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THE CONVERSION OF A DIAZOLACTAM TO AN α-METHYLENELACTAM: AN ENTRANCE TO NEW CONFORMATIONALLY RESTRICTED INHIBITORS OF ANGIOTENSIN-CONVERTING ENZYME

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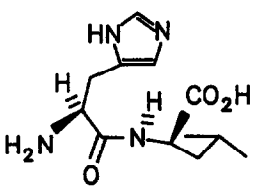
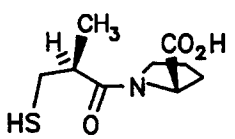
Summary: Methodology for the conversion of an α-aminolactam dipeptide mimic to an α-methylenelactam derivative was developed utilizing the decomposition of an α-diazolactam intermediate in the presence of triphenylphosphine as the key step. Conjugate addition of thiolbenzoic acid to the derived unsaturated lactam and deesterification gave two new potent sulfhydryl containing inhibitors of angiotensin-converting enzyme.

Angiotensin I-converting enzyme (ACE) is a zinc dependent dipeptidyl carboxypeptidase which cleaves the dipeptide His-Leu-OH 1 from the carboxyl terminus of angiotensin I to produce the potent vasoconstrictor octapeptide hormone angiotensin II.[1] Captopril 2 is the premier example[2] of a new class of enzyme inhibitors which combines a substrate-mimicking dipeptide fragment or surrogate with a ligand, in this case sulfhydryl, oriented to coordinate the ACE active site zinc ion.[3]



1



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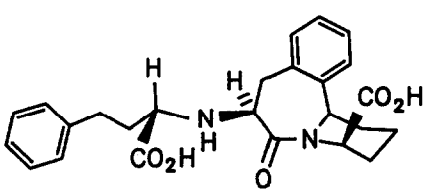

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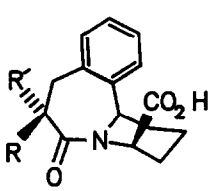


4a R=CH_2SH, R′=H

4b R=H, R′=CH_2SH

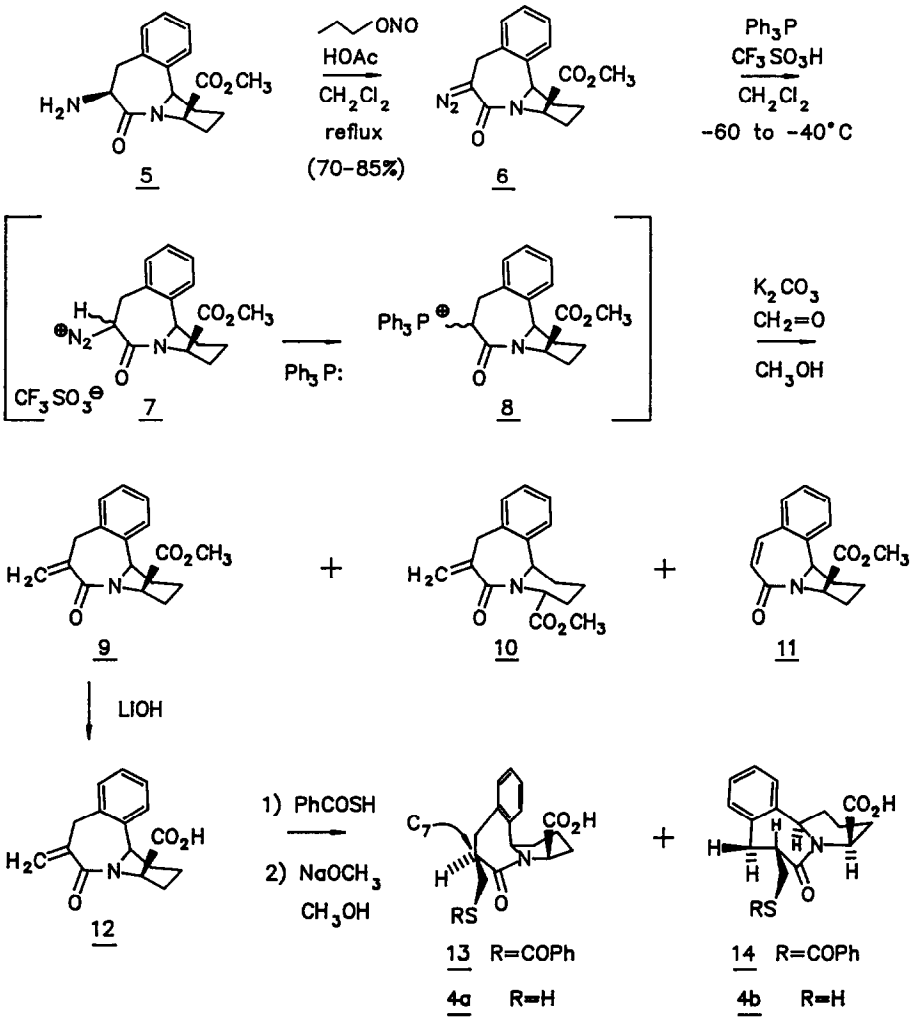
We recently described[4] the synthesis of a conformationally restricted tricyclic dipeptide surrogate which when coupled to an appropriate carboxyl ligand gave inhibitor 3 that displayed a significantly enhanced binding affinity (K_i=4 x 10^{-12}M)[5] with respect to other members of this inhibitor class. Our continuing interest in using conformationally rigid molecules as probes for the active site topography of metalloproteases prompted the design and synthesis of thiol containing inhibitors 4a and 4b.

The synthesis of mercaptomethylene inhibitors 4a and 4b was achieved as outlined in Scheme I. The key step is a direct conversion of a diazolactam to an α-methylenelactam. Tricyclic amino methyl ester 5, the chiral starting material, was prepared by modifying the esterification step of the method previously described.[4] The observed chemical shift of δ 3.05 ($CDCl_3$) for the methyl ester of 5 is a characteristic of the configuration and conformation depicted which places this methyl group in the shielding cone of the proximal aromatic ring. Treatment of 5 with 3 equivalents of n-propyl nitrite and 0.2 equivalents of acetic acid in refluxing CH_2Cl_2 for one hour provided the yellow α-diazolactam 6 as a foam in 70-85% yield. Low temperature decomposition of α-diazolactam 6 (-60 to -40°C) with trifluoromethanesulfonic acid in the presence of triphenylphosphine, followed by condensation of the presumed phosphonium salt intermediate 8 with formaldehyde in the presence of base, afforded the desired α-methylenelactam 9 in 20-34% yield after purification. Lactam 9 was accompanied by varying amounts (up to 17%) of epimer 10 and, typically, 15% of elimination product 11. The characterization of epimer 10 was based on the existence of two exo-methylene protons and the observed normal chemical shift of δ 3.7 for the methyl ester singlet in the ^{1}H NMR spectrum. Elimination product 11 could originate from diazonium salt 7.

Saponification of hindered exo-methylene ester 9 occurred quantitatively to give acid 12 and approximately 20% of its epimer at the carboxyl α-carbon. This 4:1 mixture of acids was directly treated with a 4-fold excess of thiolbenzoic acid and triethylamine in dry THF. The predominant product, diastereomer 14, was isolated in 65% yield by flash chromatography. Conjugate addition under neutral protic conditions, thiolbenzoic acid (4-fold excess) in methyl alcohol gave an 82% yield of a (1.5:1) mixture of adducts 14 and 13. Flash chromatography (30% EtOAc, 65% hexane, 5% HOAc) gave 13 (25%) and 14 (35%). The stereochemical and conformational assignments for 13 and 14 were based on the observed ^{1}H-NMR scalar coupling constants of the three methine protons and definitive NOE experiments[6]. The preference for the formation of adduct 14 under aprotic, basic conditions contrasts with the mixture of 13 and 14 observed under protic conditions. The results observed may reflect steric constraints during a cis addition pathway in an aprotic medium.

Methanolysis of 13 and 14 with sodium methoxide afforded 4a and 4b in 50% and 56% yield, respectively. Interestingly, both 4a and 4b were potent inhibitors of ACE comparable to Captopril 2. Analysis of the possible sulfhydryl orientations of the two inhibitors should give an indication of the relative location of the zinc atom in the active site of ACE. These analyses and biochemical data for these two inhibitors will be reported elsewhere.

SCHEME I


ONO
HOAc
CH2Cl2
reflux
(70-85%)
Ph3P
CF3SO3H
CH2Cl2
-60 to -40°C
CO2CH3
H2N
N2
CF3SO3⊖
Ph3P:
Ph3P⊕
K2CO3
CH2=O
CH3OH
H2C
LiOH
CO2H
1) PhCOSH
2) NaOCH3
CH3OH
C7
RS
5
6
7
8
9
10
11
12
13 R=COPh
4a R=H
14 R=COPh
4b R=H

Conclusion: Novel methodology was developed for the conversion of an α-aminolactam to an α-methylenelactam. This technology allowed the preparation of two new inhibitors of angiotensin-converting enzyme which are useful probes for studying the active sites of metalloproteases. The scope and limitations of this transformation are not fully understood and will require further studies.

References:

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4. G.A. Flynn, E.L. Giroux, and R.C. Dage, J. Am. Chem. Soc., 109, 7914 (1985).

5. E. Giroux, D.W. Beight, and R.C. Dage and G.A. Flynn, J. Enzyme Inhibition, 2, 269-277 (1989).

6. Two dimensional NOE experiments were performed on the benzhydryl esters of 13 and 14. The ester of isomer 13 exhibited a strong NOE between the methine proton at C-7 and the bridgehead methine proton. This NOE was not observed in the ester of isomer 14. Instead, NOE's were observed between the bridgehead methine proton and the α-benzylic proton at C-8, and between the β-benzylic proton and the proton at C-7. These NOE's are consistent with the stereochemistries shown in Scheme I. The ester of isomer 14 also exhibited a strong NOE between the bridgehead methine and the carboxyl α-proton indicating that this molecule adopts the ring flipped conformation shown in Scheme I. This conformation was also calculated to be the minimum energy conformation using the MM2 program Model.

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