PREPARATION OF A MODEL SYSTEM FOR A CONSTRAINED ANGIOTENSIN II RECEPTOR ANTAGONIST

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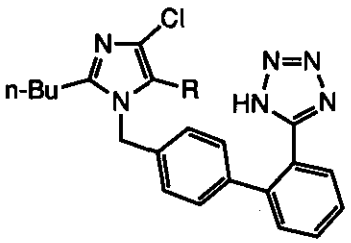
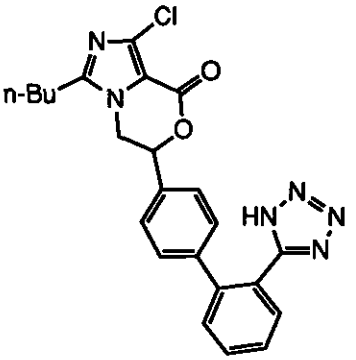
Abstract - An imidazo[5,1-*c*][1,4]oxazin-8-one system, designed to be a fused ring analog of a potent angiotensin II receptor antagonist, was prepared.

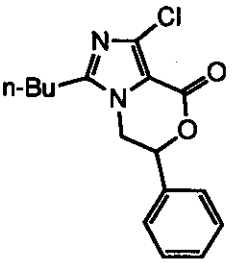
DuP 753, also known as losartan, is a nonpeptide angiotensin II receptor antagonist currently in clinical trials for the treatment of hypertension.[1] Several pharmaceutical companies are pursuing lead compounds that are structural modifications of DuP 753.[2] The major metabolite of DuP 753 is Exp 3174, arising via *in vivo* oxidation of the primary alcohol to the corresponding carboxylic acid.[3] We were interested in making a rigid analog of Exp 3174 by forming a ring between the imidazole and the biphenyl to provide **I**. In order to determine the feasibility of forming the desired imidazo [5,1-*c*][1,4]oxazin-8-one ring system we first examined a model system, namely **II**, where the biphenyl ring substituted with a tetrazole is replaced with a phenyl ring.



DuP 753 : R = CH_2OH
Exp 3174: R = COOH



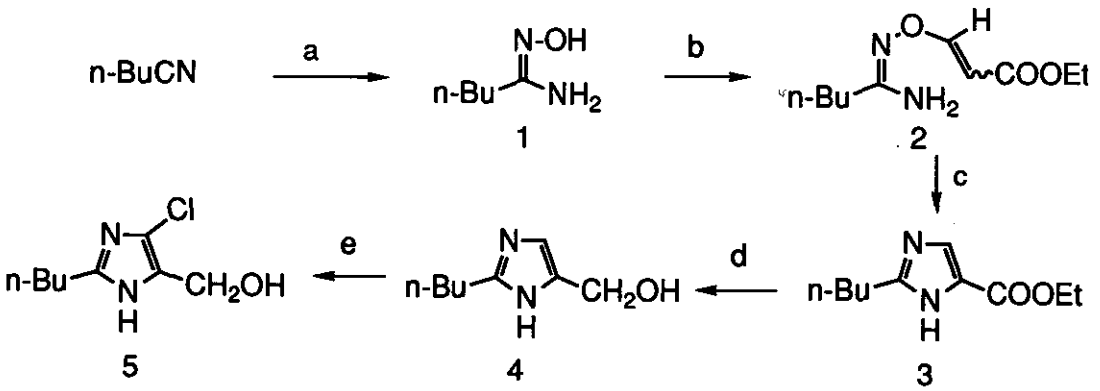
I



II

As depicted in Scheme I, valeronitrile was converted to the known amide oxime (1).[4] Addition of ethyl propiolate to 1 gave intermediate (2) as a mixture of isomers. Thermolysis of 2 provided imidazole (3).[5] Unfortunately attempts to chlorinate (3) failed.[6] Reduction of the ester group of 3 with DIBAL resulted in formation of imidazole (4), which was readily chlorinated to provide 5 as previously reported.[7]

Scheme 1

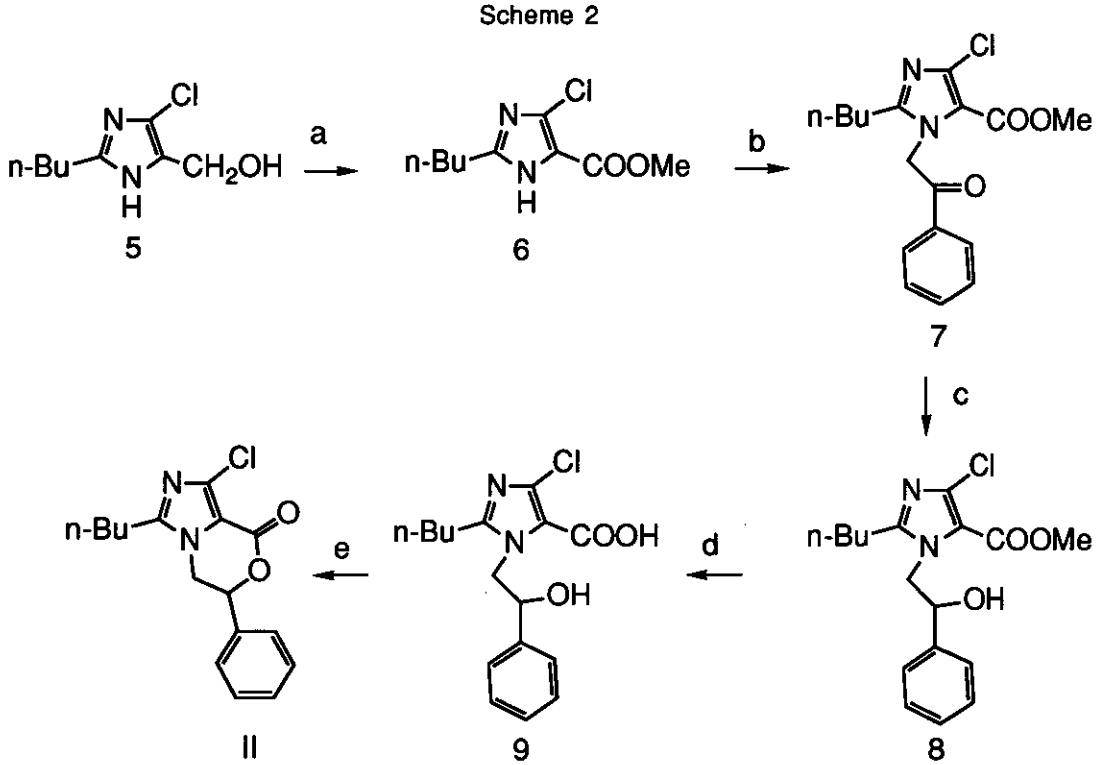


a) hydroxylamine hydrochloride[4]; b) ethyl propiolate, EtOH, reflux (75%);
c) diphenyl ether, 180°C (46%); d) DIBAL, toluene (88%); e) NCS[7]

The primary alcohol of imidazole (**5**) was converted to the corresponding methyl ester (**6**), *via* the two step oxidative protocol first utilized by DuPont.[8] As shown in Scheme 2, alkylation of **6** with Cs_2CO_3 and bromoacetophenone gave a 11 : 1 mixture of two regioisomers. These isomers were separated by chromatography with the major isomer being the desired **7**.[9] Reduction of **7** with $NaBH_4$ gave **8** which was hydrolysed to key intermediate (**9**). Ring formation to **II** readily occurred upon treatment of **9** with *p*-toluenesulfonic acid in toluene.[10]

Application of this methodology to the preparation of **I** is in progress.

Scheme 2



a) 1) MnO_2,THF; 2) MnO_2, NaCN, MeOH, HOAc [8]; b) Cs_2CO_3, bromoacetophenone (79%); c) $NaBH_4$, MeOH (81%); d) NaOH, MeOH ; e) TsOH, toluene, reflux (86% for two steps).

ACKNOWLEDGMENT
We thank the Analytical Chemistry Department for the spectral data and combustion analyses.

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6. Substitution at this position is required to obtain the desired regiochemistry in the next (alkylation) step.

7. For details of the chlorination of **4** to **5** and also an alternate route to **4** see: Y. Furukawa, S. Kishimoto, and K. Nishikawa, U. S. Patent 4,355,040 (Chem. Abstr., 1981, **95**, 132889t).

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9. We thank the Parke-Davis Analytical Chemistry Department for the nOe spectra that were used to assign the structure.

10. All new compounds had satisfactory nmr, ir and mass spectra and were within +/- .4% CHN.

Received, 17th November, 1992