Tetrahedron Letters,Vol.27,No.40,pp 4841-4844,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

The Design and Synthesis of a Nonpeptide Mimic of an Immunosuppressing Peptide

Michael Kahn*[1]

Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60607

Bruce Devens

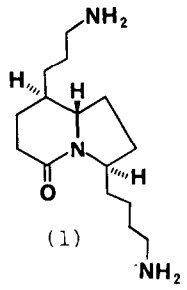
Department of Immunopharmacology, Hoffmann-La Roche Inc., Nutley, NJ 07110

Summary. The synthesis and preliminary biological evaluation of a nonpeptide mimic of the immunosuppressant tripeptide (Lys-Pro-Arg) is described.

Tuftsin, a naturally occuring tetrapeptide (Threonyl-Lysyl-Prolyl-Arginyl) isolated by Najjar and coworkers,[2] has demonstrated immunostimulating activity both *in vitro* and *in vivo*, however its biological half life, both in blood and serum,is quite short. Tuftsin is contained within the CH_2 domain of the Fc fragment (residues 289-292) of IgG. Upon liberation from IgG via the action of tuftsin-endocarboxypeptidase and leukininase, tuftsin has the ability to activate phagocytic cells, principally macrophages. In addition to phagocytic stimulation, tuftsin has shown several other effects on macrophages and granulocytes, including increasing antibody production, tumoricidal action, and bactericidal activity.[3] Interestingly both of tuftsin's initial degradation products (Thr-Lys-Pro) and (Lys-Pro-Arg) behave as competitive inhibitors of their progenitor.[4] The former has demonstrated antiinflammatory action.[4]

As part of our program concerning nonpeptide models of bioactive peptides and proteins, we have initiated a study to design and synthesize a mimetic of the tuftsin inhibitory sequence (Lys-Pro-Arg). As with most small oligopeptides, their definitive solution conformation, much less the conformation with which they bind to their receptor is ambiguous. The consensus opinion from a large array of spectroscopic[5] and computational studies[6] is that one low energy form of tuftsin exists as a turn or hairpin.[7] Based on this information, and our general interest in turns as message elements in biological systems, we have designed indolizidinone 1 as our first generation mimetic of the tripeptide (Lys-Pro-Arg). The synthesis and preliminary biological evaluation of 1 form the basis of this communication.

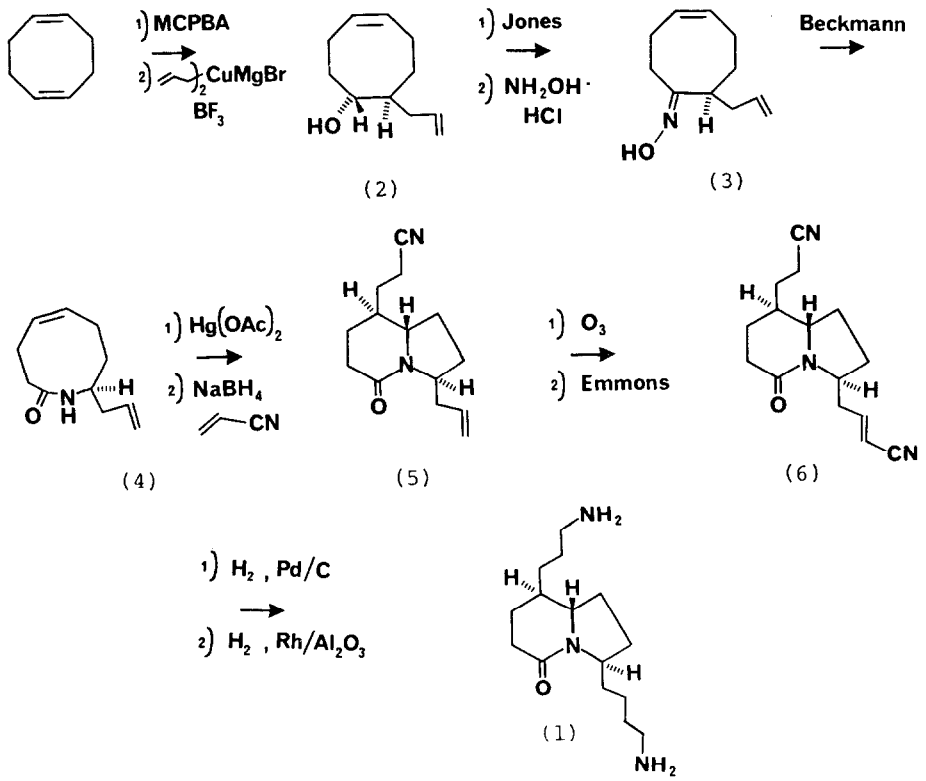
Dedicated to Professor Samuel Danishefsky on the occasion of his 50th. birthday March 10, 1986.



(1)

(Lys-Pro-Arg)

Our synthesis commences with the readily available monoepoxide of cyclooctadiene. Allylcuprate opening, utilizing the procedure of Normant,[8] 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[9], followed by stereospecific reductive trapping with acrylonitrile provides bicyclic lactam 5 in 56%.[10,11] Ozonolysis, reductive workup and subsequent Horner-Emmons condensation with diethyl cyanomethylphosphonate affords 6. Hydrogenation of the olefin and subsequent reduction of the bis-nitrile using the procedure of Baker[12] provides



mimetic 1 which was isolated as its bis hydrochloride salt in 78% yield from 6. Indolizidine 1 blocked the stimulatory effect of tuftsin on macrophages in an opsonized sheep red blood cell assay in a dose dependant fashion.[13] Further studies, including in vivo evaluation of 1 and related cogeners is in progress and will be reported in due course. These initial studies augur well for the design of nonpeptide mimics of bioactive peptides, which we anticipate will have enhanced half lives and greater bioavailability than their naturally occuring counterparts. In light of the relationship between morphine and the endogenous enkephalins, and the ability of the indolizidine skeleton to mimic the framework of a β-turn, one may anticipate the discovery of turn regions of endogenous peptides which have naturally occuring mimetics amongst the bioactive alkaloids.[14]

Acknowledgement. We wish to express our sincere appreciation to the Camille and Henry Dreyfus Foundation, Searle Scholars Program/The Chicago Community Trust, Hoffmann-La Roche Inc., the Research Corporation, the Donors of the Petroleum Research Fund administered by the American Chemical Society and the University of Illinois for generous support of our research.

References and Notes

1. Recipient of a Camille and Henry Dreyfus Distinguished Young Faculty Award 1986-1991 and a Searle Scholars Award 1986-1989.

2. V. A. Najjar, K. Nishioka, Nature 228, 672, 1970.

3. A. Capron (Institut Pasteur, Lille, France) has isolated from the serum of schistosome infected rodents the tripeptide (Thr-Lys-Pro); A. P. Capron, J. P. Dessaint, Annv. Rev. Immunol. 455, 1985, I. Z. Siemion, D. Konopinska, Mol. and Cell. Biochemistry 41, 99, 1981.

4. I. Florentin, M. Bruley-Rosset, J. L. Imbach, F. Winternitz, G. Mathe, Cancer Immunol. Immunother. 5, 211, 1978; V. A. Najjar, D.Konopinska, M. K. Chaudhuri, D. E. Schmidt, L. Linchan, Mol. Cell. Biochem, 41, 3, 1981; K. Nishioka, G. F. Babcock, J. H. Phillips, R. D. Noyes, Mol. Cell. Biochem, 41, 13, 1981; J. Martinez, F. Winternitz, Mol. Cell. Biochem, 41, 123, 1981; K. Nishioka, A. A. Amoscato, G. F. Babcock Life Sci. 28, 1081, 1981; M. Fridkin, P. Gottlieb Mol. Cell. Biochem, 41, 73, 1981.

5. I. Z. Siemion, M. Lisowski, D. Konopinska, E. Nawrocka, Eur. J. Biochem. 112, 339, 1980.

6. S. Fitzwater, Z. I. Hodes, H. A. Scheraga, Macromol. 11, 805 (1978).

7. The importance of proline residues in favoring turn conformations has been frequently investigated, see for example: M. Oka, G. T. Montelione, H. A.Scheraga, J. Am. Chem. Soc., 106, 7959, 1984.

8. A. Ghribi, A. Alexakis, J. F. Normant, Tetrahedon Lett., 3075, 1984.

9. S. R. Wilson, R. A. Sawicki, J. Org. Chem. 44, 330, 1979.

10. B. Giese, Angew. Chem. Int. Ed. Engl. 22, 753, 1983.

11. ^{13}C spectroscopy shows the presence of only one diastereomer.

12. A. Rosenthal, D. A. Baker, J. Org. Chem. 38, 193, 1973.

13. B. Devens, Hoffmann-La Roche Inc., unpublished results.

14. 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, J. P. Springer, Science 230, 177, 1985.

(Received in USA 25 June 1986)