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# Stereoselective synthesis of conformationally constrained reverse turn dipeptide mimetics

Wei Qiu, Xuyuan Gu, Vadim A. Soloshonok, Michael D. Carducci and Victor J. Hruby*

*Department of Chemistry, University of Arizona, Tucson, AZ 85721, USA*

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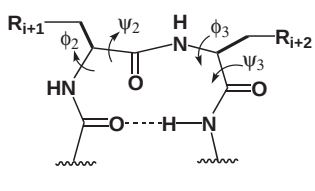
**Abstract**—Peptide side chains play critical roles in the event of molecular recognition. In order to study the bioactive conformation of parent peptides, a concise and straightforward five-step synthesis of [5.5]-bicyclic reverse turn dipeptide mimetic scaffolds with side chain functionality at the $i+1$ and $i+2$ positions has been developed. In the bicyclic structure, two dihedral angles ($\psi_2$ and $\phi_3$) are greatly restricted. 

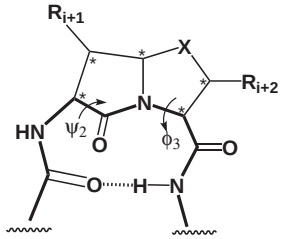
Our knowledge of how receptor–ligand interactions are manifested in biological changes often is very incomplete. A central goal in peptide and protein research is the development of systematic, predictive approaches to the design of peptidomimetics with specific conformational and topographical properties in order to obtain insights into the bioactive conformation of the native peptide on interaction with its receptor. Important peptidic mediators of biological information transduction such as hormones and neurotransmitters have great potential for medical applications, but often have inherent drawbacks such as high degrees of flexibility, biodegradability, and lack of receptor selectivity, which can complicate their use as drugs. Conformational constraints play an important role in rational design of peptides and peptidomimetics that can overcome these problems.[1]

The 'secondary structure approach' to de novo design of peptidomimetics is guided by the simple elegance which nature has employed in the molecular architecture of proteins.[2] Of the three major types of secondary structural motifs (α-helices, β-sheets and reverse turns), reverse turns offer the significant synthetic advantage that they are relatively compact, and of such a size that, in principle, they can be more readily mimicked by conformational constraint, or by use of more rigid small organic molecules.[3]

Though quite a few successes have been reported in obtaining mimetics which can force or stabilize β-turns,[4] very little success has been obtained in incorporating such mimetics into the agonist active site of peptide hormone or neurotransmitter ligands, due to the lack of appropriately positioned side chain groups. In the event of molecular recognition, the peptide backbone serves as a scaffold for the key side chain groups involved in the interaction. The side chain moieties involved directly in the binding are critical for the interaction. Their 3D architecture (topography) and




Type I β-turn

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* Corresponding author. Tel.: (520)621-6332; fax: (520)621-4964; e-mail: hruby@u.arizona.edu

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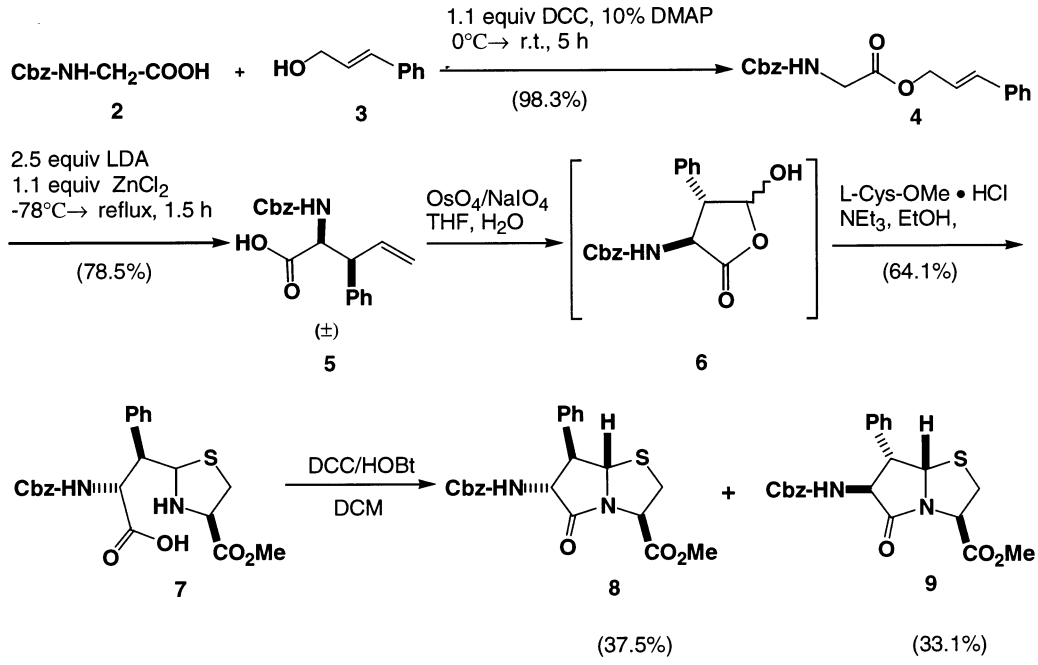



**Scheme 1.**

stereoelectronic properties provide the critical complementary shape and chemical properties that favors efficient molecular recognition. In order to truly mimic the backbone conformation and side chain orientation of different types of β-turns, a synthetic strategy requires stereocontrolled introduction of a minimum of four asymmetric centers, with different backbone geometry and side chain topography. Here we report our efforts to fulfill all the aforementioned criteria.

Extensive SAR studies on the peptide hormones/neurotransmitters α-MSH, oxytocin and their analogues have been done in our group.[5–7] Molecular dynamics simulations, molecular mechanics calculations, and NMR studies of selected potent analogues[8–10] have showed that in the low energy conformation, certain types of β-turns are preferred. Conformationally constrained bicyclic dipeptide mimetic scaffolds, such as template **1**, can provide at least 16 isomers with different backbone geometry and side chain orientation, which will greatly help us to study the bioactive conformation. Our synthesis begins with esterification of *N*-Cbz-glycine (**2**) to the amino acid ester **4**[11] (Scheme 1). A highly diastereoselective Claisen rearrangement of **4** generated a racemic mixture of β-vinyl phenylalanines (**5**).[12] The related literature procedure only gave moderate yields (~60%), but when refluxing conditions were applied after warming to room temperature, a 78.5% yield was obtained. Oxidative cleavage of **5** gave the γ-hydroxy-γ-lactone **6**. Although intermediate **6** was not purified before further reactions, its mono-methyl and trimethyl derivatives were characterized.[13] Condensation of **6** with L-cysteine methyl ester in EtOH gave a mixture of monocyclic amino acids **7**,[14] which were cyclized with DCC/HOBt in dichloromethane without further purification. Compounds **8** and **9** were separated by flash chromatography (EtOAc/hexanes 1:4 to 1:3). Their stereochemistry was assigned by 1D transient NOE experiments and confirmed by X-ray diffraction analysis. The X-ray crystal structure of compound **8** is shown in Fig. 1. Thus we have succeeded in incorporating a phenyl group into a template which mimics a phenylalanine side chain at the $i+1$ position. A Monte Carlo conformational search (MacroModel 6.0, Amber force field, aqueous environment) showed that in the lowest energy conformation, the $\psi_2$ and $\phi_3$ values are quite close to the values observed in the crystal structure.[15]

In order to incorporate an $i+2$ side chain into this [5.5]-bicyclic template, intermediate **5** was coupled with L-threonine[16] methyl ester to form a pair of diastereomers **10** and **11** (Scheme 2). Oxidative cleavage gave a mixture of γ-hydroxy lactams, which were cyclized in dry dichloromethane with catalytic amounts of TFA and 3 Å molecular sieves to give compounds **12**

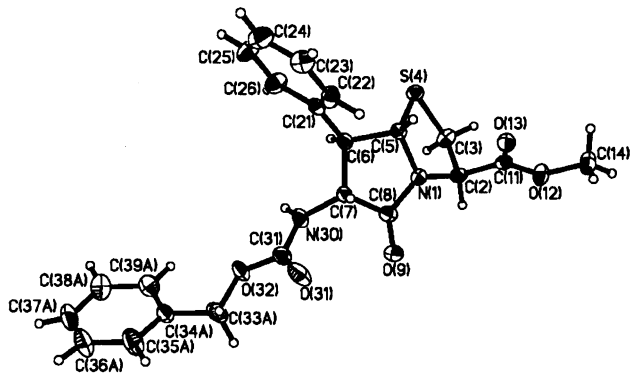
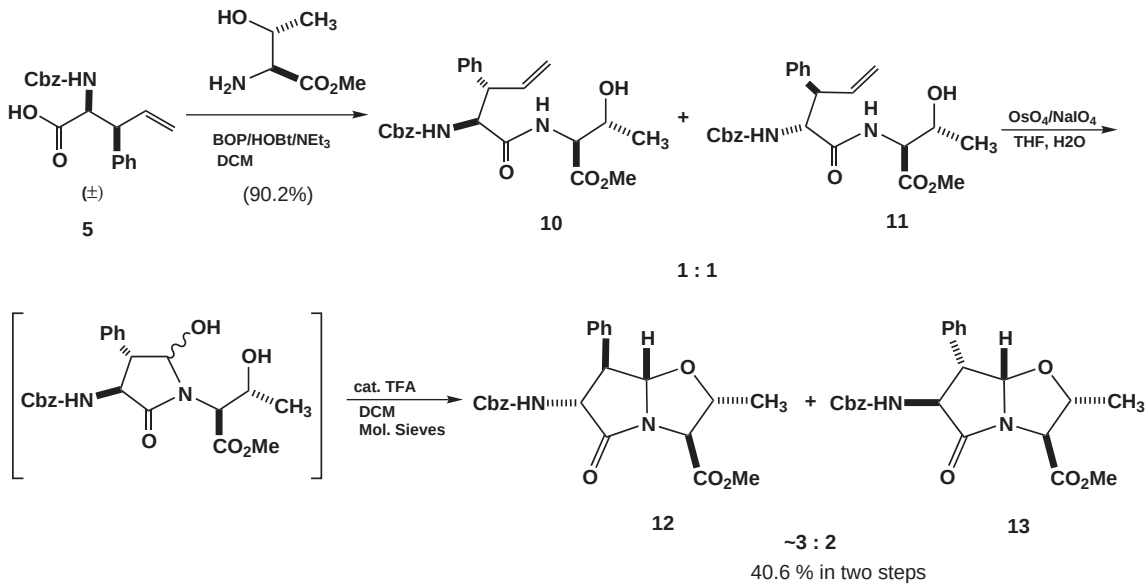



**Figure 1.** Crystal structure of (2*R*,5*S*,6*R*,7*R*)-methyl 1-aza-7-(*N*-benyloxycarbonylamino)-8-oxo-6-phenyl-4-thia-bicyclo-[5.5.0]octane-2-carboxylate (**8**).




**Scheme 2.**

and **13**. After separation by flash chromatography (EtOAc/hexanes 1:4 to 1:3), the stereochemistry of **12** and **13** was assigned by 1D transient NOE experiments.

In conclusion, a concise and straightforward five-step synthesis of [5.5]-bicyclic reverse turn dipeptide mimetic scaffolds with side chain functionality at the $i+1$ and $i+2$ positions has been developed. In the bicyclic structure, two dihedral angles ($\psi_2$ and $\phi_3$) are greatly restricted. Further development of the synthesis will enable us to prepare various types of reverse turns with different backbone geometry and side chain topography. Incorporating these conformationally and topographically constrained scaffolds into peptides will help us to understand the bioactive conformation of the parent peptides. Due to its convergent nature, this synthesis also has the potential to be applied to both solid phase chemistry and combinatorial chemistry, which is under investigation.

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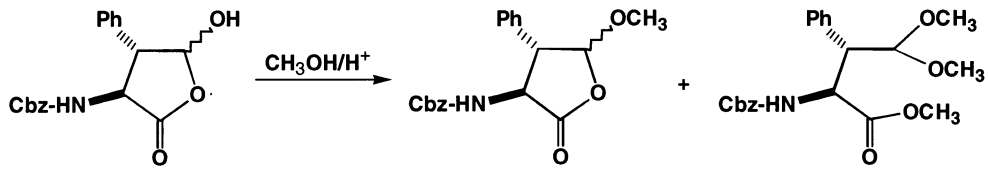


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