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SYNTHESIS OF S-DEOXO-(R)-SPARSOMYCIN

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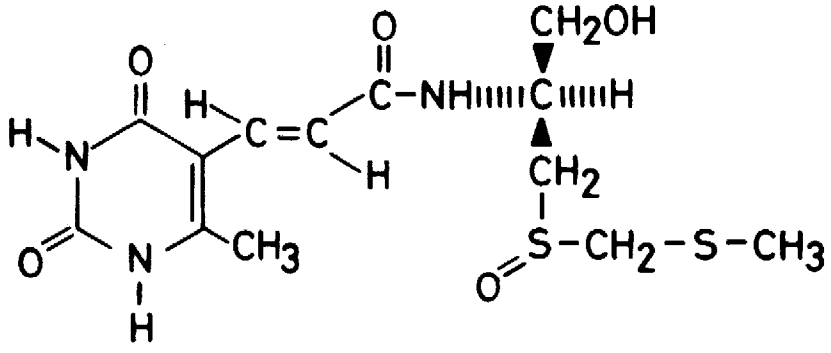
Sparsomycin, which was isolated in 1962 from *Streptomyces Sparsogenes* by Argoudelis and Herr[1], has attracted much attention because of its antitumor activity[2] and has been tested in Phase I clinical studies[3]. Not until 1970, Wiley and MacKellar[4] proposed structure 1 for this antibiotic, which has not been confirmed yet by total synthesis. We wish to report the synthesis of S-deoxo-(R)-sparsomycin 15, which definitely establishes structure 1 for the natural product and provides a practical route to analogs for further studies of structure-activity relationships.



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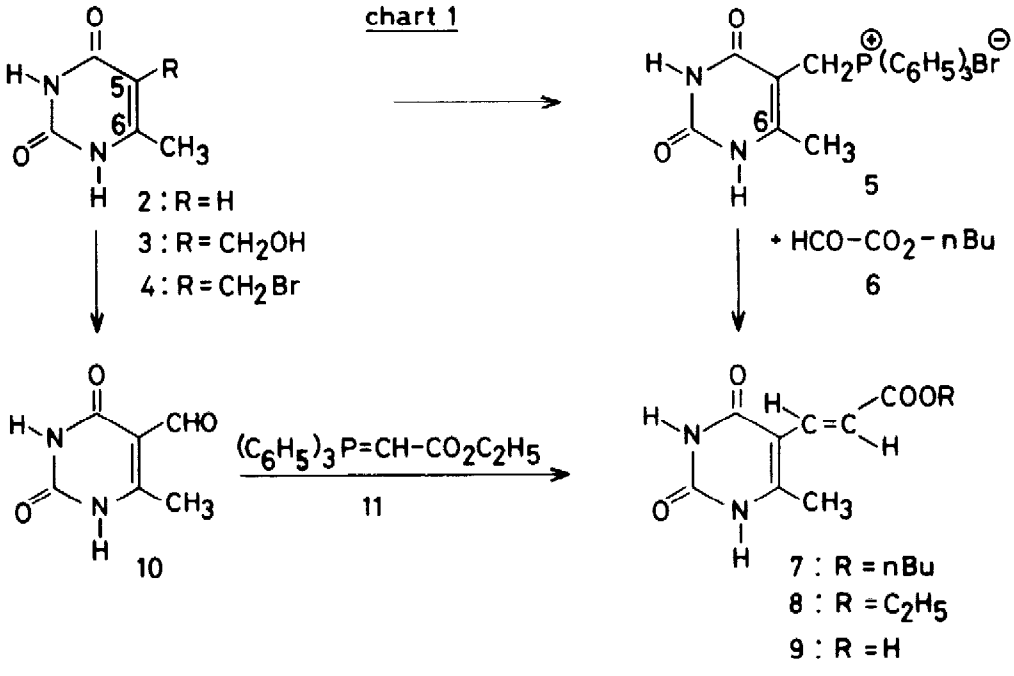
Two procedures were developed for the preparation of the β-uracil-acrylic acid 9 with a *trans*-configuration (Chart 1); both started from 5-hydroxymethyl-6-methyluracil (3), prepared from 6-methyluracil (2) with formaldehyde and aqueous NaOH (molar ratios 1:3:2)[5]. Treatment of 3 with HBr in glacial acetic acid gave 4[6] (79%), which upon reaction with $(C_6H_5)_3P$ in DMF could be converted quantitatively into the phosphonium salt 5[7]. n-Butyl glyoxylate (6) could be pre-

pared from n-butyl dimethoxyacetate[8] by distillation from P_2O_5 (variable yields). However, the method of choice[9] was found to be the oxidation of dibutyl tartrate with sodium periodate[10], followed by distillation of the hemihydrate over P_2O_5[11]. A Wittig reaction of the phosphonium salt 5 and the aldehyde 6 in DMF gave 7 in a low yield (5-15%), irrespective of the reaction conditions and base used. This low yield might be explained by deprotonation of either the uracil ring or the 6-methyl group of 5, which should give an exomethylene uracil derivative and $(C_6H_5)_3P$. Indeed, the latter could be detected on tlc, along with the expected $(C_6H_5)_3PO$.

chart 1

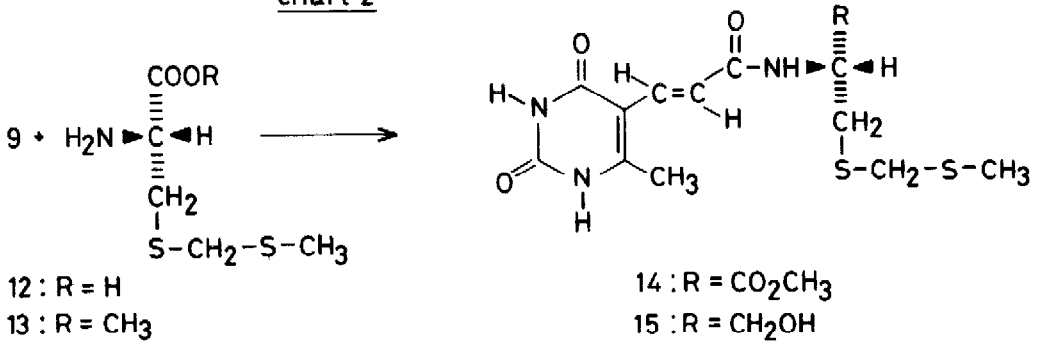


A more productive synthesis of the desired ester of 9 was found to be the inverse Wittig reaction of 10 and 11. The aldehyde 10[12], prepared from 3 (70%) by oxidation with $K_2S_2O_8$ and a trace of $AgNO_3$[13], was coupled with carbethoxymethylidenetriphenylphosphorane 11 in DMF to yield 8[4] (41%), having *trans*-configuration (J H-C=C-H, 16 Hz). Alkaline hydrolysis of 7 or 8 in dioxane-CH_3OH-water, followed by acidification gave quantitatively the acid 9 (m.p. 270°)[7].

The second key intermediate, the amino-alcohol moiety of sparsomycin, can be viewed as an S-alkylated derivative of cysteine in which the COOH function has been reduced. Accordingly, L-cystine was reduced with sodium in liquid NH_3, treated with chloromethylmethylsulfide and acidified to give 12 (61%)[14]. The amino-acid ester 13[15] was prepared (78%) by esterification of 12 with CH_3OH and $SOCl_2$, followed by treatment with $(C_2H_5)_3N$.

Coupling of 9 with 13 (Chart 2) was achieved by means of dicyclohexylcarbodiimide and hydroxybenztriazole in DMF, allowing the isolation of 14 (60%, m.p. 182°)[7], having *trans*-configuration, after chromatography on silica gel (4% CH_3OH-$CHCl_3$). Selective reduction with $LiBH_4$ in monoglyme gave the desired alcohol 15[7] (63%, m.p. 233°) after chromatography on silica gel (7% CH_3OH-$CHCl_3$) followed by chromatography on Sephadex LH-20 (15% H_2O-CH_3OH); the pmr spectrum {δ (d_6-DMSO) 11.44 (br s, 2H, uracil H), 8.20 (d, 1H, NH), 7.46 and 7.32 (AB-spectrum, 2H, H-C=C-H, J 16 Hz), 4.99 (m, 1H, OH), 4.18 (m, 1H, N-CH), 3.96 (s, 2H, $-SCH_2S-$), 3.66 (m, 2H, $-CH_2O$), 3.02 (8 lines, 2H, $-S\underline{CH_2}CH$), 2.48 (s, 3H, C_6-CH_3) and 2.31 (s, 3H, $-SCH_3$)} was identical with that reported[4] for 1, except for the singlet at δ 3.96, due to the absence of chirality at the sulfur atom.

chart 2



Now that this synthetic scheme has been established, it is possible to prepare from D-cystine the enantiomer of 15 which would have the same configuration at the chiral carbon atom as 1. Work is in progress to complete the synthesis of 1.

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7) This compound gave satisfactory spectral data and elemental analysis.
8) Prepared from dichloroacetic acid and CH_3ONa in CH_3OH, followed by esterification with n-BuOH/HCl.
9) Preparation of a pure sample of 6 according to F.J. Wolf, J. Weyland, N.J. Leonard and L.A. Miller, Org. Synth. 35, 18, failed in our hands.
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13) The tedious chromic oxide oxidation used by Wiley *et al.*[4] gave a low yield only (20%, personal communication Dr. P.F. Wiley, The Upjohn Company, Kalamazoo, Michigan, U.S.A.). We found most of the conventional reagents for the conversion of alcohols into aldehydes rather unfit for the preparation of 10.
14) This is a general method for the preparation of S-alkylated cysteine derivatives *cf.* P.J.E. Brownlee, M.E. Cox, B.O. Handford, J.C. Marsden and G.T. Young, J. Chem. Soc. 3832 (1964).
15) While this work was in progress, we became aware of the work of R.J. Dubois, C.C.L. Lin and B.L. Michel, J. Pharm. Sci. 64, 825 (1975), who, for the synthesis of N-substituted 3-aryl acrylamides, also prepared 13 in this way.