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METHODOLOGY FOR THE SYNTHESIS OF MIMETICS OF PEPTIDE β-TURNS*

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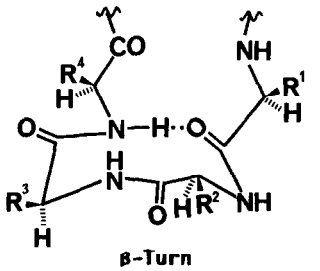
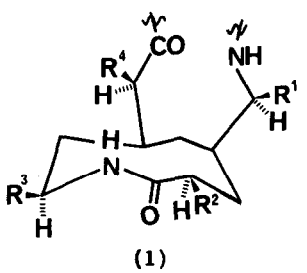
Summary This letter describes a scenario which provides for the stereospecific introduction of both the amino and carboxyl termini portion of a designed β-turn mimetic.

Peptides and proteins are ubiquitously distributed in nature, and play critical roles in the regulation of virtually all biological processes. Despite this central position, the understanding of the relationship between the structure and activity of peptides at the molecular level remains one of the important goals of contemporary biochemistry. The metabolic instability, conformational flexibility, and lack of specificity of peptides has hampered the investigation of this problem. Structural restrictions can reduce the difficulty of this determination, thereby yielding valuable information concerning the conformational requirements of a peptide at its receptor.[2]

Our investigations are focusing on the design and synthesis of systems which mimic peptide β-turns.[3] Due to a predominance of potentially reactive functional groups in their side chains and their surface localization in proteins, turns have been implicated as recognition sites which trigger complex immunological, metabolic, genomic and endocrinologic regulatory mechanisms.[4] Based on molecular modeling, we have chosen the nine-membered ring lactam 1 to mimic the pseudocyclic ten-membered system of a Type I β-turn.[5] This letter describes a strategy for the stereospecific introduction of the



β-Turn



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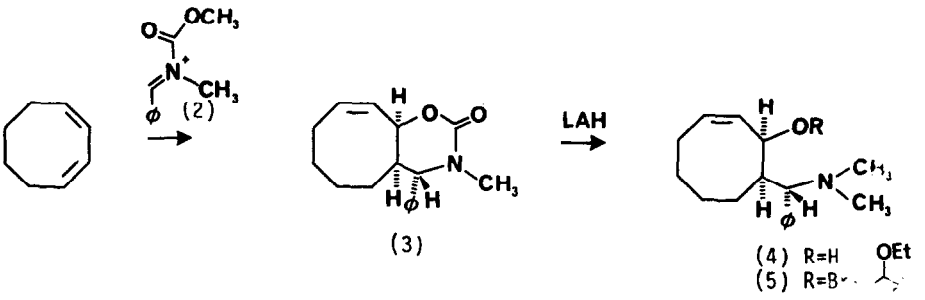
amino and carboxyl termini portion of mimetic (1).

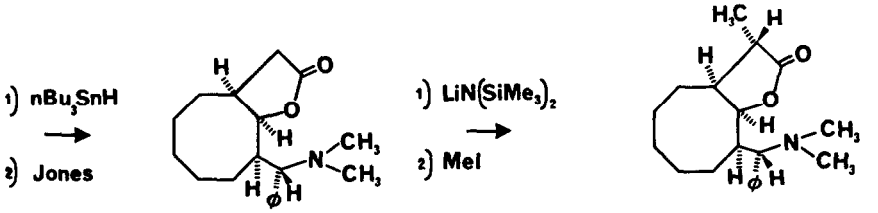
A model study to investigate the feasibility of this scenario is outlined in

*Dedicated to Professor Gilbert Stork on the occasion of his sixtyfifth birthday.

Scheme I. Cycloaddition of acyliminium species 2[6,7] with 1,3 cyclooctadiene occurs both stereo and regioselectively[8] affording carbamate 3 in 37% yield after chromatography. Lithium aluminum hydride reduction provides amino alcohol 4 in 82%

Scheme I





(6) (7)

yield, as a white solid (mp 95-8°). Treatment of 4 in CH_2Cl_2 with 1,2 dibromoethoxyethane[9] generates radical cyclization precursor 5 after neutralization. Tributyltin hydride induced cyclization[10] in refluxing benzene and subsequent Jones oxidation provides in 42% overall yield, crystalline amino lactone 6 (mp 116-118°). Stereospecific introduction of a methyl group is accomplished in 76% yield via the alkylation of the lithium enolate of lactone 6 with methyl iodide at -78°C.[11]

The synthesis of model system 7, demonstrates the utility of this methodology for the stereospecific introduction of the amino and carboxyl termini, and the R^1 and R^4 substituents of mimetic 1.[12] Incorporation of this scenario into the synthesis of nonpeptide β-turn mimetics of type (1), to mimic biologically active peptides and proteins are in progress and will be reported in due course.[13]

Acknowledgements

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References

(1) Recipient of a Camille and Henry Dreyfus Distinguished Young Faculty Award 1986-1991, a Searle Scholars Award 1986-89, and a NSF Presidential Young Investigator Award 1987-1992.

(2) See for example; Veber, D. F., and Freidinger, R. M. (1985) Trends Neuroscience, 8, 392.

(3) For previous examinations of β-turn mimics see; Feigel, M. (1986) J. Am. Chem. Soc. 108, 181-2; Kemp, D. A. and McNamara, P. E. (1984) J. Org. Chem. 49, 2286-8; Nagai, U., Sato, K. (1986) JCS Perkin I, 1231. Two studies on the design of nonpeptide mimetics of enkephalin have been reported; Belanger, P. C., Dufresne, C., Scheigetz, J., Young, R. N., Springer, J. P. and Dimtrienko, G. (1982) Can. J. Chem. 60, 1019-29; Krstenansky, J. L., Baranowski, R. L., and Currie, B. L. (1982) Biochem. Biophys. Res. Commun. 109, 1368, for the importance of turns in enkaphalins see; Schiller, P. W. (1984) in The Peptides (Udenfriend, S. and Meienhofer, J., eds.) Vol 7, Academic Press, New York.

(4) For an excellent review on turns see; Rose, G. D., Gierasch, L. M., and Smith, J. A. (1985) Adv. Prot. Chem. 37, 1-109.

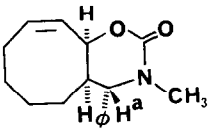
(5) Preliminary investigations were initiated during a postdoctoral year at Hoffmann-La Roche, M. Kahn, G. Olson unpublished results, to be published in due course.

(6) Schmidt, R. R. and Hoffmann, A. R. (1974) Chem. Ber. 107,78. For an excellent review on amidoalkylation see; Zaugg, H. E. (1984) Synthesis, 181. Acyliminium salt 2 is generated in situ in CH_2Cl_2 by treatment of the N-methylimine of benzaldehyde with methyl chloroformate in the presence of $TiCl_4$ at 0°C.

(7) All new structures are fully consistent with their PMR (200MHz), IR and MS data.

(8) For earlier examination of the stereo and regioselectivity of acyliminium species

see; Schmidt, R. R., and Machat, R. (1970) Angew. Chem. Int. Ed. Eng. 9, 311; Carbamate 3: H_a 3.98 δ (d, J=6Hz)



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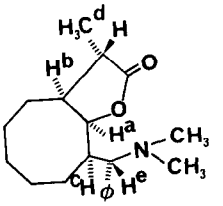
(9) Stork, G., Sher, P. M. (1983) J. Am. Chem. Soc. 105, 6765, and references therein.

(10) Stork, G., and Kahn, M. (1985) J. Am. Chem. Soc. 107, 500 and references therein.

(11) Stereochemical assignment was made via the aegis of a difference NOE experiment; lactone 7; NOE's

$H_a \rightarrow H_b$	13.6%
$H_a \rightarrow H_c$	10.2%
$H_a \rightarrow H_d$	1.6%
$H_a \rightarrow H_e$	9.5%



(7)

(12) Molecular models indicate a distance of approximately 5Å between the α-carbons of the R^1 and R^4 residues of mimetic 7, by comparison the generalized distance in a turn conformation would be 5.5-7 Å.

(13) We have recently demonstrated that utilizing a model system somewhat structurally related to 1, we can mimic the activity of the immunosuppressant tripeptide (Lys-Pro-Arg); Kahn, M. Devens, B. (1986) Tetrahedron Lett. 4841.

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