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The 'Azirine/Oxazolone Method' in Peptaibol Synthesis; Preparation of a Derivative of *Trichotoxin A-50 (G)*

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The synthesis of a mixture of epimeric derivatives of the peptaibol *Trichotoxin A-50 (G)* is described. The 'azirine/oxazolone method' has been used as a superior method for the introduction of the Aib as well as the Iva units into the peptide chain. In this protocol, 2,2-disubstituted 2*H*-azirin-3-amines are the synthons for 2,2-disubstituted glycines, which undergo the coupling with N-protected amino or peptide acids in high yield and without any need of coupling reagents. The problem of the instability of the amide function of the Gln side chain under the conditions of the acid catalyzed hydrolysis of Z-Gln-$(Aib)_n$-N(Me)Ph has been solved by using an appropriate protecting group for the amide function of the Gln side chain, *e.g.*, the triphenylmethyl (trityl) group. The structures of two intermediate peptides, *i.e.*, segment (1–5) and segment (10–13), have been establisheded by X-ray crystallography.

1. Introduction. – Peptaibols are linear, amphiphilic polypeptides of fungal origin with 11–20 amino acids [1]. In addition to proteinogenic amino acids, they contain up to 50% 2-aminoisobutyric acid (Aib) [2] and sometimes isovaline (Iva, 2-amino-2-methylbutyric acid) [3][4]. These α,α-disubstituted amino acids (2,2-disubstituted glycines) are well known for their ability to induce helical folding of the peptide chain [5–7]. This effect still dominates when amino acids such as proline (Pro) or hydroxyproline (Hyp), which often are called 'helix-breakers', are present [8]. Therefore, peptaibols exhibit an overall helical structure. Further characteristics are the acetylated N-terminus and the presence of an α-amino alcohol such as valinol (Valol), leucinol (Leuol) or phenylalaninol (Pheol) as the C-terminus [9][10]. Peptaibols are 'membrane-active' polypeptide antibiotics, which, after aggregation to bundles, form 'ion-channels' through biological membranes [11][12].

A well-known class of the peptaibols is the *Trichotoxin* family, which was isolated from the mycel of the fungus *Trichoderma viride NRRL 5242* [13]. The *Trichotoxin A-50* mixture (Tab. 1) was obtained after 'counter-current distribution' (CCD) [13a][14], the components were separated by HPLC, and their sequences could be determined by means of FAB- and FD-MS [15]. Recent work was devoted to the mechanism of formation of *Trichotoxin* channels in which the presence of octameric or hexameric bundles was proposed [16][17].

Table 1. *Sequences of* Trichotoxins A-50 [15]

Another challenge is the synthesis of peptaibols as analytically pure compounds, which can be used for the investigation of structure-activity relationships (SAR) with respect to bactericide and fungicide properties [18]. The introduction of Aib into a peptide chain had been a difficult task [19], but these difficulties have been surmounted by the development of

highly reactive coupling reagents and activated amino acids [20][21]. For example, several segments of members of the *Trichotoxin A-50* family have been synthesized, and X-ray crystal-structure determinations of Z-Aib-Gly-Aib-Leu-Aib-O^{t}Bu [22a], Z-Aib-Aib-Aib-Ala-Ala-Aib-O^{t}Bu [22b], Z-Aib-Gly-Aib-OH [22c], and Ac-Aib-Gly-Aib-OH [22c] were carried out.

The total synthesis of *Trichotoxin A-50 (E)* was reported by *Brückner* on the occasion of the '19th European Peptide Symposium' [23]. They used the Z/O^{t}Bu strategy and the water-soluble *N*-ethyl-*N*-[3-(dimethylamino)propyl]carbodiimide (EDC) as the coupling reagent. The preparation of the segment Z-Leu-Aib-Gln-Aib-Aib-Aib-Ala-O^{t}Bu (segment 4–10) was mentioned as being difficult, but the coupling reactions of the main segments to give the octadecapeptide occurred in very good yield (*Scheme 1*).

Scheme 1

Almost 20 years ago, we elaborated a different method for the introduction of hindered 2,2-disubstituted glycines into peptide chains, *i.e.*, the 'azirine/oxazolone method' [24] (and refs. cited therein). The key reaction steps are the reaction of an amino or peptide acid **1** with a 2,2-disubstituted 2*H*-azirin-3-amine **2** to yield the extended peptide **3** (*Scheme 2*). Selective hydrolysis of the C-terminal *N*,*N*-disubstituted amide bond leads to the extended peptide acid **4**, which can be coupled with a second azirine **2** to give **5** [25]. Alternatively, **4** can be used in conventional coupling reactions with an amino component, *e.g.* **7**, to give peptide **8**. The activated acid derivative is the intermediate 5(4*H*)-oxazolone **6**, which is easily formed because of the disubstitution at C(2) of the C-terminal amino acid in **4** (*Thorpe-Ingold* or *gem*-dialkyl effect [26]). The formation of the same oxazolone **6** is responsible for the selectivity of the hydrolysis of **3** to give **4** [25d].

Scheme 2

The use of the 'azirine/oxazolone method' has been demonstrated by its application to the synthesis of peptaibols or segments thereof, *e.g.*, the C-terminal nonapeptide of *Alamethicin F30* [27], segment (14–18) of *Trichotoxin A50* [28], a derivative of *Trichovirin I 1B* [29], segment (6–16) of *Zervamicin II-2* [30], and *Hypomurocin A1* [31].

Very recently, the 'azirine/oxazolone method' has been adapted to solid phase peptide synthesis [32]. This method was applied successfully to the preparation of a derivative of *Trichovirin I 1B* [32c].

In the present paper, we describe the synthesis of a mixture of epimeric derivatives of the peptaibol antibiotic *Trichotoxin A-50 (G)* (**9**) by using the 'azirine/oxazolone method'[2]).

2. Results and Discussion. – An overview of the synthesis of **9** is shown in *Scheme 3*. The peptaibol was built up from the main segments Z-Aib-Gly-Aib-Leu-Aib-OH (**10**, segment (1–5)), Z-Gln(Trt)-Aib-Aib-Aib-OH (**11a**, segment (6–9)), H-Ala-Ala-Aib-Pro-O^{t}Bu (**12**, segment (10–13)), and H-Leu-Aib-Iva-Gln-Valol (**13**, segment (14–18)) by using DCC, HOBt, and CSA or TBTU, HOBt[3]) as the coupling reagents. Our intention was to use the 'azirine/oxazolone method' for the introduction of the Aib units in positions 3,5,7,8,9,12, and 15 as well as Iva in position 16. The building blocks for the two amino acids were the 2*H*-azirin-3-amines **2a** [34] and **2b** [35].

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[2]) For a preliminary communication, see [33].

[3]) Abbreviations: *N,N'*-dicyclohexylcarbodiimid (DCC); 1-hydroxybenzotriazole (HOBt); camphor-10-sulfonic acid (CSA); *O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU); triphenylmethyl (Trt); *N*-methylmorpholine (NMM).

Scheme 3, *Formulae* **2a** *and* **2b**

2.1. Synthesis of Z-Aib-Gly-Aib-Leu-Aib-OH (**10**). – The preparation of segment (1–5) was carried out according to the general concept depicted in *Scheme 2*. Coupling of Z-Gly-OH with the Aib-synthon **2a** to give **14** and subsequent hydrolysis of the terminal amide group gave dipeptide **15** in 89% yield (*Scheme 4*). In an analogous manner, dipeptide **16** was synthesized from Z-Leu-OH and **2a**; hydrogenolysis led to the N-deprotected **17** in 93% yield. Treatment of a mixture of **15** and **17** with DCC, HOBt, and $ZnCl_2$ [25b] yielded the corresponding tetrapeptide, which was deprotected at the N-terminus to give **18** (79%). The coupling with Z-Aib-OH and subsequent selective hydrolysis gave the pentapeptide **10** in 76% yield. The analogous preparation of Ac-Aib-Gly-Aib-Leu-Aib-OH from **18** and Ac-Aib-OH proved to be less satisfactory as the product was obtained in only 12% yield. The main difficulty is the lability of the Ac-Aib terminus under the acidic conditions of the hydrolysis[4]).

Scheme 4

The conformation of **10** in the solid state was established by X-ray crystallography (*Fig. 1*). The relevant torsion angles ϕ and ψ and the H-bonding parameters are collected in *Table 2*. The OH and all NH groups of the molecule act as H-bond donors, while each of the carbonyl O-atoms acts as single H-bond acceptor. The OH group, plus N(4)–H and N(5)–H form intramolecular H-bonds with carbonyl O-atoms that are, unusually, not always the same number of atoms further along the peptide backbone. These three interactions form loops that can be described by graph set motifs [38] of S(16), S(13), and S(10), respectively. Two of the

[4]) This assumption has been proven by a series of control experiments with different N-acylated derivatives of 2,2-disubsituted glycines [36].

intermolecular interactions link the molecules into extended chains which run parallel to the [010] direction and each interaction can be described by a graph set motif of C(11). The third intermolecular interaction links the molecules into extended chains which run parallel to the [100] direction and can also be described by a graph set motif of C(11). The combination of both interactions links the molecules into two-dimensional networks, which lie parallel to (001).

Fig. 1. *ORTEP-Plot* [37] *of the molecular structure of* **10** (arbitrary numbering of atoms, 50% probability ellipsoids, H-atoms bonded to C-atoms have been omitted for clarity)

Table 2. *Torsion Angles and H-Bonding Parameters in the Crystal-Structure of* **10**

The torsion angles of Aib(1), Gly(2), and Aib(3) as well as the intramolecular H-bond N(4)–H···O(2) between NH of Leu(4) and the urethane C=O are in accordance with a right-handed α-helical structure, whereas the torsion angles of Aib(5) correspond with a left-handed α-helix (see *Table 2*). A similar conformation for Z-Aib-Gly-Aib-Leu-Aib-O^{t}Bu has been described by *Gessmann et al.* [22a].

2.2. Synthesis of Z-Gln-Aib-Aib-Aib-Ala-Ala-Aib-Pro-OH (**19**). – The octapeptide **19** (segment (6–13)) was built up by condensation of the two tetrapeptides **11a** and **12**, *i.e.*, segments (6–9) and (10–13). The latter was prepared by the reaction of Z-Ala-Ala-OH with the Aib-synthon **2a**, subsequent selective hydrolysis of the terminal amide group to give **20**, coupling with H-Pro-O^{t}Bu by using DCC and catalytic amounts of CSA to yield **21**, and

finally deprotection of the amino group (*Scheme 5*). The total yield over all four reactions was 80.3%[5]).

Scheme 5

The crystal-structure of **21** was also determined by X-ray crystallography (*Fig. 2*). The central amide group of the molecule does not partake in any H-bonds. Each of the other two amide groups forms an intermolecular H-bond with an amide O-atom of a neighboring molecule. The interaction involving N(1)–H links the molecules into extended chains which run parallel to the [010] direction and can be described by the graph set motif [38] of C(5). The interaction involving N(3)–H also links the molecules into extended chains with the C(5) motif and which also run parallel to the [010] direction. The combination of both interactions links the molecules into two-dimensional networks, which lie parallel to (100). There are no 'cross-chain' H-bonds, which are typical for helical peptide conformations. The torsion angles of Ala(1) are close to those of a 3_{10}-helical structure, and ϕ and ψ of Aib(3) are almost ideal for a left-handed α-helix. On the other hand, the torsion angles of Ala(2) correspond with those of an antiparallel β-sheet (see *e.g.* [40]).

Fig. 2. *ORTEP-Plot* [37] *of the molecular structure of* **21** (arbitrary numbering of atoms, 30% probability ellipsoids, H-atoms bonded to C-atoms have been omitted for clarity)

[5]) In the meantime we have shown that the direct introduction of the Aib-Pro sequence by azirine coupling with the dipeptide synthon **22** is a highly recommendable method [29–31][32c][39].

Formula **22**

Table 3. *Torsion Angles and H-Bonding Parameters in the Crystal-Structure of* **21**

The 'azirine/oxazolone method' is ideally suited for the synthesis of poly-Aib peptides [25c][41–43]. Therefore, the plan was to carry out the preparation of the tetrapeptide **11a** straightforwardly by repeated coupling of Z-Gln-OH with azirine **2a** and hydrolysis. A large series of preliminary experiments in connection with the syntheses of Z-Asn-Xaa-Xbb-OH (Xaa or Xbb = 2,2-disubstituted glycines) and the corresponding Gln derivatives showed that under the conditions of the hydrolysis of the terminal *N*-methyl-*N*-phenyl amide (see *Scheme 2*), the side-chain amide function of Asn and Gln was also hydrolyzed partially [36]. Therefore, a suitably protected Gln derivative had to be used. In control experiments, it was demonstrated that the bis(2,4-dimethoxybenzyl) $(DMB)_2$ [44], the 4,4'-dimethoxybenzhydryl (4,4'dimethoxydityl, Dod) [45], and the triphenylmethyl (trityl, Trt) [46][47] group are appropriate protecting groups, as they are relatively stable in 3N HCl as well as during catalytic hydrogenation, but can be removed by treatment with CF_3COOH (TFA) [36][6])[7]). The results of this study are collected in *Table 4*. The repeated coupling of the Aib-synthon **2a** with Z-Gln(X) derivatives **23a**–**23c**, as well as the selective hydrolysis of the Aib-containing

[6]) In the case of the DMB and Dod groups, addition of anisol is recommended, which intercepts the generated cation and, therefore, accelerates the reaction [45].

[7]) The deprotection of the dipeptides Z-Gln(X)-Aib-OMe by using the described conditions, *i.e.*, TFA at room temperature in the case of X = Trt, and TFA and 5–10% anisole at room temperature for X = $(DMB)_2$ and Dod, gave Z-Gln-Aib-OMe in 91, 64, and 75% yield, respectively [36].

peptide amides, occurred under mild conditions and with high yield; the total yield of the tetrapeptide acids **11a**, **11b**, and **11c** reach 62, 64, and 73%, respectively[8]).

Table 4. *Yields of the Coupling of Azirine* **2a** *and the Hydrolysis of the Terminal Amide Group of Z-Gln(X)-(Aib)*$_n$*-N(Me)Ph Derivatives*

The two tetrapeptide segments **11a** and **12** were coupled with DCC, HOBt, and CSA in DMF; the fully protected octapeptide **24** was obtained in 97% yield (*Scheme 6*). Selective deprotection of the N-terminus to give **25** was achieved by hydrogenolysis, and treatment of **24** with TFA at 0° removed the protecting groups of the C-terminus and of the Gln side chain simultaneously to yield **19**. The structures of the products were established on the basis of their ^{1}H- and ^{13}C-NMR and mass spectra. For example, the ESI- and FAB-MS of **19** are shown in *Fig. 3*.

Scheme 6

Fig. 3. *Mass-Spectra of the Octapeptide* **19**; a) *ESI-MS and* b) *FAB-MS*

[8]) The deprotection of the NH_2 group by hydrogenation (H_2, Pd/C) of the various derivatives listed in *Table 4* was achieved in 74-100% yield [36]. Furthermore, the transformation of some examples of Z-Gln(X)-(Aib)$_n$-N(Me)Ph (*Table 4*) into the corresponding methyl esters by treatment with HCl gas in MeOH was carried out at 25–65°, which led to the product in 70–96% yield [36].

2.3. *Synthesis of H-Leu-Aib-*D,L*-Iva-Gln-Valol* (**13**). – This segment was prepared as a mixture of the D- and L-Iva epimers (*Scheme 7*). Subsequent coupling of Z-Leu-OH with the Aib and Iva synthons **2a** and **2b** under standard conditions gave tripeptide **27**, which was then coupled with the terminal dipeptide **28** by using TBTU/HOBt as the coupling reagent.

Scheme 7

In preliminary studies, it has been shown that the two diastereoisomers of **27** can be separated by means of prep. HPLC (*Nucleosil 100-7*, hexane/CH_2Cl_2/EtOH), but only *ca.* 10% of the (+)-epimer could be isolated in pure form. The second epimer was obtained as a *ca.* 1:8 mixture of both isomers[9])[10]).

[9]) For this reason, we have prepared 2*H*-azirin-3-amines **2c**–**2f**, which could be used as synthons for enantiomerically pure Iva. Whereas the diastereoisomers of **2c** [36] and **2d** [48] could not be separated on a preparative scale, the optically pure diastereoisomers of **2e** and **2f** were obtained after chromatographic separation (CC). Furthermore, it has been shown that they are suitable for use in the 'azirine/oxazolone method' [49][50]. For example, the two epimers Z-Leu-Aib-D-Iva-Gln-Valol and Z-Leu-Aib-L-Iva-Gln-Valol have been synthesized [49][51].

Formulae **2c**–**2f**

[10]) *Brückner et al.* showed by means of GC methods that the two Iva units of the peptaibol '*Antiamoebin I*' have the (*R*)-configuration (*i.e.*, D-Iva) [52] (for the crystal structure of Ac-Aib-Aib-D-Iva-OMe·H_2O, see [53]).

2.4. *Coupling of the Segments* **10**, **19**, *and* **13**. – The synthesis of the *Trichotoxin A-50 (G)* derivative **9** was achieved – although in only moderate yield – by coupling of the segments (1–5), (6–13), and (14–18) under standard conditions (*Scheme 8*). First, the C-deprotected octapeptide **19** and the C-terminal pentapeptide **13** (as a mixture of two epimers) were treated with DCC, HOBt, and CSA to give the crystalline peptide **29** as a mixture of two diastereoisomers in 39% yield. The analogous condensation with TBTU/HOBt was less satisfactory and gave the same product **29** in only 28% yield. Deprotection of **29** by hydrogenolysis and subsequent coupling with the N-terminal pentapeptide **10** by using TBTU/HOBt yielded the final product **9** as a mixture of two epimers (37%). The structure of the latter was confirmed by its ESI-MS.

Scheme 8

As an alternative approach, the N-terminal pentapeptide **10** was coupled with the N-deprotected octapeptide **25** by using the TBTU/HOBt methodology to give the protected tridecapeptide Z-Aib-Gly-Aib-Leu-Aib-Gln(Trt)-$(Aib)_3$-Ala-Ala-Aib-Pro-O^{t}Bu (**30**) in 51% yield. Simultaneous deprotection of the C-terminus and the side chain of Gln was achieved in TFA at 0° in quantitative yield. The resulting segment Z-Aib-Gly-Aib-Leu-Aib-Gln-$(Aib)_3$-Ala-Ala-Aib-Pro-OH (**31**) was characterized by ESI and FAB-MS (*Fig. 4*) and ^{1}H-NMR spectroscopy. In the ESI-MS, a minor peak at *m/z* 1211 indicates the presence of small amounts of Z-Aib-Gly-Aib-Leu-Aib-Gln-$(Aib)_3$-Ala-Ala-Aib-OH, which have been formed by the treatment with TFA, *i.e.*, the acid labile Aib-Pro bond was not perfectly stable under these conditions[11]).

[11]) The coupling with the C-terminal pentapeptide **13** to give **9** has not been carried out.

Fig. 4. *Mass-Spectra of the Tridecapeptides* **30** *and* **31**; a) *ESI-MS of* **30**, b) *ESI-MS of* **31**, *and* c) *FAB-MS of* **31**

3. Conclusion. – The presented synthesis of a derivative of the peptaibol *Trichotoxin A-50 (G)* shows that the 'azirine/oxazolone method' is an attractive alternative for the preparation of Aib-containing peptides, *e.g.*, naturally occurring peptaibols and non-natural analogues. The introduction of Aib, Iva, and other 2,2-disubstituted glycines *via* the coupling reaction of N-protected amino or peptide acids with 2*H*-azirin-3-amines and subsequent selective hydrolysis are very convenient and efficient reactions. Most likely, the modest yields of the segment couplings in the presented synthesis can be improved significantly by using a different disconnection of the peptaibol, as shown in the synthesis of *Trichotoxin A-50 (E)* by *Brückner* [23].

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Experimental part

1. *General.* See [31][43a]. The starting materials 2,2-dimethyl-2*H*-azirin-3-amine (**2a**) and 2-ethyl-2-methyl-2*H*-azirin-3-amine (**2b**) were prepared according to [34c][35] from 2,*N*-dimethyl-*N*-phenylpropanamide and 2,*N*-dimethyl-*N*-phenylbutanamide by treatment with

$COCl_2$ and NaN_3 in 72 and 63% yields, respectively. The amino alcohol Valol was prepared by reduction of methyl L-valinate hydrochloride with $LiAlH_4$ (83%, $[\alpha]_D$ = +16.2 (c = 0.370, EtOH) [35]. Amino acids were purchased by *Novabiochem* and *Bachem* and are all L-configured, other reagents and solvents by *Aldrich*, *Fluka* and *Merck*. M.p. were measured on a *Mettler-FP-5* apparatus, uncorrected. $[\alpha]_D$-Values were determined at 21–23° on a *Zeiss-LEP-A2* polarimeter. IR Spectra were recorded on a *Perkin-Elmer-781* spectrometer, in KBr. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a *Bruker AC-300*, *Bruker AM-400*, and *Bruker AMX-600* spectrometer at 300, 400, and 600 (^{1}H) and 75.5, 100.8, and 151.2 MHz (^{13}C), respectively, in CD_3OD if not otherwise stated. ESI-MS were measured on a *Finnigan TSQ-700* instrument, FAB-MS on a *Finnigan MAT-90*, and CI-MS (with NH_3 or isobutane) on a *Finnigan MAT-90* or *SSQ-700* instrument. *Abbreviations*. Aib: 2-aminoisobutyric acid (2-methylalanin); CME-CDI: *N*-cyclohexyl-*N'*-[2-(4-methylmorpholin-4-ylium)ethyl]carbodiimide 4-toluolsulfonate; CSA: camphor-10-sulfonic acid; DCC: *N*,*N'*-dicyclohexylcarbodiimide; DIEA: (ethyl)(diisopropyl)amine; HOBt: 1-hydroxybenzotriazole; NMM: *N*-methylmorpholine; O^{t}Bu: *tert*-butyloxy; TBTU: *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate; TEA: triethylamine; TFA: trifluoroacetic acid; Trt: triphenylmethyl; Valol, L-valinol ((*S*)-2-amino-3-methyl-1-butanol); Z: (benzyloxy)carbonyl.

*General Procedure A (GP A, Coupling with 2*H*-Azirin-3-amines).* To a soln. of an N-protected amino acid or N-protected peptide (5 mmol) in abs. CH_2Cl_2 (30 ml) at 0°, *ca.* 1.2 equiv. of the corresponding 2*H*-azirin-3-amine in THF or CH_2Cl_2 were added, and the mixture was stirred at r.t. for several h (Ar atmosphere). After completion of the reaction, the solvent was evaporated and the product was purified by column chromatography (CC), prep. layer chromatography (PLC), or crystallization.

General Procedure B (GP B, Selective Hydrolysis of Peptide N-*Methyl*-N-*phenylamides).* A soln. of the peptide amide (5 mmol) in 3N HCl (THF/H_2O (1:1), 50 ml) was stirred at r.t. for 1–40 h. Then, aq. 2N HCl was added, and the mixture was extracted with CH_2Cl_2 (3x). The org. layers were combined, dried (Na_2SO_4), and evaporated. The product was purified by crystallization.

General Procedure C (GP C, Hydrogenolytic Deprotection). The N-protected peptide (Z-peptide) was dissolved in MeOH, and 10% Pd/C was added to the soln. The mixture was stirred at r.t. under an H_2 atmosphere overnight. After completion of the reaction (TLC), the soln. was filtered through a *Celite* pad and the solvent was evaporated. The product was dried in high vacuum (*i.v.*).

General Procedure D (GP D, Peptide Coupling). To a soln. of an N-protected amino acid or N-protected peptide in DMF at 0°, 1 equiv. of DCC, 1.1 equiv. of HOBt, *ca.* 0.1 equiv. of CSA or 2 equiv. of $ZnCl_2$, and 1.1 equiv. of a C-protected amino acid or C-protected peptide were added. The mixture was stirred overnight at r.t. (N_2 atmosphere), *N*,*N*′-dicyclohexylurea was removed by filtration through a *Celite* pad, and DMF was evaporated. The residue was dissolved in CH_2Cl_2, washed with 2N HCl (2x) and 2N NaOH soln., and dried (Na_2SO_4). The solvent was evaporated and the product was purified by CC or PLC.

General Procedure E (GP E, Deprotection with TFA). The N-protected peptide was dissolved in TFA and the soln. was stirred at 0°–r.t. for 1–8 h. Then, the TFA was evaporated, CH_2Cl_2 was added to the residue, and the procedure was repeated. The crude product was purified by CC or PLC or by crystallization after addition of Et_2O or hexane.

2. *Preparation of the Pentapeptide Z-Aib-Gly-Aib-Leu-Aib-OH* (**10**). 2.1. *Z-Gly-Aib-OH* (**15**). See [43a].

2.2. *Z-Leu-Aib-N(Me)Ph* (**16**). According to *GP A*, Z-Leu-OH (3.03 g, 11.42 mmol) in Et_2O (50 ml) was treated with **2a** (2.20 g, 12.63 mmol) for 13 h: 4.99 g (99%) of **16**. Colorless

crystals. M.p. 135.5–135.7° (Et_2O/pentane). $[\alpha]_D$ = –19.6 (c = 1.01, EtOH). IR ($CHCl_3$): 3430*w*, 3350*w*, 3070*w*, 3010*m*, 2960*m*, 1715*m*, 1680*m*, 1635*m*, 1595*m*, 1510*s*, 1495*s*, 1420*m*, 1405*m*, 1390*m*, 1370*m*, 1240*m*, 1170*m*, 1120*m*, 1055*m*, 1030*s*, 705*m*. ^{1}H-NMR (CD_3OD): 7.56–7.13 (*m*, 10 arom. H); 5.15, 5.06 (*AB*, *J* = 12.5, PhC*H*$_2$O); 4.10–3.90 (*m*, CH(2)(Leu)); 3.20 (*s*, MeN); 1.80–1.30 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.43 (*s*, Me_2C); 0.92, 0.90 (2*d*, *J* = 6.4, 2 Me(Leu)). ^{13}C-NMR (CD_3OD): 175.0, 174.1 (2*s*, 2 CO(amide)); 158.1 (*s*, CO(urethane)); 146.2, 138.1 (2*s*, 2 arom. C); 130.4, 130.0, 129.5, 129.3, 129.2, 129.0, 128.8, 128.6, 128.5, 128.3 (10*d*, 10 arom. CH); 67.6 (*t*, PhC*H*$_2$O); 58.3 (*s*, Me_2*C*); 54.5 (*d*, C(2)(Leu)); 42.5 (*t*, C(3)(Leu)); 41.3 (*q*, MeN); 26.9, 25.8 (2*q*, *Me*$_2$C); 26.6 (*d*, C(4)(Leu)); 23.6, 21.9 (2*q*, 2 Me(Leu)). CI-MS: 440 (100, $[M+1]^+$). Anal. calc. for $C_{25}H_{33}N_3O_4$ (439.56): C 68.31, H 7.57, N 9.56; found: C 68.13, H 7.70, N 9.35.

2.3. *H-Leu-Aib-N(Me)Ph* (**17**). According to *GP C*, H_2 was bubbled through a mixture of **16** (1.01 g, 2.29 mmol) and Pd/C (104 mg) in MeOH (23 ml) for 3 h: 663 mg (94%) of **17**. Colorless crystals. M.p. 111.7–112.6° (CH_2Cl_2/hexane). $[\alpha]_D$ = 2.4 (c = 0.96, EtOH). IR ($CHCl_3$): 3400*m*, 3325*m*, 3290*m*, 3030*w*, 2990*w*, 2950*m*, 2930*m*, 2870*m*, 1660*s*, 1635*s*, 1600*m*, 1510*m*, 1495*m*, 1470*m*, 1450*m*, 1440*m*, 1395*m*, 1385*m*, 1375*m*, 1090*m*, 770*m*, 710*m*. ^{1}H-NMR (CD_3OD): 7.52–7.20 (*m*, 5 arom. H); 3.26 (*s*, MeN); 3.02 (br. *s*, CH(2)(Leu)); 1.84–1.56, 1.44–1.12 (2*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.48 (*s*, Me_2C); 0.93, 0.89 (2*d*, *J* = 6.5, 2 Me(Leu)). ^{13}C-NMR (CD_3OD): 177.3, 175.1 (2*s*, 2 CO(amide)); 146.1 (*s*, 1 arom. C); 130.5, 128.8, 128.5 (3*d*, 5 arom. CH); 58.3 (*s*, Me_2*C*); 54.2 (*d*, C(2)(Leu)); 45.0 (*t*, C(3)(Leu)); 41.6 (*q*, MeN); 27.4, 27.1 (2*q*, *Me*$_2$C); 25.6 (*d*, C(4)(Leu)); 23.7, 22.1 (2*q*, 2 Me(Leu)). CI-MS: 306 (100, $[M+1]^+$). Anal. calc. for $C_{17}H_{27}N_3O_2$ (305.42): C 66.85, H 8.91, N 13.76; found: C 66.73, H 9.00, N 13.95.

2.4. *Z-Gly-Aib-Leu-Aib-N(Me)Ph*. According to *GP D*, a soln. of **15** (1.00 g, 3.40 mmol) and **17** (1.09 g, 3.58 mmol) in DMF (6 ml) was treated with DCC (702 mg, 3.40

mmol) and $ZnCl_2$ (924 mg, 6.78 mmol) for 18.5 h: 1.56 g (79%) of *Z-Gly-Aib-Leu-Aib-N(Me)Ph*. Colorless solid. M.p. 85.1–86.1°. $[\alpha]_D$ = 22.6 (c = 0.92, EtOH). IR ($CHCl_3$): 3420*w*, 3340*w*, 3000*m*, 2960*w*, 2940*w*, 2880*w*, 1670*s* (br), 1595*m*, 1510*m*, 1470*m*, 1455*m*, 1385*m*, 1365*m*, 1265*m*, 1170*w*, 1120*w*, 705*m*. ^{1}H-NMR (CD_3OD): 7.45–7.17 (*m*, 10 arom. H); 5.17, 5.04 (*AB*, *J* = 12.5, PhC*H*$_2$O); 4.36–4.20 (*m*, CH(2)(Leu)); 3.83, 3.65 (*AB*, *J* = 16.3, CH_2(Gly)); 3.29 (*s*, MeN); 1.84–1.55 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.52, 1.47, 1.42 (3*s*, 2 Me_2C); 0.96, 0.89 (2*d*, *J* = 6.5, 2 Me(Leu)). ^{13}C-NMR (CD_3OD): 176.7, 175.5, 174.2, 172.3 (4*s*, 4 CO(amide)); 159.4 (*s*, CO(urethane)); 146.8, 137.9 (2*s*, 2 arom. C); 130.4, 129.5, 129.1, 128.8, 128.3 (5*d*, 10 arom. CH); 67.9 (*t*, Ph*C*H$_2$O); 58.3, 58.0 (2*s*, 2 Me_2*C*); 53.3 (*d*, C(2)(Leu)); 45.5 (*t*, C(2)(Gly)); 41.2 (*q*, MeN); 40.8 (*t*, C(3)(Leu)); 26.9, 26.8 (2*q*, *Me*$_2$C); 26.1 (*d*, C(4)(Leu)); 24.3, 23.8, 21.2 (3*q*, *Me*$_2$C, 2 Me(Leu)). CI-MS: 475 (100, [*M*–Ph(Me)N]$^+$). Anal. calc. for $C_{31}H_{43}N_5O_6$ (581.72): C 64.01, H 7.45, N 12.04; found: C 64.00, H 7.59, N 11.82.

2.5. *H-Gly-Aib-Leu-Aib-N(Me)Ph* (**18**). According to *GP C*, a mixture of *Z-Gly-Aib-Leu-Aib-N(Me)Ph* (1.35 g, 2.32 mmol) and Pd/C (215 mg) in MeOH (20 ml) was treated with H_2 for 21.5 h: 1.04 g (quant.) of **18**. Colorless foam. M.p. 85.7–86.5°. $[\alpha]_D$ = –13.3 (c = 1.03, EtOH). IR ($CHCl_3$): 3420*w*, 3340*m*, 3005*m*, 2960*m*, 2870*w*, 1665*s*, 1590*m*, 1515*s*, 1495*s*, 1470*m*, 1455*m*, 1430*m*, 1390*m*, 1370*m*, 1270*m*, 1240*m*, 1190*m*, 1170*m*, 1120*m*, 705*m*. ^{1}H-NMR (CD_3OD): 7.45–7.16 (*m*, 5 arom. H); 4.22 (br. *s*, CH(2)(Leu)); 3.28 (*s*, MeN); 3.26 (*s*, CH_2(Gly)); 1.76–1.36 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.49, 1.47, 1.45 (3*s*, 2 Me_2C); 0.95, 0.90 (2*d*, *J* = 5.5, 2 Me(Leu)). ^{1}H-NMR ($CDCl_3$): 7.71 (*s*, NH); 7.48–7.20 (*m*, 5 arom. H); 7.04 (*s*, NH); 6.86 (*d*, *J* = 8.6, NH); 4.34–4.20 (*m*, CH(2)(Leu)); 3.31 (*s*, CH_2(Gly)); 3.26 (*s*, MeN); 1.85–1.40 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.53, 1.52, 1.47, 1.36 (4*s*, 2 Me_2C); 0.93, 0.90 (2*d*, *J* = 6.5, 2 Me(Leu)). ^{13}C-NMR (CD_3OD): 176.6, 175.4, 174.6, 174.0 (4*s*, 4 CO(amide)); 146.5 (*s*, 1 arom. C); 130.4, 128.4 (2*d*, 5 arom. CH); 58.5, 57.7 (2*s*, 2 Me_2*C*);

52.9 (*d*, C(2)(Leu)); 45.1 (*t*, C(2)(Gly)); 41.3 (*q*, MeN); 41.1 (*t*, C(3)(Leu)); 26.9, 26.5, 26.0 (3*q*, 2 *Me*$_2$C); 24.8 (*d*, C(4)(Leu)); 23.8, 21.5 (2*q*, 2 Me(Leu)). CI-MS: 448 (5, [*M*+1]$^+$), 341 (100, [*M*–Ph(Me)N]$^+$). Anal. calc. for $C_{23}H_{37}N_5O_4$ (447.58): C 61.72, H 8.33, N 15.65; found: C 61.72, H 8.29, N 15.43.

2.6. *Z-Aib-Gly-Aib-Leu-Aib-N(Me)Ph*. According to *GP D*, to a soln. of *Z-Aib-OH* (202 mg, 0.85 mmol) in DMF (1.5 ml) were added DCC (176 mg, 0.85 mmol), HOBt (129 mg, 0.96 mmol), CSA (12 mg), and **18** (437 mg, 0.98 mmol), and the mixture was stirred for 24.5 h: 478 mg (84%) of *Z-Aib-Gly-Aib-Leu-Aib-N(Me)Ph*. Colorless crystals. M.p. 193.8–194.7° (CH_2Cl_2/Et_2O/hexane). $[\alpha]_D$ = 19.1 (c = 0.92, EtOH). IR ($CHCl_3$): 3440*w*, 3320*m*, 3000*m*, 2960*w*, 2870*w*, 1710*m*, 1660*s*, 1590*w*, 1530*m*, 1500*m*, 1470*w*, 1455*w*, 1385*w*, 1365*w*, 1330*w*, 1265*m*, 1190*w*, 1170*w*, 1090*m*, 700*w*. ^{1}H-NMR ($CDCl_3$): 7.66 (br. *s*, NH); 7.55–7.10 (*m*, 10 arom. H, 3 NH); 6.09 (*s*, NH); 5.12, 5.06 (*AB*, *J* = 12.5, PhC*H*$_2$O); 4.42–4.28 (*m*, CH_2(Leu)); 3.46–3.38 (*m*, CH_2(Gly)); 3.32 (*s*, MeN); 1.90–1.45 (*m*, CH_2(3), CH(4)(Leu)); 1.53, 1.45, 1.41, 1.33 (4*s*, 3 Me_2C); 0.92, 0.86 (2*d*, *J* = 6.4, 2 Me(Leu)). ^{13}C-NMR ($CDCl_3$): 177.3, 174.8, 174.0, 172.6, 170.3 (5*s*, 5 CO(amide)); 156.1 (*s*, CO(urethane)); 145.8, 136.3 (2*s*, 2 arom. C); 129.1, 128.5, 128.1, 127.5, 127.2, 126.7 (6*d*, 10 arom. CH); 66.7 (*t*, Ph*C*H$_2$O); 57.1, 56.9, 56.6 (3*s*, 3 Me_2*C*); 52.2 (*d*, C(2)(Leu)); 45.4 (*t*, C(2)(Gly)); 40.4 (*q*, MeN); 40.0 (*t*, C(3)(Leu)); 27.3, 26.3, 25.8, 25.0, 23.5, 23.4, 20.7 (6*q* and 1*d*, 3 *Me*$_2$C, C(4)(Leu), 2 Me(Leu)). ESI-MS: 705 (40, [*M*+K]$^+$), 689 (100, [*M*+Na]$^+$), 684 (56), 667 (21, [*M*+1]$^+$). Anal. calc. for $C_{35}H_{50}N_6O_7$ (666.82): C 63.04, H 7.56, N 12.60; found: C 63.12, H 7.72, N 12.52.

2.7. *Z-Aib-Gly-Aib-Leu-Aib-OH* (**10**). According to *GP B*, a soln. of *Z-Aib-Gly-Aib-Leu-Aib-N(Me)Ph* (195 mg, 0.29 mmol) in 3N HCl (6 ml) was stirred for 30 h: 154 mg (91%) of **10**. Colorless crystals. M.p. 194.7–195.7° (CH_2Cl_2/hexane). $[\alpha]_D$ = 1.0 (c = 1.04, EtOH). IR (KBr): 3320*m* (br), 3050*w*, 2990*w*, 2930*w*, 2850*w*, 1740*m*, 1710*m*, 1670*s*, 1630*s*, 1575*m*,

1550*m*, 1535*m*, 1470*w*, 1455*w*, 1390*w*, 1370*w*, 1310*w*, 1270*m*, 1245*m*, 1180*w*, 1090*w*, 1020*w*, 740*w*. ^{1}H-NMR ($CDCl_3$): 8.68, 7.90, 7.77, 7.66, 7.64 (5*s*, 5 NH); 7.45–7.25 (*m*, 5 arom. H); 5.12 (*s*, PhC*H*$_2$O); 4.32–4.20 (*m*, CH(2)(Leu)); 3.77, 3.68 (*AB* of *ABX*, J_{AB} = 16.7, J_{AX} = 5.8, J_{BX} = 4.7, CH_2(Gly)); 1.85–1.55 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.49, 1.48, 1.45, 1.42 (4*s*, 3 Me_2C); 0.94, 0.86 (2*d*, *J* = 5.3, 2 Me(Leu)). ^{13}C-NMR (CD_3OD): 178.8, 177.7, 177.2, 174.3, 172.5 (5*s*, 5 CO(amide)); 158.0 (*s*, CO(urethane)); 138.1 (*s*, 1 arom. C); 129.5, 129.0, 128.5 (3*d*, 5 arom. CH); 67.7 (*t*, Ph*C*H$_2$O); 58.2, 57.6, 57.1 (3*s*, 3 Me_2*C*); 53.6 (*d*, C(2)(Leu)); 45.5 (*t*, C(2)(Gly)); 40.7 (*t*, C(3)(Leu)); 27.1, 26.3, 25.9, 25.7, 25.0, 24.7, 24.4, 23.7, 21.1 (8*q* and 1*d*, 3 *Me*$_2$C, C(4)(Leu), 2 Me(Leu)). ESI-MS: 638 (7), 622 (20), 616 (48, $[M+K]^+$), 600 (100, $[M+Na]^+$), 578 (4, $[M+1]^+$). Anal. calc. for $C_{28}H_{43}N_5O_8$ (577.68): C 58.22, H 7.50, N 12.12; found: C 58.31, H 7.55, N 12.16.

Suitable crystals for an X-ray crystal-structure determination were obtained from CH_2Cl_2/Et_2O/hexane by slow evaporation of the solvent.

2.8. *Ac-Aib-Gly-Aib-Leu-Aib-N(Me)Ph*. According to *GP D*, to a soln. of *Ac-Aib-OH* (100 mg, 0.68 mmol) [31] in DMF (2 ml) were added DCC (143 mg, 0.69 mmol), HOBt (105 mg, 0.78 mmol), CSA (10 mg), and **18** (355 mg, 0.79 mmol), and the mixture was stirred for 22.5 h: 209 mg (52%) of *Ac-Aib-Gly-Aib-Leu-Aib-N(Me)Ph*. Colorless crystals. M.p. 232.7–233.5° (CH_2Cl_2/hexane). ^{1}H-NMR (CD_3OD): 7.44–7.18 (*m*, 5 arom. H); 4.32–4.18 (*m*, CH(2)(Leu)); 3.72, 3.66 (*AB*, *J* = 16.8, CH_2(Gly)); 3.31 (br. *s*, MeN); 1.99 (*s*, MeCO); 1.92–1.60 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.54, 1.53, 1.50, 1.46, 1.45, 1.41 (6*s*, 3 Me_2C); 0.95, 0.88 (2*d*, *J* = 5.8, 2 Me(Leu)). ESI-MS: 613 (20, $[M+K]^+$), 597 (100, $[M+Na]^+$), 575 (6, $[M+1]^+$).

2.9. *Ac-Aib-Gly-Aib-Leu-Aib-OH*. According to *GP B*, a soln. of *Ac-Aib-Gly-Aib-Leu-Aib-N(Me)Ph* (99 mg, 0.17 mmol) in 3N HCl (2 ml) was stirred for 7.5 h: 19 mg (23%) of *Ac-Aib-Gly-Aib-Leu-Aib-OH*. Colorless crystals. ^{1}H-NMR (CD_3OD): 4.30–4.22 (*m*, CH(2)(Leu)); 3.76, 3.68 (*AB*, *J* = 16.8, CH_2(Gly)); 1.98 (*s*, MeCO); 1.80–1.30 (*m*, CH_2(3)(Leu),

CH(4)(Leu)); 1.51, 1.49, 1.47, 1.46, 1.44, 1.42 (6*s*, 3 Me_2C); 0.94, 0.87 (2*d*, *J* = 6.1, 2 Me(Leu)). ESI-MS: 524 (40, $[M+K]^+$), 508 (100, $[M+Na]^+$).

3. *Preparation of the Octapeptide Z-Gln-Aib-Aib-Aib-Ala-Ala-Aib-Pro-OH* (**19**). 3.1. *Z-Ala-Ala-Aib-N(Me)Ph*. According to *GP A*, *Z-Ala-Ala-OH* (2.34 g, 8.00 mmol) in THF (50 ml) was treated with **2a** (1.98 g, 11.00 mmol) for 24 h: 3.66 g (98%) of *Z-Ala-Ala-Aib-N(Me)Ph*. Colorless crystals. M.p. 128.3–128.9° (AcOEt/hexane). $[\alpha]_D$ = –15.9 (c = 0.74, EtOH). IR ($CHCl_3$): 3430*w*, 3340*w*, 3070*w*, 3010*m*, 2980*w*, 2940*w*, 1715*s*, 1670*s*, 1595*m*, 1495*s*, 1455*m*, 1390*m*, 1370*w*, 1290*w*, 1240*m*, 1120*w*, 1070*w*, 1030*w*, 705*m*. ^{1}H-NMR (CD_3OD): 7.46–7.12 (*m*, 10 arom. H); 5.15, 5.07 (*AB*, *J* = 12.6, PhCH_2O); 4.24–3.86 (*m*, 2 CH(2)(Ala)); 3.20 (*s*, MeN); 1.48, 1.45 (2*s*, Me_2C); 1.36 (*d*, *J* = 7.3, Me(Ala)); 1.22 (*d*, *J* = 6.8, Me(Ala)). ^{13}C-NMR (CD_3OD): 175.3, 173.6 (2*s*, 2 CO(amide)); 158.7 (*s*, CO(urethane)); 146.4, 138.1 (2*s*, 2 arom. C); 130.9, 129.8, 129.3, 129.0, 128.6 (5*d*, 10 arom. CH); 68.0 (*t*, Ph*C*H_2O); 58.6 (*s*, Me_2C); 52.8, 50.0 (2*d*, 2 C(2)(Ala)); 41.8 (*q*, MeN); 27.4, 27.2 (2*q*, Me_2C); 18.8, 18.4 (2*q*, 2 Me(Ala)). CI-MS: 362 (100, $[M+1–PhCH_2O]^+$). Anal. calc. for $C_{25}H_{32}N_4O_5$ (468.56): C 64.09, H 6.88, N 11.96; found: C 63.84, H 6.87, N 11.94.

3.2. *Z-Ala-Ala-Aib-OH* (**20**). According to *GP B*, a soln. of *Z-Ala-Ala-Aib-N(Me)Ph* (2.07 g, 4.42 mmol) in 3N HCl (45 ml) was stirred for 26 h: 1.58 g (94%) of **20**. Colorless crystals. M.p. 82.5–83.2° (MeOH/Et_2O/hexane). $[\alpha]_D$ = –42.1 (c = 1.02, EtOH). IR (KBr): 3300*w* (br), 3070*m*, 2990*m*, 2940*m*, 1730*s*, 1650*s*, 1535*s*, 1455*s*, 1385*w*, 1370*w*, 1260*s*, 1170*m*, 1075*m*, 1030*m*, 740*m*, 700*m*. ^{1}H-NMR (CD_3OD): 7.42–7.22 (*m*, 5 arom. H); 5.09 (*s*, PhCH_2O); 4.34, 4.11 (2*q*, *J* = 7.1, 2 CH(2)(Ala)); 1.47, 1.46 (2*s*, Me_2C); 1.34 (*d*, *J* = 7.1, 2 Me(Ala)). ^{13}C-NMR (CD_3OD): 177.7 (*s*, COOH); 175.3, 173.8 (2*s*, 2 CO(amide)); 158.4 (*s*, CO(urethane)); 138.1 (*s*, 1 arom. C); 129.5, 129.0, 128.8 (3*d*, 5 arom. CH); 67.7 (*t*, Ph*C*H_2O); 57.0 (*s*, Me_2C); 52.3, 50.1 (2*d*, 2 C(2)(Ala)); 25.2 (*q*, Me_2C); 18.1, 17.9 (2*q*, 2 Me(Ala)). CI-

MS: 380 (100, $[M+1]^+$). Anal. calc. for $C_{18}H_{25}N_3O_6$ (379.42): C 56.98, H 6.64, N 11.08; found: C 56.90, H 6.58, N 11.14.

3.3. *Z-Ala-Ala-Aib-Pro-O^{t}Bu* (**21**). According to *GP D*, DCC (710 mg, 3.43 mmol) was added to a stirred soln. of **20** (1.30 g, 3.43 mmol) in DMF (7 ml). After 5 min, HOBt (510 mg, 3.78 mmol), CSA (50 mg), H-Pro-O^{t}Bu dibenzenesulfimide salt (1.85 g, 3.95 mmol), and Et_3N (397 mg, 3.93 mmol) in DMF (4 ml) were added, and the mixture was stirred for 25.5 h: 1.64 g (89%) of **21**. Colorless crystals. M.p. 185.3–186.4° (CH_2Cl_2/hexane). $[\alpha]_D$ = –85.2 (c = 1.04, EtOH). IR ($CHCl_3$): 3420*w*, 3340*w*, 3040*w*, 3010*m*, 2980*m*, 2940*w*, 1725*s*, 1690*m*, 1670*s*, 1625*m*, 1500*s*, 1455*m*, 1420*m*, 1380*w*, 1370*m*, 1340*w*, 1290*w*, 1240*m*, 1150*m*, 1090*w*, 1070*w*, 1030*w*, 700*w*. ^{1}H-NMR (CD_3OD): 7.39–7.26 (*m*, 5 arom. H); 5.11, 5.07 (*AB*, *J* = 12.3, PhC*H*$_2$O); 4.35 (*q*, *J* = 7.1, CH(2)(Ala)); 4.26 (*dd*, *J* = 8.5, 3.3, CH(2)(Pro)); 4.09 (*q*, *J* = 7.1, CH(2)(Ala)); 3.66–3.44 (*m*, CH_2(5)(Pro)); 2.07–1.72 (*m*, CH_2(3)(Pro), CH_2(4)(Pro)); 1.44 (*s*, Me_2C); 1.43 (*s*, Me_3C); 1.33, 1.32 (2*d*, *J* = 7.1, 2 Me(Ala)). ^{13}C-NMR (CD_3OD): 175.7, 174.0, 173.8 (3*s*, 4 CO); 158.6 (*s*, CO(urethane)); 138.4 (*s*, 1 arom. C); 129.8, 129.3, 129.0 (3*d*, 5 arom. CH); 82.5 (*s*, Me_3C); 67.9 (*t*, PhCH_2O); 63.4 (*d*, C(2)(Pro)); 57.7 (*s*, Me_2C); 52.5, 50.2 (2*d*, 2 C(2)(Ala)); 49.5 (*t*, C(5)(Pro)); 29.2, 26.4 (2*t*, C(4)(Pro), C(3)(Pro)); 28.6 (*q*, *Me*$_3$C); 25.9, 25.1 (2*q*, *Me*$_2$C); 18.4 (*q*, 2 Me(Ala)). FAB-MS: 533 (15, $[M+1]^+$), 362 (83, [*M*–(Pro-O^{t}Bu)]$^+$). Anal. calc. for $C_{27}H_{40}N_4O_7$ (532.64): C 60.89, H 7.57, N 10.52; found: C 60.78, H 7.73, N 10.66.

Suitable crystals for an X-ray crystal-structure determination were obtained from CH_2Cl_2/hexane by slow evaporation of the solvent.

3.4. *H-Ala-Ala-Aib-Pro-O^{t}Bu* (**12**). According to *GP C*, a stirred mixture of **21** (1.10 g, 2.07 mmol) and Pd/C (154 mg) in MeOH (20 ml) was treated with H_2 for 18.5 h: 816 mg (98%) of **12**. Colorless crystals. M.p. 116.4–117.4° (MeOH/AcOEt/hexane). ^{1}H-NMR (CD_3OD): 4.36 (*q*, *J* = 7.2, CH(2)(Ala)); 4.32–4.25 (*m*, CH(2)(Pro)); 3.70–3.53 (*m*,

CH_2(5)(Pro)); 3.41 (*q*, *J* = 6.9, CH(2)(Ala)); 2.07–1.75 (*m*, CH_2(3)(Pro), CH_2(4)(Pro)); 1.45, 1.44, 1.43 (3*s*, Me_2C, Me_3C); 1.33 (*d*, *J* = 7.2, Me(Ala)); 1.24 (*d*, *J* = 6.9, Me(Ala)). ^{13}C-NMR (CD_3OD): 177.9 (*s*, CO(ester)); 173.9, 173.7, 173.5 (3*s*, 3 CO(amide)); 82.2 (*s*, Me_3C); 63.0 (*d*, C(2)(Pro)); 57.3 (*s*, Me_2C); 51.4, 49.6 (2*d*, 2 C(2)(Ala)); 49.2 (*t*, C(5)(Pro)); 28.9, 26.6 (2*t*, C(4)(Pro), C(3)(Pro)); 28.2 (*q*, Me_3C); 25.6, 24.7 (2*q*, Me_2C); 18.3 (*q*, 2 Me(Ala)). ESI-MS: 437 (4, $[M+K]^+$), 421 (9, $[M+Na]^+$), 399 (100, $[M+1]^+$).

3.5. *Z-Gln(Trt)-Aib-N(Me)Ph*. According to *GP A*, a soln. of *Z-Gln(Trt)-OH* (**23a**, 3.01 g, 5.76 mmol) in THF (25 ml) was treated with **2a** (1.25 g, 7.18 mmol) for 45 h: 3.59 g (89%) of *Z-Gln(Trt)-Aib-N(Me)Ph*. Colorless foam. M.p. 89.2–90.1°. $[\alpha]_D$ = –1.2 (c = 0.84, EtOH). IR ($CHCl_3$): 3430*w*, 3060*w*, 3010*w*, 2940*w*, 1715*m*, 1680*m*, 1635*m*, 1595*w*, 1495*s*, 1450*w*, 1420*w*, 1390*w*, 1365*w*, 1245*w*, 1195*w*, 1120*w*, 1050*w*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.43–7.06 (*m*, 25 arom. H); 6.56 (*s*, NH); 5.76 (br. *d*, *J* = 7.1, NH); 5.16, 5.06 (*AB*, *J* = 12.2, PhCH_2O); 3.76–3.63 (*m*, CH(2)(Gln)); 3.20 (*s*, MeN); 2.55–2.30 (*m*, CH_2(4)(Gln)); 2.00–1.70 (*m*, CH_2(3)(Gln)); 1.37, 1.28 (2*s*, Me_2C). ^{13}C-NMR (CD_3OD): 175.3, 174.5, 173.3 (3*s*, 3 CO(amide)); 158.5 (*s*, CO(urethane)); 146.4, 146.3, 138.5 (3*s*, 5 arom. C); 130.8, 130.3, 129.8, 129.4, 129.0, 128.8, 128.0 (7*d*, 25 arom. CH); 71.9 (*s*, Ph_3C); 68.0 (*t*, PhCH_2O); 58.7 (*s*, Me_2C); 55.6 (*d*, C(2)(Gln)); 41.7 (*q*, MeN); 33.7, 29.9 (2*t*, C(4)(Gln), C(3)(Gln)); 27.2 (*q*, Me_2C). CI-MS: 589 (15, $[M–PhCH_2O]^+$), 243 (100, Trt^+). ESI-MS: 735 (70, $[M+K]^+$), 719 (100, $[M+Na]^+$), 697 (17, $[M+1]^+$). Anal. calc. for $C_{43}H_{44}N_4O_5$ (696.85): C 74.12, H 6.36, N 8.04; found: C 73.87, H 6.34, N 7.82.

3.6. *Z-Gln(Trt)-Aib-OH*. According to *GP B*, a soln. of *Z-Gln(Trt)-Aib-N(Me)Ph* (4.93 g, 7.08 mmol) in 3N HCl (80 ml) was stirred for 8 h: 4.25 g (98%) of *Z-Gln(Trt)-Aib-OH*. Colorless crystals. M.p. 121.6–122.5° (CH_2Cl_2/hexane). $[\alpha]_D$ = –6.3 (c = 0.87, EtOH). IR (KBr): 3430*m*, 3340*m*, 3080*w*, 3060*w*, 3030*w*, 2940*w*, 1740*w*, 1700*m* (br), 1650*s*, 1520*m*, 1505*m*, 1495*m*, 1470*w*, 1400*w*, 1365*w*, 1240*w*, 1220*w*, 1150*w*, 1055*w*, 1000*w*, 700*m*. ^{1}H-

NMR ($CDCl_3$): 8.57 (*s*, NH); 8.13 (*s*, NH); 7.38–7.13 (*m*, 20 arom. H); 5.11, 5.06 (*AB*, *J* = 12.8, PhC*H*$_2$O); 4.13–4.00 (*m*, CH(2)(Gln)); 2.54–2.31 (*m*, CH_2(4)(Gln)); 2.08–1.91, 1.91–1.72 (2*m*, CH_2(3)(Gln)); 1.47, 1.42 (2*s*, Me_2C). ^{13}C-NMR (CD_3OD): 177.9 (*s*, COOH); 174.7, 173.8 (2*s*, 2 CO(amide)); 158.6 (*s*, CO(urethane)); 146.2, 138.4 (2*s*, 4 arom. C); 130.3, 129.8, 129.3, 129.2, 129.0, 128.1 (6*d*, 20 arom. CH); 71.9 (*s*, Ph_3C); 68.1 (*t*, Ph*C*H$_2$O); 57.5 (*s*, Me_2C); 55.9 (*d*, C(2)(Gln)); 33.9, 29.6 (2*t*, C(4)(Gln), C(3)(Gln)); 25.8, 25.3 (2*q*, *Me*$_2$C). ESI-MS: 646 (100, $[M+K]^+$), 630 (68, $[M+Na]^+$), 628 (90). Anal. calc. for $C_{36}H_{37}N_3O_6$ (607.71): C 71.15, H 6.14, N 6.92; found: C 71.34, H 6.07, N 6.91.

3.7. *Z-Gln(Trt)-Aib-Aib-N(Me)Ph*. According to *GP A*, a soln. of *Z-Gln(Trt)-Aib-OH* (3.98 g, 6.55 mmol) in CH_2Cl_2 (40 ml) and DMF (12 ml) was treated with **2a** (1.60 g, 9.16 mmol) for 36 h: 4.48 g (87%) of *Z-Gln(Trt)-Aib-Aib-N(Me)Ph*. Colorless foam. M.p. 111.5–112.0°. $[\alpha]_D$ = –2.0 (c = 1.06, EtOH). IR ($CHCl_3$): 3420*w*, 3350*w*, 3040*w*, 3005*m*, 2930*w*, 1715*m*, 1670*m*, 1630*m*, 1595*m*, 1495*s*, 1450*m*, 1390*m*, 1360*m*, 1240*m*, 1200*w*, 1020*w*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.57 (*s*, NH); 7.42–7.06 (*m*, 25 arom. H, NH); 6.64 (*s*, NH); 5.96 (br. *s*, NH); 5.15, 5.06 (*AB*, *J* = 12.1, PhC*H*$_2$O); 4.03 (*dd*, *J* = 12.3, 6.3, CH(2)(Gln)); 3.15 (*s*, MeN); 2.68–2.52, 2.52–2.36 (2*m*, CH_2(4)(Gln)); 2.15–2.00 (*m*, CH_2(3)(Gln)); 1.40, 1.37, 1.31 (3*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 176.2, 175.7, 174.5, 174.2 (4*s*, 4 CO(amide)); 158.9 (*s*, CO(urethane)); 147.0, 146.2, 138.6 (3*s*, 5 arom. C); 130.6, 130.3, 129.8, 129.3, 129.0, 128.9, 128.8, 128.6, 128.1 (9*d*, 25 arom. CH); 71.9 (*s*, Ph_3C); 67.9 (*t*, Ph*C*H$_2$O); 59.0, 58.4 (2*s*, 2 Me_2C); 56.7 (*d*, C(2)(Gln)); 41.5 (*q*, MeN); 34.0, 28.6 (2*t*, C(4)(Gln), C(3)(Gln)); 26.7, 26.6, 26.4, 25.3 (4*q*, 2 *Me*$_2$C). ESI-MS: 820 (10, $[M+K]^+$), 804 (100, $[M+Na]^+$). Anal. calc. for $C_{47}H_{51}N_5O_6$ (781.96): C 72.19, H 6.57, N 8.96; found: C 72.04, H 6.78, N 9.03.

3.8. *Z-Gln(Trt)-Aib-Aib-OH*. According to *GP B*, a soln. of *Z-Gln(Trt)-Aib-Aib-N(Me)Ph* (1.00 g, 1.28 mmol) in 3N HCl (16 ml) was stirred for 6.5 h: 889 mg (quant.) of *Z-Gln(Trt)-Aib-Aib-OH*. Colorless foam. M.p. 105.5–106.3°. $[\alpha]_D$ = –3.9 (c = 1.01, EtOH). IR

(KBr): 3350*m* (br), 3060*w*, 3030*w*, 2980*w*, 2930*w*, 1710*m*, 1660*s*, 1530*m*, 1515*m*, 1450*m*, 1390*w*, 1365*w*, 1315*w*, 1245*m*, 1155*w*, 1080*w*, 1000*w*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.50–7.00 (*m*, 20 arom. H, 2 NH); 6.38 (*d*, *J* = 5.5, NH); 5.09, 5.02 (*AB*, *J* = 12.2, PhC*H*$_2$O); 4.02–3.88 (*m*, CH(2)(Gln)); 2.60–2.30 (*m*, CH_2(4)(Gln)); 2.08–1.78 (*m*, CH_2(3)(Gln)); 1.45, 1.43, 1.35, 1.28 (4*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 178.3 (*s*, COOH); 176.1, 174.5, 174.3 (3*s*, 3 CO(amide)); 158.8 (*s*, CO(urethane)); 146.2, 138.5 (2*s*, 4 arom. C); 130.3, 129.8, 129.3, 129.0, 128.1 (5*d*, 20 arom. CH); 71.9 (*s*, Ph_3C); 68.0 (*t*, PhCH_2O); 58.2, 57.5 (2*s*, 2 Me_2C); 56.6 (*d*, C(2)(Gln)); 34.0, 28.6 (2*t*, C(4)(Gln), C(3)(Gln)); 26.1, 25.8, 25.7, 25.1 (4*q*, 2 *Me*$_2$C). ESI-MS: 738 (9, $[M+2Na]^+$), 731 (18, $[M+K]^+$), 715 (100, $[M+Na]^+$). FAB-MS: 693 (38, $[M+1]^+$), 243 (100). Anal. calc. for $C_{40}H_{44}N_4O_7$ (692.82): C 69.35, H 6.40, N 8.09; found: C 69.10, H 6.59, N 7.88.

3.9. *Z-Gln(Trt)-Aib-Aib-Aib-N(Me)Ph*. According to *GP A*, a soln. of *Z-Gln(Trt)-Aib-Aib-OH* (2.08 g, 3.00 mmol) in CH_2Cl_2 (25 ml) was treated with **2a** (630 mg, 3.62 mmol) for 42 h: 2.34 g (89%) of *Z-Gln(Trt)-Aib-Aib-Aib-N(Me)Ph*. Colorless foam. M.p. 199.0–199.7°. $[\alpha]_D$ = –19.6 (c = 1.07, EtOH). IR ($CHCl_3$): 3420*w*, 3340*w*, 3050*w*, 2995*w*, 2930*w*, 1675*s*, 1590*w*, 1490*s*, 1450*w*, 1390*w*, 1360*w*, 1240*w*, 1030*w*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.40–7.12 (*m*, 25 arom. H, NH); 7.05, 6.75, 6.66, 6.31 (4*s*, 4 NH); 5.10, 5.05 (*AB*, *J* = 12.3, PhC*H*$_2$O); 3.95–3.82 (*m*, CH(2)(Gln)); 3.30 (*s*, MeN); 2.66–2.52, 2.52–2.36 (2*m*, CH_2(4)(Gln)); 2.12–1.86 (*m*, CH_2(3)(Gln)); 1.46, 1.44, 1.31, 1.26 (4*s*, 3 Me_2C). ^{13}C-NMR (CD_3OD): 176.5, 175.7, 175.6, 174.6, 174.1 (5*s*, 5 CO(amide)); 147.0, 145.9, 138.0 (3*s*, 5 arom. C); 130.2, 129.9, 129.5, 129.1, 128.8, 128.7, 128.2, 128.0, 127.8 (9*d*, 25 arom. CH); 71.6 (*s*, Ph_3C); 67.8 (*t*, Ph*C*H_2O); 58.3, 58.0, 57.7 (3*s*, 3 Me_2C); 56.3 (*d*, C(2)(Gln)); 41.0 (*q*, MeN); 33.5, 27.8 (2*t*, C(4)(Gln), C(3)(Gln)); 26.8, 26.5, 26.2, 25.9, 25.0, 24.5 (6*q*, 3 *Me*$_2$C); CO(urethane) not detected. ESI-MS: 906 (30, $[M+K]^+$), 890 (100, $[M+Na]^+$). Anal. calc. for $C_{51}H_{58}N_6O_7$ (867.06): C 70.65, H 6.74, N 9.69; found: C 70.74, H 6.65, N 9.90.

3.10. *Z-Gln(Trt)-Aib-Aib-Aib-OH* (**11a**). According to *GP B*, a soln. of *Z-Gln(Trt)-Aib-Aib-Aib-N(Me)Ph* (1.31 g, 1.51 mmol) in 3N HCl (16 ml) was stirred for 5 h: 1.17 g (quant.) of *Z-Gln(Trt)-Aib-Aib-Aib-OH*. Colorless foam. M.p. 119.0–120.0°. $[\alpha]_D$ = –1.9 (c = 1.09, EtOH). IR (KBr): 3660*w*, 3420*m*, 3310*m*, 3050*w*, 2980*m*, 2940*w*, 2870*w*, 1725*m*, 1705*m*, 1670*s*, 1600*w*, 1545*m*, 1530*m*, 1510*m*, 1500*m*, 1470*m*, 1445*m*, 1375*m*, 1365*m*, 1315*m*, 1275*m*, 1240*m*, 1165*m*, 1080*w*, 1050*w*, 1000*w*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.40 (*s*, NH); 7.38–7.08 (*m*, 20 arom. H, 1 NH); 7.01, 6.97 (2*s*, 2 NH); 6.53 (*d*, *J* = 4.5, NH); 5.11, 5.04 (*AB*, *J* = 12.3, PhC*H*$_2$O); 3.95–3.80 (*m*, CH(2)(Gln)); 2.69–2.54, 2.54–2.40 (2*m*, CH_2(4)(Gln)); 2.14–1.88 (*m*, CH_2(3)(Gln)); 1.49, 1.47, 1.39, 1.38, 1.34, 1.23 (6*s*, 3 Me_2C). ^{13}C-NMR (CD_3OD): 178.1 (*s*, COOH); 176.4, 175.9, 174.6, 174.2 (4*s*, 4 CO(amide)); 158.7 (*s*, CO(urethane)); 145.8, 138.1 (2*s*, 4 arom. C); 129.9, 129.5, 129.1, 128.9, 128.7, 127.8 (6*d*, 20 arom. CH); 71.6 (*s*, Ph_3C); 68.0 (*t*, Ph*C*H$_2$O); 57.8, 57.7, 57.0 (3*s*, 3 Me_2C); 56.2 (*d*, C(2)(Gln)); 33.5, 27.8 (2*t*, C(4)(Gln), C(3)(Gln)); 26.5, 26.1, 25.8, 24.8, 24.5, 24.3 (6*q*, 3 *Me*$_2$C). ESI-MS: 822 (100, $[M+2Na]^+$), 800 (65, $[M+Na]^+$). Anal. calc. for $C_{44}H_{51}N_5O_8$ (777.92): C 67.94, H 6.61, N 9.00; found: C 67.82, H 6.79, N 8.89.

3.11. *Z-Gln(Trt)-Aib-Aib-Aib-Ala-Ala-Aib-Pro-O^{t}Bu* (**24**). According to *GP D*, to a stirred soln. of **11a** (250 mg, 0.32 mmol) in DMF (1.7 ml), DCC (68 mg, 0.33 mmol), HOBt (50 mg, 0.37 mmol), CSA (5 mg), and **12** (148 mg, 0.37 mmol) were added. The mixture was stirred for 24.5 h: 367 mg (97%) of **24**. Colorless crystals. M.p. 146.1–147.5° (AcOEt/Et_2O/hexane). ^{1}H-NMR (CD_3OD): 7.40–7.15 (*m*, 20 arom. H); 5.17, 5.09 (*AB*, *J* = 12.6, PhC*H*$_2$O); 4.36–4.26 (*m*, CH(2)(Ala), CH(2)(Pro)); 4.07 (*q*, *J* = 7.4, CH(2)(Ala)); 3.89 (*dd*, *J* = 8.4, 6.2, CH(2)(Gln)); 3.74–3.65, 3.65–3.55 (*2m*, CH_2(5)(Pro)); 2.56–2.46 (*m*, CH_2(4)(Gln)); 2.16–1.76 (*m*, CH_2(3)(Gln), CH_2(3)(Pro), CH_2(4)(Pro)); 1.54, 1.49, 1.46, 1.45, 1.44, 1.42, 1.41, 1.34, 1.33, 1.31 (10*s*, 4 Me_2C, Me_3C, 2 Me(Ala)). ESI-MS: 1196 (10,

[*M*+K]$^+$), 1180 (100, [*M*+Na]$^+$). FAB-MS: 1180 (11, [*M*+Na]$^+$), 987 (100, [*M*–(Pro-O^{t}Bu)]$^+$), 902 (23, [987–Aib]$^+$), 831 (8, [902–Ala]$^+$), 760 (9, [831–Ala]$^+$).

3.12. *H-Gln(Trt)-Aib-Aib-Aib-Ala-Ala-Aib-Pro-O^{t}Bu* (**25**). According to *GP C*, a stirred mixture of **24** (553 mg, 0.48 mmol) and Pd/C (73 mg) in MeOH (11 ml) was treated with H_2 for 21 h: 475 mg (97%) of **25**. Colorless foam. M.p. 150.2–151.3°. ^{1}H-NMR (CD_3OD): 7.32–7.06 (*m*, 15 arom. H); 4.36–4.27 (*m*, CH(2)(Ala), CH(2)(Pro)); 4.07 (*q*, *J* = 7.4, CH(2)(Ala)); 3.73–3.65, 3.65–3.55 (2*m*, CH_2(5)(Pro)); 3.25–3.18 (*m*, CH(2)(Gln)); 2.59–2.40 (*m*, CH_2(4)(Gln)); 2.16–1.66 (*m*, CH_2(3)(Gln), CH_2(3)(Pro), CH_2(4)(Pro)); 1.60–1.24 (*m*, 39 H). ESI-MS: 1046 (16, [*M*+Na]$^+$), 1038 (17), 1024 (100, [*M*+1]$^+$).

3.13. *Z-Gln-Aib-Aib-Aib-Ala-Ala-Aib-Pro-OH* (**19**). According to *GP E*, a soln. of **24** (300 mg, 0.26 mmol) in TFA (7 ml) was stirred for 3.15 h: 222 mg (quant.) of **19**. Colorless crystals. M.p. 135.0–135.6° (AcOEt/Et_2O/hexane). ^{1}H-NMR (CD_3OD): 7.89, 7.68 (2 br. *s*, 2 NH); 7.42–7.18 (*m*, 5 arom. H); 5.18, 5.08 (*AB*, *J* = 12.6, PhCH_2O); 4.42 (*dd*, *J* = 9.0, 4.0, CH(2)(Pro)); 4.33 (*q*, *J* = 7.1, CH(2)(Ala)); 4.15–4.02 (*m*, CH(2)(Ala); 3.95 (*dd*, *J* = 8.2, 6.2, CH(2)(Gln)); 3.72–3.48 (*m*, CH_2(5)(Pro)); 2.37 (*t*, *J* = 7.4, CH_2(4)(Gln)); 2.22–1.80 (*m*, CH_2(3)(Gln), CH_2(3)(Pro), CH_2(4)(Pro)); 1.58–1.20 (*m*, 4 Me_2C, 2 Me(Ala)). ^{13}C-NMR: 178.8, 177.9, 177.5, 176.9, 176.1, 174.8, 174.7, 174.1 (8*s*, COOH, 8 CO(amide)); 158.9 (*s*, CO(urethane)); 138.4 (*s*, 1 arom. C); 130.0, 129.6, 129.1, 128.7, 127.8 (5*d*, 5 arom. CH); 67.9 (*t*, Ph*C*H_2O); 62.1 (*d*, C(2)(Pro)); 57.8 (br. *s*, 4 Me_2*C*); 57.6 (*d*, C(2)(Gln)); 52.5, 50.5 (2*d*, 2 C(2)(Ala)); 49.6 (*t*, C(5)(Pro)); 32.4 (*t*, C(4)(Gln)); 29.1, 27.9, 26.8 (3*t*, C(3)(Gln), C(3)(Pro), C(4)(Pro)); 27.5, 27.0, 26.2, 25.5, 25.0, 24.1, 23.6 (7*q*, 4 *Me*$_2$C); 17.5, 16.9 (2*q*, 2 Me(Ala)). ESI-MS: 1124 (5), 882 (100, [*M*+Na]$^+$), 785 (9). FAB-MS: 882 (3, [*M*+Na]$^+$), 745 (75, [*M*–Pro]$^+$), 660 (29, [745–Aib]$^+$), 589 (35, [660–Ala]$^+$), 518 ([589–Ala]$^+$), 433 (92, [518–Aib]$^+$), 348 (100, [433–Aib]$^+$), 263 (36, [348–Aib]$^+$), 155 (26, [263–PhCH_2O+1]$^+$).

4. *Preparation of the Pentapeptide H-Leu-Aib*-D,L-*Iva-Gln-Valol* (**13**). 4.1. *Z-Leu-Aib-N(Me)Ph*. According to *GP A*, *Z-Leu-OH* (3.03 g, 11.42 mmol) in Et_2O (50 ml) was treated with **2a** (2.20 g, 12.63 mmol) for 13 h: 4.99 g (99%) of *Z-Leu-Aib-N(Me)Ph*. Colorless crystals. M.p. 135.5–135.7° (Et_2O/pentane). $[\alpha]_D$ = –19.6 (c = 1.01, EtOH). IR ($CHCl_3$): 3430*w*, 3350*w*, 3070*w*, 3010*m*, 2960*m*, 1715*m*, 1680*m*, 1635*m*, 1595*m*, 1510*s*, 1495*s*, 1420*m*, 1405*m*, 1390*m*, 1370*m*, 1240*m*, 1170*m*, 1120*m*, 1055*m*, 1030*s*, 705*m*. ^{1}H-NMR (CD_3OD): 7.56–7.13 (*m*, 10 arom. H); 5.15, 5.06 (*AB*, *J* = 12.5, PhC*H*$_2$O); 4.10–3.90 (*m*, CH(2)(Leu)); 3.20 (*s*, MeN); 1.80–1.30 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.43 (*s*, Me_2C); 0.92, 0.90 (2*d*, *J* = 6.4, 2 Me(Leu)). ^{13}C-NMR (CD_3OD): 175.0, 174.1 (2*s*, 2 CO(amide)); 158.1 (*s*, CO(urethane)); 146.2, 138.1 (2*s*, 2 arom. C); 130.4, 130.0, 129.5, 129.3, 129.2, 129.0, 128.8, 128.6, 128.5, 128.3 (10*d*, 10 arom. CH); 67.6 (*t*, Ph*C*H$_2$O); 58.3 (*s*, Me_2*C*); 54.5 (*d*, C(2)(Leu)); 42.5 (*t*, C(3)(Leu)); 41.3 (*q*, MeN); 26.9, 25.8 (2*q*, *Me*$_2$C); 26.6 (*d*, C(4)(Leu)); 23.6, 21.9 (2*q*, 2 Me(Leu)). CI-MS: 440 (100, $[M+1]^+$). Anal. calc. for $C_{25}H_{33}N_3O_4$ (439.56): C 68.31, H 7.57, N 9.56; found: C 68.13, H 7.70, N 9.35.

4.2. *Z-Leu-Aib-OH* (**26**). According to *GP B*, a soln. of *Z-Leu-Aib-N(Me)Ph* (3.50 g, 7.97 mmol) in 3N HCl (80 ml) was stirred for 18 h: 2.58 g (92%) of **26**. Colorless crystals. M.p. 118.8–119.8° (Et_2O/hexane). $[\alpha]_D$ = –23.7 (c = 1.12, EtOH). IR (KBr): 3430*w*, 3300*w*, 3030*w*, 3005*m*, 2960*m*, 1720*s*, 1680*s*, 1515*s*, 1455*m*, 1390*w*, 1370*w*, 1290*m*, 1170*m*, 1120*w*, 1050*w*, 1030*w*, 695*m*. ^{1}H-NMR (CD_3OD): 7.42–7.22 (*m*, 5 arom. H); 5.09 (*s*, PhC*H*$_2$O); 4.22–4.06 (*m*, CH(2)(Leu)); 1.86–1.50 (*m*, CH_2(3)(Leu), CH(4)(Leu)); 1.47, 1.46 (2*s*, Me_2C); 0.94, 0.90 (2*d*, *J* = 6.4, 2 Me(Leu)). ^{13}C-NMR (CD_3OD): 177.9 (*s*, COOH); 174.8 (*s*, CO(amide)); 158.6 (*s*, CO(urethane)); 138.5 (*s*, 1 arom. C); 129.7, 129.3, 129.1 (3*d*, 5 arom. CH); 67.9 (*t*, Ph*C*H$_2$O); 57.3 (*s*, Me_2*C*); 55.1 (*d*, C(2)(Leu)); 42.5 (*t*, C(3)(Leu)); 26.1 (*d*, C(4)(Leu)); 25.6, 25.3 (2*q*, *Me*$_2$C); 23.6, 21.9 (2*q*, 2 Me(Leu)). CI-MS: 351 (100, $[M+1]^+$).

Anal. calc. for $C_{18}H_{26}N_2O_5$ (350.42): C 61.70, H 7.48, N 7.99; found: C 61.60, H 7.51, N 8.11.

4.3. *Z-Leu-Aib*-D,L-*Iva-N(Me)Ph*. According to *GP A*, a soln. of **26** (3.46 g, 9.90 mmol) in CH_2Cl_2 (55 ml) was treated with **2b** (2.61 g, 13.86 mmol) for 18 h: 5.35 g (quant.) of *Z-Leu-Aib-* D,L-*Iva-N(Me)Ph*. Colorless foam. Colorless crystals were obtained after CC (SiO_2, Et_2O/hexane). M.p. 58.8–59.3°. $[\alpha]_D$ = –6.3 (c = 0.89, EtOH). IR ($CHCl_3$): 3450*w*, 3010*m*, 2960*m*, 2940*w*, 2900*w*, 2880*w*, 1715*m*, 1670*s*, 1625*m*, 1595*m*, 1495*m*, 1455*m*, 1425*s*, 1380*m*, 1365*m*, 1270*w*, 1170*w*, 1120*w*, 1050*w*, 1030*w*, 705*m*. ^{1}H-NMR (CD_3OD, 7:5 mixture of epimers): 7.43–7.17 (*m*, 10 arom. H); 5.20–5.03 (2 *AB*, *J* = 12.8, PhC*H*$_2$O); 4.03 (*t*, *J* = 7.5, CH(2)(Leu)); 3.27, 3.21 (2*s*, MeN); 2.06–1.89 (*m*, 1 H of CH_2(3)(Iva)); 1.85–1.62 (*m*, 1 H of CH_2(3)(Iva), CH(4)(Leu)); 1.56–1.48 (*m*, CH_2(3)(Leu)); 1.48, 1.43 (2*s*, Me_2C); 1.39, 1.30 (2*s*, MeC(2)(Iva)); 0.96, 0.94 (2*d*, *J* = 6.5, 2 Me(Leu)); 0.86 (*t*, *J* = 7.2, *Me*CH_2(Iva)). ^{13}C-NMR (CD_3OD): 175.8, 175.4, 174.7 (3*s*, 3 CO(amide)); 158.9 (*s*, CO(urethane)); 146.9, 138.7 (2*s*, 2 arom. C); 130.7, 129.8, 129.3, 128.9, 128.7 (5*d*, 10 arom. CH); 67.7 (*t*, Ph*C*H_2O); 62.8 (*s*, C(2)(Iva)); 58.6 (*s*, Me_2*C*); 55.8, 55.7 (2*d*, C(2)(Leu)); 41.9 (*t*, C(3)(Leu)); 41.6 (*q*, MeN); 31.1, 31.0 (2*t*, C(3)(Iva)); 26.8, 26.5 (2*q*, *Me*$_2$C); 26.1 (*d*, C(4)(Leu)); 25.3, 25.0 (2*q*, MeC(2)(Iva)); 23.6, 22.5 (2*q*, 2 Me(Leu)); 9.1, 9.0 (2*q*, C(4)(Iva)). CI-MS: 432 (100, [*M*+1–PhCH_2O]$^+$). Anal. calc. for $C_{30}H_{42}N_4O_5$ (538.69): C 66.89, H 7.86, N 10.40; found: C 66.75, H 8.06, N 10.20.

The separation of the two diastereoisomers was achieved by prep. HPLC on a *Nucleosil 100-7* column with hexane/CH_2Cl_2/EtOH 100:9:3 as the eluent. One of the epimers was obtained in pure form in *ca*. 10% yield, the second epimer was isolated as an 8:1 mixture with the first one. Data of the pure epimer: $[\alpha]_D$ = 6.1 (c = 0.85, EtOH). ^{1}H-NMR (CD_3OD): 7.45–7.20 (*m*, 10 arom. H); 5.15, 5.07 (*AB*, *J* = 12.7, PhC*H*$_2$O); 4.03 (*t*, *J* = 7.5, CH(2)(Leu)); 3.27 (*s*, MeN); 2.05–1.94 (*m*, 1 H of CH_2(3)(Iva)); 1.85–1.62 (*m*, 1 H of CH_2(3)(Iva),

CH(4)(Leu)); 1.56–1.50 (*m*, CH_2(3)(Leu)); 1.48, 1.43 (2*s*, Me_2C); 1.30 (*s*, MeC(2)(Iva)); 0.96, 0.92 (2*d*, *J* = 6.6, 2 Me(Leu)); 0.86 (*t*, *J* = 7.4, *Me*CH_2).

4.4. *Z-Leu-Aib-*D,L*-Iva-OH* (**27**). According to *GP B*, a soln. of *Z-Leu-Aib-* D,L*-Iva-N(Me)Ph* (1.52 g, 2.83 mmol) in 3N HCl (30 ml) was stirred for 23 h: 703 mg (55%) of **27**. Colorless crystals. M.p. 171.2–172.1° (AcOEt/hexane). IR (KBr): 3300*m*, 3060*w*, 3040*w*, 2960*m*, 2870*w*, 1730*s*, 1710*s*, 1660*s*, 1525*s*, 1455*m*, 1385*m*, 1365*m*, 1315*m*, 1270*m*, 1245*m*, 1165*m*, 1135*w*, 1045*m*, 1030*w*, 695*m*. ^{1}H-NMR (CD_3OD, mixture of epimers): 7.40–7.24 (*m*, 5 arom. H); 5.15–5.02 (*m*, PhCH_2O); 4.06 (*t*, *J* = 7.5, CH(2)(Leu)); 2.09–1.88, 1.88–1.61 (2*m*, CH(4)(Leu), CH_2(3)(Iva)); 1.57–1.49 (*m*, CH_2(3)(Leu)); 1.46, 1.43 (2*s*, Me_2C); 1.42, 1.41 (2*s*, MeC(2)(Iva)); 0.95, 0.93 (2*d*, *J* = 6.5, 2 Me(Leu)); 0.81, 0.78 (2*t*, *J* = 7.5, *Me*CH_2(Iva). ^{13}C-NMR (CD_3OD): 177.7, 177.4 (2*s*, COOH); 175.9, 175.4 (2*s*, 2 CO(amide)); 158.8 (*s*, CO(urethane)); 138.6 (*s*, 1 arom. C); 129.8, 129.3, 129.0, 128.9, 128.8 (5*d*, 5 arom. CH); 67.9, 67.8 (2*t*, Ph*C*H_2O); 61.6, 61.5 (2*s*, C(2)(Iva)); 58.5, 58.4 (2*s*, Me_2*C*); 55.6 (*d*, C(2)(Leu)); 42.0 (*t*, C(3)(Leu)); 31.2, 30.4 (2*t*, C(3)(Iva)); 26.3, 26.1 (2*d*, C(4)(Leu)); 25.4, 25.2 (2*q*, *Me*$_2$C); 23.6, 22.4 (2*q*, 2 Me(Leu)); 23.0, 22.7 (2*q*, *Me*CH_2(Iva)); 9.0, 8.9 (2*q*, C(4)(Iva)). CI-MS: 450 (100, [*M*+1]$^+$). Anal. calc. for $C_{23}H_{35}N_3O_6$ (449.55): C 61.45, H 7.85, N 9.35; found: C 61.35, H 8.02, N 9.30.

4.5. *Z-Gln-Valol*. To a soln. of *Z-Gln-OH* (504 mg, 1.80 mmol) in THF (12 ml) at –12°, ethyl chloroformiat (0.17 ml, 1.78 mmol) and NMM (0.2 ml, 1.80 mmol) were added. After stirring for 4 min, L-Valinol (0.2 ml, 1.80 mmol) was added and the mixture was stirred at r.t. for 2 d. Then, the solid material was filtered and washed with cold AcOEt/$CHCl_3$ and Et_2O and recrystallized from MeOH: 582 mg (88%) of *Z-Gln-Valol*. Colorless crystals. M.p. 189.8–190.5° (MeOH). $[\alpha]_D$ = –23.7 (c = 0.86, MeOH). IR (KBr): 3430*m*, 3300*s*, 3090*w*, 3060*w*, 3030*w*, 2960*w*, 2870*w*, 1680*s*, 1650*s*, 1535*s*, 1445*w*, 1415*w*, 1395*w*, 1370*w*, 1260*m*, 1245*m*, 1140*w*, 1060*w*, 1045*w*, 700*w*. ^{1}H-NMR (CD_3OD): 7.42–7.22 (*m*, 5 arom. H); 5.08 (*s*,

PhC*H*$_2$O); 4.14 (*dd*, *J* = 8.5, 5.7, CH(2)(Gln)); 3.76–3.46 (*m*, CH_2(1)(Valol), CH(2)(Valol)); 2.31 (*t*, *J* = 7.5, CH_2(4)(Gln)); 2.18–1.72 (*m*, CH_2(3)(Gln), CH(3)(Valol)); 0.93, 0.90 (2*d*, *J* = 7.2, 2 Me(Valol)). ^{13}C-NMR ((D$_6$)DMSO): 174.0, 171.6 (2*s*, 2 CO(amide)); 156.0 (*s*, CO(urethane)); 137.2 (*s*, 1 arom. C); 128.5, 127.9, 127.8 (3*d*, 5 arom. CH); 65.5 (*t*, PhC*H*$_2$O); 61.5 (*t*, CH_2OH); 55.7 (*d*, C(2)(Gln)); 54.7 (*d*, C(2)(Valol)); 31.8 (*t*, C(4)(Gln)); 28.3 (*d*, C(3)(Valol)); 28.1 (*t*, C(3)(Gln)); 19.8, 18.2 (2*q*, 2 Me(Valol)). CI-MS: 366 (100, [*M*+1]$^+$). Anal. calc. for $C_{18}H_{27}N_3O_5$ (365.43): C 59.16, H 7.45, N 11.50; found: C 59.15, H 7.22, N 11.27.

4.6. *H-Gln-Valol* (**28**). According to *GP C*, H_2 was bubbled through a soln. of *Z-Gln-Valol* (530 mg, 1.45 mmol) in MeOH (31 ml) for 4.5 h: 328 mg (98%) of **28**. Colorless foam. M.p. 144.5–145.1°. $[\alpha]_D$ = –4.5 (c = 0.84, MeOH). IR (KBr): 3360*s*, 3300*m* (br), 3180*m*, 2950*m*, 2870*m*, 1650*s*, 1620*s*, 1560*m*, 1450*m*, 1410*m*, 1380*w*, 1370*w*, 1280*w*, 1245*w*, 1200*w*, 1150*w*, 1070*m*, 1035*w*, 710*m* (br). ^{1}H-NMR (CD_3OD): 3.76–3.48 (*m*, CH_2(1)(Valol), CH(2)(Gln)); 3.42–3.32 (*m*, CH(2)(Valol)); 2.30 (*t*, *J* = 7.5, CH_2(4)(Gln)); 2.06–1.72 (*m*, CH_2(3)(Gln), CH(3)(Valol)); 0.96, 0.93 (2*d*, *J* = 6.5, 2 Me(Valol)). ^{13}C-NMR (CD_3OD): 178.6, 177.5 (2*s*, 2 CO(amide)); 63.4 (*t*, C(1)(Valol)); 58.3 (*d*, C(2)(Gln)); 56.1 (*d*, C(2)(Valol)); 33.1 (*t*, C(4)(Gln)); 32.9 (*t*, C(3)(Gln)); 30.4 (*d*, C(3)(Valol)); 20.3, 19.2 (2*q*, 2 Me(Valol)). CI-MS: 232 (100, [*M*+1]$^+$). Anal. calc. for $C_{10}H_{21}N_3O_3$ (231.30): C 51.93, H 9.15, N 18.17; found: C 51.68, H 8.89, N 17.98.

4.7. *Z-Leu-Aib*-D,L-*Iva-Gln-Valol*. To a stirred soln. of **27** (1.10 g, 2.45 mmol) and DIEA (633 mg (4.90 mmol) in DMF (7 ml) at 0°, TBTU (788 mg, 2.45 mmol) and HOBt (366 mg, 2.71 mmol) were added. After 5 min, a soln. of **28** (646 mg, 2.79 mmol) in DMF (2 ml) was added, and after 22 h, the mixture was treated according to *GP D*: 1.27 g (78%) of *Z-Leu-Aib*-D,L-*Iva-Gln-Valol*. Colorless crystals. M.p. 88.4–89.3° (AcOEt/hexane). IR (KBr): 3300*m* (br), 3060*w*, 3040*w*, 2960*m*, 2870*w*, 1705*m*, 1660*s* (br.), 1550*m*, 1535*s*, 1455*m*,

1385*w*, 1370*w*, 1310*w*, 1265*m*, 1220*w*, 1170*w*, 1120*w*, 1050*w*, 1030*w*, 695*w*. ^{1}H-NMR (CD_3OD, mixture of epimers): 7.47–7.33 (*m*, 5 arom. H); 5.18–5.03 (*m*, PhC*H*$_2$O); 4.18–4.02 (*m*, CH(2)(Gln), CH(2)(Leu)); 3.72–3.52 (*m*, CH_2(1), CH(2)(Valol)); 2.43–2.27, 2.27–2.07, 1.95–1.63, 1.63–1.48 (4*m*, CH_2(4)(Gln), CH_2(3)(Gln), CH_2(3)(Iva), CH_2(3)(Leu), CH(4)(Leu), CH(3)(Valol)); 1.40, 1.38, 1.31, 1.28 (4*s*, Me_2C, *Me*C(2)(Iva)); 1.00–0.86 (*m*, 2 Me(Leu), 2 Me(Valol)); 0.84, 0.75 (2*t*, *J* = 7.5, *Me*CH_2(Iva)). ^{13}C-NMR (CD_3OD): 177.9, 177.7, 177.6, 176.9, 176.8, 176.0, 174.4 (8*s*, 5 CO(amide)); 158.8 (*s*, CO(urethane)); 138.4, 138.2 (2*s*, 1 arom. C); 129.5, 129.0, 128.5, 128.4 (4*d*, 5 arom. CH); 67.9, 67.8 (2*t*, Ph*C*H_2O); 63.5 (*t*, CH_2OH); 61.4, 61.0 (2*s*, C(2)(Iva)); 58.5, 58.4 (2*d*, C(2)(Gln)); 57.8 (*s*, Me_2C); 56.3, 55.9, 55.6 (3*d*, C(2)(Leu), C(2)(Valol)); 41.5, 41.3 (2*t*, C(3)(Leu)); 33.6, 33.5 (2*t*, C(4)(Gln)); 32.7 (*t*, C(3)(Gln)); 30.0 (*d*, C(3)(Valol)); 28.4 (2*t*, C(3)(Iva)); 25.8 (*d*, C(4)(Leu)); 24.6, 24.5, 23.3, 23.2, 22.3, 22.1, 21.7 (7*q*, Me_2C, 2 Me(Leu), MeCH_2(Iva)); 20.1, 19.4, 19.3 (3*q*, 2 Me (Valol)); 8.7, 8.0 (2*q*, C(4)(Iva)). ESI-MS: 701 (65, $[M+K]^+$), 685 (100, $[M+Na]^+$), 663 (29, $[M+1]^+$).

The coupling of **27** and **28** with DCC/HOBt according to *GP D* gave the same product, after PLC (SiO_2, CH_2Cl_2/MeOH 95:5) in 29% yield.

4.8. *H-Leu-Aib*-D,L-*Iva-Gln-Valol* (**13**). According to *GP C*, a mixture of *Z-Leu-Aib*-D,L-*Iva-Gln-Valol* (500 mg, 0.75 mmol) and Pd/C (76 mg) in MeOH (10 ml) was treated with H_2 for 47 h: 394 mg (99%) of **13**. Colorless foam. M.p. 88.5–89.5°. ^{1}H-NMR (CD_3OD, mixture of epimers): 4.20–4.08 (*m*, CH(2)(Gln)); 3.73–3.57 (*m*, CH_2(1)(Valol), CH(2)(Valol)); 2.81 (*s*, CH(2)(Leu)); 2.45–2.05, 2.00–1.65, 1.50–1.22 (3*m*, CH_2(4)(Gln), CH_2(3)(Gln), CH_2(3)(Iva), CH_2(3)(Leu), CH(4)(Leu), CH(3)(Valol), Me_2C, *Me*C(2)(Iva)); 1.00–0.70 (*m*, 2 Me(Leu), 2 Me(Valol), *Me*CH_2(Iva)). ESI-MS: 595 (61), 567 (52, $[M+K]^+$), 551 (97, $[M+Na]^+$), 529 (100, $[M+1]^+$).

5. *Coupling of the Segments* **10**, **19**, *and* **13**. 5.1. *Z-Gln-(Aib)$_3$-Ala-Ala-Aib-Pro-Leu-Aib*-D,L-*Iva-Gln-Valol* (**29**). According to *GP D*, to a soln. of **19** (202 mg, 0.24 mmol) in DMF (2 ml) were added DCC (50 mg, 0.24 mmol), HOBt (37 mg, 0.27 mmol), CSA (8 mg), and **13** (154 mg, 0.29 mmol), and the mixture was stirred for 24 h: 125 mg (39%) of **29**. Colorless crystals. M.p. 178.6–179.8° (AcOEt/Et$_2$O/hexane). ^{1}H-NMR (CD_3OD, mixture of epimers): 8.04–7.52 (*m*, 5 NH); 7.47–7.16 (*m*, 5 arom. H, 1 NH); 5.18, 5.08 (*AB*, *J* = 12.5, PhC*H*$_2$O); 4.47–4.29 (*m*, 2 H); 4.22–4.02 (*m*, 3 H); 3.95 (*t*-like, *J* = 6.8, 1 H); 3.88–3.76 (*m*, 1 H); 3.76–3.53 (*m*, 4 H); 2.62–2.48 (*m*, 1 H); 2.43–1.22 (*m*, 56 H); 1.06–0.72 (*m*, 2 Me(Leu), 2 Me(Valol), *Me*CH$_2$(Iva)). ESI-MS: 1408 (23, $[M+K]^+$), 1393 (100, $[M+Na+1]^+$), 716 (56, $[M+K+1]^{2+}$), 708 (100, $[M+2\ Na]^{2+}$).

5.2. *H-Gln-(Aib)$_3$-Ala-Ala-Aib-Pro-Leu-Aib*-D,L-*Iva-Gln-Valol*. According to *GP C*, to a soln. of **29** (95 mg, 0.07 mmol) in MeOH (2 ml) was added Pd/C (21 mg), and the mixture was stirred under an H_2 atmosphere for 48.5 h: 85 mg (quant.) of *H-Gln-(Aib)$_3$-Ala-Ala-Aib-Pro-Leu-Aib*-D,L-*Iva-Gln-Valol*. Colorless foam. ^{1}H-NMR (CD_3OD, mixture of epimers): 7.32–7.18 (*m*, 2 NH); 4.50–4.32 (*m*, 2 H); 4.25–4.02 (*m*, 3 H); 3.87–3.77 (*m*, 1 H); 3.73–3.53 (*m*, 3 H); 3.53–3.38 (*m*, 1 H); 3.38–3.20 (*m*, 1 H); 2.65–2.45, 2.45–2.08, 2.08–1.25 (3*m*, 54 H); 1.25–1.03 (*m*, 3 H); 1.03–0.70 (*m*, 2 Me(Leu), 2 Me(Valol), *Me*CH$_2$(Iva)). ESI-MS: 1236 (34, $[M+1]^+$), 630 (100, $[M+Na+1]^{2+}$).

5.3. *Z-Aib-Gly-Aib-Leu-Aib-Gln-(Aib)$_3$-Ala-Ala-Aib-Pro-Leu-Aib*-D,L-*Iva-Gln-Valol* (**9**). To a stirred soln. of **10** (28 mg, 0.05 mmol) in DMF (1.5 ml) at 0° was added DIEA (14 mg, 0.11 mmol). After 7 min, TBTU (17 mg, 0.05 mmol), HOBt (9 mg, 0.07 mmol), and, after another 5 min, *H-Gln-(Aib)$_3$-Ala-Ala-Aib-Pro-Leu-Aib*-D,L-*Iva-Gln-Valol* (69 mg, 0.06 mmol), were added and the mixture was stirred for 25.5 h. After filtration through a Celite pad, DMF was evaporated, the residue was dissolved in AcOEt, washed with 2N HCl (2x) and 1N NaOH, and dried (Na_2SO_4). CC (SiO_2, AcOEt) and crystallization from

CH_2Cl_2/Et_2O/hexane gave 32 mg (37%) of **9**. Colorless crystals. ESI-MS: 1848 (29), 1834 (30, $[M+K+1]^+$), 1818 (100, $[M+Na+1]^+$), 1710 (31).

5.4. *Z-Aib-Gly-Aib-Leu-Aib-Gln(Trt)-(Aib)$_3$-Ala-Ala-Aib-Pro-O^{t}Bu* (**30**). According to *GP D*, to a soln. of **10** (217 mg, 0.38 mmol) in DMF (4 ml) was added DIEA (98 mg, 0.76 mmol). After stirring for 5 min, TBTU (121 mg, 0.38 mmol), HOBt (56 mg, 0.41 mmol), and, after another 9 min, **25** (408 m, 0.40 mmol) were added. The mixture was stirred for 16.5 h. Workup by CC and PLC (SiO_2, CH_2Cl_2/MeOH) gave 304 mg (51%) of **30**. Colorless foam. M.p. 168.8–169.7°. ^{1}H-NMR (CD_3OD): 8.33, 8.06 (2*s*, 2 NH); 8.02 (*d*, *J* = 5.2, NH); 7.95, 7.93, 7.91, 7.82 (4*s*, 4 NH); 7.69 (*d*, *J* = 5.6, NH); 7.50–7.00 (*m*, 20 arom. H); 5.17, 5.12 (*AB*, *J* = 12.8, PhCH_2O); 4.38–4.25 (*m*, CH(2)(Ala), CH(2)(Pro)); 4.15–3.94 (*m*, CH(2)(Leu), CH(2)(Gln), CH(2)(Ala)); 3.82–3.62 (*m*, CH_2(5)(Pro), CH_2(Gly)); 2.65–2.53, 2.46–2.35 (*m*, CH_2(4)(Gln)); 2.20–1.20 (*m*, 66 H); 0.94, 0.87 (2*d*, *J* = 6.5, 2 Me(Leu)). ESI-MS: 1644 (9, $[M+K+Na]^+$), 1622 (15, $[M+K+1]^+$), 1606 (100, $[M+Na+1]^+$).

5.5. *Z-Aib-Gly-Aib-Leu-Aib-Gln-(Aib)$_3$-Ala-Ala-Aib-Pro-OH* (**31**). According to *GP E*, a soln. of **30** (68 mg, 0.04 mmol) in TFA (1 ml) was stirred for 2.75 h: 55 mg (quant.) of **31**. Colorless crystals. M.p. 161.6–162.3° (CH_2Cl_2/Et_2O/hexane). ^{1}H-NMR (CD_3OD): 8.77, 8.02, 7.96, 7.94, 7.91, 7.81, 7.77, 7.61 (8*s*, 9 NH); 7.44–7.12 (*m*, 5 arom. H, 3 NH); 5.17, 5.12 (*AB*, *J* = 12.7, PhCH_2O); 4.44 (*dd*, *J* = 9.0, 4.1, CH(2)(Pro)); 4.38–4.25, 4.15–3.90 (2*m*, CH(2)(Leu), CH(2)(Gln), 2 CH(2)(Ala), CH_2(Gly)); 3.80–3.62 (*m*, CH_2(5)(Pro)); 2.50–2.35, 2.35–2.22, 2.22–1.82, 1.82–1.34 (4*m*, 59 H); 0.94, 0.88 (2*d*, *J* = 5.8, 2 Me(Leu)). ESI-MS: 1323 (32, $[M+K]^+$), 1307 (100, $[M+Na]^+$), 1211 (11).

6. *X-Ray Crystal-Structure Determination of* **10** *and* **21** (see *Table 5* and *Figs. 1* and *2*)[12]). The measurements were made using graphite-monochromated MoK_α radiation

[12]) CCDC-627754 & 627755 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre

(λ 0.71073 Å) on a *Nicolet-R3* diffractometer (**21**) or on a *Rigaku AFC5R* diffractometer fitted to a 12-kW rotating-anode generator (**10**). The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections, other than Friedel pairs, were merged. The data collection and refinement parameters are given in *Table 5*, and views of the molecules are shown in *Figs. 1* and *2*. Each structure was solved by direct methods using SHELXS86 [54], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amide and hydroxy H-atoms were placed in the positions indicated by difference electron density maps and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). The refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied in the case of **21**. For **10**, two reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from [55], and the scattering factors for H-atoms were taken from [56]. Anomalous dispersion effects were included in F_c [57]; the values for f' and f'' were those of [58]. The values of the mass attenuation coefficients are those of [59]. The *SHELXL97* program was used for all calculations [60].

Table 4

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via www.ccdc.cam.ac.uk/data_request/cif.

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Legends

Fig. 1. *ORTEP-Plot* [37] *of the molecular structure of* **10** (arbitrary numbering of atoms, 50% probability ellipsoids, H-atoms bonded to C-atoms have been omitted for clarity)

Fig. 2. *ORTEP-Plot* [37] *of the molecular structure of* **21** (arbitrary numbering of atoms, 30% probability ellipsoids, H-atoms bonded to C-atoms have been omitted for clarity)

Fig. 3. *Mass-Spectra of the Octapeptide* **19**; a) *ESI-MS and* b) *FAB-MS*

Fig. 4. *Mass-Spectra of the Tridecapeptides* **30** *and* **31**; a) *ESI-MS of* **30**, b) *ESI-MS of* **31**, *and* c) *FAB-MS of* **31**

Table 1. *Sequences of* Trichotoxins A-50 [15]

Table 2. *Torsion Angles and H-Bonding Parameters in the Crystal-Structure of* **10**

Table 3. *Torsion Angles and H-Bonding Parameters in the Crystal-Structure of* **21**

Table 4. *Yields of the Coupling of Azirine* **2a** *and the Hydrolysis of the Terminal Amide Group of Z-Gln(X)-(Aib)*$_n$*-N(Me)Ph Derivatives*

Table 5. *Crystallographic Data for Compounds* **10** *and* **21**

Table 1. *Sequences of* Trichotoxins A-50 [15]

Ac-Aib-Gly-Aib-Leu-Aib-Gln-Aib-Aib-Aib-Ala-Ala-Aib-Pro-Leu-Aib-Aib-Gln-Valol	(E)
Ac-Aib-Gly-Aib-Leu-Aib-Gln-Aib-Aib-Ala-Ala-Ala-Aib-Pro-Leu-Aib-Iva-Gln-Valol	(F)
Ac-Aib-Gly-Aib-Leu-Aib-Gln-Aib-Aib-Aib-Ala-Ala-Aib-Pro-Leu-Aib-Iva-Gln-Valol	(G)
Ac-Aib-Ala-Aib-Leu-Aib-Gln-Aib-Aib-Aib-Ala-Ala-Aib-Pro-Leu-Aib-Iva-Gln-Valol	(H)
Ac-Aib-Gly-Aib-Leu-Aib-Gln-Aib-Aib-Aib-Ala-Aib-Aib-Pro-Leu-Aib-Iva-Gln-Valol	(I)
Ac-Aib-Ala-Aib-Leu-Aib-Gln-Aib-Aib-Aib-Ala-Aib-Aib-Pro-Leu-Aib-Iva-Gln-Valol	(J)

Table 2. *Torsion Angles and H-Bonding Parameters in the Crystal-Structure of* **10**

Amino Acid	ϕ [°]	ψ [°]	ω [°]
Aib(1)	–56.5(3)	–51.4(3)	–174.0(2)
Gly(2)	–69.7(3)	–50.4(3)	–175.2(2)
Aib(3)	–54.9(3)	–41.8(3)	–171.4(2)
Leu(4)	–103.3(3)	16.6(3)	176.2(2)
Aib(5)	52.9(3)	47.4(3)	-

D–H···A	D···A [Å]	D–H···A [°]
N(4)–H···O(2)	3.049(3)	155(3)
N(5)–H···O(4)	3.130(3)	168(3)
O(8)–H···O(3)	2.667(3)	167(4)
N(1)–H···O(5')[a])	2.992(3)	142(3)
N(2)–H···O(6")	2.905(3)	134(3)
N(3)–H···O(7")	2.923(3)	172(3)

[a]) Primed atoms refer to the molecule in the following symmetry related positions:

' $1 + x, y, z$; " $1 - x, -1/2 + y, 1 - z$

Table 3. *Torsion Angles and H-Bonding Parameters in the Crystal-Structure of* **21**

Amino Acid	ϕ [°]	ψ [°]	ω [°]
Ala(1)	–81.9(7)	–11.4(7)	174.4(5)
Ala(2)	–133.6(5)	141.3(5)	169.9(5)
Aib(3)	52.8(7)	43.9(6)	171.5(4)
Pro(4)	–64.8(6)	–32.5(6)	–171.5(5)

D–H···A	D···A [Å]	D–H···A [°]
N(1)–H…O(3')[a])	2.893(7)	178(4)
N(3)–H…O(5")	2.835(6)	178(6)

[a]) Primed atoms refer to the molecule in the following symmetry related positions:

' 2 – *x*, 1/2 + *y*, 1 – *z*; " 2 – *x*, –1/2 + *y*, 2 – *z*

Table 4. *Yields of the Coupling of Z-Gln(X)-OH with Azirine* **2a** *and the Hydrolysis of the Terminal Amide Group of Z-Gln(X)-(Aib)$_n$ Derivatives*

Peptide	Yield [%]		
Protecting Group X	Trt	DMB	Dod
Z-Gln(X)-Aib-N(Me)Ph[a])	89	83	94
Z-Gln(X)-Aib-OH[b])	98	98	97
Z-Gln(X)-(Aib)$_2$-N(Me)Ph[a])	87	88	97
Z-Gln(X)-(Aib)$_2$-OH[b])	quant.	99	97
Z-Gln(X)-(Aib)$_3$-N(Me)Ph[a])	89	95	85
Z-Gln(X)-(Aib)$_3$-OH[b])	92 (**11a**)	95 (**11b**)	quant. (**11c**)
Total yield of **11**[c])	62.1	63.9	72.9

[a]) Coupling of Z-Gln(X)-OH (**23a**–**23c**) with **2a** in CH_2Cl_2 at r.t.

[b]) Hydrolysis in 3N HCl (THF/H_2O 1:1) at r.t.

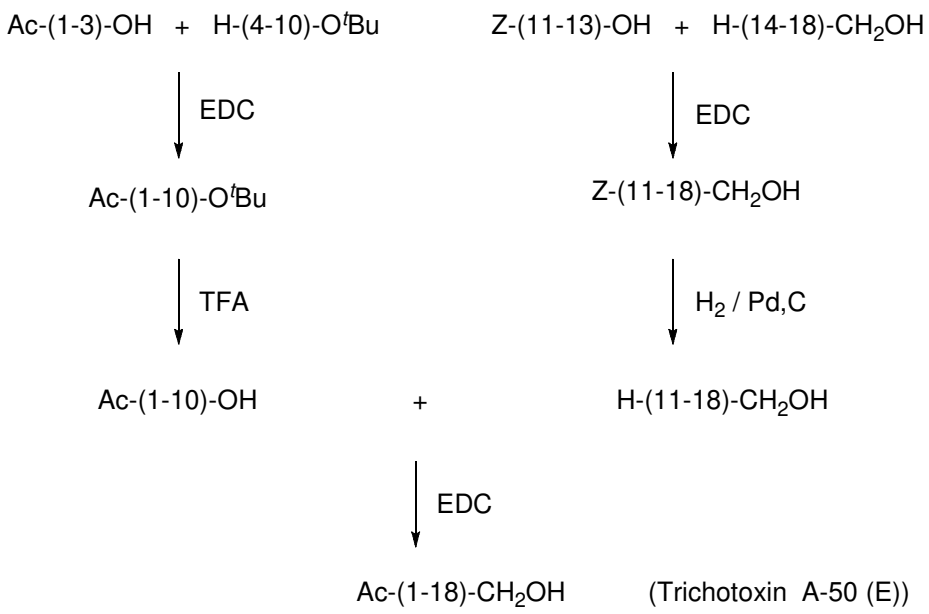
[c]) Total yield with respect to **23**.

Table 5. *Crystallographic Data for Compounds* **10** *and* **21**

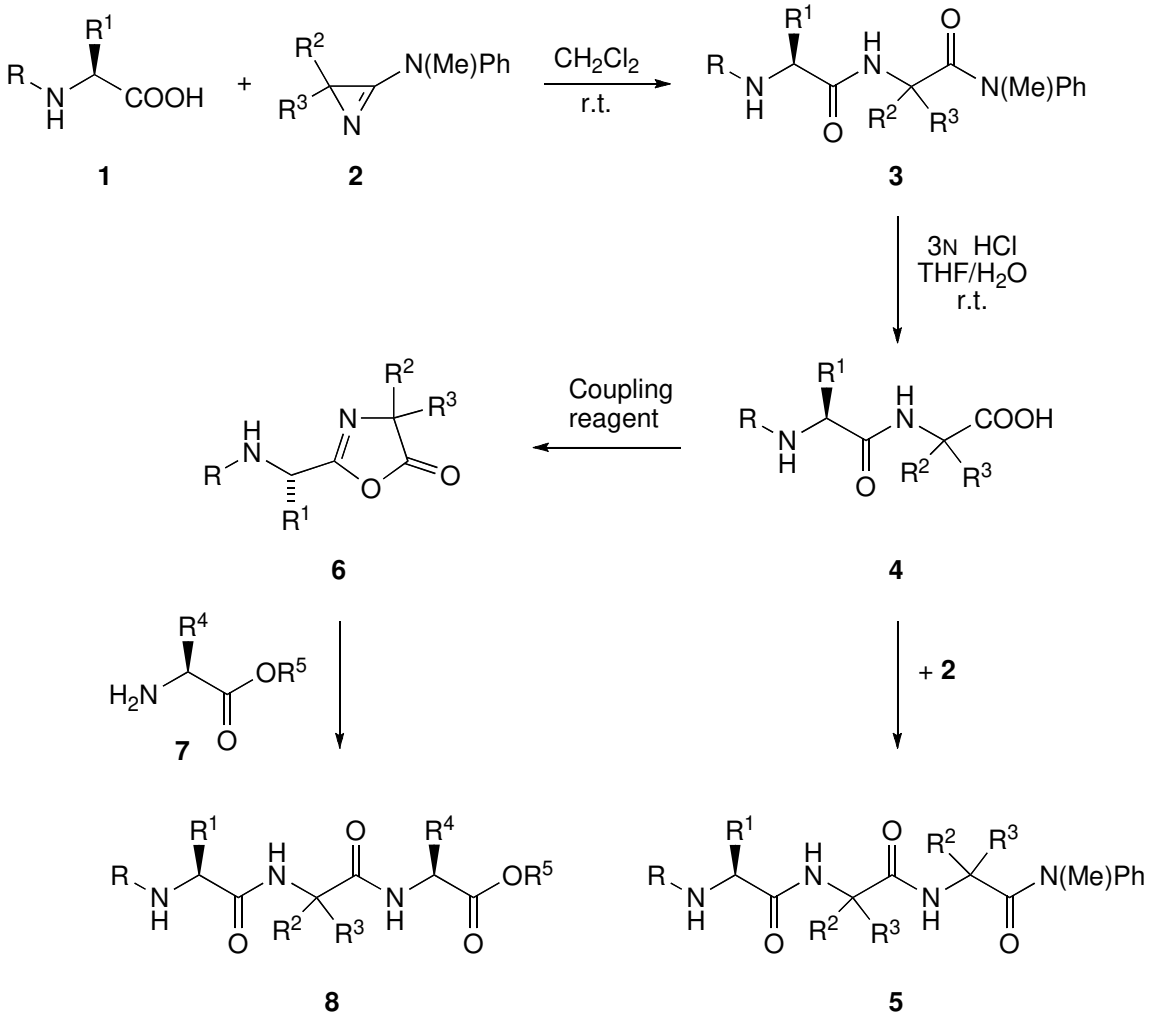
	10	**21**
Crystallized from	CH_2Cl_2/Et_2O/hexane	MeOH/H_2O/CH_2Cl_2
Empirical formula	$C_{28}H_{43}N_5O_8$	$C_{27}H_{40}N_4O_7$
Formula weight	577.67	532.63
Crystal color, habit	colorless, prism	colorless, prism
Temperature [K]	173(1)	295(1)
Crystal system	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$
Z	2	2
Reflections for cell determination	25	25
2θ range for cell determination [°]	38–40	24–28
Unit cell parameters a [Å]	9.841(4)	11.475(15)
b [Å]	16.668(4)	10.381(13)
c [Å]	10.422(6)	12.930(15)
β [°]	113.44(4)	101.07(10)
V [Å^3]	1568(1)	1512(3)
D_X [g cm^{-3}]	1.223	1.171
μ(Mo$K\alpha$) [mm^{-1}]	0.090	0.085
Scan type	$\omega/2\theta$	ω
2θ(max) [°]	60	46
Total reflections measured	4969	2952
Symmetry independent reflections	4717	2522
Reflections with $I > 2\sigma(I)$	3588	1556
Reflections used in refinement	4715	2522
Parameters refined; restraints	402; 1	363; 1
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0441	0.0472
$wR(F^2)$ (all data)	0.1092	0.0780
Weighting parameters (a; b)[a]	0.0384; 0.4557	0.0342; 0
Goodness of fit	1.025	0.986
Final Δ_{max}/σ	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.29; –0.21	0.11; –0.11

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

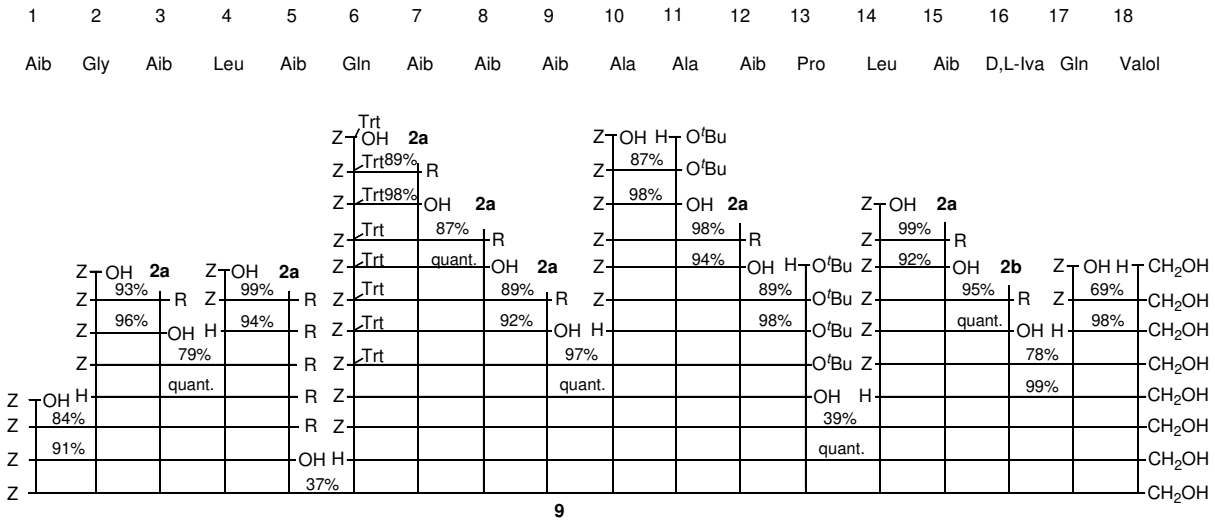
Scheme 1

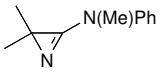

Ac-(1-3)-OH + H-(4-10)-O^{t}Bu
EDC
Ac-(1-10)-O^{t}Bu
TFA
Ac-(1-10)-OH
Z-(11-13)-OH + H-(14-18)-CH$_2$OH
EDC
Z-(11-18)-CH$_2$OH
H$_2$ / Pd,C
H-(11-18)-CH$_2$OH
+
EDC
Ac-(1-18)-CH$_2$OH
(Trichotoxin A-50 (E))

Scheme 2

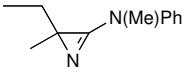

CH2Cl2
r.t.
N(Me)Ph
3N HCl
THF/H2O
r.t.
Coupling
reagent
COOH
OR5
+ 2
1
2
3
4
5
6
7
8

Scheme 3



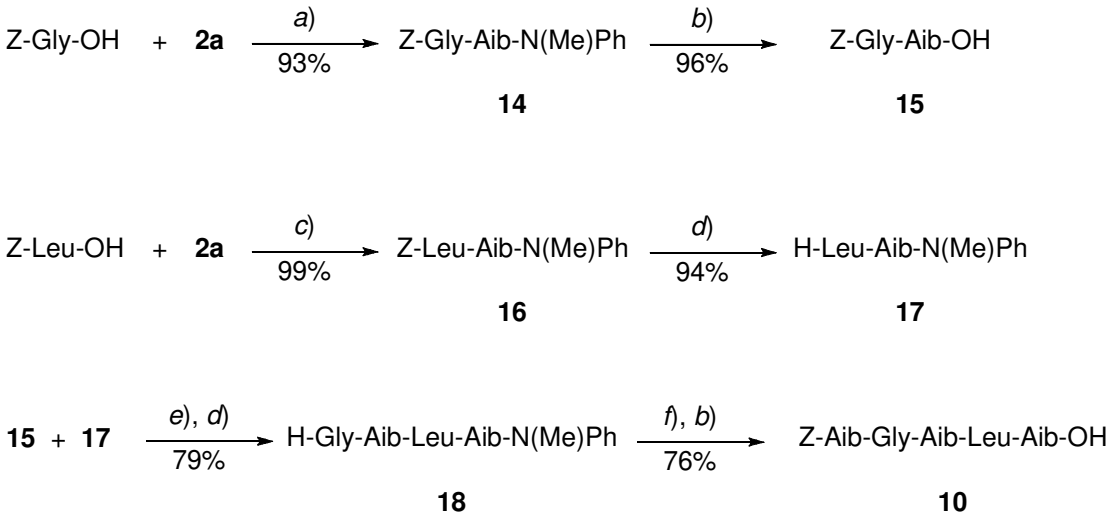


2a



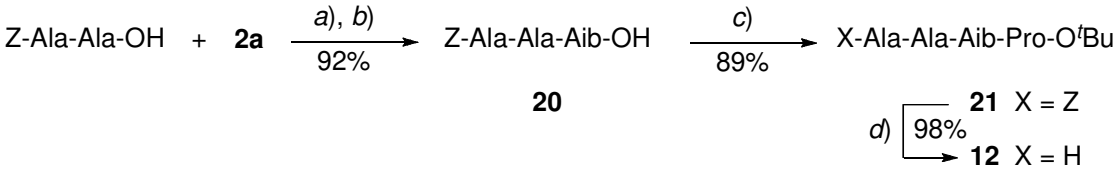
2b

Scheme 4



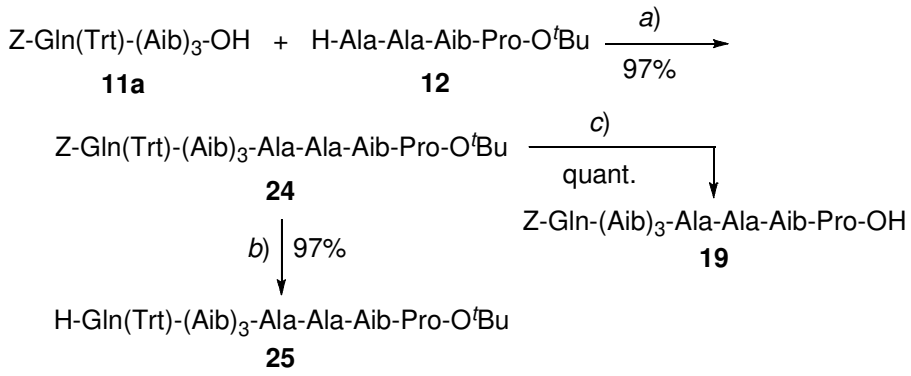
a) THF, r.t.; *b*) 3N HCl, H_2O/THF, r.t.; *c*) Et_2O, r.t.; *d*) H_2, Pd/C, MeOH, r.t.;
e) DCC, HOBt, $ZnCl_2$, DMF, 0° ⟶ r.t.; *f*) Z-Aib-OH, DCC, HOBt, CSA, 0° ⟶ r.t.

Scheme 5



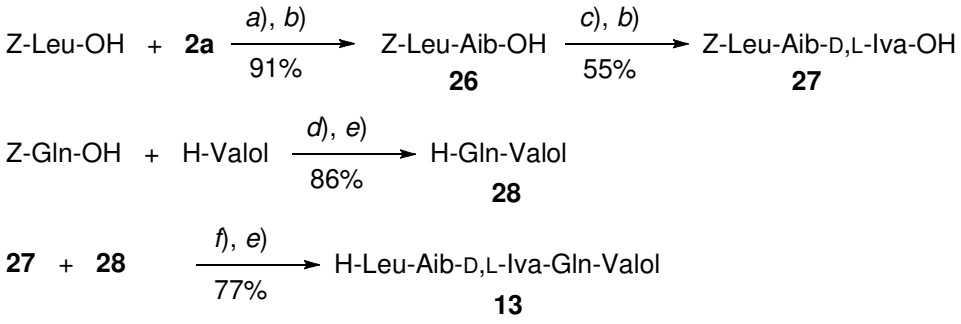
a) THF, r.t.; *b*) 3N HCl, H_2O/THF, r.t.; *c*) H-Pro-O^{t}Bu, DCC, HOBt, CSA, DMF, 0° r.t.;
d) H_2, Pd/C, MeOH

Scheme 6



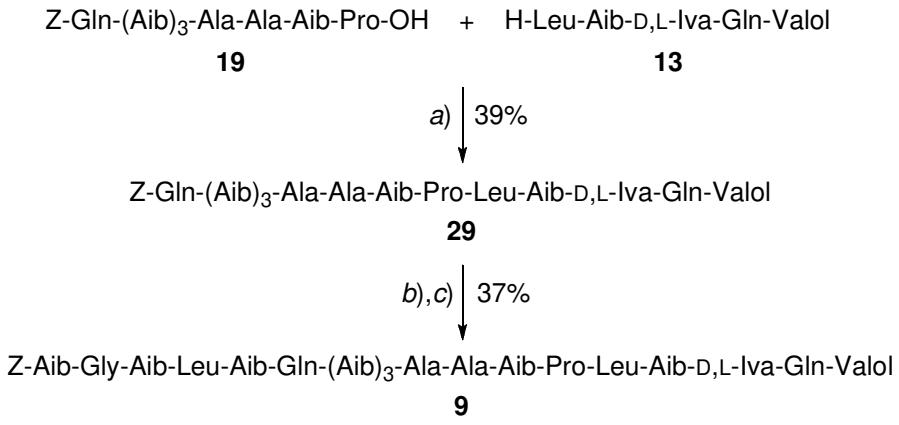
a) DCC, HOBt, CSA, DMF, 0° → r.t.; *b*) H_2, Pd/C, MeOH, r.t.
c) CF_3COOH, 0°

Scheme 7



a) Et_2O, 0° → r.t.; *b*) 3N HCl, H_2O/THF, r.t.; *c*) CH_2Cl_2, 0° → r.t.; *d*) $ClCO_2Et$, NMM, -10° → r.t.; *e*) H_2, Pd/C, MeOH, r.t.; *f*) TBTU, HOBt, DIEA, DMF, 0° → r.t.

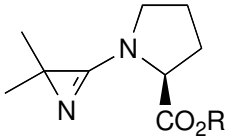
Scheme 8



a) DCC, HOBt, CSA, DMF, 0° → r.t.; *b*) H_2, Pd/C, MeOH, r.t.; *c*) **10**, DIEA, TBTU, HOBt, 0° → r.t.

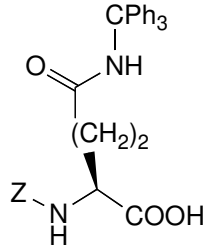
Formulae

Footnote 5)

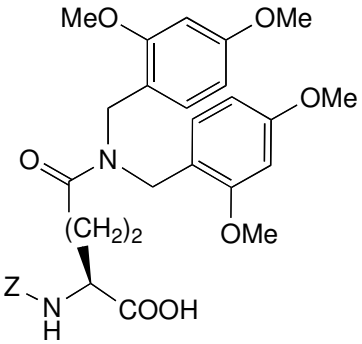


22

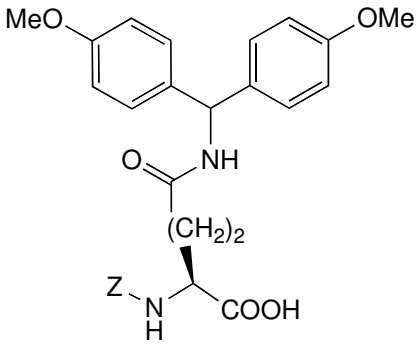
Table 4, a)



23a, Z-Gln(Trt)-OH

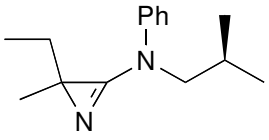


23b, Z-Gln(DMB)$_2$-OH

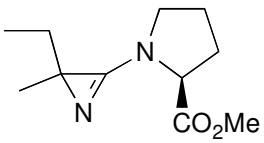


23c, Z-Gln(Dod)-OH

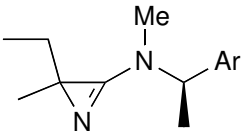
Footnote 9)



2c [36]



2d [48]



2e Ar = Ph [49]
2f Ar = 1-naphthyl [50]

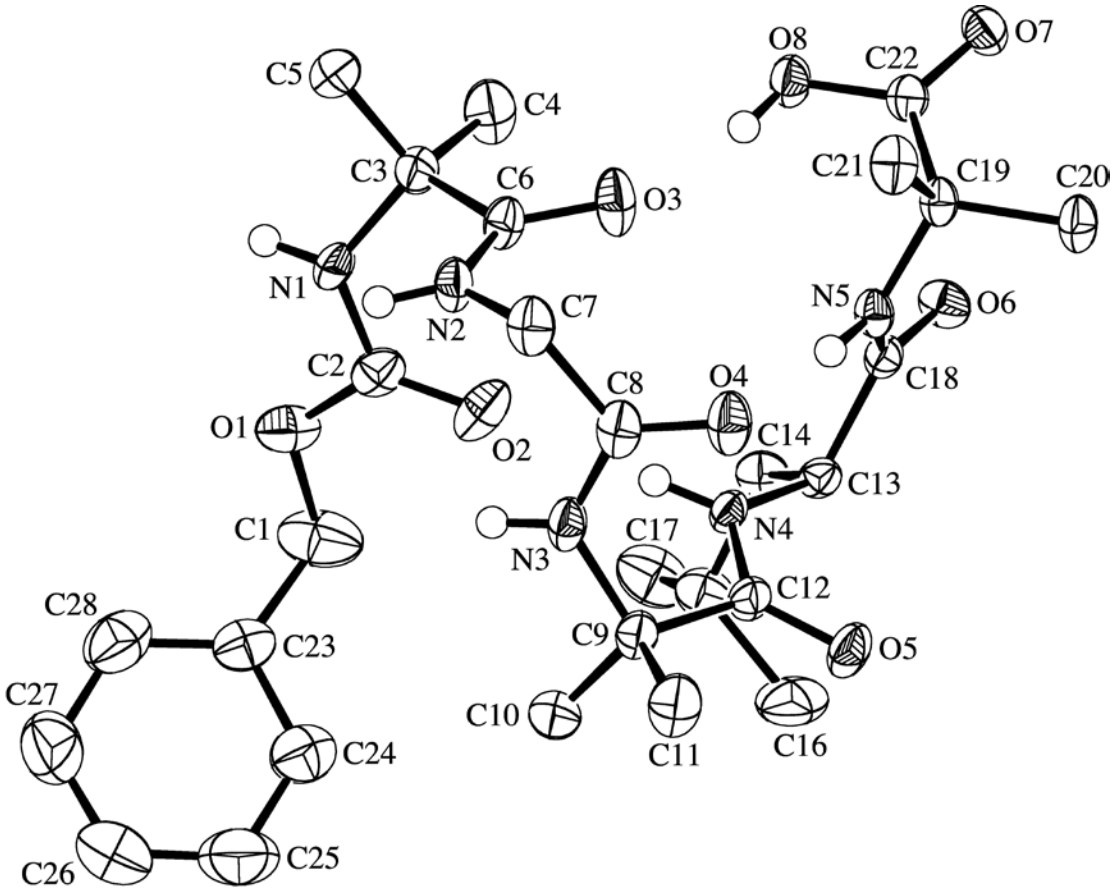

O8
O7
C22
C5
C4
C3
C6
O3
C21
C19
C20
N1
N2
C7
N5
O6
C2
C8
O4
C18
O1
O2
C14
C13
C1
N3
C17
N4
C28
C12
C23
C9
O5
C27
C10
C11
C16
C24
C26
C25

Figure 1

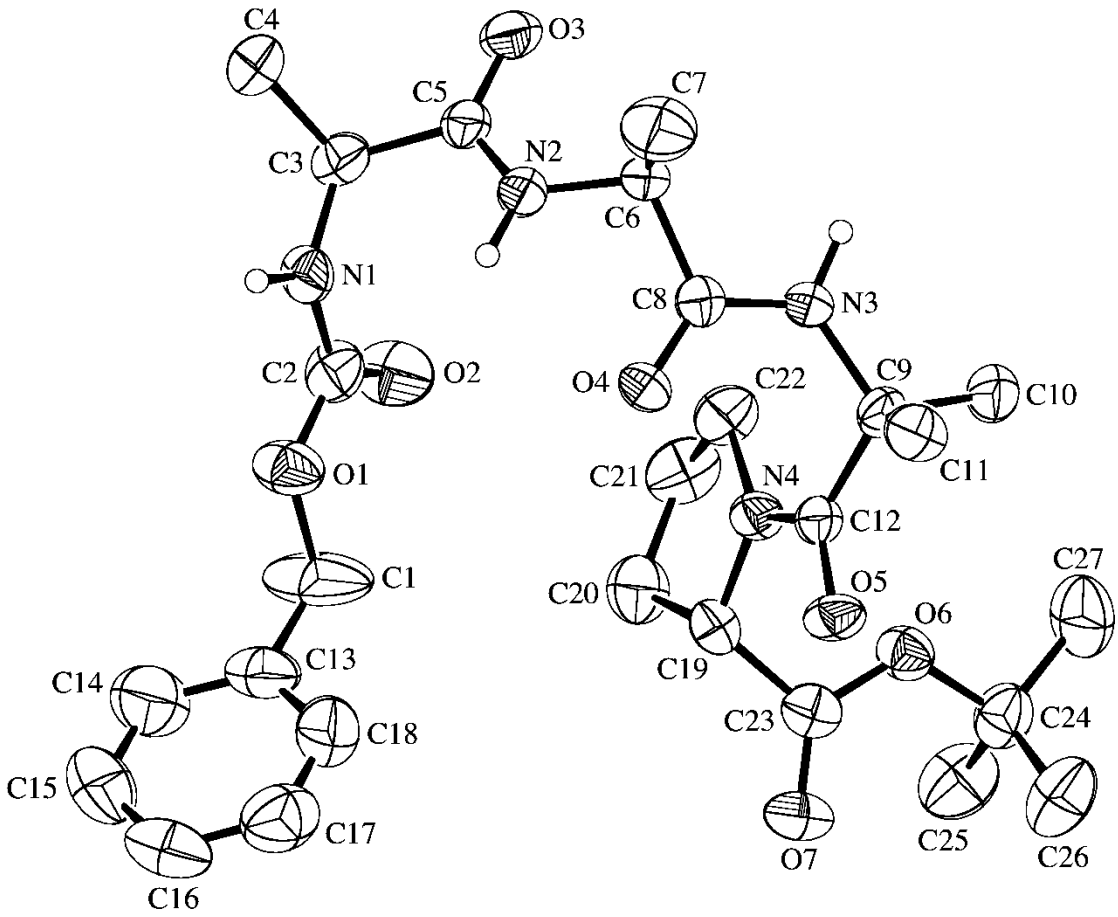

C4
O3
C5
C7
C3
N2
C6
N1
C8
N3
C2
O2
O4
C22
C9
C10
O1
C21
N4
C11
C12
C1
C20
O5
C27
O6
C19
C13
C14
C18
C23
C24
C15
C17
O7
C25
C26
C16

Figure 2

Figure 3

Figure 4

Graphical Abstract