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APPROACHES TO THE ANTIBIOTIC SPARSOMYCIN. AN EFFICIENT SYNTHESIS OF THE CYSTEINOL MONO-OXODITHIOACETAL MOIETY

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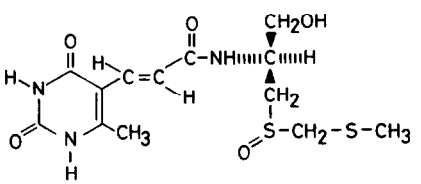
Sparsomycin (1), a fermentation product[1] of Streptomyces sparsogenes, has attracted much attention because of its biological activity and its unique $-S(O)CH_2-SCH_3$ moiety. It displays a broad spectrum of in vitro activity against bacteria and shows antifungal activity[2]. Its activity appears to be related to its ability to inhibit protein synthesis by blocking the ribosomal peptidyl transferase function[3]. In addition sparsomycin shows antitumor activity[2]. Recently, the blocking of the peptidyl transferase function[4] and antitumor activity[5] have been studied with sparsomycin analogs in which the $S(O)CH_2SCH_3$ moiety had been replaced by more easily accessible side chains.

The structure 1 has been proposed by Wiley and MacKellar[6]. Recently, this structure has been substantiated by the synthesis of S-deoxo-sparsomycin by us[7] and others[4,5]. However, a synthesis of 1, including the mono-oxodithioacetal side chain in the cysteinol moiety, has not yet appeared in literature. We wish to report an efficient synthesis of this part of the structure, which opens a practical route to sparsomycin (1) and analogs for further biochemical and pharmacological studies.



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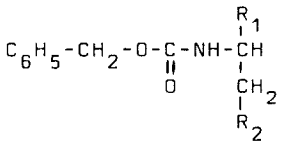
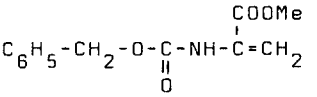
Treatment of N-benzyloxycarbonyl L-cystine methyl ester (R-configuration) in CH_2Cl_2 with three equivalents of Cl_2 in the presence of Ac_2O[8] at -10° gave the sulfinylchloride 2 as a white solid[9]. Reaction of 2 with dry CH_2N_2 according to a procedure developed by Venier *et al.*[10] gave the corresponding α-chloro-sulfoxide 3[9]. With an undried etheral CH_2N_2 solution up to 30% of 2 was converted into the sulfinate ester 4. It was found that substitution of Cl in 3 by $-SCH_3$ had to occur after reduction of the ester function: direct treatment of 3 with CH_3SNa gave the dehydro amino acid derivative 5. The ester function of 3 could be reduced selectively with $LiBH_4$ in monoglyme yielding the alcohol 6[11]. Separation by column chromatography on silica gel (Merck 60-H) using CH_2Cl_2/MeOH (94/6, v/v) as eluent gave the R_cS_s/R_cR_s diastereomers of 6

in 34% and 21% overall yield from Cbo-cystine methylester.

Direct conversion of the alcohol 6 to the desired mono-oxodithioacetal 10 failed; treatment of 6 with CH_3SNa[12] in CH_3OH at 40° for 24 hrs gave the cyclic urethane 7[11] in 30% yield after column chromatography. To circumvent this cyclisation reaction the alcohol function of 6 (mixture of diastereomers) was protected with the tetrahydropyranyl group to yield 8[9] quantitatively. Treatment of 8 with 1.2 equivalent CH_3SNa in C_2H_5OH for 2 hrs at 60° gave the mono-oxodithioacetal 9. This was converted into the desired compound 10[11] by refluxing ethanol in the presence of a trace of HCl. Separation by column chromatography as described above, gave the two possible diastereomers R_cS_s/R_cR_s in 34% and 30% overall yield from 6. On basis of the pmr spectrum [δ(CD_2Cl_2) 7.35 (s, 5H, C_6H_5), 5.82 (br, 1H, NH), 5.10 (s, 2H, $C_6H_5CH_2$), 4.20 (m, 1H, CH), 3.77 (m, 4H, CH_2OH and SCH_2SO), 3.10 (m, 2H, CH-CH_2), 2.29 (s, 3H, SCH_3)] we are inclined to consider the configuration of the major component as enantiomeric with that of sparsomycin (1), which has S configuration at the chiral carbon atom, but unknown configuration at the S(O) function.





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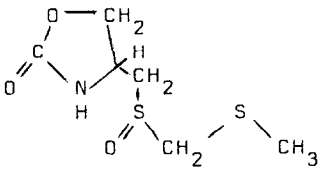

7

2 R_1 = COOMe, R_2 = S(O)Cl
3 R_1 = COOMe, R_2 = $S(O)CH_2Cl$
4 R_1 = COOMe, R_2 = SO_2Me
6 R_1 = CH_2OH, R_2 = $S(O)CH_2Cl$
8 R_1 = CH_2OTHP, R_2 = $S(O)CH_2Cl$
9 R_1 = CH_2OTHP, R_2 = $S(O)CH_2SCH_3$
10 R_1 = CH_2OH, R_2 = $S(O)CH_2SCH_3$

So far, we could not find suitable reaction conditions to remove selectively the N-protecting group. Work is in progress to solve this problem in order to complete the synthesis of sparsomycin (1) and its analogs.

References

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9. This compound gave satisfactory spectral data.
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