Synthesis of Aib- and Phe(2Me)-Containing Cyclopentapeptides

by **Franziska S. Arnhold**[1]), **Anthony Linden**, and **Heinz Heimgartner***

Institut für Chemie der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich
(phone: +41 44 635 4282; fax: +41 44 635 6812; e-mail: heinz.heimgartner@chem.uzh.ch)

Some recently described pentapeptides containing the α,α-disubstituted α-amino acids Aib and Phe(2Me) have been cyclized in DMF solution using diphenyl phosphorazidate (DPPA), *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetamethyluronium tetrafluoroborate/1-hydroxybenzotriazole (TBTU/HOBt), and diethyl phosphorocyanidate (DEPC), respectively, to give the corresponding cyclopentapeptides in fair-to-good yields. In the case of peptides with L-amino acids, and (*R*)- and (*S*)-Phe(2Me), the yields differed significantly in favor of the L/(*R*) combination. The conformations in the crystals of cyclo(Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly) and cyclo(Gly-(*R*)-Phe(2Me)-Pro-Aib-Gly) have been determined by X-ray crystallography, leading to quite different results. In the latter case, the conformation in solution has been elucidated by NMR studies.

1. Introduction. – The interest in cyclic peptides can be traced back to the 1940s, when *Synge* and co-workers established the structure of gramicidin S, cyclo[(Leu-D-Phe-Pro-Val-Orn)$_2$], a natural cyclic decapeptide with antibiotic activity [1]. Its chemical synthesis was achieved in 1957 by *Schwyzer* and *Sieber* [2]. Since then, this class of compounds has attracted continuing interest because of the diverse biological activities [3]. Well-known examples are the cyclic undecapeptide cyclosporine A, an immunosuppressant [4], the cyclodecapeptide gramicidin S with antibiotic properties [5], the glycopeptide vancomycin as an antibacterial agent used against multiresistent bacteria [6], the neuropeptide oxytocin, which acts as a neurotransmitter, as well as a hormone [7], *etc.* Another aspect of the pharmacological interest in cyclopeptides is their higher resistance against exoproteases, resulting in a higher *in vivo* stability in comparison with linear analogs [8].

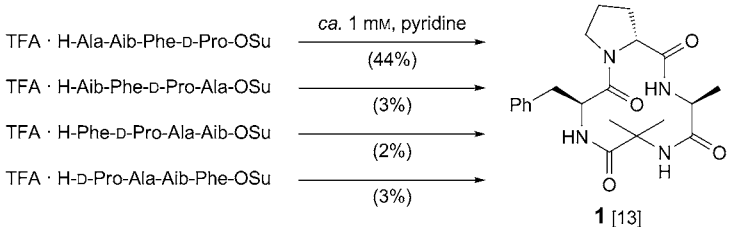
The most demanding step in the synthesis of cyclopeptides is the cyclization of the linear precursors [9]. The conditions for successful ring closures of peptides, *i.e.*, the lactamization, have been known for a long time [10]. For example, the C-terminus of a *N*-deprotected linear peptide has to be activated by a suitable coupling reagent or as an activated ester, and the requirement of high dilution (10^{-3} – 10^{-5} M) has to be fulfilled. Furthermore, efficient protocols for 'solid-phase cyclization' have been developed (*cf.*, *e.g.* [11]).

The efficiency of the cyclization depends, beside the ring size, on a series of factors such as type and configuration of the amino acids, conformation of the peptide bonds, as well as of the peptide backbone, and also the site of the ring closure. A classical

[1]) In part from the Ph.D. thesis of *F. S. A.*, Universität Zürich, 1997. Present address: *Bachem AG*, Hauptstrasse 144, CH-4416 Bubendorf.

example is the synthesis of the cyclohexapeptide cyclo(Phe-Pro-D-Phe-Pro-Phe-Pro) *via* ring closure of different linear precursors by treatment with diphenyl phosporazidate (DPPA) [12]. Whereas the cyclization of H-D-Phe-Pro-(Phe-Pro)$_2$-OH gave the desired cyclohexapeptide in 57% yield, the isomeric linear precursors H-Phe-Pro-D-Phe-Pro-Phe-Pro-OH and H-(Phe-Pro)$_2$-D-Phe-Pro-OH, under identical conditions, led to the product in 2.4 and 0.8% yield, respectively. It is important to note that the presence of one D-amino acid at the N-terminus is crucial for efficient ring closure. This was demonstrated by the cyclizations of H-(Phe-Pro)$_3$-OH and H-D-Ala-Pro-(Phe-Pro)$_2$-OH, which led to the corresponding cyclopeptides in 2 and 76% yield, respectively. A similar study was performed for the synthesis of the chlamydocin analog cyclo(Phe-D-Pro-Ala-Aib) (**1**; *Scheme 1*) [13]: whereas the cyclization of the *N*-hydroxysuccinimide ester of the tetrapeptide TFA · H-Ala-Aib-Phe-D-Pro-OSu in pyridine led to the cyclotetrapeptide **1** in 44% yield, the analogous cyclizations of the other three possible precursors gave **1** in only 2 – 3% yield.

Scheme 1

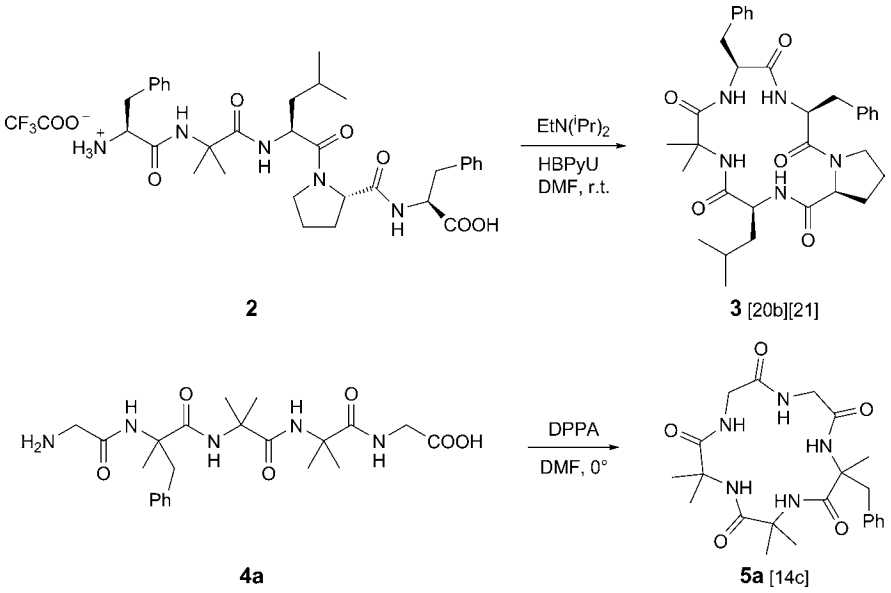


1 [13]

In the case of small cyclopeptides, the cyclodimerization presents a major problem [10][14]. For example, the cyclization of the tetrapeptide H-Gly-Phe(2Me)-Aib-Gly-OH by treatment with DPPA in DMF (10^{-3} M) led to a 1:2 mixture of the cyclic monomer and dimer [14c]. On the other hand, the synthesis of cyclotetrapeptides without formation of dimers as side-products was achieved *via* a solid-phase protocol [15]. Also in the cyclization of pentapeptides, a significant tendency to dimerization has been observed. This was a major issue in the synthesis of gramicidin S as the desired cyclodimer [2][16]. *Waki* and *Izumiya* demonstrated that the ratio of monomeric to dimeric cyclopeptide depends strongly on the bulkiness of the N-terminal amino acid [17]. Whereas, *e.g.*, in the case of the cyclization of the 4-nitrophenyl ester H-Val-Orn(δ-Z)-Leu-D-Phe-Pro-O(4-Np) the ratio was 32:78, the cyclization of the corresponding H-Gly-Orn(δ-Z)-Leu-D-Phe-Pro-O(4-Np) gave exclusively the cyclic monomer (ratio 100:0). Although to a lower extent, the steric hindrance at the C-terminus is also of importance: the cyclization of H-Val-Orn(δ-Z)-Leu-D-Phe-Gly-O(4-Np) afforded the cyclic monomer and dimer in a ratio of 79:21. Based on these results, *Kondo et al.* attempted to prepare the gramicidin S analog containing Aib instead of Val *via* the cyclodimerization strategy [18]. Surprisingly, despite the sterically unfavorable constellation, only the cyclopentapeptide cyclo(Aib-Orn(δ-Z)-Leu-D-Phe-Pro) was obtained.

A few natural cyclopeptides containing Aib are known, *i.e.*, the tetrapeptide chlamydocin and some analogs, and the heptapeptides scytalidamide A and B [19].

Scheme 2



Because of the β-turn- and helix-inducing properties of Aib, a series of Aib-containing cyclopeptides has been synthesized, and their structures in the crystal, as well as in solution, were established [20]. However, corresponding results for Aib-containing cyclopentapeptides are rare. For example, the pentapeptide TFA salt **2** was cyclized by treatment with $EtN(^iPr)_2$ and (benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-bis(tetramethylene)uronium hexafluorophosphate (HBPyU) [20b], and the structure of the product **3** was determined by NMR methods and X-ray crystallography [21] (*Scheme 2*). In our group, the pentapeptide **4a** was prepared *via* the 'azirine/oxazolone method' [22], and ring closure to give **5a** was accomplished by treatment with DPPA [14c]. On the other hand, various syntheses of cyclopentapeptides are known (*e.g.* [14b][23]), and the current interest in natural and biologically active cyclopentapeptides is remarkable (*e.g.* [24]).

In the last three decades, we have elaborated the 'azirine/oxazolone method' for the synthesis of peptides containing α,α-disubstituted α-amino acids. We have also shown that these peptides with helical conformations can be cyclized in solution to give the corresponding cyclotetra-, cyclopenta-, cyclohexa-, cycloheptа-, and cyclooctapeptides [14c][25]. Whereas the cyclopenta- to -octapeptides were formed as monomers exclusively, a mixture of monomer and dimer was formed in the case of a tetrapeptide, and only the dimer, *i.e.*, a cyclohexapeptide, was obtained from a tripeptide [14c]. Recently, we have reported the synthesis and crystal structures of Z-protected Aib- and Phe(2Me)-containing pentapeptides [26]. Herein, their cyclization to furnish cyclopentapeptides is described.

2. Results and Discussion. – 2.1. *Cyclization of Aib- and Phe(2Me)-Containing Pentapeptides.* The protected pentapeptides of type **6**, prepared *via* a combination of the 'azirine/oxazolone method' and peptide coupling [26], were deprotected at the N-

as well as at the C-terminus. For example, the ester group of Z-Gly-Aib-(*R*,*S*)-Phe(2Me)-Aib-Gly-OMe (**6a**) in MeOH was saponified by treatment with aqueous 2N NaOH at room temperature to give the Z-protected peptide acid in 85% yield. Hydrogenolysis of the latter (H_2, Pd/C) in MeOH at room temperature led to the pentapeptide **4b** in 86% yield (*Scheme 3* and *Table 1*).

Alternatively, the hydrolysis of the methyl ester of pentapeptides, *e.g.*, Z-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-OMe ((*S*)-**6d′**), was carried out with LiOH in THF/MeOH/H_2O 3:1:1 at 0° [27]. The pentapeptides with a terminal Aib-N(Me)Ph unit, resulting from the coupling with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, were transformed to the Z-pentapeptide acids by treatment with 3N HCl in THF/H_2O 1:1, *i.e.*, under the conditions of the selective amide hydrolysis [22a–22d]. For example, the hydrolysis of Z-Gly-(*R*,*S*)-Phe(2Me)-Gly-Aib-Aib-N(Me)Ph (**6c**) at room temperature gave the corresponding Z-pentapeptide acid in 98% yield.

The deprotection of the NH_2 group of the pentapeptide acids was achieved either by classic hydrogenolysis with H_2 and *ca.* 10% Pd/C in MeOH at room temperature (*ca.* 15 h) or *via* 'transfer hydrogenolysis' [28] with HCO_2NH_4 and Pd/C in boiling

Scheme 3

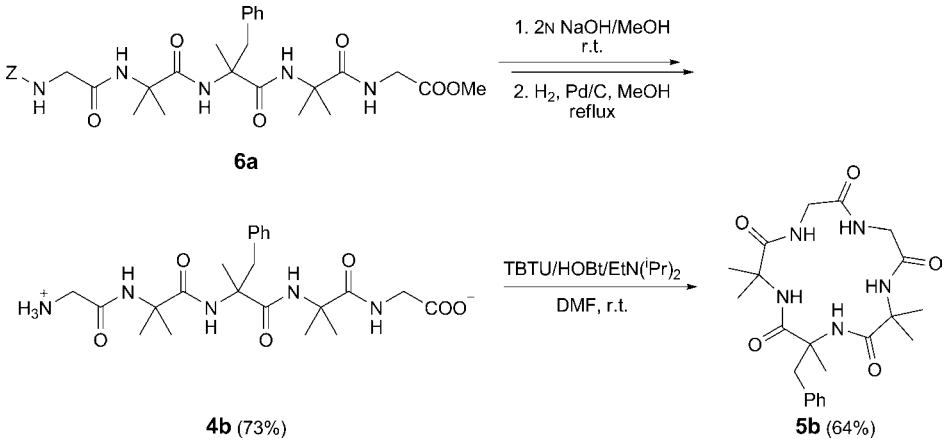


Table 1. *Linear Phe(2Me)- and Aib-Containing Pentapeptides*

Pentapeptide	**6** (X = Z) [26]	**7** (X = Z, Y = OH)	**4** (X = H, Y = OH)
X-Gly-Aib-(*R*,*S*)-Phe(2Me)-Aib-Gly-Y	**6a** Y = MeO	**7a** (85%)	**4b** (86%)
X-Gly-(*R*,*S*)-Phe(2Me)-Gly-Aib-Aib-Y	**6c** Y = Ph(Me)N	**7c** (98%)	**4c** (94%)
X-Gly-(*R*,*S*)-Phe(2Me)-Gly-Aib-Phe-Y	**6d** Y = BnO	–	**4d** (99%)
X-Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe-Y	(*R*)-**6d′** Y = MeO	(*R*)-**7d** (94%)	(*R*)-**4d** (quant.)
X-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-Y	(*S*)-**6d′** Y = MeO	(*S*)-**7d** (97%)	(*S*)-**4d** (97%)
X-Gly-(*R*,*S*)-Phe(2Me)-Pro-Aib-Aib-Y	**6e** Y = Ph(Me)N	**7e** (81%)	**4e** (96%)
X-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-Y	(*R*)-**6e** Y = Ph(Me)N	(*R*)-**7e** (82%)	(*R*)-**4e** (95%)
X-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-Y	(*S*)-**6e** Y = Ph(Me)N	(*S*)-**7e** (83%)	(*S*)-**4e** (91%)
X-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-Y	(*R*)-**6f** Y = MeO	(*R*)-**7f** (88%)	(*R*)-**4f** (96%)
X-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-Y	(*S*)-**6f** Y = MeO	(*S*)-**7f** (93%)	(*S*)-**4f** (86%)

MeOH (*ca.* 10 min). In general, the reactions proceeded to completeness, and the deprotected pentapeptides were obtained in high yields (91–100%), but, in the case of **4b** and (*S*)-**4f**, only 86% of the peptide could be isolated[2]).

For the cyclization of peptides in solution, DPPA [29a], as well as diethyl phosphorocyanidate (DEPC) [29b] proved to be suitable coupling reagents [12][14c][25a–25d]. Furthermore, *Jung*, *Kessler* and co-workers showed that the cyclization of hexapeptides with O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) in the presence of 1-hydroxybenzotriazole (HOBt) and $EtN(^iPr)_2$ in DMF at room temperature proceed smoothly leading to the cylcopeptides in high yields [30].

Based on these results, the pentapeptide **4b** in DMF was cyclized by treatment with DPPA/$NaHCO_3$, as well as with TBTU/HOBt/DIEA. In the first case, a solution of 1.5 equiv. of DPPA in DMF was slowly added to a *ca.* 1.6×10^{-3} M solution of **4b** in DMF, followed by $NaHCO_3$. After stirring for 63 h at 0° and purification by HPLC, pure **5b** was isolated in 45% yield (*Table 2*). The analogous cyclization of a 1.1×10^{-3} M solution of **4b** in DMF with 3 equiv. of TBTU and HOBt and 1% $EtN(^iPr)_2$ for 3 h at room temperature, and HPLC purification gave 64% of **5b** (*Scheme 3*).

The cyclization of **4c** (1.5×10^{-3} M solution in DMF, containing 1% of $EtN(^iPr)_2$) was performed with 2.3 equiv. of DEPC overnight. After prep. TLC, the cyclopentapeptide **5c** was isolated in excellent yield (91%; *Scheme 4* and *Table 2*). The epimeric cyclopentapeptides (*R*)-**5d** and (*S*)-**5d** were prepared from the corresponding peptides (*R*)-**4d** and (*S*)-**4d**[3]), respectively, *via* the TBTU/HOBt method. The product (*R*)-**5d**, containing (*R*)-Phe(2Me) and (*S*)-Phe, was obtained in slightly higher yield than (*S*)-**5d** with two (*S*)-configured amino acids in the backbone (64 and 55%, resp.).

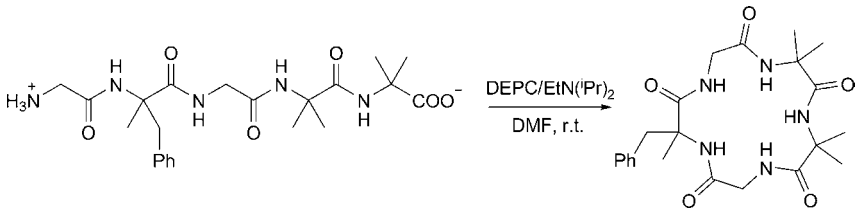
Table 2. *Cyclization of Pentapeptides* **4** *Leading to Cyclopentapeptides* **5**

Linear Pentapeptides **4**	Cyclization conditions	Cyclopentapeptides **5**		Yield [%]
4b	DPPA/$NaHCO_3$, DMF, 0°	**5b**	cyclo(Gly-Aib-(*R*,*S*)-Phe(2Me)-Aib-Gly)	45
4b	TBTU/HOBt/$EtN(^iPr)_2$, DMF, r.t.	**5b**	cyclo(Gly-Aib-(*R*,*S*)-Phe(2Me)-Aib-Gly)	64
4c	DEPC/$EtN(^iPr)_2$, DMF, r.t.	**5c**	cyclo(Gly-(*R*,*S*)-Phe(2Me)-Gly-Aib-Aib)	91
(*R*)-**4d**	TBTU/HOBt/$EtN(^iPr)_2$, DMF, r.t.	(*R*)-**5d**	cyclo(Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe)	64
(*R*)-**4d**	DEPC/$EtN(^iPr)_2$, DMF, r.t.	(*R*)-**5d**	cyclo(Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe)	61
(*S*)-**4d**	TBTU/HOBt/$EtN(^iPr)_2$, DMF, r.t.	(*S*)-**5d**	cyclo(Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe)	55
4e	DEPC/$EtN(^iPr)_2$, DMF, r.t.	**5e**	cyclo(Gly-(*R*,*S*)-Phe(2Me)-Pro-Aib-Aib)	73
(*R*)-**4e**	DEPC/$EtN(^iPr)_2$, DMF, r.t.	(*R*)-**5e**	cyclo(Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib)	78
(*S*)-**4e**	DEPC/$EtN(^iPr)_2$, DMF, r.t.	(*S*)-**5e**	cyclo(Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib)	46
(*R*)-**4f**	DEPC/$EtN(^iPr)_2$, DMF, r.t.	(*R*)-**5f**	cyclo(Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe)	47
(*S*)-**4f**	DEPC/$EtN(^iPr)_2$, DMF, r.t.	(*S*)-**5f**	cyclo(Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe)	10

[2]) Surprisingly, during the workup of (*S*)-**4d**, a sparingly soluble portion precipitated first ((*S*)-**4d′**) followed by a much more soluble second portion ((*S*)-**4d″**). Although the melting point and the spectroscopic data of the two materials were quite different, cyclization of each of the compounds led to the same cyclopentapeptide (see later).

[3]) Under the same conditions, the sparingly soluble (*S*)-**4d′** and the fairly soluble (*S*)-**4d″** gave the same cyclopentapeptide (*S*)-**5d** in 56 and 55% yield, respectively.

Scheme 4



4c **5c** (91%)

For comparison, (*R*)-**5d** was also prepared *via* cyclization of (*R*)-**4d** with DEPC/$EtN(^iPr)_2$ in almost the same yield (61%). Both cyclopentapeptides could be purified by column chromatography or prep. TLC. The advantage of the DEPC method was the easier detection of the product and side-products by TLC; therefore, this method was preferred for all other cyclizations. In the case of pentapeptide **4e**, the mixture of epimers, as well as (*R*)-**4e** and (*S*)-**4e**, were cyclized under the same conditions (DEPC) leading to **5e**, (*R*)-**5e**, and (*S*)-**5e**, respectively, in 73, 78, and 46% yield (*Table 2*). Finally, the cyclization of the epimers (*R*)-**4f** and (*S*)-**4f** gave the corresponding cyclopentapeptides (*R*)-**5f** and (*S*)-**5f** in 47 and 10% yield, respectively.

It is worth mentioning that, in all three cases of a pair of epimeric pentapeptides containing Phe(2Me) and one or two (*S*)-configured amino acids, *i.e.*, **4d**, **4e**, and **4f**, the cyclization of the (*R*)-Phe(2Me) epimer proceeded with higher efficiency. Furthermore, a dimeric cyclodecapeptide was not detected in any of the cyclization experiments, in accordance with the results reported in [17]: in all examples with a N-terminal Gly, only monomeric cyclopentapeptides were formed. The highest yields of cyclopentapeptide **5** (78–91%) were obtained, when Aib was the C-terminal amino acid. With regard to the helical conformations of derivatives of pentapeptides **4** (*cf.* [26]), with the N- and C-termini being remote from each other, the high efficiency of the cyclizations is remarkable. In the case of a C-terminal Aib, the reason may be the smooth formation of a 1,3-oxazol-5(4*H*)-one in the activation step [22], in which the C-terminal intramolecular H-bond, which contributes significantly to the stability of the helix, is broken.

2.2. *Crystal Structures of Cyclopentapeptides.* Suitable crystals of cyclo(Gly-Aib-(*R*,*S*)-Phe(2Me)-Aib-Gly) (**5b**) were obtained from $MeOH/H_2O$. The space group is non-centrosymmetric, but not polar; thus the crystals are racemic. The asymmetric unit contains two molecules, A and B, of the cyclopeptide plus one molecule of H_2O. Although the diagrams for A and B show opposite enantiomorphs (*Fig. 1*), the space group symmetry generates both enantiomorphs for each of molecules A and B. The overall conformations of molecules A and B are very similar, with only small variations in the twists within the rings and slight differences in the orientations of the Ph groups. The largest differences in the torsion angles are about the C(8)–C(9) (*ca.* 12°), C(11)–C(12) (*ca.* 21°), C(12)–N(13) (*ca.* 23°), C(14)–C(15) (*ca.* 8°), N(1)–C(15) (*ca.* 17°), C(6)–C(19) (*ca.* 16°) and C(19)–C(20) (*ca.* 16°) bonds. The Ph ring in each molecule is disordered due to in-plane-waggling of the ring about the *ipso* C–C bond. Two sets of positions were defined for the atoms of each Ph ring.

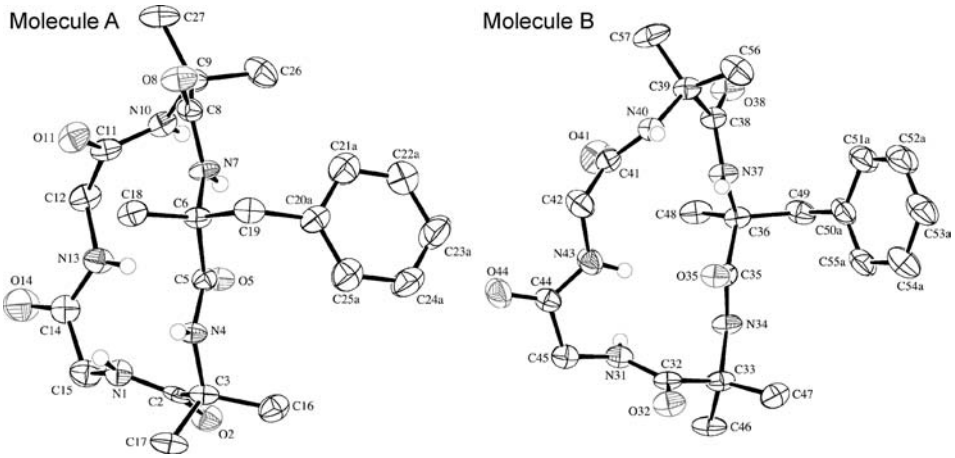


Fig. 1. *ORTEP Plot* [31] *of the molecular structure of the two symmetry-independent molecules* A (with (*R*)-Phe(2Me)) *and* B (with (*S*)-Phe(2Me)) *of cyclopentapeptide* **5b** (50% probability ellipsoids, arbitrary atom numbering, H-atoms bonded to C-atoms and the minor component of the disordered Ph ring in each molecule omitted for clarity)

Each NH group acts as a donor for H-bonding interactions (*Table 3*). All O-atoms, except O(14) of molecule A, are H-bond acceptors. In both molecules A and B, the NH group on the opposite side of the ring to the Ph substituent forms an intramolecular cross-ring H-bond with the CO O-atom immediately adjacent to the Ph substituent (N(13)–H···O(5) and N(43)–H···O(35)) to give graph set motifs [32] of *S*(10), *i.e.*, forming a β-turn of type I and I′, respectively (*Table 4*).

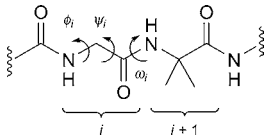
The type-A molecules are H-bonded to each other *via* both Aib NH groups (N(4)–H and N(10)–H) donating to the Aib C=O O-atoms (O(2) and O(8), resp.) of different neighboring molecules which are related by different *c*-glides. Each of these interactions link the type-A molecules into extended chains which run parallel to the [001] direction and can be described by a graph set motif of *C*(5). The combination of the two interactions also links the molecules end-to-end in the [010] direction. This

Table 3. *Intra- and Intermolecular H-Bonds of* **5b** *and* (*R*)-**5f** (for atom numbering, *cf. Figs. 1* and *2*)

5b Donor···Acceptor	N···O [Å]	N–H···O [°]	(*R*)-**5f** Donor···Acceptor	N···O [Å]	N–H···O [°]
N(1)–H···O(1^{i}) (H_2O)[a])	2.817(7)	142	N(1)–H···O(11)	2.980(4)	162(4)
N(4)–H···O(2^{ii})[b])	2.956(5)	161	N(4)–H···O(8)	2.941(4)	139(4)
N(10)–H···O(8^{iii})[c])	2.967(6)	166	N(10)–H···O(42)	2.784(4)	163(3)
N(13)–H···O(5)	3.139(6)	168	N(13)–H···O(8^{iv})[d])	2.912(4)	179(3)
N(31)–H···O(11)	2.926(6)	140	N(44)–H···O(51)	2.926(5)	154(5)
N(34)–H···O(32^{iii})	3.043(5)	169	N(53)–H···O(14)	2.965(4)	150(4)
N(40)–H···O(38^{ii})	2.851(6)	151			
N(43)–H···O(35)	3.011(6)	168			
O(1)–H(11)···O(41^{ii})	2.848(7)	174(7)			
O(1)–H(12)···O(44)	2.955(8)	144(9)			

[a]) ^{i} $x, -y, 1/2+z$. [b]) ^{ii} $x, -y, -1/2+z$. [c]) ^{iii} $x, 1-y, 1/2+z$. [d]) ^{iv} $1/2+x, 3/2-y, 2-z$.

Table 4. *Selected Torsion Angles* [°] ϕ, ψ, *and* ω *of the Backbone of the Cyclopentapeptides* **5a** [14c] *and* **5b** *in the Crystal*



	ω(Gly-Aib)	ω(Aib-Phe(2Me))	ω(Phe(2Me)-Aib)	ω(Aib-Gly)	ω(Gly-Gly)
5b Molecule A	– 176.2(5)	– 173.9(5)	– 168.0(5)	– 175.1(4)	176.3(5)
5b Molecule B	175.9(5)	176.3(5)	167.1(5)	174.9(5)	176.5(5)
	ω(Gly-Phe(2Me))	ω(Phe(2Me)-Aib)	ω(Aib-Aib)	ω(Aib-Gly)	ω(Gly-Gly)
5a [14c]	175.8(2)	165.2(3)	172.1(2)	177.3(3)	170.8(3)
	$\phi_{(i+1)}$	$\psi_{(i+1)}$	$\phi_{(i+2)}$	$\psi_{(i+2)}$	β-Turn
5b Molecule A	– 46.9(7)	– 47.3(6)	– 119.7(6)	24.5(8)	Type I
5b Molecule B	49.9(7)	45.1(6)	102.5(6)	– 16.6(7)	Type I′
5a [14c]	56.1(4)	39.9(4)	100.0(4)	– 16.1(4)	Type I′

results in two-dimensional layers of type-A molecules which lie parallel to the (100) plane and in which $R_4^4(27)$ ring motifs involving each of N(4)–H and N(10)–H twice *via* four molecules are discernable. The same type of interactions link the type-B molecules to each other, also forming layers parallel to the (100) plane.

In addition, N(1)–H of molecule A forms an intermolecular H-bond with O(1) of a neighboring H_2O molecule. The H-atoms of the H_2O molecule, in turn, donate to C=O O-atoms of two different type-B molecules (O(1)–H(11)$\cdots$O(41ii), O(1)–H(12)$\cdots$ O(44)). The corresponding NH group in molecule B, (N(31)–H), forms an intermolecular interaction with O(11) of molecule A. These four interactions serve to cross-link parallel layers of type-A and -B molecules to form an extended H-bonded bilayer. There are no interactions between these bilayers, because the Ph groups and other hydrophobic parts of the molecules face each other across the space between the bilayers.

All of the peptide bonds of the two independent molecules in **5b** are *trans*-configured as shown by the torsion angles ω (*Table 4*)[4]). The (*R*)-epimer of the previously synthesized cyclo(Gly-(*R*,*S*)-Phe(2Me)-Aib-Aib-Gly) (**5a**) [14c] shows the identical backbone conformation as molecule B of **5b** (*Table 4*), and an almost perfect superimposition of the two structures is observed. This is not surprising taking into account that the conformation of cyclopeptides is mainly determined by the sequence of the amino acids: in both cases, two unsubstituted α-amino acids (Gly) are followed by three α,α-disubstituted α-amino acids (Phe(2Me) and two Aib). On the other hand, it is astonishing that, in the case of **5b**, the epimer with (*S*)-Phe(2Me) forms a β-turn type I′, whereas in **5a** the same turn is formed by the (*R*)-Phe(2Me) epimer.

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[4]) Cyclopentapeptides are the smallest cyclopeptides with an all-*trans*-configuration, shown in a series of crystal structures (*e.g.*, [33]). A theoretical study of the minimum-energy conformations resulted in 23 conformations, including in most cases a β-turn and in a few cases one or two γ-turns [34].

Suitable crystals of the (*R*)-Phe(2Me)-containing epimer of cyclopentapeptide (*R*)-**5f** were obtained by crystallization from AcOEt/MeOH/hexane. The structure of $C_{30}H_{37}N_5O_5 \cdot MeOH$ has two molecules of the peptide in the asymmetric unit (*Fig. 2*), as well as sites for disordered MeOH and/or H_2O molecules. The solvent molecules could not be identified and modelled sufficiently well, so their contribution to the diffraction data was removed by using the *SQUEEZE* procedure (see *Exper. Part*). One of the peptide molecules has disorder of two atoms in the five-membered ring and also shows a slight conformational disorder of the peptide chain from C(45) to C(48), as well in the Ph rings.

The crystals are enantiomerically pure; however, the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the known (*S*)-configuration at C(6) (Pro) and C(15) (Phe). The configuration at C(9) (Phe(2Me)) is, therefore, (*R*). Both of the independent peptide molecules have the same configuration, but they differ quite significantly in the conformation of the peptide ring in the region between N(1) and C(6). The orientations of the Ph groups also differ between the two molecules.

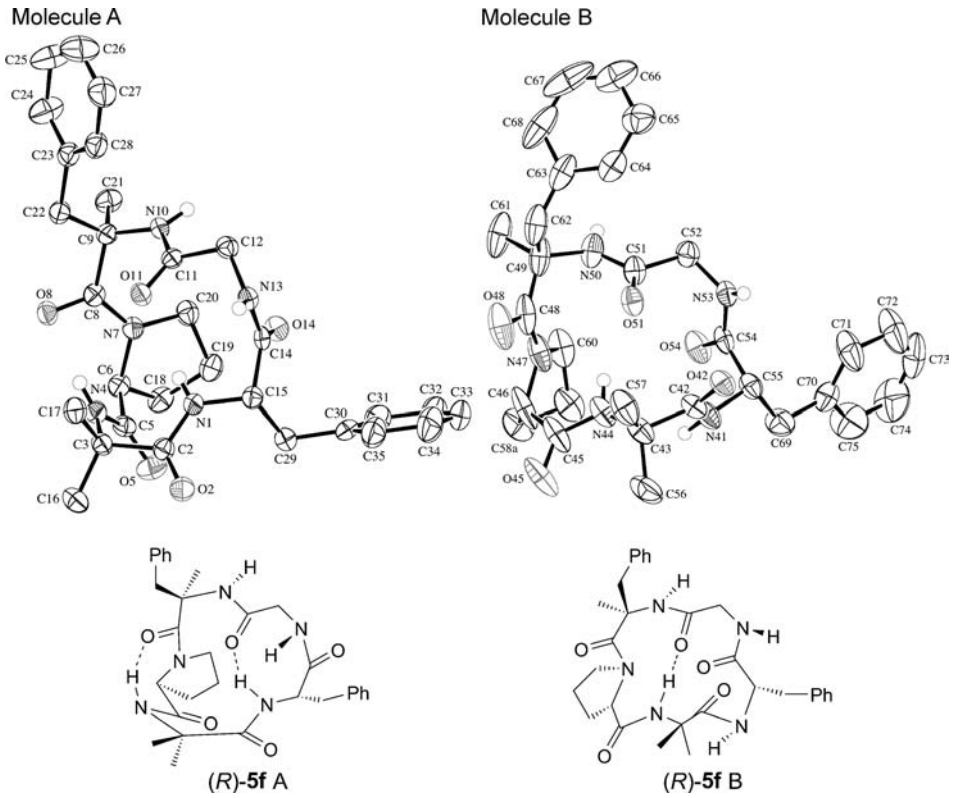

Fig. 2. *ORTEP Plot* [31] *of the molecular structure of the two symmetry-independent molecules* A *and* B *of cyclopentapeptide* (*R*)-**5f** (50% probability ellipsoids, arbitrary atom numbering, H-atoms bonded to C-atoms and one component of the disordered five-membered ring in molecule B omitted for clarity)

In molecule A, N(1)–H and N(4)–H form intramolecular H-bonds with amide O-atoms (graph sets *S*(8) and *S*(7), resp. [32]) (*Table 3*). N(10)–H and N(13)–H form intermolecular H-bonds to amide O-atoms, the former being with molecule B (graph set D) and the latter with another molecule A to form extended zig-zag A···A···A chains which run parallel to the [100] direction (graph set *C*(8)). In molecule B, only N(44)–H undergoes an intramolecular H-bonding (graph set *S*(10)), forming a β-turn (*Table 5*). N(53)–H interacts with an amide O-atom of molecule A (graph set D). Other NH donors presumably are H-bonding to solvent O-atoms. Considering only the above intermolecular interactions, the resulting network is composed of zig-zag chains of A molecules with pendant B molecules decorating the sides of the chain.

As in the cases of **5a** and **5b**, all amide bonds in both conformations of (*R*)-**5f** are *trans*-configured. Whereas the Gly-Phe(2Me) part of the two independent molecules of (*R*)-**5f** is similar, significant differences are observed in the Pro-Aib-Phe part. In conformer A, the C=O group of Gly is involved in an intramolecular H-bond with NH of Phe forming an α-turn, and the C=O group of Phe(2Me) forms an H-bond with NH of Aib (γ-turn). This conformation is quite unusual. On the other hand, in conformer B, a β-turn with an H-bond between NH of Aib and C=O of Gly stabilizes the conformation.

2.3. *Conformations of* Cyclo*pentapeptides* **5** *in Solution*. As a representative example, cyclo(Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe) ((*R*)-**5f**) was used for NMR studies in $CDCl_3$. The assignment of the ^{1}H-NMR signals was achieved by using COSY, TOCSY, HSQC, and HMBC techniques. The NH signals of Gly (6.85–6.0 ppm) and Phe (7.63 ppm) residues could be assigned on the basis of the TOCSY spectrum, and the HMBC spectrum allowed the identification of the NH signals of the α,α-disubstituted α-amino acids Phe(2Me) (6.30 ppm) and Aib (7.08 ppm). As solvent and temperature dependence of the chemical shift of amide NH signals can be used as an indication of intra- and intermolecular H-bonds [22e][35], the ^{1}H-NMR spectrum was recorded in $CDCl_3$ containing 1–10% of (D_6)DMSO (*Fig. 3*). Whereas the chemical shift of the NH signal of Phe(2Me) is strongly solvent-dependent, the NH signals of Phe, Aib, and Gly are barely influenced[5]), *i.e.*, these NH groups are not easily accessible for solvent molecules.

Table 5. *Selected Torsion Angles* [°] ϕ, ψ, *and* ω *of the Backbone of the Cyclopentapeptide* (*R*)-**5f** *in the Crystal*

(*R*)-**5f**	ω(Gly-Phe(2Me))	ω(Phe(2Me)-Pro)	ω(Pro-Aib)	ω(Aib-Phe)	ω(Phe-Gly)
Molecule A	–177.3(3)	–177.2(3)	–173.8(3)	–178.3(3)	–146.9(3)
Molecule B	–170.7(4)	–178.2(3)	179.3(4)	166.3(4)	–157.0(3)
	$\phi_{(i+1)}$	$\psi_{(i+1)}$	$\phi_{(i+2)}$	$\psi_{(i+2)}$	Turn
Molecule B	–54.2(5)	–40.2(5)	–75.5(5)	–16.1(6)	β-Turn Type I/III

[5]) The NH signal of Aib (7.08 ppm; $CDCl_3$) could not be detected after addition of 2–10% (D_6)DMSO, because it then overlaps with the *m* of the aromatic H-atoms (7.2–7.1 ppm). As the width of the aromatic *m* is only 0.2 ppm, it can be concluded that the chemical shift of NH(Aib) is rather constant and not solvent-dependent.

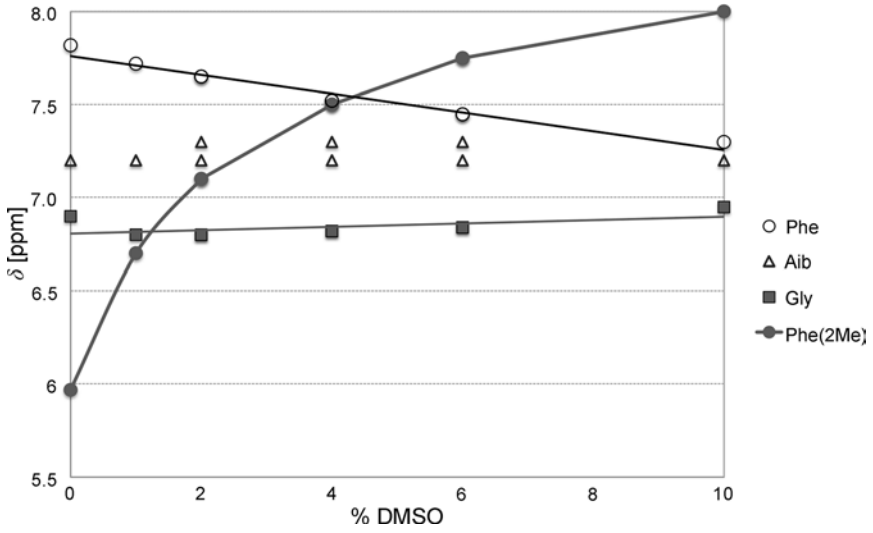

Fig. 3. *The chemical shifts of the NH resonances of* (*R*)-**5f** *as a function of the* (D_6)*DMSO concentration* (% (*v*/*v*)) *in* $CDCl_3$

A NOESY spectrum of (*R*)-**5f** in $CDCl_3$ showed cross-peaks for the interactions depicted in *Fig. 4*,*a*. Assuming that all peptide bonds adopt the *trans* conformation, this result correlates neither with conformation A nor conformation B in the crystal (*Fig. 2*). Examination of a *Dreiding* model of a conformation of (*R*)-**5f** fulfilling the special conditions resulting from the NOESY spectra and taking into consideration that NH of Phe(2Me) is not involved in an intramolecular H-bond, the presence of a γ-turn formed between NH(Aib) and CO(Phe(2Me)) as in conformation A in the crystal is likely. Furthermore, a second γ-turn formed by a H-bond between NH(Gly) and CO(Aib) seems plausible, accounting for the solvent independence of NH(Gly). The additional finding that the chemical shift of NH(Phe) is not solvent-dependent may be explained by steric shielding by the Ph group of Phe. Therefore, the conformation depicted in *Fig. 4*,*b*, with two γ-turns is proposed for the molecule in solution.

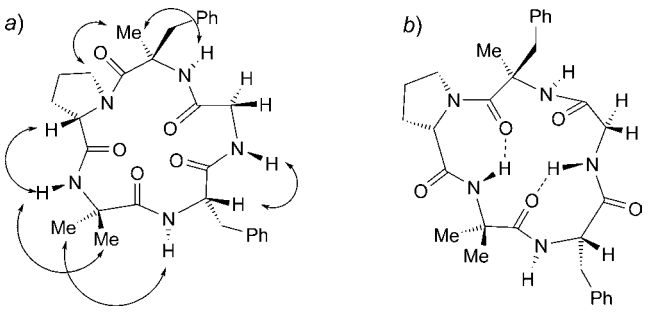

Fig. 4. a) *Observed NOE signals of* (*R*)-**5f** *in* $CDCl_3$. b) *Proposed all-*trans *conformation of* (*R*)-**5f** *in* $CDCl_3$ *solution*

3. Conclusions. – The present study shows that Aib- and Phe(2Me)-containing pentapeptides undergo smooth cyclization reactions to give the corresponding cyclopentapeptides. These 15-membered rings are generally formed in high yields. It is important to emphasize that dimerization was not observed in any of the studied cases (*cf.* [2][14c][16–18]). The best results were obtained with DEPC/EtN(^{i}Pr)$_2$ in DMF or TBTU/HOBt/EtN(^{i}Pr)$_2$ in DMF as the coupling reagent at room temperature. The highest yields were achieved in the cases of pentapeptides with a N-terminal Gly and a C-terminal Aib unit, leading to the cyclopentapeptides in 73–91% yield, whereas the yields of analogous pentapeptides with a C-terminal Gly or Phe were in the range of 45–64%. Exceptions are the two pentapeptides, H-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-OH ((*S*)-**4e**) and H-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-OH ((*S*)-**4f**), which gave the corresponding cyclopentapeptides in only 46 and 10% yield, respectively. The high efficiency of the cyclization in the case of C-terminal Aib-containing peptides may be explained by the easy formation of 4,4-dimethyl-1,3-oxazol-5(4*H*)-ones [22] as a result of the 'gem-dimethyl effect' (*Thorpe–Ingold* effect; see, *e.g.*, [36]). Furthermore, the significant difference in the yields of the cyclization of pentapeptides **4e** and **4f** containing the (*R*)-Phe(2Me)-Pro or (*S*)-Phe(2Me)-Pro-containing dipeptide unit has to be mentioned (see *Table 2*). In both cases, the ring closure of the (*R*)-Phe(2Me)-Pro-containing epimer was much more efficient than that of the (*S*)-Phe(2Me)-Pro epimer, in agreement with the known result that the formation of cyclic peptides containing a D-amino acid is easier than that of the all-L peptide (see introduction, *e.g.*, [12][13]).

The crystal structures of the two selected cyclopentapeptides, cyclo(Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly) (**5b**) and cyclo(Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe) ((*R*)-**5f**), are quite different. Whereas the racemic **5b** forms β-turns of type I and I′, respectively, the enantiomerically pure (*R*)-**5f** exists in two different conformations. In one of them, again a β-turn is formed with torsion angles between those of types I and III. In the second conformation, an inverse γ-turn and, surprisingly, an α-turn stabilize the structure of the molecule. Based on NMR studies of (*R*)-**5f** in $CDCl_3$, a conformation with two γ-turns is most likely in solution.

We thank the analytical sections of our institute for spectra and analyses, and the *Stipendienfonds der Basler Chemischen Industrie* and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Experimental Part

1. *Abbreviations.* Aib, 2-aminoisobutyric acid (2-methylalanine); DEPC, diethyl phosphorocyanidate; EtN(^{i}Pr)$_2$ (*Hünig* base); DPPA, diphenyl phosphorazidate; HOBt, 1-hydroxybenzotriazole; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate; TFA, CF_3COOH; Z, (benzyloxy)carbonyl.

2. *General.* See [25][26][37]. The synthesis of all protected pentapeptides **6** has been described in [26]. Solvents were purified by standard procedures. TLC: *Merck* TLC glass plates, silica gel *60* F_{254}. Prep. layer chromatography (PLC): *Merck* glass plates, silica gel *60* F_{254}. Column chromatography (CC): *Uetikon-Chemie*; silica gel *C-560* (0.040–0.063 mm); or *Merck 60*, 0.040–0.063 mm. High-performance liquid chromatography (HPLC): *Varian-2510* and UV detector *Varian-2550*; *Spherisorb ODS2*, 5 μm, 250 × 4.6 mm (anal.) and *Spherisorb ODS2*, 5 μm, 250 × 20 mm (prep.). M.p.: *Mettler-FP-5* apparatus, uncorrected. $[\alpha]_D$ Values: *Perkin-Elmer-241* polarimeter at 21°. IR Spectra: *Perkin-Elmer-781* spectrometer, in KBr. ^{1}H- and ^{13}C-NMR spectra: *Bruker AC-300*, *Bruker ARX-300*, or *Bruker AMX-600* spectrometer at 300 or 600 (^{1}H) and 75.5 or 150 MHz (^{13}C), in $CDCl_3$, CD_3OD, or (D_6)DMSO. The

multiplicities of ^{13}C signals were determined by the DEPT technique. ESI- and APCI-MS: *Finnigan TSQ-700* instrument; in *m/z* (rel. %).

General Procedure 1 (*GP 1; Saponification of Peptide Methyl Esters*). To a soln. of a peptide methyl ester (1 mmol) in 10 ml of THF/MeOH/H_2O 3 : 1 : 1 at 0° was added LiOH · H_2O (2.5 mmol). The mixture was stirred at 0° for 1 h. Then, it was neutralized by addition of aq. 2 N HCl, and the org. solvents were evaporated (rotavapor). The residue was dissolved in AcOEt, und the mixture was washed with aq. 0.5 N HCl. The org. phase was dried (Na_2SO_4), and the solvent was evaporated.

General Procedure 2 (*GP 2; Hydrogenolysis*). A mixture of Z-protected peptide in MeOH and *ca.* 10% Pd/C (10%) at r.t. was stirred under H_2 (balloon) overnight. The mixture was filtered through a *Celite* pad, and the solvent of the filtrate was evaporated to dryness.

General Procedure 3 (*GP 3; Transfer Hydrogenolysis*). To a mixture of Z-protected peptide (1 mmol) and the same amount of Pd/C (10%) in MeOH was added HCO_2NH_4 (5 mmol). The mixture was heated at reflux for 10 min, the hot mixture was filtered through a *Celite* pad and washed with MeOH. The solvent of the filtrate was evaporated to dryness.

General Procedure 4 (*GP 4; Hydrolysis of Peptide Amides*). A soln. of Z-protected peptide amide (1 mmol) in 3N HCl (THF/H_2O 1 : 1) was stirred at r.t. for 1 – 4.5 h. Then, 2N HCl was added, and the mixture was extracted with Et_2O. The org. phase was dried (Na_2SO_4), and the solvent was evaporated.

General Procedure 5 (*GP 5; Cyclization with DEPC*). To a *ca.* 1.5×10^{-3} M soln. of a deprotected pentapeptide (0.1 mmol) in DMF (67 ml) at 0° was added dropwise DEPC (0.2 – 0.4 mmol) and EtN(^{i}Pr)$_2$ (1% (*v*/*v*)), and the mixture was stirred overnight at r.t. Then, DMF was evaporated, and the residue was purified chromatographically and crystallized.

3. *Synthesis of the Deprotected Pentapeptides* **4**. 3.1. *H-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly-OH* (**4a**). 3.1.1. *Z-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly-OH* (**7a**). To a soln. of *Z-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly-OMe* (**6a**; 1.46 g, 2.39 mmol) in MeOH (1 ml) at r.t. was added slowly 2N NaOH (8 ml), and the mixture was stirred for 20 min. Then, 2N HCl was added until pH 1, and the mixture was extracted with CH_2Cl_2. The combined org. phase was dried (Na_2SO_4), the solvent was evaporated, and the crystalline product was dried: 1.22 g (85%) of **7a**. Colorless crystals. M.p. 95.4 – 96.9°. IR (KBr): 3310*s*, 3060*m*, 3030*m*, 2980*m*, 2940*m*, 1665*s*, 1590*s*, 1455*m*, 1385*m*, 1260*m*, 1240*m*, 1220*m*, 1190*m*, 700*m*. ^{1}H-NMR (CD_3OD): 8.21 (*s*, NH); 7.86 (*t*-like, NH); 7.77, 7.46 (2*s*, 2 NH); 7.3 – 7.2 (*m*, 8 arom. H); 7.15 – 7.1 (*m*, 2 arom. H); 5.04 (*s*, PhCH_2O); 4.1 – 3.6 (*m*, 2 CH_2(Gly)); 3.39, 3.02 (*AB*, J_{AB} = 13.6, PhCH_2); 1.49, 1.48, 1.45, 1.39, 1.34 (5*s*, 2 Me_2C, Me(Phe(2Me)). ^{13}C-NMR (CD_3OD): 178.1, 177.0, 176.1, 172.9, 172.0 (5*s*, 4 CO(amide), COOH); 159.3 (*s*, CO(urethane)); 138.0, 137.8 (2*s*, 2 arom. C); 132.1, 129.5, 129.1, 128.8, 127.9 (5*d*, 10 arom. CH); 67.8 (*t*, PhCH$_2$O); 61.2, 58.4, 58.0 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 45.1, 41.9, 41.5 (3*t*, 2 CH_2(Gly), PhCH$_2$); 26.6, 26.3, 25.1, 24.7, 24.0 (5*q*, 2 *Me*$_2$C, *Me*(Ph(2Me))). ESI-MS(neg.): 596 ([*M* – 1]$^-$). Anal. calc. for $C_{30}H_{39}N_5O_8 \cdot 0.5\ H_2O$ (606.68): C 59.39, H 6.65, N 11.45; found: C 59.25, H 6.40, N 11.56.

3.1.2. *H-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly-OH* (**4b**). According to *GP 2*, a mixture of **7a** (330 mg, 0.552 mmol) and Pd/C (33 mg) in MeOH (4 ml) was hydrogenated for 19 h: 220 mg (86%) of **4b**. Colorless solid. M.p. 138.9 – 140.7°. IR (KBr): 3380*m*, 3060*m*, 3020*m*, 2980*m*, 2940*m*, 1710*s* (br), 1535*s*, 1385*m*, 705*w*. ^{1}H-NMR (D_2O): 7.4 – 7.3 (*m*, 3 arom. H); 7.25 – 7.2 (*m*, 2 arom. H); 3.85 – 3.75 (*m*, 2 CH_2(Gly)); 3.32, 3.10 (*AB*, J_{AB} = 13.6, PhCH_2); 1.55, 1.52, 1.48, 1.44, 1.43 (5*s*, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR (D_2O): 179.7, 179.4, 178.6, 178.1, 169.4 (5*s*, 4 CO (amide), COOH); 138.5 (*s*, 1 arom. C); 133.7, 131.2, 130.1 (3*d*, 5 arom. CH); 62.9, 59.9 (2*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 46.3, 43.3, 43.2 (3*t*, 2 CH_2(Gly), PhCH$_2$); 27.2, 27.0, 26.6, 25.3 (4*q*, 2 : 1 : 1 : 1, 2 *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 502 (8, [*M* + K]$^+$), 486 (29, [*M* + Na]$^+$), 464 (100, [*M* + 1]$^+$).

3.2. *H-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Aib-OH* (**4c**). 3.2.1. *Z-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Aib-OH* (**7c**). According to *GP 4*, *Z-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Aib-N(Me)Ph* (**6c**; 425 mg, 0.619 mmol) was hydrolyzed. After 4.5 h, the mixture was extracted with AcOEt, and the solvent was evaporated: 364 mg (98%) of **7c**. Colorless solid. M.p. 122.7 – 124.2°. IR (KBr): 3310*s*, 3060*m*, 3030*m*, 2980*m*, 2940*m*, 1710*s*, 1660*s*, 1530*s*, 1470*m*, 1455*m*, 1385*m*, 1365*m*, 1280*m*, 1260*m*, 1230*m*, 1150*m*, 700*m*. ^{1}H-NMR ($CDCl_3$ + 2 drops of CD_3OD): 7.34, 7.68 (2*s*, 2 NH); 7.35 – 7.3 (*m*, 8 arom. H, 2 NH); 7.1 – 7.05 (*m*, 2 arom. H); 6.95 (*s*, NH); 5.08 (*s*, PhCH_2O); 3.8 – 3.75 (*m*, 2 CH_2(Gly)); 3.34, 3.05 (*AB*, J_{AB} = 13.6, PhCH_2); 1.52, 1.45, 1.42, 1.38 (4*s*, 2 : 1 : 1 : 1, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$ + 2 drops of CD_3OD): 176.6, 175.6, 175.1,

170.92, 170.88 (5*s*, 4 CO(amide), COOH); 157.4 (*s*, CO(urethane)); 136.0, 135.6 (2*s*, 2 arom. C); 130.5, 128.4, 128.2, 127.8, 126.9 (5*d*, 10 arom. CH); 67.1 (*t*, Ph*C*H$_2$O); 59.5, 56.8, 56.4 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 44.8, 44.4, 40.6 (3*t*, 2 CH$_2$(Gly), Ph*C*H$_2$); 25.2, 24.8, 24.5, 24.4, 22.7 (5*q*, 2 *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 602 (100, $[M+Na]^+$), 598 (5, $[M+1]^+$).

3.2.2. *H-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Aib-OH* (**4c**). According to *GP 2*, **7c** (48 mg, 0.08 mmol) in MeOH (2 ml) was treated with H_2 in the presence of Pd/C (5 mg). After 30 min, the product precipitated. After addition of DMF (40 ml), the mixture was filtered through a *Celite* pad, and the solvent was evaporated: 35 mg (94%) of **4c**.

Alternatively, transfer hydrogenolysis (*GP 3*) of **7c** (543 mg (0.91 mmol) in MeOH (20 ml) with HCO_2NH_4 (290 mg, 4.6 mmol) and Pd/C (544 mg) gave 390 mg (93%) of **4c**. Colorless solid. M.p. 172.7–173.2°. IR (KBr): 3400*m*, 3280*s*, 3060*m*, 3030*m*, 2980*m*, 2940*m*, 1680*s*, 1660*s*, 1640*s*, 1565*s*, 1535*s*, 1470*m*, 1455*m*, 1440*m*, 1425*m*, 1405*m*, 1390*m*, 1365*m*, 1330*m*, 1280*m*, 710*m*. ^{1}H-NMR (D_2O): 7.4–7.35 (*m*, 3 arom. H, 2 NH); 7.2–7.15 (*m*, 2 arom. H); 3.9–3.75 (*m*, 2 CH$_2$(Gly)); 3.31, 3.12 (*AB*, J_{AB} = 13.3, PhC*H*$_2$); 1.51, 1.44 (2*s*, 2:3, 2 Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR (D_2O): 184.6, 178.7, 177.7, 173.1, 169.5 (5*s*, 4 CO(amide), COOH); 138.1 (*s*, 1 arom. C); 133.2, 131.2 130.1 (3*d*, 5 arom. CH); 63.2, 60.8, 59.8 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 45.9, 43.6, 43.4 (3*t*, 2 CH$_2$(Gly), Ph*C*H$_2$); 27.1, 26.9, 26.8, 24.7 (4*q*, 2:1:1:1, 2 *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 486 (28, $[M+Na]^+$), 464 (100, $[M+1]^+$).

3.3. *H-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Phe-OH* (**4d**). According to *GP 2*, *Z-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Phe-OBn* (**6d**; 127 mg, 0.169 mmol) was deprotected: 88 mg (99%) **4d** (mixture of diastereoisomers). Colorless foam. M.p. 146.8–150.0°. IR (KBr): 3320*m*, 3060*m*, 3030*m*, 2930*m*, 1660*s*, 1535*m*, 1500*m*, 1200*m*, 1135*m*, 700*m*. ^{1}H-NMR (CD_3OD): 7.35–7.1 (*m*, 10 arom. H); 4.5–4.45 (*m*, CH(2)(Phe)); 3.95–3.55 (*m*, 2 CH$_2$(Gly)); 3.45–3.35, 3.25–3.0 (2*m*, 1:3, 2 PhC*H*$_2$); 1.48, 1.43, 1.39, 1.35 (4*s*, Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR (CD_3OD): 176.8, 176.6, 176.3, 171.1, 167.9, 167.8 (6*s*, 4 CO(amide), COOH); 139.1, 138.9, 137.4, 137.3 (4*s*, 2 arom. C); 131.8, 131.7, 130.7, 129.5, 129.3, 129.2, 128.9, 128.1, 127.9, 127.6, 126.8 (11*d*, 10 arom. CH); 61.5, 61.4, 58.3, 58.2 (4*s*, C(2)(Aib), C(2)(Phe(2Me))); 54.1 (*d*, CH(2)(Phe)); 44.7, 41.9, 41.0, 38.8, 38.6 (5*t*, 2 CH$_2$(Gly), 2 Ph*C*H$_2$); 25.8, 25.7, 25.5, 23.8, 23.3 (5*q*, *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 548 (100, $[M+Na]^+$], 526 (88, $[M+1]^+$), 361 (23, $[M-Phe]^+$).

3.4. *H-Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe-OH* ((*R*)-**4d**). 3.4.1. *Z-Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe-OMe* ((*R*)-**6d′**; 505 mg, 0.750 mmol) in THF/MeOH/H_2O 3:1:1 (6 ml) was treated with LiOH·H_2O (81 mg, 1.930 mmol): 464 mg (94%) (*R*)-**7d**. Colorless solid. M.p. 146.8–148.0°. $[\alpha]_D^{21} = +74.6$ (*c* = 1.02, EtOH). IR (KBr): 3300*m*, 3060*m*, 3030*m*, 2980*m*, 2930*m*, 1725*s*, 1670*s*, 1535*s*, 1455*m*, 1385*m*, 1335*m*, 1265*m*, 1225*m*, 1190*m*, 1170*m*, 1150*m*, 700*m*. ^{1}H-NMR ($CDCl_3$ + 2 drops of CD_3OD): 7.78 (br. *s*, NH); 7.72 (*s*, NH); 7.40 (*d*, *J* = 7.4, NH); 7.35–7.0 (*m*, 15 arom. H, 1 NH); 5.06, 5.04 (*AB*, J_{AB} = 12.3, PhC*H*$_2$O); 4.6–4.5 (*m*, CH(2)(Phe)); 3.8–3.55 (*m*, 2 CH$_2$(Gly)); 3.4–3.2, 3.1–3.0 (2*m*, 1:1, 2 PhC*H*$_2$); 1.44, 1.37, 1.31 (3*s*, Me$_2$C; Me(Phe(2Me))). ^{13}C-NMR (CD_3OD): 177.1, 176.8, 174.6, 172.5, 171.5 (5*s*, 4 CO(amide), COOH); 159.4 (*s*, CO(urethane)); 138.5, 138.0, 137.5 (3*s*, 3 arom. C); 131.8, 130.5, 129.5, 129.4, 129.3, 129.1, 128.9, 127.9, 127.7 (9*d*, 15 arom. CH); 68.0 (*t*, Ph*C*H$_2$O); 61.0, 58.2 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 55.2 (*d*, CH(2)(Phe)); 45.2, 44.8 (2*t*, 2 CH$_2$(Gly)); 41.6, 38.4 (2*t*, 2 Ph*C*H$_2$); 25.8, 25.5, 23.6 (3*q*, *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 682 (100, $[M+Na]^+$). Anal. calc. for $C_{35}H_{41}N_5O_8$ (659.74): C 63.72, H 6.26, N 10.62; found: C 63.42, H 6.44, N 10.61.

3.4.2. *H-Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe-OH* ((*R*)-**4d**). According to *GP 2*, (*R*)-**7d** (358 mg, 0.681 mmol) in MeOH (6 ml) was deprotected (6 h): 285 mg (quant.) of (*R*)-**4d**. Colorless solid. M.p. 169.0–171.8°. $[\alpha]_D^{21} = +67.4$ (*c* = 0.522, 2,2,2-trifluoroethanol). IR (KBr): 3280*s*, 3060*m*, 3030*m*, 2980*m*, 2930*m*, 1675*s*, 1535*s*, 1455*m*, 1440*m*, 1385*m*, 1330*m*, 1280*m*, 1245*m*, 1180*m*, 1155*m*, 700*m*. ^{1}H-NMR ($CDCl_3$ + 2 drops of TFA): 7.4–7.1 (*m*, 10 arom. H); 4.7–4.6 (*m*, CH(2)(Phe)); 3.9–3.6 (*m*, 2 CH$_2$(Gly)); 3.45–3.05 (*m*, 2 PhC*H*$_2$); 1.47, 1.42, 1.39 (3*s*, Me$_2$C; Me(Phe(2Me))). ^{13}C-NMR (CD_3OD + 2 drops of TFA): 177.0, 176.6, 174.8, 171.3, 167.7 (5*s*, 4 CO(amide), COOH); 138.5, 137.4 (2*s*, 2 arom. C); 131.8, 130.4, 129.4, 129.3, 128.1, 127.8 (6*d*, 10 arom. CH); 61.4, 58.2 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 55.3 (*d*, CH(2)(Phe)); 44.8, 41.9, 41.4, 38.3 (4*t*, 2 CH$_2$(Gly), 2 Ph*C*H$_2$); 25.6, 23.6 (2*q*, 2:1, *Me*$_2$C, *Me*(Phe(2Me))). APCI-MS: 526 ($[M+Na]^+$).

3.5. *H-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-OH* ((*S*)-**4d**). 3.5.1. *Z-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-OH* ((*S*)-**7d**). According to *GP 1*, *Z-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-OMe* ((*S*)-**6d′**; 461 mg, 0.684 mmol) in

THF/MeOH/H_2O 3:1:1 (6 ml) was treated with LiOH · H_2O (72 mg, 1.716 mmol): 439 mg (97%) (*S*)-**7d**. Colorless solid. M.p. 163.0–165.4°. $[\alpha]_D^{21} = -67.2$ ($c = 0.93$, EtOH). IR (KBr): 3290*m*, 3060*w*, 3030*w*, 2980*m*, 2930*m*, 1730*s*, 1660*s*, 1650*s*, 1535*s*, 1465*m*, 1410*m*, 1385*m*, 1365*m*, 1330*m*, 1260*m*, 1230*m*, 1195*m*, 1170*m*, 700*m*. ^{1}H-NMR (CD_3OD): 8.16 (*t*-like, NH); 8.10 (*s*, NH); 7.77 (*s*, NH); 7.54 (*d*, $J = 7.8$, NH); 7.4–7.1 (*m*, 15 arom. H); 5.10, 5.03 (*AB*, $J_{AB} = 12.4$, PhCH_2O); 4.65–4.55 (*m*, CH(2)(Phe)); 3.85–3.5 (*m*, 2 CH_2(Gly)); 3.41 (*A* of *AB*, $J_{AB} = 13.5$, 1 H of PhCH_2); 3.2–3.05 (*m*, 3 H of 2 PhCH_2); 1.46, 1.41, 1.33 (3*s*, Me_2C; Me(Phe(2Me))). ^{13}C-NMR (CD_3OD): 177.3, 177.0, 174.7, 172.5, 171.5 (5*s*, 4 CO(amide), COOH); 159.4 (*s*, CO(urethane)); 138.6, 138.1, 137.6 (3*s*, 3 arom. C); 131.9, 130.5, 129.5, 129.4, 129.2, 129.1, 128.9, 127.9, 127.7 (9*d*, 15 arom. CH); 68.0 (*t*, Ph*C*H_2O); 61.0, 58.3 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 55.6 (*d*, CH(2)(Phe)); 45.2, 44.9 (2*t*, 2 CH_2(Gly)); 41.2, 38.4 (2*t*, 2 Ph*C*H_2); 26.2, 25.1, 23.6 (3*q*, *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 682 (100, $[M + Na]^+$). Anal. calc. for $C_{35}H_{41}N_5O_8$ (659.74): C 63.72, H 6.26, N 10.62; found: C 63.83, H 6.35, N 10.31.

3.5.2. *H-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-OH* ((*S*)-**4d**). According to *GP 2*, (*S*)-**7d** (317 mg, 0.481 mmol) in MeOH (15 ml) was deprotected (4.5 h). During the evaporation of MeOH, 121 mg of sparingly soluble (*S*)-**4d′** precipitated. Evaporation of the mother liquor gave 124 mg of a much more soluble (*S*)-**4d″**. Total yield of (*S*)-**4d**: 245 mg (97%).

*Data of (*S*)-***4d′***: Colorless solid. M.p. 132.5–134.1°. $[\alpha]_D^{21} = +74.9$ ($c = 0.513$, 2,2,2-trifluoroethanol). IR (KBr): 3370*m*, 3340*m*, 3240*s*, 3015*m*, 2980*m*, 2930*m*, 1650*s*, 1570*s*, 1530*s*, 1455*m*, 1400*m*, 1385*m*, 1365*m*, 1260*m*, 1240*m*, 700*m*. ^{1}H-NMR (CD_3OD + 2 drops of TFA): 7.35–7.1 (*m*, 10 arom. H); 4.65–4.55 (*m*, CH(2)(Phe)); 3.85–3.55 (*m*, 2 CH_2(Gly)); 3.38 (*A* of *AB*, $J_{AB} = 13.5$, 1 H of PhCH_2); 3.25–3.05 (*m*, 3 H of 2 PhCH_2); 1.50, 1.47, 1.39 (3*s*, Me_2C; Me(Phe(2Me))). ^{13}C-NMR (CD_3OD + 2 drops of TFA): 177.0, 176.6, 174.9, 171.2, 167.7 (5*s*, 4 CO(amide), COOH); 138.6, 137.4 (2*s*, 2 arom. C); 131.8, 130.5, 129.4, 129.3, 128.1, 127.8 (6*d*, 10 arom. CH); 61.4, 58.3 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 55.6 (*d*, CH(2)(Phe)); 44.8, 41.9, 41.5, 38.3 (4*t*, 2 CH_2(Gly), 2 Ph*C*H_2); 26.2, 24.9, 23.4 (3*q*, *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 564 (10, $[M + K]^+$), 548 (21, $[M + Na]^+$), 526 (100, $[M + 1]^+$).

*Data of (*S*)-***4d″***: Colorless solid. M.p. 156.4–158.8°. $[\alpha]_D^{21} = -17.7$ ($c = 0.494$, 2,2,2-trifluoroethanol). IR (KBr): 3400*s*, 3300*s*, 3060*m*, 3030*m*, 2980*m*, 2930*m*, 1660*s*, 1600*s*, 1570*s*, 1455*m*, 1395*m*, 1330*m*, 1280*m*, 1240*m*, 1215*m*, 1200*m*, 1155*m*, 745*m*, 700*m*. ^{1}H-NMR (CD_3OD): 7.35–7.1 (*m*, 10 arom. H); 4.45–4.35 (*m*, CH(2)(Phe)); 3.85–3.4 (*m*, 2 CH_2(Gly)); 3.3–3.05 (*m*, 2 PhCH_2); 1.46, 1.38 (2*s*, 1:2, Me_2C; Me(Phe(2Me))). ^{13}C-NMR (CD_3OD): 178.2, 176.2, 176.1, 171.2, 168.7 (5*s*, 4 CO(amide), COOH); 139.6, 137.2 (2*s*, 2 arom. C); 131.8, 130.8, 129.3, 129.1, 128.1, 127.4 (6*d*, 10 arom. CH); 61.4, 58.2 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 57.6 (*d*, CH(2)(Phe)); 44.5, 42.8, 42.4, 38.8 (4*t*, 2 CH_2(Gly), 2 Ph*C*H_2); 26.6, 24.7, 23.2 (3*q*, *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 548 (30, $[M + Na]^+$), 526 (100, $[M + 1]^+$).

3.6. *H-Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Aib-OH* (**4e**). 3.6.1. *Z-Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Aib-OH* (**7e**). According to *GP 4*, *Z-Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph* (**6e**; 538 mg, 0.740 mmol) was hydrolyzed (1 h). Filtration of the precipitate gave 273 g of **7e**. After evaporation of the solvent and crystallization from CH_2Cl_2/Et_2O/hexane, an additional 109 mg of **7e** were obtained. Total yield: 382 mg (81%).

3.6.2. *H-Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Aib-OH* (**4e**). Hydrogenolysis of **7e** (190 mg, 0.298 mmol) in MeOH (3 ml) with HCO_2NH_4 (95 mg) and Pd/C (190 mg) according to *GP 3* gave 143 mg (96%) of **4e**.

3.7. *H-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-OH* ((*R*)-**4e**). 3.7.1. *Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-OH* ((*R*)-**7e**). According to *GP 4*, *Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph* ((*R*)-**6e**; 298 mg, 0.410 mmol) was hydrolyzed (1 h): 215 mg (82%) of (*R*)-**7e**. Colorless solid. M.p. 125.0–125.7°. $[\alpha]_D^{21} = +119.0$ ($c = 0.742$, EtOH). IR (KBr): 3420*m*, 3340*s*, 3290*s*, 3060*m*, 3030*m*, 2990*m*, 2949*m,* 1720*s*, 1675*s*, 1605*s*, 1540*s*, 1465*m*, 1420*m*, 1390*m*, 1365*m*, 1310*m*, 1285*m*, 1240*s*, 1160*m*, 1050*m*, 765*m*, 700*m*. ^{1}H-NMR (CD_3OD): 8.17, 7.76, 7.55 (3*s*, 3 NH); 7.4–7.15 (*m*, 8 arom. H); 7.15–7.1 (*m*, 2 arom. H); 5.11, 5.08 (*AB*, $J_{AB} = 12.4$, PhCH_2O); 4.26 (*t*, $J = 8.3$, CH(2)(Pro)); 3.92, 3.71 (*AB*, $J_{AB} = 17.2$, CH_2(Gly)); 3.85–3.7, 3.65–3.5 (2*m*, CH_2(5)(Pro)); 3.54, 3.06 (*AB*, $J_{AB} = 13.6$, PhCH_2); 2.35–2.2, 2.05–1.95, 1.95–1.8, 1.8–1.6 (4*m*, 1 H each, CH_2(3), CH_2(4)(Pro)); 1.52, 1.51, 1.47, 1.46, 1.31 (5*s*, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR (CD_3OD): 178.1, 176.7, 175.2, 174.4, 171.4 (5*s*, 4 CO(amide), COOH); 159.3 (*s*, CO(urethane)); 138.1 (*s*, 2 arom. C); 132.3, 129.5, 129.2, 128.9, 127.7 (5*d*, 10 arom. CH); 67.8 (*t*, Ph*C*H_2O); 65.3 (*d*, CH(2)(Pro)); 60.0, 58.1, 57.1 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 50.0 (*t*,

CH_2(5)(Pro)); 44.1 (*t*, CH_2(Gly)); 41.9 (*t*, Ph*C*H_2); 29.8 (*t*, CH_2(3)(Pro)); 27.0 (*t*, CH_2(4)(Pro)); 27.5, 26.2, 24.4, 24.1, 21.0 (5*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 660 (100, $[M+Na]^+$).

3.7.2. *H-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-OH* ((*R*)-**4e**). According to *GP 3*, (*R*)-**7e** (280 mg, 0.550 mmol) in MeOH (8 ml) was treated with HCO_2NH_4 (139 mg, 2.20 mmol) and Pd/C (281 mg): 209 mg (95%) of (*R*)-**4e**. Colorless solid. M.p. 187.3–190.4°. $[\alpha]_D^{21} = +71.8$ ($c = 0.301$, H_2O). IR (KBr): 3350*s*, 3260*s*, 3060*m*, 3030*m*, 2980*m*, 2940*m*, 2870*m*, 1730*s*, 1650*s*, 1565*s*, 1535*s*, 1455*m*, 1400*s*, 1360*m*, 1280*m*, 1240*m*, 1210*m*, 1180*m*, 1160*m*, 705*m*. ^{1}H-NMR (CD_3OD): 7.4–7.2 (*m*, 3 arom. H); 7.15–7.1 (*m*, 2 arom. H); 4.50 (*t*-like, CH(2)(Pro)); 3.8–3.7 (*m*, CH_2(Gly)); 3.65–3.35 (*m*, CH_2(5)(Pro)); 3.54, 3.13 (*AB*, $J_{AB} = 13.6$, PhCH_2); 2.2–2.05, 2.05–1.8 (2*m*, 1:3, CH_2(3), CH_2(4)(Pro)); 1.55, 1.54, 1.53, 1.49, 1.35 (5*s*, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR ((D_6)DMSO): 177.2, 172.7, 171.9, 170.5, 169.8 (5*s*, 4 CO(amide), COOH); 136.9 (*s*, 1 arom. C); 131.0, 127.8, 126.3 (3*d*, 5 arom. CH); 62.5 (*d*, CH(2)(Pro)); 58.1, 56.1, 55.5 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 47.8 (*t*, CH_2(5)(Pro)); 42.1 (*t*, CH_2(Gly)); 40.2 (*t*, Ph*C*H_2); 27.5 (*t*, CH_2(3)(Pro)); 25.2 (*t*, CH_2(4)(Pro)); 26.0, 24.4, 24.3, 24.0, 20.5 (5*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 526 (100, $[M+Na]^+$).

3.8. *H-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-OH* ((*S*)-**4e**). 3.8.1. *Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-OH* ((*S*)-**7e**). According to *GP 4*, *Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph* ((*S*)-**6e**; 242 mg, 0.333 mmol) was hydrolyzed (1 h). CC (CH_2Cl_2/MeOH/AcOH 100:10:1): 176 mg (83%) of (*S*)-**7e**. Colorless solid. M.p. 134.6–137.8°. $[\alpha]_D^{21} = -1.3$ ($c = 0.547$, EtOH). IR (KBr): 3300*m*, 3060*w*, 3030*w*, 2980*m*, 2930*m*, 1730*s*, 1660*s*, 1610*s*, 1530*s*, 1455*m*, 1410*m*, 1365*m*, 1270*m*, 1150*m*, 700*m*. ^{1}H-NMR (CD_3OD, 318K): 7.35–7.15 (*m*, 8 arom. H); 7.1–7.05 (*m*, 2 arom. H); 5.12, 5.05 (*AB*, $J_{AB} = 12.4$, PhCH_2O); 4.35–4.2 (*m*, CH(2)(Pro)); 4.1–3.85, 3.8–3.5 (2*m*, CH_2(Gly), CH_2(5)(Pro)); 3.11 (*A* of *AB*, $J_{AB} = 13.4$, 1 H of PhCH_2); 3.1–2.85 (*m*, 1 H of PhCH_2); 2.2–1.95, 1.95–1.6 (2*m*, CH_2(3), CH_2(4)(Pro)); 1.44, 1.39 (2*s*, 1:2, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR (CD_3OD, 318K): 175.3, 172.3 (2 br. *s*, 4 CO(amide), COOH); 158.9 (*s*, CO(urethane)); 138.1, 136.3 (2*s*, 2 arom. C); 131.6, 129.6, 129.2, 128.4 (4*d*, 10 arom. CH); 68.1 (*t*, Ph*C*H_2O); 64.6 (*d*, CH(2)(Pro)); 61.8, 58.7, 58.2 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 50.1 (*t*, CH_2(5)(Pro)); 45.2, 44.0 (2*t*, CH_2(Gly), Ph*C*H_2); 29.4, 27.2 (2*t*, CH_2(3), CH_2(4)(Pro)); 26.6 (br.), 25.4, 24.3 (3*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 676 (11, $[M+K]^+$), 660 (100, $[M+Na]^+$).

3.8.2. *H-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-OH* ((*S*)-**4e**). According to *GP 3*, (*S*)-**7e** (184 mg, 0.289 mmol) in MeOH (4 ml) was treated with HCO_2NH_4 (91 mg, 1.44 mmol) and Pd/C (188 mg). Crystallization from MeOH/Et_2O gave 132 mg (91%) of (*S*)-**4e**. Colorless solid. M.p. 161.2–161.9°. $[\alpha]_D^{21} = -62.4$ ($c = 0.640$, H_2O). IR (KBr): 3360*m*, 3200*m*, 3050*m*, 3030*m*, 2980*m*, 2930*m*, 2870*m*, 1730*s*, 1655*s*, 1565*s*, 1535*s*, 1455*m*, 1390*s*, 1360*m*, 1310*m*, 1280*m*, 1210*m*, 1195*m*, 1180*m*, 1150*m*, 700*m*. ^{1}H-NMR ((D_6)DMSO): 8.55 (br.), 8.37, 7.66, 7.52 (4*s*, NH); 7.35–7.2 (*m*, 3 arom. H); 7.15–7.05 (*m*, 2 arom. H); 4.25–4.2 (*m*, CH(2)(Pro)); 3.45–3.35 (*m*, CH_2(Gly), CH_2(5)(Pro)); 3.16, 3.04 (*AB*, $J_{AB} = 13.4$, PhCH_2); 2.0–1.75, 1.75–1.6 (2*m*, 3:1, CH_2(3), CH_2(4)(Pro)); 1.33, 1.31, 1.29 (3*s*, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR ((D_6)DMSO): 176.6, 172.7, 170.9, 170.6, 169.5 (5*s*, 4 CO(amide), COOH); 136.0 (*s*, 1 arom. C); 130.5, 127.9, 126.5 (3*d*, 5 arom. CH); 62.0 (*d*, CH(2)(Pro)); 59.0, 55.9, 55.3 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 47.6 (*t*, CH_2(5)(Pro)); 42.2 (*t*, CH_2(Gly)); 41.0 (*t*, Ph*C*H_2); 27.6 (*t*, CH_2(3)(Pro)); 25.2 (*t*, CH_2(4)(Pro)); 25.4, 25.2, 24.8, 24.2, 22.5 (5*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 526 (100, $[M+Na]^+$).

3.9. *H-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-OH* ((*R*)-**4f**). 3.9.1. *Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-OH* ((*R*)-**7f**). The hydrolysis of *Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-OMe* ((*R*)-**6f**; 862 mg, 1.21 mmol) with $LiOH \cdot H_2O$ (126 mg, 3.00 mmol) in THF/MeOH/H_2O 3:1:1 (25 ml) was carried out according to *GP 1* (1.5 h): 747 mg (88%) of (*R*)-**7f**. Colorless solid. M.p. 196.2–197.0°. $[\alpha]_D^{21} = +123.0$ ($c = 0.485$, EtOH). IR (KBr): 3290*s*, 3060*m*, 3030*m*, 2980*m*, 2940*m*, 1730*s*, 1660*s*, 1625*s*, 1540*s*, 1500*s*, 1455*s*, 1390*m*, 1375*m*, 1290*s*, 1235*s*, 1170*s*, 1050*m*, 735*m*, 700*s*. ^{1}H-NMR ((D_6)DMSO): 12.35 (*s*, COOH); 8.32 (*s*, NH); 7.50 (*t*-like, NH); 7.45–7.05 (*m*, 15 arom. H, 2 NH); 5.06, 5.01 (*AB*, $J_{AB} = 12.6$, PhCH_2O); 4.45–4.35 (*m*, PhCH_2); 4.21 (*t*-like, CH(2)(Pro)); 3.85–3.6 (*m*, CH_2(Gly), 1 H of CH_2(5)(Pro)); 3.55–3.4 (*m*, 1 H of CH_2(5)(Pro)); 3.41 (*A* of *AB*, $J_{AB} = 13.8$, 1 H of PhCH_2); 3.1–3.0 (*m*, 2 H of 2 PhCH_2); 2.95–2.85 (*m*, 1 H of PhCH_2); 2.2–2.05, 1.9–1.7, 1.7–1.5 (3*m*, 1:2:1, CH_2(3), CH_2(4)(Pro)); 1.36, 1.24, 1.21 (3*s*, Me_2C, Me(Phe(2Me))). ^{13}C-NMR ((D_6)DMSO): 174.0, 172.4, 172.2, 171.1, 169.2 (5*s*, 4 CO(amide), COOH); 156.6 (*s*, CO(urethane)); 137.4, 136.9, 136.8 (3*s*, 3 arom. C); 131.0, 129.1, 128.2, 127.9, 127.7, 127.6, 126.2

(7*d*, 15 arom. CH); 65.4 (*t*, Ph*C*H$_2$O); 62.8 (*d*, CH(2)(Pro)); 58.1, 56.0 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 53.5 (*d*, CH(2)(Phe)); 47.9 (*t*, CH$_2$(5)(Pro)); 42.7 (*t*, CH$_2$(Gly)); 40.2, 37.0 (2*t*, 2 Ph*C*H$_2$); 28.2 (*t*, CH$_2$(3)(Pro)); 25.3 (*t*, CH$_2$(4)(Pro)); 26.0, 24.3, 20.3 (3*q*, *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 722 (100, $[M+Na]^+$).

3.9.2. *H-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-OH* ((*R*)-**4f**). According to *GP 3*, (*R*)-**7f** (659 mg, 0.942 mmol) in MeOH (20 ml) was treated with HCO_2NH_4 (302 mg, 4.77 mmol) and Pd/C (660 mg): 511 mg (96%) of (*R*)-**4f**. Colorless solid. M.p. 171.8–173.3°. $[\alpha]_D^{21} = +111.7$ ($c = 1.075$, 2,2,2-trifluoroethanol). IR (KBr): 3380*s*, 3340*s*, 3260*s*, 3080*m*, 3030*m*, 2980*m*, 2940*m*, 2880*m*, 1680*s*, 1645*s*, 1635*s*, 1620*s*, 1615*s*, 1565*s*, 1555*s*, 1540*s*, 1515*s*, 1505*s*, 1495*s*, 1455*s*, 1440*m*, 1400*s*, 1385*s*, 1360*m*, 1320*m*, 1280*m*, 1240*m*, 1210*m*, 1190*m*, 1170*m*, 1135*m*, 1100*m*, 750*m*, 710*s*. ^{1}H-NMR (CD_3OD): 7.35–7.0 (*m*, 10 arom. H); 4.5–4.3 (*m*, CH(2)(Pro), CH(2)(Phe)); 3.85–3.6, 3.6–3.4, 3.4–3.3, 3.2–3.05 (4*m*, 2 : 2 : 1 : 3, 2 Ph*C*H$_2$, CH$_2$(Gly), CH$_2$(5)(Pro)); 2.15–1.9, 1.9–1.6 (2*m*, 1 : 3, CH$_2$(3), CH$_2$(4)(Pro)); 1.56, 1.49, 1.32 (3*s*, Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR (CD_3OD): 176.4, 174.3, 173.5, 168.8 (4*s*, 4 CO(amide), COOH); 139.2, 138.0 (2*s*, 2 arom. C); 132.2, 131.1, 129.3, 129.1, 127.9, 127.2 (6*d*, 10 arom. CH); 64.4 (*d*, CH(2)(Pro)); 60.4, 58.5 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 57.5 (*d*, CH(2)(Phe)); 49.8 (*t*, CH$_2$(5)(Pro)); 42.1, 41.9, 39.0 (3*t*, CH$_2$(Gly), 2 Ph*C*H$_2$); 29.2 (*t*, CH$_2$(3)(Pro)); 26.6 (*t*, CH$_2$(4)(Pro)); 27.4, 24.3, 21.3 (3*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 588 (5, $[M+Na]^+$), 566 (100, $[M+1]^+$).

3.10. *H-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-OH* ((*S*)-**4f**). 3.10.1. *Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-OH* ((*S*)-**7f**). The hydrolysis of *Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-OMe* ((*S*)-**6f**; 120 mg, 0.167 mmol) with LiOH · H$_2$O (18 mg, 0.429 mmol) in THF/MeOH/H$_2$O 3 : 1 : 1 (2 ml) was carried out according to *GP 1* (1.5 h): 109 mg (93%) of (*S*)-**7f**. Colorless solid. M.p. 92.0–93.1°. $[\alpha]_D^{21} = -18.2$ ($c = 0.125$, EtOH). IR (KBr): 3300*s*, 3060*m*, 3030*m*, 2980*m*, 2930*m*, 1730*s*, 1715*s*, 1670*s*, 1660*s*, 1635*s*, 1550*s*, 1540*s*, 1520*s*, 1505*s*, 1455*s*, 1410*m*, 1370*m*, 1310*m*, 1240*s*, 1165*m*, 1050*m*, 740*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.79 (*s*, NH); 7.45 (*d*, $J = 8.1$, NH); 7.4–7.05 (*m*, 15 arom. H); 7.02 (*s*, NH); 5.67 (br. *s*, NH); 5.18, 5.11 (*AB*, $J_{AB} = 12.2$, Ph*C*H$_2$O); 4.85–4.7 (*m*, Ph*C*H$_2$); 4.31 (*t*-like, CH(2)(Pro)); 3.95–3.7 (*ABX*, $J_{AB} = 17.2$, CH$_2$(Gly)); 3.6–3.45, 3.35–3.1, 3.05–2.9 (3*m*, 1 : 2 : 3, 2 Ph*C*H$_2$, CH$_2$(5)(Pro)); 2.35–2.2, 1.95–1.8, 1.7–1.5 (3*m*, 1 : 1 : 2, CH$_2$(3), CH$_2$(4)(Pro)); 1.48, 1.45, 1.20 (3*s*, Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 175.4, 173.8, 173.5, 172.1, 169.7 (5*s*, 4 CO(amide), COOH); 157.0 (*s*, CO(urethane)); 137.3, 136.1, 134.2 (3*s*, 3 arom. C); 130.2, 129.0, 128.8, 128.6, 128.5, 128.3, 128.2, 127.9, 126.6 (9*d*, 15 arom. CH); 67.3 (*t*, Ph*C*H$_2$O); 64.1 (*d*, CH(2)(Pro)); 60.2, 57.0 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 54.6 (*d*, CH(2)(Phe)); 49.1 (*t*, CH$_2$(5)(Pro)); 44.8 (*t*, CH$_2$(Gly)); 43.3, 36.9 (2*t*, 2 Ph*C*H$_2$); 28.4 (*t*, CH$_2$(3)(Pro)); 26.2 (*t*, CH$_2$(4)(Pro)); 26.5, 24.2, 23.4 (3*q*, *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 722 (100, $[M+Na]^+$).

3.10.2. *H-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-OH* ((*S*)-**4f**). According to *GP 3*, a suspension of (*S*)-**7f** (106 mg, 0.151 mmol) in MeOH (2 ml) was treated with H_2 in the presence of Pd/C (10 mg) for 44.5 h. Addition of CH_2Cl_2 and filtration afforded 74 mg (86%) of (*S*)-**4f**. Colorless solid. M.p. 166.5–167.8°. $[\alpha]_D^{21} = -0.7$ ($c = 0.420$, 2,2,2-trifluoroethanol). ^{1}H-NMR (CD_3OD): 7.35–7.15 (*m*, 8 arom. H); 7.1–7.05 (*m*, 2 arom. H); 4.6–4.55, 4.4–4.3 (2*m*, CH(2)(Pro), CH(2)(Phe)); 3.85–3.7, 3.6–3.45, 3.35–3.05 (3*m*, 1 : 1 : 2, 2 Ph*C*H$_2$, CH$_2$(Gly), CH$_2$(5)(Pro)); 2.2–2.05, 2.05–1.9, 1.9–1.7 (3*m*, 1 : 1 : 2, CH$_2$(3), CH$_2$(4)(Pro)); 1.45, 1.44, 1.40 (3*s*, Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR (CD_3OD): 176.9, 174.4, 172.9, 166.6 (4*s*, 4 CO(amide), COOH); 138.8, 137.1 (2*s*, 2 arom. C); 131.8, 130.4, 129.4, 128.1, 127.7 (5*d*, 10 arom. CH); 64.1 (*d*, CH(2)(Pro)); 61.5, 58.1 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 55.8 (*d*, C(2)(Phe)); 49.9 (*t*, CH$_2$(5)(Pro)); 42.8, 41.1, 38.6 (3*t*, CH$_2$(Gly), 2 Ph*C*H$_2$); 29.3, 27.0 (2*t*, CH$_2$(3)(Pro), CH$_2$(4)(Pro)); 26.2, 25.1, 23.2 (3*q*, *Me*$_2$C, Me(Phe(2Me))).

4. *Cyclization of Pentapeptides* **4**. 4.1. *Cyclo(Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly)* (**5b**). *a*) A soln. of **4b** (30 mg, 0.065 mmol) in DMF (40 ml) was cooled to 0°. Then, a soln. of DPPA (27 mg, 0.098 mmol) in DMF (1 ml) was added slowly within 2.5 h (syringe). After addition of $NaHCO_3$ (27 mg), the mixture was stirred for 63 h at 0°. Evaporation of DMF (high vacuum (h.v.)), filtration through *XAD* resin (type 2, 100–200 μm), and HPLC (72% H_2O/0.1% TFA; 28% MeCN/0.1% TFA; 8 ml/min; 220 nm; t_R 14.4 min) gave 13 mg (45%) of **5b**.

b) To a soln. of **4b** (21 mg, 0.045 mmol) in DMF (40 ml) were added HOBt (19 mg, 0.141 mmol), TBTU (45 mg, 0.140 mmol), and EtN(i Pr)$_2$ (0.4 ml), and the mixture was stirred at r.t. for 3 h. Then, DMF was evaporated (h.v.), and the residue was purified by HPLC: 13 mg (64%) of **5b**. Colorless solid. M.p. 286–288°. R_f (SiO_2; CH_2Cl_2/MeOH 10 : 1) 0.1. IR (KBr): 3510*m*, 3480*m*, 3350*s*, 3310*s*, 3040*w*, 2980*w*,

1680*s*, 1665*s*, 1640*s*, 1550*s*, 1515*s*, 1470*m*, 1440*m*, 1390*m*, 1365*m*, 1290*m*, 1265*m*, 1215*m*, 1205*m*, 1180*m*, 745*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO): 9.04, 8.76 (2*s*, 2 NH); 7.95–7.85 (*m*, NH); 7.55 (*s*, NH); 7.25–7.15 (*m*, 3 arom. H); 7.0–6.95 (*m*, 2 arom. H); 6.90 (*d*, J = 9.7, NH); 4.15–4.0 (*m*, CH$_2$(Gly)); 3.3–3.15 (*m*, CH$_2$(Gly), 1 H of PhCH_2); 2.90 (*B* of *AB*, J_{AB} = 13.3, 1 H of PhCH_2); 1.72, 1.40, 1.37, 1.29, 1.24 (5*s*, 2 Me$_2$C, Me(Phe(2Me)). ^{1}H-NMR (CD$_3$OD): 8.05–7.95 (*m*, NH); 7.83 (*s*, NH); 7.25 (*d*, J = 10.2, NH); 7.25–7.15 (*m*, 3 arom. H); 7.1–7.0 (*m*, 2 arom. H); 4.35–4.2 (*m*, CH$_2$(Gly)); 3.55–3.3 (*m*, CH$_2$(Gly), 1 H of PhCH_2); 3.12 (*B* of *AB*, J_{AB} = 13.6, 1 H of PhCH_2); 1.83, 1.50, 1.47, 1.36 (4*s*, 1:2:1:1, 2 Me$_2$C, Me(Phe(2Me)). ^{13}C-NMR (CD$_3$OD): 177.1, 176.7, 175.2, 172.1, 171.0 (5*s*, 5 CO(amide)); 137.4 (*s*, arom. C); 131.1, 129.0, 128.1 (3*d*, 5 arom. CH); 62.0, 59.5, 59.1 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 44.3, 44.0, 43.5 (3*t*, 2 CH$_2$(Gly), PhCH_2); 26.6, 26.3, 25.1, 24.7, 24.0 (5*q*, 2 *Me*$_2$C, *Me*(Ph(2Me))). ESI-MS: 486 (100, $[M+\mathrm{Na}]^+$).

Suitable crystals for the X-ray crystal-structure determination were grown from MeOH/H$_2$O by slow evaporation of the solvent.

4.2. *Cyclo(Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Aib)* (**5c**). Cyclization of **4c** (52.5 mg, 0.113 mmol) with DEPC (43 mg, 0.264 mmol) and EtN(i-Pr)$_2$ (0.75 ml) in DMF (75 ml) according to *GP 5* furnished 45.9 mg (91%) of **5c**. Colorless solid. M.p. 143.3–145.2°. R_f 0.2 (SiO$_2$, CH$_2$Cl$_2$/MeOH 10:1). IR (KBr): 3320*s*, 3060*m*, 3030*m*, 2980*m*, 2930*m*, 1690*s*, 1680*s*, 1660*s*, 1650*s*, 1545*s*, 1455*m*, 1445*m*, 1385*m*, 1365*m*, 1270*m*, 1225*m*, 1195*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.32, 8.00 (2*s*, 2 NH); 7.59 (*t*-like, NH); 7.51 (*s*, NH); 7.37 (*t*-like, NH); 7.35–7.2 (*m*, 3 arom. H); 7.1–7.05 (*m*, 2 arom. H); 3.91 (*dd*, J = 16.0, 6.7, 1 H of CH$_2$(Gly)); 3.81 (*dd*, J = 15.0, 6.3, 1 H of CH$_2$(Gly)); 3.60 (*dd*, J = 15.0, 3.8, 1 H of CH$_2$(Gly)); 3.46 (*dd*, J = 16.0, 3.8, 1 H of CH$_2$(Gly)); 3.31, 2.91 (*AB*, J_{AB} = 13.3, PhCH_2); 1.45, 1.42, 1.41, 1.37, 1.15 (5*s*, 2 Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR ((D$_6$)DMSO): 174.7, 174.1, 173.2, 169.3, 169.0 (5*s*, 5 CO(amide)); 136.9 (*s*, 1 arom. C); 130.5, 127.8 126.2 (3*d*, 5 arom. CH); 59.3, 57.0, 56.9 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 42.9, 42.7, 39.8 (3*t*, 2 CH$_2$(Gly), PhCH_2); 25.9, 25.1, 24.9, 24.2, 22.5 (5*q*, 2 *Me*$_2$C, *Me*(Phe(2Me))). ESI-MS: 484 (20, $[M+\mathrm{K}]^+$), 468 (100, $[M+\mathrm{Na}]^+$), 446 (37, $[M+1]^+$).

4.3. *Cyclo(Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe)* ((*R*)-**5d**). *a*) To a soln. of (*R*)-**4d** (18.7 mg, 0.036 mmol) in DMF (30 ml) were added HOBt (17 mg, 0.126 mmol), TBTU (37 mg, 0.115 mmol), and EtN(i-Pr)$_2$ (0.3 ml), and the mixture was stirred at r.t. for 3 h. Then, DMF was removed by distillation, and the residue was dissolved in AcOEt (10 ml). This soln. was extracted with 5% aq. KHSO$_4$ soln. (3 ×), 5% aq. NaHCO$_3$ soln. (3 ×), and sat. aq. NaCl soln., dried (Na$_2$SO$_4$), and purified by HPLC (65% H$_2$O/0.1% TFA; 35% MeCN/0.1% TFA, 8 ml/min; 220 nm; t_R 27.6 min): 11.6 mg (64%) of (*R*)-**5d**.

b) Cyclization of (*R*)-**4d** (18.8 mg, 0.036 mmol) with DEPC (22 mg, 0.135 mmol) and EtN(i-Pr)$_2$ (0.3 ml) in DMF (30 ml) was performed according to *GP 5*. The residue was dissolved in AcOEt (10 ml) and treated as in the previous experiment: 11.1 mg (61%) of (*R*)-**5d**. Colorless solid. M.p. 261.0–262.3°. R_f (SiO$_2$, CH$_2$Cl$_2$/MeOH 10:1) 0.2. $[\alpha]_D^{21}$ = +21.8 (c = 0.195, EtOH). IR (KBr): 3350*s*, 3310*s*, 3280*s*, 3060*m*, 3030*m*, 2990*m*, 2930*m*, 1690*s*, 1680*s*, 1670*s*, 1660*s*, 1650*s*, 1645*s*, 1550*m*, 1540*m*, 1530*m*, 1520*m*, 1505*m*, 1500*m*, 1465*m*, 1445*m*, 1435*m*, 1390*m*, 1365*m*, 1280*m*, 1260*m*, 1210*m*, 1200*m*, 1175*m*, 1130*m*, 745*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.49, 8.43 (2*s*, 2 NH); 7.75 (*t*-like, NH); 7.71 (*d*, J = 9.1, NH); 7.3–7.1 (*m*, 10 arom. H, 1 NH); 4.65–4.5 (*m*, CH(2)(Phe)); 3.92 (*dd*, J = 13.9, 6.6, 1 H of CH$_2$(Gly)); 3.83 (*dd*, J = 15.5, 5.8, 1 H of CH$_2$(Gly)); 3.63 (*dd*, J = 15.9, 3.6, 1 H of CH$_2$(Gly)); 3.46 (*dd*, J = 13.9, 3.8, 1 H of CH$_2$(Gly)); 3.34 (*d*, J = 13.4, 1 H of PhCH_2(Phe(2Me))); 3.20 (*dd*, J = 13.9, 4.2, 1 H of PhCH_2(Phe)); 2.95 (*d*, J = 13.3, 1 H of PhCH_2(Phe(2Me))); 2.77 (*dd*, J = 13.9, 10.5, 1 H of PhCH_2(Phe)); 1.19, 1.15, 1.13 (3*s*, 2 Me$_2$C, Me(Phe(2Me)). ^{13}C-NMR ((D$_6$)DMSO): 173.8, 173.4, 171.7, 169.0 (4*s*, 5 CO(amide)); 138.3, 136.6 (2*s*, 2 arom. C); 130.5, 129.1, 127.8, 126.3, 126.0 (5*d*, 10 arom. CH); 59.8, 56.1 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 53.2 (*d*, CH(2)(Phe)); 42.9, 41.6, 39.9, 36.6 (4*t*, 2 CH$_2$(Gly), 2 PhCH_2); 25.3, 23.6, 22.1 (3*q*, *Me*$_2$C, *Me*(Ph(2Me))). APCI-MS: 508 ($[M+1]^+$).

4.4. *Cyclo(Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe)* ((*S*)-**5d**). To a soln. of (*S*)-**4d** (29.5 mg, 0.056 mmol) in DMF (45 ml) were added HOBt (24 mg, 0.178 mmol), TBTU (55 mg, 0.171 mmol), and EtN(i-Pr)$_2$ (0.45 ml), and the mixture was stirred at r.t. overnight. Then, DMF was evaporated (h.v.), and the residue was purified by CC (CH$_2$Cl$_2$/MeOH 10:1) and PLC (CH$_2$Cl$_2$/MeOH 10:1): 15.8 mg (55%) of (*S*)-**5d**. Colorless solid. M.p. 162.5–164.3°. R_f (SiO$_2$, CH$_2$Cl$_2$/MeOH 10:1) 0.4. $[\alpha]_D^{21}$ = −89.1 (c = 0.430, EtOH). IR (KBr): 3300*s*, 3060*m*, 3030*m*, 2980*m*, 2930*m*, 1695*s*, 1680*s*, 1670*s*, 1660*s*, 1650*s*, 1645*s*, 1555*s*, 1540*s*, 1530*s*, 1515*s*, 1495*s*, 1470*m*, 1460*m*, 1455*m*, 1445*m*, 1390*m*, 1370*m*, 1320*m*, 1260*m*, 1230*m*, 1180*m*,

1130*m*, 1080*m*, 740*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.66, 8.53 (2*s*, 2 NH); 8.08 (*d*, *J* = 9.3, NH); 7.35–7.05 (*m*, 10 arom. H, 2 NH); 4.7–4.55 (*m*, CH(2)(Phe)); 4.15 (*dd*, *J* = 14.0, 9.2, 1 H of CH$_2$(Gly)); 4.01 (*dd*, *J* = 16.6, 5.8, 1 H of CH$_2$(Gly)); 3.55–3.35 (*m*, 2 H of 2 CH$_2$(Gly), 1 H of PhC*H*$_2$(Phe(2Me)), 1 H of PhC*H*$_2$(Phe)); 2.88 (*d*, *J* = 13.5, 1 H of PhC*H*$_2$(Phe(2Me))); 2.85–2.7 (*m*, 1 H of PhC*H*$_2$(Phe)); 1.17, 1.15, 1.01 (3*s*, 2 Me$_2$C, Me(Phe(2Me)). ^{13}C-NMR ((D$_6$)DMSO): 175.0, 173.5, 171.7, 169.8, 169.7 (5*s*, 5 CO(amide)); 139.2, 137.6 (2*s*, 2 arom. C); 131.0, 129.6, 128.21, 128.15, 126.6, 126.3 (6*d*, 10 arom. CH); 60.0, 56.5 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 53.7 (*d*, CH(2)(Phe)); 42.5, 42.2, 39.0, 36.0 (4*t*, 2 CH$_2$(Gly), 2 Ph*C*H$_2$); 26.1, 23.9, 22.8 (3*q*, *Me*$_2$C, *Me*(Ph(2Me))). APCI-MS: 508 ([*M* + 1]$^+$).

4.5. *Cyclo(Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Aib)* (**5e**). Cyclization of **4e** (22.0 mg, 0.044 mmol) with DEPC (22.0 mg, 0.135 mmol) and EtN(i-Pr)$_2$ (0.25 ml) in DMF (25 ml) was performed according to *GP 5*. After PLC (CH$_2$Cl$_2$/MeOH 10:1), 15.4 mg (73%) of **5e** were obtained.

4.6. *Cyclo(Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib)* ((*R*)-**5e**). Cyclization of (*R*)-**4e** (33.5 mg, 0.067 mmol) with DEPC (33.7 mg, 0.207 mmol) and EtN(i-Pr)$_2$ (0.45 ml) in DMF (45 ml) was performed according to *GP 5*. After PLC (CH$_2$Cl$_2$/MeOH 10:1), 25.2 mg (78%) of (*R*)-**5e** were obtained. Colorless solid. M.p. 142.6–143.6°. R_f (SiO$_2$, CH$_2$Cl$_2$/MeOH 10:1) 0.4. $[\alpha]_D^{21} = +25.0$ (*c* = 0.56, EtOH). IR (KBr): 3300*s*, 3030*m*, 2940*m*, 2915*m*, 1695*s*, 1680*s*, 1670*s*, 1660*s*, 1650*s*, 1645*s*, 1635*s*, 1555*s*, 1540*s*, 1530*s*, 1515*s*, 1505*s*, 1495*m*, 1470*m*, 1465*m*, 1455*m*, 1390*m*, 1365*m*, 1305*m*, 1265*m*, 1240*m*, 1215*m*, 1190*m*, 1130*m*, 1050*m*, 740*w*, 705*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.3 (br. *s*, NH); 7.80 (*s*, NH); 7.35–7.2 (*m*, 3 arom. H, 1 NH); 7.1–7.0 (*m*, 2 arom. H); 6.85 (br. *s*, NH); 4.6–4.5 (*m*, CH(2)(Pro)); 4.03 (*dd*, *J* = 16.6, 7.2, 1 H of CH$_2$(Gly)); 3.55–3.35 (*m*, 1 H of CH$_2$(Gly), CH$_2$(5)(Pro), 1 H of PhC*H*$_2$); 2.92 (br. *d*, *J* = 12.4, 1 H of PhC*H*$_2$); 2.0–1.7 (*m*, CH$_2$(3), CH$_2$(4)(Pro)); 1.52, 1.46, 1.45, 1.30, 1.23 (5*s*, 2 Me$_2$C, Me(Phe(2Me)). ^{13}C-NMR ((D$_6$)DMSO): 175.5, 174.0 (2*s*, 2 CO(Aib)); 171.7 (*s*, CO(Phe(2Me))); 170.0, 169.4 (2*s*, CO(Pro), CO(Gly)); 137.1 (*s*, 1 arom. C); 130.8, 127.8, 126.2 (3*d*, 5 arom. CH); 61.5 (*d*, CH(2)(Pro)); 58.4 (*s*, C(2)(Phe(2Me))); 57.5, 57.0 (2*s*, 2 C(2)(Aib)); 46.4 (*t*, CH$_2$(5)(Pro)); 41.8 (*t*, CH$_2$(Gly)); 39.9 (*t*, Ph*C*H$_2$); 26.6, 24.2 (2*t*, CH$_2$(3), CH$_2$(4)(Pro)); 24.5, 24.3, 23.3, 22.7 (4*q*, 2 *Me*$_2$C); 19.1 (*q*, *Me*(Ph(2Me))). ESI-MS: 508 ([*M* + 1]$^+$).

4.7. *Cyclo(Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib)* ((*S*)-**5e**). Cyclization of (*S*)-**4e** (27.0 mg, 0.054 mmol) with DEPC (38.0 mg, 0.233 mmol) and EtN(i-Pr)$_2$ (0.35 ml) in DMF (35 ml) was performed according to *GP 5*. After PLC (CH$_2$Cl$_2$/MeOH 10:1), 11.9 mg (46%) of (*S*)-**5e** were obtained. Colorless solid. M.p. 145.5–147.1°. R_f (SiO$_2$, CH$_2$Cl$_2$/MeOH 10:1) 0.4. $[\alpha]_D^{21} = -45.5$ (*c* = 0.38, EtOH). IR (KBr): 3300*s*, 3040*w*, 2980*w*, 1695*s*, 1690*m*, 1660*s*, 1650*s*, 1635*s*, 1555*m*, 1550*m*, 1540*m*, 1530*m*, 1520*m*, 1505*m*, 1470*m*, 1465*m*, 1455*m*, 1445*m*, 1390*m*, 1385*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO): 7.82 (br. *s*, NH); 7.35–7.15 (*m*, 3 arom. H, 1 NH); 7.15–7.05 (*m*, 2 arom. H); 4.45–4.4 (*m*, CH(2)(Pro)); 4.2–3.15 (*m*, CH$_2$(Gly), CH$_2$(5)(Pro), PhC*H*$_2$); 2.1–1.8 (*m*, CH$_2$(3), CH$_2$(4)(Pro)); 1.46, 1.44, 1.40, 1.33, 1.27 (5*s*, 2 Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR ((D$_6$)DMSO, 350K): 174.9, 174.5, 170.9, 169.4 (4*s*, 5 CO(amide)); 135.8 (*s*, 1 arom. C); 130.4, 127.8, 126.5 (3*d*, 5 arom. CH); 61.2 (*d*, CH(2)(Pro)); 60.9, 57.3, 57.2 (3*s*, C(2)(Phe(2Me)), 2 C(2)(Aib)); 47.5 (*t*, CH$_2$(5)(Pro)); 42.6, 41.6 (2*t*, CH$_2$(Gly), Ph*C*H$_2$); 24.7, 24.3, 23.7, 23.5, 22.7 (5*q*, 2 *Me*$_2$C, *Me*(Ph(2Me))); (CH$_2$(3), CH$_2$(4)(Pro) could not be detected). ESI-MS: 508 ([*M* + 1]$^+$).

4.8. *Cyclo(Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe)* ((*R*)-**5f**). Cyclization of (*R*)-**4f** (42 mg, 0.074 mmol) with DEPC (29 mg, 0.178 mmol) and EtN(i-Pr)$_2$ (0.5 ml) in DMF (50 ml) was performed according to *GP 5*. The residue was dissolved in CH$_2$Cl$_2$, and the soln. was extracted with 5% aq. KHSO$_4$ soln. (3×), 5% aq. NaHCO$_3$ soln. (3×), and sat. aq. NaCl soln., dried (Na$_2$SO$_4$), and filtered through cotton. PLC (AcOEt/MeOH 10:1) and crystallization from MeOH/AcOEt/hexane gave 19.2 mg (47%) of (*R*)-**5f**. Colorless solid. M.p. 250.3–153.1°. R_f (SiO$_2$, CH$_2$Cl$_2$/MeOH 10:1) 0.5. $[\alpha]_D^{21} = +42.5$ (*c* = 0.595, EtOH). IR (KBr): 3300*m*, 3020*w*, 2940*w*, 1695*s*, 1680*s*, 1630*s*, 1540*m*, 1530*s*, 1520*m*, 1505*m*, 1495*m*, 1470*m*, 1465*m*, 1450*m*, 1415*m*, 1400*m*, 1380*m*, 700*m*. ^{1}H-NMR (CDCl$_3$): 7.63 (*d*, *J* = 9.2, NH(Phe)); 7.2–7.1 (*m*, 8 arom. H); 7.08 (*s*, NH(Aib)); 6.9–6.85 (*m*, 2 arom. H); 6.85–6.8 (*m*, NH(Gly)); 6.30 (*s*, NH(Phe(2Me))); 4.86 (*dd*, *J* = 7.7, 1.5, CH(2)(Pro)); 4.7–4.6 (*q*-like, CH(2)(Phe)); 4.02 (*dd*, *J* = 15.9, 9.7, 1 H of CH$_2$(Gly)); 3.62 (*d*, *J* = 14.0, 1 H of PhC*H*$_2$(Phe(2Me))); 3.6–3.55, 3.55–3.45 (2*m*, CH$_2$(5)(Pro)); 3.04 (*dd*, *J* = 13.7, 8.9, 1 H of PhC*H*$_2$(Phe)); 2.89 (*d*, *J* = 13.9, 1 H of PhC*H*$_2$(Phe(2Me))); 2.84 (*dd*, *J* = 13.7, 6.7, 1 H of PhC*H*$_2$(Phe)); 2.76 (*dd*, *J* = 15.9, 3.5, CH$_2$(Gly)); 2.3–2.2, 2.1–2.0, 1.95–1.85, 1.75–1.65 (4*m*, CH$_2$(3), CH$_2$(4)(Pro)); 1.55, 1.24 (2*s*, Me$_2$C); 1.23 (*s*, Me(Phe(2Me)). ^{13}C-NMR (CDCl$_3$): 176.5 (*s*, CO(Aib));

173.9 (*s*, CO(Phe)); 173.14 (*s*, CO(Pro)); 173.06 (*s*, CO(Phe(2Me))); 168.8 (*s*, CO(Gly)); 136.94, 136.88 (2*s*, 2 arom. C); 131.1, 129.2, 128.5, 128.0, 126.8, 126.7 (6*d*, 10 arom. CH); 61.4 (*d*, CH(2)(Pro)); 59.0 (*s*, C(2)(Phe(2Me))); 58.8 (*s*, C(2)(Aib)); 54.1 (*d*, CH(2)(Phe)); 46.8 (*t*, CH_2(5)(Pro)); 42.3 (*t*, CH_2(Gly)); 40.4 (*t*, Ph*C*H_2(Phe(2Me))); 35.6 (*t*, Ph*C*H_2(Phe)); 25.5, 25.4 (2*t*, CH_2(3), CH_2(4)(Pro)); 25.1, 24.7 (2*q*, *Me*$_2$C); 19.9 (*q*, *Me*(Ph(2Me))). ESI-MS: 570 ([M + Na]$^+$). Anal. calc. for $C_{30}H_{37}N_5O_5 \cdot 1.5\ H_2O$ (574.64): C 62.70, H 7.02, N 12.19; found C 62.94, H 6.71, N 11.97.

Suitable crystals for the X-ray crystal-structure determination were grown from AcOEt/MeOH/hexane by slow evaporation of the solvent.

4.9. *Cyclo(Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe)* ((*S*)-**5f**). Cyclization of (*S*)-**4f** (22.5 mg, 0.040 mmol) with DEPC (12 mg, 0.074 mmol) and EtN(^{i}Pr)$_2$ (0.2 ml) in DMF (20 ml) was carried out according to *GP 5*. After PLC (CH_2Cl_2/MeOH 10 : 1) and CC (CH_2Cl_2/MeOH/NH_3 20 : 1 : 0.1), 2.2 mg (10%) of (*S*)-**5f** were obtained. Colorless solid. M.p. 174.0–177.5°. R_f (SiO_2, CH_2Cl_2/MeOH 10 : 1) 0.45. ^{1}H-NMR ($CDCl_3$): 7.79 (*d*, *J* = 6.9, NH); 7.4–7.15 (*m*, 10 arom. H, 1 NH); 6.65–6.55 (*m*, NH); 5.87 (*s*, NH); 5.01 (*d*, *J* = 6.0, CH(2)(Pro)); 4.7–4.65 (*m*, CH(2)(Phe)); 4.2–4.1 (*m*, 1 H of CH_2(Gly)); 3.8–3.65 (*m*, CH_2(5)(Pro)); 3.2–3.15 (*m*, 1 H of PhC*H*$_2$(Phe)); 3.1–2.95 (*m*, PhC*H*$_2$(Phe(2Me)), 1 H of CH_2(Gly)); 2.95–2.9 (*m*, 1 H of PhC*H*$_2$(Phe)); 2.45–2.35, 2.25–2.15, 2.1–2.0, 1.8–1.7 (4*m*, CH_2(3), CH_2(4)(Pro)); 1.64, 1.52, 1.45 (3*s*, Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 176.2, 173.6, 172.7, 171.9, 168.3 (5*s*, 5 CO(amide)); 136.9, 134.0 (2*s*, 2 arom. C); 130.1, 129.2, 129.0, 128.4, 127.9, 126.7 (6*d*, 10 arom. CH); 61.1 (*d*, CH(2)(Pro)); 60.3, 58.7 (2*s*, C(2)(Phe(2Me)), C(2)(Aib)); 53.8 (*d*, CH(2)(Phe)); 46.9 (*t*, CH_2(5)(Pro)); 42.5 (*t*, CH_2(Gly)); 41.3 (*t*, Ph*C*H_2(Phe(2Me))); 35.2 (*t*, Ph*C*H_2(Phe)); 25.49, 24.8 (2*t*, CH_2(3), CH_2(4)(Pro)); 25.52, 24.6, 23.2 (3*q*, *Me*$_2$C, *Me*(Ph(2Me))). ESI-MS: 570 ([M + Na]$^+$).

4. *X-Ray Crystal-Structure Determination of* **5b** *and (*R*)-***5f*** (see *Table 6* and *Figs. 1* and *2*)*[6]). The measurements were conducted using graphite-monochromated MoK_α radiation (λ 0.7107 Å) on a *Rigaku AFC5R* diffractometer fitted to a 12-kW rotating-anode generator. The data of **5b** were collected at 283 K, because cooling to a lower temp. destroyed the crystals. The intensities were corrected for *Lorentz* and polarization effects. In the case of **5b**, azimuthal scans of several reflections indicated no need for an absorption correction, whereas, in the case of (*R*)-**5f**, an empirical absorption correction, based on azimuthal scans of several reflections [38], was applied. Equivalent reflections, other than *Friedel* pairs, were merged. The data collection and refinement parameters are compiled in *Table 6*, and views of the molecules are shown in *Figs. 1* and *2*. The structures were solved by direct methods using SHELXS86 [39] for **5b**, which revealed the positions of all non-H-atoms, and *SnB* [40] for (*R*)-**5f**, which revealed the positions of most of the non-H-atoms. In the latter case, the remaining non-H-atoms were located in a subsequent difference electron-density map. For both structures, the non-H-atoms were refined anisotropically.

In the case of **5b**, the asymmetric unit contains two molecules of the peptide plus one H_2O molecule. The Ph ring in both molecules is disordered due to in-plane waggling of the ring about the *ipso* C–C bond. Two sets of positions were defined for the atoms of each disordered Ph ring and the site occupation factors of the major conformations of these groups refined to 0.52(4) and 0.55(3) for molecules A and B, resp. Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighboring atoms within and between each conformation of the disordered Ph rings were lightly restrained to have similar atomic displacement parameters.

In the case of (*R*)-**5f**, the asymmetric unit contains two molecules of the peptide, as well as sites for disordered MeOH and/or H_2O molecules. The disordered solvent molecules could not be identified or modelled adequately, so the SQUEEZE routine [41] of the program PLATON [42] was employed. When the solvent molecules are omitted from the model, each unit cell contains two cavities of 427 Å^3 and four cavities of 63 Å^3. The electron count in the unit cell was calculated to be *ca.* 198 e. One MeOH molecule has 24 e, so it has been assumed that there are eight MeOH molecules per unit cell, although it is possible that some of these might be H_2O. This approximation has been used in the subsequent calculation of the

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[6]) CCDC-1024796 and -1024797 contain the supplementary crystallographic data for this article. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

Table 6. *Crystallographic Data of Compounds* **5b** *and* (*R*)-**5f**

	5b	(*R*)-**5f**
Crystallized from	MeO/H_2O	AcOEt/MeOH/hexane
Empirical formula	$C_{22}H_{31}N_5O_5 \cdot 0.5\ H_2O$	$C_{30}H_{37}N_5O_5 \cdot MeOH$
Formula weight	454.52	591.70
Crystal color, habit	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.20 \times 0.35 \times 0.40$	$0.35 \times 0.40 \times 0.52$
Temp. [K]	283(1)	173(1)
Crystal system	monoclinic	orthorhombic
Space group	*Pc*	$P2_12_12_1$
Z	4	8
Reflections for cell determination	23	25
2θ Range for cell determination [°]	38–40	68–78
Unit cell parameters *a* [Å]	15.758(2)	13.347(4)
b [Å]	12.595(2)	23.829(3)
c [Å]	12.427(2)	35.218(3)
β [°]	105.043(9)	90
V [Å^3]	2381.8(5)	6500(2)
D_x [g cm^{-3}]	1.267	1.209
$\mu(MoK_\alpha)$ [mm^{-1}]	0.0922	0.0844
Scan type	$\omega/2\theta$	ω
$2\theta_{(max)}$ [°]	55	55
Transmission factors (min; max)	–	0.910; 1.000
Total reflections measured	5980	15792
Symmetry-independent reflections	5730	13567
Reflections with $I > 2\sigma(I)$	3664	8961
Reflections used in refinement	5730	13566
Parameters refined; restraints	714; 418	778; 42
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0553	0.0500
$wR(F^2)$ (all data)	0.1258	0.1355
Weighting parameter (a; b)[a]	0.0178; 2.4128	0.0727; 0
Goodness of fit	1.069	0.958
Final Δ_{max}/σ	0.0001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.26; −0.28	0.25; −0.22

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2F_c^2)/3$.

empirical formula, formula weight, density, linear absorption coefficient, and $F(000)$. Based on the assumption, the ratio of peptide to MeOH molecules in the structure is 1:1.

One of the peptide molecules (molecule B) has disorder of two atoms in the five-membered ring due to an alternating ring conformation. Two sets of positions were defined for these atoms, and the site occupation factor of the major conformation refined to 0.588(10). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, and the C–C bond lengths in the disordered region were restrained to 1.520(5) Å. Neighboring atoms within and between each conformation of the disordered group were restrained to have similar atomic displacement parameters. The same peptide molecule also shows a slight conformational disorder of the peptide chain from C(45) to C(48), as well as in the Ph rings, but no attempt was made to model this additional disorder. Molecule A shows no evidence for disorder. The amide H-atoms in (*R*)-**5f** and the H_2O H-atoms in **5b** were placed in the positions indicated by a difference electron-density map, and their positions were allowed to refine together with individual isotropic displacement parameters while

restraining the O–H distances in the H_2O molecule to 0.84(2) Å. All remaining H-atoms in each structure were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for the Me groups).

The refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. In the case of (*R*)-**5f**, one reflection, whose intensity was considered to be an extreme outlier, was omitted from the final refinement and the enantiomer used in the refinement was based on the known (*S*)-configurations at C(6) and C(15). Neutral atom-scattering factors for non-H-atoms were taken from [43], and the scattering factors for H-atoms were taken from [44]. Anomalous dispersion effects were included in F_c [45]; the values for f' and f'' were those of [46]. The values of the mass attenuation coefficients are those of [47]. All refinements were performed using SHELXL-2014 [48].

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