2(*S*)-Amino-3-oxo-11*b*(*R*)-hexahydroindolizino[8,7-*b*]indole-5(*S*)-carboxylate as a New Type of β-Turn Dipeptide Mimetic

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Molecular-modelling studies have shown that 2(*S*)-amino-3-oxo-11*b*(*R*)-hexahydroindolizino[8,7-*b*]indole-5(*S*)-carboxylate, stereoselectively prepared by Pictet–Spengler reaction between H-Trp-OMe and Z-Asp(H)-OBz and subsequent γ-lactamization, behaves as a type-II′ β-turn inducing mimetic.

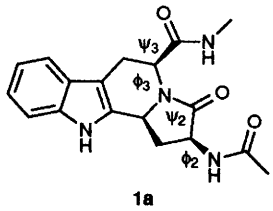
Conformationally constrained frameworks, which when incorporated into a peptide induce the adoption of a particular secondary structure, are used to delineate the biologically active conformation of a bioactive peptide.[1] Among these secondary structure mimetics, considerable attention has been paid to those mimicking the different types of β-turns,[2–8] common features in bioactive peptides, which are widely thought to act as molecular recognition sites for many biological processes.[9,10] In particular, bicyclic lactams have been shown to be effective analogues for the central dipeptide core of β-turns.[4,7] This fact and the interest in having a variety of β-turn frameworks displaying different degrees of structural flexibility, led us to consider the 2-amino-3-oxo-hexahydroindolizino[8,7-*b*]indole-5-carboxylate system as a potential β-turn mimetic. To this aim, molecular-modelling studies on those diastereoisomers having *S* configuration at C-2 and C-5 positions were carried out. Here, we report the results of these studies along with a facile and stereoselective synthetic route for their preparation.

The low-energy conformations of substituents at the C-2 and C-5 positions of the *N*-acetyl-*N*′-methylamide model compounds **1a** and **b** were explored systematically by using the conformational search option of the DISCOVER program.† The torsion angles and relative energies of the four lowest energy conformations obtained for these compounds are listed in Table 1. Although the Ψ_2 dihedral angles of all **1a** conformers are within the standard values predicted for classical β-turn of type II′, the other torsion angles did not show a similarity with this type of reverse turn. In the case of compound **1b**, conformers A and B showed calculated Ψ_2 and Φ_3 angles close to those observed in an ideal type-II′ β-turn, while the Φ_2 and Ψ_3 values suggested that extended conformations were preferred. However, the αC(1)–αC(4) distances and all the torsion angles found for the C and D minima of this derivative are in good agreement with those predicted for the classical type-II′ β-turn.‡ This indicates that the 11*b*(*R*) isomer of this system can serve as an effective type-II′ β-turn mimetic. Superposition of the eight backbone atoms from C-1 to N-4 of conformer **1b**: C and the corresponding atoms in a classical type-II′ β-turn gave a RMS fit of 0.31 Å,§ as illustrated in Fig. 1.

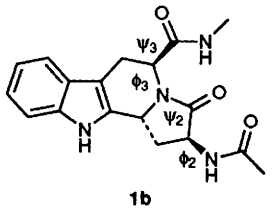
Pictet–Spengler reaction between H-L-Trp-OMe and Z-L-Asp(H)-OBz **2**,[11] in the presence of TFA at −78 °C, gave a 10:1 mixture of the tetrahydro-β-carbolines **3a** and **b** in 90% yield.[12,13] The predominantly formed *cis*-carboline **3a** could be isolated by simple precipitation from EtOAc, while the minor stereoisomer **3b** was always obtained unpurified with the corresponding major compound. When the 10:1 mixture of derivatives **3a** and **b** was refluxed in xylene for 24 h, γ-lactamization occurred to provide the tetracyclic derivatives **4a** and **b** in a similar ratio to that of the starting tetrahydro-β-carbolines (58%). Compound **4a** could be stereospecifically obtained from isolated carboline **3a** using the above indicated conditions. Epimerization of the optically pure *cis*-carboline **3a**, in refluxing xylene and in the presence of an excess of TFA (10 equiv.),[12] gave a 1:4 mixture of lactams **4a** and **b** (4 h, 89%). The absolute stereochemistry at the newly created stereocentre C-11*b* in compounds **3a**, **4a** and **4b** was assigned on the basis of NOE studies. Saponification of both **4a** and **b** with NaOH in methanol gave the free acids **5a** and **b**, respectively (>95%). Deprotection of the Z group of **4a** and **b** by hydrogenolysis, using Pd-C as catalyst, afforded the amino derivatives **6a** and **b** (94 and 88%, respectively).¶

The molecular modelling study presented here shows that the 2(*S*)-amino-3-oxo-11*b*(*R*)-hexahydroindolizino[8,7-*b*]indole-5(*S*)-carboxylate derivatie is potentially a good dipeptide mimetic of a type-II′ β-turn. This diastereoisomer can be stereoselectively prepared, in two steps, from easily available L-Trp and L-Asp derivatives. The 5 + 6 bicyclic lactam, presented here, could constitute an interesting complement to the described 5 + 5 and 6 + 5 bicyclic systems,[4,7] for probing

Table 1 Dihedral angles and relative energies of AM1 low-energy optimized conformations of structures **1a** and **b**



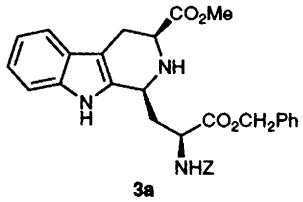
1a



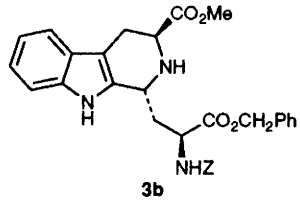
1b

Compound	Conformer	Torsion angle (°) Φ_2	Ψ_2	Φ_3	Ψ_3	Rel. energy/ kcal mol^{-1}[a]
1a	A	−126.1	−141.5	38.6	47.0	0.00
	B	168.1	−139.7	43.5	41.3	0.62
	C	−132.2	−147.0	39.4	−74.7	0.71
	D	89.5	−150.3	33.0	−73.2	2.68
1b	A	−126.2	−115.5	−133.5	−68.0	0.00
	B	−125.7	−116.9	−90.4	69.8	0.24
	C	63.9	−111.0	−117.9	6.1	1.01
	D	67.0	−111.4	−120.7	5.6	1.04
βII′	—	60.0	−120.0	−80.0	0.0	—

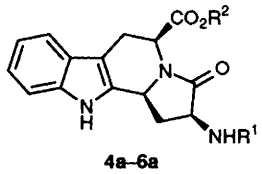
[a] 1 cal = 4.184 J.



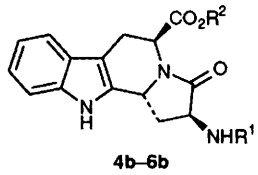
3a



3b

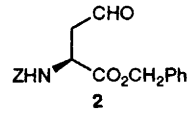


4a–6a



4b–6b

4a,4b; R^1 = Z, R^2 = Me
5a,5b; R^1 = Z, R^2 = H
6a,6b; R^1 = H, R^2 = Me



2

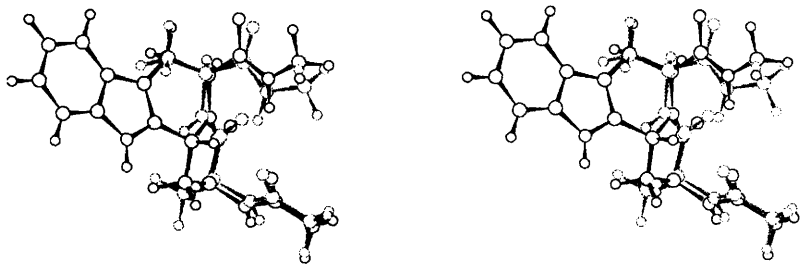


Fig. 1 Stereoview of the fit of conformer **1b**:C (black) to a model type-II′ β-turn (Ac-Ala-Ala-NHMe, grey)

the relevance of β-turn secondary structures in peptides of biological significance. The presence of the indole ring, that can be considered as the side-chain of the $i + 2$ residue, represents an additional advantage in the case of β-turn having aromatic or hydrophobic amino acids in the third residue.

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Footnotes

† DISCOVER, version 2.8. San Diego: Biosym Technologies, 1992, implemented in a Personal IRIS Workstation (Silicon Graphics). Structures **1a** and **b** were built by using the INSIGHTII, version 2.1.0, molecular modelling program. The ring conformations were initially fixed to be those provided by X-ray and NMR studies on related *N*-alkyl tetrahydro-β-carbolines (see ref. 12) and the peptide bonds were orientated in *trans* disposition. These starting structures were optimized with the molecular mechanics force field implemented in the DISCOVER program. Dihedral angles Φ_2 and Ψ_3 were rotated 360°, with 30° increments, generating 144 conformers in each case. For each conformational analysis four local minima were localized, and then, optimized with the force field above mentioned. Finally, all minima were fully optimized at the RHF, closed-shell, ground-state level using the AM1 SCF-MO semiempirical program (M. J. S. Dewar, *J. Am. Chem. Soc.*, 1985, **107**, 3002) implemented in the MOPAC (version 6.0) option of DISCOVER. The 8 stationary states obtained were verified to be real minima by force calculations.

‡ After AM1 optimization, conformer **1b**:D was equal to **1b**:C minima (RMS: 0.06§). For conformer C the topographical parameters β and ε (J. B. Ball, R. A. Hughes, P. F. Alewood and P. R. Andrews, *Tetrahedron*, 1993, **49**, 3467) were −11.4 and −24.5°, respectively.

§ Root mean square fits were performed using the INSIGHTII package of programs.

¶ All new compounds gave satisfactory analytical and spectroscopic data consistent with the assigned structures.

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