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PEPTIDIC TRIFLUOROMETHYL ALCOHOLS AND KETONES

A GENERAL SYNTHESIS AND APPLICATION AS RENIN INHIBITORS

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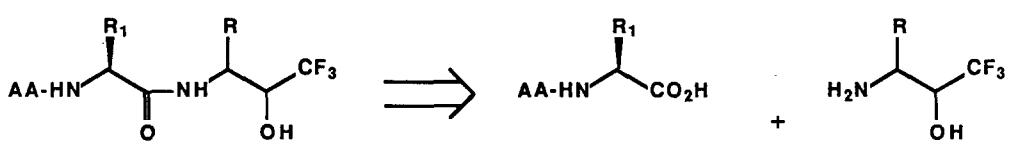
Abstract : Preparation of the tripeptidic trifluoromethyl alcohol **9** *and ketone* **10** *and their evaluation as renin inhibitors is described. The key step is the Curtius rearrangement of the beta-silyloxy acid* **6** *prepared via condensation of trifluoroacetaldehyde with the dianion of cyclohexane propionic acid.*

Fluorinated ketones, by virtue of their exceptionally high electrophilicity, exist in stable hydrated form in aqueous media and serve as ideal mimics of the tetrahedral transition state of enzymatic peptide bond hydrolysis. The pioneering work by Abeles has recently uncovered their potential as inhibitors of various proteolytic enzymes.[1] We decided to examine a novel series of peptidic trifluoromethyl alcohols and ketones as transition state analogs for inhibitory potency against the aspartyl protease, renin.[2] As alternatives to angiotensin converting enzyme (ACE) inhibitors,[3] such compounds may ultimately result in a novel therapy for the treatment of hypertension.[4]

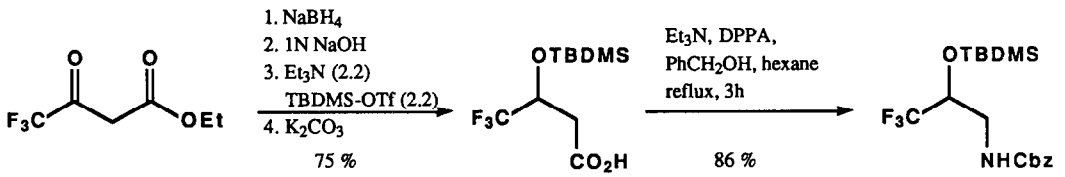
Retrosynthetic analysis reveals the amino acid **1** and the trifluoromethyl ß-amino alcohol **2** as the key components for the synthesis of these compounds.



1 **2**

The peptidic acid fragment **1** would be easily available by standard peptide coupling procedures, and we envisoned that **2** could be prepared by Curtius rearrangement of the appropriately protected carboxylic acid. Recently, Abeles[5] and Trainor[6] independently disclosed an efficient synthesis of peptidic trifluoromethyl alcohols and ketones utilizing the nitro group as an amine equivalent to arrive at an intermediate of type **2**. Our Curtius rearrangement pathway offers the added advantage that the carboxylic acid precursor can be utilized for the preparation of analogous retro-inverso peptidic trifluoromethyl alcohols and ketones.[7]

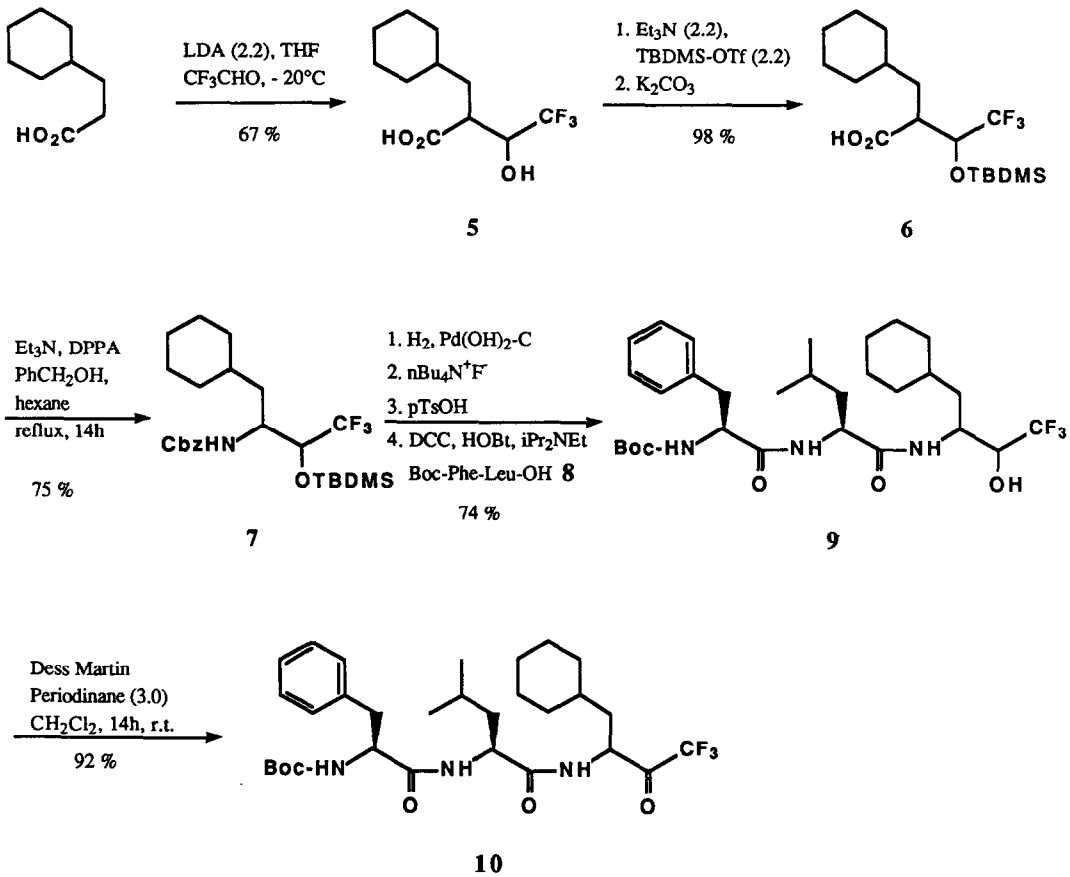
The validity of such an approach was checked by the following model study. The TBDMS protected ß-hydroxy acid **3** was prepared in three steps from ethyl 4,4,4-trifluoroacetoacetate in 75% overall yield.[8] Curtius rearrangement of **3** following classical, stepwise procedures was unsuccessful;[9] however, upon treatment with diphenylphosphoryl azide and triethylamine in toluene in the presence of benzyl alcohol,[10] the rearranged product **4** was obtained directly in 52% yield. Upon substituting hexane as the solvent for toluene, the yield improved substantially (86%).[11]



3 **4**

The tripeptidic trifluoromethyl alcohol **9** and ketone **10** were chosen for synthesis and evaluation as renin inhibitors. The amino acid residues were appropriately chosen so as to impart specificity towards the targeted enzyme, renin.[4,12] Condensation of the dianion of cyclohexane propionic acid with trifluoroacetaldehyde generated *in situ* from its ethyl hemiacetal[13] yielded the ß-hydroxy acid **5** as a racemic mixture of erythro and threo isomers in 67% yield. After protection of the alcohol as the TBDMS derivative **6**, Curtius rearrangement with DPPA (1.0 equiv) and triethyl amine (2.0 equiv) in the presence of benzyl alcohol (1.0 equiv) afforded the differentially protected amino alcohol **7** (75%). Interestingly, the addition of a second equivalent of the base was found necessary for the reaction to proceed at an appreciable rate. The free amine obtained after appropriate deprotection of **7** was coupled with the carboxylic acid **8**[14] to afford the trifluoromethyl alcohol **9**. Dess Martin oxidation[15] of **9** yielded the corresponding ketone **10** as a mixture of two diastereomers in the ratio of 1:1.2 as determined by reverse phase HPLC. As expected, the ^{13}C NMR data revealed that the ketone **10** existed completely in its hydrated form.[16]

Compound **10** was found to be a good inhibitor of human renin (I_{50} = 250 nM). Taking the diastereomeric contents of **9** and **10** into consideration, the trifluoromethyl ketone was about 10-fold more potent than its corresponding alcohol (**9**, I_{50} = 4000 nM).



5 **6** **7** **9** **10**

In summary, this communication describes a new alternative for the synthesis of peptidic trifluoromethyl alcohols and ketones and makes the first disclosure of their application as inhibitors of human renin.[17] The commercial availability of various carboxylic acids and the use of ß-hydroxy acid intermediates of type **5** or **6** for synthesis of retro-inverso analogs add to the synthetic utility of this method.

Acknowledgements : We wish to thank Dr. E.W. Petrillo Jr. for helpful discussions and Dr. Charles A. Free and his colleagues for the biological evaluation of compounds **9** and **10**.

Notes and References :

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b) Fearon, K.; Spaltenstein, A.; Hopkins, P.B.; Gelb, M.H. *J. Med. Chem.* 1987, **30**, 1617.

3 Petrillo, E.W. Jr.; Ondetti, M.A. *Med. Res. Rev.* 1982, **2**, 1.

4 Boger, J. *Annual Reports in Medicinal Chemistry* 1985, **20**, 257.

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6 Bergeson, S.H.; Edwards, P.D.; Krell, R.D.; Shaw, A.; Stein, R.L.; Stein, M.M.; Strimpler, A.M.; Trainor, D.A.; Wildonger, R.A.; Wolanin, D.J. "Abstracts of Papers" 193rd National Meeting of the American Chemical Society, Denver, Colorado, April 5-10, 1987; American Chemical Society : Washington, D.C.; 1987, MEDI 0001.

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10 Shioiri T.; Ninomiya K.; Yamada S. *J. Amer. Chem. Soc.* 1972, **94**, 6203.

11 The use of hexane was suggested to us by Prof. Spencer Knapp of Rutgers University. Also see, Ruden, R.A.; Bonjouklian, R. *J. Amer. Chem. Soc.* 1975, **97**, 6892.

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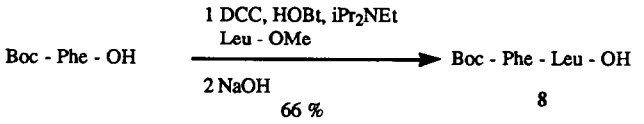
b) Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; Lamont, B. I.; Lin, T. Y.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.*, 1985, **28**, 1779.

13 Hooper, D.G.; Loucks, L.F.; Liu, M.T.H. *J. Chem. Educ.* 1975, **52**, 131.

14 The acid **8** was prepared as shown below.



15 Dess, D.B.; Martin, J.C. *J. Org. Chem.* 1983, **48**, 4155.

16 ^{13}C NMR (67.5 MHz, $CDCl_3$), **10** : The hydrated trifluoromethylketone carbonyl appeared as a quartet at 94.5 ppm.

17 A detailed account of the inhibitory potency of these and related compounds will be reported elsewhere in the near future.

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