Synthesis of a Regular 24-membered Cyclodepsipeptide by Direct Amide Cyclization

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

The synthesis of a 24-membered cyclic depsipeptide with an alternating sequence of phenyllactic acid and α-aminoisobutyric acid (Aib) is described. The linear precursor was prepared *via* the 'azirine/oxazolone method' using 2,2-dimethyl-3-amino-2*H*-azirines as building blocks for the α,α-disubstituted α-amino acid Aib. The macrolactonization leading to the cyclodepsipeptide was achieved by the 'direct amide cyclization', *i. e*., by treatment of a solution of the linear precursor in toluene with HCl gas.

Key words: Cyclodepsipeptides, Direct Amide Cyclization, Azirine/Oxazolone Method, Aminoisobutyric Acid, Crystal Structure

Introduction

Cyclic depsipeptides are macrocycles composed of both amino acids and hydroxy acids, *i. e*., containing lactam as well as lactone groups. As a result of the well known biological activity of some representatives, they are the subject of continous and current investigations. The majority of naturally occuring cyclic depsipeptides have been isolated from marine or surface cultures of the corresponding microorganisms [1]. The current efforts to find new biologically active natural examples are reflected in a large number of recent papers [2]. Two of the most well known cyclodepsipeptides are the antibiotics valinomycin [3] and enniatins [4], which act as ionophores [5]. The special feature of these 36- and 18-membered cyclodepsipeptides, respectively, is their alternating sequence of α-amino and α-hydroxy acids leading to macrocycles with alternating lactam and lactone bonds. The pharmaceutical importance of, *e. g*., natural enniatins and synthetic analogs stimulates the search for new natural examples and the attempts at synthesizing modified compounds [6]. In practically all syntheses of cyclodepsipeptides, the cyclization is the crucial step. The majority of these ring closures have been carried out by the formation of either the amide bond (lactamization) [7] or the ester bond (lactonization) [8].

A useful cyclization method for depsipeptides containing α,α-disubstituted α-amino acids, the so-called 'direct amide cyclization', has been developed in our group [9 – 13]. The basic concept is shown in Scheme 1: a solution or suspension of an amide of type **1** in toluene is treated with dry HCl gas, whereby the corresponding 1,3-oxazol-5(4*H*)-one derivative **2** is formed by ring closure and elimination of dimethylamine hydrochloride. In the absence of other nucleophiles, the oxazolone **2** undergoes a ring enlargement to yield the cyclic product **3** *via* an intramolecular attack of the ω-hydroxy group onto the lactone functionality.

Several cyclic depsipeptides which contain one hydroxy acid and several α,α-disubstituted α-amino acids have been prepared in our group by using this cyclization method [9 – 12], *e. g*., the 12-membered **4** [9b] and the 16-membered **5** [12a]. In addition, syntheses of a 12-membered [9c] as well as some 18-membered cyclodepsipeptides of type **6** [14, 15] with an alternating sequence of α-hydroxy acids and α-amino acids have been accomplished. Sterically demanding disubstituted amino acids have been incorporated into the linear precursors by the so-called 'azirine/oxazolone method' [16]. This particularly use-

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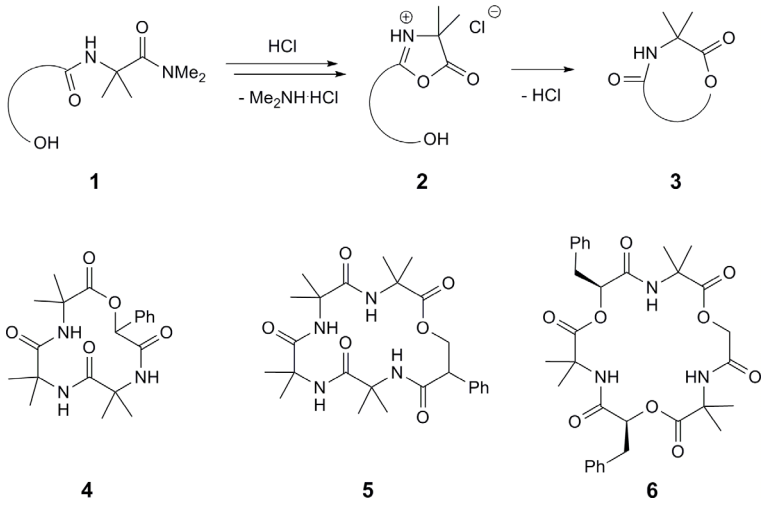


Scheme 1.

ful approach has also been applied successfully in the syntheses of peptaibols [17], endothiopeptides [18], and conformationally restricted cyclic peptides [19].

On the basis of these results it was of interest to ascertain whether cyclodepsipeptides with a larger ring size, and an alternating pattern of α-hydroxy acids and α,α-disubstituted α-amino acids can be synthesized using the 'direct amide cyclization' for the macrolactonization step. Our aim was to prepare a 24-membered cyclic depsipeptide containing four phenyllactic acid and four Aib units. The incorporation of the amino acid units into the linear precursor was again to be achieved by using the 'azirine/oxazolone method'.

Results and Discussion

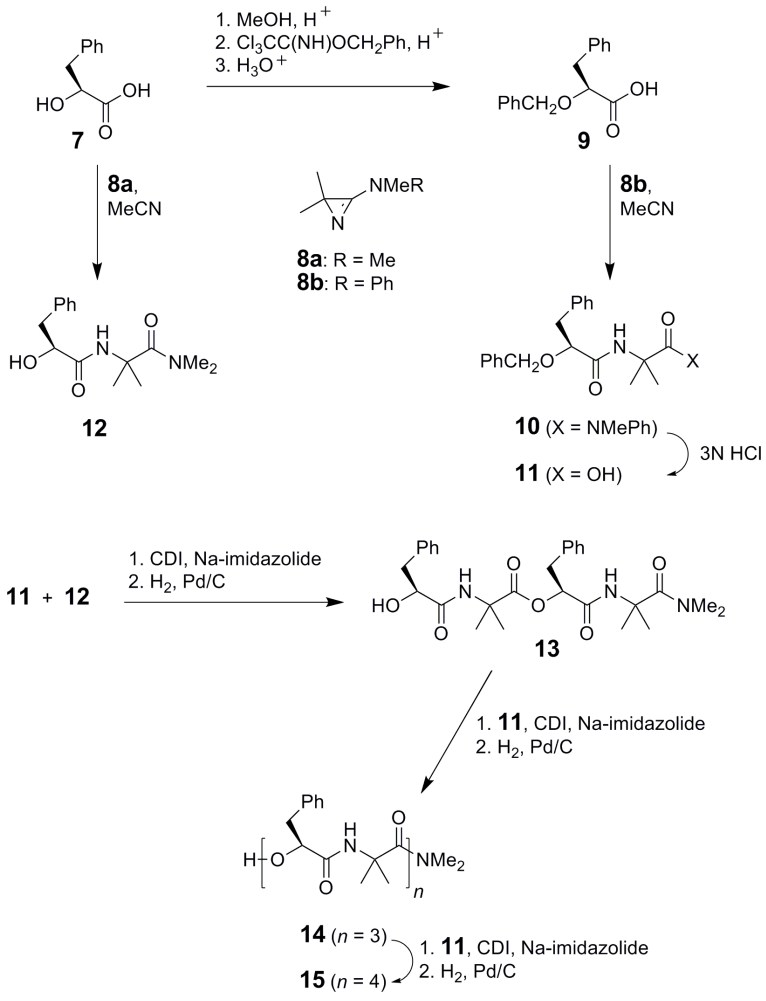
Synthesis of the linear precursor

For our model compound, we selected an α-hydroxy acid, which contained a chromophore to ensure that the final product can be detected by UV light. Furthermore, the linear precursor was to bear a sterically less congested alcohol function to facilitate the ring closure. Therefore, (–)-(*S*)-phenyllactic acid (**7**) was chosen. It was applied in its enantiopure form with the aim of generating only a single diastereoisomer of the linear precursor for the cyclization, and, hopefully, of the cyclodepsipeptide. As synthons for the introduction of the α,α-dimethyl glycine (Aib) units, 3-(*N,N*-dimethylamino)-2*H*-azirine (**8a**) and 3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine (**8b**) were used in the coupling steps to give the corresponding amides.

The synthesis of the linear depsipeptide **15** is shown in Scheme 2. The required *O*-benzyl-protected (*S*)-phenyllactic acid (**9**) could not be synthesized by standard procedures, as it turned out that the configuration at the α-carbon atom is labile under the basic conditions of the benzylation of the OH group as well as the basic ester hydrolysis. However, the enantiomerically pure building block **9** was obtained by the use of benzyl trichloroacetimidate as the benzylating agent [20] and subsequent acid-catalyzed hydrolysis of the methyl ester. The enantiomeric purity of **9** has been proved after coupling with **8b** by means of HPLC chromatography on a chiral stationary phase and comparison with the racemic compound.

The diamide **10** was obtained in excellent yield by coupling of **9** with azirine **8b**. Then, the terminal amide bond was hydrolyzed by following the standard procedure of the 'azirine/oxazolone method' (3N HCl in THF/H_2O at r. t.) leading to the enantiomerically pure building block **11** needed for the subsequent esterification reaction. The required alcohol **12** was prepared by coupling (*S*)-phenyllactic acid (**7**) with the azirine **8a**. The *N*,*N*-dimethylazirine **8a**, which affords the terminal Me_2N-amide **12**, was chosen instead of the *N*-methyl-*N*-phenyl azirine **8b**, which leads to the *N*-methyl-*N*-phenyl amide. Whereas the hydrolysis of the Ph(Me)N amides is easier and usually occurs at r. t., it had turned out in earlier experiments that the terminal Me_2N group is more suitable for the lactonization *via* 'direct amide cylization' [9 – 15].

The esterification of **11** and **12** was performed in high yield using 1,1′-carbonyldiimidazole (CDI) as the coupling reagent and sodium imidazolide as the catalyst [9c]. Deprotection of the alcohol group of the product **13** was achieved by hydrogenolysis



Scheme 2.

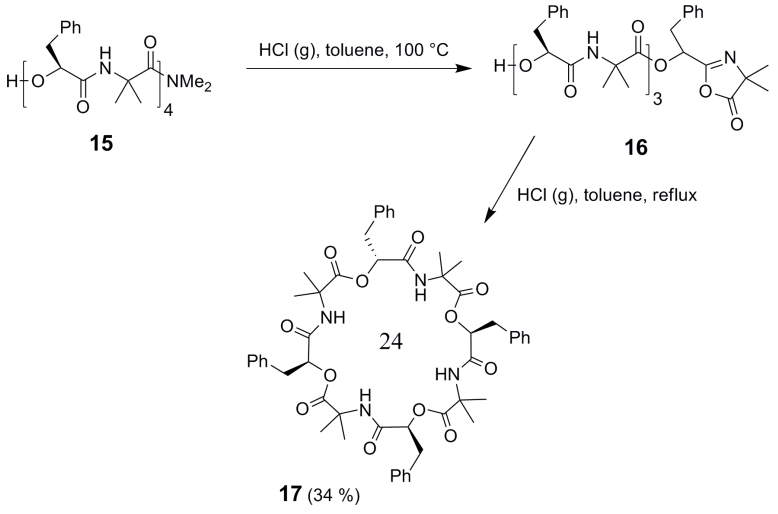
(Pd catalysis). Subsequent twofold repetition of the esterification and deprotection steps yielded the desired precursor for the macrolactonization, *viz.* the 'tetramer' **15**.

In order to obtain a 'dimeric' building block that already contains four alternating units and a carboxylic acid function at the C terminus, attempts were made to hydrolyze the terminal amide bond of **13** selectively. Unfortunately, under the conditions applied, the ester bond was also partially broken and, therefore, this shorter approach to **15** was not successful.

Macrolactonization

The first cyclization attempt was carried out by applying the optimized conditions for the ring closure to give 18-membered cyclodepsipeptides [15]. Treatment of a solution of the precursor **15** in toluene at 100 °C with a stream of dry HCl gas for 4.5 min led to a new product (TLC control). During work-up and column chromatography, the latter decomposed, so we assumed that only the oxazolone **16** was formed during this relatively short reaction time, and that the ring enlargement *via* nucleophilic addition of the ω-hydroxy group onto the oxazolone to give the desired 24-membered ring did not take place.

Therefore, in a second experiment, the reaction mixture was first treated with HCl gas as above and then stirred under reflux for another 20 min to enable the ring enlargement. Again, the same unstable intermediate was detected but could not be isolated. In the subsequent lactonization attempt, the mixture was again treated with HCl gas and then heated for 20 min under reflux while the bubbling of a gentle HCl gas stream through the solution was continued. In fact, a new



Scheme 3.

product was formed (TLC), and the desired macrocycle **17** could be isolated in 34 % yield as a colorless solid (Scheme 3).

These observations indicate a rapid formation of the oxazolone intermediate **16** during the first HCl treatment, but, in contrast to the synthesis of the corresponding 18-membered cyclodepsipeptides [15], the ring enlargement of the oxazolone *via* nucleophilic attack of the ω-hydroxy group at the oxazolone C=O group does not take place. Entropic reasons may be responsible for this difference in reactivity, as the chance for the two reaction centers to come together is smaller with increasing length of the chain. Even prolonged heating under reflux does not lead to the 24-membered ring. The ring closure/ring expansion only proceeds if HCl gas is bubbled through the reaction mixture during heating. Apparently, the intermediate oxazolone **16** has to be activated by protonation, which can be ensured by maintaining a high HCl concentration in the reaction mixture.

The yield of 34 % for the cyclodepsipeptide **17** is comparable with that of other cyclization methods for macrolactones of this ring size. Unfortunately, the ester bonds of the cyclization precursor **15** are not completely stable under the conditions of the 'direct amide cylization', as has been shown by control experiments in methanolic solution [15]. It is most likely that cleavage of ester groups in the linear depsipeptide under these acidic conditions also occurs *via* the formation of 1,3-oxazol-5(4*H*)-ones as intermediates, which, with traces of water or during workup, are transformed into the corresponding acids.

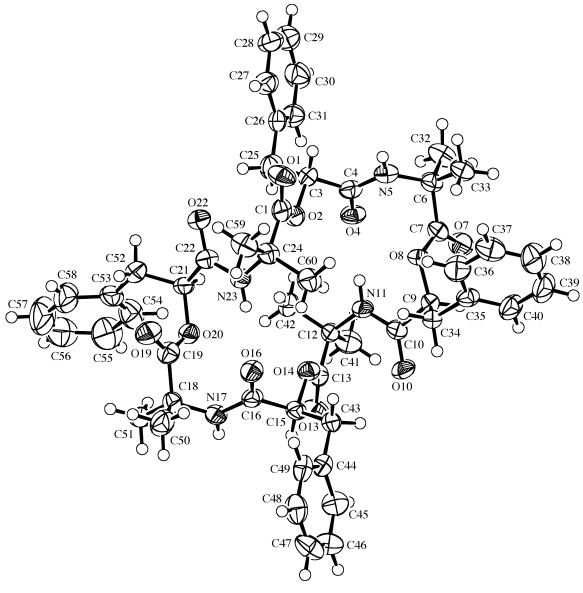


Fig. 1. ORTEP plot [21] of the molecular structure of **17** (50 % probability ellipsoids, arbitrary numbering of atoms).

Crystallization of a sample of **17** from a mixture of xylene, CCl_4 and acetone by slow evaporation of the solvent gave crystals suitable for an X-ray crystal structure determination. The molecular structure of **17** is shown in Fig. 1. It shows the cyclic depsipeptide with an epimerized configuration of one of the four stereogenic centers, *i. e.*, the molecule has the 3*R*,9*S*, 15*S*,21*S* configuration.

The available crystal was not of optimal quality and weakly diffracting, thus the refinement results are of

only moderate precision. However, the overall structure is unambiguous. The space group suggests that the compound in the crystal is enantiomerically pure, but the absolute configuration of the molecule has not been determined. The compound has either the *R,S, S,S* or the *S,R,R,R* configuration. Based on the expectation from the chemical synthesis that the compound should have the *R,S,S,S* configuration, this assumption was used to define the model used in the refinement as 3*R*,9*S*,15*S*,21*S*. Despite the obvious asymmetry arising from the chiral centers, the molecule is pseudocentrosymmetric with 97 % of the atoms closely fitting the centrosymmetric relationship. The asymmetric unit also includes two molecules of *p*-xylene. The macrocyclic molecule contains two intramolecular hydrogen bonds [N(11)–H···O(4) and N(23)–H···O(16)], which link two diametrically opposite amide N–H groups to the next amide O atom around the ring, after an intervening ester group. These interactions form loops with a graph set motif [22] of S(10), *i. e.*, β-turns. The other amide N–H groups form intermolecular hydrogen bonds to diametrically opposed ester carbonyl O atoms in adjacent molecules, one interaction being with the next molecule in the [100] direction [N(5)–H···O(13′)], and the other interaction with the next molecule in the [$\bar{1}$00] direction [N(17)–H···O(1″)]. Each of the intermolecular interactions links the molecules into extended chains which run parallel to the crystallographic *x* axis and have a graph set motif of C(11). As these interactions run antiparallel to one another and link the same pairs of molecules, the two independent intermolecular interactions combined give rise to the formation of a ring between the molecules which has a binary graph set motif of $R_2^2(14)$.

In accord with the observations for the corresponding 18-membered cyclodepsipeptides [15], epimerization also occurred in the present case at one of the stereogenic centers, and only one diastereoisomer was obtained. The stereogenic center in α-position to the oxazolone **16** (Scheme 3), *i. e.*, the first stereogenic center counting from the former amide terminus, is configurationally unstable under the applied conditions of the 'direct amide cyclization', as could be shown by control experiments in the case of the lower homologs of type **14** [15] (see also ref. [23]). Therefore, it is reasonable to assume that the epimerization also took place at this center in the case of **15**. It has not been clarified why only the product with one inverted center was obtained, as a mixture of diastereoisomers might be anticipated. But in the case of a similar 18-membered depsipeptide, a different lactonization using the Corey-Nicolaou method [24] showed that the *R*,*S*,*S* epimer undergoes the cyclization much easier than the *S*,*S*,*S* isomer [15]. The inverted configuration may promote a different conformation that is more suitable for the attack of the ω-hydroxy group onto the oxazolone moiety. A comparable observation was reported recently [25]: The base-catalyzed cyclooligomerization of (3*S*,6*S*)-3-isopropyl-6-methylmorpholine-2,5-dione led to cyclic di-, tri-, and tetramers, *i. e.*, cyclic depsipeptides with alternating lactic acid and valine units, with extensive epimerization. For example, one of the isomeric 24-membered rings was obtained in crystalline form, and the X-ray crystal structure determination established the (*R,R,R,S,R,R,R,S*)-configuration with only two valine residues showing the original (*S*)-configuration.

Conclusions

The 24-membered cylic depsipeptide **17** with an alternating sequence of an α-hydroxy acid and an α,α-disubstituted α-amino acid, *i. e.*, phenyllactic acid and aminoisobutyric acid (Aib), has been synthesized. The preparation of the linear depsipeptide **15** as the precursor of the cyclization has been accomplished by the use of the efficient 'azirine/oxazolone method' to incorporate the Aib units, followed by ester formation of the segments. The macrolactonization step was achieved *via* the 'direct amide cyclization' and yielded the desired product **17** in a yield of 34 %. The structure of the cyclic depsipeptide has been determined by X-ray analysis, which has proved that the cyclization occurs with inversion of the configuration of the α-hydroxy acid next to the amide terminus of **15**. It has thus been demonstrated that this methodology is also useful for the preparation of cyclodepsipeptides with larger rings, *i. e.*, higher homologs of the enniatins. However, the cyclization step has to be improved to avoid epimerization.

Experimental Section

General remarks

The azirines **8a** and **8b**, *i. e.*, 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine and 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, were prepared according to standard procedures (see ref. [16] and refs. cited therein). All other products used were commercially available. Solvents were purified by standard procedures. Thin-layer chromatography (TLC): Merck

TLC aluminium sheets, silica gel 60 F_{254}. Flash chromatography (FCC): Uetikon-Chemie 'Chromatographiegel' C-560. Melting points: Büchi 540 apparatus, uncorrected. IR Spectra: Perkin-Elmer Spectrum one spectrometer; in $CHCl_3$, absorption bands in cm^{-1}. ^1H NMR (300 and 600 MHz) and ^{13}C NMR (75.5 and 151 MHz) spectra: Bruker ARX-300 and Bruker DRX-600 instrument, respectively, in $CDCl_3$ at 300 K, TMS as internal standard, δ in ppm, coupling constants J in Hz, ^{13}C signal multiplicities from DEPT spectra. Mass spectrometry (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).

*General procedure 1 (GP 1). Reaction of azirines **8a** and **8b** with acids **7** and **9***

To a stirred solution of the corresponding acid in dry MeCN was added a solution of the azirine in dry MeCN. The mixture was stirred at r. t. for 16 h, the solvent was evaporated, and the residue was purified by FCC.

*General procedure 2 (GP 2). Esterification of acid **11** with the corresponding alcohols and subsequent hydrogenolysis of the benzyl ether*

A solution of **11** 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 sodium imidazolide suspension (freshly prepared by the reaction of 45 mg of a 60 % dispersion (w/w) of NaH in mineral oil and 73 mg of imidazole in 3 mL of dry THF). After completion of the reaction (monitored by TLC, 2 – 16 h), the solvent was evaporated and the mixture purified by FCC. The 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 a hydrogen atmosphere until completion of the reaction (TLC monitoring). The mixture was then filtered over Celite, the solvent evaporated, and the residue purified by FCC.

*(–)-(2S)-2-Benzyloxy-3-phenylpropanoic acid (**9**)*

To a solution of (–)-(*S*)-phenyllactic acid (**7**, 11.1 mmol, 1.84 g) in MeOH (20 mL) were added 5 drops of conc. H_2SO_4, and the mixture was heated for 1 h under reflux. Then, ethyl acetate (30 mL) was added, the mixture extracted once with 20 mL of a saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, and evaporated. Within 2 h, benzyl 2,2,2-trichloroacetimidate (2.80 g, 11.1 mmol, 2.07 mL) was added to a solution of the obtained methyl ester followed by 5 drops of CF_3SO_3H in CH_2Cl_2/hexane 1 : 1 (100 mL) in analogy to ref. [20], and the mixture was stirred for 10 h. After evaporation of the solvent, the product was separated from remaining starting material by FCC (SiO_2, hexane/Et_2O 1 : 1), and dissolved in dioxane (70 mL). Aqueous 2M HCl (70 mL) was added, and the mixture was stirred at 70 °C for 6 h. Then, brine (100 mL) was added, most of the organic solvent evaporated, and the residue extracted with ethyl acetate (3 × 80 mL). The combined organic fractions were extracted with saturated aqueous $NaHCO_3$ solution (6 × 50 mL), the combined aqueous fractions were adjusted to pH = 1 by addition of HCl and extracted with ethyl acetate (3 × 80 mL). Evaporation of the solvent after drying with $MgSO_4$ gave **9** (1.45 g, 5.66 mmol, 51 %) in pure form. Analytical data including the $[\alpha]_D$ value were in accord with the data in ref. [26].

*(–)-(S)-2-Benzyloxy-N-[1-methyl-1-(N-methyl-N-phenylcarbamoyl)ethyl]-3-phenylpropanamide (**10**)*

According to GP 1, **9** (1.0 g, 3.9 mmol) in MeCN (20 mL), **8b** (680 mg, 3.9 mmol) in MeCN (5 mL), 14 h, FCC (SiO_2, hexane/Et_2O 1 : 1): 1.49 g (89 %) of **10**. White powder, m. p. 92 °C. – IR: ν = 3407m, 3353w, 3031m, 3020s, 3013m, 2930w, 2876w, 2460w, 1952w, 1674s, 1636s, 1594m, 1496s, 1455m, 1388m, 1365m, 1245m, 1205m, 1117m, 1092s, 1030w, 912w. – ^1H NMR: δ = 1.36 (s, 6H, 2 Me), 2.89 (dd, J = 7.7, 14.1, 1H of PhCH_2), 3.14 (dd, J = 3.6, 14.1, 1H of PhCH_2), 3.25 (s, 3H, MeN), 3.86 (dd, J = 3.6, 7.7, 1H, CHO), 4.29 (s, 2H, PhCH_2O), 7.10 – 7.40 (m, 11H, NH + 2 Ph). – ^{13}C NMR: δ = 25.7, 26.3 (2q, 2 Me), 38.4 (t, Ph*C*H_2), 41.4 (q, MeN), 57.8 (s, Me_2C), 72.8 (t, Ph*C*H_2O), 81.1 (d, CHO), 126.3, 127.8, 128.1, 128.3, 129.2, 129.7 (6d, 10 arom. CH), 137.1, 137.4 (2s, 2 arom. C), 170.3, 173.0 (2s, 2 C=O). – MS (EI): *m/z* (%) = 324 (21) $[M–Ph(Me)N]^+$, 296 (36) $[M–Ph(Me)NCO]^+$, 107 (54) $[C_7H_7O]^+$, 91 (100) $[C_7H_7]^+$. – $[\alpha]_D^{25} = -51.4$ (c = 1.1, $CHCl_3$). The enantiomeric purity was proved by analytical HPLC on a Chiralcel OD-H column (hexane/*i*PrOH 13 : 1).

*(–)-(S)-2-(2-Benzyloxy-3-phenylpropanoylamino)-2-methylpropanoic acid (**11**)*

To a solution of amide **10** (1.29 g, 3.0 mmol) in THF (15 mL) was added 6N HCl (15 mL), and the mixture was stirred for 6 h at r. t. Subsequent addition of 2N HCl (15 mL), extraction with Et_2O (3 × 20 mL), drying of the combined organic fractions with $MgSO_4$, and evaporation of the solvent gave **11** (1.00 g, 98 %). White powder, m. p. 126 – 127 °C. – IR: ν = 3413m, 3066m, 3031s, 3021s, 2929m, 2876m, 1951w, 1718s, 1675s, 1517s, 1497m, 1456s, 1300m, 1228m, 1171m, 1090s, 911w. – ^1H NMR: δ = 1.45, 1.47 (2s, 2 × 3H, 2 Me), 2.94 (dd, J = 7.6, 14.1, 1H of PhCH_2), 3.18 (dd, J = 3.6, 14.1, 1H of PhCH_2), 4.10 (dd, J = 3.6, 7.6, 1H, CHO), 4.47 (s, 2H, PhCH_2O), 6.96 (s, 1H, NH), 7.18 – 7.34 (m, 10H, 2 Ph), 8.20 (br. s, 1H, CO_2H). – ^{13}C NMR: δ = 24.2, 24.8 (2q, 2 Me), 38.8 (t, Ph*C*H_2), 56.3 (s, Me_2C), 73.2 (t, Ph*C*H_2O), 80.7 (d, CHO), 126.6, 127.9, 128.1, 128.1, 128.5,

129.7 (6d, 10 arom. CH), 136.8 (s, 2 arom. C), 172.7, 177.0 (2s, 2 C=O). – MS (CI): *m/z* (%) = 359 (7) $[M + NH_4]^+$, 342 (100) $[M + H]^+$. – $[\alpha]_D^{25} = -58.7$ (*c* = 1.3, $CHCl_3$).

*(–)-(S)-N-(1-Dimethylcarbamoyl-1-methylethyl)-2-hydroxy-3-phenyl-propanamide (**12**)*

According to GP 1, **7** (2.0 g, 12.1 mmol) in MeCN (50 mL), **8a** (1.49 g, 13.3 mmol) in MeCN (15 mL), 14 h, FCC (SiO_2, CH_2Cl_2/MeOH 30 : 1): 3.06 g (91 %) of **12**. White powder, m. p. 156 – 158 °C. – IR: ν = 3603w, 3406m, 3346m, 3021s, 3012m, 2942w, 2460w, 1671s, 1629s, 1508s, 1454w, 1395m, 1242m, 1120m, 1086m. – ^{1}H NMR: δ = 1.55, 1.56 (2s, 2 × 3H, 2 Me), 2.89 (dd, *J* = 8.0, 13.9, 1H of PhCH_2), 2.98 (s, 6H, Me_2N), 3.18 (dd, *J* = 4.0, 13.9, 1H of PhCH_2), 4.27 (dd, *J* = 4.0, 8.0, 1H, CHO), 7.20 – 7.32 (m, 5H, Ph), 7.41 (s, 1H, NH). – ^{13}C NMR: δ = 24.8, 24.9 (2q, 2 Me), 38.0 (q, Me_2N), 40.6 (t, Ph*C*H_2), 56.5 (s, Me_2C), 72.6 (d, CHO), 126.8, 128.5, 129.6 (3d, 5 arom. CH), 136.9 (s, arom. C), 171.1, 172.6 (2s, 2 C=O). – MS (CI): *m/z* (%) = 279 (100) $[M + H]^+$, 234 (23) $[M–Me_2N]^+$. – $[\alpha]_D^{25} = -58.4$ (*c* = 1.0, $CHCl_3$).

*(–)-(S)-1-[(1-Dimethylcarbamoyl-1-methylethyl)carb-amoyl]-2-phenylethyl 2-((S)-2-hydroxy-3-phenylpropanoyl-amino)-2-methylpropanoate (**13**)*

According to GP 2, **11** (1.23 g, 3.60 mmol), CDI (583 mg, 3.60 mmol), **12** (1.0 g, 3.60 mmol), THF (40 mL), 2 h, FCC (SiO_2, CH_2Cl_2/MeOH 50 : 1): 1.56 g (85 %) of **13**. White powder, m. p. 96 – 97 °C. – IR: ν = 3672w, 3601w, 3413m, 3303m, 3021m, 3010m, 2462w, 1950w, 1745s, 1662s, 1624s, 1532s, 1498m, 1455m, 1396m, 1366m, 1286m, 1247m, 1147s, 1089m, 1061m, 1031w, 998w, 889w, 862w. – ^{1}H NMR: δ = 1.26, 1.33, 1.48, 1.53 (4s, 4 × 3H, 4 Me), 2.70 – 3.60 (m, 10H, Me_2N + 2 PhCH_2), 4.10 – 4.26 (m, 2H, C*H*OH + OH), 5.29 – 5.41 (m, 1H, CHOCO), 7.10 – 7.36 (m, 12H, 2 Ph + 2 NH). – ^{13}C NMR: δ = 24.4, 24.9, 25.4, 26.1 (4q, 4 Me), 37.6, 40.1 (2t, 2 Ph*C*H_2), 37.9 (q, Me_2N), 55.4, 56.5 (2s, 2 Me_2C), 72.3, 74.4 (2d, 2 CHO), 126.6, 126.7, 128.2, 128.2, 129.5, 129.6 (6d, 10 arom. CH), 136.2, 137.0 (2s, 2 arom. C), 168.1, 172.9, 173.0, 173.9 (4s, 4 C=O). – MS (ESI): *m/z* (%) = 556 (14) [M + MeOH + Na]$^+$, 534 (100) $[M + Na]^+$. – Anal. for $C_{28}H_{37}N_3O_6$ (511.61): calcd. C 65.73, H 7.29, N 8.21; found C 65.24, H 7.65, N 7.96. – $[\alpha]_D^{25} = -60.3$ (*c* = 1.0, $CHCl_3$).

*(–)-(S)-1-[(1-Dimethylcarbamoyl-1-methylethyl)carb-amoyl]-2-phenylethyl 2-{(S)-2-[2-((S)-2-hydroxy-3-phen-yl propanoylamino)-2-methylpropanoyloxy]-3-phenyl-propanoylamino}-2-methylpropanoate (**14**)*

According to GP 2, **11** (1.23 g, 3.60 mmol), CDI (583 mg, 3.61 mmol), **13** (1.84 g, 3.60 mmol), THF (40 mL), 8 h, FCC (SiO_2, CH_2Cl_2/MeOH 50 : 1): 2.22 g (83 %) of **14**. White powder, m. p. 101 – 103 °C. – IR: ν = 3671w, 3601w, 3410m, 3283s, 3066m, 3010m, 2939m, 2463w, 2338w, 1950w, 1878w, 1744s, 1650s, 1543s, 1497m, 1471m, 1455, 1440, 1388, 1366, 1269s, 1198m, 1146s, 1089m, 1063m, 1031m, 1001w, 960w, 941w, 912w, 888w, 864w, 844w. – ^{1}H NMR: δ = 1.24, 1.26, 1.38, 1.44, 1.56, 1.60 (6s, 6 × 3H, 6 Me), 2.98 – 3.45 (m, 12H, Me_2N + 3 × PhCH_2), 3.50 (br. s, 1H, OH), 4.28 – 4.35 (m, 1H, C*H*OH), 5.30 – 5.40 (m, 2H, 2 CHOCO), 7.19 – 7.41 (m, 16H, 3 Ph + 1 NH), 7.82, 8.10 (2s, 2 × 1H, 2 NH). – ^{13}C NMR: δ = 24.2, 24.3, 24.9, 25.3, 25.8, 26.2 (6q, 6 Me), 37.5, 38.0, 40.2 (3t, 3 Ph*C*H_2), 37.8 (q, Me_2N), 55.5, 56.1, 56.4 (3s, 3 Me_2C), 72.3, 74.6, 74.9 (3d, 3 CHO), 126.6, 126.8, 126.9, 128.2, 128.2, 128.4, 129.4, 129.6, 129.7 (9d, 15 arom. CH), 136.0, 136.5, 136.7 (3s, 3 arom. C), 168.4, 169.9, 172.8, 172.86, 173.3, 173.6 (6s, 6 C=O). – MS (ESI): *m/z* (%) = 767 (100) $[M + Na]^+$. – Anal. for $C_{41}H_{52}N_4O_9$ (744.89): calcd. C 66.11, H 7.04, N 7.52; found C 65.53, H 7.09, N 7.37. – $[\alpha]_D^{25} = -60.4$ (*c* = 1.4, $CHCl_3$).

*(–)-(S)-1-[(1-{1-[(1-Dimethylcarbamoyl-1-methylethyl) carbamoyl]-(S)-2-phenylethoxycarbonyl}-1-methylethyl) carbamoyl]-2-phenylethyl 2-{(S)-2-[2-((S)-2-hydroxy-3-phenylpropanoylamino)-2-methylpropanoyloxy]-3-phenylpropanoylamino}-2-methylpropanoate (**15**)*

According to GP 2, **11** (1.23 g, 3.60 mmol), CDI (583 mg, 3.61 mmol), **14** (2.68 g, 3.60 mmol), THF (40 mL), 16 h, FCC (SiO_2, CH_2Cl_2/MeOH 50 : 1): 2.81 g (80 %) of **15**. White powder, m. p. 88 – 90 °C. – IR: ν = 3601w, 3413m, 3282s, 3066m, 3021m, 3009m, 2930m, 1951w, 1744s, 1651s, 1547s, 1497m, 1471m, 1455m, 1388m, 1366m, 1269m, 1147s, 1083m, 1063m, 1031m, 1002w, 939w, 889w, 864w. – ^{1}H NMR: δ = 1.23, 1.41, 1.45, 1.52, 1.59 (5s, 8 × 3H, 8 Me), 2.90 – 3.35 (m, 14H, Me_2N + 4 PhCH_2), 4.21 – 4.29 (m, 1H, C*H*OH), 5.02 – 5.09, 5.21 – 5.31 (2m, 1H + 2H, 3 CHOCO), 7.16 – 7.39 (m, 21H, 4 Ph + 1 NH), 7.80, 8.04, 8.11 (3s, 3 × 1H, 3 NH). – ^{13}C NMR: δ = 24.3, 25.2, 25.4, 25.9, 26.3 (5q, 8 Me), 37.6, 37.8, 38.0, 40.2 (4t, 4 Ph*C*H_2), 37.9 (q, Me_2N), 55.6, 56.1, 56.6 (3s, 4 Me_2C), 72.4, 74.6, 75.1, 75.6 (4d, 4 CHO), 126.7, 126.86, 126.91, 127.0, 128.3, 128.3, 128.5, 129.6, 129.8, 129.9 (10d, 20 arom. CH), 136.1, 136.6, 136.7, 137.0 (4s, 4 arom. C), 168.6, 170.1, 170.5, 172.9, 173.1, 173.4, 173.5, 173.8 (8s, 8 C=O). – MS (ESI): *m/z* (%) = 1000 (100) $[M + Na]^+$. – Anal. for $C_{54}H_{67}N_5O_{12}$ (978.14): calcd. C 66.31, H 6.90, N 7.16; found C 65.55, H 6.88, N 7.00. – $[\alpha]_D^{25} = -58.7$ (*c* = 1.0, $CHCl_3$).

*(–)-(6R,12S,18S,24S)-6,12,18,24-Tetrabenzyl-3,3,9,9, 15,15,21,21-octamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (**17**)*

Dry HCl gas was bubbled through a solution of **15** (300 mg, 0.31 mmol) in toluene (30 mL) at 100 °C for

4.5 min. The mixture was then heated under reflux for 20 min while a gentle stream of dry HCl gas was bubbled through the solution. The mixture was allowed to cool to r.t. while bubbling N_2 through it. Evaporation of the solvent and column chromatography (SiO_2, CH_2Cl_2/MeOH 50 : 1) gave **17** (96 mg, 34 %). White powder, m.p. 133 – 134 °C. – IR: ν = 3272m, 3066w, 3031w, 3009w, 2930w, 1745s, 1645s, 1553m, 1455w, 1388m, 1309w, 1269m, 1145s, 1064m, 909w. – ^{1}H NMR: δ = 1.18 – 1.68 (m, 24H, 8 Me), 2.86 – 3.43 (m, 8H, 4 PhCH_2), 4.95 – 5.49 (m, 4H, 4 CHO), 6.90 – 7.47 (m, 20H, 4 Ph), 7.89 – 8.40 (m, 4H, 4 NH). – ^{13}C NMR (broad signals): δ = 24.8 (q, 8 Me), 37.6 (t, 4 CH_2), 56.0 (s, 4 Me_2C), 75.4 (d, 4 CHO), 126.8, 128.2, 129.7 (3d, 20 arom. CH), 136.8 (s, 4 arom. C), 170.0, 173.6 (2s, 8 C=O). – MS (ESI): *m/z* (%) = 955 (100) $[M + Na]^+$. – Anal. for $C_{52}H_{60}N_4O_{12}\cdot H_2O$ (933.04·H_2O): calcd. C 65.67, H 6.57, N 5.89; found C 65.75, H 6.89, N 5.73. – $[\alpha]_D^{25}$ = −41.0 (*c* = 0.8, $CHCl_3$).

X-Ray crystal-structure determination of ***17***

The measurement was performed on a Nonius KappaCCD area detector diffractometer [27] using graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below [28], and a view of the molecule is shown in Fig. 1. Data reduction was performed with HKL DENZO and SCALEPACK [29]. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. The structure was solved by Direct Methods using SIR92 [30], which revealed the positions of all non-H atoms. The non-H atoms were refined anisotropically. All H atoms were placed in geometrically calculated positions and refined by using a riding model where each H atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C atom (1.5 U_{eq} for the methyl 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. Neutral atom scattering factors for non-H atoms were taken from ref. [31], and the scattering factors for H atoms were taken from ref. [32]. Anomalous dispersion effects were included in F_c [33]; the values for f' and f'' were those of ref. [34]. The values of the mass attenuation coefficients are those of ref. [35]. All calculations were performed using the SHELXL-97 [36] program.

Crystal data for **17**: $C_{52}H_{60}N_4O_{12}\cdot 2C_8H_{10}$, M = 1145.39, crystallized from xylene/CCl_4/acetone, colorless, prism, crystal dimensions: 0.10 × 0.20 × 0.22 mm^3, triclinic, space group $P1$, Z = 1, reflections for cell determination: 5495, 2θ range for cell determination: 4 – 50°, a = 10.0596(4), b = 11.1402(5), c = 14.9075(7) Å, α = 76.869(2)°, β = 87.668(2)°, γ = 76.776(2)°, V = 1583.7(1) Å^3, T = 160(1) K, D_x = 1.201 g cm^{-3}, μ(MoK_α) = 0.0820 mm^{-1}, scan type ω, $2\theta_{max}$ = 50°, total reflections measured: 23521, symmetry independent reflections: 5539, reflections with $I \geq 2\sigma(I)$: 3042, reflections used in refinement: 5539, parameters refined: 770, restraints: 3, $R(F)$ [$I \geq 2\sigma(I)$ reflections] = 0.0638, $wR(F^2)$ (all data) = 0.1714 ($w = [\sigma^2(F_o^2) + (0.0568P)^2]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit: 1.037, final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.26; −0.30 e Å^{-3}, secondary extinction coefficient = 0.015(3).

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