

Synthesis and Conformational Analysis of Pentapeptides Containing Enantiomerically Pure 2,2-Disubstituted Glycines

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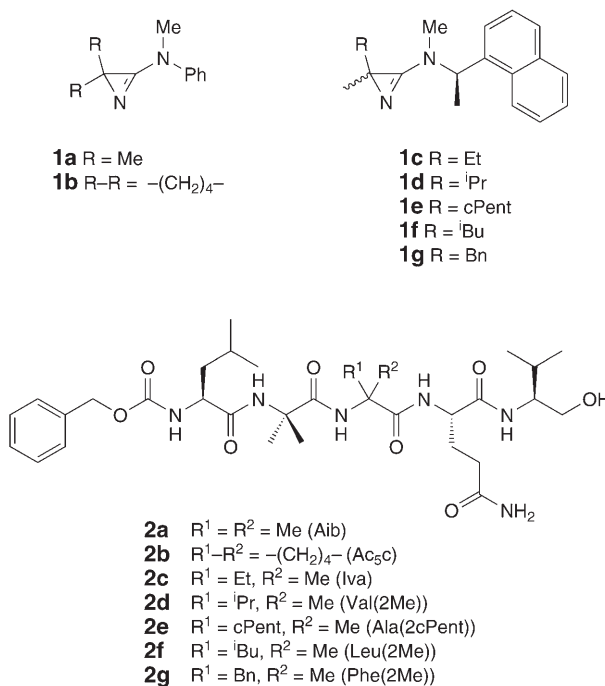
Dedicated to Professor *Dieter Seebach* on the occasion of his 70th birthday

The synthesis and conformational analysis of model pentapeptides with the sequence Z-Leu-Aib-Xaa-Gln-Valol is described. These peptides contain two 2,2-disubstituted glycines (α,α -disubstituted α -amino acids), *i.e.*, Aib (aminoisobutyric acid), and a series of unsymmetrically substituted, enantiomerically pure amino acids Xaa. These disubstituted amino acids were incorporated into the model peptides *via* the ‘azirine/oxazolone method’. Conformational analysis was performed in solution by means of NMR techniques and, in the solid state, by X-ray crystallography. Both methods show that the backbones of these model peptides adopt helical conformations, as expected for 2,2-disubstituted glycine-containing peptides.

1. Introduction. – Within the last 30 years, 2,2-disubstituted glycines (*i.e.*, α,α -disubstituted α -amino acids) attracted increasing interest as structural units in biologically active heterocycles (see, *e.g.*, [1]) and in conformationally restricted peptides (see, *e.g.*, [2]). Of special significance are the so-called peptaibols, *i.e.*, peptide antibiotics, which contain a high proportion of 2,2-dimethylglycine (α -aminoisobutyric acid (Aib)) and are produced by some filamentous fungi [3]. Due to the presence of Aib, these peptides exhibit helical conformations [4][5]. This structure is essential for their biological activity [6], *i.e.*, their ability to form ion channels through membranes [7].

For this reason, several new syntheses of achiral and optically active 2,2-disubstituted glycines have been reported in recent years [2c][8], as well as new protocols for the introduction of these sterically congested amino acids into peptides [9–11]. In our laboratory, we have developed the so-called ‘azirine/oxazolone method’ for this purpose [12][13]. It has been shown that this protocol can be used successfully in the synthesis of peptaibols and segments thereof [3i][5f][5g][13]. Therefore, a large series of 2*H*-azirin-3-amines were prepared as synthons for symmetrical 2,2-disubstituted [14] and heterocyclic α -amino acids [15], as well as dipeptide synthons [15c][16]. Furthermore, building blocks for enantiomerically pure 2-methylphenylalanine [17] and 2-ethylalanine (isovaline (Iva)) [18] were obtained after chromatographic separation of the corresponding diastereoisomeric 2*H*-azirin-3-amines bearing a chiral residue at the exocyclic N-atom. Recently, we reported the synthesis of some new optically active 2*H*-azirin-3-amines **1** as synthons for enantiomerically pure 2,2-disubstituted glycines by using (*R*)-[1-(naphthalen-1-yl)ethyl]amine (NaphthEtNH₂) as the chiral auxiliary [19].

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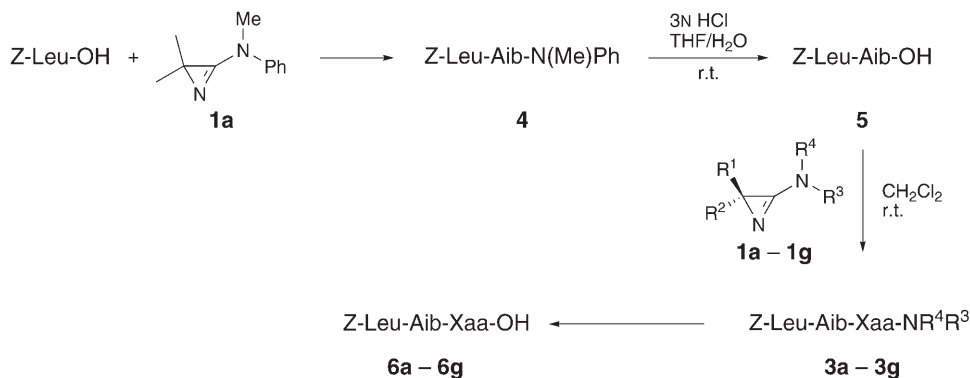


It has been shown that these 2*H*-azirin-3-amines are suitable for the successful incorporation of the corresponding enantiomerically pure 2,2-disubstituted glycines into peptides by the ‘azirine/oxazolone method’ [17–19]. In the present paper, we describe the synthesis and the results of the conformational analysis of model pentapeptides **2a–2g** with the sequence Z-Leu-Aib-Xaa-Gln-Valol. With Xaa = Aib or D-Iva, this is the C-terminal segment of the naturally occurring peptaibol family of *trichotoxin A-50* (see [3i]). As the first examples, we have already described the preparation of the pentapeptides **2c** containing D- and L-Iva [18].

2. Results and Discussion. – 2.1. *Synthesis of the Pentapeptides 2.* The model pentapeptides **2** were synthesized according to *Schemes 1* and *3*. The N-terminal tripeptides Z-Leu-Aib-Xaa-NR³R⁴ **3a–3g** were prepared by the ‘azirine/oxazolone method’. First, Z-Leu-OH was coupled with **1a**, the synthon for Aib, in Et₂O or CH₂Cl₂ at room temperature, to yield the dipeptide amide **4**, which was hydrolyzed at room temperature with 3*N* HCl (H₂O/THF 1:1) to give Z-Leu-Aib-OH (**5**) [19]. The latter was coupled with the respective azirines **1a–1g** to yield the tripeptide amides **3a–3g** (*Scheme 1* and *Table 1*; for the coupling with **1c–1g**, see [19]).

Subsequent hydrolysis gave the tripeptide acids **6a–6g**. The structure of (*R*)-**6c** was established by X-ray crystallography (*Fig. 1*). For (*R*)-**6c**, the OH group forms an intramolecular H-bond with the central amide O-atom, thereby creating a ten-membered loop and a helical turn within the molecule. This interaction can be described by the graph set motif [21] of S(10). N(1)–H forms an intermolecular H-bond with the carboxylic acid C=O O-atom of a neighboring molecule, thereby linking

Scheme 1

Table 1. Synthesis of the Tripeptide Amides **3** from Dipeptide **5**

Xaa	Azirine 1	R ¹ , R ²	R ³ , R ⁴	Tripeptide amide	
				3	Yield [%]
Aib	1a	Me, Me	Ph, Me	3a	95
Ac ₅ C	1b	–(CH ₂) ₄ –	Ph, Me	3b	97
(<i>S</i>)-Iva	(<i>2S</i>)- 1c	Me, Et	NaphthEt, Me	(<i>S</i>)- 3c	77 [19]
	(<i>2S</i>)- 1i	Me, Et	PhEt, Me	(<i>S</i>)- 3i	93 [18]
(<i>R</i>)-Iva	(<i>2R</i>)- 1c	Et, Me	NaphthEt, Me	(<i>R</i>)- 3c	83 [19]
	(<i>2R</i>)- 1i	Et, Me	PhEt, Me	(<i>R</i>)- 3i	91 [18]
(<i>S</i>)-Val(2Me)	(<i>2S</i>)- 1d	ⁱ Pr, Me	NaphthEt, Me	(<i>S</i>)- 3d	67 [19]
(<i>R</i>)-Val(2Me)	(<i>2R</i>)- 1d	Me, ⁱ Pr	NaphthEt, Me	(<i>R</i>)- 3d	69 [19]
(<i>S</i>)-Ala(2cPent)	(<i>2S</i>)- 1e	cPent, Me	NaphthEt, Me	(<i>S</i>)- 3e	39 [19]
(<i>R</i>)-Ala(2cPent)	(<i>2R</i>)- 1e	Me, cPent	NaphthEt, Me	(<i>R</i>)- 3e	38 [19]
(<i>S</i>)-Leu(2Me)	(<i>2S</i>)- 1f	ⁱ Bu, Me	NaphthEt, Me	(<i>S</i>)- 3f	64 [19]
(<i>R</i>)-Leu(2Me)	(<i>2R</i>)- 1f	Me, ⁱ Bu	NaphthEt, Me	(<i>R</i>)- 3f	60 [19]
(<i>S</i>)-Phe(2Me)	(<i>2S</i>)- 1h	Bn, Me	‘Prolinol’	(<i>S</i>)- 3h	70
	(<i>2S</i>)- 1g	Bn, Me	NaphthEt, Me	(<i>S</i>)- 3g	59 [19]
(<i>R</i>)-Phe(2Me)	(<i>2R</i>)- 1h	Me, Bn	‘Prolinol’	(<i>R</i>)- 3h	79
	(<i>2R</i>)- 1g	Me, Bn	NaphthEt, Me	(<i>R</i>)- 3g	62 [19]

the molecules into extended chains, which run parallel to the [0 1 0] direction, and which can be described by the graph set motif of C(11). N(4)–H forms an intermolecular H-bond with the amide O-atom of a neighboring molecule, thereby linking the molecules into extended chains, which run parallel to the [1 0 0] direction, and which can be described by the graph set motif of C(5). The combination of the intermolecular interactions generates a three-dimensional framework of H-bonded molecules. N(7)–H is not involved in any H-bonding interactions. The closest acceptor atom is O(12) within the same molecule, but the H⋯O and N⋯O distances of 2.65(3) and 3.330(2) Å are just outside the maximum value (2.6 and 3.2 Å, resp.) considered to be the outer limit of a significant N–H⋯O H-bonding interaction.

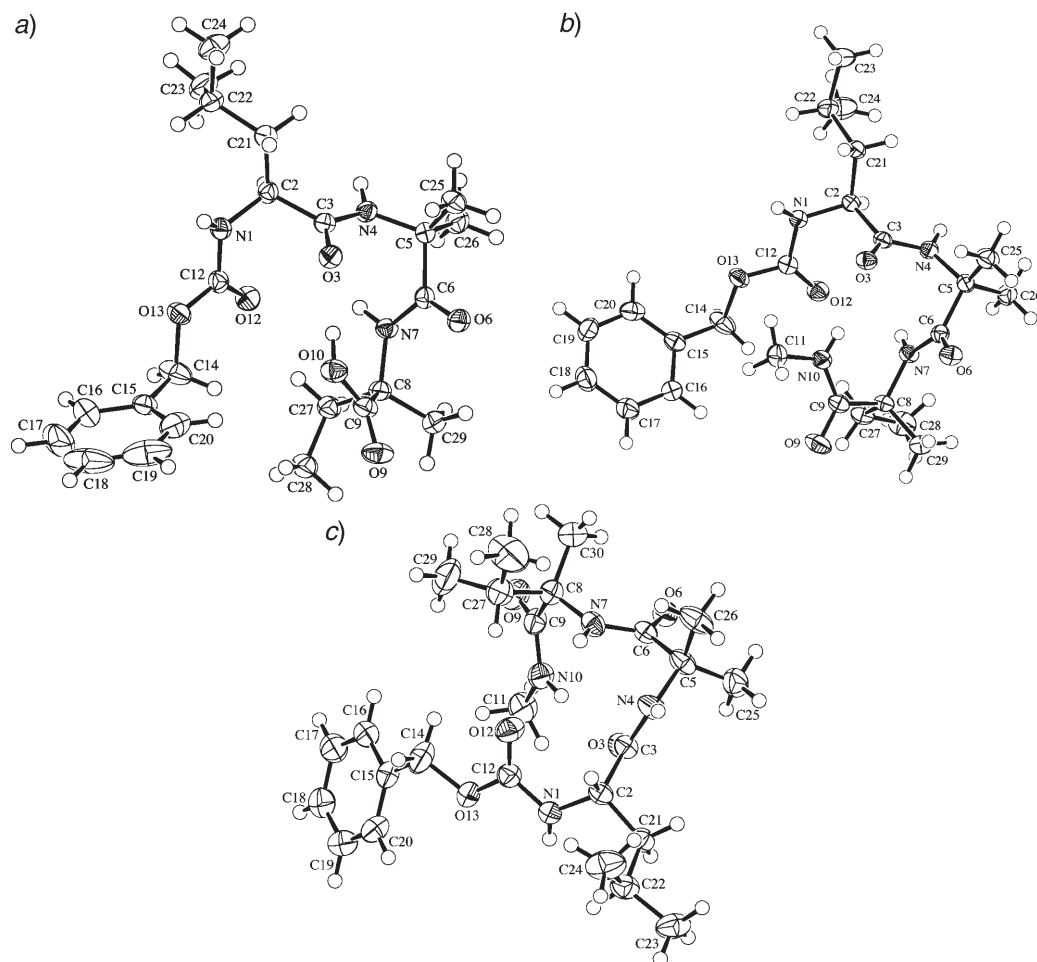


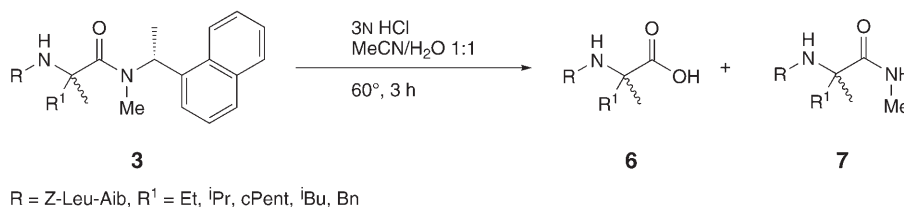
Fig. 1. ORTEP Plots [20] of the molecular structures of a) (R)-**6c** (Z-Leu-Aib-(R)-Iva-OH), b) (R)-**7c** (Z-Leu-Aib-(R)-Iva-NHMe), and c) (R)-**7d** (Z-Leu-Aib-(R)-Val(2Me)-NHMe) (50% probability ellipsoids, arbitrary numbering of atoms)

The standard conditions for the hydrolysis of peptide amides with a *N*-methyl-anilide group are 3*N* HCl (H₂O/THF 1:1) at room temperature. However, for the tripeptide amides of type **3** with NaphthEt(Me)N as the chiral auxiliary group, these conditions have proven to be too mild. Therefore, the temperature was increased, and the solvent system was changed to H₂O/MeCN 1:1. The optimized new standard conditions were 3 h at 60°.

Interestingly, the coupling of amino acids with a junction at C(3) (*i.e.*, β -branched amino acids, such as Val(2Me) and Ala(2cPent)) by the reaction of the corresponding azirine with Z-Leu-Aib-OH proceeded with lower yields than that of amino acids with a CH₂(3) group (linear or γ -branched amino acids; see Table 1). On the other hand, the hydrolysis gave better yields in the case of β -branched amino acids (see Table 2).

During this hydrolysis, a side product **7** with a *N*-methylamide group, which is similar to the side products described in [22], was formed in addition to **6** (Scheme 2 and Table 2). For example, the hydrolysis of the (*S*)-Iva- and (*R*)-Iva-containing tripeptides (*S*)-**3c** and (*R*)-**3c** gave the side products (*S*)-**7c** and (*R*)-**7c** in 30 and 29% yield, respectively. The structures of the (*R*)-Iva- and (*R*)-Val(2Me)-containing (*R*)-**7c** and (*R*)-**7d** were determined by X-ray crystallography (Fig. 1).

Scheme 2



The solid-state structures of (*R*)-**7c** and (*R*)-**7d** also exhibit the same H-bonding motifs and three-dimensional framework as described above for (*R*)-**6c** with the carboxylic acid group now replaced by the amide group involving N(10)–H. N(7)–H is positioned in approximately the correct position to interact intramolecularly with O(12), but, again, the H⋯O and N⋯O distances of 2.63(2) and 2.78(4) Å, and 3.297(2) and 3.451(3) Å, respectively, are too long to be considered as a significant N–H⋯O H-bonding interaction, particularly in the case of (*R*)-**7d**.

In the crystals of the product (*R*)-**6c** and the side product (*R*)-**7c** of the hydrolysis of (*R*)-**3c**, as well as the side product (*R*)-**7d** of the hydrolysis of (*R*)-**3d**, the molecules form a β -turn of type I' or III', which is in good agreement with the structures of the investigated pentapeptides (Fig. 1). However, as noted earlier, the interatomic distances for the intramolecular N–H⋯O interactions normally associated with such turns (N(10)–H⋯O(12) in these structures) are such that the interactions are at best extremely weak H-bonds.

The coupling of Z-Leu-Aib-OH (**5**) with (2'*R*)-**1h** and (2'*S*)-**1h**, *i.e.*, the synthons for (*R*)- and (*S*)-Phe(2Me) [17], and with (2*R*)-**1i** and (2*S*)-**1i**, the synthons for (*R*)- and (*S*)-Iva [18], to give tripeptide amides of type **3**, as well as their hydrolysis to the corresponding tripeptide acids **6**, gave better yields than in the case of **1g** and **1c** (Table 2), but their chiral auxiliary groups cannot be as widely used as the NaphthEt-(Me)N group.

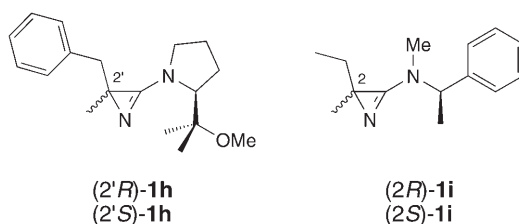
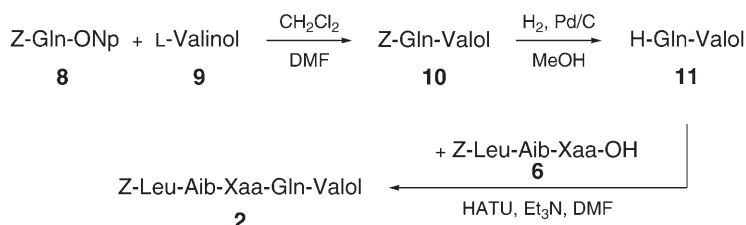


Table 2. *Synthesis of the Model Pentapeptides 2 and 13 from Tripeptide Amides 3*

Xaa	R ¹ , R ²	R ³ , R ⁴	Tripeptide acid		Side product from hydrolysis		Pentapeptide		pBrBz-Pentapeptide	
			6	Yield [%]	7	Yield [%]	2	Yield [%]	13	Yield [%]
Aib	Me, Me	Ph, Me	6a	88			2a	77	13a	78
Ac ₃ c	–(CH ₂) ₄ –	Ph, Me	6b	90			2b	87	13b	85
(S)-Iva	Me, Et	NaphthEt, Me	(S)-6c	37	(S)-7c	30				
		PhEt, Me	(S)-6i	85 [18]			(S)-2i	82 [18]		
(R)-Iva	Et, Me	NaphthEt, Me	(R)-6c	39	(R)-7c	29				
		PhEt, Me	(R)-6i	84			(R)-2i	75 [18]		
(S)-Val(2Me)	ⁱ Pr, Me	NaphthEt, Me	(S)-6d	65	(S)-7d	21				
(R)-Val(2Me)	Me, ⁱ Pr	NaphthEt, Me	(R)-6d	80	(R)-7d	9				
(S)-Ala(2cPent)	cPent, Me	NaphthEt, Me	(S)-6e	74	(S)-7e	^{a)}				
(R)-Ala(2cPent)	Me, cPent	NaphthEt, Me	(R)-6e	76	(R)-7e	^{a)}				
(S)-Leu(2Me)	ⁱ Bu, Me	NaphthEt, Me	(S)-6f	47	(S)-7f	28			(S)-13f	70
(R)-Leu(2Me)	Me, ⁱ Bu	NaphthEt, Me	(R)-6f	53	(R)-7f	35			(R)-13f	30
(S)-Phe(2Me)	Bn, Me	NaphthEt, Me	(S)-6g	25	(S)-7g	^{a)}			(S)-13g	73
		‘Prolinol’	(S)-6h	80						
(R)-Phe(2Me)	Me, Bn	NaphthEt, Me	(R)-6g	36	(R)-7g	^{a)}			(R)-13g	75
		‘Prolinol’	(R)-6h	59						

^{a)} Not isolated.

The C-terminal dipeptide H-Gln-Valol (**11**) was synthesized *via* coupling of the 4-nitrophenyl ester Z-Gln-ONp (**8**) with L-valinol (Valol, **9**) in CH₂Cl₂ and DMF (active-ester method; *Scheme 3*). The obtained Z-Gln-Valol (**10**) was deprotected by hydrogenolytic cleavage of the Z group (H₂, Pd/C) in MeOH at room temperature to give **11**. The coupling of the tripeptide acids **6** with **11** was carried out by using classical peptide coupling methods with *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) as the coupling reagent (*Table 2*).

Scheme 3

The conformations of the model peptides **2** were investigated in the crystalline state. For these studies, however, some of the peptides had to be modified by changing the N-terminal protecting group, because the Z-protected peptides did not crystallize very well. The 4-bromobenzoyl group proved to be very suitable for this purpose (*Scheme 4*). In a first step, the N-terminus of the pentapeptide **2** was deprotected by treating a solution of **2** in MeOH at room temperature with H₂ and Pd/C. After filtration over *Celite*, the deprotected pentapeptide **12** was reacted with 4-bromobenzoyl chloride in the presence of Et₃N in CH₂Cl₂ to give the new pentapeptide **13** (*Table 2*).

Scheme 4

2.2. Conformational Analysis of the Pentapeptides. The conformations of some model peptides **2** and **13**, respectively, were investigated in the solid state as well as in solution. X-Ray crystal-structure determinations were performed in the cases of **13a** (*p*BrBz-Leu-Aib-Aib-Gln-Valol), **13b** (*p*BrBz-Leu-Aib-Ac₅c-Gln-Valol), (*S*)-**2d** (Z-Leu-Aib-(*S*)-Val(2Me)-Gln-Valol), (*S*)-**2e** (Z-Leu-Aib-(*S*)-Ala(2cPent)-Gln-Valol), (*S*)-**13f** (*p*BrBz-Leu-Aib-(*S*)-Leu(2Me)-Gln-Valol), and (*S*)-**13g** (*p*BrBz-Leu-Aib-(*S*)-Phe(2Me)-Gln-Valol) (*Fig. 2*). All pentapeptides adopt a helical conformation stabilized by intramolecular H-bonds, which form two β-turns: N(10)–H and N(13)–H interact with the C=O O-atom that is seven atoms back along the peptide backbone. Each of these interactions has a graph set motif [21] of S(10).

Intermolecular H-bonds also link the molecules in each structure into infinite two-dimensional networks. In **13a**, N(1)–H and N(4)–H form intermolecular H-bonds with the carbonyl O-atom, O(12), and the hydroxy O-atom, O(15), respectively, at the

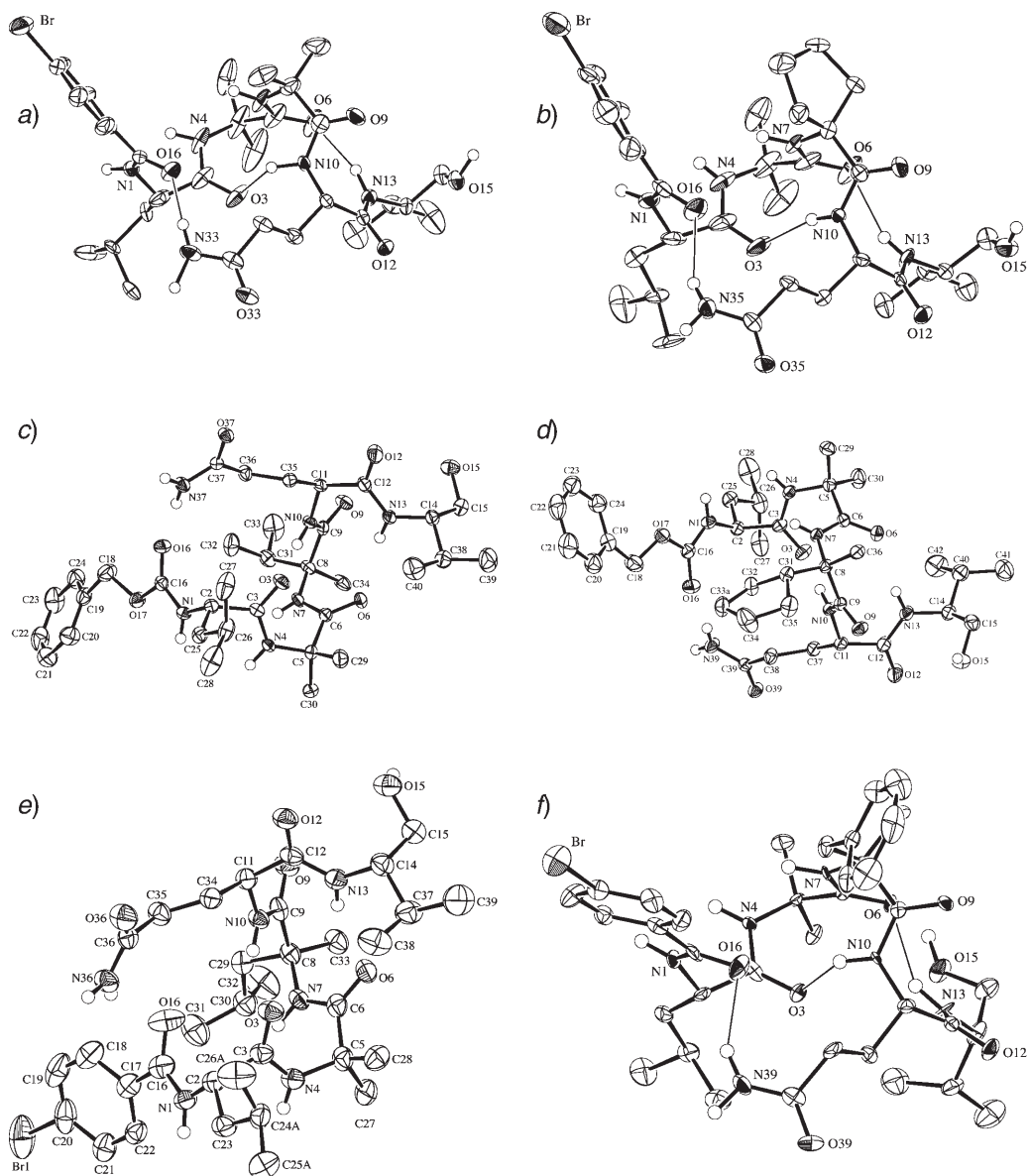


Fig. 2. ORTEP Plots [20] of the molecular structures of a) **13a** (*p*BrBz-Leu-Aib-Aib-Gln-Valol), b) **13b** (*p*BrBz-Leu-Aib-Ac₅c-Gln-Valol), c) (*S*)-**2d** (Z-Leu-Aib-(*S*)-Val(2Me)-Gln-Valol), d) (*S*)-**2e** (Z-Leu-Aib-(*S*)-Ala(2cPent)-Gln-Valol), e) one of the two symmetry-independent molecules of (*S*)-**13f** (*p*BrBz-Leu-Aib-(*S*)-Leu(2Me)-Gln-Valol), and f) (*S*)-**13g** (*p*BrBz-Leu-Aib-(*S*)-Phe(2Me)-Gln-Valol) (50% probability ellipsoids, arbitrary numbering of atoms; any solvent molecules and minor disorder components have been omitted for clarity)

opposite end of a neighboring molecule. These interactions link the peptide molecules into extended chains which run parallel to the $[1\ 0\ 1]$ direction, and which can be described by graph set motifs of $C(14)$. The OH group also forms an intermolecular H-bond with the amide O-atom, O(33), of the side chain at C(11) of a different neighboring peptide molecule, thereby linking the molecules into extended chains which run parallel to the $[1\ 0\ 0]$ direction, and which can be described by the $C(11)$ motif. The partial-occupancy H_2O molecule accepts a H-bond from N(7)–H and also donates a H-bond to O(33) in a different peptide molecule, thereby linking the peptide and H_2O molecules into extended chains which run parallel to the $[0\ 0\ 1]$ direction, and which have a $C_2^2(12)$ motif. The NH_2 group, N(33), of the amide side chain forms an intramolecular H-bond with the C=O O-atom, O(16) ($S(18)$ motif), and an intermolecular H-bond with O(9) from a neighboring molecule. This latter interaction links the molecules into extended chains which run parallel to the $[1\ 0\ 0]$ direction, and which can be described by the $C(9)$ motif. The combination of all intermolecular interactions links the molecules into infinite two-dimensional networks, which lie parallel to the $(0\ 1\ 0)$ plane.

The structure of **13b** exhibits the same pattern of H-bonding motifs and two-dimensional network to that described above for **13a**; except that with the absence of a H_2O molecule, N(7)–H is not involved in a H-bond.

For (*S*)-**2d**, the H-atoms of N(37) on the terminal amide side chain are involved in the same intra- and intermolecular interactions that were described for **13a** to give the $S(18)$ and $C(9)$ motifs. The remaining interactions, however, generate a different pattern: N(1)–H and N(4)–H form intermolecular H-bonds with the amide O-atom, O(37), of the terminal amide side chain of the same neighboring molecule. Each of these interactions links the molecules into extended chains which run parallel to the $[0\ 1\ 0]$ direction, and which can be described by graph set motifs of $C(16)$ and $C(13)$, respectively. The OH group also forms an intermolecular H-bond with the amide O-atom of the terminal amide side chain, but on a different neighboring molecule. This interaction links the molecules into extended chains which run parallel to the $[1\ 0\ 0]$ direction and have the $C(11)$ motif. N(7)–H forms an intermolecular H-bond with the OH O-atom of yet another neighboring molecule, but also links the molecules into extended chains which run parallel to the $[0\ 1\ 0]$ direction and have the $C(11)$ motif. The combination of all intermolecular interactions links the molecules into infinite two-dimensional networks, which lie parallel to the $(0\ 0\ 1)$ plane.

The structure of (*S*)-**2e** exhibits the same pattern of H-bonding motifs and two-dimensional network to that described above for (*S*)-**2d**.

The structure of (*S*)-**13f** has two molecules in the asymmetric unit, A and B. For the H-bonding, the molecules of type A interact amongst themselves, as do those of type B, and the patterns are identical with those described for **13b**, except for differences in the directionality of some chains. The chains involving N(1)–H and N(4)–H of molecule A, and those involving the corresponding atoms of molecule B, run parallel to the $[1\ 1\ 0]$ direction. The chains involving the OH group, as well as those involving the N–H group of the terminal amide side chain, run parallel to the $[0\ 1\ 0]$ and $[1\ 0\ 0]$ directions for molecules A and B, respectively. Considered overall, the intermolecular H-bonds link the molecules of (*S*)-**13f** into infinite two-dimensional layer networks, where each layer consists entirely of only one type of symmetry-independent molecule. Thus, layers

of H-bonded molecules **A** and layers of molecules **B** are stacked in an alternating fashion along the $[0\ 0\ 1]$ direction.

For (*S*)-**13g**, the NH_2 group, N(39), on the terminal amide side chain is involved in the same intra- and intermolecular interactions that were described for **13a** to give the usual S(18) and C(9) motifs. N(1)–H and N(7)–H form intermolecular H-bonds with, the amide O-atom of the side chain, O(39), and a C=O O-atom, O(12), respectively, in two different neighboring peptide molecules. These interactions link the molecules into extended chains which run parallel to the $[0\ 1\ 0]$ direction, and which can be described by graph set motifs of C(16) and C(8), respectively. N(4)–H interacts with O(43) of one of the two independent MeOH molecules, while O(43) is close enough to O(9) in a different peptide molecule to be donating a H-bond to the latter atom (the H-atoms of the solvent molecules could not be located). These interactions link the peptide and MeOH molecules into extended chains, which run parallel to the $[0\ 1\ 0]$ direction, and which can be described by a graph set motif of $\text{C}_2^2(10)$. The OH group, O(15)–H, forms an intermolecular H-bond with O(44) of the second MeOH molecule, but this solvent molecule does not appear to act as a H-bond donor. Considered overall, the intermolecular interactions combine to link the molecules into infinite two-dimensional networks, which lie parallel to the $(0\ 0\ 1)$ plane.

In Tables 3 and 4, the torsion angles ϕ_{i+1} , ψ_{i+1} , ϕ_{i+2} , and ψ_{i+2} of the β -turns are listed. The values show that two consecutive β -turns of type III/I are formed for **13a**, **13b**, (*S*)-**2d**, (*S*)-**2e**, and (*S*)-**13f**, whereas, in the case of (*S*)-**13g**, two β -turns of type III/III are observed. The III/III combination can be considered as an incipient 3_{10} -helix.

The results described above are in good agreement with previously reported results obtained for oligopeptides that contain Aib [23–29], Ac_5c [14][30][31], Val(2Me) [32], Leu(2Me) [33], and Phe(2Me) [34–36].

Table 3. Torsion Angles of the First β -Turn (amino acids i , $i+1$, $i+2$, and $i+3$)

	ϕ_{i+1} [°]	ψ_{i+1} [°]	ϕ_{i+2} [°]	ψ_{i+2} [°]	Type of β -turn
13a	–56.7(6)	–42.7(6)	–57.0(6)	–31.5(5)	III
13b	–54.9(7)	–40.2(7)	–58.2(7)	–32.3(6)	III
(<i>S</i>)- 2d	–49.6(2)	–44.6(1)	–58.9(1)	–24.9(1)	III
(<i>S</i>)- 2e	–51.3(2)	–43.3(2)	–60.1(2)	–23.1(2)	III
(<i>S</i>)- 13f , mol. A	–54.8(4)	–43.1(3)	–62.7(3)	–26.5(3)	III
(<i>S</i>)- 13f , mol. B	–54.3(4)	–42.9(4)	–59.7(4)	–28.6(4)	III
(<i>S</i>)- 13g	–53.2(6)	–44.2(6)	–54.6(7)	–37.1(7)	III

Table 4. Torsion Angles of the Second β -Turn (amino acids $i+1$, $i+2$, $i+3$, and $i+4$)

	ϕ_{i+2} [°]	ψ_{i+2} [°]	ϕ_{i+3} [°]	ψ_{i+3} [°]	Type of β -turn
13a	–57.0(6)	–31.5(5)	–78.7(5)	–4.0(5)	I
13b	–58.2(7)	–32.3(6)	–78.3(6)	–5.0(7)	I
(<i>S</i>)- 2d	–58.9(1)	–24.9(1)	–77.1(1)	–1.0(2)	I
(<i>S</i>)- 2e	–60.1(2)	–23.1(2)	–76.8(2)	–2.0(2)	I
(<i>S</i>)- 13f , mol. A	–62.7(3)	–26.5(3)	–75.6(3)	–9.3(4)	I
(<i>S</i>)- 13f , mol. B	–59.7(4)	–28.6(4)	–76.8(4)	–8.3(4)	I
(<i>S</i>)- 13g	–54.6(7)	–37.1(7)	–71.7(7)	–28.1(8)	III

The conformation of the model peptide (*S*)-**2g** was also investigated in solution by means of NMR techniques. An easy way is the observation of the signals of the amide H-atoms under different conditions. Their chemical shifts show a significantly different behavior when they are involved in an intramolecular H-bond, than when exposed to the solvent or forming intermolecular H-bonds. Intramolecularly bound NH atoms are much less influenced by temperature changes [14] or by addition of polar solvents or radicals [37].

For (*S*)-**2g**, the ^1H -NMR spectra were measured at different temperatures. Although it was not possible to assign every signal in the NMR spectrum, two strongly temperature-dependent NH signals were detected, *i.e.*, the signals for the amide H-atoms of Leu and Aib, which are not involved in the H-bonding pattern of the incipient 3_{10} -helix. One other signal was also temperature-dependent, but to a much lesser extent, *i.e.*, one of the amide H-atoms of the Gln side chain. This result is in agreement with the X-ray crystal structure of (*S*)-**13g**, *i.e.*, the corresponding *p*BrBz-protected derivative of (*S*)-**2g**, where one amide H-atom of the Gln side chain is intramolecularly involved in a H-bond with the C=O group of the N-terminal-protecting *p*BrBz-group, and the other amide H-atom of the Gln side chain is exposed to the environment and should show a significant temperature dependence. All other amide H-atoms of (*S*)-**2g** did not show a significant temperature dependence (*Fig. 3*). The amide H-atom of Phe(2Me) could not be observed and is assumed to lie in the region of the aromatic H-atoms.

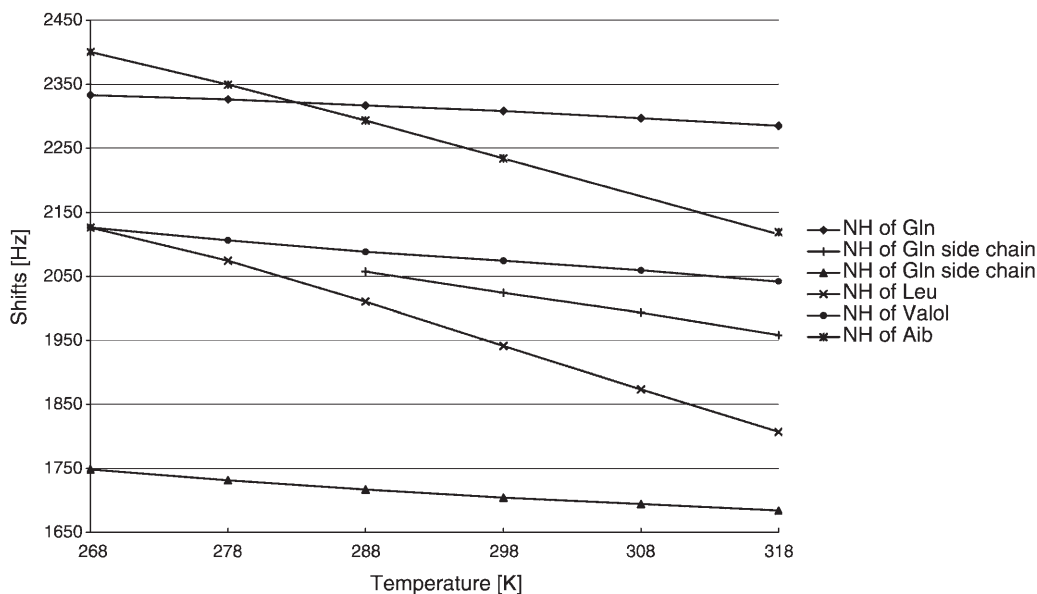


Fig. 3. Temperature dependence of the signals of the amide H-atoms of (*S*)-**2g**

As can be seen in *Fig. 3*, the temperature dependence of the amide H-atoms is linear. To compare the effects, the temperature coefficients were calculated and are listed in *Table 5*.

Table 5. *Temperature Coefficients of the Signals of the Amide H-Atoms of (S)-2g*

Amide Protons	[Hz/K]	[10 ⁻³ ppm/K]
NH of Leu	– 6.77	– 2.26
NH of Aib	– 5.54	– 1.85
NH of Phe(2Me)	not observed	not observed
NH of Gln	– 0.96	– 0.32
NH of Valol	– 1.53	– 0.51
NH(1) of Gln Side Chain	– 3.25	– 1.08
NH(2) of Gln Side Chain	– 1.27	– 0.42

As only the amide H-atoms of Leu and Aib, but not of Phe(2Me), Gln(2Me), and Valol are temperature-dependent, it is likely that the incipient 3_{10} -helix, which was observed for (S)-**13g** in the solid state, is also the dominant conformation in solution.

In conclusion, it has been shown that the model pentapeptides of the type Z-Leu-Aib-Xaa-Gln-Valol, with Xaa = 2,2-disubstituted glycine, can be prepared conveniently by the ‘azirine/oxazolone method’. They adopt a helical conformation in the solid state and in solution; the results from crystallographic and NMR investigations are in good agreement with each other.

We thank the analytical services of our institute for NMR and mass spectra, and for elemental analyses. Financial support by the *Swiss National Science Foundation*, *F. Hoffmann-La Roche AG*, Basel, the *Stiftung für wissenschaftliche Forschung an der Universität Zürich*, and the Prof. Dr. Hans E. Schmid-Stiftung is gratefully acknowledged. K. A. B. thanks the *Stipendienfonds der Basler Chemischen Industrie* for a scholarship.

Experimental Part

1. *General*. See [19]. ¹H- (600 MHz) and ¹³C-NMR (150.9 MHz) Spectra: Bruker AMX-600 instrument.

2. *Preparation of H-Gln-Valol (11)*. 2.1. *N-[(Benzyloxy)carbonyl]-glutaminyl-valinol (Z-Gln-Valol; 10)*. To a soln. of L-valinol (**9**; 0.66 g, 6.40 mmol) in abs. CH₂Cl₂ (50 ml), a soln. of Z-Gln-ONp (**8**; 2.83 g, 7.10 mmol) in abs. DMF (25 ml) was added slowly at 0°. After 6 h, the gel-like precipitate was diluted with CHCl₃ (25 ml) and stirred for 18 h at r.t.; then, additional CHCl₃ (50 ml) was added. After 2 h, the precipitate was filtered, and washed with AcOEt/CHCl₃ 1:1 and Et₂O. Recrystallization from EtOH yielded 1.717 g (73%) of **10**. Colorless crystals. M.p. 186.6–187.0°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.20. IR: 3430s, 3300s, 3200m, 3080w, 3060w, 2960m, 2930m, 2870m, 1680s, 1660s, 1645s, 1555s, 1535s, 1505m, 1470m, 1465m, 1445m, 1415m, 1390m, 1370m, 1350m, 1330m, 1260s, 1245s, 1190w, 1140w, 1060m, 1040m, 1020m, 995w, 940w, 910w, 880w, 855w, 770w, 745m. ¹H-NMR (CD₃OD): 7.35–7.3 (m, 5 arom. H); 5.08 (br. s, PhCH₂O); 4.14 (dd, *J* = 8.5, 5.8, CH(2) of Gln); 3.7–3.55 (m, CH(2) and CH₂(1) of Valol); 2.31 (t, *J* = 7.5, CH₂(4) of Gln); 2.15–1.8 (m, CH(3) of Valol, CH₂(3) of Gln); 0.93, 0.89 (2d, *J* = 6.8, 2 Me(4) of Valol). ¹³C-NMR (CD₃OD): 177.8 (s, CONH₂); 174.3 (s, CONH); 158.3 (s, OCONH); 138.1 (s, 1 arom. C); 129.4, 128.9, 128.8 (3d, 5 arom. CH); 67.6 (t, PhCH₂O); 63.0 (t, C(1) of Valol); 58.0, 56.0 (2d, C(2) of Gln, C(2) of Valol); 32.5 (t, C(4) of Gln); 30.0 (d, C(3) of Valol); 29.1 (t, C(3) of Gln); 19.9, 18.8 (2q, 2 Me(4) of Valol). ESI-MS (MeOH): 404 (31, [M + K]⁺), 388 (100, [M + Na]⁺). Anal. calc. for C₁₈H₂₇N₃O₅ (365.43): C 59.16, H 7.45, N 11.50; found: C 59.27, H 7.71, N 11.54.

2.2. *Glutaminyl-valinol (H-Gln-Valol; 11)*. A soln. of **10** (14.970 g, 40.97 mmol) and Pd/C (10% on activated charcoal, 0.550 g) in MeOH (950 ml) was treated with H₂ for 18 h at r.t. The mixture was filtered over *Celite*, and the filtrate was evaporated: 9.419 g (99%) of **11**. Colorless solid. M.p. 134.5–135.2°. IR: 3350s, 3280s, 3200s, 3110s, 2950s, 2930s, 2870m, 1690s, 1680s, 1670s, 1645s, 1630s, 1615s, 1565s, 1550s, 1515m, 1505m, 1465m, 1450m, 1415s, 1385m, 1370m, 1350m, 1335m, 1310m, 1280m, 1245m,

1200w, 1150m, 1080m, 1070m, 1025m, 975m, 950m, 875w, 845w, 815w, 780w, 770w, 715m. ¹H-NMR: 3.7–3.5 (m, CH₂(1) of Valol, CH(2) of Gln); 3.4–3.3 (m, CH(2) of Valol); 2.35–2.3 (m, CH₂(4) of Gln); 2.0–1.75 (m, CH₂(3) of Gln, CH(3) of Valol); 0.96, 0.93 (2d, *J* = 6.9, 6.8, 2 Me of Valol). ¹³C-NMR: 178.3, 177.1 (2s, CONH₂, CONH); 63.0 (t, C(1) of Valol); 57.9, 55.7 (2d, C(2) of Gln, C(2) of Valol); 32.7, 32.5 (2t, C(3), C(4) of Gln); 30.0 (d, C(3) of Valol); 19.8, 18.8 (2q, 2 Me of Valol). CI-MS (NH₃): 233 (11), 232 (100, [*M* + 1]⁺), 229 (10), 215 (20), 214 (12), 129 (5), 104 (7), 101 (6).

3. Peptides with Xaa = Aib. 3.1. Benzyl [(S)-1-([1,1-Dimethyl-2-([1,1-dimethyl-2-[methyl(phenyl)-amino]-2-oxoethyl]amino)-2-oxoethyl]amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-Aib-N(Me)Ph; **3a**). To a soln. of N-[(Benzyloxy)carbonyl]leucyl-α-aminoisobutyric acid (Z-Leu-Aib-OH [19]; **5**, 1.152 g, 3.29 mmol) in abs. CH₂Cl₂ (25 ml), 2,2,N-trimethyl-N-phenyl-2H-azirin-3-amine (**1a** [38]; 0.610 g, 3.50 mmol) was added at 0°. The soln. was stirred for 23 h at r.t. The mixture was washed with 2N HCl, 1N NaOH soln., and sat. aq. NaCl soln., dried (MgSO₄), and evaporated: 1.645 g (95%) of **3a**. Colorless solid. M.p. 57.1–57.8°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.51; *R*_f (CH₂Cl₂/MeOH 20:1) 0.18. IR: 3310s, 3060m, 3030m, 2955s, 2870m, 2140w, 1950w, 1880w, 1820w, 1705vs, 1690vs, 1680vs, 1660vs, 1640vs, 1595s, 1540–1520vs, 1495vs, 1470s, 1455s, 1390s, 1365s, 1315m, 1265–1240s, 1220s, 1170m, 1120m, 1090s, 1070m, 1045m, 1030m, 1005w, 965w, 920w, 910w, 875w, 840w, 825w, 770m, 740m, 705s. ¹H-NMR (CD₃OD): 7.4–7.2 (m, 10 arom. H); 5.15, 5.09 (AB, *J* = 12.8, PhCH₂O); 4.00 (t, *J* = 7.5, CH(2) of Leu); 3.25 (br. s, MeN); 1.7–1.65 (m, CH(4) of Leu); 1.55–1.5 (m, CH₂(3) of Leu); 1.47, 1.44, 1.41, 1.38 (4s, 4 Me of 2 Aib); 0.96, 0.93 (2d, *J* = 6.7, 6.5, 2 Me of Leu). ¹³C-NMR (CD₃OD): 176.2, 175.6, 175.2 (3s, 3 CONH); 158.8 (s, OCONH); 146.9 (s, 1 arom. CN); 138.5 (s, 1 arom. C); 130.4, 129.7, 129.1, 128.5 (4d, 10 arom. CH); 67.6 (t, PhCH₂O); 58.7, 58.2 (2s, 2 C(2) of 2 Aib); 55.7 (d, C(2) of Leu); 41.6 (t, C(3) of Leu); 41.3 (q, MeN); 26.6, 26.4, 26.0, 24.7 (d, 3q, C(4) of Leu, 4 Me of 2 Aib); 23.4, 22.4 (2q, 2 Me of Leu). ESI-MS (NaI): 547 (100, [*M* + Na]⁺). Anal. calc. for C₂₉H₄₀N₄O₅ · H₂O (530.67): C 65.64, H 7.72, N 10.56; found: C 65.90, H 7.56, N 10.73.

3.2. N-[(Benzyloxy)carbonyl]leucyl-α-aminoisobutyryl-α-aminoisobutyric Acid (Z-Leu-Aib-Aib-OH; **6a**). A soln. of **3a** (1.373 g, 2.62 mmol) in 3N HCl (THF/H₂O 1:1, 40 ml) was stirred for 2 h at r.t. Thereby, a colorless precipitate was formed. Then, 2N HCl (40 ml) was added, and the mixture was extracted with CH₂Cl₂. During this operation, the precipitate dissolved. The org. soln. was dried (MgSO₄) and evaporated. Washing of the residue with AcOEt yielded 1.005 g (88%) of **6a**. Colorless solid. M.p. 192–193°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.18–0.07. IR: 3385m, 3330s, 3290s, 3060w, 3030w, 2980w, 2950m, 2865w, 1740s, 1705vs, 1660s, 1550m, 1525s, 1500m, 1470w, 1455w, 1440w, 1385m, 1365w, 1315s, 1295m, 1270s, 1245s, 1220m, 1175w, 1130w, 1120w, 1080w, 1045m, 1030w, 990w, 970w, 945w, 910w, 850w, 785w, 765w, 755w, 740w, 730w. ¹H-NMR (CD₃OD): 7.35–7.25 (m, 5 arom. H); 5.13, 5.08 (AB, *J* = 12.6, PhCH₂O); 4.02 (t, *J* = 7.5, CH(2) of Leu); 1.7–1.65 (m, CH(4) of Leu); 1.52 (dd, *J* = 7.8, 7.2, CH₂(3) of Leu); 1.44, 1.43, 1.42, 1.40 (4s, 4 Me of 2 Aib); 0.96, 0.93 (2d, *J* = 6.5, 2 Me of Leu). ¹³C-NMR (CD₃OD): 178.0, 175.9, 175.1 (3s, COOH, 2 CONH); 158.7 (s, OCONH); 138.3 (s, 1 arom. C); 129.5, 129.0, 128.6 (3d, 5 arom. CH); 67.6 (t, PhCH₂O); 57.9, 57.1 (2s, 2 C(2) of 2 Aib); 55.5 (d, C(2) of Leu); 41.5 (t, C(3) of Leu); 25.9 (d, C(4) of Leu); 26.1, 25.5, 24.7, 24.6, 23.3, 22.2 (6q, 4 Me of 2 Aib, 2 Me of Leu). ESI-MS (NaI): 458 (100, [*M* + Na]⁺). Anal. calc. for C₂₂H₃₃N₃O₆ (435.51): C 60.67, H 7.64, N 9.65; found: C 60.55, H 7.63, N 9.59.

3.3. N-[(Benzyloxy)carbonyl]leucyl-α-aminoisobutyryl-α-aminoisobutyryl-glutaminyl-valinol (Z-Leu-Aib-Aib-Gln-Valol; **2a**). To a soln. of **6a** (100 mg, 0.230 mmol) and Et₃N (70 mg, 0.690 mmol) in abs. DMF (2.5 ml) at r.t., HATU (87 mg, 0.230 mmol) was added. After 5 min, HOBt (35 mg, 0.23 mmol), and after a further 5 min, **11** (53 mg, 0.230 mmol) was added, and the mixture was stirred for 19 h at r.t. and evaporated. The residue was dissolved in AcOEt, washed with 1N HCl and 1N NaOH soln., dried (MgSO₄), and evaporated. Recrystallization from AcOEt/hexane yielded 114 mg (77%) **2a**. Colorless crystals. M.p. 170–172°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.16. IR: 3310s, 3030w, 2960m, 2870w, 1655vs, 1535s, 1470w, 1455w, 1385w, 1365w, 1335w, 1310w, 1265m, 1230w, 1170w, 1120w, 1040w, 1030w, 925w, 850w, 790w, 740w. ¹H-NMR (CD₃OD): 7.92 (d, *J* = 6.9, NH); 7.46 (s, NH); 7.35–7.25 (m, 5 arom. H); 5.13, 5.10 (AB, *J* = 12.7, PhCH₂O); 4.15–4.05 (m, CH(2) of Gln, CH(2) of Leu); 3.7–3.65 (m, CH(2) and CH₂(1) of Valol); 2.4–2.35 (m, CH₂(4) of Gln); 2.25–2.2 (m, CH₂(3) of Gln); 1.9–1.85 (m, CH(3) of Valol); 1.75–1.7 (m, CH(4) of Leu); 1.6–1.55 (m, CH₂(3) of Leu); 1.4–1.35 (m, 4 Me of 2 Aib); 1.0–0.9 (m, 2 Me of Leu, 2 Me of Valol). ¹³C-NMR (CD₃OD): 177.9, 177.8, 176.8, 176.1, 174.4 (5s, CONH₂,

4 CONH); 158.9 (s, OCONH); 138.4 (s, 1 arom. C); 129.6, 129.0, 128.6 (3d, 5 arom. CH); 67.8 (t, PhCH₂O); 63.6 (t, C(1) of Valol); 58.6 (d, C(2) of Gln); 58.0, 57.8 (2s, 2 C(2) of 2 Aib); 56.2, 55.9 (2d, C(2) of Valol, C(3) of Leu); 41.4 (t, C(3) of Leu); 33.5 (t, C(4) of Gln); 30.1 (d, C(3) of Valol); 28.5 (t, C(3) of Gln); 25.9 (d, C(4) of Leu); 26.9, 25.8, 24.6, 24.2, 23.3, 22.2 (6q, 4 Me of 2 Aib, 2 Me of Leu); 20.1, 19.4 (2q, 2 Me of Valol). ESI-MS (MeOH): 687 (25, [M + K]⁺), 672 (94, [M + Na]⁺), 650 (100, [M + 1]⁺). Anal. calc. for C₃₂H₅₂N₆O₈ · H₂O (666.82): C 57.64, H 8.01, N 12.60; found: C 57.38, H 7.97, N 12.24.

3.4. N-[(S)-1-[(2-[(S)-4-Amino-1-[(S)-1-(hydroxymethyl)-2-methylpropyl]amino)carbonyl]-4-oxobutyl]amino]-1,1-dimethyl-2-oxoethyl]amino]-1,1-dimethyl-2-oxoethyl]amino)carbonyl]-3-methylbutyl]-4-bromobenzamide (pBrBz-Leu-Aib-Aib-Gln-Valol; **13a**). A soln. of **2a** (71 mg, 0.109 mmol) and Pd/C (10% on activated charcoal, 7 mg) in MeOH (5 ml) was treated with H₂ for 1.5 h at r.t. The mixture was filtered over cotton wool, and the filtrate was evaporated. The residue (58 mg) was dissolved in CH₂Cl₂ (5 ml), and Et₃N (30 mg, 0.297 mmol) and 4-bromobenzoyl chloride (35 mg, 0.159 mmol) were added. A precipitate formed while stirring for 30 min at r.t. The mixture was washed with 2N HCl and 1N NaOH. The precipitate dissolved after addition of a small amount of MeOH. The org. soln. was dried (MgSO₄) and evaporated. The residue (59 mg, 78%, **13a**) was recrystallized from MeOH, CH₂Cl₂, Et₂O, and petroleum ether. Colorless crystals. M.p. 232.9–233.8°. R_f (CH₂Cl₂/MeOH 10:1) 0.15. IR: 3650w, 3420s, 3340vs, 3280vs, 3060w, 2980m, 2980s, 2960s, 2870m, 2540w, 2490w, 2440w, 2400w, 1675vs, 1660vs, 1650vs, 1595s, 1540vs, 1485s, 1465s, 1455s, 1440s, 1415m, 1390s, 1365s, 1340m, 1300s, 1235m, 1200m, 1175m, 1140m, 1070m, 1010m, 980w, 940w, 925w, 900w, 870w, 860w, 825w, 790w, 765w. ¹H-NMR (CD₃OD): 7.81, 7.62 (AA'BB', J = 8.5, 4 arom. H); 4.55–4.5 (m, CH(2) of Gln); 4.15–4.1 (m, CH(2) of Leu); 3.62 (br. s, CH₂(1) and CH(2) of Valol); 2.35–2.3 (m, CH₂(4) of Gln); 2.25–2.0 (m, CH₂(3) of Gln); 1.85–1.65 (m, CH(3) of Valol, CH(4) and CH₂(3) of Leu); 1.45–1.4 (m, 4 Me of 2 Aib); 1.01, 0.99, 0.87, 0.79 (4d, J = 5.9, 6.0, 6.7, 6.8, 2 Me of Leu, 2 Me of Valol). ¹³C-NMR (CD₃OD): 178.0, 177.8, 176.9, 175.6, 174.3 (5s, CONH₂, 4 CONH); 169.6 (s, 1 CO (amide, pBrBz)); 134.0 (s, 1 arom. C); 132.8, 130.6 (2d, 4 arom. CH); 127.4 (s, 1 arom. CBr); 63.5 (t, C(1) of Valol); 58.6 (d, C(2) of Gln); 58.1, 57.9 (2s, 2 C(2) of 2 Aib); 56.1, 54.5 (2d, C(2) of Valol, C(2) of Leu); 41.2 (t, C(3) of Leu); 33.6 (t, C(4) of Gln); 30.0 (d, C(3) of Valol); 26.6 (t, C(3) of Gln); 26.1 (d, C(4) of Leu); 28.5, 25.3, 25.1, 24.6, 23.4, 22.1 (6q, 4 Me of 2 Aib, 2 Me of Leu); 20.1, 19.3 (2q, 2 Me of Valol). ESI-MS (TFA): 737 (6, [M + K]⁺, ⁸¹Br), 721 (39, [M + Na]⁺, ⁸¹Br), 699 (100, [M + 1]⁺, ⁸¹Br), 681 (13, [M – OH]⁺, ⁸¹Br), 596 (18, [M – Valol]⁺, ⁸¹Br), 468 (15, [M – Gln-Valol]⁺, ⁸¹Br). Anal. calc. for C₃₁H₄₉BrN₆O₇ (697.67): C 53.37, H 7.08, N 12.05; found: C 53.26, H 7.12, N 11.99.

Crystals suitable for an X-ray crystal-structure determination were obtained from a mixture of MeOH, CH₂Cl₂, Et₂O, and petroleum ether by slow evaporation of the solvent.

4. Peptides with Xaa = Ac₅c. 4.1. Benzyl [(S)-1-[(1,1-Dimethyl-2-[(1-[(methyl(phenyl)amino)carbonyl]cyclopentyl]amino)-2-oxoethyl]amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-Ac₅c-N(Me)Ph; **3b**). As described for **3a**, with **5** [19] (0.705 g, 2.01 mmol) in abs. CH₂Cl₂ (20 ml) and N-methyl-N-phenyl-1-azaspiro[2.4]hept-1-en-2-amine (**1b** [39]; 0.439 g (containing 12.5% amide), 1.92 mmol): 1.030 g (97%) of **3b**. Colorless solid. M.p. 67.7–69.1°. R_f (CH₂Cl₂/MeOH 10:1) 0.52; R_f (CH₂Cl₂/MeOH 20:1) 0.16. IR: 3310s, 3060m, 3030m, 2955s, 2870m, 1950w, 1810w, 1705vs, 1660vs, 1595s, 1520vs, 1495vs, 1470s, 1455s, 1380s, 1310m, 1260vs, 1220s, 1170m, 1120m, 1045s, 1030m, 1005w, 985w, 955w, 910w, 840w, 765m, 735m, 700s. ¹H-NMR (CD₃OD): 7.4–7.2 (m, 10 arom. H); 5.13, 5.11 (AB, J = 12.8, PhCH₂O); 4.00 (t, J = 7.5, CH₂(2) of Leu); 3.22 (br. s, MeN); 2.4–2.35, 2.3–2.2, 2.2–1.95 (3m, 4 H of Ac₅c); 1.75–1.65 (m, CH(4) of Leu, 4 H of Ac₅c); 1.6–1.5 (m, CH₂(3) of Leu); 1.47, 1.40 (2s, 2 Me of Aib); 0.96, 0.93 (2d, J = 6.6, 2 Me of Leu). ¹³C-NMR (CD₃OD): 176.3, 175.6, 175.3 (3s, 3 CONH); 159.0 (s, OCONH); 147.0 (s, 1 arom. CN); 138.6 (s, 1 arom. C); 130.5, 129.8, 129.3, 128.7, 128.5, 128.3 (6d, 10 arom. CH); 68.8 (s, C(2) of Ac₅c); 67.8 (t, PhCH₂O); 58.4 (s, C(2) of Aib); 55.8 (d, C(2) of Leu); 41.7 (t, C(3) of Leu); 41.1 (q, MeN); 38.7, 38.2 (2t, 2 C(3) of Ac₅c); 26.1 (d, C(4) of Leu); 25.7, 25.6 (2t, 2 C(4) of Ac₅c); 26.8, 24.9, 23.5, 22.5 (4q, 2 Me of Aib, 2 Me of Leu). ESI-MS (NaI): 573 (100, [M + Na]⁺). Anal. calc. for C₃₁H₄₂N₄O₅ · 0.33 H₂O (556.71): C 66.88, H 7.72, N 10.06; found: C 67.12, H 7.64, N 10.02.

4.2. 1-[(2-[(S)-2-[(Benzyloxy)carbonyl]amino]-4-methyl-1-oxopentyl]amino)-2-methyl-1-oxopropyl]amino)cyclopentane-1-carboxylic Acid (Z-Leu-Aib-Ac₅c-OH; **6b**). As described for **6a**, with **3b** (750 mg, 1.36 mmol), 3N HCl (THF/H₂O 1:1, 30 ml), 2.5 h at r.t., 2N HCl (15 ml), recrystallization from AcOEt/hexane: 566 mg (90%) of **6b**. Colorless crystals. M.p. 175.0–176.5°. R_f (CH₂Cl₂/MeOH 10:1)

0.13. IR: 3300s, 3060m, 3030m, 2955s, 2870m, 1740s, 1720vs, 1695vs, 1660vs, 1590w, 1530vs, 1470m, 1455s, 1410m, 1390m, 1365m, 1345m, 1330m, 1315m, 1250s, 1175m, 1120m, 1050m, 1030m, 1005w, 950w, 910w, 770w, 735m. ¹H-NMR (CD₃OD): 7.49 (br. s, NH); 7.35–7.3 (m, 5 arom. H); 5.15–5.05 (m, PhCH₂O); 4.02 (t, *J* = 7.5, CH(2) of Leu); 2.25–2.0 (m, 4 H of Ac₃c); 1.7–1.65 (m, CH(4) of Leu, 4 H of Ac₃c); 1.52 (dd, *J* = 7.5, 6.2, CH₂(3) of Leu); 1.43 (br. s, 2 Me of Aib); 0.96, 0.93 (2d, *J* = 6.7, 2 Me of Leu). ¹³C-NMR (CD₃OD): 177.8, 176.4, 175.0 (3s, COOH, 2 CONH); 158.7 (s, OCONH); 138.2 (s, 1 arom. C); 129.5, 129.1, 128.7 (3d, 5 arom. CH); 67.7 (t, PhCH₂O); 67.3 (s, C(2) of Ac₃c); 57.8 (s, C(2) of Aib); 55.5 (d, C(2) of Leu); 41.5 (t, C(3) of Leu); 38.1, 37.7 (2t, 2 C(3) of Ac₃c); 25.9 (d, C(4) of Leu); 25.6 (t, 2 C(4) of Ac₃c); 26.0, 24.7, 23.3, 22.2 (4q, 2 Me of Aib, 2 Me of Leu). ESI-MS (NaI): 506 (4, [*M* + 2 Na – 1]⁺), 484 (100, [*M* + Na]⁺). Anal. calc. for C₂₄H₃₅N₃O₆ · 0.33 H₂O (467.57): C 61.65, H 7.69, N 8.99; found: C 61.95, H 7.52, N 9.03.

4.3. Benzyl ((*S*)-1-[(2-[[1-[(*S*)-4-Amino-1-[(*S*)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-4-oxobutyl]amino]carbonyl)cyclopentyl]amino)-1,1-dimethyl-2-oxoethyl]amino]carbonyl]-3-methylbutyl]carbamate (*Z*-Leu-Aib-Ac₃c-Gln-Valol; **2b**). A soln. of **6b** (239 mg, 0.518 mmol) and Et₃N (108 mg, 1.069 mmol) in abs. DMF (3.5 ml) was stirred for 10 min at 0°, then, HATU (217 mg, 0.571 mmol) was added. After stirring at 0° for 8 min, **11** (132 mg, 0.57 mmol) was added, and the mixture was stirred for 90 min at 0° and 40 h at r.t. The solvent was evaporated, the residue dissolved in AcOEt and a small amount of MeOH, washed with 2N HCl and 1N NaOH soln., dried (MgSO₄), and evaporated. CC (CH₂Cl₂/MeOH 10:1) yielded 304 mg (87%) of **2b**. Colorless solid. M.p. 97.6–98.1°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.17. IR: 3300s, 3035w, 2960m, 2870w, 1665vs, 1535s, 1470m, 1455m, 1405w, 1390m, 1365w, 1315m, 1270m, 1220m, 1170w, 1130w, 1120w, 1045w, 1030w, 960w, 925w, 910w, 890w, 850w, 820w, 790w, 740w. ¹H-NMR (CD₃OD): 7.35–7.25 (m, 5 arom. H); 5.16, 5.11 (AB, *J* = 12.7, PhCH₂O); 4.16 (t, *J* = 7.3, CH(2) of Gln); 4.02 (t, *J* = 7.5, CH(2) of Leu); 3.7–3.6 (m, CH(2) and CH₂(1) of Valol); 2.4–2.3 (m, CH₂(4) of Gln, CH(3) of Valol); 2.25–2.15 (m, CH₂(3) of Gln); 2.0–1.85 (m, 4 H of Ac₃c); 1.75–1.55 (m, 4 H of Ac₃c, CH(4) and CH₂(3) of Leu); 1.40, 1.38 (2s, 2 Me of Aib); 1.0–0.9 (m, 2 Me of Leu, 2 Me of Valol). ¹³C-NMR (CD₃OD): 177.8, 177.4, 177.2, 176.1, 174.4 (5s, CONH₂, 4 CONH); 159.1 (s, OCONH); 138.4 (s, 1 arom. C); 129.6, 129.0, 128.4 (3d, 5 arom. CH); 68.1 (s, C(2) of Ac₃c); 67.8 (t, PhCH₂O); 63.6 (t, C(1) of Valol); 58.5 (d, C(2) of Gln); 57.8 (s, C(2) of Aib); 56.2, 56.1 (2d, C(2) of Leu, C(2) of Valol); 41.3, 38.8, 37.4 (3t, C(3) of Leu, 2 C(3) of Ac₃c); 33.4 (t, C(4) of Gln); 30.1 (d, C(3) of Valol); 28.5 (t, C(3) of Gln); 25.9 (d, C(4) of Leu); 25.7, 25.6 (2t, 2 C(4) of Ac₃c); 24.7, 23.2, 22.4 (3q, 2 Me of Aib, 2 Me of Leu); 20.1, 19.4 (2q, 2 Me of Valol). ESI-MS (TFA): 698 (20, [*M* + Na]⁺), 675 (100, [*M* + 1]⁺), 657 (15, [*M* – OH]⁺), 572 (19, [*M* – Valol]⁺), 444 (22, [*M* – Gln-Valol]⁺). Anal. calc. for C₃₄H₅₄N₈O₈ · 0.5 H₂O (683.85): C 59.72, H 8.11, N 12.29; found: C 59.48, H 8.20, N 12.28.

4.4. N-((*S*)-1-[(2-[[1-[(*S*)-4-Amino-1-[(*S*)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-4-oxobutyl]amino]carbonyl)cyclopentyl]amino)-1,1-dimethyl-2-oxoethyl]amino]carbonyl]-3-methylbutyl]-4-bromobenzamide (pBrBz-Leu-Aib-Ac₃c-Gln-Valol; **13b**). As described for **13a**, with **2b** (83 mg, 0.123 mmol), Pd/C (10% on activated charcoal, 9 mg), MeOH (5 ml), and H₂, 2 h at r.t., filtration over Celite, with CH₂Cl₂ (5 ml), Et₃N (18 mg, 0.178 mmol), 4-bromobenzoyl chloride (27 mg, 0.123 mmol), 1.5 h at r.t.; purification with CC (CH₂Cl₂/MeOH 10:1): 76 mg (85%) of **13b**. Colorless solid. M.p. 242.8–243.6°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.18. IR: 3405s, 3340vs, 3250s, 3060w, 2960s, 2875m, 1675vs, 1655vs, 1590s, 1540vs, 1485s, 1470m, 1455s, 1440m, 1410m, 1390m, 1360m, 1340m, 1315m, 1295m, 1255m, 1220m, 1180m, 1170m, 1150w, 1140w, 1130w, 1110w, 1095w, 1070w, 1020w, 1010m, 980w, 940w, 920w, 870w, 850w, 820w, 790w, 760w. ¹H-NMR (CD₃OD): 7.82, 7.63 (AA'BB', *J* = 8.4, 8.5, 4 arom. H); 4.5–4.45 (m, CH(2) of Gln); 4.15–4.1 (m, CH(2) of Leu); 3.65–3.55 (m, CH(2) and CH₂(1) of Valol); 2.35–2.3 (m, CH₂(4) of Gln); 2.3–2.0 (m, CH₂(3) of Gln, CH(3) of Valol, 2 H of Ac₃c); 1.9–1.85 (m, CH(4) of Leu); 1.85–1.65 (m, CH₂(3) of Leu, 6 H of Ac₃c); 1.43 (s, 2 Me of Aib); 1.02, 0.99, 0.86, 0.78 (4d, *J* = 6.0, 6.2, 6.8, 6.8, 2 Me of Leu, 2 Me of Valol). ¹³C-NMR (CD₃OD): 177.8, 177.4, 177.2, 175.7, 174.2 (5s, CONH₂, 4 CONH); 169.8 (s, 1 CO (amide, pBrBz)); 133.9 (s, 1 arom. C); 132.8, 130.6 (2d, 4 arom. CH); 127.5 (s, 1 arom. CBr); 68.2 (s, C(2) of Ac₃c); 63.5 (t, C(1) of Valol); 58.4 (d, C(2) of Gln); 57.9 (s, C(2) of Aib); 55.9, 55.0 (2d, C(2) of Leu, C(2) of Valol); 41.0, 38.5, 37.8 (3t, C(3) of Leu, 2 C(3) of Ac₃c); 33.4 (t, C(4) of Gln); 30.0 (d, C(3) of Valol); 28.3 (t, C(3) of Gln); 26.1 (d, C(4) of Leu); 25.7 (t, 2 C(4) of Ac₃c); 25.7, 25.3, 23.3, 22.3 (4q, 2 Me of Aib, 2 Me of Leu); 20.0, 19.3 (2q, 2 Me of Valol). ESI-MS (TFA): 763 (6, [*M* + K]⁺, ⁸¹Br), 745 (35, [*M* + Na]⁺, ⁸¹Br), 725 (100, [*M* + 1]⁺, ⁸¹Br), 707 (22, [*M* – OH]⁺, ⁸¹Br), 622

(31, $[M - \text{Valol}]^+$, ^{81}Br), 494 (33, $[M - \text{Gln-Valol}]^+$, ^{81}Br). Anal. calc. for $\text{C}_{33}\text{H}_{51}\text{N}_6\text{O}_7$: C 54.77, H 7.10, N 11.61; found: C 54.49, H 7.20, N 11.76.

Recrystallization from AcOEt, MeOH, and petroleum ether gave crystals suitable for an X-ray crystal-structure determination.

5. *Tripeptide with (S)-Iva*. N-[(Benzyloxy)carbonyl]leucyl- α -aminoisobutyryl-(S)-isovaline (Z-Leu-Aib-(S)-Iva-OH; (S)-**6c**). A soln. of (S)-**3c** [19] (438 mg, 0.710 mmol) in 3N HCl (MeCN/H₂O 1:1, 10 ml) was stirred for 3 h at 60°. The mixture was extracted with CH₂Cl₂, dried (MgSO₄), and evaporated. Prep. TLC (CH₂Cl₂/MeOH 10:1) yielded 118 mg (37%) of (S)-**6c** and 98 mg (30%) of benzyl [(S)-1-([1,1-dimethyl-2-((S)-1-methyl-1-[(methylamino)carbonyl]propyl)amino)-2-oxoethyl]-amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(S)-Iva-NHMe; (S)-**7c**).

Data of (S)-**6c**. Colorless solid. M.p. 78–80°. R_f (CH₂Cl₂/MeOH 10:1) 0.06. IR: 3320m, 2960m, 1710s, 1660s, 1525s, 1455m, 1385m, 1365w, 1315w, 1245m, 1165m, 1130w, 1050m, 945w, 800w, 780w, 740w, 700w. ¹H-NMR: 7.35–7.3 (m, 5 arom. H); 7.18 (br. s, NH); 7.08 (br. s, NH); 5.75 (d, $J = 5.7$, NH of Leu); 5.10 (br., PhCH₂O); 4.15–4.1 (m, CH(2) of Leu); 2.05–1.9 (m, CH₂(3) of Iva or Leu); 1.7–1.5 (m, CH₂(3) of Leu or Iva, Me(3) of Iva, 2 Me of Aib, CH(4) of Leu); 0.95–0.9 (m, 2 Me of Leu); 0.82 (t, $J = 7.4$, MeCH₂ of Iva). ¹³C-NMR: 173.8, 172.9 (2s, 2 CONH, COOH); 156.7 (s, OCONH); 136.0 (s, 1 arom. C); 128.5, 128.2, 127.8 (3d, 5 arom. CH); 67.1 (t, PhCH₂O); 60.3, 57.2 (2s, C(2) of Iva, C(2) of Aib); 54.3 (d, C(2) of Leu); 40.7, 29.1 (2t, C(3) of Leu, C(3) of Iva); 24.6 (d, C(4) of Leu); 25.1, 22.8, 22.0, 21.7, 8.0 (5q, 2 Me of Aib, Me(3) of Iva, Me(4) of Iva, 2 Me of Leu). ESI-MS (MeOH): 504 (15, $[M + \text{Na} + \text{MeOH}]^+$), 488 (50, $[M + \text{K}]^+$), 472 (62, $[M + \text{Na}]^+$), 450 (100, $[M + 1]^+$), 432 (14, $[M - \text{OH}]^+$), 333 (10, $[M - \text{Iva}]^+$). Anal. calc. for $\text{C}_{23}\text{H}_{35}\text{N}_3\text{O}_6$ (449.55): C 61.45, H 7.85, N 9.35; found: C 61.58, H 7.65, N 9.34.

Data of (S)-**7c**. Colorless solid. M.p. 204–205°. R_f (CH₂Cl₂/MeOH 10:1) 0.43. IR: 3385m, 3314s, 3017w, 2969m, 2871w, 1703vs, 1648vs, 1523vs, 1462m, 1442w, 1410w, 1385w, 1372w, 1362w, 1341w, 1312w, 1291w, 1271w, 1243s, 1216m, 1175w, 1134w, 1118w, 1083w, 1047m, 1030w, 969w, 944w, 916w, 846w, 804w, 790w, 749w, 737w, 699w, 670w, 630w. ¹H-NMR (CD₃OD): 7.35–7.3 (m, 5 arom. H); 5.07 (s, PhCH₂O); 4.04 (dd, $J = 8.9, 6.1$, CH(2) of Leu); 2.69 (s, MeN); 2.2–2.05, 1.85–1.65, 1.65–1.45 (3m, CH₂(3) of Iva, CH₂(3) of Leu, CH(4) of Leu); 1.42, 1.39, 1.33 (3s, Me(3) of Iva, 2 Me of Aib); 0.97, 0.95 (2d, $J = 6.8, 6.7$, 2 Me of Leu); 0.78 (t, $J = 7.5$, Me(4) of Iva). ¹³C-NMR (CD₃OD): ca. 177.5, 176, 175.5 (3s, 3 CONH); ca. 159 (s, OCONH); ca. 138 (s, 1 arom. C); 129.4, 128.9, 128.5 (3d, 5 arom. CH); 67.5 (t, PhCH₂O); 61.4, 58.0 (2s, C(2) of Iva, C(2) of Aib); 55.2 (d, C(2) of Leu); 41.2, 29.4 (2t, C(3) of Leu, C(3) of Iva); 25.7 (d, C(4) of Leu); 26.4, 26.1, 24.4, 23.2, 23.0, 22.0, 8.0 (7q, MeN, 2 Me of Aib, Me(3) of Iva, Me(4) of Iva, 2 Me of Leu). CI-MS (NH₃): 464 (16), 463 (56, $[M + 1]^+$), 432 (14, $[M - \text{HNMe}]^+$), 356 (20), 355 (10, $[M - \text{OBn}]^+$). Anal. calc. for $\text{C}_{24}\text{H}_{38}\text{N}_4\text{O}_5 \cdot 0.2 \text{H}_2\text{O}$ (466.19): C 61.83, H 8.30, N 12.02; found: C 61.85, H 8.24, N 11.94.

6. *Tripeptide with (R)-Iva*. N-[(Benzyloxy)carbonyl]leucyl- α -aminoisobutyryl-(R)-isovaline (Z-Leu-Aib-(R)-Iva-OH; (R)-**6c**). 6.1. *Hydrolysis of (R)-3c*. As described for (S)-**6c**, with (R)-**3c** [19] (437 mg, 0.710 mmol) and 3N HCl (MeCN/H₂O 1:1, 8 ml), 3 h at 60°; CC (CH₂Cl₂/MeOH 100:2, then 100:3, 20:1, 10:1) and prep. TLC (CH₂Cl₂/MeOH 10:1): 123 mg (39%) of (R)-**6c** (colorless solid) and 95 mg (29%) of benzyl [(S)-1-([1,1-dimethyl-2-((R)-1-methyl-1-[(methylamino)carbonyl]propyl)-amino)-2-oxoethyl]amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(R)-Iva-NHMe; (R)-**7c**).

6.2. *Hydrolysis of (R)-3i*. As described for (S)-**6c**, with (R)-**3i** [18] (56 mg, 0.099 mmol) and 3N HCl (MeCN/H₂O 1:1, 0.5 ml), 3 h at 60°; prep. TLC (CH₂Cl₂/MeOH 10:1): 37 mg (84%) of (R)-**6c**.

Data of (R)-**6c**. Colorless solid. M.p. 69–71°. R_f (CH₂Cl₂/MeOH 10:1) 0.06. IR: 3393s, 3344s, 3280s, 3065m, 2955s, 1738vs, 1706vs, 1664vs, 1522vs, 1456m, 1388m, 1376m, 1329m, 1272vs, 1244s, 1216s, 1172w, 1135w, 1046s, 975w, 914w, 848w, 788w, 733w, 697m. ¹H-NMR: 7.4–7.3 (m, 5 arom. H); 7.16 (br. s, NH); 6.95 (br., NH); 5.60 (br., NH); 5.11 (br., PhCH₂O); 4.11 (br., CH(2) of Leu); 2.05–1.9 (m, CH₂(3) of Iva or Leu); 1.7–1.5 (m, CH₂(3) of Leu or Iva, Me(3) of Iva, 2 Me of Aib, CH(4) of Leu); 0.95–0.9 (m, 2 Me of Leu); 0.83 (t, $J = 7.3$, MeCH₂ of Iva). ¹³C-NMR: ca. 177, 173 (2s, 2 CONH, COOH); ca. 157 (s, OCONH); ca. 136 (s, 1 arom. C); 128.5, 128.2, 127.9 (3d, 5 arom. CH); 67.2 (t, PhCH₂O); 60.4, ca. 58 (2s, C(2) of Iva, C(2) of Aib); 54.2 (d, C(2) of Leu); 40.8, 29.6 (2t, C(3) of Leu, C(3) of Iva); 24.6 (d, C(4) of Leu); 25.3, 22.8, 21.9, 7.9 (4q, 2 Me of Aib, Me(3) of Iva, Me(4) of Iva, 2 Me of Leu). ESI-MS (MeOH, NaI): 953 (10, $[2M + \text{Na} + \text{MeOH}]^+$), 921 (14, $[2M + \text{Na}]^+$), 473 (16), 472 (59, $[M + \text{Na}]^+$), 451 (26), 450

(100, $[M + 1]^+$), 432 (10, $[M - OH]^+$). Anal. calc. for $C_{23}H_{35}N_3O_6 \cdot 0.33 H_2O$ (455.56): C 60.64, H 7.89, N 9.22; found: C 60.59, H 7.61, N 9.02.

Crystals suitable for an X-ray crystal-structure determination were grown from MeOH.

Data of (R)-7c. Colorless solid. M.p. 212.8–213.6°. R_f (CH_2Cl_2 /MeOH 10:1) 0.40. IR: 3385m, 3314s, 3017w, 2969s, 2954m, 2871w, 2513w, 2483w, 1703s, 1648vs, 1523s, 1462m, 1406w, 1385w, 1372w, 1361w, 1349w, 1312w, 1291m, 1272m, 1244m, 1216m, 1175w, 1134w, 1118w, 1047m, 1030w, 968w, 944w, 917w, 848w, 789w, 748w, 699w, 629w. 1H -NMR (CD_3OD): 7.5 (br., NH); 7.35–7.3 (m, 5 arom. H); 7.13 (br. s, NH); 5.10, 5.06 (AB, $J = 12.6$, $PhCH_2O$); 4.05 (dd, $J = 8.7$, 6.4, CH(2) of Leu); 2.70 (s, MeN); 1.9–1.85 (m, 1 H of $CH_2(3)$ of Iva, $CH_2(3)$ of Leu, or CH(4) of Leu); 1.75–1.65 (m, 2 H of $CH_2(3)$ of Iva, $CH_2(3)$ of Leu, or CH(4) of Leu); 1.55–1.5 (m, 2 H of $CH_2(3)$ of Iva, $CH_2(3)$ of Leu, or CH(4) of Leu); 1.41, 1.40, 1.39 (3s, Me(3) of Iva, 2 Me of Aib); 0.96 (2d, $J = 6.4$, 6.6, 2 Me of Leu); 0.79 (t, $J = 7.5$, Me(4) of Iva). ^{13}C -NMR (CD_3OD): 177.1, 175.9, 175.3 (3s, 3 CONH); 158.3 (s, OCONH); 137.9 (s, 1 arom. C); 129.3, 128.8, 128.3 (3d, 5 arom. CH); 67.4 (t, $PhCH_2O$); 61.1, 57.8 (2s, C(2) of Iva, C(2) of Aib); 55.1 (d, C(2) of Leu); 41.1, 31.6 (2t, C(3) of Leu, C(3) of Iva); 25.6 (d, C(4) of Leu); 26.4, 25.9, 24.5, 23.1, 22.1, 21.7, 8.1 (7q, MeN, 2 Me of Aib, Me(3) of Iva, Me(4) of Iva, 2 Me of Leu). CI-MS (NH_3): 465 (10), 464 (45), 463 (100, $[M + 1]^+$), 433 (19), 432 (56, $[M - NHMe]^+$), 355 (5, $[M - OBn]^+$), 329 (8, $[M - (benzyloxy)carbonyl + 2]^+$). Anal. calc. for $C_{24}H_{38}N_4O_5 \cdot 0.25 H_2O$ (466.64): C 61.71, H 8.31, N 11.99; found: C 61.74, H 8.05, N 11.91.

Crystals of (R)-7c suitable for an X-ray crystal-structure determination were grown from MeOH/ CH_2Cl_2 .

7. Peptides with Xaa = (S)-Val(2Me). 7.1. (S)-2-((2-((S)-2-((Benzyloxy)carbonyl)amino)-4-methyl-1-oxopentyl)amino)-2-methyl-1-oxopropyl)amino)-2,3-dimethylbutanoic Acid (Z-Leu-Aib-(S)-Val(2Me)-OH); (S)-6d. As described for (S)-6c, with (S)-3d [19] (1.480 g, 2.35 mmol) and 3N HCl ($MeCN/H_2O$ 1:1, 20 ml), 90 min at 60°; CC (CH_2Cl_2 /MeOH 100:2, then 100:3) and prep. TLC (CH_2Cl_2 /MeOH 10:1): 711 mg (65%) of (S)-6d and 239 mg (21%) of benzyl [(S)-1-((1,1-dimethyl-2-((S)-1,2-dimethyl-1-((methylamino)carbonyl)propyl)amino)-2-oxoethyl)amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(S)-Val(2Me)-NHMe; (S)-7d).

Data of (S)-6d. Colorless solid. M.p. 69–70°. R_f (CH_2Cl_2 /MeOH 10:1) 0.15. IR: 3320s, 2970s, 1715s, 1670s, 1535s, 1460m, 1390m, 1370m, 1250s, 1180m, 1165m, 1130w, 1050m, 955w, 785w, 745w, 705m. 1H -NMR: 7.35–7.3 (m, 5 arom. H, NH); 6.90 (br. s, NH); 5.62 (d, $J = 6.5$, NH); 5.10 (br., $PhCH_2O$); 4.15–4.1 (m, CH(2) of Leu); 2.35–2.3 (m, CH(3) of Val(2Me)); 1.7–1.4 (m, $CH_2(3)$ and CH(4) of Leu, 2 Me of Aib, Me(3) of Val(2Me)); 0.95–0.85 (m, 2 Me of Leu, 2 Me(4) of Val(2Me)). ^{13}C -NMR: 175.4, 174.5, 173.0 (3s, 2 CONH, COOH); 156.5 (s, OCONH); 136.0 (s, 1 arom. C); 128.5, 128.2, 127.9 (3d, 5 arom. CH); 67.1 (t, $PhCH_2O$); 63.5, 57.5 (2s, C(2) of Val(2Me), C(2) of Aib); 54.3 (d, C(2) of Leu); 40.7 (t, C(3) of Leu); 33.5, 24.7 (2d, C(3) of Val(2Me), C(4) of Leu); 25.1, 24.9, 22.8, 21.7, 18.0, 17.3, 16.9 (7q, 2 Me of Aib, Me(3) and 2 Me(4) of Val(2Me), 2 Me of Leu). ESI-MS (MeOH): 502 (11, $[M + K]^+$), 486 (94, $[M + Na]^+$), 464 (100, $[M + 1]^+$), 446 (28, $[M - OH]^+$), 333 (13, $[M - Val(2Me)]^+$). Anal. calc. for $C_{24}H_{37}N_3O_6 \cdot 0.33 H_2O$ (469.58): C 61.39, H 7.94, N 8.95; found: C 61.34, H 8.17, N 8.79.

Data of (S)-7d. Colorless solid. M.p. 67–69°. R_f (CH_2Cl_2 /MeOH 10:1) 0.41. IR: 3304s, 3035w, 2964s, 2873w, 1708s, 1664vs, 1540s, 1455m, 1411w, 1370w, 1311w, 1267s, 1222m, 1173w, 1120w, 1054m, 915w, 788w, 742w, 696w, 620w. 1H -NMR (CD_3OD): 7.35–7.25 (m, 5 arom. H); 5.13, 5.09 (AB, $J = 12.6$, $PhCH_2O$); 4.05 (dd, $J = 8.7$, 6.2, CH(2) of Leu); 2.71 (s, MeN); 2.1–1.95, 1.8–1.65, 1.65–1.45 (3m, CH(3) of Val(2Me), $CH_2(3)$ of Leu, CH(4) of Leu); 1.39 (s, Me(3) of Val(2Me), 2 Me of Aib); 0.96, 0.94, 0.89 (3d, $J = 7.5$, 7.0, 6.8, 2 Me of Leu, 2 Me(4) of Val(2Me)). ^{13}C -NMR (CD_3OD): ca. 176.5, ca. 176, ca. 175.5 (3s, 3 CONH); ca. 159 (s, OCONH); 138.2 (s, 1 arom. C); 129.4, 129.0, 128.5 (3d, 5 arom. CH); 67.6 (t, $PhCH_2O$); 61.4, 58.0 (2s, C(2) of Val(2Me), C(2) of Aib); 55.6 (d, C(2) of Leu); 41.6 (t, C(3) of Leu); 36.5 (d, C(3) of Val(2Me)); 25.8 (d, C(4) of Leu); 26.4, 25.9, 24.6, 23.2, 21.9, 18.5, 17.8, 17.7 (8q, MeN, 2 Me of Aib, Me(3) of Val(2Me), 2 Me(4) of Val(2Me), 2 Me of Leu). ESI-MS (MeOH, NaI): 499 (100, $[M + Na]^+$). Anal. calc. for $C_{25}H_{40}N_4O_5 \cdot 0.25 H_2O$ (481.12): C 62.41, H 8.48, N 11.65; found: C 62.50, H 8.47, N 11.47.

7.2. Benzyl ((S)-1-((2-((S)-1-((S)-4-Amino-1-((S)-1-(hydroxymethyl)-2-methylpropyl)amino)carbonyl)-4-oxobutyl)amino)carbonyl)-1,2-dimethylpropyl)amino)-1,1-dimethyl-2-oxoethyl)amino]carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(S)-Val(2Me)-Gln-Valol; (S)-2d). To a soln. of (S)-6d

(176 mg, 0.380 mmol) and Et_3N (115 mg, 1.14 mmol) in abs. DMF (2.5 ml) at r.t., HATU (144 mg, 0.380 mmol) was added. After 2 min, HOBt (57 mg, 0.380 mmol), and after further 4 min, **11** (88 mg, 0.38 mmol) was added, and the mixture was stirred for 91 h at r.t. and evaporated. The residue was dissolved in AcOEt, washed with 1N HCl and 1N NaOH solns., dried (MgSO_4), and evaporated. From the residue, crystals formed overnight. They were separated and dried. The filtrate was purified by prep. TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). Total yield of (S)-**2d**: 94 mg (37%). Colorless solid. M.p. 202–203°. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) 0.17. IR: 3455m, 3335s, 3213m, 2957m, 2870m, 2369w, 2352w, 1706s, 1659s, 1615m, 1540s, 1456m, 1389m, 1274m, 1262m, 1171m, 1129w, 1043w, 698m. $^1\text{H-NMR}$: 7.93 (br. s, NH); 7.80 (br., NH); 7.35–7.25 (m, 5 arom. H); 7.05 (br., NH); 6.93 (br. s, NH); 6.73 (br., NH); 5.58 (br., NH); 5.15, 5.12 (AB, $J = 12.7$, PhCH_2O); 4.15–4.0, 3.85–3.8, 3.7–3.55 (3m, CH(2) of Gln, CH(2) of Leu, CH(2) and CH_2 (1) of Valol); 3.19 (br., OH); 2.45–2.2 (m, CH_2 (4) and CH_2 (3) of Gln); 1.95–1.9, 1.8–1.6 (2m, CH_2 (3) of Leu, CH(3) of Valol, CH(3) of Val(2Me)); 1.4–1.35 (m, CH(4) of Leu, 2 Me of Aib, Me(3) of Val(2Me)); 1.0–0.85 (m, 2 Me of Valol, 2 Me(4) of Val(2Me), 2 Me of Leu). $^{13}\text{C-NMR}$: 175.1, 174.9, 172.8 (3s, CONH₂, 4 CONH); 157.1 (s, OCONH); 136.5 (s, 1 arom. C); 128.5, 128.0, 127.4 (3d, 5 arom. CH); 66.8, 63.5 (2t, PhCH_2O , C(1) of Valol); 63.0, 57.0 (2s, C(2) of Aib, C(2) of Val(2Me)); 57.5, 55.8 (2d, C(2) of Gln, C(2) of Valol, C(2) of Leu); 39.9, 32.7, 27.7 (3t, C(4) and C(3) of Gln, C(3) of Leu); 35.6, 28.9, 24.6 (3d, C(3) of Valol, C(3) of Val(2Me), C(4) of Leu); 26.6, 22.9, 22.7, 21.5, 19.5, 19.2, 17.3, 17.2, 17.1 (9q, 2 Me of Aib, Me(3) of Val(2Me), 2 Me of Valol, 2 Me(4) of Val(2Me), 2 Me of Leu). ESI-MS (MeOH, AcOH): 699 (9, $[M + \text{Na}]^+$), 680 (9), 679 (36), 678 (100, $[M + 1]^+$). Anal. calc. for $\text{C}_{34}\text{H}_{56}\text{N}_6\text{O}_8 \cdot 0.33 \text{H}_2\text{O}$ (682.86): C 59.80, H 8.30, N 12.31; found: C 59.67, H 8.53, N 12.13.

8. *Peptides with Xaa = (R)-Val(2Me)*. 8.1. (R)-2-((2-((S)-2-((Benzyloxy)carbonyl)amino]-4-methyl-1-oxopentyl)amino]-2-methyl-1-oxopropyl)amino)-2,3-dimethylbutanoic Acid (Z-Leu-Aib-(R)-Val(2Me)-OH; (R)-**6d**). As described for (S)-**6c**, with (R)-**3d** [19] (1.394 mg, 2.21 mmol) and 3N HCl ($\text{MeCN}/\text{H}_2\text{O}$ 1:1, 20 ml), 2 h at 60°; CC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:2) and prep. TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1): 817 mg (80%) of (R)-**6d** and 92 mg (9%) of benzyl [(S)-1-((1,1-dimethyl-2-((R)-1,2-dimethyl-1-((methylamino)carbonyl)propyl)amino)-2-oxoethyl)amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(R)-Val(2Me)-NHMe; (R)-**7d**).

Data of (R)-6d. Colorless solid. M.p. 163–164°. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) 0.20. IR: 3320s, 2970m, 1720s, 1670s, 1540s, 1460m, 1390m, 1370m, 1250m, 1180m, 1165m, 1130w, 1050m, 745w, 707w. $^1\text{H-NMR}$: 7.4–7.3 (m, 5 arom. H); 7.03 (br., NH); 5.57 (d, $J = 6.6$, NH); 5.10 (br., PhCH_2O); 4.15–4.05 (m, CH(2) of Leu); 2.3–2.25 (m, CH(3) of Val(2Me)); 1.7–1.4 (m, CH_2 (3) and CH(4) of Leu, 2 Me of Aib, Me(3) of Val(2Me)); 0.95–0.9 (m, 2 Me of Leu, 2 Me(4) of Val(2Me)). $^{13}\text{C-NMR}$: ca. 175, 174, 173 (3s, 2 CONH, COOH); ca. 157 (s, OCONH); 135.8 (s, 1 arom. C); 128.5, 128.3, 127.9 (3d, 5 arom. CH); 67.2 (t, PhCH_2O); 63.7, 57.6 (2s, C(2) of Val(2Me), C(2) of Aib); 54.0 (d, C(2) of Leu); 41.0 (t, C(3) of Leu); 33.3, 24.6 (2d, C(3) of Val(2Me), C(4) of Leu); 25.6, 24.5, 22.8, 21.8, 17.9, 17.2, 16.7 (7q, 2 Me of Aib, Me(3) and 2 Me(4) of Val(2Me), 2 Me of Leu). ESI-MS (MeOH): 502 (12, $[M + \text{K}]^+$), 486 (90, $[M + \text{Na}]^+$), 464 (100, $[M + 1]^+$), 446 (15, $[M - \text{OH}]^+$), 333 (16, $[M - \text{Val(2Me)}]^+$). Anal. calc. for $\text{C}_{24}\text{H}_{37}\text{N}_3\text{O}_6 \cdot 0.33 \text{H}_2\text{O}$ (469.58): C 61.37, H 8.09, N 8.95; found: C 61.38, H 8.01, N 8.53.

Data of (R)-7d. Colorless solid. M.p. 195.8–196.9°. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) 0.41. IR: 3287s, 2966m, 2875w, 1703s, 1673vs, 1518s, 1463w, 1412w, 1362w, 1315w, 1271s, 1234m, 1216m, 1175w, 1117w, 1047m, 1029w, 971w, 943w, 914w, 789w, 747w, 699w, 625w. $^1\text{H-NMR}$ (CD_3OD): 7.4–7.25 (m, 5 arom. H); 5.09, 5.05 (AB, $J = 12.5$, PhCH_2O); 4.09 (dd, $J = 8.9, 6.1$, CH(2) of Leu); 2.69 (s, MeN); 2.05–1.9, 1.75–1.45 (2m, CH(3) of Val(2Me), CH_2 (3) of Leu, CH(4) of Leu); 1.40 (s, Me(3) of Val(2Me), 2 Me of Aib); 0.97, 0.95, 0.91, 0.79 (4d, $J = 7.7, 7.0, 6.8, 6.8$, 2 Me of Leu, 2 Me(4) of Val(2Me)). $^{13}\text{C-NMR}$ (CD_3OD): ca. 176.5, 176.2, ca. 175.5 (3s, 3 CONH); ca. 159 (s, OCONH); 138.1 (s, 1 arom. C); 129.4, 128.9, 128.4 (3d, 5 arom. CH); 67.3 (t, PhCH_2O); 64.1, 58.1 (2s, C(2) of Val(2Me), C(2) of Aib); 54.9 (d, C(2) of Leu); 41.4 (t, C(3) of Leu); 36.7 (d, C(3) of Val(2Me)); 25.7 (d, C(4) of Leu); 26.9, 26.4, 23.5, 23.1, 22.1, 17.6, 17.5, 17.2 (8q, MeN, 2 Me of Aib, Me(3) of Val(2Me), 2 Me(4) of Val(2Me), 2 Me of Leu). ESI-MS (MeOH, NaI): 499 (100, $[M + \text{Na}]^+$). Anal. calc. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}_5 \cdot 0.33 \text{H}_2\text{O}$ (482.63): C 62.22, H 8.49, N 11.61; found: C 62.12, H 8.47, N 12.06.

Crystals suitable for an X-ray analysis were grown from CD_3OD .

8.2. Benzyl ((S)-1-((2-((R)-1-((S)-4-Amino-1-((S)-1-(hydroxymethyl)-2-methylpropyl)amino)carbonyl)-4-oxobutyl)amino)carbonyl)-1,2-dimethylpropyl)amino]-1,1-dimethyl-2-oxoethyl)amino]-

carbonyl]-3-methylbutyl]carbamate (*Z*-Leu-Aib-(*R*)-Val(2*Me*)-Gln-Valol; (*R*)-**2d**). As described for **2a**, with (*R*)-**6d** (599 mg, 1.29 mmol), Et₃N (0.54 ml, 392 mg, 3.90 mmol), abs. DMF (13 ml), and HATU (491 mg, 1.29 mmol), 3 min at r.t., HOBt (196 mg, 1.30 mmol), 4 min at r.t., **11** (301 mg, 1.30 mmol), 65 h at r.t.; CC (CH₂Cl₂/MeOH 20:1); 357 mg (41%) of (*R*)-**2d** and 202 mg of starting material (*R*)-**6d** (34%).

Data of (R)-2d. Colorless solid. M.p. 110–111°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.15. IR: 3416s, 2962s, 1664s, 1534s, 1456m, 1388m, 1375m, 1264m, 1179w, 1122w, 1049w, 849s, 740m, 698m. ¹H-NMR: 7.70 (br., 2 NH); 7.35–7.3 (*m*, 5 arom. H); 6.94 (br., NH); 6.84 (br. *s*, NH); 6.79 (br., NH); 6.22 (br., NH); 5.15–5.05 (*m*, PhCH₂O); 4.25–4.15, 4.15–4.05, 3.75–3.55 (3*m*, CH(2) of Gln, CH(2) of Leu, CH(2) and CH₂(1) of Valol); 2.45–2.15 (*m*, CH₂(4) and CH₂(3) of Gln); 1.8–1.55 (*m*, CH₂(3) of Leu, CH(3) of Valol, CH(3) of Val(2*Me*)); 1.45–1.25 (*m*, CH(4) of Leu, 2 Me of Aib, Me(3) of Val(2*Me*)); 1.0–0.75 (*m*, 2 Me of Valol, 2 Me(4) of Val(2*Me*), 2 Me of Leu). ¹³C-NMR: *ca.* 176, 174.3, 174.1, 172.7 (4*s*, CONH₂, 4 CONH); *ca.* 157 (*s*, OCONH); 136.4 (*s*, 1 arom. C); 128.5, 128.1, 127.5 (3*d*, 5 arom. CH); 66.8, 63.2 (2*t*, PhCH₂O, C(1) of Valol); 62.2, 57.2 (2*s*, C(2) of Aib, C(2) of Val(2*Me*)); 57.1, 54.9, 54.4 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 40.1, 32.3, 27.3 (3*t*, C(4) and C(3) of Gln, C(3) of Leu); 33.4, 28.9, 24.6 (3*d*, C(3) of Valol, C(3) of Val(2*Me*), C(4) of Leu); 22.7, 21.8, 19.5, 19.1, 17.8, 17.7 (6*q*, 2 Me of Aib, Me(3) of Val(2*Me*), 2 Me of Valol, 2 Me(4) of Val(2*Me*), 2 Me of Leu). ESI-MS (MeOH, AcOH): 701 (11), 700 (46), 699 (100, [*M* + Na]⁺), 586 (10, [*M* – C₇H₇ + 1]⁺). Anal. calc. for C₃₄H₅₆N₆O₈ · 0.5 H₂O (685.86): C 59.54, H 8.38, N 12.25; found: C 59.25, H 8.52, N 12.16.

9. *Peptides with Xaa = (S)-Ala(2cPent)*. 9.1. (*S*)-2-[(2-[(*S*)-2-[(*Benzoyloxy*)carbonyl]amino]-4-methyl-1-oxopentyl)amino]-2-methyl-1-oxopropyl]amino]-2-cyclopentylpropanoic Acid (*Z*-Leu-Aib-(*S*)-Ala(2*cPent*)-OH; (*S*)-**6e**). As described for (*S*)-**6c**, with (*S*)-**3e** [19] (98 mg, 0.149 mmol) and 3*N* HCl (MeCN/H₂O 1:1, 1.5 ml), 3 h at 60°; prep. TLC (CH₂Cl₂/MeOH 10:1): 54 mg (74%) of (*S*)-**6e**. Colorless solid. M.p. 79–81°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.26. IR: 3321*m*, 2956*s*, 2871*m*, 1706*vs*, 1668*vs*, 1526*vs*, 1455*m*, 1386*w*, 1249*m*, 1047*w*, 738*w*. ¹H-NMR: 7.35–7.25 (*m*, 5 arom. H); 7.21 (br. *s*, NH); 7.06 (br. *s*, NH); 5.80 (br., NH); 5.10 (br. *s*, PhCH₂O); 4.15–4.1 (*m*, CH(2) of Leu); 2.45–2.35 (*m*, CH(3) of Ala(2*cPent*)); 1.75–1.35 (*m*, CH₂(3) and CH(4) of Leu, 2 Me of Aib, Me of Ala(2*cPent*), 4 CH₂ of Ala(2*cPent*)); 0.95–0.9 (*m*, 2 Me of Leu). ¹³C-NMR: 175.7, 174.0, 173.2 (3*s*, 2 CONH, COOH); 156.5 (*s*, OCONH); 136.1 (*s*, 1 arom. C); 128.4, 128.1, 127.7 (3*d*, 5 arom. CH); 67.0 (*t*, PhCH₂O); 61.8, 57.4 (2*s*, C(2) of Ala(2*cPent*), C(2) of Aib); 54.3 (*d*, C(2) of Leu); 46.1 (*d*, C(3) of Ala(2*cPent*)); 40.7 (*t*, C(3) of Leu); 27.0, 26.8, 25.3 (3*t*, 4 CH₂ of cPent); 25.0 (*q*, MeN); 24.6 (*d*, C(4) of Leu); 22.8, 21.7, 19.5, 14.0 (4*q*, 2 Me of Aib, Me of Ala(2*cPent*), 2 Me of Leu). ESI-MS (MeOH): 512 (100, [*M* + Na]⁺), 490 (52, [*M* + 1]⁺), 307 (13). Anal. calc. for C₂₆H₃₉N₃O₆ (489.61): C 63.78, H 8.03, N 8.58; found: C 63.80, H 8.12, N 8.24.

9.2. *Benzyl [(S)-1-[(2-[(S)-2-[(S)-4-Amino-1-[(S)-1-(hydroxymethyl)-2-methylpropyl]amino]-carbonyl]-4-oxobutyl]amino]-1-cyclopentyl-1-methyl-2-oxoethyl)amino]-1,1-dimethyl-2-oxoethyl]amino]carbonyl]-3-methylbutyl]carbamate* (*Z*-Leu-Aib-(*S*)-Ala(2*cPent*)-Gln-Valol; (*S*)-**2e**). As described for **2a**, with (*S*)-**6e** (149 mg, 0.304 mmol), Et₃N (0.1 ml, 72.6 mg, 0.720 mmol), abs. DMF (2 ml), and HATU (117 mg, 0.308 mmol), 2 min at 0°, HOAt (0.5*M* soln. in DMF, 0.6 ml, 0.3 mmol), 3 min at 0°, **11** (70.5 mg, 0.305 mmol), 20 min at 0° and 70 h at r.t.; after the washing procedure described for **2a**, crystals suitable for X-ray crystal-structure determination were obtained. Prep. TLC (CH₂Cl₂/MeOH 10:1) of the rest; total yield: 93 mg (43%) of (*S*)-**2e**. Colorless solid. M.p. 208.0–209.1°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.37. ¹H-NMR (CD₃OD): 7.35–7.3 (*m*, 5 arom. H); 5.25–5.05 (*m*, PhCH₂O); 4.1–4.05, 3.7–3.65 (2*m*, CH(2) of Gln, CH(2) of Leu, CH(2) and CH₂(1) of Valol); 2.45–2.3, 2.25–2.15, 1.95–1.85, 1.8–1.5 (4*m*, CH₂(4) and CH₂(3) of Gln, CH₂(3) of Leu, 4 CH₂ of Ala(2*cPent*), CH(4) of Leu, CH(3) of Valol, CH(3) of Ala(2*cPent*)); 1.44 (*s*, Me of Ala(2*cPent*)); 1.39 (*s*, 2 Me of Aib); 0.95–0.9 (*m*, 2 Me of Valol, 2 Me of Leu). ¹³C-NMR (CD₃OD): 177.4, *ca.* 176.5, 176.2, 174.5 (4*s*, CONH₂, 4 CONH); 158.7 (*s*, OCONH); *ca.* 143 (*s*, 1 arom. C); 129.4, 128.9, 128.4 (3*d*, 5 arom. CH); 67.5, 63.6 (2*t*, PhCH₂O, C(1) of Valol); 63.0, 58.0 (2*s*, C(2) of Aib, C(2) of Ala(2*cPent*)); 58.6, 56.6, 55.7 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 49.1 (*d*, C(3) of Ala(2*cPent*)); 41.8, 33.6, 28.4, 28.1, 27.8, 26.1, 26.1 (7*t*, 4 CH₂ of Ala(2*cPent*), C(4) and C(3) of Gln, C(3) of Leu); 29.9, 25.8 (2*d*, C(3) of Valol, C(4) of Leu); 26.4, 23.9, 23.2, 21.9, 20.0, 19.7, 19.3 (7*q*, 2 Me of Aib, Me of Ala(2*cPent*), 2 Me of Valol, 2 Me of Leu). ESI-MS (MeOH, NaI): 725 (100, [*M* + Na]⁺), 703 (100, [*M* + 1]⁺). Anal. calc. for C₃₆H₅₈N₆O₈ (702.89): C 61.52, H 8.32, N 11.96; found: C 61.33, H 8.44, N 12.04.

10. *Peptides with Xaa = (R)-Ala(2cPent)*. 10.1. (R)-2-((2-((S)-2-((Benzyloxy)carbonyl)amino)-4-methyl-1-oxopentyl)amino)-2-methyl-1-oxopropyl]amino)-2-cyclopentylpropanoic Acid (*Z*-Leu-Aib-(R)-Ala(2cPent)-OH; (S)-**6e**). As described for (S)-**6c**, with (R)-**3e** [19] (200 mg, 0.304 mmol) and 3N HCl (MeCN/H₂O 1:1, 3 ml), 3 h at 60°; prep. TLC (CH₂Cl₂/MeOH 10:1); 113 mg (76%) of (R)-**6e**. Colorless solid. M.p. 144–145°. *R_f* (CH₂Cl₂/MeOH 10:1) 0.37. IR: 3309m, 2957s, 2871w, 1724s, 1662vs, 1526s, 1455w, 1387w, 1246w, 1049w, 737w. ¹H-NMR: 7.33 (br., 5 arom. H); 7.23 (br. s, NH); 7.03 (br. s, NH); 5.52 (br., NH of Leu); 5.10 (br. s, PhCH₂O); 4.2–4.1 (*m*, CH(2) of Leu); 2.5–2.35 (*m*, CH(3) of Ala(2cPent)); 1.8–1.3 (*m*, CH₂(3) and CH(4) of Leu, 2 Me of Aib, Me of Ala(2cPent), 4 CH₂ of Ala(2cPent)); 0.95–0.9 (*m*, 2 Me of Leu). ¹³C-NMR: 173.9, 172.8 (2s, 2 CONH, COOH); 156.7 (s, OCONH); 136.0 (s, 1 arom. C); 128.5, 128.2, 127.9 (3*d*, 5 arom. CH); 67.2 (*t*, PhCH₂O); 61.9, 57.4 (2s, C(2) of Ala(2cPent)); 53.9 (*d*, C(2) of Leu); 46.2 (*d*, C(3) of Ala(2cPent)); 41.1 (*t*, C(3) of Leu); 27.0, 26.7, 25.3 (3*t*, 4 CH₂ of cPent); 24.6 (*d*, C(4) of Leu); 22.8, 21.8, 19.5 (3*q*, 2 Me of Aib, Me of Ala(2cPent), 2 Me of Leu). ESI-MS (MeOH, NaI): 525 (10), 513 (32), 512 (100, [M + Na]⁺), 503 (6), 491 (29), 490 (99, [M + 1]⁺), 472 (47, [M – OH]⁺), 333 (8, [M – Ala(2cPent)]⁺). Anal. calc. for C₂₆H₃₉N₃O₆ (489.61): C 63.78, H 8.03, N 8.58; found: C 63.50, H 8.08, N 8.53.

10.2. Benzyl ((S)-1-((2-((R)-2-((S)-4-Amino-1-((S)-1-(hydroxymethyl)-2-methylpropyl)amino)carbonyl)-4-oxobutyl)amino)-1-cyclopentyl-1-methyl-2-oxoethyl)amino)-1,1-dimethyl-2-oxoethyl]amino)carbonyl]-3-methylbutyl]carbamate (*Z*-Leu-Aib-(R)-Ala(2cPent)-Gln-Valol; (R)-**2e**). As described for **2a**, with (R)-**6e** (220 mg, 0.449 mmol), Et₃N (136 mg, 1.35 mmol), abs. DMF (3.5 ml), HATU (171 mg, 0.450 mmol), 4 min at 0°, HOAt (62 mg, 0.456 mmol), 4 min at 0°, **11** (106 mg, 0.458 mmol), 3 h at 0° and 47 h at r.t.; CC (CH₂Cl₂/MeOH 10:1) and prep. TLC (CH₂Cl₂/MeOH 10:1): 88 mg (28%) of (R)-**2e** and 78 mg of starting material (R)-**6e** (35%).

Data of (R)-2e. Colorless solid. M.p. 209.5–210.8°. *R_f* (CH₂Cl₂/MeOH 10:1) 0.23. IR: 3426vs, 2959s, 2871m, 1661vs, 1532s, 1455w, 1386w, 1261w, 1175w, 1121w, 1048w, 741w. ¹H-NMR: 8.09 (br., NH); 7.70 (br., 2 NH); 7.35–7.3 (*m*, 5 arom. H); 7.09 (br., 2 NH); 5.37 (br., 2 NH); 5.14, 5.07 (*AB*, *J* = 13.1, PhCH₂O); 4.35–4.0, 3.75–3.6 (2*m*, CH(2) of Gln, CH(2) of Leu, CH(2) of Valol); 2.65–2.45, 2.35–2.25 (2*m*, CH₂(4) and CH₂(3) of Gln); 1.85–1.25 (*m*, CH₂(3) of Leu, 4 CH₂ of Ala(2cPent), CH(4) of Leu, CH(3) of Valol, CH(3) of Ala(2cPent)); 1.45, 1.42 (2s, 2 Me of Aib); 1.28 (s, Me of Ala(2cPent)); 0.95–0.85 (*m*, 2 Me of Valol, 2 Me of Leu). ¹H-NMR (CD₃OD): 8.51 (br. s, NH); 7.74 (*d*, *J* = 7.2, NH); 7.56 (*d*, *J* = 8.9, NH); 7.4–7.25 (*m*, 5 arom. H); 7.11 (br. s, NH); 5.15–5.05 (*m*, PhCH₂O); 4.25–4.1 (*m*, CH(2) of Gln, CH(2) of Leu); 3.7–3.6 (*m*, CH(2) and CH₂(1) of Valol); 2.5–2.35, 2.2–2.15, 1.9–1.85, 1.7–1.4 (4*m*, CH(3) of Valol, CH(3) of Ala(2cPent), CH₂(3) of Leu, CH₂(4) and CH₂(3) of Gln, 4 CH₂ of Ala(2cPent), CH(4) of Leu, Me of Ala(2cPent), 2 Me of Aib); 1.0–0.9 (*m*, 2 Me of Valol, 2 Me of Leu). ¹³C-NMR: 177.5, 176.0, 174.9, 174.6, 173.5 (5s, CONH₂, 4 CONH); 157.1 (s, OCONH); *ca.* 137 (s, 1 arom. C); 128.5, 127.9, 127.2 (3*d*, 5 arom. CH); 67.0, 61.6 (2*t*, PhCH₂O, C(1) of Valol); 58.0, 55.3, 54.0 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 57.0 (s, C(2) of Aib, C(2) of Ala(2cPent)); 44.4 (*d*, C(3) of Ala(2cPent)); *ca.* 39.5, *ca.* 31, *ca.* 27, 25.0 (4*t*, 4 CH₂ of Ala(2cPent), C(4) and C(3) of Gln, C(3) of Leu); 28.8, 24.7 (2*d*, C(3) of Valol, C(4) of Leu); 22.6, 21.8, 20.3, 19.4, 19.0 (5*q*, 2 Me of Aib, Me of Ala(2cPent), 2 Me of Valol, 2 Me of Leu). ¹³C-NMR (CD₃OD): 178.1, 176.6, 176.0, 175.8, 174.2 (5s, CONH₂, 4 CONH); 158.7 (s, OCONH); 138.2 (s, 1 arom. C); 129.4, 128.9, 128.5 (3*d*, 5 arom. CH); 67.6, 63.3 (2*t*, PhCH₂O, C(1) of Valol); 62.9, 57.9 (2s, C(2) of Aib, C(2) of Ala(2cPent)); 58.3, 55.3, 55.2 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 47.6 (*d*, C(3) of Ala(2cPent)); 41.6, 33.2, 28.7, 28.4, 28.2, 26.6, 26.2 (7*t*, 4 CH₂ of Ala(2cPent), C(4) and C(3) of Gln, C(3) of Leu); 30.0, 25.8 (2*d*, C(3) of Valol, C(4) of Leu); 24.6, 23.2, 22.2, 20.0, 19.7, 19.1 (6*q*, 2 Me of Aib, Me of Ala(2cPent), 2 Me of Valol, 2 Me of Leu). ESI-MS (CH₂Cl₂, MeOH): 725 (29, [M + Na]⁺), 703 (100, [M + 1]⁺), 685 (7, [M – OH]⁺), 600 (28, [M – Valol]⁺), 472 (30, [M – Gln-Valol]⁺). Anal. calc. for C₃₆H₅₈N₆O₈ (702.89): C 61.52, H 8.32, N 11.96; found: C 61.36, H 8.31, N 11.70.

Crystals suitable for an X-ray crystal-structure determination were obtained from AcOEt/MeOH by slow evaporation of the solvent.

11. *Peptides with Xaa = (S)-Leu(2Me)*. 11.1. (S)-2-((2-((S)-2-((Benzyloxy)carbonyl)amino)-4-methyl-1-oxopentyl)amino)-2-methyl-1-oxopropyl]amino)-2,4-dimethylpentanoic Acid (*Z*-Leu-Aib-(S)-Leu(2Me)-OH; (S)-**6f**). As described for (S)-**6c**, with (S)-**3f** [19] (249 mg, 0.390 mmol) and 3N HCl

(MeCN/H₂O 1:1, 2 ml), 4 h at 60°; prep. TLC (CH₂Cl₂/MeOH 10:1): 87 mg (47%) of (S)-**6f** and 28%²⁾ of benzyl [(S)-1-((1,1-dimethyl-2-((S)-1,3-dimethyl-1-[(methylamino)carbonyl]butyl)amino)-2-oxoethyl)amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(S)-Leu(2Me)-NHMe; (S)-**7f**).

Data of (S)-6f. Colorless solid. M.p. 107–108°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.19. IR: 3306m, 2958s, 1717s, 1659s, 1523s, 1454m, 1388m, 1367m, 1237m, 1159m, 1045m, 954w, 908w, 855w, 789w, 757w, 736w, 697m. ¹H-NMR: 7.3–7.25 (*m*, 5 arom. H, NH); 7.19 (*s*, NH); 5.85 (*d*, *J* = 6.9, NH); 5.1–5.05 (*m*, PhCH₂O); 4.2–4.15 (*m*, CH(2) of Leu); 2.15–2.1 (*m*, CH(4) of Leu(2Me)); 1.8–1.5 (*m*, CH₂(3) and CH(4) of Leu, 2 Me of Aib, CH₂(3) and Me(3) of Leu(2Me)); 0.95–0.85 (*m*, 2 Me of Leu, 2 Me(5) of Leu(2Me)). ¹³C-NMR: 177.5 (*s*, COOH); 173.4, 172.8 (2*s*, 2 CONH); 156.5 (*s*, OCONH); 136.0 (*s*, 1 arom. C); 128.4, 128.1, 127.8 (3*d*, 5 arom. CH); 67.0 (*t*, PhCH₂O); 59.8, 57.3 (2*s*, C(2) of Aib, C(2) of Leu(2Me)); 54.0 (*d*, C(2) of Leu); 44.5, 40.9 (2*t*, C(3) of Leu, C(3) of Leu(2Me)); 24.6, 24.4 (2*d*, C(4) of Leu(2Me), C(4) of Leu); 25.0, 23.9, 23.5, 23.1, 22.9, 21.8 (6*q*, 2 Me of Aib, Me(3) and 2 Me(5) of Leu(2Me), 2 Me of Leu). ESI-MS (MeOH): 522 (27), 500 (100, [*M* + Na]⁺). Anal. calc. for C₂₅H₃₉N₃O₆ (477.60): C 62.87, H 8.23, N 8.80; found: C 62.77, H 8.14, N 8.68.

Data of (S)-7f. Colorless solid. M.p. 78.5–79.5°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.44. IR: 3321s, 3038w, 2957s, 2871w, 1704vs, 1652vs, 1537s, 1455m, 1411w, 1382m, 1365w, 1331w, 1261s, 1223w, 1173w, 1115w, 1051w, 1031w, 907w, 789w, 726w, 693w. ¹H-NMR (CD₃OD): 7.35–7.3 (*m*, 5 arom. H); 5.08 (br. *s*, PhCH₂O); 4.06 (*dd*, *J* = 8.4, 6.5, CH(2) of Leu); 2.69 (*s*, MeN); 2.0–1.5 (*m*, CH₂(3) of Leu(2Me), CH₂(3) of Leu, CH(4) of Leu(2Me), CH(4) of Leu); 1.40 (*s*, 2 Me of Aib); 1.38 (*s*, Me(3) of Leu(2Me)); 0.97, 0.95, 0.92, 0.86 (4*d*, *J* = 7.3, 7.5, 6.9, 6.6, 2 Me of Leu, 2 Me(5) of Leu(2Me)). ¹³C-NMR (CD₃OD): *ca.* 177.5, 175.9, 175.5 (3*s*, 3 CONH); *ca.* 158.5 (*s*, OCONH); *ca.* 138 (*s*, 1 arom. C); 129.4, 128.9, 128.5 (3*d*, 5 arom. CH); 67.5 (*t*, PhCH₂O); 61.1, 58.0 (2*s*, C(2) of Leu(2Me), C(2) of Aib); 55.1 (*d*, C(2) of Leu); 45.2, 41.4 (2*t*, C(3) of Leu(2Me), C(3) of Leu); 25.8, 24.9 (2*d*, C(4) of Leu(2Me), C(4) of Leu); 26.5, 24.6, 24.4, 24.2, 23.2, 22.0 (6*q*, MeN, 2 Me of Aib, Me(3) of Leu(2Me), 2 Me(5) of Leu(2Me), 2 Me of Leu). CI-MS (NH₃): 492 (10), 491 (32, [*M* + 1]⁺), 460 (32, [*M* – HNMe]⁺), 384 (22), 383 (32, [*M* – OBn]⁺), 357 (9), 231 (12), 214 (7). Anal. calc. for C₂₆H₄₂N₄O₅ · 0.2 H₂O (494.24): C 63.18, H 8.65, N 11.34; found: C 63.24, H 8.60, N 11.28.

11.2. Benzyl [(S)-1-[(2-[(S)-1-[(S)-4-Amino-1-[(S)-1-(hydroxymethyl)-2-methylpropyl]amino)carbonyl]-4-oxobutyl]amino)carbonyl]-1,3-dimethylbutyl]amino]-1,1-dimethyl-2-oxoethyl]amino)carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(S)-Leu(2Me)-Gln-Valol; (S)-**2f**). As described for **2a**, with (S)-**6f** (161 mg, 0.337 mmol), Et₃N (102 mg, 1.011 mmol), abs. DMF (2.5 ml), HATU (128 mg, 0.337 mmol), 4 min at r.t., HOBt (51 mg, 0.337 mmol), 5 min at r.t., **11** (78 mg, 0.337 mmol), 42 h at r.t.; CC (CH₂Cl₂/MeOH 10:1): 139 mg (60%) of (S)-**2f**. Colorless solid. M.p. 154–155°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.17. IR: 3312m, 2956m, 1653s, 1534s, 1466m, 1386w, 1360m, 1260m, 1046w, 847w, 814w, 738w. ¹H-NMR: 7.96 (br., NH); 7.81 (br., NH); 7.35–7.2 (*m*, 5 arom. H, NH); 7.04 (br., NH); 6.88 (br. *s*, NH); 6.71 (br., NH); 5.68 (br., NH); 5.15, 5.12 (*AB*, *J* = 12.7, PhCH₂O); 4.0–3.8, 3.7–3.55 (2*m*, CH(2) of Gln, CH(2) of Leu, CH(2) and CH₂(1) of Valol); 2.35–2.15 (*m*, CH₂(4) and CH₂(3) of Gln); 1.8–1.6 (*m*, CH₂(3) of Leu(2Me), CH₂(3) of Leu, CH(3) of Valol, CH(4) of Leu, CH(4) of Leu(2Me)); 1.5–1.25 (*m*, 2 Me of Aib, Me(3) of Leu(2Me)); 0.95–0.8 (*m*, 2 Me of Valol, 2 Me(5) of Leu(2Me), 2 Me of Leu). ¹³C-NMR: 175.6, 175.2, 175.1, 174.8, 172.8 (5*s*, CONH₂, 4 CONH); 157.1 (*s*, OCONH); 136.7 (*s*, 1 arom. C); 128.5, 127.9, 127.2 (3*d*, 5 arom. CH); 66.7, 63.5 (2*t*, PhCH₂O, C(1) of Valol); 59.7, 56.8 (2*s*, C(2) of Leu(2Me), C(2) of Aib); 57.5, 55.8 (2*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 48.3, 39.8, 32.6, 27.6 (4*t*, C(3) of Leu, C(3) of Leu(2Me), C(4) and C(3) of Gln); 28.9, 24.6, 23.4 (3*d*, C(3) of Valol, C(4) of Leu(2Me), C(4) of Leu); 26.3, 24.3, 24.2, 23.0, 22.7, 21.6, 20.9, 19.5, 19.2 (9*q*, 2 Me of Aib, Me(3) of Leu(2Me), 2 Me of Valol, 2 Me(5) of Leu(2Me), 2 Me of Leu). ESI-MS (MeOH): 714 (15, [*M* + Na]⁺), 691 (100, [*M* + 1]⁺). Anal. calc. for C₃₅H₅₈N₆O₈ · H₂O (708.90): C 59.30, H 8.53, N 11.85; found: C 59.31, H 8.56, N 11.49.

11.3. N-((S)-1-[(2-[(S)-1-[(S)-4-Amino-1-[(S)-1-(hydroxymethyl)-2-methylpropyl]amino)carbonyl]-4-oxobutyl]amino)carbonyl]-1,3-dimethylbutyl]amino)-1,1-dimethyl-2-oxoethyl]amino)carbon-

²⁾ The side product (S)-**7f** was not isolated in the described reaction. In another experiment, it was isolated in 28% yield; starting material (S)-**3f**: 249 mg (0.386 mmol); side product (S)-**7f**: 105 mg (0.214 mmol).

yl]-3-methylbutyl)-4-bromobenzamide (*p*BrBz-Leu-Aib-(*S*)-Leu(2Me)-Gln-Valol; (*S*)-**13f**). As described for **13a**, with (*S*)-**2f** (80 mg, 0.116 mmol), Pd/C (10% on activated charcoal, 8 mg), MeOH (5 ml), and H₂, 75 min at r.t., filtration over *Celite*, abs. CH₂Cl₂ (5 ml), Et₃N (25 mg, 0.248 mmol), 4-bromobenzoyl chloride (31 mg, 0.139 mmol), 3 h at r.t., filtration and washing with CH₂Cl₂: 60 mg (70%) of (*S*)-**13f**. Colorless solid. M.p. 246–247°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.18. IR: 3336*m*, 2959*m*, 2477*m*, 1648*vs*, 1542*s*, 1364*m*, 1278*w*, 1176*w*, 1072*w*, 1011*w*, 850*w*, 761*w*. ¹H-NMR (CD₃OD): 7.83, 7.62 (*AA'**BB'*, *J* = 8.5, 4 arom. H); 4.55–4.5, 4.1–4.05 (2*m*, CH(2) of Gln and CH(2) of Leu); 3.65–3.6 (*m*, CH₂(1) and CH(2) of Valol); 2.4–2.05, 1.85–1.65 (2*m*, CH₂(4) of Gln and CH₂(3) of Gln, CH(3) of Valol, CH(4) and CH₂(3) of Leu, CH(4) and CH₂(3) of Leu(2Me)); 1.45, 1.44, 1.41 (3*s*, 2 Me of Aib, Me(3) of Leu(2Me)); 1.01, 0.99 (2*d*, *J* = 5.6, 5.7, 2 Me); 0.95–0.9 (*m*, 3 Me); 0.81 (*d*, *J* = 6.8, 1 Me). ¹³C-NMR (CD₃OD): 177.7, 177.0, 176.7, 175.8, 174.4 (5*s*, CONH₂, 4 CONH); 169.6 (*s*, 1 CO (amide, *p*BrBz)); 134.0 (*s*, 1 arom. C); 132.8, 130.7 (2*d*, 4 arom. CH); 127.4 (*s*, 1 arom. CBr); 63.6 (*t*, C(1) of Valol); 61.2, 58.1 (2*s*, C(2) of Leu(2Me), C(2) of Aib); 58.6, 56.5, 54.5 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 48.5, 41.6, 33.8, 28.5 (4*t*, C(3) of Leu, C(3) of Leu(2Me), C(4) of Gln, C(3) of Gln); 30.1, 26.1, 24.9 (3*d*, C(3) of Valol, C(4) of Leu, C(4) of Leu(2Me)); 25.5, 25.0, 23.4, 22.7, 22.2, 20.1, 19.4 (7*q*, 2 Me of Aib, Me(3) of Leu(2Me), 2 Me of Valol, 2 Me of Leu, 2 Me(5) of Leu(2Me)). ESI-MS (NaI): 763 (24, [*M* + Na]⁺, ⁸¹Br), 741 (100, [*M* + 1]⁺, ⁸¹Br), 638 (6, [*M* – Valol]⁺, ⁸¹Br), 510 (10, [*M* – Gln-Valol]⁺, ⁸¹Br). Anal. calc. for C₃₄H₅₅BrN₆O₇ (739.75): C 55.20, H 7.49, N 11.36; found: C 55.10, H 7.53, N 11.11.

Crystals suitable for an X-ray crystal-structure determination were obtained from CD₃OD by slow evaporation of the solvent.

12. *Peptides with Xaa = (R)-Leu(2Me)*. 12.1. (R)-2-({2-[(*S*)-2-[(Benzyloxy)carbonyl]amino]-4-methyl-1-oxopentyl]amino]-2-methyl-1-oxopropyl]amino)-2,4-dimethylpentanoic Acid (*Z*-Leu-Aib-(*R*)-Leu(2Me)-OH; (*R*)-**6f**). As described for (*S*)-**6c**, with (*R*)-**3f** [19] (200 mg, 0.31 mmol) and 3*N* HCl (MeCN/H₂O 1:1, 2 ml), 3 h at 60°; prep. TLC (CH₂Cl₂/MeOH 10:1) gave 78 mg (53%) of (*R*)-**6f** and 35%³⁾ of benzyl [(*S*)-1-({[1,1-dimethyl-2-[(*R*)-1,3-dimethyl-1-[(methylamino)carbonyl]butyl]amino]-2-oxoethyl]amino]carbonyl)-3-methylbutyl]carbamate (*Z*-Leu-Aib-(*R*)-Leu(2Me)-NHMe; (*R*)-**7f**).

Data of (R)-6f. Colorless solid. M.p. 152–153°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.17. IR: 3301*s*, 2956*s*, 1727*s*, 1661*s*, 1542*s*, 1456*m*, 1366*m*, 1235*m*, 1162*m*, 1046*m*, 754*w*, 697*m*. ¹H-NMR: 7.35–7.3 (*m*, 5 arom. H); 7.2–7.05 (*m*, 2 NH); 5.75 (*d*, *J* = 6.4, NH); 5.11 (br., PhCH₂O); 4.15–4.1 (*m*, CH(2) of Leu); 2.15–2.1 (*m*, CH(4) of Leu(2Me)); 1.8–1.45 (*m*, CH₂(3) and CH(4) of Leu, CH₂(3) and Me(3) of Leu(2Me), 2 Me of Aib); 0.95–0.85 (*m*, 2 Me of Leu, 2 Me(5) of Leu(2Me)). ¹³C-NMR: 177.0 (*s*, COOH); 173.4, 172.6 (2*s*, 2 CONH); 156.6 (*s*, OCONH); 136.0 (*s*, 1 arom. C); 128.5, 128.1, 127.8 (3*d*, 5 arom. CH); 67.1 (*t*, PhCH₂O); 59.7, 57.2 (2*s*, C(2) of Leu(2Me), C(2) of Aib); 54.1 (*d*, C(2) of Leu); 44.7, 40.9 (2*t*, C(3) of Leu, C(3) of Leu(2Me)); 24.6, 24.3 (2*d*, C(4) of Leu(2Me), C(4) of Leu); 25.3, 24.9, 24.5, 23.8, 23.2, 22.8, 21.8 (7*q*, 2 Me of Aib, Me(3) and 2 Me(5) of Leu(2Me), 2 Me of Leu). ESI-MS (MeOH): 495 (14), 479 (30), 478 (100, [*M* + 1]⁺), 460 (15, [*M* – OH]⁺), 333 (12, [*M* – Leu(2Me)]⁺). Anal. calc. for C₂₅H₃₉N₃O₆ · 0.5 H₂O (486.61): C 61.71, H 8.29, N 8.64; found: C 61.77, H 8.08, N 8.30.

Data of (R)-7f. Colorless solid. M.p. 110–111°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.45. IR: 3293*s*, 2958*m*, 2873*w*, 1706*s*, 1654*vs*, 1518*vs*, 1464*m*, 1411*w*, 1386*w*, 1369*w*, 1270*s*, 1242*m*, 1175*w*, 1119*w*, 1049*m*, 1029*w*, 970*w*, 789*w*, 745*w*, 698*w*, 658*w*. ¹H-NMR (CD₃OD): 7.35–7.25 (*m*, 5 arom. H); 5.09 (br. *s*, PhCH₂O); 4.06 (*dd*, *J* = 8.9, 6.1, CH(2) of Leu); 2.69 (*s*, MeN); 1.8–1.65, 1.65–1.45 (2*m*, CH₂(3) of Leu(2Me), CH₂(3) of Leu, CH(4) of Leu(2Me), CH(4) of Leu); 1.47 (*s*, Me(3) of Leu(2Me)); 1.41, 1.39 (2*s*, 2 Me of Aib); 0.97, 0.95, 0.91, 0.89 (4*d*, *J* = 7.6, 6.9, 6.9, 6.5, 2 Me of Leu, 2 Me(5) of Leu(2Me)). ¹³C-NMR (CD₃OD): *ca.* 177.5, *ca.* 176, *ca.* 175 (3*s*, 3 CONH); *ca.* 158 (*s*, OCONH); *ca.* 138 (*s*, 1 arom. C); 129.4, 128.9, 128.5 (3*d*, 5 arom. CH); 67.5 (*t*, PhCH₂O); 61.2, 58.0 (2*s*, C(2) of Leu(2Me), C(2) of Aib); 55.2 (*d*, C(2) of Leu); 47.3, 41.4 (2*t*, C(3) of Leu(2Me), C(3) of Leu); 25.7, 25.0 (2*d*, C(4) of Leu(2Me), C(4) of Leu); 26.5, 26.0, 24.3, 24.1, 23.2, 22.5, 22.0 (7*q*, MeN, 2 Me of Aib, Me(3) of Leu(2Me), 2 Me(5) of Leu(2Me), 2 Me of Leu). CI-MS (NH₃): 491 (4, [*M* + 1]⁺), 384 (21), 383 (32, [*M* – OBn]⁺), 231 (7). Anal. calc. for C₂₆H₄₂N₄O₅ (490.64): C 63.65, H 8.83, N 11.42; found: C 63.67, H 8.62, N 11.26.

³⁾ The side product (*R*)-**7f** was not isolated in the described reaction. In another experiment, it was isolated in 35% yield; starting material (*R*)-**3f**: 909 mg (1.410 mmol); side product (*R*)-**7f**: 242 mg (0.493 mmol).

12.2. *Benzyl* [(*S*)-1-[(2-[(*R*)-1-[(*S*)-4-Amino-1-[(*S*)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-4-oxobutyl]amino]carbonyl]-1,3-dimethylbutyl]amino]-1,1-dimethyl-2-oxoethyl]amino)-carbonyl]-3-methylbutyl]carbamate (*Z*-Leu-Aib-(*R*)-Leu(2Me)-Gln-Valol; (*R*)-**2f**). As described for **2a**, with (*R*)-**6f** (240 mg, 0.503 mmol), Et₃N (153 mg, 1.515 mmol), abs. DMF (5 ml), HATU (191 mg, 0.502 mmol), 4 min at r.t., HOBt (76 mg, 0.502 mmol), 5 min at r.t., **11** (117 mg, 0.506 mmol), 94 h at r.t.; prep. TLC (CH₂Cl₂/MeOH 10:1): 177 mg (53%) of (*R*)-**2f**. Colorless foam. M.p. 105–107°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.14. IR: 3302s, 2958m, 2871m, 1659s, 1533s, 1455m, 1386m, 1356m, 1264m, 1171m, 1122w, 1055w, 852w, 786w, 740m, 697m. ¹H-NMR: 7.93 (br., NH); 7.84 (*d*, *J* = 5.1, NH); 7.4–7.25 (*m*, 5 arom. H); 7.2–7.15 (*m*, NH); 7.11 (br. s, NH); 7.02 (br., NH); 6.70 (br., NH); 5.70 (br., NH); 5.25–5.05 (*m*, PhCH₂O); 4.1–3.55 (*m*, CH(2) of Gln, CH(2) of Leu, CH(2) of Leu, CH(2) and CH₂(1) of Valol); 2.45–2.0 (*m*, CH₂(4) and CH₂(3) of Gln, CH(3) of Valol); 1.8–1.65 (*m*, CH₂(3) of Leu(2Me), CH₂(3) of Leu); 1.55–1.25 (*m*, 2 Me of Aib, Me(3) of Leu(2Me)); 0.95–0.8 (*m*, 2 Me of Valol, CH(4) of Leu, CH(4) of Leu(2Me), 2 Me(5) of Leu(2Me), 2 Me of Leu). ¹³C-NMR: 176.9, 175.1, 175.1, 174.6, 173.0 (5s, CONH₂, 4 CONH); 157.4 (s, OCONH); 136.6 (s, 1 arom. C); 128.5, 128.0, 126.9 (3*d*, 5 arom. CH); 66.6, 63.5 (2*r*, PhCH₂O, C(1) of Valol); 59.8, 56.9 (2s, C(2) of Leu(2Me), C(2) of 2 Aib); 57.5, 56.1, 55.5 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 40.6, 39.7, 32.6, 27.6 (4*t*, C(3) of Leu, C(3) of Leu(2Me), C(4) and C(3) of Gln); 28.9 (*d*, C(3) of Valol); 24.6, 23.4 (2*d*, C(4) of Leu(2Me), C(4) of Leu); 26.4, 25.0, 24.5, 24.2, 23.0, 22.7, 21.6, 19.5, 19.2 (9*q*, 2 Me of Aib, Me(3) of Leu(2Me), 2 Me of Valol, 2 Me(5) of Leu(2Me), 2 Me of Leu). ESI-MS (MeOH): 729 (10, [*M* + K]⁺), 714 (22, [*M* + Na]⁺), 691 (100, [*M* + 1]⁺), 674 (7, [*M* – OH]⁺), 588 (17, [*M* – Valol]⁺), 460 (18, [*M* – Gln-Valol]⁺). Anal. calc. for C₃₅H₅₈N₆O₈ · H₂O (708.90): C 59.30, H 8.53, N 11.86; found: C 59.08, H 8.30, N 11.42.

12.3. *N*-(*(S)*-1-[(2-[(*R*)-1-[(*S*)-4-Amino-1-[(*S*)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-4-oxobutyl]amino]carbonyl]-1,3-dimethylbutyl]amino)-1,1-dimethyl-2-oxoethyl]amino]carbonyl]-3-methylbutyl]-4-bromobenzamide (*p*BrBz-Leu-Aib-(*R*)-Leu(2Me)-Gln-Valol; (*R*)-**13f**). As described for **13a**, with (*R*)-**2f** (50 mg, 0.072 mmol), Pd/C (10% on activated charcoal, 7 mg), MeOH (4 ml), and H₂, 70 min at r.t., filtration over *Celite*, abs. CH₂Cl₂ (4 ml), Et₃N (16 mg, 0.158 mmol), 4-bromobenzoyl chloride (18.5 mg, 0.084 mmol), 2 h at r.t., evaporation and prep. TLC (CH₂Cl₂/MeOH 10:1): 16 mg (30%) of (*R*)-**13f**. M.p. 124–125°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.14. IR: 3317s, 3064w, 2959m, 1651vs, 1592m, 1483m, 1448m, 1428m, 1382m, 1335m, 1276m, 1234m, 1160w, 1140m, 1073w, 1012w, 974w, 961w, 846w, 806w, 784w, 722w, 696m. ¹H-NMR (CD₃OD): 7.95–7.9 (*m*, NH); 7.84, 7.62 (*AA'**BB'*, *J* = 8.5, 8.6, 4 arom. H); 7.45 (br. s, NH); 7.4–7.35 (*m*, NH); 4.6–4.5, 4.2–4.1 (2*m*, CH(2) of Gln, CH(2) of Leu); 3.65–3.6 (*m*, CH₂(1) and CH(2) of Valol); 2.4–1.6, 1.3–1.25 (2*m*, CH₂(4) and CH₂(3) of Gln, CH(3) of Valol, CH(4) and CH₂(3) of Leu, CH(4) and CH₂(3) of Leu(2Me)); 1.45 (s, 2 Me of Aib); 1.43 (s, Me(3) of Leu(2Me)); 1.01, 0.99 (2*d*, *J* = 5.8, 5.7, 2 Me of Valol); 0.88, 0.86, 0.83, 0.81 (4*d*, *J* = 6.9, 6.6, 5.7, 6.0, 2 Me(5) of Leu(2Me), 2 Me of Leu). ¹³C-NMR (CD₃OD): *ca.* 178, 177.5, 176.3, 175.5, 174.2, *ca.* 171 (6s, CONH₂, 5 CONH); *ca.* 134 (s, 1 arom. C); 132.7, 130.6 (2*d*, 4 arom. CH); *ca.* 127 (s, 1 arom. CBr); 63.4 (*t*, C(1) of Valol); 61.3, 58.0 (2s, C(2) of Leu(2Me), C(2) of Aib); 58.4, 55.7, 54.3 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 45.0, 41.2, 33.4, 28.8 (4*t*, C(3) of Leu, C(3) of Leu(2Me), C(4) of Gln, C(3) of Gln); 29.9, 26.0, 24.7 (3*d*, C(3) of Valol, C(4) of Leu, C(4) of Leu(2Me)); 25.2, 25.2, 25.1, 24.9, 23.8, 23.3, 22.1, 19.9, 19.2 (9*q*, 2 Me of Aib, Me(3) of Leu(2Me), 2 Me of Valol, 2 Me of Leu, 2 Me(5) of Leu(2Me)). ESI-MS (NaI): 765 (12), 764 (45), 763 (100, [*M* + Na]⁺, ⁸¹Br), 762 (41), 741 (74, [*M* + Na]⁺, ⁷⁹Br). Anal. calc. for C₃₄H₅₅BrN₆O₇ · 0.5 H₂O (748.76): C 54.54, H 7.54, N 11.22; found: C 54.29, H 7.55, N 10.21.

13. *Peptides with Xaa = (S)-Phe(2Me)*. 13.1. *Benzyl* [(*S*)-1-[(2-[(*S*)-1-Benzyl-2-[(*S*)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]-1-methyl-2-oxoethyl]amino)-1,1-dimethyl-2-oxoethyl]amino]carbonyl]-3-methylbutyl]carbamate (*Z*-Leu-Aib-(*S*)-Phe(2Me)-NCp[2-[(1-Me)(1-MeO)Et]]; (*S*)-**3h**). As described for **3a**, with **5** [19] (109 mg, 0.311 mmol), 1-[(*S*)-2-benzyl-2-methyl-2H-azirin-3-yl]-2-[(*S*)-1-methoxy-1-methylethyl]pyrrolidine ((2'*S*)-**1h** [17], 95 mg, 0.332 mmol), abs. CH₂Cl₂ (3 ml), 17 h at r.t., 2*N* HCl, 1*N* NaOH, sat. NaCl solns.; CC (CH₂Cl₂/MeOH 100:4): 140 mg (70%) of (*S*)-**3h**. M.p. 79–80°. *R*_f (CH₂Cl₂/MeOH 20:1) 0.30. IR: 3330s, 2957s, 1666vs, 1623vs, 1498s, 1454s, 1413m, 1384m, 1317m, 1243m, 1086m, 1061m, 922w, 739w, 701m. ¹H-NMR (CD₃OD): 7.3–7.1 (*m*, 10 arom. H); 5.12, 5.04 (*AB*, *J* = 12.7, PhCH₂O); 4.46 (*dd*, *J* = 8.5, 3.3, CHN of Cp); 4.04 (*t*, *J* = 7.5, CH(2) of Leu); 3.89 (*td*, *J* = 8.4, 2.5, CHN of Cp); 3.65–3.3 (*m*, CHN of Cp); 3.19, 3.07 (*AB*, *J* = 13.9, CH₂(3) of Phe(2Me)); 3.15 (s, MeO); 2.0–1.9 (*m*, CH(4) of Leu); 1.8–1.6 (*m*, 4 CH of Cp); 1.55–1.5 (*m*, CH₂(3) of Leu); 1.49 (s, Me(3) of Phe(2Me));

1.44, 1.43 (2s, 2 Me of Aib); 1.16, 1.08 (2s, Me₂(MeO)C); 0.97, 0.94 (2d, *J* = 7.3, 7.1, 2 Me of Leu). ¹³C-NMR (CD₃OD): 175.3, 172.6 (2s, CON, 2 CONH); *ca.* 158 (s, OCONH); 138.2, 137.4 (2s, 2 arom. C); 131.7, 129.4, 129.1, 128.9, 128.3, 127.9 (6d, 10 arom. CH); 80.0 (s, Me₂(MeO)C); 67.3 (t, PhCH₂O); 65.8, 55.3 (2d, C(2) of Leu, CHN of Cp); 62.2 (s, C(2) of Phe(2Me)); 58.4 (s, C(2) of Aib); 49.5 (q, MeO); 48.9, 44.1, 41.5, 26.0, 24.5 (5t, 3 CH₂ of Cp, C(3) of Leu, C(3) of Phe(2Me)); 26.9, 24.6, 24.0, 23.5, 23.2, 22.2 (6q, Me₂C, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu); 25.8 (d, C(4) of Leu). ESI-MS (MeOH, CH₂Cl₂, NaI): 659 (100, [M + Na]⁺). Anal. calc. for C₃₆H₅₂N₄O₆ · 0.25 H₂O (641.34): C 67.42, H 8.25, N 8.74; found: C 67.41, H 8.08, N 8.38.

13.2. (S)-2-Benzyl-2-((2-((S)-2-((benzyloxy)carbonyl)amino)-4-methyl-1-oxopentyl)amino)-2-methyl-1-oxopropyl)amino)propanoic Acid (*Z*-Leu-Aib-(S)-Phe(2Me)-OH; (S)-**6g**). 13.2.1. Hydrolysis of (S)-**3h**. As described for (S)-**6c**, with (S)-**3h** (140 mg, 0.219 mmol) and 3N HCl (THF/H₂O 1:1, 8 ml), 23 h at 40°; CC (CH₂Cl₂/MeOH 100:9): 90 mg (80%) of (S)-**6g**.

13.2.2. Hydrolysis of (S)-**3g**. As described for (S)-**6c**, with (S)-**3g** [19] (200 mg, 0.295 mmol) and 3N HCl (MeCN/H₂O 1:1, 6 ml), 3 h at 60°; CC (CH₂Cl₂/MeOH 100:2) and prep. TLC (CH₂Cl₂/MeOH 10:1): 37 mg (25%) of (S)-**6g**. Colorless solid. M.p. 130.2–130.6°. *R*_f (CH₂Cl₂/MeOH 20:1) 0.30. IR: 3330s, 3060m, 3030m, 2960m, 2870w, 1660vs, 1605s, 1515s, 1500s, 1455s, 1405m, 1365m, 1265m, 1245m, 1210m, 1170w, 1120w, 1045w, 1030w, 1000w, 960w, 910w, 780w, 740w, 700m. ¹H-NMR (CD₃OD): 7.45 (br. s, NH); 7.3–7.25, 7.2–7.1 (2m, 10 arom. H); 5.1–5.05 (m, PhCH₂O); 4.15 (t, *J* = 7.4, CH(2) of Leu); 3.37, 3.31 (AB, *J* = 13.3, CH₂(3) of Phe(2Me)); 1.7–1.6 (m, CH(4) of Leu); 1.6–1.55 (m, CH₂(3) of Leu); 1.51 (s, Me(3) of Phe(2Me)); 1.38, 1.33 (2s, 2 Me of Aib); 0.93, 0.91 (2d, *J* = 6.8, 2 Me of Leu). ¹³C-NMR (CD₃OD): 180.5 (s, COOH); 175.2, 174.8 (2s, 2 CONH); 158.5 (s, OCONH); 139.2, 138.0 (2s, 2 arom. C); 131.4, 129.5, 129.0, 128.8, 127.3 (5d, 10 arom. CH); 67.9 (t, PhCH₂O); 62.8 (s, C(2) of Phe(2Me)); 58.2 (s, C(2) of Aib); 55.1 (d, C(2) of Leu); 42.3, 41.8 (2t, C(3) of Phe(2Me), C(3) of Leu); 25.9 (d, C(4) of Leu); 25.8, 25.1, 24.2, 23.5, 22.0 (5q, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu). ESI-MS (NaI): 556 (12), 550 (33, [M + K]⁺), 534 (100, [M + Na]⁺), 473 (8), 466 (6, [M – COOH]⁺). Anal. calc. for C₂₈H₃₇N₃O₆ · 0.25 H₂O (516.12): C 65.16, H 7.32, N 8.14; found: C 65.28, H 7.35, N 7.81.

13.3. Benzyl ((S)-1-((2-((S)-2-((S)-4-Amino-1-((S)-1-(hydroxymethyl)-2-methylpropyl)amino)carbonyl)-4-oxobutyl)amino)-1-benzyl-1-methyl-2-oxoethyl)amino)-1,1-dimethyl-2-oxoethyl)amino)-carbonyl]-3-methylbutyl)carbamate (*Z*-Leu-Aib-(S)-Phe(2Me)-Gln-Valol; (S)-**2g**). As described for **2b**, with (S)-**6g** (83 mg, 0.162 mmol), Et₃N (33 mg, 0.327 mmol), abs. DMF (1 ml), 5 min at 0°, HATU (64 mg, 0.168 mmol), 6 min at 0°, **11** (38 mg, 0.164 mmol), 30 min at 0°, 44 h at r.t.; CC (CH₂Cl₂/MeOH 10:1): 57 mg (49%) of (S)-**2g**. Colorless solid. M.p. 102–103°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.27. IR: 3300s, 3060w, 3030w, 2960m, 2870w, 1660vs, 1530s, 1455m, 1405w, 1385w, 1370w, 1340w, 1315w, 1260m, 1170w, 1120w, 1045w, 1030w, 960w, 920w, 845w, 740w, 700m. ¹H-NMR (CD₃OD): 7.42 (d, *J* = 8.8, NH); 7.35–7.2, 7.15–7.1 (2m, 10 arom. H); 5.08, 5.05 (AB, *J* = 12.7, PhCH₂O); 4.15–4.05 (m, CH(2) of Gln, CH(2) of Leu); 3.7–3.65 (m, CH₂(1) of Valol); 3.65–3.6 (m, CH(2) of Valol); 3.22, 3.06 (AB, *J* = 13.6, CH₂(3) of Phe(2Me)); 2.3–2.25 (m, CH₂(4) of Gln); 2.25–2.2 (m, CH₂(3) of Gln); 2.2–2.05 (m, CH(3) of Valol); 1.9–1.6 (m, CH(4) of Leu); 1.6–1.5 (m, CH₂(3) of Leu); 1.43 (s, Me(3) of Phe(2Me)); 1.37 (s, 2 Me of Aib); 0.95–0.9 (m, 2 Me of Leu, 2 Me of Valol). ¹³C-NMR (CD₃OD): 178.0, 176.6, 176.3, 175.9, 174.3 (5s, CONH₂, 4 CONH); the signal for OCONH could not be detected; 138.2, 137.3 (2s, 2 arom. C); 131.7, 129.5, 129.4, 129.1, 128.7, 128.2 (6d, 10 arom. CH); 67.8 (t, PhCH₂O); 63.4 (t, C(1) of Valol); 60.7 (s, C(2) of Phe(2Me)); 58.4 (d, C(2) of Gln); 58.0 (s, C(2) of Aib); 55.9, 55.3 (2d, C(2) of Leu, C(2) of Valol); 43.4, 41.5 (2t, C(3) of Phe(2Me), C(3) of Leu); 33.5 (t, C(4) of Gln); 30.0 (d, C(3) of Valol); 28.4 (t, C(3) of Gln); 25.9 (d, C(4) of Leu); 25.6, 25.1, 23.5, 23.4, 22.2 (5q, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu); 20.1, 19.2 (2q, 2 Me of Valol). ¹H-NMR (600 MHz): 7.68 (d, *J* = 4.9, NH of Gln); 7.48 (s, NH of Aib); 7.35–7.3, 7.25–7.2, 7.1–7.05 (3m, 10 arom. H, 1 NH); 6.92 (s, NH); 6.60 (s, 1 H, NH₂ of Gln); 6.51 (d, *J* = 4.0, NH of Leu); 5.53 (s, 1 H, NH₂ of Gln); 5.11, 5.08 (AB, *J* = 12.6, PhCH₂O); 4.1–4.05 (m, CH(2) of Gln); 4.0–3.95 (m, CH(2) of Leu); 3.75–3.7 (m, CH(2) of Valol); 3.65–3.6 (m, CH₂(1) of Valol); 2.97, 2.94 (AB, *J* = 13.6, CH₂(3) of Phe(2Me)); 2.3–2.25 (m, CH₂(4) of Gln); 2.2–2.05 (m, CH₂(3) of Gln); 1.8–1.75 (m, CH(3) of Valol); 1.7–1.65 (m, CH(4) of Leu); 1.65–1.6 (m, 1 H of CH₂(3) of Leu); 1.5–1.45 (m, 1 H of CH₂(3) of Leu); 1.4–1.35 (m, 2 Me of Aib, Me(3) of Phe(2Me)); 0.93, 0.92 (2d, *J* = 6.8, 8.3, 2 Me of Leu); 0.87, 0.86 (2d, *J* = 6.9, 2 Me of Valol). ¹³C-NMR (150.9 MHz): 175.1, 174.7, 174.4, 172.6 (4s, CONH₂, 4 CONH); 157.1 (s, OCONH); 136.4 (s, 1 arom. C of PhCH₂O); 135.1 (s, 1 arom. C of

Phe(2Me)); 130.2, 128.6, 128.3, 128.2, 127.6, 127.3 (6d, 10 arom. CH); 67.1 (t, PhCH₂O); 63.4 (t, C(1) of Valol); 60.5 (s, C(2) of Phe(2Me)); 57.1 (s, C(2) of Aib); 57.6 (d, C(2) of Valol); 55.2, 55.1 (2d, C(2) of Leu, C(2) of Gln); 44.6 (t, C(3) of Phe(2Me)); 39.8 (t, C(3) of Leu); 32.5 (t, C(4) of Gln); 29.0 (d, C(3) of Valol); 27.3 (t, C(3) of Gln); 26.0, 23.7 (2q, 2 Me of Aib); 24.7 (d, C(4) of Leu); 22.9, 21.7 (2q, 2 Me of Leu); 21.5 (q, Me(3) of Phe(2Me)); 19.6, 19.2 (2q, 2 Me of Valol). ESI-MS (TFA): 748 (22, [M + Na]⁺), 726 (100, [M + 1]⁺), 706 (15, [M – OH]⁺), 624 (68, [M – Valol]⁺), 494 (30, [M – Gln-Valol]⁺). Anal. calc. for C₃₈H₅₆N₆O₈ · 1.5 H₂O (751.92): C 60.69, H 7.91, N 11.18; found: C 60.93, H 8.12, N 9.85.

13.4. N-[(S)-1-[(2-[(S)-2-[(S)-4-Amino-1-[(S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl)-4-oxobutyl]amino]-1-benzyl-1-methyl-2-oxoethyl]amino]-1,1-dimethyl-2-oxoethyl]amino]carbonyl]-3-methylbutyl]-4-bromobenzamide (pBrBz-Leu-Aib-(S)-Phe(2Me)-Gln-Valol; (S)-**13g**). As described for **13a**, with (S)-**2g** (32 mg, 0.044 mmol), Pd/C (10% on activated charcoal, 7 mg), MeOH (2 ml), and H₂, 30 min at r.t., filtration over Celite, CH₂Cl₂ (3 ml), Et₃N (10 mg, 0.099 mmol), 4-bromobenzoyl chloride (10 mg, 0.046 mmol), 20 h at r.t., the precipitate was filtered and dried: 25 mg (73%) of (S)-**13g**. Colorless solid. M.p. 236.7–237.6°. R_f (CH₂Cl₂/MeOH 10:1) 0.31. IR: 3417s, 2959m, 1682vs, 1654vs, 1608m, 1540m, 1399w, 1364w, 1230m, 1184w, 1068w, 1021w, 810w. ¹H-NMR (CD₃OD): 7.77, 7.60 (AA'BB', J = 8.6, 4 arom. H); 7.3–7.25, 7.15–7.1 (2m, 5 arom. H); 4.5–4.45, 4.15–4.1 (2m, CH(2) of Gln and CH(2) of Leu); 3.65–3.55 (m, CH₂(1) and CH(2) of Valol); 3.35, 3.05 (AB, J = 13.6, CH₂(3) of Phe(2Me)); 2.3–1.95, 1.85–1.65 (2m, CH₂(4) of Gln and CH₂(3) of Gln, CH(3) of Valol, CH₂(3) of Leu); 1.6–1.5 (m, CH(4) of Leu); 1.46, 1.40, 1.30 (3s, 2 Me of Aib, Me(3) of Phe(2Me)); 1.01, 0.98 (2d, J = 6.2, 6.3, 2 Me of Valol); 0.85, 0.78 (2d, J = 6.8, 2 Me of Leu). ¹³C-NMR (CD₃OD): 177.9, 176.5, 175.5, 174.0 (4s, CONH₂, 4 CONH); 169.5 (s, 1 CO (amide, pBrBz)); 137.3, 133.9 (2s, 2 arom. C); 132.7, 131.7, 130.6, 129.2, 128.0 (5d, 9 arom. CH); 127.3 (s, 1 arom. CBr); 63.2 (t, C(1) of Valol); 61.5, 58.0 (2s, C(2) of Phe(2Me), C(2) of Aib); 58.0, 55.4, 54.2 (3d, C(2) of Gln, C(2) of Valol, C(2) of Leu); ca. 48, 41.1, 33.3, 28.1 (4t, C(3) of Leu, C(3) of Phe(2Me), C(4) of Gln, C(3) of Gln); 29.9, 26.0 (2d, C(3) of Valol, C(4) of Leu); 24.7, 23.9, 23.3, 22.1, 19.9, 19.0 (6q, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Valol, 2 Me of Leu). ESI-MS (TFA): 813 (8, [M + K]⁺, ⁸¹Br), 798 (100, [M + Na]⁺, ⁸¹Br), 775 (86, [M + 1]⁺, ⁸¹Br), 757 (16, [M – OH]⁺, ⁸¹Br), 672 (25, [M – Valol]⁺, ⁸¹Br), 656 (12), 544 (53, [M – Gln-Valol]⁺, ⁸¹Br). Anal. calc. for C₃₇H₅₃BrN₆O₇ · 2 MeOH (837.85): C 55.91, H 7.33, N 10.03; found: C 56.23, H 7.01, N 10.57.

Recrystallization from AcOEt/MeOH/petroleum ether gave crystals suitable for an X-ray crystal structure determination.

14. Peptides with Xaa = (R)-Phe(2Me). 14.1. Benzyl [(S)-1-[(2-[(R)-1-Benzyl-2-[(S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]-1-methyl-2-oxoethyl]amino)-1,1-dimethyl-2-oxoethyl]amino]carbonyl]-3-methylbutyl]carbamate (Z-Leu-Aib-(R)-Phe(2Me)-NCp[2-[(1-Me)(1-MeO)Et]]; (R)-**3h**). As described for **3a**, with **5** [19] (159 mg, 0.45 mmol), abs. CH₂Cl₂ (4 ml), and (R)-**1h** [17] (130 mg, 0.45 mmol), abs. CH₂Cl₂ (5 ml), 18 h at r.t.; CC (CH₂Cl₂/MeOH 20:1, 25:1, 50:1); prep. TLC (CH₂Cl₂/MeOH 20:1): 229 mg (79%) of (R)-**3h**. Colorless foam. M.p. 79–80°. R_f (CH₂Cl₂/MeOH 10:1) 0.57. R_f (CH₂Cl₂/MeOH 20:1) 0.36. IR: 3323s, 3032m, 2958s, 1665vs, 1624vs, 1527vs, 1455s, 1411s, 1384s, 1316m, 1243s, 1120m, 1086s, 1061m, 921w, 737m, 700s. ¹H-NMR: 7.48 (br. s, NH); 7.4–7.3, 7.2–7.0 (2m, 10 arom. H); 6.63 (br. s, NH); 5.14 (d, NH of Leu); 5.15–5.1 (m, NH); 5.05, 4.99 (AB, J = 12.3, PhCH₂O); 4.55–4.5 (m, CHN of Cp); 4.1–3.95 (m, CH(2) of Leu, CHN of Cp); 3.6–3.4 (m, CHN of Cp, CH₂(3) of Phe(2Me)); 3.16 (s, MeO); 2.05–1.95 (m, CH₂(3) of Leu); 1.8–1.4 (m, 2 CH₂ of Cp, 2 Me of Aib, Me(3) of Phe(2Me), CH(4) of Leu); 1.17, 1.13 (2s, Me₂C); 0.92 (d, J = 6.3, 2 Me of Leu). ¹³C-NMR: 172.2, 171.5 (2s, CON, 2 CONH); the signal for OCONH could not be detected; 136.7, 136.0 (2s, 2 arom. C); 130.9, 128.4, 128.1, 127.9, 127.9, 126.6 (6d, 10 arom. CH); 67.1 (t, PhCH₂O); 64.8 (d, C(2) of Leu); 60.8, 57.7 (2s, C(2) of Phe(2Me), C(2) of Aib); 54.2 (d, CHN of Cp); 49.1 (q, MeO); 48.1 (t, CH₂N of Cp); 41.2, 40.3, 23.6 (3t, C(3) of Leu, C(3) of Phe(2Me), 2 CH₂ of Cp); 25.3 (q, Me₂C); 24.6 (d, C(4) of Leu); 22.9, 22.2, 21.7 (4q, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu). ESI-MS (MeOH, AcOH): 659 (7, [M + Na]⁺), 639 (10), 638 (39), 637 (100, [M + 1]⁺). Anal. calc. for C₃₆H₅₂N₄O₆ (636.84): C 67.90, H 8.23, N 8.80; found: C 67.73, H 8.20, N 8.61.

14.2. (S)-2-Benzyl-2-[(2-[(S)-2-[(benzyloxy)carbonyl]amino]-4-methyl-1-oxopentyl]amino]-2-methyl-1-oxopropyl]amino]propanoic Acid (Z-Leu-Aib-(R)-Phe(2Me)-OH; (R)-**6g**). 14.2.1. Hydrolysis

of (*R*)-**3h**. As described for (*S*)-**6c**, with (*R*)-**3h** (120 mg, 0.188 mmol), 3*N* HCl (THF/H₂O 1:1, 8 ml), 26 h at 40°; CC (CH₂Cl₂/MeOH 10:1); 57 mg (59%) of (*R*)-**6g**.

14.2.2. *Hydrolysis of (R)-3g*. As described for (*S*)-**6c**, with (*R*)-**3g** [19] (204 mg, 0.300 mmol) and 3*N* HCl (MeCN/H₂O 1:1, 6 ml), 3 h at 60°; CC (CH₂Cl₂/MeOH 100:2) and prep. TLC (CH₂Cl₂/MeOH 10:1); 55 mg (36%) of (*R*)-**6g**. Colorless solid. M.p. 126.8–127.3°. *R*_f (CH₂Cl₂/MeOH 20:1) 0.28. IR: 3330*m*, 3060*w*, 3030*w*, 2960*m*, 2860*w*, 1660*vs*, 1530–1510*s*, 1450*s*, 1410*m*, 1390*m*, 1365*m*, 1255*m*, 1215*m*, 1170*w*, 1120*w*, 1045*w*, 1030*w*, 1000*w*, 960*w*, 910*w*, 780*w*, 740*w*, 700*m*. ¹H-NMR (CD₃OD): 7.3–7.25, 7.15–7.1 (2*m*, 10 arom. H); 5.02, 4.97 (*AB*, *J* = 12.5, PhCH₂O); 4.13 (*t*, *J* = 6.4, CH(2) of Leu); 3.37, 3.31 (*AB*, *J* = 13.3, CH₂(3) of Phe(2Me)); 1.7–1.55 (*m*, CH(4) of Leu); 1.55–1.45 (*m*, Me(3) of Phe(2Me), CH₂(3) of Leu); 1.41, 1.38 (2*s*, 2 Me of Aib); 0.92, 0.90 (2*d*, *J* = 6.8, 2 Me of Leu). ¹³C-NMR (CD₃OD): 180.5 (*s*, COOH); 175.3, 174.9 (2*s*, 2 CONH); 158.6 (*s*, OCONH); 139.2, 138.0 (2*s*, 2 arom. C); 131.5, 129.5, 129.1, 128.9, 127.3 (5*d*, 10 arom. CH); 66.4 (*t*, PhCH₂O); 62.8 (*s*, C(2) of Phe(2Me)); 58.3 (*s*, C(2) of Aib); 55.3 (*d*, C(2) of Leu); 42.3, 41.8 (2*t*, C(3) of Phe(2Me), C(3) of Leu); 25.9 (*d*, C(4) of Leu); 26.1, 24.9, 24.2, 23.5, 22.0 (5*q*, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu). ESI-MS (NaI): 624 (18), 550 (20, [*M* + K]⁺), 534 (100, [*M* + Na]⁺). Anal. calc. for C₂₈H₃₇N₃O₆·0.25 H₂O (516.12): C 65.16, H 7.32, N 8.14; found: C 65.01, H 7.51, N 7.84.

14.3. *Benzyl N-((S)-1-((2-(((R)-2-(((S)-4-Amino-1-(((S)-1-(hydroxymethyl)-2-methylpropyl)amino)carbonyl)-4-oxobutyl)amino)-1-benzyl-1-methyl-2-oxoethyl)amino)-1,1-dimethyl-2-oxoethyl)amino)carbonyl]-3-methylbutyl)carbamate (Z-Leu-Aib-(R)-Phe(2Me)-Gln-Valol; (R)-2g)*. As described for **2b**, with (*R*)-**6g** (53 mg, 0.104 mmol), Et₃N (22 mg, 0.218 mmol), abs. DMF (1 ml), 5 min at 0°, HATU (40 mg, 0.105 mmol), 6 min at 0°, **11** (24 mg, 0.104 mmol), 40 min at 0° and 25 h at r.t. Reaction control with TLC showed still a considerable amount of (*R*)-**6g**. At 0°, additional HATU (8 mg, 0.021 mmol) was added, the mixture was stirred for 4 min, and **11** (6 mg, 0.026 mmol) was added. After a further 7 min of stirring, the mixture was warmed to r.t. and stirred for 68 h. The solvent was evaporated, the residue was dissolved in AcOEt and a small amount of MeOH, washed twice with 2*N* HCl, once with 1*N* NaOH soln. and sat. NaCl soln., dried (MgSO₄), and evaporated. A residue, which was not soluble in 50 ml of MeOH (HATU), was filtered off. CC (CH₂Cl₂/MeOH 10:1): 42 mg (56%) of (*R*)-**2g**. M.p. 94.3–95.0°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.35. ¹H-NMR (CD₃OD): 8.10 (*d*, *J* = 6.8, NH); 7.40 (*d*, *J* = 8.2, NH); 7.3–7.1 (*m*, 10 arom. H); 5.03, 4.96 (*AB*, *J* = 12.5, PhCH₂O); 4.2–4.15 (*m*, CH(2) of Gln); 4.01 (*t*, *J* = 7.5, CH(2) of Leu); 3.7–3.65 (*m*, CH₂(1) and CH(2) of Valol); 3.53, 3.09 (2*d*, *J* = 13.7, CH₂(3) of Phe(2Me)); 2.4–2.35 (*m*, CH₂(4) of Gln); 2.25–2.1 (*m*, CH₂(3) of Gln); 2.0–1.9 (*m*, CH(3) of Valol); 1.7–1.65 (*m*, CH(4) of Leu); 1.52 (*t*, *J* = 7.2, CH₂(3) of Leu); 1.42 (*s*, Me(3) of Phe(2Me)); 1.34, 1.32 (2*s*, 2 Me of Aib); 1.0–0.9 (*m*, 2 Me of Leu, 2 Me of Valol). ¹³C-NMR (CD₃OD): 177.6, 176.9, 176.2, 174.7 (4*s*, CONH₂, 4 CONH); the signal for OCONH could not be detected; 138.2, 137.8 (2*s*, 2 arom. C); 132.3, 129.5, 129.1, 128.6, 127.9 (5*d*, 10 arom. CH); 67.7 (*t*, PhCH₂O); 63.7 (*t*, C(1) of Valol); 61.3 (*s*, C(2) of Phe(2Me)); 58.8 (*d*, C(2) of Gln); 58.0 (*s*, C(2) of Aib); 56.5, 56.1 (2*d*, C(2) of Leu, C(2) of Valol); 41.3, 40.4 (2*t*, C(3) of Phe(2Me), C(3) of Leu); 33.6 (*t*, C(4) of Gln); 30.1 (*d*, C(3) of Valol); 28.6 (*t*, C(3) of Gln); 25.8 (*d*, C(4) of Leu); 26.8, 24.7, 24.3, 23.2, 22.2 (5*q*, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu); 20.1, 19.5 (2*q*, 2 Me of Valol). ESI-MS (TFA): 748 (18, [*M* + Na]⁺), 726 (77, [*M* + 1]⁺), 708 (12, [*M* – OH]⁺), 624 (100, [*M* – Valol]⁺), 494 (22, [*M* – Gln-Valol]⁺).

14.4. *N-((S)-1-((2-(((R)-2-(((S)-4-Amino-1-(((S)-1-(hydroxymethyl)-2-methylpropyl)amino)carbonyl)-4-oxobutyl)amino)-1-benzyl-1-methyl-2-oxoethyl)amino)-1,1-dimethyl-2-oxoethyl)amino)carbonyl]-3-methylbutyl)-4-bromobenzamide (pBrBz-Leu-Aib-(R)-Phe(2Me)-Gln-Valol; (R)-13g)*. As described for **13a**, with (*R*)-**2g** (25 mg, 0.035 mmol), Pd/C (10% on activated charcoal, 5 mg), MeOH (1.5 ml), and H₂, 16 h at r.t., filtration over *Celite*, CH₂Cl₂ (2 ml), Et₃N (10 mg, 0.099 mmol), 4-bromobenzoyl chloride (10 mg, 0.046 mmol), 3 h at r.t., filtration and washing with CH₂Cl₂; 20 mg (75%) of (*R*)-**13g**. Colorless solid. M.p. 127.4–128.5°. *R*_f (CH₂Cl₂/MeOH 10:1) 0.37. IR: 3422*vs*, 2929*m*, 1648*s*, 1534*m*, 1458*w*, 1388*w*, 1284*w*, 1070*w*, 1011*w*, 760*w*, 711*w*. ESI-MS (NaI): 806 (12), 798 (87, [*M* + Na]⁺, ⁸¹Br), 757 (8, [*M* – OH]⁺, ⁸¹Br), 729 (16), 655 (9), 613 (13), 589 (32), 573 (8), 514 (15), 485 (17), 441 (12).

After recrystallization from MeOH and acetone, crystals were obtained. The attempted X-ray crystal-structure determination failed, as the reflexes were not strong enough to solve the structure properly.

Table 6. Crystallographic Data of Compounds **13a**, **13b**, (*S*)-**2d**, (*S*)-**2e**, (*S*)-**13f**, and (*S*)-**13g**

	13a	13b	(<i>S</i>)- 2d	(<i>S</i>)- 2e	(<i>S</i>)- 13f	(<i>S</i>)- 13g
Crystallized from	MeOH/CH ₂ Cl ₂ /Et ₂ O/ petroleum ether	AcOEt/MeOH/ petroleum ether	CD ₃ OD	MeOH/AcOEt	CD ₃ OD	AcOEt/MeOH/ petroleum ether
Empirical formula	C ₃₁ H ₄₉ BrN ₆ O ₇ ·0.3H ₂ O	C ₃₃ H ₅₁ BrN ₆ O ₇	C ₃₄ H ₅₆ N ₆ O ₈	C ₃₆ H ₅₈ N ₆ O ₈	C ₃₄ H ₅₅ BrN ₆ O ₇	C ₃₇ H ₅₃ BrN ₆ O ₇ ·2 MeOH
Formula weight	703.67	723.70	676.85	702.89	739.75	837.85
[g mol ⁻¹]						
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism	colorless, prism	colorless, plate	colorless, needle
Crystal dimensions	0.30 × 0.35 × 0.36	0.15 × 0.30 × 0.35	0.22 × 0.25 × 0.30	0.15 × 0.30 × 0.32	0.02 × 0.15 × 0.20	0.07 × 0.17 × 0.48
[mm]						
Temp. [K]	173(1)	173(1)	160(1)	160(1)	160(1)	173(1)
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	monoclinic
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> 1	<i>P</i> 2 ₁
<i>Z</i>	2	2	2	2	2	2
Reflections for cell	18	25	5592	5774	111558	21
determination						
2θ Range for cell	39–40	24–26	4–60	4–60	4–50	20–35
determination [°]						
Unit cell parameters						
<i>a</i> [Å]	9.805(5)	9.860(3)	9.9878(1)	9.9161(1)	9.6894(1)	9.734(7)
<i>b</i> [Å]	19.077(7)	19.654(2)	17.3900(2)	17.3616(2)	9.7484(1)	17.358(5)
<i>c</i> [Å]	10.719(4)	10.608(4)	10.7563(1)	11.2766(2)	23.0357(3)	13.348(5)
<i>α</i> [°]	90	90	90	90	100.9970(7)	90
<i>β</i> [°]	114.32(3)	114.68(3)	94.2612(4)	95.3358(5)	92.7939(7)	108.22(4)
<i>γ</i> [°]	90	90	90	90	111.3514(5)	90
<i>V</i> [Å ³]	1827(1)	1868(1)	1863.07(3)	1932.96(5)	1972.62(4)	2142(2)
<i>D_x</i> [g cm ⁻³]	1.279	1.287	1.206	1.208	1.245	1.299
<i>μ</i> (MoK _α) [mm ⁻¹]	1.179	1.155	0.0862	0.0856	1.095	0.0693
Transmission factors	0.890; 1.000	0.866; 1.000	–	–	0.754; 0.915	0.918; 1.000
(min; max)						
Diffractometer	Rigaku AFC5R	Rigaku AFC5R	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD	Rigaku AFC5R
Scan type	ω/2θ	ω/2θ	φ and ω	φ and ω	φ and ω	ω/2θ
2θ _(max) [°]	55	50	60	60	50	50

Table 6 (cont.)

	13a	13b	(S)-2d	(S)-2e	(S)-13f	(S)-13g
Total reflections measured	9138	6039	55755	56770	58675	6859
Symmetry-independent reflections	8389	5461	10762	5818	13585	6154
Reflections with $I > 2\sigma(I)$	5234	3594	8966	4972	11501	3974
Reflections used in refinement	8389	5460	10754	5815	13583	6154
Parameters refined; restraints	466; 86	498; 98	465; 1	501; 7	983; 129	533; 1
$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0502	0.0453	0.0379	0.0375	0.0427	0.0491
$wR(F^2)$ (all data)	0.1009	0.0931	0.0849	0.0900	0.1024	0.1156
Weighting parameters (a ; b) ^{a)}	0; 2.2644	0.0115; 2.0792	0.04; 10.0705	0.0399; 0.1392	0.0437; 0.8945	0.0381; 0
Goodness-of-fit	1.016	1.019	1.034	1.033	1.050	1.023
Secondary extinction coefficient	–	0.0019(3)	0.025(2)	0.033(3)	0.0083(9)	–
Final A_{max}/σ	0.001	0.001	0.001	0.001	0.002	0.004
$\Delta\rho$ (max; min) [e Å ⁻³]	0.43; –0.60	0.52; –0.48	0.24; –0.16	0.20; –0.21	0.66; –0.57	0.33; –0.40
Structure solution program	DIRDIF 92 [42]	DIRDIF 92	SHELXS97 [43]	SHELXS97	SIR92 [44]	DIRDIF 92

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

15. *X-Ray Crystal-Structure Determination of 13a, 13b, (S)-2d, (S)-2e, (S)-13f, (S)-13g, (R)-6c, (R)-7c, and (R)-7d* (see Tables 6 and 7, and Figs. 1 and 2)⁴⁾. All measurements were conducted at low temp. using graphite-monochromated MoK α radiation (λ 0.71073 Å). The data collection and refinement parameters are given in Tables 6 and 7, and views of the molecules are shown in Figs. 1 and 2. The intensities were corrected for Lorentz and polarization effects, and for 13a, 13b, and (S)-13g, an empirical absorption correction, based on azimuthal scans of several reflections, was also applied [40]. For (S)-13f, a numerical absorption correction [41] was applied. Equivalent reflections, including Friedel pairs for (S)-2e, (R)-6c, and (R)-7d, were merged. Structures 13a, 13b, and (S)-13g were solved by Patterson methods using DIRDIF 92 [42], which revealed the positions of the Br-atom. All remaining non-H-atoms were located in Fourier expansions of the Patterson solution. Structures of (S)-2d, (S)-2e, (S)-13f, (R)-6c, and (R)-7c were solved by direct methods, which revealed the positions of all non-H-atoms.

In 13a, the asymmetric unit contains one peptide molecule plus a site partially occupied by a H₂O molecule. The O-atom of the H₂O molecule has a site occupation factor of ca. 0.33. The H-atom positions were not defined for the H₂O molecule. The i-Bu group is disordered. Two sets of positions were defined for each of the atoms of this group, and the site occupation factor of the major conformation of this group refined to 0.519(4). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighboring atoms within and between each conformation of the disordered group were restrained to have similar atomic displacement parameters. In 13b, the i-Bu group is also disordered and was modelled analogously to 13a; the site occupation factor of the major conformation refined to 0.629(6). In (S)-2e, the five-membered ring is disordered over two conformations. Two positions were defined for the atom C(33) of this ring, and the site occupation factor of the major conformation refined to 0.55(1). Similarity restraints were applied to the C–C bond lengths involving the disordered atom. In (S)-13f, 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 [45], but none could be found. Disorder is present in the i-Bu substituents at C(2) of molecule A, and C(42) and C(48) of molecule B. Two positions were defined for the two terminal Me groups and the methine C-atom of each disordered group, but in some cases, particularly at C(2) and C(48), the behavior of the refinement suggested that the atoms of these groups adopt several orientations which results in the electron density in these regions being smeared out. Restraints were applied to the bond lengths and the anisotropic displacement parameters of the disordered atoms. The site occupation factors of the major conformations refined to values ranging from 0.505(9) (group at C(2)) to 0.66(1) (group at C(42)). In (S)-13g, the asymmetric unit contains one molecule of the peptide and two molecules of MeOH.

The non-H-atoms were refined anisotropically, except for atom C(6) in (S)-13g, which was refined isotropically. The OH H-atoms, where present, and the amide H-atoms, except for those in 13a and (S)-13f, were placed in the positions indicated by difference electron-density maps, and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms in the structures 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 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for the Me groups). The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F^2)^2$. Corrections for secondary extinction were applied, except for 13a and (S)-13g. The crystals of each compound were enantiomerically pure, and the absolute configuration was determined experimentally for 13a, 13b, (S)-13f, and (S)-13g (absolute structure parameters [46] of $-0.005(8)$, $-0.012(10)$, $0.004(5)$, and $-0.003(11)$, resp.). The absolute configurations of the other compounds could not be determined, as no atoms exhibiting significant anomalous scattering are present. In these latter cases, the enantiomer used in each refinement was based on the known configuration derived from the synthetic precursors of the molecule.

⁴⁾ CCDC-670070–670078 contain 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.

Table 7. Crystallographic Data of Compounds (R)-**6c**, (R)-**7c**, and (R)-**7d**

	(R)- 6c	(R)- 7c	(R)- 7d
Crystallized from	MeOH	MeOH/CH ₂ Cl ₂	CD ₃ OD
Empirical formula	C ₂₃ H ₃₅ N ₃ O ₆	C ₂₄ H ₃₈ N ₄ O ₅	C ₂₅ H ₄₀ N ₄ O ₅
Formula weight [g mol ⁻¹]	449.54	462.59	476.61
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism
Crystal dimensions [mm]	0.15 × 0.25 × 0.25	0.15 × 0.20 × 0.25	0.22 × 0.28 × 0.30
Temp. [K]	160(1)	160(1)	160(1)
Crystal system	orthorhombic	orthorhombic	orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>Z</i>	4	4	4
Reflections for cell determination	3143	4170	3446
2 θ Range for cell determination [°]	4–55	4–60	4–55
Unit cell parameters			
<i>a</i> [Å]	11.2008(2)	11.0674(1)	10.7082(2)
<i>b</i> [Å]	12.6246(2)	13.3562(2)	14.3736(3)
<i>c</i> [Å]	17.0682(3)	17.2406(3)	17.3511(4)
<i>V</i> [Å ³]	2413.54(7)	2548.48(6)	2670.60(10)
<i>D_x</i> [g cm ⁻³]	1.237	1.206	1.185
μ (MoK α) [mm ⁻¹]	0.0894	0.0848	0.0828
Diffractometer	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD
Scan type	ϕ and ω	ϕ and ω	ϕ and ω
2 $\theta_{\text{(max)}}$ [°]	55	60	55
Total reflections measured	34028	51767	37349
Symmetry independent reflections	3126	7453	3430
Reflections with <i>I</i> > 2 σ (<i>I</i>)	2618	5722	2879
Reflections used in refinement	3121	7449	3426
Parameters refined	312	322	332
<i>R</i> (<i>F</i>) [<i>I</i> > 2 σ (<i>I</i>) reflections]	0.0394	0.0419	0.0451
<i>wR</i> (<i>F</i> ²) (all data)	0.1002	0.1012	0.1216
Weighting parameters (<i>a</i> ; <i>b</i>) ^a)	0.0516; 0.3241	0.0503; 0.2152	0.0643; 0.5627
Goodness-of-fit	1.052	1.025	1.036
Secondary extinction coefficient	0.015(2)	0.011(2)	0.023(3)
Final $\Delta_{\text{max}}/\sigma$	0.001	0.001	0.001
$\Delta\rho$ (max; min) [e Å ⁻³]	0.17; –0.17	0.17; –0.18	0.36; –0.17
Structure solution program	SIR92	SIR92	SIR92

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

Neutral-atom scattering factors for non-H-atoms were taken from [47], and the scattering factors for H-atoms were taken from [48]. Anomalous dispersion effects were included in F_{calc} [49]; the values for f' and f'' were those of [50]. The values of the mass attenuation coefficients are those of [51]. All calculations were performed using the SHELXL97 program [52].

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