

A TOTAL SYNTHESIS OF METHYLENOMYCIN B

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Summary: A new synthesis of methylenomycin B (1) has been accomplished in four steps starting with a $\text{Ni}(\text{CO})_4$ promoted cyclocondensation reaction of allyl chloride and 2-butyne-1-ol in MeOH, followed by hydrogenolysis of the resulting mixture to 2,3-dimethyl-5-methyloxycarbonylmethyl-2-cyclopentenone (3), which by hydrolysis and oxidative decarboxylation yielded 1.

Wide interest in bioactive cyclopentanone or cyclopentenone derivatives has led to recent developments in organic synthetic methodology. In this context, methylenomycin B (1), a structurally simple cyclopentenoid antibiotic, isolated from culture broths of *Streptomyces* species,¹ has been selected as synthetic target by different authors.² In the present communication, we report a synthesis of this antibiotic by application of an useful modification of an early reported $\text{Ni}(\text{CO})_4$ 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-butyne-1-ol, allyl chloride and $\text{Ni}(\text{CO})_4$ in methanol afforded a 4:1 isomeric mixture of cyclopentenones 2a and 2b, which without purification was hydrogenolyzed in the presence of 10% palladium on charcoal in methanol to give compound 3, isolated after flash chromatography on silica gel in 78% overall yield, as a colorless oil. IR: ν_{max} (CHCl_3): 1730, 1690, 1645 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 1.70(s, 3H), 2.05(s, 3H), 2.20-2.97(m, 5H), 3.70(s, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 7.75, 16.76, 35.08, 38.49, 41.14, 51.41, 135.15, 168.09, 172.43, 208.86. Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_3$: C, 65.93%; H, 7.69%. Found: C, 65.87%; H, 7.75%. Hydrolysis of the methyl ester moiety of 3 was achieved by refluxing for 5 hours in 0.2 N hydrochloric acid to give the corresponding carboxylic acid 4 (m.p. 76-78°C) in 91% yield. IR: ν_{max} (CHCl_3): 1710, 1700, 1650 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 1.72(s, 3H), 2.17 (s, 3H), 2.25-3.15 (m, 5H), 10.50 (br, 1H).

