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THE INCORPORATION OF β-TURN PROSTHETIC UNITS INTO MERRIFIELD SOLID PHASE PEPTIDE SYNTHESIS

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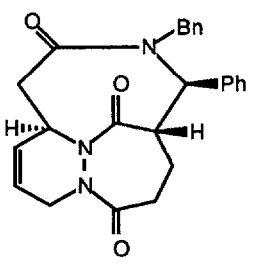
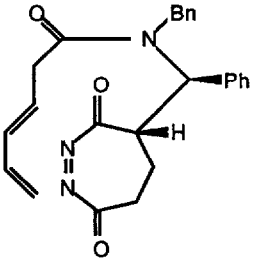
Abstract: The incorporation of designed conformationally restricted nonpeptide β-turn prosthetic units onto the amino terminus of peptides is discussed. The synthesis of the peptides, including the incorporation of the β-turn mimetic was accomplished using Merrifield solid phase automated peptide synthesis.

As part of our continuing efforts to explore the relationship between peptide structure and function, we are investigating the design and synthesis of peptide mimetics, and mimetic chimeras (i.e., peptide mimetic prosthetic units incorporated into oligopeptides).[1,2,3] This letter describes the integration of our previously described β-turn mimetic units[2] into Merrifield solid phase automated peptide synthesis.[4] These chimeric mimetics are providing unique substrates with which to examine the role of turn regions[5] in proteolytic processing[6], antigen antibody recognition[7] and the nucleation of protein folding.[8]

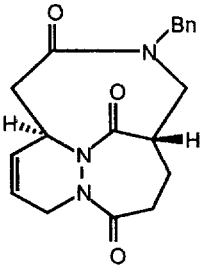
Previously, we had investigated the addition of nucleophiles (including glycine methyl ester) to the tricyclic ring system (1) which was derived from an intramolecular [4+2] cycloaddition of the diazodicarbonyl system (2).[2]



(1)



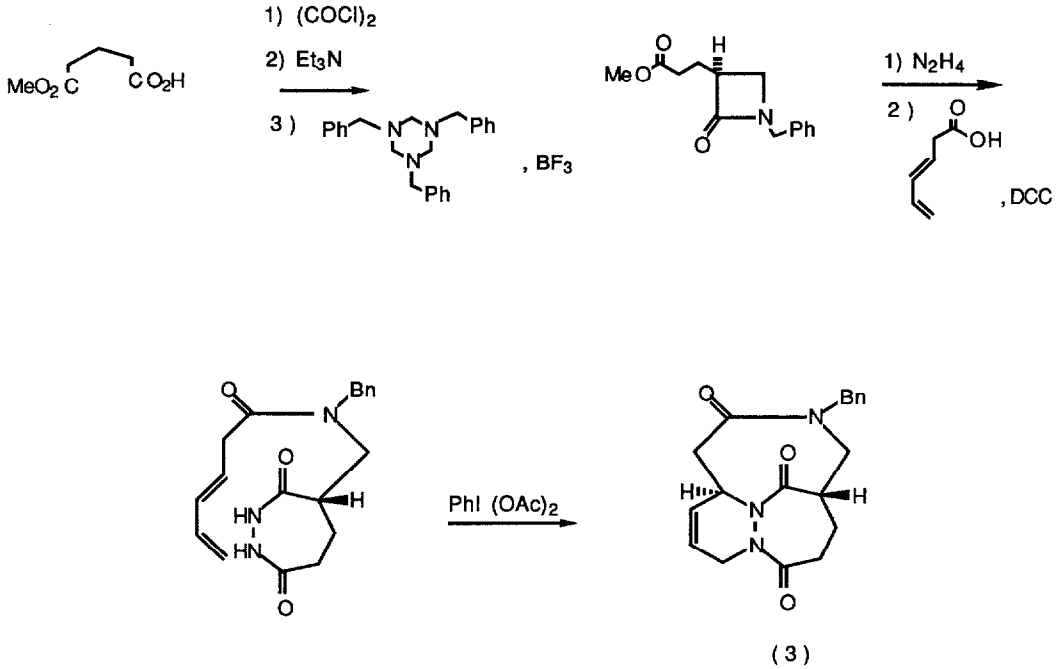
(2)



(3)

We had noted that the remarkably facile cleavage of the lactam could be readily rationalized on the basis of an IR stretching frequency of 1785 cm^{-1}, attesting to the strain and a lack of amide resonance in the unusually bridged 8-membered ring. Based on this analysis, we anticipated that the tricyclic Diels Alder adduct could be utilized as the activated ester component in a standard solid phase protocol. In the event, we have successfully incorporated into Merrifield synthesis, the synthetic turn mimic **3**. The tricyclic system **3** can be prepared in a six step process (47% overall yield) which is outlined in Scheme **1**.

Scheme 1.



(3)

After filtration through anhydrous potassium carbonate, the crude tricyclic system **3** is double coupled (2 eq.) to the free amino terminus of the growing peptide chain, whose C-terminus is attached to a polystyrene support. As can be seen from Table 1, this methodology is compatible with either BOC or FMOC strategies, and a variety of resin cleavage techniques.[4,9]

Table 1.

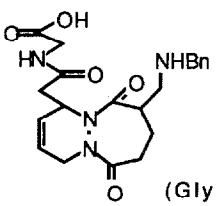
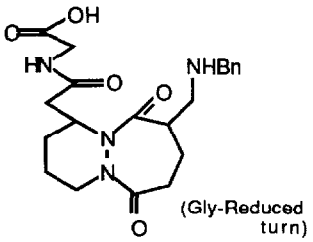
strategy used	method of cleavage from the resin	peptide sequence	product	purified yield (%)
FMOC	TFA/CH_2Cl_2	Gly	 (Gly-turn)	68
FMOC	TFA/CH_2Cl_2	Gly-Ala	Gly-Ala-turn	55

Table 1. (continued)

strategy used	method of cleavage from the resin	peptide	product	purified yield (%)
BOC	$Pd(OAc)_2/NH_4CO_2H$ [9]	Gly	 (Gly-Reduced turn)	65
BOC	HF/Anisole	Gly	Gly-turn	69
BOC	HF/Anisole	Arg-Phe-Pro-Ser	Arg-Phe-Pro-Ser-turn	42
BOC	HF/Anisole	Arg-Ala-Lys	Arg-Ala-Lys-turn	33

Cleavage of the chimeric peptide from the resin can be accomplished using several different cleavage strategies. The cleavage methods investigated to date are: 1) anhydrous HF/anisole, 2) 50% TFA in CH_2Cl_2, and 3) catalytic transfer hydrogenation with $Pd(OAc)_2/NH_4CO_2H$. [10] The reductive cleavage, as anticipated, also reduces the olefin in the nonpeptide turn portion of the molecule.

Investigations extending these studies to the continuation of the peptide synthesis on the newly generated amino terminus are in progress, as are the biological evalution of these novel chimeric peptide mimics. These results will be reported in due course. In summary, this facile procedure for generating conformationally restricted mimetic chimeras should provide unique systems with which to explore the importance of turn regions in a variety of molecular recognition processes.

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