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CONVERSION OF 1,3- INTO 1,4-DICARBONYL COMPOUNDS BY MEANS OF α-PHOSPHORYL SULPHIDES. TOTAL SYNTHESIS OF DIHYDROJASMONE AND METHYLENOMYCIN B.†

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Summary: *An effective synthesis of 1,4-dicarbonyl systems involving the Horner-Wittig reaction of α-phosphoryl sulphides with the half-protected 1,3-dicarbonyl compounds followed by hydrolysis of the vinyl sulphides formed is described. The total synthesis of dihydrojasmone and methylenomycin B employing this approach is reported.*

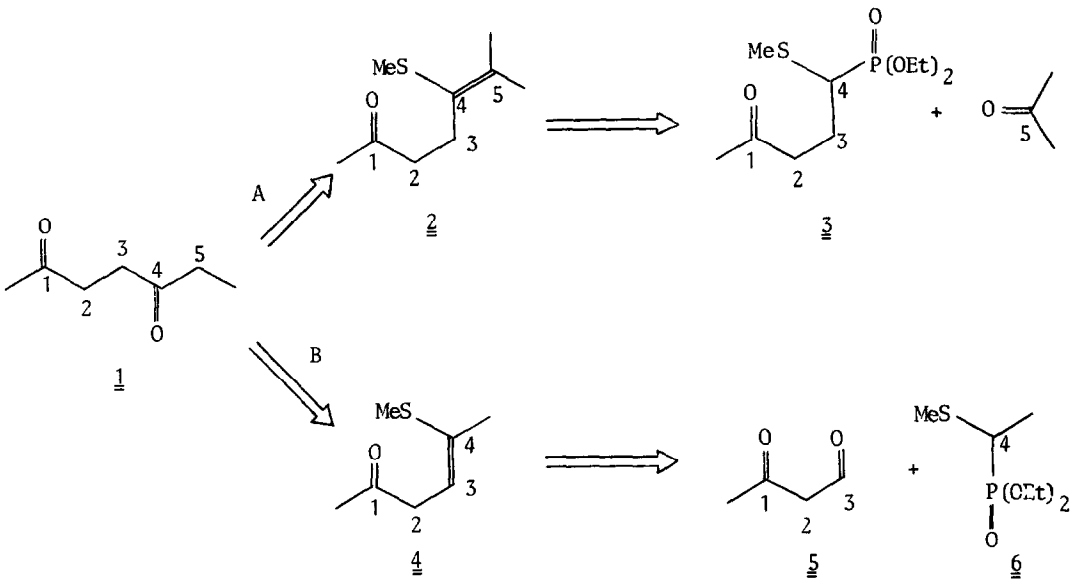
Recently, there has been considerable interest in the synthesis and biological properties of the relatively simple compounds such as prostanoids, jasmonoids, methylenomycins, pentenomycins which incorporate the cyclopentanone or cyclopentenone units[1]. The most versatile syntnesis of cyclopenten-2-ones involves the initial preparation of acyclic 1,4-dicarbonyl compounds and their subsequent intramolecular base-catalysed aldol condensation[2]. Therefore, the synthesis of 1,4-dicarbonyl compounds is still a subject of an extensive study.

In the previous paper[3] we reported a new synthesis of 1,4-dicarbonyl compounds 1 employing the Horner-Wittig reaction of the properly substituted phosphonates 3 bearing the methylthio group on the α-carbon atom. The precursor of 1 was the vinyl sulphide 2. The strategy of this approach was deduced from a retrosynthetic analysis (route A) shown in Scheme I.

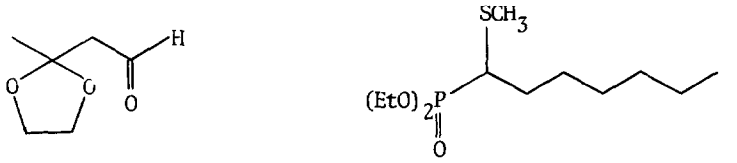
We realized, however, that the same 1,4-dicarbonyl system 1 may also be obtained from the isomeric vinyl sulphide 4 in which the double bond is located between the carbon atoms 3 and 4. According to a retrosynthetic analysis (route B, Scheme I) this sulphide can be synthesised from 1,3-dicarbonyl compounds 5 and α-phosphoryl sulphide 6 *via* the Horner-Wittig reaction.

† Presented by one of us (M.M.) as part of the lecture given at ESOC II, Stresa, Italy, 1981.

Scheme I. Retrosynthetic analysis for the construction of 1,4-dicarbonyl system

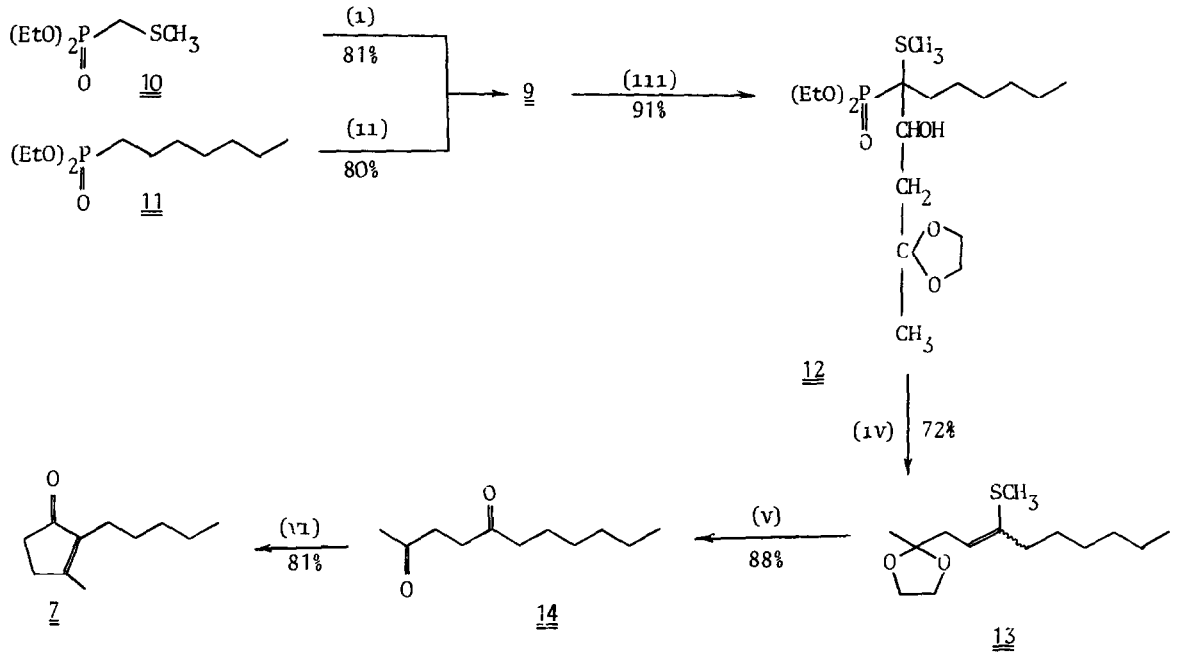


Experimental realization of this novel strategy for the construction of 1,4-dicarbonyl system is exemplified by the synthesis of dihydrojasmone 7 (Scheme II) starting from the easily available 3,3-ethylenedioxabutanal-1 8[4] and diethyl α-methylthio-n-heptanephosphonate 9 as the Horner-Wittig reaction components.



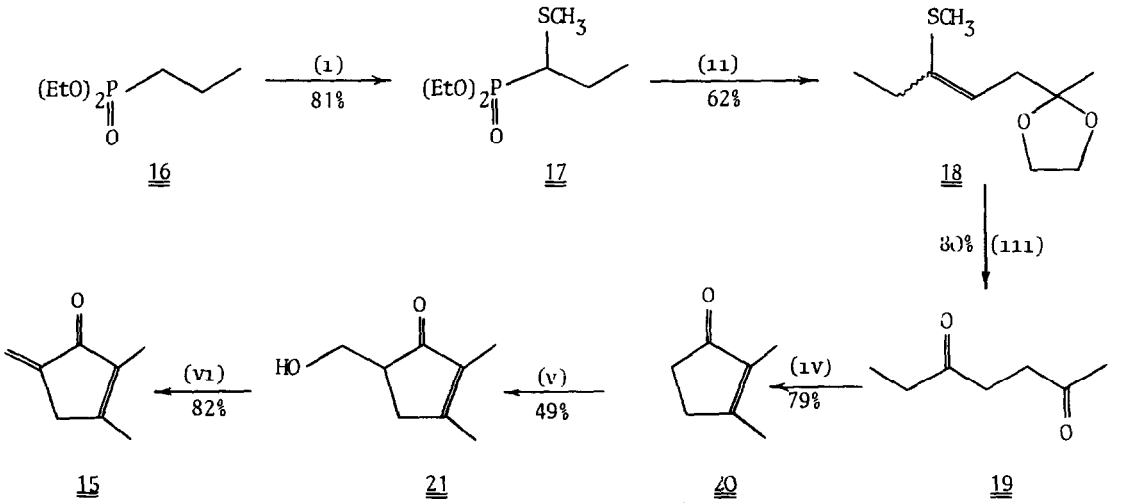
The required α-phosphoryl sulphide 9 was prepared in high yield by treating the carbanion of α-phosphoryl sulphide 10 with n-hexyl iodide[5] or alternatively *via* the sulphur addition to the carbanion derived from diethyl n-heptanephosphonate 11 followed by methylation[6]. The Horner-Wittig reaction of 9 with 8 gave the lithium salt of the addition product 12 which was rather stable and could not be decomposed to the desired vinyl sulphide 13 even on a prolonged reflux in THF solution. It was found, however, that the isolated β-hydroxyphosphonate 12 undergoes a facile decomposition at room temperature when treated with a molar ratio of sodium hydride in the presence of catalytic amount of 18-crown-6. The vinyl

Scheme II. Total synthesis of dihydrojasmone 7



(i) nBuLi, THF, -78°, n-$C_6H_{13}I$, (ii) n-BuLi, THF, -78°, S_8, CH_3I, (iii) n-BuLi, THF, -78°, 8, H_2O, (iv) NaH, 18-crown-6, (v) H_2O, CF_3COOH, (vi) NaOH, EtOH

Scheme III. Total synthesis of methylenomycin B 15



(i) n-BuLi, THF, -78°, S_8, CH_3I (ii) n-BuLi, THF, -78°, 8, H^+, NaH, 18-crown-6 (iii) H_2O, TsOH, (iv) NaOH, EtOH, (v) LDA, THF, -78°; H_2CO, H^+ (vi) DCC, Cu_2I_2

sulphide 13 formed was hydrolysed at room temperature in an aqueous THF solution containing trifluoroacetic acid[7] to give undecane-2,5-dione 14. The latter was cyclised to dihydrojasmone 7 in a standard way. The overall yield of 7 prepared as above is 47% from 8.

Our new synthetic approach to 1,4-dicarbonyl compounds was also found to be useful in the total synthesis of methylenomycin B 15, a recently isolated[8] and synthesised[9] unstable cylopentenoid antibiotic. A sub-target in this synthesis, which is outlined in Scheme III, n-heptane-2,5-dione 19, was prepared by the Horner-Wittig reaction of 8 with α-phosphoryl sulphide 17 in high yield. Its cyclisation gave 2,3-dimethylcyclopenten-2-one 20. The introduction of the exocyclic α-methylene function to 20 was accomplished according to Jernow et al.[9] *via* the hydroxymethylation followed by dehydration. After preparative TLC on silica gel (elution with Et_2O) methylenomycin B was isolated in an overall yield 16% from 8. The spectral data (^1H NMR, MS) of 15 were identical with those reported in the literature[8,9].

References and Notes

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7. Hydrolysis of 13 in the presence of titanium tetrachloride resulted only in the conversion of the vinyl sulphide grouping into the carbonyl group whereas the ethylene glycol protection of the carbonyl group is preserved.
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