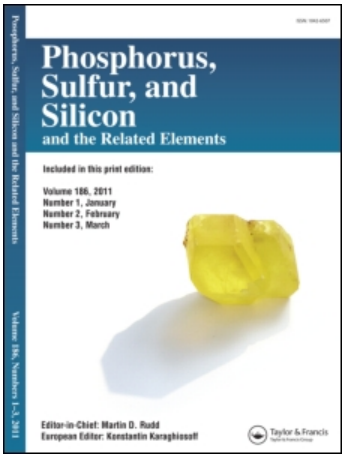


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SELECTIVE PREPARATION OF OXACYCLIC AND LINEAR PHOSPHONATES AND THE EFFECT OF DIETHYL PHOSPHONATE GROUP ON SPECTROSCOPIC DETERMINATION OF THE STRUCTURES

Jen-Wen Yu[a]; Steve K. Huang[a]
[a] Graduate School of Chemical Engineering, National Taiwan University of Science and Technology, Taipei, Taiwan, Republic of CHINA

To cite this Article Yu, Jen-Wen and Huang, Steve K.(1997) 'SELECTIVE PREPARATION OF OXACYCLIC AND LINEAR PHOSPHONATES AND THE EFFECT OF DIETHYL PHOSPHONATE GROUP ON SPECTROSCOPIC DETERMINATION OF THE STRUCTURES', Phosphorus, Sulfur, and Silicon and the Related Elements, 131: 1, 107 — 127
To link to this Article: DOI: 10.1080/10426509708031600
URL: http://dx.doi.org/10.1080/10426509708031600

Phosphorus, Sulfur, and Silicon, 1997, Vol. 131, pp. 107–127
Reprints available directly from the publisher
Photocopying permitted by license only

SELECTIVE PREPARATION OF OXACYCLIC AND LINEAR PHOSPHONATES AND THE EFFECT OF DIETHYL PHOSPHONATE GROUP ON SPECTROSCOPIC DETERMINATION OF THE STRUCTURES

JEN-WEN YU and STEVE K. HUANG*

Graduate School of Chemical Engineering, National Taiwan University of Science and Technology, Taipei, Taiwan 106, Republic of CHINA

(Received 21 January 1997; Revised 19 June 1997; In final form 19 June 1997)

The formation of either oxacyclic or linear phosphonates by alternating the synthetic condition of a single method is described. Structural identification of these two isomeric oxacyclic and linear phosphonates, **2** and **3**, were performed with IR, MS, ^{1}H & ^{13}C NMR. The ^{1}H & ^{13}C NMR spectroscopic data (*i.e.*, the chemical shifts and coupling constants) showed that the phosphonate group was the dominant factor in the conformation of oxacyclic phosphonate, with little effect from the phenyl and *p*-substituted phenyl groups. The phosphonate group with two ethoxy groups hovered over the THF-ring, thus presenting a complex ^{1}H & ^{13}C NMR spectra. The results indicated that the phenyl group stretched out and away from the THF-ring, thus exerting little electronic influence on the oxacyclic ring. For linear phosphonate **3**, McLafferty rearrangements with both C=O and P=O groups were observed in mass fragmentations. Spectroscopic data provided the information for identification of these phosphonates.

Keywords: Selective preparation; Spectroscopic data; Structural identification; 2-Aryl-2-tetrahydrofuranyl phosphonate; δ-Ketophosphonate

INTRODUCTION

A ketophosphonate, containing carbonyl and phosphonate groups, is a versatile compound for organic synthesis. The carbonyl group with an α-hydrogen shows dual character, *i.e.* as an electrophile[1] in the carbocationic carbon and as a stabilizing group for an enolate ion,[2] while the phosphonate group may activate

*Corresponding author. Fax: +886 2 7376644

the adjacent hydrogen (α-hydrogen) for the ylide formation[3] and may act as a leaving group under the RLi/O_2 condition.[4] The utilization of these functions has been illustrated in the preparation of synthetic analogs of naturally occurring materials, *e.g.* methylenomycin **B** from γ-ketophosphonate.[4] An efficient conversion of methyl δ-ketophosphonate to synthetic analogs of the biologically active 3-alkyl-cyclopentenones of allethrone and dihydrojasmone has also been reported.[4] The formation of 3-aryl-cyclopentenones, however, requires aryl δ-ketophosphonates as the starting compounds, since these aryl groups can not be formed by the synthetic procedure.

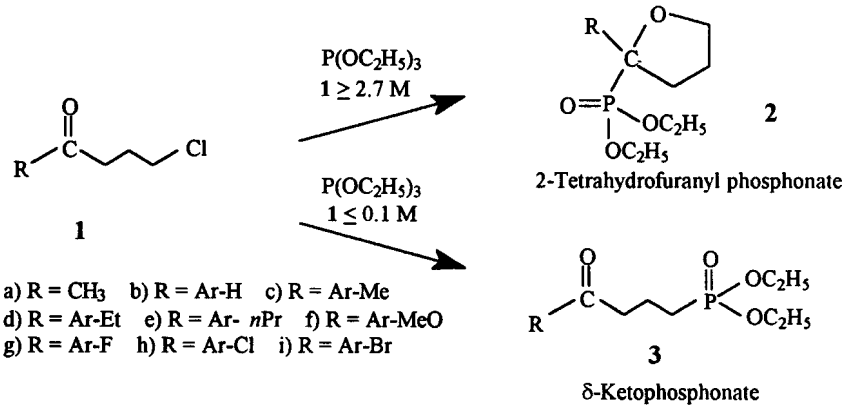
Synthesis of methyl δ-ketophosphonate has been reported by alkylation of α-copper(I) alkanephosphonates with dihalopropenes,[5a] or as a hydrolytic product of the reaction of 5-chloro-2-pentanone ethylene ketal and TEP.[5b] For an oxacyclic phosphonate, 2-methyl-2-tetrahydrofuranyl phosphonate has been obtained as a product of the reaction of 5-chloro-2-pentanone with sodium dialkylphosphite.[5c] Besides these, other phosphonates with aryl groups have not been reported. We report here the formation of methyl and new aryl δ-ketophosphonates, together with 2-methyl and new 2-aryl-2-tetrahydrofuranyl phosphonates, by a novel method in which γ-chloropropyl ketone was reacted with triethyl phosphite (TEP). It may also be interesting to study the formation of the oxacyclic phosphonates, which may be used as the starting materials for the related biological substances, since some plant biologically active metabolites, such as the stress metabolite of ipomearone[6] are known to contain oxacyclic rings. Furthermore, contamination of either oxacyclic or linear δ-ketophosphonates may produce undesirable effects. Therefore, a method for purification of these compounds is also described.

The aim of this investigation was to develop a new method for selective preparation of either oxacyclic phosphonates **2** or linear δ-ketophosphonates **3** through the variation of the synthetic condition. The effect of *p*-substituted-phenyl and phosphonate groups on the structural conformation of the products has been determined by ^1H & ^{13}C NMRs. The characteristics of oxacyclic and linear phosphonates are described and may provide useful data for differentiation of two such isomeric phosphonates.

RESULTS AND DISCUSSION

Selective Preparation of Oxacyclic and Linear Phosphonates

Phosphonation of γ-chloropropyl methyl and *p*-aryl ketones **1** was carried out with TEP as solvent and reagent (Scheme 1). The two products were identified as 2-methyl- and 2-aryl-2-tetrahydrofuranyl phosphonates **2** and the isomeric



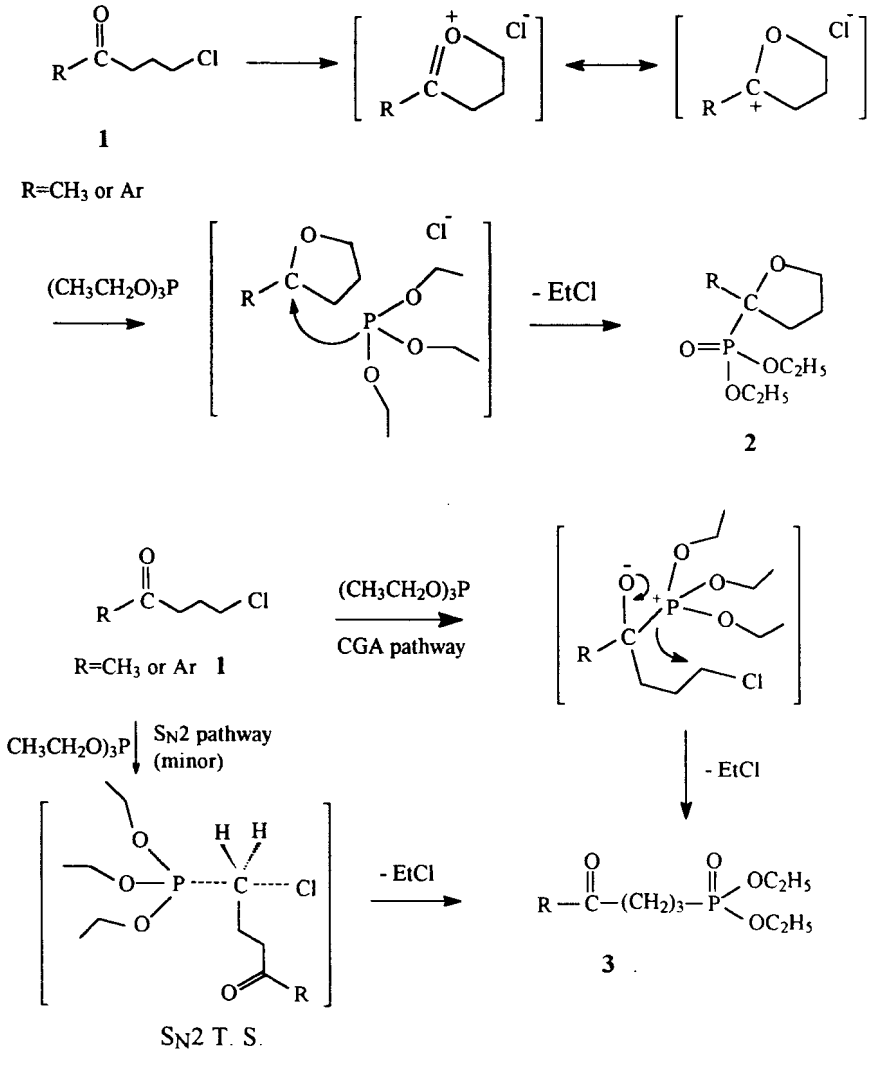
SCHEME 1 Selective preparation of oxacyclic and linear phosphonates

δ-ketophosphonates **3**. The separation of the methyl products (**2a** and **3a**) was carried out by fractional distillation under reduced pressure since the GLC analysis showed wide retention times for these two products (**2a** = 12 min; **3a** = 16 min). However, the aryl derivatives (**2b–2i** and **3b–3i**, respectively) were separated by column chromatography (Table I). Preliminary results of the kinetic study indicated that these two isomeric phosphonates, **2** and **3** were formed through different competitive pathways,[7] as shown in Scheme 2. The formation of oxacyclic phosphonate **2** occurred through the generation of nucleophilic carbonyl oxygen as the initial step, and required no participation of TEP molecules in the rate-determining step, although the TEP was needed in the latter step. On the other hand, the formation of linear δ-ketophosphonate **3** required participation of the TEP molecule in the carbonyl group-assisted (CGA) initial

TABLE I The reaction of γ-chloropropyl ketones **1** with TEP[a]

Reactant	*Total yield (%)*	*Phosphonate distribution (%)*[b]	
		Oxacyclic 2	*Linear 3*
1a	76[c]	58	42
1b	66[d]	60	40
1c	72	80	20
1d	70	84	16
1e	56	79	21
1f	82	>97	—[e]
1g	71	54	46
1h	61	42	58
1i	51	39	61

(a) The reaction was carried out with γ-chloropropyl ketones **1** (1.25 M) in excess TEP under reflux for 6–8 h. (b) The data were obtained directly by GLC analysis. (c) Obtained from the fractional distillation under vacuum. (d) Obtained from column chromatography. (e) Not found.



SCHEME 2 The proposed mechanism for the formation of oxacyclic phosphonates **2** and linear phosphonates **3**.

stage (described as a quasi-3-membered ring stage[8]). If more TEP molecules participate in this rate-determining step, the formation of **3** is likely to be favored. Therefore, the reaction was apparently dictated by the molar ratio of starting ketone **1** and TEP. The corresponding results, presented in Table II, show that δ-ketophosphonate **3b** (R = Ar-H) was formed under dilute condition ($\leq$ 0.10 M), while oxacyclic phosphonate **2b** (R = Ar-H) was produced under

TABLE II Selective formation of isomeric phosphonates[a]

Concentration of 1[b] *(M)*	*Phosphonate distribution (%)*[c]	
	2b	***3b***
2.76	>99	—[d]
1.72	73	27
1.02	51	49
0.52	28	72
0.27	15	85
0.10	—[d]	>99

(a) The reaction was carried out under reflux for 8 h. (b) The concentration was based on excess TEP as reagent and solvent. (c) The phosphonate distribution was analyzed directly by GLC. (d) Not detected.

sterically crowded conditions ($\geq$ 2.76 M). They are two different competitive pathways, such that one does not need while the other needs the participation of TEP in their individual rate-determining steps. The difference of molar ratios offers the different conditions for the formations of **2** and **3** in these solutions. Therefore, an explanation may be offered as, the more TEP molecules in the solution (dilute solution), the CGA pathway and the S_N2 mechanism are more likely to be in operation and lead to the formation of linear δ-ketophosphonate **3**. By the same argument, the reaction with the presence of a smaller number of TEP molecules proceeds through the more compact cyclic transition state and leads to the formation of oxacyclic phosphonates **2**.

Structures of phosphonates, **2** and **3**, were determined on the basis of spectroscopic data. The data of **2b** and **3b** (R = Ar-H) are presented here to illustrate the structural identifications.

Infrared Analysis

The striking absence of the carbonyl group was noticed in **2b**, while strong carbonyl absorption at 1678 cm^{-1} was noted in compound **3b** (Tables III and IV). The absorptions associated with the phosphonate group show a very strong

TABLE III The infrared absorption data of **2** (cm^{-1})

Compound	*C=C(cm⁻¹)*	*P=O(cm⁻¹)*	*P-O-C(cm⁻¹)*
2a	—	1233	1026, 960
2b	1484	1238	1038, 1023, 961
2c	1503	1238	1042, 1022, 964
2d	1502	1241	1040, 1020, 962
2e	1502	1241	1043, 1025, 959
2f	1604, 1503	1246	1044, 1026, 963
2g	1594, 1502	1224	1040, 1023, 959
2h	1583, 1484	1239	1040, 1026, 960
2i	1597, 1480	1245	1037, 1023, 966

TABLE IV The infrared absorption data of **3**

Compound	$C=O(cm^{-1})$	$C=C(cm^{-1})$	$P=O(cm^{-1})$	$P\text{-}O\text{-}C(cm^{-1})$
3a	1702	—	1231	1054, 1024, 961
3b	1678	1591	1218	1051, 1026, 960
3c	1674	1610	1224	1053, 1028, 966
3d	1676	1600	1223	1048, 1028, 959
3e	1676	1600	1224	1050, 1029, 960
3g	1681	1591	1223	1052, 1032, 959
3h	1680	1583	1217	1049, 1026, 959
3i	1679	1579	1227	1051, 1031, 958

peak at 1238–1218 cm^{-1} corresponding to P=O stretching, and a band at 960–1050 cm^{-1} corresponding to P-O-C stretching. The IR absorption peak corresponding to the THF ring is expected to be at 1085–1150 cm^{-1} for C-O-C stretching.[9] The experimental C-O-C absorption at 1096 cm^{-1} could not be distinctly observed due to the strong P=O and P-O-C absorption in this region. This result indicates that the nucleophilic attack of the carbonyl oxygen on the terminal chlorocarbon must have occurred indeed when the phosphite bonds with the carbonyl carbon, and result in the formation of a tetrahydrofuranyl ring, in the reaction of γ-chloropropyl ketone with TEP. The THF ring formation can nevertheless be clearly seen in the ^{1}H and ^{13}C NMR spectra.

GC/MS Fragmentations

Since the formation of products **2** and **3** were monitored by GLC, GC/MS was used for their identification. Two distinct fragmentation patterns were observed for **2** and **3**. Product **1** shows a strong base peak of [M-phosphonate] while **3** reveals complicated fragmentations. For **2b**, the molecular peak occurs at 284 amu and the fragmentation pattern leading to the tetrahydrofuranyl ion as base peak is shown in Figure 1.

On the other hand, the linear phosphonate **3b** undergoes fragmentation through two classic McLafferty rearrangements, involving both P=O and C=O groups, in multiple pathways as shown in Figure 2. Since the rearrangements of these groups may take place in random order, the fragmented ions resulting from different cleavage pathways complicate the spectrum.

The mass spectrum thus provides information pertaining to detection as well as identification of oxacyclic **2b** from linear **3b** by their different fragmentation patterns, even though both compounds possess the same molecular mass of 284 amu.

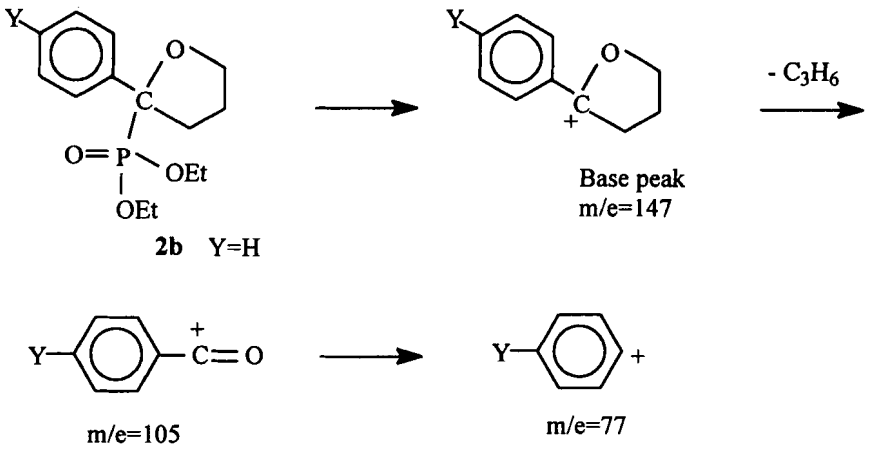


FIGURE 1 The mass fragmentations for **2b**

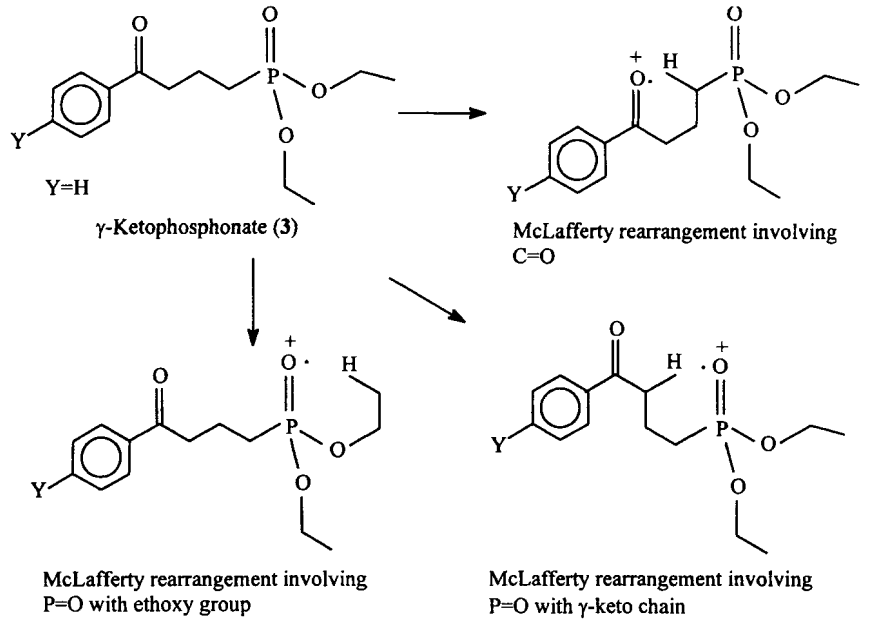
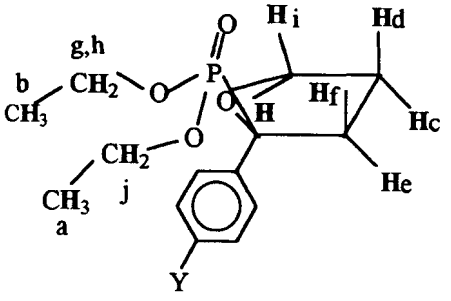


FIGURE 2 The possible McLafferty rearrangements of **3b**

TABLE V The chemical shifts of **2** in ^{1}H NMR spectrum



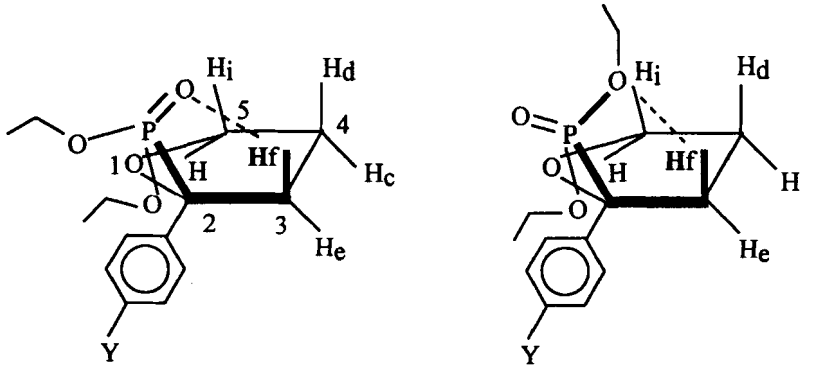
Compound	H_a *and* H_b	H_c	H_d	H_e *(Hz)*[f]	H_f *(Hz)*[g]	H_g *and* H_h	H_i	H_j	*aromatic signal*
2a[a]	1.24	1.83	1.94	1.68 (14.9)	2.30 (16.0)	4.07	3.84[h]	—	—
2b	1.26	1.77	2.04	2.28	2.74	3.74	3.99	4.09	7.24
	1.07			(12.7)	(16.4)	3.86			7.29
									7.51
2c[b]	1.30	1.79	2.07	2.30	2.75	3.81	4.03	4.14	7.14
	1.14			(13.5)	(15.7)	3.92			7.43
2d[d]	1.26	1.77	2.02	2.27	2.72	3.74	4.00	4.09	7.12
	1.09			(12.8)	(15.5)	3.86			7.41
2e[d]	1.25	1.76	2.02	2.27	2.71	3.74	3.98	4.09	7.09
	1.06			(13.5)	(16.8)	3.85			7.41
2f[e]	1.24	1.74	2.00	2.22	2.66	3.73	3.96	4.07	6.81
	1.08			(13.0)	(16.4)	3.84			7.40
2g	1.26	1.76	2.04	2.23	2.69	3.73	3.98	4.09	6.97
	1.09			(13.0)	(16.8)	3.88			7.48
2h	1.25	1.74	2.03	2.20	2.69	3.78	3.98	4.11	7.25
	1.10			(12.5)	(17.1)	3.90			7.44
2i	1.26	1.76	2.08	2.20	2.72	3.80	3.97	4.10	7.46
	1.12			(13.5)	(16.5)	3.90			7.56

(a) CH_3: 1.31 ppm, $^3J_{PH}$ = 14.9 Hz. (b) Me: 2.33 ppm. (c) Et: 2.59, 1.18 ppm. (d) *n*-Pr: 2.51, 1.58, 0.88 ppm. (e) OMe: 3.73 ppm. (f) $^3J_{PCCHe}$. (g) $^3J_{PCCHf}$. (h) Average value 3.82 and 3.86 respectively.

^{1}H NMR Analysis

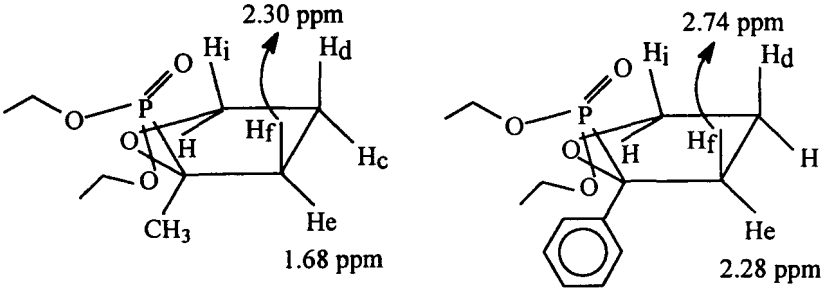
All the chemical shifts in the ^{1}H NMR spectrum for **2** are listed in Table V. H_f in **2b** is deshielded by the phosphonate group. Such deshielding effects may originate from the electronegativity as well as the relative spatial position (the steric effect). The steric compression shift through the backbone may be induced by one Et-O-P and one P=O group, or by two Et-O-P groups. The γ effect[10] through the field may also inflict an anisotropic effect on the synaxial proton H_f (see below).

The ^{1}H NMR spectrum suggests a diastereotopic,[11] chemical nonequivalence system for two hydrogens (H_f and H_e) at C-3. H_f and H_e have different chemical

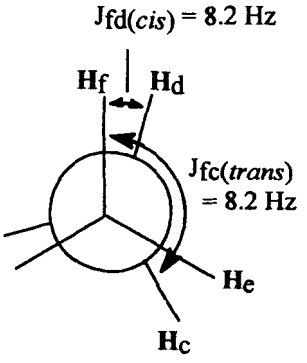


shifts because they are chemically nonequivalent since H_f is *cis* to phosphonate group, while H_e is *trans*. With the methyl homolog, **2a**, as a reference, the chemical shifts of H_f and H_e were assigned at 2.30 and 1.68 ppm respectively. In **2b**, H_f and H_e are deshield to 2.74 and 2.28 ppm, mainly by the phosphonate group and the phenyl group.

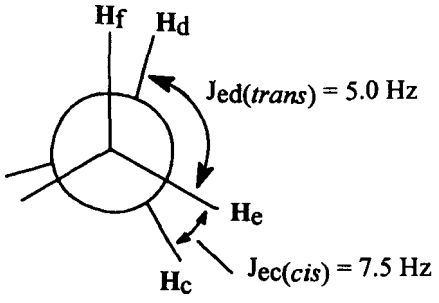
The Karplus $^3J_{HH}$ vicinal correlation[12] was used for further elucidating the relationship between hydrogens. The vicinal coupling constant $^3J_{HH}$ is a function of the dihedral angle, which reaches a maximum at 0° and 180° and a minimum at 90°. The trend of variations in the vicinal coupling constant may be useful for obtaining the relative configuration of the coupling protons. Therefore, the peak at 2.74 ppm for **2b** is assigned to H_f with the geminal coupling constant $^2J_{fe}$ = 12.7 Hz. Since the two vicinal coupling constants are 8.2 Hz, both $^3J_{fd(cis)}$ and $^3J_{fc(trans)}$ are identical. The peak at 2.28 ppm is assigned to H_e with the geminal coupling constant $^2J_{ef}$ = 12.7 Hz while the vicinal coupling constants are 5.0 and 7.5 Hz respectively. These unequal ^3J couplings show that $^3J_{ec}$ (7.5 Hz) between the *cis* protons is larger than $^3J_{ed}$ (5.0 Hz) between the *trans* pro-



2a **2b**



Vicinal couplings for **Hf**

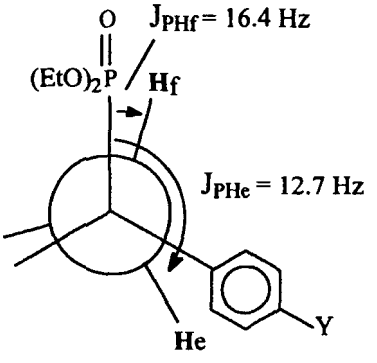


Vicinal couplings for **He**

tons, since the dihedral angle of H_e-C-C-H_d is closer to 90° than that of H_e-C-C-H_c. Both $^3J_{fc}$ and $^3J_{ed}$ are $^3J_{trans}$ couplings, and the relationship $^3J_{fc} > {}^3J_{ed}$ indicates that the dihedral angle between H_f-C-C-H_c is closer to 180° than the one between H_e-C-C-H_d, according to the Karplus correlation. This result provides further evidence against unhindered free rotation about C-C bonds of the THF ring in our system. The relative positions of the hydrogens are shown below.

The $^3J_{PH}$, like $^3J_{HH}$, is also angular dependent by the Karplus relationship. The magnitude of $^3J_{PH}$ is large for the dihedral angle of 0 or 180°, whereas it is near zero for the dihedral angle of 90°.[13] Therefore, $^3J_{PH}$ for H_f is assigned to be 16.4 Hz and that for H_e is 12.7 Hz, since the phosphonate group is in the *cis* position to H_f and *trans* position to H_e (as shown below).

With all these analyses, the ^{1}H NMR splitting patterns from the calculated couplings for H_f and H_e are in agreement with the experimental spectra as shown in Figure 3.



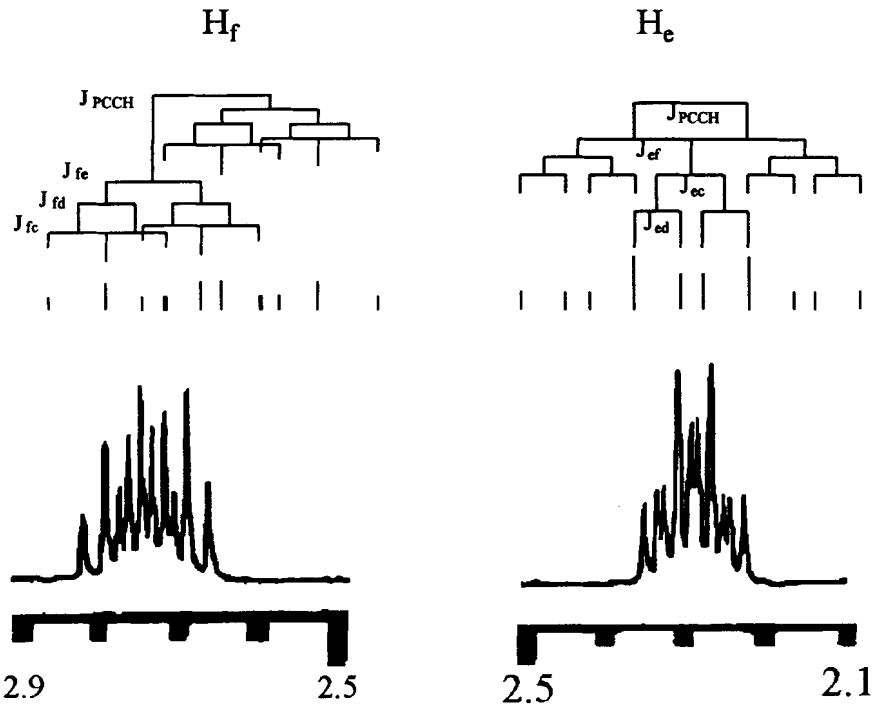


FIGURE 3 The splitting patterns of H_f and H_e in **2b**

The evaluations on other protons were also carried out. The peak at 2.04 ppm is assigned to H_d with the geminal coupling constant $^2J_{dc}$ = 13.0 Hz. It contains four vicinal coupling constants. Two $^3J_{trans}$ couplings are $^3J_{de(trans)}$ = 5.0 Hz and $^3J_{di(trans)}$ = 5.0 Hz, and two $^3J_{cis}$ couplings are $^3J_{df(cis)}$ = 8.2 Hz and $^3J_{di(cis)}$ = 7.0 Hz respectively. In addition, the peak at 1.77 ppm is assigned to H_c with the geminal coupling constant $^2J_{cd}$ = 13.0 Hz while the four vicinal coupling constants are $^3J_{cf(trans)}$ = 8.2 Hz, $^3J_{ci(trans)}$ = 7.0 Hz, $^3J_{ce(cis)}$ = 7.5 Hz and $^3J_{ci(cis)}$ = 7.0 Hz respectively. The assignments in the splitting patterns of H_d and H_c in **2b** also matched well with the experimental data (Figure 4).

In the ^{1}H NMR analysis of the linear phosphonate **3b**, two characteristic couplings of $^2J_{PH}$ and $^3J_{PH}$ were observed. The coupling of $^2J_{PH}$ is 17.4–18.6 Hz for $H_{b'}$, while the magnitude of $^3J_{PH}$ for the dihedral angle between P-C-C-$H_{c'}$ (about 60°) is 7.2–8.0 Hz (Table VI).[13b]

^{13}C NMR Analysis

The assignments and couplings of **2** in the ^{13}C NMR spectrum are shown in Tables VII and VIII. The striking characteristic of **2b** was the different chemical shifts (62.9 and 63.2 ppm), but with the same $^2J_{PC}$ coupling (7.5 Hz) at C-6 and

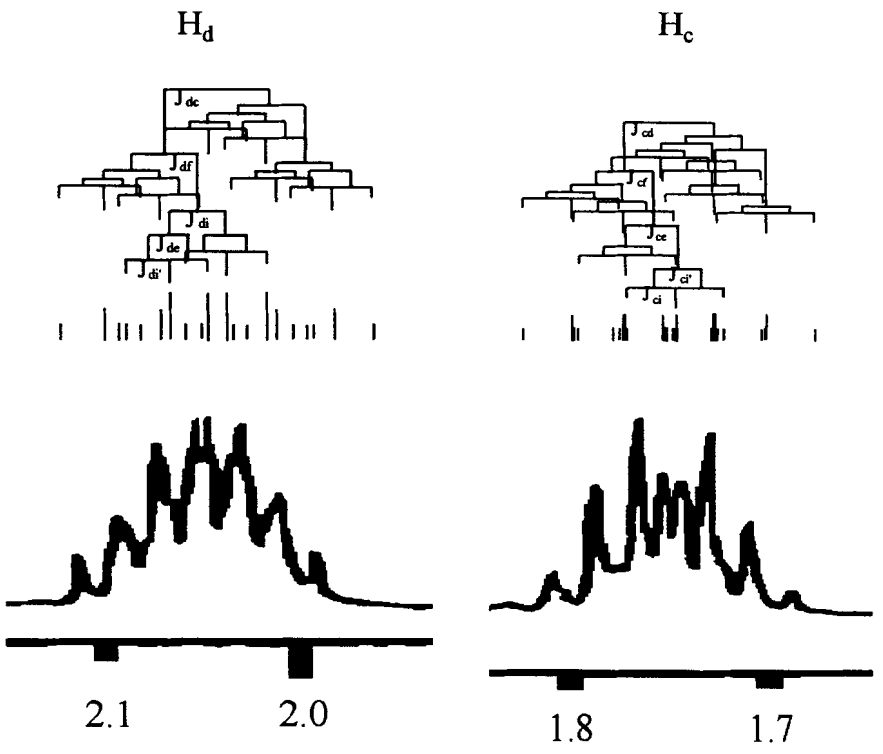
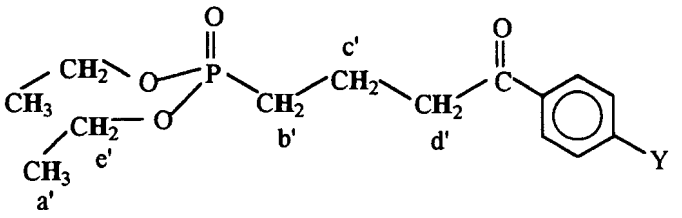


FIGURE 4 The spitting patterns of H_c and H_d in **2b**

C-7 of the two P-O-Et groups. These two chemical nonequivalent carbons may be due to the P atom being attached to a chiral carbon (C-2), thus the substituents on the P atom are diastereotropic and nonequivalent.

The ^{13}C spectrum of **2** displays two distinct characteristics of the couplings. One is the split peaks at C-2, which is greatly affected by the P atom, while another is the angular dependence of $^3J_{CP}$. Generally, the coupling of $^1J_{PC}$ is 130–145 Hz for alkylphosphonates[14] and 155–165 Hz for α-hydroxyphosphonates.[15] This implies that the couplings of $^1J_{PC}$ for the tertiary C-2 atom adjacent to the P atom should be larger. The magnitude of $^1J_{PC}$ = 171.5 Hz obtained in this study is thus consistent with this observation. The $^3J_{PC}$, *i.e.* a three-bond coupling between C and P is sensitive to the dihedral angle. The stereospecificity of $^3J_{PC}$ is probably of more general applicability and indeed has been used very widely in conformational and configurational analyses by the relative magnitudes of transoid (16–18 Hz) and the corresponding cisoid ones ($<$0.6 Hz).[16] The experimental $^3J_{PC}$ couplings were 5.7 and 7.2 Hz at C-4 and

TABLE VI The chemical shifts of **3** in the ^{1}H NMR spectrum



Compound	$H_{a'}$	$H_{b'}$ *(Hz)*[a]	$H_{c'}$ *(Hz)*[b]	$H_{d'}$	$H_{e'}$	*Aromatic signal*
3a[c]	1.32	1.75 (18.6)	1.88 (6.8)	2.59	4.08	—
3b	1.26	1.80 (18.2)	2.01 (7.3)	3.07	4.05	7.89, 7.47, 7.40
3c[d]	1.27	1.83 (18.3)	2.01 (7.5)	3.05	4.07	7.16, 7.77
3d[e]	1.31	1.86 (18.6)	2.06 (7.3)	3.10	4.10	7.88, 7.27
3e[f]	1.27	1.81 (17.9)	2.01 (7.6)	3.05	4.05	7.83, 7.21
3g	1.26	1.79 (17.4)	2.00 (8.0)	3.05	4.05	7.92, 7.06
3h	1.26	1.79 (18.0)	2.00 (7.2)	3.05	4.05	7.84, 7.37
3i	1.25	1.78 (18.2)	1.99 (8.0)	3.03	4.04	7.75, 7.52

(a) $J_{PHb'}$. (b) $J_{PHc'}$. (c) CH_3: 2.14 ppm. (d) Me: 2.31 ppm. (e) Et: 2.70, 1.26 ppm. (f) *n*-Pr: 2.59, 1.61, 0.89 ppm.

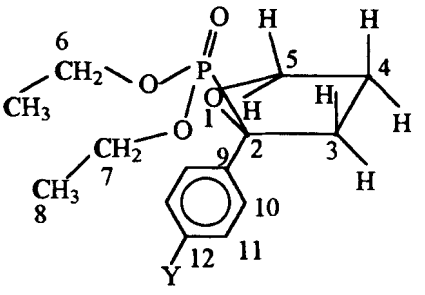
C-5 respectively, which were within the correlation data from the Karplus correlations.[15–17] Additional couplings of $^2J_{PC}$, $^3J_{PC}$, $^4J_{PC}$ and $^5J_{PC}$ were also observed between the carbons on the phenyl ring and the P atom. All the couplings between P and C are listed in Table VIII.

For **3b**, large splitted peaks at C-1′ show that the coupling of J_{PC} is 141.0 Hz. The magnitude of $^3J_{PC}$ (13.4 Hz) also suggests that transoid conformation is predominant between P-C-C-$C_{3'}$, as expected. All the chemical shifts and couplings between P and C for **3** are listed in Table IX.

^{31}P NMR Analysis

The phosphorus chemical shifts of **2** and **3** are listed in Table X. For oxacyclic phosphonates **2**, the chemical shifts are upfield at 22.5–26.4 ppm compared to those of the linear phosphonates **3** (31.8–32.3 ppm). This may be attributed to the combination of the γ effect and electronegativity. The γ effect[18] of the two carbon atoms, C-4 and C-5 on the THF ring may shield the phosphorus chemical

TABLE VII The chemical shifts of **2** in ^{13}C NMR spectrum



Compound	*2*	*3*	*4*	*5*	*6,7*	*8*	*9*	*10*	*11*	*12*
2a[a]	78.9	34.5	25.9	69.4	62.1 62.5	16.4	—	—	—	—
2b	84.3	36.2	25.7	69.4	62.9 63.2	16.2 16.4	140.8	126.3	127.8	127.2
2c[b]	84.0	36.1	25.6	69.3	62.8 63.1	16.1 16.3	137.6	126.1	128.4	136.8
2d[c]	84.2	36.2	25.7	69.4	62.8 63.2	16.2 16.4	137.9	126.3	127.3	143.3
2e[d]	84.2	36.2	25.7	69.3	62.8 63.1	16.2 16.4	137.9	126.2	127.9	141.7
2f[e]	83.9	36.1	25.6	69.3	62.7 63.1	16.2 16.1	132.6	127.5	113.2	158.9
2g	83.9	36.3	25.7	69.5	63.0 63.2	16.2 16.4	136.6	128.1	114.7	162.2
2h	83.8	36.2	25.6	69.5	63.2 63.4	16.1 16.3	139.3	127.7	128.0	133.3
2i	83.9	36.3	25.7	69.6	63.1 63.3	16.2 16.4	140.1	128.1	131.0	121.5

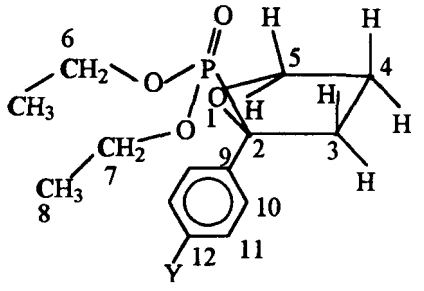
(a) CH_3: 23.2 ppm. (b) Me: 20.8 ppm. (c) Et: 28.4, 15.3 ppm. (d) *n*-Pr: 37.6, 24.3, 13.7 ppm. (e) OMe: 55.1 ppm.

shift to higher field, but does not show much difference for alkyl and cycloalkyl phosphonates.[19,20] The electronegativity of the vicinal group is also important for the ^{31}P chemical shifts. The ^{31}P chemical shift in 1-hydroxybutylphosphonate is more shielded than that in 1-methylbutylphosphonate[20] and may be attributed to the electronegativity of the hydroxyl group. Therefore the electronegativity of oxygen in the oxycyclopentyl ring may shift the ^{31}P chemical shift of **2** upfield compared to **3**. The electron-withdrawing ability of the phenyl group may move the chemical shift upfield, such as observed in **2b** (with the phenyl group) at 23.3 ppm, compared to **2a** (with the methyl group) at 26.4 ppm.

CONCLUSION

Selective preparation of oxacyclic **2** and linear **3** isomeric phosphonates is described. The formations of **2** and **3** have been found to be in competition. The spectroscopic characteristics of oxacyclic and linear phosphonates are deter-

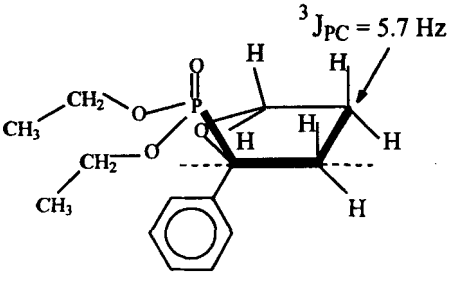
TABLE VIII J(PC) Coupling Constants of **2**



Compound	^{1}J (PC_2)	^{2}J (PC_3)	^{3}J (PC_4)	^{3}J (PC_5)	^{2}J (PC_6)	^{3}J (PC_8)	^{2}J (PC_9)	^{3}J (PC_{10})	^{4}J (PC_{11})	^{5}J (PC_{12})
2a[a]	171.5	4.4	3.7	5.2	6.9	5.4	—	—	—	—
2b	170.1	2.4	5.7	7.2	7.5	5.4	5.7	3.9	2.3	2.7
2c	171.0	3.7	5.5	7.3	7.4	5.5	5.5	3.7	—	—
2d	170.1	2.6	5.7	7.2	7.4	5.7	5.5	3.3	—	—
2e	170.0	2.7	5.6	7.3	7.4	5.7	5.7	4.2	2.6	2.9
2f	171.5	3.2	5.7	7.3	7.4	5.5	5.0	4.2	—	2.4
2g	171.4	2.3	5.7	7.1	7.3	5.7	5.7[b]	3.7[c]	2.4[d]	—[e]
2h	171.5	2.5	5.0	6.6	7.3	5.5	6.0	4.0	2.3	—
2i	171.3	2.4	4.8	6.6	7.4	5.7	6.0	4.0	—	—

(a) $J_{PCCH3} = 8.6$ Hz. (b) $J_{FCCCC} = 2.9$ Hz. (c) $J_{FCCC} = 8.4$ Hz. (d) $J_{FCC} = 21.7$ Hz. (e) $J_{FC} = 245.7$ Hz.

mined. For oxacyclic **2**, the lack of carbonyl was clearly indicated in the infrared spectrum. The mass fragmentation with the dephosphonated base peak, [M-phosphonate] was observed for **2**. The ^{1}H & ^{13}C NMR spectra showed complicated splitting patterns due to the different couplings of the P atom. These characteristics are quite different from that of its isomeric counterpart, the linear δ-phosphonate **3**. For linear δ-ketophosphonates, the strong C = O absorption at 1674–1702 was observed in the infrared spectra. Complicated mass fragmentations with multiple McLafferty rearrangements were observed in the mass spectrum. The ^{1}H & ^{13}C NMR spectra showed specific chemical shifts and coupling



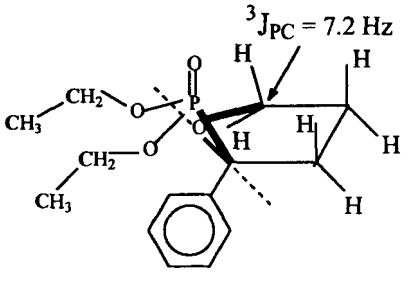
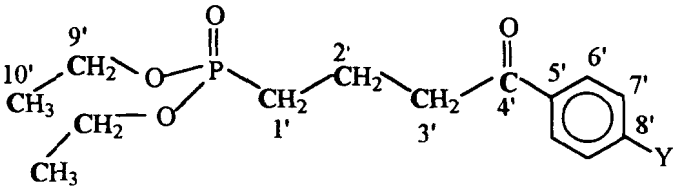


TABLE IX The chemical shifts and J(PC) coupling constants of **3**



Compound	*C1'* *(Hz)*	*C2'* *(Hz)*	*C3'* *(Hz)*	*C4'*	*C5'*	*C6'*	*C7'*	*C8'*	*C9'* *(Hz)*	*C10'* *(Hz)*
2a[a]	24.5	16.5	43.2	207.5	—	—	—	—	61.3	16.2
	(139.7)	(5.5)	(12.9)						(7.4)	(5.5)
2b	24.7	17.1	38.3	199.1	136.7	128.5	127.9	133.0	61.4	16.3
	(141.0)	(4.7)	(13.4)						(6.7)	(5.9)
2c[b]	24.8	17.2	38.2	199.0	134.2	129.1	127.9	143.8	61.4	16.3
	(140.4)	(5.1)	(13.1)						(6.6)	(5.5)
2d[c]	24.8	17.2	38.2	198.8	134.5	128.2	128.0	150.0	61.4	16.3
	(139.7)	(5.5)	(12.9)						(5.5)	(5.5)
2e[d]	24.8	17.2	38.2	198.8	134.6	128.6	128.0	148.5	61.5	16.3
	(141.0)	(4.8)	(14.2)						(6.8)	(5.8)
2g	24.7	17.1	38.2	197.5	133.2[e]	130.5[f]	115.6[g]	167.6[h]	61.4	16.3
	(141.2)	(4.5)	(13.1)						(6.0)	(5.9)
2h	24.7	17.0	38.2	197.8	135.0	129.3	128.8	139.4	61.5	16.3
	(141.1)	(4.8)	(13.1)						(6.3)	(5.8)
2i	24.6	17.0	38.2	198.0	135.4	129.4	131.8	128.1	61.5	16.3
	(141.0)	(4.9)	(13.1)						(6.3)	(5.8)

(a) CH_3: 29.7 ppm. (b) Me: 21.5 ppm. (c) Et: 28.8, 15.1 ppm. (d) *n*-Pr: 37.9, 24.1, 13.6 ppm. (e) $J_{PCCCC} = 2.9$ Hz. (f) $J_{FCCC} = 8.4$ Hz. (g) $J_{FCC} = 21.7$ Hz. (h) $J_{FC} = 245.7$ Hz.

constants. Well defined spectroscopic data for identification of the oxacyclic and linear phosphonates are provided in this article.

EXPERIMENTAL

Commercially available chemicals of reagent grade were used for all reactions. Triethyl phosphite was distilled from sodium before use.[21] 5-Chloro-2-pentanone was purchased from Janssen Chemical Co. γ-Chloropropyl phenone and

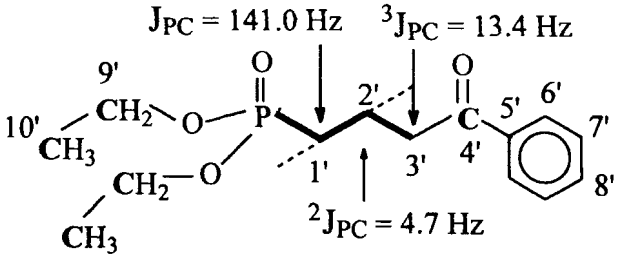


TABLE X The chemical shifts of **2** and **3** in ^{31}P NMR spectrum[a]

Compound	*$\delta^{31}P$ (ppm)*	*Compound*	*$\delta^{31}P$ (ppm)*
2a	26.4	**3a**	32.0
2b	23.3	**3b**	32.1
2c	23.3	**3c**	32.1
2d	23.4	**3d**	31.8
2e	23.4	**3e**	32.3
2f	23.4	—[b]	—
2g	23.0	**3g**	32.1
2h	22.6	**3h**	32.0
2i	22.5	**3i**	32.0

(a) Relative to 85% H_3PO_4. (b) not formed.

derivatives were prepared according to the procedure given by Westeringh and Schliemann *et al.*[22]. All the solvents and chemicals used in preparations and reactions were purified and checked by GLC before use. All reactions were carried out under inert atmosphere of N_2 and in oven dried glassware.

^1H, ^{13}C and ^{31}P NMR spertra were recorded on a Bruker AM-300WB spectrometer in deuteriochloroform using tetramethylsilane as a standard for proton spectra, solvent signals as the standard for carbon spectra and 85% H_3PO_4 as the standard for phosphorus spectra. The ^1H NMR spectrum with the ^{31}P decoupling confirmed the J_{PH} assignment for **2**. All the couplings were measured directly from the ^1H & ^{13}C NMR spectra. Infrared spectra were recorded on a Jasco IR-700 Spectrometer. Mass spectra were obtained from a VG Trio-2000 instrument with EI mode at 70 ev. HRMS were recorded on a VG *prospec* spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer.

Analytical thin-layer chromatography was performed on silica gelcoated plates using ethyl acetate/hexane as the development solvents. The R_f values presented here refer to those obtained from thin-layer chromatography on 2.5 × 10 cm analytical plates, coated with silica gel 60 F_{254} (R.D.H.). Column chromatography was performed on silica gel (ACROS Co., 0.06–0.20 mm). The solvent mixtures used for column chromatography were volume/volume mixtures.

General Prodedure for Reaction of γ-Chloroalkyl Methyl Ketone with TEP

A mixture of γ-chloropropyl ketone **1** (0.04 mol) and TEP (32 mL, 4.6 fold excess) in a round-bottomed flask, equipped with a magnetic stirrer and a condenser, was refluxed under nitrogen atmosphere for 6–8 h. The mixture was allowed to cool to room temperature and the excess unreacted TEP was distilled

off (65–70 °C, 15 mmHg). The brown residue was subjected to fractional distillation *in vacuo* or column chromatography to obtain two colorless oils. The yield, boiling point and details of other spectral data are summarized below.

Diethyl 2-methyl-2-tetrahydrofuranyl phosphonate (2a)

4.6 g, 52%, $bp_{0.005}$ = 55–57°C (lit.[5c] bp_1 = 89°C); ^{31}P NMR (300 MHz, $CDCl_3$) δ 26.4; MS (70 eV) *m/z* 222 (M^+, 0.9), 85 (100); Anal. Calc. for $C_9H_{19}PO_4$: C, 48.64; H, 8.62. Found: C, 48.45; H, 8.81.

Diethyl 2-phenyl-2-tetrahydrofuranyl phosphonate (2b)

4.6 g, 41%, $bp_{0.003}$ = 110–114 °C, R_f = 0.34 (60/40); ^{31}P NMR ($CDCl_3$) δ 23.3; MS (70 eV) *m/z* 284 (M^+, 2), 147 (100), 105 (47), 77 (22); HRMS *m/z* Calc. for $C_{14}H_{21}O_4P$: 284.1177. Found: 284.1164.

Diethyl 2-(p-methylphenyl)-2-tetrahydrofuranyl phosphonate (2c)

6.8 g, 57%, $bp_{0.003}$ = 115–119 °C, R_f = 0.43 (60/40); ^{31}P NMR ($CDCl_3$) δ 23.3; MS (70 eV) *m/z* 298 (M^+, 1), 161 (100), 119 (29), 91 (8); HRMS *m/z* Calc. for $C_{15}H_{23}O_4P$: 298.1334. Found: 298.1322.

Diethyl 2-(p-ethylphenyl)-2-tetrahydrofuranyl phosphonate (2d)

7.2 g, 58%, $bp_{0.003}$ = 117–121 °C, R_f = 0.57 (60/40); ^{31}P NMR ($CDCl_3$) δ 23.4; MS (70 eV) *m/z* 312 (M^+, 1), 175 (100), 133 (35); HRMS *m/z* Calc. for $C_{16}H_{25}O_4P$: 312.1490. Found: 312.1501.

Diethyl 2-(p-n-propylphenyl)-2-tetrahydrofuranyl phosphonate (2e)

5.7 g, 44%, $bp_{0.003}$ = 121–124 °C, R_f = 0.45 (50/50); ^{31}P NMR ($CDCl_3$) δ 23.5; MS (70 eV) *m/z* 326 (M^+, 1), 189 (100), 147 (29), 91 (12); HRMS *m/z* Calc. for $C_{17}H_{27}O_4P$: 326.1647. Found: 326.1643.

Diethyl 2-(p-methoxyphenyl)-2-tetrahydrofuranyl phosphonate (2f)

10.3 g, 82%, $bp_{0.003}$ = 123–126 °C, R_f = 0.30 (50/50); ^{31}P NMR ($CDCl_3$) δ 23.4; MS (70 eV) *m/z* 314 (M^+, 1), 177 (100), 135 (39); HRMS *m/z* Calc. for $C_{15}H_{23}O_5P$: 314.1283. Found: 314.1290.

Diethyl 2-(p-fluorophenyl)-2-tetrahydrofuranyl phosphonate (2g)

4.8 g, 40%, $bp_{0.003}$ = 111–114 °C, R_f = 0.43 (65/35); ^{31}P NMR ($CDCl_3$) δ 23.0; MS (70 eV) *m/z* 302 (M^+, 1), 165 (100), 123 (35); HRMS *m/z* Calc. for $C_{14}H_{20}FO_4P$: 302.1083. Found: 302.1085.

Diethyl 2-(p-chlorophenyl)-2-tetrahydrofuranyl phosphonate (2h)

3.8 g, 30%, $bp_{0.003}$ = 122–125 °C, R_f = 0.40 (40/60); ^{31}P NMR ($CDCl_3$) δ 22.6; MS (70 eV) *m/z* 318 (M^+, 1), 183 (33), 181 (100), 141 (15), 139 (47), 111 (19); HRMS *m/z* Calc. for $C_{14}H_{20}ClO_4P$: 318.0788. Found: 318.0790.

Diethyl 2-(p-bromophenyl)-2-tetrahydrofuranyl phosphonate (2i)

2.2 g, 15%, $bp_{0.003}$ = 129–132 °C, R_f = 0.33 (20/80); ^{31}P NMR ($CDCl_3$) δ 22.5; MS (70 eV) *m/z* 362 (M^+, 1), 364 (M+2, 1), 227 (100), 225 (100), 185 (42), 183 (42), 157 (44), 155 (44), 146 (14), 115 (10), 104 (15); HRMS *m/z* Calc. for $C_{14}H_{20}BrO_4P$: 362.0283. Found: 362.0285.

Diethyl 5-oxopentyl phosphonate (3a)

2.1 g, 24%, $bp_{0.003}$ = 76–78 °C (lit.[5a–5b] $bp_{0.5}$ = 114–117 °C); ^{31}P NMR (300 MHz, $CDCl_3$) δ 32.0; MS (70 eV) *m/z* 222 (M^+, 18), 179 (32), 152 (88), 125 (100) and 97 (30); Anal. Calc. for $C_9H_{19}PO_4$: C, 48.64; H, 8.62. Found: C, 48.37; H, 8.74.

Diethyl 4-oxo-4-phenylbutyl phosphonate (3b)

2.8 g, 25%, $bp_{0.003}$ = 139–142 °C, R_f = 0.22 (60/40); ^{31}P NMR ($CDCl_3$) δ 32.1; MS (70eV) *m/z* 284 (M^+, 3), 179 (16), 165 (12), 152 (26), 125 (19), 105 (100), 77 (50); HRMS *m/z* Calc. for CHOP: 284.1177. Found: 284.1170.

Diethyl 4-oxo-4-(p-methylphenyl)butyl phosphonate (3c)

1.8 g, 15%, $bp_{0.003}$ = 147–150 °C, R_f = 0.28 (60/40); ^{31}P NMR ($CDCl_3$) δ 32.1; MS (70eV) *m/z* 298 (M^+, 6), 179 (13), 165 (7), 152 (21), 119 (100), 91 (27); HRMS *m/z* Calc. for $C_{15}H_{23}O_4P$: 298.1334. Found: 298.1129.

Diethyl 4-oxo-4-(p-ethylphenyl)butyl phosphonate (3d)

1.5 g, 12%, $bp_{0.003}$ = 148–151 °C, R_f = 0.34 (60/40); ^{31}P NMR ($CDCl_3$) δ 31.8; MS (70eV) *m/z* 312 (M^+, 6), 179 (13), 152 (23), 133 (100), 125 (14), 105 (10); HRMS *m/z* Calc. for $C_{16}H_{25}O_4P$: 312.1490. Found: 312.1488.

Diethyl 4-oxo-4-(p-n-propylphenyl)butyl phosphonate (3e)

1.5 g, 12%, $bp_{0.003}$ = 154–156 °C, R_f = 0.30 (50/50); ^{31}P NMR ($CDCl_3$) δ 32.3; MS (70eV) *m/z* 326 (M^+, 5), 179 (20), 165 (12), 152 (32), 147 (100), 125 (13), 91 (21); HRMS *m/z* Calc. for $C_{17}H_{27}O_4P$: 326.1647. Found: 326.1651.

Diethyl 4-oxo-4-(p-fluorophenyl)butyl phosphonate (3g)

3.7 g, 31%, $bp_{0.003}$ = 141–142 °C, R_f = 0.25 (65/35); ^{31}P NMR ($CDCl_3$) δ 32.1; MS (70eV) *m/z* 302 (M^+, 4), 179 (18), 165 (12), 152 (31), 125 (24), 123 (100), 95 (35); HRMS *m/z* Calc. for $C_{14}H_{20}FO_4P$: 302.1083. Found: 302.1187.

Diethyl 4-oxo-4-(p-chlorophenyl)butyl phosphonate (3h)

4.0 g, 31%, $bp_{0.003}$ = 150–152 °C, R_f = 0.20 (40/60); ^{31}P NMR ($CDCl_3$) δ 32.0; MS (70eV) *m/z* 318 (M^+, 4), 179 (34), 165 (17), 152 (55), 139 (100), 125 (39), 111 (41), 97 (18); HRMS *m/z* Calc. for $C_{14}H_{20}ClO_4P$: 318.0788. Found: 318.0785.

Diethyl 4-oxo-4-(p-bromophenyl)butyl phosphonate (3i)

5.2 g, 36%, $bp_{0.003}$ = 158–162 °C, R_f = 0.20 (20/80); ^{31}P NMR ($CDCl_3$) δ 32.0; MS (70eV) *m/z* 362 (M^+, 3), 364 (M+2, 3), 183 (66), 185 (66), 165 (22), 152 (100), 125 (50), 108 (12), 97 (19); HRMS *m/z* Calc. for $C_{14}H_{20}BrO_4P$: 362.0283. Found: 362.0290.

References

[1] J. M. Varlet, G. Fabre, F. Sauveur, N. Collignon and P. Savignac, *Tetrahedron*, **37**, 1377 (1981); J. R. Rocca, J. H. Tumlinson, B. M. Glancey and C. S. Lofgren, *Tetra. Lett.*, **24**, 1893 (1983).

[2] C. L. McClure and K.-Y. Jung, *J. Org. Chem.*, **56**, 867 (1991).

[3] J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974); W. S. Wadsworth Jr., *Organic Reactions* (New York) **25**, 73 (1977); W. R. Roush, *J. Am. Chem. Soc.*, **102**, 1390 (1980); P. Seguineau and J. Villieras, *Tetra. Lett.*, **29**, 477 (1988).

[4] M. Mikolajczyk, S. Grzejszczak, W. Midura and A. Zatorski, *Phosphorus Sulfur*, **18**, 175 (1983).
[5] (a) P. Savignac, A. Breque and F. Mathey, *Synth. Commun.*, **9**, 287 (1979); (b) V. Sarin, B. E. Tropp and R. Engel, *Tetra. Lett.*, 351 (1977); (c) G. Sturtz, *Bull. Soc. Chim. Fr.*, 1333 (1964).
[6] L. T. Bruka, B. J. Wilson and T. M. Harris, *J. Org. Chem.*, **39**, 2212 (1974).
[7] Jen-Wen Yu and Steve K. Huang, *Phosphorus, Sulfur, and Silicon And the Related Elements*, in press.
[8] J. F. Allen and O. H. Johnson, *J. Am. Chem. Soc.*, **77**, 2871 (1955); M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, **20**, 1356 (1955).
[9] C. J. Pouchert, *The Aldrich Library of Infrared Spectra* (Aldrich Chemical Co. INC.: Wisconsin 1978), 2nd ed., pp. 127; R. M. Silverstein, G. C. Bassler and T. C. Morrill, *Spectrometric Identification of Organic Compounds* (John Wiley & Sons: New York 1991), 5th ed., Chap. 3, pp. 112–113.
[10] G. W. Buchanan and C. Benezra, *Can J. Chem.*, **54**, 231 (1976); D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964).
[11] E. Breitmaier, *Structure Elucidation by NMR in Organic Chemistry* (John Wiley & Sons: New York 1993), Chap. 2, pp. 54–56.
[12] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
[13] C. Benezra, *Tetrahedron Lett.*, 4471 (1969); C. Benezra, *J. Am. Chem. Soc.*, **95**, 6890 (1973); C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1825 (1966).
[14] A. R. Katritzky and B. Pilarski, *Org. Prep. proced. Int.*, **22**, 209 (1990); C. K. McClure and Kang-Yeoun Jung, *J. Org. Chem.*, **56**, 867 (1991).
[15] L. Ernst, *Org. Mag. Res.*, **9**, 35 (1977).
[16] G. W. Buchanan and J. H. Brown, *Can. J. Chem.*, **55**, 604 (1977).
[17] R. D. Lapper, H. H. Mantsch and I. C. P. Smith, *J. Am. Chem. Soc.*, **94**, 6243 (1972); G. W. Buchanan and F. G. Morin, *Can. J. Chem.*, **58**, 530 (1980).
[18] L. D. Quin and J. J. Breen, *Org. Magn. Res.*, **5**, 17 (1973).
[19] J. G. Verkade and L. D. Quin, *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis* (VCH Publishers Inc.: Florida 1987), Chap. 1, pp 34.
[20] M. M. Crutchfield, C. H. Pungan, J. H. Letcher, V. Mark and J. R. Van Wazer, *^{31}P Nuclear Magnetic Resonance* (John Wiley & Sons: New York 1967), Chap. 4, pp 294–297.
[21] D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals* (Pergamon Press: Oxford 1988), 3'rd ed., Chap. 3, pp. 297.
[22] C. van de Westeringh, B. Hermans, F. Raeymaekers and C. Van der Eycken, *Ind. chim. belge*, **25**, 1073 (1960); *Chem. Abstr.*, **55**, 6428b (1960); W. Schliemann, A. Buege and L. Reppel, *Pharmazie*, **35**, 140 (1980).