Oligomers of β^2- and of β^3-Homoproline: What are the Secondary Structures of β-Peptides Lacking H-Bonds?

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Dedicated to Professor *Helmut Ringsdorf* on the occasion of his 70th birthday

To study the role of H-bonds in stabilizing β-peptidic secondary structures, we have synthesized β-oligopeptides (up to the octadecamer **12**) consisting of β^2- and β^3-homoproline, *i.e.*, β-peptides lacking amide protons. The enantiomer purity of the building block β^2-homoproline (nipecotic acid, **4**) was determined by HPLC analysis of the *N*-(2,4-dinitrophenyl) derivative **5** on a *Chiralcel-OD* column (*cf. Fig. 2*). The CD spectra of the all-(*S*)-β^2- and all-(*S*)-β^3-HPro-containing β-peptides display novel and intensive CD patterns which may be indicative of a secondary structure (*cf. Fig. 3*). It is noteworthy that a distinct CD pattern was observed with the β^3-HPro derivatives containing as few as three residues (**7a**). The crystal structure of a *N*-deprotected β^3-HPro-tripeptide **7c** is presented (*cf. Figs. 4* and *5*), and a model for the structure of β-peptides consisting of β^3-HPro is discussed (*cf. Figs. 6* and *7*).

1. Introduction. – A major goal of bio-organic chemistry is the synthesis of oligomers with unnatural backbones that combine the structural diversity and functional characteristics of biopolymers (polypeptides, polynucleotides, polysaccharides, polyisoprenoides, and poly(hydroxyalkanoates) [1]) with the stability of synthetic polymers. Recent results demonstrate the potential of β-peptides as oligomers consisting of the homologues of simple proteinogenic amino acids [2]; secondary structural elements of proteins (helices [3–5], sheets [3][6], turns [7] or steps [8], and hairpins [6][9]) are formed by β-peptides as well, and they are of higher stability even with short chain lengths [5][10]. A further asset is that the secondary structures can be predicted by conformational analysis and by theoretical calculations [11–13]. Moreover, β-peptides represent an ideal combination of being stable to mammalian proteases [14][15], and yet biologically active, for instance as mimics of α-peptide hormones [16].

The following question arose in the course of rational β-peptide design which we are currently pursuing: does a β-peptidic chain without backbone H-bonds fold into stable secondary structures? Considering the importance of H-bonds in stabilizing α-peptidic structures [17], the answer may be no. However, there are several pieces of evidence indicating that stable secondary β-peptide structures may be possible without H-bonds: *i*) The preferred backbone conformation around the central C(α)–C(β) bond has been identified as a major contributor to the stabilization of β-peptide secondary struc-

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[1]) Part of the Ph. D. thesis of *S.A.*, Dissertation ETH-Zürich, No. 13203, 1999.

[2]) Part of the Master Thesis (Diplomarbeit) of *K.V.*, ETH-Zürich, 1999.

tures[3]) [5], and, in *N*-alkylated β-peptides, this staggering effect is still present. *ii*) Recent molecular-dynamics calculations suggest that spontaneous folding to give the β-peptidic 3_{14} helix occurs prior to formation of the H-bonds[4]) [11]. *iii*) 'Peptoids' (oligomers of *N*-substituted glycine [18]) containing chirality centers at the α-position of their side chains also form secondary structures in solution[5]), despite their lack of amide protons and thus of H-bonding within the backbone [19–21].

A fully *N*-methylated β-hexapeptide consisting of *N*-methyl-β-homoalanine has already been synthesized by us, but the lack of crystallinity and the presence of rotamers prevented structural analysis [22]. We have, therefore, turned to the homologues of proline: the constraints, which determine the allowed values of the backbone dihedral angles in β-peptides consisting of β^2- or β^3-homoproline, should be fundamentally different from those operating in non-*N*-alkylated β-peptides of acyclic β-amino acids, *i.e.*, distinct backbone torsion angles Φ, Θ, and Ψ (*Fig. 1,a*) are enforced, and this might compensate for the lack of H-bonding.[6])[7])

Homologation of L-proline by inserting a CH_2 group between the carbonyl C-atom and the C(α)-atom leads to (*S*)-β^3-homoproline, while insertion of CH_2 group between the C(α)-atom and the N-atom affords (*R*)-β^2-homoproline (nipecotic acid; see *Fig. 1,b*). Whereas the former transformation can be realized by classical *Arndt-Eistert* homologation, the latter can not be effected in a simple step.

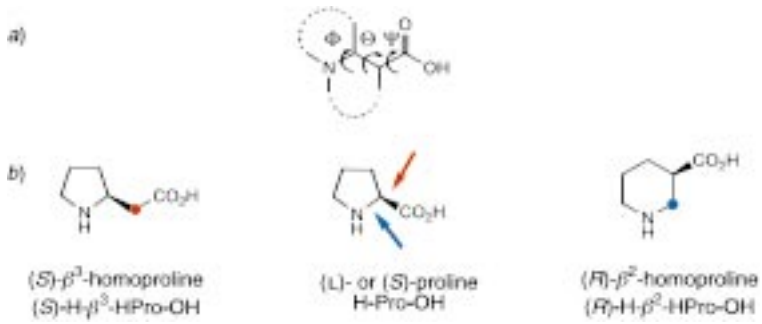

Fig. 1. a) *Torsion angles as defined in β-amino acids.* b) *Relationship between proline and β^3- and β^2-homoproline.* Arrows indicate the formal sites of homologation. The β^2-HPro-containing β-peptides described herein happen to consist of the homologs of D-proline.

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3) Actually, the failure to find a 'melting point' in temperature-dependent NMR and CD spectra of MeOH solutions of β-peptides [10] is compatible with this non-cooperative source of stability.

4) There is only a small energy difference between an intramolecular and an intermolecular H-bond in MeOH [10]!

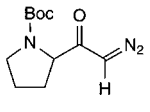
5) NMR Analysis indicated that the major conformation of a peptoid pentamer in MeOH consists of a (*P*)-3_1-helix [19].

6) *Cf.* the β-peptides having a backbone enforced by incorporated rings, studied by *Gellman* and co-workers [4][9].

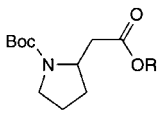
7) It is well known that proline, the only proteinogenic amino acid with a secondary amino group, imparts special conformations on a peptidic backbone by virtue of its pyrrolidine ring and of its fully substituted amide N-atom. As a consequence, the energy difference between the *cis*- and *trans*-conformation of the prolyl–peptidyl bond is decreased, accounting for 10–30% of *cis*-amide bond ($\omega = 0°$, or *ap*-conformation) in Pro-containing peptides [17]. This leads to unique structures of poly-proline [23] and of Pro-rich proteins (see collagen triple helix [24–26]).

2. Preparation of β^3- and β^2-Homoproline Derivatives. – Boc-Protected (*S*)-β^3-HPro–OH has previously been prepared by *Arndt-Eistert* [14][27–29] or C_1 homologation with cyanide [30] of L-proline[8])[9]).

We chose the classical *Arndt-Eistert* homologation for the preparation of the required building blocks. Thus, the Boc-protected diazo ketones (*R*)- and (*S*)-**1** were prepared according to published procedures [34][35]. *Wolff* rearrangement of the diazo ketones (*R*)- and (*S*)-**1** in either THF/BnOH or THF/H_2O afforded the Boc-protected β^3-homoproline benzyl esters, (*R*)- and (*S*)-**2a**, and the Boc-protected β^3-homoprolines, (*R*)- and (*S*)-**2b**, in high yields (*cf.* [22] and see *Exper. Part*).



(*R*)- or (*S*)-**1**



(*R*)- or (*S*)-**2**

a R = Bn
b R = H

The (*R*)- and (*S*)-ethyl nipecotate were prepared by classical resolution [36][10]). Only one diastereoisomeric salt (the *like*-salt) **3** precipitated upon treatment of commercially available *rac*-ethyl nipecotate (*rac*-**4a**) with either enantiomer of tartaric acid in EtOH. After two or three recrystallizations, (*R*,*R*,*R*)-**3** and (*S*,*S*,*S*)-**3** were obtained in diastereoisomerically pure form, as determined by comparison of the optical rotation and the melting points with literature values [36]. Basic extraction (pH 13) afforded (*R*)- **4a** and (*S*)-**4a**[11])[12]). Both enantiomers of ethyl nipecotate **4a** showed optical rotations similar to reported values. However, even at high concentrations, the value of the optical rotation ($[\alpha]_D^{rt.} \approx 1.3$) is too small to allow accurate determination of the enantiomer purity[13]). Consequently, other methods for determining the enantiomer purity were tested[14]).

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[8]) The synthesis of H-(*S*)-β^3-HPro-OH by *Arndt-Eistert* homologation of Z-L-Pro was first reported in 1975 [31]. However the published value and the sign of optical rotation are different from those reported by an industrial group [28], and by others [32][33].

[9]) However, both the Boc-protected diazo ketones **1**, derived from D- and L-proline, and the benzyl-ester derivatives **2** of H-β^3-HPro-OH, described herein, are new compounds.

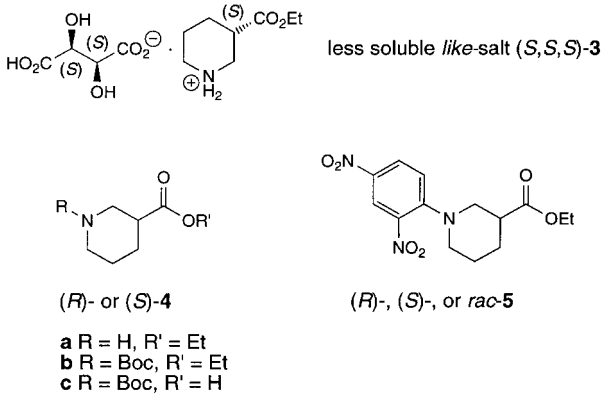
[10]) An esterase-catalyzed hydrolysis of *rac*-*N*-acetyl methyl nipecotate provides the products with poor ee values (22–24%) [37].

[11]) The absolute configuration of (–)-nipecotic acid was established by CD spectroscopy [38] and by chemical correlation [39].

[12]) This step has to be carried out rapidly at 0°, and the pH must be controlled, because complete saponification may occur.

[13]) It is noteworthy that enantiomerically pure nipecotic acid is often encountered in peptidomimetics [40–42]; the ee value was always determined by polarimetry! In independent work, (*R*)- and (*S*)-nipecotic acids were incorporated into a β-tetrapeptide, promoting hairpin formation [9].

[14]) *i*) Derivatization of **4a** with (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (= 3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride; MTPA-Cl) to give the corresponding diastereoisomeric



Eventually, reaction of *rac*-**4a** with *Sanger*'s reagent (1-fluoro-2,4-dinitrobenzene, DNPF [49][50]) in alkaline solution, to give the 2,4-dinitrophenyl (DNP) derivative of ethyl nipecotate *rac*-**5**, and chromatography on *Chiralcel-OD* (*Daicel*)[15]) was found to provide an excellent analysis of the enantiomer ratio (er; see *Fig. 2*). Integration of the peaks in the corresponding chromatograms revealed that (*R*)-**4a** and (*S*)-**4a** had been obtained by the resolution procedure with an er value of 98.9:1.1 and 99.6:0.4, respectively. With this method at hand, the diastereioisomer purity of the *l*-salts (*R*,*R*,*R*)-**3** and (*S*,*S*,*S*)-**3** was determined by liberating a small quantity of **4a**, the enantiomer purity of which was determined as outlined in *Fig. 2*[16])[17]).

The following transformations were effected with the (*S*)-enantiomer of **4a**: it was Boc-protected to give the ester **4b** as a colorless oil in 74% yield. The subsequent saponification step was considered crucial, because there was the risk of racemization (*cf.* the epimerization of $\beta^{2,3}$- [5] and β^{2}-amino-acid derivatives [52]). The mildest procedure for saponification was the hydrolysis with 2.5 equiv. of LiOH in MeOH/H_2O at r.t. for 2–3 days providing, after recrystallization, Boc-protected (*S*)-nipecotic acid **4c** in 90% yield. The enantiomeric purity of **4c** was determined by transformation to

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[14]) amides, the so-called *Mosher* amides, for ^{19}F- and ^{1}H-NMR spectroscopic analysis [43]. *ii*) The use of $\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) as chiral shift reagent for ^{13}C- and ^{1}H-NMR spectroscopy [44][45]. The ^{13}C-NMR spectrum (100 MHz) of a solution of *rac*-**4a** and TADDOL (1:2) in $CDCl_3$ showed non-equivalence of two signals after several hours. The chemical-shift differences were *ca.* 24 and 45 ppm, but the peaks showed tailing, preventing a complete separation. This enantioselective shift effect could allow for a quick, yet not accurate, determination of enantiomer purity. *iii*) Derivatization of *rac*-**4a** with 2,2,3,3,3-pentafluoropropanoyl chloride and i-PrOH [46–48] to give the corresponding isopropyl *N*-(2,2,3,3,3-pentafluoropropionyl)nipecotate for GC analysis (*α-CD, β-CD*, *γ-CD*, and *Chirasil-Val*). All of these methods failed to elucidate the enantiomer ratio.

[15]) Recently, *rac*-ethyl 4-hydroxypiperidine-3-carboxylate was successfully separated as *N*-(2,4-dinitrophenyl) derivative on a *Chiralpak AD* HPLC column [51].

[16]) In this case, the enantiomer purity of (*S*)-**4a** was 97.0% after two recrystallizations of (*S*,*S*,*S*)-**3**. A third recrystallization increased the enantiomer purity to 99.6%.

[17]) It should be noted that polarimetry with the enantiomers of **5** is suitable for a first determination of the enantiomer purity by virtue of the high values of optical rotation (+165 and −165 for (*S*)- and (*R*)-**5**, resp.; see *Exper. Part*).

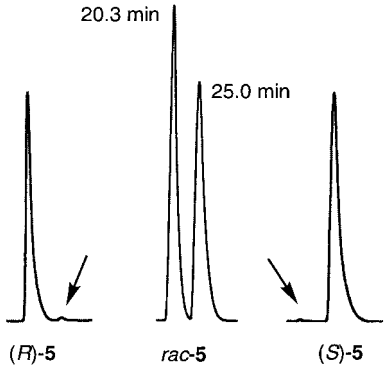

Fig. 2. *HPLC Traces of* N-*(2,4-dinitrophenyl) derivatives* **5** (*Chiralcel OD*, mobile phase: i-PrOH/hexane 35:165; see *GP 7* in *Exper. Part*). The arrows indicate the peak of the minor enantiomer. The retention times were 20.3 and 25.0 min for the (*R*)- and (*S*)-enantiomer, respectively. The er value was determined by integration of the corresponding peak: (*R*)-**5**: 98.9:1.1; (*S*)-**5**: 99.6:0.4.

the DNP derivative **5** (see *Exper. Part*); (*S*)-**4a** with an er value of 99.6:0.4 was employed in the subsequent syntheses[18]).

3. Preparation of β^3- and β^2-HPro-Peptides. – Both the all-(*S*)-β-peptides (isotactic) and the β-peptides containing an alternating sequence of (*S*)- and (*R*)-β^3-homoproline (syndiotactic) were prepared in solution, using the *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride/1-hydroxy-1*H*-benzotriazole (EDC/HOBt) procedure [3][5][7]. The benzyl-ester derivative (*S*)-**2a** was Boc-deprotected (TFA, CH_2Cl_2), and the resulting TFA salt was employed for coupling with the Boc-protected amino acid (*S*)-**2b** to give the fully protected dipeptide **6**. After *N*-deprotection, another coupling step with (*S*)-**2b** followed to give the fully protected all-(*S*)-β-tripeptide **7a** as a white foam in 91% yield. Benzyl-ester cleavage (H_2, Pd/C) provided the β-tripeptide acid **7b** and Boc deprotection yielded the TFA salt **7c**. Likewise, fully protected (*S*)/(*R*)-β-dipeptide **8a** was prepared by coupling the TFA salt derived from (*R*)-**2a** with the acid (*S*)-**2b**. Benzyl-ester cleavage (H_2, Pd/C) yielded the β-dipeptide acid **8b**, which was used for coupling with the Boc-deprotected dipeptide benzyl ester derived from **8a**, to provide (*S*)/(*R*)-β-tetrapeptide derivative **9** in 81% yield.

Fragment condensation of the tripeptide derivatives **7c** and **7b** then furnished protected isotactic β-hexapeptide **10a** (85%), which was converted to the peptide acid **10b** by hydrogenation (H_2, Pd/C). The fully protected peptide **10a** was soluble in various protic and aprotic solvents ($CHCl_3$, CH_2Cl_2, MeOH, AcOEt, Et_2O); its good solubility and the high yields in the coupling steps leading to it provided motivation for the synthesis of higher oligomers. Thus, the TFA salt obtained from hexapeptide **10a** was used for coupling with hexapeptide acid **10b** to give the fully protected β-

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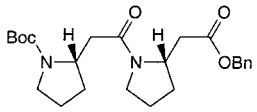
[18]) Assuming that the Boc protection (without base) occurred without racemization, the er value has been slightly reduced to 97.9:2.1 during saponification. Alternatively, saponification with the same amounts of base in refluxing MeOH/H_2O 3:1 for 3 h produced **4c** with an er of 97.3:2.7.



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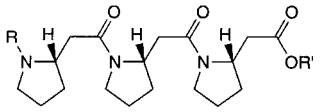
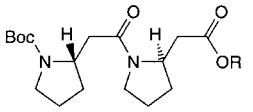
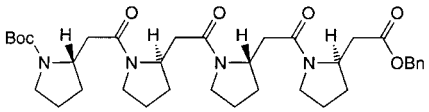


7a R = Boc, R' = Bn
7b R = Boc, R' = H
7c R = H·TFA, R' = Bn



8a R = Bn
8b R = H



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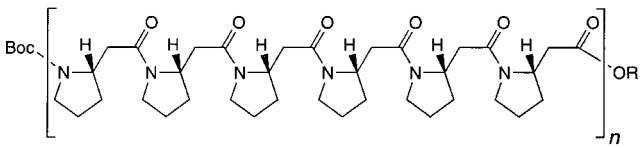
10a *n* = 1, R = Bn
10b *n* = 1, R = H
11 *n* = 2, R = Bn
12 *n* = 3, R = Bn



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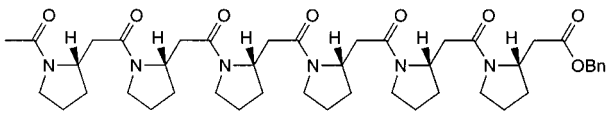

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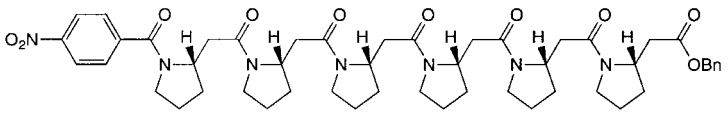

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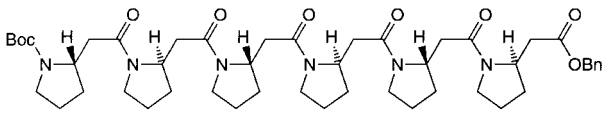

dodecapeptide **11** as a white foam in 79% yield after purification by precipitation from CH_2Cl_2/hexane. After Boc deprotection, this dodecamer was further coupled with the peptide acid **10b** to give the fully protected β-octadecapeptide **12** as a white powder. This is the longest β-peptide synthesized to date[19]).

To increase the crystallinity of the β-peptides, the Ac and *p*-nitrobenzoyl group were introduced at the N-terminus of the β-hexapeptide. The TFA salt from **10a** was used for acylation with either Ac_2O or *p*-nitrobenzoylchloride to provide the β-peptide esters **13** and **14**. In the syndiotactic series, a second fragment coupling step of the *N*-deprotected form of β-tetrapeptide **9** with the peptide acid **8b** furnished the fully protected β-hexapeptide **15** (white powder).

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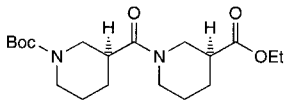
[19]) A highly insoluble β-pentadecapeptide was reported in [52].

The synthesis of the all-(*S*)-β^2-HPro-peptides began with the acylation of enantiomerically pure ethyl nipecotate (*S*)-**4a** with Boc-protected (*S*)-β^2-homoproline (*S*)-**4c** to give the dipeptide derivative **16** (waxy solid). After Boc deprotection, a further coupling with the β-amino acid (*S*)-**4c** gave fully protected β-tripeptide **17a** (white waxy solid). The following saponification was performed applying the same mild procedure as for the saponification of the monomeric building block **4b**. Thus, treatment of **17a** with LiOH in a MeOH/H_2O solution provided the tripeptide acid **17b** after precipitation from AcOEt/pentane. Final fragment coupling, with the peptide acid **17b** and the TFA salt derived from **17a**, gave the fully protected β-hexapeptide **18** (colorless 'glass', 79% yield).



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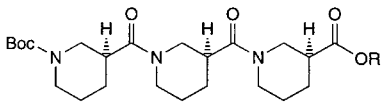
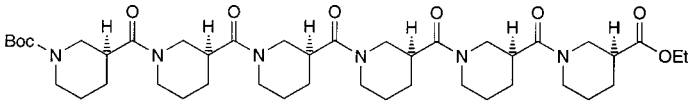


17a R = Et **17b** R = H

18



4. Structure Analysis. – 4.1. *Circular Dichroism Spectroscopy.* Circular dichroism (CD) spectroscopy is a low-resolution method that provides a first indication for the presence of secondary structures [53][54]. Compared to NMR spectroscopy, it has a very short 'time scale' (UV *vs.* radar frequency!), and, thus, an (unstable) chiral conformer present in a very small amount but with a large $\Delta\varepsilon_{R/L}$ value may contribute very strongly to the spectrum of the ensemble of all molecules present.

In comparison with the oligomers of homologues of non-cyclic L-amino acids (*Fig. 3*,*a*, shows the typical CD pattern associated with a 3_{14} helix), the β^3- and β^2-HPro oligomers give rise to a quite different *Cotton* effect (*Fig. 3*,*b* and *d*). The all-(*S*)-β^3-HPro-peptides have a characteristic, very intense minimum at 202 nm and a maximum at 223 nm, with a zero cross-over at 212 nm (*Fig. 3*,*b*)[20]. The absolute mean-residue molar ellipticity at 202 nm decreases with growing chain length (**7a** with 3 residues: $-4.40\cdot10^4$ *vs.* **12** with 18 residues: $-1.92\cdot10^4$). The same is true for the mean-residue molar ellipticity at 223 nm. This suggests that the secondary structure of longer peptide chains of this type is destabilized. However, the high molar ellipticities (for instance $-3.46\cdot10^5$ for **12** at 202 nm) still imply that a secondary structure is present in MeOH[21]). In sharp contrast to the CD spectra of the β^3-HPro oligomers consisting of

[20]) There is a conspicuous (mirror-image-type) analogy between the CD spectra of our β-HPro-containing β-peptides and the CD spectra of *Gellman*'s $\beta^{2,3}$-hexapeptide derivative consisting of *trans*-2-aminocyclopentanecarboxylic-acid building blocks [4]. However, we think that it is highly unlikely that the β-HPro-peptides adopt the same conformation (a *2.5* helix consisting of twelve-membered H-bonded rings) as the cyclopentane derivatives.

[21]) The fully protected β-hexapeptide **10a** feature the same CD pattern in CF_3CH_2OH and in aqueous buffered solution (pH 5.7), albeit with lower intensity, as compared to the CD spectra measured in MeOH.

homochiral [55] β-amino acids, the CD spectra of the β-peptides containing – in an alternating fashion – (*S*)- and (*R*)-β^3-HPro building blocks (**9** and **15**) show virtually no *Cotton* effect (*Fig. 3*,*c*), indicating that these compounds may be devoid of an ordered secondary structure[22]) – candidates for random coils in the world of β-peptides!? For both substitution patterns, the CD spectra did not change substantially with different groups at C- and N-termini. The β-peptides composed of (*S*)-β^2-HPro building blocks show weaker *Cotton* effects, but the overall CD pattern is similar to that of the β^3-HPro-peptides (*Fig. 3*,*d*). However, the mean residue molar ellipticity of β-hexapeptide derivative **18** ($+4.07\cdot10^3$) is nearly three times larger than that of β-tripeptide derivative **17a** ($+1.38\cdot10^3$) at *ca.* 230 nm. Thus, the secondary structure may be stabilized by a longer β-peptide chain, in this case. The CD curve of non-structured protected β-dipeptide **16** is included to show that the measured *Cotton* effects of the higher oligomers are due to a distinct chiral supramolecular arrangement of the β-peptide chain.

4.2. *X-Ray Crystal-Structure Analysis.* The TFA salt **7c**, which had been isolated as a colorless oil, solidified after two-weeks storage in a freezer. Suitable crystals were separated and the structure was solved. Four molecules of CF_3CO_2H are incorporated into the crystal (*Fig. 4*). The dihedral angles are given in the *Table.* Inspection of this structure revealed some interesting features (*Fig. 5*): *i*) The Ph group is parallel (at *van-der-Waals* distance) to the plane formed by the amide group of the first two β-amino acid residues[23]). *ii*) The substituents at C(α) of the second and third pyrrolidine rings are in a pseudo-axial position, a direct consequence of allylic 1,3-strain ($A^{1,3}$-strain). The exocyclic amide group pushes the neighboring substituent out of its plane into an axial position of the ring. This is in agreement with numerous structures of Pro-containing compounds, as well as with a variety of X-ray structures of simple *N*-acylated five-membered heterocycles [60]. *iii*) The pyrrolidine rings exhibit the twist conformation[24]), and the N-atoms are not pyramidalized in the crystal structure of **7c**.

5. Modelling of a Possible Secondary Structure of R-(β^3-HPro)$_n$-OR and Conclusion. – As with *N*-methyl β-peptides [22], the NMR spectra of the β-HPro oligomers show that rotamers, *i.e.*, conformers with *cis*- and *trans*-amide bonds, are present, similar to the situation with proline-containing α-peptides [17][23][64]. Structure determination by 2D-NMR techniques is thus complicated. The large coupling constant J_{AX} of the ABX system from the $CO-CH_2-CH$ units in the β^3-HPro oligomers is *ca.* 8 Hz (not quite large enough for a coupling between antiperiplanar protons). Still, this value, the crystal structure of **7c**, and the general rules of conformational analysis [17] provided guidance for the construction of a model for the structure of β-peptides composed of (*S*)-β^3-homoproline. The amide bond was fixed in

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[22]) The absence of a *Cotton* effect does *not* preclude the existence of a stable secondary structure *a priori*; for instance, γ-peptides which adopt a helical structure according to 2D-NMR analysis do not show any *Cotton* effect [56].

[23]) A similar, more twisted geometry of an α-dipeptide derivative has been reported [57]. For α-peptides with NH protons, various examples are known where this bond points to the center of the aromatic π-system of Ph groups (π-type interaction) [58][59].

[24]) For a definition of five-ring twist and envelope conformations, see [61–63].

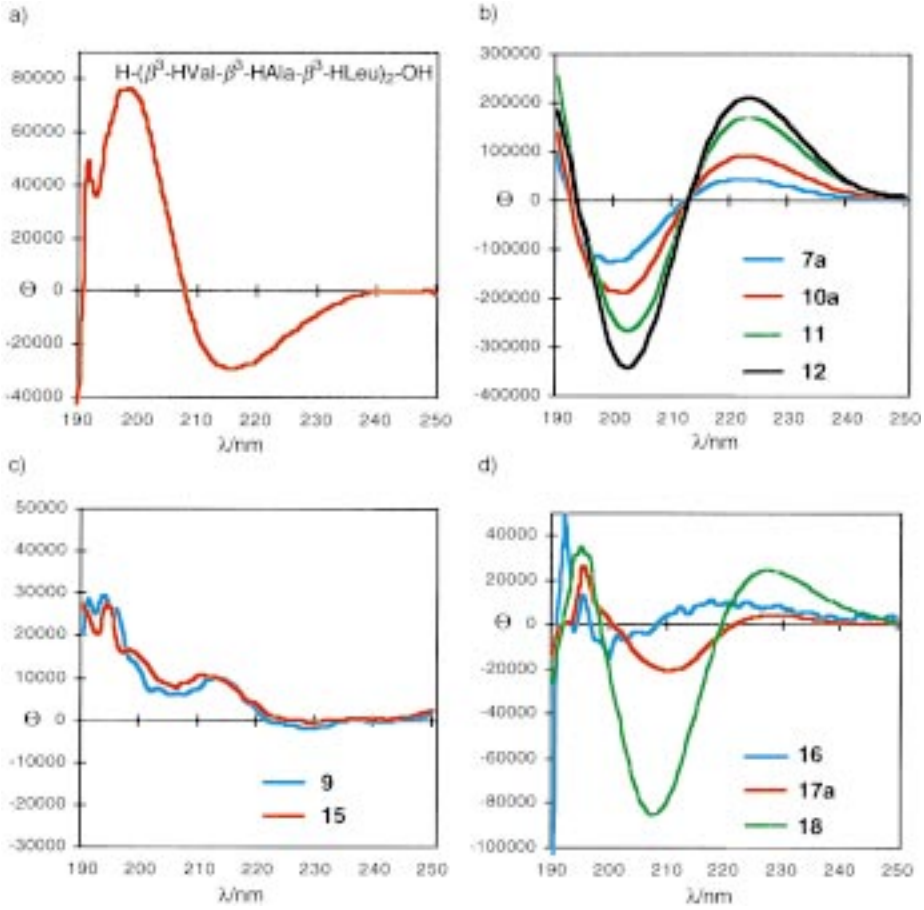

Fig. 3. *CD Spectra of β-peptides.* a) *Typical CD pattern of a* 3_{14} *β-peptide helix* [3]. b) *All-(*S*)-β-tri-* (**7a**), *-hexa-* (**10a**), *-dodeca-* (**11**), *and -octadecapeptide* (**12**), *consisting of (*S*)-β³-homoproline.* c) *(*S*)/(*R*)-β-tetra-* (**9**) *and hexapeptide* (**15**) *with alternating (*S*)- and (*R*)-β³-homoproline residues.* d) *All-(*S*)-β²-di-* (**16**), *-tri-* (**17a**) *and -hexapeptide* (**18**) *composed of (*S*)-β²-homoproline residues.* All β-peptides were measured at 0.2 mM in MeOH at r.t. The molar ellipticity [Θ] is represented in 10 $dg \cdot cm^2 \cdot mol^{-1}$, and is not normalized.

the normal *trans*-conformation. The angle Φ (*Fig. 6,a*), enforced by the pyrrolidine ring, is *ca.* $-72°$ according to the X-ray structure. An antiperiplanar conformation around the C(α)–C(β) bond ($\Theta = 180°$; *Fig. 6,b*), as encountered in the central residue of the crystal structure of **7c**, is suggested. The angle Ψ was chosen to be 180° so that the large substituents at the carbonyl C-atom and at C(α) are antiperiplanar (the C=O group lies between the γ-CH_2 group and the C(β)H atom; see *Fig. 6,c*). The resulting model is a right-handed 10_3 helix with three pitches to bring residue ($i+10$) above residue i (*Fig. 7*). The model unveils consecutive fully extended chain segments (N–C(β)–C(α)–CO–N), which are twisted by $-72°$ (*Fig. 7,c*).

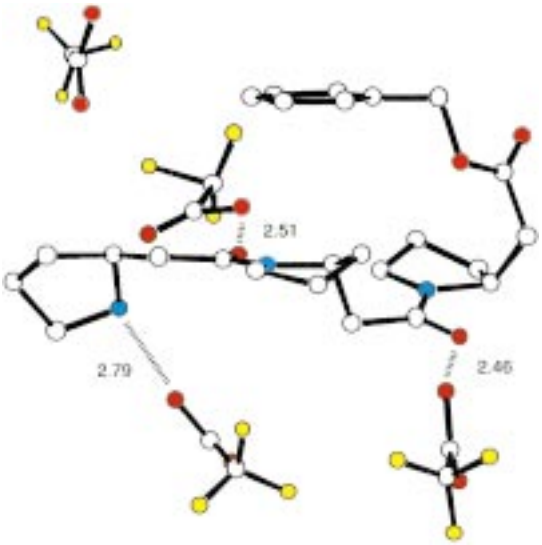

Fig. 4. *X-Ray crystal structure of β-tripeptide derivative* **7c**. The peptide crystallized with four CF_3CO_2H molecules. Two of these form H-bonds with amide-carbonyl O-atoms, and one $CF_3CO_2^-$ is the counterion of the terminal ammonium group; the distance O···O or N···O is indicated in [Å]. H-Atoms have been omitted for clarity.

Table. *Torsion Angles in the Crystal Structure of β-Tripeptide Derivative* **7c**. The torsion angles are defined in *Figs. 1, a* and *b*.

Residue[a])	Φ [°]	Θ [°]	Ψ [°]
1	–	+59.2	−175.6
2	−73.6	+171.9	−82.9
3	−71.6	−66.8	+88.2

[a]) Numbering starts from the N-terminus.

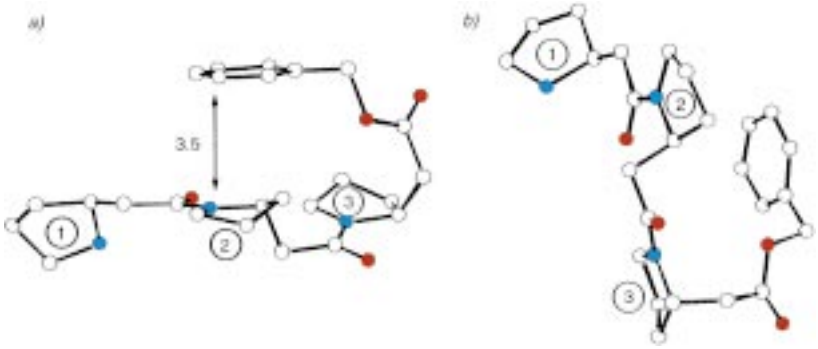

Fig. 5. *Two views of the crystal structure of the TFA salt* **7c**. a) *Projection showing the quasi-parallel arrangement of the Ph ring with the amide plane*. The distance is indicated in [Å]. b) View in which the *ap*-conformation around the C(α)–C(β) bond of the central β-amino acid is visible.

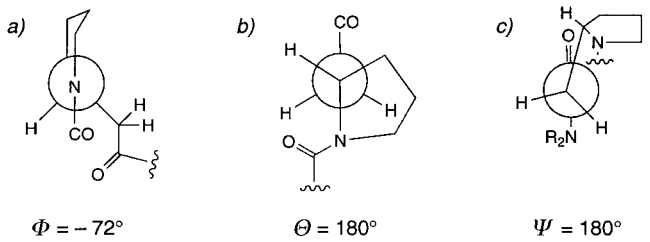

Fig. 6. *Dihedral angles Φ, Θ, and Ψ used for the construction of a model for the structure of R-(β³-HPro)ₙ-OR.* See discussion in the accompanying text and *Fig. 7.*

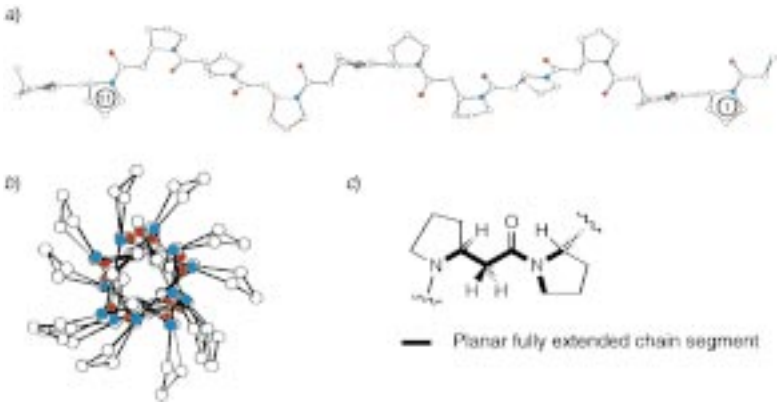

Fig. 7. *Model consisting of* (S)-*β³-HPro, constructed with the torsion angles* $\Phi = -72°$, $\Theta = \Psi = 180°$. a) *Side view of a* 10_3 *helix*. b) *Top view of a* 10_3 *helix*. Two of the pyrrolidine rings are in juxtaposition. c) *Characteristic fully extended chain segment* (N–C(β)–C(α)–CO–N) *identified in this structure.* Model constructed with MacMoMo (program by Prof. Dr. *M. Dobler*, ETH-Zürich).

Although one of the major forces that direct the self-assembly of biopolymers, *i.e.*, the formation of a H-bonding network, is lacking in β-HPro-peptides, the present results indicate that this class of β-peptides may still adopt distinct folding patterns due to the high intrinsic folding propensity of the β-peptide backbone; this is strongly suggested by the characteristic and intensive CD curves of the all-(*S*)-β²- and all-(*S*)-β³-HPro-peptides (*Fig. 3*)[25]. Efforts to crystallize larger β-peptides, such as the β-hexapeptide **10a**, and to investigate its structure by 2D-NMR spectroscopy, are in progress. The high solubility of β-HPro-peptides will facilitate the synthesis of even larger β-peptides with defined structures by the incorporation of β-homoproline residues.

We gratefully acknowledge generous supply of D-Pro from *Degussa AG*, Hanau. We would like to thank Dr. *P. Seiler* (Laboratorium für Organische Chemie, ETH-Zurich) for the determination of the X-ray crystal structure of **7c**. *A. Lerchner* has carried out some of the experiments described herein, as part of the advanced laboratory course in organic chemistry. Financial support from *Novartis Pharma* and *Agro*, Basel, is gratefully acknowledged.

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[25]) It is remarkable that the *N*-deprotected β³-HPro-tripeptide **7c**, of which an X-ray crystal structure is available (*Figs. 4* and *5*), gives rise to the same, albeit less intensive, CD pattern as the fully protected derivative **7a** (*cf. Fig. 3,b*, and *Exper. Part*).

Experimental Part

1. *General*. Abbreviations: Boc_2O: di(*tert*-butyl) dicarbonate, DMAP: 4-(dimethylamino)pyridine, EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, er: enantiomer ratio, HOBt: 1-hydroxy-1*H*-benzotriazole, h.v.: high vacuum (0.01–0.1 Torr), *β*-HXaa (*β*-homoamino acid) [3][5], TFA: trifluoroacetic acid, $CHCl_3$ employed for the coupling reactions was filtered through Al_2O_3 (Alumina *Woelm N*, activity I) to remove EtOH. Et_3N was distilled from CaH_2 and stored under Ar. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*). Boc-Pro was purchased from *Senn*, D-Pro was a gift from *Degussa*. All other reagents were used as received from *Fluka* or *Quantum Biotechnologies*, Montreuil (EDC). TLC: *Merck* silica gel *60* F_{254} plates; detection with UV, I_2 (30 g of I_2, 20 g of KI, 200 ml of EtOH, 200 ml of H_2O), anisaldehyde (9.2 ml of anisaldehyde, 3.75 ml of AcOH, 12.5 ml of conc. H_2SO_4, 350 ml of EtOH) or ninhydrine (0.6 g of ninhydrine, 2 ml of HOAc, 13 ml of H_2O, 285 ml of BuOH). FC: *Fluka* silica gel 60 (40–63 μm); at *ca*. 0.3 bar. Anal. HPLC: *Knauer* HPLC system (pump type *64*, *EuroChrom 2000* integration package, degaser, UV detector (variable-wavelength monitor)). M.p.: *Büchi-510* apparatus; uncorrected. UV Spectra: *Uvikon 860 Kontron Instruments* (1-cm rectangular cell) at r.t., λ_{max} in nm. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell) at r.t. CD Spectra: *Jasco J-710* between 190 and 250 nm in a 1-mm rectangular cell at r.t. The optical system was flushed with N_2 at a flow rate of *ca*. 10 $l \cdot min^{-1}$. Band width 1.0 nm, resolution 0.5 nm, sensitivity 100 mdeg, response 0.5 s, speed 50 $nm \cdot min^{-1}$. All spectra were the average of five scans and were corrected for the corresponding solvent spectrum. Peptide concentration: 0.2 mM in MeOH. The molar ellipticity Θ is reported in $deg \cdot cm^2 \cdot dmol^{-1}$. Smoothing was performed with the software provided by *Jasco*. IR Spectra: *Perkin-Elmer-782* spectrophotometer. NMR Spectra: *Bruker AMX 500* (^1H: 500 MHz, ^{13}C: 125 MHz), *AMX 400* (^1H: 400 MHz, ^{13}C: 100 MHz); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz; some compounds show the presence of rotamers which are indicated. MS: *VG Tribrid* (EI), *Hitachi Perkin-Elmer RHU-6M* (FAB, in a 3-nitrobenzyl alcohol matrix), or *Finnigan MAT TSQ 7000* (ESI) spectrometer; in *m/z* (% of basis peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Ester Hydrolysis: General Procedure 1* (*GP 1*). A soln. of the fully protected amino acid in MeOH (0.2M) was treated with a soln. of LiOH (2.5 equiv.) in H_2O (MeOH/H_2O 3:1 (*v/v*)) at r.t. After stirring at r.t. for 1–3 d, the mixture was diluted with H_2O (for small-scale reactions) and extracted with Et_2O (2×). The soln. was adjusted to pH 2 at 0° with 10% HCl and extracted with Et_2O (3×). The org. phase was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure.

3. *Benzyl-Ester Deprotection: General Procedure 2* (*GP 2*). The benzyl ester was dissolved in the appropriate solvent (0.1M), and a catalytic amount of 10% Pd/C was added. The apparatus was evacuated and flushed with H_2 (3×), and the mixture was stirred under H_2 for 18 h. Subsequent filtration through *Celite* and concentration under reduced pressure yielded the crude carboxylic acid, which was identified by NMR and FAB-MS and used without further purification.

4. *Boc Deprotection: General Procedure 3* (*GP 3*). Similarly to the reported procedure [3][5], the Boc-protected amino acid was dissolved in CH_2Cl_2 (0.5M) and cooled to 0°. An equal volume of TFA was added, and the mixture was allowed to warm slowly to r.t. and stirred for further 1.5 h. Concentration under reduced pressure, co-evaporation with CH_2Cl_2, and drying of the residue under h.v. yielded the crude TFA salt, which was identified by NMR and FAB-MS and used without further purification.

5. *Peptide Coupling with EDC: General Procedure 4* (*GP 4*). The appropriate TFA salt was dissolved in $CHCl_3$ (0.5M) and cooled to 0°. This soln. was treated successively with Et_3N (4 equiv.), HOBt (1.2 equiv.), a soln. of the Boc-protected fragment (1 equiv.) in $CHCl_3$ (0.25M), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t. After TLC displayed complete reaction (12 h–3 d), the mixture was subsequently diluted with $CHCl_3$, followed by thorough washing with 1N HCl, sat. aq. $NaHCO_3$ (3×), and NaCl solns. (1×). The org. phase was dried ($MgSO_4$) and the concentrated under reduced pressure. FC or recrystallization yielded the pure peptide.

6. *HPLC Analysis of* (R)- *or* (S)-**5**: a) *Derivatization of* **4a** *with 1-Fluoro-2,4-dinitrobenzene: General Procedure 5* (*GP 5*). To a soln. of **4a** in H_2O (0.5M) was added $NaHCO_3$ (1.2 equiv.) and a soln. of 1-fluoro-2,4-dinitrobenzene (1.2 equiv.) in EtOH (0.35M) at 0°. After 1 h, EtOH was evaporated and the pH adjusted to 2 with 1N HCl, and the residue was extracted with Et_2O (2×). The Et_2O phase was filtered through a *Buchner* funnel (*G4*) packed with silica gel on a $MgSO_4$ layer and evaporated to yield crude **5**. The yellow oil was dissolved in i-PrOH/hexane 35:165 (1 mg/ml) and injected onto the HPLC system according to *GP 7*.

b) *Derivatization of* **4c**: *General Procedure 6* (*GP 6*). A soln. of **4c** (5 mg, 0.022 mmol) in HCl/EtOH[26]) (1 ml, 4M) was heated to 110° for 1.5 h in a *Wheats V-Vial* (with *Teflon*-faced rubber septum) to yield **4a** · HCl. The HCl salt was further derivatized according to *GP 5*.

c) *HPLC for Determination of Enantiomer Ratio of* **5**: *General Procedure 7* (*GP 7*). HPLC Analyses were performed on a *Daicel Chiralcel OD* column (4.6 × 250 mm, 10 μm) by using an isocratic eluent of i-PrOH/hexane 35 : 165 at a flow rate of 1 ml/min with UV detection at 390 nm at 25°, t_R in min.

7. *β³-Peptides.* tert-*Butyl (*R*)-2-(Diazoacetyl)pyrrolidine-1-carboxylate* (Boc-(*R*)-Pro-CHN_2; (*R*)-**1**). Boc-D-Pro-OH (13.99 g, 65.0 mmol) was transformed with CH_2N_2 according to [35]. FC (AcOEt/pentane 1:3) yielded (*R*)-**1** (8.70 g, 56%). Yellow, waxy solid. M.p. 47–48°. R_f (AcOEt/pentane 1:3) 0.25. $[\alpha]_D^{r.t.} = +146$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3120*w*, 3008*m*, 2980*m*, 2881*w*, 2110*s*, 1690*s*, 1646*m*, 1477*w*, 1454*w*, 1394*s*, 1367*s*, 1323*m*, 1163*m*, 1123*m*. ^{1}H-NMR (400 MHz, $CDCl_3$; values for rotamers in italics): 1.44, *1.48* (*s*, *t*-Bu); 1.84–2.27 (*m*, CH_2CH_2); 3.36–3.56 (*m*, CH_2N); 4.24 (br., NCH); 5.44 (br., CHN_2). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 23.71, *24.41* (CH_2); 28.38, *28.44* (Me); 29.67, 31.27, 46.79, *47.10* (CH_2); 52.01, *53.11*, *63.60*, 64.48 (CH); *80.13*, 80.45, 109.16, *154.14*, 154.82, *195.09*, 196.06 (C). EI-MS: 170 (16.2), 114 (52.4), 70 (93.8), 57 (100). Anal. calc. for $C_{11}H_{17}N_3O_4$ (239.27): C 55.22, H 7.16, N 17.56; found: C 55.38, H 7.22, N 17.36.

tert-*Butyl (*S*)-2-(Diazoacetyl)pyrrolidine-1-carboxylate* (Boc-(*S*)-Pro–CHN_2; (*S*)-**1**). Boc-L-Pro–OH (26.9 g, 125 mmol) was transformed with CH_2N_2 according to [35]. FC (AcOEt/pentane 1:3) yielded (*S*)-**1** (22.9 g, 77%). Yellow, waxy solid. R_f (AcOEt/pentane 1:3) 0.25. $[\alpha]_D^{r.t.} = -145$ ($c = 1.0$, $CHCl_3$). Other spectroscopic data: corresponding to (*R*)-**1**.

tert-*Butyl (*S*)-2-[2-(Benzyloxy)-2-oxoethyl]pyrrolidine-1-carboxylate* (Boc-(*S*)-β³-HPro-OBn; (*S*)-**2a**). Compound (*S*)-**1** (6.00 g, 25.0 mmol) was rearranged with CF_3COOAg (10%) in BnOH/THF 15:85 (*v*/*v*) according to [22]. After removal of BnOH by distillation (0.5 mbar, 68°), FC (Et_2O/pentane 1:2) yielded (*S*)-**2a** (5.40 g, 68%). Colorless oil. R_f (Et_2O/pentane 1:2) 0.32. $[\alpha]_D^{r.t.} = -35.7$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3007*w*, 2977*m*, 2882*w*, 1730*m*, 1684*s*, 1477*w*, 1455*w*, 1403*s*, 1367*m*, 1304*w*, 1166*m*, 1125*m*. ^{1}H-NMR (400 MHz, $CDCl_3$; values for rotamers in italics): 1.45 (*s*, *t*-Bu); 1.70–1.89 (*m*, 3 CH); 2.00–2.09 (*m*, 1 CH); 2.36 (*dd*, $J = 15.1, 9.8$, COCH); 2.82–3.04 (br., COCH); 3.30–3.34 (br., CH_2N); 4.12, *4.20* (*s*, NCH); 5.12 (*s*, $PhCH_2$); 7.35 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 22.80, *23.53* (CH_2); 28.50 (Me); *30.56*, 31.27, *38.53*, 39.37, 46.20, *46.59* (CH_2); 54.05 (CH); 66.21 (CH_2); *79.27*, 79.62 (C); 128.21, 128.54 (CH); 135.92, 154.27, 171.36 (C). EI-MS: 320 (< 1, $[M+1]^+$), 319 (< 1, M^+), 218 (100), 128 (67.2), 91 (89.0), 70 (45.3). Anal. calc. for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.39; found: C 67.83, H 7.89, N 4.42.

tert-*Butyl (*R*)-2-[2-(Benzyloxy)-2-oxoethyl]pyrrolidine-1-carboxylate* (Boc-(*R*)-β³-HPro-OBn; (*R*)-**2a**). Compound (*R*)-**1** (3.00 g, 12.5 mmol) was rearranged with CF_3COOAg (10%) in BnOH/THF 15:85 (*v*/*v*) according to [22]. After removal of BnOH by distillation (0.5 mbar, 68°), FC (Et_2O/pentane 1:2) yielded (*R*)-**2a** (2.99 g, 75%). Colorless oil. $[\alpha]_D^{r.t.} = +36.3$ ($c = 1.0$, $CHCl_3$). Other spectroscopic data: corresponding to (*S*)-**2a**.

*(*R*)-1-[(*tert*-Butoxy)carbonyl]pyrrolidine-2-acetic Acid* (Boc-(*R*)-β³-HPro-OH; (*R*)-**2b**). Compound (*R*)-**1** (5.20 g, 21.7 mmol) was rearranged with CF_3COOAg (10%) in H_2O/THF 10:90 (*v*/*v*) according to [22]. Recrystallization (CH_2Cl_2/hexane) yielded (*R*)-**2b** (3.76 g, 76%). White powder. M.p. 99–100°. R_f (CH_2Cl_2/MeOH 20:1) 0.30. $[\alpha]_D^{r.t.} = +40.6$ ($c = 1.9$, DMF). IR ($CHCl_3$): 2980*m*, 2881*w*, 1711*s*, 1684*s*, 1477*w*, 1403*s*, 1368*m*, 1286*w*, 1168*s*, 1127*m*, 927*w*, 860*w*. ^{1}H-NMR (400 MHz, CD_3OCD_3): 1.44 (*s*, *t*-Bu); 1.77–1.96 (*m*, 3 CH); 2.01–2.10 (*m*, 1 CH); 2.26–2.37 (*m*, COCH); 2.75–2.95 (*m*, COCH); 3.31 (*m*, CH_2N); 4.05–4.11 (*m*, NCH). ^{13}C-NMR (100 MHz, CD_3OCD_3; values for rotamers in italics): *28.28*, 24.06 (CH_2); 28.63 (Me); 31.19, *32.00*, 38.48, *39.55*, *46.90*, 47.25 (CH_2); 54.91 (CH); 79.28, *154.45*, 154.76, 172.85 (C). FAB-MS: 481 (13.4, $[2M+Na]^+$), 459 (14.7, $[2M+1]^+$), 252 (28.6, $[M+Na]^+$), 230 (100, $[M+1]^+$), 174 (92.1), 130 (55.6). Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.63, H 8.35, N 6.11; found: C 57.51, H 8.34, N 6.04.

*(*S*)-1-[(*tert*-Butoxy)carbonyl]pyrrolidine-2-acetic Acid* (Boc-(*S*)-β³-HPro-OH; (*S*)-**2b**). Compound (*S*)-**1** (20.34 g, 85.0 mmol) was rearranged with CF_3COOAg (10%) in H_2O/THF 10:90 (*v*/*v*) according to [22]. Recrystallization (CH_2Cl_2/hexane) yielded (*S*)-**2b** (11.86 g, 61%). White powder. $[\alpha]_D^{r.t.} = -40.5$ ($c = 1.9$, DMF) ([27]: $[\alpha]_D^{r.t.} = -41.6$ ($c = 1.9$, DMF); [28]: $[\alpha]_D^{r.t.} = -39.5$ ($c = 1.9$, DMF)). Other spectroscopic data: corresponding to (*R*)-**2b**.

*Boc-(*S*)-β³-HPro-(*S*)-β³-HPro-OBn* (**6**). Compound (*S*)-**2a** (639 mg, 2.0 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with (*S*)-**2b** (459 mg, 2.0 mmol) according to *GP 4* for

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26) Freshly prepared according to [47] by the slow addition of EtOH (0.5 ml) to AcCl (0.85 ml) at 0° and dilution to 1 ml.

2.5 d. FC (AcOEt/pentane 1:1) yielded **6** (540 mg, 63%). White, waxy solid. M.p. 68–69°. R_f (AcOEt/pentane 1:1) 0.31. $[\alpha]_D^{r.t.} = -60.8$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3007*m*, 2978*m*, 2880*w*, 1730*m*, 1680*s*, 1634*m*, 1454*m*, 1401*s*, 1366*m*, 1305*w*, 1168*m*, 1124*w*, 907*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 1.81–2.55 (*m*, 8 CH, 2 COCH); 2.98–3.03 (*m*, 2 COCH); 3.31–3.68 (*m*, 4 CHN); 4.05–4.13 (*m*, NCH); 4.39–4.45 (*m*, NCH); 5.07–5.14 (*m*, PhCH_2); 7.30–7.39 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): *21.54*, 23.47, 24.00 (CH_2); 28.58 (Me); 29.91, 30.12, *31.20*, 37.55, 39.24, 45.23, 46.28 (CH_2); 53.74, *54.24*, 54.57 (CH); 66.25, *66.63* (CH_2); 79.10, *79.51* (C); 128.20, 128.32, 128.54, 128.67 (CH); 135.92, 154.40, 169.89, 171.31 (C). FAB-MS: 453 (5.9, $[M+Na]^+$), 431 (66.5, $[M+1]^+$), 331 (100), 329 (35.0). Anal. calc. for $C_{24}H_{34}N_2O_5$ (430.54): C 66.95, H 7.96, N 6.51; found: C 66.76, H 7.88, N 6.56.

*Boc-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-OBn* (**7a**). Compound **6** (5.73 g, 13.3 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with (*S*)-**2b** (3.05 g, 13.3 mmol) according to *GP 4* for 16 h. FC ($MeOH/CH_2Cl_2$ 1:22 → 1:10) yielded **7a** (6.58 g, 91%). Colorless, highly viscous oil. R_f (CH_2Cl_2/MeOH 22:1) 0.29. $[\alpha]_D^{r.t.} = -69.6$ ($c = 1.0$, $CHCl_3$). UV (0.2 mM, MeOH): λ_{max} 213 nm. CD (0.2 mM, MeOH): $-1.32 \cdot 10^5$ (202 nm), $+4.09 \cdot 10^4$ (222 nm). IR ($CHCl_3$): 3007*m*, 2977*m*, 2879*w*, 1729*m*, 1681*s*, 1632*s*, 1402*s*, 1366*m*, 1168*m*, 1124*w*, 907*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 1.74–2.36 (*m*, 16 CH); 2.94–3.02 (*m*, 2 COCH); 3.32–3.68 (*m*, 6 NCH); 4.13–4.15 (*m*, NCH); 4.27–4.30 (*m*, NCH); 4.38–4.45 (*m*, NCH); 5.07–5.14 (*m*, PhCH_2); 7.29–7.36 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 23.82, 23.93, 24.02 (CH_2); 28.57 (Me); 29.36, 29.92, 30.57, 37.61, 38.30, 39.17, 46.64, 47.18, 47.29 (CH_2); 53.72, 54.13 (CH); 66.24, *66.57* (CH_2); 79.13, *79.47* (C); 128.17, 128.32, 128.52, 128.62 (CH); 135.93, 154.39, 169.60, 169.75, 171.30 (C). FAB-MS: 542 (42.9, $[M+1]^+$), 443 (30.5), 442 (100), 91 (100). Anal. calc. for $C_{30}H_{43}N_3O_6$ (541.69): C 66.52, H 8.00, N 7.76; found: C 66.66, H 7.86, N 7.63.

*Boc-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-OH* (**7b**). Compound **7a** (3.20 g, 5.9 mmol) was debenzylated in AcOEt according to *GP 2* to yield **7b** (2.65 g, quant.). White powder. M.p. 63–68°. R_f (CH_2Cl_2/MeOH 12:1) 0.28. $[\alpha]_D^{r.t.} = -56.5$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3007*m*, 2979*m*, 2880*w*, 1728*m*, 1681*s*, 1629*s*, 1451*m*, 1401*s*, 1367*m*, 1170*m*, 1125*w*, 907*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.45 (*s*, *t*-Bu); 1.80–2.11 (*m*, 12 CH); 2.22–2.43 (*m*, 3 COCH); 2.77–3.03 (*m*, 3 COCH); 3.28–3.66 (*m*, 6 NCH); 4.10–4.15 (*m*, NCH); 4.30–4.35 (br., 2 NCH). ^{13}C-NMR (100 MHz, CD_3OD; values for rotamers in italics): 22.41, 24.54, 24.67 (CH_2); 28.85 (Me); 30.81, 30.99, 32.17, 38.03, 39.02, 40.03, 46.50, 47.33, 47.72 (CH_2); 55.45, 55.52, 55.59 (CH); 73.93, 80.70, *81.36*, 156.16, 171.92, 175.04 (C). FAB-MS: 474 (16.2, $[M+Na]^+$), 452 (24.4, $[M+1]^+$), 352 (100), 241 (48.0). Anal. calc. for $C_{23}H_{37}N_3O_6$ (451.56): C 61.18, H 8.26, N 9.31; found: C 61.09, H 8.16, N 9.11.

*TFA · H-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-OBn* (**7c**). Compound **7a** (2.59 g. 4.8 mmol) was Boc-deprotected according to *GP 3* to yield **7c** (3.41 g, quant.). Colorless oil, which crystallized after 15 d upon storage at −20°: colorless crystals, suitable for X-ray analysis. CD (0.2 mM, MeOH): $-2.83 \cdot 10^4$ (203 nm), $8.80 \cdot 10^3$ (223 nm). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.78–2.26 (*m*, 12 CH); 2.43 (*dd*, $J = 14.3$, 7.4, COCH); 2.51 (*dd*, $J =$ 15.5, 8.4, COCH); 2.70 (*dd*, $J = 14.3$, 6.8, COCH); 2.83–2.92 (*m*, 3 COCH); 3.35–3.61 (*m*, 6 NCH); 3.88–3.94 (*m*, NCH); 4.33–4.38 (*m*, NCH); 4.49–4.52 (*m*, NCH); 5.10–5.17 (*m*, PhCH_2); 7.33–7.42 (*m*, 5 arom. H); 8.55 (br., NH); 8.91 (br., NH). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 23.23, 23.36, 23.61, 29.25, 30.07, 30.19, 34.23, 37.37, 38.25, 45.58, 47.17, 47.89 (CH_2); 53.92, 55.32, 57.57 (CH); 66.78, *67.03* (CH_2); 115.23 (q, $J = 282.9$, CF_3); 128.25, 128.34, 128.42, 128.62, 128.71 (CH); *135.20*, 135.52 (C); 160.20 (q, $J = 40.0$, CCF_3); 169.90, 171.28, 171.31 (C). FAB-MS: 883 (12.1, $[2M]^+$), 443 (36.1, $[M+1]^+$), 442 (100, M^+).

*Boc-(*S*)-β³-HPro-(*R*)-β³-HPro-OBn* (**8a**). Compound (*R*)-**2a** (3.23 g, 10.1 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with (*S*)-**2b** (2.42 g, 10.1 mmol) according to *GP 4* for 2 d. FC (AcOEt/pentane 1:1) yielded **8a** (2.82 g, 62%). Colorless oil. R_f (AcOEt/pentane 1:1) 0.26. $[\alpha]_D^{r.t.} = -6.02$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3007*m*, 2978*m*, 2879*w*, 1730*m*, 1681*s*, 1635*m*, 1456*m*, 1401*s*, 1367*m*, 1168*m*, 1125*w*, 907*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; values for rotamers in italics): 1.43, *1.46* (*s*, *t*-Bu); 1.81–2.21 (*m*, 10 CH); 2.72–3.04 (*m*, 2 COCH); 3.32–3.57 (*m*, 4 NCH); 4.15 (*m*, NCH); 4.41 (*m*, NCH); 5.07–5.14 (*m*, PhCH_2); 7.30–7.38 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 23.52, 23.95 (CH_2); 28.59 (Me); 30.08, 31.26, 37.69, 39.00, 45.42, 47.19 (CH_2); 53.82, 54.28 (CH); 66.25 (CH_2); 79.09, *79.49* (C); 128.21, 128.28, 128.53 (CH); 135.94, 154.41, 169.73, *171.30* (C). FAB-MS: 430 (3.8, M^+), 329 (64.0), 91 (100). Anal. calc. for $C_{24}H_{34}N_2O_5$ (430.54): C 66.95, H 7.96, N 6.51; found: C 66.88, H 7.86, N 6.56.

*Boc-(*S*)-β³-HPro-(*R*)-β³-HPro-OH* (**8b**). Compound **8a** (3.30 g, 7.7 mmol) was debenzylated according to *GP 2* in AcOEt to yield **8b** (2.65 g, quant.). White powder. M.p. 140–141°. R_f (CH_2Cl_2/MeOH 9:1) 0.35. $[\alpha]_D^{r.t.} = -38.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3007*m*, 2980*m*, 2880*w*, 1729*m*, 1681*s*, 1627*m*, 1455*m*, 1401*s*, 1367*m*, 1169*m*, 1126*w*, 904*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.46 (*s*, *t*-Bu); 1.83-2.13 (*m*, 8 CH); 2.34–2.51 (*m*, 2 COCH); 2.68–2.89 (*m*, 2 COCH); 3.28–3.60 (*m*, 4 NCH); 4.10–4.22 (*m*, NCH). ^{13}C-NMR (100 MHz, CD_3OD; values for rotamers in italics): 22.42, 24.64 (CH_2); 28.84 (Me); 31.12, 38.12, *39.86*, 40.37, 46.60, *47.37*,

47.76 (CH_2); 55.51, 56.35 (CH); 80.74, *81.35*, 156.22, 172.02, 175.08 (C). FAB-MS: 703 (3.8, $[M+Na]^+$), 681 (7.7, $[2M+1]^+$), 363 (11.4, $[M+Na]^+$), 341 (100, $[M+1]^+$), 241 (95.8). Anal. calc. for $C_{17}H_{28}N_2O_5$ (340.42): C 59.98, H 8.29, N 8.23; found: C 60.10, H 8.12, N 8.22.

*Boc-(*S*)-β³-HPro-(*R*)-β³-HPro-(*S*)-β³-HPro-(*R*)-β³-HPro-OBn* (**9**). Compound **8a** (1.68 g, 3.9 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with **8b** (1.33 g, 3.9 mmol) according to *GP 4* for 16 h. FC ($MeOH/CH_2Cl_2$ 1:17) yielded **9** (2.08 g, 81%). White solid. M.p. 156–159°. R_f (CH_2Cl_2/MeOH 17:1) 0.30. $[\alpha]_D^{r.t.} = -2.12$ ($c = 1.0$, $CHCl_3$). CD (0.2 mM, MeOH): $+9.86 \cdot 10^3$ (214 nm). IR ($CHCl_3$): 3007*m*, 2979*m*, 2879*w*, 1730*m*, 1681*m*, 1631*s*, 1495*s*, 1366*m*, 1169*m*, 1124*w*, 1103*w*, 907*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; values for rotamers in italics): *1.42*, 1.46 (*s*, *t*-Bu); 1.70–2.21 (*m*, 19 CH); 2.40 (*dd*, $J = 15.3, 9.2$, COCH); 2.71–3.02 (*m*, 4 COCH); 3.35–3.66 (*m*, 8 NCH); 4.07–4.18 (*m*, NCH); 4.31–4.41 (*m*, 3 NCH); 5.07–5.15 (*m*, PhC*H*$_2$); 7.29–7.38 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 21.65, 23.83, 23.91, 23.98 (CH_2); 29.59 (Me); *29.71*, 29.76, 29.84, *30.07*, 30.12, *30.61*, 31.59, *37.03*, *37.63*, 37.69, 37.83, 38.18, 38.40, *39.46*, 45.57, 47.05, 47.17, 47.26 (CH_2); 53.87, *53.99*, 54.13, 54.22, 54.57 (CH); 66.26, 66.37 (CH_2); 79.16, *79.59*, 128.20, 128.24, 128.28, *128.38*, 128.54, 128.57, *128.62*, 135.94, 154.42, 169.61, 171.36 (C). FAB-MS: 653 (100, $[M+1]^+$), 554 (21.0), 553 (57.4). Anal. calc. for $C_{36}H_{52}N_4O_7$ (652.83): C 66.23, H 8.03, N 8.58; found: C 66.05, H 7.96, N 8.60.

*Boc-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-OBn* (**10a**). Compound **7a** (2.60 g, 4.8 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with **7b** (2.16 g, 4.8 mmol) according to *GP 4* for 2.5 d. FC ($MeOH/CH_2Cl_2$ 1:15) yielded **10a** (3.54 g, 85%). White foam. M.p. 65–68°. R_f (CH_2Cl_2/MeOH 15:1) 0.28. $[\alpha]_D^{r.t.} = -84.8$ ($c = 1.0$, $CHCl_3$). UV (0.2 mM, MeOH): λ_{max} 217 nm. CD (0.2 mM, MeOH): $-1.90 \cdot 10^5$ (202 nm), $+9.02 \cdot 10^4$ (222 nm). M.p. 65–68°. IR ($CHCl_3$): 3007*m*, 2978*m*, 2879*w*, 1730*w*, 1680*m*, 1632*s*, 1425*s*, 1366*w*, 1170*m*, 1123*w*, 1097*w*, 907*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 1.72–2.15 (*m*, 30 CH); 2.33 (*dd*, $J = 15.4, 9.5$, COCH); 2.96–3.05 (*m*, 5 COCH); 3.36–3.66 (*m*, 12 NCH); 4.11–4.18 (*m*, NCH); 4.29–4.44 (*m*, 5 NCH); 5.07–5.30 (*m*, PhC*H*$_2$); 7.29–7.37 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 21.57, 23.48, 23.80, 23.93, 24.01 (CH_2); 28.58 (Me), 29.40, 29.83, 29.86, 29.92, 30.61, 37.62, 38.11, 38.17, 38.31, 39.11, 45.25, 46.65, 47.11, 47.15, 47.23, 47.28, *47.37* (CH_2); 53.71, 54.03, 54.06, 54.11, 54.25, 54.49 (CH); 66.22, *66.55* (CH_2); 79.14, *79.48* (C); 128.15, 128.31, 128.38, 128.52, 128.60 (CH); *135.68*, 135.96, 154.42, 169.51, 169.62, 169.71, 169.74, 171.32 (C). FAB-MS: 898 (13.1, $[M+Na]^+$), 876 (27.1, $[M+1]^+$), 875 (52.9, M^+), 775 (100). Anal. calc. for $C_{48}H_{70}N_6O_9$ (875.12): C 65.43, H 8.69, N 9.54; found: C 65.47, H 8.87, N 9.45.

*Boc-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-OH* (**10b**). Compound **10a** (1.01 g, 1.2 mmol) was debenzylated in AcOEt according to *GP 2* to yield **10b** (1.02 g, quant.). White foam. M.p. 69–73°. R_f (CH_2Cl_2/MeOH 7:1) 0.24. $[\alpha]_D^{r.t.} = -67.3$ ($c = 1.0$, $CHCl_3$). CD (0.2 mM, MeOH): $-8.14 \cdot 10^4$ (204 nm), $+5.20 \cdot 10^4$ (224 nm). IR ($CHCl_3$): 3307*m*, 2979*m*, 2879*w*, 1728*w*, 1681*m*, 1630*s*, 1423*s*, 1366*w*, 1173*w*, 1048*w*, 881*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.45 (*s*, *t*-Bu); 1.83–2.16 (*m*, 24 CH); 2.23–2.38 (*m*, 6 COCH); 2.46–2.59 (*m*, COCH); 2.77–3.03 (*m*, 5 COCH); 3.30–3.71 (*m*, 12 NCH); 4.09–4.14 (*m*, NCH); 4.31–4.49 (*m*, 5 NCH). ^{13}C-NMR (100 MHz, CD_3OD; values for rotamers in italics): 22.41, 24.33, 24.55, 24.67 (CH_2); 28.78, 28.86 (Me); 30.85, 31.01, 31.42, 31.69, 32.16, 38.07, 39.01, 40.03, 46.50, 47.36, 47.72 (CH_2); 55.45, 55.51, 55.60, 56.11, 56.22, 57.81 (CH); 80.69, *81.35*, 156.16, 171.02, 171.14, 171.92, 172.03, 174.40, 175.11 (C). FAB-MS: 808 (39.1, $[M+Na]^+$), 807 (91.7), 786 (42.1, $[M+1]^+$), 785 (100, M^+), 685 (60.5).

*Boc-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HПgoS)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-OBn* (**11**). Compound **10a** (166 mg, 0.19 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with **10b** (150 mg, 0.19 mmol) according to *GP 4* for 40 h. Recrystallization (CH_2Cl_2/hexane) yielded **11** (233 mg, 79%). White foam. M.p. 95° (dec.). R_f (CH_2Cl_2/MeOH 9:1) 0.30. $[\alpha]_D^{r.t.} = -87.4$ ($c = 1.0$, $CHCl_3$). CD (0.1 mM, MeOH): $-2.63 \cdot 10^5$ (203 nm), $+1.82 \cdot 10^5$ (223 nm). IR ($CHCl_3$): 3005*m*, 2878*w*, 1729*m*, 1631*s*, 1525*m*, 1426*s*, 1352*m*, 857*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 1.74–2.17 (*m*, 60 CH); 2.33 (*dd*, $J = 15.3, 9.5$, COCH); 2.96–3.02 (*m*, 11 COCH); 3.36–3.67 (*m*, 24 NCH); 4.15–4.49 (*m*, 12 NCH); 5.07–5.14 (*m*, PhC*H*$_2$); 7.28–7.38 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.53, 22.66, 23.78, 24.01 (CH_2); 28.58 (Me); 29.39, 29.71, 29.88, 29.91, 31.59, 37.61, 38.10, 38.16, 38.30, 47.12, 47.28 (CH_2); 53.44, 53.71, 54.05, 54.10, 54.23, 54.52 (CH); 66.23 (CH_2); 79.16 (C); 128.16, 128.32, 128.40, 128.52, 128.61 (CH); 135.95, 154.44, 168.64, 169.32, 169.64, 169.74, 171.35 (C). FAB-MS: 1565 (4.1, $[M+Na]^+$), 1543 (100, $[M+1]^+$). ESI-MS (pos. mode): 1580.3 ($[M+K]^+$), 1564.4 ($[M+Na]^+$), 1542.3 ($[M+1]^+$).

*Boc-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-(*S*)-β³-HPro-*

(S)-β³-HPro-(S)-β³-HPro-OBn (**12**). Compound **11** (62 mg, 0.040 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with **10b** (31 mg, 0.040 mmol) according to *GP 4* for 3 d. Recrystallization (CH_2Cl_2/pentane) yielded **12** (48 mg, 54%). White powder. M.p. 228° (dec.). R_f (CH_2Cl_2/MeOH 9:1) 0.22. $[\alpha]_D^{r.t.} = -74.0$ ($c = 1.0$, $CHCl_3$). CD (0.2 mM, MeOH): $-3.46 \cdot 10^5$ (202 nm), $+2.09 \cdot 10^5$ (223 nm). IR ($CHCl_3$): 3006*m*, 2878*w*, 1728*w*, 1680*w*, 1632*s*, 1425*m*, 1360*w*, 1323*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.46 (*s*, *t*-Bu); 1.83–2.18 (*m*, 90 CH); 2.33 (*dd*, $J = 15.4$, 9.5, COCH); 2.92–3.02 (*m*, 17 COCH); 3.33–3.65 (*m*, 36 NCH); 4.12–4.52 (*m*, 18 NCH); 5.07–5.13 (*m*, PhCH_2); 7.29–7.37 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 23.78, 24.01 (CH_2); 28.60 (Me); 29.42, 29.89, 37.62, 38.12, 38.40, 47.13, 47.29 (CH_2); 53.44, 53.73, 54.06, 54.12, 54.47 (CH); 66.24 (C); 128.16, 128.31, 128.52 (CH); 135.96, 154.45, 169.67, 169.76, 171.34 (C). FAB-MS: 2208 (100, M^+), 1104 (52.2). ESI-MS (pos. mode): 2231.8 ($[M + Na]^+$).

Ac-(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-OBn (**13**). Fully protected β^3-hexapeptide **10a** (0.197 g, 0.225 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was dissolved in CH_2Cl_2 (2.3 ml) and treated at 0° with Ac_2O (0.03 ml, 0.293 mmol) and (i-Pr)$_2$EtN (0.12 ml, 0.675 mmol). After 2.5 h, the soln. was diluted with CH_2Cl_2 and washed with 1N HCl, sat. aq. $NaHCO_3$, and NaCl solns. The org. phase was dried ($MgSO_4$) and evaporated under reduced pressure. FC (MeOH/CH_2Cl_2 1:12) yielded **13** (101 mg, 55%). White foam. M.p. 63–67°. R_f (CH_2Cl_2/MeOH 12:1) 0.26. $[\alpha]_D^{r.t.} = -77.9$ ($c = 1.0$, $CHCl_3$). CD (0.2 mM, MeOH): $-1.14 \cdot 10^5$ (203 nm), $+6.42 \cdot 10^4$ (223 nm). IR ($CHCl_3$): 3004*m*, 2878*w*, 1730*w*, 1631*s*, 1503*w*, 1422*m*, 1359*w*, 1325*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.73–2.18 (*m*, 33 CH); 2.32 (*dd*, $J = 15.4$, 9.5, COCH); 2.96–3.09 (*m*, 5 COCH); 3.29–3.73 (*m*, 12 NCH); 4.29–4.44 (*m*, 6 NCH); 5.07–5.14 (*m*, PhCH_2); 7.28–7.37 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 14.05 (C); 22.21, 22.33 (CH_2); 23.03 (Me); 23.76, 23.90, 23.99, 29.38, 29.72, 29.81, 29.84, 29.90, 30.04, *31.63*, 37.59, 37.94, 38.11, 38.15, 38.29, 39.63, 45.25, 45.47. 47.13, 47.21, 47.27, 47.88 (CH_2); 53.70, 54.01, 54.05, 54.09, 54.16, 54.39, *54.48*, *55.32* (CH); 66.22 (CH_2); 128.15, 128.30, 128.38, 128.51, 128.60 (CH); 135.94, *168.64*, *169.33*, 169.57, 169.59, 169.61, 169.64, 169.73, 171.32 (C). FAB-MS: 839 (11.8, $[M + Na]^+$), 818 (45, $[M + 1]^+$), 817 (100, M^+).

(4-NO$_2$C$_6$H$_4$)CO–(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-(S)-β³-HPro-OBn (**14**). Fully protected β^3-hexapeptide **10a** (0.197 g, 0.225 mmol) was Boc-deproteced according to *GP 3*. The resulting TFA salt was dissolved in CH_2Cl_2 (1 ml) and treated at 0° with Et_3N (0.28 ml, 0.675 mmol), *p*-nitrobenzoyl chloride (50 mg, 0.270 mmol) and DMAP (2.8 mg, 0.023 mmol). The yellow suspension was stirred for 13 h at r.t. After dilution with CH_2Cl_2, the mixture was washed with sat. aq. NH_4Cl, $NaHCO_3$, and NaCl solns. The org. phase was dried ($MgSO_4$) and evaporated under reduced pressure. FC (MeOH/CH_2Cl_2 1:12) yielded **14** (166 mg, 80%). Yellow foam. M.p. 148° (dec.). R_f (CH_2Cl_2/MeOH 12:1) 0.34. $[\alpha]_D^{r.t.} = -44.1$ ($c = 1.0$, $CHCl_3$). CD (0.2 mM, MeOH): $-1.23 \cdot 10^5$ (204 nm), $+6.06 \cdot 10^4$ (225 nm). IR ($CHCl_3$): 3005*m*, 2878*w*, 1730*w*, 1632*s*, 1525*m*, 1426*s*, 1352*m*, 1045*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.73–2.08 (*m*, 27 CH); 2.12 (*dd*, $J = 15.0$, 10.5, COCH); 2.33 (*dd*, $J = 15.4$, 9.4, COCH); 2.45 (*dd*, $J = 15.1$, 9.4, COCH); 2.96–3.03 (*m*, 5 COCH); 3.12 (*dd*, $J = 15.1$, 3.1, COCH); 3.35–3.67 (*m*, 12 NCH); 4.37–4.56 (*m*, 6 NCH); 5.07–5.14 (*m*, PhCH_2); 7.28–7.38 (*m*, 5 arom. H); 7.67–7.72 (*m*, 2 arom. H); 8.25–8.29 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$; values for rotamers in italics): 21.54, 23.77, 23.79, 23.99, 24.92, 29.38, 29.69, 29.83, 29.90, 29.94, 30.40, 37.59, 38.01, 38.08, 38.14, 38.22, 38.29, 47.11, 47.14, 47.21, 47.26, 50.23 (CH_2); 53.70, 54.02, 54.10, 54.18, 54.98 (CH); 66.22 (CH_2); 123.63, 123.71, 128.15, 128.23, 128.30, 128.38, 128.51, *128.60* (CH); 135.94, 143.07, 148.53, *167.58*, *169.09*, 169.47, 169.56, 169.61, 169.71, 171.33 (C). FAB-MS: 946 (17.4, $[M + Na]^+$), 925 (49.0, $[M + 1]^+$), 924 (100, M^+).

Boc-(S)-β³-HPro-(R)-β³-HPro-(S)-β³-HPro-(R)-β³-HPro-(S)-β³-HPro-(R)-β³-HPro-OBn (**15**). Fully protected β^3-tetrapeptide **9** (1.89 g, 2.9 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with **8b** (0.98 g, 2.9 mmol) according to *GP 4* for 3 d. FC (MeOH/CH_2Cl_2 1:15) yielded **15** (632 mg, 25%). White powder. M.p. 246° (dec.). R_f (CH_2Cl_2/MeOH 17:1) 0.29. $[\alpha]_D^{r.t.} = -1.68$ ($c = 1.0$, $CHCl_3$). CD (0.2 mM, MeOH): $+1.06 \cdot 10^4$ (210 nm). IR ($CHCl_3$): 3004*m*, 2976*m*, 2880*w*, 1730*w*, 1682*m*, 1631*s*, 1421*s*, 1366*w*, 1171*m*, 1123*w*, 1103*w*, 906*w*. ^{1}H-NMR (500 MHz, $CDCl_3$; values for rotamers in italics): *1.42*, 1.46 (*s*, *t*-Bu); 1.73–2.19 (*m*, 30 CH); 2.39 (*dd*, $J = 15.3$, 9.2, COCH); 2.75–3.03 (*m*, 6 COCH); 3.36–3.65 (*m*, COCH); 4.08–4.18 (*m*, NCH); 4.29–4.41 (*m*, 5 NCH); 5.07–5.15 (*m*, PhCH_2); 5.07–5.14 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$; values for rotamers in italics): 21.63, *21.66*, *23.75*, 23.83, 23.85, 23.89, 23.92, 24.01 (CH_2); 28.60 (Me); 29.71, 29.75, 29.82, 30.14, *30.65*, 30.69, 31.62, 37.08, *37.64*, 37.69, *38.16*, 38.22, 38.41, 38.46, 39.49, 46.55, 47.01, 47.11, 47.17, 47.22, 47.26 (CH_2); 53.85, *53.97*, 54.13, 54.20, 54.22, 54.51, 54.63 (CH); 66.22, 66.33 (CH_2); 79.10, *79.56* (C); 128.18, 128.23, 128.26, 128.52, 128.56 (CH); 135.97, 154.39, 169.56, 171.33 (C). FAB-MS: 898 (14.2, $[M + Na]^+$), 877 (49.3, $[M + 1]^+$), 876 (100, M^+). Anal. calc. for $C_{48}H_{70}N_6O_9$ (875.12): C 65.88, H 8.06, N 9.60; found: C 65.62, H 8.01, N 9.58.

8. *β²-Peptides. Ethyl (S)-Piperidine-3-carboxylate (S,S)-Hydrogen Tartrate* ((S)-*Ethyl Nipecotate (S,S)-Hydrogen Tartrate*; (*S,S,S*)-**3**). According to [36], *rac*-ethyl nipecotate (28.0 g, 0.178 mol) was resolved with

(*S*,*S*)-tartaric acid (26.7 g, 0.178 mol) to yield (*S*,*S*,*S*)-**3** (15.04 g, 27%) after recrystallization from EtOH (3×). M.p. 156–157° ([36]: M.p. 155–156°). $[\alpha]_D^{r.t.} = -46.3$ ($c = 2.0$, $(NH_4)_6Mo_7O_{24}$ (0.2% aq. soln.)) ([36]: $[\alpha]_D^{r.t.} = -51.0$ ($c = 2.0$, $(NH_4)_6Mo_7O_{24}$ (0.2% aq. soln.))).

*Ethyl (*R*)-Piperidine-3-carboxylate (*R,R*)-Hydrogen Tartrate ((*R*)-Ethyl Nipecotate (*R,R*)-Hydrogen Tartrate*; (*R*,*R*,*R*)-**3**). According to [36], *rac*-ethyl nipecotate (11.28 g, 71.6 mmol) was resolved with (*R*,*R*)-tartaric acid (14.5 g, 67.0 mmol) to yield (*R*,*R*,*R*)-**3** (5.44 g, 25%) after recrystallization from EtOH (3×). M.p. 156–158° ([36]: M.p. 155–156°). $[\alpha]_D^{r.t.} = +52.3$ ($c = 2.0$, $(NH_4)_6Mo_7O_{24}$ (0.2% aq. soln.)) ([36]: $[\alpha]_D^{r.t.} = +51.0$ ($c = 2.0$, $(NH_4)_6Mo_7O_{24}$ (0.2% aq. soln.))).

*Ethyl (*S*)-Piperidine-3-carboxylate ((*S*)-Ethyl Nipecotate*; *H-(*S*)-β²-HPro-OEt*; (*S*)-**4a**). Similarly to [36], (*S*,*S*,*S*)-**3** (30 g, 97.6 mmol) was dissolved at 0° in sat. aq. NaCl soln. (50 ml). At this temp., the pH was carefully adjusted to 13, and the aq. phase was extracted rapidly with Et_2O (3×). The Et_2O phases were washed with H_2O, dried ($MgSO_4$), and evaporated to yield (*S*)-**4a** (10.0 g, 65%). Yellowish oil. $[\alpha]_D^{r.t.} = +1.38$ ($c = 5.0$, H_2O) ([36]: $[\alpha]_D^{r.t.} = +1.6$ ($c = 5.0$, H_2O)). The er was determined by derivatization according to *GP 5* and subsequent HPLC analysis according to *GP 7:* er 99.6 : 0.4.

*Ethyl (*R*)-Piperidine-3-carboxylate ((*R*)-Ethyl Nipecotate*; *H-(*R*)-β²-HPro-OEt*; (*R*)-**4a**). Similarly to [36], (*R*,*R*,*R*)-**3** (19.5 g, 64 mmol) was dissolved at 0° in sat. aq. NaCl soln. (30 ml). At this temp., the pH was carefully adjusted to 13, and the aq. phase was extracted rapidly with Et_2O (3×). The Et_2O phases were washed with H_2O, dried ($MgSO_4$), and evaporated to yield (*R*)-**4a** (4.5 g, 45%). Yellowish oil. $[\alpha]_D^{r.t.} = -1.26$ ($c = 5.0$, H_2O) ([36]: $[\alpha]_D^{r.t.} = -1.8$ ($c = 5.0$, H_2O)). The er was determined by derivatization according to *GP 5* and subsequent HPLC analysis according to *GP 7:* er 98.9 : 1.1.

*Ethyl (*S*)-1-[(*tert*-Butoxy)carbonyl]piperidine-3-carboxylate* (*Boc-(*S*)-β²-HPro-OEt*; (*S*)-**4b**). Compound (*S*)-**4a** (6.5 g, 41.3 mmol, er 99.6 : 0.4) and Boc_2O (9.5 g, 43.5 mmol) were dissolved in CH_2Cl_2 (80 ml). After stirring at r.t. for 16 h, the soln. was washed with sat. aq. NH_4Cl and NaCl solns., dried ($MgSO_4$), and evaporated under reduced pressure. FC (Et_2O/pentane 1 : 6 → 1 : 1) yielded (*S*)-**4b** (7.9 g, 74%). Colorless oil. R_f (Et_2O/pentane 1 : 6) 0.29. $[\alpha]_D^{r.t.} = +50.7$ ($c = 0.95$, $CHCl_3$). IR ($CHCl_3$): 3008*m*, 2979*m*, 1725*s*, 1683*s*, 1476*w*, 1426*s*, 1393*w*, 1367*m*, 1170*s*, 1151*s*, 1043*w*, 928*w*, 880*w*, 856*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (*t*, *J* = 7.1, Me); 1.46–1.55 (*m*, *t*-Bu, CH); 1.56–1.74 (*m*, 3 CH); 2.01–2.07 (*m*, CH); 2.39–2.46 (*m*, CH); 2.80 (*ddd*, *J* = 13.3, 11.3, 3.1, NCH); 2.97 (br., NCH); 3.92 (br. *d*, *J* = 12.9, NCH); 3.94–4.35 (*m*, NCH); 4.13 (*q*, *J* = 7.1, CH_2O). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.20 (Me); 24.30, 24.37 (CH_2); 28.43 (Me); 41.46 (CH); 44.00, 45.65, 60.50 (CH_2); 79.67, 154.70, 173.49 (C). FAB-MS: 281 (< 1, $[M + Na]^+$), 257 (< 1, M^+), 200 (18.2), 156 (38.1), 128 (38.1), 86 (51.8), 84 (100), 57 (27.1), 49 (44.3). Anal. calc. for $C_{13}H_{23}NO_4$ (257.33): C 60.68, H 9.01, N 5.44; found: C 60.71, H 8.98, N 5.45.

*(*S*)-1-[(*tert*-Butoxy)carbonyl]piperidine-3-carboxylic Acid* (*Boc-(*S*)-β²-HPro-OH*; (*S*)-**4c**). Compound (*S*)-**4b** (6.2 g, 24.1 mmol) was saponified according to *GP 1* with LiOH (1.44 g, 60.25 mmol) in MeOH (130 ml) and H_2O (43 ml) for 3 d at r.t. Recrystallization (Et_2O/pentane) yielded (*S*)-**4c** (5.01 g, 90%). Derivatization according to *GP 6* and HPLC according to *GP 7:* er 97.9 : 2.1. White powder. M.p. 165–167°. R_f (MeOH/CH_2Cl_2 1 : 10) 0.29. $[\alpha]_D^{r.t.} = +50.5$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 2980*w*, 2865*m*, 1709*s*, 1684*s*, 1467*w*, 1426*m*, 1367*m*, 1269*m*, 1173*m*, 1150*s*, 1040*w*, 1003*w*, 936*w*, 873*w*, 858*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41–1.56 (*m*, *t*-Bu, CH); 1.60–1.76 (*m*, 2 CH); 2.05–2.10 (*m*, CH); 2.45–2.53 (*m*, COCH); 2.83–2.89 (*m*, NCH); 3.05 (br., NCH); 3.86–3.91 (*m*, NCH); 4.12 (br., NCH); 7.27 (br., CO_2H). ^{13}C-NMR (100 MHz, $CDCl_3$): 24.12, 27.18 (CH_2); 28.40 (Me); 41.07 (CH); 43.83, 45.50 (CH_2); 79.92, 154.72, 178.88 (C). FAB-MS: 688 (9.6, $[3\ M + 1]^+$), 459 (16.4, $[2, M + 1]^+$), 230 (15.1, $[M + 1]^+$), 174 (100), 156 (34.9), 154 (25.0), 136 (21.5), 128 (24.9). Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.63, H 8.35, N 6.11; found: C 57.50, H 8.16, N 5.97.

Ethyl rac-N-*(2,4-Dinitrophenyl)piperidine-3-carboxylate* (*rac*-**5**). To a soln. of *rac*-ethyl nipecotate (0.671 g, 4.27 mmol) and $NaHCO_3$ (0.43 g, 5.12 mmol) in H_2O (8.5 ml) was added a soln. of 1-fluoro-2,4-dinitrobenzene (0.95 g, 5.12 mmol) in EtOH (16 ml) at 0°, similarly to [50]. After 5 h, the soln. was diluted with Et_2O and washed with 1N HCl (1×) and sat. NH_4Cl soln. (3×), dried ($MgSO_4$), and evaporated. FC (Et_2O/pentane 1 : 1) yielded *rac*-**5** (1.123 g, 81%). Orange sirup. R_f (Et_2O/pentane 1 : 1) 0.31. IR ($CHCl_3$): 3091*w*, 2961*w*, 2864*w*, 1726*m*, 1606*s*, 1530*s*, 1447*w*, 1336*s*, 1262*m*, 1178*m*, 1150*w*, 1097*m*, 1067*w*, 1030*m*, 965*w*, 943*w*, 916*w*, 858*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.25 (*t*, *J* = 7.1, Me); 1.71–1.91 (*m*, 3 CH); 2.10–2.17 (*m*, 1 CH); 2.72–2.78 (*m*, COCH); 3.07–3.13 (*m*, NCH); 3.30–3.39 (*m*, 2 NCH); 3.57–3.62 (*m*, NCH); 4.15 (*q*, *J* = 7.1, CH_2O); 7.19 (*d*, *J* = 9.4, 1 arom. H); 8.25 (*dd*, *J* = 9.3, 2.7, 1 arom. H); 8.70 (*d*, *J* = 2.7, 1 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.16 (Me); 23.93, 26.34 (CH_2); 40.95 (CH); 51.50, 52.52, 60.99 (CH_2); 119.95, 123.76, 128.17 (CH); 138.17, 138.30, 149.74, 172.61 (C). FAB-MS: 323 (7.1, M^+), 306 (100), 278 (29.7), 260 (25.5), 232 (59.9), 216 (45), 203 (67.7), 180 (45.2), 157 (29.4). Anal. calc. for $C_{14}H_{17}N_3O_6$ (323.30): C 52.01, H 5.30, N 13.00; found: C 52.27, H 5.52, N 12.85.

*Ethyl (*R*)-*N*-(2,4-Dinitrophenyl)piperidine-3-carboxylate* ((*R*)-**5**). Prepared according to *GP 5*. HPLC according to *GP 7:* t_R 20.5. Purification by FC (Et_2O/pentane 1:1). $[\alpha]_D^{r.t.} = -165.0$ ($c = 0.6$, $CHCl_3$). Other spectroscopic data: corresponding to *rac*-**5**.

*Ethyl (*S*)-*N*-(2,4-Dinitrophenyl)piperidine-3-carboxylate* ((*S*)-**5**). Prepared according to *GP 5*. HPLC according to *GP 7:* t_R 25.5. Purification by FC (Et_2O/pentane 1:1). $[\alpha]_D^{r.t.} = +164.8$ ($c = 0.6$, $CHCl_3$). Other spectroscopic data: corresponding to *rac*-**5**.

*Boc-(*S*)-β²-HPro-(*S*)-β²-HPro-OEt* (**16**). Compound (*S*)-**4a** (1.37 g, 8.72 mmol) was coupled with (*S*)-**4c** (2 g, 8.72 mmol) for 16 h according to *GP 4*. FC (AcOEt/pentane 1:2) yielded **16** (2.8 g, 87%). For anal. purposes, **16** was dried under h.v. at 35° overnight. Yellowish waxy solid. M.p. 71–72°. R_f (AcOEt/pentane 1:2) 0.25. $[\alpha]_D^{r.t.} = +61.1$ ($c = 0.365$, $CHCl_3$). IR ($CHCl_3$): 3007*w*, 2945*w*, 2866*w*, 1726*m*, 1681*s*, 1628*s*, 1468*w*, 1444*m*, 1425*m*, 1367*w*, 1306*w*, 1265*m*, 1177*m*, 1150*s*, 1031*w*, 856*w*. ^{1}H-NMR (400 MHz, $CDCl_3$, rotamers!): 1.23–1.30 (*m*, Me); 1.46–1.51 (*m*, *t*-Bu, CH); 1.62–1.88 (*m*, 6 CH); 2.05–2.08 (*m*, CH); 2.43–3.12 (*m*, 4 NCH, 2 COCH); 3.39 (br., 0.5 H, NCH); 3.73–4.21 (*m*, 5.5 H, NCH, CH_2O); 4.59 (br. *d*, $J = 10.3$, 0.5 H, NCH, rotamer). ^{13}C-NMR (100 MHz, $CDCl_3$, rotamers!): 14.19 (Me); 23.98, 24.71, 25.41, 27.35, 27.46, 27.73 (CH_2); 28.49 (Me); 38.97, 41.27 (CH); 42.02, 43.65, 45.75, 47.19, 60.62, 60.90 (CH_2); 72.51 (CH); 79.63, 154.66, 171.67, 171.99, 172.70, 173.19 (C). FAB-MS: 369 (24.2, $[M+1]^+$), 327 (18.8), 313 (100), 295 (78.8), 269 (63.9), 267 (64.1), 156 (70.1), 154 (49.6), 147 (76.1), 136 (96.1). Anal. calc. for $C_{19}H_{32}N_2O_5$ (368.47): C 61.93, H 8.75, N 7.60; found: C 61.89, H 8.74, N 7.53.

*Boc-(*S*)-β²-HPro-(*S*)-β²-HPro-(*S*)-β²-HPro-OEt* (**17a**). Compound **16** (2.53 g, 6.86 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with (*S*)-**4c** (1.57 g, 6.86 mmol) for 16 h according to *GP 4*. FC ($MeOH/CH_2Cl_2$ 1:15) yielded **17a** (2.31 g, 70%). White, waxy solid. M.p. 80° (sintering at 50–55°). R_f ($MeOH/CH_2Cl_2$ 1:15) 0.33. $[\alpha]_D^{r.t.} = +67.8$ ($c = 0.515$, $CHCl_3$). CD (0.2 mM in MeOH): $-2.09 \cdot 10^4$ (211 nm), $+4.15 \cdot 10^3$ (230 nm). IR ($CHCl_3$): 3008*m*, 2943*w*, 2865*w*, 1726*m*, 1675*m*, 1631*s*, 1443*m*, 1367*w*, 1150*m*, 855*w*. ^{1}H-NMR (500 MHz, $CDCl_3$, rotamers!): 1.23–1.30 (*m*, Me); 1.44–2.17 (*m*, *t*-Bu, 12 CH); 2.40–3.14 (*m*, 3 COCH, 6 NCH); 3.33–4.21 (*m*, CH_2O, 5 NCH); 4.49–5.30 (*m*, NCH). ^{13}C-NMR (125 MHz, $CDCl_3$, rotamers!): 14.19, 23.54, 24.00, 24.65, 25.31, 26.06, 27.05, 27.19, 27.44, 27.63, 27.76, 28.20, 28.46, 28.50, 28.61, 31.44, 36.48, 38.55, 39.04, 39.73, 41.06, 41.27, 42.01, 42.05, 42.50, 43.69, 44.49, 44.79, 45.86, 46.07, 46.78, 47.31, 48.06, 60.59, 60.70, 60.91, 60.59, 79.66, 154.63, 162.52, 171.26, 171.60, 171.69, 171.84, 172.03, 172.68, 172.95, 173.21 (C). FAB-MS: 502 (2.0, $[M+Na]^+$), 480 (62.2, M^+), 380 (100), 269 (30.0).

*Boc-(*S*)-β²-HPro-(*S*)-β²-HPro(*S*)-β²-HPro-OH* (**17b**). Compound **17a** (1.22 g, 2.54 mmol) was saponified with LiOH (0.15 g, 6.34 mmol) in MeOH (21 ml) and H_2O (7 ml) according to *GP 1*. Recrystallization (AcOEt/pentane) yielded **17b** (0.574 g, 50%). White powder. M.p. 175–177°. R_f ($MeOH/CH_2Cl_2$ 1:10) 0.25. $[\alpha]_D^{r.t.} = +52.6$ ($c = 0.50$, $CHCl_3$). IR ($CHCl_3$): 3006*w*, 2944*w*, 2863*w*, 1719*w*, 1680*m*, 1625*s*, 1444*m*, 1368*w*, 1152*m*, 855*w*. ^{1}H-NMR (500 MHz, $CDCl_3$, rotamers!): 1.44–2.17 (*m*, *t*-Bu, 9 H); 2.46–4.21 (*m*, 3 COCH, 11 NCH); 4.49–4.63 (*m*, NCH); 5.96 (br. *s*, CO_2H). ^{13}C-NMR (125 MHz, $CDCl_3$): not shown because of rotamers. FAB-MS: 474 (18.5, $[M+Na]^+$), 452 (100, $[M+1]^+$), 352 (71.2), 241 (44.7). Anal. calc. for $C_{23}H_{37}N_3O_6$ (451.56): C 61.18, H 8.26, N 9.31; found: C 60.99, H 8.17, N 9.13.

*Boc-(*S*)-β²-HPro-(*S*)-β²-HPro-(*S*)-β²-HPro-(*S*)-β²-HPro-(*S*)-β²-HPro-(*S*)-β²-HPro-OEt* (**18**). Compound **17a** (0.63 g, 1.31 mmol) was Boc-deprotected according to *GP 3*. The resulting TFA salt was coupled with **17b** (0.474 g, 1.048 mmol) for 16 h according to *GP 4*. FC (CH_2Cl_2/MeOH 9:1) yielded **18** (681 mg, 79%). Colorless glass. M.p. 116° (sintering at 104°). R_f (CH_2Cl_2/MeOH 9:1) 0.35. $[\alpha]_D^{r.t.} = +96.3$ ($c = 0.325$, $CHCl_3$). CD (0.2 mM in MeOH): $-8.54 \cdot 10^4$ (208 nm), $+2.44 \cdot 10^4$ (228 nm). IR ($CHCl_3$): 3007*m*, 2946*w*, 2860*w*, 1726*w*, 1682*m*, 1631*s*, 1442*m*, 1367*w*, 1149*m*, 856*w*. ^{1}H-NMR (500 MHz, $CDCl_3$, rotamers!): 1.23–1.29 (*m*, Me); 1.39–2.17 (*m*, *t*-Bu, 24 CH); 2.40–4.19 (*m*, 6 COCH, 20 NCH, CH_2O); 4.60 (br., 4 NCH). FAB-MS: 1649 (12.8, $[2M+Na]^+$), 1627 (19.4, $[2M]^+$), 835 (15.9, $[M+Na]^+$), 813 (37.9, $[M+1]^+$), 713 (100), 306 (26.1), 195 (34.7).

9. *X-Ray Crystal-Structure Analysis.* Compound **7c** ($C_{25}H_{35}N_9O_4 \cdot 4\,CF_3CO_2H$). Crystals were grown from a supersaturated TFA soln. at −20°. Crystal size $0.30 \times 0.20 \times 0.20$ mm. Crystal data at 243 K. Triclinic, space group *P*1, $\rho_{calc.} = 1.427$ g cm^{-3}, $Z = 1$, $a = 8.632(2)$ Å, $b = 11.739(2)$ Å, $c = 11.775(2)$ Å, $\alpha = 61.53(3)°$, $\beta = 85.08(3)°$, $\gamma = 88.90(3)°$, $V = 1044.6(3)$ Å^3. *Nonius CAD4* diffractometer, CuK_α radiation, $\lambda = 1.54178$ Å, 3208 unique reflections measured in the range $4.29 < \theta < 60.01°$. The structure was solved by direct methods (SHELXS-86 [65]), and refined by full-matrix least-squares analysis (SHELXL-97 [66]), using an isotropic extinction correction and $w = 1/[\sigma^2(F_o^2) + (0.2635P)^2 + 0.6910P]$, where $P = (F_o^2 + 2F_c^2)/3$ (heavy atoms anisotropic, H-atoms isotropic, whereby H-positions are based on stereochemical considerations). Final $R(F) = 0.1036$, $wR(F^2) = 0.2701$ for 511 variables and 3208 observations. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-129015 (**7c**). Copies of the data can be obtained, free

of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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