A TOTAL SYNTHESIS OF METHYLENOMYCIN B

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Summary: A new synthesis of methylenomycin B $(\underline{1})$ has been accomplished in four steps starting with a Ni(CO)₄ promoted cyclocondensation reaction of allyl chloride and 2-butyn-1-ol in MeOH, followed by hydrogenolysis of the resulting mixture to 2,3-dimethyl-5-methyl-oxycarbonylmethyl-2-cyclopentenone ($\underline{3}$), which by hydrolysis and oxidative decarboxylation yielded $\underline{1}$.

Wide interest in bioactive cyclopentanone or cyclopentenone derivatives has led to recent developments in organic synthetic methodology. In this context, methylenomycin B $(\underline{1})$, a structurally simple cyclopentenoid antibiotic, isolated from culture broths of <u>Streptomyces</u> species, has been selected as synthetic target by different authors? In the present communication, we report a synthesis of this antibiotic by application of an useful modification of an early reported Ni(CO)4 promoted carbonylative cycloaddition³ reaction for the synthesis of 2,3,5-trisubstituted-2-cyclopentenones, developed in our laboratory⁴.

As shown in the Scheme, the reaction of a 1:2:2 molar mixture of 2-butyn-1-ol, allyl chloride and Ni(CO)4 in methanol afforded a 4:1 isomeric mixture of cyclopentenones <u>2a</u> and <u>2b</u>, which without purification was hydrogenolyzed in the presence of 10% palladium on charcoal in methanol to give compound <u>3</u>, isolated after flash chromatography on silica gel in 78% overall yield, as a colorless oil. IR: ν_{max} (CHCl₃): 1730, 1690, 1645 cm⁻¹. ¹H-NMR(CDCl₃) & 1.70(s, 3H), 2.05(s, 3H), 2.20-2.97(m, 5H), 3.70(s, 3H). ¹³C-NMR(CDCl₃) & 7.75, 16.76, 35.08, 38.49, 41.14, 51.41, 135.15, 168.09, 172.43, 208.86. Anal. Calcd. for C₁₀H₁₄O₃: C, 65.93%; H, 7.69%. Found:C, 65.87%; H, 7.75%. Hydrolysis of the methyl ester moiety of <u>3</u> was achieved by refluxing for 5 hours in 0.2 N hydrochloric acid to give the corresponding carboxylic acid <u>4</u> (m.p. 76-78°C) in 91% yield. IR: ν_{max} (CHCl₃):1710, 1700, 1650 cm⁻¹. ¹H-NMR (CDCl₃) &1.72(s, 3H), 2.17 (s, 3H), 2.25-3.15 (m, 5H), 10.50 (br, 1H).





Completion of the synthesis was carried out by oxidative decarboxylation⁵ of acid <u>4</u> by treatment with lead tetraacetate in benzene, in the presence of a catalytic amount of cupric acetate and pyridine at 80 °C for 2 hours, to afford compound <u>1</u> in 39% yield after flash distillation (bath temperature 80 °C, 0.1 mmHg). MS Calcd. for C_8H_{10} 0: m/z 122.072594. Found: m/z 122.072599. MS: m/z: 122(M⁺), 88, 86, 84, 51, 49, 47. IR: v_{max} (CH₂Cl₂): 1690, 1660, 1630 cm⁻¹. ¹H-NMR(CDCl₃) & 1.74(bs, 3H), 2.04(bs, 3H), 3.04(bs, 2H), 5.29 (dt, J=1Hz, J=1Hz, 1H), 5.99(dt, J=1Hz, J=2Hz, 1H). ¹³C-NMR(CDCl₃) & 8.24, 16.63, 37.00, 114.89, 138.35, 141.76, 163.82 and 207.05 consisting with reported data²

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