Synthesis of Enniatin-like Cyclic Depsipeptides *via* 'Direct Amide Cyclization'

by **Peter Köttgen**[1]), **Anthony Linden**, and **Heinz Heimgartner***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

The synthesis of several 18-membered cyclodepsipeptides with an alternating sequence of α,α-disubstituted α-amino acids and α-hydroxy acids (compounds **14a**–**14e**) is described. The ring closure *via* macrolactonization was accomplished by treatment of a diluted suspension of the corresponding linear precursors **12a**–**12e** in toluene with HCl gas, *i.e.*, the so-called 'direct amide cyclization'. The incorporation of the α,α-disubstituted α-amino acids was achieved *via* the 'azirine/oxazolone method' with 2*H*-azirin-3-amines of type **6** and **9** as building blocks. The structure of the cyclic depsipeptide **14a** was established by X-ray crystallography.

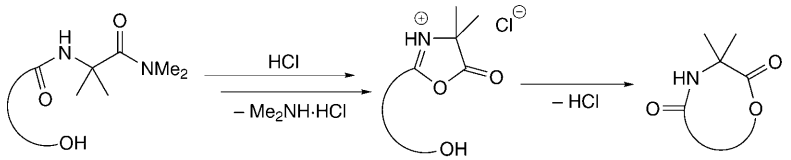
1. Introduction. – Cyclic depsipeptides are peptide analogues in which one or several lactam bonds of the cyclic skeleton are displaced by lactone bonds. The cyclization of these compounds is usually the most demanding step in their synthesis. Several successful cyclizations *via* ester bond formation (lactonization) have been reported [1–3], but ring closure *via* formation of an amide bond (lactamization) [4–6] is usually easier and, therefore, preferred [7].

Cyclization of a peptide or depsipeptide reduces its conformational freedom. This constraint can be increased further if α,α-disubstituted α-amino acids are incorporated into the peptide chain [8], and limiting the flexibility often results in higher receptor-binding affinities [7]. Effective methods for the introduction of α,α-disubstituted α-amino acids and subsequent ring closure to give a cyclic depsipeptide are, therefore, of interest. A useful cyclization method for depsipeptides containing a C-terminal α,α-disubstituted α-amino acid, the so-called 'direct amide cyclization', has been developed in our laboratory [9–20]. The basic concept is depicted in *Scheme 1*: if an amide of type **1** is treated with dry HCl gas, the corresponding 1,3-oxazol-5(4*H*)-one derivative **2** is formed *via* ring closure and elimination of $Me_2NH \cdot HCl$. In the absence of other nucleophiles, a ring enlargement to yield the cyclic product **3** occurs by an intramolecular attack of the ω-OH group of the intermediate oxazolone at the lactone group.

Several cyclic depsipeptides containing one hydroxy acid and several α,α-disubstituted α-amino acids have been prepared by this cyclization method [9–17]. A subgroup among the depsipeptides consists of the so-called regular cyclodepsipeptides [21][22], whose cyclic core shows an alternating pattern of α-amino acids and α-hydroxy acids. Some of these regular cyclodepsipeptides show high biological activity, such as the anti-

[1]) Part of the Ph.D. thesis of *P. K.*, Universität Zürich, 2006.

Scheme 1



biotics valinomycin [23–25] and the enniatins [26], which act as ionophores [27]. Some twelve-membered regular cyclodepsipeptides, which also contain α,α-disubstituted α-amino acids, have been synthesized in our group *via* 'direct amide cyclization' [11]. It was, therefore, of interest to investigate whether 18-membered regular cyclodepsipeptides of the 'enniatin type', composed of α-amino acids and α-hydroxy acids, could also be synthesized by this method. Some preliminary experiments have already been carried out [28]. The incorporation of the α,α-disubstituted α-amino acid units can be achieved *via* the elegant and efficient 'azirine/oxazolone method' that has been developed in our group [29] and successfully applied to the synthesis of peptaibols [30–35], endothiopeptides [36–39], and conformationally restricted cyclic peptides [40–44].

2. Results and Discussion. – 2.1. *Synthesis of the Linear Precursors.* The desired linear precursors **12** were synthesized according to a strategy similar to that reported for the twelve-membered depsipeptides [11] (see also [28]). The same approach has been used in the synthesis of a 24-membered cyclic depsipeptide [45][46].

Three different α-hydroxy acids, **4a**–**4c**, and six different 2*H*-azirin-3-amines **6a**–**6c** and **9a**–**9c**, which are the building blocks for the α,α-disubstituted α-amino acids, were used to prepare the precursors for the 'direct amide cyclization'. An overview of the syntheses is shown in *Scheme 2*.

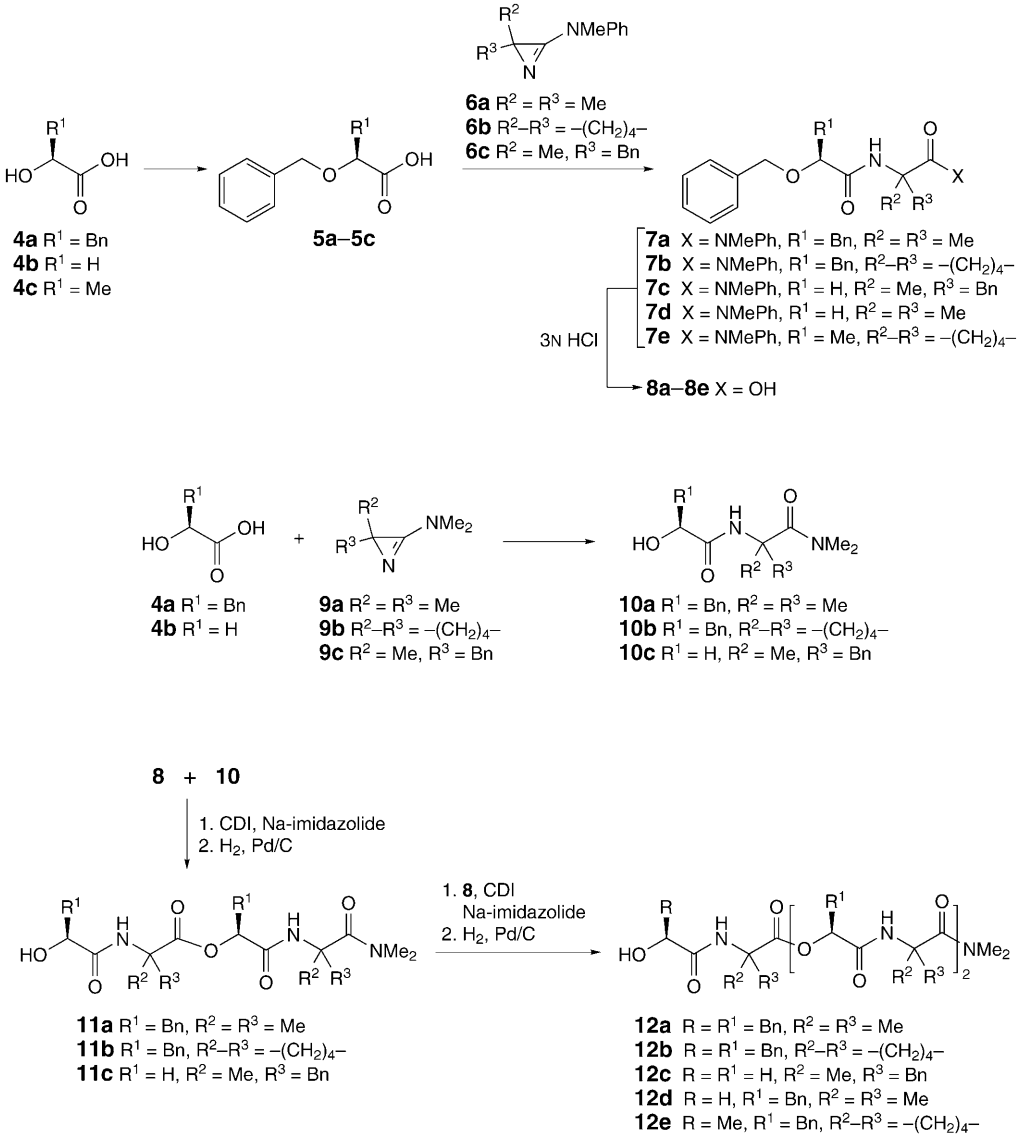
As the 2-benzyl-2-methyl-2*H*-azirin-3-amines **6c** and **9c** were employed as racemates, the synthesis yielded the precursor **12c** for the macrolactonization as a racemic mixture of four diastereoisomers.

2.2. *Macrolactonizations.* With the linear precursors **12a**–**12e** in hand, we studied their cyclizations *via* the 'direct amide cyclization' method (*Scheme 3*). Initial optimization of the reaction conditions was undertaken by using compound **12a**. The solvent and the reaction temperature were adopted from the protocols of the cyclizations that led to similar twelve-membered cyclodepsipeptides [11].

A 10–15 mM solution of **12a** in toluene was treated with a stream of dry HCl gas at 100°. The reaction mixture was then allowed to cool to room temperature, while bubbling N_2 through it. Evaporation of the solvent gave a mixture of the crude product and $Me_2NH \cdot HCl$, which was separated by column chromatography.

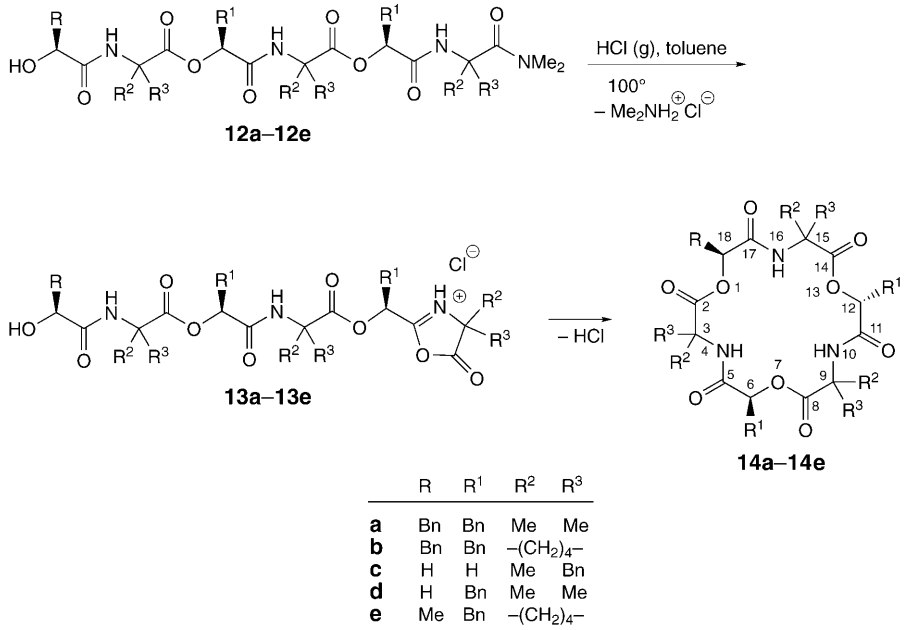
It turned out that longer reaction times reduce the yield of the desired product, probably due to decomposition of the product as well as of the starting material, caused by the limited stability of the ester bonds (see below). On the other hand, short reaction times result in a lower conversion of the starting material, so a compromise for the reaction time had to be found. The treatment with HCl gas over a period of 4.5 min proved

Scheme 2



to be the optimum, yielding 27% of the macrocycle **14a**. The ^{1}H- and ^{13}C-NMR spectra of **14a** clearly show that a single isomer is present, and epimerization had occurred at one of the three stereogenic centers. Epimerization of one of the α-hydroxy acids leads to three topologically different α-hydroxy acid units, as well as three different α,α-dimethyl α-amino acid units in **14a**. Indeed, the NMR spectra showed three different sets of signals instead of one, as would be expected without epimerization. On the other hand, it is worth mentioning that **14a** is optically active. The structure and the rel-

Scheme 3



	R	R^1	R^2	R^3
a	Bn	Bn	Me	Me
b	Bn	Bn	$-(CH_2)_4-$	
c	H	H	Me	Bn
d	H	Bn	Me	Me
e	Me	Bn	$-(CH_2)_4-$	

ative configuration of the recrystallized **14a** were established by X-ray crystallography, and the molecular structure confirms the inverted configuration at one stereogenic center (*Fig.*).

The crystals of **14a** are enantiomerically pure, and there are two molecules of the same enantiomer in the asymmetric unit; however, the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was chosen arbitrarily. This enantiomer has the (3*R*,9*S*,15*S*)-configuration[2]), but due to the absence of a strong anomalous scatterer in the structure, this enantiomer cannot be distinguished crystallographically from the (3*S*,9*R*,15*R*)-enantiomer. Although all sites were expected to have the (*S*)-configuration, it is not possible to determine if one site has inverted, or two. The two symmetry-independent molecules have almost identical conformations, with the only difference being a small rotation in the orientation of the Ph ring of the Bn substituent at C(15). Each of the two symmetry-independent molecules has the same pattern of H-bonds. Two of the amide groups in each molecule form a total of three intramolecular H-bonds. One of these is an interaction with the amide O-atom of the next amide unit around the macrocyclic ring, thereby giving rise to a ten-membered loop with a graph set motif [48] of S(10). The other two intramolecular interactions emanate from the same N-atom as weak bifurcated interactions with the ether O-atoms of the ester groups on either side of this N-atom, thereby creating small loops with graph set motifs of S(5). The third amide group forms an intermolecular H-bond

[2]) Arbitrary C-atom numbering was used in the *Figure*.

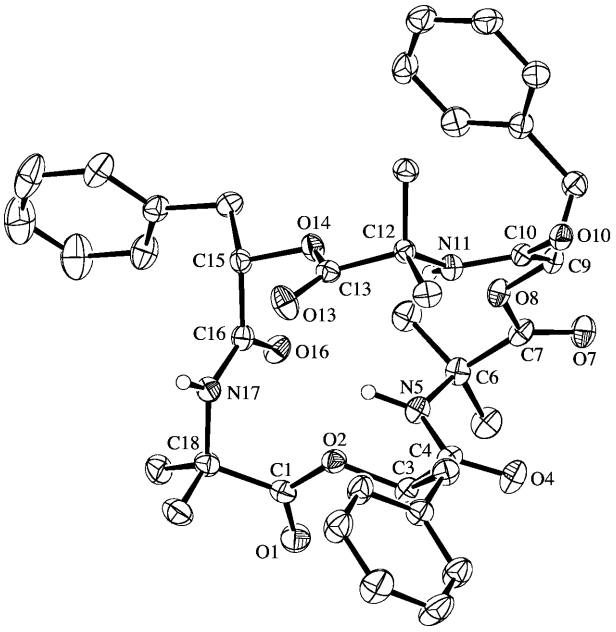


Figure. *ORTEP Plot* [47] *of the molecular structure of one of the symmetry-independent molecules of* **14a** (30% probability ellipsoids; arbitrary numbering of atoms, most H-atoms omitted for clarity)

with an amide O-atom of an adjacent symmetry-unrelated molecule, thereby linking molecules A and B alternately into extended chains which run parallel to the *z*-axis with an $\cdots A \cdots B \cdots A \cdots B \cdots$ sequence that yields a binary graph set motif of $C_2^2(20)$.

We used the optimized conditions mentioned above for the cyclization of the other linear precursors **12b**–**12e**. In the case of **12b**, which differs from **12a** only in the substituent on the α-amino acid units being a cyclopentane ring instead of the two Me groups, the desired depsipeptide **14b** was obtained in a yield of 25%, which is comparable with the cyclization yield of **12a**. Again, ^{1}H- and ^{13}C-NMR spectra show that complete epimerization at one of the stereogenic centers had occurred.

Compared with **12b**, the third hydroxy acid of the cyclization precursor **12e** (counting from the amide terminus) bears a Me group instead of the Bn residue (R = Me, R^1 = Bn). This should allow the (otherwise undistinguishable) stereogenic centres in the cyclized product to be identified, provided that this variation still leads to the same phenomenon of complete inversion at one stereogenic center. The ring-closing reaction was accomplished successfully by applying the same conditions as mentioned before, and the corresponding depsipeptide **14e** was isolated in 33% yield. The ^{1}H- and ^{13}C-NMR spectra of **14e** showed that this compound was again formed as a single diastereoisomer. As the configuration of **14e** cannot be determined by means of NMR spectroscopy, we tried to establish the structure by X-ray crystallography. Unfortunately, we were unable to grow crystals suitable for a structure determination, so the relative configurations of the stereogenic centers in **14e** could not be determined. Therefore, this experiment could not clarify the proposal that the configuration at the

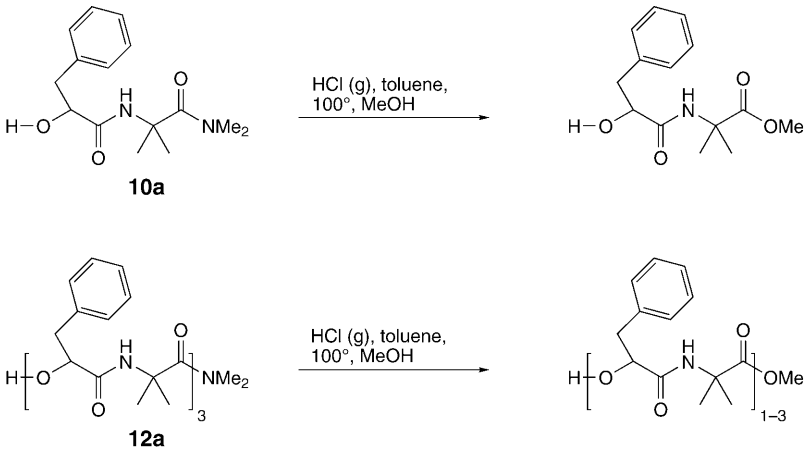
stereogenic center adjacent to the oxazolone ring of the intermediate **13** was inverted during the cyclization.

The linear precursor **12d** used for the next ring closure differs from **12a** in that there is no substituent next to the ω-OH group. The cyclization experiment, therefore, shows the difference between a primary and a secondary OH group attacking the oxazolone intermediate. When the cyclization was carried out under the same conditions as for **12a** and **12b**, the depsipeptide **14d** could be isolated with a significantly higher yield of 43%, and less by-products were formed. In contrast to **14a** and **14b**, the macrolactone **14d** was formed as a mixture of two diastereoisomers, most likely due to the configurational instability of the first stereogenic center (counting from the former amide terminus (see below)).

The linear depsipeptide **12c** also bears a primary ω-OH group and is substituted with Bn groups at the α-amino acid units to ensure the UV activity of the corresponding macrocycle. Ring closure under the usual conditions gave the desired cyclodepsipeptide **14c** in 46% yield, which is comparable with that of ring **14d**. Since the linear precursor **12c** was synthesized as a racemic mixture of different diastereoisomers, the reaction yielded **14c** as a mixture of the two possible diastereoisomers in racemic form.

Due to the lower steric hindrance, linear precursors with a primary ω-OH group seem to be more appropriate for the 'direct amide cyclization' method than those bearing a secondary OH group. The yields, ranging from 25 to 46%, are comparable with those of other cyclization methods for macrolactones of similar ring sizes. A possible explanation for the moderate yields in the present study could be the instability of the ester bonds of the cyclization precursors under the conditions of the 'direct amide cylization'. This could indeed be shown by a control experiment, in which the HCl treatment was carried out in the presence of MeOH as an external nucleophile. Under these conditions, amide **10a**, which does not contain ester bonds, was converted into the corresponding methyl ester quantitatively. On the other hand, the analogous treatment of **12a** resulted in a lower yield of products, and a mixture of the homologous esters was obtained (*cf.* also [46]; *Scheme 4*).

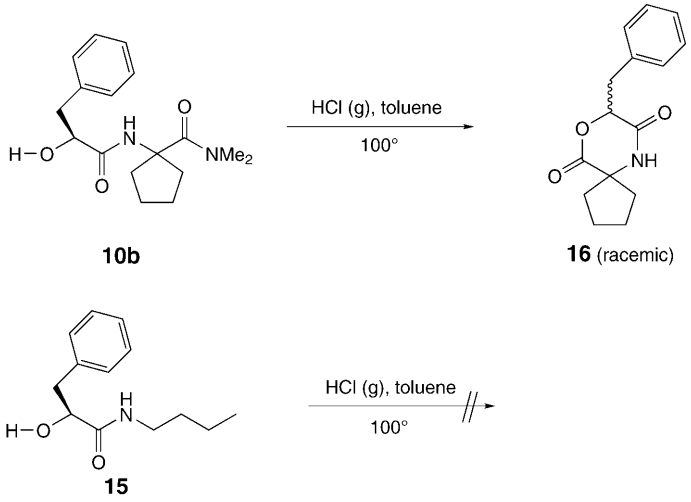
Scheme 4



Most likely, the depsipeptide bonds are cleaved *via* the intramolecular formation of 1,3-oxazol-5(4*H*)-ones as intermediates under the conditions of the 'direct amide cyclization'. Alternatively, an intermolecular attack of the free OH group of the corresponding linear precursor could cleave one of the ester bonds, thereby further reducing the yields of the cyclodepsipeptides.

As already mentioned, cyclodepsipeptides **14a** and **14b** were formed as single diastereoisomers with inverted configuration at one of the stereogenic centers. It is already known from the synthesis of six-membered cyclic depsipeptides that the 'direct amide cylization' can lead to a partial epimerization at the center in the α-position to the protonated oxazolone [10]. However, complete isomerization to give only the other diastereoisomer was surprising, as one would expect a mixture of diastereoisomers to be obtained. Therefore, we decided to examine at which position the inversion of configuration occurs. For this purpose, we subjected the optically active amide segments **10b** and **15** to the 'direct amide cylization' conditions that were used for the syntheses of the 18-membered macrocycles (*Scheme 5*).

Scheme 5



10b **16** (racemic) **15**

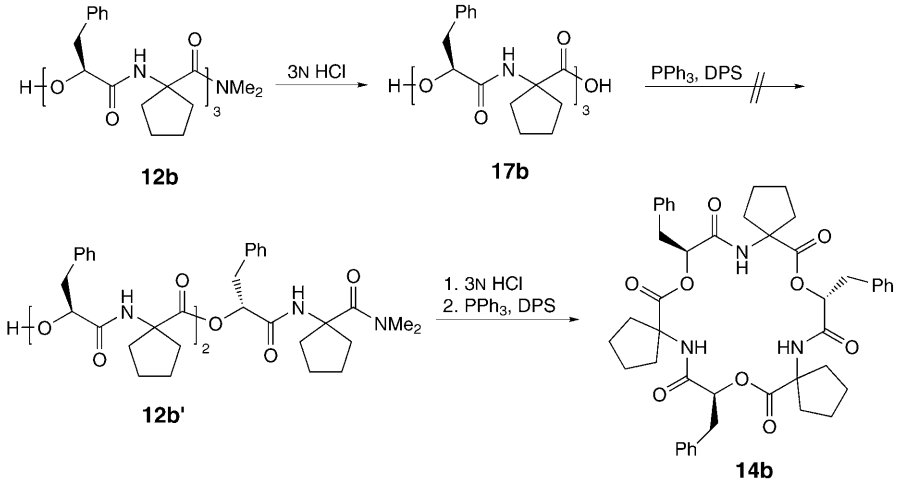
In the case of amide **10b**, which is able to form a 1,3-oxazol-5(4*H*)-one, the expected piperazine dione **16** was formed as a racemate. On the other hand, amide **15**, which cannot form an oxazolone, proved to be configurationally stable under these conditions. Even after a prolonged HCl treatment (30 min) at 100°, the other enantiomer could not be detected[3]). These results indicate that the only stereogenic center in the linear precursors **12**, where the observed epimerization occurs, is the first one, counting from the former amide terminus, *i.e.*, the stereogenic center in the α-position of the intermediate oxazolone.

---

[3]) Amide **15** and piperazine dione **16** were analyzed by means of HPLC on a chiral column with the racemic compounds as standards.

Although the position of the inversion of the configuration was clarified, the reason for the formation of a single diastereoisomer of the depsipeptide was not clear. To determine if this phenomenon is an attribute of the 'direct amide cyclization', or if other macrolactonization methods would show a similar effect, a test reaction according the *Corey–Nicolaou* method [49] was carried out. In a control experiment to synthesize piperazine dione **16**, almost no racemization occurred. Therefore, amide **12b** was hydrolyzed to give the corresponding carboxylic acid **17b** by treatment with 3N HCl in THF/H_2O (*Scheme 6*). Subsequent reaction with Ph_3P and 2,2′-dipyridyl disulfide (DPS) in CH_2Cl_2 did not yield the desired cyclodepsipeptide **14b**, and only decomposition products were found. If the same reaction sequence was performed with the epimer **12b**′ (prepared analogously to **12b** according to *Scheme 2*) under identical conditions, the macrocycle **14b** could be isolated in 16% yield (*Scheme 6*)[4]).

Scheme 6



This result indicates that the precursor with one inverted configuration is more favorable for the cyclization step than the homochiral analogue. Probably, the epimerized precursor promotes a conformation that is more suitable for the ring closure.

3. Conclusions. – Five different 18-membered regular cyclodepsipeptides of the enniatin type, which contain α,α-disubstituted α-amino acid moieties, have been synthesized. The efficient 'azirine/oxazolone method' was used to incorporate the sterically demanding amino acid units into the linear precursors. The cyclizations *via* macrolactonization were achieved by the 'direct amide cyclization' method and gave the desired products with yields ranging from 25 to 46%. The ring closure of precursors with a primary ω-OH group gave the products in higher yields than those with the corresponding compounds bearing a secondary OH group. Cyclizations of the two similar

[4]) NMR Spectra of **17b** and **17b**′ showed that no epimerization occurred during the acid-catalyzed amide hydrolysis.

compounds **12a** and **12b**, which possess three α-substituted α-hydroxy acid moieties, lead to cyclic depsipeptides with one epimerized stereogenic center. The results of some control experiments indicate that the epimerization occurs at the adjacent stereogenic center of the intermediate 1,3-oxazol-5(4*H*)-one. The structure of the cyclic depsipeptide **14a** has been established by X-ray crystallography.

We thank the analytical sections of our institue for spectra and analyses, the *Swiss National Science Foundation*, the *Betty Sassella-Keller Legat*, and *F. Hoffmann-La Roche AG*, Basel for financial support.

Experimental Part

1. *General.* See [18]. Solvents were purified by standard procedures. TLC: *Merck* TLC aluminium sheets, silica gel *60 F_{254}*. Flash column chromatography (CC): *Uetikon-Chemie* 'Chromatographiegel' *C-560*. M.p.: *Büchi 540* apparatus, uncorrected. IR Spectra: *Perkin-Elmer Spectrum One* spectrometer; in $CHCl_3$, unless otherwise stated, absorption bands in cm^{-1}. ^{1}H- (300 and 600 MHz) and ^{13}C-NMR (75.5 and 151 MHz) spectra: *Bruker ARX-300* and *DRX-600* instruments, in $CDCl_3$ at 300 K, TMS as internal standard, δ in ppm, coupling constants J in Hz; ^{13}C-signal multiplicity from DEPT spectra. MS: *Finnigan MAT 90* for electron-impact ionization (EI), *Finnigan SSQ-700* for chemical ionization (CI, with NH_3) and electrospray ionization (ESI, in MeOH + NaI).

The 2*H*-azirin-3-amines **6a**–**6c** and **9a**–**9c** were prepared according to standard procedures (*cf.* [29] and refs. cit. therein). *2-(Benzyloxy)acetic acid* (**5b**) was prepared according to [50], and *2-(benzyloxy)-propanoic acid* (**5c**) was prepared according to [51]. All other products used were commercially available. The syntheses and spectroscopic data of **5a**, **7a**, **8a**, **10a**, **11a**, and **12a** are described in [45] (see also [46]).

General Procedure 1 (*GP 1*). *Reaction of Azirines* **6** *and* **9** *with Acids* **4** *and* **5**. To a soln. of the acid in MeCN was added a soln. of the azirine in MeCN. The mixture was stirred at r.t. for 16 h, evaporated, and the residue was purified by column chromatography (CC).

General Procedure 2 (*GP 2*). *Hydrolysis of Amides* **7** *to Acids* **8**. A soln. of **7** (3.0 mmol) in THF (15 ml) was treated with aq. 6N HCl (15 ml) and stirred for 6 h at r.t. Subsequent addition of aq. 2N HCl (15 ml), extraction with Et_2O, drying ($MgSO_4$), and evaporation gave **8** in pure form.

General Procedure 3 (*GP 3*). *Esterification of Acids* **8** *with Alcohols* **10**, **11**, *and Subsequent Hydrogenolysis of the Benzyl Ether.* A soln. of **8** and 1.0 equiv. of 1,1′-carbonyldiimidazole (CDI) in dry THF was stirred for 2 h under N_2. The corresponding alcohol was then added, followed by 10 drops of a Na-imidazolide suspension (freshly prepared by the reaction of 45 mg of a 60% suspension of NaH in mineral oil with 73 mg of 1*H*-imidazole in 3 ml of dry THF). After the completion of the reaction (TLC, 2–16 h), the solvent was evaporated, and the mixture was purified by CC. The coupling product was then dissolved in THF/*i*-PrOH 1:1, a catalytic amount of Pd on charcoal was added, and the suspension was stirred under H_2 until completion of the reaction (TLC). The mixture was then filtered over *Celite*, evaporated, and purified by CC.

General Procedure 4 (*GP 4*). *Cyclization of the Linear Precursors* **12a**–**12e** *and* **10b**. A soln. of **12a**–**12e** or **10b** in toluene was treated with a strong stream of dry HCl gas for 4.5 min at 100°. The mixture was then allowed to cool to r.t., while bubbling N_2 through it. Evaporation of the solvent and purification by CC gave the corresponding cyclodepsipeptide.

2. *Synthesis of Linear Precursors.* 2.1. *1-{[(S)-2-(Benzyloxy)-3-phenylpropanoyl]amino}*-N-*methyl*-N-*phenylcyclopentane-1-carboxamide* (**7b**). According to *GP 1*, **5a** (1.0 g, 3.9 mmol) in MeCN (20 ml), **6b** (780 mg, 3.9 mmol) in MeCN (5 ml), 14 h, CC (SiO_2; hexane/Et_2O 1:1): 1.62 g (91%) of **7b**. White powder. M.p. 106–107°. $[\alpha]_D^{25} = -61.4$ ($c = 1.1$, $CHCl_3$). ^{1}H-NMR: 1.30–1.70, 2.20–2.30, 2.40–2.50 (3*m*, 6 H + 1 H + 1 H, $(CH_2)_4$); 2.92 (*dd*, $J = 7.6$, 14.1, 1 H of PhCH_2C); 3.15 (*dd*, $J = 3.8$, 14.1, 1 H of PhCH_2-C); 3.22 (*s*, MeN); 3.83 (*dd*, $J = 3.8$, 7.6, CH_2CHO); 4.10, 4.29 (2*d*, $J = 11.8$, PhCH_2O); 7.00–7.40 (*m*, 10 arom. H, NH). EI-MS: 456, (3, $M^{+\bullet}$), 350 (21, $[M - Ph(Me)N]^+$), 322 (43, $[M - CON(Me)Ph]^+$), 107 (67, $C_7H_7O^+$), 91 (100, $C_7H_7^+$).

2.2. *2-{[2-(Benzyloxy)acetyl]amino}-2,*N-*dimethyl-3,*N-*diphenylpropanamide* (**7c**). According to *GP 1*, **5b** (1.31 g, 7.9 mmol) in MeCN (30 ml), **6c** (2.2 g, 7.9 mmol) in MeCN (5 ml), 14 h, CC (SiO_2; hexane/

^{t}BuOMe 1:1): 2.67 g (81%) of **7c**. Yellowish oil. IR: 3405*m*, 3010*s*, 1770*w*, 1680*s*, 1635*s*, 1595*m*, 1520*s*, 1495*m*, 1380*s*, 1110*s*, 700*m*. ^{1}H-NMR: 1.49 (*s*, Me); 3.26 (*s*, MeN); 3.23, 3.43 (2*d*, *J* = 13.7, PhCH_2C); 3.60 (*s*, PhCH_2O); 4.21, 4.29 (2*d*, *J* = 11.7, CH_2CO); 6.60 (*s*, NH); 7.00–7.40 (*m*, 15 arom. H). ^{13}C-NMR: 24.2 (*q*, Me); 41.5 (*q*, MeN); 43.1 (*t*, PhCH_2C); 60.7 (*s*, PhCH_2(Me)*C*); 69.7, 73.0 (2*t*, PhCH_2-OCH_2); 126.8, 127.4, 127.5, 127.6, 127.9, 128.1, 128.3, 129.1, 130.4 (9*d*, 15 arom. CH); 136.2, 136.8 (2*s*, 2 arom. C); 144.6 (*s*, arom. CN); 168.3, 172.0 (2*s*, 2 C=O). CI-MS: 417 (60, $[M+1]^+$), 310 (100, $[M-$Ph(Me)N$]^+$).

2.3. *2-{[2-(Benzyloxy)acetyl]amino}-2,*N-*dimethyl*-N-*phenylpropanamide* (**7d**). According to *GP 1*, **5b** (2.86 g, 17.2 mmol) in MeCN (60 ml), **6a** (3.0 g, 17.2 mmol) in MeCN (15 ml), 14 h, CC (SiO_2; hexane/Et_2O 1:6): 5.33 g (91%) of **7d**. White powder. M.p. 76–79°. ^{1}H-NMR: 1.51 (*s*, Me); 3.25 (*s*, MeN); 3.67, 4.39 (2*s*, 2 CH_2); 6.63 (br. *s*, NH); 7.20–7.38 (*m*, 5 arom. H). ^{13}C-NMR: 26.7 (*q*, *Me*$_2$C); 41.3 (*q*, MeN); 57.5 (*s*, Me$_2$*C*); 69.7, 73.3 (2*t*, PhCH_2OCH_2); 127.5, 127.7, 127.8, 128.0, 128.4, 129.2 (6*d*, 10 arom. CH); 136.7 (*s*, arom. C); 144.6 (*s*, arom. CN); 168.1, 172.8 (2*s*, 2 C=O).

2.4. *1-{[(*S*)-2-(Benzyloxy)propanoyl]amino}*-N-*methyl*-N-*phenylcyclopentane-1-carboxamide* (**7e**). According to *GP 1*, **5c** (1.80 g, 10.0 mmol) in MeCN (50 ml), **6b** (2.0 g, 10.0 mmol) in MeCN (10 ml), 14 h, CC (SiO_2; CH_2Cl_2/MeOH 1:6): 3.27 g (86%) of **7d**. White powder. M.p. 107–108°. $[\alpha]_D^{25} = -48.4$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3314*s*, 2975*m*, 2929*m*, 2874*m*, 1686*s*, 1627*s*, 1536*m*, 1494*s*, 1388*m*, 1153*m*, 1114*m*, 1066*w*, 1023*w*, 770*w*, 745*m*, 699*m*. ^{1}H-NMR: 1.31 (*d*, *J* = 6.7, Me); 1.48–1.63, 1.64–1.88, 2.30–2.47, 2.50–2.62 (4*m*, 2 H each, $(CH_2)_4$); 3.25 (*s*, MeN); 3.67 (*q*, *J* = 6.7, MeC*H*); 4.21, 4.41 (2*d*, *J* = 11.5, PhCH_2O); 6.16 (br. *s*, NH); 7.13–7.37 (*m*, 10 arom. H). ^{13}C-NMR: 17.0 (*q*, Me); 24.1, 24.2, 38.7, 39.3 (4*t*, $(CH_2)_4$); 40.7 (*q*, MeN); 66.7 (*s*, N*C*CO); 71.3 (*t*, Ph*C*H_2O); 75.8 (*d*, Me*C*H); 127.1, 127.2, 127.3, 127.8, 128.3, 129.1 (6*d*, 10 arom. CH); 137.3 (*s*, arom. C); 144.9 (*s*, arom. CN); 171.3, 172.3 (2*s*, 2 C=O). ESI-MS: 403 (100, $[M+$Na$]^+$).

2.5. *1-{[(*S*)-2-(Benzyloxy)-3-phenylpropanoyl]amino}cyclopentane-1-carboxylic Acid* (**8b**). According to *GP 2*, **7b** (1.37 g, 3.0 mmol) in THF (15 ml), aq. 6N HCl (15 ml): 1.06 g (96%) of **8b**. White powder. M.p. 136–138°. $[\alpha]_D^{25} = -56.8$ ($c = 1.0$, $CHCl_3$). IR: 3414*m*, 3066*m*, 3021*s*, 1713*s*, 1675*s*, 1513*s*, 1454*m*, 1239*m*, 1090*s*. ^{1}H-NMR: 1.55–1.92, 2.20–2.39 (2*m*, 6 H + 2 H, $(CH_2)_4$); 2.96 (*dd*, *J* = 7.6, 14.1, 1 H of PhCH_2C); 3.16 (*dd*, *J* = 3.6, 14.1, 1 H of PhCH_2C); 4.16 (*dd*, *J* = 3.6, 7.6, CHO); 4.10, 4.29 (2*d*, *J* = 11.8, PhCH_2O); 6.94 (*s*, NH); 7.20–7.40 (*m*, 10 arom. H); 10.80 (br. *s*, CO_2H). ^{13}C-NMR: 24.4, 36.6, 37.5, 38.8 (4*t*, $(CH_2)_4$); 41.3 (*t*, PhCH_2C); 56.7 (*s*, N*C*CO); 73.1 (*t*, Ph*C*H_2O); 80.7 (*d*, CHO); 126.5, 127.9, 128.0, 128.1, 128.5, 129.7 (6*d*, 10 arom. CH); 136.8, 136.9 (2*s*, 2 arom. C); 172.9, 177.6 (2*s*, 2 C=O). CI-MS: 368 (100, $[M+1]^+$), 274 (9), 108 (6).

2.6. *2-{[2-(Benzyloxy)acetyl]amino}-2-methyl-3-phenylpropanoic Acid* (**8c**). According to *GP 2*, **7c** (1.25 g, 3.0 mmol) in THF (15 ml), aq. 6N HCl (15 ml): 883 mg (90%) of **8c**. White powder. M.p. 117–118°. IR (KBr): 3363*s*, 3030*m*, 2887*s*, 1715*s*, 1670*s*, 1542*s*, 1454*m*, 1211*s*, 1133*s*, 995*m*, 741*m*, 696*m*. ^{1}H-NMR: 1.70 (*s*, Me); 3.35, 3.50 (2*d*, *J* = 13.6, PhCH_2C); 3.94, 4.02 (2*d*, *J* = 15.6, PhCH_2O); 4.39, 4.43 (2*d*, *J* = 11.8, CH_2CO); 7.10–7.40 (*m*, 10 arom. H); 10.60 (br. *s*, CO_2H). ^{13}C-NMR: 23.1 (*q*, Me); 41.3 (*t*, Ph*C*H_2C); 60.6 (*s*, PhCH_2(Me)*C*); 69.3, 73.4 (2*t*, Ph*C*H_2OCH_2); 127.0, 127.8, 128.0, 128.3, 128.4, 129.8 (6*d*, 10 arom. CH); 135.7, 136.6 (2*s*, 2 arom. C); 170.3, 176.9 (2*s*, 2 C=O). CI-MS: 328 (100, $[M+1]^+$).

2.7. *2-{[2-(Benzyloxy)acetyl]amino}-2-methylpropanoic Acid* (**8d**). According to *GP 2*, **7d** (1.02 g, 3.0 mmol) in THF (15 ml), aq. 6N HCl (15 ml): 730 mg (97%) of **8d**. White powder. M.p. 89–90°. $[\alpha]_D^{25} = -39.8$ ($c = 0.7$, $CHCl_3$). ^{1}H-NMR: 1.60 (*s*, Me); 4.02 (*s*, PhCH_2O); 4.62 (*s*, CH_2CO); 7.05 (*s*, NH); 7.30–7.40 (*m*, 5 arom. H); 9.85 (br. *s*, CO_2H). ^{13}C-NMR: 24.6 (*q*, *Me*$_2$C); 56.3 (*s*, Me$_2$*C*); 69.4, 73.7 (2*t*, PhCH_2OCH_2); 127.9, 128.2, 128.5 (3*d*, 5 arom. CH); 136.6 (*s*, arom. C); 170.2, 177.5 (2*s*, 2 C=O). CI-MS: 259 (5, $[M+NH_4]^+$), 252 (100, $[M+1]^+$).

2.8. *1-{[(*S*)-2-(Benzyloxy)propanoyl]amino}cyclopentane-1-carboxylic Acid* (**8e**). According to *GP 2*, **7e** (2.20 g, 5.8 mmol) in THF (30 ml), aq. 6N HCl (30 ml): 1.60 g (95%) of **8e**. White powder. M.p. 96°. $[\alpha]_D^{25} = -39.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3360*s*, 2939*s*, 1706*s*, 1628*s*, 1531*s*, 1418*m*, 1337*m*, 1242*s*, 1191*s*, 1109*s*, 1062*m*, 934*m*, 773*m*, 736*s*, 695*m*. ^{1}H-NMR: 1.41 (*d*, *J* = 6.8, Me); 1.69–2.04, 2.20–2.38 (2*m*, 6 H + 2 H, $(CH_2)_4$); 3.99 (*q*, *J* = 6.8, MeC*H*); 7.06 (br. *s*, NH); 7.25–7.38 (*m*, 5 arom. H); 11.22

(br. *s*, CO_2H). ^{13}C-NMR: 18.4 (*q*, Me); 24.4, 24.5, 37.1, 37.3 (4*t*, $(CH_2)_4$); 65.6 (*s*, N*C*CO); 72.2 (*t*, Ph*C*H_2O); 76.2 (*d*, CHO); 127.8, 128.1, 128.6 (3*d*, 5 arom. CH); 137.1 (*s*, arom. C); 177.4 (*s*, C=O). ESI-MS: 314 (100, $[M+Na]^+$).

2.9. *1-{[(*S*)-2-Hydroxy-3-phenylpropanoyl]amino}-*N,N*-dimethylcyclopentane-1-carboxamide* (**10b**). According to *GP 1*, **4a** (2.0 g, 12.1 mmol) in MeCN (50 ml), **9b** (1.66 g, 12.1 mmol) in MeCN (15 ml), 14 h, CC (SiO_2; CH_2Cl_2/MeOH 30:1): 3.46 g (94%) of **10b**. White powder. M.p. 179–180°. $[\alpha]_D^{25} = -40.7$ ($c = 1.1$, $CHCl_3$). IR: 3407*m*, 3020*m*, 3011*m*, 2964*m*, 2877*m*, 1673*s*, 1632*s*, 1511*s*, 1454*m*, 1393*m*, 1242*m*, 1152*m*, 1086*m*, 1057*m*, 1031*m*, 1005*w*, 905*w*, 842*m*. ^{1}H-NMR: 1.50–1.90, 2.30–2.50 (2*m*, 6 H + 2 H, $(CH_2)_4$); 2.94 (*s*, Me_2N); 2.95 (*dd*, $J = 7.6$, 14.0, 1 H of PhCH_2); 3.21 (*dd*, $J = 4.0$, 14.0, 1 H of PhCH_2); 4.32 (*dd*, $J = 4.0$, 7.6, CHO); 6.72 (*s*, NH); 7.25–7.40 (*m*, 5 arom. H). ^{13}C-NMR: 24.1, 24.2, 37.0, 37.2 (4*t*, $(CH_2)_4$); 37.5 (*q*, Me_2N); 40.3 (*t*, PhCH_2); 66.0 (*s*, N*C*CO); 72.4 (*d*, CHO); 126.7, 128.4, 129.7 (3*d*, 3 arom. CH); 136.9 (*s*, arom. C); 171.5, 172.1 (2*s*, 2 C=O). CI-MS: 322 (13, $[M+NH_4]^+$), 305 (100, $[M+1]^+$).

2.10. *2-[(2-Hydroxyacetyl)amino]-2,*N,N*-trimethyl-3-phenylpropanamide* (**10c**). According to *GP 1*, **4b** (2.17 g, 28.6 mmol) in MeCN/THF 5:1 (100 ml), **9c** (5.40 g, 28.6 mmol) in MeCN (15 ml), 14 h, CC (SiO_2; CH_2Cl_2/MeOH 40:1): 6.05 g (80%) of **10c**. White powder. M.p. 149–150°. IR (KBr): 3293*s*, 3064*m*, 1680*s*, 1615*s*, 1550*m*, 1393*m*, 1223*m*, 1096*s*, 701*m*. ^{1}H-NMR: 1.51 (*s*, Me); 3.00 (br. *s*, Me_2N); 3.30 (*s*, PhCH_2); 3.98 (*s*, CH_2O); 4.30 (br. *s*, OH); 7.00–7.30 (*m*, 5 arom. H); 7.36 (br. *s*, NH). ^{13}C-NMR: 22.8 (*q*, Me); 38.1 (*q*, Me_2N); 41.5 (*t*, Ph*C*H_2); 59.5 (*s*, PhCH_2(Me)*C*); 61.9 (*t*, CH_2O); 126.8, 128.2, 130.2 (3*d*, 5 arom. CH); 136.1 (*s*, arom. C); 171.1, 172.0 (2*s*, 2 C=O). CI-MS: 265 (100, $[M+1]^+$).

2.11. *(*S*)-1-{[1-(Dimethylcarbamoyl)cyclopentyl]carbamoyl}-2-phenylethyl 1-{[(*S*)-2-Hydroxy-3-phenylpropanoyl]amino}cyclopentane-1-carboxylate* (**11b**). According to *GP 3*, **8b** (1.32 g, 3.60 mmol), CDI (583 mg, 3.60 mmol), **10b** (1.09 g, 3.60 mmol), THF (40 ml), 2 h, CC (SiO_2; CH_2Cl_2/MeOH 50:1): 2.07 g (88%) of **11b**, direct conversion into **13b** without further characterization.

2.12. *{[1-(Dimethylcarbamoyl)-1-methyl-2-phenylethyl]carbamoyl}methyl 2-[(2-Hydroxyacetyl)-amino]-2-methyl-3-phenylpropanoate* (**11c**). According to *GP 3*, **8c** (1.18 g, 3.60 mmol), CDI (583 mg, 3.60 mmol), **10c** (950 mg, 3.60 mmol), THF (40 ml), 2 h, CC (SiO_2; CH_2Cl_2/MeOH 60:1): 1.02 g (59%) of **11c** (mixture of 2 diastereoisomers). White powder. M.p. 84–86°. IR (KBr): 3394*w*, 3283*s*, 3029*m*, 2942*m*, 1748*s*, 1672*s*, 1540*s*, 1454*m*, 1108*s*, 740*m*, 702*m*. ^{1}H-NMR: 1.31, 1.46, 1.58, 1.58 (4*s*, 2 Me); 2.8–3.6 (*m*, Me_2N + 2 PhCH_2 + 1 H of HOCH_2 + OH); 3.73, 3.76 (2*d*, $J = 16.5$, 1 H of HOCH_2); 4.41, 4.43, 4.59, 4.71 (4*d*, $J = 15.6$, CH_2CO_2); 6.90–7.40 (*m*, 10 arom. H, NH); 7.71, 7.88 (2*s*, NH). ^{13}C-NMR: 20.6, 22.0, 22.4, 22.6 (4*q*, 2 Me); 38.2 (*q*, Me_2N); 40.5, 40.7, 41.1, 43.1 (4*t*, 2 PhCH_2); 58.4, 58.9, 60.0, 60.2 (4*s*, 2 PhCH_2(Me)*C*); 61.7, 61.8, 63.1, 63.2 (4*t*, 2 CH_2O); 126.6, 127.1, 127.3, 128.0, 128.2, 128.4, 130.1, 130.3, 130.4 (9*d*, 10 arom. CH); 134.6, 135.0, 136.5, 136.6 (4*s*, 2 arom. C); 166.0, 166.2, 171.8, 172.3, 172.4, 172.7, 172.8, 174.7 (8*s*, 4 C=O). ESI-MS: 989 (30, $[2M+Na]^+$), 506 (100, $[M+Na]^+$).

2.13. *(*S*)-1-{[1-(Dimethylcarbamoyl)cyclopentyl]carbamoyl}-2-phenylethyl 1-({(*S*)-2-[1-({[(*S*)-2-Hydroxy-3-phenylpropanoyl]amino}cyclopentyl)carbonyloxy]-3-phenylpropanoyl}amino)cyclopentane-1-carboxylate* (**12b**). According to *GP 3*, **8b** (1.32 g, 3.60 mmol), CDI (583 mg, 3.61 mmol), **11b** (2.03 g, 3.60 mmol), THF (40 ml), 16 h, CC (SiO_2; CH_2Cl_2/MeOH 50:1): 2.52 g (85%) of **11**. White powder. M.p. 117–118°. $[\alpha]_D^{25} = -69.3$ ($c = 1.0$, $CHCl_3$). IR: 3414*m*, 3292*s*, 3065*m*, 3021*m*, 2963*m*, 2876*m*, 1740*s*, 1651*s*, 1541*s*, 1497*m*, 1454*m*, 1395*m*, 1298*m*, 1238*s*, 1168*s*, 1083*s*, 1031*m*, 969*w*, 913*w*, 861*w*. ^{1}H-NMR: 1.50–1.92, 1.96–2.58 (2*m*, 18 H + 6 H, 3 $(CH_2)_4$); 2.95–3.35 (*m*, Me_2N + 3 PhCH_2); 4.30–4.35 (*m*, *C*HOH); 5.20–5.30 (*m*, 2 CHOCO); 7.20–7.40 (*m*, 15 arom. H, NH); 7.77, 8.03 (2*s*, 2 NH). ^{13}C-NMR: 23.9, 24.1, 24.1, 24.2, 24.4, 24.5, 35.7, 36.7, 36.8, 37.0, 37.3, 38.0, 38.1, 38.4, 40.2 (15*t*, 3 $(CH_2)_4$ + 3 PhCH_2); 65.2, 65.9, 66.4 (3*s*, 3 N*C*CO); 72.3, 74.7, 75.3 (3*d*, 3 CHO); 126.5, 126.8, 126.9, 128.1, 128.2, 128.3, 129.5, 129.7, 129.8 (9*d*, 15 arom. CH); 135.8, 136.6, 137.0 (3*s*, 3 arom. C); 168.5, 170.7, 172.8, 172.8, 173.3, 174.1 (6*s*, 6 C=O). ESI-MS: 845 (100, $[M+Na]^+$). Anal. calc. for $C_{47}H_{58}N_4O_9$ (823.01): C 68.59, H 7.10, N 6.81; found: C 68.51, H 7.19, N 6.59.

2.14. *(*S*)-1-{[1-(Dimethylcarbamoyl)cyclopentyl]carbamoyl}-2-phenylethyl 1-({(*S*)-2-[1-({[(*R*)-2-Hydroxy-3-phenylpropanoyl]amino}cyclopentyl)carbonyloxy]-3-phenylpropanoyl}amino)cyclopentane-1-carboxylate* (**12b′**). Synthesis as described for **12b**, with (*R*)-**10b** instead of (*S*)-**10b**. Intermediate compounds have not been characterized. White powder. M.p. 121–123°. $[\alpha]_D^{25} = -17.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3398*m*, 3283*s*, 3030*w*, 2957*s*, 2874*w*, 1743*s*, 1649*s*, 1540*s*, 1454*m*, 1264*m*, 1165*s*, 1072*s*, 745*m*,

700*m*. ^{1}H-NMR: 1.31–1.95, 1.92–2.40 (2*m*, 18 H + 6 H, 3 $(CH_2)_4$); 2.56–3.23 (*m*, Me_2N + 3 PhCH_2); 4.35–4.40 (*m*, *CH*OH); 5.28–5.38 (*m*, 2 CHOCO); 7.10–7.35 (*m*, 15 arom. H, NH); 7.70, 8.25 (2*s*, 2 NH). ^{13}C-NMR: 23.9, 24.1, 24.4, 24.5, 24.7, 35.8, 37.4, 37.6, 37.7, 38.2, 40.4 (11*t*, 3 $(CH_2)_4$); 37.0 (*q*, Me_2N); 65.3, 66.1, 66.5 (3*s*, 3 N*C*CO); 72.5, 74.7 (2*d*, 3 CHO); 126.8, 126.9, 126.9, 128.3, 128.5, 129.1, 129.8 (7*d*, 15 arom. CH); 136.4, 136.5 (2*s*, 3 arom. C); 168.3, 170.7, 172.8, 172.8, 173.4, 174.1 (6*s*, 6 C=O). ESI-MS: 845 (100, $[M+Na]^+$). Anal. calc. for $C_{47}H_{58}N_4O_9$ (823.01): C 68.59, H 7.10, N 6.81; found: C 68.13 H 7.11 N 6.69.

2.15. *{[1-({[1-(Dimethylcarbamoyl)-1-methyl-2-phenylethyl]carbamoyl}methoxycarbonyl)-1-methyl-2-phenylethyl]carbamoyl}methyl 2-[(2-Hydroxyacetyl)amino]-2-methyl-3-phenylpropanoate* (**12c**). According to *GP 3*, **8c** (1.18 g, 3.60 mmol), CDI (583 mg, 3.60 mmol), **11c** (1.74 g, 3.60 mmol), THF (40 ml), 16 h, CC (SiO_2; CH_2Cl_2/MeOH 40:1): 1.19 g (47%) of **12c** (mixture of 4 diastereoisomers). White powder. M.p. 112–115°. IR (KBr): 3275*s*, 2943*w*, 1750*s*, 1655*s*, 1548*s*, 1256*m*, 1110*s*, 910*m*, 733*m*, 703*m*. ^{1}H-NMR: 1.20–1.50 (*m*, 2.5 Me); 1.61, 1.62 (2*s*, 0.5 Me) 2.80–4.10 (*m*, Me_2N, 3 PhCH_2, HOCH_2, OH); 4.20–4.95 (*m*, 2 CH_2O); 6.95–7.40 (*m*, 15 arom. H); 7.60–8.00 (*m*, 3 NH). ^{13}C-NMR: 21.7, 22.0, 22.1, 22.4, 22.6, 22.8 (6*q*, 3 Me); 38.0, 38.3 (2*q*, Me_2N); 40.6, 40.7, 41.2, 42.2, 42.5, 42.9, 43.1 (7*t*, 3 Ph*C*H_2); 58.4, 58.7, 59.1, 59.2, 59.5, 59.7, 59.8, 60.0, 60.1 (9*s*, 3 Ph(Me)*C*); 61.9, 62.0, 62.6, 63.1, 63.2, (5*t*, 3 CH_2O); 126.4, 126.7, 127.3, 127.8, 128.0, 128.3, 128.4, 130.0, 130.1, 130.2, 130.3, 130.4, 130.7, 130.8, 130.9, 131.0 (16*d*, 15 arom. CH); 134.6, 134.8, 135.0, 135.1, 135.2, 136.5, 136.6, 136.7, 136.9 (9*s*, 3 arom. C); 165.9, 166.1, 166.7, 166.8, 167.9, 168.1, 158.3, 168.4, 168.5, 171.9, 172.0, 172.1, 172.3, 172.4, 172.6, 172.7, 172.8, 172.9 (18*s*, 6 C=O). ESI-MS: 725 (85, $[M+Na]^+$), 506 (100). Anal. calc. for $C_{38}H_{46}N_4O_9$ (702.81): C 64.94, H 6.60, N 7.97; found: C 65.32, H 6.22, N 7.85.

2.16. *(*S*)-1-({1-[({*S*)-1-{[1-(Dimethylcarbamoyl)-1-methylethyl]carbamoyl}-2-phenylethoxy)carbonyl]-1-methylethyl}carbamoyl)-2-phenylethyl 2-[(2-Hydroxyacetyl)amino]-2-methylpropanoate* (**12d**). According to *GP 3*, **8d** (904 mg, 3.60 mmol), CDI (583 mg, 3.61 mmol), **11a** (1.84 g, 3.60 mmol), THF (40 ml), 8 h, CC (SiO_2; CH_2Cl_2/MeOH 50:1): 2.14 g (91%) **12d**. White powder. M.p. 112–114°. $[\alpha]_D^{25} = -33.2$ (*c* = 1.0, $CHCl_3$). IR: 3402*m*, 3281*s*, 3066*w*, 3021*m*, 3009*m*, 2941*m*, 1745*s*, 1652*s*, 1545*s*, 1497*m*, 1471*m*, 1455*m*, 1440*m*, 1388*m*, 1367*m*, 1342*w*, 1291*m*, 1268*m*, 1146*s*, 1082*m*, 1064*m*, 1031*m*, 1001*w*, 940*w*, 888*w*, 842*w*. ^{1}H-NMR: 1.15, 1.29, 1.31, 1.52, 1.54, 1.57 (6*s*, 6 Me); 2.90–3.15 (*m*, Me_2N + 1 H of PhCH_2); 3.20–3.39 (*m*, 1 H of PhCH_2); 3.96, 4.14 (2*d*, *J* = 16.3, CH_2O); 5.20–5.30 (*m*, 2 CHO); 7.10–7.40 (*m*, 10 arom. H); 7.51, 7.79, 8.03 (3*s*, 3 NH). ^{13}C-NMR: 24.1, 24.4, 24.9, 25.2, 25.9, 26.2 (6*q*, 6 Me); 37.6, 37.9 (2*t*, 2 Ph*C*H_2); 37.4 (*q*, MeN); 55.6, 56.1, 56.6 (3*s*, 3 Me_2C); 62.1 (*t*, CH_2O); 74.6, 74.9 (2*d*, 2 CHO); 126.8, 127.1, 128.3, 128.4, 129.5, 129.7 (6*d*, 10 arom. CH); 135.9, 136.7 (2*s*, 2 arom. C); 168.8, 179.1, 173.2, 173.2, 173.3, 173.5 (6*s*, 6 C=O). ESI-MS: 677 (100, $[M+Na]^+$). Anal. calc. for $C_{34}H_{46}N_4O_9$ (645.75): C 62.37, H 7.08, N 8.56; found: C 61.58, H 7.08, N 8.34.

2.17. *(*S*)-1-{1-[(Dimethylcarbamoyl)cyclopentyl]carbamoyl}-2-phenylethyl 1-({(*S*)-2-[1-({[(*S*)-2-Hydroxypropanoyl]amino}cyclopentyl)carbonyloxy]-3-phenylpropanoyl}amino)cyclopentane-1-carboxylate* (**12e**). According to *GP 3*, **8e** (1.05 g, 3.60 mmol), CDI (583 mg, 3.61 mmol), **11b** (2.03 g, 3.60 mmol), THF (40 ml), 16 h, CC (SiO_2; CH_2Cl_2/MeOH 45:1): 2.36 g (88%) of **12e**. White powder. M.p. 137–138°. $[\alpha]_D^{25} = -36.3$ (*c* = 1.2, $CHCl_3$). IR (KBr): 3464*m*, 3304*s*, 3062*w*, 3033*w*, 2958*s*, 2874*w*, 1740*s*, 1645*s*, 1547*s*, 1454*m*, 1265*m*, 1164*m*, 1127*w*, 1072*s*, 741*m*, 699*m*. ^{1}H-NMR: 1.46 (*d*, *J* = 6.8, Me); 1.51–2.42 (*m*, 3 $(CH_2)_4$); 2.55–2.78, 3.02–3.21 (2*m*, 2 PhCH_2); 2.92 (*s*, Me_2N); 4.26 (*q*, *J* = 6.8, MeC*H*); 5.30 (*m*, 2 CHO); 7.11–7.32 (*m*, 10 arom. H); 7.49, 7.72, 8.18 (3*s*, 3 NH). ^{13}C-NMR: 20.8 (*q*, Me); 24.1, 24.2, 24.3, 24.4, 24.6, 35.7, 37.0, 37.2, 37.3, 37.5, 37.8, 38.0 (12*t*, 3 $(CH_2)_4$ + 2 PhCH_2); 37.6 (*q*, Me_2N); 65.3, 66.0, 66.4 (3*s*, 3 N*C*CO); 68.3, 74.5, 74.6 (3*d*, 3 CHO); 126.9, 127.0, 128.4, 128.5, 129.1, 129.8 (6*d*, 10 arom. CH); 136.5, 136.5 (2*s*, 2 arom. C); 168.4, 170.7, 172.8, 173.0, 173.4, 176.1 (6*s*, 6 C=O). ESI-MS: 769 (100, $[M+Na]^+$).

3. *Cyclization Reactions.* 3.1. *(6*R*,12*S*,18*S*)-6,12,18-Tribenzyl-3,3,9,9,15,15-hexamethyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone* (**14a**). According to *GP 4*, **12a** (280 mg, 0.4 mmol), toluene (30 ml), CC (SiO_2; CH_2Cl_2/MeOH 60:1): 70 mg (27%) of **14a**. White powder. M.p. 112–113°. $[\alpha]_D^{25} = -25.8$ (*c* = 1.8, $CHCl_3$). IR: 3414*w*, 3276*s*, 3031*w*, 3011*w*, 2928*m*, 2856*w*, 1746*s*, 1648*s*, 1552*s*, 1455*m*, 1388*m*, 1269*m*, 1144*s*, 1064*m*. ^{1}H-NMR: 1.19, 1.37, 1.44, 1.44, 1.46, 1.56 (6*s*, 6 Me); 2.82 (*dd*, *J* = 4.2, 6.9, 1 H of PhCH_2); 3.16 (*dd*, *J* = 2.7, 7.2, 1 H of PhCH_2); 3.33 (*dd*, *J* = 2.4, 6.9, 1 H of PhCH_2); 3.41 (*dd*, *J* = 2.7, 7.2, 1 H of PhCH_2); 3.02–3.05 (*m*, PhCH_2); 5.17 (*t*, *J* = 3.3, 1 CHO); 5.22 (*t*,

J = 3.0, 1 CHO); 5.37 (*dd*, J = 2.1, 4.2, 1 CHO); 6.71, 6.96, 6.98 (3*s*, 3 NH); 7.15–7.30 (*m*, 15 arom. H). ^{13}C-NMR: 23.0, 23.6, 24.2, 24.9, 24.9, 25.3 (6*q*, 6 Me); 36.8, 37.0, 37.5 (3*t*, 3 Ph*C*H$_2$); 56.7, 56.8, 57.6 (3*s*, 3 Me$_2$*C*); 74.8, 74.9, 75.2, (3*d*, 3 CHO); 126.9, 127.0, 127.1, 128.3, 128.4, 128.5, 129.4, 129.7, 129.8 (9*d*, 15 arom. CH); 135.1, 135.3, 135.7 (3*s*, 3 arom. C); 167.9, 168.1, 168.3, 172.0, 172.5, 173.0 (6*s*, 6 C=O). ESI-MS: 722 (100, $[M+Na]^+$). Anal. calc. for $C_{39}H_{45}N_3O_9$ (702.81): C 66.94, H 6.48, N 6.00; found: C 66.23, H 6.54, N 5.82.

3.2. *(6*R*,12*S*,18*S*)-6,12,18-Tribenzyl-3,3,9,9,15,15-tris(tetramethylene)-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone* (**14b**). According to *GP 4*, **12b** (330 mg, 0.4 mmol), toluene (30 ml), CC (SiO_2; CH_2Cl_2/Et_2O 10:1): 78 mg (25%) of **14b**. White powder. M.p. 114–115°. $[\alpha]_D^{25} = -17.2$ (c = 1.4, $CHCl_3$). IR: 3427*w*, 3318*m*, 3021*m*, 2964*m*, 2878*w*, 1744*s*, 1680*s*, 1529*s*, 1497*w*, 1454*w*, 1236*m*, 1165*s*, 1071*m*. ^{1}H-NMR: 1.52–2.12, 2.18–2.26, 2.43–2.49 (3*m*, 20 H + 3 H + 1 H, 3 $(CH_2)_4$); 2.73 (*dd*, J = 4.8, 7.2, 1 H of Ph*CH*$_2$); 3.00 (*dd*, J = 3.3, 6.9, 1 H of Ph*CH*$_2$); 3.06 (*dd*, J = 2.7, 7.2, 1 H of Ph*CH*$_2$); 3.15 (*dd*, J = 3.0, 7.2, 1 H of Ph*CH*$_2$); 3.33 (*dd*, J = 2.4, 7.2, Ph*CH*$_2$); 3.39 (*dd*, J = 2.7, 6.9, 1 H of Ph*CH*$_2$); 5.20–5.25 (*m*, 2 CHO); 5.30 (*dd*, J = 2.4, 4.8, 1 CHO); 6.72 (*s*, 1 NH); 7.10–7.30 (*m*, 15 arom. H, 2 NH). ^{13}C-NMR: 23.9, 24.0, 24.6, 24.7, 25.1, 25.2, 31.6, 34.9, 36.1, 36.5 37.0, 37.0, 37.1, 37.4, 37.9 (15*t*, 3 $(CH_2)_4$ + 3 Ph*C*H$_2$); 66.3, 66.9 (2*s*, 3 N*C*CO); 74.9, 75.0, 75.1 (3*d*, 3 CHO); 126.9, 127.0, 127.1, 128.3, 128.5, 128.5, 129.4, 129.7, 129.8 (9*d*, 15 arom. CH); 135.1, 135.5, 136.1 (3*s*, 3 arom. C); 168.2, 168.3, 168.5, 171.7, 172.7, 173.3 (6*s*, 6 C=O). ESI-MS: 800 (100, $[M+Na]^+$). Anal. calc. for $C_{45}H_{51}N_3O_9$ (777.92): C 69.47, H 6.61, N 5.40; found: C 69.12, H 6.70, N 5.27.

3.3. *3,9,15-Tribenzyl-3,9,15-trimethyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone* (**14c**). According to *GP 4*, **12c** (280 mg, 0.4 mmol), toluene (30 ml), CC (SiO_2; CH_2Cl_2/MeOH 60:1): 121 mg (46%) of **14c** as a mixture of 2 diastereoisomers. White powder. M.p. 88–89°. IR: 3279*s*, 3030*m*, 2977*m*, 1751*s*, 1654*s*, 1523*s*, 1422*s*, 1333*m*, 1112*m*, 1046*m*, 849*w*. ^{1}H-NMR[5]): 1.24–1.50 (br. *m*, 3 Me); 3.00–3.50 (br. *m*, 3 Ph*CH*$_2$); 4.10–4.75 (br. *m*, 3 CH_2O); 7.00–7.35 (*m*, 15 arom. H); 7.60–8.00 (br. *m*, 3 NH). ^{13}C-NMR (br. signals): 22.4 (*q*, Me); 41.5 (*t*, Ph*C*H$_2$); 59.4 (*s*, Ph(Me)*C*); 62.7 (*t*, CH_2O); 126.9, 128.1, 130.5 (3*d*, 15 arom. CH); 135.1 (*s*, 3 arom. C); 168.3, 172.3 (2*s*, 6 C=O). ESI-MS: 680 (100, $[M+Na]^+$). Anal. calc. for $C_{36}H_{39}N_3O_9 \cdot 0.5\ H_2O$ (657.27·0.5 H_2O): C 64.85, H 6.05, N 6.30; found: C 64.77, H 6.12, N 6.22.

3.4. *6,12-Dibenzyl-3,3,9,9,15,15-hexamethyl-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone* (**14d**). According to *GP 4*, **12d** (260 mg, 0.4 mmol), toluene (30 ml), CC (SiO_2; CH_2Cl_2/MeOH 55:1): 105 mg (43%) of **14d** as a mixture of 2 diastereoisomers. White powder. M.p. 159–162°. $[\alpha]_D^{25} = -31.9$ (c = 1.2, $CHCl_3$). IR: 3279*s*, 3067*w*, 3033*w*, 2993*m*, 2946*m*, 2857*w*, 1748*s*, 1650*s*, 1554*s*, 1471*m*, 1455*m*, 1388*m*, 1368*w*, 1308*m*, 1266*m*, 1140*s*, 1065*m*, 909*m*. ^{1}H-NMR[5]): 1.08–1.70 (br. *m*, 6 Me); 2.80–3.45 (br. *m*, 2 Ph*CH*$_2$); 4.00–4.80 (br. *m*, CH_2O); 5.10–5.50 (br. *m*, 2 CHO); 7.00–7.35 (*m*, 10 arom. H); 7.50–8.30 (br. *m*, 3 NH). ^{13}C-NMR (br. signals): 23.7 (*q*, 6 Me); 37.5 (*t*, 2 Ph*C*H$_2$); 56.1 (*s*, N*C*CO); 63.3 (*t*, CH_2O); 74.9 (*d*, 2 CHO); 126.9, 128.3, 129.4 (3*d*, 10 arom. CH); 136.2 (*s*, 2 arom. C); 170.5, 173.4 (2*s*, 6 C=O). ESI-MS: 632 (100, $[M+Na]^+$). Anal. calc. for $C_{32}H_{39}N_3O_9$ (609.67): C 63.04, H 6.45, N 6.89; found: C 62.88, H 6.77, N 6.93.

3.5. *6,12-Dibenzyl-18-methyl-3,3,9,9,15,15-tris(tetramethylene)-1,7,13-trioxa-4,10,16-triazacyclooctadecane-2,5,8,11,14,17-hexaone* (**14e**). According to *GP 4*, **12e** (250 mg, 0.34 mmol), toluene (30 ml), CC (SiO_2; CH_2Cl_2/MeOH 45:1): 79 mg (33%) of **14e**. White powder. M.p. 134–135°. $[\alpha]_D^{25} = -16.8$ (c = 1.0, $CHCl_3$). IR (KBr): 3426*w*, 3298*m*, 2959*m*, 2875*w*, 1745*s*, 1659*s*, 1545*s*, 1453*m*, 1301*m*, 1239*s*, 1166*s*, 1073*m*, 746*m*, 700*m*. ^{1}H-NMR: 1.48 (*d*, J = 6.7, Me); 1.49–2.57 (*m*, 3 $(CH_2)_4$); 2.74 (*dd*, J = 9.7, 14.1, 1 H of Ph*CH*$_2$); 3.13–3.39 (*m*, 3 H of Ph*CH*$_2$); 6.54 (br. *s*, NH); 7.11–7.38 (*m*, 10 arom. H + 2 NH). ^{13}C-NMR: 17.6 (*q*, Me); 23.9, 24.0, 24.4, 24.5, 25.3, 25.5, 34.8, 36.3, 36.4, 36.5, 36.9, 37.3, 37.5, 37.9 (14*t*, 3 $(CH_2)_4$ + 2 Ph*C*H$_2$); 66.2, 66.3, 66.8 (3*s*, 3 N*C*CO); 71.4, 74.9, 75.0 (3*d*, 3 CHO); 126.8, 127.1, 128.4, 128.5, 129.2, 129.6 (6*d*, 10 arom. CH); 134.9, 136.1 (2*s*, 2 arom. C); 168.2, 168.5, 169.6, 171.5, 172.4, 173.5 (6*s*, 6 C=O). ESI-MS: 724 (100, $[M+Na]^+$).

---

[5]) ^{1}H- and ^{13}C-NMR spectra of **14c** and **14d** show broad signals, probably due to the co-existence of different conformers that convert to one another. The same phenomenon has been observed with similar depsipeptides with 18-membered [28] and 24-membered [45][46] rings.

4. *Control Experiments.* 4.1. *8-Benzyl-9-oxa-6-azaspiro[4.5]decane-7,10-dione* (**16**). According to *GP 4*, **10b** (152 mg, 0.5 mmol), toluene (30 ml), CC (SiO_2; CH_2Cl_2/Et_2O 10:1): 66 mg (51%) of racemic **16**. White powder. M.p. 106–107°. IR (KBr): 3189*m*, 3086*m*, 2964*m*, 2926*m*, 2880*w*, 1741*s*, 1679*s*, 1454*m*, 1436*m*, 1346*m*, 1261*m*, 1185*m*, 1093*m*, 1021*w*, 828*m*, 740*w*, 694*m*. ^{1}H-NMR ((D_6)DMSO): 1.44–2.15 (*m*, $(CH_2)_4$); 3.07 (*dd*, *J*=7.5, 14.7, 1 H of PhCH_2); 3.31 (*dd*, *J*=4.0, 14.7, 1 H of PhCH_2); 5.31 (*dd*, *J*=4.0, 7.5, CHO); 7.25–7.41 (*m*, 5 arom. H); 8.76 (br. *s*, NH). ^{13}C-NMR: 23.9, 24.3, 36.4, 38.0, 39.8 (5*t*, $(CH_2)_4$+PhCH_2); 63.6 (*s*, N*C*CO); 77.8 (*d*, CHO); 126.5, 128.1, 129.6 (3*d*, 5 arom. CH); 136.1 (*s*, arom. C); 166.2, 171.0 (2*s*, 2 CO). ESI-MS: 282 (100, $[M+Na]^+$). Anal. calc. for $C_{15}H_{17}NO_3$ (259.31): C 69.47, H 6.61, N 5.40; found: C 69.50, H 6.78, N 5.38.

4.2. *(*S*)-*N*-Butyl-2-hydroxy-3-phenylpropanamide* (**15**). To a soln. of (*S*)-phenyllactic acid (300 mg, 1.81 mmol) and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU; 2 mmol, 760 mg) in CH_2Cl_2 (10 ml) was added $BuNH_2$ (396 mg, 0.54 ml, 5.5 mmol). After 4 h stirring at r.t., H_2O (10 ml) was added. The org. layer was washed with 0.5M HCl (3×5 ml) and sat. aq. $NaHCO_3$ soln. (3×5 ml), and dried ($MgSO_4$). Evaporation of the solvent and CC yielded **15** (288 mg, 72%). White powder. M.p. 83–84°. $[\alpha]_D^{25} = -43.3$ (*c*=1.1, $CHCl_3$). IR (KBr): 3335*s*, 2962*m*, 2934*m*, 2875*w*, 1627*s*, 1556*s*, 1411*m*, 1292*m*, 1084*s*, 729*m*, 699*m*. ^{1}H-NMR: 0.89 (*t*, *J*=7.2, Me); 1.21–1.47 (*m*, MeCH_2CH_2); 2.81–2.94 (*m*, 1 H of PhCH_2); 3.14–3.30 (*m*, CH_2N+1 H of PhCH_2+OH); 4.26 (*m*, CHO); 6.46 (br. *s*, NH); 7.20–7.33 (*m*, 5 arom. H). ^{13}C-NMR: 13.6 (*q*, Me); 19.9, 31.4, 38.7, 40.8 (4*t*, 4 CH_2); 72.7 (*d*, CHO); 126.9, 128.6, 129.6 (3*d*, 3 arom. CH); 137.1 (*s*, arom. C); 172.8 (*s*, C=O). ESI-MS: 244 (100, $[M+Na]^+$).

5. *X-Ray Crystal-Structure Determination of* **14a** (*Table* and *Fig.*)[6]). All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer [52] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table*, and a view of the molecule is shown in the *Figure*. Data reduction was performed with *HKL Denzo* and *Scalepack* [53]. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections were merged. The

Table. *Crystallographic Data for Compound* **14a**

Crystallized from	hexane/CH_2Cl_2	D_x [g cm^{-3}]	1.223
Empirical formula	$C_{39}H_{45}N_3O_9$	μ(MoK_α) [mm^{-1}]	0.0870
Formula weight [g mol^{-1}]	699.80	Scan type	ω
Crystal color, habit	colorless, needle	$2\theta_{(max)}$ [°]	50
Crystal dimensions [mm]	0.07×0.10×0.30	Total reflections measured	34567
Temp. [K]	160(1)	Symmetry independent reflections	6886
Crystal system	Monoclinic	Reflections with $I>2\sigma(I)$	4833
Space group	$P2_1$	Reflections used in refinement	6877
Z	4	Parameters refined; restraints	956; 1
Reflections for cell determination	6575	Final $R(F)$ [$I>2\sigma(I)$ reflections]	0.0416
2θ Range for cell determination [°]	4–50	$wR(F^2)$ (all data)	0.1007
Unit cell parameters *a* [Å]	11.3280(1)	Weights: $w=[\sigma^2(F_o^2)+(0.0514P)^2]^{-1}$ where $P=(F_o^2+2F_c^2)/3$	
b [Å]	24.3225(3)	Goodness-of-fit	1.000
c [Å]	13.7975(2)	Secondary extinction coefficient	0.0079(7)
β [°]	90.0072(6)	Final Δ_{max}/σ	0.001
V [Å^3]	3801.56(8)	$\Delta\rho$ (max; min) [e Å^{-3}]	0.32; −0.19
F(000)	1488		

[6]) CCDC-297488 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre*, *via* www.ccdc.cam.ac.uk/data_request/cif.

structure was solved by direct methods using SIR92 [54], which revealed the positions of all non-H-atoms. There are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON [55], but none could be found. The non-H-atoms were refined anisotropically. The amide H-atoms were placed in the positions indicated by a difference electron density map, and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the Me groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Nine reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral-atom-scattering factors for non-H-atoms were taken from [56a], and the scattering factors for H-atoms were taken from [57]. Anomalous dispersion effects were included in F_c [58]; the values for f' and f'' were those of [56b]. The values of the mass attenuation coefficients are those of [56c]. All calculations were performed using the SHELXL97 [59] program.

REFERENCES

[1] K. W. Li, J. Wu, W. Xing, J. A. Simpson, *J. Am. Chem. Soc.* **1996**, *118*, 7237.
[2] Y. Hirai, K. Yokota, T. Momose, *Heterocycles* **1994**, *39*, 603.
[3] S. Cerrini, E. Gavuzzo, G. Luisi, F. Pinnen, *Int. J. Pept. Protein Res.* **1993**, *41*, 282.
[4] A. M. Sefler, M. C. Kozlowski, T. Guo, P. A. Bartlett, *J. Org. Chem.* **1977**, *62*, 93.
[5] Y. L. Dory, J. M. Mellor, J. F. McAleer, *Tetrahedron Lett.* **1996**, *52*, 1343.
[6] T. Imaeda, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1994**, *35*, 591.
[7] J. S. Davies, *J. Peptide Sci.* **2003**, *9*, 471.
[8] G. E. Schulz, R. H. Schirmer, 'Principles of Protein Structure', Springer, New York, 1979.
[9] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1984**, *67*, 526.
[10] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1987**, *70*, 329.
[11] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1990**, *73*, 221.
[12] J. M. Villagordo, H. Heimgartner, *Helv. Chim. Acta* **1997**, *80*, 748.
[13] K. N. Koch, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2000**, *83*, 233.
[14] K. N. Koch, A. Linden, H. Heimgartner, *Tetrahedron* **2001**, *57*, 2311.
[15] K. N. Koch, H. Heimgartner, *Helv. Chim. Acta* **2000**, *83*, 1881.
[16] K. N. Koch, G. Hopp, A. Linden, K. Moehle, H. Heimgartner, *Helv. Chim. Acta* **2001**, *84*, 502.
[17] H. Heimgartner, F. S. Arnhold, S. P. Fritschi, K. N. Koch, J. E. F. Magirius, A. Linden, *J. Heterocycl. Chem.* **1999**, *36*, 1539.
[18] B. Iliev, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 3215.
[19] B. Iliev, A. Linden, R. W. Kunz, H. Heimgartner, *Tetrahedron* **2006**, 62, 1079.
[20] B. Iliev, Ph.D. Thesis, Universität Zürich, 2005.
[21] N. S. Wulfson, V. A. Puchkov, V. N. Bochkarev, B. V. Rozinov, A. M. Zayakoon, M. M. Shemyakin, Y. A. Ovchinnikov, V. T. Ivanov, A. A. Kiryushkin, E. I. Vinigradova, M. Y. Feigina, N. A. Aldanova, *Tetrahedron Lett.* **1964**, *5*, 951.
[22] N. S. Wulfson, V. A. Puchkov, B. V. Rozinov, A. M. Zayakoon, M. M. Shemyakin, Y. A. Ovchinnikov, A. A. Kiryushkin, V. T. Ivanov, *Tetrahedron Lett.* **1965**, *6*, 2793.
[23] K. Brockmann, G. Schmidt-Kastner, *Chem. Ber.* **1955**, *88*, 57.
[24] M. M. Shemyakin, N. A. Aldanova, R. I. Vinogradova, V. Y. Feigina, *Tetrahedron Lett.* **1963**, *4*, 1921.
[25] B. C. Pressman, E. J. Harris, W. S. Jagger, J. N. Johnson, *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *58*, 1949.
[26] Y. A. Ovchinnikov, V. T. Ivanov, A. V. Evstratov, I. I. Mikhaleva, V. F. Bystrov, S. L. Portnova, T. A. Balashova, E. N. Meshcheryakova, V. M. Tul'chinskii, *Int. J. Pept. Protein Res.* **1974**, *6*, 465.
[27] B. C. Pressman, *Ann. Rev. Biochem.* **1976**, *45*, 501.
[28] J. E. F. Magirius, Ph.D. Thesis, Universität Zürich, 1995.

[29] H. Heimgartner, *Angew. Chem., Int. Ed.* **1991**, *30*, 238.
[30] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1990**, *73*, 13.
[31] W. Altherr, Ph.D. Thesis, Universität Zürich, 1994.
[32] R. Luykx, C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1996**, *79*, 527.
[33] R. T. N. Luykx, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 4093.
[34] N. Pradeille, H. Heimgartner, *J. Peptide Sci.* **2003**, *9*, 827.
[35] N. Pradeille, O. Zerbe, K. Möhle, A. Linden, H. Heimgartner, *Chem. Biodiv.* **2005**, *2*, 1127.
[36] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1998**, *54*, 8721.
[37] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1999**, *55*, 5359.
[38] J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 888.
[39] J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 1899.
[40] F. S. Arnhold, Ph.D. Thesis, Universität Zürich, 1997.
[41] T. Jeremic, A. Linden, K. Moehle, H. Heimgartner, *Tetrahedron* **2005**, *61*, 1871.
[42] T. Jeremic, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2004**, *87*, 3056.
[43] T. Jeremic, A. Linden, H. Heimgartner, *Chem. Biodiv.* **2004**, *1*, 1730.
[44] I. Philipova, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2005**, *88*, 1711.
[45] P. Köttgen, A. Linden, H. Heimgartner, in preparation.
[46] P. Köttgen, Ph.D. Thesis, Universität Zürich, 2006.
[47] C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
[48] J. Bernstein, R. E. Davis, L. Shimoni, N.-L. Chang, *Angew. Chem., Int. Ed.* **1995**, *34*, 1555.
[49] K. C. Nicolaou, *Tetrahedron* **1977**, *33*, 683.
[50] Y. Yamashita, S. Saito, H. Ishitani, S. Kobayashi, *J. Am. Chem. Soc.* **2003**, *125*, 3793.
[51] J. J. Wen, C. M. Crews, *Tetrahedron Lett*. **1998**, *39*, 77.
[52] R. Hooft, 'KappaCCD Collect Software', *Nonius BV*, Delft, 1999.
[53] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Vol. 276, 'Macromolecular Crystallography', Part A, Eds. C. W. Carter Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.
[54] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, 'SIR92', *J. Appl. Crystallogr.* **1994**, *27*, 435.
[55] A. L. Spek, PLATON, Program for the Analysis of Molecular Geometry, University of Utrecht, 2003.
[56] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 6.1.1.1, p. 477; b) D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992 Vol. C, Table 4.2.4.3, p. 200.
[57] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[58] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[59] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, 1997.

Received February 9, 2006