Synthesis of an α-dehydro β-amino acid derived cyclic peptide as a constrained β-turn mimic

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This paper is dedicated to Prof. T. R. Govindachari on the occasion of his 80th birthday

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Abstract

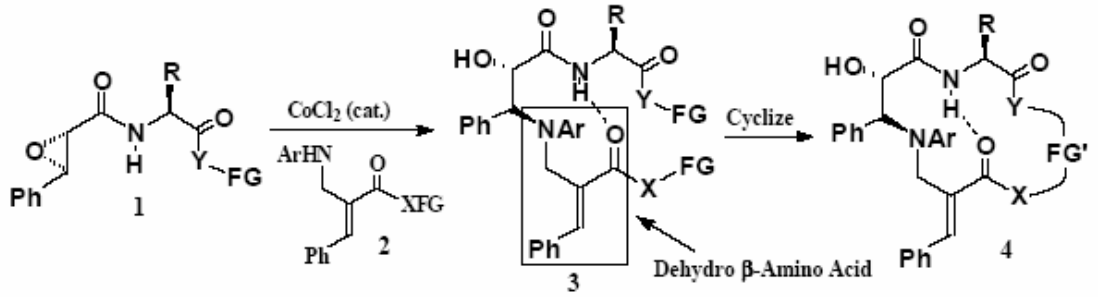
Cobalt(II) chloride catalyses the cleavage of epoxy peptides with an α-dehydro β-amino acid derivative to afford the corresponding dipeptide derivative which exhibits an intramolecular hydrogen bond and thus mimics a β-turn. This intramolecular hydrogen bonding preorganises the corresponding diallylated peptide for cyclisation via ring closing metathesis to afford the cyclic peptide as a constrained mimic of a β-turn.

Keywords: Epoxypeptides, β-turn mimic, cyclic peptide, cobalt (II) chloride catalyst, intramolecular hydrogen bond

Introduction

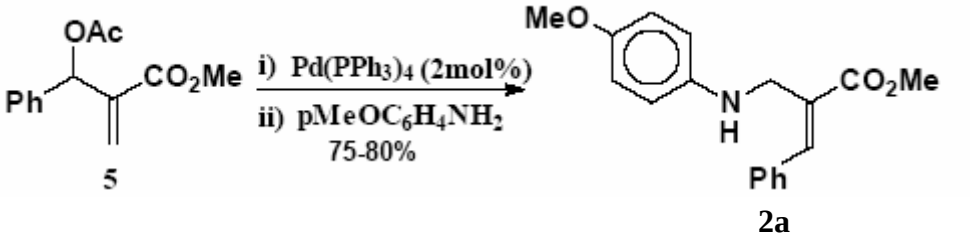
It is well known that linear peptide fragments are flexible and exhibit numerous conformations in solution and even in the solid state. However, if one can restrict the conformational freedom of these linear peptides by introducing some constraints in the structure, it may render a biologically active peptide more specific and this may give rise to species, which are therapeutically useful. In view of the importance of constrained conformations, there have been several studies1 to lock peptides into turn configurations and to synthesise molecules that might mimic a reverse turn. Among the reverse turns, the β- and γ-turn conformations in proteins have been shown 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 connection with our work on the design and synthesis of aspartyl protease inhibitors[3] (containing α-hydroxy-β-amino amide core unit) based on the β-turn mimetic concept, we reasoned that a double bond when present in the side chain of an amino acid will confer torsional restriction and in the presence of appropriate donor and acceptor sites peptides containing such amino acid residues may be constrained to adopt a turn conformation. Studies

have shown that peptides containing appropriately placed dehydro α-amino acids are capable of inducing a turn[4]. It is evident that the structural features present in an inhibitor must render a sufficient level of flexibility during its interaction with the receptor molecule.



Scheme 1

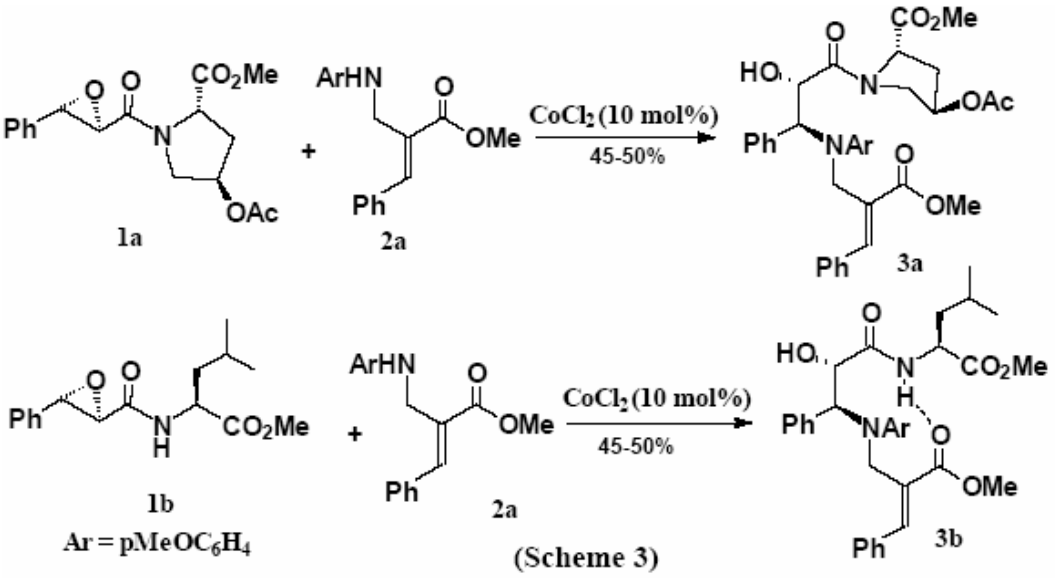
In spite of their utility as turn inducers, the dehydro α-amino a cids suffer from rigidity due to the constraint imparted by the double bond and often peptides derived from them do not possess the kind of flexibility required during binding with the host. We envisaged that incorporation of an additional carbon atom into dehydro α-amino acids would lead to α-dehydro β-amino acids and the latter might exhibit the required flexibility during its binding with a host. We now show that an α-dehydro β-amino acid derivative **2** can be used to make β-turn mimics containing an α-hydroxy β-amino residue **3** *via* a cobalt catalysed opening of epoxy peptides **1** (Scheme 1). The following section describes the synthesis and turn induced cyclization leading to the constrained mimic **4** of a β-turn. The α-dehydro β-amino acid derivative **2a** was prepared by palladium catalysed amination of the allyl acetate **5** itself prepared by Baylis-Hillman reaction (Scheme 2). The *E*-geometry of the double bond was assigned based on the ^{1}H NMR data. The anisyl group was used as a N-protecting group as it is amenable to oxidative removal without affecting the double bond of the α-dehydro β-amino acid residue.



Scheme 2

The α-dehydro β-amino acid derivative **2a** is a very good nucleophile as it cleaves epoxides in the presence of catalytic amount of cobalt(II) chloride[5]. In order to demonstrate this we have reacted epoxides[6] **1a** and **1b** with **2a** in the presence of catalytic amount of anhydrous cobalt(II) chloride in acetonitrile to afford the corresponding β-phenylisoserine derived dipeptides **3a** and **3b** respectively (Scheme 3). The dipeptides **3a-b** were isolated by column chromatography (Silicagel, EtOAc-hexane) mainly as the *trans* diastereomer. A careful analysis of the reaction mixture revealed only the presence of a minor amount (~ 5-10%) of the corresponding *syn*

diastereomer. The regio- and stereochemistry of **3a** and **3b** was unambiguously proved based on the chemical shift and the coupling constants of the methine proton [–(Ar)N-CH(Ph)-] according to our earlier studies as mentioned in reference 5b. The dipeptide **3b** derived from L-leucine exhibited an intramolecular hydrogen bond as indicated by the appearance of the amide proton at 6.94ppm (J = 8.8Hz) in the ^{1}H NMR spectrum[7]. The presence of such hydrogen bonding[1b,1c] suggests that a ten-membered cyclic structure may be formed by a non-covalent interaction between amide hydrogen and ester carbonyl.

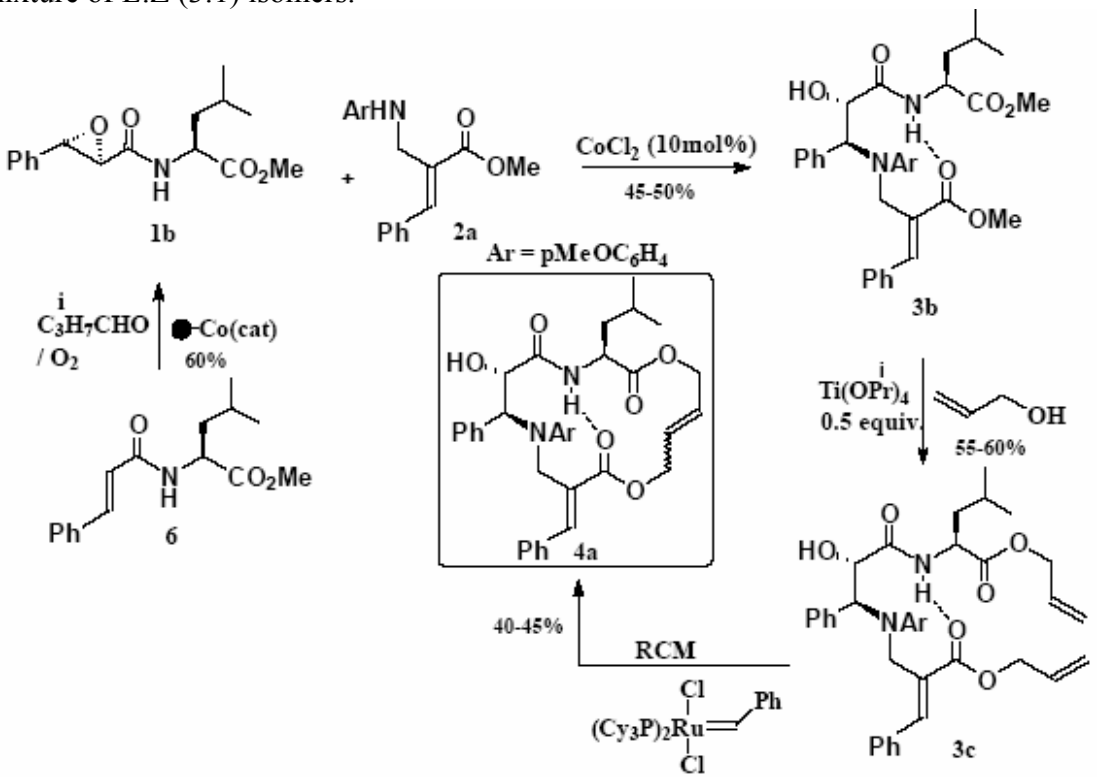


(Scheme 3)

Scheme 3

The participation of the ester carbonyl in such an interaction may be due to the enhanced electron density caused by the presence of conjugated double bond and aromatic ring. It is thus clear that the opening of an epoxy peptide with a α-dehydro β-amino acid derivative leads to an organised ten-membered structure mimicking a β-turn and it appears that the presence of a double bond may constrain the conformation leading to an intramolecular hydrogen bond. In order to demonstrate the role of α-dehydro β-amino acid **2a** in constraining the conformation via hydrogen bond, we have synthesised the cyclic peptide **4a** using a ring closing metathesis reaction (Scheme 3). Thus the epoxy peptide **1b** (single diastereomer), obtained by cobalt catalysed aerobic oxidation[8] of **6**, was reacted with **2a** in the presence of catalytic amount of cobalt(II) chloride[9] to afford **3b** after column chromatography in good yield. The ester groups in **3b** were transesterified with excess allyl alcohol in the presence of titanium isopropoxide[10] to afford the diallylated peptide **3c** (55-60%). The ^{1}H NMR spectrum of **3c** also showed the presence of an intramolecular hydrogen bond as evidenced by the appearance of signal due to the amide proton at 6.88ppm (J = 8.8Hz). The appearance of amide proton signal at ~ 7ppm in both peptides **3b** and **3c** suggests the presence of intramolecular hydrogen bond as its chemical shift does not undergo an appreciable shift on changing the concentration of the solution. The preorganized diallylated peptide **3c** was subjected to a ring closing metathesis reaction using

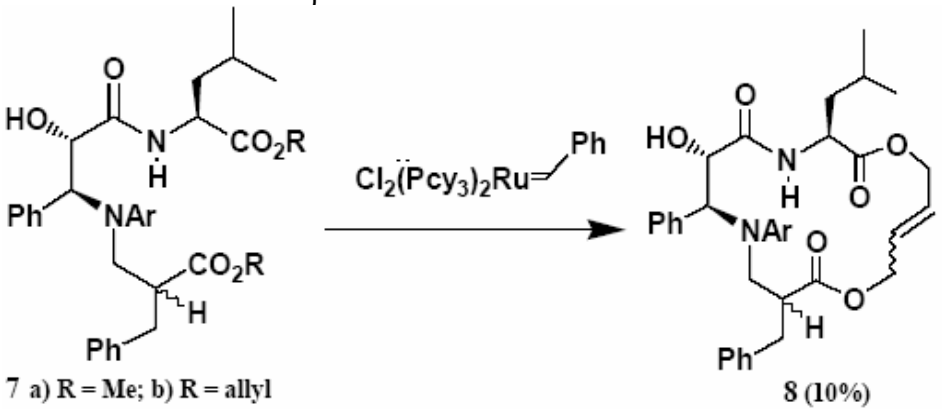
ruthenium alkylidene[11] (Grubbs Catalyst) to afford the corresponding cyclic peptide **4a** (40-45%) as a mixture of E:Z (3:1) isomers.



Scheme 3

The presence of an intramolecular hydrogen bond was also evident in the cyclic structure **4a** whose ^{1}H NMR spectrum showed[11] the appearance of an amide proton at 8.19ppm (J = 8.8Hz). The FT-IR of **4a** also indicated the presence of intramolecular hydrogen bonding as a broad signal due to this stretching appeared at 3359.8 cm^{-1}. It is not evident from ^{1}H NMR which of the geometrical isomers (***E*-4a** or ***Z*-4a**) is responsible for the intramolecular hydrogen bonding. However, it is concievable that the formation of cyclic structure **4a** may be favoured by the pre-organisation, via intramolecular hydrogen bond, of the diallylated precursor **3c** which mimics a β-turn. In order to demonstrate the role of dehydro amino acid residue in intramolecular hydrogen bonding, we have converted the peptide **3a** into the corresponding saturated analogue **7a** (Pd / H2; 25%). It is noteworthy, though not particularly surprising, that the saturated analogue **7a** and **7b** did not show the presence of any intramolecular hydrogen bonding. It is also interesting to note that the ring closing metathesis reaction on the diallylated saturated analogue **7b** did not proceed cleanly as only a small amount (10%) of the corresponding cyclic product **8** (1:1; E / Z mixture) was isolated from a complex reaction mixture (Scheme 4). These studies suggest the crucial role of double bond in **3a** in promoting the intramolecular hydrogen bonding which may in turn encourage the ring closing metathesis leading to the constrained β-turn mimic **4**. In conclusion, we have demonstrated that α-dehydro β-amino acid derivatives can be used as nucleophile to cleave epoxy peptides leading to the formation of dipeptide derivative which

mimics a β-turn by exhibiting intramolecular hydrogen bonding. This intramolecular hydrogen bonding preorganises the peptide for cyclisation via ring closing metathesis to afford a cyclic peptide as a constrained mimic of a β-turn.



7 a) R = Me; b) R = allyl

8 (10%)

Scheme 4

Acknowledgements

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References and Notes

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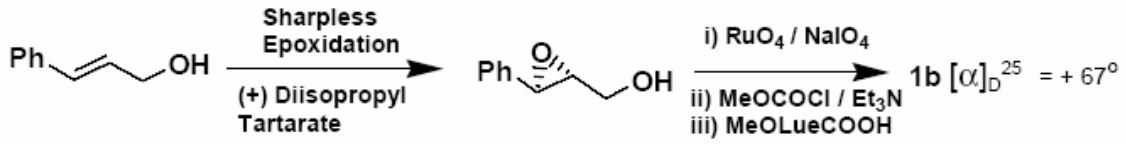
6. The relative stereochemistry of epoxides **1a** and **1b** was assigned based on the following protocol. The similarity in the sign and magnitude of optical rotation for **1b**, prepared by Sharpless's as well as by polyaniline supported cobalt catalysed procedure, helped us to assign the indicated absolute stereochemistry.



7. The presence of intramolecular hydrogen bond was proved by standard protocol as mentioned in references 1a, 1b and 1i, by FT-IR and by recording the proton NMR spectrum of **3b** dissolved in various concentration of DMSO-d_6 in $CDCl_3$. The amide protons are generally characterised by appearance of signal between 6-9ppm, a region where hydroxy protons are seldom observed. The chemical shift of the amide proton did not change appreciably with increasing concentration of DMSO-d_6 thereby indicating the presence of intramolecular hydrogen bond. A similar protocol was followed for ascertaining the intramolecular hydrogen bond in **3c** and **4a**.
8. For polyaniline supported cobalt catalysed epoxidation see: (a) Das, B. C.; Iqbal, J. *Tetrahedron Lett*. **1997**, *38*, 2903. (b) Punniyamurthy, T.; Iqbal, J. *Tetrahedron Lett*. **1997**, *38*, 4463. (c) De, A.; Basak, P.; Iqbal, J. *Tetrahedron Lett*. **1997**, *38*, 8383.
9. **General Procedure for Cobalt(II) chloride catalysed opening of epoxy amide 1 with 2a**: To a stirred solution of cobalt(II) chloride(10 mol%) in acetonitrile (15mL) was added **1a** (2mmol) and **2a** (2mmol) and the mixture stirred at ambient temperature under nitrogen atmosphere for 10-12 hours. The solvent is evaporated under reduced pressure and the residue was taken in ethyl acetate and washed thoroughly with saturated solution of sodium bicarbonate solution and water. Drying (sodium sulphate) and evaporation of solvent gave a residue which was subjected to column chromatography over silica gel (10%EtOAc / hexane) to afford **3a** as a gum in 45-50% yield. ^{1}H NMR ($CDCl_3$) **3a**: δ7.53 (m, 1H), 7.46(s, 1H), 7.12-7.34 (m, 8H), 6.94 (m, 1H), 6.83 (m, 2H),6.60 (m, 2H), 5.07 (m, 1H), 4.70 (bs, 1H), 4.42 (m, 1H), 4.35 (bs, 1H), 4.04 (d, J = 12.6Hz, 1H), 3.98 (d, J = 12.6Hz, 1H), 3.87 (m, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H), 3.37 (m, 1H), 2.21 (m, 1H), 2.07 (m, 1H),

1.95 (s, 3H). Mass (***m/z):*** 631(M+1, 20%), 386 (100%), 297 (20%), 212 (50%), 175 (15%), 126 (20%), 91 (20%).

10. Titanium tetraisopropoxide mediated transesterification with allyl alcohol was carried out according to reference: Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138. Procedure***:*** Compound **3b** (5mmol) was taken in allyl alcohol (15 mL) and Ti $(OPr^i)_4$ (50 mol%) was added to it and the resulting mixture was heated at 100 °C for 16 hours. Removal of solvent under reduced pressure gave a residue, which was taken in ethyl acetate, and the murky solution was passed through a celite pad. Removal of solvent gave a residue which was subjected to column chromatography over silica gel (EtOAc / hexane) to afford **3c** (5560%) as a gum. ^{1}H NMR ($CDCl_3$) **3c**: δ7.50 (s, 1H), 7.00-7.21 (m, 10H), 6.88 (d, J = 8.8Hz, 1H), 6.61 (d, J = 8.8Hz, 2H), 6.41 (d, J = 8.8Hz, 2H), 5.92 (m, 1H), 5.78 (m, 1H), 5.33 (d, J = 13.44Hz, 1H), 5.19 (m, 2H), 5.11 (d, 10.48Hz, 1H), 4.86 (d, J = 6.12Hz, 1H), 4.66 (d, J = 3.92Hz, 1H), 4.51 (d, J = 3.44Hz, 1H), 4.46 (d, J = 5.64Hz, 2H), 4.25 (dt, J = 9 and 5.12Hz, 1H), 3.93 (d, J = 13Hz, 1H), 3.80 (d, J = 13Hz, 1H), 3.55 (s, 3H), 1.50 (m, 1H), 0.79 (m, 2H), 0.60 (d, J = 6.56Hz, 3H), 0.52 (d, J = 6.32Hz, 3H). IR (cm^{-1}) 3404.2 (broad), 2957.5, 1741.6, 1679.5, 1509.3, 1244. Mass ***(m/z):*** 641 (M+1, 80%), 412 (100%), 323 (10%), 212 (30%).
11. **General Procedure for Ring Closure Metathesis**: To a stirring solution of ruthenium methylidene catalyst (Grubbs catalyst) (10 mol%) in dichloromethane (0.6 mm solution) under nitrogen, the diene **3c** (3mmol) was added and the mixture was refluxed for 10-12 hours. At this stage an additional ruthenium methylidine catalyst (10 mol%) was added and the mixture was further refluxed for 8 hours. The solvent was evaporated to yield a residue which was chromatographed over silica gel (30% EtOAc in hexane) to afford **4a** (40-45%) as a gum. ^{1}H NMR ($CDCl_3$) *trans* **4a**: δ8.21 (bs, 1H), 7.60 (s, 1H), 7.10-7.42 (m, 7H), 6.86-6.93 (m, 3H), 6.57 (d, *J* = 9.04Hz, 2H),6.49 (d, *J* = 9.04, 2H), 5.91 (dt, *J* = 16.72 and 5.84Hz, 1H), 5.34 (ddd, *J* = 17.3, 3 and 1.6Hz, 1H), 4.67-4.82 (m, 2H), 4.63 (bs, 2H), 4.69 (bs, 2H), 4.50 (dd, *J* = 4.88 and 12.2Hz, 1H), 4.05 (d, *J* = 13.92Hz, 1H), 3.98 (d, *J* = 13.92Hz, 1H), 3.71 (s, 3H), 1.86 (m, 1H), 1.55-1.71 (m, 2H), 0.95 (d, *J* = 6.36Hz, 3H), 0.91 (d, *J* = 6.36Hz, 3H). IR (cm^{-1}***)*** 3359.8 (broad), 2952.2, 1739.2, 1655.8, 1510.9, 1247.6. FT-IR (CH_2Cl_2): 3359.8, 2257, 2925.2, 1739.2, 1658.8, 1510.9, 1452.7. Mass *(m/z):* 613 (M^+, 100%), 555 (25%), 412 (30%), 212 (50%). ^{1}H NMR ($CDCl_3$) (**8**): δ 7.19-7.52 (m, 7H), 6.91-6.97 (m, 3H), 6.61 (d, *J* = 9.04Hz, 2H), 6.51 (d, *J* = 9.04, 2H), 5.96 (dt, *J* = 16.69 and 5.81Hz, 1H), 5.39 (ddd, *J* = 17, 3.1 and 1.8Hz, 1H), 4.72-4.88 (m, 2H), 4.71 (bs, 2H), 4.53 (dd, *J* = 4.8 and 12Hz, 1H), 4.01 (d, *J* = 14.1Hz, 1H), 3.88 (d, *J* = 14.1Hz, 1H), 3.69 (s, 3H), 3.13 (m, 2H), 2.94 (m, 1H), 2.87 (ddd, *J* = 16.7, 4.1 and 2.1Hz, 1H), 2.76 (ddd, *J* = 16.7, 4.2 and 4.3Hz, 1H), 1.86 (m, 1H), 1.55-1.71 (m, 2H), 0.95 (d, *J* = 6.36Hz, 3H), 0.91 (d, *J* = 6.36Hz, 3H). Mass (***m/z):*** 615 (M^+ , 100%), 557 (35%), 317 (25%), 214 (37%).