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New chiral polyfunctional cyclobutane derivatives from (−)-verbenone: possible surfactant behaviour

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ABSTRACT

New enantiopure cyclobutane derivatives have been synthesized from a chiral precursor derived from (−)-verbenone. The cyclobutane moiety acts as a chiral platform to afford a γ-amino acid function in a branched side-chain containing an additional stereogenic centre as well as additional C_6 or C_{16}-alkyl chains linked to the ring by means of an amine or an amide function. One of these compounds, obtained as a 1:2 mixture with its TFA salt has been investigated, suggesting behaviour as a good surfactant and its critical micellar concentration has been determined.

1. Introduction

Surfactants constitute one of the most commonly used groups of molecules. Their applications range from detergents to cosmetics, drug and food additives, and more recently have been applied in drug delivery systems. Some of them are useful in industrial processes such as those related with petrochemistry, chromatography and catalysis among others. Research is currently underway in the fields of high technology such as microelectronics and biotechnology, and also in biomedicine.[1]

Surfactants are 'surface active agents'. This term is used to describe those molecules that tend to diminish the superficial tension of an interface, namely water-air or fat-water. Their structure always implies having differentiated parts of the molecule with opposite solubility, usually an alkyl chain, which is soluble in non polar solvents (hydrophobic part), and a functional group that has a high affinity for polar solvents (hydrophilic part). These molecules in addition to adsorption also show self-aggregation. Classically, the maximum adsorption is achieved around the same concentration at which aggregates form in the bulk solution. The surface tension, which is related to the amount of adsorbed material through the Gibbs adsorption isotherm, tends to level above the critical micellar concentration because monomer activity tends to remain constant.

Amino acid based surfactants are of importance[2] due to their good levels of biodegradability and biocompatibility.[3] The combination of amino acids or peptides with hydrocarbon chains of variable length has given rise to a variety of compounds with an amphiphilic structure and with good surfactant properties. Most of the examples use natural α-amino acids.

Another important aspect is chirality in the surfactants. This issue has been exploited especially for their use as templates in the synthesis of silica materials,[4] as deracemization agents[5] and in chiral electromigration chromatography techniques[6] among others. In the case of amino acid based surfactants, chirality is directly related to some of their physicochemical and biological properties.

Our group has experience in the synthesis and structural studies of enantiopure cyclobutane containing amino acids and peptides, where the cyclobutane ring has a role as an element of constraint. Starting from chiral pool precursors such as (−)-verbenone and (−)-α-pinene, enantiopure building blocks[7] have been prepared and used in the synthesis of several derivatives including amino ethers with analgesic activity,[8] α-dehydroamino acids[9] and different types of unnatural saturated amino acids.[10] From some of these scaffolds, a wide variety of products have been synthesized such as: β-peptides,[11] γ-peptides,[12] γ-lactams and cyclobutyl GABA analogues,[13] hybrid peptides with cell-uptake properties[14] and C_3-symmetric dendrimers.[15] Some of these compounds aggregate giving vesicles[14] or show properties as organogelators.[15]

Herein we report on the stereoselective synthesis of two types of chiral cyclobutane containing γ-amino acids in which the cyclobutane ring is not a part of an amino acid main skeleton but acts as a chiral platform bearing the appropriate functional groups and side-chains. These include a C_{16}-alkyl chain that, jointly with the gem-dimethyl group of the cyclobutane, confers hydrophobicity to the molecule. Both amino acids differ in that the chain is linked to the cyclobutane moiety by means of an amine or an amide function (Chart 1). The physicochemical characterization and

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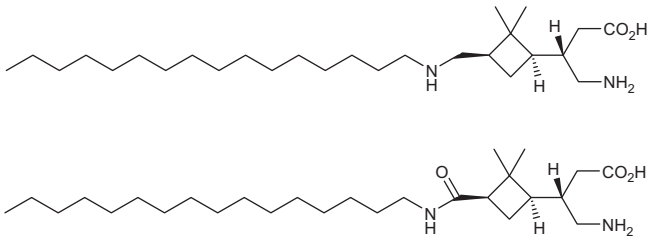


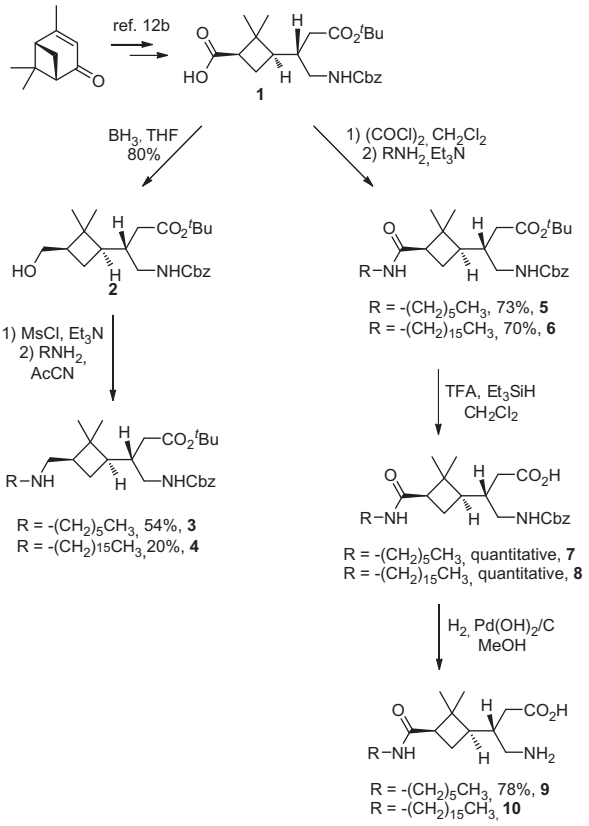
Chart 1. Types of surfactants envisioned.

properties of this new class of surfactants were investigated and some results are reported and discussed herein.

2. Results and discussion

2.1. Synthesis

The two types of amino acid derivatives were prepared through divergent synthetic routes starting from the common chiral precursor **1**, which is a γ,ε-amino diacid that has previously been synthesized in our laboratory from (−)-verbenone[12b] (Scheme 1). This compound presents a side-chain containing an orthogonally protected γ-amino acid and bearing an additional stereogenic centre with a determined absolute configuration at the β-carbonyl position. Moreover, the carboxyl group can be transformed into a functional group suitable to introduce the alkyl chain. An amine and an amide, respectively, were envisioned for this purpose. In the former case, hexadecylamine was reacted, via an S_N2 mechanism, with an appropriate derivative of the primary alcohol resulting from the reduction of the carboxylic acid. In the second case, hexadecylamine was coupled with **1** via the formation of an acid chloride.



Scheme 1.

Prior to the synthesis of the target molecules, a model system with a hydrophobic alkyl chain of only six carbon atoms was synthesized to check the viability of both routes. In order to obtain the amine substituted model compound **3**, a three step sequence was carried out (Scheme 1). First of all, the carboxylic acid was reduced to an alcohol by means of BH_3 in THF at reflux for 24 h to give **2** in 80% yield. The alcohol in **2** was then converted into a mesylate using mesyl chloride in CH_2Cl_2 in the presence of triethylamine. This mesylate was used directly in the following step without purification. Next, it was refluxed with hexylamine in acetonitrile to afford diprotected amino acid **3** in 57% yield over two steps. The same procedure was applied to prepare compound **4**, except for using hexadecylamine instead of hexylamine, although in this case the yield of the last two steps dropped to 20%. This could be related to the steric hindrance that the *gem*-dimethyl substitution in the cyclobutane ring confers to the molecule. Realizing that the yield in the target product was very poor and that larger quantities of material were needed to carry out the surfactant physico-chemical tests, this synthetic route was not useful for our purposes and, therefore, we decided to focus our efforts on the synthesis of amide derivatives **5** and **6**.

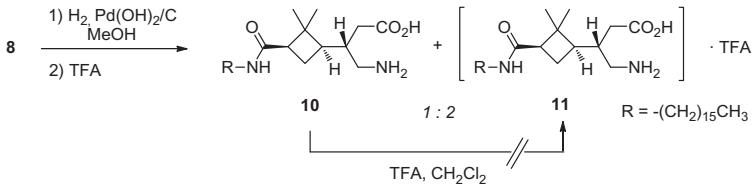
The route started with compound **1**, which was subjected to carboxylic acid activation as an acyl chloride using oxalyl chloride, to then couple the resulting intermediate with hexylamine, as a model reagent, to give compound **5** in 73% yield. When the same procedure was applied using hexadecylamine instead of the model amine, product **6** was obtained in 70% yield. As expected, the yields were higher than in the first synthetic route due to the less severe steric requirements of the coupling reaction with respect to the second order substitution process.

The model compound **5** was transformed into amphiphile **9** to check the feasibility of the synthesis. Selective removal of *tert*-butyl ester was carried out using trifluoroacetic acid (TFA) in the presence of triethylsilane in dichloromethane, with acid **7** being obtained quantitatively. Next, catalytic hydrogenation of the benzyl carbamate in the presence of $Pd(OH)_2$ in MeOH resulted in compound **9** in 78% yield.

The same procedure was applied to the synthesis of amphiphile **10**, starting from fully protected amino acid **6**. Deprotection of the carboxyl group was accomplished with TFA to yield **8** in quantitative yield. Next, hydrogenolysis of the benzyl carbamate led to the formation of what was expected to be exclusively the free γ-amino acid **10**. Nevertheless, high resolution mass spectrometry in positive and negative mode and elemental analysis of this sample (see Section 4 for details) revealed the presence of not only **10** but also salt **11** (Scheme 2), which would come from some of the TFA left in the hydrogenation step of **8**. The ratio of **10**:**11** was calculated to be 0.35:0.65. Attempts to eliminate residual acid after this step by lyophilization were unsuccessful. It is noteworthy that the much lower molecular weight of TFA compared with **7** favours the salt formation even in the presence of a very small amount of TFA. We attempted to convert the mixture into **11** by stirring it in dichloromethane in the presence of trifluoroacetic acid, but the amount of **11** was never increased suggesting that the mixture composition corresponds to the acid–base equilibrium ratio (Scheme 2).

2.2. Study of the mixture 10 + 11 as a surfactant

A preliminary test was carried out to evaluate the solubility of the obtained mixture **10** + **11** in water. The first assays determined that when an aqueous 2.5×10^{-4} M solution was prepared and shaken, foam appeared. This is a first sign of good behaviour as a surfactant.



Scheme 2.

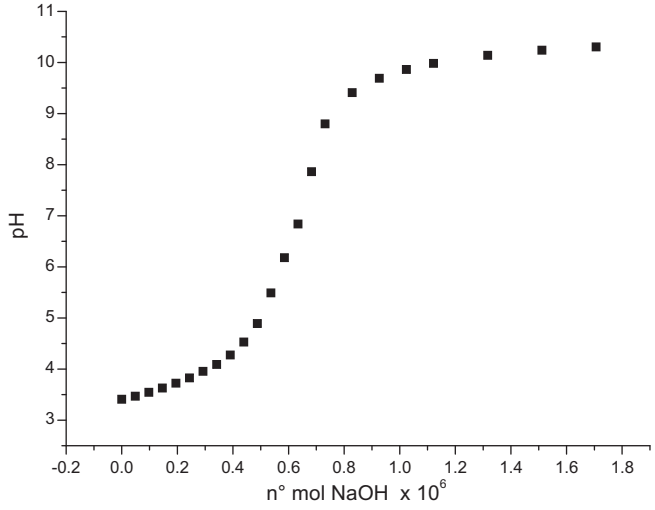


Figure 1. Titration of the surfactant mixture **10** + **11** with NaOH.

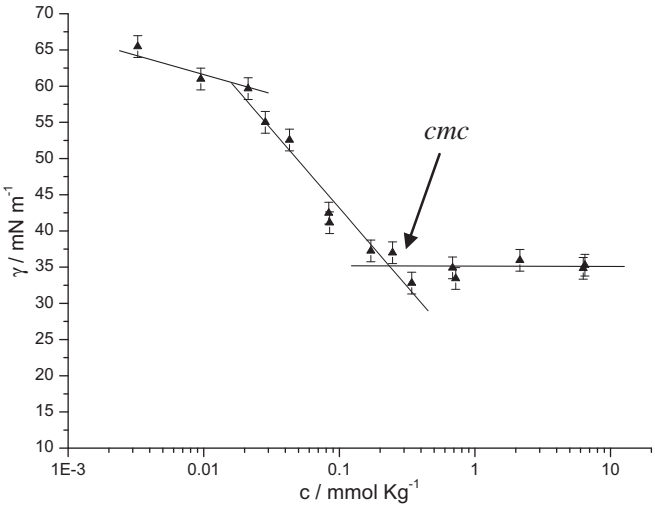


Figure 2. Plot of surface tension as a function of surfactant concentration for the **10** + **11** mixture in water at 25 °C.

Next, pH measurements were performed to gain more insight about the sample that contained the mixture **10** + **11**. At first, 1.002 g of a 0.0514 wt% solution of the surfactant was titrated with a 0.0039 wt% NaOH solution (~1 mM) under a nitrogen atmosphere to avoid carbonation. The inflection point would correspond to the titration of the carboxylic acid proton of trifluoroacetate salt **11** (6.5×10^{-6} mol of NaOH added). Taking into account the different molecular weights of the two products and the total mass of the titrated mixture, the results are in good agreement with the molar ratio for the two species inferred by the elemental analysis (Fig. 1).

The surface tension (γ) of small volumes of the surfactant mixture (**10** + **11**) was measured using a home-made pendant drop tensiometer.[16] Surface tension was followed as a function of time until equilibrium was reached (no appreciable variation of γ), which occurred within 5–6 h from sample preparation. Care was taken to ensure a saturated humidity atmosphere to prevent evaporation; the temperature was maintained at 25.0 ± 0.5 °C. The surface tension of the mixture decreased progressively upon increasing concentration (Fig. 2) until a break above which it almost leveled to a constant value (~35 mN m^{-1}). The break occurred at a concentration of 2.4×10^{-4} mol kg^{-1}, as determined from the intersection of the two fitting straight lines in the plot of γ versus log *C*, which corresponds to the critical micellar concentration (*cmc*) of the mixture. Concentrations were calculated while taking into account the weighted average molar mass of the mixture 0.35:0.65 of **10** + **11** (i.e., 526.83 g mol^{-1}). This value of *cmc* is in good agreement with the value obtained in the preliminary foaming experiment, where the maximum foaming is usually observed just above the value of *cmc*.[17] This value of *cmc*, 2.4×10^{-4} mol kg^{-1}, is in the expected range of an ionic surfactant bearing a C_{16}-alkyl chain,[18] but appears to be high if it is compared with zwitterionic surfactants of a similar hydrophobic chain length. For instance, $C_{14}H_{25}N^{+}(CH_3)_2CH_2COO^{-}$ has a *cmc* value of 2.2×10^{-4} mol kg^{-1} while $C_{14}H_{25}N^{+}(CH_3)_2CH_2SO_3^{-}$ has a *cmc* value of 3.2×10^{-4} mol kg^{-1}.[19] Based on the hydrophobicity of the hydrocarbon chain and the presence of the cyclobutane group between the amide and the terminal zwitterionic group, one would have expected this product to have a lower *cmc* value; this could be related to a significant hydration of the amide group.

This mixture also presents the other characteristic to be considered as a surfactant, that is, self-aggregation. This is shown by the significant X-ray scattering observed in 19 mmol kg^{-1} solutions, well above the *cmc* as observed from the above results. The experimental scattering pattern obtained at 25 °C is shown in Figure 3 as a function of scattering vector modulus. There is an apparent increase of intensity at small *q* and a bump at intermediate *q*. The fitting of several models did not result in perfect fitting, partly because of low signal to noise ratio due to the low concentration. However, a reasonable fitting was obtained using oligolamellar structures with a repetition distance of 3.7 nm and a few (2.5) correlated lamellae and using a core-shell ribbon model with a persistence length longer than 100 nm and width of 40 nm. Both models give a similar fitting quality, in part because at a local level both correspond to flat lamellae. Both models result in similar hydrophobic thicknesses that would correspond to only 1.2 nm, implying the strong interdigitation of the hydrophobic chains and an area per molecule of 1.2 nm^2. This value of area per molecule would be reasonable for the polar head to comprise of not only the zwitterionic group, but also the amide group, which is in agreement with the previous observation of low hydrophobicity introduced by the cyclobutane group. Whether the observed break in the surface tension plot corresponds to a monomer to a micelle or

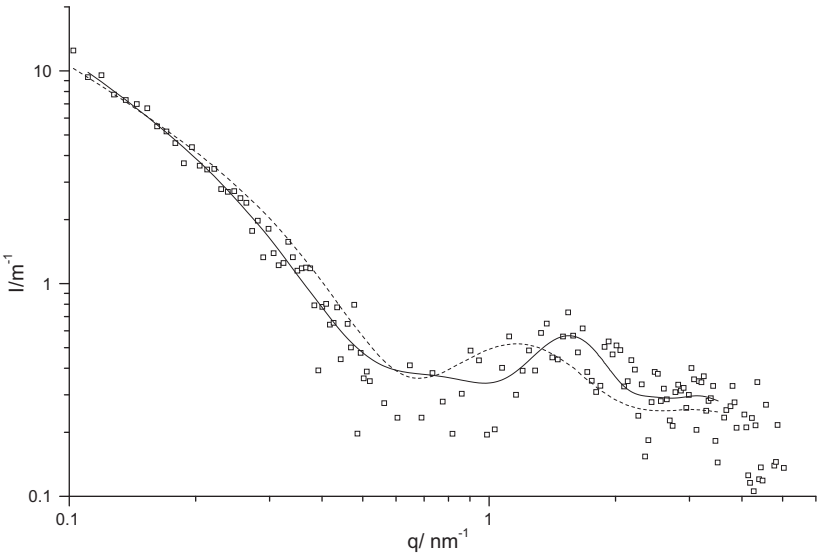


Figure 3. SAXS intensity corresponding to 19 mmol kg^{-1} of **10** + **11** mixture in water at 25 °C. The full line corresponds to the best fit result for oligolamellar structures and the dashed line corresponds to a core-shell ribbon model. From q = 0.5 nm^{-1} onward the experimental points have been adjacent averaged to reduce noise.

monomer to a vesicle transition cannot be decided with the present data and is out of the scope of the present article.

3. Conclusion

Several new enantiopure cyclobutane derivatives containing a γ-amino acid function in a side-chain and additional C_6 or C_{16}-alkyl chains have been synthesized from a chiral precursor prepared in turn from (−)-verbenone. The introduction of alkyl substituents has been achieved more efficiently by means of amide formation instead of amine alkylation involving a S_N2 process. This result is explained by the severe steric hindrance imposed by the gem-dimethyl group on the cyclobutane moiety. The basicity of the primary amine in the γ-amino acid function and that of the amide led to the unexpected formation of a TFA salt obtained jointly with the free amine in an approximate 2:1 ratio that presumably corresponds to the equilibrium ratio. Studies on this mixture suggest that it behaves as an efficient surfactant, with the critical micellar concentration being 2.4 × 10^{-4} mol kg^{-1}. At moderate concentrations, the presence of oligolamellar structures has been observed.

4. Experimental

4.1. (3*S*)-*tert*-Butyl-4-benzyloxycarbonylamino-3-((1′*R*,3′*R*)-3′-hydroxymethyl-2′,2′-dimethylcyclobutyl) butanoate 2

To a solution of acid **1** (111 mg, 0.3 mmol) in anhydrous THF (0.5 mL) was added a 1 M solution of BH_3 in THF (0.5 mL, 0.4 mmol, 1.5 equiv). The mixture was heated at reflux under a nitrogen atmosphere for 24 h. Excess hydride was eliminated by the slow addition of methanol (1 mL) and water (3 mL). The resultant solution was extracted with dichloromethane and the combined extracts were dried over $MgSO_4$. Solvents were removed at reduced pressure, and the residue was chromatographed (ethyl acetate/hexane 1:1) to provide alcohol **2** as a colourless oil (85.4 g, 80% yield). $[\alpha]_D$ = −18.6 (*c* 1.1, $CHCl_3$); IR (ATR): 3339, 2952, 1789, 1520, 1455, 1367 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.02 (s, 3H, C*H*$_3$), 1.16 (s, 3H, C*H*$_3$), 1.44 (s, 9H, ^{t}Bu), 1.61–1.76 (m, 1H), 1.78–1.90 (m, 1H), 1.96–2.09 (complex absorption, 4H), 2.19–2.30 (m, 1H), 2.90–3.05 (m, 1H), 3.18–3.31 (m, 1H), 3.49–3.65 (ca., 2H), 5.03–5.29 (ca., 3H, C*H*$_2$Bn, N*H*), 7.30–7.41 (ca., 5H, H_{Ar}); ^{13}C NMR (90 MHz, $CDCl_3$): δ 16.0, 24.0, 25.37, 28.1, 31.7, 37.3, 39.8, 42.7, 43.9, 44.0, 63.3(*C*H$_2$OH), 66.5, 80.9, 128.1, 128.4, 136.7, 156.5, 172.4; HRMS Calcd for $C_{23}H_{35}NNaO_5$ (M+Na)$^+$: 428.2407. Found: 428.2418.

4.2. (3*S*)-*tert*-Butyl-4-benzyloxycarbonylamino-3-((1′*R*,3′*R*)-3′-hexylaminomethyl-2′,2′-dimethyl-cyclobutyl)butanoate 3

Alcohol 2 (88 mg, 0.22 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and the resulting solution was cooled with an ice bath. Next, triethylamine (45 μL, 0.32 mmol) and mesyl chloride (22 μL, 0.28 mmol) were subsequently added and the reaction was stirred at 0 °C for 1 h. The resultant solution was extracted with dichloromethane, and the combined extracts were dried over $MgSO_4$. Solvents were removed at reduced pressure to afford a crude mesylate (100 mg, 95% yield), which was immediately used in the next step without purification. To the solution of the mesylate (100 mg, 0.21 mmol) in anhydrous CH_3CN (4 mL) under a nitrogen atmosphere were added Et_3N (40 μL, 0.32 mmol) and hexylamine (60 μL, 0.3 mmol). The mixture was stirred at reflux for 24 h. The solvent was evaporated under vacuum and diluted with saturated aqueous $NaHCO_3$ (5 mL). This was extracted with CH_2Cl_2 (3 × 5 mL) dried over $MgSO_4$ and evaporated at reduced pressure. The residue was chromatographed (ethyl acetate/hexane, 1:2 to 2:1) to afford pure 3 as a yellow oil (58 mg, 57% yield). $[\alpha]_D^{22}$ = −14.4 (c 1.2, $CHCl_3$); IR (ATR): 2925, 2856, 1719, 1514, 1455, 1366,1245 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, *J* = 71 Hz 3H, CH_3), 0.98 (s, 3H), 1.14 (s, 3H), 1.19–1.36 (ca., 10H, –CH_2–), 1.45 (s, 9H, ^{t}Bu), 1.55–1.76 (m, 1H), 1.82–2.17 (ca., 3H), 2.19–2.33 (m, 1H), 2.38–2.72 (ca., 4H), 2.90–3.07 (m, 1H), 3.16–3.37 (m, 1H), 5.03–5.26 (ca., 3H, CH_2Bn, NH), 7.31–7.43 (ca., 5H, H_{Ar}); ^{13}C NMR (90 MHz, $CDCl_3$): 14.2, 16.5, 22.9, 27.4, 28.1, 28.5, 30.1, 31.7, 32.1, 37.5, 40.3, 42.2, 43.1, 44.9, 50.5, 50.7, 66.9, 81.2, 128.5, 128.9, 137.1, 156.9, 172.7; HRMS Calcd for $C_{29}H_{48}N_2O_4$ (M+Na)$^+$: 489.3687. Found: 489.3683.

4.3. (3*S*)-*tert*-Butyl-4-benzyloxycarbonylamino-3-((1′*R*,3′*R*)-3′-hexadecylamino-methyl)-2′,2′-di-methylcyclobutyl)butanoate 4

To a solution of mesylate (65 mg, 0.13 mmol) (prepared as explained in Section 4.2) in anhydrous CH_3CN (2 mL) under a nitrogen atmosphere were added Et_3N (30 μL, 0.22 mmol) and hexadecylamine (47 mg, 0.19 mmol). The mixture was stirred at reflux for

24 h. The solvent was evaporated under vacuum and diluted with saturated aqueous $NaHCO_3$ (5 mL). This was extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$ and evaporated at reduced pressure. The residue was chromatographed (ethyl acetate/hexane, 1:4 to 2:1) to afford pure **4** as a colourless oil (25 mg, 30% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, J = 6.9 Hz 3H), 1.06 (s, 3H, CH_3), 1.19–1.36 (ca., 27H, –CH_2–, 3H, CH_3), 1.36–1.54 (ca., 11H, ^{t}Bu, –CH_2–), 1.88–2.11 (ca., 5H), 2.23–2.36 (ca., 1H), 2.48–2.69 (ca., 5H), 2.77–3.12 (c.a, 2H), 3.18–3.29 (ca., 1H), 4.89–5.38 (ca., 3H, CH_2Bn, NH), 7.31–7.43 (ca., 5H, *H*Ar). LMRS (ESI$^+$, *m*/*z*, %) Calcd for $C_{38}H_{66}N_2NaO_5$ (M+Na)$^+$: 637.5. Found: 637.1.

4.4. (3*S*)-*tert*-Butyl-4-benzyloxycarbonylamino-3-((1′*R*,3′*R*)-3′-hexylcarbamoyl-2′,2′-dimethyl-cyclobutyl)butanoate 5

To a solution of acid **1** (370 mg, 0.88 mmol) in anhydrous CH_2Cl_2, Et_3N (0.15 mL, 1.06 mmol), oxalyl chloride (0.53 mL, 1.06 mmol) and 3 drops of DMF, were subsequently added. The mixture was stirred at room temperature for 2 h. Next, hexylamine (0.13 mL, 0.97 mmol) was added and the resultant solution was stirred at room temperature for 8 h. The solvents were removed under reduced pressure, the crude of the reaction was extracted with dichloromethane (4 × 10 mL) and the organic extracts were dried over magnesium sulfate. The residue was chromatographed (ethyl acetate/hexane, 1:2 to 2:1) to afford pure **5** as a colourless oil (123 mg, 73% yield). $[\alpha]_D^{22}$ = +5.1 (*c* 0.9, $CHCl_3$); IR (ATR): 3308, 2928, 1706, 1647, 1528, 1455, 1366 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, J = 7.0 Hz 3H, CH_3), 1.01 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.31–1.38 (ca., –CH_2–, 5H), 1.45 (s, 9H, ^{t}Bu), 1.50–1.55 (m, 1H), 1.65–1.84 (m, 2H), 1.88–2.11 (ca., 4H), 2.16–2.31 (m, 1H), 2.38–2.55 (m, 1H), 2.98–3.14 (m, 1H), 3.18–3.38 (ca., 3H), 5.04–5.33 (ca., 3H, CH_2Bn, NH), 7.32–7.42 (ca., 5H, *H*Ar); ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.2, 17.0, 22.9, 24.5, 26.8, 28.5, 30.1, 31.7, 31.8, 37.6, 39.7, 42.8, 44.2, 47.6, 53.8, 67.0, 81.2, 128.2, 128.9, 137.1, 156.9, 171.6, 172.5; HRMS Calcd for $C_{29}H_{46}N_2NaO_5$ (M+Na)$^+$: 525.3299. Found: 525.3304.

4.5. (3*S*)-*tert*-Butyl-4-benzyloxycarbonylamino-3-((1′*R*,3′*R*)-3′-hexadecylcarbamoyl-2′,2′-di-methylcyclobutyl)butanoate 6

To a solution of acid **1** (310 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (15 mL), Et_3N (0.15 mL, 1.08 mmol), oxalyl chloride (0.44 mL, 0.88 mmol) and 3 drops of DMF, were subsequently added. The mixture was stirred at room temperature for 2 h. Next, hexadecylamine (230 mg, 0.95 mmol) was added and the resultant solution was stirred at room temperature for 8 h. Solvents were removed under reduced pressure, the crude reaction was extracted with dichloromethane (4 × 10 mL) and the organic extracts were dried over $MgSO_4$. The residue was chromatographed (ethyl acetate/hexane, 1:1) to afford pure **6** as a colourless oil (330 mg, 70% yield). $[\alpha]_D^{22}$ = +1.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz 3H, CH_3), 1.00 (s, 3H, CH_3), 1.13–1.37 (ca., 28H, –CH_2–, 3H, CH_3), 1.44 (s, 9H, ^{t}Bu), 1.68–2.08 (ca., 5H), 2.13–2.33 (m, 1H), 2.38–2.53 (m, 1H), 2.95–3.13 (m, 1H), 3.16–3.44 (ca., 3H), 5.00–5.58 (ca., 4H, CH_2Bn, N*H*), 7.30–7.41 (ca., 5H, HAr); ^{13}C NMR (90 MHz, $CDCl_3$): 14.5, 17.0, 23.1, 27.3, 28.5, 29.7, 30.1, 30.2, 31.7, 32.3, 37.6, 39.7, 42.8, 44.6, 67.0, 81.3, 128.5, 128.9, 137.1, 156.9, 171.6, 172.4. HRMS Calcd for $C_{39}H_{66}N_2NaO_5$ (M+Na)$^+$: 665.4864. Found: 665.4851.

4.6. (3*S*)-4-Benzyloxycarbonylamino-3-((1′*R*,3′*R*)-3′-hexylcarbamoyl-2′,2′-dimethyl-cyclobutyl)-butanoic acid 7

A mixture containing compound **5** (66.2 mg, 0.13 mmol), trifluoroacetic acid (0.13 mL, 1.69 mmol) and triethyl silane (50 μL, 0.31 mmol) in anhydrous dichloromethane (2 mL) was stirred at room temperature for 18 h. The solvent was evaporated and the excess trifluoroacetic acid was removed by lyophilization to afford acid **7** as a yellow oil (79 mg, quantitative yield). $[\alpha]_D^{22}$ = +15.4 (*c* 1.3, $CHCl_3$); IR (ATR): 3322, 2928, 1703, 1638, 1536, 1455, 1371 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, J = 6.4 Hz 3H, CH_3), 0.99 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.29–135 (ca., 6H, –CH_2–), 1.38–1.56 (ca., 2H), 1.59–1.93 (m, 2H), 1.97–2.13 (ca., 2H), 2.17–2.36 (m, 1H), 2.37–2.56 (m, 1H), 2.81–3.43 (ca., 4H), 5.00–5.57 (ca., 4H, CH_2Bn, N*H*), 7.28–7.54 (ca., 5H, H_{Ar}); ^{13}C NMR (90 MHz, $CDCl_3$): 14.4, 17.1, 22.9, 24.1, 26.9, 30.1, 31.6, 31.8, 35.9, 37.6, 39.8, 42.8, 44.0, 47.6, 67.3, 128.7, 128.9, 136.7, 157.4, 172.0, 177.3. HRMS Calcd for $C_{29}H_{38}N_2NaO_5$ (M+Na)$^+$: 469.2673. Found: 469.2674.

4.7. (3*S*)-4-Benzyloxycarbonylamino-3-((1′*R*,3′*R*)-3′-hexadecylcarbamoyl-2′,2′-di-methyl-cyclobutyl)butanoic acid 8

A mixture containing compound **6** (220 mg, 0.34 mmol), trifluoroacetic acid (0.34 mL, 4.41 mmol) and triethyl silane (0.14 mL, 0.88 mmol) in anhydrous dichloromethane (4 mL) was stirred at room temperature for 18 h. The solvent was evaporated and the excess trifluoroacetic acid was removed by lyophilization to afford acid **8** as a colourless oil (200 mg, quantitative yield). $[\alpha]_D^{22}$ = +14.2 (*c* 1.4, $CHCl_3$); IR (ATR): 3320, 2918–2850, 1705, 1636, 1532, 1466, 1160 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, J = 7.1 Hz 3H, CH_3), 0.95 (s, 3H, CH_3), 1.25–1.40 (ca., 30H, –CH_2–, 3H, CH_3), 1.42–1.62 (m, 1H), 1.63–1.94 (m, 1H), 1.95–2.40 (ca., 3H), 2.44–2.67 (m, 1H), 2.84–3.40 (ca., 4H), 5.00–5.48 (ca., 3H, CH_2Bn, N*H*), 5.63–5.83 (broad, 1H, N*H*) 7.30–7.47 (ca., 5H, H_{Ar});^{13}C NMR (90 MHz, $CDCl_3$): 14.5, 17.1, 23.1, 27.3, 29.8, 30.1, 31.5, 32.3, 35.9, 37.7, 40.1, 42.4, 43.1, 47.5, 67.4, 128.5, 128.9, 136.7, 157.5, 172.4, 176.63. HRMS Calcd for $C_{35}H_{58}N_2NaO_5$ (M+Na)$^+$: 609.4238. Found: 609.4249.

4.8. (3*S*)-4-Amino-3-((1′*R*,3′*R*)-3′-hexylcarbamoyl-2′,2′-dimethylcyclobutyl)butanoic acid, 9

Compound **7** (44.8 mg, 0.10 mmol) in methanol (5 mL) was hydrogenated under 5 atmospheres of pressure in the presence of 30% $Pd(OH)_2$/C (13 mg, 2% Pd in weight) overnight. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure to provide **9** (24.4 mg, 78% yield) as a colourless oil. $[\alpha]_D^{22}$ = +5.3 (*c* 1, CH_3OH); ^{1}H NMR (250 MHz, CD_3OD): δ 0.93 (t, J = 6.8 Hz 3H, CH_3), 1.00 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.33–135 (ca., –CH_2–, 6H), 1.43–1.61 (ca., 2H), 1.84–2.04 (ca., 3H), 2.11–2.38 (m, 1H), 2.39–2.65 (m, 1H), 2.66–3.01 (ca., 2H), 3.03–3.27 (ca., 2H), 3.29–3.34 (m, 1H); ^{13}C NMR (90 MHz, CD_3OD):13.4, 16.3, 18.4, 22.6, 22.81, 26.7, 29.5, 30.6, 31.7, 35.9, 39.3, 42.5, 44.2, 46.4, 50.5, 172.7. HRMS Calcd for $C_{17}H_{32}N_2NaO_3$ (M+Na)$^+$: 335.2305. Found: 335.2310.

4.9. (3*S*)-4-Amino-3-((1′*R*,3′*R*)-3′-hexadecylcarbamoyl-2′,2′-dimethylcyclobutyl) butanoic acid and (3*S*)-3-carboxy-2-((1*R*,3*R*)-3-hexadecylcarbamoyl-2′,2′-dimethylcyclobutyl)propan-1-aminium trifluoroacetate 10 and 11

Compound **8** (200 mg, 0.34 mmol) in methanol (10 mL) was hydrogenated under 5 atmospheres of pressure in the presence of 30% $Pd(OH)_2$/C (60 mg, 2% Pd in weight) overnight. The reaction mixture was filtered through Celite® and the solvent was removed under reduced pressure to provide amine **10** (180 mg) as a white solid and its corresponding salt **11**. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, J = 7.1 Hz 3H, CH_3), 0.97 (s, 3H, CH_3), 1.06–1.41 (ca., 27H, –CH_2–, 3H, CH_3), 1.59 (ca., 2H), 1.95–2.07 (ca., 3H), 2.21–2.66 (ca., 2H), 2.82–3.03 (ca., 2H), 3.10–3.32 (ca., 3H), 4.89–5.21 (broad, 2H, N*H*); ^{13}C NMR (90 MHz, CD_3OD): 13.3, 16.0, 17.72, 18.07, 22.4, 26.7, 29.1, 29.4, 29.5, 30.1, 31.5, 31.8, 39.1, 42.2, 43.1, 45.9, 50.1,

172.1. ^{13}C NMR (90 MHz, DMSO): 14.4, 17.1, 22.5, 22.9, 26.8, 28.2, 29.2, 29.5, 29.7, 31.2, 31.7, 34.4, 37.9, 38.8, 42.0, 43.0, 46.1, 100.0, 170.4, 173.8. HRMS Calcd for **10**: $C_{27}H_{51}N_2O_3$ $(M-1)^-$: 451.3905. Found: 451.3900; $C_{27}H_{53}N_2O_3$ $(M+1)^+$: 453.4051; Found: 453.4060. HRMS Calcd for **11**: $C_{29}H_{52}F_3N_2O_5$ $(M-1)^-$: 565.3907. Found: 565.3839; $C_{27}H_{51}N_2O_3$ $(M-C_2F_3O_2-2)^-$: 451.3905. Found: 451.3900. $C_{27}H_{53}N_2O_3$ $(M-C_2F_3O_2)^+$: 453.4051; Found: 453.4060. Anal. calcd for 0.35:0.65 (**10** + **11**) mixture: C, 64.52; N, 10.07%; H, 5.32%. Found: C, 64.47; N, 10.58%; H, 5.01%.

4.10. SAXS measurements

Small-angle X-ray Scattering (SAXS) measurements were carried out using a S3-MICRO (Hecus X-ray systems GMBH Graz, Austria) coupled to a GENIX-Fox 3D X-ray source (Xenocs, Grenoble), which provides a detector focussed X-ray beam with $\lambda = 0.1542$ nm Cu Kα-line with more than 97% purity and less than 0.3% K_β. Transmitted scattering was detected using a PSD 50 Hecus. The temperature was controlled by means of a Peltier TCCS-3 Hecus. The samples were inserted in a flow-through glass capillary 1 mm diameter with 20 μm wall thickness. The SAXS and WAXS scattering curves are shown as a function of the scattering vector modulus:

$$q = \frac{4\pi}{\lambda} \cdot \sin\frac{\theta}{2}$$

where, θ is the scattering angle. The q values with our setup ranged from 0.08 nm^{-1} to 6.0 nm^{-1}. The system scattering vector was calibrated by measuring a standard silver behenate sample. Since the use of a detector focused a small beam (300 × 400 μm full width at half maximum), the scattering curves are mainly smeared by the detector width. This mainly produces a widening of the peaks without a noticeable effect on the peak position. The scattering curves for liquid samples have been background subtracted and put in absolute scale by comparison with a water sample scattering.[20,21]

The instrumentally smeared experimental SAXS curves were fitted to numerically smeared models for beam size and detector width effects. A least square routine based on the Levenberg–Marquardt scheme was used. A model of core-shell ribbons (high aspect ratio ellipsoidal section cylinders[22]) and a model of bilayers based on the Modified Caillé Gaussian scheme were used.[23,24]

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