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Design and Study of Peptides Containing 1:1 Left- and Right-Handed Helical Patterns from Aminopyrancarboxylic Acids

Gangavaram V. M. Sharma,*[a] Hajari Ravindranath,[a][‡] Akkala Bhaskar,[a][‡] Shaik Jeelani Basha,[b][‡] Potti Reddy Gari Gurava Reddy,[b][‡‡] Katukuri Sirisha,[b] Akella V. S. Sarma,*[b] and Hans-Jörg Hofmann*[c]

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(*R*,*R*)- and (*S*,*S*)-aminopyrancarboxylic acids (APyCs) were used in the design of mixed β- and α/β-peptides in alternation with β-hGly and L-Ala/D-Ala, respectively. The enantiomeric β- and α/β-tetrapeptides were then coupled in a 1:1 fashion to give octapeptides with 12/10- and 9/11-mixed helices, respectively. The structure of the helices, with their characteristic hydrogen-bonding patterns and an additional stabilizing interaction between peptide-bond NH groups and pyran-ring oxygen atoms, was investigated by NMR spectroscopy, molecular dynamics, and quantum chemical studies. The presence of equal parts of left- and right-handed helices was confirmed by the cancellation of their respective CD patterns. Despite the disruption of the hydrogen bonding in the transition region, the helical conformation was maintained in the octamers. This study demonstrates the possibility of accommodating helices of opposite handedness within the same peptide.

Introduction

Oligomers containing unnatural amino acids with strong and predictable folding propensities stabilized by non-covalent interactions, referred to as foldamers,[1] enable the mimicry of large protein recognition surfaces. In the past decade, much attention has been focused on the design of oligomers with homogeneous and heterogeneous backbones, due to their well-defined folding propensities.[2] Several groups have explored unnatural peptide foldamers composed of β-amino acids[1b,2g,3] or a combination of α- and β-amino acids to mimic natural peptides and proteins.[1e,1f,2e,2f,3d,3g,4] Based on the helix-coil theory, longer sequences and several intramolecular hydrogen bonds are required to overcome the energetically demanding nucleation parameters.[5] Despite this theory, β-peptides with very small numbers of residues show helical conformations, which suggests that the nucleation parameter is different for β-peptides. Gellman et al. and Seebach et al. presented left-handed 14-helices in β-peptides built from conformationally constrained oligomers of *trans*-2-aminocyclohexanecarboxylic acid (ACHC) and homologated α-amino acids, respectively.[3d,4a,6] Gellman et al.[7] also reported a 12-helix in *trans*-2-amino cyclopentanecarboxylic acid (ACPC)-derived peptides, and Fülöp et al.[8] obtained 12-helices in β-peptides composed of amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acids (ABHC). Sharma et al. reported right- and left-handed 12/10-mixed helices in β-peptides consisting of alternating (*R*)-β-Caa/(*S*)-β-Caa and β-hGly (β-homo-glycine) constituents, and 9/11-mixed helical structures occurred in α/β-peptides with alternating L-Ala and (*S*)-β-Caa residues.[3g,3h,4d,4f] Considering the role played by additional interactions in the formation and stabilization of secondary structures in foldamers,[9] our group presented (*S*,*S*)-aminopyrancarboxylic acid [(*S*,*S*)-APyC] as a new monomer in a previous paper.[10] Peptides with alternating (*S*,*S*)-APyC and D-Ala residues were reported to form a right-handed 9/11-mixed helix, in which the pyran oxygen of APyC induced a 5-mr (five-membered ring) hydrogen bond,[9k,11] which provided additional stability for the 9/11-helix.[10]

Left-handed secondary structures are rare in nature,[12] but they are observed in peptides and proteins at active sites. However, both left- and right-handed helical structures are formed in foldamers.[13] A literature survey[14] revealed that different designs could result in a switch of the helical pattern from one handedness to the other. In earlier studies, we reported "hybrid helices" in peptides containing more than one type of secondary structure with high com-

[a] Organic and Biomolecular Chemistry Division, CSIR – Indian Institute of Chemical Technology,
Hyderabad 500007, India
E-mail: esmvee@iict.res.in
www.iictindia.org
[b] Centre for NMR & SC, CSIR – Indian Institute of Chemical Technology,
Hyderabad 500007, India
E-mail: ssav@iict.res.in
[c] Institute of Biochemistry, Faculty of Biosciences, University of Leipzig,
Brüderstrasse 34, 04103 Leipzig, Germany
E-mail: hofmann@uni-leipzig.de
[‡] These authors contributed equally.
[‡‡] Deceased
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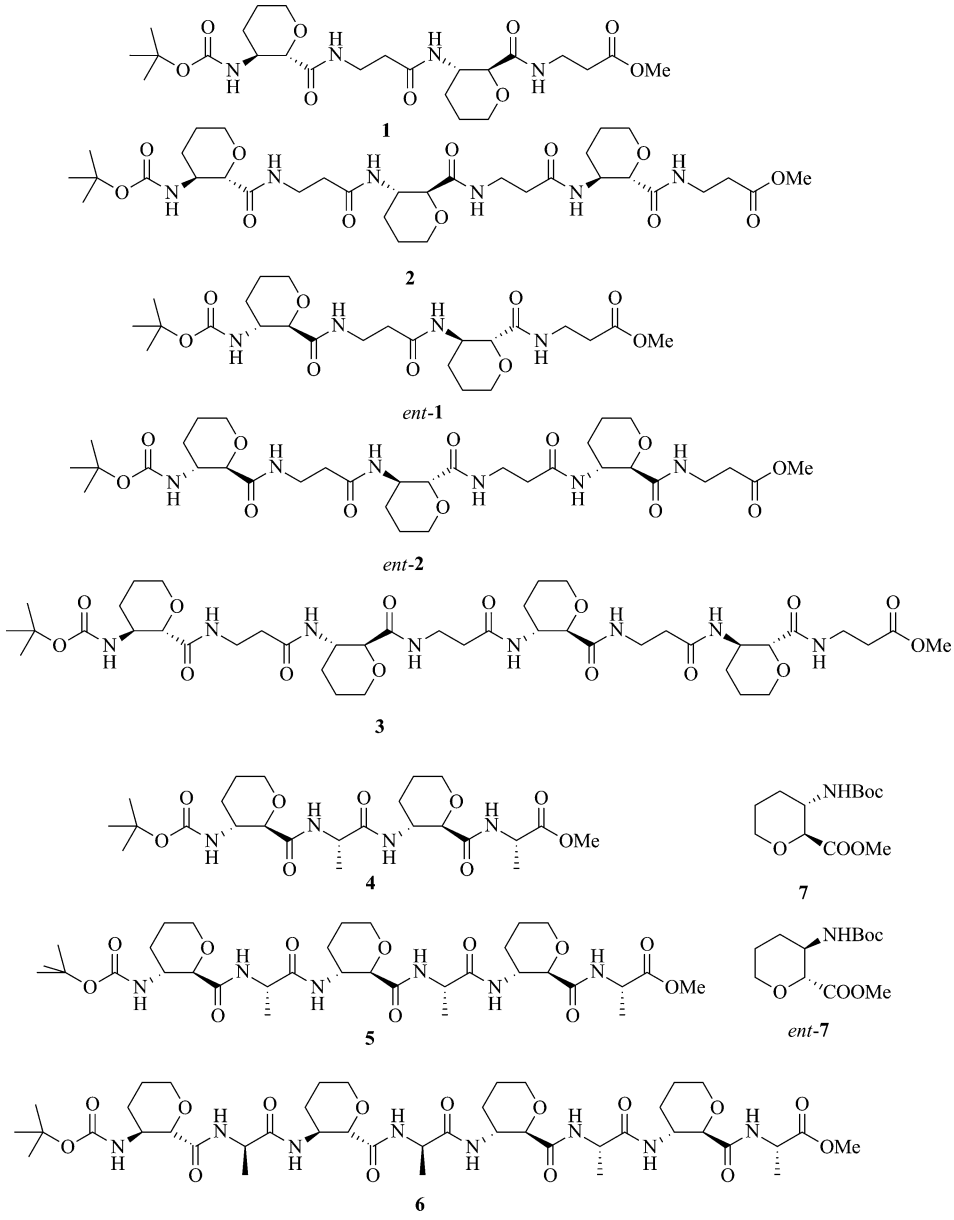


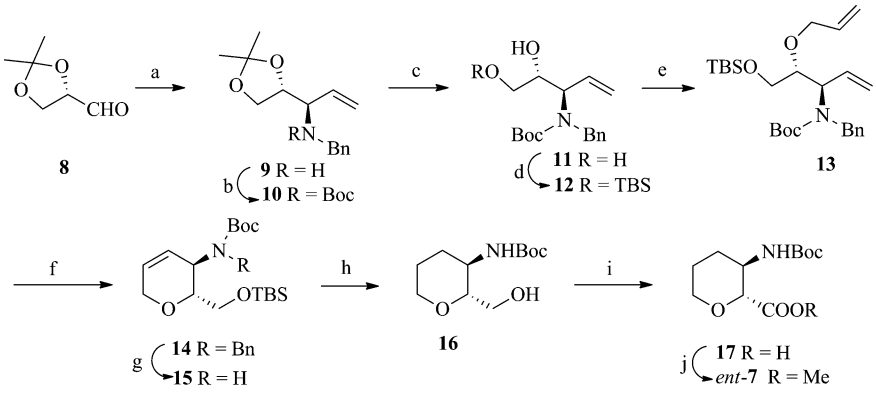
Figure 1. Structures of peptides **1**–**6**, *ent*-**1**, *ent*-**2**, (*S*,*S*)-APyC (**7**), and (*R*,*R*)-APyC (*ent*-**7**).

patibility.[15] The design and synthesis of peptides containing both left- and right-handed helical patterns have also been reported.[16] Recently, Martinek et al.[17] presented their observations of the switch in helicity in β-peptides with β-H18/20 mixed helices. In the work presented here, enantiomeric (*R*,*R*)- and (*S*,*S*)-aminopyrancarboxylic acids (APyCs) were used to synthesize β- and α/β-peptides together with alternating β-hGly and L-Ala/D-Ala constituents, respectively. The left- and right-handed structures in the peptides were examined by NMR spectroscopy, supported by molecular dynamics (MD), circular dichroism (CD), and quantum chemical studies.[18] The β- and α/β-tetrapeptides of opposite handedness were coupled in a 1:1 fashion. The resulting octapeptides also show the presence of both types of handedness. The details of the syntheses of (*R*,*R*)-aminopyrancarboxylic acid [(*R*,*R*)-APyC], β-peptides **1**, **2**, *ent*-**1**, *ent*-**2**, and **3**, and α/β-peptides **4**–**6**, as well as the conformational analysis (NMR, MD, CD, ab initio MO theory) of peptides **1**–**6**, *ent*-**1**, and *ent*-**2** (Figure 1) are described below.

Results and Discussion

Synthesis of β- and α/β-Peptides

Mixed β-peptides **1**, **2**, *ent*-**1**, and *ent*-**2** were synthesised from (*S*,*S*)- and (*R*,*R*)-aminopyrancarboxylic acids (APyC) **7** and *ent*-**7** with alternating use of β-hGly. Peptide **3** was prepared from tetrapeptides **1** and *ent*-**1**. Similarly, α/β-peptides **4** and **5** were prepared by alternating *ent*-**7** with L-Ala. Octapeptide **6** was prepared from two tetrapeptides. The required building block (*R*,*R*)-APyC *ent*-**7** was synthe-



Scheme 1. Reagents and conditions: a) i) $BnNH_2$, dry $MgSO_4$, diethyl ether, 0 °C to room temp., 2 h; ii) vinyl bromide, Mg, THF, 1,2-dibromoethane, 0 °C to r.t., 8 h; b) Et_3N, $(Boc)_2O$ (Boc = *tert*-butoxycarbonyl), CH_2Cl_2, 0 °C–r.t., 6 h; c) PTSA (*p*-toluenesulfonic acid), MeOH/H_2O (9:1), 0 °C–r.t., 6 h; d) TBSCl (*tert*-butyldimethylsilyl chloride), imidazole, CH_2Cl_2, 0 °C–r.t., 4 h; e) allyl bromide, NaH, DMF, 0 °C–r.t., 4 h; f) Grubbs I catalyst, toluene, reflux, 8 h; g) Li, liq. NH_3, THF, –78 °C, 1 h; h) Pd-C (10%), H_2, MeOH, r.t., 6 h; i) TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxy], BAIB [bis(acetoxy)iodobenzene], CH_2Cl_2/H_2O (3:1), 0 °C to r.t., 4 h; j) CH_2N_2, diethyl ether, 0 °C–r.t., 1 h.

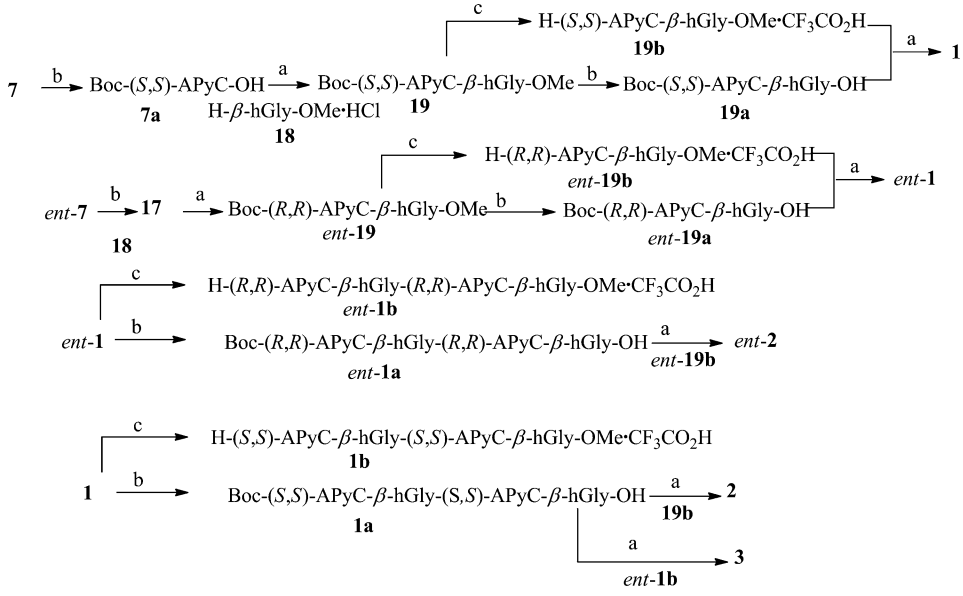
sised from (*S*)-glyceraldehyde derivative **8** by a procedure already reported for **7**,[10] according to Scheme 1 (for details, see Exp. Section).

Synthesis and Conformational Analysis of β-Peptides

Peptides **1**, **2**, *ent*-**1**, *ent*-**2**, and **3**, were prepared from β-hGly-OMe·HCl **18**, **7a**, and *ent*-**7** by standard peptide-coupling methods[19] using EDCI [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide], HOBt (hydroxybenzotriazole), and DIPEA (diisopropylethylamine) in solution phase (Scheme 2). Base hydrolysis of ester **7** with LiOH gave acid **7a**, which, on coupling with **18** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2, gave dipeptide **19** (89%). Hydrolysis of ester **19** with LiOH gave acid **19a**, while **19** was converted into salt **19b** by reaction with CF_3COOH in CH_2Cl_2. Acid **19a**, on coupling (EDCI, HOBt, and DIPEA) with salt **19b** in CH_2Cl_2, gave tetrapeptide **1** in 42% yield. Treatment of peptide **1** with LiOH gave acid **1a**, while **1** was converted into salt **1b** by reaction with CF_3COOH in CH_2Cl_2. Coupling (EDCI, HOBt, and DIPEA) of acid **1a** with salt **19b** in CH_2Cl_2 gave hexapeptide **2** (38%).

Base (LiOH) hydrolysis of ester *ent*-**7** gave acid **17**, which, on coupling (EDCI, HOBt, and DIPEA) with **18** in CH_2Cl_2, gave dipeptide *ent*-**19** (66%). Ester *ent*-**19**, on base (LiOH) hydrolysis, gave acid *ent*-**19a**, while CF_3COOH-mediated reaction of **19** in CH_2Cl_2 gave salt *ent*-**19b**.

Coupling of acid *ent*-**19a** (EDCI, HOBt, and DIPEA) and salt *ent*-**19b** in CH_2Cl_2 gave *ent*-**1** in 46% yield. Peptide



Scheme 2. Synthesis of peptides **1**, **2**, *ent*-**1**, *ent*-**2**, and **3**. Reagents and conditions: (a) HOBt (1.2 equiv.), EDCI (1.2 equiv.), DIPEA (2 equiv.), dry CH_2Cl_2, 0 °C–r.t., 8 h; (b) LiOH, THF/MeOH/H_2O (3:1:1), 0 °C–r.t., 1 h; (c) CF_3CO_2 H, dry CH_2Cl_2, 2 h.

ent-**1** gave acid *ent*-**1a** upon base hydrolysis with LiOH, while *ent*-**1** was converted into salt *ent*-**1b** by treatment with CF_3COOH in CH_2Cl_2. Acid *ent*-**1a**, on coupling (EDCI, HOBt, and DIPEA) with salt *ent*-**19b** in CH_2Cl_2, gave *ent*-**2** in 46% yield. Similarly, the coupling of acid **1a** with salt *ent*-**1b** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 gave octapeptide **3** in 75% yield.

Conformational analysis of mixed β-peptides **1**, **2**, *ent*-**1**, *ent*-**2**, and **3** (Figure 1) was carried out by NMR spectroscopy (in $CDCl_3$), CD, MD, and quantum chemical studies. Peptide **1** showed a very well-resolved amide region in the proton NMR spectrum,[18] suggesting the existence of a well-defined structure. The appearance of NH(2) and NH(3) at low field ($\delta > 7.7$ ppm) along with a small change in their chemical shift values during solvent titration studies[18] provide sufficient support for their participation in intramolecular hydrogen bonding. In addition, NH(4), resonating at $\delta = 6.9$ ppm, showed a small difference in chemical shift during titration with [D_6]DMSO, giving support for its involvement in non-covalent interactions.[18]

For (*S*,*S*)-APyC residue 1 in **1**, the coupling constant $^3J_{NH,C\beta H} \geq 9.2$ Hz shows that the NH and CβH protons are antiperiplanar to each other, corresponding to a dihedral angle ϕ[C(O)–N–Cβ–Cα] ≈ –120°. A large $^3J_{C\alpha H,C\beta H} \approx 9.6$ Hz supports a value of –60° for the dihedral angle θ, which is further supported by the presence of strong nOe correlation between the NH and CαH protons. For the β-hGly residues, the presence of a small (≤4.8 Hz) and a large (≥7.9 Hz) value for $^3J_{NH,\beta H}$ is consistent with $\phi \approx -120°$, whereas the $^3J_{C\alpha H,C\beta H}$ values (<1.9 and >12.4 Hz) are consistent with $\theta \approx -60°$. The prochiral protons of Cα and Cβ of β-hGly were assigned based on coupling constants and nOe correlations. $C\beta H_{(pro\text{-}S)}$ is assigned as the proton with a large coupling and medium nOe with the NH proton, whereas $C\beta H_{(pro\text{-}R)}$ shows a small coupling and strong nOe with the NH proton. Similarly, $C\alpha H_{(pro\text{-}S)}$ has a large coupling constant with $C\beta H_{(pro\text{-}R)}$ and a strong nOe correlation with the succeeding NH proton. NH(4) appeared as a triplet because of fraying at the terminus.

The nOe correlations CβH(1)/NH(3) and $C\alpha H_{(pro\text{-}R)}$(2)/NH(3) support a 12-membered (mr) hydrogen bond between NH(3)···O=C(Boc), whereas the nOe correlation NH(2)/NH(3) is consistent with a 10-mr hydrogen bond between NH(2)···O=C(3). From the coupling and nOe information, the presence of a 12/10-helix was unambiguously established in this peptide. This helix was found to be further stabilized by additional electrostatic interactions between NH(2)···OC(1) and between NH(4)···OC(3), which is supported by the nOe correlations CβH(1)/NH(2), CβH(3)/NH(4), CεH(1)/NH(2), and CεH(3)/NH(4).

Having defined the helical pattern (12/10-helix) and the presence of electrostatic interactions between peptide-bond NH groups and the pyran ring-oxygen atom in peptide **1**, the study was extended to higher homologue **2**. The spectral analysis of **2** showed all the characteristic nOe correlations and hydrogen-bonding information required for a propagated 12/10-mixed helix. Furthermore, the 12/10-helix was additionally stabilized by 5-mr electrostatic interactions. The ROESY spectrum of peptide **2** showing various characteristic correlations, and the characteristic hydrogen-bonding pattern are shown in Figure 2.

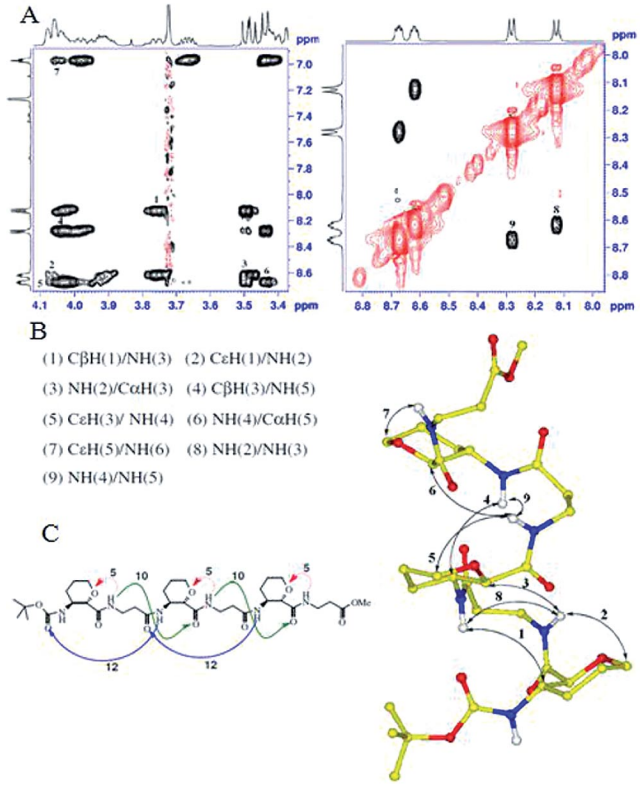


Figure 2. A) ROESY expansion of peptide **2** showing characteristic nOe correlations. B) Ball-and-stick model of peptide **2** showing characteristic nOes represented by double arrows. C) Chemical structure showing various hydrogen bonds and electrostatic interactions (red-colored arrows).

The right-handed helical structure in peptides **1** and **2** was confirmed by their CD profiles. The CD spectra of peptides **1** and **2** in methanol (0.2 mM) showed a maximum at 204 nm, which supports the presence of a right-handed 12/10-helix with molar ellipticities of ca. 10000 and ca. 15000 deg cm^2 dmol^{-1} (Figure 3). For the restrained molecular dynamics studies, the constraints were derived from the intensities of the nOe cross-peaks in the ROESY spectra using the two-spin approximation.

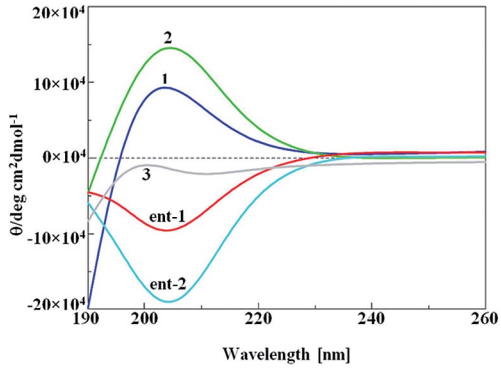


Figure 3. CD profiles of peptides **1**–**3**, *ent*-**1**, and *ent*-**2**.

The study was then extended to peptides *ent*-**1** and *ent*-**2**, prepared from the enantiomeric β-amino acid [i.e., (*R*,*R*)-APyC *ent*-**7**]. Peptides *ent*-**1** and *ent*-**2** are enantiomeric with **1** and **2**. The ^{1}H NMR spectrum[18] of peptide *ent*-**1** in $CDCl_3$ showed the features of a stable secondary structure. The amide protons NH(2) and NH(3) resonate at $\delta >$ 7.7 ppm, which indicates their participation in hydrogen bonding. This was further confirmed by their small chemical shift change (< 0.25 ppm) during solvent titration[18] with [D_6]DMSO. Furthermore, NH(4) resonated very close to $\delta = 7$ ppm and showed a small change in chemical shift ($\Delta\delta < 0.34$ ppm) during solvent titration, confirming its participation in non-covalent interactions.[18] A higher $\Delta\delta$ value of 1.94 ppm for NH(1) indicates its exposure to the solvent.

The nOe correlations, coupling constants, and changes in chemical shift values are similar to those observed for peptides **1** and **2**, but the signs of the dihedral angles are opposite. These details indicate a switch of handedness for peptides *ent*-**1** and *ent*-**2**. Support for this switch was also obtained from the CD spectra, which showed profiles opposite to those of peptides **1** and **2**. Thus, a left-handed 12/10-mixed helix is formed by *ent*-**1** and *ent*-**2**, according to NMR, CD, and MD studies.[18] Such a left-handed 12/10-helix has earlier been observed in mixed peptides made from (*S*)-β-Caa and β-hGly in a 1:1 alternating order.[3g] This study presents the first reported well-designed motif for a left-handed 12/10-helix. Since left-handed conformations in natural proteins[12c] are implicated in biological activity, this design is important in the foldamer field.

Having unequivocally analyzed the presence of right-handed 12/10-helices in peptides **1** and **2**, as well as left-handed 12/10-helices in *ent*-**1** and *ent*-**2**, we went on to study peptide **3**, whose design connects the two helices of opposite handedness. It is very interesting to investigate the structure of peptide **3**, because this gives information on the compatibility of two enantiomeric helical structures within a single peptide.

The ^{1}H NMR spectrum[18] of **3** showed a well-dispersed amide region, indicating the existence of a well-defined structure. Amide protons NH(2)–NH(3) and NH(5)–NH(7) resonated at low field ($\delta > 7.8$ ppm), while NH(4) and NH(8) resonated at $\delta > 6.8$ ppm. All the amide protons except NH(1) showed a small change in their chemical shift values during solvent titration, which indicates that they are involved in non-covalent interactions.[18]

For the APyC residue, the large $^3J_{NH,C\beta H} \geq 9.2$ Hz shows that the NH and CβH protons are antiperiplanar to each other, corresponding to a dihedral angle ϕ[C(O)–N–Cβ–Cα] ≈ |120°|. A large value for the coupling constant $^3J_{C\alpha H,C\beta H} \approx 9.6$ Hz supports a magnitude of |60°| for the dihedral angle $|\theta|$, which is further supported by the presence of strong nOe correlations between the NH and CαH protons. The dihedral angles of the β(1) and β(3) constituents have opposite signs to those of β(5) and β(7), because of the connection of two enantiomeric peptides. A similar situation is found with β-hGly, i.e., $\phi \approx 120°$ and $\theta \approx 60°$ for the β(2) and β(4) constituents, and $\phi \approx -120°$ and $\theta \approx -60°$ for the β(6) and β(8) monomers, since they have one small (≤4.8 Hz) and one large (≥7.9 Hz) coupling constant $^3J_{NH,C\beta H}$, and values of <2.2 or >12.4 Hz for $^3J_{C\alpha H,C\beta H}$.

The nOe correlations CβH(1)/NH(3), $C\alpha H_{(pro\text{-}R)}$(2)/NH(3), and NH(2)/NH(3) along with CβH(1)/NH(2), CβH(3)/NH(4), and CεH(1)/NH(2) correspond to a right-handed 12/10-helix, while CβH(5)/NH(7), $C\alpha H_{(pro\text{-}S)}$(5)/NH(6), NH(6)/NH(7), CβH(5)/NH(6), CβH(7)/NH(8), CεH(5)/NH(6), and CεH(7)/NH(8) support a left-handed 12/10-helix (Figure 4). These helical structures are further stabilized by electrostatic interactions between the amide protons of the β-hGly residues and the oxygen atoms of the pyran rings in the preceding residues. Figure 3 shows the compensation of the positive and negative profiles of the left-handed and right-handed 12/10-helices in the CD spectrum of peptide **3**. A stereoview of 20 minimum-energy structures of peptide **3** resulting from molecular dynamics can be seen in Figure 5, demonstrating the presence of the right- and left-handed 12/10-helices.[18]

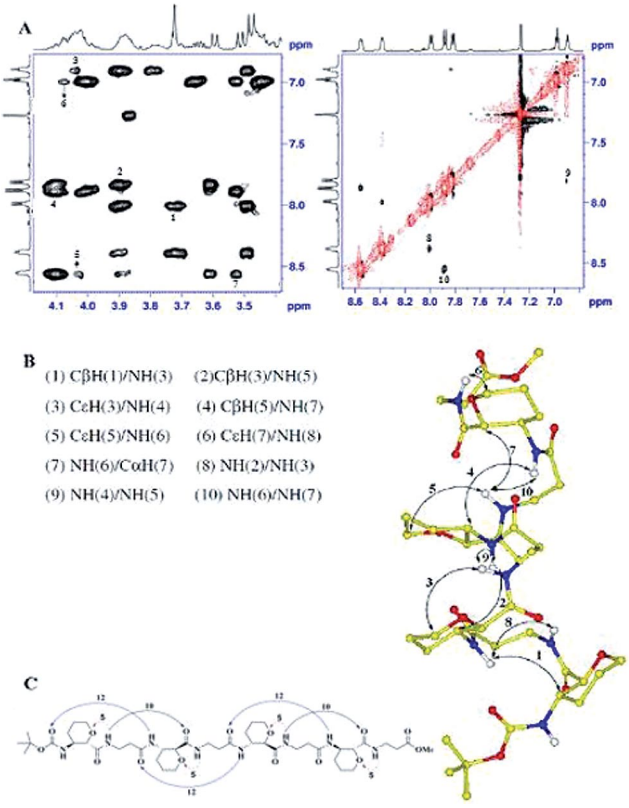


Figure 4. A) ROESY expansion of peptide **3** showing characteristic nOe correlations. B) Ball-and-stick model of peptide **3** showing characteristic nOes represented by double arrows. C) Chemical structure showing various hydrogen bonds and electrostatic interactions (red-colored arrows).

The conformational structure of peptide **3** was also confirmed by quantum chemical calculations at the B3LYP/6-31G* level of ab initio MO theory. Most striking is the smooth transition between the two helical parts of opposite handedness, such that an essentially linear helical overall shape of the peptide is maintained. A detailed inspection of the structure shows that the NH group of residue 4, which

Figure 5. Stereoview of 20 superimposed minimum energy structures of peptide **3** (hydrogens were removed after calculations for clarity).

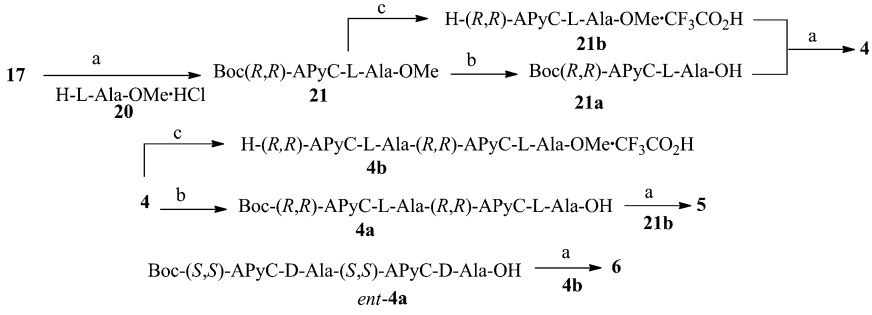
comes from peptide **1**, and the CO group of residue 5, which is the first residue of peptide *ent*-**1**, are no longer involved in the hydrogen-bonding network, as they would be if the handedness had not been changed. The approximately linear helical overall structure of the peptide results from two 12-mr hydrogen bonds between the helices of opposite handedness arising from the CO group of residue 2 (first helix) and the NH group of residue 5 (second helix), and the CO group of residue 4 (first helix) and the NH group of residue 7 (second helix), respectively. The formation of a 12-mr hydrogen bond between NH(5) with CO(2), which stabilizes the hinge region, is well documented by the NMR spectroscopic data, which indicates an nOe correlation between CβH(3)/NH(5) (Figure 4). The NH group of residue 4 keeps its stabilizing electrostatic interaction with the pyran oxygen atom of the preceding residue. According to the quantum chemical calculations, the corresponding NH···O distance is 2.18 Å. The backbone torsion angles calculated for peptide **3** are given in the Supporting Information.

Synthesis and Conformational Analysis of α/β-Hybrid Peptides 4–6

After the synthesis and analysis of peptides **1**, **2**, *ent*-**1**, *ent*-**2**, and **3** and the identification of the occurrence of left- and right-handedness in the mixed β-peptides, the study was extended to α/β-peptides with right- and left-handed 9/11-helices.

Earlier, we reported[10] a right-handed 9/11-helix in peptides containing *trans*-(*S*,*S*)-APyC. Hence, we proposed to synthesize α/β-peptides **4** and **5**, and octapeptide **6** from **4** and the known[10] tetrapeptide prepared from **7** (Scheme 3). Accordingly, acid **17**, upon coupling with **20** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 gave dipeptide **21** (90%). Hydrolysis of ester **21** with LiOH gave acid **21a**, while reaction of **21** with CF_3COOH in CH_2Cl_2 gave salt **21b**. Coupling (EDCI, HOBt, and DIPEA) of acid **21a** with salt **21b** in CH_2Cl_2 gave tetrapeptide **4** (47%). Hydrolysis of peptide **4** with LiOH gave acid **4a**, while treatment of **4** with CF_3COOH in CH_2Cl_2 gave salt **4b**. Coupling (EDCI, HOBt, and DIPEA) of acid **4a** with salt **21b** in CH_2Cl_2 provided hexapeptide **5** (38%). Similarly, coupling of known acid *ent*-**4a**[10] with **4b** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 gave octapeptide **6** in 75% yield.

Based on our earlier report,[10] we anticipated that the peptides **4** and **5** would show left-handed 9/11-helices. The proton NMR spectrum of peptide **4** was very well dispersed, and in the solvent titration study of amide protons, except for NH(1), showed small chemical shift changes,[18] indicating a well-defined secondary structure with the participation of the amide protons in hydrogen bonding. The nOe correlations and information on dihedral angles obtained from ^3J coupling constants indicate that the amide protons NH(2) and NH(3) formed 9-mr and 11-mr hydrogen bonds with the CO(3) and Boc CO groups, respectively. In addition, NH(2) and NH(4) are involved in weak electrostatic interactions with the oxygen atom of the pyran ring of APyC. Solvent titration and nOe studies on peptide **5** confirmed that the NHs of Ala(2) and Ala(4) participate in 9-mr hydrogen bonding with the CO group of APyC(3) and APyC(5), respectively, whereas the NH groups of APyC(3) and APyC(5) participate in 11-mr hydrogen bonding with the Boc CO and CO(2) groups. The amide protons of Ala(2), Ala(4), and Ala(6) showed weak interactions with the oxygen of the pyran rings of APyC(1), APyC(3), and APyC(5), respectively, which may provide further stabilization of the 9/11-helical structure. The CD spectra of **4** and **5** showed minima at 203 and 206 nm, respectively, indicating the presence of a left-handed 9/11-helical pattern, which was further confirmed by molecular dynamics simula-



Scheme 3. Synthesis of peptides **4**–**6**. Reagents and conditions: (a) HOBt (1.2 equiv.), EDCI (1.2 equiv.), DIPEA (2 equiv.), dry CH_2Cl_2, 0 °C–r.t., 8 h; (b) LiOH, THF/MeOH/H_2O (3:1:1), 0 °C–r.t., 1 h; (c) CF_3CO_2H, dry CH_2Cl_2, 2 h.

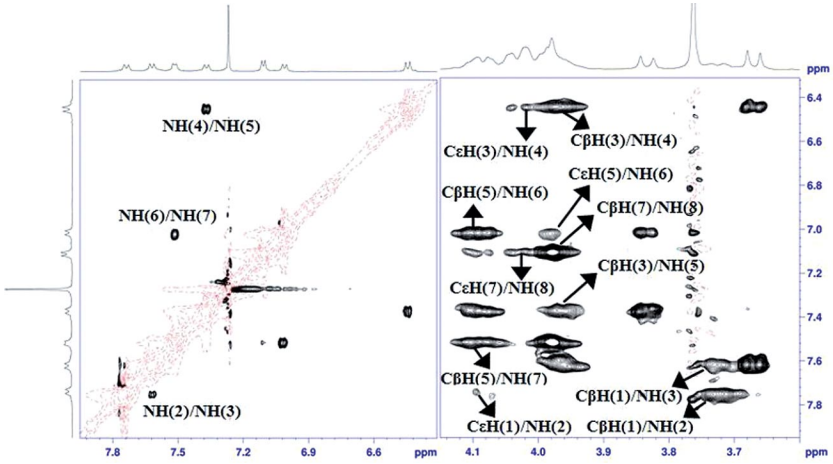


Figure 6. ROESY spectrum of peptide **6**.

tions.[18] Peptide **5** was also studied in CD_3OH, a polar solvent, and the majority of the nOe correlations that are indicative of a 9/11-helix, and which were observed in $CDCl_3$, were also observed here. The weak intensitites of the cross-peaks imply a diminishing of the ordered structure.

To understand the compatibility between two different helix types with opposite handedness, peptide **6** was studied. As was observed for peptide **3**, the amide protons of **6** resonated at low field ($\delta > 7$ ppm), and showed small changes in their chemical shifts in solvent titration,[18] except for NH(1) and NH(4). The nOe correlations CβH(1)/NH(3) and NH(2)/NH(3), along with CβH(1)/NH(2) and CβH(3)/NH(4), correspond to a right-handed 9/11-helix, while CβH(5)/NH(7), NH(6)/NH(7), CβH(5)/NH(6), and CβH(7)/NH(8) are consistent with a left-handed 9/11-helix. In addition, it was observed that the amide protons of Ala showed electrostatic interactions with the pyran oxygen atoms of the preceding residues, as indicated by the characteristic nOe correlations CεH(APyC)/NH(α) (Figure 6). This also concerns NH(4), which does not take part in the helical hydrogen-bonding system.

As observed for peptide **3**, the smooth transition of handedness in the hinge region between the two helical parts is documented by the presence of a characteristic nOe between CβH(3)/NH(5), indicating the formation of a stabilizing 11-mr hydrogen bond between NH(5) and CO(2). This finding is also supported by the absence of an nOe between NH(4)/CαH(5). All data confirm the presence of right- and left-handed 9/11-helices in peptide **6**, as can also be seen in the stereoview of a set of superimposed minimum-energy structures in Figure 7, resulting from molecular dynamics.

The CD profile of peptide **6** is similar to that of peptide **3**, reflecting the compensation of the positive and negative profiles of the connected mixed helices (Figure 8).

The discussion on the structural features of the helical pattern of peptide **3** given above, in particular in the transition range between the two 12/10-helices of opposite handedness, can be completely transferred to peptide **6** with its mixed 9/11-helices. The structure of peptide **6** with its characteristic helical folds, and the electrostatic interactions between the peptide bond NH groups and pyran ring oxygen atoms of the preceding residue, was also confirmed by MO calculations at the B3LYP/6-31G* level of ab initio MO theory. The backbone torsion angles from these calculations are given in the Supporting information.

Figure 7. Stereoview of 20 superimposed minimum-energy structures of peptide **6** (hydrogens were removed after calculations for clarity).

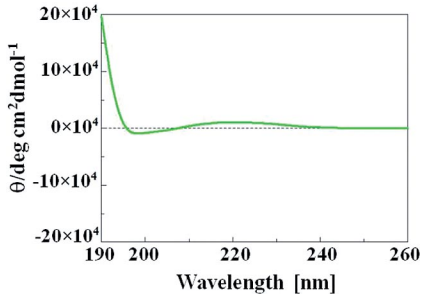


Figure 8. CD profile of peptide **6**.

Conclusions

In this paper, we report the synthesis of (*R*,*R*)-APyC, the enantiomer of the already known (*S*,*S*)-APyC. Both (*R*,*R*)- and (*S*,*S*)-APyC were used together with β-hGly to synthesize mixed β-peptides in a 1:1 alternating order to form right- and left-handed 12/10-helices. Coupling of the enantiomeric tetrapeptides **1** and *ent*-**1** gave peptide **3** showing

both right- and left-handed 12/10 hydrogen-bonding patterns. The extension of this concept to α/β-peptides composed of (*R*,*R*)-APyC/L-Ala and (*S*,*S*)-APyC/D-Ala led to enantiomeric 9/11-helical peptides. Peptide **6**, with equal portions of these oligomers, revealed the presence of the left- and right-handed helices also in this foldamer class. In both cases, the linear helical overall structure is essentially maintained, despite the change of handedness and the interruption of the hydrogen bonding network in the transition region between the helical peptide parts. These results demonstrate the design of peptides with more than one type of handedness, where the screwing sense alternates, depending on the order of the connected enantiomeric oligomers. This may pave the way for new types of peptide oligomers.

Experimental Section

General Remarks: NMR spectra were recorded with Bruker AVANCE III-700, Bruker AVANCE II-600, Bruker AVANCE III-500, Varian INOVA-500, and Bruker AVANCE-300 spectrometers at 278–303 K in chloroform, using tetramethylsilane as an internal reference. Chemical shifts were measured from 1D NMR spectra, and coupling constants were measured using resolution-enhanced 1D spectra. Chemical shift correlations were done using two-dimensional NMR experiments, such as Total Correlation Spectroscopy (TOCSY) and rotating-frame Overhauser effect spectroscopy (ROESY) in phase-sensitive mode with mixing times of 80 ms and 250–350 ms, respectively. The spectra were acquired from 2× 192 or 2× 256 experiments containing 8–16 transients with a relaxation delay of 1.5–2 s. The 2D spectra were processed with a Gaussian apodization in both dimensions. Solvent titration studies were done using sequential additions of [D_6]DMSO (33% v/v) (up to 300 μL) to solutions of peptides in chloroform (600 μL).

CD Spectra were acquired with a JASCO-810 spectrometer at room temperature in methanol, using a 2 mm path length CD cell. Spectra were recorded with an average of 2 scans (100 ms time constant, 2 nm bandwidth), background-corrected and smoothed over 2–5 data points. The scans were carried out from 250 to 193 nM, at 200 μM concentration. The molar ellipticities (θ) were normalized, and the data are presented as deg cm^2 dmol^{-1} per residue. The peptides with N-terminus B-residues showed higher molar ellipticities of 70000 deg cm^2 dmol^{-1}.

Model building and molecular dynamics simulations on **1**–**6**, *ent*-**1**, and *ent*-**2** were carried out using the Insight II (97.0)/Discover program[18] with a Silicon Graphics O2 workstation. The CVFF force field with default parameters was used throughout the simulations. Minimizations were first done with steepest descent, followed by conjugate gradient method for a maximum of 1000 iterations each or until the RMS deviation reached 0.001 kcal/mol, whichever was earlier. The molecules were initially equilibrated for 1 ps, and then subjected to a simulated annealing protocol. Starting from 300 K, they were heated to 1500 K in four steps, increasing the temperature by 300 K and simulating for 2.5 ps at each step, and then subsequently cooled back to 300 K by decreasing the temperature in four steps, and again simulating for 2.5 ps. The structure was saved and the above process was repeated 100 times. The 100 structures thus generated were energy minimized using the protocol described above, and 20 of the best structures were superimposed. For better visualization, the protons have been removed in the figures.

(*R*,*R*)-*trans*-3-Aminopyran-2-carboxylic Acid [(*R*,*R*)-APyC] (*ent*-7): Reaction of **8**[20] with benzylamine in diethyl ether, followed by treatment of the imine with vinylmagnesium bromide in THF at 0 °C to room temperature for 8 h, gave **9**[21] in 71% yield (Scheme 1). Treatment of amine **9** with $(Boc)_2O$ and Et_3N in CH_2Cl_2 at 0 °C to room temperature for 6 h gave **10** in 86% yield. Acid (PTSA)-mediated hydrolysis of **10** in MeOH/H_2O (9:1) at 0 °C to room temperature for 6 h gave diol **11** in 93% yield. Selective protection of **11** by reaction with TBSCl and imidazole in CH_2Cl_2 at 0 °C to room temperature gave TBS ether **12** (84%), which, on reaction with allyl bromide in the presence of NaH in DMF at 0 °C to room temperature for 4 h, gave allyl ether **13** in 59% yield. Ring-closing metathesis of bis-olefin **13** in the presence of Grubbs I catalyst[22] (5 mol-%) gave **14** in 89% yield. Subjection of pyrene **14** to Birch reaction conditions using Li and liquid NH_3 at –78 °C in THF for 1 h gave amide **15** (65%), which, upon hydrogenation with Pd-C (10%) in MeOH under a hydrogen atmosphere, gave alcohol **16** in 91% yield. Sequential oxidation of alcohol **16** with TEMPO and BAIB in aq. CH_2Cl_2 gave acid **17** (59%), which, upon treatment with diazomethane, generated in situ, at 0 °C for 1 h, gave ester *ent*-**7** in 55% yield.

(*R*)-*N*-Benzyl-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-amine (9): Benzylamine (14.9 mL, 137.0 mmol) was slowly added to a stirred and cooled (0 °C) suspension of **8** (18.4 g, 138.4 mmol) and dry $MgSO_4$ (5 g) in diethyl ether (100 mL), and the reaction mixture was stirred at room temperature for 2 h. A portion (50 mL) of this solution of chiral imine in diethyl ether was added dropwise over 30 min to a stirred solution of vinylmagnesium bromide [prepared from Mg (17.0 g, 709.5 mmol) and vinyl bromide (51 mL, 709 mmol) in THF (50 mL)] at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 8 h, then it was quenched with aq. NH_4Cl (70 mL) and extracted with EtOAc (3× 100 mL). The combined organic layers were washed with water (2× 100 mL) and brine (2× 100 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 5% ethyl acetate in petroleum ether) to give **9** (10 g, 71%) as a colorless liquid. $[\alpha]_D$ = –9.5 (c = 0.7, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3446, 3069, 3027, 2984, 2930, 1665, 1455, 1375, 1255, 1214, 1155, 1061, 997, 924, 756, 701, 509 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ = 7.26–7.15 (m, 5 H, ArH), 5.70–5.58 (m, 1 H, olefinic), 5.27–5.17 (m, 2 H, olefinic), 4.08 (m, 1 H, OCH), 3.97–3.84 (m, 3 H, $PhCH_2$, OCH), 3.62–3.58 (m, 1 H, OCH), 3.16 (qt, J = 4.53, 3.39 Hz, 1 H, NCH), 1.5 (br. s, 1 H, NH), 1.37 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 25.0, 26.2, 50.6, 61.9, 66.0, 78.0, 109.0, 118.7, 126.8, 128.0 (2 C), 128.2 (2 C), 136.1, 140.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.1650; found 248.1640.

***tert*-Butyl Benzyl(*R*)-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]allylcarbamate (10):** Et_3N (16.9 mL, 121.4 mmol) was added to a stirred solution of **9** (10.1 g, 40.8 mmol) in CH_2Cl_2 (50 mL) at 0 °C, and the mixture was stirred for 15 min. $(Boc)_2O$ (10.91 mL, 49.0 mmol) was added, and the reaction mixture was stirred at room temperature for 6 h. It was washed with water (2× 100 mL) and brine (100 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 2% ethyl acetate in petroleum ether) to give **10** (12.28 g, 86%) as a colorless liquid. $[\alpha]_D$ = +3.60 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3458, 2981, 2838, 1728, 1612, 1513, 1373, 1247, 1175, 1032, 833, 771 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ = 7.29–7.12 (m, 5 H, ArH), 5.92 (m, 1 H, olefinic), 5.21 (d, J = 9.8 Hz, 2 H, olefinic), 4.58–4.02 (m, 4 H, 2 OCH, $PhCH_2$), 3.78–3.36 (m, 2 H,

NCH, OCH), 1.62–1.09 (m, 15 H, acetonide, Boc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 155.5, 139.3, 132.8, 128.3, 128.1, 127.1, 126.7, 126.9, 118.9, 109.5, 80.2, 76.4, 66.9, 60.54, 48.8, 28.2 (3 C), 26.4, 25.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{29}NO_4$ [M + Na]$^+$ 370.1994; found 370.1993.

***tert*-Butyl Benzyl[(2*R*,3*R*)-1,2-dihydroxypent-4-en-3-yl]carbamate (11):** PTSA (cat.) was added to a stirred solution of **10** (12.2 g, 35.15 mmol) in MeOH/H_2O (60 mL, 9:1), and the mixture was stirred at room temperature for 6 h. The reaction was quenched with solid $NaHCO_3$ (5 g), and the mixture was extracted with EtOAc (2× 200 mL). The organic phase was washed with water (2× 100 mL) and brine (100 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 25% ethyl acetate in petroleum ether) to give **11** (10.1 g, 93%) as a colorless liquid. $[\alpha]_D$ = +50.4 (c = 0.4, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3411, 2975, 2930, 1668, 1456, 1407, 1364, 1249, 1165, 1075, 880, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (m, 5 H, ArH), 6.07–5.9 (m, 1 H, olefinic), 5.25–5.14 (m, 2 H, olefinic), 4.48–4.28 (m, 2 H, $PhCH_2$), 4.05–3.69 (m, 2 H, OCH_2), 3.4 (br. s, 2 H, NH, OCH) 2.7 (br. s, 1 H, OH), 1.8 (br. s, 1 H, OH), 1.4 (s, 9 H, Boc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 138.3, 132.7, 128.3 (3 C), 127.2 (2 C), 119.8, 81.7, 72.5, 63.1, 61.6, 50.2, 28.2 (3 C) ppm. HRMS (ESI): calcd. for $C_{17}H_{25}NO_4Na$ [M + Na]$^+$ 330.1681; found 330.1687.

***tert*-Butyl Benzyl[(3*R*,4*R*)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxypent-1-en-3-yl]carbonate (12):** Imidazole (6.6 g, 97.7 mmol) was added to a stirred and cooled (0 °C) solution of **11** (10 g, 32.5 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred for 15 min. TBSCl (5.3 g, 35.8 mmol) was added portionwise, and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with water (2× 100 mL) and brine (100 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 5% ethyl acetate in petroleum ether) to give **12** (11.1 g, 84%) as a colorless liquid. $[\alpha]_D$ = +40.7 (c = 0.4, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3423, 2933, 2861, 1678, 1463, 1416, 1362, 1251, 1165, 1112, 841, 774, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ = 7.34–7.14 (m, 5 H, ArH), 6.19–5.82 (m, 1 H, olefinic), 5.23–4.94 (m, 2 H, olefin), 4.8–3.19 (m, 2 H, NCH, PhCH), 4.17–3.25 (m, 5 H, 3 OCH, PhCH, OH), 1.46 (s, 9 H, Boc), 0.9–0.84 (m, 9 H, *t*Bu), 0.09–0.01 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 156.7, 138.3, 131.5, 128.2 (3 C), 127.4, 127.1, 118.3, 80.7, 74.1, 63.4, 63.9, 52.9, 28.2 (3 C), 25.9 (3 C), 18.0, –5.5, –5.6 ppm. HRMS (ESI): calcd. for $C_{23}H_{39}NO_4SiNa$ [M + Na]$^+$ 444.2489; found 444.2498.

***tert*-Butyl [(3*R*,4*R*)-4-(Allyloxy)-5-(*tert*-butyldimethylsilyloxy)pent-1-en-3-yl](benzyl)carbamate (13):** NaH (1.97 g, 82.3 mmol) and then allyl bromide (3.03 mL, 32.8 mmol) were added to a stirred solution of alcohol **12** (11 g, 27.4 mmol) in dry DMF (55 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with aq. NH_4Cl (30 mL) solution, and the mixture was extracted with EtOAc (2× 50 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4), and the solvents were evaporated. The residue was purified by column chromatography (60–120 mesh silica gel, 2% ethyl acetate in petroleum ether) to give **13** (7.5 g, 59%) as a colorless liquid. $[\alpha]_D$ = +36.0 (c = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3430, 2931, 2858, 1693, 1456, 1407, 1365, 1252, 1165, 928, 837, 777, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–6.56 (m, 5 H, ArH), 6.09–5.49 (m, 2 H, olefinic), 5.37–4.76 (m, 4 H, olefin), 4.67–4.98 (m, 2 H, $PhCH_2$), 4.22–3.23 (m, 6 H, 5 OCH, NCH), 1.55–1.11 (s, 9 H, Boc), 0.86 (s, 9 H, *t*Bu), 0.06 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 139.3, 135.1, 133.8, 128 (3 C), 127.2, 126.8, 118.3, 116.7, 80.8, 80.0, 72.2, 63.0, 60.8, 50.7, 28.3 (3 C), 25.9 (3 C), 18.24, –5.49, –5.41 ppm. HRMS (ESI): calcd. for $C_{26}H_{44}NO_4Si$ [M + H]$^+$ 462.3039; found 462.3029.

***tert*-Butyl Benzyl[(2*R*,3*R*)-2-(*tert*-butyldimethylsilyloxy)methyl]-[3,6-dihydro-2*H*-pyran-3-yl]carbamate (14):** A solution of **13** (7.5 g, 16.2 mmol) in freshly distilled degassed anhydrous toluene (140 mL) was treated with Grubbs I catalyst (0.14 g, 5 mol-%), and the mixture was heated at reflux for 8 h. Most of the solvent was then distilled off, and the concentrated solution was left to stir at room temperature for 8 h with air bubbling, in order to decompose the catalyst. The mixture was evaporated to dryness, and the residue was purified by column chromatography (60–120 mesh silica gel, 2.5% ethyl acetate in petroleum ether) to give **14** (6.3 g, 89%) as a pale brown liquid. $[\alpha]_D$ = –56.7 (c = 0.25, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3449, 2929, 2857, 1694, 1452, 1400, 1365, 1251, 1163, 1116, 839, 773, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.32 (m, 5 H, Ar-H), 6.05–5.52 (m, 2 H, olefinic), 4.93–4.15 (m, 5 H, $PhCH_2$, NCH, 2 OCH), 3.9–3.6 (m, 3 H, 3 OCH), 1.68–1.36 (m, 9 H, Boc), 1.04 (s, 9 H, *t*Bu), 0.19 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 139.6, 128.3, 128.1, 127.4, 126.9, 126.6, 126.5, 126.1, 80.3, 80.1, 76.4, 64.6, 64.0, 51.1, 28.1 (3 C), 26.0 (3 C) 18.4, –5.3 (2 C) ppm. HRMS (ESI): calcd. for $C_{24}H_{39}NO_4SiNa$ [M + Na]$^+$ 456.2546; found 456.2556.

***tert*-Butyl [(2*R*,3*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-3,6-dihydro-2*H*-pyran-3-yl]carbamate (15):** Lithium metal (0.43 g, 72.7 mmol) was added to a solution of liq. NH_3 (50 mL) in dry THF (20 mL) at –78 °C under a nitrogen atmosphere, and the mixture was stirred for 1 h at the same temperature. A solution of **14** (6.25 g, 14.43 mmol) in THF (30 mL) was added slowly, and the mixture was stirred for an additional 1 h. Aqueous NH_4Cl (50 mL) was then added dropwise, and the mixture was extracted with EtOAc (2× 50 mL). The organic layers were washed with brine (25 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 16% ethyl acetate in petroleum ether) to give **15** (3.1 g, 65%) as a colorless liquid. $[\alpha]_D$ = –13.57 (c = 0.14, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3391, 2928, 1701, 1517, 1380, 1252, 1161, 1086, 816, 753, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.0–5.77 (m, 2 H, olefinic), 4.6 (br. s, 1 H, NH), 4.32–4.02 (m, 3 H, 2 OCH, NCH), 3.92–3.74 (m, 3 H, 3 OCH), 1.56 (s, 9 H, Boc), 1.03 (s, 9 H, *t*Bu), 0.19 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 128.1, 126.5, 79.2, 79.5, 64.6, 64.1, 45.8, 28.3 (3 C), 25.9 (3 C), 18.4, –5.3, –5.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{34}NO_4Si$ [M + H]$^+$ 344.2293; found 344.2289.

***tert*-Butyl [(2*R*,3*R*)-Tetrahydro-2-(hydroxymethyl)-2*H*-pyran-3-yl]-carbamate (16):** Compound **15** (3.1 g, 9.0 mmol) was dissolved in MeOH (15 mL), and Pd-C (10%; cat.) was added. The mixture was stirred at room temperature for 6 h under a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad, eluting with ethyl acetate (3× 30 mL). The solvents were evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 25% ethyl acetate in petroleum ether) to give **16** (1.6 g, 91%) as a white solid, m.p. 75 °C. $[\alpha]_D$ = +0.36 (c = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3328, 2936, 2861, 1684, 1531, 1455, 1367, 1311, 1249, 1171, 1081, 1039, 982, 856, 756 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.43 (d, J = 8.4 Hz, 1 H, NH), 4.13–3.92 (m, 1 H, OCH), 3.60–3.46 (m, 3 H, 3 OCH), 3.46–3.20 (m, 2 H, NCH, OCH), 2.08 (d, J = 9.0 Hz, 1 H, OH), 1.87–1.59 (m, 4 H, 2 CH_2), 1.43 (s, 9 H, Boc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 82.6, 80.3, 67.7, 62.2, 46.1, 30.2, 28.1 (3 C), 25.5 ppm. HRMS (ESI): calcd. for $C_{11}H_{21}NO_4Na$ [M + Na]$^+$ 254.1368; found 254.1362.

(2*R*,3*R*)-3-(*tert*-Butoxycarbonylamino)tetrahydro-2*H*-pyran-2-carboxylic Acid (17): Compound **16** (1.9 g, 12.3 mmol) was dissolved in CH_2Cl_2/H_2O (3:1; 4 mL), and the solution was cooled to 0 °C. TEMPO (0.38 g, 2.46 mmol) and BAIB (7.9 g, 24.6 mmol) were added, and the mixture was stirred for 4 h. The reaction was quenched with aq. $Na_2S_2O_3$ (10 mL), and the mixture was extracted with CH_2Cl_2 (2× 100 mL). The combined organic layers were washed with water (2× 25 mL) and brine (25 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 70% ethyl acetate in petroleum ether) to give **17** (1.2 g, 59%), m.p. 110–112 °C. $[a]_D$ = –3.0 (*c* = 0.5, $CHCl_3$). IR (KBr): ṽ = 3374, 2931, 2860, 1700, 1522, 1368, 1309, 1250, 1168, 1089, 1043, 960, 756, 610 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.81 (s, 1 H, NH), 3.95 (d, *J* = 11.4 Hz, 1 H, OCH), 3.76–3.69 (m, 2 H, OCH_2), 3.43 (m, 1 H, NCH), 2.05 (m, 1 H, CH), 1.66 (m, 2 H, 2 CH), 1.47 (m, 1 H, CH), 1.36 (s, 9 H, Boc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 155.9, 78.9, 77.8, 66.8, 29.4, 28.2 (3 C), 23.8 (2 C) ppm. HRMS (ESI): calcd. for $C_{11}H_{19}NO_5Na$ $[M + Na]^+$ 268.1155; found 268.1153.

***tert*-Butyl [(2*R*,3*R*)-2-(Methoxycarbonyl)-tetrahydro-2*H*-pyran-3-yl-]carbamate (*ent*-7):** A solution of **17** (1.2 g, 48.9 mmol) in diethyl ether (15 mL) at 0 °C was treated with ethereal diazomethane [prepared from *N*-nitrosomethyl urea (3.8 g) and KOH (50%; 40 mL)], and the mixture was stirred at 0 °C for 1 h. The solvent was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 20% ethyl acetate in petroleum ether) to give *ent*-**7** (0.7 g, 55%) as a white solid, m.p. 96–98 °C. $[a]_D$ = –25.1 (*c* = 0.5, $CHCl_3$). IR (KBr): ṽ = 3373, 2981, 2940, 1752, 1681, 1519, 1440, 1369, 1246, 1171, 1115, 1088, 1038, 1012, 949, 865, 748, 702 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 293 K): δ = 4.60 (br. s, 1 H, NH), 4.01 (dt, *J* = 11.7, 4.5 Hz, 1 H, CεH), 3.79–3.75 (m, 5 H, CβH, CαH, COOMe), 3.46 (m, 1 H, Cε′H), 2.1–1.98 (m, 1 H, CγH), 1.77–1.66 (m, 2 H, CδH, Cδ′H), 1.55–1.35 (m, 10 H, Cγ′H, Boc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 154.9, 80.1 (2 C), 66.8, 52.5, 48.2, 29.3, 28.3 (3 C), 23.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{21}NO_5Na$ $[M + Na]^+$ 282.1317; found 282.1325.

Boc-(*S*,*S*)-APyC-β-hGly-OMe (19): LiOH (0.10 g, 4.4 mmol) was added to a solution of **7** (0.46 g, 1.77 mmol) in THF/MeOH/H_2O (3:1:1), at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched with HCl (1 N; 3 mL) at 0 °C, and the mixture was extracted with EtOAc (2× 50 mL). The organic layers were dried (Na_2SO_4) and evaporated to give acid **7a** as a semi-solid, which was used as such for further reaction.

A solution of acid **7a** (0.4 g, 1.63 mmol), HOBt (0.26 g, 1.95 mmol), and EDCI (0.37 g, 1.95 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C for 15 min under a nitrogen atmosphere, and then salt **18** (0.27 g, 1.95 mmol) was added. The mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with aq. NH_4Cl (10 mL) at 0 °C, and diluted with $CHCl_3$ (10 mL). The mixture was washed with HCl (1 N; 10 mL), water (10 mL), and brine (10 mL). The organic layers were dried (Na_2SO_4), the solvents were evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 50% ethyl acetate in petroleum ether) to give **19** (0.70 g, 89%) as a white solid, m.p. 104–106 °C. $[a]_D$ = +160 (*c* = 0.16, $CHCl_3$). IR (KBr): ṽ = 3340, 3311, 3093, 2954, 2855, 1733, 1680, 1656, 1558, 1523, 1446, 1388, 1313, 1250, 1173, 1091, 1030, 958, 620 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 288 K): δ = 6.91 (s, 1 H, NH-2), 5.30 (s, 1 H, NH-1), 3.96 (d, *J* = 10.38 Hz, 1 H, CαH-1), 3.69 (s, 3 H, $COOCH_3$), 3.56–3.46 (m, 5 H, CβH-1, CεH-1, Cε′H-1, CβH-2, Cβ′H-2), 2.54 (m, 2 H, CαH-2, Cα′H-2), 2.42–2.32 (m, 2 H, CγH-1, Cγ′H-1), 1.73–1.59 (m, 2 H, CδH-1, Cδ′H-1), 1.37 (s, 9 H, Boc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 170.0, 155.6, 79.6, 79.3, 67.7, 51.8, 50.4, 34.1, 33.5, 30.6, 28.2 (3 C), 24.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}N_2O_6Na$ $[M + Na]^+$ 353.1683; found 353.1681.

Boc-(*S*,*S*)-APyC-β-hGly-(*S*,*S*)-APyC-β-hGly-OMe (1): LiOH (0.02 g, 1.13 mmol) was added to a solution of ester **19** (0.15 g, 0.45 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave **19a**, which was used as such for further reaction.

A solution of acid **19a** (0.14 g, 0.45 mmol), HOBt (0.07 g, 0.55 mmol), and EDCI (0.10 g, 0.55 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under a nitrogen atmosphere for 15 min. Then salt **19b** [prepared from **19** (0.15 g, 0.45 mmol) and CF_3COOH (0.1 mL) in dry CH_2Cl_2 (1 mL) at 0 °C] and DIPEA (0.11 mL, 0.68 mmol) were added sequentially, and the mixture was stirred for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 1.5% methanol in $CHCl_3$), gave **1** (0.09 g, 42%) as a white solid, m.p. 188–190 °C. $[a]_D$ = +200 (*c* = 0.77, $CHCl_3$). IR (KBr): ṽ = 3295, 3094, 2962, 2854, 1743, 1743, 1687, 1661, 1556, 1442, 1369, 1311, 1248, 1172, 1089, 956, 684 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 278 K): δ = 8.42 (dd, *J* = 4.8, 7.9 Hz, 1 H, NH-2), 7.70 (d, *J* = 9.2 Hz, 1 H, NH-3), 6.95 (t, *J* = 6.2 Hz, 1 H, NH-4), 4.79 (d, *J* = 9.9 Hz, 1 H, NH-1), 4.04 (m, 1 H, CεH-3), 4.02 (m, 1 H, CεH-1), 3.96 (m, 1 H, CβH-3), 3.87 (dddd, *J* = 3.1, 4.7, 7.7, 12.6 Hz, 1 H, CβH-2), 3.75 (m, 1 H, CβH-1), 3.72 (s, 3 H, COOMe), 3.63 (dddd, *J* = 5.1, 6.2, 6.6, 13.3 Hz, 1 H, CβH-4), 3.48 (d, *J* = 9.5 Hz, 1 H, CαH-3), 3.46 (d, *J* = 9.8 Hz, 1 H, CαH-1), 3.43 (m, 1 H, Cβ′H-4), 3.43 (m, 1 H, Cε′H-3), 3.35 (dt, *J* = 2.1, 11.9 Hz, 1 H, Cε′H-1), 3.08 (ddt, *J* = 1.9, 4.7, 12.6 Hz, 1 H, Cβ′H-2), 2.65 (ddd, *J* = 5.2, 7.7, 17.4 Hz, 1 H, Cα′H-4), 2.55 (ddd, *J* = 5.1, 6.2, 17.4 Hz, 1 H, Cα′H-4), 2.25 (dt, *J* = 3.1, 12.4 Hz, 1 H, CαH-2), 2.13 (ddd, *J* = 1.9, 4.7, 12.4 Hz, 1 H, Cα′H-2), 2.10 (m, 1 H, CγH-1), 2.00 (m, 1 H, CγH-3), 1.77 (m, 1 H, CδH-3), 1.73 (m, 1 H, CδH-1), 1.69 (m, 1 H, Cδ′H-3), 1.69 (m, 1 H, Cδ′H-1), 1.59 (dq, *J* = 3.7, 12.4 Hz, 1 H, Cγ′H-3), 1.43 (s, 9 H, Boc), 1.39 (dq, *J* = 3.9, 12.5 Hz, 1 H, Cγ′H-1) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.3, 172.1, 169.9, 169.6, 155.7, 83.9, 81.4, 80.1, 67.4, 67.3, 51.8, 49.7, 47.8, 37.4, 36.7, 34.2, 33.3, 31.3, 29.7, 28.3 (3 C), 25.5, 25.1 ppm. HRMS (ESI): calcd. for $C_{24}H_{40}N_4O_9Na$ $[M + Na]^+$ 551.2687; found 551.2682.

(*S*,*S*)-APyC-β-hGly-(*S*,*S*)-APyC-β-hGly-(*S*,*S*)-APyC-β-hGly-OMe (2): LiOH (0.01 g, 0.46 mmol) was added to a solution of ester **1** (0.11 g, 0.18 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave **1a**, which was used as such for further reaction.

A solution of acid **1a** (0.09 g, 0.15 mmol), HOBt (0.02 g, 0.18 mmol), and EDCI (0.03 g, 0.18 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 15 min. Then **19b** [prepared from **19** (0.05 g, 0.154 mmol) and CF_3COOH (0.2 mL) in CH_2Cl_2 (2 mL)] and DIPEA (0.04 mL, 0.23 mmol) were added, and the mixture was stirred under a nitrogen atmosphere for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 3.0% methanol in $CHCl_3$), gave **2** (0.04 g, 38%) as a white solid, m.p. 212–216 °C. $[a]_D$ = +370 (*c* = 0.12, $CHCl_3$). IR (KBr): ṽ = 3298, 3092, 2940, 2855, 1732, 1887, 1653, 1553, 1443, 1365, 1310, 1177, 1090, 1054, 651 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 288 K): δ = 8.67 (dd, *J* = 4.5, 8.4 Hz, 1 H, NH-4), 8.62 (dd, *J* = 4.8,7.9 Hz, 1 H, NH-2), 8.28 (d, *J* = 9.3 Hz, 1 H, NH-5), 8.12 (d, *J* = 9.6 Hz, 1 H, NH-3), 6.97 (t, *J* = 6.3 Hz, 1 H, NH-6), 4.78 (d, *J* = 10.3 Hz, 1 H, NH-1), 4.07 (m, 1 H, CεH-1), 4.05 (m, 2 H, CεH-3, CεH-5), 4.04 (m, 1 H, CβH-3), 3.98 (m, 1 H, CβH-5), 3.93 (m, 1 H, CβH-4), 3.89 (m, 1 H, CβH-2), 3.78 (m,

1 H, CβH-1), 3.72 (s, 3 H, COOMe), 3.67 (m, 1 H, CβH-6), 3.50 (d, *J* = 9.9 Hz, 1 H, CαH-3), 3.47 (d, *J* = 9.9 Hz, 1 H, CαH-1), 3.44 (d, *J* = 9.7 Hz, 1 H, CαH-5), 3.43 (m, 1 H, Cβ′H-6), 3.40 (m, 1 H, Cε′H-3), 3.37 (m, 1 H, Cε′H-5), 3.36 (m, 1 H, Cε′H-1), 3.04 (m, 1 H, Cβ′H-4), 2.99 (m, 1 H, β′H-2), 2.70 (ddd, *J* = 4.8, 8.1, 17.3 Hz, 1 H, CαH-6), 2.57 (ddd, *J* = 4.8, 6.3, 17.4 Hz, 1 H, Cα′H-6), 2.33 (m, 2 H, CαH-2, CαH-4), 2.15 (m, 1 H, Cα′H-2), 2.12 (m, 1 H, CγH-1), 2.08 (m, 1 H, Cα′H-4), 2.06 (m, 1 H, CγH-5), 2.04 (m, 1 H, CγH-3), 1.81 (m, 1 H, CδH-1), 1.77 (m, 1 H, CδH-3), 1.73 (m, 2 H, CδH-5, Cγ′H-5), 1.70 (m, 1 H, Cδ′H-1), 1.68 (m, 2 H, Cδ′H-5, Cδ′H-3), 1.54 (m, 1 H, Cγ′H-3), 1.43 (m, 9 H, Boc), 1.42 (m, 1 H, Cγ′H-1) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): *δ* = 173.5, 173.0, 172.5, 170.1, 170.0, 169.7, 155.9, 83.5, 83.2, 82.0, 80.3, 67.6, 67.4, 67.3, 51.9, 50.0, 48.5, 47.8, 37.5, 37.0, 36.8, 34.3, 33.4, 31.4, 29.9, 29.6, 28.4, 25.7, 25.5, 25.2 ppm. HRMS (ESI): calcd. for $C_{33}H_{54}N_6O_{12}Na$ [M + Na]$^+$ 749.3691; found 749.3698.

Boc-(*R*,*R*)-APyC-β-hGly-OMe (*ent*-19): LiOH (0.10 g, 4.3 mmol) was added to a solution of *ent*-**7** (0.45 g, 1.7 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave **17**, which was used as such for further reaction.

A solution of acid **17** (0.4 g, 1.7 mmol), HOBt (0.31 g, 2.08 mmol), and EDCI (0.39 g, 2.08 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C for 15 min, and then salt **18** (0.39 g, 2.93 mmol) and DIPEA (0.45 mL, 2.6 mmol) were added under a nitrogen atmosphere. The mixture was stirred at room temperature for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 50% ethyl acetate in petroleum ether), gave *ent*-**19** (0.38 g, 66%) as a white solid, m.p. 103–105 °C. $[a]_D$ = –190 (*c* = 0.03, $CHCl_3$). IR (KBr): ṽ = 3385, 3108, 2926, 2855, 1739, 1700, 1656, 1570, 1522, 1448, 1374, 1309, 1252, 1169, 1120, 1088, 1029, 957, 900, 870, 689, 614 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 288 K): *δ* = 6.90 (s, 1 H, NH-2), 5.32 (s, 1 H, NH-1), 3.91 (d, *J* = 10.8 Hz, 1 H, CαH-1), 3.65 (s, 3 H, $COOCH_3$), 3.51–3.33 (m, 5 H, CβH-1, CεH-1, Cε′H-1, CβH-2, Cβ′H-2), 2.50 (m, 2 H, CαH-2, Cα′H-2), 2.3 (d, *J* = 10 Hz, 2 H, CγH-1, Cγ′H-1), 1.72–1.52 (m, 2 H, CδH-1, Cδ′H-1), 1.37 (s, 9 H, Boc) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 172.8, 169.8, 155.5, 79.6, 79.2, 67.6, 51.7, 50.3, 34.1, 33.4, 30.5, 28.2 (3 C), 24.5 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}N_2O_6Na$ [M + Na]$^+$ 353.1688; found 353.1687.

Boc-(*R*,*R*)-APyC-β-hGly-(*R*,*R*)-APyC-β-hGly-OMe (*ent*-1): LiOH (0.02 g, 0.98 mmol) was added to a solution of ester *ent*-**19** (0.13 g, 0.39 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave *ent*-**19a**, which was used as such for further reaction.

A solution of acid *ent*-**19a** (0.12 g, 0.39 mmol), HOBt (0.07 g, 0.47 mmol), and EDCI (0.09 g, 0.47 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under a nitrogen atmosphere for 15 min. Salt *ent*-**19b** [prepared from *ent*-**19** (0.12 g, 0.39 mmol) and CF_3COOH (0.1 mL) in dry CH_2Cl_2 (1 mL) at 0 °C] and DIPEA (0.1 mL, 0.5 mmol) were then added sequentially, and the mixture was stirred for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 1.5% methanol in $CHCl_3$), gave *ent*-**1** (0.1 g, 46%) as a white solid, m.p. 188–190 °C. $[a]_D$ = –228.1 (*c* = 0.235, $CHCl_3$). IR (KBr): ṽ = 3290, 3093, 2927, 2855, 1742, 1662, 1556, 1446, 1369, 1310, 1246, 1172, 1090, 957, 683 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): *δ* = 8.40 (dd, *J* = 4.7, 7.7 Hz, 1 H, NH-2), 7.68 (d, *J* = 9.2 Hz, 1 H, NH-3), 6.94 (t, *J* = 6.3 Hz, 1 H, NH-4), 4.80 (d, *J* = 10.1 Hz, 1 H, NH-1), 4.03 (m, 1 H, CεH-3), 4.02 (m, 1 H, CεH-1), 3.96 (m, 1 H, CβH-3), 3.86 (dddd, *J* = 3.1, 4.7, 7.7, 12.6 Hz, 1 H, CβH-2), 3.75 (m, 1 H, CβH-1), 3.71 (s, 3 H, COOMe) 3.62 (dddd, *J* = 5.1, 6.2, 6.6, 13.3 Hz, 1 H, CβH-4), 3.48 (d, *J* = 9.4 Hz, 1 H, CαH-3), 3.46 (d, *J* = 9.7 Hz, 1 H, CαH-1), 3.43 (m, 2 H, Cε′H-3, Cβ′H-4), 3.35 (dt, *J* = 2.1, 11.9 Hz, 1 H, Cε′H-1), 3.08 (ddt, *J* = 1.9, 4.7, 12.6 Hz, 1 H, Cβ′H-2), 2.65 (ddd, *J* = 5.2, 7.7, 17.4 Hz, 1 H, CαH-4), 2.56 (ddd, *J* = 5.1, 6.2, 17.4 Hz, 1 H, Cα′H-4), 2.25 (dt, *J* = 3.1, 12.4 Hz, 1 H, CαH-2), 2.13 (ddd, *J* = 1.9, 4.7, 12.4 Hz, 1 H, Cα′H-2), 2.10 (m, 1 H, CγH-1), 2.0 (m, 1 H, CγH-3), 1.77 (m, 1 H, CδH-3), 1.73 (m, 1 H, CδH-1), 1.70 (m, 1 H, Cδ′H-3), 1.68 (m, 1 H, Cδ′H-1), 1.59 (dq, *J* = 3.7, 12.4 Hz, 1 H, Cγ′H-3), 1.42 (s, 9 H, Boc), 1.39 (dq, *J* = 4.1, 12.5 Hz, 1 H, Cγ′H-1) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): *δ* = 173.1, 172.0, 169.9, 169.6, 155.7, 83.2, 81.4, 80.0, 67.4, 67.3, 51.7, 49.9, 47.9, 37.4, 36.7, 34.2, 33.4, 31.3, 29.8, 28.7 (3 C), 25.5, 25.1 ppm. HRMS (ESI): calcd. for $C_{24}H_{40}N_4O_9Na$ [M + Na]$^+$ 551.2692; found 551.2685.

(*R*,*R*)-APyC-β-hGly-(*R*,*R*)-APyC-β-hGly-(*R*,*R*)-APyC-β-hGly-OMe (*ent*-2): LiOH (0.01 g, 0.45 mmol) was added to a solution of ester *ent*-**1** (0.1 g, 0.18 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave *ent*-**1a**, which was used as such for further reaction.

A solution of acid *ent*-**1a** (0.09 g, 0.18 mmol), HOBt (0.03 g, 0.22 mmol), and EDCI (0.04 g, 0.22 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 15 min. Then *ent*-**19b** [prepared from *ent*-**19** (0.06 g, 0.18 mmol) and CF_3COOH (0.2 mL) in CH_2Cl_2 (2 mL)] and DIPEA (0.04 mL, 0.27 mmol) were added, and the mixture was stirred under a nitrogen atmosphere for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 3.0% methanol in $CHCl_3$), gave *ent*-**2** (0.06 g, 46%) as a white solid, m.p. 212–216 °C. $[a]_D$ = –380.6 (*c* = 0.31, $CHCl_3$). IR (KBr): ṽ = 3295, 3091, 2927, 2853, 1741, 1688, 1660, 1551, 1442, 1369, 1310, 1245, 1173, 1090, 1060, 1034, 956, 872, 653, 583 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 288 K): *δ* = 8.64 (dd, *J* = 8.3, 4.4 Hz, 1 H, NH-4), 8.60 (dd, *J* = 4.7, 7.8 Hz, 1 H, NH-2), 8.26 (d, *J* = 9.3 Hz, 1 H, NH-5), 8.09 (d, *J* = 9.7 Hz, 1 H, NH-3), 6.96 (t, *J* = 6.3 Hz, 1 H, NH-6), 4.77 (d, *J* = 10.4 Hz, 1 H, NH-1), 4.06 (m, *J* = 9.4 Hz, 1 H, CεH-1), 4.04 (m, 3 H, CεH-3, CεH-5, CβH-3), 3.99 (m, 1 H, CβH-5), 3.93 (m, 1 H, CβH-4), 3.90 (m, 1 H, CβH-2), 3.76 (m, 1 H, CβH-1), 3.72 (s, 3 H, COOMe), 3.66 (ddt, *J* = 13.7, 4.9, 6.3 Hz, 1 H, CβH-6), 3.50 (d, *J* = 9.7 Hz, 1 H, CαH-3), 3.47 (d, *J* = 9.9 Hz, 1 H, CαH-1), 3.44 (d, *J* = 9.6 Hz, 1 H, CαH-5), 3.42 (m, 1 H, Cβ′H-6), 3.41 (m, 1 H, Cε′H-3), 3.37 (m, 1 H, Cε′H-5), 3.35 (m, 1 H, Cε′H-1), 3.04 (ddt, *J* = 1.8, 4.6, 13.2 Hz, 1 H, Cβ′H-4), 3.0 (ddt, *J* = 1.8, 4.7, 12.8 Hz, 1 H, βH-2), 2.69 (ddd, *J* = 4.9, 8.1, 17.3 Hz, 1 H, CαH-6), 2.57 (ddd, *J* = 4.7,6.3, 17.3 Hz, 1 H, Cα′H-6), 2.33 (dt, *J* = 6.1, 12.1 Hz, 1 H, CαH-2), 2.33 (dt, *J* = 6.5, 12.2 Hz, 1 H, CαH-4), 2.14 (m, 1 H, Cα′H-2), 2.11 (m, 1 H, CγH-1), 2.07 (m, 1 H, Cα′H-4), 2.06 (m, 1 H, CγH-5), 2.03 (m, 1 H, CγH-3), 1.81 (m, 1 H, CδH-1), 1.77 (m, 1 H, CδH-5), 1.74 (m, 2 H, CδH-3, Cδ′H-3), 1.70 (m, 1 H, Cδ′H-1), 1.68 (m, 1 H, Cδ′H-5), 1.67 (m, 1 H, Cγ′H-3), 1.54 (dq, 1 H, Cγ′H-5), 1.42 (s, 9 H, Boc), 1.41 (dq, *J* = 3.7, 12.8 Hz, 1 H, Cγ′H-1) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): *δ* = 173.2, 172.7, 171.3, 169.9, 169.5, 169.4, 155.8, 82.7, 81.7, 80.0, 79.6, 67.6, 67.4 (2 C), 52.4, 50.0, 48.7, 48.4, 47.7, 47.2, 46.6, 30.6, 29.5, 29.3, 28.1 (3 C), 25.4, 25.2, 25.0, 18.1, 17.1, 17.0 ppm. HRMS (ESI): calcd. for $C_{33}H_{54}N_6O_{12}Na$ [M + Na]$^+$ 749.3687; found 749.3687.

(*S*,*S*)-APyC-β-hGly-(*S*,*S*)-APyC-β-hGly-(*R*,*R*)-APyC-β-hGly-(*R*,*R*)-APyC-β-hGly-OMe (3): LiOH (0.01 g, 0.47 mmol) was added to a solution of ester **1** (0.1 g, 0.18 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room tempera-

ture for 2 h. Work-up as described for **7a** gave **1a**, which was used as such for further reaction.

A solution of acid **1a** (0.07 g, 0.13 mmol), HOBt (0.025 g, 0.163 mmol), and EDCI (0.03 g, 0.16 mmol) in CH_2Cl_2 (15 mL) was stirred at 0 °C for 15 min. Salt *ent*-**1b** [prepared from *ent*-**1** (0.08 g, 0.16 mmol) and CF_3COOH (0.2 mL) in CH_2Cl_2 (2 mL)] and DIPEA (0.34 mL, 0.20 mmol) were added, and the mixture was stirred under a nitrogen atmosphere for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 4.5% methanol in $CHCl_3$), gave **3** (0.49 g, 75%) as a white solid, m.p. 248–250 °C. $[\alpha]_D$ = +4.5 (*c* = 0.22, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3305, 2926, 2855, 1659, 1540, 1446, 1374, 1304, 1249, 1175, 1089, 760, 577 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 278 K): δ = 8.55 (dd, *J* = 4.2, 8.1 Hz, 1 H, NH-6), 8.38 (dd, *J* = 4.7, 7.4 Hz, 1 H, NH-2), 7.99 (d, *J* = 9.4 Hz, 1 H, NH-3), 7.88 (d, *J* = 9.2 Hz, 1 H, NH-7), 7.81 (d, *J* = 19.8 Hz, 1 H, NH-5), 6.98 (t, *J* = 6.1 Hz, 1 H, NH-8), 6.89 (t, *J* = 6.3 Hz, 1 H, NH-4), 4.83 (d, *J* = 10.2 Hz, 1 H, NH-1), 4.09 (m, 1 H, CβH -5), 4.06 (m, 1 H, CεH-7), 4.04 (m, 1 H, CεH-1), 4.03 (m, 1 H, CεH-3), 4.01 (m, 1 H, CεH-5), 4.00 (m, 1 H, CβH-7), 3.88 (m, 2 H, CβH-2, CβH-3), 3.87 (m, 1 H, CβH-6), 3.78 (m, 1 H, CβH-4), 3.72 (s, 3 H, COOMe), 3.71 (m, 1 H, CβH-1), 3.64 (m, 1 H, CβH-8), 3.59 (d, *J* = 9.8 Hz, 1 H, CαH-5), 3.51 (d, *J* = 9.8 Hz, 1 H, CαH-7), 3.48 (m, 1 H, Cε′H-1), 3.48 (d, *J* = 9.8 Hz, 1 H, CαH-1), 3.48 (d, *J* = 9.8 Hz, 1 H, CαH-3), 3.44 (m, 2 H, Cε′H-3, Cε′H-7), 3.43 (m, 1 H, Cβ′H-8), 3.38 (m, 1 H, Cε′H-5), 3.24 (m, 1 H, Cβ′H-4), 3.07 (m, 2 H, Cβ′H-2, Cβ′H-6), 2.67 (ddd, *J* = 4.9, 7.9, 17.4 Hz, 1 H, CαH-8), 2.56 (ddd, *J* = 4.9, 6.2, 17.4 Hz, 1 H, Cα′H-8), 2.48 (ddd, *J* = 3.7, 10.9, 13.9 Hz, 1 H, CαH-4), 2.31 (dt, *J* = 3.2, 12.4 Hz, 1 H, CαH-2), 2.25 (ddd, *J* = 3.2, 5.0, 13.9 Hz, 1 H, Cα′H-4), 2.21 (dt, *J* = 3.3, 12.3 Hz, 1 H, CαH-6), 2.18 (m, 1 H, Cα′H-2), 2.12 (ddd, *J* = 2.2, 4.5, 12.3 Hz, 1 H, Cα′H-6), 2.10 (m, 1 H, CγH-1), 2.07 (m, 1 H, CγH-7), 2.03 (m, 2 H, CγH-3, CγH-5), 1.79 (m, 1 H, CδH-7), 1.76 (m, 1 H, CδH-3), 1.75 (m, 1 H, CδH-1), 1.74 (m, 1 H, CδH-5), 1.71 (m, 1 H, Cδ′H-1), 1.70 (m, 1 H, Cδ′H-7), 1.69 (m, 1 H, δ′H-3), 1.68 (m, 1 H, Cγ′H-3), 1.67 (m, 1 H, Cδ′H-5), 1.65 (m, 1 H, Cγ′H-5), 1.64 (m, 1 H, Cγ′H-7), 1.43 (s, 9 H, Boc), 1.41 (m, 1 H, Cγ′H-1) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 173.6, 172.5, 172.4, 172.1, 170.2, 170.1, 169.8, 169.7, 156.0, 82.9, 82.4, 81.9, 81.5, 80.1, 67.5 (2 C), 67.4, 67.2, 51.7, 50.0, 48.6, 48.5, 48.0, 37.2, 36.7, 36.6, 36.2, 36.0, 34.4, 33.5, 31.9, 29.7 (2 C), 29.6, 29.6, 28.4 (3 C), 25.5, 25.4, 25.2, 24.9 ppm. HRMS (ESI): calcd. for $C_{42}H_{68}N_8O_{15}Na$ $[M + Na]^+$ 947.4701; found 947.4683.

Boc-(*R*,*R*)-APyC-L-Ala-OMe (21): LiOH (0.106 g, 4.4 mmol) was added to a solution of *ent*-**7** (0.46 g, 1.77 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave **17**, which was used as such for the next reaction.

A solution of acid **17** (0.4 g, 1.63 mmol), HOBt (0.37 g, 1.95 mmol), and EDCI (0.26 g, 1.95 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C for 15 min. Salt **20** (0.27 g, 1.95 mmol) was added, and the mixture was stirred under a nitrogen atmosphere at room temperature for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 50% ethyl acetate in petroleum ether), gave **21** (0.72 g, 90%) as a white solid, m.p. 145–147 °C. $[\alpha]_D$ = –40.55 (*c* = 0.12, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3358, 3259, 3084, 2945, 2853, 1757, 1698, 1658, 1659, 1527, 1365, 1310, 1250, 1167, 1092, 1039, 973, 909, 856, 774, 616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 288 K): δ = 7.01 (d, 1 H, *J* = 7.17 Hz, NH-2), 5.35 (s, 1 H, NH-1), 4.58 (m, 1 H, CαH-2), 4.00 (d, *J* = 11.3 Hz, 1 H, CαH-1), 3.76 (s, 3 H, $COOCH_3$), 3.62 (m, 1 H, CβH-1), 3.56–3.44 (m, 2 H, CεH-1, Cε′H-1), 2.40 (dd, *J* = 1.8, 9.82 Hz, 1 H, CγH-1), 1.61 (m, 3 H, Cγ′H-1, CδH-1, Cδ′H-1), 1.47–1.37 (m, 12 H, Boc, CH_3-2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 169.4, 155.5, 79.2, 78.9, 67.5, 52.4, 50.0, 47.5, 30.1, 28.3 (3 C), 24.1, 18.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}N_2O_6Na$ $[M + Na]^+$ 353.1688; found 353.1680.

Boc-(*R*,*R*)-APyC-L-Ala-(*R*,*R*)-APyC-L-Ala-OMe (4): LiOH (0.02 g, 1.13 mmol) was added to a solution of ester **21** (0.15 g, 0.45 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave **21a**, which was used as such for further reaction.

A solution of acid **21a** (0.06 g, 0.31 mmol), HOBt (0.07 g, 0.55 mmol), and EDCI (0.10 g, 0.55 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under a nitrogen atmosphere for 15 min. Then salt **21b** [prepared from **21** (0.15 g, 0.45 mmol) and CF_3COOH (0.1 mL) in dry CH_2Cl_2 (1 mL) at 0 °C] and DIPEA (0.11 mL, 0.68 mmol) were added sequentially, and the mixture was stirred for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 1.5% methanol in $CHCl_3$), gave **4** (0.13 g, 47%) as a white solid, m.p. 225–228 °C. $[\alpha]_D$ = –256.1 (*c* = 0.12, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 3086, 2931, 2854, 1734, 1689, 1664, 1543, 1453, 1368, 1312, 1250, 1165, 1093, 1054, 964, 662 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 278 K): δ = 7.50 (d, *J* = 8.3 Hz, 1 H, NH-3), 7.15 (d, *J* = 9.1 Hz, 1 H, NH-2), 6.98 (d, *J* = 7.2 Hz, 1 H, NH-4), 4.76 (d, *J* = 9.2 Hz, 1 H, NH-1), 4.60 (dq, *J* = 9.1, 7.0 Hz, 1 H, CαH-2), 4.51 (q, *J* = 7.2 Hz, 1 H, CαH-4), 4.03 (m, 1 H, CεH-3), 4.01 (m, 1 H, CεH-1), 3.94 (m, 1 H, CβH-3), 3.83 (m, 1 H, CβH-1), 3.78 (d, *J* = 10 Hz, 1 H, CαH-3), 3.76 (s, 3 H, $COOCH_3$), 3.47 (d, *J* = 9.6 Hz, 1 H, CαH-1), 3.43 (dt, *J* = 2.4, 11.9 Hz, 1 H, Cε′H-3), 3.37 (dt, *J* = 2.3, 12.0 Hz, 1 H, Cε′H-1), 2.14 (m, 1 H, CγH-3), 2.11 (m, 1 H, CγH-1), 1.82 (m, 1 H, CδH-1), 1.79 (m, 1 H, CδH-3), 1.67 (m, 1 H, Cδ′H-1), 1.66 (m, 1 H, Cδ′H-3), 1.62 (dq, *J* = 3.9, 12.6 Hz, 1 H, Cγ′H-3), 1.42 (s, 9 H, Boc), 1.42 (d, *J* = 7.2 Hz, 3 H, CH_3-4), 1.39 (dq, *J* = 3.8, 12.5 Hz, 1 H, Cγ′H-1), 1.30 (d, *J* = 7.0 Hz, 3 H, CH_3-2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 171.5, 169.2, 169.4, 155.7, 82.3, 79.8, 79.9, 67.4, 67.7, 52.4, 49.7, 47.0, 47.7, 48.5, 30.7, 28.22 (3 C), 30.0, 31.5, 25.0, 16.9, 18.0 ppm. HRMS (ESI): calcd. for $C_{24}H_{40}N_4O_9Na$ $[M + Na]^+$ 551.2692; found 551.2685.

Boc-(*R*,*R*)-APyC-L-Ala-(*R*,*R*)-APyC-L-Ala-(*R*,*R*)-APyC-L-Ala-OMe (5): LiOH (0.01 g, 0.46 mmol) was added to a solution of ester **4** (0.12 g, 0.18 mmol) in THF/MeOH/H_2O (3:1:1) at 0 °C, and the mixture was stirred at room temperature for 2 h. Work-up as described for **7a** gave **4a**, which was used as such for further reaction.

A solution of acid **4a** (0.09 g, 0.15 mmol), HOBt (0.03 g, 0.18 mmol), and EDCI (0.03 g, 0.18 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under a nitrogen atmosphere for 15 min. Salt **21b** [prepared from **21** (0.05 g, 0.15 mmol) and CF_3COOH (0.1 mL) in dry CH_2Cl_2 (1 mL) at 0 °C] and DIPEA (0.04 mL, 0.23 mmol) were added sequentially, and the mixture was stirred for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 2.5% methanol in $CHCl_3$), gave **5** (0.05 g, 38%) as a white solid, m.p. 296–298 °C. $[\alpha]_D$ = –266.5 (*c* = 0.16, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3299, 3088, 2965, 2931, 2854, 1728, 1690, 1657, 1550, 1451, 1370, 1309, 1290, 1247, 1165, 1094, 1052, 964, 670 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 288 K): δ = 7.63 (d, *J* = 9.8 Hz, 1 H, NH-3), 7.43 (d, *J* = 8.4 Hz, 1 H, NH-5), 7.24 (d, *J* = 9.4 Hz, 1 H, NH-2), 7.10 (d, *J* = 7.4 Hz, 1 H, NH-6), 7.07 (d, *J* = 9.1 Hz, 1 H, NH-4), 4.79 (d, *J* = 9.9 Hz, 1 H, NH-1), 4.64 (dq, *J* = 9.4, 7.0 Hz, 1 H, CαH-2), 4.57 (dq, *J* = 9.1, 7.0 Hz, 1 H, CαH-4), 4.54 (p, *J* = 7.4 Hz, 1 H, CαH-6), 4.15

(dq, J = 4.0, 9.8 Hz, 1 H, CβH-3), 4.07 (m, 1 H, CεH-1), 4.02 (m, 1 H, CεH-3), 4.00 (m, 1 H, CεH-5), 3.98 (m, 1 H, CβH-5), 3.93 (d, J = 9.7 Hz, 1 H, CαH-5), 3.78 (s, 3 H, -$COOCH_3$), 3.76 (m, 1 H, CβH-1), 3.58 (d, J = 9.8 Hz, 1 H, CαH-3), 3.48 (d, J = 9.6 Hz, 1 H, CαH-1), 3.46 (m, 1 H, Cε′H-5), 3.43 (m, 1 H, Cε′H-3), 3.37 (m, 1 H, Cε′H-1), 2.10 (m, 1 H, CγH-1), 2.10 (m, 1 H, CγH-5), 2.20 (m, 1 H, CδH-3), 1.85 (m, 1 H, CδH-1), 1.79 (m, 1 H, CδH-3), 1.77 (m, 1 H, CδH-5), 1.76 (m, 1 H, Cγ′H-3), 1.75 (m, 1 H, Cγ′H-5), 1.7 (m, 1 H, Cδ′H-1), 1.68 (m, 1 H, Cδ′H-3), 1.66 (m, 1 H, Cδ′H-5), 1.46 (m, 1 H, Cγ′H-1), 1.42 (d, J = 7.4 Hz, 3 H, CH_3-6), 1.47 (s, 9 H, Boc), 1.33 (d, J = 7.0 Hz, 3 H, CH_3-4), 1.25 (d, J = 7.0 Hz, 3 H, CH_3-2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.1, 172.6, 171.3 169.9, 169.5, 169.3, 155.8, 82.6, 81.7, 79.9, 79.6, 67.6, 67.4 (2 C), 52.3, 50.5, 48.7, 48.4, 47.7, 47.2, 46.7, 30.6, 29.6, 29.3, 28.1 (3 C), 25.4, 25.2, 25.0, 18.1, 17.1, 16.9 ppm. HRMS (ESI): calcd. for $C_{33}H_{54}N_6O_{12}Na$ $[M + Na]^+$ 749.3697; found 749.3667.

Boc-(*S*,*S*)-APyC-L-Ala-(*S*,*S*)-APyC-L-Ala-(*R*,*R*)-APyC-L-Ala-(*R*,*R*)-APyC-L-Ala-OMe (6): A solution of acid *ent*-**4a**[10] (0.04 g, 0.87 mmol), HOBt (0.02 g, 0.10 mmol), and EDCI (0.02 g, 0.105 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under a nitrogen atmosphere for 15 min. Then salt **4b** [prepared from **4** (0.05 g, 0.10 mmol) and CF_3COOH (0.1 mL) in dry CH_2Cl_2 (1 mL) at 0 °C] and DIPEA (0.17 mL, 0.13 mmol) were added sequentially, and the mixture was stirred for 8 h. Work-up as described for **19**, and purification of the residue by column chromatography (60–120 mesh silica gel, 3.0% methanol in $CHCl_3$), gave **6** (0.15 g, 75%) as a white solid, m.p. 321–324 °C. $[\alpha]_D$ = +1.78 (c = 0.14, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3298, 2923, 2853, 1652, 1539, 1453, 1371, 1346, 1311, 1219, 1162, 1091, 965, 772 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 288 K): δ = 7.73 (d, J = 9.8 Hz, 1 H, NH-2), 7.62 (d, J = 10 Hz, 1 H, NH-3), 7.51 (d, J = 8.5 Hz, 1 H, NH-7), 7.37 (d, J = 9.5 Hz, 1 H, NH-5), 7.11 (d, J = 7.5 Hz, 1 H, NH-8), 7.0 (d, J = 9.0 Hz, 1 H, NH-7), 6.45 (d, J = 9.8 Hz, 1 H, NH-4), 4.86 (d, J = 10 Hz, 1 H, NH-1), 4.70 (dq, J = 9.8, 7.0 Hz, 1 H, CαH-2), 4.66 (dq, J = 9.8, 7.0 Hz, 1 H, CαH-4), 4.55 (dq, J = 9.0, 7.0 Hz, 1 H, CαH-6), 4.54 (dq, J = 7.5, 7.0 Hz, 1 H, CαH-8), 4.08 (m, 2 H, CεH-1, CβH-5), 4.04 (m, 1 H, CεH-7), 4.00 (m, 2 H, CεH-3, CεH-5), 3.98 (m, 2 H, CαH-7, CβH-7), 3.97 (m, 1 H, CαH-3), 3.83 (d, J = 9.8 Hz, 1 H, CαH-5), 3.76 (s, 3 H, -$COOCH_3$), 3.73 (m, 1 H, CβH-1), 3.67 (d, J = 9.8 Hz, 1 H, CαH-3), 3.52 (d, J = 9.5 Hz, 1 H, CαH-1), 3.45 (m, 1 H, Cε′H-3), 3.43 (m, 1 H, Cε′H-7), 3.39 (m, 1 H, Cε′H-5), 3.37 (m, 1 H, Cε′H-1), 2.10 (m, 1 H, CγH-1), 2.09 (m, 1 H, CγH-7), 2.0 (m, 1 H, CγH-3), 1.99 (m, 1 H, CγH-5), 2.0 (m, 1 H, CδH-5), 1.86 (m, 1 H, CδH-3), 1.85 (m, 1 H, CδH-7), 1.83 (m, 1 H, CδH-1), 1.8 (m, 1 H, Cγ′H-3), 1.79 (m, 2 H, Cδ′H-7, Cδ′H-5), 1.75 (m, 1 H, Cδ′H-3), 1.69 (m, 1 H, Cδ′H-5), 1.68 (m, 1 H, Cδ′H-1), 1.67 (m, 1 H, Cγ′H-7), 1.43 (s, 9 H, Boc), 1.42 (m, 1 H, Cγ′H-1), 1.42 (m, J = 7.0 Hz, 3 H, CH_3-8), 1.37 (d, J = 7 Hz, 6 H, CH_3-4, CH_3-6), 1.33 (s, J = 7 Hz, 3 H, CH_3-2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.3, 173.1, 171.9, 171.4, 170.2, 170, 169.9, 169.4, 155.7, 81.8, 81.1, 80.4, 79.7 (2 C), 67.8, 67.5, 67.4, 67.2, 52.4, 49.8, 49.1, 48.7, 48.5, 47.7, 47.4, 47.0, 46.4, 30.7, 29.8, 29.7, 29.4, 29.2, 28.2 (3 C), 25.4, 25.3, 25.1, 18.2, 17.5, 17.0, 16.7 ppm. HRMS (ESI): calcd. for $C_{42}H_{68}N_8O_{15}Na$ $[M + Na]^+$ 947.4701; found 947.4683.

Supporting Information (see footnote on the first page of this article): NMR (^{1}H, ^{13}C, 2D) spectra, solvent titration studies, minimum energy structures and distant constraints used in the MD calculations for all the compounds of interest are available.

Supporting Information (see footnote on the first page of this article): General; solvent titration studies; NMR data; molecular dynamics; CD spectra; quantum chemical calculations.

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[1] a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; b) J. Applequist, K. A. Bode, D. H. Appella, L. A. Christianson, S. H. Gellman, *J. Am. Chem. Soc.* **1998**, *120*, 4891; c) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893; d) C. M. Goodman, S. Choi, S. Shandler, W. F. DeGrado, *Nat. Chem. Biol.* **2007**, *3*, 252; e) D. Seebach, A. K. Beck, D. J. Bierbaum, *Chem. Biodiversity* **2004**, *1*, 1111; f) W. S. Horne, S. H. Gellman, *Acc. Chem. Res.* **2008**, *41*, 1399; g) P. Prabhakaran, G. Priya, G. J. Sanjayan, *Angew. Chem. Int. Ed.* **2012**, *51*, 4006; *Angew. Chem.* **2012**, *124*, 4079.

[2] a) M. A. Schmitt, B. Weisblum, S. H. Gellman, *J. Am. Chem. Soc.* **2004**, *126*, 6848; b) J. L. Price, W. S. Horne, S. H. Gellman, *J. Am. Chem. Soc.* **2007**, *129*, 6376; c) C. Baldauf, R. Günther, H.-J. Hofmann, *J. Org. Chem.* **2006**, *71*, 1200; d) G. V. M. Sharma, V. B. Jadhav, K. V. S. Ramakrishna, P. Jayaprakash, K. Narsimulu, V. Subash, A. C. Kunwar, *J. Am. Chem. Soc.* **2006**, *128*, 14657; e) S. Chandrasekhar, M. S. Reddy, B. Jagadeesh, A. Prabhakar, M. H. V. Ramana Rao, B. Jagannadh, *J. Am. Chem. Soc.* **2004**, *126*, 13586; f) G. Srinivasulu, S. K. Kumar, G. V. M. Sharma, A. C. Kunwar, *J. Org. Chem.* **2006**, *71*, 8395; g) D. Seebach, L. Matthews, *J. Chem. Soc. Chem. Commun.* **1997**, 2015; h) K. Gademann, T. Hintermann, J. V. Schreiber, *Curr. Med. Chem.* **1999**, *6*, 905; i) I. M. Mándity, E. Wéber, T. A. Martinek, G. Olajos, G. K. Tóth, E. Vass, F. Fülöp, *Angew. Chem. Int. Ed.* **2009**, *48*, 2171; *Angew. Chem.* **2009**, *121*, 2205; j) C. Baldauf, H.-J. Hofmann, *Helv. Chim. Acta* **2012**, *95*, 2348.

[3] a) W. F. DeGrado, J. P. Schneider, Y. Hamuro, *J. Pept. Res.* **1999**, *54*, 206; b) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219; c) D. Seebach, M. Overhand, F. N. M. Kuhnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913; d) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 13071; e) D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi, S. H. Gellman, *Nature* **1997**, *387*, 381; f) D. Seebach, K. Gademann, J. V. Schreiber, J. L. Matthews, T. Hintermann, B. Jaun, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1997**, *80*, 2033; g) G. V. M. Sharma, K. R. Reddy, P. R. Krishna, A. R. Sankar, P. Jayaprakash, B. Jagannadh, A. C. Kunwar, *Angew. Chem. Int. Ed.* **2004**, *43*, 3961; *Angew. Chem.* **2004**, *116*, 4051; h) G. V. M. Sharma, V. Subash, K. Narsimulu, A. R. Sankar, A. C. Kunwar, *Angew. Chem. Int. Ed.* **2006**, *45*, 8207; *Angew. Chem.* **2006**, *118*, 8387; i) S. Chandrasekhar, M. S. Reddy, B. N. Babu, B. Jagadeesh, A. Prabhakar, B. Jagannadh, *J. Am. Chem. Soc.* **2005**, *127*, 9664; j) K. Möhle, R. Günther, M. Thormann, N. Sewald, H.-J. Hofmann, *Biopolymers* **1999**, *50*, 167; k) S. A. W. Gruner, V. Truffault, G. Voll, E. Locardi, M. Stöckle, H. Kessler, *Chem. Eur. J.* **2002**, *8*, 4365; l) I. M. Mándity, L. Fülöp, E. Vass, G. K. Tóth, T. A. Martinek, F. Fülöp, *Org. Lett.* **2010**, *12*, 5584.

[4] a) A. Hayen, M. A. Schmitt, F. N. Ngassa, K. A. Thomasson, S. H. Gellman, *Angew. Chem. Int. Ed.* **2004**, *43*, 505; *Angew. Chem.* **2004**, *116*, 511; b) S. De Pol, C. Zorn, C. D. Klein, O. Zerbe, O. Reiser, *Angew. Chem. Int. Ed.* **2004**, *43*, 511; *Angew. Chem.* **2004**, *116*, 517; c) Y. J. Chung, L. A. Christianson, H. E. Stanger, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1998**, *120*, 10555; d) G. V. M. Sharma, P. Nagendar, P. Jayaprakash, P. R. Krishna, K. V. S. Ramakrishna, A. C. Kunwar, *Angew. Chem. Int. Ed.* **2005**, *44*, 5878; *Angew. Chem.* **2005**, *117*, 6028; e) G. V. M. Sharma, P. Nagendar, K. V. S. Ramakrishna, N.

Chandramouli, M. Choudhary, A. C. Kunwar, *Chem. Asian J.* **2008**, *3*, 969; f) G. V. M. Sharma, N. Chandramouli, S. J. Basha, P. Nagendar, K. V. S. Ramakrishna, A. V. S. Sarma, *Chem. Asian J.* **2011**, *6*, 84; g) S. H. Choi, I. A. Guzei, L. C. Spencer, S. H. Gellman, *J. Am. Chem. Soc.* **2009**, *131*, 2917; h) C. Baldauf, R. Günther, H.-J. Hofmann, *Biopolymers* **2006**, *84*, 408; i) W. S. Horne, M. D. Boersma, M. A. Windsor, S. H. Gellman, *Angew. Chem. Int. Ed.* **2008**, *47*, 2853; *Angew. Chem.* **2008**, *120*, 2895; j) Y.-H. Shin, D. E. Mortenson, K. A. Satyshur, K. T. Forest, S. H. Gellman, *J. Am. Chem. Soc.* **2013**, *135*, 8149.

[5] a) A. J. Doig, *Biophys. Chem.* **2002**, *101–102*, 281; b) A. J. Doig, *Protein Folding, Misfolding and Aggregation: Classical Themes and Novel Approaches*, Royal Society of Chemistry, Cambridge, **2008**, p. 1.

[6] a) D. H. Appella, J. J. Barchi, S. R. Durell, S. H. Gellman, *J. Am. Chem. Soc.* **1999**, *121*, 2309; b) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366.

[7] a) T. J. Peelen, Y. Chi, E. P. English, S. H. Gellman, *Org. Lett.* **2004**, *6*, 4411; b) J.-S. Park, H.-S. Lee, J. R. Lai, B. M. Kim, S. H. Gellman, *J. Am. Chem. Soc.* **2003**, *125*, 8539; c) M. G. Woll, J. D. Fisk, P. R. LePlae, S. H. Gellman, *J. Am. Chem. Soc.* **2002**, *124*, 12447; d) D. H. Appella, L. A. Christianson, D. A. Klein, M. R. Richards, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1999**, *121*, 7574.

[8] A. Hetényi, Z. Szakonyi, I. M. Mándity, E. Szolnoki, G. K. Toth, T. A. Martinek, F. Fülöp, *Chem. Commun.* **2009**, 177.

[9] a) G. V. M. Sharma, P. Sai Reddy, D. Chatterjee, A. C. Kunwar, *J. Org. Chem.* **2011**, *76*, 1562; b) E. A. Archer, H. Gong, M. J. Krische, *Tetrahedron* **2001**, *57*, 1139; c) J. Turk, G. T. Panse, G. R. Marshall, *J. Org. Chem.* **1975**, *40*, 953; d) M. Jung, *Chemistry and Biochemistry of the Amino Acids*, Chapman & Hall, **1985**, p. 227; e) D. M. Kiick, P. F. Cook, *Biochemistry* **1983**, *22*, 375; f) D. Schirlin, F. Gerhart, J. M. Hornsperger, M. Hamon, J. Wagner, M. J. Jung, *J. Med. Chem.* **1988**, *31*, 30; g) P. Heinonen, P. Virta, H. Lönnberg, *Tetrahedron* **1999**, *55*, 7613; h) D. Seebach, S. Abele, T. Sifferlen, M. Hänggi, S. Gruner, P. Seiler, *Helv. Chim. Acta* **1998**, *81*, 2218; i) M. Andreini, C. Taillefumier, F. Chrétien, V. Thery, Y. Chapleur, *J. Org. Chem.* **2009**, *74*, 7651; j) C. Tomasini, G. Luppi, M. Monari, *J. Am. Chem. Soc.* **2006**, *128*, 2410; k) I. A. Motorina, C. Huel, E. Quiniou, J. Mispelter, E. Adjadj, D. S. Grierson, *J. Am. Chem. Soc.* **2001**, *123*, 8; l) W. J. Duddy, J. W. M. Nissink, F. H. Allen, E. J. Milner-White, *Protein Sci.* **2004**, *13*, 3051; m) B. Song, P. Kibler, A. Malde, K. Kodukula, A. K. Galande, *J. Am. Chem. Soc.* **2010**, *132*, 4508.

[10] G. V. M. Sharma, K. S. Reddy, S. J. Basha, K. R. Reddy, A. V. S. Sarma, *Org. Biomol. Chem.* **2011**, *9*, 8102.

[11] a) J. P. Saludes, J. B. Ames, J. Gervay-Hague, *J. Am. Chem. Soc.* **2009**, *131*, 5495; b) J. Yang, S. H. Gellman, *J. Am. Chem. Soc.* **1998**, *120*, 9090; c) F. J. Martinez-Martinez, I. I. Padilla-Martinez, M. A. Brito, E. D. Geniz, R. J. Rojas, J. B. R. Saavedra, H. Hopfl, M. Tlahuextl, R. Contreras, *J. Chem. Soc. Perkin Trans. 2* **1998**, 401.

[12] a) F. Jourdan, S. Lazzaroni, B. L. Méndez, P. Lo Cantore, M. de Julio, P. Amodeo, N. S. Iacobellis, A. Evidente, A. Motta, *Proteins: Structure, Function, Bioinformatics* **2003**, *52*, 534; b) A. A. Adzhubei, M. J. E. Sternberg, *J. Mol. Biol.* **1993**, *229*, 472; c) M. Novotny, G. J. Kleywegt, *J. Mol. Biol.* **2005**, *347*, 231.

[13] G. V. M. Sharma, A. C. Kunwar, *Recent Research Developments in Foldamer Chemistry*, Nova Science Publishers, New York, **2012**.

[14] a) J. Solà, S. P. Fletcher, A. Castellanos, J. Clayden, *Angew. Chem. Int. Ed.* **2010**, *49*, 6836; *Angew. Chem.* **2010**, *122*, 6988; b) R. A. Brown, T. Marcelli, M. De Poli, J. Solà, J. Clayden, *Angew. Chem. Int. Ed.* **2012**, *51*, 1395; *Angew. Chem.* **2012**, *124*, 1424.

[15] G. V. M. Sharma, N. Chandramouli, M. Choudhary, P. Nagendar, K. V. Ramakrishna, A. C. Kunwar, P. Schramm, H.-J. Hofmann, *J. Am. Chem. Soc.* **2009**, *131*, 17335.

[16] a) A. A. Grauer, C. Cabrele, M. Zabel, B. König, *J. Org. Chem.* **2009**, *74*, 3718; b) M. Ueda, A. Makino, T. Imai, J. Sugiyama, S. Kimura, *Langmuir* **2011**, *27*, 4300; c) L. Jiang, T.-B. Lu, X.-L. Feng, *Inorg. Chem.* **2005**, *44*, 7056.

[17] a) É. Szolnoki, A. Hetényi, I. M. Mándity, F. Fülöp, T. A. Martinek, *Eur. J. Org. Chem.* **2013**, 3555; b) E. Szolnoki, A. Hetenyi, T. A. Martinek, Z. Szakonyi, F. Fülöp, *Org. Biomol. Chem.* **2012**, *10*, 255.

[18] See Supporting Information.

[19] a) F. Shimoma, H. Kusaka, K. Wada, H. Azami, M. Yasunami, T. Suzuki, H. Hagiwara, M. Ando, *J. Org. Chem.* **1998**, *63*, 920; b) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17.

[20] a) G. V. M. Sharma, S. Mallesham, *Tetrahedron: Asymmetry* **2010**, *21*, 2646; b) G. V. M. Sharma, S. Mallesham, C. Chandra Mouli, *Tetrahedron: Asymmetry* **2009**, *20*, 2513; c) K. V. Babu, G. V. M. Sharma, *Tetrahedron: Asymmetry* **2008**, *19*, 577; d) G. V. M. Sharma, K. Raman Kumar, *Lett. Org. Chem.* **2007**, *4*, 465; e) G. V. M. Sharma, K. Veera Babu, *Tetrahedron: Asymmetry* **2007**, *18*, 2175; f) G. V. M. Sharma, K. L. Reddy, *Tetrahedron: Asymmetry* **2006**, *17*, 3197; g) G. V. M. Sharma, K. Laxmi Reddy, J. Janardhan Reddy, *Tetrahedron Lett.* **2006**, *47*, 6537; h) G. V. M. Sharma, J. J. Reddy, K. L. Reddy, *Tetrahedron Lett.* **2006**, *47*, 6531; i) G. V. M. Sharma, G. R. Cherukupalli, *Tetrahedron: Asymmetry* **2006**, *17*, 1081.

[21] R. Badorrey, C. Cativiela, M. D. Díaz-de-Villegas, R. Díez, J. A. Gálvez, *Eur. J. Org. Chem.* **2003**, 2268.

[22] a) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746; b) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199; c) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413.

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