Synthesis of a Derivative of the Peptaibol-Antibiotic Trichovirin I 1B by Means of the 'Azirine/Oxazolone Method'

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Dedicated to Professor *Duilio Arigoni* on the occasion of his 75th birthday

According to the earlier published synthesis of the C-terminal nonapeptide of Trichovirin I 1B, Z-Ser(ᵗBu)-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**5**), the complete tetradecapeptide Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(ᵗBu)-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**11b**), a protected Trichovirin I 1B, has now been prepared by means of the 'azirine/oxazolone method'. With the exception of the N-terminal Aib(1), all Aib residues were introduced by the coupling of the corresponding amino or peptide acids with 2,2-dimethyl-2*H*-azirine-3-(*N*-methyl-*N*-phenylamine) (**1a**) and methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**3a**) as the Aib and Aib-Pro synthons, respectively. Single crystals of two segments, *i.e.*, the N-terminal hexapeptide Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(ᵗBu)-OMe (**23**) and the C-terminal octapeptide Z-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**17**), were obtained and their structures have been established by X-ray crystallography. Following the same strategy, the C-terminal nonapeptide of Trichovirin I 4A, Z-Ala-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**26**), was also synthesized and characterized by X-ray crystallography.

1. Introduction. – In the last couple of years, we have shown that 2,2-disubstituted 2*H*-azirin-3-amines of type **1** are ideal reagents for the introduction of α,α-disubstituted glycines into peptide backbones [2–5]. The coupling occurs by reacting **1** with an *N*-protected amino acid or peptide acid, leading to the amides of the corresponding di- or oligopeptides of type **2** (*Scheme 1*). Selective hydrolysis of the terminal amide group gives the elongated peptide acid, which is further used for the next azirine coupling or for segment coupling by means of common peptide-synthesis methodology. Similarly, the analogous reactions with *N*-(2*H*-azirin-3-yl)-L-prolinates of type **3** give peptides of type **4** [6–9] (*cf.* also [10–12]). These results demonstrate that, *e.g.*, 2*H*-azirin-3-amines of type **1** and **3** with $R^1 = R^2 = Me$ (**1a** and **3a**, resp.) are suitable synthons for Aib (α-aminoisobutyric acid, 2-methylalanine) and Aib-Pro, respectively, in peptide synthesis.

A group of peptide antibiotics, containing a high proportion of Aib are the peptaibols [13]. These membrane-active, linear peptides with 11–20 amino acid residues are produced by some filamentous fungi and possess an *N*-acetylated terminus and an α-amino alcohol at the C-terminus. The most-prominent member of this family is Alamethicin F-30 [14]. Nowadays, it is well documented that peptaibols adopt helical structures [15–17] essential for their biological activity [18]. Their relatively stable

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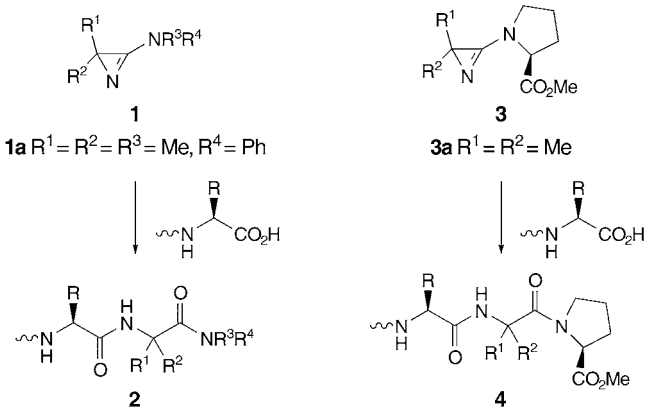
[1]) From the Ph.D. thesis of *R. T. N. L.*, Universität Zürich, 2000; presented at the 'Herbstversammlung 1999' of the *Swiss Chemical Society* [1].

Scheme 1



conformation is the result of the presence of α,α-disubstituted α-amino acids, as these amino acids induce β-turns in short oligopeptides [5][6][19–23].

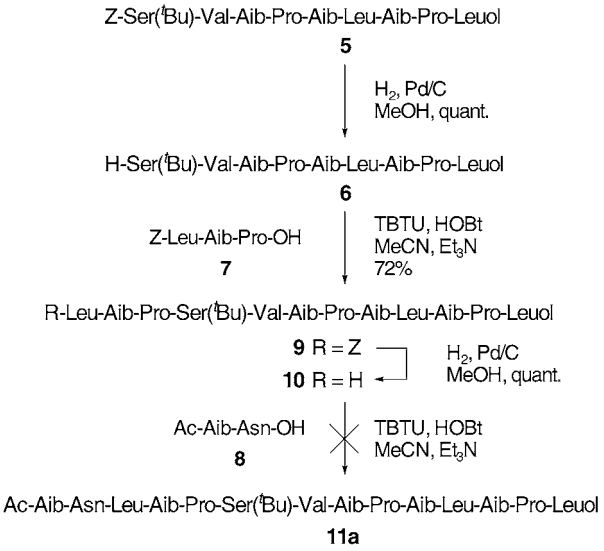
For many years, the chemical synthesis of peptaibols was a difficult task, as it was hampered by the steric hindrance in the coupling steps of Aib and Aib-containing peptide segments [24]. With the elaboration of new protocols and more-efficient coupling reagents [25], enzymatic coupling [26], and solid-phase peptide synthesis with Fmoc-protected Aib fluoride [27], the main drawbacks have been surmounted (for a more-detailed survey, see [28]). In our laboratory, we have developed the so-called 'azirine/oxazolone method' to introduce Aib and Iva (isovaline, 2-ethylalanine) residues into segments of Alamethicin F-30 [29], Trichotoxin A-50G [30], Antiamoebin I [30][31], Trichovirin I 1B [6], and Zervamicin II-2 [8].

Recently, *Brückner* and *Koza* [28] reported in detail the solution-phase preparation of the 14-residue peptaibol antibiotic Trichovirin I 4A, which is one of the major components of the microheterogeneous mixture of Trichovirin I [28]. These results prompted us to publish the synthesis of a derivative of Trichovirin I 1B by the 'azirine/oxazolone method'. Trichovirins I 1B and I 4A differ in residue 6, which is serine in the former and alanine in the latter case.

2. Results and Discussion. – According to our original strategy for the synthesis of Trichovirin I 1B, the previously prepared C-terminal nonapeptide Z-Ser(*t*Bu)-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**5**) [6] should be deprotected at the NH_2 group ($\rightarrow$ **6**) and coupled sequentially with the tripeptide Z-Leu-Aib-Pro-OH (**7**) and the dipeptide Ac-Aib-Asn-OH (**8**; *Scheme 2*).

The pentapeptide Z-Ser(*t*Bu)-Val-Aib-Pro-Aib-OH [6], which by coupling with H-Leu-Aib-Pro-Leuol (TBTU/HOBt) yielded **5**, has been prepared by a modified synthesis with a significantly improved yield of 67.1% [32] compared to 16.1% in [6]. The reaction of Z-Val-OH with **3a**, base-catalyzed hydrolysis, and coupling with **1a** gave Z-Val-Aib-Pro-Aib-N(Me)Ph in 75.2% yield. The N-terminus was deprotected (H_2/Pd/C, MeOH), and coupling with Z-Ser(*t*Bu)-OH (TBTU/HOBt), followed by hydrolysis of the C-terminal amide group (6N HCl/THF 1:1; r.t.), yielded the desired

Scheme 2



TBTU = *N*,*N*,*N*',*N*'-Tetramethyluronium tetrafluoroborate
HOBt = 1-Hydroxybenzotriazole (hydrate)

pentapeptide (89.2%). The coupling of **6** with **7** to give **9** and the deprotection to **10** proceeded in very good yields. Unfortunately, the final coupling of **10** and Ac-Aib-Asn-OH with TBTU/HOBt to give **11a** failed[2]).

Therefore, we elaborated a different route in which the N-terminal hexapeptide and the C-terminal octapeptide should be combined in the final step[3]). The corresponding coupling protocol is shown in *Scheme 3*. It is worth mentioning that cleavage of the acid-labile Aib–Pro bond was detected neither during saponification of the methyl prolinate residues nor in the acid-catalyzed hydrolysis of the terminal amide group of the tetrapeptide Z-Val-Aib-Pro-Aib-N(Me)Ph (**14**).

2.1. *Synthesis of Z-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol* (**17**). The coupling of Z-Val-OH with **3a** gave the desired tripeptide **12** in 86% yield. Subsequent basic hydrolysis with $LiOH \cdot H_2O$ led to Z-Val-Aib-Pro-OH (**13**) in 95% yield (*Scheme 4*). The coupling of the following Aib residue was achieved by reaction with azirine **1a**, yielding the tetrapeptide Z-Val-Aib-Pro-Aib-N(Me)Ph (**14**; 92%). The cleavage of the terminal *N*-methylanilido group with 3N HCl in THF/H_2O 1:1 was carried out without any problems, and the peptide acid **15** was obtained in 89% yield. The segment coupling of **15** with H-Leu-Aib-Pro-Leuol (**16**) [6] by the use of the coupling reagent TBTU in

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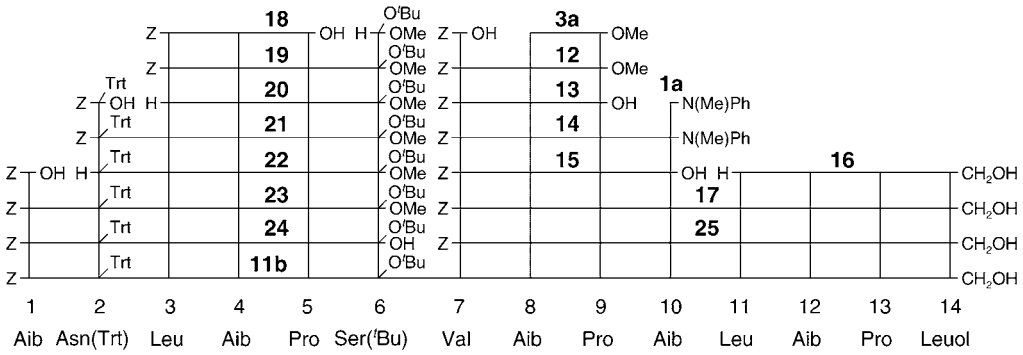
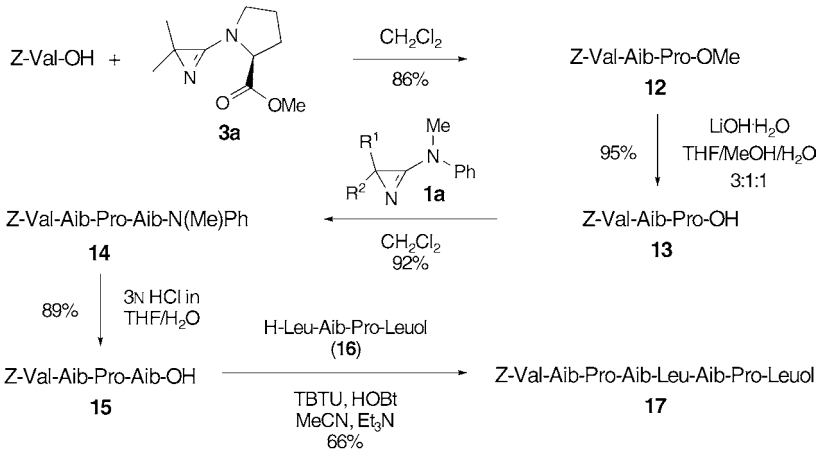
[2]) The corresponding coupling of the analogue of **10** with Ala instead of Ser(*t*Bu) in position 4 was achieved in 29–37% yield using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC)/HOBt in DMF [28].

[3]) For other approaches, see [32].

Scheme 3



Scheme 4



the presence of HOBt gave the crystalline octapeptide **17** in 66% yield[4]). By crystallization from AcOEt/MeOH, single crystals suitable for X-ray analysis were obtained. The crystal structure of **17** is shown in *Fig. 1*[5]).

The OH group and each NH group of **17** are involved mostly in intramolecular H-bonds that form a regular pattern along the peptide chain. The OH group and the N(4)–H to N(16)–H groups interact with the amide O-atom seven atoms further along the peptide backbone, *i.e.*, the $(i+3)$th amino acid. Each of these interactions has the graph-set motif [35] of S(10). This serves to maintain a fairly rigid helical conformation. The remaining two NH groups, N(22)–H and N(25)–H, which are unable to form such intramolecular interactions because of their position in the backbone, form intermolecular H-bonds with the amide and hydroxy O-atoms,

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[4]) The same coupling has been carried out by *Brückner* and *Koza* in 72% yield with EDC/HOBt; the segments had been prepared by stepwise coupling of the amino acids [28].

[5]) The crystal structure of **17** has also been published by *Gessmann et al.* [34] as its hemimethanol dihydrate.

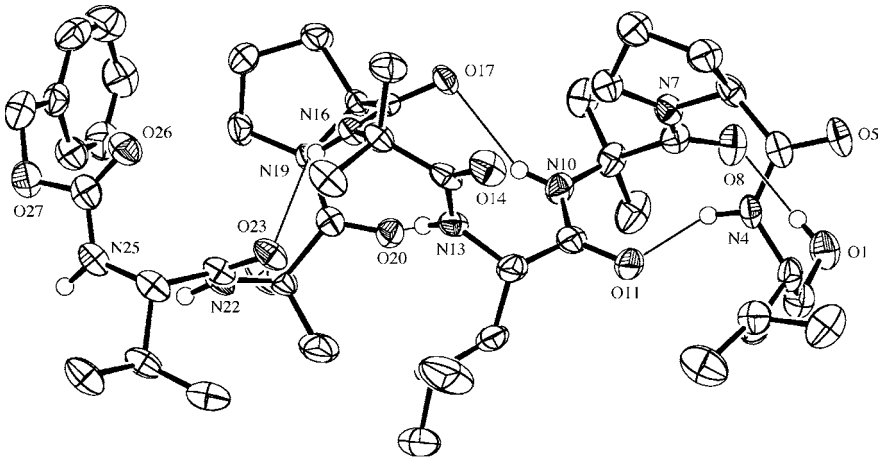


Fig. 1. *ORTEP Plot* [33] *of the molecular structure of* **17** (50% probability ellipsoids; arbitrary atom numbering; thin lines represent intramolecular H-bonds)

respectively, at the opposite end of a neighboring molecule (graph sets: C(20) and C(26), resp.). These interactions link the molecules into extended chains running parallel to the *y*-axis (*Table 1*, *Fig. 2*). Each NH group from N(4)–H to N(16)–H also forms a close contact to the next N-atom in the chain, *i.e.*, the $(i+1)^{th}$ amino acid. These weak H-bonds form in a 'sideways' fashion (acute N–H···N angle) and might result from the geometrical constraints placed on the conformation of the molecule by the other H-bonding interactions. Such close contacts are often found in peptide chains.

Table 1. *Intra- and Intermolecular H-Bonds in the Crystal Structure of* **17** (D = donor, A = acceptor)

D–H	A[a])	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O(1)–H(1)	O(8)	0.85(4)	1.97(4)	2.809(3)	169(5)
N(4)–H(4)	O(11)	0.88(3)	2.09(3)	2.893(3)	153(3)
N(10)–H(10)	O(17)	0.87(3)	2.35(3)	3.138(4)	150(3)
N(13)–H(13)	O(20)	0.84(3)	2.29(3)	3.048(4)	151(3)
N(16)–H(16)	O(23)	0.86(3)	2.19(3)	2.921(3)	142(3)
N(22)–H(22)	O(5′)	0.83(3)	2.18(3)	2.973(3)	160(3)
N(25)–H(25)	O(1′)	0.87(3)	2.03(3)	2.892(4)	169(4)
N(4)–H(4)	N(7)	0.88(3)	2.38(3)	2.800(4)	110(2)
N(10)–H(10)	N(13)	0.87(3)	2.41(3)	2.767(4)	105(3)
N(13)–H(13)	N(16)	0.84(3)	2.34(3)	2.739(4)	110(2)
N(16)–H(16)	N(19)	0.86(3)	2.42(3)	2.839(4)	111(3)

[a]) Symmetry operator for primed atoms: $\frac{3}{2}-x, -\frac{1}{2}+y, 1-z$.

2.2. *Synthesis of Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(*^{t}*Bu)-OMe* (**24**). The coupling of tripeptide Z-Leu-Aib-Pro-OH (**18**) [6] and the side-chain protected amino acid H-Ser(^{t}Bu)-OMe by use of TBTU/HOBt led to the tetrapeptide Z-Leu-Aib-Pro-Ser(^{t}Bu)-OMe (**19**) in a relatively low yield of 63% (*Scheme 5*). A possible explanation could be the steric hindrance of the *t*-Bu group in the side chain of serine and the reduced

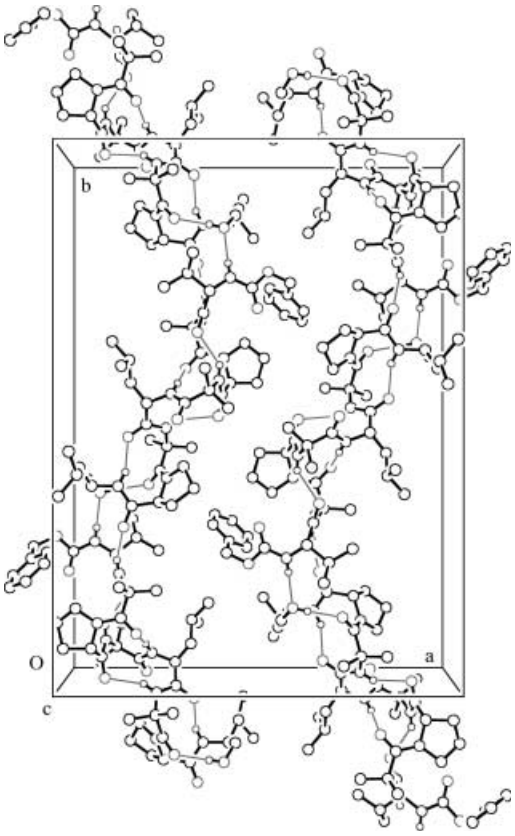
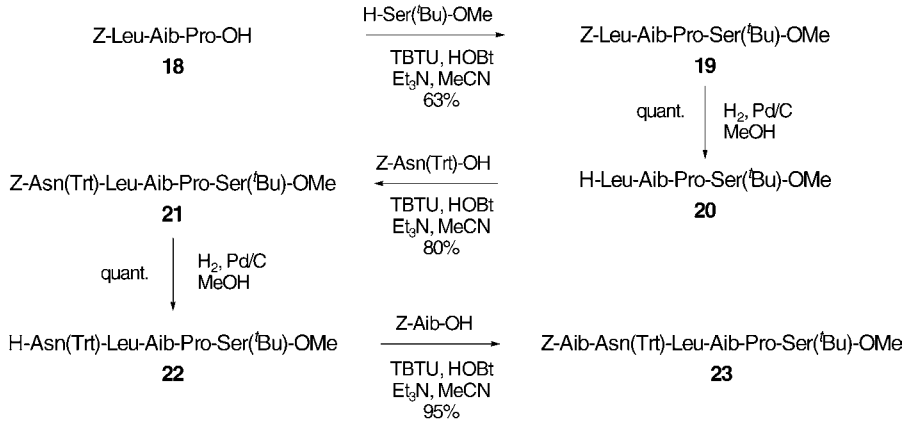


Fig. 2. *Crystal packing of* **17** *showing H-bonding interactions* (uninvolved H-atoms omitted for clarity)

Scheme 5



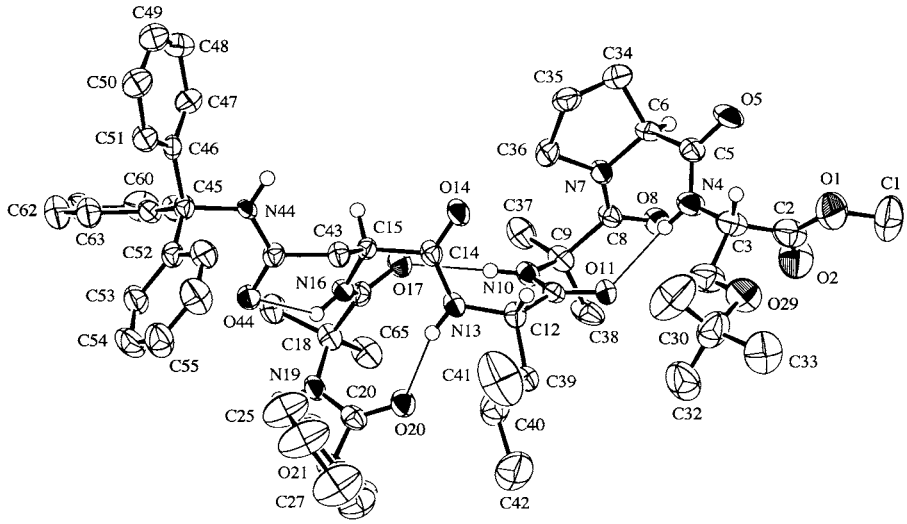


Fig. 3. *ORTEP Plot* [33] *of the molecular structure of* **23** (50% probability ellipsoids; arbitrary atom numbering; thin lines represent intramolecular H-bonds)

conformational freedom of proline[6]). The following hydrogenolysis gave **20** in quantitative yield, and the coupling with Z-Asn(Trt)-OH under standard conditions led to the pentapeptide Z-Asn(Trt)-Leu-Aib-Pro-Ser(*t*Bu)-OMe (**21**) in 80% yield. Steric interactions with the bulky trityl group in the side chain of asparagine are believed to be responsible for the lower yield of the coupling.

The deprotection of the N-terminus of **21** by hydrogenolysis led to **22** in quantitative yield. The subsequent coupling of **22** and Z-Aib-OH with TBTU/HOBt under standard conditions resulted in the hexapeptide Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(*t*Bu)-OMe (**23**) in 95% yield. Crystallization from CH_2Cl_2/hexane/EtOH provided single crystals suitable for X-ray analysis (*Fig. 3*). The five-membered ring of the proline residue is disordered in that C(35) equally occupies two sites corresponding to alternate directions for the flap of an envelope conformation. The crystal lattice contains large regions filled with solvent molecules, which appear to be disordered and to only partially occupy their sites (see *Exper. Part*).

Similar to the C-terminal octapeptide **17**, the N-terminal hexapeptide **23** shows a helical conformation stabilized by intramolecular H-bonds (*Table 2*, *Fig. 4*). While each NH group of the molecule acts as a donor for H-bonds, four of the interactions are intramolecular H-bonds. Each NH group, from N(4)–H to N(13)–H, interacts with the amide O-atom seven atoms further along the peptide backbone, and each of these interactions has the graph-set motif [35] of S(10). Two β-turns of type I are found, which are formed by the sequences Aib[1]-Asn[2]-Leu[3]-Aib[4] and Asn[2]-Leu[3]-Aib[4]-Pro[5], followed by a β-turn of type II with the sequence Leu[3]-Aib[4]-Pro[5]-Ser(*t*Bu)[6] (sequence numbering according to Trichovirin I). The N(16)–H forms an intramolecular H-bond

[6]) The corresponding coupling of **18** and H-Ala-OMe with EDC/HOBt gave 83% of Z-Leu-Aib-Pro-Ala-OMe [28].

Table 2. *Intra- and Intermolecular H-Bonds in the Crystal Structure of* **23** (D = donor, A = acceptor)

D–H	A[a])	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
N(4) –H(4)	O(11)	0.88	2.05	2.899(4)	161
N(10)–H(10)	O(17)	0.88	2.19	3.050(4)	167
N(13)–H(13)	O(20)	0.88	2.12	2.960(4)	160
N(16)–H(16)	O(44)	0.88	2.20	2.827(4)	128
N(19)–H(19)	O(8′)	0.88	1.99	2.856(4)	169
N(44)–H(44)	O(5″)	0.88	2.08	2.808(4)	140
N(4)–H(4)	N(7)	0.88	2.41	2.795(4)	107
N(10)–H(10)	N(13)	0.88	2.36	2.760(4)	108
N(13)–H(13)	N(16)	0.88	2.39	2.766(4)	106
N(16)–H(16)	N(19)	0.88	2.42	2.766(4)	104

[a]) Symmetry operators for singly (′) and doubly (″) primed atoms: $\frac{1}{2}+x,\ -\frac{1}{2}-y,\ -z$; and $1-x,\ -y,\ z$, resp.

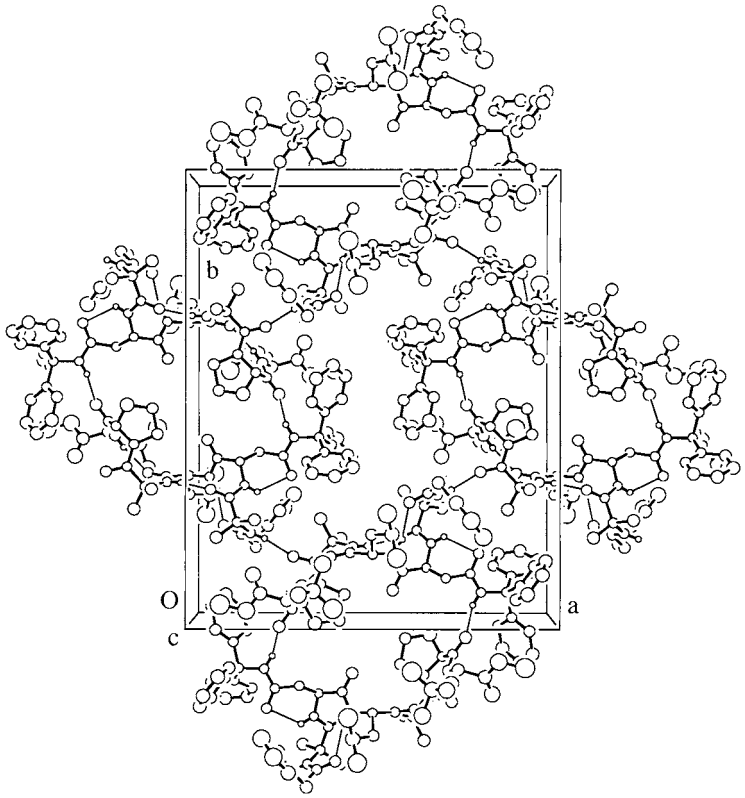


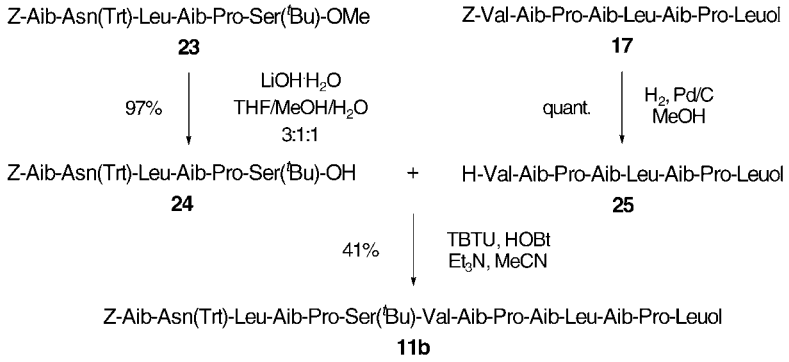
Fig. 4. *Crystal packing of* **23** *showing H-bonding interactions* (uninvolved H-atoms omitted for clarity)

with the amide O-atom of the asparagine side chain (graph set: S(6)). The remaining NH groups, N(19)–H and N(44)–H, which are unable to form intramolecular interactions because of their position in the backbone, form intermolecular H-bonds

with the amide O-atoms at the opposite end of different neighboring molecules (graph sets: C(14) and C(16), resp.). The intermolecular interactions link the molecules into infinite two-dimensional networks that lie parallel to the *xy*-plane (*Fig. 4*). Since all NH groups are involved in H-bonds, it is unlikely that there are any donor interactions with solvent molecules in the crystal. However, acceptor interactions cannot be excluded.

2.3. *Synthesis of Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(ᵗBu)-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol* (**11b**). The base-catalyzed hydrolysis of the hexapeptide **23** gave Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(ᵗBu)-OH (**24**) in 97% yield, and the free amine H-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**25**) was obtained quantitatively from **17** by hydrogenolysis under standard conditions. The final coupling of the two segments was carried out with TBTU/HOBt in MeCN and gave the tetradecapeptide **11b** in 41% yield (*Scheme 6*).

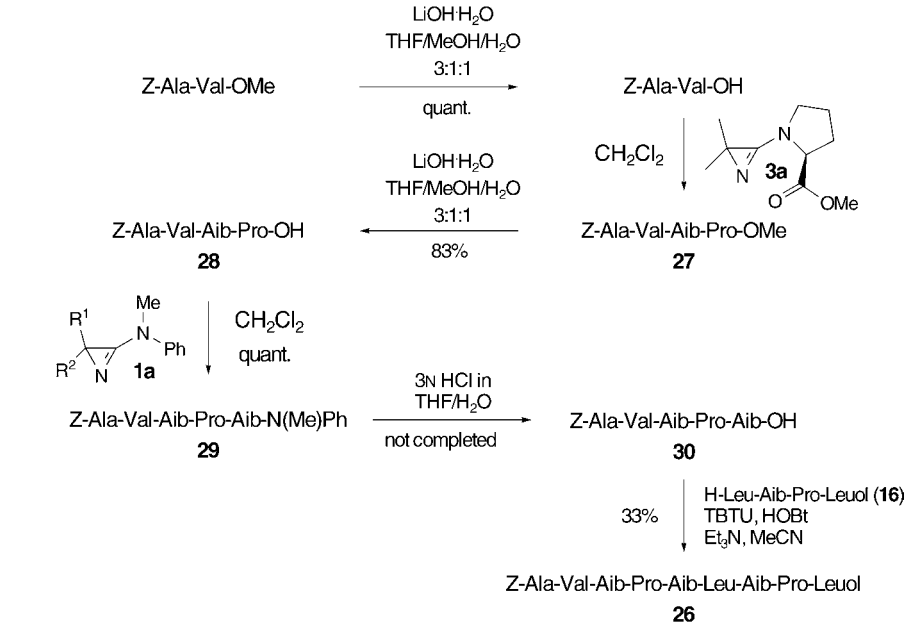
Scheme 6



The protected tetradecapeptide **11b** was thoroughly characterized by NMR spectroscopy. ^{1}H-NMR TOCSY and COSY Experiments allowed us to correlate all H-atoms. However, it was not possible to determine the positions of the multiple amino acids Aib, Leu, and Pro. On the basis of the (^{13}C,^{1}H)-correlated HSQC and HMBC 2D-spectra, it was also possible to correlate all ^{13}C-NMR signals. Unfortunately, additional experiments, such as NOE and ROESY, did not lead to further information and, therefore, the three-dimensional structure of **11a** in solution could not be determined.

2.4. *Synthesis of Z-Ala-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol* (**26**). Following the strategy described in [6], the nonapeptide **26**, which is the C-terminal nonapeptide of Trichovirin I 4A, was synthesized (*Scheme 7*). The hydrolysis of Z-Ala-Val-OMe, subsequent azirine coupling with **3a**, and hydrolysis to Z-Ala-Val-Aib-Pro-OH (**28**) were performed in an overall yield of 83%. The pentapeptide **29** was obtained in quantitative yield by coupling **28** with the azirine **1a**. Unexpectedly, the acid-catalyzed hydrolysis of the C-terminal amide group under standard conditions was not successful. The reaction could not be completed, and it was not possible to separate the starting material from the product. Therefore, the mixture was used in the next step, the coupling with H-Leu-Aib-Pro-Leuol (**16**) to obtain the nonapeptide **26** (33% yield). By crystallization from EtOH/hexane, single crystals suitable for X-ray crystallography were obtained (*Fig. 5*).

Scheme 7



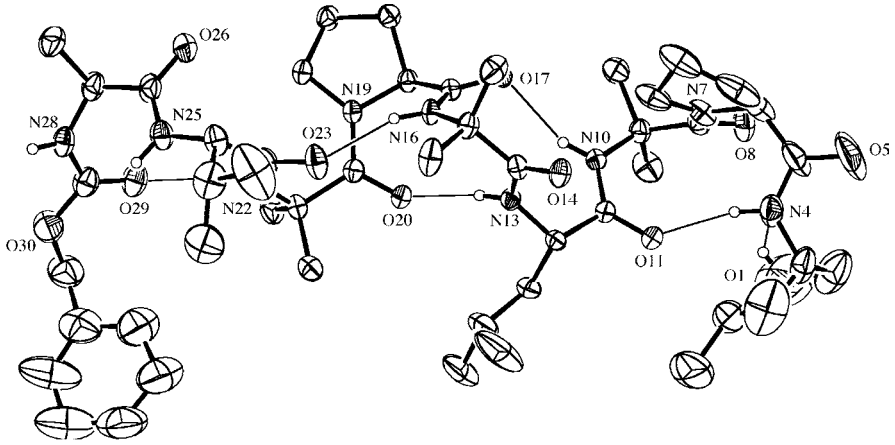


Fig. 5. *ORTEP Plot* [33] *of the molecular structure of* **26** (50% probability ellipsoids; arbitrary atom numbering; thin lines represent intramolecular H-bonds)

The crystal structure of **26** could be solved, but the results were very poor. In particular, the refinement of the terminal residues (Ala and Leuol) produced poor results, and the atoms of these groups, as well as some of the Me groups, gave rise to extremely large anisotropic displacement parameters. However, the overall backbone conformation of the peptide was clearly defined. The conformations of the end groups were less well-defined and, in particular, the positions of all atoms from the OH group

to the first 5-membered ring should be taken as being very approximate only. Disorder might be responsible for these problems, but no disordered model could be developed successfully. It might be that the molecule is extremely flexible in the crystal lattice, particularly at the ends of the chain. The nonapeptide **26** also adopts a helical conformation stabilized by intramolecular H-bonds (*Table 3*). Each NH group, except for N(25)–H and N(28)–H, acts as a donor for intramolecular H-bonds. The acceptor atoms are the amide O-atoms that are seven atoms further along the peptide chain. Each of these interactions has the graph-set motif [35] of S(10). N(25)–H does not form any H-bond, while N(28)–H forms an intermolecular H-bond with the second amide O-atom at the opposite end of a neighboring molecule. This is the sole intermolecular interaction and serves to link the molecules into extended chains running parallel to the [110] direction (graph-set motif: C(23)). The OH group forms an intramolecular H-bond with the first amide N-atom to form a closed loop with the graph set motif of S(6). Because of the uncertainty regarding the true structure of this section of the molecule, this last interaction might be incorrect.

Table 3. *Intra- and Intermolecular H-Bonds in the Crystal Structure of* **26** (D = donor, A = acceptor)

D–H	A[a])	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O(1)–H(1)	N(4)	0.82	2.53	2.85(2)	105
N(4)–H(4)	O(11)	0.86	2.18	2.990(8)	156
N(10)–H(10)	O(17)	0.86	2.18	2.996(5)	158
N(13)–H(13)	O(20)	0.86	2.23	3.085(6)	172
N(16)–H(16)	O(23)	0.86	2.08	2.901(7)	160
N(22)–H(22)	O(29)	0.86	2.27	3.104(7)	164
N(28)–H(28)	O(8′)	0.86	2.14	2.975(7)	162
N(4)–H(4)	N(7)	0.86	2.40	2.776(9)	107
N(10)–H(10)	N(13)	0.86	2.42	2.797(7)	107
N(13)–H(13)	N(16)	0.86	2.36	2.733(6)	106
N(16)–H(16)	N(19)	0.86	2.44	2.818(6)	107
N(22)–H(22)	N(25)	0.86	2.33	2.726(7)	108
N(25)–H(25)	N(28)	0.86	2.40	2.768(8)	106

[a]) Symmetry operator for primed atom: $1+x$, $1+y$, z.

3. Conclusions. – We have prepared Trichovirin I 1B by an alternative method, demonstrating the use of the 'azirine/oxazolone method'. It has been shown that the incorporation of α,α-disubstituted α-amino acids into peptide chains with the reactions described above is very convenient. The combination of this method with the classical TBTU/HOBt coupling protocol allowed the synthesis of the tetradecapeptide **11b** bearing protecting goups in the side chain of serine and asparagine, as well as the C-terminal nonapeptide of Trichovirin I 4A. The X-ray crystal structures of all prepared segments (*cf.* also [6][34]) showed helical structures formed by a sequence of β-turns. The results from 2D-NMR measurements gave only some hints regarding the three-dimensional structure in solution, but it seems very likely that these molecules possess comparable secondary structures in the crystal and in solution, *i.e.*, β-turns giving rise to an overall helical structures.

The backbones of the C-terminal nonapeptide of Trichovirin I 1B and Trichovirin I 4A have almost identical shapes. We expect that all of the seven different members of the Trichovirin I family have very similar helical structures and are able to aggregate to membrane-channel helix bundles. The chain length of the Trichovirins with only 14 residues is too short to break through the membrane of a cell. Usually, a peptide chain with 18–20 amino acids is required [36]. Assuming that Trichovirins are helical, two molecules in line could reach the length required to open up membrane channels.

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Experimental Part

1. *General*. Ethyl acetate (AcOEt), distilled over K_2CO_3; hexane, distilled; CH_2Cl_2, distilled over $CaCl_2$, K_2CO_3, or CaH_2; acetonitrile (MeCN), *Fluka* (puriss.); methanol (MeOH), *Fluka* (puriss.); ethanol (EtOH), *Kunzmann* (99.8%); tetrahydrofurane (THF), distilled over Na/benzophenone; isobutyric acid chloride, distilled; triethylamine (Et_3N), *Fluka* (purum); amino acids, from *Bachem* and *Fluka*; 1-hydroxy-1*H*-benzotriazole (HOBt), *Fluka* (purum); *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU), *Nova Biochem* or *Bachem*. TLC on TLC-Alufoil *Kieselgel 60* F_{254} (*Merck*). Column chromatography (CC) on *Kieselgel 60*, 40–60 μm (*Merck*). M.p.: *Mettler FP-5* or *Büchi B-540* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 781* instrument, in KBr; absorption bands in cm^{-1} (*s* = strong, *m* = middle, *w* = weak, *v* = very, sh = shoulder). ^{1}H-NMR Spectra (300, 500, or 600 MHz): *Bruker ARX-300*, *Bruker DRX-500*, and *Bruker AMX-600* instruments; chemical shifts δ in ppm rel. to $SiMe_4$ (= 0.0 ppm), coupling constants *J* in Hz. ^{13}C-NMR Spectra (75.5 or 150.9 MHz): *Bruker ARX-300* and *Bruker AMX-600* instruments; chemical shifts δ in ppm rel. to $CDCl_3$ (= 77.0 ppm); multiplicity from DEPT-spectra. ESI-MS: *Finnigan MAT TSQ-700* instrument.

2. *General Procedures. Procedure A* (Peptide coupling; *GPA*). One equiv. of *N*-protected amino acid or *N*-protected peptide, and one equiv. of *C*-protected amino acid or *C*-protected peptide were dissolved in MeCN (0.1–0.2M soln.). To this soln. were added TBTU and HOBt, one equiv. of each, and three equiv. of Et_3N, and the mixture was stirred at r.t. The progress of the reaction was followed by TLC. When the reaction was complete, the soln. was extracted with a sat. aq. soln. of NaCl (3×). Then, the solvent was evaporated *in vacuo*, and the crude product was purified by CC.

Procedure B (Azirine coupling; *GPB*). To a soln. of 1 equiv. of *N*-protected amino acid or peptide in CH_2Cl_2 was added one equiv. of a 2*H*-azirin-3-amine diluted in CH_2Cl_2. When the reaction was complete (TLC), the solvent was removed *in vacuo*, and the crude product was purified by CC or recrystallization.

Procedure C (Base-catalyzed hydrolysis; *GPC*). A *C*-protected peptide was dissolved in THF/H_2O/MeOH 3:1:1, and three equiv. of $LiOH \cdot H_2O$ were added. When the reaction was complete, 1N HCl was added to adjust the pH to 1, and the soln. was extracted with CH_2Cl_2. The org. phase was dried ($MgSO_4$), and the solvent removed. The crude product was dried *in vacuo* and used in the next step without further purification.

Procedure D (Hydrogenolysis; *GPD*). To a soln. of *N*-protected peptide in MeOH was added a small amount of catalyst (Pd/C), and the mixture was stirred under H_2-atmosphere. When the reaction was complete (TLC), the soln. was filtered over *Celite*, and the solvent was evaporated. The crude product was dried *in vacuo* and used without further purification.

Procedure E (Acid-catalyzed hydrolysis of peptide amides; *GPE*). To a soln. of the peptide amide in THF, the same volume of an aq. 6N HCl soln. was added at 0°. After stirring at r.t., the soln. was extracted with CH_2Cl_2, and the org. solvent was evaporated. The crude product was dried *in vacuo* and used without further purification.

3. *Synthesis of Peptide Segments.* 3.1. *Synthesis of H-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol* (**25**). *Z-Val-Aib-Pro-OMe* (**12**) [28]. According to *GPB*, Z-L-valine (111.2 mg, 0.44 mmol) and methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**3a**, 84 mg, 0.44 mmol) were dissolved in CH_2Cl_2 (10 ml) and stirred at r.t. for 15 h. The product was purified by CC (AcOEt/hexane 2:1, R_f = 0.24): 165 mg (86%) of **12**. Colorless foam. IR: 3310*m*, 3064*w*, 2964*m*, 2876*w*, 1744*vs*, 1661*vs*, 1620*vs*, 1534*vs*, 1469*m*, 1455*m*, 1411*s*, 1363*m*, 1288*m*, 1241*s*, 1170*s*, 1094*w*, 1026*m*, 741*w*, 698*w*. ^{1}H-NMR (300 MHz): 7.35–7.3 (*m*, 5 arom. H); 6.99 (*s*, NH(Aib)); 5.40 (*d*, *J* = 9, NH(Val));

5.12 (*s*, $PhCH_2$); 4.55–4.5 (*m*, CH(α)(Pro)); 3.95–3.9 (*m*, CH(α)(Val)); 3.72 (*s*, MeO); 3.7–3.5 (*m*, CH_2(δ)(Pro)); 2.15–2.0, 1.95–1.8 (2*m*, CH_2(β,γ)(Pro)); 1.65, 1.61 (2*s*, 2 Me(Aib)); 0.95, 0.91 (2*d*, *J* = 6.8, 2 Me(Val)). ^{13}C-NMR (75.5 MHz): 172.8, 172.1, 169.5 (3*s*, 3 C=O); 156.4 (*s*, O–C=O); 128.5, 128.1, 128.0 (3*d*, 5 arom. CH); 66.9 (*t*, Ph*C*H_2); 60.9, 60.5 (2*d*, CH(α)(Val), CH(α)(Pro)); 57.1 (*s*, C(α)(Aib)); 52.2 (*q*, MeO); 48.0 (*t*, CH_2(δ)(Pro)); 31.4 (*d*, CH(β)(Val)); 27.8 (*t*, CH_2(β)Pro)); 25.8 (*t*, CH_2(γ)(Pro)); 23.5, 23.0, 19.1, 17.8 (4*q*, 2 Me(Val), 2 Me(Aib)); one arom. C-atom could not be detected.

Z-Val-Aib-Pro-OH (**13**) [28]. According to *GPC*, **12** (155 mg, 0.34 mmol) and $LiOH \cdot H_2O$ (58 mg, 1.38 mmol) were dissolved in THF (5 ml), and the mixture was stirred at r.t. for 14 h: 143 mg (95%) of **13**. Colorless foam. IR: 3307*m*, 3065*w*, 2967*s*, 2877*w*, 1715*vs*, 1620*vs*, 1539*s*, 1470*m*, 1454*m*, 1418*m*, 1366*w*, 1343*w*, 1292*m*, 1237*s*, 1177*m*, 1027*w*, 739*w*, 698*w*. ^{1}H-NMR (300 MHz): 7.35–7.30 (*m*, 5 arom. H); 6.93 (*s*, NH(Aib)); 5.54 (*d*, *J* = 8.2, NH(Val)); 5.15–5.1 (*m*, $PhCH_2$); 4.6–4.5 (*m*, CH(α)(Val)); 3.96 (*dd*, *J* = 6.7, 2.0, CH(α)(Pro)); 3.8–3.7 (*m*, 1 H of CH_2(δ)(Pro)); 3.52–3.4 (*m*, 1 H of CH_2(δ)(Pro), OH); 2.15–1.7 (*m*, CH_2(β,γ)(Pro), CH(β)(Val)); 1.55, 1.53 (2*s*, 2 Me(Aib)); 0.96, 0.92 (2*d*, *J* = 6.8, 2 Me(Val)). ^{13}C-NMR (75.5 MHz): 174.1, 173.0, 170.9 (3*s*, 3 C=O); 156.7 (*s*, O–C=O); 128.5, 128.3, 127.9 (3*d*, 5 arom. CH); 67.1 (*t*, Ph*C*H_2); 61.4, 60.4 (2*d*, CH(α)(Val), CH(α)(Pro)); 57.0 (*s*, C(α)(Aib)); 48.2 (*t*, CH_2(δ)(Pro)); 30.7 (*d*, CH(β)(Val)); 27.3 (*t*, CH_2(β)(Pro)); 25.8 (*t*, CH_2(γ)(Pro)); 24.4, 24.2, 19.2, 17.9 (4*q*, 2 Me(Val); 2 Me(Aib)); one arom. C-atom could not be detected.

Z-Val-Aib-Pro-Aib-N(Me)Ph (**14**). According to *GPB*, **13** (127 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (5 ml) and a soln. of 2,2-dimethyl-2*H*-azirin-3-(*N*-methyl-*N*-phenylamine) (**1a**, 51 mg, 0.29 mmol) in CH_2Cl_2 (5 ml) was added. The soln. was stirred at r.t. overnight, and the product was purified by CC (AcOEt/MeOH 21:1; R_f 0.3): 164 mg (92%) of **14**. Colorless foam. ^{1}H-NMR (300 MHz): 7.45 (*s*, NH(Aib)); 7.35–7.2 (*m*, 10 arom. H); 6.88 (*s*, NH(Aib)); 5.43 (*d*, *J* = 8.5, NH(Val)); 5.15, 5.08 (*AB*, *J* = 12.1, $PhCH_2$); 4.49 (*t*, *J* = 6.4, CH(α)(Val)); 3.92 (*dd*, *J* = 6.4, 2.1, CH(α)(Pro)); 3.51–3.3 (*m*, CH_2(δ)(Pro)); 3.33 (*s*, MeN); 2.15–1.5 (*m*, CH_2(β,γ)(Pro), CH(β)(Val)); 1.50, 1.47, 1.43, 1.40 (4*s*, 4 Me(Aib)); 0.96, 0.91 (2*d*, *J* = 6.8, 2 Me(Val)). ^{13}C-NMR (75.5 MHz): 173.6, 171.8, 170.7 (3*s*, 4 C=O); 156.5 (*s*, O–C=O); 145.4, 136.1 (2*s*, 2 arom. C); 129.0, 128.6, 128.3, 128.1, 127.4, 126.8 (6*d*, 10 arom. CH); 67.2 (*t*, Ph*C*H_2); 62.0, 60.7 (2 *d*, CH(α)(Pro), CH(α)(Val)); 57.3, 57.0 (2*s*, 2 C(α)(Aib)); 48.0 (*t*, CH_2(δ)(Pro)); 40.2 (*q*, MeN); 30.0 (*d*, CH(β)(Val)); 27.9 (*t*, CH_2(β)(Pro); 26.3 (*t*, CH_2(γ)(Pro)); 25.6, 25.5, 25.4, 24.1 (4*q*, 4 Me(Aib)); 19.4, 17.8 (2*q*, 2 Me(Val)). ESI-MS (MeOH + NaI): 630 ($[M + Na]^+$).

Z-Val-Aib-Pro-Aib-OH (**15**) [28]. According to *GPE*, a soln. of **14** (721 mg, 1.39 mmol) in THF (10 ml) was cooled in an ice bath, treated with aq. 6N HCl (10 ml) and stirred at r.t. for 3 d: 552 mg (89%) of **15**. Colorless foam. ^{1}H-NMR (300 MHz): 7.72 (*s*, NH); 7.4–7.3 (*m*, 5 arom. H); 7.14 (br. *s*, NH); 5.56 (br. *s*, NH); 5.16, 5.09 (*AB*, *J* = 12.2, $PhCH_2$); 4.50 (*t*, *J* = 7.0, CH(α)(Val)); 4.1–3.9 (*m*, CH(α)(Pro)); 3.8–3.0 (*m*, CH_2(δ)(Pro)); 2.2–1.6 (*m*, CH_2(β,γ)(Pro), CH(β)(Val)); 1.6–1.4 (*m*, 4 Me(Aib)); 0.96, 0.91 (2*d*, *J* = 6.8, 2 Me(Val)). ^{13}C-NMR (75.5 MHz): 175.9, 172.7, 172.4, 171.3 (4*s*, 4 C=O); 156.7 (s, O–C=O); 136.3 (*s*, 1 arom. C); 128.4, 128.2, 127.9 (3*d*, 5 arom. CH); 67.8 (*t*, Ph*C*H_2); 62.4 (*d*, CH(α)(Pro), CH(α)(Val)); 61.8 (*t*, CH_2(δ)(Pro)); 56.9 (*s*, 2 C(α)(Aib)); 25.8, 25.5 (2*t*, CH_2(β,γ)(Pro)); 24.9, 24.6 (2*q*, 4 Me(Aib)); 19.3 (*q*, 2 Me(Val)).

Z-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**17**) [28]. According to *GPA*, **15** (239 mg, 0.46 mmol), H-Leu-Aib-Pro-Leuol (**16**) [6][28] (190 mg, 0.46 mmol), TBTU (148 mg), HOBt (71 mg), and Et_3N (0.25 ml) were dissolved in MeCN (25 ml), and the mixture was stirred at r.t. for 1 d. After workup, the crude product was purified by CC (AcOEt/MeOH 9:1; R_f 0.31): 278 mg (66%) of **17**. Crystallization from AcOEt/MeOH gave single crystals suitable for an X-ray crystal-structure determination. M.p.: dec. above 115°. ^{1}H-NMR (600 MHz, 2D): 7.74, 7.72, 7.66 (3*s*, 3 NH(Aib)); 7.46 (*d*, *J* = 9.1, NH(Leuol)); 7.40 (br. *s*, NH(Val)); 7.4–7.0 (*m*, 5 arom. H); 6.60 (*d*, *J* = 7.1, NH(Leu)); 5.16, 5.08 (*AB*, *J* = 12.3, $PhCH_2$); 4.35–4.3 (*m*, CH(α)(Val), CH(α)(Pro)); 4.2–4.0 (*m*, CH(α)(Pro), CH(α)(Leuol)); 3.96 (*t*, *J* = 7.3, CH(α)(Leu)); 3.8–3.7 (*m*, 1 H of CH_2(δ)(Pro)); 3.6–3.5 (*m*, CH_2O(Leuol), 2 H of CH_2(δ)(Pro)); 3.4–3.3 (*m*, 1 H of CH_2(δ)(Pro)); 2.3–2.2 (*m*, 2 CH_2(γ)(Pro)); 2.2–2.1 (*m*, CH_2(β)(Leu)); 2.0–1.9 (*m*, 1 H of CH_2(β)(Pro)); 1.9–1.8 (*m*, 1 H of CH_2(β)(Pro)); 1.8–1.6 (*m*, CH_2(β)(Pro), CH(β)(Val)); 1.6–1.5 (*m*, CH_2(β)(Leuol)); 1.55, 1.51, 1.48, 1.46, 1.45, 1.43 (6*s*, 6 Me(Aib)); 1.2–1.1 (*m*, CH(γ)(Leuol)); 1.1–1.0 (*m*, CH(γ)(Leu)); 0.98, 0.97, 0.90, 0.87 (4*d*, *J* = 6.6, 2 Me(Leu), 2 Me(Leuol)); 0.88, 0.84 (2*d*, 2 Me(Val)). ^{13}C-NMR (75.5 MHz): 175.3, 173.5, 173.3, 173.2, 172.9, 172.8, 172.3 (7*s*, 7 C=O); 156.9 (*s*, O–C=O); 136.6 (*s*, 1 arom. C); 128.4, 128.0, 127.8 (3*d*, 5 arom. CH); 66.8 (*t*, CH_2O); 65.3 (*t*, Ph*C*H_2)); 64.4, 63.4, 61.7 (3*d*, CH(α)(Val), 2 CH(α)(Pro)); 56.9, 56.5, 56.4 (3*s*, 3 C(α)(Aib)); 51.8, 49.9 (2*d*, CH(α)(Leu), CH(α)(Leuol)); 48.7, 48.4 (2*t*, 2 CH_2(δ)(Pro)); 40.0, 39.0 (2*t*, CH_2(β)(Leu), CH_2(β)(Leuol)); 29.0, 28.6 (2*t*, 2 CH_2(β)(Pro)); 27.1 (*q*, Me); 26.1 (*t*, 2 CH_2(γ)(Pro)); 25.7, 25.6 (2*q*, 2 Me); 24.8, 24.7 (2*d*, CH(γ)(Leu),

CH(γ)(Leuol)); 23.8, 23.6, 23.1, 23.0, 22.1, 20.5, 19.2, 18.4 (8*q*, 8 Me). ESI-MS (MeOH + NaI): 936 (100, [*M* + Na]$^+$).

H-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**25**). According to *GPD*, **17** (221 mg, 0.24 mmol) was dissolved in MeOH (17 ml), Pd/C was added, and the mixture was stirred under H_2-atmosphere at r.t. overnight. After workup, **25** was obtained in quant. yield (188 mg) as a sticky foam. ^{1}H-NMR (300 MHz): 8.05 (*s*, NH); 7.98 (*s*, NH); 7.68 (*s*, NH); 7.4–7.3 (*m*, NH); 4.45–4.3 (*m*, 2 CH(α)); 4.52 (*dd*, *J* = 7.9, 1.6, CH(α)); 4.1–4.0 (*m*, CH(α)); 3.85–3.7 (*m*, CH(α), CH_2(δ)(Pro)); 3.55–3.4 (*m*, CH_2(δ)(Pro)); 3.4–3.3, 3.3–3.2 (2*m*, CH_2O(Leuol)); 2.5–2.2, 2.1–1.5 (2*m*, CH_2(β,γ)(Pro), CH_2(β)(Leu), CH_2(β)(Leuol), CH(γ)(Leu), CH(γ)(Leuol)); 1.55, 1.51, 1.47, 1.46, 1.45 (5*s*, 6 Me(Aib)); 1.3–1.1 (*m*, CH(β)(Val)); 1.0–0.8 (*m*, 2 Me(Leu), 2 Me(Leuol), 2 Me(Val)).

3.2. *Synthesis of Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(^{t}Bu)-OH* (**24**). *Z-Leu-Aib-Pro-Ser(^{t}Bu)-OMe* (**19**). According to *GPA*, Z-Leu-Aib-Pro-OH (**18**, 853 mg, 1.90 mmol), H-Ser(^{t}Bu)-OMe · HCl (400 mg, 1.9 mmol), TBTU (321 mg), HOBt (153 mg), and Et_3N (1 ml) were dissolved in MeCN (15 ml), and the soln. was stirred at r.t. for 1 d. The crude product was purified by CC (AcOEt/MeOH 25 :1; R_f 0.3): 730 mg (63%) of **19**. Colorless foam. IR: 3294*m*, 2972*s*, 2874*w*, 1720*vs*, 1654*vs*, 1534*vs*, 1470*s*, 1405*s*, 1364*s*, 1246*s*, 1098*m*, 1049*m*, 1027*m*, 740*w*, 698*w*. ^{1}H-NMR (300 MHz): 7.35–7.3 (*m*, 5 arom. H); 6.98 (br. *s*, 2 NH); 5.2–5.1 (*m*, $PhCH_2$); 4.65–4.5 (*m*, CH(α)(Pro), CH(α)(Ser)); 4.2–4.1 (*m*, CH(α)(Leu)); 3.8–3.75 (*m*, 1 H of CH_2(δ)(Pro)); 3.71 (*s*, MeO); 3.65–3.5 (*m*, 1 H of CH_2(δ)(Pro), CH_2(β)(Ser)); 2.05–1.6 (*m*, CH_2(β,γ)(Pro), CH_2(β)(Leu), CH(γ)(Leu)); 1.56 (*s*, 2 Me(Aib)); 1.13 (*s*, Me_3C); 0.95–0.9 (*m*, 2 Me(Leu)). ^{13}C-NMR (75.5 MHz): 172.1, 171.6, 170.8 (3*s*, 4 C=O); 156.1 (*s*, O–C=O); 136.1 (*s*, 1 arom. C); 128.4, 128.1, 127.9 (3*d*, 5 arom. CH); 73.2 (*s*, Me_3C); 66.9 (*t*, CH_2(β)(Ser)); 61.9 (*d*, CH(α)(Ser)); 61.5 (*t*, CH_2(δ)(Pro)); 57.0 (*s*, C(α)(Aib)); 53.5 (*d*, CH(α)(Pro)); 52.9 (*d*, CH(α)(Leu)); 52.0 (*q*, MeO); 48.0 (*t*, CH_2(γ)(Pro)); 41.2 (*t*, CH_2(β)(Leu)); 28.5 (*q*, 1 Me(Aib)); 27.2 (*q*, Me_3C); 24.5 (*d*, CH(γ)(Leu)); 24.1 (*q*, 1 Me(Aib)); 22.8, 21.8 (2*q*, 2 Me(Leu)). ESI-MS (MeOH + NaI): 627 ([*M* + Na]$^+$).

H-Leu-Aib-Pro-Ser(^{t}Bu)-OMe (**20**). According to *GPD*, **19** (675 mg, 1.11 mmol) was dissolved in MeOH (10 ml), and a small amount of Pd/C was added. The mixture was stirred under H_2 at r.t. overnight: 552 mg (quant.) of **20**. Colorless foam. ^{1}H-NMR (300 MHz): 7.83 (*s*, NH); 7.12 (br. *s*, NH); 4.6–4.5 (*m*, CH(α)(Ser), CH(α)(Pro)); 3.64 (*s*, MeO); 3.7–3.5, 3.3–3.2 (2*m*, CH_2(δ)(Pro), CH_2(β)(Ser), CH(α)(Leu)); 2.1–1.6 (*m*, CH_2(β,γ)(Pro), CH_2(β)(Leu)); 1.52, 1.49 (2*s*, 2 Me(Aib)); 1.3–1.2 (*m*, CH(γ)(Leu)); 1.07 (*s*, Me_3C); 0.89, 0.84 (2*d*, *J* = 6.2, 2 Me(Leu)). ^{13}C-NMR (75.5 MHz): 174.4, 172.4, 171.8, 170.8 (4*s*, 4 C=O); 73.1 (*s*, Me_3C)); 61.8 (*d*, CH(α)(Ser)); 61.5 (*t*, CH_2(β)(Ser)); 56.3 (*s*, C(α)(Aib)); 53.4, 53.0 (2*d*, CH(α)(Pro), CH(α)(Leu)); 52.0 (*q*, MeO); 47.9 (*t*, CH_2(δ)(Pro)); 43.9 (*t*, CH_2(β)(Leu)); 27.2 (*q*, Me_3C); 25.5 (*t*, CH_2(β,γ)(Pro)); 24.7 (*d*, CH(γ)(Leu)); 24.8, 24.5, 23.2, 21.2 (4*q*, 2 Me(Aib), 2 Me(Leu)).

Z-Asn(Trt)-Leu-Aib-Pro-Ser(^{t}Bu)-OMe (**21**). According to *GPA*, **20** (525 mg, 1.12 mmol), Z-Asn(Trt)-OH (568 mg, 1.12 mmol), TBTU (359 mg), HOBt (171 mg), and Et_3N (0.6 ml) were dissolved in MeCN (50 ml). The soln. was stirred at r.t. for 1 d. After workup, the crude product was purified by CC (AcOEt/MeOH 25 :1; R_f 0.4): 828 mg (80%) of **21**. Colorless foam. IR: 3302*m*, 2971*m*, 1658*vs*, 1514*s*, 1448*m*, 1407*m*, 1365*m*, 1233*s*, 1084*m*, 752*w*, 700*s*. ^{1}H-NMR (300 MHz): 7.3–7.0 (*m*, 20 arom. H); 6.38, 6.18 (2 br. *s*, 2 NH); 4.98 (*s*, $PhCH_2$); 4.55–4.4 (*m*, 2 CH(α)); 4.3–4.2 (*m*, 2 CH(α)); 3.6–3.5 (*m*, MeO, CH_2(δ)(Pro)); 3.33 (br. *s*, 1 H of CH_2(β)(Asn)); 2.83 (*d*, *J* = 5.1, 1 H of CH_2(β)(Asn)); 2.0–1.3 (*m*, CH_2(β,γ)(Pro), CH_2(β)Leu), CH(γ)(Leu)); 1.27, 1.07 (2*s*, 2 Me(Aib)); 1.06 (*s*, Me_3C); 0.80, 0.74 (2*d*, *J* = 6.4, 2 Me(Leu)). ^{13}C-NMR (75.5 MHz): 172.3, 171.0, 170.5, 169.5 (4*s*, 6 C=O); 155.9 (*s*, O–C=O); 144.0 (*s*, 3 arom. C); 135.9 (*s*, 1 arom. C); 128.5, 128.4, 128.1, 127.8, 127.0 (5*d*, 20 arom. CH); 73.1 (*s*, Me_3C)); 70.8 (*s*, Ph_3C); 67.0 (*t*, $PhCH_2$); 61.9 (*d*, CH(α)(Ser)); 61.5 (*t*, CH_2(β)(Ser), CH_2(β)(Asn)); 56.7 (*s*, C(α)(Aib)); 53.1, 52.1 (2*d*, CH(α)(Pro), CH(α)(Leu), CH(α)(Asn)); 51.9 (*q*, MeO); 47.8 (*t*, CH_2(δ)(Pro)); 39.9 (*t*, CH_2(β)(Leu)); 38.6 (*t*, CH_2(β,γ)(Pro)); 27.3 (*q*, Me_3C); 25.2 (*q*, 1 Me(Aib)); 24.6 (*d*, CH(γ)(Leu)); 24.2, 22.9, 21.3 (3*q*, 1 Me(Aib), 2 Me(Leu)). ESI-MS (MeOH + NaI): 983 (100, [*M* + Na]$^+$), 519 (41, [*M* + 2Na]$^{2+}$).

H-Asn(Trt)-Leu-Aib-Pro-Ser(^{t}Bu)-OMe (**22**). According to *GPD*, to a soln. of **21** (298 mg, 0.31 mmol) in MeOH (10 ml) was added a small amount of Pd/C. The mixture was stirred under H_2-atmosphere at r.t. overnight: 256 mg (quant.) of **22**. Colorless foam. ^{1}H-NMR (300 MHz, CD_3OD): 7.35–7.2 (*m*, 15 arom. H); 4.6–4.3 (*m*, 3 CH(α)); 4.2–4.1 (*m*, CH(α)); 3.8–3.3 (*m*, CH_2(δ)(Pro), CH_2(β)(Ser)); 3.72 (*s*, MeO); 2.9–2.6 (*m*, CH_2(β)(Asn)); 2.25–1.5 (*m*, CH_2(β,γ)(Pro), CH_2(β)(Leu), CH_2(γ)(Leu)); 1.45, 1.27 (2*s*, 2 Me(Aib)); 1.16 (*s*, Me_3C); 1.0–0.8 (*m*, 2 Me(Leu)).

Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(^{t}Bu)-OMe (**23**). According to *GPA*, a mixture of **22** (344 mg, 0.42 mmol), Z-Aib-OH (99 mg, 0.42 mmol), TBTU (134 mg), HOBt (64 mg), and Et_3N (0.17 ml) in MeCN (15 ml) was stirred at r.t. for 1 d. After workup, the crude product was purified by CC (AcOEt/MeOH 35 :1; R_f 0.26): 413mg (95%) of **23**. Colorless crystals. Recrystallization from CH_2Cl_2/EtOH/hexane gave single crystals

suitable for an X-ray crystal-structure determination. M.p.: dec. above 98°. IR: 3308*s*, 3058*w*, 3032*w*, 2973*m*, 2873*w*, 1742*w*, 1654v*s*, 1516v*s*, 1470*m*, 1449*m*, 1385*m*, 1364*m*, 1266*s*, 1196*m*, 1147*w*, 1089*m*, 1026*w*, 1002*w*, 914*w*, 750*w*, 700*m*. ^{1}H-NMR (500 MHz, 2D, TOCSY, COSY): 7.88 (*d*, *J* = 4, NH(Asn)); 7.62 (*d*, *J* = 7.8, NH(Ser)); 7.58 (*d*, *J* = 8.3, NH(Leu)); 7.3–7.1 (*m*, 15 arom. H); 7.1–7.0 (*m*, 5 arom. H); 5.60 (*s*, NH(Aib)); 4.95, 4.84 (*AB*, *J* = 12.2, PhCH_2); 4.55–4.4 (*m*, CH(α)(Pro), CH(α)(Ser)); 4.35–4.3 (*m*, CH(α)(Leu), CH(α)(Asn)); 3.7–3.6 (*m*, CH_2(β)(Ser)); 3.55–3.5, 3.4–3.3 (2*m*, CH_2(δ)(Pro)); 2.9–2.8 (*dd*, *J* = 14.4, 4.0, 1 H of CH_2(β)(Asn)); 2.7–2.6 (*dd*, *J* = 14.4, 9.2, 1 H of CH_2(β)(Asn)); 2.05–1.9 (*m*, 1 H of CH_2(β)(Pro)); 1.9–1.8 (*m*, 1 H of CH_2(β)(Pro), 1 H of CH_2(γ)(Pro)); 1.75–1.7 (*m*, 1 H of CH_2(β)(Leu)); 1.7–1.5 (*m*, 1 H of CH_2(γ)(Pro), 1 H of CH_2(β)(Leu), CH(γ)(Leu)); 1.42, 1.41, 1.38, 1.21 (4*s*, 4 Me(Aib)); 1.08 (*s*, Me_3C)); 0.79, 0.74 (2*d*, *J* = 6.5, Me(Leu)). ^{13}C-NMR (125.7 MHz): 175.5, 172.3, 172.1, 171.5, 171.0, 169.4 (6*s*, 7 C=O); 156.0 (*s*, O–C=O); 144.0 (*s*, 3 arom. C); 135.4 (*s*, 1 arom. C); 128.5, 128.2, 127.9, 127.6, 127.0 (5*d*, 20 arom. CH); 73.0, 70.9 (2*s*, Me_3C, Ph_3C); 67.0 (*t*, PhCH_2); 61.9 (*d*, CH(α)(Pro or Ser)); 61.5 (*t*, CH_2(β)(Asn)); 56.7, 56.6 (2*s*, 2 C(α)(Aib)); 53.2 (*d*, CH(α)(Ser or Pro)); 52.4 (*d*, CH(α)(Asn or Leu)); 51.8 (*d* and *q*, CH(α)(Leu or Asn), MeO); 47.9 (*t*, CH_2(δ)(Pro)); 39.5 (*t*, CH_2(β)(Leu)); 37.3 (*t*, CH_2(β)(Asn)); 28.2 (*t*, CH_2(β)(Pro)); 27.3 (*q*, Me_3C); 26.4, 25.8 (2*q*, 2 Me(Aib)); 25.7 (*t*, CH_2(γ)(Pro)); 24.7 (*d*, CH(γ)(Leu)); 24.9, 23.7 (2*q*, 2 Me(Aib)); 23.2, 20.7 (2*q*, 2 Me(Leu)). ESI-MS (MeOH + NaI): 1068 (100, $[M + Na]^+$), 546 (17, $[M + 2Na]^{2+}$).

Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser(^{t}*Bu*)*-OH* (**24**). According to *GPC*, a soln. of **23** (184 mg, 0.18 mmol) and LiOH · H_2O (16 mg, 0.52 mmol) in THF/MeOH/H_2O 3:1:1 (10 ml) was stirred at r.t. for 2 h: 177 mg (97%) of **24**. Colorless foam. IR: 3301*s*, 2973*s*, 1650v*s*, 1525v*s*, 1194*s*, 1090*m*, 914*w*, 752*m*, 700*s*. ESI-MS (MeOH/H_2O + AcOH): 964 (22, $[M - Z + Ac + Na]^+$), 942 (38, $[M - Z + Ac + 1]^+$), 684 (100, $[M - Z - Trt + 1]^+$).

3.3. *Synthesis of Z-Aib-Asn(Trt)-Leu-Aib-Pro-Ser*(^{t}*Bu*)*-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol* (**11b**): According to *GPA*, a mixture of **24** (200 mg, 0.19 mmol), **25** (151 mg, 0.19 mmol), TBTU (63 mg), HOBt (30 mg), and Et_3N (0.08 ml) in MeCN (10 ml) was stirred at r.t. for 2 d. The crude product was purified by CC (AcOEt/MeOH/hexane 7:1:1.5): 143 mg (41%) of **11b**. Pale yellow foam. IR: 3305v*s*, 2957*s*, 2872*m*, 1650v*s*, 1536v*s*, 1470*s*, 1412*s*, 1364*s*, 1287*w*, 1172*m*, 1098*w*, 877*w*, 754*w*, 701*w*. ^{1}H-NMR (600 MHz, CD_3OD): 7.3–7.1 (*m*, 20 arom. H); 4.5–4.3 (*m*, CH(α)(Pro), 2 CH(α)(Leu), CH(α)(Ser), CH(α)(Asn)); 4.27 (*t*, *J* = 8.0, CH(α)(Pro)); 4.20 (*t*, *J* = 8.5, CH(α)(Pro)); 4.11 (*dd*, *J* = 4.5, 8.7, CH(α)(Val)); 4.0–3.9 (*m*, CH(α)(Leuol)); 3.9–3.8 (*m*, 2 H of 3 CH_2(δ)(Pro)); 3.8–3.7 (*m*, CH_2(β)(Ser)); 3.65–3.4 (*m*, 3 H of 3 CH_2(δ)(Pro), CH_2O(Leuol)); 3.4–3.3 (*m*, 1 H of 3 CH_2(δ)(Pro)); 2.96 (*dd*, *J* = 14.9, 6.7, 1 H of CH_2(β)(Asn)); 2.77 (*dd*, *J* = 14.9, 6.2, 1 H of CH_2(β)(Asn)); 2.4–2.2 (*m*, 3 H of 3 CH_2(β)(Pro)); 2.15–2.0 (*m*, 1 H of 3 CH_2(β)(Pro), CH(β)(Val)); 2.0–1.5 (*m*, 3 CH_2(β)(Pro), 3 CH_2(γ)(Pro), 2 CH_2(β)(Leu), 2 CH(γ)(Leu), CH_2(β)(Leuol)); 1.55–1.4 (*m*, 10 Me(Aib)); 1.4–1.3 (*m*, CH(γ)(Leuol)); 1.22 (*s*, Me_3C); 1.0–0.8 (*m*, 2 Me(Val), 4 Me(Leu), 2 Me(Leuol)). ^{13}C-NMR (151 MHz, CD_3OD): 177.9, 175.8, 175.6, 175.6, 175.6, 175.2, 175.1, 174.9, 174.9, 174.5, 173.3, 173.1, 171.9 (13*s*, 15 C=O); 159.7 (*s*, O–C=O); 146.0 (*s*, 3 arom. C); 136.2 (*s*, 1 arom. C); 130.2, 129.0, 128.9, 128.8, 128.0, 127.9 (6*d*, 20 arom. CH); 71.8 (*s*, Me_3C); 66.2 (*d*, CH(α)(Pro)); 65.9 (*t*, CH_2O(Leuol), PhCH_2); 65.3, 64.4 (2*d*, 2 CH(α)(Pro)); 62.4 (*t*, CH_2(β)(Ser)); 61.7 (*d*, CH(α)(Val)); 58.0 (*d*, CH(α)(Ser)); 53.4, 53.2 (2*d*, 2 CH(α)(Leu), CH(α)(Asn)); 51.2 (*d*, CH(α)(Leuol)); 50.8, 50.3, 50.0 (3*t*, 3 CH_2(δ)(Pro)); 41.3, 41.0 (2*t*, 2 CH_2(β)(Leu)); 40.6 (*t*, CH_2(β)(Leuol)); 40.0 (*t*, CH_2(β)(Asn)); 31.9 (*d*, CH(β)(Val)); 30.4 (*t*, CH_2(β)(Pro)); 28.1 (*q*, Me_3C); 27.7 (*q*, 1 Me(Aib)); 26.8, 26.1 (2*t*, CH_2(β)(Pro)); 26.3, 26.2, 26.1 (3*t*, CH_2(γ)(Pro)); 24.4, 24.2, 24.1, 24.0, 23.9, 23.8, 23.7, 23.6 (8*q*, 9 Me(Aib)); 22.2, 21.6, 21.0, 20.2, 19.9 (5*q*, 2 Me(Val), 4 Me(Leu) 2 Me(Leuol)). Some signals could not be detected. ESI-MS (MeOH + NaI): 1757 (8, $[M - Me_3C + Na]^+$), 879 (100, $[M - Me_3C + Na + 1]^{2+}$).

3.4. *Synthesis of Z-Ala-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol* (**26**). *Z-Ala-Val-Aib-Pro-OMe* (**27**). According to *GPB*, Z-Ala-Val-OH (192 mg, 0.60 mmol) and **3a** (117 mg, 0.60 mmol) were dissolved in CH_2Cl_2 (10 ml), and the mixture was stirred at r.t. overnight. Evaporation of the solvent gave crude **27** as a white foam, which was used for the next reaction without purification.

Z-Ala-Val-Aib-Pro-OH (**28**). According to *GPC*, a mixture of **27** (308 mg, 0.59 mmol) and LiOH · H_2O (99 mg, 2.38 mmol) was stirred at r.t. overnight: 250 mg (83%) of **28**. Colorless crystals. M.p.: 79.5–80.0°. IR: 3296*s*, 3066*m*, 2970*s*, 1715v*s*, 1651v*s*, 1539*s*, 1469*m*, 1454*m*, 1418*s*, 1365*m*, 1342*m*, 1241*s*, 1181*m*, 1116*w*, 1071*w*, 1027*w*, 928*w*, 777*w*, 740*w*, 698*w*. ^{1}H-NMR (300 MHz): 7.4–7.3 (*m*, 5 arom. H); 6.93 (*s*, NH(Aib)); 6.78 (*d*, *J* = 7.3, NH(Val)); 5.51 (br. *s*, NH(Ala)); 5.17, 5.09 (*AB*, *J* = 12.4, PhCH_2); 4.58 (*t*, CH(α)(Val)); 4.25–4.1 (*m*, CH(α)(Ala), CH(α)(Pro)); 3.7–3.5 (*m*, CH_2(δ)(Pro), OH); 2.3–1.8 (*m*, CH_2(β,γ)(Pro), CH(β)(Val)); 1.51, 1.47 (2*s*, 2 Me(Aib)); 1.40 (*d*, *J* = 7.3, Me(Ala)); 0.92, 0.82 (2*d*, *J* = 6.8, 2 Me(Val)).

Z-Ala-Val-Aib-Pro-Aib-N(Me)Ph (**29**). According to *GPB*, a soln. of **28** (164 mg, 0.33 mmol) and **1a** (57 mg, 0.33 mmol) in CH_2Cl_2 (10 ml) was stirred at r.t. for 20 h: 220 mg (quant.) of **29**, which was used in the next step without purification. Colorless solid. ^{1}H-NMR (300 MHz): 7.65 (br. *s*, NH); 7.4–7.1 (*m*, 10 arom. H, NH(Aib)); 6.59 (*d*, *J* = 7.7, NH(Val)); 5.75 (*d*, *J* = 4, NH(Ala)); 5.19, 5.08 (*AB*, *J* = 12.4, PhCH_2); 4.55–4.5 (*m*,

CH(α)(Val)); 4.2–4.0 (*m*, CH(α)(Ala), CH(α)(Pro)); 3.55–3.3 (*m*, CH_2(δ)(Pro)); 3.36 (*s*, MeN); 2.35–1.7 (*m*, CH_2(β,γ)(Pro), CH(β)(Val)); 1.54, 1.50, 1.43, 1.41 (4*s*, 4 Me(Aib)); 1.40 (*d*, J = 7.3, Me(Ala)); 0.93, 0.83 (2*d*, J = 6.7, 2 Me(Val)). ^{13}C-NMR (75.5 MHz): 173.8, 173.0, 171.9, 171.4, 170.7 (5*s*, 5 C=O); 156.8 (*s*, O–C=O); 145.5, 136.1 (2*s*, 2 arom. C); 129.0, 128.7, 128.5, 128.4, 127.6, 127.3 (6*d*, 10 arom. CH); 67.1 (*t*, PhCH_2); 62.1, 58.2 (2*d*, CH(α)(Pro), CH(α)(Ala)); 57.2, 56.9 (2*s*, 2 C(α)(Aib)); 52.1 (*d*, CH(α)(Val)); 48.2 (*t*, CH_2(δ)(Pro)); 48.1 (*t*, CH_2(β)(Pro)); 40.1 (*q*, MeN); 40.0 (*t*, CH_2(β)(Asn)); 29.4 (*d*, CH(β)(Val)); 28.1 (*t*, CH_2(γ)(Pro)); 26.5, 25.7 (2*q*, 2 Me(Aib)); 25.5 (*q*, Me(Ala)); 24.0, 19.4 (2*q*, 2 Me(Aib)); 17.8, 17.2 (2*q*, Me(Val)). ESI-MS (MeOH + NaI): 701 ($[M + Na]^+$).

Z-Ala-Val-Aib-Pro-Aib-OH (**30**). According to *GPE*, **29** (134 mg, 0.20 mmol) was dissolved in THF (1.5 ml), 6N HCl (1.5 ml) was added at 0°, and the mixture was stirred at r.t. overnight. Unexpectedly, the reaction was not complete, and the ^{1}H-NMR spectrum showed the presence of a *ca.* 1:1 mixture of **29** and **30**. ESI-MS (MeOH + NaI): 701 (100, $[M$(**29**) + Na$]^+$), 612 (91, $[M$(**30**) + Na$]^+$). The separation of the mixture proved to be very difficult and, therefore, the mixture was used in the next coupling step.

Z-Ala-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leuol (**26**). According to *GPA*, the mixture of **29**/**30** (*ca.* 100 mg), H-Leu-Aib-Pro-Leuol (**16**) [6][28] (*ca.* 50 mg), TBTU (40 mg), HOBt (25 mg), and Et_3N (0.1 ml) were dissolved in MeCN (10 ml), and the mixture was stirred at r.t. for 1 d. After workup, the crude product was purified by CC (AcOEt/MeOH 9:1): 28 mg of **26**. Crystallization from EtOH/hexane gave single crystals suitable for an X-ray crystal-structure determination. M.p.: dec. above 134.5°. IR: 3300*s*, 2958*m*, 2872*w*, 1643*vs*, 1620*vs*, 1541*vs*, 1469*m*, 1412*m*, 1385*m*, 1342*m*, 1364*w*, 1296*w*, 1251*m*, 1193*w*, 1171*w*, 1072*w*, 1026*w*, 928*w*, 733*w*, 697*w*. ^{1}H-NMR (300 MHz): 7.75–7.7 (*m*, NH); 7.50 (br. *s*, NH); 7.4–7.2 (*m*, 5 arom. H, NH); 7.06 (*d*, J = 7.5, NH); 6.73 (br. *s*, NH); 5.22, 5.09 (*AB*, J = 12.6, PhCH_2); 4.4–4.0 (*m*, CH(α)(Val), 2 CH(α)(Pro), CH(α)(Ala, CH(α)(Leu), CH(α)(Leuol)); 3.79–3.4 (*m*, CH_2(δ)(Pro), CH_2O(Leuol)); 2.35–1.6 (*m*, 2 CH_2(β,γ)(Pro), CH_2(β)(Leu), CH_2(β)(Leuol)); 1.6–1.1 (*m*, 6 Me(Aib), Me(Ala), CH(γ)(Leu), CH(γ)(Leuol), CH(β)(Val)); 0.95–0.8 (*m*, 2 Me(Val), 2 Me(Leu), 2 Me(Leuol)). ^{13}C-NMR (75.5 MHz): 173.5, 173.4, 173.1, 172.6, 171.4 (5*s*, 8 C=O); 157.4 (*s*, O–C=O); 136.3 (*s*, 1 arom. C); 128.7, 128.2, 127.2 (3*d*, 5 arom. CH); 66.9, 65.3 (2*t*, PhCH_2, CH_2OH); 64.6 (*d*, CH(α)(Pro)); 63.6 (*d*, CH(α)(Leuol)); 58.3 (*d*, CH(α)(Pro)); 57.0, 56.6 (2*s*, 3 C(α)(Aib)); 52.9 (2*d*, CH(α)(Leu)); 51.9 (*d*, CH(α)(Val)); 49.8 (*d*, CH(α)(Ala)); 48.9 (*t*, 2 CH_2(δ)(Pro)); 40.1, 39.1 (2*t*, CH_2(β)(Leu), CH_2(β)(Leuol)); 29.6 (*d*, CH(β)(Val)); 29.1, 28.8 (2*t*, 2 CH_2(β)(Pro)); 27.2 (*q*, 1 Me); 26.3, 26.2 (2*t*, 2 CH_2(γ)(Pro)); 25.8 (*q*, Me); 24.9, 24.8 (2*d*, CH(γ)(Leu), CH(γ)(Leuol)); 23.9, 23.5, 23.2, 23.1, 20.7, 19.0, 17.4 (7*q*, 11 Me).

4. *Crystal-Structure Determination of* **17**, **23**, *and* **26** (see *Table 4* and *Figs. 1–5*)[7]). All measurements were made on a *Rigaku AFC5R* diffractometer mounted on a 12 kW rotating-anode generator. Graphite-monochromated MoK_α radiation (λ 0.71069 Å) was used for **17** and **23**, while graphite-monochromated CuK_α radiation (λ 1.54178 Å) was employed for **26**. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are given in *Table 4*, and views of the molecules and packing diagrams are shown in *Figs. 1–5*.

In the case of **17**, the structure was solved by direct methods using SnB [37], which revealed the positions of *ca.* 90% of the non-H atoms. The remaining non-H-atoms were located by using the *Fourier*-expansion routines of DIRDIF 92 [38]. The non-H-atoms were refined anisotropically. All of the NH and OH H-atoms were placed in the positions indicated by a difference-electron-density map, and their positions were allowed to refine together with individual isotropic temperature factors. All remaining H-atoms were fixed in geometrically calculated positions, and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom. Refinement of the structure was carried out on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was not applied.

In the case of **23**, the structure was solved by direct methods using SHELXS86 [39], which revealed the positions of all non-H-atoms. The crystal lattice contains large regions filled with solvent molecules, which appear to be disordered, diffuse, and only partially occupy their sites. It was not possible to adequately model their contribution to the overall structure. An analysis of the residual electron-density peaks suggests that one or more partially occupied sites for CH_2Cl_2 molecules and additional solvent, possibly EtOH and/or H_2O are

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7) CCDC–120342–120344 contain the supplementary crystallographic data for this paper. 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, U.K. (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

present. The solvent molecules occupy a total volume of 1429.5 Å^3 per unit cell, divided into two symmetry-related regions. The best R factor obtained by attempting to model the solvent was *ca.* 0.10. Therefore, the SQUEEZE routine [40] of the PLATON program [41] was used. This procedure, which allows the disordered solvent molecules to be omitted entirely from the subsequent refinement model, significantly improved the agreement indices and the accuracy of the geometric parameters of the peptide molecule, and there were no significant peaks of residual electron density to be found in the voids of the structure. The electron count in the solvent region was calculated to be 96 e per unit cell. This corresponds to the presence of approximately one CH_2Cl_2 and two EtOH molecules (94 e), or one CH_2Cl_2, one EtOH, and three H_2O molecules (98 e) per unit cell. Other combinations are possible if one considers that these molecules appear to only partially occupy their sites. For the purposes of the calculation of the formula weight, density, $F(000)$, and the linear absorption coefficient, it was assumed that the ratio of peptide/CH_2Cl_2/EtOH is 4:1:2. The five-membered ring of the peptide molecule is disordered in that C(35) equally occupies two sites corresponding to alternate directions for the flap of an envelope conformation. This disorder was modelled successfully. Enlarged atomic-displacement ellipsoids for the i-Pr group suggest that there may also be some disorder in this region, but a disordered model

Table 4. *Crystallographic Data of* **17**, **23**, *and* **26**

	17	**26**	**23**
Crystallized from	AcOEt/MeOH	EtOH/hexane	CH_2Cl_2/hexane/EtOH
Empirical formula	$C_{47}H_{76}N_8O_{10}$	$C_{50}H_{81}N_9O_{11}$	$C_{58}H_{75}N_7O_{11}\cdot 0.25\ CH_2Cl_2\cdot 0.5\ C_2H_6O$
Formula weight [g mol^{-1}]	913.16	984.24	1090.53
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.28\times 0.33\times 0.50$	$0.15\times 0.25\times 0.35$	$0.32\times 0.45\times 0.50$
Temperature [K]	173(1)	297(1)	190(1)
Crystal system	orthorhombic	monoclinic	orthorhombic
Space group	$P2_12_12$	$P2_1$	$P2_12_12$
Z	4	2	4
Reflections for cell determination	25	23	25
2θ Range for cell determination [°]	21–25	84–93	23–28
Unit-cell parameters a [Å]	21.861(3)	15.652(1)	21.410(5)
b [Å]	29.791(7)	9.963(1)	26.392 (5)
c [Å]	8.325(6)	19.693(1)	11.954 (7)
β [°]	90	112.781(4)	90
V [Å^3]	5421(4)	2831.5(4)	6755(4)
D_x [g cm^{-3}]	1.119	1.154	1.072
μ [mm^{-1}]	0.0789	0.669	0.0935
Scan type	ω	$\omega/2\theta$	ω
$2\theta_{(max)}$ [°]	55	121	55
Total reflections measured	8118	4670	9637
Symmetry-independent reflections	7930	4479	9454
Reflections with $I>2\sigma(I)$	5356	3557	5368
Reflections used in refinement	5356	4479	9448
Parameters refined	614	645	699
Restraints	0	854	4
R [on F; $I>2\sigma(I)$ reflections]	0.0454	0.0678	0.0661
wR [on F; $I>2\sigma(I)$ reflections]	0.0365	–	–
wR [on F^2; all indept. reflections]	–	0.2046	0.1804
Weighting parameter [p][a])	0.005	–	–
Weighting parameters [a; b][b])	–	0.153; 0.19	0.1011; 0
Goodness-of-fit	1.557	1.051	0.932
Final Δ_{max}/σ	0.001	0.005	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.19; −0.20	0.90; −0.41	0.27; −0.23

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

could not be developed successfully for this group. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model, where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ for the Me groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. Six reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. A correction for secondary extinction was not applied.

For **26**, the structure was also solved by direct methods with SHELXS86 [39], which revealed the positions of most non-H atoms. All remaining non-H atoms were located in a subsequent difference-electron-density map. Although all of the non-H atoms could be located, it was very difficult to satisfactorily refine some of the atoms at each end of the peptide chain, in particular those of the Ph group and the initial chain atoms up to C(5). Disorder might be responsible for these problems, but no disordered model could be developed successfully. It seems likely that the electron density is smeared at the ends of the peptide chain, possibly due to the flexibility of these regions of the molecule. The non-H-atoms were refined anisotropically, although the atoms at the ends of the chain and many of the Me groups produced extremely large and unrealistic displacement parameters. Pseudo-isotropic and similarity restraints were applied to the atomic displacement parameters of all anisotropically refined atoms. A bond-length restraint was also applied to the O(1)–C(2) bond to prevent the bond from becoming excessively long. The H-atoms were defined analogously to **23**, and the orientation of the hydroxy O–H vector was positioned to chose the direction most likely to result in a H-bond. Refinement of the structure was carried out on F^2 analogously to **23**. A correction for secondary extinction was applied.

Neutral atom scattering factors for non-H atoms were taken from [42a], and the scattering factors for H-atoms were taken from [43]. Anomalous dispersion effects were included in F_c [44]; the values for f' and f'' were those of [42b]. Structure refinement was performed with the TEXSAN crystallographic software package [45] for **17**, and SHELXL97 [46] for both **23** and **26**.

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