FORMAL SYNTHESIS OF LAVENDAMYCIN METHYL ESTER: THE REGIOSELECTIVE SYNTHESIS TO THE BROMOQUINOLINEQUINONE SYSTEMS OF KEY INTERMEDIATE

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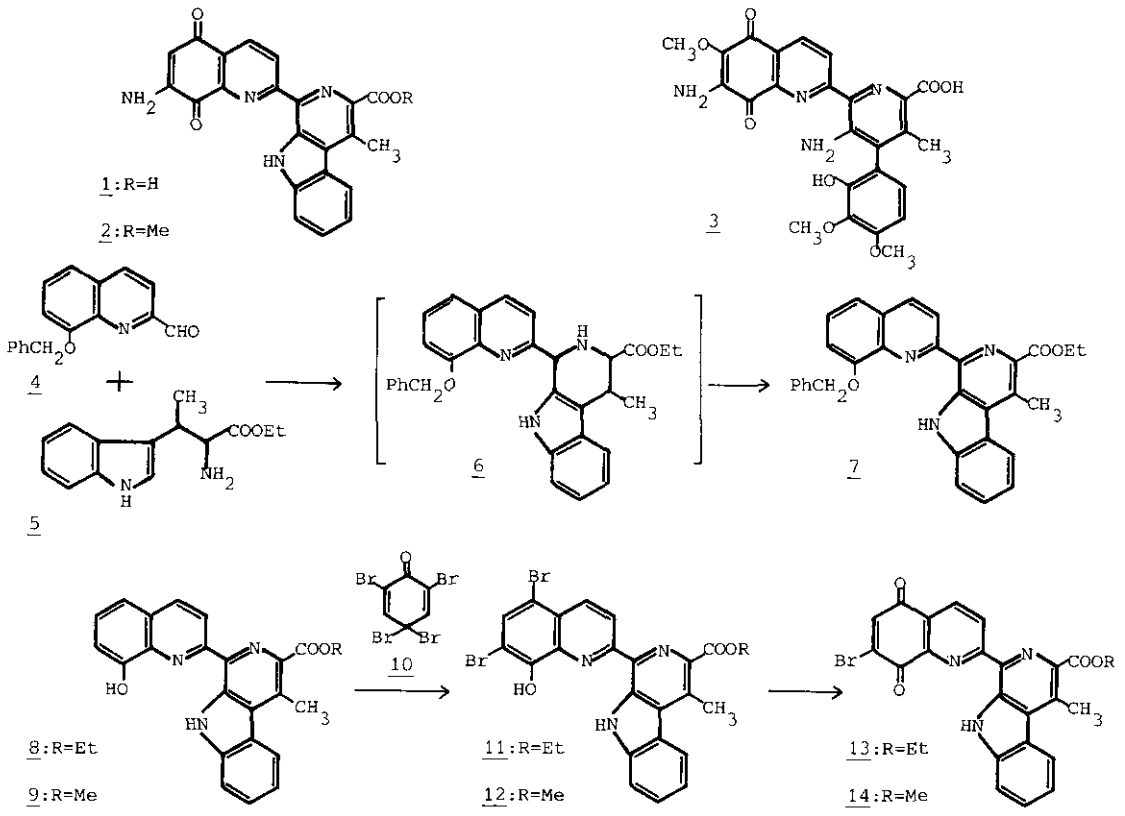
Abstract——We achieved a formal synthesis of lavendamycin methyl ester as follows. The Pictet-Spengler reaction of 8-benzyloxyquinolin-2-aldehyde 4 with β-methyltryptophan ethyl ester 5, gave pentacyclic β-carboline 7. Hydrogenolysis of benzyl ether 7 and bromination of 8-hydroxyquinoline 8 afforded 5,7-dibromo-8-hydroxyquinoline 11. Oxidation of bromophenol 11 by cerium ammonium nitrate proceeded regioselectively to the desired p-quinone system 13. On the other hand, the ethyl ester 8 was converted into its methyl ester 9 and led to the methyl ester of bromoquinolinequinone 14 regioselectively in the same way, that is, Kende's intermediate.

In 1981 Lavendamycin 1 was isolated by Doyle and co-workers[1] from fermentation broths of Streptomyces lavendulae which was structually and biogenetically related to the antitumor antibiotic streptonigrin 3[2]. Recently Kende reported a first total synthesis of lavendamycin methyl ester 2[3]. On the other hand, Boger[4] has shown an elegant approach to the tricyclic β-carboline moiety of lavendamycin 1. We now wish to report a formal synthesis of lavendamycin methyl ester 2 using the previously described synthetic pathway[5], that is, the regioselective synthesis of bromoquinolinequinone systems 13 and 14 which are synthetic precursors of lavendamycin 1. For the synthesis of pentacyclic β-carboline 7 having an appropriate quinoline moiety, we chose the Pictet-Spengler type reaction; 8-benzyloxyquinolin-2-aldehyde 4[6] (mp 92-93°C) was reacted with β-methyltryptophan ethyl ester 5 in



benzene to afford an intermediay tetrahydro-ß-carboline 6, which was followed by oxidation with 5 % Pd-C in xylene under reflux to aromatic pentacyclic ß-carboline 7[8] (75 %, mp237-239°C). Cleavage of benzyl ether 7 by 10 % Pd-C in the presence of hydrogen in tetrahydrofuran gave 95 % of 8-hydroxyquinoline derivative 8[9] (mp 227-228°C). For the confirmation of this compound, the ethyl ester 8 was converted to the known phenolic methyl ester 9 (mp 204-206°C; Lit.[3] mp 201-205°C) by hydrolysis (10 % NaOH, THF) and esterification (anhydrous MeOH, $BF_3 \cdot OEt_2$). Dibromination of both phenolic ester 8 and 9 using 2,2,4,4-tetrabromocyclohexadien-1-one 10[10] (2 equivalent) in 10 % methanolic chloroform gave the corresponding dibromophenol 11[11] (90 %, mp 259-261°C) and 12 (92 %, mp 252-254°C), respectively. Oxidation of dibromophenol 11 and 12 by cerium ammonium nitrate[12] (2.2 equivalent) in aqueous tetrahydrofuran proceeded regioselectively to give the desired p-quinone systems 13 (30 %, mp 291-294°C) and 31 %, mp 285-287°C; Lit.[3] mp 285-287°C)[13]. Physical data and ^{1}H-NMR spectrum of bromoquinolinequinone methyl ester 14 were identical in all respects with those of Kende's intermediate[3,13]. Thus a formal synthesis of

lavendamycin methyl ester 2 has been achieved and the structure of intermediate 13 has been also confirmed simultaneously.

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6. 8-Benzyloxyquinolin-2-aldehyde 4 was prepared by a 4-step sequence from 8-benzyloxyquinoline.
7. Ethyl ester of β-methyltryptophan was prepared by the reduction of ethyl α-nitro-β-(3-indole)-butanoate (mp 121-123°C) which was made from the reaction of 3-(isopropylaminoethylidene)-indole and ethyl nitroacetate. a) D. A. Lyttle, and D. I. Weisblat, J. Amer. Chem. Soc., 69, 2118 (1947), b) H. R. Snyder, and D. S. Matteson, ibid., 79, 2217 (1957).
8. Mass spectrum: m/e 487. ^{1}H-NMR($CDCl_3$) δ1.53(3H,t,J=7Hz), 2.15(3H,s), 4.52(2H, q,J=7Hz), 5.33(2H,s), 8.23 and 8.90(each 1H,d and d,J=8.5Hz).

9. For 8; mass spectrum: m/e 397. ^{1}H-NMR($CDCl_3$) δ1.55(3H,t,7Hz), 2.18(3H,s), 4.56 (2H,q,7Hz). For 9; mass spectrum: m/e 383. ^{1}H-NMR($CDCl_3$) δ2.18(3H,s), 4.11 (3H,s).

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11. Acetylation of dibromophenol 11 (m/e 553, 555, 557) by acetic anhydride and pyridine gave O-acetylated derivative in 98 % yield: mp 236-237°C, mass spectrum: m/e 595, 597, 599.

12. Although the pyridine-2,6-dicarboxylic acid N-oxide was used sometimes in the case of cerium ammonium nitrate oxidation, the yield of oxidation product did not increase in our case; L. Syper, K. Kloc, J. Mlochowski, and Z. Szulc, Synthesis, 1979, 521.

13. For 13; mass spectrum: m/e 489, 491. ^{1}H-NMR($CDCl_3$) δ1.53(3H,t,J=7Hz), 3.13 (3H,s), 4.53(2H,q,J=7Hz), 7.43(1H,s), 8.23(1H,d,J=8.0Hz), 8.35(1H,d,J=8.4Hz), 8.94(1H,d,J=8.4Hz). For 14; mass spectrum: m/e 475, 477. ^{1}H-NMR($CDCl_3$) δ3.15 (3H,s), 4.07(3H,s), 7.50(1H,s), 8.30(1H,d,J=8.0Hz), 8.42(1H,d,J=8.4Hz), 9.01 (1H,d,J=8.4Hz).

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