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Stereoselective reductive amination of chiral *trans*-3-acetyl-4-alkylpyrrolidin-2-ones

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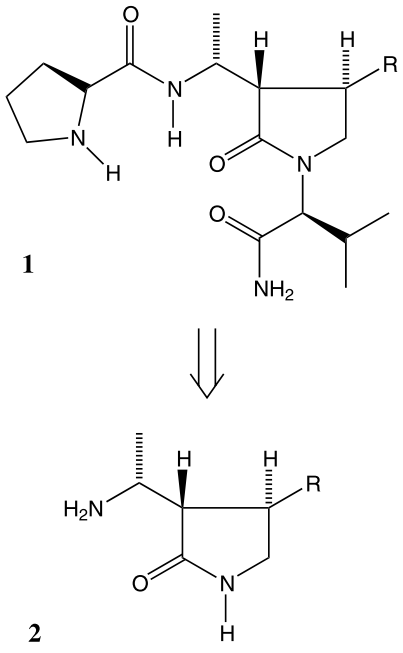
Abstract—*trans*-3-Acetyl-4-alkyl pyrrolidin-2-ones **5a**,**b** and **8a**,**b** undergo reductive amination with $NaBH_3(CN)$ in CH_3OH in the presence of CH_3COONH_4. By acylation of the reaction product the corresponding 3-acylaminoethylpyrrolidin-2-ones **9a**–**c** and **10a**,**b** were obtained with total stereoselection. The configuration of the newly formed stereogenic centre at C-1″ of the acylaminoethyl chain was assigned on the basis of ^1H NMR data supported by both molecular mechanics and quantomechanical calculations.

1. Introduction

Lactams can be considered as a useful type of conformational constraint in peptide backbones and their incorporation into pharmacologically important peptides may provide useful information regarding the bioactive conformation and enhance biological potency and/or increase metabolic stability with respect to unmodified original peptides.[1–3] Thus, a number of lactam-bridged dipeptides as conformationally constrained mimics of peptide derivatives was devised and general synthetic methodologies leading to five-membered lactam-bridged dipeptides were developed. Herein we describe preliminary results concerning a novel approach to the synthesis of mimics containing the β-aminobutyric acid moiety. In fact, a mimic containing a β-lactam ring has already reported and was found able to stabilize β-turns.[4] However, owing to the low stability of a β-lactam ring under physiological conditions, we considered a mimetic containing a more stable γ-lactam ring such as **1**, and preliminary calculations carried out on this structure showed it should induce the formation of β-turns.[5] Moreover, calculations suggested that the substituent at C-4 is non-influential in terms of conformational restrictions.[5] Therefore, an efficient stereoselective approach to a γ-lactam bearing at C-3 an aminoethyl chain such as **2** was required, in order to carry out the total synthesis of peptidomimetic **1**, and we identified pyrrolidin-2-ones **3** and **4** as attractive molecular scaffolds (Scheme 1).



Scheme 1.

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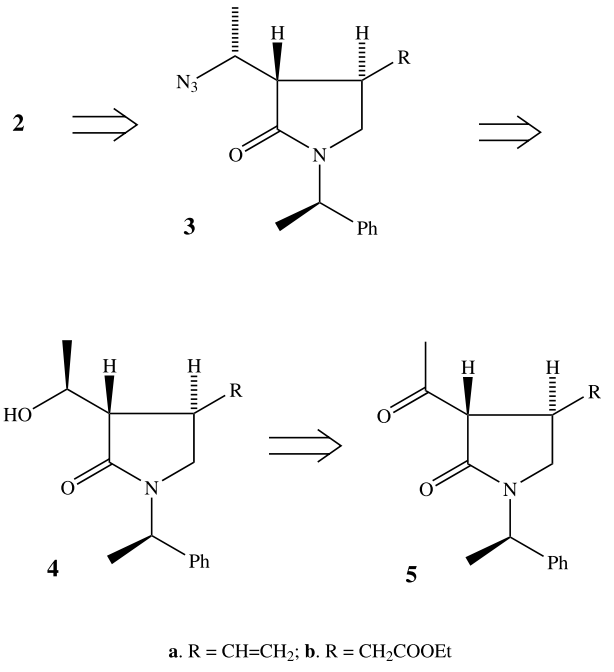
2. Results and discussion

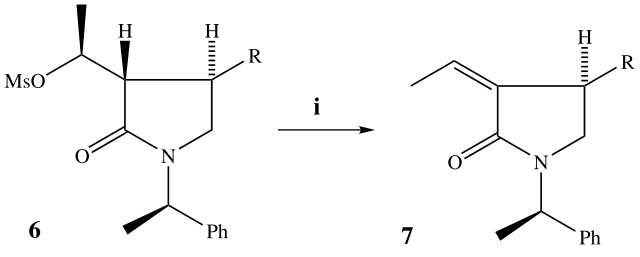
Our group recently developed new methods for the synthesis of these compounds, involving both cyclisation of chiral acyclic amides induced by Mn(III) and conjugate addition.[6] With pyrrolidin-2-ones **5a**,**b** in hand we first prepared the 3-hydroxyethyl derivatives **4** as previously reported, in order to convert these compounds into the corresponding 3-azidoethyl derivatives, **3**, which could be useful precursors for the introduction of a nitrogen atom on the C-3 chain[7] (Scheme 2).



a. R = CH=CH$_2$; **b**. R = CH$_2$COOEt

Scheme 2.

However, when the methanesulphonyl derivative **6**, obtained from **4a**, was treated with sodium azide in DMF or DMSO for 10 h at 80°C, the starting material was largely recovered, together with minor amounts of the elimination product, **7** (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) NaN_3, DMF, 70°C, 10 h, **a**, R = CH=CH$_2$, 35%. **b**, R = CH$_2$COOEt, 41%.

Next, a reductive amination reaction[8] was considered in order to achieve the synthesis of **2**, and compounds **5a**,**b** and **8a**,**b** were used as substrates: Treatment with $NaBH_3(CN)$ and CH_3COONH_4 in CH_3OH at −15°C, in the presence of molecular sieves 4 Å, converted these compounds into the corresponding 3-aminoethyl derivatives which without isolation were directly acylated with acetyl chloride or di-*t*-butoxycarbonyl anhydride. Thus the corresponding acylamino derivatives **9a**,**c** and **10a**,**b**, isolated after silica gel chromatography, were obtained in good yield and total diastereoselection (Scheme 4). In fact, only one isomer was invariably observed, as evidenced by the analysis of the ^{1}H NMR spectra of the crude products. In addition, it is worth mentioning that neither yields and diastereoselectivities were affected even on changing the substitution pattern on the pyrrolidin-2-one ring.

The configuration of the newly formed stereogenic centre of compounds **9a**,**c** and **10a**,**b** was assigned by means of ^{1}H NMR data supported by both molecular mechanics and quantomechanical calculations.

In fact, the conformational space of the intermediate imine **A** leading to **9a** was fully explored by means of a Monte Carlo search[9–11] which suggested that a hydrogen bond constrains both the imino and the lactam carbonyl group to lie *syn* to each other, whereas the conformers **B** and **C** are disfavoured over the *syn* one by 2.12 kcal/mol and 2.58 kcal/mol, respectively (Fig. 1). Examination of molecular models revealed that a hydrogen bond generates a severe crowding of the *re* face of the carbonyl, thus preventing hydride attack from this face.[12,13]

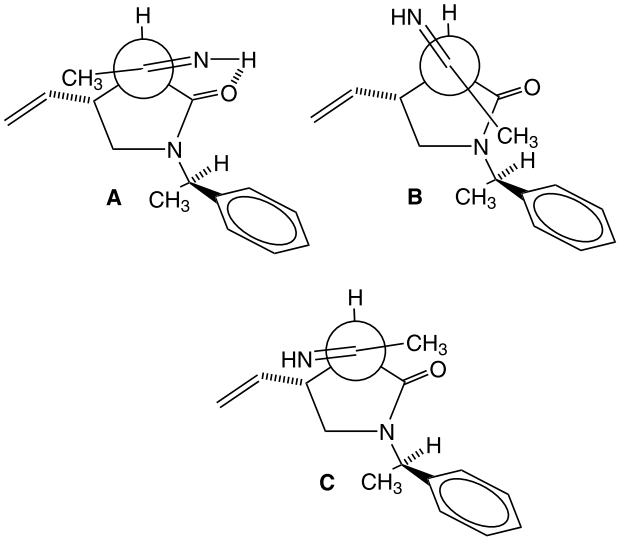
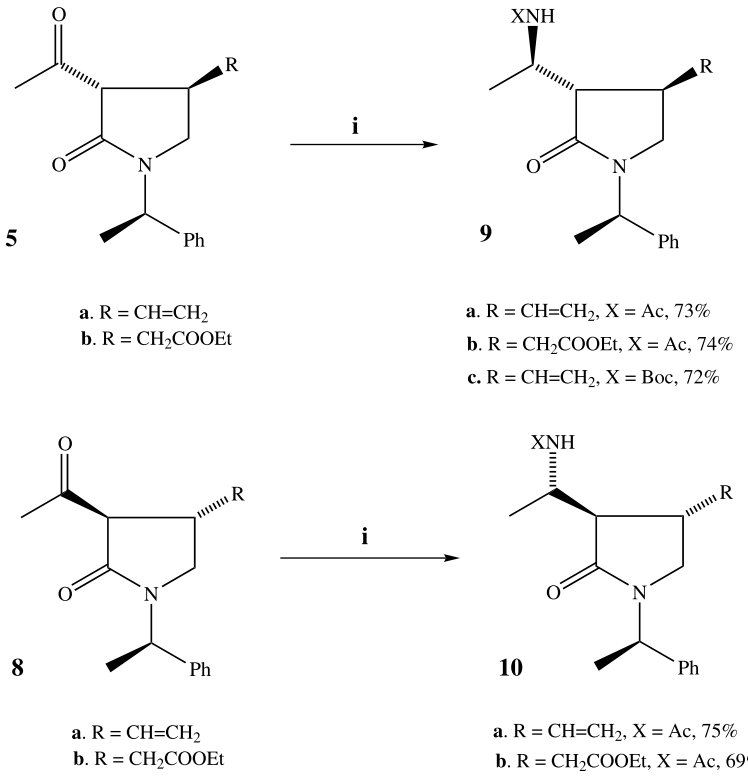


Figure 1. Calculated conformations in $CHCl_3$ for the intermediate imine.

In order to obtain further insight, calculations were carried out also by the implicit solvation GB/SA model in water,[14] in order to better mimic the solvent effect. In the minimum energy conformation, **D**, H-bonding occurs between the iminic nitrogen and carbonyl groups (Fig. 2).[15] Although conformations **E** and **F** are also present within 2.0 kcal/mol, the attack to the *re* face of the intermediate imine is strongly hindered by the phenyl group, so that they can be considered non-influential for stereoselection, and attack can occur at the *si* face, exclusively.



Scheme 4. *Reagents and conditions*. (i) **a**. $NaBH_3(CN)$, CH_3COONH_4, CH_3OH, −15°C, MS 4 Å, 12 h. **b**. CH_3COCl, Et_3N, cat. DMAP, DCM, 0°C for compounds **9a**,**b** and **10a**,**b**; Boc_2O, cat. DMAP, DCM, 0°C for compound **9c**.

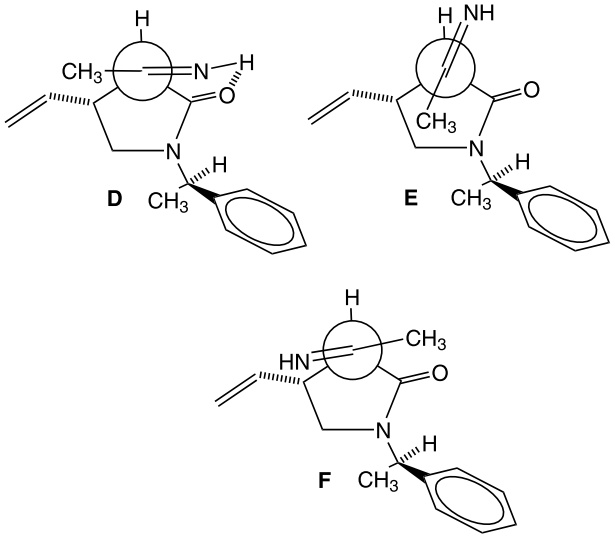
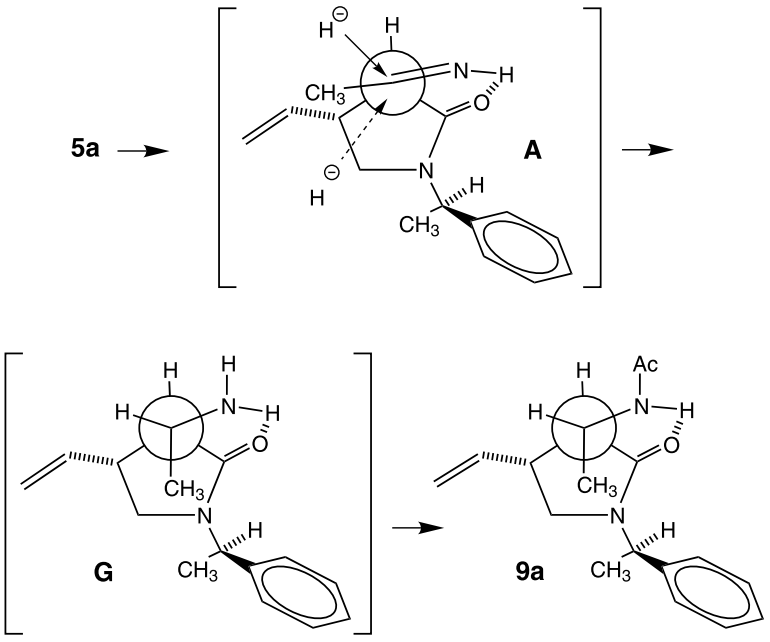


Figure 2. Calculated conformations in water for the intermediate imine.

Thus, hydride ion approaches the imino group from the less hindered *si*-face, to give the intermediate amine **G**, in which the new stereogenic centre 1″ has the *R* configuration (Scheme 5). In this case the attack onto the *re*-face of the imino group, proceeding from the concave site of the concave/convex-shaped molecule **A**, is prevented by a severe steric interaction and the corresponding product is not observed in the reaction mixture. As a consequence, the amino derivative **G** is exclusively formed and directly converted into the corresponding acetylamino derivative **9a**.

The proposed reductive amination outcome was supported by ^{1}H NMR data. In fact, in the minimum energy conformation of compound **9a**, H-3 and H-1″ lie gauche [dihedral angle (H-3)–(C-3)–(C-1″)–(H-1″) = 62.5° and d(H···O) = 2.047 Å], and this result is in agreement with the observed coupling constant value (2.1 Hz). The higher energy conformer lies at 2.34 kcal/mol, so that for compound **9a** only the gauche conformation depicted in Scheme 5 is significant. The same trend was observed even for compounds **9b**,**c** and **10a**,**b**, respectively (Scheme 4). Thus, on the basis of ^{1}H NMR data, the configuration of the newly introduced stereogenic centre at C-1″ for compounds **9a**–**c** was assigned as *R*. The opposite configuration *S* was assigned to the C-1″ of compounds **10a**,**b**, depending on the opposite configuration at C-3 in the starting **8a**,**b**. To validate further both the calculated data and structures, ^{1}H NMR chemical shift values were simulated for the B3LYP/6-31G*[16,17] optimised structure of compound **9a** in the lowest energy conformation and compared with those observed in $CDCl_3$ solution. The calculated chemical shifts were in good agreement with the experimental data, thus validating the structural assignment.[18]

In summary, the effective reductive amination leading to 3-aminoethyl pyrrolidin-2-ones **9** and **10** with good yields and complete diastereoselection represents a significant tool towards the synthesis of conformationally



Scheme 5.

restricted dipeptides. Successful work in this area is already in progress in our laboratory and full experimental details will be reported in due course.

3. Experimental

3.1. General methods and materials

^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ on a Varian Gemini 200 spectrometer. Chemical shifts are reported in the δ scale and coupling constants (J) values are given in Hz. Infrared spectra were recorded on a Nicolet 20-SX FT-IR spectrophotometer in $CHCl_3$. Diastereomeric purity was determined by GLC analysis by using a Chrompack 9001 gas-chromatograph equipped with a capillary column Chrompack 7720 (50 m×0.25 mm i.d.; stationary phase CP-Sil-5 CB). Optical rotation measurements were recorded at room temperature on a Perkin–Elmer Model 241 polarimeter at the sodium D line (concentration in g/100 mL). MS analyses were carried out on a Hewlett–Packard spectrometer model 5890, series II, Column chromatography was performed using Kieselgel 60 Merck (230–400 mesh ASTM). Compounds **6a**,**b** were prepared according to Ref. 7.

3.2. General procedure leading to compounds 7a,b

A solution of mesylate **6** (5 mmol) in DMF (15 mL) containing NaN_3 (1.0 g; 15 mmol) was stirred at 70°C for 10 h. Then the mixture was poured in water (50 mL) and extracted with ethyl acetate (2×50 mL). After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50) to give, besides starting material **6**, the elimination products **7**.

3.2.1. (*Z*,4*R*,1′*R*)-4-Etenyl-2-ethylene-1-(1′-phenylethyl) pyrrolidin-2-one 7a. Starting from **6a**, the title compound was obtained in 35% yield. Colorless oil. ^{1}H NMR ($CDCl_3$): 1.53 (d, 3H, $J=7.2$), 2.23 (dd, 3H, $J=7.3$, $J=2.4$), 3.02 (dd, 1H, $J=6.4$, $J=9.5$), 3.13 (dd, 1H, $J=9.4$, $J=9.5$), 3.20–3.34 (m, 1H), 5.02–5.20 (m, 2H), 5.58 (q, 1H, $J=7.2$), 5.66 (ddd, 1H, $J=6.5$, $J=8.3$, $J=14.7$), 5.86 (dq, 1H, $J=7.3$, $J=2.4$), 7.21–7.38 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): 13.1, 15.8, 42.3, 45.2, 48.6, 116.9, 127.0, 127.1, 127.3, 128.4, 132.9, 133.3, 138.0, 140.2, 167.7; $[\alpha]_D^{20}=+188.1$ (c 4.6, $CHCl_3$); MS (EI): m/z 241 (M^+), 226, 136, 105, 91, 79, 77. Anal. calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.60; H, 7.91; N, 5.82.

3.2.2. (*Z*,4*R*,1′*R*)-4-Ethoxycarbonylmethyl-2-ethylene-1-(1′-phenylethyl)pyrrolidin-2-one 7b. Starting from **6b**, the title compound was obtained in 41% yield. Colorless oil. ^{1}H NMR ($CDCl_3$): 1.23 (t, 3H, $J=7.2$), 1.63 (d, 3H, $J=7.2$), 2.19 (dd, 3H, $J=7.3$, $J=1.9$), 2.34 (dd, 1H, $J=8.9$, $J=16.2$), 2.54 (dd, 1H, $J=4.8$, $J=16.2$), 2.95 (dd, 1H, $J=3.9$, $J=8.7$), 2.98–3.08 (m, 1H), 3.17 (dd, 1H, $J=7.5$, $J=8.7$), 4.08 (q, 2H, $J=7.2$), 5.54 (q, 1H, $J=7.2$), 5.89 (dq, 1H, $J=7.3$, $J=1.9$), 7.19–7.35 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): 13.8, 14.7, 16.5, 33.8, 40.2, 46.0, 49.1, 61.1, 127.7, 127.9, 129.0, 132.7, 134.1, 140.5, 168.0, 172.1. $[\alpha]_D^{20}=+74.3$ (c 4.2, $CHCl_3$); MS (EI): m/z 301 (M^+), 286, 136, 105, 91, 77. Anal. calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.75; H, 7.66; N, 4.62.

3.3. General procedure for reductive amination

A solution containing compounds **5** or **9** (10 mmol), ammonium acetate (7.7 g; 100 mmol) and $NaBH_3CN$ (0.33 g; 7 mmol) in absolute ethanol (30 mL) was stirred at −15°C for 12 h. Then 6 M HCl (2 mL) was

added, ethanol was removed under reduced pressure and H_2O (10 mL) was added to the residue. The pH was adjusted to 10 by addition of 2 M NaOH and the mixture was extracted with ethyl acetate (3×150 mL). After drying (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was dissolved in DCM (30 mL) containing triethylamine (1.0 mL) and DMAP (0.2 g). Then a solution of acetyl chloride (1 mL) in DCM (10 mL) was added dropwise at 0°C and the mixture was stirred for 2 h. The mixture was poured in H_2O (100 mL) and extracted with ethyl acetate (3×100 mL). After drying (Na_2SO_4) and removal of organics, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 20:80).

3.3.1. (3*S*,4*R*,1′*R*,1″*R*)-3-(1″-Acetylaminoeth-1″-yl)-4-ethenyl-1-(1′-phenylethyl)pyrrolidin-2-one 9a. Starting from **5a**, the title product was obtained in 73%. Colorless oil. IR ($CHCl_3$): 3345, 1668, 1665, 904 cm^{-1}; ^1H NMR ($CDCl_3$): 1.40 (d, 3H, $J=7.1$), 1.50 (d, 3H, $J=7.2$), 1.90 (s, H), 2.39 (dd, 1H, $J=2.1$, $J=10.2$), 2.51–2.75 (m, 1H), 2.97–3.06 (m, 2H), 4.31 (ddq, 1H, $J=2.1$, $J=7.1$, $J=9.5$), 5.09–5.29 (m, 2H), 5.45 (q, 1H, $J=7.2$), 5.72 (ddd, 1H, $J=8.1$, $J=10.1$, $J=18.1$), 5.93 (d, 1H, NH, $J=9.5$), 7.19–7.38 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): 16.6, 20.4, 23.7, 41.1, 43.9, 46.1, 49.1, 53.3, 118.3, 127.0, 127.9, 137.5, 140.6, 170.4, 173.5; $[\alpha]_D^{20}=+91.4$ (*c* 0.5, $CHCl_3$). MS (EI): *m*/*z* 300 (M^+), 285, 105, 91, 77. Anal. calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.94; H, 8.09; N, 9.29.

3.3.2. Ethyl (3*S*,4*R*,1′*R*,1″*R*)-3-(1″-acetylaminoeth-1″-yl)-1-(1′-phenylethyl)-2-oxopyrrolidin-4-yl]acetate 9b. Starting from **5b**, the title product was obtained in 74% yield. Colorless oil. IR ($CHCl_3$): 3347, 1741, 1671, 1667 cm^{-1}; ^1H NMR ($CDCl_3$): 1.24 (t, 3H, $J=7.2$), 1.36 (d, 3H, $J=6.9$), 1.50 (d, 3H, $J=7.0$), 1.88 (s, 3H), 2.31–2.48 (m, 3H), 2.51–2.72 (m, 1H), 2.98 (dd, 1H, $J=5.8$, $J=9.4$), 3.22 (dd, 1H, $J=7.5$, $J=9.4$), 4.12 (q, 2H, $J=7.2$), 4.29 (ddq, 1H, $J=1.7$, $J=6.9$, $J=9.0$), 5.47 (q, 1H, $J=7.0$), 5.93 (d, 1H, NH, $J=9.0$), 7.21–7.42 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): 14.6, 16.7, 20.0, 23.7, 32.3, 38.1, 45.0, 46.8, 49.4, 53.2, 61.2, 127.1, 127.2, 128.1, 129.1, 140.5, 146.7, 170.4, 172.2, 173.3; $[\alpha]_D^{20}=+81.4$ (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 360 (M^+), 345, 105, 91, 77. Anal. calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.59; H, 7.85; N, 7.74.

3.3.3. (3*S*,4*R*,1′*R*,1″*R*) 3-(1″-*t*-Butoxycarbonylaminoeth-1″-yl)-4-ethenyl-1-(1′-phenylethyl)pyrrolidin-2-one 9c. Starting from **5b**, the title product was obtained in 72% yield. Low melting solid. IR ($CHCl_3$): 3345, 1743, 1711, 1670, 1665, 904 cm^{-1}; ^1H NMR ($CDCl_3$): 1.30 (d, 3H, $J=6.7$), 1.37 (s, 9H), 1.45 (d, 3H, $J=7.1$), 2.32 (dd, 1H, $J=2.2$, $J=9.6$), 2.64 (dd, 1H, $J=8.8$, $J=9.2$), 2.67–2.88 (m, 1H), 3.33 (dd, 1H, $J=7.6$, $J=9.2$), 3.98 (ddq, 1H, $J=2.2$, $J=6.7$, $J=9.5$), 4.86 (d, 1H, NH, $J=9.6$), 5.04–5.27 (m, 2H), 5.48 (q, 1H, $J=7.1$), 5.65 (ddd, 1H, $J=7.8$, $J=10.1$, $J=17.1$), 7.20–7.39 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): 16.6, 20.0, 28.6, 40.5, 45.6, 46.0, 49.3, 53.3, 79.0, 117.4, 127.4, 127.7, 127.9, 128.9, 138.0, 140.1, 155.9, 173.1; $[\alpha]_D^{20}=+74.4$ (*c* 0.5, $CHCl_3$); MS (EI): *m*/*z* 358 (M^+), 343, 105, 91, 77, 57. Anal. calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C. 70.33; H, 8.41; N, 7.85.

3.3.4. (3*R*,4*S*,1′*R*,1″*S*)-3-(1″-Acetylaminoeth-1″-yl)-4-ethenyl-1-(1′-phenylethyl)pyrrolidin-2-one 10a. Starting from **9a**, the title product was obtained in 75% yield. Colorless oil. IR ($CHCl_3$): 3345, 1669, 1665, 903 cm^{-1}; ^1H NMR: 1.35 (d, 3H, $J=7.0$), 1.48 (d, 3H, $J=7.1$), 1.93 (s, 3H), 2.29 (dd, 1H, $J=2.5$, $J=10.0$), 2.51–2.79 (m, 2H), 3.28 (dd, 1H, $J=7.2$, $J=8.8$), 4.27 (ddq, 1H, $J=2.5$, $J=7.0$, $J=9.2$), 5.00–5.25 (m, 2H), 5.41 (q, 1H, $J=7.1$), 5.58 (ddd, 1H, $J=7.9$, $J=10.1$, $J=17.1$), 6.08 (d, 1H, NH, $J=9.2$), 7.18–7.35 (m, 5 ArH); ^{13}C NMR: 16.9, 20.6, 23.9, 41.3, 43.9, 46.2, 49.6, 53.4, 118.4, 127.5, 128.1, 128.2, 128.4, 129.1, 137.5, 140.0, 170.4, 173.5; $[\alpha]_D^{20}=+98.3$ (*c* 0.4, $CHCl_3$). MS (EI): *m*/*z* 300 (M^+), 285, 105, 91. 77. Anal. calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.89; H, 7.98; N, 9.38.

3.3.5. Ethyl (3*R*,4*S*,1′*R*,1″*S*)-3-(1″-acetylaminoeth-1″-yl)-1-(1′-phenylethyl)-2-oxopyrrolidin-4-yl]acetate 10b. Starting from **9b**, the title product was obtained in 69%. Colorless oil. IR ($CHCl_3$): 3345, 1743, 1669, 1665 cm^{-1}; ^1H NMR ($CDCl_3$): 1.16 (t, 3H, $J=7.1$), 1.29 (d, 3H, $J=6.9$), 1.47 (d, 3H, $J=7.2$), 1.93 (s, 3H), 2.15–2.34 (m, 2H), 2.36–2.58 (m, 2H), 3.39–3.57 (m, 1H), 4.04 (q, 2H, $J=7.1$), 4.27 (ddq, 1H, $J=3.1$, $J=6.9$, $J=8.6$), 4.34 (q, 2H, $J=7.2$), 6.37 (d, 1H, NH, $J=8.6$), 7.17–7.35 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): 14.5, 16.6, 18.7, 23.7, 31.2, 38.5, 45.2, 46.9, 49.5, 53.2, 61.2, 127.4, 128.1, 129.0, 140.0, 170.6, 172.4, 173.3; $[\alpha]_D^{20}=+76.5$ (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 360 (M^+), 345, 105, 91. 77. Anal. calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.61; H, 7.79; N, 7.81.

3.4. Computational methods

All calculations were carried out on SGI Octane2 IRIX 6.5 workstations. Molecular mechanics calculations were performed using the implementation of MM2 force field (MM2*)[9] within the framework of Macromodel release 5.5.[10] The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search.[11] For each search, at least 1000 starting structures for each variable torsion angle was generated and minimized until the gradient was less than 0.05 kJ/Å mol. Duplicate conformations and those with an energy in excess of 5 kcal/mol above the global minimum were discarded. The solvent effect was included by using the implicit water GB/SA solvation method of Still et al.,[14] to take into account of polar solvent effects.

All DFT calculations (i.e. geometry optimizations and chemical shift simulations) were carried out using the standard tools available in the Gaussian 98 package,[16] with the DFT/B3LYP functional (i.e. Becke's three parameter hybrid functional with the Lee–Yang–Parr correlation functional)[17] at the 6-31G* level of theory. This functional and basis set have been shown to properly describe both standard hydrogen bonds, as well as non-classical, weakly bound hydrogen bonds (such as C–H···O=C interactions),[19] and to provide

reliable results for the protons chemical shifts.[20,21] Anyway, the computed data do not directly yield the chemical shift value, but only a value for the isotropic magnetic tensor. The chemical shift value is obtained from the equation $\delta_H = 32.18 - \sigma_H$, where 32.18 is the calculated isotropic magnetic tensor for the protons in tetramethylsilane and σ_H is the calculated isotropic magnetic tensor for the investigated proton.

Acknowledgements

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References

1. (a) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104–109; (b) Freidinger, R. M.; Perlow, D. S.; Randall, W. C.; Saperstein, R.; Arison, B. H.; Veber, D. F. *Int. J. Protein Res.* **1984**, *23*, 142–150; (c) Kemp, D. S.; McNamara, P. E. *J. Org. Chem.* **1985**, *50*, 5834–5838; (d) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914–7915; (e) Yu, K. L.; Rajakumar, G.; Srivastava, L. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1988**, *31*, 1430–1436.
2. For reviews of constrained peptide mimics, see: (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267; (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720; (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854; (d) Goodman, M.; Zhang, J. *Chemtracts-Org. Chem.* **1997**, *10*, 629–645.
3. (a) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164–3173; (b) Garvey, D. S.; May, P. D.; Nazdan, A. M. *J. Org. Chem.* **1990**, *55*, 936–940.
4. (a) Linder, M. L.; Podlech, J. *Org. Lett.* **1999**, *1*, 869–871; (b) Maier, T. C.; Frey, W. U.; Podlech, J. *Eur. J. Org. Chem.* **2002**, 2686–2689.
5. The conformational space was explored through Monte Carlo conformational search and molecular mechanics energy calculations of optimised structures were performed by using Amber all-atoms force field (AMBER*). These computational studies were carried out in vacuo, in chloroform and water, by using the implicit GB/SA solvation model. The results were compared and an increase of the reverse turn mimic capability of peptidomimetic **1** in $CHCl_3$ arised with respect to polar solvents such as water. Furthermore, the behaviour of this system in vacuo resulted very similar with that observed in chloroform, since there are many low-energy reverse-turn conformers with γ- or β-II′ turns. Moreover, in chloroform there is an increased population of the γ-turn conformers over the β-II′.
6. (a) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M. *Synlett* **1995**, 1159–1160; (b) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069–1084; (c) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 79–88; (d) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1997**, *8*, 133–137.
7. Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1999**, *10*, 587–605.
8. (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904; (b) Itsuni, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039–2044; (c) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1987**, 746–748; (d) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1548–1549; (e) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1859–1863; (f) Kocovsky, P. *Synlett* **1990**, 677–678; (g) Williams, D. R.; Osterhout, M. H. *J. Am. Chem. Soc.* **1992**, *114*, 8750–8751; (h) Shawe, T. T.; Sheils, C. J.; Gray, S. M.; Conard, J. L. *J. Org. Chem.* **1994**, *59*, 5841–5842; (i) Dougherty, J. T.; Flisak, J. R.; Hayes, J.; Lantos, I.; Liu, L.; Tucker, L. *Tetrahedron: Asymmetry* **1997**, *8*, 497–499; (j) Grigg, R.; Hargreves, S.; Redpath, J.; Turchi, S.; Yoganathan, G. *Synthesis* **1999**, 441–446; (k) Bhattacharyya, S.; Neidig, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781–1783; (l) Basu, B.; Jha, S.; Bhuiyan, M. H.; Das, P. *Synlett* **2003**, 555–557.
9. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134.
10. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440–467.
11. Goodman, J. M.; Still, W. C. *J. Comp. Chem.* **1991**, *12*, 1110–1117.
12. Analogous effects due to chelation were described for reductions of 2-acyloxazolidines. See, for example: (a) Colombo, L.; Di Giacomo, M.; Brusotti, G.; Delogu, G. *Tetrahedron Lett.* **1994**, *35*, 2063–2066; (b) Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron*, **1995**, *51*, 4043–4056.
13. Significant calculated data for conformations **A**, **B** and **C**. **A**: d(H···O) = 1.942 Å. **A**. (H-3)–(C-3)–(C-1″)–(NH) = −107.8°; (H-3)–(C-3)–(C-1″)–(C-2″) = 71.3°; (C-2)–(N-1)–(C-1′)–(H-1′) = −49.0°; (C-5)–(N-1)–(C-1′)–(C-2′) = 18.4°. **B**: (H-3)–(C-3)–(C-1″)–(C-2″) = 81.8°; (H-3)–(C-3)–(C-1″)–(NH) = 24.3°; (C-2)–(N-1)–(C-1′)–(H-1′) = −50.5°; (C-5)–(N-1)–(C-1′)–(C-2′) = 15.9°. **C**: (H-3)–(C-3)–(C-1″)–(C-2″) = −61.5°; (H-3)–(C-3)–(C-1″)–(NH) = 117.0°; (C-2)–(N-1)–(C-1′)–(H-1′) = −48.2°; (C-5)–(N-1)–(C-1′)–(C-2′) = 186.0°.
14. Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *12*, 6127–6129.
15. Significant calculated data for conformations **D**, **E** and **F**. **D**: d(H···O) = 1.990 Å. **A**. (H-3)–(C-3)–(C-1″)–(NH) = −111.7°; (H-3)–(C-3)–(C-1″)–(C-2″) = 68.3°; (C-2)–(N-1)–(C-1′)–(H-1′) = −47.4°; (C-5)–(N-1)–(C-1′)–(C-2′) = 19.0°. **E**: (H-3)–(C-3)–(C-1″)–(NH) = 6.5°; (H-3)–(C-3)–(C-1″)–(C-2″) = 125.5°; (C-2)–(N-1)–(C-1′)–(H-1′) = −48.6°; (C-5)–(N-1)–(C-1′)–(C-2′) = 181.0°. **F**: (H-3)–(C-3)–(C-1″)–(NH) = 121.9°; (H-3)–(C-3)–(C-1″)–(C-2″) = −56.8°; (C-2)–(N-1)–(C-1′)–(H-1′) = −46.8° (C-5)–(N-1)–(C-1′)–(C-2′) = 19.6°.
16. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.;

Adamo, C.; Clifford, S.; Ochterski, J.; Patersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malik, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzales, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. Gaussian 98, Revision A.9, Gaussian Inc., Pittsburgh, PA, 1998.

17. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
18. Calculated ^{1}H chemical shifts (ppm) for compound **9a**. C$\underline{H}_3$ (2″): 0.88–0.90; C$\underline{H}_3$CO: 1.40–1.75; C$\underline{H}_3$ (2′): 1.51–1.38; C$\underline{H}$ (3): 2.35; C$\underline{H}$ (4): 2.76; C$\underline{H}_2$ (5): 3.31; C$\underline{H}_2$ (5): 3.78;; C$\underline{H}$ (1″): 4.39; C$\underline{H}$ (1′): 4.90; C$\underline{H}_2$ (ethenyl): 5.12–5.24; C$\underline{H}$ (ethenyl): 5.85; N$\underline{H}$: 6.56.
19. (a) Gonzalez, L.; Mo, O.; Yanez, M. *J. Comp. Chem.* **1997**, *18*, 1124–1135; (b) Klein, R. A. *J. Comp. Chem.* **2002**, *23*, 585–599; (c) Novoa, J. J.; Sosa, C. *J. Phys. Chem.* **1995**, *99*, 15837–15845.
20. (a) Wolinski, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260; (b) Wolinski, K.; Sadlej, A. *Mol. Phys.* **1980**, *41*, 1419–1430; (c) Ditchfield, R. *Mol. Phys.* **1974**, *27*, 789–807; (d) McWeeny, R. *Phys. Rev.* **1962**, *126*, 1024–1028; (e) London, F. *J. Phys. Radium* **1937**, *8*, 397–409.
21. Bagno, A. *Chem. Eur. J.* **2001**, *7*, 1652–1660.