SYNTHETIC APPROACH TO THE ANTITUMOR ANTIBIOTIC LAVENDAMYCIN: A SYNTHESIS OF DEMETHYLLAVENDAMYCIN METHYL ESTER

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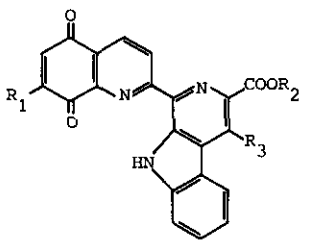
Abstract------A synthetic approach to the lavendamycin has been achieved by a formation of β-carboline derivative and oxidation of bromophenol derivative to the quinolinequinone system using cerium ammonium nitrate.

Lavendamycin, a new antitumor antibiotic isolated from *Streptomyces lavendulae*, strain C22030, was determined by spectroscopic evidences to have structure 1[1]. This structure was similar to that of antitumor antibiotic streptonigrin[2]. We have attempted to develop a total synthesis and syntheses of its congeners based on the nonacidic Pictet-Spengler type cyclization of an appropriately substituted quinoline-2-aldehyde 5 with a tryptophan methyl ester 6 to provide a demethyllavendamycin methyl ester 2 *via* oxidation of bromophenol 11. We now wish to report on this result. Initial study was aimed at the formation of pyridine ring (β-carboline 8)[3], which was successfully prepared from 8-benzyloxyquinoline-2-aldehyde 5 (mp 92-93°C)[3] with tryptophan methyl ester 6 in benzene under reflux, followed by aromatization with 5% Pd-C in xylene. Then quinolyl-β-carboline 8 (mp 219-220°C) was hydrogenated by 10% Pd-C to give 8-hydroxyquinoline 9 (mp 226-227°C), followed by bromination with 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one 10[4] to have the desired dibromo-compound 11 (mp 257-259°C) in good yields, respectively. In many oxidizing agents, we have found that cerium ammonium nitrate[5] in tetrahydrofuran was extremely effective for the oxidation of quinoline 11 to orange red bromoquinolinequinone 4 (mp >300°C). Replacement of the bromine of 4 by

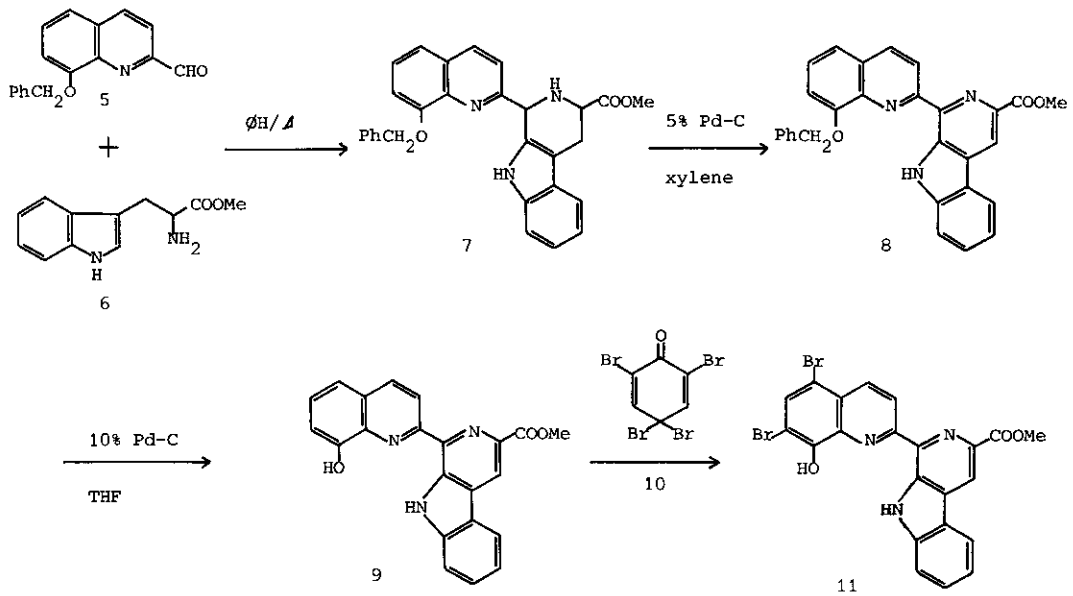


1 : R_1 = NH_2, R_2 = H, R_3 = Me

2 : R_1 = NH_2, R_2 = Me, R_3 = H

3 : R_1 = N_3, R_2 = Me, R_3 = H

4 : R_1 = Br, R_2 = Me, R_3 = H



the sodium azide gave azidoquinolinequinone 3, and reduction of the azide group of 3 with sodium hydrosulfite afforded aminoquinolinequinone 2 (demethyllavendamycin methyl ester, m/z 398, mp 250-251°C). Spectroscopic evidences of 2 were similar to those of lavendamycin[1a,6,7].

Work is now in progress on 1 and other related compounds.

REFERENCES AND NOTES

1) (a) T. W. Doyle, D. M. Balitz, R. E. Grulich, D. E. Nettleton, S. J. Gould, C.-h. Tann and A. E. Moews, *Tetrahedron Letters*, 22, 4595 (1981). (b) D. M. Balitz, J. A. Bush, W. T. Doyle, F. A. O'Herron and D. E. Nettleton, *J. Antibiotics*, 35, 259 (1982).

2) See review ; (a) S. Hibino, *Heterocycles*, 6, 1485 (1977). (b) S. J. Gould and S. M. Weinreb, *Fortschr. Chem. Org. Natur.*, 41, 77 (1982).

3) All new compounds gave satisfactory analyses and spectroscopic evidences.

4) G. J. Fox, G. Hallas, J. D. Hepworth and K. N. Paskins, *Organic Syntheses*, Vol 55, 20 (1976).

5) Oxidation of *p*-bromophenols to *p*-quinone system with cerium ammonium nitrate is first example.

6) ^{1}H-NMR and ^{13}C-NMR spectra of AB-aminoquinolinequinone portion were observed as follows: ^{1}H-NMR (DMSO-D_6/CF_3COOD), δ 5.91 (1H, S, C_6-H); ^{13}C-NMR (DMSO-D_6/CF_3COOD), δ 157.8 (C_2), 134.4 (C_3), 124.6 (C_4), 180.5 (C_5), 102.3 (C_6), 150.6 (C_7), 179.8 (C_8).

7) We wish to thank Prof. S. J. Gould, Oregon State University for sending ^{13}C-NMR spectrum of lavendamycin.

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