Synthesis of 16-Membered Cyclic Depsipeptides *via* Direct Amide Cyclization

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The 2,2-disubstituted 2*H*-azirin-3-amines **5** (3-amino-2*H*-azirines) were used as synthons for α,α-disubstituted α-amino acids in the preparation of 16-membered cyclic depsipeptides **13**. The linear precursors containing four α,α-disubstituted α-amino acids, the pentapeptides **12**, were synthesized from β-hydroxy acids **4** *via* the 'azirine/oxazolone method' (*Scheme 2*). The 16-membered cyclic depsipeptides **13** were prepared *via* 'direct amide cyclization' in good-to-excellent yields (*Schemes 3* and *4*). In addition to the desired cyclic monomer **13**, which was obtained as the main product, the cyclodimer **14** could also be isolated. The cyclization conditions were investigated and found to be optimum with HCl in toluene at 100°. The structure and conformation of the cyclic depsipeptide **13b** was established by X-ray crystallography.

1. Introduction. – Non-protein amino acids and their peptides are of considerable interest because of their biological activity. A popular modification to α-amino acids is the substitution of an alkyl group for the H-atom at the C(α)-atom. Peptides containing such α,α-disubstituted α-amino acids (α,α-disubstituted glycines) are significantly restricted in their conformational freedom. Therefore, the incorporation of one or more α,α-disubstituted α-amino acids is a convenient method for introducing rigidity to the peptide backbone, thereby promoting secondary structures such as β-turns and α- and 3_{10}-helices in the solid state and in solution [1–5]. A useful method for the introduction of α,α-disubstituted α-amino acids into peptides is the so-called 'azirine/oxazolone method', in which 2,2-disubstituted 2*H*-azirin-3-amines (3-amino-2*H*-azirines) are used as amino-acid synthons [6]. This strategy has been widely employed in the synthesis of peptaibols [7–9], endothiopeptides [10], and conformationally restricted cyclic peptides [11] [12]. A further application is the synthesis of cyclic depsipeptides containing α,α-disubstituted α-amino acids by employing a combination of the 'azirine/oxazolone method' and the so-called 'direct amide cyclization' [13–18]. This combination has been used successfully to prepare a number of conformationally restricted cyclic depsipeptides containing 9- [14], 10- [16], 12- [13–15], 15- [14], and 18-membered rings [17]. The concept of this cyclization method is outlined in *Scheme 1:* treatment of the amides of type **1** with dry HCl leads to the corresponding 1,3-oxazol-5(4*H*)-one intermediates **2** *via* ring closure to **A** and elimination of dimethylamine hydrochloride. In the absence of external nucleophiles, **2** can undergo a ring enlargement to yield the cyclic product **3** *via* an intramolecular attack of the OH group either directly at the lactone group of **2** or, after ring opening, at the oxonium group of **B**.

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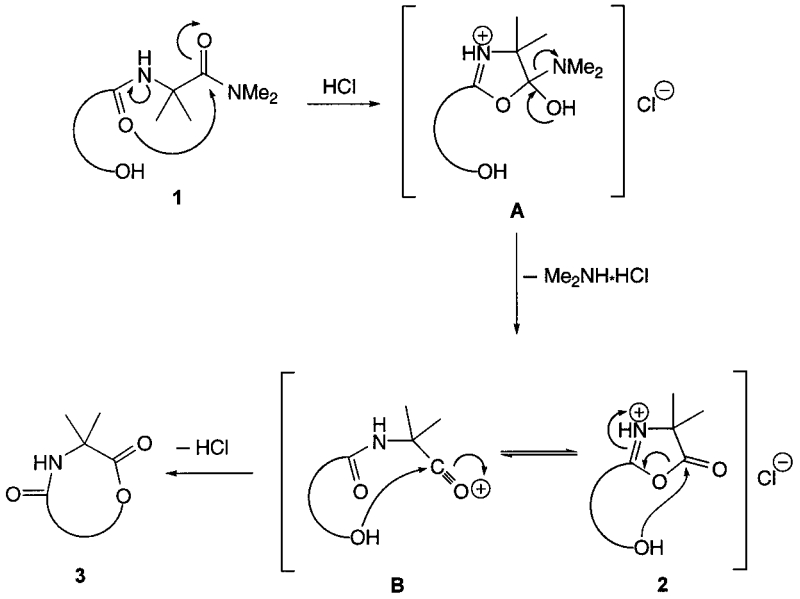
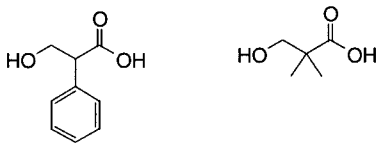
[1]) Part of the planned Ph.D. thesis of *K.N.K.*, Universität Zürich.

Scheme 1

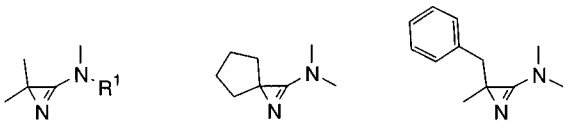


Natural cyclic depsipeptides isolated from different organisms have attracted considerable interest because of their remarkably diverse biological activities [19–24]. The crucial step in the synthesis of cyclic depsipeptides is the ring closure, which has usually been carried out *via* amide-bond formation [25–27]. On the other hand, a certain number of successful cyclizations *via* ester-bond formation have been described [28–32]. So far, 16-membered cyclic depsipeptides containing a β-hydroxy acid have received little attention [21] [33] [34]. Based on these precedents, it was of interest to expand the application of the combination of the 'azirine/oxazolone method' and the 'direct amide cyclization' to the preparation of 16-membered cyclic depsipeptides containing a β-hydroxy acid and α,α-disubstituted α-amino-acid moieties. In the present paper, the studies of an efficient synthesis of those cyclic depsipeptides *via* 'direct amide cyclization' are presented.

2. Results. – The linear pentapeptide precursors were designed with a β-hydroxy carboxylic acid at the end of the chain and four α,α-disubstituted α-amino acids connected by amide bonds. The two β-hydroxy carboxylic acids employed were 3-hydroxy-2-phenylpropanoic acid (**4a**; tropic acid, Tro) and 3-hydroxy-2,2-dimethylpropanoic acid (**4b**; Dhp). The syntheses of the pentapeptide chains were achieved *via* the so-called 'azirine/oxazolone method' [6] with the 3-amino-2*H*-azirines **5a**–**d**. The following abbreviations are used for the corresponding α,α-disubstituted α-amino acids: 2-aminoisobutyric acid (Aib), 1-aminocyclopentanecarboxylic acid (Ac_5c), and α-methylphenylalanine (Phe(2Me)).



4a **4b**



5a R^1 = Me
b R^1 = Ph

5c **5d**

2.1. *Preparation of the Linear Pentapeptides.* Five linear pentapeptides **12** were synthesized according to *Scheme 2* (*cf. Tables 1* and *2*). In contrast to the classical methods for the synthesis of peptides containing α,α-disubstituted α-amino acids [35], the 'azirine/oxazolone method' does not require additional reagents, and the coupling reaction is performed under mild conditions, where no side-products are formed. This simplifies the purification of the products considerably.

The reaction of 3-amino-2*H*-azirines **5** with the free β-hydroxy acids **4** or the peptide acids **7**, **9**, and **11** in dry MeCN at room temperature led to the corresponding amides **6**, **8**, **10**, and **12** in good-to-excellent yields (83–100%; *Table 1*). The hydrolysis of the *C*-terminal amide group was performed under standard conditions with 3N HCl/THF 1:1 at room temperature to yield the acids **7**, **9**, and **11** (86–100%; *Table 2*). In one example (hydrolysis of **10b**), it was necessary to warm the mixture to 40° to obtain the corresponding acid **11b** in good yield (95%). Generally, the coupling step was faster when 3-(dimethylamino)-2*H*-azirine **5a** was used instead of the corresponding 3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine **5b**. On the other hand, *N*-methylaniline is a better leaving group than Me_2NH, thereby making the selective hydrolysis of the *N*-methyl-*N*-phenyl amides faster than that of the *N,N*-dimethyl amides.

In one case, the selective hydrolysis of the *C*-terminal amide failed: when the tripeptide **8c** was treated with 3N HCl/THF at room temperature, not only was the C-terminal amide hydrolyzed, but also the peptide bond between the Phe(2Me) and the Aib residues. Hydrolyses of **8c** and of the corresponding tripeptide with a terminal *N,N*-dimethyl-amide group were attempted, but in both cases mixtures of dipeptide **7c** and tripeptide **9c** were formed. The best yields of tripeptide **9c** relative to dipeptide **7c** were obtained with the *N*-methyl-*N*-phenyl amide **8c**.

As already mentioned, α,α-disubstituted α-amino acids incorporated into the peptide chain severely restrict the conformational freedom of the chain. The structural preferences of Aib-containing peptides have been extensively studied by X-ray crystallography, and a series of conclusions has been drawn: Aib homopeptides, beginning at the trimer level, adopt the 3_{10}-helical structure, irrespective of the chain

Scheme 2

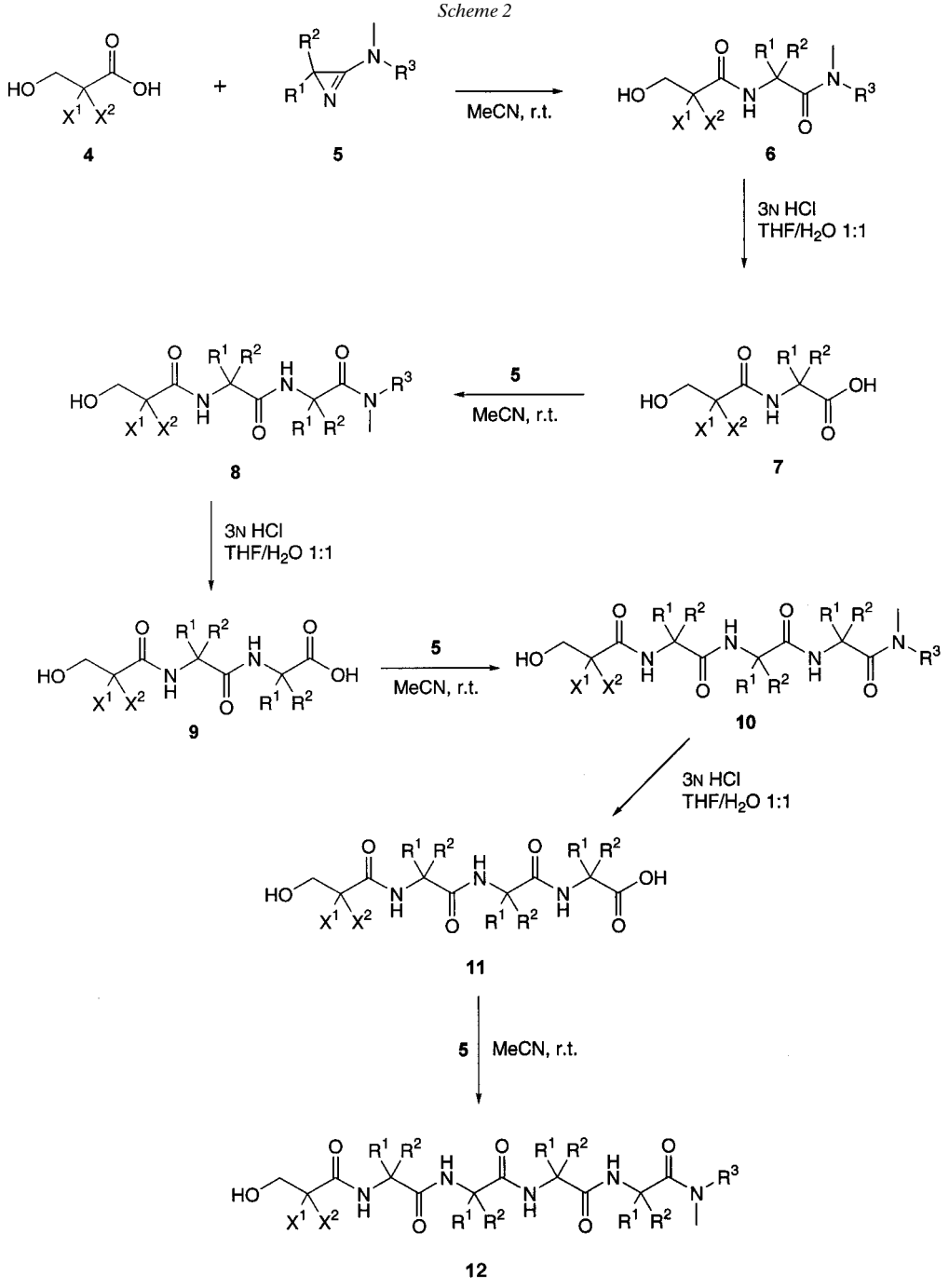

4
5
MeCN, r.t.
6
3N HCl
THF/H2O 1:1
7
5
MeCN, r.t.
8
3N HCl
THF/H2O 1:1
9
5
MeCN, r.t.
10
3N HCl
THF/H2O 1:1
11
5 MeCN, r.t.
12

Table 1. *Coupling of β-Hydroxy Acids* **4** *and of Peptide Acids* **7**, **9**, *and* **11** *with 3-Amino-2*H*-azirines* **5**

Starting material	Azirine	Product	Yield [%]
4a (Tro)	**5a**	**6a** (Tro-Aib-NMe_2)	91
4a (Tro)	**5c**	**6b** (Tro-Ac_5c-NMe_2)	93
4b (Dhp)	**5d**	**6c** (Dhp-Phe(2Me)-NMe_2)	97
7a (Tro-Aib)	**5a**	**8a** (Tro-Aib-Aib-NMe_2)	94
7b (Tro-Ac_5c)	**5c**	**8b** (Tro-Ac_5c-Ac_5c-NMe_2)	90
7c (Dhp-Phe(2Me))	**5b**	**8c** (Dhp-Phe(2Me)-Aib-N(Me)Ph)	87
7c (Dhp-Phe(2Me))	**5c**	**8d** (Dhp-Phe(2Me)-Ac_5c-NMe_2)	92
9a (Tro-Aib-Aib)	**5a**	**10a** (Tro-Aib-Aib-Aib-NMe_2)	95
9b (Tro-Ac_5c-Ac_5c)	**5c**	**10b** (Tro-Ac_5c-Ac_5c-Ac_5c-NMe_2)	92
9c (Dhp-Phe(2Me)-Aib)	**5b**	**10c** (Dhp-Phe(2Me)-Aib-Aib-N(Me)Ph)	66[a])
9d (Dhp-Phe(2Me)-Ac_5c)	**5c**	**10d** (Dhp-Phe(2Me)-Ac_5c-Ac_5c-NMe_2)	99
11a (Tro-Aib-Aib-Aib)	**5a**	**12a** (Tro-Aib-Aib-Aib-Aib-NMe_2)	94
	5b	**12e** (Tro-Aib-Aib-Aib-Aib-N(Me)Ph)	44
11b (Tro-Ac_5c-Ac_5c-Ac_5c)	**5c**	**12b** (Tro-Ac_5c-Ac_5c-Ac_5c-Ac_5c-NMe_2)	95
11c (Dhp-Phe(2Me)-Aib-Aib)	**5a**	**12c** (Dhp-Phe(2Me)-Aib-Aib-Aib-NMe_2)	96
11d (Dhp-Phe(2Me)-Ac_5c-Ac_5c)	**5c**	**12d** (Dhp-Phe(2Me)-Ac_5c-Ac_5c-Ac_5c-NMe_2)	97

[a]) Overall yield of the hydrolysis of **8c**, followed by coupling of crude **9c** with **5b**.

Table 2. *Hydrolysis of the C-Terminal Amide Groups of the Peptide Amides*

Peptide amide	Product	Yield [%]
6a (Tro-Aib-NMe_2)	**7a** (Tro-Aib)	98
6b (Tro-Ac_5c-NMe_2)	**7b** (Tro-Ac_5c)	99
6c (Dhp-Phe(2Me)-NMe_2)	**7c** (Dhp-Phe(2Me))	95
8a (Tro-Aib-Aib-NMe_2)	**9a** (Tro-Aib-Aib)	88
8b (Tro-Ac_5c-Ac_5c-NMe_2)	**9b** (Tro-Ac_5c-Ac_5c)	quant.
8c (Dhp-Phe(2Me)-Aib-N(Me)Ph)	**9c** (Dhp-Phe(2Me)-Aib)	–
8d (Dhp-Phe(2Me)-Ac_5c-NMe_2)	**9d** (Dhp-Phe(2Me)-Ac_5c)	86
10a (Tro-Aib-Aib-Aib-NMe_2)	**11a** (Tro-Aib-Aib-Aib)	99
10b (Tro-Ac_5c-Ac_5c-Ac_5c-NMe_2)	**11b** (Tro-Ac_5c-Ac_5c-Ac_5c)	95
10c (Dhp-Phe(2Me)-Aib-Aib-N(Me)Ph)	**11c** (Dhp-Phe(2Me)-Aib-Aib)	93
10d (Dhp-Phe(2Me)-Ac_5c-Ac_5c-NMe_2)	**11d** (Dhp-Phe(2Me)-Ac_5c-Ac_5c-Ac_5c)	**98**

length. The α-helical structure has never been observed [2]. Tripeptides and longer peptides containing Aib residues along with protein amino acids are folded either in the 3_{10}- or α-helical structure, depending upon the main-chain length, Aib content, sequence, and environmental conditions [2] [3]. It has been shown that Aib is the strongest known β-turn-forming residue, particularly of types I (I′) and III (III′) [1]. Several structural investigations of Phe(2Me)- and Ac_5c-containing peptides show this same strong tendency to form β-turns and helical structures [1].

The two pentapeptides **12a** and **12d** were crystallized from MeCN and MeOH/i-PrOH/Et_2O, respectively, and their structures were established by X-ray crystallography (*Figs. 1* and *2*). The relevant torsion angles are given in *Table 3*, while the intra- and intermolecular H-bond parameters are listed in *Table 4*.

The peptide **12a** adopts two consecutive β-turns, which can be considered as an incipient 3_{10}-helix conformation stabilized by two consecutive intramolecular $4 \rightarrow 1$ H-bonds between N(7)–H···O(14) and N(4)–H···O(11). The N···O distances

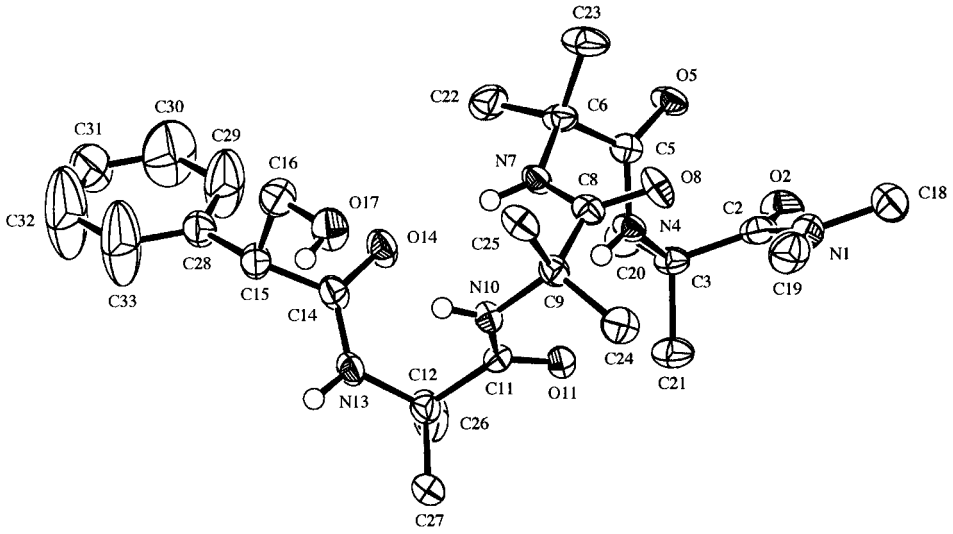


Fig. 1. *ORTEP Plot* [38] *of the molecular structure of* **12a** (arbitrary numbering of the atoms; 50% probability ellipsoids)

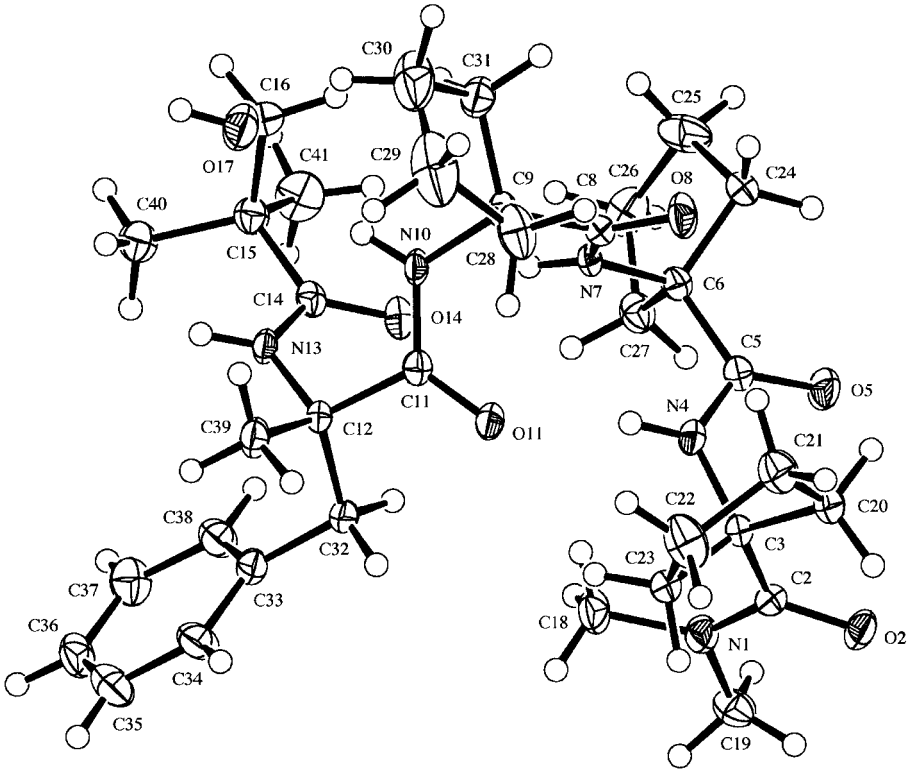
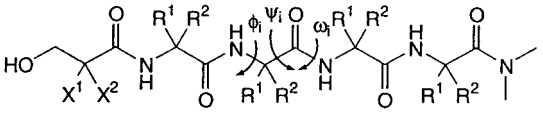


Fig. 2. *ORTEP Plot* [38] *of the molecular structure of* **12d** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Table 3. *Selected Torsion Angles* [°] *of the Pentapeptides* **12a** *and* **12d**



Angle	Peptide **12a**	Peptide **12d**
ω_0	– 177.2(3)	– 172.2(3)
ϕ_1	54.7(5)	51.4(5)
ψ_1	29.8(5)	30.5(5)
ω_1	178.6(3)	177.0(3)
ϕ_2	55.5(5)	55.7(5)
ψ_2	30.9(5)	24.1(5)
ω_2	177.4(3)	– 178.5(3)
ϕ_3	61.7(5)	62.3(5)
ψ_3	28.2(5)	21.8(5)
ω_3	160.7(3)	174.6(4)
ϕ_4	51.9(5)	– 57.7(5)
ψ_4	48.8(5)	– 58.8(5)

Table 4. *Intra- and Intermolecular H-Bond Parameters for the Pentapeptides* **12a** *and* **12d**

Compound	Type[a])	H···O [Å]	N···O [Å]	N–H···O [°]
12a	O(17)–H···O(2′)	1.92(4)	2.729(4)	173(5)
	N(13)–H···O(5′)	2.00(4)	2.888(4)	172(3)
	N(7)–H···O(14)	2.13(3)	2.959(4)	162(3)
	N(4)–H···O(11)	2.27(3)	3.051(4)	159(3)
12d	N(13)–H···O(2′)	2.05	2.876(4)	157
	O(17)–H···O(5′)	2.00(2)	2.817(4)	164(8)
	N(4)–H···O(11)	2.07	2.929(4)	166
	N(7)–H···O(14)	2.11	2.965(4)	164
	N(10)–H···O(17)	2.31	3.175(5)	169

[a]) Primed atoms refer to molecules in the following symmetry-related positions: for **12a**: $x, 1/2 - y, -1/2 + z$; for **12d**: $1 + x, y, z$.

(*Table 4*) are in good agreement with the average value determined for a large number of intramolecular H-bonds in peptides [36]. The torsion angles for the three Aib residues (ϕ_1, ϕ_2, ϕ_3 and ψ_1, ψ_2, ψ_3; *Table 3*) correspond with the values expected for two β-turns of type III′ (III) [4]. All peptide bonds (torsion angles ω) show the s-*trans*-configuration with one deviating markedly from planarity [37]. The molecules of **12a** are linked in a head-to-tail fashion by two intermolecular H-bonds (O(17)–H···O(2′) and N(13)–H···O(5′)), thus forming infinite one-dimensional chains (*cf. Fig. 4*).

In the peptide **12d**, the Phe(2Me) and the two consecutive Ac_5c residues also show torsion angles (*Table 3*), which indicate two consecutive β-turns of type III′ (III) [4] and the beginning of a 3_{10}-helix structure stabilized by two consecutive intramolecular $4 \rightarrow 1$ H-bonds between N(7)–H···O(14) and N(4)–H···O(11). The N···O distances (*Table 4*) are again in good agreement with the expected values [36]. Furthermore, there is an intramolecular H-bond between N(10)–H and the OH O-atom (O(17)),

which further stabilizes the helical conformation of the peptide. The signs of the torsion angles ϕ_4 and ψ_4 of the Ac_5c residue at the C-terminus are opposite to those of the preceding residues and also opposite to that in **12a**. This is a widely observed phenomenon for α,α-disubstituted α-amino-acid homopeptides [39] [40]. The configuration of the peptide bonds (torsion angles ω) are all s-*trans* with two of them deviating distinctly from planarity [37]. The molecules of **12d** are also linked head-to-tail by intermolecular H-bonds (O(17)–H···O(5′) and N(13)–H···O(2′)), thus forming infinite one-dimensional chains (*cf. Fig. 5*).

2.2. *Cyclization of the Linear Pentapeptides.* The ring closure *via* 'direct amide cyclization' was carried out by slowly passing dry HCl gas through a suspension of the pentapeptides **12** in toluene at 100°. Toluene was chosen as the solvent, because the pentapeptides **12** were nearly insoluble in this solvent, resulting in a low concentration of the solvated oxazolone intermediate **2**. This high dilution of the reactive intermediate is an optimum condition for the intramolecular cyclization, *i.e.*, the formation of the cyclic monomer is thereby favored over the formation of oligomers.

The pentapeptide **12b** was used as a model for the optimization of the cyclization conditions. The most successful protocol was as follows: a stream of dry HCl gas was passed through the suspension, which was prewarmed to the chosen reaction temperature. When the suspension dissolved and a clear reaction solution formed, HCl was added for another 2–3 min. Excess HCl was then removed by passing a stream of N_2 through the solution for 30 min. Then, the toluene was evaporated, the crude product was dissolved in THF/Et_2O 1:1 at room temperature, and, subsequently, the precipitated $Me_2NH \cdot HCl$ was removed by filtration. The cyclic peptides were then purified by column chromatography.

The cyclization of pentapeptide **12b** resulted in the formation and isolation of both the desired monomer **13b** (*Scheme 3*) and the dimer **14b**[2]). The experiments were carried out at four different temperatures, with two different amounts of solvent and various reaction times. The results of these cyclization experiments are depicted in *Table 5*.

The optimum conditions for maximizing the yield of monomer **13b** relative to that of the dimer **14b** are 100° with slow addition of HCl gas in a highly diluted toluene suspension. As toluene is a nonpolar solvent, it was of interest to attempt the cyclization in a polar solvent in order to compare the efficiency of the ring closure process. Previously, in the case of some ten-membered cyclic depsipeptides, the 'direct amide cyclization' was carried out in DMF at 60° [16]. Therefore, the pentapeptide **12b** was dissolved in DMF at 55°, treated with HCl gas for 30 min, and then worked up. Two experiments with different concentrations of **12b** ($c = 0.0026$M and $c = 0.001$M, resp.) were carried out. Neither the monomer **13b** nor the dimer **14b** could be detected in these two cyclization experiments. This indicated that the unique condition of an almost insoluble pentapeptide in toluene is a very important factor for obtaining the cyclopentapeptide in good yield.

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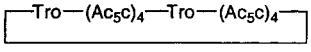
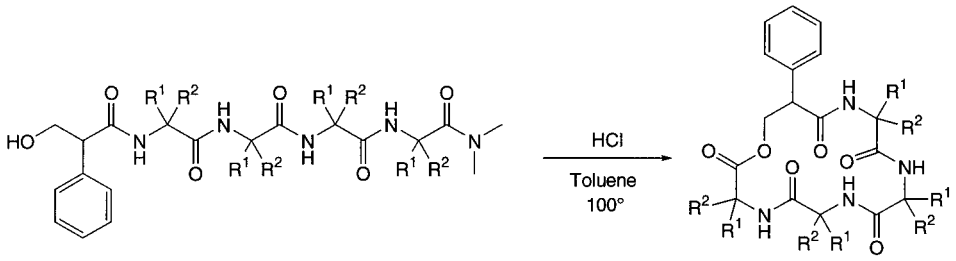
[2]) Based on the similar chromatographic properties of **14b** and **13b**, and the ESI-MS, we proposed that **14b** is a cyclodimer.



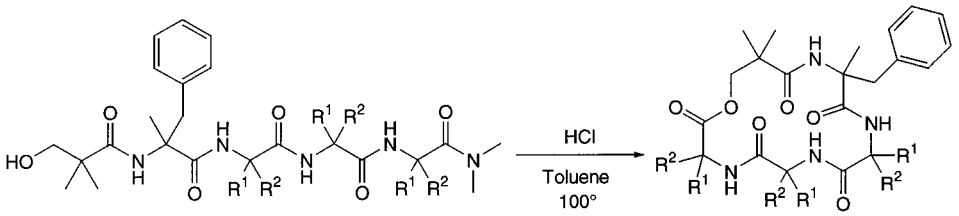
14b

Scheme 3



12a $R^1 = R^2 = Me$
b $R^1, R^2 = -(CH_2)_4-$

13a $R^1 = R^2 = Me$
b $R^1, R^2 = -(CH_2)_4-$



12c $R^1 = R^2 = Me$
d $R^1, R^2 = -(CH_2)_4-$

13c $R^1 = R^2 = Me$
d $R^1, R^2 = -(CH_2)_4-$

Table 5. *Optimization of the Conditions of the 'Direct Amide Cyclization' of* **12b**

Temp. [°]	Toluene [ml]	*t* [min]	**13b** [%]	**14b** [%]
40	15	5	0	0
60	15	5	6	17
80	15	5	15	33
100	15	5	42	13
100	15	3	34	22
100	15	10	43	11
100	30	9	60	4

The three other pentapeptides **12a**, **12c** and **12d** were then cyclized under the above optimized conditions (30 ml, toluene 100°). In each of these three examples, both the monomer **13** and the dimer **14** could be isolated, with the monomer being the main product (*cf. Table 6*).

As listed in *Table 6*, the yields of different cyclic monomers **13** vary considerably; when the yield of **13** is high, the yield of the cyclodimer **14** is low and *vice versa*. There are several possible explanations for this observation. The probability of nucleophilic attack by the OH group at one end of the peptide chain on the oxazolone group at the other terminus depends on the conformational flexibility of the peptide backbone,

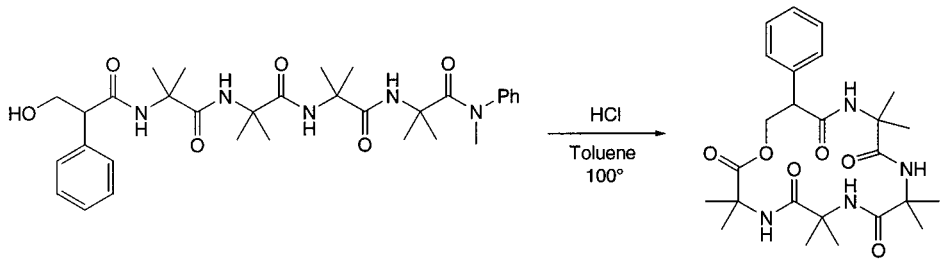
Table 6. *Cyclization of Pentapeptides* **12a**–**d** *in Toluene* (30 ml) *at 100°*

Pentapeptide	Cyclic monomer **13** [%]	Cyclodimer **14** [%]
12a	41	4
12b	60	4
12c	46	7
12d	24	19

which may vary considerably in various peptides. Another factor that influences the ratio **13**/**14** is the concentration of the oxazolone intermediate **2**: the lower the concentration of **2**, the better are the conditions for the formation of the cyclic monomer **13** relative to the cyclodimer **14**.

As previously described, *N*-methylaniline is a better leaving group than Me_2NH, which influences the reaction rate of the acid-catalyzed hydrolysis. It was of interest to determine what kind of influence the substituents on the *C*-terminal amide group would have on the 'direct amide cyclization'. Therefore, an analogue of pentapeptide **12a** was synthesized. This compound, **12e**, which contains the tropic-acid moiety, four Aib residues, and a *C*-terminal *N*-methyl-*N*-phenyl-amide group, was then cyclized in toluene (*Scheme 4*). The cyclization was performed at four different temperatures, and both the cyclic monomer **13a** and the cyclodimer **14a** could be isolated (*Table 7*).

Scheme 4



12e **13a**

Table 7. *'Direct Amide Cyclization' of* **12e** *in Toluene*

Temp. [°]	Cyclic monomer **13a** [%]	Cyclodimer **14a** [%]
40	7	7
60	13	11
80	39	17
100	48	9

In these experiments, the optimum temperature for the formation of the cyclic monomer was found to be 100°. The cyclic depsipeptide **13a** was obtained in 48% yield from pentapeptide **12e**, whereas it was isolated in 41% yield, when **12a** was used as the starting material. Therefore, the *N*-methyl-*N*-phenyl-amide group was slightly better suited for ring formation *via* 'direct amide cyclization' than the *N,N*-dimethyl-amide group.

The cyclic depsipeptides **13** were characterized by analytical and spectroscopic methods. In the IR spectra of **13a**–**13d**, the absorption of the lactone group was observed at 1722–1740 cm^{-1}. To determine the molecular mass of the cyclic depsipeptides, the soft-ionization technique ESI-MS was employed. With this technique, it was possible to differentiate between the monomer **13** and the dimer **14**. Furthermore, the structures of **13a**–**13d** were confirmed by 1D- and 2D-NMR spectroscopy. The assignment of the different ^{1}H and ^{13}C signals was carried out using HSQC and HMBC techniques. In the case of **13a** and **13c**, it was possible to assign each signal, whereas, for **13b** and **13d**, all signals could be assigned except those for the four CH_2 groups of the Ac_5c residues.

The cyclic depsipeptide **13b** was successfully crystallized from EtOH/AcOEt/CH_2Cl_2, and its structure was established by X-ray crystallography (*Fig. 3*). The structure of **13b** has four symmetry-independent molecules in the asymmetric unit. The macrocyclic rings in the four independent molecules are very similar without significant conformational differences. The major differences between the molecules are slight variations in the orientation of the Ph ring, the presence or absence of disorder in the cyclopentane rings, and the puckering of the five-membered rings. The relevant torsion angles of the four molecules are given in *Table 8*; the intra- and intermolecular H-bond parameters are listed in *Table 9*.

Table 8. *Selected Torsion Angles of the Four Crystallographically Independent Molecules A–D of* **13b**

Angle [°]	Molecule A	Molecule B	Molecule C	Molecule D
ω_0[a])	–177.5(2)	176.9(2)	175.1(2)	–176.1(2)
ϕ_1	–66.0(3)	–56.9(3)	–62.2(3)	–62.3(3)
ψ_1	132.1(2)	127.1(2)	138.4(2)	125.8(2)
ω_1	171.3(2)	165.2(2)	167.2(2)	169.6(2)
ϕ_2	56.3(3)	53.2(3)	57.8(3)	57.3(3)
ψ_2	36.6(3)	43.3(3)	33.3(3)	37.2(3)
ω_2	170.2(2)	170.0(2)	171.0(2)	171.6(2)
ϕ_3	79.2(3)	77.7(3)	75.4(3)	81.6(3)
ψ_3	–4.2(3)	–11.2(3)	–3.2(3)	–6.1(3)
ω_3	159.9(2)	160.4(2)	155.9(2)	158.1(2)
ϕ_4	–52.6(3)	–60.2(3)	–62.6(3)	–57.6(3)
ψ_4	–29.2(3)	–17.4(3)	–7.1(3)	–21.4(3)
ω_4[b])	–160.4(2)	–173.0(2)	–166.3(2)	–168.5(2)

[a]) Torsion angle of the amide bond of Tro.
[b]) Torsion angle of the lactone bond.

Each of the independent molecules A, B, C, and D adopt a β-turn conformation stabilized by an intramolecular H-bond between N(3)–H and O(10) with an average length of 3.105(6) Å, which is in good agreement with the expected values [36]. The combination of the torsion angles for the two Ac_5c residues (ϕ_2, ϕ_3, and ψ_2, ψ_3) are close to the ideal values for a β-turn conformation of type I′ (I). All of the amide bonds have the s-*trans*-configuration ($|\omega| = 155.9–177.5°$), and the ester bond in each molecule has the s-*trans*-configuration ($|\omega| = 160.4–173.0°$). Some of these amide and ester bonds deviate significantly from planarity [37]. The combination of all intermolecular H-bonds links the molecules into an infinite two-dimensional network (*cf. Fig. 6*).

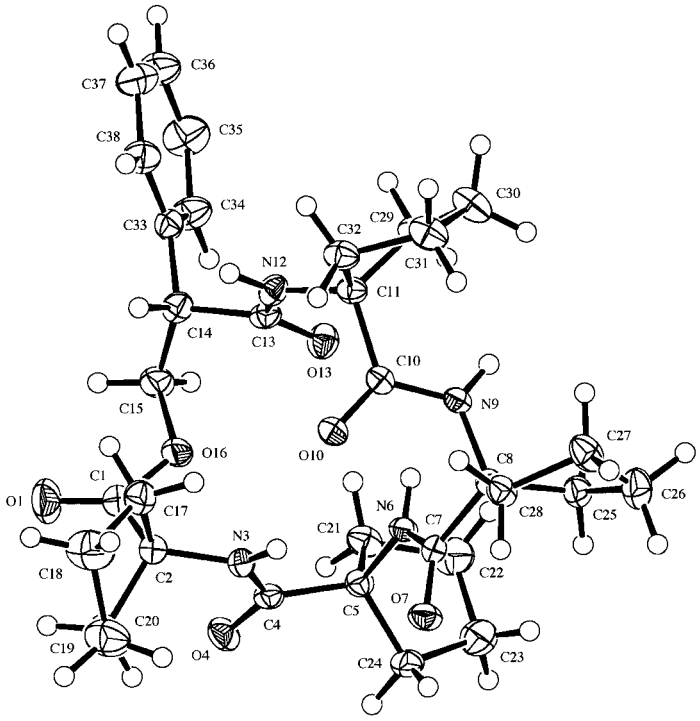


Fig. 3. *ORTEP Plot* [38] *of the molecular structure of molecule A of* **13b** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Table 9. *Selected Inter- and Intramolecular H-Bond Parameters for* **13b**

	Type [a])	H···O [Å]	N···O [Å]	N–H···O [°]
Molecule A	N(3)–H···O(10)	2.39	3.128(3)	141.4
	N(9)–H···O(4c^{i})	2.49	3.280(3)	149.6
	N(12)–H···O(7b^{ii})	2.25	3.077(3)	156.3
Molecule B	N(3a)–H···O(10a)	2.38	3.044(3)	132.8
	N(9a)–H···O(4b)	2.54	3.368(3)	157.1
	N(12a)–H···O(7c)	2.23	3.052(3)	154.9
Molecule C	N(3b)–H···O(10b)	2.46	3.131(3)	133.4
	N(9b)–H···O(4a^{iii})	2.43	3.287(3)	165.1
	N(12b)–H···O(7)	2.22	2.998(3)	147.0
Molecule D	N(3c)–H···O(10c)	2.40	3.118(3)	138.4
	N(12c)–H···O(7a^{ii})	2.22	3.055(3)	158.3

[a]) Superscripted atoms refer to molecules in the following symmetry-related positions: i: $1-x, 1-y, 1-z$; ii: $x, y, -1+z$; iii: $1-x, -y, 2-z$.

3. Conclusions. – The present study has demonstrated the application of the combination of the 'azirine/oxazolone method' and the 'direct amide cyclization' as a preparative route to 16-membered cyclic depsipeptides containing one β-hydroxy acid and four α,α-disubstituted α-amino acids. In contrast to previous results, a cyclodimer

could be isolated in addition to the cyclic monomer after ring closure *via* 'direct amide cyclization'. The optimal conditions for maximizing the yield of the cyclic monomer relative to that of the cyclodimer were determined by a number of cyclization experiments.

By X-ray crystallography, it was shown that the pentapeptide precursors **12a** and **12d** both adopt an incipient 3_{10} helix containing two consecutive β-turns of type III′ (III). This is in agreement with previous structure determinations of α,α-disubstituted α-amino-acid polypeptides [1]. For the first time, it was possible to establish the stucture of a cyclic depsipeptide prepared *via* 'direct amide cyclization' by X-ray crystallography, and it was shown that the 16-membered cyclic depsipeptide **13b** forms a β-turn conformation (N(3)–H···O(10)) which is close to type I′ (I).

Further studies of cyclization *via* 'direct amide cyclization' are in progress.

Experimental Part

1. *General*. See [41]. Unless otherwise stated, IR spectra in KBr and NMR spectra in (D_6)DMSO (^{1}H: 300 MHz and ^{13}C: 75.5 MHz). CI-MS with NH_3. The following 3-amino-2*H*-azirines were used: *2,2,*N,N-*tetramethyl-2*H-*azirin-3-amine* (**5a**), *2,2,*N-*trimethyl*-N-*phenyl-2*H-*azirin-3-amine* (**5b**), N,N-*dimethyl-1-azaspiro[2.4]hept-1-en-2-amine* (**5c**), and *2-benzyl-2,*N,N-*trimethyl-2*H-*azirin-3-amine* (**5d**) (*cf.* [6] and refs. cit. therein).

General Procedure 1 (*GP 1*). *Reaction of* **5** *with Acids* **7**, **9**, *and* **11**. To a stirred suspension of the acid in dry MeCN was added dropwise a soln. of **5** in dry MeCN. The mixture was stirred at r.t. under N_2 (16–94 h), filtered, washed with cold hexane/Et_2O 1:1, and dried under h.v.

General Procedure 2 (*GP 2*). According to *GP 1*, the mixture was stirred at r.t. under N_2 (2–30 h), evaporated, purified by column-chromatography (CC), and dried under h.v.

General Procedure 3 (*GP 3*). *Hydrolysis of Amides* **6**, **8**, *and* **10**. The amide was dissolved in 3N HCl/THF 1:1 (*v/v; ca.* 5 ml/mmol) and the soln. was stirred at r.t. (6–42 h). The solvent was evaporated, H_2O was added, and the mixture was left overnight at r.t. The product was collected by filtration, washed with cold H_2O and Et_2O, and dried under h.v.

General Procedure 4 (*GP 4*). According to *GP 3*, a soln. of the amide in 3N HCl/THF 1:1 (*v/v; ca.* 5 ml/mmol), was stirred at r.t. (2–23 h), followed by evaporation of the solvent. To the oily crude product was added brine, the mixture was extracted with AcOEt, the org. layer was dried ($MgSO_4$), evaporated, and the residue was dried under h.v.

2. *Reaction of 2*H-*Azirin-3-amines* **5** *with β-Hydroxy Acids* **4**. 2.1. *2-[(3-Hydroxy-1-oxo-2-phenylpropyl)-amino]-2,*N,N-*trimethylpropanamide* (**6a**). According to *GP 1*, **4a** (1.003 g, 6.04 mmol) in MeCN (25 ml), **5a** (0.677 g, 6.04 mmol) in MeCN (3 ml), stirred for 16 h: 1.529 g (91%) of **6a**. White powder. M.p. 176.0–177.0°. IR: 3426v*s*, 3292v*s*, 3061*m*, 2934*s*, 1648v*s*, 1622v*s*, 1540v*s*, 1499*s*, 1457*s*, 1395v*s*, 1364*s*, 1269*s*, 1212*m*, 1178*m*, 1120*s*, 1066*s*, 1054*s*, 1019*s*, 975*w*, 918*w*, 777*m*, 743*m*, 702*s*, 616*m*. ^{1}H-NMR: 8.30 (*s*, NH); 7.30–7.21 (*m*, 5 arom. H); 4.79 (*t*, J = 4.9, OH); 3.97–3.89, 3.66–3.61, 3.50–3.44 (3*m*, C*H*$_2$OH, CH); 2.71 (br. *s*, Me_2N); 1.34, 1.25 (2*s*, Me_2C). ^{13}C-NMR: 171.7, 170.2 (2*s*, 2 CO); 138.2 (*s*, 1 arom. C); 128.0, 127.8, 126.6 (3*d*, 5 arom. C); 63.2 (*t*, CH_2OH); 55.4 (*s*, Me_2C); 54.0 (*d*, CH); 37.0 (*q*, Me_2N); 25.8, 25.6 (2*q*, *Me*$_2$C). ESI-MS: 301 (100, $[M+Na]^+$).

2.2. *1-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-*N,N-*dimethylcyclopentanecarboxamide* (**6b**). According to *GP 1*, **4a** (1.002 g, 6.030 mmol) in MeCN (6 ml), **5c** (0.937 g, 6.78 mmol) in MeCN (1 ml), stirred for 48 h: 1.714 g (93%) of **6b**. White powder. M.p. 222.1–222.8°. IR: 3401v*s*, 3276v*s*, 3033*m*, 2953*s*, 2870*s*, 1656v*s*, 1615v*s*, 1540v*s*, 1490*s*, 1456*s*, 1408*s*, 1392v*s*, 1332*m*, 1313*m*, 1262*s*, 1219*m*, 1179*m*, 1090*m*, 1069*s*, 1030*m*, 962*w*, 919*w*, 782*w*, 743*m*, 702*s*, 668*m*. ^{1}H-NMR: 8.31 (*s*, NH); 7.29–7.23 (*m*, 5 arom. H); 4.78 (br. *s*, OH); 3.96–3.88, 3.66–3.61, 3.48–3.45 (3*m*, C*H*$_2$OH, CH); 2.68 (br. *s*, Me_2N); 2.18–2.04, 1.88–1.70, 1.55–1.40 (3*m*, $(CH_2)_4$). ^{13}C-NMR: 171.6, 170.2 (2*s*, 2 CO); 138.3 (*s*, 1 arom. C); 128.0, 127.7, 126.6 (3*d*, 5 arom. C); 65.4 (*s*, $(CH_2)_4C$); 63.2 (*t*, CH_2OH); 53.9 (*d*, CH); 36.9 (*q*, Me_2N); 36.3, 36.0, 23.9 (3*t*, $(CH_2)_4$). CI-MS: 305 (27, $[M+H]^+$), 260 (100, $[M-Me_2N]^+$). Anal. calc. for $C_{17}H_{24}N_2O_3$ (304.39): C 67.08, H 7.95, N 9.20; found: C 67.01, H 7.76, N 9.16.

2.3. *2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-*N,N-*dimethylpropanamide* (**6c**). According to *GP 2*, **4b** (1.015 g, 8.59 mmol) in MeCN (12 ml), **5d** (1.855 g, 8.74 mmol) in MeCN (1 ml), stirred for 30 h, CC (SiO_2, CH_2Cl_2/MeOH 20:1): 2.556 g (97%) of **6c**. White powder. M.p. 137.3–138.0°. IR: 3381v*s*, 3295v*s*, 3058*m*,

3025*s*, 2961*s*, 2930v*s*, 2870*s*, 1663v*s*, 1622v*s*, 1521v*s*, 1457v*s*, 1406v*s*, 1391v*s*, 1312*s*, 1296*m*, 1262*s*, 1234*s*, 1187*s*, 1091v*s*, 1053v*s*, 1032*m*, 988*m*, 958*m*, 905*m*, 874*w*, 836*w*, 802*w*, 762*s*, 740*m*, 709v*s*, 661*s*, 607*m*. ^{1}H-NMR: 7.38 (*s*, NH); 7.28–7.21 (*m*, 3 arom. H); 7.09–7.06 (*m*, 2 arom. H); 5.04 (*t*, $J = 5.0$, OH); 3.37–3.34 (*m*, CH_2OH); 3.27, 3.06 (*AB*, $J = 13.5$, PhCH_2); 2.92 (br. *s*, Me_2N); 1.28, 1.02 (2*s*, Me_2C, PhCH$_2$(*Me*)C). ^{13}C-NMR: 174.8, 171.2 (2*s*, 2 CO); 137.1 (*s*, 1 arom. C); 130.8, 127.6, 126.2 (3*d*, 5 arom. C); 67.7 (*t*, CH_2OH); 58.5, 43.1 (2*s*, Me_2*C*, PhCH$_2$(Me)*C*); 41.0 (*t*, PhCH_2); 37.4 (*q*, Me_2N); 22.5, 22.4 (2*q*, *Me*$_2$C, PhCH$_2$(*Me*)C). CI-MS: 307 (24, $[M+H]^+$), 262 (100, $[M-Me_2N]^+$).

3. *Hydrolysis of Dipeptide Amides* **6**. 3.1. *2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methylpropanoic Acid* (**7a**). According to *GP 3*, **6a** (1.37 g, 4.92 mmol), 25 ml of 3N HCl (H_2O/THF 1:1), stirred for 42 h, H_2O (20 ml): 1.21 g (98%) of **7a**. White powder. M.p. 212.4–214.0°. IR: 3298v*s*, 3227v*s*, 3062v*s*, 2929*s*, 2884*s*, 1710v*s*, 1650v*s*, 1557v*s*, 1490*m*, 1468*s*, 1454*s*, 1415*m*, 1380*s*, 1363*m*, 1345*m*, 1296*s*, 1272v*s*, 1235*s*, 1177*s*, 1088*m*, 1067*m*, 1051*s*, 1025*s*, 948*s*, 876*w*, 743*m*, 696v*s*, 622*m*, 604*m*. ^{1}H-NMR: 12.05 (br. *s*, COOH); 8.17 (*s*, NH); 7.32–7.18 (*m*, 5 arom. H); 4.68 (br. *s*, OH); 3.89–3.83, 3.67–3.62, 3.56–3.50 (3*m*, CH_2OH, CH); 1.35, 1.28 (2*s*, Me_2C). ^{13}C-NMR: 175.4, 170.9 (2*s*, 2 CO); 138.4 (*s*, 1 arom. C); 128.0, 127.9, 126.4 (3*d*, 5 arom. C); 63.6 (*t*, CH_2OH); 54.7 (*s*, Me_2*C*); 53.6 (*d*, CH); 24.80, 24.75 (2*q*, *Me*$_2$C). ESI-MS: 274 (100, $[M+Na]^+$). Anal. calc. for $C_{13}H_{17}NO_4$ (251.28): C 62.14, H 6.82, N 5.57; found: C 62.27, H 6.73, N 5.67.

3.2. *1-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]cyclopentanecarboxylic Acid* (**7b**). According to *GP 3*, **6b** (1.657 g, 5.44 mmol), 6 ml of 3N HCl (H_2O/THF 1:1), stirred for 24 h, H_2O (20 ml): 1.491 g (99%) of **7b**. M.p. 230.7–231.2°. IR: 3224v*s*, 3062v*s*, 2961v*s*, 2883*s*, 1707v*s*, 1648v*s*, 1559v*s*, 1490*m*, 1472*m*, 1455*s*, 1416*s*, 1377*m*, 1345*m*, 1309*s*, 1273*vs*, 1242*m*, 1193*s*, 1131*w*, 1093*m*, 1065*s*, 1049*s*, 1026*s*, 943*m*, 880*w*, 694v*s*, 603*m*. ^{1}H-NMR: 12.00 (br. *s*, COOH); 8.25 (*s*, NH); 7.32–7.17 (*m*, 5 arom. H); 3.90–3.84, 3.68–3.63, 3.57–3.51 (3*m*, CH_2OH, CH); 2.12–1.73, 1.64–1.52 (2*m*, $(CH_2)_4$). ^{13}C-NMR: 175.2, 171.2 (2*s*, 2 CO); 138.4 (*s*, 1 arom. C); 128.0, 127.9, 126.4 (3*d*, 5 arom. C); 64.8 (*s*, $(CH_2)_4$*C*); 63.5 (*t*, CH_2OH); 53.5 (*d*, CH); 36.2, 36.1, 23.92, 23.87 (4*t*, $(CH_2)_4$). CI-MS: 278 (100, $[M+H]^+$), 260 (56, $[M-OH]^+$), 232 (76, $[M-COOH]^+$). Anal. calc. for $C_{15}H_{19}NO_4$ (277.32): C 64.97, H 6.91, N 5.05; found: C 64.68, H 6.96, N 5.03.

3.3. *2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]propanoic Acid* (**7c**). According to *GP 3*, **6c** (2.52 g, 8.22 mmol), 40 ml 3N HCl (H_2O/THF 1:1), stirred for 26 h, H_2O (10 ml): 2.18 g (95%) of **7c**. White powder. M.p. 145.4–146.0°. IR: 3364v*s*, 3251v*s*, 2980v*s*, 1713v*s*, 1634v*s*, 1533v*s*, 1497*s*, 1457v*s*, 1406*s*, 1380*s*, 1367*s*, 1317*s*, 1290*s*, 1253v*s*, 1189v*s*, 1157*s*, 1128v*s*, 1092*m*, 1034v*s*, 995*m*, 936*m*, 911*m*, 885*m*, 826*m*, 789*m*, 753*s*, 734*s*, 700v*s*, 672*s*, 656v*s*, 607*s*. ^{1}H-NMR: 12.69 (*s*, COOH); 7.48 (*s*, NH); 7.28–7.20 (*m*, 3 arom. H); 7.10–7.07 (*m*, 2 arom. H); 5.05 (br. *s*, OH); 3.35, 3.29 (*AB*, $J = 10.5$, PhCH_2); 3.20 (*m*, CH_2OH); 1.37, 1.00, 0.99 (3*s*, Me_2C, PhCH$_2$(*Me*)C). ^{13}C-NMR: 175.7, 175.0 (2*s*, 2 CO); 136.8 (*s*, 1 arom. C); 130.1, 127.6, 126.3 (3*d*, 5 arom. C); 67.5 (*t*, CH_2OH); 59.0, 42.8 (2*s*, Me_2*C*, PhCH$_2$(Me)*C*); 40.2 (*t*, PhCH_2); 22.8, 22.4, 22.3 (3*q*, *Me*$_2$C, PhCH$_2$(*Me*)C). CI-MS: 280 (100, $[M+H]^+$).

4. *Reaction of 2*H*-Azirin-3-amines* **5** *with Dipeptides* **7**. 4.1. *2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2*,N,N*-trimethylpropanamide* (**8a**). According to *GP 1*, **7a** (1.133 g, 4.51 mmol) in MeCN (13 ml), **5a** (0.508 g, 4.53 mmol) in MeCN (4 ml), stirred for 18 h: 1.537 g (94%) of **8a**. White powder. M.p. 185.7–187.6°. IR: 3440*s*, 3342v*s*, 3285v*s*, 3031*m*, 2987*m*, 2941*m*, 2850*w*, 1662v*s*, 1619v*s*, 1528v*s*, 1464*m*, 1398*s*, 1364*s*, 1318*m*, 1236*m*, 1209*s*, 1179*m*, 1122*s*, 1063*s*, 1029*m*, 971*w*, 898*w*, 767*w*, 739*m*, 701*s*, 640*w*, 610*m*. ^{1}H-NMR: 8.17 (*s*, NH); 7.33–7.23 (*m*, NH, 5 arom. H); 5.10 (br. *s*, OH); 3.93–3.91, 3.75–3.72, 3.61–3.59 (3*m*, CH_2OH, CH); 2.83 (br. *s*, Me_2N); 1.34, 1.23, 1.22 (3*s*, 2 Me_2C). ^{13}C-NMR: 172.9, 171.6 (2*s*, 3 CO); 137.6 (*s*, 1 arom. C); 128.1, 127.9, 126.7 (3*s*, 5 arom. C); 63.9 (*t*, CH_2OH); 56.3, 55.5 (2*s*, 2 Me_2*C*); 53.8 (*d*, CH); 37.2 (*q*, Me_2N); 25.9, 25.4, 25.3, 24.3 (4*q*, 2 *Me*$_2$C). ESI-MS: 386 (100, $[M+Na]^+$).

4.2. *1-{1-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]cyclopentanecarboxamido}*-N,N*-dimethylcyclopentanecarboxamide* (**8b**). According to *GP 1*, **7b** (1.431 g, 5.16 mmol) in MeCN (8 ml), **5c** (0.812 g, 5.88 mmol) in MeCN (2 ml), stirred for 25 h: 1.932 g (90%) of **8b**. M.p. 233.4–234.0°. IR: 3463*s*, 3322v*s*, 3280v*s*, 3050*m*, 2957*s*, 2871*s*, 1655v*s*, 1620v*s*, 1524v*s*, 1456*s*, 1396*s*, 1330*m*, 1234*m*, 1064*s*, 1016*m*, 909*w*, 741*m*, 700*s*, 668*m*. ^{1}H-NMR: 8.20 (*s*, NH); 7.39–7.21 (*m*, 1 NH, 5 arom. H); 5.17 (*t*, $J = 4.3$, OH); 3.96–3.88, 3.77–3.72, 3.65–3.59 (3*m*, CH_2OH, CH); 2.78 (br. *s*, Me_2N); 2.11–1.85, 1.72–1.49 (2*m*, 2 $(CH_2)_4$). ^{13}C-NMR: 172.24, 172.18 171.4 (3*s*, 3 CO); 137.5 (*s*, 1 arom. C); 128.1, 127.9, 126.8 (3*d*, 5 arom. C); 66.5, 65.5 (2*s*, 2 $(CH_2)_4$*C*); 63.7 (*t*, CH_2OH); 53.8 (*d*, CH); 37.1 (*q*, Me_2N); 36.8, 36.2, 35.9, 35.3, 23.83, 23.75, 23.6 (7*t*, 2 $(CH_2)_4$). CI-MS: 371 (25, $[M+H]^+$), 371 (100, $[M-Me_2N]^+$).

4.3. *2-({2-Benzyl-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)-2*,N*-dimethyl*-N*-phenylpropanamide* (**8c**). According to *GP 2*, **7c** (0.999 g, 3.58 mmol) in MeCN (15 ml), **5b** (0.632 g, 3.63 mmol) in MeCN (2 ml), stirred for 2 h, CC (SiO_2, CH_2Cl_2/MeOH 20:1): 1.419 g (87%) of **8c**. Colorless foam. IR: 3854*w*, 3341*s*, 3029*w*, 2984*m*, 2873*m*, 1636*vs*, 1594*s*, 1495v*s*, 1456*s*, 1391*s*, 1364*s*, 1240*m*, 1201*m*, 1116*m*, 1092*s*,

1052*m*, 988*w*, 914*w*, 768*m*, 740*w*, 706*s*, 615*m*. ^{1}H-NMR: 7.72 (*s*, NH); 7.39–7.08 (*m*, NH, 10 arom. H); 5.27 (br. *s*, OH); 3.54, 3.32 (*AB*, *J* = 10.4, C*H*$_2$OH); 3.47, 3.09 (*AB*, *J* = 13.4, PhC*H*$_2$); 3.26 (*s*, MeN); 1.37, 1.34, 1.27, 1.05, 1.01 (5*s*, 2 Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C-NMR: 175.6, 173.2, 172.4 (3*s*, 3 CO); 145.8, 137.2 (2*s*, 2 arom. C); 130.5, 128.7, 127.5, 127.1, 126.2, 126.1 (6*d*, 10 arom. C); 68.4 (*t*, CH$_2$OH); 59.2, 56.6, 43.5 (3*s*, 2 Me$_2$*C*, PhCH$_2$(Me)*C*); 39.5 (*q*, MeN); 38.8 (*t*, PhCH$_2$); 25.6, 23.6, 22.3, 22.0 (4*q*, 2 *Me*$_2$C, PhCH$_2$(*Me*)C). CI-MS: 454 (20, [*M* + H]$^+$), 347 (100, [*M* – Me(Ph)N]$^+$).

4.4. *1-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)*-N,N-*dimethylcyclopentanecarboxamide* (**8d**). According to *GP 2*, **7c** (0.445 g, 1.59 mmol) in MeCN (8 ml), **5c** (0.239 g, 1.73 mmol) in MeCN (2 ml), stirred for 25 h, CC (SiO_2, CH_2Cl_2/MeOH 15:1): 0.604 g (92%) of **8d**. White powder. M.p. 156–157°. IR: 3854*w*, 3335*m*, 2960*m*, 2873*m*, 1734*w*, 1654v*s*, 1521*s*, 1456*m*, 1394*m*, 1243*m*, 1159*w*, 1053*m*, 910*w*, 739*w*, 707*m*, 668*w*. ^{1}H-NMR: 7.72 (*s*, NH); 7.27–7.05 (*m*, NH, 5 arom. H); 5.25 (*t*, *J* = 4.7, OH); 3.55–3.50, 3.30–3.25 (2*m*, C*H*$_2$OH); 3.44, 3.08 (*AB*, *J* = 13.6, PhC*H*$_2$); 2.86 (br. *s*, Me$_2$N); 2.19–1.50 (*m*, (CH$_2$)$_4$); 1.28, 1.02, 0.99 (3*s*, Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C-NMR: 175.4, 172.7, 171.6 (3*s*, 3 CO); 137.3 (*s*, 1 arom. C); 130.4, 127.5, 126.1 (3*d*, 5 arom. C); 68.3 (*t*, CH$_2$OH); 65.7, 59.1, 43.5 (3*s*, Me$_2$*C*, PhCH$_2$(Me)*C*, (CH$_2$)$_4$*C*); 38.5 (*t*, PhCH$_2$); 37.2 (*q*, Me$_2$N); 36.0, 35.9, 24.0 (3*t*, (CH$_2$)$_4$); 23.8, 22.3, 22.1 (3*q*, *Me*$_2$C, PhCH$_2$(*Me*)C). ESI-MS: 440 (100, [*M* + Na]$^+$).

5. *Hydrolysis of Tripeptide Amides* **8**. 5.1. *2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methylpropanoic Acid* (**9a**). According to *GP 4*, **8a** (0.494 g, 1.36 mmol), 9 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 23 h, 25 ml of brine, 5 × 25 ml of AcOEt: 0.404 g (88%) of **9a**. White powder. M.p. 173.5–174.2°. IR: 3410v*s*, 3339v*s*, 2985*s*, 2940*s*, 1736v*s*, 1676v*s*, 1530v*s*, 1495v*s*, 1457*s*, 1418*m*, 1390*s*, 1366*s*, 1330*s*, 1264*s*, 1237*s*, 1168*s*, 1043*s*, 1011*s*, 903*w*, 875*w*, 740*m*, 699*s*. ^{1}H-NMR[3]): 8.20 (*s*, NH); 7.36–7.20 (*m*, 5 arom. H); 7.12 (*s*, NH); 5.03 (br. *s*, OH); 3.95–3.89, 3.75–3.70, 3.60–3.55 (3*m*, C*H*$_2$OH, CH); 1.33, 1.32, 1.27, 1.22 (4*s*, 2 Me$_2$C). ^{13}C-NMR: 175.3, 173.0, 171.5 (3*s*, 3 CO); 137.6 (*s*, 1 arom. C); 128.1, 127.9, 126.7 (3*d*, 5 arom. C); 63.8 (*t*, CH$_2$OH); 56.1, 54.7 (2*s*, 2 Me$_2$*C*); 53.9 (*d*, CH); 25.5, 24.7, 24.3, 24.1 (4*q*, 2 *Me*$_2$C). ESI-MS: 359 (100, [*M* + Na]$^+$). Anal. calc. for $C_{17}H_{24}N_2O_5$ (336.38): C 60.70, H 7.19, N 8.33; found: C 60.59, H 7.19, N 8.17.

5.2. *1-{1-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]cyclopentanecarboxamido}cyclopentanecarboxylic Acid* (**9b**). According to *GP 3*, **8b** (1.763 g, 4.42 mmol), 21 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 26 h, H$_2$O (15 ml): 1.673 g (100%) of **9b**. White powder. M.p. 194.9–196.6°. IR: 3596*m*, 3376v*s*, 3277v*s*, 3061*s*, 2964*s*, 2874*s*, 1715v*s*, 1657v*s*, 1522v*s*, 1451*s*, 1323*s*, 1248*s*, 1209*s*, 1172*m*, 1046*s*, 1021*s*, 955*w*, 914*w*, 750*m*, 699*s*. ^{1}H-NMR[3]): 8.21 (*s*, NH); 7.35–7.20 (*m*, 1 NH, 5 arom. H); 3.95–3.89, 3.76–3.71, 3.63–3.58 (3*m*, C*H*$_2$OH, CH); 2.10–1.45 (*m*, 2 (CH$_2$)$_4$). ^{13}C-NMR: 175.2, 172.9, 172.0 (3*s*, 3 CO); 137.6 (*s*, 1 arom. C); 128.1, 127.9, 126.7 (3*d*, 5 arom. C); 66.1, 64.7 (2*s*, 2 (CH$_2$)$_4$*C*); 63.7 (*t*, CH$_2$OH); 53.9 (*d*, CH); 36.4, 36.3, 36.0, 35.5, 24.1, 24.0, 23.84, 23.80 (8*t*, 2 (CH$_2$)$_4$). ESI-MS: 411 (100, [*M* + Na]$^+$).

5.3. *2-({2-Benzyl-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)-2-methylpropanoic Acid* (**9c**). According to *GP 4*, **8c** (1.602 g, 3.53 mmol), 18 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 2 h, 25 ml of brine, 3 × 25 ml of AcOEt, crystallized from MeOH: 1.178 g crude **9c**. The material was used for the next reaction step without further purification.

5.4. *1-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)cyclopentanecarboxylic Acid* (**9d**). According to *GP 4*, **8d** (0.492 g, 1.18 mmol), 6 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 5 h, 25 ml of brine, 3 × 25 ml of AcOEt: 0.397 g (86%) of **9d**. Foam. IR: 3315v*s*, 3087*s*, 3062*s*, 3032*s*, 2962v*s*, 2876*s*, 1711v*s*, 1654v*s*, 1518v*s*, 1479*m*, 1454v*s*, 1418*m*, 1399*m*, 1380*m*, 1369*m*, 1318*s*, 1304*s*, 1282*s*, 1246*s*, 1185*s*, 1136*m*, 1053*s*, 1027*m*, 987*w*, 949*w*, 916*m*, 866*w*, 839*w*, 764*w*, 744*w*, 708*s*, 659*m*. ^{1}H-NMR: 12.05 (br. *s*, COOH); 7.82 (*s*, NH); 7.39 (*s*, NH); 7.22–7.17 (*m*, 3 arom. H); 7.11–7.08 (*m*, 2 arom. H); 5.13 (*m*, OH); 3.44–3.23 (*m*, C*H*$_2$OH, PhC*H*$_2$); 2.02–1.65 (*m*, (CH$_2$)$_4$); 1.37, 0.99, 0.98 (3*s*, Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C-NMR: 175.3, 175.2, 173.1 (3*s*, 3 CO); 137.2 (*s*, 1 arom. C); 130.3, 127.5, 126.1 (3*d*, 5 arom. C); 68.1 (*t*, CH$_2$OH); 65.2, 59.1, 43.5 (3*s*, Me$_2$*C*, PhCH$_2$(Me)*C*, (CH$_2$)$_4$*C*); 39.1 (*t*, PhCH$_2$); 36.04, 35.95, 24.1, 24.0 (4*t*, (CH$_2$)$_4$); 23.4, 22.2, 22.3 (3*q*, *Me*$_2$C, PhCH$_2$(*Me*)C). ESI-MS: 391 (100, [*M* + H]$^+$).

6. *Reaction of 2*H-*Azirin-3-amines* **5** *with Tripeptides* **9**. 6.1. *2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)-amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2*,N,N-*trimethylpropanamide* (**10a**). According to *GP 1*, **9a** (0.348 g, 1.03 mmol) in MeCN (4 ml), **5a** (0.104 g, 0.93 mmol) in MeCN (1 ml), stirred for 94 h: 0.442 g (95%) of **10a**. White powder. M.p. 239.0–240.0°. IR: 3287v*s*, 2988*s*, 2936*m*, 1692v*s*, 1639v*s*, 1539v*s*, 1506v*s*, 1458*s*, 1383*s*, 1363*s*, 1272*m*, 1230*s*, 1172*m*, 1122*m*, 1057*s*, 1021*m*, 924*w*, 877*w*, 744*m*, 708*s*, 668*w*, 606*w*. ^{1}H-NMR: 8.72 (*s*, NH); 7.38–7.24 (*m*, 1 NH, 5 arom. H); 6.89 (*s*, NH); 5.16 (br. *s*, OH); 3.96–3.94, 3.83–

[3]) Signal for the COOH group could not be determined.

3.78, 3.67–3.64 (3*m*, CH_2OH, CH); 2.87 (br. *s*, Me_2N); 1.35, 1.32, 1.28, 1.23, 1.16 (5*s*, 3 Me_2C). ^{13}C-NMR: 173.1, 172.9, 172.7, 172.0 (4*s*, 4 CO); 137.2 (*s*, 1 arom. C); 128.2, 127.8, 126.9 (3*d*, 5 arom. C); 63.7 (*t*, CH_2OH); 56.1, 55.7, 55.5 (3*s*, 3 Me_2C); 53.5 (*d*, CH); 37.1 (*q*, Me_2N); 25.7, 25.5, 25.4, 24.1, 23.9 (5*q*, 3 Me_2C). ESI-MS: 471 (100, $[M+Na]^+$). Anal. calc. for $C_{23}H_{36}N_4O_5$ (448.55): C 61.59, H 8.09, N 12.49; found: C 61.16, H 8.00, N 12.36.

6.2. *1-(1-{1-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]cyclopentanecarboxamido}cyclopentanecarboxamido)*-N,N-*dimethylcyclopentanecarboxamide* (**10b**). According to *GP 1*, **9b** (1.611 g, 4.15 mmol) in MeCN (10 ml), **5c** (0.612 g, 4.43 mmol) in MeCN (1 ml), stirred for 72 h: 2.015 g (92%) of **10b**. White powder. M.p. 257.8° (dec.). IR: 3325v*s*, 3272v*s*, 2952v*s*, 2873*s*, 1641v*s*, 1618v*s*, 1539v*s*, 1500v*s*, 1448*s*, 1394*s*, 1324*m*, 1266*s*, 1195*m*, 1108*w*, 1058*s*, 1021*s*, 956*w*, 911*w*, 775*w*, 747*m*, 701*s*. ^{1}H-NMR: 8.83 (*s*, NH); 7.45 (*s*, NH); 7.36–7.25 (*m*, 5 arom. H); 7.07 (*s*, NH); 5.40 (br. *s*, OH); 3.89–3.85, 3.71–3.70 (2*m*, CH_2OH, CH); 2.94, 2.75 (2 br. *s*, Me_2N); 2.07–1.52 (*m*, 3 $(CH_2)_4$). ^{13}C-NMR: 173.5, 172.6, 172.4, 171.8 (4*s*, 4 CO); 136.8 (*s*, 1 arom. C); 128.3, 127.7, 127.0 (3*d*, 5 arom. C); 66.1, 66.0, 65.6 (3*s*, 3 $(CH_2)_4C$); 63.9 (*t*, CH_2OH); 53.4 (*d*, CH); 36.7 (*q*, Me_2N); 37.6, 37.3, 35.9, 35.8, 34.8, 24.5, 24.4, 24.1, 24.0, 23.9 (10*t*, 3 $(CH_2)_4$). ESI-MS: 527 (32, $[M+H]^+$), 482 (100, $[M-Me_2N]^+$).

6.3. *2-{[2-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2,*N-*dimethyl*-N-*phenylpropanamide* (**10c**). To a stirred suspension of crude **9c** (1.135 g) in dry MeCN (10 ml) was added dropwise a soln. of **5b** (0.716 g, 4.11 mmol) in MeCN (2 ml). The mixture was stirred at r.t. for 49 h under N_2 and filtered, the solid was washed with cold hexane/Et_2O (1:1), and dried under h.v., yielding 1.08 g of **10c**. The filtrate was purified by CC (SiO_2; CH_2Cl_2/MeOH 20:1), the product was crystallized from AcOEt and dried under h.v., yielding additional 0.181 g of **10c**. Total yield of **10c**: 1.26 g (66%). White powder. M.p. 179.3–180.9°. IR: 3438*s*, 3316v*s*, 2984*m*, 2934*m*, 2870*w*, 1690v*s*, 1666v*s*, 1636v*s*, 1594*s*, 1520v*s*, 1495*s*, 1453*s*, 1393*s*, 1364*s*, 1314*m*, 1263*m*, 1236*m*, 1170*m*, 1094*s*, 1076*w*, 1054*m*, 1026*w*, 905*w*, 838*w*, 770*m*, 709*s*, 665*w*, 616*m*. ^{1}H-NMR: 7.59 (*s*, NH); 7.50 (*s*, NH); 7.35–7.09 (*m*, 1 NH, 10 arom. H); 5.37 (*m*, OH); 3.65–3.63 (*m*, 1 H of CH_2OH); 3.37–3.31 (*m*, MeN, 1 H of CH_2OH, 1 H of PhCH_2); 2.99–2.95 (*d*, $J=13.3$, 1 H of PhCH_2); 1.46, 1.37, 1.27, 1.21, 1.13, 1.06 (6*s*, 3 Me_2C, PhCH_2(*Me*)C). ^{13}C-NMR: 177.4, 173.8, 172.8, 172.6 (4*s*, 4 CO); 146.2, 137.0 (2*s*, 2 arom. C); 130.7, 128.5, 127.6, 126.8, 126.2, 125.8 (6*d*, 10 arom. C); 68.7 (*t*, CH_2OH); 59.1, 56.1, 56.0, 43.7 (4*s*, 3 Me_2C, PhCH_2(Me)*C*); 39.2 (*t*, PhCH_2); 39.1 (*q*, MeN); 26.3, 25.5, 23.9, 23.0, 22.1, 21.8 (6*q*, 3 Me_2C, PhCH_2(*Me*)C). ESI-MS: 561 (100, $[M+Na]^+$).

6.4. *1-[1-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)cyclopentanecarboxamido]*-N,N-*dimethylcyclopentanecarboxamide* (**10d**). According to *GP 1*, **9d** (0.364 g, 0.93 mmol) in MeCN (6 ml), **5c** (0.140 g, 1.01 mmol) in MeCN (1 ml), for 72 h: 0.363 g of **10d**. The filtrate was evaporated and purified by CC (SiO_2; CH_2Cl_2/MeOH 20:1), and the product was dried under h.v., yielding additional 0.123 g of **10d**. Total yield of **10d**: 0.486 g (99%). White powder. M.p. 196.7–198.0°. IR: 3854*w*, 3444*m*, 3313*s*, 2959*s*, 2872*m*, 1647v*s*, 1630v*s*, 1521v*s*, 1478*m*, 1455*s*, 1395*m*, 1320*m*, 1263*m*, 1135*w*, 1055*m*, 906*w*, 712*m*, 668*w*. ^{1}H-NMR: 7.56, 7.55 (2*s*, 2 NH); 7.34–7.07 (*m*, 1 NH, 5 arom. H); 5.50 (*t*, $J=4.5$, OH); 3.69–3.64, 3.36–3.32 (2*m*, CH_2OH, 1 H of PhCH_2); 2.97 (*d*, $J=13.3$, 1 H of PhCH_2); 2.99–2.95 (*m*, 1 Me of Me_2N); 2.76 (br. *s*, 1 Me of Me_2N); 2.18–1.47 (*m*, 2 $(CH_2)_4$); 1.19, 1.13, 1.05 (3*s*, Me_2C, PhCH_2(*Me*)C). ^{13}C-NMR: 177.5, 173.0, 172.5, 171.9 (4*s*, 4 CO); 136.9 (*s*, 1 arom. C); 130.7, 127.7, 126.3 (3*d*, 5 arom. C); 69.1 (*t*, CH_2OH); 66.1, 65.6, 59.2, 43.8 (4*s*, Me_2C, PhCH_2(Me)*C*, 2 $(CH_2)_4C$); 39.0, 37.5, 35.8, 34.8, 24.2, 24.1, 24.0, 23.9 (8*t*, PhCH_2, 2 $(CH_2)_4$); 36.5 (*q*, Me_2N); 23.3, 22.0, 21.7 (3*q*, Me_2C, PhCH_2(*Me*)C). ESI-MS: 484 (100, $[M-Me_2N]^+$).

7. *Hydrolysis of Tetrapeptide Amides* **10**. 7.1. *2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methylpropanoic Acid* (**11a**). According to *GP 3*, **10a** (0.503 g, 1.121 mmol), 6 ml of 3N HCl (H_2O/THF 1:1), stirred for 22 h, H_2O (9 ml): 0.466 g (99%) of **11a**. White powder. M.p. 240.9–241.5°. IR: 3470v*s*, 3410v*s*, 3291v*s*, 2989v*s*, 2945v*s*, 1646v*s*, 1542v*s*, 1503v*s*, 1456*s*, 1387v*s*, 1366*s*, 1269v*s*, 1230*s*, 1188v*s*, 1086*m*, 1066*s*, 1048*s*, 1020*s*, 938*m*, 911*m*, 882*m*, 862*m*, 777*m*, 748*s*, 705*s*, 677*m*, 651*m*, 614*m*. ^{1}H-NMR: 11.82 (br. *s*, COOH); 8.61 (*s*, NH); 7.37–7.21 (*m*, 1 NH, 5 arom. H); 6.95 (*s*, NH); 5.11 (br. *s*, OH); 3.96–3.90, 3.79–3.74, 3.65–3.60 (3*m*, CH_2OH, CH); 1.38, 1.35, 1.32, 1.28, 1.23, 1.17 (6*s*, 3 Me_2C). ^{13}C-NMR: 175.5, 173.1, 172.8, 172.6 (4*s*, 4 CO); 137.2 (*s*, 1 arom. C); 128.2, 127.9, 126.8 (3*d*, 5 arom. C); 63.8 (*t*, CH_2OH); 56.0, 55.5, 54.6 (3*s*, 3 Me_2C); 53.6 (*d*, CH); 25.5, 25.4, 24.8, 24.3, 24.04, 23.99 (6*q*, 3 Me_2C). ESI-MS: 444 (100, $[M+Na]^+$), 404 (48, $[M+H]^+$).

7.2. *1-(1-{1-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]cyclopentanecarboxamido}cyclopentanecarboxamido)cyclopentanecarboxylic Acid* (**11b**). Tetrapeptide amide **10b** (0.302 g, 0.573 mmol) was dissolved in 12 ml of 3N HCl (H_2O/THF 1:1), and the mixture was stirred for 4.5 h at 40°. The solvent was evaporated, H_2O (12 ml) was added, and left at r.t. overnight. The solid was collected by filtration, washed with cold H_2O and Et_2O, and dried under h.v.: 0.273 g (95%) of **11b**. White powder. M.p. 238.7° (dec.). IR: 3287v*s*, 2959*s*, 2875*m*, 1722*s*, 1653v*s*, 1535v*s*, 1473*m*, 1453*m*, 1324*m*, 1266*m*, 1018*m*, 911*w*, 744*m*, 700*m*, 668*m*. ^{1}H-NMR: 11.80 (*s*, COOH);

8.67 (*s*, NH); 7.39–7.24 (*m*, 1 NH, 5 arom. H); 7.05 (*s*, NH); 5.29 (br. *s*, OH); 3.95–3.92, 3.83–3.81, 3.78–3.65 (3*m*, CH_2OH, CH); 2.17–1.52 (*m*, 3 (CH_2)$_4$). ^{13}C-NMR: 175.3, 173.2, 172.9, 172.7 (4*s*, 4 CO); 137.0 (*s*, 1 arom. C); 128.3, 127.8, 126.9 (3*d*, 5 arom. C); 66.1, 65.6, 64.9 (3*s*, 3 (CH_2)$_4$*C*); 63.9 (*t*, CH_2OH); 53.5 (*d*, CH); 37.0, 36.8, 36.2, 36.0, 35.7, 35.2, 24.4, 24.3, 24.2, 24.0, 23.8, 23.7 (12*t*, 3 (CH_2)$_4$). ESI-MS: 522 (100, $[M+Na]^+$), 500 (83, $[M+H]^+$), 482 (45, $[M-OH]^+$).

7.3. *2-{[2-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)-2-methyl-1-oxopropyl] amino}-2-methylpropanoic Acid* (**11c**). According to *GP 3*, **10c** (0.81 g, 1.50 mmol), 8 ml of 3N HCl (H_2O/THF 1:1), stirred for 6 h, H_2O (25 ml): 0.63 g (93%) of **11c**. White powder. M.p. 203.4–204.0°. IR: 3455*s*, 3364*s*, 3318v*s*, 2981*s*, 2938*m*, 1740v*s*, 1658v*s*, 1531v*s*, 1456*s*, 1388*m*, 1365*s*, 1279*m*, 1240*s*, 1167*s*, 1044*s*, 992*w*, 910*w*, 870*w*, 804*w*, 752*m*, 716*m*, 644*m*, 604*m*. ^{1}H-NMR: 11.82 (br. *s*, COOH); 7.51 (*s*, NH); 7.38–7.08 (*m*, 2 NH, 5 arom. H); 5.34 (br. *s*, OH); 3.61 (*d*, *J* = 9.2, 1 H of CH_2OH); 3.37–3.33 (*m*, 1 H of CH_2OH, 1 H of PhCH_2); 2.96 (*d*, *J* = 13.4, 1 H of PhCH_2); 1.38, 1.36, 1.30, 1.23, 1.20, 1.10, 1.04 (7*s*, 3 Me_2C, PhCH_2(*Me*)C). ^{13}C-NMR: 177.1, 175.5, 173.3, 172.8 (4*s*, 4 CO); 137.0 (*s*, 1 arom. C); 130.7, 127.6, 126.2 (3*d*, 5 arom. C); 68.5 (*t*, CH_2OH); 59.0, 55.6, 54.6, 43.6 (4*s*, 3 Me_2*C*, PhCH_2(Me)*C*); 39.1 (*t*, PhCH_2); 26.0, 25.0, 24.2, 23.7, 23.0, 22.1, 21.8 (7*q*, 3 *Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 472 (100, $[M+Na]^+$), 450 (42, $[M+H]^+$).

7.4. *1-[1-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)cyclopentanecarboxamido]cyclopentanecarboxylic Acid* (**11d**). According to *GP 3*, **10d** (0.249 g, 0.47 mmol), 3 ml of 3N HCl (H_2O/THF 1:1), stirred for 23 h, H_2O (2 ml): 0.232 g (98%) of **11d**. White powder. M.p. 225.7–227.2°. IR: 3466*s*, 3292v*s*, 2964v*s*, 2872*s*, 1719v*s*, 1635v*s*, 1531v*s*, 1478*s*, 1451v*s*, 1383*s*, 1206*s*, 1140*m*, 1055*s*, 952*w*, 908*w*, 837*w*, 711*s*. ^{1}H-NMR[3]): 7.47 (*s*, 2 NH); 7.40 (*s*, NH); 7.30–7.22 (*m*, 3 arom. H); 7.09–7.07 (*m*, 2 arom. H); 5.42 (br. *s*, OH); 3.64 (*d*, *J* = 10.3, 1 H of CH_2OH); 3.40–3.32 (*m*, 1 H of CH_2OH, 1 H of PhCH_2); 2.96 (*d*, *J* = 13.4, 1 H of PhCH_2); 2.15–1.58 (*m*, 2 (CH_2)$_4$); 1.19, 1.12, 1.04 (3*s*, *Me*$_2$C, PhCH_2(*Me*)C). ^{13}C-NMR: 177.2, 175.3, 173.2, 173.0 (4*s*, 4 CO); 137.0 (*s*, 1 arom. H); 130.7, 127.6, 126.2 (3*d*, 5 arom. H); 68.8 (*t*, CH_2OH); 65.7, 64.9, 59.1, 43.7 (4*s*, Me_2*C*, PhCH_2(Me)*C*, 2 (CH_2)$_4$*C*); 38.9 (*t*, PhCH_2); 36.9, 36.3, 35.6, 34.9, 24.3, 24.0, 23.9, 23.8 (8*t*, 2 (CH_2)$_4$); 23.2, 22.1, 21.7 (3*q*, *Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 524 (100, $[M+Na]^+$), 502 (33, $[M+H]^+$).

8. *Reaction of 2*H*-Azirin-3-amines* **5** *with Tetrapeptides* **11**. 8.1. *2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-2*,N,N*-trimethylpropanamide* (**12a**). According to *GP 1*, **11a** (0.427 g, 1.013 mmol) in MeCN (6 ml), **5a** (0.141 g, 1.257 mmol) in MeCN (1 ml), stirred for 42 h: 0.508 g (94%) of **12a**. White powder. M.p. 261.6–262.4°. IR: 3306v*s*, 2987*s*, 2938*m*, 1652v*s*, 1527v*s*, 1457*s*, 1384*s*, 1363*s*, 1274*m*, 1225*s*, 1170*m*, 1120*m*, 1057*m*, 1020*w*, 922*w*, 746*w*, 700*m*, 606*w*. ^{1}H-NMR: 8.74 (*s*, NH); 7.41–7.22 (*m*, 3 NH, 5 arom. H); 5.13 (*t*, *J* = 4.2, OH); 3.95–3.90, 3.81–3.76, 3.67–3.62 (3*m*, CH_2OH, CH); 2.93–2.85 (br. *d*, Me_2N); 1.39, 1.38, 1.353, 1.345, 1.31, 1.24, 1.14 (7*s*, 4 Me_2C). ^{13}C-NMR: 174.7, 173.4, 173.0, 172.9, 172.0 (5*s*, 5 CO); 137.1 (*s*, 1 arom. C); 128.2, 127.9, 126.9 (3*d*, 5 arom. C); 63.8 (*t*, CH_2OH); 56.0, 55.9, 55.8, 55.4 (4*s*, 4 Me_2*C*); 53.4 (*d*, CH); 37.1 (*q*, Me_2N); 25.9, 25.5, 25.2, 24.5, 23.8, 23.7 (6*q*, 4 *Me*$_2$C). ESI-MS: 556 (100, $[M+Na]^+$), 489 (12, $[M-Me_2N]^+$). Anal. calc. for $C_{27}H_{43}N_5O_6$ (533.65): C 60.77, H 8.12; found: C 60.50, H 8.20.

8.2. *1-[1-(1-{1-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]cyclopentanecarboxamido}cyclopentanecarboxamido)cyclopentanecarboxamido]-*N,N*-dimethylcyclopentanecarboxamide* (**12b**). According to *GP 1*, **11b** (0.252 g, 0.504 mmol) in MeCN (8 ml), **5c** (0.086 g, 0.622 mmol) in MeCN (1 ml), stirred for 92 h: 0.304 g (95%) of **12b**. White powder. M.p. 281.5° (dec.). IR: 3325*s*, 2957*s*, 2874*s*, 1642v*s*, 1526v*s*, 1453*s*, 1394*m*, 1324*m*, 1266*m*, 1211*m*, 1054*m*, 1016*m*, 957*w*, 909*w*, 737*w*, 700*m*, 668*m*. ^{1}H-NMR: 8.92, 7.55, 7.45 (3*s*, 3 NH); 7.33 (br. *s*, 1 NH, 5 arom. H); 5.36 (br. *s*, OH); 4.0–3.6 (*m*, CH_2OH, CH); 2.96, 2.75 (2 br. *s*, Me_2N); 2.05–1.59 (*m*, 4 (CH_2)$_4$). ^{13}C-NMR: 174.6, 173.5, 172.8, 172.5, 171.9 (5*s*, 5 CO); 136.9 (*s*, 1 arom. C); 128.3, 127.8, 127.0 (3*d*, 5 arom. C); 66.3, 66.0, 65.9, 65.6 (4*s*, 4 (CH_2)$_4$*C*); 63.9 (*t*, CH_2OH); 53.3 (*d*, CH); 37.0, 36.6, 35.8, 35.5, 34.7, 24.3, 24.2, 24.0, 23.8 (9*t*, 4 (CH_2)$_4$). ESI-MS: 660 (38, $[M+Na]^+$), 593 (100, $[M-Me_2N]^+$).

8.3. *2-[(2-{[2-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-2*,N,N*-trimethylpropanamide* (**12c**). According to *GP 1*, **11c** (0.138 g, 0.31 mmol) in MeCN (3 ml), **5a** (0.041 g, 0.37 mmol) in MeCN (1 ml), stirred for 25 h: 0.168 g (96%) of **12c**. White powder. M.p. 254.0° (dec.). IR: 3452*m*, 3310*s*, 2988*m*, 2933*m*, 1649v*s*, 1529v*s*, 1455*m*, 1394*m*, 1382*m*, 1364*m*, 1288*m*, 1236*m*, 1170*w*, 1117*m*, 1063*m*, 713*m*. ^{1}H-NMR: 7.77, 7.68, 7.45 (3*s*, 3 NH); 7.32–7.09 (*m*, 1 NH, 5 arom. H); 5.37 (*m*, OH); 3.67–3.62 (*m*, 1 H of CH_2OH); 3.42–3.32 (*m*, 1 H of CH_2OH, 1 H of PhCH_2); 2.99–2.80 (*m*, 1 H of PhCH_2, Me_2N); 1.49, 1.41, 1.39, 1.37, 1.35, 1.30, 1.23, 1.11, 1.05 (9*s*, 4 Me_2C, PhCH_2(*Me*)C). ^{13}C-NMR: 177.5, 174.9, 173.4, 173.2, 172.0 (5*s*, 5 CO); 136.8 (*s*, 1 arom. C); 130.8, 127.7, 126.3 (3*d*, 5 arom. C); 68.7 (*t*, CH_2OH); 58.8, 56.1, 56.0, 55.5, 43.6 (5*s*, 4 Me_2*C*, PhCH_2(Me)*C*); 38.8 (*t*, PhCH_2); 38.6 (*q*, Me_2N); 26.7, 25.9, 25.5, 23.8, 23.3, 22.7, 22.0, 21.8 (8*q*, 4 *Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 584 (100, $[M+Na]^+$), 517 (19, $[M-Me_2N]^+$).

8.4. *1-{1-[1-({2-Benzyl-2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-1-oxopropyl}amino)cyclopentanecarboxamido]cyclopentanecarboxamido}*-N,N-*dimethylcyclopentanecarboxamide* (**12d**). According to *GP 1*, **11d** (0.190 g, 0.38 mmol) in MeCN (4 ml), **5c** (0.061 g, 0.44 mmol) in MeCN (1 ml), stirred for 26 h: 0.235 g (97%) of **12d**. White powder. M.p. 254.8°. IR: 3433*m*, 3302*s*, 2961*m*, 2875*m*, 1651v*s*, 1630v*s*, 1528v*s*, 1456*s*, 1391*m*, 1256*m*, 1060*m*, 707*m*, 669*w*. ^{1}H-NMR: 7.79, 7.68, 7.49, 7.44 (4*s*, 4 NH); 7.31–7.21 (*m*, 3 arom. H); 7.11–7.08 (*m*, 2 arom. H); 5.50 (*t*, J = 4.4, OH); 3.70–3.65 (*m*, 1 H of CH_2OH); 3.41–3.31 (*m*, 1 H of PhCH_2); 3.17 (*d*, J = 5.2, 1 H of CH_2OH); 3.00–2.95 (*m*, *d* at 2.97, J = 13.0, 1 Me of Me_2N, 1 H of PhCH_2); 2.73 (br. *s*, 1 Me of Me_2N); 2.32–1.49 (*m*, 3 $(CH_2)_4$); 1.23, 1.12, 1.05 (3*s*, Me_2C, PhCH_2(*Me*)C). ^{13}C-NMR: 177.7, 175.4, 172.9, 172.5, 171.8 (5*s*, 5 CO); 136.7 (*s*, 1 arom. C); 130.7, 127.7, 126.4 (3*d*, 5 arom. C); 68.9 (*t*, CH_2OH); 66.4, 66.0, 65.6, 58.9, 43.7 (5*s*, Me_2*C*, PhCH_2(Me)*C*, 3 $(CH_2)_4$*C*); 38.6, 37.1, 35.8, 35.3, 34.2, 24.4, 24.2, 24.1, 23.9, 23.7 (10*t*, Ph*C*H$_2$, 3 $(CH_2)_4$); 36.6 (*q*, Me_2N); 23.0, 22.0, 21.7 (3*q*, *Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 662 (58, $[M + Na]^+$), 595 (100, $[M - Me_2N]^+$).

8.5. *2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-2*,N-*dimethyl*-N-*phenylpropanamide* (**12e**). *a*) To a stirred suspension of **11a** (0.121 g, 0.287 mmol) in dry MeCN (1 ml) was added dropwise a soln. of **5b** (0.073 g, 0.419 mmol) in MeCN (1 ml). The mixture was stirred at r.t. for 10 days under N_2, filtered, washed with cold hexane/Et_2O (1:1), and dried under h.v. Crude **12e** was filtered through a short column (SiO_2; CH_2Cl_2/MeOH 10:1) and dried under h.v.: 0.075 g (44%) of **12e**. White powder. M.p. 255.6–256.3°. IR: 3467*m*, 3281*s*, 2990*m*, 2939*m*, 1693*s*, 1642v*s*, 1594*m*, 1542v*s*, 1492*s*, 1458*m*, 1393*s*, 1363*s*, 1275*m*, 1230*m*, 1171*m*, 1091*m*, 1062*m*, 1013*w*, 927*w*, 772*w*, 710*s*, 618*w*. ^{1}H-NMR: 8.74, 7.50, 7.42 (3*s*, 3 NH); 7.37–7.17 (*m*, 1 NH, 10 arom. H); 5.13 (*t*, J = 4.3, OH); 3.95–3.91, 3.82–3.77, 3.67–3.61 (3*m*, CH_2OH, CH); 3.31 (*s*, MeN); 1.43, 1.37, 1.32, 1.25, 1.15 (5*s*, 4 Me_2C). ^{13}C-NMR: 174.7, 173.9, 173.1, 172.9, 172.7 (5*s*, 5 CO); 146.2, 137.1 (2*s*, 2 arom. C); 128.5, 128.2, 127.9, 126.9, 126.8, 125.7 (6*d*, 10 arom. C); 63.8 (*t*, CH_2OH); 56.0, 55.9, 55.8 (3*s*, 4 Me_2*C*); 53.4 (*d*, CH); 39.1 (*q*, MeN); 25.9, 25.5, 25.2, 24.6, 23.8, 23.7 (6*q*, 4 *Me*$_2$C). ESI-MS: 618 (100, $[M + Na]^+$).

b) To a stirred soln. of **11a** (0.100 g, 0.237 mmol) in dry DMF (2 ml) was added dropwise a soln. of **5b** (0.064 g, 0.367 mmol) in DMF (1 ml). The mixture was stirred at r.t. for 48 h under N_2. The clear soln. was poured into H_2O (25 ml), stirred at r.t., filtered, washed with H_2O and hexane/Et_2O 1:1, and dried under h.v.: 0.058 g (41%) of **12e**.

9. *Cyclization of Pentapeptides* **12** *with Dry HCl to Cyclic Depsipeptides* **13**. *General Procedure 5* (*GP 5*). A stirred suspension of **12** in dry toluene (15–30 ml) was warmed to 40–100° under N_2. A stream of dry HCl gas was slowly passed through the suspension for 5–15 min at the chosen reaction temp. The resulting soln. was then purged with N_2 for 30 min to remove remaining HCl, the toluene was evaporated, and 6 ml of THF/Et_2O 1:1 were added. After 30 min of stirring at r.t., the suspension was filtered, followed by evaporation of the solvent yielding a solid crude product, which was purified by CC.

9.1. *3,3,6,6,9,9,12,12-Octamethyl-15-phenyl-1-oxa-4,7,10,13-tetraazacyclohexadecane-2,5,8,11,14-pentone* (**13a**). *a*) According to *GP 5*, **12a** (0.051 g, 0.096 mmol) in toluene (30 ml), 100°, 9 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.019 g (41%) of **13a**[4]). White powder. M.p. 281° (dec.). IR: 3362*m*, 2983*w*, 1738*s*, 1666*vs*, 1540*s*, 1518*s*,1470*m*, 1385*m*, 1364*m*, 1277*m*, 1232*m*, 1153*m*, 742*w*. ^{1}H-NMR ((D$_5$)pyridine, 600 MHz): 9.57 (*s*, NH, Aib(1)); 8.16 (*s*, NH, Aib(2)); 7.96 (*s*, NH, Aib(4)); 7.54–7.53 (*m*, 2 arom. H); 7.41 (*s*, NH, Aib(3)); 7.36–7.34 (*m*, 2 arom. H); 7.31–7.29 (*m*, 1 arom. H); 4.96–4.94, 4.43–4.40 (2*m*, CH_2O); 4.27–4.25 (*m*, CH); 2.06 (*s*, Me(b), Aib(4)); 2.06 (*s*, Me(b), Aib(3)); 1.96 (*s*, Me(a), Aib(4)); 1.96 (*s*, Me(a), Aib(3)); 1.81 (*s*, Me(b), Aib(2)); 1.79 (*s*, Me(b), Aib(1)); 1.59 (*s*, Me(a), Aib(2)); 1.46 (*s*, Me(a), Aib(1)). ^{13}C-NMR ((D$_5$)pyridine, 151 MHz): 177.3 (*s*, CO, Aib(3)); 176.5 (*s*, CO, Aib(1)); 174.8 (*s*, CO, Aib(4)); 174.7 (*s*, CO, Aib(2)); 172.2 (*s*, CO, Tro); 137.0 (*s*, 1 arom. C); 129.7, 129.0, 128.6 (3*d*, 5 arom. C); 66.0 (*t*, CH_2O); 59.2 (*s*, Me_2*C*, Aib(3)); 58.6 (*s*, Me_2*C*, Aib(4)); 58.6 (*s*, Me_2*C*, Aib(2)); 57.4 (*s*, Me_2*C*, Aib(1)); 51.8 (*d*, CH); 28.9 (*s*, Me(a), Aib(3)); 27.8 (*s*, Me(a), Aib(2)); 27.4 (*s*, Me(a), Aib(4)); 27.2 (*s*, Me(a), Aib(1)); 25.0 (*s*, Me(b), Aib(3)); 24.7 (*s*, Me(b), Aib(4)); 23.8 (*s*, Me(b), Aib(2)); 23.7 (*s*, Me(b), Aib(1)). ESI-MS: 511 (100, $[M + Na]^+$). Anal. calc. for $C_{25}H_{36}N_4O_6$ (488.57): C 61.46, H 7.43; found C 61.49, H 7.67.

b) According to *GP 5*, **12e** (0.056 g, 0.094 mmol) in toluene (30 ml), 40°, 14 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.003 g (7%) of **13a** and 0.003 g (7%) of **14a**.

c) According to *GP 5*, **12e** (0.056 g, 0.094 mmol) in toluene (30 ml), 60°, 13 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.006 g (13%) of **13a** and 0.005 g (11%) of **14a**.

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[4]) As a second product, 0.002 g of a white powder was isolated, which was identified as the cyclodimer **14a** (4%) by ESI-MS: 999 (100, $[M + Na]^+$), 511 (42, $[M + 2Na]^{2+}$).

d) According to *GP 5*, **12e** (0.056 g, 0.094 mmol) in toluene (30 ml), 80°, 15 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.018 g (39%) of **13a** and 0.008 g (17%) of **14a**.

e) According to *GP 5*, **13a** (0.056 g, 0.094 mmol) in toluene (30 ml), 100°, 12 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.022 g (48%) of **13a** and 0.004 g (9%) of **14a**.

9.2. *29-Phenyl-31-oxa-6,13,20,27-tetraazatetraspiro[4.2.4.2.4.2.4.6]dotriacontane-7,14,21,28,32-pentone* (**13b**). *a*) According to *GP 5*, **12b** (0.050 g, 0.078 mmol) in toluene (30 ml), 100°, 11 min. CC (SiO_2, CH_2Cl_2/MeOH 30:1) and crystallization from Et_2O: 0.029 g (60%) of **13b**[5]). White powder. M.p. 263° (dec.). IR: 3344*s*, 2956*s*, 2874*m*, 1740*s*, 1663v*s*, 1529v*s*, 1453*s*, 1267*s*, 1166*m*, 1122*w*, 1018*w*, 955*w*, 738*w*, 701*m*, 606*w*. ^{1}H-NMR ((D_5)pyridine, 600 MHz): 9.75 (*s*, NH, $Ac_5c(1)$); 8.58 (*s*, NH, $Ac_5c(2)$); 8.05 (*s*, NH, $Ac_5c(4)$); 7.53–7.51 (*m*, 2 arom. H); 7.41 (*s*, NH, $Ac_5c(3)$); 7.35–7.33 (*m*, 2 arom. H); 7.30–7.27 (*m*, 1 arom. H); 4.96–4.94 (*dd*-like, 1 H of CH_2O); 4.41–4.37 (*t*-like, 1 H of CH_2O); 4.27–4.24 (*dd*-like, CH); 3.16–3.13 (*m*, 1 H of $(CH_2)_4$); 3.09–3.07 (*m*, 1 H of $(CH_2)_4$); 2.92–2.83 (*m*, 3 H of $(CH_2)_4$); 2.77–2.74 (*m*, 1 H of $(CH_2)_4$); 2.63–2.51 (*m*, 3 H of $(CH_2)_4$); 2.36–2.25 (*m*, 3 H of $(CH_2)_4$); 2.19–2.09 (*m*, 3 H of $(CH_2)_4$); 2.01–1.96 (*m*, 1 H of $(CH_2)_4$); 1.87–1.50 (*m*, 16 H of $(CH_2)_4$). ^{13}C-NMR ((D_5)pyridine, 151 MHz): 177.4 (*s*, CO, $Ac_5c(3)$); 176.0 (*s*, CO, $Ac_5c(1)$); 174.5 (*s*, CO, $Ac_5c(4)$); 174.2 (*s*, CO, $Ac_5c(2)$); 172.2 (*s*, CO, Tro); 136.3 (*s*, 1 arom. C); 129.2, 128.2, 128.01 (3*d*, 5 arom. C); 68.8 (*s*, $(CH_2)_4C$, $Ac_5c(3)$); 68.4 (*s*, $(CH_2)_4C$, $Ac_5c(2)$); 68.1 (*s*, $(CH_2)_4C$, $Ac_5c(4)$); 67.6 (*s*, $(CH_2)_4C$, $Ac_5c(1)$); 65.0 (*t*, CH_2O); 51.5 (*d*, CH); 40.3, 39.3, 38.5, 37.5, 36.0, 35.4, 34.9, 34.2, 25.2, 25.1, 25.0, 24.6, 24.4, 23.9, 22.6 (15*t*, 4 $(CH_2)_4$). ESI-MS: 593 (100, $[M+H]^+$). Anal. calc. for $C_{33}H_{44}N_4O_6 \cdot 0.5\ H_2O$ (601.73): C 65.87, H 7.54, N 9.31; found: C 65.66, H 7.42, N 9.09.

Suitable crystals for the X-ray crystal structure determination were grown from EtOH/AcOEt/CH_2Cl_2.

b) According to *GP 5*, **12b** (0.050 g, 0.078 mmol) in toluene (15 ml), 40°, 5 min. No **13b** and **14b** could be detected nor isolated after CC.

c) According to *GP 5*, **12b** (0.050 g, 0.078 mmol) in toluene (15 ml), 60°, 5 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.003 g (6%) of **13b** and 0.008 g (17%) of **14b**.

d) According to *GP 5*, **12b** (0.049 g, 0.077 mmol) in toluene (15 ml), 80°, 5 min. CC (SiO_2; CH_2Cl_2/MeOH 30:1) and crystallization from Et_2O: 0.007 g (15%) of **13b** and 0.015 g (33%) of **14b**.

e) According to *GP 5*, **12b** (0.049 g, 0.077 mmol) in toluene (15 ml), 100°, 5 min. CC (SiO_2; CH_2Cl_2/MeOH 30:1) and crystallization from Et_2O: 0.020 g (42%) of **13b** and 0.006 g (13%) of **14b**.

f) According to *GP 5*, **12b** (0.050 g, 0.078 mmol) in toluene (15 ml), 100°, 10 min. CC (SiO_2; CH_2Cl_2/MeOH 30:1) and crystallization from Et_2O: 0.016 g (34%) of **13b** and 0.010 g (22%) of **14b**.

g) According to *GP 5*, **12b** (0.050 g, 0.078 mmol) in toluene (15 ml), 100°, 3 min. CC (SiO_2; CH_2Cl_2/MeOH 30:1) and crystallization from Et_2O: 0.020 g (43%) of **13b** and 0.005 g (11%) of **14b**.

9.3. *12-Benzyl-3,3,6,6,9,9,12,15,15-nonamethyl-1-oxa-4,7,10,13-tetraazacyclohexadecane-2,5,8,11,14-pentone* (**13c**). According to *GP 5*, **12c** (0.050 g, 0.089 mmol) in toluene (30 ml), 100°, 8 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.021 g (46%) of **13c**[6]). White powder. M.p. 252.2° (dec.). IR: 3389*s*, 3318*s*, 2984*m*, 2939*m*, 1722*s*, 1650v*s*, 1527v*s*, 1458*s*, 1384*s*, 1363*m*, 1277*s*, 1233*s*, 1157*s*, 1021*w*, 758*w*, 706*m*. ^{1}H-NMR ((D_5)pyridine, 600 MHz): 8.03 (*s*, NH, Phe(2Me)); 7.76 (*s*, NH, Aib(1)); 7.71 (*s*, NH, Aib(3)); 7.43 (*s*, NH, Aib(2)); 7.36–7.29 (*m*, 3 arom. H); 7.24–7.23 (*m*, 2 arom. H); 4.52–4.50, 4.25–4.23 (*AB*, $J=10.5$, CH_2O); 3.77–3.75, 3.34–3.32 (*AB*, $J=12.4$, $PhCH_2$); 1.98 (*s*, Me(a), Aib(3)); 1.93 (*s*, Me(b), Aib(3)); 1.92 (*s*, Me_2C, Aib(2)); 1.63 (*s*, Me(a), Aib(1)); 1.61 (*s*, Me(b), Aib(1)); 1.38 (*s*, Me(a), Dhp); 1.28 (*s*, Me(b), Dhp, $PhCH_2(Me)C$). ^{13}C-NMR ((D_5)pyridine, 151 MHz): 175.9 (*s*, CO, Dhp); 175.1 (*s*, CO, Aib(2)); 175.0 (*s*, CO, Phe(2Me)); 174.7 (*s*, CO, Aib(3)); 174.4 (*s*, CO, Aib(1)); 136.7 (*s*, 1 arom. C); 131.5, 128.4, 127.2 (3*d*, 5 arom. C); 72.1 (*t*, CH_2O); 60.2 (*s*, $PhCH_2(Me)C$); 58.6 (*s*, Me_2C, Aib(2)); 58.00 (*s*, Me_2C, Aib(3)); 57.97 (*s*, Me_2C, Aib(1)); 42.8 (*s*, Me_2C, Dhp); 41.5 (*t*, $PhCH_2$); 26.8 (*q*, Me(a), Aib(2)); 26.0 (*q*, Me(a), Aib(1)); 25.8 (*q*, Me(b), Aib(2)); 25.4 (*q*, Me(a), Aib(3)); 25.2 (*q*, Me(b), Aib(3)); 25.0 (*q*, Me(b), Aib(1)); 23.0 (*q*, Me(a), Dhp); 22.5 (*q*, Me(b), Dhp, $PhCH_2(Me)C$). ESI-MS: 539 (100, $[M+H]^+$). Anal. calc. for $C_{27}H_{40}N_4O_6$ (516.62): C 62.77, H 7.80, N 10.84; found: C 62.41, H 7.93, N 10.54.

9.4. *22-Benzyl-22,25,25-trimethyl-27-oxa-6,13,20,23-tetraazatrispiro[4.2.4.2.4.9]octacosane-7,14,21,24,28-pentone* (**13d**). According to *GP 5*, **12d** (0.050 g, 0.078 mmol) in toluene (30 ml), 100°, 8 min. CC (SiO_2;

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[5]) As a second product, 0.002 g of a white powder was isolated, which was identified as the cyclodimer **14b** (4%) by ESI-MS: 1208 (25, $[M+Na]^+$), 615 (100, $[M+2Na]^{2+}$).

[6]) As a second product, 0.003 g of a white powder was isolated, which was identified as the cyclodimer **14c** (7%) by ESI-MS: 539 (100, $[M+2Na]^{2+}$).

CH_2Cl_2/MeOH 35:1) and crystallization from Et_2O: 0.011 g (24%) of **13d**[7]). White powder. M.p. 249.5° (dec.). IR: 3338*s*, 2960*s*, 2874*m*, 1734*s*, 1654v*s*, 1524v*s*, 1453*s*, 1374*m*, 1270*s*, 1023*m*, 952*w*, 742*m*, 703*m*, 610*w*. ^{1}H-NMR ((D_5)pyridine, 600 MHz): 7.95 (*s*, NH, Phe(2Me)); 7.84 (*s*, NH, Ac_5c(3)); 7.74 (*s*, NH, Ac_5c(1)); 7.49 (*s*, NH, Ac_5c(2)); 7.37–7.29 (*m*, 3 arom. H); 7.25–7.24 (*m*, 2 arom. H); 4.32, 4.28 (*AB*, $J = 10.5$, CH_2O); 3.64–3.62 (*m*, 1 H of PhCH_2); 3.27 (*d*, $J = 12.3$, 1 H of PhCH_2); 2.94–1.94 (*m*, 12 H of $(CH_2)_4$); 1.93–1.55 (*m*, 12 H of $(CH_2)_4$); 1.52 (*s*, $PhCH_2(Me)C$); 1.31 (*s*, Me(a), Dhp); 1.24 (*s*, Me(b), Dhp). ^{13}C-NMR ((D_5)pyridine, 151 MHz): 176.6 (*s*, CO, Dhp); 175.7 (*s*, CO, Phe(2Me)); 175.6 (*s*, CO, Ac_5c(2)); 175.4 (*s*, CO, Ac_5c(3)); 174.9 (*s*, CO, Ac_5c(1)); 136.9 (*s*, 1 arom. C); 132.0, 128.9, 127.8 (3*d*, 5 arom. C); 72.4 (*t*, CH_2O); 69.8 (*s*, $(CH_2)_4C$, Ac_5c(2)); 69.1 (*s*, $(CH_2)_4C$, Ac_5c(1)); 67.9 (*s*, $(CH_2)_4C$, Ac_5c(3)); 60.6 (*s*, $PhCH_2(Me)C$); 43.4 (*s*, Me_2C, Dhp); 42.6 (*t*, PhCH_2); 38.2, 38.1, 37.8, 37.6, 25.53, 25.50, 25.48, 25.4, 25.3, 25.2 (10*t*, 3 $(CH_2)_4$); 23.7 (*q*, Me(a), Dhp); 23.4 (*q*, Me(b), Dhp); 22.7 (*q*, $PhCH_2(Me)C$). ESI-MS: 617 (100, $[M+Na]^+$). Anal. calc. for $C_{33}H_{46}N_4O_6$ (594.74): C 66.65, H 7.80; found C 66.81, H 7.88.

10. *X-Ray Crystal-Structure Determinations of* **12a**, **12d**, *and* **13b** (see *Table 10* and *Figs. 1–3*)[8]). All measurements were made on a *Rigaku AFC5R* diffractometer with graphite-monochromated Mo$K\alpha$ radiation ($\lambda = 0.71069$ Å) and a 12-kW rotating anode generator. The $\omega/2\theta$ scan mode was employed for data collection. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are given in *Table 10*. Views of the molecules and packing diagrams are shown in *Figs. 1–3*, and *4–6*, resp. The structures were solved by direct methods using SHELXS86 [42] in the case of **12a** and SHELXS97 [43] in the cases of **12d** and **13b**, which revealed the positions of all non-H-atoms.

The crystal lattice of **12a** contains solvent molecules disordered about a centre of inversion. As it was not clear what the solvent might be, the peaks have been arbitrarily assigned as disordered H_2O molecules, as this produces the most satisfactory refinement results. Three positions in the asymmetric unit were defined as O-atoms. The refinement showed that the sites were only partially occupied, and the best results were achieved with a total H_2O content of 1.2 molecules in the asymmetric unit. The non-H-atoms of the peptide molecule were refined anisotropically; those of the solvent molecules were refined isotropically. The NHCO and OH H-atoms were located in a difference-electron-density map, and their positions were allowed to refine together with individual isotropic displacement parameters. All of the remaining H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom. The solvent H-atoms were not included in the model.

In **12d**, one five-membered ring of the peptide molecule is disordered in that two atoms, C(25) and C(26), occupy two sites corresponding to alternate conformations of the ring. This disorder was modelled successfully by applying bond length restraints to those C–C bonds involving at least one of the disordered atoms. Refinement of the site occupation factors of the two conformations indicated that the major conformation is found in 67(2)% of the molecules. The non-H-atoms were refined anisotropically. Except for the OH group, all H-atoms were placed in geometrically calculated positions, and each was constrained to ride on its parent atom with an isotropic displacement parameter having a value equal to $1.2U_{eq}$ of the parent atom ($1.5U_{eq}$ for Me groups). The OH H-atom was located in a difference-electron-density map, and its position was allowed to refine together with an isotropic displacement parameter, but with a restraint applied to the O–H bond length.

In **13b**, there are four symmetry-independent molecules in the asymmetric unit. No additional symmetry relationship between the molecules could be found, and the lack of additional symmetry is supported by variations in the H-bonding pattern (see *Table 9*). In three of these molecules, there is evidence of conformational disorder in some of the five-membered rings. The disorder was successfully resolved for two rings in molecule B (70 and 75% site occupation for the major conformers) and one ring in molecule C (75% site occupation for the major conformer). Bond-length restraints were applied to those C–C bonds involving at least one of the disordered atoms. In other cases, the extent of the disorder was less severe, and attempts to model the disorder any further did not lead to a significant improvement in the model. Therefore, slight elongation of the atomic displacement ellipsoids is evident for the affected atoms. The non-H-atoms were refined anisotropically. All H-atoms were placed in geometrically calculated positions, and each was constrained

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7) As a second product, 0.009 g of a white powder was isolated, which was identified as the cyclodimer **14d** (19%) by ESI-MS: 1189 (7, $[M+H]^+$), 595 (100, $[M+2H]^{2+}$).

8) Crystallographic data (excluding structure factors) for structures **12a**, **12d**, and **13b** reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publications No. CCDC-137413–137415. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 10. *Crystallographic Data of Compounds* **12a**, **12d**, *and* **13b**

	12a	**12d**	**13b**
Crystallized from	MeCN	MeOH/i-PrOH/Et_2O	EtOH/AcOEt/CH_2Cl_2
Empirical formula	$C_{27}H_{43}N_5O_6 \cdot 1.2\ H_2O$	$C_{35}H_{53}N_5O_6$	$C_{33}H_{44}N_4O_6$
Formula weight [g mol^{-1}]	555.28	639.83	592.73
Crystal color, habit	colorless, rectangular prism	colorless, plate	colorless, prism
Crystal dimensions [mm]	$0.15 \times 0.25 \times 0.48$	$0.09 \times 0.40 \times 0.43$	$0.27 \times 0.37 \times 0.50$
Temp. [K]	173(1)	173(1)	173(1)
Crystal system	monoclinic	monoclinic	triclinic
Space group	$P2_1/c$	Pc	$P\bar{1}$
Z	4	2	8
Reflections for cell determination	25	25	25
2θ range for cell determination [°]	26–37	23–38	26–38
Unit cell parameters a [Å]	17.452(4)	11.273(2)	20.826(2)
b [Å]	9.210(5)	14.909(4)	21.091(2)
c [Å]	20.466(5)	10.926(2)	14.441(2)
α [°]	90	90	91.32(1)
β [°]	95.11(2)	106.73(1)	100.055(9)
γ [°]	90	90	94.568(9)
V [Å^3]	3277(2)	1758.6(6)	6222(1)
D_x [g cm^{-3}]	1.125	1.208	1.265
μ (MoK_α) [mm^{-1}]	0.0818	0.0828	0.0874
$2\theta_{(max)}$ [°]	50	55	50
Total reflections measured	6363	4405	22524
Symmetry independent reflections	5759	4250	21872
Observed reflections [$I > 2\sigma(I)$]	3171	2839	14602
Reflections used in refinement	3171	4250	21866
Restraints	0	9	14
Parameters refined	376	444	1585
Final $R(F)$ [obs. refls.]	0.0599	0.0493	0.0516
wR	0.0489 [a])	0.1329 [b])[c])	0.1465 [b])[d])
Goodness of fit	1.883	1.021	1.023
Secondary extinction coefficient	$1.6(3) \times 10^{-7}$	0.005(1)	–
Final Δ_{max}/σ	0.0004	< 0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.37; −0.36	0.23; −0.22	0.59; −0.38

[a]) Based on F and reflections with $I > 2\sigma(I)$; $w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$
[b]) Based on F^2 and all unique reflections.
[c]) $w = 1/[\sigma^2(F_o^2) + (0.0603P)^2 + 0.1055P]$ where $P = (F_o^2 + 2F_c^2)/3$.
[d]) $w = 1/[\sigma^2(F_o^2) + (0.0604P)^2 + 3.2952P]$ where $P = (F_o^2 + 2F_c^2)/3$.

to ride on its parent atom with an isotropic displacement parameter having a value equal to $1.2U_{eq}$ of the parent atom ($1.5U_{eq}$ for Me groups).

Refinement of the structure of **12a** was carried out on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$, while refinement of the structures of **12d** and **13b** was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied in the cases of **12a** and **12d**. In the case of **13b**, six reflections that were considered as extreme outliers were excluded from the final refinement.

Neutral atom scattering factors for non-H-atoms were taken from [44a], and the scattering factors for H-atoms were taken from [45]. Anomalous dispersion effects were included in F_c [46]; the values for f' and f'' were those of [44b]. Calculations were performed using the TEXSAN crystallographic software package [47] in the case of **12a**, while SHELXL97 [48], and the *teXsan* crystallographic software package [49] were used for **12d** and **13b**.

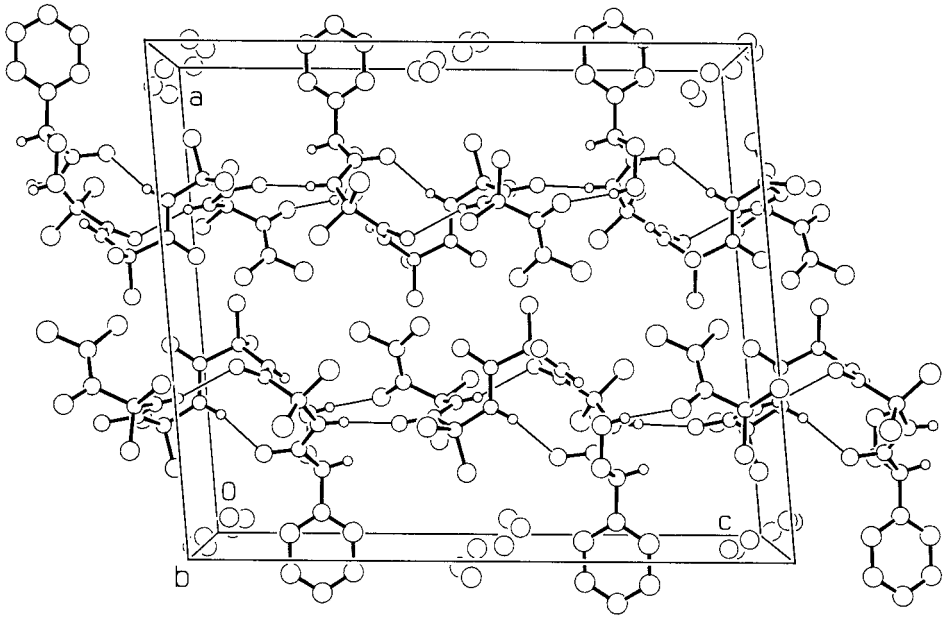

Fig. 4. *Packing diagram of compound* **12a**, *showing the H-bonding*

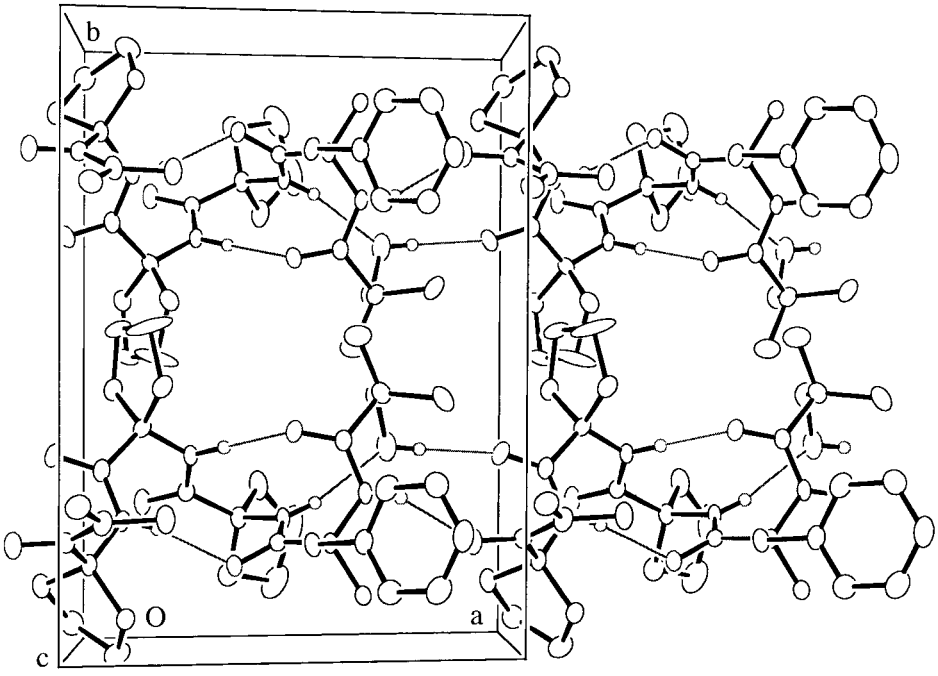

Fig. 5. *Packing diagram of compound* **12d**, *showing the H-bonding*

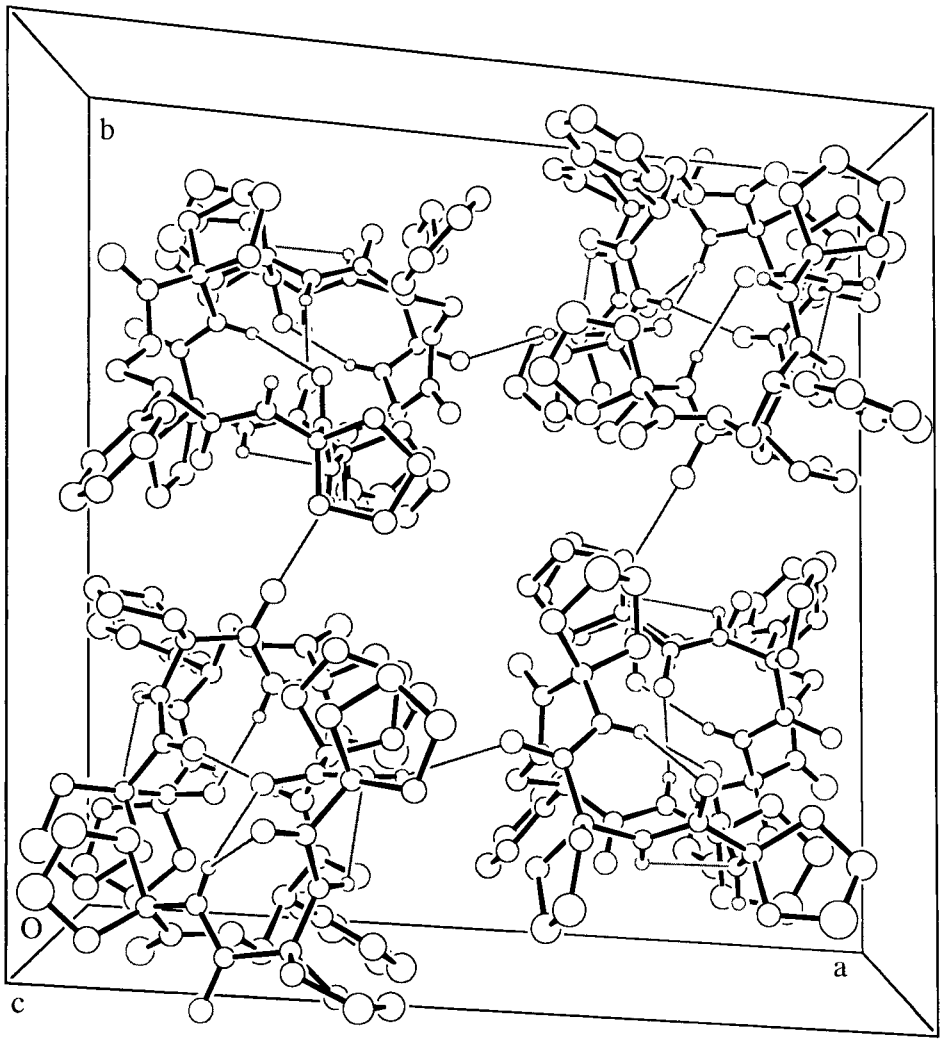

Fig. 6. *Packing diagram of compound* **13b**, *showing the H-bonding*

For **12a**, each N–H and O–H group of the molecule, excluding N(10)–H, acts as a donor for H-bonds. The OH group (O(17)–H) and the N(13)–H group form intermolecular H-bonds with the amide O-atoms, O(2) and O(5), resp., of the same neighboring molecule. Each of these interactions links the molecules into infinite one-dimensional chains which run parallel to the *z*-axis (*Fig. 4*). The chains involving O(17) and N(13) have the graph set motifs [50] of C(18) and C(11), resp. N(4)–H and N(7)–H each form intramolecular H-bonds with the amide O-atom that is seven atoms back along the peptide backbone, thus forming β-turns within the molecule; graph set: S(10) for each interaction. N(10)–H does not participate in any H-bonding interactions, but N(4)–H, N(7)–H and N(10)–H exhibit the usual weak 'sideways' contacts with one of their neighboring N-atoms.

For **12d**, each N–H group of the molecule acts as a donor for H-bonds. Three of the interactions are intramolecular H-bonds which serve to maintain a fairly rigid helical conformation of the peptide. N(4)–H and N(7)–H interact with the amide O-atom that is seven atoms further along the peptide backbone. Each of these interactions has the graph set motif [50] of S(10). N(10)–H interacts intramolecularly with the OH O-atom;

graph set: S(9). N(13)–H, which is unable to form an intramolecular interaction because of its position in the backbone, forms an intermolecular H-bond with the first amide O-atom at the opposite end of a neighboring molecule; graph set: C(14). The OH group similarly forms an intermolecular H-bond with the second amide O-atom at the opposite end of the same neighboring molecule; graph set: C(15). The intermolecular interactions link the molecules into infinite one-dimensional chains which run parallel to the *x*-axis (*Fig. 5*).

In **13b**, the pattern of H-bonds displayed by each of the four symmetry-independent molecules is similar, but there are slight differences which are probably due to small variations in the conformations of the molecules. The intramolecular interactions are generally with acceptor atoms on the opposite side of the macrocycle, thereby indicating that the peptide molecules form a rather puckered or folded cyclic system. N(3)–H forms an intramolecular H-bond with O(10) on the opposite side of each molecule to give rings with a graph set motif [50] of S(10). In molecules B and C, N(3)–H is also involved in weak intramolecular interactions with O(7) (graph set: S(7)), thereby yielding bifurcated interactions for N(3)–H. Molecules A and D show similar potential interactions, but the H···O and N···O distances are significantly longer than those normally considered to be the upper limit for N–H···O H-bonding interactions. N(6)–H appears to have the correct orientation in each molecule for an intramolecular interaction with O(13) on the opposite side of the molecule, but the distances are again too long for this to be a significant interaction. There is a shorter 'sideways' intramolecular interaction with N(9) in each molecule. Such 'neighboring' interactions are present in most peptide structures, and their significance to the H-bonding scheme is probably minimal (N(3)–H has a similar sideways interaction with N(6), but the N–H···O angles are more acute at *ca.* 103°, and these have been discarded from consideration). N(9)–H forms an intermolecular H-bond with O(4) in a neighboring symmetry-independent molecule, except for molecule D, where N(9)–H does not partake in any interactions. There are no 'sideways' interactions from N(9) to N(12), because N(12) is not positioned appropriately due to the conformation of the molecule. Molecules B and C are linked into centrosymmetric tetrameric ···B···C···B′···C′··· units by the interactions involving N(9)–H, but while molecule A donates to molecule D, the lack of an ongoing interaction from molecule D prevents the formation of a similar tetrameric sequence involving molecules A and D. N(12)–H forms an intermolecular H-bond with O(7) in a neighboring symmetry-independent molecule. These interactions link molecules A and C into infinite one-dimensional ···A···C··· chains, which run parallel to the *z*-axis and have a graph set motif of $C_2^2(16)$. Molecules B and D are similarly linked into ···B···D··· chains which also run parallel to the *z*-axis. The combination of all intermolecular H-bonding interactions links the molecules into an infinite two-dimensional network which lies parallel to the *yz*-plane (*Fig. 6*).

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