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SIMPLE TOTAL SYNTHESIS OF SARKOMYCIN

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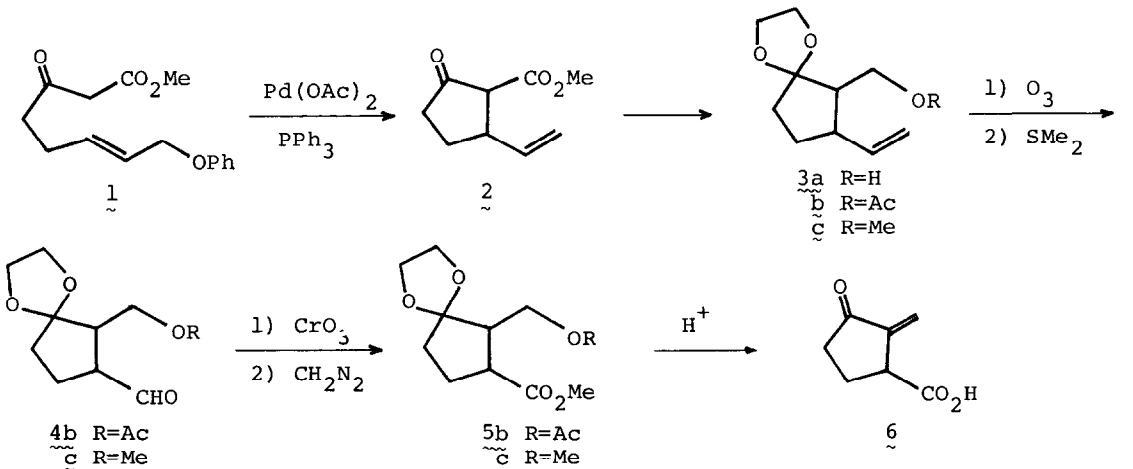
Summary: A simple total synthesis of sarkomycin starting from methyl 2-oxo-5-vinylcyclopentane-1-carboxylate is described.

Sarkomycin (6), discovered by Umezawa in 1953[1] is known to show powerful inhibitory effect on Ehrlich ascites tumors in mice. A few synthetic studies on this rather unstable compound have been carried out. Toki synthesized 6 via selective Mannich condensation of 3-oxocyclopentane-1-carboxylic acid.[2] But Hill claimed that the Mannich reaction was not regioselective.[3] Marx carried out the regioselective synthesis of 6 using very unstable 2-carbomethoxycyclopent-2-en-1-one.[4] Boeckman used 3-cyclohexenylmethyl alcohol as a starting compound.[5] However, these syntheses still have a number of problems to be solved, and further improvement seems to be necessary.

Recently we have found a new synthetic method for methyl 2-oxo-5-vinyl-1-cyclopentanecarboxylate (2) by the palladium-catalyzed cyclization of methyl 3-oxo-8-phenoxy-6-octenoate (1).[6] The compound 2 is a very useful starting material for efficient synthesis of natural products which have 2,3-disubstituted cyclopentanone framework and we have synthesized methyl dihydrojasmonate,[6] 18-functionalized steroid intermediates,[7] 18-hydroxyestrone,[8] and coronafacic acid.[9] We speculated that 2 has very suitable functionality for the simple synthesis of sarkomycin, which has been carried out by the scheme shown below.



At first the ketone of 2 was protected (87%), and the ester was reduced with $LiAlH_4$ to afford the alcohol 3a in 96% yield. Then we selected the acetylation and methyl ether formation as alcohol protections for 3a. At the final step, these protections serve as leaving groups to generate exo-methylene part. Acetylation of 3a gave the acetate 3b in 98% yield. Ozonolysis of 3b, followed by the reduction with dimethyl sulfide produced the aldehyde 4b. The aldehyde 4b was carefully oxidized using Jones reagent[10] to an acid which was converted to the methyl ester 5b in 70% yield: bp 101-104°C/2 Torr; IR (neat) 1732, 1238 cm^{-1}; NMR (CCl_4) δ 1.93 (s, 3 H), 1.62-2.75 (m, 6 H), 3.61 (m, 3 H), 3.82 (s, 4 H), 3.98 (d, J = 6 Hz, 2 H). On the other hand, the alcohol 3a was converted to the methyl ether 3c with methyl iodide and sodium hydride in 96% yield. Similar transformation of the vinyl group in 3c as above produced the ester 5c in 69% yield: bp 135-139°C/9 Torr; IR (neat) 1738, 1161, 1118 cm^{-1}; NMR (CCl_4) δ 1.58-2.70 (m, 6 H), 3.21 (s, 3 H), 3.59 (s, 3 H), 3.80 (br s, 4 H), 3.06-3.93 (m, 1 H); Anal. Calcd. for $C_{11}H_{18}O_5$; C, 57.38; H, 7.88%. Found: C, 57.47; H, 7.73%.

The ester 5b was hydrolysed with 3 N hydrochloric acid in ether (two phase system) at 25°C for 11 h to give 6 in 48% crude yield. TLC analysis showed that 6 thus obtained was almost pure and the NMR spectrum reveals two peaks centered at 5.63 and 6.17 ppm (d, J = 2.5 Hz, respectively), which are coincident thoroughly with the reported values.[4] The crude sarkomycin (6) was chromatographed on silica gel to give pure 6 in 24% yield. The low yield seems to be attributable to the instability of 6 itself. In fact, 6 was not isolated by prolonged hydrolysis (*ca.* 26 h) and decomposed merely on standing at room temperature for 24 h. Alternatively the ether 5c was hydrolyzed more slowly than 5b. After 16 h, the product was isolated and purified by chromatography on silica gel to give 6 in 20% yield: IR (neat) 3150, 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.8-2.7 (m, 4 H), 3.5-3.8 (m, 1 H), 5.63 and 6.17 (2 H, CH_2=C).

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