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Cyclic Dipeptides. A Stereocontrolled Synthesis of (2S,3R,6R)- and (2R,3R,6R)-6-*tert*-Butoxycarbonylamino-3-methoxycarbonyl-2-methyl-5-oxoperhydro-1,4-thiazepine

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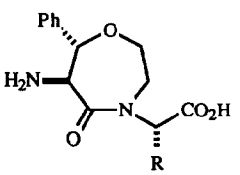
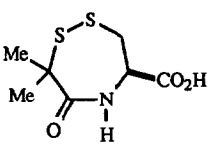
Abstract: A stereselective synthesis of the title compounds, starting from commercially available amino acids, is described. The absolute stereochemistry of **3a** and **3b** has been deduced on the basis of ^{1}H NMR and chemical degradation studies. The formation of only these two isomers has been rationalized in terms of molecular mechanics calculations.

Cyclic dipeptides like **1** have recently attracted much interest as conformationally restricted dipeptide mimetics useful for the study of the binding conformation of enzyme substrates and receptor ligands.[1] Moreover, structurally related macrocyclic sulphides and disulphides[2] (e.g. **2**) have been found to show pharmacological activities, such as hepatoprotective and immunomodulatory effects.

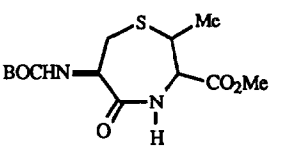
Being involved in the chemistry and the biological evaluation of sulphur containing cyclic compounds,[3] and in the light of the importance of the biological activities cited above, we are reporting here the synthesis of enantiomerically pure perhydro-1,4-thiazepinecarboxylic acid derivatives **3**, which can be regarded as relatives of **1** and **2**.



1



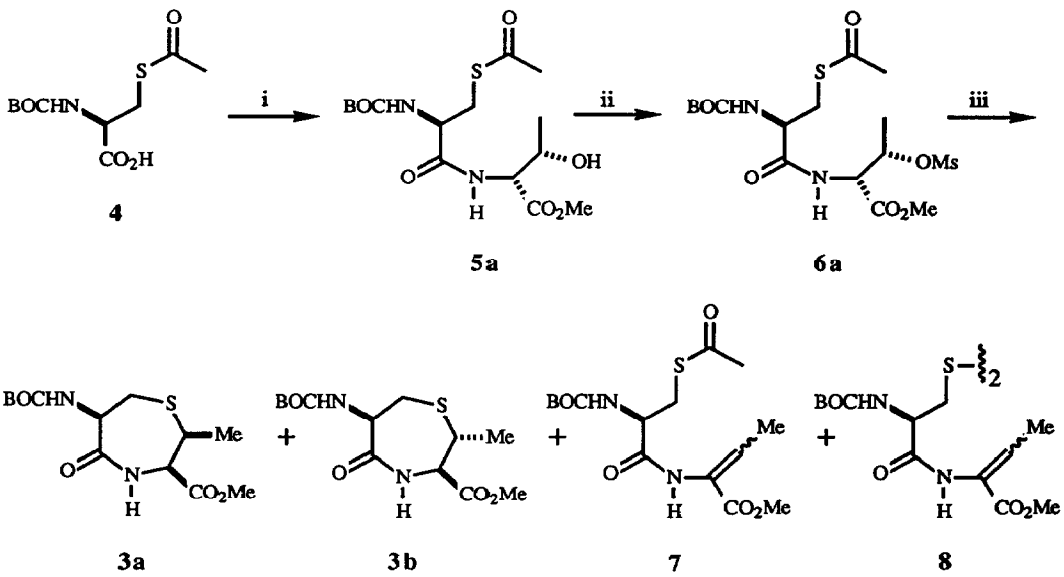
2 (SA981)



3

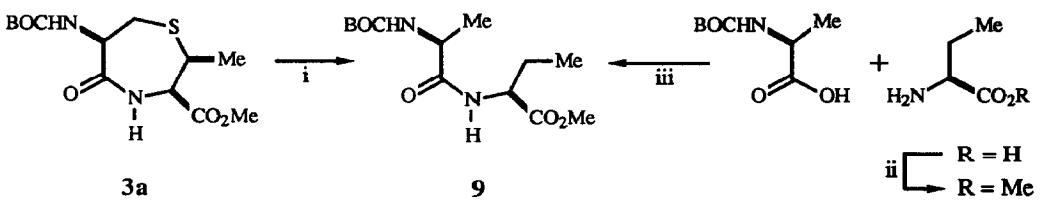
Reaction between *D*-threonine methyl ester[4] and S-acetyl-N-*tert*-butoxycarbonyl-*L*-cysteine **4** (prepared[5] from N-*tert*-butoxycarbonyl-*L*-cystine) in the presence of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl *p*-toluenesulphonate (CMC) afforded after chromatographic purification the amide **5a** ($[\alpha]_D$= +25, c=1, $CHCl_3$) in 53% yield as a single stereoisomer as determined by TLC and ^{1}H NMR spectroscopy (Scheme 1). Treatment of **5a** with methanesulphonyl chloride and diisopropylethylamine (DIPEA) at -5 °C gave the corresponding mesylate **6a** exclusively as indicated by TLC and ^{1}H NMR spectroscopy. **6a** proved to be unstable under the conditions of silica gel chromatography and was therefore used in the next reaction step without further purification. First attempts to convert **6a** into the cyclic derivative **3a** with methanolic ammonia or sodium borohydride led to a complex mixture of products from which **3a** was isolated in only very small

quantities after laborious chromatographic separations. Subsequently the deacetylation-cyclization reaction was performed with lithium trimethoxyaluminum hydride (3 molar equivalents) in dry THF. Under these conditions compounds **3a** and **3b** were obtained in 15% and 35% yield, respectively, along with the olefins **7** (E/Z mixture, 20%) and the disulphides **8** (12%). Bubbling nitrogen into the reaction mixture suppressed the formation of **8** and led to compounds **3a** and **3b** in a yield of 14% and 56%, respectively, while the olefins **7** were always present in trace amounts.



Scheme 1. Reagents: i) D-threonine methyl ester, CMC, CH_2Cl_2; ii) MsCl, DIPEA, CH_2Cl_2; iii) $LiAlH(OMe)_3$, THF.

The structures of **3a** and **3b** were determined by FAB-MS and ^1H NMR spectroscopy.[6] The stereochemistry of the methyl at C-2 and the methoxycarbonyl group at C-3 was proven to be *cis* for **3a** by a nuclear Overhauser effect (NOE) between the C-2 and C-3 protons and *trans* in the case of **3b** (where no NOE was detected). In order to establish the absolute stereochemistry at C-3, **3a** was desulphurated with Ra-Ni to compound **9**, which proved to be identical in all the respects, including specific rotation ($[\alpha]_D$= -25, c=2, CHCl3), with the material obtained from commercially available BOC-*L*-alanine and (*S*)-(+)-2-aminobutyric acid (Scheme 2).

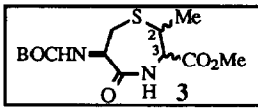


Scheme 2. Reagents: i) Ra-Ni, MeOH; ii) CH_2N_2; iii) CMC, CH_2Cl_2.

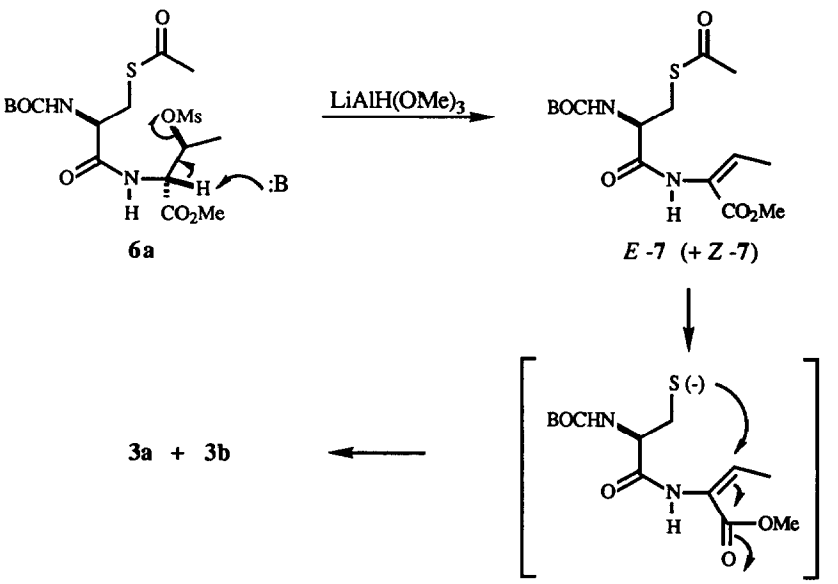
It is interesting to note that both **3a** and **3b** possess a C-3 stereochemistry inverted with respect to their precursor **6a**. In order to obtain further insight into the reasons for the exclusive formation of only these two isomers **3a** and **3b**, we resorted to molecular mechanics calculations with the programme PCMODEL (MMX force field).[7]

All possible stereoisomers[8] of 6-*tert*-butoxycarbonylamino-3-methoxycarbonyl-2-methyl-5-oxoperhydro-1,4-thiazepine were taken into account for the computational study and, after a preliminary geometry optimization, submitted to a statistical conformational search with BKM.[9] The lowest energy conformers of stereoisomers **3a** and **3b** were found to be the most stable (Table 1).

Table 1. Energy (kcal/mol) of the lowest energy conformer of the four stereoisomers of **3**.

	**3a** (2S,3R)	**3b** (2R,3R)	**3a'** (2R,3S)	**3b'** (2S,3S)
	E = 12.56	E = 12.57	E = 14.13	E = 14.33

In the light of these results, we can infer that the cyclization probably occurs through a preliminary methanesulphonic acid elimination from **6a**, followed by Michael addition of the thiolate group giving rise to the thermodynamically more stable isomers (Scheme 3) In agreement with this hypothesis, the olefins **7** were isolated and submitted to the cyclizations under the same experimental conditions as used for **6a**, leading indeed to the same products **3a** and **3b**.

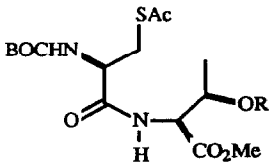


Scheme 3. Mechanism for the formation of the cyclic dipeptides **3a**, **3b**.

In order to confirm this reaction pathway, the sequence was repeated starting from **4** and *L*-threonine methyl ester to give the intermediate **5b** ($[\alpha]_D$= -10, c=1, $CHCl_3$), which was in turn subjected to mesylation

and cyclization as described for **5a**. As expected the same diastereoisomers **3a** and **3b** were obtained (51% and 25%, respectively), although the ratio of **3a** : **3b** (2 : 1) in this case was inverted with respect to the previous reaction (1 : 4).

In summary, the above studies have afforded a stereoselective synthesis of only two (**3a** and **3b**) of the four possible[8] stereoisomeric 6-*tert*-butoxycarbonylamino-3-methoxycarbonyl-2-methyl-5-oxoperhydro-1,4-thiazepines in enantiomerically pure form starting from either *D*- or *L*-threonine, with the product ratios depending on the absolute configurations of the starting amino acids.



5b R = H
6b R = Ms

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References and Notes

1. T.P. Burkholder, E.W. Huber, G.A. Flynn, *BioMed. Chem. Lett.*, **1993**, *3*, 231 and references cited therein.
2. S. Ito, A. Ota, H. Suhara, K. Tabashi, Y. Kawashima, *Chem. Pharm. Bull.*, **1993**, *41*, 1066.
3. (a) A. Garofalo, G. Balconi, M. Botta, F. Corelli, M. D'Incalci, G. Fabrizi, I. Fiorini, D. Lamba, V. Nacci, *Eur. J. Med. Chem.*, **1993**, *28*, 213. (b) A. Garofalo, V. Nacci, F. Corelli, G. Campiani, *Heterocycles*, **1990**, *31*, 1291.
4. T. Wieland, R. Sarges, *Ann.*, **1962**, *658*, 181.
5. H. Zahn, K. Hammerstrom, *Chem. Ber.*, **1969**, *102*, 1048.
6. All the new compounds gave satisfactory (±0.4% of the theoretical values) elementary analyses.
7. Serena Software, Bloomington, IN, U.S.A.
8. Assuming that the *L*-cysteinyl moiety retains its configuration throughout the synthetic pathway, four stereoisomers of **3** are possible.
9. Professor K. Steliou, Boston University, MA, U.S.A.

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