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

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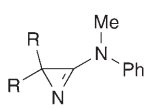
Dedicated to Professor *Dieter Seebach* on the occasion of his 70th birthday

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-disubstitued glycine-containing peptides.

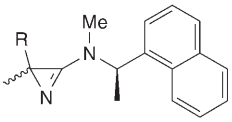
1. Introduction. – Within the last 30 years, 2,2-disubstituted glycines (*i.e.*, α,α-disubstituted α-amino acids) attracted increasing interest as structural units in biologically active heterocycles (see, *e.g.*, [1]) and in conformationally restricted peptides (see, *e.g.*, [2]). Of special significance 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 ($NaphthEtNH_2$) as the chiral auxiliary [19].

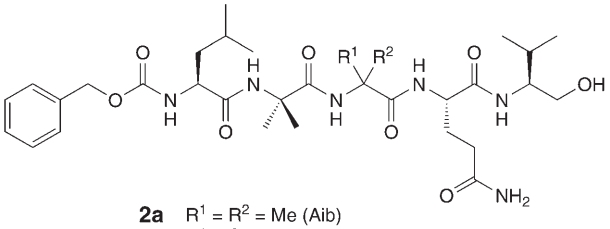
[1]) Part of the Ph.D. thesis and the Diploma thesis of *K. B.*, Universität Zürich.



1a R = Me
1b R–R = –$(CH_2)_4$–



1c R = Et
1d R = ^{i}Pr
1e R = cPent
1f R = ^{i}Bu
1g R = Bn



2a $R^1 = R^2$ = Me (Aib)
2b R^1–R^2 = –$(CH_2)_4$– (Ac_5c)
2c R^1 = Et, R^2 = Me (Iva)
2d R^1 = ^{i}Pr, R^2 = Me (Val(2Me))
2e R^1 = cPent, R^2 = Me (Ala(2cPent))
2f R^1 = ^{i}Bu, R^2 = Me (Leu(2Me))
2g R^1 = Bn, R^2 = Me (Phe(2Me))

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-NR^3R^4 **3a**–**3g** were prepared by the 'azirine/oxazolone method'. First, Z-Leu-OH was coupled with **1a**, the synthon for Aib, in Et_2O or CH_2Cl_2 at room temperature, to yield the dipeptide amide **4**, which was hydrolyzed at room temperature with 3N HCl (H_2O/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

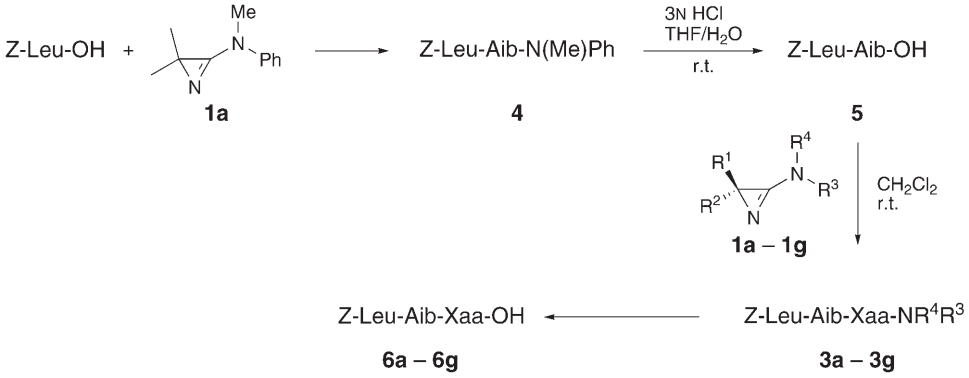


Table 1. *Synthesis of the Tripeptide Amides* **3** *from Dipeptide* **5**

Xaa	Azirine **1**	R^1, R^2	R^3, R^4	Tripeptide amide	
				3	Yield [%]
Aib	**1a**	Me, Me	Ph, Me	**3a**	95
Ac_5c	**1b**	$-(CH_2)_4-$	Ph, Me	**3b**	97
(*S*)-Iva	(2*S*)-**1c**	Me, Et	NaphthEt, Me	(*S*)-**3c**	77 [19]
	(2*S*)-**1i**	Me, Et	PhEt, Me	(*S*)-**3i**	93 [18]
(*R*)-Iva	(2*R*)-**1c**	Et, Me	NaphthEt, Me	(*R*)-**3c**	83 [19]
	(2*R*)-**1i**	Et, Me	PhEt, Me	(*R*)-**3i**	91 [18]
(*S*)-Val(2Me)	(2*S*)-**1d**	^{i}Pr, Me	NaphthEt, Me	(*S*)-**3d**	67 [19]
(*R*)-Val(2Me)	(2*R*)-**1d**	Me, ^{i}Pr	NaphthEt, Me	(*R*)-**3d**	69 [19]
(*S*)-Ala(2cPent)	(2*S*)-**1e**	cPent, Me	NaphthEt, Me	(*S*)-**3e**	39 [19]
(*R*)-Ala(2cPent)	(2*R*)-**1e**	Me, cPent	NaphthEt, Me	(*R*)-**3e**	38 [19]
(*S*)-Leu(2Me)	(2*S*)-**1f**	^{i}Bu, Me	NaphthEt, Me	(*S*)-**3f**	64 [19]
(*R*)-Leu(2Me)	(2*R*)-**1f**	Me, ^{i}Bu	NaphthEt, Me	(*R*)-**3f**	60 [19]
(*S*)-Phe(2Me)	(2*S*)-**1h**	Bn, Me	'Prolinol'	(*S*)-**3h**	70
	(2*S*)-**1g**	Bn, Me	NaphthEt, Me	(*S*)-**3g**	59 [19]
(*R*)-Phe(2Me)	(2*R*)-**1h**	Me, Bn	'Prolinol'	(*R*)-**3h**	79
	(2*R*)-**1g**	Me, Bn	NaphthEt, Me	(*R*)-**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 significiant N–H ··· O H-bonding interaction.

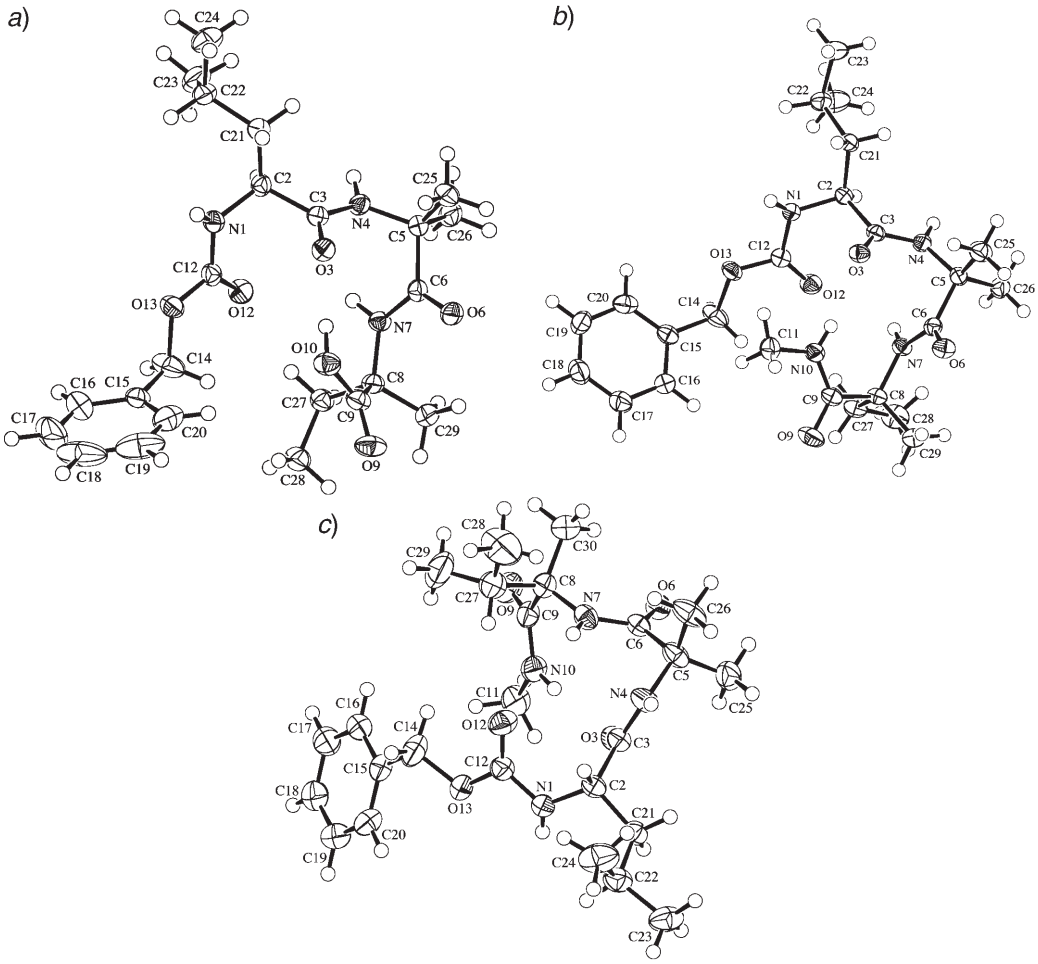


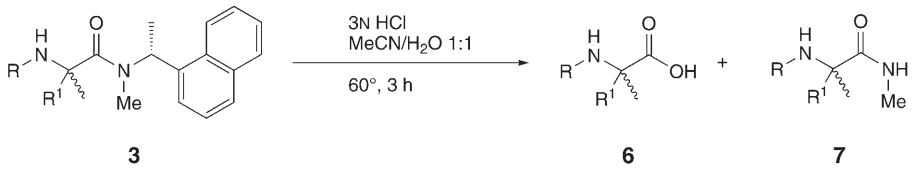
Fig. 1. *ORTEP Plots* [20] *of the molecular structures of* a) (R)-**6c** (Z-Leu-Aib-(*R*)-Iva-OH), b) (R)-**7c** (Z-Leu-Aib-(*R*)-Iva-NHMe), *and* c) (R)-**7d** (Z-Leu-Aib-(*R*)-Val(2Me)-NHMe) (50% probability ellipsoids, arbitrary numbering of atoms)

The standard conditions for the hydrolysis of peptide amides with a *N*-methylanilide group are 3N HCl (H_2O/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 H_2O/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 CH_2(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



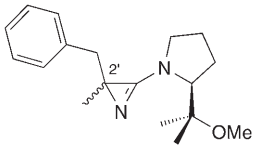
3 **6** **7**

R = Z-Leu-Aib, R^1 = Et, ^{i}Pr, cPent, ^{i}Bu, Bn

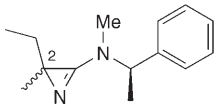
The solid-state structures of (*R*)-**7c** and (*R*)-**7d** also exhibit the same H-bonding motifs and three-dimensional framework as described above for (*R*)-**6c** with the carboxylic acid group now replaced by the amide group involving N(10)–H. N(7)–H is positioned in approximately the correct position 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 significiant 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.



(2′*R*)-**1h**
(2′*S*)-**1h**



(2*R*)-**1i**
(2*S*)-**1i**

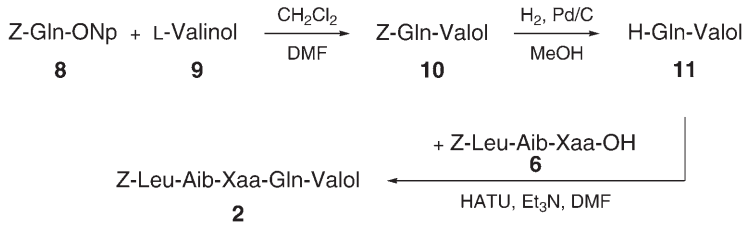
Table 2. *Synthesis of the Model Pentapeptides* **2** *and* **13** *from Tripeptide Amides* **3**

Xaa	R^1, R^2	R^3, R^4	Tripeptide acid		Side product from hydrolysis		Pentapeptide		*p*BrBz-Pentapeptide	
			6	Yield [%]	**7**	Yield [%]	**2**	Yield [%]	**13**	Yield [%]
Aib	Me, Me	Ph, Me	**6a**	88			**2a**	77	**13a**	78
Ac_5c	$-(CH_2)_4-$	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	(*S*)-**2d**	37		
(*R*)-Val(2Me)	Me, ^{i}Pr	NaphthEt, Me	(*R*)-**6d**	80	(*R*)-**7d**	9	(*R*)-**2d**	41		
(*S*)-Ala(2cPent)	cPent, Me	NaphthEt, Me	(*S*)-**6e**	74	(*S*)-**7e**	[a])	(*S*)-**2e**	43		
(*R*)-Ala(2cPent)	Me, cPent	NaphthEt, Me	(*R*)-**6e**	76	(*R*)-**7e**	[a])	(*R*)-**2e**	28		
(*S*)-Leu(2Me)	^{i}Bu, Me	NaphthEt, Me	(*S*)-**6f**	47	(*S*)-**7f**	28	(*S*)-**2f**	60	(*S*)-**13f**	70
(*R*)-Leu(2Me)	Me, ^{i}Bu	NaphthEt, Me	(*R*)-**6f**	53	(*R*)-**7f**	35	(*R*)-**2f**	53	(*R*)-**13f**	30
(*S*)-Phe(2Me)	Bn, Me	NaphthEt, Me	(*S*)-**6g**	25	(*S*)-**7g**	[a])	(*S*)-**2g**	49	(*S*)-**13g**	73
		'Prolinol'	(*S*)-**6h**	80						
(*R*)-Phe(2Me)	Me, Bn	NaphthEt, Me	(*R*)-**6g**	36	(*R*)-**7g**	[a])	(*R*)-**2g**	56	(*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 CH_2Cl_2 and DMF (active-ester method; *Scheme 3*). The obtained Z-Gln-Valol (**10**) was deprotected by hydrogenolytic cleavage of the Z group (H_2, 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 H_2 and Pd/C. After filtration over *Celite*, the deprotected pentapeptide **12** was reacted with 4-bromobenzoyl chloride in the presence of Et_3N in CH_2Cl_2 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-Ac_5c-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

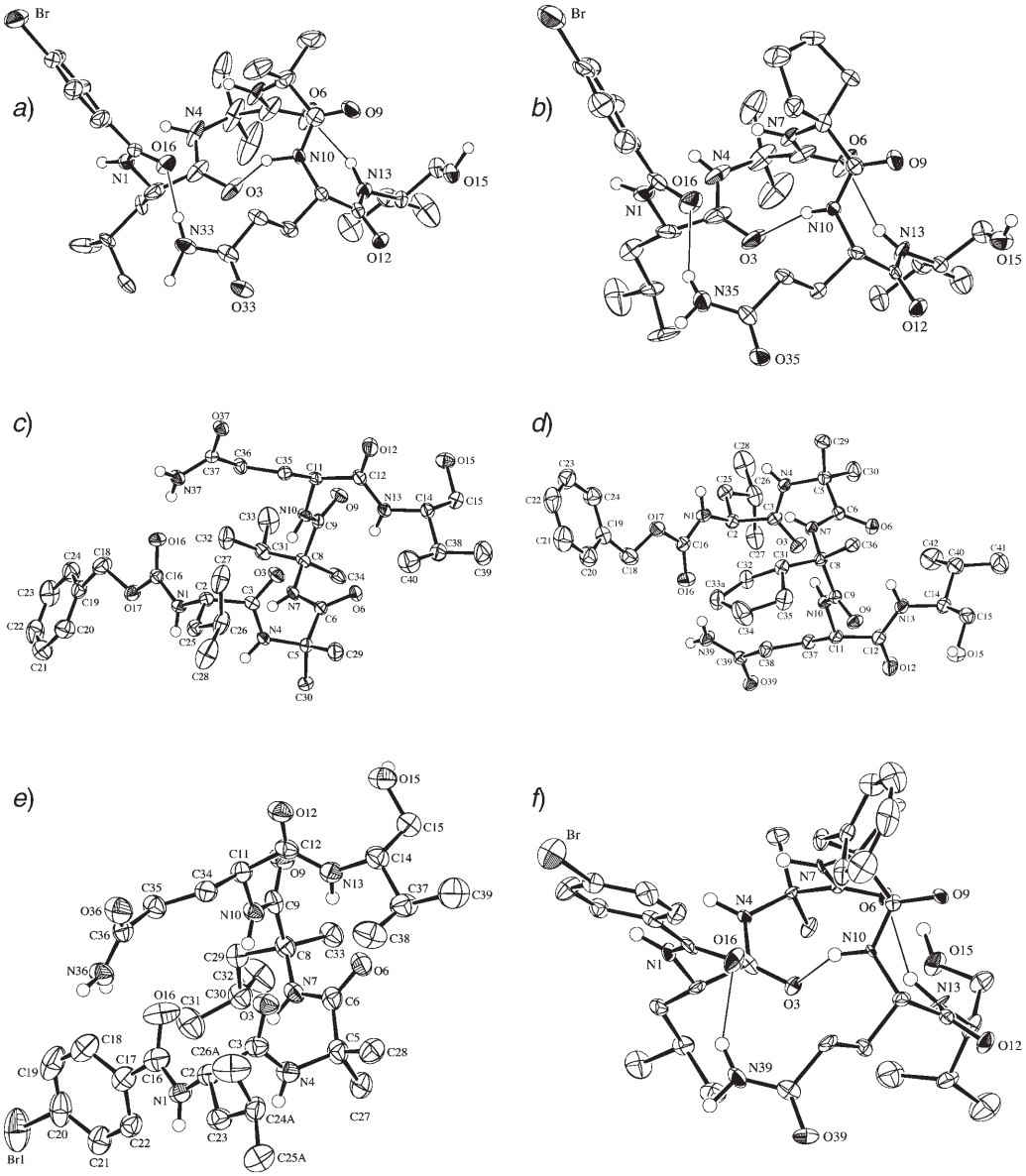


Fig. 2. *ORTEP Plots* [20] *of the molecular structures of* a) **13a** (*p*BrBz-Leu-Aib-Aib-Gln-Valol), b) **13b** (*p*BrBz-Leu-Aib-Ac$_5$c-Gln-Valol), c) (S)-**2d** (Z-Leu-Aib-(*S*)-Val(2Me)-Gln-Valol), d) (S)-**2e** (Z-Leu-Aib-(*S*)-Ala(2cPent)-Gln-Valol), e) *one of the two symmetry-independent molecules 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 $C_2^2(10)$. 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
(*S*)-**2d**	–49.6(2)	–44.6(1)	–58.9(1)	–24.9(1)	III
(*S*)-**2e**	–51.3(2)	–43.3(2)	–60.1(2)	–23.1(2)	III
(*S*)-**13f**, mol. A	–54.8(4)	–43.1(3)	–62.7(3)	–26.5(3)	III
(*S*)-**13f**, mol. B	–54.3(4)	–42.9(4)	–59.7(4)	–28.6(4)	III
(*S*)-**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
(*S*)-**2d**	–58.9(1)	–24.9(1)	–77.1(1)	–1.0(2)	I
(*S*)-**2e**	–60.1(2)	–23.1(2)	–76.8(2)	–2.0(2)	I
(*S*)-**13f**, mol. A	–62.7(3)	–26.5(3)	–75.6(3)	–9.3(4)	I
(*S*)-**13f**, mol. B	–59.7(4)	–28.6(4)	–76.8(4)	–8.3(4)	I
(*S*)-**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 ^{1}H-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.

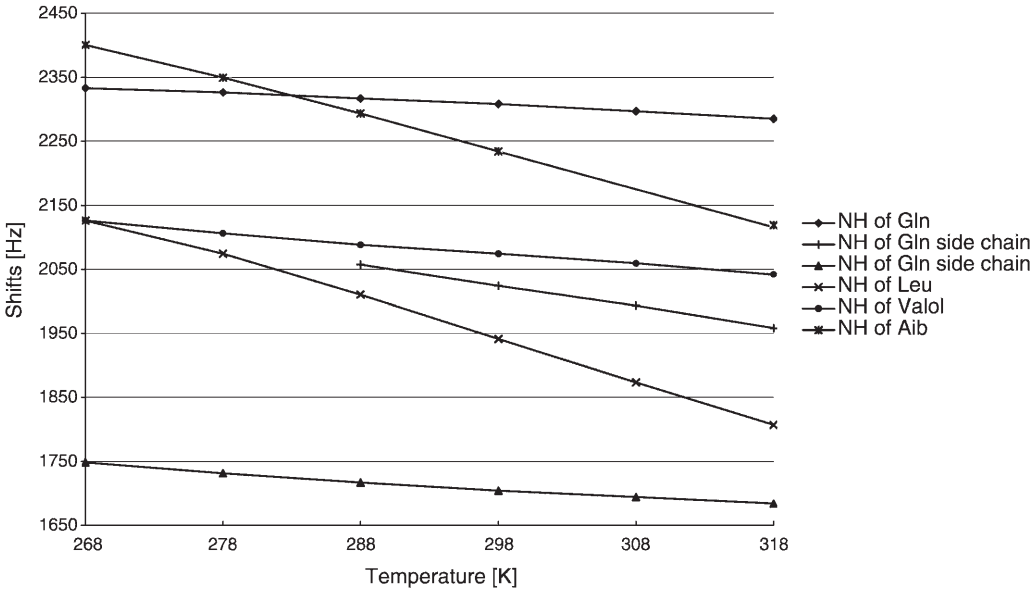


Fig. 3. *Temperature dependence of the signals of the amide H-atoms of* (S)-**2g**

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.

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Experimental Part

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

2. P*reparation 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. CH_2Cl_2 (50 ml), a soln. of Z-Gln-ON*p* (**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 $CHCl_3$ (25 ml) and stirred for 18 h at r.t.; then, additional $CHCl_3$ (50 ml) was added. After 2 h, the precipitate was filtered, and washed with AcOEt/$CHCl_3$ 1:1 and Et_2O. Recrystallization from EtOH yielded 1.717 g (73%) of **10**. Colorless crystals. M.p. 186.6–187.0°. R_f (CH_2Cl_2/MeOH 10:1) 0.20. IR: 3430*s*, 3300*s*, 3200*m*, 3080*w*, 3060*w*, 2960*m*, 2930*m*, 2870*m*, 1680*s*, 1660*s*, 1645*s*, 1555*s*, 1535*s*, 1505*m*, 1470*m*, 1465*m*, 1445*m*, 1415*m*, 1390*m*, 1370*m*, 1350*m*, 1330*m*, 1260*s*, 1245*s*, 1190*w*, 1140*w*, 1060*m*, 1040*m*, 1020*m*, 995*w*, 940*w*, 910*w*, 880*w*, 855*w*, 770*w*, 745*m*. ^{1}H-NMR (CD_3OD): 7.35–7.3 (*m*, 5 arom. H); 5.08 (br. *s*, PhCH_2O); 4.14 (*dd*, *J* = 8.5, 5.8, CH(2) of Gln); 3.7–3.55 (*m*, CH(2) and CH_2(1) of Valol); 2.31 (*t*, *J* = 7.5, CH_2(4) of Gln); 2.15–1.8 (*m*, CH(3) of Valol, CH_2(3) of Gln); 0.93, 0.89 (2*d*, *J* = 6.8, 2 Me(4) of Valol). ^{13}C-NMR (CD_3OD): 177.8 (*s*, $CONH_2$); 174.3 (*s*, CONH); 158.3 (*s*, OCONH); 138.1 (*s*, 1 arom. C); 129.4, 128.9, 128.8 (3*d*, 5 arom. CH); 67.6 (*t*, PhCH_2O); 63.0 (*t*, C(1) of Valol); 58.0, 56.0 (2*d*, 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 (2*q*, 2 Me(4) of Valol). ESI-MS (MeOH): 404 (31, $[M+K]^+$), 388 (100, $[M+Na]^+$). Anal. calc. for $C_{18}H_{27}N_3O_5$ (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 H_2 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: 3350*s*, 3280*s*, 3200*s*, 3110*s*, 2950*s*, 2930*s*, 2870*m*, 1690*s*, 1680*s*, 1670*s*, 1645*s*, 1630*s*, 1615*s*, 1565*s*, 1550*s*, 1515*m*, 1505*m*, 1465*m*, 1450*m*, 1415*s*, 1385*m*, 1370*m*, 1350*m*, 1335*m*, 1310*m*, 1280*m*, 1245*m*,

1200*w*, 1150*m*, 1080*m*, 1070*m*, 1025*m*, 975*m*, 950*m*, 875*w*, 845*w*, 815*w*, 780*w*, 770*w*, 715*m*. ^{1}H-NMR: 3.7–3.5 (*m*, CH_2(1) of Valol, CH(2) of Gln); 3.4–3.3 (*m*, CH(2) of Valol); 2.35–2.3 (*m*, CH_2(4) of Gln); 2.0–1.75 (*m*, CH_2(3) of Gln, CH(3) of Valol); 0.96, 0.93 (2*d*, *J* = 6.9, 6.8, 2 Me of Valol). ^{13}C-NMR: 178.3, 177.1 (2*s*, $CONH_2$, CONH); 63.0 (*t*, C(1) of Valol); 57.9, 55.7 (2*d*, C(2) of Gln, C(2) of Valol); 32.7, 32.5 (2*t*, C(3), C(4) of Gln); 30.0 (*d*, C(3) of Valol); 19.8, 18.8 (2*q*, 2 Me of Valol). CI-MS (NH_3): 233 (11), 232 (100, $[M+1]^+$), 229 (10), 215 (20), 214 (12), 129 (5), 104 (7), 101 (6).

3. P*eptides 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. CH_2Cl_2 (25 ml), *2,2,*N-*trimethyl*-N-*phenyl-2*H-*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 ($MgSO_4$), and evaporated: 1.645 g (95%) of **3a**. Colorless solid. M.p. 57.1–57.8°. R_f (CH_2Cl_2/MeOH 10:1) 0.51; R_f (CH_2Cl_2/MeOH 20:1) 0.18. IR: 3310*s*, 3060*m*, 3030*m*, 2955*s*, 2870*m*, 2140*w*, 1950*w*, 1880*w*, 1820*w*, 1705v*s*, 1690v*s*, 1680v*s*, 1660v*s*, 1640v*s*, 1595*s*, 1540–1520v*s*, 1495v*s*, 1470*s*, 1455*s*, 1390*s*, 1365*s*, 1315*m*, 1265–1240*s*, 1220*s*, 1170*m*, 1120*m*, 1090*s*, 1070*m*, 1045*m*, 1030*m*, 1005*w*, 965*w*, 920*w*, 910*w*, 875*w*, 840*w*, 825*w*, 770*m*, 740*m*, 705*s*. ^{1}H-NMR (CD_3OD): 7.4–7.2 (*m*, 10 arom. H); 5.15, 5.09 (*AB*, *J* = 12.8, PhCH_2O); 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*, CH_2(3) of Leu); 1.47, 1.44, 1.41, 1.38 (4*s*, 4 Me of 2 Aib); 0.96, 0.93 (2*d*, *J* = 6.7, 6.5, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 176.2, 175.6, 175.2 (3*s*, 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 (4*d*, 10 arom. CH); 67.6 (*t*, PhCH_2O); 58.7, 58.2 (2*s*, 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*, 3*q*, C(4) of Leu, 4 Me of 2 Aib); 23.4, 22.4 (2*q*, 2 Me of Leu). ESI-MS (NaI): 547 (100, $[M+Na]^+$). Anal. calc. for $C_{29}H_{40}N_4O_5 \cdot H_2O$ (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/H_2O 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 CH_2Cl_2. During this operation, the precipitate dissolved. The org. soln. was dried ($MgSO_4$) and evaporated. Washing of the residue with AcOEt yielded 1.005 g (88%) of **6a**. Colorless solid. M.p. 192–193°. R_f (CH_2Cl_2/MeOH 10:1) 0.18–0.07. IR: 3385*m*, 3330*s*, 3290*s*, 3060*w*, 3030*w*, 2980*w*, 2950*m*, 2865*w*, 1740*s*, 1705v*s*, 1660*s*, 1550*m*, 1525*s*, 1500*m*, 1470*w*, 1455*w*, 1440*w*, 1385*m*, 1365*w*, 1315*s*, 1295*m*, 1270*s*, 1245*s*, 1220*m*, 1175*w*, 1130*w*, 1120*w*, 1080*w*, 1045*m*, 1030*w*, 990*w*, 970*w*, 945*w*, 910*w*, 850*w*, 785*w*, 765*w*, 755*w*, 740*w*, 730*w*. ^{1}H-NMR (CD_3OD): 7.35–7.25 (*m*, 5 arom. H); 5.13, 5.08 (*AB*, *J* = 12.6, PhCH_2O); 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, CH_2(3) of Leu); 1.44, 1.43, 1.42, 1.40 (4*s*, 4 Me of 2 Aib); 0.96, 0.93 (2*d*, *J* = 6.5, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 178.0, 175.9, 175.1 (3*s*, COOH, 2 CONH); 158.7 (*s*, OCONH); 138.3 (*s*, 1 arom. C); 129.5, 129.0, 128.6 (3*d*, 5 arom. CH); 67.6 (*t*, PhCH_2O); 57.9, 57.1 (2*s*, 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 (6*q*, 4 Me of 2 Aib, 2 Me of Leu). ESI-MS (NaI): 458 (100, $[M+Na]^+$). Anal. calc. for $C_{22}H_{33}N_3O_6$ (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 Et_3N (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 ($MgSO_4$), and evaporated. Recrystallization from AcOEt/hexane yielded 114 mg (77%) **2a**. Colorless crystals. M.p. 170–172°. R_f (CH_2Cl_2/MeOH 10:1) 0.16. IR: 3310*s*, 3030*w*, 2960*m*, 2870*w*, 1655v*s*, 1535*s*, 1470*w*, 1455*w*, 1385*w*, 1365*w*, 1335*w*, 1310*w*, 1265*m*, 1230*w*, 1170*w*, 1120*w*, 1040*w*, 1030*w*, 925*w*, 850*w*, 790*w*, 740*w*. ^{1}H-NMR (CD_3OD): 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, PhCH_2O); 4.15–4.05 (*m*, CH(2) of Gln, CH(2) of Leu); 3.7–3.65 (*m*, CH(2) and CH_2(1) of Valol); 2.4–2.35 (*m*, CH_2(4) of Gln); 2.25–2.2 (*m*, CH_2(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*, CH_2(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). ^{13}C-NMR (CD_3OD): 177.9, 177.8, 176.8, 176.1, 174.4 (5*s*, $CONH_2$,

4 CONH); 158.9 (*s*, OCONH); 138.4 (*s*, 1 arom. C); 129.6, 129.0, 128.6 (3*d*, 5 arom. CH); 67.8 (*t*, Ph*C*H$_2$O); 63.6 (*t*, C(1) of Valol); 58.6 (*d*, C(2) of Gln); 58.0, 57.8 (2*s*, 2 C(2) of 2 Aib); 56.2, 55.9 (2*d*, C(2) of Valol, C(2) 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 (6*q*, 4 Me of 2 Aib, 2 Me of Leu); 20.1, 19.4 (2*q*, 2 Me of Valol). ESI-MS (MeOH): 687 (25, $[M+K]^+$), 672 (94, $[M+Na]^+$), 650 (100, $[M+1]^+$). Anal. calc. for $C_{32}H_{52}N_6O_8 \cdot H_2O$ (666.82): C 57.64, H 8.01, H 12.60; found: C 57.38, H 7.97, N 12.24.

3.4. N-*{(*S*)-1-[({2-[(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* (p*BrBz-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 H_2 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 CH_2Cl_2 (5 ml), and Et_3N (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 ($MgSO_4$) and evaporated. The residue (59 mg, 78%, **13a**) was recrystallized from MeOH, CH_2Cl_2, Et_2O, and petroleum ether. Colorless crystals. M.p. 232.9–233.8°. R_f (CH_2Cl_2/MeOH 10:1) 0.15. IR: 3650*w*, 3420*s*, 3340v*s*, 3280v*s*, 3060*w*, 2980*m*, 2980*s*, 2960*s*, 2870*m*, 2540*w*, 2490*w*, 2440*w*, 2400*w*, 1675v*s*, 1660v*s*, 1650v*s*, 1595*s*, 1540v*s*, 1485*s*, 1465*s*, 1455*s*, 1440*s*, 1415*m*, 1390*s*, 1365*s*, 1340*m*, 1300*s*, 1235*m*, 1200*m*, 1175*m*, 1140*m*, 1070*m*, 1010*m*, 980*w*, 940*w*, 925*w*, 900*w*, 870*w*, 860*w*, 825*w*, 790*w*, 765*w*. ^{1}H-NMR (CD_3OD): 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*, CH_2(1) and CH(2) of Valol); 2.35–2.3 (*m*, CH_2(4) of Gln); 2.25–2.0 (*m*, CH_2(3) of Gln); 1.85–1.65 (*m*, CH(3) of Valol, CH(4) and CH_2(3) of Leu); 1.45–1.4 (*m*, 4 Me of 2 Aib); 1.01, 0.99, 0.87, 0.79 (4*d*, *J* = 5.9, 6.0, 6.7, 6.8, 2 Me of Leu, 2 Me of Valol). ^{13}C-NMR (CD_3OD): 178.0, 177.8, 176.9, 175.6, 174.3 (5*s*, $CONH_2$, 4 CONH); 169.6 (*s*, 1 CO (amide, *p*BrBz)); 134.0 (*s*, 1 arom. C); 132.8, 130.6 (2*d*, 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 (2*s*, 2 C(2) of 2 Aib); 56.1, 54.5 (2*d*, 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 (6*q*, 4 Me of 2 Aib, 2 Me of Leu); 20.1, 19.3 (2*q*, 2 Me of Valol). ESI-MS (TFA): 737 (6, $[M+K]^+$, ^{81}Br), 721 (39, $[M+Na]^+$, ^{81}Br), 699 (100, $[M+1]^+$, ^{81}Br), 681 (13, $[M-OH]^+$, ^{81}Br), 596 (18, $[M-Valol]^+$, ^{81}Br), 468 (15, $[M-Gln\text{-}Valol]^+$, ^{81}Br). Anal. calc. for $C_{31}H_{49}BrN_6O_7$ (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, CH_2Cl_2, Et_2O, and petroleum ether by slow evaporation of the solvent.

4. *Peptides with Xaa = Ac$_5$c.* 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-Ac$_5$c-N(Me)Ph*; **3b**). As described for **3a**, with **5** [19] (0.705 g, 2.01 mmol) in abs. CH_2Cl_2 (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 (CH_2Cl_2/MeOH 10:1) 0.52; R_f (CH_2Cl_2/MeOH 20:1) 0.16. IR: 3310*s*, 3060*m*, 3030*m*, 2955*s*, 2870*m*, 1950*w*, 1810*w*, 1705v*s*, 1660v*s*, 1595*s*, 1520v*s*, 1495v*s*, 1470*s*, 1455*s*, 1380*s*, 1310*m*, 1260v*s*, 1220*s*, 1170*m*, 1120*m*, 1045*s*, 1030*m*, 1005*w*, 985*w*, 955*w*, 910*w*, 840*w*, 765*m*, 735*m*, 700*s*. ^{1}H-NMR (CD_3OD): 7.4–7.2 (*m*, 10 arom. H); 5.13, 5.11 (*AB*, *J* = 12.8, Ph*CH*$_2$O); 4.00 (*t*, *J* = 7.5, CH_2(2) of Leu); 3.22 (br. *s*, MeN); 2.4–2.35, 2.3–2.2, 2.2–1.95 (3*m*, 4 H of Ac$_5$c); 1.75–1.65 (*m*, CH(4) of Leu, 4 H of Ac$_5$c); 1.6–1.5 (*m*, CH_2(3) of Leu); 1.47, 1.40 (2*s*, 2 Me of Aib); 0.96, 0.93 (2*d*, *J* = 6.6, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 176.3, 175.6, 175.3 (3*s*, 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 (6*d*, 10 arom. CH); 68.8 (*s*, C(2) of Ac$_5$c); 67.8 (*t*, Ph*CH*$_2$O); 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 (2*t*, 2 C(3) of Ac$_5$c); 26.1 (*d*, C(4) of Leu); 25.7, 25.6 (2*t*, 2 C(4) of Ac$_5$c); 26.8, 24.9, 23.5, 22.5 (4*q*, 2 Me of Aib, 2 Me of Leu). ESI-MS (NaI): 573 (100, $[M+Na]^+$). Anal. calc. for $C_{31}H_{42}N_4O_5 \cdot 0.33\ H_2O$ (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-Ac$_5$c-OH*; **6b**). As described for **6a**, with **3b** (750 mg, 1.36 mmol), 3N HCl (THF/H_2O 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 (CH_2Cl_2/MeOH 10:1)

0.13. IR: 3300*s*, 3060*m*, 3030*m*, 2955*s*, 2870*m*, 1740*s*, 1720v*s*, 1695v*s*, 1660v*s*, 1590*w*, 1530v*s*, 1470*m*, 1455*s*, 1410*m*, 1390*m*, 1365*m*, 1345*m*, 1330*m*, 1315*m*, 1250*s*, 1175*m*, 1120*m*, 1050*m*, 1030*m*, 1005*w*, 950*w*, 910*w*, 770*w*, 735*m*. ^{1}H-NMR (CD_3OD): 7.49 (br. *s*, NH); 7.35–7.3 (*m*, 5 arom. H); 5.15–5.05 (*m*, PhCH_2O); 4.02 (*t*, *J* = 7.5, CH(2) of Leu); 2.25–2.0 (*m*, 4 H of Ac_5c); 1.7–1.65 (*m*, CH(4) of Leu, 4 H of Ac_5c); 1.52 (*dd*, *J* = 7.5, 6.2, CH_2(3) of Leu); 1.43 (br. *s*, 2 Me of Aib); 0.96, 0.93 (2*d*, *J* = 6.7, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 177.8, 176.4, 175.0 (3*s*, COOH, 2 CONH); 158.7 (*s*, OCONH); 138.2 (*s*, 1 arom. C); 129.5, 129.1, 128.7 (3*d*, 5 arom. CH); 67.7 (*t*, PhCH_2O); 67.3 (*s*, C(2) of Ac_5c); 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 (2*t*, 2 C(3) of Ac_5c); 25.9 (*d*, C(4) of Leu); 25.6 (*t*, 2 C(4) of Ac_5c); 26.0, 24.7, 23.3, 22.2 (4*q*, 2 Me of Aib, 2 Me of Leu). ESI-MS (NaI): 506 (4, $[M + 2\,Na - 1]^+$), 484 (100, $[M + Na]^+$). Anal. calc. for $C_{24}H_{35}N_3O_6 \cdot 0.33\ H_2O$ (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-Ac$_5$c-Gln-Valol*; **2b**). A soln. of **6b** (239 mg, 0.518 mmol) and Et_3N (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 ($MgSO_4$), and evaporated. CC (CH_2Cl_2/MeOH 10:1) yielded 304 mg (87%) of **2b**. Colorless solid. M.p. 97.6–98.1°. R_f (CH_2Cl_2/MeOH 10:1) 0.17. IR: 3300*s*, 3035*w*, 2960*m*, 2870*w*, 1665v*s*, 1535*s*, 1470*m*, 1455*m*, 1405*w*, 1390*m*, 1365*w*, 1315*m*, 1270*m*, 1220*m*, 1170*w*, 1130*w*, 1120*w*, 1045*w*, 1030*w*, 960*w*, 925*w*, 910*w*, 890*w*, 850*w*, 820*w*, 790*w*, 740*w*. ^{1}H-NMR (CD_3OD): 7.35–7.25 (*m*, 5 arom. H); 5.16, 5.11 (*AB*, *J* = 12.7, PhCH_2O); 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 CH_2(1) of Valol); 2.4–2.3 (*m*, CH_2(4) of Gln, CH(3) of Valol); 2.25–2.15 (*m*, CH_2(3) of Gln); 2.0–1.85 (*m*, 4 H of Ac_5c); 1.75–1.55 (*m*, 4 H of Ac_5c, CH(4) and CH_2(3) of Leu); 1.40, 1.38 (2*s*, 2 Me of Aib); 1.0–0.9 (*m*, 2 Me of Leu, 2 Me of Valol). ^{13}C-NMR (CD_3OD): 177.8, 177.4, 177.2, 176.1, 174.4 (5*s*, $CONH_2$, 4 CONH); 159.1 (*s*, OCONH); 138.4 (*s*, 1 arom. C); 129.6, 129.0, 128.4 (3*d*, 5 arom. CH); 68.1 (*s*, C(2) of Ac_5c); 67.8 (*t*, PhCH_2O); 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 (2*d*, C(2) of Leu, C(2) of Valol); 41.3, 38.8, 37.4 (3*t*, C(3) of Leu, 2 C(3) of Ac_5c); 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 (2*t*, 2 C(4) of Ac_5c); 24.7, 23.2, 22.4 (3*q*, 2 Me of Aib, 2 Me of Leu); 20.1, 19.4 (2*q*, 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, $[M - Gln\text{-}Valol]^+$). Anal. calc. for $C_{34}H_{54}N_6O_8 \cdot 0.5\ H_2O$ (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* (p*BrBz-Leu-Aib-Ac$_5$c-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 H_2, 2 h at r.t., filtration over *Celite*, with CH_2Cl_2 (5 ml), Et_3N (18 mg, 0.178 mmol), 4-bromobenzoyl chloride (27 mg, 0.123 mmol), 1.5 h at r.t.; purification with CC (CH_2Cl_2/MeOH 10:1): 76 mg (85%) of **13b**. Colorless solid. M.p. 242.8–243.6°. R_f (CH_2Cl_2/MeOH 10:1) 0.18. IR: 3405*s*, 3340v*s*, 3250*s*, 3060*w*, 2960*s*, 2875*m*, 1675v*s*, 1655v*s*, 1590*s*, 1540v*s*, 1485*s*, 1470*m*, 1455*s*, 1440*m*, 1410*m*, 1390*m*, 1360*m*, 1340*m*, 1315*m*, 1295*m*, 1255*m*, 1220*m*, 1180*m*, 1170*m*, 1150*w*, 1140*w*, 1130*w*, 1110*w*, 1095*w*, 1070*w*, 1020*w*, 1010*m*, 980*w*, 940*w*, 920*w*, 870*w*, 850*w*, 820*w*, 790*w*, 760*w*. ^{1}H-NMR (CD_3OD): 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 CH_2(1) of Valol); 2.35–2.3 (*m*, CH_2(4) of Gln); 2.3–2.0 (*m*, CH_2(3) of Gln, CH(3) of Valol, 2 H of Ac_5c); 1.9–1.85 (*m*, CH(4) of Leu); 1.85–1.65 (*m*, CH_2(3) of Leu, 6 H of Ac_5c); 1.43 (*s*, 2 Me of Aib); 1.02, 0.99, 0.86, 0.78 (4*d*, *J* = 6.0, 6.2, 6.8, 6.8, 2 Me of Leu, 2 Me of Valol). ^{13}C-NMR (CD_3OD): 177.8, 177.4, 177.2, 175.7, 174.2 (5*s*, $CONH_2$, 4 CONH); 169.8 (*s*, 1 CO (amide, *p*BrBz)); 133.9 (*s*, 1 arom. C); 132.8, 130.6 (2*d*, 4 arom. CH); 127.5 (*s*, 1 arom. CBr); 68.2 (*s*, C(2) of Ac_5c); 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 (2*d*, C(2) of Leu, C(2) of Valol); 41.0, 38.5, 37.8 (3*t*, C(3) of Leu, 2 C(3) of Ac_5c); 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 Ac_5c); 25.7, 25.3, 23.3, 22.3 (4*q*, 2 Me of Aib, 2 Me of Leu); 20.0, 19.3 (2*q*, 2 Me of Valol). ESI-MS (TFA): 763 (6, $[M + K]^+$, ^{81}Br), 745 (35, $[M + Na]^+$, ^{81}Br), 725 (100, $[M + 1]^+$, ^{81}Br), 707 (22, $[M - OH]^+$, ^{81}Br), 622

(31, $[M - \text{Valol}]^+$, ^{81}Br), 494 (33, $[M - \text{Gln-Valol}]^+$, ^{81}Br). Anal. calc. for $C_{33}H_{51}N_6O_7$: 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/H_2O 1:1, 10 ml) was stirred for 3 h at 60°. The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. Prep. TLC (CH_2Cl_2/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 (CH_2Cl_2/MeOH 10:1) 0.06. IR: 3320*m*, 2960*m*, 1710*s*, 1660*s*, 1525*s*, 1455*m*, 1385*m*, 1365*w*, 1315*w*, 1245*m*, 1165*m*, 1130*w*, 1050*m*, 945*w*, 800*w*, 780*w*, 740*w*, 700*w*. ^{1}H-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., PhCH_2O); 4.15–4.1 (*m*, CH(2) of Leu); 2.05–1.9 (*m*, CH_2(3) of Iva or Leu); 1.7–1.5 (*m*, CH_2(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, *Me*CH_2 of Iva). ^{13}C-NMR: 173.8, 172.9 (2*s*, 2 CONH, COOH); 156.7 (*s*, OCONH); 136.0 (*s*, 1 arom. C); 128.5, 128.2, 127.8 (3*d*, 5 arom. CH); 67.1 (*t*, PhCH_2O); 60.3, 57.2 (2*s*, C(2) of Iva, C(2) of Aib); 54.3 (*d*, C(2) of Leu); 40.7, 29.1 (2*t*, 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 (5*q*, 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 $C_{23}H_{35}N_3O_6$ (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 (CH_2Cl_2/MeOH 10:1) 0.43. IR: 3385*m*, 3314*s*, 3017*w*, 2969*m*, 2871*w*, 1703vs, 1648vs, 1523vs, 1462*m*, 1442*w*, 1410*w*, 1385*w*, 1372*w*, 1362*w*, 1341*w*, 1312*w*, 1291*w*, 1271*w*, 1243*s*, 1216*m*, 1175*w*, 1134*w*, 1118*w*, 1083*w*, 1047*m*, 1030*w*, 969*w*, 944*w*, 916*w*, 846*w*, 804*w*, 790*w*, 749*w*, 737*w*, 699*w*, 670*w*, 630*w*. ^{1}H-NMR (CD_3OD): 7.35–7.3 (*m*, 5 arom. H); 5.07 (*s*, PhCH_2O); 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 (3*m*, CH_2(3) of Iva, CH_2(3) of Leu, CH(4) of Leu); 1.42, 1.39, 1.33 (3*s*, Me(3) of Iva, 2 Me of Aib); 0.97, 0.95 (2*d*, *J* = 6.8, 6.7, 2 Me of Leu); 0.78 (*t*, *J* = 7.5, Me(4) of Iva). ^{13}C-NMR (CD_3OD): *ca.* 177.5, 176, 175.5 (3*s*, 3 CONH); *ca.* 159 (*s*, OCONH); *ca.* 138 (*s*, 1 arom. C); 129.4, 128.9, 128.5 (3*d*, 5 arom. CH); 67.5 (*t*, PhCH_2O); 61.4, 58.0 (2*s*, C(2) of Iva, C(2) of Aib); 55.2 (*d*, C(2) of Leu); 41.2, 29.4 (2*t*, 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 (7*q*, MeN, 2 Me of Aib, Me(3) of Iva, Me(4) of Iva, 2 Me of Leu). CI-MS (NH_3): 464 (16), 463 (56, $[M + 1]^+$), 432 (14, $[M - \text{HNMe}]^+$), 356 (20), 355 (10, $[M - \text{OBn}]^+$). Anal. calc. for $C_{24}H_{38}N_4O_5 \cdot 0.2\ H_2O$ (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/H_2O 1:1, 8 ml), 3 h at 60°; CC (CH_2Cl_2/MeOH 100:2, then 100:3, 20:1, 10:1) and prep. TLC (CH_2Cl_2/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/H_2O 1:1, 0.5 ml), 3 h at 60°; prep. TLC (CH_2Cl_2/MeOH 10:1): 37 mg (84%) of (*R*)-**6c**.

*Data of (*R*)-***6c***.* Colorless solid. M.p. 69–71°. R_f (CH_2Cl_2/MeOH 10:1) 0.06. IR: 3393*s*, 3344*s*, 3280*s* 3065*m*, 2955*s*, 1738vs, 1706vs, 1664vs, 1522vs, 1456*m*, 1388*m*, 1376*m*, 1329*m*, 1272vs, 1244*s*, 1216*s*, 1172*w*, 1135*w*, 1046*s*, 975*w*, 914*w*, 848*w*, 788*w*, 733*w*, 697*m*. ^{1}H-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., PhCH_2O); 4.11 (br., CH(2) of Leu); 2.05–1.9 (*m*, CH_2(3) of Iva or Leu); 1.7–1.5 (*m*, CH_2(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, *Me*CH_2 of Iva). ^{13}C-NMR: *ca.* 177, 173 (2*s*, 2 CONH, COOH); *ca.* 157 (*s*, OCONH); *ca.* 136 (*s*, 1 arom. C); 128.5, 128.2, 127.9 (3*d*, 5 arom. CH); 67.2 (*t*, PhCH_2O); 60.4, *ca.* 58 (2*s*, C(2) of Iva, C(2) of Aib); 54.2 (*d*, C(2) of Leu); 40.8, 29.6 (2*t*, C(3) of Leu, C(3) of Iva); 24.6 (*d*, C(4) of Leu); 25.3, 22.8, 21.9, 7.9 (4*q*, 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-stucture 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: 3385*m*, 3314*s*, 3017*w*, 2969*s*, 2954*m*, 2871*w*, 2513*w*, 2483*w*, 1703*s*, 1648v*s*, 1523*s*, 1462*m*, 1406*w*, 1385*w*, 1372*w*, 1361*w*, 1349*w*, 1312*w*, 1291*m*, 1272*m*, 1244*m*, 1216*m*, 1175*w*, 1134*w*, 1118*w*, 1047*m*, 1030*w*, 968*w*, 944*w*, 917*w*, 848*w*, 789*w*, 748*w*, 699*w*, 629*w*. ^{1}H-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, PhC*H*$_2$O); 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 (3*s*, Me(3) of Iva, 2 Me of Aib); 0.96 (2*d*, *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 (3*s*, 3 CONH); 158.3 (*s*, OCONH); 137.9 (*s*, 1 arom. C); 129.3, 128.8, 128.3 (3*d*, 5 arom. CH); 67.4 (*t*, PhC*H*$_2$O); 61.1, 57.8 (2*s*, C(2) of Iva, C(2) of Aib); 55.1 (*d*, C(2) of Leu); 41.1, 31.6 (2*t*, 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 (7*q*, 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: 3320*s*, 2970*s*, 1715*s*, 1670*s*, 1535*s*, 1460*m*, 1390*m*, 1370*m*, 1250*s*, 1180*m*, 1165*m*, 1130*w*, 1050*m*, 955*w*, 785*w*, 745*w*, 705*m*. ^{1}H-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., PhC*H*$_2$O); 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 (3*s*, 2 CONH, COOH); 156.5 (*s*, OCONH); 136.0 (*s*, 1 arom. C); 128.5, 128.2, 127.9 (3*d*, 5 arom. CH); 67.1 (*t*, PhC*H*$_2$O); 63.5, 57.5 (2*s*, 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 (2*d*, C(3) of Val(2Me), C(4) of Leu); 25.1, 24.9, 22.8, 21.7, 18.0, 17.3, 16.9 (7*q*, 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: 3304*s*, 3035*w*, 2964*s*, 2873*w*, 1708*s*, 1664v*s*, 1540*s*, 1455*m*, 1411*w*, 1370*w*, 1311*w*, 1267*s*, 1222*m*, 1173*w*, 1120*w*, 1054*m*, 915*w*, 788*w*, 742*w*, 696*w*, 620*w*. ^{1}H-NMR (CD_3OD): 7.35–7.25 (*m*, 5 arom. H); 5.13, 5.09 (*AB*, *J* = 12.6, PhC*H*$_2$O); 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 (3*m*, 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 (3*d*, *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 (3*s*, 3 CONH); *ca*. 159 (*s*, OCONH); 138.2 (*s*, 1 arom. C); 129.4, 129.0, 128.5 (3*d*, 5 arom. CH); 67.6 (*t*, PhC*H*$_2$O); 61.4, 58.0 (2*s*, 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 (8*q*, 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) were added, and the mixure 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 (CH_2Cl_2/MeOH 10:1). Total yield of (*S*)-**2d**: 94 mg (37%). Colorless solid. M.p. 202–203°. R_f (CH_2Cl_2/MeOH 10:1) 0.17. IR: 3455*m*, 3335*s*, 3213*m*, 2957*m*, 2870*m*, 2369*w*, 2352*w*, 1706*s*, 1659*s*, 1615*m*, 1540*s*, 1456*m*, 1389*m*, 1274*m*, 1262*m*, 1171*m*, 1129*w*, 1043*w*, 698*m*. ^{1}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 (3*m*, 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 (2*m*, 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}C-NMR: 175.1, 174.9, 172.8 (3*s*, $CONH_2$, 4 CONH); 157.1 (*s*, OCONH); 136.5 (*s*, 1 arom. C); 128.5, 128.0, 127.4 (3*d*, 5 arom. CH); 66.8, 63.5 (2*t*, PhCH_2O, C(1) of Valol); 63.0, 57.0 (2*s*, C(2) of Aib, C(2) of Val(2Me)); 57.5, 55.8 (2*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); 39.9, 32.7, 27.7 (3*t*, C(4) and C(3) of Gln, C(3) of Leu); 35.6, 28.9, 24.6 (3*d*, 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 (9*q*, 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, $[M+Na]^+$), 680 (9), 679 (36), 678 (100, $[M+1]^+$). Anal. calc. for $C_{34}H_{56}N_6O_8 \cdot 0.33\ H_2O$ (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 (MeCN/H_2O 1:1, 20 ml), 2 h at 60°; CC (CH_2Cl_2/MeOH 100:2) and prep. TLC (CH_2Cl_2/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 (CH_2Cl_2/MeOH 10:1) 0.20. IR: 3320*s*, 2970*m*, 1720*s*, 1670*s*, 1540*s*, 1460*m*, 1390*m*, 1370*m*, 1250*m*, 1180*m*, 1165*m*, 1130*w*, 1050*m*, 745*w*, 707*w*. ^{1}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}C-NMR: *ca.* 175, 174, 173 (3*s*, 2 CONH, COOH); *ca.* 157 (*s*, OCONH); 135.8 (*s*, 1 arom. C); 128.5, 128.3, 127.9 (3*d*, 5 arom. CH); 67.2 (*t*, PhCH_2O); 63.7, 57.6 (2*s*, 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 (2*d*, C(3) of Val(2Me), C(4) of Leu); 25.6, 24.5, 22.8, 21.8, 17.9, 17.2, 16.7 (7*q*, 2 Me of Aib, Me(3) and 2 Me(4) of Val(2Me), 2 Me of Leu). ESI-MS (MeOH): 502 (12, $[M+K]^+$), 486 (90, $[M+Na]^+$), 464 (100, $[M+1]^+$), 446 (15, $[M-OH]^+$), 333 (16, $[M-Val(2Me)]^+$). Anal. calc. for $C_{24}H_{37}N_3O_6 \cdot 0.33\ H_2O$ (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 (CH_2Cl_2/MeOH 10:1) 0.41. IR: 3287*s*, 2966*m*, 2875*w*, 1703*s*, 1673v*s*, 1518*s*, 1463*w*, 1412*w*, 1362*w*, 1315*w*, 1271*s*, 1234*m*, 1216*m*, 1175*w*, 1117*w*, 1047*m*, 1029*w*, 971*w*, 943*w*, 914*w*, 789*w*, 747*w*, 699*w*, 625*w*. ^{1}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 (2*m*, 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 (4*d*, $J = 7.7$, 7.0, 6.8, 6.8, 2 Me of Leu, 2 Me(4) of Val(2Me)). ^{13}C-NMR (CD_3OD): *ca.* 176.5, 176.2, *ca.* 175.5 (3*s*, 3 CONH); *ca.* 159 (*s*, OCONH); 138.1 (*s*, 1 arom. C); 129.4, 128.9, 128.4 (3*d*, 5 arom. CH); 67.3 (*t*, PhCH_2O); 64.1, 58.1 (2*s*, 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 (8*q*, 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 $C_{25}H_{40}N_4O_5 \cdot 0.33\ H_2O$ (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(2Me)-Gln-Valol*; (*R*)-**2d**). As described for **2a**, with (*R*)-**6d** (599 mg, 1.29 mmol), Et_3N (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 (CH_2Cl_2/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 (CH_2Cl_2/MeOH 10:1) 0.15. IR: 3416*s*, 2962*s*, 1664*s*, 1534*s*, 1456*m*, 1388*m*, 1375*m*, 1264*m*, 1179*w*, 1122*w*, 1049*w*, 849*s*, 740*m*, 698*m*. ^{1}H-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*, PhCH_2O); 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 CH_2(1) of Valol); 2.45–2.15 (*m*, CH_2(4) and CH_2(3) of Gln); 1.8–1.55 (*m*, CH_2(3) of Leu, CH(3) of Valol, CH(3) of Val(2Me)); 1.45–1.25 (*m*, CH(4) of Leu, 2 Me of Aib, Me(3) of Val(2Me)); 1.0–0.75 (*m*, 2 Me of Valol, 2 Me(4) of Val(2Me), 2 Me of Leu). ^{13}C-NMR: *ca.* 176, 174.3, 174.1, 172.7 (4*s*, $CONH_2$, 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*, PhCH_2O, C(1) of Valol); 62.2, 57.2 (2*s*, C(2) of Aib, C(2) of Val(2Me)); 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(2Me), 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(2Me), 2 Me of Valol, 2 Me(4) of Val(2Me), 2 Me of Leu). ESI-MS (MeOH, AcOH): 701 (11), 700 (46), 699 (100, $[M+Na]^+$), 586 (10, $[M-C_7H_7+1]^+$). Anal. calc. for $C_{34}H_{56}N_6O_8 \cdot 0.5\ H_2O$ (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-{[(Benzyloxy)carbonyl]amino}-4-methyl-1-oxopentyl)amino]-2-methyl-1-oxopropyl}amino)-2-cyclopentylpropanoic Acid* (*Z-Leu-Aib-(*S*)-Ala(2cPent)-OH*; (*S*)-**6e**). As described for (*S*)-**6c**, with (*S*)-**3e** [19] (98 mg, 0.149 mmol) and 3N HCl (MeCN/H_2O 1:1, 1.5 ml), 3 h at 60°; prep. TLC (CH_2Cl_2/MeOH 10:1): 54 mg (74%) of (*S*)-**6e**. Colorless solid. M.p. 79–81°. R_f (CH_2Cl_2/MeOH 10:1) 0.26. IR: 3321*m*, 2956*s*, 2871*m*, 1706v*s*, 1668v*s*, 1526v*s*, 1455*m*, 1386*w*, 1249*m*, 1047*w*, 738*w*. ^{1}H-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*, PhCH_2O); 4.15–4.1 (*m*, CH(2) of Leu); 2.45–2.35 (*m*, CH(3) of Ala(2cPent)); 1.75–1.35 (*m*, CH_2(3) and CH(4) of Leu, 2 Me of Aib, Me of Ala(2cPent), 4 CH_2 of Ala(2cPent)); 0.95–0.9 (*m*, 2 Me of Leu). ^{13}C-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*, PhCH_2O); 61.8, 57.4 (2*s*, C(2) of Ala(2cPent), C(2) of Aib); 54.3 (*d*, C(2) of Leu); 46.1 (*d*, C(3) of Ala(2cPent)); 40.7 (*t*, C(3) of Leu); 27.0, 26.8, 25.3 (3*t*, 4 CH_2 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(2cPent), 2 Me of Leu). ESI-MS (MeOH): 512 (100, $[M+Na]^+$), 490 (52, $[M+1]^+$), 307 (13). Anal. calc. for $C_{26}H_{39}N_3O_6$ (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(2cPent)-Gln-Valol*; (*S*)-**2e**). As described for **2a**, with (*S*)-**6e** (149 mg, 0.304 mmol), Et_3N (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 (0.5M 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 (CH_2Cl_2/MeOH 10:1) of the rest; total yield: 93 mg (43%) of (*S*)-**2e**. Colorless solid. M.p. 208.0–209.1°. R_f (CH_2Cl_2/MeOH 10:1) 0.37. ^{1}H-NMR (CD_3OD): 7.35–7.3 (*m*, 5 arom. H); 5.25–5.05 (*m*, PhCH_2O); 4.1–4.05, 3.7–3.65 (2*m*, CH(2) of Gln, CH(2) of Leu, CH(2) and CH_2(1) of Valol); 2.45–2.3, 2.25–2.15, 1.95–1.85, 1.8–1.5 (4*m*, CH_2(4) and CH_2(3) of Gln, CH_2(3) of Leu, 4 CH_2 of Ala(2cPent), CH(4) of Leu, CH(3) of Valol, CH(3) of Ala(2cPent)); 1.44 (*s*, Me of Ala(2cPent)); 1.39 (*s*, 2 Me of Aib); 0.95–0.9 (*m*, 2 Me of Valol, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 177.4, *ca.* 176.5, 176.2, 174.5 (4*s*, $CONH_2$, 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*, PhCH_2O, C(1) of Valol); 63.0, 58.0 (2*s*, C(2) of Aib, C(2) of Ala(2cPent)); 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(2cPent)); 41.8, 33.6, 28.4, 28.1, 27.8, 26.1, 26.1 (7*t*, 4 CH_2 of Ala(2cPent), 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(2cPent), 2 Me of Valol, 2 Me of Leu). ESI-MS (MeOH, NaI): 725 (100, $[M+Na]^+$), 703 (100, $[M+1]^+$). Anal. calc. for $C_{36}H_{58}N_6O_8$ (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/H_2O 1:1, 3 ml), 3 h at 60°; prep. TLC (CH_2Cl_2/MeOH 10:1): 113 mg (76%) of (*R*)-**6e**. Colorless solid. M.p. 144–145°. R_f (CH_2Cl_2/MeOH 10:1) 0.37. IR: 3309*m*, 2957*s*, 2871*w*, 1724*s*, 1662v*s*, 1526*s*, 1455*w*, 1387*w*, 1246*w*, 1049*w*, 737*w*. ^{1}H-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*, PhCH_2O); 4.2–4.1 (*m*, CH(2) of Leu); 2.5–2.35 (*m*, CH(3) of Ala(2cPent)); 1.8–1.3 (*m*, CH_2(3) and CH(4) of Leu, 2 Me of Aib, Me of Ala(2cPent), 4 CH_2 of Ala(2cPent)); 0.95–0.9 (*m*, 2 Me of Leu). ^{13}C-NMR: 173.9, 172.8 (2*s*, 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*, PhCH_2O); 61.9, 57.4 (2*s*, C(2) of Ala(2cPent), C(2) of Aib); 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 CH_2 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 $C_{26}H_{39}N_3O_6$ (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), Et_3N (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 (CH_2Cl_2/MeOH 10:1) and prep. TLC (CH_2Cl_2/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 (CH_2Cl_2/MeOH 10:1) 0.23. IR: 3426v*s*, 2959*s*, 2871*m*, 1661v*s*, 1532*s*, 1455*w*, 1386*w*, 1261*w*, 1175*w*, 1121*w*, 1048*w*, 741*w*. ^{1}H-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, PhCH_2O); 4.35–4.0, 3.75–3.6 (2*m*, CH(2) of Gln, CH(2) of Leu, CH(2) and CH_2(1) of Valol); 2.65–2.45, 2.35–2.25 (2*m*, CH_2(4) and CH_2(3) of Gln); 1.85–1.25 (*m*, CH_2(3) of Leu, 4 CH_2 of Ala(2cPent), CH(4) of Leu, CH(3) of Valol, CH(3) of Ala(2cPent)); 1.45, 1.42 (2*s*, 2 Me of Aib); 1.28 (*s*, Me of Ala(2cPent)); 0.95–0.85 (*m*, 2 Me of Valol, 2 Me of Leu). ^{1}H-NMR (CD_3OD): 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*, PhCH_2O); 4.25–4.1 (*m*, CH(2) of Gln, CH(2) of Leu); 3.7–3.6 (*m*, CH(2) and CH_2(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), CH_2(3) of Leu, CH_2(4) and CH_2(3) of Gln, 4 CH_2 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). ^{13}C-NMR: 177.5, 176.0, 174.9, 174.6, 173.5 (5*s*, $CONH_2$, 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*, PhCH_2O, 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 CH_2 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). ^{13}C-NMR (CD_3OD): 178.1, 176.6, 176.0, 175.8, 174.2 (5*s*, $CONH_2$, 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*, PhCH_2O, C(1) of Valol); 62.9, 57.9 (2*s*, 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 CH_2 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 (CH_2Cl_2, 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 $C_{36}H_{58}N_6O_8$ (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/H_2O 1:1, 2 ml), 4 h at 60°; prep. TLC (CH_2Cl_2/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 (CH_2Cl_2/MeOH 10:1) 0.19. IR: 3306*m*, 2958*s*, 1717*s*, 1659*s*, 1523*s*, 1454*m*, 1388*m*, 1367*m*, 1237*m*, 1159*m*, 1045*m*, 954*w*, 908*w*, 855*w*, 789*w*, 757*w*, 736*w*, 697*m*. ^{1}H-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*, PhCH_2O); 4.2–4.15 (*m*, CH(2) of Leu); 2.15–2.1 (*m*, CH(4) of Leu(2Me)); 1.8–1.5 (*m*, CH_2(3) and CH(4) of Leu, 2 Me of Aib, CH_2(3) and Me(3) of Leu(2Me)); 0.95–0.85 (*m*, 2 Me of Leu, 2 Me(5) of Leu(2Me)). ^{13}C-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*, PhCH_2O); 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 $C_{25}H_{39}N_3O_6$ (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 (CH_2Cl_2/MeOH 10:1) 0.44. IR: 3321*s*, 3038*w*, 2957*s*, 2871*w*, 1704v*s*, 1652v*s*, 1537*s*, 1455*m*, 1411*w*, 1382*m*, 1365*w*, 1331*w*, 1261*s*, 1223*w*, 1173*w*, 1115*w*, 1051*w*, 1031*w*, 907*w*, 789*w*, 726*w*, 693*w*. ^{1}H-NMR (CD_3OD): 7.35–7.3 (*m*, 5 arom. H); 5.08 (br. *s*, PhCH_2O); 4.06 (*dd*, J = 8.4, 6.5, CH(2) of Leu); 2.69 (*s*, MeN); 2.0–1.5 (*m*, CH_2(3) of Leu(2Me), CH_2(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)). ^{13}C-NMR (CD_3OD): *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*, PhCH_2O); 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 (NH_3): 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 $C_{26}H_{42}N_4O_5 \cdot 0.2\ H_2O$ (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), Et_3N (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 (CH_2Cl_2/MeOH 10:1): 139 mg (60%) of (*S*)-**2f**. Colorless solid. M.p. 154–155°. R_f (CH_2Cl_2/MeOH 10:1) 0.17. IR: 3312*m*, 2956*m*, 1653*s*, 1534*s*, 1466*m*, 1386*w*, 1360*m*, 1260*m*, 1046*w*, 847*w*, 814*w*, 738*w*. ^{1}H-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, PhCH_2O); 4.0–3.8, 3.7–3.55 (2*m*, CH(2) of Gln, CH(2) of Leu, CH(2) and CH_2(1) of Valol); 2.35–2.15 (*m*, CH_2(4) and CH_2(3) of Gln); 1.8–1.6 (*m*, CH_2(3) of Leu(2Me), CH_2(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). ^{13}C-NMR: 175.6, 175.2, 175.1, 174.8, 172.8 (5*s*, $CONH_2$, 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*, PhCH_2O, 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 $C_{35}H_{58}N_6O_8 \cdot H_2O$ (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-*

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[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 H_2, 75 min at r.t., filtration over *Celite*, abs. CH_2Cl_2 (5 ml), Et_3N (25 mg, 0.248 mmol), 4-bromobenzoyl chloride (31 mg, 0.139 mmol), 3 h at r.t., filtration and washing with CH_2Cl_2: 60 mg (70%) of (*S*)-**13f**. Colorless solid. M.p. 246–247°. R_f (CH_2Cl_2/MeOH 10:1) 0.18. IR: 3336*m*, 2959*m*, 2477*m*, 1648v*s*, 1542*s*, 1364*m*, 1278*w*, 1176*w*, 1072*w*, 1011*w*, 850*w*, 761*w*. ^{1}H-NMR (CD_3OD): 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*, CH_2(1) and CH(2) of Valol); 2.4–2.05, 1.85–1.65 (2*m*, CH_2(4) of Gln and CH_2(3) of Gln, CH(3) of Valol, CH(4) and CH_2(3) of Leu, CH(4) and CH_2(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). ^{13}C-NMR (CD_3OD): 177.7, 177.0, 176.7, 175.8, 174.4 (5*s*, $CONH_2$, 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, $[M+Na]^+$, ^{81}Br), 741 (100, $[M+1]^+$, ^{81}Br), 638 (6, $[M-\text{Valol}]^+$, ^{81}Br), 510 (10, $[M-\text{Gln-Valol}]^+$, ^{81}Br). Anal. calc. for $C_{34}H_{55}BrN_6O_7$ (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 CD_3OD 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 3N HCl (MeCN/H_2O 1:1, 2 ml), 3 h at 60°; prep. TLC (CH_2Cl_2/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 (CH_2Cl_2/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*. ^{1}H-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., PhCH_2O); 4.15–4.1 (*m*, CH(2) of Leu); 2.15–2.1 (*m*, CH(4) of Leu(2Me)); 1.8–1.45 (*m*, CH_2(3) and CH(4) of Leu, CH_2(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)). ^{13}C-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*, PhCH_2O); 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, $[M-\text{OH}]^+$), 333 (12, $[M-\text{Leu(2Me)}]^+$). Anal. calc. for $C_{25}H_{39}N_3O_6 \cdot 0.5\ H_2O$ (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 (CH_2Cl_2/MeOH 10:1) 0.45. IR: 3293*s*, 2958*m*, 2873*w*, 1706*s*, 1654v*s*, 1518v*s*, 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*. ^{1}H-NMR (CD_3OD): 7.35–7.25 (*m*, 5 arom. H); 5.09 (br. *s*, PhCH_2O); 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*, CH_2(3) of Leu(2Me), CH_2(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)). ^{13}C-NMR (CD_3OD): *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*, PhCH_2O); 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 (NH_3): 491 (4, $[M+1]^+$), 384 (21), 383 (32, $[M-\text{OBn}]^+$), 231 (7). Anal. calc. for $C_{26}H_{42}N_4O_5$ (490.64): C 63.65, H 8.83, N 11.42; found: C 63.67, H 8.62, N 11.26.

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[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), Et_3N (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 (CH_2Cl_2/MeOH 10:1): 177 mg (53%) of (*R*)-**2f**. Colorless foam. M.p. 105–107°. R_f (CH_2Cl_2/MeOH 10:1) 0.14. IR: 3302*s*, 2958*m*, 2871*m*, 1659*s*, 1533*s*, 1455*m*, 1386*m*, 1356*m*, 1264*m*, 1171*m*, 1122*w*, 1055*w*, 852*w*, 786*w*, 740*m*, 697*m*. ^{1}H-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*, PhC*H*$_2$O); 4.1–3.55 (*m*, CH(2) of Gln, CH(2) of Leu, CH(2) and CH_2(1) of Valol); 2.45–2.0 (*m*, CH_2(4) and CH_2(3) of Gln, CH(3) of Valol); 1.8–1.65 (*m*, CH_2(3) of Leu(2Me), CH_2(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). ^{13}C-NMR: 176.9, 175.1, 175.1, 174.6, 173.0 (5*s*, $CONH_2$, 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*t*, PhC*H*$_2$O, C(1) of Valol); 59.8, 56.9 (2*s*, 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 $C_{35}H_{58}N_6O_8 \cdot H_2O$ (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 H_2, 70 min at r.t., filtration over *Celite*, abs. CH_2Cl_2 (4 ml), Et_3N (16 mg, 0.158 mmol), 4-bromobenzoyl chloride (18.5 mg, 0.084 mmol), 2 h at r.t., evaporation and prep. TLC (CH_2Cl_2/MeOH 10:1): 16 mg (30%) of (*R*)-**13f**. M.p. 124–125°. R_f (CH_2Cl_2/MeOH 10:1) 0.14. IR: 3317*s*, 3064*w*, 2959*m*, 1651*vs*, 1592*m*, 1483*m*, 1448*m*, 1428*m*, 1382*m*, 1335*m*, 1276*m*, 1234*m*, 1160*w*, 1140*m*, 1073*w*, 1012*w*, 974*w*, 961*w*, 846*w*, 806*w*, 784*w*, 722*w*, 696*m*. ^{1}H-NMR (CD_3OD): 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*, CH_2(1) and CH(2) of Valol); 2.4–1.6, 1.3–1.25 (2*m*, CH_2(4) and CH_2(3) of Gln, CH(3) of Valol, CH(4) and CH_2(3) of Leu, CH(4) and CH_2(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). ^{13}C-NMR (CD_3OD): *ca.* 178, 177.5, 176.3, 175.5, 174.2, *ca.* 171 (6*s*, $CONH_2$, 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 (2*s*, 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, $[M+Na]^+$, ^{81}Br), 762 (41), 741 (74, $[M+Na]^+$, ^{79}Br). Anal. calc. for $C_{34}H_{55}BrN_6O_7 \cdot 0.5\ H_2O$ (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-2*H*-azirin-3-yl]-2-[(*S*)-1-methoxy-1-methylethyl]pyrrolidine* ((2′*S*)-**1h** [17], 95 mg, 0.332 mmol), abs. CH_2Cl_2 (3 ml), 17 h at r.t., 2N HCl, 1N NaOH, sat. NaCl solns.; CC (CH_2Cl_2/MeOH 100:4): 140 mg (70%) of (*S*)-**3h**. M.p. 79–80°. R_f (CH_2Cl_2/MeOH 20:1) 0.30. IR: 3330*s*, 2957*s*, 1666*vs*, 1623*vs*, 1498*s*, 1454*s*, 1413*m*, 1384*m*, 1317*m*, 1243*m*, 1086*m*, 1061*m*, 922*w*, 739*w*, 701*m*. ^{1}H-NMR (CD_3OD): 7.3–7.1 (*m*, 10 arom. H); 5.12, 5.04 (*AB*, *J* = 12.7, PhC*H*$_2$O); 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, CH_2(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*, CH_2(3) of Leu); 1.49 (*s*, Me(3) of Phe(2Me));

1.44, 1.43 (2*s*, 2 Me of Aib); 1.16, 1.08 (2*s*, Me_2(MeO)C); 0.97, 0.94 (2*d*, $J = 7.3$, 7.1, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 175.3, 172.6 (2*s*, CON, 2 CONH); *ca.* 158 (*s*, OCONH); 138.2, 137.4 (2*s*, 2 arom. C); 131.7, 129.4, 129.1, 128.9, 128.3, 127.9 (6*d*, 10 arom. CH); 80.0 (*s*, Me_2(MeO)*C*); 67.3 (*t*, Ph*C*H_2O); 65.8, 55.3 (2*d*, 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 (5*t*, 3 CH_2 of Cp, C(3) of Leu, C(3) of Phe(2Me)); 26.9, 24.6, 24.0, 23.5, 23.2, 22.2 (6*q*, *Me*$_2$C, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu); 25.8 (*d*, C(4) of Leu). ESI-MS (MeOH, CH_2Cl_2, NaI): 659 (100, $[M + Na]^+$). Anal. calc. for $C_{36}H_{52}N_4O_6 \cdot 0.25\ H_2O$ (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/H_2O 1:1, 8 ml), 23 h at 40°; CC (CH_2Cl_2/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/H_2O 1:1, 6 ml), 3 h at 60°; CC (CH_2Cl_2/MeOH 100:2) and prep. TLC (CH_2Cl_2/MeOH 10:1): 37 mg (25%) of (*S*)-**6g**. Colorless solid. M.p. 130.2–130.6°. R_f (CH_2Cl_2/MeOH 20:1) 0.30. IR: 3330*s*, 3060*m*, 3030*m*, 2960*m*, 2870*w*, 1660v*s*, 1605*s*, 1515*s*, 1500*s*, 1455*s*, 1405*m*, 1365*m*, 1265*m*, 1245*m*, 1210*m*, 1170*w*, 1120*w*, 1045*w*, 1030*w*, 1000*w*, 960*w*, 910*w*, 780*w*, 740*w*, 700*m*. ^{1}H-NMR (CD_3OD): 7.45 (br. *s*, NH); 7.3–7.25, 7.2–7.1 (2*m*, 10 arom. H); 5.1–5.05 (*m*, PhC*H*$_2$O); 4.15 (*t*, $J = 7.4$, CH(2) of Leu); 3.37, 3.31 (*AB*, $J = 13.3$, CH_2(3) of Phe(2Me)); 1.7–1.6 (*m*, CH(4) of Leu); 1.6–1.55 (*m*, CH_2(3) of Leu); 1.51 (*s*, Me(3) of Phe(2Me)); 1.38, 1.33 (2*s*, 2 Me of Aib); 0.93, 0.91 (2*d*, $J = 6.8$, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 180.5 (*s*, COOH); 175.2, 174.8 (2*s*, 2 CONH); 158.5 (*s*, OCONH); 139.2, 138.0 (2*s*, 2 arom. C); 131.4, 129.5, 129.0, 128.8, 127.3 (5*d*, 10 arom. CH); 67.9 (*t*, Ph*C*H_2O); 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 (2*t*, 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 (5*q*, 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 $C_{28}H_{37}N_3O_6 \cdot 0.25\ H_2O$ (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), Et_3N (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 (CH_2Cl_2/MeOH 10:1): 57 mg (49%) of (*S*)-**2g**. Colorless solid. M.p. 102–103°. R_f (CH_2Cl_2/MeOH 10:1) 0.27. IR: 3300*s*, 3060*w*, 3030*w*, 2960*m*, 2870*w*, 1660v*s*, 1530*s*, 1455*m*, 1405*w*, 1385*w*, 1370*w*, 1340*w*, 1315*w*, 1260*m*, 1170*w*, 1120*w*, 1045*w*, 1030*w*, 960*w*, 920*w*, 845*w*, 740*w*, 700*m*. ^{1}H-NMR (CD_3OD): 7.42 (*d*, $J = 8.8$, NH); 7.35–7.2, 7.15–7.1 (2*m*, 10 arom. H); 5.08, 5.05 (*AB*, $J = 12.7$, PhC*H*$_2$O); 4.15–4.05 (*m*, CH(2) of Gln, CH(2) of Leu); 3.7–3.65 (*m*, CH_2(1) of Valol); 3.65–3.6 (*m*, CH(2) of Valol); 3.22, 3.06 (*AB*, $J = 13.6$, CH_2(3) of Phe(2Me)); 2.3–2.25 (*m*, CH_2(4) of Gln); 2.25–2.2 (*m*, CH_2(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*, CH_2(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). ^{13}C-NMR (CD_3OD): 178.0, 176.6, 176.3, 175.9, 174.3 (5*s*, $CONH_2$, 4 CONH); the signal for OCONH could not be detected; 138.2, 137.3 (2*s*, 2 arom. C); 131.7, 129.5, 129.4, 129.1, 128.7, 128.2 (6*d*, 10 arom. CH); 67.8 (*t*, Ph*C*H_2O); 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 (2*d*, C(2) of Leu, C(2) of Valol); 43.4, 41.5 (2*t*, 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 (5*q*, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Leu); 20.1, 19.2 (2*q*, 2 Me of Valol). ^{1}H-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 (3*m*, 10 arom. H, 1 NH); 6.92 (*s*, NH); 6.60 (*s*, 1 H, NH_2 of Gln); 6.51 (*d*, $J = 4.0$, NH of Leu); 5.53 (*s*, 1 H, NH_2 of Gln); 5.11, 5.08 (*AB*, $J = 12.6$, PhC*H*$_2$O); 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*, CH_2(1) of Valol); 2.97, 2.94 (*AB*, $J = 13.6$, CH_2(3) of Phe(2Me)); 2.3–2.25 (*m*, CH_2(4) of Gln); 2.2–2.05 (*m*, CH_2(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 CH_2(3) of Leu); 1.5–1.45 (*m*, 1 H of CH_2(3) of Leu); 1.4–1.35 (*m*, 2 Me of Aib, Me(3) of Phe(2Me)); 0.93, 0.92 (2*d*, $J = 6.8$, 8.3, 2 Me of Leu); 0.87, 0.86 (2*d*, $J = 6.9$, 2 Me of Valol). ^{13}C-NMR (150.9 MHz): 175.1, 174.7, 174.4, 172.6 (4*s*, $CONH_2$, 4 CONH); 157.1 (*s*, OCONH); 136.4 (*s*, 1 arom. C of *Ph*CH_2O); 135.1 (*s*, 1 arom. C of

Phe(2Me)); 130.2, 128.6, 128.3, 128.2, 127.6, 127.3 (6*d*, 10 arom. CH); 67.1 (*t*, Ph*C*H$_2$O); 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 (2*d*, 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 (2*q*, 2 Me of Aib); 24.7 (*d*, C(4) of Leu); 22.9, 21.7 (2*q*, 2 Me of Leu); 21.5 (*q*, Me(3) of Phe(2Me)); 19.6, 19.2 (2*q*, 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, $[M-Gln\text{-}Valol]^+$). Anal. calc. for $C_{38}H_{56}N_6O_8 \cdot 1.5\ H_2O$ (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* (p*BrBz-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 H_2, 30 min at r.t., filtration over *Celite*, CH_2Cl_2 (3 ml), Et_3N (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 (CH_2Cl_2/MeOH 10:1) 0.31. IR: 3417*s*, 2959*m*, 1682v*s*, 1654v*s*, 1608*m*, 1540*m*, 1399*w*, 1364*w*, 1230*m*, 1184*w*, 1068*w*, 1021*w*, 810*w*. ^{1}H-NMR (CD_3OD): 7.77, 7.60 (*AA′BB′*, *J* = 8.6, 4 arom. H); 7.3–7.25, 7.15–7.1 (2*m*, 5 arom. H); 4.5–4.45, 4.15–4.1 (2*m*, CH(2) of Gln and CH(2) of Leu); 3.65–3.55 (*m*, CH_2(1) and CH(2) of Valol); 3.35, 3.05 (*AB*, *J* = 13.6, CH_2(3) of Phe(2Me)); 2.3–1.95, 1.85–1.65 (2*m*, CH_2(4) of Gln and CH_2(3) of Gln, CH(3) of Valol, CH_2(3) of Leu); 1.6–1.5 (*m*, CH(4) of Leu); 1.46, 1.40, 1.30 (3*s*, 2 Me of Aib, Me(3) of Phe(2Me)); 1.01, 0.98 (2*d*, *J* = 6.2, 6.3, 2 Me of Valol); 0.85,0.78 (2*d*, *J* = 6.8, 2 Me of Leu). ^{13}C-NMR (CD_3OD): 177.9, 176.5, 175.5, 174.0 (4*s*, $CONH_2$, 4 CONH); 169.5 (*s*, 1 CO (amide, *p*BrBz)); 137.3, 133.9 (2*s*, 2 arom. C); 132.7, 131.7, 130.6, 129.2, 128.0 (5*d*, 9 arom. CH); 127.3 (*s*, 1 arom. CBr); 63.2 (*t*, C(1) of Valol); 61.5, 58.0 (2*s*, C(2) of Phe(2Me), C(2) of Aib); 58.0, 55.4, 54.2 (3*d*, C(2) of Gln, C(2) of Valol, C(2) of Leu); *ca.* 48, 41.1, 33.3, 28.1 (4*t*, C(3) of Leu, C(3) of Phe(2Me), C(4) of Gln, C(3) of Gln); 29.9, 26.0 (2*d*, C(3) of Valol, C(4) of Leu); 24.7, 23.9, 23.3, 22.1, 19.9, 19.0 (6*q*, 2 Me of Aib, Me(3) of Phe(2Me), 2 Me of Valol, 2 Me of Leu). ESI-MS (TFA): 813 (8, $[M+K]^+$, ^{81}Br), 798 (100, $[M+Na]^+$, ^{81}Br), 775 (86, $[M+1]^+$, ^{81}Br), 757 (16, $[M-OH]^+$, ^{81}Br), 672 (25, $[M-Valol]^+$, ^{81}Br), 656 (12), 544 (53, $[M-Gln\text{-}Valol]^+$, ^{81}Br). Anal. calc. for $C_{37}H_{53}BrN_6O_7 \cdot 2$ 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. CH_2Cl_2 (4 ml), and (*R*)-**1h** [17] (130 mg, 0.45 mmol), abs. CH_2Cl_2 (5 ml), 18 h at r.t.; CC (CH_2Cl_2/MeOH 20:1, 25:1, 50:1); prep. TLC (CH_2Cl_2/MeOH 20:1): 229 mg (79%) of (*R*)-**3h**. Colorless foam. M.p. 79–80°. R_f (CH_2Cl_2/MeOH 10:1) 0.57. R_f (CH_2Cl_2/MeOH 20:1) 0.36. IR: 3323*s*, 3032*m*, 2958*s*, 1665v*s*, 1624v*s*, 1527v*s*, 1455*s*, 1411*s*, 1384*s*, 1316*m*, 1243*s*, 1120*m*, 1086*s*, 1061*m*, 921*w*, 737*m*, 700*s*. ^{1}H-NMR: 7.48 (br. *s*, NH); 7.4–7.3, 7.2–7.0 (2*m*, 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, PhC*H*$_2$O); 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, CH_2(3) of Phe(2Me)); 3.16 (*s*, MeO); 2.05–1.95 (*m*, CH_2(3) of Leu); 1.8–1.4 (*m*, 2 CH_2 of Cp, 2 Me of Aib, Me(3) of Phe(2Me), CH(4) of Leu); 1.17, 1.13 (2*s*, *Me*$_2$C); 0.92 (*d*, *J* = 6.3, 2 Me of Leu). ^{13}C-NMR: 172.2, 171.5 (2*s*, CON, 2 CONH); the signal for OCONH could not be detected; 136.7, 136.0 (2*s*, 2 arom. C); 130.9, 128.4, 128.1, 127.9, 127.9, 126.6 (6*d*, 10 arom. CH); 67.1 (*t*, Ph*C*H$_2$O); 64.8 (*d*, C(2) of Leu); 60.8, 57.7 (2*s*, C(2) of Phe(2Me), C(2) of Aib); 54.2 (*d*, CHN of Cp); 49.1 (*q*, MeO); 48.1 (*t*, CH_2N of Cp); 41.2, 40.3, 23.6 (3*t*, C(3) of Leu, C(3) of Phe(2Me), 2 CH_2 of Cp); 25.3 (*q*, *Me*$_2$C); 24.6 (*d*, C(4) of Leu); 22.9, 22.9, 22.2, 21.7 (4*q*, 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 $C_{36}H_{52}N_4O_6$ (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), 3N HCl (THF/H_2O 1:1, 8 ml), 26 h at 40°; CC (CH_2Cl_2/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 3N HCl (MeCN/H_2O 1:1, 6 ml), 3 h at 60°; CC (CH_2Cl_2/MeOH 100:2) and prep. TLC (CH_2Cl_2/MeOH 10:1): 55 mg (36%) of (*R*)-**6g**. Colorless solid. M.p. 126.8–127.3°. R_f (CH_2Cl_2/MeOH 20:1) 0.28. IR: 3330*m*, 3060*w*, 3030*w*, 2960*m*, 2860*w*, 1660vs, 1530–1510*s*, 1450s, 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*. ^{1}H-NMR (CD_3OD): 7.3–7.25, 7.15–7.1 (2*m*, 10 arom. H); 5.02, 4.97 (*AB*, J = 12.5, PhCH_2O); 4.13 (*t*, J = 6.4, CH(2) of Leu); 3.37, 3.31 (*AB*, J = 13.3, CH_2(3) of Phe(2Me)); 1.7–1.55 (*m*, CH(4) of Leu); 1.55–1.45 (*m*, Me(3) of Phe(2Me), CH_2(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). ^{13}C-NMR (CD_3OD): 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*, PhCH_2O); 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 $C_{28}H_{37}N_3O_6 \cdot 0.25\ H_2O$ (516.12): C 65.16, H 7.32, N 8.14; found: C 65.01, H 7.51, N 7.84.

14.3. *Benzyl {(*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), Et_3N (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 2N HCl, once with 1N NaOH soln. and sat. NaCl soln., dried ($MgSO_4$), and evaporated. A residue, which was not soluble in 50 ml of MeOH (HATU), was filtered off. CC (CH_2Cl_2/MeOH 10:1): 42 mg (56%) of (*R*)-**2g**. M.p. 94.3–95.0°. R_f (CH_2Cl_2/MeOH 10:1) 0.35. ^{1}H-NMR (CD_3OD): 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, PhCH_2O); 4.2–4.15 (*m*, CH(2) of Gln); 4.01 (*t*, J = 7.5, CH(2) of Leu); 3.7–3.65 (*m*, CH_2(1) and CH(2) of Valol); 3.53, 3.09 (2*d*, J = 13.7, CH_2(3) of Phe(2Me)); 2.4–2.35 (*m*, CH_2(4) of Gln); 2.25–2.1 (*m*, CH_2(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, CH_2(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). ^{13}C-NMR (CD_3OD): 177.6, 176.9, 176.2, 174.7 (4*s*, $CONH_2$, 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*, PhCH_2O); 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* (p*BrBz-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 H_2, 16 h at r.t., filtration over *Celite*, CH_2Cl_2 (2 ml), Et_3N (10 mg, 0.099 mmol), 4-bromobenzoyl chloride (10 mg, 0.046 mmol), 3 h at r.t., filtration and washing with CH_2Cl_2: 20 mg (75%) of (*R*)-**13g**. Colorless solid. M.p. 127.4–128.5°. R_f (CH_2Cl_2/MeOH 10:1) 0.37. IR: 3422vs, 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, $[M+Na]^+$, ^{81}Br), 757 (8, $[M-OH]^+$, ^{81}Br), 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**	(*S*)-**2d**	(*S*)-**2e**	(*S*)-**13f**	(*S*)-**13g**
Crystallized from	MeOH/CH_2Cl_2/Et_2O/ petroleum ether	AcOEt/MeOH/ petroleum ether	CD_3OD	MeOH/AcOEt	CD_3OD	AcOEt/MeOH/ petroleum ether
Empirical formula	$C_{31}H_{49}BrN_6O_7 \cdot 0.3\,H_2O$	$C_{33}H_{51}BrN_6O_7$	$C_{34}H_{56}N_6O_8$	$C_{36}H_{58}N_6O_8$	$C_{34}H_{55}BrN_6O_7$	$C_{37}H_{53}BrN_6O_7 \cdot 2$ MeOH
Formula weight [g mol^{-1}]	703.67	723.70	676.85	702.89	739.75	837.85
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism	colorless, prism	colorless, plate	colorless, needle
Crystal dimensions [mm]	$0.30 \times 0.35 \times 0.36$	$0.15 \times 0.30 \times 0.35$	$0.22 \times 0.25 \times 0.30$	$0.15 \times 0.30 \times 0.32$	$0.02 \times 0.15 \times 0.20$	$0.07 \times 0.17 \times 0.48$
Temp. [K]	173(1)	173(1)	160(1)	160(1)	160(1)	173(1)
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P1$	$P2_1$
Z	2	2	2	2	2	2
Reflections for cell determination	18	25	5592	5774	111558	21
2θ Range for cell determination [°]	39–40	24–26	4–60	4–60	4–50	20–35
Unit cell parameters						
a [Å]	9.805(5)	9.860(3)	9.9878(1)	9.9161(1)	9.6894(1)	9.734(7)
b [Å]	19.077(7)	19.654(2)	17.3900(2)	17.3616(2)	9.7484(1)	17.358(5)
c [Å]	10.719(4)	10.608(4)	10.7563(1)	11.2766(2)	23.0357(3)	13.348(5)
α [°]	90	90	90	90	100.9970(7)	90
β [°]	114.32(3)	114.68(3)	94.2612(4)	95.3358(5)	92.7939(7)	108.22(4)
γ [°]	90	90	90	90	111.3514(5)	90
V [Å^3]	1827(1)	1868(1)	1863.07(3)	1932.96(5)	1972.62(4)	2142(2)
D_x [g cm^{-3}]	1.279	1.287	1.206	1.208	1.245	1.299
μ(MoK_α) [mm^{-1}]	1.179	1.155	0.0862	0.0856	1.095	0.0693
Transmission factors (min; max)	0.890; 1.000	0.866; 1.000	–	–	0.754; 0.915	0.918; 1.000
Diffractometer	*Rigaku AFC5R*	*Rigaku AFC5R*	*Nonius KappaCCD*	*Nonius KappaCCD*	*Nonius KappaCCD*	*Rigaku AFC5R*
Scan type	$\omega/2\theta$	$\omega/2\theta$	ϕ and ω	ϕ and ω	ϕ and ω	$\omega/2\theta$
$2\theta_{(max)}$ [°]	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 Δ_{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 H_2O molecule. The O-atom of the H_2O molecule has a site occupation factor of *ca.* 0.33. The H-atom positions were not defined for the H_2O 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 isotropcially. 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.

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[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	$MeOH/CH_2Cl_2$	CD_3OD
Empirical formula	$C_{23}H_{35}N_3O_6$	$C_{24}H_{38}N_4O_5$	$C_{25}H_{40}N_4O_5$
Formula weight [g mol^{-1}]	449.54	462.59	476.61
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.15 \times 0.25 \times 0.25$	$0.15 \times 0.20 \times 0.25$	$0.22 \times 0.28 \times 0.30$
Temp. [K]	160(1)	160(1)	160(1)
Crystal system	orthorhombic	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	4	4
Reflections for cell determination	3143	4170	3446
2θ Range for cell determination [°]	4–55	4–60	4–55
Unit cell parameters a [Å]	11.2008(2)	11.0674(1)	10.7082(2)
b [Å]	12.6246(2)	13.3562(2)	14.3736(3)
c [Å]	17.0682(3)	17.2406(3)	17.3511(4)
V [Å^3]	2413.54(7)	2548.48(6)	2670.60(10)
D_x [g cm^{-3}]	1.237	1.206	1.185
$\mu(\mathrm{Mo}K_\alpha)$ [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
$2\theta_{(\max)}$ [°]	55	60	55
Total reflections measured	34028	51767	37349
Symmetry independent reflections	3126	7453	3430
Reflections with $I > 2\sigma(I)$	2618	5722	2879
Reflections used in refinement	3121	7449	3426
Parameters refined	312	322	332
$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0394	0.0419	0.0451
$wR(F^2)$ (all data)	01002	0.1012	0.1216
Weighting parameters (a; b)[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 $\Delta_{\max}/\sigma$	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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