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2-Carbomethoxycyclopentenone as a Synthon. Synthesis of Sarkomycin[1]

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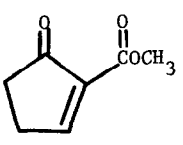
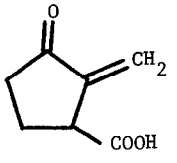
Abstract: The first regiospecific synthesis of sarkomycin (II), a compound active against ascites-type tumors, is reported. Treatment of 2-carbomythoxycyclopentenone (I) with Et_2AlCN generated the carbon skeleton; aelective functional group manipulations then gave the keto lactone X and the protected hydroxy acid XI; and mild acid treatment of these led to sarkomycin.

Several years ago, we reported[2] the first synthesis of 2-carbomethoxycyclopent-2-enone (I), a highly reactive molecule which is a potential synthon for prostaglandins and other natural products.[3] We now report its use in the first regiospecific synthesis of sarkomycin (II), an antibiotic which is active against ascites tumors.[4,5]



I



II

Previously, sarkomycin was synthesized by a Mannich condensation route[6] on 3-carboxycyclopentanone. The reaction gives a 1:2 mixture of the 2 and 5 isomers,[7] in spite of the original claims of regiospecificity.[6] The only other synthesis is an involved one by Shemyakin,[8] which gave sarkomycin semicarbazone, which could not be hydrolyzed without polymerization.

Our original route[2] to 2-carbomethoxycyclopentenone (I) involved SeO_2 oxidation of 2-carbomethoxycyclopentanone (III), followed by trapping the I formed as its cyclopentadiene adduct, purification, and the pyrolysis to give the pure compound. Reich[9] has since reported an improved synthesis of I, based on the phenylselenenyl derivative IV, but in our hands, the product formed by the reported procedure is contaminated with substantial amounts of the starting

compound (III) which appears to be formed, along with PhSeSePh, by decomposition of the desired compound IV. We have therefore improved the procedure as follows.

Treatment of 2-carbomethoxycyclopentanone (III) with NaH in THF gave the solid Na salt of III. This was suspended in fresh dry THF under N_2 and 1 eq. of PhSeCl in THF was added at 25°. After 15 min., the solvent was removed in vacuo below 25° and replaced with CH_2Cl_2, then excess O_3 was passed in until saturated at -78°, followed by O_2 to remove the O_3, then the clear solution was allowed to warm to 25°, filtered, and the solvent removed to give almost pure I, which was used directly in the next reaction.

Although 2-carbomethoxycyclopentenone (I) polymerizes readily with many reagents,[2] it reacted smoothly with a slight excess of Et_2AlCN in benzene. Purification by extraction of the product into aqueous NaOH to reverse some cyanohydrin formation and then careful reacidification gave the cyano compound V,[10] mp 47-48°, (35-40% yield from III). The ketone group in V was protected as its ketal, which gave a ca. 10:1 mixture of two isomers, (82%), mp 40-40.5°. The nmr multiplets at δ 3.2 (C-2 and C-3 H's) for the major isomer (VI) and δ 3.1 for the minor one (assigned as the cis isomer of VI) were used to differentiate them. Chromatography on silica gel partially separated them and gave the minor isomer pure, mp 73-74°. In practice, the mixture was used in subsequent steps.

Among a number of methods investigated to reduce the ester or hydrolyze the nitrile in VI, $LiBH_4$ did reduce the ester selectively, but the ketal group was not stable to this reagent. However, addition of ca. 2 eq. of H_2O-NaOH per mole of $LiBH_4$ gave a reagent mixture which effected the desired transformation cleanly in THF at room temp, to give cyano alcohol VIIIa (78%) [IR_{neat}: 3500 br, 2220; NMR ($CDCl_3$) δ 1.6-2.7, mult, 5 H; 3.06, mult, 1 H; 3.80, d, J = 8, 1 H; 3.98, s, 4 H].

Hydrolysis of the cyano group in VIIa with 5% aqueous NaOH was complete within 1 h of reflux. Acidification gave the protected keto lactone VIII, (91%), mp 67-67.5°. The hydrolysis undoubtedly involves epimerization at C-3 and neighboring group participation by the OH group, since the tetrahydropyranyl ether derivative (VIIb) required 6 h reflux with 5% NaOH to give the amide (IX), mp 144-145°, or 24 h reflux to give the acid X, mp 69-72°.

Removal of the ketal group of VIII by brief treatment with 5% HCl gave the keto lactone X (91%) mp 45-46° [IR ($CHCl_3$): 1780, 1750 cm^{-1}; NMR ($CDCl_3$): 1.95-2.75, m, 4 H; 3.15, m, 1 H; 3.44, m, 1 H; 4.44, d, J = 5.5; 4.45, d, J = 4.0]. This compound can be considered as a "protected" and more lipophilic form of sarkomycin. Surprisingly,[11] mild treatment of this ketolactone with 0.5-3 N HCl in acetone-H_2O gave slow eliminative opening to produce (±) sarkomycin (II),[12] [IR matches the published spectrum;[6] NMR δ 1.5-2.5, 5 H, m; 5.70, d, J = 2.5, 1 H; 6.24, d, J = 2.5, 1 H].

On the other hand, acid treatment of the protected keto hydroxy acid XI gave removal of the protecting groups and elimination of H_2O to give sarkomycin.[12] The compound (XI) gives

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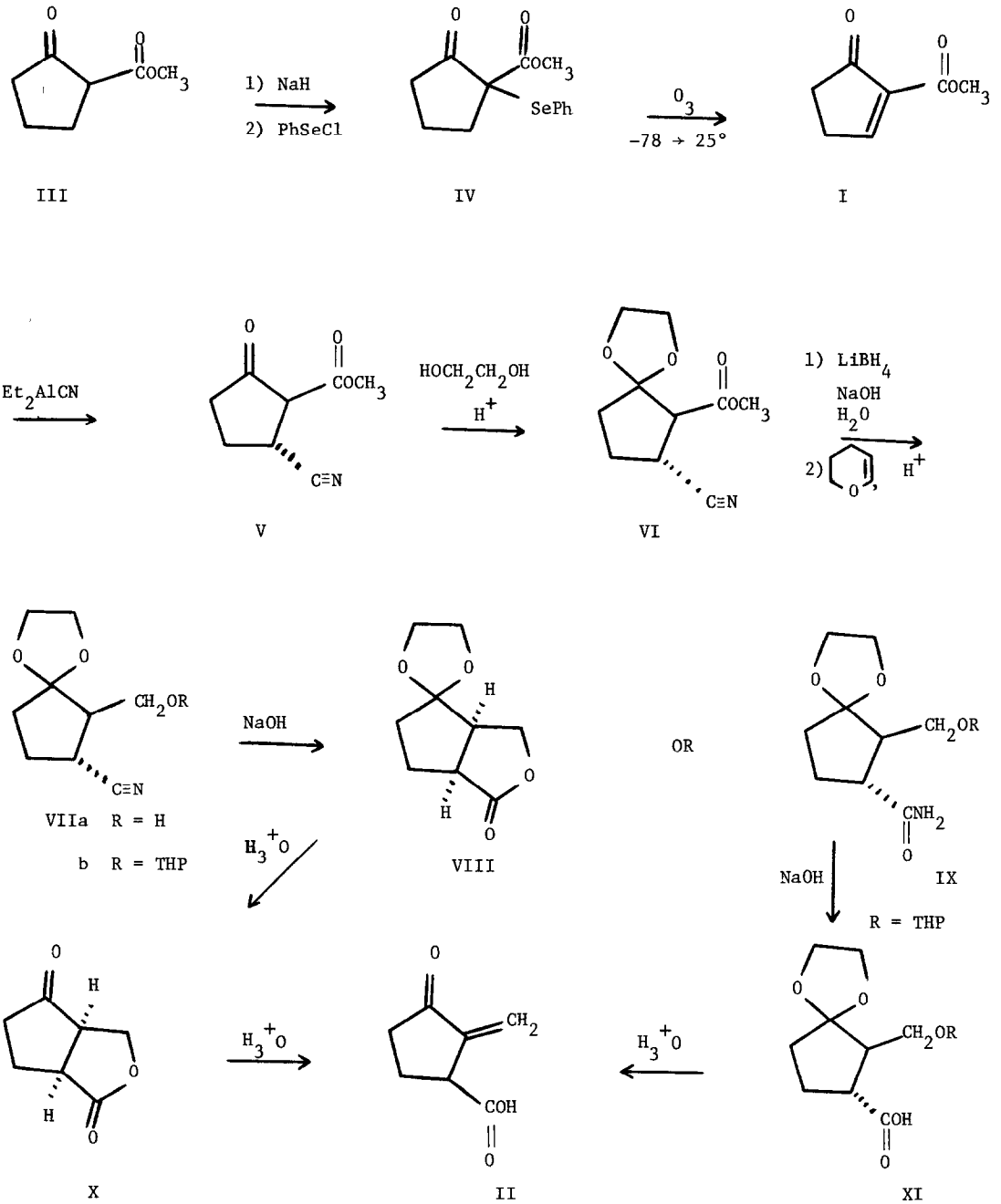

III IV I

V VI

VIIa R = H

b R = THP

VIII IX

X II XI

sarkomycin ca. ten times faster than does the keto-lactone X, and no trace of X could be detected. This behavior confirms the stereochemical assignments to all intermediates.

Modifications of the above scheme are being carried out to prepare several compounds with structural similarity to sarkomycin.

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References.

1. Presented at the ACS-CSJ Chemical Congress, Honolulu, April 2-6, 1979.
2. J. N. Marx, J. H. Cox, and L. R. Norman, J. Org. Chem., 37, 4489 (1972).
3. For recent work with I, see R. E. Schaub and M. J. Weiss, U.S. 3,884,969 (May 20, 1975); Ger Offen 2,425,573 (Dec. 11, 1975); U.S. 3,933,674 (Nov. 23, 1976); M. E. Jung et al., J. Org. Chem., 42, 3961 (1979).
4. H. Umezawa, et al., Antibiotics and Chemotherapy, 4, 514 (1954); I. R. Hooper et al., ibid., 5, 585 (1955).
5. G. B. Magill, et al., Cancer Research, 16, 960 (1965); for reviews, see S. Goto and H. Amano, Chiryo, 38, 72 (1956); S.-C. Sung, Antibiotics, 1, 156 (1967); S. Kondo, J. Antibiotics Japan Ser. B., 16, 210 (1963).
6. K. Toki, Bull. Chem. Soc., Japan, 30, 450 (1957); S. Umezawa and M. Kinoshita, Bull. Chem. Soc., Japan, 30, 267 (1957).
7. R. H. Hill, P. J. Foley, and C. A. Gardella, J. Org. Chem., 32, 2330 (1967).
8. M. M. Shemyakin, L. A. Shchukina, E. I. Vinogradova, M. N. Kolosov, R. G. Raduel, Yu B. Shretosov, E. M. Bamadas, E. S. Chanan, K. M. Ermolaev, and E. P. Semkin, Zhur Obshchei Khim., 27, 742 (1957).
9. H. J. Reich, J. M. Renga, and I. L. Reich, J. Am. Chem. Soc., 97, 5434 (1975).
10. Compound III exists in the keto form in the crystalline state: IR_{KBr}: 2225, 1770, 1730 cm^{-1}, but is a ca. 1:1 keto-enol mixture in the melt or solution: new IR peaks at 1670 and 1625 cm^{-1}; NMR ($CDCl_3$) δ 2.1-3.0, 4 H, mult; 3.5-3.7, mult, ca. 1.5 H; 3.86 and 3.88, singlets, 3 H total; 10.3, broad s, ca. 0.5 H.
11. See discussions on difficulties encountered in a similar reaction in the synthesis of methylenomycin A: R. M. Scarborough, Jr., and A. B. Smith, III, J. Am. Chem. Soc., 99, 7085 (1977).
12. With 0.5 N HCl, opening required at least a week at 25°; with 3 N HCl, about 6 h was required. Compound XI gave sarkomycin within 12 h with 0.5 N HCl. Slow decomposition occurred under the reaction conditions, and a maximum estimated yield of 30-40% of sarkomycin was produced under the conditions investigated. Rapid extraction into $NaHCO_3$ solution and reacidification gave sarkomycin essentially pure.

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