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SYNTHESIS OF PEPTIDE DERIVED AMINO ALCOHOLS II. SYNTHETIC METHODOLOGY FOR THE PREPARATION OF TERTIARY ALCOHOLS

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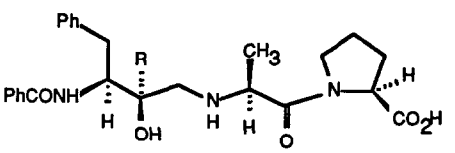
Abstract: Synthetic methods are described for the preparation of a series of tripeptide derived amino-alcohols (*i.e.*, 2). These novel peptidyl tertiary alcohols are potential inhibitors of angiotensin converting enzyme (ACE). The synthetic targets resemble acyltripeptide substrates for the enzyme, but contain a -CHOH(CH_3)-CH_2-NH- moiety, as replacement for the scissile amide bond.

Recently we described the design[1] and synthesis[2] of a new series of tripeptide derived aminoalcohols, typified by structure 1, which were shown to be potent inhibitors of angiotensin converting enzyme (ACE). In particular, the presence and absolute configuration of the secondary hydroxyl function were shown to be critical factors for the manifestation of high enzyme inhibitory activity. These designed inhibitors are reminiscent of pepstatin[3] and bestatin[4], two naturally occuring proteolytic enzyme inhibitors. Pepstatin and bestatin owe their biological activity to (different) unusual amino acids, each of which contains a critical secondary hydroxyl function. Recently, Rich has shown that the secondary hydroxyl group of statine can be replaced by a 3° alcohol, and that when such a statine analogue is incorporated into a suitable peptide backbone[5], the peptide retained potent inhibitory properties against pepsin.



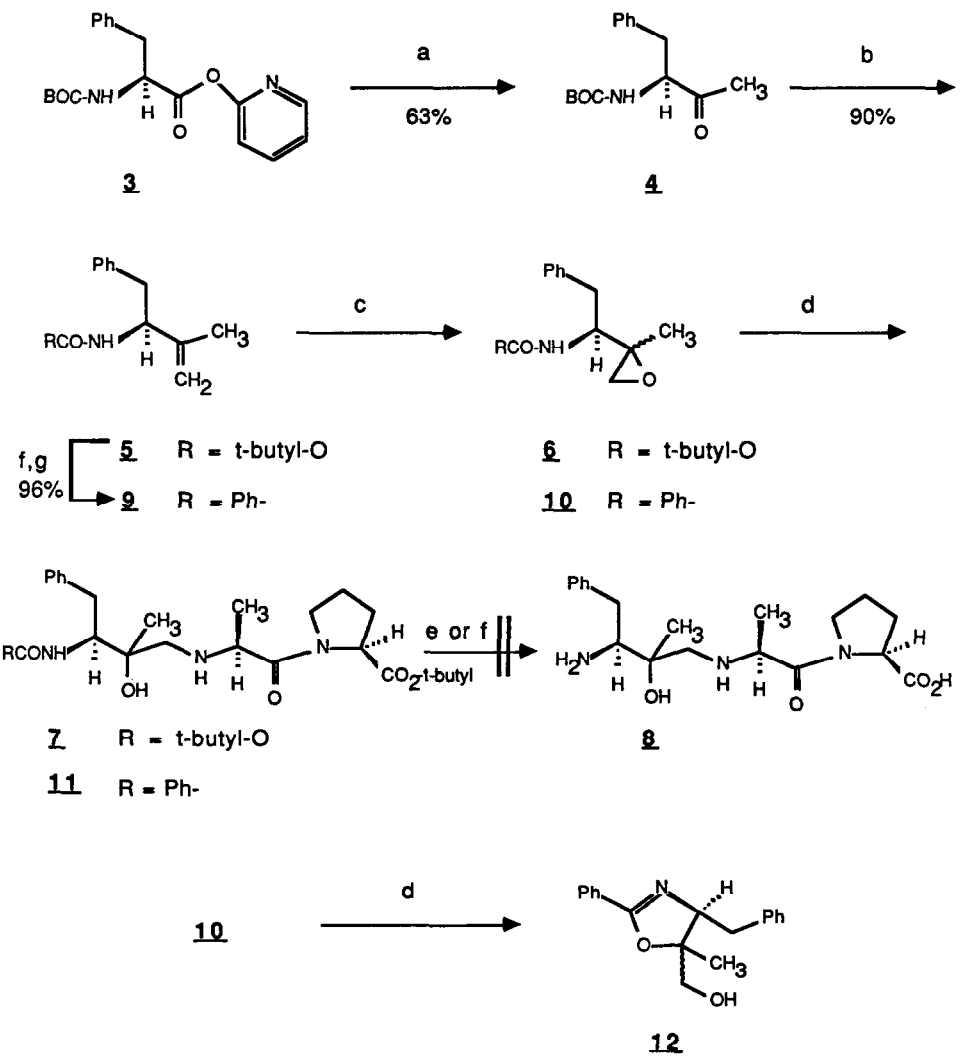
1 = -H, I_{50} = 28 nM

2 = $-CH_3$

Aminoalcohols such as 1 are the first inhibitors of ACE which rely on a hydroxyl group to forge essential inhibitor/enzyme interactions. In order to further explore the constraints of enzyme binding in this novel series of protease inhibitors, we wished to prepare the related 3° alcohol systems.

Our initial synthetic route, summarized in Scheme 1, proceeded with a BOC protected N-terminal residue. Treatment of pyridyl ester 3 with methylmagnesium bromide gave the desired, chiral methylketone (63%), which undergoes extremely rapid Wittig olefination to afford olefin 5 in excellent yield (90%). Epoxidation of 5 produced a ~2:1 mixture of diastereoisomeric epoxides (90%), which were opened regiospecifically by L-Ala-L-Pro *t*-butyl ester (CH_3OH) to yield a mixture of tertiary alcohols 7. Completion of the synthesis of 2 required the removal of the BOC and *t*-butyl ester protecting groups, followed by selective benzoylation of the resulting primary amine. Treatment of 7 with TFA/CH_2Cl_2 or HCl/dioxane

SCHEME 1



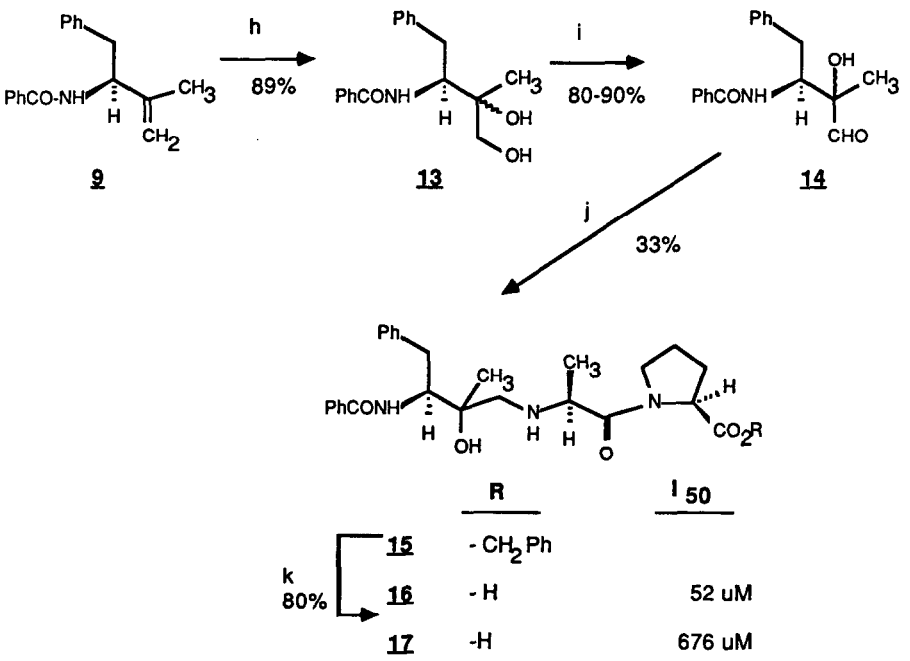
(a) CH_3MgBr, THF, -78°C; (b) CH_3PPh_3Br, $KN(SiMe_3)_2$, benzene; (c) MCPBA, CH_2Cl_2; (d) L-Ala-L-Pro-t-butyl ester, CH_3OH, 65°C; (e) HCl/dioxane; (f) TFA/CH_2Cl_2; (g) PhCOCl, diisopropylethylamine.

gave complex mixtures of products, indicating that 7 is quite unstable to acidic conditions. Therefore, it was necessary to develop a synthesis of 2 which obviates use of strongly acidic conditions in the final stages.

A second approach to amino tertiary alcohol 2 involved incorporation of the required N-benzoyl function at an earlier stage of the initial sequence. Hence, 5 was deblocked (TFA/CH_2Cl_2) and acylated (PhCOCl, diisopropylethylamine) to afford 9. Subsequent epoxidation of 9 afforded 10 as a mixture of diastereomeric epoxides. Reaction of mixture 10 with L-Ala-L-Pro-*t*-butyl ester in hot methanol did not afford the desired product 11, but lead instead (via N-benzamido participation), to a mixture of oxazolines 12[6].

A modification of the second approach led to the desired target by a path summarized in Scheme 2. Treatment of olefin 9 with osmium tetroxide[7] afforded a 89% yield of diols 13 as a nearly equal mixture of diastereomers, which were separable by chromatography. Oxidation[8] of the individual diol isomers 13 produced α-hydroxy aldehydes 14 (80-90%), both of which underwent smooth reductive amination with L-Ala-L-Pro benzyl ester to yield amino alcohols 15. Hydrogenolysis of the individual aminoalcohols 15 with Pearlman's catalyst afforded both amino tertiary alcohols 16 and 17 as pure diastereomers.[9]

SCHEME 2



(h) OsO_4, N-methylmorpholine N-oxide, THF/H_2O; (i) pyridine · SO_3, DMSO, CH_2Cl_2, diisopropylethylamine; (j) L-Ala-L-Pro benzyl ester PTSA salt, $NaHCO_3$, 3Å sieves, THF, isopropanol; $NaBH_3CN$; (k) $Pd(OH)_2/C$, H_2, EtOH, HCl.

Introduction of the methyl groups into 1 to give 16 and 17 was extremely detrimental to ACE inhibitory activity, causing nearly a 2000 fold decline in activity compared to 1. Although angiotensin converting enzyme is unable to accomodate the additional steric or conformational constraints the tertiary alcohol function imposes on the inhibitor molecule, the chemical methodology described herein should find utility in the design of inhibitors of other proteolytic enzyme systems.[10]

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6. If this approach had succeeded to yield 7, the synthesis of 2 would have required the use of an Ala-Pro ester, cleavable under nonacidic conditions.
7. J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **1967**, *89*, 5505; A. J. Mancuso and D. Swern, *Synthesis*, **1981**, 165.
8. V. Van Rheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Letters*, **1976**, 1973.
9. SELECTED DATA: 16, $[\alpha]_D$ = -71.1° (c = 1.17, CH_3OH); 17, $[\alpha]_D$ = -116.5° (c = 1.02, CH_3OH).
10. Applying the recommended nomenclature regarding amide bond replacements (Nomenclature Announcement Newsletter 1984, *Arch. Biochem. and Biophys.*, **1984**, *229*, 339), compounds 15 and 16 would be described as Bz-Phe-ψ[$C(CH_3)OHCH_2NH$]-Ala-Pro-OH, and the general class of compounds as ψ[(R,S)-$C(CH_3)OH$-CH_2-NH]. Under this system, compound 1 may be expressed as Bz-Phe-ψ[(R)-$CHOHCH_2NH$]-Ala-Pro-OH, whereas the general class may be described as ψ[(R,S)-CHOH-CH_2-NH]. We thank a referee for bringing this point to our attention.

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