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Graphical Abstract

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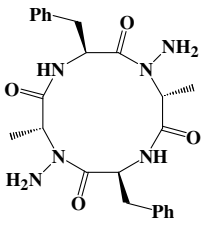

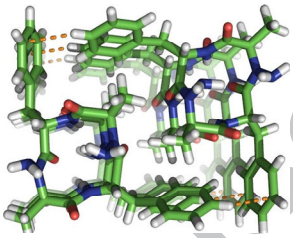

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Elaboration and structural studies of cyclo 1:1-[α/α-*N*-amino]mers

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ABSTRACT

In order to investigate the ability of self-organization of the alternance of α-amino and α-*N*-amino-acids the synthesis of cyclo 1:1-[α/α-*N*-amino]mers has been achieved by an iterative sequence of deprotection and coupling reactions followed by a macrocyclisation step. The self-assembling of *N*-amino deprotected cyclo-oligomers has been characterized using X-ray diffraction experiments and FT-IR analysis.

1. Introduction

In recent years, considerable efforts have been devoted to the synthesis of nanotubes and nanotubular structures because of their versatile uses in a variety of application; separation, recovery technologies[1] to nanomedecine[2] and biosensors.[3] One of the most favored strategies for obtaining synthetic tubular structures is the self-association of flat macrocycles by means of noncovalent processes (e.g. H-bonding, aromatic stacking).

Cyclopeptides are generally good candidates to generate nanotubes. The presence of amidic functions allows the formation of intermolecular H-bonds. Moreover, the internal diameter and surface properties can be easily tailored respectively by changing the number of units and the nature of the lateral chains.

In 1993, Ghadiri and co-workers were the first to demonstrate the formation of hollow tubular structures, by a controlled acidification of a pH responsive cyclic D,L-octapeptide[9].

The concept of peptidic nanotubes have been extended, more recently, to cyclic pseudopeptides containing β-amino-acids,[10–13] altering α- and β-amino acids,[14] oligoureas,[15,16] urea/amide hydrids[17,18] and vinylogous δ-amino-acids.[19]

Since a few years, our laboratory has focused on the synthesis of pseudopeptidic bis-nitrogen compounds. Several studies conducted on azapeptides[20,21] and hydrazinopeptides[22–24] showed that the insertion of an additional nitrogen in the main chain induced original local conformations. New strategies were developed to obtain *N*-aminopeptides, a new kind of bis-nitrogen containing pseudopeptide unit. The *N*-aminodipeptides were easily obtained tvia a Mitsunobu reaction, and their oligomerization led to the corresponding 1:1 [α/α-*N*-amino]mers (according to the nomenclature proposed by Gelmann[25]). Former conformational analyses have shown the existence of a NH-π interaction in the *N*-terminal[26] and a unique secondary structure based on a repeated C_8 pseudocycle.[27] This conformational property seems to be favorable for macrocyclization, since N- and C-terminus are close together. Moreover, De Santis and co-workers[28] predict that the cyclization of peptides is favored, by an alternation of (D)- and (L)-amino acids. Several examples, including pseudopeptides[7,29–34], have confirmed this postulate. Here, we want to report the synthesis and the conformational study of syndiotactic chiral cyclo 1:1 [α/α-*N*-amino]mers obtained after macrocyclization of the corresponding oligomers.

2. Results and discussion

2.1. Synthesis

The general stepwise strategy used for synthesizing the cyclo 1:1-[α/α-*N*-amino]mers **7** and **8,** respectively a 12- and 18-membered-ring macrocycles, is described in Scheme 1. As previously described, [35] linear tetramers **1** and hexamers **2** were synthetized starting from the corresponding dimer, following an iterative sequence of deprotection and coupling reaction using a convergent Boc/Bn strategy. The choice of these orthogonal protections for both *N*- and *C*-extremities allowed using selective conditions of deprotection. The C-terminal ester groups of compounds **1** and **2** were quantitatively removed by using classical hydrogenolysis conditions or microwaves assistance in the presence of 1,4-cyclohexadiene[36] Acidic conditions (HCl 3M in EtAc) applied to compounds **3** and **4** those obtained led to the formation of the corresponding chlorhydrate salts **5** and **6** in quantitative yield. After neutralizing of the chlorhydrate salts of **5**

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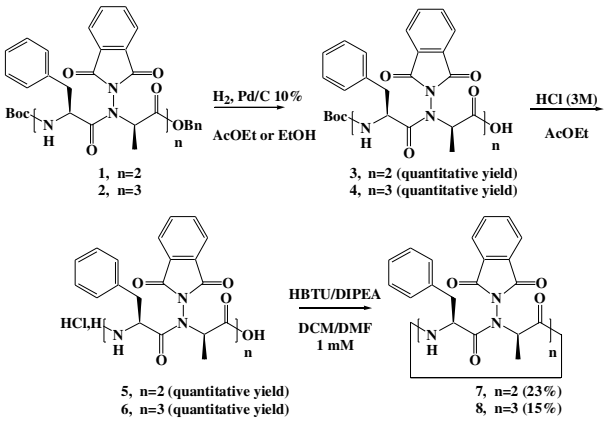
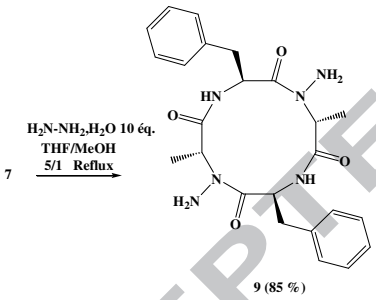
and **6**, cyclizations of the fully deprotected compounds were performed in DCM/DMF containing an excess of HBTU, These macrocyclizations were conducted under high dilution (1 mM) to minimize undesired intermolecular coupling reactions. The macrocycles **7** and **8** were obtained respectively in 23 % and 15 % yields with very high purity after chromatography.



Scheme 1. General stepwise strategy for the macrocyclisation of tetramer **1** and hexamer **2**.

The removal of the phthaloyl group of compound **7** was performed using an excess of hydrazine monohydrate (80%) in a refluxed mixture THF/Methanol (5/1). The *N*-amino deprotected product **9** was obtained in 85 % yield after purification by flash chromatography.



Scheme 2 Lateral amino group deprotection of compound **7**

The removal of the phthaloyl group of compound **8** was not attempted because of the very low global yield obtained for this compound. An improvement of the synthesis is beforehand necessary.

2.2. Structural analysis

Cyclic compound **9** crystallized in anhydrous dichloromethane and diethyl ether mixture. X-ray diffraction experiments were undertaken and the structure solved with a resolution of 0.79 Å. (figure 1). Tetracyclopeptide **9** forms a non planar cycle, shaped as a crown with the NH_2 and methyl groups oriented on the same side of the cycle. Both amide groups are on the opposite side of the cycle. Both amidic carbonyl groups pointed in the same direction as amino groups when hydrazidic carbonyl groups pointed in the opposite side. Aromatic groups of phenylalanine are rejected laterally and are responsible of interactions between columns (vide infra) (figure 1).

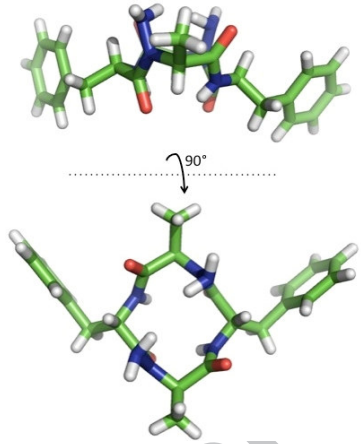


Figure 1. Crystal structure of compound **9**. Side view shows the crown shape of the cycle (top). The two aromatic rings are rejected along the cycle plane (bottom).

The distribution of hydrogen bond donors (NH_2 and NH) and acceptors (carbonyls) on either side of the cycle, allows the formation of intermolecular hydrogen bonds and then the packing of the molecules, which leads to nanotubular organization. However, due to a too small internal diameter, cyclotetramers does not allowed host molecule in the tube. Modulation of the tube diameter could be expected by enhancing the number of dimer units. The interaction between two molecules within a column is driven by intermolecular hydrogen bonds; the partners are then protons of the amino groups and carbonyls of the *N*-amino amide groups facing in the opposite molecules (figure 2). Both NH_2 groups have different behaviors. For one, both protons are involved in the hydrogen bond network while only one is involved in the other. This difference can be explained by a small shift in the stacking of molecules due to a steric hindrance of the aromatic rings.

ATR infrared spectroscopy experiments on crystals show two vibrations at 3343 cm^{-1} and 3233 cm^{-1} corresponding respectively to a free amino proton and an amino proton involved in a hydrogen bond.[37] Two additional bands located at 3395 cm^{-1} and 3364 cm^{-1} were also observed. We assigned the first one (close to 3400 cm^{-1}) to a free amidic proton, while the second was assigned to an amidic proton involved in a hydrogen bond. No intermolecular hydrogen bond involving an amidic proton was observed on the crystal structure. This proton is involved in an intramolecular H-bond and defines a C_7 pseudocycle between the amidic proton of one phenylalanine and the carbonyl of the other phenylalanine residue (figure 2). However the angle between the two atoms is not optimal and implies a weak hydrogen bond. This result is coherent with the value of 3364 cm^{-1} for the NH vibrator observed in the infrared spectrum.

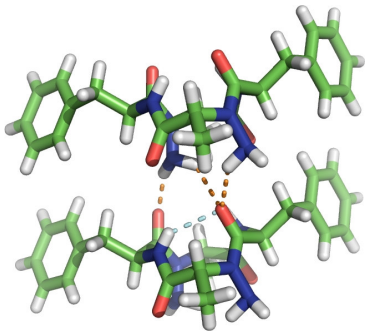


Figure 2. Crystal structure of two molecules of compound **9** stacked together. Intermolecular hydrogen bonds (orange dots) between NH_2 protons and *N*-amino amidic carbonyl group. One amidic proton is involved in an intramolecular hydrogen bond (blue dots) that stabilized a C_7 pseudocycle.

Finally, π-π stacking interactions can be detected between two columns via aromatic rings (figure 3). These π-π interactions are functions of the angle and the distance existing between both aromatic plans. For our structure, XRD analysis allows to calculate a distance of 0.98Å and an angle of 70° between plans (offset). These values are in one attraction region according to the diagram of Sanders.[38]

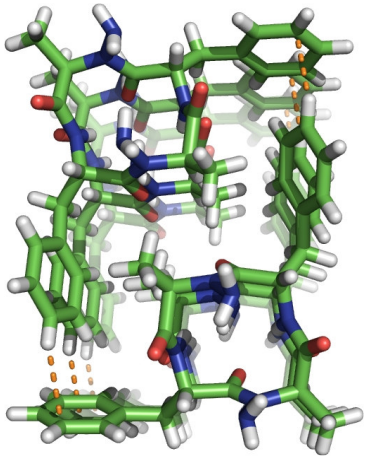


Figure 3. Crystal structure of two nanotubular structures interacting together through π-π stacking. (orange dots).

3. Conclusion

In this paper, we have reported the synthesis of the first cyclo 1:1 [α/α-*N*-amino]mers by macrocyclisation of the corresponding linear 1:1 [α/α-*N*-amino]mers. XRD structures revealed a self-organization of the macrocycles **9** in solid state by means of intermolecular hydrogen bonds and the packing of two obtained columns through π-π stacking.

This self-organization in columns is promising and the next steps will be to check the availability of the nanotubes in solution. A second point is the enlargement of the cavity by using bigger macrocycle together with the functionalization of the side chains in order to promote the interaction with ligands such as ions for example.

4. Experimental

4.1. General

All reagents were purchased as the highest purity commercially available and were used without further purification. Dry CH_2Cl_2 was obtained by distillation over diphosphorus pentoxyde P_2O_5. Methanol, acetonitrile and acetone were purchased in anhydrous form and others reagent grade solvents were used as received. The microwaves reactions were carried out in a CEM Discover SPS. Reactions were monitored by Thin Layer Chromatography (TLC) using aluminium-backed silica gel plates with fluorescent indicator UV_{254} (purchased from Macherey–Nagel: ALUGRAM® SIL G/UV_{254}). TLC spots were observed under ultraviolet light or/and by heating the plate after treatment with a staining solution of phosphomolybdic acid. Columns chromatographies were carried out on silica gel 60 (0.04-0.063 µm purchased from Macherey–Nagel). All yields were calculated from pure isolated products. NMR spectra were recorded on a Bruker Advance 300 spectrometer in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6). Chemical shift (δ) are reported in parts per million (ppm) and are referenced to the residual signals for deuterated DMSO-d_6 or $CDCl_3$, or to the signal of tetramethylsilane (TMS) as internal standard. Multiplicities are reported as follow: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (*J*) are given in Hertz (Hz). Infrared spectra (IR) were recorded on a Brucker Tensor 27 over 128 scans. Electron spray ionization mass spectra (ESI-MS) were recorded on a Brucker MicroTof-Q HR spectrometer in the "Service commun de Spectrométrie de Masse", Faculté des Sciences et Techniques, Vandoeuvre-lès-Nancy, France. HRMS spectra were obtained in ESI method.

4.2. General Procedure for benzyl ester deprotection

Deprotection with dihydrogen. A catalytic amount of palladium on charcoal (10%) was added to a strirred solution of corresponding oligomer (0.9 mmol) in ethanol (20 mL) or EtOAc (20 mL) depending of the solubility of the oligomer. The resulting mixture was flushed with H_2 and vigorously stirred at room temperature until completion (monitored by TLC). The reaction was filtered through a celite pad and the filtrate was evapored at reduced pressure. The *C*-terminal deprotected oligomer obtained was involved in the next reaction without further purification.

Deprotection with microwave heating. A 10 mL CEM microwave process tube was charged with 0.2 mmol of oligomer, palladium on charcoal (10%) and EtOAc (5 mL). 1,4-Cyclohexadiene (1.2 mmol, 6 eq) was added and the tube was capped. The mixture was stirred and heated under microwave conditions (150 W) at 100°C for runs of 5 min or 10 min until completion (monitored by TLC). The reaction mixture was filtered through a celite pad and the filtrate was evapored at reduced pressure. The *C*-terminal deprotected oligomer obtained was involved in the next reaction without further purification.

Boc((S)PheΨ[CON(Pht)](R)Ala)$_2$OH **(3)**

Formula: $C_{45}H_{44}N_6O_{11}$, Molecular weight: 844.86 g.mol^{-1}, Colorless solid, ~100%. IR (KBr) ν_{max}/cm^{-1} 3325 (NH and COOH), 1799, 1741, 1695 (CO). ^{1}H NMR ($CDCl_3$): δ (ppm) 10.61 (br, 1H, COO*H*), 8.35 (d, 0.7H, J=8.1 Hz, N*H*), 8.25 (d, 0.3H, J=8.0 Hz, N*H*), 8.10-7.80 (m, 8H, H_{Pht}), 7.33-7.00 (m, 10H, H_{arom}), 5.00-4.26 (m, 5H, 2×C*H*CH$_3$, 2×C*H*CH$_2$Ph and N*H*Boc), 3.40-2.50 (m, 4H, 2×CH_2Ph), 1.40-1.09 (m, 15 H, C(CH_3)$_3$ and 2×CHCH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 174.0, 173.0 (*C*OOH), 172.0, 171.5 (*C*ON(Pht) and *C*ONH), 167.2, 166.7, 166.0 (CO_{Pht}), 155.3 (NH*C*OOC(CH$_3$)$_3$), 137.4, 137.1, 137.0, 136.3, 136.1, 135.9, 135.7, 135.5, 130.2, 130.0, 129.9, 129.6, 127.4, 127.3, 125.6, 125.3, 124.7 (C_{arom} and CH_{arom}), 80.8, 80.3 (*C*(CH$_3$)$_3$), 59.4, 58.4 (*C*HCH$_3$), 52.1, 51.9, 50.5, 50.2 (*C*HCH$_2$Ph), 38.3, 37.5 (*C*H$_2$Ph), 28.8 (C(*C*H$_3$)$_3$), 15.2, 14.8, 14.3, 13.9 (CH*C*H$_3$).

Boc((S)PheΨ[CON(Pht)](R)Ala)$_3$OH **(4)**

Formula: $C_{65}H_{61}N_9O_{15}$, Molecular weight: 1208.23 g.mol^{-1}, Colorless solid, ~ 100%. ^{1}H NMR ($CDCl_3$): δ (ppm) 9.77 (br, 1H, COO*H*), 8.38-8.28 (m, 2H, 2×N*H*), 8.13-7.64 (m, 12H, H_{Pht}), 7.27-7.13 (m, 15H, H_{arom}), 4.91-4.15 (m, 7H, 3xC*H*CH$_3$, 3×C*H*CH$_2$Ph and N*H*Boc), 3.33-2.54 (m, 6H, 3×CH_2Ph), 1.36-1.04 (m, 18 H, C(CH_3)$_3$ and 2×CH_3).

4.3. General procedure for Boc deprotection

A solution of dry hydrogen chloride 3 M in EtOAc (10 mL) was added to the corresponding carbamate (1 mmol). The resulting solution was stirred during 2 h at room temperature and co-evapored several times with CH_2Cl_2 until dryness at reduced pressure. The *C*- and *N*-deprotected oligomer obtained was used without further purification.

HCl,H–((S)PheΨ[CON(Pht)](R)Phe)$_2$-OH **(5)**

Formula : $C_{40}H_{37}ClN_6O_9$, Molecular weight : 781.21 g.mol^{-1}, Colorless solid, ~ 100 %, m.p.= 165°C ^{1}H NMR ($CDCl_3$): δ (ppm) 9.40 (br, 1H, COO*H*), 8.29-8.13 (br s, 4H, NH_3^+ and N*H*), 7.93-7.83 (m, 8H, H_{Pht}), 7.35-6.98 (m, 10H, H_{arom}), 5.11-4.11 (m, 4H, 2×C*H*CH$_3$, 2×C*H*CH$_2$Ph), 3.38-2.92 (m, 4H, 4×CH_2Ph), 1.42-1.27 (m, 6 H, 2×CH_3).^{13}C NMR ($CDCl_3$): δ (ppm) 175.9, 173.8 (*C*OOH), 172.2, 171.2 (*C*ON and *C*ONH), 166.4, 166.3, 165.0, 164.5 (*C*O$_{Pht}$), 137.0, 136.8 (C_{arom}), 136.4, 136.0 (*C*H$_{arom}$), 133.8 (C_{arom}), 130.7, 130.1, 129.8, 129.6, 129.3, 129.1, 128.9, 128.3, 127.3, 126.1, 125.0 (*C*H$_{arom}$), 58.9, 56.8 (*C*HCH$_3$), 51.1, 50.7 (*C*HCH$_2$Ph), 38.8, 36.1 (*C*H$_2$Ph), 15.5, 14.1 (CH*C*H$_3$). HRMS (ESI) calculated for $C_{40}H_{36}N_6NaO_9$ $[M+Na]^+$ m/z 767.2436 found 767.2461

HCl,H–((S)PheΨ[CON(Pht)](R)Phe)$_3$-OH **(6)**

Formula : $C_{60}H_{54}ClN_9O_{13}$, Molecular weight : 1144.58 g.mol^{-1}, Colorless solid, ~ 100 %.^{1}H NMR ($CDCl_3$): δ (ppm) 9.83 (br, 1H, COO*H*), 8.25 (br s, 5H, NH_3^+ and 2×N*H*), 8.02-7.81 (m, 12H, H_{Pht}), 7.48-6.97 (m, 15H, H_{arom}), 5.03-4.66 (m, 6H, 3×C*H*CH$_3$, 3×C*H*CH$_2$Ph), 3.11-2.88 (m, 6H, 3×CH_2Ph), 1.26-1.20 (m, 9 H, 3×CH_3).

4.4. General procedure for the cyclization reaction

The deprotected oligomer (1.2 mmol) was dissolved in CH_2Cl_2 (100 ml) and DIPEA was added (6 mmol, 5 eq.). The mixture was added dropwise and slowly during 5 h into a solution of HBTU (2.4 mmol, 2 eq.) previously dissolved in 5 mL of DMF in CH_2Cl_2 (1 L). The total volume was calculated to obtain a concentration of 1mM in oligomer. The reaction was stirred at room temperature under nitrogen for 1 week. The volume was reduced under *vacuum* and washed successively three times with 100 mL of a solution of HCl (1N), $NaHCO_3$ sat, and brine and finally dried over $MgSO_4$ and evaporated. The resulting crude material was chromotographed on silica gel to give the expected cyclised products as colorless solids.

–((S)PheΨ[CON(Pht)](R)Phe)$_2$- **(7)**

Formula: $C_{40}H_{34}N_6O_8$, Molecular weight: 726.734 g.mol^{-1}, Colorless solid, 23 %, m.p. >250°C. Eluent for column chromatography: CH_2Cl_2/MeOH (100/0 then 92/8 then 97/3). IR (0.5 mM in $CHCl_3$) νmax/cm^{-1} 3300 (NH), 1796, 1745, 1696, 1685 (C=O). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.69 (d, 2H, J=7.5 Hz, 2×N*H*), 7.96-7.93 (m, 4H, H_{Pht}), 7.87-7.78 (m, 4H, H_{Pht}), 7.43-7.3 (m, 10H, H_{arom}), 4.82-4.74 (m, 2H, 2×C*H*CH$_2$Ph), 4.06-3.98 (m, 2H, 2×C*H*CH$_3$), 3.43-3.35 (m, 2H, CH_2Ph), 3.12-3.07 (m, 2H, CH_2Ph), 1.10 (d, 6H, J=6Hz, 2×CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 170.3, 169.4 (*C*O), 168.1, 164.2 (*C*O$_{Pht}$), 136.3 (C_{arom}), 136.0, 135.7 (*C*H$_{Pht}$), 130.7 (*C*H$_{arom}$), 130.5, 130.2 (C_{arom}), 129.5, 127.9 (*C*H$_{Ph}$), 125.5, 125.0 (*C*H$_{Pht}$), 63.9 (*C*HCH$_3$), 54.8 (*C*HCH$_2$Ph), 40.3 (CH*C*H$_2$Ph), 16.7 (CH*C*H$_3$). HRMS (ESI) calculated for $C_{40}H_{35}N_6O_8$ $[M+H]^+$ m/z 727.2511 found 727.2507.

–((S)PheΨ[CON(NH$_2$)](R)Phe)$_3$- **(8)**

Formula: $C_{60}H_{51}N_9O_{12}$, Molecular weight: 1090.10 g.mol^{-1}, Colorless solid, 15 %, m.p.= 194°C . Eluent for column chromatography: CH_2Cl_2/EtOAc (100/0 to 30/70). IR (0.3 mM in $CHCl_3$) ν_{max}/cm^{-1} 3416, 3366 (NH), 1801, 1749, 1696, 1685, 1668 (C=O). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.93-7.78 (m, 12H, H$_{Pht}$), 7.47 (d, 2H, J=4.5 Hz, N*H*), 7.21-7.09 (m, 15H, H_{arom}), 5.07 (d, 3H, J=6.6 Hz, 3×C*H*CH$_3$), 4.68 (d, 3H, J=5.1 Hz ,3×C*H*CH$_2$Ph), 3.23-3.17 (m, 3H, CH_2Ph), 2.95-2.89 (m, 3H, CH_2Ph), 1.19 (d, 9H, J=6.9 Hz, 3×CH_3).^{13}C NMR ($CDCl_3$): δ (ppm) 174.3, 168.4 (*C*O), 166.1, 163.8 (*C*O$_{Pht}$), 136.3 (C_{arom}), 135.6, 135.5 (*C*H$_{Pht}$), 130.2 (*C*H$_{arom}$), 130.0, 129.9 (C_{arom}), 128.8, 127.5. (*C*H$_{Ph}$), 125.8, 124.8 (*C*H$_{Pht}$), 55.8 (*C*HCH$_3$), 52.3 (*C*HCH$_2$Ph), 38.3 (*C*H$_2$Ph), 13.7 (*C*H$_3$). HRMS (ESI) calculated for $C_{60}H_{51}N_9NaO_{12}$ $[M+H]^+$ m/z 1112.3549 found 1112.3528.

4.5. -[(S)Phe Ψ [CON(NH$_2$)](R)Ala]$_2$- **(9)**

To -[(S)Phe Ψ [CON(Pht)](R)Ala]$_2$-cyclotetramer (100 mg, 0.14 mmol) in 12 mL of THF/Methanol (5/1) was added hydrazine monohydrate (0.82 mmol, 6 eq.) at room temperature. After refluxing the mixture for 1 day, solvents were removed under *vacuum*. Acetonitrile (15 mL) was added and insoluble material was removed by filtration. After concentration of the filtrate, the crude product was purified by column chromatography, eluting with CH_2Cl_2/MeOH 95/5 to give the deprotected cyclooligomer **9**.

Formula: $C_{24}H_{30}N_6O_4$, Molecular weight: 466.533 g.mol^{-1}, Colorless solid, 85 %, m.p. >250°C. IR (0.5 mM in $CHCl_3$) νmax/cm^{-1} 3385, 3369, 3340 (NH), 1696, 1684, 1652 (C=O). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.26-7.18 (m, 10H, H_{arom}), 6.56 (d, 2H, J=10.2Hz, 2×N*H*), 6.14-6.05 (m, 2H, 2×C*H*CH$_2$Ph), 5.1-5.03 (q, 2H, 2×C*H*CH$_3$), 3.76 (br, 2H, 2xNH_2), 3.21-3.13 (m, 2H, CH_2Ph), 2.98-2.91 (m, 2H, CH_2Ph), 1.23 (d, 6H, J=6.9Hz, 2×CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 178.0, 170.7 (*C*O), 137.4 (*C*$_{Ph}$), 129.8, 129.2, 127.3 (*C*H$_{Ph}$), 52.8 (*C*HCH$_3$), 49.5 (*C*HCH$_2$Ph), 37.5 (CH*C*H$_2$Ph), 11.7 (CH*C*H$_3$). HRMS (ESI) calculated for $C_{24}H_{30}N_6NaO_4$ $[M+Na]^+$ m/z 489.2221 found 489.2219.

Crystallographic data (excluding structure factor) for the structure of this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 1000338. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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Supplementary Material

Supplementary data related to this article can be found in the online version, at doi: