THE DESIGN AND SYNTHESIS OF A NONPEPTIDE MIMIC OF ERABUTOXIN†

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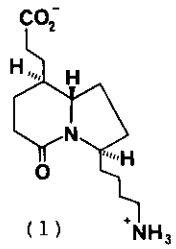
Abstract - The synthesis of indolizidinone 1, a designed mimic of the proposed bioactive region of erabutoxin, a lethal venom protein, is detailed.

Peptides and proteins are ubiquitously distributed in nature, and play vital roles in the regulation of virtually all biological processes. The understanding of the relationship between the conformation and activity of these peptides is one of the important goals of contemporary biochemistry. In this regard, we are engaged in the design and synthesis of conformationally restricted mimetics of bioactive peptides and proteins.

Erabutoxin b, whose x-ray structure has been determined,[2] is a 62 amino acid lethal neurotoxic venom protein isolated from the broad-banded blue sea snake. Erabutoxin acts through the blockade of the post-synaptic nicotinic acetylcholine receptor ($K_D \tilde{=} 10^{-11}$ M) in a nondepolarizing curare-like manner.[3] Venoms from both hydrophiidae (sea snakes) and elapidae families (cobras, kraits, mambas) exhibit a common mode of action and strong structural homology. The highly conserved region Asp-Phe-Arg-Gly (residues 31-34) is contained within a β-turn region at the end of the longest of three loops of β-pleated sheet, and has been proposed to contain the residues critical for binding to the acetylcholine receptor protein.[4] It is this region which we have chosen to mimic.

Based on molecular modeling, we have designed a first generation β-turn mimetic 1, incorporating the functionality representative of the aspartyl and arginyl side chains, the synthesis of which is the subject of this communication.

†This paper is warmly dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.



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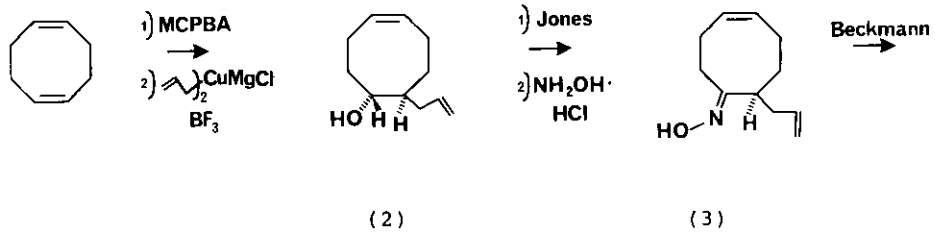
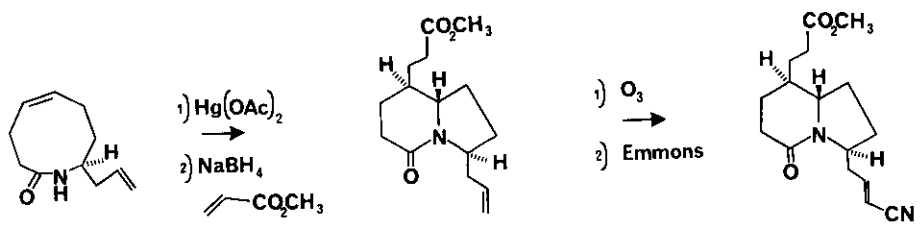
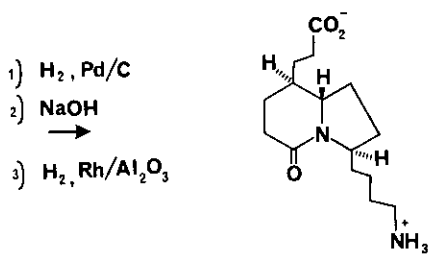
Our synthesis commences with the readily available monoepoxide of cyclooctadiene. Allylcuprate opening, utilizing the procedure of Normant,[5] affords in 87% yield the cyclooctenol derivative 2. Jones oxidation and subsequent oxime formation provides anti-oxime 3. Beckmann rearrangement via the tosyloxime generates the nine membered ring lactam 4 in 52% yield. Amidomercuration[6], followed by stereospecific reductive trapping with methyl acrylate affords the bicyclic lactam 5 in 57%.[7,8] Ozonolysis, reductive workup and subsequent Horner-Emmons condensation with diisopropyl cyanomethylphosphonate affords nitrile ester 6.



(2) (3)



(4) (5) (6)



(1)

Hydrogenation of the olefin, hydrolysis of the ester, and catalytic reduction of the nitrile using the procedure of Baker[9] provides mimetic 1 in 82% yield from 6.

The biological evaluation of erabutoxin mimetic 1, in a nicotinic acetylcholine binding assay is in progress and will be reported in due course. In light of the relationship between morphine and the endogenous enkephalins, and the ability of the indolizidine skeleton to mimic the framework of a ß-turn, one may anticipate the discovery of turn regions of endogenous peptides which have naturally occuring mimetics amongst the bioactive alkaloids.[10]

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REFERENCES

1) Recipient of a Camille and Henry Dreyfus Distinguished Young Faculty Award 1986-1991, and Searle Scholars Award 1986-89.

2) G. A. Petsko,and D. Tsernoglou, FEBS Letters, 68, 1 (1976); B. W. Low, H. S. Preston, A. Sato, L. S. Rosen, J. E. Searl, A. D. Rudko, and J. S. Richardson, Proc. Natl. Acad. Sci. USA, 73, 2991 (1976).

3) C. Y. Lee, Ann. Rev. Pharmacol., 12, 265 (1972).

4) L. Ryden, D. Gabel, and D. Eaker, Int. J. Peptide Prot. Res,. 5, 261 (1973).

5) A. Ghribi, A. Alexakis, and J. F. Normant, Tetrahedron Lett., 3075 (1984).

6) S. R. Wilson, and R. A. Sawicki, J. Org. Chem., 44, 330, 1979.

7) B. Giese, Angew. Chem. Int. Ed. Engl., 22, 753 (1983).

8) ^{13}C spectroscopy shows the presence of only one diastereomer.

9) A. Rosenthal, and D. A. Baker, J. Org. Chem., 38, 193 (1973).

10) For a recent example see: R. S. L. Chang, V. J. Lotti, R. L. Monahan, J. Birnbaum, E. O. Stapely, M. A. Goetz, G. Albersi Schönberg, A. A. Patchett, J. M. Leisch, O. D. Hensens, and J. P. Springer, Science, 230, 177 (1985).

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