Tetrahedron Letters No. 42, pp 3987 - 3988. 0040-4039/78/1015-3987$02.00/0

A CONVENIENT SYNTHESIS OF PENICILLIC ACID

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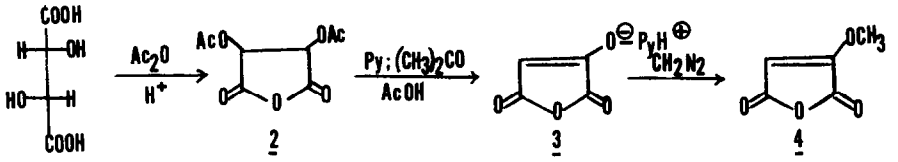
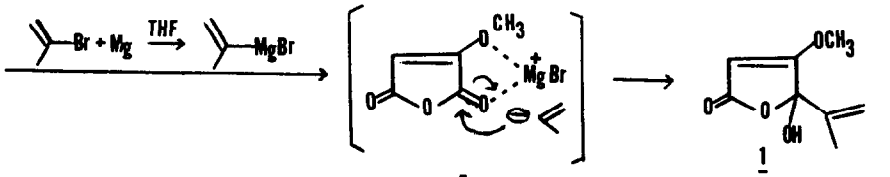
The mycotoxin, penicillic acid (1), was discovered by Alsberg and Black[1] in 1913 during their study of pellagra. This substance was produced by varieties of fungi including the genus Penicillin and Aspergillus. The structure was elucidated by Birkinshaw in 1936[2]. Penicillic acid possesses antimicrobial and antitumor activities[3], shows a dilating effect upon blood vessels, and exhibits an antidiuretic effect[4].

Raphael described the courses of several attempted syntheses and reported a successful route from methylallyl alcohol requiring more than 12 steps[5]. We wish to report a convenient 4-step synthetic route starting from tartaric acid.

As shown in the following scheme, tartaric acid was treated with acetic anhydride in the presence of sulfuric acid to afford diacetyltartaric anhydride (2)[6], which after treatment with pyridine in acetone, and then, acetic acid gave the crystalline (m.p. 108-110°C)[7] pyridine salt of hydroxymaleic anhydride (3). The key intermediate, methoxymaleic anhydride (4) (m.p. 154-156°C, lit.[8] 154°C) was obtained by reaction of the pyridine salt (3) with ethereal diazomethane in 85% yield. Treatment of 4 with 2-propenylmagnesium bromide at -15°C in tetrahydrofuran afforded penicillic acid (1) in 52% yield after purification by preparative high pressure liquid chromatography. The compound, m.p. 57-65° (hydrate), showed identical HPLC behavior with authentic material (Aldrich Chemical) on Porasil (hexane-methanol, 98:2). The synthetic compound likewise showed identical spectra as authentical material; ir (nujol) cm^{-1}: 3270, 1730, 1645, 1350, 1225, 908, and 805; nmr ($CDCl_3$) δ: 1.8 (s, 3H), 3.94 (s, 3H), 5.12 (s, 1H), 5.24 (broad, 1H), 5.5 (broad s. 1H); ms (70 ev): m/e 170 (M^+, 5%), 129 (37), 69 (100), 41 (42).





The strategy for the synthetic approach was based upon two viewpoints. First, one of the carbonyl groups of methoxymaleic anhydride (4) is conjugated through the methoxyl oxygen and would be expected to be less reactive toward Grignard reagents as a result of charge delocalization. Second, the location of the methoxyl oxygen with a proximal carbonyl group suggested a potential coordinating effect on the attacking magnesium reagent as in the complex (5). Although other reaction products were not isolated or identified we apparently obtained a high degree of regioselectivity as shown by the NMR spectrum of the crude product. Pattenden et al.[9] have studied the reactivity of 2-methoxy-3-methylmaleic anhydride toward reduction with metal hydrides and condensation with Wittig reagents, such as carbethoxymethyltriphenylphosphorane. Similar results were obtained in that high regioselectivity was observed for reaction at the 1-carbonyl. Since these diverse reagents (hydride, Wittig, Grignard) all showed such a distinct preference for the 1-carbonyl we attribute the regioselectivity to the electronic effects rather than metal-oxygen coordination. The pronounced acidity of tetronic acids tends to support the strong delocalization inherent in these β-oxyacrylate systems.

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(Received in USA 17 July 1978; received in UK for publication 22 August 1978)