Synthesis of Conformationally Restricted Cyclic Hexadepsipeptides *via* Direct Amide Cyclization

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Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

Ring closure by direct amide cyclization was used in the synthesis of 19-membered cyclic depsipeptides **27** (*Schemes 1* and *3*). The linear hexapeptide precursors **4**, containing the β-hydroxy acid 3-hydroxy-2-phenylpropanoic acid (Tro), and five α-amino acids of the type Aib, Gly, and Pro, were prepared according to *Scheme 2*. The α,α-disubstituted α-amino acid Aib was incorporated into the peptide chain *via* the azirine/oxazolone method, and Gly and Pro were introduced by using the TBTU/HOBt coupling method. The cyclic depsipeptides **27a**–**27f** were obtained in reasonable-to-excellent yields (*Scheme 3* and *Table 1*).

1. Introduction. – Cyclic hexadepsipeptides have been isolated from a variety of sources, and some have been shown to exhibit significant biological activity [1–3]. They are the most common naturally occurring depsipeptides, the smallest ones that act as ionophores, of which the family of the enniatins is the most well-known [4].

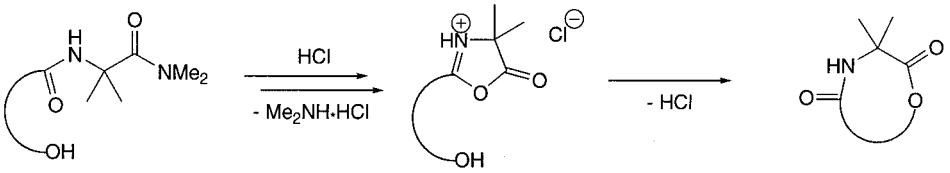
The synthesis of cyclic peptides and depsipeptides containing conformationally restricted amino acids like α,α-disubstituted α-amino acids (α,α-disubstituted glycines) has received little attention [5–8]. A number of such cyclic peptides [9][10] and cyclic depsipeptides [11–16] have been prepared in our group. Peptides containing α,α-disubstituted α-amino acids are significantly restricted in their conformational freedom because of the tetrasubstituted α-C-atom. Therefore, the incorporation of one or several α,α-disubstituted α-amino acids is a convenient method for introducing rigidity into the peptide backbone, thereby promoting secondary structures such as β-turns and α- and 3_{10}-helices [17–21].

The cyclization is traditionally the yield-limiting step in the preparation of cyclic peptides. This is particularly true for smaller peptides in which the rigidity of the linear peptide precursor often makes cyclization a demanding step. Generally, ring closure becomes more difficult as the number of side chains in the peptide increases, and yields vary greatly depending on the amino-acid sequence of the linear peptide precursor [22–25]. Cyclization yields are frequently enhanced by the presence of glycine, (*R*)-amino acids, and *N*-substituted amino acids [22]. In general, cyclic depsipeptides have been cyclized *via* amide-bond formation [26–28], but there are a number of successful ring closures *via* ester-bond formation known [29–33]. A useful method for the cyclization of conformationally restricted depsipeptides *via* ester-bond formation has been developed in our laboratory, the so-called 'direct amide cyclization' [13][34]. The concept of this cyclization method is outlined in *Scheme 1* (*cf.* [15]): treatment of the

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

amides of type **1** with dry HCl leads to the corresponding 1,3-oxazol-5(4*H*)-one intermediates **2** *via* ring closure and elimination of $Me_2NH \cdot HCl$. 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**.

Scheme 1



1 **2** **3**

In a recently published paper [15], we have shown that 16-membered cyclic pentadepsipeptides containing one β-hydroxy acid and four α,α-disubstituted α-amino acids can be conveniently prepared *via* 'direct amide cyclization'. From the results presented, it was obvious that the use of different β-hydroxy acids and/or combinations of different α,α-disubstituted α-amino acids influences the yield of cyclic monomer considerably [15][16].

Based on these precedents, it was of interest to further explore and develop the applicability of the 'direct amide cyclization' to the synthesis of cyclic hexadepsipeptides. Therefore, a linear hexapeptide containing one β-hydroxy acid and five α,α-disubstituted α-amino acids was prepared and cyclized with the aim of comparing this ring closure with previously reported results to determine the influence of an additional α,α-disubstituted α-amino acid. A series of similar linear hexapeptides were prepared in which selected α,α-disubstituted α-amino acids in the peptide chain were substituted with glycine and/or proline with the goal to determine in which way this exchange of amino-acid residues in the peptide backbone influences the cyclization.

2. Results and Discussion. – Six hexapeptides **4a**–**4f**, of which **4c** and **4d** are diastereoisomers, containing one β-hydroxy carboxylic acid and five α-amino acids, were synthesized. The monomers used were the racemic 3-hydroxy-2-phenylpropanoic acid (tropic acid, Tro), the α,α-disubstituted α-amino acid 2-aminoisobutyric acid (Aib), and the proteinogenic α-amino acids (*S*)-proline (Pro) and glycine (Gly). The hexapeptides **4** were all designed with *N*-terminal Tro residues, amide-protected *C*-terminal Aib residues, and various combinations of Aib, Gly, and Pro residues in the positions 2–5[2]). The intention was to explore how different combinations of these amino acids with distinct conformational requirements in positions 2–5 would influence the cyclization reaction.

2.1. *Preparation of the Linear Hexapeptides.* The peptides were synthesized in the N → C direction starting with 3-hydroxy-2-phenylpropanoic acid (Tro) (*cf. Scheme 2*).

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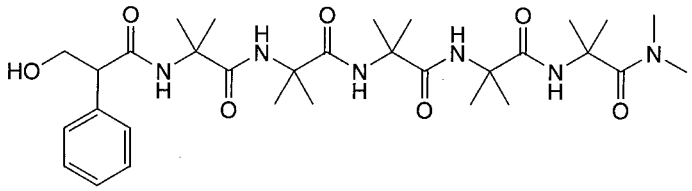
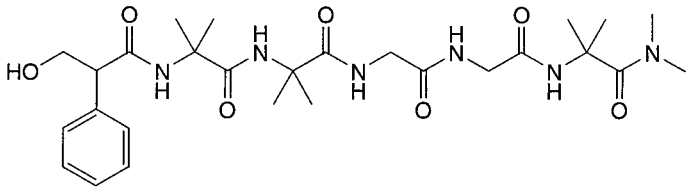
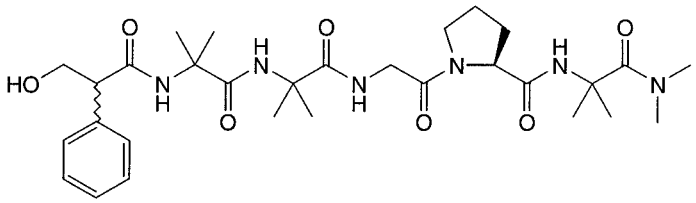
[2]) No hexapeptide containing the acid-labile Aib-Pro linkage [35] was prepared. Previous cyclization reactions have shown that this linkage is not stable under the conditions of the 'direct amide cyclization' (HCl gas in toluene 100°) [36].



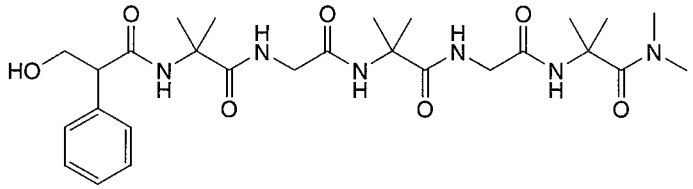
4a



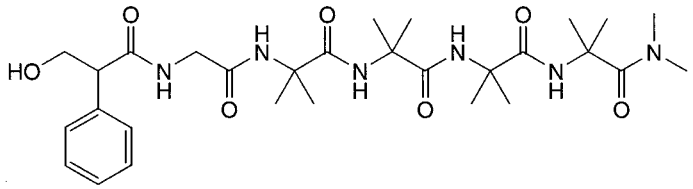
4b



4c, 4d

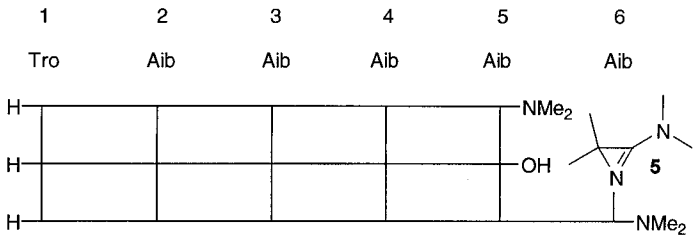


4e



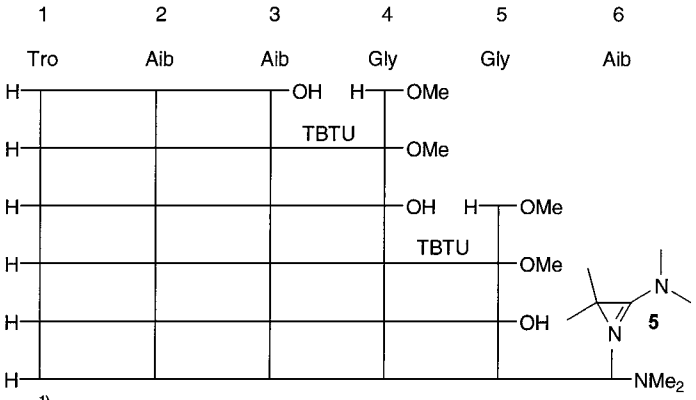
4f

Scheme 2



6 (93%)

4a (93%)



7 (71%)

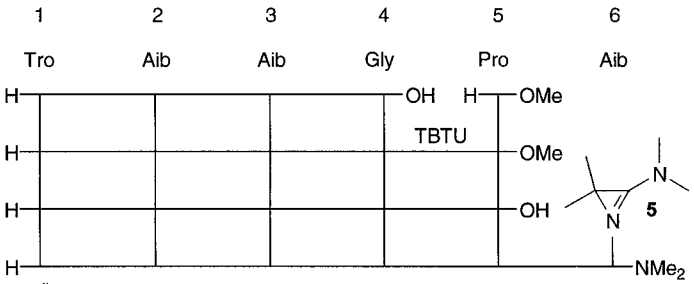
8 (91%)

9 (50%)

10 (-)

4b (52%)[1)]

[1)]Overall yield with respect to **9**.



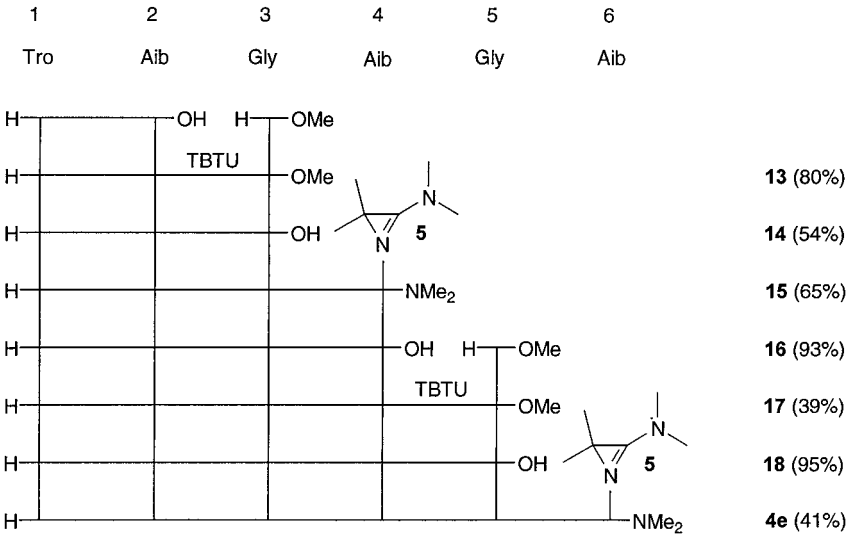
11a/11b (74%)

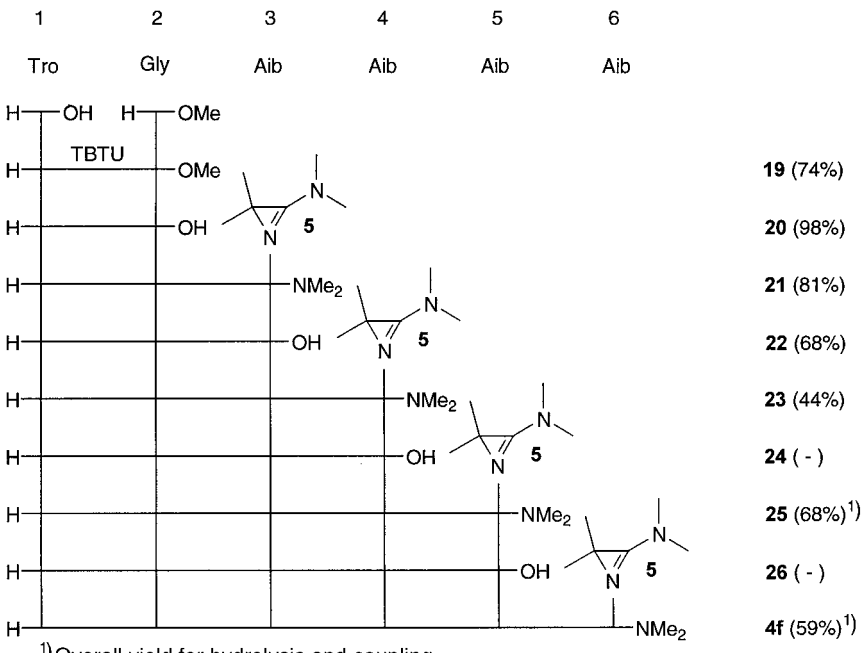
12a/12b (98%)

4c/4d (68%)[1)]

[1)]The diastereoisomers were separated by RP-HPLC.

Scheme 2 (cont.)





1) Overall yield for hydrolysis and coupling.

All Aib units have been inserted into the peptide chain by the so-called 'azirine/oxazolone method' [37] with 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (**5**) (a 3-amino-2*H*-azirine) as the synthon for the α,α-disubstituted α-amino acid. This method supplements the classical methods for incorporating α,α-disubstituted α-amino acids into peptide chains [38–40] and has been widely employed in the synthesis of peptaibols [41–43] and endothiopeptides [44]. In the azirine/oxazolone method, the free acid group of the amino acid or peptide is coupled directly with the chosen 3-amino-2*H*-azirine at room temperature without the use of coupling reagents, and no side-products are formed. This simplifies the purification of the products considerably compared to the classical methods. The *C*-terminal dimethylamide group was removed by hydrolysis under standard conditions with 3N HCl/THF 1:1 at room temperature [15][45].

The α-amino acids H-Gly-OMe and (*R*)-H-Pro-OMe were added to the peptide chains by using the *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU)/1-hydroxy-1*H*-benzotriazole (HOBt)/NEt_3 coupling method [46][47]. Free aliphatic OH groups are not affected under these conditions [47], obviating the need to protect the OH group of Tro. The *C*-terminal methyl-ester group was removed by saponification with LiOH at room temperature.

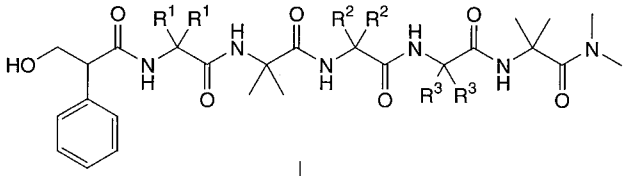
In a first attempt, the hexapeptides **4b** and **4c**/**4d** were prepared by the fragment condensation of Tro-Aib-Aib-Gly-OH with H-Gly-Aib-NMe_2 and H-Pro-Aib-NMe_2, respectively. For both examples, the yields of the required hexapeptides were very low and, therefore, this condensation strategy was dropped.

2.2. *Cyclization of the Linear Hexapeptides.* The optimum conditions for the 'direct amide cyclization' were investigated in previous work [15]. The following general procedure was used in the present work: a stream of dry HCl gas was slowly passed through a suspension or solution of the hexapeptide **4** in toluene at 100°. In the case of a suspension, HCl gas was added until the suspension gave way to a clear solution, and then HCl gas addition was continued for another 4 min. When the hexapeptide **4** was dissolved in toluene at 100°, HCl gas was added for 20 min. Excess HCl was then removed by passing a stream of N_2 through the solution for 30 min, then, toluene was evaporated and the crude product **27** was suspended in THF/Et_2O (1:1) at room temperature, and subsequently the precipitated $Me_2NH \cdot HCl$ was removed by filtration. The monomers were then isolated by column chromatography and further purified by reversed-phase HPLC (RP-HPLC) if necessary.

The structures of the cyclic depsipeptides **27** were elucidated on the basis of the following spectroscopic data. In the IR spectra, the absorption of the lactone CO group was observed at 1736–1751 cm^{-1}. The molecular mass of the cyclic depsipeptides was determined by the soft-ionization technique ESI-MS. By means of 2D-NMR spectroscopy, the assignment of the different H- and C-signals was accomplished by TOCSY, HSQC, and HMBC experiments.

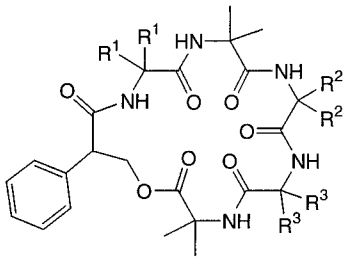
The cyclization of the linear hexapeptide **4a** was first performed with 50 mg (0.08 mmol) in 30 ml of toluene to give the cyclic monomer **27a** in 4% yield (*Scheme 3*; *cf. Table*). With the aim of increasing the yield of **27a**, the amount of toluene was increased to 120 ml and 240 ml, yielding **27a** in 13 and 24%, respectively. This considerable improvement in the yield of cyclic monomer can be explained by the higher dilution of the reactive intermediate of type **2**, thereby favoring the intramolecular cyclization to intermolecular reactions.

Scheme 3

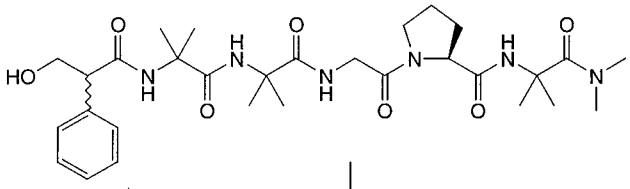


4a $R^1 = R^2 = R^3 = Me$
4b $R^1 = Me$, $R^2 = R^3 = H$
4f $R^1 = H$, $R^2 = R^3 = Me$

HCl | Toluene, 100°

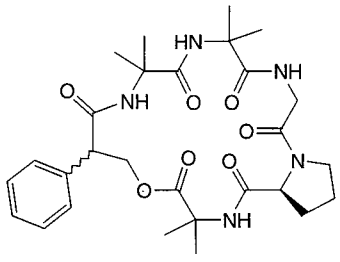


27a $R^1 = R^2 = R^3 = Me$
27b $R^1 = Me$, $R^2 = R^3 = H$
27f $R^1 = H$, $R^2 = R^3 = Me$



4c, **4d**

HCl | Toluene, 100°



27c, **27d**

Table. *Cyclization of Hexapeptides* **4a**–**f** (*ca.* 50 mg (0.08–0.1 mmol)) *in Toluene at 100°*

Hexapeptide **4**	Toluene [ml]	Cyclic monomer **27** (Yield [%])
a	30	4
a	120	13
a	240	24
b	30	26
b	120	36
b	240	79
c	240	41
d	240	43
e	240	22
f	240	30

The previously described cyclization of the linear pentapeptide Tro-Aib-Aib-Aib-Aib-NMe_2 led to the corresponding cyclic pentadepsipeptide in 41% yield [15]. The effect of adding one more Aib residue to the peptide chain is profound, as the yield of cyclic monomer drops by half. The explanation for this difference shall probably be found in the rigid conformation of such poly-Aib peptides. In the *Ramachandran* plot, the allowed torsion angles for the Aib residue are located in two very restricted regions, near $\phi = \pm 57°$ and $\psi = \pm 47°$, which correspond to the helical conformation [19]. The solid-state molecular structures of the $(Aib)_n$ homopeptides with $n = 1-12$ have been studied in detail. Beginning at the trimer level, they adopt the 3_{10}-helical structure stabilized by consecutive β-turns of type III (III′), irrespective of the main-chain length. The 3_{10}-helix is fully developed at the pentamer level [17]. Solution studies show that Aib homopeptides, as in the solid state, also adopt the 3_{10}-helix [48]. The crystal structure of the linear pentapeptide Tro-Aib-Aib-Aib-Aib-NMe_2 has also been established by X-ray crystallography [15]. As expected, the peptide adopts two consecutive β-turns, which can be considered an incipient 3_{10}-helix conformation. Adding one Aib residue to this chain should result in the formation of a fully developed 3_{10}-helical conformation of the hexapeptide **4a** with three consecutive β-turns in the peptide chain.

The yield of cyclic monomer from the intramolecular cyclization certainly depends on the conformation of the reactive intermediate **2**. The rigidity of this conformation determines whether or not the two ends of the peptide chain can easily contact each other. In the 'direct amide cyclization', the addition of HCl gas to the suspension of the peptide leads to the formation of the oxazolone intermediate of type **2**, which results in the breaking of the *C*-terminal β-turn. This means that the reactive intermediate of the pentapeptide Tro-Aib-Aib-Aib-Aib is stabilized by only one β-turn and that of the hexapeptide **4a** by two consecutive β-turns. Apparently, the conformation of the former intermediate is better suited for intramolecular cyclization than the latter. These conformational considerations can explain the almost twofold difference in the yield of cyclic monomer from pentapeptide Tro-Aib-Aib-Aib-Aib-NMe_2 and hexapeptide **4a**.

As the hexapeptide **4a** with five conformationally restricted Aib residues has a very rigid backbone, it was of interest to determine whether the yield of the 'direct amide cyclization' could be improved by the substitution of selected Aib residues by conformationally less-restricted amino acids or amino acids that are known to favor intramolecular cyclization.

Therefore, the Aib residues in positions 4 and 5 were substituted by Gly residues to yield the hexapeptide **4b**. Lacking a side chain Gly is more flexible, and the allowed torsion angles occupy a larger region in the *Ramachandran* plot. Because of the absence of a side chain, no steric obstacle during cyclization is created, and Gly fits well into secondary structures where amino acids with large substituents would be excluded [49]. The two Gly residues in the hexapeptide **4b** result in a more flexible region of the peptide backbone, which should be an advantage for the cyclization. Gly is normally described as a helix breaker, but it should be noted that a number of peptides containing both Aib and Gly had their structures established as α-helical and/or 3_{10}-helical by X-ray crystallography [50].

The hexapeptide **4b** (51–55 mg) was cyclized in 30, 120, and 240 ml of toluene and the cyclic monomer **27b** was isolated in 26, 36, and 79% yield, respectively (*Scheme 3*; *cf. Table*). These cyclization experiments show again a considerable increase in the yield of **27b** with increased dilution of the reactive intermediate **2** of the hexapeptide. In comparison with **27a**, the yield of monomer **27b** is increased by a factor of three, and the cyclization of **4b** to give **27b** in 79% yield is by any standard an exceptionally good result. This result clearly documents that the higher flexibility of the hexapeptide backbone considerably increased the yield of cyclodepsipeptide, as the conformation leading to ring closure was favored due to the substitution of Aib by Gly at positions four and five.

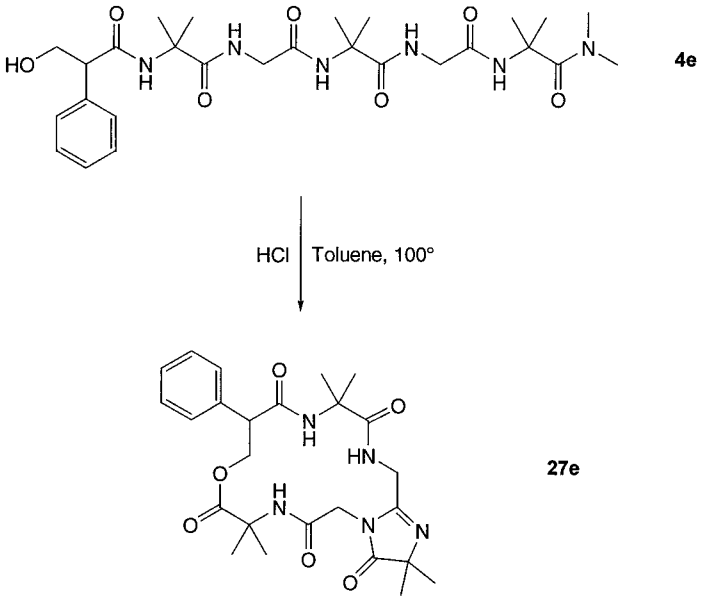
N-Substituted amino acids, of which Pro is the best-known, have been described to promote the cyclization of peptides. The *cis*- and *trans*-conformations of the amide bonds of proline are of comparable stability. Additionally, the Pro side chain severely restricts rotation about the N–C(α) bond and limits the rotations of neighboring groups [49]. These factors often provide a favorable geometry for ring closure. Pro is also well-known as a helix breaker because of the lack of an NH for a H-bond. Recently, some crystal structures of peptides containing Aib and Pro have been established. They have been found to adopt a helical conformation despite the presence of Pro. The bulk of the pyrrolidine ring in Pro causes a bend of *ca.* 30° in the helix [50].

With these results in mind, it was of interest to incorporate a Pro residue into the hexapeptide chain to study its influence on the cyclization. Based on the success of substituting two Aib residues of **4a** in positions 4 and 5 with two Gly residues, the comparable hexapeptides **4c**/**4d** were prepared with Gly and Pro in positions 4 and 5, respectively. The use of racemic Tro in the synthesis results in the formation of two diastereoisomeric hexapeptides **4c** and **4d**, which were separated by reversed-phase HPLC. Each of the hexapeptides **4c** and **4d** was cyclized *via* the 'direct amide cyclization' according to *Scheme 3* (*cf. Table*). The cyclic monomers **27c** and **27d** were isolated with RP-HPLC and obtained in 41 and 43% yield, respectively. The yields of the two diastereoisomers **27c** and **27d** are almost equal indicating no preference for either diastereoisomer in the cyclization reaction. The yields of **27c** and **27d** were increased nearly twofold compared with the previously prepared **27a**, but they were approximately half of the yield of **27b**. This shows that the substitution of the two Aib residues at position 4 and 5 with Gly and Pro, respectively, also favors a conformation of the reactive intermediate of type **2** suitable for the cyclization.

The hexapeptide **4e** with Gly residues in positions 3 and 5 has an alternating sequence of Aib and Gly residues in the peptide chain. It was cyclized *via* 'direct amide

cyclization' according to *Scheme 4* (*cf. Table*). Surprisingly, the isolated product was not the expected 19-membered cyclic hexadepsipeptide, but the 16-membered cyclodepsipeptide **27e** with a fused imidazole ring. This compound is also a monomeric product of **4e**, which, apart from undergoing the expected cyclization *via* lactone-bond formation, had undergone a second ring closure leading to the formation of the imidazole ring. The structure of **27e** was determined by ESI-MS and 2D-NMR spectroscopy. The imidazolone ring has been formed by nucleophilic attack of the NH group of Gly in position 5 onto the C=O group of Gly in position 3 followed by elimination of H_2O. Which of the two intramolecular cyclizations happens first is not clear. Apparently, the flexibility of the peptide backbone with Gly in positions 3 and 5 results in a unique conformation that allows the intramolecular imidazolone formation under the reaction conditions. Product **27e** was obtained in 22% yield (*cf. Table*) as the only monomer. The substitution of two Aib residues in positions 3 and 5 of hexapeptide **4a** by Gly does not lead to the preference of a conformation of the peptide backbone that was more favorable for the cyclization compared with the hexapeptide **4a**.

Scheme 4



4e

27e

The hexapeptide **4f** has a Gly residue in position 2, which should make the *N*-terminal part of the peptide backbone more flexible. It was also cyclized according to *Scheme 3*, and the cyclic hexadepsipeptide **27f** was isolated in 30% yield (*cf. Table*). This yield is only slightly better than the yield of **27a**. Therefore, the substitution of the Aib residue in position 2 of **4a** with Gly seems to have a negligible effect on the flexibility of the peptide backbone.

3. Conclusions. – As a model compound, the conformationally rigid hexapeptide **4a** containing one β-hydroxy acid (Tro) and five α,α-disubstituted α-amino acids (Aib)

was prepared and cyclized *via* 'direct amide cyclization'. By comparison with a previously prepared 16-membered cyclic pentadepsipeptide containing one Aib residue fewer, it could be determined that the elongation of the peptide chain with one Aib residue influenced the cyclization reaction considerably, leading to a significantly lower yield of cyclic monomer for the hexapeptide.

We have shown that, by substituting Aib residues of the model peptide **4a** with different combinations of Gly and Pro at positions 2–5, the cyclization ability can be influenced considerably up to a threefold improvement of the yield of cyclic monomer. In another example, no improvements in the formation of cyclic monomer compared to the model hexapeptide **4a** were found. Therefore, it can be concluded that the effect on the 'direct amide cyclization' of building Gly and Pro residues into a peptide chain instead of only Aib residues, apart from the β-hydroxy acid Tro, is very dependent on the combination and the position of these amino acids.

In two examples, the influence of dilution of the reactive intermediates leading to the formation of cyclic monomer was investigated. Not unexpectedly, the yield of cyclic monomer increases with higher dilution.

The present study has shown that the 'direct amide cyclization' is a suitable method for obtaining 19-membered cyclic hexadepsipeptides containing α,α-disubstituted α-amino acids in reasonable-to-excellent yield.

We thank the analytical units of our institute for spectra and analyses, especially Dr. *G. Hopp-Rentsch*, Miss *N. Walch*, and Mr. *M. Binder* for performing NMR measurements and for useful discussions, and the *Swiss National Science Foundation*, the *Stiftung für wissenschaftliche Forschung an der Universität Zürich*, and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Experimental Part

1. *General*. See [51]. Unless otherwise stated, IR spectra in KBr and NMR spectra in (D_6)DMSO (^{1}H: 300 MHz and ^{13}C: 75.5 MHz).

General Procedure 1 (*GP 1*). *Coupling of Amino Acids with Tropic Acid and Peptides.* To a stirred suspension of the acid, the *C*-terminal-protected amino acid hydrochloride, TBTU, and HOBt in dry MeCN was added excess Et_3N. The mixture was stirred at r.t. under N_2 (4.5–22 h), followed by evaporation of the solvent. The crude product was dissolved in AcOEt and washed with $2 \times 5\%$ $KHSO_4$ and $2 \times 5\%$ $NaHCO_3$. The aq. layers were extracted with AcOEt. The combined org. layer was washed with brine, dried ($MgSO_4$), evaporated, purified by column chromatography (CC), and dried under h.v.

General Procedure 2 (*GP 2*). *Reaction of* 2,2,*N*,*N*-*Tetramethyl-2*H-*azirin-3-amine with Peptide Acids.* To a stirred suspension of the acid in dry MeCN was added dropwise a soln. of 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (**5**) in dry MeCN. The mixture was stirred at r.t. under N_2 (20 min–66 h), filtered, washed with cold hexane/Et_2O 1:1, and dried under h.v.

General Procedure 3 (*GP 3*). According to *GP 2*, the mixture was stirred at r.t. under N_2 (17–72 h), evaporated, purified by CC, and dried under h.v.

General Procedure 4 (*GP 4*). *Hydrolysis of Peptide Esters.* A suspension of the ester and $LiOH \cdot H_2O$ in THF/MeOH/H_2O 3:1:1 was stirred at r.t. under N_2 (17–39 h). The mixture was cooled to 0°, 2N HCl was added dropwise until pH 1 was reached, and the solvent was evaporated. To the crude product was added brine, the mixture was extracted with AcOEt, the org. layer was dried ($MgSO_4$), evaporated, and the residue dried under h.v.

General Procedure 5 (*GP 5*). *Hydrolysis of Peptide Amides.* The amide was dissolved in 3N HCl/THF 1:1 (*v*/*v*: *ca.* 5 ml/mmol), and the soln. was stirred at r.t. (40 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 6 (*GP 6*). According to *GP 5*, a soln. of the amide in 3N HCl/THF 1:1 (*v*/*v*; *ca.* 5 ml/mmol) was stirred at r.t. (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. *Preparation of the Hexapeptide* **4a**. 2.1. *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-methyl-1-oxopropyl)amino]-2-methylpropanoic Acid* (**6**). According to *GP 5*, Tro-Aib-Aib-Aib-Aib-NMe_2[3]) (1.805 g, 3.38 mmol), 18 ml of 3N HCl (H_2O/THF 1:1), stirred for 40 h: 1.596 g (93%) of **6**. White powder. M.p. 225.9° (dec.). IR: 3426*s*, 3337v*s*, 3064*m*, 2985*s*, 2939*m*, 2878*w*, 1741*s*, 1670v*s*, 1539v*s*, 1457*s*, 1387*s*, 1364*s*, 1270*m*, 1229*s*, 1164*s*, 1046*m*, 1026*w*, 756*w*, 701*m*, 656*w*, 606*w*. ^{1}H-NMR: 11.79 (br. *s*, COOH); 8.72 (*s*, NH); 7.38–7.22 (*m*, 3 NH, 5 arom. H); 5.13 (br. *s*, OH); 3.99–3.93, 3.81–3.76 (2*m*, CH_2OH); 3.66–3.61 (*m*, CH); 1.351, 1.345, 1.31, 1.23 (4*s*, 4 Me_2C). ^{13}C-NMR: 175.5, 174.4, 173.5, 173.1, 172.8 (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); 55.9, 55.7, 55.6, 54.5 (4*s*, 4 Me_2C); 53.5 (*d*, CH); 25.5, 25.2, 24.8, 24.4, 23.9, 23.8 (6*q*, 4 Me_2C). ESI-MS: 507 (100, $[M+H]^+$).

2.2. *2-({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-methyl-1-oxopropyl}amino)-2-*N,N-*trimethylpropanamide* (**4a**). According to *GP 2*, **6** (1.495 g, 2.95 mmol) in MeCN (30 ml) and **5** (0.385 g, 3.43 mmol) in MeCN (1 ml), stirred for 66 h: 1.693 g (93%) of **4a**. White powder. M.p. 243.2° (dec.). IR: 3421*m*, 3269v*s*, 2986*m*, 2939*m*, 1655v*s*, 1622v*s*, 1539v*s*, 1466*m*, 1397*m*, 1384*s*, 1363*m*, 1293*m*, 1228*m*, 1171*m*, 1121*m*, 1058*w*, 1012*w*, 749*w*, 700*m*, 614*w*. ^{1}H-NMR: 8.76 (*s*, NH); 7.68 (*s*, NH); 7.52 (*s*, NH); 7.40–7.25 (*m*, 2 NH, 5 arom. H); 5.14 (*m*, OH); 3.97–3.93, 3.82–3.78 (2*m*, CH_2OH); 3.67–3.65 (*m*, CH); 1.36, 1.31, 1.27, 1.19 (4*s*, 5 Me_2C). ^{13}C-NMR: 175.0, 174.7, 173.4, 172.9, 172.0 (5*s*, 6 CO); 137.1 (*s*, 1 arom. C); 128.2, 127.9, 126.9 (3*d*, 5 arom. C); 63.8 (*t*, CH_2OH); 56.04, 55.95, 55.8, 55.7, 55.5 (5*s*, 5 Me_2C); 53.4 (*d*, CH); 37.2 (*q*, Me_2N); 25.8, 25.5, 25.2, 24.9, 24.6, 24.2, 23.6 (7*q*, 5 Me_2C). ESI-MS: 641 (100, $[M+Na]^+$).

3. *Preparation of the Hexapeptide* **4b**. 3.1. *Methyl 2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}ethanoate* (**7**). According to *GP 1*, Tro-Aib-Aib-OH[3]) (0.369 g, 1.10 mmol), glycine methyl ester hydrochloride (0.151 g, 1.20 mmol), TBTU (0.358 g, 1.12 mmol), HOBt (0.152 g, 1.13 mmol), and Et_3N (0.337 g, 3.33 mmol) in MeCN (5 ml), stirred for 15 h, 25 ml of AcOEt, 2 × 10 ml of 5% $KHSO_4$, 2 × 20 ml of AcOEt, 2 × 10 ml of 5% $NaHCO_3$, 2 × 20 ml of AcOEt, 20 ml of brine, CC (SiO_2, CH_2Cl_2/MeOH 20:1): 0.316 g (71%) of **7**. White powder. M.p. 163.6–165.4°. IR: 3295v*s*, 3065*w*, 2987*m*, 2950*m*, 1751v*s*, 1645v*s*, 1540v*s*, 1440*m*, 1417*m*, 1385*s*, 1363*s*, 1265*s*, 1213v*s*, 1061*m*, 1027*m*, 749*w*, 720*m*, 702*m*, 668*m*. ^{1}H-NMR (CD_3OD): 7.40–7.23 (*m*, 5 arom. H); 4.15–3.70 (*m*, CH_2OH, CH_2(Gly), CH, MeO); 1.43, 1.41, 1.37, 1.35 (4*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 177.8, 176.1, 175.6, 172.1 (4*s*, 4 CO); 137.9 (*s*, 1 arom. C); 129.7, 129.2, 128.6 (3*d*, 5 arom. C); 65.4 (*t*, CH_2OH); 58.04, 57.98 (2*s*, 2 Me_2C); 55.8 (*d*, CH); 52.6 (*q*, MeO); 42.0 (*t*, CH_2(Gly)); 26.1, 26.0, 25.0, 24.6 (4*q*, 2 Me_2C). ESI-MS: 430 (100, $[M+Na]^+$).

3.2. *2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}ethanoic Acid* (**8**). According to *GP 4*, **7** (0.316 g, 0.78 mmol), LiOH · H_2O (0.101 g, 2.41 mmol), and 5 ml of THF/MeOH/H_2O (3:1:1), stirred for 19 h, 5 ml of brine, 4 × 20 ml of AcOEt: 0.279 g (91%) of **8**. Colorless foam. IR: 3319v*s*, 2987*s*, 2939*s*, 1744*s*, 1658v*s*, 1540v*s*, 1456*s*, 1386*s*, 1365*s*, 1223v*s*, 1048*m*, 1022*m*, 875*w*, 744*m*, 701*s*. ^{1}H-NMR (CD_3CD): 7.40–7.22 (*m*, 5 arom. H); 4.17–3.68 (*m*, CH_2OH, CH_2(Gly), CH); 1.43, 1.41, 1.37 (3*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 177.6, 176.3, 175.6, 173.3 (4*s*, 4 CO); 137.9 (*s*, 1 arom. C); 129.8, 129.2, 128.6 (3*d*, 5 arom. C); 65.4 (*t*, CH_2OH); 58.0 (*s*, 2 Me_2C); 55.8 (*d*, CH); 41.9 (*t*, CH_2(Gly)); 26.2, 26.0, 25.0, 24.6 (4*q*, 2 Me_2C). ESI-MS: 416 (100, $[M+Na]^+$), 394 (50, $[M+H]^+$).

3.3. *Methyl 2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-1-oxoethyl)amino]ethanoate* (**9**). According to *GP 1*, **8** (0.439 g, 1.12 mmol), glycine methyl ester hydrochloride (0.158 g, 1.26 mmol), TBTU (0.373 g, 1.16 mmol), HOBt (0.160 g, 1.18 mmol), and Et_3N (0.341 g, 3.37 mmol) in MeCN (10 ml), stirred for 17 h, 100 ml of AcOEt, 2 × 10 ml of 5% $KHSO_4$, 2 × 20 ml of AcOEt, 2 × 10 ml of 5% $NaHCO_3$, 2 × 20 ml of AcOEt, 20 ml of brine, CC (SiO_2, CH_2Cl_2/MeOH 25:1): 0.262 g (50%) of **9**. Colorless foam. IR: 3305*s*, 3062*w*, 2987*w*, 2939*w*, 1749*m*, 1655v*s*, 1536*s*, 1456*m*, 1439*m*, 1408*w*, 1385*m*, 1365*m*, 1336*w*, 1273*m*, 1218*s*, 1049*w*, 1020*w*, 744*w*, 702*m*. ^{1}H-NMR (CD_3OD): 7.40–7.22 (*m*, 5 arom. H); 4.16–3.68 (*m*, CH_2OH, 2 CH_2(Gly), CH, MeO); 1.43, 1.39, 1.37, 1.36 (4*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 177.7, 177.3, 175.5, 172.8, 171.3 (5*s*, 5 CO); 137.8 (*s*, 1 arom. C); 129.7, 129.2, 128.6 (3*d*, 5 arom. C); 65.4 (*t*, CH_2OH); 58.03, 57.97 (2*s*, 2 Me_2C); 55.7 (*d*, CH); 52.6 (*q*, MeO); 43.8, 41.8 (2*t*, 2 CH_2(Gly)); 26.1, 26.0, 24.8, 24.3 (4*q*, 2 Me_2C). ESI-MS: 487 (100, $[M+Na]^+$), 465 (46, $[M+H]^+$).

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[3]) The synthesis of the compound is described in [15].

3.4. *2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-1-oxoethyl)amino]ethanoic Acid* (**10**). According to *GP 4*, **9** (0.256 g, 0.55 mmol), LiOH · H_2O (0.076 g, 1.81 mmol) and 5 ml of THF/MeOH/H_2O (3:1:1), stirred for 39 h, 15 ml of brine, 4 × 100 ml of AcOEt: 0.253 g of crude **10**. The material was used for the next reaction step without further purification.

3.5. *2-({2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-1-oxoethyl)amino]-1-oxoethyl}amino)-2,*N,N*-trimethylpropanamide* (**4b**). According to *GP 3*, crude **10** (0.214 g) in MeCN (3 ml) and **5** (0.061 g, 0.54 mmol) in MeCN (1 ml), stirred for 29 h, CC (SiO_2; CH_2Cl_2/MeOH 10:1) and crystallization from MeCN/AcOEt/Et_2O: total yield of **4b**: 0.160 g (52%). White powder. M.p. 224.3° (dec.). IR: 3453*s*, 3277v*s*, 3053*w*, 2987*m*, 2936*m*, 2876*w*, 1656v*s*, 1629v*s*, 1542v*s*, 1463*m*, 1440*m*, 1398*s*, 1363*m*, 1331*m*, 1290*m*, 1219*m*, 1200*m*, 1176*w*, 1119*m*, 1082*w*, 1049*m*, 1025*w*, 749*w*, 703*m*, 671*w*, 646*w*, 603*m*. ^{1}H-NMR (CD_3OD): 7.40–7.25 (*m*, 5 arom. H); 4.16–3.71 (*m*, CH_2OH, 2 CH_2(Gly), CH); 3.07, 2.90 (2 br, *s*, Me_2N); 1.49, 1.47, 1.45, 1.41, 1.39, 1.37 (6*s*, 3 Me_2C). ^{13}C-NMR (CD_3OD): 178.4, 177.5, 175.6, 174.7, 172.7, 170.4 (6*s*, 6 CO); 137.7 (*s*, 1 arom. C); 129.7, 129.1, 128.6 (3*d*, 5 arom. C); 65.3 (*t*, CH_2OH); 57.8, 57.7 (2*s*, 3 Me_2C); 55.5 (*d*, CH); 44.6, 43.3 (2*t*, 2 CH_2(Gly)); 38.7, 38.2 (2*q*, Me_2N); 26.2, 26.1, 26.0, 25.9, 24.5, 24.3 (6*q*, 3 Me_2C). ESI-MS: 585 (100, $[M+Na]^+$), 518 (28, $[M-Me_2N]^+$).

4. *Preparation of the Hexapeptides* **4c**/**4d**. 4.1. *Methyl (*R,S*)- and (*S,S*)-1-(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-1-oxoethyl)pyrrolidine-2-carboxylate* (**11a**/**11b**). According to *GP 1*, **7** (0.500 g, 1.27 mmol), (*S*)-proline methyl ester hydrochloride (0.224 g, 1.35 mmol), TBTU (0.419 g, 1.30 mmol), HOBt (0.190 g, 1.41 mmol), and Et_3N (0.402 g, 3.97 mmol) in MeCN (10 ml), stirred for 17 h, 200 ml of AcOEt, 2 × 30 ml of 5% $KHSO_4$, 2 × 60 ml of AcOEt, 2 × 30 ml of 5% $NaHCO_3$, 2 × 60 ml of AcOEt, 60 ml of brine, CC (SiO_2; CH_2Cl_2/MeOH 15:1): 0.471 (74%) of **11a**/**11b** (*ca.* 1:1). White powder. IR: 3459*m*, 3303*s*, 3058*w*, 2985*w*, 2950*w*, 2878*w*, 1756*s*, 1651v*s*, 1538*s*, 1454*s*, 1380*m*, 1365*m*, 1330*w*, 1285*w*, 1223*m*, 1196*m*, 1169*m*, 1059*w*, 1023*w*, 722*w*, 705*w*. ^{1}H-NMR: 8.53–8.48, 7.53–7.43 (2*m*, 4 NH); 7.35–7.20 (*m*, 10 arom. H); 7.03, 7.00 (2*s*, 2 NH); 5.06–5.02 (*m*, 2 OH); 4.34–4.30, 4.13–3.17 (2*m*, 2 CH_2OH, 2 CH_2(Pro), 2 CH_2(Gly), 2 CH(Tro), 2 CH(Pro)); 3.60, 3.59 (2*s*, 2 MeO); 2.19–2.09, 1.97–1.79 (2*m*, 4 CH_2(Pro)); 1.33, 1.30, 1.280, 1.2875, 1.25 (5*s*, 4 Me_2C). ^{13}C-NMR: 174.1, 173.1, 172.6, 172.5, 172.2, 167.4, 167.1 (7*s*, 10 CO); 137.3, 137.2 (2*s*, 2 arom. C); 128.1, 128.0, 126.7 (3*d*, 10 arom. C); 63.7 (*t*, 2 CH_2OH); 58.4 (*d*, 2 CH); 56.1, 55.9, 55.8 (3*s*, 4 Me_2C); 53.7 (*d*, 2 CH); 51.7 (*q*, 2 MeO); 45.5 (*t*, 2 CH_2); 41.4, 41.2 (2*t*, 2 CH_2); 28.5 (*t*, 2 CH_2); 25.82, 25.76, 25.5, 25.2, 24.4, 24.1, 24.0, 23.8 (8*q*, 4 Me_2C); 24.3 (*t*, 2 CH_2). ESI-MS: 505 (100, $[M+H]^+$).

4.2. *(*R,S*)- and (*S,S*)-1-(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-2-methyl-1-oxopropyl]amino}-1-oxoethyl)pyrrolidine-2-carboxylic Acid* (**12a**/**12b**). According to *GP 4*, **11a**/**11b** (0.428 g, 0.85 mmol), LiOH · OH (0.107 g, 2.55 mmol), and 10 ml of THF/MeOH/H_2O 3:1:1, stirred for 21 h, 20 ml of brine, 4 × 100 ml of AcOEt: 0.409 g (98%) of **12a**/**12b** (*ca.* 1:1). White powder. IR: 3295*s*, 3060*w*, 2985*m*, 2943*w*, 2878*w*, 1748*m*, 1655v*s*, 1538*s*, 1455*m*, 1385*m*, 1364*w*, 1330*w*, 1293*w*, 1226*m*, 1197*m*, 1057*w*, 1022*w*, 721*w*, 702*w*. ^{1}H-NMR (CD_3OD): 8.58, 8.54 (2*s*, 2 NH); 8.0–7.9, 7.8–7.7 (2*m*, 2 NH); 7.35–7.24 (*m*, 2 NH, 10 arom. H); 4.47–3.57 (*m*, 2 CH_2OH, 2 CH_2(Gly), 2 CH_2(Pro), 2 CH(Pro), 2 CH(Tro)); 2.25–1.91 (*m*, 4 CH_2); 1.47, 1.41, 1.40, 1.36 (4*s*, 4 Me_2C). ^{13}C-NMR (CD_3OD): 177.6, 176.5, 176.4, 175.5, 170.1, 169.8 (6*s*, 10 CO); 137.8, 137.7 (2*s*, 2 arom. C); 129.7, 129.2, 128.5 (3*d*, 10 arom. C); 65.4 (*t*, 2 CH_2OH); 60.5 (*d*, 2 CH); 58.2, 58.1 (2*s*, 4 Me_2C); 47.5, 42.7, 30.1 (3*t*, 2 CH_2 each); 27.3, 26.7, 26.3, 24.7, 24.2, 23.9 (6*q*, 4 Me_2C); 25.7 (*t*, 2 CH_2). ESI-MS: 491 (100, $[M+H]^+$).

4.3. *(*R,S*)- and (*S,S*)-2-[1-(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}-amino)-2-methyl-1-oxopropyl]amino}-1-oxoethyl)pyrrolidine-2-carboxamido]-2,*N,N*-trimethylpropanamide* (**4c**/**4d**). According to *GP 3*, **12a**/**12b** (0.409 g, 0.83 mmol) in MeCN (4 ml) and **5** (0.101 g, 0.90 mmol) in MeCN (1 ml), stirred for 42 h, CC (SiO_2; CH_2Cl_2/MeOH 20:1, CH_2Cl_2/MeOH 15:1, CH_2Cl_2/MeOH 10:1): 0.427 g of crude **4c**/**4d** (*ca.* 1:1). Crude **4c**/**4d** was purified, and a portion of the diastereoisomers was separated by prep. RP-HPLC. Conditions: stationary phase, *Nucleosil 100-7 C8*; column, 250 × 21 mm; mobile phase, 10 ml/min, H_2O/MeOH/MeCN 5:1:1; UV detector, 254 nm. Total yield of **4c**/**4d**: 0.340 g (68%).

Data of **4c**: White powder. M.p. 154.2° (dec.). $[\alpha]_D = -22.3$ ($c = 0.31$, EtOH). IR: 3311*s*, 3059*w*, 2985*w*, 2938*w*, 1652v*s*, 1540*s*, 1454*m*, 1385*m*, 1364*m*, 1333*w*, 1266*w*, 1201*w*, 1121*w*, 1055*w*, 702*w*. ^{1}H-NMR ((D$_5$)pyridine): 9.69, 8.57 (2*s*, 2 NH); 8.49–8.43 (*m*, NH); 7.75 (*s*, NH); 7.67–7.59, 7.40–7.22 (2*m*, 5 arom. H); 4.72–4.70, 4.40–4.30, 4.12–4.01, 3.60–3.53, 3.34–3.26 (5*m*, CH_2OH, CH_2(Gly), CH_2(Pro), CH(Pro), CH(Tro)); 3.08 (br *s*, Me_2N); 2.13–1.62 (*m*, 2 CH_2); 1.78, 1.74, 1.70, 1.68 (4*s*, 3 Me_2C). ^{13}C-NMR ((D$_5$)pyridine): 175.8, 174.6, 174.4, 172.8, 170.9, 169.3 (6*s*, 6 CO); 137.8 (*s*, 1 arom. C); 129.1, 128.8, 127.7 (3*d*, 5 arom. C); 65.7 (*t*, CH_2OH); 60.7 (*d*, CH); 57.7, 57.4, 56.8 (3*s*, 3 Me_2C); 55.5 (*d*, CH); 46.8, 43.0 (2*t*, 2 CH_2); 38.0 (*q*, Me_2N); 29.2 (*t*, CH_2); 26.5, 26.4, 26.3, 25.4, 24.6 (5*q*, 3 Me_2C); 24.9 (*t*, CH_2). ESI-MS: 625 (100, $[M+Na]^+$), 558 (30, $[M-Me_2N]^+$).

Data of **4d**. Foam. $[\alpha]_D = -73.0$ ($c = 0.46$, EtOH). IR: 3424*s*, 2985*w*, 2935*m*, 2878*w*, 1648v*s*, 1539*m*, 1436*s*, 1363*m*, 1330*w*, 1265*w*, 1208*m*, 1122*w*, 1054*w*, 702*w*. ^{1}H-NMR ((D$_5$)pyridine): 9.72 (*s*, NH); 8.52 (*t*, $J = 5.2$, NH); 8.35, 7.83 (2*s*, 2 NH); 7.66–7.63, 7.38–7.28 (2*m*, 5 arom. H); 4.77–4.74 (*m*, CH); 4.69–4.62 (*m*, 1 H of CH_2OH); 4.32–4.28 (*m*, 1 H of CH_2, CH); 4.12–4.06 (*m*, 1 H of CH_2OH, 1 H of CH_2); 3.62–3.60 (*m*, 1 H of CH_2); 3.28–3.23 (*m*, 1 H of CH_2); 3.12 (*m*, Me_2N); 2.19–2.14 (*m*, 1 H of CH_2); 1.99–1.82 (*m*, 2 H of CH_2); 1.88, 1.76, 1.73, 1.71, 1.70, 1.65 (6*s*, 3 Me_2C); 1.72–1.64 (*m*, 1 H of CH_2). ^{13}C-NMR ((D$_5$)pyridine): 176.1, 174.6, 174.4, 172.8, 170.9, 169.4 (6*s*, 6 CO); 137.7 (*s*, 1 arom. C); 129.0, 128.8, 127.7 (3*d*, 5 arom. C); 65.8 (*t*, CH_2OH); 60.8 (*d*, CH); 57.7, 57.4, 56.9 (3*s*, 3 Me_2C); 55.4 (*d*, CH); 46.9, 43.3 (2*t*, 2 CH_2); 38.0 (*q*, Me_2N); 29.2 (*t*, CH_2); 27.5, 26.8, 26.4, 26.3, 24.5, 24.2 (6*q*, 3 *Me*$_2$C); 24.9 (*t*, CH_2). ESI-MS: 625 (23, $[M + Na]^+$), 558 (100, $[M - Me_2N]^+$).

5. *Preparation of the Hexapeptide* **4e**. 5.1. *Methyl 2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)ethanoate* (**13**). According to *GP 1*, Tro-Aib-OH[3]) (0.293 g, 1.17 mmol), glycine methyl ester hydrochloride (0.155 g, 1.23 mmol), TBTU (0.395 g, 1.23 mmol), HOBt (0.164 g, 1.21 mmol), and Et_3N (0.358 g, 3.54 mmol) in MeCN (3 ml), stirred for 22 h, 25 ml of AcOEt, 2 × 10 ml of 5% $KHSO_4$, 2 × 20 ml of AcOEt, 2 × 10 ml of 5% $NaHCO_3$, 2 × 20 ml of AcOEt, 20 ml of brine, CC (SiO_2; CH_2Cl_2/MeOH 20:1): 0.301 g (80%) of **13**. Colorless foam. IR: 3323*s*, 3062*m*, 2987*m*, 2951*m*, 2881*w*, 1754v*s*, 1661v*s*, 1602*m*, 1537v*s*, 1455*s*, 1438*s*, 1408*m*, 1385*s*, 1365*s*, 1219v*s*, 1049*m*, 1023*m*, 984*w*, 747*w*, 702*s*. ^{1}H-NMR: 8.14 (*s*, NH); 7.79 (*t*, $J =$ 5.8, NH); 7.34–7.19 (*m*, 5 arom. H); 4.93 (*t*, $J = 4.8$, OH); 3.94–3.54 (*m*, C*H*$_2$OH, CH_2(Gly), CH); 1.36, 1.35 (2*s*, Me_2C). ^{13}C-NMR: 174.5, 171.5, 170.2 (3*s*, 3 CO); 137.9 (*s*, 1 arom. C); 128.0, 126.6 (2*d*, 5 arom. C); 63.8 (*t*, CH_2OH); 56.1 (*s*, Me_2C); 53.8 (*d*, CH); 51.5 (*q*, MeO); 40.8 (*t*, CH_2(Gly)); 25.9, 24.0 (2*q*, *Me*$_2$C). ESI-MS: 323 (100, $[M + H]^+$).

5.2. *2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)ethanoic Acid* (**14**). According to *GP 4*, **13** (1.527 g, 4.74 mmol) LiOH · H_2O (0.597 g, 14.2 mmol) and 10 ml of THF/MeOH/H_2O 3:1:1, stirred for 20 h, 20 ml of brine, 4 × 100 ml of AcOEt: 0.795 g (54%) of **14**. Colorless foam. IR: 3340*s*, 3062*m*, 2986*m*, 2938*m*, 1737*s*, 1660v*s*, 1538v*s*, 1455*m*, 1388*m*, 1366*m*, 1227*s*, 1193*s*, 1045*m*, 1022*m*, 745*w*, 701*m*. ^{1}H-NMR[4]): 8.14 (*s*, NH); 7.65 (*t*, $J = 5.7$, NH); 7.34–7.19 (*m*, 5 arom. H); 3.93–3.54 (*m*, C*H*$_2$OH, CH_2(Gly), CH); 1.36, 1.35 (2*s*, Me_2C). ^{13}C-NMR: 174.2, 171.5, 171.0 (3*s*, 3 CO); 137.9 (*s*, 1 arom. C); 128.04, 127.99, 126.6 (3*d*, 5 arom. C); 63.8 (*t*, CH_2OH); 56.1 (*s*, Me_2C); 53.9 (*d*, CH); 40.9 (*t*, CH_2(Gly)); 25.9, 24.0 (2*q*, 2 *Me*$_2$C). ESI-MS: 309 (100, $[M + H]^+$).

5.3. *2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-1-oxoethyl]amino}-2*,N,N-*trimethylpropanamide* (**15**). According to *GP 3*, **14** (0.746 g, 2.42 mmol) in MeCN (3 ml) and **5** (0.298 g, 2.66 mmol) in MeCN (1 ml), stirred for 17 h, CC (SiO_2; CH_2Cl_2/MeOH 20:1, CH_2Cl_2/MeOH 10:1): 0.666 g (65%) of **15**. Colorless foam. IR: 3289v*s*, 3060*m*, 2988*m*, 2936*m*, 1652v*s*, 1543v*s*, 1456*m*, 1396*s*, 1364*m*, 1543v*s*, 1456*m*, 1396*s*, 1364*m*, 1335*w*, 1287*m*, 1202*m*, 1122*m*, 1054*m*, 1021*w*, 751*w*, 702*m*, 652*w*. ^{1}H-NMR: 8.62 (*s*, NH); 7.92 (*t*, $J = 6.0$, NH); 7.64 (*s*, NH); 7.36–7.20 (*m*, 5 arom. H); 4.99 (*t*, $J = 4.7$, OH); 3.97–3.43 (*m*, C*H*$_2$OH, CH_2(Gly), CH); 2.85 (br. *s*, Me_2N); 1.37, 1.36, 1.31, 1.28 (4*s*, 2 Me_2C). ^{13}C-NMR: 173.9, 172.7, 171.7, 167.8 (4*s*, 4 CO); 137.5 (*s*, 1 arom. C); 128.1, 127.9, 126.7 (3*d*, 5 arom. C); 63.6 (*t*, CH_2OH); 55.8, 55.4 (2*s*, 2 Me_2C); 53.5 (*d*, CH); 42.5 (*t*, CH_2(Gly)); 37.2 (*q*, Me_2N); 25.9, 25.6, 25.4, 23.9 (4*q*, 2 *Me*$_2$C). ESI-MS: 443 (100, $[M + Na]^+$), 376 (50, $[M - Me_2N]^+$).

5.4. *2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-1-oxoethyl]amino}-2-methylpropanoic Acid* (**16**). Amide **15** (0.626 g, 1.49 mmol) was dissolved in 8 ml of 3N HCl/THF (1:1) and the soln. was stirred at r.t. for 45 h and at 40° for 6 h. The solvent was evaporated, 10 ml of brine were added, the mixture was extracted with 5 × 50 ml of AcOEt, the org. layer was dried ($MgSO_4$), evaporated, and the residue was dried under h.v.: 0.542 g (93%) of **16**. White powder. M.p. 203.2° (dec.). IR: 3394*m*, 3328*s*, 3276*s*, 3056*m*, 2991*m*, 2934*m*, 2641*w*, 1714*s*, 1672v*s*, 1652v*s*, 1625v*s*, 1556*s*, 1527*s*, 1493*w*, 1474*m*, 1462*m*, 1440*w*, 1403*m*, 1381*m*, 1364*w*, 1316*m*, 1268*s*, 1218*m*, 1186*s*, 1068*w*, 1050*w*, 1025*m*, 926*w*, 794*w*, 740*w*, 702*m*. ^{1}H-NMR[4]): 8.50 (*s*, NH); 7.83 (*t*, $J = 5.9$, NH); 7.61 (*s*, NH); 7.35–7.19 (*m*, 5 arom. H); 3.96–3.90, 3.78–3.42 (2*m*, C*H*$_2$OH, CH_2(Gly), CH); 1.37, 1.36, 1.32, 1.29 (4*s*, 2 Me_2C). ^{13}C-NMR: 175.2, 173.8, 172.4, 168.2 (4*s*, 4 CO); 137.7 (*s*, 1 arom. C); 128.1, 128.0, 126.6 (3*d*, 5 arom. C); 63.7 (*t*, CH_2OH); 55.9, 54.7 (2*s*, 2 Me_2C); 53.7 (*d*, CH); 42.5 (*t*, CH_2(Gly)); 25.9, 24.73, 24.66, 24.1 (4*q*, 2 *Me*$_2$C). ESI-MS: 394 (100, $[M + H]^+$).

5.5. *Methyl 2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-1-oxoethyl]amino}-2-methyl-1-oxopropyl)amino]ethanoate* (**17**). According to *GP 1*, **16** (0.477 g, 1.21 mmol), glycine methyl ester hydrochloride (0.170 g, 1.35 mmol), TBTU (0.403 g, 1.26 mmol), HOBt (0.172 g, 1.27 mmol), and Et_3N (0.376 g, 3.72 mmol) in MeCN (10 ml), stirred for 13 h, 50 ml of AcOEt, 2 × 10 ml of 5% $KHSO_4$,

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[4]) The signals for the COOH group and the OH group could not be located.

2×20 ml of AcOEt, 2×10 ml of 5% $NaHCO_3$, 2×20 ml of AcOEt, 20 ml of brine, CC (SiO_2; CH_2Cl_2/MeOH 10:1): 0.220 g (39%) of **17**. Foam. IR: 3309*s*, 3061*w*, 2986*w*, 2937*w*, 1737*m*, 1654v*s*, 1542v*s*, 1468*w*, 1439*w*, 1386*m*, 1365*m*, 1335*w*, 1266*m*, 1221*m*, 1196*m*, 1046*w*, 1023*w*, 701*w*. ^{1}H-NMR: 8.53 (*s*, NH); 7.82 (*t*, $J = 5.4$, NH); 7.70 (*t*, $J = 5.7$, NH); 7.62 (*s*, NH); 7.34–7.21 (*m*, 5 arom. H); 5.01 (*t*, $J = 4.7$, OH); 4.04–3.47 (*m*, MeO, CH_2OH, 2 CH_2(Gly), CH); 1.41, 1.39, 1.32, 1.31 (4*s*, 2 Me_2C). ^{13}C-NMR: 174.5, 172.4, 170.1, 168.5 (4*s*, 5 CO); 137.5 (*s*, 1 arom. C); 128.1, 127.9, 126.7 (3*d*, 5 arom. C); 63.8 (*t*, CH_2OH); 55.9 (*s*, 2 Me_2C); 53.6 (*d*, CH); 51.5 (*q*, MeO); 43.2, 40.8 (2*t*, 2 CH_2(Gly)); 26.0, 25.2, 24.8, 23.8 (4*q*, 2 Me_2C). ESI-MS: 465 (100, $[M+H]^+$).

5.6. *2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-1-oxoethyl]-amino}-2-methyl-1-oxopropyl)amino]ethanoic Acid* (**18**). According to *GP 4*, **17** (0.200 g, 0.43 mmol), LiOH·H_2O (0.057 g, 1.36 mmol) and 5 ml of THF/MeOH/H_2O 3:1:1, stirred for 19 h, 10 ml of brine, 4×50 ml of AcOEt: 0.184 g (95%) of **18**. Colorless foam. IR: 3311*s*, 3061*w*, 2987*m*, 2938*m*, 1736*m*, 1659v*s*, 1540*s*, 1456*w*, 1387*m*, 1366*m*, 1338*w*, 1220*m*, 1194*m*, 1046*w*, 1021*w*, 701*w*. ^{1}H-NMR: 12.28 (br. *s*, COOH); 8.53 (*s*, NH); 7.83 (*t*, $J = 5.3$, NH); 7.63–7.59 (*m*, 2 NH); 7.32–7.22 (*m*, 5 arom. H); 5.03 (br. *s*, OH); 3.96–3.47 (*m*, CH_2OH, 2 CH_2(Gly), CH); 1.41, 1.39, 1.33, 1.31 (4*s*, 2 Me_2C). ^{13}C-NMR (151 MHz): 174.5, 174.3, 172.4, 171.0, 168.6 (5*s*, 5 CO); 137.5 (*s*, 1 arom. C); 128.1, 127.9, 126.7 (3*d*, 5 arom. C); 63.8 (*t*, CH_2OH); 55.9 (*s*, 2 Me_2C); 53.5 (*d*, CH); 43.2, 40.9 (2*t*, 2 CH_2); 26.0, 25.2, 24.8, 23.8 (4*q*, 2 Me_2C). ESI-MS: 451 (90, $[M+H]^+$), 376 (100, $[M-NHCH_2COOH]^+$).

5.7. *2-({2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-methyl-1-oxopropyl}amino)-1-oxoethyl]-amino}-2-methyl-1-oxopropyl)amino]-1-oxoethyl}amino)-2*,N,N-*trimethylpropanamide* (**4e**). According to *GP 3*, **18** (0.168 g, 0.37 mmol) in MeCN (4 ml), **5** (0.081 g, 0.72 mmol) in MeCN (1 ml), stirred for 44 h, CC (SiO_2; CH_2Cl_2/MeOH 10:1): 0.086 (41%) of **4e**. White powder. M.p. 209.5–212.9°. IR: 3304*s*, 3060*w*, 2987*w*, 2936*w*, 1655v*s*, 1541*s*, 1467*w*, 1396*m*, 1385*m*, 1364*w*, 1334*w*, 1284*w*, 1196*w*, 1120*w*, 1053*w*, 1020*w*, 700*w*. ^{1}H-NMR: 8.59 (*s*, NH); 7.91 (*t*, $J = 5.6$, NH); 7.85 (*s*, NH); 7.81 (*t*, $J = 6.1$, NH); 7.55 (*s*, NH); 7.33–7.22 (*m*, 5 arom. H); 4.99 (*t*, $J = 4.8$, OH); 3.94–3.89, 3.78–3.70, 3.64–3.53 (3*m*, CH_2OH, 2 CH_2(Gly), CH); 2.9, 2.8 (2 br. *s*, Me_2N); 1.39, 1.36, 1.35, 1.33, 1.30 (5*s*, 3 Me_2C). ^{13}C-NMR: 174.6, 174.0, 172.5, 171.6, 170.0, 167.7 (6*s*, 6 CO); 137.5 (*s*, 1 arom. C); 128.1, 127.9, 126.7 (3*d*, 5 arom. C); 63.7 (*t*, CH_2OH); 55.9, 55.8, 55.4 (3*s*, 3 Me_2C); 53.5 (*d*, CH); 43.4, 42.5 (2*t*, 2 CH_2); 37.3 (*q*, Me_2N); 25.9, 25.7, 25.6, 24.9, 24.8, 23.8 (6*q*, 3 Me_2C). ESI-MS: 518 (100, $[M-Me_2N]^+$).

6. *Preparation of the Hexapeptide* **4f**. 6.1. *Methyl 2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]ethanoate* (**19**). According to *GP 1*, tropic acid (1.214 g, 7.31 mmol), glycine methyl ester hydrochloride (0.955 g, 7.61 mmol), TBTU (2.349 g, 7.32 mmol), HOBt (0.995 g, 7.36 mmol), and Et_3N (2.214 g, 21.9 mmol) in MeCN (25 ml), stirred for 4.5 h, 100 ml of AcOEt, 2×10 ml of 5% $KHSO_4$, 2×20 ml of AcOEt, 2×10 ml of 5% $NaHCO_3$, 2×20 ml of AcOEt, 20 ml of brine, CC (SiO_2; CH_2Cl_2/MeOH 20:1, CH_2Cl_2/MeOH 10:1): 1.286 g (74%) of **19**. Colorless oil. IR: 3308*s*, 3063*m*, 3030*w*, 2952*m*, 2882*m*, 1748v*s*, 1659v*s*, 1538v*s*, 1454*s*, 1438*s*, 1408*m*, 1381*s*, 1212v*s*, 1181*s*, 1151*m*, 1061*s*, 1024*m*, 980*w*, 742*m*, 702*s*. ^{1}H-NMR: 8.42 (*t*, $J = 5.8$, NH); 7.32–7.21 (*m*, 5 arom. H); 4.76 (*t*, $J = 5.2$, OH); 3.95–3.82, 3.70–3.51 (2*m*, CH_2OH, CH_2(Gly), CH). ^{13}C-NMR: 172.1, 170.2 (2*s*, 2 CO); 138.1 (*s*, 1 arom. C); 128.0, 126.6 (2*d*, 5 arom. C); 63.3 (*t*, CH_2OH); 54.0 (*d*, CH); 51.5 (*q*, MeO); 40.5 (*t*, CH_2(Gly)). ESI-MS: 260 (100, $[M+Na]^+$), 238 (38, $[M+H]^+$).

6.2. *2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]ethanoic Acid* (**20**). According to *GP 4*, **19** (1.286 g, 5.42 mmol), LiOH·H_2O (0.693 g, 16.5 mmol), 10 ml THF/MeOH/H_2O 3:1:1, stirred for 17 h, 25 ml of brine, 4×100 ml of AcOEt: 1.183 g (98%) of **20**. Colorless foam. IR: 3414*s*, 3251*s*, 3067*s*, 2932*m*, 2878*m*, 1725v*s*, 1659v*s*, 1557*s*, 1488*m*, 1454*w*, 1436*m*, 1408*m*, 1380*m*, 1306*w*, 1269*m*, 1249v*s*, 1213*m*, 1181*m*, 1112*w*, 1053*s*, 1028*m*, 931*w*, 879*w*, 747*m*, 708*s*. ^{1}H-NMR[4]): 8.30 (*t*, $J = 5.7$, NH); 7.34–7.19 (*m*, 5 arom. H); 3.95–3.89, 3.71–3.66 (2*m*, CH_2OH); 3.76 (*d*, $J = 5.8$, CH_2(Gly)); 3.59–3.53 (*m*, CH). ^{13}C-NMR: 171.9, 171.1 (2*s*, 2 CO); 138.2 (*s*, 1 arom. C); 128.02, 128.00, 126.6 (3*d*, 5 arom. C); 63.4 (*t*, CH_2OH); 54.0 (*d*, CH); 40.6 (*t*, CH_2(Gly)). ESI-MS: 246 (100, $[M+Na]^+$).

6.3. *2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-1-oxoethyl}amino)-2*,N,N-*trimethylpropanamide* (**21**). According to *GP 2*, **20** (1.183 g, 5.30 mmol) in MeCN (8 ml) and **5** (0.605 g, 5.39 mmol) in MeCN (1 ml), stirred for 20 min: 1.433 g (81%) of **21**. White powder. M.p. 110.5–111.2°. IR: 3344v*s*, 3060*m*, 2984*m*, 2933*m*, 1651v*s*, 1619v*s*, 1533v*s*, 1454*m*, 1397*s*, 1365*s*, 1263*m*, 1209*m*, 1121*m*, 1060*m*, 1020*m*, 733*m*, 701*s*, 616*m*. ^{1}H-NMR: 8.33 (*t*, $J = 5.6$, NH); 7.91 (*s*, NH); 7.35–7.19 (*m*, 5 arom. H); 4.96 (*t*, $J = 4.8$, OH); 3.98–3.90, 3.78–3.55 (2*m*, CH_2OH, CH_2(Gly), CH); 2.82 (br. *s*, Me_2N); 1.30 (*s*, Me_2C). ^{13}C-NMR: 172.0, 171.5, 167.3 (3*s*, 3 CO); 137.9 (*s*, 1 arom. C); 128.04, 127.98, 126.7 (3*d*, 5 arom. C); 63.5 (*t*, CH_2OH); 55.4 (*s*, Me_2C); 54.0 (*d*, CH); 41.8 (*t*, CH_2(Gly)); 37.2 (*q*, Me_2N); 25.7, 25.6 (2*q*, Me_2C). ESI-MS: 358 (100, $[M+Na]^+$).

6.4. *2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-1-oxoethyl}amino)-2-methylpropanoic Acid* (**22**). According to *GP 6*, **21** (1.338 g, 3.99 mmol) and 20 ml of 3N HCl (H_2O/THF 1:1), stirred for 23 h, 10 ml of brine, 4×100 ml of AcOEt: 0.832 g (68%) of **22**. White powder: M.p. 190.4–192.5°. IR: 3495*s*, 3361v*s*, 3279*s*,

3039*m*, 2883*m*, 2540*m*, 1716v*s*, 1665v*s*, 1621v*s*, 1533v*s*, 1465v*s*, 1392*m*, 1376*w*, 1361*w*, 1344*m*, 1315*m*, 1238*s*, 1204v*s*, 1177*s*, 1056*s*, 1039*m*, 994*w*, 974*w*, 956*w*, 866*w*, 799*m*, 751*m*, 700*m*, 670*w*. ^{1}H-NMR[4]): 8.27 (*t*, *J* = 5.5, NH); 7.79 (*s*, NH); 7.35–7.19 (*m*, 5 arom. H); 3.97–3.91, 3.79–3.55 (2*m*, C*H*$_2$OH, CH$_2$(Gly), CH); 1.32, 1.31 (2*s*, Me$_2$C). ^{13}C-NMR: 175.2, 171.9, 167.9 (3*s*, 3 CO); 138.0 (*s*, 1 arom. C); 128.04, 128.00, 126.6 (3*d*, 5 arom. C); 63.5 (*t*, CH$_2$OH); 54.7 (*s*, Me$_2$*C*); 54.0 (*d*, CH); 41.8 (*t*, CH$_2$(Gly)); 24.8, 24.7 (2*q*, *Me*$_2$C). ESI-MS: 309 (100, [*M* + Na]$^+$).

6.5. *2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-1-oxoethyl}amino)-2-methyl-1-oxopropyl]amino}-2*,N,N-*trimethylpropanamide* (**23**). According to *GP 2*, **22** (0.775 g, 2.51 mmol) in MeCN (10 ml) and **5** (0.300 g, 2.67 mmol) in MeCN (1 ml), stirred for 18 h: 0.464 g (44%) of **23**. White powder. M.p. 130.8–132.3°. IR: 3299v*s*, 3063*m*, 2986*m*, 2937*m*, 1661v*s*, 1538v*s*, 1467*s*, 1395*s*, 1365*s*, 1329*m*, 1260*m*, 1204*s*, 1176*m*, 1121*m*, 1058*s*, 1021*w*, 748*w*, 701*s*, 613*w*. ^{1}H-NMR: 8.54 (*t*, *J* = 5.2, NH); 7.62 (*s*, NH); 7.35–7.29 (*m*, 5 arom. H); 4.94 (*t*, *J* = 4.6, OH); 3.96–3.90, 3.76–3.61 (2*m*, C*H*$_2$OH, CH$_2$(Gly), CH); 2.84 (br. *s*, Me$_2$N); 1.31, 1.30 (2*s*, 2 Me$_2$C). ^{13}C-NMR: 172.9, 172.7, 171.8, 168.3 (4*s*, 4 CO); 137.7 (*d*, 1 arom. C); 128.1, 128.0, 126.7 (3*d*, 5 arom. C); 63.4 (*t*, CH$_2$OH); 56.0, 55.6 (2*s*, 2 Me$_2$*C*); 53.9 (*d*, CH); 43.4 (*t*, CH$_2$(Gly)); 37.2 (*q* Me$_2$N); 25.3, 25.2, 24.8 (3*q*, 2 *Me*$_2$C). ESI-MS: 443 (24, [*M* + Na]$^+$), 376 (100, [*M* + Na]$^+$).

6.6. *2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-1-oxoethyl}amino)-2-methyl-1-oxopropyl]amino}-2-methylpropanoic Acid* (**24**). Amide **23** (0.431 g, 1.025 mmol) was dissolved in 5 ml of 3N HCl/THF 1:1, and the soln. was stirred at r.t. for 18 h. The solvent was evaporated, 15 ml of brine was added, the mixture was extracted with 3 × 100 ml of AcOEt, evaporated, and the residue was dried under h.v. The material was used for the next reaction step without further purification.

6.7. *2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-1-oxoethyl}amino)-2-methyl-1-oxopropyl]-amino}-2-methyl-1-oxopropyl)amino]-2*,N,N-*trimethylpropanamide* (**25**). To a stirred suspension of crude **24** in MeCN was added a soln. of **5** (0.196 g, 1.75 mmol) in MeCN. The mixture was stirred at r.t. under N_2, evaporated, 25 ml of brine was added, the mixture was extracted with 5 × 100 ml of AcOEt, and purified by CC (SiO_2; CH_2Cl_2/MeOH 10:1). The product was crystallized from MeCN and dried under h.v. Yield of **25**: 0.352 g (68%). White powder. M.p. 208.4–212.3°. IR: 3286*s*, 2985*w*, 2936*w*, 1661v*s*, 1625*s*, 1534*s*, 1466*m*, 1386*m*, 1365*m*, 1330*w*, 1259*w*, 1204*w*, 1173*w*, 1121*w*, 1055*w*, 701*w*. ^{1}H-NMR: 7.40–7.25 (*m*, 5 arom. H); 4.16–4.08, 3.82–3.72 (2*m*, C*H*$_2$OH, CH$_2$(Gly), CH); 3.07, 2.91 (2 br. *s*, Me$_2$N); 1.46, 1.44, 1.43, 1.41, 1.37, 1.35 (6*s*, 3 Me$_2$C). ^{13}C-NMR (CD_3OD): 176.5, 176.1, 175.6, 175.4, 171.8 (5*s*, 5 CO); 138.2 (*s*, 1 arom. C); 129.7, 129.3, 128.6 (3*d*, 5 arom. C); 65.4 (*t*, CH$_2$OH); 58.1, 57.8 (2*s*, 3 Me$_2$*C*); 56.1 (*d*, CH); 39.0 (*t*, CH$_2$(Gly)); 39.0, 38.1 (2*q*, Me$_2$N); 26.2, 26.0, 25.6, 25.5, 25.1 (5*q*, 3 *Me*$_2$C). ESI-MS: 528 (11, [*M* + Na]$^+$), 461 (100, [*M* − Me$_2$N]$^+$).

6.8. *2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-1-oxoethyl}amino)-2-methyl-1-oxopropyl]-amino}-2-methyl-1-oxopropyl)amino]-2-methylpropanoic Acid* (**26**). Amide **25** (0.340 g, 0.672 mmol) was dissolved in 4 ml of 3N HCl/THF 1:1, and the soln. was stirred at r.t. for 45 h. The solvent was evaporated, 5 ml of brine was added, the mixture was extracted with 3 × 40 ml of AcOEt, evaporated, and the residue was dried under h.v.: 0.255 g of crude **26**. The material was used for the next reaction step without further purification.

6.9. *2-({2-[(2-{[2-({2-[(3-Hydroxy-1-oxo-2-phenylpropyl)amino]-1-oxoethyl}amino)-2-methyl-1-oxopropyl]-amino}-2-methyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}amino)-2*,N,N-*trimethylpropanamide* (**4f**). According to *GP 3*, crude **26** (0.255 g) in MeCN (4 ml) and **5** (0.068 g, 0.61 mmol) in MeCN (1 ml), stirred for 72 h, CC (SiO_2; CH_2Cl_2/MeOH 10:1), and crystallization from MeCN: 0.235 g (59%) of **4f**. White powder. M.p. 237.2° (dec.). IR: 3406*s*, 3296v*s*, 2985*m*, 2939*m*, 1656v*s*, 1535v*s*, 1468*m*, 1383*m*, 1363*s*, 1336*w*, 1284*w*, 1259*w*, 1224*m*, 1172*w*, 1119*w*, 1058*m*, 703*w*, 667*w*, 606*w*. ^{1}H-NMR: 8.46 (*m*, NH); 8.18, 7.64, 7.40 (3*s*, 3 NH); 7.34–7.20 (*m*, 5 arom. H); 4.93 (*t*, *J* = 5.0, OH); 3.97–3.89, 3.73–3.60 (2*m*, C*H*$_2$OH, CH$_2$(Gly), CH); 2.86 (br. *s*, Me$_2$N); 1.33, 1.30, 1.29, 1.28 (4*s*, 4 Me$_2$C). ^{13}C-NMR: 174.5, 173.5, 173.1, 172.8, 172.0, 169.9 (6*s*, 6 CO); 137.8 (*s*, 1 arom. C); 128.1, 128.0, 126.7 (3*d*, 5 arom. C); 63.4 (*t*, CH$_2$OH); 56.0, 55.9, 55.7, 55.4 (4*s*, 4 Me$_2$*C*); 54.0 (*d*, CH); 43.1 (*t*, CH$_2$(Gly)); 37.1 (*q*, Me$_2$N); 25.4, 25.1, 25.0, 24.6 (4*q*, 4 *Me*$_2$C). ESI-MS: 613 (67, [*M* + Na]$^+$), 546 (100, [*M* − Me$_2$N]$^+$).

7. *Cyclization of Hexapeptides* **4** *with HCl to Cyclic Depsipeptides* **27**. *General Procedure 7* (*GP 7*). A stirred suspension of **4** in dry toluene (30–240 ml) was warmed to 100° under N_2, and a stream of dry HCl gas was slowly passed through the suspension for 14–20 min at 100°. The resulting soln. was then purged with N_2 for 30 min to remove remaining HCl, the toluene was evaporated, and 10 ml of THF/EtO_2 1:1 was added. After 30 min of stirring at r.t., the suspension was filtered, followed by evaporation of the solvent to yield a solid crude product, which was purified by CC.

7.1. *3,3,6,6,9,9,12,12,15,15-Decamethyl-18-phenyl-1-oxa-4,7,10,13,16-pentaazacyclononadecane-2,5,8,11,14,17-hexone* (**27a**). *a*) According to *GP 7*, **4a** (0.050 g, 0.081 mmol) in toluene (240 ml), 14 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.011 g (24%) of **27a**. White powder. M.p. 223.5° (dec.). IR: 3639*w*,

3426*m*, 3354*m*, 3286*m*, 2984*m*, 2940*w*, 1751*m*, 1651v*s*, 1538*s*, 1456*m*, 1386*m*, 1364*m*, 1263*m*, 1232*m*, 1172*w*, 1143*m*, 702*w*. ^{1}H-NMR ((D$_5$)pyridine, 600 MHz)[5]): 9.56 (*s*, NH, Aib(1)); 8.49 (*s*, NH, Aib(5)); 8.41 (*s*, NH, Aib(4)); 8.08 (*s*, NH, Aib(2)); 7.76 (*s*, NH, Aib(3)); 7.37–7.36, 7.34–7.28 (2*m*, 5 arom. H); 4.77–4.69 (*m*, CH$_2$O); 4.19–4.17 (*m*, CH); 2.04 (*s*, Me(a), Aib(3)); 2.00 (*s*, Me(a), Aib(4)); 1.94 (*s*, Me(b), Aib(4)); 1.93 (*s*, Me(b), Aib(3)); 1.84 (*s*, Me(a), Aib(5)); 1.78 (*s*, Me(a), Aib(2)); 1.65 (*s*, Me(b), Aib(5)); 1.63 (*s*, Me(a), Aib(1)); 1.60 (*s*, Me(b), Aib(2)); 1.36 (*s*, Me(b), Aib(1)). ^{13}C-NMR ((D$_5$)pyridine, 151 MHz)[5]): 176.5 (*s*, CO, Aib(3)); 176.2 (*s*, CO, Aib(1)); 175.14 (*s*, CO, Aib(4)); 175.06 (*s*, CO, Aib(5)); 174.5 (*s*, CO, Aib(2)); 171.8 (*s*, CO, Tro); 138.4 (*s*, 1 arom. C); 129.6, 128.6, 128.3 (3*d*, 5 arom. C); 65.5 (*t*, CH$_2$O); 58.5 (*s*, Me$_2$*C*, Aib(3)); 58.4 (*s*, Me$_2$*C*, Aib(4)); 58.2 (*s*, Me$_2$*C*, Aib(2)); 57.00 (*s*, Me$_2$*C*, Aib(5)); 56.98 (*s*, Me$_2$*C*, Aib(1)); 52.1 (*d*, CH); 28.5 (*q*, Me(b), Aib(3)); 27.62 (*q*, Me(b), Aib(2)); 27.58 (*q*, Me(b), Aib(4)); 26.9 (*q*, Me(b), Aib(1)); 26.2 (*q*, Me(b), Aib(5)); 24.8 (*q*, Me(a), Aib(3)); 24.72 (*q*, Me(a), Aib(5)); 24.66 (*q*, Me(a), Aib(4)); 23.9 (*q*, Me(a), Aib(2)); 22.9 (*q*, Me(a), Aib(1)). ESI-MS: 596 (62, $[M+Na]^+$), 574 (100, $[M+H]^+$).

b) According to *GP 7*, **4a** (0.050 g, 0.081 mmol) in toluene (120 ml), 12 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 25:1) and crystallization from EtO: 0.006 g (13%) of **27a**.

c) According to *GP 7*, **4a** (0.050 g, 0.081 mmol) in toluene (30 ml), 15 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 20:1): 0.002 g (4%) of **27a**.

7.2. *3,3,12,12,15,15-Hexamethyl-18-phenyl-1-oxa-4,7,10,13,16-pentaazacyclononadecane-2,5,8,11,14,17-hexone* (**27b**). *a*) According to *GP 7*, **4b** (0.055 g, 0.098 mmol) in toluene (240 ml), 20 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 25:1) and crystallization from Et$_2$O: 0.040 g (79%) of **27b**. White powder. M.p. 176.0° (dec.). IR: 3319v*s*, 3063*w*, 2986*m*, 2938*w*, 1741*s*, 1660v*s*, 1533v*s*, 1456*s*, 1407*w*, 1387*s*, 1366*m*, 1335*w*, 1277*s*, 1151*s*, 1045*w*, 1021*w*, 737*w*, 701*m*. ^{1}H-NMR ((D$_5$)pyridine, 600 MHz)[5]): 9.64 (*s*, NH, Aib(1)); 18.98–8.96 (*m*, NH, Gly(1)); 8.94–8.92 (*m*, NH, Gly(2)); 8.30 (*s*, NH, Aib(3)); 8.27 (*s*, NH, Aib(2)); 7.40–7.38, 7.32–7.26 (2*m*, 5 arom. H); 4.84–4.80, 4.61–4.59 (2*m*, CH$_2$O); 4.73–4.69, 4.11–4.07 (2*m*, CH$_2$, Gly(1)); 4.51–4.47, 3.69–3.65 (2*m*, CH$_2$, Gly(2)); 4.29–4.27 (*m*, CH); 1.85 (*s*, Me(a), Aib(2)); 1.76 (*s*, Me(a), Aib(3)); 1.66 (*s*, Me(a), Aib(1)); 1.64 (*s*, Me(b), Aib(2)); 1.48 (*s*, Me(b), Aib(1), Me(b), Aib(3)). ^{13}C-NMR ((D$_5$)pyridine, 151 MHz)[5]): 176.6 (*s*, CO, Aib(1)); 175.5 (*s*, CO, Aib(2)); 175.1 (*s*, CO, Aib(3)); 172.2 (*s*, CO, Tro); 171.7 (*s*, CO, Gly(1)); 169.6 (*s*, CO, Gly(2)); 138.2 (*s*, 1 arom. C); 129.2, 128.2, 127.8 (3*d*, 5 arom. C); 66.0 (*t*, CH$_2$O); 58.0 (*s*, Me$_2$*C*, Aib(2)); 57.0 (*s*, Me$_2$*C*, Aib(1)); 56.1 (*s*, Me$_2$*C*, Aib(3)); 51.6 (*d*, CH); 44.7 (*t*, CH$_2$, Gly(2)); 44.3 (*t*, CH$_2$, Gly(1)); 27.2 (*q*, Me(b), Aib(2)); 26.2 (*q*, Me(b), Aib(3)); 26.1 (*q*, Me(b), Aib(1)); 24.4 (*q*, Me(a), Aib(3)); 24.1 (*q*, Me(a), Aib(2)); 23.2 (*q*, Me(a), Aib(1)). ESI-MS: 540 (74, $[M+Na]^+$), 518 (100, $[M+H]^+$).

b) *According to GP 7*, **4b** (0.051 g, 0.091 mmol) in toluene (120 ml), 20 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 25:1) and crystallization from Et$_2$O: 0.017 g (36%) of **27b**.

c) *According to GP 7*, **4b** (0.051 g, 0.091 mmol) in toluene (30 ml), 18 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 25:1) and crystallization from Et$_2$O: 0.012 g (26%) of **27b**.

7.3. *(6S,18R/S)-3,3,12,12,15,15-Hexamethyl-6,7-trimethylen-18-phenyl-1-oxa-4,7,10,13,16-pentaazacyclononadecane-2,5,8,11,14,17-hexone* (Isomer 1, **27c**). According to *GP 7*, **4c** (0.047 g, 0.078 mmol) in toluene (240 ml), 20 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 30:1, CH$_2$Cl$_2$/MeOH 20:1) and crystallization from Et$_2$O: 0.020 g of crude **27c**. The crude **27c** (0.020 g) was purified by prep. RP-HPLC. Conditions: stationary phase, *Nucleosil 100-7 C8*; column, 250 × 21 mm; mobile phase, 10 ml/min, H$_2$O/MeCN 1:1; UV detector, 254 nm. Total yield of **27c**: 0.015 g (41%). White powder. M.p. 160.6° (dec.). $[\alpha]_D = -8.0$ ($c = 0.60$, EtOH). IR: 3347*s*, 3061*w*, 2984*m*, 2937*m*, 1742*s*, 1660v*s*, 1539v*s*, 1453*s*, 1387*m*, 1364*m*, 1334*m*, 1279*s*, 1226*m*, 1144*s*, 1046*w*, 1019*w*, 995*w*, 701*m*. ^{1}H-NMR ((D$_5$)pyridine, 600 MHz)[5]): two conformers A and B: 10.01 (*s*, NH, Aib(3), B); 9.62 (*s*, NH, Aib(1), B); 9.30 (*s*, NH, Aib(1), A); 8.68 (*s*, NH, Aib(3), A); 8.68–8.67 (*m*, NH, Gly, B); 8.65–8.64 (*m*, NH, Gly, A); 8.01 (*s*, NH, Aib(2), A); 7.84 (*s*, NH, Aib(2), B); 7.43–7.42, 7.34–7.21 (2*m*, 5 arom. H, A, 5 arom. H, B); 5.05–5.00 (*m*, 1 H of CH$_2$O, B, 1 H of CH$_2$(Gly), B); 4.80–4.77 (*m*, 1 H of CH$_2$O, A); 4.73–4.70 (*m*, 1 H of CH$_2$O, A, 1 H of CH$_2$O, B, CH(Pro), A); 4.66–4.64 (*m*, CH(Pro), B); 4.46–4.44 (*m*, CH(Tro), A); 4.40–4.34 (*m*, 1 H of CH$_2$(Gly), A, 1 H of CH$_2$(Gly), B); 4.18–4.15 (*m*, 1 H of CH$_2$(Gly), A); 4.03–4.01 (*m*, CH(Tro), B); 3.83–3.80, 3.68–3.62 (2*m*, CH$_2$(Pro), B); 3.61–3.53, 3.25–3.21 (2*m*, CH$_2$(Pro), A); 2.23–2.17 (*m*, 1 H of CH$_2$(Pro), A); 2.15–2.05 (*m*, 2 H of 2 CH$_2$(Pro), B); 1.99–1.93 (*m*, 1 H of CH$_2$(Pro), A); 1.97 (*s*, Me(a), Aib(2), A); 1.92 (*s*, Me(a), Aib(2), B); 1.91–1.85 (*m*, 1 H of CH$_2$(Pro), B); 1.84 (*s*, Me(b), Aib(2), A); 1.84–1.79 (*m*, 1 H of CH$_2$(Pro), A); 1.74 (*s*, Me(a), Aib(1), A, Me(a), Aib(3), A); 1.71 (*s*, Me(a), Aib(3), B); 1.70–1.65 (*m*, 1 H of CH$_2$(Pro), A); 1.66 (*s*, Me(b), Aib(2), B); 1.64 (*s*, Me(a), Aib(1), B); 1.61 (*s*, Me(b), Aib(3), A); 1.52–1.45 (*m*, 1 H of CH$_2$(Pro), B); 1.47 (*s*, Me(b), Aib(1), A); 1.46 (*s*, Me(b), Aib(3), B); 1.42 (*s*, Me(b), Aib(1), B).

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[5]) The assignment of the signals was accomplished by 2D-NMR spectroscopy (TOCSY, HSQC, and HMBC).

^{13}C-NMR ((D$_5$)pyridine, 151 MHz)[5]): two conformers A and B: 176.1 (*s*, CO, Aib(2), B); 175.6 (*s*, CO, Aib(2), A); 175.2 (*s*, CO, Aib(3), A); 174.5 (*s*, CO, Aib(1), B); 174.3 (*s*, CO, Aib(3), B); 174.1 (*s*, CO, Aib(1), A); 172.5 (*s*, CO, Tro, A); 172.2 (*s*, CO, Pro, B); 172.1 (*s*, CO, Tro, B); 171.4 (*s*, CO, Pro, A); 169.1 (*s*, CO, Gly, A, CO, Gly, B); 138.0, 137.7 (2*s*, 1 arom. C, A and B); 129.3, 129.1, 128.4, 128.1, 127.9, 127.8 (6*d*, 5 arom. C, A, 5 arom. C, B); 66.7 (*t*, CH$_2$O, A); 64.7 (*t*, CH$_2$O, B); 60.3 (*d*, CH(Pro), A); 59.4 (*d*, CH(Pro), B); 58.2 (*s*, Me$_2$*C*, Aib(2), A); 57.9 (*s*, Me$_2$*C*, Aib(1), A); 57.7 (*s*, Me$_2$*C*, Aib(2), B); 56.8 (*s*, Me$_2$*C*, Aib(1), B); 56.4 (*s*, Me$_2$*C*, Aib(3), A); 55.8 (*s*, Me$_2$*C*, Aib(3), B); 52.0 (*d*, CH(Tro), B); 51.6 (*d*, CH(Tro), A); 47.3 (*t*, CH$_2$(Pro), B); 46.6 (*t*, CH$_2$(Pro), A); 43.6 (*t*, CH$_2$(Gly), B); 42.8 (*t*, CH$_2$(Gly), A); 31.7 (*t*, CH$_2$(Pro), B); 28.2 (*t*, CH$_2$(Pro), A); 27.9 (*q*, Me(b), Aib(2), B); 26.6 (*q*, Me(b), Aib(1), B); 26.4 (*q*, Me(b), Aib(1), A); 26.0 (*q*, Me(b), Aib(2), A); 25.9 (*q*, Me(b), Aib(3), B); 25.8 (*q*, Me(b), Aib(3), A); 25.3 (*q*, Me(a), Aib(2), A); 25.0 (*t*, CH$_2$(Pro), A); 24.79 (*q*, Me(a), Aib(3), B); 24.76 (*q*, Me(a), Aib(3), A); 24.0 (*q*, Me(a), Aib(2), B); 23.5 (*q*, Me(a), Aib(1), A); 23.1 (*t*, CH$_2$(Pro), B); 22.5 (*q*, Me(a), Aib(1), B). ESI-MS: 580 (100, $[M+Na]^+$), 558 (12, $[M+H]^+$).

Isomer 2, **27d**. According to *GP 7*, **4d** (0.047 g, 0.078 mmol) in toluene (240 ml), 20 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 30:1, CH$_2$Cl$_2$/MeOH 20:1) and crystallization from Et$_2$O: 0.029 g of crude **27d**. The crude **27d** (0.020 g) was purified by prep. RP-HPLC. Conditions: stationary phase, *Nucleosil 100-7 C8*; column, 250 × 21 mm; mobile phase, 10 ml/min, H$_2$O/MeCN 1:1; UV detector, 254 nm. Total yield of **27d**: 0.013 g (43%). White powder. M.p. 171.7° (dec.). $[\alpha]_D = +9.2$ ($c = 0.65$, EtOH). IR: 3338*s*, 3061*w*, 2984*m*, 2939*m*, 2879*w*, 1743*s*, 1658v*s*, 1535v*s*, 1452*s*, 1386*m*, 1364*m*, 1334*m*, 1278*s*, 1226*m*, 1144*s*, 1046*w*, 1020*w*, 996*w*, 736*w*, 701*m*. ^{1}H-NMR ((D$_5$)pyridine, 600 MHz)[5]): two conformers A and B: 10.01 (*s*, NH, Aib(3), B); 9.62 (*s*, NH, Aib(1), B); 9.30 (*s*, NH, Aib(1), A); 8.69–8.67 (*m*, NH, Gly, B); 8.68 (*s*, NH, Aib(3), A); 8.66–8.64 (*m*, NH, Gly, A); 8.00 (*s*, NH, Aib(2), A); 7.83 (*s*, NH, Aib(2), B); 7.43–7.41, 7.34–7.33, 7.30–7.24 (3*m*, 5 arom. H, A, 5 arom. H, B); 5.04–5.00 (*m*, 1 H of CH$_2$(Gly), B, 1 H of CH$_2$O, B); 4.80–4.77 (*m*, 1 H of CH$_2$O, A); 4.73–4.70 (*m*, 1 H of CH$_2$O, A, 1 H of CH$_2$O, B, CH(Pro), A); 4.65–4.63 (*m*, CH(Pro), B); 4.45–4.43 (*m*, CH(Tro), A); 4.39–4.34 (*m*, 1 H of CH$_2$(Gly), A, 1 H of CH$_2$(Gly), B); 4.18–4.15 (*m*, 1 H of CH$_2$(Gly), A); 4.02–4.00 (*m*, CH(Tro), B); 3.83–3.79 (*m*, 1 H of CH$_2$(Pro), B); 3.68–3.63 (*m*, 1 H of CH$_2$(Pro), B); 3.56–3.52 (*m*, 1 H of CH$_2$(Pro), A); 3.25–3.21 (*m*, 1 H of CH$_2$(Pro), A); 2.22–2.18 (*m*, 1 H of CH$_2$(Pro), A); 2.14–2.05 (*m*, 1 H of CH$_2$(Pro), A); 2.14–2.05 (*m*, 2 H of 2 CH$_2$(Pro), B); 2.01–1.94 (*m*, 1 H of CH$_2$(Pro), A); 1.97 (*s*, Me(a), Aib(2), A); 1.92 (*s*, Me(a), Aib(2), B); 1.89–1.85 (*m*, 1 H of CH$_2$(Pro), B); 1.84 (*s*, Me(b), Aib(2), A); 1.83–1.78 (*m*, 1 H of CH$_2$(Pro), A); 1.74 (*s*, Me(a), Aib(1), A, Me(a), Aib(3), A); 1.70 (*s*, Me(a), Aib(3), B); 1.69–1.68 (*m*, 1 H of CH$_2$(Pro), A); 1.66 (*s*, Me(b), Aib(2), B); 1.64 (*s*, Me(a), Aib(1), B); 1.61 (*s*, Me(b), Aib(3), A); 1.52–1.48 (*m*, 1 H of CH$_2$(Pro), B); 1.46 (*s*, Me(b), Aib(1), A); 1.45 (*s*, Me(b), Aib(3), B); 1.42 (*s*, Me(b), Aib(1), B). ^{13}C-NMR ((D$_5$)pyridine, 151 MHz)[5]): two conformers A and B: 176.1 (*s*, CO, Aib(2), B); 175.6 (*s*, CO, Aib(2), A); 175.1 (*s*, CO, Aib(3), A); 174.5 (*s*, CO, Aib(1), B); 174.3 (*s*, CO, Aib(3), B); 174.1 (*s*, CO, Aib(1), A); 172.5 (*s*, CO, Tro, A); 172.2 (*s*, CO, Pro, B); 172.1 (*s*, CO, Tro, B); 171.4 (*s*, CO, Pro, A); 169.1 (*s*, 2 CO, Gly, A, Gly, B); 138.0, 137.7 (2*s*, 1 arom. C, A and B); 129.3, 129.1, 128.4, 128.1, 127.9, 127.8 (6*d*, 5 arom. C, A and B); 66.7 (*t*, CH$_2$O, A); 64.7 (*t*, CH$_2$O, B); 60.3 (*d*, CH, Pro, A); 59.4 (*d*, CH, Pro, B); 58.2 (*s*, Me$_2$*C*, Aib(2), A); 57.9 (*s*, Me$_2$*C*, Aib(1), A); 57.7 (*s*, Me$_2$*C*, Aib(2), B); 56.8 (*s*, Me$_2$*C*, Aib(1), B); 56.4 (*s*, Me$_2$*C*, Aib(3), A); 55.9 (*s*, Me$_2$*C*, Aib(3), B); 52.1 (*d*, CH(Tro), B); 51.6 (*d*, CH(Tro), A); 47.3 (*t*, CH$_2$(Pro), B); 46.6 (*t*, CH$_2$(Pro), A); 43.6 (*t*, CH$_2$(Gly), B); 42.8 (*t*, CH$_2$(Gly), A); 31.7 (*t*, CH$_2$(Pro), B); 28.2 (*t*, CH$_2$(Pro), A); 27.9 (*q*, Me(b), Aib(2), B); 26.6 (*q*,Me(b), Aib(1), B); 26.4 (*q*, Me(b), Aib(1), A); 26.0 (*q*, Me(b), Aib(2), A); 25.9 (*q*, Me(b), Aib(3), B); 25.8 (*q*, Me(b), Aib(3), A); 25.3 (*q*, Me(a), Aib(2), A); 25.0 (*t*, CH$_2$(Pro), A); 24.79, 24.77 (2*q*, Me(a), Aib(3), A, Me(a), Aib(3), B); 24.0 (*q*, Me(a), Aib(2), B); 23.5 (*q*, Me(a), Aib(1), A); 23.1 (*t*, CH$_2$(Pro), B); 22.5 (*q*, Me(a), Aib(1), B). ESI-MS: 580 (77, $[M+Na]^+$), 558 (100, $[M+H]^+$).

7.4. *5,5,12,12,18,18-Hexamethyl-9-phenyl-7-oxa-1,4,11,14,17-pentaazabicyclo[14.3.0]nonadec-16-ene-3,6,10,13,19-pentone* (**27e**). According to *GP 7*, **4e** (0.052 g, 0.092 mmol) in toluene (240 ml), 20 min. CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 20:1) and crystallization from Et$_2$O: 0.010 g (22%) of **27e**. White powder. M.p. 252.0° (dec.). IR: 3313*s*, 3063*w*, 2984*m*, 2937*w*, 1736v*s*, 1678v*s*, 1532*s*, 1456*m*, 1438*m*, 1386*m*, 1364*m*, 1331*m*, 1279*m*, 1206*m*, 1151*s*, 702*w*, 640*w*, 601*w*. ^{1}H-NMR ((D$_5$)pyridine, 500 MHz)[5]): 10.20 (*s*, NH, Aib(2)); 9.47 (*s*, NH, Aib(1)); 8.53–8.52 (*m*, NH, Gly(1)); 7.54–7.51, 7.35–7.28 (2*m*, 5 arom. H); 5.15–5.10 (*m*, 1 H of CH$_2$(Gly(1))); 4.99–4.95 (*m*, 1 H of CH$_2$O); 4.76–4.74 (*m*, CH); 4.62 (*d*, $J = 16.4$, 1 H of CH$_2$(Gly(2))); 4.45–4.39 (*m*, 1 H of CH$_2$O, 1 H of CH$_2$(Gly(2))); 4.26 (*d*, $J = 13.6$, 1 H of CH$_2$(Gly(1))); 1.81 (*s*, Me(a), Aib(2)); 1.77 (*s*, Me(a), Aib(1)); 1.45 (*s*, Me(b), Aib(2)); 1.38 (*s*, Me(b), Aib(1)); 1.37 (*s*, Me(a), C(18)); 1.36 (*s*, Me(b), C(18)). ^{13}C-NMR ((D$_5$)pyridine, 126 MHz)[5]): 186.4 (*s*, CO, C(19)); 175.3 (*s*, CO, Aib(1)); 175.0 (*s*, CO, Aib(2)); 171.5 (*s*, CO, Tro); 168.7 (*s*, CO, Gly(2)); 159.1 (*s*, CN, C(16)); 137.8 (*s*, 1 arom. C); 129.3, 128.3, 127.9 (3*d*, 5 arom. C); 67.5 (*s*, Me$_2$*C*, C(18)); 67.4 (*t*, CH$_2$O); 57.3 (*s*, Me$_2$*C*, Aib(1)); 56.3 (*s*, Me$_2$*C*, Aib(2)); 50.9 (*d*, CH); 43.6 (*t*, CH$_2$,

Gly(2)); 39.0 (*t*, CH_2, Gly(1)); 28.3 (*q*, Me(b), Aib(1)); 26.7 (*q*, Me(b), Aib(2)); 24.7 (*q*, Me(a), Aib(2)); 24.2 (*q*, Me(a), C(18)); 23.4 (*q*, Me(b), C(18)); 23.0 (*q*, Me(a), Aib(1)). ESI-MS: 500 (100, $[M+H]^+$).

7.5. *3,3,6,6,9,9,12,12-Octamethyl-18-phenyl-1-oxa-4,7,10,13,16-pentaazacyclononadecane-2,5,8,11,14,17-hexone* (**27f**). According to *GP 7*, **4f** (0.054 g, 0.091 mmol) in toluene (240 ml), 20 min. CC (SiO_2; CH_2Cl_2/MeOH 25:1) and crystallization from Et_2O: 0.015 g (30%) of **27f**. White powder. M.p. 210.1° (dec.). IR: 3326*s*, 3064*w*, 2986*m*, 2940*w*, 1737*m*, 1658v*s*, 1538v*s*, 1470*m*, 1455*m*, 1387*m*, 1364*m*, 1273*m*, 1229*m*, 1157*m*, 701*w*, 602*w*. ^{1}H-NMR ((D_5)pyridine, 600 MHz)[5]): 9.85 (*s*, NH, Aib(1)); 9.40–9.39 (*m*, NH, Gly); 8.19 (*s*, NH, Aib(4)); 7.84 (*s*, NH, Aib(3)); 7.77 (*s*, NH, Aib(2)); 7.56–7.54, 7.30–7.25 (2*m*, 5 arom. H); 5.06–5.02, 3.68–3.64 (2*m*, CH_2, Gly); 4.97–4.94, 4.46–4.44 (2*m*, CH_2O); 4.29–4.27 (*m*, CH); 1.994 (*s*, Me(a), Aib(3)); 1.989 (*s*, Me(b), Aib(3)); 1.95 (*s*, Me(a), Aib(4)); 1.84 (*s*, Me(a), Aib(1)); 1.83 (*s*, Me(b), Aib(4)); 1.81 (*s*, Me(a), Aib(2)); 1.62 (*s*, Me(b), Aib(2)); 1.54 (*s*, Me(b), Aib(1)). ^{13}C-NMR ((D_5)pyridine, 151 MHz)[5]): 175.4 (*s*, CO, Aib(1), CO, Aib(4)); 174.7 (*s*, CO, Aib(3)); 174.1 (*s*, CO, Aib(2)); 171.5 (*s*, CO, Tro); 170.3 (*s*, CO, Gly); 136.7 (*s*, 1 arom. C); 129.0, 128.7, 128.0 (3*d*, 5 arom. C); 67.3 (*t*, CH_2O); 57.8 (*s*, Me_2C, Aib(2)); 57.4 (*s*, Me_2C, Aib(3)); 56.7 (*s*, Me_2C, Aib(1)); 56.4 (*s*, Me_2C, Aib(4)); 51.8 (*d*, CH); 42.3 (*t*, CH_2, Gly); 28.4 (*q*, Me(b), Aib(3)); 27.0 (*q*, Me(b), Aib(2)); 26.9 (*q*, Me(b), Aib(4)); 26.7 (*q*, Me(b), Aib(1)); 24.3 (*q*, Me(a), Aib(2)); 24.0 (*q*, Me(a), Aib(4)); 23.8 (*q*, Me(a), Aib(3)); 23.5 (*q*, Me(a), Aib(1)). ESI-MS: 568 (85, $[M+Na]^+$), 546 (100, $[M+H]^+$).

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