Attempts toward the Synthesis of the Peptaibol Antiamoebin I by Using the 'Azirine/Oxazolone Method'¹)

by Pia Blaser²), Werner Altherr³)[†], Anthony Linden, and Heinz Heimgartner*

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich (phone: +41-44-6354282; fax: +41-44-6356836; e-mail: heimgart@oci.uzh.ch)

The two segments, 1–9 and 10–16, of the peptaibol antibiotic antiamoebin I, *i.e.*, the nonapeptide Ac-Phe-Aib-Aib-Aib-D,L-Iva-Gly-Leu-Aib-Aib-OH (**15**) and the heptapeptide Z-Hyp-Gln-D,L-Iva-Hyp-Aib-Pro-Pheol (**34**), have been prepared as mixtures of the epimers containing D,L-Iva. All a,a-disubstituted a-amino acids were introduced by the 'azirine/oxazolone method', in which amino or peptide acids are coupled with the corresponding 2*H*-azirin-3-amines, followed by selective hydrolysis of the terminal amide bond. The amino acids Hyp and Gln were introduced as Z-protected⁴) (2*S*,4*R*)-4-(*tert*-butoxy)proline (**19**) and methyl *N*-[bis(4-methoxyphenyl)methyl]glutamine (**26**). Coupling of peptide segments was achieved *via* the 'mixed anhydride' method, the DCC/HOBt or TBTU/HOBt strategy. The crystal structure of the segment 6–9 was determined by X-ray crystallography and displayed the presence of a β -turn conformation.

1. Introduction. – The reaction of 2*H*-azirine-3-amines of type **1** with *N*-protected α -amino acids or peptides proved to be useful for the synthesis of peptides containing α , α -disubstituted α -amino acids, *e.g.*, α -aminoisobutyric acid (Aib) [2]. It has been shown that the so-called 'azirine/oxazolone method' [3] is an attractive tool for the preparation of peptaibol segments [4] and peptaibols [5]. Furthermore, a solid-phase protocol of the 'azirine/oxazolone method' has been developed [6].

Peptaibols are naturally occurring linear, bioactive **pept**ides, produced by filamentous fungi such as *Trichoderma* and *Gliocladium* (with teleomorphs in *Hypocrea*), *Emericillopsis*, *Stilbella*, and *Acremonium*. According to definition, these *N*-acylated peptides contain **Aib**, frequently together with other α, α -disubstituted α -amino acids, as well as a C-terminal β -amino alcohol such as Pheol, Valol, or Leuol [7–9]. They attracted increasing interest because of their biological activities as antifungal, antibacterial, and anticancer compounds [10]. Recently, it has been shown that they are synthesized by non-ribosomal peptide synthetases [11]. These oligopeptides are well-known to occur in rather stable helical conformations, *i.e.*, α -helix, 3_{10} -helix, and β -bend ribbon spiral, as a result of the high content of Aib residues [12] (for some exceptions, see [13]). Based on these structural properties, peptaibols are 'membrane-active'

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²) In part from the Diploma thesis of *P. B.*, Universität Zürich, 1990.

³) Part of the Ph.D. thesis of *W. A.*, Universität Zürich, 1994. [†] Dr. *Werner Altherr* passed away on October 4, 2012.

⁴⁾ For all abbreviations, cf. the Exper. Part.

polypeptide antibiotics, which, after aggregation to bundles, form 'ion-channels' through biological membranes [7a][14][15].

The natural peptaibol *Antiamoebin* was reported initially as a mixture of two compounds (antiamoebins I and II (AAM I and AAM II, resp.); *Fig. 1*) in a ratio of *ca.* 98:2. The antibiotic activity of this peptaibol was described for the first time by *Thirumalachar* [16], and the primary structure was established stepwise by *Vaidya et al.*, *Pandey et al.*, and *Brückner et al.* [17]. It was shown that antiamoebin consists of mixtures of up to 16 microheterogeneous 16-mer peptaibols with varying compositions depending on the source of the natural material [17e]. The crystal structure of AAM I has been solved by X-ray crystallography independently by *Karle et al.* and *Snook et al.* [18], establishing the presence of a right-handed helix. On the other hand, it was reported that the *N*-terminus of AAM I in solution (DMSO or MeOH) forms a left-handed helical structure [14b][19]. A recent study of the conformation in MeOH solution showed a rapid exchange between the right-handed and left-handed 3_{10} -helical conformation of the N-terminal segment Ac-Phe-Aib-Aib-Aib-Iva-Gly [20]. Furthermore, several studies on the ability of antiamoebin to form ion channels have been published [19][21].

Ac-Phe-Aib-Aib-Aib-D-Iva-Gly-Leu-Aib-Aib-Hyp-Gln-D-Iva-Hyp-Aib-Pro-Pheol (AAM I) Ac-Phe-Aib-Aib-Aib-D-Iva-Gly-Leu-Aib-Aib-Hyp-Gln-D-Iva-Pro-Aib-Pro-Pheol (AAM II)

Fig. 1. Sequences of antiamoebins I and II [18]

The aim of the present study was the elaboration of a practical synthesis of the segments 1-9 and 10-16 of AAM I by applying the 'azirine/oxazolone method'.

2. Results and Discussion. -2.1. Synthesis of Ac-Phe-Aib-Aib-Aib-D,L-Iva-Gly-Leu-Aib-Aib-OH (1). – Based on our experience, the 'azirine coupling' should be ideally suited for the synthesis of the segment 1-5 (*i.e.*, Ac-Phe-Aib₃-D,L-Iva-OH, **2**)) with four consecutive a,a-disubstituted a-amino acids. We have shown that similar peptide segments could be prepared conveniently by repeating the sequence 'azirine coupling' and selective hydrolysis [3c][5b][22]. Therefore, N-acetylated L-phenylalanine, Ac-Phe-OH, in THF was reacted with 2,2,N-trimethyl-N-phenyl-2H-azirin-3-amine (**1a**) at $20-35^{\circ}$, leading to dipeptide amide **3** in quantitative yield (Scheme 1). Subsequent hydrolysis under standard conditions (3N HCl, THF/H₂O 1:1, r.t.) gave the corresponding peptide acid **4** in 90% yield. These two reaction steps were repeated to give tripeptide **6** and tetrapeptide **8**⁵). The reaction of the latter with the racemic isovaline (Iva) synthon **1b** [5b] was carried out at $20-50^{\circ}$ to give pentapeptide amide **2** as a mixture of the epimers in 96% yield⁶). Selective hydrolysis then yielded **2** as

⁵) This tetrapeptide has been prepared previously by conventional coupling methods within the synthesis of emerimicins III and IV [23].

⁶⁾ An attempted separation of the epimers by means of preparative HPLC (*LiChrosorb RP18*, MeOH/H₂O gradient) gave the epimers in enriched form (8:1 and 1:7, resp.). In the mean time, we have elaborated a preparative method for the synthesis of enantiomerically pure Iva synthons [4b][24].



In a similar manner, the protected segment 6-9, **10**, was prepared, starting with Z-Gly-Leu-OH, by azirine coupling with **1a** to give **11**, hydrolysis to **12**, and again coupling with the Aib-synthon **1a** to yield **10** (*Scheme 2*). Finally, the N-terminus was deprotected by hydrogenolysis to give tetrapeptide amide **13**.

For the coupling of the two segments 2 and 13, different conditions were evaluated, *i.e.*, *via* the 'mixed anhydride' [25] or *via* a 1,3-oxazol-5(4*H*)-one by treatment with DCC⁴) or CME-CDI [26] in the presence of CSA or ZnCl₂ [3b] (see *Exper. Part*). The best result was obtained when a solution of 2 in THF/DMF 1:1 was treated subsequently with equimolar amounts of *N*-methylmorpholine (NMM), isobutyl chloroformate, and 13, to give 14 in 69% yield (*Scheme 2*). Hydrolysis of the latter with 3N HCl (THF/H₂O 1:1) at room temperature afforded 15 in 67% yield as a mixture of epimers.

In addition to these reactions, hydrolysis of **10** was performed with 3N HCl under standard conditions to yield Z-Gly-Leu-Aib-Aib-OH (**16**; 82%), and subsequent deprotection of the NH₂ group (H₂, Pd/C) gave tetrapeptide H-Gly-Leu-Aib-Aib-OH (**17**) in almost quantitative yield (*Scheme 3*).

Single crystals of **16**, of modest quality for an X-ray crystal-structure analysis, were obtained from CH_2Cl_2 . Although the results have low precision, the overall composition of the molecule has been determined unambiguously. The crystal structure of **16** is shown in *Fig.* 2. The space group of **16** permits the compound in the crystal to be enantiomerically pure, but the absolute configuration has not been





determined. The enantiomer used in the refinement was based on the known (*S*)configuration of Leu. Both ends of the molecule are disordered over two approximately equally occupied conformations. The N(1)–H group of Aib⁴ forms an intramolecular H-bond with O(4) of Gly¹ thus creating a loop that can be described by the graph set motif [28] of S(10) (β -turn). The N(4)–H and N(3)–H groups form intermolecular Hbonds with an amide O-atom (N(4)–H···O(2')) and the C=O group of the acid function (N(3)–H···O(1')), respectively, of the same neighboring molecule. These interactions link the molecules into extended chains running parallel to the [110] direction, and each interaction can be described by the C(11) graph set motif [28]. The chains also include an intermolecular H-bond between the OH group and an adjacent amide O-atom (O(11)–H···O(3^), graph set motif C(10)), but the direction of propagation of this interaction is opposite to that of the other two interactions. The three-fold screw axis parallel to [001] results in two additional sets of symmetry-related chains running parallel to [100] and [010]. The interaction of N(2)–H with an amide Oatom in a different neighboring molecule (N(2)–H···O(5'')) serves at the local level to



Fig. 2. ORTEP Plot [27] of the molecular structure of one of the disordered conformations of **16** (50% probability ellipsoids; arbitrary numbering of atoms; H-atoms bonded to C-atoms have been omitted for clarity)

link pairs of molecules into dimers in which the $R_2^2(20)$ ring motif is evident. At the extended level, these latter interactions cross-link the above-mentioned chains to yield overall a three-dimensional H-bonded network of peptide molecules.

2.2. Synthesis of Z-Hyp-Gln-D,L-Iva-Hyp-Aib-Pro-Pheol (34). The synthesis of segment 10–16 of AAM I started with the preparation of the C-terminal tetrapeptide **18** (*Scheme 4*). Although the coupling of Z-Hyp-OH with the Aib synthon **1a** and the subsequent hydrolysis furnished Z-Hyp-Aib-OH in good yield [29], the attempted coupling with H-Pro-Pheol *via* the mixed anhydride [25] failed. Therefore, the *O*-protected Hyp derivative **19** was used, and the reaction with **1a** in CH₂Cl₂ at room temperature gave dipeptide amide **20** in 96% yield, and subsequent hydrolysis afforded the acid **21** (86%). Hydrogenolytic deprotection of **20** to give **22** was achieved in 90% yield. The segment H-Pro-Pheol (**24**) was obtained from Z-Pro-OH and H-Pheol *via* the mixed anhydride and deprotection of **23**. The coupling of **21** with **24** by using DCC/HOBt in the presence of CSA yielded **25** (78%). Hydrogenolytic deprotection of the amino group led to the desired **18**.

For the preparation of segment 10-12, Gln derivative **26** with the Dod-protected [30] amide function was chosen [5b]. Treatment of **19** and **26** with DCC/HOBt/CSA in DMF at 0° led to the fully protected dipeptide **27**, which was saponified to give the dipeptide acid **28** in 88% yield (*Scheme 5*). Reaction of the latter with the Iva synthom



1b gave tetrapeptide **29** as a mixture of epimers in 80% yield⁷), and subsequent selective hydrolysis led to the tripeptide acid **30** (95%).

Unfortunately, the attempted coupling of the segments **30** and **18** by treatment with DCC/HOBt/CSA in DMF failed. It is worth mentioning that, under the same conditions, the related tripeptide Z-Hyp('Bu)-Gln(Dod)-Aib-OH reacted with **18** to give Z-Hyp('Bu)-Gln(Dod)-Aib-Hyp('Bu)-Aib-Pro-Pheol [29], *i.e.*, the protected C-terminal heptapeptide of zervamicin IA [32], albeit in only 11% yield.

Finally, the desired segment 10-16 of AAM I was prepared by the 3+2+2 condensation depicted in *Scheme 6*. The coupling of the tripeptide **30** with the dipeptide

7) Attempts to separate the diastereoisomers by prep. HPLC (*Nucleosil 100-7*) were not successful. Therefore, the analogous reaction of **28** with the Iva synthons **1c** [29] and **1d** [31] bearing a chiral auxiliary group were carried out, leading to the corresponding tripeptides of type **29** in 75 and 76% yield, respectively. Again, in each case two epimers were formed in almost equal amounts, which could not be separated [29].





22 by using TBTU/HOBt/EtNⁱPr₂ was successful and gave the pentapeptide **31** in a yield of $60\%^8$). Subsequent selective hydrolysis of the terminal amide group was accomplished under the usual conditions (3N HCl, H₂O/THF 1:1, r.t.), and the peptide acid **32** was obtained in 94% yield. The latter was coupled with the earlier prepared C-terminal dipeptide **24**, with DCC/HOBt/CSA as the coupling reagents, to yield the protected terminal heptapeptide **33** (60%). All side-chain functional groups, *i.e.*, the 'BuO groups of two Hyp and the Dod group of Gln, were deprotected simultaneously by treating **33** with CF₃COOH in the presence of a small amount of anisole. The heptapeptide Z-Hyp-Gln-D,L-Iva-Hyp-Aib-Pro-Pheol (**34**) was obtained in 93% yield as a crystalline material, which was purified by preparative HPLC without separation of the two epimers.

3. Conclusions. – The presented results show that the 'azirine/oxazolone method' offers a convenient approach to the synthesis of the peptaibol antibiotic antiamoebin AAM I. Epimer mixtures of the two main segments 1-9 and 10-16 containing D,L-isovaline were obtained in reasonable yields. Whereas the introduction of the a,a-disubstituted a-amino acids Aib and D,L-Iva via coupling with the corresponding 2*H*-azirin-3-amines occurred smoothly and with high yields, the coupling of the segments was much more demanding. The success of this reaction strongly depended on the

⁸⁾ The attempted coupling with DCC/HOBt/CSA gave the desired 31 in only 15% yield.



chosen strategy, *i.e.*, the disconnection of the target molecule into segments. The separation of epimeric segments containing D,L-Iva seems to be possible by HPLC but proved to be rather difficult. As enantiomerically pure 2*H*-azirin-3-amines as D- and L-Iva synthons are now available [4b][24], the synthesis of the natural AAM I should be possible according to the presented method.

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Experimental Part

1. *Abbreviations*. Aib, 2-Aminoisobutyric acid (2-methylalanine); CME-CDI, *N*-cyclohexyl-*N'*-[2-(4-methylmorpholin-4-ylium)ethyl]carbodiimide 4-toluenesulfonate; CSA, camphor-10-sulfonic acid; DCC, *N*,*N'*-dicyclohexylcarbodiimide; Dod, '4,4'-dimethoxydityl' (=4,4'-dimethoxybenzhydryl (Mbh)); HOBt, 1-hydroxybenzotriazole; Hyp, *trans*-4-hydroxyproline; Iva, 'isovaline' (=2-ethylalanine); NMM, 4-methylmorpholine; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N'*,*N'*-tetramethyluronium

tetrafluoroborate; TFA, trifluoroacetic acid; Pheol, L-phenylalaninol (=(S)-2-amino-3-phenylpropan-1-ol); Z, (benzyloxy)carbonyl.

2. General. See [5b]. Amino acids, Ac-Phe-OH, and Pheol were purchased from Novabiochem and Bachem, and are all L-configured; other reagents and solvents from Aldrich, Bachem, Fluka, and Merck, resp. Solvents were dried according to known protocols. The syntheses of 2,2,N-trimethyl-N-phenyl-2H-azirin-3-amine (**1a**) and rac-2-ethyl-2,N-dimethyl-N-phenyl-2H-azirin-3-amine (**1b**) have been described previously [5b][33]. M.p.: Mettler-FP-5 apparatus, uncorrected. Optical rotations ($[a]_D$): Zeiss-LEP-A2 or Perkin-Elmer-241 polarimeter at 21–23°. IR Spectra: Perkin-Elmer 781 spectrometer, in KBr; $\tilde{\nu}$ in cm⁻¹. ¹H- and ¹³C-NMR spectra: Bruker AC-300, Bruker AM-400, and Bruker AMX-600 spectrometer at 300, 400, and 600 (¹H), and 75.5, 100.8, and 151.2 MHz (¹³C), resp., in CD₃OD or (D₆)DMSO, if not otherwise stated; δ in ppm rel. to Me₄Si as internal standard, J in Hz. ESI-MS: Finnigan MAT-90 or SSQ-700 instrument with NH₃ or isobutane; in m/z (rel. %).

General Procedure 1 (GP 1): Coupling with 2H-Azirin-3-amines. To a soln. of an N-protected amino acid or N-protected peptide in THF or CH_2Cl_2 at 0°, ca. 1.2 equiv. of the corresponding 2H-azirin-3-amine in THF or CH_2Cl_2 were added, and the mixture was stirred at r.t. for several hours under Ar. 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 2 (GP 2): Selective Hydrolysis of Peptide N-Methyl-N-phenylamides. A soln. of the peptide amide in 3N HCl (THF/H₂O 1:1) was stirred at r.t. for 1-50 h. Then, aq. 2N HCl was added, and the mixture was extracted with CH₂Cl₂ ($3 \times$). The org. layers were combined, dried (Na₂SO₄), and evaporated. The product was purified by crystallization.

General Procedure 3 (GP 3): 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 H_2 overnight. After completion of the reaction (TLC), the soln. was filtered through a pad of *Celite*, and the solvent was evaporated. The product was dried in high vacuum (*i.v.*).

2. Preparation of the Pentapeptide Ac-Phe-Aib-Aib-Aib-D,L-Iva-OH (2). 2.1. Ac-Phe-Aib-N(Me)Ph (3). According to GP 1, Ac-Phe-OH (3.04 g, 14.7 mmol) in THF (80 ml) at 0° was treated with **1a** (2.82 g, 16.2 mmol); stirring at r.t. for 49 h and at 35° for 3 h. The solvent was evaporated, the residue was dissolved in a small amount of AcOEt, and the product precipitated by addition of hexane: 5.54 g (99%) of **3**. Colorless crystals. M.p. 140.8–142.2°. $[a]_{D}^{22} = +7.1$ (c=0.91, EtOH). IR (KBr): 3375s, 3060s, 3030m, 2990m, 2930m, 1650s, 1595s, 1565s, 1550s, 1535s, 1495s, 1390s, 1360s, 1290s, 1250s, 1200s, 1170m, 1115m, 1090s, 1075m, 1030m, 770m, 745s, 700s. ¹H-NMR ((D₆)DMSO): 7.95 (d, J=8.9, NH); 7.94 (s, NH); 7.38–7.12 (m, 10 arom. H); 4.40 (td, J=8.8, 5.5, CH(2) (Phe)); 3.12 (s, MeN); 2.91, 2.71 (AB of ABM, $J_{AB}=$ 13.7, $J_{AM}=8.9$, $J_{BM}=5.5$, PhCH₂); 1.78 (s, MeCO); 1.32, 1.28 (2s, Me₂C). ¹³C-NMR ((D₆)acetone): 173.0, 170.9, 170.2 (3s, 3 CO (amide)); 146.3, 138.5 (2s, 2 arom. C); 130.3, 129.9, 128.9, 128.5, 127.8, 127.1 (6d, 10 arom. CH); 57.9 (s, Me₂C); 54.9 (d, C(2) (Phe)); 40.8 (q, MeN); 38.6 (t, PhCH₂); 26.84, 26.75 (2q, Me_2 C); 22.8 (q, MeCO). CI-MS: 382 (21, $[M+1]^+$), 276 (17, $[M-Ph(Me)N+1]^+$), 275 (100, $[M-Ph(Me)N]^+$), 178 (23), 175 (35), 108 (20, [Ph(Me)N+2]^+), 107 (14, [Ph(Me)N+1]⁺), 89 (18). Anal. calc. for C₂₂H₂₇N₃O₃ (381.47): C 69.27, H 7.13, N 11.02; found: C 69.23, H 7.14, N 11.21.

2.2. *Ac-Phe-Aib-OH* (4) [23b]. According to *GP* 2, a soln. of **3** (7.30 g, 19.0 mmol) in 3N HCl (192 ml) was stirred at r.t. for 21 h. The solvent was evaporated, and the precipitate was filtered and washed with Et₂O: 5.04 g (90%) of **4**. Colorless crystals. M.p. 197.3–202.8°. $[\alpha]_{12}^{22} = +2.0$ (*c*=0.75, EtOH). IR (KBr): 3290s, 3060m, 3030m, 2990m, 2930m, 1720s, 1660m, 1640s, 1565s, 1500w, 1440m, 1380m, 1356w, 1310w, 1290w, 1265w, 1220w, 1190w, 1170w, 1120w, 1040w, 1020w, 995w, 745w, 700w. ¹H-NMR ((D₆)DMSO): 8.17 (*s*, NH); 8.03 (*d*, *J*=8.7, NH); 7.41–7.15 (*m*, 5 arom. H); 4.51 (*td*, *J*=9.1, 4.6, CH(2) (Phe)); 2.94, 2.68 (*AB* of *ABM*, J_{AB} =13.7, J_{AM} =9.8, J_{BM} =4.6, PhCH₂); 1.73 (*s*, MeCO); 1.33, 1.30 (2*s*, Me₂C). ¹³C-NMR ((D₆)acetone): 177.6 (*s*, COOH); 172.9, 172.7 (2*s*, 2 CO (amide)); 138.4 (*s*, 1 arom. C); 130.4, 129.3, 127.7 (3*d*, 5 arom. CH); 57.0 (*s*, Me₂C); 55.8 (*d*, C(2) (Phe)); 39.1 (*t*, PhCH₂); 25.2, 25.1 (2*q*, *Me*₂C); 22.4 (*q*, MeCO). CI-MS: 294 (17), 293 (100, [*M*+1]⁺), 275 (15, [*M*-H₂O+1]⁺), 190 (15, [AcPhe]⁺), 104 (11). Anal. calc. for C₁₅H₂₀N₂O₄ (292.33): C 61.63, H 6.90, N 9.58; found: C 61.76, H 6.98, N 9.53.

2.3. *Ac-Phe-Aib-Aib-N(Me)Ph* (**5**). According to *GP 1*, to a soln. of **4** (385 mg, 132 mmol) in THF (9 ml) at 0° was added **1a** (253 mg, 1.45 mmol); stirring at r.t. for 65 h. The solvent was evaporated, and the crude **5** was used for the hydrolysis. IR (KBr): 3300s, 3060m, 2980m, 2940m, 1650s, 1590m, 1560m, 1550s, 1535s, 1515s, 1495s, 1470m, 1455m, 1390m, 1365m, 1280m, 1220m, 1090m, 1025w, 970w, 745m, 705s. ¹H-NMR ((D₆)DMSO): 8.25 (d, J = 6.4, NH); 8.08 (s, NH); 7.36 – 7.16 (m, 10 arom. H, NH); 4.33 (dt, J = 8.9, 6.3, CH(2) (Phe)); 3.21 (s, MeN); 2.91, 2.77 (*AB* of *ABM*, J_{AB} = 13.7, J_{AM} = 8.9, J_{BM} = 6.2, PhC*H*₂); 1.80 (s, MeCO); 1.36, 1.31, 1.27. 1.22 (4s, 2 Me₂C). ¹³C-NMR (CD₃OD): 176.1, 175.5, 173.5, 173.4 (4s, 4 CO (amide)); 146.8, 137.9 (2s, 2 arom. C); 130.5, 130.3, 129.5, 128.4, 128.3, 127.9 (6d, 10 arom. CH); 58.6, 58.0 (2s, 2 Me₂C); 57.3 (d, C(2) (Phe)); 41.1 (q, MeN); 3.22 (t, PhCH₂); 26.8, 26.4, 26.2, 23.9 (4q, 2 Me_2 C); 22.3 (q, MeCO). CI-MS: 361 (11, [M – Ph(Me)N + 1]⁺), 360 (53, [M – Ph(Me)N]⁺), 108 (100, [Ph(Me)N + 2]⁺), 107 (25, [Ph(Me)N + 1]⁺).

2.4. *Ac-Phe-Aib-Aib-OH* (**6**). According to *GP* 2, a soln. of **5** (350 mg, 0.75 mmol) in 3N HCl (7.5 ml) was stirred at r.t. for 23 h. Then, 2N HCl (3.5 ml) was added, the mixture was extracted with CH₂Cl₂ (3 ×), and the org. phase was dried (Na₂SO₄). The solvent was evaporated, Et₂O was added, and the precipitate was filtered: 216 mg (87%, two steps) of **6**. Colorless crystals. M.p. 197.0–198.2°. $[a]_{12}^{25}$ = +39.3 (*c* = 1.13, EtOH). IR (KBr): 3390s, 3330s, 3290s, 3060*m*, 2980*m*, 2930*m*, 1745*s*, 1735*m*, 1680*s*, 1645*s*, 1625*s*, 1560*m*, 1550*s*, 1500*m*, 1465*m*, 1450*m*, 1380*m*, 1370*m*, 1290*m*, 1245*m*, 1210*m*, 1175*m*, 1160*s*, 1120*w*, 1050*w*, 1030*w*, 1005*w*, 960*w*, 730*m*, 695*m*. ¹H-NMR ((D₆)DMSO): 12.04 (*s*, COOH); 8.24 (*d*, *J* = 6.7, NH); 8.14 (*s*, NH); 7.27–7.15 (*m*, 5 arom. H, NH); 4.33 (*dt*, *J* = 9.1, 6.4, CH(2) (Phe)); 2.91, 2.75 (*AB* of *ABM*, *J*_{AB} = 13.7, *J*_{AM} = 9.1, *J*_{BM} = 5.9, PhCH₂); 1.78 (*s*, MeCO); 1.32, 1.27, 1.25, 1.23 (4*s*, 2 Me₂C). ¹³C-NMR (CD₃OD): 178.3 (*s*, COOH); 176.2, 176.1, 173.7 (3*s*, 3 CO (amide)); 138.2 (*s*, 1 arom. C); 130.8, 129.8, 128.2 (3*d*, 5 arom. CH); 58.1, 57.3 (2*s*, 2 Me₂C); 57.8 (*d*, C(2) (Phe)); 38.6 (*t*, PhCH₂); 26.8, 25.9, 24.9, 24.2 (4*q*, 2 *Me*₂C); 22.7 (*q*, MeCO). CI-MS: 379 (22), 378 (100, [*M*+1]⁺), 361 (6, [*M*-H₂O+1]⁺), 360 (31, [*M*-H₂O]⁺), 275 (18). Anal. calc. for C₁₉H₂₇N₃O₅ (377.44): C 60.46, H 7.21, N 11.13; found: C 60.32, H 7.21, N 11.06.

2.5. *Ac-Phe-Aib-Aib-N(Me)Ph* (**7**). According to *GP 1*, to a soln. of **6** (419 mg, 1.11 mmol) in THF (6 ml) at 0° was added **1a** (206 mg, 1.18 mmol); stirring at r.t. for 51 h. The solvent was evaporated, the residue was dissolved in AcOEt, Et₂O was added, and the precipitate was filtered: 590 mg (96%) of **7**. Colorless crystals. M.p. 181.5–184.5°. $[a]_{D}^{22} = +24.7$ (c=0.55, EtOH). IR (KBr): 3440m, 3350s, 3290s, 3060m, 2990m, 2935w, 1660s, 1635s, 1595m, 1535s, 1510m, 1490m, 1470m, 1455m, 1395m 1380m, 1365m, 1280w, 1230w, 1090m, 1070w, 1025w, 980w, 745w, 705m. ¹H-NMR ((D₆)DMSO): 8.55 (s, NH); 8.34 (d, J = 5.5, NH); 8.08 (s, NH); 7.37–7.18 (m, 10 arom. H, NH); 7.13 (s, NH); 4.35–4.28 (m, CH(2) (Phe)); 3.27 (s, MeN); 2.93, 2.84 (AB of ABM, $J_{AB} = 13.7$, $J_{AM} = 8.8$, $J_{BM} = 6.5$, PhC H_2); 1.81 (s, MeCO); 1.41, 1.37, 1.31, 1.22. 1.19 (5s, 3 Me₂C). ¹³C-NMR (CD₃OD): 176.8, 175.8, 175.7, 174.1, 173.4 (5s, 5 CO (amide)); 147.0, 137.9 (2s, 2 arom. C); 130.5, 130.2, 129.5, 128.3, 128.1, 127.9 (6d, 10 arom. CH); 58.5, 58.2, 57.7 (3s, 3 Me₂C); 57.2 (d, C(2) (Phe)); 41.0 (q, MeN); 38.0 (t, PhCH₂); 27.5, 26.58, 26.57, 26.2, 24.2, 23.7 (6q, 3 Me_2 C); 22.4 (q, MeCO). CI-MS: 446 (28, [M - Ph(Me)N+1]⁺), 445 (100, [M - Ph(Me)N]⁺), 361 (8), 360 (41), 108 (44, [Ph(Me)N+2]⁺), 107 (11, [Ph(Me)N+1]⁺). Anal. calc. for C₃₀H₄₁N₅O₅ (551.68): C 65.32, H 7.49, N 12.69; found: C 65.11, H 7.35, N 12.78.

2.6. *Ac-Phe-Aib-Aib-OH* (8). According to *GP* 2, a soln. of **7** (368 mg, 0.67 mmol) in 3N HCl (7.0 ml) was stirred at r.t. for 39 h. Then, 2N HCl (3.5 ml) was added, the mixture was extracted with $CH_2Cl_2(3 \times)$, and the org. phase was dried (Na_2SO_4) . The solvent was evaporated, Et_2O was added, and the precipitate was filtered: 259 mg (84%) of **8**. Colorless crystals. M.p. 216.0–217.5°. $[a]_{12}^{25} = +31.9$ (*c*= 0.86, EtOH). IR (KBr): 3440*s*, 3300*s*, 3065*m*, 3030*m*, 3000*s*, 2980*s*, 2940*m*, 2880*m*, 1710*s*, 1680*s*, 1675*s*, 1640*s*, 1560*s*, 1550*s*, 1495*m*, 1470*m*, 1455*m*, 1450*s*, 1435*m*, 1415*m*, 1370*s*, 1365*s*, 1310*s*, 1275*m*, 1245*s*, 1220*m*, 1180*s*, 1125*w*, 1085*w*, 1060*w*, 1005*w*, 985*w*, 750*m*, 700*m*. ¹H-NMR ((D₆)DMSO): 8.52 (*s*, NH); 8.31 (*d*, *J* = 5.8, NH); 7.45–7.18 (*m*, 5 arom. H, NH); 7.10 (*s*, NH); 4.34–4.27 (*m*, CH(2) (Phe)); 2.90, 2.81 (*AB* of *ABM*, *J_{AB}*=13.7, *J_{AM}*=8.7, *J_{BM}*=6.5, PhC*H*₂); 1.82 (*s*, MeCO); 1.35, 1.33, 1.32, 1.26, 1.21, 1.18 (6*s*, 3 Me₂C). ¹³C-NMR (CD₃OD): 178.4 (*s*, COOH); 176.7, 176.2, 174.5, 174.0 (4*s*, 4 CO (amide)); 138.1 (*s*, 1 arom. C); 130.8, 129.8, 128.2 (3*d*, 5 arom. CH); 58.1, 58.0, 57.5 (3*s*, 3 Me₂C); 57.3 (*d*, C(2) (Phe)); 38.3 (*t*, PhCH₂); 2.74, 26.9, 26.4, 24.8, 24.4, 24.0 (6*q*, 2 *Me*₂C); 22.6 (*q*, MeCO). CI-MS: 446 (21), 445 (72, [*M* – H₂O + 1]⁺), 361 (22), 360 (100, [445 – Aib]⁺). Anal. calc. for C₂₃H₃₄N₄O₆ (462.54): C 59.73, H 7.41, N 12.11; found: C 59.48, H 7.50, N 12.27.

2.7. Ac-Phe-Aib-Aib-Aib-D,L-Iva-N(Me)Ph (9). According to GP1, to a soln. of 8 (185 mg, 0.40 mmol) in THF (6 ml) and abs. DMF (1 ml) at 0° was added **1b** (83 mg, 0.44 mmol); stirring at r.t. for 24 h and at 50° for 94 h. Then, Et₂O was added, the precipitate was filtered and washed with Et₂O: 251 mg (96%) of **9** as a *ca.* 1:1 mixture of diastereoisomers. Colorless crystals. M.p. $247.0-252.0^{\circ}$. $[a]_{12}^{22} =$ +11.4 (c=0.54, EtOH). IR (KBr): 3440m, 3310s, 3024w, 2990w, 2940m, 1665s, 1650s, 1595m, 1530s, 1495m, 1470m, 1455m, 1415m, 1380m, 1360m, 1310w, 1290w, 1225w, 1175w, 1110w, 1090w, 1070w, 1030w, 1010w, 765w, 705m. ¹H-NMR ((D₆)DMSO): 8.57 (d, J=8.1, NH); 8.26 (s, NH); 7.48-7.16 (m, 10 arom. H, 3 NH); 4.37-4.24 (m, CH(2) (Phe)); 3.29 (s, MeN); 2.94-2.76 (m, PhCH₂); 1.95-1.73 (m, MeCH₂) (Iva)); 1.81 (s, MeCO); 1.41, 1.40, 1.35, 1.34, 1.29, 1.27, 1.26, 1.25, 1.23, 1.21 (10s, 3 Me₂C, Me (Iva)); 0.82 (t, J=7.4, MeCH₂ (Iva)). ¹³C-NMR ((D₆)DMSO): 174.83, 174.75, 173.7, 173.6, 173.5, 173.4, 172.63, 172.56, 172.2, 172.1, 170.5, 170.4 (12s, 6 CO (amide)); 146.5, 137.50, 137.46 (3s, 2 arom. C); 129.3, 128.8, 128.2, 127.0, 126.5, 126.0 (6d, 10 arom. CH); 59.5, 59.4 (2s, C(2) (Iva)); 56.3, 56.2, 56.1, 56.0, 55.9 (5s, 3 Me₂C); 55.3 (d, C(2) (Phe)); 39.3 (q, MeN); 36.4 (t, PhCH₂); 29.3 (t, MeCH₂ (Iva)); 26.9, 26.4, 26.0, 25.9, 25.7, 24.9, 24.5, 24.0, 23.7, 23.5, 23.3, 22.3, 22.2 (12q, 3 Me₂C, Me (Iva), MeCO); 8.04, 7.99 (2q, MeCH₂ (Iva)). CI-MS: 546 (24), 545 (73), 544 (100, $[M - Ph(Me)N]^+$), 446 (13), 445 (32, $[544 - Iva]^+$), 380 (12), 360 (16, [445 – Aib]⁺), 285 (13), 284 (50), 282 (10), 256 (38), 190 (19, [AcPhe]⁺), 181 (17), 109 (13), 108 $(90, [Ph(Me)N+2]^+), 107 (34, [Ph(Me)N+1]^+), 91 (27).$ Anal. calc. for $C_{35}H_{50}N_6O_5 (650.82)$: C 64.59, H 7.74, N 12.91; found: C 64.40, H 8.00, N 12.86.

The epimers of **9** were separated by prep. HPLC (*LiChrosorb RP18*; gradient MeOH/H₂O). *Epimer* **9a** (*ca.* 8 : 1 mixture). $[\alpha]_D^{22} = +8.6$ (c=0.95, EtOH). ¹H-NMR (CD₃OD): 7.83 (s, NH); 7.58 (s, NH); 7.39–7.20 (m, 10 arom. H, 3 NH); 4.37 (t-like, J=8.0, 7.8, CH(2) (Phe)); 3.41 (s, MeN); 3.02, 2.94 (*AB* of *ABM*, $J_{AB}=13.6, J_{AM,BM}=8.0, 7.8$, PhCH₂); 2.12–1.95 (m, MeCH₂ (Iva)); 1.94 (s, MeCO); 1.56, 1.54, 1.48, 1.38, 1.36, 1.29, 1.25 (7s, 3 Me₂C, Me (Iva)); 0.95 (t, J=7.5, *Me*CH₂ (Iva)).

Epimer **9b** (*ca.* 1:7 mixture): $[a]_{D}^{2D} = +13.0$ (*c* =0.90, EtOH). ¹H-NMR (CD₃OD): 7.72 (br. *s*, NH); 8.62 (*s*, NH); 7.54 (*s*, NH); 7.42–7.26 (*m*, 10 arom. H, 2 NH); 4.35 (*t*-like, *J* = 7.9, 7.8, CH(2) (Phe)); 3.40 (*s*, MeN); 3.04–2.95 (*m*, PhCH₂); 2.11–1.95 (*m*, MeCH₂ (Iva)); 1.95 (*s*, MeCO); 1.55, 1.54, 1.48, 1.39, 1.35, 1.28, 1.20 (7*s*, 3 Me₂C, Me (Iva)); 0.95 (*t*, *J* = 7.4, *Me*CH₂ (Iva)). ¹³C-NMR ((D₆)DMSO): 174.7, 173.6, 173.3, 172.5, 172.0, 170.4 (6*s*, 6 CO (amide)); 146.3, 137.4 (2*s*, 2 arom. C); 129.2, 128.6, 128.0, 126.9, 126.4, 125.9 (6*d*, 10 arom. CH); 59.4 (*s*, C(2) (Iva)); 56.2, 56.1, 55.8 (3*s*, 3 Me₂C); 55.2 (*d*, C(2) (Phe)); 39.2 (*q*, MeN); 36.3 (*t*, PhCH₂); 29.2 (*t*, MeCH₂ (Iva)); 26.8, 25.9, 25.8, 24.4, 23.6, 23.2, 22.2, 22.0 (8*q*, 3 *Me*₂C, Me (Iva), *Me*CO); 7.93 (*q*, *Me*CH₂ (Iva)).

2.8. Ac-Phe-Aib-Aib-Aib-D,L-Iva-OH (2). According to GP 2, a soln. of 9 (277 mg, 0.43 mmol) in 3N HCl (4.5 ml) was stirred at r.t. for 25 h. Then, 2N HCl (2.2 ml) was added, the mixture was extracted with CH_2Cl_2 (4 ×), and the org. phase was dried (Na₂SO₄). The solvent was evaporated, and the residue was crystallized from AcOEt/Et₂O: 222 mg (92%) of **2**. Colorless crystals. M.p. 234.8–236.0°. $[\alpha]_{D}^{22} = +16.6$ (c=0.61, EtOH). IR (KBr): 3370m, 3320s, 3060w, 3030w, 2980s, 2935m, 1750m, 1740m, 1660s, 1535s, 1455m, 1445m, 1385m, 1365m, 1230m, 1170w, 750w, 700w. ¹H-NMR ((D₆)DMSO): 11.93 (br. s, COOH); 8.54 (s, NH); 8.28 (s, NH); 7.37 (d, J=4.8, NH (Phe)); 7.29-7.19 (m, 5 arom. H); 7.16 (s, NH); 7.13 (s, NH); 4.31-4.29 (m, CH(2) (Phe)); $2.93, 2.82 (AB of ABM, J_{AB} = 13.6, J_{AM} = 8.9, J_{BM} = 6.2, PhCH_2)$; 2.05-100 + 11.60 (m, MeCH₂ (Iva)); 1.81 (s, MeCO); 1.31, 1.28, 1.26, 1.24, 1.21 (5s, 3 Me₂C, Me (Iva)); 0.77 (m, MeCH₂ (Iva)). ¹³C-NMR (CD₃OD): 177.7, 177.3, 176.5, 176.4, 176.3, 174.02, 173.97, 173.6 (8s, COOH, 5 CO (amide)); 137.8 (s, 1 arom. C); 130.4, 129.5, 127.9 (3d, 5 arom. CH); 60.83, 60.76 (2s, C(2) (Iva)); 57.94, 57.90, 57.1 (3s, 3 Me₂C); 57.6 (d, C(2) (Phe)); 37.9 (t, PhCH₂); 31.3 (t, MeCH₂ (Iva)); 27.0, 26.71, 26.68, 26.46, 26.43, 26.3, 25.0, 24.8, 24.3, 24.0, 23.8, 22.6, 22.4, 22.2 (14q, 3 Me₂C, Me (Iva), MeCO); 8.68, 8.38 (2q, MeCH₂ (Iva)). CI-MS: 562 (18, $[M+1]^+$), 545 (33, $[M-H_2O+1]^+$), 544 (100, $[M-H_2O]^+$), 463 (17), 446 (20, $[544-Iva+1]^+$), 445 (20, $[544-Iva]^+$), 360 (38, $[445-Aib]^+$). Anal. calc. for C₂₈H₄₃N₅O₇ (561.68): C 59.88, H 7.72, N 12.47; found: C 59.93, H 7.75, N 12.65.

3. Preparation of the Tetrapeptide H-Gly-Leu-Aib-Aib-N(Me)Ph (13). 3.1. Z-Gly-Leu-Aib-N(Me)Ph (11). According to GP 1, Z-Gly-Leu-OH (3.51 g, 10.7 mmol) in THF (70 ml) at 0° was treated with 1a (2.08 g, 11.9 mmol); stirring at r.t. for 3 d. The solvent was evaporated, the residue was dissolved in a small amount of AcOEt, and the product precipitated by addition of petroleum ether: 5.25 g (98%) of 11. Colorless crystals. M.p. $150.0-151.0^{\circ}$. $[\alpha]_D^{22} = -20.4$ (c=0.53, EtOH). IR (KBr): 3290s, 3080m, 2960m, 1740s, 1685s, 1660s, 1620s, 1595s, 1560s, 1540s, 1495s, 1470m, 1455m, 1395m,

1365*m*, 1260*s*, 1235*s*, 1210*m*, 1170*w*, 1120*w*, 1090*w*, 1075*w*, 1050*m*, 775*m*. ¹H-NMR ((D₆)DMSO): 7.99 (br. *s*, NH); 7.89 (*d*, *J* = 8.5, NH); 7.52 (*t*, *J* = 6.0, NH); 7.34–7.15 (*m*, 10 arom. H); 5.02 (*s*, PhCH₂O); 4.25– 4.16 (*m*, CH(2) (Leu)); 3.65 (*d*, *J* = 6.0, CH₂ (Gly)); 3.14 (*s*, MeN); 1.56–1.23 (*m*, CH(4) (Leu), CH₂(3) (Leu)); 1.34 (*s*, Me₂C); 0.84 (*t*-like, *J* = 8.2, 6.7, *Me*₂CH). ¹³C-NMR ((D₆)acetone): 173.1, 171.9, 169.9 (3*s*, 3 CO (amide)); 157.7 (*s*, CO (urethane)); 146.4, 138.0 (2*s*, 2 arom. C); 129.9, 129.2, 128.6, 128.51, 128.45, 127.8 (6*d*, 10 arom. CH); 66.9 (*t*, PhCH₂O); 57.9 (*s*, Me₂C); 51.9 (*d*, C(2) (Leu)); 45.1 (*t*, C(2) (Gly)); 42.0 (*t*, C(3) (Leu)); 40.9 (*q*, MeN); 26.8, 25.2 (*d*, C(4) (Leu) and *q*, *Me*₂C); 23.6, 22.0 (2*q*, *Me*₂CH). CI-MS: 391 (14), 390 (67, [*M* – PhCH₂O + 1]⁺), 282 (18), 256 (15), 245 (9), 200 (13), 108 (100, [PhCH₂O + 1]⁺ or [Ph(Me)N+2]⁺), 107 (42, [Ph(Me)N+1]⁺ or [PhCH₂O]⁺), 91 (26). Anal. calc. for C₂₇H₃₆N₄O₅ (496.61): C 65.30, H 7.31, N 11.28; found: C 65.28, H 7.42, N 11.26.

3.2. *Z*-*Gly*-*Leu*-*Aib*-*OH* (**12**). According to *GP* 2, a soln. of **11** (4.45 g, 8.95 mmol) in 3N HCl (90 ml) was stirred at r.t. for 12 h. Then, 2N HCl (45 ml) was added and the mixture was extracted with CH₂Cl₂ (5 ×). The combined org. phases were dried (Na₂SO₄), the solvent was evaporated, the residue was dissolved in a small amount of acetone, and hexane was added. The precipitate was filtered: 3.07 g (84%) of **12**. Colorless crystals. M.p. 151.9–153.9°. $[a]_{D}^{22} = -37.5$ (c=0.75, EtOH). IR (KBr): 3435*m*, 3280*s*, 3080*m*, 2960*m*, 1720*s*, 1670*s*, 1630*s*, 1565*s*, 1550*s*, 1510*m*, 1470*m*, 1455*m*, 1420*w*, 1385*w*, 1370*m*, 1295*m*, 1275*s*, 1245*s*, 1170*m*, 1155*m*, 1100*w*, 1085*w*, 1050*w*, 1030*w*, 735*m*, 695*m*. ¹H-NMR ((D₆)DMSO): 12.13 (br. *s*, COOH); 8.07 (*s*, NH); 7.87 (*d*, J=8.6, NH); 7.46 (*t*, J=6.0, NH); 7.35–7.33 (*m*, 5 arom. H); 5.03 (*s*, PhCH₂O); 4.39–4.31 (*m*, CH(2) (Leu)); 3.63 (*d*, J=6.0, CH₂ (Gly)); 1.60–1.34 (*m*, CH(4) (Leu), CH₂(3) (Leu)); 1.34, 1.31 (2*s*, Me₂C); 0.85 (*t*-like, J=8.4, 6.7, *Me*₂CH). ¹³C-NMR (CD₃OD): 177.6 (*s*, COOH); 173.8, 172.0 (2*s*, 2 CO (amide)); 159.1 (*s*, CO (urethane)); 138.1 (*s*, arom. C); 129.5, 129.0, 128.8 (3*d*, 5 arom. CH); 67.8 (*t*, PhCH₂O); 57.0 (*s*, Me₂C); 52.8 (*d*, C(2) (Leu)); 4.50 (*t*, C(2) (Gly)); 4.19 (*t*, C(3) (Leu)); 25.7, 25.3 (*d*, C(4) (Leu); *q*, *Me*₂C); 23.4, 22.0 (2*q*, *Me*₂CH). CI-MS: 409 (23), 408 (100, [*M*+1]⁺), 391 (14), 390 (61, [*M*-H₂O+1]⁺), 305 (17, [390 – Aib]⁺), 277 (9), 104 (12), 91 (11). Anal. calc. for C₂₀H₁₉N₃O₆ (407.47): C 58.95, H 7.17, N 10.31; found: C 59.00, H 7.08, N 10.41.

3.3. *Z*-*Gly*-*Leu*-*Aib*-*N*(*Me*)*Ph* (**10**). According to *GP* 1, **12** (1.18 g, 2.9 mmol) in THF (15 ml) at 0° was treated with **1a** (0.56 g, 3.19 mmol); stirring at r.t. for 50 h. The solvent was evaporated, and the crude product was obtained as a foam: 1.68 g (quant.) of **10**. IR (KBr): 3310s, 3060m, 3030m, 2950m, 2770m, 1710s, 1660s, 1590m, 1545s, 1530s, 1495s, 1470m, 1455m, 1390m, 1365m, 1250s, 1170m, 1115w, 1090m, 1070w, 1050m, 770w, 740w, 705w. ¹H-NMR (CDCl₃): 7.60 (*s*, NH); 7.40–7.17 (*m*, 10 arom. H); 6.83 (*s*, NH); 6.56 (*d*, J = 8.2, NH); 6.04 (br. *s*, NH); 5.13, 5.11 (*AB*, J_{AB} = 12.2, PhCH₂O); 4.39 (*dt*, J = 8.3, 6.2, CH(2) (Leu)); 4.09, 3.79 (*AB* of *ABX*, J_{AB} = 17.8, J_{AX} = 7.1, J_{BX} = 4.7, CH₂ (Gly)); 3.23 (*s*, MeN); 1.73–1.42 (*m*, CH(4) (Leu), CH₂(3) (Leu)); 1.51, 1.46, 1.41, 1.38 (4*s*, 2 Me₂C); 0.91 (*m*, *Me*₂CH). ¹³C-NMR (CD₃OD): 176.0, 175.6, 174.4, 172.6 (4*s*, 4 CO (amide)); 159.0 (*s*, CO (urethane)); 146.8, 138.0 (2*s*, 2 arom. C); 130.3, 129.5, 129.1, 128.8, 128.4, 128.3 (6*d*, 10 arom. CH); 67.8 (*t*, PhCH₂O); 58.6, 58.2 (2*s*, 2 Me₂C); 54.3 (*d*, C(2) (Leu)); 23.3, 22.2 (2*q*, *Me*₂CH). CI-MS: 476 (18), 475 (59, [*M* – PhCH₂O + 1]⁺ or [*M* – Ph(Me)N]⁺), 390 (9, [475 – Aib]⁺), 360 (42), 108 (100, [PhCH₂O + 1]⁺ or [Ph(Me)N + 2]⁺), 107 (36, [Ph(Me)N + 1]⁺ or [PhCH₂O]⁺).

3.4. *H*-*Gly*-*Leu*-*Aib*-*Aib*-*N*(*Me*)*Ph* (13). According to *GP* 3, a mixture of 10 (2.03 g, 3.5 mmol) in MeOH (28 ml) and Pd/C (206 mg) under H₂ was stirred at r.t. for 15 h. The crude product 13 was obtained as an oil: 1.57 g (quant.), and the pure product was obtained after crystallization from CH₂Cl₂/ Et₂O. Colorless crystals. M.p. 64.5–68.5°. $[a]_{12}^{25} = +2.3$ (c=0.48, EtOH). IR (KBr): 3300s, 3060m, 2950m, 2870w, 1655s, 1595s, 1560m, 1550s, 1530s, 1495s, 1470m, 1390m, 1365m, 1285m, 1255m, 1220m, 1200m, 1170m, 1110m, 1090m, 1070w, 1025w, 770w, 740w, 710w. ¹H-NMR (CDCl₃): 7.57 (d, J=7.9, NH); 7.52 (s, NH); 7.45–7.17 (m, 5 arom. H); 6.93 (s, NH); 4.32 (dt, J=8.2, 5.9, CH(2) (Leu)); 3.40, 3.34 (AB, $J_{AB}=7.2$, CH₂ (Gly)); 3.27 (s, MeN); 1.89 (br. s, NH₂); 1.78–1.52 (m, CH(4) (Leu), CH₂(3) (Leu)); 1.50, 1.45, 1.44, 1.41 (4s, 2 Me₂C); 0.94 (d, J=8.0, Me (Leu)); 0.92 (d, J=7.8, Me (Leu)). ¹³C-NMR (CDCl₃): 173.8, 173.6, 172.7, 171.2 (4s, 4 CO (amide)); 144.4 (s, arom. C); 129.3, 128.2, 127.8 (3d, 5 arom. CH); 58.2, 57.4 (2s, 2 Me₂C); 51.9 (d, C(2) (Leu)); 44.7 (t, C(2) (Gly)); 41.2 (q, MeN); 40.0 (t, C(3) (Leu)); 25.7, 24.91, 24.85, 24.78, 24.3 (4q, 2 Me_2 C; d, C(4) (Leu)); 22.3, 22.0 (2q, Me_2 CH). CI-MS: 342 (19, [M – Ph(Me)N+1]⁺), 341 (100, [M – Ph(Me)N]⁺), 178 (37), 177 (56), 151 (15), 108 (13, [Ph(Me)N+2]⁺), 107 (7, 12) (4, 12) $[Ph(Me)N+1]^+$), 89 (28). Anal. calc. for $C_{23}H_{37}N_5O_4$ (447.58): C 61.72, H 8.33, N 15.65; found: C 61.68, H 8.44, N 15.45.

3.5. Z-Gly-Leu-Aib-Aib-OH (16). According to GP2, a soln. of 10 (332 mg, 0.57 mmol) in 3N HCl (7 ml) was stirred at r.t. for 25 h. Then, 2N HCl (3.5 ml) was added, and the mixture was extracted with CH_2Cl_2 (4 ×). The combined org. phases were dried (Na₂SO₄), the solvent was evaporated, and the oily residue dissolved in a small amount of CH₂Cl₂ was left standing at r.t. The formed precipitate was filtered: 211 mg (82%) of **16**. Colorless crystals. M.p. 159.5–162.0°. $[\alpha]_D^2 = -20.9$ (c = 0.89, EtOH). IR (KBr): 3320s, 3060m, 3030m, 2990m, 2930m, 2870m, 1710s, 1660s, 1650s, 1550s, 1530s, 1470m, 1450m, 1405m, 1385m, 1365w, 1335w, 1300m, 1265s, 1220m, 1160s, 1125w, 1015w, 735m, 695m. ¹H-NMR ((D₆)DMSO): 12.05 (s, COOH); 8.07 (d, J=6.5, NH); 8.03 (s, NH); 7.44 (t, J=6.0, NH); 7.39-7.26 (m, 5 arom. H); 7.21 (s, NH); 5.01 $(s, PhCH_2O)$; 4.12 (q-like, $J \approx 7.1$, CH(2) (Leu)); 3.68, 3.60 (AB of ABX, $J_{AB} = 16.9, J_{AX} = 16.9$ $6.3, J_{BX} = 6.0, CH_2 (Gly); 1.64 - 1.50 (m, CH(4) (Leu)); 1.48 - 1.41 (m, CH_2(3) (Leu)); 1.32, 1.30, 1.27 (3s, 1.20); 1.21, 1.22, 1.20); 1.22, 1.20, 1.27 (3s, 1.20); 1.20, 1.20; 1.$ 2 Me₂C); 0.89, 0.84 (2d, J=6.5, Me₂CH). ¹³C-NMR (CD₃OD): 178.3 (s, COOH); 176.2, 174.7, 172.9 (3s, 3 CO (amide)); 159.3 (s, CO (urethane)); 138.3 (s, arom. C); 129.7, 129.3, 129.1 (3d, 5 arom. CH); 68.2 (t, PhCH₂O); 58.2, 57.5 (2s, 2 Me₂C); 54.5 (d, C(2) (Leu)); 45.1 (t, C(2) (Gly)); 41.5 (t, C(3) (Leu)); 26.1, 25.6, 25.2 (d, C(4) (Leu); 2q, 2 Me₂C); 23.6, 22.4 (2q, Me₂CH). CI-MS: 493 (10, [M+1]⁺), 476 (13), 475 $(53, [M-H_2O+1]^+), 408 (26), 391 (23, [M-H_2O-Aib+2]^+), 390 (100, [Z-Gly-Leu-Aib+1]^+), 305 (100, [Z-Gly-Leu+Aib+1]^+), 305 (100, [Z-Gly-Leu+Aib+1]^+), 30$ $(8, [Z-Gly-Leu+1]^+), 277 (9), 104 (60).$ Anal. calc. for $C_{24}H_{36}N_4O_7 (492.57)$: C 58.52, H 7.37, N 11.37; found: C 58.38, H 7.22, N 11.47.

Suitable crystals of **16** for an X-ray crystal-structure determination were obtained from MeOH/ Et_2O by slow evaporation of the solvent.

3.6. *H-Gly-Leu-Aib-Aib-OH* (**17**). According to *GP* 3, a mixture of **16** (270 mg, 0.55 mmol) in MeOH (4 ml) and Pd/C (30 mg) under H₂ was stirred at r.t. for 5.5 h. The crude product **17** was obtained as a colorless solid: 204 mg (quant.). ¹H-NMR ((D_6)DMSO): 8.50 (d, J = 9.0, NH); 8.37, 7.80 (2*s*, 2 NH); 4.48 (*q*-like, $J \approx 7.8$, CH(2) (Leu)); 3.92 (br. *s*, NH[±]₃); 3.40, 3.30 (*AB*, J_{AB} = 7.0, CH₂ (Gly)); 1.52–1.37 (*m*, CH(4) (Leu), CH₂(3) (Leu)); 1.32, 1.28, 1.25 (3*s*, 2 Me₂C); 0.90, 0.85 (2*d*, J = 6.0, *Me*₂CH). ¹³C-NMR (CD₃OD): 181.8 (*s*, COO⁻); 175.0, 172.7, 167.7 (3*s*, 3 CO (amide)); 58.9, 58.3 (2*s*, 2 Me₂C); 53.1 (d, C(2) (Leu)); 42.0 (t, C(2) (Gly)); 41.1 (t, C(3) (Leu)); 27.2, 26.0, 24.3, 24.2, 24.0 (4*q*, 2 *Me*₂C; d, C(4) (Leu)); 22.0, 22.6 (2*q*, *Me*₂CH). CI-MS: 360 (20), 359 (100, [M + 1]⁺), 341 (14, [M – H₂O + 1]⁺), 256 (12, [341 – Aib]⁺), 189 (6), 171 (6).

4. Coupling of **2** and **13** to Give Ac-Phe-Aib-Aib-Aib-D,L-Iva-Gly-Leu-Aib-Aib-N(Me)Ph (**14**). 4.1. Via the Mixed Anhydride. To a stirred soln. of **2** (265 mg, 0.47 mmol) in a mixture of THF (0.5 ml) and DMF (0.5 ml) at -15° , NMM (48 mg, 0.47 mmol) and isobutyl chloroformate (64 mg, 0.47 mmol) were added. After stirring for 4 min at -15° , **13** (213 mg, 0.47 mmol) in THF (1 ml) was added, and the mixture was stirred for 3 h in an ice-bath and for 50 h at r.t. To the suspension was added CH₂Cl₂, and the mixture was extracted with an aq. soln. of citric acid (5%), 1N NaOH, and sat. aq. NaCl soln. The org. phase was dried (Na₂SO₄), the solvent evaporated, and the product precipitated by addition of Et₂O: 321 mg (69%) of **14**.

4.2. With DCC and Catalytic Amounts of CSA. To a stirred soln. of **2** (175 mg, 0.31 mmol) in DMF (1.4 ml) at 0° was added DCC (65 mg, 0.32 mmol). After stirring for 10 min at 0°, HOBt (47 mg, 0.35 mmol) and CSA (20 mg) were added, and, after 2 min, **13** (162 mg, 0.36 mmol), and the mixture was stirred for 50 h at r.t. Then, the mixture was filtered through a pad of *Celite* and washed with DMF. The filtrate was dissolved in CH₂Cl₂, and the soln. was extracted with an aq. soln. of citric acid (5%), 1N NaOH, and sat. aq. NaCl soln. The org. phase was dried (Na₂SO₄), and the solvent was evaporated: 284 mg (92%) of crude **14**, which still contained dicyclohexylurea (¹H-NMR). Part of the crude material (78 mg) was purified by column chromatography (CC; SiO₂, CH₂Cl₂/MeOH 19:1) to give 46 mg of pure **14**.

4.3. With DCC and Catalytic Amounts of $ZnCl_2$. To a stirred soln. of 2 (63 mg, 0.11 mmol) in abs. DMF (10.5 ml) at 0° was added DCC (25 mg, 0.12 mmol). After stirring for 3 min at 0°, $ZnCl_2$ (31 mg, 0.23 mmol), and a soln. of 13 (57 mg, 0.13 mmol) and Et₃N (20 mg, 0.20 mmol) in abs. DMF (0.5 ml) were added, and the mixture was stirred for 77.5 h at r.t. Then, the mixture was filtered through a pad of *Celite* and washed with DMF. The filtrate was dissolved in CH₂Cl₂ and the soln. was extracted with 2N HCl, 1N NaOH, and sat. aq. NaCl soln. The org. phase was dried (Na₂SO₄), and the solvent was

evaporated. The residue was dissolved in a small amount of CH_2Cl_2 , and the product was crystallized by addition of hexane: 25 mg (23%) of **14**.

4.4. With CME-CDI and Catalytic Amounts of CSA. To a stirred soln. of **2** (293 mg, 0.52 mmol) in DMF (1.5 ml) at 0° was added CME-CDI (221 mg, 0.52 mmol). After stirring for 5 min at 0°, HOBt (72 mg, 0.53 mmol) and CSA (30 mg) were added, and, after another 5 min, **13** (238 mg, 0.53 mmol) was added. The mixture was stirred for 5 h at r.t., CH_2Cl_2 (0.5 ml) was added, and stirring at r.t. was continued for 98 h. Then, the mixture was diluted with CH_2Cl_2 , and the soln. was extracted with an aq. soln. of citric acid (5%), 1N NaOH, and sat. aq. NaCl soln. The org. phase was dried (Na₂SO₄), and the solvent was evaporated: 132 mg (26%) of **14**.

Data of 14. Colorless crystals. M.p. 230.0–232.5°. $[\alpha]_{12}^{22} = +7.3$ (c = 0.48, EtOH). IR (KBr): 3460m, 3300s, 3060w, 2980m, 2940m, 1660s, 1595m, 1545s, 1535s, 1495m, 1465m, 1440m, 1385m, 1365m, 1280w, 1220w, 1170w, 1090w, 770w, 745w, 705m. ¹H-NMR ((D₆)DMSO): 8.61, 8.60 (2s, NH (Aib²)); 8.30 (d, J= 5.8, NH (Phe)); 7.91 (t-like, J=5.6, NH (Gly)); 7.70, 7.69 (2s, NH (Aib⁴)); 7.62-7.59 (m, NH (Aib³), NH (Aib⁹), NH (Leu)); 7.49, 7.47 (2s, NH (Iva)); 7.34–7.17 (m, 10 arom. H, NH (Aib⁸)); 4.35–4.29 (m, CH(2)) (Phe)); 4.04-4.02 (m, CH(2) (Leu)); 3.75-3.56 (m, CH₂ (Gly)); 3.23 (s, MeN); 2.96, 2.82 (AB of ABMX, $J_{AB} = 13.7, J_{AM} = 8.9, J_{BM} = 6.0, J_{BX} = 2.5, PhCH_2$; 2.04–1.91 (*m*, 1 H of MeCH₂ (Iva)); 1.81 (*s*, MeCO); 1.76-1.44 (m, 1 H of MeCH₂ (Iva), CH(4) (Leu), CH₂(3) (Leu)); 1.37, 1.35, 1.32, 1.300, 1.296, 1.27, 1.26, 1.25 (8s, 5 Me₂C, Me (Iva)); 0.88 (d, J = 5.9, (Me (Leu)); 0.84 (d, J = 5.5, Me (Leu)); 0.80-0.74 (m, MeCH₂ (Iva)). ¹³C-NMR ((D₆)DMSO): 175.8, 175.7, 175.5, 175.21, 175.18, 175.0, 173.5, 172.63, 172.58, 171.7, 170.5, 170.1 (12s, 10 CO (amide)); 146.2, 137.6 (2s, 2 arom. C); 129.4, 128.8, 128.2, 127.2, 126.5, 126.2 (6d, 10 arom. CH); 59.3, 59.2 (2s, C(2) (Iva)); 56.5, 56.4, 56.1, 56.0 (4s, 5 Me₂C); 55.4 (d, C(2) (Phe)); 52.5 (d, C(2) (Leu)); 43.4 (t, C(2) (Gly)); 39.7 (q, MeN); 37.4 (t, C(3) (Leu)); 36.5 (t, C(3) (Phe)); 29.2, 28.8 (2t, MeCH₂ (Iva)); 25.83, 25.75, 25.6, 25.4, 25.2, 24.9, 24.7, 24.2, 23.9, 23.7, 23.0, 22.5, 21.6, 21.4, 21.3 (d, C(4) (Leu), 14q, 5 Me₂C, Me₂CH, Me (Iva), MeCO); 7.77, 7.67 (2q, MeCH₂ (Iva)). FAB-MS: 1013 $(5, [M+Na]^+), 886 (14), 885 (36, [M-Ph(Me)N+1]^+), 884 (65, [M-Ph(Me)N]^+), 800 (11, [884-100])^+), 800 (11, [884-100])^+)$ Aib+1]⁺), 799 (18, [884-Aib]⁺), 714 (10, [799-Aib+1]⁺), 601 (18, [714-Leu]⁺), 545 (25, [601- $Gly+1]^+$, 544 (65, $[601-Gly]^+$), 446 (27, $[544-Iva+1]^+$), 445 (100, $[544-Iva]^+$). Anal. calc. for C₅₁H₇₈N₁₀O₁₀ (991.24): C 61.80, H 7.93, N 12.13; found: C 61.60, H 8.22, N 13.93.

4.5. Hydrolysis of 14 to Give Ac-Phe-Aib-Aib-Aib-D,L-Iva-Gly-Leu-Aib-Aib-OH (15). According to GP 2, a soln. of 14 (170 mg, 0.17 mmol) in 3N HCl (2 ml) was stirred at r.t. for 10 h. Then, 2N HCl (1 ml) was added, and the mixture was extracted with CH_2Cl_2 (4 ×). The combined org. phases were dried (Na_2SO_4) , the solvent was evaporated, and the product precipitated by addition of Et₂O: 103 mg (67%) of 15. Colorless crystals. M.p. 208.0–210.5°. $[a]_{D}^{22} = +7.3$ (c = 0.30, EtOH). ¹H-NMR ((D_{6})DMSO): 12.05 (br. s, COOH); 8.63, 8.62 (2s, NH (Aib²)); 8.31 (d, J=5.9, NH (Phe)); 7.93 (dd-like, J=5.9, 5.4, NH (Gly)); 7.71 (s, NH (Aib⁴)); 7.61, 7.59 (2s, NH (Aib³), NH (Aib⁹), NH (Leu)); 7.51, 7.49 (2s, NH (Iva)); 7.30–7.20 (*m*, 5 arom. H); 7.04 (*s*, NH (Aib⁸)); 4.34 (*M* of *ABMX*, J_{MX} =6.0, J_{MA} =8.6, J_{MB} =6.1, CH(2) (Phe)); 4.10-4.03 (m, CH(2) (Leu)); 3.76-3.58 (m, CH₂ (Gly)); 2.98, 2.83 (AB of ABMX, J_{AB}=13.7, $J_{AM} = 9.0, J_{BM} = 6.0, J_{BX} = 3.0, PhCH_2$; 2.04–1.96 (m, 1 H of MeCH₂ (Iva)); 1.83 (s, MeCO); 1.75–1.47 (m, 1 H of MeCH₂ (Iva), CH(4) (Leu), CH₂(3) (Leu)); 1.39, 1.37, 1.35, 1.33, 1.31, 1.30, 1.29, 1.27 (8s, 5 Me_2C , Me (Iva)); 0.89 (d, J = 5.7, Me (Leu)); 0.83 (d, J = 6.1, Me (Leu)); 0.80–0.75 ($m, MeCH_2$ (Iva)). ¹³C-NMR ((D₆)DMSO): 175.8, 175.7, 175.6, 175.31, 175.27, 175.1, 173.2, 172.6, 171.7, 170.7, 170.0 (11s, COOH, 9 CO (amide)); 137.6 (s, arom. C); 129.4, 128.3, 126.6 (3d, 5 arom. CH); 59.4, 59.3 (2s, C(2)) (Iva)); 56.2, 56.1, 55.0 (3s, 5 Me₂C); 55.4 (d, C(2) (Phe)); 52.4 (d, C(2) (Leu)); 43.5 (t, C(2) (Gly)); 38.5 (t, C(3) (Leu)); 36.6 (t, C(3) (Phe)); 29.3, 28.9 (2t, MeCH₂ (Iva)); 25.6, 25.5, 25.2, 24.9, 24.7, 24.3, 23.9, 23.7, 23.1, 22.5, 21.6, 21.4, 21.3 (d, C(4) (Leu), 12q, 5 Me₂C, Me₂CH, Me (Iva), MeCO); 7.85, 7.69 $(2q, MeCH_2 (Iva))$. FAB-MS: 903 (7), 902 (15, $[M+1]^+$), 886 (12), 800 (12), 799 (25, $[M-H_2O-Aib+1]^+$), 886 (12), 800 (12), 799 (25, $[M-H_2O-Aib+1]^+$) 1^{+} , 714 (11, [798 – Aib + 1]⁺), 601 (14, [714 – Leu]⁺), 545 (17, [601 – Gly + 1]⁺), 544 (50, [601 – Gly]⁺), 446 (27, [544–Iva+1]⁺), 445 (58, [544–Iva]⁺), 361 (21, [445–Aib+1]⁺), 360 (81, [445–Aib]⁺), 276 (11, [360 - Aib + 1]⁺), 275 (49, [360 - Aib]⁺), 190 (12, [275 - Aib]⁺), 171 (16), 169 (14), 162 (27), 155 (14), 141 (12), 128 (12), 127 (18), 126 (12), 120 (62), 112 (15). Anal. calc. for C₄₄H₇₁N₉O₁₁ (902.10): C 58.58, H 7.93, N 13.97; found: C 58.29, H 8.21, N 13.88.

5. Synthesis of the Heptapeptide Z-Hyp-Gln-D,L-Iva-Hyp-Aib-Pro-Pheol (**34**). 5.1. Z-Hyp('Bu)-Aib-N(Me)Ph (**20**). According to GP 1, Z-Hyp('Bu)-OH (**19**, 2.51 g, 7.8 mmol) in CH₂Cl₂ (30 ml) at 0° was

treated with **1a** (1.70 g, 9.75 mmol); stirring at r.t. for 17.5 h. The solvent was evaporated, and the residue was purified by CC (AcOEt/hexane $3:2 \rightarrow 4:2$): 3.73 g (96%) of **11**. Colorless foam. M.p. 53.5–54.2°. $[\alpha]_{D}^{21} = -22.1$ (c=1.09, EtOH). IR (KBr): 3440w, 2990w, 2970w, 1685s, 1635m, 1590m, 1530w, 1490m, 1450m, 1410m, 1385m, 1355m, 1290w, 1240w, 1180m, 1120m, 1065m, 1020w, 900w, 700w. ¹H-NMR (CD₃OD; two conformers): 7.43–7.12 (m, 10 arom. H); 5.17–5.00 (m, PhCH₂O); 4.43–4.18 (m, CH(2) (Hyp), CH(4) (Hyp)); 3.72–3.60, 3.43–3.23 (2m, CH₂(5) (Hyp)); 3.15 (s, MeN); 2.20–1.98 (m, CH₂(3) (Hyp)); 1.46, 1.43, 1.35 (3s, Me₂C); 1.20, 1.18 (2s, 'Bu). ¹³C-NMR (CD₃OD; two conformers): 175.0, 173.7, 173.6 (3s, 2 CO (amide)); 156.8, 156.4 (2s, CO (urethane)); 146.4, 146.3, 138.1, 137.7 (4s, 2 arom. C); 130.3, 129.5, 129.0, 128.7 (4d, 10 arom. CH); 75.3 (s, Me₃C); 70.7, 70.0 (2d, C(4) (Hyp)); 68.3, 68.1 (2t, PhCH₂O); 60.2, 60.0 (2d, C(2) (Hyp)); 28.5 (q, Me_3 C); 26.8, 26.6, 26.4, 26.3 (4q, Me_2 CH). ESI-MS: 534 (9, [M+K]⁺), 518 (100, [M+Na]⁺). Anal. calc. for C₂₈H₃₇N₃O₅ (495.62): C 67.86, H 7.53, N 8.48; found: C 67.95, H 7.62, N 8.32.

5.2. *Z*-*Hyp*('*Bu*)-*Aib*-*OH* (**21**). According to *GP* 2, a soln. of **20** (2.95 g, 5.95 mmol) in 3N HCl (60 ml) was stirred at r.t. for 23 h. Then, 2N HCl (3.5 ml) was added, and the mixture was extracted with $CH_2Cl_2(4 \times)$. The combined org. phases were dried (Na₂SO₄), the solvent was evaporated, and the residue was recrystallized from CH_2Cl_2 /hexane: 2.10 g (86%) of **21**. Colorless crystals. M.p. 144.1–145.2°. $[\alpha]_{D}^{22} = -32.5$ (*c*=1.01, EtOH). IR (KBr): 3430*w*, 3390*w*, 3220*w*, 2980*m*, 2880*w*, 1690*s*, 1545*w*, 1515*w*, 1455*m*, 1420*m*, 1390*w*, 1355*m*, 1310*w*, 1260*w*, 1170*m*, 1130*m*, 1100*m*, 1070*w*, 998*w*, 915*w*, 900*w*, 695*w*. ¹H-NMR (CDCl₃; two conformers): 7.35 (br. *s*, 5 arom. H); 5.30–5.02 (*m*, PhCH₂O); 4.55–4.22 (*m*, CH(2) (Hyp), CH(4) (Hyp)); 3.72–3.55, 3.55–3.35, 3.35–3.20 (3*m*, CH₂(5) (Hyp)); 2.50–2.32, 2.28–2.02, 2.02–1.83 (3*m*, CH₂(3) (Hyp)); 1.54, 1.52, 1.50 (3*s*, Me₂C); 1.18 (*s*, 'Bu). ¹³C-NMR (CD₃OD; two conformers): 177.6, 177.5, 174.1, 173.9 (4*s*, COOH, CO (amide)); 156.7, 156.3 (*s*, CO (urethane)); 137.9, 137.8 (2*s*, arom. C); 129.5, 129.4, 128.9 (3*d*, 5 arom. CH); 75.3 (*s*, Me₃C); 70.6, 70.0 (2*d*, C(4) (Hyp)); 68.5, 68.2 (2*t*, PhCH₂O); 60.3, 60.2 (2*d*, C(2) (Hyp)); 57.0, 56.9 (2*s*, Me₂C); 55.4, 54.0 (2*t*, C(5) (Hyp)); 40.0, 38.9 (2*t*, C(3) (Hyp)); 28.5 (*q*, Me₃C); 25.8, 24.7 (2*q*, Me₂CH). CI-MS: 407 (100, $[M+1]^+$). Anal. calc. for C₂₁H₃₀N₂O₆ (406.48): C 62.05, H 7.44, N 6.89; found: C 62.14, H 7.18, N 7.09.

5.3. *H*-*Hyp*(*'Bu*)-*Aib*-*N*(*Me*)*Ph* (**22**). According to *GP* 3, a mixture of **20** (700 mg, 1.41 mmol) in MeOH (15 ml) and Pd/C (91 mg) under H₂ was stirred at r.t. for 23 h. The crude product was purified by CC (AcOEt/hexane 95 :5) to give **22** (463 mg, 90%). Yellowish resin. $[a]_{D}^{11} = -30.2$ (c=1.24, EtOH). IR (KBr): 3320w, 2960m, 2920w, 2860w, 1660s, 1635s, 1590m, 1510m, 1490m, 1455m, 1415w, 1385m, 1360m, 1290w, 1240w, 1185m, 1115m, 1090m, 1070m, 1020m, 995m, 900w, 700w. ¹H-NMR (CDCl₃): 7.50–7.20 (m, 5 arom. H); 4.19 (br. *s*, CH(2) (Hyp)); 3.52–3.35 CH(4) (Hyp)); 3.23 (s, MeN); 3.00 (dd, J=11.3, 4.8, 1 H of CH₂(5) (Hyp)); 2.68 (dd, J=11.3, 3.0, 1 H of CH₂(5) (Hyp)); 2.05–1.85, 1.85–1.60 (2m, CH₂(3) (Hyp)); 1.47, 1.46 (2s, Me₂C); 1.17 (s, 'Bu). ¹³C-NMR (CD₃OD; two conformers): 175.5, 175.3, 174.8, 174.7 (4s, 2 CO (amide)); 146.7 (s, arom. C); 130.6, 130.5, 128.8, 128.4 (4d, 5 arom. CH); 74.7, 74.6 (2s, Me₃C); 70.9, 70.8 (2d, C(4) (Hyp)); 60.7, 60.6 (2d, C(2) (Hyp)); 58.6, 58.0 (2s, Me₂C); 55.5 (t, C(5) (Hyp)); 41.8, 41.6 (2 br. q, MeN); 40.4, 39.7 (2t, C(3) (Hyp)); 28.7 (q, Me_3 C); 27.4, 27.1, 26.8, 26.5 (4q, Me_2 CH). ESI-MS: 384 (15, [M+Na]⁺), 362 (100, [M+1]⁺); FAB-MS: 362 (100, [M+1]⁺). Anal. calc. for C₂₀H₃₁N₃O₃ (361.49): C 66.45, H 8.64, N 11.62; found: C 66.17, H 8.45, N 11.39.

5.4. *Z*-*Pro-Pheol* (23). To a stirred soln. of Z-Pro-OH (4.00 g, 16.06 mmol) in THF (80 ml) at -9° , NMM (1.77 ml, 16.06 mmol) and isobutyl chloroformate (2.09 ml, 16.00 mmol) were added. After 6 min stirring at -5° , H-PheOH (2.57 mg, 16.99 mmol) was added. The mixture was stirred for 10 min at -5° and for 20 h at r.t. Then, the solvent was evaporated, the residue was dissolved in CH₂Cl₂, and the soln. extracted with 2N HCl (2×) and 1N NaOH (2×), dried (Na₂SO₄), and evaporated: 5.86 g (95%) of 23. Colorless crystals. M.p. 135.1–135.4°. $[a]_{21}^{21} = -67.0$ (*c* =1.02, EtOH). IR (KBr): 3420*w*, 3000*w*, 2960*w*, 2890*w*, 1680*s*, 1515*m*, 1500*w*, 1450*w*, 1420*m*, 1355*m*, 1180*w*, 1115*m*, 1090*w*, 1040*w*, 985*w*, 920*w*, 700*m*. ¹H-NMR (CD₃OD): 7.45–7.05 (*m*, 10 arom. H); 5.16, 5.10 (*AB*, *J*=12.6, PhCH₂O); 5.01 (*s*, PhCH₂O); 4.28–4.02 (*m*, CH(2) (Pro), CH(2) (Pheol)); 3.58–3.35 (*m*, CH₂(3) (Pro), CH₂(4) (Pro)). ¹³C-NMR (CD₃OD); two conformers): 174.9, 174.6 (2*s*, CO (amide)); 156.5 (*s*, CO (urethane)); 139.7, 137.9 (2*s*, 2 arom. C); 130.3, 129.3, 129.0, 127.3 (4*d*, 10 arom. CH); 68.2, 68.1 (2*t*, PhCH₂O); 63.9 (*t*, CH₂OH); 62.1, 61.6 (2*d*, C(2) (Pro)); 54.2, 53.9 (2*d*, C(2) (Pheol)); 48.6, 48.2 (2*t*, C(5) (Pro)); 37.7 (*t*, C(3) (Pheol)); 32.6,

31.3, 25.1, 24.2 (4t, C(3) (Pro), C(4) (Pro)). CI-MS: 401 (21), 400 (100, $[M+1+NH_3]^+$), 384 (15), 383 (71, $[M+1]^+$). Anal. calc. for C₂₂H₂₆N₂O₄ (382.46): C 69.09, H 6.85, N 7.32; found: C 69.03, H 6.83, N 7.16.

5.5. *H-Pro-Pheol* (24). According to *GP* 3, a mixture of 23 (3.00 g, 7.85 mmol) in MeOH (70 ml) and Pd/C (412 mg) under H₂ was stirred at r.t. for 21 h. The crude product was crystallized from CH₂Cl₂/ hexane to give 24 (1.79 g, 91%). Colorless crystals $[\alpha]_D^2 = -54.1$ (c=0.99, EtOH). IR (KBr): 3350*m*, 3260*m*, 3060*w*, 3020*w*, 2960*w*, 2940*m*, 2860*m*, 1650*s*, 1600*w*, 1520*m*, 1480*w*, 1455*m*, 1435*w*, 1300*w*, 1240*w*, 1220*w*, 1100*w*, 1080*w*, 1055*m*, 1000*w*, 920*w*, 740*m*, 700*m*. ¹H-NMR (CD₃OD): 7.32–7.10 (*m*, 5 arom. H); 4.18–4.05 (*m*, CH(2) (Pheol)); 3.62–3.45 (*m*, CH(2) (Pro), CH₂OH); 3.01–2.65 (*m*, CH₂(3) (Pheol), CH₂(5) (Pro)); 2.10–1.90, 1.71–1.41 (2*m*, CH₂(3) (Pro), CH₂(4) (Pro)). ¹³C-NMR (CDCl₃): 176.1 (*s*, CO (amide)); 137.7 (*s*, arom. C); 129.1, 128.4, 126.4 (3*d*, 5 arom. CH); 65.1 (*t*, CH₂OH); 60.3 (*d*, C(2) (Pro)); 52.7 (*d*, C(2) (Pheol)); 47.0 (*t*, C(5) (Pro)); 37.0 (*t*, C(3) (Pheol)); 30.5 (*t*, C(3) (Pro)); 25.8 (*t*, C(4) (Pro)). CI-MS: 249 (100, [*M*+1]⁺). Anal. calc. for C₁₄H₂₀N₂O₂ (248.33): C 67.72, H 8.12, N 11.28; found: C 67.58, H 7.95, N 10.99.

5.6. Z-Hyp('Bu)-Aib-Pro-Pheol (25). To a soln. of 21 (1.75 g, 4.31 mmol) in DMF (7 ml) at 0° was added DCC (889 mg, 4.31 mmol), and the mixture was stirred for 6 min. Then, HOBt (643 mg, 7.76 mmol), CSA (60 mg), and 24 (1.23 g, 4.95 mmol) were added, and the mixture was stirred at r.t. for 18.5 h. Usual workup (see 5.4) and CC (AcOEt/MeOH 95:5) afforded 25 (2.16 g, 78%). Colorless foam. M.p. $73.1-74.0^{\circ}$. $[a]_{21}^{21} = -37.4$ (c = 1.03, EtOH). IR (KBr): 3450w, 3400w, 3320w, 3050w, 2980w, 2870w, 1675s, 1655s, 1540m, 1530m, 1495w, 1465m, 1450m, 1410m, 1360m, 1350m, 1305w, 1240w, 1170m, 1125m, 1100m, 1065m, 970w, 945w, 910w, 695m. ¹H-NMR (CDCl₃; two conformers): 8.03, 7.65 (2s, 2 NH); 7.47 (d, J=8.6, NH); 7.45-7.15 (m, 10 arom. H); 5.23, 5.17 (AB, J=12.5, PhCH₂O); 4.63-4.43, 4.43-4.18 (2m, CH(2) (Hyp), CH(4) (Hyp), CH(2) (Pro), CH(2) (Pheol)); 3.95-3.66, 3.66-3.46, 3.46-3.18 (3m, CH₂(3) (Pheol), CH₂OH, CH₂(5) (Hyp)); 3.02–2.79 (m, CH₂(5) (Pro)); 2.53–2.24, 2.08–1.92, 1.92– 1.72, 1.72–1.52 (4m, CH₂(3) (Hyp), CH₂(3) (Pro), CH₂(4) (Pro)); 1.41, 1.37 (2s, Me₂C); 1.18, 1.17 (2s, ¹³C-NMR (CD₃OD; two conformers): 174.6, 174.4, 174.3, 174.2, 174.1, 174.0 (6s, 3 CO (amide)); 157.0, 156.4 (2s, CO (urethane)); 139.9, 138.1, 137.8 (3s, 2 arom. C); 130.3, 130.2, 129.5, 129.3, 129.1, 128.7, 127.3 (7d, 10 arom. CH); 75.4, 75.3 (2s, Me₃C); 70.9, 70.2 (2d, C(4) (Hyp)); 68.3, 68.2 (2t, PhCH₂O); 64.3, 64.2 (2t, CH₂OH); 64.1 (d, C(2) (Pro)); 60.8, 60.0 (2d, C(2) (Hyp)); 57.9 (s, Me₂C); 56.1, 55.5 (2t, C(5) (Hyp)); 54.1, 53.9 (2d, C(2) (Pheol)); 49.6 (t, C(5) (Pro)); 40.8, 39.4 (2t, C(3) (Hyp)); 37.6, 37.5 (2t, C(3) (Pheol)); 29.8, 26.5 (2t, C(3) (Pro), C(4) (Pro)); 28.6 (q, Me₃C); 26.3, 26.1, 24.2, 24.0 (4q, Me₂C). ESI-MS: 675 (11, $[M + K]^+$), 659 (100, $[M + Na]^+$). Anal. calc. for $C_{35}H_{48}N_4O_7$ (636.79): C 66.02, H 7.60, N 8.80; found: C 65.79, H 7.74, N 8.83.

5.7. *H*-*Hyp*('*Bu*)-*Aib*-*Pro*-*Pheol* (**18**). According to *GP* 3, a mixture of **25** (802 mg, 1.26 mmol) in abs. MeOH (10 ml) and Pd/C (104 mg) under H₂ was stirred at r.t. for 25 h. After filtration, the solvent was evaporated, and the product **18** was dried *i.v.* (633 mg, quant.). Colorless foam: M.p. 52.3–53.1°. IR (KBr): 3440w, 3380w, 3050w, 3060w, 3005m, 2980m, 2870w, 1655s, 1535m, 1510m, 1470w, 1455w, 1405m, 1365m, 1340w, 1305w, 1240w, 1190m, 1170w, 1150w, 1095w, 1070w, 1040w, 1000w, 945w, 900w, 865w, 700w. ¹H-NMR (CDCl₃; two conformers): 7.42 (*s*, NH); 7.30–7.05 (*m*, 5 arom. H); 4.85–4.70, 4.70–4.55, 4.55–4.28, 4.28–4.05 (4m, CH(2) (Hyp), CH(4) (Hyp), CH(2) (Pro), CH(2) (Pheol)); 3.95–3.40, 3.40–3.15 (2m, CH₂(3) (Pheol), CH₂OH, CH₂(5) (Hyp)); 2.97–2.75 (*m*, CH₂(5) (Pro)); 2.45–1.90, 1.90–1.35 (2m, CH₂(3) (Pheol), CH₂(3) (Pro), CH₂(4) (Pro), Me₂C); 1.18, 1.16 (2*s*, 'Bu). ¹³C-NMR (CD₃OD; two conformers): 176.2, 175.9, 174.4, 174.0 (4*s*, 3 CO (amide)); 140.0 (*s*, arom. C); 130.3, 129.2, 127.3 (3*d*, 5 arom. CH); 74.9 (*s*, Me₃C); 73.6 (*d*, C(4) (Hyp)); 64.6, 64.4 (2*t*, CH₂OH); 64.1, 64.0 (2*d*, C(2) (Pro)); 60.8 (*d*, C(2) (Hyp)); 57.8, 57.5 (2*s*, Me₂C); 55.9 (*t*, C(5) (Hyp)); 53.9, 53.8 (2*d*, C(2) (Pheol)); 49.7 (*t*, C(5) (Pro)); 40.7, 40.5 (2*t*, C(3) (Hyp)); 37.5 (*t*, C(3) (Pheol)); 29.7, 26.5 (2*t*, C(3) (Pro), C(4) (Pro)); 28.8, 28.7 (2*q*, Me₃C); 26.4, 24.2 (2*q*, Me₂C). ESI-MS: 541 (15, [*M*+K]⁺), 525 (100, [*M*+Na]⁺).

5.8. *Z*-*Hyp*('*Bu*)-*Gln*(*Dod*)-*OMe* (**27**). A mixture of *Z*-*Hyp*('*Bu*)-*OH* (**19**, 204 mg, 0.64 mmol) and DCC (130 mg, 0.63 mmol) in DMF (3 ml) was stirred at 0° for 6 min. Then, HOBt (96 mg, 0.71 mmol), CSA (10 mg), and a soln. of H-Gln(Dod)-OMe ·HCl (**26**, 304 mg, 0.72 mmol) and Et₃N in DMF (1 ml) were added. The mixture was stirred for 19 h at r.t. The solvent was evaporated, the residue was dissolved in CH₂Cl₂, the soln. was extracted with 2N HCl (2 ×) and 1N NaOH (2 ×), dried (Na₂SO₄), and purified by CC (AcOEt/hexane 4:1): 385 mg (88%) of **27**. Colorless foam. M.p. 62.8–63.7°. [a]₂²¹ = -20.0 (c=

1.15, EtOH). IR (KBr): 3430w, 3340w, 3000w, 2980w, 2840w, 1740m, 1680s, 1610w, 1585w, 1510s, 1465w, 1455w, 1420m, 1390w, 1355m, 1305m, 1250m, 1175m, 1120m, 1085m, 1065w, 1035m, 830w, 700w. ¹H-NMR (CDCl₃; two conformers): 7.36–7.04, 6.85–6.68 (2m, 14 H); 6.14 (d, J=8.1, 1 H); 5.15–5.00, 4.82, 4.61 (m, AB, J=12.6, PhCH₂O); 4.43–4.27 (m, 1 H); 4.24 (dd, J=8.1, 4.8, 1 H); 3.82–3.58 (m, 10 H); 3.25 (dd, J=10.7, 5.1, 1 H); 2.47–1.83 (m, CH₂(3) (Hyp), CH₂(4) (Gln), CH₂(3) (Gln)); 1.17 (s, 'Bu). ¹³C-NMR (CDCl₃): 172.0, 171.9, 171.0 (3s, 2 CO (amide), 1 CO (ester)); 158.6, 158.5 (2s, 2 arom. C (Dod)); 155.3 (s, CO (urethane)); 136.1, 134.2, 134.1 (3s, 3 arom. C); 128.5, 128.4, 128.3, 127.9, 126.6 (5d, 9 arom. CH); 113.7 (d, 4 arom. H (Dod)); 73.9 (s, Me₃C); 69.3 (d, C(4) (Hyp)); 67.0 (t, PhCH₂O); 59.3 (d, C(2) (Hyp)); 55.5 (d, CH (Dod)); 55.1 (q, 2 MeO (Dod)); 53.5 (t, C(5) (Hyp)); 52.3 (q, MeO (Gln)); 51.7 (d, C(2) (Gln)); 37.3 (t, C(3) (Hyp)); 32.0, 28.4 (2t, C(4) (Gln), C(3) (Gln)); 28.1 (q, Me_3 C). CI-MS: 690 (6, [M+1]⁺), 227 (100). Anal. calc. for C₃₈H₄₇N₃O₉ (689.81): C 66.17, H 6.87, N 6.09; found: C 66.11, H 6.95, N 5.96.

5.9. Z-Hyp('Bu)-Gln(Dod)-OH (28). To a soln. of 27 (401 mg, 0.58 mmol) in dioxane (4.5 ml), was added 1N NaOH (4.5 ml) and the mixture was stirred at r.t. for 4.5 h. Then, excess 2N HCl was added, and the mixture was extracted with CH_2Cl_2 (3×). The org. phase was dried (Na₂SO₄), the solvent was evaporated, and the residue was dried in high vacuum: 392 mg (quant.) of 28. Colorless foam. M.p. 72.6-73.6°. IR (KBr): 3420w, 3310w, 3060w, 3030w, 3000m, 2980m, 2940w, 2840w, 1680s (br.), 1660m, 1590w, 1510s, 1465m, 1455m, 1440m, 1425m, 1390w, 1355m, 1305w, 1250m, 1175m, 1120w, 1085w, 1065w, 1035m, 915w, 830w, 695w. ¹H-NMR (CDCl₃; two conformers): 7.79 (d, J=8.4, NH); 7.38-7.16, 7.16-7.03, 6.88-6.68 (3m, 14 H); 6.18 (d, J=8.5, 1 H); 4.63-4.47, 4.37-4.17 (2m, PhCH₂O, CH(2) (Gln), CH(2) (Hyp), CH(4) (Hyp)); 3.72, 3.64 (2s, 2 MeO); 3.80-3.57 (m, 1 H of CH₂(5) (Hyp)); 3.25 (dd, J=10.9, 3.9, 1 H of CH₂(5) (Hyp)); 2.72-2.54, 2.54-2.32, 2.32-2.00 (3m, CH₂(3) (Hyp), CH₂(4) (Gln), CH₂(3) (Gln)); 1.15 (s, 'Bu). ¹³C-NMR (CD₃OD; two conformers): 175.2, 174.9, 174.6, 174.4, 173.9, 173.6 (6s, 2 CO (amide), 1 CO (ester)); 160.2 (s, 2 arom. C (Dod)); 156.6, 156.4 (2s, CO (urethane)); 137.7, 135.3, 135.2 (3s, 3 arom. C); 129.7, 129.5, 129.1, 128.8 (4d, 9 arom. CH); 114.8 (d, 4 arom. CH (Dod)); 75.3 (s, Me₃C); 70.8, 70.0 (2d, C(4) (Hyp)); 68.2 (t, PhCH₂O); 60.4, 60.1 (2d, C(2) (Hyp)); 57.1, 57.0 (2d, CH (Dod)); 55.7 (q, 2 MeO); 55.5 (t, C(5) (Hyp)); 53.4, 52.9 (2d, C(2) (Gln)); 40.2, 39.2 (2t, C(3) (Hyp)); 33.4, 33.1 (2t, C(4) (Gln)); 28.9 (t, C(3) (Gln)); 28.5 (q, Me_3 C). ESI-MS: 714 (7, $[M+K]^+$), 698 (100, $[M+Na]^+$).

5.10. Z-Hyp('Bu)-Gln(Dod)-D,L-Iva-N(Me)Ph (29). According to GP 1, 28 (1.20 g, 1.76 mmol) in CH_2Cl_2 (15 ml) at 0° was treated with **1b** (468 mg, 2.49 mmol); stirring at r.t. for 21 h. The solvent was evaporated, and the residue was purified by CC (AcOEt/hexane $95:5 \rightarrow 100:0$): 1.23 g (80%) of **29**. Colorless foam. M.p. 95.7-96.5°. IR (KBr): 3420w, 3330w, 3060w, 3000m, 2970m, 2930w, 2880w, 2840w, 1665s (br.), 1610m, 1595m, 1510s, 1465m, 1455m, 1420m, 1390w, 1360m, 1305w, 1245m, 1175m, 1120w, 1075w, 1030w, 970w, 900w, 830w, 810w, 700w. ¹H-NMR (CD₃OD; two conformers): 7.43-7.07 (m, 14 arom. H); 6.90-6.79 (m, 5 H); 6.12-6.02 (m, 1 H); 5.10-4.86 (m, PhCH₂O); 4.50-4.25 (m, 2 H); 4.20-4.03 (m, 1 H); 3.75, 3.74, 3.72, 3.70, 3.69 (5s, 2 MeO); 3.80-3.56, 3.42-3.30 (2m, CH₂(5) (Hyp)); 3.22, 3.21 (2s, MeN); 2.65-2.30, 2.30-1.96, 1.96-1.58 (3m, CH₂(3) (Hyp), MeCH₂ (Iva), CH₂(4) (Gln), CH₂(3) (Gln)); 1.41, 1.39, 1.33 (3s, MeC(2) (Iva)); 1.16 (s, Bu); 0.92–0.76 (m, MeCH₂ (Iva)). ¹³C-NMR (CD₃OD; two conformers): 174.8, 174.7, 174.6, 174.1, 172.3, 172.2 (6s, 4 CO (amide)); 160.2 (s, 2 arom. C (Dod)); 156.9, 156.3 (2s, CO (urethane)); 146.0 (br. s, 1 arom. C); 137.8, 137.7, 135.4, 135.2 (4s, 3 arom. C); 130.6, 130.5, 129.8, 129.0, 128.6 (5d, 14 arom. CH); 114.9 (d, 4 arom. CH (Dod)); 75.3 (s, Me₃C); 70.8, 70.4 (2d, C(4) (Hyp)); 68.4 (t, PhCH₂O); 62.0, 61.7 (2s, C(2) (Iva)); 60.8, 60.0 (2d, C(2) (Hyp)); 57.1, 57.0 (2d, CH (Dod)); 55.7 (q, 2 MeO); 55.7 (t, C(5) (Hyp)); 53.8, 53.7 (2d, C(2) (Gln)); 41.5 (br. q, MeN); 40.4, 39.5 (2t, C(3) (Hyp)); 32.8, 31.4 (2t, C(4) (Gln)); 30.7, 29.3, 29.2, 28.8 (4t, C(3) (Gln), MeCH₂ (Iva)); 28.6 (q, Me₃C); 23.4, 23.3 (2q, MeC(2) (Iva)); 8.6, 8.4 (2q, MeCH₂ (Iva)). ESI-MS: 902 (8, [M+K]⁺), 866 $(100, [M + Na]^+)$. Anal. calc. for $C_{49}H_{61}N_5O_9$ (864.06): C 68.11, H 7.12, N 8.11; found: C 68.10, H 7.22, N 7.97.

5.11. Z-Hyp(¹Bu)-Gln(Dod)-D,L-Iva-OH (**30**). According to GP 2, a soln. of **29** (1.10 g, 1.27 mmol) in 3N HCl (20 ml) was stirred at r.t. for 24 h. Then, 2N HCl (3.5 ml) was added, and the mixture was extracted with CH₂Cl₂ (4×). The combined org. phases were dried (Na₂SO₄), the solvent was evaporated, and the residue was recrystallized from CH₂Cl₂/hexane: 939 mg (95%) of **30**. Colorless crystals. M.p. 103.4–104.3°. IR (KBr): 3320w, 3060w, 3020w, 3000m, 2970m, 2930w, 2830w, 1680s, 1660s, 1610m, 1585m, 1510s, 1465m, 1455m, 1420m, 1390w, 1355m, 1305w, 1245m, 1175m, 1130w, 1085w, 1065w,

1035*w*, 870*w*, 830*w*, 810*w*, 695*w*. ¹H-NMR (CDCl₃; two conformers): 8.34 (br. *s*, NH); 7.85 (*d*, J=8.9, NH); 7.38–7.00, 6.91–6.68 (2*m*, 14 arom. H); 6.07 (*d*, J=6.0, 1 H); 5.13–4.72, 4.72–4.18 (2*m*, PhCH₂O), CH(2) (Gln), CH(2) (Hyp), CH(4) (Hyp)); 3.88–3.61 (*m*, 1 H of CH₂(5) (Hyp), 2 MeO)); 3.41–3.24 (*m*, 1 H of CH₂(5) (Hyp)); 2.68–2.36, 2.36–1.67, 1.55–1.20 (3*m*, CH₂(3) (Hyp), MeCH₂ (Iva), CH₂(4) (Gln), CH₂(3) (Gln), MeC(2) (Iva)); 1.15, 1.14 (2*s*, 'Bu); 0.98–0.64 (*m*, *Me*CH₂ (Iva)). ¹³C-NMR (CD₃OD; two conformers): 176.9, 176.8, 174.7, 174.1, 173.6, 172.3 (6*s*, 4 CO (amide)); 160.0 (*s*, 2 arom. C (Dod)); 156.7 (*s*, CO (urethane)); 137.5, 137.4, 135.2, 134.9 (4*s*, 3 arom. C); 129.6, 129.2, 129.1, 128.9, 128.6, 128.4 (6*d*, 9 arom. CH); 114.2 (*d*, 4 arom. CH (Dod)); 75.2 (*s*, Me₃C); 70.6, 69.8 (2*d*, C(4) (Hyp)); 68.2, 68.1 (2*t*, PhCH₂O); 61.1, 60.9 (2*s*, C(2) (Iva)); 60.6, 59.8 (2*d*, C(2) (Hyp)); 56.9 (*d*, CH (Dod)); 55.6 (*q*, 2 MeO); 55.2 (*t*, C(5) (Hyp)); 54.4, 54.0 (2*d*, C(2) (Gln)); 40.0, 39.2 (2*t*, C(3) (Hyp)); 33.0, 32.8 (2*t*, C(4) (Gln)); 30.8, 30.5, 30.2, 28.7 (4*t*, C(3) (Gln), MeCH₂ (Iva)); 28.5 (*q*, *Me*₃C); 22.5, 22.3 (2*q*, *Me*C(2) (Iva)); 8.6, 8.5 (2*q*, *Me*CH₂ (Iva)). ESI-MS: 813 (12, $[M+K]^+$), 797 (100, $[M+Na]^+$), 741 (22). Anal. calc. for C₄₂H₅₄N₄O₁₀ (774.92): C 65.10, H 7.02, N 7.23; found: C 64.89, H 7.31, N 7.18.

5.12. Z-Hyp('Bu)-Gln(Dod)-D,L-Iva-Hyp('Bu)-Aib-N(Me)Ph (**31**). To a soln. of **30** (100 mg, 0.13 mmol) in CH₂Cl₂ (2 ml) at 0° was added EtNⁱPr₂ (Hünig's base; 34 mg, 0.26 mmol). After stirring for 3 min, TBTU (43 mg, 0.13 mmol), HOBt (21 mg, 0.16 mmol), and **22** (55 mg, 0.15 mmol) were added, and the mixture was stirred at r.t. for 48 h. Then, the solvent was evaporated, the residue was dissolved in AcOEt, the soln. was extracted with 2N HCl (2 ×) and 1N NaOH (2 ×), dried (Na₂SO₄), and the product was purified by PLC (CH₂Cl₂/MeOH 9:1): 87 mg (60%) of **31**. Pale-yellow solid. M.p. 103.6–104.6°. ¹H-NMR (CD₃OD; two conformers): 7.42–7.02 (*m*, 14 arom. H); 6.92–6.78 (*m*, 4 arom. H); 6.12, 6.10 (2*s*, 1 H); 5.14–4.88 (*m*, PhCH₂O); 4.60–4.46, 4.46–4.20, 4.20–4.03 (3*m*, CH(2) (Gln), 2 CH(2) (Hyp), 2 CH(4) (Hyp)); 3.75, 3.74, 3.721, 3.718 (4*s*, 2 MeO); 3.70–3.53, 3.46–3.34 (2*m*, 2 CH₂(5) (Hyp)); 3.32 (*s*, MeN); 2.57–2.40, 2.27–1.70 (2*m*, 2 CH₂(3) (Hyp), MeCH₂ (Iva), CH₂(4) (Gln), CH₂(3) (Gln)); 1.51, 1.50 (2*s*, Me₂C (Aib)); 1.40, 1.25 (2*s*, MeC(2) (Iva)); 1.18, 1.16 (2*s*, 2 'Bu); 0.82, 0.76 (2*t*, *J*=7.5, *Me*CH₂ (Iva)). ESI-MS: 1157 (24, [*M*+1+K]⁺), 1141 (100, [*M*+1+Na]⁺); FAB-MS: 1011 (100, [*M* – Ph(Me)N]⁺).

5.13. *Z*-*Hyp*(¹*Bu*)-*Gln*(*Dod*)-D,L-*Iva*-*Hyp*(¹*Bu*)-*Aib*-*OH* (**32**). According to *GP* 2, a soln. of **31** (315 mg, 0.28 mmol) in 3N HCl (10 ml) was stirred at r.t. for 20 h. Usual workup and crystallization from CH₂Cl₂/hexane gave 274 mg (94%) of **32**. Colorless crystals. M.p. 111.3–112.2°. ¹H-NMR (CD₃OD; two conformers): 7.36–7.20, 7.20–7.05, 6.92–6.78 (3*m*, 13 arom. H); 6.11, 6.08, 6.07 (3*s*, 1 H); 5.06, 4.92 (*AB*, *J*=12.6, PhCH₂O); 5.05 (*s*, PhCH₂O); 4.55–4.43, 4.43–4.20, 4.20–4.08 (3*m*, CH(2) (Gln), 2 CH(2) (Hyp), 2 CH(4) (Hyp)); 3.76, 3.75, 3.74, 3.72 (4*s*, 2 MeO); 3.72–3.33 (*m*, 2 CH₂(5) (Hyp)); 2.57–2.38, 2.27–1.70 (2*m*, 2 CH₂(3) (Hyp), MeCH₂ (Iva), CH₂(4) (Gln), CH₂(3) (Gln)); 1.49, 1.48, 1.47, 1.41, 1.27 (5*s*, Me₂C (Aib), MeC(2) (Iva)); 1.18, 1.17, 1.16 (3*s*, 2 'Bu); 0.95–0.73 (*m*, MeCH₂ (Iva)). ESI-MS: 1007 (24, [M+K]⁺), 1051 (100, [M+Na]⁺), 995 (14).

5.14. *Z*-*Hyp*('*Bu*)-*Gln*(*Dod*)-D,L-*Iva*-*Hyp*('*Bu*)-*Aib*-*Pro*-*Pheol* (**33**). To a soln. of **32** (219 mg, 0.21 mmol) in DMF (3 ml) at 0° was added DCC (45 mg, 0.22 mmol). After stirring for 6 min, HOBt (33 mg, 0.24 mmol), CSA (8 mg), and **24** (62 mg, 0.25 mmol) were added, and the mixture was stirred at r.t. for 43 h. Workup as described in *Sect.* 5.12 and purification by CC (AcOEt/MeOH 95:5 \rightarrow 9:1) gave 163 mg (60%) of **33**. Colorless foam. M.p. 122.8–123.3°. ¹H-NMR (CD₃OD; two conformers): 7.36–7.20, 7.20–7.05, 6.92–6.80 (3*m*, 20 H); 6.12, 6.10 (2*s*, 1 H); 5.09, 4.96 (*AB*, *J*=12.6, PhCH₂O); 5.08 (*s*, PhCH₂O); 4.73–4.62, 4.44–4.20, 4.20–4.07 (3*m*, CH(2) (Gln), 2 CH(2) (Hyp), 2 CH(4) (Hyp), CH(2) (Pheol), CH(2) (Pro)); 3.75, 3.74, 3.73, 3.72 (4*s*, 2 MeO); 3.70–3.52, 3.52–3.34 (2*m*, 2 CH₂(5) (Hyp), CH₂(5) (Pro), CH₂OH); 3.03–2.93, 2.80–2.68 (2*m*, CH₂(3) (Pheol)); 2.58–2.42, 2.28–1.95, 1.95–1.75, 1.75–1.52 (4*m*, 2 CH₂(3) (Hyp), MeCH₂ (Iva), CH₂(4) (Gln), CH₂(3) (Gln), CH₂(3) (Pro), CH₂(4) (Pro)); 1.48, 1.47, 1.45, 1.42, 1.41 (5*s*, Me₂C (Aib)); 1.31, 1.28 (2*s*, MeC(2) (Iva)); 1.19, 1.17, 1.158, 1.156 (4*s*, 2 'Bu); 0.92–0.82 (*m*, MeCH₂ (Iva)); 0.79 (*t*, *J*=7.5, MeCH₂ (Iva)). ESI-MS: 1299 (12, [*M*+1+K]⁺), 1282 (100, [*M*+1+Na]⁺), 652 (66, [*M*+Na]²⁺).

5.15. Z-Hyp-Gln-D,L-Iva-Hyp-Aib-Pro-Pheol (34). To a soln. of 33 (63 mg, 0.05 mmol) in TFA (1.2 ml) at 0° was added anisol (0.1 ml), and the soln. was stirred at r.t. for 4 h. Then, TFA was evaporated, the residue was dissolved in CH₂Cl₂, and the solvent was evaporated again. This procedure was repeated several times. The crude product was purified by prep. HPLC (*LiChrosorb RP18*, 7 μ m, MeCN/H₂O 100:0 \rightarrow 97:3 \rightarrow 9:1, 8 ml/min): 43 mg (93%) of 34. Colorless crystals. M.p. 130.7–131.7°.

¹H-NMR (CD₃OD; two conformers): 8.10–7.96 (*m*, NH); 7.92–7.82 (*m*, NH); 7.42–7.08 (*m*, 10 arom. H); 5.28–5.07 (*m*, PhCH₂O); 4.78–4.66, 4.54–4.25, 4.18–4.07 (3*m*, CH(2) (Gln), 2 CH(2) (Hyp), 2 CH(4) (Hyp), CH(2) (Pro), CH(2) (Pheol)); 3.95–3.72, 3.72–3.53, 3.53–3.43 (3*m*, 2 CH₂(5) (Hyp), CH₂(5) (Pro), CH₂OH); 3.05–2.82 (*m*, CH₂(3) (Pheol)); 2.44–2.24, 2.24–2.08, 2.08–1.92, 1.92–1.75, 1.75–1.57 (5*m*, 2 CH₂(3) (Hyp), MeCH₂ (Iva), CH₂(4) (Gln), CH₂(3) (Gln), CH₂(3) (Pro), CH₂(4) (Pro)); 1.50, 1.49, 1.48, 1.42, 1.36, 1.28 (6*s*, Me₂C (Aib), MeC(2) (Iva)); 1.00–0.75 (*m*, MeCH₂ (Iva)). ESI-MS: 943 (100, $[M+Na]^+$), 921 (21, $[M+1]^+$), 483 (36, $[M+Na]^{2+}$).

6. X-Ray Crystal-Structure Determination of **16** (see the Table and Fig. 2)⁹). All measurements were carried out on a Nicolet diffractometer using graphite-monochromated MoK_a radiation (λ =0.71073 Å). The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. The data collection and refinement parameters are given in the Table, and a view of the molecule is shown in Fig. 2. The structure was solved by direct methods using SHELXS86 [34], which revealed the positions of all non-H-atoms. The atoms of the terminal acid function, from the CH₂ group onwards, and the atoms of the benzoyl function, from the amide group onwards, are

Table 1. Crystallographic Data for Compound 1	.6
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Crystallized from	MeOH/Et ₂ O
Empirical formula	$C_{24}H_{36}N_4O_7$
Formula weight	492.57
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	$0.36 \times 0.37 \times 0.75$
Temp. [K]	295(1)
Crystal system	trigonal
Space group	P3 ₁ 21
Ζ	6
Reflections for cell determination	25
2θ Range for cell determination [°]	48-52
Unit cell parameters:	
a [Å]	13.144(15)
<i>c</i> [Å]	29.41(4)
V [Å ³]	4401(13)
D_x [g cm ⁻³]	1.115
$\mu(MoK_a) [mm^{-1}]$	0.0823
Scan type	ω
$2\theta_{(\max)}$ [°]	50
Total reflections measured	16229
Symmetry-independent reflections	5190
Reflections with $I > 2\sigma(I)$	2892
Reflections used in refinement	5190
Parameters refined; restraints	478; 505
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0894
$wR(F^2)$ (all data)	0.2929
Weights	$w = [\sigma^2(F_o^2) + (0.1830P)^2]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness-of-fit	1.057
Final $\Delta_{\rm max}/\sigma$	0.001
$\Delta \rho_{(\max; \min)} [e \text{ Å}^{-3}]$	0.50; -0.31

⁹⁾ CCDC-910784 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/ data_request/cif.

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disordered. Two sets of overlapping positions were defined for the atoms of each disordered fragment. The site occupation factors of the major conformations of these fragments refined to similar values and were then refined as a common value yielding a final value of 0.53(1). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered atoms, while neighboring atoms within and between each conformation of the disordered fragments were restained to have similar atomic displacement parameters. The non-H-atoms were refined anisotropically. All of the 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 1.2 U_{eq} of its parent atom (1.5 U_{eq} for the Me and OH groups). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w (F_o^2 - F_o^2)^2$. A correction for secondary extinction was not applied. Neutral atom-scattering factors for non-H-atoms were taken from [36], and the scattering factors for H-atoms were taken from [36]. Anomalous dispersion effects were included in F_c [37]; the values for f' and f'' were those of [38]. The values of the mass-attenuation coefficients are those of [39]. The SHELXL97 program was used for all calculations [40].

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