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Abstract

The protected poly-Aib oligopeptides Z-(Aib)n-N(Me)Ph with n = 2 - 6 were prepared according to the 'azirine/oxazolone method', i.e., by coupling amino or peptide acids with 2,2,N-trimethyl-N-phenyl-2H-azirin-3-amine (1a) as an Aib synthon (Scheme 2). Following the same concept, the segments Z-(Aib)3-OH (9) and H-L-Pro-(Aib)3-N(Me)Ph (20) were synthesized, and their subsequent coupling with N,N'-dicyclohexylcarbodiimide (DCC)/ZnCl2 led to the protected heptapeptide Z-(Aib)3-L-Pro-(Aib)3-N(Me)Ph (21; Scheme 3). The crystal structures of the poly-Aib oligopeptide amides were established by X-ray crystallography confirming the 310-helical conformation of Aib peptides.

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Synthesis of Poly-Aib-Oligopeptides and Aib-Containing Peptides *via* the 'Azirine/Oxazolone Method' and their Crystal Structures

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[1]) Part of the PhD thesis of *I.D.-D.*, University of Zürich, 1995.

The protected poly-Aib oligopeptides Z-$(Aib)_n$-N(Me)Ph with n = 2 – 6 were prepared according to the 'azirine/oxazolone method', *i.e.*, by coupling of amino or peptide acids with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1a**) as an Aib synthon (*Scheme 2*). Following the same concept, the segments Z-$(Aib)_3$-OH (**9**) and H-L-Pro-$(Aib)_3$-N(Me)Ph (**20**) were synthesized, and their subsequent coupling with DCC/$ZnCl_2$ led to the protected heptapeptide Z-$(Aib)_3$-L-Pro-$(Aib)_3$-N(Me)Ph (**21**, *Scheme 3*). The crystal structures of the poly-Aib oligopeptide amides were established by X-ray crystallography confirming the 3_{10}-helical conformation of Aib peptides.

1. Introduction. – The broad interest in Aib-containing oligopeptides is well documented [1], and a large number of recent articles show that this type of peptides still attract attention because of their structural (*e.g.* [2]) and antimicrobial properties (*e.g.* [3]). In the last twenty years, we have shown that *N,N*-disubstituted 2,2-dimethyl-2*H*-azirin-3-amines **1** are useful building blocks for 2-aminoisobutyric acid (Aib) in the syntheses of heterocycles and peptides [4]. The so-called 'azirine/oxazolone method' proved to be a convenient synthetic approach for the introduction of Aib into peptides [5] (*Scheme 1*). After the coupling of an amino acid or peptide acid with **1**, the resulting dipeptide amide **2** was hydrolyzed selectively to give the dipeptide acid **3**. Subsequent coupling with an amino acid ester by using DCC/$ZnCl_2$ led, *via* the intermediate 1,3-oxazol-5(4*H*)-one **4**, to the tripeptide **5**. This method has been used successfully in the syntheses of model peptides and naturally occurring peptaibols[2]), *e.g.*, segments of alamethicin [8] and zervamicin II-2 [9], derivatives of trichovirin I 1B [10] and trichotoxin A-50(G) [11], as well as hypomurocin A1 [12].

Recently, the 'azirine/oxazolone method' has been adopted for solid phase synthesis [13].

Scheme 1

The repetition of the reaction sequence of azirine coupling and selective hydrolysis of the C-terminal amide group allows the direct coupling of Aib segments with a peptide chain. This convenient and efficient approach has been used for the preparation of peptides like HO–

[2]) The term 'peptaibol' is used for amphiphilic, membrane-active Aib-containing peptides with an acylated N-terminus and a C-terminal amino alcohol, which show antibiotic properties [6][7].

CHR^1–CO–(NH–CMe_2–CO)$_n$–N(Me)R^2 [14] and Z–NH–CHR^1–CO–(NH–CMe_2–CO)$_n$–N(Me)R^2 [15] as precursors of cyclic depsipeptides and peptides, respectively.

The goal of the present study was to demonstrate the usefulness of 2,2-dimethyl-2*H*-azirin-3-amines for the preparation of poly-Aib peptides and the determination of the conformation of these oligopeptides in the crystalline state.

2. Results and Discussion. – *2.1. Synthesis of Poly-Aib-Oligopeptides.* The synthesis of the poly-Aib-oligopeptides was carried out in analogy to the preparations of the linear peptides of type X–CHR^1–CO–(NH–CMe_2–CO)$_n$–N(Me)R^2 mentioned above [14][15]. The Z-protected 2-aminoisobutyric acid (Z-Aib-OH) [16], which had been prepared in 95% yield by treatment of Aib with benzyl chloroformate in a mixture of 2N aqueous NaOH and dioxane, was dissolved in Et_2O and reacted with 1.1 equiv. 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1a**) at room temperature to give Z-Aib-Aib-N(Me)Ph (**6a**) in quantitative yield (*Scheme 2*). The dipeptide amide crystallized directly from the mixture and was isolated by filtration. Selective hydrolysis of the terminal amide group was achieved in THF/6N HCl (1:1) at room temperature and led to the dipeptide acid Z-Aib-Aib-OH (**7**) in 94% yield.

Scheme 2

The reaction sequence of azirine coupling and hydrolysis was repeated with **7** and subsequently three times in addition. A suitable solvent for the coupling step with **7** was THF; in the cases of the higher homologues **9**, **11**, and **13**, DMF was used. To obtain a clear solution, the mixtures in DMF were heated to 40–70° and then cooled to 0°. After addition of **1a**, the solution was allowed to warm to room temperature. The peptide amides **8a** and **12** crystallized directly from the mixture, whereas **10** and **14** were obtained as yellow oils, but

crystallized after treatment with Et_2O/petroleum ether and Et_2O, respectively. The pure peptide amides were isolated in 85–100% yield. The selective hydrolysis of **8a** and **10** occurred smoothly at room temperature to give the peptide acids **9** and **11** in 85 and 98% yield, respectively. In the case of the rather insoluble **12**, the hydrolysis was carried out at 60° and gave **13** in 98% yield.

2.2. Synthesis of the Heptapeptide Z-(Aib)$_3$-Pro-(Aib)$_3$-N(Me)Ph (**21**). The protected heptapeptide amide **21** was synthesized *via* a combination of the azirine coupling/hydrolysis described above and the segment condensation *via* a 1,3-oxazol-5(4*H*)-one (*Scheme 3*), *i.e.* with the 'azirine/oxazolone method'. The first segment Z-(Aib)$_3$-OH (**9**) was prepared analogously to *Scheme 2*, but by using 2,2,*N*,*N*,tetramethyl-2*H*-azirin-3-amine (**1b**) as the Aib synthon. The azirine coupling gave **6b** and **8b** in 87 and 92% yield, respectively, and the selective hydrolysis to **7** and **9** was almost quantitative. The second segment, Z-L-Pro-(Aib)$_3$-N(Me)Ph (**19**) was obtained in a total yield of 51% by repeated coupling of Z-L-Pro-OH with **1a**, followed by the selective hydrolysis. The reason for the choice of **1a** was the faster hydrolysis of the *N*-methyl-*N*-phenylamides in 6N HCl/THF in comparison with that of the corresponding *N*,*N*-dimethylamides. Therefore, the racemization of Pro as well as the acid-catalyzed cleavage of Pro-Aib [5b][17] was minimized. The hydrolysis of **15** and **17** were complete already after 3 and 3.5 h, respectively, and afforded the products in 80 and 94% yield.

Scheme 3

Finally, the Z-protecting group of the tetrapeptide **19** was removed by hydrogenolysis with Pd/C yielding **20**, and the segments **9** and **20** were condensed by using the coupling reagent DCC/$ZnCl_2$ [5a] to give **21** in 75% yield.

2.3. Crystal Structures of the Poly-Aib-Oligopeptide Amides. Nowadays it is well known that the preferred conformation of peptides containing Aib (and some other α,α-dialkylated glycines) is the 3_{10}-helix, which is a sequence of β-turns of type III or III', in which the ideal values for all torsion angles ϕ (CO–N–C_α–CO) and ψ (N–C_α–CO–N) are ± 60° and ± 30°, respectively. The negative values stand for the right-handed helix (β-turns of type III) and the positive ones for the left-handed helix (β-turns of type III'). An additional characteristic feature consists of the intramolecular H-bonds between CO of amino acid *i* and NH of amino acid *i*+4, which form 10-membered rings, and thereby stabilize the helical structure.

A rather large series of poly-Aib-oligopeptide derivatives have been prepared and their structures analyzed (see *e.g.* [16][18]). In most cases, peptide esters were investigated. The crystal structures of the present set of Z-$(Aib)_n$-N(Me)Ph (n = 3 – 6)[3]), *i.e.* poly-Aib amides, are in good agreement with the 3_{10}-helical structures of analogous derivatives: the average magnitudes of ϕ_i and ψ_i are 55.3° and 31.5°, *i.e.* they correspond well with the typical values of ± 60° and ± 30° (see, *e.g.* [16b][18b,e,f]).

Z-$(Aib)_2$-N(Me)Ph (**6a**). The molecular structure of **6a** in the crystal is shown in *Fig. 1*. The torsion angles ω of the amide groups are in the allowed region for *trans*-amide bonds (*Table 1*). The values of the torsion angle-pair ϕ/ψ for Aib(2) are + 55.2(3)° and + 41.9(3)°, *i.e.*, compatible with a left-handed 3_{10}-helix, but the corresponding ψ-value for Aib(1) is far from the allowed values. Note that since the space group is centrosymmetric, the crystal also contains the equal number of molecules existing in a right-handed helix.

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[3]) The dipeptide derivative Z-$(Aib)_2$-N(Me)Ph (**6a**) is not able to form a β-turn and, therefore, is not included in this comparison.

Fig. 1. *ORTEP Plots* [19] *of the molecular structures of a)* **6a** *and b) one of the two symmetry-independent molecules of* **8a** (50% probability ellipsoids, arbitrary numbering of the atoms)

The molecule **6a** does not form intramolecular H-bonds. Each N–H group of the molecule acts as a donor for intermolecular H-bonds: N(2)–H forms an intermolecular H-bond with the amide O(1)-atom at the Ph(Me)N end of a neighboring peptide molecule and thereby links the molecules into extended chains which run parallel to the [010] direction and which can be described by a graph set motif [20] of C(5). N(3)–H forms an intermolecular H-bond with the amide O(2)-atom in the middle of a different neighboring peptide molecule and thereby links the molecules into centrosymmetric dimers, in which the interactions can be described by a graph set motif of $R^2_2(10)$. The combination of these interactions links the molecules into two-dimensional networks which lie parallel to the (1 0 -1) plane.

Table 1. *Torsion Angles* ω, ϕ, and ψ *of the Backbone of Compounds* **6a**, **8a**, **10**, **12**, *and* **14** *in the Crystal* (atom numbering refers to *Figs. 1 – 3*)

Z-(Aib)$_3$-N(Me)Ph (**8a**). There are two molecules with almost identical conformations but with opposite helicity in the asymmetric unit. As the space group is centrosymmetric, both of the independent molecules exist in the crystal in their left- and right-handed forms. A view of molecule A is shown in *Fig. 1*. Both molecules form a β-turn, stabilized by an intramolecular H-bond between N(2)–H of Aib(2) and C=O(4) of the Z-protecting group (*Table 2*). This corresponds with the observation of *Toniolo et al.* that polypeptides with a Z-protected N-terminal Aib form a β-turn of type III with a $4 \rightarrow 1$ H-bond between NH of the third amino acid and C=O of the Z-group [21]. All torsion angles ω of the amide groups show

characteristic values for *trans*-amide bonds (*Table 1*). The average magnitudes of the torsion angle-pairs ϕ_{1-3}/ψ_{1-2} are 57.3° and 33.8°, typical for a 3_{10}-helix. The torsion angles ψ_{3A} and ψ_{3B} of the C-terminal Aib differ significantly from the ideal value of ± 30°, a fact that has also been described earlier [21a].

Each N–H group of each independent molecule acts as a donor for H-bonds. In molecule A, N(2)–H forms an intramolecular H-bond with the urethane O(4)-atom that is seven atoms along the peptide backbone. This interaction has a graph set motif [20] of S(10) and serves to maintain a fairly rigid helical conformation of the peptide. N(3)–H and N(4)–H, which are unable to form an intramolecular interaction because of their positions in the backbone, form intermolecular H-bonds with the amide O(31') and O(32')-atoms closest to the Ph(Me)N end of the same neighboring B molecule. Molecule B exhibits an identical pattern of H-bonds. Each of these specific donors links molecules A and B alternately into extended chains which run parallel to the [101] direction, and which can be described by a graph set motif of $C^2_{,2}(16)$. The double-bridge between adjacent molecules resulting from both the interactions forms a ring with a graph set motif of $R^2_{,2}(12)$.

Table 2. *Intramolecular H-bonds in* **8a**, **10**, **12**, and **14** *in the Crystal* (atom numbering refers to *Figs. 1 – 3*)

Z-(Aib)$_4$-N(Me)Ph (**10**). The asymmetric unit of the centrosymmetric structure contains one molecule of the peptide **10** and one molecule of H_2O. A view of the molecule is shown in *Fig. 2*. The right-handed 3_{10}-helical conformation of the reference molecule is stabilized by two intramolecular 4 → 1 H-bonds, which form *β*-turns of type III' (N(2)–H···O(4), N(3)–H···O(5)). As in the previous case, N(3)–H forms a H-bond with the C=O(5) group of the urethane. All torsion angles *ω* are in the region of *trans* amide bonds, and the

magnitudes of the torsion angles ϕ_{1-4} and ψ_{1-3} are those of a 3_{10}-helical conformation (*Table 1*; average values –55.3° and –29.0°, resp.). Again, the value of ψ_4 deviates significantly from ± 30°. It is worth mentioning that ϕ_4 and ψ_4 are positive whereas ϕ_{1-3} and ψ_{1-3} are all negative, *i.e.* the helicity of the last Aib is inverted.

Fig. 2. *ORTEP Plots* [19] *of the molecular structures of a)* **10** *and b)* **12** (50% probability ellipsoids, arbitrary numbering of the atoms, H_2O molecule in **10** omitted)

Each N–H group of the molecule **10** acts as a donor for H-bonds. N(2)–H and N(3)–H form intramolecular H-bonds with the amide O(4) and O(5)-atoms that are seven atoms along the peptide backbone. Each of these interactions has a graph set motif [20] of S(10). N(5)–H, which is unable to form an intramolecular interaction because of its position in the backbone, forms an intermolecular H-bond with the amide O(1')-atom at the Ph(Me)N end of a neighboring peptide molecule. These interactions link the molecules into extended chains which run parallel to the [010] direction and which can be described by a graph set motif of C(14). N(4)–H forms an intermolecular H-bond with the O-atom of the H_2O molecule, which, in turn, donates a H-bond to the amide O(1')-atom at the Ph(Me)N end of the next peptide molecule in the chain. These interactions can be described by a binary graph set motif of $C^2_{,2}(13)$.

Z-(Aib)$_5$-N(Me)Ph (**12**). The molecular structure is shown in *Fig. 2*. The reference molecule in the asymmetric unit of the centrosymmetric structure forms a left-handed 3_{10}-helix, stabilized by three intramolecular H-bonds of type 4 → 1, *i.e.* three β-turns of type III: N(2)–H$^{\cdots}$O(4), N(3)–H$^{\cdots}$O(5), and N(4)–H$^{\cdots}$O(6), the last one including the C=O of the urethane (*Table 2*). The torsion angles ω are typical for *trans* amide bonds, and the magnitudes of the torsion angles ϕ_{1-4} and ψ_{1-4} are characteristic for a 3_{10}-helical conformation

(*Table 1*; average values +56.3° and +28.5°, resp.). The values of the last pair ϕ_5 and ψ_5 are quite different and have the opposite sign (–47.6(6)° and –54.1(5)°) compared with ϕ_{1-4} and ψ_{1-4}.

Each N–H group of the molecule acts as a donor for H-bonds. N(2)–H, N(3)–H, and N(4)–H form intramolecular H-bonds with the amide O(4), O(5), and O(6)-atoms that are seven atoms along the peptide backbone. Each of these interactions has a graph set motif [20] of S(10). These H-bonds stabilize the peptide in a fairly rigid helical conformation. N(5)–H and N(6)–H, which are unable to form an intramolecular interaction because of their positions in the backbone, form intermolecular H-bonds with the amide O(1') and O(2')-atoms closest to the Ph(Me)N end of the same neighboring molecule. Each of these specific donors links the molecules into extended chains which run parallel to the [100] direction and which can be described by a graph set motif of C(14). The double-bridge between adjacent molecules resulting from both the interactions forms a ring with a graph set motif of $R^2_2(12)$.

Z-(Aib)$_6$-N(Me)Ph (**14**). The molecular structure is shown in *Fig. 3*. The asymmetric unit contains one molecule of **14** plus a site, which is approximately 25% occupied by a H_2O molecule. Four intramolecular H-bonds of type 4 → 1, *i.e.* four β-turns of type III' (N(2)–H···O(4), N(3)–H···O(5), N(4)–H···O(6), and N(5)–H….O(7), *Table 2*), stabilize a right-handed 3_{10}-helix. The compound crystallizes in a chiral space group, so all molecules exclusively posses a right-handed helix. As in the cases of **8a**, **10**, and **12**, the acceptor of the last H-bond is the C=O group of the urethane. All torsion angles ω are compatible with *trans* amide bonds, and the values of the torsion angles ϕ_{1-5} and ψ_{1-5} are characteristic for a 3_{10}-helical conformation (*Table 1*; average values –54.6° and –35.1°, resp.). Again, the values of the last pair ϕ_6 and ψ_6 differ and have the opposite sign (+49.3(4)° and +52.7(4)°).

Fig. 3. *ORTEP Plot* [19] *of the molecular structure of* **14** (50% probability ellipsoids, arbitrary numbering of the atoms, the H_2O molecule has been omitted)

Each N–H group of the molecule acts as a donor for H-bonds. The four interactions involving N(2)–H, N(3)–H, N(4)–H, and N(5)–H are intramolecular H-bonds with the amide O(4), O(5), O(6), and O(7)-atoms that are seven atoms along the peptide backbone. Each of these interactions has a graph set motif [20] of S(10). This serves to maintain a fairly rigid helical conformation of the peptide. N(7)–H, which is unable to form an intramolecular interaction because of its position in the backbone, forms an intermolecular H-bond with the amide O-atom at the Ph(Me)N end of a neighboring peptide molecule. These interactions link the molecules into extended chains which run parallel to the [001] direction and which can be described by a graph set motif of C(20). N(6)–H forms an intermolecular H-bond with the O-atom of the H_2O molecule, which, in turn, donates a H-bond to the first amide O-atom in the next peptide molecule in the chain. These interactions can be described by a binary graph set motif of $C^2_{,2}(19)$.

3. Conclusions. – With the presented syntheses of poly-AIB-oligopeptides and an Aib-containing heptapeptide, the usefulness of 2,2-dimethyl-2*H*-azirin-3-amines as Aib synthons in peptide synthesis was proved. Repeated azirine coupling with Z-protected α-aminoisobutyric acid (Aib) allowed the smooth and efficient preparation of the Aib-oligomers (Z-$(Aib)_{2–6}$-N(Me)Ph) with a C-terminal amide function. The X-ray crystal-structure analyses of these oligomers confirmed the high preference of β-turns and the 3_{10}-helical conformation. It is worth mentioning that the dimer Z-Aib-Aib-N(Me)Ph is not able to form a β-turn with the corresponding $4 \rightarrow 1$ H-bond because it is to short, but the values of the torsion angles of Aib(2) are close to those of an Aib involved in a β-turn. As expected, in all oligomers the

terminal amide group is not involved in intramolecular H-bonding and, therefore, does not influence the structure of the peptide backbone significantly (*cf.* [18]). Furthermore, the conformation of the Z-protecting group, which is involved in a 4 → 1 H-bond stabilizing the first β-turn, is similar for all investigated oligopeptides and shows the *trans*,*trans*-conformation (*cf.* [21b]). The torsion angles ω of the peptide bonds of the studied Aib-oligomers are typically in the range of 171 – 180° (*trans* amide bonds), and only in the two crystallographically independent molecules of Z-$(Aib)_3$-N(Me)Ph were values of *ca.* 164° observed for ω_2.

With the synthesis of Z-$(Aib)_3$-Pro-$(Aib)_3$-N(Me)Ph it was demonstrated once more that the combination of azirine coupling, selective hydrolysis, and coupling of a peptide segment *via* an 5(4*H*)-oxazolone, *i.e.* the 'azirine/oxazolone method', is very suitable for the synthesis of Aib-rich oligopeptides.

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Experimental Part

1. *General*. Solvents were purified by standard procedures; THF was distilled from Na/benzophenone, Et_2O from Na, and CH_2Cl_2 from $CaCl_2$; DMF, puriss. was dried over molecular sieves. All commercially available chemicals were of analytical grade and were

used without purification. The 2*H*-azirin-3-amines **1a** and **1b** were prepared according to the references cited in [4]. TLC: aluminium sheets, silica gel 60 F_{254} (*Merck*). Prep. TLC: glass plates, silica gel 60 F_{254} (2 mm; *Merck*). Column chromatography (CC, flash chromatography [22]): silica gel *Merck* 60 (0.040–0.063 mm). High performance liquid chromatography (HPLC) with a *Varian* 2510 instrument and *Varian* 2550 UV detector (254 nm) or *Waters* 600 E instrument with *Waters* 484 UV detector (254 nm); Lichrosorb RP 18 or LichroCast RP 18 (reversed phase) columns. M.p.: *Mettler-FP-5* apparatus; uncorrected. IR Spectra: *Perkin-Elmer*-297 or 781 spectrophotometer; in KBr, in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian* XL-200 or *Bruker*-AM-400 instrument (200 and 50.4 MHz, or 400 and 100.7 MHz, resp.); δ in ppm, coupling constants *J* in Hz; multiplicity of C-atoms from DEPT spectra. MS: *Finnigan* MAT-90 (EI) or *Finnigan* SSQ-700 (CI with NH_3) instrument. Elemental analyses were performed at the Institute of Organic Chemistry of the University of Zürich.

Abbreviations: AcOEt = ethyl acetate, Aib = 2-aminoisobutyric acid, Bn = benzyl, DCC = *N*,*N*'-dicyclohexyl carbodiimide, Z = benzyloxycarbonyl.

General Procedure 1 (*GP 1*, *azirine coupling*). To a 0.5M soln. of the peptide acid in Et_2O, THF, or DMF at 0° was added azirine **1a** or **1b** (1.1 equiv.) dropwise, and the mixture was stirred at 0° for 10 min and at r.t. for several h. The precipitated product was filtered and washed with Et_2O and petroleum ether. The solvent of the mother liquor was evaporated and the oily residue crystallized by treatment with petroleum ether at 0°. The combined crystals were dried in h.v.

General Procedure 2 (*GP 2*, *selective hydrolysis*). A 0.1M soln. of the peptide amide in THF/6N HCl (1:1) was stirred at r.t. or at 60° and the progress of the reaction followed by TLC. When the reaction was complete, the same volume of 2N HCl was added, the product was extracted with Et_2O, and the combined org. phase was dried (Na_2SO_4). After evaporation of the solvent, the product was dried in h.v.

2. *Synthesis of Poly-Aib-Oligopeptides*. 2.1. N-*Benzyloxycarbonyl-2-methylalanine* (Z-Aib-OH) [16]. To a vigorously stirred soln. of Aib (20 g, 194 mmol) in 2N HCl/dioxane (2:1, 145.5 ml) at 0° were added simultaneously a soln. of benzyl chloroformate (79.4 g, 466 mmol) in toluene and 4N NaOH (37 ml) to keep the pH basic. Then, the mixture was warmed to r.t., and stirring was continued overnight. After addition of Et_2O, the org. phase was separated, and 6N HCl was added to the cooled aq. phase, which was then extracted with Et_2O (3×). The combined org. phase was evaporated, and the oily residue was crystallized by addition of petroleum ether at reflux temperature and subsequent cooling to r.t. The crystalline solid was washed with petroleum ether and dried in h.v. Yield of Z-Aib-OH: 44.5 g (95%). M.p. 75.5°. ^{1}H-NMR (90 MHz, $CDCl_3$): 10.65 – 10.35 (br. *s*, COOH); 7.35 (*s*, 5 arom. H); 5.65 – 5.25 (br. *s*, NH); 1.60 (*s*, Me_2C).

2.2. N-*Benzyloxycarbonyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-$(Aib)_2$-N(Me)Ph, **6a**). According to *GP 1*, to a soln. of Z-Aib-OH (1.30 g, 5.5 mmol) in Et_2O (10 ml), azirine **1a** (1.0 g, 6.0 mmol) was added. After 5 min, a precipitate formed. The mixture was kept at 4° overnight and then filtered. Yield of **6a**: 2.28 g (quant.). Colorless solid. M.p. 152 – 154°. IR ($CHCl_3$): 3430*w*, 3370*w*, 2940*w*, 1725*m*, 1670*m*, 1630*m*, 1595*w*, 1495*s*, 1455*m*, 1390*w*, 1365*w*, 1170*w*, 1120*w*, 1090*w*, 1075*w*, 705*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.48 (br. *s*, NH); 7.42 – 7.30, 7.30 – 7.20 (2*m*, 10 arom. H); 5.36 (br. *s*, NH urethane); 5.07 (*s*, PhCH_2O); 3.28 (*s*, MeN); 1.47, 1.42 (2*s*, 2 Me_2C). ^{13}C-NMR (50 MHz, $CDCl_3$): 173.6, 172.7 (2*s*, 2 CO(amide)); 154.9 (*s*, CO(urethane)); 144.3, 136.5 (2*s*, 2 arom. C); 129.3, 128.4, 128.3, 128.03, 128.0, 127.9 (6*d*, 10 arom. CH); 66.4 (*t*, PhCH_2O); 58.4, 57.0 (2*s*, 2 Me_2C); 41.5 (*q*, MeN); 25.2, 25.1 (2*q*, 2 Me_2C). Anal. calc. for $C_{23}H_{29}N_3O_4$ (411.51): C 67.13, H 7.10, N 10.21; found: C 67.25, H 7.03, N 10.30.

Suitable crystals for the X-ray crystal-structure determination were grown from DMSO/H_2O by slow evaporation of the solvent.

2.3. N-*Benzyloxycarbonyl-2-methylalanyl-2-methyalanine* (Z-(Aib)$_2$-OH, **7**). According to *GP 2*, **6a** (3.74 g, 9.1 mmol) was hydrolysed. After evaporation of Et_2O, **7** was obtained as a colorless, crystalline solid. Yield: 2.75 g (94%). M.p. 154 – 158°. IR (KBr): 3430*m*, 3300*m*, 3040*w*, 2990*w*, 2950*w*, 1725*s*, 1705*s*, 1655*s*, 1535*s*, 1510*m*, 1470*w*, 1460*w*, 1445*w*, 1420*w*, 1380*w*, 1360*w*, 1300*w*, 1255*m*, 1230*m*, 1210*w*, 1185*w*, 1170*w*, 1080*m*, 970*w*, 855*w*, 785*w*, 750*w*, 700*w*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 12.27 – 12.20 (br. *s*, COOH); 7.48 (*s*, NH); 7.37 – 7.26 (*m*, 5 arom. H, NH); 5.02 (*s*, PhC*H*$_2$O); 1.33 (*s*, 2 Me_2C). ^{13}C-NMR (50 MHz, (D_6)DMSO): 175.8 (*s*, COOH); 173.4 (*s*, CO(amide)); 154.7 (*s*, CO(urethane)); 137.2 (*s*, arom. C); 128.3, 127.7, 127.5 (3*d*, 5 arom. CH); 65.0 (*t*, Ph*C*H$_2$O); 56.0, 55.1 (2*s*, 2 Me_2*C*); 25.0, 24.4 (2*q*, 2 *Me*$_2$C). CI-MS: 323 (100, [*M*+1]$^+$). Anal. calc. for $C_{16}H_{22}N_2O_5$ (322.36): C 59.62, H 6.88, N 8.69; found: C 59.54, H 6.82, N 8.49.

2.4. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-(Aib)$_3$-N(Me)Ph, **8a**). According to *GP 1*, to a soln. of **7** (2.0 g, 6.2 mmol) in THF (14 ml) was added **1a** (1.14 g, 6.5 mmol). After warming to r.t., a precipitate formed. The mixture was stirred at r.t. for 4 h and kept at 4° overnight. Yield of **8a**: 2.95 g (95%). Colorless solid. M.p. 177 – 178°. IR (KBr): 3340*m*, 3290*m*, 3040*w*, 2990*w*, 2940*w*, 1710*m*, 1690*m*, 1660*s*, 1635*s*, 1595*w*, 1540*m*, 1515*m*, 1495*m*, 1465*m*, 1270*m*, 1225*w*, 1205*w*, 1170*w*, 1100*m*, 1090*m*, 915*w*, 740*w*, 710*w*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 7.75, 7.66 (2*s*, 2 NH); 7.40 – 7.15 (*m*, 10 arom. H, NH); 5.11 (*s*, PhC*H*$_2$O); 3.16 (*s*, MeN); 1.31, 1.30, 1.29 (3*s*, 3 Me_2C). ^{13}C-NMR (50 MHz, (D_6)DMSO): 173.7, 173.1, 172.4 (3*s*, 3 CO(amide)); 155.5 (*s*, CO(urethane)); 146.0, 137.2 (2*s*, 2 arom. C); 128.6, 128.3, 127.6, 126.9, 126.8, 125.9 (6*d*, 10 arom. CH); 65.1 (*t*, Ph*C*H$_2$O); 56.2, 56.1, 55.9 (3*s*, 3 Me_2*C*); 39.1 (*q*, MeN); 25.4, 24.8, 24.7 (3*q*, 3 *Me*$_2$C). Anal. calc. for $C_{27}H_{36}N_4O_5$ (496.61): C 65.30, H 7.31, N 11.28; found: C 65.52, H 7.54, N 11.05.

Suitable crystals for the X-ray crystal-structure determination were grown from

DMSO/H_2O by slow evaporation of the solvent.

2.5. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methyalanine* (Z-$(Aib)_3$-OH, **9**). According to *GP 2*, **8a** (4.95 g, 10.0 mmol) was hydrolyzed. After 2 h, the precipitate was filtered. The aq. phase was extracted with Et_2O, the org. phase was dried (Na_2SO_4), then Et_2O was evaporated, the combined solid material was washed wit Et_2O and dried in h.v. Yield of **9**: 3.43 g (85%). Colorless solid. M.p. 195 – 196°. IR (KBr): 3470*m*, 3410*m*, 3320*m*, 3300*s*, 3080*w*, 3020*w*, 2990*w*, 2930*w*, 1730*s*, 1700*s*, 1660*s*, 1635*s*, 1550*m*, 1535*s*, 1470*w*, 1455*m*, 1390*m*, 1345*m*, 1310*m*, 1275*s*, 1225*w*, 1210*w*, 1180*m*, 1100*s*, 1080*w*, 740*m*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 7.62 (br. *s*, 2 NH); 7.39 – 7.31 (*m*, 5 arom. H, NH); 5.07 (*s*, PhC*H*$_2$O); 1.30 (br. *s*, 3 Me_2C). ^{13}C-NMR (50 MHz, (D_6)DMSO): 175.5 (*s*, COOH); 173.4, 173.2 (2*s*, 2 CO(amide)); 155.4 (*s*, CO(urethane)); 137.0 (*s*, arom. C); 128.3, 127.8, 127.6 (3*d*, 5 arom. CH); 65.3 (*t*, Ph*C*H_2O); 56.2, 55.7, 54.8 (3*s*, 3 Me_2*C*); 24.9, 24.5 (2*q*, 3 *Me*$_2$C). CI-MS: 408 (100, $[M+1]^+$). Anal. calc. for $C_{20}H_{29}N_3O_6$ (407.47): C 58.95, H 7.17, N 10.31; found: C 58.87, H 7.33, N 10.55.

2.6. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-$(Aib)_4$-N(Me)Ph, **10**). At *ca*. 40°, **9** (3.20 g, 7.85 mmol) was dissolved in DMF (17 ml). After cooling to 0°, according to *GP 1*, **1a** (1.55 g, 8.2 mmol) was added and the mixture stirred at r.t. for 4 h. The solvent was evaporated and the yellow oily residue was treated with Et_2O. The formed solid was filtered, dissolved in DMF, precipitated by addition of Et_2O (3×), and dried in h.v. Yield of **10**: 4.24 g (93%). Colorless solid. M.p. 194 – 195°. IR (KBr): 3420*w*, 3330*m*, 3300*m*, 3030*w*, 2990*w*, 2940*w*, 1705*s*, 1680 – 1650*s* (br), 1630*m*, 1595*m*, 1530*s*, 1495*m*, 1470*m*, 1455*m*, 1395*m*, 1380*m*, 1365*m*, 1270*m*, 1220*w*, 1170*w*, 1090*m*, 710*m*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 8.21, 7.84, 7.55 (3 br. *s*, 3 NH); 7.38 – 7.16 (*m*, 10 arom. H, NH); 5.08 (*s*, PhC*H*$_2$O); 3.28 (*s*, MeN); 1.42, 1.34, 1.28, 1.26 (4*s*, 4 Me_2C). ^{13}C-NMR (50 MHz, (D_6)DMSO): 175.1, 173.9, 173.1, 172.7 (4*s*, 4

CO(amide)); 155.7 (*s*, CO(urethane)); 146.2, 137.5 (2*s*, 2 arom. C); 128.6, 128.3, 127.7, 127.2, 126.8, 125.8 (6*d*, 10 arom. CH); 65.5 (*t*, Ph*C*H_2O); 56.04, 56.0 (2*s*, 4 Me_2C); 39.1 (*q*, MeN); 25.5, 25.1, 24.6 (3*q*, 4 *Me*$_2$C). Anal. calc. for $C_{31}H_{43}N_5O_6$ (581.72): C 64.01, H 7.45, N 12.04; found: C 64.15, H 7.48, N 12.02.

Suitable crystals for the X-ray crystal-structure determination were grown from DMSO/H_2O by slow evaporation of the solvent.

2.7. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methylalanlyl-2-methyalanine* (Z-(Aib)$_4$-OH, **11**). According to *GP 2*, **10** (8.81 g, 15.1 mmol) was hydrolyzed in THF/6N HCl (152 ml). After 2.5 h, 2N HCl (150 ml) was added and the precipitate was filtered. The solid material was washed with CH_2Cl_2 and dried in h.v. Yield of **11**: 7.31 g (98%). Colorless solid. M.p. 232 – 233°. IR (KBr): 3370*w*, 3300*m*, 3070*w*, 3000*w*, 1730*m*, 1710*s*, 1660*s*, 1545*m*, 1530*m*, 1515*m*, 1455*w*, 1400*w*, 1390*w*, 1365*w*, 1300*w*, 1280*w*, 1260*m*, 1230*w*, 1170*w*, 1080*m*, 955*w*, 810*w*, 790*w*, 700*w*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 11.83 (br. *s*, COOH); 8.07, 7.78 (2*s*, 2 NH); 7.41 – 7.25 (*m*, 5 arom. H, NH); 7.18 (*s*, NH); 5.09 (*s*, PhC*H*$_2$O); 1.33, 1.25, 1.22 (3*s*, 4 Me_2C). ^{13}C-NMR (50 MHz, (D_6)DMSO): 175.6 (*s*, COOH); 174.8, 173.5, 173.1 (3*s*, 3 CO(amide)); 155.7 (*s*, CO(urethane)); 137.1 (*s*, arom. C); 128.3, 127.7, 127.3 (3*d*, 5 arom. CH); 65.5 (*t*, Ph*C*H_2O); 56.01, 56.0, 55.5, 54.6 (4*s*, 4 Me_2C); 24.8, 24.6 (2*q*, 4 *Me*$_2$C). FAB-MS: 493 (100, [*M*+1]$^+$). Anal. calc. for $C_{24}H_{36}N_4O_7$ (492.57): C 58.52, H 7.37, N 11.37; found: C 58.56, H 7.10, N 11.56.

2.8. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methylalanyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-(Aib)$_5$-N(Me)Ph, **12**). At *ca*. 70°, **11** (6.50 g, 13.2 mmol) was dissolved in DMF (30 ml). After cooling to 0°, according to *GP 1*, **1a** (2.60 g, 13.7 mmol) was added and the mixture stirred at r.t. overnight. The formed solid was filtered and dried in h.v. Yield of **12**: 8.02 g (91%). Colorless solid. M.p. 235 – 236°. IR (KBr): 3420*w*, 3300*s*, 3250*m*, 3040*w*, 2990*w*, 2940*w*, 1695*m*, 1675*s*, 1650*s*, 1595*w*,

1555*s*, 1530*s*, 1495*m*, 1465*m*, 1455*m*, 1395*m*, 1385*m*, 1365*m*, 1270*m*, 1225*w*, 1215*w*, 1170*w*, 1090*m*, 1080*m*, 770*w*, 755*w*, 710*m*. ^{1}H-NMR (400 MHz, (D_6)DMSO, 100°): 7.75, 7.55, 7.42 (3 br. *s*, 3 NH); 7.38 – 7.16 (*m*, 10 arom. H, 2 NH); 5.09 (*s*, PhC*H*$_2$O); 3.31 (*s*, MeN); 1.45, 1.42, 1.39, 1.37, 1.34, 1.32, 1.30 (7*s*, 5 Me$_2$C). ^{13}C-NMR (50 MHz, (D_6)DMSO, 100°): 174.4, 174.1, 173.3, 172.8, 172.2 (5*s*, 5 CO(amide)); 155.3 (*s*, CO(urethane)); 145.9, 136.5 (2*s*, 2 arom. C); 127.9, 127.7, 127.2, 126.8, 126.3, 125.2 (6*d*, 10 arom. CH); 65.2 (*t*, Ph*C*H$_2$O); 56.0, 55.81, 55.80, 55.7, 55.6 (5*s*, 5 Me$_2$*C*); 39.1 (*q*, MeN); 25.2, 24.8, 24.2, 24.0 (4*q*, 5 *Me*$_2$C). FAB-MS: 560 (20, [*M*+1–Ph(Me)NH]$^+$). Anal. calc. for $C_{35}H_{50}N_6O_7$ (666.82): C 63.04, H 7.56, N 12.60; found: C 63.08, H 7.48, N 12.44.

Suitable crystals for the X-ray crystal-structure determination were grown from DMSO by slow evaporation of the solvent.

2.9. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methylalanlyl-2-methylalanyl-2-methyalanine* (Z-(Aib)$_5$-OH, **13**). According to *GP 2*, a suspension of **12** (200 mg, 0.3 mmol) in THF/6N HCl (3 ml) was stirred at *ca*. 60° for 1.5 h. After usual workup, the product was dried in h.v. Yield of **13**: 169 mg (98%). Colorless solid. M.p. 234 – 235°. IR (KBr): 3300*m*, 3080*w*, 3030*w*, 299*w*, 2940*w*, 1730*m*, 1710*m*, 1660*s*, 1530*s*, 1455*w*, 1385*w*, 1365*w*, 1300*w*, 1260*m*, 1230*w*, 1170*w*, 1080*m*, 750*w*, 700*w*. ^{1}H-NMR (200 MHz, (D_6)DMSO, 50°): 11.83 (br. *s*, COOH); 8.24, 7.85, 7.48 (3*s*, 3 NH); 7.34 – 7.30 (*m*, 5 arom. H, NH); 7.29 (br. *s*, NH); 5.10 (*s*, PhC*H*$_2$O); 1.33, 1.27, 1.22 (3*s*, 5 Me$_2$C). ^{13}C-NMR (50 MHz, (D_6)DMSO, 80°): 174.8, 174.4, 174.0, 173.1, 173.0 (5*s*, COOH, 4 CO(amide)); 155.4 (*s*, CO(urethane)); 136.7 (*s*, arom. C); 127.8, 127.3, 126.9 (3*d*, 5 arom. CH); 65.3 (*t*, Ph*C*H$_2$O); 55.8, 55.60, 55.59, 55.5, 54.5 (5*s*, 5 Me$_2$*C*); 24.6, 24.3, 24.25, 24.1 (4*q*, 5 *Me*$_2$C). Anal. calc. for $C_{28}H_{43}N_5O_8$ (577.68): C 58.12, H 7.50, N 12.12; found: C 58.35, H 7.57, N 11.95.

2.10. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methylalanyl-2-*

methylalanyl-2-methylalanlyl-2-methyalanine-N-*methyl*-N-*phenylamide* (Z-(Aib)$_6$-N(Me)Ph, **14**). At *ca*. 70°, **13** (3.0 g, 5.2 mmol) was dissolved in DMF (11 ml). After cooling to 0°, according to *GP 1*, was added **1a** (950 mg, 5.45 mmol) and the mixture stirred at r.t. for 20 h. The obtained oil was treated with Et_2O, and the formed solid was dried in h.v. Yield of **14**: 3.58 g (92%). Colorless solid. M.p. 222 – 223°. IR (KBr): 3320*m*, 3040*w*, 2990*w*, 2940*w*, 1745*w*, 1700*m*, 1670*s*, 1595*w*, 1525*s*, 1455*w*, 1385*w*, 1365*w*, 1270*m*, 1230*w*, 1170*w*, 1090*m*, 1100*w*, 740*w*, 715*w*, 700*w*. ^{1}H-NMR (200 MHz, (D_6)DMSO + 5% H_2O, 85°)[4]): 7.89, 7.61, 7.50, 7.48 (4 br. *s*, 4 NH); 7.44 – 7.12 (*m*, 10 arom. H, 2 NH); 5.10 (*s*, PhC*H*$_2$O); 3.31 (*s*, MeN); 1.45, 1.42, 1.40, 1.37, 1.36, 1.35, 1.32, 1.31, 1.28 (9*s*, 6 Me_2C). ^{13}C-NMR (50 MHz, (D_6)DMSO, 70°)[4]): 174.9, 174.7, 174.5, 174.45, 174.1, 173.5, 173.14, 173.1, 172.3 (9*s*, 6 C=O(amide)); 155.5, 155.4 (2*s*, C=O(urethan)); 146.0, 136.7 (2*s*, 2 arom. C); 128.1, 127.9, 127.4, 127.0, 126.5, 125.4 (6*d*, 10 arom. CH); 65.3 (*t*, PhC*H*$_2$O); 56.0, 55.9, 55.8, 55.7, 55.6, 55.5 (6*s*, 6 Me_2*C*); 38.8 (*q*, MeN); 25.3, 25.0, 24.5, 24.4, 24.3, 24.1 (6*q*, 6 *Me*$_2$C). Anal. calc. for $C_{39}H_{57}N_7O_8$ (751.93): C 62.30, H 7.64, N 13.04; found: C 62.08, H 7.62, N 12.82.

Suitable crystals for the X-ray crystal-structure determination were grown from DMSO/H_2O by slow evaporation of the solvent.

3. *Synthesis of Z-(Aib)$_3$-*L*-Pro-(Aib)$_3$-N(Me)Ph* (**21**). 3.1. N-*Benzyloxycarbonyl-2-methylalanyl-2-methyalanine*-N,N-*dimethylamide* (Z-(Aib)$_2$-NMe_2, **6b**). According to *GP 1*, to a soln. of Z-Aib-OH (4.0 g, 16.9 mmol) in Et_2O (36 ml) at 0°, azirine **1b** (2.1 g, 18.6 mmol) was added, and the mixture was stirred at r.t. After 1 h, a precipitate formed, and after 24 h, the reaction was complete. The solid was filtered, washed with Et_2O, and dried in h.v. Yield of **6b**: 5.13 g (87%). Colorless solid. M.p. 159 – 161°. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.56 (br. *s*, NH); 7.40 – 7.30 (*m*, 5 arom. H); 5.44 (br. *s*, NH urethane); 5.09 (*s*, PhC*H*$_2$O); 3.03 (*s*, Me_2N); 1.58, 1.53 (2*s*, 2 Me_2C). CI-MS: 350 (45, [*M*+1]$^+$), 305 (100).

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[4]) Some of the signals were doubled, most likely because of the presence of conformers.

3.2. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methyalanine*-N,N-*dimethylamide* (Z-(Aib)$_3$-NMe$_2$, **8b**). According to *GP 2*, **6b** (5.0 g, 14.0 mmol) was hydrolyzed to give **7** (4.40 g, 13.65 mmol; see section 2.3). The crude material was dissolved in a mixture of Et_2O (28 ml) and THF (10 ml), and azirine **1b** (1.77 g, 15.7 mmol) was added. After 42 h, the precipitate was filtered, the product washed with Et_2O, and dried in h.v. Yield of **8b**: 5.46 g (92%). Colorless solid. M.p. 185 – 186°. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.43 (br. *s*, NH); 7.36 – 7.32 (*m*, 5 arom. H, NH); 6.72 (br. *s*, NH); 5.13 (*s*, PhC*H*$_2$O); 2.97 (br. *s*, Me$_2$N); 1.43, 1.42, 1.38 (3*s*, 3 Me$_2$C). CI-MS: 435 (17, $[M+1]^+$), 390 (100).

3.3. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methyalanine* (Z-(Aib)$_3$-OH, **9**). The hydrolysis of **8b** (5.32 g, 12.2 mmol) according to *GP 2* gave **9** (4.10 g, 96%; see section 2.5).

3.4. N-*Benzyloxycarbonyl*-L-*prolyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-Pro-Aib-N(Me)Ph, **15**). According to *GP 1*, to a soln. of Z-Pro-OH (5.0 g, 20.06 mmol) in abs. THF (50 ml) at 0°, azirine **1a** (3.7 g, 21.06 mmol) was added and the mixture was stirred under Ar at r.t. for 5 d. The solvent was evaporated and the residue was crystallized by treatment with Et_2O and hexane. The product was washed with Et_2O and dried in h.v. Yield of **15**: 7.90 g (93%). Colorless solid. M.p. 119 – 120°. $[\alpha]_D^{20}$ = – 51.0 (EtOH, c = 0.97). IR (KBr): 3420*w*, 3280*m*, 3040*w*. 3000*w*, 2970*w*, 2880*w*, 1710*s*, 1675*s*, 1625*s*, 1590*m*, 1535*m*, 1495*m*, 1470*w*, 1455*w*, 1420*s*, 1390*m*, 1375*w*, 1355*m*, 1250*m*, 1215*w*, 1170*w*, 1120*m*, 1090*m*, 1070*w*, 1030*w*, 1020*w*, 995*w*, 960*w*, 915*w*, 870*w*, 775*w*, 710*m*, 700*w*. ^{1}H-NMR (200 MHz, (D_6)DMSO): 8.12 (br. *s*, NH); 7.40 – 7.10 (*m*, 10 arom. H); 5.20 – 4.85 (*m*, PhC*H*$_2$O); 4.30 – 4.10 (*m*, CH(2) Pro); 3.45 – 3.30 (*m*, CH$_2$(5) Pro); 3.32 (*s*, MeN); 2.30 – 1.70 (*m*, CH$_2$(3), CH$_2$(4) Pro); 1.35, 1.31 (2*s*, Me$_2$C). CI-MS: 424 (43, $[M+1]^+$), 317 (100). Anal. calc. for $C_{24}H_{29}N_3O_4$ (423.52): C 68.00, H 6.90, N 9.92; found: C 67.33, H 6.89, N 10.03.

3.5. N-*Benzyloxycarbonyl*-L-*prolyl-2-methyalanine* (Z-Pro-Aib-OH, **16**). The

hydrolysis of **15** (6.63 g, 15.65 mmol) according to *GP 2* for 2.75 h gave **16** (4.19 g, 80%) as a colorless foam. ^{1}H-NMR (90 MHz, $CDCl_3$): 9.30 (br. *s*, COOH); 7.50 – 7.10 (*m*, 5 arom. H, NH); 5.10 (br. *s*, PhC*H*$_2$O); 4.50 – 4.10 (*m*, CH(2) Pro); 3.85 – 3.30 (*m*, CH_2(5) Pro); 2.30 – 1.80 (*m*, CH_2(3), CH_2(4) Pro); 1.50 (br. *s*, Me_2C).

3.6. N-*Benzyloxycarbonyl*-L-*prolyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-Pro-(Aib)$_2$-N(Me)Ph, **17**). According to *GP 1*, to a soln. of **16** (4.20 g, 12.56 mmol) in Et_2O (130 ml) at 0°, **1a** (2.53 g, 14.45 mmol) was added and the mixture was stirred under Ar at 0° overnight. The precipitate was filtered, washed with Et_2O, and dried in h.v. Yield of **17**: 5.69 g (89%). Colorless solid. M.p. 147 – 148°. $[\alpha]_D^{22}$ = – 23.1 (EtOH, c = 0.943). IR (KBr): 3400*m*, 3310*m*, 2990*w*, 2940*w*, 2870*w*, 1695*s*, 1685*s*, 1625*s*, 1595*w*, 1530*w*, 1495*w*, 1440*w*, 1425*m*, 1395*w*, 1365*w*, 1335*m*, 1280*w*, 1240*w*, 1225*w*, 1205*w*, 1110*w*, 1090*w*, 1000*w*, 995*w*, 980*w*, 770*w*, 730*w*, 705*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.17, 7.86 (2*s*, 2 NH); 7.50 – 7.10 (*m*, 10 arom. H); 5.09 (*s*, PhC*H*$_2$O); 4.20 – 4.10 (*m*, CH(2) Pro); 3.60 – 3.30 (*m*, CH_2(5) Pro); 3.32 (*s*, MeN); 2.20 – 1.70 (*m*, CH_2(3), CH_2(4) Pro); 1.36, 1.35, 1.29, 1.27 (4*s*, 2 Me_2C). CI-MS: 509 (2, $[M+1]^+$), 402 (100). Anal. calc. for $C_{28}H_{36}N_4O_5$ (508.62): C 66.12, H 7.13, N 11.02; found: C 65.89, H 7.22, N 11.19.

3.7. N-*Benzyloxycarbonyl*-L-*prolyl-2methylalanyl-2-methyalanine* (Z-Pro-(Aib)$_2$-OH, **18**). The hydrolysis of **17** (5.45 g, 10.72 mmol) according to *GP 2* for 3.5 h gave **18** (4.49 g, 94%) as a colorless foam. $[\alpha]_D^{22}$ = – 36.0 (EtOH, c = 1.197). IR (KBr): 3330*m*, 3300*m*, 3030*w*, 2990*w*, 2980*w*, 2940*w*, 2880*w*, 1730*m*, 1685*s*, 1650*s*, 1530*m*, 1500*w*, 1470*m*, 1440*m*, 1395*w*, 1385*w*, 1360*m*, 1315*w*, 1280*w*, 1260*w*, 1240*w*, 1170*m*, 1130*w*, 1090*w*, 1040*w*, 990*w*, 975*w*, 770*w*, 750*w*, 700*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.21 (*s*, NH); 7.50 – 7.20 (*m*, 5 arom. H); 7.18 (*s*, NH); 5.07 (*s*, PhC*H*$_2$O); 4.20 – 4.10 (*m*, CH(2) Pro); 3.50 – 3.20 (*m*, CH_2(5) Pro); 2.20 – 1.70 (*m*, CH_2(3), CH_2(4) Pro); 1.33, 1.32, 1.31, 1.29 (4*s*, 2 Me_2C). CI-MS: 420 (100, $[M+1]^+$). Anal. calc. for $C_{21}H_{29}N_3O_6$ (419.48): C 60.13, H 6.97, N 10.02;

found: C 59.79, H 6.84, N 9.80.

3.8. N-*Benzyloxycarbonyl*-L-*prolyl-2-methylalanyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-Pro-(Aib)$_3$-N(Me)Ph, **19**). According to *GP 1*, to a soln. of **18** (4.0 g, 9.54 mmol) in a mixture of abs. THF (19 ml) and abs. DMF (10 ml) at 0°, **1a** (1.94 g, 11.15 mmol) was added slowly and the mixture was stirred under Ar at r.t. for 45 h. The precipitate was filtered, washed with Et_2O, and dried in h.v. Yield of **19**: 4.64 g (82%). Colorless solid. $[\alpha]_D^{22}$ = – 46.0 (EtOH, c = 1.062). IR (KBr): 3400*w*, 3300*w*, 3070*w*, 3040*w*, 2990*w*, 2950*w*, 2880*w*, 1670*s* (br), 1640*s* (br), 1595*w*, 1535*s*, 1495*s*, 1470*w*, 1455*s*, 1425*s*, 1395*s*, 1365*s*, 1340*w*, 1290*w*, 1275*w*, 1245*w*, 1215*w*, 1170*w*, 1125*m*, 1100*m*, 1025*w*, 985*w*, 935*w*, 775*w*, 740*w*, 715*m*, 700*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.68, 7.43 (2*s*, 2 NH); 7.40 – 7.10 (*m*, 10 arom. H); 7.02 (*s*, NH); 5.12, 4.98 (*AB*, J_{AB} = 12.8, PhC*H*$_2$O); 4.25 – 4.15 (*m*, CH(2) Pro); 3.55 – 3.35 (*m*, CH_2(5) Pro); 3.30 (*s*, MeN); 2.20 – 1.75 (*m*, CH_2(3), CH_2(4) Pro); 1.36, 1.34 (2*s*, 3 Me_2C). ^{13}C-NMR (50 MHz, CD_3OD): 177.0, 176.1, 176.0, 175.4 (4*s*, 4 C=O(amide)); 157.0 (*s*, C=O(urethane)); 147.4, 138.2 (2*s*, 2 arom. C); 130.5, 129.9, 129.5, 129.0, 128.5, 128.3 (6*d*, 10 arom. CH); 68.6 (*t*, Ph*C*H$_2$O); 62.2 (*d*, C(2) Pro); 58.7, 58.4, 58.1 (3*s*, 3 Me_2*C*); 48.2 (*t*, CH_2(5) Pro); 41.3 (*q*, MeN); 31.4, 26.0 (2*t*, CH_2(3), CH_2(4) Pro); 27.5, 26.8, 26.7, 26.3, 24.9, 24.4 (6*q*, 3 *Me*$_2$C). CI-MS: 487 (96, [*M*+1–Ph(Me)NH]$^+$), 108 (100). Anal. calc. for $C_{32}H_{43}N_5O_6$ (593.73): C 64.74, H 7.30, N 11.80; found: C 64.53, H 7.20, N 12.01.

3.9. L-*Prolyl-2-methylalanyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (H-Pro-(Aib)$_3$-N(Me)Ph, **20**). To a stirred soln. of **19** (500 mg, 0.84 mmol) in MeOH (5.5 ml) was added in small portions Pd/C 10% (50 mg) at r.t., and a stream of H_2 was bubbled through the mixture for 2 h. Then, the mixture was filtered through Celite, the filtrate evaporated, the residue crystallized by treatment with Et_2O, and dried in h.v. Yield of **20**: 345 mg (89%). Colorless solid. $[\alpha]_D^{22}$ = – 24.3 (EtOH, c = 0.420). IR (KBr): 3440*m* (br), 3300*m* (br), 2980*w*, 2930*w*, 1660*s* (br), 1595*w*, 1530*m* (br), 1495*m*, 1460*w*, 1390*w*, 1365*w*, 1280*w*,

1225*w*, 1170*w*, 1095*w*, 770*w*, 710*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.02, 7.05 (2*s*, 2 NH); 7.40 – 7.20 (*m*, 5 arom. H, NH); 6.83 (br. *s*, NH); 3.96 (*dd*, *J* = 9.1, 5.3, CH(2) Pro); 3.31 (*s*, MeN); 3.10 – 2.85 (*m*, CH_2(5) Pro); 2.20 – 1.65 (*m*, CH_2(3), CH_2(4) Pro); 1.49, 1.48, 1.47 (3*s*, 3 Me_2C). ^{13}C-NMR (50 MHz, $CDCl_3$): 175.8, 173.7, 173.2, 173.0 (4*s*, 4 C=O(amide)); 145.2 (*s*, C arom.); 129.1, 127.9, 127.2 (3*d*, 5 arom. CH); 60.7 (*d*, C(2) Pro); 57.9, 57.1, 56.7 (3*s*, 3 Me_2C); 47.2 (*t*, CH_2(5) Pro); 40.8 (*q*, MeN); 30.6, 26.2 (2*t*, CH_2(3), CH_2(4) Pro); 25.7, 25.5, 25.4, 25.0, 24.9 (5*q*, 3 Me_2C). FAB-MS: 460 (20, $[M+1]^+$), 353 (92).

3.10. N-*Benzyloxycarbonyl-2-methylalanyl-2-methylalanyl-2-methylalanyl*-L-*prolyl-2-methylalanyl-2-methylalanyl-2-methyalanine*-N-*methyl*-N-*phenylamide* (Z-$(Aib)_3$-Pro-$(Aib)_3$-N(Me)Ph, **21**). To a stirred soln. of **9** (80.6 mg, 0.20 mmol) in DMF (1 ml) at 0°, dicyclohexyl carbodiimide (CCD, 41 mg, 0.20 mmol) was added. After 3 min, $ZnCl_2$ (55 mg, 0.40 mol) and then **20** (100 mg, 0.22 mmol) were added in small portions, and the mixture was stirred under Ar at r.t. for 40 h. Then, aq. Na_2CO_3 soln. (2.5%) was added and the mixture was extracted with CH_2Cl_2 (3×). The combined org. phase was washed with 2N HCl (3×). The org. phase was dried (Na_2SO_4), the solvent evaporated, and the residue dried in h.v. Yield of **21**: 125 mg (75%). Colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.77, 7.45, 7.40, 7.23, 6.35, 5.82 (6*s*, 6 NH); 7.50 – 7.10 (*m*, 10 arom. H); 5.19, 5.08 (*AB*, J_{AB} = 12.6, PhCH_2O); 4.22 (*t*, *J* = 8.1, CH(2) Pro); 3.75 – 3.55 (*m*, CH_2(5) Pro); 3.45 (*s*, MeN); 2.40 – 2.25, 2.10 – 1.70 (2*m*, CH_2(3), CH_2(4) Pro); 1.61, 1.59, 1.55, 1.51, 1.49, 1.46, 1.45, 1.42, 1.41, 1.34, 1.27, 1.26 (12*s*, 6 Me_2C). ^{13}C-NMR (50 MHz, $CDCl_3$): 174.9, 174.8, 174.5, 174.1, 173.6, 173.2, 173.1 (7*s*, 7 C=O(amide)); 156.2 (*s*, C=O(urethane)); 146.2, 136.7 (2*s*, 2 arom. C); 128.9, 128.6, 128.1, 127.2, 127.1, 126.3 (6*d*, 10 arom. CH); 66.5 (*t*, PhCH_2O); 64.0 (*d*, C(2) Pro); 57.1, 57.0, 56.8, 56.6 (4*s*, 6 Me_2C); 48.4 (*t*, CH_2(5) Pro); 40.1 (*q*, MeN); 28.8, 26.2 (2*t*, CH_2(3), CH_2(4) Pro); 27.8, 27.1, 26.7, 26.1, 25.8, 25.7, 25.5, 24.2, 23.9, 23.4, 23.2 (11*q*, 6 Me_2C). FAB-MS: 871 (15, $[M+Na]^+$), 742 (100, [*M*+1–Ph(Me)NH), 390 (100), 305 (100).

4. *X-Ray Crystal-Structure Determination of* **6a**, **8a**, **10**, **12**, and **14** (*Table 3* and *Figs. 1 – 3*)[5]). All measurements were performed on a *Nicolet R3* diffractometer using graphite-monochromated MoK_α radiation (λ 0.71073 Å). The data collection and refinement parameters are given in *Table 3*, and views of the molecules are shown in *Figs. 1 – 3*. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The structures were solved by direct methods using SHELXS86 [23], which revealed the positions of all non-H-atoms. In the case of **8a**, there are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON [24], but none could be found. In the case of **10**, the asymmetric unit contains one molecule of the peptide plus one molecule of H_2O. In the case of **14**, one significant electron density peak (*ca.* 0.5 e/Å^3) remained after all other atoms were accounted for. This peak was assigned as a partially occupied site for a H_2O molecule [O(9)], with a site occupation factor of 0.25. The non-H-atoms were refined anisotropically. The amide H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. The H-atoms of the H_2O molecule in **14** could not be located. Bond lengths restraints were applied to the N(5)–H and N(6)–H bonds in compound **12**. All remaining H-atoms were fixed in geometrically calculated positions and refined by using a rigid 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 Me groups). The refinements of the structures were carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary

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[5]) CCDC-817459–817463 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

extinction was applied in the cases of **6a**, **8a**, and **10**. Neutral atom scattering factors for non-H-atoms were taken from [25a], and the scattering factors for H-atoms were taken from [26]. Anomalous dispersion effects were included in F_c [27]; the values for f' and f'' were those of [25b]. The values of the mass attenuation coefficients are those of [25c]. All calculations were performed using the *SHELXL97* [28] program.

Table 3. *Crystallographic Data for Compounds* **6a**, **8a**, **10**, **12**, and **14**

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Legends

Fig. 1. *ORTEP Plots* [20] *of the molecular structures of a)* **6a** *and b) one of the two symmetry-independent molecules of* **8a** (50% probability ellipsoids, arbitrary numbering of the atoms)

Fig. 2. *ORTEP Plots* [20] *of the molecular structures of a)* **10** *and b)* **12** (50% probability ellipsoids, arbitrary numbering of the atoms)

Fig. 3. *ORTEP Plot* [20] *of the molecular structure of* **14** (50% probability ellipsoids, arbitrary numbering of the atoms)

Table 1. *Torsion Angles* ω, ϕ, and ψ *of the Backbone of Compounds* **6a**, **8a**, **10**, **12**, *and* **14** *in the Crystal* (atom numbering refers to *Figs. 1 – 3*)

Compound	Amino Acid		Atoms	Torsion Angles (°)
6a	Aib(1)	ϕ_1	C(5)–N(3)–C(4)–C(3)	–62.9(3)
		ψ_1	N(3)–C(4)–C(3)–N(2)	165.6(2)
		ω_1	C(4)–C(3)–N(2)–C(2)	171.1(2)
	Aib(2)	ϕ_2	C(3)–N(2)–C(2)–C(1)	55.2(3)
		ψ_2	N(2)–C(2)–C(1)–N(1)	41.9(3)
		ω_2	C(2)–C(1)–N(1)–C(12)	179.0(2)
8a[a])	Aib(1)	ϕ_1	C(7)–N(4)–C(6)–C(5)	52.5(3); –52.1(3)
		ψ_1	N(4)–C(6)–C(5)–N(3)	37.3(2); –37.3(3)
		ω_1	C(6)–C(5)–N(3)–C(4)	174.4(2); –172.9(2)
	Aib(2)	ϕ_2	C(5)–N(3)–C(4)–C(3)	61.7(3); –60.4(3)
		ψ_2	N(3)–C(4)–C(3)–N(2)	29.7(3); –30.8(3)
		ω_2	C(4)–C(3)–N(2)–C(2)	164.5(2); –163.9(2)
	Aib(3)	ϕ_3	C(3)–N(2)–C(2)–C(1)	58.0(3); –59.0(3)
		ψ_3	N(2)–C(2)–C(1)–N(1)	58.5(3); –56.7(3)
		ω_3	C(2)–C(1)–N(1)–C(16)	161.7(2); –165.4(2)
10	Aib(1)	ϕ_1	C(9)–N(5)–C(8)–C(7)	–54.8(3)
		ψ_1	N(5)–C(8)–C(7)–N(4)	–29.4(3)
		ω_1	C(8)–C(7)–N(4)–C(6)	–179.9(2)
	Aib(2)	ϕ_2	C(7)–N(4)–C(6)–C(5)	–54.8(3)
		ψ_2	N(4)–C(6)–C(5)–N(3)	–28.4(4)
		ω_2	C(6)–C(5)–N(3)–C(4)	179.6(2)
	Aib(3)	ϕ_3	C(5)–N(3)–C(4)–C(3)	–56.6(4)
		ψ_3	N(3)–C(4)–C(3)–N(2)	–29.2(4)
		ω_3	C(4)–C(3)–N(2)–C(2)	174.7(3)
	Aib(4)	ϕ_4	C(3)–N(2)–C(2)–C(1)	54.6(4)
		ψ_4	N(2)–C(2)–C(1)–N(1)	53.4(4)
		ω_4	C(2)–C(1)–N(1)–C(20)	168.7(3)

[a]) Two symmetry-independent molecules

Table 1. *Torsion Angles* ω, ϕ, and ψ *of the Backbone of Compounds* **6a**, **8a**, **10**, **12**, *and* **14** *in the Crystal* (atom numbering refers to *Figs. 1 – 3*) (continued)

Compound	Amino Acid		Atoms	Torsion Angles (°)
12	Aib(1)	ϕ_1	C(11)–N(6)–C(10)–C(9)	55.3(6)
		ψ_1	N(6)–C(10)–C(9)–N(5)	32.5(6)
		ω_1	C(10)–C(9)–N(5)–C(8)	174.8(4)
	Aib(2)	ϕ_2	C(9)–N(5)–C(8)–C(7)	55.2(6)
		ψ_2	N(5)–C(8)–C(7)–N(4)	28.9(6)
		ω_2	C(8)–C(7)–N(4)–C(6)	–179.3(5)
	Aib(3)	ϕ_3	C(7)–N(4)–C(6)–C(5)	54.2(7)
		ψ_3	N(4)–C(6)–C(5)–N(3)	25.9(7)
		ω_3	C(6)–C(5)–N(3)–C(4)	178.1(4)
	Aib(4)	ϕ_4	C(5)–N(3)–C(4)–C(3)	60.4(7)
		ψ_4	N(3)–C(4)–C(3)–N(2)	26.5(7)
		ω_4	C(4)–C(3)–N(2)–C(2)	–172.1(5)
	Aib(5)	ϕ_5	C(3)–N(2)–C(2)–C(1)	–47.6(6)
		ψ_5	N(2)–C(2)–C(1)–N(1)	–54.1(5)
		ω_5	C(2)–C(1)–N(1)–C(24)	178.3(4)
14	Aib(1)	ϕ_1	C(13)–N(7)–C(12)–C(11)	–50.8(6)
		ψ_1	N(7)–C(12)–C(11)–N(6)	–35.8(5)
		ω_1	C(12)–C(11)–N(6)–C(10)	–178.2(3)
	Aib(2)	ϕ_2	C(11)–N(6)–C(10)–C(9)	–50.4(5)
		ψ_2	N(6)–C(10)–C(9)–N(5)	–39.6(5)
		ω_2	C(10)–C(9)–N(5)–C(8)	–172.0(3)
	Aib(3)	ϕ_3	C(9)–N(5)–C(8)–C(7)	–57.8(4)
		ψ_3	N(5)–C(8)–C(7)–N(4)	–31.4(4)
		ω_3	C(8)–C(7)–N(4)–C(6)	–175.8(3)
	Aib(4)	ϕ_4	C(7)–N(4)–C(6)–C(5)	–55.5(4)
		ψ_4	N(4)–C(6)–C(5)–N(3)	–33.6(4)
		ω_4	C(6)–C(5)–N(3)–C(4)	–176.5(3)
	Aib(5)	ϕ_5	C(5)–N(3)–C(4)–C(3)	–58.3(4)
		ψ_5	N(3)–C(4)–C(3)–N(2)	–35.0(4)
		ω_5	C(4)–C(3)–N(2)–C(2)	174.1(3)
	Aib(6)	ϕ_6	C(3)–N(2)–C(2)–C(1)	49.3(4)
		ψ_6	N(2)–C(2)–C(1)–N(1)	52.7(4)
		ω_6	C(2)–C(1)–N(1)–C(28)	–179.4(3)

Table 2. *Intramolecular H-Bonds of Compounds* **8a**, **10**, **12**, and **14** (atom numbering refers to *Figs. 1* – 3)

Compound	H-Bond	N–H (Å)	H⋯⋯O (Å)	N⋯⋯O (Å)	N–H⋯⋯O (°)
8a (A)	N(2)–H⋯⋯O(4)	0.79(2)	2.26(2)	3.027(3)	162(2)
8a (B)	N(32)–H⋯⋯O(34)	0.83(2)	2.28(2)	3.070(3)	160(2)
10	N(2)–H⋯⋯O(4)	0.85(3)	2.11(3)	2.950(3)	166(2)
	N(3)–H⋯⋯O(5)	0.88(3)	2.13(3)	3.001(4)	168(2)
12	N(2)–H⋯⋯O(4)	0.83(4)	2.25(5)	3.077(5)	171(4)
	N(3)–H⋯⋯O(5)	0.87(5)	2.04(5)	2.906(6)	172(4)
	N(4)–H⋯⋯O(6)	0.91(4)	2.19(5)	3.087(6)	168(4)
14	N(2)–H⋯⋯O(4)	0.86(3)	2.22(4)	3.031(4)	156(3)
	N(3)–H⋯⋯O(5)	0.87(4)	2.30(4)	3.133(4)	160(3)
	N(4)–H⋯⋯O(6)	0.88(4)	2.27(4)	3.094(4)	156(3)
	N(5)–H⋯⋯O(7)	0.81(4)	2.22(4)	3.012(4)	167(4)

Table 3. *Crystallographic Data for Compounds* **6a**, **8a**, **10**, **12**, and **14**

		6a	**8a**	**10**
Crystallized from		DMSO/H_2O	DMSO/H_2O	DMSO/H_2O
Empirical formula		$C_{23}H_{29}N_3O_4$	$C_{27}H_{36}N_4O_5$	$C_{31}H_{43}N_5O_6.H_2O$
Formula weight		411.50	496.60	599.72
Crystal color, habit		colorless, prism	colorless, prism	colorless, prism
Temperature [K]		294(1)	294(1)	294(1)
Crystal system		monoclinic	triclinic	triclinic
Space group		$P2_1/n$	$P\bar{}$,1	$P\bar{}$,1
Z		4	4	2
Reflections for cell determination		25	25	25
2θ range for cell determination [°]		20 – 28	20 – 28	24 – 28
Unit cell parameters	a [Å]	13.875(3)	13.171(1)	8.660(4)
	b [Å]	10.796(4)	14.694(3)	11.731(5)
	c [Å]	15.499(4)	15.546(3)	16.839(7)
	α [°]	90	99.42(1)	103.25(3)
	β [°]	103.27(2)	109.99(1)	96.22(3)
	γ [°]	90	91.07(1)	90.81(3)
	V [Å^3]	2259(1)	2780.2(8)	1653(1)
D_X [g cm^{-1}]		1.211	1.186	1.204
μ(MoK_α) [mm^{-1}]		0.0835	0.0825	0.0858
Scan type		ω	ω	ω
$2\theta_{(max)}$ [°]		46	46	46
Total reflections measured		3952	8238	5013
Symmetry independent reflections		2833	7745	4601
Reflections with $I > 2\sigma(I)$		2080	5540	3184
Reflections used		2833	7745	4601
Parameters refined; restraints		285; 0	688; 0	426; 0
Final $R(F)$ [$I > 2\sigma(I)$]		0.0431	0.0431	0.0514
$wR(F^2)$ (all data)		0.1092	0.1069	0.1465
Weights: a and b[a])		0.0543; 0.4155	0.0503; 0.3506	0.0776; 0.2280
Goodness of fit		1.022	1.027	1.029
Secondary extinction coefficient		0.008(1)	0.0046(5)	0.008(2)
Final Δ_{max}/σ		0.001	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]		0.12; –0.13	0.20; –0.14	0.22; –0.18

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

Table 3. *Crystallographic Data for Compounds* **6a**, **8a**, **10**, **12**, and **14** (continued)

		12	**14**
Crystallized from		DMSO	DMSO/H_2O
Empirical formula		$C_{35}H_{50}N_6O_7$	$C_{39}H_{57}N_7O_8$.0.25 H_2O
Formula weight		666.82	756.43
Crystal color, habit		colorless, prism	colorless, prism
Temperature [K]		294(1)	294(1)
Crystal system		monoclinic	monoclinic
Space group		$P2_1/c$	$P2_1$
Z		4	2
Reflections for cell determination		25	25
2θ range for cell determination [°]		20 – 24	20 – 26
Unit cell parameters	a [Å]	11.585(4)	9.092(2)
	b [Å]	18.943(5)	16.052(4)
	c [Å]	17.718(7)	14.968(4)
	α [°]	90	90
	β [°]	103.67(2)	100.93(2)
	γ [°]	90	90
	V [Å^3]	3778(2)	2144.9(9)
D_X [g cm^{-1}]		1.172	1.171
μ(MoK_α) [mm^{-1}]		0.0824	0.0829
Scan type		ω	ω
$2\theta_{(max)}$ [°]		46	52
Total reflections measured		5831	4749
Symmetry independent reflections		5258	4378
Reflections with $I > 2\sigma(I)$		2454	3232
Reflections used		5258	4378
Parameters refined; restraints		464; 2	534; 1
Final $R(F)$ [$I > 2\sigma(I)$]		0.0734	0.0443
$wR(F^2)$ (all data)		0.1883	0.1137
Weights: a and b[a])		0.0845; 0	0.0620; 0.1035
Goodness of fit		0.943	1.020
Secondary extinction coefficient		-	-
Final Δ_{max}/σ		0.002	0.001

$\Delta\rho$ (max; min) [e Å^{-3}]	0.27; –0.19	0.13; –0.12

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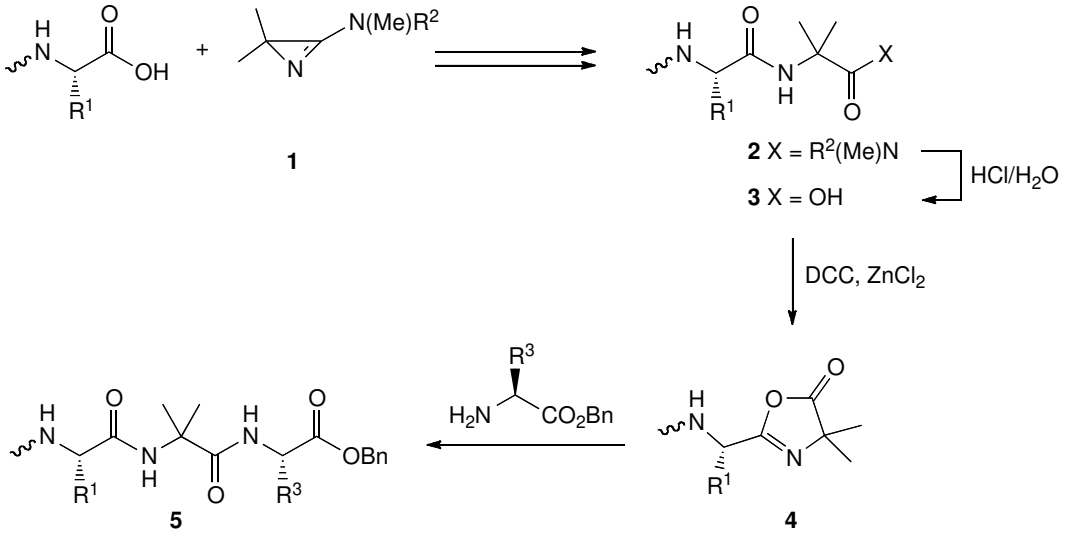
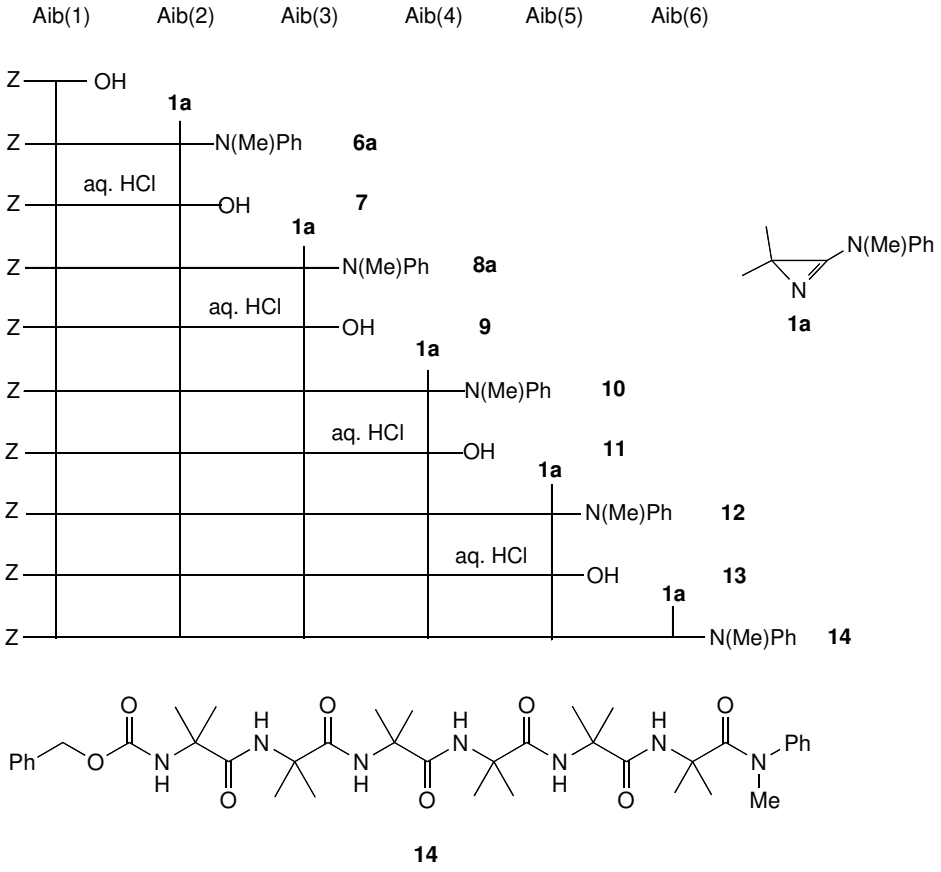
[a]) $w = [\sigma^2 (F_o^2) + (aP)^2 + bP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$

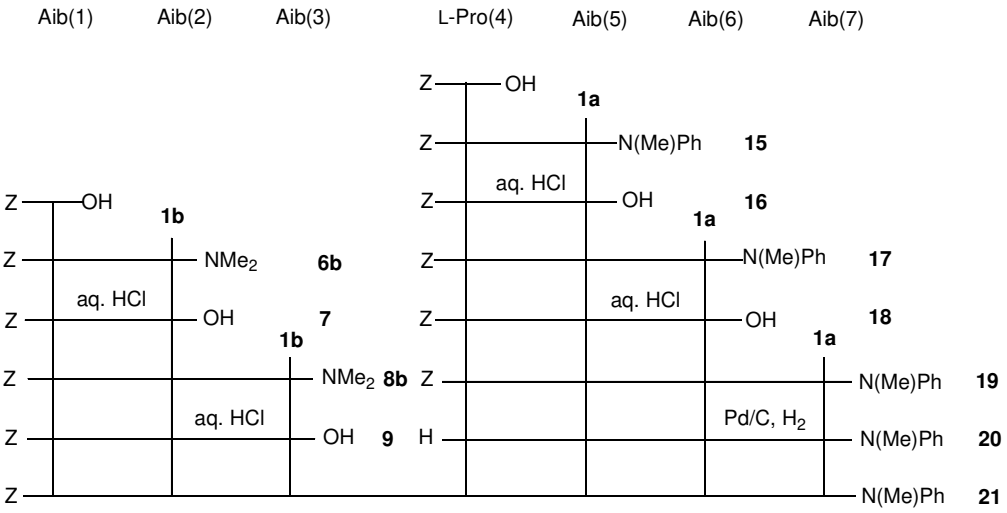
Scheme 1

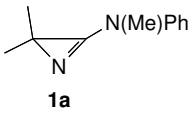


Scheme 2

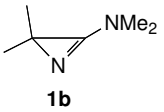


Scheme 3

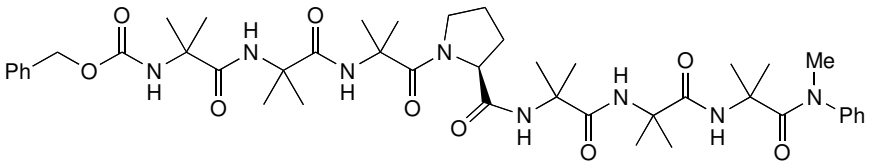




1a



1b



21

Figure 1a (**6a**)

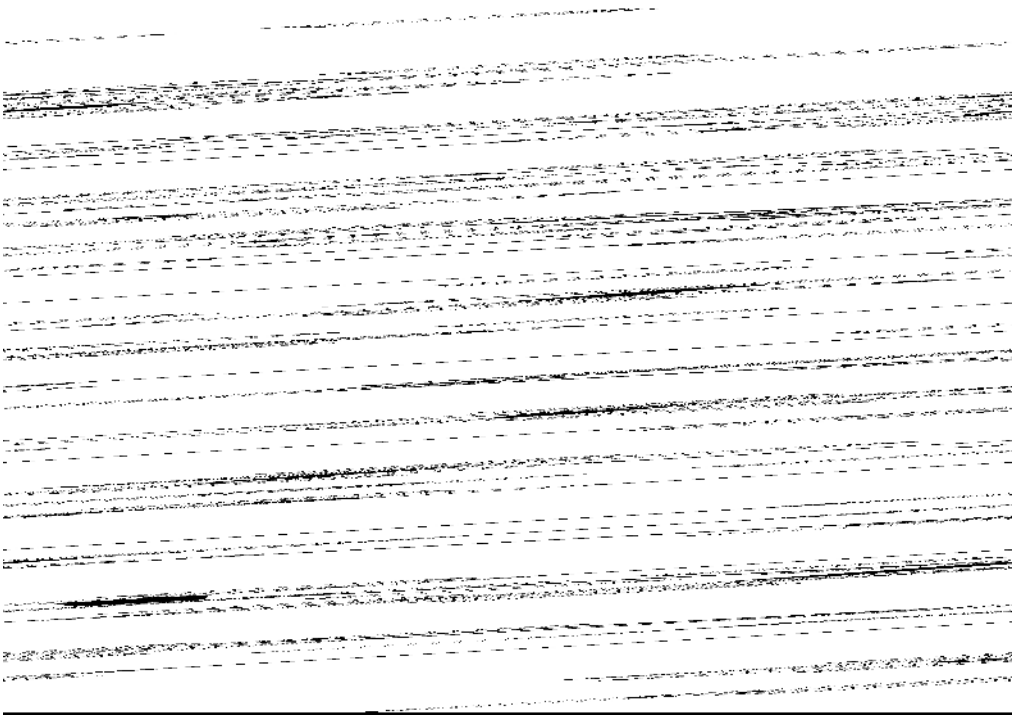


Figure 1b (**8a**)

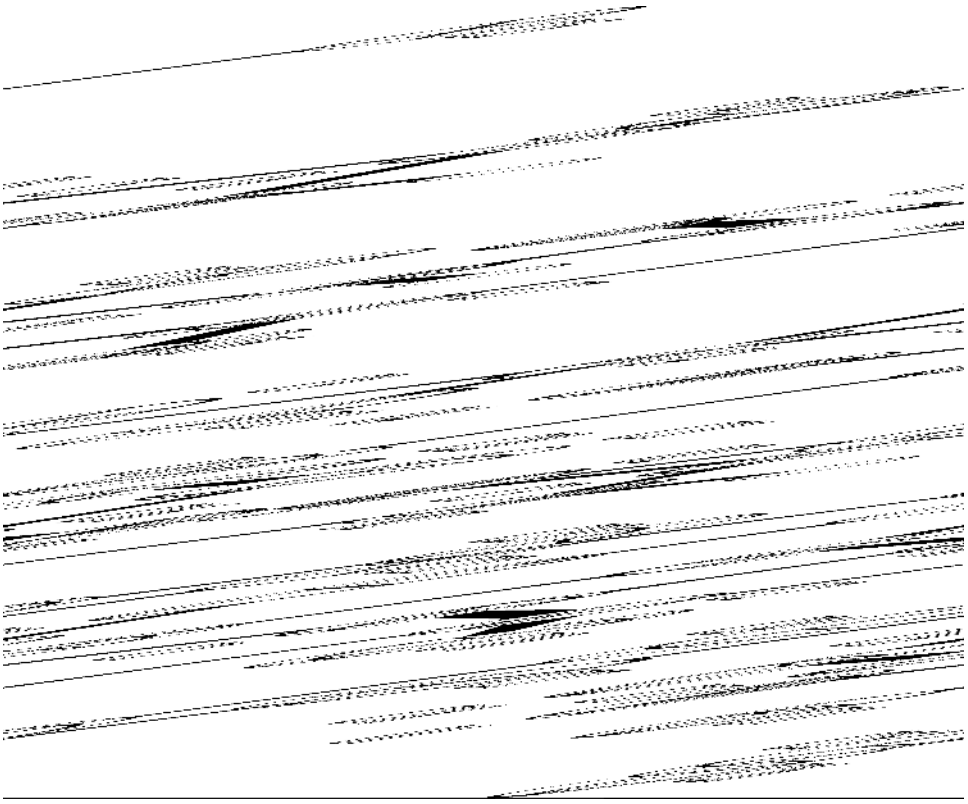


Figure 2a (**10**)

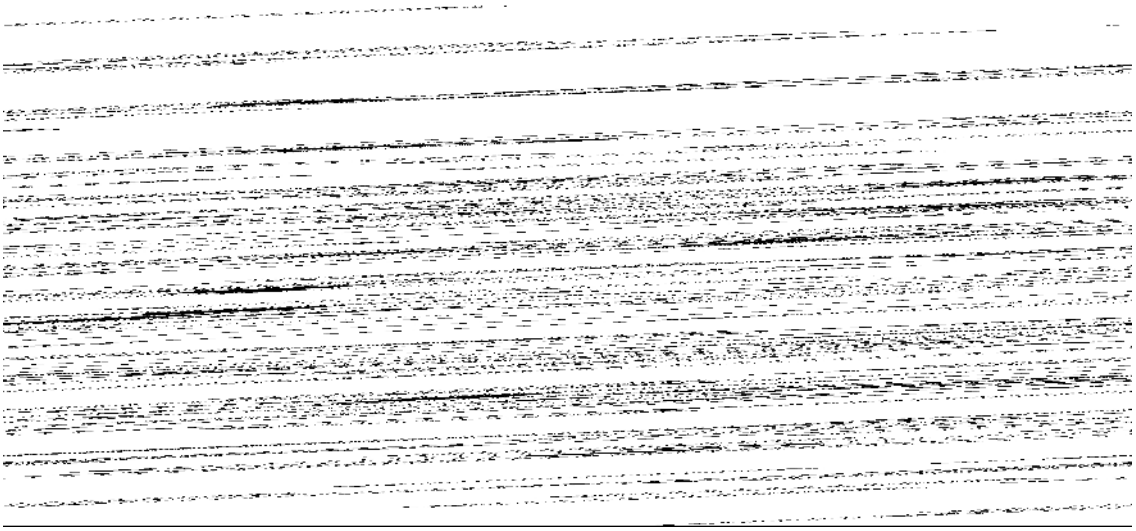


Figure 2b (**12**)

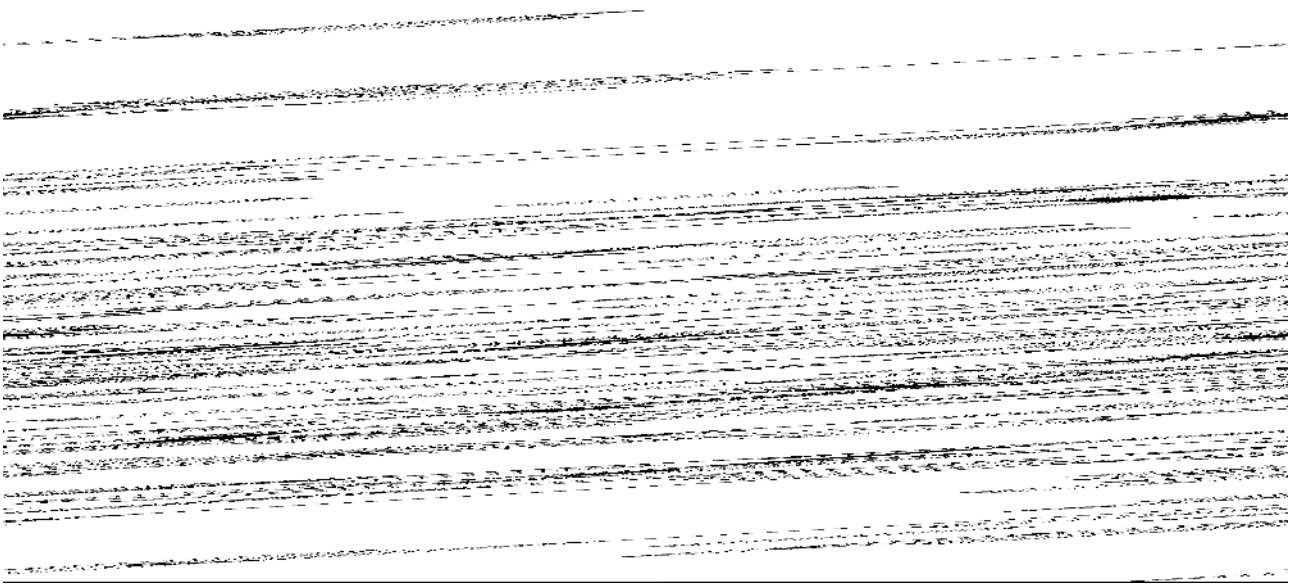
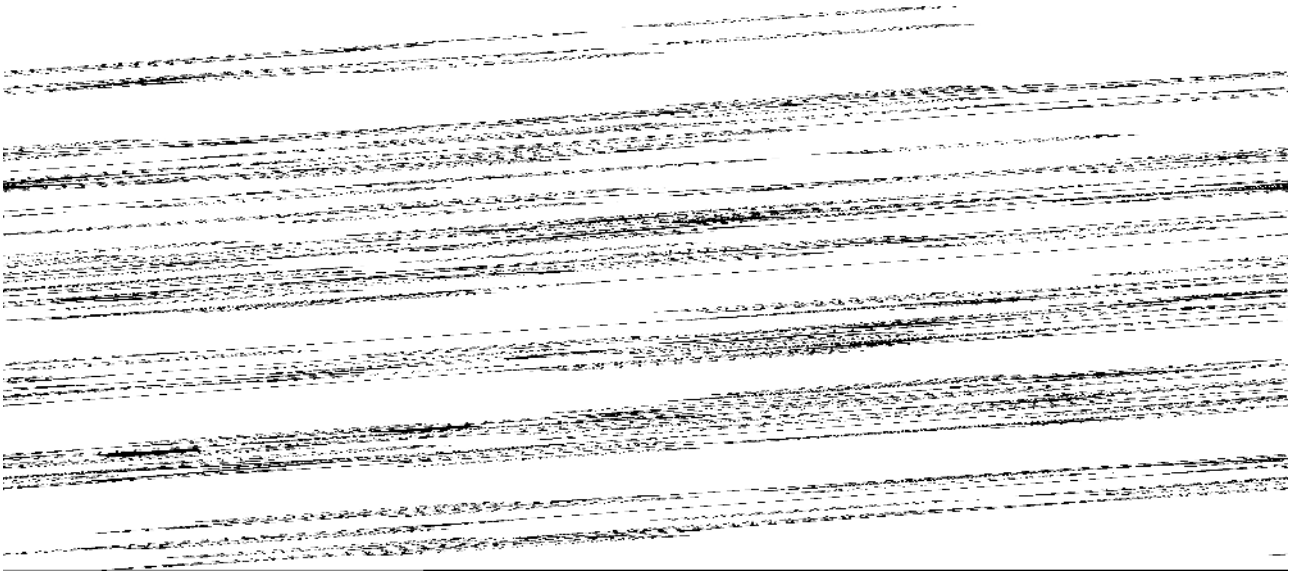


Figure 3 (**14**)



Graphical Abstract