Cyclobutane-Containing Scaffolds as Useful Intermediates in the Stereoselective Synthesis of Suitable Candidates for Biomedical Purposes: Surfactants, Gelators and Metal Cation Ligands

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Abstract: Efficient and versatile synthetic methodologies are reported for the preparation of products that are suitable candidates to be used as surfactants, gelators for hydroxylic solvents or metal cation ligands, with potential use in several fields including biomedical applications. The common structural feature of all the synthesized products is the presence of a cis or trans-1,2- or cis-1,3-difunctionalized cyclobutane ring. In the two first cases, the key intermediates including enantiomerically pure 1,3-diamines and 1,3-amino alcohols have been prepared from β-amino acid derivatives obtained, in turn, from a chiral half-ester. This compound is also precursor of γ-amino esters. Furthermore, two kind of polydentate ligands have also been synthesized from a symmetric 1,5-diamine obtained from norpinic acid, which was easily prepared from commercial verbenone.

Keywords: cyclobutane; amphiphiles; surfactants; gelators; cation ligands

1. Introduction

Search for new molecules with suitable properties for biological purposes needs a rational synthetic design involving stereo- and chemoselective methodologies. Among target products, amphiphiles in general and, especially, surfactants and gelators play a key role in biomedicine. In addition, appropriate ligands to chelate cations are crucial for imaging technologies and radiopharmacy.

Amphiphiles are interesting and versatile compounds with usefulness in different fields. They can be classified in different families regarding their structure. Single head–single tail amphiphiles consist of an apolar tail and a polar head. Depending on the nature of the latter, they are classified as cationic, anionic or non-ionic amphiphiles [1]. They present a great potential for biomedical applications in targeted drug delivery systems (DDS) [1] and as non-viral vectors for gene therapy [2]. For the last purpose, cationic surfactants are especially interesting due to the fact of their properties that make them suitable to interact with DNA. Indeed, controlled DNA compaction and neutralization of their negatively charged phosphate groups is crucial to transfect into cells avoiding repulsive interactions with phospholipids in the cell membrane [3].

Otherwise, amphiphiles with properties as gelators and, in particular low–molecular-weight gelators (LMWG) are also valuable for the design and preparation of soft materials with utility in biochemical and biophysical studies [4] and applications in biomedicine, which include DDS, biosensors and tissue regeneration [5].

Imaging is nowadays a powerful tool in diagnosis and personalized medicine. In this area, contrast agents play a relevant role [6]. Many of them consist of appropriate metal complexes that must present specific requirements to assure their thermodynamic and kinetic stability to avoid metal leaching into the body. For this reason, the search for modifications in the structure of the ligands,
trying to improve the properties and the effectiveness of the corresponding complexes, is the subject of a very active interdisciplinary research [7].

Previously, we have developed efficient synthetic methodologies to prepare both 1,2- and 1,3- disubstituted cyclobutane derivatives, whose exploitation in the synthesis of several kinds of amphiphiles [8–10], organogelators producing chiral aggregates [11,12] and metal ligands [13] has been explored. The presence of the cyclobutane ring confers all these types of molecules with rigidity as well as with two stereogenic centers, the relative and absolute configurations of which can be controlled. Scheme 1 summarizes synthetic strategies to prepare some cis- and trans-1,2-cyclobutane derivatives from a chiral half-ester that is the common precursor to cis- [14] and trans-β-amino acids [15,16]. From these compounds, we synthesized peptides with properties as foldamers in solution [16–18] and/or LMWG [19,20] as well as neuropeptide Y (NPY) analogues [21]. Amino alcohols [22] and diamines [22,23] have also been prepared, some of them with application in organocatalysis [22,23]. The 1,3-diamine motif is found in natural products and also in the structure of ligands for metal catalysts. Despite the many synthetic methods described to prepare 1,2-diamine building blocks, the synthetic approaches to 1,3-diamines are more limited [24–26].

Scheme 1. Retrosynthetic strategies to prepare the target products from suitable precursors.

Concerning cis-1,3-disubstituted cyclobutane derivatives, we prepared organocatalysts [27] and other products as dendrimers [28] and cell penetrating peptides [29] starting from commercial verbenone, which provides polyfunctional chemical platforms that are highly useful scaffolds for synthetic applications.

In this article, we describe the utilization of cis- and trans-cyclobutane β-amino acids (β-CBAA) [30] in the stereoselective synthesis of novel chiral cationic surfactants and LMWG. Moreover, a new synthesis of cis-γ-CBAA derivatives is provided along with their application as synthetic precursors to anionic or non-ionic amphiphiles. Some examples are described herein to illustrate the usefulness of these methodologies (Scheme 1).
Moreover, highly rigid polydentate ligands for metal cations were synthesized as well from norpinic acid [31], which is easily obtained from verbenone (Scheme 1) or pinene. Related ligands, previously described in the literature, have formed gadolinium complexes with interesting properties as potential candidates to contrast agents for magnetic resonance imaging [32–34], or complexes with other cations of application in radiopharmacy [35] or for industrial purposes [36].

2. Results and Discussion

2.1. Amphiphiles from 1,2-Disubstituted Cyclobutane Scaffolds: Surfactants and LMWG

Scheme 1 shows two retrosynthetic strategies to prepare different families of single head–single tail amphiphiles. Cationic derivatives were synthesized from 1,3-diamines and 1,3-amino alcohols, respectively, as the immediate precursors. These compounds, in turn, were obtained from orthogonally protected cis-β-CBAA through selective transformations of the functional groups. A second synthetic route leads to the formation of cis-γ-CBAA as the key intermediates, which allows the preparation of anionic or non-ionic amphiphiles. Moreover, trans-β-CBAA, obtained through regioselective epimerization of the cis diastereomers, led to molecules which had structural features that conferred on them possible properties as organogelators (Scheme 1). Indeed, these compounds bear functional groups suitable for intermolecular hydrogen bonding and appropriate long alkyl-chains for van der Waals interactions. In addition, trans stereochemistry precludes the formation of intramolecular hydrogen bonds, thus favouring the interactions with solvents.

The synthetic route towards non-ionic or anionic amphiphiles is depicted in Scheme 2. The carboxyl group in half-ester 1 [14] was selectively reduced with diborane in tetrahydrofuran, at 0 °C, providing primary alcohol 2 in 63% yield, which was activated towards nucleophilic displacement to introduce the amino group. Thus, treatment of 2 with tosyl chloride in the presence of triethylamine (TEA), giving tosylate 3 in 77% yield, and subsequent reaction with sodium azide followed by hydrogenation in the presence of 20% Pd(OH)2 on activated charcoal as a catalyst provided amino ester 4. Reaction of this intermediate with lauryl chloride led to 5 in 51% yield (3 steps), which is representative of non-ionic amphiphiles. Moreover, deprotection of the carboxyl group, by acid cleavage of the tert-butyl ester with trifluoroacetic acid and triethylsilane in dichloromethane, afforded quantitatively 6, which would be the direct precursor of an anionic amphiphile via deprotonation of the carboxylic acid.

Scheme 2. Synthetic route towards non-ionic or anionic amphiphiles.

Scheme 3 shows the synthetic pathways to prepare cationic amphiphiles 12 and 14 and LMWG 18 and 19 from cis- and trans-CBAA, respectively. The methyl ester in precursor 7 [14] was reduced with lithium borohydride in ether to afford alcohol 8 in 75% yield. This compound was submitted to similar transformations as those described above, giving diamine 10.
Scheme 3. Synthesis of cationic amphiphiles and organogelators from cis- or trans-β-CBAA.

Separate reactions of amino alcohol 8 and diamine 10 with lauryl chloride and TEA under reflux of dichloromethane led to compounds 11 and 13, respectively, in 66–68% yield. Treatment of these products with 2 N HCl in dichloromethane allowed to obtain cationic surfactants 12 and 14 in 84% and 64%, respectively.

The synthetic route for the preparation of LMWG 16 and 17 (Scheme 3) starts with coupling of previously described trans-β-CBAA 15 [15] with dodecyl- or hexadecylamine, using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as a coupling agent in the presence of diisopropylethylamine (DIPEA) in dichloromethane, at room temperature, afforded the corresponding amides that, in separate processes, were submitted to amine deprotection by treatment with HCl followed of aqueous NaOH to provide the free amines. Further coupling with lauric or palmitic acid, under similar conditions as before, led to diamides 16 and 17, respectively, in 27–28% yield from 15. Preliminary experiments showed that these compounds are good gelators for alcohols (MeOH, EtOH, i-PrOH) with minimum gelation concentration (mgc) values 8–47 mg/mL and biocompatible EtOH–water mixtures (up to 30% water) with mgc = 10–16 mg/mL. These data differentiate these LMWG from alkyl bisamides prepared from cyclobutane-1,2-dicarboxylic acid, which were insoluble in alcohols [11], and confer these products with very interesting features for future applications.

2.2. Highly Rigid Polydentate Ligands From 1,3-disubstituted Cyclobutane Scaffolds

1,5-Diamine 19 was synthesized from previously known dimesylate 18 (Scheme 4), which had been obtained from norpinic acid [31]. The procedure was similar to that described above for the preparation of amines 4 and 10.

Tetraalkylation of diamine 19 with tert-butyl bromoacetate, in the presence of KI and DIPEA, using DMF as a solvent, afforded tetraester 20 in 26% yield. Tetraacid 21 was quantitatively obtained after treatment of 20 with 4 M HCl in dioxane.

Otherwise, cyclic or open-chain ligands bearing picolinate moieties have shown enhanced ability to coordinate metal cations making them useful for manifold applications including highly stable and
kinetically inert contrast agents [33,34]. For this reason, we decided to synthesize ligand 25 according to Scheme 4.

![Scheme 4. Synthesis of ligands from 1,3-disubstituted cyclobutane scaffolds.](image)

Methyl 6-formylpicolinate, 22 [37], was submitted to reductive amination by treatment with 0.5 equivalents of diamine 19 and subsequent in situ reduction of the resultant double Schiiff-base with sodium borohydride in methanol at 0 °C. Subsequent dialkylation was carried out as described before for the preparation of 20, giving the analogue 24 in 11% yield for the two steps. Finally, saponification of the two methyl esters with 1.2 equivalents of LiOH in a 1:1 THF/water mixture at room temperature followed by treatment with 4 M HCl in dioxane, to remove the Boc protecting groups, led to ligand 25 in quantitative yield.

3. Materials and Methods

3.1. General Procedures

Melting points were determined using a Kofler apparatus model Reicher Austria™ and are uncorrected. Specific rotations were recorded on a JASCO-715 optical polarimeter. Infrared spectra were recorded on a Bruker Tensor 27 spectrophotometer with sapphire-ATR (Golden Gate). Nuclear magnetic resonance spectra were recorded on an AC 250, AVANCE 360, or ARX Bruker apparatus. Mass spectra (MS) were obtained on a Bruker Squire 3000 micrOTOF spectrometer using ESI-MS (QTOF). Thin-layer chromatography was performed using ALUGRAM® SIL G/UV254 aluminium...
sheets pre-coated with silica gel 60 (0.20 mm thickness) containing a fluorescent indicator at 254 nm (Macherey-Nagel, Düren, Germany). The TLC spots were visualized with a UV lamp or by staining with vanillin in 96% EtOH or with an acid KMnO₄ solution. Column chromatography was carried out using PanReac® silica gel (230–400 mesh) (Castellar del Vallès, Spain). Nitrogen was used as driving gas.

3.2. Experimental Section

3.2.1. Synthesis of tert-Butyl (1S,2R)-2-Hydroxymethylcyclobutane-1-Carboxylate (2)

1 M B₂H₆ in THF (10.5 mL, 10.5 mmol) was added to a solution of half-ester 1 [14] (1.4 g, 6.9 mmol) in anhydrous THF (70 mL) and the resultant mixture was stirred at 0 °C for 2 h under nitrogen atmosphere and 2 h at room temperature. The reaction was quenched with aqueous saturated NH₄Cl (50 mL), then water (50 mL) was added and the mixture was extracted with EtOAc (4 × 80 mL). The combined organic layers were dried over MgSO₄ and solvent was removed at reduced pressure. The residue was purified by flash chromatography (2:1 hexane/ethyl acetate) to afford alcohol 2 (0.85 g, 63% yield) as an oil. Rp = 0.27 (2:1 hexane/ethyl acetate); [α]D = −21.7 (c = 1.01 in CH₂Cl₂); 1H NMR (250 MHz, CDCl₃) δ = 1.42 (s, 9H, O-tBu); 1.68 (m, 1H, H3); 1.99 (m, 2H, H3, H4); 2.23 (m, 1H, H3); 2.73 (m, 1H, H2); 3.02 (m, 1H, OH); 3.16 (m, 1H, H1); 3.58 (m, 1H, H5); 3.71 (m, 1H, H5) ppm; 13C NMR (62.5 MHz, CDCl₃) δ = 21.3 (C3); 22.1 (C4); 40.1 (C2); 41.2 (C1); 64.1 (C5); 81.3 (C7); 174.6 (C6) ppm; IR ν_{max} = 3411, 1720, 1152 cm⁻¹; HRMS (ESI⁺) calcd m/z for C₁₀H₁₈O₃ [M + Na]⁺: 209.1148, found: 209.1152 (Supplementary Materials).

3.2.2. Synthesis of tert-Butyl (1R,2S)-2-Tosyloxymethylcyclobutane-1-Carboxylate (3)

A solution containing alcohol 2 (0.62 g, 3.3 mmol), p-toluenesulfonyl chloride (0.85 g, 4.3 mmol), 4-DMAP (0.1 g, 0.8 mmol) and TEA (0.7 mL, 5.0 mmol) in dry CH₂Cl₂ (30 mL) was stirred at room temperature overnight under nitrogen atmosphere. Then water (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 60 mL). Phases were separated and the organic layer was dried over MgSO₄. Solvent was removed and the residue was purified by flash column chromatography (3:1 hexane/ethyl acetate) to afford tosylate 3 (0.87 g, 77% yield) as an oil. Rp = 0.30 (3:1 hexane/EtOAc); [α]D +223.6 (c = 1.03 in CH₂Cl₂); 1H NMR (360 MHz, CDCl₃) δ = 1.41 (s, 9H, tBu); 1.72 (m, 1H, H3); 2.02 (m, 2H, H4, H3); 2.23 (m, 1H, H3); 2.44 (s, 3H, H7⁺); 2.88 (m, 1H, H1); 3.16 (m, 1H, H2); 4.13 (dd, 1H, H5, J = 10.5 Hz, J’ = 7.2 Hz); 4.21 (dd, 1H, H5, J = 10.5 Hz, J’ = 7.2 Hz); 7.34 (d, J = 11.7 Hz, 2H, H3’, H5’); 7.75 (d, J = 11.7 Hz, 2H, H2’, H6’); 13C NMR (90 MHz, CDCl₃) δ = 21.0, 21.3, 21.4 (C4, C7’, C3); 27.7 (C2boc); 35.6 (C1); 39.8 (C2); 70.5 (C5); 80.7 (C7); 127.6 (C2’, C6’); 129.5 (C3’, C5’); 132.8 (C4’); 144.4 (C1’); 172.1 (C6); IR ν = 2979.3, 1721.17, 1600.6 cm⁻¹; HRMS (ESI⁺) calcd m/z for C₁₇H₂₂NO₄S [M + Na]⁺: 363.1237, found: 363.1239.

3.2.3. Synthesis of tert-Butyl (1S,2R)-2-Dodecanamidomethylcyclobutane-1-Carboxylate (5) through amine 4

A mixture of tosylate 3 (0.84 g, 2.4 mmol) and sodium azide (0.48 g, 7.4 mmol) in anhydrous DMF (30 mL) was stirred and heated at 75 °C for 3 h under nitrogen atmosphere. Then EtOAc (60 mL) was added and the resultant solution was washed with water (5 × 50 mL). The combined aqueous layers were extracted with EtOAc (100 mL) and extract was washed with water (5 × 50 mL). The combined organic layers were dried over MgSO₄ and concentrated (caution: azides can be explosive, so their solutions must be never evaporated to dryness). The residue was purified by column chromatography (6:1 hexane/ethyl acetate) to afford yellowish oil (Rp = 0.44, 6:1 hexane/ethyl acetate). The obtained oil in THF (20 mL) was hydrogenated under 1.9 atmospheres pressure in the presence of 20% Pd(OH)₂/C as a catalyst (0.10 g). After 5 h the mixture was filtered over celite® (Sigma-Aldrich, Darmstadt, Germany), which was washed with methanol (30 mL). Solvents were removed to afford a solid corresponding
to partially protected diamine 4 that was used in the next step without further purification due to its instability.

A light protected solution of crude diamine 4 (0.10 g) dodecanoyl chloride (0.12 mL, 1.5 mmol) and TEA (0.16 mL, 1.9 mmol) in dry CH₂Cl₂ (10 mL) was stirred overnight under nitrogen atmosphere. The reaction mixture was successively washed with aqueous saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄ and solvent was evaporated to dryness. The residue was washed with pentane affording compound 5 (0.1 g, 51% yield for the 3 steps) as a solid. m. p. 55–57 °C (pentane);

[α]D +10.7 (c = 1.06 in CH₂Cl₂); 1H NMR (250 MHz, CDCl₃) δ = 0.90 (t, 3H, H12'); 1.28 (m, 16H, H4', H5', H6', H7', H8', H9', H10', H11'); 1.51 (s, 9H, tBu); 1.75 (m, 1H, H3); 2.07 (m, 2H, H3, H4); 2.18 (m, 3H, H2', H4); 2.80 (m, 1H, H2); 3.19 (m, 2H, H3, H4); 3.56 (m, 1H, H5); 6.10 (broad s, 1H, NH–C(Boc); 41.9 (C2); 48.1 (C1); 62.8 (C5); 80.1 (C7); 156.9 (C6) ppm; IR ν = 3309, 2916, 1715, 1644, 1153 cm⁻¹; HRMS (ESI⁺) calcd m/z for C₂₂H₄₁NO₃ [M + Na]⁺: 390.2979, found: 390.2981.

3.2.4. Synthesis of (1S,2R)-2-Dodecanamidomethylcyclobutane-1-Carboxylic Acid (6)

A solution containing ester 5 (90 mg, 0.2 mmol), TFA (0.25 mL, 3.8 mmol), and triethylsilane (0.10 mL, 0.6 mmol) in dry CH₂Cl₂ (5 mL) was stirred at room temperature overnight under nitrogen atmosphere. Most of solvent was removed and the residue was lyophilized to afford acid 6 (74 mg, quantitative yield) as a solid. m. p. 48–50 °C; [α]D +19.0 (c = 1.10 in CH₂Cl₂); 1H NMR (250 MHz, CDCl₃) δ = 0.90 (t, 3H, H12', J = 6.8 Hz); 1.27 (m, 16H, H4', H5', H6', H7', H8', H9', H10', H13'); 1.61 (m, 2H, H3'); 1.81 (m, 1H, H3); 2.12 (m, 2H, H3, H4); 2.21 (t, 2H, H2', J = 6.7 Hz); 2.35 (m, 1H, H4); 2.90 (m, 1H, H2); 3.29 (m, 1H, H5); 3.46 (m, 2H, H5, H1); 6.36 (broad s, 1H, NH–C=O); 7.61 (broad s, 1H, HO–C=O) ppm; 13C NMR (62.5 MHz, CDCl₃) δ = 14.6 (C12'); 21.2 (C3); 23.1 (C4); 26.2–32.3 (C3', C4', C5', C6', C7', C8', C9', C10', C11'); 37.0 (C2'); 38.0 (C2'); 40.7 (C5); 41.7 (C1); 175.1 (C1'); 178.6 (C6) ppm; IR ν = 3309, 1740, 1702, 1174 cm⁻¹.

3.2.5. Synthesis of tert-Butyl (1S,2R)-2-Hydroxymethylcyclobutane-1-Carbamate (8)

A solution of 2 M LiBH₄ in THF (2.6 mL, 5.2 mmol) was added to a solution of amino ester 7 (1 g, 4.4 mmol) in Et₂O (100 mL). The mixture was stirred at 0 °C for 3 h under nitrogen atmosphere. Aqueous saturated NH₄Cl was added (60 mL) and the resultant mixture was stirred for 30 min, then water (50 mL) was added and the mixture was consecutively extracted with EtOAc (3 × 80 mL); the organic layer was dried over MgSO₄ and evaporated to dryness. The residue was chromatographed on silica gel (3:1 hexane/EtOAc) to afford alcohol 8 (0.67 g, 75%) as a solid (Rf = 0.24, 3:1 hexane/EtOAc); crystals, m. p. 79–81 °C (hexane/EtOAc); [α]D −77.8 (c = 1.02 in CH₂Cl₂); 1H NMR (250 MHz, CDCl₃) δ = 1.46 (s, 9H, tBu); 1.63 (m, 1H, H3); 1.88 (m, 2H, H4, H3); 2.36 (m, 1H, H4); 2.71 (m, 1H, H2); 3.63 (dd, 1H, H5, J = 11.3 Hz, J' = 4.3 Hz); 3.78 (dd, 1H, H5, J = 11.3 Hz, J' = 4.3 Hz); 3.75 (m, 1H); 4.21 (m, 1H, H1); 5.12 (broad s, 1H, NH–Boc) ppm; 13C NMR (62.5 MHz, CDCl₃) δ = 19.2 (C3); 28.8 (C4); 28.7 (C5); 41.9 (C2); 48.1 (C1); 62.8 (C5); 80.1 (C7) ppm; IR ν = 3311, 2976, 1691, 1174 cm⁻¹; HRMS (ESI⁺) calcd m/z for C₁₉H₂₁NO₃ [M + Na]⁺: 224.1257, found: 224.1260.

3.2.6. Synthesis of (1S,2R)-1-tert-Butyloxycarbonylaminocyclobutane-1-Methyl Dodecanoate (11)

A solution of alcohol 8 (0.3 g, 1.5 mmol), lauryl chloride (0.36 mL, 1.5 mmol), and TEA (0.27 mL, 1.9 mmol) in dry CH₂Cl₂ (15 mL) was heated to reflux overnight under nitrogen atmosphere. The reaction mixture was cooled to room temperature, washed once with aqueous saturated NaHCO₃ (10 mL) and twice with brine, and dried over MgSO₄. Solvent was removed and the residue was purified by flash chromatography (CH₂Cl₂) to give pure 11 (0.4 g, 68%) as a solid. m. p. 44–46 °C (CH₂Cl₂); [α]D −63.9 (c = 0.97 in CH₂Cl₂); 1H NMR (360 MHz, CDCl₃) δ = 0.87 (t, 3H, H12', J = 8.4 Hz); 1.25 (m, 16H, H4', H5', H6', H7', H8', H9', H10', H11'); 1.43 (s, 9H, tBu); 1.63 (m, 3H, H4, H3); 1.92 (m, 2H, H3, H4); 2.33 (m, 3H, H2', H3); 2.81 (m, 1H, H1); 4.16 (dd, 1H, H5, J = 13.8 Hz, J' = 7.2 Hz); 4.31 (dd, 3H, H2', H3); 4.96 (m, 1H, H12'); 5.11 (m, 2H, H2', H3); 5.12 (broad s, 1H, NH–C(Boc); 41.9 (C2); 48.1 (C1); 62.8 (C5); 80.1 (C7); 156.9 (C6) ppm; IR ν = 3311, 2976, 1691, 1174 cm⁻¹; HRMS (ESI⁺) calcd m/z for C₁₉H₂₁NO₃ [M + Na]⁺: 224.1257, found: 224.1260.
1H, H5; J = 13.8 Hz, J′ = 7.2 Hz); 4.30 (m, 1H, H2); 4.79 (broad s, 1H, NHBoc) ppm; \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) δ = 13.8 (C12′); 17.7 (C4); 22.2−31.6 (C3′, C4′, C5′, C6′, C7′, C8′, C9′, C10′, C11′); 26.6 (C4); 28.1 (C10); 34.1 (C2′); 38.6 (C1); 45.8 (C2); 63.4 (C5); 79.0 (C7); 154.7 (C6); 173.7 (C1′) ppm; IR ν = 3342, 2919, 1679, 1166 cm\(^{-1}\); HRMS (ESI\(^+\)) calcd m/z for C\(_{22}\)H\(_{41}\)NO\(_4\) [M + Na\(^+\)]: 406.2928, found: 406.2930.

3.2.7. Synthesis of (1S,2R)-2-Dodecanoyloxyethylcycllobutane-1-Ammonium Chloride (12)

A solution of compound 11 (0.2 g, 0.5 mmol) and 2 N HCl in Et\(_2\)O (1.56 mL, 3.1 mmol) in dry CH\(_2\)Cl\(_2\) (15 mL) was stirred at room temperature for 24 h under nitrogen atmosphere. Most solvent was removed, and the residue was lyophilized to afford quantitatively a solid that was crystallized in pentane to provide surfactant 12 (0.14 g, 84% yield) as crystals. m.p. 86−88 °C (pentane); [α]D \(+9.6\) (c = 1.01 in MeOH); \(^1\)H NMR (360 MHz, CD\(_3\)OD) δ = 0.91 (m, 3H, H12′); 1.30 (m, 16H, H4′, H5′, H6′, H7′, H8′, H9′, H10′, H11′); 1.63 (m, 2H, H3′); 1.81 (m, 1H, H3); 2.17 (m, 2H, H4, H3); 2.39 (m, 3H, H2′, H4); 2.95 (m, 1H, H2); 3.95 (m, 1H, H1); 4.32 (m, 2H, H5); \(^{13}\)C NMR (90 MHz, CD\(_3\)OD) δ = 13.1 (C12′); 17.9 (C3); 22.3−29.3 (C3′, C4′, C5′, C6′, C7′, C8′, C9′, C10′, C11′); 31.7 (C4); 33.4 (C2′); 36.4 (C2); 46.6 (C5); 62.3 (C1); 173.8 (C1′) ppm; IR ν = 3370, 2919, 1740, 1112 cm\(^{-1}\); HRMS (ESI\(^+\)) calcd m/z for C\(_{17}\)H\(_{23}\)ClNO\(_2\) [M\(^+\)]: 319.2348, found: 319.2346.

3.2.8. Synthesis of tert-Butyl (1S,2R)-2-Tosloyloxymethylcycllobutane-1-Carboxylate (9)

Following a procedure similar to that described above for the preparation of tosylate 3, compound 9 (0.57 g, 62% yield) was obtained as a solid. Rf = 0.28 (6:1 hexane/EtOAc); crystals, m.p. 87−88 °C (ethyl acetate/hexane); [α]D \(-10.2\) (c = 1.05 in CH\(_2\)Cl\(_2\)); \(^1\)H NMR (360 MHz, CDCl\(_3\)) δ = 1.41 (s, 9H, \(\text{tBu}\)); 1.58 (m, 1H, H3); 1.88 (m, 2H, H4, H3); 2.27 (m, 1H, H3); 2.45 (s, 3H, H7); 2.75 (m, 1H, H1); 4.17 (m, 2H, H5); 4.33 (m, 1H, H2); 4.77 (broad s, 1H, NHBoc); 7.34 (d, J = 11.7 Hz, 2H, H3′, H5′); 7.75 (d, J = 11.7 Hz, 2H, H2′, H6′) ppm; \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) δ = 17.6 (C4); 21.4 (C7′); 28.0 (C10); 28.1 (C3); 38.7 (C1); 45.8 (C2); 69.8 (C5); 79.1 (C7); 127.6 (C2′, C6′); 129.6 (C3′, C5′); 132.6 (C4′); 144.6 (C1′); 154.8 (C6) ppm; IR ν = 3311, 2976, 1691, 1174 cm\(^{-1}\); HRMS (ESI\(^+\)) calcd m/z for C\(_{12}\)H\(_{14}\)O\(_2\)N\(_2\) [M + Na\(^+\)]: 378.1346, found: 378.1344.

3.2.9. Synthesis of tert-Butyl (1S,2S)-2-Dodecanamidomethylcyclobutane-1-Carbamate (13) through diamine 10

Following a similar procedure than that described above for the preparation of 5, compound 13 (66% overall yield for the three steps) was obtained as crystals. m.p. 102−104 °C (pentane); [α]D \(+40.2\) (c = 1.01 in CH\(_2\)Cl\(_2\)); \(^1\)H NMR (360 MHz, CDCl\(_3\)) δ = 0.89 (t, 3H, H12′, J=5.7 Hz); 1.25 (m, 16H, H4′, H5′, H6′, H7′, H8′, H9′, H10′, H11′); 1.44 (s, 9H, tBu); 1.61 (m, 3H, H3, H3′); 1.80 (m, 1H, H4); 1.92 (m, 1H, H3); 2.13 (t, 2H, H2′, J = 6.3 Hz); 2.36 (m, 1H, H4); 2.59 (m, 1H, H2); 3.15 (m, 1H, H5); 3.52 (m, 1H, H5); 4.17 (m, 1H, H1); 4.99 (broad s, 1H, NHBoc); 6.12 (broad s, 1H, NH-C=O) ppm; \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) δ = 14.1 (C12′); 20.1 (C3); 26.6 (C4); 22.7−29.6 (C2′, C3′, C4′, C5′, C6′, C7′, C8′, C9′, C11′); 28.4 (C10); 36.9 (C10′); 39.1−40.0 (C2, C5); 47.2 (C1); 79.7 (C7); 156.2 (C6); 173.3 (C1′) ppm; IR ν = 3342, 2919, 1679 cm\(^{-1}\); HRMS (ESI\(^+\)) calcd m/z for C\(_{22}\)H\(_{42}\)N\(_2\)O\(_3\) [M + Na\(^+\)]: 405.3088, found: 405.3088.

3.2.10. Synthesis of (1S,2R)-2-Dodecanamidomethylcyclobutane-1-Ammonium Chloride (14)

A solution of compound 13 (0.2 g, 0.5 mmol) and 2 N HCl in Et\(_2\)O (1.56 mL, 3.1 mmol) in dry CH\(_2\)Cl\(_2\) (15 mL) was stirred at room temperature for 24 h under nitrogen atmosphere. Most solvent was removed, and the residue was lyophilized to afford quantitatively a solid that was crystallized in pentane to provide amphiophile 14 (0.1 g, 64% yield). Crystals, m.p. 98−100 °C (pentane); [α]D \(+8.7\) (c = 1.05 in MeOH); \(^1\)H NMR (360 MHz, CD\(_3\)OD) δ = 0.91 (m, 3H, H12′); 1.30 (m, 16H, H4′, H5′, H6′, H7′, H8′, H9′, H10′ H11′); 1.61 (m, 2H, H3′); 1.98 (m, 2H, H3, H4); 2.09 (m, 1H, H3); 2.23 (t, 2H, H2′, J=6.3 Hz); 2.39 (m, 1H, H4); 2.79 (m, 1H, H1); 3.16 (m, 1H, H5); 3.44 (m, 1H, H5); 3.75 (m, 1H, H1) ppm; \(^{13}\)C NMR (90 MHz, CD\(_3\)OD) δ = 13.0 (C12′); 20.2 (C3); 22.3 (C4); 22.7−29.6 (C3′, C4′, C5′, C6′, C7′, C8′,
C9\textsuperscript{′}, C10\textsuperscript{′}, C11\textsuperscript{′}); 35.5 (C2\textsuperscript{′}); 37.8–38.6 (C2, C5); 47.2 (C1); 176.2 (C1\textsuperscript{′}) ppm; IR ν = 3342, 2918, 1679 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) calcld m/z for C\textsubscript{17}H\textsubscript{35}N\textsubscript{2}O\subscript{2} [M\textsuperscript{+}]: 283.2744, found: 283.2745.

3.2.11. Synthesis of Diamides 16 and 17. General Procedure

To a solution of compound 15 [15] (0.18 g, 0.84 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (27.0 mL), DIPEA (0.44 mL, 2.52 mmol) and PyBOP (0.55 g, 1.06 mmol) were added. After 15 min stirring at room temperature, dodecylamine or hexadecylamine (0.92 mmol) dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (10.0 mL) was added and the resulting mixture was stirred at room temperature for 18 h. The solution was diluted with CH\textsubscript{2}Cl\textsubscript{2} (10.0 mL) and washed with aqueous saturated NaHCO\textsubscript{3} (30.0 mL). The organic layer was dried over MgSO\textsubscript{4} and evaporated under vacuum. The residue was purified by column chromatography (1:1 hexane-EtOAc) to afford the corresponding pure amide. A mixture containing this compound (0.40 mmol), 2 N HCl in Et\textsubscript{2}O (20 mmol) and anhydrous CH\textsubscript{2}Cl\textsubscript{2} (10.0 mL) was stirred at room temperature for 36 h. The solvent was evaporated at reduced pressure to afford the corresponding amine hydrochloride, which was dissolved in a 1:1 mixture of 0.25 M NaOH-Et\textsubscript{2}O and stirred vigorously for 15 min. Then the reaction mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL). The combined organic layers were dried over MgSO\textsubscript{4} and solvent was removed to afford the respective free amine. This was coupled with lauryl or palmitic acid, respectively, as described above for the first coupling procedure. After purification by column chromatography (5% MeOH-CH\textsubscript{2}Cl\textsubscript{2}) the corresponding pure diamides were obtained as solid products.

(1S,2S)-N-Dodecyl-2-Dodecanamidocyclobutane-1-Carboxamide (16)

27% overall yield from 15. Crystals, m.p. 74–79 °C (CH\textsubscript{2}Cl\textsubscript{2}); [α]\textsubscript{D} +2.1 (c = 1.05 in CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) δ = 0.92 (t, J = 6.4 Hz, 6H, H19, H18\textsuperscript{′}), 1.28 (s, 34H, H10-18, H10-17\textsuperscript{′}), 1.60 (m, 4H, H9, H9\textsuperscript{′}), 1.81–2.00 (m, 2H, H4-3), 2.19 (m, 4H, H3-4, H8\textsuperscript{′}), 2.90 (q, J = 9.1 Hz, 1H, H5), 3.24 (m, 2H, H8), 4.33 (m, 1H, H2), 5.88 (broad s, 1H, N1H), 8.36 (broad s, 1H, N7H) ppm; \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) δ = 13.8 (C19, C19\textsuperscript{′}); 18.6 (C4); 22.3 (C18, C18\textsuperscript{′}); 24.1 (C9-16,C10-16\textsuperscript{′}); 25.4 (C9-16, C10-16\textsuperscript{′}); 26.8 (C3); 29.0-29.4 (C9-16,C10-16\textsuperscript{′}); 31.7 (C17,C17\textsuperscript{′}); 36.1 (C17, C17\textsuperscript{′}); 39.1 (C8); 47.7 (C2); 49.7 (C5, C9\textsuperscript{′}); 172.5 (C7); 174.1 (C8\textsuperscript{′}) ppm; IR ν = 2952, 1685, 1638 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) calcld m/z for C\textsubscript{29}H\textsubscript{56}N\textsubscript{2}O\textsubscript{2} [M + H\textsuperscript{+}]: 465.4415, found: 465.4397.

(1S,2S)-N-Hexadecyl-2-Palmitamidocyclobutane-1-Carboxamide (17)

28% overall yield from 15. Crystals, m.p. 116-118 °C (CH\textsubscript{2}Cl\textsubscript{2}); [α]\textsubscript{D} +6.0 (c = 1.04 in CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) δ = 0.88 (t, J = 5.5 Hz, 6H, H23, H22\textsuperscript{′}), 1.26 (s, 50H, H10-22, H10-21\textsuperscript{′}), 1.61 (m, 4H, H9, H9\textsuperscript{′}), 1.77–2.00 (m, 2H, H4-3), 2.18 (m, 4H, H3-4, H8\textsuperscript{′}), 2.89 (q, J = 8.7 Hz, 1H, H5), 3.21 (m, 2H, H8), 4.32 (m, 1H, H2), 5.80 (d, J = 6.6 Hz, 1H, N1H), 8.34 (s, 1H, N7H) ppm; \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) δ = 13.9 (C23, C23\textsuperscript{′}); 18.6 (C4); 22.2 (C22, C22\textsuperscript{′}); 24.1 (C9-20, C10-20\textsuperscript{′}); 25.4 (C9-20, C10-20\textsuperscript{′}); 26.8 (C3); 29.0-29.4 (C9-20, C10-20\textsuperscript{′}); 31.6 (C21, C21\textsuperscript{′}); 39.3 (C8); 47.4 (C2); 49.7 (C5, C9\textsuperscript{′}); 172.2 (C7); 173.9 (C8\textsuperscript{′}) ppm; IR ν = 3293, 2955, 2849, 1686, 1644 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) calcld m/z for C\textsubscript{37}H\textsubscript{72}N\textsubscript{2}O\textsubscript{2} [M + Na\textsuperscript{+}]: 599.5486, found: 599.5478.

3.2.12. Synthesis of Tetra-
ter-
-Butyl N,N,N′,N′-\textsuperscript{′}-\textsuperscript{′}-(\textsuperscript{′}(15,3R)-2,2-Dimethylcyclobutane-1,3-diyl) Bis(Methylene)Bis(Azanetriyl)] Tetraacetate (20)

Diamine 19 was prepared from dimesylate 18 [31] as described above for the synthesis of diamine 4 and used in the next step without further purification. tert-Butyl bromoacetate (3.7 mL, 25.1 mmol) was added dropwise to a mixture of crude diamine 19 (0.45 g, 3.2 mmol), potassium iodide (2.8 g, 17 mmol), and DIPEA (8.7 mL, 50.2 mmol) in anhydrous DMF (15 mL). The resultant solution was stirred at room temperature for 96 h under nitrogen atmosphere. The mixture was diluted with dichloromethane (150 mL) and washed with sat. K\textsubscript{2}CO\textsubscript{3} (2 x 30 mL) and brine (40 mL). The organic phase was dried over MgSO\textsubscript{4} and the solvent was evaporated to afford a yellow oil. The crude product was purified by column chromatography (4:1 Hexane/EtOAc) to obtain a colourless oil (0.48 g, 26% overall yield from dimesylate
3.2.13. Synthesis of $N,N,N',N'$-bis(methylene)-bis(azanetriyl) tetraacetic acid (21)

A solution of tetraester 20 (0.20 g, 0.3 mmol) in 4 M HCl in dioxane (12 mL, 48 mmol) was stirred at room temperature for 20 h. Solvent was removed at reduced pressure, then water (2 mL) was added and the mixture was lyophilized to afford 21 as a solid (0.13 g, quantitative). $^1$H NMR (250 MHz, CDCl$_3$) $\delta = 0.92$ (s, 3H, H6/5); 1.09 (s, 3H, H5/6); 1.47 (s, 3H, H11); 2.06 (m, 3H, H1, H3, H4); 2.66 (m, 4H, H7); 3.39 (s, 8H, H8); ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta = 16.0$ (C6); 28.0 (C5); 29.6 (C11); 30.0 (C2); 40.0 (C4); 40.9 (C1, C3); 54.5 (C7); 55.9 (C8); 80.8 (C10); 170.7 (C9) ppm; IR $\nu = 2951, 2862, 2360, 1723, 1139$ cm$^{-1}$; HRMS (ESI$^+$) calcd m/z for C$_{32}$H$_{58}$N$_2$O$_8$ [M + H]$^+$: 599.4266, found: 599.4252.

3.2.14. Synthesis of Dimethyl 6,6′-[(2,2-Dimethylcyclobutane-1,3-diylbis(methylene)]bis(azanemethylenediyl)] dipicolinic acid (24)

A solution of diamine 19 (0.6 g, 4.3 mmol) and methyl 6-formyl picolinate 22 [37] (0.14 g, 8.6 mmol) in MeOH (20 mL) was stirred at room temperature for 5 h. Then, the solution was cooled with ice and NaBH$_4$ (0.26 g, 7 mmol) and MeOH (20 mL) were added. The resultant ice-cooled mixture was stirred for 2 h. Aqueous saturated NaHCO$_3$ (30 mL) was added and most methanol was removed. The solution was extracted with CH$_2$Cl$_2$ (4 x 50 mL), the combined organic layers were dried over MgSO$_4$ and solvent was removed to afford crude compound 23 that was identified by its $^1$H NMR spectrum and used in the next step without further purification. $^1$H NMR (250 MHz, CDCl$_3$) $\delta = 0.91$ (s, 3H, H4/5); 1.09 (s, 3H), 1.14–1.29 (m, 1H, H1); 1.94–2.11 (m, 3H, H1,2,3); 2.48 (m, 2H, H7); 2.62 (m, 2H, H7); 3.95 (s, 6H, H15); 7.54 (m, 2H, H9); 7.77 (m, 2H, H10); 7.97 (m, 2H, H11) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta = 15.1$ (C6); 27.6 (C5); 29.5 (C4); 37.0 (C2); 41.2 (C3); 55.5 (C7); 56.9 (C8); 168.7 (C9) ppm; IR $\nu = 1730$ cm$^{-1}$; HRMS (ESI$^+$) calcd m/z for C$_{16}$H$_{26}$N$_2$O$_8$ [M - H]$^-$: 373.1616, found: 373.1626.

3.2.15. Synthesis of 6,6′-[(2,2-dimethylcyclobutane-1,3-diylbis[(carboxymethyl) azane methylene diyl]]-bis(methylene)] dipicolinic acid (25)

A mixture containing compound 24 (200 mg, 0.30 mmol) and LiOH (45 mg, 1.19 mmol) in 1:1 THF/H$_2$O (5 mL) was stirred at room temperature for 4 h. Solvent was removed, the residue was poured into 4 M HCl in dioxane (8 mL) and the mixture was stirred for 20 h. Solvent was evaporated under vacuo, water (2 mL) was added and the resultant mixture was lyophilized to afford quantitatively tetraacid 25 (170 mg) as a brown solid. $^1$H NMR (250 MHz, D$_2$O) $\delta = 0.78$ (s, 3H, H5/6), 0.97 (s, 3H, H5/6), 1.78 (m, 1H, H4), 2.10 (m, 1H, H1/3/4), 2.30 (m, 2H, H1/3/4), 3.32 (m, 4H, H7), 3.98 (s, 4H, H8/16), 4.57 (s, 4H, H8/16), 7.62 (d, $J = 7.6$ Hz, 2H, H10), 8.00 (t, $J = 7.7$ Hz, 2H, H11), 8.09 (d, $J = 7.7$ Hz, 2H, H12) ppm; $^{13}$C NMR (62.5 MHz, D$_2$O) $\delta = 14.8$ (C5,6); 27.4 (C4); 29.5 (C5,6); 36.7 (C1/3); 41.0 (C2); 54.1 (C7); 56.2 (C16); 27.8 (C8); 125.4 and 127.8 (C10/12); 139.8 (C11); 146.2 (C13); 149.1 (C9); 166.8 and 167.7.
(C14/17) ppm; IR ν = 3363, 2360, 1730, 1630, 1400 cm\(^{-1}\); HRMS (ESI\(^+\)) calcd m/z for C\(_{26}\)H\(_{32}\)N\(_{4}\)O\(_{8}\) [M + H]\(^+\): 529.2293, found: 529.2283.

### 4. Conclusions

In this work, we showed the suitability of several cyclobutane scaffolds for the preparation of different families of products with potential usefulness in the fields of surfactants, gelators and metal cation ligands. Enantiomerically pure cis-1,2-disubstituted cyclobutane derivatives have been efficient and selectively obtained from a common chiral half-ester. From this precursor, synthetic routes to amphiphiles as possible surfactants have been achieved through a cis-β-CBAA as a convenient intermediate. In addition, compounds with appropriate structures to behave as gelators have been synthesized from an orthogonally protected trans-β-CBAA. Otherwise, symmetric cis-1,3-cyclobutane scaffolds have been prepared from verbenone through norpinic acid that provided a cis-1,5-diamine, which is a key intermediate in the synthesis of different poly(amino acids). These compounds are valuable candidates to be investigated as polydentate ligands for lanthanide complexes. The properties of these families of compounds as well as their likely applications are the subject of active investigation in our laboratory.

**Supplementary Materials:** Supplementary materials can be found at [http://www.mdpi.com/1422-0067/20/18/4333/s1](http://www.mdpi.com/1422-0067/20/18/4333/s1).

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**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| ATR          | Attenuated Total Reflection |
| CBAA         | Cyclobutane Amino Acid |
| DDS          | Drug Delivery Systems |
| DIPEA        | Diisopropylethylamine |
| DMAP         | Dimethylaminopyridine |
| DMF          | Dimethylformamide |
| DNA          | Deoxyribonucleic Acid |
| ESI          | Electrospray Ionization |
| HRMS         | High-Resolution Mass Spectrometry |
| IR           | Infrared |
| LMWG         | Low Molecular-Weight Gelator |
| MS           | Mass Spectrometry |
| NMR          | Nuclear Magnetic Resonance |
| NPY          | Neuropeptide Y |
| PyBOP        | (Benzotriazol-1-yl-oxy)tripyrrolidinophosphonium hexafluorophosphate |
| QTOF         | Quadrupole Time-of-Flight |
| TEA          | Triethylamine |
| TFA          | Trifluoroacetic Acid |
| THF          | Tetrahydrofuran |
| TLC          | Thin layer chromatography |

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