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SYNTHESIS OF DIDEHYDROPEPTIDES FROM PEPTIDES CONTAINING 3-ALKYLTHIO-AMINO ACID RESIDUES

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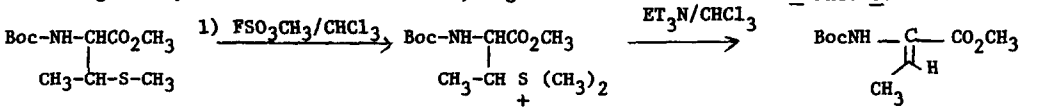
The α,β-didehydroamino acid system is found frequently in microbial peptides[1] and may be important in both the biosynthesis[2] and the biological mechanism of action[3] of these peptides. Although several methods have been developed for the synthesis of the α,β-didehydroamino acids,[4-6] elimination of O-tosyl derivatives of 3-hydroxy amino acids 1a is used most frequently.[4] However peptides which contain the O-tosyl derivative of threonine (1b) are converted into aziridine peptides 3 rather than α,β-didehydro peptides 2 upon treatment with triethylamine.[7]

1a R_1=H; b R_1=CH_3 — 2a R_1=H; b R_1=CH_3 — 3 R_1=CH_3

Thus other methods are needed to prepare complex dehydropeptides which contain β-substituted unsaturated residues like 2b. We report here a convenient method for synthesizing protected didehydropeptides in high yield by the base catalyzed elimination of sulfonium derivatives of peptides containing 3-alkylthioamino acid residues, e.g. the transformation of 5 into 6.



5 — 6

The following experiment illustrates the procedure used to prepare the didehydropeptides. Boc-MeAla-Leu-Cys(Me)-Gly-OMe (650 mg, 1.29 mmol) was dissolved in 10 ml methylene chloride and treated with methyl fluorosulfonate for 8-10 hrs at 0°C under nitrogen. Skelly B was added and the mixture was cooled to -78°C to complete the precipitation of the sulfonium salt. The supernatant was decanted and the salt resuspended in methylene chloride. Triethylamine (0.39 g, 3.9 mmol) was added and the reaction mixture was stirred at 0°C for 30 min. The solution was evaporated to dryness, redissolved in ethylacetate and filtered through silica gel to remove salts. The solvent was evaporated to give the didehydrotetrapeptide 20 in 89% yield. Examples of

compounds which have been prepared by this procedure are given in the table.

Table[11]

Sulfide	Didehydro Derivative	% Yield
7. Boc-Cys(Me)-OMe	15. Boc-ΔAla-OCH_3	85
8. Boc-Pen(Me)-OMe	16. Boc-ΔVal-OMe	93
9. Boc-Ala-Cys(Me)-OMe	17. Boc-Ala-ΔAla-OMe	80
10. Boc-Ala-But(3-SMe)-OMe	18. Boc-Ala-ΔBut-OMe	82
11. Boc-Ala-Leu(Me)-OMe	19. Boc-Ala-ΔVal-OMe	85
12. Boc-NMeAla-Leu-Cys(Me)-Gly-OMe	20. Boc-NMeAla-Leu-Δ-Ala-Gly-OMe	89
13. Boc-Cys(Bzl)-O-Me	21. Boc-Δ-Ala-OMe	86
14. Boc-But(3-SMe)-Gly-OMe	22. Boc-ΔBut-Gly-OMe(Z+E)	79

This procedure is convenient for synthesizing didehydropeptides which do not contain the alkylatable residues, Cys, His, Met. The starting 3-alkylthio-amino acids are readily prepared by addition of the thiol to the corresponding unsatuarated azlactone.[10] The sulfur protecting group is stable to the usual coupling and deprotection conditions employed in peptide synthesis and requires no further protection or deprotection prior to sulfonium formation as is required for a 3-hydroxyl group. Furthermore, the base catalyzed elimination of sulfonium derivatives of 3-alkylthio butyrine peptides (14) has been found to give only the α,β-didehydrobutyrine peptides (22). No peptides were detected which contained the aziridine carboxylic acid derivative (eg 2b).

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11. Abbreviations used are: But, butyrine (3-methylalanine); Pen, penicillamine (3-mercaptovaline).