths, P. C.; Whatton, M. L.; Abbott, R. J.; Kwan, W.; Pitt, A. R.; Howe, A. M.; King, S. M.; Heenan, R. K. *J. Colloid Interface Sci.* **1999**, *215*, 114−123.
(24) Söderlind, E.; Karlsson, L. *Eur. J. Pharm. Biopharm.* **2006**, in press.
(25) Lindman, B. In *Handbook of Applied Surface and Colloid Chemistry*; Holmberg, K., Ed.; Wiley: Chichester, 2002; Vol. 1, pp 421−443.
(26) Patist, A. In *Handbook of Applied Surface and Colloid Chemistry*; Holmberg, K., Ed.; Wiley: Chichester, 2002; Vol. 2, p 239−249.
(27) Viklund, F. Ph.D. Thesis, Royal Institute of Technology, 2003.
(28) Jones, M. N. *Int. J. Pharm.* **1999**, *177*, 137−159.
(29) Kondo, T. *Adv. Colloid Interface Sci.* **1976**, *6*, 139−172.
(30) Shalel, S.; Streichman, S.; Marmur, A. *J. Colloid Interface Sci.* **2002**, *255*, 265−269.
(31) Ohnishi, M.; Sagitani, H. *J. Am. Oil Chem. Soc.* **1993**, *70*, 679−684.
(32) Söderlind, E.; Wollbratt, M.; von Corswant, C. *Int. J. Pharm.* **2003**, *252*, 61−71.
(33) Isomaa, B.; Hägerstrand, H.; Paatero, G. *Biochim. Biophys. Acta* **1987**, *899*, 93−103.
(34) Isomaa, B.; Hägerstrand, H.; Paatero, G.; Engblom, A. C. *Biochim. Biophys. Acta* **1986**, *860*, 510−524.
(35) Reinhart, T.; Bauer, K. H. *Pharmazie* **1995**, *50*, 403−407.
(36) Claesson, P. M.; Kjellin, U. R. M. In *Encyclopedia of Surface and Colloid Science*; Hubbard, A. T., Ed.; Marcel Dekker: New York, 2002; pp 4909−4925.
(37) Yalkowsky, S. H. *Solubilization by surfactants*; Oxford University Press: New York, 1999.

Brij, and Triton.[7] In conclusion, surfactants **1**−**3** are equally or less hemolytic in relation to CMC than previously reported sugar surfactants, but they are expected to have a higher solubilization capacity. Still the differences in hemolytic activity between the three investigated surfactants are marginal, and the influence of a C2−C6 acyloxy group in the hydrophobic part is not significant. In comparison to commercially available surfactants such as Solutol, Brij, and Triton, surfactants **1**−**3** are more hemolytic, and their use in pharmaceutical formulations is therefore limited. However, surfactants with this type of structure appear as promising alternatives to existing solubilizing agents. A less hemolytic surfactant with unchanged micellar properties is desired, which may be obtained by exchanging the acyloxy group. To compensate for the increased hydrophobicity of such surfactants the head group structure needs to be modified, e.g., by introducing larger sugar groups.

Experimental Section

General Methods. The general experimental procedures have been published before.[10] The study was approved by the Animals Ethics Committee of Gothenburg, ethics approval no. 120200.

Bis(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside)-amine (9). Aldehyde **8** (1.36 g, 2.94 mmol) and amine **7** (1.36 g, 2.94 mmol) in MeOH (45 mL) was added $Ti(O^iPr)_4$ (1.75 mL, 5.88 mmol) and the mixture was stirred for 3 h at rt. $NaBH_3CN$ (278 mg, 4.41 mmol) was added to the solution, and the mixture was stirred for 2 days at rt. The reaction was quenched by the addition of H_2O (100 mL) and diluted with Et_2O (50 mL). The inorganic precipitate was filtered off and washed thoroughly with aq NH_4-OH and Et_2O. The filtrate was collected, and the phases were separated. The organic layer was dried (Na_2SO_4) and concentrated to give **9** in 88% yield (2.34 g, 2.57 mmol). An analytical sample was purified with preparative HPLC, and the remaining material was taken to the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.27 (m, 30H), 5.02 (d, J = 10.8 Hz, 2H), 4.92 (d, J = 11.1 Hz, 2H), 4.87 (d, J = 10.8 Hz, 2H), 4.83 (d, J = 12.2 Hz, 2H), 4.69 (d, J = 12.2 Hz, 2H), 4.66 (d, J = 11.1 Hz, 2H), 4.56 (d, J = 3.5 Hz, 2H), 4.02 (t, J = 9.6 Hz, 2H), 3.81−3.73 (m, 2H), 3.50 (dd, J = 9.6, 3.7 Hz, 2H), 3.44 (t, J = 9.6 Hz, 2H), 3.38 (s, 6H), 2.89 (dd, J = 12.3, 2.5 Hz, 2H), 2.75 (dd, J = 12.3, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.3, 138.2, 128.40, 128.37, 128.35, 128.03, 128.00, 127.8, 127.7, 127.6, 97.8, 82.0, 80.1, 79.6, 75.8, 75.0, 73.3, 69.9, 55.0, 50.5; IR (neat) 2914, 1454, 1360, 1072, 737, 698 cm^{-1}; $[\alpha]_D$ +62.3 (*c* 1.06, CH_2Cl_2); HRMS (FAB+) calcd for $C_{56}H_{63}NNaO_{10}$ (M + Na) 932.4350, found 932.4354.

(12*R*)-12-Hydroxystearylbis(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside)amine (10). To a solution of amine **9** (1.05 g, 1.15 mmol) in CH_2Cl_2 (20 mL) were added (*R*)-12-hydroxystearic acid (415 mg, 1.38 mmol) and EDC (265 mg, 1.38 mmol), and the reaction mixture was stirred for 1 day at rt. The mixture was washed with 2 M HCl (50 mL), H_2O (2 × 50 mL), and brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting pale yellow wax was adsorbed on silica (CH_2Cl_2) and purified by flash chromatography (pentane/EtOAc 4:1 → 2:1 →1 :1) to give **10** in 64% yield (872 mg, 0.736 mmol): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.20 (m, 30H), 5.00−4.55 (m, 12H), 4.47 (d, J = 3.5 Hz, 1H), 4.45 (d, J = 3.5 Hz, 1H), 4.02−3.99 (m, 1H), 3.96 (t, J = 9.5 Hz, 1H), 3.95 (t, J = 9.5 Hz, 1H), 3.77 (t, J = 9.6 Hz, 1H), 3.59−3.55 (m, 3H), 3.45 (t, J = 10.0 Hz, 1H), 3.44 (t, J = 10.5 Hz, 1H), 3.19 (s, 3H), 3.18 (s, 3H), 3.16−3.09 (m, 4H), 2.22 (t, J = 7.0 Hz, 2H), 1.57−1.23 (m, 28H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 138.7, 138.5, 138.3, 138.2, 138.0, 137.9, 128.5, 128.44, 128.41, 128.35, 128.2, 128.07, 128.06, 128.04, 128.02, 127.98, 127.9, 127.7, 127.6 127.5, 97.6, 97.5, 82.2, 81.8, 79.7, 79.5, 79.0, 75.8, 75.7, 74.8, 74.0, 73.31, 73.25, 72.0, 71.6, 69.9, 55.2, 54.6, 49.5, 47.3, 37.5, 33.2, 31.8, 29.7, 29.64, 29.59, 29.54, 29.50, 29.42, 29.37, 25.7, 25.6, 25.5, 22.6, 14.1; IR (neat) 2926, 1647, 1454, 1072, 737, 698 cm^{-1}; $[\alpha]_D$ +45.0 (*c* 1.00, CH_2Cl_2); HRMS (FAB+) calcd for $C_{74}H_{97}NNaO_{12}$ (M + Na) 1214.6909, found 1214.6907.

(12*R*)-12-Acetoxystearylbis(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside)amine (11). To a cooled solution of alcohol **10** (150 mg, 126 μmol) in dry CH_2Cl_2 (10 mL) were added successively pyridine (204 μL, 2.52 mmol) and acetyl chloride (90 μL, 1.26 mmol). After being stirred for 2 h at rt, the mixture was quenched with HCl (0.1 M). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 7 mL). The combined organic phases were washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting yellow vitreous solid was subjected to flash chromatography (pentane/EtOAc 5:1 → 3:1 → 2:1) to give **11** in 93% yield (145 mg, 118 μmol) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19−7.35 (m, 30H) 5.01−4.54 (m, 13H), 4.47 (d, J = 3.6 Hz, 1H), 4.45 (d, J = 3.6 Hz, 1 H), 4.02−3.99 (m, 1H), 3.96 (t, J = 9.3 Hz, 1H), 3.95 (t, J = 9.2 Hz, 1H), 3.77 (td, J = 9.8, 1.8 Hz, 1H), 3.59−3.54 (m, 2H), 3.46 (dd, J = 9.6, 3.5 Hz, 1H), 3.43 (dd, J = 9.6, 3.6 Hz, 1H), 3.19 (s, 3H), 3.18 (s, 3H), 3.24−3.09 (m, 4H), 2.22 (m_c, 2H), 2.04 (s, 3H), 1.55−1.22 (m, 28H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 171.1, 138.8, 138.6, 138.44, 138.40, 138.2, 138.1, 128.7, 128.61, 128.58, 128.53, 128.4, 128.24, 128.22, 128.20, 128.15, 128.0, 127.9, 127.8, 127.6, 97.8, 97.7, 82.3, 81.9, 79.8, 79.7, 79.2, 77.4, 76.0, 75.9, 75.0, 74.6, 74.2, 73.5, 73.4, 71.8, 70.1, 55.3, 54.8, 49.4, 47.5, 34.31, 34.29, 33.4, 31.9, 29.79, 29.75, 29.7, 29.6, 29.4, 25.7, 25.5, 25.4, 22.7, 21.5, 14.2; IR (neat) 2960, 1732, 1649, 1090, 737, 698 cm^{-1}; $[\alpha]_D$ +52.5 (*c* 1.04, CH_2Cl_2); HRMS (FAB+) calcd for $C_{76}H_{99}NNaO_{13}$ (M + Na) 1256.7015, found 1256.7019.

(12*R*)-12-Hydroxystearylbis(methyl 6-deoxy-α-D-glucopyranoside)amine (1). Compound **10** (1.88 g, 1.58 mmol) was dissolved in dry MeOH (90 mL), and to this solution was added Pd/C (10 wt %, 310 mg). The solvent was degassed at −78 °C, and a hydrogen gas balloon was then connected to the reaction flask. After 48 h at rt, the reaction mixture was filtered through a small plug of Florisil to remove the catalyst, and the filtrate was concentrated. This afforded surfactant **1** as a waxy solid in 98% yield (1.01 g, 1.55 mmol): ^{1}H NMR (400 MHz, MeOD): δ 4.64 (d, J = 3.5 Hz, 1H), 4.62 (d, J = 3.8 Hz, 1H), 3.98 (d, J = 14.4 Hz, 1H), 3.90 (dd, J = 13.7, 1.6 Hz, 1H), 3.78−3.70 (m, 1H), 3.69−3.61 (m, 3H), 3.61−3.54 (m, 2H), 3.53−3.44 (m, 1H), 3.42−3.34 (m, 2H), 3.33 (s, 3H), 3.31 (s, 3H), 3.10 (t, J = 9.1 Hz, 1H), 3.03 (t, J = 9.3 Hz, 1H), 2.60−2.39 (m, 2H), 1.68−1.54 (m, 2H), 1.48−1.22 (m, 26H), 0.90 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, MeOD): δ 177.0, 101.0, 75.0, 74.5, 73.8, 73.5, 73.3, 72.5, 72.3, 71.8, 55.5, 55.4, 51.8, 49.8, 38.4, 34.0, 33.0, 30.8, 30.71, 30.66, 30.61, 30.51, 30.49, 30.45, 26.74, 26.71, 23.6, 14.4; IR (neat) 3367 (br), 2926, 1624, 1049 cm^{-1}; $[\alpha]_D$ +92.9 (*c* 0.51, MeOH); HRMS (FAB+) calcd for $C_{32}H_{61}NNaO_{12}$ (M + Na) 674.4092, found 674.4099.

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Supporting Information Available: Experimental data for compounds **2**−**4**, **7**, **8**, **12**, **13**, determination of CMC and haemolytic activity, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) Bauer, K. *J. Clin. Chem. Clin. Biochem.* **1981**, *19*, 971−976.