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CONJUGATE ADDITION TO THE ETHYLENE KETAL OF 2-CARBOMETHOXY-2-CYCLOPENTENONE A SYNTHESIS OF SARKOMYCIN

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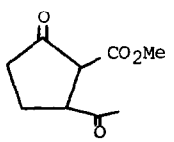
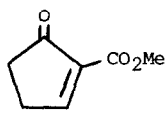
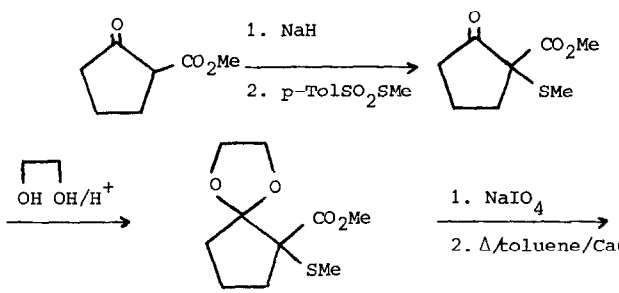
Summary: 1,4-addition of nitronate anions to the title ketal ester (III) is described; one of the adducts is converted to sarkomycin.

During work aimed at the synthesis of bicyclo[3.3.0]octanes we required a source of the diketo ester (I).[1]

(I)   (II)

Retrosynthetic analysis suggests that (I) should be available from keto ester (II) by 1,4-addition of an acyl anion equivalent. The unstable nature of (II) has been described, although it has recently been shown that cyanide ion can be added in a 1,4 sense.[2] We decided to investigate the use of the potentially more stable ketal (III)[3] which was readily obtained as shown below.

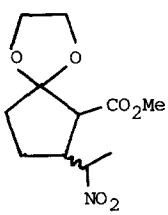


(III)

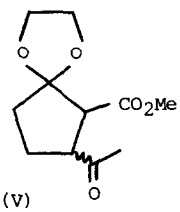
In this manner 2-carbomethoxycyclopentanone was converted to (III) in 64% overall yield (IR (neat) 1725, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9-2.5, m, 4H; 3.6, s, 3H; 3.75-4.15, m, 4H; 6.9, t, 1H).

Reaction between (III) and the acyl anion equivalent $CH_3SOCH(Li)SCH_3$, under aprotic conditions, resulted only in extensive decomposition of (III). This failure could be a result of the intermediate anion in the addition being destroyed by ketal opening. Thus it was felt that use of an acyl anion equivalent which could be used in a solvent capable of acting as a proton donor might overcome this problem. Reaction of (III) with

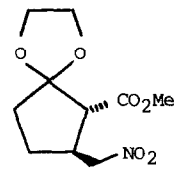
excess nitroethane in the presence of tetramethylguanidine[4] resulted in the production of (IV) (92%; 5:3 mixture of isomers). The mixture (IV) was directly treated with sodium methoxide followed by buffered $TiCl_3$[5] to give the mixture (V) (95%) which was converted with aqueous TFA into (I) (79%; m. 81-82 °; IR (KBr) 1760, 1735, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7-2.6, m, 7H; 3.5-4.0, m, 2H; 3.20, s, 3H).



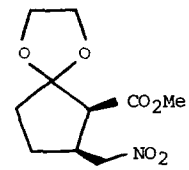
(IV)



(V)

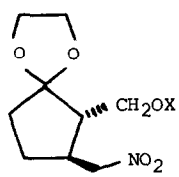


(VI)

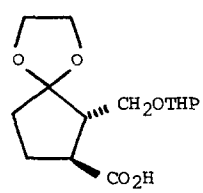


(VII)

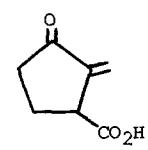
We have also used a similar method in a synthesis of sarkomycin, an antibiotic-antitumour agent.[2,6] Reaction of (III) with excess nitromethane in the presence of tetramethylguanidine afforded (VI) (71%; IR (neat) 1730, 1555, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2-2.0, m, 4H; 2.68, d, 1H; 2.95-3.4, m, 1H; 3.62, s, 3H; 3.7-3.95, m, 4H; 4.3, d, 2H), together with a small quantity of the cis compound (VII). Reduction of (VI) with AlH_3 afforded the alcohol (VIII) (69%) which was protected as its THP ether (IX) (79%). Oxidation of (IX) with alkaline $KMnO_4$ gave the acid (X) (50%; m. 68-70 °, lit.[2] 69-72 °) whose spectral data were identical with those described. Sarkomycin (XI) was obtained by treatment of (X) with HCl as described by Marx.



(VIII), X = H
(IX), X = THP



(X)



(XI)

Acknowledgement

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References

1. B.M. Trost and W.C. Vladuchick, J. Org. Chem., 1979, 44, 148.
2. J.N. Marx and G. Minaskanian, J. Org. Chem., 1982, 47, 3306, and references cited therein.
3. S.J. Branca and A.B. Smith, J. Am. Chem. Soc., 1978, 100, 7767.
4. G.P. Pollini, A. Barco and G. De Giuli, Synthesis, 1972, 44.
5. J.E. McMurry and J. Melton, J. Org. Chem., 1973, 38, 4367.
6. B.A. Wexller, B.H. Toder, G. Minaskanian and A.B. Smith, J. Org. Chem., 1982, 47, 3333; E.J. Barreiro, Tet. Let., 1982, 3605.

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