Tetrahedron Letters,Vol.27,No.16,pp 1757-1758,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain 

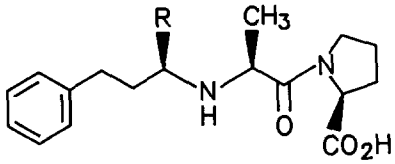
# THE SYNTHESIS OF AN AMINOPHOSPHONIC ACID CONVERTING ENZYME INHIBITOR

Gary A. Flynn and Eugene L. Giroux

Merrell Dow Research Institute
2110 East Galbraith Road
Cincinnati, Ohio 45215

ABSTRACT: The phosphonic acid analog of potent angiotensin-converting enzyme inhibitor MK-422 has been prepared.

N-(1-(S)-carboxy-3-phenylpropyl)-(S)-alanyl-(S)-proline, MK-422[1], is a potent inhibitor of angiotensin-converting enzyme (ACE). Modifications of this basic structure have been made in hopes of improving enzyme affinity and pharmacological properties. Although potent in-chain phosphinate[2] and phosphoramidate[3] analogs have been prepared, syntheses involving direct substitution of a phosphonic acid moiety for the internal carboxyl ligand of MK-422 have not been reported.[4] Our interest in the synthesis of α-aminophosphonic acids[5] as enzyme inhibitors led us to synthesize 1 as a potential ACE inhibitor.



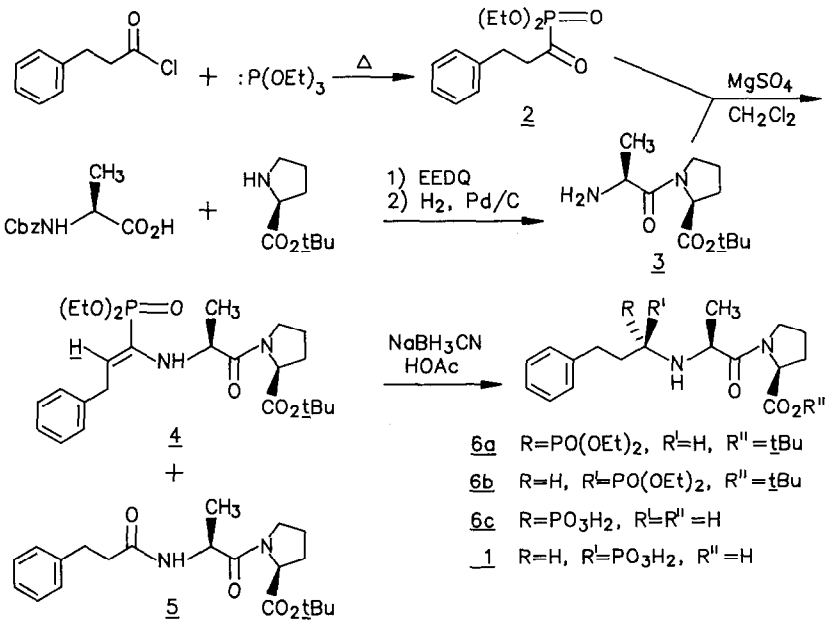

MK-422 R=$CO_2H$
1 R=$PO_3H_2$

Condensation of equimolar amounts (30 mM) of readily prepared α-ketophosphonic diester 2 and (S)-alanyl-(S)-proline t-butyl ester 3 (prepared by standard methods, Scheme I) in $CH_2Cl_2$ (200 ml) containing $MgSO_4$ for 72 hours gave a mixture of products which was not easily separated by chromatography. NMR analysis of this mixture revealed the presence of diethyl phosphite and a doublet of triplets centered at 5.62 ppm ($J_d$ = 15 Hz, $J_t$ = 7 Hz) which was assigned to the vinyl proton of enamine 4.

Reduction of the filtered reaction mixture with excess $NaBH_3CN$ (30 mM) in glacial acetic acid (100 mL, 25°C, 18 h) gave, after work-up, a more easily separable mixture of amide 5 (38%), diethyl phosphite, and isomeric aminophosphonic esters 6a and 6b (20% overall yield). Partial separation of 6a and 6b was realized during flash chromatography (60-100% EtOAc/Hexane); instability of the phosphonic ester analogs precluded further separation by recycling HPLC techniques. Sequential hydrolysis of the t-butyl and phosphonic esters of pure 6a and 6b was effected with trifluoroacetic acid (neat, 25°C, 1 h) and trimethylsilyl bromide (10 eq., neat, 25°C, 48 h) respectively. The resulting triacids 6c and 1, obtained in 80% yield, could be inefficiently purified by ion-exchange chromatography on Amberlite IR-120$^+$ resin and isolated as their monohydrated hydrochloride salts.

The triacid 1 derived from the least polar triester 6b was found to be the most potent inhibitor of rabbit lung ACE (Ki = 2.9 x $10^{-9}$M) while the isomeric amino phosphonic acid was 1500 fold less potent. The R,S,S-configuration was tentatively assigned to 1 based on analogy with the configuration of MK-422 (Ki = 5 x $10^{-11}$M).[6] It is clear that, although 1 is a good inhibitor of ACE, significant loss of binding affinity results from the substitution of a phosphonic acid residue for the carboxy ligand of MK-422.[7]

Scheme I




REFERENCES

1. A.A. Patchett, et al. Nature, 288, 280-283 (1980).
2. G.B. MacKaness, J. Cardiovascular Pharm., 7, S30-S34 (1985).
3. R.E. Galardy and D. Grobelny, J. Med. Chem., 28, 1422-1427 (1985).
4. Substitution of phosphonic acid for the terminal proline carboxyl has been reported: R.G. Almquist, W-R. Chao, C.J. White, J. Med. Chem., 28, 1067-1071 (1985).
5. G.A. Flynn, D.W. Beight, E.H.W. Bohme, and B.W. Metcalf, Tetrahedron Lett., 285-288 (1985).
6. P. Bünning, Arzneim-Forsch./Drug Res., 34 (II), 1406-1410 (1984).
7. The Merck group has recently alluded to unpublished data for phosphonate analogs of MK 422; M.J. Wyvratt and A.A. Patchett, Med. Research Rev., 5, 483-531 (1985).

(Received in USA 24 January 1986)