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Stereoselective Synthesis of Polyhydroxyl Surfactants. Stereochemical Influence on Langmuir Monolayers

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Received December 1, 2003

Herein is described the synthesis of surfactants featuring polyhydroxylated head groups. Three head groups were prepared via consecutive stereoselective dihydroxylations of a diene. By coupling of these with lipophilic tail groups six novel surfactants have been prepared. The monolayers prepared from four of these have been investigated at the air−water interface. Significant differences were observed between monolayers consisting of enantiomerically pure surfactants contra racemates as well as between diastereomers.

Introduction

Surfactants, also called tensides, belong to a class of compounds that carry a hydrophilic part (often called the head group) and a hydrophobic part (the tail group) in the same molecule. This feature enables the molecules to adsorb at interfaces where the head group is oriented toward the hydrophilic media and the tail group toward the hydrophobic milieu. Adsorption of the surfactant to the interphase is spontaneous, and the driving force is the lowering of interfacial energy.[1,2] The ability of surfactants to lower the energy of a surface in a system makes their use valuable in a wide variety of applications, e.g., as solubilizers and emulsifying agents in pharmaceutical and food industry, as components in paints and detergents, as well as in the manufacturing of papers.[1] With a growing concern for environmental issues, the field of sugar-based surfactants has lately drawn much attention, as sugars are readily available, cheap, nontoxic starting materials.[3,4] Surfactants of this class carry a sugar-based moiety as head group, to which a hydrophobic tail group of choice is coupled. The head group can be a naturally occurring ring-closed sugar or an open-chain sugar derivative.[5−12] The tail group is typically an aliphatic chain of six to twelve carbons, while the linkage between head and tail group can be an ester, ether, or amide bond.[13] The surface chemical properties of several sugar surfactants are well mapped, but only a few studies have considered the influence of stereochemistry of the sugar head groups on the physical properties of the surfactants.[14−19]

This study describes the preparation of the novel polyhydroxyl surfactants **1a**,**b**, *ent*-**1a**,**b**, and **2a**,**b** in which the head groups are natural and non-natural sugar derivatives (Figure 1). The last isomers, *ent*-**2a**,**b** can be prepared following the same route as described for **2a**,**b**, using AD-mix α in place of AD-mix β. Surfactants **1b**, *ent*-**1b**, *rac*-**1b**, and **2b** were then selected for studying the influence of stereoisomerism on Langmuir monolayers.

To minimize the synthetic input it is important that all surfactants can be made from a common starting material through a divergent synthetic route, featuring simple and reliable transformations. Our approach in-

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10.1021/jo0357566 CCC: $27.50
Published on Web 04/30/2004

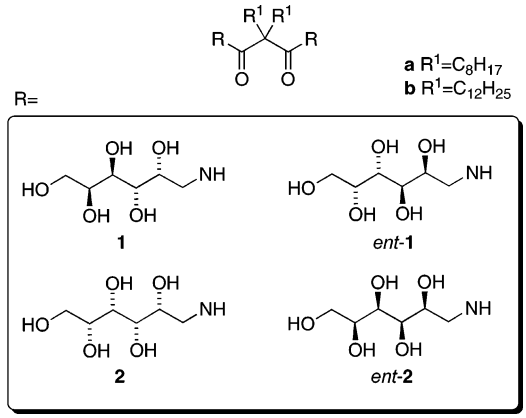


FIGURE 1. Target surfactants.

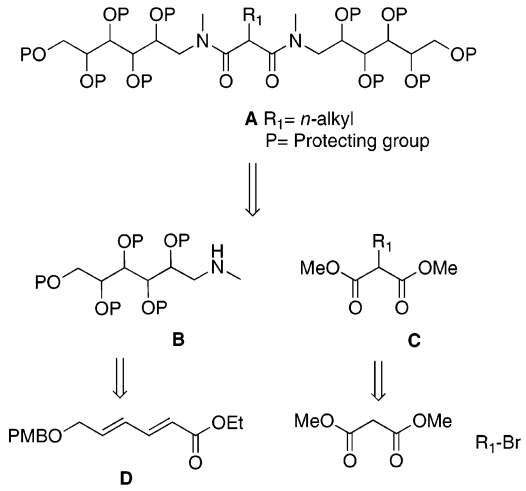


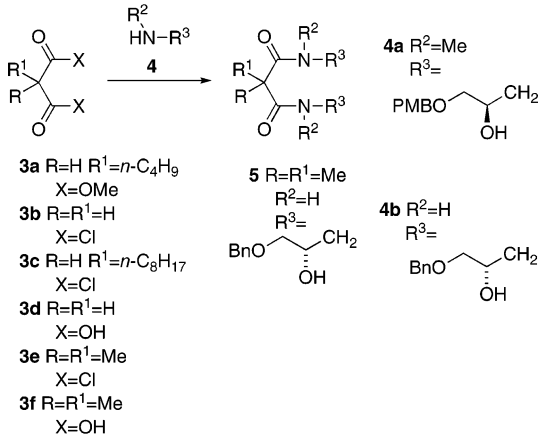
FIGURE 2. Retrosynthetic analysis of surfactant **A**.

volved the preparation of surfactants with the generic structure **A** (Figure 2, stereochemistry not outlined). Compound **A** can be considered as consisting of three parts, the two head groups **B** and the hydrophobic tail group **C**. Introducing a suitable alkyl chain into the α position of dimethyl malonate will give **C**. The key steps in the selected strategy are the stereocontrolled synthesis of **B** and the amide coupling between head groups **B** and tail group **C**. The desired stereoisomers of **B** would be accessed in a stereocontrolled fashion by consecutive asymmetric dihydroxylations[20] from diene **D**.[21] Tail group **C** could be formed by α-alkylation of dimethyl malonate. This strategy has the potential of delivering a large number of products from a limited pool of starting materials, thus meeting any requirement on the surfactant.

Results and Discussions

Investigation of Reaction Conditions for Amide Formation. The formation of the amide bond between the hydrophilic and hydrophobic parts was thoroughly investigated in model systems prior to the synthesis of the desired head and tail groups (Scheme 1). Amines **4a**,**b**

SCHEME 1. Investigation of Reaction Conditions for Amide Formation



and ester **3a** were prepared and used as model substrates in the studies. When ester **3a** was heated together with amine **4a** as previously described for similar substrates, only recovered starting material was obtained.[22] Similarly, reflux in methanol using NaOMe or NaCN as catalysts was not successful.[23,24] It has been described that Lewis acids such as $MgCl_2$, $MgBr_2$, and $AlCl_3$ can be used to promote the acylation of amines with esters,[25−27] but application of these as catalysts was not successful. Since it is known that secondary amines are indeed difficult substrates to acylate, especially with nonactivated carboxylic esters such as **3a**,[28,29] the investigation was limited to primary amines. Some improvements were observed when amine **4b** was subjected to the same reaction conditions; however, the conversions were far from synthetically useful. As a result, it was decided to investigate alternative carboxylic acid derivatives in the coupling reaction and compounds **3b**−**f** were thus selected. When the more reactive electrophile **3b** was reacted with **4b** (Et_3N or K_2CO_3, cat. DMAP, 0 °C) the formation of a new compound was observed, but the reaction never reached completion. Treating a monosubstituted acid chloride (**3c**)[30] as reported above for **3b** gave only 50% conversion. Similar results were obtained when attempting to couple acid **3d** with **4b** using various coupling reagents.[31−34] Gratifyingly, when **3e** was reacted with **4b** (Et_3N, DMAP, CH_2Cl_2), the corresponding amide

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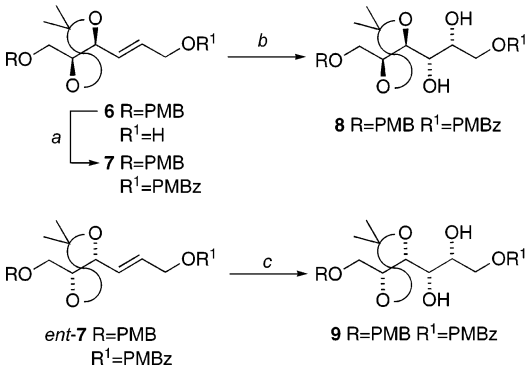
SCHEME 2. Synthesis of Alcohols 8 and 9[a]



[a] Reaction conditions: (a) PMBzCl, Et_3N, DMAP, CH_2Cl_2, 89%. (b) AD-mix β, $K_2OsO_4 \cdot H_2O$, *t*-BuOH/H_2O (1:1), 91%. (c) AD-mix β, $K_2OsO_4 \cdot H_2O$, *t*-BuOH/H_2O (1:1), 82%.

5 was smoothly formed.[35] Also, dimethyl malonic acid (**3f**) could be coupled with **4b** using DMT−MM,[33,36] giving amide **5** in high yield, but problems encountered in the workup made us favor the use of acid chlorides for this type of acylation reaction. In conclusion, to achieve a synthetically applicable route to the desired class of surfactants, a 2,2-dialkylated malonyl dichloride and a primary amine should be used in the coupling reaction and, consequently, the structures of the projected target molecules were revised to incorporate these requirements (Figure 1).

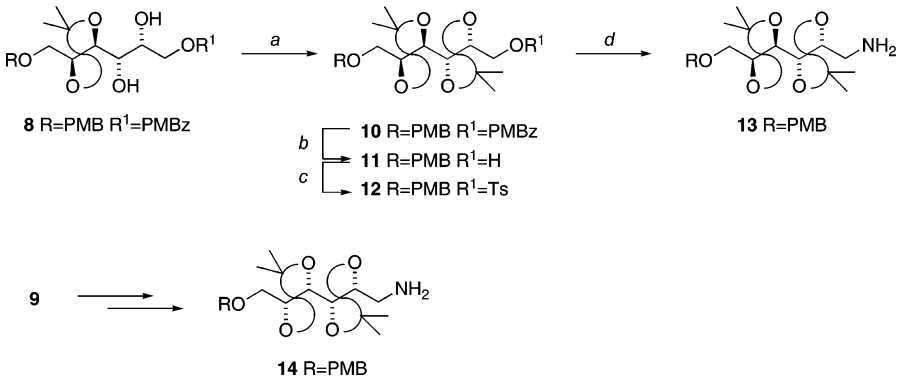
Synthesis of Head Groups 13, 14, and 17. The synthesis of the required polyols is summarized in Scheme 2. Protection of alcohol **6** (ee >99%), prepared from diene **D** as previously described,[37] as the *p*-methoxybenzoyl (PMBz) ester gave **7**. The PMBz ester was the protecting group of choice since it has proven to interact favorably with the chiral ligands most commonly employed in the Sharpless asymmetric dihydroxylation and since it is not prone to undergo migration to adjacent hydroxyls.[38] Diol **8** was accessed with good diastereoselectivity (*syn*/*anti* 1:20) by treating **7** with AD-mix β.[39] The dr could be further improved by flash chromatography (*syn*/*anti* 1:97). Similarly, diol **9** was obtained with equally good *syn*/*anti* diastereoselectivity (33:1) when *ent*-**7**[40] was subjected to AD-mix β.

The transformation of alcohol **8** to the protected head group **13** is depicted in Scheme 3. The diol moiety in **8** was protected as an acetonide to give **10**, which was subsequently hydrolyzed to the primary alcohol **11**. Conversion of this material into tosylate **12** proceeded smoothly and the final transformation into the corresponding amine **13** was accomplished by heating in aq NH_4OH using THF as a cosolvent. Amine **14** was obtained from **9** by following an analogous sequence.[40]

The remaining head group **17** was prepared from compound **10** by removal of the PMB protecting group, affording alcohol **15** (Scheme 4). Tosylation of this material was performed to give compound **16**, the aminolysis of which gave the corresponding amine but also resulted in partial removal of the PMBz ester. Since the PMBz protecting group had fulfilled its mission the crude reaction mixture was treated with NaOH to afford amine **17** in good overall yield.

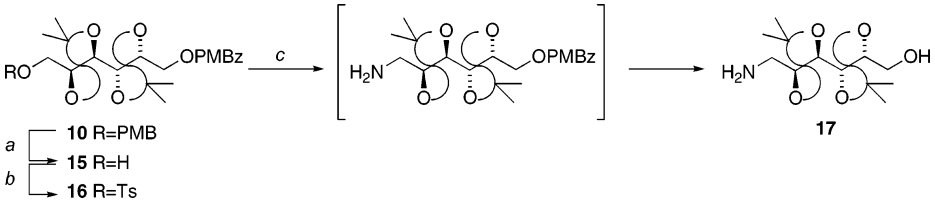
Coupling of Amines 13, 14, and 17 with Acid Chlorides 19a,b. As discussed above, 2,2-disubstituted malonic acid chlorides were the electrophiles of choice, and consequently, the hydrophobic parts **18a** and **18b**,[40] incorporating two C_8 and C_{12} tails, respectively, were selected (Scheme 5). Acids **18a** and **18b** were converted into acid chlorides **19a** and **19b**, which without further purification were coupled with amino alcohol **13** to afford

SCHEME 3. Completion of the Synthesis of Head Groups 13 and 14[a]



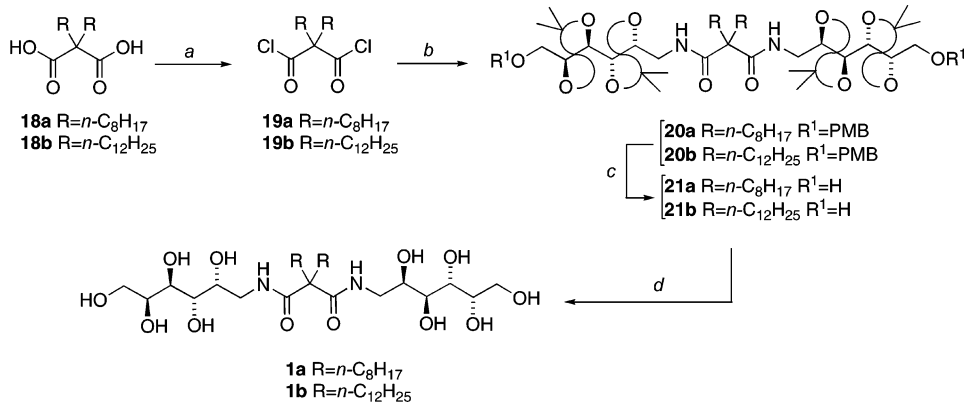
[a] Reaction conditions: (a) 2-methoxypropene, TsOH, DMF, 74%; (b) NaOH, MeOH, 99%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, 85%; (d) NH_4OH, THF, 100 °C, 99%.

SCHEME 4. Synthesis of Head Group 17[a]



[a] Reaction conditions: (a) H_2, Pd(C), MeOH, 30 min, 99%; (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 68%; (c) (i) NH_4OH, THF, 100 °C, (ii) NaOH (2M), THF, 50−60 °C, 81% (two steps).

SCHEME 5. Completion of the Synthesis of the Target Surfactants[a]



[a] Reaction conditions: (a) $(CClO)_2$, DMF, CH_2Cl_2; (b) **13**, Et_3N, DMAP, CH_2Cl_2; **a**: 63%; **b**: 56%;. (c) H_2, Pd(C), MeOH; **a**: 98%; **b**: >99%; (d) Dowex-50W, MeOHl, Δ; **a**: 92%; **b**: 73%.

the fully protected surfactant precursors **20a** and **20b**. The C_8 and C_{12} aliphatic chains imparted highly hydrophobic character to **20a** and **20b** resulting in difficult purifications. The isolated yields thereby dropped, but as purification after deprotection might be even more troublesome, it was considered easier to purify at this stage. The PMB-protecting groups were removed by hydrogenolysis to form **21a** and **21b**, respectively, in high yields. Finally, stirring **21a** and **21b** together with strongly acidic ion-exchange resin (Dowex-50W) in refluxing methanol gave surfactants **1a** and **1b**, respectively. It is noteworthy that the workup of the final steps in this sequence only required filtration and evaporation.

The remaining isomers *ent*-**1** and **2** were prepared from amino alcohols **17** and **14**, respectively, following the procedure outlined in Scheme 5.[40] This afforded in total six new surfactants, with three stereochemically different head groups. The head groups of surfactants **1** and *ent*-**1** are stereochemically analogous to L-galactose and D-galactose respectively, while the head groups of **2** have the stereochemistry corresponding to D-iodose.

Surface Pressure−Area (*π*−A) Isotherms. The measurement of surface pressure (π) versus molecular area at constant temperature is a widely used method for the investigation of monolayers at the air−water interface, first used by Langmuir.[41] Chiral Langmuir monolayers at the air−water interface provide a unique and simple model to study the effects of stereochemical differences on intermolecular interactions.[42,43] Although sugar surfactants belong to a field of growing interest, surprisingly few investigations have considered the chiral discriminations of these amphiphiles.[14−17] Since we had prepared stereoisomeric surfactants it was of interest to study their physical properties, and herein is reported on a surface pressure−area ($\pi-A$) investigation of compounds **1b**, *ent*-**1b**, **1b** + *ent*-**1b** (racemate), and **2b**.

Figure 3 depicts the $\pi-A$ isotherms for surfactants **1b**, *ent*-**1b**, **1b** + *ent*-**1b** (racemate[44]), and **2b**. The discrepancy between the isotherms of surfactant **1b** and *ent*-**1b** can be attributed to the very small amount of material used in the measurement and the sensitivity of the method toward impurities.[45] Interestingly, **2b** appears to be much more expanded than its diastereomer **1b**. Furthermore, there is a clearly visible phase transition for surfactant **1b**, which is absent for isomer **2b**, and these differences can only be attributed to the difference in stereochemistry of the head groups. Interestingly, the racemic mixture (**1b** + *ent*-**1b**) also exhibits a significant difference compared to **1b** and *ent*-**1b**. The pronounced sinuous curvature at the phase transition region (from a liquid expanded to a liquid condensed phase) for the racemate (**1b** + *ent*-**1b**), that is visible only as a small decrease in surface pressure for **1b** can be ascribed to an equilibrium effect, i.e., the relaxation speed of the molecules in the monolayer is much slower than the compression speed of the barrier.[15,46] Further studies to rationalize these observations are ongoing and will be reported elsewhere.

Conclusions

We have developed a simple and reliable synthetic route for the preparation of diastereomeric and enantiomeric surfactants from a limited number of starting materials. The selected route permits the preparation of head and tail groups separately, thereby allowing for a flexible approach to the surfactants. The protecting group strategy circumvents the solubility problems often encountered in surfactant synthesis, and the deprotection steps employed solid-supported reagents to avoid tedious purification steps.

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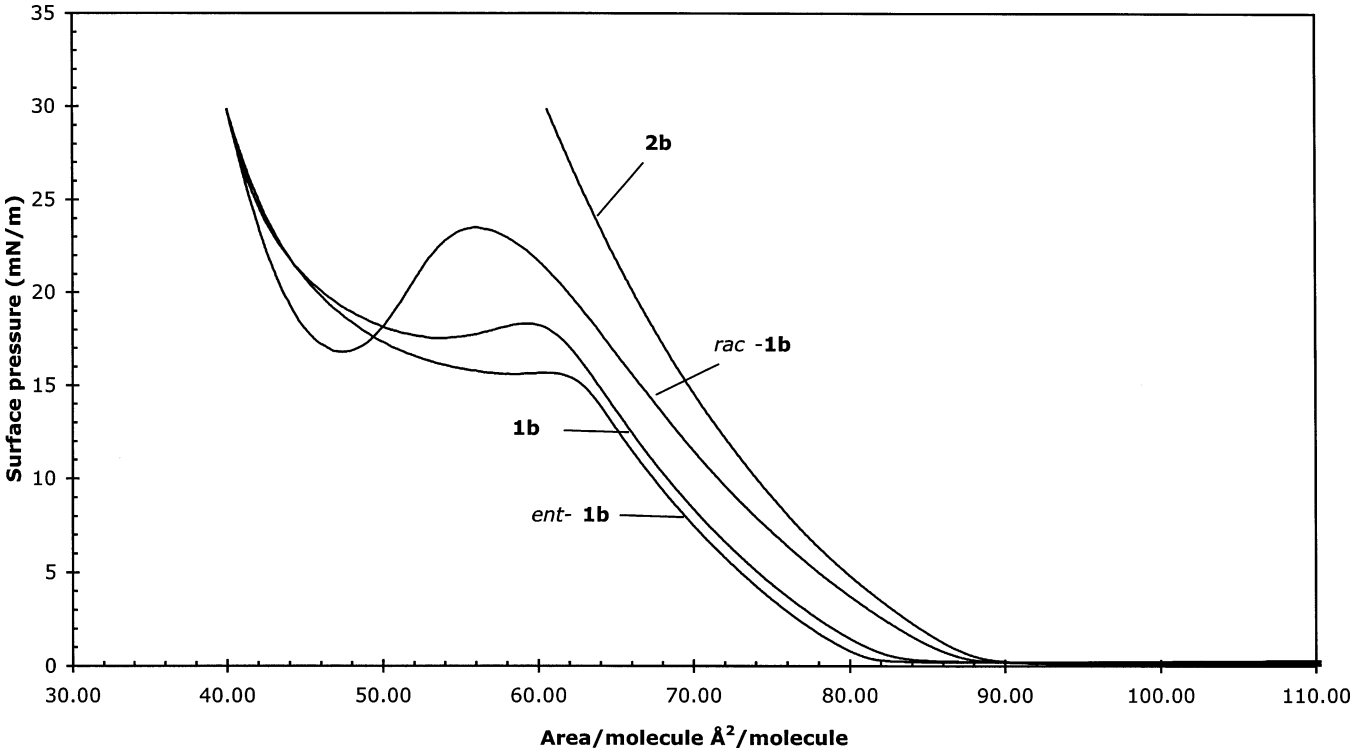

FIGURE 3. Surface pressure−area isotherms for **1b**, *ent*-**1b**, **1b** + *ent*-**1b** (racemate), and **2b**.

Preliminary results demonstrate that there is an important difference in molecular packing at the air−water interface between stereoisomeric surfactants.

Experimental Section

(*E*)-3-((4*S*,5*S*)-5-((4-Methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl 4-Methoxybenzoate (7). Alcohol **6**[37] (640 mg, 2.1 mmol), *p*-methoxybenzoyl chloride (553 mg, 3.24 mmol), Et_3N (290 μL, 2.1 mmol), and DMAP (cat.) were stirred in dry CH_2Cl_2 (100 mL) under nitrogen overnight. Et_2NH (0.3 mL) was added to remove unreacted *p*-methoxybenzoyl chloride, and the reaction mixture was stirred for 1 h at rt. The solvent was evaporated and the residue purified by flash chromatography (EtOAc/pentane 1:2 → 1:1) to give **7** as a colorless oil (812 mg, 1.8 mmol, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 9.0, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.98 (td, J = 15.5, 5.5 Hz, 1H), 5.84 (dd, J = 15.5, 7.3 Hz, 1H), 4.78 (d, J = 5.5 Hz, 2H), 4.52 (s, 2H), 4.28 (t, J = 7.3 Hz, 1H), 3.94−3.89 (m, 1H), 3.86 (s, 3H), 3.61−3.54 (m, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 163.9, 159.7, 132.1, 131.1, 130.4, 129.7, 129.0, 122.8, 114.2, 114.1, 109.9, 80.2, 78.8, 73.6, 69.5, 64.4, 55.8, 55.6, 27.4, 27.4; IR (neat) 2986, 1712, 1608 cm^{-1}; $[\alpha]_D$ −14.2 (*c* 1.00, CH_2Cl_2); HRMS (FAB+) calcd for $C_{25}H_{31}O_7$ (M + H) 443.2070, found 443.2070.

1-(4-Methoxybenzyl)-2,3-*O*-isopropylidene-D-galactitol-6-(4-methoxybenzoat) (8). AD-mix β (27 g), $K_2OsO_4 \cdot 2H_2O$ (10 mg, 27 μmol) and methanesulfonamide (2.15 g, 22.6 mmol) were added to a stirred solution of **7** (11.0 g, 22.6 mmol) in *t*-BuOH/H_2O (1:1, 300 mL). The reaction mixture was stirred overnight at 0 °C and then quenched by the addition of Na_2SO_3(s). The mixture was stirred for an additional 2 h at room temperature and then diluted with EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed once with KOH (2 M). Drying ($MgSO_4$) and concentration gave the desired *anti*-diol (**8**) as an oil that was purified by flash chromatography (EtOAc/pentane 1:2 → 1:1). This afforded **8** as a white solid with a diastereomeric ratio of 97:1 in 91% yield (9.8 g, 20.6 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, J = 8.9 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 4.58 (s, 2H), 4.49−4.47 (m, 2H), 4.22−4.12 (m, 2H), 3.95 (t, J = 7.8 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.80 (dd, J = 9.3, 4.8 Hz, 1H), 3.73 (ddd, J = 7.8, 4.0, 1.9 Hz, 1H), 3.66 (d, J = 4.0 Hz, 1H), 3.60 (dd, J = 9.3, 7.2 Hz, 1H), 2.92 (d, J = 7.6 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 163.9, 159.9, 132.2, 130.1, 129.4, 122.8, 114.4, 114.1, 109.9, 80.2, 78.7, 74.0, 72.5, 70.7, 69.8, 66.5, 55.9, 55.7, 27.3; IR (neat) 3415 (br), 1710, 1607 cm^{-1}; $[\alpha]_D$ +8.1 (*c* 1.55, CH_2Cl_2); HRMS (FAB+) calcd for $C_{25}H_{33}O_9$ (M + H) 477.2125, found 477.2122.

General Procedure for Acetonide Protection of 1,2-Diols. 2,3:4,5-Di-*O*-isopropylidene-1-(4-methoxybenzyl)-D-galactitol-6-(4-methoxybenzoate) (10). To a solution of **8** (9.8 g, 20.6 mmol) and *p*-TsOH (cat.) in DMF (200 mL) at 0 °C was added 2-methoxypropene (7.7 mL, 82.4 mmol) under an atmosphere of nitrogen. The reaction mixture was stirred for 30 min at 0 °C, the temperature was raised to rt, and the reaction mixture was stirred until completion (3 h). The crude reaction mixture was extracted between water and Et_2O, the water phase was extracted twice with Et_2O, and the combined organic layers were dried ($MgSO_4$) and evaporated. The obtained yellow oil was triturated with pentane to give the protected alcohol **10** as an off-white solid in 74% yield (11.2 g, 15.2 mmol): mp 88−90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.63 (dd, J = 11.6, 2.3 Hz, 1H), 4.58 (AB-d, J = 11.8 Hz, 1H), 4.55 (AB-d, J = 11.8 Hz, 1H), 4.40 (m, 2H), 4.25 (m, 1H), 3.95 (t, J = 7.7 Hz, 1H), 3.88 (s, 3H), 3.86 (t, J = 7.7 Hz, 1H), 3.82 (s, 3H), 3.76 (dd, J = 10.6, 2.8 Hz, 1H), 3.61 (dd, J = 10.6, 6.0 Hz, 1H), 1.43 (s, 6H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 163.8, 159.6, 132.2, 130.6, 129.7, 122.6, 114.1, 114.0, 110.7, 110.6, 80.4, 79.1, 79.0, 78.7, 73.5, 70.5, 64.9, 55.9, 55.7, 27.53, 27.51, 27.48, 27.39; IR (neat) 2988, 1715, 1607 cm^{-1}; $[\alpha]_D$ −1.9 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{28}H_{36}O_9$ (M) 516.2359, found 516.2363.

General Procedure for Ester Hydrolysis of PMBz Group. 2,3:4,5-Di-*O*-isopropylidene-1-(4-methoxylbenzyl)-D-galactitol (11). 10 (4.0 g, 7.74 mmol) was dissolved in MeOH (200 mL). Finely powdered NaOH (1.5 g 39 mmol) was added, and the mixture was gently warmed until everything was completely dissolved. The reaction was stirred for 1 h at rt, the MeOH was removed under reduced pressure, and water (200 mL) was added. The reaction mixture was stirred vigorously overnight and then extracted twice with Et_2O. The combined organic phases were dried ($MgSO_4$) and evaporated. The product (**11**) was obtained as a low-melting solid in 99% yield (2.9 g, 7.6 mmol). No further purification was needed: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.57 (AB-d, J = 11.8 Hz, 1H), 4.52 (AB-d, J = 11.8 Hz, 1H), 4.21−4.17 (m, 1H), 4.05−4.01 (m, 1H), 3.80 (s, 3H), 3.79−3.71 (m, 4H), 3.58 (dd, J = 10.6, 5.8 Hz, 1H), 2.28 (dd, J = 8.6, 4.3 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 130.6, 129.8, 114.2, 110.7, 110.1, 81.4, 80.8, 79.7, 78.4, 73.6, 70.4, 63.1, 55.7, 27.5, 27.4, 27.4, 27.3; IR (neat) 3474 (br), 1612 cm^{-1}; $[\alpha]_D$ −13.3 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{20}H_{30}O_7$ (M) 382.1992, found 382.1994.

General Procedure for the Tosylation of Alcohols 11 and 15. 2,3:4,5-Di-*O*-isopropylidene-1-(4-methoxybenzyl)-D-galactitol-6-(4-methylbenzenesulfonate) (12). *p*-TsCl (548 mg, 2.9 mmol), Et_3N (405 μL, 2.9 mmol), and DMAP (cat.) was added to a solution of **11** (1.0 g, 2.9 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was allowed to stir overnight and then diluted with CH_2Cl_2 and washed sequentially with H_2O and brine. Drying ($MgSO_4$), evaporation, and flash chromatography (EtOAc/pentane 1:3) afforded **12** as a solid in 85% yield (1.19 g, 2.2 mmol): mp 68.6−69.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.52 (AB-d, J = 11.8 Hz, 1H), 4.49 (AB-d, J = 11.8 Hz, 1H), 4.30−4.25 (m, 1H), 4.11−4.06 (m, 3H), 3.78 (s, 3H), 3.76−3.70 (m, 2H), 3.66 (dd, J = 10.7, 2.7 Hz, 1H), 3.52 (dd, J = 10.7, 5.9 Hz, 1H), 2.43 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 145.2, 133.4, 130.6, 130.2, 129.7, 128.5, 114.1, 111.1, 110.6, 80.6, 78.6, 78.5, 78.1, 73.5, 70.3, 69.7, 55.7, 27.5, 27.4, 27.4, 27.2, 22.0; IR (neat) 1612, 1369, 1177 cm^{-1}; $[\alpha]_D$ +2.8 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{27}H_{36}O_9S$ (M) 536.2080, found 536.2087.

General Procedure for the Aminolysis of Tosylates. 6-Amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-1-(4-methoxybenzyl)-D-galactitol (13). In a vessel were added **12** (1.08 g, 2.0 mmol), aq NH_4OH (25%, 20 mL), and THF (10 mL). The vessel was sealed and the reaction mixture heated to 100 °C for 24 h, diluted with Et_2O, and washed with water. The water phase was extracted two times with Et_2O, and the organic layers were dried (Na_2SO_4) and evaporated to afford amine **13** as a colorless oil in quantitative yield (771 mg, 2.0 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 9.2 Hz, 2H), 6.87 (d, J = 9.2, 2H) 4.55 (AB-d, J = 11.8 Hz, 1H), 4.53 (AB-d, J = 11.8 Hz, 1H), 4.20−4.15 (m, 1H), 3.97−3.93 (m, 1H), 3.80 (s, 3H), 3.78−3.66 (m, 3H), 3.56 (dd, J = 10.6, 6.1 Hz, 1H), 3.00 (dd, J = 13.4, 3.8 Hz), 2.85 (dd, J = 13.4, 6.3 Hz, 1H), 1.41 (s, 3H), 1.38 (s, 6H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 130.7, 129.7, 114.1, 110.3, 109.7, 83.0, 80.6, 79.9, 78.6, 73.5, 70.6, 55.6, 44.7, 27.7, 27.5, 27.5, 27.3; IR (neat) 2987, 1514 cm^{-1}; $[\alpha]_D$ −5.1 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{20}H_{32}NO_6$ (M + H) 382.2230, found 382.2220.

Hydrogenation of PMB Ester 2,3:4,5-Di-*O*-isopropylidene-D-galactitol-6-(4-methoxybenzoate) (15). Compound **10** (3.76 g, 7.27 mmol) was dissolved in dry MeOH (50 mL) and degassed at −78 °C. Pd on charcoal (10 wt % loading cat. amount) was added and a hydrogen gas balloon connected to the reaction flask. The reaction mixture was allowed to stir at rt for 30 min and then filtered through a plug of Celite. The solvent was evaporated to afford the deprotected alcohol **15** in quantitative yield (890 mg, 7.27 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 4.64 (dd, J = 11.4, 2.6 Hz, 1H), 4.42−4.36 (m, 2H), 4.12−4.09 (m, 1H), 3.94−3.84 (m, 6H), 3.81−3.75 (m, 1H), 2.30 (br d, J = 6.0 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 163.9, 132.2, 122.6, 114.0, 110.9, 110.3, 81.5, 79.5, 79.3, 78.8, 64.7, 62.9, 55.8, 27.5, 27.5, 27.4, 27.2; IR (neat) 3435 (br), 2988, 1713, 1607 cm^{-1}; $[\alpha]_D$ +9.4 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{20}H_{37}O_8$ (M + H) 397.1862, found 397.1864.

2,3:4,5-Di-*O*-isopropylidene-D-galactitol-6-(4-methoxybenzoate)-1-(4-methylbenzenesulfonate) (16) was prepared from **15** as described for **12** and obtained in 68% yield after flash chromatography (EtOAc/pentane 1:2 → 1:1): mp 85−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 4.60 (dd, J = 11.7, 3.2 Hz, 1H), 4.38−4.29 (m, 3H), 4.18 (m, 2H), 3.88 (s, 3H), 3.87−3.81 (m, 2H), 2.47 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 163.9, 145.3, 133.3, 132.2, 130.2, 128.5, 122.7, 114.0, 111.2, 110.9, 79.7, 78.9, 78.7, 78.0, 69.5, 64.6, 55.9, 27.5, 27.4, 27.4, 27.1, 22.1; IR (neat) 1713, 1606, 1370, 1176 cm^{-1}; $[\alpha]_D$ −3.0 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{27}H_{35}O_{10}S$ (M + H) 551.1951, found 551.1948.

1-Amino-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactitol (17). Tosylate **16** (2.5 g, 4.54 mmol) was dissolved in THF (10 mL). NH_4OH (25%, 20 mL) was added, and the vessel was sealed and heated to 100 °C for 24 h. The crude reaction mixture was diluted with Et_2O and washed with water. The Et_2O was evaporated, the residue was redissolved in THF (10 mL), and aq NaOH (2 M, 20 mL) was added. The biphasic mixture was stirred vigorously at 60 °C for 30 h, the water phase was extracted three times with EtOAc, and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent gave **17** in 81% yield (923 mg, 3.67 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05−3.96 (m, 2H), 3.83−3.66 (m, 4H), 3.04 (d, J = 13.0 Hz, 1H), 2.86 (dd, J = 13.0, 6.3 Hz, 1H), 1.81 (br s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.37 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.13, 110.07, 83.2, 81.6, 79.7, 79.6, 63.1, 44.6, 27.6, 27.4, 27.3, 27.3; $[\alpha]_D$ −7.9 (*c* 1.00, $CHCl_3$ IR (neat) 3186, 2987, 2861, cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{28}NO_5$ (M + H) 262.1654, found 262.1654.

General Procedure for the Amide Coupling between 18 and Amines 13, 14, and 17. N^1,N^3-Bis-(1-deoxy-2,3:4,5-di-*O*-isopropylidene-6-(4-methoxybenzyl)-L-galactitol)-2,2-dioctylmalonamide (20a). Oxalyl chloride (283 μL, 3.27 mmol) was added to a solution of **18a** (215 mg, 0.655 mmol) and DMF (5.1 μL, 65.5 μmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 h. Solvent and excess oxalyl chloride were evaporated, and the oily residue was redissolved in CH_2Cl_2 (10 mL). To this solution were added Et_3N (183 μL, 1.31 mmol), DMAP (cat.), and **13** (500 mg, 1.31 mmol). The reaction mixture was allowed to stir at rt overnight. Water was added, and the phases were separated. The organic layer was washed with brine and dried ($MgSO_4$). The solution was concentrated, and the residue was purified by flash chromatography (EtOAc/pentane 1:4 → 1:1) to give **20a** as an oil in 63% yield (605 mg, 0.413 mmol): ^{1}H NMR (400 MHz, C_6D_6) δ 7.94 (br dd, J = 6.5, 4.1 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 4.57 (AB-d, J = 11.7 Hz, 2H), 4.53 (AB-d, J = 11.7 Hz, 2H), 4.46−4.42 (m, 2H), 4.25−4.21 (m, 2H), 4.12−4.06 (m, 4H), 3.91−3.84 (m, 4H), 3.76 (dd, J = 10.7, 5.1 Hz, 2H), 3.71 (td, J = 13.8, 4.3 Hz, 2H), 3.40 (s, 6H), 2.18−2.10 (m, 4H), 1.63−1.50 (m, 24H) 1.40−1.37 (m, 24H), 1.00 (t, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.6, 130.7, 129.7, 114.1, 110.8, 110.0, 80.7, 80.6, 79.6, 78.3, 73.5, 70.4, 57.5, 55.7, 41.4, 38.0, 32.3, 30.3, 29.8, 29.7, 27.6, 27.6, 27.5, 27.2, 25.4, 23.1, 14.5; IR (neat) 3368, 1672, 1514 cm^{-1}; $[\alpha]_D$ −11.1 (*c* 2.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{59}H_{94}N_2O_{14}Na$ (M + Na) 1077.6603, found 1077.6600.

N^1,N^3-Bis(1-deoxy-2,3:4,5-di-*O*-isopropylidene-6-(4-methoxybenzyl)-L-galactitol)-2,2-dididecylmalonamide (20b) was prepared from **18b** and **13** as described for **20a** and obtained as a clear oil in 56% yield: ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.55 (t, J = 4.9 Hz, 2H), 7.27 (d, J = 8.5 Hz, 4H), 6.87 (d, J = 8.5 Hz, 4H), 4.55 (AB-d, J = 11.8 Hz, 2H), 4.53 (AB-d, J = 11.8 Hz, 2H), 4.19−4.16 (m, 2H), 4.01−3.97 (m, 2H), 3.80 (s, 6H), 3.76−3.60 (m, 8H), 3.55 (dd, J = 10.7, 6.0 Hz, 2H), 3.47 (td, J = 13.8, 4.9 Hz, 2H), 1.82−1.78 (m, 4H), 1.44 (s, 6H), 1.41−1.38 (m, 12H), 1.28 (s, 6H), 1.24−1.15 (m, 40H), 0.88 (t, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 159.6, 130.6, 129.7, 114.1, 110.8, 110.0, 80.64, 80.59, 79.6, 78.3, 73.5, 70.4, 57.4, 55.7, 41.4, 37.9, 32.3, 30.3, 30.09, 30.07, 30.07, 29.87, 29.77, 27.6, 27.5, 27.4, 27.2, 25.4, 23.1, 14.5; one signal is not visible; IR (neat) 2986, 2925, 2855, 1672, 1513, 1462, 1371, 1090 cm^{-1}; $[\alpha]_D$ −10.4 (*c* 0.87, $CHCl_3$); HRMS (FAB+) calcd for $C_{67}H_{110}N_2O_{14}Na$ (M + Na) 1189.7855, found 1189.7856.

General Procedure for the Hydrogenation of the PMB Ether to the Alcohol. *N*^{1},*N*^{3}-Bis(1-deoxy-2,3:4,5-di-*O*-isopropylidene-L-galactitol)-2,2-dioctylmalonamide (21a). Compound **20a** (50 mg, 0.0474 mmol) was dissolved in anhydrous MeOH (3.5 mL). At −78 °C, under an atmosphere of nitrogen, Pd on charcoal (11 mg, 10 wt % Pd) was added to the solution. The solvent was evaporated and connected to a hydrogen gas balloon. The cooling bath was removed and the reaction allowed reaching room temperature. After 45 min, the starting material was completely consumed and the catalyst removed by filtration through a small plug of Celite. The desired alcohol **21a** was obtained, after evaporation of the solvent, as clear oil in 98% yield (38 mg, 0.0465 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br s, 2H), 4.06−4.03 (m, 4H), 3.84−3.69 (m, 8H), 3.65 (t, J = 7.9 Hz, 2H), 3.51 (td, J = 13.7, 4.1 Hz, 2H), 2.33 (br s, 2H), 1.83 (br s, 4H), 1.44 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.23 (br s, 24H), 0.88 (t, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 173.9, 110.4, 110.0, 81.7, 80.3, 79.7, 79.3, 62.9, 57.8, 41.4, 38.5, 32.6, 30.6, 30.1, 30.0, 27.55, 27.50, 27.4, 27.0, 25.9, 23.3, 14.6; IR (neat) 3376, 1667, 1530 cm^{-1}; $[\alpha]_D$ −5.2 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{43}H_{78}N_2O_{12}Na$ (M + Na) 837.5452, found 837.5455.

***N*^{1},*N*^{3}-Bis-(1-deoxy-2,3:4,5-di-*O*-isopropylidene-L-galactitol)-2,2-didodecylmalonamide (21b)** was prepared from **20b** as described for **21a** and obtained in quantitative yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (br dd, J = 6.3, 4.3 Hz, 2H), 4.09−4.05 (m, 4H), 3.85−3.71 (m, 8H), 3.65 (t, J = 7.9 Hz, 2H), 3.50 (td, J = 13.9, 4.3 Hz, 2H), 2.37 (br s, 2H), 1.86−1.80 (m, 4H), 1.45 (s, 6H), 1.44 (s, 6H), 1.41 (s, 6H), 1.38 (s, 6H), 1.26−1.18 (m, 40H), 0.89 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 110.5, 110.2, 81.3, 80.2, 79.6, 79.0, 62.9, 57.5, 41.2, 37.9, 32.3, 30.3, 30.07, 30.05, 30.04, 29.9, 29.8, 27.5, 27.4, 27.3, 27.2, 25.4, 23.1, 14.6; one signal is not visible; IR (neat) 3350 (br), 1665, 1530 cm^{-1}; $[\alpha]_D$ −5.9 (*c* 1.00, $CHCl_3$); HRMS (FAB+) calcd for $C_{51}H_{94}N_2O_{12}Na$ (M + Na) 949.6704, found 949.6715.

General Procedure for the Deprotection of the Acetonides To Give the Final Surfactants 1a,b, *ent*-1a,b, and 2a,b. *N*^{1},*N*^{3}-Bis(1-deoxy-L-galactitol)-2,2-dioctylmalonamide (1a). In a round-bottomed flask was placed **21a** (317 mg, 0.389 mmol) dissolved in MeOH (10 mL). Dowex 50W (cat.) was added, and the mixture was refluxed overnight. The ion-exchange resin was removed by filtration, and the MeOH was evaporated to give the desired product as a fine white powder (234 mg, 0.357 mmol, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (t, J = 6.1 Hz, 2H), 3.94 (br t, J = 6.7 Hz, 2H), 3.69−3.64 (m, 6H), 3.56 (dd, J = 9.7, 1.4 Hz, 2H), 3.49 (dd, J = 13.5, 5.5 Hz, 2H), 3.39−3.34 (m, 2H), 1.90−1.85 (m, 4H), 1.36−1.16 (m, 24H), 0.91 (t, J = 6.8 Hz, 6H); ^{13}C NMR (500 MHz, MeOD) δ 176.0, 72.0, 71.9, 71.3, 70.0, 65.0, 58.8, 44.2, 36.0, 33.1, 31.1, 30.4, 25.6, 23.8, 14.5; $[\alpha]_D$ +11.3 (*c* 1.00, MeOH); IR (neat) 3317 (br), 1625, 1440 cm^{-1}; HRMS (FAB+) calcd for $C_{31}H_{63}N_2O_{12}$ (M + H) 655.4381, found 655.4384.

***N*^{1},*N*^{3}-Bis-(1-deoxy-L-galactitol)-2,2-diododecylmalonamide (1b)** was prepared from **21b** as described for **1a** and obtained as a white powder in 73% yield: ^{1}H NMR (400 MHz, MeOD) δ 3.98−3.91 (m, 4H), 3.70−3.63 (m, 6H), 3.52−3.43 (m, 4H), 1.87−1.82 (m, 4H), 1.32−1.12 (m, 40H), 0.89 (t, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, MeOD:$CDCl_3$ 1:1, 313K): δ 174.8, 71.2, 70.9, 70.9, 69.2, 64.3, 58.1, 49.4, 43.2, 34.3, 32.1, 30.2, 29.86, 29.83, 29.81, 29.6, 29.5, 24.5, 22.8, 13.8; IR (neat) 3226 (br), 1635, 1521 cm^{-1}; HRMS (FAB+) calcd for $C_{39}H_{79}N_2O_{12}$ (M + H) 767.5633, found 767.5632.

Acknowledgment. The Centre for Surfactants Based on Natural Products (SNAP) and the Swedish Research Council are acknowledged for financial support.

Supporting Information Available: Preparation of compound **14** from *ent*-**6**, preparation of compounds **3a**, **4a**,**b**, preparation of **18a**,**b**, preparation of **2a**,**b** from **14**, analytical data for compounds *ent*-**21a**, *ent*-**21b**, *ent*-**1a**, and *ent*-**1b**, 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.

JO0357566