Polylithiated β-Peptides: *like*-Selective *C*-Terminal Alkylation of Boc-β-HVal-β-HAla-β-HLeu-OMe

Tobias Hintermann[1], Christian Mathes[2], and Dieter Seebach*

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland
Fax: (internat.) + 411 6321144
E-mail: seebach@org.chem.ethz.ch

Received June 30, 1998

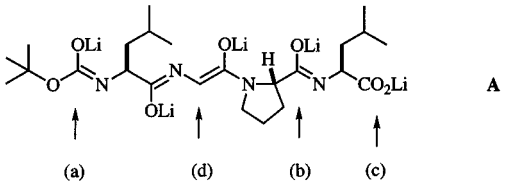
Keywords: β-Peptides / Polylithiation of peptides / Li-enolates of peptides / Back-bone alkylation of β-peptides / Diastereoselective alkylation of β-peptide enolates

A series of *N*-Boc-protected β-tripeptide derivatives with or without *N*-methyl groups and with free or Me-ester-protected C terminus has been prepared (**8**–**14**, **16**, **17**). As with α-peptides (→ **A**), the β-peptide derivatives can be polylithiated (→ **B**, **C**). No epimerization of stereogenic centers and no β elimination (exception **17** → **24**) is observed upon treatment with bases as strong as *t*BuLi. The C terminal ester Li-enolate moiety of tetralithio β-tripeptides (cf. **C**) can be selectively alkylated with methyl, benzyl and allyl halides, and with *tert*-butyl bromoacetate in yields ranging from 35–80% (**8** → **18**, **14** → **20**–**23**).

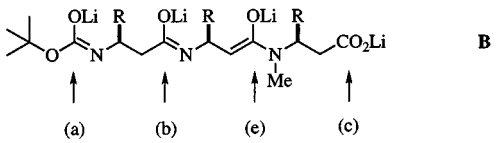
Introduction

The modification of peptides by *C*-alkylation has proven to be a useful alternative of the classical procedure which involves incorporation of proteinogenic or non-proteinogenic amino acids or other building blocks in solution or solid-phase peptide syntheses[3]. More than a decade ago we have initiated a program towards the modification of peptides through Li-enolates[4]. We have shown that linear oligopeptides containing either a glycine or a sarcosine unit can be selectively alkylated[5]. Although deprotonation, and concomitant epimerization of non-glycine or -sarcosine amino acid residues in polylithiated species such as **A**[6] could have occured under the conditions applied (bases such as *t*BuLi were used!), the process of enolization and alkylation was not complicated by such side reactions. Obviously, the bases first deprotonate CONH [→ Li-aza-carbonate (a) or Li-aza-enolate (b) in **A**] and CO_2H groups [→ Li-carboxylate (c)] within the chain and at the termini, and this leads to a protection of the neighbouring stereogenic centers, thus allowing for selective alkylation of the Li_2-4-amino-2-aza-diene-1,4-diolate unit (d) in **A**. The polylithiated species and, sometimes, the peptide precursors, were solubilized in the non polar solvent THF used for those reactions by addition of Li salts[7].

Recently, there has been much interest in β-peptides (peptides built exclusively from β-amino acids) because of their unique tendency to form stable secondary structures in solution[8][9] and because of their resistance to common proteases[10]. This has prompted us to also investigate the possibility of modifying β-peptides by *C*-alkylation of the corresponding polylithiated derivatives, such as **B**. In these



A



B

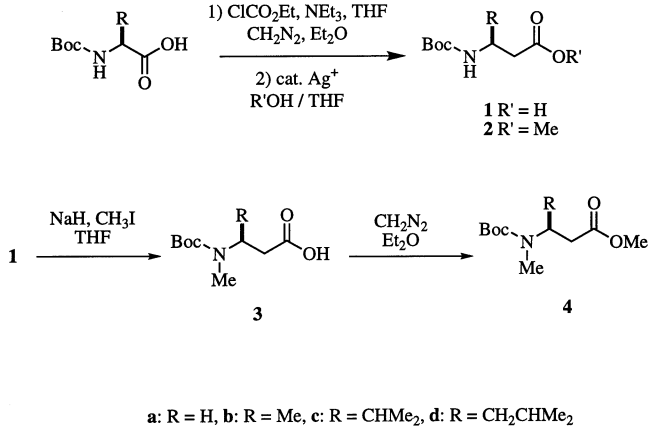
polylithiated species ("homologs" of **A**), the risk of deprotonation at stereogenic centers is much lower than with α-peptides. On the other hand, there is now a risk for β-elimination to occur, with formation of the corresponding α,β-unsaturated carboxylic acid derivatives (after all, β-amino acids have the same functionality pattern as Mannich bases!). In the same way in which we may consider the NH deprotonations of α-peptides as a means of protecting the stereogenic centers from beeing deprotonated (see **A**), we could expect the NH deprotonations of β-peptides as a way of preventing β-elimination in **B**: after all, the moiety R′-C(OLi)=NLi should not be a good leaving group! The strong base should, again, first deprotonate CONH [→ Li-aza-carbonate (a) or Li-aza-enolate (b)] and CO_2H [→ Li-carboxylate (c) in **B**], and thus allow for formation and alkylation of a Li-amino-enolate unit (e). There was precedence for such a process in our previous alkylation studies of doubly lithiated amide- and carbamate-protected simple β-amino acid esters[11][12][13].

  1434−193X/98/1111−2379 $ 17.50+.50/0

Synthesis of the β-Amino Acid Building Blocks and Peptides

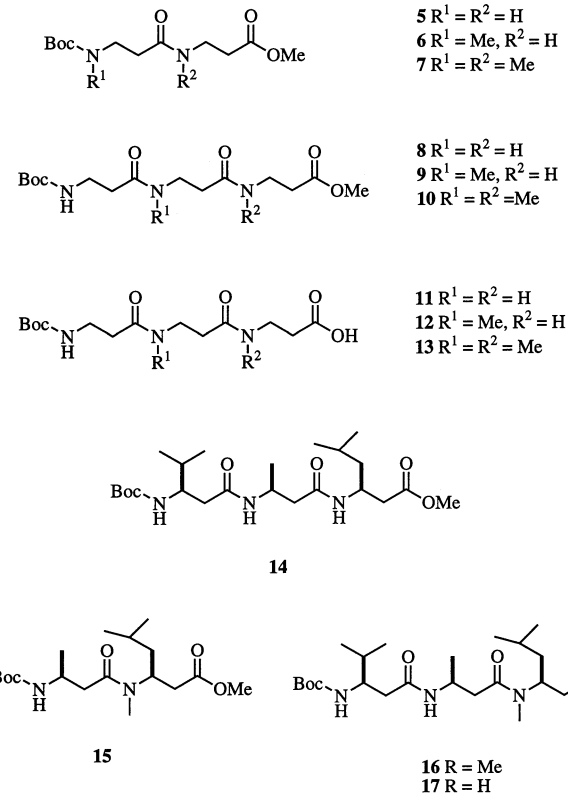
The β-amino acids required for the construction of the peptides to be used as substrates for the alkylation experiments were prepared by known procedures. While Boc-β-HGly-OH (**1a**) is commercially available, Boc-β-HAla-OH (**1b**), Boc-β-HVal-OH (**1c**), Boc-β-HLeu-OH (**1d**), and Boc-β-HLeu-OMe (**2d**), were prepared from the corresponding Boc-protected α-amino acids by Arndt-Eistert homologation[14][15] (Scheme 1). The homologation of Boc-protected *N*-methyl α-amino acids is also possible, but we have previously found, that the synthesis of *N*-methyl-Boc-β-HAla-OH (**3b**) by methylation of Boc-β-HAla-OH (**1b**) is more convenient[16]. The *N*-methyl Boc-β-amino acids **3a**−**d** were thus prepared in good yields (66−94%) by *N*-methylation of Boc-β-amino acids **1a**−**d** using Benoitons procedure[17] originally developed for the methylation of α-amino acids (Scheme 1). The β-amino acid esters **4a** and **4d** were obtained by esterification of the corresponding *N*-methyl amino acids **3a** and **3d** with diazomethane (Scheme 1).

Scheme 1



a: R = H, **b**: R = Me, **c**: R = $CHMe_2$, **d**: R = CH_2CHMe_2

For the preparation of peptides from the building blocks thus available, we followed the standard coupling procedures (EDC/HOBt as coupling reagent, NMM as base, THF or CH_2Cl_2 as solvent) that have proved to be well suited for the solution synthesis of β-peptides[12]. No significant differences with respect to yields obtained in the coupling reactions of *N*-methylated building blocks as compared to their non-methylated counterparts were observed. Dipeptides **5**−**7** were obtained by coupling of the respective amino acids Boc-β-HGly-OH (**1a**), *N*-methyl-Boc-β-HGly-OH (**3a**), $HCl{\cdot}H_2N$-β-HGly-OMe, and $CF_3CO_2H{\cdot}HN$-(Me)-β-HGly-OMe (70−94%). Boc-Deprotection (CF_3COOH/CH_2Cl_2) and coupling with Boc-β-homoglycine (**1a**) gave the tripeptides **8**−**10** in excellent yields (93−96%). Finally, saponification of the methyl ester group (NaOH/MeOH) led to the free acids **11**−**13**. Tripeptide **14** was prepared as previously described in the literature[18]. The synthesis of *N*-methylated tripeptide **17** started with the Boc-deprotection (CF_3COOH/CH_2Cl_2) of *N*-methyl-Boc-β-HLeu-OMe (**4d**). Coupling with Boc-β-HAla-OH (**1b**) using EDC/HOBt led to Boc-dipeptide ester **15** in 83% yield, and this, in turn, was Boc-deprotected and coupled with Boc-β-HVal-OH (**1c**) to give tripeptide ester **16** (89% yield), which was saponified (NaOH/MeOH) to the free carboxylic acid **17** in 94% yield.



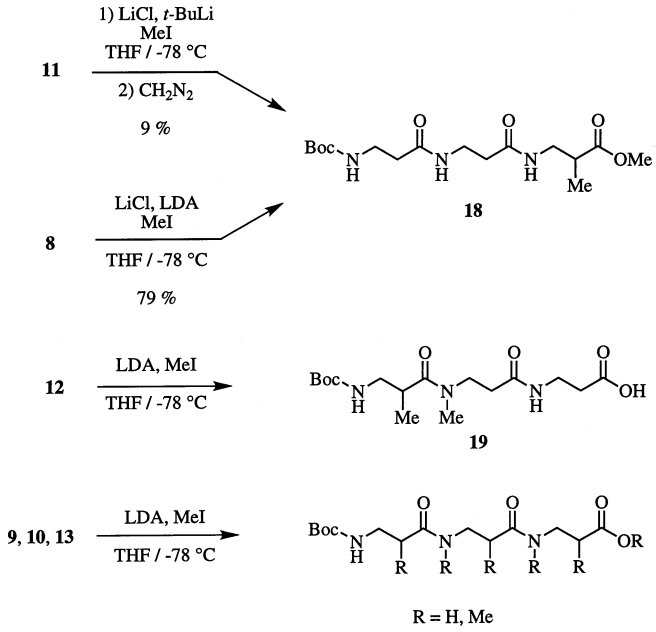
Lithiation of the β-Peptides and Reactions with Electrophiles

As substrates for the metalations we first chose the tripeptide acids **11**−**13** and **17** for the following reasons: with peptides **11**−**13**, containing three β-HGly units with different *N*-methyl substitution patterns, the absence of stereogenic centers was expected to simplify the analysis of the product mixtures (degree of methylation, regioselectivity). To study the diastereoselectivity of the alkylation reaction, however, a β-peptide with stereogenic centers was required. We chose tripeptide **17** with the sequence Val-Ala-Leu because the lipophilic nature of the side-chains should increase the solubility of the starting peptide derivative and of its polylithiated form in THF. In addition, this special sequence has previously been used by us for structural studies on β-peptides, and we thought that our experience should facilitate the analysis of the alkylation products[8][12][18].

The most useful procedure from a general synthetic point of view would be the alkylation of peptides that contain no *N*-alkyl amino acids, a task that has never been achieved with α-peptides[19]. Our first attempts with β-peptides were thus directed towards the (per)alkylation of tripeptide **11**.

In a typical experiment, the peptides (solids) were solubilized in THF by the addition of 7−8 equivalents of dry LiCl[7], whereas in the case of oily β-peptides the reaction was conducted without addition of salt. The polylithiated species was generated at −78°C by treatment with a strong base (LDA, *t*BuLi, LDA/KO*t*Bu) for three hours. Attempted methylation of tripeptide **11** with LDA (7 equiv.) and MeI (15 equiv., −78°C for 20 h) failed; starting material was recovered. Thus, deprotonation of the four $-CO_2H$ and −CONH protons by LDA probably causes, at least under these conditions, "protection" against further deprotonation. We then tried lithiation and alkylation of tripeptide **11** at higher temperature (−15°C). Under otherwise identical conditions, a complex, non separable mixture of *C*- and *N*-alkylated products was obtained[20]. Next we used stronger bases at low temperature (−78°C)[21]: Treatment of tripeptide **11** with Schlosser's base (*t*BuOK/LDA[22]) at −78°C resulted in partial decomposition, and no methylation at all (ca. 60% starting material recovery). A slightly better result was obtained with *t*BuLi (6 equiv.)/MeI: after esterification of the crude product (diazomethane) and flash chromatography, a modest yield of 9% of the monoalkylated tripeptide methyl ester **18** was isolated (Scheme 2). Perhaps not surprisingly, the alkylation took place at the C terminal carboxylate group of the peptide (through the doubly lithiated carboxylic acid group), and not in α-position to an amide group (through a doubly lithiated azacarboxylate, cf. the alkylation of α-peptides[23]).

Scheme 2



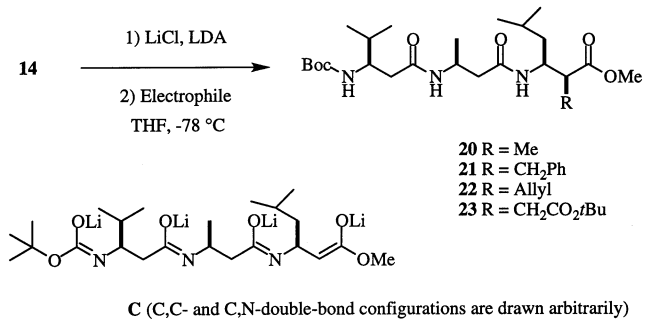
As a consequence of these disappointing results in the alkylation of β-peptide **11**, lacking *N*-alkyl groups, we turned our attention to the tripeptides **12** and **13**, containing one and two *N*-methyl β-amino acid residues. Lithiation and methylation of peptide **12** (5 equiv. LDA/MeI, −78°C) led to a selective *C*-alkylation, presumably in α-position of the *N*-methyl carboxamide unit (→ tripeptide acid **19**), but we were unable to separate the product from starting material (2:1 mixture). The lithiation/methylation (5 equiv. LDA) of doubly *N*-methylated tripeptide **13** under the same conditions yielded a complex mixture of *C*-alkylation products (mono- and dialkylation, various stereoisomers)[24].

From these preliminary experiments, we concluded that alkylation of *N*-methylated β-peptides is, in principle, feasible without causing β-elimination, and we extended the investigation to the tripeptide methyl esters **8**−**10**. With the successful alkylation of *N*-acyl β-amino acid esters[11] in mind, we were confident, that alkylation of the carboxy-terminal methyl ester group[25] in β-peptides is also possible, and, indeed, lithiation of non-*N*-methylated tripeptide methyl ester **8** (7 equiv. LDA, 3 h, −78°C) and subsequent reaction with MeI (15 equiv.) afforded the alkylated tripeptide **18** in good yield (79%, see Scheme 2). On the other hand, selective alkylation of methyl ester enolates in the *N*-methylated β-peptides **9** and **10** turned out to be impossible: treatment with two to five equivalents of LDA followed by addition of MeI resulted in the formation of complex mixtures containing mono-, di- and trimethylated products.

With the chiral peptide ester Boc-β-HVal-β-HAla-β-HLeu-OMe (**14**) methylation (under the conditions specified for **8**, above) gave the product **20** in good yield as a single isomer (Scheme 3, entry 1). In order to determine the configuration at the newly formed stereogenic center, the tripeptide **20** was synthesized from (2*S*,3*S*)-β-HLeu(αMe)-OMe, Boc-β-HAla-OH (**1b**), and Boc-β-HVal-OH (**1c**). Comparison of the independently obtained samples (NMR spectra, optical rotations) showed, that they were identical. Thus, the *C*-terminal β-amino acid residue in **20** has *like*-configuration. We next tried alkylations of peptide **14**, through Li_4 derivative **C**, with various other electrophiles. The use of benzyl and allyl bromide (Scheme 3, entries 2,3) led to the tripeptides **21** (70%) and **22** (66%), both as single isomers (supposedly of the same rel. configuration as **20**). With the more reactive *tert*-butyl bromoacetate (entry 4) the diastereoselectivity of the alkylation dropped to 4:1, and the major isomer **23** was isolated in 35% yield. Reaction with methyl acrylate (6 equiv., entry 5) led to a mixture of oligo methyl acrylate peptide conjugates. No reaction took place with the less reactive electrophiles iodobutane and 2-iodopropane (entries 6, 7).

Having shown that *C*-terminal alkylation with reactive electrophiles can be a useful way for modifying β-peptides, we also tried to achieve alkylation of an internal β-amino acid residue: tripeptide **17**, containing one *N*-methyl-β-amino acid moiety, was treated with LDA (5 equiv.) at −78°C for six hours, followed by addition of MeI. No reaction took place in 20 h at the low temperature, and upon warming (ca. −30°C) decomposition occured. We isolated the β-dipeptide methylamide **24** (53%) and *trans*-5-methylhex-2-enoic acid (detected in the ^{1}H-NMR spectrum of the crude product, see Scheme 4). This is actually the first instance of such a β-elimination in all of our work on β-amino acids and β-peptides!

Scheme 3

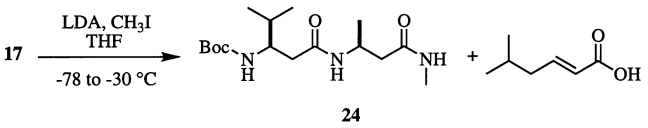


C (C,C- and C,N-double-bond configurations are drawn arbitrarily)

Entry	Electrophile	Product	Yield (%)[a]	Diastereomer ratio[b] (*l*/*u*)
1	MeI	**20**	75	> 97:3
2	$PhCH_2Br$	**21**	70	> 97:3
3	AllylBr	**22**	66	> 97:3
4	$BrCH_2CO_2tBu$	**23**	35	> 4:1
5	$CH2{=}CHCO_2Me$	– [c]	–	> –
6	$Me(CH_2)_3I$	– [d]	–	> –
7	Me_2CHI	– [d]	–	> –

[a] Diastereomerically pure product. – [b] Determined by ^1H NMR (300 MHz) of the crude product. – [c] A mixture of multiple-alkylation products was isolated. – [d] The starting material was recovered.

Scheme 4



24

Conclusions

The experiments described here show that linear β-peptide esters can be modified by alkylation with a variety of electrophiles on their C terminus. The solubilisation by LiCl of β-peptides and their polylithiated derivatives in THF proved to be as effective as with α-peptides. The alkylation reaction, proceeding via polylithiated species such as **C**, proceeds with good yields and excellent diastereoselectivities. The lithiation of amide and carbamate groups proved to be an efficient way of preventing β-elimination. However, while the lithiation/methylation of β-HGly residues on positions other than the *C*-terminus of β-peptides, as long as they are adjacent to *N*-methyl-β-HGly, was successful (see **19**), the alkylation of β-tripeptide Boc-β-HVal-β-HAla-Me-β-HLeu-OH (**17**) at the β-HAla residue failed. Instead, the main reaction was elimination of dipeptide methylamide **24**. It seems that, for some reason, the β-HAla residue in tripeptide **17**, containing side-chains, is not deprotonated to a Li-aza-enolate so that no alkylation takes place, and elimination of the amide unit – not protected by lithiation – occurs. More experiments need to be done, in order to gain further insight into the influence of side-chains and the position of *N*-alkyl groups on alkylation *vs.* elimination of β-peptides.

We gratefully acknowledge the donation of amino acids from *Degussa AG*, Hanau. We thank *A. K. Beck* for his help in the course of the lithiation experiments and *S. Abele* for the donation of a sample of (2*S*,3*S*)-Boc-β-HLeu(αMe)-OMe. We thank the *Novartis Pharma AG* (Basel) for continuing support of our research.

Experimental Section

General: DIPA = diisopropylamine, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, FC = Flash Chromatography, GP = General Procedure, HOBt = 1-hydroxy-1*H*-benzotriazole, HV = High Vacuum (0.01–0.1 Torr), β-HXxx = β-homoamino acid, LDA = lithium diisopropylamide, NMM = *N*-methylmorpholine. THF was freshly distilled from K and DIPA from CaH_2 under Argon before use. Electrophiles for alkylations were filtered through basic Al_2O_3 (activity I) directly prior to use. Solvents for chromatography and work-up procedures were distilled from Sikkon (anhydrous $CaSO_4$, Fluka). LiCl was dried under HV at ca. 150°C for at least 20 h. All other reagents were used as received from Fluka. The β-amino acid derivatives **1b**–**d**, **2d**, and β-tripeptide **14** were prepared according to literature procedures[14][18]. Alkylations and peptide coupling reactions were carried out under Argon. – TLC: Merck silica gel 60 F_{254} plates, detection by dipping into a soln. of anisaldehyde (9.2 ml), AcOH (3.75 ml), conc. H_2SO_4 (12.5 ml), and EtOH (338 ml), followed by heating. – FC: Fluka silica gel 60 (40–63 μm), at ca. 0.3 bar. – M.p.: Büchi-510 apparatus, uncorrected. – Optical rotations: Perkin-Elmer 241 polarimeter (10 cm, 1 ml cell) at room temp. – IR: Perkin-Elmer-782 spectrophotometer. – NMR: Bruker AMX 400 (^1H 400 MHz, ^{13}C 100 MHz), Varian Gemini 300 (^1H 300 MHz, ^{13}C 75 MHz). TMS as internal standard. *J* values are given in Hz. – Mass Spectra: VG Tribrid (EI) or Hitachi Perkin-Elmer RHU-6M (FAB, in a 3-nitrobenzyl alcohol matrix) spectrometer, in *m/z* (% of basis peak). – Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

General Procedure for the N-Methylation of Boc-Protected β-Amino Acids (GP 1)[17]: The β-amino acid was dissolved in THF (0.1 M), CH_3I (8 equiv.) added, the solution cooled to 0°C, and NaH (3 equiv.) was added in portions. The reaction mixture was allowed to warm to room temp. and stirred for 22 h, then cooled to –10°C to hydrolyse excess NaH with ice. The solvent was removed under reduced pressure and the residue dissolved in water. The aq. phase was washed with Et_2O, the pH adjusted to ca. 2 with sat. aq. $KHSO_4$ solution, and extracted with Et_2O. The org. phase was washed with 0.5 M HCl solution and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the Boc-protected *N*-methyl-β-amino acid which was used without further purification.

General Procedure for Peptide Coupling (GP 2): The appropriate trifluoroacetate or hydrochloride salt was dissolved in CH_2Cl_2 or THF (0.5 M) and cooled to 0°C. The solution was treated successively with the Boc-protected amino acid, NMM (2.8 equiv.), HOBt (1.2 equiv.), and EDC (1 equiv.). The mixture was allowed to warm to room temp. and stirred for 15 h. THF was then removed under reduced pressure, the residue dissolved in CH_2Cl_2 and washed thoroughly with 0.5 M HCl, sat. aq. $NaHCO_3$ and NaCl solutions. The org. phase was dried ($MgSO_4$) and then concentrated under reduced pressure. FC yielded the pure peptide.

General Procedures for Boc-Deprotection (GP 3). – GP 3a: The Boc-protected compound was dissolved in CH_2Cl_2 (0.5 M) and cooled to 0°C. An equal volume of CF_3COOH was added and the

mixture was allowed to warm to room temp. and then stirred for 1.5 h. Concentration under reduced pressure and drying of the residue under HV yielded the crude trifluoroacetate salt, which was used without further purification. – *GP 3b:* The Boc-protected compound was dissolved in HCl-saturated dioxane (0.25 M) at 0°C. The mixture was allowed to warm to room temp. and then stirred for 1.5 h. Concentration under reduced pressure and drying of the residue under HV yielded the crude hydrochloride salt, which was used without further purification.

General Procedure for the Cleavage of Methyl Esters (GP 4): The peptide was dissolved in MeOH (1.2 M) and 0.75 M aq. NaOH solution (1.2 equiv.) was added. The mixture was stirred at room temp. for 5 h. The pH was adjusted to 2–3 with 1 M HCl solution and the aq. phase extracted with EtOAc. The org. phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dried under HV and used without further purification.

General Procedure for the Alkylation of β-Peptides (GP 5). – Preparation of LDA: DIPA (1 equiv.) was dissolved in THF (0.75 M) and cooled to −78°C. A solution of BuLi (1 equiv.) in hexane (ca. 1.6 M) was added. The mixture was stirred at −78°C for 30 min. – *Alkylation:* The peptide was suspended in THF (0.08 M), dry LiCl added at room temp. and the mixture stirred for ca. 20 min. The resulting clear solution was cooled to −78°C and transferred via syringe to the LDA solution (internal temp. < −70°C). The mixture was stirred for ca. 3 h at −78°C and then the electrophile was added. After 20 h at −78°C, sat. NH_4Cl solution was added, the solvent was removed under reduced pressure, the residue dissolved in CH_2Cl_2, and washed with 0.5 M HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl solutions. The org. phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by FC.

3-[(tert-Butoxy)carbonylmethylamino]propanoic Acid [*Boc-(Me)-β-HGly-OH,* **3a**]: Boc-β-Ala-OH (**1a**) (15.2 g, 80 mmol) was transformed according to GP 1 to yield the *N*-methyl amino acid **3a** as a yellowish oil (15.1 g, 93%). For analytical purposes, a sample was esterified with CH_2N_2, purified by FC (pentane/Et_2O) and saponified to the title compound. – IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1}, 2980, 2925, 2875, 1713, 1687, 1431, 1394, 1367, 1166. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.60 [t, *J* = 6.9, 2 H, $C(O)CH_2$], 2.89 (s, 3 H, NCH_3), 3.51 (t, *J* = 6.9, 2 H, NCH_2), 9.50 (br., 1 H, COOH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 33.1, 34.9, 44.9, 80.0, 156.0, 177.1. – MS (EI); *m/z* (%): 204 (1) [M + H^+], 203 (1) [M^+], 130 (33), 104 (17), 130 (23), 57 (100), 29 (37). – $C_9H_{17}NO_4$ (203.2): calcd. C 53.19, H 8.43, N 6.89; found C 53.39, H 8.20, N 6.82.

(S)-3-[(tert-Butoxy)carbonylmethylamino]butanoic Acid [*Boc-(Me)-β-HAla-OH,* **3b**]: Boc-β-HAla-OH (**1b**) (1.63 g, 8 mmol) was transformed according to GP 1 to yield the *N*-methyl amino acid **3b** as a yellowish oil (1.54 g, 88%). For analytical purposes, a sample was esterified with CH_2N_2, purified by FC (pentane/Et_2O) and saponified to the title compound. – $[\alpha]_D^{RT}$ = +8.1 (*c* = 1.09, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1}, 2974, 2933, 2884, 1713, 1682, 1482, 1456, 1395, 1369, 1153. ^1H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 1.20, 1.24 (d, *J* = 6.8, 3 H, CH_3), 1.44, 1.45 [s, 9 H, $C(CH_3)_3$], 2.43 [dd, *J* = 15.0, 6.7, 1 H, $C(O)CH_2$], 2.59 [dd, *J* = 15.0, 8.1, 1 H, $C(O)CH_2$], 2.75 (s, 3 H, NCH_3), 4.53 (br., 1 H, CH), 10.54 (br., 1 H, COOH). – ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 18.2, 20.4, 28.4, 28.7, 39.2, 48.8, 79.9, 155.6, 176.7. – MS (EI), *m/z* (%): 218 (1) [M + H^+], 217 (1) [M^+], 162 (18), 146 (47), 161 (14), 144 (16), 118 (13), 102 (84), 57 (100), 41 (56).

(R)-3-[(tert-Butoxy)carbonylmethylamino]-4-methylpentanoic Acid [*Boc(Me)-β-HVal-OH,* **3c**]: Boc-β-HVal-OH (**1c**) (1.85 g, 8 mmol) was transformed according to GP 1 to yield the *N*-methyl amino acid **3c** as a yellowish oil (1.29 g, 66%). For analytical purposes, a sample was esterified with CH_2N_2, purified by FC (pentane/Et_2O) and saponified to the title compound. – $[\alpha]_D^{RT}$ = −8.3 (*c* = 0.96, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1}, 2974, 2960, 2884, 1712, 1682, 1635, 1480, 1445, 1389, 1369, 1149. – ^1H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 0.88 (d, *J* = 6.6, 3 H, CH_3), 0.94 (d, *J* = 6.6, 3 H, CH_3), 1.45, 1.46 [2 s, 9 H, $C(CH_3)_3$], 1.78–1.87 [m, 1 H, $CH(CH_3)_2$], 2.48–2.67 [m, 2 H, $C(O)CH_2$], 2.72, 2.75 (2 s, 3 H, NCH_3), 3.93–4.06 (m, 1 H, NCH), 9.35 (br., 1 H, COOH). – ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 19.5, 19.6, 20.0, 20.1, 28.4, 30.5, 30.6, 30.9, 35.9, 36.2, 59.3, 60.1, 79.6, 79.8, 156.0, 156.2, 176.8, 177.3. – MS (EI), *m/z* (%): 246 (1) [M + H^+], 245 (1) [M^+], 202 (30), 146 (47), 130 (23), 102 (100), 84 (24), 57 (96), 42 (30). – $C_{12}H_{23}NO_4$ (245.3): calcd. C 58.75, H 9.45, N 5.71; found C 58.66, H 9.61, N 5.61.

(S)-3-[(tert-Butoxy)carbonylmethylamino]-5-methylhexanoic Acid [*Boc(Me)-β-HLeu-OH,* **3d**]: Boc-β-HLeu-OH (**1d**) (1.23 g, 5 mmol) was transformed according to GP 1 to yield the *N*-methyl amino acid **3d** as white solid (1.22 g, 94%). For analytical purposes, a sample was esterified with CH_2N_2, purified by FC (pentane/Et_2O) and saponified to the title compound, m.p. 60°C. – $[\alpha]_D^{RT}$ = −2.6 (*c* = 0.95, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1}, 2964, 2930, 2870, 1712, 1682, 1456, 1394, 1360, 1149. – ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.6, 3 H, CH_3), 0.93 (d, *J* = 6.5, 3 H, CH_3), 1.09–1.29 [br. m, 1 H, $CH(CH_3)_2$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.45–1.61 (m, 2 H, $CHCH_2$), 2.37–2.49 [m, 1 H, $C(O)CH_2$], 2.52–2.56 [m, 1 H, $C(O)CH_2$], 2.71 (br. s, 3 H, NCH_3), 4.54 (br. m, 1 H, NCH), 10.10 (br., 1 H, COOH). – ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 21.6, 21.8, 22.9, 23.4, 24.7, 24.9, 28.4, 28.9, 38.1, 38.4, 41.7, 42.2, 50.4, 50.9, 79.7, 79.8, 155.8, 176.6, 177.0. – MS (EI), *m/z* (%): 259 (1) [M^+], 203 (5), 186 (4), 160 (3), 144 (30), 102 (87), 57 (100). – $C_{13}H_{25}NO_4$ (259.3): calcd. C 60.21, H 9.72, N 5.40; found C 60.30, H 9.61, N 5.40.

Methyl 3-[(tert-Butoxy)carbonylmethylamino]propanoate [*Boc-(Me)-β-HGly-OMe,* **4a**]: *N*-Methyl amino acid **3a** (4.47 g, 22 mmol) was dissolved in Et_2O (50 ml). A solution of CH_2N_2 in Et_2O was added until the yellow color persisted. The solvent was removed under reduced pressure and the residue dried under HV to yield methyl ester **4a** (4.64 g, 97%) as colorless liquid. R_f (Et_2O/pentane 1:5) = 0.31. – IR($CHCl_3$): $\tilde{\nu}$ = 2991 cm^{-1}, 2960, 2850, 1733, 1687, 1482, 1394, 1369, 1169. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.55 [t, *J* = 7.0, 2 H, $C(O)CH_2$], 2.87 (s, 3 H, NCH_3), 3.50 (t, *J* = 6.9, 2 H, NCH_2), 3.68 (s, 3 H, OCH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 33.2, 34.7, 45.1, 51.7, 79.7, 155.5, 172.4. – MS (EI), *m/z* (%): 217 (1) [M^+], 161 (13), 144 (11), 130 (13), 117 (7), 102 (26), 57 (60), 44 (100). – $C_{10}H_{19}NO_4$ (217.3): calcd. C 55.28, H 8.81, N 6.45; found C 55.15, H 8.91, N 6.45.

Methyl (3S)-3-[(tert-Butoxy)carbonylmethylamino]-5-methylhexanoate [*Boc(Me)-β-HLeu-OMe,* **4d**]: *N*-Methyl amino acid **3d** (1.22 g, 4.7 mmol) was dissolved in Et_2O (12 ml). A solution of CH_2N_2 in Et_2O was added until the yellow color persisted. The solvent was removed under reduced pressure and the residue dried under HV. FC (pentane/Et_2O 5:1) yielded methyl ester **4d** (1.25 g, 97%) as colorless liquid. R_f (Et_2O/pentane 1:5) = 0.31. – $[\alpha]_D^{RT}$ = −6.4 (*c* = 1.01, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 2994 cm^{-1}, 2952, 2861, 1732, 1682, 1435, 1394, 1364, 1148. – ^1H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 0.91 (d, *J* = 6.6, 3 H, CH_3), 0.93 (d, *J* = 6.5, 3 H, CH_3), 1.05–1.30 [m, 1 H, $CH(CH_3)_2$], 1.45, 1.46 [2 s, 9 H, $C(CH_3)_3$], 1.43–1.61 [m, 2 H, $CH_2CH(CH_3)_2$], 2.32–2.40 [m, 1 H, $C(O)CH_2$], 2.45–2.53 [m, 1 H, $C(O)CH_2$], 2.68, 2.70 (2 s, 3 H,

NCH_3), 3.65, 3.66, 3.68 (3 s, 3 H, OCH_3), 4.46−4.63 (br. m, 1 H, NCH). − ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 21.6, 21.8, 23.2, 23.4, 24.6, 24.9, 28.1, 28.4, 28.6, 38.2, 38.5, 41.2, 41.7, 51.1, 51.5, 51.5, 51.6, 79.2, 79.6, 155.6, 171.6, 171.8. − MS (EI), *m/z* (%): 273 (1) [M + H^+], 217 (6), 200 (6), 186 (6), 172 (3), 160 (21), 144 (27), 116 (100), 100 (36), 84 (13), 57 (88). − $C_{14}H_{23}NO_4$ (272.4): calcd. C 61.51, H 9.95, N 5.12; found C 61.66, H 9.58, N 4.97.

Methyl N-[(tert-Butoxy)carbonyl]-β-homoglycyl-β-homoglycinate (*Boc-β-HGly-β-HGly-OMe*, **5**): A solution of methyl 3-aminopropanoate hydrochloride (3.07 g, 22 mmol) in THF was treated with Boc-β-HGly-OH (**1a**) (4.16 g, 22 mmol) according to GP 2. FC (pentane/Et_2O 4:1) yielded dipeptide **5** (5.15 g, 85%) as white solid, m.p. 79°C. − R_f (Et_2O/pentane 1:4) = 0.27. − IR ($CHCl_3$): $\tilde{\nu}$ = 3448 cm^{-1}, 2981, 2954, 2871, 1706, 1503, 1439, 1411, 1392, 1367, 1178. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 2.38 [t, *J* = 6.0, 2 H, $C(O)CH_2$], 2.54 [t, *J* = 6.0, 2 H, $C(O)CH_2$], 3.39 (q, *J* = 6.1, 2 H, NCH_2), 3.52 (q, *J* = 6.1, 2 H, NCH_2), 3.71 (s, 3 H, OCH_3), 5.40 (br. s, 1 H, BocNH), 6.14 (br. s, 1 H, NH). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 33.9, 34.8, 36.2, 36.6, 51.9, 79.3, 156.1, 171.4, 172.9. − MS (FAB), *m/z* (%): 571 (1) [2 M + Na^+], 549 (13) [2 M + H^+], 297 (5) [M + Na^+], 275 (85) [M + $H]^+$, 219 (74), 175 (100). − $C_{12}H_{22}N_2O_5$ (274.3): calcd. C 52.54, H 8.08, N 10.21; found C 52.46, H 8.12, N 10.21.

Methyl N-[(tert-Butoxy)carbonyl]-N-methyl-β-homoglycyl-β-homoglycinate [*Boc(Me)-β-HGly-β-HGly-OMe*, **6**]: A solution of methyl 3-aminopropanoate hydrochloride (3.07 g, 22 mmol) in THF was treated with Boc-protected amino acid **3a** (4.47 g, 22 mmol) according to GP 2. FC (pentane/Et_2O 3:1) yielded dipeptide **6** (4.44 g, 70%) as white solid, m.p. 47.5°C. − R_f (Et_2O/pentane 1:3) = 0.25. − IR ($CHCl_3$): $\tilde{\nu}$ = 3446 cm^{-1}, 2994, 2964, 2923, 2871, 1728, 1671, 1518, 1482, 1394, 1369, 1174. − ^{1}H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.35−2.46 [m, 2 H, $C(O)CH_2$], 2.53−3.56 [m, 2 H, $C(O)CH_2$], 2.85 (s, 3 H, NCH_3), 3.48−3.54 (m, 4 H, NCH_2), 3.70 (s, 3 H, OCH_3), 6.16, 6.64 (2 br. s, 1 H, NH). − ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 28.4, 34.8, 33.8, 34.9, 35.4, 45.3, 51.8, 79.8, 156.0, 170.9, 172.0. − MS (FAB), *m/z* (%): 577 (6) [2 M + H^+], 311 (20) [M + Na^+], 289 (72) [M + H^+], 233 (25), 189 (100). − $C_{13}H_{24}N_2O_5$ (288.3): calcd. C 54.15, H 8.39, N 9.72; found C 54.09, H 8.51, N 9.67.

Methyl N-[(tert-Butoxy)carbonyl]-N-methyl-β-homoglycyl-N-methyl-β-homoglycinate [*Boc(Me)-β-HGly-Me-β-HGly-OMe*, **7**]: Boc-Protected amino acid ester **4a** (3.67 g, 16.9 mmol) was deprotected according to GP 3b. Treatment of a solution of the resulting hydrochloride salt in THF with Boc-protected amino acid **3a** (3.43 g, 16.9 mmol) according to GP 2 gave after FC (pentane/Et_2O 6:1) dipeptide **7** (4.80 g, 94%) as colorless oil. R_f (Et_2O/pentane 1:6) = 0.30. − IR ($CHCl_3$): $\tilde{\nu}$ = 2994 cm^{-1}, 2964, 2851, 1733, 1682, 1641, 1482, 1394, 1369, 1317, 1169. − ^{1}H NMR (400 MHz , $CDCl_3$, rotamers!): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.48−2.64 [m, 4 H, $C(O)CH_2$], 2.88, 2.88, 2.91, 3.05 (4 s, 6 H, NCH_3), 3.48−3.54 (m, 2 H, NCH_2), 3.61−3.66 (m, 2 H, NCH_2), 3.68, 3.69 (2 s, 3 H, OCH_3). − ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 28.5, 31.5, 32.4, 36.4, 44.4, 45.4, 45.2, 45.8, 51.7, 51.9, 79.5, 156.0, 171.3, 172.5. − MS (FAB), *m/z* (%): 627 (4) [2 M + Na^+], 605 (7) [2 M + H^+], 325 (15) [M + Na^+], 303 (100) [M + H^+], 247 (11), 229 (11), 203 (57). − $C_{14}H_{26}N_2O_5$ (302.4): calcd. C 55.61, H 8.67, N 9.26; found C 55.65, H 8.66, N 8.99.

Methyl N-[(tert-Butoxy)carbonyl]-β-homoglycyl-β-homoglycyl-β-homoglycinate (*Boc-β-HGly-β-HGly-β-HGly-OMe*, **8**): Boc-Protected dipeptide **5** (4.72 g, 17.2 mmol) was deprotected according to GP 3b. Treatment of a solution of the resulting hydrochloride salt in THF with Boc-protected amino acid **1a** (3.58 g, 18.9 mmol) according to GP 2 gave after FC (CH_2Cl_2/MeOH 97:3) tripeptide **8** (5.50 g, 93%) as white solid, m.p. 149°C. − R_f (CH_2Cl_2/MeOH 97:3) = 0.25. − IR ($CHCl_3$): $\tilde{\nu}$ = 3446 cm^{-1}, 2994, 2973, 2933, 1702, 1666, 1507, 1441, 1393, 1369, 1174. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 2.36−2.39 [m, 4 H, $C(O)CH_2$], 2.52−2.57 [m, 2 H, $C(O)CH_2$], 3.37−3.42 (q, *J* = 6.1, 2 H, NCH_2), 3.49−3.55 (m, 4 H, NCH_2), 3.71 (s, 3 H, OCH_3), 5.27 (br. s, 1 H, NH), 6.49 (br. s, 1 H, NH), 6.59 (br. s, 1 H, NH). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 33.8, 34.9, 35.5, 35.7, 36.3, 36.8, 51.9, 79.3, 156.1, 171.6, 173.4. − MS (FAB), *m/z* (%): 713 (2) [2 M + Na^+], 691 (5) [2 M + H^+], 368 (30) [M + Na^+], 346 (100) [M + H^+], 290 (14), 246 (69), 175 (10). − $C_{15}H_{27}N_3O_6$ (345.4): calcd. C 52.16, H 7.88, N 12.17; found C 52.00, H 7.84, N 12.14.

Methyl N-[(tert-Butoxy)carbonyl]-β-homoglycyl-N-methyl-β-homoglycyl-β-homoglycinate (*Boc-β-HGly-Me-β-HGly-β-HGly-OMe*, **9**): Boc-Protected dipeptide **6** (3.83 g, 13.3 mmol) was deprotected according to GP 3b. Treatment of a solution of the resulting hydrochloride salt in THF with Boc-protected amino acid **1a** (2.77 g, 14.6 mmol) according to GP 2 gave after FC (CH_2Cl_2/EtOAc/MeOH 87:10:3) tripeptide **9** (4.61 g, 96%) as colorless oil. R_f (CH_2Cl_2/AcOEt/MeOH 87:10:3) = 0.26. − IR ($CHCl_3$): $\tilde{\nu}$ = 3446 cm^{-1}, 2994, 2930, 2875, 1728, 1702, 1635, 1502, 1441, 1369, 1174. − ^{1}H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 2.39−2.59 [m, 6 H, $C(O)CH_2$], 2.91, 2.99 (2 s, 3 H, NCH_3), 3.37−3.43 (m, 2 H, NCH_2), 3.48−3.54 (m, 2 H, NCH_2), 3.60−3.65 (m, 2 H, NCH_2), 3.70, 3.71 (s, 3 H, OCH_3), 5.35 (br., 1 H, NH), 6.43, 6.68 (2 br., 1 H, NH). − ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 28.4, 33.3, 33.7, 33.8, 34.8, 35.0, 35.4, 33.0, 35.9, 36.2, 36.6, 44.7, 45.9, 51.8, 51.9, 79.1, 156.1, 169.0, 170.8, 171.7, 172.2, 172.8, 173.0. − MS (FAB), *m/z* (%): 719 (8) [2 M + H^+], 382 (12) [M + Na^+], 360 (100) [M + H^+], 307 (7), 260 (87), 189 (23). − $C_{16}H_{29}N_3O_6$ (359.4): calcd. C 53.47, H 8.13, N 11.69; found C 53.34, H 8.07, N 11.70.

Methyl N-[(tert-Butoxy)carbonyl]-β-homoglycyl-N-methyl-β-homoglycyl-N-methyl-β-homoglycinate (*Boc-β-HGly-Me-β-HGly-Me-β-HGly-OMe*, **10**): Boc-Protected dipeptide **7** (3.80 g, 12.6 mmol) was deprotected according to GP 3b. Treatment of a solution of the resulting hydrochloride salt in CH_2Cl_2 with Boc-protected amino acid **1a** (2.62 g, 13.9 mmol) according to GP 2 gave after FC (CH_2Cl_2/MeOH 97:3) tripeptide **10** (4.38 g, 93%) as colorless oil. R_f (CH_2Cl_2/MeOH 97:3) = 0.31. − IR ($CHCl_3$): $\tilde{\nu}$ = 3452 cm^{-1}, 2950, 2930, 2875, 1733, 1705, 1639, 1501, 1440, 1410, 1367, 1171. − ^{1}H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 1.42, 1.43 [2 s, 9 H, $C(CH_3)_3$], 2.46−2.69 [m, 6 H, $C(O)CH_2$], 2.91, 2.93, 2.93, 3.03, 3.04, 3.05 (6 s, 6 H, NCH_3), 3.39−3.42 (m, 2 H, NCH_2), 3.60−3.66 (m, 4 H, NCH_2), 3.68, 3.69, 3.70 (3 s, 3 H, OCH_3), 5.34 (br., 1 H, NH). − ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 28.4, 31.1, 31.2, 31.9, 31.9, 32.4, 32.4, 32.8, 33.1, 33.2, 33.2, 33.8, 36.3, 36.3, 36.4, 36.4, 44.4, 44.5, 44.9, 45.1, 45.2, 45.4, 45.5, 45.8, 51.8, 51.8, 51.9, 52.1, 79.1, 156.0, 170.1, 171.1, 171.1, 171.4, 171.9, 172.4, 172.4. − MS (FAB), *m/z* (%): 748 (2) [2 M + H^+], 396 (11) [M + Na^+], 374 (100) [M + H^+], 274 (56), 203 (17), 201 (25). − $C_{17}H_{31}N_3O_6$ (373.5): calcd. C 54.68, H 8.37, N 11.23; found C 54.56, H 8.30, N 11.19.

N-[(tert-Butoxy)carbonyl]-β-homoglycyl-β-homoglycyl-β-homoglycine (*Boc-β-HGly-β-HGly-β-HGly-OH*, **11**): Methyl ester **8** (173 mg, 0.5 mmol) was treated according to GP 4 to yield tripepdide **11** (157 mg, 95%) as white solid. − ^{1}H NMR (200 MHz, CD_3OD): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 2.29−2.41 [q, *J* = 6.0, 4 H, $C(O)CH_2$], 2.50 [t, *J* = 6.8, 2 H, $C(O)CH_2$], 3.23−3.33 (m, 2 H, NCH_2), 3.35−3.47 (m, 4 H, NCH_2). − ^{13}C NMR (75 MHz, CD_3OD): δ =

28.9, 34.8, 36.5, 36.6, 36.8, 37.2, 37.5, 80.4, 158.6, 174.2, 174.4, 175.7. − MS (FAB), *m/z* (%): 685 (12) [2 M + Na^+], 663 (18) [2 M + H^+], 354 (46) [M + Na^+], 332 (100) [M + H^+], 276 (18), 258 (7), 232 (79).

N-[(tert-Butoxy)carbonyl]-β-homoglycyl-N-methyl-β-homoglycyl-β-homoglycine (*Boc-β-HGly-Me-β-HGly-β-HGly-OH* **12**): Methyl ester **9** (2.70 g, 7.5 mmol) was treated according to GP 4 to yield tripepdide **12** (1.73 g, 67%) as colorless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3600−2400 cm^{-1}, 3442, 3008, 1708, 1636, 1505, 1407, 1368, 1170. − ^1H NMR (400 MHz, CD_3OD, rotamers!): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 2.40 [t, *J* = 6.8, 1 H, $C(O)CH_2$], 2.45−2.55 [m, 4 H, $C(O)CH_2$], 2.63 [t, *J* = 6.8, 1 H, $C(O)CH_2$], 2.89, 3.03 (2 s, 3 H, NCH_3), 3.28−3.32 (m, 2 H, NCH_2), 3.39−3.43 (m, 2 H, NCH_2), 3.58−3.78 (m, 2 H, NCH_2). − ^{13}C NMR (100 MHz, CD_3OD, rotamers!): δ = 28.8, 33.6, 34.0, 34.6, 34.7, 35.2, 35.8, 36.5, 36.7, 37.6, 37.9, 46.2, 47.4, 80.2, 158.3, 173.2, 173.7, 173.8, 174.0, 175.1, 175.2. − MS (FAB), *m/z* (%): 692 (10) [2 M + H^+], 368 (23) [M + Na^+], 346 (100) [M + H^+], 246 (84).

N-[(tert-Butoxy)carbonyl]-β-homoglycyl-N-methyl-β-homoglycyl-N-methyl-β-homoglycine (*Boc-β-HGly-Me-β-HGly-Me-β-HGly-OH*, **13**): Methyl ester **10** (0.75 g, 2.0 mmol) was treated according to GP 4 to yield tripeptide **13** (0.69 g, 96%) as colorless oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 3600−3400 cm^{-1}, 3444, 3007, 1719, 1639, 1501, 1408, 1368, 1169. − ^1H NMR (400 MHz, CD_3OD, rotamers!): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 2.52−2.56 [m, 2 H, $C(O)CH_2$], 2.60−2.86 [m, 4 H, $C(O)CH_2$], 2.90, 2.91, 2.91, 3.06, 3.09, 3.09 (6 s, 6 H, NCH_3), 3.28−3.33 (m, 2 H, NCH_2), 3.58−3.70 (m, 4 H, NCH_2). − ^{13}C NMR (100 MHz, CD_3OD, rotamers!): δ = 28.8, 31.7, 32.2, 32.4, 32.8, 33.0, 33.1, 33.3, 33.5, 33.6, 33.7, 33.7, 33.8, 34.0, 34.7, 36.6, 36.8, 37.6, 37.9, 45.6, 45.6, 45.8, 46.1, 46.7, 46.8, 47.0, 47.3, 80.2, 158.3, 172.9, 173.6, 173.6, 173.7, 173.7, 173.8, 174.8, 175.4. − MS (FAB), *m/z* (%): 741 (13) [2 M + Na^+], 719 (14) [2 M + H^+], 382 (41) [M + Na^+], 360 (100) [M + H^+], 260 (74).

Methyl N-[(tert-Butoxy)carbonyl]-(S)-β-homoalanyl-(S)-N-methyl-β-homoleucinate (*Boc-β-HAla-Me-β-HLeu-OMe*, **15**): The Boc-protected *N*-methyl amino acid **4d** (1.20 g, 4.4 mmol) was deprotected according to GP 3a. Treatment of a solution of the resulting trifluoroacetate salt in THF with Boc-β-HAla-OH (**2b**) (0.98 g, 4.8 mmol) according to GP 2 yielded after FC (pentane/EtOAc/MeOH 50:50:0.5) dipeptide **15** (1.30 g, 83%) as colorless liquid. R_f (pentane/AcOEt/MeOH 50:50:0.5) = 0.15. − $[\alpha]_D^{RT}$ = −16.0 (*c* = 0.96, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3450 cm^{-1}, 2980, 2925, 2875, 1740, 1705, 1635, 1497, 1470, 1390, 1366, 1174. − ^1H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 0.90−0.96 (m, 6 H, CH_3), 1.20−1.33 [m, 1 H, $CH(CH_3)_2$], 1.24, 1.24 (2 d, *J* = 6.7, 3 H, CH_3), 1.38−1.55 [m, 2 H, $CH_2CH(CH_3)_2$], 1.43 [s, 9 H, $C(CH_3)_3$], 2.38−2.49 [m, 2 H, $C(O)CH_2$], 2.52−2.68 [m, 2 H, $C(O)CH_2$], 2.72, 2.83 (2 s, 3 H, NCH_3), 3.64, 3.66 (2 s, 3 H, OCH_3), 3.92−4.00, 4.01−4.09 (2 m, 1 H, NCH), 4.25−4.32, 5.01−5.08 (2 m, 1 H, NCH), 5.42 (br., 1 H, NH). − ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 24.7, 25.0, 26.3, 28.4, 29.8, 37.2, 37.8, 39.3, 41.1, 42.0, 43.9, 48.7, 51.8, 51.9, 78.9, 155.3, 155.4, 171.2, 171.3, 171.5. − MS (FAB), *m/z* (%): 739 (4) [2 M + Na^+], 717 (1) [2 M + H^+], 617 (3), 381 (36) [M + Na^+], 359 (67) [M + H^+], 259 (100). − $C_{18}H_{34}N_2O_5$ (358.5): calcd. C 60.31, H 9.56, N 7.81; found C 60.21, H 9.30, N 7.58.

Methyl N-[(tert-Butoxy)carbonyl]-(R)-β-homovalyl-(S)-β-homoalanyl-(S)-N-methyl-β-homoleucinate (*Boc-β-HVal-β-HAla-Me-β-HLeu-OMe*, **16**): Dipeptide **15** (0.79 g, 2.2 mmol) was deprotected according to GP 3a. Treatment of a solution of the resulting trifluoroacetate salt in CH_2Cl_2 with Boc-β-HVal-OH (**2c**) (0.53 g, 2.4 mmol) according to GP 2 yielded after FC (CH_2Cl_2/EtOAc/MeOH 30:15:1) tripeptide **16** (0.92 g, 89%) as white solid, m.p. 85−86°C. − R_f (CH_2Cl_2/AcOEt/MeOH 30:15:1) = 0.5. − $[\alpha]_D^{RT}$ = −34.5 (*c* = 1.01, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3436 cm^{-1}, 2964, 2933, 2871, 1733, 1702, 1646, 1497, 1456, 1390, 1369, 1169. − ^1H NMR (400 MHz, $CDCl_3$, rotamers!): δ = 0.88−1.06 (m, 12 H, CH_3), 1.23 (d, *J* = 6.7, 3 H, CH_3), 1.24−1.28 [m, 1 H, $CH(CH_3)_2$], 1.35−1.55 [m, 2 H, $CH_2CH(CH_3)_2$], 1.42 [s, 9 H, $C(CH_3)_3$], 1.78−1.86 [m, 1 H, $CH(CH_3)_2$], 2.23−2.65 [m, 6 H, $C(O)CH_2$], 2.73, 2.83 (2 s, 3 H, NCH_3), 3.64, 3.66 (s, 3 H, OCH_3), 4.24−4.39 (m, 2 H, NCH), 4.97−5.08 (m, 1 H, NCH), 5.28−5.38 (br., 1 H, NH), 6.85−6.92 (br., 1 H, NH). − ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 19.5, 19.5, 19.8, 20.0, 21.9, 22.7, 22.9, 23.2, 24.7, 25.0, 26.3, 28.4, 29.8, 31.9, 32.0, 37.6, 37.7, 38.1, 38.6, 38.9, 41.1, 48.9, 42.4, 48.8, 51.8, 51.9, 51.9, 53.5, 78.9, 155.9, 170.3, 170.4, 171.2, 171.5. − MS (FAB), *m/z* (%): 966 (16) [2 M + Na^+], 494 (100) [M + Na^+], 472 (89) [M + H^+], 372 (63), 259 (9), 174 (10). − $C_{24}H_{45}N_3O_6$ (471.6): calcd. C 61.12, H 9.62, N 8.91; found C 60.98, H 9.60, N 8.88.

N-[(tert-Butoxy)carbonyl]-(R)-β-homovalyl-(S)-β-homoalanyl-(S)-N-methyl-β-homoleucine (*Boc-β-HVal-β-HAla-Me-β-HLeu-OH*, **17**): Methyl ester **16** (0.50 g, 1.1 mmol) was treated according to GP 4 to yield tripeptide **17** (0.46 g, 94%) as white solid, m.p. 193−194°C. − R_f (CH_2Cl_2/AcOEt/MeOH 30:15:3) = 0.31. − $[\alpha]_D^{RT}$ = −8.6 (*c* = 1.13, MeOH). − IR (Nujol): $\tilde{\nu}$ = 3300 cm^{-1}, 1702, 1682, 1635, 1395, 1365, 1374, 1184. − ^1H NMR (400 MHz, CD_3OD, rotamers!): δ = 0.88−0.97 (m, 12 H, CH_3), 1.17, 1.18 (2 d, *J* = 6.6, 3 H, CH_3), 1.20−1.30 [m, 1 H, $CH_2CH(CH_3)_2$], 1.42, 1.43 [2 s, 9 H, $C(CH_3)_3$], 1.32−1.61 [m, 2 H, $CH_2CH(CH_3)_2$], 1.69−1.77 [m, 1 H, $CH(CH_3)_2$], 2.15−2.81 [m, 6 H, $C(O)CH_2$], 2.73, 2.94 (s, 3 H, NCH_3), 3.68−3.77 (m, 1 H, NCH), 4.16−4.39, 5.00−5.11 (m, 2 H, NCH). − ^{13}C NMR (100 MHz, CD_3OD, rotamers!): δ = 18.4, 19.7, 20.1, 20.4, 22.3, 23.3, 23.3, 23.7, 27.2, 30.3, 28.9, 33.5, 33.8, 38.6, 38.8, 40.1, 40.3, 41.8, 41.9, 42.9, 44.0, 44.1, 50.1, 53.7, 54.9, 55.0, 79.9, 158.0, 173.2, 173.3, 174.4, 174.7. − MS (FAB), *m/z* (%): 938 (4) [2 M + Na^+], 496 (13) [M + K^+], 480 (98) [M + Na^+], 458 (100) [M + H^+], 358 (60), 245 (8). − $C_{23}H_{43}N_3O_6$ (457.6): calcd. C 60.37, H 9.47, N 9.18; found C 60.25, H 9.49, N 9.17.

Methyl N-[(tert-Butoxy)carbonyl]-β-homoglycyl-β-homoglycyl-2-methyl-β-homo-glycinate [*Boc-β-HGly-β-HGly-β-HGly(αMe)-OMe*, **18**]: Tripeptide **8** (173 mg, 0.50 mmol) was treated with LDA (3.5 mmol), LiCl (163 mg, 3.8 mmol) and CH_3I (0.47 ml, 7.5 mmol) according to GP 5. FC (CH_2Cl_2/MeOH 97:3) yielded tripeptide **18** (142 mg, 79%) as white solid, m.p. 105°C. − R_f (CH_2Cl_2/MeOH 97:3) = 0.31. − IR ($CHCl_3$): $\tilde{\nu}$ = 3445 cm^{-1}, 2994, 2943, 2982, 1707, 1666, 1505, 1461, 1437, 1392, 1367, 1171. − ^1H NMR (400 MHz, $CHCl_3$): δ = 1.11 (d, *J* = 7.2, 3 H, CH_3), 1.36 [s, 9 H, $C(CH_3)_3$], 2.29−2.35 [m, 4 H, $C(O)CH_2$], 2.57−2.67 [m, 1 H, C(O)CH], 3.23−3.35 (m, 3 H, NCH_2), 3.40−3.47 (m, 3 H, NCH_2), 3.64 (s, 3 H, OCH_3), 5.19 (br. s, 1 H, NH), 6.31 (br. s, 1 H, NH), 6.49 (br. s, 1 H, NH). − ^{13}C NMR (100 MHz, $CHCl_3$): δ = 14.8, 23.7, 28.4, 35.6, 35.7, 36.3, 36.7, 39.6, 41.8, 52.0, 79.2, 156.1, 171.6, 171.7, 175.9, 174.7. − MS (FAB), *m/z* (%): 719 (6) [2 M + H^+], 430 (6), 382 (4) [M + Na^+], 374 (11), 360 (100) [M + H^+], 304 (7), 286 (5), 274 (7), 260 (41). − $C_{16}H_{29}N_3O_6$ (359.4): calcd. C 53.47, H 8.13, N 11.69; found C 53.40, H 7.96, N 11.48.

Methyl N-[(tert-Butoxy)carbonyl]-(R)-β-homovalyl-(S)-β-homoalanyl-(2S,3S)-2-methyl-β-homoleucinate [*Boc-β-HVal-β-HAla-(2S,3S)-β-HLeu(αMe)-OMe*, **20**]: Tripeptide **14** (183 mg, 0.40 mmol) was treated with LDA (2.8 mmol), LiCl (182 mg, 4.3 mmol) and CH_3I (0.38 ml, 6.0 mmol) according to GP 5. FC (CH_2Cl_2/EtOAc/MeOH 50:40:1) yielded tripeptide **20** (169 mg, 90%) as white solid, m.p. 174−175°C. − R_f (CH_2Cl_2/AcOEt/MeOH

50:40:1) = 0.25. – $[\alpha]_D^{RT}$ = −33.4 (*c* = 1.02, $CHCl_3$). – IR($CHCl_3$): $\tilde{\nu}$ = 3427 cm^{-1}, 2967, 2923, 2871, 1707, 1661, 1502, 1461, 1390, 1369, 1169. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.5, 3 H, CH_3), 0,91 (d, *J* = 6.7, 3 H, CH_3), 0.92 (d, *J* = 6.8, 6 H, CH_3), 1.19 (d, *J* = 7.2, 3 H, CH_3), 1.21 (d, *J* = 6.6, 3 H, CH_3), 1.17−1.25 [m, 1 H, $CH_2CH(CH_3)_2$], 1.34−1.45 [m, 1 H, $CH_2CH(CH_3)_2$], 1.43 [s, 9 H, $C(CH_3)_3$], 1.51−1.61 [m, 1 H, $CH_2CH(CH_3)_2$], 1.77−1.84 [m, 1 H, $CH(CH_3)_2$], 2.27- 2.46 [m, 4 H, $C(O)CH_2$], 2.53−2.60 [m, 1 H, C(O)CH], 3.60−3.72 (m, 1 H, NCH), 3.70 (s, 3 H, OCH_3), 4.17−4.30 (m, 2 H, NCH), 5.20 (br. d, 1 H, NH), 6.41 (d, *J* = 7.9, 1 H, NH), 7.01 (d, *J* = 9.6, 1 H, NH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 18.5, 19.4, 19.9, 21.5, 22.1, 23.1, 23.9, 24.99, 28.4, 32.0, 32.2, 38.0, 38.9, 39.2, 42.4, 42.7, 42.8, 42.9, 49.2, 51.8, 53.4, 79.1, 156.0, 170.5, 170.9, 176.1. – MS (FAB), *m/z* (%): 966 (11) [2 M + Na^+], 494 (100) [M + Na^+], 472 (73) [M + H^+], 372 (37), 259 (12). – $C_{24}H_{45}N_3O_6$ (471.6): calcd. C 61.12, H 9.62, N 8.91; found C 61.19, H 9.68, N 8.87.

Methyl N-[(tert-Butoxy)carbonyl]-(R)-β-homovalyl-(S)-β-homoalanyl-(2S,3S)-2-benzyl-β-homoleucinate [*Boc-β-HVal-β-HAla-(2S,3S)-β-HLeu(αBn)-OMe*, **21**]: Tripeptide **14** (183 mg, 0.40 mmol) was treated with LDA (2.0 mmol), LiCl (131 mg, 3.1 mmol) and BnBr (0.47 ml, 4.0 mmol) according to GP 5. FC (CH_2Cl_2/EtOAc/MeOH 50:44:3) yielded tripeptide **21** (180 mg, 82%) as white solid, m.p. 188−189°C. – R_f (CH_2Cl_2/AcOEt/MeOH 30:15:3) = 0.31. – $[\alpha]_D^{RT}$ = −63.1 (*c* = 1.07, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3415 cm^{-1}, 3005, 2964, 2920, 2871, 1707, 1661, 1497, 1456, 1380, 1369, 1169. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.7, 3 H, CH_3), 0.89 (d, *J* = 6.5, 3 H, CH_3), 0.90 (d, *J* = 6.8, 6 H, CH_3), 1.19−1.24 [m, 1 H, $CH_2CH(CH_3)_2$], 1.26 (d, *J* = 6.7, 3 H, CH_3), 1.29−1.37 [m, 1 H, $CH_2CH(CH_3)_2$], 1.42 [s, 9 H, $C(CH_3)_3$], 1.51−1.62 [m, 1 H, $CH_2CH(CH_3)_2$], 1.76−1.84 [m, 1 H, $CH(CH_3)_2$], 2.28−2.49 [m, 4 H, $C(O)CH_2$], 2.79−2.95 [m, 3 H, $PhCH_2$, C(O)CH], 3.58 (s, 3 H, OCH_3), 3.59−3.68 (m, 1 H, NCH), 4.26−4.35 (m, 2 H, NCH), 5.19 (br. d, 1 H, NH), 6.54 (d, *J* = 9.6, 1 H, NH), 7.00 (d, *J* = 8.0, 1 H, NH), 7.12- 7.35 (m, 5 H, arom. H). – ^{13}C NMR (100 MHz, $CDCl_3$, rotamers!): δ = 19.5, 19.5, 19.8, 20.0, 21.9, 22.7, 22.9, 23.2, 24.7, 25.0, 26.3, 28.4, 29.8, 31.9, 32.0, 37.6, 37.7, 38.1, 38.6, 38.9, 41.1, 48.9, 42.4, 48.8, 51.8, 51.9, 51.9, 53.5, 78.9, 155.9, 170.3, 170.4, 171.2, 171.5. – MS (FAB), *m/z* (%): 1095 (4) [2 M + H^+], 570 (14) [M + Na^+], 548 (100) [M + H^+], 448 (73), 335 (10). – $C_{30}H_{49}N_3O_6$ (547.8): calcd. C 65.79, H 9.02, N 7.67; found C 65.53, H 9.08, N 7.62.

Methyl N-[(tert-Butoxy)carbonyl]-(R)-β-homovalyl-(S)-β-homoalanyl-(2S,3S)-2-allyl-β-homoleucinate [*Boc-β-HVal-β-HAla-(2S,3S)-β-HLeu(αAllyl)-OMe*, **22**]: Tripeptide **14** (183 mg, 0.40 mmol) was treated with LDA (2.0 mmol), LiCl (152 mg, 3.6 mmol) and allyl bromide (0.34 ml, 4.0 mmol) according to GP 5. FC (CH_2Cl_2/EtOAc/MeOH 60:40:3) yielded tripeptide **22** (131 mg, 66%) as white solid, m.p. 167−168°C. – R_f (CH_2Cl_2/AcOEt/MeOH 30:20:1.5) = 0.31. – $[\alpha]_D^{RT}$ = −44.0 (*c* = 1.20, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3420 cm^{-1}, 3005, 2964, 2930, 2850, 1770, 1702, 1661, 1502, 1390, 1340, 1174. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6, 3 H, CH_3), 0.91 (d, *J* = 6.0, 3 H, CH_3), 0.91 (d, *J* = 7.4, 6 H, CH_3), 1.17−1.27 [m, 1 H, $CH_2CH(CH_3)_2$], 1.22 (d, *J* = 6.7, 3 H, CH_3), 1.30−1.37 [m, 1 H, $CH_2CH(CH_3)_2$], 1.43 [s, 9 H, $C(CH_3)_3$], 1.53−1.63 [m, 1 H, $CH_2CH(CH_3)_2$], 1.77−1.85 [m, 1 H, $CH(CH_3)_2$], 2.25−2.46 [m, 6 H, $C(O)CH_2$, CH_2), 2.59−2.64 [m, 1 H, C(O)CH], 3.65−3.68 (m, 1 H, NCH), 3.69 (s, 3 H, OCH_3), 4.25−4.31 (m, 2 H, NCH), 5.00−5.10 (m, 2 H, CH_2=CH), 5.21 (br. d, 1 H, NH), 5.70−5.81 (m, 1 H, CH_2=CH), 6.47 (d, *J* = 9.7, 1 H, NH), 6.99 (d, *J* = 8.0, 1 H, NH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 19.5, 19.8, 22.3, 22.9, 24.9, 28.4, 32.2, 34.3, 39.2, 41.9, 42.8, 43.4, 47.5, 48.8, 51.7, 53.4, 79.1, 117.5, 134.6, 156.0, 170.5, 170.7, 175.3. – MS (FAB), *m/z* (%): 1018 (5) [2 M + Na^+], 521 (100) [M + H + Na^+], 520 (33) [M + Na^+], 498 (91) [M + H^+], 398 (87), 285 (20), 243 (10), 243 (11). – $C_{26}H_{47}N_3O_6$ (497.7): calcd. C 62.75, H 9.52, N 8.44; found C 62.49, H 9.64, N 8.41.

Methyl N-[(tert-Butoxy)carbonyl]-(R)-β-homovalyl-(S)-β-homoalanyl-(2S,3S)-2-[(tert-butoxy)carbonyl]-methyl-β-homoleucinate [*Boc-β-HVal-β-HAla-(2S,3S)-β-HLeu(αCH$_2$CO$_2$tBu)-OMe*, **23**]: Tripeptide **14** (183 mg, 0.40 mmol) was treated with LDA (2.0 mmol), LiCl (139 mg, 3.2 mmol) and *tert*-butyl bromoacetate (0.35 ml, 2.4 mmol) according to GP 5. FC (CH_2Cl_2/EtOAc/MeOH 10:5:1) yielded tripeptide **23** (81 mg, 35%) as white solid, m.p. 165−166°C. – R_f (CH_2Cl_2/AcOEt/MeOH 30:15:3) = 0.31. – $[\alpha]_D^{RT}$ = −34.3 (*c* = 1.00, $CHCl_3$) . – IR ($CHCl_3$): $\tilde{\nu}$ = 3425 cm^{-1}, 2964, 2935, 2880, 1723, 1661, 1502, 1390, 1369, 1153. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.7, 6 H, CH_3), 0.91 (d, *J* = 6.7, 6 H, CH_3), 1.25 (d, *J* = 6.7, 3 H, CH_3), 1.22−1.49 [m, 3 H, $CH_2CH(CH_3)_2$], 1.44 [s, 9 H, $C(CH_3)_3$], 1.44 [s, 9 H, $C(CH_3)_3$], 1.51−1.65 [m, 1 H, $CH(CH_3)_2$], 1.78−1.88 [m, 1 H, $CH(CH_3)_2$], 2.26−2.48 [m, 4 H, $C(O)CH_2$], 2.45 [dd, *J* = 16.5, 6.0, 1 H, $C(O)CH_2$], 2.61 [dd, *J* = 16.5, 9.0, 1 H, $C(O)CH_2$], 2.96−3.04 [m, 1 H, C(O)CH), 3.66−3.73 (m, 1 H, NCH), 3.73 (s, 3 H, OCH_3), 4.23−4.34 (m, 2 H, NCH), 5.19 (br. d, 1 H, NH), 6.28 (d, *J* = 9.7, 1 H, NH), 6.93 (d, *J* = 7.9, 1 H, NH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 19.5, 20.0, 22.1, 22.9, 24.9, 28.0, 28.4, 32.2, 35.7, 39.3, 42.1, 42.8, 42.9, 44.9, 47.7, 51.9, 53.3, 79.1, 156.0, 170.5, 170.7, 174.3. – MS (FAB), *m/z* (%): 1166 (8) [2 M + Na^+], 594 (100) [M + Na^+], 572 (73) [M + H^+], 472 (43), 416 (46), 303 (13), 218 (8). – $C_{29}H_{53}N_3O_8$ (571.8): calcd. C 60.92, H 9.34, N 7.35; found C 60.91, H 9.13, N 8.40.

Methyl N-[(tert-Butoxy)carbonyl]-(R)-β-homovalyl-(S)-β-homoalaninamide (*Boc-β-HVal-β-HAla-NHMe*, **24**): Tripeptide **17** (183 mg, 0.40 mmol) was treated with LDA (1.8 mmol), LiCl (150 mg, 3.5 mmol) and CH_3I (0.47 ml, 7.5 mmol) in the fashion described in GP 5 with the exception that the reaction mixture was allowed to warm to −30°C before addition of sat. NH_4Cl solution. Workup yielded crude dipeptide **24** (70 mg, 53%) as white solid, m.p. 208−210°C. – $[\alpha]_D^{RT}$ = −9.2 (*c* = 0.30, $CHCl_3$) . – IR ($CHCl_3$): $\tilde{\nu}$ = 3434 cm^{-1}, 2974, 1702, 1662, 1368, 1170. – ^{1}H NMR (500 MHz, $CDCl_3$, rotamers!): δ = 0.91 (d, *J* = 6.8, 3 H, CH_3), 0.91 (d, *J* = 6.8, 3 H, CH_3), 1,22 (d, *J* = 6.7, 3 H, CH_3), 1.43 [s, 9 H, $C(CH_3)_2$], 1.75−1.83 [m, 1 H, $CH(CH_3)_2$], 2.28−2.44 [m, 4 H, $C(O)CH_2$], 2.79, 2.80 (2 s, 3 H, NCH_3), 3.62−3.71 (m, 1 H, NCH), 4.23−4.30 (m, 1 H, NCH), 5.10 (d, *J* = 8.4, 1 H, NH), 6.17 (br. s, 1 H, NH), 6.81 (d, *J* = 7.30, 1 H, NH). – ^{13}C NMR (125 MHz, $CDCl_3$, rotamers!): δ = 18.4, 19.4, 20.3, 26.2, 28.4, 32.3, 39.6, 42.6, 42.9, 53.4, 79.3, 156.1, 170.8, 171.5. – MS (FAB), *m/z* (%): 659 (15) [2 M + H^+], 330 (100) [M + H^+], 230 (82).

---

[1] Part of the projected Ph. D. thesis of T. H., ETH Zürich.

[2] Part of the master thesis of C. M. (Universität Erlangen-Nürnberg), carried out in Laboratorium für Organische Chemie, ETH Zürich, August **1997** until January **1998**.

[3] Reviews with chapters concerning peptide Li-enolates: D. Seebach, *Angew. Chem.* **1988**, *100*, 1685−1715. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624−1654. – D. Seebach, *Aldrichimica Acta* **1992**, *25*, No. 3, 59−66. – D. Seebach, A. K. Beck, A. Studer in *Modern Synthetic Methods 1995* (Eds. B. Ernst, C. Leumann), VHCA Basel, VCH Weinheim, **1995**, p. 1−178.

[4] First successful experiments with cyclosporin A by R. Naef, ETH Zürich, **1983**, were published ten years later: D. Seebach, A. K. Beck, H. G. Bossler, C. Gerber, S. Y. Ko, C.W. Murtiashaw, R. Naef, S. Shoda, A. Thaler, M. Krieger, R. Wenger, *Helv. Chim. Acta* **1993**, *76*, 1564−1590.

[5] D. Seebach, H. Bossler, H. Gründler, S. Shoda, *Helv. Chim. Acta* **1991**, *74*, 197- 224.

[6] H.G. Bossler, D. Seebach, *Helv. Chim. Acta* **1994**, *77*, 1124−1165.
[7] D. Seebach, A. Thaler, A. K. Beck, *Helv. Chim. Acta* **1989**, *72*, 857−867. − A. Thaler, D. Seebach, F. Cardinaux, *Helv. Chim. Acta* **1991**, *74*, 617−627. − A. Thaler, D. Seebach, F. Cardinaux, *Helv. Chim. Acta* **1991**, *74*, 628−643. M. Köck, H. Kessler, D. Seebach, A. Thaler, *J. Am. Chem. Soc.* **1992**, *114*, 2676−2686. − D. Seebach, H. G. Bossler, R. Flowers, E. M. Arnett, *Helv. Chim. Acta* **1994**, *77*, 291−305.
[8] D. Seebach, J. L. Matthews, *J. Chem. Soc., Chem. Commun.* **1997**, 2015−2022.
[9] B. L. Iverson, *Nature (London)*, **1997**, *385*, 113−115. − S. Borman, *Chem. Eng. News*, June 16, **1997**, 32−35. − U. Koert, *Angew. Chem.* **1997**, *109*. 1922−1923; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1836−1837. − S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173−180.
[10] T. Hintermann, D. Seebach, *Chimia* **1997**, 244−247.
[11] D. Seebach, H. Estermann, *Tetrahedron Lett.* **1987**, *28*, 3103−3106. − H. Estermann, D. Seebach, *Helv. Chim. Acta* **1988**, *71*, 1824−1839.
[12] D. Seebach, S. Abele, K. Gademann, G. Guichard, T. Hintermann, B. Jaun, J. L. Matthews, J. V. Schreiber, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1998**, *81*, 932−982.
[13] For Li_2 derivatives of β-hydroxyesters see: D. Seebach, J. Aebi, D. Wasmuth, *Organic Syntheses* **1985**, *63*, 109−120; *Collective Volume VII*, **1990**, 153−159. and earlier work by Kraus, Taschner and Frater cited therein. Review article: G. Frater in *Alkylation of Ester Enolates*, Houben Weyl *Methods of Organic Chemistry* (Eds:. G. Helmchen, R.W. Hoffmann, J. Mulzer, E. Schaumann) 4th edition, vol. E 21a, , Thieme, Stuttgart, New York, **1995**, p. 723−790.
[14] J. Podlech, D. Seebach, *Liebigs Ann.* **1995**, 1217−1228.
[15] J.L. Matthews, C. Braun, G. Guibourdenche, M. Overhand, D. Seebach in *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi) Wiley-VCH, New York, **1997**, p. 105−126.
[16] J. L. Matthews, M. Overhand, F. N. M. Kühnle, P. E. Ciceri, D. Seebach, *Liebigs Ann.* **1997**, 1371−1379.
[17] S. T. Cheung, N. L. Benoiton, *Can. J. Chem.* **1977**, *55*, 916−921. − S. T. Cheung, N. L. Benoiton, *ibid.* **1977**, *55*, 906−910. − J. R. McDermott, N. L. Benoiton, *ibid.* **1972**, *51*, 1915−1919.
[18] D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, L. Oberer, U. Hommel, R. Amstutz, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 2043−2066.
[19] The necessity of the presence of *N*-alkyl groups is a major drawback in the alkylation reaction of α-peptides: It is not possible to remove *N*-methyl groups, the best suited *N*-alkyl groups, from the modified peptides. A way to circumvent this problem is the use of *N*-benzyl amino acids (the benzyl group of which can be cleaved with Na in liquid NH_3), or of proline (the only proteinogenic *N*-alkyl amino acid)[6].
[20] So far, it is not clear, whether *C*-alkylation proceeds via a doubly lithiated aza- carboxylate or whether *N*-alkylation preceeds *C*-alkylation.
[21] *N*-methylation is supposed to occur only at elevated temperatures.
[22] M. Schlosser in *Modern Synthetic Methods 1992* (Ed.: R. Scheffold), VHCA Basel, VCH Weinheim, **1992**, p. 227−271.
[23] H. Bossler, master thesis, ETH Zürich, **1989**.
[24] From the ^{1}H-NMR spectrum of the crude product [integration of *t*Bu vs. C(O)Me signals], we could deduce, that an average of more than one methyl group per molecule was introduced.
[25] The rest of the peptide can be considered as an extended amide protecting group!

[O98297]