2. Synthesis of Peptides Containing α,α-Disubstituted α-Amino Acids by the Azirine/Oxazolone Method: The (12–20)-Nonapeptide of the Ionophore Alamethicin

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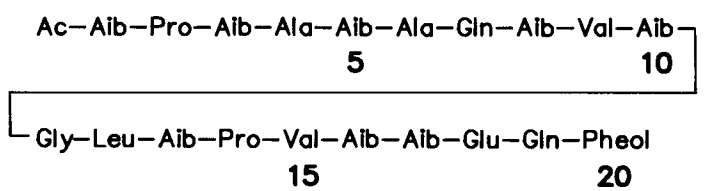
The (12–20)-nonapeptide Z-Leu-Aib-Pro-Val-Aib-Aib-Glu (OBzl)-Gln-Pheol (**10**) of the ionophor alamethicin was synthesized by a new strategy, using 3-amino-2,2-dimethyl-2*H*-azirines **2** as synthons for the α-aminoisobutyric acid (Aib) moieties.

1. Introduction. – In 1967, *Meyer* and *Reusser* isolated the peptide antibiotic alamethicin from the culture medium of a strain of the fungus *Trichoderma viride* [1]. Since the discovery of their unique membrane-modifying properties [2], considerable attention has been focused on alamethicin and its analogues [3–5]. The high content of non-proteinogenic α,α-disubstituted amino acids (up to 50% Aib; Iva), a *C*-terminal amino alcohol and a *N*-terminal acetyl group is characteristic of this new class of amphiphilic polypeptide ionophores and antibiotics, the so-called peptaibols [6] *(Table)*.

Table. *Some Members of the Peptaibol Family*

	Number of amino acids		C-Terminal amino alcohol
	total	α,α-disubstituted	
Alamethicin F30 [3]	20	8	Pheol
Suzukacillin A [7]	20	9	Pheol
Trichotoxin A40 [3] [8]	18	9	Valol
Emerimicin IV [9]	15	6	Pheol
Antiamöbin [10]	16	8	Pheol
Hypelcin A [11]	20	10	Leuol
Paracelsin A [12]	20	9	Pheol
Trichorzianin A IIIc [13]	19	8	Trpol



Alamethicin (Pheol = phenylalaninol)

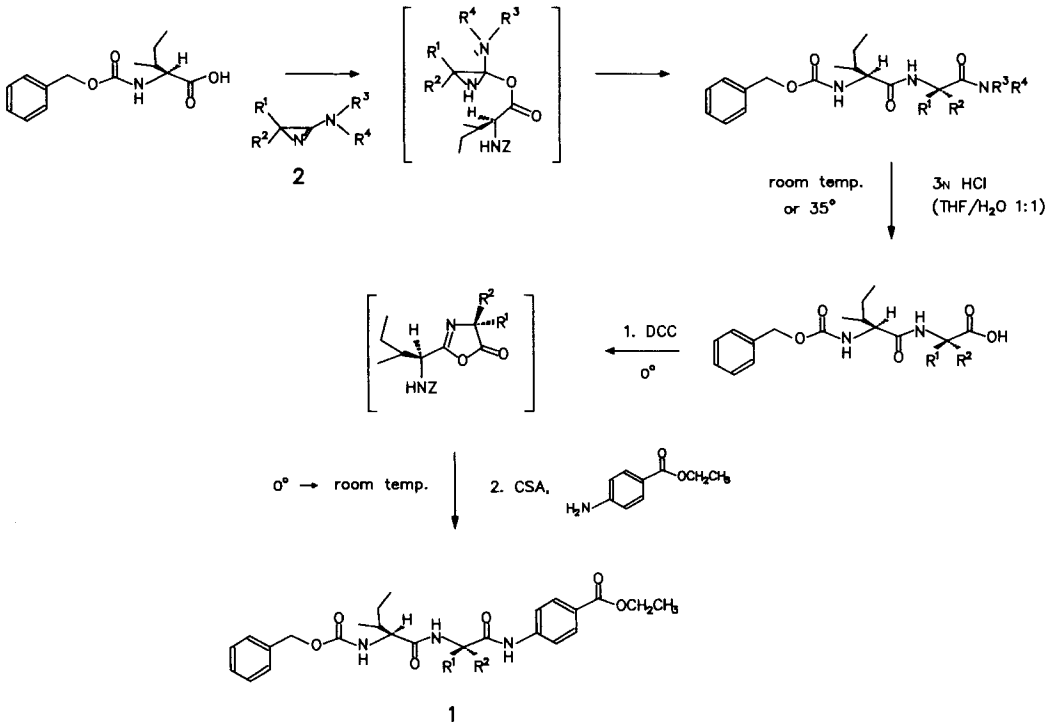
[1]) Part of the Ph.D. thesis of *P. W.*, University of Zürich, 1987. Current address: University of Virginia, Department of Chemistry, Charlottesville, VA 22901, USA.

Beside the peptaibol sequences, peptides containing α,α-disubstituted α-amino acids are currently the object of extensive studies because of their extraordinary stereochemical properties [14–19]: The presence of disubstitution at C(α) induces a significant constraint on the conformational freedom and offers the possibility to stabilize selectively certain secondary structures in oligopeptide segments [20] [21]. Thus, such modifications may become an important tool not only for the elucidation of structure/activity relationships but also for the construction of artificial proteins (see, *e.g.*, [22]).

However, the considerable steric hindrance of α,α-disubstituted α-amino acids complicates their use in synthesis because coupling yields of conventional procedures are usually low, and racemization can become a serious side reaction [23–25]. Lately, the advantages of the azirine/oxazolone method [25–29] over conventional procedures have been demonstrated in the synthesis of tripeptides **1** [20] [27] *(Scheme 1)* and tetrapeptides [28].

This new method for the insertion of α,α-disubstituted α-amino acids into peptide chains was developed in the course of studies on the use of 3-amino-2*H*-azirines **2** as reactive synthons [29]. After the coupling of *N*-terminal-protected peptides or amino acids with 3-amino-2*H*-azirines and selective hydrolysis of the *C*-terminal amide bond [23], the peptide chain is lengthened by the condensation with amino components *via in situ* generated oxazol-5(4*H*)-ones and additives like camphor-10-sulfonic acid (=(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid, CSA), benzotriazol-

Scheme 1. *Synthesis of Tripeptides* **1** *by the Azirine/Oxazolone Method*



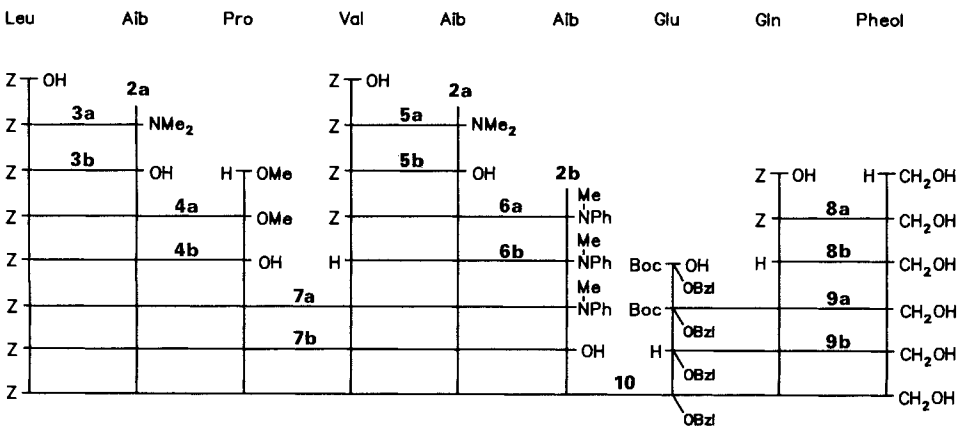
1-ol (HOBt), $ZnCl_2$, or $CuCl_2$ [25]. The reaction conditions are especially mild; condensations and hydrolysis occur between 0 and 35° and usually yield pure products without need of chromatographic separations. The function of the amino azirine is that of a N-activated amino acid synthon, and no additional activation of the carboxy component is necessary. The new peptide bond is formed in an intramolecular rearrangement, and so the degree of racemization is extremely low (in fact no racemized or epimerized products have ever been detected).

2. Results and Discussions. – With the synthetic approach for the protected alamethicin-(12–20)-nonapeptide Z-Leu-Aib-Pro-Val-Aib-Aib-Glu(OBzl)-Gln-Pheol (**10**; see *Scheme 2*), we intended to test the ability of the azirine/oxazolone method for the generation of longer peptide sequences and to develop strategies for the total synthesis of other peptaibols[2]). It turned out to be a good choice; the same nonapeptide was also used by *Jung* and *Schmitt* as a main segment in their total synthesis of alamethicin and thus allowed a direct comparison with conventional procedures; moreover, a lot of spectroscopic data are available [31]. The nonapeptide **10** was shown by X-ray analysis to adopt in the crystal almost the same helical structure as when it is an integrated part of alamethicin [32].

The synthetic route to this segment **10**, based on the azirine/oxazolone method, is outlined in *Scheme 2*.

Reaction of Z-leucine and 3-(dimethylamino)-2,2-dimethyl-2*H*-azirine (**2a**; → **3a**) followed by selective hydrolysis of the C-terminal disubstituted amide group in 3N HCl (THF/H_2O 1:1) at 35° led to acid **3b** (Z-Leu-Aib) in 98% yield. The corresponding oxazol-5(4*H*)-one, formed by addition of dicyclohexylcarbodiimide (DCC) to an ice-cooled solution of **3b** in DMF, was coupled *in situ* with Pro-OMe using HOBt catalysis (→ **4a**). Saponification of methyl ester **4a** (Z-Leu-Aib-Pro-OMe) in 1N NaOH/MeOH 3:7

Scheme 2. *Synthesis of* **10**, *the Sequence 12–20 of Alamethicin*



[2]) Alamethicin is still the only synthesized member of the peptaibol family. For the latest, well documented total synthesis, based on a conventional approach, see [30].

yielded 91% of the *C*-terminal-deprotected segment **4b** (Z-Leu-Aib-Pro). The acid hydrolysis of the corresponding *tert*-butyl ester **4c** (see *Exper. Part*) yielded only 74% of the desired **4b** along with significant amounts of **3b** which resulted from the hydrolysis of the acid-labile Aib-Pro bond.

The dipeptide **5b** (Z-Val-Aib) was prepared in 95% yield by the reaction of **2a** and Z-Val (→ **5a**) and subsequent hydrolysis. The coupling of **5b** with 3-(*N*-methyl-*N*-phenylamino)-2,2-dimethyl-2*H*-azirine (**2b**) quantitatively led to the tripeptide **6a** (Z-Val-Aib-Aib-NMe(Ph)) and thus demonstrated particularly well the high reactivity of aminoazirines even towards sterically hindered residues. A total segment yield of 95% stands here against a 38% yield in the conventional synthesis [30]!

After hydrogenolysis of **6a** (→ **6b**) and condensation with **4b** (*via* the mixed anhydride of **4b** and isobutyl chloroformate using *Anderson*'s conditions [33]), the hexapeptide **7a** (Z-Leu-Aib-Pro-Val-Aib-Aib-NMe(Ph)) was isolated in 74% yield. Besides three Aib residues, this segment contained again an especially sensitive Aib-Pro bond that can be easily hydrolyzed under acidic conditions [34]. However, the deprotection of the C-terminus succeeded very selectively and gave **7b** (Z-Leu-Aib-Pro-Val-Aib-Aib) in 93% yield. It is indeed noteworthy that in this sequence with six more or less labile amide bonds such a high selectivity of cleavage is achieved. This result can only be explained with the extremely mild hydrolysis of *N*-methylanilides [26] (3N HCl (H_2O/THF 1:1), 3 h, room temperature)[3]). Aminoazirines thus provide not only the backbone of α,α-disubstituted α-amino acids but also a new kind of carboxy-protecting group that is easier to handle than benzyl and methyl esters which are sometimes difficult to remove [30].

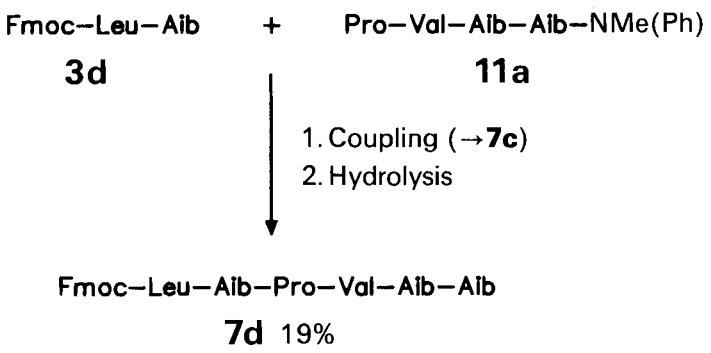
The tripeptide **9a** (Boc-Glu(OBzl)-Gln-Pheol) containing the *C*-terminal amino alcohol Pheol was prepared in 73% yield using standard procedures (mixed-anhydride coupling; Z-Gln + Pheol → **8a** → **8b** → **9a**). Dissolving **9a** in 1.5N HCl (Et_2O/CH_2Cl_2 1:1) cleanly removed the Boc group (→ **9b**), whereas deprotection with CF_3COOH led to formation of side products.

For the final segment coupling, the carboxy component Z-Leu-Aib-Pro-Val-Aib-Aib (**7b**) was cyclized to the corresponding oxazol-5(4*H*)-one by addition of *N*-cyclohexyl-*N'*-[2-(4-methylmorpholin-4-ylio)ethyl] carbodiimide 4-toluenesulfonate (= 4-{2-{[(cyclohexylimino)methylidene]amino}ethyl}-4-methylmorpholin-4-ium *p*-toluenesulfonate; CME-CDI), reacted *in situ* with **9b**/HOBt, and after 20 h at 0° to room temperature, the target nonapeptide **10** was isolated by column chromatography in 65% yield. The structure of **10** was proven by 2D-NMR and comparison of the ^{13}C-NMR signals with published data [31].

In the synthesis of the *N*-[(fluoren-9-yl)methoxycarbonyl]-protected (Fmoc) hexapeptide Fmoc-Leu-Aib-Pro-Val-Aib-Aib-NMe(Ph) (**7c**), the condensation of Fmoc-Leu-Aib (**3d**; from Fmoc-Leu and **2a** *via* **3c** (see *Exper. Part*)) and **11a** led to a mixture of products *(Scheme 3)*. After hydrolysis, only 19% of **7d** (Fmoc-Leu-Aib-Pro-Val-Aib-Aib) could be isolated by chromatography. The presumed reason for this poor yield is the partial cleavage of the Fmoc protective group by the amino component on segment condensation with longer peptides where the coupling speed is relatively low [35]. In the

[3]) In general, higher temperatures and longer reaction times (typically *ca.* 35° and 20 h) are needed for the hydrolysis of the corresponding *N,N*-dimethylamides.

Scheme 3



condensation of Fmoc-Val-Aib-Aib (**6c**) or Fmoc-Pro-Val-Aib-Aib (**11b**) with **9b**, the same side reaction also led to complex mixtures that were not analyzed in detail. The use of the Fmoc protective group in segment condensations is, therefore, not recommended, especially with sterically hindered acyl components or longer segments.

Several other related protected di-, tri-, and tetrapeptides are described in the *Exper. Part*: Fmoc-Leu-Aib-NMe_2 (**3c**), Fmoc-Val-Aib-NMe_2 (**5c**), Fmoc-Val-Aib (**5d**), Fmoc-Val-Aib-Aib-NMe_2 (**6c**), Fmoc-Val-Aib-Aib (**6d**), Z-Val-Aib-Aib-NMe_2 (**6e**), Val-Aib-Aib-NMe_2 (**6f**), Z-Pro-Val-Aib-Aib-NMe(Ph) (**11c**), Z-Pro-Val-Aib-Aib-NMe_2 (**11d**), Z-Pro-Val-Aib-Aib (**11e**), and Fmoc-Pro-Val-Aib-Aib-NMe_2 (**11f**).

3. Conclusion. – Using the azirine/oxazolone method, the target molecule Z-Leu-Aib-Pro-Val-Aib-Aib-Glu(Bzl)-Gln-Pheol (**10**), the sequence 12–20 of the peptide ionophore alamethicin, was synthesized in high yield (29%; *cf.* classical procedure, yield 12% [30]). In particular, it was demonstrated that the synthetic strategy based on the use of aminoazirines can be successfully applied to the straightforward preparation of important peptaibol segments. This method is not limited to Aib residues but works as well with many other α,α-disubstituted α-amino acids and will certainly hasten their use as important building blocks for chemical synthesis of oligo- and polypeptide sequences with extraordinary properties.

Our thanks are due to the analytical services of our institute, especially to Mr. *H. Frohofer* for elemental analyses, Mrs. *E. Patterson-Vykoukal* for running IR spectra, Dr. *R. W. Kunz*, Dr. *U. Piantini*, and Mr. *M. Hofer* for NMR spectra, and Mrs. Dr. *A. Lorenzi* and Mr. *N. Bild* for mass spectra. Financial support by the *Swiss National Science Foundation* and by *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged.

Experimental Part

General. See also [25]. Solvents and liquid reagents were purified by distillation or drying shortly before use. Flash chromatography (FC) [36]: silica gel *Merck 60*, 0.040–0.063 mm. M.p.: uncorrected. $[\alpha]_D$ Values: *Zeiss-LEP-A_2* spectrometer; at 20–22°. IR spectra (cm^{-1}): in KBr; *Perkin-Elmer-297* or *Perkin-Elmer-781* instrument. ^{1}H-NMR spectra: in CD_3OD; *Varian-XL-200* and *Bruker-AM-400* spectrometers; chemical shifts in ppm rel. to internal *TMS* (=*0* ppm), coupling constants *J* in Hz. ^{13}C-NMR spectra: in CD_3OD; *Varian-XL-200* instrument;

multiplicities from ^{1}H-decoupled or DEPT spectra. MS: *Varian-MAT-711* or *Varian-MAT-112* systems; electron impact (EI) and chemical ionisation (CI); peaks in *m/z* [%].

Abbreviations [37]: Aib = 2-methylalanine (=2-aminoisobutyric acid), Boc = [(*tert*-butyloxy)carbonyl]-, CME-CDI = *N*-cyclohexyl-*N'*-[2-(4-methylmorpholin-4-ylio)ethyl]carbodiimide 4-toluenesulfonate, DCC = dicyclohexylcarbodiimide, Fmoc = [(fluoren-9-yl)methoxycarbonyl]-, HOBt = benzotriazol-1-ol, Iva = 2-ethylalanine (=(*S*)-isovaline), Leuol = L-Leucinol (=L-leucine with CH_2OH instead of COOH), Pheol = L-phenylalaninol, Trpol = L-tryptophanol, Valol = L-valinol, Z = (benzyloxy)carbonyl-.

General Procedure A. To a soln. of *N*-protected amino acid (10 mmol) in Et_2O (50 ml) was added, at 0°, the aminoazirine (11 mmol) under stirring. After 0.5–6 h at r.t., petroleum ether (50 ml) was added. The precipitated dipeptide was filtered, washed with petroleum ether, and dried *in vacuo*. The mother liquor was evaporated and the residue recrystallized from Et_2O/petroleum ether.

General Procedure B. A soln. of peptide amide (5 mmol) in 50 ml of 3N HCl (THF/H_2O 1:1) was stirred at r.t. or 35° for 1–24 h. After addition of 25 ml of 2N HCl, the mixture was thoroughly extracted with Et_2O. The combined org. phase was dried (Na_2SO_4) and the solvent evaporated.

General Procedure C. A soln. of *N*-(benzyloxy)carbonyl-protected peptide (Z-peptide; 5 mmol) in MeOH (40 ml) was hydrogenated in the presence of 8–10% Pd (10% Pd/C) without addition of acid. After complete hydrogenation (3–4 h), the mixture was filtered over *Celite* and the solvent evaporated to give chromatographically (TLC) uniform N-deprotected amine that was used without further purification.

1. Segment 12–13. – 1.1. N-*[(Benzyloxy)carbonyl]*-L-*leucyl-2-methylalanine Dimethylamide* (= *Z-Leu-Aib-NMe$_2$*; **3a**). Reaction of Z-Leu (2.20 g, 8.29 mmol) and 3-(dimethylamino)-2,2-dimethyl-2*H*-azirine (**2a**; 1.02 g, 9.10 mmol) in Et_2O (50 ml) according to *General Procedure A* yielded 3.12 g (100%) of **3a**. Colorless crystals. M.p. 114–115° (Et_2O). $[\alpha]_D = -47.0$ (*c* = 1.0, EtOH). IR: 3275*s*, 3065*w*, 3035*w*, 2955*m*, 2870*w*, 1723*s*, 1674*s*, 1622*s*, 1549*s*, 1470*m*, 1455*m*, 1395*s*, 1364*m*, 1262*s*, 1244*s*, 1177*w*, 1121*m*, 1047*w*, 1029*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.33 (*s*, 5 arom. H); 7.26 (br. *s*, NH); 5.37 (*d*, *J* = 8, NH); 5.10 (*s*, PhCH_2O); 4.2–4.1 (*m*, CH(2) of Leu); 2.98 (*s*, $(CH_3)_2$N); 1.75–1.45 (*m*, CH_2(3), CH(4) of Leu); 1.59, 1.57 (2*s*, $(CH_3)_2$C of Aib); 0.93 (*d*, *J* = 6, CH_3(5), CH_3(5') of Leu). ^{13}C-NMR (50.4 MHz, $CDCl_3$): 172.6, 170.6 (2*s*, 2 amide CO); 156.1 (*s*, urethane CO); 136.3 (*s*, arom. C); 128.4, 128.1, 127.9 (3*d*, 5 arom. C); 66.9 (*t*, PhCH_2O); 56.7 (*t*, C(2) of Aib); 53.8 (*d*, C(2) of Leu); 41.3 (*t*, C(3) of Leu); 38.0 (*q*, $(CH_3)_2$N); 24.8, 24.59 (2*q*, $(CH_3)_2$C of Aib); 24.64 (*d*, C(4) of Leu); 22.8, 21.9 (2*q*, C(5), C(5') of Leu). CI-MS: 378 ($[M + 1]^+$).

1.2. N-*[(Benzyloxy)carbonyl]*-L-*leucyl-2-methylalanine* (= *Z-Leu-Aib*; **3b**). Hydrolysis of **3a** (2.80 g, 7.42 mmol) according to *General Procedure B* (14 h at 35°) yielded 2.55 g (98%) of chromatographically uniform **3b**. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.33 (*s*, 5 arom. H); 7.02 (*s*, NH); 6.0–5.3 (br. *s*, COOH); 5.61 (*d*, *J* = 9, NH); 5.11 (*s*, PhCH_2O); 4.4–4.25 (*m*, CH(2) of Leu); 1.8–1.3 (*m*, CH_2(3), CH(4) of Leu); 1.56, 1.54 (2*s*, $(CH_3)_2$C of Aib); 0.93 (*d*, *J* = 6, CH_3(5), CH_3(5') of Leu).

1.3. N-*[(Fluoren-9-yl)methoxycarbonyl]*-L-*leucyl-2-methylalanine Dimethylamide* (= *Fmoc-Leu-Aib-NMe$_2$*; **3c**). Reaction of Fmoc-Leu (3.00 g, 8.49 mmol) and **2a** (1.05 g, 9.37 mmol) in abs. CH_2Cl_2 (40 ml) according to *General Procedure A* yielded 3.84 g (97%) of **3c**. Colorless crystals. M.p. 158.5–159° (CH_2Cl_2/Et_2O/hexane). $[\alpha]_D = -49.1$ (*c* = 0.9, EtOH). IR: 3420*w*, 3280*m*, 3065*w*, 2955*w*, 1715*m*, 1713*m*, 1676*m*, 1669*m*, 1624*s*, 1550*m*, 1452*w*, 1399*w*, 1367*w*, 1283*w*, 1265*m*, 1245*m*, 1124*m*, 1052*m*, 756*m*, 737*m*. ^{1}H-NMR (200 MHz): 7.8–7.6, 7.45–7.25 (2*m*, 8 arom. H); 4.4–4.35, 4.25–4.1 (2*m*, C*H*CH_2O, CH(2) of Leu); 2.94 (br. *s*, $(CH_3)_2$N); 1.75–1.4 (*m*, CH_2(3), CH(4) of Leu); 1.45, 1.44 (2*s*, $(CH_3)_2$C of Aib); 0.96, 0.93 (2*d*, *J* = 6, CH_3(5), CH_3(5') of Leu). ^{13}C-NMR (50.4 MHz): 174.7, 174.1 (2*s*, 2 amide CO); 158.3 (*s*, urethane CO); 145.3, 145.1, 142.6, 128.8, 128.1, 126.1, 120.9 (12 arom. C); 67.6 (*t*, CH_2O); 57.5 (*s*, C(2) of Aib); 54.5 (*d*, C(2) of Leu); 48.4 (*d*, CHCH_2O); 42.0 (*t*, C(3) of Leu); 38.4 (*q*, $(CH_3)_2$N); 26.3, 25.8, 25.7 (2*q*, *d*, $(CH_3)_2$C of Aib, CH(4) of Leu); 23.4, 21.9 (2*q*, C(5), C(5') of Leu). Anal. calc. for $C_{27}H_{35}N_3O_4$ (465.60): C 69.65, H 7.58, N 9.02; found: C 69.82, H 7.45, N 8.98.

1.4. N-*[(Fluoren-9-yl)methoxycarbonyl]*-L-*leucyl-2-methylalanine* (= *Fmoc-Leu-Aib*; **3d**). Hydrolysis of **3c** (1.50 g, 3.22 mmol) according to *General Procedure B* (16 h at 35°) yielded 1.37 g (97%) of colorless **3d**. ^{1}H-NMR (200 MHz): 7.8–7.6, 7.45–7.25 (2*m*, 8 arom. H); 4.4–4.35, 4.25–4.1 (2*m*, C*H*CH_2O, CH(2) of Leu); 1.75-1.4 (*m*, CH_2(3), CH(4) of Leu); 1.48, 1.46 (2*s*, $(CH_3)_2$C of Aib); 0.95, 0.91 (2*d*, *J* = 6, CH_3(5), CH_3(5') of Leu).

2. Segment 12–14. – 2.1. N-*[(Benzyloxy)carbonyl)]*-L-*leucyl-2-methylalanyl*-L-*proline Methyl Ester* (= *Z-Leu-Aib-Pro-OMe*; **4a**). To a soln. of **3b** (2.45 g, 7.00 mmol) in dry DMF (7 ml) was added at 0° DCC (1.44 g, 7.00 mmol). After 5 min, HOBt (1.00 g, 7.40 mmol), CSA (100 mg), and a soln. of proline methyl ester hydrochloride (1.35 g, 8.15 mmol) and *N*-methylmorpholine (750 mg, 7.41 mmol) in dry DMF (3 ml) were added. The mixture was allowed to warm up to r.t. and stirred for 24 h. Then, Et_2O was added, the mixture filtered and twice washed

with 2N HCl, 1N NaOH, and sat. NaCl soln. The org. layer was dried (Na_2SO_4) and evaporated and the residue taken up in some CH_2Cl_2 and filtered. The colorless **4a** crystallized after addition of hexane: 2.53 g (72%). M.p. 127–128°. $[\alpha]_D = -84.7$ ($c = 0.9$, EtOH). IR: 3290*m*, 3065*w*, 3035*w*, 2955*w*, 1755*m*, 1716*m*, 1669*s*, 1626*s*, 1539*m*, 1470*w*, 1454*w*, 1434*w*, 1412*m*, 1385*w*, 1364*w*, 1267*w*, 1240*m*, 1205*w*, 1165*m*, 1044*w*, 1028*w*, 750*w*, 740*w*, 698*w*. ^{1}H-NMR (200 MHz): 7.33 (*s*, 5 arom. H); 5.13, 5.02 (*AB*, $J = 13$, PhCH_2O); 4.45–4.35 (*m*, CH(2) of Pro); 4.25–4.15 (*m*, CH(2) of Leu); 3.67 (*s*, CH_3O); 3.6–3.55 (*m*, CH_2(5) of Pro); 2.0–1.3 (*m*, CH_2(3), CH(4) of Leu, CH_2(3), CH_2(4) of Pro); 1.42, 1.41 (2*s*, $(CH_3)_2$C of Aib); 0.95, 0.93 (2*d*, $J = 7$, CH_3(5), CH_3(5′) of Leu). ^{13}C-NMR (50.4 MHz): 174.7, 174.4, 173.9 (3*s*, 2 amide CO, ester CO); 158.3 (*s*, urethane CO); 138.4 (*s*, arom. C); 129.5, 129.0, 128.6 (3*d*, 5 arom. C); 67.4 (*t*, PhCH_2O); 62.0 (*d*, C(2) of Pro); 57.3 (*s*, C(2) of Aib); 54.3 (*d*, C(2) of Leu); 52.4 (*q*, CH_3O); 49.1 (*t*, C(5) of Pro); 42.0 (*t*, C(3) of Leu); 34.7 (*t*, C(3) of Pro); 26.7 (*t*, C(4) of Pro); 25.9, 25.6, 24.4 (2*q*, *d*, $(CH_3)_2$C of Aib, C(4) of Leu); 23.4, 21.8 (2*q*, C(5), C(5′) of Leu). CI-MS: 462 ($[M + 1]^+$). Anal. calc. for $C_{24}H_{35}N_3O_6$ (461.56): C 62.45, H 7.64, N 9.10; found: C 62.25, H 7.86, N 9.28.

2.2. *N-[(Benzyloxy)carbonyl]-*L*-leucyl-2-methylalanyl-*L*-proline* (= *Z-Leu-Aib-Pro*; **4b**). *From Hydrolysis of* **4a**. A soln. of **4a** (1.65 g, 3.57 mmol) in MeOH (28 ml) was saponified with 1N NaOH (12 ml) at r.t. After 7 h, the mixture was acidified with 2N HCl, evaporated and, after addition of 2N HCl, extracted with Et_2O. The combined org. phase was dried (Na_2SO_4), evaporated, and crystallized from Et_2O/hexane: 1.45 g (91%) of **4b**. ^{1}H-NMR (200 MHz): 7.33 (*s*, 5 arom. H); 5.14, 5.02 (*AB*, $J = 13$, PhCH_2O); 4.4–4.3, 4.25–4.15 (2*m*, CH(2) of Pro, CH(2) of Leu); 3.65–3.5 (*m*, CH_2(5) of Pro); 2.0–1.3 (*m*, CH_2(3), CH(4) of Leu, CH_2(3), CH_2(4) of Pro); 1.43, 1.42 (2*s*, $(CH_3)_2$C of Aib); 0.95, 0.93 (2*d*, $J = 6$, 7, CH_3(5), CH_3(5′) of Leu).

From Hydrolysis of **4c**. A soln. of **4c** (770 mg, 1.53 mmol) in 16 ml of 3N HCl (H_2O/THF 1:1) was stirred for 48 h at r.t., acidified with 2N HCl, and extracted with Et_2O. The combined org. phase was dried (Na_2SO_4) and evaporated. The residue contained some **3b** that could be removed by crystallization from Et_2O/hexane to yield 510 mg (74%) of **4b**.

2.3. *N-[(Benzyloxy)carbonyl]-*L*-leucyl-2-methylalanyl-*L*-proline* tert-*Butyl Ester* (= *Z-Leu-Aib-Pro-OBu*^{t}; **4c**). Condensation of **3b** (0.50 g, 1.43 mmol) and proline *tert*-butyl ester dibenzenesulfimide salt (1.00 g, 2.13 mmol) according to *Exper. 2.1* yielded 550 mg (76%) of **4c**. M.p. 144–145° (CH_2Cl_2/Et_2O/hexane). $[\alpha]_D = -82.2$ ($c = 0.7$, EtOH). IR: 3385*m*, 3030*w*, 2975*m*, 2930*m*, 2870*w*, 2850*w*, 1722*s*, 1651*s*, 1623*s*, 1538*s*, 1469*w*, 1454*w*, 1410*m*, 1367*m*, 1291*w*, 1266*m*, 1221*w*, 1154*m*, 1046*w*, 1029*w*. ^{1}H-NMR (200 MHz): 7.33 (*s*, 5 arom. H); 5.13, 5.02 (*AB*, $J = 13$, PhCH_2O); 4.3–4.15 (*m*, CH(2) of Pro, CH(2) of Leu); 3.65–3.5 (*m*, CH_2(5) of Pro); 1.95–1.35 (*m*, CH_2(3), CH(4) of Leu, CH_2(3), CH_2(4) of Pro); 1.43 (*s*, $(CH_3)_2$C of Aib, $(CH_3)_3$C); 0.95, 0.93 (2*d*, $J = 7$, CH_3(5), CH_3(5′) of Leu). ^{13}C-NMR (50.4 MHz): 174.3, 173.6, 173.5 (3*s*, 2 amide CO, ester CO); 158.3 (*s*, urethane CO); 138.4 (*s*, arom. C); 129.4, 129.0, 128.7 (3*d*, 5 arom. C); 82.1 (*s*, $(CH_3)_3C$); 67.4 (*t*, PhCH_2O); 62.9 (*d*, C(2) of Pro); 57.3 (*s*, C(2) of Aib); 54.3 (*d*, C(2) of Leu); 49.1 (*t*, C(5) of Pro); 42.0 (*t*, C(3) of Leu); 34.7 (*t*, C(3) of Pro); 28.2 (*q*, $(CH_3)_3$C); 26.6 (*t*, C(4) of Pro); 25.9, 25.7, 24.6 (2*q*, *d*, $(CH_3)_2$C of Aib, C(4) of Leu); 23.4, 21.9 (2*q*, C(5), C(5′) of Leu). CI-MS: 504 ($[M + 1]^+$). Anal. calc. for $C_{27}H_{41}N_3O_6$ (503.64): C 64.39, H 8.21, N 8.34; found: C 64.52, H 8.05, N 8.53.

3. Segment 15–16. – 3.1. *N-[(Benzyloxy)carbonyl]-*L*-valyl-2-methylalanine Dimethylamide* (= *Z-Val-Aib-NMe*$_2$; **5a**). See [26].

3.2. *N-[(Benzyloxy)carbonyl]-*L*-valyl-2-methylalanine* (= *Z-Val-Aib*; **5b**). Hydrolysis of **5a** (2.50 g, 6.88 mmol) according to *General Procedure B* (24 h at 35°) yielded 2.20 g (95%) of **5b**. M.p. 146.8–147.5° (Et_2O/hexane). ^{1}H-NMR (200 MHz): 7.34 (*s*, 5 arom. H); 5.11 (*s*, PhCH_2O); 3.94 (*d*, $J = 7$, CH(2) of Val); 2.08 (*m*, CH(3) of Val); 1.49 (*s*, $(CH_3)_2$C of Aib); 0.98, 0.93 (2*d*, $J = 7$, CH_3(4), CH_3(4′) of Val).

3.3. *N-[(Fluoren-9-yl)methoxycarbonyl]-*L*-valyl-2-methylalanine Dimethylamide* (= *Fmoc-Val-Aib-NMe*$_2$; **5c**). Reaction of Fmoc-Val (1.0 g, 2.94 mmol) and **2a** (365 mg, 3.25 mmol) in Et_2O (20 ml) according to *General Procedure A* yielded 1.32 g (99%) of **5c**. M.p. 113–115° (CH_2Cl_2/Et_2O). $[\alpha]_D = -56.8$ ($c = 0.7$, EtOH). IR ($CHCl_3$): 3425*w*, 3345*w*, 3005*w*, 2965*w*, 1718*s*, 1672*m*, 1630*s*, 1496*s*, 1464*m*, 1452*m*, 1403*w*, 1378*w*, 1235*m*, 1119*w*, 1097*w*, 1053*w*, 1032*w*. ^{1}H-NMR (200 MHz): 7.85–7.8, 7.7–7.6, 7.45–7.25 (3*m*, 8 arom. H); 4.55–4.15 (*m*, CHCH_2O); 3.87 (*d*, $J = 8$, CH(2) of Val); 2.90 (br. *s*, $(CH_3)_2$N); 2.05–1.85 (*m*, CH(3) of Val); 1.46, 1.43 (2*s*, $(CH_3)_2$C of Aib); 0.93 (2*d*, $J = 7$, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz): 174.7, 173.0 (2*s*, 2 amide CO); 158.4 (*s*, urethane CO); 145.2, 145.1, 142.6, 128.8, 128.1, 126.1, 120.9 (12 arom. C); 67.7 (*t*, CH_2O); 61.8 (*d*, C(2) of Val); 57.6 (*s*, C(2) of Aib); 48.4 (*d*, $CHCH_2$O); 38.3 (br. *q*, $(CH_3)_2$N); 31.8 (*d*, C(3) of Val); 26.5, 25.5 (2*q*, $(CH_3)_2$C of Aib); 19.8, 18.7 (2*q*, C(4), C(4′) of Val). Anal. calc. for $C_{26}H_{33}N_3O_4$ (451.57): C 69.16, H 7.37, N 9.31; found: C 69.00, H 7.21, N 9.47.

3.4. *N-[(Fluoren-9-yl)methoxycarbonyl]-*L*-valyl-2-methylalanine* (= *Fmoc-Val-Aib*; **5d**). Hydrolysis of **5c** (1.20 g, 2.66 mmol) according to *General Procedure B* (24 h at 35°) yielded 1.00 g (89%) of pure (TLC) **5d** that was used without further purification.

4. Segment 15–17. – 4.1. N-*[(Benzyloxy)carbonyl]*-L-*valyl-2-methylalanyl-2-methylalanine* N-*Methylanilide* (= *Z-Val-Aib-Aib-NMe(Ph)*; **6a**). Reaction of **5b** (590 mg, 1.75 mmol) and 3-(*N*-methyl-*N*-phenylamino)-2,2-dimethyl-2*H*-azirine (**2b**; 336 mg, 1.93 mmol) in CH_2Cl_2 (30 ml) according to *General Procedure A* yielded 890 mg (100%) of **6a**. M.p. 71–74° (CH_2Cl_2/Et_2O). $[\alpha]_D = 1.5$ ($c = 0.9$, EtOH). IR: 3310*m*, 3065*w*, 3035*w*, 2965*w*, 2935*w*, 2875*w*, 1716*s*, 1670*s*, 1637*s*, 1597*m*, 1570*s*, 1497*s*, 1471*w*, 1457*m*, 1394*m*, 1366*m*, 1290*w*, 1288*m*, 1172*w*, 1119*w*, 1092*m*, 1029*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.45–7.3 (*m*, 8 arom. H, NH); 7.3–7.2 (*m*, 2 arom. H); 6.69 (*s*, NH); 5.42 (*d*, $J = 8$, NH); 5.11 (*s*, PhCH_2O); 3.91 (*dd*, $J = 6, 8$, CH(2) of Val); 3.28 (*s*, CH_3N); 2.2–2.0 (*m*, CH(3) of Val); 1.51, 1.49, 1.44, 1.42 (4*s*, 2 $(CH_3)_2$C of Aib); 0.96, 0.91 (2*d*, $J = 7$, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz, $CDCl_3$): 173.5, 172.7, 170.6 (3*s*, 3 amide CO); 156.4 (*s*, urethane CO); 144.4, 136.3 (2*s*, 2 arom. C); 129.3, 128.4, 128.2, 128.1, 127.9 (5*d*, 10 arom. C); 66.9 (*t*, PhCH_2O); 60.8 (*d*, C(2) of Val); 58.4, 57.5 (2*s*, 2 C(2) of Aib); 41.3 (*q*, CH_3N); 31.0 (*d*, C(3) of Val); 25.3, 25.2, 24.9, 24.6 (4*q*, 2 (CH_3)$_2$C of Aib); 19.1, 17.8 (2*q*, C(4), C(4′) of Val). Anal. calc. for $C_{28}H_{38}N_4O_5$ (510.63): C 65.86, H 7.50, N 10.97; found: C 65.96, H 7.78, N 11.07.

4.2. L-*Valyl-2-methylalanyl-2-methylalanine* N-*Methylanilide* (= *Val-Aib-Aib-NMe(Ph)*; **6b**). Deprotection of **6a** (1.92 g, 3.76 mmol) according to *General Procedure* C yielded pure (TLC) **6b** that was immediately used for coupling.

4.3. N-*[(Fluoren-9-yl)methoxycarbonyl]*-L-*valyl-2-methylalanyl-2-methylalanine Dimethylamide* (= *Fmoc-Val-Aib-Aib-NMe$_2$*; **6c**). Reaction of **5d** (0.95 g, 2.24 mmol) and **2a** (280 mg, 2.50 mmol) in THF (15 ml) according to *General Procedure A* yielded 1.15 g (96%) of **6c**. M.p. 139–140° (CH_2Cl_2/Et_2O/petroleum ether). $[\alpha]_D = -20.8$ ($c = 0.9$, EtOH). IR ($CHCl_3$): 3430*w*, 3360*w*, 3005*m*, 2965*w*, 2935*w*, 1716*m*, 1680*m*, 1628*m*, 1500*s*, 1463*m*, 1452*m*, 1394*w*, 1367*w*, 1235*m*, 1169*w*, 1120*w*, 1032*w*, 924*w*. ^{1}H-NMR (200 MHz): 7.85–7.8, 7.75–7.6, 7.45–7.25 (3*m*, 8 arom. H); 4.5–4.25 (*m*, CHCH_2O); 3.67 (*d*, $J = 8$, CH(2) of Val); 2.99, 2.91 (2*s*, $(CH_3)_2$N); 2.05–1.9 (*m*, CH(3) of Val); 1.49, 1.41, 1.39, 1.35 (4*s*, 2 $(CH_3)_2$C of Aib); 1.02, 0.97 (2*d*, $J = 7$, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz): 175.9, 174.9, 174.1 (3*s*, 3 amide CO); 158.9 (*s*, urethane CO); 145.2, 145.1, 142.6, 142.5, 128.8, 128.2, 126.2, 126.0 (12 arom. C); 68.1 (*t*, CH_2O); 63.0 (*d*, C(2) of Val); 58.1, 57.7 (2*s*, 2 C(2) of Aib); 48.3 (*d*, CHCH$_2$O); 38.5 (*q*, $(CH_3)_2$N); 31.1 (*d*, C(3) of Val); 27.1, 26.0, 24.0 (3*q*, 2 (CH_3)$_2$C of Aib); 19.6, 19.5 (2*q*, C(4), C(4′) of Val). Anal. calc. for $C_{30}H_{40}N_4O_5$ (536.68): C 67.14, H 7.51, N 10.44; found: C 66.86, H 7.81, N 10.24.

4.4. N-*[(Fluoren-9-yl)methoxycarbonyl]*-L-*valyl-2-methylalanyl-2-methylalanine* (= *Fmoc-Val-Aib-Aib*; **6d**). Hydrolysis of **6c** (0.80 g, 1.49 mmol) according to *General Procedure B* (28 h at 35°) yielded 0.73 g (96%) of **6d**. ^{1}H-NMR (200 MHz): 7.85–7.8, 7.75–7.6, 7.45–7.25 (3*m*, 8 arom. H); 4.35–4.2 (*m*, CHCH_2O); 3.73 (*d*, $J = 8$, CH(2) of Val); 2.05–1.9 (*m*, CH(3) of Val); 1.46, 1.42, 1.40 (3*s*, 2 $(CH_3)_2$C of Aib); 0.99, 0.96 (2*d*, $J = 7$, CH_3(4), CH_3(4′) of Val).

4.5. N-*[(Benzyloxy)carbonyl]*-L-*valyl-2-methylalanyl-2-methylalanine Dimethylamide* (= *Z-Val-Aib-Aib-NMe$_2$*; **6e**). Reaction of **5b** (2.0 g, 5.95 mmol) and **2a** (730 mg, 6.51 mmol) in THF (30 ml) according to *General Procedure A* yielded 2.65 g (99%) of **6e**. M.p. 77–78° (CH_2Cl_2/Et_2O). $[\alpha]_D = -1.8$ ($c = 0.9$, EtOH). IR: 3388*m*, 3030*w*, 2960*m*, 2932*m*, 1659*s*, 1625*s*, 1529*s*, 1417*m*, 1404*m*, 1392*m*, 1363*m*, 1278*m*, 1238*m*, 1171*w*, 1119*m*, 1038*w*, 1028*w*, 740*w*, 698*w*. ^{1}H-NMR (200 MHz): 7.34 (*s*, 5 arom. H); 5.15, 5.10 (*AB*, $J = 12$, PhCH_2O); 3.68 (*d*, $J = 8$, CH(2) of Val); 2.95 (*s*, $(CH_3)_2$N); 2.1–1.9 (*m*, CH(3) of Val); 1.48, 1.42, 1.41, 1.35 (4*s*, 2 $(CH_3)_2$C of Aib); 1.01, 0.97 (2*d*, $J = 7$, 8, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz): 175.9, 175.0, 174.1 (3*s*, 3 amide CO); 158.9 (*s*, urethane CO); 138.3 (*s*, arom. C); 129.5, 129.0, 128.4 (3*d*, 5 arom. C); 67.5 (*t*, PhCH_2O); 63.1 (*d*, C(2) of Val); 58.1, 57.7 (2*s*, 2 C(2) of Aib); 38.4 (br. *q*, $(CH_3)_2$N); 31.1 (*d*, C(3) of Val); 26.9, 26.0, 24.3 (3*q*, 2 (CH_3)$_2$C of Aib); 19.5 (*q*, C(4), C(4′) of Val). Anal. calc. for $C_{23}H_{36}N_4O_5$ (448.57): C 61.59, H 8.09, N 12.49; found: C 61.59, H 8.02, N 12.25.

4.6. L-*Valyl-2-methylalanyl-2-methylalanine Dimethylamide* (= *Val-Aib-Aib-NMe$_2$*; **6f**). Deprotection of **6e** (1.50 g, 3.34 mmol) according to *General Procedure C* yielded pure (TLC) **6f** that was immediately used for coupling.

5. Segment 12–17. – 5.1. N-*[(Benzyloxy)carbonyl]*-L-*leucyl-2-methylalanyl*-L-*prolyl*-L-*valyl-2-methylalanyl-2-methylalanine* N-*Methylanilide* (= *Z-Leu-Aib-Pro-Val-Aib-Aib-NMe(Ph)*; **7a**). To a soln. of **4b** (1.80 g, 4.02 mmol) in dry THF (8 ml) were added, at −15°, *N*-methylmorpholine (405 mg, 4.00 mmol) and isobutyl chloroformate (550 mg, 4.02 mmol). After 4 min stirring, **6b** (*ca.* 3.76 mmol, see *Exper. 4.2*) in dry THF (4 ml) was added dropwise so that the temp. did not rise above −10°. After an additional 10 min, the mixture was allowed to reach r.t. and after 2 h stirring, the solvent was evaporated, the residue dissolved in CH_2Cl_2 and washed with 2N HCl, 1N NaOH, and sat. NaCl soln. The org. layer was dried (Na_2SO_4) and evaporated: 2.25 g (74% starting from **6a**) of **7a**. M.p. 101–103° (CH_2Cl_2/Et_2O/hexane). $[\alpha]_D = -16.5$ ($c = 0.9$, EtOH). IR: 3310*m*, 3065*w*, 3035*w*, 2960*m*, 2940*w*, 2875*w*, 1724*m*, 1652*s*, 1595*m*, 1533*s*, 1470*m*, 1456*m*, 1393*w*, 1363*w*, 1251*m*, 1218*w*, 1162*w*, 1118*w*, 1091*w*, 1047*w*, 1028*w*, 768*w*, 740*w*, 705*w*. ^{1}H-NMR (200 MHz): 7.45–7.2 (*m*, 10 arom. H); 5.16, 5.07 (*AB*, $J = 13$, PhCH_2O); 4.4–4.3 (*m*, CH(2) of Pro); 4.25–4.1 (*m*, CH(2) of Leu); 3.77 (*d*, $J = 9$, CH(2) of Val); 3.7–3.5 (*m*, CH_2(5) of Pro); 3.37 (*s*, CH_3N); 2.35–2.15, 1.9–1.3 (2*m*, CH_2(3), CH(4) of Leu, CH_2(3), CH_2(4) of Pro, CH(3) of Val); 1.52, 1.51,

1.45, 1.44 (4*s*, 3 $(CH_3)_2C$ of Aib); 1.05–0.9 (*m*, $CH_3(5)$, $CH_3(5')$ of Leu, $CH_3(4)$, $CH_3(4')$ of Val). ^{13}C-NMR (50.4 MHz)[4]): 176.23, 176.17, 175.6, 175.5, 174.3, 173.7 (6*s*, 6 amide CO); 158.3 (*s*, urethane CO); 147.0, 138.3, 130.2, 129.5, 129.1, 128.8, 128.3, 128.1 (12 arom. C); 67.7 (*t*, Ph*C*H_2O); 64.6 (*d*, C(2) of Val); 63.1, 63.0 (2*d*, C(2) of Pro); 58.6, 58.5, 58.1, 57.8 (4*s*, 3 C(2) of Aib); 55.3 (*d*, C(2) of Leu); 49.8 (*t*, C(5) of Pro); 41.8 (*t*, C(3) of Leu); 41.2 (*q*, CH_3N); 30.6 (*d*, C(3) of Val); 30.0 (*t*, C(3) of Pro); 27.4, 26.81, 26.4, 26.1, 25.9, 24.2, 23.8 (6*q*, *d*, 3 (CH_3)$_2$C of Aib, C(4) of Leu); 26.84 (*t*, C(4) of Pro); 23.3, 21.9 (2*q*, C(5), C(5') of Leu); 20.2, 19.6 (2*q*, C(4), C(4') of Val). FAB-MS: 806 ($[M + 1]^+$).

5.2. N-*[(Benzyloxy)carbonyl]*-L-*leucyl-2-methylalanyl*-L-*prolyl*-L-*valyl-2-methylalanyl-2-methylalanine* (= *Z-Leu-Aib-Pro-Val-Aib-Aib*; **7b**). Hydrolysis of **7a** (1.82 g, 2.26 mmol) according to *General Procedure B* (3 h at r.t.) yielded 1.50 g (93%) of **7b**. M.p. 104–107° (Et_2O/hexane). ^1H-NMR (200 MHz): 7.4–7.3 (*m*, 5 arom. H); 5.15, 5.06 (*AB*, *J* = 13, PhCH_2O); 4.45–4.35 (*m*, CH(2) of Pro); 4.25–4.15 (*m*, CH(2) of Leu); 3.87 (*d*, *J* = 8, CH(2) of Val); 3.7–3.45 (*m*, $CH_2(5)$ of Pro); 2.35–2.15, 1.9–1.2 (2*m*, $CH_2(3)$, CH(4) of Leu, $CH_2(3)$, $CH_2(4)$ of Pro, CH(3) of Val); 1.48, 1.46, 1.45, 1.43 (4*s*, 3 $(CH_3)_2C$ of Aib); 1.05–0.85 (*m*, $CH_3(5)$, $CH_3(5')$ of Leu, $CH_3(4)$, $CH_3(4')$ of Val).

5.3. N-*[(Fluoren-9-yl)methoxycarbonyl]*-L-*leucyl-2-methylalanyl*-L-*prolyl*-L-*valyl-2-methylalanyl-2-methylalanine* N-*Methylanilide* (= *Fmoc-Leu-Aib-Pro-Val-Aib-Aib-NMe(Ph)*; **7c**). To a soln. of **3d** (600 mg, 1.37 mmol) in dry CH_2Cl_2 (3 ml) was added, at 0°, DCC (282 mg, 1.37 mmol). After 3 min, HOBt (400 mg, 2.72 mmol), CSA (60 mg), and a soln. of **11a** (*ca.* 1.37 mmol; see *Exper. 9.4*) in dry DMF (3 ml) were added. The mixture was stirred for 24 h at 0° to r.t., filtrated, diluted with CH_2Cl_2, and washed with 2N HCl, 1N NaOH, and sat. NaCl soln. The org. layer was dried (Na_2SO_4), the residue dissolved in CH_2Cl_2, filtrated, and evaporated: 920 mg of a mixture that was hydrolyzed without further purification.

5.4. N-*[(Fluoren-9-yl)methoxycarbonyl]*-L-*leucyl-2-methylalanyl*-L-*prolyl*-L-*valyl-2-methylalanyl-2-methylalanine* (= *Fmoc-Leu-Aib-Pro-Val-Aib-Aib*; **7d**). Hydrolysis of 920 mg of mixture from *Exper. 5.3* according to *General Procedure B* (3 h at r.t.) yielded 215 mg (19% starting from **11c**; see *Exper. 9.1* and *9.4*) of **7d** after chromatographic separation (CH_2Cl_2/MeOH/AcOH 250:20:1). ^1H-NMR (200 MHz): 7.85–7.25 (*m*, 8 arom. H); 4.55–4.35, 4.3–4.1 (2*m*, *CHCH*$_2$O, CH(2) of Pro, CH(2) of Leu); 3.95–3.85 (*m*, CH(2) of Val); 3.75–3.4 (*m*, $CH_2(5)$ of Pro); 2.35–2.2, 1.95–1.1 (2*m*, $CH_2(3)$, CH(4) of Leu, $CH_2(3)$, $CH_2(4)$ of Pro, CH(3) of Val); 1.48, 1.47, 1.45 (3*s*, 3 $(CH_3)_2C$ of Aib); 1.05–0.85 (*m*, $CH_3(5)$, $CH_3(5')$ of Leu, $CH_3(4)$, $CH_3(4')$ of Val).

6. Segment 19–20. – 6.1. N-*[(Benzyloxy)carbonyl]*-L-*glutaminyl*-L-*phenylalaninol* (= *Z-Gln-Pheol*; **8a**). Condensation of Z-Gln (9.30 g, 33.18 mmol) and L-phenylalaninol (3.35 g, 33.12 mmol) according to *Exper. 9.1* yielded 12.4 g (93%) of **8a**. M.p. 180–181° (MeOH/AcOEt). $[\alpha]_D = -39.7$ (*c* = 0.9, MeOH). IR: 3415*s*, 3380*s*, 3085*w*, 3060*w*, 3030*w*, 2955*m*, 2875*w*, 2775*w*, 1690*s*, 1657*s*, 1538*s*, 1496*m*, 1453*s*, 1415*m*, 1383*m*, 1314*m*, 1307*m*, 1266*s*, 1242*s*, 1182*w*, 1153*w*, 1050*s*, 1036*m*, 1016*m*, 920*w*, 899*w*, 736*s*, 701*s*, 697*s*. ^1H-NMR (200 MHz): 7.34 (*s*, 5 arom. H); 7.21 (*s*, 5 arom. H); 5.08 (*s*, PhCH_2O); 4.15–4.05 (*m*, CH(2) of Gln, CH(2) of Pheol); 3.55–3.45 (*m*, CH_2OH of Pheol); 2.88, 2.74 (*AB* of *ABX*, $J_{AB} = 14$, $J_{AX} = 4$, $J_{BX} = 3$, $CH_2(3)$ of Pheol); 2.3–2.1 (*m*, $CH_2(4)$ of Gln); 2.05–1.75 (*m*, $CH_2(3)$ of Gln). ^{13}C-NMR (50.4 MHz): 177.8, 173.8 (2*s*, 2 amide CO); 158.2 (*s*, urethane CO); 139.6, 138.1, 130.3, 129.4, 129.3, 129.0, 128.9, 127.3 (12 arom. C); 67.8 (*t*, Ph*C*H_2O); 64.0 (*t*, *C*H_2OH of Pheol); 56.3 (*d*, C(2) of Pheol); 54.2 (*d*, C(2) of Gln); 38.0 (*t*, C(3) of Pheol); 32.5 (*t*, C(4) of Gln); 29.3 (*t*, C(3) of Gln). Anal. calc. for $C_{22}H_{27}N_3O_5$ (413.48): C 63.91, H 6.58, N 10.16; found: C 63.96, H 6.40, N 10.24.

6.2. L-*Glutaminyl*-L-*phenylalaninol* (= *Gln-Pheol*; **8b**). Deprotection of **8a** (6.00 g, 14.51 mmol) according to *General Procedure C* yielded pure (TLC) **8b** that was immediately used for coupling.

7. Segment 18–20. – 7.1. N-*[(*tert*-Butyloxy)carbonyl]*-O^5-*benzyl*-L-*glutam-1-yl*-L-*glutaminyl*-L-*phenylalaninol* (= *Boc-Glu(OBzl)-Gln-Pheol*; **9a**). Reaction of Boc-Glu(OBzl) (*ca.* 2.51 mmol; prepared from Boc-Glu-(OBzl) dicyclohexylamine salt (1.30 g, 2.51 mmol) by addition of a $KHSO_4$ soln. and extraction) with **8b** (*ca.* 2.42 mmol) according to *Exper. 9.1* yielded 1.14 g (79% starting from **8a**) of **9a**. M.p. 141–143° (AcOEt/Et_2O). $[\alpha]_D = -31.7$ (*c* = 1.0, EtOH). IR: 3412*m*, 3295*s*, 3063*w*, 3028*w*, 2971*w*, 2930*m*, 1731*m*, 1713*m*, 1688*s*, 1659*s*, 1640*s*, 1549*m*, 1525*m*, 1497*w*, 1453*w*, 1392*w*, 1367*w*, 1282*w*, 1251*w*, 1168*m*, 1049*w*, 1030*w*, 864*w*, 749*w*, 699*w*. ^1H-NMR (400 MHz): 7.35–7.3 (*m*, 5 arom. H); 7.25–7.2 (*m*, 5 arom. H); 5.12 (*s*, PhCH_2O); 4.3–4.25, 4.05–3.95 (2*m*, CH(2) of Glu, CH(2) of Gln); 4.15–4.05 (*m*, CH(2) of Pheol); 3.55–3.45 (*m*, CH_2OH of Pheol); 2.95–2.85, 2.8–2.7 (2*m*, $CH_2(3)$ of Pheol); 2.45 (*t*, *J* = 8, $CH_2(4)$ of Glu); 2.23 (*t*, *J* = 7, $CH_2(4)$ of Gln); 2.1–1.95 (*m*, $CH_2(3)$ of Glu); 1.95–1.85 (*m*, $CH_2(3)$ of Gln); 1.44 (*s*, $(CH_3)_3C$). ^{13}C-NMR (50.4 MHz): 177.9, 174.4, 174.3, 173.1 (4*s*, 3 amide CO, ester CO); 158.0 (*s*, urethane CO); 139.5, 137.5, 130.3, 129.5, 129.4, 129.2, 127.3 (12 arom. C); 80.8 (*s*, $(CH_3)_3C$); 67.4 (*t*, Ph*C*H_2O); 63.9 (*t*, CH_2OH of Pheol); 55.5 (*d*, C(2) of Pheol); 54.35, 54.28 (2*d*, C(2) of Gln, C(2)

[4]) The splitting of some signals in the ^{13}C-NMR of Pro-containing peptides results from (*Z*/*E*)-isomerization of X-Pro peptide bonds.

of Glu); 37.9 (*t*, C(3) of Pheol); 32.4 (*t*, C(4) of Gln); 31.4 (*t*, C(4) of Glu); 29.1 (*t*, C(3) of Gln); 28.7 (*q*, $(CH_3)_3C$); 28.2 (*t*, C(3) of Glu). Anal. calc. for $C_{31}H_{42}N_4O_8$ (598.70): C 62.19, H 7.07, N 9.36; found: C 61.94, H 7.12, N 9.36.

7.2. *O^5-Benzyl-L-glutam-1-yl-L-glutaminyl-L-phenylalaninol* (= *Glu(OBzl)-Gln-Pheol*; **9b**). A soln. of **9a** (2.00 g, 3.34 mmol) in CH_2Cl_2 (20 ml) was deprotected by addition of 20 ml of 3N HCl (Et_2O) and 30 min stirring at r.t. After addition of Et_2O, 1.76 g (98%) of colorless **9b**·HCl was isolated by filtration. ^{1}H-NMR (200 MHz): 7.4–7.3 (*m*, 5 arom. H); 7.25–7.2 (*m*, 5 arom. H); 5.13 (*s*, PhCH_2O); 4.45–4.35 (*m*, CH(2) of Glu); 4.15–4.05 (*m*, CH(2) of Pheol); 4.0–3.95 (*m*, CH(2) of Gln); 3.6–3.45 (*m*, CH_2OH of Pheol); 2.95–2.7 (*m*, CH_2(3) of Pheol); 2.6–2.45 (*m*, CH_2(4) of Glu); 2.32 (*t*, J = 7, CH_2(4) of Gln); 2.2–1.9 (*m*, CH_2(3) of Glu, CH_2(3) of Gln).

8. Segment 12–20. – *N-[(Benzyloxy)carbonyl]-L-leucyl-2-methylalanyl-L-prolyl-L-valyl-2-methylalanyl-2-methylalanyl-O^5-benzyl-L-glutam-1-yl-L-glutaminyl-L-phenylalaninol* (= *Z-Leu-Aib-Pro-Val-Aib-Aib-Glu(OBzl)-Gln-Pheol*; **10**). To a soln. of **7b** (1.00 g, 1.39 mmol) in dry DMF (2 ml) was added, at 0°, CME-CDI (591 mg, 1.39 mmol). After 5 min stirring at 0°, HOBt (189 mg, 1.40 mmol) and after another 5 min, a soln. of **9b**·HCl (748 mg, 1.40 mmol) and *N*-methylmorpholine (141 mg, 1.40 mmol) in dry DMF (2 ml) was added. The mixture was stirred for 20 h at 0° to r.t., diluted with CH_2Cl_2, and washed with 2N HCl and sat. NaCl soln. The org. layer was dried (Na_2SO_4) and evaporated: 1.26 g (76%) of colorless product. Chromatography (CH_2Cl_2/MeOH 9:1) gave 1.09 g (65%) of **10**. M.p. 100–102°. $[\alpha]_D = -18.4$ (c = 1.2, EtOH). IR: 3440*m*, 3030*w*, 3975*w*, 2930*w*, 2870*w*, 1723*m*, 1651*s*, 1537*s*, 1468*w*, 1453*w*, 1386*w*, 1363*w*, 1250*w*, 1213*w*, 1170*w*, 1116*w*, 1043*w*, 740*w*. ^{1}H-NMR (400 MHz): 7.4–7.1 (*m*, 15 arom. H); 5.18, 5.09 (*AB*, J = 13, PhCH_2O of Z); 5.12, 5.08 (*AB*, J = 12, PhCH_2O of Glu); 4.30 (*dd*, J = 6, 9, CH(2) of Pro); 4.2–4.1 (3*m*, CH(2) of Pheol, CH(2) of Gln, CH(2) of Leu); 4.04 (*dd*, J = 5, 10, CH(2) of Glu); 3.65–3.5 (*m*, CH(2) of Val, CH_2(5) of Pro, CH_2OH of Pheol); 2.93, 2.73 (*AM* of *AMX*, J = 13, 8, 5, CH_2(3) of Pheol); 2.9–2.8, 2.65–2.55 (2*m*, CH_2(4) of Glu); 2.4–2.25, 2.25–2.15 (2*m*, CH_2(3) of Glu); 2.4–2.0 (*m*, CH_2(4), CH_2(3) of Gln); 2.25–2.15 (*m*, CH(3) of Val); 2.2–2.1, 1.9–1.6 (2*m*, CH_2(3) of Pro); 1.9–1.6 (*m*, CH_2(4) of Pro); 1.9–1.5 (*m*, CH_2(3), CH(4) of Leu); 1.50, 1.48, 1.47, 1.46 (4*s*, 3 $(CH_3)_2$C of Aib); 0.98, 0.91 (2*d*, J = 7, 7, CH_3(5), CH_3(5′) of Leu); 0.95, 0.90 (2*d*, J = 7, 7, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz)[4]): 178.8, 177.6, 177.2, 176.1, 176.0, 175.4, 175.3, 175.2, 174.5, 174.3, 174.1 (11*s*, 9 amide CO, ester CO); 158.3 (*s*, urethane CO); 139.3, 138.3, 137.6, 130.5, 129.5, 129.2, 129.1, 128.7, 127.2 (18 arom. C); 67.7, 67.2 (2*t*, PhCH_2O of Z, PhCH_2O of Glu); 64.9 (*t*, CH_2OH of Pheol); 64.7, 64.5 (2*d*, C(2) of Val, C(2) of Pro); 57.9, 57.8, 57.6, 57.5 (4*s*, 3 C(2) of Aib); 56.9 (*d*, C(2) of Pheol); 55.9, 55.7, 54.5 (3*d*, C(2) of Glu, C(2) of Gln, C(2) of Leu); 49.9 (*t*, C(5) of Pro); 41.8 (*t*, C(3) of Leu); 38.1 (*t*, C(3) of Pheol); 33.0, 32.0 (2*t*, C(4) of Glu, C(4) of Gln); 30.3 (*d*, C(3) of Val); 29.8 (*t*, C(3) of Pro); 28.2, 27.2 (2*t*, C(3) of Glu, C(3) of Gln); 27.5, 27.4, 26.9, 25.9, 23.6, 23.5, 23.3 (6*q*, *d*, 3 $(CH_3)_2$C of Aib, C(4) of Leu); 26.9 (*t*, C(4) of Pro); 23.1, 22.0 (2*q*, C(5), C(5′) of Leu); 20.7, 19.5 (2*q*, C(4), C(4′) of Val). FAB-MS: 1197 ($[M + 1]^+$). Anal. calc. for $C_{62}H_{88}N_{10}O_{14}$ (1197.44): C 62.19, H 7.41, N 11.70; found: C 61.89, H 7.43, N 11.92.

9. Segment 14–17. – 9.1. *N-[(Benzyloxy)carbonyl]-L-prolyl-L-valyl-2-methylalanyl-2-methylalanine N-Methylanilide* (= *Z-Pro-Val-Aib-Aib-NMe(Ph)*; **11c**). A soln. of Z-Pro (1.85 g, 7.42 mmol) in dry THF (25 ml) was treated at −15° with *N*-methylmorpholine (751 mg, 7.42 mmol) and isobutyl chloroformate (1.01 g, 7.39 mmol). After 4 min, **6b** (*ca.* 7.44 mmol; see *Exper. 4.2*) in dry THF (10 ml) was added and the mixture stirred for 2 min at −15° and for 30 min at r.t. The solvent was evaporated and the residue, after addition of CH_2Cl_2, washed with 2N HCl, 1N NaOH, and sat. NaCl soln. The org. phase was dried (Na_2SO_4) and evaporated: 3.90 g (86% starting from **6a**) of **11c**. $[\alpha]_D = -37.4$ (c = 0.9, EtOH). IR: 3320*m*, 3060*w*, 2960*m*, 1665*s*, 1594*m*, 1535*m*, 1496*m*, 1453*m*, 1418*m*, 1391*m*, 1360*m*, 1212*m*, 1170*m*, 1119*m*, 1091*m*. ^{1}H-NMR (200 MHz): 7.45–7.25 (*m*, 10 arom. H); 5.15–5.05 (*m*, PhCH_2O); 4.45–4.35 (*m*, CH(2) of Pro); 3.95–3.85 (*m*, CH(2) of Val); 3.6–3.5 (*m*, CH_2(5) of Pro); 3.31 (*s*, CH_3N); 2.35–2.25 (*m*, CH(3) of Val); 2.1–1.85 (*m*, CH_2(3), CH_2(4) of Pro); 1.49, 1.45, 1.43, 1.42 (4*s*, 2 $(CH_3)_2$C of Aib); 1.0–0.85 (*m*, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz)[4]): 176.0, 175.4, 175.2, 173.2 (4*s*, 4 amide CO); 157.0, 156.4 (2*s*, urethane CO); 146.7, 138.0, 137.8, 130.3, 129.5, 129.0, 128.8, 128.7, 128.5, 128.3 (12 arom. C); 68.2 (*t*, PhCH_2O); 61.7, 61.4 (2*d*, C(2) of Pro); 60.8 (*d*, C(2) of Val); 58.8, 58.3 (2*s*, 2 C(2) of Aib); 48.7, 48.3 (2*t*, C(5) of Pro); 41.3 (*q*, CH_3N); 32.5, 31.2 (2*t*, C(3) of Pro); 31.3 (*d*, C(3) of Val); 26.3, 24.7, 24.6, 24.3 (4*q*, 2 (CH_3)$_2$C of Aib); 25.5 (*t*, C(4) of Pro); 19.6, 19.3 (2*q*, C(4), C(4′) of Val).

9.2. *N-[(Benzyloxy)carbonyl]-L-prolyl-L-valyl-2-methylalanyl-2-methylalanine Dimethylamide* (= *Z-Pro-Val-Aib-Aib-NMe_2*; **11d**). Reaction of Z-Pro (920 mg, 3.69 mmol) and **6f** (*ca.* 3.34 mmol; see *Exper. 4.6*) according to *Exper. 9.1* yielded 1.68 g (92% starting from **6b**) of **11d**. M.p. 196–197° (CH_2Cl_2/Et_2O). $[\alpha]_D = -41.8$ (c = 1.0, EtOH). IR ($CHCl_3$): 3430*w*, 3355*w*, 3003*w*, 2940*w*, 1682*s*, 1629*m*, 1503*m*, 1453*w*, 1413*m*, 1295*w*, 1258*w*, 1122*w*. ^{1}H-NMR (200 MHz): 7.4–7.3 (*m*, 5 arom. H); 5.15–5.0 (*m*, PhCH_2O); 4.45–4.3 (*m*, CH(2) of Pro); 3.9–3.8 (*m*, CH(2) of Val); 3.6–3.5 (*m*, CH_2(5) of Pro); 3.2–2.8 (br. *s*, $(CH_3)_2$N); 2.4–2.15 (*m*, CH(3) of Val); 2.1–1.8 (*m*, CH_2(3), CH_2(4) of Pro); 1.49, 1.45, 1.42 (3*s*, 2 $(CH_3)_2$C of Aib); 1.05–0.9 (*m*, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz)[4]): 175.9, 175.4, 175.2, 175.0, 173.2 (5*s*, 4 amide CO); 156.9, 156.3 (2*s*, urethane CO); 138.0, 137.8, 129.5,

129.1, 129.0, 128.8, 128.7 (6 arom. C); 68.2 (*t*, $PhCH_2O$); 61.7, 61.5 (2*d*, C(2) of Pro); 60.7 (*d*, C(2) of Val); 58.1, 57.8 (2*s*, 2 C(2) of Aib); 48.8, 48.3 (2*t*, C(5) of Pro); 38.5 (*q*, $(CH_3)_2N$); 32.5 31.1 (2*t*, C(3) of Pro); 31.1 (*d*, C(3) of Val); 27.0, 26.7, 26.1, 26.0, 24.6, 24.1 (6*q*, 2 $(CH_3)_2C$ of Aib); 25.5, 24.7 (2*t*, C(4) of Pro); 19.5 (*q*, C(4), C(4′) of Val). Anal. calc. for $C_{28}H_{43}N_5O_6$ (545.69): C 61.63, H 7.94, N 12.83; found: C 61.71, H 7.99, N 12.59.

9.3. *N-[(Benzyloxy)carbonyl]-*L*-prolyl-*L*-valyl-2-methylalanyl-2-methylalanine* (= *Z-Pro-Val-Aib-Aib*; **11e**). Hydrolysis of **11d** (1.30 g, 2.38 mmol) according to *General Procedure B* (24 h at 35°) yielded 1.20 g (95%) of **11e**. ^{1}H-NMR (200 MHz): 7.35–7.3 (*m*, 5 arom. H); 5.15–5.0 (*m*, $PhCH_2O$); 4.45–4.3 (*m*, CH(2) of Pro); 3.95–3.85 (*m*, CH(2) of Val); 3.6–3.45 (*m*, CH_2(5) of Pro); 2.35–2.1 (*m*, CH(3) of Val); 2.15–1.8 (*m*, CH_2(3), CH_2(4) of Pro); 1.47, 1.45, 1.42 (3*s*, 2 $(CH_3)_2C$ of Aib); 1.0–0.85 (*m*, CH_3(4), CH_3(4′) of Val).

9.4. *L-Prolyl-*L*-valyl-2-methylalanyl-2-methylalanine N-Methylanilide* (= *Pro-Val-Aib-Aib-NMe(Ph)*; **11a**). Deprotection of **11c** (1.00 g, 1.65 mmol) according to *General Procedure C* yielded pure (TLC) **11a** that was immediately used for coupling.

9.5. *N-[(Fluoren-9-yl)methoxycarbonyl]-*L*-prolyl-*L*-valyl-2-methylalanyl-2-methylalanine Dimethylamide* (= *Fmoc-Pro-Val-Aib-Aib-NMe$_2$*; **11f**). Condensation of Fmoc-Pro (600 mg, 1.78 mmol) and **6f** (*ca.* 1.55 mmol) according to *Exper. 9.1* yielded 930 mg (95% starting from **6e**) of **11f**. M.p. 105–106° (CH_2Cl_2/Et_2O/petroleum ether). $[\alpha]_D = -52.7$ (*c* = 1.0, EtOH). IR: 3310*m*, 3055*w*, 2960*m*, 2935*m*, 2875*m*, 1675*s*, 1621*s*, 1532*s*, 1458*m*, 1453*s*, 1418*s*, 1393*m*, 1362*m*, 1336*m*, 1285*w*, 1239*w*, 1205*m*, 1170*w*, 1120*m*, 1091*w*, 989*w*. ^{1}H-NMR (200 MHz): 7.85–7.8, 7.7–7.6, 7.45–7.3 (3*m*, 8 arom. H); 4.55–4.15 (*m*, $CHCH_2O$, CH(2) of Pro); 3.95–3.8 (*m*, CH(2) of Val); 3.6–3.4 (*m*, CH_2(5) of Pro); 2.95 (br. *s*, $(CH_3)_2N$); 2.45–1.85 (*m*, CH(3) of Val, CH_2(3), CH_2(4) of Pro); 1.48, 1.43, 1.41 (3*s*, 2 $(CH_3)_2C$ of Aib); 1.05–0.85 (*m*, CH_3(4), CH_3(4′) of Val). ^{13}C-NMR (50.4 MHz)[4]: 176.0, 175.2, 175.0, 173.2 (4*s*, 4 amide CO); 156.9 (*s*, urethane CO); 145.3, 145.1, 142.6, 128.9, 128.2, 126.1, 121.0 (12 arom. C); 69.1, 68.7 (2*t*, CH_2O); 61.8, 61.6 (2*d*, C(2) of Pro, C(2) of Val); 58.2, 57.9 (2*s*, 2 C(2) of Aib); 48.4 (*d*, $CHCH_2O$); 48.2 (*t*, C(5) of Pro); 38.4 (*q*, $(CH_3)_2N$); 31.2 (*t*, *d*, C(3) of Pro, C(3) of Val); 26.9, 26.1, 26.0, 24.5 (4*q*, 2 $(CH_3)_2C$ of Aib); 25.5 (*t*, C(4) of Pro); 19.6, 19.5 (2*q*, C(4), C(4′) of Val). Anal. calc. for $C_{35}H_{47}N_5O_6$ (633.80): C 66.33, H 7.47, N 11.05; found: C 65.98, H 7.82, N 11.02.

9.6. *N-[(Fluoren-9-yl)methoxycarbonyl]-*L*-prolyl-*L*-valyl-2-methylalanyl-2-methylalanine* (= *Fmoc-Pro-Val-Aib-Aib*; **11b**). *From Hydrolysis of* **11f**. Hydrolysis of **11f** (300 mg, 0.473 mmol) according to *General Procedure B* (16 h at 35°) yielded 180 mg (63%) of extremely badly soluble **11b**.

From **11e**. The solid crude product from the deprotection of **11e** (1.10 g, 2.08 mmol) according to *General Procedure C* was treated with 5.5 ml of a 10% Na_2CO_3 soln. and THF (2.7 ml). At 0°, a soln. of Fmoc-Cl (0.59 g, 2.28 mmol) in THF (4 ml) was added. After 2 h stirring at r.t., the mixture was treated with H_2O and extracted with Et_2O. The H_2O layer was acidified at 0° with 2N HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated: 850 mg (67%) of extremely badly soluble **11b**.

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