177. Synthesis of Tri-, Penta-, and Heptapeptides Containing an (*R*)-2-Alkyl-2-amino-3-(methylamino)-propionic Acid Residue in the Central Position[1])

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By conventional peptide-coupling methods (C to N direction; mixed anhydride, bis(2-oxooxazolidin-3-yl)phosphinoyl chloride (Bop-Cl), or dicyclohexylcarbodiimide (DCC), 2-amino-2-methyl-3-(methylamino)-propionic acid and 2-amino-2-ethyl-3-(methylamino)propionic acid (= 2-amino-2-[(methylamino)methyl]butanoic acid) are incorporated in the central position of tri-, penta-, and heptapeptides (see **3**–**7**, **21**, and **22**). The fragment coupling of the β-amino group of the diamino-acid moiety in a tetrapeptide led to partial epimerization, and thus, two epimeric heptapeptide derivatives were actually obtained (**7** and epi-**7**). The final deprotection to the free heptapeptide (involving a Me_3SiI cleavage of BocNH and MeOCONH, a saponification with NaOH, and HPLC purification) gave both the desired product (isopeptide **21**), with the β-amino group inside the peptide backbone, and a product (peptide **22**) of transpeptidation, with the α-amino group of the diamino acid incorporated and a (methylamino)methyl group as the side chain. Peptide **22** is completely converted to the isopeptide **21** by prolonged treatment with base. The heptapeptide **21** was analyzed by elaborate 2QF-COSY and NOESY NMR measurements in H_2O/CD_3OD at $-5°$ (*Table*, *Fig.*); there is no indication for β-sheet or helical structures, a fact which was also confirmed by CD measurements.

Introduction. – During the last twenty years, many new biologically active peptides were discovered. Structural analogues were synthesized for studying structure/activity correlations. Especially the relationship of conformation and activity is of great importance. Non-proteinogenic amino acids such as α-aminoisobutyric acid (Aib) [1], α,β-didehydrophenylalanine (ΔPhe) or other dehydroamino acids [2], dibenzofuran-based amino acids [3] and spiro-lactam systems [4] were introduced into the peptide chain, in order to stabilize a defined conformation.

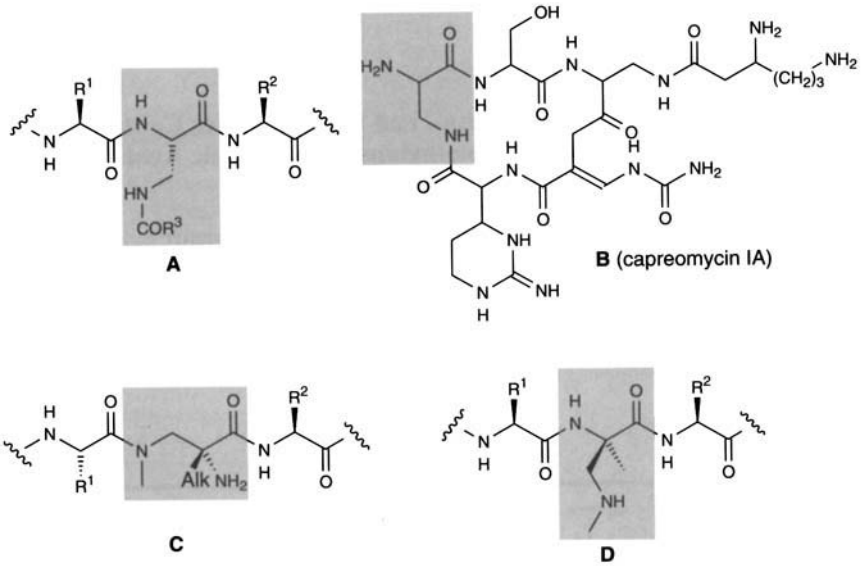
A special amino acid, also occurring naturally [5], is 2,3-diaminopropionic acid (A_2pr). Normally, it is found to be a peptide residue with an aminomethyl side chain[4]) (see, *e.g.*, **A**). In a *Chemical Abstract* search, we found only one example, a family of cyclic peptides with antibiotic activity (capreomycin, viomycin, tuberactinomycin) in which A_2pr is incorporated with the β-amino group as part of the backbone [5b] (*Formula* **B**; containing a total of five β-amino acid units!).

[1]) This project was supported by the *Swiss National Science Foundation*, project No. 20-30770.91.

[2]) Part of the Diplomarbeit (1991) and of the projected Doktorarbeit of *A.S.*

[3]) Part of the Doktorarbeit of *E.P.*, Dissertation No. 9703, ETH-Zürich, 1992.

[4]) There are numerous peptides with this side chain ('aza-serine derivatives'). For two recently isolated fungizides containing A_2pr, see [5a].



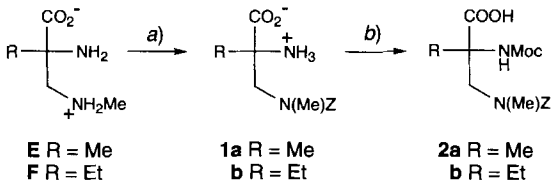
In the course of our work on synthetic methodology for the preparation of amino acids, we also found a simple access to α-branched α-amino-β-(methylamino) acids [6][5]), and we incorporated two of them into linear peptides, with either the β- or the α-amino group as part of the backbone (see **C** and **D**). We chose the sequence Val-Ala-Leu-Xaa-Val-Ala-Leu for the investigations described here. The tripeptide moiety Val-Ala-Leu was used in the classical work by *Karle et al.* [1d,e] for studying the effect of α-amino-isobutyric-acid incorporation on the conformation of linear peptides, *e.g.* Val-Ala-Leu-Aib-Val-Ala-Leu. This led to the discovery that α-branched amino-acid residues in this kind of small peptides enforce helical conformations [1d,e]. Thus, we incorporated diaminopropionic-acid moieties in the Xaa position of the above mentioned heptapeptide and studied the conformational effects of this structural variation by CD and NMR spectroscopy.

In addition, peptides containing our α-alkyl-α-amino-β-(methylamino)-propionic-acid residues might also be interesting peptidic drugs.

Preparative Results. – Starting from the chiral glycine derivative Boc-BMI ((*S*)-2-(*tert*-butyl)-1-(*tert*-butoxycarbonyl)-3-methylimidazolidin-4-one) [8], the α,β-diamino-propionic acids (2*R*)-2-amino-2-methyl-3-(methylamino)propionic acid ((*R*)-Aib(NHMe), **E**) and (2*R*)-2-amino-2-[(methylamino)methyl]butanoic acid ((*R*)-Abu(CH_2NHMe), **F**) were easily prepared in multi-gram amounts in four steps, as described previously [6]. They were used for the synthesis of the tripeptides **3**–**5**, pentapeptide **6**, and the heptapeptide derivatives **7** and epi-**7**. All peptides were constructed in the C to N direction. Following a procedure by *Kjaer* and *Larsen* [9], the acids **E** and **F** were selectively protected with benzyloxycarbonyl chloride (Z-Cl) in a two-phase system (phosphate buffer (pH 7)/toluene) in high yield (*Scheme 1*). The protection of the amino

[5]) For a different approach to α-branched α,β-diamino acids, see [7].

Scheme 1. *Protection of the Diamino Acids* **E** *and* **F**

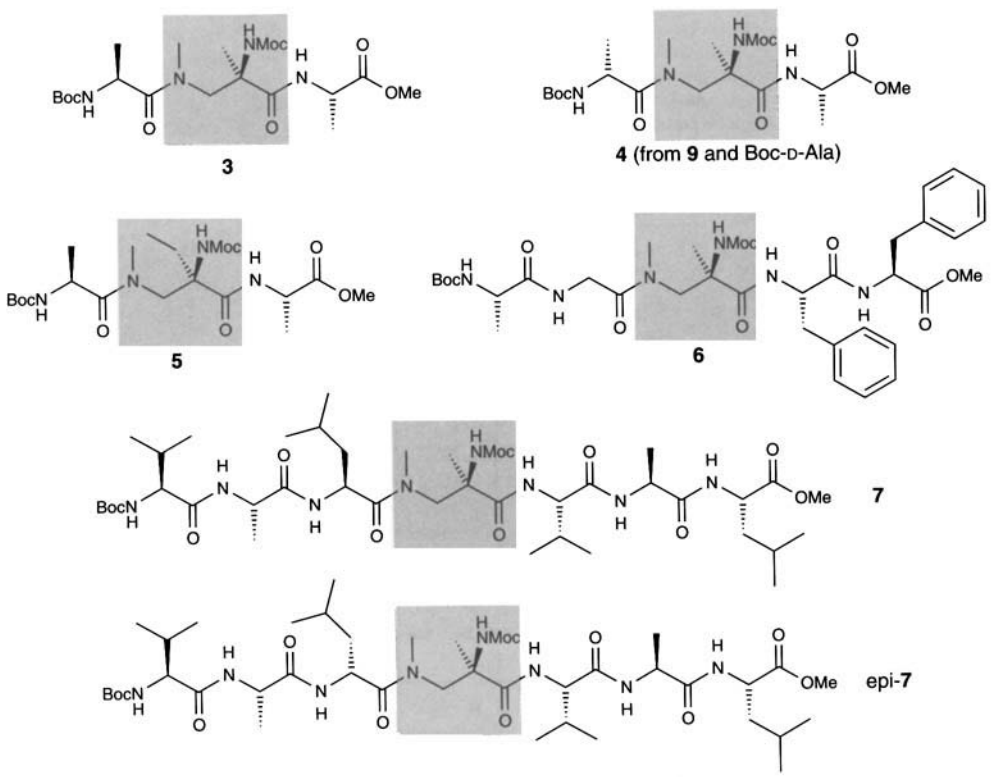


E R = Me, **F** R = Et; **1a** R = Me, **b** R = Et; **2a** R = Me, **b** R = Et

a) Z-Cl, toluene, phosphate buffer pH 7. *b*) Moc-Cl, 1N NaOH, dioxane.

functionality at the branched α-position caused some problems. Carbamoylation with di(*tert*-butyl) dicarbonate ($(Boc)_2O$) failed. Only with the small methoxycarbonyl chloride (Moc-Cl; NaOH/dioxane), we succeeded in forming the doubly protected acids **2a** and **2b**.

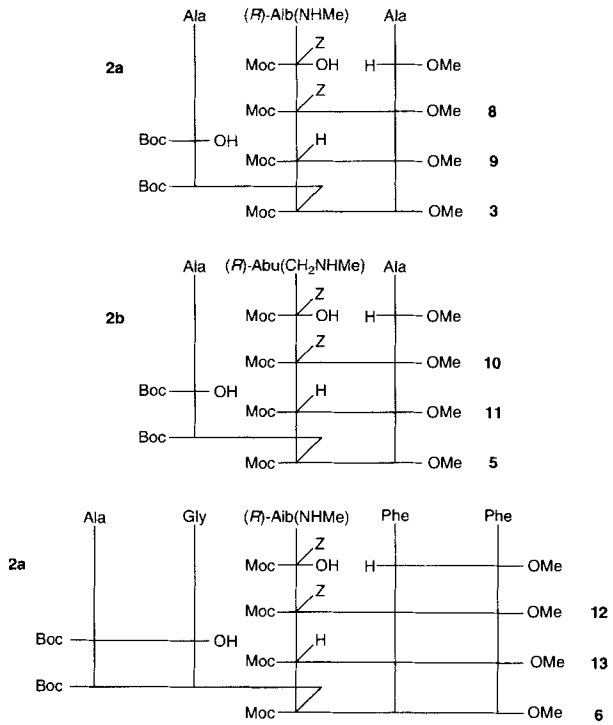
The synthesis of peptides containing the diamino acids **E** and **F** is outlined in *Schemes 2* and *3*. For the tripeptide derivatives **3**–**5**, we first coupled the protected methyl- and ethyl-branched diamino acids **2a** and **2b** with H-Ala-OMe using bis(2-oxooxazolidin-3-yl)phosphinoyl chloride (Bop-Cl) [10] (→ **8**, **10**). After removal of the Z group (→ **9**, **11**), the β-amino group was coupled, using the same reagent, with Boc-Ala-OH (→ **3**, **5**) or with Boc-D-Ala-OH (**9**→ **4**). The pentapeptide derivative **6** was put together from our



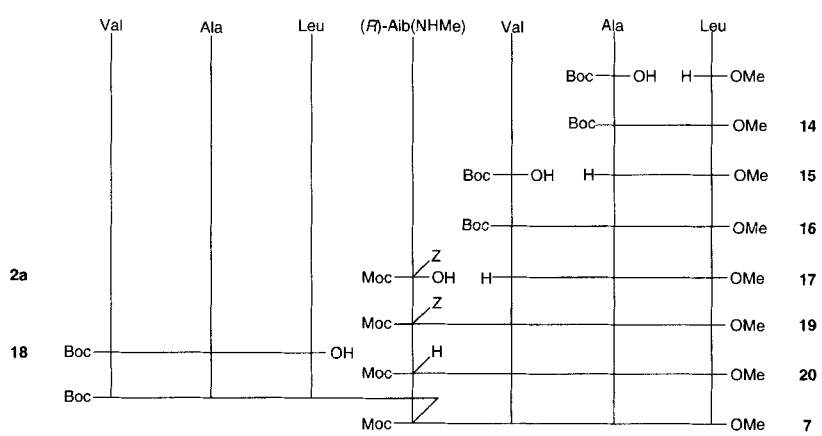
diamino-acid building block **2a** and the commerical dipeptides H-Phe-Phe-OMe and Boc-Ala-Gly-OH, again using the same coupling procedures, through the intermediates **12** and **13** (*Scheme 2*).

Finally, the heptapeptide **7** with three protecting groups was assembled in the following way (*Scheme 3*): it contains the repeating sequence Val-Ala-Leu on both sides of the

Scheme 2. *Synthesis of the Tripeptides* **3** *and* **5** *and of Pentapeptide* **6**



Scheme 3. *Synthesis of Heptapeptide* **7**



diamino-acid residue, thus the tripeptides H-Val-Ala-Leu-OMe (**17**) and Boc-Val-Ala-Leu-OH (**18**) were first prepared. Peptides containing the repeating sequence Val-Ala-Leu were described in the literature, but without experimental detail [1e]. We used the mixed-anhydride method [11] for the Ala-Leu coupling (→ **14**), cleaved off the Boc group with HCl in Et_2O (→ **15**·HCl), and coupled with Boc-Val-OH using the dicyclohexylcarbodiimide (DCC) procedure (→ **16**). Removal of the Boc group from **16** (CF_3COOH) gave the C-terminal tripeptide **17** and ester saponification the N-terminal tripeptide **18**[6]). All steps were carried out on a 10–20-g scale and gave yields of 85–97%. It is well known that the incorporation of α-branched- or *N*-methylated amino acids into peptides is difficult (a useful comparison of different coupling methods for this type of amino acids is given in [12]). For coupling the Moc- and Z-protected diamino acid **2a** with the tripeptide ester **17**, the DCC/HOBt (1-hydroxy-1*H*-benzotriazole) method [13] gave better yields (90% of **19**) than the Bop-Cl method (50%). After hydrogenolytic removal of the Z group (→**20**), the tetrapeptide was ready to be joined with the Boc-protected tripeptide **18**. This type of segment coupling is not often used in peptide chemistry. One reason is the risk of epimerization at the activated residue. Additional problems are caused by lack of solubility of the two segments and the low yields frequently observed. All this turned out to be true in the present case. The reaction of **18** with **20** was carried out in $HCONMe_2$ at *ca.* −18° (when solutions of **18** and **20** in the commonly used solvents CH_2Cl_2 or THF were mixed in the presence of DCC, a non-stirrable gel formed). Even at this low temperature, epimerization of the Leu residue occurred with all activation methods tested. Best results were obtained with DCC/HOBt at −20°. With Bop-Cl in CH_2Cl_2, the yields were low, and the degree of epimerization was *ca.* 42%. With the recently proposed system DCC/$CuCl_2$ [14], which is supposed to minimize epimerization, we did not observe any product formation. The two isomers (**7** and epi-**7**) formed were separated by careful flash column chromatography on silica gel. To identify the epimers, they were hydrolyzed to the component amino acids, and these were transformed to *N*-(pentafluoropropionyl)-substituted isopropyl esters and analyzed on the chiral GC column *Chirasil-Val* [15] [16]. In this way, the major, less polar epimer **7** (2:1) with higher specific rotation ($[\alpha]_D = -30.9$ *vs.* +4.9) was identified as having an L-Leu in position 3, the minor epi-**7** having a D-Leu.

Both carbamate protecting groups (Boc and Moc) of **7** were easily removed in quantitative yield with trimethyliodosilane (Me_3SiI) [17] in CH_2Cl_2 at room temperature (HPLC monitoring)[7]). The diamino peptide ester thus obtained, was saponified without further purification (1N NaOH/MeOH, 12 h). The fully deprotected heptapeptide **21** was isolated (54%) by prep. reversed-phase HPLC (*Nucleosil 500-7 C4*). There was a second major product isolated in 22% yield which turned out to be the rearranged isomeric heptapeptide **22** (*Scheme 4*). The assignment of the structures to **21** (79 mg isolated) and **22** (32 mg) rests mainly upon the NMR analyses of **21** (see below).

The ready acyl shift from the Me-substituted N^{β}-atom to the N^{α}-atom of amino-acid moiety **E** in the heptapeptide under basic conditions was surprising to us, but we found

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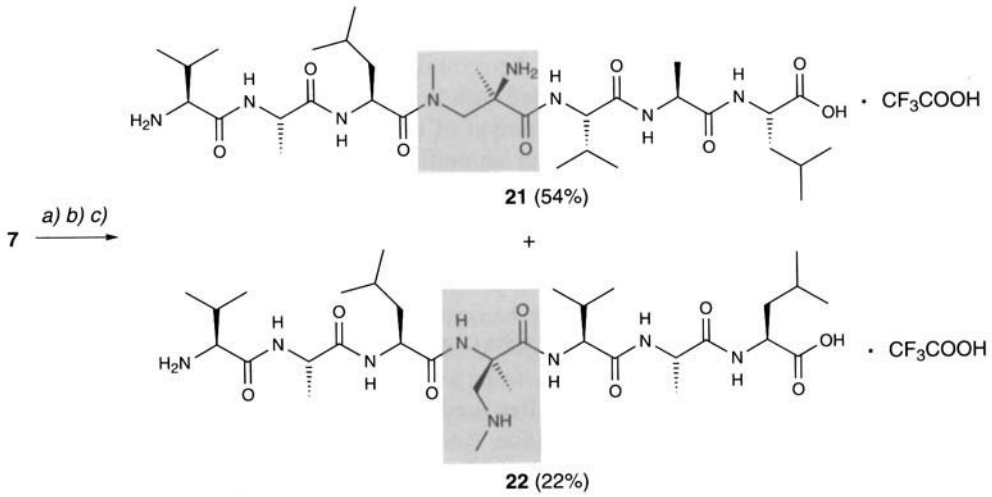
[6]) No epimerization was observed during saponification as checked by GC of derivatives of the different amino acids obtained after hydrolysis of the peptide. Details on the formation of these derivatives are given below.

[7]) Deprotection with the *in situ* prepared Me_3SiI as proposed by *Olah et al.* [18] failed in this case: peptide cleavage occurred, as confirmed by the isolation of smaller fragments.

Scheme 4. *Deprotection of Heptapeptide Derivative* 7



a) Me_3SiI, CH_2Cl_2, r.t. *b*) NaOH, MeOH, r.t. *c*) Reversed-phase HPLC (15% MeCN, 85% H_2O, 0.1% CF_3COOH).

that this transpeptidation is a well studied phenomenon [19]. The so-called iso-peptide **21** can be expected to be more stable than peptide **22** in basic media[8])[9]), as shown for a series of model peptides [19]. To test whether the observed *ca.* 2.5:1 ratio of iso-peptide **21** and peptide **22** is the equilibrium ratio, we kept stirring the mixture of the saponification step (NaOH/MeOH) for prolonged periods of time and analyzed samples. After 24 h, the peptide was completely converted to the iso-peptide, and no change was observed after 10 days. This result proves that peptide **22** had not been formed under the basic conditions of saponification, but rather during the preceding Me_3SiI cleavage of the Boc and Moc groups. From the supposed mechanism of the Boc cleavage, we expect that HI is formed, and acidic conditions will undoubtedly convert an iso-peptide to a peptide[9]). We did not succeed in determining the peptide/iso-peptide ratio of the corresponding diamino esters by anal. HPLC after Me_3SiI treatment.

NMR Spectroscopy. – A 9-mM solution of iso-peptide **21** was prepared in H_2O buffered with 50 mM phosphate (pH 3.2), and 15% CD_3OD was added to avoid sample freezing at the NMR measurement temperature of −5°.

2QF-COSY [20] and NOESY [21] spectra using H_2O presaturation were recorded with 512 increments corresponding to 51.2 ms in t_1: the acquisition time in t_2 was 164 ms with a recycle time per scan of 1.8 s. The NOESY spectrum was measured with a 120-ms mixing time. Scalar coupling constants $J(H-C(\alpha), NH)$ were measured in 1D experiments under the same conditions as 2D spectra. The data were processed on an *Aspect X 32*

[8]) This is reasonable, since the amino group of the iso-peptide (here **21**) is less basic than the one of the peptide (here **22**).

[9]) *Cf.* the N to O acyl shift in serine- or threonine-containing peptides under acidic conditions (*e.g.* in CF_3CO_2H).

computer using *Bruker UXNMR* software. Cosine window functions were applied in both dimensions of the NOESY data, and the frequency domain spectrum was baseline-corrected with a polynomial of third degree. For the 2QF-COSY spectrum, sine window functions were used.

The δ(H)'s of peptide **21** were completely assigned from the 2D-NMR spectra (2QF-COSY, NOESY). In the *Table*, the chemical shifts of the amide protons and their coupling constants to the H–C(α)'s are listed. The coupling constants $J(H\text{–}C(\alpha), NH)$ are correlated with the intervening torsion angle *via* a *Karplus*-type relation [22]. The J values are small (< 5 Hz) for helical structures and large (> 8 Hz) for β-sheets. The observed values for Val-5 and Leu-7 (7.3 and 6.7 Hz) were in between these two typical regions, indicating that the torsion angle ϕ is flexible (no defined conformation). For

Table. *^{1}H-NMR Chemical Shifts and Coupling Constants of the* H–*C(α)'s of Heptapeptide* **21**. The spectrum was measured in H_2O/D_3COD at pH 3.2 at −5°. See also text.

Amino acid	Chemical shift [ppm] of CONH	$J(H\text{–}C(\alpha), NH)$ [Hz]
Ala-2	8.93	4.9
Leu-3	9.16	4.9
Val-5	8.01	7.3
Ala-6	8.72	5.5
Leu-7	8.60	6.7

Ala-2 and Leu-3, the coupling constants are small (4.9 Hz), corresponding to a torsion angle of *ca.* −60°. This could be evidence for the prevalence of helical structures; however, the NOE pattern is typical for a peptide with no defined overall conformation. In the $H\text{–}C(\alpha)/NH$ region of the NOESY spectrum, only intra-residual and sequential NOE's are observed, but no NOE over more than one residue (*Fig.*).

There are two weak NH/NH NOE's (Ala-2/Leu-3; Val-5/Ala-6). They indicate that there might be some short-lived turn or helical conformations, especially for the region Ala-2/Leu-3, in agreement with their coupling constants. However, this is not a stable helix in this region, since the NH/NH NOE intensities are significantly lower than the $H\text{–}C(\alpha)/NH$ NOE intensities.

CD Spectroscopy. – The circular dichroism (CD) spectra of the peptides **7**, epi-**7**, and the fully deprotected heptapeptide **21** were recorded in MeOH. The epimers **7** and epi-**7** have very similar spectra. For the peptide **7**, a minimum at 195 nm ($-6.7\cdot10^4$ deg cm^{2}dmol^{-1}), a zero-crossover at 205 nm, a maximum at 213.5 nm ($+1.7\cdot10^4$ deg cm^{2}dmol^{-1}), a zero-crossover at 225 nm, and a weak negative *Cotton* effect at 234.5 nm ($-0.5\cdot10^4$ deg cm^{2}dmol^{-1}) are observed. The CD spectrum of epi-**7** shows similar CD effects at 195 nm and 213 nm. The only difference is the missing weak negative *Cotton* effect at 234 nm. The spectra of **7** and epi-**7** are those expected for peptides with an unordered chain [23]. For heptapeptide **21**, a zero-crossover at 193 nm, a minimum at 203 nm ($-5.3\cdot10^4$ deg cm^{2}dmol^{-1}), an additional maximum at 220 nm ($-0.9\cdot10^4$ deg cm^{2}dmol^{-1}), and a weak negative *Cotton* effect at 238 nm ($-2.3\cdot10^4$ deg cm^{2}dmol^{-1}) are observed. There is no indication for a stable conformation, in agreement with the results of the NMR analysis (see above).

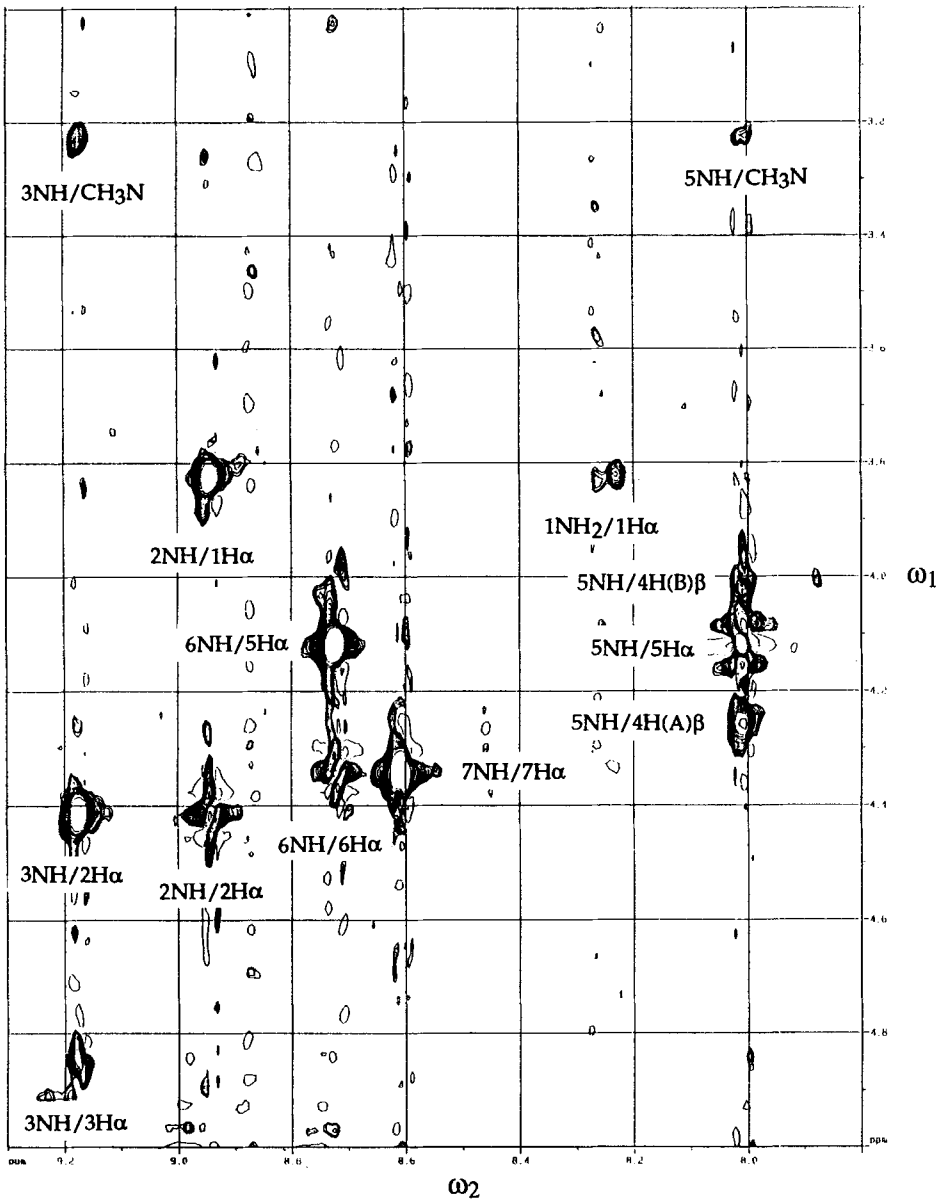


Figure. *Region from the NOESY spectrum of peptide* **21** *showing NOE's between* H–*C*(α)*'s* (ω_1) *and amide protons* (ω_2). The numbers preceding NH, Hα (= *H*–C(α)), and H(A)β or H(B)β (= H_A– or H_B–C(β)) are the residue numbers.

Conclusions. – The results described herein show that α-branched 2-amino-3-(methylamino)carboxylic acids can be incorporated into oligopeptides, and that non-protected iso-peptides such as **21** can be isolated and are stable under neutral or basic conditions

(no cyclizing peptide cleavage!)[10]). Peptide **22** with a (methylamino)methyl side chain is completely converted to the iso-peptide **21** under basic conditions. It is not too surprising that the additional CH_2 group of the unnatural amino acid **E** in the peptide backbone destabilizes the formation of a helical structure in peptide **7** in comparison with the analogous peptide containing α-aminoisobutyric acid (Aib) at that special site of the peptide. However, we hoped that this diamino acid might act as a conformationally fixed linker of two defined substructures, with at least one helical part (the C-terminal one). But neither for peptide **7** nor for the fully deprotected peptide **21** with an additional NH_3^+ group, which might provide additional conformational fixing, was the formation of a defined secondary structure in H_2O/MeOH detected by CD or NMR analysis. Thus, the incorporation of (*R*)-Aib(NHMe) (**E**) into the heptapeptide Val-Ala-Leu-Xaa-Val-Ala-Leu does not have any pronounced effect on the conformation as does Aib itself.

Experimental Part

1. *General.* THF used for coupling reactions was freshly distilled over Na under Ar. TLC: *Merck* silica gel *60* F_{254} anal. plates; detection either with UV and 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, or by dipping into a soln. of I_2 (30 g), KI (2 g) in H_2O (200 ml) and EtOH (200 ml); amino acids and free amines by dipping into a soln. of BuOH (285 ml), AcOH (2 ml), H_2O (13 ml), and ninhydrine (0.6 g), followed by heating. LC: *Merck* silica gel *60* (40–63 μm). GC: *Chirasil-Val*® column (*Macherey-Nagel*, 25 m, 0.4 mm); *Carlo-Erba-Fractovap 4160-HRGC*; temp. program, 3 min 85°, 4°/min. Anal. HPLC: *Kontron* HPLC system; UV detector *Uvikon LCD-75*, programmer *200*, integrator *Shimadzu C-R 1B Chromatopak*; *Macherey-Nagel* C_4-column (*Nucleosil 500-7 C_4* (250 × 4 mm)). Prep. HPLC; *Knauer* HPLC system; pump type *64*, programmer *50*, UV detektor variable-wavelength monitor, *Macherey-Nagel* C_4-column (*Nucleosil 500-7 C_4* (250 × 20 mm)). Optical rotations: 10-cm, 1-ml cell, at r.t.; *Perkin-Elmer-241* polarimeter. Circular dichroism (CD): *Jobin-Yvon-Mark-III* system: total molar ellipticity $[\Theta]$ in $°cm^2 dmol^{-1}$, λ in nm in parentheses (190–270 nm); peptide concentrations 0.41 mM in MeOH). IR Spectra: *Perkin-Elmer-782* spectrophotometer. ^{1}H-NMR: *Bruker-AMX-II-500* (500 MHz), *Bruker-AMX-400* (400 MHz), *Bruker-ARX-300* (300 MHz), or *Varian-Gem-200* (200 MHz) spectrometer. ^{13}C-NMR: *Bruker-AMX-II-500* (125 MHz), *Bruker-AMX-400* (100 MHz), or *Varian-XL-300* (75 MHz) spectrometer.

2. *General Procedure for GC Analysis.* In a screw-capped vial, 10–20 mg of peptide were hydrolyzed with conc. HCl soln. at 100–110° for 6–15 h. Then, H_2O was removed in an airflow and *ca.* 1 ml of anh. 4M HCl in i-PrOH added. The soln. was heated at 100° for 1 h, then the solvent removed in an airflow, and *ca.* 0.1 ml of CH_2Cl_2 and 0.05 ml of pentafluoropropionic anhydride were added. Heating at 100° for 15 min followed by removal of excess pentafluoropropionic anhydride in an airflow gave the derivatives of the individual amino acids.

3. *General Procedure for the Coupling with Isobutyl Chloroformate* (*G.P.1*). To a soln. of the carboxyl component in dry THF, *N*-methylmorpholine (NMM) and isobutyl chloroformate were added at −15°. After 2 min, a cold soln. of the salt of the amino component and NMM in DMF or THF was added dropwise. After 30–60 min, the soln. was warmed to r.t., and stirring was continued für 2 h. The mixture was evaporated and the residue taken up in AcOEt and washed with 5% citric acid, sat. aq. $NaHCO_3$, and sat. aq. NaCl soln. All aq. layers were additionally extracted twice with AcOEt. The combined org. layers were dried ($MgSO_4$) and evaporated.

4. *General Procedure for the Coupling with Bis[2-oxooxazolidin-3-yl]phosphinoyl Chloride* (Bop-Cl, *G.P.2*). The suspension of the acid component, Et(i-Pr)$_2$N, and Bop-Cl in CH_2Cl_2 was stirred for 2 h at −18°. The amino component and Et(i-Pr)$_2$N in CH_2Cl_2 were added at −18° and stirred for 2 h at −18°. The mixture was allowed to warm up to r.t., and stirring was continued for 12 h. Workup according to *G.P.1*.

5. *General Procedure for the Coupling with Dicyclohexylcarbodiimide* (DCC; *G.P.3*). To the suspension of the acid component, the salt of the amino component, 1-hydroxy-1*H*-benzotriazole (HOBt), and NMM in dry THF,

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[10]) The amino group of the α-branched amino-acid residue of **21** could attack the carbonyl group of the neighboring valine residue and thus cleave the peptide backbone.

DCC was added at −18°. The suspension was stirred for 2 h at −18°. The mixture was allowed to warm up to r.t., and stirring was continued for 12 h. The *N,N'*-dicyclohexylurea which separated was filtered off and the filtrate evaporated. Workup according to *G.P.1*.

(2R)-2-Amino-3-[N-(benzyloxycarbonyl)-N-methylamino]-2-methylpropanoic Acid (H-(R)-Aib(N(Z)Me)-OH; **1a**). To a soln. of 2,3-diamino-2-methylpropanoic acid (500 mg, 3.8 mmol **E**) in phosphate-buffer soln. (pH 7, *Fluka*; 135 ml), benzyl chloroformate (0.64 ml, 4.4 mmol) in toluene (0.7 ml) was added at r.t. After stirring for 16 h, the precipitate was filtered off and washed with pentane and a small amount of H_2O: 910 mg (90%) of colorless powder. For anal. purposes, **1a** was recrystallized from H_2O/MeOH. M.p. 211°. $[\alpha]_D^{r.t.} = +21.3$ ($c = 0.80$, 3N HCl). IR (KBr): 3440*s*(br.), 3160*w*, 3100*w*, 2815*w*, 2505*m* (br.), 2005*w*, 1675*w*, 1610*s*, 1540*m*, 1495*s*, 1455*s*, 1440*m*, 1425*s*, 1400*s*, 1360*w*, 1340*s*, 1325*w*, 1315*s*, 1270*w*, 1260*w*, 1215*m*, 1195*s*, 1120*m*, 1085*w*, 1030*w*, 970*m*, 935*w*, 870*m*, 820*w*, 785*w*, 775*m*, 765*s*, 710*s*. ^{1}H-NMR (300 MHz, D_2O): 1.31, 1.42, 1.45 (3*s*, Me–C(2), rotamers); 2.81, 2.88, 2.94 (3*s*, Me–N(4), rotamers); 3.4–3.6 (*m*, H–C(3), rotamers); 3.8–3.9 (*m*, H–C(3), rotamers); 5.0–5.25 (*m*, PhCH_2, rotamers); 7.42 (*s*, *Ph*CH_2). ^{13}C-NMR (75 MHz, D_2O): 22.98 (Me); 38.82 (Me); 57.36, 57.98 (CH_2, rotamers); 70.73 (CH_2); 130.13, 130.30 (CH, rotamers); 130.50 (CH); 130.93 (CH); 131.18, 131.35 (CH, rotamers); 131.50 (CH); 138.76 (C); 161.84 (C); 177.59 (C). FAB-MS: 533.1 (11.77, $[2M + 1]^+$), 307.0 (11.55), 289.0 (20.30, $[M + Na]^+$), 267.1 (100, $[M + H]^+$), 221.1 (16.51), 154.0 (44.69), 136.0 (34.90), 120.0 (6.61), 107.0 (12.82), 91.0 (59.34), 89.0 (14.20), 77.0 (13.30), 56.9 (11.28).

(2R)-2-Amino-2-{[N-(benzyloxycarbonyl)-N-methylamino]methyl}butanoic Acid (H-(R)-Abu(CH$_2$N(Z)Me)-OH; **1b**). As described for **1a**, with 2-amino-2-[(methylamino)methyl]butanoic acid (500 mg, 3.42 mmol, **F**), phosphate-buffer soln. (pH 7, *Fluka*; 135 ml), benzyl chloroformate (0.61 ml, 4.2 mmol), and toluene (0.7 ml): 720 mg (75%) of **1b**. The colorless foam was used for the following reaction without further purification. ^{1}H-NMR (200 MHz, D_2O): 0.93 (*m*, Me(4)); 1.5–2.1 (*m*, CH_2(3)); 2.9–3.0 (2*s*, MeN, rotamers); 3.4–3.8 (*m*, 1 H, MeNCH_2, rotamers); 3.8–4.0 (*m*, 1 H, MeNCH_2, rotamers); 5.16 (*s*, PhCH_2); 7.47 (*s*, *Ph*CH_2).

(2R)-3-[N-(Benzyloxycarbonyl)-N-methylamino]-2-[N-(methoxycarbonyl)amino]-2-methylpropanoic Acid (Moc-(R)-Aib(N(Z)Me)-OH; **2a**). A soln. of **1a** (400 mg, 1.5 mmol) in H_2O (20 ml), dioxane (6.4 ml), and 1N NaOH (3.3 ml) was cooled to 0°. The soln. was treated with methyl chloroformate (0.26 ml, 3.3 mmol). By adding 1N NaOH, the pH was kept alkaline. The mixture was allowed to warm up to r.t., stirred for 14 h, and evaporated. The resulting oil was acidified with phosphoric acid to pH 2 and extracted with AcOEt and the combined extract washed with sat. aq. NaCl soln. and dried ($MgSO_4$), filtered, and evaporated: 389 mg (80%) of **2a**. Oil. $[\alpha]_D^{r.t.} = +47.9$ ($c = 1.35$, MeOH). IR ($CHCl_3$): 3410*w*, 3010*m*, 2960*m*, 1720*s*, 1510*m*, 1455*m*, 1400*m*, 1365*w*, 1220*s*, 1120*m*, 1080*m*, 875*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.60 (br. *s*, Me–C(2)); 2.98 (*s*, MeN); 3.6–3.9 (*m*, CH_2(3), MeO); 5.14 (*s*, PhCH_2); 6.84 (br. *s*, NH); 7.34 (*s*, *Ph*CH_2); 9.2–9.6 (br. *s*, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.98 (Me); 37.30 (Me); 52.25 (Me); 56.38 (CH_2); 61.19 (C); 67.04, 68.01 (CH_2, rotamers); 127.91 (CH); 128.21 (CH); 128.55 (CH); 136.09 (C); 156.74 (C); 158.64 (C); 175.77 (C). FAB-MS: 347.1 (12.92, $[M + Na]^+$), 325.1 (41.25, $[M + H]^+$), 281.1 (33.08), 178.1 (10.97), 134.1 (21.44), 115.0 (10.45), 92.0 (19.00), 91.0 (100), 76.9 (10.84).

(2R)-2-{[N-(Benzyloxycarbonyl)-N-methylamino]methyl}-2-[N-(methoxycarbonyl)amino]butanoic Acid (Moc-(R)-Abu(CH$_2$N(Z)Me)-OH; **2b**). As described for **1a**, with **1b** (1.34 g, 4.8 mmol), H_2O (80 ml), dioxane (22 ml), 1N NaOH (12 ml), and methyl chloroformate (0.81 ml, 10.6 mmol): 1.18 g (73%) of **2b**. The oil was used for the following reaction without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.87 (*m*, Me(4)); 1.8–2.4 (*m*, CH_2(3)); 3.65 (*s*, MeN); 3.7–4.0 (*m*, MeNCH_2, rotamers); 5.11 (*s*, PhCH_2); 6.34 (*s*, NH); 7.33 (*s*, *Ph*CH_2); 8.5–9.0 (br. *s*, COOH).

{(2R)-3-N-[N-(tert-Butoxycarbonyl)alanyl]-2-[N-(methoxycarbonyl)amino]-2-methyl-3-(methylamino)-propanoyl}alanine Methyl Ester (Boc-Ala-Moc-(R)-Aib(NMe)-Ala-OMe; **3**). Coupling and workup according to *G.P.2*, with Boc-Ala-OH (359 mg, 1.90 mmol), Bop-Cl (509 mg, 2.00 mmol), Et(i-Pr)$_2$N (0.65 ml, 3.80 mmol), CH_2Cl_2 (11 ml), Moc-(*R*)-Aib(NHMe)-Ala-OMe (523 mg, 1.90 mmol; **9**), Et(i-Pr)$_2$N (0.32 ml, 1.90 mmol), and CH_2Cl_2 (11 ml). The crude peptide was purified by FC (AcOEt/hexane 2:1): **3** (470 mg, 56%). Colorless foam. M.p. 53–54°. $[\alpha]_D^{r.t.} = +68.7$ ($c = 1.0$, CH_2Cl_2). IR: 3360*s* (br.), 2980*s*, 2940*m*, 1730*s*, 1700*s*, 1680*s*, 1645*s*, 1520*s*, 1450*m*, 1420*w*, 1370*m*, 1320*m*, 1260*s*, 1210*w*, 1170*s*, 1105*w*, 1080*s*, 1020*w*, 860*w*, 785*w*, 755*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.28 (*d*, $J = 6.9$, Me(3.3) or Me(3.1)); 1.41–1.44 (*m*, *t*-Bu, Me(3.3) or Me(3.1)); 1.56 (*s*, Me–C(2.2)); 3.15 (*s*, MeN); 3.34 (*d*, $J = 14.7$, H–C(3.2)); 3.60 (*s*, MeO); 3.73 (*s*, MeO); 4.06 (*d*, $J = 14.1$, H–C(3.2)); 4.5–4.56 (*m*, H–C(2.1), H–C(2.3)); 5.26 (*d*, $J = 6.6$, NHCOO); 7.28 (2*s*, 2 NH). ^{13}C-NMR: 17.37 (Me); 17.74 (Me); 21.00 (Me); 28.39 (Me); 38.39 (Me); 46.91 (CH); 48.75 (CH); 51.83 (Me); 52.20 (Me); 56.62 (CH_2); 62.50 (C); 79.85 (C); 155.32 (C); 155.83 (C); 172.08 (C); 173.14 (C); 176.52 (C). FAB-MS: 448.2 (24.96), 447.2 (83.78, $[M + H]^+$), 348.1 (21.68), 347.1 (89.31), 316.1 (40.48), 277.1 (16.26), 276.1 (85.75), 260.1 (23.55), 244.1 (10.11), 232.1 (10.31), 145.1 (41.19), 141.1 (50.41), 116.0 (10.44), 115.0 (18.75), 113.0 (27.96), 104.0 (22.83), 102.0 (19.05), 89.0 (10.39), 87.9

(22.10), 69.9 (11.94), 57.9 (11.22), 56.9 (100), 55.9 (13.72), 54.9 (10.67). Anal. calc. for $C_{19}H_{34}N_4O_8$ (446.5): C 51.11, H 7.68, N 12.55; found: C 50.77, H 7.49, N 12.36.

*{(2R)-3-*N*-[*N*-(*tert*-Butoxycarbonyl)-*D*-alanyl]-2-[*N*-(methoxycarbonyl)amino]-2-methyl-3-(methylamino)propanoyl}alanine Methyl Ester* (*Boc-D-Ala-Moc-(R)Aib(NMe)-Ala-OMe*; **4**). Coupling and workup according to *G.P.2*, with Boc-D-Ala-OH (397 mg, 2.10 mmol), Bop-Cl (560 mg, 2.20 mmol), Et(i-Pr)$_2$N (0.72 ml, 4.2 mmol), CH_2Cl_2 (11 ml), Moc-(*R*)-Aib(NHMe)-Ala-OMe (580 mg, 2.1 mmol; **9**), Et(i-Pr)$_2$N (0.36 ml, 2.10 mmol), and CH_2Cl_2 (11 ml). The crude peptide was purified by FC (AcOEt/hexane 2:1): **4** (511 mg, 55%). Colorless foam. M.p. 50–52°. $[\alpha]_D^{r.t.} = +85.3$ ($c = 0.95$, CH_2Cl_2). IR: 3340*s* (br.), 2980*s*, 2950*m*, 1730*s*, 1710*s*, 1670*s*, 1645*s*, 1515*s*, 1450*m*, 1420*w*, 1370*m*, 1350*m*, 1315*w*, 1260*s*, 1220*w*, 1170*s*, 1080*s*, 1060*s*, 1020*w*, 980*w*, 935*w*, 865*m*, 830*m*, 785*w*, 755*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.3–1.5 (*m*, *t*-Bu; Me(3.3), Me(3.1)); 1.57 (*s*, Me–C(2.2)); 3.08 (*s*, MeN); 3.41 (*d*, $J = 14.7$, H–C(3.2)); 3.65 (*s*, MeO); 3.74 (*s*, MeO); 4.01 (*d*, $J = 14.4$, H–C(3.2)); 4.5–4.7 (*m*, H–C(2.3), H–C(2.1)); 5.32 (*d*, $J = 4.5$, NHCOO); 7.09 (*d*, NH); 7.24 (*s*, N*H*COOMe). ^{13}C-NMR: 18.08 (Me); 18.48 (Me); 20.73 (Me); 28.36 (Me); 38.10 (Me); 46.64 (CH); 48.39 (CH); 52.08 (Me); 52.41 (Me); 57.05 (CH_2); 62.61 (C); 79.82 (C); 155.18 (C); 156.09 (C); 171.86 (C); 173.22 (C); 176.88 (C). FAB-MS: 447.3 (56.70, $[M + H]^+$), 348.2 (13.29), 347.2 (72.36), 316.2 (24.75), 277.2 (12.29), 276.2 (82.18), 147.1 (16.48), 145.1 (42.36), 143.1 (12.50), 141.1 (44.42), 132.9 (12.21), 115.0 (16.45), 113.1 (22.57), 104.0 (17.92), 102.0 (16.43), 88.0 (21.18), 72.9 (44.48), 70.0 (12.10), 68.9 (12.04), 57.9 (11.59), 56.9 (100), 55.9 (12.85), 54.9 (17.16). Anal. calc. for $C_{19}H_{34}N_4O_8$ (446.5): C 51.11, H 7.68, N 12.55; found: C 50.81, H 7.67, N 12.26.

*{(2R)-2'-*N*-[*N*-(*tert*-Butoxycarbonyl)alanyl]-2-[*N*-(methoxycarbonyl)amino]-2-[(methylamino)methyl]-butanoyl}alanine Methyl Ester* (*Boc-Ala-Moc-(R)-Abu(CH$_2$NMe)-Ala-OMe*; **5**). Coupling and workup according to *G.P.2*, with Boc-Ala-OH (64.3 mg, 0.34 mmol), Bop-Cl (102 mg, 0.40 mmol), Et(i-Pr)$_2$N (0.12 ml, 0.68 mmol), CH_2Cl_2 (2.5 ml), Moc-(*R*)-Abu(CH_2NHMe)-Ala-OMe (99 mg, 0.34 mmol; **11**), (Et(i-Pr)$_2$N (0.06 ml, 0.34 mmol), CH_2Cl_2 (2.5 ml). The crude peptide was purified by FC (AcOEt/hexane 2:1): **5** (93 mg, 60%). Colorless foam. M.p. 54–55°. $[\alpha]_D^{r.t.} = +13.5$ ($c = 1.00$, CH_2Cl_2). IR: 3360*s* (br.), 2980*s*, 2880*m*, 1725*s*, 1710*s*, 1670*s*, 1645*s*, 1520*s*, 1495*s*, 1460*w*, 1370*m*, 1320*m*, 1295*w*, 1250*s*, 1210*w*, 1165*s*, 1085*s*, 1065*s*, 1030*w*, 940*w*, 900*w*, 865*m*, 830*m*, 785*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83 (*t*, $J = 6.8$, *Me*CH$_2$–C(2.2)); 1.25 (*d*, $J = 4.6$, Me); 1.43 (2*s*, *t*-Bu, Me); 1.80–2.20 (*m*, CH$_2$–C(2.2)); 3.14 (*s*, MeN); 3.6–3.8 (*m*, H–C(3.2)); 3.63 (*s*, MeO); 3.72 (*s*, MeO); 4.18 (*d*, $J = 9.8$, H–C(3.2)); 4.44 (*m*, H–C(2.3) or H–C(2.1)); 4.57 (*m*, H–C(2.3) or H–C(2.1)); 5.32 (*d*, $J = 5$, NHCOO); 6.84 (br. *s*, NH); 7.24 (*s*, N*H*COOMe). ^{13}C-NMR: 7.38 (Me); 17.44 (Me); 17.98 (Me); 26.63 (CH_2); 28.29 (Me); 37.67 (Me); 46.65 (CH); 48.75 (CH); 51.89 (Me); 52.20 (Me); 52.87 (CH_2); 65.00 (C); 79.76 (C); 155.17 (C); 155.57 (C); 171.66 (C); 172.96 (C); 175.71 (C). FAB-MS: 462.2 (11.51), 461.2 (47.93, $[M + H]^+$), 362.2 (15.08), 361.2 (76.65), 330.1 (34.33), 290.1 (72.57); 288.1 (12.35), 274.1 (17.15), 159.1 (32.69), 157.1 (15.97), 155.1 (25.18), 132.9 (32.69), 127.1 (20.13), 116.0 (20.12), 104.0 (17.09), 100.0 (10.41), 88.0 (21.65), 69.9 (19.35), 57.9 (11.98), 56.9 (100), 55.9 (19.98), 54.9 (12.74). Anal. calc. for $C_{20}H_{36}N_4O_8$ (460.5): C 52.16, H 7.88, N 12.17; found: C 51.99, H 7.90, N 11.97.

*{(2R)-3-*N*-[*N*-(*tert*-Butoxycarbonyl)-alanyl-glycyl]-2-[*N*-(methoxycarbonyl)amino]-2-methyl-3-(methylamino)propanoyl}-phenylalanyl-phenylalanine Methyl Ester* (*Boc-Ala-Gly-Moc-(R)-Aib(NMe)-Phe-Phe-OMe*; **6**). Coupling and workup according to *G.P.2*, with Boc-Ala-Gly-OH (280 mg, 1.15 mmol), Bop-Cl (300 mg; 1.18 mmol), Et(i-Pr)$_2$N (0.40 ml, 2.30 mmol), CH_2Cl_2 (5 ml), Moc-(*R*)-Aib(NHMe)-Phe-Phe-OMe (590 mg, 1.18 mmol; **13**), Et(i-Pr)$_2$N (0.20 ml, 1.20 mmol), and CH_2Cl_2 (3 ml): **6** (240 mg, 30%). Colorless foam. $[\alpha]_D^{r.t.} = +32.9$ ($c = 0.99$, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.36–1.57 (*m*, *t*-Bu, Me–C(2.3), Me–C(2.1)); 2.57 (*s*, MeN); 2.92–3.11 (*m*, CH$_2$–C(2.5), CH$_2$–C(2.4)); 3.35 (*d*, $J = 14.3$, H–C(3.3)); 3.61–3.68 (3*s*, 2 MeO); 3.80–3.84 (*d*, $J = 14.4$, H–C(3.3)); 3.93–4.05 (*m*, H–C(2.2)); 4.19–4.24 (*m*, H–C(2.1)); 4.63 (*dd*, $J = 7.6$, 2.0, H–C(2.5) or H–C(2.4)); 4.75 (*dd*, $J = 7.6$, 2.0, H–C(2.5) or H–C(2.4)); 5.08 (*d*, $J = 7.5$, NH); 6.86–7.03 (*m*, 4 NH); 7.18–7.28 (*m*, arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.82 (Me); 21.01 (Me); 28.35 (Me); 36.74, 36.99 (Me, rotamers); 37.87 (CH_2); 41.49 (CH_2); 50.15 (CH); 52.18 (Me); 52.34 (Me); 53.48 (CH); 54.57 (CH); 55.22 (CH_2); 56.46 (CH_2); 60.85, 62.11 (C, rotamers); 80.11 (C); 127.08 (CH); 128.57 (CH); 128.64 (CH); 128.7 (CH); 129.16 (CH); 129.41 (CH); 129.84 (CH); 136.02 (C); 136.51 (C); 155.31 (C); 156.21 (C); 170.30 (C); 171.46 (C); 171.59 (C); 172.04 (C); 172.76 (C). FAB-MS: 749 (0.4, $[M + Na]^+$), 727 (0.2, $[M + H]^+$), 207 (12.7), 147 (32.8), 145 (23.3), 136 (16.8), 133 (15.0), 131 (10.2), 125 (10.7), 120 (29.2), 90 (19.8), 89 (10.7), 73 (100.0), 69 (16.3), 57 (31.7), 55 (21.8).

*{(2R)-3-*N*-[*N*-(*tert*-Butoxycarbonyl)-valyl-alanyl-*ambo*-leucyl]-2-[*N*-(methoxycarbonyl)amino]-2-methyl-3-(methylamino)propanoyl}-valyl-alanyl-leucine Methyl Ester* (*Boc-Val-Ala-*ambo*-Leu-Moc-(R)-Aib(NMe)-Val-Ala-Leu-OMe*; **7**/epi-**7**). A soln. of Moc-(*R*)-Aib(NHMe)-Val-Ala-Leu-OMe (500 mg, 1.05 mmol; **20**) and Boc-Val-Ala-Leu-OH (422 mg, 1.05 mmol; **18**) in DMF (5 ml) was cooled to −20° and HOBt (142 mg, 1.05 mmol) added. The soln. was treated with DCC (217 mg, 1.05 mmol) and stirring continued for 5 days at −20°. Workup

according *G.P.3* gave an epimer mixture. The epimers were separated by FC (AcOEt) yielding 210 mg (31.4%) of **7** as a colorless solid and 93 mg (14%) of epi-**7** as a colorless foam. The isomers were identified by GC.

*Boc-Val-Ala-*L*-Leu-Moc-(*R*)-Aib(NMe)-Val-Ala-OMe* (**7**). M.p. 178–181°. $[\alpha]_D^{r.t.} = -30.9$ ($c = 0.68$, MeOH). CD: $-6.74 \cdot 10^{-4}$ (195.0), $+1.70 \cdot 10^{-4}$ (213.5), $-5.14 \cdot 10^{-3}$ (234.5). IR ($CHCl_3$): 3670*w*, 3420*m*, 3320*s*, 3010*s*, 2960*s*, 2940*w*, 2870*m*, 1725*w*, 1665*s*, 1510*s*, 1470*w*, 1455*w*, 1420*m*, 1390*m*, 1370*m*, 1260*m*, 1240*m*, 1165*s*, 1110*w*, 1080*m*, 870*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89–0.99 (*m*, Me(Val,Leu)); 1.32–1.39 (2 Me(Ala)); 1.44 (*s*, Me–C(2.4)); 1.47–1.65 (*m*, CH_2–C(2.7), CH_2–C(2.3), CH–C(3.7), CH–C(3.3)); 2.0–2.2 (*m*, CH(Val)); 2.2–2.4 (br. *s*, CH(Val)); 3.10 (*s*, MeN); 3.54 (*d*, $J = 14.5$, H–C(3.4)); 3.61 (*s*, MeO); 3.72 (*s*, MeO); 3.99 (*d*, $J = 14.4$, H–C(3.4)), 3.9–4.1 (br. *s*, H–C(α)); 4.27–4.31 (*m*, H–C(α)); 4.52–4.62 (*m*, 2 H–C(α)); 4.64–4.69 (*m*, H–C(α)); 4.80–4.95 (br. *s*, H–C(α)); 5.23 (*d*, $J = 7.6$, NHCOO); 6.87–6.88 (br. *s*, NH); 7.14–7.27 (br. *s*, 3 NH); 7.3–7.4 (br. *s*, 2 NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.51 (Me); 17.68 (Me); 18.19 (Me); 19.29 (Me); 21.06 (Me); 21.76 (Me); 21.85 (Me); 22.80 (Me); 23.34 (Me); 24.75 (CH); 28.33 (Me); 30.50 (CH); 31.11 (CH); 38.13 (Me); 40.95 (CH_2); 41.31 (CH_2); 48.54 (CH); 48.90 (CH); 50.80 (CH); 52.10 (Me); 52.25 (Me); 56.19, 56.28 (CH_2, rotamers); 59.46 (CH); 59.83 (CH); 62.48 (C); 79.96 (C); 155.92 (C); 156.09 (C); 171.13 (C); 171.53 (C); 172.03 (C); 172.35 (C); 173.03 (C); 173.25 (C); 175.61 (C). FAB-MS: 893.4 (21.81, $[M + Na]^+$), 871.4 (12.40, $[M + H]^+$), 771.4 (11.51), 489.2 (13.66), 488.2 (49.18), 244.2 (14.58), 215.1 (14.82), 146.1 (12.34), 145.1 (36.55), 116.0 (10.30), 98.0 (10.67), 86.0 (100), 72.0 (42.94), 56.9 (40.90), 54.9 (13.29). Anal. calc. for $C_{41}H_{74}N_8O_{12}$ (871.09): C 56.53, H 8.56, N 12.86; found: C 56.63, H 8.43, N 12.69.

*Boc-Val-Ala-*D*-Leu-Moc-(*R*)-Aib(NMe)-Val-Ala-OMe* (epi-**7**). $[\alpha]_D^{r.t.} = +4.9$ ($c = 0.575$, MeOH). CD: $+2.91 \cdot 10^{-4}$ (213.0). IR (KBr): 3670*w*, 3420*m*, 3320*m*, 3010*s*, 2960*s*, 2940*w*, 2870*m*, 1710*s*, 1670*s*, 1500*s*, 1470*w*, 1455*w*, 1420*m*, 1390*m*, 1370*s*, 1260*w*, 1240*m*, 1160*m*, 1080*m*, 870*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.8–1.0 (*m*, Me(Val,Leu)); 1.34 (*d*, $J = 7.1$, Me(Ala)); 1.39 (*d*, $J = 7.1$, Me(Ala)); 1.44, 1.45 (2*s*, Me–C(2.4), rotamers); 1.47–1.71 (*m*, CH_2–C(2.7), CH_2–C(2.3), CH–C(3.7), CH–C(3.3)); 2.08–2.19 (*m*, CH(Val)); 2.22–2.31 (*m*, CH(Val)); 2.89, 3.09, 3.12 (3*s*, MeN, rotamers); 3.59 (*d*, $J = 10.8$, H–C(3.4)); 3.63 (*s*, MeO); 3.65–3.70 (*m*, H–C(3.4)); 3.72 (*s*, MeO); 3.8–4.0 (br. *m*, H–C(α)); 4.2–4.3 (*m*, H–C(α)); 4.45–4.65 (*m*, 3 H–C(α)); 4.8–4.9 (*m*, H–C(α)); 5.1–5.2 (br. *s*, NHCOO); 6.8–6.9 (*m*, 2 NH); 6.9–7.0 (br. *s*, NH); 7.15–7.25 (br. *s*, NH); 7.25–7.30 (br. *s*, NH); 7.30–7.40 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.35 (Me); 17.55 (Me); 18.66 (Me); 19.33 (Me); 19.55 (Me); 21.14 (Me); 21.47 (Me); 21.59 (Me); 21.84 (Me); 22.76 (Me); 23.30 (Me); 23.37 (Me); 24.72 (CH_2); 24.81 (CH_2); 28.32 (Me); 30.24, 30.59 (CH, rotamers); 30.82, 31.04 (CH, rotamers); 36.42, 38.21 (MeN, rotamers); 40.82, 40.94 (CH_2, rotamers); 41.24 (CH_2); 47.99 (CH); 48.56, 48.62 (CH, rotamers); 48.84 (CH); 50.76, 50.84 (CH, rotamers); 52.05 (Me); 52.22 (Me); 55.78 (Me); 59.08, 59.26, 59.37 (CH, rotamers); 59.82, 59.98 (CH, rotamers); 61.88, 62.61 (C, rotamers); 80.02, 80.14 (C, rotamers); 155.93, 156.04 (C, rotamers); 156.48 (C); 170.88 (C); 171.34, 171.56 (C, rotamers); 171.93 (C); 172.18, 172.32 (C, rotamers); 172.81, 172.90 (C, rotamers); 173.02, 173.21 (C, rotamers); 175.29, 175.57 (C, rotamers). FAB-MS: 894.4 (23.60), 893.4 (48.49, $[M + Na]^+$), 871.4 (15.59, $[M + H]^+$), 771.4 (18.81), 489.2 (22.58), 488.2 (84.44), 343.1 (11.43), 244.2 (13.48), 215.1 (19.49), 147.1 (18.46), 145.1 (34.69), 132.9 (14.48), 116.0 (11.79), 86.0 (100), 72.9 (45.80), 71.9 (45.89), 56.9 (58.84), 54.9 (17.13).

{(2R)-3-[N-(Benzyloxycarbonyl)-N-methylamino]-2-[N-(methoxycarbonyl)amino]-2-methylpropanoyl}-alanine Methyl Ester (Moc-(R)-Aib(N(Z)Me)-Ala-OMe; **8**). Coupling and workup according to *G.P.2* with **2a** (700 mg, 2.63 mmol), Bop-Cl (687 mg, 2.65 mmol), Et(i-Pr)$_2$N (0.91 ml, 5.26 mmol), CH_2Cl_2 (11 ml), H-Ala-OMe·HCl (510 mg, 2.7 mmol), Et(i-Pr)$_2$N (0.46 ml, 2.7 mmol), and CH_2Cl_2 (8 ml). The crude peptide was used for the following deprotecting procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.37 (*d*, $J = 7.0$, Me(3.2)); 1.50–1.51 (*m*, Me–C(2.1)); 2.92 (*s*, MeN); 3.52 (*d*, $J = 15.4$, H–C(3.1)); 3.65 (*s*, MeO); 3.71 (*s*, MeO); 3.72 (*d*, $J = 14.2$, H–C(3.1)); 4.4–4.6 (*m*, H–C(2.2)); 5.16 (*s*, PhCH_2); 7.0–7.2 (*m*, 2 NH).

{(2R)-2-[N-(Methoxycarbonyl)amino]-2-methyl-3-(methylamino)propanoyl}alanine Methyl Ester (Moc-(R)-Aib(NHMe)-Ala-OMe; **9**). To a soln. of **8** (700 mg, 1.70 mmol) in EtOH (7 ml) under Ar, 10% Pd/C (70 mg) was added. The Ar atmosphere was replaced by H_2. The suspension was stirred for 14 h, the catalyst removed by filtration over *Celite*, and the filtrate evaporated: **9** (462 mg, 99%). The slight green oil was used for the following coupling procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.40 (*d*, $J = 7.4$, Me–C(3.2)); 1.55 (*s*, Me–C(2.1)); 2.46 (*s*, MeN); 2.61 (*d*, $J = 12.4$, H–C(3.1)); 3.24 (*d*, $J = 12.2$, H–C(3.1)); 3.64 (*s*, MeO); 3.72 (*s*, MeO); 4.4–4.6 (*m*, H–C(2.2)); 6.20 (br. *s*, NH); 6.25 (*s*, NH).

{(2R)-2-{[N-(Benzyloxycarbonyl)-N-methylamino]methyl}-2-[N-(methoxycarbonyl)amino]butanoyl}alanine Methyl Ester (Moc-(R)-Abu(CH$_2$N(Z)Me)-Ala-OMe; **10**). Coupling and workup according to *G.P.2* with **2b** (1.18 g, 3.5 mmol), Bop-Cl (917 mg, 3.6 mmol), Et(i-Pr)$_2$N (1.24 ml, 7.0 mmol), CH_2Cl_2 (15 ml), H-Ala-OMe·HCl (750 mg, 4.0 mmol), Et(i-Pr)$_2$N (0.71 ml, 3.5 mmol) and CH_2Cl_2 (15 ml). The crude **10** was used for the following deprotecting procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.70–0.95 (*m*, Me(4.1)); 1.32 (*d*, $J = 7.2$, Me(3.2)); 1.60–2.40 (*m*, CH_2(3.1)); 2.94 (*s*, MeN); 3.8–4.3 (*m*, 1 H, MeNCH_2–C(2.1));

3.65 (*s*, MeO); 3.71 (*s*, MeO); 4.4–4.5 (*m*, 1 H, MeNC*H*$_2$–C(2.1)); 5.29 (*s*, PhC*H*$_2$); 6.7 (*s*, NH); 7.1–7.3 (*m*, NH); 7.34 (*s*, *Ph*CH$_2$).

{(2R)-2-[N-(Methoxycarbonylamino]-2-[(methylamino)methyl]butanoyl}alanine Methyl Ester (*Moc-(R)-Abu(CH$_2$NHMe)-Ala-OMe*; **11**). As described for **9**, with **10** (1.3 g, 3.8 mmol), EtOH (13 ml), and 10% Pd/C (130 mg): 874 mg (99%) of **11**. The slight green oil was used for the following coupling procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.70–0.90 (*m*, Me(4.1)); 1.2–1.4 (*m*, Me–C(3.2)); 1.7–2.4 (*m*, CH$_2$(3.1)); 2.6–2.9 (*m*, ^{1}H, MeNC*H*$_2$–C(2.1)); 2.9–3.0 (2*s*, MeN, rotamers); 3.3–3.5 (*m*, 1 H, MeNC*H*$_2$–C(2.1)); 3.63 (*s*, MeO); 3.72 (*s*, MeO); 4.4–4.5 (*m*, H–C(2.2)); 6.27 (br. *s*, NH); 6.25 (*s*, NH); 8.75 (br. *s*, NH).

{(2R)-3-[N-(Benzyloxycarbonyl)-N-methylamino]-2-[N-(methoxycarbonyl)amino]-2-methylpropanoyl}-phenylalanyl-phenylalanin Methyl Ester (*Moc-(R)-Aib(N(Z)Me)-Phe-Phe-OMe*; **12**). Coupling and workup according to *G.P.2*, with **2a** (404 mg, 1.50 mmol), Bop-Cl (380 mg, 1.50 mmol), Et(i-Pr)$_2$N (0.52 ml, 3.10 mmol), CH_2Cl_2 (8 ml), H-Phe-Phe-OMe·HCl (640 mg, 1.76 mmol), Et(i-Pr)$_2$N (0.30 ml, 1.80 mmol), and CH_2Cl_2 (5.2 ml): **12** (800 mg, 85%). Colorless foam. $[\alpha]_D^{r.t.} = +36.5$ ($c = 1.00$, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23–1.64 (3*s*, Me–C(2.1), rotamers); 2.82 (*s*, MeN); 2.92–3.08 (*m*, CH$_2$–C(2.3), CH$_2$–C(2.2)); 3.46–3.72 (*m*, 2 MeO, 2 H–C(3.1)); 4.55–4.58 (*m*, H–C(2.3) or H–C(2.2)); 4.70–4.72 (*m*, H–C(2.3) or H–C(2.2)); 5.13–5.18 (br. *s*, PhC*H*$_2$); 6.40–6.50 (*s*, NH); 6.96–7.05 (*m*, 2 NH); 7.17–7.36 (*m*, arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$); 20.28 (Me); 37.48 (Me); 37.56 (CH$_2$); 37.74 (CH$_2$); 52.21 (2 Me); 54.80 (CH); 56.84 (CH); 57.13 (CH$_2$); 62.24 (C); 67.97 (CH$_2$); 126.98 (CH); 127.91 (CH); 128.05 (CH); 128.22 (CH); 128.52 (CH); 128.63 (CH); 129.12 (CH); 135.35 (C); 136.15 (C); 136.66 (C); 156.22 (C); 158.90 (C); 170.19 (C); 171.40 (C); 172.37 (C). FAB-MS: 633.3 (25.1, $[M + H]^+$), 454.2 (14.7), 307.1 (24.6), 180.1 (11.1), 154.0 (12.1), 136.0 (11.8), 134.1 (17.7), 120.0 (33.5), 92.0 (100.0).

{(2R)-2-[N-(Methoxycarbonyl)amino]-2-methyl-3-(methylamino)propanoyl}-phenylalanyl-phenylalanin Methyl Ester (*Moc-(R)-Aib(NHMe)-Phe-Phe-OMe*; **13**). As described for **9**, with **12** (780 mg, 1.24 mmol), EtOH (5 ml), and 10% Pd/C (50 mg): 615 mg (99%) of **13**. The oil was used for the following coupling procedure without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.54 (*s*, Me–C(2.1)); 2.22 (*s*, MeN); 2.90–3.14 (*m*, CH$_2$–C(2.3), CH$_2$–C(2.2)); 3.59–3.70 (2*s*, 2 MeO); 4.61–4.82 (*m*, H–C(2.3), H–C(2.2)); 5.95 (*s*, NH); 6.61–6.64 (*d*, $J = 7.0$, NH); 6.94–7.18 (*m*, NH); 7.20–7.37 (*m*, arom. H); 8.07–8.10 (*m*, NH).

N-(tert-Butoxycarbonyl)-alanyl-leucine Methyl Ester (*Boc-Ala-Leu-OMe*; **14**). Coupling and workup according to *G.P.1*, with Boc-Ala-OH (3 g, 15.9 mmol), NMM (1.55 ml, 16.5 mmol), THF (80 ml), isobutyl chloroformate (2.07 ml, 15.9 mmol), H-Leu-OMe·HCl (3 g, 16.5 mmol), NMM (1.55 ml, 16.5 mmol), and DMF (30 ml). The resulting oil was purified by FC (AcOEt/hexane 1:1): **14** (4.25 g, 85%). Colorless solid. M.p. 66°. $[\alpha]_D^{r.t.} = -54.4$ ($c = 1.1$, MeOH). IR (KBr): 3320*s*, 2980*m*, 2960*m*, 2940*m*, 2870*w*, 1760*s*, 1750*s*, 1630*s*, 1610*s*, 1535*s*, 1510*s*, 1455*m*, 1390*m*, 1370*s*, 1340*w*, 1310*w*, 1285*m*, 1275*m*, 1255*m*, 1220*m*, 1200*m*, 1160*s*, 1070*w*, 1005*m*, 855*w*, 790*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95 (*d*, $J = 5.7$, 2 Me–C(4.2)); 1.36 (*d*, $J = 6.9$, Me(3.1)); 1.45 (*s*, *t*-Bu); 1.5–1.7 (*m*, CH$_2$(3.2), CH(4.2)); 3.73 (*s*, MeO); 4.18 (*m*, CH(2.2)); 4.59 (*m*, CH(2.1)); 5.05 (*d*, $J = 6.9$, NHCOO); 6.59 (*d*, $J = 6.6$, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.92 (Me); 21.82 (Me); 22.85 (Me); 24.76 (CH); 28.29 (Me); 41.53 (CH$_2$); 49.92 (CH); 50.68 (CH); 52.28 (Me); 80.14 (C); 155.55 (C); 172.43 (C); 173.25 (C). FAB-MS: 318.1 (12.24), 317.1 (53.73, $[M + H]^+$), 262.1 (22.56), 261.1 (100), 229.1 (12.81), 218.1 (11.96), 217.1 (65.38), 201.1 (17.16), 146.1 (45.74), 144.1 (14.18), 87.9 (24.86), 86.0 (72.79), 56.9 (60.98).

Alanyl-leucine Methyl Ester Hydrochloride (*H-Ala-Leu-OMe·HCl*; **15**·HCl). A soln. of **14** (3.75 g, 11.86 mmol) in 3 ml of an Et$_2$O soln. sat. with HCl was stirred at r.t. for 2 h and then evaporated: 2.95 g (99%) of **15**·HCl. Colorless powder. M.p. 62°. $[\alpha]_D^{r.t.} = -25.8$ ($c = 1.0$, MeOH). IR (KBr): 3500–2500 (br.), 1740*s*, 1680*s*, 1555*s*, 1500*m*, 1470*m*, 1440*m*, 1390*w*, 1370*w*, 1160*m*, 1125*m*. ^{1}H-NMR (300 MHz, CD_3OD): 0.9–1.0 (*m*, 2 Me–C(4.2)); 1.53 (*d*, $J = 6.9$, Me(3.1)); 1.6–1.8 (*m*, CH$_2$(3.2), CH(4.2)); 3.71 (*s*, MeO); 3.96 (*m*, CH(2.1)); 4.48 (*t*, $J = 7.2$, CH(2.2)). ^{13}C-NMR (75 MHz, CD_3OD): 17.64 (Me); 21.72 (Me); 23.29 (Me); 25.96 (CH); 41.24 (CH$_2$); 50.11 (CH); 52.31 (CH); 52.80 (Me); 171.27 (C); 174.19 (C). FAB-MS: 649.2 (13.55, $[3(M - HCl) + H]^+$), 434.1 (15.27), 433.1 (48.83, $[2(M - HCl) + H]^+$), 218.1 (23.30), 217.1 (100, $[(M - HCl) + H]^+$), 146.1 (44.70), 85.9 (25.21).

N-(tert-Butoxycarbonyl)-valyl-alanyl-leucine Methyl Ester (*Boc-Val-Ala-Leu-OMe*; **16**). Coupling and workup according to *G.P.3* with Boc-Val-OH (1.736 g, 8 mmol), H-Ala-Leu-OMe·HCl (2.016 g, 8 mmol), HOBt (1.224 g, 8 mmol), NMM (0.76 ml, 8 mmol), THF (10 ml), and DCC (1.691 g). The crude peptide was purified by FC (AcOEt/hexane 1:1): **16** (2.79 g, 84%). Colorless solid. M.p. 157°. $[\alpha]_D^{r.t.} = -68.1$ ($c = 1.1$, MeOH). IR (KBr): 3310*s*, 2970*m*, 2930*w*, 2870*w*, 1745*s*, 1700*s*, 1675*s*, 1640*s*, 1530*s*, 1450*m*, 1430*w*, 1390*m*, 1365*m*, 1335*w*, 1285*m*, 1245*s*, 1220*s*, 1170*s*, 1090*w*, 1040*w*, 1015*w*, 680*m*. ^{1}H-NMR (300 MHz, CD_3OD): 0.9–1.0 (*m*, 2 Me–C(4.3), 2 Me–C(3.1)); 1.35 (*d*, $J = 7.2$, Me(3.2)); 1.44 (*s*, *t*-Bu); 1.5–1.8 (*m*, CH$_2$(3.3), CH(4.3)); 1.8–2.2 (*m*, CH(3.1)); 3.69 (*s*, MeO); 3.7–3.9 (*m*, CH(2.3)); 4.38–4.46 (*m*, CH(2.2), CH(2.1)). ^{13}C-NMR (75 MHz, CD_3OD): 18.22 (Me); 18.34

(Me); 19.78 (Me); 21.84 (Me); 23.34 (Me); 25.86 (CH); 28.74 (Me); 32.14 (CH); 41.50 (CH_2); 49.98 (CH); 52.08 (CH); 52.67 (CH); 61.29 (CH); 80.60 (C); 158.04 (C); 174.06 (C); 174.51 (C); 174.80 (C). FAB-MS: 831.5 (17.21, $[2M + H]^+$), 417.3 (24.45), 416.3 (82.88, $[M + H]^+$), 361.2 (15.15), 360.2 (64.95), 316.2 (18.25), 217.2 (35.98), 215.1 (28.63), 171.2 (19.87), 146.2 (100), 116.1 (21.92), 86.0 (68.63), 72.0 (56.68), 56.9 (55.10), 54.9 (14.29).

Valyl-alanyl-leucine Methyl Ester (*H-Val-Ala-Leu-OMe*; **17**). A soln. of **16** (1 g, 2.4 mmol) in CH_2Cl_2 (16 ml) was treated with CF_3COOH (3 ml, 7.2 mmol) and stirred at r.t. for 3 h. The mixture was evaporated, the resulting oil taken up in AcOEt and washed with sat. aq. $NaHCO_3$ soln., the aq. layer additionally extracted twice with AcOEt and the combined org. layer dried ($MgSO_4$) and evaporated: 730 mg (97%) of **17**. Colorless solid. M.p. 97°. $[\alpha]_D^{r.t.} = -75.1$ ($c = 0.71$, $CHCl_3$). IR ($CHCl_3$): 3430*m*, 3350*m*, 3000*w*, 2975*m*, 2890*w*, 1750*s*, 1690*s*, 1660*s*, 1510*s*, 1490*m*, 1460*m*, 1380*m*, 1285*w*, 1270*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83 (*d*, $J = 6.9$, Me–C(4.3) or Me–C(3.1)); 0.88–0.93 (*m*, Me–C(4.3) or Me–C(3.1)); 0.99 (*d*, $J = 7.0$, Me–C(4.3) or Me–C(3.1)); 1.39 (*d*, $J = 7.0$, Me–C(2.2)); 1.50–1.76 (*m*, CH_2–C(2.3), CH–C(3.3), NH_2); 2.2–2.4 (*m*, CH–C(2.1)); 3.25 (*d*, $J = 3.8$, CH–C(1.2)); 3.73 (*s*, MeO); 4.5–4.65 (*m*, 2 H–C(α)); 6.96 (*d*, $J = 7.8$, NH); 7.84 (*d*, $J = 7.7$, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 16.09 (Me); 18.03 (Me); 19.62 (Me); 21.92 (Me); 22.76 (Me); 24.86 (CH); 30.95 (CH); 41.24 (CH_2); 48.36 (CH); 50.92 (CH); 52.25 (Me); 60.04 (CH); 172.18 (C); 173.22 (C); 174.51 (C). FAB-MS: 317.2 (16.37), 316.2 (69.01, $[M + H]^+$), 217.1 (46.31), 171.1 (32.40), 146.1 (56.54), 143.1 (16.85), 86.0 (34.25), 71.9 (100), 69.9 (12.33), 54.9 (16.08).

N-(tert-*Butoxycarbonyl*)-*valyl-alanyl-leucine* (*Boc-Val-Ala-Leu-OH*; **18**). To a soln. of **16** (1 g, 2.4 mmol) in MeOH (8 ml), 1N NaOH (5 ml) was added and the mixture stirred for 4 h at r.t. The soln. was neutralized with 1N HCl (5 ml) and evaporated. The resulting oil was acidified with 1N HCl to pH 2 and extracted with AcOEt and the combined extract washed with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated: 935 mg (97%) of **18**. Colorless foam. $[\alpha]_D^{r.t.} = -46.9$ ($c = 1.05$, MeOH). IR ($CHCl_3$): 3300*m*, 3220*m*, 2875*w*, 2840*m*, 2820*w*, 1670*s*, 1615*s*, 1450*s*, 1410*w*, 1325*s*, 1115*s*, 960*m*, 820*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.7–0.95 (*m*, Me(Val), Me(Leu)); 1.36 (*d*, $J = 6.9$, Me–C(2.2)); 1.43 (*s*, *t*-Bu); 1.55–1.80 (*m*, CH_2–C(2.3), CH–C(3.3)); 2.0–2.2 (*m*, CH–C(2.1)); 3.95–4.10 (*m*, H–C(α)); 4.45–4.55 (*m*, H–C(α)); 4.55–4.65 (*m*, H–C(α)); 5.43 (*d*, $J = 7.8$, NHCOO); 6.5–7.3 (br. *s*, COOH); 7.29 (*d*, $J = 7.8$, NH); 7.46 (*d*, $J = 6.8$, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.81, 18.30 (Me, rotamers); 19.21 (Me); 20.65 (Me); 21.81 (Me); 22.85 (Me); 24.83 (CH); 28.33 (Me); 31.13 (CH); 40.95 (CH_2); 48.82 (CH); 51.11 (CH); 59.85 (CH); 80.23 (C); 156.16 (C); 172.04 (C); 172.59 (C); 175.36 (C). FAB-MS: 703.4 (22.49), 424.2 (29.11, $[M + Na]^+$), 403.2 (13.64), 402.2 (51.46, $[M + H]^+$), 347.2 (16.08), 346.2 (68.36), 303.1 (15.04), 302.1 (61.91), 271.1 (10.88), 215.1 (60.67), 203.1 (52.59), 171.1 (45.13), 143.1 (18.09), 132.1 (62.12), 116.0 (31.52), 98.0 (14.02), 86.0 (81.42), 71.9 (100), 56.9 (82.09).

{(2R)-3-[N-(*Benzyloxycarbonyl*)-N-*methylamino*]-2-[N-(*methoxycarbonyl*)*amino*]-2-*methylpropanoyl*}-*valyl-alanyl-leucine Methyl Ester* (*Moc-(R)-Aib(N(Z)Me)-Val-Ala-Leu-OMe*; **19**). Coupling and workup according to *G.P.3* with **2a** (80 mg, 0.25 mmol), **17** (85 mg, 0.27 mmol), HOBt (38 mg, 0.25 mmol), CH_2Cl_2 (4 ml), and DCC (51.5 mg, 0.25 mmol). The crude peptide was purified by FC (AcOEt/hexane 4:1): **19** (143 mg, 93%). Colorless solid. M.p. 146°. $[\alpha]_D^{r.t.} = +10.4$ ($c = 0.985$, MeOH). IR (KBr): 3320*s*, 3060*w*, 3030*w*, 2960*s*, 2870*w*, 1730*s*, 1705*s*, 1680*s*, 1640*s*, 1520*s*, 1455*s*, 1400*m*, 1370*m*, 1315*m*, 1260*s*, 1210*s*, 1170*s*, 1080*s*, 1030*w*, 870*w*, 770*w*, 700*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92 (*s*, Me); 0.94 (*s*, Me); 0.98 (*d*, $J = 6.8$, Me); 1.36 (*d*, $J = 7.0$, MeC(2.3)); 1.56 (*s*, Me–C(2.1)); 1.60–1.65 (*m*, CH–C(3.4)); 1.92 (*s*, CH); 2.2–2.4 (br. *m*, CH–C(2.2)); 2.91 (*s*, MeN); 3.64 (*s*, MeO); 3.72 (*s*, MeO); 3.5–3.7 (br. *m*, H–C(3.1), rotamers); 3.8–3.9 (br. *m*, H–C(3.1), rotamers); 4.20–4.24 (*m*, H–C(α)); 4.45–4.58 (*m*, 2 H–C(α)); 5.0–5.25 (*m*, PhCH_2, rotamers); 5.71 (br. *s*, NH, rotamers); 6.72 (*d*, $J = 7.6$, NH); 6.93 (*s*, NHCOO); 6.8–7.0 (br. 2*s*, NH); 7.3–7.4 (*s*, arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.29 (Me); 17.46 (Me); 19.39 (Me); 20.94 (Me); 21.79 (Me); 22.79 (Me); 24.73 (CH); 29.46, 30.28 (CH, rotamers); 37.48 (Me); 41.24 (CH_2); 48.81 (CH); 50.85 (CH); 52.24, 52.49, 52.62 (2 Me, rotamers); 56.97 (CH_2); 59.17 (CH); 62.18 (C); 67.98 (CH_2); 127.93 (CH); 128.22 (CH); 128.55 (CH); 136.18 (C); 156.44 (C); 158.84 (C); 170.63 (C); 171.83 (C); 172.95 (C); 173.05 (C). FAB-MS: 644.2 (15.40, $[M + Na]^+$), 622.2 (19.90, $[M + H]^+$), 488.2 (21.45), 477.1 (15.01), 406.1 (28.96), 307.1 (34.91), 217.2 (12.51), 146.1 (13.62), 145.1 (12.48), 341.1 (13.91), 91.0 (100), 86.0 (13.41), 72.0 (37.17).

{(2R)-2-[N-(*Methoxycarbonyl*)*amino*]-2-*methyl*-3-(*methylamino*)*propanoyl*}-*valyl-alanyl-leucine Methyl Ester* (*Moc-(R)-Aib(NHMe)-Val-Ala-Leu-OMe*; **20**). As described for **9**, with **19** (366 mg, 0.58 mmol), EtOH (7 ml), and 10% Pd/C (40 mg): 279 mg (99%) of colorless **20**. M.p. 67–68°. $[\alpha]_D^{r.t.} = -49.2$ ($c = 0.9$, MeOH). IR (KBr): 3310*s*, 3070*w*, 2960*s*, 2880*m*, 1730*s*, 1645*s*, 1540*s*, 1450*m*, 1385*w*, 1370*w*, 1255*s*, 1210*w*, 1170*m*, 1100*w*, 1080*m*, 780*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91–0.95 (*m*, Me–C(4.4), Me–C(3.2)); 0.98 (*d*, $J = 6.8$, Me–C(4.4) or Me–C(3.2)); 1.38 (*d*, $J = 7.1$, Me–C(2.3)); 1.56 (*s*, Me–C(2.1)); 1.57–1.59 (*m*, CH_2–C(2.4), CH–C(3.4)); 1.76 (br. *s*, NH); 2.2–2.4 (*m*, CH–C(2.2)); 2.45 (*s*, MeN); 2.72 (*d*, $J = 12.2$, CH–C(2.1)); 3.18 (*d*, $J = 12.2$, CH–C(2.1)); 3.64 (*s*, MeO); 3.71 (*s*, MeO); 4.22–4.26 (*m*, H–C(α)); 4.49–4.57 (*m*, 2 H–C(α)); 6.10 (*s*, NHCOO); 6.82 (*d*,

J = 8.1, NH); 7.12 (*d*, J = 7.6, NH); 8.11–8.13 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.35, 17.57 (Me, rotamers); 17.82 (Me); 19.41, 19.52 (Me, rotamers); 21.75 (Me); 21.84 (Me); 22.79 (Me); 24.76 (CH); 29.88 (CH); 36.81 (Me); 41.15 (CH_2); 48.62, 48.75 (CH, rotamers); 50.91 (CH); 52.18 (Me); 52.25 (Me); 57.38 (CH_2); 58.64 (CH); 59.02, 59.17 (C, rotamers); 156.42 (C); 170.95 (C); 172.07 (C); 173.12 (C); 174.67 (C). FAB-MS: 516.7 (10.23), 500.5 (26.36), 489.5 (37.65), 488.5 (100, $[M + H]^+$), 244.3 (11.38), 157.2 (11.20), 146.2 (11.16), 145.2 (13.35), 72.0 (61.05).

{(2R)-3-N-[Valyl-alanyl-leucyl]-2-amino-2-methyl-3-(methylamino)propanoyl}-valyl-alanyl-leucine Trifluoroacetate (H-Val-Ala-Leu-(R)-Aib(NMe)-Val-Ala-Leu-OH·CF$_3$COOH; **21**). A soln. of **7** (188 mg, 0.208 mmol) in CH_2Cl_2 (8 ml) and Me_3SiI (0.209 ml, 1.535 mmol) was stirred for 8 h at r.t. and then evaporated. The resulting oil was taken up in MeOH (1.5 ml) and 1N NaOH (1.664 ml) and stirred for 12 h. After evaporation, the crude peptide was purified by reversed-phase HPLC (11% MeCN, 0.1% CF_3COOH, 89% H_2O): **21** (79 mg, 54%). Colorless salt. M.p. 102–104°. $[\alpha]_D^{r.t.} = -115.3$ (c = 0.505, MeOH). CD: $-5.27 \cdot 10^4$ (203.0), $-2.34 \cdot 10^4$ (238.0). ^{1}H-NMR (400 MHz, D_2O): 0.87 (*d*, J = 6.2, Me(Val) or Me(Leu)); 0.91–1.02 (*m*, Me(Val), Me(Leu)); 1.37 (*d*, J = 7.2, Me–C(2.6)); 1.40 (*d*, J = 7.2, Me–C(2.2)); 1.63 (*s*, Me–C(2.4)); 1.7–1.8 (*m*, H–C(4.7)); 1.8–1.9 (*m*, H–C(4.3)); 2.0–2.1 (*m*, H–C(3.5)); 2.1–2.2 (*m*, H–C(3.1)); 3.18 (*s*, MeN); 3.79 (*d*, J = 5.8, H–C(2.1)); 3.97 (*d*, J = 12.4, H–C(3.4)); 4.11 (*d*, J = 7.8, H–C(2.5)); 4.21 (*d*, J = 12.4, H–C(3.4)); 4.3–4.4 (*m*, H–C(2.6), H–C(2.7)); 4.40 (*q*, J = 7.1, H–C(2.2)); 4.7–4.8 (*m*, H–C(2.3)). ^{13}C-NMR (100 MHz, D_2O): 19.03 (Me); 19.07 (Me); 19.39 (Me); 20.23 (Me); 20.60 (Me); 20.97 (Me); 23.06 (Me); 23.17 (Me); 24.67 (Me); 24.84 (Me); 26.50 (Me); 26.79 (CH); 27.04 (CH); 32.67 (CH); 33.03 (CH); 35.50 (CH); 40.96 (CH_2); 41.89 (CH_2); 47.24 (CH); 51.97 (CH); 52.03 (CH); 54.01 (CH); 60.86 (CH); 62.25 (CH); 64.56 (CH_2); 67.16 (C); 118.99 (*q*, J = 291.8, CF_3); 165.64 (*q*, J = 35.7, CF_3COOH); 170.71 (C); 171.67 (C); 175.07 (C); 175.26 (C); 177.24 (C); 177.35 (C); 179.01 (C). FAB-MS: 683.6 (12.38), 682.6 (42.37), 681.5 (100, $[M - H_2O + H]^+$), 496.4 (18.60), 452.3 (29.53), 451.35 (26.14), 352.3 (30.15), 222.2 (11.90), 196.2 (12.00), 167.2 (18.32), 166.2 (13.60), 165.1 (52.47), 124.1 (20.95), 123.1 (70.35), 112.1 (12.03), 111.0 (17.02), 110.0 (18.10), 109.0 (40.07), 98.0 (30.65), 97.0 (54.18), 96.00 (12.96), 86.00 (53.75), 71.95 (68.35), 69.9 (48.69), 68.9 (39.08), 67.9 (21.26), 56.9 (15.09), 55.9 (17.21), 54.9 (20.28).

{(2R)-2-N-[Valyl-alanyl-leucyl]-2-amino-2-methyl-3-(methylamino)propanoyl}-valyl-alanyl-leucine Trifluoroacetate (H-Val-Ala-Leu-(R)-Aib(NHMe)-Val-Ala-Leu-OH·CF$_3$COOH; **22**). As a by-product in the deprotecting procedure, **22** (32 mg, 22%) was obtained after reversed-phase HPLC (11% MeCN, 0.1% CF_3COOH, 89% H_2O). ^{1}H-NMR (500 MHz, D_2O): 0.83–0.99 (*m*, 4 Me(Val), 4 Me(Leu)); 1.33–1.36 (*m*, 2 Me(Ala)); 1.5–1.75 (*m*, 4–C(β)(Leu), 2 H–C(γ)(Leu)); 1.62 (*s*, Me–C(2.4)); 2.02–2.07 (*m*, CH(Val)); 2.14–2.20 (*m*, CH(Val)); 2.71, 2.81, 2.96, 3.11, 3.15 (5*s*, MeN, rotamers); 3.35–3.50 (*m*, H–C(2.1)); 3.69 (*d*, J = 15.2, H–C(3.4)); 3.75–3.77 (*m*, H–C(α)(Ala)); 3.99 (*d*, J = 8.1, H–C(2.5)); 4.08 (*d*, J = 15.2, H–C(3.4)); 4.20–4.35 (*m*, H–C(α)(Ala), H–C(2.7)); 4.37–4.41 (*m*, H–C(α)(Ala)); 4.7–4.8 (*m*, H–C(2.3)). ^{13}C-NMR (125 MHz, D_2O): 19.10 (Me); 19.11 (Me); 19.52 (Me); 20.24 (Me); 20.97 (Me); 21.36 (Me); 22.27 (Me); 22.93 (Me); 23.19 (Me); 24.86 (Me); 25.16 (Me); 27.02 (CH); ; 27.08 (CH); 32.37, 32.67 (CH, rotamers); 33.05 (CH); 40.22 (Me); 41.62 (CH_2); 41.97 (CH_2); 51.71 (CH); 52.02 (CH); 52.07 (CH); 54.21 (CH); 57.25 (CH_2); 60.99 (CH); 63.49 (CH); 63.59 (C); 171.52 (C); 173.23 (C); 175.37 (C); 176.82 (C); 177.19 (C); 178.83 (C); 179.27 (C). FAB-MS: 699.4 (23.6, $[M + H]^+$), 699.1 (18.58), 681.2 (12.17), 572.2 (10.04), 416.1 (12.67), 171.1 (30.22), 170.1 (12.05), 143.1 (15.16), 142.1 (12.18), 141.1 (13.15), 127.1 (11.04), 126.01 (10.43), 123.1 (14.43), 115.0 (11.83), 112.0 (10.70), 99.0 (13.84), 98.0 (29.56), 97.0 (15.49), 87.0 (55.44), 86.0 (89.53), 72.0 (100), 70.0 (30.24), 69.0 (33.38), 56.9 (33.38), 55.9 (22.14), 54.9 (39.36).

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