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An Improved Synthesis of 3,4-(Aminomethano)proline and Its Incorporation into Small Oligopeptides[‡]

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Starting from the readily available Garner aldehyde, a new synthesis of diastereomerically and enantiomerically pure 3,4-(aminomethano)prolinol (2*R*,1′*S*,3*S*,4*S*)-**17** has been developed using simple and easily scalable transformations. The protected diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**17** has been shown to be an appropriate compound for the exchange of protecting groups. Final Jones oxidation furnished the correspondingly protected diamino acids in high yields. The newly synthesized Fmoc/Boc-protected 3,4-(aminomethano)-proline (Amp) derivatives, which are proline mimics as well as bicyclic γ-amino acids, depending on the orthogonal protecting group pattern, were employed for solid-phase peptide synthesis with the Fmoc strategy. Thus, the features of Amp as a γ-amino acid residue (γ-Amp) were investigated in the preparation of alternating α/γ-amino acid sequences. The obtained highly homogeneous products were characterized by circular dichroism spectroscopy. The fact that the dichroic properties of the α/γ-oligopeptides were independent from the solvent used (water or methanol) suggests the presence of a preferred conformation. These results are encouraging for the development of foldamers based on γ-Amp units.

Introduction

First isolated in 1968 from seeds of *aesculus parviflora*,[1] the 3,4-methanoproline (**1**) has been found to be a potent inhibitor of the proline metabolism. Since then, several syntheses of 3,4-methanoproline (**1**) have been developed, offering approaches to racemic[2] as well as enantiomerically pure[3] **1**. Numerous synthetic analogs of **1** have been synthesized and attracted considerable attention as pharmaceutically relevant compounds and conformationally constrained scaffolds for peptide chemistry. Among these are the 1′-carboxy-3,4-methanoproline (**2**)[4] and 1′,1′-dicarboxy-3,4-methanoproline (**3**), which was found to be a potent NMDA- (*N*-methyl-D-aspartate) and KA (kainate) receptor agonist.[5] The 1′,1′-dimethyl- (**4**) and 1′-guanidinylmethyl- (**5**) as well as **2** have been used for an extensive study of peptide mimics based on the 3,4-methanoproline system (Figure 1).[6]

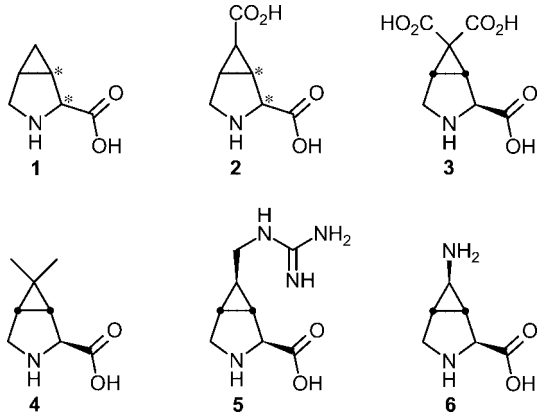

Figure 1. 3,4-Methanoproline (**1**) and examples of known 1′-substituted 3,4-methanoproline derivatives **2**–**6**.

Recently, we described the first synthesis of 3,4-(aminomethano)proline (**6**).[7] Starting from (2*S*,4*R*)-*N*-Boc-4-hydroxyproline, protected 3,4-(aminomethano)proline could be obtained in a remarkably short synthesis of four steps only, furnishing a single diastereomer of this diamino acid. However, this synthesis caused inevitable difficulties related to reasonable yields upon an attempted scale-up concerning its purification and modification of the protecting groups. Therefore, we developed an improved synthesis employing easily scalable, high yielding transformations, which offers an access to 3,4-(aminomethano)proline equipped with various protecting groups.

In this context, we focused on a strategy to develop *N*-Fmoc/Boc-protected 3,4-(aminomethano)proline (Amp) as

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a possible candidate for solid-phase peptide synthesis. Indeed, Amp represents an interesting building block for the development of peptido-mimetics, as it can be used not only as a modified proline, but also as a bicyclic γ-amino acid, depending on the nature of the two amino-protecting groups. In the last decade,[8] many efforts have been made to design and develop new oligopeptides, so-called foldamers, which exist in a well-ordered conformation in solution. These fully synthetic molecules aim to mimic or even to expand the functions of nature. The pioneering work of Gellman[9] and Seebach[10] on β-peptides designing oligomers of cyclic or acyclic β-amino acids has shown the power of these chemical tools in a number of biological applications. Besides β-peptides, also alternating α/β-peptides,[11] γ-peptides[12] and δ-peptides[13] have been described, and many other foldamers are rapidly emerging. Here, we report our first results concerning the use of Amp as a γ-amino acid to prepare alternating α/γ-peptides by the solid-phase Fmoc methodology.

Results and Discussion

The envisaged synthetic route was conceived to start from a vinylglycine derivative **7** which ought to be *N*-allylated to furnish the *N*-allylvinylglycine **8**. Ring-closing metathesis of the latter would afford the 3,4-dehydroproline **9**, which would be an appropriate substrate for a titanium-mediated aminocyclopropanation to give **10** (Figure 2).[7] Initial attempts to prepare the intermediates **7** and **8**, respectively, turned out to be rather futile and were usually accompanied by significant racemization. An attractive possibility to circumvent this problem appeared to be the use of the analogous amino alcohol, vinylglycinol in an appropriately protected form **11**, the products of which would have to be oxidized to the corresponding amino acid towards the end of the synthesis.

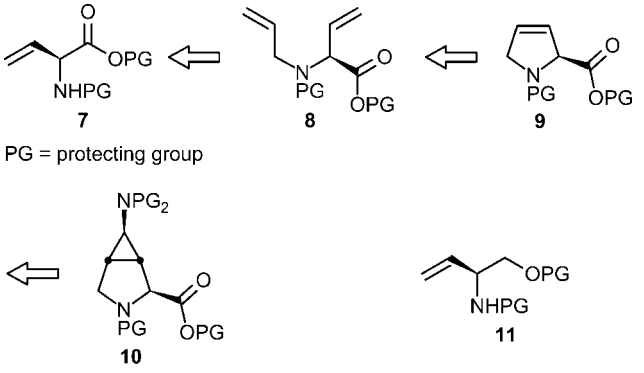


Figure 2. Retrosynthetic considerations concerning 3,4-(aminomethano)proline **10**.

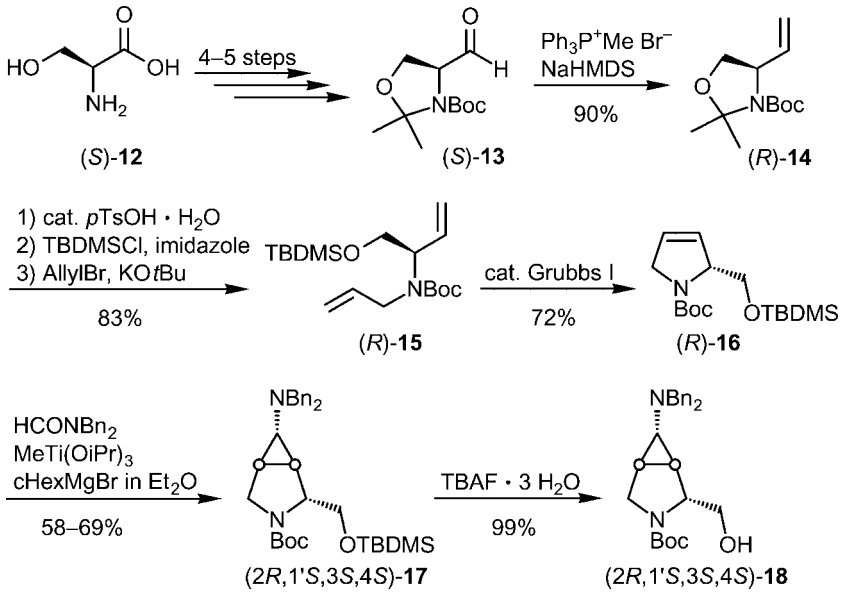
A fairly simple route to **11** starts from (*S*)-*N*-Boc-methionine which can be transformed to the methyl ester followed by reduction to (*S*)-*N*-Boc-methioninol[14] and oxidation to the corresponding sulfoxide[15] in nearly quantitative yield over three steps. Thermal elimination of this sulfoxide is known to proceed in 56–65% yield.[16] Unfortunately, this yield dropped dramatically to 36% on a 10 mmol and to only 11% on a 100 mmol scale, showing that (*S*)-*N*-Boc-methionine is an unsuitable starting material en route to 3,4-(aminomethano)proline.

An alternative synthesis of protected vinylglycinol **11** starts from (*S*)-serine, (*S*)-**12**, which can easily be converted into the Garner aldehyde (*S*)-**13** on a 20 g scale.[17] Wittig olefination of the latter using sodium bis(trimethylsilyl)-amide as a base furnished the protected vinylglycinol derivative (*R*)-**14** with virtually the same optical purity as described previously with use of the considerably more expensive potassium bis(trimethylsilyl)amide.[17,18] Cleavage of the *N*,*O*-dimethyl acetal group using 12 mol-% of *p*-toluenesulfonic acid monohydrate, subsequent protection of the alcohol function as a *tert*-butyldimethylsilyl ether followed by *N*-allylation using potassium *tert*-butoxide as the base, afforded the protected *N*-allylvinylglycinol derivative (*R*)-**15** in 83% yield over three steps (Scheme 1).

Albeit an analogous ring-closing cross-metathesis reaction[19] of the precursor (*R*)-**15** without a *tert*-butyldimethylsilyl group using Grubbs I catalyst[20a] has been described to give the corresponding 3,4-dehydroprolinol derivative in 95% yield,[21] the same ring closure of (*R*)-**15** turned out to be more difficult. With the Grubbs I catalyst, an incomplete conversion occurred, and this could not be improved significantly employing the Grubbs II[20b] or the Hoveyda–Grubbs catalyst.[20c] However, (*R*)-**15** and the product (*R*)-**16** could easily be separated by column chromatography furnishing (*R*)-**16** in 72% yield. Astonishingly, the recovered (*R*)-**15** proved to be unreactive in an attempted second run (Scheme 1).

Titanium-mediated aminocyclopropanation[22] of the 3,4-dehydroprolinol derivative (*R*)-**16** with dibenzylformamide gave the protected 3,4-(aminomethano)prolinol derivative (2*R*,1′*S*,3*S*,4*S*)-**17** in up to 69% yield as a single diastereomer. The only side product formed was 7-(dibenzylamino)bicyclo[4.1.0]heptane which was inevitably obtained due to reductive cyclopropanation of dibenzylformamide with the titanacyclopropane intermediate derived from cyclohexylmagnesium bromide. Removal of the silyl-protecting group succeeded in virtually quantitative yield[23] furnishing the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18** which proved to be a suitable starting material for the introduction of different protecting groups (Scheme 1).

First, oxidation of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18** was investigated. With potassium permanganate in a mixture of *tert*-butyl alcohol and sodium hydroxide, complete decomposition of the substrate was observed,[24] probably because of the high acidity of the proton in the α-position of (2*R*,1′*S*,3*S*,4*S*)-**19**, the abstraction of which does not only cause racemization, but could also lead to ring-opening reactions. Using Jones reagent, the desired diamino acid (2*R*,1′*S*,3*S*,4*S*)-**19** was obtained, albeit in 49% yield only.[25] Surprisingly, subsequent hydrogenolysis of (2*R*,1′*S*,3*S*,4*S*)-**19** under palladium catalysis led to complete decomposition instead of removal of the *N*-benzyl groups. This was rather astonishing, as debenzylation of an analogous substrate without acid function has been re-

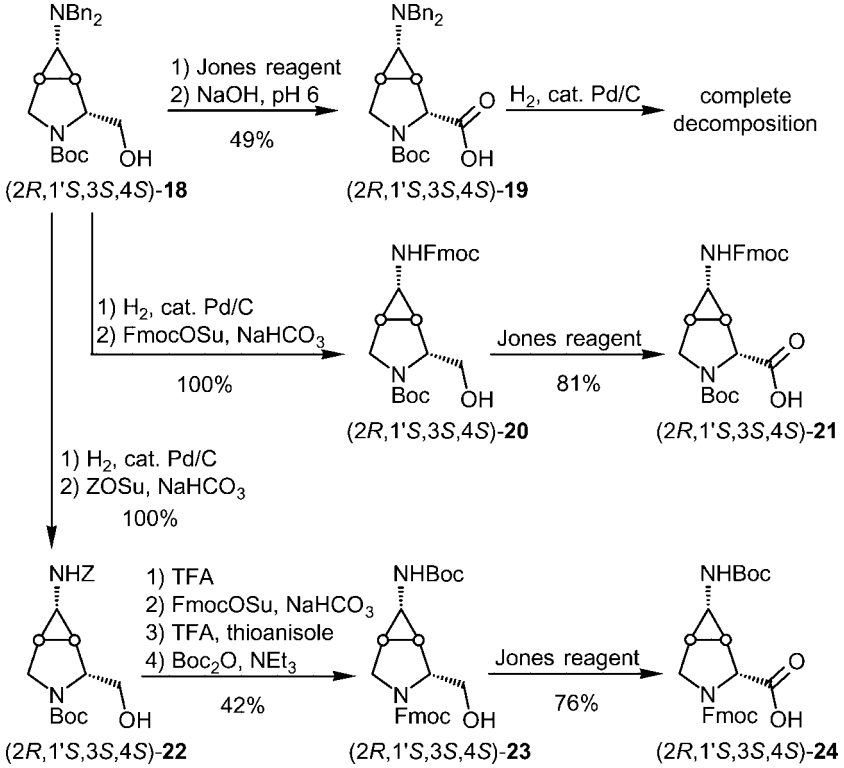


Scheme 1. Synthesis of protected 3,4-(aminomethano)prolinol (2*R*,1′*S*,3*S*,4*S*)-**18**.

ported to succeed under the same conditions in almost quantitative yield (Scheme 2).[22a]

An alternative starting material for the preparation of the target amino acid with modified protecting groups ought to be the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18**. In contrast to the diamino acid (2*R*,1′*S*,3*S*,4*S*)-**19**, hydrogenolysis of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18** could be carried out without any difficulties, and it furnished, after Fmoc-protection of the newly created primary amino group, the protected diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**20** in quantitative yield. Jones oxidation of the latter gave the 3,4-(aminomethano)proline derivative (2*R*,1′*S*,3*S*,4*S*)-**21** in 81% yield, having incorporated the Boc group on the secondary and the Fmoc group on the primary amino function (Scheme 2).

Introduction of the reverse protection pattern, i.e. with the Fmoc-protecting group on the secondary and the Boc-protecting group on the primary amino function, turned out to be much more difficult. Early attempts had proven



Scheme 2. Modification of protection groups in (2*R*,1′*S*,3*S*,4*S*)-**18** and oxidation to diamino acid derivatives.

that a titanium-mediated aminocyclopropanation with an Fmoc-containing substrate (e.g. *N*-Fmoc-dihydropyrrole) could not be performed, probably due to the instability of the Fmoc group under the basic reaction conditions of such a cyclopropanation reaction.[26] Consequently, the Fmoc group had to be introduced at a later stage in the synthesis, and again, the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18** was chosen as the starting material for the exchange of the protecting groups.

Hydrogenolysis of (2*R*,1′*S*,3*S*,4*S*)-**18** followed by Boc protection of the primary amino function led into a blind alley since, in contrast to a literature procedure,[27] the Boc group could not be removed selectively from the secondary amino function, but stayed intact along with that on the primary amine. When the Boc group in (2*R*,1′*S*,3*S*,4*S*)-**18** was cleaved off first, followed by Fmoc protection, removal of the benzyl groups by hydrogenolysis only led to decomposition.

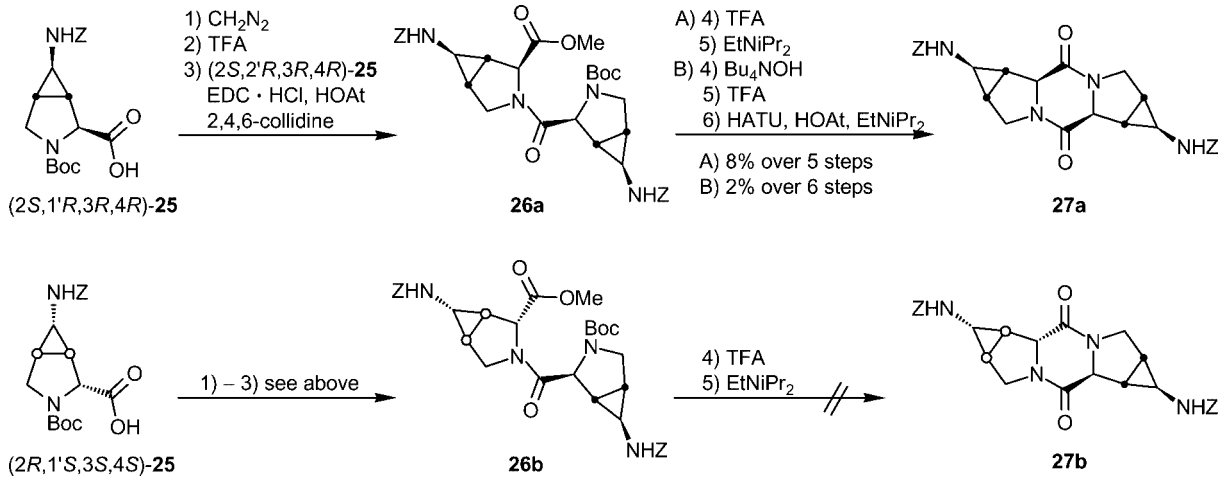
As the direct exchange of the desired protecting groups failed, an indirect access was chosen. Cleavage of the *N*-benzyl groups in (2*R*,1′*S*,3*S*,4*S*)-**18** and introduction of the Z group gave the protected diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**22** in quantitative yield. Exchange of the Boc group with the Fmoc group furnished the N^{α}-Fmoc-3,4-(Z-aminomethano)prolinol which was subjected to hydrogenolysis. Surprisingly, after Boc protection, the desired prolinol derivative (2*R*,1′*S*,3*S*,4*S*)-**23** holding the Fmoc- and Boc-protecting groups, was formed along with the bis-Boc-protected derivative in a ratio of 2:1, corresponding to a yield of 60 and 32%, respectively. The fact that not only the Z-protecting group, but also the Fmoc group is cleaved off upon hydrogenolysis, has been described in literature, but does usually occur as a minor side reaction only.[28] However, if the Z group was not cleaved-off by hydrogenolysis, but under acidic conditions with trifluoroacetic acid and thioanisole[29] followed by Boc protection, the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**23** could be isolated in 42% yield as a single product. Subsequent Jones oxidation of the latter furnished the desired 3,4-(aminomethano)proline (2*R*,1′*S*,3*S*,4*S*)-**24** with the Fmoc group on the secondary and the Boc group on the primary amino function in 76% yield (Scheme 2).

Having completed the synthesis of (2*R*,1′*S*,3*S*,4*S*)-**21** and (2*R*,1′*S*,3*S*,4*S*)-**24**, suitable starting materials for standard solid-phase peptide coupling with 3,4-(aminomethano)proline **6** were available.

An interesting aspect in connection with the available 3,4-(aminomethano)proline (**6**) appeared to be the synthesis of its diketopiperazine as a rigid scaffold for pharmacophores. Since especially 2,5-diketopiperazines are known to often exhibit remarkable biological activities,[30] their synthesis as well as their application in peptide chemistry have been well established.[31] A diketopiperazine consisting of 3,4-(aminomethano)proline subunits might hold interesting properties due to the almost complete conformational constraint in the diketopentacyclic skeleton.

An established access to diketopiperazines starts with the synthesis of the corresponding dipeptide which is subsequently cyclized to the diketopiperazine. Therefore, the free acid function of (2*S*,1′*R*,3*R*,4*R*)-**25**[17,32] was esterified with diazomethane followed by removal of the Boc group. Subsequent peptide coupling with a second equivalent of (2*S*,1′*R*,3*R*,4*R*)-**25** under standard conditions furnished an impure dipeptide **26a** (44% crude yield) which was used without further purification. Removal of the Boc group in **26a** and subsequent cyclization in the presence of Hünig's base, succeeded in only 8% yield over five steps. When, the methyl ester function of the crude dipeptide **26a** was hydrolyzed and then the cyclization was initiated by addition of HATU and HOAt in the presence of Hünig's base, the yield of the desired diketopiperazine **27a** was even lower (2% over six steps).

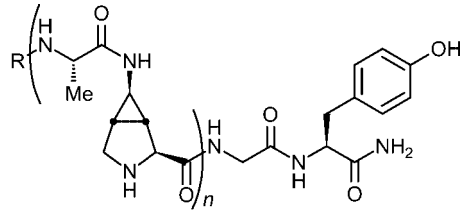
The analogous reaction sequence carried out with the second enantiomer (2*R*,1′*S*,3*S*,4*S*)-**25** gave the crude dipeptide **26b**. In contrast to the reaction of **26a**, removal of the Boc group from **26b** followed by treatment with Hünig's base did not result in cyclization to the corresponding diketopiperazine **27b**. Instead, a dipeptide corresponding to **26b**, but without a Boc-protecting group was obtained in 18% yield starting from (2*R*,1′*S*,3*S*,4*S*)-**25** (Scheme 3).



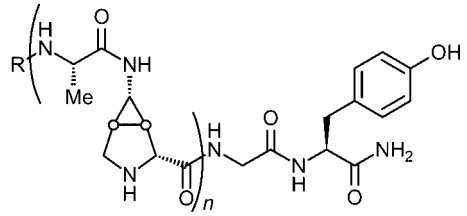
Scheme 3. En route to diketopiperazines derived from 3,4-(aminomethano)proline.

These results indicate that a peptide coupling of two 3,4-(aminomethano)proline units as well as cyclization reactions to obtain a pentacyclic system as **27** are particularly disfavored. However, the first diketopiperazine **27a** consisting of two 3,4-(aminomethano)proline subunits has successfully been synthesized.

Both enantiomers of N^{γ}-Fmoc/N^{α}-Boc-protected Amp ([2*S*,1′*R*,3*R*,4*R*]-**21a** and [2*R*,1′*S*,3*S*,4*S*]-**21b**) were used for the solid-phase synthesis of alternating α/γ peptides (Figure 3). The chain assembly was performed manually on Rink amide resin with an initial loading of 0.7 mmol/g. The dipeptide Gly-Tyr was chosen as a general *C*-terminal motif for two reasons: (*i*) Tyr provides the oligomer with an internal chromophore, which is advantageous for the determination of the concentration by UV spectroscopy, and (*ii*) Gly can function as a short spacer between the *C* end and the core sequence. As the oligomers presented here were cleaved-off from the resin before removing the last Fmoc group, their concentration was determined from the UV absorption of the fluorene moiety at 301 nm. The synthesis of fully deprotected peptide chains in order to determine the influence of the nature of the *N* and *C* ends on the conformation will have to be investigated in future.



28a (*n* = 2)
29a (*n* = 3)



28b (*n* = 2)
29b (*n* = 3)

R = Fmoc

Figure 3. Chemical structure of the synthesized α/γ-peptides containing the γ-Amp unit ([2*S*,1′*R*,3*R*,4*R*]-**21a** in **28a** and **29a**, [2*R*,1′*S*,3*S*,4*S*]-**21b** in **28b** and **29b**).

The core sequence of the oligomers consisted of repeats of Ala-γ-Amp. A single-coupling procedure was applied for the building block as well as for the natural amino acids in the presence of HOBt and DIC; however, whereas the acylation steps involving the building block were carried out using a moderate molar excess (2.5 equiv.) and a longer reaction time (16 h), those involving the commercially available amino acids were carried out using higher molar excesses (4 equiv.) and shorter reaction times (4 h). To monitor the peptide chain growth, a small amount of peptidyl-resin was taken after each γ-Amp coupling, treated with TFA in the presence of 10% (v/v) scavengers (TIS/water 1:1), and the cleaved-off product was characterized by analytical HPLC and mass spectrometry. The Fmoc cleavage steps were accomplished with a mixture containing DBU and HOBt in DMF. With this synthetic procedure, hexamers **28a/b** and octamers **29a/b** could be obtained in high purities already after TFA cleavage from the resin and precipitation from ice-cold diethyl ether (Figure 4).

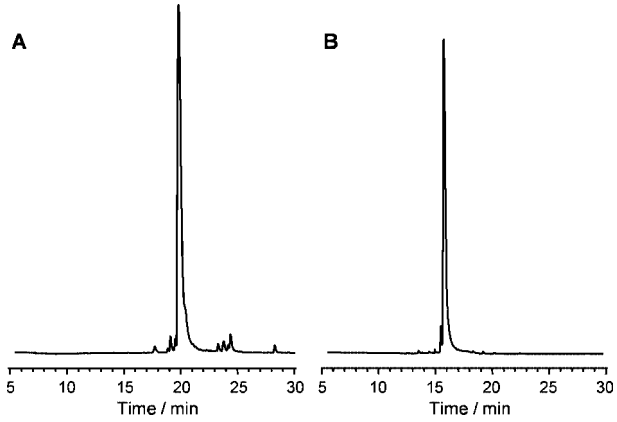


Figure 4. Analytical HPLC profiles of hexamer **28a** (A) and octamer **29a** (B) after TFA cleavage from Rink amide resin and precipitation from ice-cold diethyl ether. The HLPC peaks were detected at 220 nm.

The synthesized α/γ-peptides were investigated by circular dichroism (CD) spectroscopy in water and methanol. The CD spectra were analyzed in the far-UV region of 195–260 nm, in which the amide bond transitions can be observed. Both the hexamer **28a** and the octamer **29a** containing the γ-Amp unit with the (2*S*,1′*R*,3*R*,4*R*) configuration were characterized in water by a positive signal in the range of 200–240 nm, with a maximum at 208 nm for **28a** or 212 for **29a**, followed by a shoulder at 225 nm. The CD signal became negative below 198 nm (Figure 5, A). The same CD shape was found in methanol, in which, however, the positive maximum for both oligomers was slightly blue-shifted to 205 nm (Figure 5, B).

In contrast to **28a** and **29a**, oligomers **28b** and **29b** containing the γ-Amp unit with the (2*R*,1′*S*,3*S*,4*S*)-configuration presented completely different CD spectra which were characterized by a negative CD signal in the range of 195–225 nm. In water **28b** and **29b** displayed an intense minimum near 207 nm, which was slightly red-shifted in methanol (to 211 nm for **28b** and to 209 nm for **29b**). Additionally, a weak positive band was detected near 230 nm for the two peptides in both solvents, with a cross-over close to 225 nm (Figure 5, C–D).

The dichroic properties of the oligomers **28a/b** and **29a/b** indicate that the enantiomers of γ-Amp induced two different conformations that were described by opposite Cotton effects in the region 200–225 nm, which was positive in the case of the (2*S*,1′*R*,3*R*,4*R*)-configuration and negative in the case of the (2*R*,1′*S*,3*S*,4*S*) configuration. Moreover, the induced conformations appeared to be not significantly

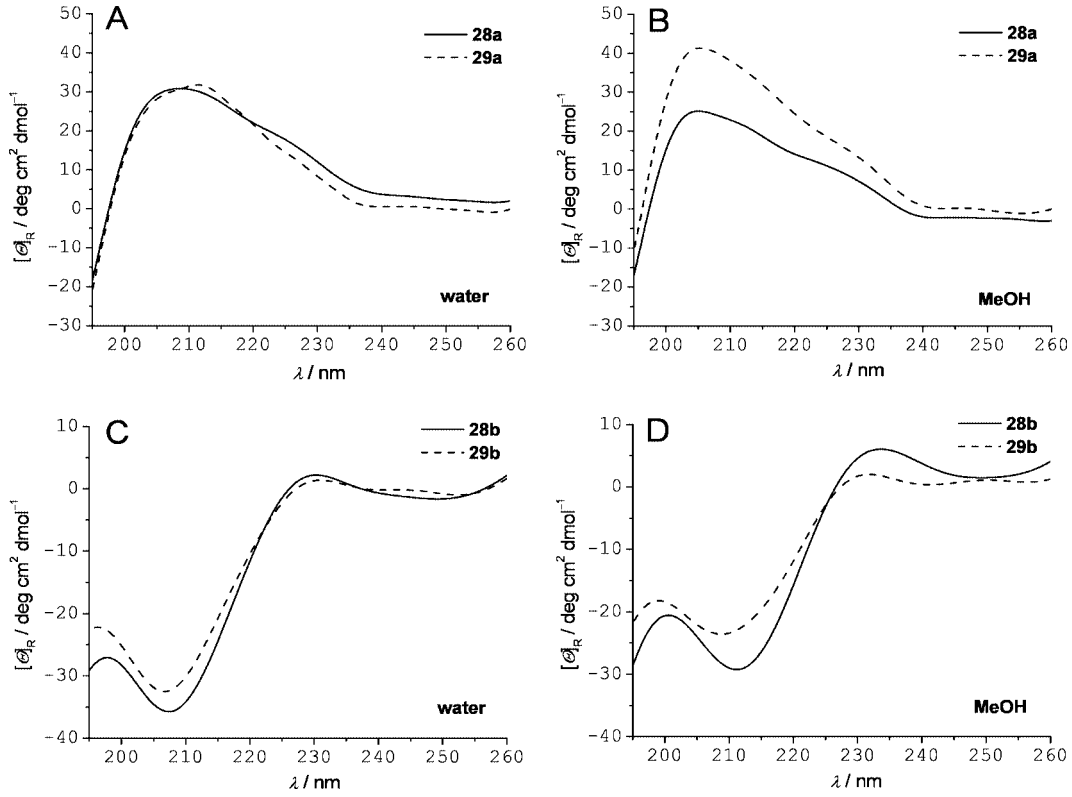


Figure 5. Far-UV CD spectra of the α/γ-hexamers **28a** (100 μM) and **28b** (50 μM) and α/γ-octamers **29a** (100 μM) and **29b** (50 μM) in water and methanol.

affected by the change of the solvent from water to methanol. NMR investigations are currently carried out to elucidate the structure adopted by the presented α/γ-peptides.

Conclusions

The newly prepared *N*γ-Fmoc/*N*α-Boc-protected Amp has been shown to be compatible with the solid-phase peptide chemistry and, therefore, represents a valuable tool to introduce peptide-backbone modifications. In particular, its combination with natural α-amino acids appears to be promising for the development of oligomers with ordered conformations which are dictated by the stereochemistry of the byciclic system.

Experimental Section

General Remarks: $[a]_D^{20}$ values: Polarimeter 241 Perkin–Elmer. IR: Bruker Vector 22 (FT-IR) spectrophotometer, measured as KBr pellets or oils between NaCl plates. NMR spectra were recorded with a Varian Mercury 200 (200 MHz for ^{1}H and 50.2 MHz for ^{13}C NMR) or a Varian UNITY 300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR) instrument. Proton chemical shifts are reported in ppm relative to residual peaks of deuterated solvents. Multiplicities were determined by APT (Attached Proton Test). Whenever necessary, HSQC (Heteronuclear Single Quantum Coherence) was also measured. MS (EI at 70 eV or DCI with NH_3): Finnigan MAT 95 spectrometer. MS (ESI): Finnigan LCQ. MS(HR-ESI): APEX IV 7T FTICR, Bruker Daltonic spectrometer. MS (MALDI-TOF): Future GSG mass spectrometer (Bruchsal, Germany). Melting points: Büchi 510 capillary melting point apparatus, values are uncorrected. Analytical HPLC: L-6200A Intelligent Pump from Merck, HP detector Series 1050 from Agilent, Luna C-18(2) column from Phenomenex (90 Å, 3 μm, 150×4.60 mm) with the following binary elution system: (A) 0.012% (v/v) TFA in water and (B) 0.01% TFA in acetonitrile. The gradient was 5% B for 5 min, 5–60% B over 40 min. UV detection was done at 220 nm (amide bond) and 301 nm (fluorene moiety). Preparative HPLC: Kromasil C18 column (5 μm, 20 mm×250 mm), Jasco PU-1587 pump, Jasco UV/Vis 1575 detector, Jasco Borwin data system (version 1.50). TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV$_{254}$. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie, Universität Göttingen. CD spectroscopy: JASCO J710 spectropolarimeter. Starting materials: 1-hydroxy-7-azabenzotriazole (HOAt) was prepared according to published procedures.[33] *N*-(benzyloxycarbonyloxy)succinimide was recrystallyzed from hexane/EtOAc before use. Anhydrous THF was obtained by distillation from sodium benzophenone ketyl, DMF from CaH_2 and CH_2Cl_2 from P_4O_{10}. All other chemicals were used as commercially available. All operations in anhydrous solvents were performed under a nitrogen atmosphere in flame-dried glassware. Organic extracts were dried with $MgSO_4$. Abbreviations: Boc_2O = di-*tert*-butyl dicarbonate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIC = *N*,*N*′-diisopropylcarbodiimide, DMF = dimethylformamide, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, FmocOSu = *N*-9-fluorenylmethoxycarbonyloxy succinimide, HATU = *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole, HOBt = *N*-hydroxybenzotriazole, MBHA = 4-methyl-

benzhydrylamine, NaHMDS = sodium hexamethyldisilazide, TBAF = tetrabutylammonium fluoride, TBDMSCl = *tert*-butyldimethylsilyl chloride, TFA = trifluoroacetic acid, TIS = triisopropylsilane, *p*TsOH = *p*-toluenesulfonic acid, ZOSu = benzyloxycarbonyloxy succinimide.

(*R*)-*N*-Boc-Vinylglycinol Acetonide [(*R*)-14]: A suspension of methyltriphenylphosphonium bromide (39.3 g, 110 mmol) in anhydrous THF (200 mL) was treated with NaHMDS (53.0 mL, 106 mmol, 2 M soln. in THF) and stirred for 1 h. The reaction mixture was cooled to –78 °C. A solution of the Garner aldehyde (*S*)-**13** (19.4 g, 84.6 mmol) in anhydrous THF (100 mL) was added. The reaction mixture was stirred at –78 °C for 15 min, the cooling bath was removed, and stirring was continued for an additional 2.5 h. H_2O (150 mL) was added, the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed with brine (200 mL), dried and evaporated under reduced pressure. The residue was suspended in pentane (2 × 100 mL), filtered and the solvents evaporated in vacuo. Filtration through silica gel (120 g, 3 × 20 cm column, hexane/EtOAc, 15:1) furnished 17.3 g (76.1 mmol, 90%) of (*R*)-**14** as a colorless oil. The spectroscopic data correspond to the ones described in literature.[11]

(*R*)-*N*-Allyl-*N*-Boc-*O*-(*tert*-butyldimethylsilyl)vinylglycinol [(*R*)-15]: A solution of (*R*)-*N*-Boc-vinylglycinol acetonide [(*R*)-**14**] (17.3 g, 76.1 mmol) in MeOH (150 mL) was treated with H_2O (1.37 mL, 76.1 mmol) and *p*TsOH·H_2O (1.81 g, 9.51 mmol, 12 mol-%). The reaction mixture was stirred for 17 h, before all volatile compounds were evaporated under reduced pressure. The residue was dissolved in anhydrous DMF (100 mL). Imidazole (12.9 g, 190 mmol) was added, and the reaction mixture was stirred for 5 min. After addition of TBDMSCl (12.6 g, 83.7 mmol), stirring was continued for 2.5 h. The reaction mixture was treated with H_2O (100 mL) and extracted with EtOAc (3 × 80 mL). The combined organic extracts were washed with H_2O (3 × 100 mL) and brine (100 mL), dried and concentrated under reduced pressure. The residue was dissolved in anhydrous DMF (50 mL), and the solution cooled to –20 °C. Allyl bromide (9.92 mL, 117 mmol) was added, and then a solution of KO*t*Bu (10.2 g, 91.3 mmol) in anhydrous DMF (100 mL) was added dropwise over a period of 25 min. The cooling bath was removed, and the reaction mixture was stirred for 1.5 h. The reaction mixture was treated with a mixture of ice/H_2O (100 mL) and extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with H_2O (3 × 100 mL) and brine (100 mL), dried and the solvents evaporated in vacuo. The residue was filtered through silica gel (185 g, 4 × 30 cm column, hexane/EtOAc, 30:1, R_f = 0.34) to yield 21.7 g (63.5 mmol, 83%) of (*R*)-**15** as a pale yellow oil, $[\alpha]_D^{20}$ = +2.5 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2976 cm^{-1} (C–H), 2957 (C–H), 2930 (C–H), 2887 (C–H), 2858 (C–H), 1697 (C=O), 1473, 1454, 1402, 1366, 1252, 1176, 1157, 1110, 1072, 921, 838, 776. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 0.09 (s, 6 H, $SiMe_2$), 0.93 [s, 9 H, $SiC(CH_3)_3$], 1.47 [s, 9 H, $C(CH_3)_3$], 3.72–3.94 (m, 4 H, 1,1′′-H), 4.32–4.44 (m, 1 H, 2-H), 5.04–5.22 (m, 4 H, 2′,3′′-H), 5.78–6.00 (m, 2 H, 1′,2′′-H) ppm. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): δ = –5.6 (+, $SiMe_2$), 17.8 [–, $SiC(CH_3)_3$], 25.6 [+, $SiC(CH_3)_3$], 28.3 [+, $OC(CH_3)_3$], 48.2 (–, C-1′′), 60.7 (+, C-2), 63.6 (–, C-1), 79.2 [–, $OC(CH_3)_3$], 115.0, 116.3 (–, C-2′,3′′), 135.2, 136.0 (+, C-1′,2′′), 155.0 (–, NCO) ppm. MS (DCI): *m*/*z* (%) = 342 (100) [M^+ + H], 286 (7), 242 (14). $C_{18}H_{35}NO_3Si$ (341.56): calcd. C 63.30, H 10.33, N 4.10; found C 63.36, H 10.19, N 4.04.

(*R*)-*N*-Boc-*O*-*tert*-Butyldimethylsilyl-3,4-dehydroprolinol [(*R*)-16]: A solution of the vinylglycinol (*R*)-**15** (16.7 g, 48.9 mmol) in anhydrous CH_2Cl_2 (75 mL) was added to a solution of Grubbs I catalyst (100 mg, 122 μmol, 0.25 mol-%) in anhydrous CH_2Cl_2 (25 mL). The reaction mixture was stirred for 17 h and then evaporated under reduced pressure. Column chromatography of the residue (200 g of silica gel, 4 × 30 cm column, hexane/EtOAc, 20:1, starting product fraction 5:1) furnished 11.1 g (35.4 mmol, 72%) of (*R*)-**16** as a pale yellow oil, $[\alpha]_D^{20}$ = +70 (*c* = 0.7, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2956 cm^{-1} (C–H), 2930 (C–H), 2886 (C–H), 2858 (C–H), 1705 (C=O), 1682, 1473, 1463, 1394 (*t*Bu), 1368 (*t*Bu), 1339, 1319, 1256, 1174, 1128, 1106. ^1H NMR (200 MHz, $CDCl_3$, rotamers): δ = 0.00, 0.01 (s, 6 H, $SiMe_2$), 0.84, 0.86 [s, 9 H, $SiC(CH_3)_3$], 1.45, 1.47 [s, 9 H, $C(CH_3)_3$], 3.44–3.58 (m, 1 H, 5-H), 3.67–4.30 (m, 3 H, 1,5-H), 4.35–4.50 (m, 1 H, 2-H), 5.70–5.90 (m, 2 H, 3,4-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, rotamers): δ = –5.5, –5.4 (+, $SiMe_2$), 18.2 [–, $SiC(CH_3)_3$], 25.8, 25.9 [+, $SiC(CH_3)_3$], 28.4, 28.5 [+, $OC(CH_3)_3$], 53.9, 54.1 (–, C-5), 63.2, 64.6 (–, C-1), 65.5, 65.7 (+, C-2), 79.2, 79.5 [–, $OC(CH_3)_3$], 125.8, 126.0 (+, C-4*), 128.8, 128.9 (+, C-3*), 154.1, 154.2 (–, NCO) ppm. MS (EI): *m*/*z* (%) = 313 (3) [M^+], 312 (10), 272 (16), 256 (6) [$M^+ - t$Bu], 232 (100), 212 (38) [$M^+ - CO_2t$Bu], 188 (30), 170 (37), 154 (51), 89 (41), 73 (29) [O*t*Bu$^+$], 57 (59) [*t*Bu$^+$]. $C_{16}H_{31}NO_3Si$ (313.51): calcd. C 61.30, H 9.97, N 4.47; found C 61.01, H 9.64, N 4.20.

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Boc-*O*-*tert*-Butyldimethylsilyl-3,4-(dibenzylaminomethano)prolinol [(2*R*,1′*S*,3*S*,4*S*)-17]: Cyclohexylmagnesium bromide (58.5 mL, 80.7 mmol, 1.38 M soln. in Et_2O) was added over a period of 2 h (syringe pump) to a solution of dibenzylformamide (12.4 g, 55.1 mmol), $MeTi(OiPr)_3$ (11.5 mL, 47.7 mmol) and the dehydroprolinol derivative (*R*)-**16** (11.5 g, 36.7 mmol) in anhydrous THF (70 mL). The reaction mixture was stirred for 17 h, cooled to 0 °C treated with H_2O (5 mL) and stirred for 30 min. The major fraction of the volatile compounds was removed in vacuo. The sticky residue was treated with pentane (200 mL) and stirred until a powder-like precipitate was formed (ca. 2 h). The reaction mixture was filtered through Celite, dried and concentrated under reduced pressure. Column chromatography of the residue [200 g of silica gel, 4 × 30 cm column, hexane/EtOAc, 20:1, R_f = 0.25, starting product fraction 5:1, R_f (20:1) = 0.25] gave 11.1 g (21.2 mmol, 58%) of (2*R*,1′*S*,3*S*,4*S*)-**17** as a pale yellow oil, $[\alpha]_D^{20}$ = +46 (*c* = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2955 cm^{-1} (C–H), 2929 (C–H), 2883 (C–H), 2857 (C–H), 1698 (C=O), 1494, 1472, 1455, 1396 (*t*Bu), 1366 (*t*Bu), 1254, 1177, 1116, 1094, 837, 776, 750, 699. ^1H NMR (300 MHz, $C_2D_2Cl_4$, HSQC, 125 °C): δ = 0.07 (s, 3 H, $SiMe_2$), 0.08 (s, 3 H, $SiMe_2$), 0.93 [s, 9 H, $SiC(CH_3)_3$], 1.35–1.60 (m, 3 H, 1′,3,4-H), 1.47 [s, 9 H, $C(CH_3)_3$], 3.25 (dd, ^2J = 12.0, ^3J = 5.5 Hz, 1 H, 5-H), 3.40–3.48 (m, 1 H, 5-H), 3.54–3.63 (m, 2 H, 1-H), 3.70–3.74 (m, 1 H, 2-H), 3.76 (s, 4 H, NCH_2Ph), 7.24–7.38 (m, 10 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, HSQC, 100 °C): δ = –5.6 (+, $SiMe_2$), 17.8 [C_{quat}, $SiC(CH_3)_3$], 24.5 (+, C-4*), 24.7 (+, C-3*), 25.6 [+, $SiC(CH_3)_3$], 28.4 [+, $OC(CH_3)_3$], 46.8 (+, C-1′), 48.0 (–, C-5), 59.0 (–, NCH_2Ph), 60.5 (+, C-2), 63.8 (–, C-1), 78.8 [C_{quat}, $OC(CH_3)_3$], 126.7 (+, Ph-C), 127.8 (+, Ph-C), 129.1 (+, Ph-C), 138.4 (C_{quat}, Ph-C), 153.6 (C_{quat}, NCO) ppm. MS (DCI): *m*/*z* (%) = 523 (100) [M^+ + H].

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Boc-3,4-(Dibenzylaminomethano)prolinol [(2*R*,1′*S*,3*S*,4*S*)-18]: A solution of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**17** (2.98 g, 5.70 mmol) in THF (20 mL) was treated with TBAF·3H_2O (2.15 g, 6.84 mmol), and the resulting solution was stirred for 3.5 h. H_2O (50 mL) was added and the reaction mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (50 mL), dried and the solvents evaporated in vacuo. The residue was either filtered through silica gel [25 g, hexane/EtOAc, 5:1, starting product fraction 1:1, R_f (1:1) = 0.52] or recrystallized from hexane/Et_2O to yield 2.30 g (5.63 mmol, 99%) of (2*R*,1′*S*,3*S*,4*S*)-**18** as a colorless solid, m.p.

112–114 °C, $[\alpha]_D^{20}$ = +42.9 (*c* = 0.85, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3485 cm^{-1} (O–H), 3022 (C–H), 2997 (C–H), 2978 (C–H), 2943 (C–H), 2931 (C–H), 2912 (C–H), 2877 (C–H), 2843 (C–H), 2813 (C–H), 1670 (C=O), 1493, 1479, 1454, 1433, 1416, 1366 (*t*Bu), 1168, 1123, 1088, 1076. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.14–1.25 (m, 1 H, 3-H*), 1.35–1.42 (m, 1 H, 4-H*), 1.48 [s, 9 H, $C(CH_3)_3$], 1.54–1.58 (m, 1 H, 1′-H), 3.28 (dd, ^2J = 12.0 Hz, ^3J = 6.0 Hz, 1 H, 5-H), 3.43–3.56 (m, 3 H, 1,5-H), 3.71 (s, 2 H, NCH_2Ph), 3.73 (s, 2 H, NCH_2Ph), 3.78–3.87 (m, 1 H, 2-H), 7.24–7.38 (m, 10 H, Ph-H) ppm. The signal of the OH proton could not be assigned. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 24.5 (+, C-3*), 28.1 (+, C-4*), 28.3 [+, $C(CH_3)_3$], 46.9 (+, C-1′), 47.7 (–, C-5), 59.1 (–, NCH_2Ph), 61.1 (+, C-2), 65.3 (–, C-1), 79.7 [–, $OC(CH_3)_3$], 126.8, 127.9, 129.1 (+, Ph-C), 138.4 (–, Ph-C) ppm. The signal of the NCO carbon could not be detected. MS (EI): *m*/*z* (%) = 408 (5) $[M^+]$, 317 (10) $[M^+ - Bn]$, 261 (25) $[M^+ - Bn - C_4H_8]$, 217 (26) $[M^+ - Bn - CO_2 - C_4H_8]$, 91 (100) $[Bn^+]$, 57 (56) $[tBu^+]$, 43 (50). $C_{25}H_{32}N_2O_3$ (408.54): calcd. C 73.50, H 7.89, N 6.86; found C 73.24, H 8.06, N 6.90.

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Boc-3,4-(Dibenzylaminomethano)proline [(2*R*,1′*S*,3*S*,4*S*)-19]: Jones reagent (0.32 mL, 854 μmol, 2.67 M solution in H_2O) was added dropwise at 0 °C to a solution of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18** (204 mg, 500 μmol) in acetone (5 mL) until the reaction mixture stayed orange for >5 min. It was then stirred at 0 °C for 30 min, the cooling bath was removed, and stirring was continued for an additional 45 min. *i*PrOH (0.1 mL) and H_2O (5 mL) were added, and 1 M aq. NaOH soln. was added until the pH value was adjusted to 6. The mixture was extracted with EtOAc (5 × 10 mL). The combined organic extracts were dried and concentrated under reduced pressure. Column chromatography of the residue (10 g of silica gel, 1 × 5 cm column, hexane/EtOAc, 1:1, R_f = 0.06) yielded 104 mg (246 mmol, 49%) of (2*R*,1′*S*,3*S*,4*S*)-**19** as a pale beige, voluminous solid. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.40–1.58 (m, 1 H, 3-H*), 1.46 [s, 9 H, $C(CH_3)_3$], 2.23–2.34 (m, 2 H, 1′,4-H*), 3.36–3.52 (m, 2 H, 5-H), 3.52 (s, 2 H, NCH_2Ph), 3.54 (s, 2 H, NCH_2Ph), 4.18–4.25 (m, 1 H, 2-H), 6.16 (br. s, 1 H, COOH), 7.24–7.42 (m, 10 H, Ph-H) ppm. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 25.0 (+, C-3*), 28.2, 28.3 [+, C-4*, $C(CH_3)_3$,], 46.8 (+, C-1′), 47.7 (–, C-5), 59.8 (–, NCH_2Ph), 60.9 (+, C-2), 80.4 [–, $OC(CH_3)_3$], 126.9, 127.9, 129.0 (+, Ph-C), 138.2 (–, Ph-C), 154.5 (–, NCO) ppm. The signal of the COOH carbon could not be detected. MS (EI): *m*/*z* (%) = 422 (4) $[M^+]$, 331 (8) $[M^+ - Bn]$, 275 (18) $[M^+ - Bn - C_4H_8]$, 231 (11), 106 (34), 91 (100) $[Bn^+]$, 57 (17) $[tBu^+]$.

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Boc-3,4-(Fmoc-Aminomethano)prolinol [(2*R*,1′*S*,3*S*,4*S*)-20]: A suspension of Pd (86 mg, 81.0 μmol, 3 mol-%, 10% on charcoal) in MeOH (5 mL) was shaken under an atmosphere of H_2 for 5 min. A solution of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18** (1.10 g, 2.70 mmol) in MeOH (25 mL) was added, and the mixture was shaken under an atmosphere of H_2 for 17 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was dissolved in acetone/H_2O (10 mL/5 mL), the solution treated with $NaHCO_3$ (250 mg, 2.97 mmol) and FmocOSu (1.00 g, 2.97 mmol), and then stirred for 4 h. After concentration to a volume of ca. 5 mL, H_2O (10 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried and evaporated under reduced pressure. Column chromatography of the residue (40 g of silica gel, 2 × 25 cm column, hexane/EtOAc, 2:1, R_f = 0.25) furnished 1.22 g (2.70 mmol, 100%) of (2*R*,1′*S*,3*S*,4*S*)-**20** as a colorless, voluminous solid, m.p. 77–82 °C, $[\alpha]_D^{20}$ = +30.5 (*c* = 0.57, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3424 cm^{-1} (O–H, N–H), 2974 (C–H), 2934 (C–H), 2882 (C–H), 1696 (C=O), 1676 (C=O), 1403. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.48–1.72 (m, 2 H, 3,4-H), 1.50 [s, 9 H, $C(CH_3)_3$], 2.24–2.32 (m, 1 H, 1′-H), 3.41 (dd, ^2J = 8.0, ^3J = 5.0 Hz, 1 H, 5-H), 3.62–3.74 (m, 3 H, 1,5-H), 4.01–4.09 (m, 1 H, 2-H), 4.24 (t, ^3J = 8.0 Hz, 1 H, 9-H, *Fmoc*), 4.50 (d, ^3J = 8.0 Hz, 2 H, 1′-H, *Fmoc*), 4.80 (br. s, 1 H, NH), 7.30–7.48 (m, 4 H, Ph-H), 7.57–7.64 (m, 2 H, Ph-H), 7.76–7.84 (m, 2 H, Ph-H) ppm. The signal of the OH proton could not be assigned. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 24.0 (+, C-3*), 27.1 (+, C-4*), 28.2 [+, $C(CH_3)_3$], 32.8 (+, C-1′), 47.3 (+, C-9, *Fmoc*), 47.5 (–, C-5), 60.7 (+, C-2), 64.9 (–, C-1*), 66.5 (–, C-1′*, *Fmoc*), 79.9 [–, $C(CH_3)_3$], 119.7, 124.6, 126.8, 127.5 (+, Ph-C), 141.1, 143.7 (–, Ph-C), 156.2 (–, NCO) ppm. MS (ESI): positive, *m*/*z* (%) = 1374 (15) $[3M + Na^+]$, 923 (100) $[2M + Na^+]$, 473 (89) $[M + Na^+]$.

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Boc-3,4-(Fmoc-Aminomethano)proline [(2*R*,1′*S*,3*S*,4*S*)-21]: Jones reagent (1.2 mL, 3.20 mmol, 2.67 M soln. in H_2O) was added dropwise at 0 °C to a solution of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**20** (1.08 g, 2.40 mmol) in acetone (24 mL), until the solution stayed orange for >5 min. The reaction mixture was stirred at 0 °C for 30 min, the cooling bath was removed, and stirring was continued for an additional 1 h. *i*PrOH (0.5 mL) and H_2O (20 mL) were added, and the solution was concentrated to a volume of ca. 25 mL. The reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried and concentrated under reduced pressure. Column chromatography of the residue (40 g of silica gel, 2 × 25 cm column, hexane/EtOAc/HOAc, 25:25:1, R_f = 0.38) gave 901 mg (1.94 mmol, 81%) of (2*R*,1′*S*,3*S*,4*S*)-**21** as a colorless, voluminous solid, m.p. 97–104 °C, $[\alpha]_D^{20}$ = +48.1 (*c* = 0.47, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3322 cm^{-1} (O–H, N–H), 3067 (C–H), 2977 (C–H), 2937 (C–H), 2888 (C–H), 1704 (C=O), 1397, 1368, 1338, 1253, 1175. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 1.66–1.76 (m, 1 H, 3-H*), 1.92–2.02 (m, 1 H, 4-H*), 2.33–2.44 (m, 1 H, 1′-H), 3.52 (dd, ^2J = 8.0, ^3J = 5.0 Hz, 1 H, 5-H), 3.60–3.72 (m, 1 H, 5-H), 4.24 (t, ^3J = 8.0 Hz, 1 H, 9-H, *Fmoc*), 4.40–4.50 (m, 1 H, 2-H), 4.52 (d, ^3J = 8.0 Hz, 2 H, 1′-H, *Fmoc*), 4.92 (br. s, 1 H, NH), 5.40 (br. s, 1 H, COOH), 7.30–7.47 (m, 4 H, Ph-H), 7.55–7.64 (m, 2 H, Ph-H), 7.74–7.82 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 24.1 (+, C-3*), 27.3 (+, C-4*), 28.1 [+, $C(CH_3)_3$], 32.8 (+, C-1′), 47.3 (+, C-9, *Fmoc*), 47.7 (–, C-5), 60.4 (+, C-2), 66.6 (–, C-1′, *Fmoc*), 81.1 [–, $C(CH_3)_3$], 119.7, 124.5, 126.8, 127.5 (+, Ph-C), 141.1, 143.6 (–, Ph-C), 156.2 (–, 2 C, NCO), 171.8 (–, COOH) ppm. MS (ESI, positive): *m*/*z* (%) = 951 (71) $[2M + Na^+]$, 487 (100) $[M + Na^+]$; MS (ESI, negative): *m*/*z* (%) = 927 (100) $[2M - H^+]$, 463 (14) $[M - H^+]$. HRMS (ESI) calcd. for $C_{26}H_{28}N_2O_6Na$ $[M + Na^+]$ 487.18396, found 487.18393.

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Boc-3,4-(Z-Aminomethano)prolinol [(2*R*,1′*S*,3*S*,4*S*)-22]: A suspension of Pd (86 mg, 81.0 μmol, 3 mol-%, 10% on charcoal) in MeOH (5 mL) was shaken under H_2 for 5 min. A solution of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**18** (1.10 g, 2.70 mmol) in MeOH (25 mL) was added, and the mixture was shaken under H_2 for 17 h. The reaction mixture was filtered through celite and concentrated in vacuo. The residue was dissolved in acetone/H_2O (10 mL/5 mL), treated with $NaHCO_3$ (250 mg, 2.97 mmol) and ZOSu (740 mg, 2.97 mmol) and stirred for 3 h. After concentration to a volume of ca. 5 mL, H_2O (10 mL), was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried and evaporated under reduced pressure. Column chromatography of the residue (40 g of silica gel, 2 × 25 cm column, hexane/EtOAc, 2:1, R_f = 0.25) furnished 980 mg (2.70 mmol, 100%) of (2*R*,1′*S*,3*S*,4*S*)-**22** as a colorless, highly viscous oil, $[\alpha]_D^{20}$ = +41.2 (*c* = 0.49, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3316 cm^{-1} (O–H, N–H), 2975 (C–

H), 2933 (C–H), 2882 (C–H), 1695 (C=O), 1674 (C=O), 1531, 1478, 1455, 1427, 1404, 1368, 1253, 1175, 1122, 1072. ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 1.60–1.66 (m, 1 H, 3-H*), 1.66–1.78 (m, 1 H, 4-H*), 2.34–2.38 (m, 1 H, 1′-H), 3.44 (dd, ^2J = 8.0, ^3J = 5.0 Hz, 1 H, 5-H), 3.64–3.77 (m, 3 H, 1,5-H), 4.06–4.14 (m, 1 H, 2-H), 4.88 (br. s, 1 H, NH), 5.12 (s, 2 H, OCH_2Ph), 7.28–7.42 (m, 5 H, Ph-H) ppm. The signal of the OH proton could not be assigned. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 24.0 (+, C-3*), 27.1 (+, C-4*), 28.2 [+, $C(CH_3)_3$], 32.9 (+, C-1′), 47.5 (–, C-5), 60.8 (+, C-2), 64.9 (–, C-1*), 66.6 (–, OCH_2Ph), 79.9 [–, $C(CH_3)_3$], 127.5, 127.8, 128.2 (+, Ph-C), 136.4 (–, Ph-C), 156.2 (–, 2 C, NCO) ppm. MS (ESI, positive): *m*/*z* (%) = 1109 (23) [3M + Na$^+$], 747 (100) [2M + Na$^+$], 385 (48) [M + Na$^+$]. $C_{19}H_{26}N_2O_5$ (362.42): calcd. C 62.97, H 7.23, N 7.73; found C 62.76, H 7.12, N 7.60.

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Fmoc-3,4-(Boc-Aminomethano)prolinol [(2*R*,1′*S*,3*S*,4*S*)-23]: Diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**22** (1.13 g, 3.12 mmol) was treated with TFA (2 mL) and the mixture stirred for 30 min. All volatile compounds were evaporated in vacuo. Toluene (2 mL) was added to the residue, and the mixture was concentrated under reduced pressure. This operation was repeated three times. The residual oily trifluoroacetate was dissolved in acetone/H_2O (10 mL/10 mL), $NaHCO_3$ (512 mg, 6.09 mmol) was added portionwise, and the reaction mixture was stirred for 5 min. After treatment with FmocOSu (1.03 g, 3.05 mmol), stirring was continued for an additional 4 h. The reaction mixture was concentrated to a volume of ca. 5 mL, H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried and evaporated under reduced pressure. The residue was filtered through silica gel (20 g, hexane/EtOAc, 1:1). The obtained *N*α-Boc-3,4-(Z-aminomethano)-prolinol (798 mg) was treated with TFA (2 mL) and thioanisole (100 μL) and stirred for 2 d. All volatile compounds were evaporated under reduced pressure. Toluene (2 mL) was added to the residue, and the mixture was concentrated under reduced pressure. This operation was repeated three times. The residue was dissolved in MeOH (3 mL). After addition of NEt_3 (696 μL, 4.95 mmol) and Boc_2O (792 mg, 3.63 mmol), the resulting mixture was stirred for 17 h and then concentrated in vacuo. H_2O (10 mL) was added to the residue, and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried and evaporated under reduced pressure. Column chromatography of the residue (30 g of silica gel, 2 × 20 cm column, hexane/EtOAc, 1:1, R_f = 0.25) furnished 590 mg (1.31 mmol, 42%) (2*R*,1′*S*,3*S*,4*S*)-**23** as a colorless, voluminous solid, m.p. 77–82 °C, $[\alpha]_D^{20}$ = +33.0 (*c* = 0.6, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3412 cm^{-1} (O–H, N–H), 2975 (C–H), 2934 (C–H), 2882 (C–H), 1686 (C=O), 1452, 1429, 1366, 1167. ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 1.56–1.64 (m, 1 H, 3*-H), 1.64–1.74 (m, 1 H, 4*-H), 2.17–2.26 (m, 1 H, 1′-H), 3.44 (dd, ^2J = 8.0, ^3J = 5.0 Hz, 1 H, 5-H), 3.52–3.66 (m, 2 H, 1,5-H), 3.66–3.76 (m, 1 H, 1-H), 3.90–4.12 (m, 1 H, 2-H), 4.24 (t, ^3J = 8.0 Hz, 1 H, 9-H, *Fmoc*), 4.43–4.56 (m, 2 H, 1′-H, *Fmoc*), 4.66 (br. s, 1 H, NH), 7.28–7.46 (m, 4 H, Ph-H), 7.56–7.63 (m, 2 H, Ph-H), 7.75–7.82 (m, 2 H, Ph-H) ppm. The signal of the OH proton could not be assigned. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 24.0 (+, C-3*), 27.1 (+, C-4*), 28.2 [+, $C(CH_3)_3$], 32.8 (+, C-1′), 47.4 (+, C-9, *Fmoc*), 47.7 (–, C-5), 60.8 (+, C-2), 65.0 (–, C-1*), 66.8 (–, C-1′*, *Fmoc*), 79.5 [–, $C(CH_3)_3$], 119.7, 124.6, 126.9, 127.4 (+, Ph-C), 141.2, 143.8 (–, Ph-C), 155.5, 155.6 (–, NCO) ppm. MS (ESI, positive): *m*/*z* (%) = 1374 (77) [3M + Na$^+$], 923 (100) [2M + Na$^+$], 473 (46) [M + Na$^+$]. HRMS (ESI) calcd. for $C_{26}H_{31}N_2O_5$ [M + H$^+$] 451.22275, found 451.22265.

(2*R*,1′*S*,3*S*,4*S*)-*N*α-Boc-3,4-(Fmoc-Aminomethano)proline [(2*R*,1′*S*,3*S*,4*S*)-24]: In analogy to the conversion of the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**20**, the diamino alcohol (2*R*,1′*S*,3*S*,4*S*)-**23** (590 mg, 1.31 mmol) was oxidized with Jones reagent (550 μL, 1.47 mmol, 2.67 M soln. in H_2O) to furnish, after purification by column chromatography (20 g of silica gel, 2 × 10 cm column, hexane/EtOAc/HOAc, 25:25:1, R_f = 0.41), 461 mg (992 μmol, 76%) of (2*R*,1′*S*,3*S*,4*S*)-**24** as a pale yellow, voluminous solid which contained small amounts of EtOAc and HOAc, m.p. 95–105 °C, $[\alpha]_D^{20}$ = +38.0 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3342 cm^{-1} (O–H, N–H), 3067 (C–H), 2977 (C–H), 2937 (C–H), 2888 (C–H), 1711 (C=O), 1452, 1422, 1367, 1251, 1164, 1121. ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 1.73–1.84 (m, 1 H, 3-H*), 1.90–2.00 (m, 1 H, 4-H*), 2.32–2.43 (m, 1 H, 1′-H), 3.62 (dd, ^2J = 8.0, ^3J = 5.0 Hz, 1 H, 5-H), 3.70–3.82 (m, 1 H, 5-H), 4.24 (t, ^3J = 8.0 Hz, 1 H, 9-H, *Fmoc*), 4.40–4.60 (m, 3 H, 2-H, 1′-H, *Fmoc*), 4.80 (br. s, 1 H, NH), 4.98 (br. s, 1 H, COOH), 7.28–7.46 (m, 4 H, Ph-H), 7.56–7.62 (m, 2 H, Ph-H), 7.73–7.83 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 24.0 (+, C-3*), 27.4 (+, C-4*), 28.1 [+, $C(CH_3)_3$], 32.8 (+, C-1′), 47.2 (+, C-9, *Fmoc*), 47.9 (–, C-5), 60.5 (+, C-2), 67.5 (–, C-1′, *Fmoc*), 80.0 [–, $C(CH_3)_3$], 119.7, 124.6, 126.9, 127.5 (+, Ph-C), 141.1, 143.6 (–, Ph-C), 155.7 (–, NCO), 172.0 (–, COOH) ppm. MS (ESI, positive): *m*/*z* (%) = 1415 (57) [3M + Na$^+$], 951 (100) [2M + Na$^+$], 487 (100) [M + Na$^+$]; MS (ESI, negative): *m*/*z* (%) = 927 (84) [2M – H$^+$]. HRMS (ESI) calcd. for $C_{26}H_{28}N_2O_6Na$ [M + Na$^+$] 487.18396, found 487.18385.

(1*R*,5*S*,6*R*,7*R*,8*R*,12*S*,13*R*,14*R*)-7,14-Di-Z-amino-3,10-diazapentacyclo[11.1.0.0^{3,12}.0^{5,10}.0^{6,8}]tetradecane-4,11-dione (27a): A solution of CH_2N_2 in Et_2O was added dropwise to a solution of (2*S*,1′*R*,3*R*,4*R*)-**25** (89 mg, 237 μmol) in Et_2O (5 mL) until the mixture stayed yellow for more than 5 min. The reaction mixture was stirred for 20 min before removing the solvent under reduced pressure. The residue was treated with TFA (0.25 mL) and stirred for 45 min. Toluene (2 mL) was added, and the mixture was concentrated under reduced pressure. This operation was repeated three times. The residual oil was dissolved in anhydrous CH_2Cl_2 and the solution cooled to 0 °C. After addition of EDC·HCl (43 mg, 224 μmol), HOAt (31 mg, 228 μmol), (2*S*,1′*R*,3*R*,4*R*)-**25** (82 mg, 218 μmol) and 2,4,6-collidine (120 μL, 903 μmol), the reaction mixture was stirred at 0 °C for 4 h. The cooling bath was removed, and stirring was continued for an additional 14 h, before evaporating all volatile compounds under reduced pressure. The residue was taken up in EtOAc (10 mL), washed with H_2O (2 × 5 mL), 1 M aq. $KHSO_4$ soln. (2 × 5 mL), satd. aq. $NaHCO_3$ soln. (2 × 5 mL), H_2O (5 mL) and brine (5 mL), then dried. The solvent was removed in vacuo. The residue was filtered through silica gel (7 g, hexane/EtOAc, 1:2). The resulting crude 3,4-(aminomethano)proline dipeptide **26a** (68 mg) was treated with TFA (0.25 mL) and stirred for 45 min. Toluene (2 mL) was added and the mixture was concentrated under reduced pressure. This operation was repeated three times. The residue was dissolved in THF (2 mL), EtN*i*Pr$_2$ (74 μg, 432 μmol) was added, and the reaction mixture was stirred for 3 d. All volatile compounds were removed in vacuo. The residue was taken up in EtOAc (10 mL), washed with H_2O (5 mL), 1 M aq. $KHSO_4$ soln. (2 × 5 mL), satd. aq. $NaHCO_3$ soln. (2 × 5 mL), H_2O (5 mL) and brine (5 mL), then dried. After purification using preparative HPLC[34] 9.0 mg (17.4 μmol, 8%) of **27a** was obtained as a colorless, voluminous solid, $[\alpha]_D^{20}$ = +15 (*c* = 0.058, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80–1.98 (m, 2 H, 1,8-H*), 2.42–2.60 (m, 4 H, 6,7,13,14-H*), 3.54–3.52 (m, 2 H, 2,9-H), 3.74–3.86 (m, 2 H, 2,9-H), 4.00–4.14 (m, 2 H, 5,12-H), 5.06 (br. s, 4 H, CH_2O), 5.34 (br. s, 2 H, NH), 7.22–7.40 (m, 10 H, Ph-H) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 26.0 (+, C-1,8), 36.9 (+, C-,6,7,13,14), 48.6 (–, C-2,9), 63.1 (+, C-5,12), 67.1 (–, OCH_2Ph), 128.3, 128.6 (+, Ph-C), 136.1 (–, Ph-C), 156.4 (–, NCO_2), 165.1 (–, C-4,11) ppm. MS MS (ESI, positive): *m*/*z* (%) = 1571 (12) [3M + Na^+], 1055 (100) [2M + Na^+], 539 (11) [M + Na^+]. HRMS (ESI) calcd. for $C_{28}H_{28}N_4O_6Na$ [M + Na^+] 539.19011, found 539.19008.

General Procedure for the Solid-Phase Synthesis of 28–29: Each oligomer was synthesized manually starting from 30 mg of MBHA Rink amide resin (loading: 0.7 mmol/g). The side chain of Tyr was protected as a *tert*-butyl ether. Single coupling of the N^{α}-Fmoc amino acids was performed using a mixture amino acid/HOBt/DIC (each 4 equiv.) in DMF for 4 h. Single coupling of the N^{γ}-Fmoc Amp was carried out with only 2.5 equiv. of the amino acid in excess in the presence of equimolar HOBt and DIC in DMF for 16 h. The Fmoc group was removed with 5% DBU in a solution of 60 μmol HOBt in DMF (2 × 3 min). Each coupling and Fmoc-cleavage step was followed by washes (3 ×) with DMF. After peptide chain completion, the peptidyl-resin was treated with TFA/TIS/water (90:5:5 v/v) for 2.5 h, the resin was filtered off, ice-cold diethyl ether was added to the filtrate to induce peptide precipitation. The precipitate was then recovered by centrifugation at 3 °C for 8 min, washed several times with ice-cold ether and finally dried in vacuo. The peptides were characterized by analytical HPLC and MALDI-TOF mass spectrometry. **28a:** t_R = 20 min. MS: calcd. for $C_{44}H_{51}N_9O_9$ 849.38 Da, found 850.8 Da [M + H^+], 873.7 Da [M + Na^+], 889.7 Da [M + K^+]. **28b:** t_R = 21.5 min. MS: calcd. for $C_{44}H_{51}N_9O_9$ 849.38 Da, found 851.5 Da [M + H^+], 874.3 Da [M + Na^+]. **29a:** t_R = 16.2 min. MS: calcd. for $C_{53}H_{64}N_{12}O_{11}$ 1044.48 Da, found 1044.0 Da [M + H^+], 1067.7 Da [M + Na^+], 1083.8 Da [M + K^+]. **29b:** t_R = 17.8 min. MS: calcd. for $C_{53}H_{64}N_{12}O_{11}$ 1044.48 Da, found 1044.0 Da [M + H^+], 1066.0 Da [M + Na^+], 1082 Da [M + K^+].

CD Spectroscopy: The CD spectra of **28a/b** and **29a/b** were recorded at room temperature using a quartz cell with a path length of 0.02 cm. Peptide concentration of the solutions in water and in methanol were determined by measuring the UV absorbance of the fluorene group at 301 nm (ε = 7800 $mol^{-1}\,cm^{-1}$). For each CD spectrum ten scans were accumulated using the following parameters: 1 nm step resolution and band width, 2 sec response time, 20 nm/min scan speed, and 20 mdeg sensitivity. The CD spectrum of the solvent was subtracted from that of the peptide to eliminate interferences from the cell, solvent and optical equipment. Noise reduction was achieved by a Fourier transform filter with the program Origin (OriginLab Corporation, Northampton, MA, USA). The CD intensity is expressed in terms of mean-residue molar ellipticity $[\Theta]_R$ ($deg\,cm^2\,dmol^{-1}$).

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