Tetrahedron Letters,Vol.24,No.11,pp 1133-1134,1983 0040-4039/83/111133-02$03.00/0
Printed in Great Britain

DETERMINATION OF THE ABSOLUTE CONFIGURATION OF (-)-S-(2-CARBOXYPROPYL)-L-CYSTEINE

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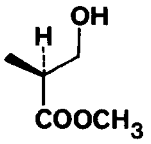
Abstract: The absolute configuration of the naturally occurring amino acid (-)-S-(2-carboxypropyl)-L-cysteine has been determined by asymmetric synthesis.

(-)-S-(2-Carboxypropyl)-L-cysteine (9 or 10) is a component of the naturally occurring tripeptide S-(2-carboxypropyl)glutathione that occurs in the onion[1] and in garlic.[2] Granroth[3] has shown that (-)-S-(2-carboxypropyl)-L-cysteine is the precursor of trans-S-(prop-1-enyl)-L-cysteine sulfoxide which is in turn the progenitor of lacrymatory principle of onions. In addition, S-(2-carboxypropyl)-L-cysteine has recently been found to be an intermediate in the biosynthesis of the nematicidal 1,2-dithiolane of *Asparagus*, asparagusic acid.[4] The important role played by this amino acid in sulfur metabolism in the *Liliaceae* makes a knowledge of its absolute configuration highly desirable. We therefore report assignment of the absolute configuration by asymmetric synthesis.

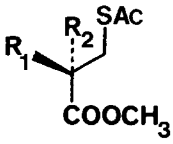
Methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate (1) was converted to methyl (*R*)-(+)-3-acetylthio-2-methylpropanoate (2)[5] by treatment with thiolacetic acid in the presence of DEAD and triphenylphosphine.[6] Methyl (*S*)-(-)-3-acetylthio-2-methylpropanoate (3)[7] was obtained from the commercially available[8] acid by esterification with diazomethane. Deacetylation of 2 and 3 with sodium ethoxide in ethanol yielded methyl (*R*)-3-mercapto-2-methylpropanoate (4) and (*S*)-3-mercapto-2-methylpropanoate (5), respectively. The benzyl ester of (S)-aziridinecarboxylic acid was prepared from L-serine by the method of Nakajima *et al.*[9] and acylated with ethyl chloroformate to yield the optically active aziridine derivative 6. The two enantiomeric thiol esters 4 and 5 were then each reacted with the aziridine 6 in the presence of boron trifluoride etherate[10] to produce the respective diastereomeric adducts 7 and 8. Finally, 7 and 8 were deprotected by sequential treatment with trimethylsilyl iodide,[11] which removed the urethane and benzyl ester moieties, followed by 1 N potassium hydroxide to hydrolyze the methyl ester function. In this way, the two diastereomeric forms of S-(2-carboxylpropyl)-L-cysteine 9 and 10 were obtained. The diastereomer 9 prepared from the (*R*)-(+)-acetylthio ester 2 exhibited $[\alpha]_D^{25} = +34.5°$ (c 0.04, H_2O) while the diastereomer 10 prepared from the (*S*)-(-)-acetylthio ester 3 exhibited $[\alpha]_D^{25} = -58.3°$ (c 0.04, H_2O). S-(2-Carboxypropyl)-L-cysteine isolated from hydrolysis of S-(2-carboxypropyl)glutathione has been reported[1] to show $[\alpha]_D^{21} = -50.1°$ (H_2O). Furthermore, Carson[12] resolved the two diastereomeric forms of S-(2-carboxypropyl)-L-cysteine and reported rotations for the two isomers of $[\alpha]_D^{25} = -66.1°$ (c 2.5, H_2O) and $[\alpha]_D^{25} = +35.8$ (c 1.25, H_2O). From these data, we conclude that naturally occurring (-)-S-(2-carboxypropyl)-L-cysteine has the (S) configuration at C-2 and corresponds to structure 10.

Acknowledgment. We thank Dr. Noal Cohen of Hoffmann-La Roche, Inc., for a generous gift of methyl (S)-(+)-3-hydroxy-2-methylpropanoate and the National Science Foundation for financial support.

The author is very pleased to dedicate this paper to Dr. Ulrich Weiss on the occasion of his 75th birthday.

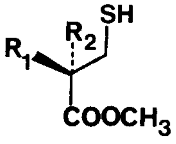


1



2, R_1 = Me, R_2 = H

3, R_1 = H, R_2 = Me



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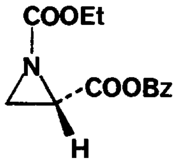
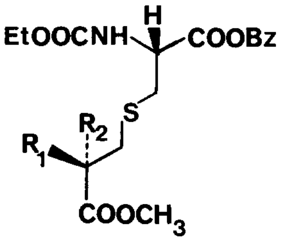
5, R_1 = H, R_2 = Me

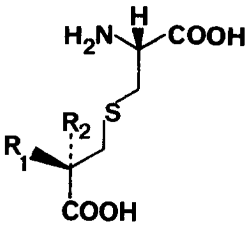


6



7, R_1 = Me, R_2 = H

8, R_1 = H, R_2 = Me



9, R_1 = Me, R_2 = H

10, R_1 = H, R_2 = Me

References and Notes

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5. The rotation exhibited by 2 was $[\alpha]_D^{25} = +59.8°$ (c 0.16, EtOH).
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7. The rotation exhibited by 3 was $[\alpha]_D^{25} = -54.7°$ (c 0.15, EtOH).
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(Received in USA 23 December 1982)