Fine Tuning of the Cation Affinity of Artificial Receptors Based on Cyclic Peptides by Intramolecular Conformational Control

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A series of cyclic hexapeptides consisting of alternating 4-substituted 3-aminobenzoic acid units (R = CH_3, Cl, CH_2OCH_3, OCH_3, $COOCH_3$) and residues of the natural amino acid proline has been prepared and their ion affinities have been investigated. Whereas the unsubstituted parent compound (R = H) is able to bind cations through cation–π interactions with the aromatic subunits, as well as anions through hydrogen bonding with the peptide NH groups, the introduction of substituents at the 4-positions of the aromatic rings results in complete loss of the anion affinity. The cation complex stabilities depend on the substituents and cover a wide range from K_a = 140 M^{-1} for R = CH_3 to K_a = 10800 M^{-1} for R = $COOCH_3$ (K_a = 1260 M^{-1} for R = H) with *n*-butyltrimethylammonium picrate. The conformations of the peptides in solution have been determined by one- and two-dimensional NMR techniques and FT-IR spectroscopy. It was found that all the substituents prevent the peptides from adopting the necessary conformation for anion binding. For one receptor (R = OCH_3), the results have been corroborated by a crystal structure determination. AM1 calculations have been used to estimate the electrostatic potential surfaces of the substituted aromatic subunits. The variation in the cation complex stabilities can be mainly attributed to the effects of the substituents on the solution conformations of the peptides. The influence of the substituents on the electrostatic potentials of the aromatic peptide subunits appears to be less important.

Introduction

The biological activity of a protein is critically dependent on the folding of the peptide chain. The chain folding process itself is highly complex and is controlled by a large number of cooperative interactions between the individual protein subunits,[1] the most important factors being electrostatic or hydrophobic interactions, hydrogen bonding, and the steric demand of the various amino acid residues. In supramolecular chemistry, such interactions are utilized to control the conformations and binding properties of artificial receptors.[2,3] For example, calixarenes are relatively flexible and adopt a number of different conformations in solution, but by introducing bulky substituents on the lower rim of these macrocycles it is possible to stabilize a symmetrical, so-called *cone* conformation, which is best suited for substrate binding.[4−7] In this case, the conformational stabilization stems from the steric bulk of the substituents, which prevents ring inversion of the aromatic subunits. In the self-folding cavitands described by Rebek and coworkers, a seam of hydrogen bonds at the open end of these container molecules is used to stabilize a vase-like conformation with a well-defined cavity.[8,9] These receptors form kinetically very stable complexes with suitable guests, and it has been shown that complex formation is even possible in water.[10] Another receptor in which conformational control is based on intramolecular hydrogen bonds has been introduced by ourselves.[11]

In 1995, Ishida et al. described a cyclic peptide that acted as a receptor for phosphomonoesters in [D_6]DMSO,[12] but in the same solvent the complexation of cations was not observed. We recently described a similar cyclic peptide made up of L-glutamic acid and 3-aminobenzoic acid residues, for which an association constant of 300 M^{-1} with *n*-butylammonium iodide in chloroform was determined.[13] Subsequently, we prepared the receptor **1d**, based on a cyclic peptide composed of alternating proline and 3-aminobenzoic acid subunits.[14] Peptides of this general structure bind cations, such as quaternary ammonium ions, through cation−π interactions.[15,16] The cations are held in the shallow dish-shaped cavity of the peptide, the conformation of which resembles the *cone* conformation of calixarenes. Interestingly, anions can also interact with these peptides, i.e. when they are able to form hydrogen bonds to the peptide amide groups. Anion complexation results in the stabilization of a receptor conformation where all the NH groups point towards the center of the cavity. In the absence of suitable anions, the peptides are more flexible due to the large number of rotatable bonds between their aromatic subunits. Although the flexibility can be somewhat reduced by using proline subunits as the natural amino acid, cyclopeptide **1d** is not completely rigid as there is still conformational flexibility of the bonds around the secondary amide groups.[14]

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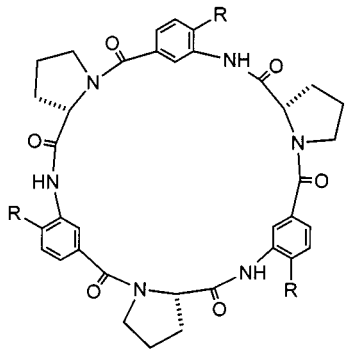


1a: R = CH_3
1b: R = Cl
1c: R = CH_2OCH_3
1d: R = H
1e: R = OCH_3
1f : R = $COOCH_3$

More recently, we have succeeded in suppressing amide rotation through the introduction of methoxycarbonyl groups at the 4-positions of the aromatic peptide subunits (**1f**).[11] These groups form strong intramolecular hydrogen bonds to neighboring NH groups, and lock the amides in a fixed conformation.[17] The introduction of such substituents into the cyclopeptide leads to a significant reduction in its flexibility, thereby resulting in improved cation binding ability. An interesting consequence of this is that, because the NH groups are locked in an orientation unsuitable for interaction with anions, no anion complexation can be detected.[11]

In this paper, we extend the series of new substituted cyclic peptides, and study the influence of substituents on the conformations and complexing abilities of these compounds.

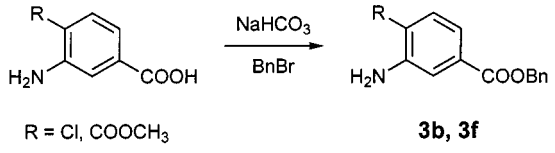
Results and Discussion

Preparation of Cyclopeptides 1a−1f

Following our findings that methoxycarbonyl substituents have a significant effect on the conformation and ion binding properties of the cyclic hexapeptide **1f**,[11] we decided to prepare and study a series of these cyclopeptides with various substituents in the 4-position with the aim of gaining some insight into the nature of the influence of the substituent type on the properties.

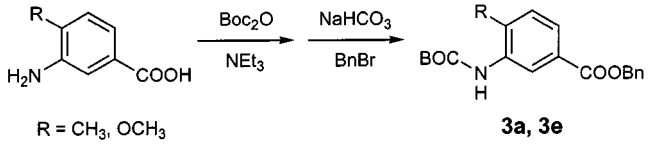
We chose to examine five derivatives, specifically those with methyl (**1a**), chloro (**1b**), methoxymethyl (**1c**), methoxy (**1e**), and methoxycarbonyl substituents (**1f**). The latter four contain an electronegative atom, i.e. oxygen or chlorine, which can interact with an NH group through hydrogen bonding. The conformational stabilization of **1f** by hydrogen bonding between the methoxycarbonyl substituents and the amide groups has already been demonstrated.[11] We expected similar, albeit probably weaker effects, in all the other cyclopeptides except **1a**, where only steric effects are expected to play a role. We include the unsubstituted peptide **1d**[14] in this discussion for comparison purposes.

The syntheses of the peptides **1a**, **1b**, **1c**, **1e**, and **1f** are straightforward because, in most cases, the corresponding 3-aminobenzoic acid derivatives are commercially available. 1-Methyl aminoterephthalate and 3-amino-4-chlorobenzoic acid were directly converted into the corresponding benzyl esters by reaction with benzyl bromide/$NaHCO_3$ in DMF (Scheme 1). 3-Amino-4-methylbenzoic acid and 3-amino-4-methoxybenzoic acid were converted into the benzyl esters via their Boc-protected derivatives (Scheme 2). Benzyl 3-amino-4-(methoxymethyl)benzoate was obtained from the Boc-protected methyl 3-amino-4-methylbenzoate by a sequence of NBS bromination, nucleophilic substitution of the bromine by methylate, and transesterification, followed by cleavage of the Boc group (Scheme 3).



R = Cl, $COOCH_3$ **3b, 3f**

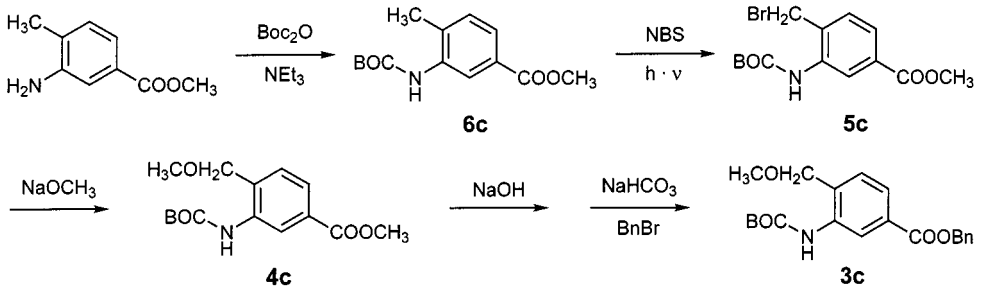
Scheme 1



R = CH_3, OCH_3 **3a, 3e**

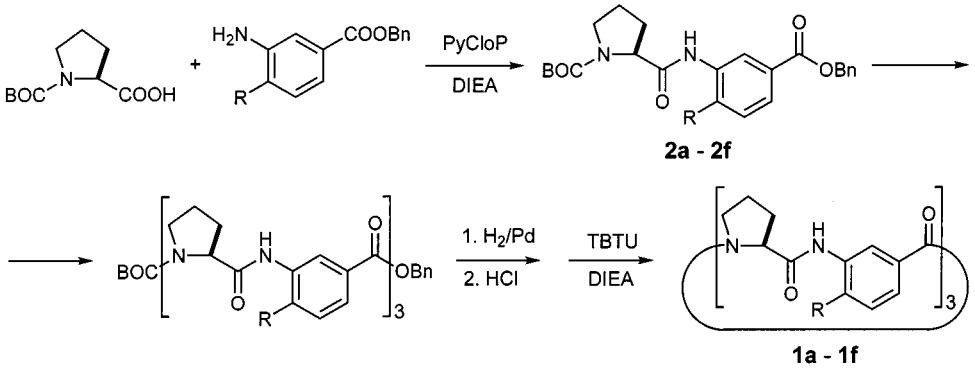
Scheme 2

All the benzyl esters were coupled with Boc-(L)-proline using PyCloP as the coupling reagent. The dipeptides were chain elongated to give the linear hexapeptides according to standard peptide synthesis protocol. The fully deprotected hexapeptides were cyclized under high dilution conditions and were typically obtained in yields in the range 20−50% (Scheme 4).



6c **5c** **4c** **3c**

Scheme 3



Scheme 4

Complexation of Various *n*-Butyltrimethylammonium Salts by 1a−1f

Complex formation between the cyclopeptides and cationic guests was followed both qualitatively and quantitatively by NMR spectroscopy. As representative guest molecules, the picrate, iodide, and tosylate salts of the *n*-butyltrimethylammonium cation ($BTMA^+$) were chosen. The same salts were also used in our investigations on the complexing behavior of **1d**[14] and **1f**[11] and hence comparisons with previous results can easily be made.

As in the case of cyclopeptide **1d**,[14] the addition of $BTMA^+$ salts to solutions of the substituted peptides in $CDCl_3$ resulted in significant upfield shifts of all the $BTMA^+$ proton signals of up to ca. 0.6 ppm. This effect has been explained in terms of the inclusion of the cationic guest in the receptor cavity, which brings the guest protons in close proximity to the aromatic subunits, where they experience a shielding.[15,16]

The stabilities of the $BTMA^+$ complexes of the various peptides were quantitatively determined by means of NMR titrations.[18,19] Increasing amounts of the host were added to a solution of the $BTMA^+$ salt in $CDCl_3$ and the shifts of the guest proton resonances were followed in the ^1H NMR spectra. Stability constants were calculated from the resulting saturation curves using a nonlinear least-squares fitting method for 1:1 complexes. Representative titration curves are depicted in Figure 1a. The 1:1 complex stoichiometry for the complex between **1f** and $BTMA^+$ picrate was confirmed by using Job's method of continuous variations (Figure 1b).[18,20] In view of the excellent fits between the calculated and observed saturation curves in our titrations, it seems reasonable to assume that the same stoichiometry holds for all the complexes. The titrations were usually repeated several times, and the error limit of the method is well below 20%. Since the ^1H NMR spectra of the peptides are not significantly affected by varying the concentration in the range 2.0−0.2 mM, intermolecular association of the receptors under these conditions can be ruled out. For all the substituted cyclopeptides, the calculated stability constants (K_a) proved to be independent of the choice of the $BTMA^+$ proton which was followed during the titrations. Consequently, only the results derived from the shift of the $BTMA^+$ *N*-methyl proton resonances are summarized in Table 1. Stability constants below 50 M^{-1} could not be determined accurately by our method because of the low solubility of the cyclopeptides in $CDCl_3$ at higher concentrations, so that in the case of $BTMA^+$ iodide with **1a** only the general trend is indicated in the table.

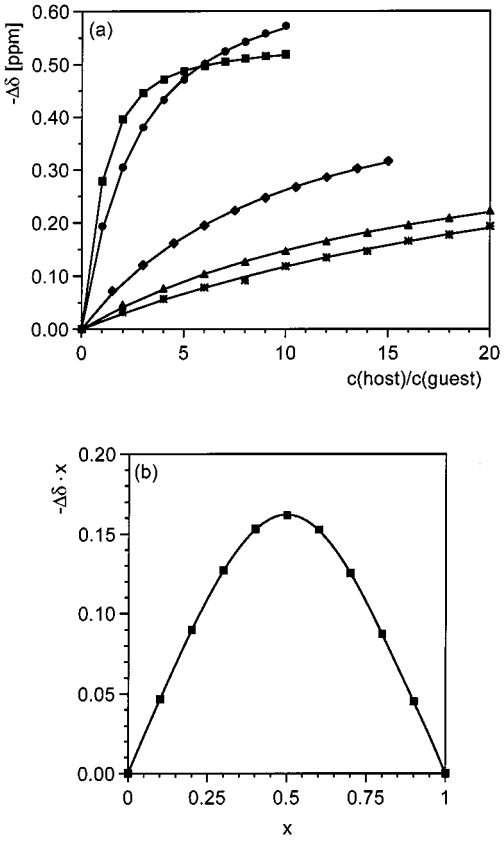


Figure 1. (a) ^1H NMR titration curves of complexes of peptides **1a** (stars), **1b** (triangles), **1c** (diamonds), **1e** (circles), and **1f** (squares) with $BTMA^+$ picrate; (b) Job plot of the complex between **1f** and $BTMA^+$ picrate

It is evident from these results that the various substituents on the investigated cyclopeptides have a marked influence on cation complex formation. The stability constants of the $BTMA^+$ picrate complexes vary over two orders of magnitude from ca. 100 M^{-1} for **1a** to ca. 10000 M^{-1} for **1f**. Furthermore, it is clear that whereas the stability constants for unsubstituted cyclopeptide **1d** increase on going from the picrate to the iodide and to the tosylate, for all the other

Table 1. $BTMA^+$ complex stabilities in $CDCl_3$ at 298 K (K_a stability constant in M^{-1}, error limits for $K_a < 20\%$; $\Delta\delta_{max}$ maximum chemical shift; ΔG_H = Gibbs free energy of hydration of the anions in $kJ \cdot mol^{-1}$)

	$BTMA^+$ picrate		$BTMA^+$ iodide		$BTMA^+$ tosylate	
	K_a	$-\Delta\delta_{max}$	K_a	$-\Delta\delta_{max}$	K_a	$-\Delta\delta_{max}$
1a	140	0.51	< 50		100	0.54
1b	290	0.42	110	0.34	60	0.30
1c	550	0.51	230	0.60	140	0.52
1d[14]	1260	0.70	21100	1.11	5050000	1.16
1e	2700	0.68	850	0.73	340	0.56
1f[11]	10800	0.54	3310	0.59	740	0.54
$-\Delta G_H$	197		283		318	

cyclic peptides they decrease. Only in the case of **1a** (R = Me) is a slight deviation from this sequence observed. In the case of the unsubstituted cyclopeptide **1d**, the increase in cation complex stability with iodide as the counterion, and even more so with tosylate, has been attributed to a simultaneous complexation of the anion and cation, which is possible with these anions but not with picrate.[14] Since none of the other cyclopeptides exhibit a similar K_a dependence, we assume that these receptors are not capable of anion complexation. FT-IR spectroscopic investigations support this assumption, since no dependence of the NH vibrational frequencies of the various substituted cyclopeptides on the nature of the anion could be detected.

In the case of **1f** (R = CO_2Me), a reduced anion affinity has been attributed to hydrogen-bonding interactions between the peptide NH groups and the adjacent methoxycarbonyl substituents.[11] Such interactions are certainly not possible in **1a** (R = Me), and therefore other factors must be invoked to account for the lack of anion affinity of this cyclopeptide. The crystal structure of the iodide complex of the unsubstituted **1d** shows that for anion complexation the aromatic subunits and the secondary amide groups have to adopt an almost coplanar conformation, with the amide carbonyl group pointing towards the proton in the 4-position.[14] We assume that unfavorable steric interactions between the aromatic methyl substituent and the neighboring carbonyl groups prevent **1a** from adopting such a structure. This assumption is supported by the results of molecular modeling calculations. When methyl groups are introduced into the structure of the anion complex of parent compound **1d**, the secondary amide groups tilt away from the center of the cavity upon energy minimization and possible anion interactions are lost. Clearly, the steric effects of suitably positioned substituents on the aromatic rings of **1d** are sufficient to eliminate its anion affinity. Only the slight deviation of the dependence of cation complex stability on the type of anion from the order picrate > iodide > tosylate may account for the weak anion complexation by **1a**. With all the other substituted cyclopeptides, steric effects of the substituents certainly also contribute to the loss of anion affinity of these receptors.

The fact that the stability constants of the complexes of the substituted cyclopeptides decrease in the order picrate > iodide > tosylate probably stems from various factors. Bartsch et al. have reported that the extraction efficiency of certain crown ether salt complexes shows an inverse correlation with the hydration enthalpy of the anion.[21] In accordance with these findings, the stabilities of the $BTMA^+$ complexes of the substituted cyclopeptides decrease with increasing Gibbs free energy of hydration of the anion.[22] Roelens et al. recently described a similar anion dependence with regard to cation−π interactions between salts of quaternary ammonium ions and cyclophane hosts.[23] They concluded that the higher the charge density on the anion, the stronger the charge polarization of the quaternary ammonium cation, and the less available the cation becomes for interactions with the host. Ion-pair aggregation thus strongly influences the cation complex stabilities of artificial receptors in non-polar solvents. In addition, the high stability of the cyclopeptide complexes with $BTMA^+$ picrate may be a consequence of the so-called "picrate effect".[24] This effect is due to π−π interactions between the picrate anions and aromatic subunits of an artificial receptor, which occur when cations are incorporated into the receptor cavity. In agreement with these observations, we found a small but characteristic upfield shift of the picrate proton signals in the ^1H NMR spectra of the $BTMA^+$ picrate complexes of our cyclopeptides.

In summary, the dependence of the stabilities of cation complexes of the substituted cyclopeptides on the nature of the anion is mainly influenced by ion-pair aggregation and to a lesser extent by specific interactions of the anions with the receptors. In the following discussion, we therefore focus on the effects of the aromatic substituents on the $BTMA^+$ picrate complex stabilities. Two major factors may be responsible for the observed dependence of complex stability on the type of substituent. Firstly, there is the effect of the substituents on the solution conformation of the peptides, and secondly, the different electrostatic potentials of the aromatic peptide subunits. Both factors will affect the cation−π interactions with the guests.

Conformational Studies of 1a−1f

The solution conformations of the substituted cyclopeptides were studied by NMR and FT-IR spectroscopy. The ^1H NMR spectra of **1c** and **1f** in $CDCl_3$ are rather complex, which indicates that interconversion of the various cyclopeptide conformers is slow on the NMR time scale, and hence that these peptides are conformationally relatively rigid. The reduced flexibility is probably due to hydrogen bonds between the amide NH groups and the oxygen atoms of the corresponding substituents, which would prevent amide rotation. This assumption is corroborated by the FT-IR spectroscopic investigations described below.

The remaining substituted cyclopeptides exhibit NMR spectra consistent with averaged C_3-symmetric conformations, and hence their solution conformations can easily be investigated by NOESY NMR. The most important indications of the preferred conformation are the NOEs involving the secondary amide NH groups. In peptide **1a** (R = Me), the NH protons exhibit NOEs with H(α) of the adjacent proline residues, as well as with H(2) of the aromatic rings

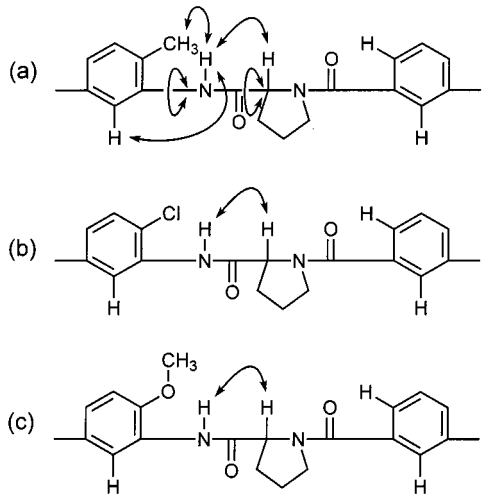


Figure 2. Intramolecular NOEs in the NOESY NMR spectra of **1a** (a), **1b** (b), and **1e** (c) in $CDCl_3$

(Figure 2a). A weaker NOE between NH and the aromatic methyl group is also in evidence. Such multiple effects can be accounted for in terms of conformational flexibility of the secondary amides that results from the NH groups being oriented either towards or away from the aromatic methyl group. In contrast, in the NOESY NMR spectra of peptides **1b** (R = Cl) and **1e** (R = OCH_3), cross-peaks are only visible between the NH groups and the proline H(α) (Figures 2b and 2c).

In these peptides, the secondary amide moieties are thus preferentially oriented towards the corresponding aromatic substituents, possibly because of hydrogen-bonding interactions with the oxygen or chlorine atom. In the case of **1e** (R = OCH_3), this observation could be confirmed by a crystal structure determination of the compound (Figure 3).

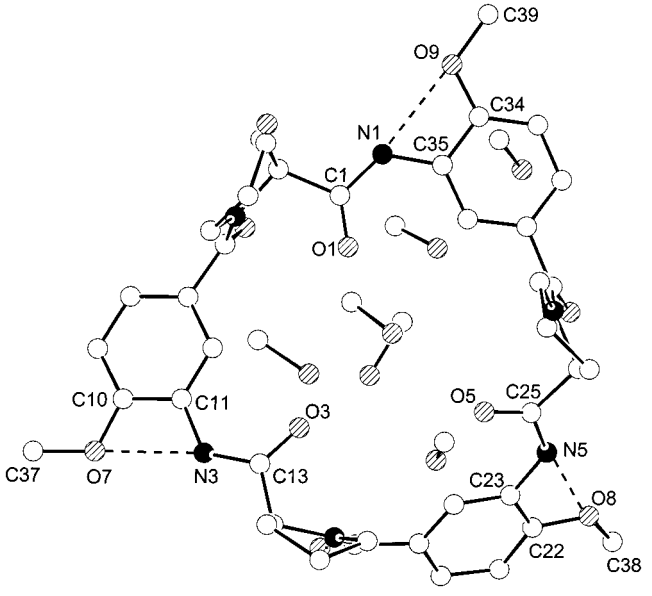


Figure 3. Molecular structure of cyclopeptide **1e**·7MeOH viewed perpendicular to a plane through the amide N atoms N1, N3, and N5 showing the near C_3 point symmetry of the cyclopeptide; the following groups of atoms are approximately coplanar: O1, C1, N1, C35, C34, O9, C39 (r.m.s. deviation 0.04 Å); O3, C13, N3, C11, C10, O7, C37 (r.m.s. deviation 0.07 Å); O5, C25, N5, C23, C22, O8, C38 (r.m.s. deviation 0.07 Å)

1e crystallizes from methanol with seven solvent molecules per peptide unit. In spite of the appreciable polarity of this solvent, no interactions of the NH protons with solvent molecules are apparent in the crystal. Indeed, all three peptide NH groups are oriented towards the adjacent methoxy substituents and are only involved in hydrogen bonding to the oxygen atoms of these substituents. As a result, the overall peptide conformation is highly symmetrical. Similar conformational stabilization of peptides by aromatic methoxy substituents has recently been demonstrated by Nowick et al.[25] as well as by Gong et al.[26,27]

Hydrogen-bonding interactions in solution between the Cl and NH groups in **1b** and between the OCH_3 and NH groups in **1e** are also evident from the FT-IR spectra of these peptides. The results of the FT-IR spectroscopic investigations on all the cyclopeptides are summarized in Table 2. In the spectra of the unsubstituted cyclopeptide **1d**, the weak bands at 3425 cm^{-1} and 3408 cm^{-1} have been assigned to the vibrations of free NH groups.[14] Another weak band appears in the same spectral region at 3268 cm^{-1}, which can be attributed to NH groups involved in intramolecular hydrogen bonds with the carbonyl groups of the adjacent tertiary amides.[28] This interaction does not appear to be strong. No band due to free NH groups is visible in the FT-IR spectra of **1b** or **1e** and the sharp, strong bands at 3410 cm^{-1} for **1b** and 3414 cm^{-1} for **1e** can be attributed to the respective NH···Cl and NH···OCH_3 interactions. The second band at lower frequency is much stronger in the FT-IR spectra of these cyclopeptides than in the case of **1d**. Clearly, other hydrogen-bonding interactions besides those involving the aromatic substituents also occur.

Table 2. NH and C=O vibration bands in the FT-IR spectra of cyclopeptides **1a**−**1f** (c = 2 mM in 1% [D_6]DMSO/$CDCl_3$) (s = strong, w = weak, b = broad)

	ν(N−H)	$\nu(C{=}O)_{tert.\ amide}$
1a	3430 (w)/3276 (b, s)	1620/1608 (shoulder)
1b	3410 (s)/3271 (b)	1618 (b)
1c	3340 (b)/3282 (b)	1624/1617 (shoulder)
1d	(3425/3408) (w)/3268 (w)	1622
1e	3414 (s)/3314 (b)	1619/1613 (shoulder)
1f	3305 (b)/3260 (b)	1635/1619

Since interaction of the NH protons with the methyl substituent in **1a** is not possible, a weak band due to the free NH groups is visible at 3430 cm^{-1} in the spectrum of this compound. Again, the second band at 3276 cm^{-1} is much more intense than in the spectrum of the parent compound **1d** and presumably can also be assigned to $NH\cdots(O{=}C)_{tert.\ amide}$ interactions (Figure 4).

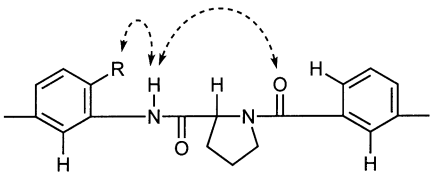


Figure 4. Possible hydrogen bonds between two aromatic subunits of the cyclopeptides in a peptide chain fragment

Because of the steric effects of the methyl groups, the conformational equilibrium of **1a** seems to be significantly shifted towards conformers in which the NH groups are involved in hydrogen bonds. Peptides **1c** (R = CH_2OCH_3) and **1f** (R = CO_2CH_3) possess two strong, broad bands in the NH vibration region of their FT-IR spectra. These may be attributed to both possible interactions of the NH groups, i.e. one with the aromatic substituent and the other with the carbonyl groups on the adjacent proline subunits.

If the bands at ca. 3270 cm^{-1} in the spectra of the substituted peptides do indeed represent NH groups that are involved in intramolecular hydrogen bonds with the tertiary amides, then an effect on the vibrational frequencies of the corresponding carbonyl groups should also be visible. Table 2 shows that this is indeed the case. In the unsubstituted cyclopeptide **1d**, the carbonyl group of the tertiary amide gives rise to a single band at 1622 cm^{-1}, which indicates that intramolecular hydrogen bonds between adjacent amino acid residues are either absent or at least very weak. In contrast, peptides **1a**, **1c**, **1e**, and **1f** exhibit split bands of their tertiary amide carbonyl vibrations, with a maximum at ca. 1620 cm^{-1} (1635 cm^{-1} in the case of **1f**) and another one significantly shifted to lower frequencies. This second band can be attributed to carbonyl groups that are involved in hydrogen-bonding interactions. In the case of peptide **1b**, the carbonyl band is rather broad, hence an assignment of individual bands is difficult.

The FT-IR spectroscopic results clearly indicate a shift of the conformational equilibria of the substituted cyclopeptides towards conformations with $NH\cdots(O=C)_{tert.\ amide}$ hydrogen bonds. The conformational shift is, however, most marked in the case of **1a**, where only steric effects of the substituent are important, and it is not so pronounced when the substituents are themselves able to form hydrogen bonds with the secondary amides as in **1c**, **1e**, and **1f**.

The addition of 1 equiv. of $BTMA^+$ picrate to a solution of **1e** (R = OCH_3) in $CDCl_3$ was found to have an interesting effect on the FT-IR spectrum. Thus, the NH band at 3314 cm^{-1} almost completely disappeared, while the CO band at 1619 cm^{-1} intensified at the expense of that at 1613 cm^{-1} (Figure 5).

Complex formation with the cation and anion clearly results in a loss of the $NH\cdots(O=C)_{tert.\ amide}$ hydrogen bonds. The resulting conformational reorganization may slightly increase the size of the receptor cavity so that it can better accommodate the guests. The NH groups are nevertheless still held in the previous orientation through the interaction with the methoxy groups. A similar effect was also observed upon addition of $BTMA^+$ picrate to solutions of **1c** and **1f**. The requirement for intramolecular $NH\cdots(O=C)_{tert.\ amide}$ hydrogen bond breaking for optimal cation complexation would explain the low affinity of **1a** towards this guest. Table 2 shows that in **1a** these hydrogen bonds are the strongest among all the cyclopeptides. It would appear that

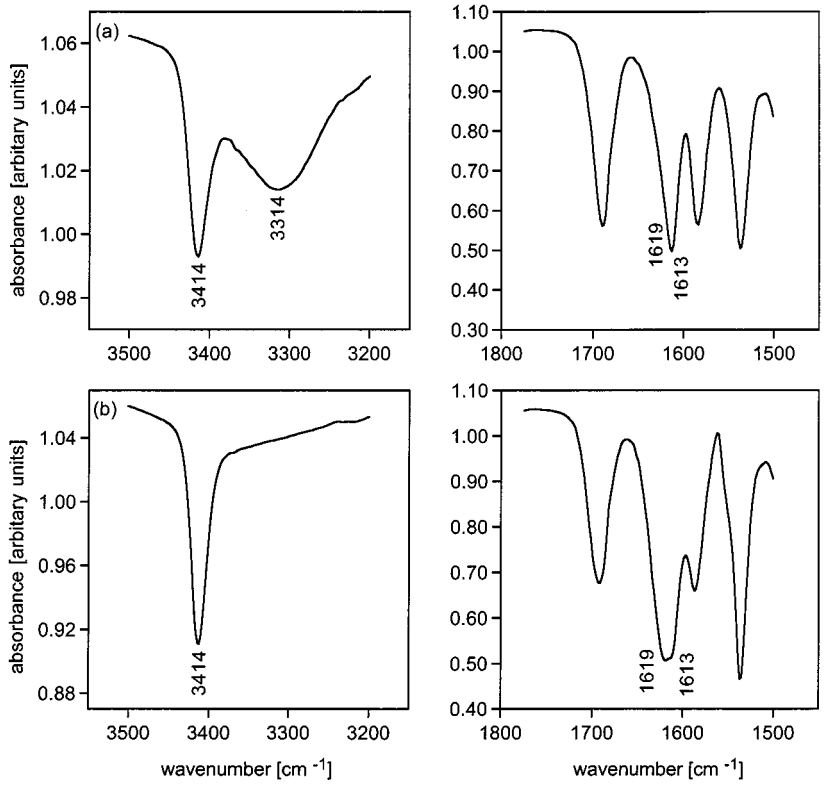


Figure 5. NH and C=O vibration regions of the FT-IR spectrum of **1e** in 1% $[D_6]DMSO/CDCl_3$ (c = 2 mM) (a) before and (b) after the addition of 1 equiv. of $BTMA^+$ picrate

complex formation between **1a** and $BTMA^+$ cannot compensate for the energy needed to cleave these bonds.

Calculations of the Electrostatic Potential Surfaces of 1a−1f

The results described above demonstrate the pronounced influence of the substituents on the conformational equilibrium of the cyclopeptides. Interaction of the substituent with the NH groups provides an adequate explanation for the loss of the anion affinity of all the substituted cyclopeptides, the low cation affinity of **1a**, and also the high affinity of **1f**. We have assumed all along, however, that cation−π interactions between the cations and the aromatic peptide subunits are not affected by the substituents. This is certainly not the case since a substituent may increase or decrease the electrostatic potentials of the aromatic systems and thereby influence cation affinity. It is directly evident from Table 1, however, that the dependence of cation complex stability on the type of aromatic substituent cannot be adequately explained in terms of electronic effects alone. If this were to be the case, one would expect, for example, a much lower affinity of peptide **1f** towards cations because a methoxycarbonyl substituent should reduce the electrostatic potential of the aromatic ring more than, say, a methoxy group.

Dougherty et al. have shown that the electronic effects of aromatic systems on cation−π interactions can be estimated by AM1 calculations of the electrostatic potential surfaces (EPS) of the aromatics.[29] We carried out similar calculations on 3-(acetylamino)-*N*-methylbenzamides with the same substituents in the 4-position as in the cyclopeptides **1a**−**1f**. The results show that the incorporation of the methyl substituent has little effect on the EPS of the aromatic rings as compared with the unsubstituted parent compound. Chloro and methoxycarbonyl substituents decrease the EPS of the aromatic rings somewhat. Methoxy and, to an even greater extent, methoxymethyl groups increase the EPS of the aromatic rings. Although the potential surfaces alone cannot account for the sequence of cation complex stabilities of the peptides **1a**−**1f**, they do explain the much lower cation affinity of **1b** in comparison with **1e**, since the solution conformations of both of these peptides are quite similar. Analogously, the higher cation affinity of **1e** as compared with **1d** may be partly due to the electronic effects of the methoxy substituents.

In order to see whether these effects might be mirrored in the cyclopeptides themselves, we carried out similar AM1 calculations on the cyclopeptides for which crystal structures have been determined. For **1d**, the crystal structure of the *N*-quinuclidinium iodide complex[14] was used as a model, and for **1f** that of the acetone complex.[11] In both cases, the guest molecules were removed. Similarly, the structure depicted in Figure 3 was used for the calculations on peptide **1e**. Figure 6 shows the results.

The views clearly illustrate that the majority of the negative potential (red) resides on the inside of the cavities as the concave surface curvature inside the receptor cavity of the cyclopeptides strongly enhances the EPS. This effect has been explained in detail by Klärner et al. using the example of their pincette receptors.[30] In the cyclopeptides, however, the cavity walls are lined by at least three, and, in the case of **1f**, six carbonyl groups, which further contribute to the negative potential inside the cavities. Interestingly, we have not observed any effect of cation complexation on the vibrational frequencies of these carbonyl groups. We therefore believe the interactions responsible for cation binding do not involve hydrogen bonding but rather are purely electrostatic.[31] The more positive EPS (blue) on the outside of **1d**, as compared with **1e** and **1f**, is due to the different orientations of the secondary amide groups in this peptide.

The AM1 calculations thus provide us with valuable information concerning the interaction of the cyclopeptides with the cations. They explain the electronic effects of the aromatic substituents on cation complexation, and they also show where the majority of the negative potential resides. Although the substituents have some influence on the electrostatic potential inside the cyclopeptides, their most important contribution to cation affinity is the effect they have on the peptide conformation in solution.

Conclusions

The nature of the substituent in the 4-position of the aromatic peptide subunits has been shown to have a significant effect on the conformational and receptor properties of the cyclic hexapeptides **1a**−**1f**. Whereas the parent compound can bind both anions and cations, the introduction of a substituent results in a complete loss of anion affinity since the NH groups are prevented from pointing towards the center of the cavity, a necessary prerequisite for anion binding. In the case of a methyl substituent, the reason is steric, while for the other compounds the NH groups are additionally engaged in hydrogen-bonding interactions with the substituents. In contrast, the cation affinities show a large substituent dependence. The cation complex stability is lowest for the methyl substituent. This is because the conformational change required for cation binding requires the rupture of intramolecular $NH\cdots(O=C)_{tert.\ amide}$ hydrogen bonds. In the other compounds, such prior bond breaking is less important since the NH groups are more involved in hydrogen-bonding interactions with the substituents. Substituents that interact most strongly with the NH groups stabilize a peptide conformation with a high cation affinity. Although the substituents also affect the electrostatic potential inside the cyclopeptides, their most important contribution to cation affinity is the effect they have on the peptide conformation in solution. The ease with which structural variation of the aromatic subunits of the peptide can be introduced, coupled with the effects of substituents as investigated herein, enables a facile fine tuning of the affinity of receptors of this type towards cationic guests. **1e** and **1f** are particularly promising candidates for further investigation as they are not only suitably pre-organized for guest binding, but additional binding sites can be introduced on the methoxy and methoxycarbonyl groups

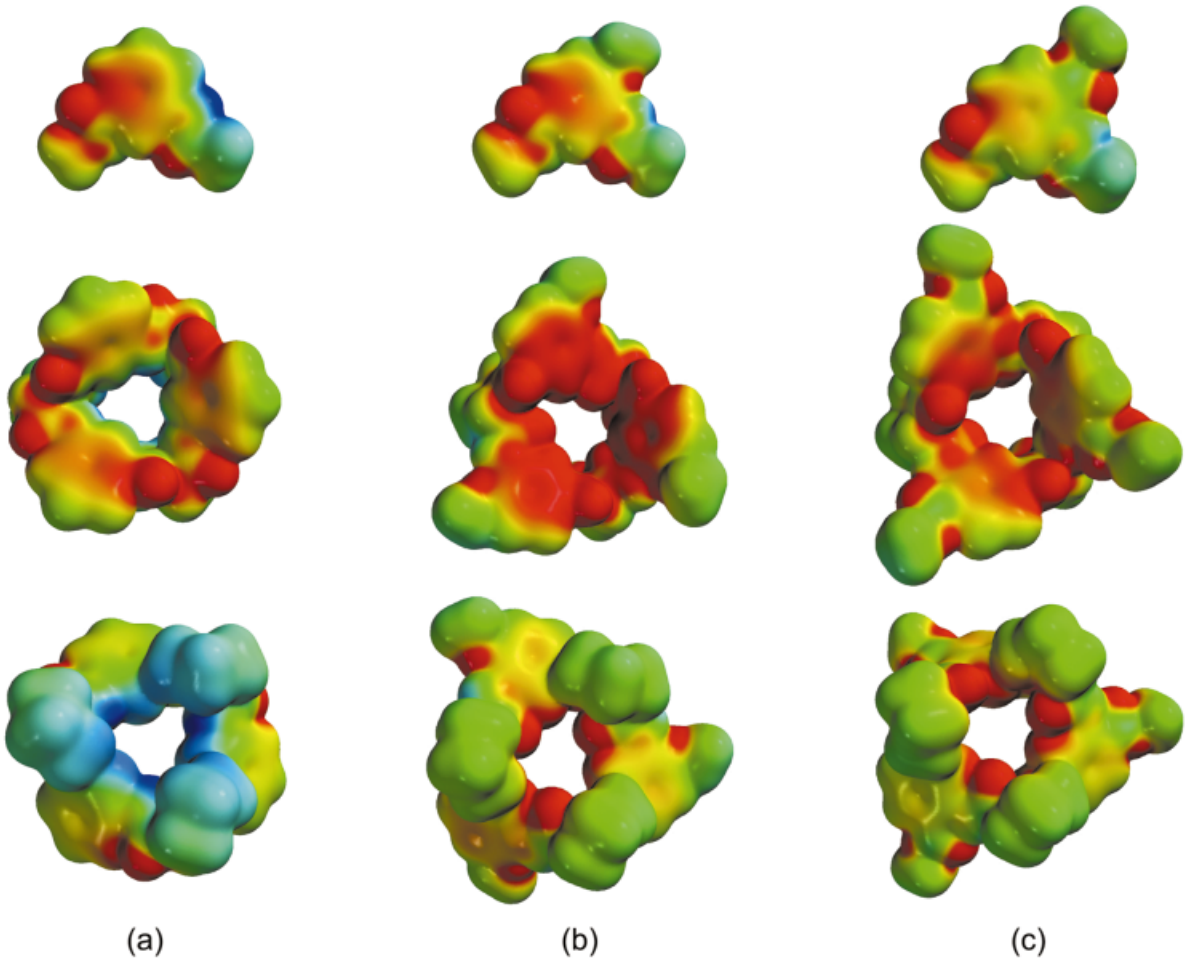


Figure 6. AM1 electrostatic potential surfaces of cyclopeptides **1d** (a), **1e** (b), and **1f** (c)

through ether or ester linkages. We will report on our progress in this area in due course.

Experimental Section

General Methods: Analyses were carried out as follows: Melting points: Büchi 510 apparatus. − Optical rotations: Perkin−Elmer 241 MC digital polarimeter (d = 10 cm). − NMR: Varian VXR 300 or Bruker DRX 500 equipped with an automatic sampler (the chemical shifts in the NMR titrations were referenced to the $CHCl_3$ signal at δ = 7.27 as an internal standard). − FT-IR: Bruker Vector 22 FT-IR spectrometer; cuvette d = 5 mm (NaCl). − Elemental analysis: Pharmaceutical Institute of the Heinrich-Heine-University, Düsseldorf. − Mass spectrometry: Finnigan INCOS 50. − Chromatography: ICN silica gel 32−63 μm (ICN Biomedicals), Merck LiChroprep RP-8 (40−63 μm) prepacked column, size B (310−25). The following abbreviations are used: TsOH = 4-toluenesulfonic acid, Bn = benzyl, Boc = *tert*-butyloxycarbonyl, DIEA = *N*-ethyldiisopropylamine, TFA = trifluoroacetic acid, PyCloP = chlorotripyrrolidinophosphonium hexafluorophosphate, TBTU = *O*-(1*H*-benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate, Pro = proline, AB = 3-aminobenzoic acid, NBS = *N*-bromosuccinimide.

Computational Methods: Most of the calculations were performed with a Silicon Graphics workstation using the program CERIUS^2 (Molecular Simulations Inc.). For molecular modeling, the Dreiding force field 2.21 was used.[32] Geometry optimization of the 3-(acetylamino)-*N*-methylbenzamide derivatives was carried out at the AM1 level. Electrostatic potential surfaces of the aromatic rings were generated with the program Spartan (Wavefunction, Inc.) by mapping AM1 electrostatic potentials onto surfaces of molecular electron density (0.002 electron/Å) followed by color-coding. Over all the surfaces, the potential energy values range from +40 to −20 kcal/mol, with red signifying a value greater than or equal to the maximum in negative potential and blue signifying a value greater than or equal to the maximum in positive potential.

Materials: All solvents were dried according to standard procedures prior to use. DMF p.A. was purchased from Fluka and was used without further purification. PyCloP was prepared according to the literature procedure.[33] TBTU, 3-amino-4-chlorobenzoic acid, methyl 3-amino-4-methylbenzoate, 3-amino-4-methoxybenzoic acid, and 1-methyl aminoterephthalate are commercially available. The synthesis of *cyclo*-[(L)-Pro-AB]$_3$ (**1d**) has been described elsewhere.[14]

Job Plot: Equimolar solutions (1 mM) of *n*-butyltrimethylammonium picrate (BTMA$^+$ picrate) and cyclopeptide **1f** in 1% [D_6]DMSO/$CDCl_3$ were prepared and mixed in various ratios. ^{1}H NMR spectra of the resulting solutions were recorded, and the change in chemical shift of the *N*-methyl proton signals of the guest was analyzed.[18,20]

Host−Guest Titrations: Stock solutions of the guest (0.2 μmol/100 μL) in 1% [D_6]DMSO/$CDCl_3$ and the cyclopeptide (**1a**, **1b**: 4 μmol/800 μL; **1c**: 3 μmol/800 μL; **1e**, **1f**: 2 μmol/800 μL) in $CDCl_3$ were prepared. In total, 11 NMR tubes were set up by adding increasing amounts of the host solution (0−800 μL) to 100 μL aliquots of the guest solution. All samples were made up to a volume of 1 mL with $CDCl_3$ and the respective ^{1}H NMR spectra were recorded. The chemical shifts of prominent guest protons were plotted against the host concentration. From the resulting saturation curves, K_a and $\Delta\delta_{max}$ were calculated by a nonlinear least-squares fitting method for 1:1 complexes using the SIGMA Plot 3.0 (Jandel Scientific) software package.[18,19]

General Procedure for the Cleavage of Benzyl Esters: The ester was dissolved in methanol (50 mL/mmol). After the addition of 10% Pd/C (100 mg) [in the case of compounds with a chloro substituent on the aromatic moieties, Raney nickel (1 g) was used], the reaction mixture was subjected to hydrogenation at 1 atm for about 2 h. That the reaction had reached completion was checked by TLC. The catalyst was then filtered off by passage through a layer of Celite and washed with methanol. The combined filtrate and washings were concentrated to dryness in vacuo.

General Procedure for the Cleavage of *tert*-Butyloxycarbonyl Groups. − Method A: The carbamate was dissolved in CH_2Cl_2 (5 mL). The resulting solution was cooled in an ice bath, and then trifluoroacetic acid (5 mL) was added dropwise. The reaction mixture was stirred for 1.5 h at 0−5 °C and then the solvent was evaporated in vacuo. The residue was redissolved in ethyl acetate and this solution was extracted twice with 10% Na_2CO_3 solution and three times with water. The organic layer was dried, 1 N HCl was added (1 mL/mmol), and then it was concentrated to dryness in vacuo. The resulting crude product was redissolved in CH_2Cl_2, the solvent was evaporated, and the residue was dried in vacuo. It was used without further purification. − **Method B:** The carbamate was suspended in 1,4-dioxane (20 mL). This suspension was cooled in an ice bath and a 6 N solution of HCl in 1,4-dioxane (40 mL) was added dropwise. The reaction mixture was stirred for 2 h at 0−5 °C and then concentrated to dryness in vacuo.

3-[(*tert*-Butyloxycarbonyl)amino]-4-methylbenzoic Acid (4a): 3-Amino-4-methylbenzoic acid (7.55 g, 50 mmol) was suspended in 1,4-dioxane/water (2:1; 150 mL). Triethylamine (6.96 mL, 50 mmol) was added and the mixture was cooled in an ice bath. A solution of di-*tert*-butyl dicarbonate (11.99 g, 55 mmol) in 1,4-dioxane (50 mL) was then added dropwise over a period of 30 min under stirring. Stirring was continued for 2 h at ca. 5 °C and then overnight at room temperature. Thereafter, the dioxane was removed in vacuo, and the remaining aqueous solution was diluted with water and 10% aqueous Na_2CO_3 solution (50 mL). The resulting mixture was extracted three times with diethyl ether. The organic layers were discarded. The aqueous layer was then acidified with 20% aqueous $KHSO_4$ and extracted three times with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated to dryness in vacuo. The residue was triturated with hexane, collected by filtration, and dried. It was used for the next step without further purification. Yield 10.92 g (87%); m.p. > 190 °C (dec.). − ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 1.48 (s, 9 H, tBuCH$_3$), 2.26 (s, 3 H, PhCH$_3$), 7.28 [d, ^3J = 8.1 Hz, 1 H, ABH(5)], 7.60 [dd, ^3J = 7.8 Hz, ^4J = 1.8 Hz, 1 H, ABH(6)], 7.99 [d, ^4J = 1.5 Hz, 1 H, ABH(2)], 8.69 (br. s, 1 H, NH), 12.86 (br. s, 1 H, COOH).

Benzyl 3-[(*tert*-Butyloxycarbonyl)amino]-4-methylbenzoate (3a): A mixture of **4a** (2.51 g, 10 mmol) and $NaHCO_3$ (1.68 g, 20 mmol) was suspended in DMF (25 mL). Benzyl bromide (2.37 mL, 20 mmol) was then added and the reaction mixture was stirred for 48 h at room temperature. After the addition of 10% aqueous Na_2CO_3 (75 mL), the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and dried. The solvent was removed in vacuo and the residue was recrystallized from hexane/ethyl acetate. Yield 2.90 g (85%); m.p. 136−138 °C. − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.51 (s, 9 H, tBuCH$_3$), 2.28 (s, 3 H, PhCH$_3$), 5.35 (s, 2 H, PhCH$_2$), 6.32 (br. s, 1 H, NH), 7.20 [d, ^3J = 8.1 Hz, 1 H, ABH(5)], 7.37 (br. m, 5 H, PhH), 7.71 [dd, ^3J = 7.9 Hz, ^4J = 1.8 Hz, 1 H, ABH(6)], 8.43 [s, 1 H, ABH(2)]. − $C_{20}H_{23}NO_4$ (341.4): calcd. C 70.36, H 6.79, N 4.10; found C 70.36, H 6.81, N 4.17.

Benzyl 3-Amino-4-chlorobenzoate (3b): A mixture of 3-amino-4-chlorobenzoic acid (8.58 g, 50 mmol) and $NaHCO_3$ (5.04 g, 60 mmol) was suspended in DMF (125 mL). Benzyl bromide (7.12 mL, 60 mmol) was added and the reaction mixture was stirred for 72 h at room temperature. After the addition of 10% aqueous Na_2CO_3 (375 mL), the resulting mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and dried. The solvent was removed in vacuo and the product was isolated from the residue by chromatographic workup (hexane/ethyl acetate, 6:1). It was finally recrystallized from hexane/ethyl acetate. Yield 2.87 g (22%); m.p. 74−75 °C. − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.10 (br. s, 2 H, NH), 5.32 (s, 2 H, PhCH$_2$), 7.28 [d, ^3J = 8.3 Hz, 1 H, ABH(5)], 7.37 [br. m, 6 H, PhH + ABH(6)], 7.46 [d, ^4J = 2.0 Hz, 1 H, ABH(2)]. − $C_{14}H_{12}ClNO_2$ (261.7): calcd. C 64.25, H 4.62, N 5.35; found C 64.42, H 4.71, N 5.34.

Methyl 3-[(*tert*-Butyloxycarbonyl)amino]-4-methylbenzoate (6c): Methyl 3-amino-4-methylbenzoate (5.28 g, 32 mmol) and di-*tert*-butyl dicarbonate (7.41 g, 34 mmol) were dissolved in dry THF (100 mL). The resulting solution was heated to reflux for 48 h. After cooling, it was concentrated to dryness in vacuo. The residue was stirred with hexane. The undissolved material was collected by filtration and recrystallized from hexane/ethyl acetate. Yield 7.41 g (87%); m.p. 130−132 °C. − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.53 (s, 9 H, tBuCH$_3$), 2.29 (s, 3 H, PhCH$_3$), 3.89 (s, 3 H, OCH$_3$), 6.45 (br. s, 1 H, NH), 7.20 [d, ^3J = 7.9 Hz, 1 H, ABH(5)], 7.68 [dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1 H, ABH(6)], 8.44 [s, 1 H, ABH(2)]. − $C_{14}H_{19}NO_4$ (265.3): calcd. C 63.38, H 7.22, N 5.28; found C 63.50, H 7.26, N 5.47.

Methyl 4-(Bromomethyl)-3-[(*tert*-butyloxycarbonyl)amino]benzoate (5c): Compound **6c** (6.63 g, 25 mmol) was dissolved in dry CCl_4 (100 mL) under gentle heating. NBS (4.89 g, 27.5 mmol) was added and the reaction mixture was heated to reflux for 1 h under irradiation by a UV lamp (500 W). After cooling, the succinimide produced was filtered off. The filtrate was concentrated in vacuo and the residue was recrystallized from hexane/ethyl acetate. The hot solution was filtered through a glass frit (P4) to remove insoluble material. Yield 6.39 g (74%); m.p. 114−116 °C (dec.). − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.55 (s, 9 H, tBuCH$_3$), 3.91 (s, 3 H, OCH$_3$), 4.50 (s, 2 H, PhCH$_2$Br), 6.73 (br. s, 1 H, NH), 7.36 [d, ^3J = 8.0 Hz, 1 H, ABH(5)], 7.74 [dd, ^3J = 8.0 Hz, ^4J = 1.7 Hz, 1 H, ABH(6)], 8.48 [s, 1 H, ABH(2)].

Methyl 3-[(*tert*-Butyloxycarbonyl)amino]-4-(methoxymethyl)benzoate (4c): Compound **5c** (5.16 g, 15 mmol) was dissolved in dry methanol (200 mL). After the addition of sodium methoxide (1.62 g, 30 mmol), the reaction mixture was heated to reflux for 4 h. After cooling, diethyl ether (750 mL) was added, and the mixture was washed with water, dried, and concentrated in vacuo. The

product was isolated from the residue by chromatographic workup (hexane/ethyl acetate, 4:1). It was finally recrystallized from hexane. Yield 3.25 g (73%); m.p. 79−80 °C. − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.54 (s, 9 H, *t*BuCH$_3$), 3.36 (s, 3 H, CH_2OCH_3), 3.91 (s, 3 H, $COOCH_3$), 4.54 (s, 2 H, CH_2OCH_3), 7.22 [d, ^3J = 7.8 Hz, 1 H, ABH(5)], 7.68 [dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1 H, ABH(6)], 7.77 (br. s, 1 H, NH), 8.65 [s, 1 H, ABH(2)]. − $C_{15}H_{21}NO_5$ (295.3): calcd. C 61.00, H 7.17, N 4.74; found C 61.05, H 7.29, N 4.63.

Benzyl 3-[(*tert*-Butyloxycarbonyl)amino]-4-(methoxymethyl)benzoate (3c): Compound **4c** (2.95 g, 10 mmol) was stirred in a mixture of 1,4-dioxane/1 N aqueous NaOH (1:1; 100 mL) for 4 h at room temperature. Thereafter, the reaction mixture was concentrated to half of its original volume in vacuo. Water was added, and the resulting solution was extracted twice with ethyl acetate. The organic layers were discarded. The aqueous layer was acidified with 20% aqueous $KHSO_4$ and then extracted three times with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated to dryness in vacuo. The residue was triturated with hexane, collected by filtration, and dried. The crude product and $NaHCO_3$ (1.68 g, 20 mmol) were suspended in DMF (25 mL). Benzyl bromide (2.37 mL, 20 mmol) was added, and the reaction mixture was stirred for 48 h at room temperature. After the addition of 10% aqueous Na_2CO_3 (75 mL), the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and dried. The solvent was removed in vacuo, and the product was isolated from the residue by chromatographic workup (hexane/ethyl acetate, 6:1). It was finally recrystallized from hexane. Yield 3.13 g (84%); m.p. 78−80 °C. − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.52 (s, 9 H, *t*BuCH$_3$), 3.34 (s, 3 H, CH_2OCH_3), 4.52 (s, 2 H, CH_2OCH_3), 5.37 (s, 2 H, PhCH$_2$), 7.20 [d, ^3J = 7.8 Hz, 1 H, ABH(5)], 7.37 (br. m, 5 H, PhH), 7.70 [dd, 1 H, ^3J = 7.8 Hz, ^4J = 1.7 Hz, ABH(6)], 7.72 [s, 1 H, ABH(2)], 8.67 (br. s, 1 H, NH). − $C_{21}H_{25}NO_5$ (371.4): calcd. C 67.91, H 6.78, N 3.77; found C 67.74, H 6.83, N 3.80.

3-[(*tert*-Butyloxycarbonyl)amino]-4-methoxybenzoic Acid (4e): 3-Amino-4-methoxybenzoic acid (3.34 g, 20 mmol) was suspended in 1,4-dioxane/water (2:1; 60 mL). After the addition of triethylamine (2.78 mL, 20 mmol), the mixture was cooled in an ice bath. A solution of di-*tert*-butyl dicarbonate (5.23 g, 24 mmol) in 1,4-dioxane (20 mL) was then added dropwise over a period of 30 min under stirring. Stirring was continued for 2 h at ca. 5 °C and then overnight at room temperature. The dioxane was subsequently removed in vacuo and the remaining aqueous solution was diluted with water and 10% aqueous Na_2CO_3 (20 mL). The resulting mixture was extracted three times with diethyl ether. The organic layers were discarded. The aqueous layer was acidified with 20% aqueous $KHSO_4$ and extracted three times with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated to dryness in vacuo. The residue was triturated with hexane, collected by filtration, and dried. It was used for the next step without further purification. Yield 4.50 g (84%); m.p. 193−194 °C (dec.). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.47 (s, 9 H, *t*BuCH$_3$), 3.88 (s, 3 H, OCH$_3$), 7.09 [d, ^3J = 8.7 Hz, 1 H, ABH(5)], 7.67 [dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1 H, ABH(6)], 8.08 (br. s, 1 H, NH), 8.35 [d, ^4J = 1.8 Hz, 1 H, ABH(2)], 12−13 (v br., 1 H, COOH).

Benzyl 3-[(*tert*-Butyloxycarbonyl)amino]-4-methoxybenzoate (3e): A mixture of **4e** (2.67 g, 10 mmol) and $NaHCO_3$ (1.68 g, 20 mmol) was suspended in DMF (25 mL). Benzyl bromide (2.37 mL, 20 mmol) was added and the reaction mixture was stirred for 48 h at room temperature. After the addition of 10% aqueous Na_2CO_3 (75 mL), the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and dried. The solvent was removed in vacuo, and the product was isolated from the residue by chromatographic workup (hexane/ethyl acetate, 3:1). It was dried in vacuo. Yield 3.32 g (93%); oil. − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.52 (s, 9 H, *t*BuCH$_3$), 3.90 (s, 3 H, OCH$_3$), 5.35 (s, 2 H, PhCH$_2$), 6.85 [d, ^3J = 8.6 Hz, 1 H, ABH(5)], 7.04 (br. s, 1 H, NH), 7.37 (br. m, 5 H, PhH), 7.75 [dd, 1 H, ^3J = 8.5 Hz, ^4J = 2.1 Hz, ABH(6)], 8.75 [s, 1 H, ABH(2)]. − $C_{20}H_{23}NO_5$ (357.4): calcd. C 67.21, H 6.49, N 3.92; found C 67.28, H 6.54, N 3.85.

1-Methyl-4-benzyl 2-Aminoterephthalate (3f): A mixture of 1-methyl 2-aminoterephthalate (3.90 g, 20 mmol) and $NaHCO_3$ (2.02 g, 24 mmol) was suspended in DMF (50 mL). Benzyl bromide (2.85 mL, 24 mmol) was added and the reaction mixture was stirred for 72 h at room temperature. After the addition of 10% aqueous Na_2CO_3 (150 mL), the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water and dried. The solvent was removed in vacuo, and the product was isolated from the residue by chromatographic workup (hexane/ethyl acetate, 6:1). It solidified on drying. Yield 3.58 g (63%); m.p. 79−80 °C. − ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.88 (s, 3 H, OCH$_3$), 5.34 (s, 2 H, PhCH$_2$), 5.80 (br. s, 2 H, NH), 7.28 [dd, ^3J = 8.4 Hz, ^4J = 1.7 Hz, 1 H, ABH(6)], 7.39 [br. m, 6 H, PhH + ABH(2)], 7.89 [d, ^3J = 8.3 Hz, 1 H, ABH(5)]. − $C_{16}H_{15}NO_4$ (285.3): calcd. C 67.36, H 5.30, N 4.91; found C 67.53, H 5.30, N 4.71.

Dipeptides: Prior to coupling, **3a**, **3c**, and **3e** were deprotected at the terminal amino group according to Method A. The aromatic amine (7.50 mmol), Boc-(L)-proline (1.2 equiv., 9.00 mmol, 1.94 g), and PyCloP (1.2 equiv., 9.00 mmol, 3.79 g) were dissolved in CH_2Cl_2 (150 mL). At room temperature, DIEA (2.4 equiv., 18.0 mmol, 3.13 mL) was added dropwise, and then the reaction mixture was stirred overnight. The solvent was subsequently evaporated in vacuo, and the product was isolated from the residue by chromatographic workup. In the case of dipeptides **2b** and **2f**, 1.5 equiv. of Boc-(L)-proline, 1.5 equiv. of PyCloP, and 3.0 equiv. of DIEA were used and the reaction time was extended to 7 d.

Boc-(L)-Pro-AB(4-CH$_3$)-OBn (2a): Eluent for the chromatographic purification: hexane/ethyl acetate, 2:1. Yield 3.21 g (98%); oil; $[\alpha]_D^{25}$ = −55.1 (*c* = 2, MeOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 100 °C, TMS): δ = 1.38 (s, 9 H, *t*BuCH$_3$), 1.76−2.02 [m, 3 H, ProC(β)H + ProC(γ)H$_2$], 2.20 [m, 1 H, ProC(β)H], 2.27 (s, 3 H, PhCH$_3$), 3.39 [m, 2 H, ProC(δ)H$_2$], 4.33 [dd, $^3J(H_{ax},H_{ax})$ = 8.5 Hz, $^3J(H_{ax},H_{eq})$ = 3.9 Hz, 1 H, ProC(α)H], 5.33 (s, 2 H, PhCH$_2$), 7.37 [br. m, 6 H, PhH + ABH(5)], 7.70 [dd, ^3J = 7.9 Hz, ^4J = 1.8 Hz, 1 H, ABH(6)], 8.06 [d, ^4J = 1.7 Hz, 1 H, ABH(2)], 9.17 (s, 1 H, ABNH). − $C_{25}H_{30}N_2O_5$ (438.5): calcd. C 68.47, H 6.90, N 6.39; found C 68.31, H 6.96, N 6.37.

Boc-(L)-Pro-AB(4-Cl)-OBn (2b): Eluent for the chromatographic purification: hexane/ethyl acetate, 3:1. Yield 3.37 g (98%); oil; $[\alpha]_D^{25}$ = −66.7 (*c* = 2, MeOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 100 °C, TMS): δ = 1.38 (s, 9 H, *t*BuCH$_3$), 1.85 [m, 2 H, ProC(γ)H$_2$], 2.02 [m, 1 H, ProC(β)H], 2.25 [m, 1 H, ProC(β)H], 3.40 [m, 2 H, ProC(δ)H$_2$], 4.41 [dd, $^3J(H_{ax},H_{ax})$ = 8.4 Hz, $^3J(H_{ax},H_{eq})$ = 4.0 Hz, 1 H, ProC(α)H], 5.36 (s, 2 H, PhCH$_2$), 7.38 (br. m, 5 H, PhH), 7.61 [d, ^3J = 8.4 Hz, 1 H, ABH(5)], 7.76 [dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz, 1 H, ABH(6)], 8.45 [d, ^4J = 2.0 Hz, 1 H, ABH(2)], 9.33 (s, 1 H, ABNH). − $C_{24}H_{27}ClN_2O_5$ (458.9): calcd. C 62.81, H 5.93, N 6.10; found C 62.56, H 5.95, N 5.85.

Boc-(L)-Pro-AB(4-CH$_2$OCH$_3$)-OBn (2c): Eluent for the chromatographic purification: hexane/ethyl acetate, 2:1. Yield 3.29 g (94%);

oil; $[\alpha]_D^{25} = -60.5$ (c = 2, MeOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 100 °C, TMS): δ = 1.39 (s, 9 H, tBuCH$_3$), 1.84−2.02 [m, 3 H, ProC(β)H + ProC(γ)H$_2$], 2.22 [m, 1 H, ProC(β)H], 3.33 (s, 3 H, CH$_2$OCH_3), 3.42 [m, 2 H, ProC(δ)H$_2$], 4.28 [dd, ^3J(H$_{ax}$,H$_{ax}$) = 8.6 Hz, ^3J(H$_{ax}$,H$_{eq}$) = 3.9 Hz, 1 H, ProC(α)H], 4.48 + 4.52 (2 d, ^2J = 13.3 Hz, 2 H, CH_2OCH$_3$), 5.35 (s, 2 H, PhCH$_2$), 7.37 [br. m, 6 H, PhH + ABH(5)], 7.76 [dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1 H, ABH(6)], 8.34 [d, ^4J = 1.8 Hz, 1 H, ABH(2)], 9.25 (s, 1 H, ABNH). − C$_{26}$H$_{32}$N$_2$O$_6$ (468.5): calcd. C 66.65, H 6.88, N 5.98; found C 66.38, H 7.01, N 5.99.

Boc-(L)-Pro-AB(4-OCH$_3$)-OBn (2e): Eluent for the chromatographic purification: hexane/ethyl acetate, 1:1. Yield 3.28 g (96%); oil; $[\alpha]_D^{25} = -79.8$ (c = 2, MeOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 100 °C, TMS): δ = 1.37 (s, 9 H, tBuCH$_3$), 1.86 [m, 2 H, ProC(γ)H$_2$], 2.02 [m, 1 H, ProC(β)H], 2.17 [m, 1 H, ProC(β)H], 3.39 [m, 2 H, ProC(δ)H$_2$], 3.91 (s, 3 H, OCH$_3$), 4.39 [dd, ^3J(H$_{ax}$,H$_{ax}$) = 8.4 Hz, ^3J(H$_{ax}$,H$_{eq}$) = 4.0 Hz, 1 H, ProC(α)H], 5.33 (s, 2 H, PhCH$_2$), 7.14 [d, ^3J = 8.7 Hz, 1 H, ABH(5)], 7.37 (br. m, 5 H, PhH), 7.75 [dd, ^3J = 8.6 Hz, ^4J = 2.2 Hz, 1 H, ABH(6)], 8.69 [d, ^4J = 2.1 Hz, 1 H, ABH(2)], 8.95 (s, 1 H, ABNH). − C$_{25}$H$_{30}$N$_2$O$_6$ (454.5): calcd. C 66.06, H 6.65, N 6.16; found C 65.81, H 6.59, N 5.98.

Boc-(L)-Pro-AB(4-COOCH$_3$)-OBn (2f): Eluent for the chromatographic purification: hexane/ethyl acetate, 2:1. Yield 3.14 g (87%); oil; $[\alpha]_D^{25} = -78.1$ (c = 2, MeOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 100 °C, TMS): δ = 1.34 (s, 9 H, tBuCH$_3$), 1.87 [m, 2 H, ProC(γ)H$_2$], 1.99 [m, 1 H, ProC(β)H], 2.25 [m, 1 H, ProC(β)H], 3.46 [m, 2 H, ProC(δ)H$_2$], 3.90 (s, 3 H, OCH$_3$), 4.24 [dd, ^3J(H$_{ax}$,H$_{ax}$) = 8.7 Hz, ^3J(H$_{ax}$,H$_{eq}$) = 4.3 Hz, 1 H, ProC(α)H], 5.39 (s, 2 H, PhCH$_2$), 7.39 (br. m, 5 H, PhH), 7.74 [dd, ^3J = 8.3 Hz, ^4J = 1.7 Hz, 1 H, ABH(6)], 8.05 [d, ^3J = 8.3 Hz, 1 H, ABH(5)], 9.04 [d, ^4J = 1.7 Hz, 1 H, ABH(2)], 10.81 (s, 1 H, ABNH). − C$_{26}$H$_{30}$N$_2$O$_7$ (482.5): calcd. C 64.72, H 6.27, N 5.81; found C 64.57, H 6.28, N 5.71.

Cyclopeptides: The synthesis of the linear hexapeptides was carried out analogously to the previously described procedures starting from the appropriate dipeptide.[13,14] The hexapeptide (2.00 mmol) was then hydrogenated according to the general procedure. The product was triturated with diethyl ether/hexane, 1:1, to afford a white solid. It was deprotected at the terminal amino group according to Method B. The product obtained was triturated with diethyl ether. The resulting completely deprotected peptide was dissolved in a mixture of DMF (100 mL/mmol) and DIEA (3.2 equiv.) and the solution was heated to 80 °C. A solution of TBTU (1.1 equiv.) in DMF (20 mL) was then slowly added dropwise. Stirring was continued for 2 h at 80 °C and then the solvent was evaporated in vacuo. The product was isolated from the mixture by chromatographic workup. An initial purification step was carried out using a silica gel column (CH$_2$Cl$_2$/MeOH, 15:1) (in the case of **1e**, CH$_2$Cl$_2$/MeOH, 5:1, was used). The material recovered was further purified on an RP-8 column. For this, it was dissolved in a small amount of DMF (in the case of **1f**, DMSO was used) and applied to a column conditioned with 1,4-dioxane/H$_2$O, 1:10. The eluent composition was gradually changed until the pure product eluted.

***cyclo*-[(L)-Pro-AB(4-CH$_3$)]$_3$ (1a):** The product eluted with 1,4-dioxane/H$_2$O, 1:2.5. If it was not obtained white after the RP-8 column step, it was subjected to further column chromatography on silica gel eluting with acetone. Yield 0.58 g (42%); m.p. > 250 °C (dec.) (softening from 245 °C); $[\alpha]_D^{25} = +26.3$ (c = 2, DMF). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.84−2.00 [m, 9 H, ProC(β)H + ProC(γ)H$_2$], 2.56 [m, 3 H, ProC(β)H], 2.30 (s, 9 H, PhCH$_3$), 3.39 + 3.63 [2 m, 2 × 3 H, ProC(δ)H$_2$], 4.71 [d, ^3J(H$_{ax}$,H$_{ax}$) = 9.1 Hz, 3 H, ProC(α)H], 7.27 [s, 6 H, ABH(5) + ABH(6)], 7.80 [s, 3 H, ABH(2)], 9.57 (s, 3 H, ABNH). − ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 17.6 (PhCH$_3$), 24.4 [ProC(γ)], 29.8 [ProC(β)], 49.3 [ProC(δ)], 59.9 [ProC(α)], 122.1 [ABC(6)], 124.4 [ABC(2)], 129.4 [ABC(5)], 132.1 [ABC(4)], 134.6 [ABC(1)], 136.2 [ABC(3)], 168.0 (ABCO), 170.5 (ProCO). − C$_{39}$H$_{42}$N$_6$O$_6$ · 2 H$_2$O (726.8): calcd. C 64.45, H 6.38, N 11.56; found C 64.69, H 6.46, N 11.70. − CI-MS (NH$_3$): m/z (%): 708 (100) [M + NH$_4^+$].

***cyclo*-[(L)-Pro-AB(4-Cl)]$_3$ (1b):** The product eluted with 1,4-dioxane/H$_2$O, 1:1. If it was not obtained white after the RP-8 column step, it was subjected to further column chromatography on silica gel eluting with acetone. The product was finally triturated with methanol. Yield 0.39 g (26%); m.p. > 250 °C; $[\alpha]_D^{25} = +43.1$ (c = 2, DMF). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.85−1.98 [m, 9 H, ProC(β)H + ProC(γ)H$_2$], 2.26 [m, 3 H, ProC(β)H], 3.40 [m, 3 H, ProC(δ)H], 3.61 [m, 3 H, ProC(δ)H], 4.84 [dd, ^3J(H$_{ax}$,H$_{ax}$) = 8.2 Hz, ^3J(H$_{ax}$,H$_{eq}$) = 2.2 Hz, 3 H, ProC(α)H], 7.39 [dd, ^3J = 8.3 Hz, ^4J = 1.9 Hz, 3 H, ABH(6)], 7.58 [d, ^3J = 8.2 Hz, 3 H, ABH(5)], 8.03 [d, ^4J = 2.0 Hz, 3 H, ABH(2)], 9.94 (s, 3 H, ABNH). − ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 24.4 [ProC(γ)], 29.7 [ProC(β)], 49.3 [ProC(δ)], 59.8 [ProC(α)], 123.2 [ABC(6)], 125.0 [ABC(2)], 126.4 [ABC(4)], 128.9 [ABC(5)], 134.9 [ABC(1)], 135.9 [ABC(3)], 166.9 (ABCO), 170.7 (ProCO). − C$_{36}$H$_{33}$Cl$_3$N$_6$O$_6$ (752.1): calcd. C 57.50, H 4.42, N 11.17; found C 57.58, H 4.63, N 11.02. − CI-MS (NH$_3$): m/z (%): 770 (100) [M + NH$_4^+$], 733 (20) [M − Cl + NH$_4^+$].

***cyclo*-[(L)-Pro-AB(4-CH$_2$OCH$_3$)]$_3$ (1c):** The product eluted with 1,4-dioxane/H$_2$O, 1:2. If it was not obtained white after the RP-8 column step, it was subjected to further column chromatography on silica gel eluting with acetone. Yield 0.55 g (35%); m.p. 216 °C (softening from 189 °C); $[\alpha]_D^{25} = -198.6$ (c = 2, MeOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 100 °C, TMS): δ = 1.84−2.00 [m, 9 H, ProC(β)H + ProC(γ)H$_2$], 2.47 [m, 3 H, ProC(β)H], 3.32 (s, 9 H, CH$_2$OCH_3), 3.55 [m, 6 H, ProC(δ)H$_2$], 4.51 (m, 6 H, CH_2OCH$_3$), 4.75 [m, 3 H, ProC(α)H], 7.28 [dd, ^3J = 7.9 Hz, 3 H, ABH(6)], 7.38 [d, ^3J = 7.7 Hz, 3 H, ABH(5)], 7.88 [s, 3 H, ABH(2)], 9.18 (s, 3 H, ABNH). − ^{13}C NMR (75 MHz, [D$_6$]DMSO, 100 °C, TMS): δ = 24.3 [ProC(γ)], 29.6 [ProC(β)], 49.1 [ProC(δ)], 57.7 (CH$_2$OCH$_3$), 60.6 [ProC(α)], 70.6 (CH$_2$OCH$_3$), 122.3 [ABC(6)], 123.6 [ABC(2)], 128.0 [ABC(5)], 131.8 [ABC(4)], 136.0 [ABC(1)], 136.6 [ABC(3)], 168.5 (ABCO), 170.5 (ProCO). − C$_{42}$H$_{48}$N$_6$O$_9$ (780.9): calcd. C 64.60, H 6.20, N 10.76; found C 64.42, H 6.18, N 10.72. − CI-MS (NH$_3$): m/z (%): 798 (100) [M + NH$_4^+$], 768 (50) [M − OCH$_3$ + H + NH$_4^+$], 738 (15) [M − 2 OCH$_3$ + 2 H + NH$_4^+$], 708 (2) [M − 3 OCH$_3$ + 3 H + NH$_4^+$], 781 (3) [M + H$^+$], 751 (5) [M − OCH$_3$ + H + H$^+$], 721 (4) [M − 2 OCH$_3$ + 2 H + H$^+$].

***cyclo*-[(L)-Pro-AB(4-OCH$_3$)]$_3$ (1e):** The product eluted with 1,4-dioxane/H$_2$O, 1:2.5. It was finally recrystallized from methanol. Yield 0.61 g (41%); m.p. > 250 °C (dec.) (softening from 245 °C); $[\alpha]_D^{25} = +31.2$ (c = 2, DMF). − ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.75−1.98 [m, 9 H, ProC(β)H + ProC(γ)H$_2$], 2.27 [m, 3 H, ProC(β)H], 3.48 [m, 6 H, ProC(δ)H$_2$], 3.90 (s, 9 H, OCH$_3$), 4.87 [dd, ^3J(H$_{ax}$,H$_{ax}$) = 8.4 Hz, ^3J(H$_{ax}$,H$_{eq}$) = 2.1 Hz, 3 H, ProC(α)H], 7.06 [d, ^3J = 8.7 Hz, 3 H, ABH(5)], 7.21 [dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz, 3 H, ABH(6)], 8.29 [d, ^4J = 1.9 Hz, 3 H, ABH(2)], 9.53 (s, 3 H, ABNH). − ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 24.5 [ProC(γ)], 29.7 [ProC(β)], 49.4 [ProC(δ)], 55.7 (PhOCH$_3$), 59.4 [ProC(α)], 110.2 [ABC(5)], 121.4 [ABC(2)], 121.9 [ABC(6)], 127.0 [ABC(1)], 129.5 [ABC(3)], 150.0 [ABC(4)], 168.1 (ABCO), 170.7 (ProCO). − C$_{39}$H$_{42}$N$_6$O$_9$·H$_2$O (756.8): calcd.

C 61.89, H 5.86, N 11.10; found C 62.18, H 5.98, N 11.40. – CI-MS (NH_3): *m/z* (%): 756 (100) [M + NH_4^+], 739 (5) [M + H^+].

***cyclo*-[(L)-Pro-AB(4-COOCH$_3$)]$_3$ (1f):** The product eluted with 1,4-dioxane/H_2O, 1:1. It was finally recrystallized from acetone. Yield 0.43 g (26%); m.p. > 250 °C (dec.) (softening from 234 °C); $[\alpha]_D^{25}$ = −139.5 (*c* = 2, $CHCl_3$); $[\alpha]_D^{25}$ = +19.9 (*c* = 2, DMF). – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.92 [m, 6 H, ProC(γ)H$_2$], 2.08 + 2.35 [2 m, 2 × 3 H, ProC(β)H$_2$], 2.09 (s, 6 H, acetone), 3.44 [m, 6 H, ProC(δ)H$_2$], 3.92 (s, 9 H, OCH_3), 4.76 [dd, ^3J(H$_{ax}$,H$_{ax}$) = 8.7 Hz, ^3J(H$_{ax}$,H$_{eq}$) = 3.3 Hz, 3 H, ProC(α)H], 7.33 [dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 3 H, ABH(6)], 8.00 [d, ^3J = 8.1 Hz, 3 H, ABH(5)], 8.54 [d, ^4J = 1.4 Hz, 3 H, ABH(2)], 10.71 (s, 3 H, ABNH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 24.4 [ProC(γ)], 29.1 [ProC(β)], 30.6 (acetone-CH_3), 49.0 [ProC(δ)], 52.6 (OCH_3), 60.4 [ProC(α)], 118.5 [ABC(4)], 120.4 [ABC(2)], 120.5 [ABC(6)], 130.7 [ABC(5)], 139.3 [ABC(1)], 142.0 [ABC(3)], 166.9 + 167.3 (ABCO), 169.9 (ProCO), 206.4 (acetone-CO). – $C_{42}H_{42}N_6O_{12} \cdot C_3H_6O \cdot 0.5\ H_2O$ (889.9): calcd. C 60.74, H 5.55, N 9.44; found C 60.72, H 5.53, N 9.18. – CI-MS (NH_3): *m/z* (%): 841 (100) [M + H + NH_4^+], 808 (5) [M − OCH_3 + NH_2 + H^+].

X-ray Crystallographic Structure Determination of 1e · 7 MeOH: Crystal data: $C_{39}H_{42}N_6O_9 \cdot 7\ (CH_4O)$, M_w = 963.1, colorless plate 0.40 × 0.22 × 0.08 mm, orthorhombic $P2_12_12_1$ (No. 19), *a* = 13.9313(8), *b* = 16.0836(8), *c* = 21.118(1) Å, *V* = 4731.8(4) Å^3, *T* = 100 K, D_X = 1.352 g cm^{-3}, λ = 0.71073 Å, μ = 1.02 cm^{-1}, Nonius Kappa CCD diffractometer, 2.16° < θ < 30.97°, 22862 measured reflections, 13045 independent, 6052 with $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXS-97) and refined by least-squares (SHELXL-97) using Chebyshev weights on F_o^2 to R_1 = 0.089 [$I > 2\sigma(I)$], wR_2 = 0.267, 546 parameters, H atoms on peptide constrained, H atoms on methanol solvate molecules not located, *S* = 0.965, residual electron density 0.87 e Å^{-3} (1.65 Å from C42). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-144565. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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