(*S*)-β^3-Homolysine- and (*S*)-β^3-Homoserine-Containing β-Peptides: CD Spectra in Aqueous Solution

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For further structural studies and for physiological investigations of β-peptides, it is necessary to have H_2O-soluble derivatives. Thus, we have prepared β-hexa-, β-hepta-, and β-nonapeptides (**1**–**6**) with two, three, and seven side chains of lysine and serine. To detect possible π-π interactions, we also included the β-amino acid β^2-HHop, resulting from homologation of so-called homophenylalanine (Hop) (**5** and **6**). The Fmoc-β^2- and β^3-amino-acid derivatives (**11**–**14** and **19**), and the corresponding β-peptides were prepared by methods previously described (solid-phase peptide coupling; HPLC-pure samples, *Fig. 1*). Circular-dichroism spectra (*Fig. 2*) indicate the presence of less pronounced secondary structures (especially of the lysine analogues with multiple positive charge) in H_2O as compared to MeOH. The β^3-heptapeptide (**3**) with two serine side chains is well soluble in H_2O and exhibits the CD pattern typical of the 3_1-helical structure.

1. Introduction. – Short-chain ω-peptides [1] that can form stable folded structures have recently joined the rapidly growing family of structurally defined non-natural oligomers [2]. We and others have demonstrated that peptides consisting exclusively of β- [3–7] or γ- [8] [9] rather than α-amino acids, can form stable and novel helical structures in MeOH, pyridine, or in the solid state. More recently, further structural diversity has been achieved with the successful design and synthesis of parallel [4] [10] and antiparallel [11] pleated-sheet-type structures based on β^3- and $\beta^{2,3}$-amino acids.

With respect to potential applications of β-peptides in biological systems, the current challenge is to design, based on secondary structural elements, β-peptides with a given secondary structure and with specific biological functions. For example, cyclo-β^3-tetrapeptides that have been found to form nanotubes in the solid state [12], have recently been used as transmembrane ion channels [13]. The elucidation of structural propensities of linear β-peptides in aqueous environment represents a further important issue that still needs to be addressed for future developments in bioorganic chemistry. Here, we report the synthesis and CD measurements in organic solvents and aqueous solution of β-hepta- and β-nonapeptides **1**–**6** containing two or more polar hydrophilic side chains of Lys or Ser, with β^3-amino-acid residues (**1**–**5**) or with mixed sequences of β^2- and β^3-amino-acid residues (**6**).

From our previous studies [4] [5] [14], β-peptides **1**–**6** are expected to adopt the (*M*)-3_1-helical structure. Compound **1** can be considered as a section of the β-peptide

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[1] Part of the projected Ph. D. thesis of *S.A.*, ETH-Zürich.

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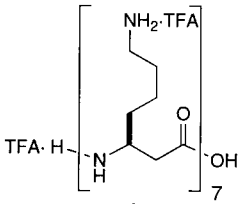

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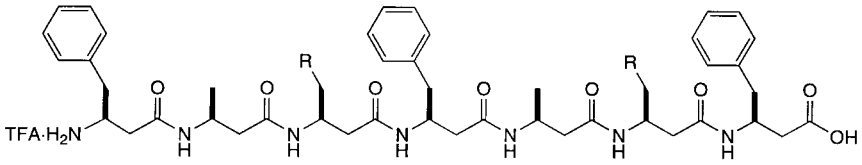
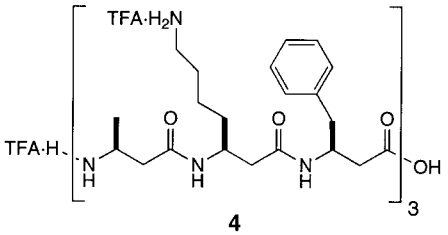


2 R = $(CH_2)_4NH_2$·TFA
3 R = CH_2OH



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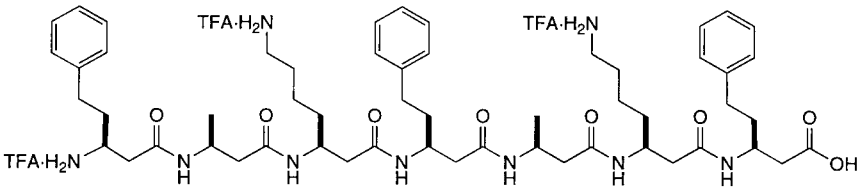

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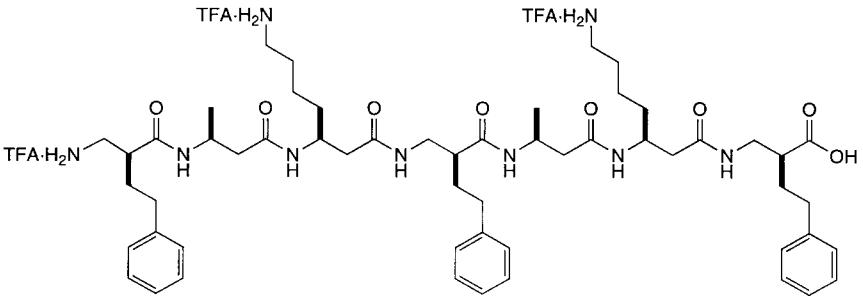

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analogue of poly-α-lysine, a cationic polymer that has been widely used to study the transition between α-helical and pleated-sheet structures by CD spectroscopy [15–17], and to explore its complexation with anionic partners, including DNA [18] or bilirubin [19]. Peptides **2** and **3** were prepared in order to examine the effect of lysine and serine side chains on the helix stability. A comparison of the β-heptapeptide **2** with the homologous β-nonapeptide **4** should allow us to assess the stabilizing effect of growing chain length[3]). Analysis of the 3_1-helix model suggests that the incorporation of an additional CH_2 group in the side chain of β^2- and β^3-HPhe might favor the stacking of the Ph rings. In addition to electrostatic, H-bonding, and hydrophobic interactions, aromatic interactions may also contribute to the stabilization of helical secondary structures. For example, in the case of oligo-*N*-substituted-glycines ('peptoids') with aromatic side chains, π-stacking and dipole-dipole repulsion between side chains and the C=O groups of the backbone have been suggested to account for the stabilization of helical structures in H_2O [21]. Hence, compound **5** and **6**, containing the β-amino-acid analogue of so-called homophenylalanine (Hop), were thought to be suitable for evaluating the influence of aromatic side chains on folding propensities of β-peptides.

2. Preparation of the β^2- and β^3-Amino-Acid Building Blocks. – For rendering β-peptides H_2O-soluble, incorporation of polar side-chains is a prerequisite. For this purpose, we synthesized several new β-amino acids with the appropriate orthogonally protected functional groups. Diazo ketones **7**–**10** were prepared by procedures used in our laboratory [4] [22] [23], starting from the corresponding commercially available enantiomerically pure α-amino acids. The β^3-amino acids **11**–**14** were obtained in good yields (40–50% from the α-amino acids) by *Arndt-Eistert* homologation. Whereas the Boc-protected β^3-amino acids **11a** and **12** were prepared for coupling in solution, Fmoc-protected acids **11b**, **13**, and **14** are the appropriate building blocks for solid-phase synthesis[4]). The *N,N′*-diphthalyl-[25a], *N,N′*-dibenzyloxy-, and *N,N′*-bis(*tert*-butyloxy)carbonyl [25b] derivatives of **13** have already been synthesized in order to confirm the structure of 'isolysine'[5]), a hydrolysis product of several antibiotics. However, since orthogonality of the amino protecting groups in these compounds is not secured, we prepared the β-Fmoc-/ε-Boc-protected amino acid **13** that can be employed in Fmoc-coupling reactions.

Evans' enolate chemistry was used for the synthesis of β^2-amino-acid derivatives (*Scheme*). Unlike in our previous syntheses [6] [26], we used benzyl *N*-(methoxymethyl) carbamate [27] for the amidomethylation of (*R*)-4-benzyl-3-(4-phenylbutanoyl)-1,3-oxazolidin-2-one (**15**), through the $TiCl_4$-enolate to give the *unlike*-product **16**[6]). The somewhat lower yield (44%), as compared to the previously used electrophile (benzoylamino)methyl chloride, is more than compensated for by the

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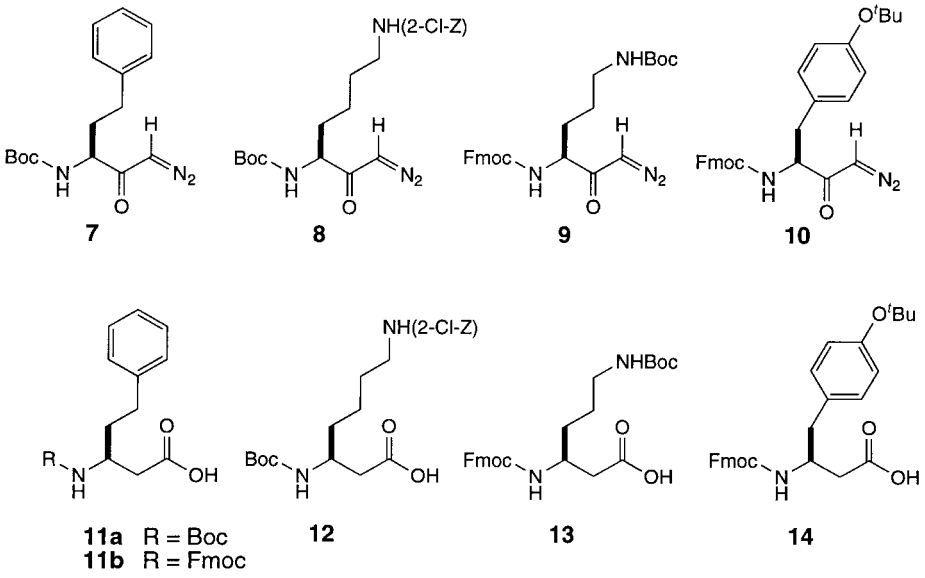
[3]) β-Peptides **2** and **4** are also promising candidates for the inhibition of cholesterol uptake through brush border membrane [20].

[4]) Like its α-analogues [24], the β^3-homotyrosine derivative **14** has a low solubility in common organic solvents (CH_2Cl_2, $CHCl_3$, AcOEt).

[5]) 3,6-Diaminohexanoic acid, often called β-lysine, is a constitutional isomer of lysine. According to the nomenclature used for β-amino acids [4] [6] [14], this compound is β^3-HOrn

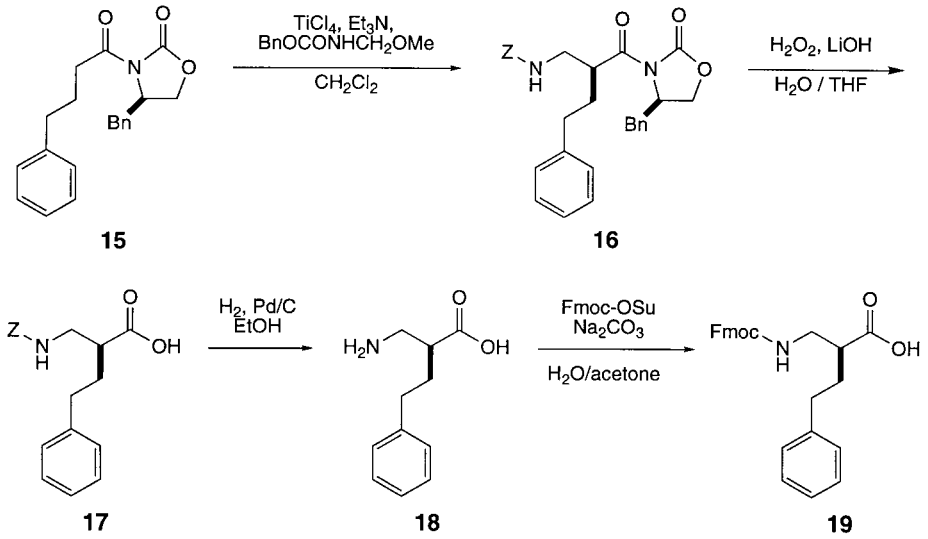
[6]) The configurational purity of the chromatographed product was >97:3 (by ^{1}H-NMR).



milder conditions of *N*-deprotection. Hydrolytic removal of the auxiliary group with $LiOH/H_2O_2$ led to the Z-protected acid **17** which was *N*-deprotected by hydrogenolysis (H_2, Pd/C) to yield the free β^2-amino acid **18** which was converted to the desired Fmoc-protected β^2-amino acid **19** (33% starting from **16**).

3. Preparation of β-Peptides. – β^3-Heptapeptides **1**–**3** and **5**, **6**, and β^3-nonapeptide **4** were synthesized on *ortho*-chlorotrityl chloride [28] resin by conventional solid-phase

Scheme. *Preparation of (S)-β²-Amino Acid Derivatives* **17**–**19** *by Aminomethylation of Acyl-oxazolidinones*



peptide-synthesis procedures [29] [30] (BOP/HOBt/(i-Pr)$_2$EtN)[7]). The yields of the crude peptides, obtained after cleavage from the resin and precipitation with Et_2O, were between 45 and 99%[8]). The crude products had a purity of 48–80%, as determined by reversed-phase (RP) HPLC (see *Exper. Part*). The HPLC profiles of purified β-peptides **1**–**3**, **5** and **6** are shown in *Fig. 1*. FAB-MS Analysis of the major impurities isolated by preparative RP-HPLC revealed that poor purities were due to incomplete Fmoc removal[9]). It seems that this complication may arise during the synthesis of β^3-HLys-containing β-peptides exceeding seven residues. An elemental analysis was performed with β^3-heptahomolysine **1** in order to determine the amount of CF_3COOH present after purification and lyophilization. The values found correspond to the heptapeptide with eight molecules of CF_3COOH. This result is of importance for other β-peptides containing free amino groups[10]). It shows that all free amino groups form a CF_3COOH salt. All the β-peptides were white powders except the polycationic β-peptide **1** which was obtained as a colorless highly viscous oil.

4. CD Spectroscopy. – CD Spectra of β-peptides **1**–**6** (*Fig. 2*) were measured in MeOH, in CF_3CH_2OH (TFE), and in buffered aqueous solutions at different pH in the range of 195–250 nm[11]) (0.2 mM concentration, see *Exper. Part*). In MeOH, all β-peptides showed the typical CD pattern (positive *Cotton* effect at 200 nm, negative *Cotton* effect at 215–220 nm) that we previously assigned to the (*M*)-3_1 helix [6] [14][12])[13]). The weakest negative *Cotton* effect (*ca.* $-1.2\cdot10^4$ at 219 nm) was measured for β^3-hepta(homolysine) **1** suggesting that the large number of neighboring cationic side chains destabilizes the secondary structure (*Fig. 2,a*). It is noteworthy that the β^3-HSer-containing peptide **3** displays a more intensive negative *Cotton* effect (*ca.* $-6.1\cdot10^4$ at 219 nm) than its β^3-HLys-containing analogue **2** (*ca.* $-3.7\cdot10^4$ at 219 nm) (*Fig. 2,b* and *c*). Obviously, the OH groups in **3** do not destabilize the 3_1 helix, while the NH_3^+ groups in **2** do. A comparison of the mean residue molar ellipticity of β-heptapeptide **2** and β-nonapeptide **4** ($-5.2\cdot10^3$ and $-5.3\cdot10^3$, resp.) shows that there is no stabilization of the 3_1 helix due to longer chain length, in this case (*Fig. 2,b* and *d*). We then tested the effect of aromatic side-chain interaction on the *Cotton* effect (see **2** *vs.* **5** and **6**): CD curves of β-peptides **2** and **5** in MeOH do not differ substantially ($-3.7\cdot10^4$ *vs.* $4.2\cdot10^4$ at 220 nm resp.) (*Fig. 2,b* and *e*). This indicates that the presence of an additional CH_2 group in the aromatic side chains (*vide supra*) (β-peptides **5** and **6**), although it could favor π-stacking, does not stabilize the 3_1 helix in MeOH.

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[7]) Abbreviations are defined in the *Exper. Part*.

[8]) % Mass recovered based on polymer loading.

[9]) The corresponding Fmoc-protected octa- and hexapeptides were identified by mass spectroscopy as impurities in **4** and **5**, respectively, indicating that incomplete Fmoc deprotection had taken place in the penultimate coupling step. Use of the stronger base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) instead of 20% piperidine in DMF [29] did not substantially improve the purity of crude products **4** and **5**.

[10]) The molar ellipticity Φ can only be determined accurately from the CD spectra if the exact mass of the sample is known.

[11]) Because of inherent absorption of buffer solutions, data were recorded for $\lambda > 195$ nm. Changes of the CD spectra in the range 195–200 nm are not discussed.

[12]) When measured in TFE, the CD spectra exhibit a stronger negative *Cotton* effect (*Fig. 2*).

[13]) The high content of aromatic chromophors (up to 45% of the side chains) did not alter the magnitude of the *Cotton* effect, compared with previously reported 3_1-helical β-peptides [4] [6] [14] [29].

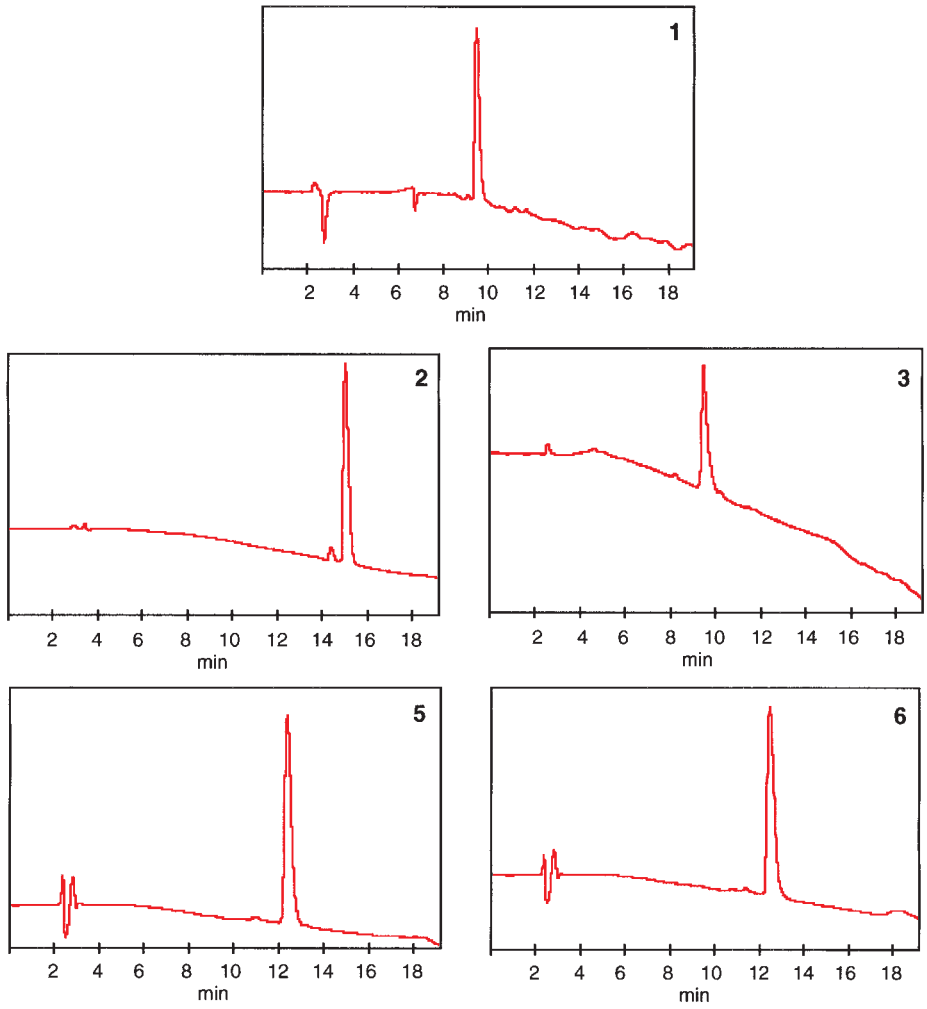

Fig. 1. *HPLC Profiles of purified β-heptapeptides* **1**–**3**, **5**, *and* **6** (*RP-C_{18}* column, linear gradient of 0.1% CF_3COOH in H_2O and MeCN; see *GP 7* in *Exper. Part*)

β-Peptide **6** has a novel sequence pattern ((β²-HXaa-β³HXaa-β³HXaa)$_n$) that is compatible with a 3_1-helical structure, and this is confirmed by its CD spectrum (*Fig. 2,f*).

Next, we compared the CD spectra of the new β-peptides in aqueous solution. The trough at *ca.* 220 nm is only observed with compounds **3** and **6**, albeit with much lower intensities ($-2.4\cdot10^4$ and $-1.1\cdot10^4$ at pH 5.6) than in MeOH. In the case of compounds **3** and **6**, the intensity of the *Cotton* effect increases at high pH values ($-3.0\cdot10^4$ and $-2.1\cdot10^4$, at pH 11). Taken together, these data and those obtained in MeOH suggest that β-HSer has a smaller helix-disrupting effect in H_2O than β-HLys. In the case of β-peptides **1**, **2**, **4**, and **5**, the molar ellipticity at 215 nm is only slightly

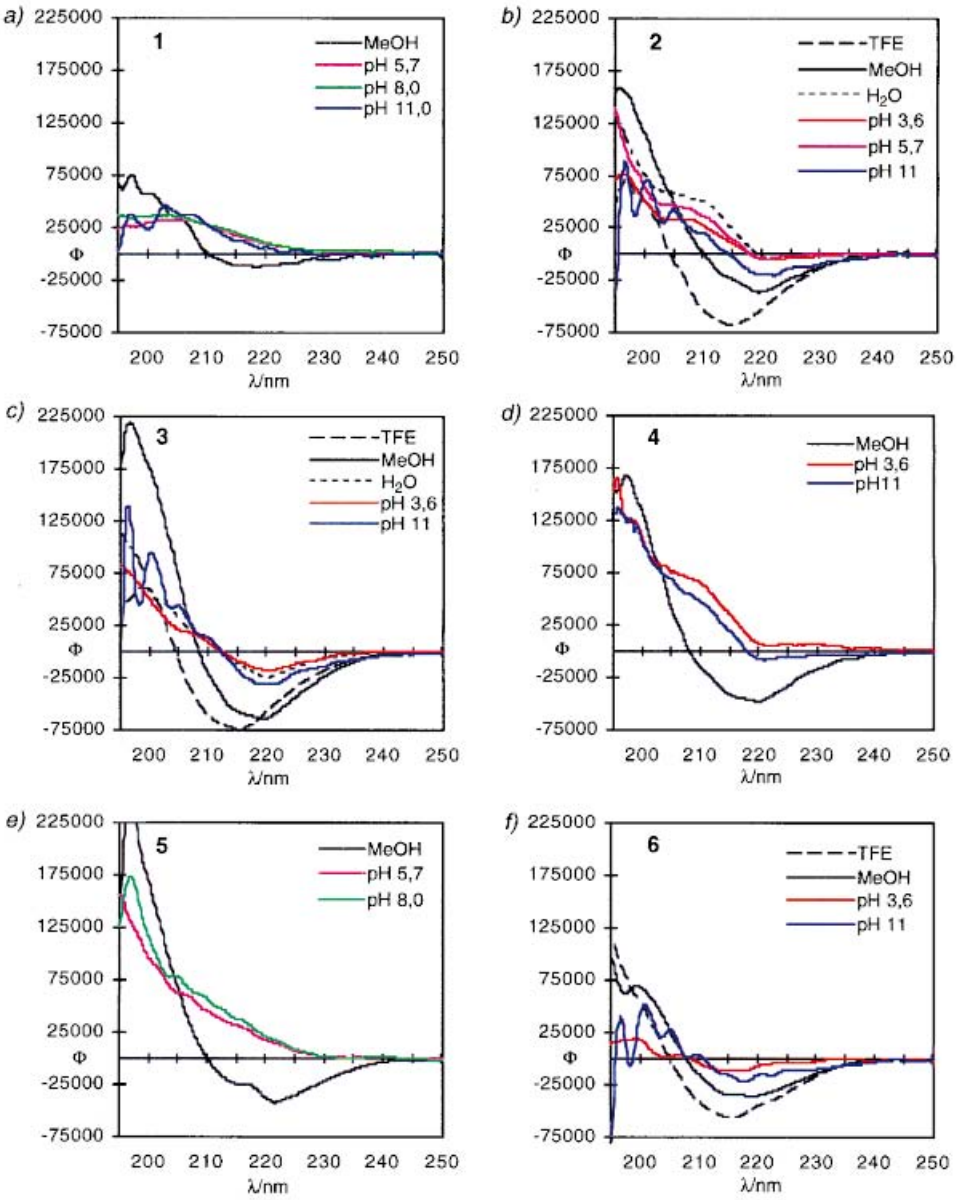

Fig. 2. *Overlay of CD spectra of β-peptides* **1**–**6** *under various solvent conditions. a*) β-Peptide **1**. *b*) β-Peptide **2**. *c*) β-Peptide **3**. *d*) β-Peptide **4**. *e*) β-Peptide **5**. *f*) β-Peptide **6**. Molar ellipticity $[\Theta]$ in 10 deg · cm^2 · mol^{-1}. The curves specified by pH values all refer to aqueous solutions.

negative or even positive[14]). A common feature of peptides **2**, **4**, and **6** is the occurrence of a positive shoulder at 205–210 nm, that might reflect either a single new conformation or the co-existence of several conformational isomers. Surprisingly, the CD spectrum of the highly basic β-peptide **1** did not show any significant pH dependence.

5. Conclusion. – We have investigated by CD spectroscopy the conformational features of short-chain β-peptides **1**–**6** in aqueous environment. In contrast to CD spectra measured in MeOH, spectra of β^3-HLys-containing β-peptides **1** and **2**, and **4** and **5** recorded in H_2O and in buffered solutions do not display the typical pattern assigned to the 3_1-helical structure. This may be due to a destabilization of the helix caused by partial or total disruption of the H-bond network[15]). In contrast, CD spectra of both β^3-heptapeptide **3** (with side chains of Ala, Phe, and Ser) and mixed β^2, β^3-heptapeptide **6** (with side chains of Ala, Hop, and Lys) show, although with a moderate intensity, the helix-specific trough at 215–220 nm. In this peptide series, the apparent order of stabilization of the 3_1 helix in H_2O would then be β^3-HSer > β^3-HLys for polar residues in positions 3 and 6, and β^2-HHop > β^3-HHop = β^3-HPhe for aromatic residues in 1-, 4-, and 7-position. A more systematic approach based on combinatorial libraries would be of interest to determine the 3_1-helix-disrupting and -generating propensities of all β^2- and β^3-amino acids with proteinaceous side chains in H_2O. This would be in analogy to the existing scales describing the effect of an α-amino-acid side chain on α-helix formation [31].

Alternative strategies that could be used to achieve 3_1-helix stabilization in aqueous solution would include: *i*) The creation of ion pairs or salt bridges between side chains of two β-amino-acid residues *i* and $(i+3)$ (*i.e.*, side chains of Glu and Lys). *ii*) Since the 3_1 helix has a resulting dipole moment with the positive pole near the C- and the negative near the N-terminus [6], the ideal situation would be to insert the negatively charged side chains near the C- and the positively charged ones near the N-terminus. *iii*) The design of covalent macrocycles between *i* and $(i+3)$ side chains. *iv*) The design of H_2O-soluble β-peptides built completely from $\beta^{2,3}$-amino acids ($\beta^{2,3}$-peptides have very slow NH/ND exchange kinetics, probably due to the diminished solvent accessibility of the NH protons [6]). *v*) The design of H_2O-soluble long-chain β-peptides [6] [29b].

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Experimental Part

1. *General. Abbreviations:* BOP: benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, DMAP: 4-(dimethylamino)pyridine. FC: flash chromatography, GP: general procedure, HOBt: 1-hydroxy-1*H*-benzotriazole, h.v.: high vacuum, 0.01–0.1 Torr, NMM: *N*-methylmorpholin, TFA: CF_3COOH, TIS: triisopropylsilane, β-HXaa: β-homoamino acid. THF was freshly distilled over K under Ar before use. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*). Et_3N was

[14]) A first demonstration of the disruptive effect of H_2O on β-peptide secondary structures was described in one of our previous studies on β-peptides [29b].

[15]) This effect is well-known for α-helices which are more stable in MeOH and TFE than in H_2O.

distilled from CaH_2 and stored over KOH. *i*-BuOCOCl was distilled and stored at $+4°$ under Ar. All indicated temp. were monitored with an internal thermometer (*Ebro* TTX 690 digital thermometer). Amino-acid derivatives were purchased from *Bachem*, *Senn*, or *Degussa*. *ortho*-Chlorotrityl chloride and *Wang* resins were purchased from *Novabiochem*. All other reagents were used as received from *Fluka*. ***Caution***: The generation and the handling of CH_2N_2 requires special precautions [32]. TLC was performed on *Merck* silica gel *60* F_{254} plates; detection with UV and ninhydrine. FC: *Fluka* silica gel *60* (40–63 μm) at *ca.* 0.2 bar. Anal. HPLC: *Knauer* HPLC system (pump type 64, *EuroChrom 2000 Integration Package, degaser*, UV detector (variable-wavelength monitor)). Prep. HPLC: *Knauer* HPLC system (pump typ 64, programmer *50*, UV detector (variable-wavelength monitor)). M.p.: *Büchi 510* apparatus; uncorrected. 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. All spectra were the average of five scans and were corrected for the baseline. (Peptide concentration 0.2 mM). The molar ellipticity (Θ) is reported in $deg \cdot cm^2 \cdot dmol^{-1}$. Smoothing was performed using 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), *Varian Gemini 300* (^1H: 300 MHz, ^{13}C: 75 MHz), or *Varian Gemini 200* (^1H: 200 MHz, ^{13}C: 50 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 nitrobenzyl-alcohol matrix), *LDI 1700* (MALDI), or *Finnigan MAT TSQ 7000* (ESI) spectrometer. Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Diazo Ketones* **7**–**10**: *General Procedure 1* (*GP 1*). Similarly to the procedure reported in [23], the *N*-protected amino acid was dissolved in THF (0.35M) under Ar and cooled to $-20°$. After addition of *i*-BuOCOCl (1.05 equiv.) and NMM (1.05 equiv.), the mixture was stirred at $-20°$ for 20 min. The resulting white suspension was allowed to warm up to $-5°$, and a soln. of CH_2N_2 in Et_2O was added until the rich yellow color persisted. Stirring was continued for 4 h as the mixture was allowed to warm to r.t. Excess CH_2N_2 was destroyed by vigorous stirring and by the addition of a few drops of AcOH. The mixture was then diluted with Et_2O and washed with sat. $NaHCO_3$ soln., 1N HCl, and sat. NaCl soln. The org. phase was dried ($MgSO_4$) and concentrated under reduced pressure. FC and/or recrystallization afforded the pure diazo ketone.

3. *Homologated Carboxylic Acids* **11**–**14**: *General Procedures 2* (*GP 2*). *GP 2a.* Similar to the procedures reported in [4] [23], the diazo ketone was dissolved in THF (0.25M) containing 10% H_2O and then cooled to $-25°$ under Ar with the exclusion of light. A soln. of CF_3COOAg (0.11 equiv.) in Et_3N (2.8 equiv.) was added, and the resulting mixture was allowed to warm to r.t. in 4–5 h in the dark. After removing the bulk of THF under reduced pressure, the mixture was diluted with aq. sat. $NaHCO_3$ soln. and extracted with Et_2O. The aq. phase was then carefully adjusted to pH 2–3 at 0° with 1N HCl and extracted with AcOEt. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure. FC and/or recrystallization afforded the pure *N*-protected β^3-amino acids.

GP 2b. The diazo ketone was dissolved in THF (0.25M) containing 10% H_2O and then cooled to 0° under Ar with the exclusion of light. A soln. of CF_3COOAg (0.11 equiv.) in NMM (2.5 equiv.) was added and the resulting mixture was allowed to warm to r.t. in 4 h in the dark. Workup as in *GP 2a*. FC and/or recrystallization afforded the pure *N*-protected β^3-amino acids.

4. N-*Fmoc Protection: General Procedure 3* (*GP 3*). A stirred soln. of the β-amino acid in 0.15M aq Na_2CO_3 (2–3 equiv.) was treated with a soln. of Fmoc-OSu (1.2 equiv.) in acetone (0.1M). After 2 h, the mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The aq. phase was carefully adjusted to pH 2–3 at 0° with 1N HCl and extracted with AcOEt. The org. layer was dried ($MgSO_4$) and evaporated. FC and/or recrystallization afforded the pure *N*-Fmoc-protected β-amino acid.

5. *Anchoring of* N-*Fmoc-Protected β-Amino Acids on the Resin: General Procedure 4* (*GP 4*). *ortho*-Chlorotrityl-chloride resin was esterified according to [28]. The resin (initial loading: 1.00 or 1.30 mmol Cl/g) was dried under h.v. for 30 min and swelled in CH_2Cl_2 (10 ml/mmol) for 10 min. A soln. of the β-amino acid (0.8–1.0 equiv.) in CH_2Cl_2 (10 ml/mmol) and $(i\text{-}Pr)_2EtN$ (3.2–4.0 equiv.) were then added successively, and the suspension was mixed under Ar for 4 h. Subsequently, the resin was filtered, washed (10 ml/mmol) with CH_2Cl_2/MeOH/$(i\text{-}Pr)_2EtN$ 17:2:1 (3 × 3 min), CH_2Cl_2 (3 × 3 min), DMF (2 × 3 min), CH_2Cl_2 (3 × 3 min), MeOH (2 × 3 min) and finally dried over KOH under h.v. for 12 h. The loading of the resin was then determined on a 3–5 mg sample (after treatment with 20% piperidine in DMF for 20 min), by measuring the absorbance of the dibenzofulvene-piperidine adduct (formed during deprotection) at 300, 289, and 266 nm (ε = 7800, 5800, and 17500, resp.), taking the average absorbance from the three measurements.

6. *β-Peptide on Solid Support: General Procedures 5* (*GP 5*). *GP 5a* (*cf. Scheme*). The Fmoc group of the first amino acid attached to the resin was removed using 20% piperidine in DMF (30 ml/mmol, 2 × 20 min)

under Ar bubbling. The resin was then filtered and washed with DMF (30 ml/mmol, 6 × 3 min). For each coupling step, a soln. of the Fmoc-*β*-amino acid (2–3 equiv.), BOP (2–3 equiv.), and HOBt (2–3 equiv.) in DMF (2 ml) and (i-Pr)$_2$EtN (6–9 equiv.) were added successively to the resin, and the suspension was mixed for 15–60 min under Ar. Monitoring of the coupling reaction was performed with 2,4,6-trinitrobenzenesulfonic acid (TNBS). In case of a positive TNBS test (indicating incomplete coupling), the suspension was allowed to react further for 15–60 min. The resin was then filtered and washed (12 ml/mmol) with DMF (3 × 3 min) prior to the following Fmoc deprotection step. After the removal of the last Fmoc protecting group, the resin was washed (12 ml/mmol) with DMF (6 × 3 min), CH_2Cl_2 (3 × 3 min), Et_2O (5 × 1 min), and dried under h.v. over KOH for 4 h.

GP 5b. As in *GP 5a*, except that the Fmoc group is removed using 30 ml/mmol DBU/piperidine/DMF (1:1:48, 1 × 3 min and 1 × 8 min) under Ar bubbling.

7. *Resin Cleavage and Final Deprotection: General Procedures 6* (*GP 6*). *GP 6a*. The dry Fmoc-deprotected peptide-resin was treated with CF_3COOH/H_2O 95:5 (20 ml/mmol, 5 × 15 min) under Ar bubbling. The resin was removed by filtration, washed with CF_3COOH and the org. phase containing the peptide was concentrated under reduced pressure. The precipitate, which formed upon addition of cold Et_2O to the oily residue, was collected by filtration or centrifugation. The solid was then dissolved in H_2O or H_2O/AcOH 9:1 and lyophilized to afford a crude product which was analyzed and purified by RP-HPLC.

8. *Reversed Phase (RP) HPLC Analysis and Purification of β-Peptides: General Procedure 7* (*GP 7*). RP-HPLC Analysis was performed on a *Macherey-Nagel C$_8$ column/Nucleosil 100-5 C$_8$* (250 × 4 mm) or *Macherey-Nagel C$_{18}$ column/Nucleosil 100-5 C$_8$* (250 × 4 mm) by using a linear gradient of *A* (0.1% CF_3COOH in H_2O) and *B* (MeCN) at a flow rate of 1 ml/min with UV detection at 220 nm. t_R in min. Crude products were purified by prep. RP-HPLC (*Macherey-Nagel C$_{18}$ column/Nucleosil 100-7 C$_{18}$* (250 × 21 mm)) using gradient of *A* and *B* at a flow rate of 4 ml/min with UV detection at 214 nm and then lyophilized.

9. *Diazo Ketones* **7**–**10.** *(*S*)-3-[[(*tert*-Butoxy)carbonyl]amino}-1-diazo-5-phenylpentan-2-one* (**7**). (*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-phenylbutyric acid (4.8 g, 17.18 mmol) was transformed according to *GP 1*. Recrystallization from Et_2O/hexane yielded **7** (3.6 g, 69%). Yellowish solid. M.p. 83–84°. $[\alpha]_D^{r.t.} = +12.6$ (c = 0.97, $CHCl_3$). IR ($CHCl_3$): 3438*w*, 3008*w*, 2111*s*, 1708*s*, 1643*m*, 1496*s*, 1455*w*, 1369*s*, 1241*w*, 1164m, 1046*w*, 1021*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (*s*, *t*-Bu); 1.79–1.91 (*m*, 1 H, CHCH_2); 2.06–2.18 (*m*, 1 H, CHCH_2); 2.68 (*t*, J = 7.5, PhCH_2); 4.21 (br., CHN); 5.15 (*d*, J = 6.53, NH); 5.40 (*s*, CHN_2); 7.17–7.32 (*m*, 5 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 25.9 (Me); 29.2, 31.7 (CH_2); 51.6, 54.5 (CH); 123.9, 126.0, 126.2 (CH); 138.5, 153.1, 191.5 (C). FAB-MS: 304 (7, $[M+1]^+$). Anal. calc. for $C_{16}H_{21}N_3O_3$ (303.36): C 63.35, H 6.98, N 13.85; found: C 63.50, H 6.89, N 13.58.

*(*S*)-3-[[(*tert*-Butoxy)carbonyl]amino}-7-[[(2-chlorobenzyloxy)carbonyl]amino}-1-diazoheptan-2-one* (Boc-(*S*)-Lys(2-Cl-Z)-CHN_2; **8**). Boc-(*S*)-Lys(2-Cl-Z)-OH (30.0 g, 72.0 mmol) was transformed according to *GP 1*. FC (AcOEt/pentane 2:3) yielded **8** (28.09 g, 89%). Yellow solid. M.p. 72–74°. R_f 0.29 (AcOEt/pentane 2:3). IR ($CHCl_3$): 3446*w*, 3008*w*, 2960*w*, 2940*w*, 2110*s*, 1800*w*, 1711*s*, 1642*m*, 1500*m*, 1446*w*, 1368*m*, 1248*w*, 1163*w*, 1042*w*, 859*w*, 630*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.36–1.69 (*m*, *t*-Bu, 5 CH); 1.74–1.83 (*m*, CH); 3.17–3.23 (*m*, CH_2); 4.14 (br., CHN), 4.91 (br., NH); 5.21 (br. *s*, CH_2, NH); 5.45 (br. *s*, CHN_2); 7.23–7.29 (*m*, 2 arom. H); 7.35–7.43 (*m*, 2 arom. H). ^{13}C-NMR (76 MHz, $CDCl_3$): 22.33, 28.36, 29.55, 32.10, 40.56, 53.97, 57.34, 64.05, 80.21, 127.11, 129.51, 129.61, 129.77, 130.01, 133.83, 134.57, 155.86, 156.62, 193.48. FAB-MS: 877 (1.7, $2M^+$), 439 (23.1, $[M+1]^+$), 355 (100), 339 (24.7), 311 (27.8), 252 (50.2), 154.1 (23.8), 127 (33.8). Anal. calc. for $C_{20}H_{27}ClN_4O_5$ (438.91): C 54.73, H 6.20, N 12.76; found: C 54.65, H 6.17, N 12.50.

*(*S*)-6-[[(*tert*-Butoxy)carbonyl]amino}-1-diazo-3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)hexan-2-one* (Fmoc-(*S*)-Orn(Boc)-CHN_2; **9**). Fmoc-(*S*)-Orn(Boc)-OH (5.0 g, 11.0 mmol) was transformed according to *GP 1*. FC (Et_2O/CH_2Cl_2 1:8) and recrystallization (AcOEt/hexane) yielded **9** (3.18 g, 60%). Bright-yellow powder. M.p. 115° (dec., sintering at 86°). R_f 0.09 (Et_2O/CH_2Cl_2 1:8). $[\alpha]_D^{r.t.} = -24.0$ (c = 1.0, $CHCl_3$). IR ($CHCl_3$): 3453*w*, 3007*w*, 2111*m*, 1712*s*, 1641*m*, 1507*s*, 1450*m*, 1391*m*, 1367*s*, 1166*m*, 1044*w*, 867*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44 (*s*, *t*-Bu); 1.47–1.60 (*m*, 3 CH); 1.81–1.87 (*m*, 1 CH); 3.13–3.16 (*m*, CH_2N); 4.21 (*t*, J = 7.0, CHO); 4.27 (br. *s*, NH); 4.39–4.49 (*m*, CH_2O); 4.60 (br. *s*, NH); 5.43 (br. *s*, CHN_2); 5.62 (br. *d*, J = 7.0, NH); 7.30–7.34 (*m*, 2 arom. H); 7.38–7.43 (*m*, 2 arom. H); 7.59–7.62 (*m*, 2 arom. H); 7.77 (*d*, J = 7.5, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 26.25 (CH_2); 28.42 (Me); 29.56, 39.74 (CH_2); 47.29, 54.02, 57.35 (CH); 66.77 (CH_2); 79.36 (C); 120.0, 124.71, 125.06, 125.13, 127.10, 127.73 (CH); 141.37, 143.76, 156.05, 156.20, 193.37 (C). FAB-MS: 479 (3.2, $[M+1]^+$), 178 (78.0), 165 (34.3), 132 (100). Anal. calc. for $C_{26}H_{30}N_4O_5$ (478.55): C 65.26, H 6.32, N 11.71; found: C 65.20, H 6.42, N 11.52.

*(*S*)-4-[(4-*tert*-Butoxy)phenyl]-1-diazo-3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)butan-2-one* (Fmoc-(*S*)-Tyr(*t*-Bu)-CHN_2; **10**). Fmoc-(*S*)-Tyr(*t*-Bu)-OH (20.0 g, 43.5 mmol) was transformed according to *GP 1*. FC

(AcOEt/pentane 1:3) and recrystallization (CH_2Cl_2/hexane) yielded **10** (14.4 g, 69%). Yellow powder. M.p. 120.5–121.5°. R_f 0.18 (AcOEt/pentane 1:3). $[\alpha]_D^{r.t.} = +3.5$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3426*w*, 3005*w*, 2985*m*, 2113*s*, 1718*s*, 1641*m*, 1503*s*, 1451*m*, 1390*m*, 1364*s*, 1318*m*, 1159*m*, 1108*w*, 1082*w*, 1041*w*, 918*w*, 897*m*, 851*w*, 826*w*. ^{1}H-NMR (400 MHz, CD_3COCD_3, signals of rotamers in italics): 1.25 (*s*, *t*-Bu); 2.86 (*dd*, $J = 14.0$, 9.6, H–C(4)); 3.14 (*dd*, $J = 14.0$, 4.9, H–C(4)); 4.16 (*t*, $J = 6.9$, CHO); 4.31 (*d*, $J = 7.0$, CH_2O); 3.32–4.44 (*m*, CHN); 5.86, *6.16* (*s*, CHN_2); 6.80 (*d*, $J = 8.4$, NH); 6.88 (*d*, $J = 8.4$, 2 arom. H); *7.09*, 7.19 (*d*, $J = 8.3$, 2 arom. H); 7.30–7.34 (*m*, 2 arom. H); 7.39–7.43 (*m*, 2 arom. H); 7.65 (*d*, $J = 7.3$, 2 arom. H); 7.85 (*d*, $J = 8.5$, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3COCD_3, signals of rotamers in italics): 29.11 (Me); 37.31, 48.07 (CH_2); 53.71, 60.81, 67.01 (CH); 78.41 (C); 120.79, 124.66, 126.11, 126.14, 127.93, 128.51, 130.61 (CH); 133.12, 142.15, 142.16, 144.92, 145.07, 155.23, *156.74*, 194.59 (C). FAB-MS: 967 (8.6, $2M^+$), 484 (40.6, $[M + 1]^+$), 456 (41.4), 399 (13.5), 222 (83.5), 179 (100), 165 (14.7), 154 (53.1), 136 (34.4). Anal. calc. for $C_{29}H_{29}N_3O_4$ (483.57): C 72.03, H 6.04, N 8.69; found: C 72.11, H 6.17, N 8.58.

10. *β³-Amino Acids* **11–14**. *(*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-5-phenylpentanoic Acid* (Boc-(*S*)-β³-HHop-OH; **11a**) [33]. Diazo ketone **7** (1.4 g, 4.6 mmol) was transformed according to *GP 2a*. FC ($CHCl_3$/MeOH 10:1) and recrystallization from AcOEt/hexane yielded **11a** (890 mg, 66%). White solid. M.p. 81–82°. $[\alpha]_D^{r.t.} = -4.0$ ($c = 0.75$, $CHCl_3$). IR ($CHCl_3$): 3439*w*, 3018*s*, 2978*w*, 2400*m*, 1708*m*, 1510*m*, 1422*m*, 1210*m*, 1047*w*, 928*w*. ^{1}H-NMR (200 MHz, $CDCl_3$, signals of rotamers in italics): 1.46 (*s*, *t*-Bu); 1.71–2.02 (*m*, $CHCH_2$); 2.59–2.81 (*m*, $PhCH_2$, $COCH_2$); 3.96 (br., CHN); 4.98, *5.84* (br., NH); 7.17–7.32 (*m*, 5 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 28.4 (Me); 32.6, 36.4, 39.3 (CH_2); 47.4 (CH); 79.7 (C); 126.0, 128.4, 128.5 (CH); 141.4, 155.6, 176.6 (C). FAB-MS: 304 (7, $[M+1]^+$). Anal. calc. for $C_{16}H_{23}NO_4$ (293.36): C 65.51, H 7.90, N 4.77; found: C 65.62, H 7.85, N 4.83.

*(*S*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-5-phenylpentanoic Acid* (Fmoc-(*S*)-β³-HHop-OH; **11b**). Diazoketone **11a** (541 mg, 1.84 mmol) was dissolved in CF_3COOH (0.25M) at 0°. After stirring at r.t. for 1 h and concentration under reduced pressure, the crude trifluoroacetate salt which precipitated upon addition of Et_2O, was collected by filtration, dried under h.v., and used without further purification. The trifluoroacetate salt (440 mg, 1.43 mmol) was transformed according to *GP 3*. FC (AcOEt/hexane/AcOH 4:6:0.3) and recrystallization from $CHCl_3$/hexane yielded **11b** (490 mg, 64%). White solid. M.p. 177.5–178°. R_f 0.47 (AcOEt/hexane/AcOH 4:6:0.3). $[\alpha]_D^{r.t.} = -7.62$ ($c = 0.79$, $CHCl_3$). IR ($CHCl_3$): 3434*w*, 3008*w*, 2944*w*, 1717*s*, 1510*m*, 1451*w*, 1405*w*, 1339*w*, 1248*m*, 1127*w*, 1082*w*, 1051*w*. ^{1}H-NMR (400 MHz, CD_3COCD_3): 1.88–1.91 (*m*, $CHCH_2$); 2.53–2.79 (*m*, $PhCH_2$, $COCH_2$); 4.01–4.09 (*m*, CHN); 4.24 (*t*, $J = 7.0$, $CHCH_2O$); 4.32–4.41 (*m*, $CHCH_2O$); 6.51 (*d*, $J = 8.8$, NH); 7.14–7.42 (*m*, 4 arom. H); 7.70 (*d*, $J = 7.5$, 2 arom. H); 7.85 (*d*, $J = 7.6$, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3COCD_3): 33.1, 37.4, 40.1 (CH_2); 48.2, 49.0 (CH); 66.7 (CH_2); 120.8, 126.1, 126.5, 128.1, 128.5, 129.2 (CH); 142.1, 143.0, 145.3, 156.7, 172.7 (C). FAB-MS: 416.2 (100, $[M+1]^+$), 415.1 (14, M^+). Anal. calc. for $C_{26}H_{25}NO_4$ (415.49): C 75.16, H 6.06, N 3.37; found: C 75.04, H 5.98, N 3.41.

*(*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-7-{[(2-chlorobenzyloxy)carbonyl]amino}heptanoic Acid* (Boc-(*S*)-β³-HLys(2-Cl-Z)-OH; **12**). Diazo ketone **8** (6.85 g, 15.61 mmol) was transformed according to *GP 2a*. Recrystallization (CH_2Cl_2/pentane) yielded **12** (5.05 g, 75%). White powder. M.p. 72–78°. R_f 0.3 (CH_2Cl_2/MeOH 12:1). $[\alpha]_D^{r.t.} = -11.43$ ($c = 1.19$, $CHCl_3$). IR ($CHCl_3$): 3448*w*, 3326*w*, 2981*m*, 2941*m*, 2859*w*, 1709*s*, 1597*w*, 1506*s*, 1445*m*, 1393*m*, 1368*m*, 1167*s*, 1039*m*, 867*w*. ^{1}H-NMR (400 MHz, CD_3COCD_3): 1.39 (*s*, *t*-Bu); 2.45 (*dd*, $J = 15.4$, 6.7, H–C(2)); 2.54 (*dd*, $J = 15.4$, 6.0, H–C(2)); 3.14–3.19 (*m*, CH_2N); 3.91 (br., CHN); 5.16 (*s*, $PhCH_2$); 5.86 (br. *s*, NH); 6.43 (br. *s*, NH); 7.32–7.37 (*m*, 2 arom. H); 7.40–7.44 (*m*, 1 arom. H); 7.48–7.50 (*m*, 1 arom. H); 10.74 (br., COOH). ^{13}C-NMR (100 MHz, CD_3COCD_3): 23.92 (CH_2); 28.64 (Me); 30.42, 35.00, 40.13, 41.45 (CH_2); 48.50 (CH); 63.63 (CH_2); 78.60 (C); 127.99, 130.13, 130.20, 130.33 (CH); 133.57, 136.05, 156.22, 156.91, 172.94 (C). FAB-MS: 857 (5.2, $2M^+$), 451 (10.4, $[M+Na]^+$), 429 (20.8, M^+), 329 (100), 125 (60.0). Anal. calc. for $C_{20}H_{29}ClN_2O_6$ (428.91): C 56.01, H 6.81, N 6.53; found: C 56.02, H 6.79, N 6.36.

*(*S*)-6-{[(*tert*-Butoxy)carbonyl]amino}-3-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)hexanoic Acid* (Fmoc-(*S*)-β³-Orn(Boc)-OH; **13**). Diazo ketone **9** (2.65 g, 5.54 mmol) was transformed according to *GP 2b*. Recrystallization ($CHCl_3$/hexane) yielded **13** (1.63 g, 63%). White powder. M.p. 104° (dec.). R_f 0.27 (MeOH/CH_2Cl_2 1:9). $[\alpha]_D^{r.t.} = -8.0$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3436*w*, 3008*w*, 2981*w*, 1710*s*, 1511*m*, 1450*m*, 1406*w*, 1367*w*, 1169*m*, 1107*w*, 1082*w*, 1046*w*, 872*w*. ^{1}H-NMR (400 MHz, CD_3COCD_3; signals of rotamers in italics): 1.40 (*s*, *t*-Bu); 1.52–1.66 (*m*, 2 CH_2); 2.51 (*dd*, $J = 15.6$, 6.5, H–C(2)); 2.58 (*dd*, $J = 15.6$, 6.6, H–C(2)); 3.09–3.18 (*m*, CH_2N); 3.95–4.05 (*m*, CHN); 4.22 (*t*, $J = 7.1$, CHO); 4.29–4.40 (*m*, CH_2O); *5.58*, 5.95 (br., NH); 6.46 (*d*, $J = 8.7$, NH); 7.30–7.34 (*m*, 2 arom. H); 7.39–7.43 (*m*, 2 arom. H); 7.60–7.70 (*m*, 2 arom. H); 7.86 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3COCD_3; signals of rotamers in italics): *14.34*, 28.67 (Me); 23.28, 27.55, 32.58, 40.17, 40.90 (CH_2); 48.16, 49.10 (CH); 66.72 (CH_2); 78.38 (C); 120.79, 126.13, 126.16, 127.93, 128.48 (CH); 142.11, 145.12, 145.23, 156.65, 156.71, 172.79 (C). FAB-MS: 938 (6.2, $[2M+1]^+$), 491 (4.9, $[M+$

Na]$^+$), 469 (30.3, [$M+1$]$^+$), 369 (50.9), 307 (47.0), 289 (24.8), 178 (100). Anal. calc. for $C_{26}H_{32}N_2O_6$ (468.55): C 66.65, H 6.88, N 5.98; found: C 66.53, H 6.79, N 5.84.

*(S)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-[4-(*tert*-butoxy)phenyl]butanoic Acid* (Fmoc-(*S*)-β^3-HTyr(*t*-Bu)-OH; **14**). Diazo ketone **10** (8.0 g, 16.5 mmol) was transformed according to *GP 2b*. FC (CH_2Cl_2/MeOH 15:1 → 6:1) and recrystallization (AcOEt/pentane) yielded **14** (5.81 g, 74%). White powder. M.p. 190–191° (dec.). R_f 0.44 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{rt} = -20.8$ ($c = 0.5$, DMF). IR (KBr): 3500–2700 (br.), 1695*s*, 1656*m*, 1606*w*, 1562*m*, 1534*m*, 1506*s*, 1451*m*, 1367*m*, 1262*m*, 1234*s*, 1162*m*, 1106*m*, 1084*m*, 1045*m*, 901*m*, 851*w*, 756*m*, 734*m*, 623*w*, 573*w*. ^{1}H-NMR (400 MHz, $CDCl_3$, signals of rotamers in italics): *1.25*, 1.30 (*s*, *t*-Bu); 2.10–2.95 (*m*, 2 H–C(2), $PhCH_2$); *3.90*, 4.16–4.20 (*m*, CHO, CHN); 4.30–4.51 (*m*, CH_2O); 5.25, *5.79* (br., NH); 6.89 (*d*, $J = 7.5$, 2 arom. H); 7.00–7.10 (*m*, 2 arom. H); 7.28–7.31 (*m*, 2 arom. H); 7.36–7.40 (*m*, 2 arom. H); 7.55 (*d*, $J = 7.4$, 2 arom. H); 7.74 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$, signals of rotamers in italics): 28.82, *29.70* (Me); 37.37, 39.51 (CH_2); 47.25, *49.25* (CH); 66.72 (CH_2); 78.42, 119.98, 124.26, 125.05, 127.07, 127.70, 129.77, 132.03 (CH); 141.33, 143.87, 154.17, 155.74, 176.10 (C). FAB-MS: 1497 (41.4, [$3M-1+2$ K]$^+$), 985 (8.8, [$2M+$K]$^+$), 512 (17.9, [$M+$K]$^+$), 496 (43.8, [$M+$Na]$^+$), 474 (78.3, [$M+1$]$^+$), 307 (22.3), 179 (100). Anal. calc. for $C_{29}H_{31}NO_5 \cdot 0.75\ H_2O$ (487.09): C 71.51, H 6.73, N 2.88; found: C 71.54, H 6.81, N 2.92.

11. *β^2-Amino Acid* **19**. *(*R*)-4-Benzyl-3-(4-phenyl-1-oxobutyl)oxazolidin-2-one* (**15**). Similarly to the procedure reported in [34], 4-phenylbutyric acid (4.08 g, 24.87 mmol) and Et_3N (3.6 ml, 26.07 mmol) were dissolved in THF (50 ml) under Ar. After cooling to −78° (internal temp.), pivaloyl chloride (3.2 ml, 26.1 mmol) was slowly added, and the white suspension was stirred at 0° for 1 h. In a separate flask, (*R*)-4-benzyloxazolidin-2-one (4.2 g, 23.7 mmol) was dissolved in THF (100 ml) at r.t. and treated with a cat. amount of DMAP (144 mg, 1.19 mmol) and Et_3N (3.3 ml, 23.7 mmol). The resulting soln. was added to the mixed pivalic anhydride at −78° over 5 min. After stirring for 12 h at r.t., the mixture was diluted with 1M NaOH and extracted with CH_2Cl_2. The org. layer was washed with sat. NaCl soln., H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. FC (AcOEt/hexane 3:7) yielded (*R*)-4-benzyloxazolidin-2-one (1.0 g, 24%) and **15** (5.0 g, 65%). White solid. M.p. 108–109°. $[\alpha]_D^{rt} = -48.5$ ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 2924*w*, 1781*s*, 1698*m*, 1497*w*, 1454*w*, 1385*m*, 1352*m*, 1291w, 1108*w*, 1080*w*, 1051*w*, 1014*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.99–2.14 (*m*, CH_2); 2.71–2.84 (*m*, CH_2CO, 1 H, $PhCH_2$); 2.92–3.10 (*m*, $PhCH_2$); 3.31 (*dd*, $J = 13.3$, 3.3, 1 H, $PhCH_2$); 4.16–4.21 (*m*, CH_2O); 4.62–4.74 (*m*, CHN); 7.18–7.41 (*m*, 5 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 23.39, 32.53, 32.69, 35.49 (CH_2); 52.72 (CH); 63.77 (CH_2); 123.66, 125.03, 126.08, 126.20, 126.65, 127.09 (CH); 133.00, 139.22, 151.15, 170.77 (C). FAB-MS: 324.1 (100, [$M+1$]$^+$), 423.1 (7, M^+). Anal. calc. for $C_{20}H_{21}NO_3$ (323.39): C 74.28, H 6.54, N 4.33; found: C 74.31, H 6.59, N 4.48.

*(4*S*)-4-Benzyl-3-[(2*R*)-2-({[(benzyloxy)carbonyl]amino}methyl)-1-oxo-4-phenylbutyl]oxazolidin-2-one* (**16**). Compound **15** (4.8 g, 14.86 mmol) was dissolved in CH_2Cl_2 under Ar and cooled to −5° (internal temp.). $TiCl_4$ (1.64 ml, 15 mmol) was slowly added (internal temp. < 1°) and the resulting orange soln. stirred for 10 min. Et_3N (2.09 ml, 15 mmol) was then added and the resulting dark red soln. stirred for 45 min at −5°. Benzyl *N*-(methoxymethyl) carbamate (4.35 g, 22.29 mmol) [27] was added, and the mixture was stirred at 0° for 3 h. The mixture was quenched with sat. NH_4Cl soln. and the org. phase washed twice with 1M HCl and sat. NaCl soln., dried ($MgSO_4$), and evaporated. FC (Et_2O/pentane 1:1) yielded **15** (960 mg, 20%) and **16** (3.19 g, 44%). Colorless oil. $[\alpha]_D^{rt} = -41.1$ ($c = 1.3$, $CHCl_3$). IR ($CHCl_3$): 3450*w*, 3010*s*, 2977*w*, 1779*m*, 1720*m*, 1515*m*, 1422*w*, 1389*w*, 1351*w*, 1215w, 1046*w*, 928*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.76–1.88 (*m*, 1 H, $PhCH_2CH_2$); 2.06–2.12 (*m*, 1 H, $PhCH_2CH_2$); 2.60–2.70 (*m*, 3 H, $PhCH_2CH_2$, $PhCH_2CHN$); 3.21 (*dd*, $J = 13.4$, 3.4, 1 H, $PhCH_2CHN$); 3.52–3.60 (*m*, CH_2N); 3.96–3.98 (*m*, CHCO); 4.04–4.12 (*m*, CH_2O); 4.46 (*m*, CHN); 5.10 (*s*, $PhCH_2$); 5.15 (br., NH); 7.14–7.61 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.7, 31.1, 35.4, 40.0 (CH_2); 40.1, 53.0 (CH); 63.8, 64.3 (CH); 123.7, 124.9, 125.7, 125.9, 126.1, 126.2, 126.5, 127.0 (CH); 132.9, 134.1, 138.7, 150.7, 153.9, 172.3 (C). FAB-MS: 509 (100, [M + Na]$^+$), 487 (54, [M + 1]$^+$).

(S)-2-({[(Benzyloxy)carbonyl]amino}methyl)-4-phenylbutanoic Acid (Z-(*S*)-β^2-HHop-OH; **17**). Compound **16** (3.0 g, 6.16 mmol) was dissolved in THF/H_2O 4:1 (0.2M) and cooled (ice-bath). H_2O_2 (30% aq. soln., 2.5 ml, 25 mmol) followed by $LiOH \cdot H_2O$ (414 mg, 9.86 mmol.), was added, and the soln. was stirred for 90 min at 0°. The mixture was treated with 1M Na_2SO_3 soln. (20 ml), concentrated and extracted with CH_2Cl_2 (3×). The chiral auxiliary was recovered from the CH_2Cl_2 phase (590 mg, 60%). The aq. phase was acidified (pH 1–2) with 6M HCl and extracted with AcOEt (3×). The combined AcOEt phases were dried ($MgSO_4$) and evaporated. Recrystallization from $CHCl_3$/hexane yielded **17** (1.40 g, 70%). Colorless needles. M.p. 103–103.5°. $[\alpha]_D^{rt} = -4.7$ ($c = 0.96$, $CHCl_3$). IR ($CHCl_3$): 3446*w*, 3011*w*, 2948*w*, 1717*s*, 1515*m*, 1455*w*, 1410*w*, 1328*w*, 1261w, 1143*w*, 1082*w*, 1046*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.74–1.83 (*m*, 1 H, $PhCH_2CH_2$); 1.84–1.93 (*m*, 1 H, $PhCH_2CH_2$); 2.55–2.71 (*m*, 3 H, $PhCH_2CH_2$, CHCO); 3.27–3.41 (*m*, CH_2N); 4.84 (*s*, $PhCH_2$); 7.04 (br., NH);

7.12–7.34 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, CD_3OD): 32.5, 34.4, 43.4 (CH_2); 46.6 (CH); 67.5 (CH_2); 127.1, 129.1, 129.2, 129.5 (CH); 138.4, 143.0, 158.9, 177.9 (C). FAB-MS: 655.3 (2, $[2M+1]^+$), 350.1 (13, $[M+Na]^+$), 328.1 (100, $[M+1]^+$), 327.1 (7, M^+). Anal. calc. for $C_{19}H_{21}NO_4$ (327.38): C 69.71, H 6.47, N 4.28; found: C 69.75, H 6.61, N 4.31.

*(*S*)-2-(Aminomethyl)-4-phenylbutanoic Acid* (H-(*S*)-β^2-HHop-OH; **18**). Compound **17** (600 mg, 1.83 mmol) was dissolved in EtOH (0.1M), and a cat. amount of 10% Pd/C was added. The apparatus was evacuated, flushed three times with H_2, and the mixture was stirred under an atmosphere of H_2, for 3 h. Filtration, concentration under reduced pressure, and recrystallization from EtOH/H_2O yielded **18** (222 mg, 63%). Colorless needles. M.p. 228–230°. $[\alpha]_D^{r.t.} = -26.4$ ($c = 0.6$, 1M HCl). IR (KBr): 2948*s*, 1633*s*, 1506*s*, 1261*w*. ^{1}H-NMR (200 MHz, D_2O): 1.71–2.00 (*m*, $PhCH_2CH_2$); 2.47–2.72 (*m*, 3 H, $PhCH_2CH_2$, CHCO); 3.00–3.20 (*m*, CH_2N); 7.22–7.40 (*m*, 5 arom. H). ^{13}C-NMR (50 MHz, D_2O): 31.9, 32.6, 41.1 (CH_2); 45.0 (CH); 67.5 (CH_2); 126.5, 128.7, 128.9 (CH); 142.1, 180.6 (C). ESI-MS: 232.0 (10, $[M+K]^+$), 216.0 (28, $[M+Na]^+$), 194.0 (100, $[M+1]^+$). Anal. calc. for $C_{11}H_{15}NO_2$ (193.25): C 68.37, H 7.82, N 7.25; found: C 68.17, H 7.72, N 7.21.

*(*S*)-2-[([[(9*H*-Fluoren-9-yl)methoxy]carbonyl]amino)methyl]-4-phenylbutanoic Acid* (Fmoc-(*S*)-β^2-HHop-OH; **19**). The free β^2-amino acid **18** was transformed according to *GP 3*. Recrystallization from $CHCl_3$/hexane yielded **17** (310 mg, 75%). White solid. M.p. 182–184°. R_f 0.41 (AcOEt/hexane/AcOH 4:6:0.3). $[\alpha]_D^{r.t.} = -9.7$ ($c = 1.2$, CH_3COCH_3). IR ($CHCl_3$): 3451*w*, 3019*s*, 2400*m*, 1522*w*, 1477*w*, 1423*w*, 1410*w*, 1328*w*, 1215*s*, 1046*w*, 929*w*. ^{1}H-NMR (400 MHz, CD_3COCD_3): 1.81–1.98 (*m*, $PhCH_2CH_2$); 2.62–2.77 (*m*, 3 H, $PhCH_2CH_2$, CHCO); 3.36–3.48 (*m*, CH_2N); 4.22 (*t*, $J = 7.0$, $CHCH_2O$); 4.33 (*d*, $J = 6.9$, $CHCH_2O$); 6.59 (br., NH); 7.14–7.42 (*m*, 9 arom. H); 7.69 (*d*, $J = 7.5$, 2 arom. H); 7.85 (*d*, $J = 7.5$, 2 arom. H). ^{13}C-NMR (100 MHz, CD_3COCD_3): 32.3, 34.0, 43.0 (CH_2); 45.9, 48.1 (CH); 67.0 (CH_2); 120.8, 126.1, 126.6, 127.7, 128.5, 129.3 (CH); 142.1, 142.4, 145.2, 157.3, 175.7 (C). FAB-MS: 832.5 (1, $[2M+1]^+$), 416.2 (100, $[M+1]^+$). Anal. calc. for $C_{26}H_{25}NO_4$ (415.49): C 75.16, H 6.06, N 3.37; found: C 75.08, H 5.95, N 3.39.

12. *β-Peptides. H-(*S*)-β³-HLys-(*S*)-β³-HLys-(*S*)-β³-HLys-(*S*)-β³-HLys-(*S*)-β³-HLys-(*S*)-β³-HLys-(*S*)-β³-HLys-OH · 8 CF_3COOH* (**1**). According to *GP 4* the *ortho*-chlorotrityl-chloride resin (189 mg, 1.00 mmol Cl/g) was esterified with Fmoc-(*S*)-β^3-HLys(Boc)-OH [29] (64.0 mg, 0.168 mmol). Loading 0.338 mmol/g (57%) corresponding to 64 μmol of anchored Fmoc-(*S*)-β^3-HLys(Boc)-OH. Synthesis according to *GP 5b* and cleavage from the resin according to *GP 6* afforded crude **1** as CF_3COOH salt (112 mg, 91%), purity 79% (RP-HPLC). The peptide was purified by prep. RP-HPLC (2–30% *B* in 20 min) according to *GP 7:* CF_3COOH salt of **1** (67.8 mg, 55%). Colorless high viscous liquid. RP-HPLC (0–25% *B* in 20 min) t_R 10.0 min, purity > 99%. M.p. 235° (dec., sintering at 200°). CD (0.2 mM in MeOH): $-1.2 \cdot 10^4$ (219 nm). IR (KBr): 3600–3000 (br.), 2956*m*, 2867*m*, 2362*s*, 2340*s*, 1850–1350*br*, 1206*m*, 1172*m*, 1128*m*, 839*w*, 800*w*, 722*w*, 666*m*, 606*w*, 522*w*. ^{1}H-NMR (400 MHz, D_2O): 1.29–1.70 (*m*, 21 CH_2); 2.28–2.46 (*m*, 11 CHCO); 2.50–2.66 (*m*, 3 CHCO); 3.55–3.59 (*m*, CHN); 4.07–4.17 (*m*, 6 CHN). ^{13}C-NMR (100 MHz, D_2O): 24.34, 24.89, 29.07, 29.13, 29.17, 34.35, 35.69, 35.81, 39.68, 41.77, 41.88, 41.97, 43.73, 43.79, 43.93 (CH_2); 49.02, 49.70, 49.75, 51.43 (CH); 119.07 (*q*, $J =$ 583.5, 291.6, CF_3); 165.61 (*q*, $J = 70.7$, 35.1, CF_3CO); 173.85, 175.14, 175.20, 175.27, 178.05 (C). FAB-MS: 1052 (4.9, $[M+K]^+$), 1036 (14.9, $[M+Na]^+$), 1015 (100, $[M+1]^+$), 307 (19), 137 (63.5), 84 (62.5). Anal. calc. for $C_{49}H_{100}N_{14}O_8 \cdot 8\ CF_3COOH$ (1925.61): C 40.54, H 5.65, N 10.18; found: C 39.42, H 5.39, N 9.82.

*H-(*S*)-β³-HPhe-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HPhe-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HPhe-OH* (**2**). According to *GP 4* the *ortho*-chlorotrityl-chloride resin (200 mg, 1.30 mmol Cl/g) was esterified with Fmoc-β^3-(*S*)-HPhe-OH (104.0 mg, 0.260 mmol). Loading 0.42 mmol/g (48%). Synthesis (62 μmol) according to *GP 5b* and cleavage from the resin according to *GP 6* afforded crude **2** as CF_3COOH salt (58.1 mg, 72%), purity 81% (RP-HPLC). The peptide was purified by prep. RP-HPLC (10–60% *B* in 10 min) according to *GP 7:* CF_3COOH salt of **2** (46 mg, 57%). White solid. RP-HPLC (30–90% *B* in 20 min) t_R 12.0 min, purity > 96%. M.p. 225.2–236.4°. CD (0.2 mM in MeOH): $-3.7 \cdot 10^4$ (219 nm). IR (KBr): 3600–3000 (br.), 2960*m*, 1650*s*, 1550*s*, 1205*m*, 1133*m*, 800*m*, 722*m*. ^{1}H-NMR (400 MHz, CD_3OD): 1.12 (*d*, $J = 6.7$, Me); 1.13 (*d*, $J = 6.7$, Me); 1.35–1.50 (*m*, $CHCH_2CH_2CH_2$); 1.56–1.75 (*m*, $CHCH_2CH_2CH_2$); 2.25–3.07 (*m*, 24 H, CH_2CO, CH_2NH_2, $PhCH_2$); 3.75–3.82 (*m*, CHN); 4.16–4.18 (*m*, CHN); 4.29–4.35 (*m*, CHN); 4.36–4.53 (*m*, 2 CHN); 4.57–4.64 (*m*, 2 CHN); 7.16–7.36 (*m*, 15 arom. H); 7.62 (*d*, $J = 8.6$, NH); 7.77 (*d*, $J = 9.0$, NH); 7.97 (*d*, $J = 9.1$, NH); 8.21 (*d*, $J = 9.2$, NH); 8.25 (*d*, $J = 8.8$, NH). ^{13}C-NMR (100 MHz, D_2O): 17.1, 17.5 (Me); 20.1, 24.3, 30.5, 30.6, 34.8, 36.1, 37.2, 37.3, 37.9, 38.9, 39.0, 40.0, 40.1, (CH_2); 41.3, 41.4, 44.5, 44.6, 46.0, 46.7, 48.1 (CH); 124.8, 125.8, 126.7, 127.1, 127.5 (CH); 133.1, 136.1, 168.5, 170.1, 170.2, 170.6, 173.6 (C). FAB-MS: 958 (57, $[M+1]^+$), 957 (100, M^+).

*H-(*S*)-β³-HPhe-(*S*)-β³-HAla-(*S*)-β³-HSer-(*S*)-β³-HPhe-(*S*)-β³-HAla-(*S*)-β³-HSer-(*S*)-β³-HPhe-OH* (**3**). According to *GP 4* the *ortho*-chlorotrityl-chloride resin (250 mg, 1.00 mmol Cl/g) was esterified with Fmoc-β^3-(*S*)-

HPhe-OH (90.0 mg, 0.225 mmol). Loading 0.68 mmol/g (92%). Synthesis (62 μmol) according to *GP 5a* and cleavage from the resin according to *GP 6* afforded crude **3** as CF_3COOH salt (35.4 mg, 58%), purity 70% (RP-HPLC). The peptide was purified by prep. RP-HPLC (10–60% *B* in 120 min) according to *GP 7:* CF_3COOH salt of **3** (15 mg, 25%). White solid. RP-HPLC (30–90% *B* in 20 min) t_R 9.9 min, purity >96%. M.p. 115.2–149.4°. CD (0.2 mM in MeOH): $-6.1\cdot10^4$ (219 nm). IR (KBr): 3600–3000 (br.), 3286*s*, 3086*m*, 2929*m,* 1653*s*, 1546*s*, 1455*m*, 1378*m*, 1260*w*, 1205*m*, 1134*m*, 1055*w*, 968*w*, 834*w*, 800*w*, 750*w*, 721*w,* 700*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.13 (*d*, *J* = 6.2, Me); 2.25–3.07 (*m*, 20 H, CH_2CO, $PhCH_2$); 3.42–3.52 (*m*, CH_2O); 3.75–3.82 (*m*, CHN); 4.16–4.22 (*m*, CHN); 4.44–4.55 (*m*, 3 CHN); 4.63–4.71 (*m*, 2 CHN); 7.16–7.38 (*m*, 15 arom. H); 7.45 (*d*, *J* = 8.5, NH); 7.60 (*d*, *J* = 9.0, NH); 7.97 (*d*, *J* = 9.0, NH); 8.44 (*d*, *J* = 9.7, NH); 8.50 (*d*, *J* = 8.9, NH). ^{13}C-NMR (100 MHz, D_2O): 20.9, 21.3 (Me); 38.2, 38.3, 38.9, 39.2, 40.2, 41.4, 42.3, 43.2, 43.3, 43.4 (CH_2); 43.6, 43.8, 52.0 (CH); 64.9 (CH_2); 127.7, 128.6, 129.6, 130.1, 130.6 (CH); 136.9, 139.3, 139.8, 171.2, 171.5, 171.6; 171.9, 172.3, 173.7, 175.2 (C). FAB-MS: 912 (4.7, $[M+K]^+$), 896 (26.5, $[M+Na]^+$), 875 (93.6, $[M+1]^+$), 874 (100, M^+).

*H-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HPhe-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HPhe-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HPhe-OH* (**4**). According to *GP 4* , the *ortho*-chlorotrityl-chloride resin (158.6 mg, 1.00 mmol Cl/g) was esterified with Fmoc-β³-(*S*)-HPhe-OH (48 mg, 0.12 mmol). Loading 0.38 mmol/g (65%) corresponding to 60 μmol of anchored Fmoc-β³-(*S*)-HPhe-OH. Synthesis according to *GP 5b* and cleavage from the resin according to *GP 6* afforded crude **4** as CF_3COOH salt (99 mg, quant.), purity 49% (RP-HPLC). The peptide was purified by RP-HPLC (10–35% *B* in 20 min, then 35–45% *B* in 15 min; C_8) according to *GP 7:* CF_3COOH salt of **4** (25.7 mg, 26%). White solid. HPLC (15–65% *B* in 20 min; C_8) t_R 11.7 min, purity >95%. M.p. 137° (dec.). CD (0.2 mM in MeOH): $-4.8\cdot10^4$ (219 nm). IR (KBr): 3293 (br.), 3096*m*, 2974*m*, 2947*m*, 1676*s*, 1654*s*, 1560*m*, 1541*m*, 1437*w*, 1265*w*, 1205*s*, 1136*m*, 1031*w*, 838*w*, 800*w*, 723*m*, 701*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.12 (*d*, *J* = 6.7, Me); 1.14 (*d*, *J* = 6.6, Me); 1.29–1.76 (*m*, Me, 9 CH_2); 2.25–2.70 (*m*, 9 CH_2CO); 2.74–2.96 (*m*, 3 $PhCH_2$, 3 CH_2N); 3.69–3.75 (*m*, CHN); 4.38–4.68 (*m*, 8 CHN); 7.16–7.28 (*m*, 15 arom. H); 7.77 (*d*, *J* = 9.0, NH); 8.16 (*d*, *J* = 9.8, NH); 8.23 (*d*, *J* = 8.8, NH); 8.41–8.44 (*m*, NH). ^{13}C-NMR (100 MHz, CD_3OD): 18.84, 20.93, 21.56 (Me); 23.90, 24.09, 24.45, 28.03, 28.73, 28.82, 35.89, 36.54, 40.64, 40.67, 40.70, 41.11, 41.57, 41.65, 42.25, 43.23, 43.37 (CH); 43.49, 43.64, 43.81, 46.67, 46.99, 47.26, 47.41, 127.70, 129.50, 129.57, 130.52, 130.62, 130.65 (CH); 139.40, 139.52, 139.66, 171.43, 171.46, 171.64, 171.75, 171.91, 172.13, 172.21, 173.11. FAB-MS: 1222 (18.0, $[M+K]^+$), 1206 (39.8, $[M+Na]^+$), 1184 (100, $[M+1]^+$), 1042 (13.4).

*H-(*S*)-β³-HHop-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HHop-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β³-HHop-OH* (**5**). According to *GP 4* the *ortho*-chlorotrityl-chloride resin (150 mg, 1.00 mmol Cl/g) was esterified with **11b** (56 mg, 0.135 mmol). Loading 0.61 mmol/g (91%) corresponding to 0.123 mmol of anchored **11b**. Synthesis according to *GP 5b* and cleavage from the resin according to *GP 6* afforded crude **5** as AcOH salt (60.4 mg, 45%), purity 48% (RP-HPLC). The peptide was purified by prep. RP-HPLC (20–80% *B* in 20 min, C_8) according to *GP 7:* CF_3COOH salt of **5** (15 mg, 25%). White solid. RP-HPLC (20–80% *B* in 20 min): t_R 12.94 min, purity >98%. M.p. 101.5–108.4°. CD (0.2 mM in MeOH): $-4.2\cdot10^4$ (220 nm). IR (KBr): 3600–3000 (br.), 3283*s*, 3066*s*, 2955*s,* 1650*s*, 1555*s*, 1433*m*, 1383*m*, 1261*w*, 1206*s*, 1133*s*, 978*w*, 833*w*, 800*m*, 750*w*, 722*m,* 700*m*. ^{1}H-NMR (500 MHz, CD_3OD): 1.18 (*d*, *J* = 6.7, Me); 1.21 (*d*, *J* = 6.7, Me); 1.37–1.83 (*m*, 16 H, $PhCH_2CH_2$, $CHCH_2CH_2CH_2$); 1.95–2.12 (*m*, $PhCH_2CH_2$); 2.28–2.95 (*m*, 24 H, $PhCH_2$, CH_2N, CH_2CO); 3.64–3.69 (*m*, CHN); 4.29–4.57 (*m*, 6 CHN); 7.16–7.38 (*m*, 15 arom. H); 7.63 (*d*, *J* = 9.0, NH); 7.77 (*d*, *J* = 9.2, NH); 7.92 (*d*, *J* = 9.2, NH); 8.35 (*d*, *J* = 9.3, NH); 8.37 (*d*, *J* = 9.1, NH). ^{13}C-NMR (125 MHz, CD_3OD): 21.0, 21.2 (Me); 24.0, 24.2, 28.3, 28.6, 32.4, 33.7, 33.9, 35.9, 36.2, 36.3, 38.4, 39.0, 39.1, 39.9, 40.6, 40.7, 42.0, 43.3 (CH_2); 43.6 (CH); 43.7(CH_2); 44.0, 47.1, 47.3, 47.4, 48.2, 50.7 (CH); 127.0, 127.5, 129.3, 129.4, 129.5, 129.8 (CH); 141.8, 142.8, 142.9, 171.2, 171.7, 171.9, 172.0, 172.6, 173.4, 175.1 (C). FAB-MS: 1021 (5.0, $[M+Na]^+$), 999 (70.3, $[M+2]^+$), 998 (100, $[M+1]^+$).

*H-(*S*)-β²-HHop-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β²-HHop-(*S*)-β³-HAla-(*S*)-β³-HLys-(*S*)-β²-HHop-OH* (**6**). According to *GP 4* the *ortho*-chlorotrityl-chloride resin (150 mg, 1.00 mmol Cl/g) was esterified with **19** (56 mg, 0.135 mmol). Loading 0.66 mmol/g (99%) corresponding to 0.133 mmol of anchored **19**. Synthesis according to *GP 5a* and cleavage from the resin according to *GP 6* afforded crude **6** as AcOH salt (72 mg, 46%), purity 80% (RP-HPLC). The peptide was purified by prep. RP-HPLC (20–80% *B* in 20 min, C_{18}) according to *GP 7:* CF_3COOH salt of **6** (59 mg, 33%). White solid. RP-HPLC (20–80% *B* in 20 min): t_R 12.6 min, purity >97%. M.p. 76.5–106.7°. CD (0.2 mM in MeOH): $-4.8\cdot10^4$ (219.8 nm). IR (KBr): 3600–3000 (br.), 3277*s*, 3067*s*, 2966*s,* 1650*s*, 1555*s*, 1456*m*, 1394*m*, 1261*m*, 1200*s*, 1133*s*, 833*m*, 800*m*, 750*w*, 722*m,* 700*m*. ^{1}H-NMR (500 MHz, CD_3OD): 1.22 (*d*, *J* = 6.7, Me); 1.23 (*d*, *J* = 6.6, Me); 1.36–1.96 (*m*, 18 H, $PhCH_2CH_2$, $CHCH_2CH_2CH_2$); 2.30–2.73 (*m*, 16 H, $PhCH_2$, CH_2CO, CHCO); 2.87–2.97 (*m*, 5 H, CH_2CH_2N, CHCO); 3.09–3.29 (*m*, 4 H, CH_2N); 3.55 (*dd*, *J* = 13.5, 9.0, 1 H, CH_2N); 3.62 (*dd*, *J* = 13.2, 10.8, 1 H, CH_2N); 4.25–4.36 (*m*, 2 CHN); 4.43–4.53

(*m*, 2 CHN); 7.05–7.26 (*m*, 15 arom. H). ^{13}C-NMR (125 MHz, CD_3OD): 21.2, 21.4 (Me); 24.0, 24.1, 28.3, 28.5, 33.5, 33.6, 34.0, 34.4, 34.5, 34.8, 35.5, 36.0, 40.7, 40.8, 41.8, 41.9, 42.0, 42.3, 42.9, 43.4, 43.4, 43.5 (CH_2); 44.1, 44.4, 45.6, 46.2, 47.3, 47.4, 47.7 (CH); 127.1, 127.2, 127.3, 129.3, 129.5, 129.6 (CH); 142.4, 142.7, 172.4, 172.8, 173.4, 173.8, 174.8, 177.9 (C). FAB-MS: 1021 (9.6, $[M+Na]^+$), 999 (58.6, $[M+2]^+$), 998 (100, $[M+1]^+$).

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