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Synthesis of the Nonpeptide Renin Inhibitor A-68064 and the ACE Inhibitor Methyl Enalaprilat from (5S)-2,3,5,6-Tetrahydro-5-alkyl-N-(*tert*-butyloxycarbonyl-4H-1,4-oxazine-2-ones

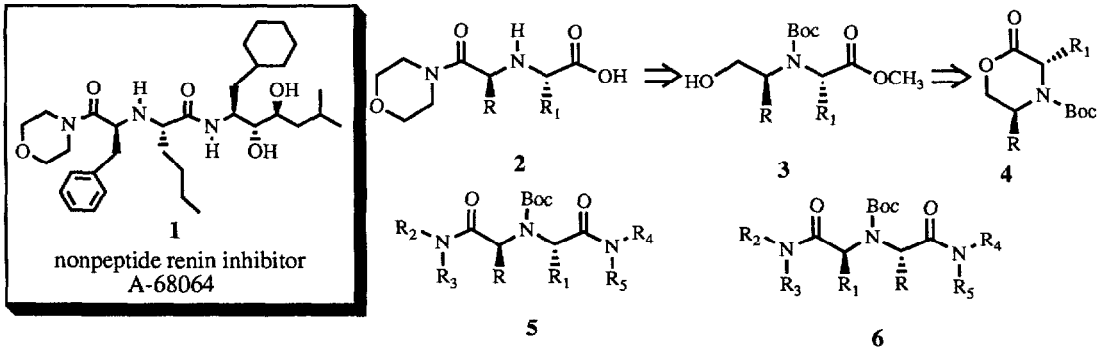
William R. Baker* and Stephen L. Condon

Pharmaceutical Products Division, Abbott Laboratories, One Abbott Park Road, Abbott Park, IL 60064

Key words: nonpeptide renin inhibitor; ACE inhibitor

Abstract: The nonpeptide renin inhibitor, A-68064, and the ACE inhibitor methyl enalaprilat were synthesized from (5S) 2,3,5,6-tetrahydro-5-benzyl(butyl)-N-(tert-butoxycarbonyl)-4H-1,4-oxazine-2-ones **7a** *and* **7b**, *and (5S) 2,3,5,6-tetrahydro-5-methyl-N-(tert-butoxycarbonyl)-4H-1,4-oxazine-2-one* **12**, *respectively.*

We have recently identified a novel series of renin inhibitory compounds whose structure is typified by A-68064 (**1**).[1] These nonpeptide inhibitors possessed a novel (2S,4S)-3-aza-2,4-disubstituted glutaric acid moiety **2** at the P_2/P_3 position of the molecule, a moiety also found in the ACE inhibitor, enalaprilat (**16**). We have developed

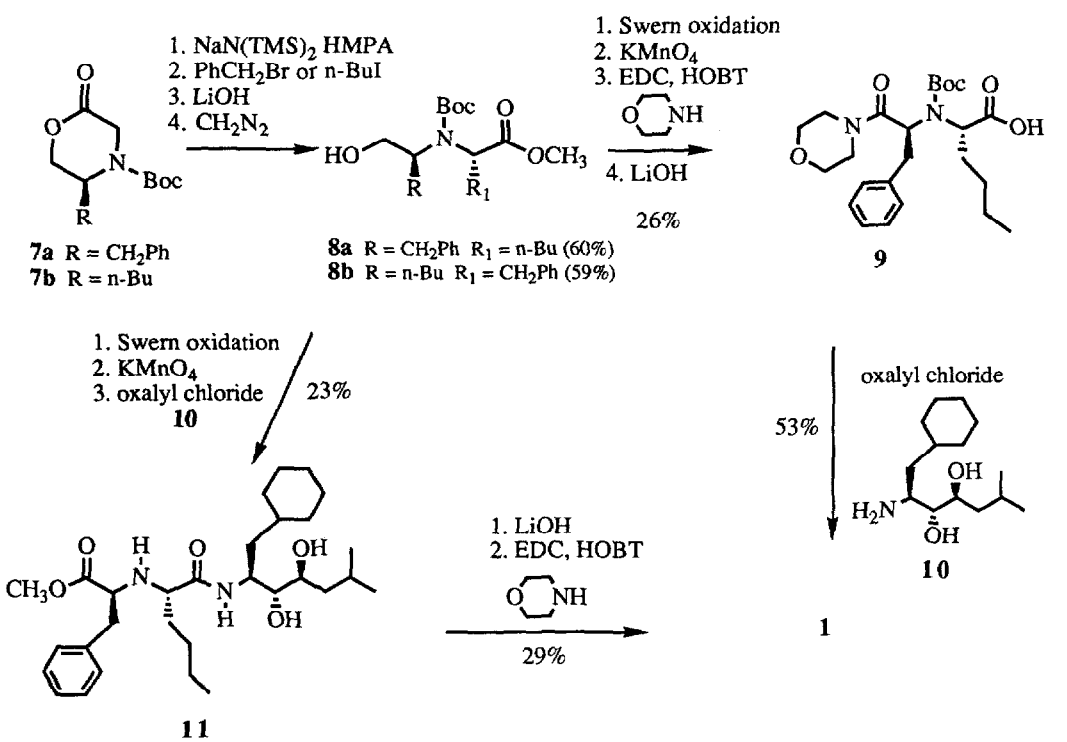


a general synthetic approach to the 3-aza-2,4-dialkyl glutaric acid structures **5** and **6** which depends on the stereoselective alkylation of (5S) 2,3,5,6-tetrahydro-5-benzyl or butyl-N-(tert-butoxycarbonyl)-4H-1,4-oxazine-2-ones (**7a** and **b**).[2] The versatility of the approach relied on the intrinsic C_2 symmetry available to lactone **4** and complimentary synthetic protocols for the preparation of **5** and **6** from **3**. Thus, the hydroxyester **3**, available from **4** by hydrolysis of lactone **4** and esterification of the resulting acid, was oxidized to the carboxylic acid. Transformation of the carboxylic acid ester into the bisamide **5** was achieved by following a three step protocol; 1) amine (R_2R_3NH) coupling, 2) hydrolysis of the methyl ester, and 3) amine (R_4R_5NH) coupling. Reversal of the protocol (couple amine R_4R_5NH, methyl ester hydrolysis, and then couple amine R_2R_3NH) produced the isomeric bisamide **6** and interchanged the R and R_1 substituents. Application of both synthetic protocols for the synthesis of renin inhibitor, A-68064 (**1**) is shown in scheme 1. The methodology was also employed for the synthesis of the ACE inhibitor, methyl enalaprilat (**15**, scheme 2).

Alkylation of **7a** with *n*-butyl iodide, hydrolysis of the resulting dialkyl lactone (LiOH, aq. THF, 24 h, rt), and esterification with diazomethane gave hydroxy ester **8a** in 60% overall yield. A parallel series of reactions were performed on the butyl lactone **7b** to produce the hydroxy ester **8b** in 59% overall yield. Renin inhibitor, A-68064 (**1**) was prepared from both hydroxy esters **8a** and **8b** by the two protocols described. A two step oxidation (Swern oxidation followed by 1M $KMnO_4$, pH 5-6, *t*-BuOH[3]) of alcohol **8a** was employed for the synthesis of the carboxylic acid. Coupling the crude acid with morpholine (EDC, HOBT, DMF, 18 h, -23 °C to rt) and hydrolysis of the methyl ester (LiOH, aq. dioxane, 24 h, rt) gave acid **9** in 26% overall yield from **8a**. All attempts to couple acid **9** with the amine diol **10**[4] using standard peptide coupling procedures failed. However, the coupling reaction was successfully performed by first forming the cyclic anhydride intermediate from acid **9** (9 eq. of oxalyl chloride, 2h, rt) and reacting the anhydride with amine **10** (0 °C to rt, 18 h) in $CHCl_3$. Compound **1** was isolated as a white amorphous solid in 53% isolated yield.

The synthesis of inhibitor **1** from hydroxy ester **8b** was also accomplished. Oxidation of **8b** gave the carboxylic acid which was reacted with **10** via the cyclic anhydride intermediate to give **11** in 23% yield. Conversion of ester **11** to inhibitor **1** was completed in 29% overall yield by hydrolysis of the methyl ester (aq. LiOH dioxane, 18 h, rt) and coupling the resulting acid with morpholine (EDC, HOBT, DMF, 18h -23 °C to rt). The ^1H NMR and ^{13}C NMR spectra for compound **1** obtained from both synthetic routes were identical.

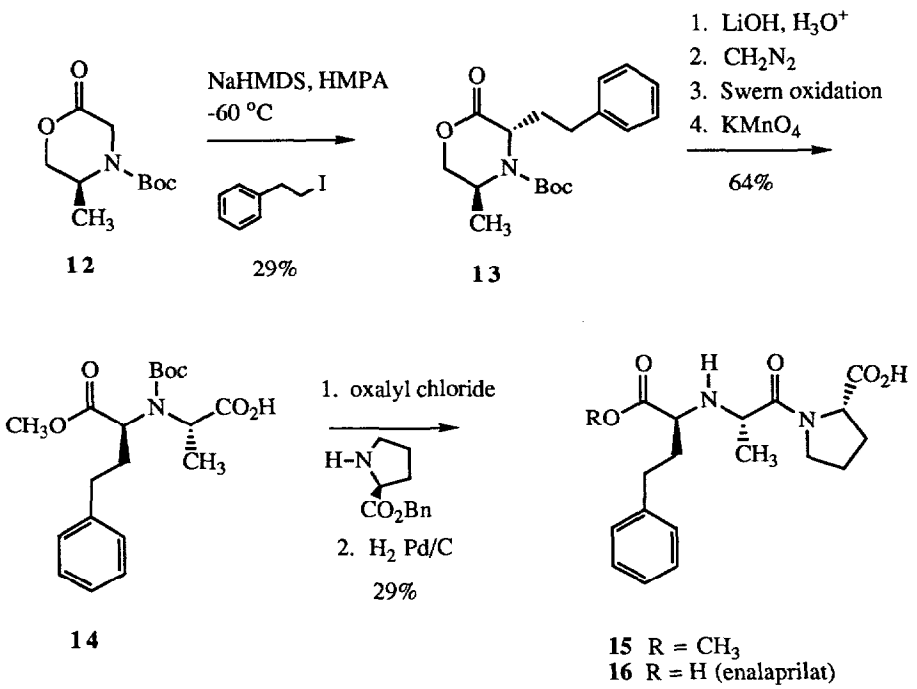
Scheme 1



The synthesis of the ACE inhibitor methyl enalaprilat **15** was achieved in seven steps starting from (5S) 2,3,5,6-tetrahydro-5-methyl-N-(tert-butoxycarbonyl)-4H-1,4-oxazine-2-one (**12**, scheme 2). Alkylation of **12** with phenethyl iodide using the standard conditions gave lactone **13** in 29% isolated. The low yield of compound **13** was expected since phenethyl iodide is known to undergo a β-elimination side reaction to form styrene during alkylation reactions. Methyl ester **14** was obtained in 64% yield from **13** by the procedures previously described. The synthesis of methyl enalaprilat **15** was completed by coupling L-proline benzyl ester to acid **14** and cleavage of the benzyl ester by hydrogenolysis. Correlation of **15** to enalaprilat (**16**) was accomplished by reaction of **15** with diazomethane to give the dimethyl ester which was identical (^{1}H NMR, ^{13}C NMR, and TLC) to a sample of dimethyl ester prepared from enalaprilat (**16**) and diazomethane.

In conclusion, (3S, 5S) 2,3,5,6-tetrahydro-3,5-dialkyl-N-(tert-butoxycarbonyl)-4H-1,4-oxazine-2-ones served as useful starting materials for the synthesis of nonpeptide renin and ACE inhibitors. The ring opened 1,4-oxazine-2-ones were transformed by two synthetic protocols into the bisamides **5** or **6**. Application of this methodology for structure-activity relationship (SAR) studies of nonpeptide renin inhibitors are underway and will be reported in due course.

Scheme 2



References and Notes

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2. See the preceding article in this issue.
3. Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537-40.
4. For a synthesis of the amine diol **10** see the following article in this issue and references cited therein.

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