The 'Azirine/Oxazolone Method' on Solid Phase: Introduction of Various α,α-Disubstituted α-Amino Acids

by **Simon Stamm**[1]), **Anthony Linden**, and **Heinz Heimgartner***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

Peptides containing various α,α-disubstituted α-amino acids, such as α-aminoisobutyric acid (Aib), 1-aminocyclopentane-1-carboxylic acid, α-methylphenylalanine, and 3-amino-3,4,5,6-tetrahydro-2*H*-pyran-3-carboxylic acid have been synthesized from the N- to the C-terminus by the 'azirine/oxazolone method' under solid-phase conditions. In this convenient method for the synthesis of sterically demanding peptides on solid-phase, 2*H*-azirin-3-amines are used to introduce the α,α-disubstituted α-amino acids without the need for additional reagents. Furthermore, the synthesis of poly(Aib) sequences has been explored.

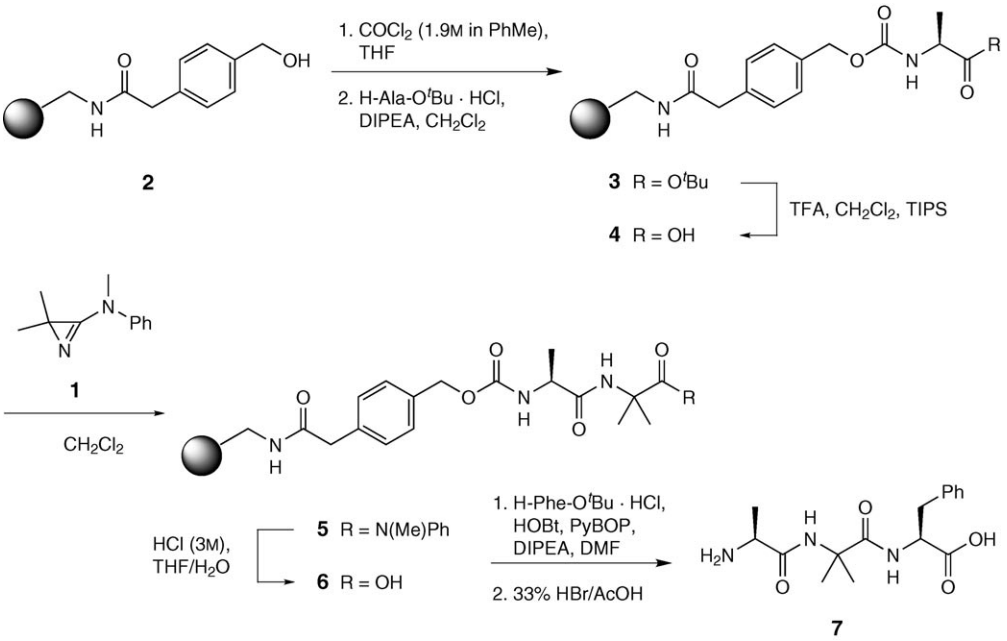
1. Introduction. – Due to the restrictions in their conformational freedom, α,α-disubstituted α-amino acid-containing peptides form stabilized secondary structures, such as β-turns and helices [1–4]. One useful method for the introduction of α,α-disubstituted α-amino acids into peptides is the 'azirine/oxazolone method' [5–7]. Thus, the reaction of 2*H*-azirin-3-amines, *e.g.*, the Aib synthon **1**, with an amino or peptide acid proceeds smoothly and in high yield. The terminal amide bond of the resulting peptide amide can be hydrolyzed selectively to give the extended peptide acid. In solution-phase chemistry, the 'azirine/oxazolone method' has proven to be successful for the introduction of a multitude of sterically demanding α,α-disubstituted α-amino acids into peptides, and it has found application in the synthesis of some antibiotic peptaibols or segments thereof [8–15].

Since solid-phase synthesis offers rapid access to peptides without the need for the isolation of the sometimes cumbersome peptide acid intermediates, we adapted the 'azirine/oxazolone method' to solid-phase conditions (*Scheme 1*) [16].

In this convenient method for the synthesis of sterically demanding peptides on solid phase, the first amino acid was attached through a carbamate linker to a [4-(hydroxymethyl)phenyl]acetamidomethyl (PAM) polystyrene resin (**2**). Deprotection of the ^{t}Bu ester **3** with TFA afforded resin **4**, which was treated with a solution of *N*,2,2-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1**). Unconsumed **1** could easily be recovered and reused. Selective hydrolysis of the terminal amide with 3M HCl in THF/H_2O afforded peptide acid resin **6**. Further extension of the peptide chain could be achieved either with a ^{t}Bu ester protected amino acid and a coupling reagent, *e.g.*, PyBOP, or with **1**. Cleavage from the resin was achieved with HBr (33%) in AcOH to give the tripeptide **7**.

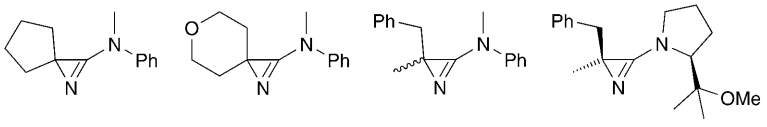
[1]) Part of the projected Ph.D. thesis of *S. S.*, Universität Zürich.

Scheme 1



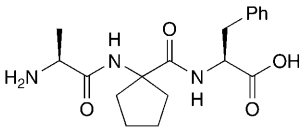
DIPEA = $EtN(i\text{-}Pr)_2$; HOBt: 1-Hydroxybenzotriazole; PyBOP = (1*H*-Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; TFA = CF_3COOH; TIPS = $(i\text{-}Pr)_3SiH$.

It was of interest to ascertain if this method is restricted to the α-aminoisobutyric acid (Aib) synthon **1**, or if it can be extended to other 2*H*-azirin-3-amines. Herein, we report the use of the 1-aminocyclopentane-1-carboxylic acid (Acp) synthon **8**, the 3-amino-3,4,5,6-tetrahydro-2*H*-pyran-3-carboxylic acid (Thp) synthon **9**, and the α-methylphenylalanine (Phe(2Me)) synthon **10** in peptide synthesis by the 'azirine/oxazolone method' under solid-phase conditions. Furthermore, a limitation of the method in the synthesis of poly(Aib) sequences is revealed.

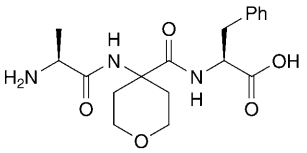


8 **9** **10** **12**

2. Results and Discussion. – In analogy to the model peptide H-Ala-Aib-Phe-OH (**7**), which had been used to establish the viability of the 'azirine/oxazolone method' under solid-phase conditions, the tripeptides H-Ala-Acp-Phe-OH (**11a**) and H-Ala-Thp-Phe-OH (**11b**) were synthesized on solid-phase in 37 and 38% yield (after prep. HPLC, based on resin loading), respectively (see *Scheme 1*; instead of **1**, the Acp and Thp synthons **8** and **9**, resp., were used; *Table 1*). Both α,α-disubstituted residues



11a



11b

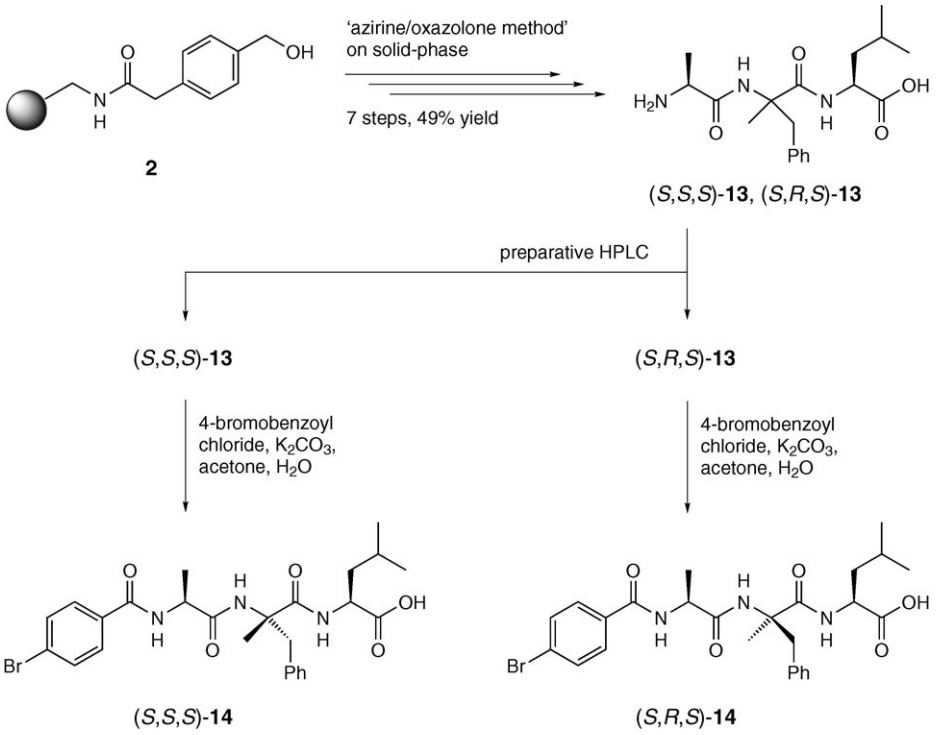
were introduced by the 'azirine/oxazolone method', and Phe with PyBOP as the coupling reagent.

When (*S*)-1-[(*S*)-2-benzyl-2-methyl-2*H*-azirin-3-yl]-2-(1-methoxy-1-methylethyl)-pyrrolidine (**12**) was used as an optically pure Phe(2Me) synthon, the syntheses of H-Ala-Phe(2Me)-Phe-OH and H-Ala-Phe(2Me)-Leu-OH failed, although this 2*H*-azirin-3-amine has been used successfully in solution-phase chemistry. *N*-Methyl-*N*-phenyl-2*H*-azirin-3-amines belong to the most reactive 2*H*-azirin-3-amines. Therefore, the racemic Phe(2Me)-synthon **10** was used in a second, successful attempt to synthesize the tripeptide H-Ala-Phe(2Me)-Leu-OH (**13**) as a mixture of two diastereoisomers. The diastereoisomers (*S*,*S*,*S*)-**13** and (*S*,*R*,*S*)-**13** were separated by means of preparative HPLC, which gave the two isomers in a 1:1 ratio in 49% yield.

X-Ray crystallography would have allowed the determination of the configuration at C(α) of the Phe(2Me) residue, but all attempts to crystallize at least one of the two diastereoisomeric tripeptides **13** failed. Therefore, (*S*,*S*,*S*)-**13** and (*S*,*R*,*S*)-**13** were derivatized with 4-bromobenzoyl chloride (*Scheme 2*). Crystals suitable for an X-ray crystal-structure determination were obtained from (*S*,*S*,*S*)-**14** (*Fig.*), and the absolute configuration of the molecule was determined independently by the diffraction experiment. This confirmed the (*S*)-configurations of the alanine and leucine residues, and revealed the (*S*)-configuration of the Phe(2Me) residue. The knowledge of the absolute configuration of (*S*,*S*,*S*)-**14** allowed the assignment of the absolute configurations of the primarily isolated tripeptides (*S*,*S*,*S*)-**13** and (*S*,*R*,*S*)-**13**.

The asymmetric unit in the structure of (*S*,*S*,*S*)-**14** contains two symmetry-independent peptide and two MeOH molecules. The two peptide molecules have very similar conformations and differ primarily in the orientation of the plane of the 4-bromophenyl ring. Each peptide molecule is involved in one intramolecular and four intermolecular H-bonds. The amide group closest to the COOH group in each peptide molecule forms an intramolecular H-bond with the amide O-atom adjacent to the 4-bromophenyl moiety thereby stabilizing a β-turn. Each of these interactions has a graph set motif [18] of *S*(10). The OH group in each peptide molecule forms an intermolecular H-bond with the O-atom of a neighboring MeOH molecule. In turn, each of these MeOH molecules forms an intermolecular H-bond to one of the symmetry-independent peptide molecules. These interactions link the peptide and MeOH molecules alternately into extended chains which run parallel to the [0 1 0] direction in the sequence ···peptideA···MeOH2···peptideB···MeOH1···peptideA···. The quaternary graph set motif that describes this sequence is $C_4^4(26)$. The amide group closest to the 4-bromophenyl moiety in peptide molecule A forms an intermolecular H-bond with the carboxylate carbonyl O-atom of a neighboring molecule B. In turn, molecule B interacts in an identical fashion with another molecule A. These interactions link peptide molecules A and B

Scheme 2



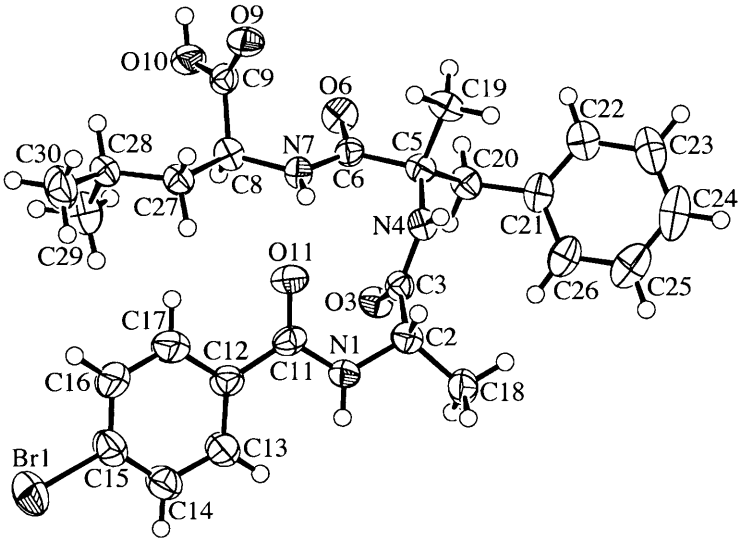


Figure. *ORTEP Plot* [17] *of the molecular structure of one of the two symmetry-independent molecules of (*S,S,S*)*-**14** (50% probability ellipsoids; arbitrary numbering of atoms; the MeOH molecules are not shown).

alternately into extended chains, which run parallel to the [0 – 1 1] direction and can be described by a binary graph set motif of $C_2^2(22)$. The central amide group in peptide molecule A forms an intermolecular H-bond with the carbonyl O-atom of the amide group closest to the carboxylic acid end of a neighboring molecule A. This interaction links the peptide molecules A into centrosymmetric dimers and can be described by a graph set motif of $R_2^2(10)$. The peptide molecules B display identical interactions that also link the molecules into centrosymmetric dimers. The combination of all intermolecular H-bonding interactions links the peptide and MeOH molecules into extended two-dimensional networks which lie parallel to the (1 0 0) plane.

Some longer model peptides containing up to three α,α-disubstituted residues were synthesized successfully on solid phase (*Table 1*). The pentapeptides H-Val-Thp-Gly-Acp-Ala-OH (**15**) and H-Ala-Thp-Val-Thp-Phe-OH (**16**) were obtained in 23 and 16% yield, respectively. All α,α-disubstituted residues were introduced by the 'azirine/oxazolone method', while the other amino acids were introduced by using PyBOP as the coupling reagent. The ^{1}H-NMR spectrum of **15** showed partial doubling of the signals. The contribution of the minor signals is *ca.* 20%. Unexpectedly, while increasing the temperature in the NMR experiment, the chemical shifts of the minor and major NH signals did not coalesce or converge. The convergence of the NH signals with increasing temperature would have been strong evidence for the existence of conformers and not diastereoisomers. To rule out the presence of diastereoisomers, however, an amino acid analysis was performed [19]: to determine the extent of racemization/epimerization of the C(α)-center(s), the pentapeptide was hydrolyzed, and the amino acids were analyzed by capillary gas chromatography with enantiomer labelling. The results showed that alanine and valine had racemized by 0.4 and 0.8%, respectively. Thus, the doubling of the signals in the ^{1}H-NMR was caused by different conformers and not by diastereoisomers. Furthermore, this analysis shows that, although the peptide was synthesized from the N- to the C-terminus, the product was obtained with an acceptably low degree of racemization.

Table 1. *Synthesized Peptides Containing Aib, Acp, Thp, and Phe(2Me) Residues*

Sequence	Yield [%][a])
H-Ala-Acp-Phe-OH (**11a**)	37
H-Ala-Thp-Phe-OH (**11b**)	38
H-Ala-Phe(2Me)-Leu-OH (**13**)	49
H-Val-Thp-Gly-Acp-Ala-OH (**15**)	23
H-Ala-Thp-Val-Thp-Phe-OH (**16**)	16
H-Ala-Aib-Val-Acp-Gly-Thp-Leu-OH (**17**)	21
H-Ala-Aib-Val-Acp-Phe-Thp-Leu-OH (**18**)	13

[a]) Yield of product isolated after HPLC purification, based on resin loading.

The heptapeptides H-Ala-Aib-Val-Acp-Gly-Thp-Leu (**17**) and H-Ala-Aib-Val-Acp-Phe-Thp-Leu (**18**) were synthesized analogously on solid-phase with yields of 21 and 13%, respectively. The two peptides only differ in one amino acid (Gly(4) → Phe(4)). While the coupling of the α,α-disubstituted α-amino acid is a difficult step (which has been solved by using 2*H*-azirin-3-amines), the following coupling can be dif-

ficult too, so we assume that this might be the reason for the noticeably lower yield of **18** compared with **17**.

Peptides containing α,α-disubstituted α-amino acids stabilize or even promote secondary structures, such as helices or β-turns. Therefore, poly(Aib) motifs with an accumulation of helix-stabilizing residues are of some interest. The repeated coupling of 2*H*-azirin-3-amines in solution is an efficient method for the preparation of this type of sterically highly congested oligopeptides [20][21]. The tripeptide H-$(Aib)_3$-OH (**19**) was synthesized by the 'azirine/oxazolone method' on solid-phase in 33% yield (*Table 2*), but the preparation of H-$(Aib)_4$-OH failed. A similar result was obtained in the extension from H-Ala-$(Aib)_2$-OH (**20**) to H-Ala-$(Aib)_3$-OH (**21**). While **20** could be prepared in 41% yield, **21** was obtained in a conspicuously lower yield (*ca.* 12%, not pure; additionally, 35% of **20** were obtained). The introduction of the fourth amino acid in H-Ala-Aib-Aib-Val-OH with conventional coupling by using PyBOP as the coupling reagent was also in vain. All attempts to improve the introduction of the fourth amino acid, such as performing the reaction in different solvents (CH_2Cl_2, THF, DMF, PhMe, H_2O), raising the temperature to 50° or using a *Tentagel* resin were not effective. Since the most probable reason for the failure is aggregation, we also performed the reaction by using the 'magic mixture' [22] (CH_2Cl_2/DMF/*N*-methylpyrrolidinone (NMP) 1:1:1, *Triton X-100*, ethylenecarbonate (2M)) and in $CHCl_3$/$(CF_3)_2CHOH$ 1:1, but no improvement could be achieved.

Table 2. *Synthesized Peptides Containing Poly(Aib) Motifs*

Sequence	Yield [%][a])
H-Aib-Aib-Aib-OH (**19**)	33
H-Ala-Aib-Aib-OH (**20**)	41
H-Ala-Aib-Aib-Aib-OH (**21**)	12[b])
H-Ala-Val-Aib-Aib-Aib-OH (**22**)	16
H-Ala-Val-Phe-Aib-Aib-Leu-OH (**23**)	6
H-Ala-Val-Phe-Aib-Aib-Aib-Leu-OH (**24**)	9

[a]) Yield of product isolated after HPLC purification, based on resin loading. [b]) Not pure.

A slight improvement was observed when proteinogenic α-amino acids were introduced prior to the poly(Aib) motif, *e.g.*, H-Ala-Val-Aib-Aib-Aib-OH (**22**) was prepared in 16% yield. Furthermore, the poly(Aib)-containing peptides H-Ala-Val-Phe-Aib-Aib-Leu-OH (**23**) and H-Ala-Val-Phe-Aib-Aib-Aib-Leu-OH (**24**) were synthesized, although in low yield (6 and 9%, resp.). All Aib residues were introduced by the 'azirine/oxazolone method', while all other amino acids were introduced by using PyBOP as the coupling reagent.

3. Conclusions. – Peptide synthesis by the 'azirine/oxazolone method' on solid phase was carried out from the N- to the C-terminus. 2*H*-Azirin-3-amines were used to introduce α,α-disubstituted α-amino acids into the peptides without the need for further reagents. It was shown that the method is not limited to the Aib synthon **1**, and it was extended successfully to the 1-aminocyclopentane-1-carboxylic acid (Acp) synthon **8**, the 3-amino-3,4,5,6-tetrahydro-2*H*-pyran-3-carboxylic acid (Thp) synthon **9**, and the

α-methylphenylalanine (Phe(2Me)) synthon **10**. Peptides with up to seven residues, of which three are α,α-disubstituted α-amino acids, have been prepared. In contrast, the synthesis of peptides containing the poly(Aib) motif was not successful, most probably due to aggregation.

We thank Dr. *Daniel Obrecht, Polyphor Ltd*, CH-Allschwil, for continous advice and valuable discussions, as well as the analytical sections of our institute for 2D-NMR measurements and mass spectra. Financial support of the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged.

Experimental Part

1. *General*. See [16], except anal. HPLC/MS: the system consists of a *Rheos 2000* pump, a *Rheos CPS-LC* degasser (*Flux Instruments*, CH-Basel), and a *Thermo Finnigan Surveyor* photo-diode array detector (*Thermo Finnigan*, San Jose, CA, USA). The HPLC system is equipped with a *HTS PAL* autosampler (*CTC Analytics*, CH-Zwingen) and connected to a *Thermo Finnigan MSQ* linear quadrupole instrument. *Method A*: *Interchim Uptisphere C18-NEC*, 120 Å, 3 μm, 50×2.0 mm column (*Interchim*, F-Montluçon); eluents: $A = H_2O$, $B =$ MeCN, $C =$ HCOOH (1%) in H_2O; flow rate: 0.2 ml/min, gradient (A/B/C): 0.0–10.0 min: 85:5:10–75:15:10. *Method B*: *Interchim Uptisphere C18-ODB*, 120 Å, 3 μm, 50×2.0 mm column; eluents: $A = H_2O$, $B =$ MeCN, $C =$ HCOOH (1%) in H_2O; flow rate: 0.2 ml/min, gradient (A/B/C): 0.0–15.0 min: 87:3:10–40:50:10. N*,2,2-Trimethyl*-N-*phenyl-2*H-*azirin-3-amine* (**1**), N-*methyl*-N-*phenyl-1-azaspiro[2.4]hept-1-en-2-amine* (**8**), N-*methyl*-N-*phenyl-6-oxa-1-azaspiro[2.5]oct-1-en-2-amine* (**9**), and *2-benzyl*-N,*2-dimethyl*-N-*phenyl-2*H-*azirin-3-amine* (**10**) were synthesized by *Villalgordo* and *Heimgartner*'s method [23–25]. *(*S*)-1-[(*S*)-2-Benzyl-2-methyl-2*H-*azirin-3-yl]-2-(1-methoxy-1-methylethyl)pyrrolidine* (**12**) was synthesized according to [26]. In the NMR data, the integer *n* in Xaa^n corresponds to the position of the amino acid within the peptide, but is only given if the amino acid was present more than once in the peptide, and if the NMR signal could be assigned unambigously. In some ^{1}H-NMR spectra, the broad COOH signal could not be detected. In the ^{1}H- and ^{13}C-NMR spectra of **15**, the descriptor (w) means the weaker, (s) the stronger signal of the two conformers observed.

2. *Abbreviations*. Aib: α-aminoisobutyric acid; CC: column chromatography; Acp: 1-aminocyclopentane-1-carboxylic acid; DIPEA: EtN(i-Pr)$_2$; HOBt: 1-hydroxybenzotriazole; PAM: [4-(hydroxymethyl)phenyl]acetamidomethyl; Phe(2Me): 2-amino-2-methyl-3-phenylpropanoic acid; PyBOP: (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; Thp: 3-amino-3,4,5,6-tetrahydro-2*H*-pyran-3-carboxylic acid; TIPS: (i-Pr)$_3$SiH.

3. *General Procedures 1–6* (*GP 1–GP6*). *GP 1*: *Attachment of the First Amino Acid*. All manipulations were carried out under N_2. PAM resin was swollen in THF. After filtration, a soln. of $COCl_2$ in toluene (1.9M, 10 equiv.) and THF (*ca*. 2.5 ml/1 g resin) were added to the resin, which was agitated at r.t. for 2 h, then washed with THF (2×) and CH_2Cl_2 (2×). In a separate vial, H-Xaa-O^{t}Bu·HCl (4 equiv.) was dissolved in DIPEA (8 equiv.) and CH_2Cl_2 (conc. of H-Xaa-O^{t}Bu·HCl = 0.2M). This mixture was added to the resin, and any ammonium salt that occured was removed by filtration. The resin was agitated at r.t. overnight, then washed with DMF (3×) and CH_2Cl_2 (3×).

GP 2: *Removal of the* ^{t}*Bu Protecting Group*. The resin was swollen in CH_2Cl_2. TFA in CH_2Cl_2 (1×5 s, 25%; 1×30 min, 50%) and TIPS (5%, in each case) were added, and the resin was agitated at r.t. Afterwards, the resin was washed with CH_2Cl_2 (3×), DMF (2×) and CH_2Cl_2 (3×).

GP 3: *Coupling with 2*H-*Azirin-3-amines* **1**, **8**, **9**, *and* **10**. The resin was swollen in CH_2Cl_2. A soln. of 2*H*-azirin-3-amine (4 equiv.) in CH_2Cl_2 (conc. of 2*H*-azirin-3-amine 0.2M) was added, and the resin was agitated at r.t. overnight, then washed with CH_2Cl_2 (3×). Unconsumed 2*H*-azirin-3-amine can easily be recovered.

GP 4: *Hydrolysis of the Terminal Amide*. The resin was swollen in THF. Aq. HCl (*ca*. 3–4 ml/200 mg resin, 3M in THF/H_2O, prepared from conc. HCl and THF) was added, and the resin was agitated at r.t. overnight, then washed with THF (3×), DMF (3×), and CH_2Cl_2 (3×).

GP 5: *Coupling with H-Xaa-O*^{t}*Bu·HCl.* The resin was swollen in DMF. HOBt (6 equiv.) in DMF, PyBOP (4 equiv.) in DMF, H-Xaa-O^{t}Bu·HCl (4 equiv.) in DMF and DIPEA (12 equiv.) were added (conc. of H-Xaa-O^{t}Bu·HCl 0.2M), and the resin was agitated at r.t. overnight, then washed with DMF (3×) and CH_2Cl_2 (3×).

GP 6: *Cleavage.* The resin was swollen in CH_2Cl_2. HBr in AcOH (33%, 1 ml/100 mg resin), two drops of H_2O were added, and the resin was agitated for 6 h. The resin was separated by filtration and washed with AcOH/CH_2Cl_2 1:1 (3×) and MeCN/CH_2Cl_2 1:1 (3×). The solvents were evaporated under reduced pressure, and the crude product was purified by HPLC. The purified product was lyophilized.

4. *Synthesis of Peptides.* *(*S*)-2-{[({[(*S*)-2-Amino-1-oxopropyl]amino}cyclopentyl)carbonyl]amino}-3-phenylpropanoic Acid* (*H-Ala-Acp-Phe-OH*; **11a**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–6* to yield **11a** (21.0 mg, 37%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3397*m*, 3262*s*, 3076*s*, 2962*m*, 2876*m*, 1731*s*, 1664 (sh), 1647v*s*, 1561*m*, 1517*s*, 1490*m*, 1455*m*, 1442*m*, 1382*w*, 1331*w*, 1266*m*, 1238*m*, 1202v*s*, 1141*s*, 1004*w*, 982*w*, 845*w*, 802*w*, 734*w*, 724*w*, 699*w*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): 12.84 (br. *s*, COOH); 8.53, 8.48 (2*s*, NH(Acp)); 8.06 (br. *s*, NH_3(Ala)); 7.36 (*d*, *J* = 7.7, NH(Phe)); 7.27–7.17 (*m*, 5 arom. H); 4.44 (*ddd*, *J* = 7.7, 7.7, 5.6, CH(α)(Phe)); 3.82 (br. *s*, CH(α)(Ala)); 3.07 (*dd*, ^2J = 13.8, *J* = 5.6, 1 H of CH_2(Phe)); 2.94 (*dd*, ^2J = 13.8, *J* = 7.7, 1 H of CH_2(Phe)); 2.14–2.09 (*m*, 1 H of 4 CH_2(Acp)); 1.89–1.82 (*m*, 3 H of 4 CH_2(Acp)); 1.60–1.59 (*m*, 4 H of 4 CH_2(Acp)); 1.33 (*d*, *J* = 7.0, Me(Ala)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 172.7 (*s*, CO(Phe)); 172.2 (*s*, CO(Acp)); 169.3 (*s*, CO(Ala)); 137.4 (*s*, arom. C); 129.3, 128.1, 126.4 (3*d*, 5 arom. CH); 66.4 (*s*, C(α)(Acp)); 53.4 (*d*, CH(α)(Phe)); 48.3 (*d*, CH(α)(Ala)); 36.9 (*t*, CH_2(Phe)); 36.3, 35.3, 23.7 (3*t*, 4 CH_2(Acp)); 16.9 (*q*, Me(Ala)). ESI-MS: 370 (8, $[M+Na]^+$), 348 (100, $[M+H]^+$), 183 (13, $[M-Phe]^+$), 151 (24). HPLC/MS. (*Method B*): t_R 7.7 min, *m*/*z* 348 (100, $[M+H]^+$), 183 (76, $[M-Phe]^+$), 155 (20, $[M-Phe-CO]^+$).

*(*S*)-2-{[(4-{[(*S*)-2-Amino-1-oxopropyl]amino}-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)carbonyl]amino}-3-phenylpropanoic Acid* (*H-Ala-Thp-Phe-OH*; **11b**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–6* to yield **11b** (22.5 mg, 38%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3425*s*, 3243*s*, 3061v*s*, 3033v*s*, 2875*s*, 2616*w*, 1724v*s*, 1678v*s*, 1533v*s*, 1499*s*, 1455*m*, 1444*m*, 1429*m*, 1394*m*, 1356*m*, 1331*w*, 1302*m*, 1261*s*, 1244*s*, 1202v*s*, 1141*s*, 1102*s*, 1029*w*, 1019*w*, 969*w*, 843*w*, 800*w*, 723*m*, 701*m*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): 12.79 (br. *s*, COOH); 8.43 (*s*, NH(Thp)); 8.06 (br. *s*, NH_3(Ala)); 7.52 (*d*, *J* = 8.0, NH(Phe)); 7.28–7.51 (*m*, 5 arom. H); 4.46 (*ddd*, *J* = 8.3, 8.0, 5.4, CH(α)(Phe)); 3.95 (*q*, *J* = 6.7, CH(α)(Ala)); 3.68–3.65, 3.59–3.59, 3.52–3.46 (3*m*, 2 CH_2O(Thp)); 3.08 (*dd*, ^2J = 13.8, *J* = 5.4, 1 H of CH_2(Phe)); 2.95 (*dd*, ^2J = 13.8, *J* = 8.3, 1 H of CH_2(Phe)); 1.99–1.94, 1.87–1.76 (2*m*, 2 CH_2CH$_2$O(Thp)); 1.38 (*d*, *J* = 7.0, Me(Ala)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 172.6 (*s*, CO(Phe)); 171.9 (*s*, CO(Thp)); 169.5 (*s*, CO(Ala)); 137.4 (*s*, arom. C); 129.3, 128.1, 126.4 (3*d*, 5 arom. CH); 62.6, 62.3 (2*t*, 2 CH_2O(Thp)); 57.0 (*s*, C(α)(Thp)); 53.3 (*d*, CH(α)(Phe)); 48.4 (*d*, CH(α)(Ala)); 36.9 (*t*, CH_2(Phe)); 31.9, 31.3 (2*t*, 2 CH_2CH$_2$O(Thp)); 17.1 (*q*, Me(Ala)). ESI-MS: 364 (100, $[M+H]^+$). HPLC/MS (*Method B*): t_R 6.1 min, *m*/*z* 364 (100, $[M+H]^+$), 199 (58, $[M-Phe]^+$).

*(*S*)-2-[((*S*)-2-{[(*S*)-2-Amino-1-oxopropyl]amino}-2-benzyl-1-oxopropyl)amino]-4-methylpentanoic Acid and (*S*)-2-[((*R*)-2-{[(*S*)-2-Amino-1-oxopropyl]amino}-2-benzyl-1-oxopropyl)amino]-4-methylpentanoic Acid* (*H-Ala-Phe(2Me)-Leu-OH*; (*S*,*S*,*S*)-**13** and (*S*,*R*,*S*)-**13**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–6* to yield (*S*,*S*,*S*)-**13** and (*S*,*R*,*S*)-**13** in a 1:1 ratio as colorless powders after prep. HPLC purification and lyophilization (29 mg, 49% altogether).

*Data of (*S,S,S*)-***13***.* IR (KBr): 3045 (sh), 3281*s*, 3066*s*, 3033*s*, 2960*s*, 2874*s*, 2623*w*, 1672v*s*, 1528v*s*, 1454*m*, 1388*m*, 1329*w*, 1268*m*, 1238*m*, 1202v*s*, 1141v*s*, 1031*w*, 1004*w*, 969*w*, 928*w*, 879*w*, 838*w*, 800*w*, 740*w*, 722*m*, 706*m*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca.* 9.5–8.0 (br. *s*, NH_3(Ala)); 8.09 (*s*, NH(Phe(2Me))); 7.82 (*d*, *J* = 8.2, NH(Leu)); 7.27–7.21, 7.12–7.11 (2*m*, 5 arom. H); 4.36–4.32 (*m*, CH(α)(Leu)); 3.81–3.80 (*m*, CH(α)(Ala)); 3.36, 3.18 (*AB*, *J* = 13.5, PhCH_2); 1.68–1.59 (*m*, CH(γ)(Leu), 1 H of CH_2(Leu)); 1.52–1.41 (*m*, 1 H of CH_2(Leu)); 1.31 (*s*, Me(Phe(2Me))); 1.30 (*d*, *J* = 7.0, Me(Ala)); 0.88, 0.86 (2*d*, *J* = 6.5, 2 Me(Leu)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 174.3 (*s*, CO(Leu)); 172.5 (*s*, CO(Phe(2Me))); 169.4 (*s*, CO(Ala)); 136.8 (*s*, arom. C); 130.6, 127.8, 126.4 (3*d*, 5 arom. CH); 59.6 (*s*, C(α)(Phe(2Me))); 50.5 (*d*, CH(α)(Leu)); 48.8 (*d*, CH(α)(Ala)); 40.1 (*t*, CH_2(Leu)); 38.8 (*t*, PhCH_2); 24.0 (*d*, CH(γ)(Leu)); 23.7 (*q*, Me(Phe(2Me))); 23.0, 21.4 (2*q*, 2 Me(Leu)); 17.1 (*q*, Me(Ala)). ESI-

MS: 408 (12, $[M-H+2\,Na]^+$), 386 (100, $[M+Na]^+$), 364 (11, $[M+H]^+$), 293 (7, $[M-Ala+H]^+$), 233 (8, $[M-Leu]^+$), 205 (23, $[M-Leu-CO]^+$), 134 (28). HPLC/MS (*Method B*): t_R 8.8 min, *m/z* 364 (100, $[M+H]^+$).

Data of (S,R,S)-**13**. IR (KBr): 3291*s*, 3066*s*, 3034*s*, 2961*s*, 2875*s*, 2618*w*, 1720*s*, 1670v*s*, 1525v*s*, 1468*m*, 1454*m*, 1387*m*, 1329*w*, 1269*m*, 1202v*s*, 1143v*s*, 1031*w*, 1004*w*, 968*w*, 927*w*, 838*w*, 800*w*, 742*w*, 723*m*, 703*m*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): 8.11 (*s*, NH_3(Ala)); 8.02 (*s*, NH(Phe(2Me))); 8.00 (*d*, *J* = 7.9, NH(Leu)); 7.25–7.19, 7.10–7.09 (2*m*, 5 arom. H); 4.29–4.25 (*m*, CH(α)(Leu)); 3.93–3.91 (*m*, CH(α)(Ala)); 3.34 (*s*, PhCH_2); 1.71–1.65 (*m*, CH(γ)(Leu), 1 H of CH_2(Leu)); 1.55–1.52 (*m*, 1 H of CH_2(Leu)); 1.45 (*s*, Me(Phe(2Me))); 1.24 (*d*, *J* = 6.9, Me(Ala)); 0.92, 0.88 (2*d*, *J* = 6.4, 2 Me(Leu)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 173.9 (*s*, CO(Leu)); 172.5 (*s*, CO(Phe(2Me))); 168.8 (*s*, CO(Ala)); 136.7 (*s*, arom. C); 130.1, 127.8, 126.4 (3*d*, 5 arom. CH); 60.2 (*s*, C(α)(Phe(2Me))); 50.8 (*d*, CH(α)(Leu)); 48.4 (*d*, CH(α)(Ala)); 39.8 (*t*, CH_2(Leu)); 39.7 (*t*, PhCH_2); 24.3 (*d*, CH(γ)(Leu)); 23.0 (*q*, Me(Phe(2Me))); 23.0, 21.1 (2*q*, 2 Me(Leu)); 17.2 (*q*, Me(Ala)). ESI-MS: 408 (5, $[M-H+2\,Na]^+$), 386 (100, $[M+Na]^+$), 364 (96, $[M+H]^+$), 293 (23, $[M-Ala+H]^+$), 233 (24, $[M-Leu]^+$), 205 (43, $[M-Leu-CO]^+$), 134 (63). HPLC/MS (*Method B*): t_R 9.7 min, *m/z* 364 (100, $[M+H]^+$).

*(*S*)-2-[({[(2-{[(4-{[(*S*)-2-Amino-3-methyl-1-oxobutyl]amino}-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)carbonyl]amino}-1-oxoethyl)amino]cyclopentyl}carbonyl)amino]propanoic Acid* (*H-Val-Thp-Gly-Acp-Ala-OH*; **15**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–5* and *GP 2–6* to yield **15** (17.0 mg, 23%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3337*s*, 3056*s*, 2971*s*, 2880*m*, 2642*w*, 1720 (sh), 1670v*s*, 1534v*s*, 1455*m*, 1430*w*, 1400*w*, 1379*w*, 1333*w*, 1297*m*, 1240*m*, 1202v*s*, 1141*s*, 1103*m*, 1027*w*, 961*w*, 935*w*, 840*w*, 800*w*, 722*m*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz; 2 conformers): *ca.* 13.0–12.0 (br. *s*, COOH); 8.82 (*s*, NH(Thp)); 8.57 (w) (*s*, NH(Acp)); 8.11 (*s*, NH_3(Val)); 8.04 (*s*, NH(Gly)); 7.73 (s) (*s*, NH(Acp)); 7.53 (w), 7.38 (s) (2*d*, *J* = 7.3, NH(Ala)); 4.26 (w), 4.14 (s) (2*dq*, *J* = 7.3, 7.3, CH(α)(Ala)); 3.77–3.71, 3.66–3.53, 3.47–3.43 (3*m*, CH(α)(Val), CH_2(Gly), 2 CH_2O(Thp)); 2.23–2.18, 2.14–2.07 (2*m*, CH(β)(Val), 1 H of 2 CH_2CH$_2$O(Thp), 1 H of 2 CH_2CH_2C(α)(Acp)); 1.97–1.76 (*m*, 3 H of 2 CH_2CH$_2$O(Thp), 3 H of 2 CH_2CH_2C(α)(Acp)); 1.69–1.56 (*m*, 2 CH_2CH$_2$C(α)(Acp)); 1.27 (s), 1.24 (w) (2*d*, *J* = 7.3, Me(Ala)); 0.99 (s), 0.95 (s), 0.94 (w) (3*d*, *J* = 6.9, Me(Val)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz; 2 conformers): 173.9 (*s*, CO(Ala)); 173.3 (*s*, CO(Thp)); 173.2 (*s*, CO(Acp)); 168.7 (*s*, CO(Gly)); 168.5 (*s*, CO(Val)); 66.4 (w), 65.9 (s) (2*s*, C(α)(Acp)); 62.5, 62.4 (2*t*, 2 CH_2O(Thp)); 57.6 (s), 57.6 (w) (2*d*, CH(α)(Val)); 56.9 (*s*, C(α)(Thp)); 47.7 (s), 47.6 (w) (2*d*, CH(α)(Ala)); 43.2 (*t*, CH_2(Gly)); 37.1, 35.2 (2*t*, 2 CH_2CH_2C(α)(Acp)); 32.8, 30.1 (2*t*, 2 CH_2CH$_2$O(Thp)); 29.6 (s), 29.5 (w) (2*d*, CH(β)(Val)); 24.1 (s), 24.0 (s), 23.9 (w), 23.8 (w) (4*t*, 2 CH_2-CH$_2$C(α)(Acp)); 18.6 (s), 18.2 (w), 17.5 (w), 17.2 (s) (4*q*, 2 Me(Val)); 17.1 (w), 17.0 (s) (2*q*, Me(Ala)). ESI-MS: 484 (100, $[M+H]^+$), 300 (20). HPLC/MS (*Method B*): t_R 4.9 min, *m/z* 484 (100, $[M+H]^+$).

*(*S*)-2-[({4-[((*S*)-2-{[(4-{[(*S*)-2-Amino-1-oxopropyl]amino}-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)carbonyl]amino}-3-methyl-1-oxobutyl)amino]-3,4,5,6-tetrahydro-2*H*-pyran-4-yl}carbonyl)amino]-3-phenylpropanoic Acid* (*H-Ala-Thp-Val-Thp-Phe-OH*; **16**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–5*, and *GP 2–6* to yield **16** (14.3 mg, 16%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3426*s*, 3306*s*, 3061*s*, 2967*s*, 2875*m*, 2620*w*, 1720*s*, 1671v*s*, 1533v*s*, 1469*m*, 1444*m*, 1429*m*, 1393*m*, 1356*w*, 1302*m*, 1259*m*, 1245*m*, 1203v*s*, 1189 (sh), 1142*s*, 1104*s*, 1029*w*, 968*w*, 946*w*, 917*w*, 838*w*, 800*w*, 722*m*, 702*w*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca.* 13.0–12.5 (br. *s*, COOH); 8.52 (*s*, NH(Thp^1)); 8.07 (*s*, NH_3(Ala)); 8.03 (*s*, NH(Thp^2)); 7.45 (*d*, *J* = 7.9, NH(Phe)); 7.38 (*d*, *J* = 7.7, NH(Val)); 7.27–7.16 (*m*, 5 arom. H); 4.43 (*ddd*, *J* = 7.9, 7.9, 5.9, CH(α)(Phe)); 4.17 (*dd*, *J* = 7.3, 7.3, CH(α)(Val)); 3.99–3.97 (*m*, CH(α)(Ala)); 3.71–3.41 (*m*, 4 CH_2O(Thp)); 3.02 (*dd*, ^2J = 13.8, *J* = 5.9, 1 H of CH_2(Phe)); 2.95 (*dd*, ^2J = 13.8, *J* = 7.5, 1 H of CH_2(Phe)); 2.07–2.04 (*m*, CH(β)(Val)); 2.01–1.84 (*m*, 4 CH_2CH$_2$O(Thp)); 1.39 (*d*, *J* = 7.0, Me(Ala)); 0.87, 0.82 (2*d*, *J* = 6.7, 2 Me(Val)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 172.5 (*s*, 2 CO(Thp)); 172.4 (*s*, CO(Phe)); 171.1 (*s*, CO(Val)); 169.7 (*s*, CO(Ala)); 137.2 (*s*, arom. C); 129.1, 128.1, 126.3 (3*d*, 5 arom. CH); 62.4, 62.3, 62.3 (3*t*, 4 CH_2O(Thp)); 58.4 (*d*, CH(α)(Val)); 57.1, 56.9 (2*s*, 2 C(α)(Thp)); 53.3 (*d*, CH(α)(Phe)); 48.5 (*d*, CH(α)(Ala)); 36.9 (*t*, CH_2(Phe)); 31.9, 31.7, 31.3, 31.1 (4*t*, 4 CH_2CH$_2$O(Thp)); 30.0 (*d*, CH(β)(Val)); 19.5, 18.2 (2*q*, 2 Me(Val)); 17.1 (*q*, Me(Ala)). ESI-MS: 590 (100, $[M+H]^+$), 425 (27, $[M-Phe]^+$). HPLC/MS (*Method B*): t_R 8.3 min, *m/z* 590 (100, $[M+H]^+$), 425 (98, $[M-Phe]^+$), 298 (48, $[M-(Thp-Phe)]^+$).

*(*S*)-2-{[(4-{[(*S*)-2-({[({[(*S*)-2-[(2-{[(*S*)-2-Amino-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-3-methyl-1-oxobutyl}amino)cyclopentyl]carbonyl}amino)-1-oxoethyl]amino}-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)carbonyl]amino}-4-methylpentanoic Acid* (*H-Ala-Aib-Val-Acp-Gly-Thp-Leu-OH*; **17**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–5*, *GP 2–5*, and *GP 2–6* to yield **17** (20.2 mg, 21%) as a colorless powder after prep. HPLC purification and lyophilization. For the 'conventional' coupling of Gly and Leu, the coupling was performed two times (1 × 2 h and 1 × overnight). IR (KBr): 3314*s*, 3054*m*, 2962*s*, 2874*m*, 1722 (sh), 1662v*s*, 1536v*s*, 1470*m*, 1448*m*, 1389*m*, 1368*w*, 1329*w*, 1295*m*, 1267*m*, 1250 (sh), 1202*s*, 1172*m*, 1141*m*, 1107*w*, 1062*w*, 1029*w*, 977*w*, 947*w*, 929*w*, 851*w*, 835*w*, 800*w*, 722*w*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca*. 12.6–12.1 (br. *s*, COOH); 8.69 (*s*, NH(Aib)); 8.49 (*s*, NH(Acp)); 8.23 (br. *s*, NH$_3$(Ala)); 8.10 (*t*, *J* = 5.6, NH(Gly)); 7.90 (*d*, *J* = 6.1, NH(Val)); 7.47 (*s*, NH(Thp)); 7.42 (*d*, *J* = 8.1, NH(Leu)); 4.23–4.19 (*m*, CH(α)(Leu)); 3.90–3.88 (*m*, CH(α)(Ala)); 3.79 (*m*, CH(α)(Val)); 3.68–3.64 (*m*, 3 H of 2 CH$_2$O(Thp)); 3.60 (*d*, *J* = 5.6, CH$_2$(Gly)); 3.57–3.45 (*m*, 1 H of 2 CH$_2$O(Thp)); 2.30–2.28 (*m*, 1 H of 2 CH$_2$C*H*$_2$C(α)(Acp)); 2.19–2.16 (*m*, CH(β)(Val)); 2.09–2.02 (*m*, 2 H of 2 C*H*$_2$CH$_2$O(Thp)); 2.00–1.88 (*m*, 1 H of 2 C*H*$_2$CH$_2$O(Thp), 3 H of 2 CH$_2$C*H*$_2$C(α)(Acp)); 1.84–1.80 (*m*, 1 H of 2 C*H*$_2$-CH$_2$O(Thp)); 1.72–1.60 (*m*, CH(γ)(Leu), 1 H of CH$_2$(Leu), 4 H of 2 C*H*$_2$CH$_2$C(α)(Acp)); 1.49–1.46 (*m*, 1 H of CH$_2$(Leu)); 1.44, 1.40 (2*s*, 2 Me(Aib)); 1.37 (*d*, *J* = 6.9, Me(Ala)); 0.88, 0.87 (2*d*, *J* = 6.7, 2 Me(Val)); 0.86, 0.82 (2*d*, *J* = 6.4, 2 Me(Leu)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 175.0 (*s*, CO(Acp)); 174.7 (*s*, CO(Aib)); 173.8 (*s*, CO(Leu)); 173.1 (*s*, CO(Thp)); 172.4 (*s*, CO(Val)); 169.5 (*s*, CO(Ala)); 168.9 (*s*, CO(Gly)); 66.1 (*s*, C(α)(Acp)); 62.4, 62.3 (2*t*, 2 CH$_2$O(Thp)); 60.1 (*d*, CH(α)(Val)); 57.1 (*s*, C(α)(Thp)); 56.4 (*s*, C(α)(Aib)); 50.3 (*d*, CH(α)(Leu)); 48.5 (*d*, CH(α)(Ala)); 44.1 (*t*, CH$_2$(Gly)); 39.8 (*t*, CH$_2$(Leu)); 36.9, 35.7 (2*t*, 2 CH$_2$*C*H$_2$C(α)(Acp)); 32.7, 30.3 (2*t*, 2 *C*H$_2$CH$_2$O(Thp)); 28.3 (*d*, CH(β)(Val)); 25.4, 24.5 (2*q*, 2 Me(Aib)); 24.1, 24.1, 24.0 (*d*, 2*t*, CH(γ)(Leu), 2 *C*H$_2$CH$_2$C(α)(Acp)); 23.0, 21.3 (2*q*, 2 Me(Leu)); 19.4, 19.3 (2*q*, 2 Me(Val)); 16.7 (*q*, Me(Ala)). ESI-MS: 682 (100, $[M+H]^+$). HPLC/MS (*Method B*): t_R 11.9 min, *m*/*z* 682 (100, $[M+H]^+$).

*(*S*)-2-{[(4-{[(*S*)-2-({[({[(*S*)-2-[(2-{[(*S*)-2-Amino-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-3-methyl-1-oxobutyl}amino)cyclopentyl]carbonyl}amino)-3-phenyl-1-oxopropyl]amino}-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)carbonyl]amino}-4-methylpentanoic Acid* (*H-Ala-Aib-Val-Acp-Phe-Thp-Leu-OH*; **18**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–5*, *GP 2–5*, and *GP 2–6* to yield **18** (14.2 mg, 13%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3431*s*, 3319*s*, 3062*m*, 3032*m*, 2962*s*, 2874*m*, 1726 (sh), 1662v*s*, 1532v*s*, 1469*m*, 1454*m*, 1445*m*, 1389*w*, 1367*w*, 1326*w*, 1293 (sh), 1266*m*, 1244*m*, 1202*s*, 1140*s*, 1108*w*, 1029*w*, 978*w*, 927*w*, 838*w*, 800*w*, 722*w*, 700*w*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca*. 12.8–12.2 (br. *s*, COOH); 8.78 (br. *s*, NH(Aib)); 8.15 (br. *s*, NH$_3$(Ala)); 8.04 (br. *s*, NH(Val), NH(Acp)); 7.72 (br. *s*, NH(Phe)); 7.61 (*s*, NH(Thp)); 7.26–7.24 (*m*, 2 arom. CH); 7.21–7.17 (*m*, NH(Leu), 3 arom. CH); 4.34–4.30 (*m*, CH(α)(Leu)); 4.23 (br. *s*, CH(α)(Phe)); 3.87 (br. *s*, CH(α)(Ala)); 3.83–3.81 (*m*, CH(α)(Val)); 3.68–3.65 (*m*, 3 H of 2 CH$_2$O(Thp)); 3.34–3.31 (*m*, 1 H of CH$_2$(Phe)); 3.26–3.22 (*m*, 1 H of 2 CH$_2$O(Thp)); 2.92–2.87 (*m*, 1 H of CH$_2$(Phe)); 2.16–2.15 (*m*, 2 H of 2 C*H*$_2$CH$_2$O(Thp)); 2.08–2.04 (*m*, CH(β)(Val), 1 H of 4 CH$_2$(Acp)); 1.99–1.94 (*m*, 1 H of 2 C*H*$_2$CH$_2$O(Thp), 1 H of 4 CH$_2$(Acp)); 1.79–1.71 (*m*, CH(γ)(Leu), 1 H of 2 C*H*$_2$CH$_2$O(Thp), 2 H of 4 CH$_2$(Acp)); 1.69–1.58 (*m*, 1 H of CH$_2$(Leu), 4 H of 4 CH$_2$(Acp)); 1.49–1.44 (*m*, 1 H of CH$_2$(Leu)); 1.49 (*s*, 1 Me of 2 Me(Aib)); 1.37 (*d*, *J* = 6.9, Me(Ala)); 1.36 (*s*, 1 Me of 2 Me(Aib)); 0.91 (*d*, *J* = 6.8, 1 Me of 2 Me(Val)); 0.88 (*d*, *J* = 6.7, 1 Me of 2 Me(Leu)); 0.85 (*d*, *J* = 6.7, 1 Me of 2 Me(Val), 1 Me of 2 Me(Leu)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 175.9 (*s*, CO(Aib)); 174.2 (*s*, CO(Acp)); 173.9 (*s*, CO(Leu)); 172.9 (*s*, CO(Thp)); 172.6 (*s*, CO(Val)); 170.3 (*s*, CO(Phe)); 169.4 (*s*, CO(Ala)); 138.4 (*s*, arom. C); 129.0, 128.2, 126.1 (3*d*, 5 arom. CH); 66.3 (*s*, C(α)(Acp)); 62.5, 62.3 (2*t*, 2 CH$_2$O(Thp)); 60.8 (*d*, CH(α)(Val)); 57.1 (*s*, C(α)(Thp)); 56.2 (*s*, C(α)(Aib)); 54.9 (*d*, CH(α)(Phe)); 49.8 (*d*, CH(α)(Leu)); 48.4 (*d*, CH(α)(Ala)); 40.2 (*t*, CH$_2$(Leu)); 36.1, 36.0 (2*t*, 2 CH$_2$*C*H$_2$C(α)(Acp)); 35.5 (*t*, CH$_2$(Phe)); 33.7, 28.7 (2*t*, 2 *C*H$_2$CH$_2$O(Thp)); 28.5 (*d*, CH(β)(Val)); 25.3, 24.3 (2*q*, 2 Me(Aib)); 24.1, 24.0 (2*t*, 2 *C*H$_2$CH$_2$C(α)(Acp)); 23.7 (*d*, CH(γ)(Leu)); 23.1, 21.1 (2*q*, 2 Me(Leu)); 19.3, 18.4 (2*q*, 2 Me(Val)); 16.7 (*q*, Me(Ala)). ESI-MS: 772 (100, $[M+H]^+$). HPLC/MS (*Method B*): t_R 11.4 min, *m*/*z* 772 (100, $[M+H]^+$).

2-({2-[(2-Amino-2-methyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methylpropanoic Acid (*H-Aib-Aib-Aib-OH*; **19**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–4*, *3*, and *6* to yield **19** (15.9 mg, 33%) as a colorless powder after prep. HPLC purification and lyophilization.

IR (KBr): 3508*m*, 3359*s*, 3262*m*, 3119*s*, 3064*s*, 2994*s*, 2947*s*, 2604*w*, 1719v*s*, 1667v*s*, 1519v*s*, 1472*m*, 1440*m*, 1406*w*, 1390*w*, 1367*w*, 1258*s*, 1203v*s*, 1179v*s*, 1144v*s*, 947*w*, 925*w*, 911*w*, 839*w*, 801*w*, 773*w*, 723*m*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): *ca*. 9.0–7.0 (br. *s*, NH$_3$); 8.00, 7.38 (2*s*, 2 NH); 1.49, 1.41, 1.38 (3*s*, 6 Me). ^{13}C-NMR ((D$_6$)DMSO, 75 MHz): 175.8, 172.6, 170.7 (3*s*, 3 CO); 56.6, 56.5, 55.2 (3*s*, 3 C(α)); 24.5, 24.4, 23.3 (3*q*, 6 Me). ESI-MS: 274 (100, $[M+H]^+$), 170 (4, $[M-\text{Aib}]^+$). HPLC/MS (*Method A*): t_R 1.3 min, *m*/*z* 274 (100, $[M+H]^+$).

*2-[(2-{[(*S*)-2-Amino-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-2-methylpropanoic Acid* (*H-Ala-Aib-Aib-OH*; **20**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–4*, *3*, and *6* to yield **20** (19.0 mg, 41%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3284*s*, 3072*s*, 2993*s*, 2945*s*, 2631*w*, 1726v*s*, 1673v*s*, 1530v*s*, 1471*m*, 1458*m*, 1441*m*, 1389*m*, 1368*m*, 1264*s*, 1204v*s*, 1141v*s*, 1005*w*, 930*w*, 880*w*, 838*m*, 801*m*, 768*w*, 723*m*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca*. 8.8–7.5 (br. *s*, NH$_3$(Ala)); 8.38 (*s*, NH(Aib^2)); 7.46 (*s*, NH(Aib^3)); 3.85 (*q*, *J* = 6.9, CH(α)(Ala)); 1.41–1.34 (*m*, 4 Me(Aib), Me(Ala)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 175.7 (*s*, CO(Aib^3)); 172.5 (*s*, CO(Aib^2)); 168.9 (*s*, CO(Ala)); 56.3 (*s*, C(α)(Aib^2)); 55.2 (*s*, C(α)(Aib^3)); 48.3 (*d*, CH(α)(Ala)); 24.8, 24.5, 24.5, 24.4 (4*q*, 4 Me(Aib)); 17.1 (*q*, Me(Ala)). ESI-MS: 519 (36, $[2M+H]^+$), 260 (100, $[M+H]^+$). HPLC/MS (*Method A*): t_R 1.3 min, *m*/*z* 260 (100, $[M+H]^+$).

*2-({2-[(2-{[(*S*)-Amino-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}-amino)-2-methylpropanoic Acid* (*H-Ala-Aib-Aib-Aib-OH*; **21**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1–4*, *3*, *4*, *3*, and *6* to yield **21** (7 mg, 12%) as a colorless powder after prep. HPLC purification and lyophilization. Additional **20** was isolated as a colorless powder (16 mg, 35%). IR(KBr): 3432v*s*, 3262v*s*, 3120v*s*, 2992v*s*, 2939*s*, 1670v*s*, 1543v*s*, 1535v*s*, 1469*s*, 1460*s*, 1399v*s*, 1367*m*, 1261*m*, 1204v*s*, 1182*s*, 1141*s*, 1089*w*, 1048*w*, 1025*w*, 1005*w*, 722*w*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca*. 12.2–11.8 (br. *s*, COOH); 8.61 (*s*, NH(Aib)); 8.04 (br. *s*, NH$_3$(Ala)); 7.44, 7.31 (2*s*, 2 NH(Aib)); 3.87 (br. *s*, CH(α)(Ala)); 1.39–1.34 (*m*, 6 Me(Aib), Me(Ala)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 174.4, 172.2, 171.1, 168.1 (4*s*, 4 CO); 55.2, 54.6, 53.8 (3*s*, 3 C(α)(Aib)); 47.1 (*d*, CH(α)(Ala)); 23.9, 23.6, 23.5, 23.3, 23.3, 23.2 (6*q*, 6 Me(Aib)); 15.8 (*q*, Me(Ala)). ESI-MS: 345 (100, $[M+H]^+$). HPLC/MS (*Method A*): t_R 1.5 min, *m*/*z* 345 (100, $[M+H]^+$).

*2-{[2-({2-[((*S*)-2-{[(*S*)-Amino-1-oxopropyl]amino}-3-methyl-1-oxobutyl)amino]-2-methyl-1-oxopropyl}ami no)-2-methyl-1-oxopropyl]amino}-2-methylpropanoic Acid* (*H-Ala-Val-Aib-Aib-Aib-OH*; **22**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1*, *2*, *5*, *2–4*, *3*, *4*, *3*, and *6* to yield **22** (11.0 mg, 16%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3431*s*, 3304*s*, 3063*s*, 2987*s*, 2942*s*, 2883*m*, 2629*w*, 1720 (sh), 1667v*s*, 1534v*s*, 1469*m*, 1389*m*, 1366*m*, 1203v*s*, 1181v*s*, 1140*s*, 1010*w*, 935*w*, 837*w*, 800*w*, 776*w*, 722*m*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca*. 9.5–7.5 (br. *s*, NH$_3$(Ala)); 8.40 (*s*, NH(Aib^3)); 8.33 (*d*, *J* = 7.6, NH(Val)); 7.34 (*s*, NH(Aib^5)); 7.13 (*s*, NH(Aib^4)); 4.11 (*dd*, *J* = 7.2, 7.2, CH(α)(Val)); 3.95 (*q*, *J* = 6.9, CH(α)(Ala)); 2.05 (*dsept*., *J* = 6.8, 6.8, CH(β)(Val)); 1.33–1.29 (*m*, 6 Me(Aib), Me(Ala)); 0.93, 0.91 (2*d*, *J* = 7.0, 2 Me(Val)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 175.6 (*s*, CO(Aib^5)); 173.3 (*s*, CO(Aib^4)); 172.6 (*s*, CO(Aib^3)); 170.9 (*s*, CO(Val)); 169.8 (*s*, CO(Ala)); 58.3 (*d*, CH(α)(Val)); 56.1 (*s*, C(α)(Aib^3)); 55.7 (*s*, C(α)(Aib^4)); 54.8 (*s*, C(α)(Aib^5)); 47.9 (*d*, CH(α)(Ala)); 30.0 (*d*, CH(β)(Val)); 25.0 (*q*, 1 Me of 2 Me(Aib^3)); 24.9 (*q*, 1 Me of 2 Me(Aib^4)); 24.8, 24.5 (2*q*, 2 Me(Aib^5)); 24.4 (*q*, 1 Me of 2 Me(Aib^4)); 24.2 (*q*, 1 Me of 2 Me(Aib^3)); 19.2, 18.2 (2*q*, 2 Me(Val)); 17.4 (*q*, Me(Ala)). ESI-MS: 444 (100, $[M+H]^+$). HPLC/MS (*Method A*): t_R 8.4 min, *m*/*z* 444 (100, $[M+H]^+$).

*(*S*)-2-[(2-{[2-({(*S*)-2-{[(*S*)-Amino-1-oxopropyl]amino}-3-methyl-1-oxobutyl)amino]-3-phenyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-4-methylpentanoic Acid* (*H-Ala-Val-Phe-Aib-Aib-Leu-OH*; **23**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1*, *2*, *5*, *2*, *5*, *2–4*, *3–6* to yield **23** (5.3 mg, 6%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3421*s*, 3312*s*, 3065*m*, 3034*m*, 2964*s*, 2939*m*, 2876*m*, 1668v*s*, 1534v*s*, 1468*m*, 1460*m*, 1442*m*, 1388*m*, 1367*w*, 1203v*s*, 1190 (sh), 1140*s*, 837*w*, 800*w*, 745*w*, 722*w*, 700*w*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca*. 12.4–12.1 (br. *s*, COOH); 8.32 (*d*, *J* = 5.7, NH(Phe)); 8.26 (*d*, *J* = 8.6, NH(Val)); 8.19 (*s*, NH(Aib^4)); 8.04 (br. *s*, NH$_3$(Ala)); 7.32 (*s*, NH(Aib^5)); 7.30–7.18 (*m*, 5 arom. H, NH(Leu)); 4.41 (*ddd*, *J* = 8.1, 6.3, 6.3, CH(α)(Phe)); 4.15 (*dd*, *J* = 8.2, 8.2, CH(α)(Val)); 4.13–4.10 (*m*, CH(α)(Leu)); 3.93–3.90 (*m*, CH(α)(Ala)); 2.95 (*dd*, *J* = 13.9, 6.5, 1 H of CH$_2$(Phe)); 2.88 (*dd*, *J* = 13.9, 8.5, 1 H of CH$_2$(Phe)); 1.92 (*dsept*., *J* = 7.0, 7.0, CH(β)(Val)); 1.72–1.63 (*m*, CH(γ)(Leu), 1 H of

CH_2(Leu)); 1.47–1.42 (*m*, 1 H of CH_2(Leu)); 1.34, 1.31 (2*s*, 2 Me(Aib^5)); 1.26 (*d*, *J* = 7.0, Me(Ala)); 1.19, 1.12 (2*s*, 2 Me(Aib^4)); 0.90 (*d*, *J* = 6.7, 1 Me of 2 Me(Val)); 0.87 (*d*, *J* = 6.5, 1 Me of 2 Me(Leu)); 0.84 (*d*, *J* = 6.7, 1 Me of 2 Me(Val)); 0.81 (*d*, *J* = 6.5, 1 Me of 2 Me(Leu)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 174.1 (*s*, CO(Aib^5)); 173.8 (*s*, CO(Leu)); 172.6 (*s*, CO(Aib^4)); 171.0 (*s*, CO(Phe)); 170.7 (*s*, CO(Val)); 169.2 (*s*, CO(Ala)); 137.0 (*s*, arom. C); 129.1, 127.9, 126.2 (3*d*, 5 arom. CH); 57.8 (*d*, CH(α)(Val)); 55.9 (*s*, C(α)(Aib^4)); 55.6 (*s*, C(α)(Aib^5)); 54.5 (*d*, CH(α)(Phe)); 50.3 (*d*, CH(α)(Leu)); 47.8 (*d*, CH(α)(Ala)); 39.6 (*t*, CH_2(Leu)); 36.9 (*t*, CH_2(Phe)); 30.3 (*d*, CH(β)(Val)); 25.9 (*q*, 1 Me of 2 Me(Aib^5)); 25.8 (*q*, 1 Me of 2 Me(Aib^4)); 23.8 (*d*, CH(γ)(Leu)); 23.5 (*q*, 1 Me of 2 Me(Aib^5)); 23.4 (*q*, 1 Me of 2 Me(Aib^4)); 23.0, 21.0 (2*q*, 2 Me(Leu)); 19.2, 18.5 (2*q*, 2 Me(Val)); 17.3 (*q*, Me(Ala)). ESI-MS: 619 (100, $[M+H]^+$), 488 (21, $[M-\text{Leu}]^+$), 403 (10, $[M-(\text{Aib-Leu})]^+$). HPLC/MS (*Method B*): t_R 11.1 min, *m*/*z* 619 (100, $[M+H]^+$).

*(*S*)-2-({2-[(2-{[2-({(*S*)-2-[((*S*)-2-{[(*S*)-2-Amino-1-oxopropyl]amino}-3-methyl-1-oxobutyl)amino]-3-phenyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-2-methyl-1-oxomethyl}amino)-4-methylpentanoic Acid* (*H-Ala-Val-Phe-Aib-Aib-Aib-Leu-OH*; **24**). PAM Resin (200 mg, 0.124 mmol) was treated as described in *GP 1*, *2*, *5*, *2*, *5*, *2–4*, *3*, *4*, *3–6* to yield **24** (8.6 mg, 9%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3422*s*, 3307*s*, 3065*s*, 3033*s*, 2964*s*, 2941*s*, 2875*m*, 1667v*s*, 1532v*s*, 1468*m*, 1458*m*, 1442*m*, 1387*m*, 1366*m*, 1276*m*, 1203v*s*, 1188*s*, 1140*s*, 945*w*, 923*w*, 837*w*, 800*w*, 722*w*, 700*w*. ^{1}H-NMR ((D$_6$)DMSO, 600 MHz): *ca*. 12.3–12.1 (br. *s*, COOH); 8.44 (*s*, NH(Aib^4)); 8.42 (*d*, *J* = 4.9, NH(Phe)); 8.26 (*d*, *J* = 8.6, NH(Val)); 8.04 (br. *s*, NH_3(Ala)); 7.53, 7.41 (2*s*, NH(Aib^5), NH(Aib^6)); 7.40 (*d*, *J* = 7.9, NH(Leu)); 7.28–7.20 (*m*, 5 arom. H); 4.41 (*td*, *J* = 7.6, 5.1, CH(α)(Phe)); 4.20 (*dd*, *J* = 8.1, 8.1, CH(α)(Val)); 4.18–4.14 (*m*, CH(α)(Leu)); 3.91 (br. *s*, CH(α)(Ala)); 2.96–2.89 (*m*, CH_2(Phe)); 1.93 (*dsept*., *J* = 7.0, 7.0, CH(β)(Val)); 1.78–1.75 (*m*, CH(γ)(Leu)); 1.73–1.69, 1.44–1.39 (2*m*, CH_2(Leu)); 1.34, 1.33, 1.30, 1.26 (4*s*, 4 Me of 6 Me(Aib)); 1.26 (*d*, *J* = 6.5, Me(Ala)); 1.20, 1.14 (2*s*, 2 Me of 6 Me(Aib)); 0.94, 0.88 (2*d*, *J* = 6.8, 2 Me(Val)); 0.83, 0.81 (2*d*, *J* = 6.6, 2 Me(Leu)). ^{13}C-NMR ((D$_6$)DMSO, 150 MHz): 174.3, 174.1 (2*s*, 2 CO of 3 CO(Aib)); 174.0 (*s*, CO(Leu)); 173.0 (*s*, 1 CO of 3 CO(Aib)); 171.7 (*s*, CO(Phe)); 170.8 (*s*, CO(Val)); 169.2 (*s*, CO(Ala)); 136.8 (*s*, arom. C); 129.2, 127.9, 126.3 (3*d*, 5 arom. CH); 57.6 (*d*, CH(α)(Val)); 56.1, 55.8, 55.7 (3*s*, 3 C(α)(Aib)); 54.5 (*d*, CH(α)-(Phe)); 50.2 (*d*, CH(α)(Leu)); 47.8 (*d*, CH(α)(Ala)); 39.8 (*t*, CH_2(Leu)); 36.7 (*t*, CH_2(Phe)); 30.3 (*d*, CH(β)(Val)); 26.7, 26.1, 25.9 (3*q*, 3 Me of 6 Me(Aib)); 23.6 (*d*, CH(γ)(Leu)); 23.4, 23.2 (2*q*, 2 Me of 6 Me(Aib)); 23.0 (*q*, 1 Me of 2 Me(Leu)); 22.9 (*q*, 1 Me of 6 Me(Aib)); 21.0 (*q*, 1 Me of 2 Me(Leu)); 19.2, 18.5 (2*q*, 2 Me(Val)); 17.3 (*q*, Me(Ala)). ESI-MS: 704 (100, $[M+H]^+$), 573 (21, $[M-\text{Leu}]^+$). HPLC/MS (*Method B*): t_R 11.1 min, *m*/*z* 704 (100, $[M+H]^+$).

5. *Derivatization of (*S,S,S*)-***13*** and (*S,R,S*)-***13***. (S)-2-{[(S)-2-({(S)-2-[4-(Bromobenzoyl)amino]-1-oxopropyl}amino)-2-benzyl-1-oxopropyl]amino}-4-methylpentanoic Acid* (p-*BrBz-Ala-Phe(2Me)-Leu-OH*; (*S,S,S*)-**14**) *and (*S*)-2-{[(*R*)-2-({(*S*)-2-[4-(Bromobenzoyl)amino]-1-oxopropyl}amino)-2-benzyl-1-oxopropyl]amino}-4-methylpentanoic Acid* (p-*BrBz-Ala-Phe(2Me)-Leu-OH*; (*S,R,S*)-**14**). At 0°, 4-bromobenzoyl chloride (8 mg, 0.036 mmol) was added to a mixture of (*S,S,S*)-**13** (*ca*. 12 mg, 0.025 mmol) and K_2CO_3 (12 mg, 0.087 mmol), and (*S,R,S*)-**13** (*ca*. 12 mg, 0.025 mmol) and K_2CO_3 (12 mg, 0.087 mmol), resp., in acetone (5 ml) and H_2O (1 ml), then stirred at r.t. for 2 h. The org. solvent was removed under reduced pressure, and the residue was acidified with dil. aq. HCl. The resulting precipitation was filtered and purified by prep. TLC (CH_2Cl_2/MeOH 10 : 1; 2 × dev.) to yield colorless powders (8 mg (59%) and 6 mg (44%), resp.). Suitable crystals for the X-ray crystal-structure determination of (*S,S,S*)-**14** were grown from MeOH/$CHCl_3$/Et_2O.

*Data of (*S,S,S*)-***14***.* ESI-MS: 593 (10), 592 (30, $[M(^{81}\text{Br})-H+2\,Na]^+$), 591 (10), 590 (33, $[M(^{79}\text{Br})-H+2\,Na]^+$), 571 (42), 570 (100, $[M(^{81}\text{Br})+Na]^+$), 569 (34), 568 (86, $[M(^{79}\text{Br})+Na]^+$).

*Data of (*S,R,S*)-***14***.* ESI-MS: 593 (5), 592 (11, $[M(^{81}\text{Br})-H+2\,Na]^+$), 591 (5), 590 (11, $[M(^{79}\text{Br})-H+2\,Na]^+$), 571 (29), 570 (100, $[M(^{81}\text{Br})+Na]^+$), 569 (26), 568 (72, $[M(^{79}\text{Br})+Na]^+$).

6. *X-Ray Crystal-Structure Determination of (*S,S,S*)-***14***,* (see *Table 3* and *Fig.*)[2]). A crystal of $C_{26}H_{32}BrN_3O_5 \cdot$MeOH, obtained from MeOH/$CHCl_3$/Et_2O, was used for a low-temp. X-ray crystal-struc-

---

[2]) CCDC-287054 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Center via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 3. *Crystallographic Data of Compound (*S,S,S*)-***14***

Crystallized from		$MeOH/CHCl_3/Et_2O$
Empirical formula		$C_{27}H_{36}BrN_3O_6$
Formula weight [g mol^{-1}]		578.50
Crystal color, habit		colorless, plate
Crystal dimensions [mm]		$0.03\times0.15\times0.22$
Temp. [K]		160(1)
Crystal system		monoclinic
Space group		$P2_1$
Z		4
Reflections for cell determination		84590
2θ Range for cell determination [°]		4–50
Unit cell parameters	a [Å]	15.2292(6)
	b [Å]	10.1998(4)
	c [Å]	18.6076(8)
	β [°]	91.810(2)
	V [Å^3]	2889.0(2)
D_x [g cm^{-3}]		1.330
$\mu(MoK_\alpha)$ [mm^{-1}]		1.470
Scan type		ω
$2\theta_{(max)}$ [°]		50
Transmission factors (min; max)		0.737; 0.982
Total reflections measured		43528
Symmetry independent reflections		10174
Reflections with $I>2\sigma(I)$		6247
Reflections used in refinement		10163
Parameters refined; restraints		693; 1
Final	$R(F)$ [$I>2\sigma(I)$ reflections]	0.0646
	$wR(F^2)$ (all data)	0.1480
Weights: $w=[\sigma^2(F_o^2)+(0.0518P)^2+1.5382P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$		
Goodness-of-fit		1.036
Final Δ_{max}/σ		0.001
$\Delta\rho$ (max; min) [e Å^{-3}]		0.49; −0.44

ture determination. All measurements were made on a *Nonius KappaCCD* area-detector diffractometer [27] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in *Table 3*, and a view of the molecule is shown in the *Figure*.

Data reduction was performed with *HKL Denzo* and *Scalepack* [28]. The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [29] was applied. Equivalent reflections, other than *Friedel* pairs, were merged.

The structure was solved by direct methods using SHELXS97 [30], which revealed the positions of all non-H-atoms. There are two symmetry-independent peptide and two MeOH molecules in the asymmetric unit. The atomic coordinates were tested carefully for a relationship from a higher symmetry space group by using the program PLATON [31], but none could be found. The non-H-atoms were refined anisotropically. The OH H-atoms of the peptide and MeOH molecules 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. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the Me groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures,

which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. Eleven reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Refinement of the absolute structure parameter [32] yielded a value of 0.00(1), which confidently confirms that the refined model represents the true enantiomorph. Neutral-atom scattering factors for non-H-atoms were taken from [33a], and the scattering factors for H-atoms were taken from [34]. Anomalous dispersion effects were included in F_c [35]; the values for f' and f'' were those of [33b]. The values of the mass attenuation coefficients are those of [33c]. All calculations were performed using the SHELXL97 [36] program.

REFERENCES

[1] W. F. DeGrado, *Adv. Prot. Chem.* **1988**, *39*, 51.
[2] J. Rizo, L. M. Gierasch, *Annu. Rev. Biochem.* **1992**, *61*, 387.
[3] V. J. Hruby, F. Al-Obeidi, W. Kazmierski, *Biochem. J.* **1990**, *268*, 249.
[4] M. Mutter, *Angew. Chem., Int. Ed.* **1985**, *24*, 639.
[5] H. Heimgartner, *Angew. Chem., Int. Ed.* **1991**, *30*, 238.
[6] J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* **1997**, *97*, 2243.
[7] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1986**, *69*, 1153; P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1987**, *70*, 354.
[8] N. Pradeille, A. Linden, K. Möhle, O. Zerbe, H. Heimgartner, *Chem. Biodiv.* **2005**, *2*, 1127.
[9] R. T. N. Luykx, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 4093.
[10] N. Pradeille, H. Heimgartner, *J. Pept. Sci.* **2003**, *9*, 827.
[11] S. Stamm, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 1371.
[12] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1998**, *54*, 8721.
[13] C. B. Bucher, H. Heimgartner, *Helv. Chim. Acta* **1996**, *79*, 1903.
[14] W. Altherr, Ph.D. thesis, Universität Zürich, 1994.
[15] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1990**, *73*, 13.
[16] S. Stamm, H. Heimgartner, *Eur. J. Org. Chem.* **2004**, 3820.
[17] C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
[18] J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem., Int. Ed.* **1995**, *34*, 1555.
[19] Performed by *C.A.T. GmbH & Co.*, Tübingen, Germany.
[20] I. Dannecker-Dörig, Ph.D. thesis, Universität Zürich, 1995.
[21] S. A. Stoykova, Ph.D. thesis, Universität Zürich, 2004.
[22] L. Zhang, C. Goldammer, B. Henkel, F. Zuehl, G. Panhaus, G. Jung, E. Bayer, in 'Innovation Perspect. Solid Phase Synth. Collect. Pap.', 3rd Int. Symp. (1993), 1994, p. 711.
[23] J. M. Villalgordo, H. Heimgartner, *Tetrahedron* **1993**, *49*, 7215.
[24] J. M. Villalgordo, H. Heimgartner, *Helv. Chim. Acta* **1993**, *76*, 2830.
[25] C. Strässler, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1997**, *80*, 1528.
[26] C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1995**, *78*, 935.
[27] R. Hooft, *KappaCCD Collect Software*, *Nonius BV*, Delft, The Netherlands, 1999.
[28] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Vol. 276, 'Macromolecular Crystallography', Part A, Eds. C. W. Carter Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.
[29] R. H. Blessing, *Acta Crystallogr., Sect A* **1995**, *51*, 33.
[30] G. M. Sheldrick, SHELXS97, Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1997.
[31] A. L. Spek, PLATON, Program for the Analysis of Molecular Geometry, University of Utrecht, The Netherlands, 2005.
[32] a) H. D. Flack, G. Bernardinelli, *Acta Crystallogr., Sect A* **1999**, *55*, 908; b) H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143.
[33] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477; b) D. C.

Creagh, W. J. McAuley, *ibid*. Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, *ibid*. Table 4.2.4.3, p. 200.
[34] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[35] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[36] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

Received October 22, 2005