Pergamon

Tetrahedron Letters, Vol. 35, No. 10, pp. 1493-1496, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0075-9

DESIGN, SYNTHESIS AND EVALUATION OF A NOVEL BICYCLIC LACTAM AS A GLY-PRO TYPE VI BETA-TURN MIMIC

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Abstract The stereoselective synthesis and conformational evaluation of Gly-Pro type VI turn mimic **7**, the first mimetic to constrain the central three bonds and incorporate the side chain groups of a beta-turn, is described. A superimposition of the crystallographically determined structure of **7** with the structure of a typical type VI turn revealed exceptional similarity in backbone and side chain atom positions. The temperature dependence of the chemical shift of the amide proton of the derivative **8** in DMSO confirmed the presence of a remarkably stable *i*, *i*+3 intramolecular hydrogen bond.

Conformationally constrained polypeptides forced to adopt beta turn conformations have been the focus of substantial research activity.[1,2] There is great interest in such compounds since turns are present in the active conformations of numerous biologically important peptides.[3] The design strategies toward turn-constrained analogs have been diverse,[4] and their successes in duplicating the structural features of turns have been varied.[5] In particular the type VI turn has attracted considerable interest as a result of its unique structural and functional properties (Figure 1).[6] The characteristic feature of the type VI turn is the presence of a *cis*-proline residue at the *i*+2 position. Type VI turns have been spectroscopically detected in the solution conformations of several highly potent peptide hormone analogs,[7] and have been implicated in the function of important proteins.[8] Structure-activity relationships of these molecules would be significantly clarified through functional analysis of analogs constrained to the type VI turn conformation using rigid mimics that incorporate side chain functional groups.

As part of a program to synthesize polypeptides as scaffolds for functional groups, we required a rigid mimic that possessed the conformational characteristics and side chain functional groups of the central two residues of the type VI turn and that would be amenable to solid phase peptide synthetic procedures. Inspection of the structure of the type VI turn[6] revealed that the Cα-H bond vectors of the *i*+1 and *i*+2 residues are disposed such that connection of the alpha carbons with a two atom covalent bridge would result in a conformationally stable bicyclic structure, as in compound **II** (Figure 1). Incorporation of the two atom bridge removes the possibility of rotation about the ψ_1, ω, and ϕ_2 bonds. Herein we report the synthesis and conformational evaluation of bicyclic lactam **II** (X=CH_2, R=H), a

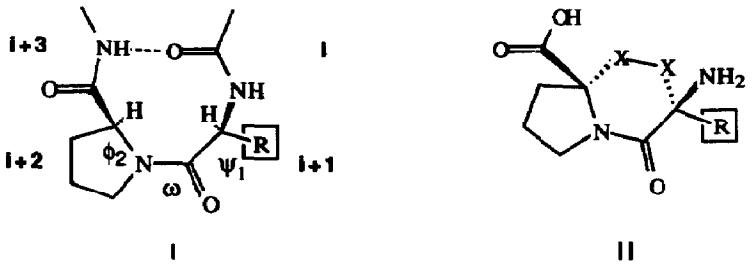


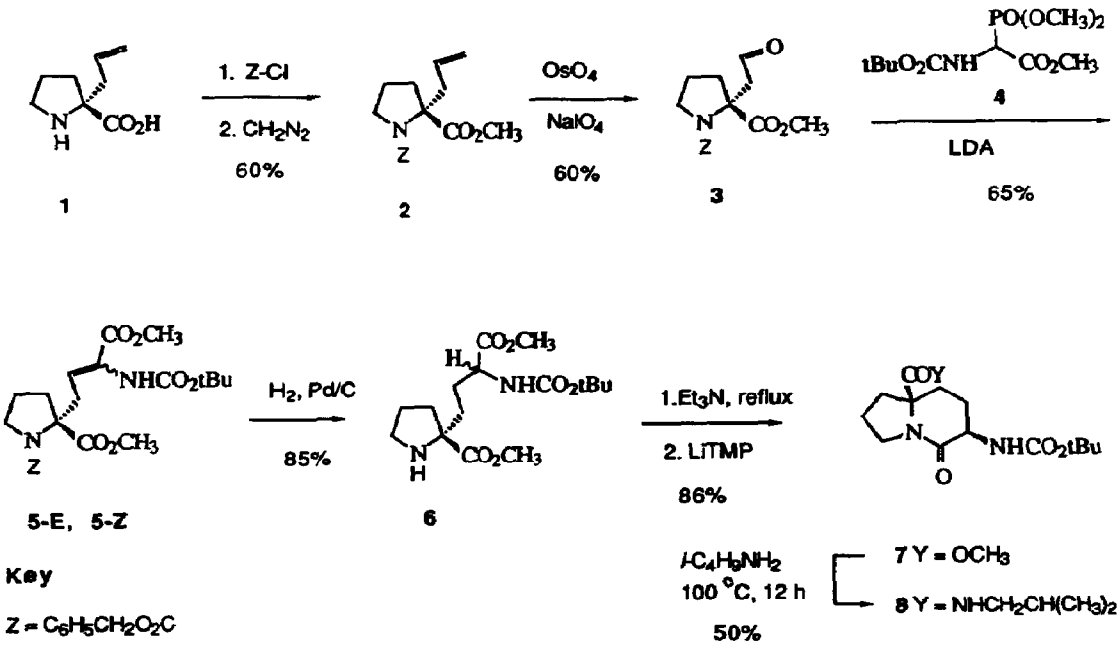
Figure 1. Structures of the type VI turn (I) and dipeptide mimic (II).

constrained Gly-Pro type VI turn[9] that is the first mimic to restrict the three central backbone torsion angles and to incorporate side chain functional groups.[10]

The starting material for the synthesis was (R)-2-(2'-propenyl)proline (**1**), available in optically pure form from (S)-proline following the procedure developed by Seebach and co-workers.[11] Protection of the secondary amino group of **1** as a benzyloxycarbamate and esterification of the carboxyl group proceeded smoothly to afford ester **2** in 60% overall yield.[12] Oxidative cleavage of the double bond of ester **2** was effected with sodium periodate and catalytic osmium tetroxide, resulting in aldehyde **3** (60%).

Attachment of a protected glycine synthon to the aldehyde function of the intermediate **3** proved non-trivial, but was successfully accomplished by a Wittig-Horner reaction. Condensation of **3** with phosphonate **4**[13] afforded dehydroamino acid **5** as an equimolar mixture of *E* and *Z* isomers (65%). The high yield of this transformation demonstrates the value of Wittig reactions to construct highly functionalized amino acid derivatives. Subsequent hydrogenolysis of the secondary amino protecting group of **5** occurred with concomitant alkene reduction to furnish amino ester **6** as a 1:1 mixture of diastereomers (85%). Cyclization of **6** was achieved with complete regioselectivity in refluxing triethylamine, resulting in a mixture of epimeric bicyclic lactams which could be completely converted to the thermodynamically more stable *cis* isomer **7** in 86% overall yield, completing the stereoselective synthesis.

The ability of bicyclic lactam **7** to duplicate the conformational features of the central two residues of a type VI turn was evaluated by crystallographic, computational and spectroscopic techniques. The structure of lactam **7** was determined by X-ray crystallography.[14] To assess the conformational similarity between mimic **7** and a typical type VI turn, a superimposition of the main chain and side chain atoms of **7** with the corresponding atoms of the type VI turn from RNase (Tyr92-Pro93)[15] was carried out using a computational overlay algorithm[16] that minimizes the deviation between the positions of analogous atoms of the two structures. The two structures displayed exceptional similarity, with 0.15 Å RMS overall deviation (Figure 2).



Further indication of the utility of the bicyclic structure of 7 as a mimic of the type VI turn was obtained from ^{1}H NMR spectroscopy of derivative 8. The temperature dependence of the chemical shift of the amide resonance of isobutylamide 8 in DMSO (-1.3 ppb/K) was consistent with an intramolecular hydrogen bond from the amide NH to the carbamate carbonyl oxygen.[17] The uncommonly low value for this number reflects the the exceptional stability of the *i*, *i*+3 hydrogen bond of the mimetic, which most likely is due to the substantial rigidity of the bicyclic structure.

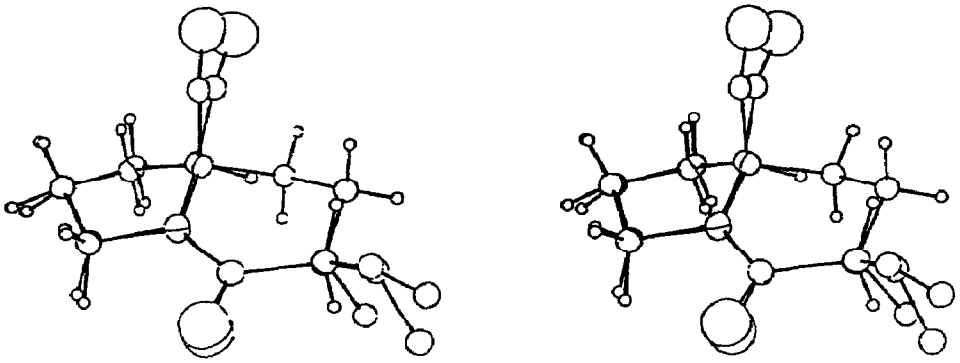


Figure 2. Stereoview of the overlay of the side chain and backbone atoms of 7 (X-ray structure) with those of the type VI turn (Tyr 92-Pro 93) of RNase. Positional deviations of the ester carbonyl carbon and carbamate nitrogen are 0.21 and 0.13 Å, respectively.

In conclusion we have shown that lactam **7** is a dipeptide mimetic of high rigidity and similarity in backbone and side chain conformation to the type VI turn. It is anticipated that turn mimics incorporating *i+1* side chain functional groups should be accessible through stereoselective alkylation of enolates derived from **7**. Studies are underway to prepare such functionalized mimics and to use these compounds to obtain constrained peptides.

Acknowledgment. Financial support from the University of Houston and American Cyanamid (Faculty Research Award to J. P. G.) is gratefully acknowledged.

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(Received in USA 3 *September* 1993; *revised* 10 *November* 1993; *accepted* 21 *December* 1993)