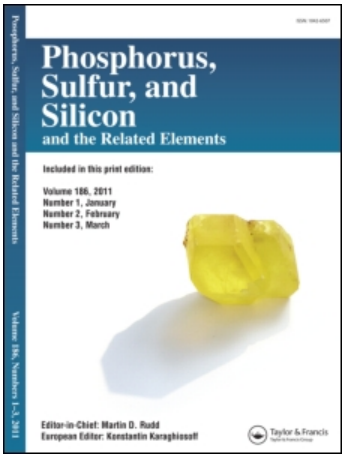

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Horner Olefination Reaction in Organic Sulfur Chemistry and Synthesis of Natural and Bioactive Products

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This article outlines the results of our work on the application of the Horner olefination reaction for the synthesis of unsaturated sulfur compounds. A general synthesis of racemic and optically-active α,β-unsaturated sulfoxides by the Horner reaction with α-sulfinylmethylphosphonates as olefination reagents is presented. We demonstrated how the structure of the phosphonate moiety may control the E- and Z-stereoselectivity in the above reaction. The use of racemic and optically-active α-sulfinylvinylphosphonates in tandem Michael addition / Horner olefination reaction leads to a wide range of carbocyclic and heterocyclic vinyl sulfoxides. In second part of this account a new strategy for the synthesis of functionalized cyclopentenones is briefly described. The synthesis and reactivity of 3-phosphorylmethyl-cyclopentenones is discussed as a platform for developing the synthesis of racemic rosaprostol, enantiomeric prostaglandin B_1 methyl esters, enantiopure isoterreins, natural and unnatural neplanocin A and enantiomeric forms of phytoprostane B_1 type I.

Keywords Horner reaction; α-sulfinylalkylphosphonates; vinyl sulfoxides; 3-phosphorylmethyl-cyclopentenones; total synthesis; natural products; phytoprostane B_1 type I

INTRODUCTION

Among many methods for the formation of the olefinic carbon-carbon bond, P(O)-activated olefination gained a wide application in different

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This paper is based on the keynote lecture presented at the 17th International Conference on Phosphorus Chemistry (Xiamen, China), and it is dedicated to the late Professor Leopold Horner.

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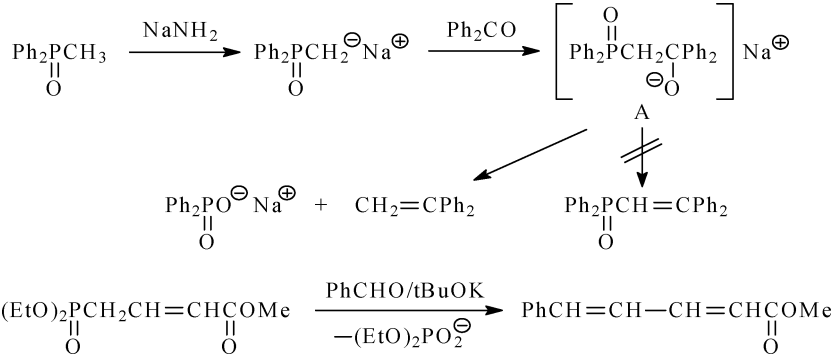
fields of organic chemistry, especially in the total synthesis of natural products and biologically active compounds. Horner[1] was the first who discovered—as early as 1958—that the reaction of the sodium salt of diphenylmethylphosphine oxide with benzophenone afforded 1,1-diphenyl-ethylene and sodium diphenylphosphinate (Scheme 1). No formation of (2,2-diphenylvinyl)diphenyl-phosphine oxide was observed which could be formed from the oxy-adduct A on elimination of sodium hydroxide. One year later, Horner[2] extended his olefination reaction to phosphonates which became very useful CH acidic olefination reagents (Scheme 1).



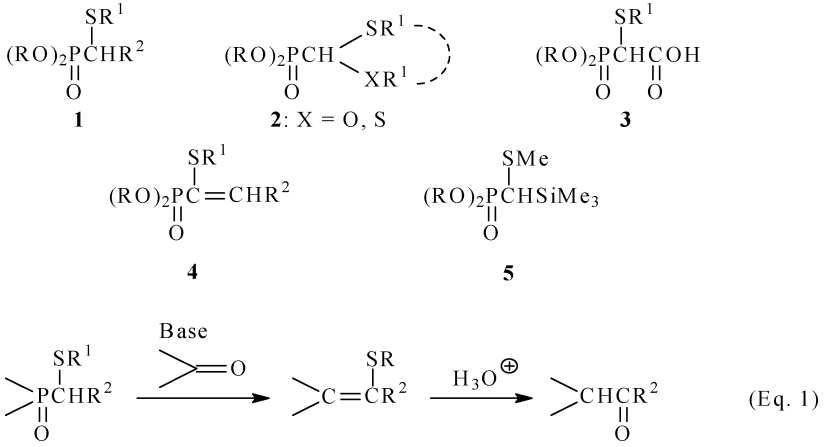
SCHEME 1

In 1961, Wadsworth and Emmons[3] published their initial experiments on the Horner reaction, and in subsequent papers they described the scope and limitations of this new olefination method. Therefore, nowadays the P(O)-activated olefination method is very often called Horner-Wadsworth-Emmons reaction (HWE) and its importance in preparative organic chemistry is still increasing. The main advantage of the Horner olefination reaction over the closely related Wittig reaction is that phosphorus acid salts formed also as products in the former reaction are easily removed while the separation of olefins from neutral phosphine oxides, that are produced in the Wittig reaction, is very often difficult.

In this account, we wish to demonstrate a great utility of the Horner olefination reaction in our work focused on the synthesis of selected unsaturated organosulfur compounds and natural products containing the cyclopentenone and cyclopentanone structural unit.

MIXED PHOSPHORUS AND SULFUR COMPOUNDS AS P(O)-ACTIVATED OLEFINATION REAGENTS

A long-term interest of our laboratory in the chemistry of phosphonates and various sulfur compounds led us to extensive studies on organic compounds containing both heteroatoms in one molecule. Since the Horner reaction became one of the most important synthetic methods, in our early work we prepared various phosphonates bearing the sulfur functionalities at the α-phosphonate carbon atom. Typical examples of such mixed phosphorus-sulfur structures are: α-sulfanyl-alkylphosphonates **1**,[4] S,S-dithio- and O,S-thioacetals of formylphosphonates **2**,[5] α-sulfanyl-α-carboxy-methylphosphonate **3**,[6] α-sulfanylvinylphosphonates **4**[7] and αmethtylsulfanyl-α-trimethylsilyl-methylphosphonate **5**[8] (Scheme 2).

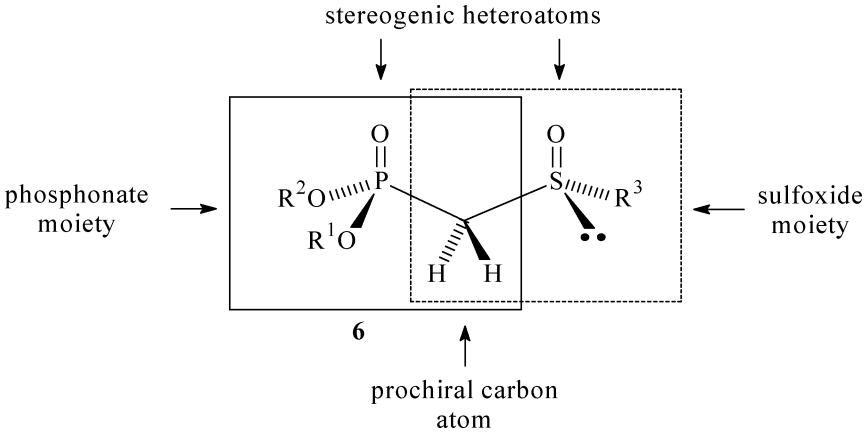


SCHEME 2

Phosphonates **1**, **2**, and **3** undergo the Horner olefination reaction with carbonyl compounds to give the corresponding vinyl sulfides which upon hydrolysis form mono-carbonyl (from **1** and **2**) or 1,2-dicarbonyl (from **3**) products. As the α-phosphoryl sulfide moiety may be regarded as a masked carbonyl group [Eq. (1) in Scheme 2], three consecutive reactions involving Michael addition of enolate anion to **4**, Horner reaction of the adduct with a carbonyl electrophile and hydrolysis of the vinyl sulfide formed represents a general method for the synthesis of 1,4-dicarbonyl compounds which may be transformed into cyclopent-2-enones.[7] The α-phosphonate carbanion generated from **5** reacts with carbonyl compounds in a different way. It affords the Peterson reaction product via elimination of the trimethylsilyloxy group. Therefore,

phosphonate **5** is a key reagent for the synthesis of vinylphosphonates **4**.

A very important class of mixed P,S-compounds is α-sulfinyl phosphonates **6** first synthesized in racemic[9] and enantiomeric forms[10] in our laboratory. As shown in Scheme 3, the structure of **6** contains the phosphonate and sulfoxide moieties. Both of them are chiral. It should be pointed out that the chiral sulfinyl group has proved to be one of the most efficient chiral auxiliaries because of its extraordinary ability to control stereoselectivity of asymmetric reactions.

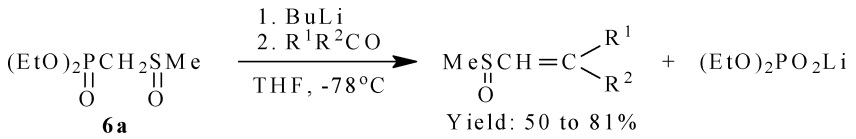


SCHEME 3

Among many transformations of α-sulfinyl phosphonates **6**, the most important is their Horner P(O)-olefination reaction leading to α,β-unsaturated sulfoxides.[11] Due to the presence of highly electron-withdrawing phosphoryl and sulfinyl groups, proton elimination from the bridging methylene group readily occurs on treatment with a base yielding the appropriate stabilized α-phosphonate carbanions, which afford α,β-unsaturated sulfoxides when reacted with carbonyl compounds. They were formed in good to high yields as separable mixtures of E and Z isomers. Selected experimental results obtained with **6a** are depicted in Scheme 4.

With the aim at the synthesis of optically active vinylic sulfoxides, we prepared enantiopure (+)-(*S*)-(dimethoxyphosphoryl)methyl *p*-tolyl sulfoxide **6b** which has become a reagent of choice for the synthesis of variously substituted optically active α,β-unsaturated sulfoxides.[10] Its synthesis and Horner reaction are shown in Scheme 5.

The only drawback of the synthesis of vinyl sulfoxides presented above is that a mixture of geometrical E- and Z-isomers is produced.

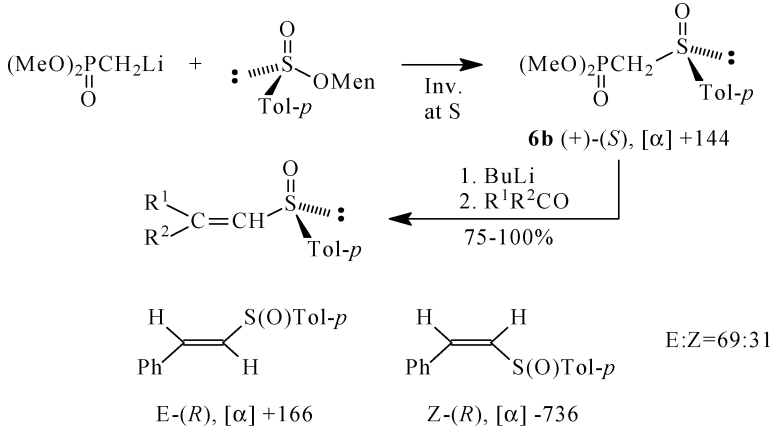


R^1	R^2	E:Z
Ph	H	58:42
$Cl_2C_6H_3$	H	45:55
MeC_6H_4	H	54:46
$Me_2NC_6H_4$	H	82:18
Ph	Me	45:55
$Cl_2C_6H_3$	Me	27:73

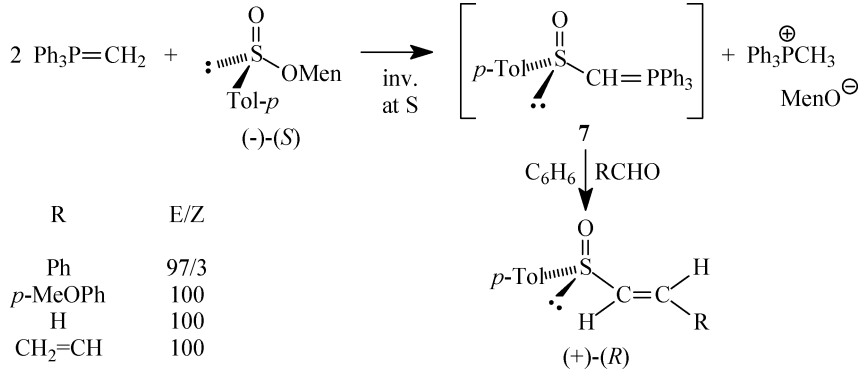
SCHEME 4

We found, however, that the Wittig reaction of the in situ generated α-sulfinylphosphonium ylide **7** with carbonyl compounds affords racemic or optically active vinyl sulfoxides with the E-geometry[12] (Scheme 6).

Recently, extensive effort has been devoted to the stereoselective synthesis of Z-α,β-unsaturated esters. These isomers were found to be preferentially formed when bis(trifluoroethyl)phosphono-acetates and diarylphosphono-acetates[14] are used as the Horner olefination reagents. Moreover, Kokin et al.[15] reported that bis(trifluoroethyl) α-sulfinylmethylphosphonates reacted with aromatic aldehydes with predominant formation of Z-vinyl sulfoxides. Prompted by these observations, we decided to synthesize racemic and optically-active diphenyl α-*p*-tolylsulfinylmethylphosphonate **6c** in the hope to achieve

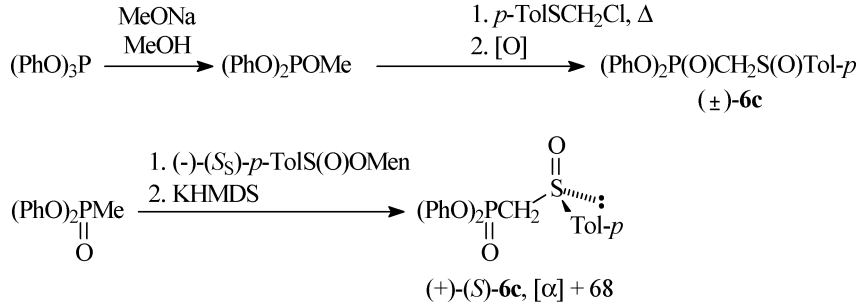


SCHEME 5



SCHEME 6

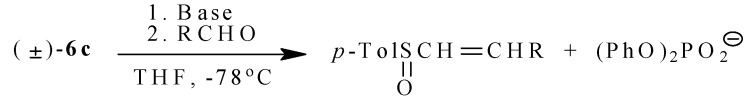
Z-stereoselectivity in the Horner reaction. The synthesis of (±)-**6c**[16] was performed according to the procedure described earlier by us for diphenyl α-phenylsulfinylmethylphosphonate[17] and is shown in Scheme 7. Optically active (+)–(S)-**6c** was prepared in a standard way from (-)-(S_S)-menthyl *p*-toluenesulfinate and diphenyl methylphosphonate carbanion[16] (Scheme 7).



SCHEME 7

Horner reaction of (±)-**6c** was first carried out with benzaldehyde using different bases such as: *n*BuLi, NaH, KH, *t*-BuOK and KHMDS. It was found that with NaH and KHMDS the reaction gave quantitatively 2-phenylvinyl *p*-tolyl sulfoxide with predominant Z-selectivity, 66 and 64%, respectively. When the reaction was performed in the presence of 18-crown-6 the Z-selectivity was increased. For example, treatment of (±)-**6c** with benzaldehyde in the presence of KHMDS and 5 equivalents of 18-crown-6 afforded the product with 78% Z-selectivity. Furthermore, the structure of the aldehyde component has also an influence on the reaction stereoselectivity. Thus, with *o*-bromobenzaldehyde the Horner

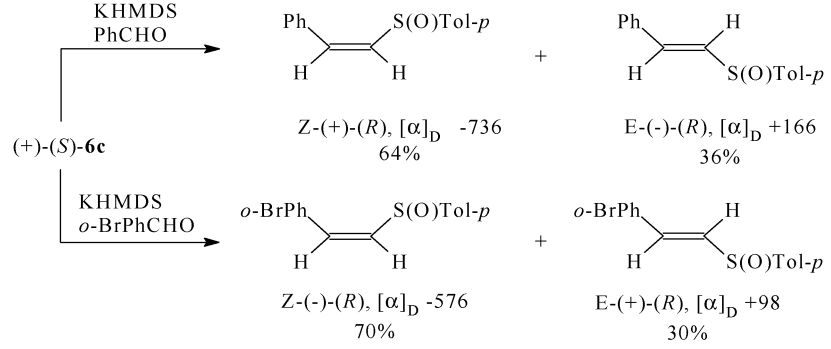
reaction carried out in the presence of 18-crown-6 gave the corresponding vinyl sulfoxide as a mixture of Z and E isomers in a ratio of 93:7 (Scheme 8).



R	Base	Z:E
Ph	NaH	66:34
Ph	t-BuOH	60:40
Ph	KHMDS + 18-c-6	78:22
p-BrPh	KHMDS + 18-c-6	76:24
o-BrPh	KHMDS	70:30
o-BrPh	KHMDS + 18-c-6	93:7

SCHEME 8

Although the olefination of phosphono sulfoxide **6c** with aromatic aldehydes showed higher Z-selectivity in the presence of 18-crown-6, the Horner reaction of optically active (+)–(*S*)-**6c** with aromatic aldehydes was carried out in its absence to avoid some problems connected with the product separation. In Scheme 9, some experimental data for this reaction with benzaldehyde and *o*-bromobenzaldehyde are given.



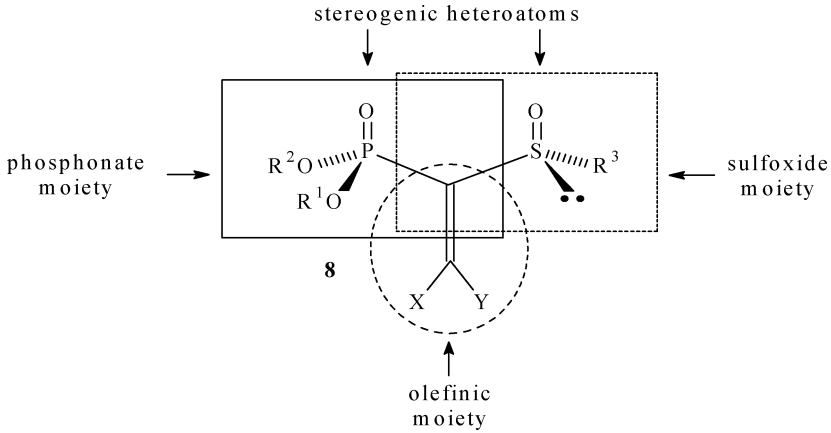
SCHEME 9

It is interesting to note that, in spite of the same absolute configuration at sulfur, the Z- and E-isomers of vinyl sulfoxides have opposite sign of optical rotation and differ distinctly in its magnitude.

To complete discussion on the utilization of the Horner olefination reaction in the synthesis of unsaturated sulfoxides, it is desirable to describe briefly our new approach to the synthesis of racemic and optically

active carbocyclic and heterocyclic vinyl sulfoxides.[18] In this case we used α-sulfinylvinylphosphonates **8** as olefination reagents.

A distinctive feature of this new chiral structure (Scheme 10) is the presence of a very reactive carbon-carbon double bond with two electron-withdrawing P(O) and S(O) groups at the olefinic α-carbon atom. As the nucleophilic addition to α-sulfinylvinylphosphonates **8** generates the corresponding α-phosphonate carbanion, reactions of these phosphonates with carbonyl compounds bearing a nucleophilic center in a β- or γ-position to the carbonyl group can provide a useful means for the synthesis of cyclic vinylic sulfoxides as depicted in Scheme 11.

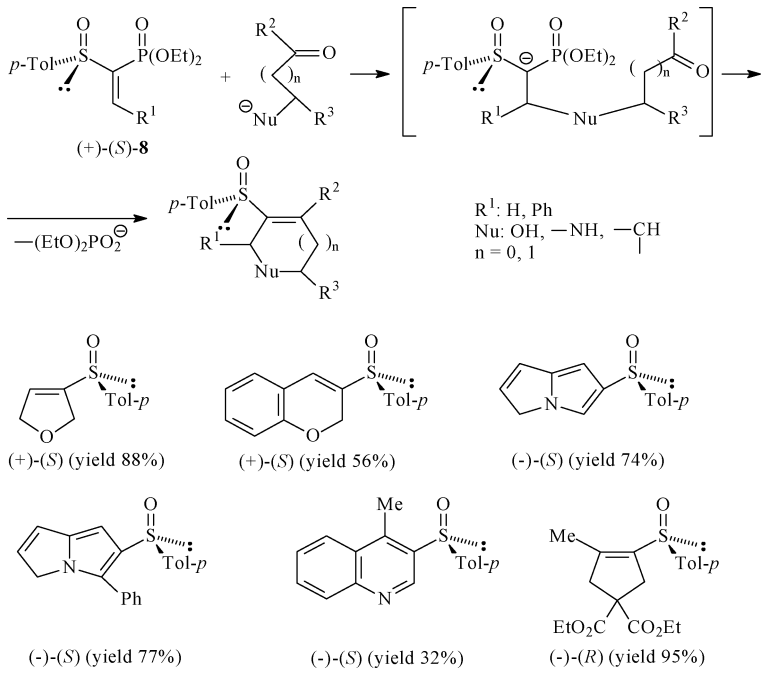


SCHEME 10

A wide scope and usefulness of this tandem Michael addition/Horner olefination reaction is demonstrated by the synthesis of a variety of optically active chromene, pyrrolizine, chinoline and cyclopentene sulfoxides prepared from (+)-(*S*)-**8** and listed in Scheme 11.[18]

PHOSPHONATE-BASED STRATEGY FOR SYNTHESIS OF CYCLOPENTENONE AND CYCLOPENTANONE NATURAL PRODUCTS AND BIOACTIVE COMPOUNDS

As part of our program on the application of phosphorus compounds in organic synthesis,[19] we have been involved over the last two decades or so in the invention and development of general methods for the synthesis of functionalized cyclopentenones and cyclopentanones.[20] These structural units are present in a wide range of important natural products such as jasmonoids, cyclopentanoid antibiotics, and

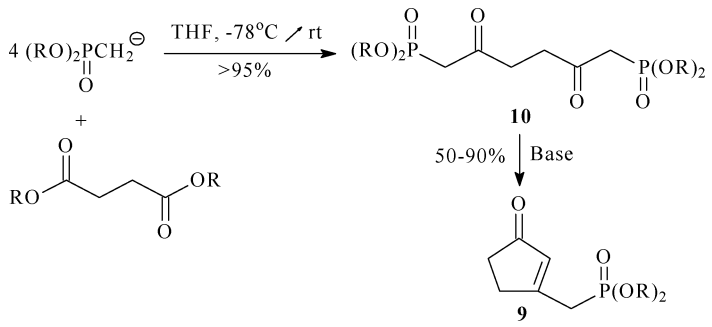


SCHEME 11

prostaglandins. Our efforts resulted in the elaboration of general approaches to 3-(phosphorylmethyl)cyclopent-2-enones **9** which turned out to be excellent building blocks in the synthesis of a variety of interesting target compounds.

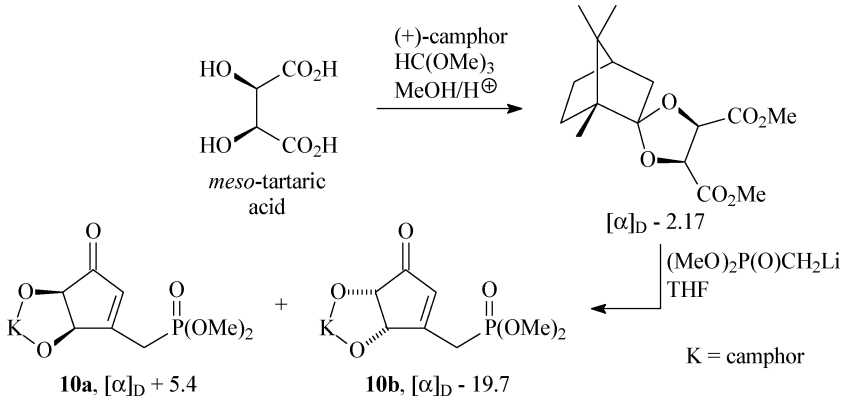
The cyclopentenones **9** were easily obtained in the reaction between α-phosphonate carbanions and dicarboxylic acid esters[21] (Scheme 12). This reaction affords in the first step the corresponding bis-β-ketophosphonates **10**, which under basic conditions undergo intramolecular Horner reaction to produce the desired cyclopentenones **9**. As a matter of fact, the later reaction is a little more complicated because the kinetically controlled product is the Knoevenagel product which can be converted into the Horner reaction product **9** under basic conditions.

A similar strategy was applied in the synthesis of optically active 3-phosphorylmethyl-4,5-dihydroxy-cyclopentenones **10a** and **10b**.[22] In this case, the first important step was complete desymmetrization of *meso*-tartaric acid, which gave on treatment with (+)-camphor and methyl orthoformate the corresponding protected dimethyl ester as a single diastereomer. Its reaction with dimethyl



SCHEME 12

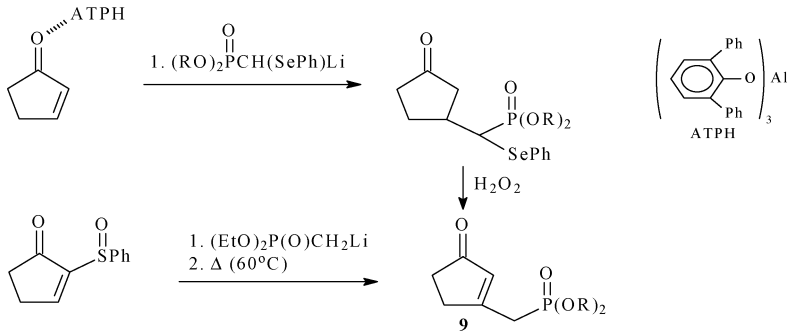
lithiomethylphosphonate under proper conditions afforded a separable mixture of the diastereomeric cyclopentenones **10a** and **10b** (Scheme 13).



SCHEME 13

Quite recently, two new synthetic approaches to **9** have been elaborated which involve in a key step so-called forced conjugate addition of α-phosphonate carbanions to appropriate cyclopentenones[23] (Scheme 14).

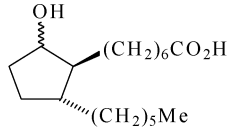
The cyclopentenones **9** and **10** offer interesting possibilities for further functionalization of the five-membered ring. First of all, the anion derived from 3-phosphorylmethyl-cyclopentenones might be described by three mesomeric forms in which the negative charge is located on the α-phosphoryl carbon atom, α-carbonyl carbon atom and carbonyl oxygen atom. Our study on reactivity of this anion revealed that alkylation occurs mainly at the α-carbonyl carbon atom, carbonyl electrophiles



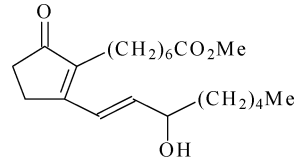
SCHEME 14

react at the α-phosphoryl carbon atom producing the Horner olefination products and acylation takes place at carbonyl oxygen.[21]

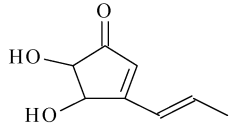
Hence, combination of the alkylation and Horner reaction of the anion under discussion paved the way for the synthesis of 2,3-difunctionalized cyclopentenones. This method has been exploited in the total synthesis of some natural products and bioactive compounds (Scheme 15). For instance, the cyclopentenone **9** was converted in three steps (alkylation, Horner olefination, hydrogenation) into racemic



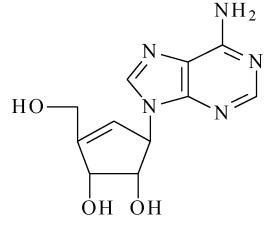
(±)-Rosaprostol



$PB_{1\alpha}$
(-)-(*R*), $[\alpha]_D$ - 18.2
(+)-(*S*), $[\alpha]_D$ + 19.0



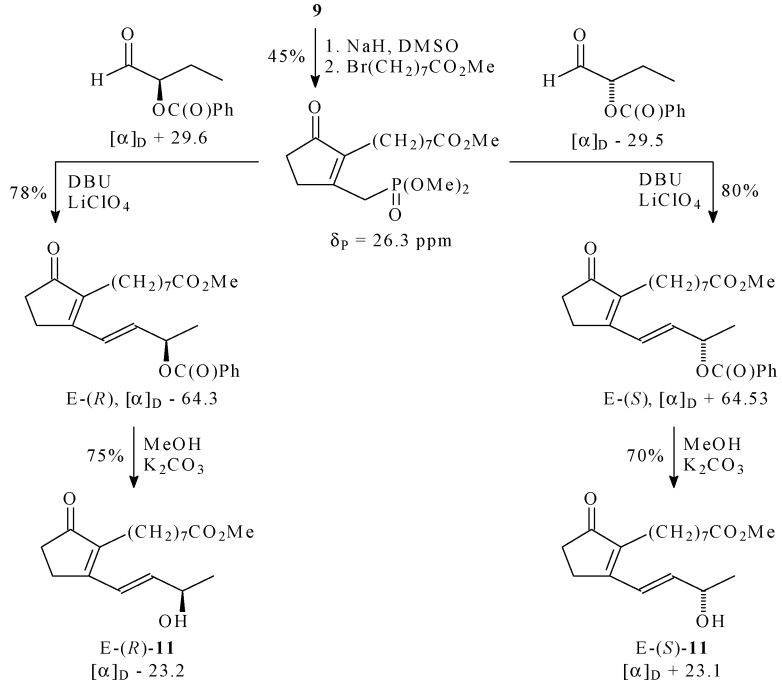
Isoterrein
(-)-(4*S*, 5*S*), [ ]$_D$ - 113.0
(+)-(4*R*, 5*R*), [ ]$_D$ + 111.0



Neplanocin A
Natural, $[\alpha]_D$ - 150.0
Unnatural, $[\alpha]_D$ + 155.2

SCHEME 15

rosaprostol—an antiulcer drug.[24] In a similar way, two enantiomers of prostaglandin $B_{1\alpha}$ methyl ester were synthesized form **9**.[25] On the other hand, the diastereomers of **10** were successfully used as starting materials in the synthesis of enantiomeric isoterreins which belong to the family of cyclopentanoid antibiotics.[22] Starting from **10** the synthesis of natural (-)-neplanocin A and its unnatural (+)-enantiomer was also executed.[26]



SCHEME 16

To illustrate the usefulness, simplicity and effectiveness of our strategy, the synthesis of both enantiomers of phytoprostane B_1 type I, **11**,[27] is presented in detail (Scheme 16). Phytoprostanes B_1 type I and II are a new class of compounds that occur in plants and are formed from α-linolenic acid. They display a wide spectrum of biological activity including activation of mitogen-activated protein kinase (MAPK) and the induction of glutathione-S-transferase (GTS), defense genes and phytoalexins. The first step in our synthesis is the alkylation of the cyclopentenone **9** anion with methyl 8-bromooctanoate. Although this reaction was not very efficient due to competitive O-alkylation, the Horner reaction of the mono-alkylated product with the enantiomeric

benzoyl protected α-hydroxy butanals occurred in excellent yield affording the desired olefination products in a straightforward way. After deprotection of the hydroxyl group, the enantiopure forms of phytoprostane **11** were obtained in ca. 25% overall yield.

The synthesis of prostaglandins and therapeutically important prostaglandin analogues according to our strategy is under current study.

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