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Synthesis of new β-turn dipeptide mimetic based on tetrahydroisoquinoline moiety

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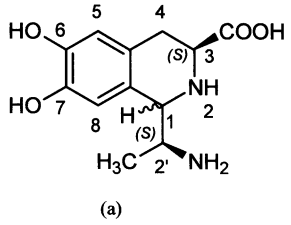
Abstract—A new β-turn dipeptide mimetic was performed by a Pictet–Spengler condensation, starting from *L*-DOPA and the corresponding aldehyde derived from Fmoc-*L*-Ala-OH.

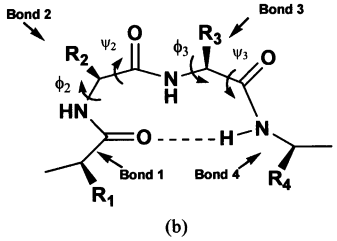
Among the different secondary structure of peptides the β-turn play a central role due to its common occurrence in the active site of peptides.[1,2] β-turns is defined as a tetrapeptide sequence in which the interatomic distance $C\alpha_1$–$C\alpha_4$ is <7 Å. A hydrogen bond is often present between CO(1) and NH(4), although open turns lacking this hydrogen bond also exist (Fig. 1).[3]

The β-turn is an attractive motif for intervention by low molecular weight, conformationally constrained peptidomimetic scaffolds.[4] In order to attain high affinity and selective binding to a target receptor, a β-turn mimetic must reproduce both the functionality and the orientation of the side chains of the receptor-bound peptide ligand.[5] A great effort has therefore been focused on design and synthesis of constrained dipeptide motifs those that would nicely mimic the natural β-turn in a given target molecule, particularly if it incorporates a carboxyl and amino group in geometrical suitable position for peptide coupling.[6] As part of a project directed towards development of syntheses of turn mimetic we wish to report the synthesis of a new β-turn dipeptide mimetic based on tetrahydroisoquinoline moiety, as shown in Fig. 1. The synthesis of the compound **1** was performed by a Pictet–Spengler[7,8] condensation from *L*-DOPA and the appropriate aldehyde. In our case, the starting aldehyde was prepared from Fmoc-Ala-OH by reduction as previously reported.[9,10] *L*-DOPA hydrochloride and Fmoc-*L*-Ala-H were dissolved in MeOH and stirred at room temperature under nitrogen for 4 day. Then, the mixture was evaporated in vacuo obtaining a white solid (Scheme 1).[11]

Compound **1** was obtained as epimeric mixture (3:2, **1a** and **1b**) and was resolved by reversed-phase HPLC technique[12] obtaining the corresponding diastereoisomers **1a** and **1b** (Fig. 3). Detailed inspection of the 1D and 2D NMR spectra permitted the complete assignment of the proton and carbon resonance for the products.[13] The determination of the configuration at



(a)



(b)

Figure 1. (a) New β-turn dipeptide; (b) a β-turn motif.

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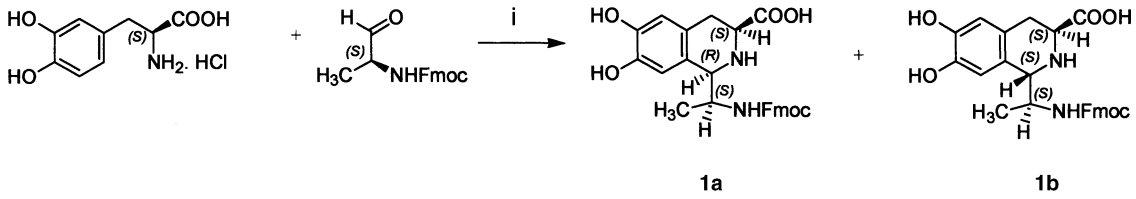

Scheme 1. *Reagents and conditions*: (i) MeOH, rt, 4 days.

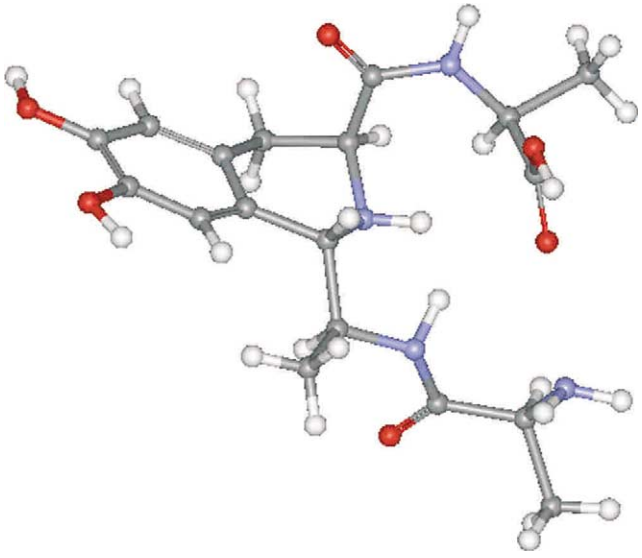

Figure 2. Model of **1b** in a tetrapeptide sequence.

the new asymmetric center C-1 was deduced from the NOESY experiments.

In fact strong exchanges of magnetization among the H-3 and H-1 in compound **1a** indicated that these protons were in *cis* disposition. This NOE effect was not observed in compound **1b** suggesting that the H-1 proton has a *trans* disposition with respect to the H-3 proton. Thus we assigned as *R* the absolute configuration at C-1 in **1a** (1*R*,2′*S*,3*S*) and *S* in its epimer **1b** (1*S*,2′*S*,3*S*).

Subsequently, in order to determine which one isomer has more propensity to adopt a β-turn conformation we performed on structure **1** a molecular modeling study using the MacroModel v7.0 program[14] on a Silicon Graphic O2 workstation. The results obtained suggest that the absolute configuration C-1 can affect the conformation of the backbone and than ultimately influence the overall structure. We found that while the isomer **1a** (1*R*,2′*S*,3*S*) shows an extended conformation, as deduced from the $C\alpha_1$–$C\alpha_4$ distance, calculation for isomer **1b** (1*S*,2′*S*,3*S*) reveal a $C\alpha_1$–$C\alpha_4$ distance of <7 Å (5.25 Å) and therefore a β-turn-like conformation. Also, an intramolecular hydrogen bound between CO(1) and NH(4) can be inferred by the interatomic distance of 2.95 Å. In Fig. 2 is shown a representative model of dipeptide mimetic **1b** in a tetrapeptide sequence with *L*-Ala.

Thus, NMR and modeling studies confirmed the proposed β-turn characteristic of the structure **1b**. In conclusion, the short synthetic approach described in this paper allows to prepare several β-turn dipeptides modifying the starting aldehyde.

Incorporation of new constrained dipeptide β-turn mimetic **1b** into biologically active peptides, such as opioids, substance P and melanocortins, where reverse-turn motif is important for activity, is currently underway in our laboratory.

Acknowledgements

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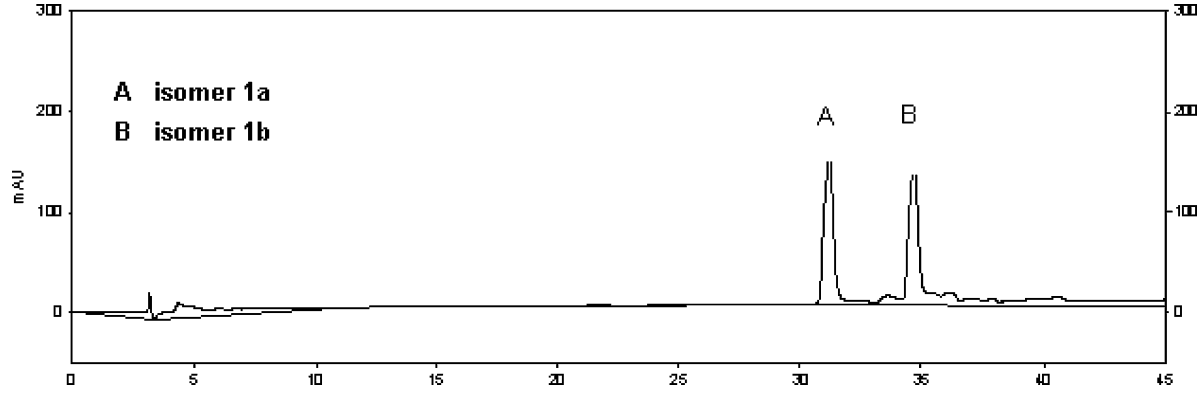

Figure 3. Analytical HPLC of compounds **1a** and **1b**.

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11. Synthesis of compound **1**: Fmoc-Ala-H (3.40 mM) was added to a solution of *L*-DOPA hydrochloride (3.40 mM) in methanol (50 mL) and the solution was stirred at room temperature for 4 days. Then, the solution was evaporated under reduced pressure and the residue was purified by HPLC.
12. Preparative RP-HPLC was performed on C18 column (Vydac 218TP152010) using a gradient of acetonitrile in 0.1% aqueous TFA at 5 mL/min. The following gradient was used: 10–40% acetonitrile in 45 min. Analytical RP-HPLC was performed on a C18 column using same gradient (Vydac 218TP54).
13. Final yield for compound **1**: 35%. Significant analytical and ^{1}H NMR data of **1a**: white crystalline solid, mp 138°C; MW 474.51.27, MS = 475.18, ^{1}H NMR (500 MHz, CD_3OD): δ 6.70 (s, 1H, 5-H), 6.60 (s, 1H, 8-H), 4.43–4.41 (brs, 1H, 1-H), 3.48–3.43 (m, 1H, 2′-H), 3.15–3.12 (m, 1H, 3-H), 2.93–2.91 and 2.81–2.78 (m, 2H, 4-H). ^{13}C NMR (125 MHz, CD_3OD): δ 63.9 (3-C), 57.4 (1-C), 42.1 (2′-C), and 25.6 (4-C). $k' = 7.75$ **1b**: white crystalline solid, mp 146°C; MW 474.51, MS = 475.30, ^{1}H NMR (500 MHz, CD_3OD): δ 6.63 (s, 1H, 5-H), 6.59 (s, 1H, 8-H), 4.33–4.32 (brs, 1H, 1-H), 4.04–4.01 (m, 1H, 2′-H), 3.67–3.65 (m, 1H, 3-H), 2.95–2.90 (m, 2H, 4-H), 4.16–4.13 (m, 2H, CH_2 ester) 3.67–3.65 (m, 1H, 4-H). ^{13}C NMR (125 MHz, CD_3OD): δ 61.4 (3-C), 54.0 (1-C), 46.9 (2′-C) and 27.3 (4-C). $k' = 8.07$
14. MacroModel v/7.0 software, Schrödinger, Framingham, MA, USA