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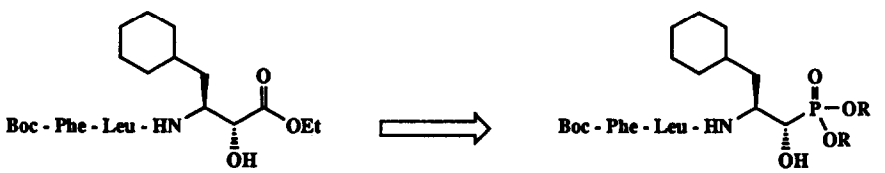
PREPARATION OF PEPTIDIC α-HYDROXY PHOSPHONATES A NEW CLASS OF TRANSITION STATE ANALOG RENIN INHIBITORS

Dinesh V. Patel,* Katherine Rielly-Gauvin and Denis E. Ryono

The Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000

Abstract : A stereoselective synthesis of α-hydroxy phosphonates, a new class of transition state analog inhibitors is described. Methods of incorporating neutral and basic amino acid residues at the N-terminus of α-hydroxy-β-amino dimethyl phosphonate 8 are discussed. Incorporation of this novel functionality in a tripeptidic framework suitable for the aspartyl protease renin has led to the development of potent inhibitors of this enzyme.

During the course of our work on activated ketone based renin inhibitors,[1,2] we realized that α-hydroxy esters of type **1** were good renin inhibitors, a finding that was soon reported in the literature by other research groups as well.[3] We envisioned that replacement of the ester moiety in **1** by its bioisostere, a phosphonate group, would preserve all the important binding interactions present in a carboxylic ester group and thus result in novel and potent inhibition of the enzyme. This led us to propose the α-hydroxy phosphonate group as a new transition state mimic, whose synthesis, general scope with regard to the N-terminal modifications and specific application to renin inhibition are discussed in this communication.

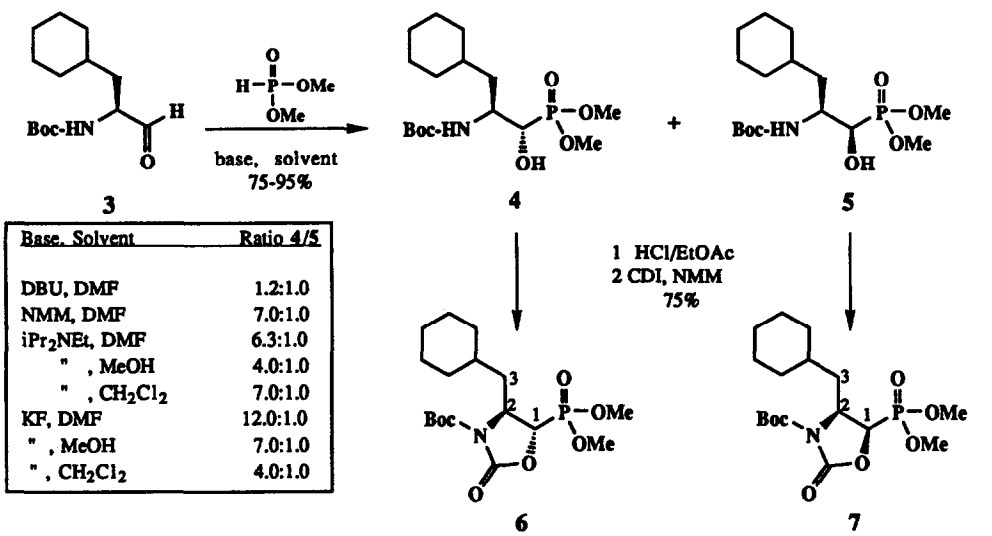


1 **2**

At the onset of this project, we were uncertain about the chemical stability of an α-hydroxy phosphonate group when incorporated into a peptidic framework. A simple approach for preparing compounds of the type **2** would involve coupling an appropriate amino acid or peptidic fragment with a β-amino-α-hydroxy-phosphonate

intermediate like **8**. A critical issue in the preparation of **8** would be the relative and absolute stereocontrol of the two adjacent chiral centers.

Reaction of the chiral aldehyde **3** derived from L-phenylalanine,[4] with dimethyl phosphite and DBU in dimethylformamide proceeded well and gave essentially an equimolar ratio of the *syn* and *anti* isomers, as determined by ^{31}P NMR.[5] For stereochemical assignment, diastereomers **4** and **5** were converted to the corresponding oxazolidinones **6** and **7** respectively. Based on the ^{1}H NMR[6] and ^{13}C NMR[7] data, and the 10% NOE observed for the H_2 proton with **7**, oxazolidinones **6** and **7** were designated as the *trans* and *cis* isomers respectively. This translates to the hydroxyl bearing carbon of the diastereomer **4** as having the S (*anti, threo*) stereochemistry, the one that is prefered for biological activity in the statine[8] and α-hydroxy ester[3] based renin inhibitors. After considerable experimentation, best yields and stereoselection in favor of the desired *anti* isomer **4** were realized by employing potassium fluoride as a base in dimethylformamide (95%, **4**/**5** = 12:1).

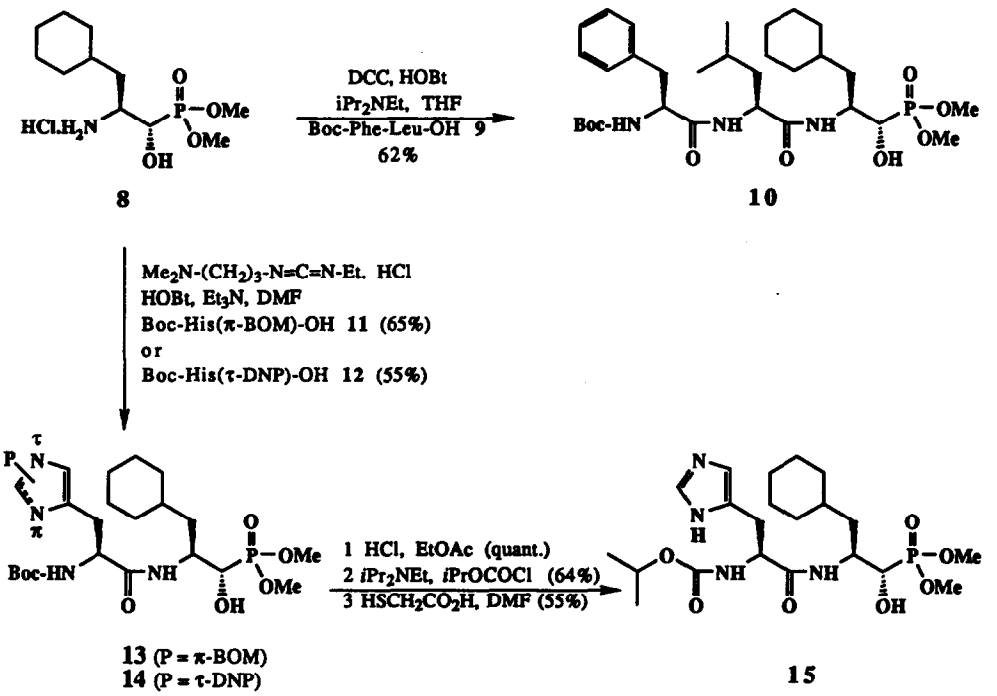


Base, Solvent	Ratio 4/5
DBU, DMF	1.2:1.0
NMM, DMF	7.0:1.0
iPr_2NEt, DMF	6.3:1.0
" , MeOH	4.0:1.0
" , CH_2Cl_2	7.0:1.0
KF, DMF	12.0:1.0
" , MeOH	7.0:1.0
" , CH_2Cl_2	4.0:1.0

^{1}H NMR :	H-1	4.30 ppm (J = 6.3 Hz)	4.75 ppm (J = 8.4 Hz)
^{13}C NMR :	C-1	75.5 ppm (J = 172 Hz)	74.0 ppm (J = 172 Hz)
	C-3	38.3 ppm (J = 4.72 Hz)	34.1 ppm (J = 13.3 Hz)

Deprotection of **4** under strongly acidic conditions led to substantial monodealkylation of the dimethyl phosphonate group.[9] This side reaction could be minimized by employing lower temperatures and avoiding prolonged reaction times (1.5 N anhydrous HCl in EtOAc, 0°C, 2 hrs). The amine **8** also gradually monodealkylated upon storage and it was found best to utilize it immediately in the subsequent coupling reaction. Thus, reaction of **8** with the carboxylic acid **9**[10] afforded **10** in 61% overall yield from **4**.

Similar instability problems were also encountered during the incorporation of basic amino acid residues at the N-terminus. Thus, compound **13**, the coupled product arising from the reaction of **8** with the benzyloxymethyl (BOM) protected histidine **11**[10] was unstable and underwent slow monodealkylation upon storage. This problem was overcome by utilizing the 2,4-dinitrophenyl (DNP) protected histidine **12**[10] wherein the highly electron withdrawing nature of the DNP group drastically reduces the overall basicity of the imidazole ring system. Unlike **13**, compound **14** was a stable synthetic intermediate which could be conveniently utilized for further modifications at the amino terminus. As an example, selective Boc removal from **14** by anhydrous HCl in EtOAc and acylation with isopropyl chloroformate[11] followed by removal of the DNP group by treatment with mercaptoacetic acid gave the histidine bearing α-hydroxy phosphonate **15**.



It was gratifying to realize that compound **10** was a very good inhibitor of human renin (I_{50} = 10 nM). In summary, this communication describes the synthesis of peptidic α-hydroxy phosphonates, a promising and structurally unique class of transition state analog inhibitors of proteolytic enzymes and makes the first disclosure of their application in preparing inhibitors of human renin. The ability to incorporate neutral or basic amino acid residues at the N-terminus makes this functionality attractive for application to various other classes of proteolytic enzymes as well.

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We wish to thank Dr. M. Porubcan and Mrs. Alicia Kahle for all the NMR data and NOE experiments, Dr. Charles A. Free and Mrs. W. Lynn Rogers for the biological evaluation of compound **2**, and Dr. E. W. Petrillo Jr. for helpful discussions.

Notes and References :

1 Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* 1988, **29**, 4665.

2 a) Orally active angiotensin converting enzyme (ACE) inhibitors have demonstrated that interruption of the renin-angiotensin system is an effective way of treating hypertension and congestive heart failure. See Petrillo, E. W. Jr.; Ondetti, M. A. *Med. Res. Rev.* 1982, **2**, 1.
b) Inhibition of the aspartyl protease renin, the enzyme that precedes ACE in the pathway, would be expected to have a similar effect and has currently been an area of intense research. See Hamilton, H. W.; Hodges, J. C.; Taylor, D. G. *Jr. Annual Reports in Medicinal Chemistry* 1989, **24**, 51.

3 We found the α-hydroxy ester **1** to be a potent human renin inhibitor (I_{50} = 5 nM, unpublished data). Also see Iizuka, K.; Kamijo, T.; Kubota, T.; Akahane, K.; Umeyama, H.; Kiso, Y. *J. Med. Chem.* 1988, **31**, 704.

4 Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; Lamont, B. I.; Lin, T-Y.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.* 1985, **28**, 1779.

5 ^{31}P NMR was found to be the most convenient method for determining the isomeric contents and purities of various synthetic intermediates and final products. ^{31}P NMR : **4** = 25.28 ppm, **5** = 24.66 ppm w.r.t. H_3PO_4 = 0 ppm as the external reference.

6 In the ^1H NMR, the H_1 proton of *cis* oxazolidinones normally appears downfield and has a larger coupling constant compared to the *trans* oxazolidinones. a) Rich. D. H.; Sun, E. T. O.; Ulm, E. *J. Med. Chem.* 1980, **23**, 27. b) Defour, M.; Jouin, P.; Poncet, J.; Pantalino, A.; Castro, B. *J. Chem. Soc., Perkin Trans I*, 1986, 1895.

7 One of the remote substituent effects in ^{13}C NMR is the steric compression effect according to which, sterically perturbed carbon atoms appear at higher field than similar carbons that are not crowded. For example, see Cardillo, G.; Orena, M.; Sandri, S.; Tamasini, C.; *Tetrahedron* 1985, **41**, 163.

8 Boger, J.; Lohr, N. S.; Ulm, E. H.; Poe, M.; Blaine, E. H.; Fanelli, G. M.; Lin, T-Y.; Payne, L. S.; Schorn, T. W.; Lamont, B. I.; Vassil, T. C.; Stabilito, I. I.; Veber, D. F.; Rich, D. H.; Bopari, A. S. *Nature (London)* 1983, **303**, 81.

9 For example, deprotection of **4** with 3.0 N anhydrous HCl in methanol at room temperature is accompanied by 10% monodealkylation as determined by ^{31}P NMR.

10 The acid **9** was prepared as described in reference 1, note 14. The acid **11** was prepared according to literature procedure (Brown, T.; Jones, J. H.*J. Chem. Soc., Chem. Comm.* 1981, 648) and **12** is commercially available.

11 Interestingly, attempted acylation with isopropyl p-nitrophenylcarbonate in the presence of diisopropylethylamine and DMAP (0.1 equiv.) afforded the diacylated compound resulting from both O- & N-acylation as the major product (60%).

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