γ^2-, γ^3-, and $\gamma^{2,3,4}$-Amino Acids, Coupling to γ-Hexapeptides: CD Spectra, NMR Solution and X-ray Crystal Structures of γ-Peptides

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Abstract: There are numerous possible γ-amino acids with different degrees of substitution and with various constitutions and configurations. Of these the γ^4- and the *like*- and *unlike*-$\gamma^{2,4}$-amino acids have been previously used as building blocks in γ-peptides. The synthesis of γ^2-, γ^3-, and $\gamma^{2,3,4}$-peptides is now described. The corresponding amino acids have been prepared by Michael addition of chiral *N*-acyl-oxazolidinone enolates to nitro-olefins, with subsequent reduction of the NO_2 to NH_2 groups. Such additions to *E*-2-methyl-nitropropene provide (2*R*,3*R*,4*R*)-2-alkyl-3-methyl-4-amino-pentanoic acid derivatives (**9**, **10**, **11**). Stepwise coupling and fragment coupling lead to γ-di-, tri-, and hexapeptides (**12**–**23**), which were fully characterized. The crystal structures of one of the γ-amino acids (2,3-dimethyl-4-amino-pentanoic acid·HCl, **9a**), of a $\gamma^{2,3,4}$-di- and a $\gamma^{2,3,4}$-tetrapeptide (**20**, **22**) are described, and the NMR solution structure in MeOH of a $\gamma^{2,3,4}$-hexapeptide (**3**) has been determined (using TOCSY, COSY, HSQC, HMBC and ROESY measurements and a molecular dynamics simulated-annealing protocol). A linear conformation (sheet-like), a novel (*M*) helix built of nine-membered hydrogen-bonded rings, and (*M*) 2.6_{14} helices have thus been identified. NMR measurements at different temperatures (298–393 K) and H/D-exchange rates obtained for the $\gamma^{2,3,4}$-hexapeptide are interpreted as evidence for the stability of the 2.6_{14} helix (no "melting") and for its non-cooperative folding mechanism. CD Spectra of the γ-peptides have been measured in MeOH and CH_3CN, indicating that only the protected and unprotected $\gamma^{2,3,4}$-hexapeptide is present as the 2.6_{14} helix in solution. The structures of the γ^2- and γ^3-hexapeptides (**1**, **2**) could not be determined.

Keywords: amino acids · circular dichroism · helical structures · peptides

Introduction

The biological functions of proteins are based on the property of the peptide chain to fold into definite three-dimensional structures.[2] Different secondary structural motifs such as helices, sheets, and turns are found in these biomacromolecules, although they all consist of only L-α-amino acid residues. Among synthetic oligomers investigated so far, only a few show a similar diversity of secondary structures. An outstanding position in this regard occupy oligomers consisting entirely of β-amino acids.[3] These so-called β-peptides have been extensively investigated over the last few years. Most interestingly, they do not only form secondary structures similar to those found in proteins, but these structures are also more stable, and they are adopted with short chain lengths. This feature, together with the possibility of designing the folding by employing appropriate β-amino acid residues, will allow for the rational construction of novel, complex protein-like structures.

Introduction of a further carbon atom into the backbone of each residue of β-peptides leads to γ-peptides. This kind of molecules has not been studied as intensively as β-peptides, so far. Still, various secondary structures of γ-peptidic chains have already been identified. Schreiber and co-workers have reported on oligomers consisting of α,β-unsaturated γ-amino acids, so-called vinylogous polypeptides.[4] They have observed parallel sheet structures for γ-peptides of type **A** (Figure 1) and antiparallel sheet structures for γ-peptides of type **B** in the crystalline state.[5] Hanessian's[6] and our group[7] have found that oligomers of type **C** form stable 2.6_{14} helices in solution, at chain lengths as short as four residues.[8] This finding was rather unexpected, since the propylene unit of each residue is a conformationally flexible element, which makes the formation of a specific conformer entropically unfavorable. On the other hand, 2,4-disubstituted γ-amino acid residues are known to have pronounced conformational preferences.[9] Thus, these building blocks can be used to stabilize or destabilize certain secondary structures of γ-peptides. In fact, oligomers of type **D** form even more stable

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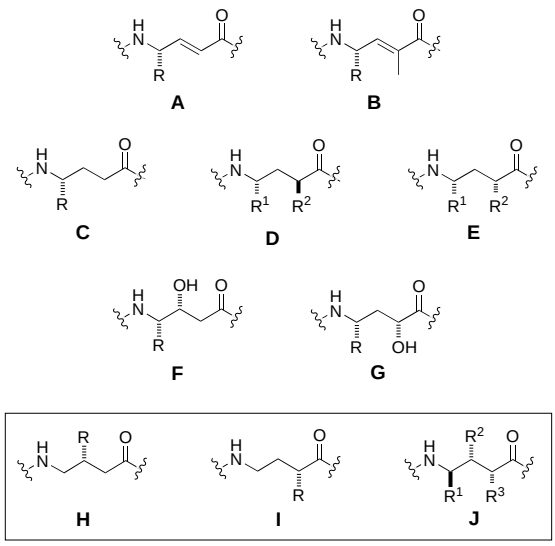

Figure 1. Types of γ-peptides investigated so far (**A**–**G**) and described in this paper (**H**–**J**). For details and references, see text.

2.6_{14}-helical structures than those of type **C**, while γ-peptides of type **E** cannot form such helices at all.[6, 10] Hanessian has described a turn structure for a γ-tetrapeptide of type **E**,[10] and we have recently reported on a stable turn structure of an *N*-acyl-γ-dipeptide amide consisting of two residues of type **E** with opposite chirality.[11] In order to investigate the influence of heteroatom substituents on the conformation of γ-peptides, we have also prepared oligomers of type **F** and **G**.[12]

Here, we report on the synthesis and structural characterization of γ-peptides with the substitution pattern **H**, **I**, and **J**. To facilitate comparisons between the different γ-peptides, we chose compounds **1** and **2**, which are isomers of the known helix forming γ-peptide **C′**, and **3** for this study (Figure 2).[13] The substitution patterns of these γ-peptides tolerate the formation of 2.6_{14}-helical structures without massive van der Waals interactions. While γ-peptide **C′** forms an (*M*) 2.6_{14} helix, γ-peptides **2** and **3** would fit into a (*P*) 2.6_{14} helix and γ-peptide **1** into both, an (*M*)- and a (*P*)- 2.6_{14} helix.

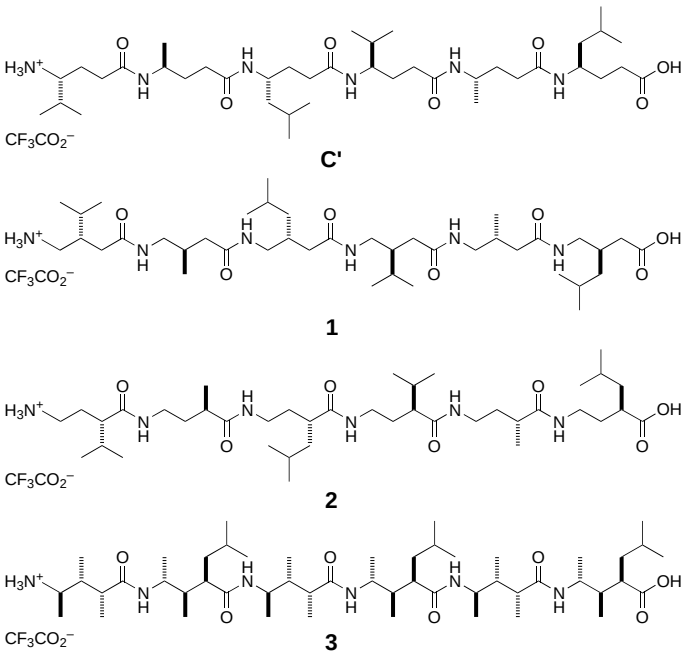

Figure 2. Formulae of the known helix-forming γ-peptide **C′**[7] and of γ-peptides **1**–**3** described herein.

Results and Discussion

Synthesis of γ-amino acids: The γ-amino acid derivatives **4a**–**c** and **5a**–**c**, which are required for the preparation of the γ-peptides **1** and **2**, respectively, were prepared as previously described by us (Figure 3).[14] The building blocks for γ-peptide **3** were obtained following a related route (see Scheme 1). Since we originally envisaged the introduction of a residue with an *i*Pr side chain into γ-peptide **3**, we also prepared the corresponding γ-amino acid derivatives.

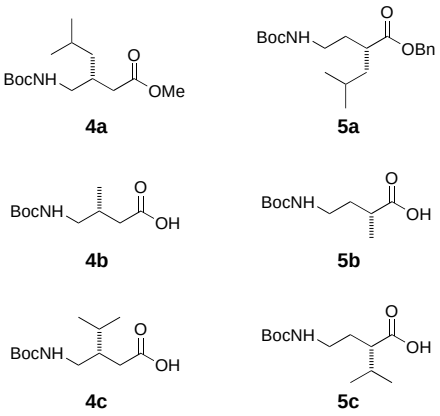

Figure 3. γ-Amino acid derivatives[14] used for the preparation of peptides **1** and **2**.

Addition of the Ti-enolates of the chiral acyloxazolidinones **6a**–**c** to (*E*)-2-nitro-but-2-ene yielded mixtures of nitro compounds **7a**–**c** and their respective diastereoisomers (4′-*epi*-**7a**–**c**) in ratios ranging from 4:1 to 6:1.[15] After separation by column chromatography or crystallization, the major stereoisomers **7a**–**c** were obtained in 50–60% yield. The nitro compounds were then subjected to catalytic hydrogenation over neutral Raney-Ni, a reaction, which was accompanied by some epimerization, and mixtures of pyrrolidinones **8a**–**c** and 5-*epi*-**8a**–**c** (dr = 91:9–86:14) were isolated.[16] These mixtures were used in the next step without separation of the diastereoisomers. Treatment of the *N*-Boc derivatives of **8a** and 5-*epi*-**8a** with LiOH, following a procedure by Grieco,[17, 18] did not furnish **10a**. Rather, hydrochlorides **9a** and **9c** (of dr > 98:2) had to be prepared in a first step, by heating the corresponding pyrrolidinones in refluxing 6N HCl and recrystallizing the crude products.[19] Even under these strongly acidic conditions we observed an equilibrium between the pyrrolidinones and the γ-amino acid hydrochlorides, depending on the substituent R in the 3-position of the γ-lactam. Thus, while hydrolysis of **8a**/5-*epi*-**8a** went almost to completion, the equilibrium was reached at 80% conversion for **8c**/5-*epi*-**8c** and at 65% conversion for **8b**/5-*epi*-**8b**. *N*-Boc Protection finally furnished acids **10a** and **10c**. Compound **10b** was obtained in only

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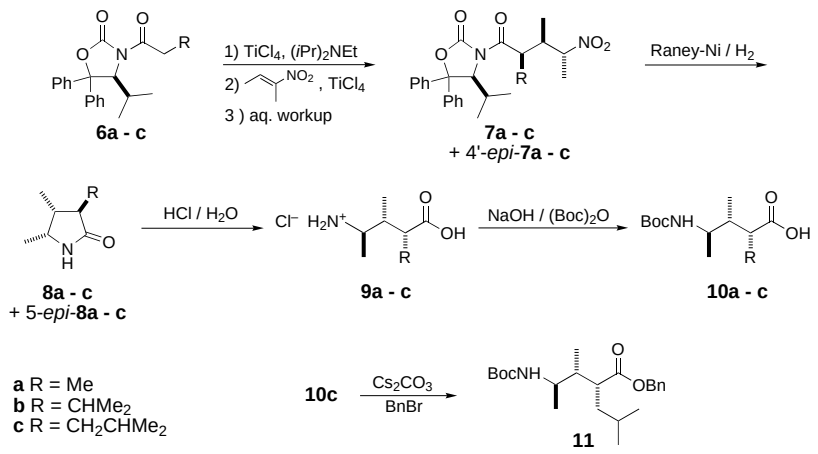

Scheme 1. Preparation of 2,3-disubstiuted-4-amino-pentanoic acid derivatives.

moderate yield from **8b**/5-*epi*-**8b** without isolation of the intermediate **9b**. Finally, **10c** was converted to the benzyl ester **11**.

Synthesis of the γ-peptides: γ-Peptides **1** and **2** were prepared from the corresponding γ-amino acids in solution by using EDC (1-[3-dimethylamino]propyl-3-ethylcarbodiimide hydrochloride) and HOBt (1-hydroxy-1*H*-benzotriazole) as coupling reagents. For the synthesis of γ-peptide **1**, a methyl ester was used as C-terminal protecting group. Thus, compound **4a** was coupled with acid **4b** to yield γ-dipeptide **12**, which was coupled with acid **4c** to γ-tripeptide **13** (Figure 4). Methyl ester hydrolysis yielded acid **14**. It turned out that the basic conditions used for methyl ester hydrolysis also led to cyclization of the C-terminal γ-amino acid, resulting in an *N*-acyl pyrrolidinone. Coupling of γ-tripeptides **13** and **14** furnished the fully protected γ-hexapeptide **15**, from which the free γ-peptide **1** was obtained by deprotection and purification by HPLC. Again, pyrrolidinone formation was observed as a side reaction during hydrolysis of the methyl ester. Thus, we decided to use a benzyl ester as C-terminal protecting group for the preparation of the other γ-peptides.

For the synthesis of **2** with the side chains in 3-position of the amino acids, we first coupled compound **5a** with acid **5b** to the γ-dipeptide derivative **16**, which was then coupled with acid **5c** to γ-tripeptide **17**. Hydrogenolysis of **17** furnished acid **18** in quantitative yield. γ-Hexapeptide **19** was obtained by coupling of γ-tripeptide **17** with acid **18**. Deprotection of **19** and purification by HPLC finally yielded γ-peptide **2**.

The coupling of γ-amino acids having side chains in the 2-, 3-, and 4-position, turned out to be more difficult than coupling of mono-substituted γ-amino acids. Aminoester **11** was coupled with acid **10a** to the γ-dipeptide **20**, using HATU (1-[bis-(dimethylamino)methyliumyl]-1*H*-1,2,3-triazolo[4,5-b]-pyridin-3-oxide hexafluorophosphate) as coupling reagent, since this gave better yields than EDC/HOBt. All our attempts to couple acid **10b** with γ-dipeptide **20** were unsuccessful. On the other hand, acid **21** could by coupled with **20** in good yield, using EDC/DMAP as reagents. Finally, the protected γ-tetrapeptide **22** and γ-dipeptide **21** were used, by appropriate deprotection and coupling steps, to prepare the fully protected γ-hexapeptide **23**, from which compound **3** was obtained.

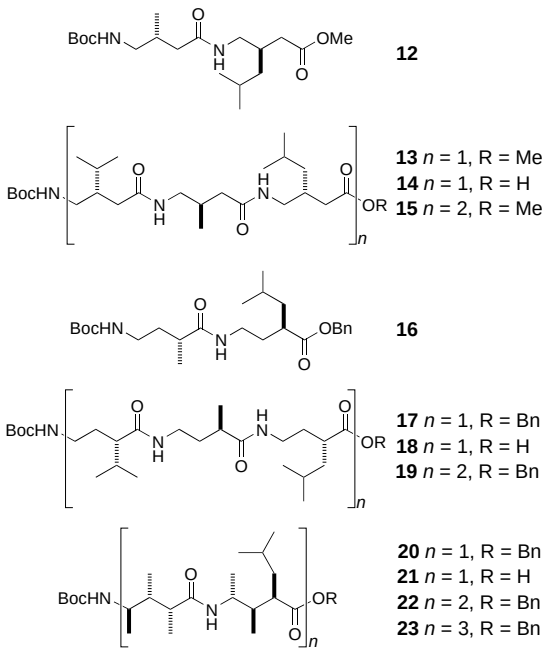

Figure 4. γ-Peptide intermediates in the syntheses of **1**–**3**.

X-ray Crystal structures: The X-ray crystal structure of hydrochloride **9a** shows an extended conformation of the γ-amino acid backbone (Figure 5). Each Cl ion forms three hydrogen bonds to NH_3^+ groups (Cl···N distances: 3.18, 3.31 and 3.22 Å), and one hydrogen bond to a COOH group (Cl···O distance: 3.06 Å). Despite the absence of hydrogen bonds between the amino acids, the crystal structure resembles that of a parallel pleated sheet.

In the crystal structure of γ-dipeptide **20** a different backbone conformation of the residues is found. Rather than forming a sheet-like structure, left-handed helices with nine-membered H-bonded rings are observed (Figure 6). Dado and Gellman have previously identified such intramolecular hydrogen bonds of γ-amino acid derivatives in CH_2Cl_2 solution.[20] The crystal packing of **20** shows stacks of helices, connected by hydrogen bonds between the ester CO and the carbamate NH of neighboring molecules.

We also obtained crystals suitable for single-crystal X-ray structure analysis of the γ-tetrapeptide **22**. Again, a helical structure was found, but with two 14-membered H-bonded rings (Figure 7). The formation of such a ring is not possible for γ-dipeptide **20**. Nevertheless, the backbone conformation of residues 1–3 in the crystal structure of the tetrapeptide

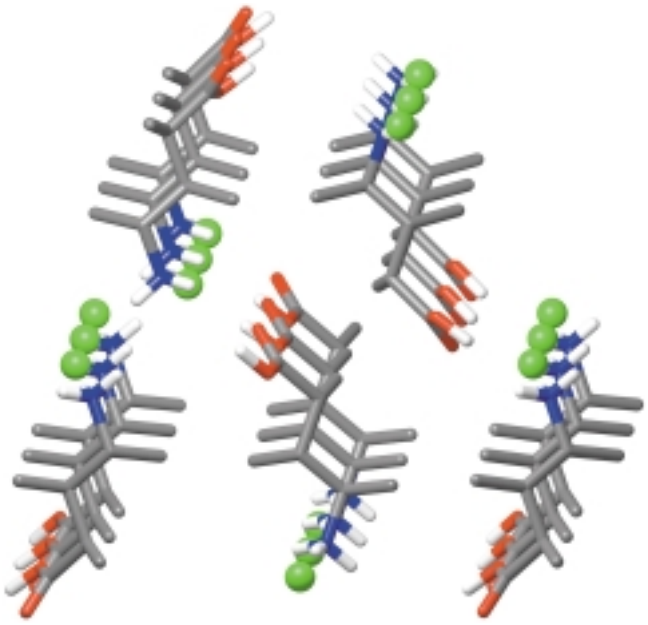

Figure 5. X-ray crystal structure of γ-amino acid hydrochloride **9a**; C atoms in gray, H atoms in white, N atoms in blue, O atoms in red, and Cl ions in green.

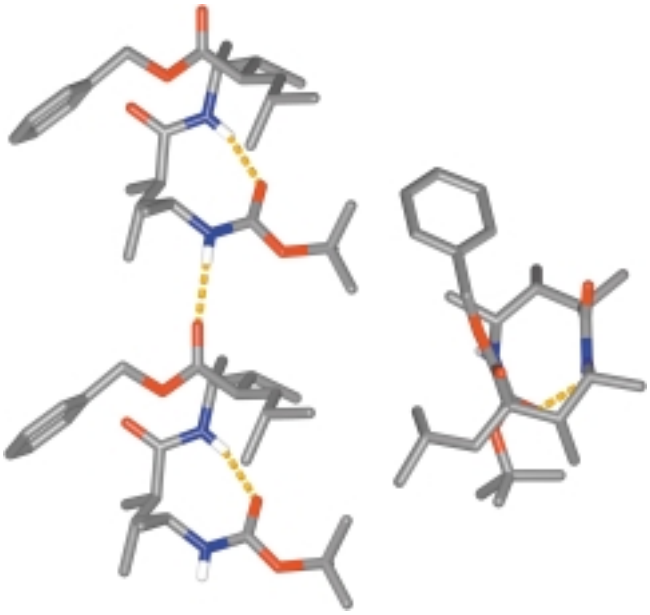

Figure 6. X-ray crystal structure of γ-dipeptide **20;** left: side view of two molecules showing the formation of stacks; right: view of a molecule along the helix axis; for color coding (atom specification) see caption of Figure 5.

derivative **22** is very similar to the one found in the crystal structure of the dipeptide analogue **20**, while residue 4 adopts an extended conformation, similar to the one found in the crystal structure of hydrochloride **9a**. Since the C-terminal ester group cannot act as a H-bond donor, the formation of a third 14-membered H-bonded ring is not possible. Thus, the conformation of residue 4 may mainly be determined by interactions with neighboring molecules. In fact, the ester CO is involved in an intermolecular hydrogen bond to the carbamate NH of the neigboring molecule. A second intermolecular hydrogen bond is formed between CO of residue 3

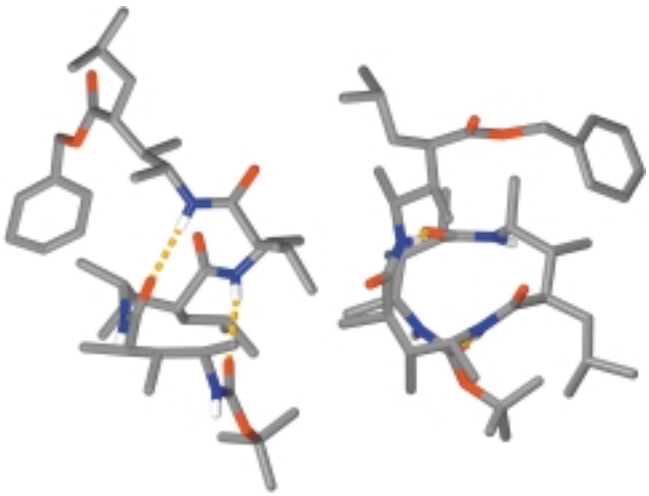

Figure 7. X-ray crystal structure of γ-tetrapeptide **22;** left: side view of the helical structure; right: view along the helix axis; for color coding (atom specification) see caption of Figure 5.

and NH of residue 2 of another neighbor. The H-bonding pattern and the backbone conformation of residues 1–3 fit perfectly into the pattern of a 2.6_{14} helix, similar to the one found in solution for γ-peptide **C′**, but—as expected—with opposite sense of chirality.

Remarkably, in all three crystal structures described here, only two distinguished conformations of the γ-amino acid residue backbones were observed. In fact, only these two conformations do not suffer from unfavorable *syn*-pentane interactions.[21]

NMR spectroscopy: γ-Peptides have been shown to fold into stable secondary structures in solution.[6, 7, 10] The γ-peptides **1**–**3**, soluble in a variety of organic solvents, were investigated by NMR experiments. Two-dimensional ^{1}H NMR measurements were performed in methanol and pyridine solutions in order to allow for comparison of these peptides with the already known structures determined in the same solvents. Complete proton resonance assignment of the individual residues was achieved using TOCSY, COSY and HSQC measurements. Sequence-specific assignment was accomplished by HMBC measurements and a combination of TOCSY and ROESY experiments analyzing short range NOEs between H(α)i and NH(i+1). To determine the three-dimensional structure, ROESY spectra at different mixing times (150 ms, 300 ms) were recorded. However, for γ-peptides **1** and **2**, limited dispersion of the chemical shifts and resonance overlap made the assignment of the NOEs impossible. This was also true for pyridine solutions, which in earlier measurements of other γ-peptides had shown greater dispersion.

For γ-peptide **3** a complete assignment of the NOEs in methanol solution was achieved. The NOEs obtained were classified into three distance categories: strong, medium and weak based upon their volume. These NOE-derived distances as well as the dihedral angles derived from coupling constants and NOEs were used in a restrained molecular dynamics simulated-annealing protocol, yielding 25 structures that could be clustered to a left-handed helix. The structures show

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a well-defined 2.6-helical structure with 14-membered hydrogen-bonded rings from C=O of residue *i* to NH of residue *i*+3 (Figure 8).

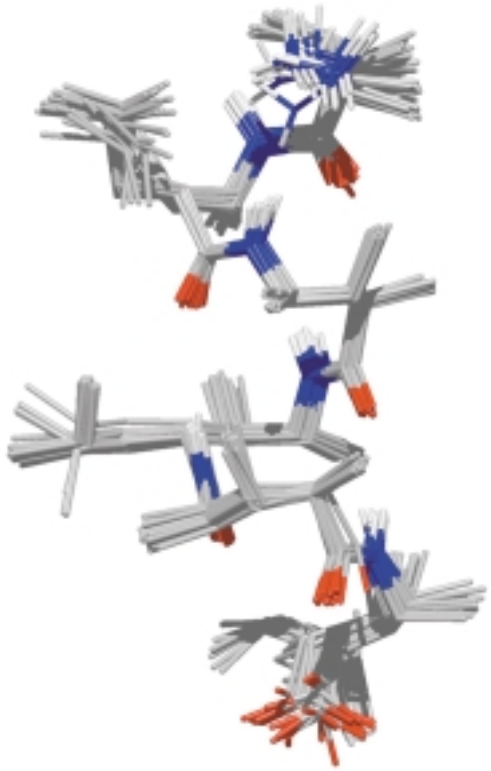

Figure 8. NMR solution structure of γ-peptide **3** in methanol. The peptide forms a left-handed 2.6-helical structure with 14-membered hydrogen-bonded rings from C=O of residue i to NH of residue *i*+3.

In order to probe the stability of the helix, temperature-dependent NMR measurements in methanol were performed at intervals of 10 K up to 393 K. The experiments were carried out in a sealed NMR tube and the solvent was suppressed by presaturation. Figure 9 shows the temperature dependence of the chemical shifts of the amide protons.

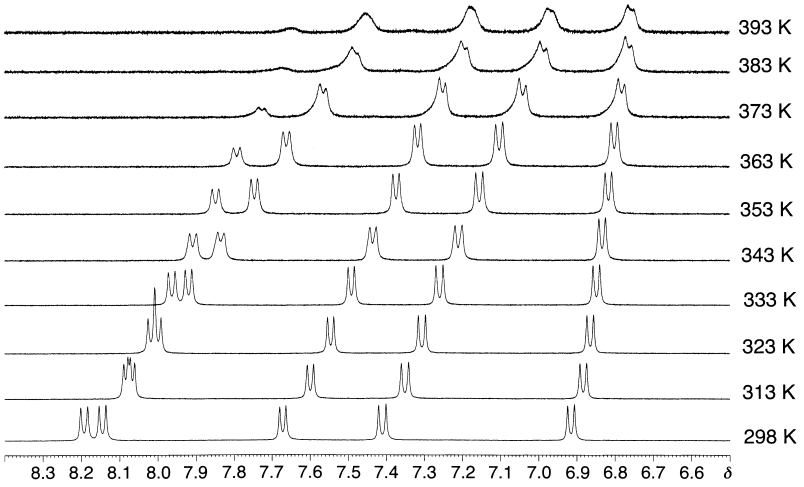

Figure 9. Temperature-dependent ^{1}H NMR spectra (NH region) of γ-peptide **3** in methanol. Measurements were performed at intervals of 10 K up to 393 K. The *J* values remain large, the dispersion of the chemical shifts is maintained, the temperature coefficients are linear (Table 1) and the NH signals are not disappearing by exchange with the solvent. See also Supporting Information.

The backbone $^3J_{HN,HC\gamma}$-coupling constants listed in Table 1 decrease only slowly upon increase of temperature;[22] this is an indication that the helical structure is still present at 363 K.[23] The observed temperature coefficients (Table 1) show a linear relationship of δ versus T for all residues. As anticipated for a helical structure, the C-terminal residue has a high $d\delta/dT$ value (ca. 8 ppb K^{-1}) which is characteristic of solvent exposed groups. Residues 2–5 have a low $d\delta/dT$ value, suggesting that they are part of a stable secondary structure, which is in agreement with the H/D exchange experiment,[24] carried out by dissolving the peptide in CD_3OD:[25] the residues 3–5 exchange at lower rates than the terminal residues (Table 1).

Table 1. Characteristic ^{1}H NMR parameters for γ-peptide **3**. For further details see Supporting Information.

Residue of γ-peptide **3**	NH δ[a]	$^3J_{HN,HC\gamma}$ [Hz][a]	$d\delta/dT$ [ppb K^{-1}]	Half life values [min]
Ala[1]	8.20[b]	–	–	–
Leu[2]	8.12	9.2	−6.0	<5
Ala[3]	7.41	9.6	−6.0	240
Leu[4]	6.90	8.9	−1.7	453
Ala[5]	7.65	8.2	−5.8	197
Leu[6]	8.18	8.8	−7.9	35

[a] Solvent: CD_3OH, T = 298 K. [b] Assigned by COSY measurements.

All of these data indicate that 2,3,4-substituted γ-hexapeptides with the relative configuration of the residues as in **3** adopt stable secondary structures that are maintained even at high temperatures. As with β-peptides, there is no cooperative melting of the helix.[26] In contrast to γ-peptides **1** and **2**, carrying one substituent only in each residue, and showing intensive resonance overlap, γ-peptide **3** contains three aliphatic side chains in each residue and shows a much larger dispersion of signals. This may be a consequence of the helical secondary structure. The conformational constraint imposed by the three substituents sets the conformation of the individual amino acid residue in the backbone[9, 11] towards helix formation.

CD Spectroscopy: Circular dichroism (CD) spectroscopy is a widely used method for the structural characterization of oligopeptides consisting of α-amino acids.[27] This technique has also proven to be useful for the investigation of unnatural oligomers forming secondary structures.[28]

The CD spectra of γ-peptides **C′**, **1**, and **2** in methanol solution show only weak intensities at wavelengths longer then 210 nm (Figure 10, left). It is obvious, that such uncharacteristic spectra are not useful for structural assignments. The γ-peptides **C′** and **2** have very similar CD

spectra. The CD spectrum of the γ-peptide **1** shows a weak minimum around 212 nm. In contrast, the CD spectrum of γ-peptide **3** has a pronounced maximum near 213 nm, but, interestingly, it has no resemblance to the CD spectrum of the γ-peptide **C′**, despite the fact that we know from NMR investigations that both peptides form a 2.6_{14} helix in solution (see above).

Even though it turned out to be difficult to gain structural information by comparing CD spectra of different γ-peptides, comparisons of CD spectra within one type of γ-peptides may be useful. Thus, we measured the CD spectra of the fully protected γ-peptides **20**, **22** and **23**, as well as of the deprotected γ-peptide **3** in methanol solution (Figure 10, middle). All of these γ-peptides consist of the same two residues. The spectra of γ-dipeptide **20** and γ-tetrapeptide **22** are almost superimposable. Both have a maximum near 215 nm and a zero-crossing at 208 nm (the more intensive Cotton effect of **22** reflects the larger number of residues, as compared to **20**). Upon going from γ-tetrapeptide **22** to γ-hexapeptide **23**, a drastic change of the CD pattern occurs. The maximum at 215 nm becomes much more intense and the $\pi \rightarrow \pi^*$ transition is split into a couplet, leading to a shoulder at 203 nm—caused by the low-energy component of the couplet—and a zero-crossing at 197 nm. The CD spectrum of the unprotected γ-peptide **3** is similar to the one of its protected precursor **23**, but the intensity is reduced.

With due care, we draw the following conclusions from these CD spectra: i) both, the protected (**23**) and the unprotected (**3**) γ-hexapeptides are present as 2.6_{14}-helical structures in methanol solutions (unambiguously proven by NMR analysis of **3**); ii) the γ-tetrapeptide **22**, which was found as a 2.6_{14} helix in crystals does not appear to fold to such a helix to a any larger extend in methanol solution; iii) rather, the γ-tetra- (**22**) and the γ-dipeptides (**20**) might have similar structures in methanol, which can not be 2.6_{14}-helical, because the latter can not possibly from a single turn of such a helix (it adopts a nine-membered ring with a next-neighbor hydrogen bond in the crystal).

In aprotic solvents, such as acetonitrile, secondary structures with intramolecular hydrogen bonds are stabilized, relative to methanol, which competes strongly for hydrogen bonding. Nevertheless, the CD spectra in acetonitrile indicate that only a minor population of a 2.6_{14}-helical structure for γ-tetrapeptide **22** is present (Figure 10, right). Again, the CD spectra of the γ-hexapeptides **3** and **23** show a couplet for the $\pi \rightarrow \pi^*$ transition, but with higher intensities than in methanol solution, while the intensities for the maxima at 215 nm are similar in both solvents. In the spectrum of **3**, the long wavelength component of the $\pi \rightarrow \pi^*$ band at $\approx$200 nm is most intense.

Conclusion

We have shown, that a γ-hexapeptide consisting of residues with side chains in the 2, 3, and 4-position form stable 2.6_{14}-helical structures in methanol solution. A γ-tetrapeptide consisting of the same residues forms a 2.6_{14} helix in the solid state, but probably not to a larger extend in methanol or acetonitrile solution. A new kind of helical structure with a nine-membered H-bonded ring was found in the crystalline state for a γ-dipeptide.

Structural assignments of γ-peptides consisting of mono substituted residues with the side chains in the 2- or in the 3-positions were hampered by strong overlap of the NMR signals and uncharacteristic CD spectra.

Experimental Section

General: Starting materials and reagents: Acyl-oxazolidinones **6a–c**,[29] (*E*)-2-nitro-but-2-ene[30] and γ-amino acids **4a–c** and **5a–c**[14] were prepared according to literature procedures. THF was distilled from Na under an Ar atmosphere prior to use. Solvents for chromatography and workup procedures were distilled from Sikkon (anhydrous $CaSO_4$; Fluka Chemie AG) or KOH (Et_2O). All other solvents and reagents were used as received from Fluka. Acronyms: Boc_2O = di(*tert*-butyl) dicarbonate, DMAP = dimethyl-pyridin-4-yl-amine, dr = diastereoisomer ratio (determined by ^1H NMR), EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HATU = (1-[bis-(dimethylamino)methyliumyl]-1*H*-1,2,3-triazolo[4,5-b]pyridin-3-oxide hexafluorophosphate), HOBt = 1-hydroxy-1*H*-benzotriazole, NMM = 4-methylmorpholine.

Equipment: Thin-layer chromatography (tlc): silica gel 60 F_{254} glass plates (Merck); visualization by UV_{254} light and development with $KMnO_4$ solution (NaOH (12 g), $KMnO_4$ (1.5 g), H_2O (300 mL)) or anisaldehyde solution (anisaldehyde (9.2 mL), AcOH (3.75 mL), H_2SO_4 conc. (12.5 mL), EtOH (340 mL)). Flash column chromatography: silica gel 60 (40–63 μm, Fluka), pressure 0.2–0.3 bar. Preparative HPLC: Knauer HPLC system (pump type 64, programmer 50, UV detection (variable-wavelength

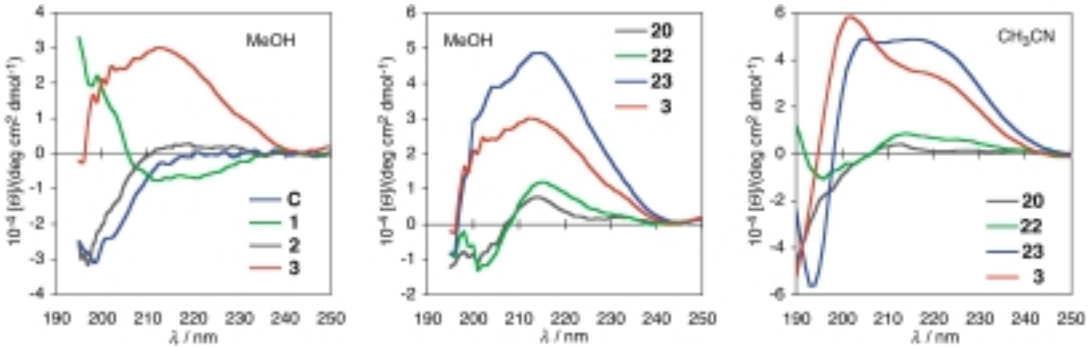

Figure 10. CD Spectra of γ-peptides; left: fully deprotected γ-hexapeptides **C′** and **1–3** in methanol; middle: protected γ-di-, γ-tetra-, and γ-hexapeptides (**20**, **22**, and **23**), as well as deprotected γ-hexapeptide **3** in methanol; right: γ-peptides **20**, **22**, **23**, and **3** in acetonitrile. The spectra were recorded with 0.2 M peptide solutions and are not normalized to the number of residues.

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monitor)); column: Nucleosil 100-7 C_8 (250 × 21 mm, Macherey–Nagel). M.p.: Büchi-510 apparatus, uncorrected. Optical rotations: Perkin-Elmer 241 polarimeter (10 cm, 1 mL cell) at rt. Circular dichroism (CD) spectra: Jasco J-710 recording from 190 to 250 nm at 20 °C; 1 mm cell; average of five scans, corrected for the baseline; peptide concentration 0.2 mM; smoothing by Jasco software. IR Spectra: Perkin–Elmer-782 spectrophotometer. NMR Spectra: Bruker AMX 500 (^{1}H 500 MHz, ^{13}C 125 MHz), AMX 400 (^{1}H 400 MHz, ^{13}C 100 MHz); δ in ppm downfield from internal TMS ($\delta = 0$); MS: VG Tribrid (EI), VG ZAB2-SEQ (FAB, in a 3-nitrobenzyl alcohol matrix), Finnigan-MAT-TSQ 7000 (ESI) and InoSpec Ultima (MALDI FT-MS, high resolution MS (HRMS), in a 2,5-dihydroxybenzoic acid matrix). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

Addition of 3-acyl-4-isopropyl-5,5-diphenyl-oxazolidin-2-ones to (*E*)-2-nitro-but-2-ene—General procedure 1 (GP 1): $TiCl_4$ (1.1 equiv) was added at −78 °C to a solution of the respective 3-acyl-4-isopropyl-5,5-diphenyl-oxazolidin-2-one in CH_2Cl_2 (0.25 M). After stirring for 5 min, $(i\mathrm{Pr})_2\mathrm{NEt}$ (1.2 equiv) was added at −78 °C and the resulting dark red solution was stirred at 0 °C for 30 min. A solution of (*E*)-2-nitro-but-2-ene in CH_2Cl_2 (1.1 equiv, 1.5 M) and $TiCl_4$ (1.1 equiv) were successively added at −78 °C. The mixture was stirred for 5 h at −78 °C and treated with aq. NH_4F solution (20 %). The organic layer was separated and washed with aq. NH_4F solution (1 ×). To the resulting yellow solution was added 1 N NaOH (5 equiv). After stirring the emulsion for 10 min, sat. $NaHCO_3$ solution (10 mL per 1 mmol oxazolidinone) was slowly added under vigorous stirring over a period of 2 h. The organic layer was separated, washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography.

Reduction of the nitro compounds to pyrrolidin-2-ones—General procedure 2 (GP 2): The respective nitro compound was added to a suspension of W2 Raney/nickel (freshly prepared from 600 mg Al/Ni alloy per 1 mmol nitro compound[31]) in EtOH/AcOEt 1:2 (15 mL 1 mmol^{-1}). The mixture was stirred in an autoclave for 3 d at 50 °C under H_2 (30 bar). The precipitated oxazolidinone auxiliary was dissolved by adding CH_2Cl_2. The catalyst was removed by filtration through Celite and the filtrate was evaporated to yield a white solid residue. Trituration in boiling Et_2O followed by filtration yielded pure recovered oxazolidinone auxiliary as a white solid. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

Boc Deprotection of γ-amino acids and γ-peptides—General procedure 3 (GP 3): To a solution of the respective γ-amino acid (or γ-peptide) in CH_2Cl_2 (0.5 M) was added an equal volume of CF_3CO_2H at 0 °C. The mixture was allowed to warm to rt and stirred for further 1.5 h. Concentration under reduced pressure yielded the crude CF_3CO_2H salt, which was used without further purification.

Peptide coupling with EDC/HOBt—General procedure 4 (GP 4): The respective CF_3CO_2H salt (1 equiv) was dissolved in THF, CH_2Cl_2 or $CHCl_3$ (0.5 M) and cooled to 0 °C. To the resulting solution was added successively NMM (5 equiv), HOBt (1.2 equiv), a solution of the Boc-protected fragment (1 equiv) in THF, CH_2Cl_2 or $CHCl_3$ (0.5 M) and EDC (1.2 equiv). The mixture was allowed to warm to rt and stirred until TLC indicated complete reaction. After dilution with AcOEt the mixture was washed with 1 M HCl (3 ×), sat. aq. $NaHCO_3$ solution (3 ×) and sat. aq. NaCl solution (3 ×). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography.

Peptide coupling with EDC/DMAP—General procedure 5 (GP 5): The respective CF_3CO_2H salt was dissolved in CH_2Cl_2 (0.3 M) and cooled to 0 °C. The Boc-protected fragment (1 equiv), DMAP (3 equiv) and EDC (1.2 equiv) were added and the resulting mixture was stirred for 3 h at 0 °C. The mixture was allowed to warm to rt and stirring was continued until TLC indicated complete reaction. The mixture was diluted with AcOEt and washed with 1 M HCl (3 ×), sat. aq. $NaHCO_3$ solution (3 ×) and sat. aq. NaCl solution (3 ×). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography.

Benzyl ester deprotection—General procedure 6 (GP 6): The respective benzyl ester was dissolved in MeOH (0.1 M) and 10 % (m/m) Pd/C (10 %) was added. The resulting mixture was stirred at rt under an atmosphere of H_2 (1 bar) for 12 h. Subsequent filtration through Celite and concentration under reduced pressure yielded the crude carboxylic acid which was used without further purification.

Reversed-phase (RP) HPLC purification of γ-peptides—General procedure 7 (GP 7): Crude products were purified by preparative RP-HPLC using a gradient of A (0.1 % CF_3CO_2H in H_2O) and B (CH_3CN) at a flow rate of 20 mL min^{-1} with UV detection at 220 nm. The products were isolated and dried by lyophilization.

(*S*)-4-Isopropyl-3-((2*R*,3*R*,4*R*)-2,3-dimethyl-4-nitro-pentanoyl)-5,5-diphenyl-oxazolidin-2-one (7a) and **4′-*epi*-7a**: Reaction of propionyl-oxazolidinone **6a** (13.5 g, 40.0 mmol) with (*E*)-2-nitro-but-2-ene according to GP 1 yielded after trituration (Et_2O) a mixture of **7a** and 4′-*epi*-**7a** (9.5 g, 54 %, dr = 92:8) as a white solid (dr of the crude product = 4:1). $R_f = 0.38$ (pentane/Et_2O 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): **7a**: $\delta = 0.77$ (d, J(H,H) = 6.9 Hz, 3H; CH_3), 0.82 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 0.91 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 0.94 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 1.59 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.99 (app sept.d, J(H,H) = 6.9, 3.2 Hz, 1H; C*H*(CH_3)$_2$), 2.39–2.47 (m, 1H; C*H*CHNO$_2$), 3.70–3.77 (m, 1H; CHCO), 4.59–4.65 (m, 1H; $CHNO_2$), 5.41(d, J(H,H) = 3.2 Hz, 1H; CHNCO), 7.26–7.48 (m, 10H; 2Ph); 4′-*epi*-**7a**: 0.77 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 0.77 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 0.87 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 0.90 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 1.47 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.95–2.03 (m, 1H; C*H*(CH_3)$_2$), 2.79 (dqd, J(H,H) = 8.3, 7.0, 5.3 Hz, 1H; C*H*CHNO$_2$), 3.63 (dq, J(H,H) = 8.3, 6.9 Hz, 1H; CHCO), 4.62 (qd, J(H,H) = 6.8, 5.3 Hz, 1H; $CHNO_2$), 5.34 (d, J(H,H) = 3.6 Hz, 1H; CHNCO), 7.25–7.40 (m, 10H, 2Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7, 12.8, 16.3, 17.2, 21.8, 29.8, 38.8, 39.1, 64.6, 86.1, 89.5, 125.6, 125.9, 128.0, 128.4, 128.7, 128.9, 137.9, 142.3, 152.6, 175.1; 4′-*epi*-**7a**: 10.6, 13.2, 14.4, 16.6, 29.5, 38.7, 39.4, 65.0, 84.3, 89.7, 125.6, 125.8, 128.1, 128.5, 128.7, 137.7, 142.1, 152.8, 175.1; IR ($CHCl_3$): $\tilde{\nu}$ = 2974 (m), 1781 (s), 1709 (s), 1550 (s), 1494 (w), 1450 (m), 1391 (m), 1363 (s), 1316 (m), 1093 (w), 1052 (w), 990 cm^{-1} (w); MS (FAB): *m*/*z* (%): 439 (100) $[M+H]^+$, 392 (47), 348 (32), 238 (43); elemental analysis calcd (%) for $C_{25}H_{30}N_2O_5$ (438.52): C 68.47, H 6.90, N 6.39; found: C 68.39, H 6.98, N 6.42.

(*S*)-4-Isopropyl-3-((2*R*,3*R*,4*R*)-2-isopropyl-3-methyl-4-nitro-pentanoyl)-5,5-diphenyl-oxazolidin-2-one (7b): Reaction of acyl-oxazolidinone **6b** (11.0 g, 30.0 mmol) with (*E*)-2-nitro-but-2-ene according to GP 1 yielded after purification by flash column chromatography (pentane/Et_2O 7:1 → 3:1) compound **7b** (6.7 g, 47 %, dr > 97:3) as a white solid (dr of the crude product = 4:1). $R_f = 0.45$ (pentane/Et_2O 3:1); m.p. 196–167 °C; $[\alpha]_D^{RT} = -146.1$ ($c = 0.98$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.37$ (d, J(H,H) = 7.0 Hz, 3H; CH_3), 0.48 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 0.85 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 0.96 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 1.04 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 1.59 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.77–1.89 (m, 1H; (CH_3)$_2$C*H*CHCO), 2.04 (app sept.d, J(H,H) = 6.9, 3.0 Hz, 1H; (CH_3)$_2$C*H*CHN), 2.28–2.34 (m, 1H; C*H*CHNO$_2$), 3.92 (dd, J(H,H) = 8.1, 6.1 Hz, 1H; CHCO), 4.65 (qd, J(H,H) = 6.7, 5.0 Hz, 1H; $CHNO_2$), 5.47 (d, J(H,H) = 3.0 Hz, 1H; CHNCO), 7.23–7.56 (m, 10H; 2Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 16.2, 18.0, 18.3, 19.5 21.9, 28.4, 30.0, 38.4, 49.4, 65.4, 85.8, 88.8, 125.4, 125.7, 127.9, 128.4, 128.5, 128.8, 137.9, 142.7, 152.7, 174.0; IR ($CHCl_3$): $\tilde{\nu}$ = 2970 (m), 1782 (s), 1709 (m), 1549 (s), 1494 (w), 1450 (m), 1395 (m), 1363 (s), 1316 (m), 1103 (w), 1052 (w), 1002 cm^{-1} (w); MS (FAB): *m*/*z* (%): 933 (5) $[2M+H]^+$, 467 (100) $[M+H]^+$, 420 (29), 376 (16); elemental analysis calcd (%) for $C_{27}H_{34}N_2O_5$ (466.58): C 69.51, H 7.34, N 6.00; found: C 69.28, H 7.44, N 6.02.

(*S*)-3-((2*R*,3*R*,4*R*)-2-Isobutyl-3-methyl-4-nitro-pentanoyl)-4-isopropyl-5,5-diphenyl-oxazolidin-2-one (7c): Reaction of acyl-oxazolidinone **6c** (17.5 g, 46.0 mmol) with (*E*)-2-nitro-but-2-ene according to GP 1 yielded after purification by flash column chromatography (pentane/Et_2O 10:1) compound **7c** (11.1 g, 50 %, dr > 97:3) as a white solid (dr of the crude product = 4:1). $R_f = 0.44$ (pentane/Et_2O 5:1); $[\alpha]_D^{RT} = -102.7$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.38$ (d, J(H,H) = 6.5 Hz, 3H; CH_3), 0.60 (d, J(H,H) = 6.6 Hz, 3H; CH_3), 0.67–0.74 (m, 1H; C*H*HCH(CH_3)$_2$), 0.77–0.89 (m, 1H; CH_2C*H*(CH_3)$_2$), 0.79 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 0.85 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 0.93 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.64 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.80 (ddd, J(H,H) = 13.4, 11.8, 4.4 Hz, 1H; CH*H*CH(CH_3)$_2$), 2.02 (app sept.d, J(H,H) = 6.9, 3.6 Hz, 1H; CHC*H*(CH_3)$_2$), 2.49 (dqd, J(H,H) = 9.6, 6.9, 3.0 Hz, 1H; C*H*CHNO$_2$), 3.69–3.74 (m, 1H; CHCO), 4.49 (dq, J(H,H) = 9.5, 6.7 Hz, 1H; $CHNO_2$), 5.39 (d, J(H,H) = 3.6 Hz, 1H; CHNCO), 7.25–7.51 (m, 10H; 2Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 16.5, 17.7, 21.2, 21.7, 23.3, 26.2,

29.6, 33.4, 38.6, 41.2, 65.1, 88.0, 89.8, 125.4, 125.8, 128.1, 128.5, 128.6, 128.9, 137.6, 142.2, 152.8, 173.5; IR ($CHCl_3$): $\tilde{\nu}$ = 2961 (m), 1777 (s), 1698 (m), 1553 (s), 1494 (w), 1450 (m), 1390 (m), 1364 (m), 1119 (w), 1053 (w), 1036 (w), 988 (w), 900 cm^{-1} (w); MS (FAB): *m/z* (%): 961 (12) $[2M+H]^+$, 481 (100) $[M+H]^+$, 434 (50), 390 (23); elemental analysis calcd (%) for $C_{28}H_{36}N_2O_5$ (480.60): C 69.98, H 7.55, N 5.83; found: C 70.16, H 7.52, N 5.66.

(3*R*,4*R*,5*R*)-3,4,5-Trimethyl-pyrrolidin-2-one (8a) and **5-*epi*-8a**: Compound **7a** (9.47 g, 21.6 mmol) was hydrogenated according to GP 2. After purification by flash column chromatography (Et_2O/MeOH 60:1 → 25:1) a mixture of **8a** and 5-*epi*-**8a** (2.59 g, 94%, dr = 87:13) was obtained as a white solid. R_f = 0.34 (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$, **8a**): δ = 1.04 (d, *J*(H,H) = 6.8 Hz, 3H; CH_3), 1.07 (d, *J*(H,H) = 6.6 Hz, 3H; CH_3), 1.16 (d, *J*(H,H) = 6.8 Hz, 3H; CH_3), 2.00–2.14 (m, 2H; CHCHCO), 3.62–3.67 (m, 1H; CHN), 6.82 (br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$, **8a**): δ = 13.5, 13.6, 16.5, 41.0, 41.1, 51.1, 180.1; IR ($CHCl_3$): $\tilde{\nu}$ = 3431 (m), 3007 (m), 2970 (m), 2932 (w), 2877 (w), 1693 (s), 1457 (m), 1417 (m), 1382 (m), 1343 (w), 1295 (w), 1086 (w), 1056 (w), 1011 (w), 968 cm^{-1} (w); MS (EI): *m/z* (%): 127 (16) $[M]^+$, 112 (93), 84 (6), 69 (100), 56 (47), 55 (16), 44 (79), 42 (16), 41 (36), 28 (16); elemental analysis calcd (%) for $C_7H_{13}NO$ (127.19): C 66.11, H 10.30, N 11.01; found: C 66.27, H 10.26, N 11.15.

(3*R*,4*R*,5*R*)-3-Isopropyl-4,5-dimethyl-pyrrolidin-2-one (8b) and **5-*epi*-8b**: Compound **7b** (8.21 g, 17.6 mmol) was hydrogenated according to GP 2. After purification by flash column chromatography (CH_2Cl_2/MeOH 50:1 → 35:1) a mixture of **8b** and 5-*epi* **8b** (2.58 g, 94%, dr = 86:14) was obtained as a white solid. R_f = 0.43 (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$, **8b**): δ = 0.99 (d, *J*(H,H) = 6.9 Hz, 3H; CH_3), 1.03 (d, *J*(H,H) = 7.0 Hz, 3H; CH_3), 1.03 (d, *J*(H,H) = 7.1 Hz, 3H; CH_3), 1.08 (d, *J*(H,H) = 6.6 Hz, 3H; CH_3), 1.97 (dd, *J*(H,H) = 7.6, 3.9 Hz, 1H; CHCO), 2.11–2.22 (m, 1H; C*H*(CH_3)$_2$), 2.33–2.42 (m, 1H; C*H*CHN), 3.64–3.71 (m, 1H; CHN), 6.34 (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, **8b**): δ = 15.8, 16.9, 19.1, 20.2, 27.8, 33.9, 51.1, 53.8, 179.0; IR ($CHCl_3$): $\tilde{\nu}$ = 3426 (m), 3000 (m), 2965 (m), 2933 (m), 2875 (m), 1687 (s), 1465 (m), 1417 (m), 1385 (m), 1279 (w), 1084 (w), 1007 cm^{-1} (w); MS (EI): *m/z* (%): 155 (0.6) $[M]^+$, 113 (32), 98 (100), 69 (35), 55 (21), 44 (23), 42 (14), 41 (37), 39 (19), 28 (43); elemental analysis calcd (%) for $C_9H_{17}NO$ (155.24): C 69.63, H 11.04, N 9.02; found: C 69.76, H 11.21, N 8.92.

(3*R*,4*R*,5*R*)-3-Isobutyl-4,5-dimethyl-pyrrolidin-2-one (8c) and **5-*epi*-8c**: Compound **7c** (11.0 g, 22.8 mmol) was hydrogenated according to GP 2. After purification by flash column chromatography (Et_2O/MeOH 100:1 → 30:1) a mixture of **8c** and 5-*epi*-**8c** (3.50 g, 91%, dr = 91:9) was obtained as a white solid. R_f = 0.36 (Et_2O/MeOH 50:1); ^{1}H NMR (400 MHz, $CDCl_3$, **8c**): δ = 0.92 (d, *J*(H,H) = 6.6 Hz, 3H; CH_3), 0.93 (d, *J*(H,H) = 6.6 Hz, 3H; CH_3), 1.04 (d, *J*(H,H) = 7.0 Hz, 3H; CH_3), 1.09 (d, *J*(H,H) = 6.6 Hz, 3H; CH_3), 1.26–1.33 (m, 1H; C*H*H), 1.62 (ddd, *J*(H,H) = 13.8, 7.9, 5.8 Hz, 1H; CH*H*), 1.83–1.93 (m, 1H; C*H*(CH_3)$_2$), 2.04 (app td, *J*(H,H) = 7.9, 5.8 Hz, 1H; CHCO), 2.14–2.23 (m, 1H; C*H*CHN), 3.65–3.72 (m, 1H; CHN); 7.28 (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, **8c**): δ = 14.6, 16.7, 22.3, 23.0, 25.9, 39.1, 39.4, 45.2, 50.9, 180.3; IR ($CHCl_3$): $\tilde{\nu}$ = 3429 (m), 2963 (m), 1691 (s), 1466 (m), 1416 (m), 1384 (m), 1086 cm^{-1} (m); MS (EI): *m/z* (%): 170 (31) $[M+H]^+$, 154 (13), 126 (23), 113 (65), 112 (25), 98 (100), 69 (8); elemental analysis calcd (%) for $C_{10}H_{19}NO$ (169.27): C 70.96, H 11.31, N 8.27; found: C 70.95, H 11.32, N 8.28.

(2*R*,3*R*,4*R*)-4-{[(*tert*-Butoxy)carbonyl]amino}-2,3-dimethyl-pentanoic acid (10a): Lactam **8a** (1.53 g, 12.0 mmol, dr = 87:13,) was dissolved in 6N HCl (90 mL) and stirred for 2 h under reflux. The solvent was evaporated and the residue was triturated (acetone). After filtration hydrochloride **9a** (1.55 g, 71%, dr > 98:2) was obtained as a white solid. A solution of hydrochloride **9a** (1.24 g, 6.8 mmol) in 1N NaOH (14 mL) was cooled to 0 °C and a solution of Boc_2O (1.92 g, 8.8 mmol) in dioxane (5 mL) was added. The resulting mixture was stirred at rt for 18 h, with pH being retained at 10–12 by adding small amounts of 1N NaOH. 1N NaOH was then added until pH 14 was reached and the reaction mixture was washed with Et_2O (2×). AcOEt was added to the aqueous layer and the resulting mixture was acidified at 0 °C with aq. $KHSO_4$ solution (10%) to pH 2–3. The aqueous layer was separated and extracted with AcOEt (3×). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by recrystallisation (AcOEt/hexane) yielded acid **10a** (1.41 g, 84% from **9a**) as a white solid. M.p. 143–144 °C; $[\alpha]_D^{RT} = -8.4$ (*c* = 0.52 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.86 (d, *J*(H,H) = 7.0 Hz, 3H; CH_3), 1.06 (d, *J*(H,H) = 7.1 Hz, 3H; CH_3), 1.12 (d, *J*(H,H) = 6.7 Hz, 3H; CH_3), 1.43 (s, 9H; *t*Bu), 1.89–1.97 (m, 1H; CHO), 2.49–2.56 (m, 1H; C*H*CHN), 3.54–3.61 (m, 1H; CHN); ^{13}C NMR (100 MHz, CD_3OD): δ = 11.6, 12.1, 19.6, 28.8, 41.6, 42.3, 50.3, 79.9, 158.2, 180.0; IR ($CHCl_3$): $\tilde{\nu}$ = 3439 (m), 2980 (s), 1705 (s), 1510 (s), 1454 (m), 1392 (m), 1368 (m), 1083 (m), 1020 (w), 857 cm^{-1} (w); MS (ESI pos.): *m/z* (%): 513 (48) $[2M+Na]^+$, 268 (100) $[M+Na]^+$; MS (ESI neg.): *m/z* (%): 511 (17) $[2M+Na-2H]^-$, 489 (33) $[2M-H]^-$, 280 (6) $[M+Cl]^-$, 244 (100) $[M-H]^-$; elemental analysis calcd (%) for $C_{12}H_{23}NO_4$ (245.32): C 58.75, H 9.45, N 5.71; found: C 58.77, H 9.61, N 5.77.

(2*R*,3*R*,4*R*)-4-{[(*tert*-Butoxy)carbonyl]amino}-2-isopropyl-3-methyl-pentanoic acid (10b): Lactam **8b** (1.09 g, 7.0 mmol, dr = 86:14,) was dissolved in 6N HCl (50 mL) and stirred under reflux for 5 h. The solvent was evaporated and the residue (light yellow oil consisting of a 2:1 mixture of **8b** and **9b**) was dissolved in H_2O (20 mL). The resulting solution was cooled to 0 °C. 1N NaOH (7 mL) and a solution of Boc_2O (1.09 g, 5.0 mmol) in THF (1 mL) was added. The resulting mixture was stirred at rt for 18 h, with pH being retained at 10–12 by adding small amounts of 1N NaOH. 1N NaOH was then added until pH 14 was reached and the reaction mixture was washed with Et_2O (5×). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to yield recovered lactam **8b** (730 mg, 67%, dr = 84:16). AcOEt was added to the aqueous layer and the resulting mixture was acidified at 0 °C with aq. $KHSO_4$ solution (10%) to pH 2–3. The aqueous layer was separated and extracted with AcOEt (5×). Concentration of the aqueous layer yielded a mixture of **9b** and inorganic salts. The organic layers were combined, dried over $MgSO_4$ and evaporated. Purification by trituration (Et_2O) yielded acid **10b** (279 mg, 15% from **8b**, *dr* > 98:2) as a white solid. M.p. 171–172 °C (decomp); $[\alpha]_D^{RT} = +12.1$ (*c* = 0.62 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.90 (d, *J*(H,H) = 7.1 Hz; 3H; CH_3), 0.91 (d, *J*(H,H) = 6.8 Hz, 3H; CH_3), 1.01 (d, *J*(H,H) = 6.9 Hz, 3H; CH_3), 1.11 (d, *J*(H,H) = 6.8 Hz, 3H; CH_3), 1.43 (s, 9H; *t*Bu), 1.93–2.07 (m, 2H; C*H*(CH_3)$_2$, C*H*CHN), 2.24 (dd, *J*(H,H) = 10.4, 4.6 Hz, 1H; CHCO), 3.72 (qd, *J*(H,H) = 6.8, 3.2 Hz, 1H; CHN); ^{13}C NMR (100 MHz, CD_3OD): δ = 11.4, 17.4, 19.8, 22.5, 28.0, 28.8, 38.7, 49.9, 55.2, 79.9, 158.1, 180.0; IR ($CHCl_3$): $\tilde{\nu}$ = 3442 (m), 2973 (s), 1698 (s), 1504 (m), 1456 (m), 1392 (m), 1368 (s), 1088 (m), 1055 cm^{-1} (w); MS (ESI pos.): *m/z* (%): 569 (100) $[2M+Na]^+$, 296 (28) $[M+Na]^+$; MS (ESI neg.): *m/z* (%): 567 (6) $[2M+Na-2H]^-$, 545 (100) $[2M-H]^-$, 308 (10) $[M+Cl]^-$, 272 (50) $[M-H]^-$; elemental analysis calcd (%) for $C_{14}H_{27}NO_4$ (273.37): C 61.51, H 9.95, N 5.12; found: C 61.27, H 9.80, N 4.97.

(2*R*,3*R*,4*R*)-4-{[(*tert*-Butoxy)carbonyl]amino}-2-isobutyl-3-methyl-pentanoic acid (10c): Lactam **8c** (2.20 g, 13.0 mmol, dr = 91:9,) was dissolved in 6N HCl (80 mL) and stirred for 24 h under reflux. The solvent was evaporated and the residue coevaporated with acetone (2×) and triturated in Et_2O. The hydrochloride **9c** (1.76 g, 61%, dr > 98:2) was obtained as a white solid. Repeating the same procedure with the residue of the mother liquid yielded a second amount of **9c** (462 mg, 16%). To a solution of **9c** (2.13 g, 9.5 mmol) in 1N NaOH (20 mL) was added a solution of Boc_2O (3.12 g, 14.3 mmol) in dioxane (8 mL). The resulting mixture was stirred at rt for 18 h, with pH being retained at 10–12 by adding small amounts of 1N NaOH. 1N NaOH was added until pH 14 was reached and the resulting reaction mixture was washed with Et_2O (2×). AcOEt was added to the aq. layer and the mixture was acidified at 0 °C with aq. $KHSO_4$ solution (10%) to pH 2–3. The aq. layer was separated and extracted with AcOEt (3×). The organic layers were combined, dried over $MgSO_4$ and evaporated. The residue was purified by recrystallisation (AcOEt/hexane) to yield acid **10c** (2.34 g, 86% from **9c**) as a white solid. M.p. 126–127 °C; $[\alpha]_D^{RT} = +13.5$ (*c* = 0.81 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD 4:1): δ = 0.88 (d, *J*(H,H) = 6.6 Hz, 3H; CH_3), 0.91 (d, *J*(H,H) = 7.1 Hz, 3H; CH_3), 0.91 (d, *J*(H,H) = 6.5 Hz, 3H; CH_3), 1.12–1.18 (m, 1H; C*H*H), 1.14 (d, *J*(H,H) = 6.7 Hz, 3H; CH_3), 1.44 (s, 9H; *t*Bu), 1.51–1.64 (m, 2H; CH*HCH*(CH_3)$_2$), 1.80–1.95 (m, 1H; C*H*CHN), 2.40–2.50 (m, 1H; CHCO), 3.60–3.70 (m, 1H; CHN); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD 4:1): δ = 12.0, 19.0, 21.4, 24.0, 26.6, 28.4, 37.3, 41.0, 46.2, 79.7, 156.4, 178.7; IR ($CHCl_3$): $\tilde{\nu}$ = 3440 (m), 2959 (m), 1707 (s), 1511 (s), 1455 (m), 1368 (s), 1111 cm^{-1} (m); MS (ESI pos.): *m/z* (%): 597 (4) $[2M+Na]^+$, 310 (100) $[M+Na]^+$; MS (ESI neg.): *m/z* (%): 595 (8) $[2M+Na-2H]^-$, 286 (100) $[M-H]^-$; elemental analysis calcd (%) for $C_{15}H_{29}NO_4$ (287.4): C 62.69, H 10.17, N 4.87; found: C 62.90, H 10.18, N 4.58.

(2*R*,3*R*,4*R*)-4-{[(*tert*-Butoxy)carbonyl]amino}-2-isobutyl-3-methyl-pentanoic acid benzyl ester (11): Similar to a reported procedure,[32] amino acid **10c** (1.44 g, 5.00 mmol) was dissolved in MeOH (50 mL). Aq. Cs_2CO_3 solution (20%) was added until a pH of 7–8 was reached. The solvent was

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evaporated and the residue coevaporated with DMF (2×) and dissolved in DMF (50 mL). To the resulting solution BnBr (0.65 mL, 5.5 mmol) was added. After stirring for 1 h at rt the solvent was evaporated and the residue purified by flash column chromatography (pentane/Et_2O 5:1). Ester **11** (1.80 g, 95%) was obtained as a colorless oil. $R_f = 0.32$ (pentane/Et_2O 4:1); $[\alpha]_D^{RT} = \pm 0.0$ ($c = 0.98$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (d, J(H,H) = 6.5 Hz, 3H; CH_3), 0.86 (d, J(H,H) = 6.6 Hz, 3H; CH_3), 0.88 (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.11 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.17 (ddd, J(H,H) = 13.4, 10.1, 3.3 Hz, 1H; C*H*HCH), 1.41 (*s*, 9H; *t*Bu), 1.38–1.48 (m, 1H; C*H*(CH_3)$_2$), 1.61–1.68 (m, 1H; CH*H*CH), 1.67–1.95 (m, 1H; C*H*CHN), 2.49 (ddd, J(H,H) = 11.6, 7.4, 3.3 Hz, 1H; CHO), 3.63–3.73 (m, 1H; CHN), 4.28–4.38 (br d, 1H; NH), 5.11 (d, J(H,H) = 12.5 Hz, 1H; C*H*HPh), 5.14 (d, J(H,H) = 12.5 Hz, 1H; CH*H*Ph), 7.28–7.37 (m, 5H; Ph); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.5$, 18.6, 21.4, 23.8, 26.4, 28.4, 37.5, 40.6, 45.6, 49.3, 66.1, 79.1, 128.0, 128.1, 128.4, 136.1, 155.3, 175.8; IR ($CHCl_3$): $\tilde{\nu} = 3620$ (m), 3445 (w), 3008 (m), 2975 (s), 1709 (s), 1499 (m), 1454 (m), 1391 (m), 1368 (m), 1046 (s), 877 cm^{-1} (m); MS (MALDI): *m*/*z* (%): 400 (100) $[M+Na]^+$, 344 (78), 300 (44), 278 (31), 273 (28), 192 (39); elemental analysis calcd (%) for $C_{22}H_{35}NO_4$ (377.52): C 69.99, H 9.34, N 3.71; found: C 69.93, H 9.50, N 3.69.

Dipeptide 12: Compound **4a** (1.23 g, 4.50 mmol) was Boc-deprotected according to GP 3 and coupled with acid **4b** (0.98 g, 4.50 mmol) in THF according to GP 4. After purification by flash column chromatography (AcOEt/pentane 5:2) dipeptide **12** (1.57 g, 94%) was obtained as a white solid. $R_f = 0.50$ (AcOEt/pentane 5:1); m.p. 53–54 °C; $[\alpha]_D^{RT} = +3.6$ ($c = 0.61$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.88$ (d, J(H,H) = 6.6 Hz, 3H; CH_3), 0.90 (d, J(H,H) = 6.6 Hz, 3H; CH_3), 0.95 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.08–1.16 (m, 1H; C*H*HCH(CH_3)$_2$), 1.20–1.27 (m, 1H; CH*H*CH(CH_3)$_2$), 1.44 (s, 9H; *t*Bu), 1.62–1.70 (m, 1H; C*H*(CH_3)$_2$), 2.02–2.22 (m, 4H, CH_2CO, 2C*H*CH_2CO), 2.25–2.35 (m, 2H, CH_2CO), 3.00–3.35 (m, 4H, 2CH_2N), 3.68 (s, 3H; OCH_3), 4.90 (br t, 1H; N*H*Boc), 6.72 (br t, 1H; NH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.0$, 22.6, 22.7, 25.2, 28.4, 31.9, 33.1, 37.4, 41.1, 41.6, 43.1, 45.5, 51.6, 79.5, 156.8, 172.6, 173.8; IR ($CHCl_3$): $\tilde{\nu} = 3452$ (w), 2959 (m), 1704 (s), 1660 (m), 1513 (s), 1438 (w), 1368 (m), 1171 cm^{-1} (m); MS (FAB): *m*/*z* (%): 395 (27) $[M+Na]^+$, 373 (97) $[M+H]^+$, 371 (16), 317 (17), 273 (100), 256 (31), 142 (29); elemental analysis calcd (%) for $C_{19}H_{36}N_2O_5$ (372.50): C 61.26, H 9.74, N 7.52; found: C 61.39, H 9.74, N 7.49.

Tripeptide 13: Dipeptide **12** (1.44 g, 3.86 mmol) was Boc-deprotected according to GP 3 and coupled with acid **4c** (947 mg, 3.86 mmol) in THF according to GP 4. After purification by flash column chromatography (CH_2Cl_2/MeOH 20:1) tripeptide **13** (1.61 g, 83%) was obtained as a colorless glass. $R_f = 0.51$ (CH_2Cl_2/MeOH 10:1); m.p. 64–65 °C; $[\alpha]_D^{RT} = -1.4$ ($c = 0.60$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$–1.00 (m, 15H; 5CH_3), 1.10–1.16 (m, 1H; C*H*HCH(CH_3)$_2$), 1.18–1.24 (m, 1H; CH*H*CH(CH_3)$_2$), 1.43 (s, 9H; *t*Bu), 1.63–1.71 (m, 2H), 1.80–1.90 (m, 1H), 2.04–2.36 (m, 8H), 3.07–3.35 (m, 6H; 3CH_2N), 3.67 (s, 3H; OCH_3), 4.99 (br t, 1H; N*H*Boc), 6.72 (br t, 1H, NH), 6.77 (br t, 1H; NH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.4$, 19.5, 20.0, 22.7, 22.7, 25.2, 28.5, 29.3, 31.2, 33.2, 36.7, 37.5, 41.4, 41.7, 42.0, 42.2, 43.1, 44.7, 51.6, 79.3, 156.7, 172.4, 173.4, 173.8; IR ($CHCl_3$): $\tilde{\nu} = 3449$ (w), 2962 (m), 1702 (s), 1657 (s), 1514 (s), 1438 (w), 1368 (m), 1171 cm $^{-1}$ (m); MS (FAB): *m*/*z* (%): 500 (100) $[M+H]^+$, 400 (42); elemental analysis calcd (%) for $C_{26}H_{49}N_3O_6$ (499.69): C 62.50, H 9.88, N 8.41; found: C 62.56, H 9.77, N 8.36.

Tripetide (14): A solution of tripeptide **13** (375 mg, 0.750 mmol) in MeOH (1 mL) was treated with 0.75 N NaOH (1 mL). After stirring for 5.5 h at rt the mixture was diluted with H_2O and AcOEt and acidified to pH 2 with 1N HCl. The aq. layer was separated and extracted with AcOEt (2×). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. After purification by flash column chromatography (CH_2Cl_2/MeOH 10:1) peptide **14** (345 mg, 95%) was obtained as a white solid. $R_f = 0.40$ (CH_2Cl_2/MeOH 7:1); m.p. 173–174 °C (decomp); $[\alpha]_D^{RT} = +9.9$ ($c = 0.98$ in MeOH); ^1H NMR (500 MHz, CD_3OD): $\delta = 0.88$–0.97 (m, 15H; 5CH_3), 1.10–1.30 (m, 2H; CH_2CH(CH_3)$_2$), 1.43 (s, 9H; *t*Bu), 1.63–1.80 (m, 2H; 2C*H*(CH_3)$_2$), 1.89–1.97 (m, 1H; C*H*CH_2N), 2.04–2.26 (m, 8H; 3CH_2CO, 2C*H*CH_2N), 2.97–3.07 (m, 3H; CH_2N, C*H*HN), 3.10–3.14 (m, 1H; C*H*HN), 3.21–3.26 (m, 2H; 2C*H*HN); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 18.2$, 19.0, 19.9, 23.0, 23.5, 26.4, 28.9, 29.6, 32.4, 35.0, 36.5, 40.2, 41.7, 42.7, 42.9, 43.1, 44.3, 46.1, 80.2, 158.7, 175.2, 176.0, 180.8; IR (KBr): $\tilde{\nu} = 3333$ (m), 2976 (s), 1686 (s), 1654 (s), 1541 (s), 1458 (m), 1389 (m), 1367 (m), 1249 (m), 1170 (s), 1076 (w), 1021 (w), 668 cm^{-1}(w); MS (MALDI): *m*/*z* (%): 508 (10) $[M+Na]^+$, 408 (21), 390 (22), 231 (100); HR-MS: calcd for $[C_{25}H_{47}N_3O_6Na]^+$: 508.3357; found: 508.3356 $[M+Na]^+$.

Hexapeptide (15): Tripeptide **13** (225 mg, 0.450 mmol) was Boc-deprotected according to GP 3 and coupled with **14** (219 mg, 0.450 mmol) in THF according to GP 4. After purification by flash column chromatography (CH_2Cl_2/MeOH 15:1) hexapeptide **15** (221 mg, 57%) was obtained as a colorless glass. $R_f = 0.47$ (CH_2Cl_2/MeOH 10:1); m.p. 122–123 °C; $[\alpha]_D^{RT} = -1.9$ ($c = 0.52$ in MeOH); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$–1.01 (m, 30H; 10CH_3), 1.09–1.26 (m, 4H, 2CH_2CH(CH_3)$_2$), 1.43 (s, 9H; *t*Bu), 1.63–1.72 (m, 4H), 1.75–1.90 (m, 2H), 2.03–2.37 (m, 16H), 3.12–3.39 (m, 12H; 6CH_2N), 3.66 (s, 3H; OCH_3), 4.98 (br t, 1H; N*H*Boc), 6.95 (br t, 1H; NH), 7.03 (br t, 1H; NH), 7.37 (br t, 1H; NH), 7.49 (br t, 1H; NH), 7.70 (br t, 1H; NH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.2$, 18.3, 18.4, 19.4, 19.7, 19.9, 20.1, 20.2, 22.6, 22.7, 22.8, 25.1, 25.2, 28.4, 29.1, 29.3, 31.3, 31.4, 31.5, 33.3, 34.0, 36.4, 36.9, 37.0, 37.5, 39.3, 40.8, 41.4, 41.6, 41.7, 41.9, 42.1, 42.3, 43.1, 44.2, 44.6, 44.7, 51.6, 79.6, 156.8, 172.5, 173.1, 173.6, 173.7, 173.8; IR ($CHCl_3$): $\tilde{\nu} = 3448$ (w), 3321 (m), 2961 (s), 1699 (m), 1654 (s), 1518 (m), 1466 (m), 1387 (w), 1368 (m), 1100 (m), 1016 cm^{-1} (m); MS (FAB): *m*/*z* (%): 890 (11) $[M+Na]^+$, 868 (100) $[M+H]^+$, 768 (40); HR-MS: calcd for $[C_{46}H_{86}N_6O_9Na]^+$: 889.6349; found: 889.6344 $[M+Na]^+$.

Dipeptide 16: Compound **5a** (1.22 g, 3.50 mmol) was Boc-deprotected according to GP 3 and coupled with acid **5b** (760 mg, 3.50 mmol) in CH_2Cl_2 according to GP 4. After purification by flash column chromatography (Et_2O/pentane 3:1 → 5:1) dipeptide **16** (1.47 g, 94%) was obtained as a colorless oil. $R_f = 0.29$ (Et_2O/pentane 5:1); $[\alpha]_D^{RT} = -26.7$ ($c = 0.93$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (d, J(H,H) = 6.5 Hz, 3H; CH_3), 0.87 (d, J(H,H) = 6.5 Hz, 3H; CH_3), 1.11 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.24–1.31 (m, 1H; C*H*HCH(CH_3)$_2$), 1.43 (s, 9H; *t*Bu), 1.43–1.57 (m, 1H; C*H*(CH_3)$_2$), 1.59–1.66 (m, 1H; CH*H*CH(CH_3)$_2$), 1.68–1.83 (m, 4H; 2C$H_2$$CH_2$N), 2.14–2.29 (m, 1H; C*H*(CH_3)CO); 2.53–2.60 (m, 1H; C*H*i Bu), 2.96–3.03 (m, 1H; C*H*HN), 3.18–3.50 (m, 3H; 3C*H*HN), 4.71 (br t, 1H; N*H*Boc), 5.12 (app s, 2H; CH_2Ph), 6.35 (br t, 1H; NH), 7.30–7.39 (m, 5H; Ph); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.1$, 22.0, 22.9, 26.1, 28.4, 32.3, 35.2, 37.5, 38.3, 38.6, 41.4, 41.5, 66.3, 79.4, 128.2, 128.3, 128.6, 136.0, 156.6, 175.8, 176.1; IR ($CHCl_3$): $\tilde{\nu} = 3452$ (w), 2961 (m), 1706 (s), 1665 (m), 1512 (s), 1455 (w), 1368 (m), 1167 cm^{-1} (m); MS (FAB): *m*/*z* (%): 471 (91) $[M+Na]^+$, 449 (100) $[M+H]^+$, 349 (81); elemental analysis calcd (%) for $C_{25}H_{40}N_2O_5$ (448.60): C 66.94, H 8.99, N 6.24; found: C 66.93, H 8.78, N 6.27.

Tripeptide 17: Dipeptide **16** (1.30 g, 2.90 mmol) was Boc-deprotected according to GP 3 and coupled with acid **5c** (711 mg, 2.90 mmol) in $CHCl_3$ according to GP 4. After purification by flash column chromatography (AcOEt/hexane 2:1 → AcOEt) tripeptide **17** (1.05 g, 63%) was obtained as a white solid. $R_f = 0.35$ (CH_2Cl_2/MeOH 20:1); m.p. 129–130 °C; $[\alpha]_D^{RT} = -23.5$ ($c = 1.04$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.85$ (d, J(H,H) = 6.6 Hz, 3H; CH_3), 0.87 (d, J(H,H) = 6.5 Hz, 3H; CH_3), 0.90 (d, J(H,H) = 6.4 Hz, 3H; CH_3), 0.92 (d, J(H,H) = 6.5 Hz, 3H; CH_3), 1.11 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.26–1.31 (m, 1H; C*H*HCH(CH_3)$_2$), 1.43 (s, 9H; *t*Bu), 1.47–1.55 (m, 2H), 1.55–1.64 (m, 2H), 1.68–1.86 (m, 6H), 2.28–2.53 (m, 1H; C*H*(CH_3)CO), 2.54–2.59 (m, 1H; C*H*i Bu), 2.98–3.08 (m, 1H; C*H*HN), 3.08–3.19 (m, 2H; 2C*H*HN), 3.19–3.30 (m, 2H; 2C*H*HN), 3.32–3.42 (m, 1H; C*H*HN), 4.74 (br t, 1H; N*H*Boc), 5.09–5.14 (m, 2H; CH_2Ph), 6.34 (br t, 1H; NH), 6.80 (br t, 1H; NH), 7.30–7.43 (m, 5H; Ph); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.0$, 20.3, 21.0, 22.0, 23.0, 26.1, 28.4, 30.4, 30.8, 32.4, 34.4, 37.4, 37.5, 38.2, 38.9, 41.4, 41.5, 51.9, 66.2, 79.5, 128.2, 128.6, 136.0, 156.7, 175.3, 175.9, 176.0; IR ($CHCl_3$): $\tilde{\nu} = 3448$ (w), 2962 (m), 1703 (s), 1662 (s), 1514 (s), 1454 (m), 1391 (w), 1368 (m), 1166 cm^{-1} (m); MS (FAB): *m*/*z* (%): 598 (24) $[M+Na]^+$, 576 (100) $[M+H]^+$, 476 (76); elemental analysis calcd (%) for $C_{32}H_{53}N_3O_6$ (575.79): C 66.75, H 9.28, N 7.30; found: C 66.87, H 9.39, N 7.38.

Tripeptide 18: Debenzylation of tripeptide **17** (461 mg, 0.800 mmol) according to GP 6 yielded tripeptide **18** (387 mg, 99%) as a white solid. M.p. 108–110 °C; $[\alpha]_D^{RT} = +0.2$ ($c = 1.00$ in $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): $\delta = 0.89$ (d, J(H,H) = 6.6 Hz, 3H; CH_3), 0.90 (d, J(H,H) = 6.3 Hz, 3H; CH_3), 0.91 (d, J(H,H) = 6.4 Hz, 3H; CH_3), 0.94 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.11 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.23–1.31 (m, 1H), 1.43 (s, 9H; *t*Bu), 1.50–1.94 (m, 10H), 2.36–2.50 (m, 2H; 2CHCO), 2.71–3.08 (m, 3H; 3C*H*HN), 3.14–3.28 (m, 3H; 3C*H*HN); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 18.4$, 20.7, 21.3, 22.5, 23.5, 27.4, 28.9, 31.0, 31.8, 33.5, 34.6, 38.4, 38.6, 39.5, 40.0, 42.7, 42.9, 52.7, 80.0, 158.5, 177.7, 178.7, 180.0; IR ($CHCl_3$): $\tilde{\nu} = 3447$ (w), 2963 (m), 1699 (s), 1660 (s), 1516 (s), 1453 (m), 1392 (m), 1368 (m), 1168 cm^{-1} (m); MS (FAB): *m*/*z* (%): 508 (100) $[M+Na]^+$,

486 (15) $[M+H]^+$, 386 (22); HR-MS: calcd for $[C_{25}H_{47}N_3O_6Na]^+$: 508.3357; found: 508.3349 $[M+Na]^+$.

Hexapeptide 19: Tripeptide **17** (288 mg, 0.500 mmol) was Boc-deprotected according to GP 3 and coupled with **18** (243 mg, 0.500 mmol) in CH_2Cl_2 according to GP 4. After purification by flash column chromatography (CH_2Cl_2/MeOH 30:1 → 7:1) hexapeptide **19** (401 mg, 85 %) was obtained as a white solid. $R_f = 0.56$ (CH_2Cl_2/MeOH 7:1); m.p. 199–201 °C; $[\alpha]_D^{RT} = -47.3$ ($c = 0.81$ in CF_3CH_2OH); ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$ 1:1): $\delta = 0.86$ (d, J(H,H) = 6.6 Hz, 3H; CH_3), 0.87 (d, J(H,H) = 6.5 Hz, 3H; CH_3), 0.88 (d, J(H,H) = 6.5 Hz, 3H; CH_3), 0.90 (d, J(H,H) = 6.7 Hz, 9H; 3CH_3), 0.92 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 0.94 (d, J(H,H) = 6.6 Hz, 3H; CH_3), 1.09 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.11–1.19 (m, 1H), 1.13 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.26–1.32 (m, 1H; C*H*HCH$(CH_3)_2$), 1.45 (s, 9H; *t*Bu), 1.45–1.63 (m, 16H), 1.68–1.86 (m, 12H), 1.96–2.02 (m, 1H), 2.30–2.39 (m, 3H; 3CHCO), 2.55–2.61 (m, 1H; CHCO), 2.97–3.40 (m, 12H; 6CH_2N), 5.10 (d, J(H,H) = 12.3 Hz, 1H; C*H*HPh), 5.15 (d, J(H,H) = 12.3 Hz, 1H; CH*H*Ph), 7.28–7.38 (m, 5H; Ph); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$ 1:1): δ = 17.7, 18.4, 20.3, 20.4, 20.8, 21.0, 22.1, 22.5, 23.1, 23.4, 26.4, 26.4, 28.6, 29.6, 30.3, 30.8, 30.9, 32.6, 33.1, 34.0, 34.1, 37.4, 37.5, 37.7, 37.9, 38.2, 39.3, 41.8, 41.9, 42.3, 42.4, 51.3, 52.1, 66.7, 79.7, 128.5, 128.6, 128.8, 136.3, 157.3, 176.5, 176.5, 176.7, 177.0, 177.6, 177.7; IR (KBr): $\tilde{\nu}$ = 3298 (s), 3089 (w), 2960 (s), 1734 (m), 1685 (s), 1639 (s), 1552 (s), 1451 (m), 1388 (m), 1367 (m), 1248 (m), 1208 (m), 1171 (m), 991 (w), 872 (w), 698 cm^{-1} (m); MS (FAB): *m*/*z* (%): 965 (100) $[M+Na]^+$, 943 (92) $[M+H]^+$, 843 (70); HR-MS: calcd for $[C_{52}H_{90}N_6O_9Na]^+$: 965.6662; found: 965.6657 $[M+Na]^+$.

Dipeptide 20: Amino acid **11** (1.09 g, 2.90 mmol) was Boc-deprotected according to GP 3. The resulting CF_3CO_2H salt was dissolved in CH_2Cl_2 (28 mL). The solution was cooled to 0 °C and amino acid **10a** (711 mg, 2.90 mmol), NMM (1.6 mL, 14.5 mmol) and HATU (1.33 g, 3.50 mmol) were added. The mixture was stirred for 2 h at 0 °C and for 16 h at rt. After dilution with AcOEt the mixture was washed with 1M HCl (3 ×), sat. aq. $NaHCO_3$ solution (3 ×) and sat. aq. NaCl solution (3 ×). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (pentane/Et_2O 2:1) yielded peptide **20** (1.23 g, 84 %) as a white solid. $R_f = 0.44$ (pentane/Et_2O 2:3); m.p. 133–134 °C; $[\alpha]_D^{RT} = -0.86$ ($c = 1.01$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.75$ (d, J(H,H) = 7.0 Hz, 3H; CH_3), 0.81–0.86 (m, 9H; 3CH_3), 1.01 (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.05 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.13 (d, J(H,H) = 6.6 Hz, 3H; CH_3), 1.19–1.29 (m, 1H; C*H*HCH), 1.36–1.46 (m, 1H; C*H*$(CH_3)_2$), 1.42 (s, 9H; *t*Bu), 1.55–1.69 (m, 2H; CH*H*CH$(CH_3)_2$, C*H*CHN), 1.83–1.92 (m, 1H; C*H*CHN), 2.05 (dq, J(H,H) = 10.3, 6.8 Hz, 1H; C*H*(CH_3)CO), 2.73–2.79 (m, 1H; C*H*/*i*Bu), 3.89–3.96 (m, 1H, CHN), 4.00–4.08 (m, 1H; CHN), 4.27 (d, J(H,H) = 9.2 Hz, 1H; N*H*Boc); 5.00 (d, J(H,H) = 12.3 Hz, 1H; C*H*HPh), 5.24 (d, J(H,H) = 12.3 Hz, 1H; CH*H*Ph), 7.05 (d, J(H,H) = 8.0 Hz, 1H; NH), 7.27–7.37 (m, 5H; Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.9, 10.3, 15.3, 19.8, 20.0, 21.1, 24.0, 26.5, 28.4, 38.7, 40.5, 41.1, 43.8, 46.6, 47.1, 48.2, 66.2, 79.3, 128.0, 128.4, 128.6, 136.3, 156.2, 175.9, 176.3; IR ($CHCl_3$): $\tilde{\nu}$ = 3619 (m), 3443 (w), 2976 (s), 1701 (s), 1654 (m), 1506 (m), 1454 (m), 1391 (m), 1368 (m), 1166 (m), 1046 (s), 877 cm^{-1} (m); MS (MALDI): *m*/*z* (%): 543 (10) $[M+K]^+$, 527 (15) $[M+Na]^+$, 427 (100); elemental analysis calcd (%) for $C_{29}H_{48}N_2O_5$ (504.71): C 69.01, H 9.59, N 5.55; found: C 68.89, H 9.52, N 5.46.

Dipeptide 21: Debenzylation of dipeptide **20** (606 mg, 1.20 mmol) according to GP 6 yielded dipeptide **21** (498 mg, quantitative) as a white solid. M.p. 77–81 °C; $[\alpha]_D^{RT} = -11.4$ ($c = 0.95$ in MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.84$ (d, J(H,H) = 7.0 Hz, 3H; CH_3), 0.89 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 0.91 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.01 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.01 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 1.09 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.14 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.18–1.28 (m, 1H; C*H*$(CH_3)_2$), 1.44 (s, 9H; *t*Bu), 1.49–1.60 (m, 2H; CH_2), 1.67–1.75 (m, 1H; C*H*CHO), 1.80–1.88 (m, 1H; C*H*CHO), 2.22–2.30 (m, 1*H*; CH(CH_3)CO), 2.66–2.71 (m, 1H; C*H*/*i*Bu), 3.81–3.91 (m, 1H; CHN), 3.91–3.98 (m, 1H; CHN), 6.29 (d, J(H,H) = 9.0 Hz, 1H; N*H*Boc), 7.87 (d, J(H,H) = 7.6 Hz, 1H; NH); ^{13}C NMR (100 MHz, CD_3OD): δ = 10.8, 11.4, 15.0, 19.5, 20.1, 21.9, 24.4, 27.8, 28.9, 39.1, 41.7, 42.4, 44.7, 47.5, 48.8, 49.7, 79.8, 158.4, 178.9, 179.9; IR (KBr): $\tilde{\nu}$ = 3316 (m), 2963 (s), 1686 (s), 1654 (s), 1560 (s), 1458 (m), 1368 (m), 1254 (w), 1183 (m), 1141 (m), 836 (w), 722 cm^{-1} (w); MS (MALDI): *m*/*z* (%): 437 (28) $[M+Na]^+$, 337 (100), 301 (60), 298 (56), 210 (80); HR-MS: calcd for $[C_{22}H_{42}N_2O_5Na]^+$: 437.2986; found: 437.2985 $[M+Na]^+$.

Tetrapeptide 22: Dipeptide **20** (298 mg, 0.590 mmol) was Boc-deprotected according to GP 3 and coupled with dipeptide **21** (245 mg, 0.590 mmol) according to GP 5. After purification by flash column chromatography (hexane/AcOEt 3:2) tetrapeptide **22** (404 mg, 85 %) was obtained as a white solid. $R_f = 0.31$ (hexane/AcOEt 1:1); m.p. 160–161 °C; $[\alpha]_D^{RT} = +3.8$ ($c = 0.53$ in $CHCl_3$); CD (0.2 M in MeOH): $+1.2 \times 10^4$ deg cm^2 dmol^{-1} (215 nm); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.82$ (d, J(H,H) = 6.6 Hz, 6H; 2CH_3), 0.82 (d, J(H,H) = 6.5 Hz, 3H; CH_3), 0.85 (d, J(H,H) = 7.2 Hz, 3H; CH_3), 0.85 (d, J(H,H) = 6.6 Hz, 6H; 2CH_3), 0.88 (d, J(H,H) = 7.1 Hz, 3H; CH_3), 0.98 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.01 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 1.04 (d, J(H,H) = 7.0 Hz, 3H; CH_3), 1.05 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.06 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.08–1.22 (m, 2H; 2C*H*HCH$(CH_3)_2$), 1.10 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.14 (d, J(H,H) = 6.6 Hz, 3H; CH_3), 1.27–1.49 (m, 2H; 2C*H*$(CH_3)_2$), 1.42 (s, 9H; *t*Bu), 1.52–1.59 (m, 1H; CH*H*CH$(CH_3)_2$), 1.61–1.90 (m, 5H; CH*H*CH$(CH_3)_2$, 4C*H*CHN), 2.01–2.09 (m, 1H; CHCO), 2.17–2.29 (m, 2H; 2CHCO), 2.60–2.66 (m, 1H; CHCO), 3.75–3.85 (m, 1H; CHN), 4.00–4.10 (m, 2H; 2CHN), 4.15–4.21 (m, 1H; CHN), 4.30 (d, J(H,H) = 9.6 Hz, 1H; N*H*Boc), 5.00 (d, J(H,H) = 12.3 Hz, 1H; C*H*HPh), 5.21 (d, J(H,H) = 12.3 Hz, 1H; CH*H*Ph), 6.13 (d, J(H,H) = 8.5 Hz, 1H; NH), 6.83 (d, J(H,H) = 8.4 Hz, 1H; NH); 7.25–7.36 (m, 5H; Ph), 7.83 (d, J(H,H) = 8.7 Hz, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 10.0, 10.1, 11.2, 15.5, 16.3, 19.7, 19.7, 19.9, 20.7, 21.3, 21.9, 23.9, 24.3, 26.0, 26.6, 28.4, 36.9, 39.4, 40.4, 40.5, 40.6, 40.9, 43.4, 44.5, 46.4, 47.1, 47.4, 47.7, 47.9, 48.1, 66.2, 79.3, 127.9, 128.4, 128.5, 136.4, 156.0, 175.6, 175.9, 176.1, 176.7; IR ($CHCl_3$): $\tilde{\nu}$ = 3306 (m), 2974 (s), 1702 (s), 1659 (s), 1506 (s), 1454 (m), 1368 (m), 1166 (s), 1129 (w), 1077 cm^{-1} (w); MS (MALDI): *m*/*z* (%): 824 (34) $[M+Na]^+$, 724 (100); elemental analysis calcd (%) for $C_{46}H_{80}N_4O_7$ (801.16): C 68.96, H 10.06, N 6.99; found: C 68.87, H 10.24, N 7.03.

Hexapeptide 23: Tetrapeptide **22** (160 mg, 0.200 mmol) was Boc-deprotected according to GP 3 and coupled with dipeptide **21** (91 mg, 0.220 mmol) according to GP 5. After flash column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH 20:1) hexapeptide **23** (181 mg, 82 %) was obtained as a white solid. $R_f = 0.55$ (CH_2Cl_2/MeOH 20:1); m.p. 95–115 °C; $[\alpha]_D^{RT} = +22.1$ ($c = 0.56$ in $CHCl_3$); CD (0.2 M in MeOH): $+4.9 \times 10^4$ deg cm^2 dmol^{-1} (215 nm); CD (0.2 M in CH_3CN): 4.9×10^4 deg cm^2 dmol^{-1} (205 nm), -5.6×10^4 deg cm^2 dmol^{-1} (193 nm); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.82-0.92$ (m, 33H; 11CH_3), 0.99–1.02 (m, 9H; 3CH_3), 1.05–1.20 (m, 24H; 7CH_3, 3C*H*H), 1.44 (s, 9H; *t*Bu), 1.44–1.56 (m, 5H; 3C*H*Me_2, 2CH*H*), 1.66–1.73 (m, 1H; CH*H*), 1.75–1.92 (m, 6H; 6C*H*CHN), 2.00–2.06 (m, 1H; CHCO), 2.18–2.36 (m, 4H; 4CHCO), 2.62–2.66 (m, 1H; CHCO), 3.70–3.85 (m, 1H; CHN), 3.94–4.07 (m, 3H; 3CHN), 4.15–4.23 (m, 2H; 2CHN), 4.30 (d, J(H,H) = 9.9 Hz, 1H; N*H*Boc), 5.00 (d, J(H,H) = 12.3 Hz, 1H; C*H*HPh), 5.18 (d, J(H,H) = 12.3 Hz, 1H; CH*H*Ph), 5.89 (d, J(H,H) = 8.6 Hz, 1H; NH), 6.34 (d, J(H,H) = 8.4 Hz, 1H; NH), 6.43 (d, J(H,H) = 9.4 Hz, 1H; NH), 7.26–7.36 (*m*, 5H; Ph), 7.39 (d, J(H,H) = 8.1 Hz, 1H; NH), 8.01 (d, J(H,H) = 8.7 Hz, 1H; NH); ^{13}C NMR (125 MHz, $CDCl_3$): 9.2, 9.5, 9.5, 9.8, 10.0, 11.6, 16.1, 16.6, 17.1, 19.4, 19.5, 19.8, 20.5, 20.9, 21.0, 21.4, 21.8, 22.0, 23.9, 24.3, 24.5, 25.8, 25.9, 26.6, 28.4, 35.8, 39.3, 39.7, 40.1, 40.2, 40.3, 40.4, 40.9, 43.5, 43.7, 44.7, 46.0, 46.5, 46.9, 47.2, 47.3, 47.4, 47.7, 47.9, 48.4, 66.1, 79.3, 127.9, 128.4, 128.5, 136.4, 155.9, 175.1, 175.6, 175.8, 176.4, 176.6, 177.0; IR ($CHCl_3$): $\tilde{\nu}$ = 3311 (w), 2972 (m), 1710 (s), 1650 (s), 1506 (m), 1452 (m), 1366 (m), 1166 (m); MS (MALDI): *m*/*z* (%): 1120 (93) $[M+Na]^+$, 1098 (19) $[M+H]^+$, 1020 (100); HR-MS: calcd for $[C_{63}H_{112}N_6O_9Na]^+$: 1119.8383; found: 1119.8385 $[M+Na]^+$.

Hexapeptide 1: 5N NaOH (1.5 mL) was added to a solution of hexapeptid **15** (70 mg, 0.081 mmol) in CF_3CH_2OH (0.6 mL). After stirring at rt for 12 h the mixture was acidified with 1N HCl to pH 2 and extracted with AcOEt (3 ×). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was Boc-deprotected according to GP 3. After purification by preparative HPLC (30 → 40 % B in 15 min, t_R = 13.0 min) according to GP 7, peptide **1** (37 mg, 53 %) was obtained as a white solid. CD (0.2 M in MeOH) = -7×10^3 deg cm^2 dmol^{-1} (212 nm); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.87-1.00$ (m, 30H; 10CH_3), 1.08–1.25 (m, 4H; 2CH_2CH$(CH_3)_2$), 1.63–1.85 (m, 4H; 4C*H*$(CH_3)_2$), 1.93–2.34 (m, 17H), 2.45–2.51 (m, 1H), 2.90–2.94 (m, 1H), 3.00–3.03 (m, 1H), 3.09–3.15 (m, 7H), 3.19–3.27 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ = 18.1, 18.2, 18.7, 19.1, 19.7, 19.9, 23.1, 23.2, 23.3, 26.4, 26.4, 29.8, 31.1, 32.5, 32.7, 34.7, 35.2, 36.8, 37.3, 38.4, 40.7, 41.1, 41.7, 42.1, 42.2, 42.7, 42.8, 42.9, 43.3, 44.0, 46.1, 46.3, 175.1, 175.2, 175.2, 175.3, 175.8,

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176.7; MS (FAB): *m/z* (%): 791 (27) $[M+K]^+$, 775 (42) $[M+Na]^+$, 753 (100) $[M+H]^+$; HR-MS: calcd for $[C_{40}H_{77}N_6O_7]^+$: 753.5848; found: 753.5837 $[M+H]^+$.

Hexapeptide 2: Hexapeptide **18** (132 mg, 0.140 mmol) was debenzylated according to GP 6. The resulting carboxylic acid was Boc-deprodected according to GP 3. After purification by preparative HPLC (25 → 35% B in 35 min, $t_R = 15.8$ min) according to GP 7 hexapeptide **2** (98 mg, 81%) was obtained as a white solid. $[\alpha]_D^{RT} = -17.6$ ($c = 0.68$ in MeOH); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.88-0.95$ (*m*, 21H; 7CH_3), 0.97 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.10 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.12 (d, J(H,H) = 6.9 Hz, 3H; CH_3), 1.16–1.19 (m, 1H; C*H*HCH(CH_3)$_2$), 1.20–1.30 (m, 1H; C*H*HCH(CH_3)$_2$), 1.48–2.00 (m, 20H), 2.29–2.50 (m, 4H; 4CHCO), 2.77–2.89 (m, 2H; CH_2N), 3.03–3.29 (m, 10H; 5CH_2N); ^{13}C NMR (125 MHz, CD_3OD): δ = 18.3, 18.4, 20.4, 20.8, 21.2, 21.2, 22.5, 22.6, 23.5, 23.7, 27.2, 27.4, 28.4, 30.6, 31.6, 31.9, 33.5, 33.6, 34.1, 34.6, 34.9, 38.4, 38.6, 38.7, 38.8, 39.2, 39.5, 40.0, 42.6, 42.9, 43.3, 43.8, 52.4, 52.6, 176.4, 177.4, 178.0, 178.5, 178.8, 179.7; IR (KBr): $\tilde{\nu} = 3303$ (s), 3085 (m), 2963 (s), 1646 (s), 1559 (s), 1458 (m), 1388 (m), 1202 (s), 1139 (m), 836 (w), 799 (w), 721 cm^{-1} (w); MS (FAB): *m/z* (%): 791 (15) $[M+K]^+$, 775 (30) $[M+Na]^+$, 753 (100) $[M+H]^+$; HR-MS: calcd for $[C_{40}H_{76}N_6O_7Na]^+$: 775.5679; found: 775.5672 $[M+Na]^+$.

Hexapeptide 3: Hexapeptide **22** (60 mg, 0.055 mmol) was debenzylated according to GP 6. The resulting carboxylic acid was Boc-deprodected according to GP 3. Purification by preparative HPLC (35 → 75% B in 30 min, $t_R = 12.7$ min) according to GP 7 yielded hexapeptide **3** (47 mg, 84%) as a white solid. $[\alpha]_D^{RT} = +8.5$ ($c = 0.42$ in MeOH); CD (0.2 mM in MeOH): $+3.0 \times 10^4$ deg cm^2 dmol^{-1} (213 nm); CD (0.2 mM in CH_3CN): 5.8×10^4 deg cm^2 dmol^{-1} (202 nm); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.87-1.24$ (m, 63H; 20CH_3, 3C*H*H), 1.34 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.42–1.57 (m, 4H; CH*H*, 3C*H*(CH_3)$_2$), 1.60–1.66 (m, 1H; CH*H*), 1.71–1.96 (m, 7H; 6 C*H*CHN, CH*H*), 2.15–2.21 (m, 1H; CHCO), 2.39–2.46 (m, 2H; 2CHCO), 2.49–2.54 (m, 1H; CHCO), 2.56–2.64 (m, 1H; CHCO), 2.64–2.69 (m, 1H; CHCO), 3.52–3.54 (m, 1H; CHN), 3.91–3.98 (m, 3H; 3CHN), 4.05–4.10 (m, 1H; CHN), 4.22–4.26 (m, 1H; CHN); ^{13}C NMR (125 MHz, CD_3OD): δ = 10.7, 10.9, 11.0, 11.9, 12.5, 13.1, 16.0, 16.3, 16.8, 18.4, 19.6, 19.9, 20.0, 20.3, 21.2, 22.0, 22.1, 22.9, 24.3, 24.4, 24.9, 27.3, 27.7, 27.9, 37.3, 37.5, 40.5, 40.8, 41.4, 41.4, 41.7, 42.0, 42.8, 44.6, 45.1, 45.9, 47.1, 47.5, 47.9, 176.5, 178.0, 178.3, 178.9, 179.0, 179.4; IR (KBr): $\tilde{\nu} = 2969$ (m), 1645 (s), 1541 (s), 1458 (m), 1388 (m), 1203 (m), 1136 cm^{-1} (m); MS (ESI pos.): *m/z* (%): 930 (6) $[M+Na]^+$, 908 (38) $[M+H]^+$, 466 (100) $[M+Na+H]^{2+}$; MS (ESI neg.): *m/z* (%): 1020 (66) $[M+CF_3CO_2]^-$, 942 (33) $[M+Cl]^-$, 906 (100) $[M-H]^-$; HR-MS: calcd for $[C_{51}H_{97}N_6O_7Na_2]^+$: 951.7209; found: 951.7163 $[M-H+2Na]^+$.

X-ray crystal structure analysis of 9a, 20, and 22: The reflections were measured on an Enraf Nonius CAD-4 Diffractometer with Cu*K*α radiation (graphite monochromator, $\lambda = 1.54184$ Å). Structures of **9a** and **20** was solved by direct method with SIR97.[33] The non-H atoms were refined anisotropically with SHELXL-97[34] (full-matrix last-squares on F^2). Part of the structure of **22** was solved by direct methods with SIR97, the remaining non hydrogen atoms were found from a difference Fourier map. The non-H atoms were refined isotropically with SHELXL-97. The number of observed reflections did not allow anisotropic refinement. Hydrogen atoms were calculated at idealised positions and included in the structure factor calculation with fixed isotropic displacement parameters.

Crystal data for **9a** ($C_7H_{16}ClNO_2$): $M = 181.66$, $T = 293(2)$ K, orthorhombic, space group $P2_12_12_1$, $a = 6.318(2)$, $b = 11.889(4)$, $c = 13.944(4)$ Å, $V = 1047.4(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.152$ g cm^{-3}, $\mu = 2.926$ mm^{-1}, crystal size $0.40 \times 0.40 \times 0.25$ mm. A total of 1805 reflections were collected ($4.89 < 2\Theta < 66.92°$) of which 1529 were independent and 1336 were considered significant with $I_{net} > 3\sigma(I_{net})$. Final residuals were $R = 0.0486$ and $wR2 = 0.1358$ (GOF = 1.270) for 105 parameters. $\Delta\rho$ (max, min) = 0.316, −0.199 e A^{-3}.

Crystal data for **20** ($C_{29}H_{48}N_2O_5$): $M = 504.71$, $T = 293(2)$ K, monoclinic, space group $P2_1$, $a = 9.320(2)$, $b = 12.176(5)$, $c = 13.426(4)$ Å, $\beta = 93.93(2)°$, $V = 1521.6(6)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.102$ g cm^{-3}, $\mu = 0.592$ mm^{-1}, crystal size $0.30 \times 0.10 \times 0.10$ mm. A total of 2590 unique reflections ($3.30 < 2\Theta < 64.82°$) were processed of which 2006 were considered significant with $I_{net} > 3\sigma(I_{net})$. Final residuals were $R = 0.0398$ and $wR2 = 0.1119$ (GOF = 1.036) for 326 parameters. $\Delta\rho$ (max, min) = 0.175, −0.124 e A^{-3}. Crystal data for **22** ($C_{46}H_{80}N_4O_7$): $M = 801.14$, $T = 293(2)$ K, monoclinic, space group $P2_1$, $a = 9.462(2)$, $b = 20.472(6)$, $c = 13.866(4)$ Å, $\beta = 106.14(2)°$, $V = 2580.1(12)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.031$ g cm^{-3}, $\mu = 0.543$ mm^{-1}, crystal size $0.30 \times 0.20 \times 0.02$ mm. A total of 4479 unique reflections ($3.32 < 2\Theta < 66.23°$) were processed of which 1140 were considered significant with $I_{net} > 3\sigma(I_{net})$. Final residuals were $R = 0.0898$ and $wR_2 = 0.1961$ (GOF = 1.525) for 243 parameters. $\Delta\rho$ (max, min) = 0.242, −0.256 e A^{-3}.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-167172 (**9b**), CCDC-167171 (**20**) and CCDC-182/1874 (**22**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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