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Novel 1-Phosphonyl Radicals Derived From 1-Mono and 1,1-Di-heterosubstituted 2-Oxoalkylphosphonates as Useful Phosphoroorganic Intermediates in Organic Synthesis[1].

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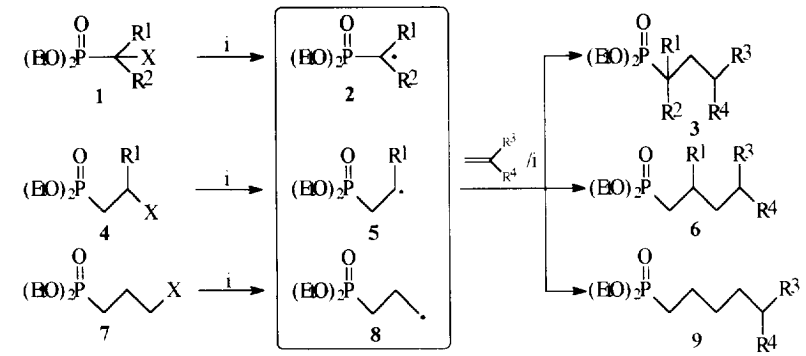
Abstract: Novel 1-phosphonyl radicals **17** were obtained from 1-mono(Y=H. X=Cl. Br. SMe) and 1.1-di (Y=X=Cl) hetero substituted 2-oxoalkylphosphonates **16** under the reductive conditions (*n*-Bu_3SnH/AIBN) and utilized in the reactions with alkenes for the free-radical synthesis of highly functionalized phosphonates **19** and **20**. The utility of the new approach has been demonstrated by the synthesis of methylenomycin B **13**, a cyclopentanoid antibiotic, using the phosphonate **19d** as well as by the synthesis of 4-diethoxyphosphoryl-2,3-dihydrofuran **22** and 2-diethoxyphosphoryloxy-heptan-5-one **23**. © 1997, Elsevier Science Ltd. All rights reserved.

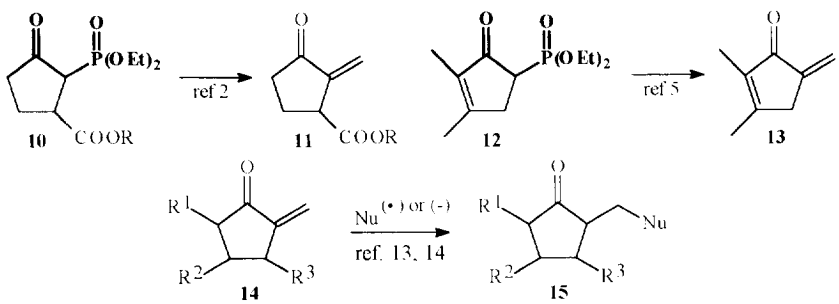
INTRODUCTION

A search for new, synthetic methodologies and their applications involving organophosphorus and organosulfur reagents is one of the aims in research of our laboratory.[2] So far, this aim was realized in numerous syntheses of natural products containing cyclopentenone and cyclopentanone frameworks, such as dihydrojasmone,[3] Z-jasmone,[4] methylenomycin B,[5] (±) sarkomycin[6] and (+), (-) isoterrein[7] based on reactions involving 1-phosphonyl carbanions and 1-phosphonyl carbenes. A significant potential inhering in radical chemistry,[8] as well as a lack of systematic and parallel investigations in the field of the radical chemistry[9] of phosphonates has recently been utilized in this laboratory in a successful synthesis of 1-, 2- and 3-phosphonyl radicals **2**, **5**, **8** starting from the corresponding heterosubstituted phosphonates **1**, **4**, **7** as the radical precursors[1,5,9-11] (Scheme 1). A large number of 1-heterosubstituted 1-phosphonyl radicals were also obtained during the selective desulfenylation and deselenylation reactions of 1-mono or 1,1-diheterosubstituted phosphonates[11]. All of these findings enabled elaboration of new, free radical methodology for the synthesis of the C_1, C_2...Cn-C phosphonate bonds from the C_1, C_2...Cn radical species and compounds possessing multiple bonds. Thus, it was shown that from radicals **2**, **5**, **8**, the corresponding highly substituted phosphonates **3**, **6**, **9** could be obtained.[1, 9, 10] These successful results prompted us to further investigate the unknown, electrophilic radicals **17**, derived from 2-oxoalkylphosphonates **16** (see Scheme 3 and Table 1). It seemed essential to devolop this chemistry because the intermediate radicals **17** possess two important

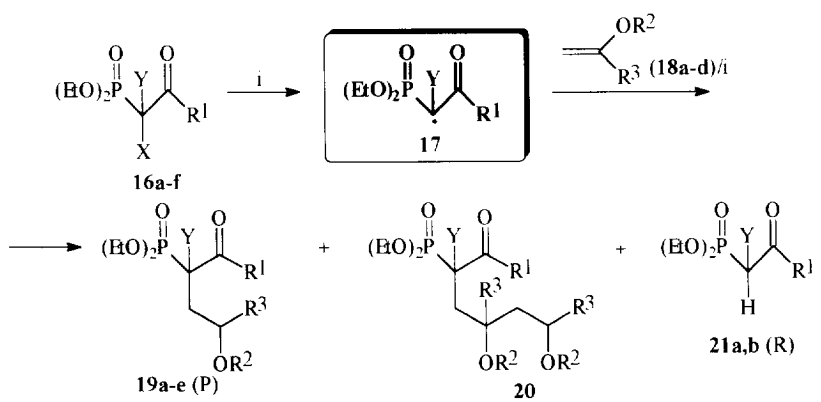


i: n-Bu$_3$SnH/AIBN; X-Cl, Br, I, SR, SeR, SC(=S)NMe$_2$
R^1, R^2 - alkyl, aryl, C(=O)R [Cl, OR, SR, (EtO)$_2$P(O)]

Scheme 1



Scheme 2



X=Cl, Br, SMe; Y=H, Me, Cl; R^1=Me, Et
i: n-Bu$_3$SnH/AIBN

Scheme 3

functional groups:[2, 12] a) the keto group, present in lots of natural products and their synthetic precursors, and b) diethoxyphosphoryl group, allowing introduction of the exo-methylene moiety in sarkomycin[2] and methylenomycin B,[5] two cylopentanoid antibiotics (**10**→**11**, **12**→**13**; Scheme 2 and also Scheme 3) and in a large number of their congeners. Moreover, the exo-methylene grouping could be further functionalized by the radical or anionic 1,4-addition reactions (**14**→**15**; Scheme 2) what was well documented in the literature concerning the prostaglandin chemistry.[13,14]

RESULTS AND DISCUSSION

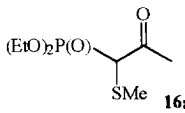
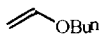
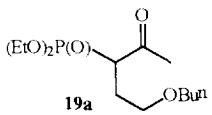
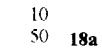
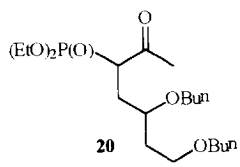
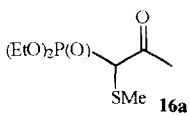
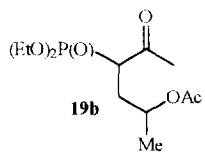
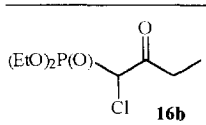
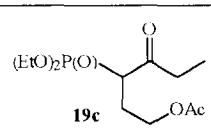
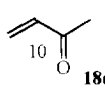
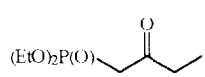
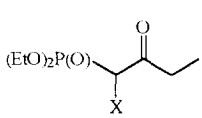
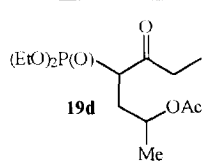
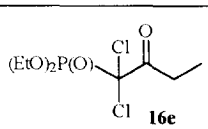
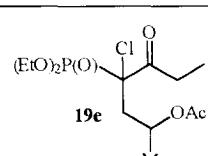
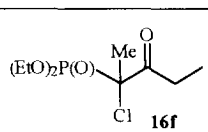
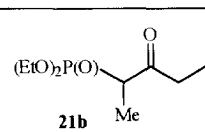
A series of 1-mono(Y=H, Me, X=Cl, Br, SMe) and 1,1-di(X=Y=Cl) heterosubstituted diethyl 2-oxoalkylphosphonates **16a-f** were prepared for the generation of the corresponding 1-phosphonyl radicals **17** under the Giese reductive conditions[8] (*n*-Bu_3SnH/AIBN) and for their further reactions with electron rich alkenes **18**. The 1-chloro derivative **16b** was synthesized from diethyl 1,1-dichloro-2-oxo-*n*-butylphosphonate **16e** by the demonohalogenation reaction with the $Na_2S_2O_5$/$NaHCO_3$/H_2O/MeOH reagent system[15]. Such a procedure was necessary because the direct chlorination of diethyl 2-oxo-*n*-butylphosphonate **21a** (Y=H, R^1=Et) with stoichiometric amount of sulfuryl chloride (O°C, CCl_4) produced a mixture of the substrate, mono- and di-chloro derivatives. The presence of the latter was even detected when 0.5eq of sulfuryl chloride was used. Diethyl 1-bromo-2-oxo-*n*-butylphosphonate **16c** was prepared by bromination of the corresponding 1-lithio derivative with bromine. Diethyl 1-methylthio-2-oxo-alkylphosphonates **16a** and **16d** were obtained by acylation of diethyl 1-lithio-1-(methylthio)methylphosphonate with the corresponding carboxylic esters[16].

The electrophilic, radical precursors **16a-f** synthesized in that way were reacted with an excess of vinyl ethers **18a-d**. With 10 equivalents of **18**, the corresponding monoadducts **19** (P) were obtained in 30-70% yields (Table 1 and Scheme 3). The reduced substrates **21** (R) in the given P/R ratios (Table 1) and bisadducts **20** were also formed as the minor reaction products. The yields of **20** (usually 12-17% with 10 equivalents of **18**) could be significantly reduced with 6-7 equivalents of the alkene used, but these results were achieved at the expense of the worse P/R ratios. On the other hand, the raction yields of **20** could be doubled, to almost 40% with 50 equivalents of the alkene used (Table1). The bisadducts of the type **20** seem to be interesting compounds because they are the first examples of the intermolecular, tandem reaction products involving 1-phosphonyl radicals.

It was also confirmed for the verification of the selectivity requirements[8], that 2-oxoalkylphosphonyl radicals **17** (for instance: Y=Cl; R^1=Et), due to significant, electrophilic character, did not react with electron-poor 3-buten-2-one **18d**, affording quantitatively the reduction product **21a** (Table 1). For a comparison, it was previously found[10] that alkyl-substituted 1-phosphonyl radicals **2** possessing a less electrophilic nature than radicals **17** reacted with both electron-rich and -deficient alkenes, although, with the latter, much less effectively.

In order to demonstrate the utility of the new, free-radical approach to the synthesis of functionalized

Table 1. Reaction of 1-Phosphonyl Radicals **17** with Alkenes **18**

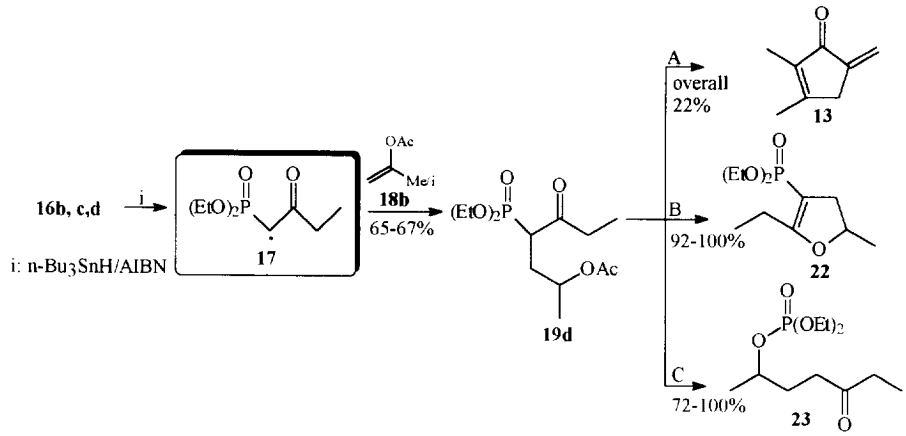
Phosphonate	Alkene [equivs]	Product	Yield [%]	P/R
 **16a**	 10	 **19a** +	51-70	65/25
	50 **18a**		46	74/26
	 10	 **20**	17	56/44
	50		37	69/21
 **16a**	 10 **18b**	 **19b**	42	50/50
 **16b**	 10 **18c**	 **19c**	32	38/62
16b	 **18d**	 **21a**	100	100/0
 **16b**: X=Cl	 10 **18b**	 **19d**	51 (67)	62/38
	6		43	50/50
16c: X=Br	10		48 (65)	56/44
16d: X=SMe	10		53 (65)	76/26
	7		35	33/67
 **16e**	 10 **18b**	 **19e** + **19d**	30	38/62
			15	
 **16f**	**18a**	 **21b**	100	100/0

2-oxoalkylphosphonates, we planned to synthesize the phosphonate **19d**, aimed at the total synthesis of methylenomycin B **13**[5]. It was found, together with methylenomycin A, in a soil sample collected at Sagamihara, Kanagawa Prefecture, Japan and isolated from the culture filtrate of a streptomycete strain No 2416, which was further identified as a strain of *Streptomyces violaceoruber*[17]. This deceptively simple, natural molecule is a highly functionalized cyclopentenone antibiotic with the inhibitory activity against gram-positive and gram-negative bacteria[18]. Although relatively unstable, methylenomycin-B is often utilized for testing new synthetic methodologies[5]. The instability of **13** results from the presence of the conjugated *exo*-methylene moiety which therefore should be introduced in the last step of a total synthesis. Application of phosphonates and in particular phosphoryl group, as the synthetic equivalent of the *exo*-methylene moiety (introduced through the Horner-Wittig reaction), allows one to handle stable compounds from the first to the penultimate step of the synthesis (Scheme 4). Moreover, the reaction progress can be easily monitored by ^{31}P-NMR spectroscopy.

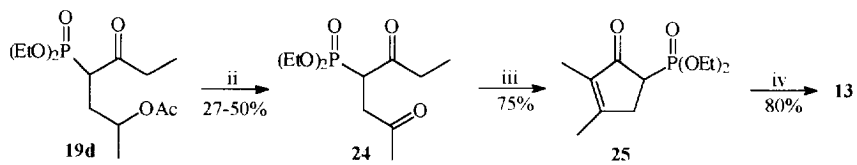
Thus, starting from different radical precursors **16** (Y=H, Me, Cl; X=Cl, Br, SMe) and commercially available isopropenyl acetate, the phosphonate **19d** was obtained as a mixture of two diastereoisomers under the free-radical, reductive conditions (*n*-Bu_3SnH/AIBN, toluene, reflux, 3-4 hrs, syringe pump) in 48-53% yields (65-67% based on the substrate recovered). Then, the acetate function in the resulting phosphonate **19d** was hydrolyzed under acidic conditions to the corresponding 4-hydroxy ketone[19] which immediately was "in situ" oxidized with chromium salts (VI) to give the known 1,4-diketone **24**[5] (path A, Scheme 4). Cyclization of the latter under basic conditions gave the stable, phosphonate precursor **25** of the methylenomycin B **13**. Finally, the conversion of **25** to **13** was achieved through the Horner-Wittig reaction with formaldehyde[5].

It is interesting to note that hydrolysis of the acetate **19d** under acidic conditions (conc. HCl, MeOH, 24 hrs, reflux) in the absence of oxidant, led unexpectedly to the formation of 4-phosphorylated 2,3-dihydrofuran **22** in a quantitative yield[19]. Performance of the reaction at room temperature (2 days) led to the full recovery of the substrate. The chemical structure of **22** was established by ^{1}H-, ^{13}C-, ^{31}P-NMR, UV, IR, MSCI techniques and finally by elemental analysis, 2D ^{1}H-^{1}H (COSY) and ^{1}H-^{13}C-NMR correlations. The formation of **22** may involve two reversible processes (removal of the acetate function and nucleophilic attack of the free hydroxy group at the carbonyl moiety) and irreversible removal of water from the intermediate cyclic hemiketal formed (path B, Scheme 4). An alterntive mechanism that would involve the carbophilic attack of the enol hydroxyl at the protonated C-OH or C-OAc is less probable since the formation of the enol form of 2-oxoalkylphosphonate is suppressed in methanol (confirmed by ^{31}P-NMR spectroscopy). In summary, the oxidative hydrolysis of the acetate function in **19d** under acidic conditions leads to two different processes: formation of the 1,4-diketone **24** (path A, Scheme 4), and the much more favoured formation of the dihydrofuran **22** (path B).

On the other hand, the hydrolysis of the acetate **19d** under basic conditions (KOH or NH_4OH or KCN/alcoholic solution, Method A-C, see Experimental) led to the quantitative formation of the phosphate **23**[19] (path C, Scheme 4). The reaction proceeds via two steps, the first undoubtely being hydrolysis of the

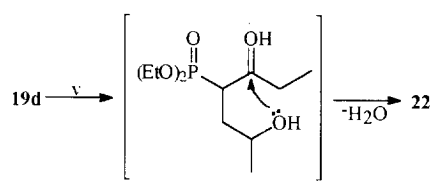


A



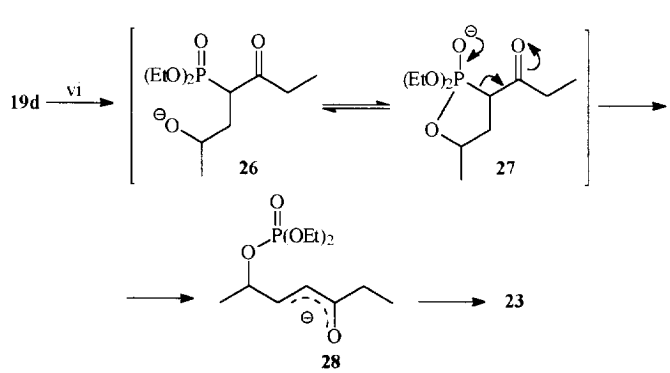
ii: $Na_2Cr_2O_7/H_2SO_4/H_2O$; iii:2% NaOH/EtOH (ref. 5); iv: K_2CO_3/36%(aq.) HCHO/EtOH (ref. 5)

B



v: conc. HCl/MeOH/reflux

C



vi: 3% KOH/EtOH or KCN/EtOH or 25%(aq.) NH_4OH/MeOH

Scheme 4

acetate function. The second consists in nucleophilic attack of the oxyanion **26** at the phosphoryl phosphorus leading most probably via a five-membered oxyphosphorane intermediate **27** to the rearranged product **28**, and after protonation to the phosphate **23**. The driving force for this new example of the phosphoryl group migration from carbon to oxygen is a high nucleophilicity of the oxyanion towards phosphorus and stabilization of the enolate anion formed. It is interesting to note that the hydrolysis/oxidation step under basic, phase-transfer conditions (pyridinium dichromate-PDC/3% $KOH/H_2O/CH_2Cl_2$; n-$Bu_4N^+Br^-$ (cat.); 2 hrs, 25°C) led to the formation of the 1,4-diketone **24** in 27% yield.

In conclusion, in this paper the first report on the synthetically useful 2-oxoalkylphosphonyl radicals **17** derived from 1-mono(Y=H; X=Cl, Br, SMe) and 1,1-di(Y=Cl, X=Cl) heterosubstituted phosphonates **16** and generated under the Giese reductive conditions (n-Bu_3SnH/AIBN) is described. The radicals **17** were utilized for the elaboration of the free-radical synthesis of highly functionalized phosphonates **19** and **20**. In particular, the utility of the new approach was demonstrated in the synthesis of the phosphonate **19d** obtained in the reaction of the radical **17** (R^1=Et, Y=H) and the commercially available isopropenyl acetate **18b**. The phosphonate **19d** was hydrolyzed and oxidized under acidic conditions to the 1,4-diketone **24**, a key substrate in the synthesis of methylenomycin B **13**[5]. The acidic hydrolysis of **19d** without the oxidant led to the quantitative formation of 4-diethoxyphosphoryl 2,3-dihydrofuran **22**, while basic hydrolysis of **19d** led to the P-C→P-O rearrangement which results in a quantitative formation of the phosphate **23**.

Acknowledgement: Financial support by the State Committee for Scientific Research (Grant No 2 2684 9203) is gratefully acknowledged.

EXPERIMENTAL SECTION

The ^{1}H-NMR (200 MHz) and ^{31}P-NMR (81 MHz) spectra were recorded using a Bruker AC-200 spectrometer. The mass spectra were obtained using a Finnigan Mat 95 spectrometer. The models A and A-D of a syringe pump (Razel Scientific Instruments Inc.) were employed for a slow addition of tin reagents. The preparative thin layer chromatography was performed using 20x20cm Merck silica-gel plates with concentrated zone. Organic solvents were purified by standard procedures. Toluene was deaerated with stirring under vacuum (2-3 times) and kept under argon. All alkenes were commercial reagents (Aldrich Chemical Co.)

Diethyl 1-Methylthio-2-oxo-n-propylphosphonate **16a**

To a stirred solution of diethyl 1-(methylthio)methylphosphonate (0.07 mol, 13.86 g) in dry tetrahydrofuran (70 ml), a solution of n-butyllithium in diethyl ether (0.077 mol) was added dropwise at -78°C under argon atmosphere. After stirring for 45 mins. at this temperature, a solution of ethyl acetate (0.035 mol, 3.08 g) in tetrahydrofuran (35 ml) was added and the resulting mixture was additionally stirred at -78°C for 1 hr. Then, the temperature was raised to 0°C and the reaction mixture was acidified with 10% aqueous solution of

hydrochloric acid. The solvents were evaporated and the water layer was extracted with chloroform (3x100 ml). The combined chloroform solutions were washed with 10% aqueous solution of sodium hydroxide to remove sodium enolate of **16a** from the starting material (3x50ml). The combined alkaline solutions were additionally washed with chloroform (1x50ml), acidified with 10% HCl to free **16a** and finally extracted with chloroform (3x80ml). The combined chloroform solutions were washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The crude **16a** (13.1g, 78% yield) was purified by distillation or column chromatography over silicagel (toluene or benzene/acetone in a gradient as eluent).

Yield: 10.9g (65%)[16]: b.p. 54-56°C/0.05 Torr; n_D^{24}=1.4697. ^{31}P-NMR ($CDCl_3$), δ=26.4 ppm (8%, the keto form), 18.3 ppm (92%, the enol form). ^{1}H-NMR (C_6D_6), δ=1.01 (t, 6H, $^3J_{H-H}$=7.1 Hz, $POCH_2C\underline{H}_3$, ketone); 1.04 (t, 6H, $^3J_{H-H}$=7.1 Hz, $POCH_2C\underline{H}_3$, enol); 1.87 (d, 3H, $^4J_{H-P}$= 1.0 Hz, SCH_3, ketone); 1.90 (d, 3H, $^4J_{H-P}$=1.0 Hz, SCH_3, enol); 2.19 (s, 3H, $C(O)CH_3$); 2.20 (d, 3H, $^4J_{H-P}$=1.4 Hz, =C-CH_3, enol); 3.50 (d, 1H, $^2J_{H-P}$=19.4 Hz, PCH, ketone); 3.71-4.03 (m, 4H, $POC\underline{H}_2CH_3$, enol); 3.98 (2xdq, 4H, $^3J_{H-H}$=7.1 Hz, $^3J_{H-P}$=10.4 Hz, $POC\underline{H}_2CH_3$, ketone); 12.93 (brs, 1H, OH, enol). ^{13}C-NMR ($CDCl_3$), δ=15.31 (d, $^3J_{C-P}$=6.3 Hz)+15.56 (one arm of a doublet)+15.75 (d, $^3J_{C-P}$=5.4 Hz)-SCH_3 and $POC\underline{H}_2CH_3$, enol+ketone; 19.09, 18.82 (2xs, $\underline{C}H_3$-C=C, enol); 27.23 (s, $C(O)\underline{C}H_3$); 52.57 (d, $^1J_{C-P}$=138.0 Hz, P-C, ketone); 61.95 (d, $^2J_{C-P}$=4.8 Hz, $POC\underline{H}_2CH_3$, enol); 63.03 (d, $^2J_{C-P}$=5.3 Hz, $POC\underline{H}_2CH_3$, ketone); 198.99 (s, C=O). IR (film), ν(cm^{-1})-1590 (C=C), 1705 (C=O). Anal. for $C_8H_{17}O_4PS$=240.0; Calcd/Found: C-39.99/39.96, H-7.13/7.13, P-12.89/13.40; S-13.34/13.53.

Diethyl 1-Chloro-2-oxo-n-butylphosphonate **16b**

This compounds was prepared according to the modified procedure of Nicholson and Vaughn[15]. To a stirred solution of **16e** (4g, 14.4 mmol) in methanol (6 ml), sodium hydrogen carbonate-$NaHCO_3$ (1.21g, 14.4 mmol +10-15% excess) was added at room temperature. Then, to the resulting suspension, a solution of sodium hyposulfite-$Na_2S_2O_5$ (1.37g, 7.2 mmol +10-15% excess) in water (6 ml) was added dropwise. Stirring was continued for 4.5 hrs. The precipitate was removed by filtration and the filtrate was evaporated to give the crude **16b** (75-89%, ^{31}P-NMR). This material was dissolved in chloroform, washed with water, dried over anhydrous $MgSO_4$, filtered, evaporated and finally distilled to give analytically pure **16b**.

Yield: 68-80%, 130°C/0.005 Torr (Kugelrohr), n_D^{20}=1.4538. ^{31}P-NMR ($CDCl_3$), δ=13.1 ppm (Lit.[20]: δ=10.0 ppm, $CDCl_3$). ^{1}H-NMR ($CDCl_3$), δ=1.07 (t, 3H, $^3J_{H-H}$=7.1 Hz, $C(O)CH_2C\underline{H}_3$); 1.32, 1.33 (2xdt, 6H, $^3J_{H-H}$=7.1 Hz, $^4J_{H-P}$=0.7 Hz, $POCH_2C\underline{H}_3$); 2.70 (q, 1H, $^3J_{H-H}$=7.1 Hz, $C(O)C\underline{H}_2CH_3$); 2.88 (dq, 1H, $^3J_{H-H}$=7.1 Hz, $^4J_{H-P}$=0.4 Hz, $C(O)C\underline{H}_2CH_3$); 4.23, 4.24 (2xdq, 4H, $^3J_{H-H}$=7.1 Hz, $^3J_{H-H}$=10.0 Hz, $POC\underline{H}_2CH_3$); 4.49 (d, 1H, $^2J_{H-P}$=17.4 Hz, PCH). Anal. for $C_8H_{16}O_4PCl$=242.63; Calcd/Found: 39.60/39.73; H-6.65/6.90.

Diethyl 1-Bromo-2-oxo-n-butylphosphonate **16c**

To a stirred solution of diethyl 2-oxo-n-butylphosphonate (2.08g, 0.01 mol) in anhydrous tetrahydrofuran (50ml) , a solution of n-butyllithium (0.01 mol+3% excess, 6.8 ml, 1.54 M) in n-heksane was added dropwise at -78°C. The resulting solution was stirred for 20 mins and bromine (0.01 mol, 1.6g) was added. The

temperature of the reaction mixture was raised to 25°C within 30 mins and saturated, aqueous solution of NH_4Cl was added. The solvents were evaporated and the residue was dissolved in chloroform (100ml). The chloroform solution was washed with water, dried over $MgSO_4$, filtered, evaporated and finally distilled. Yield: 50%.

The employment of other bases and reaction conditions gave lesser yields of **16c** (NaH/Br, diethyl ether, 0°C↗25°C-32%; Et_3N/Br_2, diethyl ether, 0°C↗25°C-28%).

100°C/0.05 Torr. ^{31}P-NMR ($CDCl_3$), δ=13.7 ppm, ^{1}H-NMR ($CDCl_3$), δ=1.06 (t, 3H, $^3J_{H-H}$=7.1 Hz, $C(O)CH_2C\underline{H}_3$); 1.32 (2xdt, 6H, $^3J_{H-H}$=7.0 Hz, $^4J_{H-P}$=0.7 Hz, $POCH_2CH_3$); 2.61-3.11 (m, 2H, $C(O)CH_2$); 4.20 (m, 4H, $POCH_2C\underline{H}_3$); 4.37 (d, 1H, $^2J_{H-P}$= 15.1 Hz, PCH). MSEI (15ev, m/z, %)-286, 288 (6); 230, 232 (100); 203, 205 (26); 151 (11). Anal. for $C_8H_{16}O_4PBr$=287.1; Calcd/Found: C-33.47/33.88; H-5.62/5.77.

Diethyl 1-Methylthio-2-oxo-n-butylphosphonate **16d**

This compound was prepared from diethyl 1-(methylthio)methylphosphonate and ethyl propionate according to the procedure applied for the synthesis of **16a**.

Yield: 44% (Kugelrohr distillation); b.p. 105°C/0.1 Torr; n_D^{20}=1.4725. ^{31}P-NMR ($CDCl_3$), δ=26.4 ppm (9%, enol), 18.3 ppm (91%, ketone). ^{1}H-NMR ($CDCl_3$): δ=1.09 (t, 3H, $^3J_{H-H}$=7.2 Hz, $C(O)CH_2C\underline{H}_3$, ketone), 1.18 (dt, 3H, $^3J_{H-H}$=7.5 Hz, $^5J_{H-H}$=0.4 Hz, $=CCH_2C\underline{H}_3$, enol); 1.33 (2xdt, 6H, $^3J_{H-H}$=7.1 Hz, $^4J_{H-P}$=1.6 Hz, $POCH_2C\underline{H}_3$, ketone); 2.15 (d, 3H, $^4J_{H-P}$=1.0 Hz, SCH_3, enol), 2.20 (d, 3H, $^4J_{H-P}$=1.0 Hz, SCH_3, ketone); 2.63-2.87 (m, 4H, $(O)C-C\underline{H}_2CH_3$, enol+ketone); 3.62 (d, 1H, $^2J_{H-P}$=19.4 Hz, PCH, ketone); 4.09-4.28 (m, 4H, $POC\underline{H}_2CH_3$, ketone+enol), 12.03 (m, 1H, OH). Anal. for $C_9H_{19}O_4PS$=254.29; Calcd/Found: C-42.51/42.45, H-7.53/7.44.

Diethyl 1,1-Dichloro-2-oxo-n-butylphosphonate **16e**

To a stirred solution of diethyl 2-oxo-n-butylphosphonate (2.08g, 0.01 mol) in anhydrous carbon tetrachloride (50ml), a solution of sulfuryl chloride (2.70g, 1.6ml, 0.02 mol) in the same solvent (20ml) was added dropwise at 0°C (water-ice bath) within 20 mins. The resulting solution was refluxed for further 20 mins, cooled, evaporated and distilled (Kugelrohr).

Yield: 80%; 0.01 Torr/110°C; n_D^{20}=1.4612 (crude:n_D^{20}=1.4610). ^{31}P-NMR ($CDCl_3$), δ=8.47 ppm. ^{1}H-NMR ($CDCl_3$), δ=1.15 (t, 3H, $^3J_{H-H}$=7.2 Hz, $C(O)CH_2C\underline{H}_3$); 1.38 (dt, 6H, $^3J_{H-H}$=7.1 Hz; $^4J_{H-H}$=0.9 Hz; $POCH_2C\underline{H}_3$); 3.00 (q, 2H, $^3J_{H-H}$=7.2 Hz; $C(O)CH_2$); 4.28-4.40 (m, 4H, $POC\underline{H}_2CH_3$).

Anal. for $C_8H_{15}O_4PCl_2$=277.08. Calcd/Found: C-34.68/34.88, H-5.46/5.68.

Diethyl 1-Chloro-1-methyl-2-oxo-n-butylphosphonate **16f**

To a stirred solution of diethyl 1-methyl-2-oxo-n-butylphosphonate (407 mg, 1.38 mmol) dissolved in anhydrous carbon tetrachloride (10 ml), sulfuryl chloride (190 µl, 320 mg, 2.38 mmol) was added dropwise through a microsyringe at 0°C. The resulting solution was stirred for 2 hrs at room temperature, next refluxed for 20 mins, evaporated and then kept under high vacuum for 1 hr to give the crude **16f** in the quantitative

yield. This product was used for the free-radical reactions without further purification; n_D^{30}=1.4484. ^{31}P-NMR ($CDCl_3$), δ=17.15 ppm. ^{1}H-NMR ($CDCl_3$), δ=1.05 (t, 3H, $^3J_{H-H}$=7.1 Hz, C(O)$CH_2\underline{CH_3}$); 1.31 (dt, 6H, $^3J_{H-H}$=7.1 Hz, $^4J_{H-P}$=2.3 Hz, $POCH_2\underline{CH_3}$), 1.81 (d, 3H, $^3J_{H-P}$=14.9 Hz, P-C-Me); 2.91 (2xq, 2H, $^3J_{H-H}$=7.1 Hz, C(O)$\underline{CH_2}CH_3$); 4.23 (dq, 4H, $^3J_{H-H}$=$^3J_{H-P}$=7.1 Hz, $POCH_2CH_3$); MSEI (70ev, m/z, %)-275 (M^+, 0.3), 202 (27), 200 (100), 174 (7), 172 (20), 165 (18), 147 (3), 146 (17), 145 (11), 144 (56), 57 (11). MS-HRCI-Anal. for $C_9H_{19}PO_4Cl$: Calcd/Found-257.0709/257.0700.

General procedure for preparation of phosphonates **19a-e** *and* **20**.

To a stirred solution of the appropriate phosphonate **16** (1 mmol) and alkene **18** (6-50 mmol, see Table 1) in refluxing and deaerated toluene (30ml), a solution of n-Bn_3SnH (404-485 μl, 437-524 mg, 1.5-1.8 mmol) and α, α'-azabisisobutyronitrile-AIBN (26-33 mg, 0.16-0.20 mmol) in toluene (17ml) was added dropwise through the syringe pump within 4 hours. Heating was continued for additional 1 hr and toluene was evaporated to give the crude material which was first distilled (Kugelrohr) and then chromatographed using silicagel (column or TLC plates; toluene/acetone as eluent).

Diethyl 1-(2-n-Butoxyethyl)-2-oxo-n-propylphosphonate **19a**

oil; 170°C/0.001 Torr (Kugelrohr). ^{31}P-NMR ($CDCl_3$), δ=23.2 ppm. ^{1}H-NMR ($CDCl_3$), δ=0.88 (t, 3H, $^3J_{H-H}$=7.2 Hz, $(CH_2)_3\underline{CH_3}$); 1.29; 1.30 (2xdt, 6H, $^3J_{H-H}$=7.1 Hz, $^4J_{H-P}$=0.4 Hz; $POCH_2\underline{CH_3}$); 1.18-1.55 (m, 4H, $(CH_2)_2$); 1.89-2.10 (m, 2H, P-CH-$\underline{CH_2}$); 2.15-2.38 (m, 1H, PCH); 2.31 (s, 3H, C(O)CH_3); 3.26-3.41 (m, 4H, CH_2OCH_2); 4.03-4.18 (m, 4H, $POCH_2CH_3$). ^{13}C-NMR ($CDCl_3$), δ=13.8 (s, $(CH_2)_3\underline{C}H_3$); 16.25 (d, $^3J_{C-P}$=5.5 Hz, $POCH_2\underline{C}H_3$); 19.24 (s, $(CH_2)_2\underline{C}H_2CH_3$); 26.61, 26.71 (2xs, $PCH\underline{C}H_2$; $OCH_2\underline{C}H_2CH_2CH_3$), 31.5 (d, $^2J_{C-P}$=13.0 Hz, C(O)$\underline{C}H_3$); 50.15 (d, $^1J_{C-P}$=125.9 Hz, PCH); 62.4, 62.6 (2xd; $^2J_{C-P}$=10.6 Hz, $PO\underline{C}H_2CH_3$); 68.3 (d, $^3J_{C-P}$=15.3 Hz, $PCHCH_2\underline{C}H_2O$); 70.6 (s, $O\underline{C}H_2$-n-Pr); 203.44 (s, (O)C). ^{13}C-NMR (DEPT) technique was also applied to distinguish carbon frequencies. MSEI (m/z, %): 294 (M^+, 2); 194 (100); 180 (11); 179 (24); 167 (24); 165 (35); 109 (22); 84 (11); 43 (57); 41 (40); 29 (55); 27 (22). MSCI (isobutane); MH^+=295. Anal. for $C_{13}H_{27}O_5P$=294.32, Calcd/Found: C-53.05/52.60; H-9.25/9.21; P-10.52/10.16.

Diethyl 1-Acetyl-3,5-di-n-butyoxy-n-pentylphosphonate **20**

Yield 17% (Method A with 10eqs of alkene); Yield 37% (Method B with 50eqs of alkene); oil; 170°C/0/001 Torr (Kugelrohr). ^{31}P-NMR ($CDCl_3$), δ=23.7 ppm. ^{1}H-NMR ($CDCl_3$), δ=0.89, 0.90 (2xt, 6H, $^3J_{H-H}$=7.2 Hz; 2x$(CH_2)_3\underline{CH_3}$); 1.31; 1.32 (2xt, 6H, $^3J_{H-H}$=7.1 Hz, 2x$OCH_2\underline{CH_3}$); 1.25-1.80 (m, 12H, 2x$(\underline{CH_2})_2CH_3$; $\underline{CH_2}$-CH-$\underline{CH_2}$); 2.32, 2.33 (2xs, 3H, (O)CCH_3); 3.19-3.47 (m, 8H, 2x$O\underline{CH_2}$n-Pr, $CH\underline{O}CH_2$, PCH); 4.11 (m, 4H, 2x$O\underline{CH_2}CH_3$). MSCI (isobutane) MH^+=395. MSEI (70ev, m/z, %)-395(M^++1; 0.6); 293 (50); 263 (18); 219 (26); 207 (66); 201 (20); 195 (28); 194 (100); 191 (21); 179 (23); 167 (23); 165 (61); 163 (23); 126 (61); 115 (35); 109 (20); 57 (54); 43 (16); 41 (23). MS-HRCI-Anal for $C_{19}H_{40}O_6P$: Calcd/Found-395.2563/395.2557.

Diethyl 3-Acetoxy-1-acetyl-n-butylphosphonate **19b**

oil; ^{31}P-NMR ($CDCl_3$), δ=22.5, 22.4 ppm: diasteroisomers in a ratio 7/10 (after TLC, ethyl acetate as eluent). ^{1}H-NMR ($CDCl_3$), δ=1.18, 1.21 (2xd, 3H, $^3J_{H-H}$=6.2 Hz; CHC<u>H</u>$_3$); 1.30 (dt, 6H, $^3J_{H-H}$=7.3 Hz, $^4J_{H-P}$=0.3 Hz, C<u>H</u>$_3$CH$_2$OP in one diastereomer); 1.31 (dt, 6H, $^3J_{H-H}$=7.5 Hz, $^4J_{H-P}$=0.4 Hz, C<u>H</u>$_3$CH$_2$OP in the second diastereomer); 1.95, 1.99 (2xs, 3H, OAc); 1.82-2.45 (m, 2H, P-CH-C<u>H</u>$_2$); 2.30, 2.31 (2xs, (O)CCH$_3$); 3.07-3.38 (m, 1H, PCH); 4.10 (m, 4H, CH$_3$C<u>H</u>$_2$OP); 4.70-4.95 (m, 1H, CH-OAc). MS-GC (m/z, %)-one diastereomer: M+1 (0.3; 295); 252 (6); 207 (5); 165 (100); 137 (16); 109 (17); 43 (84); second diasteromer: 294 (0.2); 293 (0.8); 292 (7); 207 (7); 165 (40); 137 (5); 43 (100). ^{13}C-NMR ($CDCl_3$), δ=16.20 (d, $^3J_{C-P}$=5.3 Hz; POCH$_2$<u>C</u>H$_3$); 19.92, 20.20, 20.98 (3 frequencies, PCH<u>C</u>H$_2$, <u>C</u>H$_3$CH); 30.53, 31.58, 32.26, 32.37, (4xs, <u>C</u>H$_3$C(O), OC(O)<u>C</u>H$_3$); 49.16, 50.52 (2xd. $^1J_{C-P}$=124.4, 124.8 Hz, PCH); 62.54, 62.75 (2xd, $^2J_{C-P}$=10.9, 10.2 Hz, PO<u>C</u>H$_2$CH$_3$); 68.55, 70.20 (2xd, $^3J_{C-P}$=15.7; 14.0 Hz, CHOAc); 170.22, 170.49 (2xs, CH$_3$<u>C</u>(O)O); 202.75 (s, <u>C</u>(O)CH$_3$). Anal.for $C_{12}H_{23}O_6P$=294.28; Calcd/Found: C-48.97/48.97; H-7.87/7.84.

Diethyl 1-(2-Acetoxyethyl)-2-oxo-n-butylphosphonate **19c**

oil; prep. TLC-toluen/acetone, v/v=2/1. ^{31}P-NMR ($CDCl_3$), δ=22.5 ppm. ^{1}H-NMR ($CDCl_3$), δ=1.07 (t, 3H, $^3J_{H-H}$=7.2 Hz, C(O)CH$_2$C<u>H</u>$_3$); 1.31 (dt, 6H, $^3J_{H-H}$=7.1 Hz, $^4J_{H-P}$=1.9 Hz, POCH$_2$CH$_3$); 2.01 (s, 3H, OAc); 2.28-2.59 (m, 3H, C(O)C<u>H</u>$_2$CH$_3$(1H)+PCHC<u>H</u>$_2$); 2.83, 2.92 (2xq, 1H, $^3J_{H-H}$=7.2 Hz, C(O)C<u>H</u>$_2$CH$_3$(1H)); 3.30 (ddd, 1H, $^2J_{H-P}$=24.9 Hz, $^3J_{H-H}$=10.5, 3.4 Hz, PC<u>H</u>CH$_2$); 4.03 (t, 2H, $^3J_{H-H}$=6.1 Hz, CH$_2$OAc); 4.05-4.19 (m, 4H, POC<u>H</u>$_2$CH$_3$). MSEI (70ev, m/z, %)-294 (M$^+$, 0.7), 223 (12), 179 (16), 167 (14), 165 (100), 149 (13), 137 (11), 108 (11), 109 (16), 57 (16), 41 (16), 43 (27), 29 (23). Anal. for $C_{12}H_{23}O_6P$=294.28. Calcd/Found-48.97/49.20; H-7.87/7.92.

Diethyl 1-(2-Acetoxy-n-propyl)-2-oxo-n-butylphosphonate **19d**

oil; 0.01 Torr /150°C (Kugelrohr); a mixture of diasteromers in a ratio 1/1. ^{31}P-NMR ($CDCl_3$), δ=22.8, 22.7 ppm. ^{1}H-NMR ($CDCl_3$), δ=1.04, 1.05 (2xt, 3H, $^3J_{H-H}$=7.2 Hz, C(O)CH$_2$C<u>H</u>$_3$); 1.18, 1.20 (2xd, 3H, $^3J_{H-H}$=6.2 Hz, CHC<u>H</u>$_3$); 1.30 (t, 6H, $^3J_{H-H}$=7.1 Hz, C<u>H</u>$_3$CH$_2$OP in one diastereomer); 1.31 (dt, 6H, $^3J_{H-H}$=6.9 Hz, $^4J_{H-P}$=0.3 Hz; C<u>H</u>$_3$CH$_2$OP in the second diastereomer); 1.95, 2.00 (2xs, 3H, OAc); 1.78-2.10 (m, 2H, P-CHC<u>H</u>$_2$); 2.29-2.52 (m, 2H, C(O)C<u>H</u>$_2$CH$_3$); 3.19 (ddd, 1H, $^3J_{H-H}$=2.2, 11.8 Hz; $^2J_{H-P}$=25.4 Hz, P-CH in the first diastereomer); 3.30 (ddd, 1H, $^3J_{H-H}$=3.5, 9.3 Hz; $^2J_{H-P}$=24.2 Hz; PCH in the second diastereomer); 4.00-4.20 (m, 4H, CH$_3$C<u>H</u>$_2$OP); 4.70-4.92 (m, 1H, CH-OAc). ^{13}C-NMR ($CDCl_3$), δ=7.25 (s, C(O)CH$_2$<u>C</u>H$_3$); 16.25 (d, $^3J_{C-P}$=5.2 Hz, POCH$_2$<u>C</u>H$_3$); 20.2, 21.07 (2xs, PCH<u>C</u>H$_2$); 32.49 (2xs, C(O)<u>C</u>H$_3$); 36.9, 37.8, (2xs, C(O)<u>C</u>H$_2$); 48.2, 49.8 (2xd, $^1J_{C-P}$=124.6, 125.7 Hz, PCH); 62.48-62.85 (m, PO<u>C</u>H$_2$CH$_3$); 68.6, 70.30 (2xd, $^3J_{C-P}$=15.6, 13.3 Hz, CHOAc); 170.30, 170.50 (2xs, O<u>C</u>(O)Me); 205.57, 205.65 (2xs, <u>C</u>(O)Et). MSEI (70ev, m/z, %)-308 (M$^+$, 0.2), 252 (7), 237 (8), 208 (5), 165 (100), 163 (6), 137 (12), 109 (13), 57 (8), 43 (43), 29 (22). Anal. for $C_{13}H_{25}O_6P$=308.31; Calcd/Found: C-50.56/50.42, H-8.17/8.29.

Diethyl 1-(2-Acetoxy-n-propyl)-1-chloro-2-oxo-n-butylphosphonate **19e**

oil (diastereoisomers in a ratio 1/1 after the preparative TLC using toluene/acetone=2/1 as eluent). ^{31}P-NMR ($CDCl_3$), δ=15.4, 14.9 ppm. ^{1}H-NMR ($CDCl_3$), δ=1.07 (t, 3H, $^3J_{H-H}$=7.1 Hz, C(O)$CH_2C\underline{H}_3$); 1.19 (2xd, 3H, $^3J_{H-H}$=6.2 Hz, $CHC\underline{H}_3$); 1.28-1.39 (m, 6H, $POCH_2C\underline{H}_3$); 1.90, 1.98 (2xs, 3H, OAc); 2.80-3.10 (m, 2H, $C\underline{H}_2CH$); 4.13-4.32 (m, 4H, $POC\underline{H}_2CH_3$); 4.94-5.24 (m, 1H, $C\underline{H}CH_3$). Anal. for $C_{13}H_{24}O_4PCl$=342.75; Calcd/Found: C-45.55/45.57; H-7.05/6.91.

Compounds **16b** (50-60%) and **19d** (8-20%) accompanied **19e** and were also separated from the crude reaction mixture.

4-Diethoxyphosphoryl-5-ethyl-2-methyl-2,3-dihydrofuran **22**

To a stirred solution of the phosphonate **19d** (30.8 mg, 0.1 mmol) in methanol (100 ml), concentrated hydrochloric acid (1 drop) was added at room temperature and the resulting mixture was refluxed for 24 hrs. Then methanol was evaporated and to the residue chloroform (50 ml) and water (10 ml) were added. The chloroform solution was again washed with water (10 ml), dried over anhydrous $MgSO_4$, filtered and evaporated to give pure **22** in the quantitative yield. In some cases, 5-8% of the starting material was left. Separation of **22** from **19d** was then achieved by the preparative TLC (benzene/acetone as eluent, v/v=2/1). oil. ^{31}P-NMR ($CDCl_3$), δ=19.8 ppm.^{1}H-NMR ($CDCl_3$, 300 MHz), δ=1.08 (t, 3H, $^3J_{H-H}$=7.5 Hz, C(O)$CH_2C\underline{H}_3$); 1.29 (t, 6H, $^3J_{H-H}$=7.0 Hz, $C\underline{H}_3CH_2OP$); 1.31 (d, 3H, $^3J_{H-H}$=6.7 Hz, CH-$C\underline{H}_3$); 2.35 (dddt, 1H, $^3J_{H-P}$=14.0, $^3J_{H-H}$=7.2, $^2J_{H-H}$=2.4, $^3J_{H-H}$=1.1 Hz, $PCC\underline{H}_A$); 2.52 (qdt, 2H, $^3J_{H-H}$=7.5, $^4J_{H-P}$=1.6, $^5J_{H-H}$=1.1 Hz, =C-$C\underline{H}_2CH_3$; 2.89 (dddt, 1H, $^3J_{H-P}$=13.4, $^3J_{H-H}$=9.8, $^2J_{H-H}$=2.4, $^5J_{H-H}$=1.1 Hz, $PCC\underline{H}_B$); 3.95-4.10 (m, 4H, $CH_3C\underline{H}_2OP$); 4.67-4.78 (m, 1H, CH-O). ^{13}C-NMR ($CDCl_3$), δ=11.67 (s, =$CCH_2\underline{C}H_3$); 16.28 (d, $^3J_{C-P}$=6.1 Hz, $\underline{C}H_3CH_2OP$); 20.87 (s, =C-$\underline{C}H_2$); 21.53 (s, $OCH\underline{C}H_3$); 38.49 (d, $^2J_{C-P}$=9.8 Hz, P-C=$\underline{C}H_2$); 60.97 (d, $^2J_{C-P}$=4.8 Hz; $CH_3\underline{C}H_2OP$); 78.33 (d, $^3J_{C-P}$=12.0 Hz, CH-O); 91.17 (d, $^1J_{C-P}$=217.4 Hz, P-C=). UV (MeOH), λ=228 nm. IR (film), ν=1630 cm^{-1}. MSCI (isobutane), M+1=249. MSEI (70ev, m/z, %), 248 (M^+, 100), 233 (20), 220 (30), 219 (26), 205 (17), 192 (31), 191 (54), 177 (25), 55 (16).

2-Diethoxyphosphoryloxy-heptan-5-one **23**

Method A: A solution of **19d** (30.8 mg, 0.1 mmol) in 3% ethanolic solution of KOH (3 ml) was stirred for 24 hrs at room temperature. Then, the solution was neutralized with 10% aqueous solution of HCl and extracted with chloroform (2x15 ml). The combined chloroform solutions were washed with water, dried over $MgSO_4$, filtered and evaporated to give **23** in the quantitative yield.

Method B: A solution of **19d** (30.8 mg, 0.1 mmol) in a mixture of methanol (0.6 ml) and 25% aqueous solution of ammonia (0.6 ml) was stirred for 24 hrs at room temperature. Then, methanol was evaporated and the residue was extracted with chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, filtered and evaporated to give **23** in 85-100% yield. In case of a lesser yield than quantitative, the crude sample was purified by TLC (toluene/acetone as eluent, v/v=2/1).

Method C: To a stirring solution of **19d** (120 mg, 0.38 mmol) in 95% ethanol, potassium cyanide (114 mg, 1.71 mmol) was added and the resulting mixture was refluxed for 6 hrs. Then, ethanol was evaporated and the residue was dissolved in chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, filtered and evaporated to give **23** in 72-100% yield. In case of a lesser yield than quantitative, the crude sample was purified by TLC (toluene/acetone as eluent, v/v=2/1.

oil. ^{31}P-NMR ($CDCl_3$), δ=-0.84 ppm. ^{1}H-NMR ($CDCl_3$), δ=1.05 (t, 3H, $^3J_{H-H}$=7.3 Hz, C(O)$CH_2C\underline{H}_3$); 1.19-1.36 (m, 9H, 2x$C\underline{H}_3CH_2OP$, $C\underline{H}_3CH$); 1.78-2.00 (m, 2H, $CHC\underline{H}_2$); 2.44 (q, 2H, $^3J_{H-H}$=7.3 Hz, C(O)$C\underline{H}_2CH_3$); 2.56 (t, 2H, $^3J_{H-H}$=7.3 Hz, $C\underline{H}_2C(O)CH_2CH_3$); 4.08 (2xdq, 4H, $^3J_{H-H}$=$^3J_{H-P}$=7.1 Hz; 2x$CH_3C\underline{H}_2OP$); 4.47 (m, 1H, CHOP). MSEI (15ev, m/z, %)-266 (M^+, 1) 195 (32), 155 (74), 127 (16), 113 (12), 112 (100), 83 (57), 57 (20). Anal. for $C_{11}H_{23}O_5P$=266.09: Calcd/Found-49.65/49.51; H-8.71/8.84.

Diethyl 1-Methoxymethyl-2-oxo-n-butylphosphonate **24**

Method A: To a stirring solution of **19d** (111 mg, 0.35 mmol) in diethyl ether, a solution of sodium dichromate dihydrate (53 mg, 0.178 mmol) in a mixture of water (260 µl) and concentrated H_2SO_4 (40 µl) was added dropwise and the resulting solution was stirred for 2 hrs. Then the solvent was evaporated. The residue was dissolved in methylene chloride, washed with water, dried over $MgSO_4$, filtered and evaporated to give the crude **24** which was purified by TLC (toluene/acetone as eluent). Yield: 50%. Spectral data were identical with those reported by us earlier[5], for instance: ^{31}P-NMR ($CDCl_3$), δ=22.1 ppm [Lit.[5]: δ ($CHCl_3$)=21.9 ppm, δ (THF)=21.7-22.2 ppm].

Method B: To a stirring solution of **19d** (10 mg, 0.03 mmol) in methylene chloride (2 ml), a solution of 3% aqueous solution of potassium hydroxide (2 ml) and tetrabutyl ammonium bromide (2-3 mg) were added. Then, pyridinium dichromate (100 mg, 0.34 mmol) was added and the resulting mixture was vigorously stirred for 2 hours. Next, methylene chloride (20 ml) and water (20 ml) were added. The water layer was neutralized with 5% aqueous solution of hydrogen chloride and the two-phase mixture was vigorously stirred for 5 mins. Finally, the methylene chloride layer was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by TLC as in Method A. Yield 27%. ^{31}P-NMR ($CDCl_3$), δ=22.0 ppm. The rest of organic material constituted unreacted **19d**. The prolonged reaction time (21 hrs) caused a loose of phosphoroorganic material during the aqueous work-up.

The synthesis of methylenomycin B **13** from **24** is described in our previous paper[5].

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