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Synthesis of Functionalized Phenolic Derivatives *via* the Benzannulation of Dienylketenes Formed by a Thermal Wolff Rearrangement of α-Diazo-β-keto Compounds

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Abstract: Eleven conjugated dienyl α-diazo-β-keto derivatives were prepared from α,β-unsaturated carbonyl compounds. Their thermolysis induced a Wolff rearrangement generating an intermediate dienyl ketene whose isomer which has the required configuration of the *internal* double bond underwent a benzannulation thus forming the corresponding phenolic derivatives. When γ-substituted by a methoxy group both stereoisomers of the diazo compounds gave rise to the phenolic derivatives due to the reversible formation of an intermediate cyclobutenone which permitted the isomerization of the nonproductive transient dienylketene into the productive one. Copyright © 1996 Elsevier Science Ltd

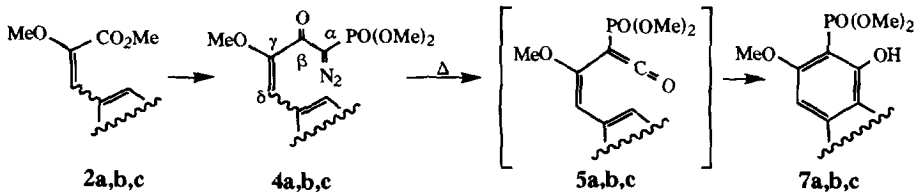
INTRODUCTION

α–Diazocarbonyl compounds are useful intermediates in organic chemistry. They are easily prepared from readily accessible precursors and can be induced to undergo a variety of chemical transformations.[1] Among the most useful reactions are cyclopropanation, insertion into O-H, S-H, N-H or unactivated C-H bonds[2] and Wolff rearrangement generating a ketene.[1,3] This rearrangement can be initiated by thermolysis, photolysis or metal ion catalysis and the ketene thus formed may then undergo further reactions such as radical, electrophilic or nucleophilic additions[4], cycloaddition to unsaturated systems[5] or electrocyclizations.[6]

A remarkably efficient new aromatic annulation method has been developed by Danheiser and co-workers. It is based on the generation of vinyl or arylketenes either from the reversible 4π electrocyclic ring opening of a cyclobutenone[7] or from the photochemical Wolff rearrangement of unsaturated α-diazo ketones,[8] followed by a cascade of three pericyclic reactions, of which the final one consists in the electrocyclization of a dienylketene. A variety of highly substituted polycyclic aromatic and heteroaromatic compounds can be prepared using this method. Independently Moore[9] and Liebeskind[10] have reported related strategies for the synthesis of highly substituted quinones or phenols.[11]

Pursuing our investigation into the synthetic usefulness of 2-methoxy-2-alkenoates[12] and of their 2-trimethylsilyloxy analogues,[13] we recently prepared, in two steps from dienyl esters **2a-c**, the corresponding α-diazo-β-ketophosphonates **4**. We expected that a thermally induced Wolff rearrangement[14] of the latter

compounds would generate intermediate dienylketenes **5** susceptible to electrocyclic ring closure as observed by Danheiser and others. In accordance with our predictions, when compounds **4a-c** were heated in refluxing toluene, they led to the corresponding phenolic derivatives **7** in good yields.[15]



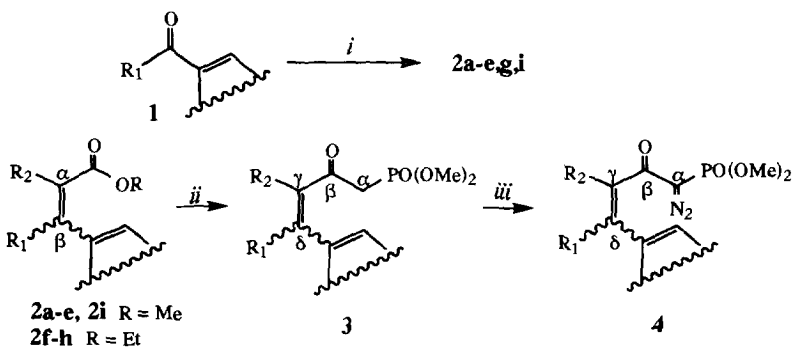
2a,b,c **4a,b,c** **5a,b,c** **7a,b,c**

To determine the scope and limitations of this new access to functionalized phenolic derivatives,[16] we have now examined the influence of the nature of the γ and δ positioned substituents and also the effect of replacing the dimethoxyphosphinyl group by other functionalities.

RESULTS AND DISCUSSION

Benzannulation of γ-methoxy-α-diazo-β-ketophosphonates 4a-e

The diazo compounds **4a** to **4e** were obtained from commercially available starting materials using the three-step sequence depicted in scheme 1.



2a-e, 2i R = Me
2f-h R = Et

3 **4**

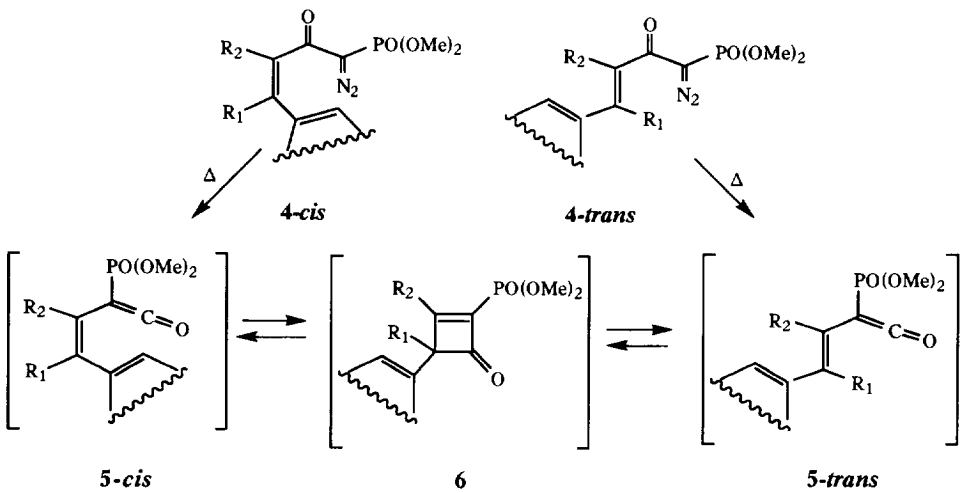
i) Wittig reaction (see text); *ii)* $LiCH_2PO(OMe)_2$ (2 eq), THF; *iii)* TsN_3, K_2CO_3, CH_3CN.

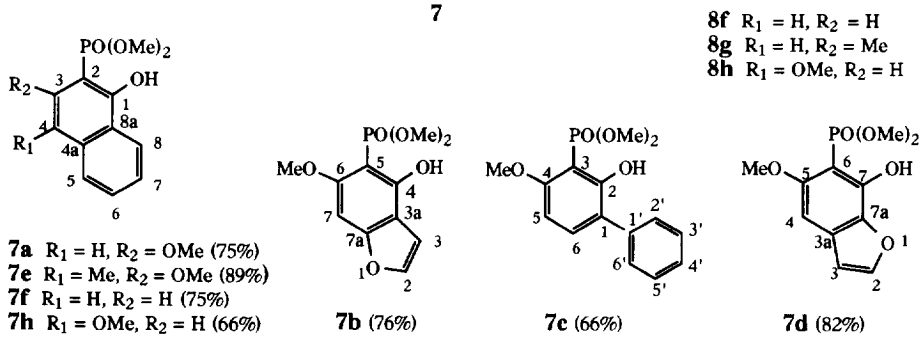
		R_1	R_2	2 → 4
a	Ph	H	OMe	65%
b	2-furyl	H	OMe	62%
c	(E) -CH=CH-Ph	H	OMe	61%
d	3-furyl	H	OMe	56%
e	Ph	Me	OMe	86%
f-cis	Ph	H	H	87%
f-trans	Ph	H	H	68%
g	Ph	H	Me	80%
h	Ph	MeO	H	80%
i	Ph	H	$N(CH_2)_5$	*

*Compound **4i** was not obtained (see text).

Scheme 1

A Wadsworth-Horner-Emmons reaction between the α,β-unsaturated carbonyl compound **1a-e** and methyl 2-dimethoxyphosphinyl-2-methoxy acetate[17] led to the corresponding methyl 2-methoxy-2-alkenoates **2** obtained as a mixture of *cis* and *trans*[18] stereoisomers, the former being the major product.[19, 20] When *cis-trans* mixtures of compounds **2** were submitted to the action of dimethyl lithiomethylphosphonate (2 eq), they were transformed into β-ketophosphonates **3**. Compound **3a** was purified and fully characterized whereas **3b-e** were used as crude products in the following step. The diazo-transfer reaction was conducted using tosyl azide and potassium carbonate in acetonitrile according to the conditions reported by Koskinen and Munoz for the preparation of α-diazo-β-ketoesters.[21] The α-diazo-β-ketophosphonates **4a-e** were thus obtained from compounds **2** in overall yields ranging from 56% to 86%.





Scheme 2

As previously reported,[15] when the stereoisomers **4a-*cis*** and **4a-*trans*** were heated separately in refluxing toluene, they were both completely decomposed after the same reaction time and led to the naphthol **7a** in similar yield (75%). Therefore we then treated a mixture of *cis* and *trans* isomers of compounds **4b** to **4e** under the same conditions. We thus obtained the corresponding phenolic derivatives **7b-e** in fairly good yields (66% to 85%) (scheme 2).

Benzannulation of both stereoisomers of **4a-e** can be explained as follows. The *cis* isomer can give rise to **7** by direct electrocyclisation of the corresponding intermediate dienylketene **5-*cis*** having the required stereochemistry. The *trans* isomer would first lead to a vinyl cyclobutenone **6** which would reopen in either **5-*cis*** or **5-*trans*** and finally lead to compound **7** (scheme 1).[22]

The reversibility in electrocyclic ring opening of 3-trialkylsilyloxy cyclobutenones into the corresponding dienylketenes has been recently put forward by Danheiser and co-workers to explain related benzannulations.[8b] However the electrocyclic ring closure of dienylketene into cyclobutenones is not a general process and largely depends on the nature of the substituents both on the ketene and vinyl moieties.[5a,6c,23] It was therefore interesting to examine the behaviour of diazo ketophosphonates **4** variously substituted in γ and δ positions.

Thermolysis of α-diazo-β-ketophosphonates 4f, 4g and 4h

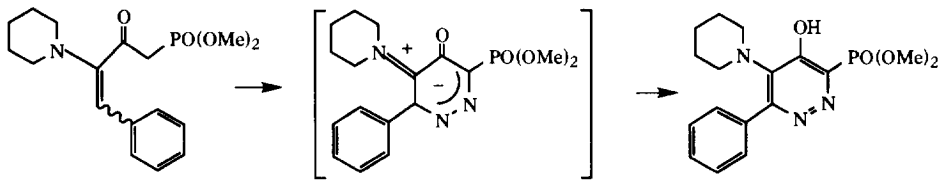
The two diastereoisomers of diazo compound **4f** were prepared from Z-ethyl cinnamate **2f-*cis***[24] or its commercially available isomer **2f-*trans*** (scheme 1). Thermolysis of **4f-*cis*** in refluxing toluene (4 h) led to expected phenol **7f** in 75% yield (scheme 2).[25] Under the same conditions **4f-*trans*** was surprisingly recovered almost unchanged. However, when the thermolysis was conducted in the presence of a catalytic amount of rhodium acetate[26] in refluxing benzene (30 mn), the Wolff rearrangement did take place. Indeed, if methanol was then added to the reaction mixture, the *persistent* dienylketene **5f-*trans*** was transformed into the methyl ester **8f** in 87% yield. Since the presence of the phenol **7f** could not be detected, it appeared that the cyclobutenone **6** was no longer formed in this case.[27] A similar result was obtained with diazo compound **4g-*trans*** prepared from ester **2g-*trans***[19,20] resulting from a Wittig reaction between benzaldehyde and commercially available ethyl 2-(triphenylphosphoranylidene)propionate. The Wolff rearrangement took place only in the presence of a catalytic amount of rhodium acetate and after treatment of the reaction mixture with methanol, we isolated the methyl ester **8g** (72%) as the sole product.

These results showed that the γ-positioned methoxy group plays a crucial role in the formation of cyclobutenones **6**. To determine if the intermediate cyclobutenone **6** would still be formed when the methoxy group was differently positioned on the carbon-carbon double bond, we decided to examine the thermal behaviour of **4h**. Ester **2h** was prepared from ethyl benzoylacetate according to Arndt and Loewe procedure[28] and transformed into the corresponding diazo ketophosphonate **4h** in the usual way (scheme 1). Though compounds **2h** and crude **4h** were formed only in the expected[28] *trans* configuration, after column chromatography of the the latter compound we obtained a mixture of *cis* (major) and *trans* (minor) isomers. When heated in refluxing toluene, only **4h-*cis*** led to the phenol **7h** (66%). Under the same conditions **4h-*trans*** did not lead to **7h**, but treatment of the reaction mixture with methanol led to the formation of the methyl ester **8h** in 64% yield (scheme 2). Hence the dienylketene **5h-*trans*** was no longer in equilibrium with its stereoisomer **5h-*cis*** via the cyclobutenone **6**. As a result the formation of the phenol **7h** could not take place.

From the above results it could be predicted that the *cis/trans* equilibration of stereoisomeric intermediate dienylketenes **5**, *via* the cyclobutenones **6**, could only take place if the former compounds were derived from diazo compounds **4** bearing a mesomeric donating group in the vicinal position of the keto function. To try to

confirm this hypothesis we decided to prepare the enamino diazo compound **4i** whose thermolysis of both *cis* and *trans* isomers was expected to give rise to the corresponding phenol.

Reaction between benzaldehyde and methyl 2-dimethoxyphosphinyl-2-piperidinylacetate[17] furnished the enamino ester **2i**, as a mixture of *cis* and *trans* isomers, which were then transformed into the β-ketophosphonate **3i** (scheme 1). Unfortunately, when submitted to the usual conditions of diazo transfer reaction, **3i** did not lead to the expected diazo compound **4i**. From the complex crude mixture we were able to isolate the pyridazine **10** (scheme 3). This compound results from a nucleophilic attack of the enamino carbon-carbon double bond on the diazo moiety followed by aromatization of the intermediate zwitterion **9**. A related mechanism has been proposed by Regitz et al. for the formation of aminopyridazines, resulting from the reaction of aminocyclopropenylium salts with diazomethyl compounds.[29]

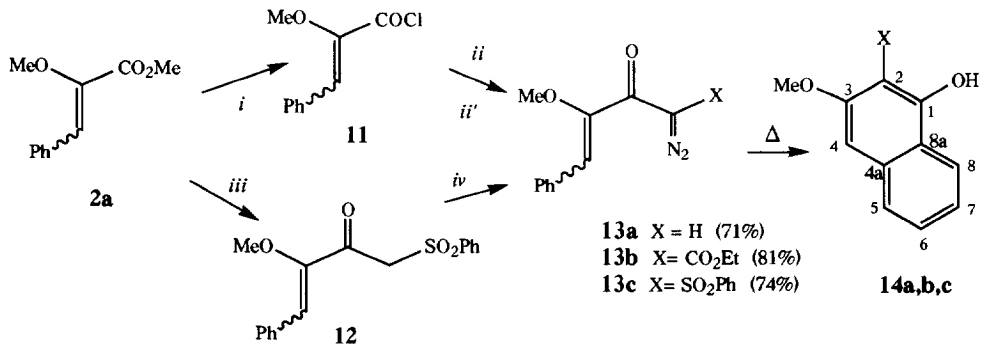


3i **9** **10**

Scheme 3

Benzannulation of γ-methoxy-α-diazo-β-keto compounds 13

In the second part of our study we examined the thermal behaviour of analogues of **4a** bearing functionalities other than the dimethoxyphosphinyl group. They were obtained according to the sequences depicted in scheme 4. The ester **2a** was hydrolyzed into the corresponding acid which was not isolated but directly converted into the acid chloride **11**, using oxalyl chloride as chlorinating agent. The α-diazoketone **13a** was prepared in the usual way by adding an ethereal solution of diazomethane to the acid chloride **11**. The α-diazo-β-ketoester **13b** was obtained by reacting ethyl diazoacetate with **11**. The α-diazo-β-ketosulphone **13c** was obtained in two steps from ester **2a** by reaction with the bis-lithium derivative[30] of methyl phenyl sulphone leading to the β-ketosulphone **12** and then diazo transfer under the usual conditions.



i) KOH/MeOH, H^+, $(ClCO)_2$, toluene, Δ; *ii)* CH_2N_2; *ii')* N_2CHCO_2Et;
iii) $MeSO_2Ph$, BuLi (2 eq), THF, - 80 °C; *iv)* TsN_3, K_2CO_3, CH_3CN.

Scheme 4

As for compound **4a** the *cis* and *trans* isomers of compounds **13** were separated (column chromatography) and separately thermolyzed. We observed that both isomers underwent benzannulation. This demonstrates that isomerization of the intermediate dienyl ketenes occurs regardless of the terminal functional group, and even with the non electron-deficient ketene obtained from **13a**. The thermolysis of compounds **13b** and **13c** in refluxing toluene afforded the corresponding phenols **14b** and **14c** in 68% and 78% yields respectively. Under the same conditions the thermolysis of **13a** was rather sluggish, but when heated in refluxing xylene[31] compound **13a** gave rise to **14a** in 75% yield.

Structural determination of phenolic compounds 7, 14

The structures of phenolic compounds **7** and **14** are completely consistent with their IR, ^{1}H- and ^{13}C-NMR spectra (Tables 1 and 2) and microanalysis.

Table (1): Pertinent ^{1}H-NMR Data of Phenolic Compounds **7**, **14** and **15** [δ (ppm) and J (Hz)]

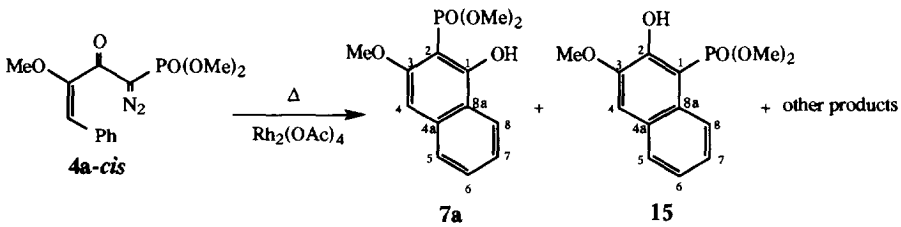
7a	**7b**	**7c**	**7d**	**7f**	**7h**	**14a**	**14b**	**14c**	**15**
-	-	-	-	H-3 7.30 (dd) $^3J_{HP}$=12.1 $^3J_{HH}$ = 8.5	H-3 6.41 (d) $^3J_{HP}$ = 13.7	-	-	-	-
H-4 6.62 (d) $^4J_{HP}$ = 5.7	H-7 6.58 (dd) $^4J_{HP}$ = 4.7 $^5J_{HH}$ = 0.7	H-5 6.48 (dd) $^4J_{HP}$ = 6.0 $^3J_{HH}$ = 8.6	H-4 6.55 (d) $^4J_{HP}$ = 5.6	H-4 7.39 (dd) $^4J_{HP}$ = 3.4 $^3J_{HH}$ = 8.5	-	H-4 6.53 (d) $^4J_{HH}$ = 2.2	H-4 6.59 (s)	H-4 6.55 (s)	H-4 7.27 (s) $^5J_{HP}$ = 0

Attribution of the resonances in the NMR spectra of **7a** was made utilizing *HH* COSY, *HC* COSY and *HC* Multibond Correlation. The bicyclic structure of **7a** resulting from a Wolff transposition is in agreement with the observed resonance of the proton H-4 (doublet at 6.62 ppm, $^4J_{HP}$ = 5.7 Hz) and with the chemical shifts of carbons C-1, C-2, C-3, C-4, C-4a and C-8a. The $^nJ_{CP}$ values for carbons C-2, C-1, C-8a and C-4a are well within the expected ranges for such coupling constants ($^1J_{CP} >> {}^3J_{CP} > {}^2J_{CP} > {}^4J_{CP}$). Surprisingly no coupling was observed between the phosphorus atom and the carbon C-3 ($^2J_{CP}$ = 0) and only a weak three-bond coupling constant was measured between the phosphorus atom and the carbon C-4 ($^3J_{CP}$ = 8.1 Hz).

In order to confirm the structure of **7a**, especially the relative positions of the hydroxy and dimethoxyphosphinyl substituents, we decided to synthesize the isomeric naphthol **15** which could result from the insertion of a carbenoid[32] species into a C-H bond of the aromatic ring.[26] Thus the α-diazo-β-ketophosphonate **4a-*cis*** was heated in refluxing fluorobenzene in the presence of a catalytic amount of rhodium acetate.[26] After refluxing for 8 h the starting material was totally transformed into a mixture containing the expected naphtol **15** (48%), the same naphthol **7a** (28%) as that obtained under thermal conditions and other unidentified products (scheme 5).

Table (2) : ^{13}C-NMR Data of Phenolic Compounds **7a-e,f,h; 14a-c** and **15** [δ (ppm) and $^{n}J_{CP}$ (Hz)]

7a	C-1 163.1 $^{2}J_{CP}$ = 6.4	C-2 99.2 $^{1}J_{CP}$ = 178.2	C-3 157.1 $^{2}J_{CP}$ = 0	C-4 96.5 $^{3}J_{CP}$ = 8.1	C-4a 137.4 $^{4}J_{CP}$ = 1.2	C-5 126.2 $^{5}J_{CP}$ = 0.5	C-6 129.8 $^{6}J_{CP}$ = 0.5	C-7 123.4 $^{5}J_{CP}$ = 1.4	C-8 123.9 $^{4}J_{CP}$ = 1.3	C-8a 121.0 $^{3}J_{CP}$ = 13.6	PO(OMe)$_2$ 53.2 $^{2}J_{CP}$ = 5.0	OMe 55.7
7b	C-4 159.1 $^{2}J_{CP}$ = 6.7	C-5 90.1 $^{1}J_{CP}$ = 180.8	C-6 160.1 $^{2}J_{CP}$ = 1.8	C-7 86.8 $^{3}J_{CP}$ = 9.3	C-7a 160.2 $^{4}J_{CP}$ = 1.1		-	C-2 143.0	C-3 104.6 $^{4}J_{CP}$ = 2.0	C-3a 111.3 $^{3}J_{CP}$ = 15.6	PO(OMe)$_2$ 52.9 $^{2}J_{CP}$ = 4.3	OMe 56.5
7c	C-2 161.2 $^{2}J_{CP}$ = 5.8	C-3 96.1 $^{1}J_{CP}$ = 176.6	C-4 161.4 $^{2}J_{CP}$ = 0	C-5 101.4 $^{3}J_{CP}$ = 9.1	C-6 137.0 $^{4}J_{CP}$ = 1.3	C-1' 137.8 $^{4}J_{CP}$ = 1.9	C-2',C-6' 126.8	C-3',C-5' 128.0 -	C-4' 129.3 -	C-1 123.3 $^{3}J_{CP}$ = 12.3	PO(OMe)$_2$ 53.3 $^{2}J_{CP}$ = 5.1	OMe 56.0
7d	C-7 150.1 $^{2}J_{CP}$ = 6.8	C-6 91.8 $^{1}J_{CP}$ = 180.2	C-5 157.4 $^{2}J_{CP}$ = 0	C-4 92.3 $^{3}J_{CP}$ = 10.1	C-3a 133.6 $^{4}J_{CP}$ = 0	C-3 107.2	C-2 147.8	-	-	C-7a 138.9 $^{3}J_{CP}$ = 20.8	PO(OMe)$_2$ 53.2 $^{2}J_{CP}$ = 5.0	OMe 56.2
7e	C-1 161.5 $^{2}J_{CP}$ = 5.6	C-2 95.8 $^{1}J_{CP}$ = 182.2	C-3 154.7 $^{2}J_{CP}$ = 0	C-4 115.0 $^{3}J_{CP}$ = 8.2	C-4a 137.2 $^{4}J_{CP}$ = 0	C-5 124.5	C-6 129.6	C-7 123.5	C-8 124.3 $^{4}J_{CP}$ = 1.6	C-8a 122.8 $^{3}J_{CP}$ = 14.3	PO(OMe)$_2$ 53.1 $^{2}J_{CP}$ = 5.1	OMe 62.0 Me 11.3
7f	C-1 161.8 $^{2}J_{CP}$ = 7.5	C-2 99.5 $^{1}J_{CP}$ = 181.4	C-3 125.7 $^{2}J_{CP}$ = 6.3	C-4 119.7 $^{3}J_{CP}$ = 13.4	C-4a 137.5 $^{4}J_{CP}$ = 2.0	C-5 127.9	C-6 129.6	C-7 126.4 $^{5}J_{CP}$ = 1.2	C-8 123.7 $^{4}J_{CP}$ = 1.6	C-8a 125.1 $^{3}J_{CP}$ = 13.8	PO(OMe)$_2$ 53.3 $^{2}J_{CP}$ = 4.7	-
7h	C-1 155.8 $^{2}J_{CP}$ = 6.6	C-2 97.0 $^{1}J_{CP}$ = 183.0	C-3 101.3 $^{2}J_{CP}$ = 7.5	C-4 148.5 $^{3}J_{CP}$ = 16.3	C-4a 129.6 $^{4}J_{CP}$ = 2.3	C-5 121.8 $^{5}J_{CP}$ = 0.5	C-6 128.8	C-7 126.6	C-8 123.5 $^{4}J_{CP}$ = 2.2	C-8a 125.7 $^{3}J_{CP}$ = 15.9	PO(OMe)$_2$ 52.8 $^{2}J_{CP}$ = 4.5	OMe 55.7
14a	C-1 157.9	C-2 101.5	C-3 152.9	C-4 98.9	C-4a 135.5	C-5, C-6, C-7, C-8 121.8, 123.1, 126.7, 127.2				C-8a 120.8	-	OMe 55.5
14b	C-1 163.9	C-2 100.2	C-3 156.4	C-4 97.6	C-4a 136.7	C-5, C-6, C-7, C-8 123.4, 124.1, 126.0, 130.0				C-8a 120.7	CO_2Et 171.0, 61.7, 14.2	OMe 55.9
14c	C-1 157.4	C-2 108.3	C-3 153.5	C-4 98.2	C-4a 137.0	C-5, C-6, C-7, C-8 124.1, 124.3, 126.2, 130.4				C-8a 121.1	SO_2Ph 142.2,133.3, 128.6,127.7	OMe 55.8
15	C-1 97.7 $^{1}J_{CP}$ = 175.2	C-2 157.3 $^{2}J_{CP}$ = 7.9	C-3 148.5 $^{3}J_{CP}$ = 19.1	C-4 112.2 $^{4}J_{CP}$ = 2.7	C-4a 128.4 $^{3}J_{CP}$ = 13.7	C-5 127.3 $^{4}J_{CP}$ =2.1	C-6 124.1	C-7 125.6	C-8 123.9 $^{3}J_{CP}$ = 4.2	C-8a 127.6 $^{2}J_{CP}$ = 6.9	PO(OMe)$_2$ 52.9 $^{2}J_{CP}$ = 4.3	OMe 56.0



Scheme 5

Attribution of the resonances in the NMR spectra of **15** was made in the same way as for **7a**. The NMR spectra are in perfect agreement with the structure of **15**. The proton H-4 appears as a singlet at 7.27 ppm ($^5J_{HP}$ = 0) whereas the $^nJ_{CP}$ values and chemical shifts of carbons C-1, C-2, C-3, C-4, C-4a and C-8a confirm the relative positions of the hydroxy and dimethoxyphosphinyl substituents. The weak coupling constant between P and C-8 in compound **15** ($^3J_{CP}$ = 4.2 Hz) is related to the cis positions of carbon C-8 and phosphorus atoms with respect to the C1-C8a bond. The C-4a and C-8a chemical shifts (137.4/121.0 ppm for **7a** and 128.4/127.6 ppm for **15**) can be compared with the corresponding values in 1,3-dihydroxynaphthalene (135.4/119.8 ppm) and 2,3-dihydroxynaphthalene (128.8 ppm).[33] Thus the spectral comparison of **7a** and **15** establishes unambiguously their structures.

The structures of compounds **7b-e, f, h** were supported by the similarities of their NMR spectra with those of **7a**. Coupling constants $^3J_{HP}$ = 12.1-13.7 Hz and $^4J_{HP}$ = 3.4-6.0 Hz and expected proton chemical shifts are observed when the corresponding protons are present. As for compound **7a** the ^{13}C-NMR spectra provided evidence for the influence of the methoxy group as an R_2 substituent on some $^2J_{CP}$ and $^3J_{CP}$ coupling constants. If the R_2 substituent is a methoxy group (**7b-e**), the $^2J_{CP}$ related to carbon [C-6 or C-3 or C-5 or C-3] are in the range 0-1.8 Hz and the $^3J_{CP}$ related to carbon [C-7 or C-4] are in the range 8.2-10.1 Hz. If the R_2 substituent is a hydrogen atom (**7f,h**), expected values are observed for the $^2J_{CP}$ related to carbon C-3 (6.3 and 7.5 Hz) and for the $^3J_{CP}$ related to carbon C-4 (13.4 and 16.3 Hz).

The NMR data of compounds **14** are to be compared with those of **7a.** Concerning the relative positions of the 1-hydroxy group and C-2 substituent, the structures are well supported by the chemical shifts of proton H-4 (6.53-6.59 ppm) and carbons C-4a (135.5-137.0 ppm) and C-8a (120.7-121.1 ppm).

CONCLUSION

In conclusion we report here a new access to variously functionalized phenolic derivatives in a three step sequence from α,β-unsaturated esters. The method is particularly attractive for the preparation of *meta*-methoxy phenolic compounds since they are obtained from both stereoisomers of the starting 2-methoxy-2-alkenoates. In addition our results point out the crucial role of an alkoxy group and its position on the vinyl moiety, in the interconversion of vinylketenes into cyclobutenones.

EXPERIMENTAL SECTION

General.

Diethyl ether was distilled from potassium hydroxide, pentane from phosphorus pentoxide, tetrahydrofuran from sodium benzophenone ketyl. Benzene and toluene were dried over sodium. Organic solutions were dried over anhydrous sodium sulfate. Column chromatographies were performed using Merck Silica gel 60 (70-230 mesh) and TLC were carried out using Merck Kieselgel 60 F254 plates. Melting points were determined on a Kofler block apparatus. IR spectra were recorded on a Perkin Elmer 1310 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ on a Brucker AC200 (200/50 MHz) spectrometer and for specified cases on a Brucker AM300 (300/75 MHz). All NMR recordings were referenced to $CHCl_3$ resonances (7.26 and 77.0 ppm). Splitting patterns abbreviations are: s, singulet; d, doublet; t, triplet; m, multiplet; b, broad; p, pseudo. Multiplicity (^{13}C NMR) was determined by DEPT sequencies. Diazo carbons were often not observed due to their long relaxation time. Elemental analyses and Mass spectra (recorded on a Fisons VG 70E) were performed by Service Central d'Analyse, Centre National de la Recherche Scientifique, 69300 Vernaison, France.

SYNTHESIS OF ALKENOATES (2)

Esters (2a-e).

To a stirred solution of methyl (2-dimethoxyphosphinyl-2-methoxy) acetate[17] (2.12 g, 10 mmol) in anhydrous THF (30 ml), cooled at - 40°C was added, under nitrogen, a 1M solution of LHMDS in THF (10 ml). The mixture was allowed to warm to 5°C and a solution of aldehyde (9 mmol) in anhydrous THF (20 ml) was added dropwise. The reaction mixture was stirred for 3 h at room temperature and was then hydrolysed with a satured ammonium chloride solution (10 ml). The aqueous phase was extracted with diethyl ether (3 x 30 ml) and the combined organic extracts were dried, filtered and concentrated. The crude oil was purified by flash chromatography.

Methyl 2-methoxy-3-phenyl-2-propenoate (2a).

From benzaldehyde (0.95 g), after flash chromatography (pentane/diethyl ether 90:10) of crude **2a** (E/Z, 74:26)[34] we obtained 0.44 g of **2a-Z** and 1.25 g of **2a-E** (total yield: 87%). (Z-isomer): R_f = 0.35. Oil. IR (neat): 1710, 1625. ^1H-NMR δ 3.77 (s, 3H); 3.85 (s, 3H); 6.99 (s, 1H); 7.25-7.41 (m, 3H); 7.69-7.77 (m, 2H). ^{13}C-NMR δ 52.1; 59.2; 124.1; 128.6 (2C); 129.0; 130.2 (2C); 133.4; 145.5; 164.9. (E-isomer): R_f = 0.20. Oil. IR (neat): 1725, 1625. ^1H-NMR δ 3.65 (s, 3H); 3.72 (s, 3H); 6.10 (s, 1H); 7.15-7.38 (m, 5H). ^{13}C-NMR δ 52.1; 55.9; 109.2; 126.9 (2C); 128.1; 128.6 (2C); 134.6; 147.6; 164.6. Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.30. Found: C, 68.59; H, 6.03.

Methyl 3-(2'-furyl)-2-methoxy-2-propenoate (2b).

From 2-furaldehyde (0.86 g) after flash chromatography (pentane/diethyl ether 90:10) we obtained 1.23 g (75%) of **2b** (E/Z, 60:40). (Z-isomer): *Rf* =0.40. Oil. IR (neat): 1710, 1625. ^1H-NMR δ 3.82 (s, 3H); 3.83 (s, 3H); 6.49 (ddd, J = 0.6, 1.8, 3.4, 1H); 6.92 (dd, J = 0.6, 3.4, 1H); 7.00 (s, 1H); 7.47 (dd, J = 0.6, 1.8, 1H). ^{13}C-NMR δ 52.1; 59.2; 112.4; 113.6; 114.1; 143.1; 143.4; 149.3, 164.3. (E-isomer): R_f = 0.30. Oil. IR (neat): 1730, 1640. ^1H-NMR δ 3.72 (s, 3H); 3.85 (s, 3H); 6.03 (s, 1H); 6.40 (dd, J = 1.8, 3.4, 1H); 6.80 (dd, J = 0.6, 3.4, 1H); 7.36 (dd, J = 0.6, 1.8, 1H). ^{13}C-NMR δ 52.2; 56.1; 100.8; 110.5; 111.8; 142.0; 145.5; 148.9; 163.0. LRMS (EI) m/z (rel int) 182 (100), 167 (6), 151 (6), 139 (39), 123 (7), 111 (45), 83 (45). HRMS (EI) m/z calcd. for $C_9H_{10}O_4$ (M^+) 182.0579, found 182.0580.

Methyl 2-methoxy-5-phenyl-2,4(E)-pentadienoate (2c).

From (E)-cinnamaldehyde (1.19 g) after flash chromatography (pentane/diethyl ether 85:15) we obtained 1.76 g (90%) of **2c** (2(E),4(E)/2(Z),4(E)), 64:36). (2(Z),4(E)-isomer): R_f = 0.35. Oil. IR ($CHCl_3$): 1715, 1615. ^{1}H-NMR δ 3.79 (s, 3H); 3.81 (s, 3H); 6.80 (d, J = 15.7, 1H); 6.88 (d, J = 11.2, 1H); 7.18 (dd, J = 11.2, 15.7, 1H); 7.26-7.38 (m, 3H); 7.45-7.50 (m, 2H). ^{13}C-NMR δ 52.0; 60.7; 121.5; 126.2; 127.1 (2C); 128.6; 128.7 (2C); 136.6; 137.6; 145.2; 164.4. (2(E),4(E) isomer): R_f = 0.25. mp 86-88°C. IR (neat): 1735, 1590. ^{1}H-NMR δ 3.73 (s, 3H); 3.88 (s, 3H); 6.07 (d, J = 11.3, 1H); 6.65 (d, J = 15.7, 1H); 7.26-7.45 (m, 5H); 7.86 (dd, J = 11.3, 15.7, 1H). ^{13}C-NMR δ 52.1; 55.8; 115.0; 124.0; 126.8 (2C); 127.8; 128.6 (2C); 134.9; 135.8; 145.3; 163.6. Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.36; H, 6.17.

Methyl 3-(3'-furyl)-2-methoxy-2-propenoate (2d).

From 3-furaldehyde (0.86 g) after flash chromatography (pentane/diethyl ether 90:10) we obtained 1.36 g (83%) of **2d** (E/Z, 57:43). (Z-isomer): R_f = 0.40. Oil. IR (neat): 1710, 1635. ^{1}H-NMR δ 3.78 (s, 3H); 3.83 (s, 3H); 6.72 (d, J = 1.9, 1H); 6.93 (s, 1H); 7.43 (pt, J = 0.4, 1.9, 1H); 7.81 (t, J = 0.7, 1H). ^{13}C-NMR: 52.0; 59.1; 110.7; 116.0; 119.3; 143.4; 144.4; 144.7; 164.5. (E-isomer): R_f = 0.30. mp 82-84 °C. IR (neat): 1725, 1635. ^{1}H-NMR δ 3.73 (s, 3H); 3.84 (s, 3H); 5.95 (s, 1H); 6.53 (d, J = 1.6, 1H); 7.37 (pt, J = 1.6, 1H); 7.73 (t, J = 0.7, 1H). ^{13}C-NMR: 52.2; 56.1; 102.8; 111.5; 118.7; 142.6 (2C); 145,7; 164.0. LRMS (EI) m/z (rel int) 182 (100), 167 (7), 151 (8), 139 (37), 123 (21), 111 (56), 83 (55). HRMS (EI) m/z calcd. for $C_9H_{10}O_4$ (M^+) 182.0579, found 182.0580.

Methyl 2-methoxy-3-methyl-3-phenyl-2(E)-propenoate (2e).

From acetophenone (1.08 g) after flash chromatography (pentane/dichloromethane 50:50) we obtained 1.43 g (77%) of **2e** (E-isomer): Oil. IR (CCl_4): 1715, 1630. ^{1}H-NMR δ 2.12 (s, 3H); 3.51 (s, 3H), 3.67 (s, 3H); 7.12-7.36 (m, 5H). ^{13}C-NMR δ 19.3; 51.4; 59.0; 127.2 (2C); 127.3; 128.1 (2C); 134.3; 140.7; 143.0; 164.8. Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.83; H, 7.22.

Methyl 2-methyl-3-phenyl-2(E)-propenoate (2g).

To a stirred suspension of ethyl 2-(triphenylphosphoranylidene)propionate (0.94 g, 2.6 mmol) in dry benzene (20 ml) was added a solution of benzaldehyde (230 mg, 2.2 mmol) in benzene (10 ml). The mixture was refluxed for 8 h. The solvent was evaporated and the crude product was flash chromatographied (pentane/diethyl ether 95:5) to afford 405mg (97%) of **2g** (E/Z, 97:3). (E-isomer): Oil. IR (neat): 1700, 1630. ^{1}H-NMR δ 1.36 (t, 3H); 2.14 (d, J = 1.3, 3H); 4.29 (q, 2H); 7.26-7.41 (m,5H); 7.71 (q, J = 1.3, 1H). ^{13}C-NMR:δ 14.3; 14.5; 61.1; 128.2; 128.3 (2C); 128.6; 129.5 (2C); 135.9; 138.9; 168.9. Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.62; H, 7.49.

Ethyl 3-methoxy-3-phenyl-2(Z)-propenoate (2h).

Following the Arndt-Loewe procedure[28]: to an etheral solution of diazomethane (100 ml) (prepared from N-methyl-N-nitroso-*p*-toluene-sulfonamide 12.8 g (60 mmol)), cooled in a water ice bath, was added dropwise a solution of ethyl benzoylacetate (3.84 g, 20 mmol) in diethyl ether (25 ml). The ice bath was removed and the mixture stirred at room temperature for 3 days. The solvent was evaporated, diethyl ether (200 ml) was added and evaporated over again to ensure a total removal of diazomethane. The crude oil was distilled and gave 3.1 g (75%) of **2h**. bp 118-120 °C / 1Torr. Oil. IR (neat): 1710, 1615. ^{1}H-NMR δ 1.31 (t, 3H); 3.83 (s, 3H); 4.21 (q, 2H); 5.53 (s, 1H); 7.38-7.44 (m, 3H); 7.51-7.56 (m, 2H). ^{13}C-NMR δ 14.4; 59.7; 60.4; 100.0; 127.5 (2C);

128.6 (2C); 130.3; 134.9; 165.2; 168.7.Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.94; H, 6.95.

SYNTHESIS OF β-KETOPHOSPHONATES (3)

β-Ketophosphonates (3a-h).

To a stirred solution of dimethyl methylphosphonate (1.24 g, 10 mmol) in anhydrous THF (30 ml) cooled at -80°C, was added dropwise, under nitrogen, 6.25 ml (10 mmol) of *n*-butyllithium 1.6M in hexanes. The mixture was kept for 45 mn at -80 °C and then a solution of the ester **2** (Z/E mixtures or **2a-Z** or **2a-E**; 5 mmol) in anhydrous THF (30 ml) was added slowly. The reaction mixture was allowed to react at room temperature for 3 h, and was then quenched with a satured ammonium chloride solution (10 ml). The aqueous phase was extracted with ethyl acetate (3 x 30 ml), the organic layers were washed with brine, dried, filtered and concentrated. The resulting crude compounds **3** were used in the following step except for **3a-Z** or **3a-E** wich were purified by chromatography (ethyl acetate).

Dimethyl 3-methoxy-2-oxo-4-phenyl-3-butenylphosphonate (3a).

(Z-isomer). Yield: 77%. R_f= 0.35. Oil. IR (neat): 1700, 1610, 1260, 1060, 1030. ^{1}H-NMR δ 3.47 (d, $^2J_{HP}$ = 22.5, 2H); 3.75 (s, 3H); 3.82 (d, $^3J_{HP}$= 11.2, 6H); 6.98 (s, 1H); 7.34-7.45 (m, 3H); 7.73-7.78 (m, 2H). ^{13}C-NMR δ 36.6 (d, $^1J_{CP}$ = 131.6); 53.2 (d, $^2J_{CP}$ = 6.4, 2C); 59.3; 125.5; 128.7 (2C); 129.7; 130.6 (2C); 133.0; 152.6 (d, $^3J_{CP}$ = 2.7); 190.3 (d, $^2J_{CP}$ = 6.8). (E-isomer). Yield: 71%. R_f= 0.25. Oil. IR (neat): 1700, 1610, 1260, 1060, 1030. ^{1}H-NMR δ: 3.30 (d, $^2J_{HP}$ = 22.9, 2H); 3.76 (d, $^3J_{HP}$ = 11.4, 6H); 3.77 (s, 3H); 6.08 (s, 1H); 7.26 (m, 5H). ^{13}C-NMR δ 38.6 (d, $^1J_{CP}$ = 129.6); 52.9 (d, $^2J_{CP}$ = 6.4, 2C); 55.8; 109.9; 127.4 (2C); 128.2; 129.1 (2C); 134.1; 151.9 (d, $^3J_{CP}$ = 2.0); 190.5 (d, $^2J_{CP}$ = 6.4). Anal. Calcd. for $C_{13}H_{17}O_5P$: C, 54.93; H, 6.03. Found: C, 54.21; H, 6.12.

Dimethyl 3-piperidinyl-2-oxo-4-phenyl-3-butenylphosphonate (3i). To a stirred suspension of sodium hydride (60% in oil; 340 mg, 8.5 mmol) in anhydrous THF (10 ml) was added at room temperature a solution of methyl 2-(dimethoxyphosphinyl)-2-piperidinylacetate[17] (2.25 g, 8.5 mmol) in THF (20 ml). After 1h, a solution of benzaldehyde (680 mg, 6.4 mmol) in THF (25 ml) was added dropwise. The reaction mixture was stirred overnight and then hydrolyzed with brine (10 ml), extracted with diethyl ether (3 x 20 ml), dried and concentrated. Due to its relative unstability the crude ester **2i** was not purified but directly transformed into the corresponding β-ketophosphonate **3i** following the procedure described for **3a-h**. The crude product was purified by flash chromatography (ethyl acetate) to yield 540 mg (25%) of **3i** as a mixture of isomers (Z/E 63:37). The E and Z configurations were determined, as for compounds **2**, by the H-4 chemical shifts. IR (neat): 1730, 1665, 1590, 1560, 1260, 1050, 1020. ^{1}H-NMR δ 1.56-1.66 (m, 6H); 2.77-2.80 (m, 4H for Z-isomer); 2.88-2.93 (m, 4H for E-isomer); 3.11 (d, $^2J_{HP}$ = 22.0, 2H for E-isomer); 3.46 (d, $^2J_{HP}$ = 22.3, 2H for Z-isomer); 3.71 (d, $^3J_{HP}$ = 11.3, 6H for E-isomer); 3.80 (d, $^3J_{HP}$ = 11.2, 6H for Z-isomer); 5.94 (s, 1H for E-isomer); 6.62 (s, 1H for Z-isomer); 7.10-7.19 (m, 3H for Z-isomer); 7.22-7.39 (m, 5H for E-isomer); 7.48-7.51 (m, 2H for Z-isomer). ^{13}C-NMR δ 22.9 (E); 24.0 (Z); 25.9 (E); 26.4 (Z); 37.7 (Z) (d, $^1J_{CP}$ = 131.5); 41.0 (E) (d, $^1J_{CP}$ = 129.7); 50.4 (E); 51.6 (Z); 52.8 (E) (d, $^2J_{CP}$ = 6.3, 2C); 53.0 (Z) (d, $^2J_{CP}$ = 6.3, 2C); 112.2 (E); 125.5 (Z); 126.7 (E); 127.9 (Z); 128.1 (Z); 128.3 (E); 128.5 (E); 129.8 (E); 135.5 (Z); 136.6 (E); 148.3 (Z) (d, $^3J_{CP}$ = 2.7); 150.5 (E) (d, $^3J_{CP}$ = 3.2); 194.5 (E) (d, $^2J_{CP}$ = 6.4); 197.1 (Z) (d, $^2J_{CP}$ = 6.7). LRMS (EI) m/z (rel int) 337 (28), 228 (37), 186 (40), 170 (28), 84 (100).

SYNTHESIS OF α-DIAZO-β-KETOPHOSPHONATES (4)

α-Diazo-β-ketophosphonates (4a-e,g).

To a suspension of pure (**3a-Z** or **3a-E**) or crude (**3b-e,g**) β-ketophosphonate **3** (5 mmol) and potassium carbonate (825 mg, 6 mmol) in acetonitrile (20 ml) was added a solution of tosyl azide[35] (1.18 g, 6 mmol) in acetonitrile (20 ml). The reaction mixture was stirred at room temperature until the reaction was complete as judged by TLC and then quenched with a saturated ammonium chloride solution (10 ml). The aqueous phase was extracted with ethyl acetate (3 x 30 ml), the combined organic extracts were dried, filtered and concentrated. All crude products were purified by flash chromatography (ethyl acetate).

Dimethyl 1-diazo-3-methoxy-2-oxo-4-phenyl-3-butenylphosphonate (4a).

(Z-isomer). Yield: 85%. R_f = 0.45. Oil. IR (neat): 2120, 1610, 1240, 1060, 1010. ^{1}H-NMR δ 3.73 (s, 3H); 3.88 (d, $^3J_{HP}$ = 12.0, 6H); 6.82 (s, 1H); 7.28-7.43 (m, 3H); 7.46-7.70 (m, 2H). ^{13}C-NMR δ 54.2 (d, $^2J_{CP}$ = 6.1, 2C); 59.3; 121.4; 128.7 (2C); 129.3; 130.3 (2C); 132.6; 152 (d, $^3J_{CP}$ = 4.8); 183.2 (d, $^2J_{CP}$ = 8.8). (E-isomer). Yield: 85%. R_f = 0.40. Oil. IR (neat): 2120, 1630, 1260, 1050, 1020. ^{1}H-NMR δ 3.73 (d, $^3J_{HP}$ = 11.4, 6H); 3.76 (s, 3H); 5.99 (s, 1H); 7.19-7.33 (m, 5H). ^{13}C-NMR δ 53.9 (d, $^2J_{CP}$ = 5.7, 2C), 55.8; 105.8; 127.4; 128.5 (4C); 133.5; 151.3 (d, $^3J_{CP}$ = 4.6); 183.1. Anal. Calcd. for $C_{13}H_{15}O_5N_2P$: C, 50.33; H, 4.87; N, 9.03; P, 9.98. Found: C, 50.53; H, 4.84; N, 9.33; P, 10.17.

Dimethyl 1-diazo-4-(2'-furyl)-3-methoxy-2-oxo-3-butenylphosphonate (4b).

Yield (Z+E): 62%. (Z-isomer): R_f = 0.40. Oil. IR (neat): 2110, 1725, 1640, 1290-1250, 1060, 1020. ^{1}H-NMR δ 3.81 (s, 3H); 3.87 (d, $^3J_{CP}$ = 11.9, 6H); 6.52 (dd, J = 1.7, 3.4, 1H); 6.83 (d, J = 3.4, 1H); 6.88 (s, 1H); 7.54 (dd, J = 0.4, 1.7, 1H). ^{13}C-NMR δ 54.2 (d, $^3J_{CP}$ = 6.0, 2C); 59.8; 111.2; 112.6, 115.3; 144.5; 148.7; 149.8 (d, $^3J_{CP}$ = 5.1); 182.0 (d, $^2J_{CP}$ = 8.8). (E-isomer): R_f = 0.35. Oil. IR (neat): 2120, 1730, 1640, 1270, 1250, 1070-1020. ^{1}H-NMR δ 3.73 (s, 3H); 3.81 (d, $^3J_{HP}$ = 11.9, 6H); 5.85 (s, 1H); 6.38 (dd, J = 1.7, 3.4, 1H); 6.63 (d, J = 3.4, 1H); 7.35 (dd, J = 0.6, 1.7, 1H). ^{13}C-NMR δ 53.9 (d, $^2J_{CP}$ = 5.6, 2C); 55.6; 97.2; 109.9; 111.8; 142.2; 148.6; 150.1 (d, $^3J_{CP}$ = 3.5); 182.2 (d, $^2J_{CP}$ = 9.5). Anal. Calcd. for $C_{11}H_{13}O_6N_2P$: C, 44.01; H, 4.36; N, 9.33; P, 10.32. Found: C, 44.17; H, 4.27; N, 9.09; P, 11.06.

Dimethyl 1-diazo-3-methoxy-2-oxo-6-phenyl-3,5-hexadienylphosphonate (4c).

Yield (Z+E): 61 %. (3(Z),5(E)-isomer: R_f = 0.40. Oil. IR (CCl_4): 2120, 1735, 1650, 1630, 1590, 1280, 1230, 1060, 1030. ^{1}H-NMR δ 3.82 (s, 3H); 3.87 (d, $^3J_{HP}$ = 11.9, 6H); 6.77 (d, J = 11.2, 1H); 6.88 (d, J = 15.5, 1H); 7.09 (dd, J = 11.2, 15.5, 1H); 7.29-7.40 (m, 3H); 7.45-7.51 (m, 2H). ^{13}C-NMR δ 54.2 (d, $^2J_{CP}$ = 6.0, 2C); 61.5; 120.4; 123.3; 127.2 (2C); 128.8 (2C); 129.0; 136.4; 139.6; 151.8 (d, $^3J_{CP}$ = 4.8); 182.0 (d, $^2J_{CP}$ = 8.8). (3(E),5(E)-isomer): R_f = 0.30. Oil. IR ($CHCl_3$): 2120, 1635, 1600, 1580, 1280, 1250, 1050, 1030. ^{1}H-NMR δ 3.86 (d, $^3J_{HP}$ = 11.3, 6H); 3.89 (s, 3H); 5.92 (d, J = 11.1, 1H); 6.70 (d, J = 15.7, 1H); 7.21-7.56 (m, 5H); 7.71 (dd, J = 11.1, 15.7, 1H). ^{13}C-NMR δ 54.1 (d, $^2J_{CP}$ = 5.8, 2C); 55.1; 112.7; 123.4; 126.7 (2C); 127.9; 128.6 (2C); 135.9; 137.2; 150.4 (d, $^3J_{CP}$ = 3.8); 181.4 (d, $^2J_{CP}$ = 8.9). LRMS (EI) m/z (rel int) 340 (20), 308 (100), 276 (15). HRMS (EI) m/z calcd for $C_{15}H_{17}O_5P$ ($M^+ - N_2$) 308.0813, found 308.0810.

Dimethyl 1-diazo-4-(3'-furyl)-3-methoxy-2-oxo-3-butenylphosphonate (4d).

Yield (Z+E): 56%. (Z-isomer): R_f = 0.30. mp 88-90 °C. IR ($CHCl_3$): 2110, 1715, 1640, 1290, 1070, 1020. ^{1}H-NMR δ 3.75 (s, 3H); 3.88 (d, $^3J_{HP}$ = 12.0, 6H); 6.72 (d, J = 1.7, 1H); 6.80 (s, 1H); 7.46 (m, 1H); 7.79 (pt, J = 0.7, 1H). ^{13}C-NMR δ 54.2 (d, $^2J_{CP}$ = 6.1, 2C); 59.4; 110.4; 114.0; 118.7; 143.9; 145.1; 151.5 (d, $^3J_{CP}$ = 5.1); 182.4 (d, $^2J_{CP}$ = 8.7). (E-isomer): R_f = 0.20. Oil. IR (neat): 2120, 1725, 1640, 1270, 1220, 1070-

1020. ^{1}H-NMR δ 3.72 (s, 3H); 3.82 (d, $^3J_{HP}$ = 12.1, 6H); 5.75 (s, 1H); 6.45 (d, J = 1.6, 1H); 7.36 (pt, J = 1.7, 1H); 7.68 (d, J = 0.8, 1H). ^{13}C-NMR δ 53.9 (d, $^2J_{CP}$ = 5.7, 2C); 55.3; 98.8; 110.9; 118.1; 142.1; 142.9; 150.3 (d, $^3J_{CP}$ = 3.9); 182.5 (d, $^2J_{CP}$ = 8.9). Anal. Calcd. for $C_{11}H_{13}O_6N_2P$: C, 44.01; H, 4.36; N, 9.33; P, 10.32. Found: C, 43.59; H, 4.45; N, 8.68; P, 9.65.

Dimethyl 1-diazo-3-methoxy-4-methyl-2-oxo-4-phenyl-3(E)-butenylphosphonate (4e). Yield: 86%. Oil. IR (neat): 2120, 1630, 1280, 1210, 1070, 1030. ^{1}H-NMR δ 2.10 (s, 3H); 3.67 (d, $^3J_{HP}$ = 12.0, 6H); 3.69 (s, 3H); 7.22-7.38 (m, 5H). ^{13}C-NMR δ 17.6; 53.9 (d, $^2J_{CP}$ = 6.0, 2C); 58.6; 127.9; 128.1; 128.2 (2C); 128.4 (2C); 138.6; 146.6; 185.0 (d, $^2J_{CP}$ = 7.9); one resonance is missing. Anal. Calcd. for $C_{14}H_{17}N_2O_5P$: C, 51.86; H, 5.28; N, 8.64; P, 9.55. Found: C, 51.74; H, 5.28; N, 8.58; P, 9.37.

Dimethyl 1-diazo-3-methyl-2-oxo-4-phenyl-3(E)-butenylphosphonate (4g). Yield: 80%. Oil. IR (neat): 2110, 1720, 1620, 1260, 1040. ^{1}H-NMR δ 2.10 (d, J = 1.5, 3H); 3.82 (d, $^3J_{HP}$ = 11.9, 6H); 7.06 (q, J = 1.5, 1H); 7.31-7.38 (m,5H). ^{13}C-NMR δ 14.9; 54.1 (d, $^2J_{CP}$ = 5.9, 2C); 62.2 (d, $^1J_{CP}$ = 220.0); 128.4 (2C); 128.5; 129.3 (2C); 134.9; 135.0 (d, $^3J_{CP}$ = 2.0); 135.5; 189.9 (d, $^2J_{CP}$ = 9.6). Anal. Calcd. for $C_{13}H_{15}N_2O_4P$: C, 53.07; H, 5.14; N, 9.52; P, 10.53. Found: C, 53.06; H, 5.27; N, 9.33; P, 10.54.

Dimethyl 1-diazo-2-oxo-4-phenyl-3(Z)-butenylphosphonate (4f-Z).
Treatment of (Z)-ethyl cinnamate[24] following the general procedure for β-ketophosphonate and subsequent diazo transfer gave, after chromatography (ethyl acetate), **4f-Z**. Yield: 87%. Oil. IR (neat): 2115, 1635, 1265, 1200, 1025. ^{1}H-NMR δ 3.81 (d, $^3J_{HP}$ = 12.0, 6H); 6.28 (d, J = 12.6, 1H); 6.89 (d, J = 12.6, 1H); 7.27-7.38 (m, 3H); 7.55-7.58 (m, 2H). ^{13}C-NMR δ 53.7 (d, $^2J_{CP}$ = 5.6, 2C); 64.6 (d, $^1J_{CP}$ = 216.5); 123.9; 128.4 (2C); 129.5; 129.6 (2C); 134.7; 140.8; 184.7 (d, $^2J_{CP}$ = 8.5). Anal. Calcd. for $C_{12}H_{13}N_2O_4P$: C, 51.44; H, 4.68; N, 10.00; P, 11.05. Found: C, 51.23; H, 4.80; N, 10.25; P, 10.81.

Dimethyl 1-diazo-2-oxo-4-phenyl-3(E)-butenylphosphonate (4f-E).
Treatment of commercially available (E)-ethyl cinnamate following the general procedure for β-ketophosphonate and subsequent diazo transfer gave after chromatography (ethyl acetate) **4f-E**. Yield: 68%. IR (neat): 2120, 1645, 1265, 1200, 1025. ^{1}H-NMR δ 3.88 (d, $^3J_{HP}$ = 12.0, 6H); 7.12 (d, J = 15.5, 1H); 7.38-7.44 (m, 3H); 7.53-7.61 (m, 2H); 7.76 (d, J = 15.5, 1H). ^{13}C-NMR: 53.6 (d, $^2J_{CP}$ = 6.5, 2C); 120.8; 128.6 (2C); 129.0; 130.8 (2C); 134.3; 143.2; 181.8 (d, $^2J_{CP}$ = 13.1). Anal. Calcd. for $C_{12}H_{13}N_2O_4P$: C, 51.44; H, 4.68; N, 10.00; P, 11.05. Found: C, 51.61; H, 4.80; N, 10.02; P, 10.98.

Dimethyl 1-diazo-4-methoxy-2-oxo-4-phenyl-3-butenylphosphonate (4h).
Treatment of ester **2h** (Z-isomer) (1.23g, 6mmol) following the general procedure for β-ketophosphonate and subsequent diazo-transfer afforded a crude product containing only the Z-isomer of **4h** as judged by TLC. Isomerisation occured during the purification by flash chromatography (ethyl acetate) which gave 1.48g (80%) of **4h** as a mixture of two isomers (Z/E: 16/84). (Z-isomer): R_f = 0.45. mp 51-53°C. IR (CCl_4): 2105, 1620, 1270, 1050, 1025. ^{1}H-NMR δ 3.81 (d, $^3J_{HP}$ = 12.0, 6H); 3.91 (s, 3H); 6.06 (s, 1H); 7.41-7.46 (m, 2H); 7.57-7.62 (m, 3H). ^{13}C-NMR δ 53.8 (d, $^2J_{CP}$ = 5.3, 2C); 61.9; 102.5; 128.1 (2C); 129.0 (2C); 131.1; 135.6; 168.2; 180.2 (d, $^2J_{CP}$ = 6.1). (E-isomer): R_f = 0.40. Oil. IR (CCl_4): 2105, 1640, 1270, 1050, 1030. ^{1}H-NMR δ 3.84 (s, 3H); 3.86 (d, $^3J_{HP}$ = 11.8, 6H); 5.96 (s, 1H); 7.37-7.48 (m, 5H). ^{13}C-NMR δ 53.5 (d, $^2J_{CP}$ = 5.4, 2C); 56.6; 97.0 (d, $^3J_{CP}$ = 1.8); 127.8 (2C); 128.7 (2C); 130.1; 135.0; 170.8; 180.7 (d, $^2J_{CP}$ = 6.3). Anal. Calcd. for $C_{13}H_{15}O_5N_2P$: C, 50.33; H, 4.87; N, 9.03; P, 9.98. Found: C, 50.15; H, 4.98; N, 9.24; P, 9.79.

SYNTHESIS OF β-KETO SULFONE (12) AND α-DIAZO-β-KETO COMPOUNDS (13)

(3-Methoxy-2-oxo-4-phenyl-3-butenyl) phenyl sulfone (12)

To a stirred solution of methylphenylsulfone (270 mg, 1.7 mmol) in anhydrous THF (20 ml), cooled at -78°C, was added dropwise a solution of *n*-butyllithium 1.6M in hexanes (2 ml). After stirring for 45 mn at -78 °C, a solution of methylester **2a** (E/Z, 74:26) (307 mg, 1.6 mmol) in THF (20 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. A satured ammonium chloride solution (10 ml) was added. The aqueous phase was extracted with ethyl acetate (2 x 25 ml) and the combined organic extracts were dried, filtered and concentrated. Purification of the crude oil by flash chromatography (pentane/ethyl acetate 80:20) afforded 440mg (87%) of **12** (E/Z, 74:26). (Z-isomer): R_f = 0.25. mp 116-118°C. IR (CCl_4): 1680, 1665, 1605, 1330, 1160. ^{1}H-NMR δ 3.68 (s, 3H); 4.58 (s, 2H); 6.94 (s, 1H); 7.34-7.42 (m, 3H); 7.51-7.73 (m, 5H); 7.92-7.97 (m, 2H). ^{13}C-NMR δ 59.4; 64.3; 127.0; 128.5 (2C); 128.7 (2C); 129.2 (2C); 130.0; 130.7 (2C); 132.6; 134.2; 139.0; 152.3; 186.5. (E-isomer): R_f = 0.20. mp 105-108°C. IR (neat): 1720, 1700, 1605,1320, 1150. ^{1}H-NMR δ 3.59 (s, 3H); 4.37 (s, 2H); 6.05 (s, 1H); 7.20-7.45 (m, 5H); 7.49-7.66 (m, 3H); 7.81-7.95 (m, 2H). ^{13}C-NMR δ 56.4; 65.0; 112.2; 128.4; 129.0 (2C); 129.1 (2C); 129.8 (2C); 129.9 (2C); 134.4; 134.7; 139.9; 151.7; 187.1. Anal. Calcd. for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10; S, 10.13. Found: C, 64.76; H, 5.01; S, 10.09.

1-Diazo-3-methoxy-4-phenyl-3-butene-2-one (13a).

A solution of ester **2a** (E/Z, 74:26) (288 mg, 1.5 mmol) in 1M methanolic potassium hydroxyde (10 ml) was stirred for 24 h at room temperature. The reaction mixture was acidified to pH 2 with Dowex W50X8 H^+. After filtration and evaporation of the solvent in vacuo, anhydrous toluene (10 ml) was added and rotoevaporated. Anhydrous toluene (10 ml) was added to the crude carboxylic acid and then freshly distilled oxalyl chloride (1.3 ml, 15 mmol). The mixture was stirred under reflux for 6 h. After evaporation of toluene, the crude acyl chloride **11** was dissolved in anhydrous diethyl ether (5 ml) and the solution was added dropwise to an ethereal solution of diazomethane (prepared from 3.2 g of N-methyl-N-nitroso *p*-toluenesulfonamide (15 mmol)) cooled in a water ice bath. After 1.5 h at 0 °C, the solvent was evaporated, diethyl ether (70 ml) was added and evaporated to ensure a total removal of diazomethane. The residue was purified by flash chromatography (pentane/acetone 95:5) to afford 215 mg (71%) of **13a** (E/Z, 74:26). (Z-isomer): R_f = 0.40. mp 76-78°C. IR (CCl_4): 2100, 1645, 1605. ^{1}H-NMR δ 3.67 (s, 3H); 5.87 (s, 1H); 6.89 (s, 1H); 7.33-7.37 (m, 3H); 7.67-7.71 (m, 2H). ^{13}C-NMR δ 54.2; 59.5; 119.3; 128.7 (2C); 129.0; 130.3 (2C); 133.1; 152.0; 184.5. (E-isomer): R_f = 0.30. Oil. IR (CCl_4): 2110, 1670, 1605. ^{1}H-NMR δ 3.74 (s, 3H); 5.51 (s, 1H); 6.01 (s, 1H); 7.23-7.32 (m, 5H). ^{13}C-NMR: 55.6; 56.6; 107.7; 126.9 (2C); 128.0 (2C); 129.1; 134.3; 151.5; 184.1. Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85; O, 15.82. Found C, 65.27; H, 5.17; N, 13.93; O, 15.60.

Ethyl (2-diazo-4-methoxy-3-oxo-5-phenyl)-4-pentenoate (13b).

Ethyl diazoacetate (570 mg, 5 mmol) was added to the crude acyl chloride **11** (1mmol) (prepared as described for **13a**). The mixture was kept at room temperature for a week. The residue was purified by flash chromatography (pentane/diethyl ether 90:10) to afford 222mg (81%) of diazoester **13b** (E/Z, 74:26). (Z-isomer): R_f = 0.25. Oil. IR (neat): 2120, 1720, 1680, 1610. ^{1}H-NMR δ 1.33 (t, 3H); 3.74 (s, 3H); 4.33 (q, 2H); 6.60 (s, 1H); 7.27-7.40 (m, 3H); 7.67-7.71 (m, 2H). ^{13}C-NMR δ 14.3; 58.9; 61.9; 73.0; 121.2; 128.6 (2C); 129.0; 130.2 (2C); 133.1; 151.7; 161.4; 181.3. (E-isomer): R_f = 0.15. Oil. IR (neat): 2115, 1720, 1690, 1630. ^{1}H-NMR δ 1.26 (t,

3H); 3.76 (s, 3H); 4.23 (q, 2H); 5.92 (s, 1H); 7.17-7.29 (m,5H). ^{13}C-NMR δ 14.3; 56.0; 61.7; 78.4; 104.8; 126.8; 128.3 (2C); 128.4 (2C); 134.0; 152.3; 160.0; 183.0. Anal Calcd. for $C_{14}H_{14}O_4N_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.00; H, 5.18; N, 10.06.

(1-Diazo-3-methoxy-2-oxo-4-phenyl-3-butenyl) phenyl sulfone (13c)

Treatment of **12** (380 mg, 1.2 mmol) with tosyl azide (295 mg, 1.5 mmol) and potassium carbonate (207 mg, 1.5 mmol) in acetonitrile as described in the general procedure for the diazo transfer of β-ketophosphonates afforded, after flash chromatography (pentane/ethyl acetate 80:20), 349mg (85%) of **13c** (E/Z, 74:26). (Z-isomer): R_f = 0.30. mp 83-86°C. IR (CCl_4): 2110, 1655, 1610, 1350, 1160. ^{1}H-NMR δ 3.64 (s, 3H); 6.80 (s, 1H); 7.26-7.35 (m, 3H); 7.56-7.76 (m, 5H); 8.09-8.13 (m, 2H). ^{13}C-NMR δ 59.4; 82.1; 122.5; 128.3 (2C); 128.8 (2C); 129.1 (2C); 129.7; 130.4 (2C); 132.2; 134.1; 141.4; 151.2; 178.6. (E-isomer): R_f = 0.25. mp 139-141°C. IR ($CHCl_3$): 2110, 1720, 1650, 1610, 1340, 1150. ^{1}H-NMR δ 3.67 (s, 3H); 5.98 (s, 1H); 6.97-7.25 (m, 5H); 7.25-7.49 (m, 3H); 7.96-8.00 (m, 2H). ^{13}C-NMR δ 55.8; 84.6; 107.8; 127.6; 128.1 (2C); 128.3 (2C); 128.5 (2C); 129.1 (2C); 132.7; 134.1; 141.0; 150.5; 178.6. LRMS (EI) m/z (rel int) 342 (2), 314 (100), 250 (7), 173 (16), 157 (39), 145 (58). HRMS (EI) m/z calcd. for $C_{17}H_{14}O_4N_2S$ (M^+) 342.0674, found 342.0670.

SYNTHESIS OF PHENOLIC DERIVATIVES (7), (14) AND (15)

Compounds (7a-e,f,h) and (14b,c).

A solution of diazo compound **4** or **13** (1.5 mmol) in anhydrous toluene (50 ml) was refluxed for a time t, until the disappearance of the diazo was complete as judged by TLC. The solvent was then evaporated in vacuo and the residue was purified by flash chromatography. For ^{13}C-NMR data, see Table-2.

Dimethyl 1-hydroxy-3-methoxy-2-naphthalenephosphonate (7a).

From diazo **4a-E** or **4a-Z** (465 mg, t = 3 h), we obtained after flash chromatography (dichloromethane/diethyl ether 80:20), respectively 315 mg (75%) or 303 mg (72%) of **7a**. mp 92-94°C. IR (CCl_4): 3500-2500, 1620, 1595, 1580, 1500, 1460, 1430, 1315, 1290, 1190, 1090, 1030, 900, 840. ^{1}H-NMR (300 MHz) δ 3.83 (d, $^3J_{HP}$ = 11.9, 6H); 3.92 (s, 3H); 6.62 (d, $^4J_{HP}$ = 5.7, 1H); 7.34 (ddd, J = 1.2, 6.7, 8.3, 1H); 7.52 (ddd, J = 1.2, 6.7, 8.2, 1H); 7.62 (dd, J = 1.2, 8.2, 1H); 8.28 (dd, J = 1.2, 8.3, 1H); 12.26 (d, $^4J_{HP}$ = 1.3, 1H). Anal. Calcd. for $C_{13}H_{15}O_5P$: C, 55.32; H, 5.36; P, 10.97. Found: C, 55.18; H, 5.35; P, 11.08.

Dimethyl 4-hydroxy-6-methoxy-5-benzo[b]furanphosphonate (7b).

From diazo **4b** (E/Z, 60:40, 450 mg, t = 1.5 h), we obtained after flash chromatography (diethyl ether) 310mg (76%) of **7b**. mp 63-65°C. IR (CCl_4): 3500-2500, 1620, 1590, 1540, 1455, 1420, 1380, 1290, 1190, 1170, 1100, 1070, 1030, 840, 790. ^{1}H-NMR (300 MHz) δ 3.75 (d, $^3J_{HP}$ = 11.9, 6H); 3.88 (s, 3H); 6.58 (dd, J = 0.7, $^4J_{HP}$ = 4.7, 1H); 6.86 (dd, J = 0.7, 2.2, 1H); 7.46 (d, J = 2.2, 1H); 11.86 (d, $^4J_{HP}$ = 1.4, 1H). Anal. Calcd. for $C_{11}H_{13}O_6P$: C, 48.54; H, 4.81; P, 11.38. Found: C, 48.66; H, 4.87; P, 11.21.

Dimethyl 2-hydroxy-4-methoxy-3-biphenylylphosphonate (7c).

From diazo **4c** (E/Z, 64:36, 500 mg, t = 3 h), we obtained after flash chromatography (diethyl ether) 305 mg (66%) of **7c**. Oil. IR (CCl_4): 3500-2500, 1610, 1580, 1450, 1410, 1290, 1190, 1090, 1030, 840, 780, 700. ^{1}H-NMR δ 3.79 (d, $^3J_{HP}$ = 11.8, 6H); 3.88 (s, 3H); 6.48 (dd, $^4J_{HP}$ = 6.0, J = 8.6, 1H); 7.25-7.56 (m, 6H); 11.61 (s, 1H). Anal. Calcd. for $C_{15}H_{17}O_5P$: C, 58.44; H, 5.56; O, 25.95; P, 10.05. Found: C, 58.51; H, 5.47; P, 9.99.

Dimethyl 7-hydroxy-5-methoxy-6-benzo[b]furanphosphonate (7d).

From diazo **4d** (E/Z, 57:43, 450 mg, t = 1.5 h), we obtained after flash chromatography (diethyl ether) 335mg (82%) of **7d**. mp 62-64°C. IR (CCl_4): 3500-2500, 1635, 1580, 1540, 1460,1380, 1290, 1250, 1200, 1100, 1035, 1000, 980, 890, 850. ^{1}H-NMR (300 MHz) δ 3.77 (d, $^3J_{HP}$ = 11.9, 6H); 3.88 (s, 3H); 6.55 (d, $^4J_{HP}$ = 5.6, 1H); 6.70 (d, J = 2.0, 1H); 7.69 (d, J = 2.0, 1H); 11.78 (d, $^4J_{HP}$ = 1.3, 1H). Anal. Calcd. for $C_{11}H_{13}O_6P$: C, 48.54; H, 4.81; P, 11.38. Found: C, 48.59; H, 4.65; P, 11.36.

Dimethyl 1-hydroxy-3-methoxy-4-methyl-2-naphthalenephosphonate (7e).

From diazo **4e-E** (485 mg, t = 1 h), we obtained after flash chromatography (diethyl ether) 395mg (89%) of **7e**. mp 56-58 °C. IR (CCl_4): 3500-2500, 1620, 1590, 1500, 1460, 1425, 1400, 1370, 1310, 1275, 1170, 1115, 1030, 930, 850. ^{1}H-NMR (300 MHz) δ 2.47 (s, 3H); 3.82 (s, 3H); 3.82 (d, $^3J_{HP}$ = 11,7, 6H); 7.43 (ddd, J = 1.1, 7.2, 8.4, 1H); 7.61 (ddd, J = 1.1, 7.2, 8.4, 1H); 7.86 (dd, J = 1.1, 8.4, 1H); 8.36 (dd, J = 1.1, 8.4, 1H); 11.96 (d, $^4J_{HP}$ = 1.3, 1H). Anal. Calcd. for $C_{14}H_{17}O_5P$: C, 56.76; H, 5.78; P, 10.45. Found: C, 56.98; H, 5.83; P, 10.53.

Dimethyl 1-hydroxy-2-naphthalenephosphonate (7f).

From diazo **4f-Z**(420 mg, t = 4 h), we obtained after chromatography (ethyl acetate) 285mg (75%) of **7f**. mp = 38-39 °C. IR (neat): 3500-2500, 1625, 1590, 1565, 1495, 1455, 1395, 1220, 1180, 1050, 1030, 890, 865, 840, 805. ^{1}H-NMR (300 MHz) δ 3.77 (d, $^3J_{HP}$ = 11.5, 6H); 7.30 (dd, J = 8.5, $^3J_{HP}$ = 12.1, 1H); 7.39 (dd, $^4J_{HP}$ = 3.4, J = 8.5, 1H); 7.56 (m, 1H); 7.63 (m, 1H); 7.81 (br d, J = 8.3, 1H); 8.41 (br d, J = 8.2, 1H); 11.36 (d, J = 1.1, 1 H). Anal. Calcd. for $C_{12}H_{13}O_4P$: C, 57.15; H, 5.20; P, 12.28. Found: C, 57.50; H, 5.48; P, 12.18.

Dimethyl 1-hydroxy-4-methoxy-2-naphthalenephosphonate (7h).

From diazo **4h-E** (465 mg, t = 1.5 h), we obtained after flash chromatography (ethyl acetate) 280 mg (66%) of **7h**. Oil. IR (CCl_4): 3500-2500, 1620, 1590, 1570, 1440, 1390, 1350, 1300, 1160, 1110, 1040, 980, 880, 830. ^{1}H-NMR (300 MHz) δ 3.70 (d, $^3J_{HP}$ = 11.5, 6H); 3.86 (s, 3H); 6.41 (d, $^3J_{HP}$ = 13.7, 1H); 7.49 (ptd, J = 1.3, 7.0, 7.9, 1H); 7.55 (ptd, J = 1.3, 7.0, 7.9, 1H); 8.12 (dd, J = 1.3, 7.9, 1H); 8.27 (dd, J = 1.3, 7.9, 1H); 10.65 (d, $^4J_{HP}$ = 0.9, 1H). Anal. Calcd. for $C_{13}H_{15}O_5P$: C, 55.32; H, 5.36; P, 10.97. Found: C, 55.33; H, 5.46; P, 10.80.

Ethyl 1-hydroxy-3-methoxy-2-naphthalenecarboxylate (14b).

From diazo **13b** (E/Z, 74:26, 410 mg, t = 5 h), we obtained after flash chromatography (pentane/diethyl ether 95:5) 260 mg (70%) of **14b**. mp = 46-48 °C. IR (CCl_4): 3500-2500, 1635, 1595, 1460, 1425, 1370, 1325, 1295, 1260, 1195, 1160, 1110, 1020, 865, 670. ^{1}H-NMR δ 1.42 (t, 3H); 1.44 (q, 2H); 3.89 (s, 3H); 6.59 (s, 1H); 7.31 (ptd, J = 1.5, 8.3, 1H); 7.45-7.59 (m, 2H); 8.28 (d, J = 8.3, 1H); 12.88 (s, 1H). Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.52; H, 5.67.

(1-Hydroxy-3-methoxy-2-naphthalenyl) phenyl sulfone (14c)

From diazo **13c** (E/Z, 74:26, 510 mg, t = 5 h), we obtained after flash chromatography (pentane/ethyl acetate 90:10) 365 mg (78%) of **14c**. mp 160-162 °C. IR (CCl_4): 3500-2500, 1630, 1605, 1580, 1505, 1410, 1315, 1300, 1270, 1200, 1170, 1130, 1090, 1025, 690, 650, 630. ^{1}H-NMR δ 3.69 (s, 3H); 6.55 (s, 1H); 7.39 (ddd, J = 2.3, 5.9, 8.3, 1H); 7.48-7.62 (m,5H); 7.97-8.00 (m, 2 H); 8.32 (dd, J = 0.7, 8.3, 1H); 11.52 (s, 1H). Anal. Calcd. for $C_{17}H_{14}O_4S$: C, 64.95; H, 4.49; S, 10.20. Found: C, 65.20; H, 4.34; S, 10.19.

3-Methoxy-1-naphthol (14a).

A solution of the diazoketone **13a** (E/Z, 74:26, 150 mg, 0.75 mmol) in xylene (20 ml) was added dropwise, over a period of 1 h, to refluxing xylene (10 ml).[31] The reaction mixture was then refluxed overnight. Evaporation of the solvent and purification by flash chromatography (pentane/acetone 80:20) gave 100 mg (77%) of **14a**. Reddish oil. IR (CCl_4): 3500-2500, 1630, 1600, 1590, 1510, 1460, 1410, 1350, 1295, 1240, 1230, 1200, 1160, 1150, 1140, 1080, 1040, 1020, 955, 890, 650. ^{1}H-NMR δ 3.86 (s, 3H); 6.30 (bs, 1H); 6.53 (d, J = 2.2, 1H); 6.74 (d, J = 2.2, 1H); 7.30 (ptd, J = 1.2, 7.0; 1H), 7.42 (ptd, J = 1.2, 7.0, 1H); 7.67 (d, J = 8.2, 1H); 8.10 (d, J = 8.0, 1H). Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 74.98; H, 6.27.

Dimethyl 2-hydroxy-3-methoxy-1-naphthalenephosphonate (15).

A solution of diazophosphonate **4a-E** (930 mg, 3 mmol) in anhydrous fluorobenzene (80 ml) was refluxed with stirring for 1.5 h in the presence of rhodium acetate (55 mg, 4 % mol). The solvent was evaporated and the residue was purified by flash chromatography (ethyl acetate) to afford 235 mg (28%) of **7a** and 413 mg (48%) of **15**. Compound **7a**: R_f = 0.65. Compound **15**: R_f = 0.55. mp 114-116 °C. IR (CCl_4): 3500-2500, 1620, 1600, 1580, 1500, 1460, 1425, 1305, 1280, 1250, 1195, 1100, 1050, 1020, 890. ^{1}H-NMR (300 MHz) δ 3.75 (d, $^3J_{HP}$ = 11.8, 6H); 4.01 (s, 3H); 7.27 (s, 1H); 7.38 (m, 2H); 7.68 (m, 1H); 7.93 (br d, J = 8.0, 1H); 12.15 (dd, J = 0.7, 1.3, 1H). Anal. Calcd. for $C_{13}H_{15}O_5P$: C, 55.32; H, 5.36; P, 10.97. Found: C, 55.38; H, 5.36; P, 10.94.

SYNTHESIS OF PHOSPHONATE ESTERS (8)

Methyl 2-(dimethoxyphosphinyl)-4-phenyl-3(E)-butenoate (8f).

A solution of diazophosphonate **4f-E** (280 mg, 1 mmol) in anhydrous benzene (20 ml) was refluxed for 0.5 h in the presence of rhodium acetate (10 mg, 2.2 % mol). After quenching with anhydrous methanol (3 ml), the solvent was evaporated. The crude green residue was dissolved in ethyl acetate (100 ml) and washed with a 0.5 M aqueous hydrochloric solution (10 ml). The organic extracts were washed with a saturated sodium hydrogenocarbonate solution (10 ml), dried and rotoevaporated. Purification of the residue by flash chromatography (ethyl acetate) afforded 245 mg (87%) of **8f**. Oil. IR (neat): 1730, 1255, 1050, 1030. ^{1}H-NMR δ 3.80 (s, 3H); 3.81 (d, $^3J_{HP}$ = 11.0, 3H); 3.83 (d, $^3J_{HP}$ = 11.0, 3H); 3.94 (dd, J = 9.5, $^2J_{HP}$ = 24.3, 1H); 6.35 (ddd, $^3J_{HP}$ = 6.3, J = 9.5, 15.9, 1H); 6.61 (dd, J = 4.9, 15.9, 1H); 7.22-7.44 (m, 5H). ^{13}C-NMR δ 49.9 (d, $^1J_{CP}$ = 131.9); 52.9; 53.7 (d, $^2J_{CP}$ = 7.0); 54.1 (d, $^2J_{CP}$ = 6.7); 118.3 (d, $^2J_{CP}$ = 12.2); 126.6; 128.2 (2C); 128.6 (2C); 135.4 (d, $^3J_{CP}$ = 13.0); 136.1 (d, $^4J_{CP}$ = 3.5); 167.9 (d, $^2J_{CP}$ = 5.5). Anal. Calcd. for $C_{13}H_{17}O_5P$: C, 54.93; H, 6.03; P, 10.90. Found: C, 54.71; H, 6.18; P, 10.74.

Methyl 2-(dimethoxyphosphinyl)-3-methyl-4-phenyl-3(E)-butenoate (8g).

From diazoketophosphonate **4g-E** (295 mg, 1 mmol) following the procedure described for **8f**, but with a refluxing time of 2.5 h, we obtained after purification by chromatography (ethyl acetate) 216 mg (72%) of **8g**. Oil. IR (CCl_4): 1740, 1260, 1060, 1030. ^{1}H-NMR δ 2.00 (dd, J = 1.3, $^4J_{HP}$ = 3.0, 3H); 3.71 (s, 3H); 3.75 (d, $^3J_{HP}$ = 10.9, 3H); 3.76 (d, $^3J_{HP}$ = 11.0, 3H); 3.80 (d, $^2J_{HP}$ = 23.8, 1H); 6.56 (d, J = 4.5, 1H); 7.15-7.26 (m, 5H). ^{13}C-NMR δ 17.7 (d, $^3J_{CP}$ = 3.1); 52.7; 53.6 (d, $^2J_{CP}$ = 7.0); 53.8 (d, $^2J_{CP}$ = 6.7); 54.7 (d, $^1J_{CP}$ = 137.9); 126.9; 128.1 (2C); 128.5 (d, $^2J_{CP}$ = 10.2); 128.9 (d, $^5J_{CP}$ = 2.4, 2C); 131.8 (d, $^3J_{CP}$ = 11.8); 137.0

(d, $^4J_{CP}$ = 2.9); 168.0 (d, $^2J_{CP}$ = 3.4). Anal. Calcd. for $C_{14}H_{19}O_5P$: C, 56.38; H, 6.42; P, 10.38. Found: C, 55.93; H, 6.49; P, 9.59

Methyl 2-(dimethoxyphosphinyl)-4-methoxy-4-phenyl-3-(Z)-butenoate (8h).
A solution of diazo compound **4h-Z** (100 mg, 0.3 mmol) in anhydrous toluene (25 ml) was refluxed for 3 h. The solvent was rotoevaporated and the residue was purified by flash chromatography (ethyl acetate) to afford 62 mg (64%) of **8h**. Oil. IR (neat): 1700, 1615, 1250, 1060, 1030. ^{1}H-NMR δ 3.54 (s, 3H); 3.79 (s, 3H); 3.83 (d, $^3J_{HP}$ = 11.5, 6H); 4.53 (dd, J = 10.2, $^2J_{HP}$ = 24.2, 1H); 5.43 (dd, $^3J_{HP}$ = 6.4, J = 10.2, 1H); 7.43-7.49 (m, 5H). ^{13}C-NMR δ 43.0 (d, $^1J_{CP}$ = 133.5); 52.9; 53.6 (d, $^2J_{CP}$ = 6.9); 53.9 (d, $^2J_{CP}$ = 6.6); 58.5 (d, $^4J_{CP}$ = 2.5); 102.3 (d, $^2J_{CP}$ = 11.3); 126.8 (2C); 128.5 (2C); 128.9; 134.3; 158.1 (d, $^2J_{CP}$ = 12.9); 168.3. Anal. Calcd. for $C_{14}H_{19}O_6P$: C, 53.51; H, 6.09; P, 9.86. Found: C, 53.48; H, 6.00; P, 9.32.

Dimethyl 4-hydroxy-6-phenyl-5-piperidinyl-3-pyridazinephosphonate (10).
To a stirred suspension of **3i** (400 mg, 1.18 mmol) and potassium carbonate (210 mg, 1.5 mmol) in acetonitrile (20 ml) was added a solution of tosyl azide (300 mg, 1.5mmol) in acetonitrile (10 ml) The reaction mixture was stirred at room temperature overnight and hydrolysed with a saturated ammonium chloride solution (10 ml). The aqueous phase was extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were dried, filtered and evaporated in vacuo. Purification by flash chromatography (dichloromethane/methanol 95:5) afforded 146 mg (34%) of **10**. R_f = 0.25. Oil. IR ($CHCl_3$): 3600-2500, 1580, 1550, 1520, 1440, 1380, 1040, 970. ^{1}H-NMR δ 1.40 (bs, 6H); 2.72 (m, 4H); 3.75 (d, $^3J_{HP}$ = 11.2, 6H); 7.40-7.43 (m, 3H); 7.53-7.55 (m, 2H); 13.2 (bs, 1H). ^{13}C-NMR δ 24.1; 26.2 (2C); 51.1 (2C); 53.8 (d, $^2J_{CP}$ = 5.7, 2C); 128.4 (2C); 129.2 (2C); 129.6; 131.5; 141.4 (d, $^3J_{CP}$ = 9.7); 143.7; 144.2 (d, $^1J_{CP}$ = 221.0); 169.8 (d, $^2J_{CP}$ = 14.8). LRMS (EI) m/z (rel int) 363 (100), 348 (18), 268 (78), 240 (16), 84 (32). HRMS (EI) m/e Calcd for $C_{17}H_{22}N_3O_4P$ (M^+) 363.1347, found 363.1350.

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18. For generality's sake the geometric isomers of compounds **2**, **3** and **4** will be designed as *cis* or *trans* if the unsaturated moiety (β-positioned for **2** or δ-positioned for **3** and **4**) and the carbonyl group are "cis"or "trans" with respect to the carbon-carbon double bond.
19. The configuration of the α,β carbon-carbon double bond in compounds **2a-d** was established by the chemical shift of the β-proton: 5.96-6.10 ppm for the *cis* isomer and 6.88-7.00 for the *trans* isomer (see ref. 12a). The *cis* configuration of compound **2e** was established by the chemical shifts of its aromatic protons (7.12-7.36) which appeared similar to those of **2a-*cis*** (7.15-7.38) and different from those of **2a-*trans*** (7.25-7.41 and 7.69-7.77). The configuration of **2g-*trans*** was established on the basis of the chemical shift.of its vinylic proton.
20. Pure analytical samples for NMR spectroscopy of each stereoisomer of compounds **2**, **3a** and **4** were obtained by column chromatography. In the case of **2e** only the *cis* isomer was obtained. In the case of **2g** the *cis* isomer was formed in a very small amount and was not characterized; the sequence was then

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34. The Z/E ratio was determined from the ^{1}H-NMR spectra of crude products. When compounds **3** and **4** were prepared from a mixture of steroisomers of compounds **2**, we observed no significative modification in this ratio, excepted for **4h** after purification (see text).
35. Caution! This compound is potentially explosive.

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