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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,

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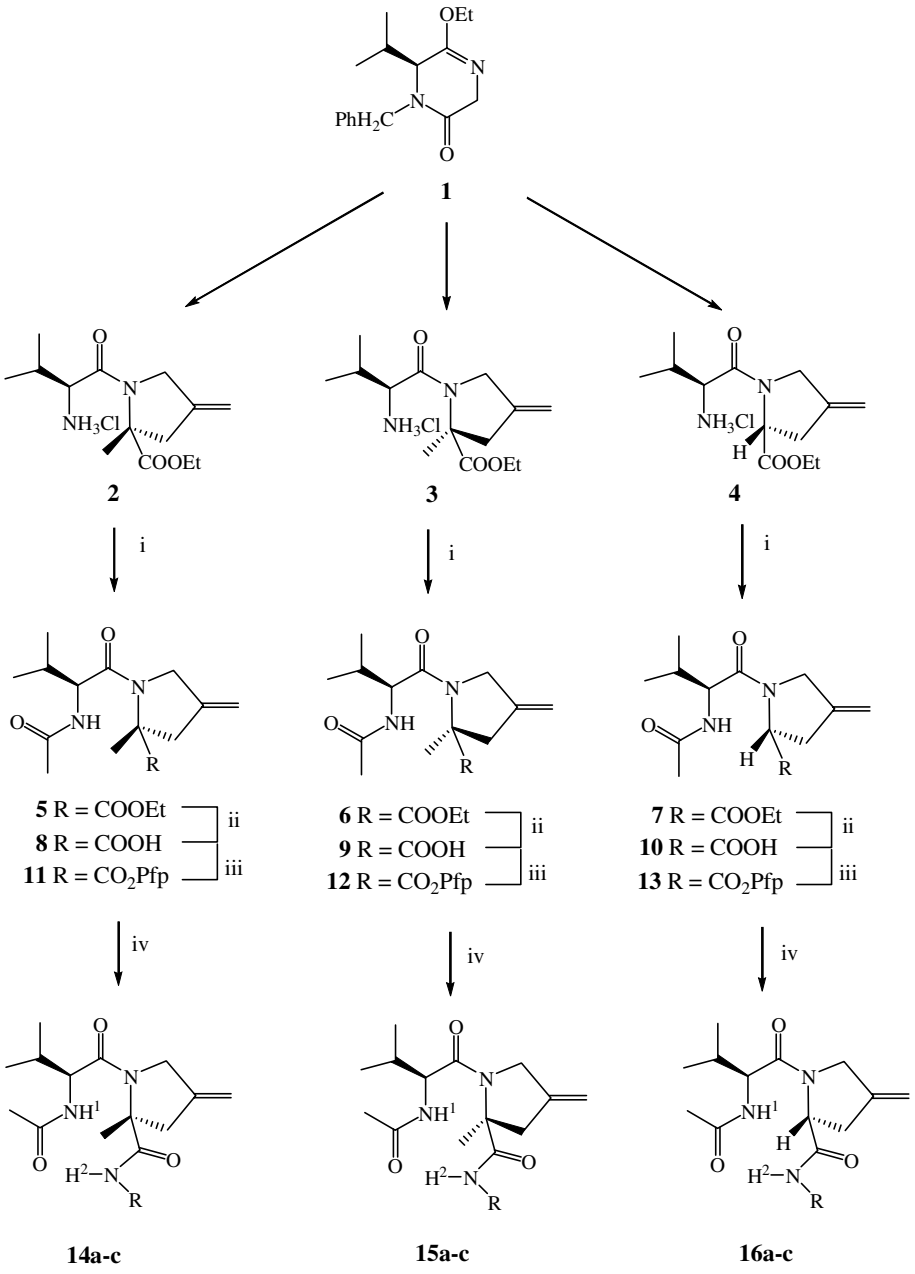

Scheme 1. Reagents and conditions: (i) CH_3COCl/Et_3N in CH_2Cl_2; (ii) 2 M NaOH in EtOH, 2 h at rt; (iii) pentafluorophenyl trifluoroacetate (CF_3CO_2Pfp) in CH_2Cl_2, Py; (iv) R–NH_2 in DMF.

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-