Tetrahedron Letters No. 4, pp 387 - 390. 0040-4039/79/0122-0387$02.00/0

TOTAL SYNTHESIS OF ENANTIOMERIC SPARSOMYCIN

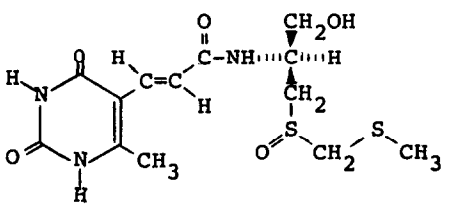
H.C.J. Ottenheijm*, R.M.J. Liskamp and M.W. Tijhuis

Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED Nijmegen, the Netherlands

Sparsomycin (1) has been isolated[1] in 1962 from streptomyces sparsogenes and more recently from streptomyces cuspidosporus[2]. This compound has attracted much attention because of its biological activity and its unique $-S(O)-CH_2-S-CH_3$ moiety. It displays a broad spectrum of in vitro activity against bacteria[3] and shows antifungal[4] and antitumor activity[3,4,5]. As its activity appears to be related to its ability to inhibit protein synthesis by blocking the ribosomal peptidyl transferase function[6], sparsomycin has been used in studies of peptide biosynthesis. Recently, the blocking of the peptidyl transferase function[7] and antitumor activity[8] have been studied with sparsomycin analogs in which the mono-oxo-dithioacetal moiety ($-S(O)-CH_2-S-CH_3$) had been replaced by more easily accessible side chains.

The structure 1 has been proposed by Wiley and MacKellar[9], mainly on the basis of spectroscopic and degradation studies. The chiral carbon atom has S-configuration as depicted, whereas that of the chiral sulfur atom is unknown. Although the synthesis of S-deoxo-sparsomycin has been reported by us[10] and others[7,8], a synthesis of 1 has not yet appeared in literature. Recently[11] we developed a practical preparation of the hitherto elusive cysteinol mono-oxo-dithioacetal moiety 2 of sparsomycin.

We wish to report a total synthesis of the enantiomer of sparsomycin (1), having the R configuration at the chiral carbon atom. This synthesis confirms the structure as proposed by Wiley and MacKellar, and will provide a practical source of sparsomycin and its analogs for further biochemical and pharmacological studies.

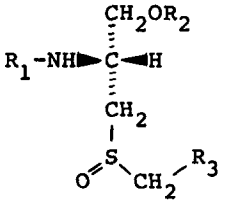


1

Previously[11] we have reported the synthesis of the α-chlorosulfoxide 3, starting from (L)-cystine with R-configuration. The reaction mixture showed two spots on tlc, with rf-values of 0.34 and 0.37 respectively (Merck precoated silica gel plates F-254, thickness 0.25 mm, CH_2Cl_2/MeOH,

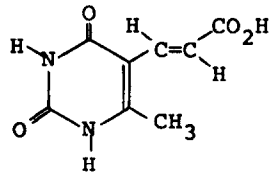
90/10, v/v) due to the presence of the diastereomers R_cR_s and R_cS_s. Separation could be achieved by column chromatography on silica gel (Merck 60-H) using CH_2Cl_2/MeOH (94/6, v/v) as eluant. *The diastereomer with the lowest rf-value* was converted quantitatively into the alcohol-protected mono-oxo-dithioacetal 4 as has been reported previously[11].

We then faced the problem of selective removal of the benzyloxycarbonyl group. This amine protecting group had to be removed under neutral or basic reaction conditions, as the $-S(O)-CH_2-S-CH_3$ function is acid labile[12]. Therefore, we investigated the removal by reduction. Palladium catalysed hydrogenation in liquid ammonia[13] according to Meienhofer[14] gave only starting material. However, when a refluxing ammonia solution of 4 was treated carefully[15] with sodium in liquid ammonia[16], the desired amine 5 could be isolated in 24% yield[17] after column chromatography on silica gel (CH_2Cl_2/MeOH, 90/10, v/v), besides 30%[18] of a ninhydrin positive side-product with lower rf-value on tlc (CH_2Cl_2/MeOH, 80/20, v/v). The pmr spectrum of 5 {δ ($CDCl_3$, int. TMS) 4,62 (1H, br. s, OCHO), 3.85 and 3.67 (2H, AB-spectrum, $OS-CH_2-S$), 3.55 (5H, mult., $NH-CH-\underline{CH_2}-O$, $\underline{CH}-NH_2$ and $O\underline{CH_2}CH_2$), 2.95 and 2.85 (2H, part of ABX-spectrum, $CH-\underline{CH_2}-SO$), 2.33 (3H, s, SCH_3), 1.78 (2H, br. s., NH_2) and 1.60 (6H, br. mult., $CH_2CH_2CH_2$)} showed the presence of only one diastereomer. By an independant synthesis[19] it was shown that the side product is the methylsulfoxide 6, formed by a reductive scission of the C-S bond.

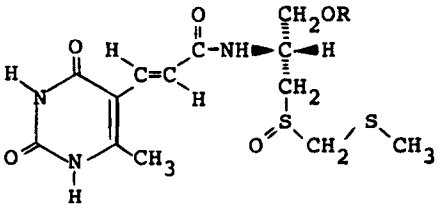


2: $R_1 = C_6H_5CH_2OCO$; $R_2 = H$; $R_3 = SCH_3$
3: $R_1 = C_6H_5CH_2OCO$; $R_2 = H$; $R_3 = Cl$
4: $R_1 = C_6H_5CH_2OCO$; $R_2 = THP$; $R_3 = SCH_3$
5: $R_1 = H$; $R_2 = THP$; $R_3 = SCH_3$
6: $R_1 = H$; $R_2 = THP$; $R_3 = H$

Coupling of 5 with β-(6-methyluracil-)acrylic acid 7[10] was achieved by means of dicyclohexylcarbodiimide and hydroxybenztriazole in DMF, allowing the isolation of 8 in 45% yield[17] after column chromatography on silica gel (CH_2Cl_2/MeOH, 92/8, v/v). The tetrahydropyranyl group could be removed by refluxing an acidified ethanol solution (1 ml of 0.1N aq. HCl in 100 ml EtOH) of 8 for 15 min, to give 9 in 74% yield after column chromatography on Sephadex LH-20 (MeOH/H_2O, 85/15, v/v). The product thus obtained was found to be identical in all respects (pmr[9], tlc, ir[1]) with an authentic sample of sparsomycin (1)[20] except for the sign of the specific rotation[21]. Thus compound 9 is the enantiomer of sparsomycin; this was anticipated, as the configuration of the chiral carbon atom of the starting material, i.e. (L)-cystine, is opposite to that of 1.



7



8: R = THP
9: R = H

The diastereomer of sparsomycin, having R configuration at the chiral carbon atom, and the same, but unknown chirality at the sulfur atom as sparsomycin, was also prepared by the same sequence of reactions, starting from the less polar diastereomer of 3. This diastereomer of 1 has a higher rf-value on tlc (i.e. 0.32, CH_2Cl_2/MeOH, 4/1, v/v; for sparsomycin rf: 0.28), whereas the pmr spectrum shows slightly different chemical shifts for the four methylene protons adjacent to the sulfoxide function.

Work is in progress to establish the configuration at the chiral sulfur atom of 1.

REFERENCES AND FOOTNOTES

1. A.D. Argoudelis and R.R. Herr, Antimicrob. Ag. Chemotherapy, 780 (1962).
2. E. Higashide, T. Hasegawa, M. Shibata, K. Mizuno and H. Akaike, Takeda Kenkyusho Nempo 25, 1 (1966); Chem. Abstr. 66, 54238 q (1967).
3. L. Slechta, Antibiotics 1, 10 (1967).
4. S.P. Owen, A. Dietz and G.W. Camiener, Antimicrob. Ag. Chemotherapy, 772 (1962).
5. H.P. Close and J.R. McFarlane, Cancer Chemotherapy Reports 43, 29 (1964).
6. R.E. Monro and D. Vazques, J. Mol. Biol. 28, 161 (1967).
7. C.K. Lee and R. Vince, J. Med. Chem. 21, 176 (1978).
8. C.C.L. Lin and R.J. Dubois, ibid, 20, 337 (1977).
9. P.F. Wiley and F.A. MacKellar, J. Amer. Chem. Soc. 92, 417 (1970); P.F. Wiley and F.A. MacKellar, J. Org. Chem. 41, 1858 (1976).
10. H.C.J. Ottenheijm, S.P.J.M. van Nispen and M.J. Sinnige, Tet. Letters, 1899 (1976).
11. H.C.J. Ottenheijm and R.M.J. Liskamp, ibid, 2437 (1978).
12. K. Ogura and G. Tsuchihashi, Tet. Letters, 3151 (1971).

13. In general, catalytic hydrogenation of compounds containing bivalent sulfur fails, due to catalyst poisening.
14. J. Meienhofer and K. Kuromizu, Tet. Letters, 3259 (1974).
15. The procedure of H. Nesvadba and H. Roth, Monatshefte 98, 1432 (1967) was applied, using a simplified apparatus.
16. R.H. Sifferd and V. du Vigneaud, J. Biol. Chem. 108, 753 (1935).
17. Work is in progress to optimize the reaction conditions.
18. The product ratio is dependant upon the reaction conditions.
19. Compound 6 was prepared as follows: S-methyl-(L)-cysteine was converted to N-benzyloxycarbonyl-S-methyl-(L)-cysteine methylester by conventional methods. Oxidation with one equivalent $NaIO_4$ in acetonitril/water afforded the corresponding sulfoxide in 92% yield. Reduction with $LiBH_4$ of the ester to the corresponding alcohol, protection with the tetrahydropyranyl group, and careful treatment with sodium in refluxing ammonia (ref. 15) gave in 40% overall yield the two diastereomers of 6, i.e. R_cR_s and R_cS_s, which could be seperated by column chromatography on silica (CH_2Cl_2/MeOH, 9/1, v/v). The diastereomer with the highest rf-value on tlc (CH_2Cl_2/MeOH, 4/1, v/v) was found to be identical (tlc, pmr) with the side product.
20. We are gratefull to Dr. P.F. Wiley, Upjohn Co, for a sample of 1.
21. For 9: $[\alpha]_D^{25}$ -60^o (C 0.47, water), Lit.[1]: $[\alpha]_D^{25}$ $+69^o$ (C 0.50, water).

(Received in UK 20 October 1978)