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ORIGINAL ARTICLE

β-Peptoids: synthesis of a novel dimer having a fully extended conformation

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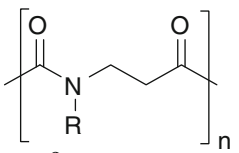
Abstract Chiral imines **1a,b**, already synthesized in our laboratory, were converted in good yield by reduction into the corresponding *N*-benzyl-γ-lactams **2a,b**. Desilylation followed by oxidation of the hydroxymethyl functionality gave the *N*-benzyl-β-amino acids **5a,b** in good yield and high purity. Starting from compound **6a**, the corresponding β-peptoid dimer **8** was prepared, together with its derivatives **9** and **10**, these latter displaying conformational restriction about the peptide bond, as evidenced by NMR data.

Keywords Peptoid · Lactam · Foldamer · Imines · Conformational restrictions

Introduction

Peptoids, a class of biomimetic polymers displaying poly-*N*-substituted glycine backbones, are designed to mimic peptides and proteins (Simon et al. 1992; Fowler and Blackwell 2009). In fact, owing to their resistance to proteolysis (Miller et al. 1994) and rapid cellular uptake (Kwon and Kodadek 2007), they are attractive candidates for interesting biological applications, in particular as antibiotics (Olsen et al. 2010; Huang et al. 2012). In solution, peptoids can form well-defined three-dimensional folds like helices (Kirshenbaum et al. 1998; Armand et al. 1998; Wu et al. 2003) and loops (Huang et al. 2006). Understanding the factors that affect peptoid conformation is a central topic within this research field, since formation of helical or threaded loop conformations relies on oligomer sequence, chain length and solvent composition. More recently, the role of monomer units on peptoid folding has been evidenced because $n - \pi^*$ and steric interactions allow the control of s-*cis*/s-*trans* isomerism in the monomer (Gorske et al. 2009).

Among peptoids, β-peptoids represent a new class of synthetic polyamides structurally related to β-peptides in which the amino acid side chain lies on amide nitrogen in place of C_α or C_β carbons.



β-Peptoid

Since the introduction of these structures (Hamper et al. 1998), very few reports deal to this class of compounds (Baldauf et al. 2006; Norgren et al. 2006; Cardoso et al. 2009). The lack of the amidic hydrogen and three rotable bonds in the backbone can greatly modify the folding properties of β-peptoids related to β-peptides. Of great concern is the relationship between β-peptoid sequence and secondary structure displayed. Thus, it is very important to have chemically different monomers not only for a deeper insight of the factors affecting peptoid conformation, but also to obtain new molecules with interesting biological activity. The conformational stability of dimers about the amide bond is generally low, and two conformations generally take place, as revealed by ^{1}H NMR spectra, leading to reduced conformational stability of the final peptoid. We

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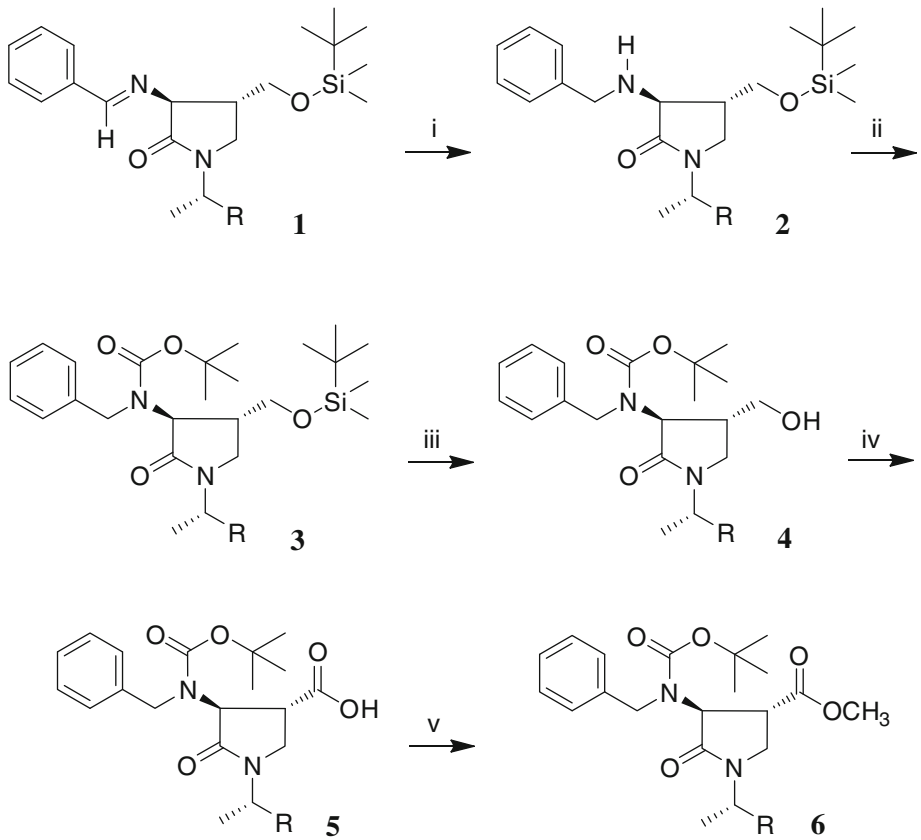
have already reported the preparation of monomers of foldamers tethered on a pyrrolidin-2-one ring, and stable secondary structures have been observed, such as 12-helix and 8-helix (Menegazzo et al. 2006; Galeazzi et al. 2011). Therefore, the preparation of highly conformationally restricted monomers for β-peptoids can be of interest, and we devised that useful starting units can be novel 3-aminoalkyl substituted pyrrolidin-2-ones.

Results and discussion

Within a program directed towards the synthesis of isosteres of proteinogenic and non-proteinogenic amino acids (Galeazzi et al. 2005; Crucianelli et al. 2010), we already reported the synthesis of analogs of (*R*)-2-methylhomoserine and (*R*)-2-methylaspartic acid by alkylation of chiral imines **1a,b** (Crucianelli et al. 2009) and we devised that these compounds could be also useful as starting materials suitable for the preparation of new monomers of β-peptoids. Thus, imines **1a,b** were reduced with $NaBH_4$ in methanol to give the corresponding amines **2a,b** in good yield and high purity. The protection of the amino functionality was carried out with di-*t*-butyl dicarbonate in CH_2Cl_2 in the presence of TEA leading to the pyrrolidin-2-ones 3,4-*trans*-disubstituted **3a,b** in good yield after chromatography on silica gel, which were then treated with NH_4F in methanol to give the desired alcohols **4a,b** used without any further purification. The next synthetic step was the oxidation of hydroxymethyl functionality with TEMPO and NaOCl solution in CH_2Cl_2 (Anelli et al. 1987) to give the corresponding acids **5a,b** in quantitative yield. Eventually, treatment of **5a,b** with CH_2N_2 in methanol afforded *N*-benzyl-β-amino esters **6a**,**b**, which can be useful monomers for the synthesis of novel β-peptoids (Scheme 1).

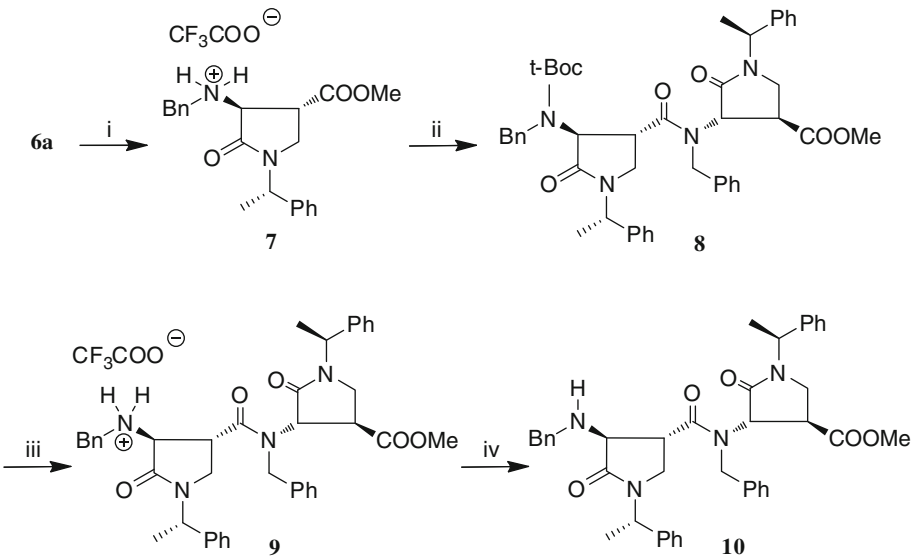
According to this project, in an attempt to investigate the behavior of monomer **6a**, we have synthesized the dimer **8** and its derivatives **9** and **10**. Thus, compound **6a** bearing the chiral inducer (*S*)-phenylethyl group underwent selective deprotection of the amino functionality with TFA in DCM to give the corresponding ammonium salt **7** in 95 % yield. The reaction of **7** with the corresponding acid **5a** in DCM in the presence of PyBrop (Coste et al. 1994) and DIPEA allowed to obtain the dimer **8** in moderate yield. After removal of the *t*-Boc group by treatment with TFA in DCM, the trifluoroacetate **9** was obtained in quantitative yield and, in the event, the corresponding amino derivative **10** was obtained by treatment with TEA (Scheme 2).

In fact, by inspection of ^{1}H-NMR spectra of compounds **6a**, two rotamers have been evidenced, due to hindered rotation of the *t*-butoxycarbonyl group, giving



Scheme 1 (a) R = C_6H_5, (b) R = 4-$CH_3OC_6H_4$. Reagent and conditions. (**i**) $NaBH_4$, dry CH_3OH, (a) R = C_6H_5, 72 %, (b) R = 4-$CH_3OC_6H_4$, 87 %; (**ii**) Boc_2O, TEA, DCM, (a) R = C_6H_5, 91 %, (b) R = 4-$CH_3OC_6H_4$, 73 %; (**iii**) NH_4F, CH_3OH, (a) R = C_6H_5, 90 %, (b) R = 4-$CH_3OC_6H_4$, 90 %; (**iv**) TEMPO, NaOCl, DCM, 0 °C, (a) R = C_6H_5, 98 %, (b) R = 4-$CH_3OC_6H_4$, 98 %; (**v**) CH_2N_2, CH_3OH, 0 °C, (a) R = C_6H_5, 98 %, (b) R = 4-$CH_3OC_6H_4$, 98 %

Scheme 2 Reagents and conditions. (**i**) TFA, DCM, 95 %; (**ii**) **5a**, PyBroP, DIPEA, DCM, 44 %; (**iii**) TFA, DCM, 96 %; (**iv**) TEA, DCM, 98 %



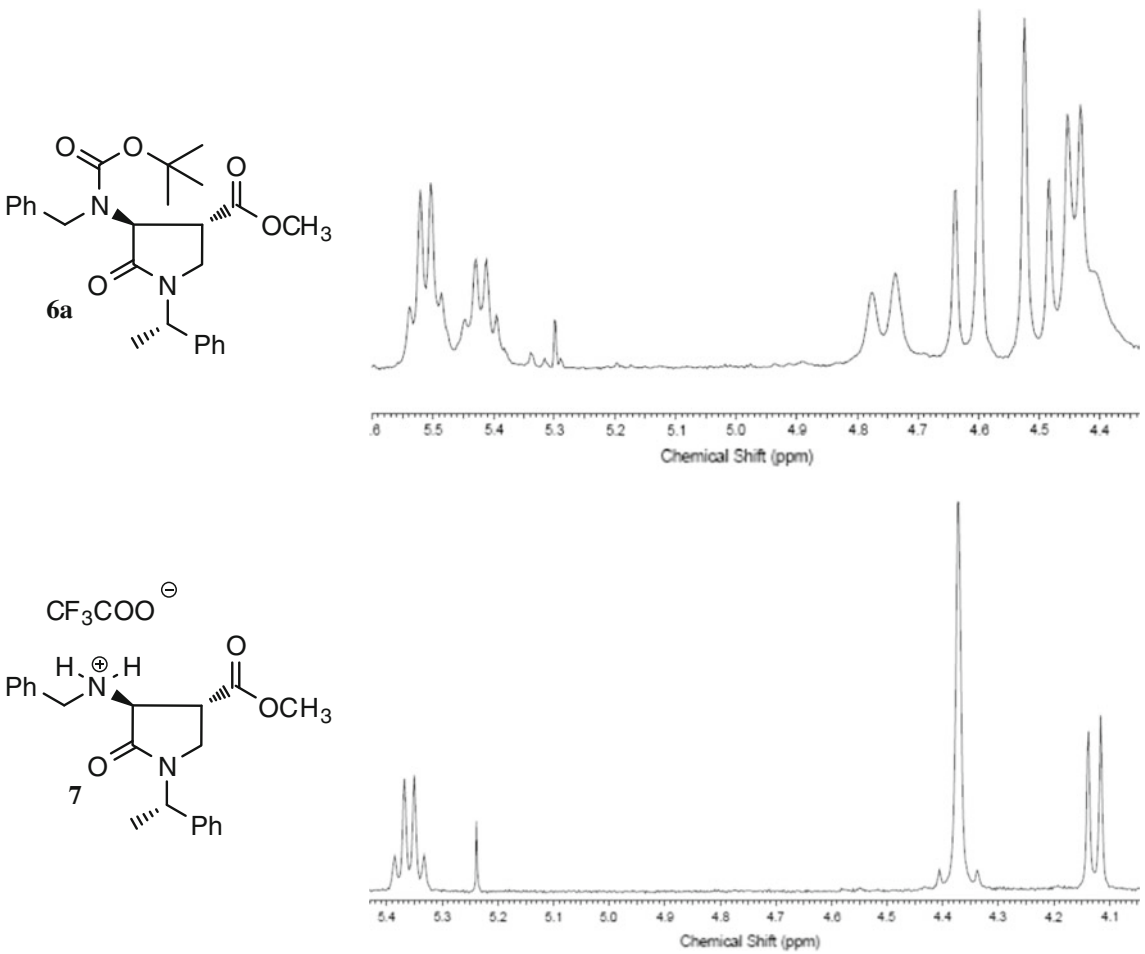


Fig. 1 Structures of compounds **6a** and **7**, with part of the corresponding ^{1}H NMR spectra recorded at 25 °C, 5 mM solution in $CDCl_3$

rise to two different signal patterns for the quartet of the proton of the chiral inducer and for the peak relative to N-CH_2Ph protons. On the other hand, the ammonium salt **7** shows only one signal pattern for the same kind of protons (Fig. 1). These findings are significant because the conformational properties of the monomer unit strongly affect the secondary structure of the corresponding peptoid oligomers.

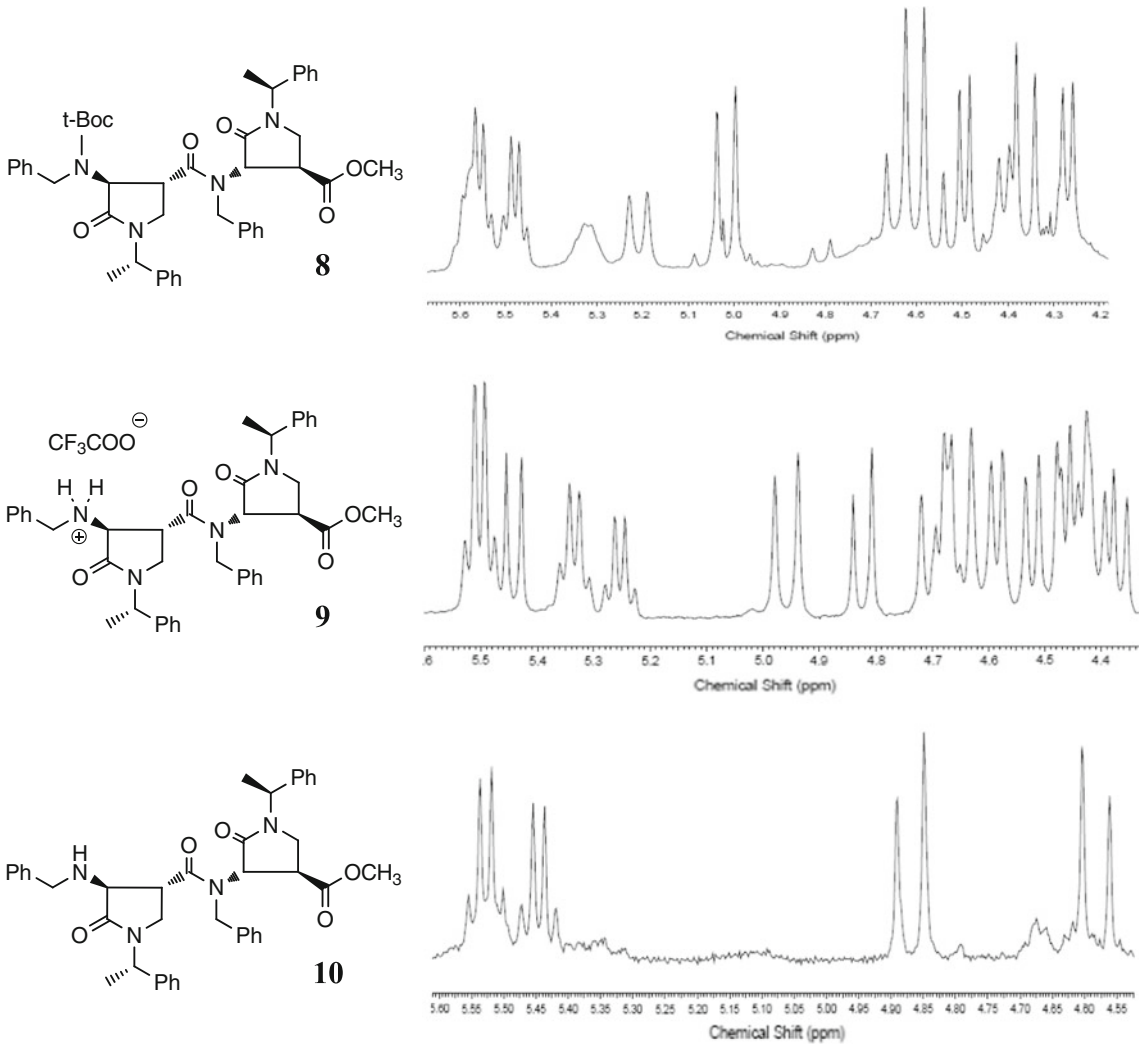


Fig. 2 Structures of dimers **8**–**10**, with part of ^{1}H NMR spectra (recorded at 25 °C, 5 mM solution in $CDCl_3$) evidencing the conformational changes

Thus, having in hands the monomer **6a**, we directed our investigation towards the conformational behavior of the dimer, with the aim to ascertain whether restricted rotation about C3–C4 bond in the nearly planar five-membered ring is able to reduce the conformational freedom at dimer level.

In fact, the ^{1}H-NMR spectra of dimer **8**, the corresponding ammonium salt **9** and the free amino derivative **10** has given useful information about this question. The presence of two rotamers has been evidenced for molecules **8** and **9**. On the other hand, when *t*-butoxycarbonyl group is removed from **8**, leading to the corresponding ammonium salt **9**, spectrum displays narrow signals. Eventually, in the spectrum of the dimer **10**, signals due to a single rotamer are present, exclusively (Fig. 2). These results show the importance of steric interactions for the *cis*/*trans* isomerism at the amide bond in particular when bulky *t*-butoxycarbonyl group is missing, thus favoring the evidence of a sole conformer.

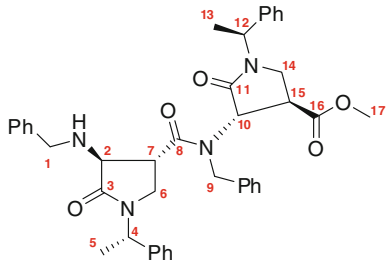
To have more information on the in-solution preferred conformation, **10** was further analyzed by two-dimensional NMR techniques. gCOSY, gHSQC and gHMBC were used to attribute all the ^{1}H and ^{13}C chemical shifts, that are reported in Table 1.

The preferential conformation of **10** was then attributed by 2D ROESY experiments performed on a 10 mM solution of **10** in $CDCl_3$ (Fig. 3a). As reported in Fig. 3b, no cross peaks have been detected between the side chains or between the two heterocyclic rings. So, we can deduce that this compound preferentially lies in a fully extended conformation, similar to a β-sheet conformation.

Conclusions

We reported the synthesis of novel chiral dimers for the preparation of β-peptoids exploiting a very simple

Table 1 ^{1}H and ^{13}C chemical shifts of all the atoms of **10**



Carbon atom number	δ C (ppm)	δ H (ppm)
1	51.6	3.88 (d, J = 14.0 Hz, 1H)
		4.01 (d, J = 14.0 Hz, 1H)
2	62.4	4.12 (d, J = 8.0 Hz, 1H)
3	171.9	–
4	49.5	5.43 (q, J = 7.0 Hz, 1H)
5	16.1	1.47 (d, J = 7.0 Hz, 3H)
6	42.6	2.87 (m, 1H)
		3.24 (m, 1H)
7	52.3	3.37 (m, 1H)
8	170.9	–
9	53.3	4.57 (d, J = 17.0 Hz, 1H)
		4.86 (d, J = 17.0 Hz, 1H)
10	63.5	4.40 (d, J = 9.0 Hz, 1H)
11	168.1	–
12	49.4	5.52 (q, J = 7.0 Hz, 1H)
13	16.0	1.49 (d, J = 7.0 Hz, 3H)
14	45.0	3.23 (m, 1H)
		3.28 (m, 1H)
15	41.0	3.47 (m, 2H)
16	172.8	–
17	52.4	3.57 (s, 3H)

methodology, which proceeds with very high yields to the corresponding dimers. Then, by inspection of the ^{1}H NMR spectra, we further observed rotamers are missing for both monomer **7** and dimer **10**. This result suggests that insertion of these units into peptoids or mixed peptide–peptoid sequences could give rise to conformationally stable structures. The ROESY 2D analysis suggests that the preferred conformation of the dimer **10** is a fully extended conformation, useful for the formation of β-sheet layers. Thus, we think that this work can open a promising path to rational β-peptoid design, which we are currently pursuing.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a Varian MR 400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, in $CDCl_3$ unless otherwise reported. Chemical shifts are given as ppm from tetramethylsilane and coupling constants J are given in Hertz. The proton and carbon signals were assigned by gCOSY, gHSQC, gHMBC spectra. 2D spectra were recorded in the phase sensitive mode and processed using a 90°-shifted, squared sine-bell apodization. 2D ROESY experiments were recorded with a 200 ms mixing time with a proton spectral width of 4,032.3 Hz.

Optical rotations were measured on a Perkin Elmer 241 polarimeter at the sodium D line (concentration in g/100 ml). The purity of the products was determined with a liquid chromatography Agilent Technologies HP1100 equipped with a Zorbax Eclipse XDB-C8 Agilent and Technologies column (flow rate 0.5 cm^3/min) using a diode-array UV detector (220 and 254 nm). Acetonitrile and methanol for HPLC were purchased from a commercial supplier. For every analysis the products (1 mg) were dissolved in 5 ml of H_2O/acetonitrile mixture 1:1 or methanol. The MSD1100 mass detector was utilized under the following conditions: mass range 100–2,500 amu, positive scanning, energy of fragmentor 50 V, drying gas flow (N_2) 10.0 cm^3/min, nebulizer pressure 310 kPa, drying gas temperature 350 °C, capillary voltage 4,500 V. Elemental analyses (C, H, N) were conducted using a Carlo

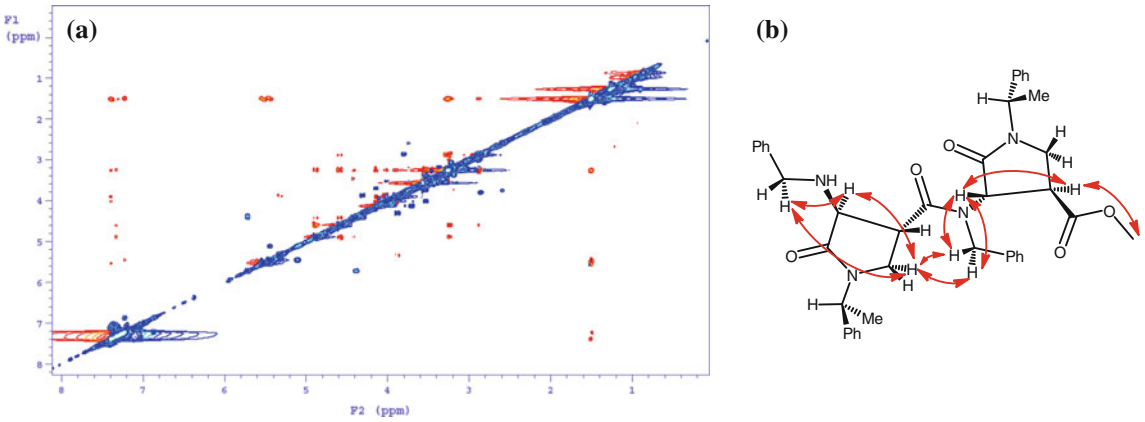


Fig. 3 **a** ROESY 2D spectrum of **10** (10 mM solution in $CDCl_3$, mixing time 200 ms); **b** NOE enhancements as gathered from the spectrum

Erba 1106 elemental analyser, and their results were found to be in good agreement (±0.2 %) with the calculated values. Column chromatography was performed using Kieselgel 60 Merck.

General procedure for the preparation of amines **2a,b**

To a solution of imine **1a** or **1b** (1 mmol) in dry methanol (3 ml) was added, at 0 °C, $NaBH_4$ (2 mmol) under nitrogen atmosphere and the solution was stirred at r.t. for 3 h. Then the reaction mixture was poured in H_2O (10 ml) and extracted with ethyl acetate (3 × 20 ml). The organic phase was dried over Na_2SO_4 and evaporated under reduce pressure to give a residue purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30) to obtain compounds **2a,b**.

*(3S,4R)-3-(Benzylamino)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1-((S)-1-phenylethyl)pyrrolidin-2-one (**2a**)*

Starting from **1a**, compound **2a** (0.31 g, 72 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.85 (s, 9H), 1.51 (d, $J = 6.8$ Hz, 3H), 1.82 (br, 1H), 2.20 (m, 1H), 2.98 (dd, $J = 8.8$ Hz, $J = 9.6$ Hz), 3.07 (dd, $J = 8.0$ Hz, $J = 9.6$ Hz, 1H), 3.42 (d, $J = 8.4$ Hz, 1H), 3.64 (m, 2H), 3.94 (s, 2H), 5.49 (q, $J = 6.8$ Hz, 1H), 7.22–7.37 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.8, 16.4, 18.3, 26.0, 27.1, 42.0, 42.3, 49.0, 52.1, 61.0, 62.8, 127.0, 128.0, 128.1, 128.2, 132.1, 140.3, 173.8; $[\alpha]_D = -105.0$ ($c = 0.1$, $CHCl_3$). ESI-MS: $m/z = 438.27$ $[M^+]$, 461.27 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{38}N_2O_2Si$: C, 71.19; H, 8.73; N, 6.39;. Found: C, 71.23; H, 8.75; N, 6.41.

*(3S,4R)-3-(Benzylamino)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1-((S)-1-(4methoxyphenyl) ethyl)pyrrolidin-2-one (**2b**)*

Starting from **1b**, compound **2b** (0.41 g, 87 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 1.50 (d, $J = 6.8$ Hz, 3H), 2.08 (br, 1H), 2.19 (m, 1H), 3.01 (dd, $J = 13.6$ Hz, $J = 8.4$ Hz), 3.06 (dd, $J = 7.6$ Hz, $J = 9.6$ Hz, 1H), 3.42 (d, $J = 8.0$ Hz, 1H), 3.65 (m, 2H), 3.79 (s, 3H, OCH_3), 3.95 (s, 2H), 5.45 (q, $J = 6.8$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, ArH), 7.22–7.38 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.6, 16.1, 18.1, 25.7, 26.8, 41.8, 42.2, 48.5, 51.8, 55.1, 60.5, 62.7, 113.7, 126.9, 128.1, 128.2, 128.3, 131.9, 140.1, 158.8, 173.6; $[\alpha]_D = -123.0$ (c 0.13, $CHCl_3$). ESI-MS: $m/z = 468.28$ $[M^+]$, 491.28 $[M + Na]^+$. Anal. Calcd. for $C_{27}H_{40}N_2O_3Si$: C, 69.19; H, 8.60; N, 5.98. Found: C, 69.23; H, 8.62; N, 5.89.

General procedure for the preparation of *t*-Boc-protected amines **3a,b**

To a solution of amine **2a** or **2b** (1 mmol) in CH_2Cl_2 (2 ml) TEA (1.1 mmol) and di-*t*-butyl-dicarbonate (1.1 mmol) were added. After stirring for 3 h, H_2O (10 ml), ethyl acetate (20 ml) and 1 M HCl were added until neutral pH obtained. The reaction mixture was extracted with ethyl acetate (2 × 20 ml). The organic residue was dried over Na_2SO_4 and concentrated under reduced pressure to give pure compound **3a,b**.

*Tert-butyl-benzyl ((3S,4R)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxo-1-((S)-1-phenylethyl) pyrrolidin-3-yl)carbamate (**3a**)*

Starting from **2a**, compound **3a** (0.49 g, 91 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.06 (s, 6H), 0.81 (s, 9H), 1.30 (s, 9H, 30 %), 1.42 (s, 9H, 70 %), 1.49 (d, $J = 7.2$ Hz, 3H, 70 %), 1.60 (d, $J = 7.2$ Hz, 3H, 30 %), 2.30–2.47 (m, 1H), 2.98 (dd, $J = 4.8$ Hz, $J = 17.0$ Hz 2H, 70 %), 3.06 (dd, $J = 4.8$ Hz, $J = 17.0$ Hz 2H, 30 %), 3.22–3.48 (m, 2H), 4.41 (d, $J = 16.0$ Hz, 2H, 30 %), 4.55 (d, $J = 16.0$ Hz, 2H, 70 %), 5.45 (q, $J = 7.2$ Hz, 1H, 30 %), 5.51 (q, $J = 7.2$ Hz, 1H, 70 %), 7.10–7.40 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ −6.2, −6.4, 13.6, 15.4, 15.8, 17.4, 20.0, 25.1, 26.2, 27.8, 30.0, 40.9, 41.0, 48.0, 48.7, 51.4, 59.3, 59.4, 60.4, 61.1, 61.7, 79.3, 79.7, 126.3, 126.4, 127.0, 127.4, 127.7, 128.0, 131.1, 138.0, 138.5, 154.2, 154.7, 169.5, 170.0; $[\alpha]_D = -58.5$ ($c = 0.5$, $CHCl_3$); ESI-MS: $m/z = 538.32$ $[M^+]$, 561.32 $[M + Na]^+$. Anal. Calcd. for $C_{31}H_{46}N_2O_4Si$: C, 69.10; H, 8.61; N, 5.20; Found: C, 69.11; H, 8.64; N, 5.16.

*Tert-butyl-benzyl((3S,4R)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1-((S)-1-(4-methoxyphenyl) ethyl)-2-oxopyrrolidin-3-yl)carbamate (**3b**)*

Starting from **2b**, compound **3b** (0.41 g, 73 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.02 (s, 6H), 0.82 (s, 9H), 1.35 (s, 9H, 35 %), 1.41 (s, 9H, 65 %), 1.43 (m, 3H), 2.40 (m, 1H), 2.93–3.10 (m, 2H), 3.24–3.48 (m, 2H), 3.81 (s, 3H), 4.23 (m, 1H), 4.36–4.68 (m, 2H), 5.38–5.50 (m, 1H), 6.85–6.89 (m, 2H, ArH), 7.22–7.34 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ −6.3, −6.2, 13.5, 15.6, 15.9, 17.5, 20.2, 25.2, 26.2, 27.6, 30.3, 40.8, 41.1, 47.9, 49.0, 51.3, 54.3, 59.4, 59.8, 60.5, 61.2, 61.9, 79.4, 79.7, 113.0, 113.2, 126.5, 126.6, 127.1, 127.6, 127.7, 128.1, 131.2, 138.2, 138.6, 154.4, 154.9, 158.2, 158.5, 169.7, 170.1; $[\alpha]_D = -79.0$ ($c = 0.6$, $CHCl_3$); ESI-MS: $m/z = 568.33$ $[M^+]$, 581.33 $[M + Na]^+$.

Anal. Calcd. for $C_{32}H_{48}N_2O_5Si$: C, 67.57; H, 8.51; N, 4.92. Found: C, 67.61; H, 8.54; N, 4.96.

General procedure for the preparation of alcohols **4a,b**

To a solution of **3a** or **3b** (1 mmol) in methanol (3 ml) was added NH_4F (5 mmol). The reaction mixture was refluxed for 6 h, then was added H_2O (10 ml) and extracted with ethyl acetate (3 × 20 ml). The organic residue was dried over Na_2SO_4 and evaporated to give alcohols **4a,b**.

*tert-Butyl-benzyl ((3S,4R)-4-(hydroxymethyl)-2-oxo-1-((S)-1-phenylethyl)pyrrolidin-3-yl)car-bamate (**4a**)*

Starting from **3a**, compound **4a** (0.38 g, 90 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.49 (d, $J = 7.2$ Hz, 3H), 1.94 (m, 1H), 2.30 (br, 1H), 2.78 (dd, $J = 8.8$ Hz, $J = 18.0$ Hz, 1H), 2.97 (dd, $J = 8.8$ Hz, $J = 18.0$ Hz, 1H), 3.30 (dd, $J = 4.8$ Hz, $J = 12.0$ Hz, 1H), 3.52 (dd, $J = 4.8$ Hz, $J = 18.0$ Hz, 1H), 4.27 (d, $J = 16.4$ Hz, 1H), 4.78 (m, 1H), 5.51 (q, $J = 7.2$ Hz, 1H), 7.17–7.38 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 28.2, 29.7, 40.5, 40.9, 48.9, 49.5, 60.1, 61.1, 81.4, 127.0, 127.2, 127.3, 128.4, 128.6, 139.2, 139.7, 165.9, 165.9; $[\alpha]_D = -49.3$ (c 0.5, $CHCl_3$); ESI-MS: $m/z = 424.24$ $[M^+]$, 467.24 $[M + Na]^+$. Anal. Calcd. for $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 70.75; H, 7.66; N, 6.56.

*tert-Butyl-benzyl((3S,4R)-4-(hydroxymethyl)-1-((S)-1-(4-methoxyphenyl)ethyl)-2-oxopyrrolidin-3-yl)carbamate (**4b**)*

Starting from **3b**, compound **4b** (0.41 g, 90 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.47 (d, $J = 7.2$ Hz, 3H), 1.95 (m, 1H), 2.78 (m, 1H), 2.94 (m, 1H), 3.26 (br, 1H), 3.41–3.60 (m, 2H), 4.28 (d, $J = 16.0$ Hz, 1H), 4.77–4.86 (m, 2H), 5.47 (q, $J = 7.2$ Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 2H, ArH), 7.18–7.37 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9, 27.9, 39.8, 40.8, 48.6, 49.3, 55.0, 60.2, 60.9, 80.8, 113.6, 126.9, 127.0, 127.7, 127.9, 128.1, 131.4, 138.9, 156.2, 158.7, 169.8; $[\alpha]_D = -64.0$ ($c = 0.2$, $CHCl_3$); ESI-MS: $m/z = 454.25$ $[M^+]$, 477.25 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found C, 68.73; H, 7.57; N, 6.14.

General procedure for the preparation of carboxylic acids **5a,b**

To a solution containing compound **4a** or **4b** (1 mmol) in CH_2Cl_2 (2 ml) at 0 °C, TEMPO (0.01 mmol), 0.5 M NaBr (0.2 ml) and 0.35 M NaOCl (7 ml) were added at pH = 8.6 (the pH of the sodium hypochlorite was adjusted at 8.6 just before use by dissolving 350 mg of solid $NaHCO_3$) under vigorous stirring. After 10 min, 0.35 M NaOCl (7 ml) was added and the mixture was stirred for 10 min. Then temperature was raised to r.t. and ethyl acetate (20 ml) and 1 M HCl (10 ml) were added. The reaction mixture was extracted with ethyl acetate (2 × 20 ml) and the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give acids **5a,b**.

*(3R,4S)-4-(Benzyl(tert-butoxycarbonyl)amino)-5-oxo-1-((S)-1-phenylethyl)pyrrolidine-3-carboxylic acid (**5a**)*

Starting from **4a**, compound **5a** (0.43 g, 98 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H, 30 %), 1.42 (s, 9H, 70 %), 1.42–1.54 (m, 3H), 3.04–3.39 (m, 3H), 4.32 (d, $J = 16.0$ Hz, 1H, 30 %), 4.38 (d, $J = 16.0$ Hz, 1H, 70 %), 4.56 (d, $J = 8.4$ Hz, 1H), 4.70 (d, $J = 16.0$ Hz, 1H, 70 %), 4.86 (d, $J = 16.0$ Hz, 1H, 30 %), 5.42 (q, $J = 7.2$ Hz, 1H, 30 %), 5.51 (q, $J = 7.2$ Hz, 1H, 70 %), 7.12–7.40 (m, 10H, ArH), 9.41 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.9, 15.7, 16.2, 20.6, 20.8, 25.9, 27.7, 27.9, 28.0, 29.5, 41.4, 41.5, 41.6, 49.4, 50.7, 52.2, 60.3, 61.5, 62.3, 65.6, 80.9, 81.2, 127.0, 127.2, 127.4, 127.5, 127.7, 127.9, 128.1, 128.2, 128.3, 128.5, 138.7, 138.8, 154.9, 168.9, 169.5, 171.2, 175.1, 175.8; $[\alpha]_D = -61.0$ ($c = 0.1$, $CHCl_3$); ESI-MS: $m/z = 438.52$ $[M^+]$, 461.52 $[M + Na]^+$. Anal. Calcd. for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.49; H, 6.92; N, 6.35.

*(3R,4S)-4-(Benzyl(tert-butoxycarbonyl)amino)-1-((S)-1-(4-methoxyphenyl)ethyl)-5-oxopyrroli-dine-3-carboxylic acid (**5b**)*

Starting from **4b**, compound **5b** (0.46 g, 98 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.50 (m, 12H), 2.92 (m, 1H, 20 %), 3.05 (m,1H, 80 %), 3.10–3.25 (m, 2H, 80 %), 3.30–3.39 (m, 2H, 20 %), 3.86 (s, 3H, 20 %), 3.87 (s, 3H, 80 %), 4.26–4.55 (m, 3H), 4.72 (d, $J = 15.6$ Hz, 1H, 80 %), 4.86 (d, $J = 15.6$ Hz, 1H, 20 %), 5.28–5.43 (m, 1H), 6.86 (d, $J = 8.4$ Hz, 2H, ArH), 7.18–7.42 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8, 16.3, 17.9, 18.3, 28.1, 29.5, 41.5, 41.8, 48.5, 51.9, 56.0, 56.1, 60.4, 61.6, 62.3, 80.9, 81.2, 117.7, 122.4, 126.3, 126.8, 127.0, 127.2, 127.4, 127.6, 127.8, 128.2, 132.3, 132.6, 137.9, 138.0, 154.2, 154.6, 154.9, 155.2, 169.1, 169.5, 171.2, 171.3; $[\alpha]_D = -79.5$ (c 0.2, $CHCl_3$); ESI-MS: $m/z = 468.23$ $[M^+]$, 491.23 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 65.70; H, 6.92; N, 5.92.

General procedure for preparation of the methyl esters **6a,b**

A solution of acid **5a** or **5b** (1 mmol) in methanol (3 ml) was treated at 0 °C with an ethereal solution of CH_2N_2

until nitrogen evolution ceased and the solvent was evaporated under reduced pressure to give a residue which was purified by silica gel chromatography (cycloexane/ethyl acetate 70:30) affording the esters **6a,b**.

*Methyl (3R,4S)-4-(benzyl(tert-butoxycarbonyl)amino)-5-oxo-1-((S)-1-phenylethyl)pyrrolidine-3-carboxylate (**6a**)*

Starting from **5a**, compound **6a** (0.44 g, 98 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H, 40 %),1.42 (s, 9H, 60 %), 1.45–1.51 (m, 3H), 3.10–3.22 (m, 3H, 40 %), 3.23–3.34 (m, 3H, 60 %), 3.55 (s, 3H), 4.38–4.80 (m, 3H), 5.41 (q, $J = 6.8$ Hz, 1H, 40 %), 5.50 (q, $J = 6.8$ Hz, 1H, 60 %), 7.18–7.40 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8, 16.2, 28.0, 28.1, 41.4, 41.8, 49.2, 50.5, 52.2, 52.3, 61.7, 61.9, 62.5, 66.4, 71.4, 80.6, 81.1, 127.0, 127.1, 127.4, 127.5, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 137.8, 138.4, 139.0, 139.2, 154.7, 168.4, 168.9, 172.9;$[\alpha]_D = -108.1$ ($c = 0.1$, $CHCl_3$); ESI-MS: $m/z = 452.23$ $[M^+]$, 575.23 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 69.04; H, 7.17; N, 6.17.

*Methyl (3R,4S)-4-(benzyl(tert-butoxycarbonyl)amino)-1-((S)-1-(4-methoxyphenyl)ethyl)-5-oxopyr-rolidine-3-carboxylate (**6b**)*

Starting from **5b**, compound **6b** (0.47 g, 98 % yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28–1.51 (m, 12H), 3.10–3.32 (m, 3H), 3.55 (s, 3H), 3.80 (s, 3H, OCH_3, 70 %), 3.89 (s, 3H, OCH_3, 30 %), 4.30 (d, $J = 8.8$ Hz, 1H, 30 %), 4.42 (d, $J = 8.8$ Hz, 1H, 70 %), 4.45–4.80 (m, 2H), 5.37 (q, $J = 7.2$ Hz, 1H, 30 %), 5.46 (q, $J = 7.2$ Hz, 1H, 70 %), 6.86 (d, $J = 7.2$ Hz, 2 H, ArH), 7.20–7.40 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 16.5, 28.2, 28.3, 41.3, 41.4, 41.5, 41.6, 48.9, 50.1, 52.3, 52.4, 55.2, 56.1, 62.1, 62.8, 65.4, 66.6, 67.8, 71.4, 80.7, 81.2, 113.7, 113.9, 127.1, 127.2, 127.4, 127.5, 127.9, 128.3, 128.8, 131.3, 132.2, 137.9, 138.3, 154.8, 155.0, 158.9, 159.2, 168.4, 168.9, 172.7, 173.1; $[\alpha]_D = -125.0$ (c 0.1, $CHCl_3$); ESI-MS: $m/z = 482.24$ $[M^+]$, 505.24 $[M + Na]^+$. Anal. Calcd. for $C_{27}H_{34}N_2O_6$: C, 67.20; H, 7.10; N, 5.81. Found C, 67.24; H, 7.13; N, 5.77.

*(3S,4R)-N-benzyl-4-(methoxycarbonyl)-2-oxo-1-((S)-1-phenylethyl)pyrrolidin-3-aminium 2,2,2-trifluoroacetate (**7**)*

To a solution of compound **6a** (1 mmol) in DCM (2 mL), TFA (2.40 mL, 0.5 mL/100 mg) was slowly added and the clear solution was stirred for 1 h at r.t. After removal of organics under reduced pressure, the residue was washed with ethyl ether to give compound **7** (0.44 g, 95 %) as a white solid. M.p. 42–44 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, $J = 7.2$ Hz, 3H), 3.12 (br, 2H), 3.23 (d, $J = 8.8$ Hz, 2H), 3.58 (m, 1H), 3.66 (s, 3H), 4.18 (d, $J = 9.2$ Hz, 1H), 4.43 (s, 2H), 5.41 (q, $J = 7.2$ Hz, 1H), 7.25–7.46 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 41.6, 49.8, 51.3, 55.2, 60.9, 62.3, 117.3 (q, J = 282.0 Hz), 127.1, 127.3, 128.2, 128.6, 139.2, 140.1, 160.9 (q, $J = 41.3$ Hz), 172.3; $[\alpha]_D = -92.5$ ($c = 0.1$, $CHCl_3$); ESI-MS: $m/z = 466.17$ $[M^+]$, 489.17 $[M + Na]^+$. Anal. Calcd. for $C_{23}H_{25}F_3N_2O_5$: C, 59.22; H, 5.40; N, 6.01. Found: C, 59.26; H, 5.45; F, 1.24; N, 5.97.

General procedure for the synthesis of dimers **8**, **9** and **10**

To a solution of the acid **5a** (1 mmol) and ammonium salt **7** (1.1 mmol) in CH_2Cl_2 (1 ml), PyBroP (1 mmol) and DIPEA (1 mmol) were added at 0 °C under nitrogen atmosphere. After 1 min at 0 °C, the mixture was stirred for 12 h at r.t., then ethyl acetate (20 ml) and 1 M HCl (10 ml) were added. The reaction mixture was extracted with ethyl acetate (2 × 20 ml) and the organic phase was washed with Brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cycloexane/ethyl acetate 60:40) to give dimer **8** (0.34 g, 44 %) as a colorless oil. The compound **8** (1 mmol) was then dissolved in CH_2Cl_2 (2 ml) and treated with TFA (2.40 mL, 0.5 mL/100 mg). The solution was stirred for 1 h at r.t. After removal of organics under reduced pressure, the residue was washed with ethyl ether to give compound **9** (0.55 g, 96 %) as a white solid. This ammonium salt was treated with TEA (1 mmol) in CH_2Cl_2 (2 ml) for 30 min at r.t., then concentrated under reduced pressure and purified by silica gel chromatography (cycloexane:ethyl acetate 70:30) to give compound **10** (0.66 g, 98 %) as colorless oil.

*Methyl (3R,4S)-4-((3R,4S)-N-benzyl-4-(benzyl(tert-butoxycarbonyl)amino)-5-oxo-1-((S)-1-phenylethyl)pyrrolidine-3-carboxamido)-5-oxo-1-((S)-1-phenylethyl)pyrrolidine-3-carboxylate (**8**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H, 60 %), 1.41 (d, $J = 6.8$ Hz, 3 H 40 %), 1.42 (s, 9H, 40 %), 1.46 (d, $J = 6.8$ Hz, 3H, 60 %), 1.51 (d, $J = 6.8$ Hz, 3H, 60 %), 1.53 (d, $J = 6.8$ Hz, 3H, 40 %), 3.06 (dd, $J = 9.6$ Hz, $J = 9.2$ Hz, 1H), 3.16 (dd, $J = 9.6$ Hz, $J = 9.2$ Hz, 1H), 3.27 (m, 2H), 3.50 (m, 1H), 3.62 (s, 3H, 60 %), 3.64 (s, 3H, 40 %), 3.86 (m, 1H), 4.25–4.67 (m, 5H), 5.02 (d, $J = 16$ Hz, 1H, 60 %), 5.22 (d, $J = 16$ Hz, 1H, 40 %), 5.32 (q, $J = 6.8$ Hz, 1H, 40 %), 5.48 (q, $J = 6.8$ Hz, 1H, 60 %), 5.56 (m, 1H), 7.20–7.40 (m, 20H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8, 15.9, 16.6, 22.7, 26.9, 27.9,

28.1, 28.3, 29.3, 29.6, 29.7, 30.3, 31.9, 39.6, 40.1, 41.0, 41.1, 41.4, 41.5, 42.2, 49.1, 49.2, 49.3, 50.7, 52.5, 52.8, 52.9, 53.1, 62.3, 62.6, 63.4, 63.5, 80.3, 80.7, 125.5, 126.2, 126.9, 127.0, 127.1, 127.2, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.0, 135.6, 135.7, 137.9, 138.3, 139.1, 139.3, 139.5, 139.6, 154.4, 154.6, 167.9, 168.0, 168.9, 169.3, 172.8, 172.9, 173.0, 173.2; $[\alpha]_D = -110.1$ (c 0.2, $CHCl_3$); ESI-MS: $m/z = 772.93$ $[M^+]$, 795.93 $[M + Na]^+$. Anal. Calcd. for $C_{46}H_{52}N_4O_7$: C, 71.48; H, 6.78; N, 7.25. Found C, 71.45; H, 6.75; N, 7.27.

*(3S,4R)-N-benzyl-4-(benzyl((3S,4R)-4-(methoxycarbonyl)-2-oxo-1-((S)-1-phenylethyl)pyrrolidin-3-yl)carbamoyl)-2-oxo-1-((S)-1-phenylethyl)pyrrolidin-3-aminium 2,2,2-trifluoroacetate (**9**)*

m.p. 45–47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, $J = 6.8$ Hz, 3H, 60 %), 1.36 (d, $J = 6.8$ Hz, 3H, 40 %), 1.42 (d, $J = 6.8$ Hz, 3H, 60 %), 1.48 (d, $J = 6.8$ Hz, 3H, 40 %), 2.44 (m, 1H), 2.95 (m, 1H), 3.16 (m, 1H), 3.32 (m, 2H), 3.49 (s, 3H, 40 %), 3.65 (s, 3H, 60 %), 4.12 (m, 1H), 4.36–4.96 (m, 5H), 5.24 (q, $J = 6.8$ Hz, 1H, 40 %), 5.33 (q, $J = 6.8$ Hz, 1H, 60 %), 5.41 (d, $J = 11.0$ Hz, 1H), 5.50 (q, $J = 6.8$ Hz, 1H), 7.05–7.45 (m, ArH + NH, 22H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 16.4, 16.5, 16.8, 30.1, 30.9, 32.0, 32.3, 39.1, 40.2, 40.6, 41.0, 49.1, 49.3, 50.1, 50.3, 55.0, 55.3, 55.8, 56.0, 62.2, 62.5, 62.8, 63.1, 65.4, 65.6, 66.0, 66.2, 118.1 (q, $J = 285.0$ Hz), 118.3 (q, $J = 285.0$ Hz), 127.9, 128.0, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.1, 129.3, 129.4, 129.5, 129.6, 129.7, 129.8, 131.9, 132.1, 132.2, 132.4, 139.8, 139.9, 140.1, 140.3, 160.8 (q, $J = 40.2$ Hz), 161.0 (q, $J = 40.2$ Hz), 172.4, 172.7, 172.9, 173.2; $[\alpha]_D = -81.7$ ($c = 0.2$, $CHCl_3$); ESI-MS: $m/z = 786.32$ $[M^+]$, 809.32 $[M + Na]^+$. Anal. Calcd. for $C_{43}H_{45}F_3N_4O_7$: C, 65.64; H, 5.76; N, 7.12. Found C, 65.61; H, 5.72; N, 7.27.

*(3R,4S)-methyl 4-((3R,4S)-N-benzyl-4-(benzylamino)-5-oxo-1-((S)-1-phenylethyl)pyrrolidine-3-carboxamido)-5-oxo-1-((S)-1-phenylethyl)pyrrolidine-3-carboxylate (**10**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, $J = 7.0$ Hz, 3H), 1.49 (d, $J = 7.0$ Hz, 3H), 2.56 (bs, 2H), 3.23 (m, 1H), 3.24 (m, 1H), 3.28 (m, 1H), 3.37 (m, 1H), 3.47 (m, 2H) 3.57 (s, 3H), 3.88 (d, $J = 14.0$ Hz, 1H), 4.01 (d, $J = 14.0$ Hz, 1H), 4.12 (d, $J = 8.0$ Hz, 1H), 4.40 (d, $J = 9.0$ Hz, 1H), 4.57 (d, $J = 17.0$ Hz, 1H), 4.86 (d, $J = 17.0$ Hz, 1H), 5.43 (q, $J = 7.0$ Hz, 1H) 5.52 (q, $J = 7.0$ Hz, 1H), 7.11–7.35 (m, ArH, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 16.1, 41.0, 42.6, 45.0, 49.4, 49.5, 51.6, 52.3, 52.4, 53.3, 62.4, 63.5, 127.0, 127.1, 127.2, 127.4, 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.0, 136.4, 140.2, 140.8, 140.9, 168.1, 170.9, 171.9, 172.8; $[\alpha]_D = -98.3$ (c 0.1, $CHCl_3$); ESI-MS: $m/z = 672.33$ $[M^+]$, 695.33 $[M + Na]^+$. Anal. Calcd. for $C_{41}H_{44}N_4O_5$: C, 73.19; H, 6.59; N, 8.33. Found C, 73.16; H, 6.54; N, 8.34.

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References

Anelli PL, Biffi C, Montanari F, Quici S (1987) Fast and selective oxidation of primary alcohols to aldehydes or to carboxylic acids and of secondary alcohols to ketones mediated by oxoammonium salts under two-phase conditions. J Org Chem 52:2559–2562

Armand P, Kirshenbaum K, Goldsmith RA, Farr-Jones S, Barron AE, Truong KTV, Dill KA, Mierke DF, Cohen FE, Zuckermann RN, Bradley EK (1998) NMR determination of the major solution conformation of a peptoid pentamer with chiral side chains. Proc Natl Acad Sci USA 95:4309–4314

Baldauf C, Gunther R, Hofmann HJ (2006) Helices in peptoids of α- and β-peptides. Phys Biol 3:S1–S9

Cardoso AL, Lopes SMM, Beja AM, Silva MR, de los Santos JM, Pinho e Melo TMVD, Palacios F (2009) New chiral building blocks of β-peptoid analogs. Tetrahedron 65:9116–9124

Coste J, Frerot E, Jouin P (1994) Coupling N-methylated amino acids using PyBroP and PyCloP halogenophosphonium salts: mechanism and fields of application. J Org Chem 59:2437–2446

Crucianelli E, Martelli G, Orena M, Rinaldi S, Sgolastra F (2009) New isosteres of (*R*)-2-methylhomoserine and (*R*)-2-methylaspartic acid by alkylation of a chiral imine leading stereoselectively to a quaternary stereogenic center. Tetrahedron Asymmetry 20:1824–1827

Crucianelli E, Galeazzi R, Martelli G, Orena M, Rinaldi S, Sabatino P (2010) A novel conformationally restricted analogue of 3-methylaspartic acid via stereoselective methylation of chiral pyrrolidin-2-ones. Tetrahedron 66:400–405

Fowler SA, Blackwell HE (2009) Structure–function relationships in peptoids: recent advances toward deciphering the structural requirements for biological function. Org Biomol Chem 7:1508–1524

Galeazzi R, Martelli G, Orena M, Rinaldi S, Sabatino P (2005) Conformationally restricted analogues of both (*S*)-β-homoserine and (*S*)-aspartic acid from chiral 3-acylamino pyrrolidin-2-ones. Tetrahedron 61:5465–5473

Galeazzi R, Martelli G, Mazzanti A, Orena M, Rinaldi S (2011) Quaternary centres as a tool for modulating foldamer conformation. Chem Eur J 17:12564–12568

Gorske BC, Stringer JR, Bastian BL, Fowler SA, Blackwell HE (2009) New strategies for the design of folded peptoids revealed by a survey of noncovalent interactions in model systems. J Am Chem Soc 131:16555–16567

Hamper BC, Kolodziej SA, Scates AM, Smith RG, Cortez E (1998) Solid phase synthesis of β-peptoids: N-substituted β-aminopropionic acid oligomers. J Org Chem 63:708–718

Huang K, Wu CW, Sanborn TJ, Patch JA, Kirshenbaum K, Zuckermann RN, Barron AE, Radhakrishnan I (2006) A threaded loop conformation adopted by a family of peptoid nonamers. J Am Chem Soc 128:1733–1738

Huang ML, Shin SBY, Benson MA, Torres VJ, Kirshenbaum K (2012) A comparison of linear and cyclic peptoid oligomers as potent antimicrobial agents. ChemMedChem 7:114–122

Kirshenbaum K, Barron AE, Goldsmith RA, Armand P, Bradley EK, Truong KTV, Dill KA, Cohen FE, Zuckermann RN (1998) Sequence-specific polypeptoids: a diverse family of heteropolymers with stable secondary structure. Proc Natl Acad Sci USA 95:4303–4308

Kwon YU, Kodadek T (2007) Quantitative evaluation of the relative cell permeability of peptoids and peptides. J Am Chem Soc 129:1508–1509

Menegazzo I, Fries A, Mammi S, Galeazzi R, Martelli G, Orena M, Rinaldi S (2006) Synthesis and structural characterisation as 12-helix of the hexamer of a β-amino acid tethered to a pyrrolidin-2-one ring. Chem Commun 47:4915–4917

Miller SM, Simon RJ, Ng S, Banville SC, Zuckermann RN, Kerr JM, Moos WH (1994) Proteolytic studies of homologous peptide and N-substituted glycine peptoid oligomers. Bioorg Med Chem Lett 4:2657–2662

Norgren AS, Zhang S, Arvidsson PI (2006) Synthesis and circular dichroism spectroscopic investigations of oligomeric β-peptoids with α-chiral side chains. Org Lett 8:4533–4536

Olsen CA, Ziegler HL, Nielsen HM, Frimodt-Møller N, Jaroszewski JW, Franzyk H (2010) Antimicrobial, hemolytic, and cytotoxic activities of b-peptoid–peptide hybrid oligomers: improved properties compared to natural AMPs. ChemBioChem 11:1356–1360

Simon RJ, Kania RS, Zuckermann RN, Huebner VD, Jewell DA, Banville S, Ng S, Wang L, Rosenberg S, Marlowe CK (1992) Peptoids: a modular approach to drug discovery. Proc Natl Acad Sci USA 89:9367–9371

Wu CW, Kirshenbaum K, Sanborn TJ, Patch JA, Huang K, Dill KA, Zuckermann RN, Barron AE (2003) Structural and spectroscopic studies of peptoid oligomers with α-chiral aliphatic side chains. J Am Chem Soc 125:13525–13530