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Cyclic Dipeptides. 2[1]. A Simple Synthesis of Methyl (6*R*)-6-*tert*-Butoxycarbonylamino-4,5,6,7-tetrahydro-2-methyl-5-oxo-1,4-thiazepine-3-carboxylate, A Useful Intermediate for the Preparation of Potential Antihypertensive Agents

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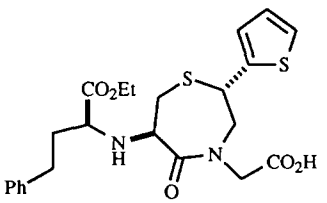
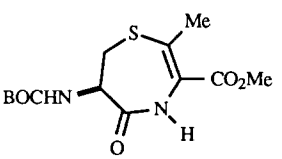
Abstract: A stereoselective synthesis of the title compound **2**, starting from readily accessible intermediates, is described. The absolute stereochemistry of **2** has been deduced through X-ray crystallographic analysis of the corresponding sulphoxide **14**. © 1997 Elsevier Science Ltd.

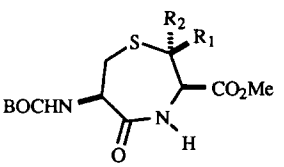
In recent years intensive efforts have been made to develop peptidomimetics, that is agents that can imitate or block the biological functions of bioactive peptides.[2] They can serve either as aids for the investigation of peptidergic systems and of the binding conformation of enzyme substrates and receptor ligands, or as therapeutic agents endowed with possibly improved pharmacological properties over the parent peptidal drugs.[3] In particular, modulation of the renin-angiotensin system through inhibition of angiotensin converting enzyme has assumed increasing importance in the therapy of hypertension and of congestive heart failure.[4] Temocapril (**1**) is one of the latest finding in this area.[5]



Temocapril (**1**)



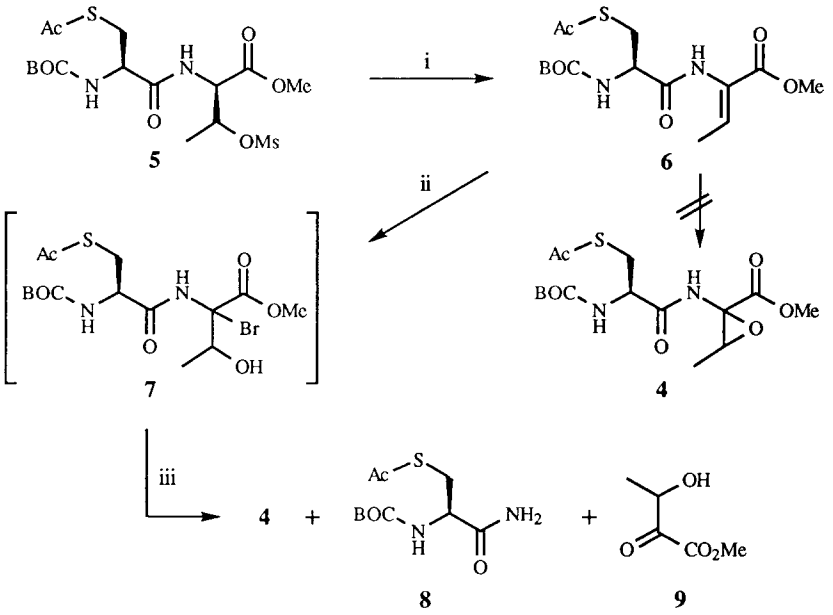
2



3a: R_1 = H, R_2 = Me
3b: R_1 = Me, R_2 = H

Being involved in the chemistry and biological evaluation of sulphur containing cyclic compounds[1,6] as well as in the development of antihypertensive agents[7] we are reporting here the synthesis of enantiomerically pure 1,4-thiazepine-3-carboxylic acid derivative **2**, which can be regarded as a relative of compounds **3** previously described by us[1] and a good synthon for the preparation of analogs of **1**.

As a first approach, we identified in an epoxide **4** a possible precursor of the target compound **2** (Scheme 1). Thus, the mesylate **5**[1] was subjected to elimination reaction to provide the olefin **6**, which had already been obtained (mixture of *E* and *Z* isomers) as a by-product during the synthesis of compounds **3**.[1] The use of bases such as diisopropylethylamine (DIPEA) or DBU consistently afforded a diolefinic product deriving from the elimination of both methanesulphonic acid and thiolacetic acid, whereas the use of finely ground potassium carbonate in refluxing chloroform gave the desired olefin **6** in 66% yield as a single isomer ($[\alpha]_D$= -30.0, c=1.0, $CHCl_3$) as indicated by TLC and ^1H NMR spectroscopy.[8] Unexpectedly, all attempts to directly convert **6** into the corresponding epoxide **4** under different experimental conditions were unsuccessful, leading to degradation products, even when the urea-hydroperoxide (UHP)/trifluoroacetic anhydride system was used, which had found to efficiently epoxidize the analogue substrate methyl 2-benzyloxycarbonylamino-2-butenoate.[9]

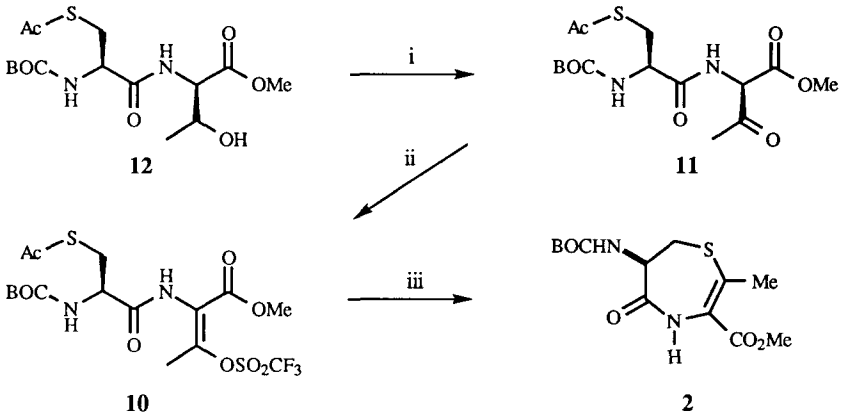


Scheme 1. Reagents: i) K_2CO_3, $CHCl_3$; ii) NBS, DMSO, H_2O.

Alternatively, treatment of **6** with NBS and wet DMSO to obtain the bromohydrin **7** (or the isomeric 2-bromo-3-hydroxy bromohydrin) afforded a complex mixture of products, from which **4** was isolated after laborious chromatographic separation in less than 10% yield, along with degradation products **8** and **9**. Unfortunately, **4** was found to be too unstable to be fully characterized and used as a synthetic intermediate.

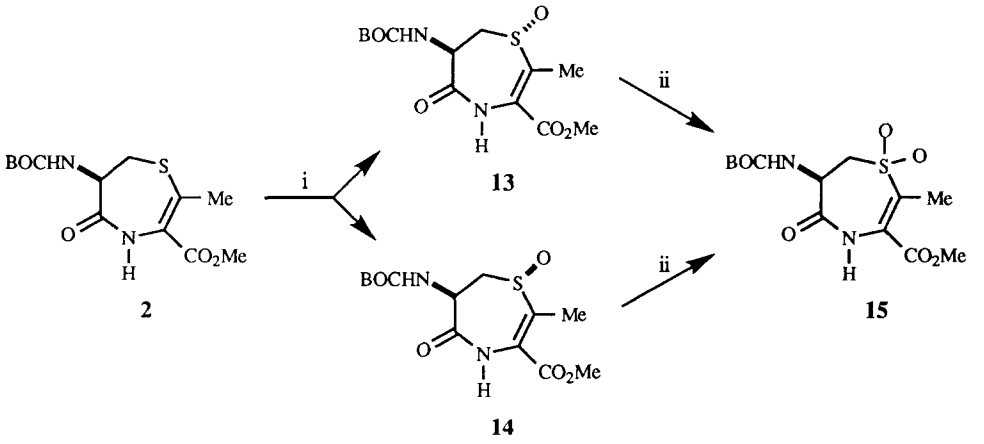
In the light of these findings, we sought a different approach to **2**. The ability of alkenyl triflates to undergo solvolytic displacement through the intermediacy of the corresponding vinyl cations is well documented in the literature.[10] Therefore, we devised a new avenue to our target molecule entailing the preparation of enol triflate **10**, followed by its intramolecular displacement by an *in situ* generated thiol group (Scheme 2).To this end, ketone **11** ($[\alpha]_D$= +10.0, c=1.0, $CHCl_3$), in turn obtained in 80% yield by PCC oxidation of alcohol **12**,[1] was transformed by means of triflic anhydride and DIPEA into the corresponding enol triflate **10** in 88% yield. TLC

and ^{1}H NMR spectroscopy revealed that only one isomer of **10** ($[\alpha]_D$= -31.3, c=1.0, $CHCl_3$) was obtained (double bond geometry not determined).



Scheme 2. Reagents: i) PCC, CH_2Cl_2; ii) Tf_2O, DIPEA, CH_2Cl_2; iii) $CH(OEt)_3$, CSA, 4A MS.

Having secured an easy access to **10**, several procedures were investigated to deprotect the thiol group selectively under conditions consistent with the presence of the enol triflate functionality and it was gratifying to find that this could be easily accomplished by reaction with triethyl orthoformate catalyzed by camphorsulphonic acid in the presence of 4A molecular sieves. Under these conditions, complete conversion of substrate **10** was obtained in 6 hours and **2** was isolated in 52% yield ($[\alpha]_D$= -20.7, c=0.8, $CHCl_3$) after chromatographic purification.[11] Attempts to cyclize **10** using the procedure (lithium trimethoxyaluminum hydride, THF) recently described[1] by us for the synthesis of derivatives **3** were unsuccessful, giving complex reaction mixtures in which thiazepine **2** was never detected.



Scheme 3. Reagents: i) MCPBA, CH_2Cl_2, -30 °C; ii) MCPBA, CH_2Cl_2, 0 °C.

Compound **2** was oxidized with MCPBA at -30 °C to give quantitatively a mixture of the two sulphoxides **13** ($[\alpha]_D$= -250.0, c=0.3, $CHCl_3$) and **14** ($[\alpha]_D$= -9.0, c=27, $CHCl_3$) in the ratio 1:3 (Scheme 3). Further oxidation of each sulphoxide led to the same sulphone **15** ($[\alpha]_D$= -154.5, c=0.3, $CHCl_3$).[12]

The absolute stereochemistry of compound **14** was determined by X-ray crystallographic analysis (Figure 1). Compounds **14** and **15** exhibited *in vitro* cytotoxic activity in the MTT test at 50 μM concentration.

In summary, the above studies have afforded a stereoselective synthesis of methyl 6-*tert*-butoxycarbonylamino-4,5,6,7-tetrahydro-2-methyl-5-oxo-1,4-thiazepine-3-carboxylate, a highly functionalized intermediate for the preparation of new biologically active peptidomimetics.

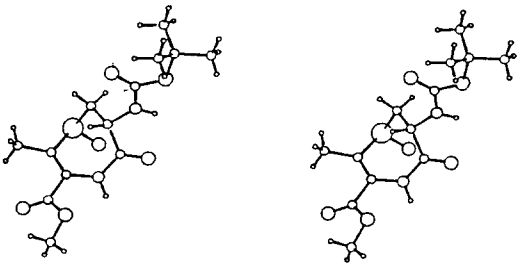


Figure 1. Stereoview of the X-ray structure of **14**.

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References and Notes

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8. The double bond geometry has not been determined. Compound **6** is arbitrarily drawn in Sheme 1 as the *Z*-isomer. It is interesting to note that the diastereomeric mesylate[1] prepared from *L*-threonine led to the same olefin **6**.
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10. See for example: (a) R. H. Summerville, P. V. R. Schleyer, *J. Am. Chem. Soc.*, **1972**, *94*, 3629. (b) T. C. Clarke, D. R. Kelsey, R. G. Bergman, *J. Am. Chem. Soc*, **1972**, *94*, 3626.
11. No attempt has been yet made to assess the actual mechanism of the cyclization reaction.
12. The structures of the new compounds were determined by FAB-MS and ^1H NMR spectroscopy. All the new compounds gave satisfactory (±0.4% of the theoretical values) elementary analyses, with the only exception of **4** which resulted too unstable to be analyzed.

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