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Synthesis of conformationally restricted cyclic pentadepsipeptides via direct amide cyclization

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Abstract—The 2,2-disubstituted 2*H*-azirin-3-amines **6** (3-amino-2*H*-azirines) were used as building blocks for α,α-disubstituted α-amino acids in the preparation of 16-membered cyclic depsipeptides **14**. The linear precursors containing four α,α-disubstituted α-amino acids, the pentapeptides **13**, were synthesized starting with β-hydroxy acids **5** via the 'azirine/oxazolone method'. The cyclic depsipeptides **14** were formed via 'direct amide cyclization' and the influence of several factors on this cyclization was investigated in the following way: (a) using the same composition of α,α-disubstituted α-amino acids, but changing their respective positions in the peptide chain; (b) using different C-terminal α,α-disubstituted α-amino acids in the peptide chain; (c) using different β-hydroxy acids; and (d) using different diastereoisomers of the peptides.

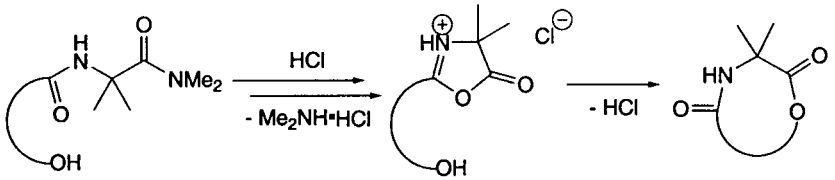
1. Introduction

Cyclic depsipeptides are well known for their biological activity. They contain, in addition to the amide bonds, one or more ester bonds. A large number of them have been isolated from different natural sources.[1–5] The majority of naturally occurring cyclic depsipeptides are produced on surface or marine cultures of an appropriate micro-organism. Two of the most well-known examples are the antibiotics valinomycin[6–8] and enniatins,[9] which act as ionophores.[10]

The crucial step in the synthesis of cyclic depsipeptides is the cyclization. Traditionally, it has been carried out via amide bond formation,[11–13] although, several examples are known where the cyclization has been performed via ester bond formation.[14–18] A useful method for the cyclization via ester bond formation, the so-called 'direct amide cyclization', has been developed in our laboratory.[19–25] The concept is shown in Scheme 1: treatment of an amide of type **1** with dry HCl gas leads to the corresponding 1,3-oxazol-5(4*H*)-one derivative **2** via ring closure and elimination of dimethylamine hydrochloride. In the absence of external nucleophiles, **2** undergoes a ring enlargement to yield the cyclic product **3** via an intramolecular attack of the OH group at the lactone group of **2**.

Several cyclic depsipeptides containing one α- or β-hydroxy acid and two to four α,α-disubstituted α-amino acids (2,2-disubstituted glycines) have been prepared via this cyclization method.[19–25] The α,α-disubstituted α-amino acids have been incorporated into the peptide chains of the linear precursors by using the so-called 'azirine/oxazolone method'.[26] This particularly useful method has been successfully used in the synthesis of peptaibols,[27–29] endothiopeptides[30] and conformationally restricted cyclic peptides.[31,32]

The tetrasubstitution of the α-carbon in these α-amino acids results in severe steric hindrance. Peptides containing



Scheme 1.

Keywords: α,α-disubstituted α-amino acids; 3-amino-2*H*-azirines; azirine/oxazolone method; cyclic pentadepsipeptides; direct amide cyclization.

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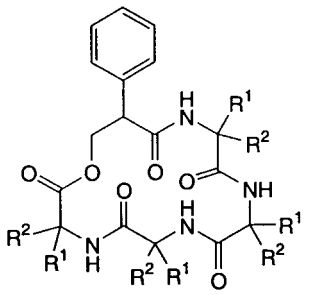
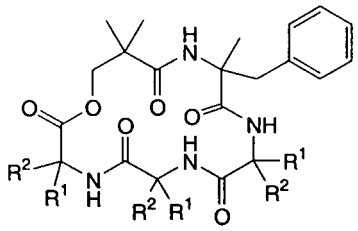


4a: $R^1 = R^2 = Me$; 41%
b: $R^1, R^2 = -(CH_2)_4-$; 60%



4c: $R^1 = R^2 = Me$; 46%
d: $R^1, R^2 = -(CH_2)_4-$; 24%

α,α-disubstituted α-amino acids therefore possess significant constraints on their conformational freedom and secondary structures such as β-turns and α- and 3_{10}-helices are promoted in the solid state and in solution.[33–37]

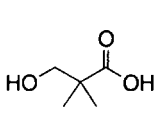
Recently, we reported on the synthesis of four cyclic pentadepsipeptides **4a–d** containing one β-hydroxy acid and four α,α-disubstituted α-amino acids[25] via 'direct amide cyclization', and the yield of monomer **4** varied considerably (24–60%).

On the basis of these results, it was of interest to investigate the influence of specific changes in the pentapeptide chain on the cyclization, especially the yield of cyclic monomer. The following factors were examined: (a) same composition of α,α-disubstituted α-amino acids but different respective position in the peptide chain; (b) different C-terminal α,α-disubstituted α-amino acids; (c) different β-hydroxy acids; and (d) different diastereoisomers of the linear pentapeptides.

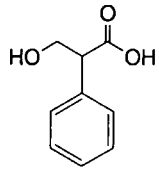
2. Results and discussion

The desired linear pentapeptides containing one β-hydroxy acid and four α,α-disubstituted α-amino acids were synthesized according to the same strategy as previously reported.[25] With 3-amino-2*H*-azirines as building blocks for α,α-disubstituted α-amino acids, the pentapeptides could be prepared without the use of coupling reagents,[38] thereby eliminating the formation of side products and simplifying the purification procedures considerably.

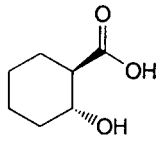
Three β-hydroxy acids were selected, namely 3-hydroxy-2,2-dimethylpropanoic acid (**5a**; Dhp), 3-hydroxy-2-phenylpropanoic acid (**5b**, tropic acid (Tro)) and *trans*-2-hydroxycyclohexanecarboxylic acid (**5c**; Hcc). The 3-amino-2*H*-azirines **6a–e** were used as building blocks for 2-aminoisobutyric acid (Aib), 1-aminocyclopentanecarboxylic acid (Ac_5c), and α-methylphenylalanine (Phe(2Me)), respectively.



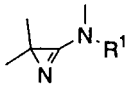
5a



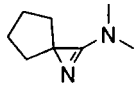
5b



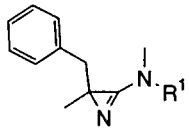
5c



6a: $R^1 = Me$
b: $R^1 = Ph$



6c



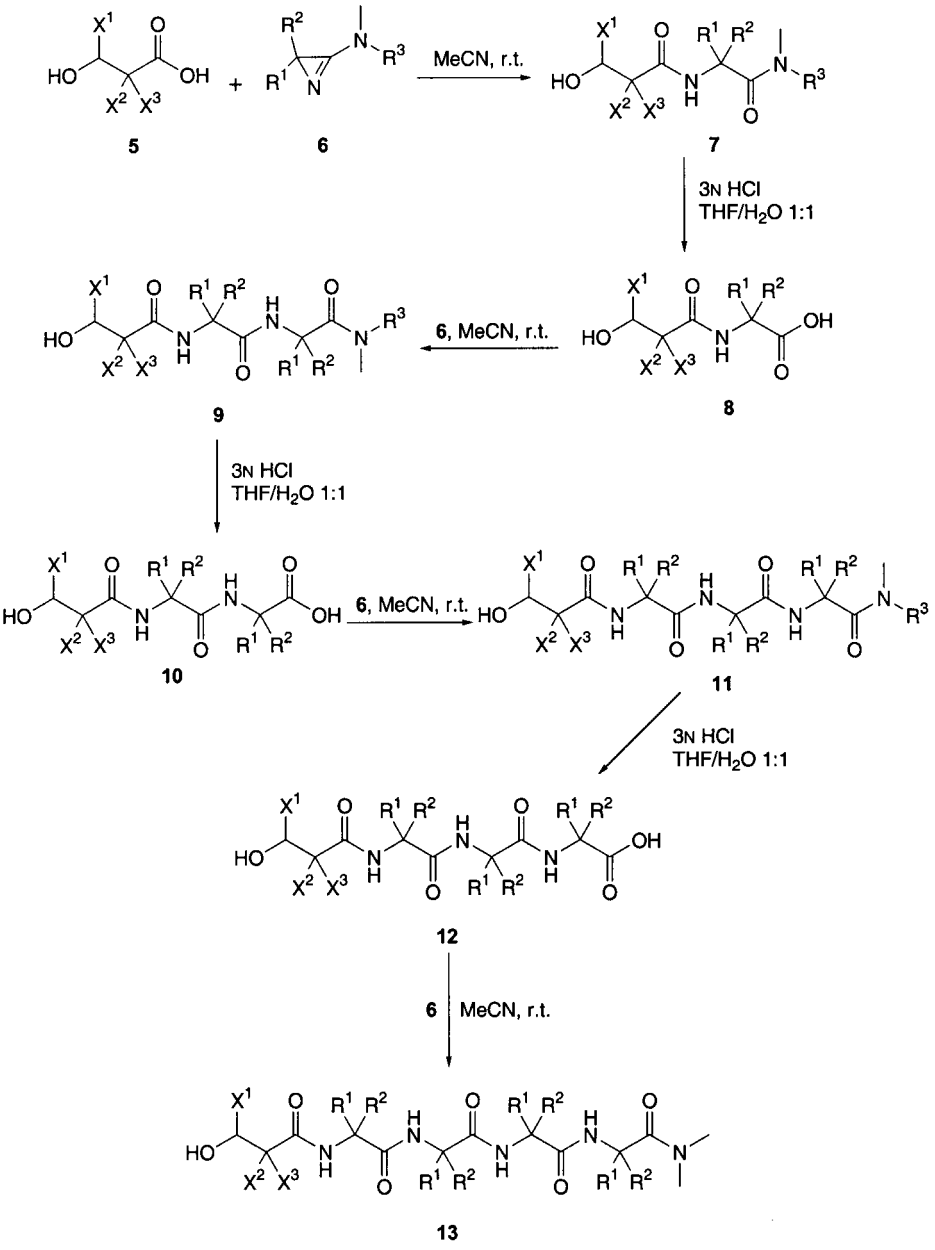
6d: $R^1 = Me$
e: $R^1 = Ph$

2.1. Preparation of the linear pentapeptides

Seven linear pentapeptides of type **13** were synthesized using the 'azirine/oxazolone method' according to Scheme 2 (cf. Tables 1 and 2). The amides **7**, **9**, **11** and **13** were prepared via coupling of 3-amino-2*H*-azirines **6** with the β-hydroxy acids or the free peptide acids in good to excellent yields (Table 1). Hydrolysis of the C-terminal amide was performed under standard conditions in 3N HCl/THF at rt yielding the acids **8**, **10** and **12** (Table 2). In three examples, the selective hydrolysis of the C-terminal amide was less satisfying: treatment of the tripeptide **9a** and the two tetrapeptides **11b** and **d** under standard conditions resulted in hydrolysis not only of the C-terminal amide, but also of other amide bonds of the peptide chain. Therefore, the yields of the desired carboxylic acids were low and, for practical reasons, the crude products were used for the following coupling reaction.

Generally, the coupling step is faster when 3-(*N*,*N*-dimethylamino)-2*H*-azirines **6a** and **d** are used instead of the corresponding 3-(*N*-methyl-*N*-phenylamino)-2*H*-azirines **6b** and **e**. On the other hand, *N*-methylaniline is a better leaving group than dimethylamine, thereby making the selective hydrolysis of the *N*-methyl-*N*-phenylamide faster than that of the *N*,*N*-dimethylamide.

In two examples, the diastereoisomeric peptides were separated. In the first case, the diastereoisomers **9b/9c** were separated by means of MPLC, and the two



Scheme 2. For X^1–X^3 and R^1–R^3 see Schemes 3–5 and Tables 1 and 2.

diastereoisomeric pentapeptides **13f** and **g** were then prepared independently of each other from **9b** (→**10b**→**11c**→**12d**→**13f**) and **9c** (→**10c**→**11d**→**12e**→**13g**), respectively. In the second case, RP-HPLC was used for the separation of the diastereoisomeric pentapeptides **13d** and **e**.

The structural preferences of Aib-containing peptides have been studied extensively by X-ray crystallography, and the following conclusions have been drawn: (a) Aib homopeptides, beginning at the trimer level, adopt the 3_{10}-helical structure stabilized by β-turns of type III (III′), irrespective of the chain length;[33] the α-helical structure has never been observed;[34] (b) 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;[34,35] (c) Aib is the strongest known β-turn-forming residue, particularly of types I (I′) and III (III′);[33] (d) Phe(2Me)- and Ac_5c-containing peptides show the same strong tendency to form β-turns and helical structures.[33]

The pentapeptide **13f** (Scheme 2, Table 1) and the previously prepared pentapeptide **13h**[25] have the same combination of α,α-disubstituted α-amino acids and differ only in the β-hydroxy acid. It was of interest to determine whether and how the different β-hydroxy acids

Table 1. Coupling of β-hydroxy acids **5** and peptide acids **8**, **10**, and **12** with 3-amino-2*H*-azirines **6**

Starting material	Azirine	Product	Yield (%)
5a (Dhp)	**6b**	**7a** (Dhp–Aib–N(Me)Ph)	93
5c (Hcc)	**6e**	**7b/c** (Hcc–Phe(2Me)–N(Me)Ph)	73
8a (Dhp–Aib)	**6b**	**9a** (Dhp–Aib–Aib–N(Me)Ph)	90
8b/c (Hcc–Phe(2Me))	**6b**	**9b/c** (Hcc–Phe(2Me)–Aib–N(Me)Ph)	88
10a (Dhp–Aib–Aib)	**6d**	**11a** (Dhp–Aib–Aib–Phe(2Me)–NMe_2)	35[a]
10a (Dhp–Aib–Aib)	**6b**	**11b** (Dhp–Aib–Aib–Aib–N(Me)Ph)	48[b]
10b (Hcc–Phe(2Me)–Aib) (*RS*,*RS*,*SR*)-Isomer	**6a**	**11c** (Hcc–Phe(2Me)–Aib–Aib–NMe_2) (*RS*,*RS*,*SR*)-Isomer	85
10c (Hcc–Phe(2Me)–Aib) (*RS*,*RS*,*RS*)-Isomer	**6b**	**11d** (Hcc–Phe(2Me)–Aib–Aib–N(Me)Ph) (*RS*,*RS*,*RS*)-Isomer	92
12a (Dhp–Aib–Aib–Phe(2Me))	**6a**	**13a** (Dhp–Aib–Aib–Phe(2Me)–Aib–NMe_2)	77
12b (Dhp–Aib–Aib–Aib)	**6d**	**13b** (Dhp–Aib–Aib–Aib–Phe(2Me)–NMe_2)	46[c]
12c ((*R*)-Tro–Aib–Aib–Aib)	**6c**	**13c** ((*R*)-Tro–$(Aib)_3$–Ac_5c–NMe_2)	87
12c ((*R*)-Tro–Aib–Aib–Aib)	**6d**	**13d/e** ((*R*)-Tro–$(Aib)_3$–Phe(2Me)–NMe_2)	82
12d (Hcc–Phe(2Me)–Aib–Aib) (*RS*,*RS*,*SR*)-Isomer	**6a**	**13f** (Hcc–Phe(2Me)–Aib–Aib–Aib–NMe_2) (*RS*,*RS*,*SR*)-Isomer	71
12e (Hcc–Phe(2Me)–Aib–Aib) (*RS*,*RS*,*RS*)-Isomer	**6a**	**13g** (Hcc–Phe(2Me)–Aib–Aib–Aib–NMe_2) (*RS*,*RS*,*RS*)-Isomer	42[d]

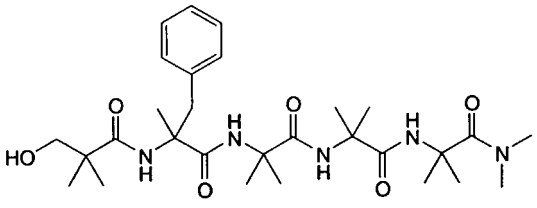
[a] Overall yield of the hydrolysis of **9a** followed by coupling of crude **10a** with **6d**.
[b] Overall yield of the hydrolysis of **9a** followed by coupling of crude **10a** with **6b**.
[c] Overall yield of the hydrolysis of **11b** followed by coupling of crude **12b** with **6d**.
[d] Overall yield of the hydrolysis of **11d** followed by coupling of crude **12e** with **6a**.

Table 2. Hydrolysis of the C-terminal amide group of the peptide amides

Peptide amides	Product	Yield (%)
7a (Dhp–Aib–N(Me)Ph)	**8a** (Dhp–Aib)	36
7b/c (Hcc–Phe(2Me)–N(Me)Ph)	**8b/c** (Hcc–Phe(2Me))	90
9a (Dhp–Aib–Aib–N(Me)Ph)	**10a** (Dhp–Aib–Aib)	–[a]
9b (Hcc–Phe(2Me)–Aib–N(Me)Ph) (*RS*,*RS*,*SR*)-Isomer	**10b** (Hcc–Phe(2Me)–Aib) (*RS*,*RS*,*SR*)-Isomer	88
9c (Hcc–Phe(2Me)–Aib–N(Me)Ph) (*RS*,*RS*,*RS*)-Isomer	**10c** (Hcc–Phe(2Me)–Aib) (*RS*,*RS*,*RS*)-Isomer	91
11a (Dhp–Aib–Aib–Phe(2Me)–NMe_2)	**12a** (Dhp–Aib–Aib–Phe(2Me))	83
11b (Dhp–Aib–Aib–Aib–N(Me)Ph)	**12b** (Dhp–Aib–Aib–Aib)	–[a]
11c (Hcc–Phe(2Me)–Aib–Aib–NMe_2) (*RS*,*RS*,*SR*)-Isomer	**12d** (Hcc–Phe(2Me)–Aib–Aib) (*RS*,*RS*,*SR*)-Isomer	93
11d (Hcc–Phe(2Me)–Aib–Aib–N(Me)Ph) (*RS*,*RS*,*RS*)-Isomer	**12e** (Hcc–Phe(2Me)–Aib–Aib) (*RS*,*RS*,*RS*)-Isomer	–[a]

[a] Yield not determined, cf. Table 1.

influence the conformation.



13h

The two pentapeptides were crystallized from H_2O/MeOH/$CHCl_3$ and H_2O/MeOH, 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 pentapeptides **13f** and **h** adopt helical conformations containing two distorted consecutive β-turns of type III (III′) (ϕ_1, ϕ_2, ϕ_3 and ψ_1, ψ_2, ψ_3; Table 3). The β-turns are stabilized by two consecutive intramolecular 4 → 1 H-bonds between N(7)–H···O(14) and N(4)–H···O(11). In **13f**, the N···O distances (Table 4) are slightly longer than the average value determined for a large number of intramolecular H-bonds in peptides,[40] whereas in **13h**, they are in good agreement with the expected values. All the peptide bonds (torsion angles ω) show the *s-trans*-configuration with two (in the case of **13f**) and one (in the case of **13h**), respectively, deviating markedly from planarity.[41]

The molecules of **13f** also form two intermolecular H-bonds, N(10)–H···O(2″) and N(13)–H···O(5″), linking neighboring molecules into infinite one-dimensional chains. Furthermore, there is an intermolecular H-bond between the hydroxy group O(16)–H and O(14′) at the cyclohexane end of a different neighboring molecule. This interaction links adjacent cyclohexane ends of neighboring molecules into centrosymmetric dimeric loops. These loops crosslink the H-bonded chains described above. Thus, the combination of all intermolecular H-bond interactions results in the formation of infinite two-dimensional networks.

In **13h**, there is an additional intramolecular H-bond

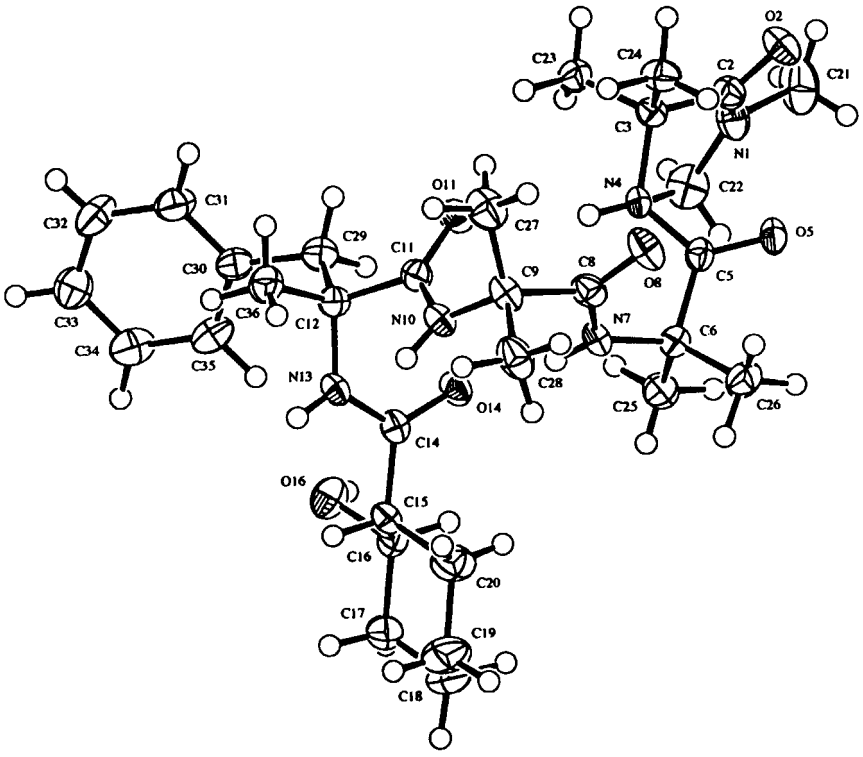


Figure 1. ORTEP Plot[39] of the molecular structure of **13f** (arbitrary numbering of the atoms; 50% probability ellipsoids).

between N(10)–H and O(17) of the OH group, which further stabilizes the helical conformation of the peptide. The molecules of **13h** are 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.

The signs of the torsion angles ϕ_4 and ψ_4 of the Aib residue at the C-terminal position of **13f** and **h** are opposite to those of the proceeding residues. This is a widely observed phenomenon for homopeptides of α,α-disubstituted α-amino acids.[42,43]

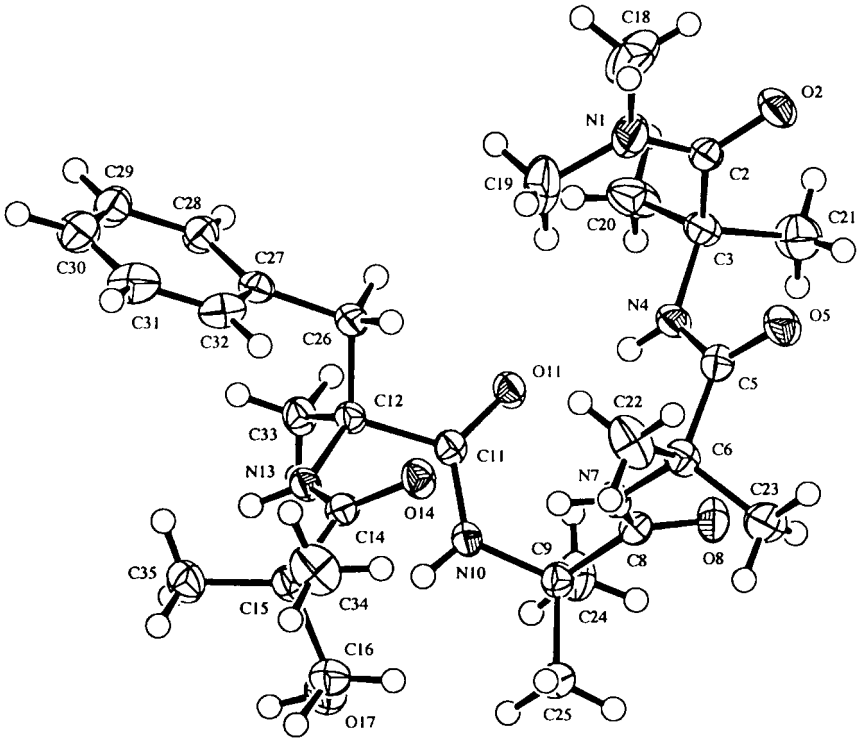
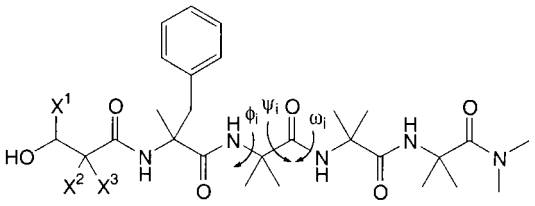
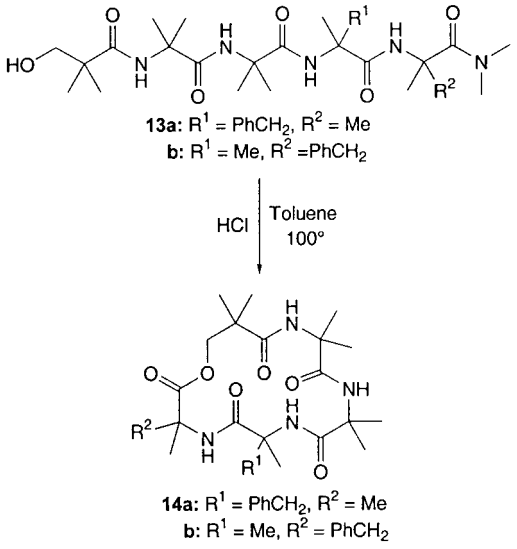


Figure 2. ORTEP Plot[39] of the molecular structure of **13h** (arbitrary numbering of the atoms; 50% probability ellipsoids).

Table 3. Selected torsion angles (°) of pentapeptides **13f** and **h**



Angle	Peptide **13f**	Peptide **13h**
ω_0	−178.9(2)	−178.1(1)
ϕ_1	−51.8(3)	55.2(2)
ψ_1	−51.1(3)	29.2(2)
ω_1	−166.2(2)	178.4(1)
ϕ_2	−64.7(3)	46.7(2)
ψ_2	−24.5(3)	36.9(2)
ω_2	−179.3(2)	+113.9(2)
ϕ_3	−54.7(3)	66.4(2)
ψ_3	−34.2(3)	12.3(2)
ω_3	167.2(2)	−179.8(2)
ϕ_4	45.0(3)	−55.4(2)
ψ_4	61.6(3)	−57.4(2)



Scheme 3.

In conclusion, both peptides, **13f** and **h**, adopt the conformation of an incipient 3_{10}-helix stabilized by two distorted consecutive β-turns of Type III′ (III). This conformation appears to be independent of the kind of β-hydroxy acid present.

2.2. Cyclization of the linear pentapeptides

The optimum reaction conditions for the cyclization to give 16-membered cyclic pentadepsipeptides of type **14** via the 'direct amide cyclization' were elaborated in the previous work.[25] The general procedure was as follows: a stream of dry HCl gas was slowly passed through a suspension of the pentapeptide **13** in toluene at 100°C. When a clear solution was formed, HCl was added for another 2–3 min. Then, excess HCl was removed by passing a stream of N_2 through the solution for 30 min, toluene was evaporated, the residue was suspended in THF/Et_2O 1:1 at rt, and, subsequently, the precipitated $Me_2NH{\cdot}HCl$ was removed by filtration. The products were then purified by column chromatography.

All cyclic depsipeptides of type **14** were characterized by spectroscopic methods. In the IR spectra of **14a–g**, the absorption of the lactone group was observed at 1715–1749 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 cyclic monomer **14** and the corresponding cyclodimer. The structures of **14a–g** were confirmed by one- and two-dimensional NMR spectroscopy. The assignment of the different ^1H and ^{13}C signals was carried out using HSQC and HMBC techniques.[25]

A possible influence of the amino acid sequence in the pentapeptide chain with the same composition of α,α-disubstituted α-amino acids on the cyclization was examined. Therefore, the formation of cyclic depsipeptides of type **14** containing the β-hydroxy acid **5a**, three Aib residues and one Phe(2Me) residue was studied. The first example **4c** with Phe(2Me) in position 2 has been prepared from **13h** earlier and was obtained in good yield (46%).[25] Under the same conditions, the analogous pentapeptides **13a** and **b**, with Phe(2Me) in positions 4 and 5, respectively, were cyclized according to Scheme 3, and the cyclic monomers, **14a** and **b**, respectively, were obtained, although in rather low yield (Table 5). In the case of **13a**, the cyclodimer **15a**[‡] was also isolated in similar yield.

The results of these cyclizations were compared with those previously described. The yield of **14a** is less than half of that of **4c**, and the formation of the cyclodimer **15a** is favored. In the case of **14b**, the difference is even more pronounced as the yield is only a fifth of that of **4c**. This indicates that different positions of Phe(2Me) in the pentapeptide chain influence the conformation and/or solubility of **13** and/or the intermediates of the cyclization

Table 4. Intra- and intermolecular H-bond parameters for the pentapeptides **13f** and **h**

Compound	Type[a]	H···O (Å)	X^b···O (Å)	X^b–H···O (°)
13f	O(16)–H···O(14′)	1.93(3)	2.855(2)	172(3)
	N(10)–H···O(2″)	2.54(2)	3.350(3)	154(2)
	N(13)–H···O(5″)	2.03(2)	2.829(2)	162(2)
	N(4)–H···O(11)	2.32(2)	3.121(2)	167(2)
	N(7)–H···O(14)	2.48(2)	3.235(3)	156(2)
13h	N(13)–H···O(2′)	2.06(2)	2.908(2)	160(2)
	O(17)–H···O(5′)	1.99(3)	2.847(2)	177(3)
	N(4)–H···O(11)	2.13(2)	2.958(2)	167(2)
	N(7)–H···O(14)	2.20(2)	3.047(2)	167(2)
	N(10)–H···O(17)	2.45(2)	3.302(2)	167(2)

[a] Primed atoms refer to molecules in the following symmetry-related positions: for **13f**: $'1-x, 2-y, -z$; $''-(1/2)+x, (3/2)-y, -(1/2)+z$; for **13h**: $'-1+x, y, z$.

[b] X=O or N.

[‡] Based on the similar chromatographic properties of **15a** and **14a** and the ESI-MS, we propose that **15a** is a cyclodimer:

15a

Table 5. Cyclization of pentapeptides **13a–g** in toluene (30 ml) at 100°C

Pentapeptide	Cyclic monomer	Yield (%)	Cyclodimer	Yield (%)
13a	**14a**	20	**15a**	24
13b	**14b**	9	**15b**	–[a]
13c	14c	30	**15c**	20
13d	**14d**	58	**15d**	–[a]
13e	**14e**	57	**15e**	21
13f	**14f**	50	**15f**	2
13g	**14g**	28	**15g**	11

[a] The proposed cyclodimers **15b** and **d** were isolated together with other non-identified products (detected by ESI-MS).

considerably, resulting in large variations in the yields of **14**.

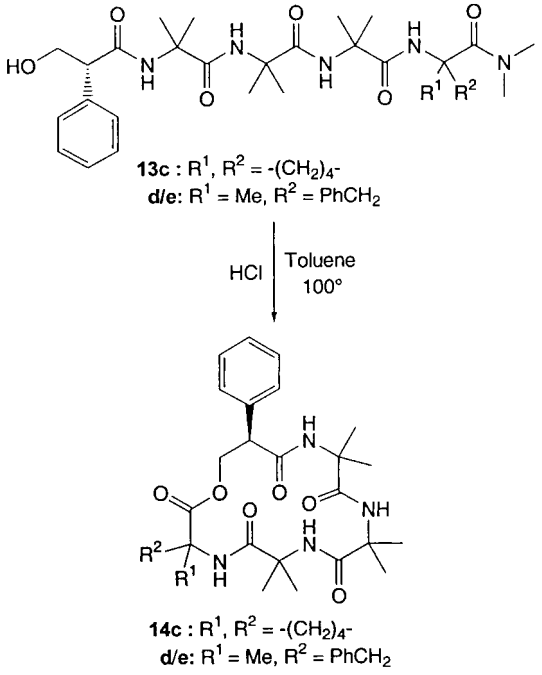
It was also of interest to know how different C-terminal α,α-disubstituted α-amino acids would influence the cyclization, when the rest of the peptide chain remained identical. The cyclic depsipeptide **4a**, containing only one type of α,α-disubstituted α-amino acid, i.e. Aib, was chosen as the reference. The new pentapeptides **13c–e** were synthesized with enantiomerically pure tropic acid ((*R*)-Tro), three Aib residues, and a C-terminal Ac_5c and Phe(2Me) residue, respectively, as described above. Ring closure of the three pentapeptides was carried out via 'direct amide cyclization' according to Scheme 4. In each of these examples, both the monomer **14** and the dimer **15** were formed. The yields are summarized in Table 5.

Comparing the yields of the monomers **14** (Table 5) with that of **4a** (41%), it is evident that the C-terminal α,α-disubstituted α-amino acid also influences the yield of cyclic monomer. The lowest yield was obtained in the case of pentapeptide **13c** containing a C-terminal Ac_5c residue (formation of **14c** in only 30% yield), the highest yield resulted with **13d** containing a C-terminal Phe(2Me) residue (58% yield of **14d**). The difference between the lowest and highest yield of cyclic monomer is nearly twofold. Another interesting result is the similarity of the yields of the two diastereoisomeric monomers **14d** and **e** (58% and 57%, respectively), i.e. the formation of the monomers **14d** and **e** is not significantly influenced by the chirality of the C-terminal α,α-disubstituted α-amino acid.

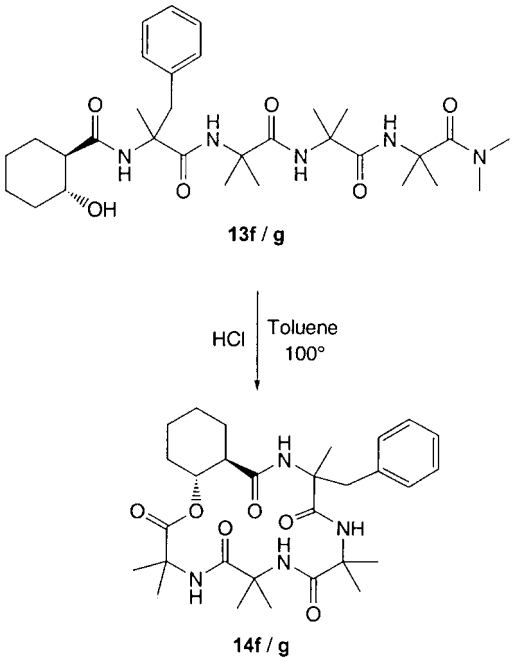
A further point of interest was the effect of different β-hydroxy acids on the ring closure via 'direct amide cyclization'. Pentapeptide **13b** and the diastereoisomers **13d** and **e** contain the same sequence of α,α-disubstituted α-amino acids and differ only in the β-hydroxy acid, with Dhp (**5a**) in the former and Tro (**5b**) in the latter case. The cyclic monomer **14b** was obtained in 9% yield, whereas **14d** and **e** were formed in 58% and 57% yield, respectively. The sixfold difference in yield shows the distinctive effect of the β-hydroxy acid on the ring closure.

In the above-described examples, β-hydroxy acids with a primary hydroxy group were used. Therefore, it was of interest to investigate whether or not a sterically more hindered β-hydroxy acid with a secondary hydroxy group could be used to prepare cyclic depsipeptides. Furthermore, it was attractive to cyclize diastereoisomeric pentapeptides **13** containing the chiral Phe(2Me) within the peptide chain. The β-hydroxy acid **5c**, with the secondary hydroxy group in a *trans* relationship to the carboxylic acid functionality, was chosen. The cyclic monomer **4c** with the racemic Phe(2Me) residue in position 2 of the pentapeptide was used as the reference. The two diastereoisomeric pentapeptides **13f** and **g** were cyclized via the 'direct amide cyclization' according to Scheme 5. In both cases, the corresponding monomer **14** and dimer **15** could be isolated (Table 5).

The diastereoisomeric cyclic monomers **14f** and **g** were



Scheme 4.



Scheme 5.

formed in 50% and 28% yield, respectively. This indicates that the ease of cyclization in this case is influenced remarkably by the configuration of the chiral Phe(2Me) residue next to the β-hydroxy acid. The model peptide monomer **4c** has been obtained in 46% yield, thus **14f** was obtained in slightly higher yield. These results show that a sterically more hindered β-hydroxy acid can also be used successfully for ring closure via 'direct amide cyclization'.

3. Conclusions

In the present study, a number of factors which influence the formation of cyclic depsipeptides via the 'direct amide cyclization' have been investigated. The following modifications of the pentapeptide chain were found to have a profound influence on the yield of cyclic monomer **4/14**: (a) keeping the β-hydroxy acid and four α,α-disubstituted α-amino acids in the peptide chain unchanged, but varying the position of the different α,α-disubstituted α-amino acids in the peptide chain; (b) using different α,α-disubstituted α-amino acids at the C-terminal position while keeping the β-hydroxy acid and three α,α-disubstituted α-amino acids unchanged; (c) preserving the chain of four α,α-disubstituted α-amino acids, but using different β-hydroxy acids. Apart from these three factors, it was found that a sterically hindered β-hydroxy acid containing a secondary hydroxy group could be successfully used in the 'direct amide cyclization'. The cyclization of diastereoisomeric pentapeptides was found to be influenced by the position of the chiral Phe(2Me) residue in the pentapeptide chain, whereas no influence was observed with the chiral Phe(2Me) residue at the C-terminal position; the yields of the cyclizations of the diastereoisomers with the chiral Phe(2Me) residue next to the β-hydroxy acid differ significantly.

In summary, all ring closures of pentapeptides **13** containing a β-hydroxy acid and four α,α-disubstituted α-amino acids via 'direct amide cyclization' gave the corresponding cyclic monomer **4/14**, but the yields vary considerably ranging from 9 to 60%. We believe that the explanation for this result shall be found in the difference of the conformation and/or solubility of the linear precursors and the intermediates of the cyclization.

4. Experimental

4.1. General

See Ref. 44. 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 (**6a**), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**6b**), *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine (**6c**), 2-benzyl-2,*N*,*N*-trimethyl-2*H*-azirin-3-amine (**6d**) and 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine (**6e**) (cf. Ref. 26 and references cited therein).

*General procedure 1 (GP 1). Reaction of **6** with acids **5**, **8**, **10** and **12***. To a stirred suspension of the acid in dry MeCN was added dropwise a solution of **6** in dry MeCN. The mixture was stirred at rt under N_2 (18–44 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 rt under N_2 (17–92 h), evaporated, purified by column chromatography (CC), and dried under h.v.

*General procedure 3 (GP 3). Hydrolysis of amides **7**, **9** and **11***. The amide was dissolved in 3N HCl/THF 1:1 (v/v; ca. 5 ml/mmol) and the solution was stirred at rt (19–24 h). The solvent was evaporated, H_2O was added, and the mixture left overnight at rt. 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 solution of the amide in 3N HCl/THF 1:1 (v/v; ca. 5 ml/mmol) was stirred at rt (18–23 h), followed by evaporation of the solvent. Brine was added to the oily crude product, the mixture was extracted with AcOEt, the organic layer dried ($MgSO_4$), evaporated, and the residue dried under h.v.

4.2. Reaction of 2*H*-azirin-3-amines 6 with β-hydroxy acids 5

4.2.1. 2-[(3-Hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2,*N*-dimethyl-*N*-phenylpropanamide (7a). According to GP 2, **5a** (1.01 g, 8.50 mmol) in MeCN (10 ml), **6b** (1.54 g, 8.84 mmol) in MeCN (2 ml), stirred for 17 h, CC (SiO_2, CH_2Cl_2/MeOH 25:1, CH_2Cl_2/MeOH 10:1): 2.32 g (93%) of **7a**. White powder. Mp 103.4–104.0°C. IR: 3353vs, 3257vs, 3058m, 2965s, 2867s, 1645vs, 1592vs, 1548vs, 1493vs, 1472s, 1415vs, 1384vs, 1359vs, 1309m, 1260s, 1218s, 1196s, 1172s, 1156m, 1116s, 1074m, 1058vs, 1024m, 990m, 962m, 927w, 902m, 859m, 811w, 778s, 709vs, 632m. ^{1}H NMR: 7.39–7.19 (m, NH, 5 arom. H); 4.96 (t, *J*=5.1 Hz, OH); 3.26 (d, *J*=5.0 Hz, CH_2OH); 3.19 (s, MeN); 1.36, 0.96 (2s, 2Me$_2$C). ^{13}C NMR: 175.5, 172.4 (2s, 2CO); 145.6 (s, 1 arom. C); 128.8, 127.2, 126.5 (3d, 5 arom. C); 67.6 (t, CH_2OH); 56.2, 42.9 (2s, 2Me$_2$*C*); 40.0 (q, MeN); 26.1, 22.1 (2q, 2*Me*$_2$C). CI-MS: 293 (36, $[M+H]^+$), 186 (100, $[M-Me(Ph)N]^+$).

4.2.2. (1′*RS*,2′*RS*,2*RS*)- and (1′*RS*,2′*RS*,2*SR*)-2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}-*N*-methyl-*N*-phenylpropanamide (7b/7c). According to GP 2, **5c** (0.693 g, 4.81 mmol) in MeCN (10 ml), **6e** (1.31 g, 5.22 mmol) in MeCN (2 ml), stirred for 40 h, CC (SiO_2, CH_2Cl_2/MeOH 25:1): 1.33 g (73%) of **7b/7c** (ca. 1:1 mixture of diastereoisomers). White powder. Mp 143.6–171.2°C. IR: 3854w, 3545m, 3430m, 3301s, 3060m, 2931s, 2858m, 2362w, 1646vs, 1593s, 1539s, 1494vs, 1452s, 1390s, 1370s, 1310m, 1258m, 1238m, 1220m, 1105m, 1068s, 1007w, 930w, 868w, 765m, 703vs, 655m, 565w. ^{1}H NMR: 7.98 (s, NH); 7.83 (s, NH); 7.37–7.11 (m, 2×10 arom. H); 4.76 (d, *J*=4.4 Hz, OH); 4.60 (d, *J*=4.5 Hz, OH); 3.57 (m, 2C*H*OH); 3.23 (s, 2MeN); 3.23–3.22 (m, 2H of 2PhCH_2); 3.10–3.00 (m, 2H of 2PhCH_2); 2.06–2.04 (m, 2CH); 1.83–1.11 (m, 2×4CH_2); 1.28, 1.21 (2s, 2PhCH_2(*Me*)C). ^{13}C NMR: 173.4, 173.3, 171.9 (3s, 2×2CO); 146.2 (s, 2 arom. C); 137.1, 137.0 (2s, 2 arom. C); 131.2, 131.0, 128.6, 127.6, 127.2, 127.0, 126.2, 126.1

(8d, 2×10 arom. C); 69.4 (d, 2CHOH); 58.8 (s, 2PhCH$_2$(Me)*C*); 51.7, 51.5 (2d, 2CH); 41.5 (t, 2Ph*C*H$_2$); 39.7, 39.5 (2q, 2MeN); 35.1, 28.7, 24.7, 24.1 (4t, 2×4CH$_2$); 22.4, 22.2 (2q, 2PhCH$_2$(*Me*)C). CI-MS: 395 (28, $[M+H]^+$), 288 (100, $[M-Me(Ph)N]^+$).

4.3. Hydrolysis of dipeptide amides 7

4.3.1. 2-[(3-Hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methylpropanoic acid (8a). According to GP 4, **7a** (2.25 g, 7.68 mmol), 40 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 23 h, 50 ml of brine, 4×50 ml of AcOEt: 0.569 g (36%) of **8a**. White powder. Mp 142.8–144.0°C. IR: 3852m, 3403vs, 3339vs, 2977vs, 2626m, 1715vs, 1620vs, 1539vs, 1468s, 1457s, 1404vs, 1365s, 1279s, 1254vs, 1234s, 1179vs, 1048vs, 1019s, 980m, 942m, 916m, 896s, 873s, 767s, 628s. ^{1}H NMR:[§‖] 7.52 (s, NH); 3.36 (s, C*H*$_2$OH); 1.35, 1.00 (2s, 2Me$_2$C). ^{13}C NMR: 175.7 (s, 2CO); 67.7 (t, CH$_2$OH); 54.7, 42.7 (2s, 2Me$_2$*C*); 24.7, 22.2 (2q, 2*Me*$_2$C). ESI-MS: 204 (100, $[M+H]^+$).

4.3.2. (1′*RS*,2′*RS*,2*RS*)- and (1′*RS*,2′*RS*,2*SR*)-2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}propanoic acid (8b/8c). According to GP 3, **7b/7c** (0.700 g, 1.77 mmol), 10 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 24 h, H$_2$O (5 ml): 0.485 g (90%) of **8b/8c** (ca. 1:1 mixture of diastereoisomers). White powder. Mp 191.3–193.0°C. IR: 3459s, 3261s, 3064s, 2937vs, 2861s, 1737vs, 1643vs, 1624vs, 1552vs, 1496m, 1450s, 1396s, 1320m, 1269s, 1249s, 1223s, 1122s, 1079m, 1062m, 1006w, 950w, 927w, 858w, 815w, 769w, 737w, 703s, 660m. ^{1}H NMR[§‖]: 7.70 (s, NH); 7.60 (s, NH); 7.28–7.12 (m, 2×10 arom. H); 3.59–3.42 (m, 2C*H*OH); 3.35 (d, *J*=13.2 Hz, 1H of PhC*H*$_2$); 3.23 (d, *J*=13.1 Hz, 1H of PhC*H*$_2$); 3.08 (d, *J*=13.1 Hz, 1H of PhC*H*$_2$); 3.04 (d, *J*=13.2 Hz, 1H of PhC*H*$_2$); 2.07–2.00 (m, 2CH); 1.86–1.62 (m, 4CH$_2$); 1.38–1.07 (m, 4CH$_2$); 1.28, 1.19 (2s, 2PhCH$_2$(*Me*)C). ^{13}C NMR: 175.3, 175.0, 173.7, 173.7 (4s, 2×2CO); 137.0, 136.7 (2s, 2 arom. C); 130.7, 130.4, 127.6, 127.5, 126.3, 126.1 (6d, 2×5 arom. C); 69.8, 69.5 (2d, 2CHOH); 58.7, 58.3 (2s, 2PhCH$_2$(Me)*C*); 51.7 (d, 2CH); 40.6, 39.6, 35.1, 34.7, 28.4, 28.2, 24.6, 24.2, 24.1 (9t, 2×5CH$_2$); 22.6, 22.4 (2q, 2PhCH$_2$(*Me*)C). CI-MS: 306 (100, $[M+H]^+$), 288 (13, $[M-OH]^+$), 260 (36, $[M-COOH]^+$).

4.4. Reaction of 2*H*-azirin-3-amines 6 with dipeptides 8

4.4.1. 2-({2-[(3-Hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxo-propyl}amino)-2,*N*-dimethyl-*N*-phenylpropanamide (9a). According to GP 1, **8a** (0.503 g, 2.48 mmol) in MeCN (5 ml), **6b** (0.580 g, 3.33 mmol) in MeCN (1 ml), stirred for 19 h: 0.840 g (90%) of **9a**. White powder. Mp 152.1–153.5°C. IR: 3417vs, 3325vs, 2987s, 2960s, 2934s, 2871m, 2361w, 1668vs, 1645vs, 1595s, 1522vs, 1495vs, 1465s, 1393vs, 1362vs, 1307m, 1281m, 1250s, 1220s, 1171s, 1091vs, 1068m, 1050vs, 964w, 930w, 900w, 855w, 770m, 743w, 706vs, 662m, 616m. ^{1}H NMR: 7.50, 7.44 (2s, 2NH); 7.38–7.19 (m, 5 arom. H); 5.23 (m, OH); 3.43 (d, *J*=4.4 Hz, C*H*$_2$OH); 3.23 (s, MeN); 1.36, 1.34, 1.04 (3s, 3Me$_2$C). ^{13}C NMR: 175.3, 173.6, 172.3 (3s, 3CO); 145.7 (s, 1 arom. C); 128.6, 127.0, 126.2 (3d, 5 arom. C); 68.5 (t, CH$_2$OH); 56.3, 56.0, 43.4 (3s, 3Me$_2$*C*); 39.5 (q, MeN); 25.5, 24.8, 22.1 (3q, 3*Me*$_2$C). ESI-MS: 400 (100, $[M+Na]^+$), 271 (62, $[M-Me(Ph)N]^+$).

4.4.2. (1″*RS*,2″*RS*,2′*RS*)- and (1″*RS*,2″*RS*,2′*SR*)-2-[(2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}-1-oxopropyl)amino]-2,*N*-dimethyl-*N*-phenylpropanamide (9b/9c). According to GP 1, **8b/8c** (0.433 g, 1.48 mmol) in MeCN (5 ml), **6b** (0.290 g, 1.66 mmol) in MeCN (1 ml), stirred for 20 h: 0.627 g (88%) of **9b/9c** (ca. 1:1 mixture of diastereoisomers). White powder. The diastereoisomers were separated by means of MPLC. Conditions: stationary phase: SiO$_2$, mobile phase: 48 ml/min, CH$_2$Cl$_2$/MeOH 20:1; UV detector, 254 nm.

Data of **9b** (*RS*,*RS*,*SR* isomer). White powder. Mp 177.3–175.5°C. IR: 3333vs, 3028m, 2987m, 2934vs, 2859m, 1636vs, 1592s, 1523vs, 1493vs, 1454vs, 1392s, 1364s, 1276m, 1259m, 1242m, 1212s, 1132m, 1094s, 1071s, 1014m, 932m, 851w, 773m, 745w, 710vs, 614m. ^{1}H NMR: 7.67, 7.49 (2s, 2NH); 7.40–7.18 (m, 10 arom. H); 4.88 (d, *J*=5.1 Hz, OH); 3.63–3.57 (m, C*H*OH); 3.44, 3.00 (AB, *J*=13.4 Hz, PhC*H*$_2$); 3.27 (s, MeN); 2.13–2.04 (m, CH); 1.91–1.07 (m, 4CH$_2$); 1.36, 1.35, 1.19 (3s, Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C NMR: 174.1, 173.2, 172.5 (3s, 3CO); 145.8, 137.1 (2s, 2 arom. C); 130.9, 128.7, 127.5, 127.1, 126.2, 126.0 (6d, 10 arom. C); 70.2 (d, CHOH); 59.3, 56.5 (2s, Me$_2$*C*, PhCH$_2$(Me)*C*); 52.9 (d, CH); 39.5 (q, MeN); 39.3, 35.1, 27.9, 24.6, 24.2 (5t, 4CH$_2$, Ph*C*H$_2$); 25.6, 25.5, 23.1 (3q, *Me*$_2$C, PhCH$_2$(*Me*)C).

Data of **9c** (*RS*,*RS*,*RS* isomer). White powder. Mp 179.4–181.4°C. IR: 3378s, 3029m, 2986m, 2937s, 2853m, 1681vs, 1619vs, 1592s, 1494vs, 1452s, 1394s, 1365s, 1267m, 1216s, 1094s, 1070s, 1017w, 951w, 924w, 870w, 752m, 709vs, 618m. ^{1}H NMR: 7.72 (s, NH); 7.44–7.07 (m, 1NH, 10 arom. H); 4.98 (d, *J*=4.1 Hz, OH); 3.71, 2.97 (AB, *J*=13.3 Hz, PhC*H*$_2$); 3.56–3.43 (m, C*H*OH); 3.29 (s, MeN); 2.13–2.02 (m, CH); 2.00–1.12 (m, 4CH$_2$); 1.38, 1.36, 1.12 (3s, Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C NMR: 174.2, 173.7, 172.4 (3s, 3CO); 146.1, 137.4 (2s, 2 arom. C); 130.7, 128.6, 127.6, 126.9, 126.1, 125.9 (6d, 10 arom. C); 71.7 (d, CHOH); 59.1, 56.4 (2s, Me$_2$*C*, PhCH$_2$(Me)*C*); 51.8 (d, CH); 39.3 (q, MeN); 37.5, 34.8, 27.2, 24.3, 24.0 (5t, 4CH$_2$, Ph*C*H$_2$); 25.7, 25.6, 24.1 (3q, *Me*$_2$C, PhCH$_2$(*Me*)C). ESI-MS: 480 (14, $[M+H]^+$), 373 (100, $[M-Me(Ph)N]^+$).

4.5. Hydrolysis of tripeptide amides 9

4.5.1. 2-({2-[(3-Hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxo-propyl}amino)-2-methylpropanoic acid (10a). According to GP 4, **9a** (0.765 g, 2.03 mmol), 10 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 23 h, 25 ml of brine, 5×25 ml of AcOEt: 0.311 g of crude **10a**. The material was used for the next reaction step without further purification.

4.5.2. (1″*RS*,2″*RS*,2′*SR*)- and (1″*RS*,2″*RS*,2′*RS*)-2-[(2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}-1-oxopropyl)amino]-2-methylpropanoic acid (10b and 10c, respectively). Data of **10b**. According to GP 4, **9b** (0.178 g, 0.371 mmol), 2 ml of 3N HCl (H$_2$O/THF 1:1), stirred for 23 h, 5 ml of brine, 5×5 ml of AcOEt: 0.128 g

§ The signal for the COOH group could not be determined.
‖ The signal for the OH group could not be determined.

(88%) of **10b**. White powder. Mp 181.2–181.4°C. IR: 3416vs, 3311vs, 2984s, 2935vs, 2859s, 2551m, 1699s, 1656vs, 1522vs, 1456s, 1388s, 1302s, 1240s, 1220s, 1178s, 1129m, 1051s, 1004m, 857w, 793w, 744w, 703s, 631w. ^{1}H NMR (CD_3OD, 300 MHz): 7.25–7.19 (m, 5 arom. H); 3.68–3.65 (m, C*H*OH); 3.35, 3.12 (AB, *J*= 13.6 Hz, PhCH_2); 2.16–2.06 (m, CH); 2.02–1.65, 1.51–1.14 (2m, 4CH_2); 1.49, 1.46, 1.37 (3s, Me_2C, $PhCH_2$(*Me*)C). ^{13}C NMR (CD_3OD, 75.5 MHz): 178.0, 177.2, 175.4 (3s, 3CO); 137.6 (s, 1 arom. C); 132.1, 129.0, 127.7 (3d, 5 arom. C); 72.3 (d, CHOH); 61.4, 57.3 (2s, Me_2C, $PhCH_2$(Me)*C*); 54.7 (d, CH); 42.3, 36.1, 29.6, 26.0, 25.6 (5t, 4CH_2, $PhCH_2$(*Me*)C); 25.1, 25.0, 23.4 (3q, *Me*$_2$C, $PhCH_2$(*Me*)C). ESI-MS: 413 (26, $[M+Na]^+$), 391 (100, $[M+H]^+$).

Data of **10c**. According to GP 3, **9c** (0.272 g, 0.567 mmol), 3 ml of 3N HCl (H_2O/THF 1:1), stirred for 20 h, H_2O (3 ml): 0.201 g (91%) of **10c**. White powder. Mp 201.3–202.3°C. IR: 3854w, 3821w, 3751w, 3736w, 3712w, 3690w, 3676w, 3635s, 3423s, 3344vs, 3289vs, 3057m, 2944s, 2857s, 1717vs, 1653vs, 1544vs, 1496m, 1458s, 1387s, 1364m, 1328m, 1314m, 1294m, 1243s, 1224s, 1162s, 1060s, 1014w, 936m, 870w, 780m, 750m, 707s, 671m, 610m. ^{1}H NMR:[§‖] 7.70, 7.39 (2s, 2NH); 7.27–7.05 (m, 5 arom. H); 3.57, 2.94 (AB, *J*=13.3 Hz, PhCH_2); 3.52–3.45 (m, C*H*OH); 2.09–2.02 (m, CH); 1.93–1.12 (m, 4CH_2); 1.33, 1.28, 1.12 (3s, Me_2C, $PhCH_2$(*Me*)C). ^{13}C NMR: 175.4, 174.1, 173.1 (3s, 3CO); 137.4 (s, 1 arom. C); 130.6, 127.6, 126.0 (3d, 5 arom. C); 71.4 (d, CHOH); 58.8, 54.8 (2s, Me_2C, $PhCH_2$(Me)*C*); 51.8 (d, CH); 37.8, 34.9, 27.3, 24.3, 24.1 (5t, 4CH_2, Ph*C*H_2); 25.4, 23.8 (2q, *Me*$_2$C, $PhCH_2$(*Me*)C). ESI-MS: 413 (100, $[M+Na]^+$), 391 (56, $[M+H]^+$).

4.6. Reaction of 2*H*-azirin-3-amines 6 with tripeptides 10

4.6.1. 2-Benzyl-2-{[2-({2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-*N*,*N*-dimethylpropanamide (11a). According to GP 2, crude **10a** (0.272 g) in MeCN (5 ml), **6d** (0.288 g, 1.36 mmol) in MeCN (1 ml), stirred for 23 h, CC (SiO_2, CH_2Cl_2/MeOH 25:1, CH_2Cl_2/MeOH 10:1): 0.297 g (35% with respect to **9a**). Foam. IR: 3310s, 2985m, 2936m, 2362w, 1652vs, 1528vs, 1457s, 1383s, 1362m, 1229m, 1189m, 1091m, 1054m, 977w, 915w, 767w, 736w, 704m, 658m. ^{1}H NMR ((d$_5$)pyridine, 600 MHz): 8.25, 8.08, 7.69 (3s, 3NH); 7.44–7.23 (m, 5 arom. H); 3.88–3.80 (m, CH_2OH, PhCH_2); 3.39, 3.01 (2brs, Me_2N); 1.88, 1.772, 1.770, 1.68, 1.65, 1.36, 1.31 (7s, 3Me_2C, $PhCH_2$(*Me*)C). ^{13}C NMR ((d$_5$)pyridine, 151 MHz): 178.7, 174.9, 174.5, 172.3 (4s, 4CO); 138.4 (s, 1 arom. C); 132.1, 128.7, 127.3 (3d, 5 arom. C); 70.5 (t, CH_2OH); 61.3, 58.0, 57.9, 44.9 (4s, 3Me_2C, $PhCH_2$(Me)*C*); 44.0 (t, Ph*C*H_2); 38.8 (q, Me_2N); 26.8, 26.4, 26.3, 25.9, 24.4, 22.92, 22.91 (7q, 3*Me*$_2$C, $PhCH_2$(*Me*)C). ESI-MS: 499 (100, $[M+Na]^+$), 432 (45, $[M-Me_2N]^+$).

4.6.2. 2-{[2-({2-[(3-Hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxo-propyl}amino)-2-methyl-1-oxopropyl]amino}-2,*N*-dimethyl-*N*-phenylpropanamide (11b). According to GP 2, crude **10a** (0.580 g) in MeCN (5 ml), **6b** (0.366 g, 2.10 mmol) in MeCN (1 ml), stirred for 78 h, CC (SiO_2, CH_2Cl_2/MeOH 25:1, CH_2Cl_2/MeOH 10:1): 0.540 g (48% with respect to **9a**). Oil. IR (Film): 3306s, 2985s, 2937s, 1652vs, 1594s, 1531vs, 1391s, 1362s, 1226s, 1170s, 1092s, 1027vs, 823m, 765s, 709s. ^{1}H NMR: 7.79, 7.51 (2s, 2NH); 7.37–7.18 (m, 1NH, 5 arom. H); 5.33 (t, *J*=4.5 Hz, OH); 3.51 (d, *J*=4.2 Hz, CH_2OH); 3.29 (s, MeN); 1.44, 1.34, 1.32, 1.09 (4s, 4Me_2C). ^{13}C NMR: 177.2, 174.0, 173.3, 172.8 (4s, 4CO); 146.3 (s, 1 arom. C); 128.6, 126.9, 125.9 (3d, 5 arom. C); 68.9 (t, CH_2OH); 56.2, 56.0, 43.7 (3s, 4Me_2C); 39.2 (q, MeN); 25.5, 25.2, 24.9, 22.0 (4q, 4*Me*$_2$C). ESI-MS: 485 (100, $[M+Na]^+$).

4.6.3. (1″′*RS*,2″′*RS*,2″*SR*)-2-({2-[(2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2,*N*,*N*-trimethylpropanamide (11c). According to GP 1, **10b** (0.124 g, 0.318 mmol) in MeCN (2 ml), **6a** (0.041 g, 0.366 mmol) in MeCN (1 ml), stirred for 18 h: 0.136 g (85%) of **11c**. White powder. Mp 235.3–237.1°C. IR: 3330vs, 3283vs, 2990m, 2938s, 2861m, 2362w, 1651vs, 1538vs, 1452s, 1392s, 1381s, 1364s, 1286m, 1260m, 1207s, 1170m, 1118s, 1073m, 1017w, 951w, 924w, 871w, 743m, 703m. ^{1}H NMR ((d$_5$)pyridine, 300 MHz): 8.89, 8.16, 7.63 (3s, 3NH); 7.49–7.25 (m, 5 arom. H); 6.78 (brs, OH); 4.11 (m, C*H*OH); 3.64, 3.41 (AB, *J*=13.4 Hz, PhCH_2); 3.16 (brs, Me_2N); 2.65–2.55 (m, CH); 2.23–1.10 (m, 4CH_2); 1.93, 1.91, 1.72, 1.68, 1.65 (5s, 2Me_2C, $PhCH_2$(*Me*)C). ^{13}C NMR ((d$_5$)pyridine, 75.5 MHz): 176.8, 174.5, 173.5, 172.8 (4s, 4CO); 137.1 (s, 1 arom. C); 131.6, 128.4, 127.1 (3d, 5 arom. C); 72.3 (d, CHOH); 60.8, 57.4, 57.0 (3s, 2Me_2C, $PhCH_2$(Me)*C*); 54.4 (d, CH); 42.8, 35.9, 28.5, 25.2, 25.0 (5t, 4CH_2, Ph*C*H_2); 38.1 (q, Me_2N); 26.6, 26.4, 26.2, 25.7, 23.2 (5q, 2*Me*$_2$C, $PhCH_2$(*Me*)C). ESI-MS: 525 (100, $[M+Na]^+$), 458 (35, $[M-Me_2N]^+$), 373 (15, $[M-NHC(CH_3)_2CONMe_2]^+$).

4.6.4. (1″′*RS*,2″′*RS*,2″*RS*)-2-({2-[(2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2,*N*-dimethyl-*N*-phenylpropanamide (11d). According to GP 1, **10c** (0.173 g, 0.443 mmol) in MeCN (3 ml), **6b** (0.084 g, 0.482 mmol) in MeCN (1 ml), stirred for 44 h: 0.229 g (92%) of **11d**. White powder. Mp 211°C (dec.). IR: 3635w, 3415m, 3274s, 3062w, 2985m, 2938s, 2861m, 2360w, 1716m, 1672vs, 1639vs, 1595m, 1542vs, 1495s, 1455s, 1394s, 1364m, 1265m, 1221m, 1199m, 1131w, 1093m, 1070m, 1013w, 933w, 871w, 753w, 707s. ^{1}H NMR: 8.17 (s, NH); 7.49–7.05 (m, 2NH, 10 arom. H); 4.91 (d, *J*=4.0 Hz, OH); 3.54–3.43 (m, C*H*OH, 1H of PhCH_2); 2.94 (d, *J*=13.3 Hz, 1H of PhCH_2); 2.17–1.12 (m, CH, 4CH_2); 1.47, 1.45, 1.43, 1.28, 1.14 (5s, 2Me_2C, $PhCH_2$(*Me*)C). ^{13}C NMR: 175.5, 173.7, 173.1, 172.7 (4s, 4CO); 146.2, 137.2 (2s, 2 arom. C); 130.7, 128.5, 127.7, 126.8, 126.2, 125.8 (6d, 10 arom. C); 71.6 (d, CHOH); 58.8, 56.1 (2s, 2Me_2C, $PhCH_2$(Me)*C*); 51.7 (d, CH); 39.2 (q, MeN); 38.0, 34.8, 27.3, 24.3, 24.1 (5t, 4CH_2, Ph*C*H_2); 27.2, 25.5, 23.4, 23.2 (4q, 2*Me*$_2$C, $PhCH_2$(*Me*)C). ESI-MS: 587 (34, $[M+Na]^+$), 458 (100, $[M-Me(Ph)N]^+$), 373 (78, $[M-NHC(CH_3)_2CON(Me)Ph]^+$).

4.7. Hydrolysis of tetrapeptide amides 11

4.7.1. 2-Benzyl-2-{[2-({2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}propanoic acid (12a). According to

GP 4, **11a** (0.285 g, 0.598 mmol), 3 ml of 3N HCl (H_2O/THF 1:1), stirred for 18 h, 5 ml of brine, 5×15 ml of AcOEt: 0.224 g (83%) of **12a**. White powder. Mp 186.0–187.7°C. IR: 3302s, 2985s, 2362w, 1741vs, 1651vs, 1526vs, 1456s, 1385s, 1364s, 1299s, 1227s, 1116m, 1053m, 912w, 744m, 703m. ^{1}H NMR:[§] 7.65, 7.34, 7.31 (3s, 3NH); 7.26–7.14 (m, 5 arom. H); 5.26 (m, OH); 3.52–3.21 (m, CH_2OH); 3.26, 3.12 (AB, J=13.4 Hz, PhCH_2); 1.33, 1.27, 1.23, 1.01, 0.99 (5s, 3Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C NMR: 176.5, 174.7, 173.6, 173.5 (4s, 4CO); 136.6 (s, 1 arom. C); 130.4, 127.6, 126.2 (3d, 5 arom. C); 68.5 (t, CH$_2$OH); 58.8, 56.0, 55.8, 43.4 (4s, 3Me$_2$*C*, PhCH$_2$(Me)*C*); 40.9 (t, Ph*C*H$_2$); 25.1, 24.9, 24.7, 24.6, 21.9 (5q, 3*Me*$_2$C, PhCH$_2$(*Me*)C). ESI-MS: 472 (100, [M+Na]$^+$), 450 (78, [M+H]$^+$).

4.7.2. 2-{[2-({2-[(3-Hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methylpropanoic acid (12b). According to GP 4, **11b** (0.188 g, 0.406 mmol), 4 ml of 3N HCl (H_2O/Et_2O 1:1), stirred for 19 h, 5 ml of brine, 5×15 ml of AcOEt: 0.082 g of crude **12b**. The material was used for the next reaction step without further purification.

4.7.3. (1″′*RS*,2″′*RS*,2″*SR*)- and (1″′*RS*,2″′*RS*,2″*RS*)-2-({2-[(2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methylpropanoic acid (12d and e, respectively). Data of **12d**. According to GP 4, **11c** (0.127 g, 0.253 mmol), 2 ml of 3N HCl (H_2O/THF 1:1), stirred for 22 h, 1 ml of brine, 5×5 ml of AcOEt: 0.112 g (93%) of **12d**. White powder. Mp 193.9°C (dec.). IR: 3332vs, 2986s, 2936s, 2858m, 1721s, 1652vs, 1533vs, 1455s, 1384s, 1363m, 1305m, 1259m, 1220s, 1168s, 1059m, 1013w, 941w, 743w, 701m, 614m. ^{1}H NMR ((d$_5$)pyridine, 300 MHz): 8.79, 8.25, 7.85 (3s, 3NH); 7.60–7.30 (m, 5 arom. H); 4.18 (m, C*H*OH); 3.75, 3.46 (AB, J=13.2 Hz, PhCH_2); 2.58 (m, CH); 2.16–1.11 (m, 4CH$_2$); 2.05, 2.04, 1.79, 1.79, 1.68 (5s, 2Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C NMR ((d$_5$)pyridine, 75.5 MHz): 177.7, 176.7, 174.8, 173.3 (4s, 4CO); 137.3 (s, 1 arom. C); 131.7, 128.4, 127.0 (3d, 5 arom. C); 72.0 (d, CHOH); 60.8, 57.3, 56.6 (3s, 2Me$_2$*C*, PhCH$_2$(Me)*C*); 54.4 (d, CH); 42.5 (t, Ph*C*H$_2$); 35.9, 28.6, 25.3, 25.0 (4t, 4CH$_2$); 25.9, 25.8, 23.4 (3q, 2*Me*$_2$C, PhCH$_2$(*Me*)C). ESI-MS: 498 (27, [M+Na]$^+$), 476 (100, [M+H]$^+$).

Data of **12e**. According to GP 3, **11d** (0.200 g, 0.354 mmol), 4 ml of 3N HCl (H_2O/THF 1:1), stirred for 19 h, H_2O (2 ml): 0.155 g of crude **12e**. The material was used for the next reaction step without further purification.

4.8. Reaction of 2*H*-azirin-3-amines 6 with tetrapeptides 12

4.8.1. 2-[(2-Benzyl-2-{[2-({2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-1-oxopropyl)amino]-2,*N*,*N*-trimethylpropanamide (13a). According to GP 1, **12a** (0.178 g, 0.396 mmol) in MeCN (3 ml), **6a** (0.060 g, 0.535 mmol) in MeCN (1 ml), stirred for 21 h, CC (SiO_2, CH_2Cl_2/MeOH 25:1, CH_2Cl_2/MeOH 10:1): 0.171 g (77%) of **13a**. White powder. Mp 252.7–254.9°C. IR: 3295vs, 2984m, 2935m, 2362w, 1646vs, 1533vs, 1456s, 1383s, 1363s, 1282m, 1243m, 1215m, 1173m, 1117m, 1052m, 985w, 742w, 712m, 668w, 603w. ^{1}H NMR: 7.76, 7.64, 7.62 (3s, 3NH); 7.23–7.04 (m, 1NH, 5 arom. H); 5.21 (t, J=4.5 Hz, OH); 3.58, 2.94 (AB, J=13.5 Hz, PhCH_2); 3.47–3.42, 3.20–3.15 (2m, CH_2OH); 2.88 (brs, Me$_2$N); 1.40, 1.39, 1.35, 1.333, 1.326, 1.23, 1.22, 0.91, 0.80 (9s, 4Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C NMR: 177.0, 175.1, 173.5, 173.1, 172.0 (5s, 5CO); 137.3 (s, 1 arom. C); 130.6, 127.3, 125.9 (3d, 5 arom. C); 68.3 (t, CH$_2$OH); 59.1, 56.0, 55.9, 55.6, 43.2 (5s, 4Me$_2$*C*, PhCH$_2$(Me)*C*); 37.9 (t, Ph*C*H$_2$); 37.1 (q, Me$_2$N); 26.5, 25.7, 25.6, 25.4, 24.1, 23.2, 23.1, 21.6, 21.5 (9q, 4*Me*$_2$C, PhCH$_2$(*Me*)C). ESI-MS: 584 (46, [M+Na]$^+$), 517 (100, [M−Me$_2$N]$^+$).

4.8.2. 2-Benzyl-2-[(2-{[2-({2-[(3-hydroxy-2,2-dimethyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2-methyl-1-oxopropyl)amino]-*N*,*N*-dimethylpropanamide (13b). According to GP 2, crude **12b** (0.075 g) in MeCN (3 ml), **6d** (0.065 g, 0.285 mmol) in MeCN (1 ml), stirred for 92 h, CC (SiO_2, CH_2Cl_2/MeOH 20:1, CH_2Cl_2/MeOH 10:1): 0.093 g (46% with respect to **11b**). White powder. Mp 205.6–209.2°C. IR: 3289vs, 2983m, 2934m, 1644vs, 1533vs, 1457s, 1383s, 1362s, 1269m, 1229s, 1188m, 1166m, 1091m, 1064m, 976w, 924w, 824w, 767w, 737w, 703m, 658w. ^{1}H NMR: 7.83, 7.65, 7.49, 7.34 (4s, 4NH); 7.21–7.07 (m, 5 arom. H); 5.29 (t, J=4.6 Hz, OH); 3.50 (d, J=4.5 Hz, CH_2OH); 3.26, 3.14 (AB, J=13.7 Hz, PhCH_2); 3.07, 2.80 (2brs, Me$_2$N); 1.45, 1.40, 1.34, 1.27, 1.25, 1.23, 1.08 (7s, 4Me$_2$C, PhCH$_2$(*Me*)C). ^{13}C NMR: 177.1, 175.0, 173.4, 173.3, 170.3 (5s, 5CO); 136.6 (s, 1 arom. C); 130.6, 127.6, 126.1 (3d, 5 arom. C); 68.6 (t, CH$_2$OH); 59.3, 56.3, 55.9, 43.5 (4s, 4Me$_2$*C*, PhCH$_2$(Me)*C*); 42.2 (t, Ph*C*H$_2$); 37.5 (q, Me$_2$N); 25.6, 25.3, 24.9, 24.6, 24.5, 24.3, 22.7, 21.9 (8q, 4*Me*$_2$C, PhCH$_2$(*Me*)C). ESI-MS: 584 (100, [M+Na]$^+$).

4.8.3. (*R*)-1-(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-*N*,*N*-dimethylcyclopentanecarboxamide (13c). According to GP 2, (*R*)-Tro–Aib–Aib–Aib–OH (**12c**)[¶] (0.151 g, 0.358 mmol) in MeCN (3 ml), **6c** (0.079 g, 0.572 mmol) in MeCN (1 ml), stirred for 19 h, CC (SiO_2, CH_2Cl_2/MeOH 20:1, CH_2Cl_2/MeOH 10:1) and crystallization from AcOEt: 0.175 g (87%) of **13c**. White powder. Mp 245.6°C (dec.). $[\alpha]_D$=+25.0 (c=1.0, EtOH). IR: 3312vs, 2942s, 2874m, 1652vs, 1527vs, 1456s, 1384s, 1362s, 1272m, 1230s, 1169m, 1056m, 1012m, 923w, 743w, 701m, 668m. ^{1}H NMR: 8.75, 7.48, 7.40 (3s, 3NH); 7.37–7.22 (m, 1NH, 5 arom. H); 5.11 (t, J=4.3 Hz, OH); 3.98–3.90, 3.81–3.76, 3.67–3.61 (3m, CH_2OH, CH); 2.98, 2.75 (2brs, Me$_2$N); 2.07–2.06, 1.68–1.64, 1.57–1.49 (3m, (CH$_2$)$_4$); 1.38, 1.37, 1.36, 1.31, 1.24, 1.13 (6s, 3Me$_2$C). ^{13}C NMR: 174.8, 173.2, 172.9, 171.9 (4s, 5CO); 137.1 (s, 1 arom. C); 128.2, 127.9, 126.9 (3d, 5 arom. C); 65.5, 55.9, 55.8 (3s, 3Me$_2$*C*, (CH$_2$)$_4$*C*); 63.8 (t, CH$_2$OH); 53.5 (d, CH); 37.3, 36.6 (2q, Me$_2$N); 35.8, 24.0 (2t, (CH$_2$)$_4$); 25.9, 25.13, 25.06, 24.5, 23.8, 23.6 (6q, 3*Me*$_2$C). ESI-MS: 582 (100, [M+Na]$^+$).

[¶] The tetrapeptide **12c** was prepared as previously described[25] starting with (*R*)-**5b**.[45]

4.8.4. (*R*,*S*)- and (*R*,*R*)-2-Benzyl-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]-*N*,*N*-dimethylpropanamide (13d/13e). According to GP 2, (*R*)-Tro–Aib–Aib–Aib–OH (**12c**)[¶] (0.151 g, 0.358 mmol) in MeCN (3 ml), **6d** (0.100 g, 0.473 mmol) in MeCN (1 ml), stirred for 18 h, CC (SiO_2, CH_2Cl_2/MeOH 25:1, CH_2Cl_2/MeOH 10:1) and crystallization from MeCN/AcOEt: 0.178 g (82%) of **13d/13e**. The diastereoisomers were separated by means of HPLC. Conditions: stationary phase: SPHERISORB ODS2 5.0 μm, column: 250×20 mm, mobile phase: 5 ml/min, MeOH/H_2O 2:1, 43 kg/cm^2; UV detector, 254 nm.

Data of **13d**. White powder. Mp 242.9–243.5°C. $[\alpha]_D$=+6.3 (*c*=1.0, EtOH). IR: 3399s, 3354s, 3308vs, 3029w, 2985m, 2938m, 1685vs, 1636vs, 1617vs, 1534vs, 1456s, 1382s, 1363m, 1278m, 1233s, 1180m, 1093m, 1056s, 1018m, 924w, 740w, 701s, 660m. ^{1}H NMR: 8.77, 7.51 (2s, 2NH); 7.41–7.08 (m, 2NH, 10 arom. H); 5.15 (brs, OH); 3.99–3.93, 3.82–3.77, 3.68–3.63 (m, C*H*$_2$OH, CH); 3.29, 3.11 (AB, *J*=13.6 Hz, PhC*H*$_2$); 3.08, 2.82 (2brs, Me_2N); 1.47, 1.41, 1.30, 1.29, 1.26, 1.21, 1.15 (7s, 3Me_2C, PhCH_2(*Me*)C). ^{13}C NMR: 174.6, 173.4, 173.1, 172.8, 170.3 (5s, 5CO); 137.2, 136.6 (2s, 2 arom. C); 130.6, 128.2, 127.9, 127.6, 126.9, 126.1 (6d, 10 arom. C); 63.8 (t, CH_2OH); 59.4, 56.3, 55.9 (3s, 3Me_2*C*, PhCH_2(Me)*C*); 53.5 (d, CH); 42.3 (t, PhCH_2); 37.4 (q, Me_2N); 25.9, 25.1, 24.9, 24.0, 23.8, 22.8 (6q, 3*Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 632 (41, [M+Na]$^+$), 565 (100, [M−Me_2N]$^+$).

Data of **13e**. White powder. Mp 240.1°C (dec.). $[\alpha]_D$=−22.2 (*c*=0.5, EtOH). IR: 3370s, 3304vs, 3029m, 2983s, 2938m, 1691vs, 1638vs, 1532vs, 1454s, 1436s, 1382s, 1363s, 1269m, 1236s, 1178m, 1090m, 1055s, 1008m, 923w, 818w, 762w, 739m, 704s, 644m. ^{1}H NMR: 8.73 (s, NH); 7.42–7.05 (m, 3NH, 10 arom. H); 5.13 (t, *J*=4.3 Hz, OH); 3.95–3.90, 3.82–3.77, 3.68–3.63 (3m, C*H*$_2$OH, CH); 3.22–3.17 (m, PhC*H*$_2$); 3.07, 2.80 (2brs, Me_2N); 1.46, 1.42, 1.32, 1.25, 1.24, 1.19, 1.15 (7s, 3Me_2C, PhCH_2(*Me*)C). ^{13}C NMR: 174.6, 173.4, 173.1, 172.7, 170.4 (5s, 5CO); 137.1, 136.6 (2s, 2 arom. C); 130.6, 128.2, 127.9, 127.6, 126.9, 126.0 (6d, 10 arom. C); 63.8 (t, CH_2OH); 59.3, 56.2, 55.8 (3s, 3Me_2*C*, PhCH_2(Me)*C*); 53.4 (d, CH); 42.1 (t, PhCH_2); 37.4 (q, Me_2N); 26.3, 25.5, 25.3, 24.5, 23.6, 23.4, 22.7 (7q, 3*Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 632 (100, [M+Na]$^+$).

4.8.5. (1‴*RS*,2‴*RS*,2″′*SR*)- and (1‴*RS*,2‴*RS*,2″′*RS*)-2-{[2-({2-[(2-Benzyl-2-{[*trans*-(2-hydroxycyclohexyl)carbonyl]amino}-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-2,*N*,*N*-trimethylpropanamide (13f and 13g, respectively). Data of **13f**. According to GP 1, **12d** (0.104 g, 0.219 mmol) in MeCN (2 ml), **6a** (0.030 g, 0.267 mmol) in MeCN (1 ml), stirred for 42 h: 0.091 g (71%) of **13f**. White powder. Mp 275.7°C (dec.). IR: 3308vs, 2986m, 2936s, 2858m, 1660vs, 1621vs, 1537vs, 1456s, 1383s, 1364s, 1304m, 1216s, 1170m, 1121m, 1074m, 967w, 947w, 867w, 826w, 742w, 704m, 678m. ^{1}H NMR ((d$_5$)pyridine, 300 MHz): 9.06, 8.28, 8.12, 8.04 (4s, 4NH); 7.56–7.27 (m, 5 arom. H); 4.15 (m, C*H*OH); 3.72, 3.46 (AB, *J*=13.4 Hz, PhC*H*$_2$); 3.31, 3.01 (2brs, Me_2N); 2.72–2.61 (m, CH); 2.24–1.06 (m, 4CH_2); 1.91, 1.89, 1.86, 1.67, 1.653, 1.649 (6s, 3Me_2C, PhCH_2(*Me*)C). ^{13}C NMR ((d$_5$)pyridine, 75.5 MHz): 177.0, 175.1, 175.1, 174.4, 173.8 (5s, 5CO); 137.0 (s, 1 arom. C); 131.7, 128.4, 127.1 (3d, 5 arom. C); 72.2 (d, CHOH); 60.4, 57.5, 57.4, 56.9 (4s, 3Me_2*C*, PhCH_2(Me)*C*); 54.3 (d, CH); 42.1 (t, PhCH_2); 38.0 (q, Me_2N); 35.8, 28.5, 25.2, 25.0 (4t, 4CH_2); 26.42, 26.36, 25.9, 25.6, 23.0 (5q, 3*Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 610 (100, [M+Na]$^+$).

Data of **13g**. According to GP 2, crude **12e** (0.120 g) in MeCN (4 ml), **6a** (0.031 g, 0.276 mmol) in MeCN (1 ml), stirred for 20 h, CC (SiO_2, CH_2Cl_2/MeOH 15:1): 0.125 g of crude **13g**. 0.097 g of the crude **13g** was purified by means of preparative HPLC. Conditions: stationary phase: SPERISORB ODS2 5.0 μm, column: 250×20 mm, mobile phase: 20 ml/min, H_2O/MeOH 1:2; UV detector, 254 nm: Total yield of **13g**: 0.068 g (42% with respect to **11d**). White powder. Mp 290.5°C (dec.). IR: 3305vs, 2986m, 2936s, 2861m, 2362w, 1647vs, 1527vs, 1456s, 1383s, 1363m, 1284m, 1217s, 1170m, 1120m, 1072m, 1017w, 928w, 867w, 754w, 707m, 602w. ^{1}H NMR ((d$_5$)pyridine, 300 MHz): 9.37, 8.26, 8.09, 8.03 (4s, 4NH); 7.41–7.38 (m, 5 arom. H); 6.71 (s, OH); 4.12–4.08 (m, C*H*OH, 1H of PhC*H*$_2$); 3.46 (d, *J*=13.3 Hz, 1H of PhC*H*$_2$); 3.20 (brs, Me_2N); 2.49–2.43 (m, CH); 2.21–0.97 (m, 4CH_2); 1.99, 1.94, 1.92, 1.89, 1.78, 1.59, 1.47 (7s, 3Me_2C, PhCH_2(*Me*)C). ^{13}C NMR ((d$_5$)pyridine, 75.5 MHz): 176.8, 176.1, 174.9, 174.3, 173.5 (5s, 5CO); 138.2 (s, 1 arom. C); 131.7, 128.5, 127.0 (3d, 5 arom. C); 72.8 (d, CHOH); 59.9, 57.5, 57.4, 57.0 (4s, 3Me_2*C*, PhCH_2(Me)*C*); 53.1 (d, CH); 40.0 (q, Me_2N); 39.0 (t, PhCH_2); 35.9, 27.9, 25.0, 24.8 (4t, 4CH_2); 28.7, 27.6, 26.6, 26.5, 24.0, 23.8, 23.4 (7q, 3*Me*$_2$C, PhCH_2(*Me*)C). ESI-MS: 610 (100, [M+Na]$^+$), 543 (16, [M−Me_2N]$^+$). Anal. calcd for $C_{31}H_{49}N_5O_6$·H_2O (605.75): C 61.47, H 8.49, N 11.56; found: C 61.28, H 8.45, N 11.41.

4.9. Cyclization of pentapeptides 13 to cyclic depsipeptides 14

General procedure 5 (GP 5). A stirred suspension of **13** in dry toluene (30 ml) was warmed to 100°C under N_2. A stream of dry HCl gas was slowly passed through the suspension at 100°C for 7–15 min. The resulting solution was then purged with N_2 for 30 min to remove remaining HCl, the toluene was evaporated, and 6 ml THF/Et_2O 1:1 were added. After 30 min of stirring at rt, the suspension was filtered, followed by evaporation of the solvent yielding a solid crude product, which was purified by CC.

4.9.1. 6-Benzyl-3,3,6,9,9,12,12,15,15-nonamethyl-1-oxa-4,7,10,13-tetraazacyclohexadecane-2,5,8,11,14-pentone (14a). According to GP 5, **13a** (0.050 g, 0.089 mmol) in toluene (30 ml), 10 min, CC (SiO_2, CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.009 g (20%) of **14a**.[**] White powder. Mp 170.5°C (dec.). IR: 3396s, 2984m, 2939m, 2362w, 1734s, 1662vs, 1522vs, 1456m, 1384m, 1365m, 1281s, 1159s, 1022w, 945w, 768w, 710m. ^{1}H NMR ((d$_5$)pyridine, 600 MHz): 8.21 (s, NH, Aib(1)); 7.75

[**] As a second product, 0.011 g of a white powder was isolated, which was identified as the cyclodimer **15a** (24%) by ESI-MS: 1055 (19, [M+Na]$^+$), 539 (100, [M+2Na]$^{2+}$).

(s, NH, Aib(3)); 7.63 (s, NH, Aib(2)); 7.52–7.51 (m, 2 arom. H); 7.32–7.30 (m, 2 arom. H); 7.26–7.24 (m, 1 arom. H); 7.22 (s, NH, Phe(2Me)); 4.48, 4.30 (AB, J=10.4 Hz, CH_2O); 4.13, 3.53 (AB, J=13.5 Hz, PhCH_2); 2.01 (s, Me(a), Aib(3)); 2.01 (s, Me(b), Aib(3)); 1.84 (s, PhCH$_2$(*Me*)C); 1.59 (s, 2Me, Aib(1)); 1.56 (s, Me(a), Aib(2)); 1.55 (s, Me(b), Aib(2)); 1.33 (s, Me(a), Dhp); 1.33 (s, Me(b), Dhp). ^{13}C NMR ((d$_5$)pyridine, 151 MHz): 176.1 (s, CO, Dhp); 175.8 (s, CO, Aib(1)); 174.7 (s, CO, Aib(3)); 174.6 (s, CO, Phe(2Me)); 174.2 (s, CO, Aib(2)); 138.3 (s, 1 arom. C); 131.7, 128.2, 126.8 (3d, 5 arom. C); 72.2 (t, CH_2O); 61.5 (s, PheCH$_2$(Me)*C*); 58.4 (s, Me$_2$*C*, Aib(3)); 57.8 (s, Me$_2$*C*, Aib(2)); 56.9 (s, Me$_2$*C*, Aib(1)); 42.7 (s, Me$_2$*C*, Dhp); 41.8 (t, Ph*C*H$_2$); 25.5 (q, Me(a), Aib(2)); 25.4 (q, Me(a), Aib(1)); 25.4 (q, Me(a), Aib(3)); 25.2 (q, Me(b), Aib(2)); 25.1 (q, Me(b), Aib(3)); 25.0 (q, Me(b), Aib(1)); 23.0 (q, PhCH$_2$(*Me*)C); 22.7 (q, 2Me, Dhp). ESI-MS: 539 (100, [M+Na]$^+$).

4.9.2. 3-Benzyl-3,6,6,9,9,12,12,15,15-nonamethyl-1-oxa-4,7,10,13-tetraazacyclohexadecane-2,5,8,11,14-pentone (14b). According to GP 5, **13b** (0.050 g, 0.089 mmol) in toluene (30 ml), 11 min, CC (SiO_2, CH_2Cl_2/MeOH 25:1): 0.004 g (9%) of **14b**. Foam. IR: ($CHCl_3$): 3454w, 3397w, 3010m, 2967w, 1738m, 1670vs, 1503s, 1457w, 1385m, 1366m, 1262s, 1238m, 1199w, 1169w, 1101m, 1015m. ^{1}H NMR ((d$_5$)pyridine, 600 MHz): 8.33 (s, NH, Aib(1)); 7.77 (s, NH, Aib(2)); 7.48–7.42 (m, NH of Aib(3), NH of Phe(2Me), 2 arom. H); 7.35–7.30, 7.26–7.22 (m, 3 arom. H); 4.69, 3.80 (AB, J=10 Hz, CH_2O); 4.33, 3.51 (AB, J=13 Hz, PhCH_2); 2.06 (s, PhCH$_2$(*Me*)C); 1.91 (s, Me(a), Aib(3)); 1.82 (s, Me(b), Aib(3)); 1.77 (s, Me(a), Aib(1)); 1.66 (s, Me(a), Aib(2)); 1.54 (s, Me(b), Aib(2)); 1.42 (s, Me(b), Aib(1)); 1.27 (s, Me(a), Dhp); 1.03 (s, Me(b), Dhp). ^{13}C NMR ((d$_5$)pyridine, 151 MHz): 176.1 (s, CO, Dhp); 175.6 (s, CO, Aib(1)); 175.2 (s, CO, Aib(3)); 174.2 (s, CO, Aib(2)); 173.3 (s, CO, Phe(2Me)); 137.9 (s, 1 arom. C); 130.9, 128.3, 126.9 (3d, 5 arom. C); 72.1 (t, CH_2O); 63.0 (s, PhCH$_2$(Me)*C*); 57.9 (s, Me$_2$*C*, Aib(3)); 57.4 (s, Me$_2$*C*, Aib(2)); 56.8 (s, Me$_2$*C*, Aib(1)); 42.8 (t, Ph*C*H$_2$); 42.3 (s, Me$_2$*C*, Dhp); 27.1 (q, Me(b), Aib(3)); 26.6 (q, Me(b), Aib(2)); 26.1 (q, Me(b), Aib(1)); 24.4 (q, Me(a), Aib(1), Me(a), Aib(3)); 23.9 (q, Me(a), Aib(2)); 23.2 (q, PhCH$_2$(*Me*)C); 22.5 (q, Me(a), Dhp); 22.4 (q, Me(b), Dhp). ESI-MS: 517 (100, [M+H]$^+$).

4.9.3. (15*R*)-6,6,9,9,12,12-Hexamethyl-15-phenyl-3,3-tetramethylen-1-oxa-4,7,10,13-tetraazacyclohexadecane-2,5,8,11,14-pentone (14c). According to GP 5, **13c** (0.050 g, 0.089 mmol) in toluene (30 ml), 15 min, CC (SiO_2, CH_2Cl_2/MeOH 30:1) and crystallization from Et$_2$O: 0.014 g (30%) of **14c**.[††] White powder. Mp 279.3°C (dec.). $[\alpha]_D$=+14.0 (c=0.4, EtOH). IR: 3361s, 2981m, 2874w, 1715s, 1669vs, 1533vs, 1473m, 1378m, 1366m, 1271s, 1233s, 1183s, 1076w, 1021w, 748m, 700m. ^{1}H NMR ((d$_5$)pyridine, 600 MHz): 9.55 (s, NH, Aib(1)); 8.14 (s, NH, Aib(2)); 8.11 (s, NH, Ac$_5$c); 7.52–7.51 (m, 2 arom. H); 7.35–7.33 (m, NH of Aib(3), 2 arom. H); 7.30–7.28 (m, 1 arom. H); 4.94–4.93, 4.40–4.36 (2m, CH_2O); 4.26–4.23 (m, CH); 2.90–2.87, 2.40–2.35, 1.90–1.67 (3m, (CH$_2$)$_4$); 2.07 (s, Me(a), Aib(3)); 1.95 (s, Me(b), Aib(3)); 1.80 (s, Me(a), Aib(2)); 1.79 (s, Me(a), Aib(1)); 1.58 (s, Me(b), Aib(2)); 1.46 (s, Me(b), Aib(1)). ^{13}C NMR ((d$_5$)pyridine, 151 MHz): 176.8 (s, CO, Aib(3)); 176.3 (s, CO, Aib(1)); 174.3 (s, CO, Ac$_5$c); 174.1 (s, CO, Aib(2)); 171.8 (s, CO, Tro); 136.4 (s, 1 arom. C); 129.2, 128.4, 128.1 (3d, 5 arom. C); 67.9 (s, (CH$_2$)$_4$*C*); 65.3 (t, CH_2O); 58.8 (s, Me$_2$*C*, Aib(3)); 58.2 (s, Me$_2$*C*, Aib(2)); 56.9 (s, Me$_2$*C*, Aib(1)); 51.4 (d, CH); 39.2, 35.0, 25.0, 24.46 (4t, (CH$_2$)$_4$); 28.6 (q, Me(b), Aib(3)); 27.4 (q, Me(b), Aib(2)); 26.7 (q, Me(b), Aib(1)); 24.48 (q, Me(a), Aib(3)); 23.3 (q, Me(a), Aib(2)); 23.1 (q, Me(a), Aib(1)). ESI-MS: 537 (100, [M+Na]$^+$). Anal. calcd for $C_{27}H_{38}N_4O_6$ (514.61): C 63.02, H 7.44, N 10.89; found: C 62.98, H 7.61, N 10.88.

4.9.4. (3*R*,15*R*- and 3*S*,15*R*)-3-Benzyl-3,6,6,9,9,12,12-heptamethyl-15-phenyl-1-oxa-4,7,10,13-tetraazacyclohexadecane-2,5,8,11,14-pentone (14d/14e). Data of **14d** (isomer 1). According to GP 5, **13d** (0.050 g, 0.082 mmol) in toluene (30 ml), 15 min, CC (SiO_2, CH_2Cl_2/MeOH 30:1) and crystallization from Et$_2$O: 0.027 g (58%) of **14d**.[‡‡] Mp 235.2°C (dec.). $[\alpha]_D$=−1.0 (c=0.5, EtOH). IR (KBr): 3343s, 2984m, 2938m, 1749s, 1661vs, 1521vs, 1456s, 1382m, 1364m, 1275s, 1230s, 1116m, 1043w, 741w, 702s, 600w. ^{1}H NMR ((d$_5$)pyridine, 500 MHz): 9.68 (s, NH, Aib(1)); 8.16 (s, NH, Aib(2)); 8.07 (s, NH, Phe(2Me)); 7.63–7.61 (m, 2 arom. H of Phe(2Me)); 7.55–7.54 (m, 2 arom. H of Tro); 7.49 (s, NH, Aib(3)); 7.38–7.34 (m, 2 arom. H of Phe(2Me), 2 arom. H of Tro); 7.32–7.26 (m, 1 arom. H of Phe(2Me), 1 arom. H of Tro); 4.93–4.90, 4.51–4.46 (2m, CH_2O); 4.37–4.33 (m, CH); 3.91, 3.70 (AB, J=13.3 Hz, PhCH_2); 2.00 (s, Me(a), Aib(3)); 1.97 (s, PhCH$_2$(*Me*)C); 1.95 (s, Me(b), Aib(3)); 1.89 (s, Me(a), Aib(2)); 1.78 (s, Me(a), Aib(1)); 1.61 (s, Me(b), Aib(2)); 1.44 (s, Me(b), Aib(1)). ^{13}C NMR: 176.8 (s, CO, Aib(3)); 176.1 (s, CO, Aib(1)); 174.3 (s, CO, Aib(2)); 173.4 (s, CO, Phe(2Me)); 171.9 (s, CO, Tro)); 137.0 (s, 1 arom. C, Phe(2Me)); 136.5 (s, 1 arom. C, Tro); 131.5 (d, 2 arom. C of Phe(2Me)); 129.3, 128.5 (2d, 2 arom. C of Phe(2Me), 2 arom. C of Tro); 128.1 (d, 1 arom. C of Tro); 127.1 (d, 1 arom. C of Phe(2Me)); 65.8 (t, CH_2O); 62.2 (s, PhCH$_2$(Me)*C*); 58.8 (s, Me$_2$*C*, Aib(3)); 58.2 (s, Me$_2$*C*, Aib(2)); 57.0 (s, Me$_2$*C*, Aib(1)); 51.3 (d, CH); 44.4 (t, Ph*C*H$_2$); 28.2 (q, Me(b), Aib(3)); 27.4 (q, Me(b), Aib(2)); 26.6 (q, Me(b), Aib(1)); 24.5 (q, Me(a), Aib(3)); 23.2 (q, Me(a), Aib(1)); 23.2 (q, Me(a), Aib(2)); 20.8 (q, PhCH$_2$(*Me*)C). ESI-MS: 587 (100, [M+Na]$^+$). Anal. calcd for $C_{31}H_{40}N_4O_6$ (564.67): C 65.94, H 7.14, N 9.92; found: C 65.43, H 7.56, N 9.42.

Data of **14e** (isomer 2). According to GP 5, **13e** (0.051 g, 0.084 mmol) in toluene (30 ml), 14 min, CC (SiO_2, CH_2Cl_2/MeOH 30:1) and crystallization from Et$_2$O: 0.027 (57%) of **14e**.[§§] White powder. Mp 241.6°C (dec.). $[\alpha]$=+4.4 (c=0.5, EtOH). IR: 3639w, 3416s, 3370s, 3325s, 3062w,

[††] As a second product, 0.010 g of a white powder was isolated, which was identified as the cyclodimer **15c** (20%) by ESI-MS: 1051 (32, [M+Na]$^+$), 537 (100, [M+2Na]$^{2+}$).

[‡‡] As a second fraction, 0.004 g of a material containing cyclodimer **15d** among other non-identified products was obtained. **15d** was identified by ESI-MS: 1151 (34, [M+Na]$^+$), 587 (100, [M+2Na]$^{2+}$).

[§§] As a second product, 0.010 g of a white powder was isolated, which was identified as the cyclodimer **15e** (21%) by ESI-MS: 1151 (37, [M+Na]$^+$), 587 (100, [M+2Na]$^{2+}$).

3029w, 2983m, 2938m, 1747vs, 1663vs, 1604w, 1542vs, 1497vs, 1455s, 1384s, 1365s, 1325m, 1280vs, 1218vs, 1170s, 1119s, 1074w, 1044w, 1027w, 974w, 933w, 770w, 743m, 704s. ^{1}H NMR ((d$_5$)pyridine, 600 MHz): 9.82 (s, NH, Aib(1)); 8.38 (s, NH, Aib(3)); 8.30 (s, NH, Phe(2Me)); 7.83–7.82 (m, 2 arom. H of Phe(2Me)); 7.60–7.58 (m, 2 arom. H of Tro); 7.46–7.41 (m, 2 arom. H of Phe(2Me), 2 arom. H of Tro); 7.39–7.36 (m, 1 arom. H of Tro); 7.35 (s, NH, Aib(2)); 7.29–7.26 (m, 1 arom. H of Phe(2Me)); 4.88–4.86, 4.71–4.67 (2m, CH_2O); 4.47–4.45 (m, CH); 4.27, 3.75 (AB, J=13.9 Hz, PhCH_2); 2.13 (s, Me(a), Aib(3)); 2.01 (s, Me(b), Aib(3)); 1.72 (s, Me(a), Aib(2)); 1.65 (s, Me(a), Aib(1)); 1.65 (s, PhCH$_2$(*Me*)C); 1.35 (s, Me(b), Aib(1)); 1.13 (s, Me(b), Aib(2)). ^{13}C NMR ((d$_5$)pyridine, 151 MHz): 176.3 (s, CO, Phe(2Me)); 176.3 (s, CO, Aib(3)); 174.6 (s, CO, Aib(1)); 173.8 (s, CO, Aib(2)); 172.2 (s, CO, Tro); 138.0 (s, 1 arom. C, Phe(2Me)); 136.4 (s, 1 arom. C, Tro); 132.3 (d, 2 arom. C of Phe(2Me)); 129.6, 128.4 (2d, 2 arom. C of Phe(2Me), 2 arom. C of Tro)); 128.5 (d, 1 arom. C of Tro); 128.2 (d, 2 arom. C of Tro); 126.5 (d, 1 arom. C of Phe(2Me)); 66.6 (t, CH_2O); 59.8 (s, PhCH$_2$(Me)*C*); 57.6 (s, Me$_2$*C*, Aib(3)); 57.2 (s, Me$_2$*C*, Aib(1)); 57.1 (s, Me$_2$*C*, Aib(2)); 51.3 (d, CH); 41.0 (t, Ph*C*H$_2$); 28.5 (q, Me(b), Aib(3)); 27.3 (q, Me(b), Aib(2)); 25.8 (q, Me(b), Aib(1)); 24.2 (q, Me(a), Aib(1)); 23.6 (q, Me(a), Aib(2)); 23.3 (q, Me(a), Aib(3)); 23.2 (q, PhCH$_2$(*Me*)C). ESI-MS: 587 (100, [M+Na]$^+$). Anal. calcd for $C_{31}H_{40}N_4O_6$ (564.67): C 65.94, H 7.14, N 9.92; found: C 65.49, H 7.39, N 9.49.

4.9.5. (12*RS*,15*SR*,16*SR*)- and (12*RS*,15*RS*,16*RS*)-12-Benzyl-3,3,6,6,9,9,12-heptamethyl-15,16-tetramethylen-1-oxa-4,7,10,14-tetraazacyclohexadecane-2,5,8,11,14-pentone (14f and g, respectively). Data of **14f**. According to GP 5, **13f** (0.050 g, 0.085 mmol) in toluene (30 ml), 7 min, CC (SiO_2, CH_2Cl_2/MeOH 30:1) and crystallization from Et_2O: 0.023 g (50%) of **14f**.[||||] White powder. Mp 325.7°C (dec.). IR: 3400m, 3339m, 2983w, 2938m, 2863w, 2361w, 1748m, 1729m, 1664vs, 1538s, 1456m, 1382m, 1364w, 1276m, 1231m, 1163m, 1042w, 914w, 767w, 701w, 668w, 602w. ^{1}H NMR ((d$_5$)pyridine, 600 MHz): 8.62 (s, NH, Phe(2Me)); 7.98 (s, NH, Aib(1)); 7.71 (s, NH, Aib(3)); 7.53 (s, NH, Aib(2)); 7.40–7.34 (m, 3 arom. H); 7.25–7.24 (m, 2 arom. H); 5.35 (dt, J=11.0, 4.4 Hz, CHO); 4.21, 3.27 (AB, J=12.1 Hz, PhCH_2); 2.75 (m, CH(CO)); 2.18–2.11, 1.67–1.60, 1.47–1.42, 1.23–1.17, 1.14–1.06, 0.91–0.85 (6m, 4CH$_2$); 2.16 (s, Me(b), Aib(3)); 2.03 (s, Me(a), Aib(3)); 1.95 (s, Me(b), Aib(2)); 1.93 (s, Me(a), Aib(2)); 1.76 (s, Me(b), Aib(1)); 1.55 (s, Me(a), Aib(1)); 1.20 (s, PhCH$_2$(*Me*)C). ^{13}C NMR ((d$_5$)pyridine, 151 MHz): 175.9 (s, CO, Phe(2Me)); 174.5 (s, CO, Aib(2)); 174.4 (s, CO, Aib(3)); 174.2 (s, CO, Hcc); 173.7 (s, CO, Aib(1)); 137.4 (s, 1 arom. C); 131.6, 128.3, 127.0 (3d, 5 arom. C); 75.1 (d, CHO); 59.6 (s, PhCH$_2$(Me)*C*); 58.9 (s, Me$_2$*C*, Aib(3)); 57.9 (s, Me$_2$*C*, Aib(2)); 57.6 (s, Me$_2$*C*, Aib(1)); 53.3 (d, CH(CO)); 38.9 (t, Ph*C*H$_2$); 31.5, 28.0, 25.0, 24.0 (4t, 4CH$_2$); 28.2 (q, Me(a), Aib(2)); 27.3 (q, Me(a), Aib(1)); 25.3 (q, Me(b), Aib(3)); 24.6 (q, Me(a), Aib(3)); 23.5 (q, Me(b), Aib(2)); 23.4 (q, Me(b), Aib(1)); 23.2 (q, PhCH$_2$(*Me*)C). ESI-MS: 565 (18, [M+Na]$^+$), 543 (100, [M+H]$^+$). Anal. calcd for $C_{29}H_{42}N_4O_6$ (542.66): C 64.19, H 7.80, N 10.32; found: C 64.04, H 8.03, N 10.15.

Data of **14g**. According to GP 5, **13g** (0.050 g, 0.085 mmol) in toluene (30 ml), 11 min, CC (SiO_2, CH_2Cl_2/MeOH 30:1) and crystallization from Et_2O: 0.013 g (28%) of **14g**.[¶¶] White powder. Mp 272.3°C (dec.). IR: 3392s, 2984m, 2939s, 2861w, 1728s, 1664vs, 1531vs, 1455s, 1382s, 1363m, 1282s, 1231m, 1167s, 1125m, 1037w, 914w, 866w, 769w, 741w, 702m. ^{1}H NMR ((d$_5$)pyridine, 500 MHz): 8.64 (s, NH, Phe(2Me)); 7.81 (s, NH, Aib(1)); 7.64 (s, NH, Aib(3)); 7.53 (s, NH, Aib(2)); 7.34–7.27 (m, 3 arom. H); 7.26–7.24 (m, 2 arom. H); 5.35 (dt, J=11.0, 4.3 Hz, CHO); 3.45 (d, J=12.6 Hz, 1H of PhCH_2); 3.21 (d, J=11.7 Hz, 1H of PhCH_2); 2.69 (m, CH(CO)); 2.26–2.21, 2.11–2.04, 1.86–1.78, 1.53–1.47, 1.27–1.17, 1.06–0.99 (6m, 4CH$_2$); 2.11 (s, Me(a), Aib(3)); 2.08 (s, Me(b), Aib(3)); 1.92 (s, 2Me, Aib(2); 1.82 (s, PhCH$_2$(*Me*)C); 1.66 (s, Me(a), Aib(1)); 1.40 (s, Me(b), Aib(1)). ^{13}C NMR ((d$_5$)pyridine, 126 MHz): 174.7 (s, CO, Phe(2Me)); 174.6 (s, CO, Aib(2)); 174.4 (s, CO, Aib(3)); 174.1 (s, CO, Hcc); 173.9 (s, CO, Aib(1)); 135.8 (s, 1 arom. C); 131.6, 128.5, 127.5 (3d, 5 arom. C); 75.4 (d, CHO); 60.5 (s, PhCH$_2$(Me)*C*); 58.9 (s, Me$_2$*C*, Aib(3)); 58.2 (s, Me$_2$*C*, Aib(2)); 57.9 (s, Me$_2$*C*, Aib(1)); 53.0 (d, CH(CO)); 44.2 (t, Ph*C*H$_2$); 31.5, 29.2, 25.2, 24.2 (4t, 4CH$_2$); 26.8 (q, Me(b), Aib(1)); 25.3 (q, Me(a), Aib(3)); 25.2 (q, Me(b), Aib(3)); 24.5 (q, Me(a), Aib(1)); 21.4 (q, PhCH$_2$(*Me*)C); 27.2 (q, Me(a), Aib(2)); 24.5 (q, Me(b), Aib(2)). ESI-MS: 565 (47, [M+Na]$^+$), 543 (100, [M+H]$^+$).

4.10. Crystal structure determination of 13f and h

See Figs. 1 and 2.[46] The intensities were collected on a Rigaku AFC5R diffractometer using graphite-monochromated MoK$_\alpha$ radiation and a 12 kW rotating anode generator. The intensities were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods using SIR92,[47] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amide and hydroxy H-atoms 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 were fixed in geometrically calculated positions [d(C–H)=0.95 ?] and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent atom. Refinement of the structure was carried out on F using full-matrix least-squares procedures, which minimized the function $\sum w(|F_o|-|F_c|)^2$. A correction for secondary extinction was applied in both cases. Neutral atom scattering factors for non-H-atoms were taken from Ref. 48a, and scattering factors for H-atoms were taken from Ref. 49. Anomalous dispersion effects were included in F_c;[50] the values for f' and f'' were those of Ref. 48b. The values of the mass attenuation coefficients were taken from Ref. 48c. All calculations were performed using the teXsan crystallographic software package.[51]

[||||] As a second product, 0.002 g of a white powder was isolated, which was identified as the cyclodimer **15f** (2%) by ESI-MS: 1107 (100, [M+Na]$^+$).

[¶¶] As a second product, 0.005 g of a white powder was isolated, which was identified as the cyclodimer **15g** (11%) by ESI-MS: 1107 (100, [M+Na]$^+$).

4.10.1. Crystal data for 13f. A crystal of dimension 0.40×0.45×0.48 mm^3 was grown from H_2O/MeOH/$CHCl_3$. $C_{31}H_{49}N_5O_6$, M_r=587.76, monoclinic, space group $P2_1/n$, a=14.978(4), b=12.363(3), c=18.507(3) Å, β=108.19(1)°, V=3256(1) $Å^3$, Z=4, D_x=1.199 g/cm^3, μ (MoK_α)=0.0835 mm^{-1}; T=193(1) K, λ=0.71069 Å. Cell dimension from 25 reflections in the range 2θ=39–40°, $\omega/2\theta$ scans, $2\theta_{(max)}$=50°, 6259 reflections measured, 5724 symmetry-independent reflections, 4001 reflections with $I>2\sigma(I)$ used in the refinement of 400 parameters. Final R=0.0462, wR=0.0403 ($w=[\sigma^2(F_o)+(0.005F_o)^2]^{-1}$), GoF=2.177, Δ_{max}/σ=0.0002, $\Delta\rho$ (max; min)=0.27; −0.19e $Å^{-3}$.

4.10.2. Crystal data for 13h. A crystal of dimension 0.32×0.33×0.50 mm^3 was grown from H_2O/MeOH. $C_{29}H_{47}N_5O_6$, M_r=561.72, Triclinic, space group $P\bar{1}$, a=11.2403(9), b=14.127(2), c=10.155(2) ÅÅ, α=90.86(1), β=102.374(9), γ=89.865(8)°, V=1574.8(3) $Å^3$, Z=2, D_x=1.185 g/cm^3, μ (MoK_α)=0.0832 mm^{-1}; T=173(1) K, λ=0.71069 Å. Cell dimension from 25 reflections in the range 2θ=37–40°, $\omega/2\theta$ scans, $2\theta_{(max)}$=55°, 7606 reflections measured, 7239 symmetry-independent reflections, 5247 reflections with $I>2\sigma(I)$ used in the refinement of 382 parameters. Final R=0.0479, wR=0.0446 ($w=[\sigma^2(F_o)+(0.005F_o)^2]^{-1}$), GoF=2.102, Δ_{max}/σ=0.0005, $\Delta\rho$(max; min)=0.35; −0.21e $Å^{-3}$.

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