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Synthesis and conformational preferences of cyclic unnatural di- and tripeptides containing an L-valine unit: Part 2☆

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Abstract—Stereoselective syntheses of non-proteinogenic di- **14a**,**b**, **15a**,**b** and **16a**,**b** and tripeptides **14c**, **15c** and **16c** containing an L-valine unit and a cyclic unnatural α-amino acid have been accomplished starting from the L-valine derived chiral synthon **1**. The conformational preferences of these unnatural peptides were investigated by ^{1}H NMR and IR spectroscopies and by molecular modelling calculations. X-ray analysis of pseudopeptides **15a** and **15b** is also reported.

1. Introduction

In a preceding paper,[1] we described a stereoselective approach to a series of unusual dipeptides containing the L-valine unit. Our interest in this field is because peptidomimetic structures could exhibit therapeutic effects similar to natural peptides with the advantage of metabolic stability.[2] In addition, non-proteinogenic dipeptides could be useful building blocks for preparing higher peptides or components to use as starting materials in the organic synthesis.

Thus, in connection with our interest in these structural derivatives, we undertook the synthesis of new pseudopeptide derivatives **14**–**16** containing L-valine and a cyclic non-proteinogenic α-amino acid (proline derived). To determine if these unnatural peptide analogues behave as a scaffold, giving rise to conformationally constrained cyclic structures through the formation of intramolecular hydrogen bonds, studies were performed by ^{1}H NMR and IR spectroscopies and by molecular modelling calculations.[1,3–6]

The strategy followed to accomplish the asymmetric synthesis of these pseudopeptide derivatives is that previously acquired on the stereoselective approach to analogous substrates,[1,3–5] that is starting from the chiral synthon **1**, a monolactim ether easily obtained from L-valine.

2. Synthesis

As previously reported, the stereoselective synthesis followed makes use of the chiral synthon **1**, (6*S*)-1-benzyl-5-ethoxy-3,6-dihydro-6-isopropyl-pyrazin-2-one,[3] a monolactim ether easily obtained starting from L-valine (Scheme 1). The cyclic unnatural dipeptides **2**, **3** and **4**, obtained in good overall yield as previously reported,[1] were converted into the corresponding acetamides **5**, **6** and **7**. After hydrolysis of the ester group, the carboxylic acid function was activated by conversion of intermediates **8**, **9** and **10** into pentafluorophenylester **11**, **12** and **13** derivatives, respectively. Finally, the activated esters were converted into the respective pseudodipeptides, **14a**,**b**, **15a**,**b** and **16a**,**b**, by treatment with cyclohexylamine or benzylamine and the pseudotripeptides **14c**, **15c** and **16c** by reaction with L-valine methylester. The final products were all obtained in good overall yields.

3. ^{1}H NMR and IR studies

To determine the structural features of the unnatural peptides **14**–**16**, we performed conformational investigations by both ^{1}H NMR and IR spectroscopies[3–7] as well as by molecular modelling studies. Essentially,

☆ Ref. 1 is considered to be Part 1.
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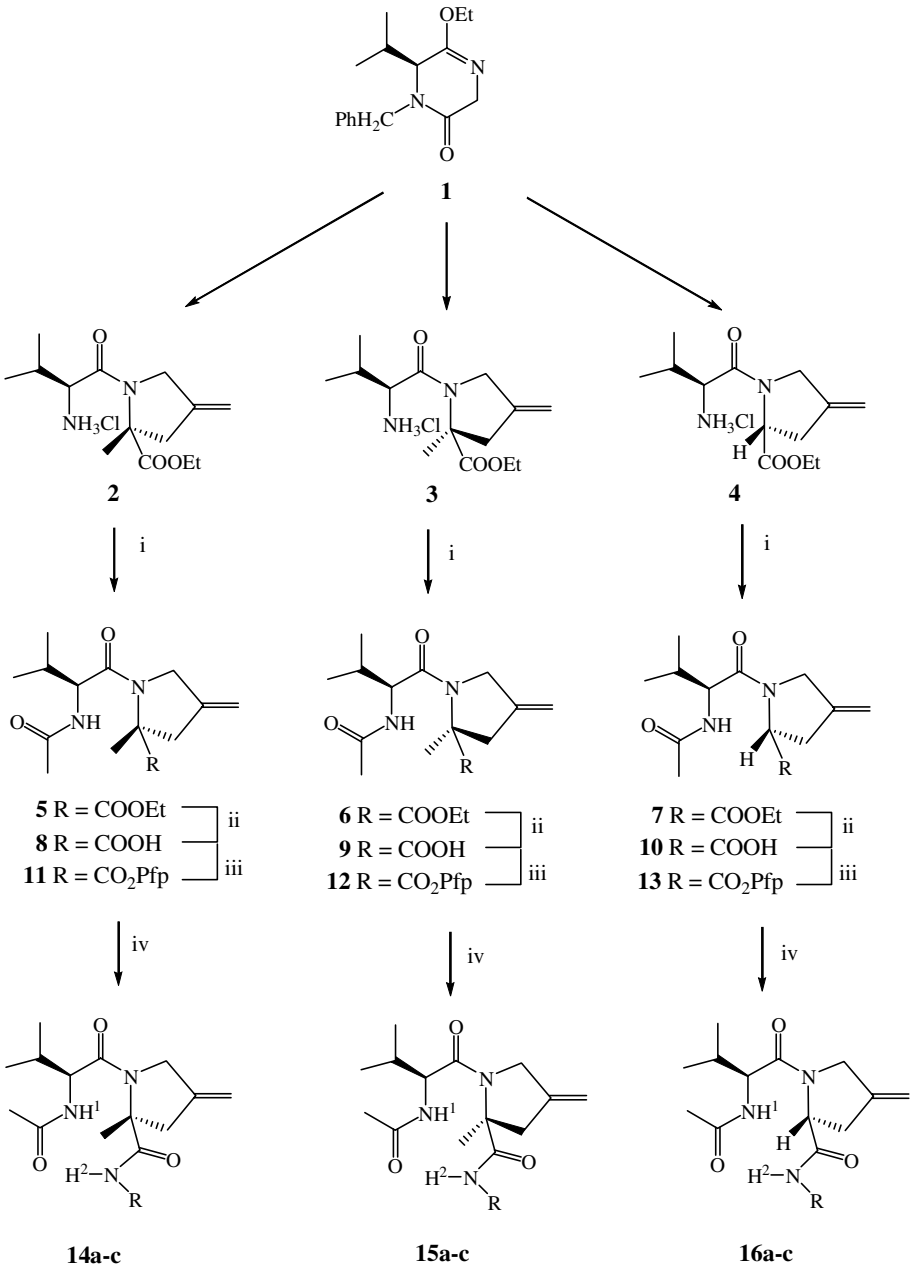

Scheme 1. Reagents and conditions: (i) CH_3COCl/Et_3N in CH_2Cl_2; (ii) 2 M NaOH in EtOH, 2 h at rt; (iii) pentafluorophenyl trifluoroacetate (CF_3CO_2Pfp) in CH_2Cl_2, Py; (iv) R–NH_2 in DMF.

information on the intramolecular hydrogen bonds existence was derived from the chemical shift value (δ_{NH}), the magnitude of temperature coefficient ($\Delta\delta_{NH}/\Delta T$) and solvent titration studies by adding up to 20% of DMSO, a strongly competitive solvent in hydrogen bond formation. Participation in hydrogen bonding can be further confirmed by a broad band in the range 3300–3350 cm^{-1} for the infrared stretching absorption of the amidic NH, taking into account that a sharp band higher than 3400 cm^{-1} is attributable to hydrogen-bond-free NH groups. In Table 1 are listed the meaningful ^1H NMR and IR data of substrates investigated in dilute solutions and for clarity their amide protons are labelled as $\mathbf{H^1}$ and $\mathbf{H^2}$ (see Scheme 1).

From the spectroscopic data in Table 1, it can be inferred that in all pseudopeptides studied, the $\mathbf{H^1}$ proton does not form hydrogen bonds because the chemical shifts are <7 ppm and the signals undergo a significant downfield shift (1.3–2 ppm) upon addition of 20% DMSO. Further support for this deduction comes from the IR spectra that show sharp bands at $\nu > 3400$ cm^{-1}, that is in the region characteristic of free NH amide absorbance.

Conversely, the spectroscopic data allowed us to conclude that most probably the $\mathbf{H^2}$ proton in some substrates is involved in an intramolecular hydrogen bond. Although the chemical shift of $\mathbf{H^2}$ in pseudopep-

Table 1. Meaningful ^{1}H NMR and IR data of pseudopeptides **14–16**

	δ_{NH} (ppm) (in 2 mM $CDCl_3$)		δ_{NH} (ppm) (in 2 mM $CDCl_3$/DMSO 4:1)		$\Delta\delta_{NH}/\Delta T$(ppb/°C) (in $CDCl_3$)		IR (cm^{-1}) (2 mM $CHCl_3$)
	H^1	H^2	H^1	H^2	H^1	H^2	
14a	5.96	6.34	7.96	6.55	2.0	0.9	3436 (sharp) 3369 (broad)
15a	6.10	6.36	7.40	6.64	1.7	1.2	3431 (sharp) 3305 (broad)
16a	6.16	6.63	8.03	6.92	3.6	1.6	3432 (sharp) 3356 (broad)
14b	5.91	7.05	7.76	7.48	2.9	2.9	3434 (sharp) 3363 (broad)
15b	6.01	6.71	7.40	7.49	2.2	1.1	3461 (shoulder) 3425 (sharp)
16b	5.99	7.28	7.86	7.73	2.6	1.4	3437 (sharp) 3349 (broad)
14c	6.08	7.03	7.73	6.88	2.5	1.0	3430 (sharp) 3290 (shoulder)
15c	6.11	6.96	7.67	7.30	2.4	0.2	3449 (shoulder) 3429 (sharp)
16c	6.26	7.47	7.60	7.49	2.9	2.1	3422 (sharp) 3315 (broad)

tides **14a**, **15a** and **16a** is below 7 ppm, the small change in δ_{NH^2} after addition of 20% DMSO (0.21–0.28 ppm) and the small value of the temperature coefficient (0.9–1.6 ppb/°C) are in agreement with the participation of $\mathbf{H^2}$ in an intramolecular hydrogen bonding state. Such a conjecture is supported by the IR spectra that show broad bands in the range 3305–3369 cm^{-1} in comparable intensity with the sharp bands at higher ν values, that is in the range 3431–3436 cm^{-1} (Table 1). Thus, it is reasonable to infer that most probably, in pseudopeptides **14a**, **15a** and **16a**, $\mathbf{H^2}$ is involved in an intramolecular hydrogen bond although the chemical shifts are in the range 6.34–6.63 ppm. We believe that the δ_{NH^2} value below 7 ppm, registered for these pseudopeptides, could be due to the shielding effect induced by the nearby cyclohexane ring.

Also in substrates **14b** and **16b**, we believe that $\mathbf{H^2}$ is engaged in an intramolecular hydrogen bond because δ_{NH^2} values are greater than 7 ppm and the IR spectra show a consistent broad band attributable to the hydrogen bonded amidic NH. Nevertheless, the solvent titration value (a downshift of ≈0.44 ppm) suggests that the added solvent (DMSO) competes with the carbonyl oxygen in the intramolecular hydrogen bonding formation. So, probably in pseudopeptides **14b** and **16b** $\mathbf{H^2}$ forms hydrogen bonds weaker than those in **14a**, **15a** and **16a**.

Conversely, the spectroscopic parameters reported in Table 1 for **15b**, $\delta_{NH^2} = 6.71$ ppm, an appreciable downshift of ≈0.8 ppm upon addition of 20% DMSO, a small temperature coefficient (1.1 ppb/°C) and the absence of a broad band around 3310 cm^{-1}, typical of a hydrogen bonding state, are consistent with $\mathbf{H^2}$ does not participate in an intramolecular hydrogen bond.

In pseudopeptide **15c**, the ^{1}H NMR data do not allow us to assert if the $\mathbf{H^2}$ proton is or not engaged in an intramolecular hydrogen bond. However, because the IR spectrum shows only a sharp band at 3429 cm^{-1}, typical of a free amidic NH (with a shoulder at 3449 cm^{-1}), we hypothesize that the $\mathbf{H^2}$ probably does not form a hydrogen bond.

In the case of pseudopeptides **14c** and **16c**, we infer that the $\mathbf{H^2}$ proton is involved in hydrogen bond because the δ_{NH^2} remains unchanged on adding 20% DMSO, or is rather shifted upfield as for **14c**, the temperature coefficients are small and the IR spectra show a broad shoulder at 3290 and a broad band at 3310 cm^{-1}, respectively, attributable to amidic NH in hydrogen bonding states.

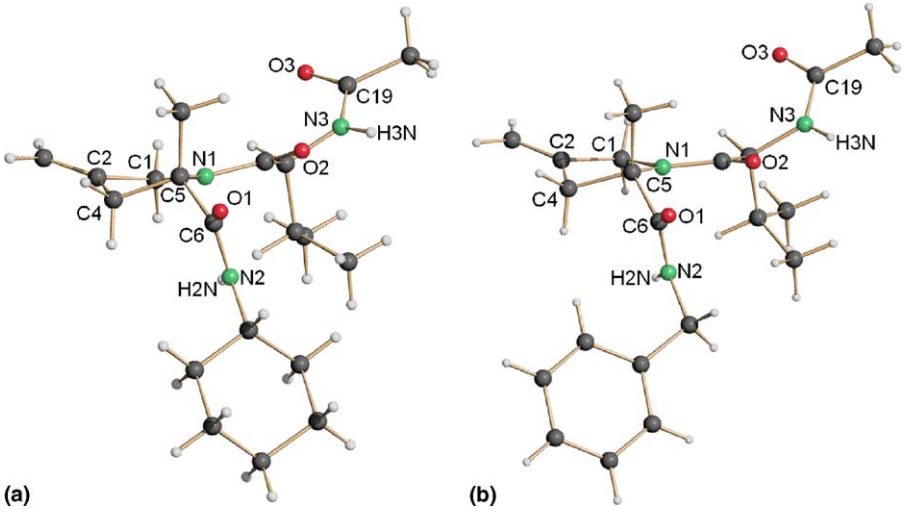

Figure 1. Molecular structure of (a) **15a** and (b) **15b**.

4. X-ray analysis

The two compounds **15a** and **15b** differ only for the substituent bonded to N(2) (cyclohexyl and benzyl, respectively) and adopt the same conformation in the solid state.

The inner part of compounds **15a** and **15b** consists of a five-membered ring [C(1)–C(2)–C(4)–C(5)–N(1)] in an envelope conformation with the flap occupied by C(4), which is placed 0.508(4) Å out of the average plane described by C(1)–C(2)–C(5)–N(1) in compound **15a** [0.486(2) Å in compound **15b**] (Fig. 1a and b).

The molecules possess three amidic functional groups: one tertiary (central) and two secondary ones. The two secondary groups O(1)–C(6)–N(2)–H(2N) and O(3)–C(19)–N(3)–H(3N) are almost perpendicular to each other. The spatial arrangement of the amido groups does not allow formation of intramolecular hydrogen bonds in the solid state. Interestingly, the orientations of the secondary amido groups in each molecules give rise to four intermolecular hydrogen bonds: two by using the amidic protons [H(2N) and H(3N)] and two by using the oxygens [O(1) and O(3)].

Furthermore, each hydrogen bond is only established with another molecule and as a consequence, each molecule is connected through hydrogen bonds to four distinct molecules. This kind of intermolecular interactions produces, in both molecular structures, a peculiar structural motif that consists of a complex 3D network made of macrocycles containing six molecules linked to each other through six hydrogen bonds (Fig. 2a and b).

Since the two molecules crystallize with a similar crystal packing only that of molecule **15b** is shown (Fig. 3).

The strength of the N(2)–H(2N)···O(3) hydrogen bond is slightly different in the two molecules being weaker in **15a** [N(2)–H(2N), 0.861(3) Å, N(2)–H(2N)···O(3), 147.25(7)°, H(2N)···O(3) 2.348(6) Å for **15a** and N(2)–H(2N), 0.967(3) Å, N(2)–H(2N)···O(3), 163.87(4)°, H(2N)···O(3) 1.977(2) Å for **15b**] presumably because of small differences in the crystal. The two remaining intermolecular interactions are almost identical [N(3)–H(3N), 0.904(5) Å, N(3)–H(3N)···O(1), 166.42(9)°, H(3N)···O(1) 2.231(9) Å for **15a** and N(3)–H(3N), 0.903(2) Å, N(3)–H(3N)···O(1), 175.38(6)°, H(3N)···O(1) 2.145(3) Å for **15b**].

5. Molecular modelling

In an attempt to obtain some clues to the interpretation of the spectroscopic data regarding the pseudopeptides described above, we carried out a molecular modelling conformational analysis. Particularly, we studied **14b**, **16b** and **15c**, not only as representative compounds of the set, but also because the conclusions about their intramolecular H-bonding profile seemed not completely unequivocal. For each molecule, conformations were generated by means of the Monte Carlo method,

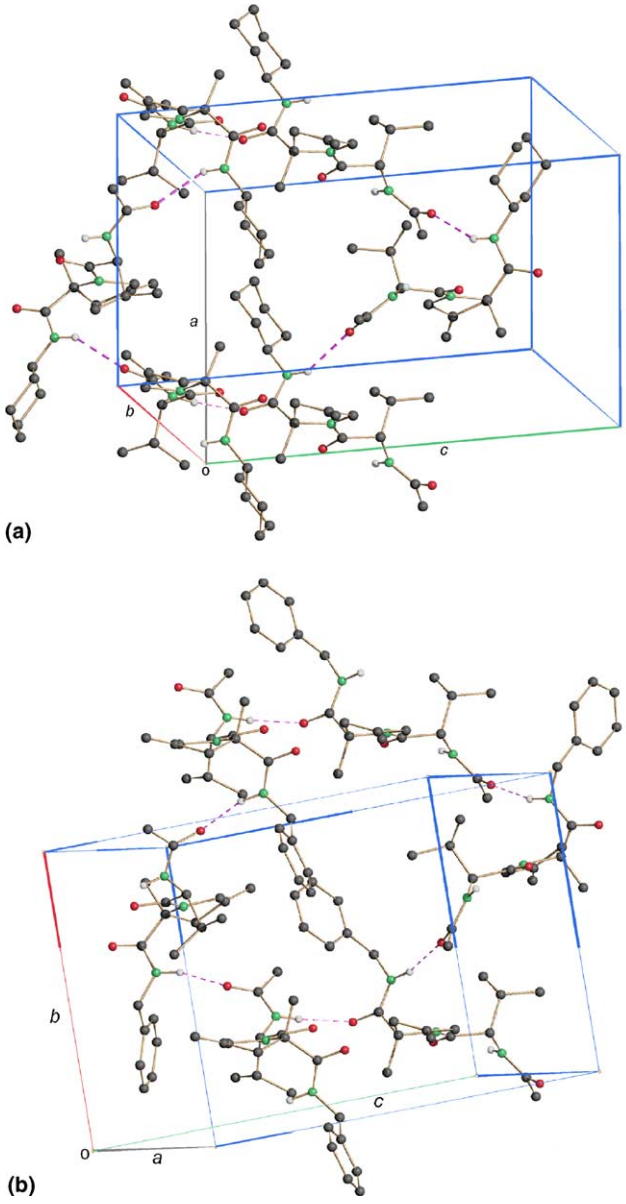

Figure 2. Structural motif in the crystal structure of (a) **15a** and (b) **15b**.

and those within 50 kJ/mol from the global minimum were then minimized through a molecular mechanics force field approach simulating the $CHCl_3$ solvation environment (see experimental section 7.8). The compounds **14b** and **16b** produced 72 and 49 conformations, respectively, whereas compound **15c** generated 57 conformations. By inspection of the minimized conformations, it can be inferred that all the three molecules are able to form an intramolecular hydrogen bond using the $\mathbf{H^2}$ proton. In no case does the $\mathbf{H^1}$ proton seems to be involved in a hydrogen bond. From the conformational analysis, it appears that pseudopeptides **14b** and **16b** behave in a similar manner, both forming a hydrogen bond in their minimum energy conformation. In the case of **14b**, it is a seven-membered hydrogen bond, while a ten-membered H-bond is detected in the global minimum of **16b**. However, for both molecules, several conformations displaying hydrogen bonds via seven-

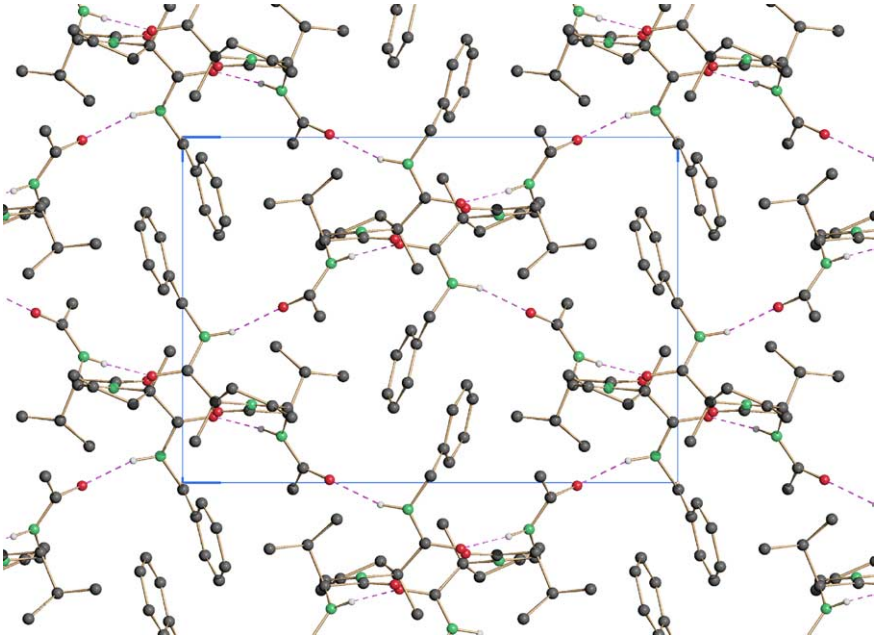

Figure 3. Crystal packing of **15b** (view down the *a* axis).

Table 2. Energetic and geometric parameters of the lowest energy hydrogen-bonded conformations of pseudopeptides **14b**, **16b** and **15c**

Molecule		Energy (kJ/mol)	ΔE (kcal/mol)	Hydrogen bond geometry		
				Cycle members	O–H Distance (Å)	O–H–N Angle (°)
14b	Conf. 1[a]	84.642	0.24	7	1.810	92.71
	Conf. 4	85.064		10	2.398	105.90
16b	Conf. 1[a]	45.114	0.21	10	2.192	105.53
	Conf. 3	45.982		7	1.881	90.79
15c	Conf. 1[a]	194.01	0.74	0	—	—
	Conf. 2	197.12		7	1.820	95.85

[a] Lowest energy conformation.

or ten-membered rings are present within a few kJ/mol from the minimum.

The pseudopeptide **15c** does not show a hydrogen bond in its global minimum, but a conformation containing a seven-membered hydrogen bond is accessible within 3 kJ/mol. For this molecule, no conformation forming a ten-membered hydrogen bond was found.

In Table 2, the energetic and geometric parameters of some representative conformations of **14b**, **16b** and **15c** are reported; the same conformations of the three molecules are shown in Figure 4a–f.

6. Conclusion

We have accomplished the synthesis of new enantiomerically pure unnatural peptides containing L-valine and a cyclic non-proteinogenic α-amino acid, that is a proline derived. The approach, carried out by starting from L-valine, might also represent a new and simple synthetic path to more complex pseudopeptides with potential biological activities. In fact, peptidomimetic structures are interesting because they could exhibit therapeutic effects similar to natural peptides with the advantage of a metabolic stability.

Interestingly, X-ray analysis performed on **15a** and **15b** showed that the amide groups do not form intramolecular hydrogen bonds, but rather each molecule is connected through intermolecular hydrogen bonds to four distinct molecules giving rise to a complex tridimensional network consisting of macrocycles containing six molecules linked to each other through hydrogen bonds.

Nevertheless, X-ray structural information, that is the existence of intermolecular hydrogen bonds, is only apparently in disagreement with the spectroscopic data showing the $\mathbf{H^2}$ involved in an intramolecular hydrogen bond. In fact, the molecular geometry deduced by X-ray analysis concerns the compound in the crystalline state, while the spectroscopic measurements are performed on sufficiently diluted solution where the intermolecular hydrogen bonds are broken. As a consequence, the single molecule of **15a** can adopt such a geometry (evidently not allowed in the crystal packing), which

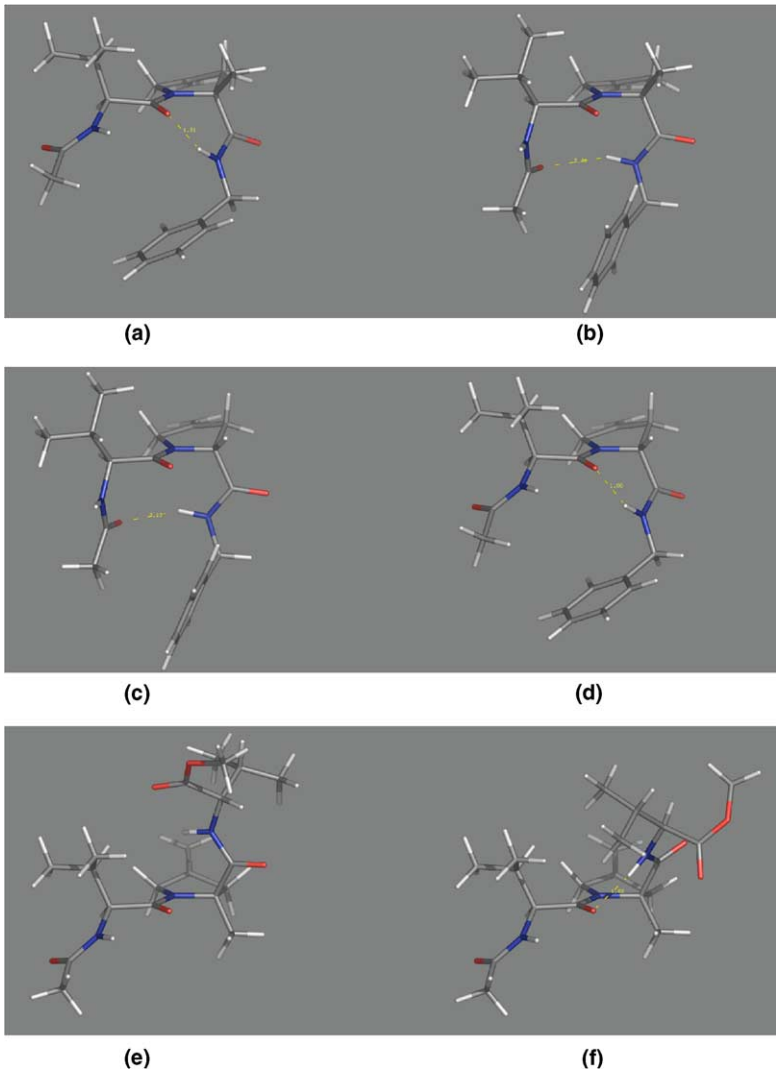

Figure 4. Representative conformations of pseudopeptides **14b** (a, b), **16b** (c, d) and **15c** (e, f). Structures shown in (a), (c), and (e) represent the minimum energy conformation of **14b**, **16b** and **15c**, respectively. Structures shown in (b), (d) and (f) represent the closest hydrogen-bonded conformation.

makes possible the formation of an intramolecular hydrogen bond through $\mathbf{H}^2$. Conversely, in the case of **15b** the spectroscopic data, obtained in dilute solution, suggested that the single molecule forms neither inter- nor intramolecular hydrogen bonds.

In reasonable agreement with the spectroscopic data, conformational analysis shows that both pseudodipeptides **14b** and **16b** form a hydrogen bond in their minimum energy conformations, giving rise to a seven- or a ten-membered ring, respectively. Conversely, pseudotripeptide **15c** shows a seven-membered hydrogen bond structure, which lies 3 kJ/mol higher than the global minimum.

7. Experimental

7.1. General information

^{1}H and ^{13}C NMR spectra were recorded on a Gemini spectrometer at 300 MHz using $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million relative to $CDCl_3$ and the coupling constants (J) are in hertz. IR spectra were recorded on a Nicolet 210 spectrometer. Optical rotation values were measured at 25 °C on a Perkin–Elmer 343 polarimeter. Dry THF was distilled from sodium benzophenone ketyl. Chromatographic separations were performed with silica gel 60 (230–400 mesh).

Synthesis and spectroscopic data of compounds **1**–**4** have been previously reported.[1]

7.2. Acylation of 2–4

Acetyl chloride (0.55 mL, 7.5 mmol) was added to a stirred solution of **2**, **3** or **4** (5 mmol) and triethylamine (2.1 mL, 15 mmol) in CH_2Cl_2 (20 mL) cooled at 0–5 °C. After about 2 h, 2 M HCl (5 mL) was added and the reaction product extracted by ethyl acetate. The organic solution was dried on Na_2SO_4 and the solvent completely evaporated under vacuum. The residue was

then submitted to purification by silica gel chromatography eluting with hexane/ethyl acetate and the product was isolated in good yield as an oil.

7.2.1. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid ethyl ester, 5. It was obtained starting from **2** in 80% yield. ^{1}H NMR δ: 0.92 (d, 3H, $J = 6.6$); 0.97 (d, 3H, $J = 6.6$); 1.21 (t, 3H, $J = 6.8$); 1.54 (s, 3H); 1.98 (m, 1H); 2.00 (s, 3H); 2.52 (dd, 1H, $J = 1.4$, 15.4); 2.89 (d, 1H, $J = 15.4$); 4.15 (m, 2H); 4.23 (d, 1H, $J = 14.2$); 4.56 (d, 1H, $J = 14.2$); 4.56 (dd, 1H, $J = 7$, 9.2); 5.07 (m, 2H); 6.22 (d, 1H, $J = 9.2$). ^{13}C NMR δ: 13.7, 17.6, 18.9, 20.9, 22.6, 31.0, 44.4, 52.1, 55.3, 60.7, 65.8, 108.4, 141.3, 169.8, 170.3, 172.5. $[\alpha]_D = +2.8$ (c 0.5, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.11; H, 8.42; N, 9.01.

7.2.2. (2′*S*,2*S*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid ethyl ester, 6. It was obtained starting from **3** in 82% yield. ^{1}H NMR δ: 0.92 (d, 3H, $J = 6.6$); 1.0 (d, 3H, $J = 6.6$); 1.23 (t, 3H, $J = 7.4$); 1.46 (s, 3H); 1.97 (s, 3H); 2.03 (m, 1H); 2.43 (d, 1H, $J = 14.8$); 2.88 (d, 1H, $J = 14.8$); 4.15 (m, 2H); 4.32 (br s, 2H); 4.48 (dd, 1H, $J = 7$, 9.2); 5.06 (m, 2H); 6.2 (d, 1H, $J = 9.2$). ^{13}C NMR δ: 13.2, 17.7, 18.0, 19.6, 21.5, 29.8, 43.9, 51.0, 55.6, 60.1, 65.0, 108.2, 141.0, 169.8, 170.2, 171.5. $[\alpha]_D = -35.5$ (c 0.9, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.82; H, 8.46; N, 9.05.

7.2.3. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-4-methylene-pyrrolidine-2-carboxylic acid ethyl ester, 7. It was obtained starting from **4** in 78% yield. ^{1}H NMR δ: 0.93 (d, 3H, $J = 7$); 0.97 (d, 3H, $J = 7$); 1.24 (t, 3H, $J = 7.2$); 2.02 (s, 3H); 2.04 (m, 1H); 2.65 (m, 1H); 2.96 (m, 1H); 4.18 (q, 2H, $J = 7.2$); 4.29 (d, 1H, $J = 14.2$); 4.46 (d, 1H, $J = 14.2$); 4.55–4.7 (m, 2H); 5.05 (m, 2H); 6.3 (d, 1H, $J = 8.8$). ^{13}C NMR δ: 13.9, 17.6, 19.3, 22.9, 31.1, 35.2, 51.1, 55.3, 58.5, 61.0, 108.9, 141.7, 169.9, 171.1. The product was not isolated in sufficiently pure form to measure the specific rotation.

7.3. Hydrolysis of 5–7

NaOH (2 M, 10 mmol, 5 mL) was added to a stirred solution of **5**, **6** or **7** (5 mmol) in ethanol at rt and the reaction was monitored by TLC. After 2 h, ethanol was evaporated under vacuum and the residue solution extracted with ethyl acetate. The aqueous solution was acidified to pH = 2–3 with diluted HCl and then extracted with ethyl acetate. The organic solution was dried and the solvent completely evaporated in vacuo. The product was isolated in semisolid state in good yield.

7.3.1. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid, 8. It was obtained pure in 90% yield starting from **5**. ^{1}H NMR δ: 0.95 (d, 6H, $J = 6.6$); 1.56 (s, 3H); 1.99 (s, 3H); 2.06 (m, 1H); 2.54 (d, 1H, $J = 15.4$); 3.0 (d, 1H, $J = 15.4$); 4.26 (d, 1H, $J = 14$); 4.52 (t, 1H, $J = 8.4$); 4.65 (d, 1H, $J = 14$); 5.09 (m, 2H); 7.43 (d, 1H, $J = 8.8$); 7.8–8.2 (s, OH). ^{13}C NMR δ: 18.1, 19.0, 21.1, 22.5, 31.1, 44.6, 52.7, 55.9, 66.5, 109.0, 141.2, 171.3, 171.6, 175.4. $[\alpha]_D = +5.6$ (c 0.5, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.35; H, 7.87; N, 9.95.

7.3.2. (2′*S*,2*S*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid, 9. It was obtained pure in 95% yield starting from **6**. ^{1}H NMR δ: 0.91 (d, 3H, $J = 6.6$); 0.98 (d, 3H, $J = 6.6$); 1.5 (s, 3H); 2.0 (s, 3H); 2.08 (m, 1H); 2.48 (d, 1H, $J = 14.6$); 3.03 (d, 1H, $J = 14.6$); 3.08–3.50 (s, OH); 4.33 (d, 1H, $J = 14$); 4.44–4.53 (m, 2H); 5.09 (m, 2H); 6.51 (d, 1H, $J = 9$). ^{13}C NMR δ: 18.9, 20.4, 22.7, 31.0, 44.9, 52.2, 55.9, 66.3, 109.4, 141.0, 171.0, 171.2, 176.3. $[\alpha]_D = -33.7$ (c 0.2, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.84; H, 7.82; N, 9.88.

7.3.3. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-4-methylene-pyrrolidine-2-carboxylic acid, 10. It was obtained in 90% yield starting from **7**. ^{1}H NMR δ: 0.97 (d, 6H, $J = 7$); 1.97 (s, 3H); 2.03 (m, 1H); 2.75–3.05 (m, 2H); 4.31 (d, 1H, $J = 14.4$); 4.5–4.7 (m, 3H); 5.12 (m, 2H); 5.36–5.68 (s, OH); 7.11 (d, 1H, $J = 9.2$). ^{13}C NMR δ: 17.9, 19.2, 22.2, 30.9, 35.2, 51.5, 55.7, 58.6, 109.1, 141.4, 171.5, 171.9, 173,3. The product was not isolated in sufficiently pure form to measure the specific rotation.

7.4. Activation of the carboxylic function

To a stirred solution of **8**, **9** or **10** (5 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, pyridine (1.2 mL, 15 mmol) was added followed by pentafluorophenyl trifluoroacetate (1.3 mL, 7.5 mmol). After removing from the cooling bath, the reaction was stirred at rt for about 10 h and monitored by TLC. When the reaction was complete, CH_2Cl_2 (10 mL) was added and the organic solution washed with water. The organic extract was then dried over $CaCl_2$ and evaporated to dryness in vacuo. The crude reaction product was purified by silica gel chromatography eluting with hexane/ethyl acetate and the product was obtained in good yield as a wax.

7.4.1. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid pentafluorophenyl ester, 11. It was obtained in 90% yield starting from **8**. ^{1}H NMR δ: 0.99 (d, 3H, $J = 6$); 1.03 (d, 3H, $J = 6$); 1.7 (s, 3H); 2.04 (s, 3H); 2.08 (m, 1H); 2.75 (d, 1H, $J = 15.6$); 3.18 (d, 1H, $J = 15.6$); 4.35 (d, 1H, $J = 13.8$); 4.62 (dd, 1H, $J = 7.5$, 9.3); 4.69 (d, 1H, $J = 13.8$); 5.19 (m, 2H); 6.14 (d, 1H, $J = 9.3$). ^{13}C NMR δ: 17.8, 19.0, 21.2, 22.8, 31.3, 44.1, 52.0, 55.3, 65.8, 109.7, 125 (m), 140 (m), 140.6, 168.7, 170.1, 170.7. $[\alpha]_D = -6.9$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}F_5N_2O_4$: C, 53.57; H, 4.72; N, 6.25. Found: C, 53.82; H, 4.71; N, 6.23.

7.4.2. (2′*S*,2*S*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid pentafluorophenyl ester, 12. It was obtained in 88% yield starting from **9**. ^{1}H NMR δ: 0.96 (d, 3H, $J = 6$); 1.03

(d, 3H, $J = 6$); 1.57 (s, 3H); 2.03 (s, 3H); 2.07 (m, 1H); 2.68 (d, 1H, $J = 15$); 3.17 (d, 1H, $J = 15$); 4.36–4.61 (m, 3H); 5.2 (m, 2H); 6.12 (d, 1H, $J = 8.4$). ^{13}C NMR δ: 18.3, 18.4, 20.2, 22.1, 30.5, 44.4, 51.5, 56.7, 65.5, 109.7, 125 (m), 139 (m); 140.6, 168.5, 170.6, 171.6. $[\alpha]_D = -38.7$ (c 0.4, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}F_5N_2O_4$: C, 53.57; H, 4.72; N, 6.25. Found: C, 53.48; H, 4.73; N, 6.24.

7.4.3. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-4-methylene-pyrrolidine-2-carboxylic acid pentafluorophenyl ester, 13. It was obtained in 85% yield starting from **10**. ^{1}H NMR δ: 0.97 (d, 3H, $J = 6.6$); 1.01 (d, 3H, $J = 6.6$); 2.0 (s, 3H); 2.04 (m, 1H); 2.9 (m, 1H); 3.17 (m, 1H); 4.34 (d, 1H, $J = 15.4$); 4.58 (d, 1H, $J = 15.4$); 4.65 (dd, 1H, $J = 7.4$, 8.8); 4.91 (dd, 1H, $J = 3.4$, 9.4); 5.18 (m, 2H); 6.31 (d, 1H, $J = 8.8$). ^{13}C NMR δ: 17.6, 18.8, 22.0, 30.6, 35.0, 51.0, 55.6, 57.9, 109.4, 140.7, 124.4 (m), 139 (m), 167.0, 170.3, 171.8. The product was not isolated in sufficiently pure form to measure the specific rotation.

7.5. Pseudopeptides 14a–c, 15a–c and 16a–c

To a stirred solution of activated esters **11**, **12** or **13** (0.6 mmol) in dry CH_2Cl_2 (6 mL) cyclohexylamine, benzylamine or L-valine methylester (0.12 mmol) was added under an inert atmosphere and the reaction monitored by TLC. After about 1 h CH_2Cl_2 (6 mL) was added and the organic solution washed with dilute HCl and then water. The organic extract was dried over $CaCl_2$ and evaporated to dryness in vacuo in a water bath at about 50 °C. The crude reaction product was purified by the silica gel chromatography eluting with hexane/ethyl acetate.

7.5.1. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid cyclohexylamide, 14a. It was obtained as an oil in 60% yield by reacting **11** with cyclohexylamine. ^{1}H NMR δ: 1.05 (d, 3H, $J = 6.9$); 1.07 (d, 3H, $J = 6.9$); 1.10–1.95 (m, 10H); 1.67 (s, 3H); 2.03 (m, 1H); 2.05 (s, 3H); 2.55 (d, 1H, $J = 15.6$); 2.96 (d, 1H, $J = 15.6$); 3.7 (m, 1H); 4.12 (dd, 1H, $J = 6.6$, 8.7); 4.26 (d, 1H, $J = 13.5$); 4.75 (d, 1H, $J = 13.5$); 5.09 (m, 2H); 6.07 (d, 1H, $J = 6.6$); 6.39 (d, 1H, $J = 8.4$). ^{13}C NMR δ: 18.5, 19.2, 21.6, 22.3, 24.7, 25.4, 29.9, 32.3, 46.4, 48.3, 53.1, 58.3, 68.2, 108.3, 140.9, 171.3, 171.7. $[\alpha]_D = +6.9$ (c 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{33}N_3O_3$: C, 66.08; H, 9.15; N, 11.56. Found: C, 65.85; H, 9.17; N, 11.6.

7.5.2. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid benzylamide, 14b. It was obtained as an oil in 63% yield by reacting **11** with benzylamine. ^{1}H NMR δ: 1.02 (d, 3H, $J = 7$); 1.03 (d, 3H, $J = 7$); 1.67 (s, 3H); 1.76 (s, 3H); 2.05 (m, 1H); 2.62 (d, 1H, $J = 15.8$); 3.03 (d, 1H, $J = 15.8$); 4.06 (dd, 1H, $J = 7$, 9.2); 4.24 (dd, 1H, $J = 4.8$, 15); 4.31 (d, 1H, $J = 14.6$); 4.60 (dd, 1H, $J = 7$, 15); 4.76 (d, 1H, $J = 14.6$); 5.07 (m, 2H); 6.07 (d, 1H, $J = 4.8$); 7.09 (m, 1H); 7.28 (m, 5ArH). ^{13}C NMR δ: 18.8, 19.1, 22.1, 22.2, 30.3, 43.4, 46.4, 53.3, 58.2, 68.6, 108.8, 126.8, 127.4, 128.2, 138.8, 140.8, 171.4, 172.0, 173.0. $[\alpha]_D = +4.9$ (c 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{29}N_3O_3$: C, 67.9; H, 7.87; N, 11.31. Found: C, 68.2; H, 7.84; N, 11.27.

7.5.3. (2*S*,2′*S*,2″*R*)-2-{[1-(2′-Acetylamino-3′-methyl-butyryl)-2″-methyl-4″-methylene-pyrrolidine-2″-carbonyl]-amino}-3-methyl-butyric acid methyl ester, 14c. It was obtained as an oil in 60% yield by reacting **11** with L-valine methylester. ^{1}H NMR δ: 0.9 (d, 3H, $J = 6.6$); 0.97 (d, 3H, $J = 6.6$); 1.03 (d, 6H, $J = 6.6$); 1.71 (s, 3H); 1.99 (s, 3H); 2.07 (m, 1H); 2.15 (m, 1H); 2.52 (d, 1H, $J = 15.9$); 3.10 (d, 1H, $J = 15.9$); 3.69 (s, 3H); 4.32 (d, 1H, $J = 13.8$); 4.35 (t, 1H, $J = 8.1$); 4.46 (dd, 1H, $J = 5.1$, 8.4); 4.61 (d, 1H, $J = 13.8$); 5.07 (m, 2H); 6.16 (d, 1H, $J = 6.9$); 7.0 (d, 1H, $J = 8.7$). ^{13}C NMR δ: 17.7, 18.5, 18.7, 21.5, 22.4, 30.3, 45.3, 51.6, 52.9, 57.1, 57.5, 68.0, 108.6, 140.5, 170.7, 171.2, 172.0, 172.7. $[\alpha]_D = +3.7$ (c 0.9, $CHCl_3$). Anal. Calcd for $C_{20}H_{33}N_3O_5$: C, 60.74; H, 8.41; N, 10.62. Found: C, 61.02; H, 8.39; N, 10.6.

7.5.4. (2′*S*,2*S*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid cyclohexylamide, 15a. It was obtained pure as a solid in 62% yield by reacting **12** with cyclohexylamine. ^{1}H NMR δ: 0.98 (d, 3H, $J = 6.9$); 1.04 (d, 3H, $J = 6.9$); 1.10–1.98 (m, 10H); 1.6 (s, 3H); 2.03 (s, 3H); 2.05 (m, 1H); 2.42 (d, 1H, $J = 15$); 3.2 (d, 1H, $J = 15$); 3.75 (m, 1H); 4.3 (d, 1H, $J = 13$); 4.5 (d, 1H, $J = 13$); 4.58 (dd, 1H, $J = 6.6$, 8.7); 5.1 (m, 2H); 6.08 (d, 1H, $J = 8.4$); 6.4 (d, 1H, $J = 7.8$). ^{13}C NMR δ: 17.9, 19.3, 21.4, 22.8, 24.6, 25.4, 30.9, 32.69, 32.72, 44.9, 48.2, 52.8, 56.1, 68.2, 108.5, 141.1, 170.1, 171.5, 171.6. $[\alpha]_D = -59.7$ (c 0.3, $CHCl_3$). Mp 167.5–168.5 °C. Anal. Calcd for $C_{20}H_{33}N_3O_3$: C, 66.08; H, 9.15; N, 11.56. Found: C, 66.15; H, 9.12; N, 11.53.

7.5.5. (2′*S*,2*S*)-1-(2′-Acetylamino-3′-methyl-butyryl)-2-methyl-4-methylene-pyrrolidine-2-carboxylic acid benzylamide, 15b. It was obtained pure as an oil in 60% yield by reacting **12** with benzylamine. ^{1}H NMR δ: 0.89 (d, 3H, $J = 6.9$); 0.96 (d, 3H, $J = 6.9$); 1.63 (s, 3H); 2.01 (m, 1H); 2.05 (s, 3H); 2.47 (dd, 1H, $J = 1.5$, 15.9); 3.23 (d, 1H, $J = 15.9$); 4.32 (d, 1H, $J = 13.8$); 4.52 (m, 4H); 5.01 (m, 2H); 6.23 (d, 1H, $J = 8.7$); 6.72 (t, 1H, $J = 5.1$); 7.33 (m, 5H). ^{13}C NMR δ: 17.7, 19.1, 21.1, 22.8, 30.8, 43.7, 45.0, 52.7, 56.0, 67.9, 108.7, 127.2, 127.5, 128.4, 138.0, 141.0, 170.1, 171.4, 172.5. $[\alpha]_D = -39.6$ (c 0.6, $CHCl_3$). Mp 158.5–159.5 °C. Anal. Calcd for $C_{21}H_{29}N_3O_3$: C, 67.9; H, 7.87; N, 11.31. Found: C, 67.79; H, 7.89; N, 11.34.

7.5.6. (2*S*,2′*S*,2″*S*)-2-{[1-(2′-Acetylamino-3′-methyl-butyryl)-2″-methyl-4″-methylene-pyrrolidine-2″-carbonyl]-amino}-3-methyl-butyric acid methyl ester, 15c. It was obtained pure as an oil in 65% yield by reacting **12** with L-valine methylester. ^{1}H NMR δ: 0.92 (d, 3H, $J = 6.9$); 0.94 (d, 3H, $J = 6.9$); 0.96 (d, 3H, $J = 6.9$); 1.03 (d, 9H, $J = 6.9$); 1.66 (s, 3H); 2.03 (s, 3H); 2.08 (m, 1H); 2.18 (m, 1H); 2.45 (d, 1H, $J = 15$); 3.18 (d, 1H, $J = 15$); 3.72 (s, 3H); 4.30 (d, 1H, $J = 13$); 4.56 (m, 3H); 5.06 (m, 2H); 6.24 (d, 1H, $J = 9.2$); 6.96 (d, 1H, $J = 8.4$). ^{13}C NMR δ: 17.6, 17.8, 18.9, 19.5, 21.5, 23.2,

31.1, 31.3, 45.1, 52.0, 52.9, 55.8, 57.5, 68.2, 108.8, 141.1, 170.0, 171.3, 172.3, 172.6. $[\alpha]_D = -54.4$ (c 0.6, $CHCl_3$). Anal. Calcd for $C_{20}H_{33}N_3O_5$: C, 60.74; H, 8.41; N, 10.62. Found: C, 60.55; H, 8.43; N, 10.65.

7.5.7. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-4-methylene-pyrrolidine-2-carboxylic acid cyclohexylamide, 16a. It was obtained pure as a wax in 60% yield by reacting **13** with cyclohexylamine. ^{1}H NMR δ: 0.96 (d, 3H, $J = 6.9$); 1.01 (d, 3H, $J = 6.9$); 1.16–1.95 (m, 10H); 2.04 (s, 3H); 2.01 (m, 1H); 2.7–3.0 (m, 2H); 3.68 (m, 1H); 4.17 (dd, 1H, $J = 7.2$, 9); 4.3 (d, 1H, $J = 14.4$); 4.6 (d, 1H, $J = 14.4$); 4.75 (dd, 1H, $J = 1.8$, 8.4); 5.14 (m, 2H); 6.5 (d, 1H, $J = 6.6$); 6.5 (d, 1H, $J = 8.1$). ^{13}C NMR δ: 18.9, 19.1, 22.7, 24.9, 25.5, 29.9, 32.5, 32.7, 36.0, 48.3, 51.3, 57.8, 60.1, 108.9, 142.1, 169.3, 171.5, 171.7. $[\alpha]_D = +53.2$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{19}H_{31}N_3O_3$: C, 65.3; H, 8.94; N, 12.02. Found: C, 65.58; H, 8.92; N, 11.98.

7.5.8. (2′*S*,2*R*)-1-(2′-Acetylamino-3′-methyl-butyryl)-4-methylene-pyrrolidine-2-carboxylic acid benzylamide, 16b. It was obtained pure as an oil in 65% yield by reacting **13** with benzylamine. ^{1}H NMR δ: 1.02 (d, 3H, $J = 7$); 1.04 (d, 3H, $J = 7$); 1.68 (s, 3H); 2.03 (m, 1H); 2.75–3.05 (m, 2H); 4.13 (dd, 1H, $J = 6.2$, 9.2); 4.20–4.34 (m, 2H); 4.6 (m, 2H); 4.87 (dd, 1H, $J = 3.6$, 6.8); 5.14 (m, 2H); 6.46 (d, 1H, $J = 6.2$); 7.3 (m, 5ArH); 7.39 (t, 1H, $J = 5.6$). ^{13}C NMR δ: 18.9, 21.9, 29.7, 36.0, 43.1, 51.4, 58.2, 60.3, 109.6, 126.9, 127.1, 128.2, 137.9, 141.4, 171.0, 172.0, 172.7. $[\alpha]_D = +50.1$ (*c* 1.8, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}N_3O_3$: C, 67.2; H, 7.61; N, 11.76. Found: C, 67.53; H, 7.59; N, 11.73.

7.5.9. (2*S*,2′*S*,2″*R*)-2-{[1-(2′-Acetylamino-3′-methyl-butyryl)-4″-methylene-pyrrolidine-2″-carbonyl]-amino}-3-methyl-butyric acid methyl ester, 16c. It was obtained pure as an oil in 60% yield by reacting **13** with L-valine methylester. ^{1}H NMR δ: 0.89 (d, 3H, $J = 6.9$); 0.96 (d, 3H, $J = 6.9$); 1.00 (d, 3H, $J = 6.9$); 1.02 (d, 3H, $J = 6.9$); 2.03 (s, 3H); 2.17 (m, 2H); 2.70 (m, 1H); 3.12 (d, 1H, $J = 15$); 3.69 (s, 3H); 4.31 (s, 2H); 4.47 (m, 2H); 4.91 (d, 1H, $J = 9$); 5.12 (m, 2H); 6.47 (d, 1H, $J = 8.4$); 7.44 (d, 1H, $J = 8.7$). ^{13}C NMR δ: 17.7, 18.3, 19.1, 19.4, 22.8, 30.5, 30.6, 33.6, 51.1, 51.9, 56.5, 57.4, 59.1, 108.8, 142.3, 170.4, 171.7, 172.4. $[\alpha]_D = +8.7$ (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{19}H_{31}N_3O_5$: C, 59.82; H, 8.19; N, 11.02. Found: C, 59.93; H, 8.17; N, 10.98.

7.6. Crystallographic data of 15a

Single crystal X-ray diffraction data: $C_{20}H_{33}N_3O_3$, Fw 363.49, colourless parallelepiped, size: $0.45 \times 0.32 \times 0.25$ mm, Orthorhombic, space group $P2_12_12_1$, $a = 11.1449(8)$ Å, $b = 11.5597(9)$ Å, $c = 17.0747(13)$ Å, $V = 2199.8(3)$ Å^3, theta range for data collection 2.13–26.08°, $Z = 4$, $F(000) = 792$, $D_x = 1.098$ Mg/m^3, $\mu = 0.074$ mm^{-1}, data collected on a Bruker APEX II CCD diffractometer (Mo-Kα radiation, $\lambda = 0.71073$ Å) at 293(2) K, total of 17,225 reflections, of which 4358 unique [$R_{(int)} = 0.0211$]. Empirical absorption correction was applied, initial structure model by direct methods. Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms yielded $R_1 = 0.0427$ and $wR_2 = 0.1271$ for [$I > 2\sigma(I)$] and $R_1 = 0.0535$ and $wR_2 = 0.1337$ for all intensity data. All hydrogen atoms were added in calculated position except the amidic hydrogens that were located in the Fourier map. Goodness-of-fit = 1.085. CCDC number is 278479.

7.7. Crystallographic data of 15b

Single crystal X-ray diffraction data: $C_{21}H_{29}N_3O_3$, Fw 371.47, colourless parallelepiped, size: $0.50 \times 0.30 \times 0.20$ mm, Orthorhombic, space group $P2_12_12_1$, $a = 10.6448(7)$ Å, $b = 11.8037(8)$ Å, $c = 16.9260(11)$ Å, $V = 2126.7(2)$ Å^3, theta range for data collection 2.10–28.65°, $Z = 4$, $F(000) = 800$, $D_x = 1.160$ Mg/m^3, $\mu = 0.078$ mm^{-1}, data collected on a Bruker APEX II CCD diffractometer (Mo-Kα radiation, $\lambda = 0.71073$ Å) at 100(2) K, total of 17,283 reflections, of which 5008 unique [$R_{(int)} = 0.0196$]. Empirical absorption correction was applied, initial structure model by direct methods. Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms yielded $R_1 = 0.0315$ and $wR_2 = 0.0825$ for [$I > 2\sigma(I)$] and $R_1 = 0.0342$ and $wR_2 = 0.0838$ for all intensity data. All hydrogen atoms were added in calculated position except the amidic hydrogens that were located in the Fourier map. Goodness-of-fit = 1.052. CCDC number is 278478.

7.8. Computational method

All the calculations were performed using the Macro-Model Version 5.5[9] package. The initial structure of each compound was energy minimized with the MMFF[8] force field by means of the Conjugate Gradient algorithm using a derivative convergence of 0.1 kJ/(Å mol), along with the GB/SA[10] continuum solvation model for chloroform. Conformational searches were carried out using internal coordinate Metropolis Monte Carlo simulations at the reference temperature of 300 K. For each compound a total of 15000 conformations were sampled, and then they were energy minimized according to the above mentioned criteria. All of the conformations within about 50 kJ/mol above the global minimum were kept.

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