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Synthesis and Structure of α/δ-Hybrid Peptides—Access to Novel Helix Patterns in Foldamers

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Abstract: Stimulated by an overview on all periodic folding patterns of α/δ-hybrid peptides with 1:1 alternating backbone provided by ab initio molecular orbital theory, the first representatives of this foldamer class were synthesized connecting novel C-linked carbo-δ-amino acid constituents and L-Ala. In agreement with theoretical predictions, extensive NMR spectroscopic analyses confirm the formation of new motifs of 13/11-mixed helical patterns in these peptides supported by the rigidity of the D-xylose side chain in the selected δ-amino acid constituents. Relationships between possible helix types in α/δ-hybrid peptides and their counterparts in other 1:1 hybrid peptide classes and native α-peptides are discussed; these indicate the high potential of these foldamers to mimic native peptide secondary structures. The design of α/δ-hybrid peptides provides an opportunity to expand the domain of foldamers and allows the introduction of desired functionalities through the α-amino acid constituents.

Keywords: ab initio calculations · amino acids · foldamers · mixed helices · peptides

Introduction

The generation of new systems by using non-natural polymers provides an excellent opportunity to test the rules that govern protein folding and function.[1] Proteins carry out diversified functions in biological systems by adopting compact and well-defined three-dimensional folding patterns. Thus, the creation of novel structural diversity by designing new scaffolds allows us to obtain systems with desirable features in non-natural oligomers. β-Peptides, the oligomers of β-amino acids, are by far the most extensively studied class of foldamers.[1a–c,j,k] Studies involving the higher homologues of these amino acids are increasing, but are still rather scarce.[1a,j,k,2] To broaden the size of the foldamer domain, hybrid peptides composed of various homologous amino acids were suggested.[3] In particular, the strategy of employing dipeptide repeats represents an attractive option. Thus, α/β-hybrid peptides containing a 1:1 alternation of α- and β-amino acid constituents in the backbone displayed a variety of helical structures.[4] Recently, some very interesting biological applications of this class of peptides were demonstrated.[5] In earlier efforts, we have synthesized new β- and γ-amino acids,[6,7c] namely, the C-linked carbo-β- and γ-amino acids (β-Caas and γ-Caas), and used them to obtain the especially interesting mixed or β-helical folding patterns, which include the left- and right-handed 10/12-helices in β-peptides[7a,b] and α/γ-hybrid peptides,[7c] 9/11-mixed helices in α/β-hybrid peptides,[7d,e] and 11/13-mixed helices in β/γ-hybrid peptides.[7c] Here, the foldamers with the new β- and γ-Caas not only resulted in new mixed helices, but also in new motifs. From the very beginning, foldamer research was successfully supported by application of quantum chemical and molecular dynamics methods to verify and predict possible folding patterns of novel foldamer classes.[8] Encouraged by the close correspondence of experimental findings and

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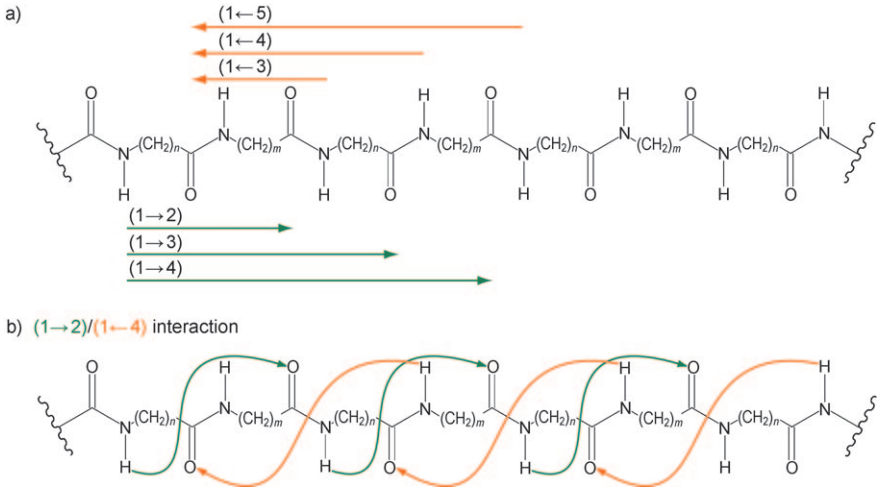
theoretical predictions, we have explored the possibility of obtaining novel helical patterns in the foldamer class of α/δ-hybrid peptides with a 1:1 alternating backbone by a concerted strategy of theoretical and experimental methods. Selecting δ-amino acid constituents is especially tempting, since they can be viewed as isoesters of α-amino acid dipeptides.[1a,3a,8i] Thus, closer relationships to secondary structure formation in native α-peptides could be expected than in other foldamer classes. Experimental hints for the formation of ordered structures in oligomers of δ-amino acids were obtained, but detailed structure information is still missing.[2g,9] This report describes the experimental and theoretical results of synthesis and structures of the first representatives of α/δ-hybrid peptides.



Scheme 1. Possible hydrogen-bonding patterns for helices of α/δ-hybrid peptides a) with exclusively forwards or backwards hydrogen bonds and b) with hydrogen bonds alternately changing their directions ($n/m=1$: α-amino acid, $n/m=4$: δ-amino acid).

Results and Discussion

Theoretical studies: Looking at a sequence of α/δ-hybrid peptides with dimer periodicity (Scheme 1), numerous folding patterns are imaginable that are characterized by hydrogen-bonded pseudocycles of different size (Table 1). Among these helices, there are representatives with all hydrogen bonds formed only in forward or in backward directions of the sequence (Scheme 1a), respectively, but also the particularly interesting mixed or β-helices, in which the hydrogen bonds are alternately formed in forward and backward directions (Scheme 1b).[8b,c,g,k] Scheme 1b shows only the pattern for mixed helices resulting from the interaction between the amino acids i and $i+1$ in the forward and the amino acids i and $i+3$ in the backward direction. Table 2 considers also the representatives with the next larger ring sizes arising from $i\rightarrow i+3/i\leftarrow i+5$ amino acid interactions. To get a complete overview on all potential possibilities of periodic backbone folding, a systematic conformational search was performed on blocked α/δ-peptide octamers following strategies already employed for other peptide foldamers.[8f,g,i,j,l,m] To avoid any restriction of the conformational space, side chains were omitted. The complete catalogue on all periodic backbone folding alternatives and their stability relationships, which we can expect from this search, opens up the possibility to find substitution patterns that favor special helix types.

For our α/δ-hybrid peptide model, a pool of 2657205 conformations was generated by a systematic variation of the backbone torsion angles (φ,ψ) of the α- and ($\varphi,\theta,\zeta,\rho,\psi$) of the δ-amino acid constituents in intervals of 45° considering

Table 1. Formal possibilities of hydrogen-bonded helices in α/δ-hybrid peptides.

Relative position[a]	Type of interacting amino acids[a,b]	Alternating pseudocycles C_x/C_y[c]	Helix notation	Number of helix representatives[d]
1→2/1←4	α→δ/α←δ	C_{11}/C_{13}	$H_{11/13}$	4
	δ→α/δ←α	C_{13}/C_{11}	$H_{13/11}$	4
1→4/1←6	α→δ/α←δ	C_{20}/C_{22}	$H_{20/22}$	2
	δ→α/δ←α	C_{22}/C_{20}	$H_{22/20}$	3
1→2	α→δ/δ→α	C_{11}/C_{11}	H_{11}	2
1→3	α→α/δ→δ	C_{14}/C_{17}	$H_{14/17}$	4
1→4	α→δ/α→δ	C_{20}/C_{20}	H_{20}	1
1←4	α←δ/δ←α	C_{13}/C_{13}	H_{13}	6
1←5	α←α/δ←δ	C_{16}/C_{19}	$H_{16/19}$	1

[a] Relative position of the interacting amino acids; the arrows indicate the forward (→) and backward (←) directions of the hydrogen bonds. [b] α: α-amino acid; δ: δ-amino acid. [c] x,y: number of atoms in the alternating hydrogen-bonded pseudocycles. [d] Resulting from the conformational search.

Table 2. Relative energies and free enthalpies of the most stable helices of alternating α/δ-hybrid peptide octamers obtained by ab initio MO theory in vacuum (HF/6-31G*, B3LYP/631G*) and in an aqueous environment (PCM//HF/6-31G*).

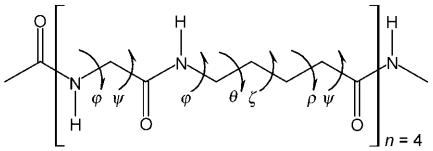
	ΔE [kJ mol^{-1}]			
Helix[a]	HF/6-31G*	B3LYP/6-31G*	PCM//HF/6-31G*[b]	ΔG[c] [kJ mol^{-1}]
$H^{I}_{11/13}$	38.4	30.1	76.1	37.7
$H^{I}_{13/11}$	**0.0**[d]	**0.0**[e]	**0.0**[f]	2.1
$H^{I}_{20/22}$	21.1	20.6	59.7	17.6
$H^{I}_{22/20}$	4.6	6.8	41.7	**0.0**[g]
H^{I}_{11}	86.8	83.6	60.4	75.9
$H^{I}_{14/17}$	118.1	120.7	74.3	109.3
H^{I}_{20}	149.3	159.4	103.3	130.4
H^{I}_{13}	60.4	64.3	21.0	56.8
$H^{I}_{16/19}$	106.4	119.2	51.4	90.1

[a] See Table 1. [b] $\varepsilon=78.4$. [c] HF/6-31G* level. [d] $E_T=-2370.010398$ a.u. [e] $E_T=-2384.451607$ a.u. [f] $E_T=-2369.994021$ a.u. [g] $G=-2369.135411$ a.u.

the dipeptide periodicity (Scheme 1). On the basis of general geometry criteria for hydrogen bonds, all conformations corresponding to the described hydrogen-bonding patterns were selected (Table 1, Scheme 1). From this procedure, 216 conformations resulted, which were starting points for complete geometry optimizations of blocked octa- and hexamers at the HF/6-31G* level of ab initio molecular orbital (MO) theory. Correlation effects on the structure were estimated by reoptimization of the HF/6-31G* conformers at the B3LYP/6-31G* level of density functional theory (DFT). The minimum character of all structures was confirmed by vibration analysis, which was also the basis for the estimation of free enthalpy differences. To estimate the solvent influence, single-point calculations on the HF/6-31G* conformers were performed for an aqueous environment employing a polarizable continuum model (PCM).

The conformational search provided 27 helical conformers. Their distribution on the various helix types is given in the fifth column of Table 1. In Table 2 the relative energies of the most stable helical octamer conformers of each helix pattern are given. Table 3 contains the HF/6-31G* backbone torsion angles. The corresponding data for all other helix conformers at all approximation levels are given in the Supporting Information together with the data for the hexamers. The stability order of the various helix types found for the octamers is retained within the hexamer series (Table 2 and Table S14 in the Supporting Information), but it is striking that most helix alternatives are destabilized relative to the most stable 13/11-conformer as the sequence length increases. Figure 1 shows representative examples of the various helix types. Two mixed helices, $H^{I}_{13/11}$ and $H^{I}_{22/20}$, are most stable in vacuum. Following our convention with β/γ-hybrid peptides,[7c,8m] a mixed 11/13-helix results when the amide protons of the α residues take part in the hydrogen bonding of 11-membered rings and those of the δ residues in the formation of 13-membered rings. The reverse situation leads to a 13/11-helix (Scheme 1). The energies and free enthalpies of the two mixed helices are closely together at all approximation levels. Mixed or β-helices are generally disadvantaged in more polar environments over helix types with all hydrogen bonds pointing into the same direction due to their smaller macrodipole moments resulting from the alternate change of the hydrogen-bond directions.[8b,g,k,l,m] Nevertheless, in the case of α/δ-hybrid peptides the mixed 13/11-helix, but not the 22/20-helix, remains most stable in an aqueous environment. Now, it is followed in the stability order by H^{I}_{13}, which

Table 3. Backbone torsion angles of the most stable helices of alternating α/δ-hybrid peptide octamers at the HF/6-31G* level of ab initio MO theory.



Helix[a]	φ [°]	θ [°]	ζ [°]	ρ [°]	ψ [°]	Helix[a]	φ [°]	θ [°]	ζ [°]	ρ [°]	ψ [°]
$H^{I}_{11/13}$	−86.0				63.6	$H^{I}_{14/17}$	−107.2				−137.6
	61.8	58.9	−150.1	72.4	−121.8		−99.3	54.8	178.7	159.6	−82.8
	−133.6				56.6		−102.9				−129.7
	65.3	59.1	−145.6	71.3	−124.7		−96.7	51.0	172.4	162.9	−92.5
	−134.0				57.8		−93.6				−127.6
	65.3	59.3	−146.3	71.5	−124.8		−95.6	53.9	175.2	157.6	−96.6
	−134.2				59.0		−95.5				−129.7
	67.9	60.7	−147.1	68.4	−119.4		−94.5	70.3	179.3	−179.8	161.6
$H^{I}_{13/11}$	−73.8				153.8	H^{I}_{20}	−101.1				−144.3
	136.8	−78.3	63.9	57.1	−143.0		−105.6	−59.9	−157.8	−54.1	−78.3
	−68.6				150.9		−102.3				−130.3
	139.8	−79.9	63.9	57.5	−140.3		−72.5	−57.8	−170.4	−64.2	−99.8
	−68.9				151.7		−126.6				−68.0
	138.9	−79.8	63.7	57.9	−141.6		−96.0	−72.9	175.4	−81.1	−152.6
	−70.3				156.5		−72.5				−30.6
	135.9	−79.1	63.1	60.8	−146.0		−115.9	−59.6	−164.8	−66.4	155.3
$H^{I}_{20/22}$	−85.6				63.9	H^{I}_{13}	−86.2				−12.6
	69.1	55.6	175.5	173.3	−162.1		−71.8	−66.3	77.4	63.1	−139.9
	−86.8				70.9		−88.0				−10.0
	75.4	57.3	174.4	172.9	−126.1		−71.3	−66.0	76.4	63.2	−139.5
	−142.7				115.2		−90.2				−7.0
	61.9	49.1	174.2	167.1	−128.3		−70.7	−65.3	75.6	63.3	−143.9
	−152.6				134.9		−101.9				10.1
	55.3	49.1	−177.6	171.4	−164.9		−80.9	−71.5	75.9	64.6	−139.2
$H^{I}_{22/20}$	−130.3				154.9	$H^{I}_{16/19}$	−88.3				−16.6
	78.1	−179.2	175.9	65.6	−125.7		−106.4	62.0	−92.8	168.1	168.8
	−125.6				152.3		−87.1				−20.8
	74.5	174.6	170.5	62.0	−136.5		−110.6	57.6	−94.7	172.4	171.9
	−90.2				96.4		−80.8				−21.2
	86.4	−175.6	179.4	70.9	−137.1		−119.3	59.1	−101.2	177.4	−178.0
	−80.7				92.5		−92.9				5.5
	87.9	179.5	177.4	70.2	−148.5		−162.4	74.7	−74.5	−172.1	134.7
H^{I}_{11}	−103.2				−137.1						
	−102.7	66.2	−128.1	70.3	−115.7						
	−106.2				−130.4						
	−106.0	65.7	−128.1	70.2	−116.2						
	−104.1				−131.6						
	−105.4	64.9	−126.6	69.7	−114.9						
	−108.3				−120.0						
	−97.8	72.6	−146.9	72.3	−153.9						

[a] See Table 1.

has all hydrogen bonds along the sequence in the backwards direction.

Peptide synthesis: The considerable stability of the mixed $H_{13/11}$ conformer according to the theoretical predictions in vacuum, and even in polar solvents, encourages verification by experiment. From our earlier work on the β-, α/β-, α/γ-, and β/γ-peptides using the β- and γ-Caas, it was evident that the carbohydrate side chain in the β- and γ-Caas plays a prominent role in the design control to derive a variety of mixed helical structures. Additionally, mass spectral fragmentation studies[10] on the dipeptides derived from β-Caa and γ-Caa monomers indicate that the rigidity of the side chain and the stereochemistry around the amine center are important for the control of the design. The differential rigidities in the *S* and *R* epimeric Caa residues play a crucial role in defining the helical conformations, making them the preferred choice in the present designs. Based on these findings and considering the possible orientations in the theoretical model, the α/δ-hybrid peptides **2**–**7** (Scheme 2) from the proposed δ-Caa$_{(x)}$[C-linked carbo-δ-amino acid] (**1**) and L-Ala in the above design are likely to provide helices with 11/13- or 13/11-hydrogen-bonding patterns.

The requisite δ-Caa$_{(x)}$ **1** (Scheme 3) was synthesized from the known aldehyde **1a**,[11a] prepared from β-Caa$_{(x)}$,[6] designed on the basis of a C-(ribofuranoside)-linked glycine moiety present in nikkomycins.[11b] Accordingly, aldehyde **1a** was treated with (methoxycarbonylmethylene)triphenylphosphorane in CH_2Cl_2 at room temperature for 6 h to give the α,β-unsaturated ester **1b** in 86 % yield. This ester gave **1**[12]

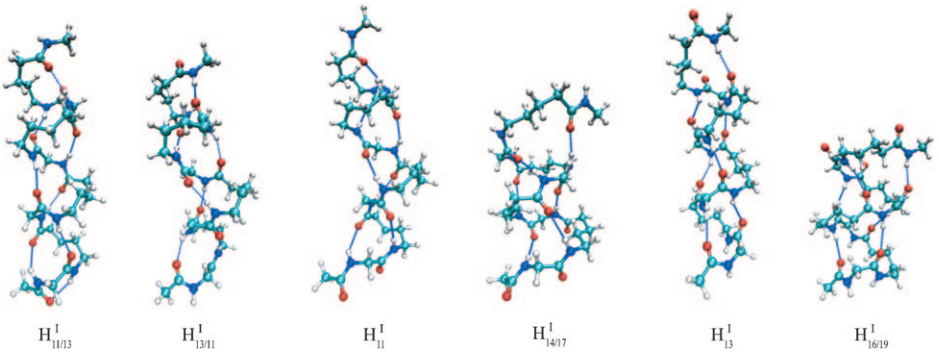
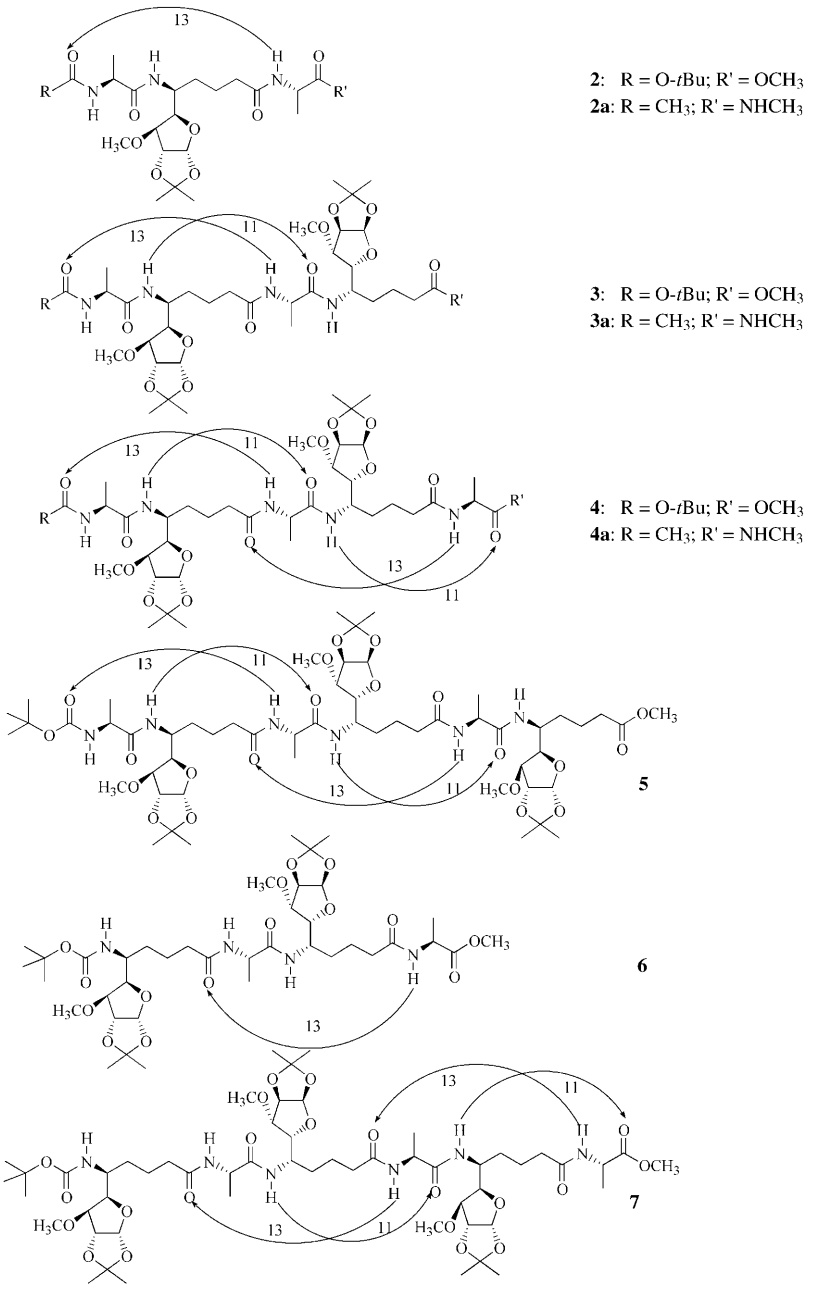
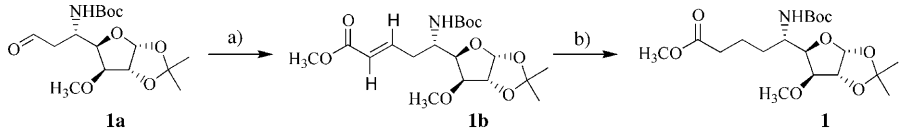


Figure 1. Most stable helix types of α/δ-hybrid peptides.



Scheme 2. Structures of the synthesized peptides **2**–**7** and **2a**–**4a** (arrows show hydrogen bonding).



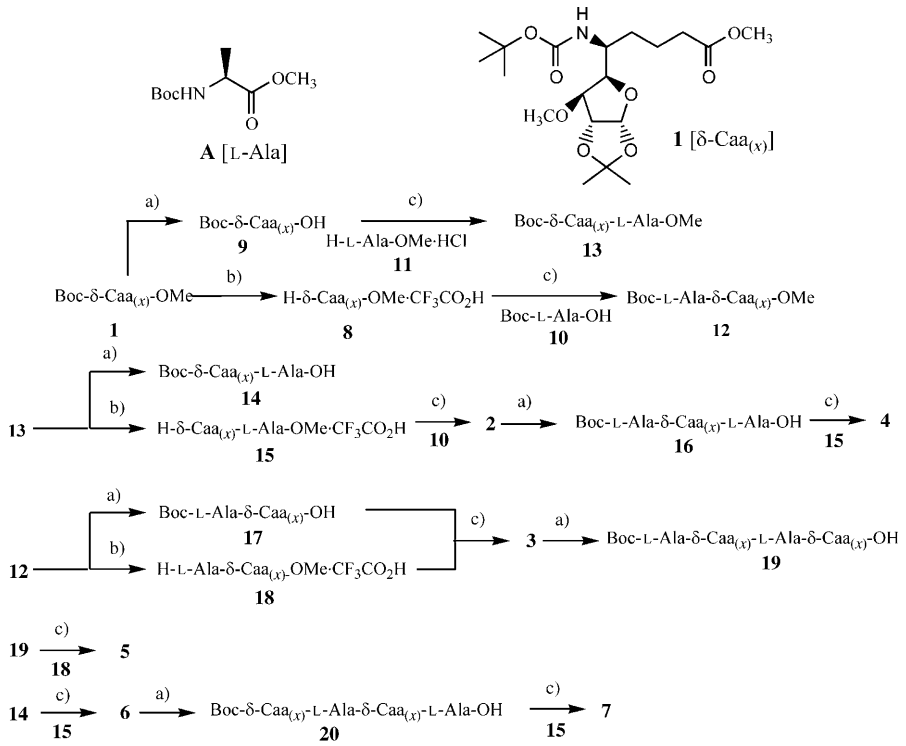
Scheme 3. Synthesis of **1** (Reagents and conditions: a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 0 °C→RT, 6 h; b) 10% Pd/C, MeOH, RT, 6 h).

on catalytic hydrogenation in the presence of 10% Pd/C at room temperature for 6 h in 82% yield (Scheme 3).

Monomer **1** was used to synthesize peptides **2–7** (Scheme 2) alternating with L-Ala (**A**) by standard peptide coupling methods by using *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), and diisopropylethylamine (DIPEA) in solution phase (see the Experimental Section and Supporting Information). The synthetic strategy (Scheme 4) starts with the preparation of the two dipeptides **12** and **13**. Thus, amine salt **8**, obtained from **1** on exposure to CF_3COOH in CH_2Cl_2, afforded dipeptide **12** on condensation with acid **10** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 in 74% yield. Similarly, acid **9**, obtained by base-mediated hydrolysis of **1** (by using 4 N NaOH (aq.)), was treated with amine salt **11** under standard reaction conditions (EDCI, HOBt and DIPEA in CH_2Cl_2) to give dipeptide **13** in 90% yield. Peptide **13** provided the corresponding acid **14** on base-mediated hydrolysis (4 N NaOH (aq.)), whereas it was converted into salt **15** by treatment with CF_3COOH in CH_2Cl_2. Furthermore, reaction of the salt **15** with the acid **10** under peptide coupling conditions gave tripeptide **2** in 85% yield. Hydrolysis of peptide **2** with base and further treatment of the resulting acid **16** with salt **15** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 provided pentapeptide **4** in 36% yield. Likewise, dipeptide **12** on exposure to CF_3COOH in CH_2Cl_2 afforded the salt **18**, whereas it gave the acid **17** on base hydrolysis. Coupling of acid **17** with salt **18** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 led to tetrapeptide **3** in 65% yield, which gave acid **19** upon base hydrolysis (4 N NaOH (aq.)). Coupling of acid **19** with salt **18** resulted in hexapeptide **5** in 46% yield. Similarly, acid **14** on coupling with salt **15** afforded tetrapeptide **6** in 55% yield. Base hydrolysis of **6** gave acid **20**, which on further condensation with salt **15** provided the hexapeptide **7** in 48% yield. Thus, peptides **2**, **4**, **6**, and **7** were prepared from dipeptide **13** and peptides **3** and **5** from dipeptide **12**.

Conformational analysis: Based on our experience with α/β-, α/γ-, and β/γ-hybrid peptides from experimental and theoretical studies, we were tempted to expect that the most probable structure generated by α/δ-hybrid peptides could stem from the 11/13- or, alternatively, 13/11-helix family—remembering that we denote a mixed helix as the 11/13-helix when the amide protons of the α-amino acids take part in hydrogen bonding of 11-membered rings and those of δ-residues in the formation of 13-membered rings. In the reverse situation, we speak of a 13/11-helix (Scheme 1).

Important information on the structure of the α/δ-hybrid peptides comes from NMR spectroscopy. The NMR spectra of **2–7** were investigated as 3–10 mM solutions in $CDCl_3$.[12] Distinctive signatures of a defined structure were gleaned from well-dispersed amide proton resonances at low field with chemical shifts $\delta > 7$ ppm and a large number of medium-range NOE correlations. In particular, backbone NOE correlations NH(i)/C_γH(i), NH(i)/C_βH(i), C_δH(i)/C_βH(i), C_δH(i)/$C_\alpha H_{(pro\text{-}R)}$(i), in which i is the δ-Caa residue, as well as strong C3H/CγH, C3H/Cγ′H, C4H/CγH, C4H/Cγ′H, and NH/C4H intraresidue



Scheme 4. Synthesis of **2–7** (Reagents and conditions: a) 4 N NaOH (aq.), MeOH, 0 °C→RT, 2 h; b) CF_3COOH, dry CH_2Cl_2, 2 h; c) HOBt (1.2 equiv), EDCI (1.2 equiv), DIPEA (1.5 equiv), dry CH_2Cl_2, 0 °C→RT, 4 h).

NOEs involving the sugar ring proton were helpful for structure assignment (Figure 2).

Based on these data, nucleation of a well-defined structure was indicated in the shortest peptide **2** and continues in

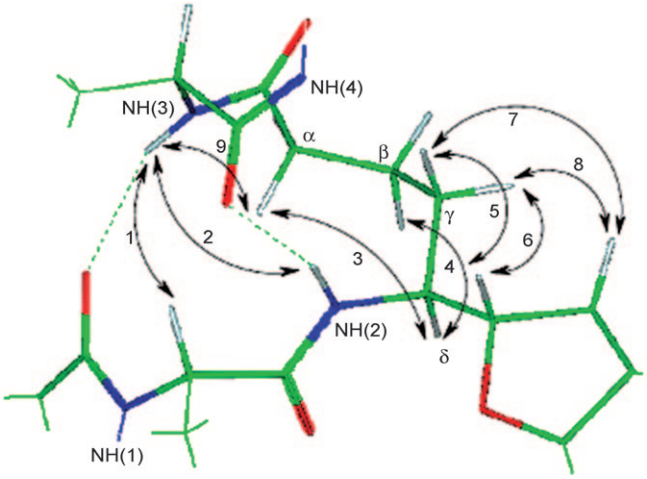


Figure 2. Characteristic NOEs 1) CαH(1)/NH(3), 2) NH(2)/NH(3), 3) CδH(2)/CαH(2), 4) CδH(2)/CβH(2), 5) C4H/CγH, 6) C4H/Cγ′H, 7) C3H/CγH, 8) C3H/Cγ′H, and 9) CαH(2)/NH(3), supporting 13- and 11-membered hydrogen bonding (shown in dotted lines) in an α/δ-hybrid dipeptide repeat employed for structure determination on the basis of the NMR spectroscopic measurements in $CDCl_3$.

the longer peptides **3**–**7**.[12] Data analysis unequivocally shows the formation of 13/11-helices in all 6 peptides. Since data acquisition and interpretation follows the same principles in all cases, we selected the shortest peptide **2**, peptide **4** of medium length, and the longest peptide **7** for detailed discussion. The NMR spectroscopy data for peptides **3**, **5**, and **6** can be found in the Supporting Information. For **2**, a large δ value of 7.21 ppm for NH(3) suggests its involvement in hydrogen bonds. A small change of 0.54 ppm in the chemical shift ($\Delta\delta$) during solvent titration studies,[12] when 33% v/v [D_6]DMSO was added to the solution in $CDCl_3$, confirms this observation (for details, see the Supporting Information). Though NH(2) appears at $\delta = 6.62$ ppm, it has a modest $\Delta\delta$ of 0.71 ppm (during solvent titration), which suggests that it might be taking brief excursions to conformations that involve it in hydrogen bonding. Due to a very well-resolved spectrum, overlap of spectral lines was minimal, thus permitting unique assignment of the chemical shifts along with many of the coupling constants (J). For the δ-residue, the coupling constant $^3J(\mathrm{NH,C\delta H}) = 9.6$ Hz is consistent with an antiperiplanar arrangement of the NH and the CδH, corresponding to a value of $\approx 120°$ for the torsion angle φ (C(O)-N-Cδ-Cγ). Similarly, the $^3J(\mathrm{C\gamma H,C\delta H})$ values of 3.4 and 10.5 Hz as well as NH(2)/CγH(2), CγH(2)/C4H(2) NOE correlations permit us to assign CγH, with a large coupling to CδH ($^3J(\mathrm{C\gamma H,C\delta H}) = 10.5$ Hz), as $\mathrm{C\gamma H}_{(pro\text{-}R)}$ and deduce a value of about $-60°$ for the backbone torsion angle θ (N-Cδ-Cγ-Cβ). The NOE correlations involving NH(3) and CαH(2), one very strong and the other rather weak, support values of $\pm 120°$ for ψ (Cβ-Cα-C(O)-N) in the second δ-residue. We could also locate another medium-range NOE, CαH(2)/CδH(2) (the same CαH(2) with strong NH(3)/CαH(2) NOE correlation) involving backbone protons, which suggests constrained values of the intervening dihedral angles θ, ζ (Cδ-Cγ-Cβ-Cα), and ρ (Cγ-Cβ-Cα-C(O)). Spectral overlap prevented an estimation of the actual values of ζ and ρ. However, by using $\varphi = 120°$, $\theta = -60°$, and $\psi = \pm 120°$ and further assuming that only the staggered conformations, with values of 60, −60, and 180°, are populated for ζ and ρ, we searched the conformational space for possible structures. Taking into account the medium-range NOEs, CαH(1)/NH(3), CγH(2)/NH(2), CδH(2)/CαH(2), and CδH(2)/CβH(2), permitted us to reduce the available options to only four structures. Resorting to an energy-minimization protocol using the distance constraints from the ROESY spectra, in which two-spin approximation was utilized (see the Supporting Information), enabled us to reduce the structures consistent with the NMR spectroscopy observations to just one with the backbone dihedral angles ζ and ρ of $\approx 60°$. For the α-residues, although the $^3J(\mathrm{NH,C\alpha H})$ values of 7.9 and 7.5 Hz are not distinctive, suggesting averaging over several conformations, strong CαH(1)/NH(2) NOE correlation corresponds to ψ at about 120° for the N-terminal α-residue. The restrained molecular dynamics (MD) calculations,[13] undertaken with starting structures having these dihedral angles and the distance constraints obtained from the ROESY spectra, brought out a structure with a 13-membered (mr) hydrogen-bonded pseudocycle involving NH(3) and *tert*-butyloxycarbonyl (Boc) CO.

For peptide **3**, which has been discussed in detail in the Supporting Information, the presence of a 13/11-helix was adequately supported by a 13-mr hydrogen-bonded ring between NH(3) Boc CO and an 11-mr pseudocycle closed between NH(2) and CO(3). It was noticed that peptide **4** had the optimal balance between the achievable information and the spectral resolution, despite the enhanced spectral complexity. Although the ROESY spectrum shows exchange peaks between two isomers, the ^{1}H NMR spectrum indicates the presence of only one isomer. The large δ values (> 6.90 ppm) and small changes $\Delta\delta$ (< 0.56 ppm) in solvent titration found for all amide protons, except the first one, support their involvement in hydrogen bonding. For δ-Caa(2) and δ-Caa(4) residues, $^3J(\mathrm{NH,C\delta H})$ values of 9.5 and 9.3 Hz, respectively, suggest a value for φ of about 120°. Due to spectral overlaps, it was not possible to get individual chemical shifts and most of the coupling constants involving the CαH and CβH protons of δ-Caa. The value of $^3J(\mathrm{NH,C\alpha H}) = 6.3$ Hz for Ala(3) suggests a preponderance of a single structure with constrained φ, whereas the corresponding values for Ala(1) and Ala(5) of about 7.5 Hz may arise either from a single predominant conformation or from fraying in the termini, resulting in averaging due to structures with several values of φ. Strong CαH(1)/NH(2) and CαH(3)/NH(4) NOEs further suggest ψ at $\approx 120°$ for the Ala(1) and Ala(3) residues. Like earlier observations on

other mixed helices,[7] the tell-tale medium-range NOEs, CαH(1)/NH(3), NH(2)/NH(3), CαH(3)/NH(5), and NH(4)/NH(5), provide the distinctive signatures of a 13/11-helix. The structures from the MD studies very clearly bring out a 13/11-helix with an alternating 13/11/13/11 hydrogen-bonded configuration. Figure 3a shows a stereoview of the 20

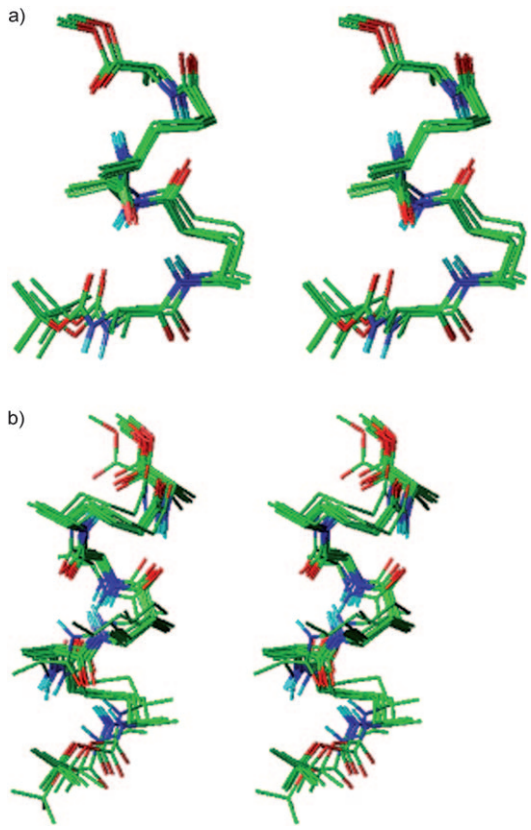


Figure 3. Stereoviews of the superimposition of the 20 lowest-energy structures determined on the basis of the NMR spectroscopy measurements in $CDCl_3$ of a) peptide **4** and b) peptide **7** (sugar residues are replaced by methyl groups after the calculations for clarity).

lowest-energy superimposed structures. The root-mean-square deviation (rmsd) values of the backbone and the heavy atoms for **4** are 0.26 and 0.32 Å, respectively. The average values of the backbone dihedral angles in **4** are $\varphi = (-75 \pm 5)°$, $\psi = (143 \pm 2)°$ for the α-amino acid constituents and $\varphi = (140 \pm 8)°$, $\theta = (-77 \pm 6)°$, $\zeta = (74 \pm 1)°$, $\rho = (51 \pm 2)°$, and $\psi = (-137 \pm 5)°$ for the δ-residues. The formation of 13/11-helices is also confirmed in peptides **5** and **6**.[12]

We also undertook NMR spectroscopy studies on **4** and **5** in CD_3OH. For **5**, the solvent-exchange studies in CD_3OD, in which all of the amide proton resonances disappeared in <2 h, indicates lack of hydrogen bonds. However, it is pertinent to mention that in the ROESY spectrum (in CD_3OH) few weak medium-range NOEs CαH(1)/NH(3), CαH(3)/NH(5), CδH(2)/CβH(2), and CδH(2)/CαH(2) were still present, indicating the presence of some population of a nascent structure. For **4**, the amide proton resonances lasted for less than half an hour in CD_3OD and support the lack of a robust secondary structure. Yet, like **5**, ample evidence for preponderance of a structure is reflected in the ROESY data.[12]

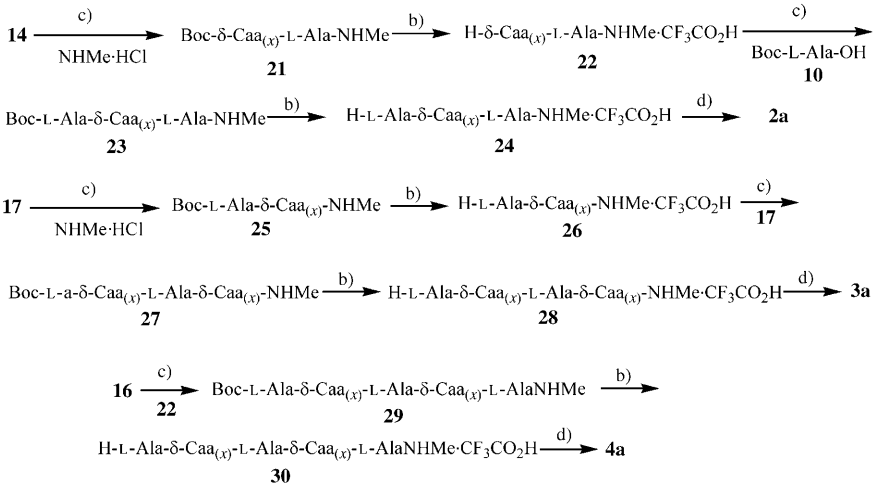
In the ^{1}H NMR spectrum of hexapeptide **7** in $CDCl_3$, the NH(2)-NH(6) amide resonances appeared at $\delta > 6.92$ ppm, which along with the solvent titration[12] studies ($\Delta\delta < 0.46$ ppm) confirmed their participation in hydrogen bonding. For the δ-Caa residues, the values of ^3J(NH,CδH) > 8.3 Hz indicated that the NH and CδH protons are antiperiplanar, which implies a value of about 120° for φ. The values of ^3J(CδH,CγH) could not be obtained due to spectral overlap. The ^3J(NH,CαH) values < 7.5 Hz for the Ala residues are not distinctive enough to deduce the conformational preferences about the N–Cα bond. Strong CαH(2)/NH(3) and CαH(4)/NH(5) NOEs, however, suggest ψ at approximately 120° for the Ala(2) and Ala(4) residues. The characteristic medium-range NOE correlations CγH(1)/NH(1), CδH(1)/CβH(1), CδH(1)/CαH(1), CαH(2)/NH(4), NH(3)/NH(4), CγH(3)/NH(3), CδH(3)/CβH(3), CδH(3)/CαH(3), CαH(4)/NH(6), NH(5)/NH(6), CγH(5)/NH(5), CδH(5)/CβH(5), and CδH(5)/CαH(5) provide an emphatic support for a 13/11/13/11-hydrogen-bonded pattern. The superimposition of the 20 lowest-energy structures obtained from MD calculations for **7** provides backbone and heavy-atom rmsd values of 0.32 and 0.42 Å, respectively (Figure 3b).

The following average values of the backbone dihedral angles for **7** were obtained by removing the terminal residues to reduce the effect of fraying: $\varphi = (-87 \pm 2)°$, $\psi = (133 \pm 4)°$ for the α-amino acid constituents and $\varphi = (138 \pm 4)°$, $\theta = (-72 \pm 3)°$, $\zeta = (73 \pm 1)°$, $\rho = (56 \pm 1)°$, and $\psi = (-135 \pm 4)°$ for the δ-residues. The backbone torsion angles estimated from the NMR spectroscopy studies for the synthesized peptides agree well with the torsion angles for the most stable $H^{I}_{13/11}$ helix of the model octapeptides in Table 3. To get still closer correspondence to the synthesized peptides, we repeated our HF/6-31G* calculations for the actual hexapeptide **7** and obtained the following average backbone torsion angles for a right-handed 13/11-helix in fair agreement with the experimental data: $\varphi = -68.1°$, $\psi = 149.4°$ for the α-amino acid constituents, and $\varphi = 135.5°$, $\theta = -72.3°$, $\zeta = 66.8°$, $\rho = 54.8°$, and $\psi = -139.2°$ for the δ-residues.

Synthesis and conformational analysis of the peptides 2a, 3a, and 4a: The above-presented peptides **2**–**7**, with a Boc group at the N termini and a methyl ester at the C termini, possess three types of hydrogen-bonding acceptors, namely, carbamate carbonyl and ester carbonyl along with the amide carbonyl.

They have shown preponderance of robust 13/11-helical patterns. In the hydrogen-bonding-acceptor scale the following trends are observed: amide carbonyl ≈ carbamate carbonyl > carboxyl carbonyl, which implies that the amide proton–carboxyl carbonyl hydrogen bonds are weaker than the other two hydrogen-bond types.[14] To have hydrogen

bonds of similar strength and to understand the impact of N capping (at the C and N termini) on the robustness of the conformations, peptides **2a**, **3a**, and **4a** (Scheme 2) with the N termini capped by an acetyl group and the C termini capped with an *N*-methyl group, were synthesized starting from the acids **14**, **17**, and **16**, respectively (Scheme 5).



Scheme 5. Synthesis of **2a**–**4a** (Reagents and conditions: a) 4N NaOH (aq.), MeOH, 0°C→RT, 2 h; b) CF_3COOH, dry CH_2Cl_2, 2 h; c) HOBt, EDCI, DIPEA, dry CH_2Cl_2, 0°C→RT, 4 h; d) Ac_2O, Et_3N, dry CH_2Cl_2, 0°C→RT, 15 h).

Accordingly, acid **14** on treatment with NHMe·HCl in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 gave dipeptide **21** in 79% yield. Amide **21** on exposure to CF_3COOH in CH_2Cl_2 afforded salt **22**, which on condensation (EDCI, HOBt, and DIPEA in CH_2Cl_2) with **10** afforded **23** (61%). Peptide **23** was converted into trifluoroacetate (TFA) salt **24** and acetylated with Ac_2O in the presence of Et_3N in CH_2Cl_2 to give tripeptide **2a** in 63% yield. Similarly, condensation (EDCI, HOBt, and DIPEA in CH_2Cl_2) of acid **17** with NHMe·HCl gave amide **25** in 84% yield. Reaction of acid **17** with the salt **26** (obtained from **25** on exposure to CF_3COOH in CH_2Cl_2) afforded tetrapeptide **27** in 64% yield. Treatment of **27** with CF_3COOH in CH_2Cl_2 and acetylation (Ac_2O, Et_3N) of the resulting amine salt **28** in CH_2Cl_2 gave **3a** in 44% yield. Likewise, tripeptide acid **16** gave pentapeptide **29** in 47% yield upon treatment with dipeptide salt **22** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2. Removal of the Boc group in **29** with CF_3COOH in CH_2Cl_2 and treatment of salt **30** with Ac_2O and Et_3N in CH_2Cl_2 gave **4a** in 43% yield.

In general, the spectra[12] of peptides **2a**, **3a**, and **4a**, were found to be not well resolved. The reason for such behavior may be attributed to the decreased difference in the chemical environment of various residues due to the terminal cappings, thus leading to a very similar local environment for each residue. For peptide **2a**,[12] although several of the spectral signatures (derived couplings, the hydrogen-bonding information, and the NOE correlations) are very much like those for corresponding trimer **2**, the NOE correlations CγH(2)/NH(2), CγH(2)/C3H(2), CγH(2)/C4H(2), and NH(2)/CβH(2) were conspicuous by their absence. The values of ^3J(CδH,CγH) could not be obtained due to spectral overlaps, which in turn did not permit stereospecific assignments for the CγH protons. The spectral information that was available at this stage was inadequate to deduce more definitive conclusions on the secondary structure. Therefore, we took recourse to some trends observed for trimer **2**. The chemical shifts of CαH and CγH in the δ-Caa residue follow a pattern: $\delta C\alpha H_{(pro\text{-}R)} > \delta C\alpha H_{(pro\text{-}S)}$ and $\delta C\gamma H_{(pro\text{-}S)} > \delta C\gamma H_{(pro\text{-}R)}$, which was also noted for peptides **3**–**7**. The above surmise was used to obtain the stereospecific assignments for CαH and CγH in **2a**. The restrained MD calculations on **2a** reveal the presence of a 13-membered hydrogen-bonded pseudocycle involving NH(3) and Boc CO (Figure S60 in the Supporting Information) with average pairwise backbone and rmsd values of 0.36 and 0.47 Å, respectively.[12] Tetrapeptide **3a** provided almost all of the signatures observed for the corresponding tetramer **3** and the finding of the 13/11-helix has been discussed in detail in the Supporting Information. Furthermore, the NMR spectroscopy study on peptide **3a** in CD_3OH indicated the presence of a weakened 13/11-helix.[12]

From the ^{1}H spectrum of **4a**, hydrogen bonding of NH(2)–NH(5) was inferred from their large δ values and small $\Delta\delta$ values in the solvent titration studies.[12] For the δ-Caa(2) and δ-Caa(4) residues, the ^3J(NH,CδH) values of 9.5 and 9.3 Hz, respectively, correspond to $\varphi \approx 120°$, whereas the value of $^3J(NH,C\alpha H) = 6.6$–7.0 Hz for the Ala residues is consistent with the preponderance of a single structure with $\varphi \approx -60°$. Strong CαH(1)/NH(2), CαH(3)/NH(4) NOEs further suggest $\psi \approx 120°$ for the Ala(1) and Ala(3) residues. Due to spectral overlap of the signals, individual chemical shifts and most of the coupling constants involving the CαH, CβH, and CγH protons of δ-Caas could not be arrived at. However, the NOE correlations CαH(1)/NH(3), CαH(3)/NH(5), and NH(4)/NH(5) as signatures of a 13/11-helix were present in the ROESY spectrum.[12] The 13/11-helical structure is also consistent with strong C3H/CγH, C3H/Cγ′H, C4H/CγH, C4H/Cγ′H, and NH/C4H intraresidue NOEs involving sugar ring protons of δ-Caa(2) and δ-Caa(4). Following the arguments presented for **2a**, stereospecific assignments of CαH and CγH protons were obtained, which in turn resulted in required distance constraints for the MD calculations to provide a 13/11-helix with a 13/11/13-hydrogen-bonding pattern. The superposi-

tion of the 20 lowest-energy structures[12] of **4a** obtained from restrained MD calculations revealed the backbone and heavy-atom rmsd values of 0.28 and 0.34 Å, respectively.

The circular dichroism (CD) spectra of **2–7** in CH_3OH are shown in Figure 4 and the CD spectra for peptides for **2a–4a** are presented in the Supporting Information. The molar

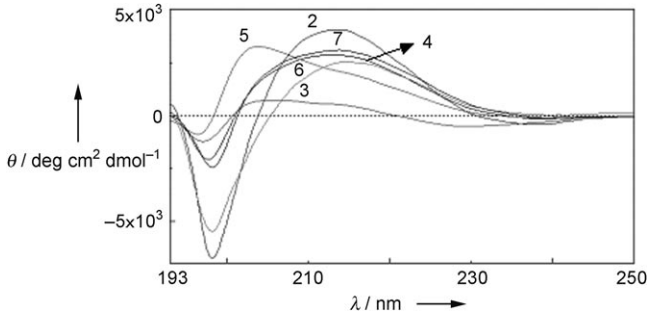


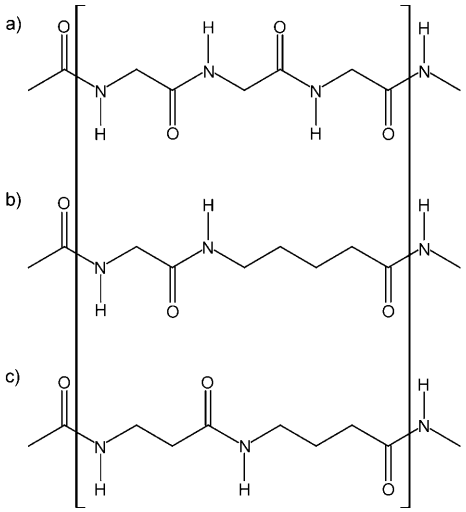
Figure 4. CD spectra of peptides **2–7** (in MeOH).

ellipticities (θ) have been normalized and the data are presented as $deg\,cm^2\,dmol^{-1}$ per residue. Interestingly, they appear different when compared with other mixed helices.[1k,7,15] Furthermore, there are differences amongst peptides **2–7**, although all display at least one minimum and maximum. Peptides **2, 4**, **6**, and **7** have well-defined minima and maxima at about 198 and 214 nm, respectively, whereas **3** and **5** have the corresponding values at $\approx$196 and $\approx$205 nm, respectively. The CD spectra of **2a–4a** show very similar trends (Figure S68 in the Supporting Information). Few CD spectra of δ-peptides have been reported to date,[9h,16] and this is the first report for α/δ-hybrid peptides.

Relationships to helices of other hybrid peptides: It is interesting to compare the conformational properties of α/δ-hybrid peptides with those of other hybrid peptides, for instance, α/β-, α/γ-, and β/γ-hybrid peptides. Similar to our α/δ-hybrid peptides, mixed or β-helices were also experimentally found in the other hybrid peptide classes as an important helix type.[7c–e] Theoretical estimations for all these hybrid peptide classes show that mixed helices generally lose stability when changing from apolar to polar environments due to their small macrodipole compared with helices with all hydrogen bonds pointing in the same direction.[8g,l,m] Thus, it can be expected that solvent influence may change the stability relationships between the various helix types in the different hybrid peptide classes. In any case, the most stable representatives of mixed helices always belong to the group of most stable helix alternatives. For the unsubstituted backbone of α/β-hybrid peptides, it was estimated that the three most important helix types, a mixed 11/9-helix and the 11- and 14/15-helices with backwards orientation of all hydrogen bonds, are closely together, within an energy range of $\Delta E = 15.8\,kJ\,mol^{-1}$ in an aqueous environment, however, with a slight preference for the mixed helix.[8l] In view of these small energy differences it is not surprising that all three helix types were indeed experimentally found.[4a,c,7d,e] Obviously, special backbone substitution may easily shift the stability order between the most stable helix alternatives. It was also shown for α/β-hybrid peptides that mixed helices can be generated both with carbohydrate backbones and with side chains of natural amino acids.[7c–e] Mixed helices with 12/10- or 10/12- and 13/11- or 11/13-hydrogen-bonding patterns, respectively, were experimentally found in α/γ- and β/γ-hybrid peptides in agreement with theoretical predictions.[7c,8m] Additionally, a helix with backwards orientation of all hydrogen bonds and 12-membered hydrogen-bonded rings, was obtained in experimental studies on α/γ-hybrid peptides;[3i] this was theoretically predicted to be the most stable in a polar medium.[8m]

In case of the α/δ-hybrid peptides, the 13/11-hydrogen-bond pattern is even a bit more stable than the mixed helices in the other hybrid peptide classes with reference to the helix alternatives and predominates also in a polar environment according to the theoretical estimations for the unsubstituted backbone. This is confirmed by the NMR spectroscopy studies on our α/δ-hybrid peptides consisting of L-Ala and a carbo-δ-amino acid alternating in a ratio of 1:1, which indicate this helix type both in chloroform and in methanol. As theoretically predicted, the NMR spectroscopy data show that the mixed 13/11-helix is weakened in the more polar solvent methanol. It is also interesting to see the 13-turn already realized in the blocked trimer unit of compound **2** and the two alternating 13- and 11-turns with only two dimer units in compound **3**. Despite the general preference for the 13/11-helix in α/δ-hybrid peptides, the energy difference of $21.0\,kJ\,mol^{-1}$ to the next stable octamer helix H^{I}_{13}, with all hydrogen bonds in the backward direction is still small enough to imagine backbone modifications favoring this helix type (Table 2). This might be especially important because this hydrogen-bond pattern corresponds to that of the α-helix in native peptides. This correspondence was already shown for β/γ-hybrid peptides,[7c,8m] which generally exhibit the same helix types as the α/δ-hybrid peptides with the 11/13- and 13/11-hydrogen-bonding patterns among the most stable ones. Scheme 6 demonstrates this for the dimer repeats of both hybrid peptide classes and shows also their correspondence to a trimer unit of the native α-peptides. The helix parameters of the experimentally found 13/11-helices of α/δ- and β/γ-hybrid peptides are very similar. The pitch of 5.8 Å, the number of residues per turn of 2.7, and the rise per turn of about 2.1 Å for the α/δ-helix compare well with the corresponding values of approximately 5.9, 2.7, and 2.2 Å, respectively, for the 13/11-β/γ-helix.[7c] Figure 5a shows a superimposition of both helices.

For an examination of the possibility to mimic an α-helix by an α/δ-hybrid peptide sequence, we have to look at the two most stable 13-helices, H^{I}_{13} and H^{II}_{13}, found for α/δ-hybrid peptides. Both helices are not very different in energy. There is even an interesting stability change between both helices with increasing sequence length. Thus, H^{I}_{13} is $12.2\,kJ\,mol^{-1}$ more stable than H^{II}_{13} in the octamer, whereas H^{II}_{13} is $4.3\,kJ\,mol^{-1}$ more stable than H^{I}_{13} in the hexamer. The corresponding values for a polar environment are $5.7\,kJ\,mol^{-1}$ in favor of the H^{I}_{13} octamer, but $13.6\,kJ\,mol^{-1}$ in



Scheme 6. Schematic comparison between an α-peptide trimer (a) and the dimer repeats of α/δ- (b) and β/γ-hybrid peptides (c).

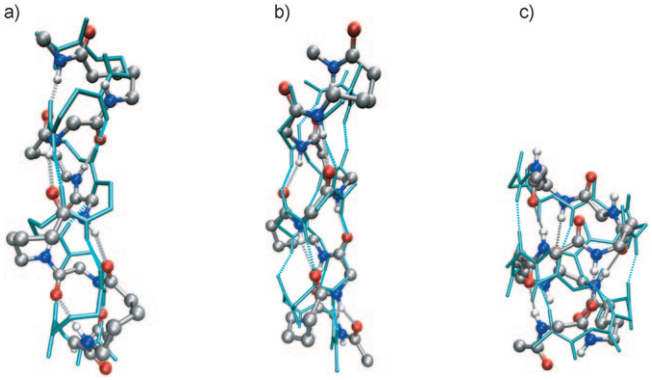


Figure 5. Superimposition of a) the 13/11-helices of α/δ- and β/γ-hybrid peptides (rmsd = 0.3 Å); b) the H^{II}_{13}-helix of α/δ-hybrid peptides and the native α-helix (rmsd = 0.7 Å); and c) the most stable mixed $H^{I}_{20/22}$ helix of α/δ-hybrid peptides and the gramicidin A helix (rmsd = 0.9 Å).

favor of the H^{II}_{13} hexamer. The dependence of the relative stabilities of different folding patterns on sequence length was already mentioned above when comparing the stabilities of all helix types of α/δ-hybrid peptides for the octamers and hexamers (Table 2 and Table S14 in the Supporting Information) and also experimentally found in α/β-hybrid peptides comparing the 11- and 14/15-helices there.[4e] Moreover, it is also well known for native α-peptides when studying the relationships between the α- and 3_{10}-helices. Conformer H^{II}_{13} (average backbone torsion angles: $\varphi = -73.7°$, $\psi = -27.9°$ for the α-amino acid constituents and $\varphi = -68.1°$, $\theta = -57.9°$, $\zeta = 171.2°$, $\rho = -62.9°$, and $\psi = -44.5°$ for the δ-amino acid constituent, detailed values are given in Table S11 in the Supporting Information) shows the closest correspondence to the α-helix. Here, the torsion angle ζ, which describes the rotation around the Cβ–Cγ bond in the δ-amino acid constituents, agrees with the value of about 180° for the torsion angle ω of a *trans* peptide bond in α-peptides. The Cβ–Cγ bond of δ-amino acids corresponds to the peptide bond in an α-amino acid dimer (Scheme 6). On the contrary, the value of ζ in H^{I}_{13} denotes a *gauche* conformation (Table 3).[8i] These relationships also explain why δ-amino acid constituents easily fit into sequences of α-amino acids.[3m,8i] The superimposition in Figure 5b shows the similarities between H^{II}_{13} and the native α-helix.

There is also close correspondence between the rather stable mixed helices $H^{I}_{20/22}$ and $H^{I}_{22/20}$ and the structure of the gramicidin A membrane channel (Figure 5c).[17] These remarkable relationships demonstrate the considerable potential for α/δ-hybrid peptides to mimic native peptide and protein structures.

Conclusion

In a concerted theoretical and experimental study, we present α/δ-hybrid peptides as a novel foldamer class. Taking advantage of the rigidity of the side chain in the design control, the new δ-Caa$_{(x)}$, prepared from D-glucose with a D-xylose furanoside side chain, has been very efficiently utilized in the synthesis of these foldamers. Detailed structure analyses show the formation of a novel 13/11-motif corresponding to a mixed or β-helix. Despite the flexibility of the backbone, the stereochemistry around the amine center and the side chain in δ-Caa allow these α/δ-hybrid peptides to adopt robust 13/11-helices, even in peptides with very few residues. The theoretical conformational search for all periodic hydrogen-bonded secondary structures employing ab initio MO theory provides a complete overview on the helix-forming potential of these hybrid peptide sequences. The pool of predicted folding patterns may serve to find further secondary structure types by the introduction of suitable substituents in the backbone. There are interesting relationships between helices of α/δ-hybrid peptides and helices of other hybrid peptide classes and native α-peptides, respectively. The new design of α/δ-hybrid peptides provides an opportunity to expand the domain of foldamers and allows the introduction of desired functionalities through the α-amino acid constituents. Thus, the addition of δ-Caas to the array of already available β- and γ-Caas leads to novel folding motifs, which could be important for secondary and tertiary structure formation.

Experimental Section

NMR spectra (1D and 2D experiments) for peptides **2–7** and **2a–4a** were obtained at 500 and 600 MHz (^{1}H), and at 75, 100, and 150 MHz (^{13}C). Chemical shifts are reported in δ with respect to the internal TMS reference. IR spectra were recorded with a FTIR spectrometer between 400 and 4000 cm^{-1} as KBr pellets. Melting points were determined in open capillaries and were not corrected.

The CD spectra were obtained with a Jasco J-810 spectropolarimeter in rectangular fused quartz cells of 0.2 cm path length as 200 mM solutions in methanol. The binomial method was used for smoothening the spectra. The values are expressed in terms of θ, the total molar ellipticity, and are given in $deg\,cm^2\,dmol^{-1}$.

Restraint MD studies were carried out by using the INSIGHT-II Discover[13] module employing an SGI workstation. The constraints were derived from the volume integrals obtained from the ROESY spectra by

using a two-spin approximation and a reference distance of 1.8 Å for the geminal protons. The upper and lower boundary of the distance constraints have been obtained by enhancing and reducing the derived distance by 10%.

Boc-L-Ala-δ-Caa$_{(x)}$-OMe (12): A solution of **1** (0.45 g, 1.11 mmol) and CF_3COOH (0.45 mL) in CH_2Cl_2 (3 mL) was stirred at room temperature. After 2 h, the solvent was evaporated under reduced pressure to get **8**, which was dried under high vacuum and used without any further purification. A cooled (0 °C) solution of **10** (0.211 g, 1.11 mmol), HOBt (0.18 g, 1.33 mmol), and EDCI (0.26 g, 1.33 mmol) in CH_2Cl_2 (6 mL) was stirred under N_2 atmosphere for 15 min and treated sequentially with the salt **8**, DIPEA (0.3 mL, 1.67 mmol), and stirred for another 8 h. The reaction mixture was cooled to 0 °C, treated with a saturated aqueous solution of NH_4Cl (10 mL), and stirred for 10 min. The reaction mixture was diluted with $CHCl_3$ (10 mL), washed sequentially with 1 N HCl (10 mL), water (10 mL), a saturated aqueous solution of $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), evaporated, and the residue obtained was purified by column chromatography (silica gel, 50% ethyl acetate in petroleum (pet.) ether) to give **12** as a white solid (0.394 g, 74%). M.p. 133–136 °C; $[\alpha]_D = -7.9$ ($c = 0.25$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.16$ (d, 1H, $J = 8.0$ Hz; NH-2), 5.88 (d, 1H, $J = 3.7$ Hz; C_1H-2), 5.11 (brs, 1H; NH-1), 4.54 (d, 1H, $J = 3.8$ Hz; C_2H-2), 4.31–4.20 (m, 1H; C_δH-2), 4.11 (m, 1H; C_αH-1), 4.08 (dd, 1H, $J = 3.1$, 6.2 Hz; C_4H-2), 3.65 (s, 3H; COOMe), 3.64 (brs, 1H; C_3H-2), 3.34 (s, 3H; OMe), 2.43–2.24 (m, 2H; C_αH-2), 1.62 (m, 2H; C_βH-2), 1.46 (m, 2H; C_γH-2), 1.44 (s, 9H; Boc), 1.32 (d, 3H, $J = 7.1$ Hz; CH_3-1), 1.31 (s, 6H; Me), 1.28 ppm (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta =$ 173.8, 172.2, 155.4, 111.5, 104.7, 84.6, 81.3, 80.6, 79.7, 57.6, 51.5, 50.1, 47.5, 33.4, 32.1, 28.3, 26.7, 26.1, 20.7, 18.2 ppm; IR (KBr): $\tilde{\nu} = 3356$, 2987, 2941, 1717, 1686, 1539, 1507, 1453, 1374, 1230, 1171, 1086 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{38}N_2O_9Na$ [M^++Na]: 497.2475; found: 497.2482.

Boc-δ-Caa$_{(x)}$-L-Ala-OMe (13): A solution of **1** (0.43 g, 1.06 mmol) in methanol (4 mL) was cooled to 0 °C and treated with a 4 N aqueous solution of NaOH (4 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated, the pH was adjusted to 2–3 with a 1 N aqueous solution of HCl at 0 °C and extracted with ethyl acetate (2×10 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford **9** (0.41 g, 98%), which was used without any further purification. A solution of **9** (0.4 g, 1.02 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C, treated with HOBt (0.166 g, 1.23 mmol), EDCI (0.236 g, 1.23 mmol), salt **11** prepared from L-Ala (0.14 g, 1.02 mmol) and AcCl (0.16 mL, 2.35) in MeOH (2 mL), and DIPEA (0.27 mL, 1.54 mmol), as described for the synthesis of **12**. Workup and purification by column chromatography (silica gel, 50% ethyl acetate in pet. ether) gave **13** as a white solid (0.44 g, 90%). M.p. 166–168 °C; $[\alpha]_D = -27.99$ ($c = 0.25$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.36$ (d, 1H, $J = 6.5$ Hz; NH-2), 5.88 (d, 1H, $J = 3.9$ Hz; C_1H-1), 4.76 (d, 1H, $J = 8.0$ Hz; NH-1), 4.70–4.60 (m, 1H; C_αH-2), 4.53 (d, 1H, $J = 3.9$ Hz; C_2H-1), 4.03–3.92 (m, 2H; C_4H-1, C_δH −1), 3.75 (s, 3H; COOMe), 3.63 (d, 1H, $J = 3.2$ Hz; C_3H-1), 3.40 (s, 3H; OMe), 2.44–2.35 (m, 1H; C_αH-1), 2.24–2.14 (m, 1H; C_αH-1), 1.76 (m, 2H; C_βH-1), 1.55 (m, 2H; C_γH-1), 1.48 (s, 3H; Me), 1.46 (s, 3H; Me), 1.46 (s, 9H; Boc), 1.42 ppm (d, 1H, $J = 7.2$ Hz; CH_3-2); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 173.5$, 172.8, 156.2, 111.6, 104.6, 84.3, 81.3, 81.2, 79.1, 57.6, 52.5, 52.3, 47.9, 35.6, 32.0, 28.4, 26.7, 26.1, 21.6, 18.5, 18.1 ppm; IR (KBr): $\tilde{\nu} = 3362$, 2983, 2937, 1756, 1695, 1652, 1525, 1458, 1385, 1260, 1171, 1076 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{38}N_2O_9Na$ [M^+ + Na]: 497.2475; found: 497.2468.

Boc-L-Ala-δ-Caa$_{(x)}$-L-Ala-OMe (2): A solution of **13** (0.188 g, 0.4 mmol) and CF_3COOH (0.2 mL) in CH_2Cl_2 (1.5 mL) was stirred at room temperature as described for **8**, to give **15**, which was used without any further purification. As described for the synthesis of **12**, a mixture of **10** (0.075 g, 0.4 mmol), HOBt (0.064 g, 0.48 mmol), and EDCI (0.092 g, 0.48 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min; followed by the salt **15** and DIPEA (0.1 mL, 0.6 mmol). Workup and purification by column chromatography (silica gel, 90% ethyl acetate in pet. ether) afforded **2** as a white solid (0.185 g, 85%). M.p. 160–162 °C; $[\alpha]_D = -57.9$ ($c = 0.25$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.22$ (d, 1H, $J =$ 7.5 Hz; NH-3), 6.62 (d, 1H, $J = 9.6$ Hz; NH-2), 5.89 (d, 1H, $J = 3.8$ Hz; C_1H-2), 5.32 (d, 1H, $J = 7.9$ Hz; NH-1), 4.66–4.60 (m, 1H; C_αH-3), 4.54 (d, 1H, $J = 3.8$ Hz; C_2H-2), 4.37–4.31 (m, 1H; C_δH-2), 4.10–4.04 (m, 1H; C_αH-1), 4.03 (dd, 1H, $J = 3.4$, 7.4 Hz; C_4H-2), 3.74 (s, 3H; COOMe), 3.62 (d, 1H, $J = 3.4$ Hz; C_3H-2), 3.35 (s, 3H; OMe), 2.44 (ddd, 1H, $J = 6.5$, 6.5, 14.0 Hz; $C_\alpha H_{(pro\text{-}R)}$-2), 2.14 (ddd, 1H, $J = 7.9$, 7.9, 14.0 Hz; $C_\alpha H_{(pro\text{-}S)}$-2), 1.73 (m, 1H; C_βH-2), 1.67 (m, 1H; $C_{\beta'}$H-2), 1.55 (m, 1H; $C_\gamma H_{(pro\text{-}S)}$-2), 1.48 (s, 3H; Me), 1.46 (m, 1H; $C_{\gamma'}H_{(pro\text{-}R)}$-2), 1.42 (s, 9H; Boc), 1.41 (d, 3H, $J = 7.2$ Hz; CH_3-3), 1.33 (d, 3H, $J = 7.1$ Hz; CH_3-1), 1.31 ppm (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 174.9$, 173.3, 173.2, 155.9, 111.3, 104.8, 84.2, 81.5, 81.2, 79.9, 57.5, 52.4, 50.4, 47.5, 47.4, 35.0, 30.1, 28.2 (3), 26.7, 26.2, 21.7, 17.7, 17.5 ppm; IR (KBr): $\tilde{\nu} = 3344$, 3340, 2988, 2952, 1745, 1686, 1663, 1530, 1457, 1372, 1319, 1266, 1210, 1167, 1073, 1024, 855 cm^{-1}; HRMS (ESI): m/z calcd for $C_{25}H_{44}N_3O_{10}$ [M^++H]: 546.3026; found: 546.3023.

Boc-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-OMe (3): As described for the synthesis of **9**, a solution of **12** (0.155 g, 0.32 mmol) on reaction with a 4 N aqueous solution of NaOH (1.28 mL) and workup gave **17** (0.148 g, 99%), which was used without further purification. A solution of **12** (0.144 g, 0.3 mmol) and CF_3COOH (0.15 mL) in CH_2Cl_2 (1 mL) was stirred at room temperature as described for **8** to give **18**, which was used without any further purification. As described for the synthesis of **12**, a mixture of acid **17** (0.14 g, 0.3 mmol), HOBt (0.05 g, 0.36 mmol) and EDCI (0.07 g, 0.36 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min followed by the salt **18** and DIPEA (0.07 mL, 0.45 mmol). Workup and purification by column chromatography (silica gel, 1.6% MeOH in $CHCl_3$) afforded **3** as a white solid (0.161 g, 65%). M.p. 143–145 °C; $[\alpha]_D = -42.5$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.16 (d, 1H, $J =$ 7.5 Hz; NH-3), 6.85 (d, 1H, $J = 9.6$ Hz; NH-2), 6.16 (d, 1H, $J = 9.3$ Hz; NH-4), 5.89 (d, 1H, $J = 4.0$ Hz; C_1H-4), 5.87 (d, 1H, $J = 3.9$ Hz; C_1H-2), 5.50 (d, 1H, $J = 8.5$ Hz; NH-1), 4.54 (d, 1H, $J = 4.0$ Hz; C_2H-4), 4.53 (d, 1H, $J = 3.9$ Hz; C_2H-2), 4.41–4.35 (m, 1H; C_αH-3), 4.35–4.29 (m, 1H; C_δH-2), 4.26–4.20 (m, 1H; C_δH-4), 4.18–4.12 (m, 1H; C_αH-1), 4.10 (dd, 1H, $J = 3.4$, 6.4 Hz; C_4H-4), 4.04 (dd, 1H, $J = 3.4$, 7.0 Hz; C_4H-2), 3.66 (d, 1H, $J = 3.4$ Hz; C_3H-4), 3.65 (d, 1H, $J = 3.4$ Hz; C_3H-2), 3.65 (s, 3H; COOMe), 3.35 (s, 3H; OMe), 3.34 (s, 3H; OMe), 2.44 (ddd, 1H, $J = 5.9$, 7.8, 14.1 Hz; $C_\alpha H_{(pro\text{-}R)}$-2), 2.35 (m, 1H; $C_\alpha H_{(pro\text{-}R)}$-4), 2.31 (m, 1H; $C_\alpha H_{(pro\text{-}S)}$-4), 2.11 (ddd, 1H, $J = 7.5$, 7.9, 14.1 Hz; $C_\alpha H_{(pro\text{-}S)}$-2), 1.74 (m, 2H; C_βH-2), 1.68 (m, 2H; C_βH-4), 1.57 (m, 2H; C_γH-4), 1.53 (m, 1H; $C_\gamma H_{(pro\text{-}S)}$-2), 1.49 (s, 3H; Me), 1.47 (s, 3H; Me), 1.43 (s, 9H; Boc), 1.42 (m, 1H; $C_\gamma H_{(pro\text{-}R)}$-2), 1.36 (d, 3H, $J = 6.2$ Hz; CH_3-1), 1.34 (d, 3H, $J =$ 6.2 Hz; CH_3-3), 1.32 (s, 3H; Me), 1.30 (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.9$, 173.5 (2), 172.8, 156.0, 111.5, 111.3, 104.8 (2), 104.7 (2), 84.6, 84.3, 81.5, 81.4, 81.3, 80.7, 79.7, 57.5, 51.5, 50.3, 49.1, 47.7, 47.3, 35.1, 33.5, 32.0, 30.4, 28.3 (3), 26.7, 26.2, 26.1, 21.9, 20.7, 17.6, 17.2 ppm; IR (KBr): $\tilde{\nu} = 3356$, 3076, 2983, 2935, 1739, 1662, 1528, 1454, 1374, 1246, 1168, 1076, 1023, 857, 699, 651 cm^{-1}; HRMS (ESI): m/z calcd for $C_{38}H_{64}N_4O_{15}Na$ [M^++Na]: 839.4265; found: 839.4253.

Boc-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-L-Ala-OMe (4): As described for the synthesis of **9**, treatment of **2** (0.15 g, 0.27 mmol) with a 4 N aqueous solution of NaOH (1 mL) and workup gave **16** (0.14 g, 96%), which was used as such for the next reaction. A solution of **13** (0.107 g, 0.22 mmol) and CF_3COOH (0.1 mL) in CH_2Cl_2 (1 mL) was stirred at room temperature as described for **8** to give **15**, which was used without any further purification. As described for the synthesis of **12**, a mixture of acid **16** (0.12 g, 0.22 mmol), HOBt (0.036 g, 0.27 mmol), and EDCI (0.051 g, 0.27 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 15 min followed by the addition of **15** and DIPEA (0.06 mL, 0.33 mmol). Workup and purification by column chromatography (silica gel, 3.0% MeOH in $CHCl_3$) afforded **4** as a white solid (0.073 g, 36%). M.p. 158–160 °C; $[\alpha]_D = -47.9$ ($c = 0.25$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz and 600 MHz): $\delta = 8.02$ (d, 1H, $J =$ 6.7 Hz; NH-5), 7.79 (d, 1H, $J = 6.3$ Hz; NH-3), 7.29 (d, 1H, $J = 9.5$ Hz; NH-2), 6.90 (d, 1H, $J = 9.3$ Hz; NH-4), 5.89 (d, 1H, $J = 4.0$ Hz; C_1H-4), 5.88 (d, 1H, $J = 3.9$ Hz; C_1H-2), 5.56 (d, 1H, $J = 7.8$ Hz; NH-1), 4.66–4.60 (m, 1H; C_αH-5), 4.56 (d, 1H, $J = 4.0$ Hz; C_2H-4), 4.53 (d, 1H, $J = 3.9$ Hz; C_2H-2), 4.33 (m, 1H; C_δH-2), 4.30 (m, 1H; C_δH-4), 4.27 (m, 1H; C_αH-3), 4.20–4.14 (m, 1H; C_αH-1), 4.02 (dd, 1H, $J = 3.4$, 8.6 Hz; C_4H-4), 4.0 (dd, 1H, $J = 3.3$, 8.2 Hz; C_4H-2), 3.74 (s, 3H; COOMe), 3.61 (d, 1H, $J =$ 3.4 Hz; C_3H-4), 3.57 (d, 1H, $J = 3.2$ Hz; C_3H-2), 3.35 (s, 6H; 2×OMe), 2.45 (m, 1H; $C_\alpha H_{(pro\text{-}R)}$-2), 2.42 (m, 1H; $C_\alpha H_{(pro\text{-}R)}$-4), 2.17 (m, 1H;

$C_\alpha H_{(pro\text{-}S)}$-4), 2.08 (m, 1H; $C_\alpha H_{(pro\text{-}S)}$-2), 1.73 (m, 2H; C_βH-4), 1.70 (m, 2H; C_βH-2), 1.58 (m, 1H; $C_\gamma H_{(pro\text{-}S)}$-4), 1.50 (m, 1H; $C_\gamma H_{(pro\text{-}S)}$-2), 1.49 (s, 6H; 2×Me), 1.46 (s, 3H; Me), 1.43 (s, 9H; Boc), 1.42 (d, 3H, J=7.3 Hz; CH_3-5), 1.40 (m, 1H; $C_\gamma H_{(pro\text{-}R)}$-4), 1.37 (d, 3H, J=7.0 Hz; CH_3-3), 1.36 (d, 3H, J=6.9 Hz; CH_3-1), 1.31 (m, 1H; $C_\gamma H_{(pro\text{-}R)}$-2), 1.30 (s, 6H; 2×Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=175.6, 174.3, 173.9, 173.7, 173.4 (2), 156.2, 111.3, 104.7 (3), 84.2, 84.0, 81.8, 81.7, 81.2, 79.7, 57.5, 57.3, 52.4, 50.5, 49.8, 48.2, 47.7, 47.6, 47.5, 34.8, 29.7, 29.2, 28.9, 28.3 (3), 26.7, 26.6, 26.2, 21.9, 21.6, 17.6, 17.1, 17.0 ppm; ^{1}H NMR (CD_3OH, 600 MHz): δ= 8.32 (d, 1H, J=5.9 Hz; NH-5), 8.08 (d, 1H, J=5.8 Hz; NH-3), 7.91 (d, 1H, J=9.3 Hz; NH), 7.87 (d, 1H, J=9.2 Hz; NH), 6.68 (d, 1H, J= 7.2 Hz; NH-1), 5.79 (d, 1H, J=3.4 Hz; C_1H), 5.77 (d, 1H, J=3.8 Hz; C_1H), 4.61 (brs, 1H; C_2H-2, 4), 4.41–4.35 (m, 1H; C_αH-5), 4.32–4.27 (m, 1H; C_αH-3), 4.20–4.14 (m, 2H; C_δH-2,4), 4.07 (m, 1H; C_αH-1), 4.06 (dd, 2H, J=3.4, 8.8 Hz; C_4H-2, 4), 3.68 (d, 2H, J=3.3 Hz; C_3H-2, 4), 3.65 (s, 3H; COOMe), 3.36 (s, 6H; 2×OMe), 2.29 (m, 2H; C_αH-2, 4), 2.21 (m, 2H; C_αH-2, 4), 1.72 (m, 2H; C_βH-2, 4), 1.65 (m, 2H; C_γH-2, 4), 1.56 (m, 2H; C_γH-2, 4), 1.42 (s, 9H; Boc), 1.40 (m, 2H; C_γH-2, 4), 1.38 (d, 3H, J=7.4 Hz; CH_3-5), 1.34 (d, 3H, J=7.0 Hz; CH_3-3), 1.31 (d, 3H, J= 7.0 Hz; CH_3-1), 1.28 (s, 6H; 2×Me), 1.27 ppm (s, 6H; 2×Me); IR (KBr): $\tilde{\nu}$=3312, 2984, 2937, 1744, 1655, 1539, 1454, 1382, 1219, 1167, 1079, 1025, 854, 782, 679 cm^{-1}; HRMS (ESI): m/z calcd for $C_{41}H_{69}N_5O_{16}Na$ [M^++Na]: 910.4637; found: 910.4632.

Boc-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-OMe (5): As described for the synthesis of **9**, a solution of **3** (0.14 g, 0.17 mmol) on treatment with a 4N aqueous solution of NaOH (0.68 mL) and workup gave **19** (0.132 g, 96%), which was used without further purification. A solution of **12** (0.065 g, 0.13 mmol) and CF_3COOH (0.1 mL) in CH_2Cl_2 (0.7 mL) was stirred at room temperature as described for **8** to give **18**, which was used without any further purification. As described for the synthesis of **12**, a mixture of **19** (0.11 g, 0.13 mmol), HOBt (0.022 g, 0.16 mmol), and EDCI (0.031 g, 0.16 mmol) in CH_2Cl_2 (2 mL) was stirred at 0°C for 15 min followed by the addition of **18** and DIPEA (0.03 mL, 0.2 mmol). Workup and purification by column chromatography (silica gel, 2.5% MeOH in $CHCl_3$) afforded **5** as a white solid (0.073 g, 46%). M.p. 160–162°C; $[\alpha]_D$=−29.2 (c=0.32 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz and 600 MHz): δ=7.88 (d, 1H, J=7.5 Hz; NH-5), 7.80 (d, 1H, J=7.1 Hz; NH-3), 7.32 (d, 1H, J=9.7 Hz; NH-2), 7.19 (d, 1H, J=9.4 Hz; NH-4), 6.26 (d, 1H, J=8.1 Hz; NH-6), 5.89 (d, 1H, J=3.8 Hz; C_1H-6), 5.87 (d, 2H, J=3.9 Hz; C_1H-2, 4), 5.50 (d, 1H, J=7.2 Hz; NH-1), 4.59 (d, 1H, J=3.9 Hz; C_2H-6), 4.54 (d, 2H, J=4.0 Hz; C_2H-4, 6), 4.52 (d, 1H, J= 3.9 Hz; C_2H-2), 4.37 (m, 2H; C_αH-3, 5), 4.32 (m, 1H; C_δH-2), 4.30 (m, 1H; C_δH-4), 4.25 (m, 1H; C_δH-6), 4.20–4.14 (m, 1H; C_αH-1), 4.08 (dd, 1H, J=3.3, 6.8 Hz; C_4H-6), 4.01 (dd, 1H, J=3.4, 7.3 Hz; C_4H-2), 3.99 (dd, 1H, J=3.4, 8.1 Hz; C_4H-4), 3.68 (s, 3H; COOMe), 3.65 (d, 1H, J= 3.3 Hz; C_3H-6), 3.62 (d, 1H, J=3.4 Hz; C_3H-4), 3.57 (d, 1H, J=3.4 Hz; C_3H-2), 3.37 (s, 6H; 2×OMe), 3.36 (s, 3H; OMe), 2.42 (m, 1H; C_αH-2), 2.41 (m, 1H; C_αH-4), 2.33 (m, 2H; C_αH-6), 2.11 (m, 1H; C_αH-4), 2.10 (m, 1H; C_αH-2), 1.73 (m, 2H; C_βH-6), 1.70 (m, 4H; C_βH-2, 4), 1.55 (m, 2H; C_γH-6), 1.52 (m, 1H; C_γH-4), 1.49 (m, 1H; C_γH-2), 1.43 (s, 9H; Boc), 1.45 (s, 9H; 3×Me), 1.39 (d, 3H, J=7.0 Hz; CH_3-3), 1.36 (d, 3H, J=7.1 Hz; CH_3-1), 1.34 (m, 2H; C_γH-2, 4), 1.33 (m, 3H; CH_3-5), 1.30 (s, 6H; 2×Me), 1.28 (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=174.1, 174.0, 173.9, 173.6, 173.5, 156.1, 111.4, 111.3, 111.2, 105.0, 104.7, 84.5, 84.1, 83.9, 81.9, 81.8, 81.3, 81.2, 80.9, 79.7, 57.5, 57.3, 51.5, 50.5, 49.8, 49.5, 47.9, 47.7, 35.1, 34.9, 33.6, 31.9, 29.1, 28.3, 26.8, 26.7, 26.6, 26.3, 26.2, 26.1, 22.0, 21.9, 20.8, 17.9, 17.3, 17.0 ppm; ^{1}H NMR (CD_3OH, 600 MHz): δ= 8.22 (d, 1H, J=7.0 Hz; NH-5), 8.20 (d, 1H, J=6.5 Hz; NH-3), 8.15 (d, 1H, J=9.7 Hz; NH-2), 8.01 (d, 1H, J=9.2 Hz; NH), 8.00 (d, 1H, J= 9.4 Hz; NH), 6.78 (d, 1H, J=7.2 Hz; NH-1), 5.82–5.79 (m, 3H; C_1H-2, 4, 6), 4.67 (d, 1H, J=3.9 Hz; C_2H-2), 4.66 (d, 2H, J=3.9 Hz; C_2H-4, 6), 4.33–4.28 (m, 2H; C_αH-3, 5), 4.21 (m, 1H; C_δH-2), 4.19 (m, 2H; C_δH-4, 6), 4.08 (m, 1H; C_αH-1), 4.06 (dd, 2H, J=3.3, 9.1 Hz; C_4H-4, 6), 4.03 (dd, 1H, J=3.3, 9.4 Hz; C_4H-2), 3.69 (d, 1H, J=3.3 Hz; C_3H-2), 3.67 (d, 2H, J=3.3 Hz; C_3H-4, 6), 3.65 (s, 3H; COOMe), 3.38 (s, 3H; OMe), 3.37 (s, 6H; 2×OMe), 2.39–2.28 (m, 3H; C_αH-2, 4, 6), 2.21 (m, 1H; C_αH-4, 6), 2.16 (m, 1H; C_αH-6), 1.70 (m, 6H; C_βH-2, 4, 6), 1.54 (m, 2H; C_γH-4, 6), 1.53 (m, 1H; C_γH-2), 1.45 (s, 3H; Me), 1.44 (s, 3H; Me), 1.43 (s, 9H; Boc), 1.39 (m, 2H; C_γH-4, 6), 1.34 (m, 1H; C_γH-2), 1.35 (d, 1H, J= 7.3 Hz; CH_3-3, 5), 1.31 (d, 3H, J=7.0 Hz; CH_3-1), 1.30 (s, 3H; Me), 1.29 ppm (s, 9H; 3×Me); IR (KBr): $\tilde{\nu}$=3362, 2984, 2934, 1738, 1642, 1537, 1453, 1381, 1247, 1168, 1079, 1024, 855, 698, 651 cm^{-1}; HRMS (ESI): m/z calcd for $C_{54}H_{90}N_6O_{21}Na$ [M^++Na]: 1181.6056; found: 1181.6021.

Boc-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-L-Ala-OMe (6): As described for the synthesis of **9**, a solution of **13** (0.18 g, 0.22 mmol) on treatment with a 4N aqueous solution of NaOH (0.8 mL) and workup gave **14** (0.172 g, 97%), which was used without further purification. A solution of **13** (0.154 g, 0.32 mmol) and CF_3COOH (0.2 mL) in CH_2Cl_2 (1.5 mL) was stirred at room temperature as described for **8** to give **15**, which was used without any further purification. According to the procedure described for **12**, a mixture of **14** (0.15 g, 0.32 mmol), HOBt (0.052 g, 0.39 mmol), and EDCI (0.074 g, 0.39 mmol) in CH_2Cl_2 (3 mL) was stirred at 0°C for 15 min and treated with **15** and DIPEA (0.08 mL, 0.48 mmol) under an N_2 atmosphere for 8 h. Workup and purification by column chromatography (silica gel, 2% MeOH in $CHCl_3$) gave **6** as a white solid (0.147 g, 55%). M.p. 171–173°C; $[\alpha]_D$=−22.85 (c=0.17 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=7.62 (d, 1H, J=7.7 Hz; NH-4), 6.85 (d, 1H, J=9.5 Hz; NH-3), 6.84 (d, 1H, J=7.3 Hz; NH-2), 5.92 (d, 1H, J=3.9 Hz; C_1H-1), 5.91 (d, 1H, J=3.9 Hz; C_1H-3), 4.95 (d, 1H, J=9.0 Hz; NH-1), 4.65–4.60 (m, 1H; C_αH-4), 4.58 (d, 2H, J=3.9 Hz; C_2H-1, 3), 4.36 (m, 1H; C_αH-2), 4.35 (m, 1H; C_δH-3), 4.01 (dd, 1H, J=3.4, 7.4 Hz; C_4H-1, 3), 3.98–3.93 (m, 1H; C_δH-1), 3.75 (s, 3H; COOMe), 3.62 (d, 1H, J=3.4 Hz; C_3H-1), 3.60 (d, 1H, J=3.4 Hz; C_3H-3), 3.36 (s, 6H; 2×OMe), 2.48 (ddd, 1H, J=6.4, 7.8, 13.8 Hz; $C_\alpha H_{(pro\text{-}R)}$-3), 2.32 (ddd, 1H, J=6.4, 8.3, 14.5 Hz; $C_\alpha H_{(pro\text{-}R)}$-1), 2.20 (ddd, 1H, J=7.2, 8.2, 14.5 Hz; $C_\alpha H_{(pro\text{-}S)}$-1), 2.13 (ddd, 1H, J=7.9, 7.6, 13.8 Hz; $C_\alpha H_{(pro\text{-}S)}$-3), 1.75 (m, 1H; C_βH-1), 1.73 (m, 1H; C_βH-3), 1.68 (m, 1H; $C_{\beta'}$H-1), 1.60 (m, 1H; $C_{\beta'}$H-3), 1.50 (m, 1H; C_γH-3), 1.48 (m, 2H; C_γH-1), 1.49 (s, 12H; 4×Me), 1.43 (s, 9H; Boc), 1.41 (m, 1H; C_γH-3), 1.40 (d, 3H, J=7.3 Hz; CH_3-4), 1.35 ppm (d, 3H, J=6.9 Hz; CH_3-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=175.2, 173.6, 173.3, 172.9, 156.1, 111.5, 111.4, 104.8, 104.7, 84.3, 84.1, 81.5, 81.3, 81.2, 81.1, 79.0, 57.7, 57.6, 57.5, 52.5, 49.1, 48.9, 47.8, 47.5, 47.3, 47.2, 35.5, 34.9, 31.9, 30.2, 28.4 (3), 26.7, 26.2, 26.1, 21.9, 21.6, 17.7, 17.0 ppm; IR (KBr): $\tilde{\nu}$= 3335, 2984, 2935, 1742, 1699, 1644, 1455, 1382, 1218, 1171, 1079, 1025, 856 cm^{-1}; HRMS (ESI): m/z calcd for $C_{38}H_{64}N_4O_{15}Na$ [M^++Na]: 839.4265; found: 839.4281.

Boc-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-L-Ala-OMe (7): As described for the synthesis of **9**, a solution of **6** (0.08 g, 0.09 mmol) on treatment with a 4N aqueous solution of NaOH (0.4 mL) and workup gave **20** (0.073 g, 94%), which was used without further purification. A solution of **13** (0.029 g, 0.062 mmol) and CF_3COOH (0.1 mL) in CH_2Cl_2 (0.5 mL) was stirred at room temperature as described for **8** to give **15**, which was used without any further purification. As described for the synthesis of **12**, a mixture of **20** (0.05 g, 0.062 mmol), HOBt (0.01 g, 0.074 mmol), and EDCI (0.014 g, 0.074 mmol) in CH_2Cl_2 (1.5 mL) was stirred at 0°C for 15 min and treated with **15** and DIPEA (0.02 mL, 0.09 mmol). Workup and purification by column chromatography (Silica gel, 3.4% MeOH in $CHCl_3$) afforded **7** as a white solid (0.034 g, 48%). M.p. 195–197°C; $[\alpha]_D$=−28.33 (c=0.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz and 600 MHz): δ=8.12 (d, 1H, J=7.5 Hz; NH-6), 7.7 (d, 1H, J=7.1 Hz; NH-4), 7.23 (d, 1H, J=7.5 Hz; NH-2), 7.16 (d, 1H, J=9.7 Hz; NH-3), 6.97 (d, 1H, J=9.5 Hz; NH-5), 5.89 (d, 1H, J=3.9 Hz; C_1H-5, 1), 5.88 (d, 1H, J=3.9 Hz; C_1H-3), 4.90 (d, 1H, J=8.3 Hz; NH-1), 4.64–4.59 (m, 1H; C_αH-6), 4.56 (d, 1H, J=3.9 Hz; C_2H-5), 4.54 (d, 2H, J=3.9 Hz; C_2H-1, 3), 4.53–4.48 (m, 1H; C_αH-2), 4.34 (m, 1H; C_δH-3), 4.27 (m, 1H; C_δH-5), 4.23 (m, 1H; C_αH-4), 4.02 (m, 1H; C_4H-1), 4.00 (m, 2H; C_4H-3, 5), 3.95–3.90 (m, 1H; C_δH-1), 3.74 (s, 3H; COOMe), 3.63 (d, 1H, J=3.3 Hz; C_3H-1), 3.60 (d, 1H, J=3.4 Hz; C_3H-5), 3.58 (d, 1H, J=3.4 Hz; C_3H-3), 3.36 (s, 3H; OMe), 3.35 (s, 3H; OMe), 3.34 (s, 3H; OMe), 2.48 (ddd, 1H, J=5.2, 8.6, 14.8 Hz; C_αH-3), 2.40 (ddd, 1H, J=5.9, 7.4, 14.8 Hz; C_αH-5), 2.34–2.21 (m, 2H; C_αH-1), 2.17 (ddd, 1H, J=6.4, 8.2, 14.4 Hz; $C_{\alpha'}$H-5), 2.03 (ddd, 1H, J=7.4, 8.4, 14.8 Hz; $C_{\alpha'}$H-3), 1.81 (m, 2H; C_γH-1), 1.74 (m, 1H; C_βH-5), 1.71 (m, 2H; C_βH-1), 1.70 (m, 2H; C_βH-3), 1.67 (m, 1H; $C_{\beta'}$H-5), 1.57 (m, 1H; C_γH-5), 1.56 (s, 9H; Boc), 1.51 (m, 1H; C_γH-3), 1.49 (s, 3H; Me), 1.48 (s, 3H; Me), 1.47 (s, 6H; 2×Me), 1.44 (s, 3H; Me), 1.43 (m, 1H; C_γH-3), 1.42 (s, 3H; Me), 1.40 (d, 3H, J=7.2 Hz; CH_3-6), 1.39 (m, 1H; C_γH-5), 1.37 (d, 3H, J=7.1 Hz; CH_3-4), 1.35 ppm

(d, 3H, $J=6.9$ Hz; CH_3-2); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=175.7$, 174.3, 174.0, 173.9, 173.5, 173.4, 156.0, 111.4, 111.3, 105.3, 104.8, 104.7, 104.6, 85.0, 84.5, 84.1, 84.0, 81.7, 81.4, 81.2, 81.0, 75.2, 73.5, 67.6, 57.5, 57.4, 52.4, 49.8, 49.1, 48.9, 48.3, 47.7, 47.0, 35.4, 34.8, 34.5, 32.0, 29.7, 28.8, 28.4, 26.7, 26.6, 26.2, 26.1, 25.1, 22.2, 21.8, 21.7, 17.2, 17.0, 16.8 ppm; IR (KBr): $\tilde{\nu}=$ 3310, 2985, 2930, 1745, 1693, 1641, 1530, 1456, 1379, 1248, 1219, 1168, 1077, 1026, 852, 785, 642 cm^{-1}; HRMS (ESI): m/z calcd for $C_{54}H_{90}N_6O_{21}Na$ [M^++Na]: 1181.6051; found: 1181.6048.

Boc-δ-Caa$_{(x)}$-L-Ala-NHMe (21): A solution of **14** (0.5 g, 1.08 mmol) in CH_2Cl_2 (5 mL) was cooled to 0°C, treated with HOBt (0.176 g, 1.3 mmol), EDCI (0.25 g, 1.3 mmol), NHMe·HCl salt (0.146 g, 1.23 mmol), and DIPEA (0.28 mL, 1.63 mmol), as described for the synthesis of **12**. Workup and purification by column chromatography (silica gel, 3% Methanol in ethyl acetate) gave **21** as a white solid (0.41 g, 79%). M.p. 186–188°C; $[\alpha]_D=-115.45$ ($c=0.55$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=6.40$ (d, 1H, $J=7.9$ Hz; NH-2), 6.35 (brs, 1H; NH-3), 5.90 (d, 1H, $J=3.8$ Hz; C_1H-1), 4.78 (d, 1H, $J=9.1$ Hz; NH-1), 4.57 (d, 1H, $J=3.8$ Hz; C_2H-1), 4.47–4.37 (m, 1H; C_δH −1), 4.01 (dd, 1H, $J=3.2$, 6.7 Hz; C_4H-1), 3.95 (s, 3H; C_αH-2), 3.63 (d, 1H, $J=3.2$ Hz; C_3H-1), 3.36 (s, 3H; OMe), 2.79 (d, 1H, $J=4.6$ Hz; Me), 2.43–2.33 (m, 1H; C_αH-1), 2.23–2.13 (m, 1H; C_αH-1), 1.77 (m, 2H; C_βH-1), 1.49 (m, 1H; C_γH-1), 1.48 (s, 3H; Me), 1.44 (m, 1H; C_γH-1), 1.43 (s, 9H; Boc), 1.36 (d, 1H, $J=7.2$ Hz; CH_3-2), 1.35 (s, 6H; 2×Me), 1.33 (s, 3H; Me), 1.32 ppm (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=173.2$, 172.9, 156.2, 111.4, 104.6, 84.3, 81.3, 81.1, 79.2, 57.6, 48.7, 35.7, 35.6, 32.3, 32.1, 28.4, 26.7, 26.2, 26.1, 21.6, 17.8 ppm; IR (KBr): $\tilde{\nu}=3354$, 3317, 2980, 2945, 1696, 1643, 1528, 1457, 1384, 1248, 1171, 1075, 1022, 951 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{39}N_3O_8Na$ [M^++Na]: 496.2628; found: 496.2634.

Boc-L-Ala-δ-Caa$_{(x)}$-L-Ala-NHMe (23): A solution of **21** (0.09 g, 0.19 mmol) and CF_3COOH (0.09 mL) in CH_2Cl_2 (1.1 mL) was stirred at room temperature as described for **8** to give **22**, which was used without any further purification. As described for the synthesis of **12**, a mixture of **10** (0.036 g, 0.19 mmol), HOBt (0.031 g, 0.22 mmol), and EDCI (0.044 g, 0.22 mmol) in CH_2Cl_2 (3 mL) was stirred at 0°C for 15 min followed by the addition of **22** and DIPEA (0.05 mL, 0.28 mmol). Workup and purification by column chromatography (silica gel, 2% methanol in chloroform) gave **23** as a white solid (0.063 g, 61%). M.p. 165–167°C; $[\alpha]_D=-189.26$ ($c=0.225$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=$ 7.34 (d, 1H, $J=7.1$ Hz; NH-3), 6.90 (d, 1H, $J=9.2$ Hz; NH-2), 6.21 (brs, 1H; NH-4), 5.92 (d, 1H, $J=3.6$ Hz; C_1H-2), 5.69 (d, 1H, $J=6.9$ Hz; NH-1), 4.56 (d, 1H, $J=3.6$ Hz; C_2H-2), 4.43–4.31 (m, 2H; C_αH-3, C_δH-2), 4.21–4.15 (m, 1H; C_αH-1), 4.03 (dd, 1H, $J=3.2$, 7.4 Hz; C_4H-2), 3.62 (d, 1H, $J=3.2$ Hz; C_3H-2), 3.36 (s, 3H; OMe), 2.50–2.44 (m, 1H; C_αH-2), 2.11–2.05 (m, 1H; C_αH-2), 1.75 (m, 2H; C_βH-2), 1.51 (m, 1H; C_γH-2), 1.49 (s, 3H; Me), 1.41 (s, 9H; Boc), 1.38 (d, 3H, $J=6.4$ Hz; CH_3-1), 1.36 (d, 3H, $J=6.4$ Hz; CH_3-3), 1.34 (m, 1H; C_γH-2), 1.31 (s, 3H; Me), 1.25 ppm (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=173.8$, 173.6, 111.5, 104.8, 84.3, 81.4, 81.3, 57.6, 54.1, 50.2, 48.7, 47.0, 42.4, 35.1, 30.6, 29.7, 28.3, 26.7, 26.3, 26.2, 21.9, 18.6, 17.5, 17.3, 16.9 ppm; IR (KBr): $\tilde{\nu}=$ 3354, 2980, 1696, 1643, 1527, 1457, 1384, 1248, 1171, 1075, 952 cm^{-1}; HRMS (ESI): m/z calcd for $C_{25}H_{44}N_4O_9Na$ [M^++Na]: 567.3005; found: 567.3005.

Ac-L-Ala-δ-Caa$_{(x)}$-L-Ala-NHMe (2a): A solution of **23** (0.03 g, 0.05 mmol) and CF_3COOH (0.03 mL) in CH_2Cl_2 (0.5 mL) was stirred at room temperature as described for **8** to give **24**, which was used without any further purification. A solution of **24** in CH_2Cl_2 (3 mL) was cooled to 0°C, treated with Et_3N (0.045 mL, 0.33 mmol) and Ac_2O (0.007 mL, 0.08 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 12 h and treated with an aqueous solution of NH_4Cl (5 mL). The organic layer was separated, washed with water (5 mL), brine (5 mL), and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 2.5% methanol in chloroform) to give **2a** as a white solid (0.017 g, 63%). M.p. 158–160°C; $[\alpha]_D=-80.33$ ($c=0.25$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.34$ (d, 1H, $J=8.1$ Hz; NH-1), 7.22 (d, 1H, $J=7.7$ Hz; NH-3), 6.72 (d, 1H, $J=9.6$ Hz; NH-2), 6.28 (brs, 1H; NH-4), 5.90 (d, 1H; C_1H-2), 4.55 (d, 1H, $J=4.0$ Hz; C_2H-2), 4.54 (m, 1H; C_αH-1), 4.37 (m, 1H; C_δH-2), 4.36 (m, 1H; C_αH-3), 4.03 (dd, 1H, $J=3.2$, 7.4 Hz; C_4H-2), 3.62 (d, 1H, $J=3.2$ Hz; C_3H-2), 3.35 (s, 3H; OMe), 2.80 (s, 3H; Me), 2.51 (ddd, 1H, $J=4.2$, 10.1, 13.8 Hz; C_αH-2), 2.05 (m, 1H; C_αH-2), 1.76 (m, 1H; C_βH-2), 1.48 (s, 3H; Me), 1.46 (m, 1H; C_γH-2), 1.40 (m, 1H; C_γH-2), 1.39 (d, 3H, $J=7.2$ Hz; CH_3-3), 1.38 (d, 3H, $J=7.1$ Hz; CH_3-1), 1.31 ppm (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=173.9$, 173.3, 111.5, 104.8, 97.8, 84.2, 81.4, 81.2, 74.2, 57.5, 48.7, 46.2, 34.9, 31.9, 31.0, 29.7, 26.7, 26.2, 22.8, 22.1, 17.6, 16.3, 14.1 ppm; IR (KBr): $\tilde{\nu}=3664$, 3435, 2927, 2678, 1732, 1643, 1532, 1454, 1378, 1258, 1214, 1072, 1028, 798 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{38}N_4O_8Na$ [M^++Na]: 509.2590; found: 509.2587.

Boc-L-Ala-δ-Caa$_{(x)}$-NHMe (25): A solution of **17** (0.31 g, 0.67 mmol) in CH_2Cl_2 (5 mL) was cooled to 0°C, treated with HOBt (0.109 g, 0.8 mmol), EDCI (0.155 g, 0.8 mmol), the NHMe·HCl salt (0.091 g, 1.34 mmol) and DIPEA (0.175 mL, 1.01 mmol), as described for the synthesis of **12**. Workup and purification by column chromatography (silica gel, 3% methanol in ethyl acetate) gave **25** as a white solid (0.27 g, 84%). M.p. 150–152°C; $[\alpha]_D=-121.09$ ($c=0.375$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=6.15$ (d, 1H, $J=9.2$ Hz; NH-2), 6.09 (brs, 1H; NH-3), 5.88 (d, 1H, $J=4.0$ Hz; C_1H-2), 5.03 (d, 1H, $J=7.0$ Hz; NH-1), 4.55 (d, 1H, $J=4.0$ Hz; C_2H-2), 4.32–4.22 (m, 1H; C_δH-2), 4.11–4.02 (m, 1H; C_αH-1), 4.05 (dd, 1H, $J=3.1$, 6.4 Hz; C_4H-2), 3.64 (d, 1H, $J=$ 4.0 Hz; C_3H-2), 3.35 (s, 3H; OMe), 2.77 (d, 1H, $J=4.6$ Hz; Me), 2.38–2.28 (m, 1H; C_αH-2), 2.17–2.08 (m, 1H; C_αH-2), 1.74 (m, 2H; C_βH-2), 1.56 (m, 2H; C_γH-2), 1.48 (s, 3H; Me), 1.43 (s, 9H; Boc), 1.33 (d, 3H, $J=7.0$ Hz; CH_3-1), 1.31 ppm (s, 6H; 2×Me); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=173.7$, 172.8, 155.4, 111.5, 104.7, 84.5, 81.3, 80.9, 79.7, 57.6, 50.4, 47.2, 35.6, 31.8, 28.3, 26.7, 26.2, 26.1, 21.7, 18.1 ppm; IR (KBr): $\tilde{\nu}=$ 3349, 3317, 2980, 2939, 1791, 1665, 1530, 1456, 1371, 1320, 1261, 1168, 1112, 1074, 1025, 858 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{39}N_3O_8Na$ [M^++Na]: 496.2624; found: 496.2634.

Boc-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-NHMe (27): A solution of **25** (0.123 g, 0.26 mmol) and CF_3COOH (0.12 mL) in CH_2Cl_2 (1.2 mL) was stirred at room temperature, as described for **8**, to give **26**, which was used without any further purification. A solution of **17** (0.12 g, 0.26 mmol) in CH_2Cl_2 (3 mL) was cooled to 0°C, treated with HOBt (0.042 g, 0.31 mmol), EDCI (0.06 g, 0.31 mmol), followed by **26** and DIPEA (0.067 mL, 0.39 mmol), as described for the synthesis of **12**. Workup and purification by column chromatography (silica gel, 3.2% methanol in chloroform) gave **27** as a white solid (0.137 g, 64%). M.p. 171–173°C; $[\alpha]_D=-90.1$ ($c=0.275$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=8.13$ (d, 1H, $J=$ 6.9 Hz; NH-3), 7.57 (d, 1H, $J=9.5$ Hz; NH-2), 7.20 (brs, 1H; NH-5), 6.01 (d, 1H, $J=9.2$ Hz; NH-4), 5.93 (d, 1H, $J=4.1$ Hz; C_1H-2), 5.91 (d, 1H, $J=4.2$ Hz; C_1H-4), 5.54 (d, 1H, $J=7.1$ Hz; NH-1), 4.60 (d, 1H, $J=$ 4.1 Hz; C_2H-4), 4.36 (d, 1H, $J=4.1$ Hz; C_2H-2), 4.33 (m, 1H; C_δH-4), 4.31 (m, 1H; C_δH-2), 4.22–4.16 (m, 1H; C_αH-3), 4.11–4.05 (m, 1H; C_αH-1), 3.99 (dd, 1H, $J=3.2$, 7.6 Hz; C_4H-4), 3.94 (dd, 1H, $J=3.2$, 8.9 Hz; C_4H-2), 3.64 (d, 1H, $J=3.2$ Hz; C_3H-4), 3.49 (d, 1H, $J=3.2$ Hz; C_3H-2), 3.36 (s, 3H; OMe), 3.35 (s, 3H; OMe), 2.80 (d, 3H, $J=4.8$ Hz; CH_3-5), 2.55–2.49 (m, 1H; C_αH-2), 2.32–2.26 (m, 1H; C_αH-2), 2.15 (m, 1H; C_αH-4), 2.04 (m, 1H; C_αH-2), 1.75 (m, 2H; C_βH-2), 1.71 (m, 2H; C_βH-4), 1.63 (m, 1H; C_γH-2), 1.58 (m, 1H; C_γH-4), 1.51 (s, 3H; CH_3), 1.45 (m, 1H; C_γH-4), 1.42 (s, 9H; Boc), 1.41 (m, 1H; C_γH-2), 1.37 (d, 3H, $J=6.9$ Hz; CH_3-3), 1.36 (d, 3H, $J=7.0$ Hz; CH_3-1), 1.33 (s, 6H; 2×Me), 1.31 ppm (s, 6H; 2×Me); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=174.4$, 173.8, 173.6, 173.3, 156.1, 111.5, 111.3, 104.8, 104.7, 84.4, 84.2, 81.3, 79.9, 57.6, 53.9, 50.5, 49.9, 47.5, 36.2, 35.0, 31.6, 29.6, 28.3, 26.7, 26.3, 26.2, 26.1, 21.9, 19.0, 17.7, 17.5, 16.9 ppm; IR (KBr): $\tilde{\nu}=3329$, 2927, 1643, 1538, 1453, 1378, 1347, 1317, 1273, 1240, 1211, 1167, 1135, 1079, 1025, 858, 807 cm^{-1}; HRMS (ESI): m/z calcd for $C_{38}H_{65}N_5O_{14}$ [M^++H]: 815.45473; found: 815.4528.

Ac-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-NHMe (3a): A solution of **27** (0.105 g, 0.12 mmol) and CF_3COOH (0.105 mL) in CH_2Cl_2 (1.05 mL) was stirred at room temperature, as described for **8**, to give **28**, which was used without any further purification. A solution of **28** in CH_2Cl_2 (2 mL) was cooled to 0°C, treated with Et_3N (0.107 mL, 0.77 mmol) and Ac_2O (0.018 mL, 0.19 mmol), as described for the synthesis of **3a**. Workup and purification by column chromatography (silica gel, 4.2% methanol in chloroform) gave **3a** as a white solid (0.043 g, 44%). M.p. 160–162°C; $[\alpha]_D=-203.08$ ($c=0.2$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.67$ (d, 1H, $J=6.3$ Hz; NH-3), 7.49 (d, 1H, $J=7.5$ Hz*; NH-1, * $T=273$ K),

7.19 (d, 1H, J=10.0 Hz; NH-2), 7.01 (brs, 1H; NH-5), 6.10 (d, 1H, J=10.0 Hz; NH-4), 5.91 (d, 2H, J=4.0 Hz; C_1H-2, 4), 4.59 (d, 2H, J=4.0 Hz; C_2H-2, 4), 4.53–4.47 (m, 1H; C_αH-1), 4.41–4.35 (m, 1H; C_δH-2), 4.34–4.28 (m, 1H; C_δH-4), 4.21–4.15 (m, 1H; C_αH-3), 4.00 (dd, 2H, J=3.1, 9.0 Hz; C_4H-2, 4), 3.64 (d, 1H, J=3.1 Hz; C_3H-4), 3.59 (d, 1H, J=3.1 Hz; C_3H-2), 3.35 (s, 3H; OMe), 3.34 (s, 3H; OMe), 2.80 (s, 3H; Me), 2.55–2.49 (m, 1H; C_αH-2), 2.28–2.22 (m, 1H; C_αH-4), 2.13 (m, 1H; C_αH-4), 2.03 (m, 1H; C_αH-2), 1.72 (m, 2H; C_βH-2), 1.68 (m, 2H; C_βH-4), 1.58 (m, 2H; C_γH-4), 1.49 (s, 3H; Me), 1.47 (s, 3H; Me), 1.45 (m, 1H; C_γH-4), 1.41 (m, 2H; C_γH-2), 1.38 (d, 3H, J=7.2 Hz; CH_3-3), 1.36 (d, 3H, J=7.1 Hz; CH_3-1), 1.32 (s, 3H; Me), 1.30 ppm (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.9, 173.3, 172.8, 111.5, 111.3, 104.7, 84.3, 84.1, 81.2, 81.4, 81.3, 71.5, 57.8, 51.5, 49.8, 48.8, 47.6, 46.7, 36.1, 34.7, 31.5, 30.4, 29.7, 26.7, 26.2, 24.9, 21.9, 16.9 ppm; ^{1}H NMR (CD_3OH, 600 MHz): δ=8.31 (d, 1H, J=6.4 Hz; NH-3), 8.28 (d, 1H, J=6.6 Hz; NH-3), 8.19 (d, 1H, J=9.8 Hz; NH-2), 8.14 (d, 1H, J=9.8 Hz; NH-4), 8.03 (d, 1H, J=4.9 Hz; NH-5), 5.78 (d, 2H, J=3.3 Hz; C_1H-2, 4), 4.66 (d, 2H, J=3.3 Hz; C_2H-2, 4), 4.23 (m, 1H; C_αH-3), 4.22 (m, 1H; C_αH-1), 4.17 (m, 2H; C_δH-2, 4), 4.03 (dd, 1H, J=3.2, 9.3 Hz; C_4H-4), 4.00 (dd, 1H, J=3.2, 9.2 Hz; C_4H-2), 3.63 (d, 2H, J=3.3 Hz; C_3H-2, 4), 3.36 (s, 3H; OMe), 3.35 (s, 3H; OMe), 2.69 (d, 3H, J=4.8 Hz; CH_3-4), 2.31 (m, 1H; C_αH-2), 2.33–2.29 (m, 1H; C_αH-4), 2.12 (m, 1H; C_αH-4), 1.43 (s, 6H; 2×Me), 1.62–1.68 (m, 4H; C_βH-2, 4), 1.49 (m, 4H; C_γH-2, 4), 1.43 (s, 6H; 2×Me), 1.36 (m, 2H; C_γH-2, 4), 1.31 (d, 6H, J=7.1 Hz; CH_3-1, 3), 1.28 (s, 3H; Me), 1.27 ppm (s, 3H; Me); IR (KBr): $\tilde{\nu}$=3278, 2924, 2853, 1739, 1644, 1545, 1457, 1375, 1217, 1163, 1077, 1020, 856 cm^{-1}; HRMS (ESI): m/z calcd for $C_{35}H_{59}N_5O_{13}$ [M^++H]: 757.4123; found: 757.4109.

Boc-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-L-Ala-NHMe (29): A solution of **21** (0.053 g, 0.11 mmol) and CF_3COOH (0.05 mL) in CH_2Cl_2 (0.5 mL) was stirred at room temperature, as described for **8**, to give **22**, which was used without any further purification. As described for the synthesis of **12**, a mixture of **16** (0.06 g, 0.11 mmol), HOBt (0.018 g, 0.13 mmol), and EDCI (0.025 g, 0.13 mmol) in CH_2Cl_2 (3 mL) was stirred at 0°C for 15 min followed by the addition of **22** and DIPEA (0.03 mL, 0.16 mmol). Workup and purification by column chromatography (silica gel, 3.6% methanol in chloroform) gave **29** as a white solid (0.047 g, 47%). M.p. 156–158°C; $[\alpha]_D$=−168.11 (c=0.15 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=8.21 (d, 1H, J=6.8 Hz; NH-3), 7.34 (d, 1H, J=7.6 Hz; NH-5), 7.30 (d, 1H, J=9.6 Hz; NH-2), 7.07 (brs, 1H; NH-6), 6.86 (d, 1H, J=9.4 Hz; NH-4), 5.91 (d, 1H, J=4.0 Hz; C_1H-4), 5.88 (d, 1H, J=3.9;Hz, C_1H-2), 5.51 (d, 1H, J=8.0 Hz; NH-1), 4.58 (d, 1H, J=4.0 Hz; C_2H-4), 4.55 (d, 1H; J=3.9 Hz, C_2H-2), 4.48 (m, 1H; C_αH-3), 4.46 (m, 1H; C_αH-5), 4.45–4.37 (m, 3H; C_αH-1, C_δH-2, 4), 4.02 (dd, 2H, J=3.3, 8.1 Hz; C_4H-2, 4), 3.66 (d, 2H, J=3.3 Hz; C_3H-2, 4), 3.57 (d, 1H, J=3.2 Hz; C_3H-2), 3.36 (s, 6H; 2×OMe), 2.75 (d, 3H, J=4.6 Hz; CH_3-6), 2.52–2.46 (m, 1H; C_αH-4), 2.37–2.31 (m, 1H; C_αH-2), 2.11–2.00 (m, 2H; C_αH-4, C_αH-2), 1.75 (m, 2H; C_βH-4), 1.64 (m, 2H; C_βH-2), 1.50 (s, 3H; Me), 1.47 (s, 3H; Me), 1.44 (m, 4H; C_γH-4), 1.43 (s, 9H; Boc), 1.41 (d, 6H, J=6.9 Hz; CH_3-3, 5), 1.39 (d, 3H, J=7.3 Hz; CH_3-1), 1.33 (s, 3H; Me), 1.31 (s, 3H; Me), 1.27 ppm (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=174.4, 174.1, 173.5, 173.4, 156.2, 114.5, 111.2, 104.8, 104.7, 84.0, 83.8, 81.8, 81.3, 81.2, 81.1, 79.8, 57.5, 50.1, 49.0, 47.1, 46.5, 36.4, 34.7, 31.1, 29.9, 29.7, 29.3, 28.3, 26.7, 26.2, 22.7, 22.2, 22.0, 18.9, 18.4, 16.0 ppm; IR (KBr): $\tilde{\nu}$=3622, 2928, 1653, 1543, 1456, 1378, 1260, 1166, 1083, 1023, 858 cm^{-1}; HRMS (ESI): m/z calcd for $C_{41}H_{70}N_6O_{15}$Na [M^++Na]: 886.4906; found: 886.4899.

Ac-L-Ala-δ-Caa$_{(x)}$-L-Ala-δ-Caa$_{(x)}$-L-Ala-NHMe (4a): A solution of **29** (0.03 g, 0.03 mmol) and CF_3COOH (0.03 mL) in CH_2Cl_2 (0.3 mL) was stirred at room temperature, as described for **8**, to give **30**, which was used without any further purification. A solution of **30** in CH_2Cl_2 (2 mL) was cooled to 0°C, treated with Et_3N (0.027 mL, 0.2 mmol) and Ac_2O (0.004 mL, 0.05 mmol), as described for the synthesis of **2a**. Workup and purification by column chromatography (silica gel, 4.8% methanol in chloroform) gave **4a** as a white solid (0.012 g, 43%). M.p. 178–180°C; $[\alpha]_D$=−123.66 (c=0.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$+40 μL [D_6]DMSO, 500 MHz): δ=7.99 (d, 1H, J=6.6 Hz; NH-3), 7.89 (d, 1H, J=7.0 Hz; NH-5), 7.73 (d, 1H, J=7.0 Hz; NH-1), 7.56 (d, 1H, J=9.3 Hz; NH-4), 7.51 (brs, 1H; NH-5), 7.46 (d, 1H, J=9.5 Hz; NH-2), 5.88 (d, 2H, J=4.0 Hz; C_1H-2, 4), 4.58 (d, 2H, J=4.0 Hz; C_2H-2, 4), 4.55 (m, 1H; C_αH-1), 4.44 (m, 1H; C_αH-5), 4.40 (m, 1H; C_αH-3), 4.33 (m, 1H; C_δH-2), 4.28 (m, 1H; C_δH-4), 4.02 (dd, 1H, J=3.1, 8.7 Hz; C_4H-4), 4.00 (dd, 1H, J=3.1, 8.7 Hz; C_4H-2), 3.60 (d, 1H, J=3.1 Hz; C_3H-2), 3.59 (d, 1H, J=3.1 Hz; C_3H-4), 3.35 (s, 6H; 2×OMe), 2.74 (s, 3H; Me), 2.43 (m, 1H; C_αH-4), 2.42 (m, 1H; C_αH-2), 2.10 (m, 1H; C_αH-4), 2.04 (m, 1H; $C_\alpha H_J$-2), 1.70 (m, 2H; C_βH-4), 1.68 (m, 2H; C_βH-2), 1.49 (s, 6H; 2×Me), 1.46 (m, 1H; C_γH-4), 1.44 (m, 2H; C_γH-2), 1.39 (d, 3H, J=7.0 Hz; CH_3-3), 1.37 (d, 3H, J=7.3 Hz; CH_3-1), 1.36 (d, 3H, J=6.9 Hz; CH_3-5), 1.34 (m, 1H; C_γH-4), 1.31 (s, 3H; Me), 1.30 ppm (s, 3H; Me); IR (KBr): $\tilde{\nu}$=3664, 3436, 2924, 2854, 1732, 1686, 1635, 1533, 1460, 1376, 1217, 1214, 761 cm^{-1}; HRMS (ESI): m/z calcd for $C_{38}H_{64}N_6O_{14}$Na [M^++Na]: 828.4487; found: 828.4480.

Theoretical calculations: All quantum chemical calculations were performed by employing the program package Gaussian 03.[18]

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