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Peptidomimetics with tunable tertiary amide bond containing substituted β-proline and β-homoproline

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ABSTRACT

Tunable *cis*/*trans* prolyl amide bond configuration in substituted β-proline (β-Pro) and β-homoproline (β-Hpro) homodimers was explored, based on position and nature of the substituent. Tertiary amide bond in β-proline ($\beta^{2,3}$-substituted) dimers show distinct *trans* configuration and β-homoproline (β^3-substituted) dimers preferably exhibited *cis* configuration.

1. Introduction

Oligomers with well-defined conformations, known as foldamers,[1] mostly contain backbone intramolecular H-bonding network, which majorly contributes to the structural shape and stability in the foldamers.[2] Occasionally we come across certain class of oligomers, i.e., polyprolines[3–5] and peptoids,[6,7] which cannot have backbone H-bonding network as they lack backbone amide protons. Nevertheless, these classes of foldamers also form well-defined stable structures as noticed in PPII helices with poly prolines[4,5] and in peptoids with chiral centres at α-position of their *N*-substituents.[8]

In an ongoing study in our laboratory toward the development of short collagen related peptides (CRPs)[9] containing β-prolines and β-homoprolines that may spontaneously self assemble into the bioactive form of collagen to interact with collagen receptor sites with an aim to have new anti-thrombotic therapy, we were interested to understand the folding preferences of differently substituted β-Pro and β-Hpro containing short peptides. Controlling tertiary amide bond *cis*/*trans* isomerism is crucial in generating ordered structures in these classes of peptides, despite the fact that the energy difference between the two isomers is not significantly different. In nature, *cis*/*trans* isomerism of the prolyl–peptide bonds plays pivotal role in determining the structure, function of certain proteins and peptides.[10] Studies carried out in non-natural oligomers containing proline chimeras showed that the tertiary amide bond configuration correlates well with the nature and position of the substituent of the pyrrolidine ring.[11a–d] Fine tuning *cis*/*trans* isomerism in prolyl–peptide bonds remains a challenging task. While the *cis*/*trans* isomerization of α-proline derivatives and their control on structures have been studied extensively,[12] that of β-Hpro has been poorly explored. In 1998, Seebach et al. studied the conformational preferences of β-Hpro oligomers containing unsubstituted β^3-homoproline,[13] and crystal studies revealed that these oligomers formed conformations with exclusive *trans* amide bonds. Later Gellman et al., in 2003, conducted studies on β-peptides containing 2,2-disubstituted β^2-Hpro oligomers, and helical structures were demonstrated.[14] It was proposed that the disubstituted products will favour *cis* amide bonds preferably, thus favouring ordered structures. In PPII helices, both proline and hydroxyproline play predominant roles due to their predisposed backbone dihedral angles. However, to the best of our knowledge, there is no report, to date, related to any stable conformation formed from $\beta^{2,3}$- and β^3-substituted prolines. In an effort to understand the conformational preferences of substituted β-Pro and β-Hpro, we have carried out synthesis and solution conformational

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analysis on two varieties of β-prolines, i.e., $\beta^{2,3}$- (1) and β^3-substituted (2) monomers and their homodimers 3 and 4, respectively, supported by density functional theory (DFT)[15] calculations (Fig. 1).

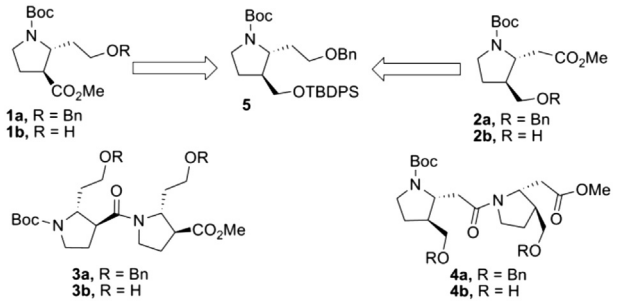
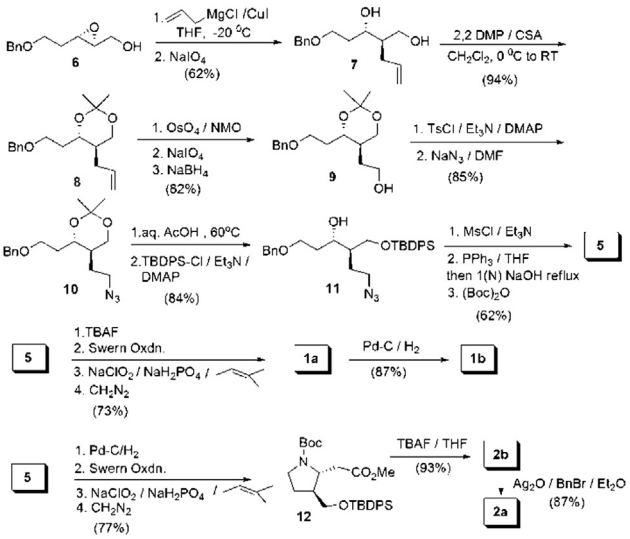


Fig. 1. Schematic representation of substituted β-Pro **1** and β-Hpro **2** and their homodimers, **3** and **4**, respectively.

2. Results and discussion

2.1. Synthesis of substituted $\beta^{2,3}$-proline 1 and β^3-homoproline 2

Monomers **1** and **2** were derived from a common precursor **5**, a 2,3-disubstituted pyrrolidine molecule having orthogonally protected groups that could be easily manipulated to prepare the desired β-prolines (Scheme 1). Syntheses of pyrrolidine precursor **5**, substituted β-proline **1** and β-homoproline **2** are depicted in Scheme 1. Treatment of the epoxide[16] **6** with 2.0 equiv of allylmagnesium chloride in THF at −80 °C produced 1,2-diol, exclusively. When this epoxide was reacted with Gilman reagent, prepared from 2.0 equiv of allylmagnesium bromide and 0.1 equiv of CuI, at −20 °C in THF, a mixture 1,2- and 1,3-diols was obtained. The crude reaction mixture was treated with $NaIO_4$ to remove the unwanted 1,2-diol and gave 1,3-diol **7** in 62% yield from epoxy-alcohol **6**. The diol **7** was converted into acetonide **8** on treatment with 2,2-dimethoxypropane in CH_2Cl_2 in presence of catalytic amount of CSA in 94% yield. Dihydroxylation of the double bond on **8** with OsO_4 and oxidation of the resulting 1,2-diol with $NaIO_4$ furnished an aldehyde. Reduction of the aldehyde with $NaBH_4$ in MeOH gave the alcohol **9** in 82% yield from **8**. Compound **9** was converted into the azide **10** in 85% yield in two steps—tosylation with TsCl, Et_3N and catalytic amount of DMAP followed by reaction with NaN_3 in DMF at elevated temperature. The acetonide group on azide **10** was deprotected by treating it with an aqueous acetic acid solution at elevated temperature. Primary hydroxyl group of the diol, thus obtained, was selectively protected as its silyl-ether using TBDPS-Cl, Et_3N and catalytic amount of DMAP to produce azido-alcohol **11** in 84% yield from **10**. The azido-alcohol **11** on intramolecular cyclization provided the pyrrolidine **5** in 62% overall yield using the following steps—first treatment with MsCl and Et_3N in CH_2Cl_2 to give a mesylate, followed by reduction of the azido group with PPh_3 in THF with the resulting amine undergoing smooth intramolecular cyclization in situ on addition of 1(N) NaOH under reflux to produce the pyrrolidine backbone. Finally the amine group on the pyrrolidine ring was protected as Boc carbamate to provide **5**. Silyl-ether on **5** was cleaved with TBAF in THF to produce a primary alcohol. This alcohol was oxidized into an acid in two steps, Swern oxidation followed by oxidation of the resulting aldehyde using $NaClO_2$ along with $NaH_2PO_4{\cdot}2H_2O$ in a mixture of 2-methyl-2-butene and ^{t}BuOH (1:2) gave an acid. Acid was transformed into its ester **1a**, on treatment with excess of diazomethane in Et_2O, in 73% yield from **5**. Cleavage of benzyl ether of 1**a** with Pd–C in MeOH using a H_2-filled balloon produced **1b** in 87% yield.



Scheme 1. Syntheses of substituted $\beta^{2,3}$-proline **1** and β^3-homoproline **2**.

Synthesis of **2b** started with cleavage of benzyl ether on **5** with Pd–C under hydrogen in MeOH to provide a primary alcohol. Two step oxidation of the alcohol to an acid followed by esterification with diazomethane furnished the ester **12** in 77% yield from **5**. Silyl-ether on **12** was cleaved with TBAF in THF to produce the substituted β^3-Hpro **2b** in 93% yield. Free hydroxyl group of **2b** was further protected as benzyl ether with BnBr and Ag_2O in Et_2O to produce the side-chain benzylated β^3-Hpro **2a** in 87% yield.

Dimers **3a** and **4a** were obtained from **1a** and **2a**, respectively, following solution phase peptide coupling procedures using EDCI, HOBt and DIPEA. Hydrogenation of **3a** and **4a** with Pd–C in MeOH produced **3b** and **4b**, respectively.

2.2. Conformational studies

Conformational analyses of monomers (**1a**–**b** and **2a**–**b**) and dimers (**3a**–**b** and **4a**–**b**), with 10 mM concentration in $CDCl_3$, were performed using two-dimensional NMR techniques (Figs. 2 and 3) supported with DFT calculations. In **1a**–**b**, coupling constant value of $^3J_{C\alpha H-C\beta H}$ ~6.2 Hz was attributed to the dihedral angle 'θ' [N–Cβ–Cα–C(O)] of about 120°.[17] The characteristic NOEs between $C\beta H \leftrightarrow C\gamma' H_{(pro\text{-}R)}$, $C\alpha H \leftrightarrow C\gamma' H_{(pro\text{-}S)}$ support that the pyrrolidine ring takes $^{\beta}$E (Cβ-*endo*) conformation in both **1a**–**b** (Fig. 2A). Variation in the intensity of the $C\alpha H \leftrightarrow C\delta H$ NOE, strong in **1a** and weak in **1b**, suggests that χ^2 is varying to a value of 180° and 60° in **1a** and **1b**, respectively. DFT calculations were carried out, where potential energy surfaces for monomers, **1a**–**b** (tertiary butyl group at N-terminal replaced with CH_3) were explored at B3LYP[7c,18]/6-31G(d,p) level of theory in gas phase, to suggest that the *trans* conformation is the lowest energy conformations for both **1a**–**b**, shown in Tables S27–S29.[17]

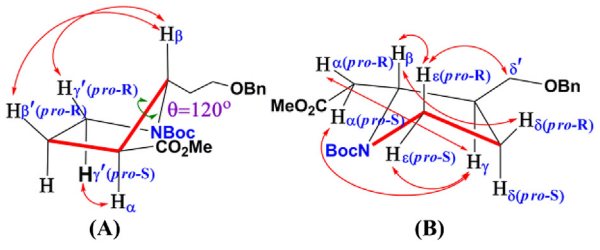


Fig. 2. Schematic representation of the proposed conformations with NOEs shown in arrows for (A) $^{\beta}$E (Cβ-*endo*) conformation of **1a**; (B) E_N (*N-exo*) conformation of **2a**.

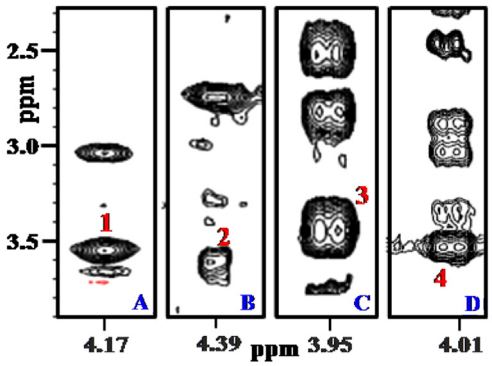


Fig. 3. NOESY spectra of monomers (A) **1a**, (B) **1b**; (C) **2a** and (D) **2b**. Characteristic NOEs, CβH↔Cγ′H$_{(pro\text{-}R)}$ of **1a**, CβH↔Cγ′H$_{(pro\text{-}R)}$ of **1b**, CβH↔CεH$_{(pro\text{-}R)}$ of **2a**, CβH↔CεH$_{(pro\text{-}R)}$ **2b** are depicted as **1**–**4**, respectively.

Conformational analysis carried out on **2a**–**b** showed differences in their NOE patterns, which suggest that the pyrrolidine ring conformations vary based on the nature of the substitution. However, in both **2a**–**b** $^{3}J_{C\beta H-C\alpha H}$ values, >9.5 Hz and <3 Hz,[17] indicate that of a predominant single conformation around the dihedral angle '*θ*' [N–Cβ–Cα–C(O)]. Further, based on the NOE CαH$_{(pro\text{-}R)}$↔CγH and $^{3}J_{C\beta H-C\varepsilon H(pro\text{-}R)}$ ~9.5 Hz, a value of 180° may be attributed to '*θ*'.[17] For **2a**, strong NOEs between CβH↔CεH$_{(pro\text{-}R)}$, CγH↔CεH$_{(pro\text{-}S)}$ support that the pyrrolidine ring takes E_N (N-*exo*) conformation (Fig. 2B). In **2b**, NOEs between CγH↔CεH$_{(pro\text{-}S)}$, CβH↔Cδ′H, CβH↔CδH$_{(pro\text{-}R)}$ support $^{\delta}$E (Cδ-*endo*) conformation for the pyrrolidine ring. Also, the coupling constants and NOEs support a value of 180° for the dihedral angle '*θ*', as in **2a**. In DFT calculations[7c,18] (Tables S30–S32), it was observed that for **2a**–**b** the value of '*θ*' for minimum energy conformation is about 180°.

Conformational analysis on both the monomers suggested that preferred conformations exist in the β^{3}-, β^{2,3}-substituted prolines. It would be rather intriguing to study the configurational preferences of the oligomers containing these monomeric blocks and to begin with studies were carried on homodimers **3a**–**b** and **4a**–**b**. For dimers **3a**–**b**, characteristic NOEs, as given in Fig. 4A–B, between CβH↔Cγ′H$_{(pro\text{-}R)}$, CαH↔Cγ′H$_{(pro\text{-}S)}$ support $^{\beta}$E (Cβ-*endo*) conformation for the pyrrolidine ring similar as in **1a**–**b**. Further strong NOEs between ^{1}CαH↔^{2}Cγ′H$_{(pro\text{-}R)}$ and ^{2}Cγ′H$_{(pro\text{-}S)}$ support the amide bond between residue 1 and 2 in *trans* configuration. These observations are reflected in the DFT calculations, which suggest that for both dimers **3a**–**b**, the *trans* configuration for the peptide bonds is the lowest energy conformation. Profiles of potential energy surfaces for *trans*–*trans* (type I) and *trans*–*cis* (type II) conformations of **3a** explored at B3LYP/6-31G(d,p) level of theory in gas phase are similar, and the low energy minima are observed at *ψ*=−80°. On the other hand, the type I, II minima for **3b** are seen at different angles, i.e., *ψ*=−80° and −50°, respectively. As suggested by earlier studies,[19] in such cases the tertiary amide bond

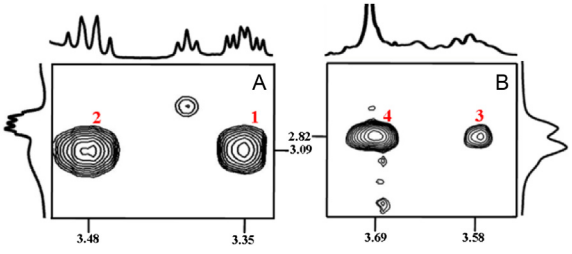


Fig. 4. Expansions of NOESY spectra for (A) **3a** and (B) **3b**. Characteristic NOEs ^{2}Cγ′H$_{(pro\text{-}R)}$↔^{1}CαH, ^{2}Cγ′H$_{(pro\text{-}S)}$↔^{1}CαH for **3a**; and ^{2}Cγ′H$_{(pro\text{-}R)}$↔^{1}CαH, ^{2}Cγ′H$_{(pro\text{-}S)}$↔^{1}CαH for **3b** are depicted as **1**–**4**, respectively.

preferred to be in *trans* orientation as *cis* orientation will be less favourable due to steric repulsions. However, it is worth mentioning that **3a** being a substituted β-proline containing dimer, certain resonances in the proton spectrum appeared as broad lines suggesting intermediate exchange of at least two populations in the NMR timescale. While exploring for the possible second isomer we detected a weak NOE peak between ^{1}CαH↔^{2}CβH suggesting that the second isomer population is coming due to the rotation at the amide bond between the two rings. Also, at high energy minimum region (*ψ*=60°, Fig. 5), while the electronic energy (E_{el}) difference between both the types of **3a** is less than 1 kcal/mol, for **3b** it is about 4 kcal/mol. These inferences conclude that though major population for the amide bond in the NMR timescale exists in *trans* configuration, however, certain population also exists in *cis*/*trans* isomerism as reflected in the NMR analysis of **3a**. However, no such isomerism was noticed in **3b** (Figs. 6 and 7).

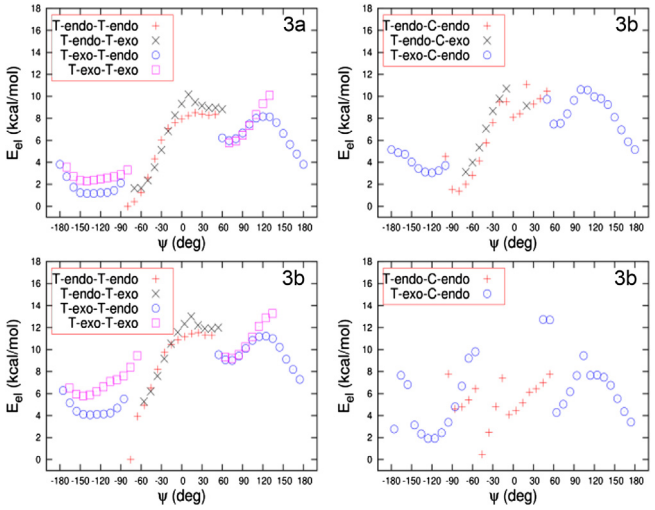


Fig. 5. Potential energy surfaces for *trans*–*trans* and *trans*–*cis* conformations of dimers, **3a**–**b**, explored at B3LYP/6-31G(d.p) level of theory in gas phase with respect to the torsion, *ψ*, about Cβ$_{(i-1)}$–Cα$_{(i-1)}$–C(O)$_{(i-1)}$–N$_i$. 'C' and 'T' refer to *cis* and *trans*, respectively. The torsion χ^1 about N–Cβ–Cα–Cβ′ describes pucker conformation of proline ring, where χ^1>0 denotes '*endo*' and χ^1<0 denotes '*exo*'. Each residue in the dimer is represented as C/T-*endo*/*exo*. E_{el} is electronic energy.

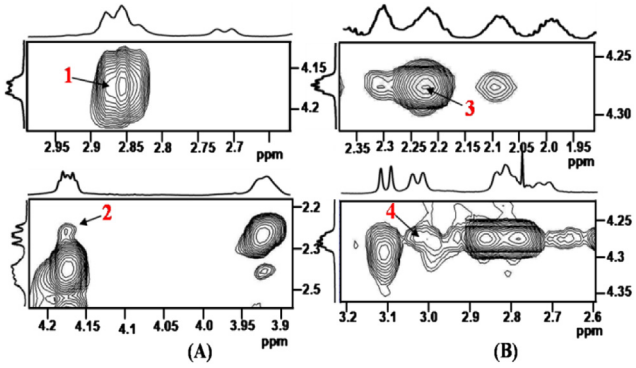


Fig. 6. Expansions of NOESY spectra for (A) **4a** and (B) **4b**. Characteristic NOEs ^{2}CβH↔^{1}CαH$_{(pro\text{-}R)}$, ^{2}CβH↔^{1}CαH$_{(pro\text{-}S)}$ of **4a**, ^{2}CβH↔^{1}CαH$_{(pro\text{-}R)}$, ^{2}CβH↔^{1}CαH$_{(pro\text{-}S)}$ of **4b** are depicted as **1**–**4**, respectively.

For dimers **4a**–**b**, variation in the intra residual NOE patterns suggests that the puckering of the pyrrolidine ring varies from their monomers. For **4a**, NOEs between CγH↔CεH$_{(pro\text{-}S)}$ and CβH↔CδH$_{(pro\text{-}R)}$, support that the pyrrolidine ring takes $^{\delta}$E (Cδ-*endo*) conformation. For **4b**, NOEs between CβH↔CεH$_{(pro\text{-}R)}$,

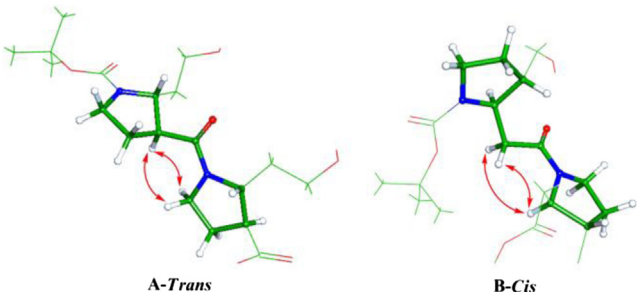


Fig. 7. Schematic representation with characteristic NOEs for *trans* configuration (A) of **3b** and *cis* configuration (B) of **4b**.

CβH↔Cδ′H$_{(pro\text{-}R)}$, CγH↔CεH$_{(pro\text{-}S)}$ support that the pyrrolidine ring takes ^{E}N (N-*exo*) conformation similar to its monomer **2a**. Theoretically, dimers with both the ring conformations are found to be minima on the potential energy surface. In both **4a** and **4b**, the characteristic inter residual NOEs between ^{1}CαH↔^{2}CβH suggest that the peptide bond between the rings is predominantly in *cis* configuration (Fig. 7B). Calculations at B97D[20]/6-31G(d,p) level of theory showed that, while **4a** with *cis* configuration is close to the minimum (relative free energy, *G*=2.07 kcal/mol), for **4b**, *cis* configuration is the lowest energy conformation as given in Tables S35–S36.[15]

The restrained molecular dynamics (MD) calculations on **1**–**4** were performed on Discovery studio 3.0 client Program using the CHARMm force field[21] with default parameters throughout the simulation. Fig. 8A–D depicts the superimposition of the 15 lowest energy structures of peptides **3a**–**b**, **4a**–**b** obtained from 1 nS MD simulation runs. The average pair wise heavy atom and backbone RMSD is 2.16 and 1.83 Å for **3a**, 0.94 and 0.73 Å for **3b**, 2.20 and 2.06 Å for **4a**, and 0.54 and 0.32 Å for **4b**, respectively. *trans* Amide bond in **3a**–**b** and *cis* amide bond in **4a**–**b** are observed as major conformers throughout the MD simulations.

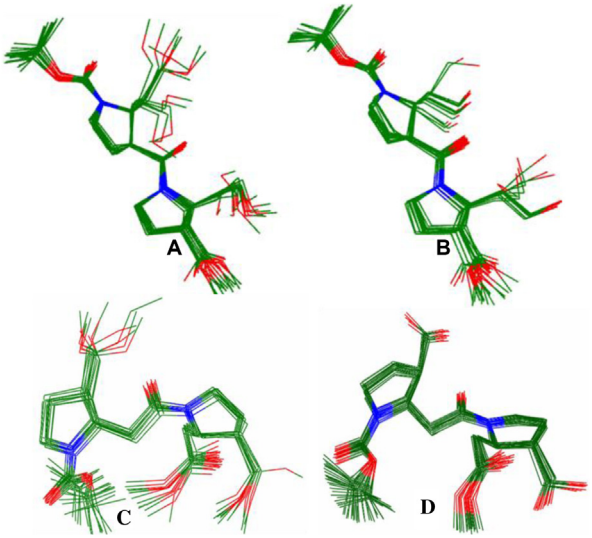


Fig. 8. Ensemble of 15 superimposed lower energy structures from restrained MD studies of (A) **3a**; (B) **3b**; (C) **4a** and (D) **4b**. Side-chains are removed for clarity, after superposition in all the dimers.

3. Conclusion

Generating tunable *cis*/*trans* isomerism in prolyl tertiary amide bonds remains a challenging task. Despite the lack of H-bonding network in this class of β-peptides, conformational analysis carried out on β^{2,3}- and β^{3}-substituted β-proline foldamers displayed distinctly preferred either *cis* or *trans* configurations. Conformational studies for **3a**–**b** indicate that in these molecules *trans* configuration for the peptide bond between the rings is preferred, where as for **4a**–**b** *cis* configuration is favoured. These distinct preferences in the dimers may be attributed to the intrinsic preferences of their backbone and the stability of these preferences may further increase with the increase in the chain lengths of the peptides. Further work is currently in progress.

4. Experimental section

4.1. General

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concd H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. IR spectra were recorded as thin films on FTIR. Mass spectra were obtained under high resolution mass spectrometric (HRMS) and electrospray ionization (ESI) techniques. Optical rotations were measured with a digital polarimeter. 1D and 2D NMR were recorded on 300 MHz, 400 MHz, 500 MHz and 700 MHz spectrometers.

4.2. Preparation of β^{2,3}-proline 1 and β^{3}-homoproline 2

*4.2.1. (2R,3S)-2-Allyl-5-(benzyloxy)pentane-1,3-diol (**7**).* To a solution of allylmagnesium chloride (2 M in THF) (48.1 mL, 96.153 mM) was added CuI (1.83 g, 9.614 mM) and the resulting mixture was stirred for 30 min at room temperature. Then the temperature was brought down to −40 °C and stirring was continued for another 10 min Epoxide**6** (10 g, 48.07 mM) was dissolved in THF (96 mL) and it was cannulated slowly into the solution of the Gilman's reagent at −40 °C. After 30 min, temperature was raised to 0 °C and kept stirring for another 1 h. Then the reaction was quenched with satd. NH_4Cl (10 mL) and extracted with EtOAc (500 mL). EtOAc layer was washed sequentially with aq NH_3 (3×50 mL), H_2O (2×50 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in vacuo to provide a crude mixture of 1,2- and 1,3-diols as a liquid.

The mixture of diols were dissolved in a 1:1 solution of THF:H_2O (80 mL) and cooled to 0 °C. $NaIO_4$ (10.3 g, 48 mM) was added to the resulting solution. Temperature was allowed to rise to room temperature and stirring was continued for 30 min. Then the reaction mixture was diluted with EtOAc and solid Na_2SO_4 was added into it. The resulting reaction mixture was filtered and the solids were washed with EtOAc. The filtrate was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (50% EtOAc/hexane) gave 1,3-diol **7** (7.45 g, 62%) as a liquid. R_f 0.4 (50% EtOAc/hexane); $[\alpha]_D^{25}$ −1.86 (*c* 0.76, $CHCl_3$); ν_{max} (liquid film) 3426, 2922, 1649, 1439, 1096 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.40–7.29 (m, 5H), 5.70 (m, 1H), 5.01–4.93 (m, 2H), 4.44 (s, 2H), 3.85–3.76 (m, 2H), 3.67 (dt, *J*=9.37, 4.85 Hz, 1H), 3.62–3.55 (m, 2H), 2.19–1.98 (m, 2H), 1.95–1.80 (m, 1H), 1.76–1.65 (m, 1H), 1.56–1.44 (m, 1H) ppm; δ_C (75 MHz, $CDCl_3$): 136.4, 128.4, 127.8, 127.6, 116.5, 75.5, 73.4, 69.6, 63.8, 44.6, 34.5, 33.2 ppm; HRMS (ESI) (*m*/*z*): calcd for $C_{15}H_{23}O_3$ $[M+H]^+$, 251.1647; found 251.1638.

*4.2.2. (4S,5R)-5-Allyl-4-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (**8**).* To a solution of diol **7** (7.45 g, 29.8 mM) in CH_2Cl_2

(90 mL) was added 2,2-dimethoxypropane (14.62 mL, 119.2 mM) and CSA (692.25 mg, 2.98 mM) at room temperature. The resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with EtOAc (300 mL) and washed sequentially with water (2×50 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexane) gave the acetonide **8** (8.2 g, 94%) as a liquid. R_f 0.5 (10% EtOAc/hexane); $[\alpha]_D^{25}$ −47.73 (*c* 0.57, $CHCl_3$); ν_{max} (liquid film) 3022, 2361, 1635, 1216, 909, 766, 671 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.39–7.28 (m, 5H), 5.69 (m, 1H), 5.05–4.99 (m, 2H), 4.54 (d, *J*=12.18 Hz, 1H), 4.46 (d, *J*=12.18 Hz, 1H), 3.81–3.70 (m, 2H), 3.64–3.50 (m, 3H), 2.18–2.11 (m, 1H), 2.07–1.97 (m, 1H), 1.85–1.75 (m, 1H), 1.73–1.57 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H) ppm; δ_c (75 MHz, $CDCl_3$): 135.0, 128.2, 127.5, 127.4, 116.7, 72.9, 70.2, 66.3, 64.0, 38.6, 33.3, 32.7, 29.3, 19.3 ppm; MS (ESI) (*m*/*z*) (%): 251 (55) $[M+H-C_3H_4]^+$, 291 (80) $[M+H]^+$, 308 (100) $[M+NH_4]^+$.

*4.2.3. 2-((4S,5R)-4-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl)ethanol (**9**).* To a solution of acetonide **8** (8.2 g, 28.3 mmol) in acetone–water mixture (3:1, 60 mL) were added NMO (6.63 g, 56.6 mmol) and OsO_4 (0.04 M in toluene) (7 mL, 0.283 mM) sequentially at room temperature. After being stirred for 4 h at the same temperature the reaction mixture was concentrated in vacuo and diluted with EtOAc (200 mL), washed with water (2×50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and preceded to the next reaction. R_f 0.3 (50% EtOAc/hexane).

The diol obtained above was dissolved in THF/H_2O (1:1, 60 mL), with pH around 7 maintained by adding phosphate buffer, was treated with $NaIO_4$ (12.11 g, 56.6 mM) at 0 °C and stirred for 45 min at the same temperature. Then the reaction mixture was diluted with EtOAc and solid Na_2SO_4 was added into it. The resulting reaction mixture was filtered and the solids were washed with EtOAc. The filtrate was dried over anhydrous Na_2SO_4 and concentrated in vacuo; R_f 0.5 (30% EtOAc/hexane). The crude reaction mixture was dissolved in MeOH (56 mL) and cooled to 0 °C. Then $NaBH_4$ (2.15 g, 56.6 mM) was added to it and stirred for another 1 h. After completion of the reaction, it was quenched with satd. NH_4Cl and extracted with EtOAc (300 mL). The organic layer was washed sequentially with water (2×40 mL), brine (60 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in vacuo. Purification by column chromatography (30% EtOAc/hexane) gave the alcohol **9** (6.82 g, 82%) as a colourless liquid. R_f 0.5 (50% EtOAc–hexane); $[\alpha]_D^{25}$ −38.92 (*c* 0.49, $CHCl_3$); ν_{max} (liquid film) 3434, 2926, 1215, 756 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.33 (m, 5H), 4.54 (d, *J*=12.03 Hz, 1H), 4.46 (d, *J*=12.03 Hz, 1H), 3.84 (dd, *J*=11.55, 4.92 Hz, 1H), 3.74 (t, *J*=9.47 Hz, 1H), 3.67–3.55 (m, 5H), 2.04–1.93 (m, 1H), 1.75–1.60 (m, 4H), 1.40 (s, 3H), 1.35 (s, 3H) ppm; δ_c (75 MHz, $CDCl_3$): 138.4, 128.2, 127.6, 127.5, 98.0, 73.0, 70.3, 66.2, 64.3, 60.2, 36.5, 33.3, 31.0, 29.6, 29.3, 19.3 ppm; MS (ESI) *m*/*z* (%): 255 (10) $[M+H-C_3H_4]^+$, 295 (35) $[M+H]^+$.

*4.2.4. (4S,5R)-5-(2-Azidoethyl)-4-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (**10**).* To the solution of the alcohol **9** (6.82 g, 23.2 mM) in CH_2Cl_2 (70 mL) was added Et_3N (6.451 mL, 46.4 mM), TsCl (5.267 g, 27.63 mM) and DMAP (283 mg, 2.32 mM) sequentially at room temperature. The reaction was stirred for another 2 h at the same temperature. Then it was quenched with satd. NH_4Cl (20 mL) and extracted with EtOAc (300 mL). The organic layer was washed sequentially with water (2×40 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and preceded to the next reaction.

The tosylate was dissolved in DMF (40 mL) and NaN_3 (4.52 g, 69.6 mM) was added to it. The resulting mixture was heated to 80 °C and stirring was continued for 6 h at that temperature. Then the temperature of the reaction mixture was brought down to room temperature and water was added into it. The reaction mixture was extracted with diethyl ether (300 mL) and washed sequentially with water (2×40 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in vacuo. Purification by column chromatography (SiO_2, with EtOAc/hexane, 1:10) gave the azide **10** (6.29 g, 85%) as a colourless liquid. R_f 0.3 (10% EtOAc/hexane); $[\alpha]_D^{25}$ −44.7 (*c* 0.55, $CHCl_3$); ν_{max} (liquid film) 2856, 2096, 1260, 1075, 798, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.30 (m, 5H), 4.53 (d, *J*=11.93 Hz, 1H), 4.46 (d, *J*=11.93 Hz, 1H), 3.82 (dd, *J*=11.65, 4.83 Hz, 1H), 3.72 (dt, *J*=9.66, 2.27 Hz, 1H), 3.64–3.52 (m, 3H), 3.25 (ddd, *J*=19.54, 12.37, 7.38 Hz, 2H), 2.00–1.91 (m, 1H), 1.72–1.57 (m, 4H), 1.40 (s, 3H), 1.35 (s, 3H) ppm; δ_c (75 MHz, $CDCl_3$): 138.6, 128.4, 127.6, 127.5, 98.3, 73.1, 70.1, 66.1, 63.8, 49.0, 37.2, 33.5, 29.2, 27.4, 19.4 ppm; HRMS (ESI) (*m*/*z*): calcd for $C_{17}H_{25}N_3O_3Na$ $[M+Na]^+$, 342.1794; found 342.1791.

*4.2.5. (3S,4R)-6-Azido-1-(benzyloxy)-4-((tert-butyldiphenylsilyloxy)methyl)hexan-3-ol (**11**).* To the azide **10** (6.29 g, 19.72 mM) a solution AcOH–H_2O (7:3, 100 mL) was added and the resulting mixture was heated at 100 °C for 3 h. Then the reaction mixture was concentrated in vacuo and residual AcOH was quenched with solid $NaHCO_3$. The reaction mixture was diluted with EtOAc (250 mL) and washed sequentially with water (3×40 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic extract was concentrated under reduced pressure and preceded to the next reaction.

To the solution of the diol in CH_2Cl_2 (50 mL) was added Et_3N (7.7 mL, 55.26 mM), TBDPS-Cl (7.9 mL, 30.393 mM), and DMAP (337 mg, 2.763 mM) sequentially at room temperature. After stirring for 5 h at the same temperature, it was quenched with satd. NH_4Cl and extracted with EtOAc (250 mL). The organic layer was washed sequentially with water (2×50 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in vacuo. Purification by column chromatography (10% EtOAc/hexane) gave the silyl-ether **11** (12.02 g, 84%) as a colourless liquid. R_f 0.6 (20% EtOAc/hexane); $[\alpha]_D^{25}$ 2.6 (*c* 1.035, $CHCl_3$); ν_{max} (liquid film) 3019, 2099, 1716, 1639, 1375, 1218, 1048, 759 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.65–7.63 (m, 4H), 7.46–7.25 (m, 11H), 4.51 (s, 2H), 3.90 (m, 1H), 3.848 (dd, *J*=10.67, 3.77 Hz, 1H), 3.73–3.60 (m, 3H), 3.22 (ddd, *J*=19.57, 12.56, 7.10 Hz, 2H), 1.88–1.63 (m, 5H), 1.06 (s, 9H) ppm; δ_c (75 MHz, $CDCl_3$): 138.0, 132.9, 129.8, 128.4, 127.6, 73.2, 72.0, 68.9, 63.8, 49.6, 42.6, 34.3, 27.3, 19.1 ppm; HRMS (ESI) (*m*/*z*): calcd for $C_{30}H_{40}N_3O_3Si$ $[M+H]^+$, 518.2839; found 518.2833.

*4.2.6. (2R,3S)-tert-Butyl 2-(2-(benzyloxy)ethyl)-3-((tert-butyldiphenylsilyloxy)methyl)pyrrolidine-1-carboxylate (**5**).* To the solution of the silyl-ether **11** (12.02 g, 23.2 mM) in CH_2Cl_2 (55 mL) were added Et_3N (6.5 mL, 46.4 mM) and methanesulphonyl chloride (2.2 mL, 27.84 mM) sequentially at 0 °C. After stirring for 30 min at the same temperature, it was quenched with satd. NH_4Cl and extracted with EtOAc (300 mL). The organic layer was washed sequentially with water (2×40 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated in vacuo. Purification by column chromatography (SiO_2, with EtOAc/hexane, 1:9) gave the mesylated compound (12.7 g, 92%) as a viscous liquid; R_f=0.5 (silica, EtOAc–hexane, 1:5).

The mesylate (12.7 g, 21.344 mM) was dissolved in THF (160 mL) and PPh_3 (28 g, 106.7 mM) was added to it at room temperature and stirred for 4 h at the same temperature. After complete consumption of the mesylate, a solution of 1(N) NaOH (20 mL) was added into it and the resulting mixture was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and $(Boc)_2O$ (7.3 mL, 32.02 mM) was added into it and it was stirred for 12 h at the same temperature. The reaction mixture was diluted with EtOAc (250 mL) and washed sequentially with water (2×50 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. The reaction

mixture was concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexane) gave the pyrrolidine **5** (8.36 g, 62% from silyl-ether **60**) as a colourless liquid. R_f 0.4 (10% EtOAc–hexane); $[\alpha]_D^{25}$ 1.67 (*c* 0.925, $CHCl_3$); ν_{max} (liquid film) 3020, 1729, 1375, 1217, 1046, 759 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.65–7.61 (m, 4H), 7.41–7.23 (m, 11H), 4.45 (t, *J*=12.36 Hz, 2H), 3.81 (br, 1H), 3.49 (br, 5H), 3.26 (br, 1H), 2.29–2.27 (m, 1H), 2.01–1.89 (m, 2H), 1.77–1.64 (m, 2H), 1.43 (s, 9H), 1.04 (s, 9H) ppm; δ_c (75 MHz, $CDCl_3$): 154.51, 138.46, 135.52, 133.56, 133.49, 129.63, 128.26, 127.65, 127.50, 127.40, 79.12, 72.94, 68.01, 64.96, 57.15, 46.21, 45.45, 44.57, 34.66, 34.13, 28.48, 26.82, 25.19, 19.20 ppm; HRMS (ESI) (*m*/*z*): calcd for $C_{35}H_{48}NO_4Si$ $[M+H]^+$, 574.3353; found 574.3344.

*4.2.7. (2R,3S)-1-tert-Butyl 3-methyl 2-(2-(benzyloxy)ethyl)pyrrolidine-1,3-dicarboxylate (**1a**).* To a solution of pyrrolidine **5** (3.3 g, 5.73 mM) in THF (20 mL) was added drop-wise TBAF in THF (8.6 mL, 8.6 mM) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature and quenched by the addition of saturated aqueous NH_4Cl solution. Then it was extracted with EtOAc (100 mL), washed with water (2×20 mL), brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification by column chromatography (30% EtOAc/hexane) gave the alcohol (1.84 g, 95%) as a colourless liquid; R_f 0.5 (60% EtOAc/hexane).

To a solution of oxalyl chloride (0.7 mL, 8.16 mM) in dry CH_2Cl_2 (25 mL) at −78 °C, DMSO (1.25 mL, 17.41 mM) was added slowly in a drop-wise manner with stirring under nitrogen atmosphere. After 15 min stirring, alcohol (1.84 g, 5.44 mM, dissolved in 15 mL of dry CH_2Cl_2) was added to the reaction mixture. After 0.5 h of stirring at −78 °C, Et_3N (3.8 mL, 27.2 mM) was added and stirred for another 0.5 h at −78 °C and then for 0.5 h at 0 °C. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (100 mL). The combined organic layers were washed with water (2×30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo, R_f 0.5 (30% EtOAc/hexane). The aldehyde, thus obtained, was directly used for the next reaction.

To the solution of the aldehyde in 2-methyl-2-butene (4 mL) and ^{t}BuOH (8 mL), the mixture of $NaClO_2$ (1.48 g, 16.32 mM) and NaH_2PO_4 (2.54 g, 16.32 mM), dissolved in minimum amount of water, was added and stirring continued for 3 h at room temperature. The solvents of reaction mixture were evaporated under vacuum; the residue was diluted with EtOAc (100 mL), washed with 1 N HCl (2×20 mL), water (2×20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. Crude acid was dissolved in Et_2O and treated with excess CH_2N_2 in ether at 0 °C. Then the solvent was evaporated and purification by column chromatography (15% EtOAc/hexane) afforded methyl ester **1a** (1.52 g, 73% from pyrrolidine). R_f 0.3 (20% EtOAc/hexane); $[\alpha]_D^{25}$ 2.27 (*c* 0.545, $CHCl_3$); ν_{max} (liquid film) 3020, 2400, 1729, 1374, 1216, 1046, 756, 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.35–7.29 (m, 5H), 4.49 (d, *J*=11.89 Hz, 1H), 4.45 (d, *J*=11.89 Hz, 1H), 4.16 (br, 1H), 3.67 (s, 3H), 3.55 (br, 3H), 3.32–3.26 (m, 1H), 3.04–3.03 (m, 1H), 2.11–2.07 (m, 3H), 1.81–1.73 (m, 1H), 1.44 (s, 9H) ppm; δ_C (175 MHz, $CDCl_3$): 174.2, 154.5, 137.9, 128.4, 127.7, 127.6, 127.5, 79.5, 73.3, 68.1, 59.3, 52, 47.1, 45.6, 29.7, 28.5, 27.0 ppm; HRMS (ESI) (*m*/*z*): calcd for $C_{20}H_{30}NO_5$ $[M+H]^+$, 364.2124; found 364.2115.

*4.2.8. (2R,3S)-1-tert-Butyl 3-methyl 2-(2-hydroxyethyl)pyrrolidine-1,3-dicarboxylate (**1b**).* To a stirred solution of ester **1a** (300 mg, 0.826 mM) in MeOH (10 mL), 10% Pd–C (100 mg) were added and subjected to hydrogenation under atmospheric pressure using a hydrogen filled balloon. After 6 h the reaction mixture was filtered through a short Celite pad and the filter cake was washed with methanol. The filtrate and the washings were combined and concentrated in vacuo. Purification by column chromatography (30% EtOAc/hexane) afforded methyl ester **1b** (196 mg, 87%). R_f 0.4 (50% EtOAc/hexane); $[\alpha]_D^{25}$ 11.213 (*c* 0.51, $CHCl_3$); ν_{max} (liquid film) 3019, 1669, 1404, 1215, 756, 669 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 4.39 (br, 1H), 3.71 (s, 3H), 3.63–3.57 (m, 3H), 3.33–3.28 (m, 1H), 2.78–2.74 (m, 1H), 2.19 (br, 1H), 2.14–2.07 (m, 2H), 1.85 (br, 1H), 1.47 (s, 9H) ppm; δ_C (100 MHz, $CDCl_3$):173.9, 156.2, 80.3, 58.7, 56.9, 52.1, 48.5, 38.8, 31.9, 29.6, 28.4, 26.8, 22.7, 14.1 ppm; HRMS (ESI) (*m*/*z*): calcd for $C_{13}H_{23}NO_5Na$ $[M+Na]^+$, 296.1474; found 296.1496.

*4.2.9. (2R,3S)-tert-Butyl 3-((tert-butyldiphenylsilyloxy)methyl)-2-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (**12**).* To a stirred solution of pyrrolidine **5** (2.0 g, 3.47 mM) in MeOH (15 mL), 10% Pd–C (200 mg) were added and subjected to hydrogenation under atmospheric pressure using a hydrogen filled balloon. After 6 h the reaction mixture was filtered through a short Celite pad and the filter cake was washed with methanol. The filtrate and the washings were combined and concentrated in vacuo. Purification by column chromatography (silica gel, 18% EtOAc in hexane eluant) afforded alcohol (1.53 g, 91%); R_f 0.4 (30% EtOAc/hexane).

To a solution of oxalyl chloride (0.407 mL, 4.73 mM) in dry CH_2Cl_2 (18 mL) at −78 °C, DMSO (0.716 mL, 10.1 mM) was added slowly in a drop-wise manner, with stirring under nitrogen atmosphere. After 15 min stirring, alcohol (1.53 g, 3.154 mM, dissolved in 15 mL of dry CH_2Cl_2) was added to the reaction mixture. After 0.5 h of stirring at −78 °C, Et_3N (2.19 mL, 15.77 mM) was added and stirred for another 0.5 h at −78 °C and then for 0.5 h at 0 °C. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (100 mL). The combined organic layers were washed with water (2×30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo; R_f 0.6 (10% EtOAc/hexane) The aldehyde, thus obtained, was directly used for the next reaction.

To the solution of aldehyde in 2-methyl-2-butene (4 mL) and ^{t}BuOH (8 mL), the mixture of $NaClO_2$ (904 mg, 10 mM) and NaH_2PO_4 (1.56 g, 10 mM), dissolved in minimum amount of water, was added and stirring continued for 3 h at room temperature. The solvents of reaction mixture were evaporated under vacuum; the residue was diluted with EtOAc (100 mL), washed with 1 N HCl (2×20 mL), water (2×20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. Crude acid was dissolved in Et_2O and treated with excess CH_2N_2 in ether at 0 °C. Then the solvent was evaporated and purification by column chromatography (8% EtOAc/hexane) afforded methyl ester **12** (1.37 g, 77% from pyrrolidine **70**). R_f 0.4 (20% EtOAc/hexane); $[\alpha]_D^{25}$ −0.697 (*c* 2.7, $CHCl_3$); ν_{max} (liquid film) 3019, 1731, 1401, 1248, 1217, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.64 (m, 4H), 7.42–7.37 (m, 6H), 4.02(m, 1H), 3.61 (s, 3H), 3.55–3.49 (m, 2H), 3.40–3.30 (m, 2H), 2.85–2.70 (m, 1H), 2.49–2.36 (m, 2H), 2.01–1.89 (m, 1H), 1.77 (m, 1H), 1.45 (s, 9H), 1.05 (s, 9H); δ_C (75 MHz, $CDCl_3$): 171.8, 154.2, 135.6, 133.53, 133.50, 129.76, 127.77, 79.67, 79.31, 65.21, 64.83, 56.66, 56.39, 51.57, 46.23, 45.38, 44.91, 39.08, 38.36, 29.75, 28.54, 26.89, 26.18, 26.04, 25.18, 19.30; HRMS (ESI) (*m*/*z*): calcd for $C_{29}H_{41}NO_5SiNa$ $[M+Na]^+$, 534.2652; found 534.2610.

*4.2.10. (2R,3S)-tert-Butyl 3-(hydroxymethyl)-2-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (**2b**).* To a solution of methyl ester **12** (1.01 g, 1.94 mM) in THF (8 mL) was added drop-wise TBAF in THF (4.0 mL, 4.0 mM) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature and quenched by the addition of saturated aqueous NH_4Cl solution. Then it was extracted with EtOAc (40 mL), washed with water (2×10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification by column chromatography (30% EtOAc/hexane) gave the alcohol **2b** (503 mg, 93%) as a colourless liquid. R_f 0.4 (50% EtOAc/hexane); $[\alpha]_D^{25}$ −27.36 (*c* 1.345, $CHCl_3$); ν_{max} (liquid film) 3019, 1669, 1404, 1215, 756, 669 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 4.00 (m, 1H), 3.68 (s, 3H), 3.57 (br, 2H), 2.91 (m, 1H), 2.45 (m, 1H), 2.28 (m, 1H), 1.99 (m, 1H), 1.70 (m, 1H), 1.47 (m, 1H) ppm; δ_C (100 MHz, $CDCl_3$): 172.5, 154.2, 79.9, 79.6, 64.1, 56.7, 51.8, 47.0, 46.2, 45.2, 44.9, 29.7, 28.5,

26.1, 25.3 ppm; HRMS (ESI) (m/z): calcd for $C_{13}H_{23}NO_5Na$ $[M+Na]^+$, 296.1474; found 296.1496.

*4.2.11. (2R,3S)-tert-Butyl 3-(benzyloxymethyl)-2-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (**2a**).* The alcohol **2b** (400 mg, 1.47 mM) obtained in the above reaction was dissolved in Et_2O (15 ml) and BnBr (1.74 mL, 14.7 mM) and Ag_2O (3.41 g, 14.7 mM) was added to it simultaneously at room temperature. After 36 h, the reaction mixture was filtered through a short Celite pad and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in vacuo. Purification by column chromatography (16% EtOAc/hexane) afforded benzyl ether **2a** (344 mg, 65% from **2b**) and 85 mg of unreacted alcohol **2b**. R_f 0.4 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −14.3 (c 0.69, $CHCl_3$); ν_{max} (liquid film) 3023, 2400, 1725, 1374, 1216, 1046, 756, 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.34–7.32 (m, 5H), 4.50 (s, 2H), 3.97–3.91 (m, 1H), 3.64 (s, 3H), 3.43–3.34 (m, 4H), 2.82–2.77 (m, 1H), 2.49 (m, 2H), 1.99–1.94 (m, 1H), 1.77 (m, 1H), 1.45 (s, 9H) ppm; δ_C (100 MHz, $CDCl_3$): 171.9, 154.5, 136.0, 134.8, 130.0, 128.1, 79.9, 79.8, 65.5, 65.3, 56.8, 56.5, 52.0, 46.5, 45.8, 45.2, 39.0, 38.4, 28.7, 27.0, 26.3, 25.4, 19.1 ppm; HRMS (ESI) (m/z): calcd for $C_{20}H_{30}NO_5$ $[M+H]^+$, 364.2124; found 364.2115.

*4.2.12. Dimers **3a**–**b** and **4a**–**b**.* Syntheses and analytical data of the dimeric peptides are included in Supplementary data.

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Supplementary data

Electronic Supplementary data (ESD) available: Details of synthesis of dimers, NMR, MD calculations and energy calculations from DFT. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.078.

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