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SYNTHESIS OF CADEGUOMYCIN (7-DEAZAGUANOSINE-7-CARBOXYLIC ACID)

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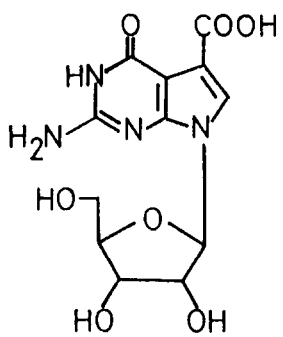
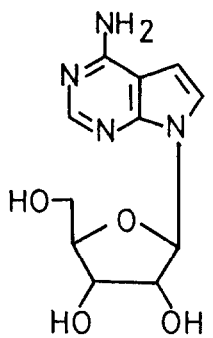
Cadeguomycin, 2-amino-3,4-dihydro-4-oxo-7-(β-D-ribofuranosyl)-7H-pyrrolo-[2,3-d]pyrimidine-5-carboxylic acid, was synthesized from 2-diacetylamino-3-methoxymethyl-5-methyl-6-bromo-3,4-dihydro-4-oxo-7-(β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine.

Cadeguomycin (1) has been isolated from the culture filtrate of Streptomyces hygroscopicus IM7912T together with tubercidin (2).[1] The antibiotic (1) stimulated immune response and exhibited inhibitory effects on transplantable animal tumors, but no significant antimicrobial activity against bacteria and fungi in contrast to tubercidin (2), which showed antimicrobial and antitumor effects.[1] The structure of cadeguomycin has a strong resemblance to that of nucleoside Q.[2] We now describe a total synthesis of the antibiotic (1) starting from the key intermediate 3 of the total synthesis of nucleoside Q.[3]



Cadeguomycin (1)



Tubercidin (2)

A suspension of the protected 8-bromo-7-methyl-7-deazaguanosine 3 (33.7 mg)[3], N-bromosuccinimide (NBS) (20 mg) and K_2CO_3 (51 mg) in CCl_4 (10 ml) containing benzoyl peroxide (4 mg) was refluxed under stirring for 3 h. After filtration, the solvent was evaporated in vacuo to dryness. The residue was dissolved in dioxane-water (3:1, 8 ml) and then

Ag_2CO_3 (150 mg) was added to it under stirring at room temp. After stirring for 2 days, the mixture was filtered and evaporated to dryness. The residue was subjected to silica gel tlc [acetone-benzene (1:6)] to give the bromo-alcohol 4 (15.6 mg)[EI-MS m/z 600 and 602 (M^+); UV (MeOH) λ_{max}(nm) 304 and 271; PMR ($CDCl_3$) δ(ppm) 1.36, 1.61, 2.06, 2.36, 2.40 and 3.42 (each 3H, s), 4.0-4.5 (3H, m), 4.73 (2H, s), 4.85 (1H, dd, J = 4 & 7 Hz), 5.26 (1H, dd, J = 2 & 7 Hz), 5.32 (2H, s), 6.26 (1H, d, J = 2 Hz)].

To a solution of the bromo-alcohol 4 (25.5 mg) in acetonitrile (2.5 ml) was added active MnO_2 (300 mg) in portions at room temp. during 3.5 h under stirring. After stirring for 12 h, the mixture was diluted with acetonitrile and filtered. The filtrate was evaporated in vacuo and the residue, which contained a partially hydrolyzed product, was treated with Ac_2O and pyridine at room temp. The mixtue was evaporated to dryness and subjected to silica gel tlc [EtOAc-C_6H_6 (1:2)] to afford the bromo-aldehyde 5 (18.3 mg) [EI-MS m/z 598 and 600 (M^+); UV (MeOH) λ_{max}(nm) 320sh, 300, 271sh, 249sh; PMR ($CDCl_3$) δ(ppm) 1.37, 1.62, 2.07, 2.38, 2.41 and 3.44 (each 3H, s), 4.0-4.5 (3H, m), 4.86 (1H, dd, J = 4 & 7 Hz), 5.30 (1H, dd, J = 2 & 7 Hz), 5.35 (2H, s), 6.38 (1H, d, J = 2 Hz), 10.50 (1H, s)].

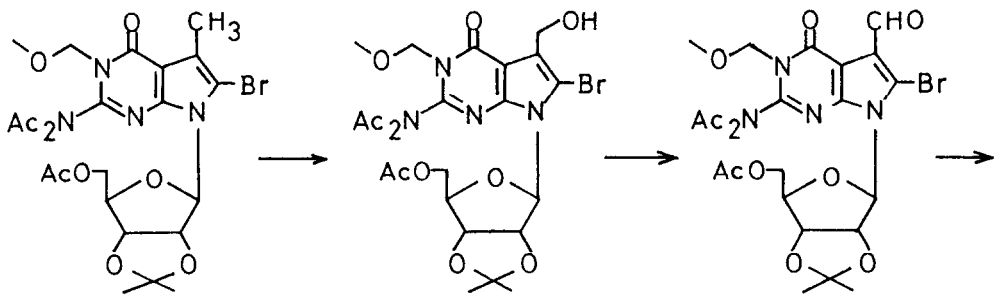
To a solution of the bromo-aldehyde 5 (18.0 mg) in CCl_4 (6 ml) was added NBS (6.0 mg) and anhydrous K_2CO_3 (60 mg) with stirring. Under nitrogen atmosphere the mixture was arradiated by 500W effexing photo-lamp at 10-40 °C.[4] When the starting material disappeared (monitored by silica gel tlc), dioxane-water (4:1, 0.3 ml) was added and after 30 min the mixture was partitioned between CH_2Cl_2 and water at pH 2-3 (addition of 2N HCl). The organic layer was evaporated to dryness and the residue was treated with triethylamine-water-dioxane (0.5:1:3). The mixture was dried up and subjected to silica gel tlc [MeOH-CH_2Cl_2 (1:20)] to give the bromo-carboxylic acid 6 (9.9 mg) [EI-MS m/z 574 and 572 (M^+); UV (MeOH) λ_{max}(nm) 305sh, 285, 223; PMR ($CDCl_3$) δ(ppm) 1.41, 1.62, 2.04, 2.30 and 3.54 (each 3H, s), 4.0-4.5 (3H, m), 5.22 (1H, dd, J = 4 & 7 Hz), 5.44 (1H, d, J = 11 Hz), 5.56 (1H, dd, J = 2 & 7 Hz), 5.84 (1H, d, J = 11 Hz), 6.40 (1H, d, J = 2 Hz), 8.75 (1H, br.s)].

The bromo-carboxylic acid 6 (9 mg), which was dissolved in methanol (3 ml) and water (0.4 ml) containing CH_3CO_2K (85 mg), was hydrogenated at room temp. in the presence of 10% Pd-C (30 mg) with hydrogen gas for 15 min. After removal of the catalyst by filtration, the mixture was dried up in vacuo, and partitioned between CH_2Cl_2 and water at pH 2-3 (addition of 2N HCl). The organic layer was evaporated and tlc separation of the residue [acetone-C_6H_6 (1:4)] gave the carboxylic acid 7 (3.2 mg) [PMR ($CDCl_3$) δ(ppm) 1.37, 1.61. 2.14, 2.50 and 3.52 (each 3H, s), 4.1-4.6 (3H, m), 4.8-5.1 (2H, m), 5.60 (1H, d, J = 11 Hz), 5.65 (1H, d, J = 11 Hz), 6.13 (1H, d, J = 2 Hz), 7.81 (1H, s), 8.60 (1H, br.s)].

A solution of the protected cadeguomycin 7 (3.5 mg) in CF_3CO_2H-H_2O (2:1, 4 ml) was heated at 65 - 70 °C for 24 h under nitrogen atmosphere. The reaction mixture was evaporated in vacuo to dryness and subjected to ODS HPLC (JASCO Finepak SIL C_{18}; eluent: 30% MeOH containing 1% AcOH) to give cadeguomycin 1 (1.5mg) [SI-MS m/z 327 (M+1); UV λ_{max} (nm) (Fig. 1) (in H_2O) 299, 272, 233, (in dil NaOH) 282sh, 268, 225sh; PMR(D_2O-CF_3CO_2D = 4:1) δ(ppm) (Fig. 2) (internal standard: t-BuOH as 1.23 ppm; at 60 °C; 200 MHz) 7.83 (1H,s), 5.93 (1H, d, J = 5.5 Hz), 4.52 (1H, t, J = 5.5 Hz), 4.35 (1H, dd, J = 4 & 5.5 Hz), 4.26 (1H,

q, J = 4 Hz), 3.93 (1H, dd, J = 4 & 12 Hz), 3.88 (1H, dd, J = 4 & 12 Hz)].

The synthetic cadeguomycin (1) showed PMR (Fig. 2) and UV (Fig. 1) spectra superimposable to those of natural cadeguomycin.



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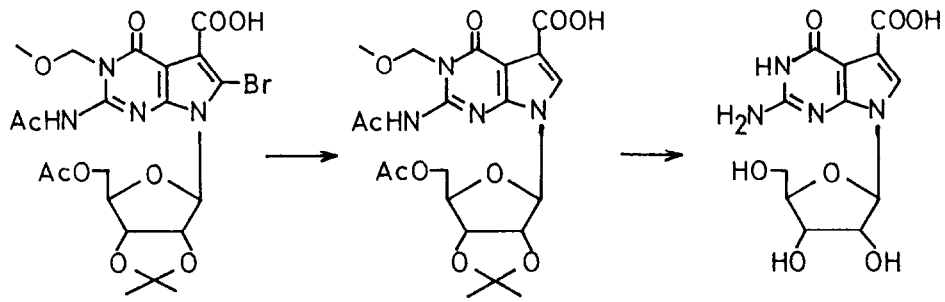

(6) (7) (1)

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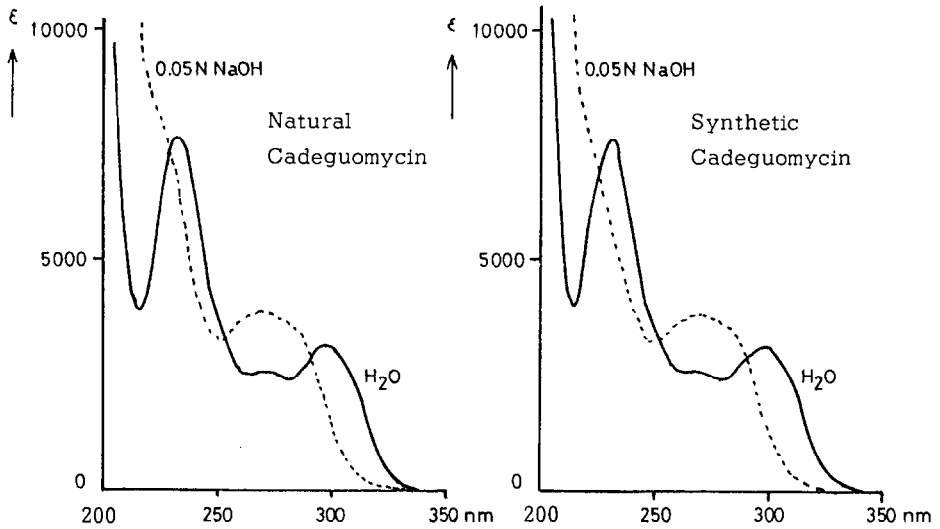

Fig. 1. UV Spectra of Natural and Synthetic Cadeguomycin (1)

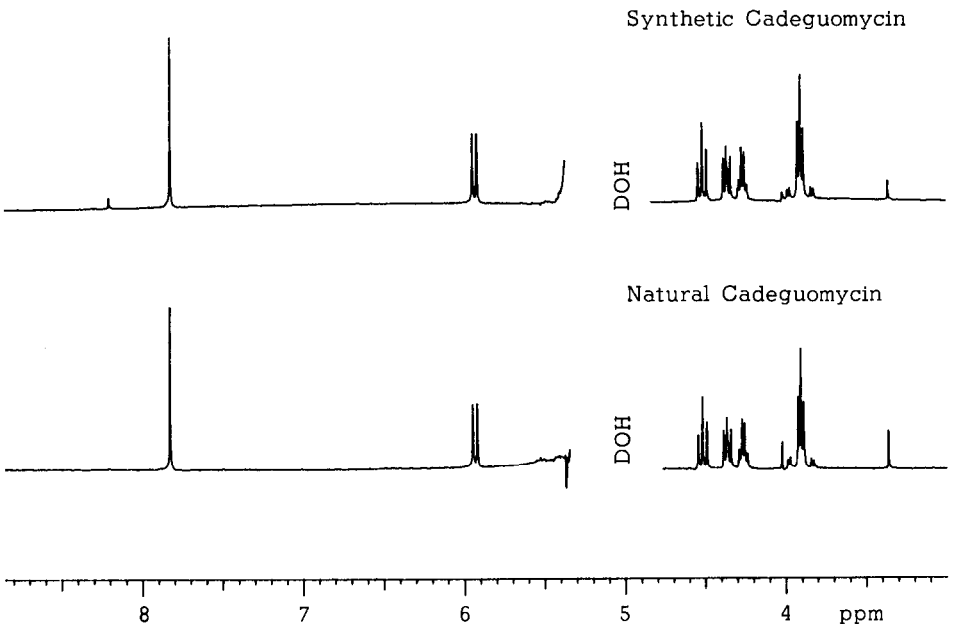

Fig. 2. PMR Spectra of Natural and Synthetic Cadeguomycin (1) in D_2O-CF_3CO_2D (4:1) at 60 °C (200 MHz)

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