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Rapid Communication

α-Dehydro β-amino acid derivatives as turn inducer: Synthesis of potential HIV protease inhibitors based on structural mimicry†

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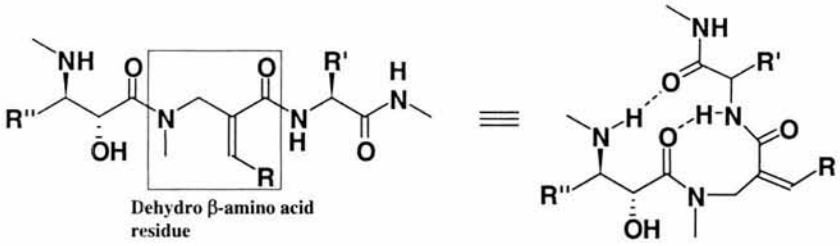
α-Dehydro β-amino acid derivatives derived di- and tripeptides **4-7** adopt eight-member turn conformations in $CDCl_3$ solutions. These peptides show similar hydrogen bonding characterstics as compared to the corresponding L-proline containing peptides **8**. Thus the dehydro β-amino acid derived tripeptides **7** may behave as the structural mimic of the L-proline containing tripeptides **8c** which are structural analogues of HIV protease inhibitors.

The β- and γ-turn conformations in proteins have been shown[1] to play important roles during the biochemical recognition process. It has been shown that when peptides are used as an inhibitor they adopt a turn conformation[2] while bound to their protein receptors. In view of their importance a number of peptides and non-peptides that confer a β- or γ-turn conformations have been synthesised[3]. In connection with our work on the design and synthesis of aspartyl protease inhibitors (containing α-hydroxy-β-amino amide core unit) based on β-turn mimetic concept, we conceptualised that a double bond when present in the side chain of an amino acid will confer torsional restriction and peptides containing such amino acid residues may be constrained to adopt a turn conformation. Also, in order for it to be a meaningful aspartyl protease inhibitor[4], we reasoned that the core unit consisting of α-hydroxy-β-amino amide group should be the part of the constrained portion of such an organised structure (**Scheme I**). Studies have shown that peptides containing appropriately placed dehydro α-amino acids are capable of inducing a turn. For example, if a dehydro residue of class I is placed at (i+1) position with a flexible residue (Gly, Ala) at (i+2) position, the dehydro residue[5] adopts a conformation which correspond to the torsional angle values of an (i+1) residue in a β-turn II conformation. It is axiomatic that the structural features present in an inhibitor must render sufficient level of flexibility during its interaction with the receptor molecule. Inspite of their utility as turn inducer, the dehydro α-amino acid suffers from the rigidity due to the constraints imparted by the double bond and often peptides derived from it does not possess the kind of flexibility required during binding with the host. We envisaged that incorporation of an additional carbon atom in dehydro α-amino acid will lead to α-dehydro β-amino acids and the latter may exhibit the required flexibility expected during its binding with the host. We now show that a tripeptide **7** containing a α-dehydro β-amino acid residue at (i+1) position is a turn inducer and leads to the formation of a psuedo-eight-membered ring (**Scheme I**). These results are compared by synthesising L-proline containing tripeptide **9** which is structural analogue of HIV protease inhibitors. The following section describes the synthesis and turn inducing characterstics of α-dehydro β-amino acid derived peptides which may behave as the structural mimic of the structural analogue of HIV protease inhibitors.

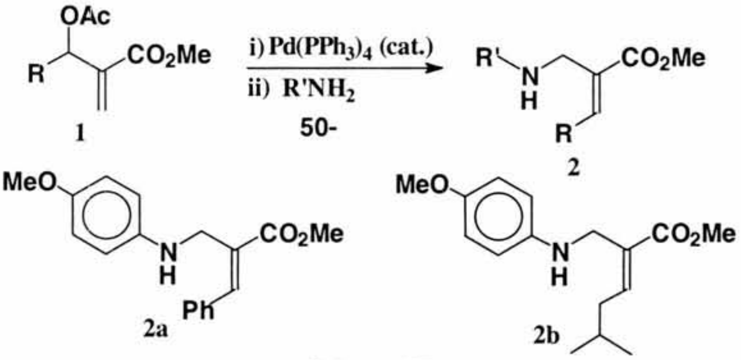
The α-dehydro β-amino acid derivatives **2** were prepared by palladium catalysed amination of allyl acetates **1** with aniline derivatives (**Scheme II**). In most of the cases, the (*E*)-isomer was formed predominantly. The α-dehydro β-amino acid derivatives **2a** and **2b** were transformed quantitatively to the corresponding *N*-cinnamoyl amide **3a** and **3b** respectively on treatment with cinnamoyl chloride (**Scheme III**). Hydrolysis of the ester in **3a** and **3b** followed by mixed anhydride coupling with the methyl ester hydrochloride of L-leucine, afforded the corresponding peptides **4a** and **4b** respectively in good yields (**Scheme III**). The proton NMR and IR of these peptides showed[6] the presence of intramolecular hydrogen bond (**Table I**).

In each case the chemical shift of the amide hydrogen was sensitive to concentration and temperature and the chemical shift cited in the **Table I** were obtained from samples at concentration (~1.5 mM) and ambient temperature at which no significant aggregation was evident. It is interesting to note that ^{1}H NMR of compounds **4a** and **4b** showed a down field chemical shifts (7-8.5 ppm) for the amide

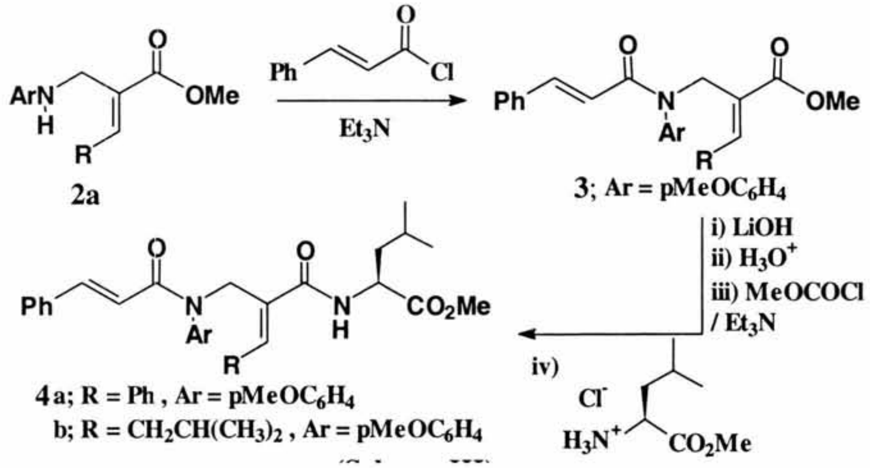
† Dedicated to Prof.U. R. Ghatak on his 70th birthday



Scheme I



Scheme II



Scheme III

Table I—[1]H NMR chemical shifts and coupling constants of amide hydrogens for compounds **4-7**

Compd	δ NH (ppm)[a]	*J* NH(Hz)
4a	8.45	7.08
4b	8.44	7.32
4c	7.61	8.56
5	8.14	7.43
6	7.86	7.60
7	7.95	7.54

[a] NMR were recorded with a sample concentrations of $CDCl_3$ at room temperature

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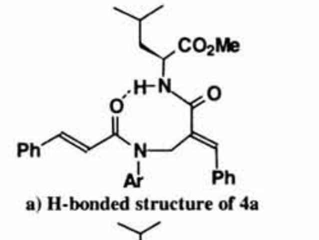
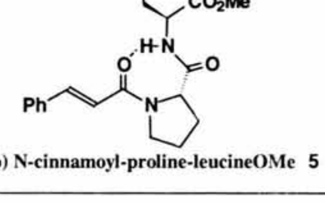


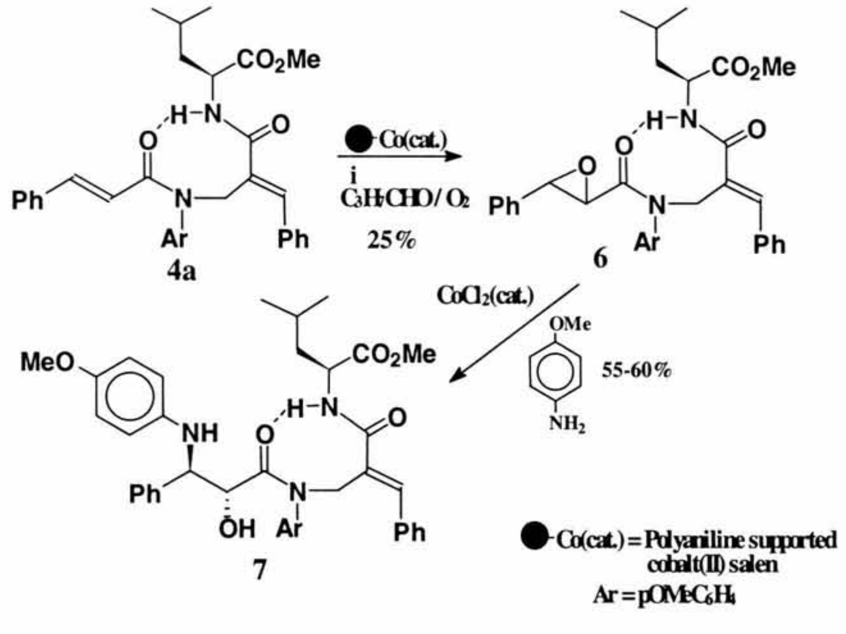
a) H-bonded structure of 4a



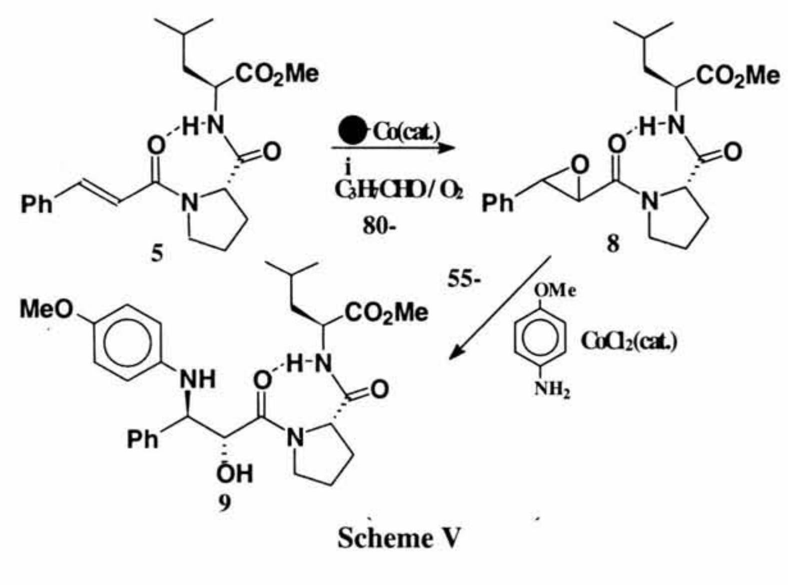
b) N-cinnamoyl-proline-leucineOMe 5

hydrogen and their coupling constants were also consistent with the literature[6] values. The de-shielding of the amide hydrogen in **4a** and **4b** suggested that they were involved in hydrogen bond interaction and the ^{1}H NMR of these also indicated the absence of any unbound structure as the high field signal due to the free amide hydrogen was not observed.

The turn inducing behaviour of α-dehydro β-amino acids **2** in peptides **4** was evident when comparing it with the peptide *N*-cinnamoyl-L-proline-L-leucine **5**. The ^{1}H NMR of **5** indicated a downfield appearance of the amide hydrogen indicating an intramolecular hydrogen bonding leading to the well known γ-turn that may have resulted if the prolyl amide[7] residue existed as *trans*-isomer. Thus the role played by the α-dehydro β-amino acid residue in **4** is comparable to the one exhibited by L-proline residue in peptide **5**. It is important to note that the ^{1}H NMR of the amide derived from L-proline residue in **5** showed the presence of geometric mixtures of *cis* and *trans* isomers whereas the presence of the N-aryl group in **4** was mainly responsible for the formation of one isomer of the tertiary amide **4a** . Thus it appears that the aromatic ring present on nitrogen in **4** influences the geometry of the tertiary amide such that it adopts a conformation suitable for the intramolecular hydrogen bonding. The existence of the eight-membered intramolecular hydrogen bonding was also



Scheme IV



Scheme V

observed in epoxide **6** (**Table I**) which was obtained from **4a** on polyaniline supported cobalt(II) salen catalysed[8] aerobic epoxidation (**Scheme IV**).

The cobalt(II) chloride catalysed opening of the epoxide **6** with anisidine led to the corresponding β-phenylisoserine derived tripeptide **7** which also showed the presence of intramolecular hydrogen bonding as evidenced from the appearance of amide hydrogen at 7.9 ppm in ^{1}H NMR (**Table I**). The tripeptide **7** has the α-hydroxy β-amino amide core structure which is shown to be present in HIV protease inhibitors[9]. In order to draw analogy between structure **7** and the proline containing structural analogue of HIV protease inhibitors, we have synthesised the tripeptide **9** from **8** (**Scheme V**) using the epoxidation and its opening protocol as described for **7** in scheme 4. The tripeptide **9** also showed the intramolecular hydrogen bonding as evidenced[10] from the appearance of low field signal for amide hydrogen in proton NMR. This observation suggests that **7** may function as a structural mimic of **9**. In conclusion, the α-dehydro β-amino acid **2** is an efficient turn inducer when present at i+1 position of tripeptide **7** and can mimic the L-proline residue at this position as indicated by its comparison with **9**.

Acknowledgement

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10 ^{1}H NMR and Mass for tripeptide **7**; ^{1}H NMR ($CDCl_3$): δ 7.95 (bs, 1H), 7.76 (s, 1H), 7.13-7.27 (m, 10H), 6.61 (d, J = 4.8Hz, 2H), 6.59 (d, J = 9Hz, 2H), 6.33 (d, J = 8.76Hz, 2H), 5.11 (d, J = 15.1Hz, 1H), 4.72 (m, 1H), 4.41 (m, 1H), 4.36 (d, J = 14.88Hz, 1H), 4.17 (d, J =), 3.78 (s, 3H), 3.68 (s, 3H), 1.67 (m, 2H), 1.25 (m, 1H), 0.98 (d, J = 5.84Hz, 6H). Mass: 680 (M+1, 10%), 468 (15%), 212 (60%). **9;** ^{1}H NMR ($CDCl_3$): δ 7.14-7.35 (m, 5H), 7.15 (d, J = 7.6Hz, 1H), 6.66 (d, J = 8.8Hz, 2H), 6.39 (d, J = 4.2Hz, 2H), 4.89 (d, J = 5.6Hz, 1H), 4.47-4.52 (m, 1H), 4.41 (d, J = 5.6Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 2.13-2.20 (m, 1H), 1.84-1.96 (m, 2H), 1.46-1.77 (m, 4H), 0.88 (d, J = 6.4Hz, 3H), 0.91 (d, J = 5.6Hz, 3H).