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A synthetic strategy for novel nonsymmetrical bola amphiphiles based on carbohydrates

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Abstract—A number of novel nonionic bolaform amphiphiles with nonidentical alditol head groups, 1-(1-deoxy-D-galactitol-1-ylamino)-6-(1-deoxy-D-glucitol-1-ylamino)hexane (**4a**), 1-(1-deoxy-D-mannitol-1-ylamino)-6-(1-deoxy-D-glucitol-1-ylamino)hexane (**4b**), and 1-(1-deoxy-D-galactitol-1-ylamino)-6-(1-deoxy-D-mannitol-1-ylamino)hexane (**4c**) were synthesized by two successive reductive aminations involving 1,6-diaminohexane (**1**) and the appropriate D-aldohexoses (D-glucose, D-mannose, and D-galactose) using 5% Pd on carbon as the catalyst. Typical reaction conditions were 40 °C, 4 MPa hydrogen and a reaction time of 4.5 h. The compounds were isolated as white solids in yields ranging from 39% to 72%. The intermediate aminoalditols, 1-(1-deoxy-D-glucitol-1-ylamino)-6-aminohexane (**3a**) and 1-(1-deoxy-D-galactitol-1-ylamino)-6-aminohexane (**3b**) were obtained as off-white solids in 80–85% yield. The bolaform amphiphiles containing 1-deoxy-D-glucitol head group(s) showed markedly lower melting points than the compounds with the 1-deoxy-D-mannitol and 1-deoxy-D-galactitol head groups, due to the presence of 1,3-syn interactions within the carbohydrate moiety. The novel bolaform compounds are potential starting materials for the synthesis of a broad range of gemini surfactants with nonidentical, carbohydrate-based head groups.

Keywords: Nonionic bolaform amphiphiles; Reductive amination; Carbohydrates

1. Introduction

Bolaform and gemini amphiphiles are novel classes of surface-active components. Bolaform amphiphiles have a hydrophilic head group at both ends of a hydrophobic chain (Fig. 1), and have been shown biological activity, might be applicable as ultra-thin monolayer synthetic membranes, and have potential as supramolecular gelling agents for water.[1,2]

Gemini surfactants, commonly containing two hydrophilic head groups and two hydrophobic chains linked by a spacer (Fig. 1), have physical properties that differ from conventional surfactants with similar hydrophobicity, showing lower critical micelle concentrations (cmc)[2] and larger decreases in surface tension. Gemini surfactants have potential uses in cosmetics, detergent compositions, synthesis of high porosity materials, solubilization processes, emulsions for photographic light sensitive emulsions, and gene therapy.[2]

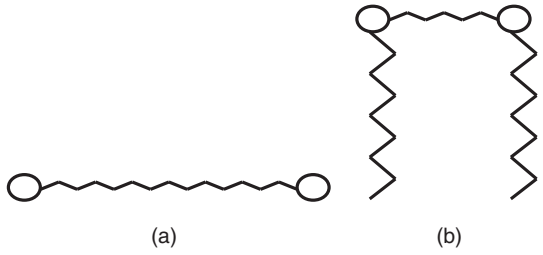

Figure 1. Schematic representation of (a) bolaform and (b) gemini surfactants (circles: hydrophilic head group; lines: hydrophobic tail).

Current interest in bolaform and gemini amphiphiles based on carbohydrate building blocks is growing rapidly.[2–11] Besides their proven physical properties, they are biologically compatible in an ecologically sensitive environment, are biodegradable and, to a certain extent,

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preparable from such renewable resources as sugars and natural fats.

Extensive research has been conducted on bolaform and gemini amphiphiles based on D-aldohexoses and α,ω-diaminoalkanes.[3,12–16] Synthetic methodology has been developed, and such important physical properties as aggregation behavior have been studied in detail. The application of these gemini amphiphiles based on D-aldohexoses and α,ω-diaminoalkanes for gene transfection has been assessed, and very good transfection activity in vitro has been observed.[17]

Research on gemini surfactants has thus far been dominated by those having two identical head groups.[18] We anticipated that gemini surfactants having two nonidentical head groups might have unique aggregation properties and have high potential for use in the area of gene transfection. In addition, their structural diversity increases dramatically, which is beneficial for structure–performance studies. Here, we report a highly flexible, broadly applicable synthetic methodology for preparing novel carbohydrate-based bola amphiphiles containing two different carbohydrate head groups and a diamine linker. These offer access to a wide range of nonsymmetrical gemini surfactants.[3]

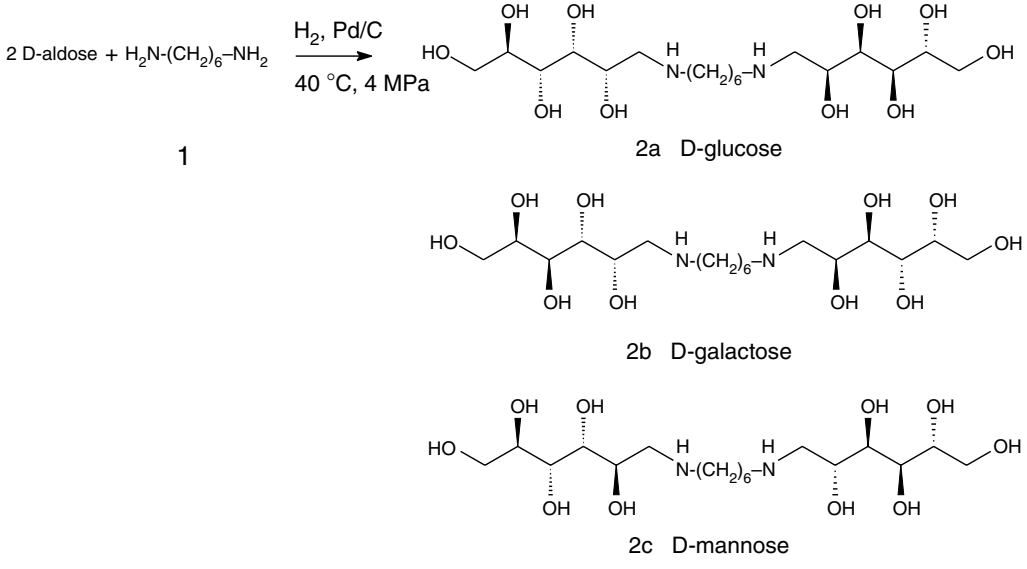
2. Results and discussion

Our target was to develop a flexible, broadly applicable synthetic route for nonionic bolaform amphiphiles having two different carbohydrate head groups connected by a diamine spacer. The route should also be applicable for preparing libraries of bolaform and gemini compounds for screening purposes, using high throughput experimentation. Two pathways have been explored, both based on the successive introduction of two different aldohexoses on 1,6-diaminohexane. The first attempts involved reductive amination of a monoprotected diamine with an aldohexose, using Pd/C as the catalyst, followed by deprotection and a second reductive amination using a different aldohexose. However, the attempted reaction of D-glucose with *N*-Boc-protected 1,6-diaminohexane (40 °C, 5 MPa H_2, Pd/C 5%) gave a deep brown mixture, from which no pure compounds could be isolated.

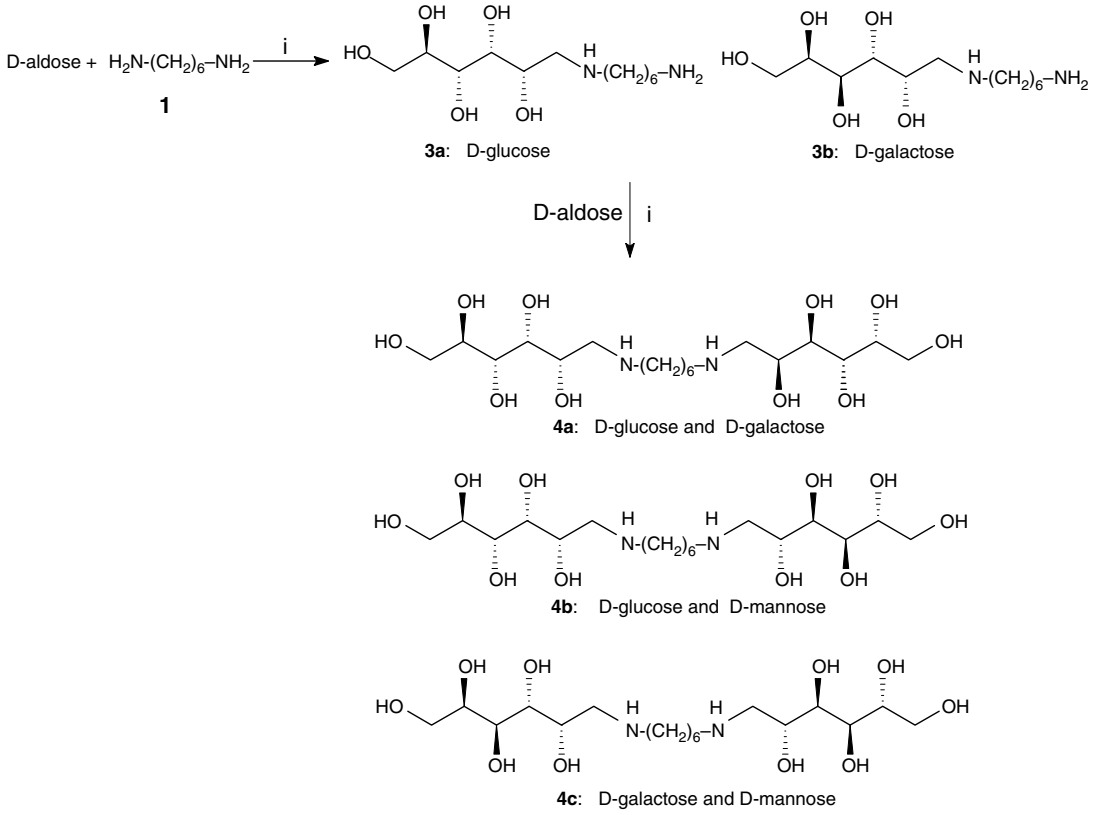
The second synthetic pathway was successful and was explored in detail. It extends the strategy for the synthesis of bolaform amphiphiles with 2 equiv aldohexose head groups linked by an amine spacer (Scheme 1).[3]

The original route involves reductive amination of a D-aldohexose with a diamine (such as **1**) using Pd on carbon as the catalyst. Using this approach, sugar-based bola amphiphiles (for example, **2a**–**c**) with different spacer lengths could be obtained in a one-pot synthesis. The reaction is typically carried out in methanol–water mixtures using a 2:1 molar ratio of D-aldohexose and diamine at 40 °C and 4 MPa of hydrogen pressure and a reaction time of 24 h. The results of extensive process research conducted to improve the product yields and reduce reaction times will be reported separately,[19] but it is noteworthy that the bolaform amphiphiles could be isolated in yields of >80% after significantly shorter reaction times (4.5 instead of 24 h).

We envisaged that adaptation of the substrate ratios could lead to the intermediate 1-(1-deoxy-D-alditol-1-ylamino)-6-aminohexane, namely, a diamine with one free amine and a sugar-derived head group (Scheme 2). This was realized, and the reductive amination of either D-glucose or D-galactose with an excess of 1,6-diaminohexane (aldohexose–diaminohexane molar ratio of



Scheme 1.



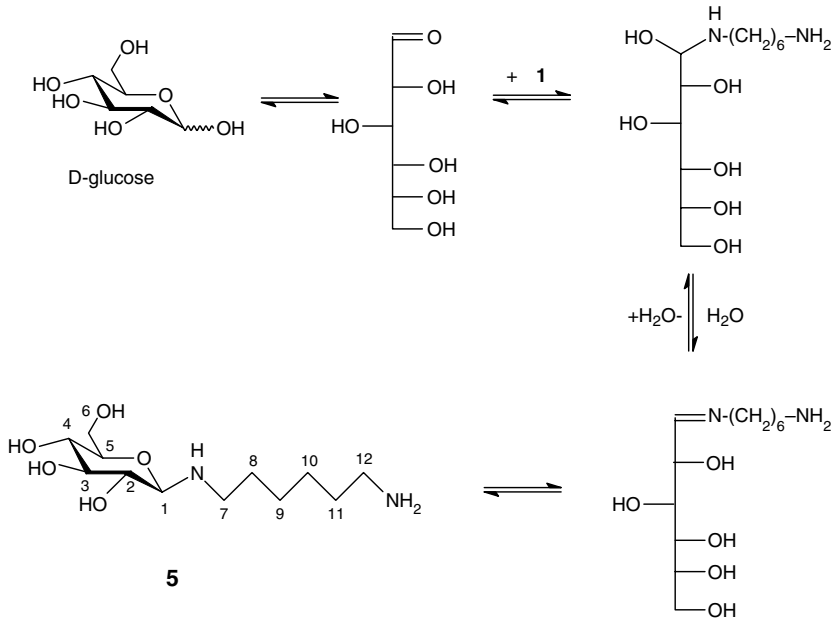
Scheme 2. Reagents and conditions: (i) H_2, 4 MPa, 40 °C, H_2O/MeOH, 5% Pd/C.

1:6.6) gave the aminoalditol products, 1-(1-deoxy-D-glucitol-1-ylamino)-6-aminohexane (**3a**) and 1-(1-deoxy-D-galactitol-1-ylamino)-6-aminohexane (**3b**) in 80–85% yields. The hydrogen uptake was monitored with time to establish suitable reaction times. Hydrogen uptake ceased after 4.5 h of reaction, suggesting that aldohexose conversion is essentially quantitative and that the isolated yields are lower due to losses in work-up. Very low amounts of symmetrical bola amphiphiles (<1%) were isolated during the work-up procedure. D-Glucitol and D-galactitol, the direct hydrogenation products of the parent aldoses, could not be detected in the crude product mixtures (^{1}H and ^{13}C NMR).

Characteristic ^{13}C NMR peaks arising from the 1-deoxy-D-alditol-1-yl fragments were observed between δ 50 and 73 ppm. As expected, all spacer carbons are nonequivalent, and six different peaks were observed between δ 26 and 50 ppm. Further derivatization chemistry (see later) suggests that **3a** and **3b** were contaminated with small amounts (<7%) of *N*-β-D-glucopyranosyl-1,6-diaminohexane (**5**) (Scheme 3). Direct evidence for the presence of **5** in samples of **3a** and **3b** by ^{13}C NMR was not obtained because of its low concentration, and ^{1}H NMR was also not conclusive.

Three novel bolaform amphiphiles with different carbohydrate-based head groups were synthesized by a second reductive amination, using the intermediate amines **3a** and **3b** and the appropriate aldohexoses (Scheme 2). The second reductive amination was carried out at 40 °C, 4 MPa hydrogen pressure, and 5% palladium on carbon as catalyst. The products, 1-(1-deoxy-D-galactitol-1-ylamino)-6-(1-deoxy-D-glucitol-1-ylamino)hexane (**4a**), 1-(1-deoxy-D-mannitol-1-ylamino)-6-(1-deoxy-D-glucitol-1-ylamino)hexane (**4b**), and 1-(1-deoxy-D-galactitol-1-ylamino)-6-(1-deoxy-D-mannitol-1-ylamino)-hexane (**4c**) were isolated as off-white solids in yields ranging from 39–72%. Yields at the low end of the range are due to excessive adhesion of the product to the catalyst, which significantly hampered work-up.

^{13}C NMR clearly indicated that **4a–c** contain two different 1-deoxy-alditol-1-yl head groups. This is especially evident when considering the number of resonances for the carbon atoms of the spacer between the two nitrogen atoms. In the case of identical head groups, a maximum of three carbon atoms is possible because of symmetry within the molecule. For **4a–c**, more than three resonances were observed for this fragment. For instance for **4c**, five resonances were found at δ 26.60, 29.32, 29.40, 49.13, and 49.19 ppm. Quantitative ^{13}C NMR shows that the peak at δ 26.60 ppm has an intensity twice of that of the other resonances, a clear indication that this resonance arises from two different carbon atoms, bringing the total carbon atoms to the expected number of six.



Scheme 3.

With these NMR data, it cannot be excluded a priori that compounds **4a**–**c** are not single compounds but are actually 1:1 molar mixtures of the corresponding symmetrical compounds. However, support to the statement that **4a**–**c** are indeed single compounds is obtained when comparing ^{13}C NMR spectra (Me_2SO-d_6, 50 °C) of **4a**–**c** with spectra of 1:1 molar mixtures of the corresponding symmetrical compounds (such as **4c** and a 1:1 molar mixture of **2b** and **2c**). As expected, the total number of carbon resonances is equal for both samples, but small, albeit significant, shift differences of up to 0.4 ppm were observed.

Additional evidence for **4a**–**c** being single compounds and not 1:1 mixtures of two symmetrical compounds was obtained by comparing the melting points of **4a**–**c** and the corresponding 1:1 molar mixtures of the symmetrical compounds. For the latter, extremely wide melting trajectories were observed, for example, 143–189 °C for a 1:1 mixture of 1,6-bis-(1-deoxy-D-glucitol-1-ylamino)hexane (**2a**) and 1,6-bis-(1-deoxy-D-galactitol-1-ylamino)hexane (**2b**) as compared to a melting point of 153–156 °C for compound **4a**. In addition, the melting point of the bolaform amphiphile **4c** (180–182 °C), containing both a 1-deoxy-D-galactitol-1-yl and a 1-deoxy-D-mannitol-1-yl head group is lower than found for the two symmetrical analogues, **2b** (197–198 °C) and **2c** (193–194 °C).

In the initial stage of the work-up procedure for compounds **4a** and **4b**, small amounts of bolaform amphiphiles with two identical head groups crystallized from the reaction mixture as off-white solids. For **4a**, 7% of the symmetric bolaform amphiphile 1,6-bis-(1-deoxy-D-galactitol-1-ylamino)hexane (**2b**) was isolated. For **4b**, 6% 1,6-bis-(1-deoxy-D-mannitol-1-ylamino)hexane (**2c**) was obtained. Both components were characterized by NMR and elemental analyses.[15]

The formation of these symmetrical bolaform amphiphiles containing 1-deoxy-D-galactitol and 1-deoxy-D-mannitol groups is rather surprising, as the monoaminoalditol precursor (**3a**) only contains a 1-deoxy-D-glucitol-1-yl group. A possible explanation for the formation of these symmetrical products could be the presence of small amounts of *N*-β-D-glucopyranosyl-1,6-diaminohexane (**5**) in samples of **3a**. Recent studies on reductive aminations of carbohydrates with amines have indicated that glycosylamines are indeed intermediate products in the sequence,[20] see Scheme 3. All steps in the sequence are reversible,[20] and it is therefore likely that **5**, present as impurities in **3a**, is reacting in the reverse manner to form the starting materials, D-glucose and 1,6-diaminohexane. Subsequently, the 1,6-diaminohexane is reacting with 2 mol equiv of the aldohexose reactant to form the symmetrical bola components.

^{13}C NMR experiments were performed to investigate whether **5** is an intermediate in the reaction between D-glucose and 1,6-diaminohexane (**1**). A solution of **1** (0.19 mol/L) and D-glucose (0.41 mol/L) in MeOH-d_4–D_2O mixtures (65:35 vol ratio) was monitored with time at 40 °C. Characteristic signals of α,β-D-glucose and **1** slowly diminished over a period of 3 h. A new set of signals appeared at δ 27.6, 28.0, 30.7, 33.4, 42.2, 46.9, 62.6, 78.5, 78.6, and 91.5 ppm. These carbon resonances are assigned to compound **5**.[20] The latter is especially characteristic for an *N*-β-D-glucopyranosyl-1,6-diaminoalkane and arises from C-1 of the glucopyranosyl ring.[20] The presence of six resonances arising from the amine carbons (δ 27.6–46.9 ppm) indicate that the amine groups have different substituent patterns.

Additional proof that **5** is indeed formed under reductive elimination conditions and may be present as an impurity in the precursor **3a** is obtained by analyzing ^{13}C NMR samples from reductive amination reactions terminated before hydrogenation was complete. Significant amounts of **5** were indeed detected.

An alternative explanation for the formation of the symmetrical products with two identical alditol-1-yl head groups is the presence of free 1,6-diaminohexane in the precursor **3a**. However, this is rather unlikely as the work-up procedure for **3a** consists of a number of washing and crystallization steps, which are expected to result in very efficient removal of 1,6-diaminohexane from the solid products.

Considering all information, it is likely that the isolated monoaminoalditol precursor **3a** is contaminated with small amounts (6–7%) of *N*-β-D-glucopyranosyl-1,6-diaminohexane (**5**).

2.1. Melting points

The melting points of **4a** (153–156 °C) and **4b** (135–142 °C) are significantly lower than for **4c** (180–182 °C). This feature can be explained by taking 1,3-syn interactions[21] into consideration. In the 1-deoxy-D-glucitol-1-yl units of **4a** and **4b**, the hydroxyl groups at C-2 and C-4 are both at the same side of the molecule. This results in steric hindrance, leading to a bending within the head group and, subsequently, distortion of the crystal packing. The stereochemistry of the 1-deoxy-D-mannitol and 1-deoxy-D-galactitol units differs from the 1-deoxy-D-glucitol unit at C-2 and C-4, respectively. As a result, 1,3-syn interactions are absent in **4c**, leading to a higher melting point. The previously reported[3] melting point (151–153 °C) of the symmetrical glucose-based bola amphiphile **2a** is, as expected on the basis of this explanation, significantly lower than that of **2b** (197–198 °C) and **2c** (193–194 °C).

The melting point of the mixed bolaform amphiphile, **4c**, containing a 1-deoxy-D-galactitol and a 1-deoxy-D-mannitol head group is lower than found for the two symmetrical analogues, **2b** and **2c**. The asymmetry in **4c** probably results in a less ideal crystal packing and thus a lowering of the melting point.

2.2. Conclusions

We have developed a flexible synthetic strategy for the synthesis of a broad range of novel bolaform amphiphiles with nonidentical sugar derived head groups linked by a diamine spacer. The methodology has been demonstrated for such D-aldohexoses as D-glucose, D-mannose, and D-galactose but is expected to be applicable also for such disaccharides as lactose and maltose, allowing the synthesis of bolaform amphiphiles with head groups differing in size and structure. The nonsymmetrical bolaform compounds are potentially useful starting materials for the synthesis of novel classes of gemini surfactants, which are expected to have potential in such areas as gene transfection.

3. Experimental

3.1. General procedures

All reductive aminations were carried out in a 385-mL autoclave equipped with a mechanical hollow axis gas induced stirrer operated at 800 rotations/min. The reactor was operated isothermally using electrical heating combined with air cooling. Reactions were carried out at constant hydrogen pressure. Consumed hydrogen was replenished from a buffer vessel. The pressure in the buffer vessel was continuously monitored, allowing determination of the uptake of hydrogen as a function of the batch time. Details of the set-up are described in Ref. 22.

The NMR spectra were recorded on a Varian VXR 300 spectrometer. Unless stated otherwise, the ^{13}C NMR spectra were recorded at 25 °C using Me_2SO-d_6 as solvent and the ^1H NMR spectra were recorded at 50 °C using D_2O. Carbon atoms are numbered as follows: C-1 to C-6: first aldohexose unit, C-7 to C-12: diamine spacer, C-13 to C-18: second aldohexose unit. A representative example is given in Figure 2.

The melting points of the compounds **2b**–**c** and **4a**–**c** were determined using a standard melting point microscope. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

3.2. 1-(1-Deoxy-D-glucitol-1-ylamino)-6-aminohexane (3a)

1,6-Diaminohexane (**1**, 21.40 g, 0.184 mol) was dissolved in MeOH (150 mL). D-Glucose (5.01 g, 0.0278 mol) was dissolved in water (50 mL) and wet Pd on carbon (5%, 6 g) was added. The solutions were combined in the autoclave. The content was heated to 40 °C and subsequently the autoclave was pressurized with 4 MPa of hydrogen. After 4.5 h, the reaction was stopped by releasing the hydrogen pressure and cooling down the contents to room temperature. The catalyst was filtered off and the solvents were evaporated under reduced pressure (40 °C, 2500 Pa). The residue was washed three

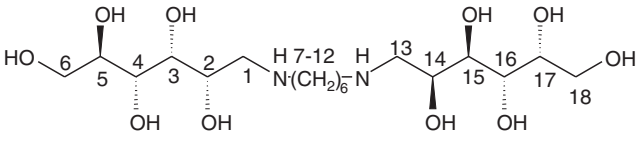


Figure 2. Carbon numbering for the bolaform compounds (e.g., **4a**).

times with Et_2O (100 mL) to extract the excess of **1**. The first washing step was carried out with Et_2O containing MeOH (1 mL). A total of 17.7 g (0.152 mol) of **1** was extracted this way (97% of the theoretical value in case of 100% aldohexose conversion). The residue was dissolved in MeOH (50 mL) at about 50 °C. Cooling down resulted in the formation of about 10 mg (23 μmol) of a white solid, which was identified as the symmetrical compound 1,6-bis-(1-deoxy-D-glucitol-1-ylamino)hexane (**2a**). The filtrate was evaporated to dryness (40 °C, 2500 Pa), resulting in a yellow viscous substance. Et_2O (75 mL) was added to this residue and the mixture was stirred for 1.5 h during which a white crystalline material formed. The solvent was decanted and the residue was dried under vacuum (20 °C, 2000 Pa), resulting in the desired product **3a** (6.522 g, 84%) in approximately 93% purity (see Section 2).

Mp 65–75 °C; ^{1}H NMR (Me_2SO-d_6): δ 1.28 (m, 6H), 2.52 (m, 4H), 3.48 (m, 10H); ^{13}C NMR (Me_2SO-d_6): δ 26.39, 26.76, 29.34, 33.18, 41.54, 49.24 (C-7–12), 50.66, 63.80, 70.45, 70.64, 71.12, 71.21 (C-1–6). Anal. Calcd for $C_{12}H_{28}N_2O_5 \cdot 0.5H_2O$: C, 49.81; H, 10.10; N, 9.68. Found: C, 49.60; H, 9.66; N, 9.57. Compound **3a** was used in the next step without further purification.

3.3. 1-(1-Deoxy-D-galactitol-1-ylamino)-6-aminohexane (3b)

A similar procedure as described for **3a** was applied, employing **1** (14.37 g, 0.124 mol) and D-galactose (5.00 g, 0.0278 mol). Compound **3b** (6.483 g, 83%) was obtained as a white powder in approximately 93% purity (see Section 2).

Mp 120–138 °C, ^{1}H NMR (Me_2SO-d_6): δ 1.27 (m, 6H), 2.51 (m, 4H), 3.19 (m, 10H). ^{13}C NMR (Me_2SO-d_6): δ 26.44, 26.82, 29.60, 33.28, 41.59, 49.40 (C-7–12), 53.17, 63.15, 68.30, 69.49, 70.09, 71.81 (C-1–6). Anal. Calcd for $C_{12}H_{28}N_2O_5 \cdot H_2O$: C, 48.30; H, 10.13; N, 9.39. Found: C, 49.25; H, 10.45; N, 9.17. Compound **3b** was used in the next step without further purification.

3.4. 1-(1-Deoxy-D-galactitol-1-ylamino)-6-(1-deoxy-D-glucitol-1-ylamino)hexane (4a)

Compound **3a** (5.96 g, 0.0213 mol) and D-galactose (3.99 g, 0.0221 mol) were dissolved in MeOH (160 mL) and water (40 mL), respectively, mixed in the autoclave reactor and wet Pd on carbon (5%, 6 g) was added. When a reaction temperature of 40 °C was reached, the hydrogen pressure was set at 4 MPa to start the reduction. After 4.5 h, the reaction was stopped by releasing the hydrogen pressure and cooling down the contents to room temperature. The catalyst was filtered off and the solvents were partly evaporated under reduced pressure (40 °C, 7000 Pa). During this procedure, a white solid crystallized out, which was filtered off and dried (0.67 g, 0.0015 mol, 7%). This component was identified as the symmetric bolaform amphiphile **2b**. The desired compound, **4a**, was obtained from the filtrate by partly evaporating the solvent under reduced pressure (2500 Pa, 40 °C), leading to the formation of a white powder. Compound **4a** was isolated by filtration and obtained in 48% yield (4.54 g).

Compound **4a**: mp 153–156 °C; $[\alpha]_D^{25}$ −8.0° (*c* 0.61, water); ^{1}H NMR (D_2O): δ 1.23 (m, 4H), 1.41 (m, 4H), 2.54 (m, 4H), 2.73 (m, 4H), 3.55 (m, 12H); ^{13}C NMR (Me_2SO-d_6, 50 °C): δ 26.74, 29.15, 29.27, 49.23 (C-7–12), 50.56, 53.00, 63.13, 63.78, 68.11, 69.43, 70.04, 70.40, 70.61, 71.00, 71.20, 71.71 (C-1–6 and C-13–18). Anal. Calcd for $C_{18}H_{40}N_2O_{10} \cdot H_2O$: C, 46.74; H, 9.15; N, 6.06. Found: C, 46.98; H, 9.19; N, 6.09.

Compound **2b**: mp 197–198 °C; ^{1}H NMR (D_2O): δ 1.47 (m, 4H), 1.62 (m, 4H) 2.75 (m, 4H), 2.93 (m, 4H), 3.82 (m, 8H), 4.08 (m, 4H); ^{13}C NMR (Me_2SO-d_6, 60 °C): δ 26.55, 29.37, 49.14 (C-7–12), 52.82, 63.11, 68.42, 69.78, 70.17, 71.83 (C-1–6 and C-13–18). Anal. Calcd for $C_{18}H_{40}N_2O_{10}$: C, 48.64; H, 9.07; N, 6.30. Found: C, 48.64; H, 9.17; N, 6.14.

3.5. 1-(1-Deoxy-D-mannitol-1-ylamino)-6-(1-deoxy-D-glucitol-1-ylamino)hexane (4b)

A similar procedure was applied as described for **4a**. Compound **3a** (8.41 g, 0.030 mol) and D-mannose (5.42 g, 0.030 mol) were dissolved in MeOH (170 mL) and water (90 mL), respectively, mixed in the reactor and wet Pd on carbon catalyst (5%, 6 g) was added. The desired compound **4b** was isolated as a white powder (5.20 g, 39%). By-product **2c** was obtained in 6% yield (0.83 g).

Compound **4b**: mp 135–142 °C; $[\alpha]_D^{25}$ −4.4° (*c* 0.61, water); ^{1}H NMR (D_2O): δ 1.23 (m, 4H), 1.40 (m, 4H), 2.56 (m, 6H), 2.86 (m, 2H), 3.63 (m, 12H); ^{13}C NMR (Me_2SO-d_6, 50 °C): δ 26.68, 28.91, 49.02 (C-7–12), 50.57, 52.83, 63.77, 63.99, 68.56, 70.01, 70.45, 70.62, 70.90, 71.22, 72.17 (C-1–6 and C-13–18). Anal. Calcd for $C_{18}H_{40}N_2O_{10} \cdot 0.5H_2O$: C, 47.67; H, 9.11; N, 6.18. Found: C, 47.63; H, 9.29; N, 6.27.

Compound **2c**: mp 193–194 °C; ^{1}H NMR (D_2O, 60 °C): δ 1.56 (m, 4H), 1.71 (m, 4H), 2.83 (m, 6H), 3.10 (m, 2H), 3.97 (m, 12H); ^{13}C NMR (Me_2SO-d_6): δ 26.52, 29.29, 49.06 (C-7–12), 52.82, 63.71, 68.95, 70.18, 71.28, 72.21 (C-1–6 and C-13–18). Anal. Calcd for $C_{18}H_{40}N_2O_{10}$: C, 48.64; H, 9.07; N, 6.30. Found: C, 48.64; H, 9.16; N, 6.19.

3.6. 1-(1-Deoxy-D-galactitol-1-ylamino)-6-(1-deoxy-D-mannitol-1-ylamino)hexane (4c)

A similar procedure was applied as described for **4a**. Compound **3b** (3.51 g, 0.0125 mol) and D-mannose (2.28 g, 0.0127 mol) were dissolved in MeOH (170 mL)

and water (90 mL), respectively, mixed in the reactor and wet Pd on carbon catalyst (5%, 6 g) was added. After reaction, the catalyst was filtered off and washed several times with hot water. The combined solvent fractions were (partly) evaporated under reduced pressure (40 °C, 2500 Pa), during which a white product crystallized out. Isolation gave 4.03 g (72%) of compound **4c**.

Mp 180–182 °C; $[\alpha]_D^{25}$ −3.7° (*c* 0.61, water); ^{1}H NMR (D_2O): δ 1.52 (m, 4H), 1.69 (m, 4H), 2.81 (m, 6H), 2.94 (m, 2H), 3.94 (m, 12H); ^{13}C NMR (Me_2SO-d_6, 50 °C): δ 26.60, 29.32, 29.40, 49.13, 49.19 (C-7–12), 52.90, 63.11, 63.79, 68.37, 68.93, 69.69, 70.15, 71.26, 71.82, 72.23 (C-1–6 and C-13–18). Anal. Calcd for $C_{18}H_{40}N_2O_{10}\cdot H_2O$: C, 46.72; H, 9.15; N, 6.06. Found: C, 46.54; H, 9.40; N, 6.05.

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