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Solid-Supported Synthesis of a Peptide β-Turn Mimetic

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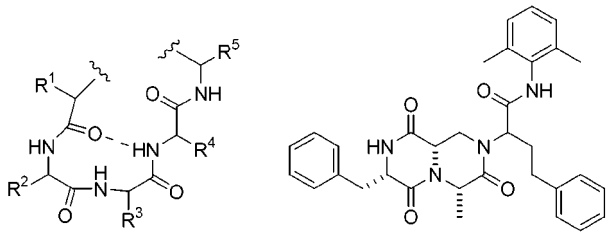
ABSTRACT



The solid-supported synthesis of a bicyclic diketopiperazine, a potential peptide β-turn mimetic, is described. The Ugi reaction between the resin ester of α-*N*-Boc-diaminopropionic acid (an amine input), α-bromo acid, aldehyde, and isocyanide is the key step in the proposed protocol.

We recently described our efforts in the high-throughput organic synthesis of peptide turn mimetic libraries based on piperazinic acid scaffold **1** (Figure 1).[1] While studying methods that would allow us to introduce the missing R^3 substituent, we turned our attention to diaminopropionic acid as a source of the central framework on which we hoped to build our libraries.[2] Another approach using diaminopropionic acid in the solid-phase synthesis of pyridones and pyridopyrazines as a peptidomimetic scaffold has also been reported.[3] While working on this manuscript we became aware of Kahn and co-workers approach to conformationally restricted peptide secondary structure mimetics utilizing a similar bicyclic heterocyclic scaffold.[4] A cyclopropyl derivative of this heterocycle was recently reported by Belov and co-workers.[5] The β-turn is a common feature in biologically active peptides and is defined as any tetrapeptide sequence

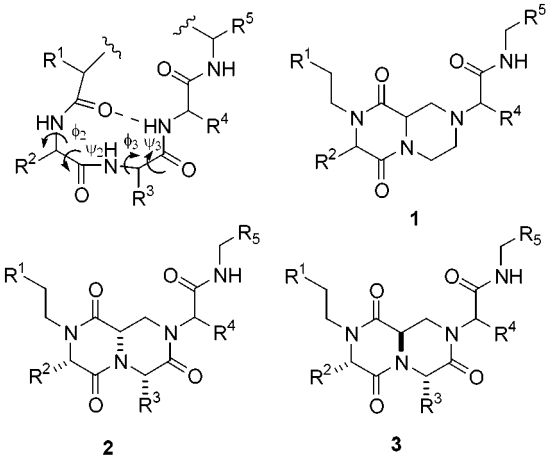


Figure 1. Peptide β-turn and the evolution of our peptide turn mimetic concept.

with a 10-membered intramolecularly H-bonded ring, in which the $C_\alpha{}^i-C_\alpha{}^{i+3}$ distance varies from 4 to 7 Å.[6] Contingent upon the dihedral angle values for ϕ_2, ψ_2, ϕ_3,

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(2) Recent, improved synthesis of diamino propionic acid: Zhang, L. H.; Kauffman, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem*. **1997**, *62*, 6918−6920.

(3) Creighton, C. J.; Zapf, C. W.; Bu, J. H.; Goodman, M. *Org. Lett*. **1999**, *1*, 1407−1409.

(4) Kim, H. O.; Nakanishi, H.; Lee, M. S.; Kahn, M. *Org. Lett*. **2000**, *2*, 301−302.

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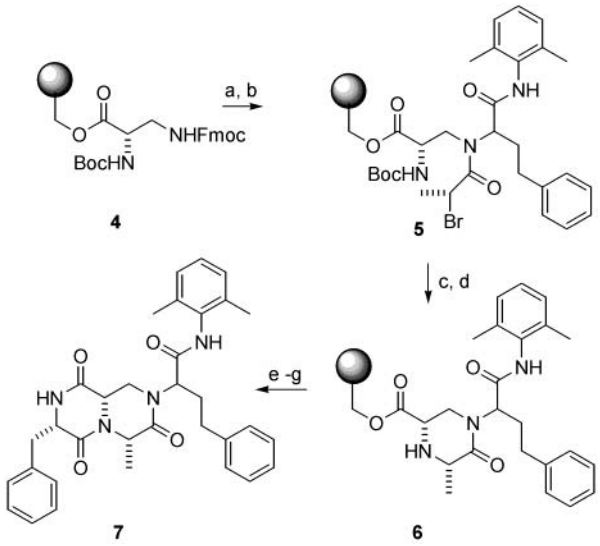
and ψ_3, there are at least 14 types of β-turn structures described in the literature.[7] Preliminary modeling using the SYBYL 6.6 molecular modeling program was performed on structures **2** and **3** (Figure 1) to determine their propensity to adopt a β-turn. It consisted of energy minimizing both structures in a distance dependent dielectric and then constraining the dihedral angles in a β-turn followed by energy minimization of the fully unconstrained structures. The root-mean-square deviation calculated for the heavy atoms between a type I β turn and the structure **2** (R^1,R^5 = H, R^4 = CH_3) was 1.1 Å, and the deviation was 0.9 Å with structure **3**. The root-mean-square deviations between type II β turns and structures **2** and **3** were 0.7 and 0.9 Å, respectively.

These results suggest that the absolute stereochemistry of diaminopropionic acid can slightly affect the conformation of the backbone which will ultimately influence the overall positioning of the side chains. This should allow us to tune our mimetic into a given β-turn target. Figure 2 presents compound **7** overlapped with a type II β-turn peptide.

Figure 2. Compound **7**, (*S*)-diaminopropionic acid, as the substrate, overlapped with a type II β-turn peptide (magenta).

α-*N*-Boc-β-*N*-Fmoc-L-diaminopropionic acid was attached to Merrifield's hydroxymethyl resin using Mitsunobu conditions to provide resin ester **4**.[8] Standard Fmoc-group deprotection exposed an amine group which was applied as one of the inputs in solid-phase Ugi reaction (Scheme 1).

Scheme 1[a]



[a] Reagents and conditions: (a) 25% piperidine, DMF, 30 min; (b) hydrocinnamaldehyde (5 equiv), 2,6-dimethylphenyl isocyanide (5 equiv), (*R*)-(+)-2-bromopropionic acid, MeOH/$CHCl_3$ (1:4; v/v), rt, 2 × 2 h; (c) 25% TFA in DCM; (d) 10% DIPEA, DCM, rt, 18 h; (e) Boc-Phe-OH, NMM, isobutyl chloroformate, THF/DMF; (f) 25% TFA, DCM; (g) 2 M AcOH, i-PrOH, 50 °C, 18 h.

Optically active (*R*)-(+)-2-bromopropionic acid, hydrocinnamaldehyde, and 2,6-dimethylphenylisocyanide were used in excess (5 equiv) to drive the reaction to completion. Boc group removal followed by base-catalyzed cyclization afforded resin-bound product **6**. The second ring system was elaborated via Boc-amino acid coupling, amino group deprotection, and cyclitive cleavage induced by heating the resin in 2 M acetic acid in 2-propanol. We tested several coupling procedures, and the mixed anhydride method was found to be the optimum. As expected, the application of a cyclitive cleavage step afforded the crude product **7** with a relatively high level of purity (85% pure HPLC/UV detector).

After HPLC purification, the product **7** was isolated in overall 20% yield (calculated on the Merrifield-OH resin)—82% average yield.

The diastereoselectivity of the Ugi reaction was not very high, and as a consequence the crude product **7** was isolated as a 1:1.5 mixture of diastereoisomers (**7a** and **7b**) at the R^4 center.[9] However, it should be pointed out that the present method allows for control of all the remaining chiral centers. Both enantiomers of diaminopropionic acid are readily available from L- and D-asparagine.[2] Optically active α-bromo acids are readily prepared from related α-amino acids.[10] The bromine displacement occurs via an S_N2 mechanism with inversion of the configuration on the R^3 stereocenter.[11] No

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(11) As proven by NOESY experiment: see Supporting Information.

epimer at the R^2 chiral center was isolated. Substituents R^4 and R^5 are not conformationally constrained, but they are presented in the right distance and position to the remaining R^1, R^2, and R^3 side chains. Simulated annealing was performed on structure **7**. The protocol consisted of 50 cycles of annealing from 1000 to 300 K, with a 10 ps annealing time. This process yielded 50 structures whose energy-minimized average structure is presented in Figure 2. This compound overlapped well with a type II β turn as indicated by the small root-mean-square deviation of the heavy atoms (0.5 Å).

In conclusion, we have developed an efficient solid-supported synthesis of a peptide β-turn mimetic. The key multicomponent reaction is carried out under mild conditions utilizing readily available components. The final product is obtained in high yield and good purity. The scope and limitations of the proposed method as well as its demonstration in the high-throughput mode are currently being studied in our group and will be reported shortly.

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Supporting Information Available: Experimental procedures and characterization details (^{1}H and ^{13}C NMR, NOESY, LC-MS) for products **7a** and **7b**. This material is available free of charge via the Internet at http://pub.acs.org.

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