Synthesis of Cyclohexapeptides Containing Pro and Aib Residues

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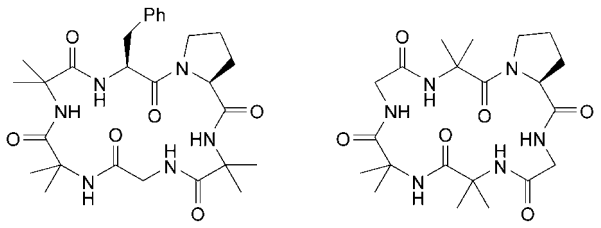
Cyclization reactions on hexapeptides containing several α-aminoisobutyric acid (= 2-amino-2-methylpropanoic acid; Aib) residues and the turn-promoting glycine (Gly) and proline (Pro) residues were investigated. Eight linear hexapeptides were synthesized, and their cyclization was attempted with various coupling reagents. The macrolactamization step proved to be difficult since only three hexapeptides could be cyclized. Two of these latter peptides were the linear precursors of the same cyclic hexapeptide, cyclo(Aib-Aib-Phe-Pro-Aib-Gly) (**1**). Surprisingly, they gave **1** in almost the same yield. Thus, **1** was obtained in 35% yield upon ring closure at the Phe/Pro site by using DEPBT as the coupling reagent, whereas the cyclization at the Aib/Phe site led to **1** in 28 and 34% yield by using PyAOP and DEPC, respectively (DEPBT = 3-[(diethoxyphosphoryl)oxy]-1,2,3-benzotriazin-4(3*H*)-one, PyAOP = (1*H*-7-azabenzotriazol-1-yloxy)tripyrrolidin-1-ylphosphonium hexafluorophosphate, DEPC = diethyl phosphorocyanidate). Another cyclic hexapeptide, cyclo(Aib-Aib-Gly-Aib-Pro-Gly) (**2**) was prepared in 34% yield when DEPC was used in the cyclization step. The solid-state conformation of **1** was established by X-ray crystallography.

1. Introduction. – Cyclic peptides usually exist in more clearly defined conformations than their linear counterparts, and often they have increased receptor affinity and metabolic stability. Out of this arises their potential to serve as lead structures in drug design [1]. Cyclization can also constrain a short amino acid sequence to a turn conformation [2]. In particular, cyclic penta- and hexapeptides have frequently been used as models for reverse turns although the cyclization of these small peptides is often troublesome [3]. Since peptide bonds possess pronounced π character and preferentially adopt a *trans* conformation ($\omega_i = 180°$), the linear precursor has the terminal acid and amine functions in remote positions, which is unfavorable for cyclization. Incorporation of residues such as glycine (Gly), L-proline (Pro), or D-amino acids are known to enhance cyclization yields [4].

Recently, we have focused our interest on the cyclization of model hexapeptides containing Aib (α-aminoisobutyric acid = 2-amino-2-methylpropanoic acid) residues, and we were also interested in the propensity of these cyclic peptides to form certain types of β-turns. Since we have successfully cyclized hexapeptides containing several Aib residues and one or two Gly residues [5], the aim of this work was to investigate the cyclization tendencies of hexapeptides containing Aib and Pro residues. Pro is believed to prefer turn-forming *cis*-peptide bonds, which should facilitate the ring closure. In this paper, we report the synthesis of cyclo(Aib-Aib-Phe-Pro-Aib-Gly) (**1**) and cyclo(Aib-Aib-Gly-Aib-Pro-Gly) (**2**) and the attempted cyclizations of four additional hexapeptides containing Aib and Pro residues (Phe = L-phenylalanine). Furthermore, three different linear precursors of the cyclic peptide **1** were synthesized to study the influence of the amino acid sequence on the cyclization yield.

[1]) Part of the Ph.D. thesis of *T. J.*, Universität Zürich, 2004.



1 **2**

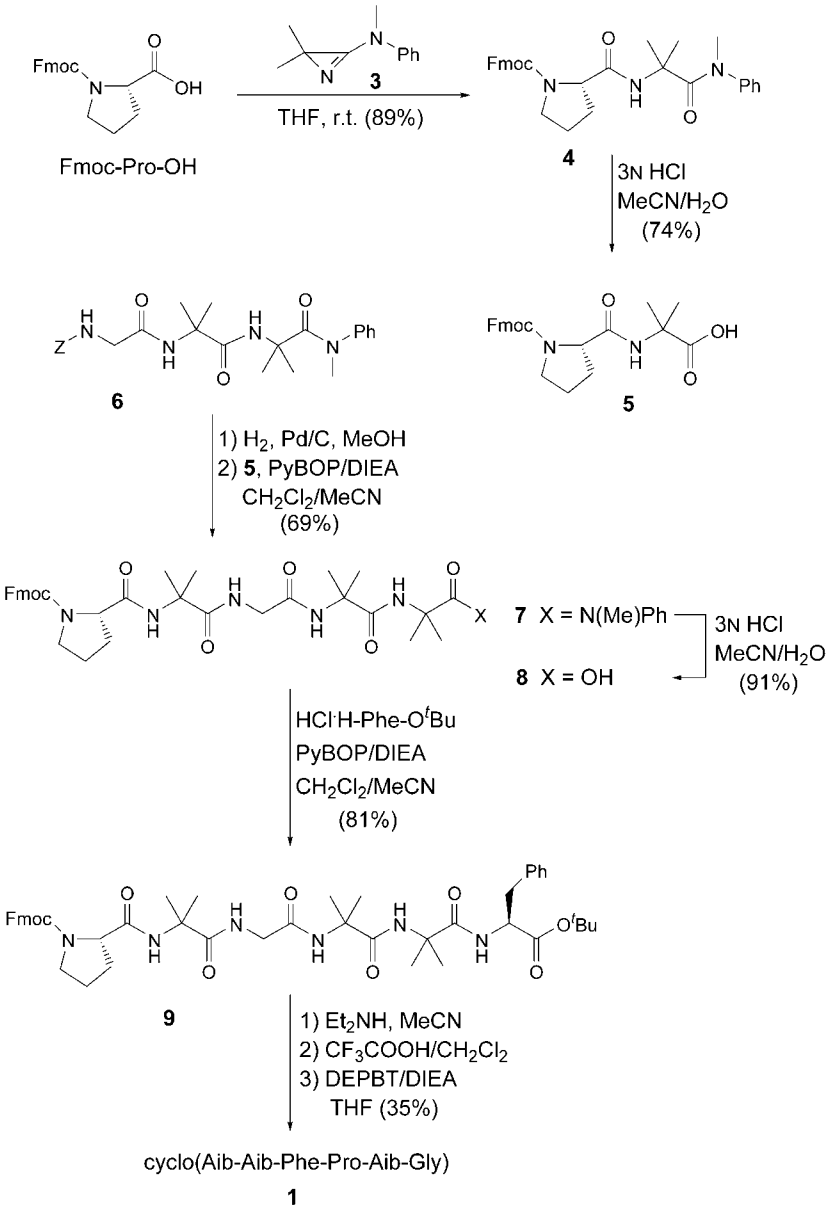
2. Results and Discussion. – 2.1. *Linear Peptides and Their Cyclization.* The amino acid sequence of the linear precursor and the choice of the coupling reagent are two of the most important factors that affect the result of the cyclization reaction [6][7]. The cyclic hexapeptide cyclo(Aib-Aib-Phe-Pro-Aib-Gly) (**1**) was chosen as a model for the investigation of the significance of the linear amino acid sequence on the success of the macrolactamization. In the retrosynthetic analysis, three amide bonds were selected for the final ring-closure step, *i.e.*, between Phe/Pro, Aib/Phe, and Aib/Gly. These three disconnections were likely to give different yields for the cyclization, but it was impossible to predict with appropriate certainty which one would be optimal.

The synthesis of the linear precursor for the Phe/Pro cyclization site was carried out by stepwise elongation from the N-terminal Pro derivative (*Scheme 1*). The synthesis started by coupling Fmoc-Pro-OH (Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl) with the 2*H*-azirin-3-amine **3**, our synthon for Aib, to give the dipeptide amide **4**, which was then hydrolyzed with 3N HCl (MeCN/H_2O 1:1) to give the dipeptide acid Fmoc-Pro-Aib-OH (**5**). The N-terminal tripeptide Z-Gly-Aib-Aib-N(Me)Ph (**6**) was prepared analogously from Z-Gly-OH (Z = (benzyloxy)carbonyl) by use of the 'azirine/oxazolone method' [8]. After removal of the Z group from **6**, PyBOP/DIEA-mediated[2]) coupling with **5** gave pentapeptide amide **7** in 69% yield. The latter was hydrolyzed to yield the peptide acid **8**, which was then coupled with H-Phe-O^{t}Bu to give the linear precursor Fmoc-Pro-Aib-Gly-Aib-Aib-Phe-O^{t}Bu (**9**) in high yield. The coupling reaction was again accomplished by use of PyBOP/DIEA. Finally, after removal of the Fmoc group at the N-terminus of **9** by treatment with Et_2NH and then deprotection of the ^{t}Bu ester group at the C-terminus with CF_3COOH, the free linear precursor as its CF_3COO^- salt was subjected to macrolactamization.

The cyclic hexapeptide **1** was initially obtained in low yield (20%) by ring closure with TBTU/HOBt/DIEA[2]); however, due to the long reaction time of 6 d, significant epimerization of the C-terminal Phe residue occurred affording **1** as an inseparable mixture of two diastereoisomers. For this reason, the DEPBT[2]) coupling reagent was chosen for the cyclization reaction. This reagent has proven to be very efficient in the synthesis of cyclic peptides [9][10] with remarkable resistance to racemization [11]. The cyclization was carried out with 3 equiv. of DEPBT in THF and high dilution (1.5 mM) and in the presence of DIEA for 3 d. This procedure afforded cyclo(Aib-Aib-Phe-Pro-Aib-Gly) (**1**) in 35% yield. No side reactions such as dimerization of the linear

[2]) For abbreviations see *Exper. Part.*

Scheme 1

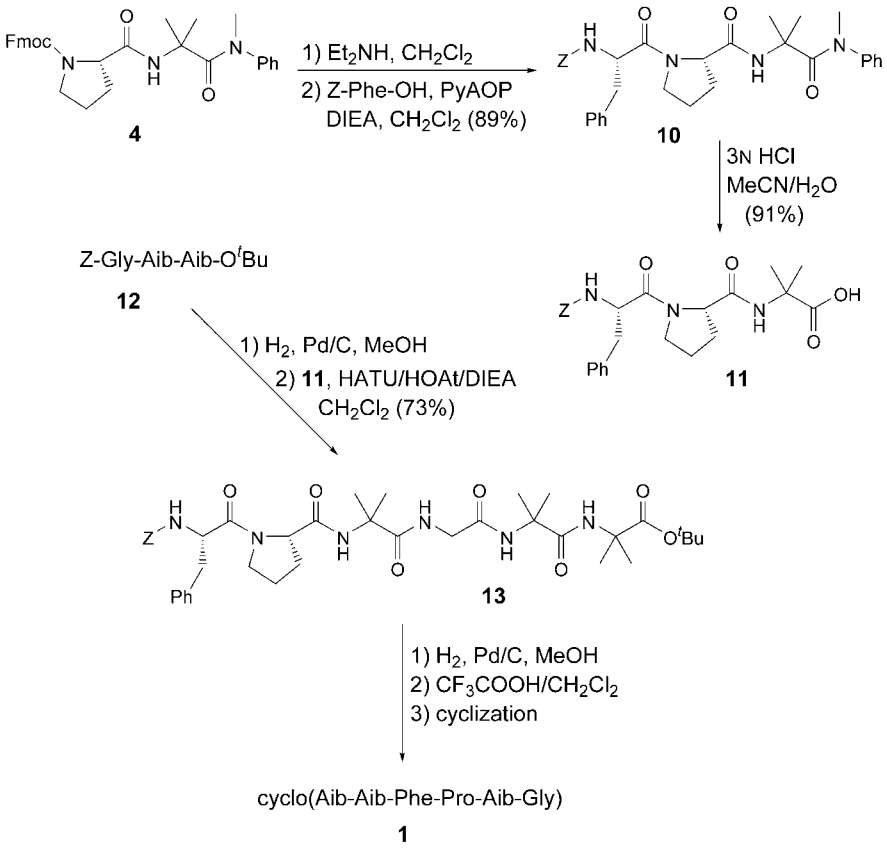


precursor or epimerization of the C-terminal Phe residue were observed, which allowed the desired cyclic peptide **1** to be purified easily.

The cyclization at the Aib/Phe site should be advantageous because epimerization is not possible when Aib is the C-terminal residue, and the steric hindrance should be

reduced compared with that of the Phe/Pro cyclization site. Therefore, the linear precursor for this cyclization was prepared as shown in *Scheme 2*. The dipeptide amide Fmoc-Pro-Aib-N(Me)Ph (**4**) was first *N*-deprotected (Et_2NH in CH_2Cl_2) and then coupled with Z-Phe-OH by using PyAOP[2]), which led to the tripeptide Z-Phe-Pro-Aib-N(Me)Ph (**10**) in high yield. The hydrolysis of **10** with 3N HCl (MeCN/H_2O 1:1) provided tripeptide acid **11**. After deprotection of the N-terminus of Z-Gly-Aib-Aib-O^{t}Bu (**12**), the reaction with **11** using HATU/HOAt[2]) as activating agents afforded hexapeptide Z-Phe-Pro-Aib-Gly-Aib-Aib-O^{t}Bu (**13**) in good yield. After the removal of the Z group of **13** and subsequent cleavage of the ^{t}Bu group by CF_3COOH, the linear precursor was cyclized by means of different coupling reagents. The best result among the reagents explored was achieved when DEPC ($(EtO)_2P(O)CN$) [12] was used. The cyclic hexapeptide **1** was obtained in 34% yield when a diluted solution (1.0 mM) of the deprotected hexapeptide in DMF was exposed to DEPC and DIEA for 6 d at room temperature. It should be noted that the yield of the crude cyclic product was higher and the reaction was faster (24 h) when PyAOP/HOAt[2]) was used as the cyclization reagent, but the purification was difficult, which resulted in a slightly lower

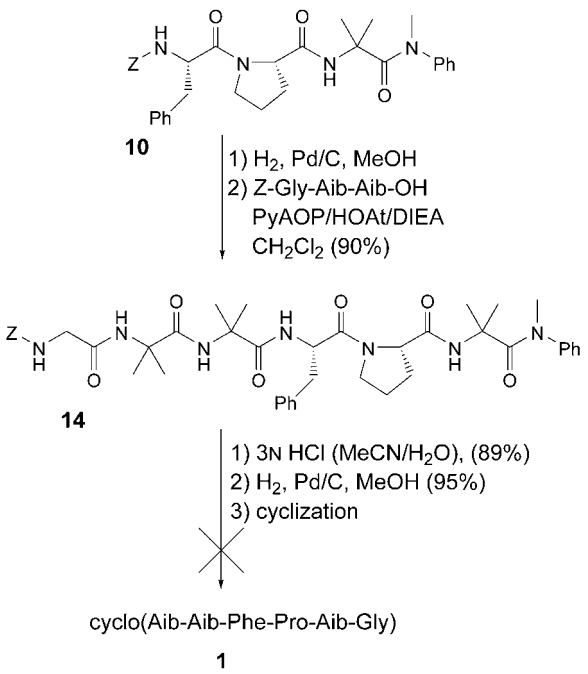
Scheme 2



yield (28%) of pure **1**. An additional fraction of **1**, contaminated with some (Et^iPr_2NH)PF_6, was obtained but could not be purified. We were unable to completely remove this by-product by washing with aqueous citric acid and $NaHCO_3$, or by two successive chromatographic purifications (AcOEt/MeOH 10:1, followed by CH_2Cl_2/MeOH 15:1), or by crystallization. The only single crystals suitable for X-ray crystallographic analysis that could be grown from this mixture were co-crystals of (Et^iPr_2NH)PF_6 and **1**. The formation of **1** was also attempted with the DEPBT[2]) coupling reagent, but, surprisingly, the linear precursor remained unaltered after a period of 3 d.

The linear precursor for the cyclization at the Aib/Gly site was prepared as outlined in *Scheme 3*. After removal of the Z group in Z-Phe-Pro-Aib-N(Me)Ph (**10**), condensation with Z-Gly-Aib-Aib-OH by using PyAOP/HOAt[2]) provided the linear hexapeptide **14** in 90% yield. The deprotection of **14** afforded the free linear precursor, which was subjected to macrolactamization with four different coupling reagents, *i.e.*, DEPC, DEPBT, PyAOP/HOAt, and HATU/HOAt[2]). Unfortunately, all four attempts failed, and only decomposition of the coupling reagents was observed. This result was very surprising since we have previously successfully cyclized several Aib-containing hexapeptides at an Aib/Gly site in good yields (45–57%) [5][13]. We assume that the Pro residue at position 5 of the sequence makes the peptide more rigid, thereby completely preventing cyclization.

Scheme 3



cyclo(Aib-Aib-Phe-Pro-Aib-Gly)

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The incorporation of Gly or Pro residues as turn-inducing elements is generally considered a prerequisite for the ring closure of short peptides [14]. Since the cyclic peptide **1** contains both of these residues, the cyclization was expected to proceed in high yield. The observed moderate yields (28–35%) were presumably caused by the presence of three conformationally constrained Aib units in the sequence, in addition to one conformationally restricted Pro residue, thus evoking highly constrained linear precursors. Based on these precedents, we decided to prepare a similar cyclohexapeptide, *i.e.*, cyclo(Aib-Aib-Gly-Aib-Pro-Gly) (**2**), which contains an additional Gly instead of Phe. Furthermore, one Gly residue is placed adjacent to the Pro unit, which should hopefully decrease the conformational constraint and enhance the cyclization yield. The synthesis of the linear precursor of **2** and its cyclization are shown in *Scheme 4*. After removal of the Z group of tripeptide **6**, condensation with Fmoc-Pro-OH by using PyAOP[2]) yielded the linear tetrapeptide Fmoc-Pro-Gly-Aib-Aib-N(Me)Ph (**15**). Treatment of **15** with Et_2NH gave the *N*-deprotected tetrapeptide, which, on subsequent coupling with Z-Gly-Aib-OH by means of PyAOP led to the linear hexapeptide Z-Gly-Aib-Pro-Gly-Aib-Aib-N(Me)Ph (**16**). The latter was hydrolyzed to give the peptide acid **17**, the Z group was removed hydrogenolytically, and the free linear precursor subjected to cyclization in DMF (1.5 mM) by using DEPC (4 equiv.) as the coupling reagent in the presence of DIEA[2]). The cyclopeptide **2** was obtained as a white precipitate, which was almost insoluble in organic solvents and H_2O. Since chromatographic purification was not possible, **2** was collected by filtration, washed with H_2O, MeOH, and CH_2Cl_2 to remove excess coupling reagent and some by-products, and recrystallized from hot H_2O/MeOH/EtOH solution. In this way, pure cyclohexapeptide **2** was obtained in 34% yield[3]). Due to the low solubility of **2**, the NMR spectra were performed in (D_6)DMSO containing small amounts of CF_3COOH. Surprisingly, although the linear precursor of **2** possesses the turn-inducing Pro-Gly segment in the middle of the sequence and two residues (Aib and Gly) at the C- and N-terminus, which can both be considered as pseudo-D- and -L-amino acids, the cyclization was no more-effective than in the case of **1**.

Recently, we have synthesized a cyclic hexapeptide in which Aib residues alternate with proteinogenic amino acids, *i.e.*, cyclo(Aib-Gly-Aib-Leu-Aib-Phe) [15]. The conformation of this cyclic peptide in solution was well defined, and it was shown that it is very similar to the conformation adopted in the solid state. Furthermore, the cyclization yield was surprisingly high (53%), although the Aib unit situated between the two large Leu and Phe residues was forced to assume a fully extended conformation, as shown by X-ray crystallography and MD simulations. It is unfavorable and highly uncommon for an Aib residue to adopt extended conformations. Thus, we decided to replace Leu by Pro to see how this modification would affect the cyclization yield and the conformational preference of the Aib residues. The synthesis of the linear precursor is outlined in *Scheme 5*. After Fmoc deprotection of dipeptide amide **4**, the

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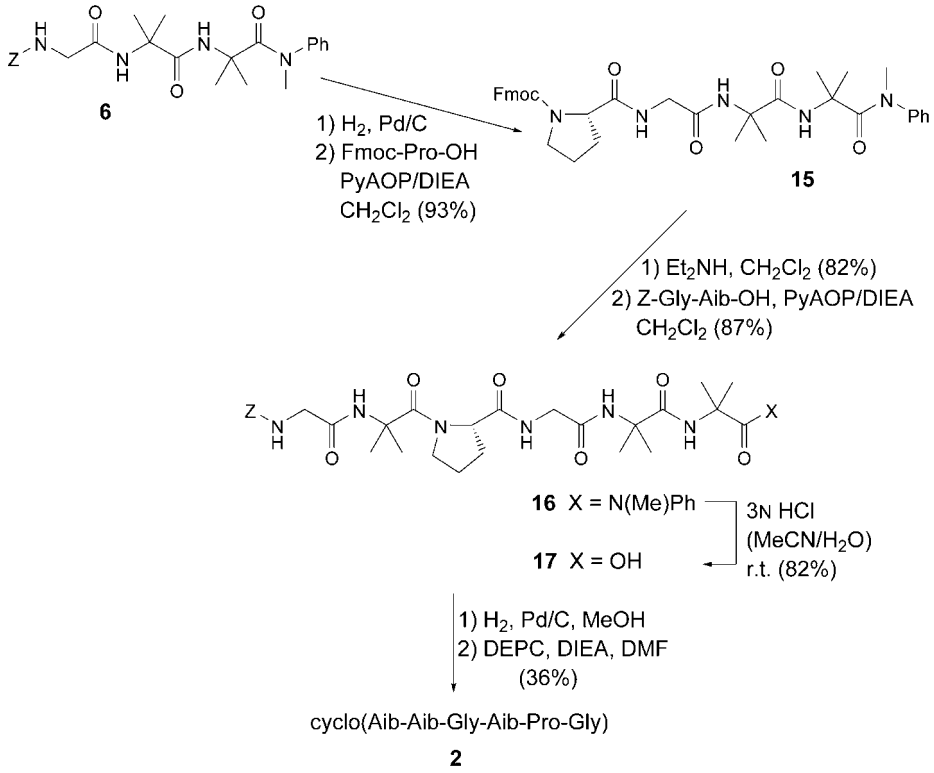
[3]) The cyclization was not repeated with other coupling reagents such as PyAOP, DEPBT, or HATU because, in contrast to DEPC, they are solid materials, and it would not be possible to remove them from the cyclic product merely by filtration and washing. In addition, they usually generate much more of the by-products during cyclization or workup, with some by-products arising from the decomposition of excess coupling reagent.

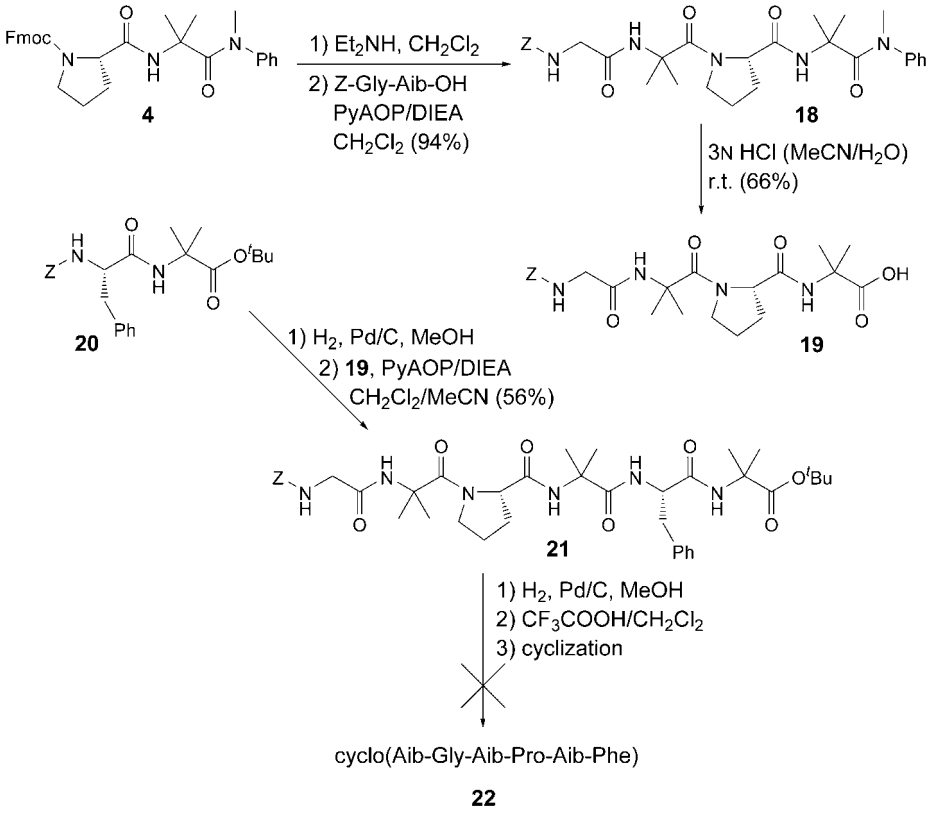
Scheme 4



coupling with Z-Gly-Aib-OH by using the PyAOP[2]) reagent gave tetrapeptide Z-Gly-Aib-Pro-Aib-N(Me)Ph (**18**) in high yield. The latter was hydrolyzed (3N HCl (MeCN/H_2O 1:1)) to give peptide acid **19**. The Z group of Z-Phe-Aib-O^{t}Bu (**20**) was removed, and the subsequent coupling with **19** by using PyAOP provided hexapeptide Z-Gly-Aib-Pro-Aib-Phe-Aib-O^{t}Bu (**21**) in moderate yield. After the removal of the protecting groups, the linear precursor was subjected to cyclization, but both DEPBT and PyBOP[2]) failed to give cyclo(Aib-Gly-Aib-Pro-Aib-Phe) (**22**). Unfortunately, we were unable to grow crystals of the linear hexapeptide suitable for an X-ray crystal-structure analysis to evaluate the conformational constraints of the linear precursor.

Next, we prepared a similar hexapeptide, with Pro at the N-terminus and the Gly residue in the middle of the sequence, with the aim of facilitating the cyclization (*Scheme 6*). By starting with the dipeptide amide **23** and Fmoc-Pro-Aib-OH (**5**) and by using HATU/HOAt[2]) as the coupling reagent, the tetrapeptide amide Fmoc-Pro-Aib-Gly-Aib-N(Me)Ph (**24**) was obtained and hydrolyzed to give **25**. Coupling of H-Phe-Aib-N(Me)Ph, generated by hydrogenolysis from Z-Phe-Aib-N(Me)Ph (**26**) [16], with **25** by using TBTU/HOBt[2]) afforded Fmoc-Pro-Aib-Gly-Aib-Phe-Aib-N(Me)Ph (**27**). After deprotection, the linear precursor was subjected to cyclization. Unfortunately, neither PyAOP nor DEPBT[2]) led to cyclo(Aib-Gly-Aib-Phe-Aib-Pro) (**28**). Since the

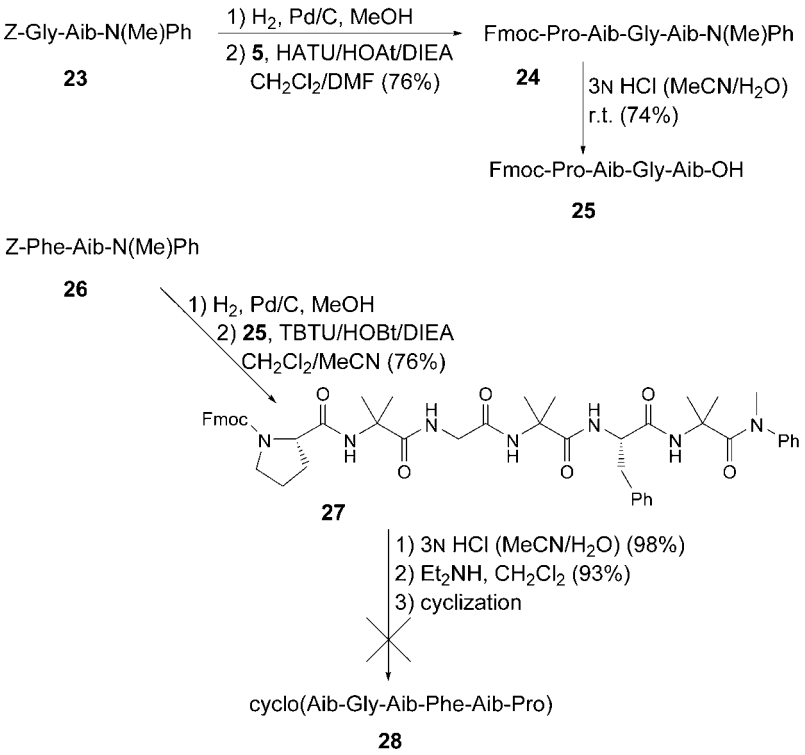
Scheme 5



linear precursor of **28**, as in the case of **22**, remained unaltered upon exposure to the coupling reagents and the base over a period of several days, we suppose that these hexapeptide sequences form rigid extended conformations that prevent cyclization.

The cyclic Pro- and Aib-containing pentapeptide cyclo(Aib-Aib-Gly-Aib-Pro) has previously been synthesized in excellent yield (89%) with DEPC/DIEA[2]) in DMF in an overnight reaction [16]. The linear precursor of this cyclic pentapeptide apparently possesses a cyclization-prone conformation in DMF solution. Although it is known that minor changes in peptide sequence can significantly affect cyclization, we hoped that, by incorporation of an additional Aib residue into the above sequence, the conformational preference of the linear precursor would not be altered too much and would, therefore, lead to the cyclic hexapeptide in good yield. The synthesis of the linear precursor containing Gly, Pro, and four Aib residues is outlined in *Scheme 7*. PyBOP-Mediated[2]) condensation of Fmoc-Pro-Aib-OH (**5**) with H-Aib-O^{t}Bu gave tripeptide Fmoc-Pro-Aib-Aib-O^{t}Bu (**29**) in good yield. Removal of the Fmoc group of **29** followed by a second PyBOP-mediated coupling with Z-Gly-Aib-Aib-OH provided Z-Gly-Aib-Aib-Pro-Aib-Aib-O^{t}Bu (**30**) in moderate yield. Finally, the protecting groups were removed, and the linear precursor was subjected to cyclization. However, all

Scheme 6

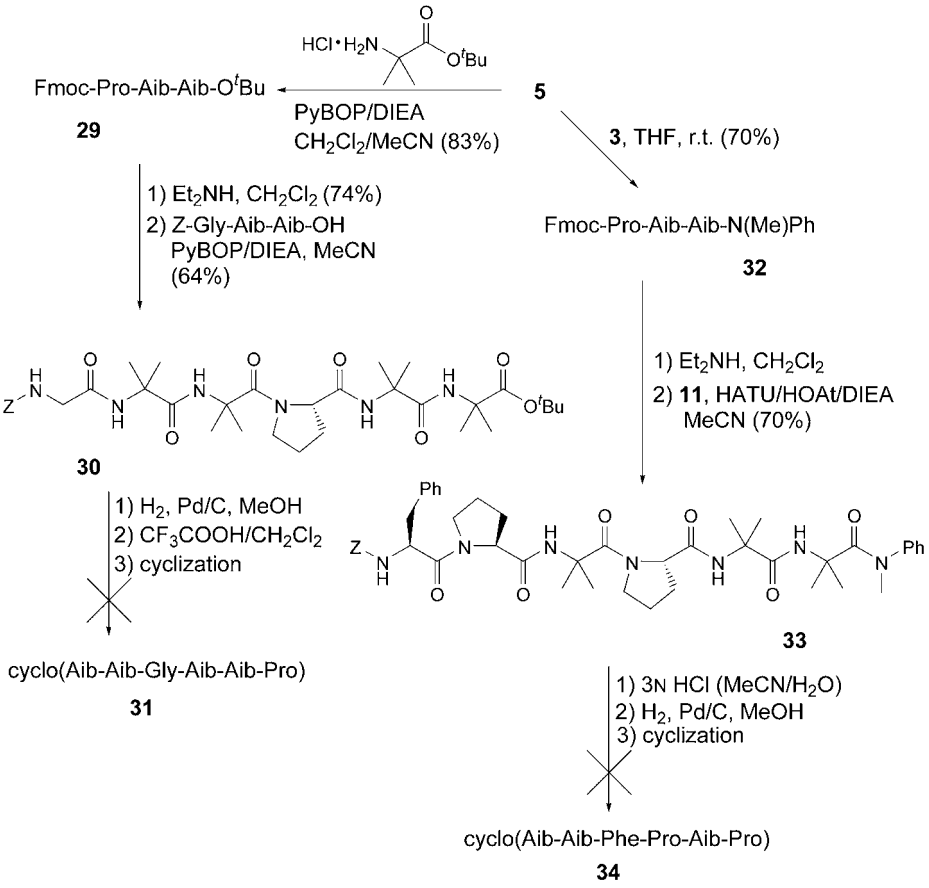


attempts by using either DEPBT/DIEA/DMF or DEPC/DIEA/DMF[2]) and prolonged reaction time (3–10 d) failed to give cyclopeptide **31**.

Since the cyclization of hexapeptides containing one Pro and several Aib residues remained difficult, the incorporation of two Pro units seemed reasonable. As cyclo(Aib-Aib-Phe-Pro-Aib-Gly) (**1**) was synthesized successfully, although in moderate cyclization yields (28–35%), an analogous peptide with Gly replaced by an additional Pro residue was prepared (*Scheme 7*). Thus, the reaction of **5** with **3** in THF (6 d) afforded tripeptide amide Fmoc-Pro-Aib-Aib-N(Me)Ph (**32**) in good yield. After removal of the Fmoc group of **32**, the HATU/HOAt-mediated[2]) coupling with Z-Phe-Pro-Aib-OH (**11**) gave hexapeptide Z-Phe-Pro-Aib-Pro-Aib-Aib-N(Me)Ph (**33**). The protecting groups were removed and the linear precursor subjected to cyclization, but no cyclic peptide **34** was formed after treatment with either PyAOP/HOAt[2]) or EDCI/HOAt for 3 d.

In summary, the cyclization of various hexapeptides containing Pro and three or four Aib residues was investigated. In contrast to the general rule that Pro residues in linear peptides promote the formation of cyclization-prone conformations, our experimental data showed that the introduction of Pro into the peptide sequence containing Aib residues drastically hinders the formation of cyclic hexapeptides regardless of the position of Pro in the linear sequence. A total of 18 cyclization

Scheme 7



reactions were carried out to study the propensity of these hexapeptides to form cyclomonomers, but only three reactions were successful and resulted in moderate yields of cyclopeptides **1** or **2**. During cyclizations that fail to produce cyclomonomers, the formation of cyclic dimers or oligomers is commonly observed, but, in the present study, the linear precursors either formed cyclomonomers in moderate yields or remained unaltered. One possible explanation for this observation might be the preference for rigid extended conformations when conformationally restricted proline along with conformationally constrained Aib units are incorporated in short peptide sequences (*cf.* also [17]).

2.2. *Solid-State Conformation of Cyclo(Aib-Aib-Phe-Pro-Aib-Gly)* (**1**). Cyclic hexapeptides generally adopt conformations consisting of two β-turns, often referred to as the turn-extended-turn conformation [18]. A proline residue, in which the N–C(α) torsion angle ϕ is restricted to -60° ($\pm 20^\circ$) induces characteristic turn motifs within the cyclic peptides. As a consequence of this reduced conformational space, Pro strongly prefers the $(i+1)$-position of most β-turns [19]. In Pro-Xaa sequences, the

preference for a certain type of β-turn conformation depends on the structure of the Xaa residue, such as L/D configuration and side-chain nature, as well as on the environment (solid or solution state, solvent polarity) [20].

We carried out an X-ray crystallographic investigation of the molecular structure of **1** to study the effect that the Pro and Aib residues might have on the conformation of small cyclic peptides. Crystals were grown from the fraction containing **1** and some $(Et^iPr_2NH)PF_6$ by slow evaporation of a solution in AcOEt/EtOH/hexane. The cyclic peptide **1** co-crystallized with $(Et^iPr_2NH)PF_6$ and H_2O in a ratio 1:1:1. The ORTEP plot [21] of the molecular structure with the atom numbering scheme is presented in the *Figure*. The relevant torsion angles for **1** are summarized in *Table 1*, and the H-bond parameters are shown in *Table 2*.

Table 1. *Torsion Angles* [°] *for Cyclo(Aib-Aib-Phe-Pro-Aib-Gly)* (=*Cyclo(Pro*[1]*-Aib*[2]*-Gly*[3]*-Aib*[4]*-Aib*[5]*-Phe*[6]*)*; **1**)

Residue[a])	ϕ	ψ	ω
Pro[1]	−54.7(4)	−35.4(5)	+179.5(3)
Aib[2]	−65.1(5)	−13.8(5)	−165.9(4)
Gly[3]	+118.6(4)	+169.5(3)	+173.0(4)
Aib[4]	+53.9(5)	+46.7(5)	+173.1(3)
Aib[5]	+80.2(5)	+10.1(5)	+170.6(4)
Phe[6]	−122.0(4)	+168.0(3)	+176.9(3)

[a]) Arbitrary residue numbering.

Table 2. *Hydrogen-Bonding Geometry for Cyclo(Aib-Aib-Phe-Pro-Aib-Gly)* (**1**)

Donor (D−H)[a])	Acceptor (A)[b])	D−H [Å]	H···A [Å]	D···A [Å]	D−H···A [°]
N(1)−H(1)	O(12)	0.88	2.25	3.063(5)	153
N(1)−H(1)	N(16)	0.88	2.23	2.684(5)	112
N(7)−H(7)	N(4)	0.88	2.43	2.793(5)	105
N(7)−H(7)	F(3a)	0.88	2.42	3.220(5)	152
N(7)−H(7)	F(2b)	0.88	2.43	2.904(9)	114
N(7)−H(7)	F(3c)	0.88	2.20	2.916(8)	139
N(10)−H(10)	O(3)	0.88	2.01	2.852(4)	159
N(10)−H(10)	N(7)	0.88	2.32	2.748(5)	110
N(13)−H(13)	O(6^i)	0.88	2.08	2.924(5)	159
N(16)−H(16)	N(13)	0.88	2.53	2.868(5)	104
N(16)−H(16)	O(44)	0.88	2.18	3.032(5)	162
N(37)−H(37)	O(18^{ii})	0.93	1.92	2.829(5)	165
O(44)−H(441)	O(6^i)	0.84(1)	1.97(1)	2.808(6)	173(10)
O(44)−H(442)	O(9^{iii})	0.84(1)	2.05(4)	2.842(5)	156(9)

[a]) Arbitrary numbering, *cf. Figure.* [b]) Superscripts in atom labels refer to the peptide molecule in the following symmetry-related positions: ^{i} $-1/2+x,\ -1/2+y,\ -z$; ^{ii} $-1/2+x,\ 1/2-y,\ -z$; ^{iii} $1/2+x,\ -1/2-y,\ -z$.

The overall conformation of cyclo(Pro[1]-Aib[2]-Gly[3]-Aib[4]-Aib[5]-Phe[6]) (=cyclo(Aib-Aib-Phe-Pro-Aib-Gly); **1**) consists of two β-turns stabilized by a pair of intramolecular H-bonds involving the CO and NH groups of the Gly and Phe residues. The torsion angles ϕ and ψ of the Aib[4] and Aib[5] residues in the Gly[3]-Aib[4]-Aib[5]-Phe[6] segment show values close to those for a type-I′ β-turn (*Table 1*). The sequence Phe[6]-Pro[1]-Aib[2]-Gly[3]

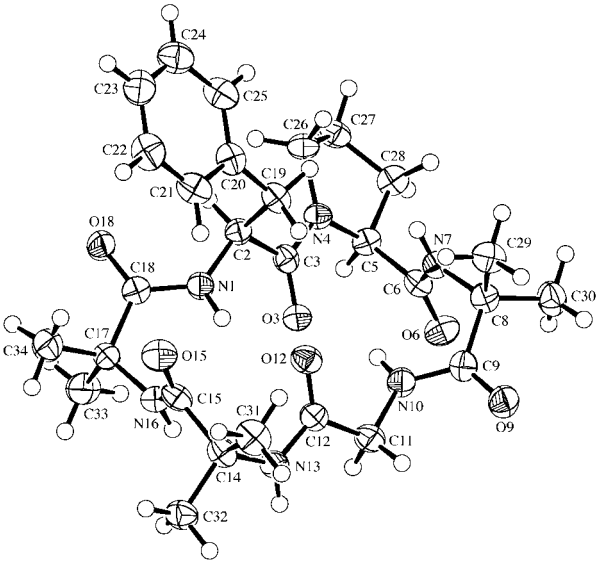


Figure. *ORTEP Plot* [21] *of the molecular structure of* **1**. The co-crystallized $(Et^iPr)_2NH)PF_6$ and H_2O are not shown; 50% probability ellipsoids; arbitrary numbering of the atoms.

adopts a type-III β-turn conformation with Pro[1] at the $(i+1)$ position of the turn, as expected for this residue. All three Aib residues show torsion angles which are in good agreement with the expected values in the helical region of the conformational space. In addition, all the amide bonds have the *trans* conformation. Since structural information about the conformational preferences of Aib- and Pro-containing cyclic hexapeptides is scarce, our results cannot be compared with other data. To the best of our knowledge, the solution structure of *cyclo*(Aib-Pro-Leu)$_2$ is, so far, the only example of an Aib- and Pro-containing cyclic hexapeptide with a known conformation [22]. The NMR spectra and temperature coefficients of this cyclic peptide indicate an asymmetric conformation that contains both *cis* and *trans* Aib-Pro bonds. Therefore, the overall conformation consists of two β-turns of type II′ and VI with Pro residues occupying the $(i+2)$ positions of the turns.

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Experimental Part

1. *General.* Abbreviations: DEPBT = 3-[(diethoxyphosphoryl)oxy]-1,2,3-benzotriazin-4(3*H*)-one, DEPC = diethyl phosphorocyanidate, DIEA = *N*-ethyl-diisopropylamine, EDCI = *N*-ethyl-*N*′-[3-(dimethylamino)propyl]carbodiimide, Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl, HATU = 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-1*H*-7-azabenzotriazole, HOBt = 1-hydroxy-1*H*-benzotriazole, PyAOP = (1*H*-7-azabenzotriazol-1-yloxy)tripyrrolidin-1-ylphosphonium hexafluorophosphate, PyBOP = (1*H*-benzotriazol-1-yloxy)tripyrrolidin-1-ylphosphonium hexafluorophosphate, TBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, Z = (benzyloxy)carbonyl. Solvents were purified by standard procedures. The Aib-synthon used was 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**3**) [23]. TLC: *Merck* TLC aluminium sheets, silica gel *60 F_{254}*. Column chromatography (CC): *Uetikon-*

Chemie 'Chromatographiegel' *C-560*. M.p.: *Büchi 510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 1600* FT-IR spectrophotometer; in KBr; absorptions in cm^{-1}. ^{1}H- (300 MHz) and ^{13}C-NMR (75.5 MHz) Spectra: *Bruker ARX-300* instrument; in (D_6)DMSO at 300 K unless otherwise stated; δ in ppm, coupling constants J in Hz. MS: *Finnigan SSQ-700* or *MAT-90* instrument for CI; *Finnigan TSQ-700* triple quadrupole spectrometer for ESI; *m*/*z* (rel.%).

General Procedure 1 (*GP 1*). To a soln. of an *N*-protected amino acid or peptide acid in abs. THF or MeCN was added the 2*H*-azirin-3-amine **3** (1.1 equiv.) in abs. THF, and the mixture was stirred at r.t. under N_2. After completion of the reaction (TLC), the solvent was evaporated and the residue purified by CC (SiO_2).

General Procedure 2 (*GP 2*). The peptide amide was dissolved in 3N HCl/MeCN 1:1 (*v*/*v*; 10 ml/mmol), and the soln. was stirred at r.t. overnight. The mixture was extracted with CH_2Cl_2 or AcOEt, the org. phase dried (Na_2SO_4) and evaporated, and the crude product purified by CC or crystallization and dried under high vacuum (h.v.).

General Procedure 3 (*GP 3*). To a soln. of a Z-protected peptide in MeOH was added 10% Pd/C, and the mixture was hydrogenated overnight under atmospheric pressure by means of an H_2-filled balloon. The catalyst was removed by filtration through a pad of *Celite* and the solvent evaporated. The residue was purified by CC (short plug of SiO_2, CH_2Cl_2/MeOH/NH_3 soln. 12:1:0.1).

General Procedure 4 (*GP 4*). To a soln. of an *N*-protected peptide acid in the given solvent were added the amino component (1.1 equiv.), coupling reagent (1.0–1.1 equiv.), additive (HOAt or HOBt, 1.0–1.1 equiv.) if indicated, and DIEA (2 equiv. without and 3 equiv. with hydrochloride salts present). The mixture was stirred at r.t. under N_2 until the starting material was consumed (TLC). After evaporation, the residue was dissolved in AcOEt, the soln. washed with 5% aq. $KHSO_4$ soln., 5% aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the residue purified by CC and dried *in vacuo* (*i.v.*).

General Procedure 5 (*GP 5*): *DEPBT-Mediated Cyclization.* Free linear hexapeptide was dissolved in abs. DMF (1.5 mM) under stirring. DEPBT (3–5 equiv.) and DIEA (1% *v*/*v*) were then added at r.t., and the soln. was stirred for an additional 3 d. The solvent was evaporated, and the crude cyclopeptide purified by CC and prep. TLC.

General Procedure 6 (*GP 6*): *DEPC-Mediated Cyclization.* Free linear hexapeptide was dissolved in abs. DMF (1.0–1.5 mM), and the soln. was cooled to 0° in an ice bath. A soln. of 3–5 equiv. of DEPC in abs. DMF (1 ml) was added under stirring. Then, DIEA (1% *v*/*v*) was added slowly within 15 min. The soln. was warmed to r.t. and stirred for an additional 6 d. The solvent was then evaporated, the residue taken up in AcOEt, the soln. washed with 5% aq. $KHSO_4$ soln., 5% aq. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the crude cyclohexapeptide purified by CC.

General Procedure 7 (*GP 7*): *PyAOP-Mediated Cyclization.* Free linear hexapeptide was dissolved in abs. DMF (0.5–1.0 mM) under stirring. PyAOP (3 or 5 equiv.), 0.5M HOAt in DMF (3 or 5 equiv.), and DIEA were then added at r.t. The soln. was stirred at r.t. for an additional 3 d. After evaporation, the residue was dissolved in AcOEt, the soln. washed with 10% citric acid soln., 5% $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and evaporated, and the yellow oil purified by CC.

2. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*prolyl-2-amino-2-methylpropanoylglycyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoyl*-L-*phenylalanine* tert-*Butyl Ester* (*Fmoc-Pro-Aib-Gly-Aib-Aib-Phe-O*^{t}*Bu*; **9**). 2.1. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*prolyl-2-amino*-N,*2-dimethyl*-N-*phenylpropanamide* (*Fmoc-Pro-Aib-N(Me)Ph*; **4**). According to *GP 1*, with Fmoc-Pro-OH (4.0 g, 11.85 mmol) in THF (50 ml) and **3** (2.272 g, 13.04 mmol) in THF (5 ml) for 60 h. CC (AcOEt/hexane 2:1) yielded 5.39 g (89%) of **4**. White foam. IR: 3305*s*, 3063*m*, 2980*m*, 2948*m*, 2880*m*, 1703*s*, 1635*s*, 1594*s*, 1535*m*, 1493*s*, 1451*s*, 1417*s*, 1359*s*, 1289*m*, 1243*m*, 1192*m*, 1118*s*, 1090*s*, 988*m*, 760*s*, 741*s*, 705*m*.^{1}H-NMR: 8.09 (*s*, NH); 7.91–7.18 (*m*, 13 arom. H); 4.34–4.11 (*m*, C*H*CH_2O of Fmoc, CH(2) of Pro); 3.48–3.35 (*m*, CH_2(5) of Pro); 3.24 (*s*, MeN); 2.19–1.82 (*m*, CH_2(3) and CH_2(4) of Pro); 1.37, 1.35 (2*s*, 2 Me of Aib). ^{13}C-NMR: 172.1, 170.6 (2*s*, 2 CO); 154.0 (*s*, CO (urethane)); 145.6, 143.8, 143.6, 140.6 (4*s*, 5 arom. C); 128.5, 127.5, 127.3, 127.0, 126.2, 125.0, 120.0 (7*d*, 13 arom. CH); 66.4 (*t*, CHCH_2O of Fmoc); 59.4 (*d*, C(2) of Pro); 56.1 (*s*, C(2) of Aib); 46.5 (*d*, *C*HCH_2O of Fmoc); 46.3 (*t*, C(5) of Pro); 39.6 (*q*, MeN); 29.7 (*t*, C(3) of Pro); 26.0, 25.7 (2*q*, 2 Me of Aib); 23.7 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 534 (100, $[M + Na]^+$). Anal. calc. for $C_{31}H_{33}N_3O_4$ (511.62): C 72.78, H 6.50, N 8.21; found: C 72.71, H 6.59, N 8.17.

2.2. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*prolyl-2-amino-2-methylpropanoic Acid* (*Fmoc-Pro-Aib-OH*; **5**). According to *GP 2*, with **4** (5.3 g, 10.35 mmol) in 3N HCl (MeCN/H_2O 1:1, 100 ml). After extraction with AcOEt, CC (AcOEt/MeOH 20:1) gave 3.22 g (74%) of pure **5**. White powder. M.p. 170.0–171.5°. IR: 3364*m*, 2987*m*, 2946*m*, 2895*m*, 2536*w*, 1706*s*, 1628*s*, 1528*s*, 1463*s*, 1451*s*, 1408*s*, 1356*m*, 1345*s*, 1328*s*, 1270*m*, 1252*m*, 1204*s*, 1175*s*, 1128*m*, 988*w*, 925*w*, 862*w*, 760*s*, 741*s*. ^{1}H-NMR: 8.21 (br. *s*, NH); 8.00–7.30 (*m*, 8 arom. H);

4.40–4.00 (*m*, C*HCH*$_2$O of Fmoc, CH(2) of Pro); 3.44–3.32 (*m*, CH$_2$(5) of Pro); 2.24–1.82 (*m*, CH$_2$(3) and CH$_2$(4) of Pro); 1.36, 1.33 (2*s*, 2 Me of Aib). ^{13}C-NMR: 175.3, 171.2 (2*s*, 2 CO); 153.8 (*s*, CO (urethane)); 144.0, 143.7, 143.4, 140.6 (4*s*, 4 arom. C); 127.5, 127.0, 125.5, 125.2, 125.0, 120.0 (6*d*, 8 arom. CH); 66.7 (*t*, CH*C*H$_2$O of Fmoc); 59.2 (*d*, C(2) of Pro); 54.8 (*s*, C(2) of Aib); 47.0 (*t*, C(5) of Pro); 46.5 (*d*, *C*HCH$_2$O of Fmoc); 31.0 (*t*, C(3) of Pro); 25.1, 24.4 (2*q*, 2 Me of Aib); 22.7 (*t*, C(4) of Pro). ESI-MS (MeOH): 445 (48, $[M+Na]^+$), 423 (100, $[M+H]^+$). Anal. calc. for $C_{24}H_{26}N_2O_5$ (422.48): C 68.23, H 6.20, N 6.63; found: C 68.10, H 6.28, N 6.42.

2.3. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*prolyl-2-amino-2-methylpropanoylglycyl-2-amino-2-methylpropanoyl-2-amino-*N,*2-dimethyl-*N*-phenylpropanamide* (*Fmoc-Pro-Aib-Gly-Aib-Aib-N(Me)Ph*; **7**). According to *GP 3*, with Z-Gly-Aib-Aib-N(Me)Ph [5] (**6**; 0.54 g, 1.15 mmol), Pd/C (60 mg), and MeOH (6 ml), overnight). CC (CH_2Cl_2/MeOH 15:1) yielded 0.385 g (100%) of H-Gly-Aib-Aib-N(Me)Ph as a white foam, which was used directly in the next step.

According to *GP 4*, with Fmoc-Pro-Aib-OH (**5**; 0.442 g, 1.05 mmol), H-Gly-Aib-Aib-N(Me)Ph (0.385 g, 1.15 mmol), PyBOP (0.544 g, 1.05 mmol), and DIEA (0.27 g, 2.1 mmol) in abs. CH_2Cl_2/MeCN 4:1 (10 ml). CC (AcOEt/MeOH 13:1, CH_2Cl_2/MeOH 15:1) yielded 0.536 g (69%) of **7**. White powder. M.p. 136–138°. IR: 3323*m*, 3064*w*, 2984*m*, 2940*m*, 1673*s*, 1594*m*, 1534*s*, 1494*m*, 1452*s*, 1425*m*, 1391*m*, 1361*m*, 1336*m*, 1281*m*, 1244*m*, 1195*m*, 1168*m*, 1125*m*, 1091*m*, 1017*w*, 991*w*, 760*m*, 741*m*, 708*m*. ^{1}H-NMR: 8.77, 8.04, 7.90, 7.88 (4*s*, 4 NH); 7.64–7.15 (*m*, 13 arom. H); 4.37–4.12 (*m*, C*HCH*$_2$O of Fmoc, CH(2) of Pro); 3.52–3.41 (*m*, CH$_2$ of Gly, CH$_2$(5) of Pro); 3.22 (*s*, MeN); 2.15–1.85 (*m*, CH$_2$(3) and CH$_2$(4) of Pro); 1.39, 1.36, 1.28, 1.21 (4*s*, 6 Me of 3 Aib). ^{13}C-NMR (CD_3OD): 178.1, 176.2, 175.5, 175.2, 171.6 (5*s*, 5 CO); 156.8 (*s*, CO (urethane)); 147.0, 145.0, 144.9, 142.5 (4*s*, 5 arom. C); 130.2, 128.9, 128.1, 126.2, 125.9, 121.0 (6*d*, 13 arom. CH); 69.0 (*t*, CH*C*H$_2$O of Fmoc); 61.5 (*d*, C(2) of Pro); 58.4, 58.2, 57.6 (3*s*, 3 C(2) of 3 Aib); 48.24 (*t*, C(5) of Pro); 48.20 (*d*, *C*HCH$_2$O of Fmoc); 45.4 (*t*, C(2) of Gly); 41.0 (*q*, MeN); 31.0 (*t*, C(3) of Pro); 25.6 (*t*, C(4) of Pro); 27.1, 26.5, 26.4, 26.1, 24.4, 24.0 (6*q*, 6 Me of 3 Aib). ESI-MS (MeOH/CH_2Cl_2): 784 (32, $[M+K]^+$), 632 (100, $[M-N(Me)Ph]^+$). Anal. calc. for $C_{41}H_{50}N_6O_7 \cdot 1/2\,H_2O$ (747.89): C 65.84, H 6.87, N 11.24; found: C 65.87, H 6.80, N 11.25.

2.4. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*propyl-2-amino-2-methylpropanoylglycyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoic Acid* (*Fmoc-Pro-Aib-Gly-Aib-Aib-OH*; **8**). According to *GP 2*, with **7** (0.478 g, 0.65 mmol) in 3N HCl (MeCN/H_2O 1:1, 6 ml). The solvent was evaporated, H_2O (5 ml) added, and the precipitated product filtered, washed with H_2O and Et_2O, and dried under h.v.: 0.38 g (91%) of pure **8**. White powder. M.p. 185.5–187.5°. IR: 3325*m*, 2983*m*, 2938*m*, 1662*s*, 1603*m*, 1525*s*, 1452*s*, 1362*m*, 1338*m*, 1289*m*, 1210*m*, 1133*m*, 1019*w*, 989*w*, 942*w*, 868*w*, 759*m*, 741*m*. ^{1}H-NMR (CD_3OD): 7.80–7.28 (*m*, 8 arom. H); 4.43–4.21 (*m*, C*HCH*$_2$O of Fmoc, CH(2) of Pro); 3.76–3.50 (*m*, CH$_2$ of Gly, CH$_2$(5) of Pro); 2.22–1.88 (*m*, CH$_2$(3) and CH$_2$(4) of Pro); 1.48, 1.43, 1.31, 1.19 (4*s*, 6 Me of 3 Aib). ^{13}C-NMR (CD_3OD): 181.3, 179.9, 176.1, 174.6, 169.7 (5*s*, 6 CO); 156.4 (*s*, CO (urethane)); 144.8, 143.1, 142.4 (3*s*, 4 arom. C); 128.9, 128.0, 127.7, 126.0, 125.7, 121.0, 120.9 (7*d*, 8 arom. CH); 70.2 (*t*, CH*C*H$_2$O of Fmoc); 60.7 (*d*, C(2) of Pro); 58.6, 58.3, 57.1 (3*s*, 3 C(2) of 3 Aib); 48.6 (*t*, C(5) of Pro); 47.4 (*d*, *C*HCH$_2$O of Fmoc); 44.7 (*t*, C(2) of Gly); 31.3 (*t*, C(3) of Pro); 25.7 (*t*, C(4) of Pro); 25.0, 24.3, 24.1, 22.9 (4*q*, 6 Me of 3 Aib). ESI-MS (MeOH + NaI): 672 (100, $[M+Na]^+$).

2.5. *Fmoc-Pro-Aib-Gly-Aib-Aib-Phe-O*^{t}*Bu* (**9**). According to *GP 4*, with **8** (0.338 g, 0.52 mmol), HCl·H-Phe-O^{t}Bu (0.147 g, 0.57 mmol), PyBOP (0.27 g, 0.52 mmol), and DIEA (0.2 g, 1.56 mmol) in abs. CH_2Cl_2/MeCN 3:2 (10 ml) for 20 h. CC (CH_2Cl_2/MeOH 20:1) yielded 0.358 g (81%) of **9**. White powder. M.p. 166.5–167.5°. IR: 3323*m*, 2981*m*, 2936*m*, 1671*s*, 1535*s*, 1453*s*, 1425*m*, 1363*m*, 1336*m*, 1283*m*, 1247*m*, 1160*s*, 1128*m*, 990*w*, 847*w*, 759*m*, 741*m*, 701*m*. ^{1}H-NMR (CD_3OD): 7.79–7.15 (*m*, 13 arom. H); 4.44–4.17 (*m*, C*HCH*$_2$O of Fmoc, CH(2) of Phe, CH(2) of Pro); 3.87–3.50 (*m*, CH$_2$ of Gly, CH$_2$(5) of Pro); 3.07–3.02 (*m*, CH$_2$ of Phe); 2.25–1.85 (*m*, CH$_2$(3) and CH$_2$(4) of Pro); 1.44, 1.42, 1.41, 1.35, 1.30, 1.15 (6*s*, 6 Me of 3 Aib, Me$_3$C). ^{13}C-NMR (CD_3OD): 177.9, 176.9, 175.8, 175.2, 172.2, 172.1 (6*s*, 6 CO); 156.8 (*s*, CO (urethane)); 145.0, 144.9, 142.6, 138.5 (4*s*, 5 arom. C); 130.4, 129.2, 128.9, 128.1, 127.5, 126.1, 125.9, 121.0 (8*d*, 13 arom. CH); 82.4 (*s*, Me$_3$*C*); 69.0 (*t*, CH*C*H$_2$O of Fmoc); 61.5, 56.5 (2*d*, C(2) of Pro, C(2) of Phe); 48.3 (*t*, C(5) of Pro); 48.2 (*d*, *C*HCH$_2$O of Fmoc); 45.3, 38.4 (2*t*, C(2) of Gly, C(3) of Phe); 31.0 (*t*, C(3) of Pro); 28.1 (*q*, *Me*$_3$C); 26.9, 26.8, 26.7 (3*q*, 6 Me of 3 Aib); 25.6 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 876 (100, $[M+Na]^+$). Anal. calc. for $C_{47}H_{60}N_6O_9 \cdot 1/3\,H_2O$ (859.03): C 65.71, H 7.12, N 9.78; found: C 65.70, H 7.26, N 9.72.

3. N-*[(Benzyloxy)carbonyl]*-L-*phenylalanyl*-L-*prolyl-2-amino-2-methylpropanoylglycyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoic Acid* tert-*Butyl Ester* (*Z-Phe-Pro-Aib-Gly-Aib-Aib-O*^{t}*Bu*; **13**). 3.1. N-*[(Benzyloxy)carbonyl]*-L-*phenylalanyl-2-amino-*N,*2-dimethyl-*N*-phenylpropanamide* (*Z-Phe-Pro-Aib-N(Me)Ph*; **10**). A soln. of Fmoc-Pro-Aib-N(Me)Ph (**4**; 2.479 g, 4.84 mmol) in CH_2Cl_2/Et_2NH 1:1 (20 ml) was stirred for 3 h at r.t. After evaporation, CC (CH_2Cl_2/MeOH 12:1) gave 1.21 g (86%) of H-Pro-Aib-N(Me)Ph, which was used directly in the next step.

According to *GP 4*, with H-Pro-Aib-N(Me)Ph (1.21 g, 4.18 mmol), Z-Phe-OH (1.138 g, 3.8 mmol), PyAOP (2.19 g, 4.2 mmol), and DIEA (1.36 g, 10.5 mmol) in abs. CH_2Cl_2 (15 ml) for 24 h. CC (AcOEt/MeOH 15:1, CH_2Cl_2/MeOH 35:1) yielded 1.94 g (89%) of pure **10**. White foam. IR: 3416*m*, 3304*s*, 3061*m*, 3031*m*, 2981*m*, 2946*m*, 1715*s*, 1683*s*, 1643*s*, 1593*m*, 1531*s*, 1494*s*, 1453*s*, 1389*m*, 1361*m*, 1245*s*, 1211*m*, 1116*m*, 1089*m*, 1044*m*, 1027*m*, 1002*w*, 845*w*, 774*m*, 748*m*, 701*s*. ^{1}H-NMR: 8.06 (*s*, NH of Aib); 7.64 (*d*, $J = 8.2$, NH of Phe); 7.37–7.14 (*m*, 15 arom. H); 4.96 (*s*, PhCH_2O); 4.47–4.31 (*m*, CH(2) of Phe, CH(2) of Pro); 3.69–3.50 (*m*, CH_2(5) of Pro); 3.27 (*s*, MeN); 3.04–2.73 (*m*, CH_2 of Phe); 2.05–1.77 (*m*, CH_2(3) and CH_2(4) of Pro); 1.38, 1.37 (2*s*, 2 Me of Aib). ^{13}C-NMR: 172.1, 170.2, 170.1 (3*s*, 3 CO); 155.8 (*s*, CO (urethane)); 145.7, 137.8, 136.9 (3*s*, 3 arom. C); 129.1, 128.6, 128.1, 128.0, 127.6, 127.4, 127.3, 126.2 (8*d*, 15 arom. CH); 65.1 (*t*, Ph*C*H_2O); 59.1 (*d*, C(2) of Pro); 56.0 (*s*, C(2) of Aib); 54.3 (*d*, C(2) of Phe); 46.6 (*t*, C(5) of Pro); 39.6 (*q*, MeN); 36.3 (*t*, C(3) of Phe); 28.7 (*t*, C(3) of Pro); 26.1, 25.4 (2*q*, 2 Me of Aib); 24.3 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 593 (100, $[M + Na]^+$). Anal. calc. for $C_{33}H_{38}N_4O_5 \cdot 1/2\,H_2O$ (579.70): C 68.37, H 6.78, N 9.66; found: C 68.50, H 6.76, N 9.58.

3.2. N-*[(Benzyloxy)carbonyl]*-L-*phenylalanyl-2-amino-2-methylpropanoic Acid (Z-Phe-Pro-Aib-OH*; **11**). According to *GP 2*, with **10** (0.68 g, 1.19 mmol) in 3N HCl (MeCN/H_2O 1:1, 12 ml). CC (CH_2Cl_2/MeOH 15:1) yielded 0.519 g (91%) of **11**. White foam. IR: 3416*s*, 3063*m*, 3031*m*, 2982*m*, 1714*s*, 1640*s*, 1529*s*, 1454*s*, 1341*m*, 1247*s*, 1214*s*, 1162*s*, 1081*m*, 1051*m*, 1003*w*, 913*w*, 749*m*, 700*s*. ^{1}H-NMR: 7.94 (*s*, NH of Aib); 7.58 (*d*, $J = 8.4$, NH of Phe); 7.36–7.18 (*m*, 10 arom. H); 4.95 (br. *s*, PhCH_2O); 4.46–4.28 (*m*, CH(2) of Pro and CH(2) of Phe); 3.67–3.23 (*m*, CH_2(5) of Pro); 3.04–2.73 (*m*, CH_2(3) of Phe); 2.03–1.64 (*m*, CH_2(3) and CH_2(4) of Pro); 1.37, 1.35 (2*s*, 2 Me of Aib). ^{13}C-NMR: 175.9, 170.1, 170.0 (3*s*, 3 CO); 155.8 (*s*, CO (urethane)); 137.8, 136.9 (2*s*, 2 arom. C); 129.1, 128.1, 127.9, 127.5, 127.3, 126.1 (6*d*, 10 arom. CH); 65.1 (*t*, Ph*C*H_2O); 59.4 (*d*, C(2) of Pro); 55.0 (*s*, C(2) of Aib); 54.3 (*d*, C(2) of Phe); 46.6 (*t*, C(5) of Pro); 36.3 (*t*, C(3) of Phe); 28.5 (*t*, C(3) of Pro); 24.8, 24.2 (2*q*, 2 Me of Aib); 24.3 (*t*, C(4) of Pro). CI-MS (NH_3): 482 (27, $[M + H]^+$), 464 (100, $[M - OH]^+$). Anal. calc. for $C_{26}H_{31}N_3O_6 \cdot 1/2\,H_2O$ (490.55): C 63.66, H 6.57, N 8.56; found: C 63.57, H 6.32, N 8.37.

3.3. *Z-Phe-Pro-Aib-Gly-Aib-Aib-O^{t}Bu* (**13**). According to *GP 3*, with Z-Gly-Aib-Aib-O^{t}Bu [5] (**12**; 0.425 g, 0.98 mmol), Pd/C (50 mg), and MeOH (6 ml): 0.294 g (100%) of H-Gly-Aib-Aib-O^{t}Bu, which was used directly in the next step without further purification.

According to *GP 4*, with H-Gly-Aib-Aib-O^{t}Bu (0.294 g, 0.98 mmol), **11** (0.427g, 0.89 mmol), HATU (0.342 g, 0.9 mmol), 0.5M HOAt in DMF (0.9 mmol, 1.8 ml), and DIEA (0.232 g, 1.8 mmol) in abs. CH_2Cl_2 (10 ml) for 20 h. CC (CH_2Cl_2/MeOH 15:1) gave 0.495 g (73%) of pure **13**. White foam. IR: 3328*s*, 3063*w*, 3031*w*, 2982*m*, 2937*m*, 1670*s*, 1529*s*, 1454*s*, 1386*m*, 1367*m*, 1310*m*, 1252*m*, 1149*s*, 1083*w*, 1044*m*, 919*w*, 850*s*, 751*m*, 699*m*. ^{1}H-NMR: 8.90 (*s*, NH of Aib); 8.27 (*t*-like, NH of Gly); 7.74 (*d*, $J = 8.5$, NH of Phe); 7.46 (*s*, NH of Aib); 7.35–7.21 (*m*, 10 arom. H); 7.13 (*s*, NH of Aib); 4.93–4.92 (*m*, PhCH_2O); 4.45–4.37 (*m*, CH(2) of Pro, CH(2) of Phe); 3.81–3.50 (*m*, CH_2(5) of Pro, CH_2 of Gly); 2.89–2.66 (*m*, CH_2 of Phe); 2.18–1.80 (*m*, CH_2(3) and CH_2(4) of Pro); 1.43, 1.37, 1.32, 1.30, 1.29, 1.26 (6*s*, 6 Me of 3 Aib, Me_3C). ^{13}C-NMR: 175.7, 173.0, 172.8, 171.0, 168.5 (5*s*, 6 CO); 155.9 (*s*, CO (urethane)); 137.5, 136.8 (2*s*, 2 arom. C); 129.1, 128.2, 128.1, 127.7, 127.5, 126.4 (6*d*, 10 arom. CH); 78.9 (*s*, Me_3C); 65.3 (*t*, Ph*C*H_2O); 60.0 (*d*, C(2) of Pro); 56.0, 55.7, 55.2 (3*s*, 3 C(2) of 3 Aib); 54.5 (*d*, C(2) of Phe); 47.0 (*t*, C(5) of Pro); 44.4 (*t*, C(2) of Gly); 36.4 (*t*, C(3) of Phe); 28.3 (*t*, C(3) of Pro); 27.4 (*q*, *Me*$_3$C); 25.0 (*t*, C(4) of Pro); 26.6, 25.9, 25.1, 23.8, 23.6, 23.4 (6*q*, 6 Me of 3 Aib). ESI-MS (MeOH + NaI): 788 (100, $[M + Na]^+$).

4. *Cyclo(2-amino-2-methylpropanoyl-2-amino-2-methylpropanoyl*-L-*phenylalanyl*-L-*prolyl-2-amino-2-methylpropanoylglycyl)* (*cyclo(Aib-Aib-Phe-Pro-Aib-Gly)*; **1**). 4.1. *Cyclo(Aib-Aib-Phe-Pro-Aib-Gly)* (**1**) *from* **9**. To a soln. of **9** (0.318 g, 0.37 mmol) in MeCN (4 ml) was added Et_2NH (1.2 ml) at r.t., and the mixture was stirred for 3 h. After evaporation, CC (CH_2Cl_2/MeOH 15:1) gave 0.227 g (96%) of H-Pro-Aib-Gly-Aib-Aib-Phe-O^{t}Bu as a white foam.

This *N*-deprotected hexapeptide (0.227 g, 0.35 mmol) was dissolved in CH_2Cl_2 (10 ml), and CF_3COOH (10 ml) was then added. The mixture was stirred for 5 h at r.t. Excess CF_3COOH was evaporated, and the remaining CF_3COOH was removed by co-evaporation with Et_2O (3 × 5 ml). The residue was triturated with Et_2O, the soln. decanted, and the operation was repeated twice to afford, after drying *i.v.*, 0.257 g (0.35 mmol, 100%) of the deprotected hexapeptide as its CF_3COO^- salt.

A sample 0.117 g (0.15 mmol) of this material was dissolved in abs. THF (100 ml) and subjected to cyclization according to *GP 5*, with DEPBT (0.14 g, 0.46 mmol) and DIEA (1 ml) for 3 d. CC (CH_2Cl_2/MeOH 12:1, 2 ×) and prep. TLC (CH_2Cl_2/MeOH 10:1) afforded 30 mg (35%) of pure **1**. White powder. M.p. > 280° (dec.). Data of **1** see *4.2*.

4.2. *Cyclo(Aib-Aib-Phe-Pro-Aib-Gly)* (**1**) *from* **13**. According to the *GP 3*, with **13** (0.4 g, 0.52 mmol), Pd/C (45 mg), and MeOH (10 ml)): 0.328 g (100%) of H-Phe-Pro-Aib-Gly-Aib-Aib-O^{t}Bu. Pale yellow foam.

This material was dissolved in CH_2Cl_2/CF_3COOH 1:1 (30 ml) and stirred for 4 h at r.t. Excess CF_3COOH was removed as described in *Exper. 4.1*, and 0.404 g (0.52 mmol, 100%) of the deprotected linear hexapeptide was obtained as its CF_3COO^- salt, which was used in the cyclization reactions without further purification.

DEPC-Mediated Cyclization: According to *GP 6*, with deprotected hexapeptide (0.135 g, 0.17 mmol) in abs. DMF (175 ml), DEPC (0.141 g, 0.86 mmol), and DIEA (1.75 ml) for 6 d. CC (CH_2Cl_2/MeOH 13:1, then CH_2Cl_2/MeOH 17:1) afforded 33 mg (34%) of pure **1**. White foam.

PyAOP-Mediated Cyclization: According to *GP 7*, with deprotected hexapeptide (0.135 g, 0.17 mmol) in abs. DMF (220 ml), PyAOP (0.361 g, 0.69 mmol), and DIEA (2.2 ml) for 24 h. CC (AcOEt/MeOH 10:1, then CH_2Cl_2/MeOH 15:1) afforded 27 mg (28%) of pure **1** as a white foam, besides 15 mg of **1** contaminated with some $(Et^iPr_2NH)PF_6$ which could not be purified by CC. Crystals suitable for an X-ray crystal-structure analysis were obtained from this mixture by crystallization from AcOEt/EtOH/hexane.

DEPBT-Mediated Cyclization: According to *GP 5*, with deprotected hexapeptide (0.134 g, 0.17 mmol) in abs. DMF (175 ml), DEPBT (0.26 g, 0.86 mmol), and DIEA (1.75 ml) for 3 d: no cyclic product was obtained.

Data of cyclo(Aib⁴-Aib⁵-Phe⁶-Pro¹-Aib²-Gly³) (**1**): IR: 3317*s*, 3061*w*, 1985*m*, 2938*m*, 1665*s*, 1536*s*, 1444*m*, 1385*m*, 1363*m*, 1285*m*, 1216*m*, 1191*m*, 1101*w*, 1019*w*, 923*w*, 875*w*, 825*w*, 747*w*, 701*w*. ^{1}H-NMR: 9.30 (*s*, NH of Aib²); 8.46 (*t*-like, NH of Gly³); 7.90 (*s*, NH of Aib⁴); 7.42 (*d*, $J = 8.4$, NH of Phe⁶); 7.40–7.31 (*m*, 2 arom. H of Phe⁶); 7.25–7.12 (*m*, NH of Aib⁵, 3 arom. H of Phe⁶); 4.58–4.55 (*m*, CH(2) of Phe⁶); 4.36–4.33 (*m*, CH(2) of Pro¹); 3.86–3.79 (*m*, 1 H of CH_2 of Gly³, 1 H of CH_2(5) of Pro¹); 3.73–3.66 (*m*, 1 H of CH_2 of Gly³, 1 H of CH_2(5) of Pro¹); 2.86–2.67 (*m*, CH_2 of Phe⁶); 2.20–2.11 (*m*, 1 H of CH_2(3), 1 H of CH_2(4) of Pro¹); 1.98–1.93 (*m*, 1 H of CH_2(4) of Pro¹); 1.89–1.82 (*m*, 1 H of CH_2(3) of Pro¹); 1.46, 1.39 (2*s*, 2 Me of Aib²); 1.35 (*s*, Me of Aib⁴); 1.31, 1.30 (2*s*, 2 Me of Aib⁵); 1.18 (*s*, Me of Aib⁴). ^{13}C-NMR: 176.3 (*s*, CO of Aib²); 174.4 (*s*, CO of Aib⁵); 173.8 (*s*, CO of Pro¹); 172.5 (*s*, CO of Aib⁴); 171.7 (*s*, CO of Phe⁶); 170.1 (*s*, CO of Gly³); 137.3 (*s*, 1 arom. C of Phe⁶); 129.3, 128.1, 126.2 (3*d*, 5 arom. CH of Phe⁶); 59.7 (*d*, C(2) of Pro¹); 56.1 (*s*, C(2) of Aib⁴); 56.0 (*s*, C(2) of Aib²); 55.8 (*s*, C(2) of Aib⁵); 53.1 (*d*, C(2) of Phe⁶); 47.3 (*t*, C(5) of Pro¹); 45.1 (*t*, C(2) of Gly³); 36.9 (*t*, C(3) of Phe⁶); 28.4 (*t*, C(3) of Pro¹); 27.8 (*q*, Me of Aib⁵); 27.4 (*q*, Me of Aib⁴); 26.5 (*q*, Me of Aib²); 24.9 (*t*, C(4) of Pro¹); 23.1 (*q*, Me of Aib²); 22.4 (*q*, Me of Aib⁴); 22.3 (*q*, Me of Aib⁵). ESI-MS (MeOH + NaI): 579 (100, $[M + Na]^+$).

5. N-*[(Benzyloxy)carbonyl]glycyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoyl*-L-*phenylalanyl*-L-*prolyl-2-amino*-N,*2-dimethyl*-N-*phenylpropanamide* (*Z-Gly-Aib-Aib-Phe-Pro-Aib-N(Me)Ph*; **14**). 5.1. *Synthesis of* **14**. According to *GP 3*, with **10** (0.728 g, 1.27 mmol), Pd/C (80 mg), and MeOH (10 ml). CC (CH_2Cl_2/MeOH 10:1) yielded 0.519 g (93%) of H-Phe-Pro-Aib-N(Me)Ph, which was used directly in the next step.

According to *GP 4*, with H-Phe-Pro-Aib-N(Me)Ph (0.519 g, 1.19 mmol) in abs. CH_2Cl_2 (10 ml), Z-Gly-Aib-Aib-OH [5] (0.41 g, 1.08 mmol), PyAOP (0.573 g, 1.1 mmol), 0.5M HOAt in DMF (0.15 g, 1.1 mmol, 2.2 ml), and DIEA (0.284 g, 2.2 mmol) for 20 h. CC (CH_2Cl_2/MeOH 15:1) yielded 0.78 g (90%) of pure **14**. White foam. IR: 3322*s*, 3061*m*, 3031*m*, 2984*m*, 2937*m*, 1650*s*, 1593*m*, 1522*s*, 1496*s*, 1454*s*, 1385*m*, 1362*m*, 1237*s*, 1172*m*, 1116*m*, 1090*m*, 1048*m*, 1001*w*, 922*w*, 774*w*, 742*m*, 702*m*. ^{1}H-NMR: 8.09, 7.94 (2*s*, 2 NH); 7.53–7.12 (*m*, 15 arom. H, 3 NH); 5.02 (*s*, PhC*H*$_2$O); 4.65–4.60, 4.25–4.23 (2*m*, CH(2) of Phe, CH(2) of Pro); 3.68–3.41 (*m*, CH_2 of Gly, CH_2(5) of Pro); 3.23 (*s*, MeN); 3.06–2.81 (*m*, CH_2 of Phe); 1.98–1.78 (*m*, CH_2(3) and CH_2(4) of Pro); 1.35, 1.30, 1.27, 1.23 (4*s*, 6 Me of Aib). ^{13}C-NMR: 173.8, 172.8, 172.2, 170.4, 169.3, 169.1 (6*s*, 6 CO); 156.6 (*s*, CO (urethane)); 145.7, 137.8, 136.9 (3*s*, 3 arom. C); 129.3, 128.6, 128.2, 127.9, 127.7, 127.5, 127.2, 126.8, 126.2, 126.0 (10*d*, 15 arom. CH); 66.5 (*t*, PhCH_2O); 59.3 (*d*, C(2) of Pro); 56.0, 55.8 (2*s*, 3 C(2) of 3 Aib); 52.3 (*d*, C(2) of Phe); 46.4, 43.9 (2*t*, C(2) of Gly, C(5) of Pro); 39.5 (*q*, MeN); 36.6 (*t*, C(3) of Phe); 28.6 (*t*, C(3) of Pro); 26.1, 25.5, 24.7, 24.3 (4*q*, 6 Me of 3 Aib); 24.2 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 820 (100, $[M + Na]^+$). Anal. calc. for $C_{43}H_{55}N_7O_8 \cdot 1/2\,H_2O$ (806.96): C 64.00, H 6.99, N 12.15; found: C 63.86, H 6.96, N 12.07.

5.2. *Cyclization of* **14**. According to *GP 2*, with **14** (0.68 g, 0.85 mmol) in 3N HCl (MeCN/H_2O 1:1, 10 ml) for 15 h. Then, the MeCN was evaporated, 2N HCl (5 ml) added, the mixture extracted with CH_2Cl_2, the extract dried (Na_2SO_4) and evaporated, and the residue dried *i.v.:* 0.54 g (89%) of peptide acid. White foam.

According to *GP 3*, with this acid (0.464 g, 0.65 mmol) Pd/C (50 mg), and MeOH (8 ml): 0.358 g (95%) of H-Gly-Aib-Aib-Phe-Pro-Aib-OH as a pale yellow foam, which was used in the cyclization reactions without further purification.

DEPC-Mediated Cyclization: According to *GP 6*, with the deprotected hexapeptide (90 mg, 0.16 mmol) abs. DMF (160 ml), DEPC (0.128 g, 0.78 mmol), and DIEA (1.6 ml) for 3 d: no **1** was obtained.

DEPBT-Mediated Cyclization: According to *GP 5*, with the deprotected hexapeptide (90 mg, 0.16 mmol) abs. DMF (100 ml), DEPBT (0.141 g, 0.47 mmol) and DIEA (1 ml) for 3 d: no cyclic product was obtained.

PyAOP-Mediated Cyclization: According to *GP 7*, with the deprotected hexapeptide (90 mg, 0.16 mmol) abs. DMF (160 ml), PyAOP (0.328 g, 0.63 mmol), 0.5M HOAt in DMF (0.63 mmol, 1.4 ml), and DIEA (1.6 ml): no cyclic product was obtained.

HATU-Mediated Cyclization: The deprotected hexapeptide (74 mg, 0.13 mmol) in abs. DMF (130 ml) was cooled to 0° in an ice bath. HATU (54 mg, 0.14 mmol), 0.5M HOAt in DMF (0.14 mmol, 0.3 ml), and collidine (0.157 g, 13 mmol) were then added under stirring. The mixture was allowed to warm to r.t. within 2 h, and was stirred for a further 3 d: no **1** was observed.

6. *Cyclo(2-amino-2-methylpropanoyl-2-amino-2-methylpropanoylglycyl-2-amino-2-methylpropanoyl-*L*-prolylglycyl)* (*Cyclo(Aib-Aib-Gly-Aib-Pro-Gly)*; **2**). 6.1. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*L*-prolylglycyl-2-amino-2-methylpropanoyl-2-amino-*N*,2-dimethyl-*N*-phenylpropanamide* (*Fmoc-Pro-Gly-Aib-Aib-N(Me)Ph*; **15**). According to *GP 3*, with **6** (0.4 g, 0.85 mmol), Pd/C (45 mg), and MeOH (10 ml): H-Gly-Aib-Aib-N(Me)Ph (0.285 g, 100%), which was used directly in the next step without further purification.

According to *GP 4*, with Fmoc-Pro-OH (0.262 g, 0.78 mmol), H-Gly-Aib-Aib-N(Me)Ph (0.285 g, 0.85 mmol), PyAOP (0.47 g, 0.9 mmol), and DIEA (0.233 g, 1.8 mmol) in abs. CH_2Cl_2 (10 ml) for 24 h. CC (AcOEt/MeOH 15:1, CH_2Cl_2/MeOH 20:1) yielded 0.47 g (93%) of pure **15**. White foam. IR: 3748*m*, 3671*m*, 3647*m*, 3419*s*, 3064*m*, 2983*m*, 2934*m*, 1675*s*, 1594*m*, 1524*s*, 1494*s*, 1452*s*, 1423*s*, 1391*m*, 1360*s*, 1339*m*, 1195*m*, 1168*m*, 1124*m*, 1092*m*, 1040*w*, 1022*w*, 989*w*, 759*m*, 740*m*, 706*m*. ^{1}H-NMR (CD_3OD): 7.81–7.18 (*m*, 13 arom. H); 4.47–4.20 (*m*, C*H*C*H*$_2$O of Fmoc and CH(2) of Pro); 3.74–3.47 (*m*, CH_2 of Gly and CH_2(5) of Pro); 3.22 (*s*, MeN); 2.30–1.80 (*m*, CH_2(3) and CH_2(4) of Pro); 1.46, 1.45, 1.41, 1.39 (4*s*, 4 Me of 2 Aib). ^{13}C-NMR (CD_3OD): 175.9, 175.3, 171.0 (3*s*, 4 CO); 157.0 (*s*, CO (urethane)); 145.1, 142.5 (2*s*, 5 arom. C); 130.2, 128.8, 128.4, 128.1, 125.9, 120.9 (6*d*, 13 arom. CH); 68.8 (*t*, CH*C*H$_2$O of Fmoc); 62.1 (*d*, C(2) of Pro); 58.6, 58.2 (2*s*, 2 C(2) of 2 Aib); 48.3 (*d*, *C*HCH$_2$O of Fmoc); 48.1, 44.6 (2*t*, C(5) of Pro and C(2) of Gly); 41.2 (*q*, MeN); 31.1 (*t*, C(3) of Pro); 26.2, 25.9, 25.3 (3*q*, 4 Me of 2 Aib); 25.5 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 676 (100, $[M+Na]^+$), 534 (70, $[M-N(Me)Ph]^+$). Anal. calc. for $C_{37}H_{43}N_5O_6 \cdot 1/3\,H_2O$ (659.78): C 67.36, H 6.67, N 10.61; found: C 67.27, H 6.90, N 10.61.

6.2. N-*[(Benzyloxy)carbonyl]glycyl-2-amino-2-methylpropanoyl-*L*-prolylglycyl-2-amino-2-methylpropanoyl-2-amino-N,2-dimethyl-N-phenylpropanamide* (*Z-Gly-Aib-Pro-Gly-Aib-Aib-N(Me)Ph*; **16**). To a soln. of **15** (0.47 g, 0.72 mmol) in CH_2Cl_2 (7 ml), Et_2NH (5 ml) was added under stirring. After 5 h at r.t., the mixture was evaporated and the residue purified by CC (CH_2Cl_2/MeOH 10:1): 0.253 g (82%) of H-Pro-Gly-Aib-Aib-N(Me)Ph, which was used directly in the next step.

According to *GP 6*, with Z-Gly-Aib-OH (0.157 g, 0.53 mmol), H-Pro-Gly-Aib-Aib-N(Me)Ph (0.253 g, 0.58 mmol), abs. CH_2Cl_2 (10 ml), PyAOP (0.313 g, 0.6 mmol), and DIEA (0.156 g, 1.2 mmol) for 24 h. CC (CH_2Cl_2/MeOH 15:1) gave 0.33 g (87%) of **16**. White foam. IR: 3745*m*, 3418*s*, 3062*m*, 2985*m*, 2936*m*, 1659*s*, 1594*m*, 1529*s*, 1471*m*, 1455*m*, 1395*s*, 1364*m*, 1244*s*, 1171*m*, 1115*m*, 1092*m*, 1053*m*, 769*w*, 741*w*, 706*w*. ^{1}H-NMR (CD_3OD): 7.55–7.24 (*m*, 10 arom. H); 5.13–5.03 (*m*, PhC*H*$_2$O); 4.39–4.34 (*m*, CH(2) of Pro); 3.92–3.43 (*m*, 2 CH_2 of 2 Gly, CH_2(5) of Pro); 3.34 (*s*, MeN); 2.27–1.74 (*m*, CH_2(3) and CH_2(4) of Pro); 1.52, 1.49, 1.48, 1.47, 1.45 (5*s*, 6 Me of 3 Aib). ^{13}C-NMR (CD_3OD): 176.2, 175.6, 175.5, 174.9, 172.2, 171.3 (6*s*, 6 CO); 158.5 (*s*, CO (urethane)); 146.8, 138.0 (2*s*, 2 arom. C); 130.2, 129.4, 129.1, 128.8, 128.3, 128.1 (6*d*, 10 arom. CH); 67.7 (*t*, PhC*H*$_2$O); 64.5 (*d*, C(2) of Pro); 58.6, 58.3, 57.7 (3*s*, 3 C(2) of 3 Aib); 49.7 (*t*, C(5) of Pro); 44.5, 44.3 (2*t*, 2 C(2) of 2 Gly); 41.1 (*q*, MeN); 29.5, 26.8 (2*t*, C(3) and C(4) of Pro); 26.5, 26.4, 25.0, 23.9 (4*q*, 6 Me of 3 Aib). ESI-MS (MeOH + NaI): 730 (100, $[M+Na]^+$). Anal. calc. for $C_{36}H_{49}N_7O_8 \cdot 1/2\,H_2O$ (716.83): C 60.32, H 7.03, N 13.68; found: C 60.27, H 6.99, N 13.61.

6.3. N-*[(Benzyloxy)carbonyl]glycyl-2-amino-2-methylpropanoyl-*L*-prolylglycyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoic Acid* (*Z-Gly-Aib-Pro-Gly-Aib-Aib-OH*; **17**). According to *GP 2*, with **16** (0.25 g, 0.35 mmol) in 3N HCl (MeCN/H_2O 1:1, 4 ml). The product was extracted with CH_2Cl_2 and the extract dried (Na_2SO_4) and evaporated: 0.177 g (82%) of pure **17**. White foam. IR: 3304*s*, 3061*m*, 2986*m*, 2940*m*, 1719*s*, 1657*s*, 1534*s*, 1470*m*, 1455*m*, 1410*m*, 1365*m*, 1243*s*, 1165*s*, 1051*m*, 910*w*, 777*w*, 745*w*, 697*m*. ^{1}H-NMR (CD_3OD): 8.61, 7.99, 7.62 (3br. *s*, 3 NH); 7.36–7.27 (*m*, 5 arom. H); 5.14–5.03 (*m*, PhC*H*$_2$O); 4.40–4.35 (*m*, CH(2) of Pro); 3.92–3.30 (*m*, CH_2(5) of Pro, 2 CH_2 of 2 Gly); 2.26–1.73 (*m*, CH_2(3) and CH_2(4) of Pro); 1.50, 1.475, 1.468, 1.46, 1.44 (5*s*, 6 Me of 3 Aib). ^{13}C-NMR (CD_3OD): 177.9, 176.0, 175.5, 174.9, 172.3, 171.3 (6*s*, 6 CO); 159.0 (*s*, CO (urethane)); 138.1 (*s*, 2 arom. C); 129.4, 129.1, 128.8 (3*d*, 5 arom. CH); 67.7 (*t*, PhC*H*$_2$O); 64.4 (*d*, C(2) of Pro); 58.1, 57.8, 57.1 (3*s*, 3 C(2) of 3 Aib); 49.7 (*t*, C(5) of Pro); 44.3, 44.2 (2*t*, 2 C(2) of 2 Gly); 29.5, 26.8 (2*t*, C(3) and C(4) of Pro); 26.4, 25.9, 25.3, 25.1, 25.0, 23.9 (6*q*, 6 Me of 3 Aib). ESI-MS (MeOH + NaI): 641 (100, $[M+Na]^+$). Anal. calc. for $C_{29}H_{42}N_6O_9$ (618.69): C 56.29, H 6.84, N 13.58; found: C 55.98, H 6.68, N 13.46.

6.4. *Cyclo(Gly*^{1}*-Aib*^{2}*-Pro*^{3}*-Gly*^{4}*-Aib*^{5}*-Aib*^{6}*)* (= *Cyclo(Aib-Aib-Gly-Aib-Pro-Gly)*; **2**). According to *GP 3*, with **17** (0.162 g, 0.26 mmol), Pd/C (25 mg), and MeOH (6 ml): 0.125 g (0.26 mmol, 100%) of the deprotected hexapeptide as a pale yellow foam, which was used in the next step without further purification.

According to *GP 6*, with the deprotected hexapeptide (0.125 g, 0.26 mmol) in abs. DMF (170 ml), DEPC (0.168 g, 1.03 mmol), and DIEA (1.7 ml) for 7 d. During the evaporation of DMF, an extremely insoluble white precipitate formed. This precluded purification by CC. The precipitate was collected by filtration and washed with H_2O, MeOH, and CH_2Cl_2 to remove excess DEPC and some by-products. Recrystallization from hot H_2O/MeOH/EtOH yielded 43 mg (36%) of pure **2**. White powder. M.p. $>320°$ (dec.). IR: 3487*m*, 3365*m*, 3324*s*, 3283*s*, 3044*w*, 2990*w*, 2937*w*, 1683*s*, 1650*s*, 1598*s*, 1545*s*, 1470*m*, 1418*m*, 1385*m*, 1366*m*, 1337*w*, 1252*m*, 1194*w*, 1178*w*, 1021*w*, 944*w*, 919*w*, 811*w*, 705*w*. ^{1}H-NMR ((D_6)DMSO + 3 drops of CF_3COOH): 8.78 (*s*, NH of Aib^2); 8.31 (*s*, NH of Aib^5); 7.49 (*s*, NH of Aib^6); 7.42 (br. *d*, *J* = 9.4, NH of Gly^4); 7.36 (br. *d*, *J* = 9.1, NH of Gly^1); 4.67–4.61 (*m*, CH(2) of Pro^3); 4.30 (*dd*, *J* = 9.8, 17.5, 1 H of CH_2 of Gly^4); 4.22 (*dd*, *J* = 9.2, 17.8, 1 H of CH_2 of Gly^1); 3.73–3.67 (*m*, 1 H of CH_2(5) of Pro^3); 3.53 (br. *d*, *J* = 17.3, 1 H of CH_2 of Gly^1); 3.48–3.35 (*m*, 1 H of CH_2 of Gly^4, 1 H of CH_2(5) of Pro^3); 1.99–1.92 (*m*, 1 H of CH_2(3) of Pro^3); 1.88–1.79 (*m*, 1 H of CH_2(3), 1 H of CH_2(4) of Pro^3); 1.71–1.62 (*m*, 1 H of CH_2(4) of Pro^3); 1.45 (*s*, Me of Aib^6); 1.36, 1.34 (2*s*, 2 Me of Aib^2); 1.31 (*s*, Me of Aib^5); 1.27 (br. *s*, Me of Aib^5, Me of Aib^6). ^{13}C-NMR ((D_6)DMSO + 3 drops of CF_3COOH): 174.1 (*s*, CO of Aib^6); 173.5 (*s*, CO of Aib^5); 171.8 (*s*, CO of Aib^2); 171.1 (*s*, CO of Pro^3); 169.7 (*s*, CO of Gly^4); 169.1 (*s*, CO of Gly^1); 61.1 (*d*, C(2) of Pro^3); 56.9 (*s*, C(2) of Aib^6); 56.3 (*s*, C(2) of Aib^5); 55.9 (*s*, C(2) of Aib^2); 46.8 (*t*, C(5) of Pro^3); 39.7 (*t*, C(2) of Gly^4); 39.2 (*t*, C(2) of Gly^1); 28.5 (*q*, Me of Aib^6); 27.7 (*t*, C(3) of Pro^3); 26.4 (*q*, Me of Aib^5); 26.0 (*q*, Me of Aib^2); 24.3 (*t*, C(4) of Pro^3); 23.4 (*q*, Me of Aib^2); 23.25 (*q*, Me of Aib^5); 23.1 (*q*, Me of Aib^6). ESI-MS (MeOH + NaI): 489 (100, $[M + Na]^+$).

7. N-*[(Benzyloxy)carbonyl]glycyl-2-amino-2-methylpropanoyl*-L-*prolyl-2-amino-2-methylpropanoyl*-L-*phenylalanyl-2-amino-2-methylpropanoic Acid* tert-*Butyl Ester* (*Z-Gly-Aib-Pro-Aib-Phe-Aib-O*^{t}*Bu*; **21**). 7.1. N-*[(Benzyloxy)carbonyl]glycyl-2-amino-2-methylpropanoyl*-L-*prolyl-2-amino*-N,*2-dimethyl*-N-*phenylpropanamide* (*Z-Gly-Aib-Pro-Aib-N(Me)Ph*; **18**). *A* soln. of **4** (0.71 g, 1.39 mmol) in CH_2Cl_2 (10 ml) and Et_2NH (5 ml) was stirred for 3 h at r.t. Evaporation and CC (CH_2Cl_2/MeOH/NH_3(l) 10:1:0.1) gave 0.322 g (80%) of H-Pro-Aib-N(Me)Ph, which was used directly in the next step.

According to *GP 4*, with H-Pro-Aib-N(Me)Ph (0.23 g, 0.79 mmol), Z-Gly-Aib-OH (0.213 g, 0.72 mmol), abs. CH_2Cl_2 (6 ml) and abs. MeCN (2 ml), PyAOP (0.417 g, 0.8 mmol), and DIEA (0.206 g, 1.6 mmol) for 18 h. CC (CH_2Cl_2/MeOH 20:1, 2 ×) yielded 0.385 g (94%) of **18**. White foam. IR: 3423*s*, 3299*s*, 3062*m*, 3037*m*, 2985*m*, 2939*m*, 2878*w*, 1722*s*, 1647*s*, 1594*m*, 1534*s*, 1495*s*, 1470*m*, 1454*m*, 1399*s*, 1363*s*, 1242*s*, 1212*m*, 1168*m*, 1115*m*, 1090*m*, 1051*m*, 927*w*, 769*w*, 741*w*. ^{1}H-NMR: 8.53, 7.58 (2*s*, 2 NH); 7.49 (*t*, *J* = 6.1, NH of Gly); 7.39–7.15 (*m*, 10 arom. H); 5.10–4.96 (*m*, PhCH_2O); 4.33–4.28 (*m*, CH(2) of Pro); 3.84, 3.78 (2*d*, *J* = 6.3, CH_2 of Gly); 3.67–3.45 (*m*, CH_2(5) of Pro); 3.26 (*s*, MeN); 2.09–1.60 (*m*, CH_2(3) and CH_2(4) of Pro); 1.40, 1.37, 1.36, 1.32 (4*s*, 4 Me of 2 Aib). ^{13}C-NMR: 172.5, 171.4, 170.8, 169.1 (4*s*, 4 CO); 156.4 (*s*, CO (urethane)); 146.1, 136.8 (2*s*, 2 arom. C); 128.5, 128.2, 127.7, 127.5, 126.7, 125.7 (6*d*, 10 arom. CH); 65.3 (*t*, PhCH_2O); 61.5 (*d*, C(2) of Pro); 55.7, 55.6 (2*s*, 2 C(2) of 2 Aib); 47.4, 42.6 (2*t*, C(5) of Pro, C(2) of Gly); 39.1 (*q*, MeN); 28.2 (*t*, C(3) of Pro); 25.7, 25.5, 25.2, 23.8 (4*q*, 4 Me of 2 Aib); 25.1 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 588 (100, $[M + Na]^+$). Anal. calc. for $C_{30}H_{39}N_5O_6 \cdot 1/3\,H_2O$ (571.67): C 63.03, H 6.99, N 12.25; found: C 63.04, H 6.91, N 12.28.

7.2. N-*[(Benzyloxy)carbonyl]glycyl-2-amino-2-methylpropanoyl*-L-*prolyl-2-amino-2-methylpropanoic Acid* (*Z-Gly-Aib-Pro-Aib-OH*; **19**). According to *GP 2*, with 0.47 g (0.83 mmol) of **18** in 3N HCl (MeCN/H_2O 1:1, 10 ml) for 24 h. Extraction with CH_2Cl_2 and CC (CH_2Cl_2/MeOH 11:1) yielded 0.26 g (66%) of **19**. White foam. IR: 3415*s*, 3311*s*, 3063*m*, 2986*s*, 2942*s*, 1723*s*, 1657*s*, 1536*s*, 1470*m*, 1455*m*, 1406*s*, 1365*s*, 1343*m*, 1245*s*, 1161*s*, 1051*m*, 977*w*, 931*w*, 778*w*, 741*m*, 698*m*. ^{1}H-NMR (CD_3OD): 7.97, 7.78 (2*s*, 2 NH); 7.34–7.28 (*m*, 5 arom. H, NH); 5.13–5.01 (*m*, PhCH_2O); 4.41–4.37 (*m*, CH(2) of Pro); 3.90–3.57 (*m*, CH_2 of Gly, CH_2(5) of Pro); 2.14–1.81 (*m*, CH_2(3) and CH_2(4) of Pro); 1.48, 1.45, 1.41 (3*s*, 4 Me of 2 Aib). ^{13}C-NMR (CD_3OD): 178.5, 174.4, 173.7, 171.2 (4*s*, COOH, CO); 159.0 (*s*, CO (urethane)); 67.7 (*t*, PhCH_2O); 63.8 (*d*, C(2) of Pro); 57.6, 57.1 (2*s*, 2 C(2) of 2 Aib); 49.5, 44.2 (2*t*, C(5) of Pro and C(2) of Gly); 29.5, 26.4 (2*t*, C(3) and C(4) of Pro); 26.1, 26.0, 24.5, 24.3 (4*q*, 4 Me of 2 Aib). ESI-MS (MeOH + NaI): 499 (100, $[M + Na]^+$). Anal. calc. for $C_{23}H_{32}N_4O_7 \cdot 1/3\,H_2O$ (482.53): C 57.25, H 6.82, N 11.61; found: C 57.28, H 6.72, N 11.37.

7.3. *Z-Gly-Aib-Pro-Aib-Phe-Aib-O*^{t}*Bu* (**21**). According to *GP 3*, with Z-Phe-Aib-O^{t}Bu [15] (**20**; 0.25 g, 0.57 mmol) Pd/C (30 mg), and MeOH (10 ml) for 24 h. CC (AcOEt/MeOH 12:1) yielded 0.168 g (97%) of H-Phe-Aib-O^{t}Bu, which was used directly in the next step.

According to *GP 4*, with **19** (0.24 g, 0.5 mmol), H-Phe-Aib-O^{t}Bu (0.168 g, 0.55 mmol), abs. CH_2Cl_2 (8 ml) and abs. MeCN (2 ml), PyAOP (0.262 g, 0.55 mmol), and DIEA (0.129 g, 1.0 mmol) for 20 h. CC (AcOEt/MeOH 15:1) followed by prep. TLC (AcOEt/MeOH 16:1) yielded 0.213 g (56%) of **21**. White foam. IR: 3314*s*,

3030*w*, 2983*m*, 2935*m*, 2878*w*, 1729*s*, 1662*s*, 1623*s*, 1533*s*, 1470*m*, 1455*m*, 1409*m*, 1384*m*, 1366*m*, 1271*m*, 1248*m*, 1148*s*, 1050*m*, 980*w*, 940*w*, 849*w*, 754*m*, 699*m*. ^{1}H-NMR (CD_3OD): 7.70, 7.62, 7.57 (3*s*, 3 NH); 7.34–7.12 (*m*, 10 arom. H, 2 NH); 5.08 (br. *s*, PhCH_2O); 4.55–4.45, 4.25–4.18 (2*m*, CH(2) of Pro, CH(2) of Phe); 3.95–3.52 (*m*, CH_2 of Gly, CH_2(5) of Pro); 3.43–3.34 (*m*, 1 H of CH_2 of Phe); 2.90–2.80 (*m*, 1 H of CH_2 of Phe); 2.30–1.60 (*m*, CH_2(3), CH_2(4) of Pro); 1.54, 1.47, 1.46, 1.45, 1.37, 1.12 (6*s*, 6 Me of 3 Aib and Me_3C). ^{13}C-NMR (CD_3OD): 177.3, 177.2, 175.0, 174.8, 172.8, 171.2 (6*s*, 6 CO); 159.1 (*s*, CO (urethane)); 139.3, 138.0 (2*s*, 2 arom. C); 130.0, 129.4, 129.2, 129.0, 128.7, 127.4 (6*d*, 10 arom. CH); 81.7 (*s*, Me_3C); 67.6 (*t*, PhCH_2O); 65.4 (*d*, C(2) of Pro); 58.0, 57.6, 57.5 (3*s*, 3 C(2) of 3 Aib); 56.3 (*d*, C(2) of Phe); 50.0, 44.0 (2*t*, C(5) of Pro, C(2) of Gly); 38.4 (*t*, C(3) of Phe); 29.7 (*t*, C(3) of Pro); 28.2 (*q*, Me_3C); 26.9 (*t*, C(4) of Pro); 27.2, 26.8, 25.7, 24.7, 23.84, 23.77 (6*q*, 6 Me of 3 Aib). ESI-MS (MeOH + NaI): 788 (100, $[M+Na]^+$). Anal. calc. for $C_{40}H_{56}N_6O_9 \cdot 1/2\,H_2O$ (773.93): C 62.08, H 7.42, N 10.86; found: C 62.19, H 7.55, N 10.85.

7.4. *Attempted Cyclization of* **21**. According to *GP 3*, with **21** (0.193 g, 0.25 mmol) Pd/C (25 mg) and MeOH (6 ml). CC (CH_2Cl_2/MeOH/NH_3(l) 10 : 1 : 0.1) yielded 0.145 g (0.23 mmol, 91%) of H-Gly-Aib-Pro-Aib-Phe-Aib-O*t*Bu as a white foam. This peptide was dissolved in CH_2Cl_2/CF_3COOH (20 ml) at r.t. and stirred for 5 h. Excess CF_3COOH was removed as described in *Exper. 4.1* to give, after drying *i.v.*, 0.19 g (0.23 mmol, 100%) of the deprotected hexapeptide as its CF_3COO^- salt.

DEPBT-Mediated Cyclization: According to *GP 5*, with the linear hexapeptide (91 mg, 0.11 mmol), abs. DMF (80 ml), DEPBT (0.137 g, 0.46 mmol), and DIEA (0.8 ml) for 3 d: no cyclopeptide **22** was obtained.

PyBOP-Mediated Cyclization: According to *GP 7*, with the linear hexapeptide (91 mg, 0.11 mmol), abs. DMF (230 ml), PyBOP (0.18 g, 0.34 mmol), and DIEA (2.3 ml) for 3 d: no cyclic product was formed.

8. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*prolyl-2-amino-2-methylpropanoylglycyl-2-amino-2-methylpropanoyl*-L-*phenylalanyl-2-amino*-N,*2-dimethyl*-N-*phenylpropanamide* (*Fmoc-Pro-Aib-Gly-Aib-Phe-Aib-N(Me)Ph*; **27**). 8.1. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*prolyl-2-amino-2-methylpropanoylglycyl-2-amino*-N,*2-dimethyl*-N-*phenylpropanamide* (*Fmoc-Pro-Aib-Gly-Aib-N(Me)Ph*; **24**). According to *GP 3*, with **23** (0.385 g, 1.0 mmol) Pd/C (40 mg), and MeOH (6 ml): 0.25 g (100%) of H-Gly-Aib-N(Me)Ph as a pale yellow foam, which was used directly in the next step.

According to *GP 4*, with **5** (0.385 g, 0.91 mmol), H-Gly-Aib-N(Me)Ph (0.25 g, 1.0 mmol), abs. CH_2Cl_2 (6 ml) and abs. DMF (2 ml), HATU (0.38 g, 1.0 mmol), 0.5M HOAt in DMF (0.136 g, 1.0 mmol, 2 ml), and DIEA (0.258 g, 2.0 mmol) for 24 h. CC (CH_2Cl_2/MeOH 15 : 1, then AcOEt/MeOH 12 : 1) afforded 0.45 g (76%) of **24**. White foam. IR: 3423*s*, 3063*m*, 2982*m*, 2932*m*, 1670*s*, 1593*m*, 1537*s*, 1495*s*, 1468*m*, 1451*s*, 1423*s*, 1389*m*, 1359*s*, 1337*m*, 1284*m*, 1244*m*, 1192*m*, 1171*m*, 1122*m*, 1091*m*, 1022*w*, 991*w*, 874*w*, 760*m*, 741*m*, 704*m*. ^{1}H-NMR ($CDCl_3$): 7.76, 7.74 (2br. *s*, 2 NH); 7.58–7.20 (*m*, 13 arom. H); 6.84 (br. *s*, NH); 4.42–4.08 (*m*, C*H*CH_2O of Fmoc, CH(2) of Pro); 3.86–3.48 (*m*, CH_2(5) of Pro, CH_2 of Gly); 3.26 (*s*, MeN); 2.08–1.80 (*m*, CH_2(3) and CH_2(4) of Pro); 1.50, 1.47, 1.42 (3*s*, 4 Me of 2 Aib). ^{13}C-NMR ($CDCl_3$): 173.5, 173.0, 172.5, 168.4 (4*s*, 4 CO); 156.0 (*s*, CO (urethane)); 145.1, 143.5, 141.2 (3*s*, 5 arom. C); 129.0, 127.7, 127.3, 127.1, 127.0, 124.9, 119.9 (7*d*, 13 arom. CH); 67.9 (*t*, CHCH_2O of Fmoc); 61.0 (*d*, C(2) of Pro); 57.25, 57.20 (2*s*, 2 C(2) of 2 Aib); 47.1 (*t*, C(5) of Pro); 46.9 (*d*, *C*HCH_2O of Fmoc); 43.3 (*t*, C(2) of Gly); 40.4 (*q*, MeN); 29.1 (*t*, C(3) of Pro); 26.6, 26.1, 24.5 (3*q*, 4 Me of 2 Aib); 24.7 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 676 (100, $[M+Na]^+$). Anal. calc. for $C_{37}H_{43}N_5O_6 \cdot 1/2\,H_2O$ (662.78): C 67.05, H 6.69, N 10.56; found: C 67.10, H 6.63, N 10.50.

8.2. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]*-L-*prolyl-2-amino-2-methylpropanoylglycyl-2-amino-2-methylpropanoic Acid* (*Fmoc-Pro-Aib-Gly-Aib-OH*; **25**). According to *GP 2*, with **24** (0.387 g, 0.59 mmol) in 3N HCl (MeCN/H_2O 1 : 1, 6 ml) for 20 h. CC (CH_2Cl_2/MeOH 10 : 1) yielded 0.247 g (74%) of **25**. White foam. IR: 3319*s*, 3066*m*, 2984*m*, 2940*m*, 2882*m*, 1673*s*, 1539*s*, 1470*m*, 1451*s*, 1427*s*, 1390*m*, 1357*m*, 1337*m*, 1286*m*, 1244*m*, 1213*m*, 1167*m*, 1127*m*, 1091*m*, 1043*w*, 1020*w*, 989*w*, 939*w*, 915*w*, 876*w*, 759*m*, 740*m*. ^{1}H-NMR: 8.62 (*s*, NH); 7.90–7.88 (*m*, 2 arom. H); 7.78 (*t*, $J = 5.9$, NH of Gly); 7.71–7.31 (*m*, 6 arom. H, NH); 4.43–4.14 (*m*, C*H*CH_2O of Fmoc, CH(2) of Pro); 3.67–3.32 (*m*, CH_2 of Gly, CH_2(5) of Pro); 2.30–1.80 (*m*, CH_2(3) and CH_2(4) of Pro); 1.37, 1.33, 1.31, 1.28 (4*s*, 4 Me of 2 Aib). ^{13}C-NMR: 175.1, 173.7, 172.7, 168.1 (4*s*, 4 CO); 154.2 (*s*, CO (urethane)); 143.7, 143.5, 140.6 (3*s*, 4 arom. C); 127.5, 127.0, 125.3, 125.2, 125.0, 120.0 (6*d*, 8 arom. CH); 66.6 (*t*, CHCH_2O of Fmoc); 59.6 (*d*, C(2) of Pro); 55.9, 54.5 (2*s*, 2 C(2) of 2 Aib); 47.1 (*t*, C(5) of Pro); 46.5 (*d*, *C*HCH_2O of Fmoc); 42.6 (*t*, C(2) of Gly); 29.3 (*t*, C(3) of Pro); 25.6, 24.7, 24.4, 24.3 (4*q*, 4 Me of 2 Aib); 24.0 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 587 (100, $[M+Na]^+$), 565 (15, $[M+H]^+$). Anal. calc. for $C_{30}H_{36}N_4O_7 \cdot 1/2\,H_2O$ (573.65): C 62.81, H 6.50, N 9.77; found: C 62.70, H 6.57, N 9.77.

8.3. *Fmoc-Pro-Aib-Gly-Aib-Phe-Aib-N(Me)Ph* (**27**). According to *GP 3*, with Z-Phe-Aib-N(Me)Ph [16] (**26**; 0.515 g, 1.09 mmol) Pd/C (60 mg), and MeOH (10 ml). CC (AcOEt/MeOH 15 : 1) yielded 0.365 g (99%) of H-Phe-Aib-N(Me)Ph as a white foam, which was used directly in the next step.

According to *GP 4*, with **25** (0.198 g, 0.35 mmol), H-Phe-Aib-N(Me)Ph (0.13 g, 0.38 mmol), abs. CH_2Cl_2 (8 ml) and abs. MeCN (2 ml), TBTU (0.128 g, 0.4 mmol), HOBt (0.054 g, 0.4 mmol), and DIEA (0.103 g, 0.8 mmol) for 48 h. CC (CH_2Cl_2/MeOH 20 :1, then AcOEt/MeOH/hexane 8 :1 :0.5) yielded 0.237 g (76%) of **27**. White foam. IR: 3423*s*, 3060*m*, 3025*m*, 2980*m*, 2936*m*, 1665*s*, 1594*m*, 1533*s*, 1496*s*, 1470*m*, 1453*s*, 1424*m*, 1386*m*, 1361*m*, 1338*m*, 1277*m*, 1244*m*, 1191*m*, 1121*m*, 1091*m*, 758*w*, 741*m*, 704*m*. ^{1}H-NMR (CD_3OD): 7.81 – 7.78, 7.62 – 7.59, 7.41 – 7.06 (3*m*, 18 arom. H, 5 NH); 4.42 – 4.17 (*m*, C*HCH*$_2$O of Fmoc, CH(2) of Phe, CH(2) of Pro); 3.74 – 3.45 (*m*, CH_2 of Gly, CH_2(5) of Pro, 1 H of CH_2 of Phe); 3.26 (*s*, MeN); 2.98 – 2.80 (*m*, 1 H of CH_2 of Phe); 2.20 – 1.80 (*m*, CH_2(3) and CH_2(4) of Pro); 1.50, 1.49, 1.45, 1.43, 1.27, 1.11 (6*s*, 6 Me of 3 Aib). ^{13}C-NMR (CD_3OD): 178.0, 176.3, 175.3, 174.9, 172.5, 171.9 (6*s*, 6 CO); 157.0 (*s*, CO (urethane)); 146.6, 145.3, 145.1, 142.5, 139.2 (5*s*, 6 arom. C); 130.3, 129.2, 128.8, 128.1, 127.4, 126.1, 126.0, 121.0 (8*d*, 18 arom. CH); 68.8 (*t*, CH*C*H$_2$O of Fmoc); 61.9 (*d*, C(2) of Pro); 58.3, 57.9, 57.7 (3*s*, 3 C(2) of 3 Aib); 61.9, 56.4 (2*d*, C(2) of Pro, C(2) of Phe); 48.3 (*d*, *C*HCH$_2$O of Fmoc); 48.1, 45.2 (2*t*, C(5) of Pro, C(2) of Gly); 41.2 (*q*, MeN); 37.7 (*t*, C(3) of Phe); 31.0 (*t*, C(3) of Pro); 26.6, 25.6, 25.2 (3*q*, 6 Me of 3 Aib); 25.5 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 909 (100, $[M+Na]^+$). Anal. calc. for $C_{50}H_{59}N_7O_8 \cdot 1/3\,H_2O$ (892.06): C 67.32, H 6.74, N 10.99; found: C 67.32, H 6.78, N 11.04.

8.4. *Attempted Cyclization of* **27**. According to *GP 2*, with **27** (0.222 g, 0.25 mmol) in 3N HCl (MeCN/H_2O 1 :1, 4 ml) for 24 h. Extraction with CH_2Cl_2 and drying *i.v.* yielded 0.195 g (98%) of peptide acid as a white foam. This acid was then dissolved in CH_2Cl_2 (5 ml), and Et_2NH (1 ml) was added. After 4 h of stirring at r.t., the mixture was evaporated. The product was triturated with Et_2O, collected by filtration, and washed with Et_2O to give 0.13 g (93%) of deprotected hexapeptide as a pale yellow foam, which was used in the cyclization without further purification.

According to *GP 7*, with the deprotected hexapeptide (0.13 g, 0.23 mmol), abs. CH_2Cl_2/DMF (450 ml) 2 :1, PyAOP (0.59 g, 1.13 mmol), 0.5M HOAt in DMF (1.13 mmol, 2.5 ml), and DIEA (4.5 ml) for 3 d: no cyclic product was obtained. Purification on *Sephadex LH-20*, eluting with MeOH, gave 90 mg (0.16 mmol) of recovered starting material.

According to *GP 5*, with the recovered linear peptide (90 mg, 0.16 mmol), abs. DMF (160 ml), DEPBT (0.233 g, 0.78 mmol), and DIEA (1.6 ml) for 3 d: no cyclic product was formed.

9. N-*[(Benzyloxy)carbonyl]glycyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoyl-*L*-prolyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoic Acid* tert-*Butyl Ester* (*Z-Gly-Aib-Aib-Pro-Aib-Aib-O*^{t}*Bu*; **30**). 9.1. N-*[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*L*-prolyl-2-amino-2-methylpropanoyl-2-amino-2-methylpropanoic Acid* tert-*Butyl Ester* (*Fmoc-Pro-Aib-Aib-O*^{t}*Bu*; **29**). According to *GP 4*, with **5** (0.414 g, 0.98 mmol), HCl · H-Aib-O^{t}Bu (0.211 g, 1.08 mmol), abs. CH_2Cl_2 (8 ml) and abs. MeCN (2 ml), PyBOP (0.51 g, 0.98 mmol), and DIEA (0.388 g, 3.0 mmol) for 24 h. CC (CH_2Cl_2/MeOH 35 :1, then AcOEt/hexane 2 :1) afforded 0.459 g (83%) of pure **29**. White powder. M.p. 153 – 154°. IR: 3416*m*, 3281*m*, 3041*w*, 2981*m*, 2942*m*, 2876*m*, 1731*s*, 1710*s*, 1687*s*, 1648*s*, 1530*s*, 1470*m*, 1450*s*, 1416*s*, 1389*m*, 1360*s*, 1331*m*, 1307*m*, 1242*m*, 1152*s*, 1097*m*, 1033*w*, 991*w*, 939*w*, 855*w*, 760*m*, 739*m*. ^{1}H-NMR: 8.21 (*s*, NH); 7.91 – 7.89 (*m*, 2 arom. H); 7.64 – 7.61 (*m*, 2 arom. H); 7.43 – 7.32 (*m*, 4 arom. H); 7.20 (*s*, NH); 4.32 – 4.13 (*m*, C*HCH*$_2$O of Fmoc, CH(2) of Pro); 3.47 – 3.38 (*m*, CH_2(5) of Pro); 2.20 – 1.80 (*m*, CH_2(3) and CH_2(4) of Pro); 1.37, 1.32, 1.31, 1.22 (4*s*, 4 Me of 2 Aib and Me_3C). ^{13}C-NMR: 172.7, 171.2 (2*s*, 3 CO); 154.1 (*s*, CO (urethane)); 143.6, 143.5, 140.6 (3*s*, 4 arom. C); 127.6, 127.0, 124.9, 120.0 (4*d*, 8 arom. CH); 79.0 (*s*, Me_3C); 66.5 (*t*, CH*C*H$_2$O of Fmoc); 59.8 (*d*, C(2) of Pro); 55.7, 55.2 (2*s*, 2 C(2) of 2 Aib); 46.5 (*d*, *C*HCH$_2$O of Fmoc); 46.4 (*t*, C(5) of Pro); 29.4 (*t*, C(3) of Pro); 27.3 (*q*, *Me*$_3$C); 26.2, 24.8, 23.7, 23.6 (4*q*, 4 Me of 2 Aib); 24.0 (*t*, C(4) of Pro). ESI-MS (MeOH + NaI): 586 (100, $[M+Na]^+$). Anal. calc. for $C_{32}H_{41}N_3O_6$ (563.69): C 68.18, H 7.33, N 7.45; found: C 67.85, H 7.34, N 7.41.

9.2. *Z-Gly-Aib-Aib-Pro-Aib-Aib-O*^{t}*Bu* (**30**). Prior to coupling, **29** (0.382 g, 0.68 mmol) was deprotected with Et_2NH (1 ml) in CH_2Cl_2 (5 ml) by stirring for 6 h. Evaporation and CC (CH_2Cl_2/MeOH/NH_3(l) 11 :1 :0.1) afforded 0.172 g (74%) of H-Pro-Aib-Aib-O*t*Bu, which was used directly in the next step.

According to *GP 4*, with Z-Gly-Aib-Aib-OH (0.19 g, 0.5 mmol), H-Pro-Aib-Aib-O^{t}Bu (0.172 g, 0.5 mmol), abs. MeCN (8 ml), PyBOP (0.29 g, 0.56 mmol), and DIEA (0.143 g, 1.1 mmol) for 24 h. CC (AcOEt/MeOH 10 :1, then CH_2Cl_2/MeOH 15 :1) yielded 0.248 g (64%) of pure **30**. White foam. IR: 3336*s*, 3033*m*, 2983*s*, 2937*m*, 2877*w*, 1658*s*, 1627*s*, 1521*s*, 1469*s*, 1455*s*, 1413*m*, 1384*m*, 1366*m*, 1305*m*, 1276*s*, 1234*s*, 1148*s*, 1048*m*, 987*w*, 939*w*, 850*w*, 751*w*, 698*m*. ^{1}H-NMR (CD_3OD): 7.54 (br. *s*, NH); 7.36 – 7.28 (*m*, 5 arom. H, 4 NH); 5.13 (br. *s*, PhC*H*$_2$O); 4.20 (*t*, *J* = 7.9, CH(2) of Pro); 3.71 – 3.62 (*m*, CH_2 of Gly, CH_2(5) of Pro); 2.30 – 1.65 (*m*, CH_2(3) and CH_2(4) of Pro); 1.51, 1.49, 1.45, 1.42, 1.40 (5*s*, 8 Me of 4 Aib, Me_3C). ^{13}C-NMR (CD_3OD): 176.3, 176.0, 175.3, 174.9, 174.4, 171.6 (6*s*, 6 CO); 159.0 (*s*, CO (urethane)); 138.2 (*s*, 1 arom. C); 129.5, 128.9, 128.4 (3*d*, 5 arom. CH); 81.5 (*s*, Me_3C); 67.6 (*t*, PhC*H*$_2$O); 64.8 (*d*, C(2) of Pro); 57.9, 57.8, 57.45, 57.36 (4*s*, 4 C(2) of 4 Aib); 49.7, 45.5 (2*t*, C(5) of Pro, C(2) of Gly); 29.7 (*t*, C(3) of Pro); 28.1 (*q*, *Me*$_3$C); 26.9 (*t*, C(4) of Pro); 27.4, 25.9, 25.3, 24.2, 24.1

(6*q*, 8 Me of 4 Aib). ESI-MS (MeOH + NaI): 741 (15, $[M+K]^+$), 725 (100, $[M+Na]^+$), 703 (100, $[M+H]^+$). Anal. calc. for $C_{35}H_{54}N_6O_9 \cdot 1/2\ H_2O$ (708.85): C 59.30, H 7.77, N 11.85; found: C 59.07, H 7.78, N 11.83.

9.3. *Attempted Cyclization of* **30**. According to *GP 3*, with **30** (0.188 g, 0.27 mmol), Pd/C (20 mg), and MeOH (6 ml). CC (CH_2Cl_2/MeOH/NH_3 soln. 11:1:0.1) gave 0.146 g (97%) of H-Gly-Aib-Aib-Pro-Aib-Aib-O*t*Bu as a white foam. This foam was then dissolved in CH_2Cl_2/CF_3COOH 1:1 (22 ml) and stirred for 5 h at r.t. Excess CF_3COOH was removed as described in *Exper. 4.1* to give, after drying *i.v.*, 0.17 g (0.26 mmol) of deprotected hexapeptide as its CF_3COO^- salt.

According to *GP 5*, with the deprotected hexapeptide (0.26 mmol), abs. DMF (170 ml), DEPBT (0.308 g, 1.03 mmol), and DIEA (1.7 ml) for 3 d: no reaction was observed. The linear precursor (not as its CF_3COO^- salt) was fully recovered from the mixture by purification on *Sephadex LH-20*, eluting with MeOH.

According to *GP 6*, with the recovered linear peptide (0.134 g, 0.26 mmol), DEPC (0.17 g, 1.04 mmol), DIEA (1.9 ml), and abs. DMF (190 ml) for 10 d: no cyclic product was formed.

10. N-*[(Benzyloxy)carbonyl]*-L-*phenylalanyl*-L-*prolyl*-2-*amino*-2-*methylpropanoyl*-L-*prolyl*-2-*amino*-2-*methylpropanoyl*-2-*amino*-N,2-*dimethyl*-N-*phenylpropanamide* (*Z-Phe-Pro-Aib-Pro-Aib-Aib-N(Me)Ph*; **33**). 10.1. N-*[(9*H-*Fluoren*-9-*ylmethoxy)carbonyl]*-L-*prolyl*-2-*amino*-2-*methylpropanoyl*-2-*amino*-N,2-*dimethyl*-N-*phenylpropanamide* (*Fmoc-Pro-Aib-Aib-N(Me)Ph*; **32**). According to *GP 1*, with **5** (0.484 g, 1.14 mmol) in THF (15 ml) and **3** (0.22 g, 1.26 mmol) in THF (1 ml) for 6 d. CC (AcOEt → AcOEt/MeOH 10:1) gave 0.475 g (70%) of **32**. White powder. M.p. 151.0–151.8°. IR: 3384*s*, 3303*s*, 3062*w*, 3039*w*, 2983*m*, 2945*m*, 2890*w*, 1712*s*, 1689*s*, 1648*s*, 1594*m*, 1539*s*, 1494*s*, 1450*s*, 1423*s*, 1392*m*, 1360*s*, 1334*m*, 1285*m*, 1242*m*, 1215*m*, 1203*m*, 1165*m*, 1122*m*, 1088*m*, 1033*w*, 1022*w*, 991*w*, 877*w*, 759*m*, 740*m*, 707*m*. ^{1}H-NMR ($CDCl_3$): 7.77–7.19 (*m*, 13 arom. H, NH); 6.83 (br. *s*, NH); 4.42–4.17 (*m*, $CHCH_2O$ of Fmoc, CH(2) of Pro); 3.64–3.47 (*m*, CH_2(5) of Pro); 3.24 (*s*, MeN); 2.20–1.89 (*m*, CH_2(3) and CH_2(4) of Pro); 1.48, 1.45, 1.42, 1.41 (4*s*, 4 Me of 2 Aib). ^{13}C-NMR ($CDCl_3$): 173.5, 172.6, 171.1 (3*s*, 3 CO); 156.4 (*s*, CO (urethane)); 144.5, 143.7, 141.2 (3*s*, 5 arom. C); 129.2, 128.0, 127.7, 127.0, 124.9, 119.9 (6*d*, 13 arom. CH); 67.6 (*t*, $CHCH_2O$ of Fmoc); 61.2 (*d*, C(2) of Pro); 58.1, 57.4 (2*s*, 2 C(2) of 2 Aib); 47.1 (*d*, $CHCH_2O$ of Fmoc); 46.9 (*t*, C(5) of Pro); 41.0 (*q*, MeN); 28.7 (*t*, C(3) of Pro), 25.4, 24.7 (2*q*, 4 Me of 2 Aib); C(4) of Pro not detectable. ESI-MS (MeOH + NaI): 619 (100, $[M+Na]^+$). Anal. calc. for $C_{35}H_{40}N_4O_5$ (596.73): C 70.45, H 6.76, N 9.39; found: C 70.35, H 6.75, N 9.32.

10.2. *Z-Phe-Pro-Aib-Pro-Aib-Aib-N(Me)Ph* (**33**). As described in *Exper. 9.2*, with **32** (0.375 g, 0.63 mmol), Et_2NH (2 ml), and CH_2Cl_2 (8 ml) for 5 h. CC (CH_2Cl_2/MeOH/NH_3 soln. 12:1:0.1) yielded H-Pro-Aib-Aib-N(Me)Ph (0.22 g, 94%) as a white foam, which was used directly in the next step.

According to *GP 4*, with **11** (0.257 g, 0.53 mmol), H-Pro-Aib-Aib-N(Me)Ph (0.22 g, 0.59 mmol), HATU (0.223 g, 0.59 mmol), 0.5M HOAt in DMF (80 mg, 0.59 mmol, 1.2 ml), DIEA (0.142 g, 1.07 mmol), and MeCN (6 ml) for 24 h. CC (AcOEt/MeOH 12:1) yielded 0.312 g (70%) of **33**. White foam. IR: 3422*s*, 3321*s*, 3061*w*, 3030*m*, 2983*m*, 2940*m*, 2876*m*, 1718*s*, 1659*s*, 1594*m*, 1532*s*, 1496*s*, 1453*s*, 1416*s*, 1391*m*, 1362*m*, 1282*m*, 1244*m*, 1213*m*, 1173*m*, 1089*m*, 1053*m*, 1028*m*, 925*w*, 880*w*, 767*w*, 749*w*, 702*m*. ^{1}H-NMR (CD_3OD): 7.78, 7.68 (2br. *s*, 2 NH); 7.36.7.19 (*m*, 15 arom. H, 2 NH); 4.99 (br. *s*, $PhCH_2O$); 4.64–4.13 (*m*, CH(2) of Phe, 2 CH(2) of 2 Pro); 3.94–3.38 (*m*, 2 CH_2(5) of 2 Pro); 3.33 (br. *s*, MeN); 3.04–2.71 (*m*, CH_2 of Phe); 2.27–1.67 (*m*, 2 CH_2(3) and 2 CH_2(4) of 2 Pro); 1.54, 1.52, 1.50, 1.49, 1.45 (5*s*, 6 Me of 3 Aib). ^{13}C-NMR (CD_3OD): 176.6, 175.6, 174.7, 174.5, 173.7, 172.6 (6*s*, 6 CO); 158.2 (*s*, CO (urethane)); 146.9, 138.1, 137.6 (3*s*, 3 arom. C); 130.2, 130.1, 129.4, 129.3, 128.9, 128.6, 128.1, 127.9, 127.7 (9*d*, 15 arom. CH); 67.5 (*t*, $PhCH_2O$); 64.8, 61.4 (2*d*, 2 C(2) of 2 Pro); 58.4, 58.3, 57.6 (3*s*, 3 C(2) of 3 Aib); 55.7 (*d*, C(2) of Phe); 49.8, 48.6 (2*t*, 2 C(5) of 2 Pro); 41.0 (*q*, MeN); 38.3 (*t*, C(3) of Phe); 30.5, 29.6 (2*t*, 2 C(3) of 2 Pro); 27.2 (*q*, Me of Aib); 27.0 (*t*, C(4) of Pro); 26.3, 26.2 (2*q*, 2 Me of Aib); 26.1 (*t*, C(4) of Pro); 26.0, 24.9, 24.4 (3*q*, 3 Me of Aib). ESI-MS (MeOH + NaI): 861 (100, $[M+Na]^+$).

10.3. *Attempted Cyclization of* **33**. According to *GP 2*, with **33** (0.255 g, 0.3 mmol) and 3N HCl (MeCN/H_2O 1:1, 4 ml) for 5 h. Extraction with CH_2Cl_2, and drying of the residue under h.v. gave 0.212 g (93%) of peptide acid as a white foam, which was used in the next step without further purification.

According to *GP 3*, with this peptide acid, Pd/C (23 mg), and MeOH (10 ml) for 16 h. 0.172 g of the deprotected linear hexapeptide as a pale yellow foam.

According to *GP 7*, with the deprotected linear hexapeptide (86 mg, 0.14 mmol), abs. DMF (140 ml), PyAOP (0.292 g, 0.56 mmol), 0.5M HOAt in DMF (0.56 mmol, 1.2 ml), and DIEA (1.4 ml) for 3 d: no cyclic product was obtained.

The deprotected linear hexapeptide (86 mg, 0.14 mmol) was dissolved in abs. DMF (140 ml) under stirring. The mixture was cooled to 0°, and EDCI · HCl (0.134 g, 0.7 mmol), 0.5M HOAt in DMF (0.7 mmol, 1.4 ml), and DIEA (1.4 ml) were added. After 2 h at 0°, the mixture was warmed to r.t. and stirred for an additional 3 d: no cyclic product could be isolated.

11. *X-Ray Crystal-Structure Determination of* **1**·(Et^iPr_2NH)PF_6·H_2O (see *Table 3* and *Fig.*)[4]). All measurements were made on a *Nonius-KappaCCD* area-detector diffractometer [24] with graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream-700* cooler. Data reduction was performed with HKL Denzo and Scalepack [25]. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. Data collection and refinement parameters are given in *Table 3*, and a view of the molecule is shown in the *Figure*. The structure was solved by direct methods by using SIR92 [26], which revealed the positions of all non-H-atoms. The asymmetric unit contains one molecule of peptide **1**, one H_2O molecule, and one unit of ethyl(diisopropyl)ammonium hexafluorophosphate. The PF_6^- anion is highly disordered. Three sets of P- and F-atoms were defined for this anion, and refinement of the site-occupation factors of each set led to values of 0.648(3), 0.157(4), and 0.195(4). The P–F and F···F distances were restrained tightly, so as to maintain octahedral geometry and uniform P–F bond lengths. Finally, neighboring atoms within and between each conformation of the disordered anion were restrained to have similar atomic-displacement parameters. The non-H-atoms were refined anisotropically. The H-atoms of the H_2O molecule 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 and H···H distances to reasonable values. All remaining H-atoms were placed in geometrically calculated positions and

Table 3. *Crystallographic Data of* **1**·(Et^iPr_2NH)PF_6·H_2O

Crystallized from		AcOEt/EtOH/hexane
Empirical formula		$C_{36}H_{62}F_6N_7O_7P$
M [g mol^{-1}]		849.89
Crystal color, habit		colorless, plate
Crystal dimensions [mm]		0.05 × 0.15 × 0.30
Temperature [K]		160(1)
Crystal system		orthorhombic
Space group		$P2_12_12_1$
Z		4
Reflections for cell determination		4318
2θ Range for cell determination [°]		4–50
Unit-cell parameters	a [Å]	8.7953(1)
	b [Å]	18.4796(2)
	c [Å]	26.6501(4)
	V [Å^3]	4331.54(9)
D_x [g cm^{-3}]		1.303
μ(MoK_α) [mm^{-1}]		0.142
Scan type		ϕ and ω
$2\theta_{(max)}$ [°]		50
Total reflections measured		45195
Symmetry-independent reflections		4296
Reflections with $I > 2\sigma(I)$		3478
Reflections used in refinement		4287
Parameters refined; restraints		668; 997
Final	$R(F)$ ($I > 2\sigma(I)$ reflections)	0.0549
	$wR(F^2)$ (all data)	0.1547
Weights: $w = [\sigma^2(F_o^2) + (0.0900P)^2 + 2.2715P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$		
Goodness-of-fit		1.049
Secondary extinction coefficient		0.004(1)
Final Δ_{max}/σ		0.012
$\Delta\rho$ (max; min) [e Å^{-3}]		0.51; −0.27

[4]) CCDC-246353 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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 atom (1.5 U_{eq} for the Me groups). Refinement of the 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 applied. Nine reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. The absolute configuration of the peptide molecule could not be confirmed crystallographically, as refinement of the absolute structure factor yielded an inconclusively imprecise value of 0.08(15). Therefore, all equivalent reflections, including the *Friedel* pairs, were merged, and the peptide enantiomer used in the refinement was chosen to give the (*S*)-configuration at each chiral center in the peptide molecule, which was known from the synthesis of the compound. Neutral-atom scattering factors for non-H-atoms from [27], and those for H-atoms from [28]. Anomalous dispersion effects were included in F_c [29]; the values for f' and f'' were those of [30]. The values of the mass attenuation coefficients are those of [31]. All calculations were performed by using the SHELXL97 program [32].

In **1**, each NH group of the peptide molecule acts as a donor for H-bonds. Two of the interactions, N(1)–H and N(10)–H, are intramolecular H-bonds with the amide O-atoms that are diagonally opposed in the peptide ring. Each of these interactions has the graph set motif [33] S(10). This corresponds with the usual spacing along the peptide chain between the donor and acceptor atoms in open-chain peptide turns. N(7)–H forms a H-bond with an F-atom in each of the disordered orientations of the PF_6^- anion; graph set motif D. N(13)–H forms an intermolecular H-bond with the amide O-atom of the peptide unit adjacent to the five-membered ring of a neighboring peptide molecule and thereby links the peptide molecules into extended chains which run parallel to the *x*-axis and have the graph set motif C(10). N(16)–H forms an intermolecular H-bond with the O-atom of the H_2O molecule. In turn, the H_2O molecule donates H-bonds to amide O-atoms in two different neighboring peptide molecules. One of these interactions embeds the H_2O molecule between two peptide molecules in the same chain created by the N(13)–H···O H-bond. The other interaction also involves these chains but with the sense of the interaction running along the chain in the opposite direction. The chains incorporating H_2O and peptide molecules alternately have the binary graph set motifs $C_2^2(13)$ and $C_2^2(12)$. The cation forms an intermolecular H-bond *via* N(37)–H with an amide O-atom of an adjacent peptide molecule; graph set motif D. Finally, most amide NH groups in the peptide molecule have a close intramolecular 'sideways' contact with an adjacent amide N-atom. These interactions have very sharp N–H···O angles and, therefore, may be simply a result of the geometrical arrangement within the molecule rather than being true H-bonds.

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