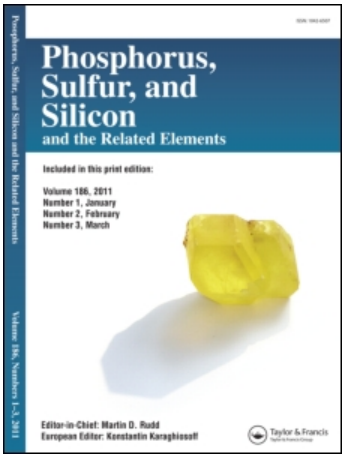

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α-Phosphoryl Cyclopentanones as Possible Intermediates in the Total Synthesis of Sarkomycin

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α-PHOSPHORYL CYCLOPENTANONES AS POSSIBLE INTERMEDIATES IN THE TOTAL SYNTHESIS OF SARKOMYCIN

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Abstract In an effort to synthesize sarkomycin **1** trans-2-diphenylphosphinoyl-3-tris(methylthio)methyl-cyclopentanone **7** and trans-2-diphenylphosphinoyl-3-carbomethoxy-cyclopentanone **8** were prepared. The Horner-Wittig reaction of the latter with formaldehyde failed. (±)-Sarkomycin **1** was prepared by a sequence of reactions starting from diethyl 2-oxopropanephosphonate. The key steps in this synthesis involve the intramolecular carbenoid cyclization of 1-diazo-2-oxopropanephosphonate **10** and the Horner-Wittig reaction of 2-diethoxyphosphoryl-3-carboxy-cyclopentanone **12** with formaldehyde.

INTRODUCTION

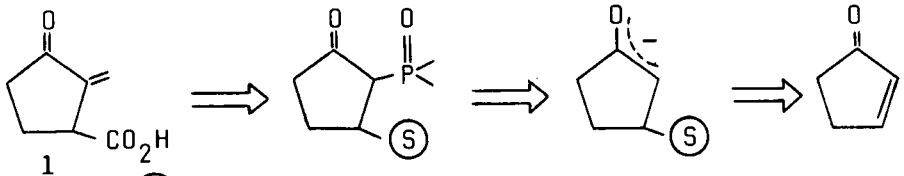
In recent years α-phosphoryl ketones have become valuable intermediates in organic synthesis, mainly as substrates in the Horner-Wittig olefination reactions. The preparation of acyclic α-phosphoryl ketones is rather simple and may be easily achieved by acylation of α-phosphonate anions[1]. In contrast to that, α-phosphoryl cycloalkanones cannot be prepared in this way. The most reasonable method of their preparation, which would consist in phosphorylation of the enolate anions, produces undesired enol phosphates[2]. Only recently, Wiemer et al. have succeeded in the synthesis of α-phosphoryl cycloalkanones either by phosphorylation of the dilithiated derivatives of cyclic ketones[3] or by the base-induced rearrangement of the corresponding enol phosphonates[4]. The severe drawback of the latter method is however, the lack of regioselectivity of the rearrangement.

RESULTS AND DISCUSSION

Synthesis and Properties of α-Phosphinoyl Cyclopentanones

In a continuation of our studies on the synthesis of cyclopentanoid antibiotics[5] we became interested in the preparation of an antitumour agent-sarkomycin **1**. The synthesis of **1** was based on a retrosynthetic analysis shown in Scheme I.

Scheme I

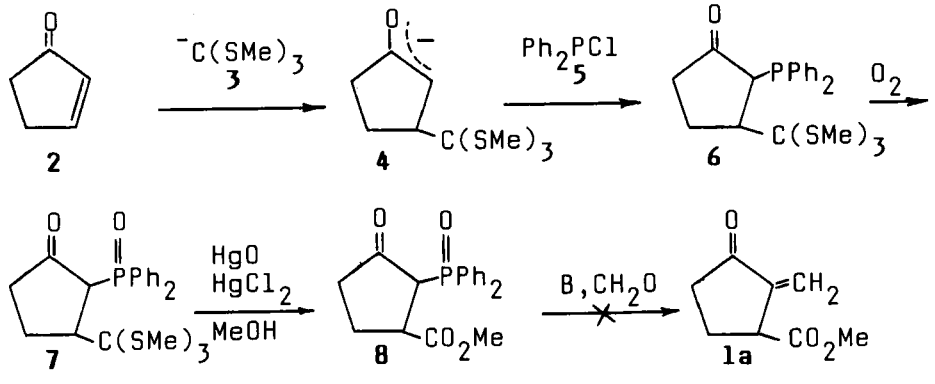


1

where (S) -carboxylic group synthon

The practical realisation of the above strategy for the synthesis of sarkomycin is outlined in Scheme II.

Scheme II



Trimethyl trithioorthoformate was used as the carboxylic group synthon, whose anion **3** reacted with 2-cyclopentenone **2** in an 1,4-fashion to give the enolate anion **4**. Searching for a phosphorylating agent which would react on the carbon atom of the enolate anion we turned our attention to the series of publications of Lutsenko et al.[6] These authors have exhaustively investigated the reaction between acyclic enolate anions and tricoordinated phosphorus acid halogenides and found that the use of dialkylchlorophosphines leads in some cases to the exclusive C-phosphorylation.

Having this in mind, we used in our work chlorodiphenylphosphine **5** which is commercially available and much more easy to handle in comparison with dialkylchlorophosphines. It was gratifying to find that phosphorylation with **5** took place exclusively at the carbon atom of the enolate anion **4**, as evidenced by ^{31}P-NMR spectra. Oxidation of the β-oxophosphine **6** was achieved by simple bubbling dry air through the reaction solution. It is interesting to note that all the transformations from **2** to **7** were performed in an one-pot procedure and the total yield of 2-diphenylphosphinoyl-3--tris(methylthio)-methyl-cyclopentanone **7** after column chromatography was 40%. The next step, involving methanolysis of the trithioorthoester moiety, gave 2-diphenylphosphinoyl-3-carbomethoxy-cyclopentanone **8** in 80% yield. An X-ray analysis of the cyclopentanones **7** and **8** revealed the trans arrangement of the 2,3-substituents in both cases. The cyclopentanone **7** was found to exist in the solid state in an envelope (C_S) conformation with the diaxial disposal of exocyclic substituents; the $Ph_2P(O)$-group occupies the flap of the envelope. The five-membered ring in **8** adopts in the crystal a half-chair (C_2) conformation with both exocyclic substituents being axial.

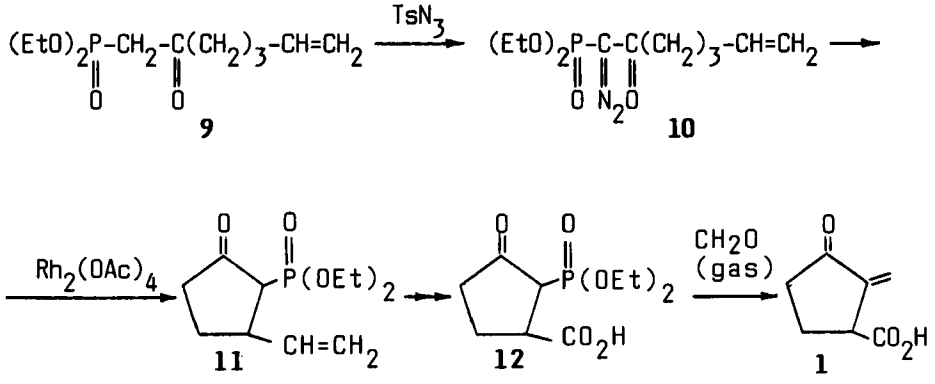
Unfortunately, it turned out that the β-oxo phosphinoxide **8** did not undergo the Horner-Wittig reaction with formaldehyde and other carbonyl compounds under the various conditions applied[7].

Synthesis of (±)-Sarkomycin

Because the phosphonate carbanions are known to be more reactive than the phosphinoxide carbanions towards carbonyl compounds in the Horner-Wittig reaction, we decided to synthesize the P-dialkoxy analogue of the cyclopentanone **8**. This was realized by the reaction sequence depicted in Scheme III. The important step of this synthesis was the intramolecular carbenoid cyclization of α-diazo-β-oxophosphonate **10**, prepared from **9** by the diazo-transfer reaction[8]. The phosphonate **11** thus obtained was then transformed into

12 by a series of standard procedures. To complete the preparation of **1**, cyclopentanone **12** was treated with two equi-

Scheme III



valents of sodium hydride and then with gaseous formaldehyde at room temperature and the reaction mixture was refluxed for 2 h in THF. After usual work-up and column chromatography (±)sarkomycin **1** was obtained in 45%[9]. The spectral data of **1** were fully consistent with the literature data.

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