A General Approach to 3-Phosphorylmethyl Cycloalkenones by Intramolecular Horner–Wittig Reaction of Bis-β-ketophosphonates[1]

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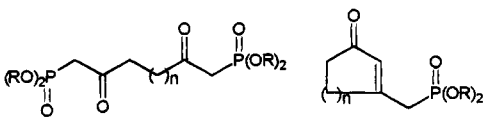
The reaction of dicarboxylic acid diesters with lithiomethylphosphonates was found to give bis-β-keto phosphonates **1** $[(RO)_2P(O)CH_2C(O)]_2(CH_2)_n$ (n = 2, 3, 4), a new class of compounds. Their cyclization under basic conditions provides an easy access to five-, six- and seven-membered 3-phosphorylmethyl cycloalkenones **2**. The cyclization of 1,6-bis(dialkoxyphosphoryl)hexan-2,5-dione (**1a,d**) was found to be bidirectional in course and a competition between the intramolecular Horner–Wittig and Knoevenagel reaction was observed. It was demonstrated that the latter reaction is reversible which allows conversion of the Knoevenagel reaction product into the Horner–Wittig reaction product (for example **5b** into **2d**). Two efficient methods for the synthesis of 2- and 3-functionalized cycloalkenones **6** and **7** involving alkylation and olefination of the cycloalkenones **2** anion were devised.

Introduction

Development of new synthetic methods leading to the formation of five- and six-membered rings is currently one of the most focal points in organic synthesis. Among carbocyclic compounds, cyclopentenones are of considerable interest due to the presence of this structural unit in many natural products with outstanding biological activity as well as to their usefulness for further transformations.[2] In the course of our studies directed toward the synthesis of cyclopentanoid antibiotics,[3] the cyclopentenone skeleton was formed by base-catalyzed cyclization of 1,4-dicarbonyl compounds[4] or by carbenoid cyclization of α-diazo-β-keto phosphonates.[5] The Horner–Wittig reaction was applied for efficient introduction of the exocyclic methylene moiety present in the structure of methylenomycins and sarkomycin.

Bearing in mind that the intramolecular Horner–Wittig reaction of β,ω-diketo phosphonates has been applied for the ring closure leading to cyclopentenones[6] and searching for new possibilities of modification of simple cyclopentanoid precursors, we turned our attention on bis-β-keto phosphonates **1**. This class of compounds is practically unknown[7,8] and to the best of our knowledge they have never been isolated and characterized. The intramolecular Horner–Wittig reaction of bis-β-ketophosphonates **1** should provide a general approach to the cycloalkenones **2** containing the 3-phosphorylmethylene moiety that can be utilized for further structural modifications.



1, n=1,2,3 **2**, n=1,2,3

We report here the synthesis and characterization of bis-β-keto phosphonates **1**, their cyclization to the cycloalkenones **2** and some reactions of the anions derived from the latter compounds.

Results and Discussion

We found that bis-β-keto phosphonates **1** may be easily prepared by treatment of dicarboxylic acid esters **3** with 4 equiv of the lithium salts of dialkyl methanephosphonates **4** at −78 °C. As in the case of the synthesis of simple β-keto phosphonates from carboxylic acid esters,[9] 2 mol excess of lithio phosphonates is necessary for deprotonation of the bis-β-keto phosphonates **1** formed (see Scheme 1). It is important to point out that the alkoxy groups in both reaction partners **3** and **4** must be the same to avoid the alkoxy exchange at the carbonyl and phosphoryl group which takes place under basic

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(6) (a) Henrick, C. A.; Böhme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926. (b) Piers, E.; Abeysekera, B.; Scheffer, J. R. *Tetrahedron Lett.* **1979**, *20*, 3279. (c) Altenbach, H.-J.; Korff, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 371. (d) Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synth. Commun.* **1975**, *5*, 1. (e) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. (f) Altenbach, H.-J.; Holzapfel, W.; Smerat, G.; Finkler, S. H. *Tetrahedron Lett.* **1985**, *26*, 6329. (g) Begley, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron Lett.* **1981**, *22*, 257. (h) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325. (i) Lim, M.-J.; Marquez, V. E. *Tetrahedron Lett.* **1983**, *24*, 4051, 5559.

(7) The reaction between the *tert*-butyldimethylsilyl-protected diethyl (−)-tartrate and diethyl lithiomethylphosphonate described recently by Altenbach and Holzapfel[8] proceeds undoubtedly via the corresponding bis-β-keto phosphonate that, however, under the reaction conditions applied by the above-mentioned authors underwent a fast cyclization to a mixture of the Horner–Wittig and Knoevenagel reaction products.

(8) Altenbach, H.-J.; Halzapfel, W. *Angew Chem., Int. Ed. Engl.* **1990**, *29*, 67.

(9) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5652. *Ibid.* **1968**, *90*, 6816.

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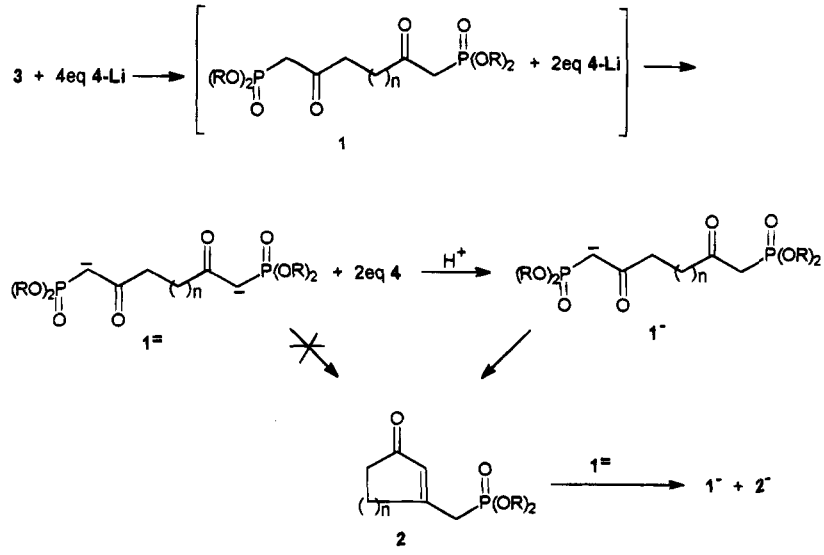
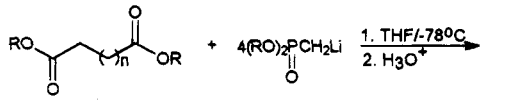
Scheme 1



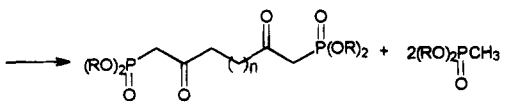
reaction conditions and leads to a hardly separable mixture of products.



3 a, R=Me, n=1
b, R=Me, n=2
c, R=Me, n=3
d, R=Et, n=1
e, R=Et, n=2
f, R=Et, n=3

4-Li a, R=Me
b, R=Et

(eq. 1)

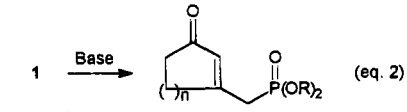


1 a, R=Me, n=1
b, R=Me, n=2
c, R=Me, n=3
d, R=Et, n=1
e, R=Et, n=2
f, R=Et, n=3

In order to obtain tetramethyl bis-β-keto phosphonates **1** (R = Me) as the only reaction products, the reaction mixtures, after stirring for a 0.5 h, should be quenched at −78 °C and worked up. Under these conditions the subsequent intramolecular Horner−Wittig reaction is supressed and the desired bis-β-keto phosphonates **1a−c** are obtained in almost quantitative yields (>95%, the ^{31}P NMR assay). The crude products are spectrally pure and may be used for further reactions without purification. Analytically and spectrally pure **1a−f** are obtained by flash chromatography in 50−67%. However, when the reaction mixtures are allowed to stand overnight at room temperature, the reaction course is dependent on the structure of dimethyl dicarboxylate **3**. Dimethyl succinate (**3a**) gives two products: the corresponding bis-β-keto phosphonate **1a** in 60% yield and the cyclopentenone **2a** which is formed in 40% as a result of the subsequent intramolecular Horner−Wittig reaction of **1a**. Dimethyl glutarate (**3b**) affords under these conditions only the corresponding cyclohexenone **2b** (90% yield) while the adipic ester **3c** yields the bis-β-keto phosphonate **1c** exclusively. In contrast to the methyl esters **3a**, diethyl dicarboxylates **3b** react with lithiated diethyl methanephosphonate (**4b**) to form the corresponding bis-β-keto phosphonates **1d−f** as the only reaction products irrespective of the reaction time.

The formation of the cyclic products **2** in the reaction under discussion may be explained by assuming that the reaction mixture contains trace amounts of the phosphonate monoanion derived from **1** which, in contrast to the corresponding bis-β-keto phosphonate dianion 1^{2-} resulting from the condensation of **3** with **4-Li**, can undergo the intramolecular Horner−Wittig reaction to form the cycloalkenone **2**. As the latter possesses an acidic methylene group α to phosphorus, it can protonate the dianion 1^{2-}. In this way the whole primary reaction product **1** can be transformed into a cycloalkenone **2**.

Having in our hands bis-β-keto phosphonates **1a-f** we could study their cyclization to the corresponding cycloalkenones **2** via the intramolecular Horner−Wittig reaction.

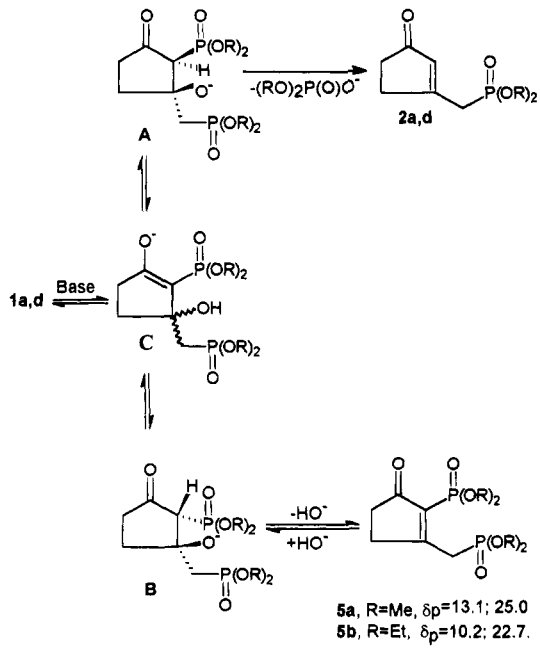


n=1,2,3

2 a, R=Me, n=1
b, R=Me, n=2
c, R=Me, n=3
d, R=Et, n=1
e, R=Et, n=2

Thus, the cyclohexenone **2b** was easily formed directly from **3b** and **4a-Li** under the above mentioned conditions and was isolated in 90% yield. The best conditions to obtain the cyclopentenone **2a** (90% yield) involve refluxing **1a** in a benzene solution in the presence of potassium carbonate and crown ether for 12 h. In order to prepare the cycloheptenone **2c** it is necessary to reflux the monoanion of **1c** generated by sodium hydride for 20 h in a toluene solution. Under these optimized conditions the yield of the isolated **2c** was 50%. Moreover, the cyclization reactions of **1a−e** should be carried out under dilution conditions to prevent intermolecular condensations. In contrast to tetramethyl bis-β-keto phosphonates **1a−c**, their ethyl analogues **1d−f** undergo very slow cyclization under comparable reaction conditions. The cyclopentenone **2d** and cyclohexenone **2e** were isolated in 25 and 50% yield, respectively. The cycloheptenone

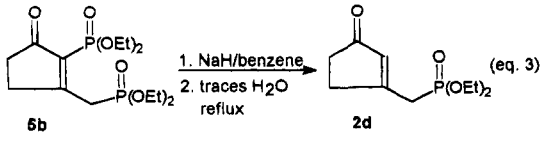
Scheme 2



was practically not formed as evidenced by ^{31}P NMR and TLC. The difference in reactivity between the methyl and ethyl derivatives of **1** is most probably steric in nature.

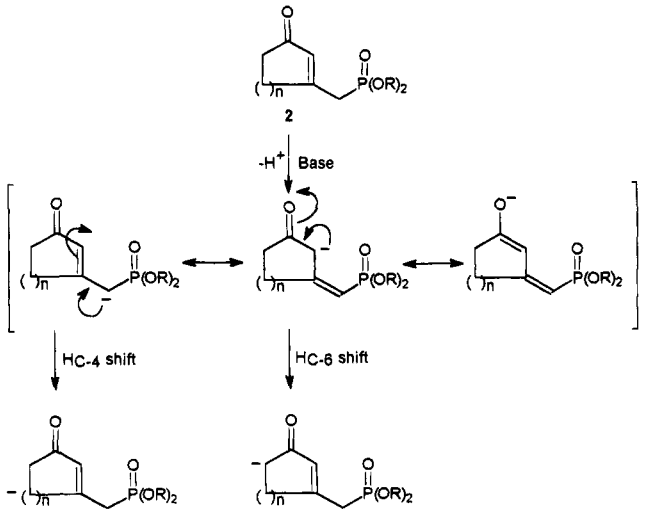
With regards to intramolecular cyclization of bis-β-keto phosphonate **1a** it is interesting to point out that depending on the experimental conditions this reaction results in the formation of two products containing phosphorus i.e. cyclopentenone **2a** and cyclopentenone **5a** (R = Me) (see Scheme 2).

The first is the expected Horner–Wittig reaction product while the latter results from the Knoevenagel reaction. Moreover, when a benzene solution of the anion of **1a** is refluxed for 0.5 h the formation of the Knoevenagel reaction product **5a** is practically observed in ^{31}P NMR spectra in addition to a small amount of **1a**. However, when the reaction time is elongated the Horner–Wittig reaction product **2a** is almost exclusively present in the reaction mixture. This indicates that **5a** is formed faster and is then converted into the desired cyclopentenone **2a**. That this conversion indeed occurs was corroborated by an independent experiment in which the isolated Knoevenagel product **5b** (R = Et) was transformed into an anion with sodium hydride and refluxed in a benzene solution in the presence of traces of water. After a few hours the reaction mixture contained the cyclopentenone **2d** (eq 3).



The above observations may reasonably be explained by assuming reversibility of the Knoevenagel reaction and formation of two diastereomeric alkoxides **A** and **B** as intermediates (see Scheme 2). The first of them having the 2-phosphoryl group and 3-oxy anion cis-oriented undergoes irreversible elimination of the dialkyl phosphate anion to give the cyclopentenones **2a** or **2d**. Stabilization of the second intermediate **B** occurs by

Scheme 3



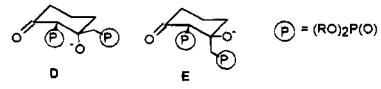
elimination of hydroxide leading to the Knoevenagel reaction product **5a** or **5b**.[10,12] However, this step is reversible and due to nonstereoselectivity of the reverse reaction a mixture of **A** and **B** is formed. It is also possible that the alkoxides **A** and **B** are equilibrated via the enolate form **C**.

As was mentioned above, the cycloalkenones **2** offer new possibilities for further functionalization of the carbocyclic ring mainly due to the presence of the exocyclic 3-phosphorylmethylene group. Particularly interesting is the reactivity of the anion generated from **2** upon treatment with base since it may be described at first sight by three mesomeric forms in which the negative charge is located on the α-phosphoryl carbon atom, α-carbonyl carbon atom, and oxygen atom. Scheme 3.

To get better insight into reactivity of the cycloalkenones **2** and their anions the hydrogen–deuterium exchange was first investigated. It was found that quenching the anion of **2b** generated by sodium hydride in a benzene solution with D_2O/D_2SO_4 results in incorporation of only one deuterium into the exocyclic 3-methylene group.

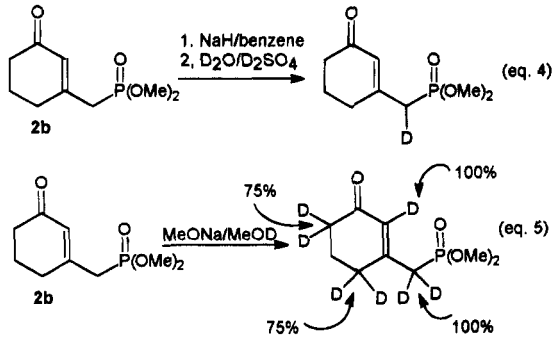
However, when the cyclohexenone **2b** was subjected to action of sodium methoxide in deuterium methanol, i.e. the hydrogen–deuterium exchange was carried out under thermodynamically controlled conditions, the protons in the exocyclic 3-methylene group and a methine proton at C-2 were fully exchanged by deuterium. More-

(10) Presumably preferential formation of the Knoevenagel product is connected with steric requirements for cyclization of **1a** or **1d** and greater stability of the transient alkoxide **B**. However, due to our ignorance of a conformation of both alkoxides **A** and **B** the reasons for differences in their stability are obscure. On the contrary, it seems possible to account for a clean cyclization of bis-β-keto phosphonates **1b** to the cyclohexenone **2b** on the grounds of difference in energy of the corresponding diastereomeric alkoxides **D** and **E** which adopt most probably a chair conformation.[11] The structure **D**, which is responsible for the formation of **2b**, should be more stable since two bulky phosphorus substituents at C-2 and C-3 are equatorial.



(11) For a conformation of cyclohexanones see: Eliel, E. L.; Allinger, M. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; John Wiley & Sons, Inc.: New York, 1967.

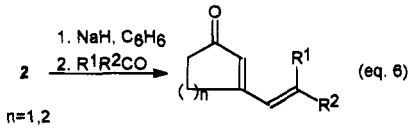
(12) For a recent, similar example of a competition between the Horner–Wittig and Knoevenagel reaction see: Aloni, M.; Lygo, B.; Trabsa, H. *Synlett* **1994**, 115.



over, we observed also that the methylene protons at C-4 and C-6 were 75% replaced by deuterium. This means that in addition to the three anionic centers of the anion shown in Scheme 3 two carbanionic centers at C-4 and C-6 are formed under basic conditions. Their formation may occur by direct deprotonation or by prototropic shift as shown in Scheme 3. Therefore, the reaction of this cycloalkenone **2** anion can be expected to give five different products depending on the nature of electrophilic reagent used.

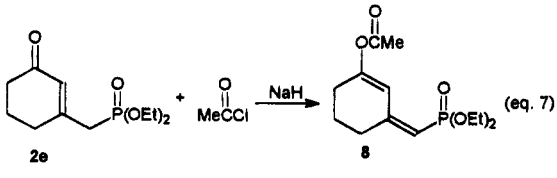
In spite of the fact that the anion derived from cycloalkenones **2** may react with electrophilic reagents at different positions as shown by deuterium experiments, the reaction of the cyclohexenone anion **2b**$^-$ with methyl iodide is fully regioselective and gives the C-2 methylated product **6a** in 67% yield. Unexpectedly, the use of methyl triflate instead of methyl iodide leads also to the same compound **6a** even in a better yield (90%). Alkylation of **2e** with methyl triflate gave **6b**. Similarly, alkylation of **2b** with ethyl iodide and benzyl chloride gave the C-2 alkylated products **6c** and **6d**.

In accord with expectations, the reaction of the cycloalkenone anions with carbonyl compounds occurs at the α-phosphonate carbon atom and affords the Horner–Wittig olefination products. Some illustrative examples of the Horner–Wittig reaction of **2** are summarized in eq 6. It should be noted that the reaction conditions and yields of the products were not optimized in this case.



	Yield (%)
7a, n=1, R^1=R^2H	61
7b, n=1, R^1=R^2=Me	51
7c, n=2, R^1=H, R^2=Me	59
7d, n=2, R^1=R^2=Ph	21

As expected, the reaction of the anion derived from **2e** with acetyl chloride occurred at the oxygen atom and gave the O-acetylation product **8**. However, silylation with trimethylchlorosilane and phosphorylation with diethyl chlorophosphate failed most probably due to steric bulk of these electrophilic agents.



The work on application of the cycloalkenones **2** and their reactions described here for the synthesis of natural products is in progress.

Experimental Section

^{31}P NMR spectra were recorded using 85% H_3PO_4 as an external standard. Reaction mixtures were analyzed by TLC using Merck 60 F_{254} TLC plates. Column chromatography was performed using Merck 60 (70–230 mesh) silica gel. Flash chromatography was carried out on Merck 60 (230–400 mesh) silica gel. Mixtures of hexane and acetone were used as eluents. Benzene and toluene were dried by standing over sodium wire, following by distillation. THF was freshly distilled over potassium/benzophenone.

General Procedure for Synthesis of Bis-β-keto Phosphonates 1a–f. To a magnetically stirred solution of 0.2 mol of methanephosphonate **4** in dry THF (1 L) under nitrogen at −78 °C is added dropwise 0.2 mol of BuLi in hexane. After 15 min a solution of 0.05 mol of dicarboxylic acid ester **3** in 20 mL of dry THF is added. The mixture is stirred at −78 °C for an additional 0.5 h and a solution of ammonium chloride in water is added. After removal of solvent in vacuum the residue is extracted with $CHCl_3$ (3 × 50 mL). The extract is dried ($MgSO_4$) and concentrated under vacuum. An excess of methanephosphonate **4** is removed under vacuum using a kugelrohr apparatus (80 °C/0.01 mmHg). The remaining oil is used without purification for the next reaction. Analytically pure sample was obtained by flash chromatography using Merk 60 (230–400 mesh) silica gel and a hexane/acetone (1:1) mixture as eluent.

1,6-Bis(dimethoxyphosphoryl)hexane-2,5-dione (1a): 52% yield of isolated product; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.78 (d, 12H, J = 11.2 Hz), 3.13 (d, 4H, J = 22.6 Hz), 2.90 (s, 4H), ^{13}C-NMR (50 MHz, $CDCl_3$) δ 199.7 (d, J = 6.7 Hz), 52.6 (d, J = 6.6 Hz), 40.8 (d, J = 128 Hz), 37.2; ^{31}P-NMR (81 MHz, $CDCl_3$) δ 22.9; HR-MS (CI) (M + H)$^+$ calcd for $C_{10}H_{21}P_2O_8$ 331.0712, obsd 331.0713.

1,7-Bis(dimethoxyphosphoryl)heptane-2,6-dione (1b): 50% yield of isolated product; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.72 (d, 12H, J = 11.0 Hz), 3.06 (d, 4H, J = 22.7 Hz), 2.65 (t, 4H, J = 7.0 Hz), 1.85 (q, 2H, J = 7.0 Hz) ^{13}C-NMR (50 MHz, $CDCl_3$) δ 200.9 (d, J = 6.5 Hz), 52.6 (d, J = 6.8 Hz), 42.1, 40.8 (d, J = 131 Hz), 16.6; ^{31}P-NMR (81 MHz, $CDCl_3$) δ 23.1; HR-MS (CI) (M + H)$^+$ calcd for $C_{11}H_{23}P_2O_8$ 345.0868, obsd 345.0864.

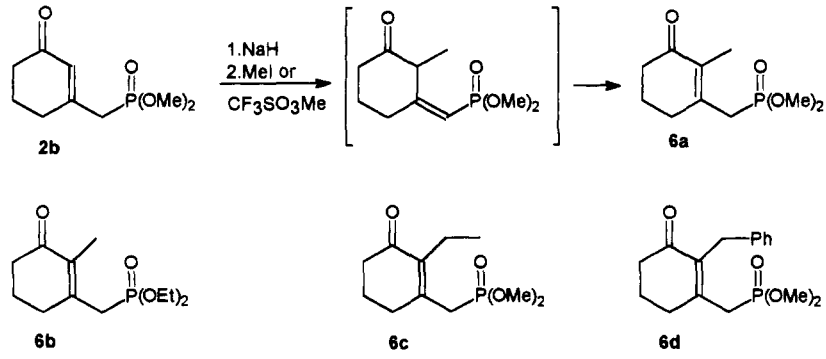
1,8-Bis(dimethoxyphosphoryl)octane-2,7-dione (1c): 54% yield of isolated product; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.72 (d, 12H, J = 11.0 Hz), 3.07 (d, 4H, J = 22.7 Hz), 2.57–2.67 (m, 4H), 1.52–1.62 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 201.1 (d, J = 5.6 Hz), 52.6 (d, J = 6.5 Hz), 43.3, 40.8 (d, J = 128Hz), 22.1; ^{31}P-NMR (81 MHz, $CDCl_3$) δ 23.1; HR-MS (CI) (M + H)$^+$ calcd for $C_{12}H_{25}P_2O_8$ 359.1025, obsd 359.1021.

1,6-Bis(diethoxyphosphoryl)hexane-2,5-dione (1d): 58% yield of isolated product; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.16 (q, 4H, J = 7.1 Hz), 4.12 (q, 4H, J = 7.1 Hz), 3.12 (d, 4H, J = 22.6 Hz), 2.91 (s, 4H), 1.33 (t, 12H, J = 7.1 Hz); ^{13}C-NMR (50 MHz, C_6D_6) δ 200.6 (d, J = 5.4 Hz), 62.4 (d, J = 6.1 Hz), 42.8 (d, J = 126 Hz) 38.0, 16.5 (d, J = 6.0 Hz), ^{31}P-NMR (81 MHz, $CDCl_3$) δ 20.3; HR-MS (CI) (M + H)$^+$ calcd for $C_{14}H_{29}P_2O_8$ 387.1338, obsd 387.1341.

1,7-Bis(diethoxyphosphoryl)heptane-2,6-dione (1e): 54% yield of isolated product; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 4.14 (q, 4H, J = 7.1 Hz), 4.10 (q, 4H, J = 7.1 Hz) 3.06 (d, 4H, J = 22.7 Hz), 2.66 (t, 4H, J = 7.5 Hz), 1.85 (q, 2H, J = 7.5 Hz), 1.33 (t, 12H, J = 7.0 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 200.8 (d, J = 5.8 Hz), 61.9 (d, J = 6.7 Hz), 42.0, 41.7 (d, J = 127 Hz), 16.6, 15.7 (d, J = 5.5 Hz); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 20.5; HR-MS (CI) (M + H)$^+$ calcd for $C_{15}H_{31}P_2O_8$ 401.1494, obsd 401.1490.

1,8-Bis(diethoxyphosphoryl)octane-2,7-dione (1f): 67% yield of isolated product; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.13 (q, 4H, J = 7.1 Hz), 4.09 (q, 4H, J = 7.1 Hz), 3.06 (d, 4H, J = 22.8 Hz), 2.60–2.67 (m, 4H), 1.54–1.61 (m, 4H), 1.33 (t, 12H, J = 7.0 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 201.1 (d, J = 6.4 Hz), 62.0 (d, J = 6.0 Hz), 43.1, 41.9 (d, J = 127 Hz), 22.1, 15.8

Scheme 4



(d, J = 6.2 Hz); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 20.6; HR-MS (CI) (M + H)$^+$ calcd for $C_{16}H_{33}P_2O_8$ 415.1651, obsd 415.1649.

3-[(Dimethoxyphosphoryl)methyl]cyclopent-2-enone (2a). To a magnetically stirred solution of **1a** (3.31 g, 0.01 mol) in dry benzene (1 L) are added 3.72 g (0.01 mol) of DCH-18-C6 and 2.76 g (0.02 mol) of K_2CO_3. The reaction mixture is refluxed for 12 h, and then benzene is removed under vacuum. A solution of ammonium chloride in water is added to the residue and extracted with $CHCl_3$ (3 × 20 mL). The extract is dried ($MgSO_4$). After removal of solvent under vacuum the residue is chromatographed on silica gel using a mixture of hexane and acetone (2:1) as eluent to give 1.84 g (90%) of **2a** as a colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.11 (brd, 1H, J = 5.0 Hz), 3.77 (d, 6H, J = 11.1 Hz), 3.01 (d, 2H, J = 23.5 Hz), 2.71–2.75 (m, 2H), 2.42–2.47 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 208.6, 170.6 (d, J = 10.7 Hz), 133.0 (d, J = 9.2 Hz), 52.7 (d, J = 6.7 Hz), 35.2, 32.1 (d, J = 3.0 Hz), 30.5 (d, J = 137 Hz); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 25.8; HR-MS (EI) M$^+$ calcd for $C_8H_{13}PO_4$ 204.0551, obsd 204.0537.

3-[(Dimethoxyphosphoryl)methyl]cyclohex-2-enone (2b). A solution of **1b** obtained as described in a general procedure for **1a–f** is additionally stirred overnight at room temperature. Further workup is analogous to the isolation of **1a–f**. Crude product is chromatographed on silica gel using a mixture of acetone and hexane (1:2) as eluent to give **2b** (90%) as a colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.94 (brd, 1H, J = 4.9 Hz), 3.74 (d, 6H, J = 11.0 Hz), 2.75 (dd, 2H, J = 23.6 Hz, J = 0.7 Hz), 2.41–2.47 (m, 2H), 2.32–2.39 (m, 2H), 2.00 (q, 2H, J = 6.9 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 198.8, 155.5 (d, J = 11.5 Hz), 129.3 (d, J = 10.8 Hz), 52.8 (d, J = 6.8 Hz) 36.7, 34.9 (d, J = 135 Hz), 30.2, 22.3; ^{31}P-NMR (81 MHz, $CDCl_3$) δ 26.9; HR-MS (EI), M$^+$ calcd for $C_9H_{15}PO_4$ 218.0708, obsd 218.0712.

3-[(Dimethyloxyphosphoryl)methyl]cyclohept-2-enone (2c). To a magnetically stirred solution of **1c** (1.79 g, 0.005 mol) in dry toluene (1 L) is added 0.12 g (0.005 mol) of NaH (washed with hexane). After 12 h stirring at room temperature the reaction mixture is refluxed for 20 h. Further workup is performed analogously as for **2a** and yields the product as a colorless oil: 0.58 g (50%); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.94 (brd, 1H, J = 5.1 Hz), 3.73 (d, 6H, J = 11.0 Hz), 2.70 (d, 2H, J = 23.5 Hz), 2.48–2.62 (m, 4H), 1.72–1.86 (m, 4H), ^{13}C-NMR (50 MHz, $CDCl_3$) δ 202.8, 151.2 (d, J = 11.2 Hz), 132.8 (d, J = 11.9 Hz), 52.7 (d, J = 6.9Hz), 42.2, 37.5 (d, J = 135 Hz), 33.8, 25.0, 21.0, ^{31}P-NMR (81 MHz, $CDCl_3$) δ 27.6; HR-MS (EI) M$^+$ calcd for $C_{10}H_{17}PO_4$ 232.0865, obsd 232.0862.

3-[(Diethoxyphosphoryl)methyl]cyclopent-2-enone (2d). It is obtained and isolated as described for **2a** using 3.87 g (0.01 mol) of **1d**, 3.72 g (0.01 mol) of DCH-18-C6, 2.76 g (0.02 mol) of K_2CO_3, and 1 L of dry benzene (yield 0.58 g, 25%): ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.99 (brd, 1H, J = 5.4 Hz), 3.82 (q, 2H, J = 7.1 Hz), 3.78 (q, 2H, J = 7.1 Hz) 2.44 (d, 2H, J = 23.2 Hz), 2.18–2.25 (m, 2H), 1.98–2.04 (m, 2H), 0.96 (t, 6H, J = 7.1 Hz); ^{13}C-NMR (50 MHz, C_6D_6) δ 207.8, 171.3 (d, J = 10.2 Hz), 133.8 (d, J = 10.1 Hz), 62.7 (d, J = 6.3 Hz), 36.2, 33.0 (d, J = 3.1 Hz), 32.5 (d, J = 136 Hz), 17.0 (d, J = 5.6 Hz); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 23.1; HR-MS (EI) M$^+$ calcd for $C_{10}H_{17}PO_4$ 232.0865, obsd 232.0873.

3-[(Diethoxyphosphoryl)methyl]cyclohex-2-enone (2e). It is obtained and isolated as described for **2a** using 4.01g (0.01 mol) of **1e**, 3.72 g (0.01 mol) of DCH-18-C6, 2.76 g (0.02 mol) of K_2CO_3, and 1 L of dry benzene (yield 1.24 g, 50%): ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.23 (brd, 1H, J = 5.6 Hz), 4.09 (q, 2H, J = 7.1 Hz), 4.05 (q, 2H, J = 7.1 Hz), 2.32 (d, 2H, J = 23.5 Hz), 2.04–2.13 (m, 4H), 1.49 (q, 2H, J = 6.1 Hz), 0.98 (t, 6H, J = 7.1 Hz); ^{13}C-NMR (50 MHz, C_6D_6) δ 198.0, 156.2 (d, J = 10.5 Hz), 130.3 (d, J = 11.4 Hz), 62.8 (d, J = 6.7 Hz), 37.9, 36.9 (d, J = 134 Hz), 31.1, 23.5, 17.1 (d, J = 6.0 Hz); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 24.2; HR-MS (EI) M$^+$ calcd for $C_{11}H_{19}PO_4$ 246.1021, obsd 246.1018.

2-(Dimethoxyphosphoryl)-3-[(dimethoxyphosphoryl)-methyl]cyclopent-2-enone (5a). To a magnetically stirred solution of sodium methoxide (0.01 mol) in 10 mL of dry methanol is added 3.30 g (0.01 mol) of **1a**. The reaction mixture is refluxed for 3 h, and then 0.01 mol of hydrochloric acid is added. Methanol is removed under vacuum and the residue is washed with $CHCl_3$ (5 × 20 mL). The organic layer is dried ($MgSO_4$) and concentrated under vacuum yielding almost quantitatively cyclic bis-phosphonate **5a**. The analytically pure sample is obtained in 64% yield by chromatography on silica gel using acetone as eluent: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.78 (d, J = 11.2 Hz, 6H), 3.77 (d, J = 11.4 Hz, 6H), 3.73 (dd, 2H, J = 25.3 Hz, J = 2.0 Hz), 2.88–2.98 (m, 2H), 2.46–2.54 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 204.6 (d, J = 9.9 Hz), 184.4 (dd, J = 13.1 Hz, J = 10.1 Hz), 130.5 (dd, J = 187.9 Hz, J = 10.0 Hz), 52.2 (d, J = 6.4 Hz), 52.2 (d, J = 6.1 Hz), 34.6 (d, J = 10.5 Hz), 33.3 (d, J = 17.7 Hz), 30.1 (d, J = 130.5 Hz); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 25.0 (d, J = 8.3 Hz), 13.1 (d, J = 8.3 Hz); HR-MS (EI) M$^+$ calcd for $C_{10}H_{18}P_2O_7$ 312.0528, obsd 312.0512.

2-(Diethoxyphosphoryl)-3-[(diethoxyphosphoryl)methyl]cyclopent-2-enone (5b). It is obtained and isolated in 72% yield as described for **5a** using 0.01 mol of sodium ethoxide in 10 mL of dry ethanol and 3.87 g (0.01 mol) of **1d**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.05–4.25 (m, 8H), 3.75 (dd, 2H, J = 24.8 Hz, J = 2.0 Hz), 2.90–3.00 (m, 2H), 2.45–2.54 (m, 2H), 1.33 (t, 6H, J = 7.1 Hz), 1.32 (t, 6H, J = 7.1 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 204.6 (dd, J = 10.6 Hz, J = 2.3 Hz), 183.6 (dd, J = 11.8 Hz, J = 10.8 Hz), 131.3 (dd, J = 187.9 Hz, J = 10.3 Hz), 61.9 (d, J = 7.4 Hz), 61.7 (d, J = 6.4 Hz), 34.5 (d, J = 10.4 Hz), 33.0 (d, J = 17.7 Hz), 31.0 (d, J = 130.8 Hz), 15.7 (d, J = 5.7 Hz); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 22.7 (d, J = 9.1 Hz); 10.2 (d, J = 9.1 Hz), HR-MS (EI) M$^+$ calcd for $C_{14}H_{26}P_2O_7$ 368.1154, obsd 368.1156.

Transformation of Knoevenagel Reaction Product 5a into Horner Reaction Product 2a. To a magnetically stirred solution of **5a** (3.68 g, 0.01 mol) in 50 mL of benzene is added 0.24 g (0.01 mol) of NaH (washed with hexane). After 0.5 h 0.2 mL of water is added and reaction mixture is refluxed for 6 h. Further workup is analogous to the isolation of **2a** mentioned above. The Horner reaction product **2a** is obtained in 45% yield (0.92 g).

Transformation of Knoevenagel Reaction Product 5b into Horner Reaction Product 2d. In a similar way using 3.68 g (0.01 mol) of **5b**, 0.01 mol of NaH, and 0.2 mL of water the Horner reaction product **2d** was obtained in 30% yield (0.70 g).

Alkylation of Cycloalkenones 2. General Procedure. To a magnetically stirred solution of **2** (0.004 mol) in 10 mL of dry benzene is added 0.096 g (0.004 mol) of NaH (washed with

hexane). After 1 h 0.004 mol of alkyl halide or sulfonate is added. The reaction mixture is stirred at room temperature overnight. A solution of ammonium chloride in water is added. The organic layer is separated and water solution is additionally extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers are dried ($MgSO_4$) and concentrated under vacuum. The residue is chromatographed on silica gel using a mixture of hexane and acetone (2:1) as eluent to give the products as a colorless oil.

2-Methyl-3-[(dimethoxyphosphoryl)methyl]cyclohex-2-enone (6a): 65% yield using methyl iodide; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.75 (d, 6H, J = 11.0 Hz), 2.84 (d, 2H, J = 24.4 Hz), 2.45–2.54 (m, 2H), 2.38–2.45 (m, 2H), 1.88–2.04 (m, 2H), 1.78–1.86 (m, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 198.1 (d, J = 3.1 Hz), 147.5 (d, J = 11.6 Hz), 133.5 (d, J = 10.7 Hz), 52.4 (d, J = 6.9 Hz), 37.1, 32.4 (d, J = 135 Hz), 31.4, 21.8, 10.8; ^{31}P-NMR (81 MHz, $CDCl_3$) δ 28.0; HR-MS (EI) M^+ calcd for $C_{10}H_{17}PO_4$ 232.0865, obsd 232.0845.

2-Methyl-3-[(diethoxyphosphoryl)methyl]cyclohex-2-enone (6b): 90% yield using methyl triflate; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.10 (q, 2H, J = 7.0 Hz), 4.06 (q, 2H, J = 7.0 Hz), 2.80 (d, 2H, J = 24.0 Hz), 2.43–2.53 (m, 2H), 2.35–2.42 (m, 2H), 1.86–1.99 (m, 2H), 1.77–1.81 (m, 3H), 1.28 (t, 6H, J = 7.0 Hz); ^{13}C-NMR (50 MHz, C_6D_6) δ 197.6, 148.4 (d, J = 11.6 Hz), 129.9 (d, J = 10.5 Hz), 62.5 (d, J = 6.4 Hz), 38.5, 35.1, (d, J = 134 Hz), 32.6, 23.2, 17.1, (d, J = 5.2 Hz), 15.0; ^{31}P-NMR (81 MHz, $CDCl_3$) δ 25.4; HR-MS (EI) M^+ calcd for $C_{12}H_{21}PO_4$ 260.1177, obsd 260.1168.

2-Ethyl-3-[(dimethoxyphosphoryl)methyl]cyclohex-2-enone (6c): 69% yield using ethyl iodide; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.73 (d, 6H, J = 11.0 Hz), 2.81 (d, 2H, J = 24.3 Hz), 2.40–2.52 (m, 2H), 2.22–2.40 (m, 4H), 1.80–2.05 (m, 2H), 0.91 (t, 3H, J = 7.5 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 197.4 (d, J = 2.8 Hz), 146.8 (d, J = 10.8 Hz), 139.1 (d, J = 11.5 Hz), 52.3 (d, J = 6.9 Hz), 37.4, 31.7 (d, J = 135 Hz), 31.2, 21.8, 18.3, 12.7 (d, J = 2.6 Hz); HR-MS (EI) M^+ calcd for $C_{11}H_{19}PO_4$ 246.1021, obsd 246.1014.

2-Benzyl-3-[(dimethoxyphosphoryl)methyl]cycloheptan-2-enone (6d): 62% yield using benzyl chloride; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.05–7.28 (m, 5H), 3.60–3.80 (m, 2H), 3.73 (d, 6H, J = 11.0 Hz), 2.83 (d, 2H, J = 23.9 Hz), 2.45–2.60 (m, 4H), 1.70–1.80 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 205.8 (d, J = 3.0 Hz), 142.2 (d, J = 12.1 Hz), 140.1 (d, J = 13.1 Hz), 139.1 (d, J = 2.9 Hz), 128.0, 127.7, 125.6, 52.4, 41.1, 33.9, 33.4, 32.7, 23.5, 20.5; ^{31}P-NMR (81 MHz, $CDCl_3$) δ 28.3; HR-MS (EI) M^+ calcd for $C_{17}H_{23}PO_4$ 322.1333, obsd 322.1328.

Horner–Wittig Reaction of Cycloalkenones 2. General Procedure. To a magnetically stirred solution of **2** (0.004 mol) in 100 mL of dry benzene is added 0.096 g (0.004 mol) of NaH (washed with hexane). After 1 h 0.008 mol of a carbonyl compound is added. The reaction mixture is stirred for 12 h at room temperature and additionally refluxed for 10 h. A solution of ammonium chloride in water is added. The organic layer is separated and water solution is additionally extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers are dried ($MgSO_4$) and concentrated under vacuum. The residue is chromatographed on silica gel using a mixture of hexane and acetone as eluent (5:1) yielding olefinic product as a colorless oil.

3-Vinylcyclopent-2-enone (7a): 61% yield; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.28 (dd, 1H, J = 17.4 Hz, J = 10.7 Hz), 5.82 (s, 1H), 5.16 (d, 1H, J = 17.4 Hz), 4.97 (d, 1H, J = 10.7 Hz), 1.88–2.03 (m, 4H); ^{13}C-NMR (50 MHz, C_6D_6) δ 208.4, 171.6, 133.7, 132.1, 122.0, 35.3, 26.9, HR-MS (EI) M^+ calcd for C_7H_8O 108.0575, obsd 108.0567.

3-(2,2-Dimethylvinyl)cyclopent-2-enone (7b): 51% yield; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.04 (s, 1H), 6.01 (s, 1H), 2.72–2.82 (m, 2H0, 2.36–2.45 (m, 2H), 1.96 (s, 3H), 1.95 (s, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 209.9, 173.2, 147.4, 129.5, 121.7, 34.8, 31.9, 28.2, 20.9; HR-MS (EI) M^+ calcd for $C_9H_{12}O$ 136.0888, obsd 136.0895.

***trans*-3-(2-Methylvinyl)cyclohex-2-enone (7c):** 58% yield; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.95 (s, 1H), 5.82 (d, 1H, J = 15.6 Hz), 5.63 (dq, 1H, J = 15.6 Hz, J = 6.3 Hz), 2.14 (t, 2H, J = 6.2 Hz) 1.81 (t, 2H, J = 6.2 Hz), 1.45 (d, 3H, J = 6.3 Hz), 1.44 (q, 2H, J = 6.2 Hz); ^{13}C-NMR (50 MHz, C_6D_6) δ 198.8, 156.6, 133.9, 133.0, 127.7, 38.6, 25.6, 23.2, 19.2; HR-MS (EI) M^+ calcd for $C_9H_{12}O$ 136.0888, obsd 136.0912.

3-(2,2-Diphenylvinyl)cyclohex-2-enone (7d): 21% yield; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.15–7.43 (m, 5H), 6.69 (q, 1H, J = 0.9 Hz), 6.01 (q, 1H, J = 1.1 Hz), 2.26–2.45 (m, 2H), 1.72–2.05 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 199.9, 158.8, 148.4, 142.2, 139.8, 130.0, 129.8, 128.8, 128.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.3, 127.0, 37.4, 28.9, 23.1; HR-MS (EI) M^+ calcd for $C_{20}H_{18}O$ 274.1357, obsd 274.1333.

1-Acetoxy-3-[(diethoxyphosphoryl)methyl]cyclohex-1-ene (8). In a 5-mm NMR tube is placed a solution of 24.6 mg (0.0001 mol) of **2e** in 1 mL of benzene-d_6, and then 2.4 mg (0.0001 mol) of NaH (washed with hexane) is added. After 1 h 7.9 mg (0.0001 mol) of acetyl chloride is added. The formation of the title product was observed based on ^{1}H- and ^{31}P-NMR spectra of the reaction mixture. The acetoxy compound **8** cannot be isolated by chromatography due to its fast hydrolysis: ^{1}H-NMR (200 MHz, C_6D_6) δ 5.99 (brd, 1H, J = 5.1 Hz), 5.28 (brd, 1H, J = 16.2 Hz), 3.90–4.08 (m, 4H), 2.04 (s, 3H), 1.85–1.98 (m, 2H), 1.25–1.40 (m, 4H), 1.08 (t, 6H, J = 7.1 Hz); ^{31}P-NMR (81 MHz, C_6D_6) δ 17.6.

Hydrogen–Deuterium Exchange under Kinetically Controlled Conditions. To a magnetically stirred solution of **2b** (21.8 mg, 0.0001 mol) in dry benzene (2 mL) is added 2.4 mg (0.0001 mol) of NaH. After 1 h a small excess of D_2SO_4 in D_2O (0.5 N) is added. The layers are separated. The organic layer is dried ($MgSO_4$) and concentrated under vacuum. The sample of **2b** was analyzed by NMR spectroscopy.

Hydrogen–Deuterium Exchange under Thermodynamically Controlled Conditions. To a magnetically stirred solution of **2b** (21.8 mg, 0.0001 mol) in MeOD (1 mL) is added a trace of NaH. After five days a small excess of D_2SO_4 in D_2O (0.5 N) is added. Solution is concentrated under vacuum, extracted with $CHCl_3$, dried ($MgSO_4$), and evaporated to give **2b** which was analyzed with NMR spectroscopy.

Supplementary Material Available: ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra of **1a-f**, **2a-e**, **5a,b**, and **6a-d**; ^{1}H- and ^{13}C-NMR spectra of **7a-d**; ^{1}H- and ^{31}P-NMR spectra of the mixture of **2e** and **8**, and ^{31}P-NMR spectrum of sodium salt of **2e** (61 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.