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Efficient Synthesis and Astonishing Supramolecular Architectures of Several Symmetric Macrolactams

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Abstract: The synthesis of four C_n symmetric macrocyclic lactams cyclo-[NH-CH_2-CH=CH-CH_2-CO]$_n$ (**1**, $n=2$; **2**, $n=3$; **3**, $n=4$) and cyclo-[NH-CH_2-CH_2-CH=CH-CO]$_3$ (**4**) has been achieved by two approaches. A linear route leads to precursors that are subsequently macrocyclized in a separate step. The second, convergent approach relies on the symmetry of the targets: it includes suitably activated subunits, which are subjected to macrocyclization conditions. The subunits first oligomerize, then cyclize to form either pure macrolactams or mixtures. The macrolactam units **1**, **2** and **4** stack on top each other through weak interactions (hydrogen bond and van der Waals), to form endless square, rectangular and triangular prisms, respectively. These stacks are further packed side by side in crystals grown from isotropic media. The overall dipoles in the crystals from lactams **1** and **4**, which result mostly from the alignment of amide groups, are zero and large, respectively. Macrolactam **2** displays an astonishing isomorphism when allowed to cool down in anisotropic liquid crystal solutions. Large hollow hexagonal tubes are then obtained through a fractal process. Contrary to the three previous rings, **3** yields crystals where prisms of any shape are absent.

Keywords: crystal engineering · lactams · oligomerization · supramolecular chemistry · synthetic methods

Introduction

Non-covalent synthesis[1,2] is a rapidly growing field of research, because the resulting supramolecular objects may find numerous applications as new materials endowed with very diverse properties.[3–11] Among the different shapes that can be sculptured, tubular supramolecules of various dimensions occupy a privileged position.[12–23] One such natural molecule, gramicidin A, is a channel acting as an efficient ion transporter across cell membranes.[24] Other much larger proteins similarly shaped as tubes yield pores in lipid bilayers for the same purpose of transport.[25] Synthetic supramolecular tubes[26–31] could find many uses in medicine as drugs[22] or drug delivery systems.[32] However, the applications of such aggregates are not at all limited to the biology realm. A plethora of domains such as catalysis, photonics, material science, can also be targeted.[33–36]

We have been particularly interested in synthesizing tubes through controlled stacking of sufficiently rigid ring units **1**–**4**; each unit consisted of a macrolactam[37–44] of C_n symmetry ($n=2$, 3, 4, Figure 1).[45,46]

Owing to the vast potential of such compounds we looked for expedient and efficient syntheses. We also tried to scrutinize the relationships between structure of macrocycles and how they assemble to supramolecular objects. Such understanding is obviously of much value for any work dealing with closely related or even more remote supramolecular tubes.

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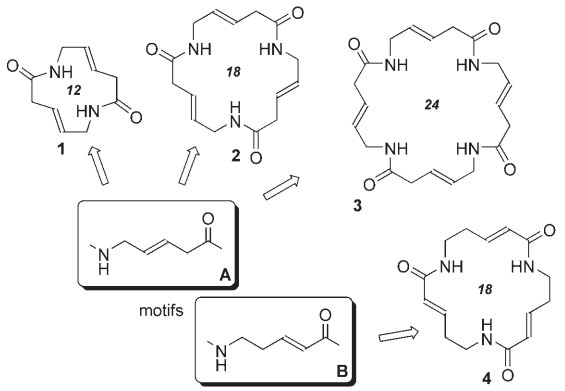


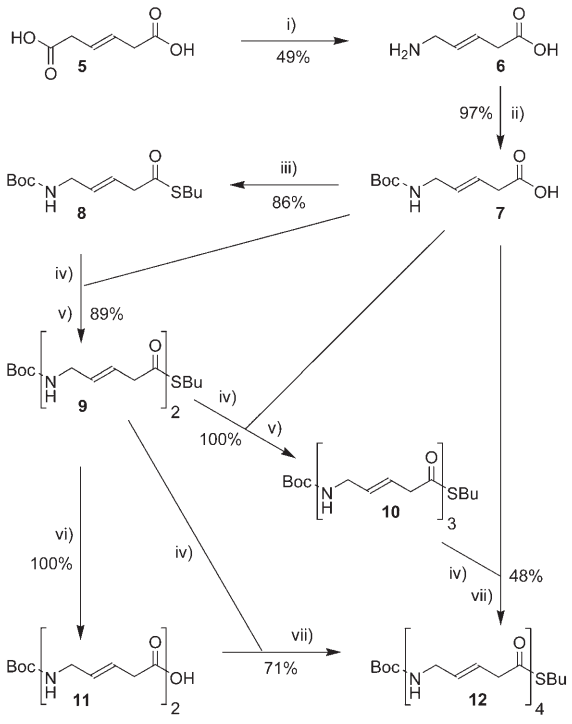
Figure 1. C_n symmetric macrolactams **1**–**4** (ring size in italics) and their repeating motifs.

Results and Discussion

Synthesis: We tackled the synthesis of targets **1**–**4** in two ways: macrocyclization,[47] or cyclooligomerization[48,49] of repeating subunits **A** and **B** (Figure 1) to take advantage of their symmetry. The thioesters **9**, **10** and **12**, based on the same δ-amino acid **6** (corresponding to subunit **A**), were selected as linear precursors to macrocycles **1**–**3** (Scheme 1). Thus, *trans*-β-hydromuconic acid **5** was transformed into the unsaturated δ-amino-acid **6** (49%) and then into its corresponding Boc-protected amine **7** (97%).[50] *n*-Butanethiol was coupled with **7** by means of EDCI, DMAP and HOBt at −17°C to yield the thioester **8** (86%). Many other conditions involving DCC and higher temperatures led to various amounts of conjugated thioester **17** (Scheme 3). TFA treatment of **8** gave the corresponding ammonium salt, that was coupled with acid **7** by means of DCC to afford the dimeric thioester **9** (89%). Boc cleavage of **9**, followed by coupling (DCC) of the resulting ammonium salt with **7**, gave the trimeric thioester **10** (100%).

Acid **7** was DCC-coupled with the ammonium salt corresponding to **10** to give **12** (48%). Alternatively, the same tetrameric thioester **12** was better prepared by DCC coupling of two dimers: the ammonium salt obtained from thioester **9** and acid **11** (71%), the latter resulting from KOH hydrolysis of thioester **9** (100%).

Since preliminary cyclooligomerization attempts from thioester **8** proved unsuccessful (Table 1), we then selected pentafluorophenyl (Pfp) esters as cyclooligomerization and/or macrocyclization precursors.[51,52] The first Pfp ester **13**, equivalent to the thioester **8** (Scheme 2), was prepared from acid **7** with DCC and an equal molar amount of pentafluorophenol (96%). The previously prepared dimeric acid **11** (Scheme 1) was obtained by a new very efficient method by simply stirring a mixture of Pfp ester **13**, amino acid **6** and K_2CO_3 in acetone and water (79%). The dimeric Pfp ester **14** was prepared from **11** (83%) as before (DCC, PfpOH). Amino acid **6** was coupled with dimeric Pfp ester to produce trimeric acid **15** (85% from **11**). Alternatively, Boc cleavage of carbamate **11** afforded its corresponding dimeric zwitterionic amino acid, that was allowed to react with monomeric Pfp ester **13** to produce the same acid **15** (82% from **11**). Although both routes are in effect two-step sequences, the latter proved more effective since it involves a quantitative cleavage of the Boc group with TFA. All attempts to prepare Pfp ester **16** in the usual way (DCC and equal amount of PfpOH) from the corresponding acid **15** yielded various amounts of an undesired and practically inseparable isomer of **16**, in which the alkene at the C-terminal side of the tri-

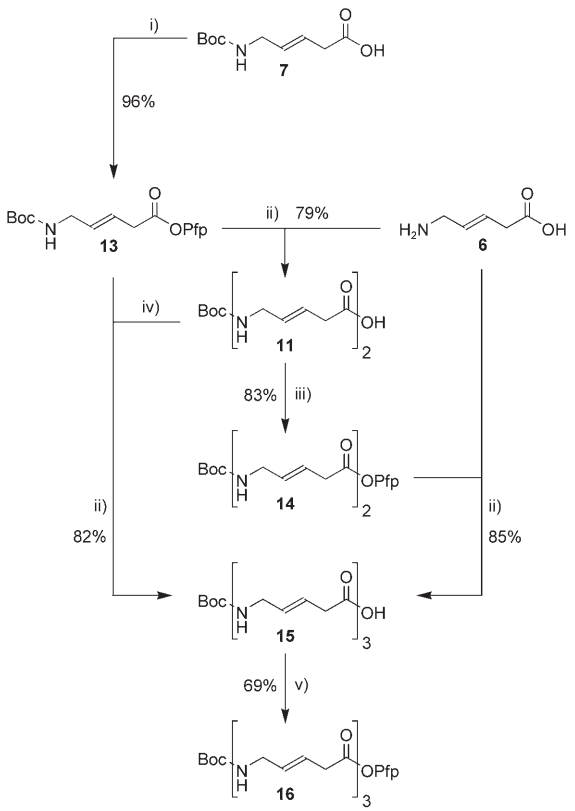


Scheme 1. Preparation of thioester precursors **8**–**10** and **12**. i) H_2SO_4, NaN_3, $CHCl_3$, 45°C; ii) Boc_2O, NaOH, *t*BuOH, H_2O, RT; iii) *n*BuSH, EDCI, DMAP, HOBt, CH_2Cl_2, −17°C; iv) TFA, CH_2Cl_2, RT; v) DCC, DMAP, NMM, CH_2Cl_2, 0°C; vi) KOH, H_2O, MeOH, RT; vii) DCC, DMAP, NMM, EtOAc, 0°C.

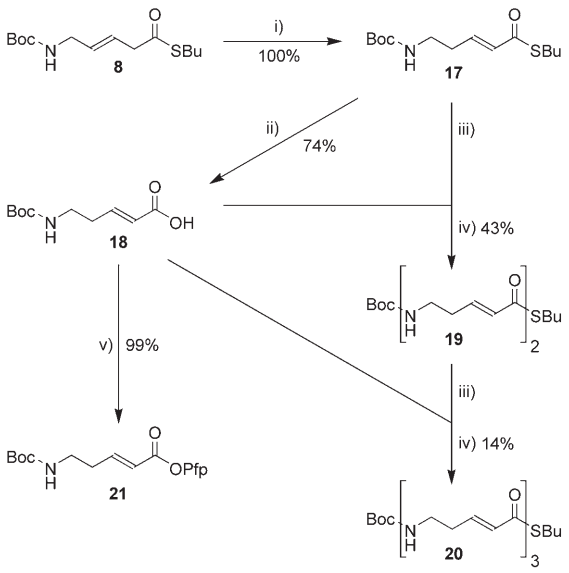
Table 1. Results of macrocyclization and cyclooligomerization.

Starting ester[a,b]	Ring product	Yield [%]
monomeric thioester **8**	–	
monomeric Pfp ester **13**	dimer **1**	21
	trimer **2**	37
	tetramer **3**	12
dimeric thioester **9**	–	
dimeric Pfp ester **14**	dimer **1**	22
	tetramer **3**	49
trimeric thioester **10**	trimer **2**	55
trimeric Pfp ester **16**	trimer **2**	88
tetrameric thioester **12**	tetramer **3**	67
monomeric Pfp ester **21**	trimer **4**	41
	(monomer) **24**	7
trimeric thioester **20**	trimer **4**	50

[a] Conditions for thioesters: i) TFA, ii) AgTFA (3 equiv), DIPEA, DMF, 45°C. [b] Conditions for Pfp esters: i) TFA, ii) NMM, dioxane, 80°C.



Scheme 2. Preparation of Pfp ester precursors **13**, **14** and **16**. i) DCC, PfpOH, EtOAc, RT; ii) K_2CO_3, MeAc, H_2O, RT; iii) DCC, PfpOH, EtOAc, DMF, RT; iv) TFA, CH_2Cl_2, RT; v) EDCI·3PfpOH (complex), CH_2Cl_2, RT.



Scheme 3. Preparation of ester precursors **20** and **21**. i) DBU, CH_2Cl_2, RT; ii) 2,6-lutidine, THF, H_2O, $AgNO_3$, reflux; iii) TFA, CH_2Cl_2, RT; iv) DCC, DMAP, NMM, CH_2Cl_2, 0 °C; v) DIC·3PfpOH (complex), dioxane, MeCN, 0 °C.

peptide had shifted to become conjugated. It is worth noting that this side reaction had not been observed during the preparation of its smaller congeners **13** and **14**. This synthetic drawback was solved by using the DCC·3PfpOH complex,[53] since no conjugated isomer had been observed with this reagent. Nevertheless, it was very tedious to get rid of dicyclohexyl urea (DCU) formed as a side product. The same purification problem was present with DIC·3PfpOH complex. Finally, adaptation of the complex methodology to EDCI afforded the much sought for Pfp ester **16** (69%).

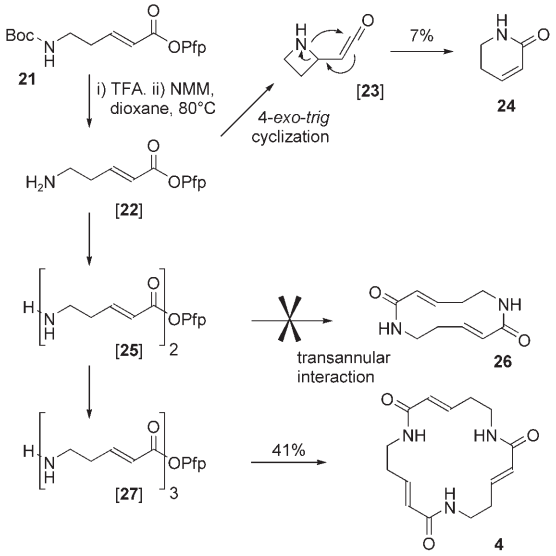
The last macrocyclic target **4** was based on motif **B** (Figure 1) that differs from motif **A** only by the position of the alkene. Thus, in order to make its corresponding macrocyclization thioester precursor **20** (Scheme 3), the alkene of **8** was first conjugated with DBU (100%).[54] The resulting thioester **17** was hydrolyzed (74%) with 2,6-lutidine and $AgNO_3$ to trap released *n*BuSH and prevent it from adding to unreacted thioester.[55] Acid **18** thus obtained was coupled with DCC to the TFA salt issued from **17** to give the dimeric conjugated thioester **19** (43%). TFA treatment of **19**, then DCC coupling of the resulting TFA salt with acid **18**, gave the macrocyclization precursor thioester **20** with a very disappointing yield (14%). On the other hand, the Pfp ester cyclooligomerization precursor **21** was prepared from acid **18** using DIC·3PfpOH complex (99%).

We then studied the formation of macrolactams **1**–**4**. The macrocyclizations and cyclooligomerizations were carried out in similar way. All Boc groups from carbamates **8**–**10**, **12**–**13**, **16**, **20** and **21** were cleaved with TFA. The resulting ammonium salts were added to solutions of DIPEA and AgTFA in DMF at 45 °C (thioesters)[56,57] or to solutions of NMM in dioxane at 80 °C (Pfp esters). All rings **1**–**4** were obtained with various yields (Table 1).

It immediately appears that the thioester methodology is much less efficient than the Pfp ester methodology since thioester **8** did not produce any of the expected lactam products **1**–**3**. Contrarily, its equivalent Pfp activated esters **13** afforded mixture of three macrolactams **1**–**3** with good yields (total yield of 70%). Thus, cyclooligomerization appears to be favored in the case of Pfp esters but disfavored in the case of thioesters. The limitation of the thioester methodology is also clearly visible at the direct macrocyclization level, since dimeric Pfp ester **14** yielded both cyclic dimer **1** (22% of macrocyclization) and cyclic tetramer **3** (49% of cyclodimerization); dimeric thioester **9** produced nothing. This latter experiment confirms that thioesters do not cyclooligomerize, but it also demonstrates that cyclization to strained rings such as 12-membered lactam **1** is not possible either. Even for macrocyclizations to stain-free lactams, the Pfp approach remains more efficient, as shown in the results from trimeric esters **10** and **16** to 18-membered lactam **2** (yields of 55% from thioester **10** and 88% from Pfp ester **16**). The thioester **12** led also to the larger 24-membered macrolactam **3** with a similar yield (67%).

Another 18-membered ring, the conjugated macrolactam **4**, was obtained by the same route from trimeric thioester **20** and with a comparable yield as that obtained in the case of isomeric unconjugated lactam **2** from trimeric thioester **10**

(50% for **4** and 55% for **2**). We also attempted the cyclooligomerization of monomeric Pfp activated ester **21** to prepare the same target **4**. TFA treatment of **21** gave its corresponding salt which was immediately injected to a hot solution of base in dioxane (Scheme 4).



Scheme 4. Cyclooligomerization of monomeric Pfp ester **21**.

Under these conditions, released free amine [**22**] produced small amounts of six-membered lactam **24**, possibly through four-membered ring intermediate [**23**] resulting from a favored amine 4-*exo*-*trig* cyclization.[58] But [**22**] mostly gave linear dimer [**25**] which cannot cyclize to medium 12-membered ring **26** (isomeric to **1**), as it would be very strained, suffer transannular interactions and would likely have more energetic s-*cis* amides or distorted s-*trans* amides. Consequently, [**25**] had no other choice but to add statistically another monomer [**22**] (obviously in higher concentration than itself) to yield Pfp activated trimer [**27**] that readily cyclized to finally afford **4** (41%).

Structures of supramolecular assemblies: We managed to crystallize all four rings **1**–**4** from common solvents, although smaller macrocycle **1** crystallization proved much more difficult (Table 2). The macrocycles **2**, **3** and **4** had already been crystallized by diffusion of diethyl ether in ethanol, isopropanol and ethanol, respectively.[45] The unconjugated trimer **3** yielded long hexagonal hollow nanotubes when it was dissolved into some liquid crystals at high temperature, then allowed to slowly cool down.[46] New crystallization conditions were applied to rings **2** and **3** in order to study possible polymorphism and to improve the structural precision for **3**. Indeed the length of the double bounds previously found for **3** were rather short at 1.28 Å and even 1.22 Å. In the new crystal, obtained by diffusion of *tert*-butyl methyl ether into a solution of **3** in *n*-butanol, the refined alkene bond lengths are 1.30 and 1.31 Å as expected.

Table 2. Structural information for rings **1**–**4**.

Ring	Crystal growth	Unit symmetry	Tubular shape	Crystal polarity
1[a]	MeOH	C_i	square	zero
2[b]	EtOH/Et_2O	C_1	rectangle	small
2[a]	EtOAc	C_1	rectangle	small
2[c]	liquid crystal	C_3	hexagone	zero
3[b]	*i*PrOH/Et_2O	C_i	no tubes	zero
3[a]	*n*BuOH/*t*BuOMe	C_i	no tubes	zero
4[b]	EtOH/Et_2O	C_3	triangle	large

[a] Crystal data in ref. [59]. [b] Crystal data in ref. [45]. [c] Structure described in ref. [46].

The large 24-membered ring **3** did not produce tubes, but an interlaced network of rings (Figure 2). Two related conformations **3a** and **3b** are observed in the crystal; their only difference being the orientation of two opposing alkene groups. Although the shape of individual macrocycles with C_i symmetry is roughly circular, they are linked through hydrogen bonds to four neighboring macrocycles instead of only two as would be expected for nanotubes. All possibilities for hydrogen bonding amounting to eight are totally fulfilled. The doughnut molecules (inner cavity of about 5 Å) manage to fill all available room by adopting an edge to centre geometry relationship in the crystal. Obviously, no tubes could ever form from such large rings, unless other objects could be inserted into the resulting hollow cylinder. For that reason, we tried to crystallize **3** with another set of solvents (*tert*-butyl methyl ether and *n*-butanol) to obtain porous materials with inclusion of solvent molecules. However, **3** crystallized in a very similar way as before with exclusion of solvent.[59]

A similar attempt to provoke polymorphism by using different solvent systems for crystal growth was tried with the 18-membered macrocycle **2**.[59] However, both systems

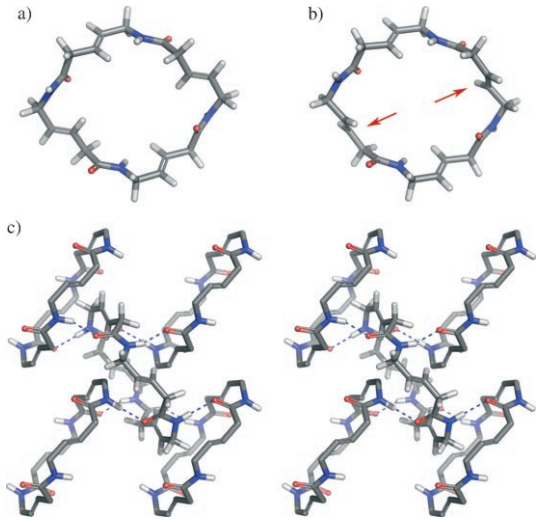


Figure 2. a) and b) Two crystal C_i symmetric conformations **3a** and **3b** of **3** (*n*BuOH/*t*BuOMe) (arrows show rotating alkenes); c) Parallel stereoviews. C*H* are omitted.

(EtOH/Et_2O and EtOAc) produced crystals with similar 3D arrangements of C_1 symmetric molecules (Figure 3). Two conformers, **2a** and **2b**, are present in the crystals grown in

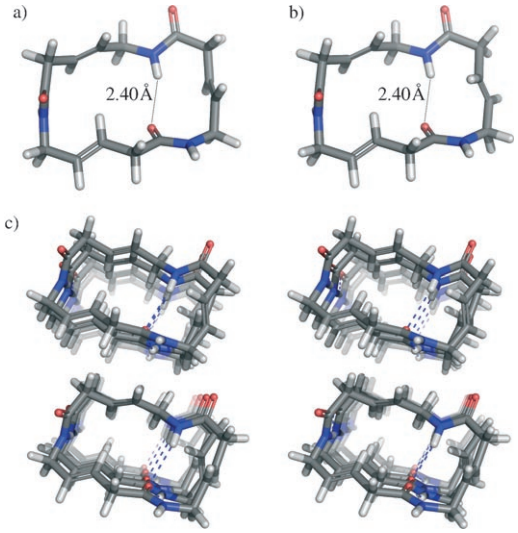


Figure 3. a) and b) Two crystal conformations **2a** and **2b** of **2** (EtOAc); c) Parallel stereoviews of tubes formed by stacking of conformers **2a** and **2b**.

ethyl acetate. Noteworthy, these conformations differ only from each other by rotation of an alkene moiety. These conformations share also a common important feature: a β-turn that is responsible for the flat rectangular shape of the ring.

Polymorphism for such compounds is not too surprising since a crystal of cyclohexaglycine isosteric[60] to **2** (the three alkenes of the latter being replaced by amides in the former) is also polymorphous (Figure 4).[61] In this case, however, there are as many as four different conformations present in the same crystal. These conformers belong to two groups in terms of distinctive features. Thus, conformer **a** is held rectangular by means of two β-turns, whereas, conformers **b**, **c** and **d** which have no such intramolecular bonds tend to adopt more hexagonal shapes. It is worth noting that conformers **b** and **c** differ from each other by the orientation of two opposite amides; conformer **d** represents an intermediate geometry between **b** and **c** where only one of the floppy amides has rotated. Consequently, **a**, **b** and **c** are all C_i symmetric molecules whereas conformer **d** has no symmetry. Interestingly, conformer **a** has very much the same backbone geometry as that of **b**. Simply the intramolecular hydrogen bonds present in **a** are disrupted in **b** and the two floppy amides adopt a slightly different orientation. Conformer **a** of cyclo-$(Gly)_6$ corresponds to conformer **2b** of cyclo-(δ-aminoacyl)$_3$ **2** (Figure 3). A cooperative effect is obviously at work in cyclo-$(Gly)_6$ (conformer **a**): its two β-turn CO–HN distances are very short at 2.07 and 2.12 Å. Only one such β-turn exists in the corresponding conformer **2b** of **2** with a much longer CO–HN bond length of 2.40 Å.

Both crystals of cyclo-(δ-aminoacyl)$_3$ **2** and cyclo-$(Gly)_6$ are constituted of parallel stacks of cyclopeptide rings held

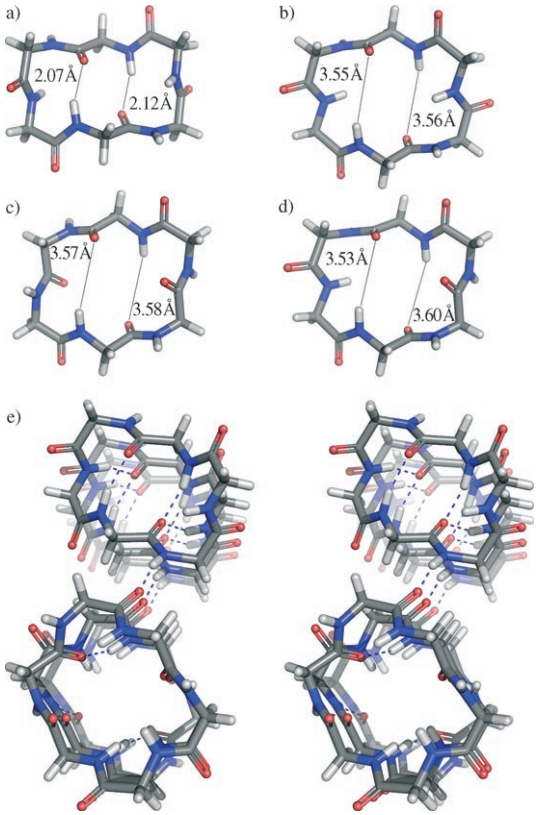


Figure 4. a), b), c) and d) Four crystal conformations **a**, **b**, **c** and **d** of cyclohexaglycine; e) Parallel stereoviews of tubes formed by stacking of conformers **a** (top) and **b**, **c** and **d** (bottom).

together by intra-stacked hydrogen bonds. These stacks can be compared to endless tubes. Only one kind of flat tube is observed in **2**, and there are no interstacked hydrogen bonds that could bring more strength to the whole architecture. In the case of cyclo-$(Gly)_6$ the same shape of rectangular tube is also present. This rectangular tube arises from conformation **a** only. The three other more hexagonal conformers **b**–**c** lead to another more hollow tube in which some molecules of water are trapped. Contrarily to **2**, all cyclo-$(Gly)_6$ tubes have developed inter-stack hydrogen bonds (Figure 4e).

When a hot solution of macrolactam **2** in a lipophilic liquid crystal (BL006) was left to cool down to room temperature, very long and thick fibres crystallized out.[46] These fibres later proved to be hexagonal hollow tubes when observed by scanning electron microscopy (SEM) after the liquid crystal matrix had been removed with hexane (Figure 5a). Obviously this type of hexagonal object could not be obtained from the same rectangular conformers of **2** as those obtained from crystal grown from isotropic media (Table 2 and Figure 3). A quick study of polymorphism for the macrolactam **2** successfully proved that several forms can coexist. Thus, crystals of **2** could be grown on an ITO substrate by diffusion of diethyl ether into a solution of **2** in methanol (ITO coated glass plate in MeOH solution). Scanning electron microscopy showed tiny crystals shaped-like

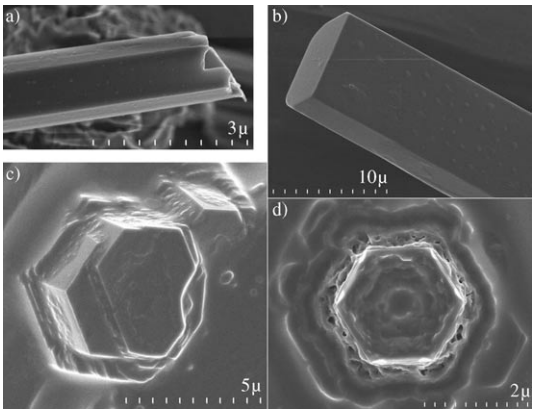


Figure 5. SEM images of a) a hollow hexagonal tube resulting from cooling down of a hot solution of ring **2** in a liquid crystal; and b), c) and d) crystals of the same macrocycle **2** grown on the ITO substrate from a methanol solution.

rectangular prisms (Figure 5b) similar to those also obtained from isotropic media.[45,59] Aside from this first type of crystal, many smaller hexagonal crystalline objects were also present (Figure 5c and d).

Conformation analysis calculations (HF/6-31Gd and MM2) to fit micro-Raman data from tubes extracted from the liquid crystal matrix showed that such hexagonal hollow tubes could result from two conformers **2c** and **2d** of **2** (Figure 6a and b).[41] These two conformers, which present many similarities with cyclohexaglycine conformers **b–d** (Figure 4b–d), stack on top of each other in an alternate way (···**2c**–**2d**···) to fulfil their hydrogen-bonding capabilities. The resulting so-called first-generation tubes pack side by side in an antiparallel fashion by means of interstack hydrogen bonds (Figure 6c); the surrounding aggregates of liquid crystals act as templates for the lipophilic faces of the first generation tubes (Figure 6d). A second-generation tube of six first-generation tubes is then constructed. The same fractal self-assembly process is carried on until mesoscopic hexagonal tubes appear (Figures 5a and 7).

Thus, the macrocycle **2** proved very flexible, since it could adopt numerous different conformations. Although polymorphism can be sometimes an asset, it can also be troublesome as in the case of marketed drugs.[62] We wanted to address this matter in the next generation by conceiving a ring monomer for which stacking and packing processes are completely controlled and limited to only one possibility.

In order to gain control over the shape of the macrocyclic monomers and consequently also over the shape of their aggregates, we designed the conformationally restricted macrocyclic **4**. Although ring **4** has the same ring size as **2** (18 atoms), its conformation is entirely locked in a triangular crown (Figure 8a). All intramolecular hydrogen bond as β-turns found in **2** and cyclohexaglycine (Figures 3 and 4) are prevented. Conjugation of the alkenes with the amide carbonyls imposes all three amides plans to be parallel to the C_3 axis of the cyclotripeptide. The s-*trans* conformation of the enamides brings also control over the conformation of

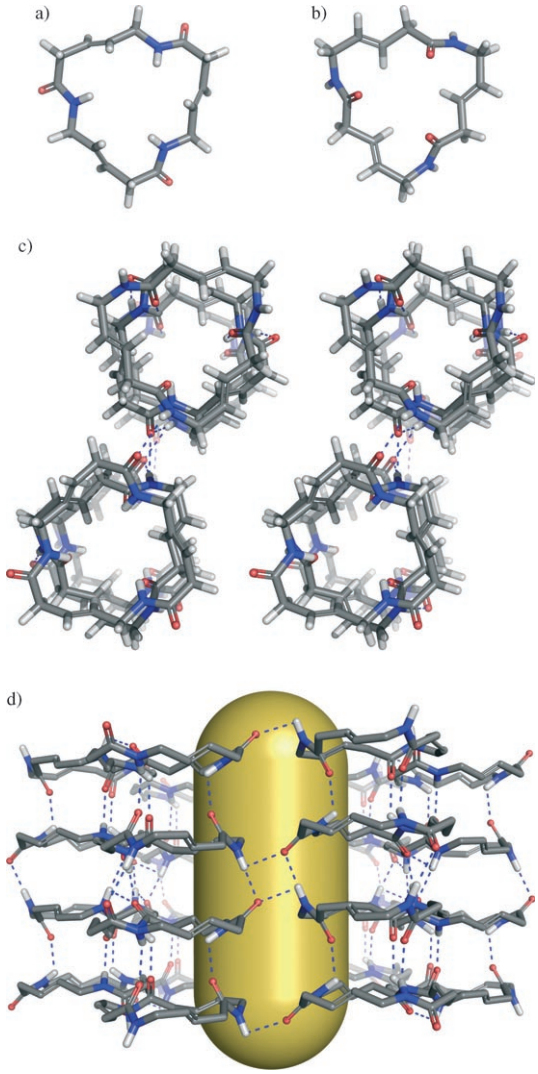


Figure 6. a) and b) calculated conformers **2c** and **2d** found in hollow hexagonal microscopic tubes formed from solution of **2** in a lipophilic liquid crystal; c) Parallel stereoviews of two antiparallel tubes constituted of alternating conformers **2c** and **2d**; d) 3D arrangement via interstack hydrogen bonds of six antiparallel tubes around bundles of oriented liquid crystal chains (shown as a yellow object).

the three ethane tethers. As a whole all the regions of the entire molecule are conformationally coupled, resulting in a very rigid macrocycle. A direct consequence of the conformational coupling is that the three amides are oriented in the same direction. Therefore, all amide dipoles add up and the molecule displays a very strong electric dipole moment of 9.08 D from B3LYP/6-31G(d) calculations.[63] By comparison the calculated dipole moments of conformers **2a** and **2b** of the isomeric ring **2** (Figure 3) are 7.22 and 7.40 D, respectively. Such a high dipole is rather surprising for a neutral molecule; it is in fact equivalent to the extremely polar NaCl molecule having a experimental dipole of 9.00 D.[64] The extreme polarity of the molecule is also clearly visible from its 3D molecular electrostatic potential map (MEP map).[65] The MEP map indicates that all three carbonyl

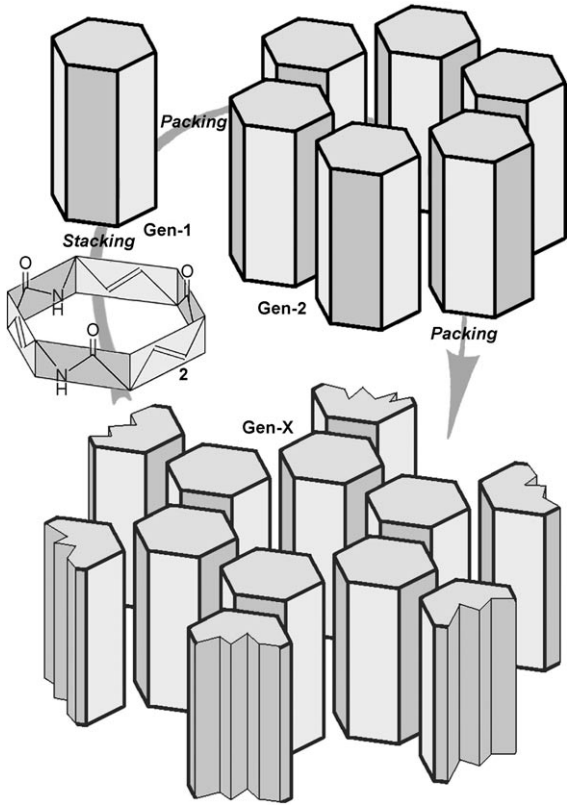


Figure 7. Fractal self-assembly of ring **2** in a lipophilic liquid crystal matrix. Stacking of **2** leads to a first generation tube **Gen-1**. A second generation tube **Gen-2** is built through side by side packing of six **Gen-1** tubes. Repetition of the same self-assembly process eventually produces larger objects **Gen-X**.

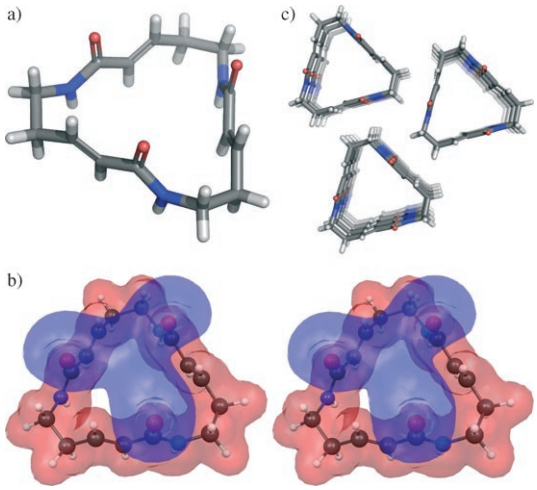


Figure 8. a) Crystal conformation of C_3 symmetric ring **4**. b) Parallel stereoviews of the 3D molecular electrostatic potential map of **4**. c) Its crystal stacking and packing.

work cooperatively and impart large charge separation to the triangular lactam (Figure 8b). The preformed polar monomeric units stack perfectly on top of each other like coins could do (e.g. all faces up and all tails down). Consequently, the same C_3 symmetry of the ring constituents is retained in the resulting stack and the dipole is amplified. Intuitively, we were expecting that all the highly polar stacks would pack in such a way that the gross crystal dipole would be minimized. On the contrary, all dipoles moments aligned perfectly in the crystal (Figure 8c). Monocrystals of that type are very anisotropic;[21,23] they belong to the very rare trigonal R_3 space group.[66]

Cyclo-(δ-aminoacyl)$_2$ **1** and cyclo-(Gly)$_4$ are isosteric, in the same way as cyclo-(δ-aminoacyl)$_3$ **2** and cyclo-(Gly)$_6$.[60] However, no crystallography reports exist for such a simple molecule as cyclotetraglycine. In fact cyclotetrapeptides in general are rather scarce in the literature. This is not too surprising since these 12-membered rings are very strained as can be inferred from the fact that most of them crystallize with either 25%[67] or even 50%[68–76] of their amide bonds in a more energetic *cis* conformation. It is therefore amazing that macrolactam **1** crystallizes from MeOH solution in a C_2 conformation corresponding to a cyclotetrapeptide with four *trans* amides (Figure 9a). Nevertheless, it appears that there is much tension in the C_2 conformation of **1**, since amides are distorted by as much as 21° from planarity. This tension even shows up in the alkenes also twisted by a quite large value of 18°. There exists only one known crystallized cyclotetrapeptide whose backbone is conformationally isosteric to that of **1**, the natural product dihydrochlamydocin monohydrate.[77] However, one of the residues being a proline, stacking of the rings is completely hindered. This is not the

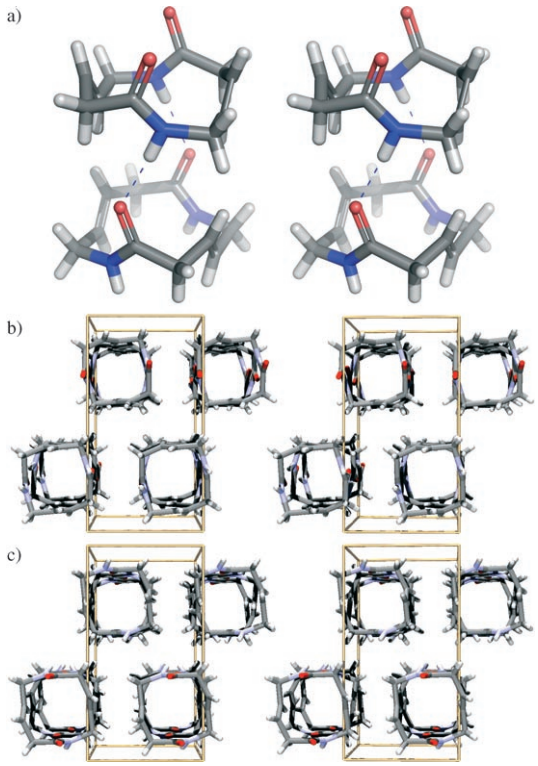


Figure 9. Parallel stereoviews of a) stacked C_2 symmetric rings **1** and, b) and c) its crystal unit cell with two possible orientations of the macrocycles.

case for macrolactam **1**, for which no such steric interactions exist. Thus, stacking of units **1** along the C_2 axis is favored (Figure 9a). However, this process occurs in the same way as for antiparallel β-sheets. This is opposite to the case of **4**, for which stacking is the same as in parallel β-sheets. The calculated electric dipole moment of **1** is 5.94 D, corresponding roughly to 2/3 of the value calculated for ring **4** (9.08 D). This comes as no surprise since only two amides participate to the dipole of **1**; three are involved in the case of **4**. The highly polar stacks further pack side by side like **4**. However, the order in the crystal is far from being perfect. Contrarily to **4**, there are two possible orientations for each ring with an average occupancy of 50% (Figure 9b and c). The two possible orientations at each ring position result from 90° rotation around the C_2 axis (z axis) followed by xy plan inversion. This is obviously a major difference with **4**, where the order can be considered to be perfect. But, the most striking difference resides in the relative orientation of the stacks dipoles. All these dipoles are parallel in the case of **4**, resulting in a strong monocrystal gross dipole. Whereas, they contrary each other in the crystal of **1**. There are at present no clear reasons for this.

Conclusion

Cyclooligomerization is a rapid method to prepare conjugated trimers like **4**; it is also efficient to synthesize unconjugated dimeric, trimeric and even tetrameric lactams like **1**–**3**, although mixtures of these products cannot be avoided. Despite this apparent drawback, this technique remains attractive because the three products **1**–**3** can be very easily purified. Introduction of side chains and groups to these C_n symmetric frameworks to obtain specific properties is the current goal from now on.

The polymorphism of crystals constituted of cyclic peptides can be controlled by reducing the mobility of the ring. It is possible to achieve that goal when the conformational shapes of all regions of the macrocycle are interdependent. Such total rigidity was reached in the conjugated ring **4**. In that particular case, the molecular charge distribution was also completely controlled. Our data (for **1** and **4**) suggest that ring rigidity coupled with well separated charges might be the major contributors to monomorphism. However, these simple rules apply only to stacking, since it seems impossible for now to explain why some stacks prefers to pack in parallel fashion (**4**), while other prefer an antiparallel arrangement (**1**). For more floppy systems (**2** and **3**), conformational flexibility is present so that polymorphs are likely. Nevertheless, the medium of crystallization has a great influence on the final outcome as shown in the case of **2** where rectangular or hexagonal conformers are selectively sorted in isotropic and anisotropic media, respectively.

Experimental Section

General methods: 1,4-Dioxane was distilled over pellets of KOH. Italic integral figures for ^{1}H NMR signals indicate that they vary with time because of D/H exchange; selected ^{1}H NMR spectra are shown in the Supporting Information.

Amino acid 6: Commercially available *trans*-β-hydromuconic acid **5** (30 g, 207.9 mmol) was dissolved in $CHCl_3$ (900 mL) at 45 °C under stirring. Concentrated H_2SO_4 (90 mL) was then added, followed by small portions of NaN_3 (13.5 g, 207.9 mmol) over a period of 35 min. The viscous solution was stirred for 5 h at 45 °C and further overnight at RT. The resulting solution was extracted with H_2O (3×250 mL) and the combined aqueous layers were diluted with H_2O (400 mL) to dissolve small floating particles. Meanwhile, Dowex resin 50WX8-100 (about 650 mL) was washed with de-ionized H_2O (1.5 L) and HCl (0.1 N, 1.0 L). The resulting resin was then loaded with the aqueous extract, rinsed with de-ionized H_2O until pH 7 (about 1.0 L). The product was finally eluted with pyridine (0.1 N, 2.0 L). All washings and elutions were performed under atmospheric pressure. The fractions with the desired product **6** were concentrated. The resulting white precipitate was filtered, rinsed with *i*PrOH and dried under vacuum (11.7 g, 49%). M.p. 166–167 °C; ^{1}H NMR (300 MHz, D_2O, TMS): δ = 5.86 (m, 1H), 5.50 (m, 1H), 3.45 (d, J = 6.5 Hz, 2H), 2.87 ppm (d, 2H, 7 Hz); ^{13}C NMR (75 MHz, D_2O, TMS): δ = 180.0, 132.8, 123.0, 40.8 ppm; IR (KBr): $\tilde{\nu}$ = 2800 br, 1630, 1560, 1490, 1370, 980 cm^{-1}; MS (70 eV): m/z: 114 [$M-H^+$], 116 [$M+H^+$]; HRMS (70 eV): m/z: calcd for $C_5H_8NO_2$: 114.0555; found: 114.0553 [$M-H^+$], 116.0709 [$M+H^+$].

Carbamate 7: Di-*tert*-butyl dicarbonate (2.89 g, 13.2 mmol) in *t*BuOH (5 mL) was added to a solution of amine **6** (1.69 g, 14.7 mmol) and 2.1 N aqueous NaOH (7 mL, 14.7 mmol) in *t*BuOH (5 mL). The solution was stirred for 5 min, then 2.1 N aqueous NaOH (7 mL, 14.7 mmol) was added. The mixture was subsequently stirred for an additional 17 h at RT. The solution was concentrated under reduced pressure, and the residue was acidified with 6 N aqueous HCl until pH 3 was reached. The aqueous phase was extracted with Et_2O (3×20 mL). The combined organics extracts were dried over Na_2SO_4, filtrated and concentrated to give the title compound as a white solid (2.75 g, 97%). R_f = 0.30 (EtOAc/hexane/AcOH 60:39:1); m.p. 59–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.39 (br, 1H), 5.75–5.55 (m, 2H), 4.69 (br, 1H), 3.70 (br, 2H), 3.09 (d, J = 6.5 Hz, 2H), 1.43 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 176.8, 154.5, 130.8, 122.8, 81.0, 41.3, 37.0, 27.6 ppm; ^{13}C NMR (75 MHz, CD_3OD, TMS): δ = 174.1, 156.9, 130.2, 123.6, 78.6, 41.4, 36.9, 27.3 ppm; IR (NaCl): $\tilde{\nu}$ = 3335, 3000 br, 1715, 1520, 1170, 970 cm^{-1}; MS (70 eV): m/z: 159 [$M^+-C_4H_8$]; HRMS (70 eV): m/z: calcd for $C_6H_9NO_4$: 159.0532; found: 159.0536 [$M^+-C_4H_8$].

Thioester 8: Acid **7** (600 mg, 2.79 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled with an ice bath. The reagents were added in the following order: HOBt (452 mg, 3.35 mmol), DMAP (851 mg, 6.97 mmol), *n*BuSH (313 μL, 2.93 mmol) and EDCI (639 mg, 3.35 mmol). The flask was sealed with a rubber septum and purged with N_2. The resulting mixture was stirred until a clear homogenous solution was obtained and immediately placed in the freezer at −17 °C for 18 h without stirring. Some starting material **7** was still present, and more *n*BuSH (60 μL, 0.56 mmol) and EDCI (106 mg, 0.56 mmol) were quickly added to the reaction mixture placed in an ice bath. The flask was sealed and purged with nitrogen and set at −17 °C for another 18 h, after that time the reaction was complete. The reaction mixture was poured directly from the freezer into saturated aqueous NH_4Cl (30 mL). The CH_2Cl_2 layer was isolated and the remaining aqueous solution was extracted with CH_2Cl_2 (3×20 mL). The combined organics layers were dried on Na_2SO_4, filtrated and concentrated. The rude residue was purified by flash chromatography on silica gel eluting with Et_2O/hexane 7:3 to yield a colorless oil (688 mg, 86%). R_f = 0.80 (Et_2O/hexane 7:3); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 5.75–5.5 (m, 2H), 4.64 (br, 1H), 3.72 (br, 2H), 3.24 (d, J = 5.5 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 1.52 (m, 2H), 1.42 (s, 9H), 1.38 (m, 2H), 0.89 ppm (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 197.5, 155.7, 131.9, 123.4, 79.4, 47.0, 42.1, 31.5, 28.7, 28.3, 21.9, 13.5 ppm; IR (NaCl): $\tilde{\nu}$ = 3355, 2965, 2930, 2870, 1695, 1515, 1250, 1170, 970 cm^{-1}; MS (70 eV):

m/z: 214 [$M^+-C_4H_9O$]; HRMS (70 eV): *m/z*: calcd for $C_{10}H_{16}NO_2S$: 214.0902; found: 214.0909 [$M^+-C_4H_9O$].

Dipeptide 9: Carbamate **8** (0.98 g, 3.41 mmol) was dissolved in a mixture of TFA (5 mL) and CH_2Cl_2 (5 mL) and stirred for 45 min at RT. Toluene (5 mL) was added to the solution and concentrated in order to remove the excess of TFA. This operation was repeated four more times to give the corresponding ammonium salt. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=7.68 (br, 3H), 5.96 (m, 1H), 5.70 (m, 1H), 3.64 (br, 2H), 3.31 (d, J=6.5 Hz, 2H), 2.86 (t, J=7.5 Hz, 2H), 1.54 (m, 2H), 1.38 (m, 2H), 0.90 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=198.2, 130.1, 125.3, 46.5, 41.5, 31.2, 28.9, 21.8, 13.4 ppm; IR (NaCl): $\tilde{\nu}$=3000 br, 1675, 1530, 1200, 1140, 975 cm^{-1}; MS (70 eV): *m/z*: 188 [M+H$^+$]; HRMS (70 eV): *m/z*: calcd for $C_9H_{18}NOS$: 188.1109; found: 188.1115 [M+H$^+$].

The salt was dissolved in CH_2Cl_2 (10 mL) and NMM (1.5 mL, 13.6 mmol) was added. The resulting solution was stirred for 10 min before addition of DMAP (42 mg, 0.34 mmol) and the acid **7** (807 mg, 3.75 mmol). The mixture was cooled to 0°C and a 1 M solution of DCC in cyclohexane (3.75 mL, 3.75 mmol) was added. It was stirred for 5 min at 0°C and for 17 h at RT. The reaction mixture was filtered on Celite and concentrated before being purified by flash chromatography on silica gel eluting with hexane/EtOAc 2:3 to afford the title compound as a white solid (1.17 g, 89%). R_f=0.27 (EtOAc/hexane 7:3); m.p. 75–76°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=6.03 (br, 1H), 5.75–5.55 (m, 4H), 4.78 (br, 1H), 3.85 (t, J=5.5 Hz, 2H), 3.71 (t, J=5.5 Hz, 2H), 3.25 (d, J=6 Hz, 2H), 2.97 (d, J=6.5 Hz, 2H), 2.85 (t, J=7.5 Hz, 2H), 1.52 (m, 2H), 1.42 (s, 9H), 1.38 (m, 2H), 0.90 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=197.5, 170.6, 155.9, 132.1, 131.0, 124.6, 124.0, 79.5, 47.0, 42.3, 41.1, 39.9, 31.5, 28.7, 28.4, 21.9, 13.6 ppm; IR (NaCl): $\tilde{\nu}$=3350, 3295, 2930, 1685, 1640, 1525, 1245, 1170, 970 cm^{-1}; MS (70 eV): *m/z*: 328 [M^+ $-C_4H_8$]; HRMS (70 eV): *m/z*: calcd for $C_{15}H_{24}N_2O_4S$: 328.1457; found: 328.1451 [$M^+-C_4H_8$].

Tripeptide 10: Carbamate **9** (131 mg, 0.34 mmol) was dissolved in TFA (5 mL) and CH_2Cl_2 (5 mL) and stirred for 45 min at RT. Toluene (5 mL) was added to the solution and concentrated. This operation was repeated four more times to give the corresponding ammonium salt. M.p. 107–110°C; ^{1}H NMR (300 MHz, CD_3OD, TMS): δ=8.10 (br, 1H), 5.99 (dt, J=15.5 Hz, 7 Hz, 1H), 5.8–5.55 (m, 3H), 3.78 (m, 2H), 3.53 (d, J=6.5 Hz, 2H), 3.30 (m, 2H), 3.05 (d, J=7 Hz, 2H), 2.87 (t, J=7 Hz, 2H), 1.54 (m, 2H), 1.39 (m, 2H), 0.92 ppm (t, J=7 Hz, 3H); IR (KBr): $\tilde{\nu}$=3290, 3100 br, 1685, 1640, 1545, 1140, 975 cm^{-1}.

The compound was dissolved in CH_2Cl_2 (10 mL) followed by NMM (112 μL, 1.0 mmol). The resulting solution was stirred for 30 min. DMAP (4 mg, 0.03 mmol) and acid **7** (81 mg, 0.37 mmol) were added. The resulting solution was cooled to 0°C. A 1 M solution of DCC in cyclohexane (370 μL, 0.37 mmol) was added to the reaction mixture, that was stirred for 5 min at 0°C and then for 19 h at RT. The mixture was filtered on Celite and concentrated before being purified by flash chromatography on silica gel eluting with MeOH/EtOAc 1:9. The desired product was obtained as a white solid (164 mg, 100%). R_f=0.31 (MeOH/EtOAc 1:9); m.p. 140–143°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=6.53 (br, 1H), 6.32 (br, 1H), 5.75–5.5 (m, 6H), 4.98 (br, 1H), 3.85–3.75 (m, 4H), 3.67 (br, 2H), 3.24 (d, J=6 Hz, 2H), 2.97 (d, J=6.5 Hz, 4H), 2.83 (t, J=7.5 Hz, 2H), 1.6–1.2 (m, 4H), 1.40 (s, 9H), 0.88 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=197.7, 171.3, 170.9, 156.1, 132.2, 131.0, 130.9, 125.0, 124.4, 123.9, 79.6, 47.0, 42.3, 41.2, 41.1, 39.7, 31.4, 29.7, 28.7, 28.3, 21.9, 13.6 ppm; IR (KBr): $\tilde{\nu}$=3335, 3300, 2960, 1685, 1635, 1530, 1170, 970 cm^{-1}; MS (70 eV): *m/z*: 408 [M^+−O*t*Bu], 425 [M^+ $-C_4H_8$]; HRMS (70 eV): *m/z*: calcd for $C_{24}H_{39}N_3O_5S$: 481.2610; found: 481.2616 [M^+].

Acid 11: Thioester **9** (100 mg, 0.26 mmol) was dissolved in MeOH (4 mL). 2% w/v aqueous KOH (900 μL, 0.31 mmol) was added and the resulting mixture was stirred at RT for 23 h. The solvent was removed under reduced pressure and H_2O (10 mL) was added to the residue. The aqueous solution was washed with EtOAc (5 mL), acidified with 1 N aqueous HCl until pH 2 was reached, then extracted with EtOAc (3× 10 mL). The combined organics layers were dried on Na_2SO_4, filtrated and concentrated. The product was recovered as a white solid (81 mg, 100%). M.p. 109–118°C; ^{1}H NMR (300 MHz, CD_3OD, TMS): δ=8.03 (br, 1H), 5.8–5.5 (m, 4H), 3.76 (m, 2H), 3.62 (d, J=5 Hz, 2H), 3.04 (d, J=7 Hz, 2H), 2.94 (d, 4H, 6 Hz), 1.43 ppm (s, 9H); IR (KBr): $\tilde{\nu}$=3340, 3310, 2900 br, 1685, 1635, 1530, 1170, 970 cm^{-1}.

Tetrapeptide 12: ***Method 1***: A solution of carbamate **9** (20 mg, 53 μmol) in TFA (2 mL) and CH_2Cl_2 (2 mL) was stirred for 45 min at RT. Toluene (2 mL) was added to the solution and concentrated. This operation was repeated four more times to give the corresponding ammonium salt, that was dissolved in a mixture of CH_2Cl_2 (2 mL), EtOAc (1 mL) and DMF (100 μL). NMM (17 μL, 0.16 mmol) was added and the mixture was stirred for 30 min. DMAP (1 mg, 8 μmol) and acid **11** (18 mg, 58 μmol) were added and the resulting solution was cooled to 0°C. DIC (9 μL, 58 μmol) was added to the mixture, that was stirred for 30 min at 0°C and for 7 d at RT. The reaction was filtered on Celite and concentrated before being purified by flash chromatography on silica gel eluting with MeOH/EtOAc 1:9. **12** was obtained as a white solid (22 mg, 71%).

Method 2: Carbamate **10** (38 mg, 79 μmol) in TFA (2 mL) and CH_2Cl_2 (2 mL) was stirred for 45 min at RT. Toluene (2 mL) was added to the solution and concentrated (same operation repeated 4×) to yield the corresponding salt. M.p. 134–137°C; ^{1}H NMR (300 MHz, $CDCl_3$/TFA 1:1, TMS): δ=6.89 (br, 3H), 6.04 (m, 1H), 5.95–5.55 (m, 5H), 4.05–3.85 (m, 4H), 3.80 (t, J=6 Hz, 2H), 3.41 (d, J=7 Hz, 2H), 3.35–3.2 (m, 4H), 2.96 (t, J=7.5 Hz, 2H), 1.60 (m, 2H), 1.41 (m, 2H), 0.93 ppm (t, J=7 Hz, 3H); IR (KBr): $\tilde{\nu}$=3290, 3100 br, 1690, 1640, 1545, 1140, 970 cm^{-1}.

The compound was dissolved in EtOAc (3 mL) and DMF (1 mL). NMM (26 μL, 0.24 mmol) was added and the resulting solution was stirred for 10 min. DMAP (5 mg, 40 μmol) and acid **7** (19 mg, 87 μmol) were added. The solution was cooled to 0°C before addition of a 1 M solution of DCC in CH_2Cl_2 (87 μL, 87 μmol). The resulting mixture was stirred for 5 min at 0°C and for 3 h at RT. The mixture was filtered on Celite and concentrated before being purified by flash chromatography on silica gel eluting with MeOH/EtOAc 1:9. The peptide **12** was obtained as a white solid (22 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=6.45 (br, 1H), 6.28 (br, 1H), 6.19 (br, 1H), 5.8–5.5 (m, 8H), 4.88 (br, 1H), 3.9–3.75 (m, 6H), 3.70 (m, 2H), 3.27 (d, J=6 Hz, 2H), 2.98 (d, J=6 Hz, 6H), 2.86 (t, J=7.5 Hz, 2H), 1.65–1.2 (m, 4H), 1.43 (s, 9H), 0.91 ppm (m, 3H); IR (NaCl): $\tilde{\nu}$=3300, 2960, 1685, 1635, 1530, 970 cm^{-1}.

Pentafluorophenyl ester 13: Acid **7** (1.00 g, 4.65 mmol) was dissolved at RT in EtOAc (30 mL) and PfpOH (898 mg, 4.88 mmol) was added. A solution of DCC (1.01 g, 4.88 mmol) in EtOAc (30 mL) was added to the reaction by means of an addition funnel. The solution became cloudy after a few minutes and a white precipitate appeared. The solution was allowed to stir overnight. Hexane (20 mL) was added and the precipitate of DCU was filtered off. The clear solution was concentrated and the residue purified by flash chromatography on silica gel eluting with EtOAc/hexane 3:7 to afford the title compound as a white solid (1.64 g, 96%). R_f=0.67 (EtOAc/hexane 3:7); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=5.85–5.65 (m, 2H), 4.64 (br, 1H), 3.79 (br, 2H), 3.43 (m, 2H), 1.45 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=167.4, 155.7 (5 very weak signals around 140 from Pfp ring), 132.7, 121.3, 79.5, 41.9, 36.3, 28.3 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, TMS): δ=−76.55 (d, J=18.5 Hz, 2F), −82.60 (t, J=21.5 Hz, 1F), −86.40 ppm (t, J=19.5 Hz, 2F); IR (NaCl): $\tilde{\nu}$=3350, 2980, 2935, 1795, 1700, 1525, 1175, 1095, 1005 cm^{-1}; MS (70 eV): *m/z*: 325 [$M^+-C_4H_8$]; HRMS (70 eV): *m/z*: calcd for $C_{12}H_8F_5NO_4$: 325.0373; found 325.0367 [$M^+-C_4H_8$].

Acid 11: The activated ester **13** (589 mg, 1.61 mmol) was dissolved in a mixture of MeAc (30 mL) and H_2O (2 mL) along with the zwitterionic amino acid **6** (204 mg, 1.77 mmol) and K_2CO_3 (222 mg, 1.77 mmol). The reaction was complete after 2 h. The solution was concentrated under reduced pressure and the residue was taken in CH_2Cl_2 (50 mL) and 1 N aqueous HCl (50 mL). The organic phase was isolated and the remaining aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organics layers were dried on Na_2SO_4, filtrated and hexane (50 mL) was added before the solution was concentrated. The white solid that formed during the concentration was filtrated before complete evaporation of the solvent and rinsed with hexane to afford pure product. More product precipitated in the mother liquor; it was filtered and rinsed in the same way. The combined powder gave pure white product **11** (382 mg, 79%).

Pentafluorophenyl ester 14: Acid **11** (120 mg, 0.38 mmol) and PpfOH (70 mg, 0.38 mmol) were added to a mixture of EtOAc (25 mL) and DMF (2 mL) at RT. DCC (78 mg, 0.38 mmol) in EtOAc (10 mL) was added to the reaction dropwise with an addition funnel. The solution was allowed to stir overnight. Hexane (20 mL) was added and the solution was then filtrated to remove the white precipitate. The clear solution was concentrated and the residue purified by flash chromatography on silica gel eluting with CH_2Cl_2/EtOAc 1:1. The title product was obtained as a white solid (152 mg, 83%). R_f=0.45 (CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, CD_3OD, TMS): δ=8.10 (br, 1H), 6.70 (br, 1H), 5.85–5.55 (m, 4H), 3.81 (m, 2H), 3.63 (m, 2H), 3.51 (d, J=4.5 Hz, 2H), 2.96 (d, J=6.5 Hz, 2H), 1.42 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=170.8, 167.4, 166.0, 156.0, 132.2, 131.9, 124.5, 121.9, 79.5, 42.4, 41.0, 39.8, 37.7, 28.3 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, TMS): δ=−76.55 (d, J=18.5 Hz, 2F), −82.60 (t, J=21.5 Hz, 1F), −86.40 ppm (t, J=19.5 Hz, 2F); IR (NaCl): $\tilde{\nu}$=3355, 2990, 1790, 1705, 1655, 1520, 1000 cm^{-1}; MS (70 eV): m/z: 422 [M^+−C_4H_8]; HRMS (70 eV): m/z: calcd for $C_{17}H_{15}F_5N_2O_5$: 422.0901; found 422.0911 [M^+−C_4H_8].

Acid 15: ***Method 1***: Acid **11** (376 mg, 1.20 mmol) was dissolved in a mixture of TFA (1 mL) and CH_2Cl_2 (3 mL) and stirred for 35 min. Toluene (5 mL) was added to the solution and concentrated in order to remove TFA. This operation was repeated four more times to ensure complete azeotropic removal of TFA. To the resulting residue was added a solution of activated ester **13** (505 mg, 1.32 mmol) in MeAc (20 mL). Aqueous K_2CO_3 (530 mg in 1.5 mL H_2O, 384 mmol) was slowly added and the reaction mixture was stirred for 5 h. The reaction was found to be complete after that time and the solution was concentrated under reduced pressure to remove the MeAc. The residue was diluted with H_2O (5 mL) and washed three times with CH_2Cl_2. The aqueous phase was acidified with 1N aqueous HCl until pH 4 was reached and the acid **15** was simply filtrated and rinsed with H_2O then dried to afford a white powder (405 mg, 82%).

Method 2: A mixture of activated ester **14** (200 mg, 418 μmol), zwitterionic amino acid **6** (50 mg, 439 μmol) and K_2CO_3 (63 mg, 459 μmol) in MeAc (20 mL) and H_2O (1 mL) was stirred for 18 h. The solution was concentrated to remove MeAc and the residue was diluted with H_2O (5 mL) and washed three times with CH_2Cl_2. The aqueous phase was acidified with 1N aqueous HCl until pH 4 was reached and the precipitate was filtrated, rinsed with H_2O then dried to afford the title compound as a white powder (145 mg, 85%). ^{1}H NMR (300 MHz, CD_3OD, TMS): δ=8.1–7.95 (br, 2H), 5.8–5.5 (m, 6H), 3.8–3.75 (m, 4H), 3.62 (d, J=5 Hz, 2H), 3.05 (d, J=7 Hz, 2H), 2.94 (d, J=6 Hz, 4H), 1.43 ppm (s, 9H); IR (NaCl): $\tilde{\nu}$=3335, 3290, 2900 br, 1685, 1630, 1530, 965 cm^{-1}; MS (70 eV): m/z: 409; HRMS (70 eV): m/z: calcd for $C_{20}H_{31}N_3O_6$: 409.2213; found: 409.2206 [M^+].

Pentafluorophenyl ester 16: PfpOH (797 mg, 4.32 mmol) and EDCI (276 mg, 1.44 mmol) were added to dioxane (15 mL). The mixture was heated by means of a heat gun to ensure complete dissolution of the suspension. The resulting clear solution was stirred for 6 h at RT. Dioxane was removed and a thick yellowish oil was obtained. Some of this resulting EDCI·3PFP complex (653 mg, 0.88 mmol) was dissolved in dioxane (2 mL) and added to solution of the acid **15** (120 mg, 0.29 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 24 h and concentrated under reduced pressure to afford a white paste. The crude product was purified by flash chromatography on silica gel starting with CH_2Cl_2 only to elute first the PfpOH, then with MeOH/CH_2Cl_2 1:9 to yield the title product as a white powder (115 mg, 69%). R_f=0.70 (MeOH/CH_2Cl_2 1:9); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=6.24 (br, 1H), 6.12 (br, 1H), 5.8–5.5 (m, 6H), 4.84 (br, 1H), 3.90 (m, 2H), 3.84 (t, J=5 Hz, 2H), 3.70 (t, J=5 Hz, 2H), 3.44 (m, 2H), 2.99 (d, J=8 Hz, 2H), 2.97 (d, J=8 Hz, 2H), 1.44 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=170.9, 170.6, 167.5, 156.1, 132.4, 131.9, 131.4, 124.9, 124.4, 121.9, 79.6, 41.3, 41.0, 39.9, 39.8, 36.3, 28.3 ppm; IR (NaCl): $\tilde{\nu}$=3440, 3355, 3000, 1785, 1705, 1655, 1515, 995 cm^{-1}; MS (70 eV): m/z: 476 [M^+−Boc]; HRMS (70 eV): m/z: calcd for $C_{21}H_{23}F_5N_3O_4$: 476.1609; found: 476.1615 [M^+−Boc].

Conjugated alkene 17: DBU (2 mL, 13.1 mmol) was added to a solution of conjugated thioester **8** (7.81 g, 27.2 mmol) in CH_2Cl_2 (140 mL) and the resulting solution was allowed to stir at RT for 3 d. The solution was washed with aqueous 1N HCl (2×60 mL) and with brine. The organic layer was dried on Na_2SO_4, filtrated and concentrated to afford the title product as an orange oil (7.81 g, 100%). R_f = 0.75 (Et_2O/hexane/AcOH 70:29:1); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=6.81 (td, J=7 Hz, 15.5 Hz, 1H), 6.15 (td, J=1.5 Hz, 15.5 Hz, 1H), 4.56 (br, 1H), 3.27 (m, 2H), 2.94 (t, J=7 Hz, 2H), 2.39 (m, 2H), 1.58 (m, 2H), 1.44 (s, 9H), 1.39 (m, 2H), 0.92 ppm (t, J=7 Hz, 3H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, TMS): δ=189.1, 156.0, 143.3, 129.8, 77.9, 38.7, 32.6, 31.7, 28.6, 28.0, 21.8, 13.8 ppm; IR (NaCl): $\tilde{\nu}$=3340, 3000 br, 1700, 1170 cm^{-1}; MS (70 eV): m/z: 231 [M^+−C_4H_8]; HRMS (70 eV): m/z: calcd for $C_{10}H_{17}NO_3S$: 231.0929; found: 231.0924 [M^+−C_4H_8].

Acid 18: $AgNO_3$ (19.8 g, 117 mmol) was added to a solution of thioester **17** (2.23 g, 7.8 mmol) in THF (72 mL), H_2O (18 mL) and 2,6-lutidine (6.8 mL, 58.2 mmol). The mixture was heated under reflux for 24 h. Glacial acetic acid (20 mL) and Et_2O (400 mL) were added. The solution was filtrated on Celite and washed successively with saturated aqueous $CuSO_4$ (100 mL) and brine (100 mL). Organic layer was dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The crude product (1.31 g) was dissolved in EtOAc (50 mL) and extracted with 3M aqueous K_2CO_3 (50 mL). 1N aqueous HCl was added to the aqueous layer until pH 3 was reached. It was then extracted with EtOAc (3×50 mL). Combined organic extract was dried (Na_2SO_4), filtrated and concentrated to give **18** as a yellow solid (1.26 g, 74%). ^{1}H NMR (300 MHz, CD_3OD, TMS): δ=6.96 (td, J=7 Hz, 15.5 Hz, 1H), 5.84 (td, J=1.5 Hz, 15.5 Hz, 1H), 4.95 (br, 1H), 3.17 (t, J=7 Hz, 2H), 2.37 (qd, J=7 Hz, 1.5 Hz, 2H), 1.42 ppm (s, 9H); ^{13}C NMR (75 MHz, CD_3OD, TMS): δ=168.3, 157.0, 146.3, 122.8, 78.6, 38.5, 32.3, 27.3 ppm; IR (KBr): $\tilde{\nu}$=3365, 3000 br, 1685, 1520, 1280, 1165 cm^{-1}; MS (70 eV): m/z: 159 [M^+−C_4H_8], 200 [M^+−CH_3]; HRMS (70 eV): m/z: calcd for $C_6H_9NO_4$: 159.0532; found: 159.0528 [M^+−C_4H_8], 200.0916 [M^+−CH_3].

Dipeptide 19: TFA (10 mL) was added to a solution of the carbamate **17** (2.0 g, 6.96 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 45 min. Toluene (5 mL) was added to the solution and concentrated. This operation was repeated four more times to ensure complete azeotropic removal of TFA and to yield the corresponding ammonium salt. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=8.15 (br, 3H), 6.74 (m, 1H), 6.20 (d, J=5.5 Hz, 1H), 3.10 (m, 2H), 2.92 (t, J=7.5 Hz, 2H), 2.59 (br q, J=7 Hz, 2H), 1.55 (m, 2H), 1.39 (m, 2H), 0.91 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=190.4, 162.4, 148.1, 143.7, 137.7, 131.5, 38.2, 31.4, 29.7, 28.6, 21.9, 13.6 ppm; IR (NaCl): $\tilde{\nu}$=3000 br, 1680, 1205, 1140, 1020 cm^{-1}; MS (70 eV): m/z: 188 [M+H$^+$]; HRMS (70 eV): m/z: calcd for $C_9H_{18}NOS$: 188.1109; found: 188.1113 [M+H$^+$].

The compound was dissolved in CH_2Cl_2 (60 mL) and NMM (2.3 mL, 20.9 mmol) was added. DMAP (85 mg, 0.7 mmol) and the acid **18** (1.65 g, 7.66 mmol) were added 10 min later. The resulting solution was cooled to 0°C and 1M DCC in CH_2Cl_2 (7.7 mL, 7.7 mmol) was added and stirred for 1 h. The reaction mixture was allowed to warm up to RT and was stirred for 15 h. It was filtered on Celite and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with hexane/EtOAc 30:70 to yield the title product as a white solid (1.15 g, 43%). R_f=0.48 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=6.8–6.6 (m, 3H), 6.07 (d, J=15.5 Hz, 1H), 5.81 (d, J=15.5 Hz, 1H), 4.96 (br, 1H), 3.35 (q, J=6.5 Hz, 2H), 3.13 (br q, J=6.5 Hz, 2H), 2.84 (t, J=7.5 Hz, 2H), 2.35 (q, J=6.5 Hz, 2H), 2.27 (q, J=6.5 Hz, 2H), 1.48 (m, 2H), 1.33 (s, 9H), 1.31 (m, 2H), 0.82 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ=189.8, 165.7, 155.9, 141.0, 140.9, 130.4, 125.3, 79.2, 39.2, 37.9, 32.5, 35.1, 28.4, 28.3, 29.1, 13.5 ppm; IR (KBr): $\tilde{\nu}$=3360, 3300, 2960, 1685, 1625, 1535, 1280, 1175, 975 cm^{-1}; MS (70 eV): m/z: 328 [M^+−C_4H_8]; HRMS (70 eV): m/z: calcd for $C_{15}H_{24}N_2O_4S$: 328.1457; found 328.1451 [M^+−C_4H_8].

Tripeptide 20: TFA (10 mL) was added to a solution of the carbamate **19** (1.15 g, 2.99 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 45 min. Toluene (5 mL) was added to the solution and concentrated. This operation was repeated four more times to ensure complete azeotropic removal of TFA and to yield the corresponding ammonium salt. ^{1}H NMR (300 MHz, CD_3OD, TMS): δ=8.23 (br, 3H), 6.84 (td, J=7 Hz, 15.5 Hz, 1H), 6.68 (td, J=7 Hz, 15.5 Hz, 1H), 6.20 (d, J=15.5 Hz, 1H), 6.07 (d, J=15.5 Hz, 1H), 3.39 (m, 2H), 3.07 (t, J=7 Hz, 2H), 2.92 (t, J=

7 Hz, 2H), 2.55 (q, $J=7$ Hz, 2H), 2.44 (q, $J=6.5$ Hz, 2H), 1.56 (m, 2H), 1.40 (m, 2H), 0.92 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, TMS): $\delta=190.0$, 166.4, 141.5, 137.9, 129.8, 126.5, 38.0, 37.5, 31.5, 29.4, 27.7, 21.5, 12.5 ppm; IR (NaCl): $\tilde{\nu}=2900$ br, 2930, 1670, 1625, 1460, 1210, 1140, 980 cm^{-1}; MS (70 eV): m/z: 285 [M+H$^+$]; HRMS (70 eV): m/z: calcd for $C_{14}H_{25}N_2O_2S$: 285.1637; found: 285.1643 [M+H$^+$].

The salt was dissolved in CH_2Cl_2 (35 mL) and NMM (0.99 mL, 8.97 mmol) was added. DMAP (37 mg, 0.1 mmol) and the acid **18** (708 mg, 3.29 mmol) were added 10 min later. The solution was cooled to 0 °C and 1 M DCC in CH_2Cl_2 (3.29 mL, 3.29 mmol) was added. It was stirred for 1 h, left to warm up to RT and stirred for 15 h. The reaction mixture was filtered on Celite and concentrated under reduced pressure to give a residue that was purified by flash chromatography on silica gel eluting with MeOH/EtOAc 1:9. The desired product **20** was obtained as a white solid (365 mg, 14 %). $R_f=0.42$ (MeOH/hexane 1:9); ^{1}H NMR (300 MHz, CD_3OD, TMS): $\delta=6.9$–6.6 (m, 3H), 6.20 (d, $J=15.5$ Hz, 1H), 5.95 (d, $J=15.5$ Hz, 1H), 5.93 (d, $J=15.5$ Hz, 1H), 3.45–3.25 (m, 4H), 3.15 (q, $J=6.5$ Hz, 2H), 2.93 (t, $J=7$ Hz, 2H), 2.5–2.3 (m, 6H), 1.56 (m, 2H), 1.42 (s, 9H), 1.38 (m, 2H), 0.92 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, TMS): $\delta=190.0$, 167.0, 166.9, 157.0, 141.5, 141.0, 140.8, 129.8, 124.9, 124.9, 78.6, 39.0, 37.8, 37.5, 32.2, 31.6, 31.5, 31.4, 27.7, 27.4, 21.5, 12.6 ppm; IR (KBr): $\tilde{\nu}=3300$, 2935, 1675, 1620, 1455, 1170, 970 cm^{-1}; MS (70 eV): m/z: 482 [M+H$^+$], 499 [M+NH$_4^+$]; HRMS (70 eV): m/z: calcd for $C_{24}H_{40}N_3O_5S$: 482.2688; found: 482.2693 [M+H$^+$], 499.2960 [M+NH$_4^+$].

Pentafluorophenyl ester 21: DIC (1.6 mL, 10.21 mmol) was added to a solution of PfpOH (5.62 g, 30.53 mmol) in EtOAc (10 mL) at 0 °C. The resulting solution was stirred for 15 min, then added to a solution of the acid **18** (1.99 g, 9.25 mmol) in MeCN (20 mL) and dioxane (20 mL) at 0 °C. The reaction was stirred for 17 h at RT, then filtered on Celite. The solution was concentrated and the residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane 3:7 to yield the title product as a colorless oil (3.52 g, 99 %). $R_f=0.4$ (EtOAc/hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta=7.22$ (dt, $J=15.5$ Hz, 7 Hz, 1H), 6.10 (d, $J=15.5$ Hz, 1H), 4.84 (br, 1H), 3.31 (br q, $J=6$ Hz, 2H), 2.51 (br q, $J=6.5$ Hz, 2H), 1.41 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta=161.6$, 155.8, 151.5, 119.7, 79.5, 38.7, 33.4, 28.1 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, TMS): $\delta=-76.55$ (d, $J=18.5$ Hz, 2F), −82.60 (t, $J=21.5$ Hz, 1F), −86.40 ppm (t, $J=19.5$ Hz, 2F); IR (NaCl): $\tilde{\nu}=3355$, 2980, 2935, 1765, 1695, 1655, 1520, 1370, 1255, 1170, 1005 cm^{-1}; MS (70 eV): m/z: 399 [M+NH$_4^+$]; HRMS (70 eV): m/z: calcd for $C_{16}H_{20}F_5N_2O_4$: 399.1343; found: 399.1352 [M+NH$_4^+$].

Cyclo-oligomerisation of pentafluophenyl ester 13 to lactams 1–3: Carbamate **13** (106 mg, 0.29 mmol) was dissolved in a mixture of CH_2Cl_2 (3 mL) and TFA (1 mL) and stirred for 45 min at RT. The resulting mixture was concentrated under reduced pressure and the residual TFA was co-evaporated with toluene under reduced pressure. The same procedure was repeated four more times. The corresponding ammonium salt was dissolved in dioxane (112 mL) and a solution of NMM (320 μL, 2.9 mmol) in dioxane (1 mL) was added to the reaction mixture. The solution was then stirred for 18 h at 80 °C and then concentrated. The crude residue was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 1:9 to 3:7. Pure macrolactams **1** (6 mg, 21 %), **2** (10 mg, 37 %) and **3** (3 mg, 12 %) were obtained as solids.

Lactam **1**: $R_f=0.70$ (MeOH/CH_2Cl_2 1:4), 0.36 (MeOH/EtOAc 1:4); m.p. degradation at 275 °C; ^{1}H NMR (300 MHz, CD_3OD, TMS): $\delta=6.15$–5.85 (m, 4H), 3.51 (d, $J=7$ Hz, 4H), 2.68 ppm (d, $J=7$ Hz, 4H); ^{13}C NMR (75 MHz, CD_3OD, TMS): $\delta=176.56$, 133.44, 130.29, 39.19, 39.09 ppm; IR (KBr): $\tilde{\nu}=3300$, 2930, 1680, 1640, 1530, 1440, 1230, 1170, 970 cm^{-1}; MS (70 eV): m/z: 194 [M^+]; HRMS (70 eV): m/z: calcd for $C_{10}H_{14}N_2O_2$: 194.1055; found: 194.1058 [M^+].

Lactam **2**: $R_f=0.55$ (MeOH/CH_2Cl_2 1:4), 0.72 (MeOH/CH_2Cl_2 3:7); m.p. degradation at 250 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): $\delta=7.75$ (br t, $J=5.5$ Hz, 3H), 5.60–5.45 (m, 6H), 3.63 (br d, $J=4.5$ Hz, 6H), 2.81 ppm (br d, $J=2.5$ Hz, 6H); ^{1}H NMR (300 MHz, CD_3OD, TMS): $\delta=7.92$ (br, 3H), 5.75–5.55 (m, 6H), 3.79 (m, 6H), 2.95 ppm (m, 6H); ^{13}C NMR (75 MHz, CD_3OD, TMS): $\delta=172.6$, 130.2, 124.2, 40.0, 39.3 ppm; IR (KBr): $\tilde{\nu}=3360$, 3300, 3070, 2905, 1645, 1545, 1420, 1285, 975 cm^{-1}; MS (70 eV): m/z: 291 [M^+]; HRMS (70 eV): m/z: calcd for $C_{15}H_{21}N_3O_3$: 291.1583; found 291.1585 [M^+].

Lactam **3**: $R_f=0.45$ (MeOH/CH_2Cl_2 1:4); m.p. degradation at 250 °C; ^{1}H NMR (300 MHz, CD_3OD, TMS): $\delta=8.10$ (m, 4H), 5.75–5.55 (m, 8H), 3.76 (d, $J=4$ Hz, 8H), 2.94 ppm (d, $J=6$ Hz, 8H); ^{13}C NMR (75 MHz, CD_3OD, TMS): $\delta=172.4$, 129.9, 124.2, 40.2, 39.2 ppm; IR (NaCl): $\tilde{\nu}=2950$, 1685, 1650, 1545, 1440, 1205, 1135, 970 cm^{-1}; MS (70 eV): m/z: 388 [M^+]; HRMS (70 eV): m/z: calcd for $C_{20}H_{28}N_4O_4$: 388.2110; found 388.2104 [M^+].

Macrocyclization and cyclooligomerisation of pentafluorophenyl ester 14 to lactams 1 and 3: Carbamate **14** (102 mg, 0.21 mmol) was dissolved in a mixture of CH_2Cl_2 (5 mL) and TFA (1 mL) and stirred for 45 min at RT until complete removal of the *tert*-butyl carbamate protecting group. The resulting mixture was concentrated under reduced pressure and the residual TFA was co-evaporated with toluene under reduced pressure. The same procedure was repeated four more times. The crude ammonium salt was dissolved in dioxane (100 mL) and a solution of NMM (230 μL, 2.1 mmol) in dioxane (1 mL) was added. The solution was then stirred for 18 h at 80 °C and then concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 1:9 to 1:4 to afford the pure lactams **1** (9 mg, 22 %) and **3** (20 mg, 49 %) as solids.

Macrocyclization of thioester 10 to lactam 2: Carbamate **10** (197 mg, 0.41 mmol) was dissolved in a mixture of CH_2Cl_2 (3 mL) and TFA (1 mL) and stirred for 45 min at RT. The resulting mixture was concentrated under reduced pressure and the residual TFA was co-evaporated with toluene under reduced pressure. The same procedure was repeated 4 more times. The corresponding ammonium salt was dissolved in DMF (60 mL). DIPEA (78 μL, 0.45 mmol) was then added followed by AgTFA (272 mg, 1.23 mmol). The solution was heated to 45 °C during 45 min and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with MeOH/EtOAc 15:85 to give lactam **2** (66 mg, 55 %) as a white solid.

Macrocyclization of pentafluorophenyl ester 16 to lactam 2: The activated ester **16** (45 mg, 0.078 mmol), dissolved in a mixture of CH_2Cl_2 (1 mL) and TFA (0.2 mL), was stirred for 45 min at RT until complete removal of the *tert*-butyl carbamate group. The resulting mixture was concentrated under reduced pressure and the residual TFA was co-evaporated with toluene under reduced pressure. The same procedure was repeated four more times. The resulting ammonium salt was dissolved in dioxane (30 mL) and NMM (86 μL, 0.780 mmol) was added in the reaction. The solution was then stirred for 18 h at 80 °C and then concentrated. The crude residue was purified by flash chromatography on silica gel eluting MeOH/CH_2Cl_2 1:9 to 1:4 to give pure lactam **2** (20 mg, 88 %).

Macrocyclisation of thioester 12 to lactam 3: Carbamate **12** (14 mg, 24 μmol) was dissolved in a mixture of CH_2Cl_2 (3 mL) and TFA (1 mL) and stirred for 45 min at RT. The resulting mixture was concentrated under reduced pressure and the residual TFA was co-evaporated with toluene under reduced pressure. The same procedure was repeated four more times. The corresponding ammonium salt was dissolved in DMF (5 mL). DIPEA (17 μL, 96 μmol) was then added followed by AgTFA (16 mg, 72 μmol). The solution was kept at 45 °C and stirred during 80 min, then concentrated. The crude residue was purified by flash chromatography on silica gel eluting with MeOH/EtOAc 3:7 to give lactam **3** (7 mg, 67 %) as a white solid.

Cyclooligomerization of pentafluorophenyl ester 21 to lactams 4 and 24: Carbamate **21** (294 mg, 0.77 mmol) was dissolved in a mixture of CH_2Cl_2 (2 mL) and TFA (1 mL) and stirred for 45 min at RT until complete removal of the protecting group. The resulting mixture was concentrated under reduced pressure and the residual TFA was co-evaporated with toluene under reduced pressure. The same procedure was repeated 4 more times. The resulting ammonium salt was dissolved in dioxane (10 mL) and added over a 1 h period to a solution of NMM (980 μL, 8.91 mmol) in dioxane (440 mL). The solution was then stirred for 18 h at 80 °C, then concentrated. The crude residue was purified by flash chromatography on silica gel eluting with MeOH/EtOAc 3:7 to 1:3. The pure lactams **4** (36 mg, 41 %) and six-membered lactam **24** (6 mg, 7 %) were obtained as a white solid and as a colorless oil, respectively.

Lactam **4**: $R_f = 0.55$ (MeOH/EtOAc 1:1); m.p. degradation at 250 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS): $\delta = 7.56$ (br t, $J = 6$ Hz, 3H), 6.33 (dt, $J = 15.5$ Hz, $J = 7$ Hz, 6H), 5.68 (d, $J = 15.5$ Hz, 3H), 3.24 (br q, $J = 6$ Hz, 6H), 2.25 ppm (br m, 6H); ^{1}H NMR (300 MHz, CD$_3$OD, TMS): $\delta = 7.82$ (3H, m), 6.56 (dt, $J = 15.5$ Hz, $J = 7$ Hz, 6H), 5.79 (dt, $J = 15.5$ Hz, $J = 1.5$ Hz, 3H), 3.42 (m, 6H), 2.41 ppm (m, 6H); ^{13}C NMR (75 MHz, CD$_3$OD, TMS): $\delta = 166.5$, 140.4, 125.8, 36.6, 31.4 ppm; IR (KBr): $\tilde{\nu} = 3300$, 3095, 2915, 1675, 1635, 1560, 980 cm^{-1}; MS (70 eV): m/z: calcd for $C_{15}H_{21}N_3O_3$: 291.1583; found 291.1571 [M^+].

Lactam **24**: $R_f = 0.68$ (MeOH/EtOAc 1:1); ^{1}H NMR (300 MHz, CD$_3$OD, TMS): $\delta = 6.78$ (dt, $J = 10$ Hz, $J = 4$ Hz, 1H), 5.83 (dt, $J = 10$ Hz, $J = 0.5$ Hz, 1H), 3.38 (t, $J = 7.5$ Hz, 2H), 2.36 ppm (m, 2H); ^{13}C NMR (75 MHz, CD$_3$OD, TMS): $\delta = 167.1$, 142.8, 123.2, 38.6, 23.5 ppm; IR (KBr): $\tilde{\nu} = 3350$, 1670, 1603, 1490, 1430, 1380, 1345, 1210, 1140, 810 cm^{-1}; MS (70 eV): m/z: 98 [M+H$^+$]; HRMS (70 eV): m/z: calcd for C_5H_8NO: 98.1095; found 98.1092 [M+H$^+$].

Macrocyclization of thioester 20 to lactam 4: Carbamate **20** (365 mg, 0.76 mmol) was dissolved in a mixture of CH_2Cl_2 (20 mL) and TFA (10 mL) and stirred for 45 min at RT. The resulting mixture was concentrated under reduced pressure and the residual TFA was co-evaporated with toluene (5 mL) under reduced pressure (same procedure repeated four times) to afford the corresponding ammonium salt. ^{1}H NMR (300 MHz, CD$_3$OD, TMS): $\delta = 8.15$ (br, 3H), 6.84 (dt, 1H, $J = 15.5$ Hz, $J = 7$ Hz, 1H), 6.75–6.6 (m, 2H), 6.20 (d, $J = 15.5$ Hz, 1H), 6.06 (d, $J = 15.5$ Hz, 1H), 5.95 (d, $J = 15.5$ Hz, 1H), 3.4–3.3 (m, 4H), 3.06 (t, $J = 6.5$ Hz, 2H), 2.93 (t, $J = 7$ Hz, 2H), 2.55 (q, $J = 6.5$ Hz, 2H), 2.5–2.35 (m, 4H), 1.56 (m, 2H), 1.40 (m, 2H), 0.93 ppm (t, $J = 7.5$ Hz, 3H); IR (KBr): $\tilde{\nu} = 2930$, 1670, 1625, 1460, 1210, 1140, 980 cm^{-1}. The ammonium salt was dissolved in DMF (70 mL). DIPEA (146 μL, 0.84 mmol) was then added followed by AgTFA (503 mg, 2.28 mmol). The solution was stirred at 45 °C during 45 min and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with MeOH/EtOAc 1:9 to 3:7 to give lactam **4** as a white solid (111 mg, 50 %).

Crystallography (Table 3)[59]

Ring 1: The data were collected on a Nonius CAD4 diffractometer; $Cu_{K\alpha}$; ω and θ scan; the structure was solved by the application of direct methods and refined using SHELX97;[78] the refinements were against $|F^2|$, the data were reduced using XCAD4 (K. Harms, S. Wocadlo, University of Marburg, Germany), all programs included in the WinGX package;[79] the H atoms were geometrically placed.

Rings 2 and 3: A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer; CCD area detector; $Mo_{K\alpha}$; ω and ϕ scans with a scan width of 0.3° and 40 s (**2**) or 30 s (**3**) exposure times; The detector distance was 6 cm (**2**) or 5 cm (**3**). The data were reduced (SAINT 6.02, 1997–1999, Bruker AXS, Inc., Madison, Wisconsin, USA.) and corrected for absorption (SADABS, George Sheldrick, 1999, Bruker AXS, Inc., Madison, Wisconsin, USA). The structures were solved by direct methods and refined by full-matrix least squares on F^2 (SHELXTL 5.1, George Sheldrick, 1997, Bruker AXS, Inc., Madison, Wisconsin, USA).

Table 3. Crystallographic data for rings **1**–**3**.

	1	**2**	**3**
formula	$C_{10}H_{14}N_2O_2$	$C_{15}H_{21}N_3O_3$	$C_{20}H_{28}N_4O_4$
F_w	194.23	291.35	388.46
T [K]	293(2)	198(1)	198(1)
λ [Å]	1.54176	0.71073	0.71073
crystal system	orthorhombic	triclinic	monoclinic
space group	*Pbnb*	*P*1	*P*2(1)/*c*
a [Å]	7.557(3)	4.6797(18)	11.295(3)
b [Å]	9.662(5)	7.606(3)	10.301(3)
c [Å]	14.100(6)	10.983(5)	9.437(2)
α [°]	90	72.878(6)	90
β [°]	90	78.027(4)	113.020(4)
γ [°]	90	88.016(4)	90
V [Å^3]	1029.5(8)	365.3(3)	1010.6(4)
Z	4	1	2
ρ_{calcd} [mg m^{-3}]	1.253	1.324	1.277
μ [mm^{-1}]	0.723	0.094	0.090
F(000)	416	156	416
crystal size [mm]	0.4 × 0.25 × 0.15	0.6 × 0.35 × 0.05	0.3 × 0.2 × 0.025
θ range [°]	6.65–69.76	1.98–25.69	1.96–27.49
completeness [%]	95.9	90.4	97.4
index ranges	$0 < h < 9$	$-5 < h < 5$	$-13 < h < 14$
	$0 < k < 11$	$-8 < k < 8$	$-12 < k < 13$
	$0 < l < 17$	$-12 < l < 13$	$-12 < l < 12$
reflns collected	935	1717	6816
independent reflns	935	1170	2255
R(int)	0.0000	0.0109	0.0317
absorb correction	empirical	SADABS	SADABS
max/min transmission	0.9753/0.6734	0.9953/0.9460	Ratio 0.688
data/restraints/params	935/38/129	1170/3/209	2255/5/227
GOF on F^2	0.984	1.103	1.022
final R indices [$I > 2\sigma(I)$]			
R_1	0.0751	0.040	0.0399
wR_2	0.1829	0.1051	0.0892
R indices (all data)			
R_1	0.1286	0.0438	0.0761
wR_2	0.2156	0.1108	0.0972
largest diff. peak/hole [e Å^{-3}]	0.248/−0.187	0.291/−0.199	0.179/−0.156

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