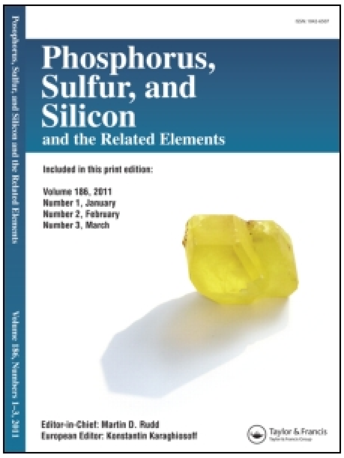

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A General Approach to the Synthesis of Functionalized Cycloalkenones. Total Synthesis of Iso-Terrein

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A GENERAL APPROACH TO THE SYNTHESIS OF FUNCTIONALIZED CYCLOALKENONES. TOTAL SYNTHESIS OF ISO-TERREIN.

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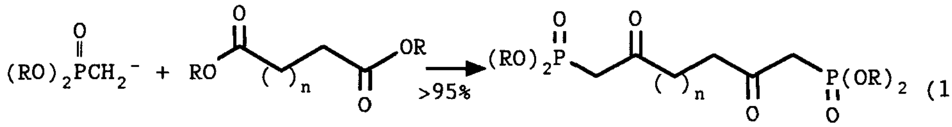
Abstract The synthesis and chemical behaviour of bis-β-ketophosphonates are described. A new approach to the synthesis of chiral iso-terrein has been developed which utilizes the bis-β-ketophosphonate chemistry.

Intramolecular Horner reaction of β-ketophosphonates containing additional carbonyl group is well known and has been utilized for the synthesis of cycloalkenones[1,2] which are an important group of compounds used in the natural product synthesis. Recently, cycloalkenones and their derivatives have attracted particular attention as potent anti-tumor and anti-viral agents.

In the course of our studies on the synthesis of biologically active cyclopentenones using phosphorus and sulfur reagents,[3] we turned our attention to the bis-β-ketophosphonate system, **1**, which is practically unknown and, as we found, may be easily synthesized from dicarboxylic acid esters and α-phosphonate carbanions.



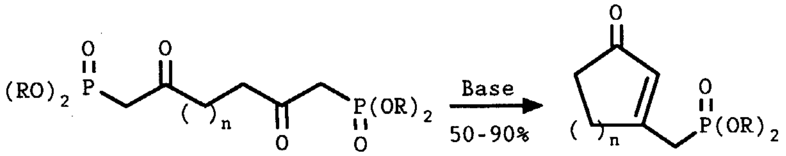
1

(1)

n=1,2,3 R=Me,Et

It was found that some bis β-ketophosphonates **1** undergo intramolecular Horner reaction even in the absence of crown ethers which were claimed to be necessary for other intramolecular Horner reactions mentioned above.

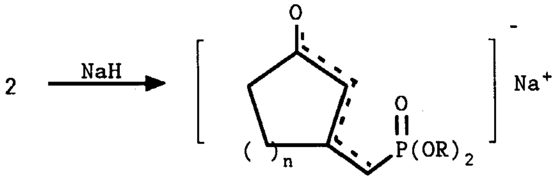
The cycloalkenones **2** obtained in this way are interesting compounds for further elaboration especially due to the presence of the phosphonate moiety. For instance, treatment of **2** with sodium hydride leads to generation of the



1 2

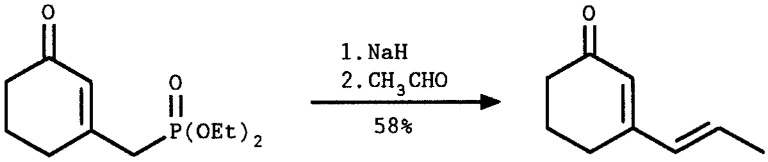
(2)

corresponding anion in which the negative charge is distributed between three atoms: α-phosphonate carbon, α-carbonyl carbon and oxygen. Therefore, depending on the nature of an electrophile used three different products can be formed.



(3)

Preliminary experiments (Eq. 4÷6) clearly illustrate the ambivalent reactivity of such an anion. Thus, the anion derived from cyclohexenone **3** gives on treatment with acetaldehyde only the Horner reaction product having the trans-geometry of a newly formed carbon-carbon double bond.



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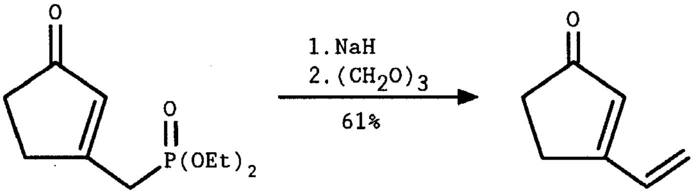
(4)

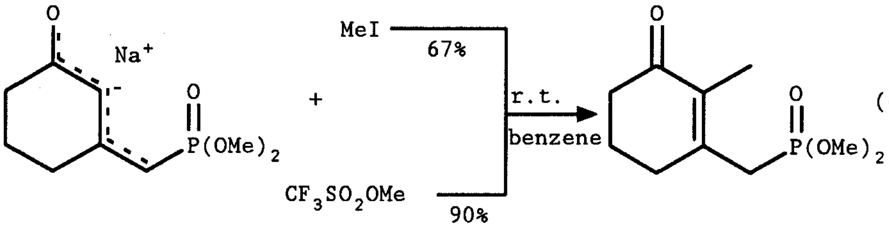
Similarly, the reaction between the anion derived from cyclopentenone **4** and formaldehyde affords the Horner reaction product.



4

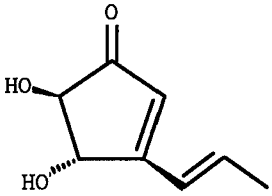
(5)

When methyl iodide was reacted with the anion generated from **3** exclusive methylation at the α-carbonyl carbon atom was taking place. Unexpectedly, the use of methyl triflate in this reaction gave the same product even in higher yield. The formation of the O-alkylation product was not observed.



(6)

The ketophosphonate chemistry briefly presented above was tested in the synthesis of chiral terrein **5**. Terrein was isolated as a metabolite of Aspergillus terreus by Raistrick and Smith[4] in 1935 and its structure was established by Grove[5] and Barton[6]. The synthesis of racemic terrein has been reported by Weinreb[7], Barton[8] and Zwanenburg.[9]



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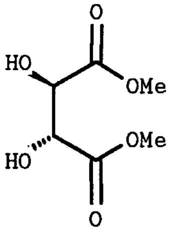

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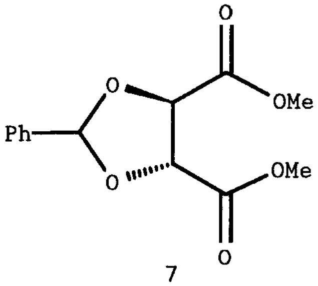
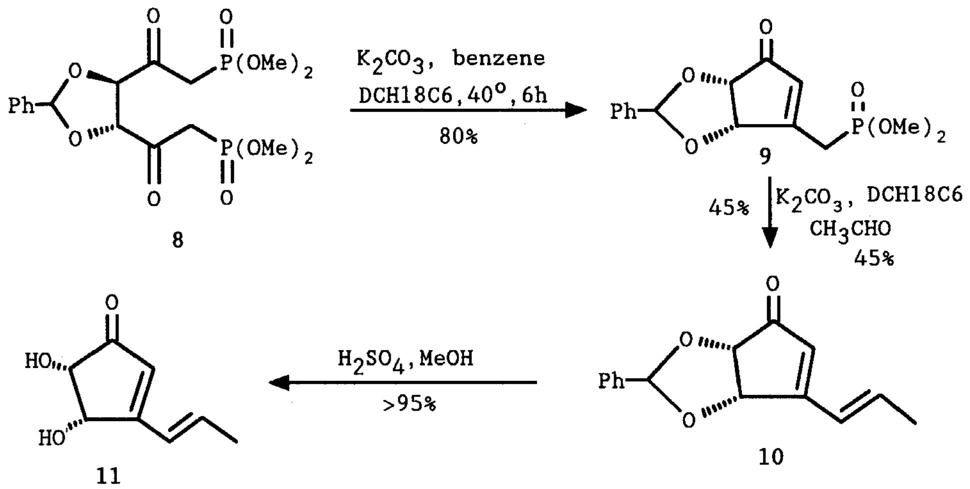


7

In our attempted approach to **5** (-)-(R,R)-dimethyl tartrate **6**, in which configurations of both carbon atoms correspond to the configuration of the diol moiety in terrein, was used as substrat. After it's protection and reaction of **7** with the dimethyl methanephosphonate anion the corresponding bis-β-ketophosphonate **8** was obtained. The next step was the base - catalyzed cyclization of **8** affording the cyclopentenone **9**. The Horner reaction of **9** with acetaldehyde was utilized for introduction of the desired alkene chain. In the final step of the synthesis the acetal protecting group was removed by treatment of **10** with a catalytic amount of sulfuric acid in methanol.



Unexpectedly, the obtained product **11** exhibited different properties from those of the natural (+)-terrein. For example, optical rotation of our product is -14.4° whereas that of the isolated (+)-terrein is +185°. Moreover, the coupling constant between protons at C(4) and C(5) in **11** is equal to 5.8 Hz. This value is similar to that reported for racemic iso-terrein[8] (6.0 Hz) and different from that of terrein **5** equal to 2.6 Hz.[9] Therefore, based on the coupling constant values we may conclude that our synthesis resulted in the formation of chiral iso-terrein having the cis configuration of the diol moiety. Most probably, the trans to cis isomerization at chirality centres takes place during the intramolecular Horner cyclization of **8** to **9**.

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