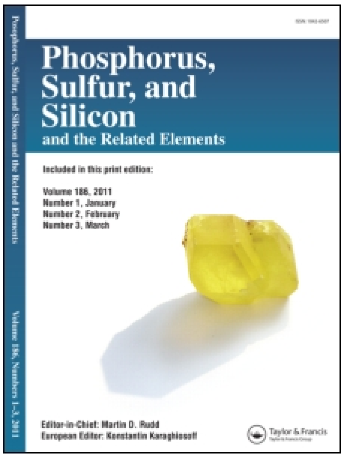

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Synthesis, Characterizations, and Crystal Structures of α-Hydroxyphosphonic Acid Esters

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SYNTHESIS, CHARACTERIZATIONS, AND CRYSTAL STRUCTURES OF α-HYDROXYPHOSPHONIC ACID ESTERS

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This article describes the synthesis of α-hydroxyphosphonic acid esters using the Pudovik reaction. IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, MS, and elemental analysis were employed to confirm their structures. X-ray structure analysis is reported for six compounds. The antibacterial activities of these compounds are also reported.

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Keywords Crystal structure; phosphonate; synthesis

INTRODUCTION

In recent years, α-hydroxyphosphonic acids esters have attracted much attention due to their wide biological activity[1–4] and pharmaceutical interest.[5,6] They are useful as synthetic intermediates for other biologically important α-substituted phosphoryl compounds.[7,8] The addition of compounds containing a P—H bond to aldehydes or ketones, the Pudovik reaction, is the most versatile pathway to these compounds. This reaction mainly proceeds in the presence of a basic catalyst,[9,10] acid catalyst,[11] or a metal fluoride.[12] However, to the best of our knowledge, only a few reports have dealt with Pudovik reaction in

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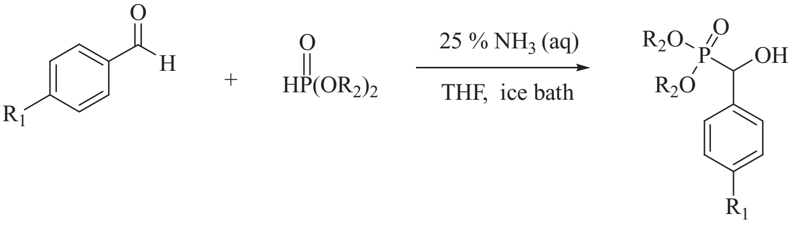
a THF-aqueous ammonia system.[13] The approach to the synthesis of the title compounds has been already described in Fang et al.[14] and is shown in Scheme 1.



Where: R_1 = OCH_3 (**1**), H (**2**), Cl (**3**), NO_2 (**4**);
R_2 = -Me (**a**), -Et (**b**), -^{i}Pr (**c**), Ph (d)

Scheme 1 Synthetic pathway of α-hydroxyphosphonic acid esters.

RESULTS AND DISUSSION

^{31}P NMR

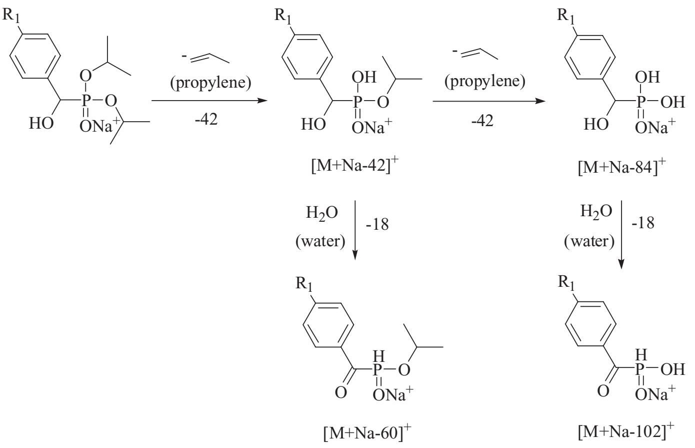
As can be seen from Table I, the phosphorus chemical shift of all the compounds ranged from 18 to 24 ppm. As the size of the alkyl group is increased with the order Me < Et < ^{i}Pr, the phosphorus signals shift downfield. When the phenyl substituent is changed, no appreciable effect on the phosphorus chemical shift is observed.

Mass Spectroscopy

The ion scan of the sodiated molecules $[M+Na]^+$ afforded the product ions a, b, c, and d (Table II, Scheme 2). The genesis of the product ions a and c was obtained directly from the precursor ion by the consecutive elimination of one and/or two molecules of propylene. The product ions b and d were dehydrated ions. We have found that MS/MS fragmentation of the sodiate molecules obtained from this series of phosphorylated compounds **1c**–**4c** was identical to that of the product ion scan of the sodiate DIPP-Ala (N-diisopropyloxyphosphoryl alanine) molecule reported earlier in our laboratory.[15–17]

Table I ^{31}P NMR of α-hydroxyphosphonic acid esters **1a–4a**, **1b–4b**, and **1c–4c**

	R_2		
R_1	-Me	-Et	-^{i}Pr
OCH_3	23.98 (**1a**)	21.74 (**1b**)	20.08 (**1c**)
H	23.76 (**2a**)	21.68 (**2b**)	20.18 (**2c**)
Cl	22.95 (**3a**)	20.89 (**3b**)	19.18 (**3c**)
NO_2	21.85 (**4a**)	19.82 (**4b**)	18.04 (**4c**)



Where: $R_1 = OCH_3$ (**1c**), H (**2c**), Cl (**3c**), NO_2 (**4c**);

Scheme 2 Fragmentation pattern obtained from the product ion scan of the sodiated adducts from compounds **1c–4c**.

X-Ray Crystallography

X-ray data of all the six compounds were collected on a Bruker SMART CCD X-ray area detector diffractometer at room temperature using Mo Kα radiation ($\lambda = 0.7173$ Å) with ϕ and ω scans. All the crystal systems belong to monoclinic space group $P2_{1/n}$, $Z = 4$, with $R_1 = 0.068$, 0.049, 0.067 0.101, 0.061, and 0.051, respectively. The structures were solved by direct methods using the SHELXS program.[18] All H atoms were placed in geometrically idealized positions and were treated as riding on their parent atoms. Anisotropic temperature factors were introduced for all non-hydrogen atoms, and least-squares refinements were carried out by minimizing the function $\sum w\,(\|F_o|-|F_c\|)^2$, where F_o and F_c are the observed and calculated structure factors. A weighting scheme was used.[19] The model reached convergence with $R = \sum(\|F_o|-|F_c\|)/\sum|F_o|$ and $Rw = [\sum w(\|F_o|-|F_c\|)^2/\sum w(|F_o|)^2]^{1/2}$.

The crystal data and the final refinement details of compounds (**1b**, **1c**, **2a**, **2b**, **2c**, **2d**) are given in Tables III and IV,[20] and selected bond distances and angles are shown in

Table II ESI-MS/MS of $[M+Na]^+$ ions of compounds **1c–4c** [*m/z* with relative abundance (%) in parentheses, m = MW + 23]

		Product ions *m/z* (%)			
		a	b	c	d
Compound (MW)	Precursor ions	m-42	m-60	m-84	m-102
1c (302)	325	283 (100)	265 (8)	241 (17)	223 (34)
2c (272)	295	253 (100)	235 (11)	211 (23)	193 (29)
3c (306)	329	287 (100)	269 (21)	245 (27)	227 (31)
4c (317)	340	298 (100)	280 (9)	256 (16)	238 (25)

Table III Crystal data and refinement details for compounds **1b**, **1c**, and **2a**

	1b	**1c**	**2a**
CCDC number	659488	659487	605054
Empirical formula	$C_{12}H_{19}O_5P$	$C_{14}H_{23}O_5P$	$C_9H_{13}O_4P$
Formula weight	274.24	302.29	216.16
Crystal size	0.30 × 0.20 × 0.18	0.20 × 0.18 × 0.16	0.46 × 0.20 × 0.18
Unit cell dimensions			
a (Å)	10.454 (4)	10.529 (2)	8.400 (3)
b (Å)	7.745 (3)	8.424 (2)	7.373 (3)
c (Å)	18.021 (7)	19.448 (4)	16.477 (7)
α (°)	90	90	90.0
β (°)	105.2287 (7)	105.25 (3)	98.949 (7)
γ (°)	90	90	90.0
Volume (Å^3)	1407.9 (9)	1664.1 (6)	1057.8 (7)
D (Mg/m^3)	1.294	1.207	1.357
μ (mm^{-1})	0.205	0.180	0.246
F(000)	584	648	456
θ range (°)	2.05 to 26.50	2.00 to 25.50	2.50 to 26.49
Limiting indices	$-12 = h = 13$ $-9 = k = 9$ $-18 = l = 22$	$-10 = h = 12$ $-10 = k = 10$ $-23 = l = 22$	$-10 = h = 10$; $-9 = k = 9$; $-12 = l = 20$
Reflections collections	7612	4896	5687
Independent reflections	2891 [R(int) = 0.068]	2897 [R(int) = 0.048]	2179 [R(int) = 0.044]
Data/restraints/parameters	2891/0/158	2897/0/186	2179/0/127
Goodness-of-fit on F^2	0.90	1.00	1.09
R indices [I>2σ(I)]	$R_1 = 0.068$, $wR_2 = 0.180$	$R_1 = 0.049$, $wR_2 = 0.102$	$R_1 = 0.067$, $wR_2 = 0.143$
R indices (all data)	$R_1 = 0.097$, $wR_2 = 0.195$	$R_1 = 0.092$, $wR_2 = 0.113$	$R_1 = 0.083$, $wR_2 = 0.187$
Refinement methods	Full-matrix least-squares	Full-matrix least-squares	Full-matrix least-squares
Largest diff. Peak/hole (e Å^{-3})	0.39 and −0.32	0.24 and −0.22	0.49/−0.33

Table V. The crystal structures are shown in Figures 1–6.[21] Bond lengths and angles in the compounds are in agreement with the values reported in the literature.[22] The packing of the molecules is assumed to be dictated by van der Waal interactions and by intermolecular hydrogen bonds. For example, one of the ester types (Me, Et, iPr, and Phe), the hydroxy group, is involved in hydrogen-bonding interactions with the phosphoryl O atom of a neighboring molecule. In compounds **1b**, **1c**, **2a**, **2b**, **2c**, and **2d**, one pair hydrogen bond formed, and the length of the intermolecular hydrogen bonds (O-1···O-2) are 2.685 (3) Å, 2.693 (7) Å, 2.689 (5) Å, 2.685 (5) Å, 2.715 (2) Å, and 2.691 (3) Å, respectively.

Biological Activities

In our previous work, many α-aminophosphonate derivatives were synthesized and were found to have moderate antimicrobial activities.[23,24] Hence, it is naturally interesting whether or not the α-hydroxyphosphonate derivatives will display or improve their antimicrobial activities. Antibacterial activities of α-hydroxyphosphonic acid esters were also determined.[25] (See the Supplemental Materials, available online, and Table S1.)

Table IV Crystal data and refinement details for compounds **2b**, **2c**, and **2d**

	2b	**2c**	**2d**
CCDC number	659489	298432	608519
Empirical formula	$C_{11}H_{17}O_4P$	$C_{13}H_{21}O_4P$	$C_{19}H_{17}O_4P$
Formula weight	244.22	272.27	340.30
Crystal size	0.32 × 0.20 × 0.16	0.49 × 0.21 × 0.11	0.29 × 0.20 × 0.18
Unit cell dimensions			
a (Å)	9.128 (3)	9.680 (3)	10.349 (3)
b (Å)	7.986 (3)	9.579 (3)	7.881 (2)
c (Å)	17.238 (6)	18.007 (6)	20.362 (6)
α(°)	90.0	90.0	90
β (°)	94.99 (7)	100.217 (6)	102.075 (5)
γ (°)	90.0	90.0	90
Volume (Å^3)	1251.8 (8)	1471.6 (9)	1624.0 (8)
D (Mg/m^3)	1.296	1.229	1.392
μ (mm^{-1})	0.216	0.154	0.189
F(000)	520	584	712
θ range (°)	2.37 to 25.00	2.24 to 25.00	2.05 to 25.00
Limiting indices	$-10 = h = 10$	$-10 = h = 11$	$-12 = h = 11$;
	$-8 = k = 9$	$-8 = k = 10$	$-9 = k = 9$;
	$-20 = l = 19$	$-21 = l = 21$	$-24 = l = 23$
Reflections collections	6139	7150	7898
Independent reflections	2204	2591	2857
	[R(int) = 0.056]	[R(int) = 0.025]	[R(int) = 0.043]
Data/restraints/parameters	2204/0/145	2591/0/163	2857/0/217
Goodness-of-fit on F^2	1.06	1.09	1.03
R indices [I > 2σ(I)]	$R_1 = 0.101$,	$R_1 = 0.061$,	$R_1 = 0.051$,
	$wR_2 = 0.250$	$wR_2 = 0.148$	$wR_2 = 0.137$
R indices (all data)	$R_1 = 0.119$,	$R_1 = 0.075$,	$R_1 = 0.058$,
	$wR_2 = 0.260$	$wR_2 = 0.158$	$wR_2 = 0.142$
Refinement methods	Full-matrix least-squares	Full-matrix least-squares	Full-matrix least-squares
Largest diff. Peak/hole (e Å^{-3})	0.47/−0.29	0.38/−0.20	0.36 and −0.39

EXPERIMENTAL

Materials and Methods

Aqueous ammonia (25%) and substituted benzaldehydes are commercially available (they were obtained from Aldrich and were used without further purification). The melting points were obtained with a Yanaco micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet AVATAR 360 FT-IR spectrophotometer using KBr discs. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker 400 MHz spectrometer operating at 400, 100, and 160 MHz, respectively. The chemical shifts are reported in ppm with respect to the references and were stated relative to tetramethylsilane (TMS) for ^{1}H and ^{13}C NMR, and to 85% phosphoric acid for ^{31}P NMR. Elemental analyses were performed with a Flash EA 1112. All mass spectra were acquired with a Bruker ESQUIRE-3000 plus ion trap spectrometer equipped with a gas nebulizer probe in the positive ion mode. A Bruker SMART CCD X-ray diffractometer was used.

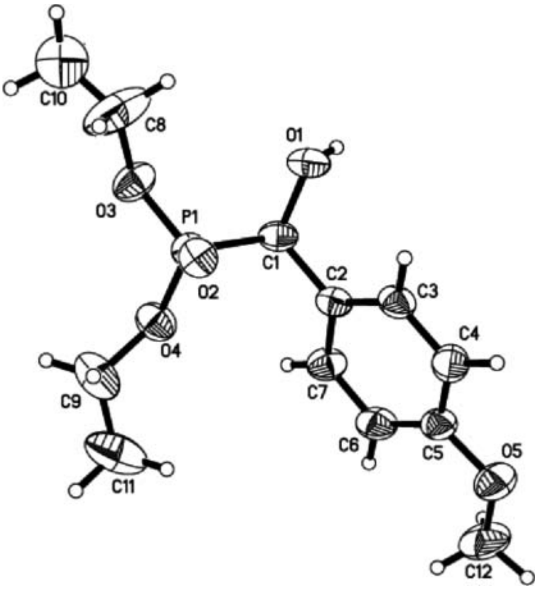


Figure 1 ORTEP drawing of the molecular structure **1b**. Displacement ellipsoids are at the 30% probability level.

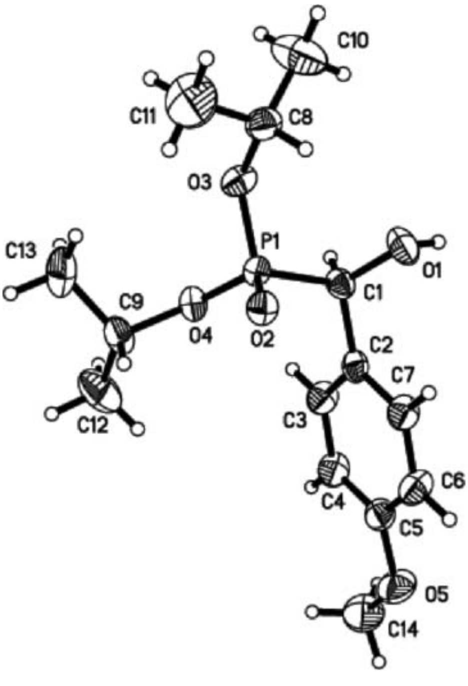


Figure 2 ORTEP drawing of the molecular structure **1c**. Displacement ellipsoids are at the 30% probability level.

Table V Selected bond lengths (Å) and angles (°) for compounds **1b**, **1c**, **2a**, **2b**, **2c**, and **2d**

	Compounds					
Bond	**1b**	**1c**	**2a**	**2b**	**2c**	**2d**
P(1)—O(2)	1.452(2)	1.468(2)	1.448(2)	1.453(3)	1.451(2)	1.454(2)
P(1)—O(4)	1.538(2)	1.567(2)	1.550(2)	1.549(3)	1.553(2)	1.564(6)
P(1)—O(3)	1.541(2)	1.573(7)	1.559(2)	1.549(3)	1.549(2)	1.567(2)
P(1)—C(1)	1.789(3)	1.820(2)	1.798(3)	1.803(4)	1.806(3)	1.806(2)
C(1)—O(1)	1.408(3)	1.420(3)	1.418(3)	1.410(4)	1.422(3)	1.404(3)
C(1)—C(2)	1.487(4)	1.521(3)	1.477(4)	1.491(6)	1.483(4)	1.512(3)
O(3)—C(8)	1.382(5)	1.464(3)	1.438(4)	1.433(6)	1.443(3)	1.402(3)
O(4)—C(9)	1.426(4)	1.464(3)	1.410(4)	1.438(5)	1.453(3)	1.398(3)
O(4)—P(1)—O(2)	115.8(3)	115.7(2)	113.3(2)	116.2(2)	114.5(2)	115.7(1)
O(3)—P(1)—O(2)	113.3(5)	114.3(30	116.2(1)	114.5(2)	116.3(1)	114.0(2)
C(1)—P(1)—O(2)	115.4(3)	115.1(1)	114.9(4)	114.9(1)	115.4(7)	1154.1()
P(1)—C(1)—O(1)	105.4(2)	103.8(2)	104.3(1)	103.7(3)	105.4(2)	103.7(3)
P(1)—O(3)—C(8)	124.3(3)	123.7(1)	120.3(2)	121.9(3)	123.7(2)	128.3(1)
P(1)—O(4)—C(9)	125.4(2)	124.2(5)	123.2(2)	121.8(4)	125.4(2)	124.2(5)

Synthesis

General procedure for the preparation of α-hydroxyphosphonic acid esters. To a solution of substituted-benzaldehyde (50 mmol) and dialkyl phosphite (50 mmol) in tetrahydrofuran (30 mL) at 0°C, aqueous ammonia (16 mL) was added. The mixture was left to stand at ambient temperature for 2 h, during which time a precipitate separated. The precipitate was filtered off and washed rapidly with cold diethyl ether.[26] Single crystals were obtained by crystallization of a dichloromethane/petroleum ether (v/v = 1:6) solution (Scheme 1).

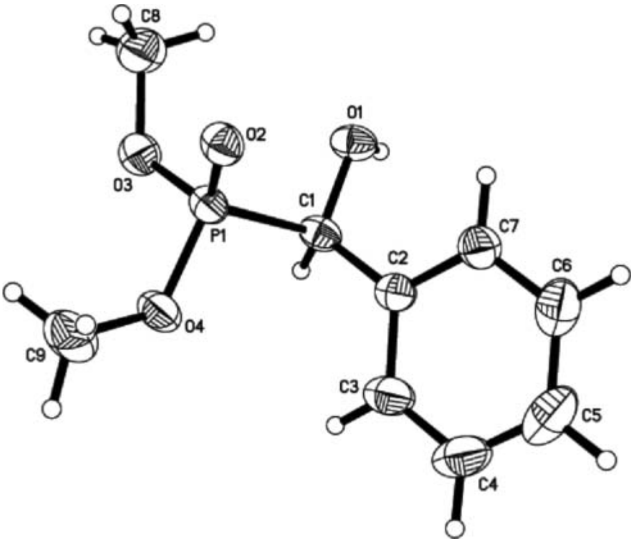


Figure 3 ORTEP drawing of the molecular structure **2a**. Displacement ellipsoids are at the 30% probability level.

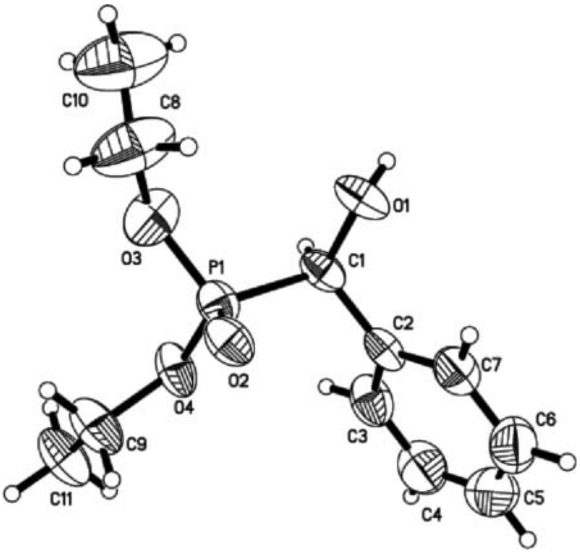


Figure 4 ORTEP drawing of the molecular structure **2b**. Displacement ellipsoids are at the 30% probability level.

[Hydroxy-(4-methoxy-phenyl)-methyl]-phosphonic acid dimethyl ester (**1a**) white solid, Yield: 72%; mp 74–75°C (Lit. 74–76°C^{27}); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.43 (d, 2H, $J = 5.2$ Hz, ArH), 6.89 (d, 2H, $J = 5.2$ Hz, ArH), 4.99 (d, 1H, $^2J_{P-C\underline{H}} = 5.6$ Hz, CH), 4.78 (br, 1H, OH), 3.81 (s, 3H, OCH$_3$), 3.78–3.66 (m, 6H, 2OCH$_3$); ^{13}C NMR: 159.4, 128.5, 128.5, 113.8 (Ar), 70.8 (d, $^1J_{P-\underline{C}H} = 162$ Hz, CH), 55.2 (PhOCH$_3$), 53.9 (d, $^2J = 10$

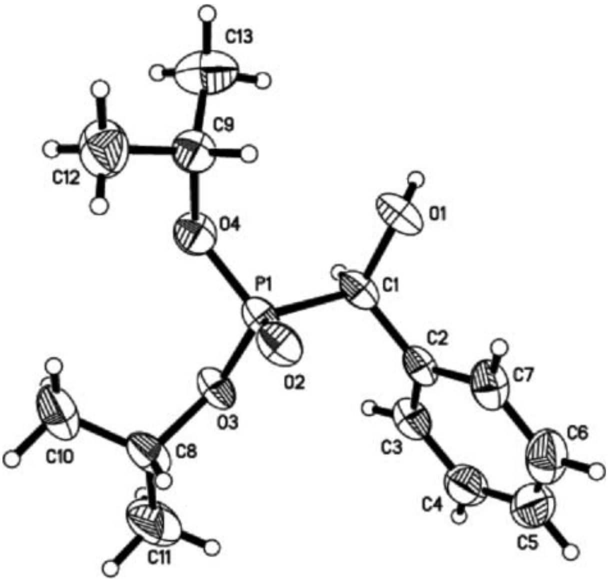


Figure 5 ORTEP drawing of the molecular structure **2c**. Displacement ellipsoids are at the 30% probability level.

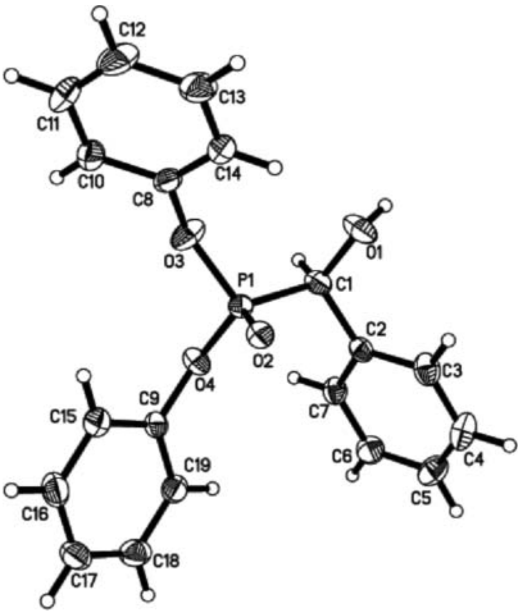


Figure 6 ORTEP drawing of the molecular structure **2d**. Displacement ellipsoids are at the 30% probability level.

Hz, OCH$_3$), 53.5 (d, $^2J = 10$ Hz, OCH$_3$); ^{31}P NMR: 23.98; MS *m/z* 247 [M+H]$^+$; Anal. calcd for $C_{10}H_{15}O_5P$: C 48.78, H 6.14; Found C 48.81, H 6.28.

[Hydroxy-(4-methoxy-phenyl)-methyl]-phosphonic acid diethyl ester (1b). White crystal, yield: 92%; mp 124–125°C (Lit. 120–121°C[28]); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.42 (d, 2H, $J = 4.4$ Hz, ArH), 6.89 (d, 2H, $J = 4.4$ Hz, ArH), 4.95 (d, 1H, $^2J_{P-C\underline{H}} = 5.6$ Hz, CH), 4.23 (br, 1H, OH), 4.08–4.02 (m, 4H, 2OC$\underline{H}_2$CH$_3$), 3.81 (s, 3H, OCH$_3$), 1.27 (t, 3H, $J = 7.2$ Hz, OCH$_2$C$\underline{H}_3$), 1.22 (t, 3H, $J = 7.2$ Hz, OCH$_2$C$\underline{H}_3$); ^{13}C NMR: 159.5, 132.0, 130.3, 128.6, 114.3, 113.7 (Ar), 71.1 (d, $^1J_{P-\underline{C}H} = 160$ Hz, CH), 63.2 (d, $^2J = 12$ Hz, O$\underline{C}$H$_2$CH$_3$), 62.9 (d, $^2J = 12$ Hz, O$\underline{C}$H$_2$CH$_3$), 55.4 (OCH$_3$), 16.4 (d, $^3J = 5$ Hz, OCH$_2\underline{C}$H$_3$), 16.3 (d, $^3J = 5$ Hz, OCH$_2\underline{C}$H$_3$); ^{31}P NMR: 21.74; MS *m/z* 275 [M+H]$^+$; Anal. calcd for $C_{12}H_{19}O_5P$: C 52.55, H 6.98; Found C 52.81, H 7.18.

[Hydroxy-(4-methoxy-phenyl)-methyl]-phosphonic acid diisopropyl ester (1c). White crystal, yield: 86%; mp 145–146°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.43 (d, 2H, $J = 4.2$ Hz, ArH), 6.89 (d, 2H, $J = 4.2$ Hz, ArH), 4.90 (d, 1H, $^2J_{P-C\underline{H}} = 5.4$ Hz, CH), 4.65–4.60 (m, 2H, 2OC$\underline{H}$(CH$_3$)$_2$), 3.81 (s, 3H, OCH$_3$), 3.72 (br, 1H, OH), 1.28–1.14 (m, 12H, 2OCH(C$\underline{H}_3$)$_2$); ^{13}C NMR: 159.4, 128.9, 128.7, 128.6, 113.6, 113.6 (Ar), 71.8 (d, $^2J = 10$ Hz, O$\underline{C}$H(CH$_3$)$_2$), 71.6 (d, $^2J = 10$ Hz, O$\underline{C}$H(CH$_3$)$_2$), 71.5 (d, $^1J_{P-\underline{C}H} = 161$ Hz, CH), 55.2 (OCH$_3$), 23.9, 23.6 (d, $^3J = 4$ Hz, OCH($\underline{C}$H$_3$)$_2$), 24.2, 24.1 (d, $^3J = 4$ Hz, OCH($\underline{C}$H$_3$)$_2$); ^{31}P NMR: 20.08; MS *m/z* 303 [M+H]$^+$; Anal.calcd for $C_{14}H_{23}O_5P$: C 55.62, H 7.67; Found C 55.65, H 7.69.

(Hydroxy-phenyl-methyl)-phosphonic acid dimethyl ester (2a). White crystal, yield: 64%; mp 102–105°C (Lit. 102–103°C[27]); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.50–7.30 (m, 5H, ArH), 5.41 (br, 1H, OH), 5.06 (d, 1H, $^2J_{P-C\underline{H}} = 11.6$ Hz, CH), 3.65–3.70 (m, 6H, 2OCH$_3$); ^{13}C NMR: 136.5, 135.8, 128.5, 128.1, 127.8 (Ar), 71.2 (d, $^1J_{P-\underline{C}H} = 159$ Hz, CH), 53.8 (d, $^2J = 8$ Hz, OCH$_3$), 53.5 (d, $^2J = 8$ Hz, OCH$_3$); ^{31}P NMR:

23.76; MS *m/z* 217 [M+H]$^+$; Anal. calcd for $C_9H_{13}O_4P$: C 50.01, H 6.06; Found C 49.99, H 6.30.

(Hydroxy-phenyl-methyl)-phosphonic acid diethyl ester (2b). White crystal, yield: 76%; mp 83–85°C (Lit. 83–84°C[28]); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18–7.24 (m, 5H, ArH), 4.91(t, 1H, $^2J_{P-C\underline{H}} = 12.5$ Hz, CH), 4.28 (br, 1H, OH), 3.90 (d, 4H, $^2J =$ 7.5 Hz, $2OC\underline{H}_2CH_3$), 1.07–1.17 (m, 6H, $2OCH_2C\underline{H}_3$); ^{13}C NMR: 13.7, 128.2, 127.9, 127.0 (Ar), 71.5 (d, $^1J_{P-\underline{C}H} = 158$ Hz, CH), 63.3 (d, $^2J = 12$ Hz, $O\underline{C}H_2CH_3$), 63.0 (d, $^2J = 12$ Hz, $O\underline{C}H_2CH_3$), 16.4 (d, $^3J = 5$ Hz, $OCH_2\underline{C}H_3$), 16.3 (d, $^3J = 5$ Hz, $OCH_2\underline{C}H_3$); ^{31}P NMR: 21.68; MS *m/z* 245 [M+H]$^+$; Anal. calcd for $C_{11}H_{17}O_4P$: C 54.10, H 7.02; Found C 54.33, H 7.19.

(Hydroxy-phenyl-methyl)-phosphonic acid diisopropyl ester (2c). White crystal, yield: 96%; mp 93–94°C (Lit. 95–97°C[27]); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20–7.40 (m, 5H, ArH), 4.85 (t, $^2J_{P-C\underline{H}} = 11.3$ Hz, CH), 4.50–4.55 (m, 2H, $2OC\underline{H}(CH_3)_2$), 2.96 (br, 1H, OH), 1.00–1.18 (m, 12H, $2OCH(C\underline{H}_3)_2$); ^{13}C NMR: 136.9, 127.9, 127.7, 127.2 (Ar), 71.7 (d, $^1J_{P-\underline{C}H} = 160$ Hz, CH), 71.6 (d, $^2J = 8$ Hz, $O\underline{C}H(CH_3)_2$), 71.5 (d, $^2J = 8$ Hz, $O\underline{C}H(CH_3)_2$), 23.8, 23.5 (d, $^3J = 4$ Hz, $OCH(\underline{C}H_3)_2$), 24.0, 23.9 (d, $^3J = 4$ Hz, $OCH(\underline{C}H_3)_2$); ^{31}P NMR: 20.18; MS *m/z* 273 [M+H]$^+$; Anal. calcd for $C_{13}H_{21}O_4P$: C 57.35, H 7.77; Found C 57.04, H 7.80.

(Hydroxy-phenyl-methyl)-phosphonic acid diphenyl ester (2d). White crystal, yield: 64%; mp 94–96°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61–6.81 (m, 15H, ArH), 5.34 (d, 1H, $^2J_{P-C\underline{H}} = 4.6$ Hz, CH), 3.93 (br, 1H, OH); ^{13}C NMR: 150.3, 135.4, 129.7, 129.6, 129.5, 128.6, 128.5, 128.4, 127.5, 127.5, 125.3, 125.2, 120.6, 120.6, 115.4 (Ar), 71.5 (d, $^1J_{P-\underline{C}H} = 161$ Hz, CH); ^{31}P NMR: 14.17; MS *m/z* 341 [M+H]$^+$; Anal. calcd for $C_{19}H_{17}O_4P$: C 67.06, H 5.04; Found C 67.00, H 5.06.

[(4-Chloro-phenyl)-hydroxy-methyl]-phosphonic acid dimethyl ester (3a). White solid, yield: 62%; mp 47–48°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53–7.46 (m, 2H, ArH), 7.36–7.33 (m, 2H, ArH), 5.06 (d, 1H, $^2J_{P-C\underline{H}} = 5.4$ Hz, CH), 4.32 (br, 1H, OH), 3.74 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3); ^{13}C NMR: 140.9, 134.8, 128.6, 128.5, 128.4, 128.3 (Ar), 70.8 (d, $^1J_{P-\underline{C}H} = 162$ Hz, CH), 54.0 (d, $^2J = 8$ Hz, OCH_3), 53.7 (d, $^2J = 8$ Hz, OCH_3); ^{31}P NMR: 22.95; MS *m/z* 251 [M(35)+H]$^+$, 253 [M(37)+H]$^+$.

[(4-Chloro-phenyl)-hydroxy-methyl]-phosphonic acid diethyl ester (3b). Colorless oil, yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.39 (m, 2H, ArH), 7.29–7.26 (m, 2H, ArH), 4.99 (d, 1H, $^2J_{P-C\underline{H}} = 5.6$ Hz, CH), 4.27 (br, 1H, OH), 4.11–3.98 (m, 4H, $2OC\underline{H}_2CH_3$), 1.33–1.18 (m, 6H, $2OCH_2C\underline{H}_3$); ^{13}C NMR: 140.9, 135.6, 134.7, 133.9, 128.5, 128.3 (Ar), 70.8 (d, $^1J_{P-\underline{C}H} = 160$ Hz, CH), 63.4 (d, $^2J = 12$ Hz, $O\underline{C}H_2CH_3$), 61.8 (d, $^2J = 12$ Hz, $O\underline{C}H_2CH_3$), 16.4 (d, $^3J = 5$ Hz, $OCH_2\underline{C}H_3$), 16.2 (d, $^3J = 5$ Hz, $OCH_2\underline{C}H_3$); ^{31}P NMR: 20.89; MS *m/z* 279 [M(35)+H]$^+$, 281 [M(37)+H]$^+$.

[(4-Chloro-phenyl)-hydroxy-methyl]-phosphonic acid diisopropyl ester (3c). White solid, yield: 86%; mp 105–107°C (Lit. 101–102°C[27]); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, 2H, $J = 4.2$ Hz, ArH), 7.43 (d, 2H, $J = 4.2$ Hz, ArH), 4.57 (br, 1H, OH), 4.94 (d, 1H, $^2J_{P-C\underline{H}} = 5.4$ Hz, CH), 4.80–4.62 (m, 2H, $2OC\underline{H}(CH_3)_2$), 1.28–1.25 (m, 9H, $OCH(C\underline{H}_3)_2$), 1.20–1.18 (m, 3H, $OCH(C\underline{H}_3)_2$); ^{13}C NMR: 140.9, 135.4, 134.7, 133.6 (Ar), 72.2 (d, $^2J = 10$ Hz, $O\underline{C}H(CH_3)_2$), 71.8 (d, $^2J = 10$ Hz, $O\underline{C}H(CH_3)_2$), 71.2 (d, $^1J_{P-\underline{C}H} = 162$ Hz, CH), 24.1, 24.0 (d, $^3J = 4$ Hz, $OCH(\underline{C}H_3)_2$), 23.9, 23.7 (d, $^3J = 4$ Hz, $OCH(\underline{C}H_3)_2$); ^{31}P NMR: 19.18; MS *m/z* 307 [M(35)+H]$^+$, 309 [M(37)+H]$^+$.

[Hydroxy-(4-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester (4a). Yellow solid, yield: 18%; mp 129–131°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, 2H, $J =$ 4.4 Hz, ArH), 7.69 (d, 2H, $J = 4.4$ Hz, ArH), 5.23 (d, 1H, $^2J_{P-C\underline{H}} = 4.2$ Hz, CH), 4.88

(br, 1H, OH), 3.81–3.76 (m, 6H, 2OCH$_3$); ^{13}C NMR: 147.8, 143.8, 127.6, 123.5 (Ar), 70.8 (d, $^1J_{\mathrm{P-\underline{C}H}}$ = 158 Hz, CH), 54.4 (d, ^2J = 10 Hz, OCH$_3$), 53.8 (d, ^2J = 10 Hz, OCH$_3$); ^{31}P NMR: 21.85; MS *m/z* 262 [M+H]$^+$.

[Hydroxy-(4-nitro-phenyl)-methyl]-phosphonic acid diethyl ester (4b). Yellow solid, yield: 20%; mp 100–101°C; ^{1}H NMR (400 Hz, CDCl$_3$) δ: 8.22 (d, 2H, J = 4.2 Hz, ArH), 7.68 (d, 2H, J = 4.2 Hz, ArH), 5.22 (d, 1H, $^2J_{\mathrm{P-C\underline{H}}}$ = 6.4 Hz, CH), 4.23 (br, 1H, OH), 4.14–4.10 (m, 4H, 2OC$\underline{\mathrm{H}}_2$CH$_3$), 1.33–1.26 (m, 6H, 2OCH$_2$C$\underline{\mathrm{H}}_3$); ^{13}C NMR: 147.5, 144.3, 132.2, 127.7, 123.3, 113.8 (Ar), 70.9 (d, $^1J_{\mathrm{P-\underline{C}H}}$ = 158 Hz, CH), 64.0 (d, ^2J = 12 Hz, O$\underline{\mathrm{C}}$H$_2$CH$_3$), 63.4 (d, ^2J = 12 Hz, O$\underline{\mathrm{C}}$H$_2$CH$_3$), 16.4 (d, ^3J = 5 Hz, OCH$_2\underline{\mathrm{C}}$H$_3$), 16.4 (d, ^3J = 5 Hz, OCH$_2\underline{\mathrm{C}}$H$_3$); ^{31}P NMR: 19.82; MS *m/z* 290 [M+H]$^+$.

[Hydroxy-(4-nitro-phenyl)-methyl]-phosphonic acid diisopropyl ester (4c). Yellow solid, yield: 43%; mp 105–107°C; ^{1} H NMR (400 MHz, CDCl$_3$) δ: 7.75 (d, 2H, J = 4.3 Hz, ArH), 7.22 (d, 2H, J = 4.3 Hz, ArH), 5.27 (br, 1H, OH), 4.67 (d, 1H, $^2J_{\mathrm{P-C\underline{H}}}$ = 6.4 Hz, CH), 4.29–4.20 (m, 2H, 2OC$\underline{\mathrm{H}}$(CH$_3$)$_2$), 0.88–0.78 (m, 12H, 2OCH(C$\underline{\mathrm{H}}_3$)$_2$); ^{13}C NMR 147.3, 144.9, 129.5, 123.0 (Ar), 72.7 (d, ^2J = 10 Hz, O$\underline{\mathrm{C}}$H(CH$_3$)$_2$), 72.1 (d, ^2J = 10 Hz, O$\underline{\mathrm{C}}$H(CH$_3$)$_2$), 71.0 (d, $^1J_{\mathrm{P-\underline{C}H}}$ = 160 Hz, CH), 24.0, 23.9 (d, ^3J = 4 Hz, OCH($\underline{\mathrm{C}}$H$_3$)$_2$), 23.8, 23.6 (d, ^3J = 4 Hz, OCH($\underline{\mathrm{C}}$H$_3$)$_2$); ^{31}P NMR 18.04; MS *m/z* 318 [M+H]$^+$; Anal. calcd for C$_{13}$H$_{20}$NO$_6$P: C 49.21, H 6.35, N 4.41; Found C 49.99, H 6.30, N 5.10.

Supplementary Data

Crystallographic data of the structural analyses (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center: CCDC nos. 659488, 659487, 605054, 659489, 298432, 608519. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ UK on request (fax: +44 1223–336-033; email: deposit @ ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk), by quoting the deposition numbers for compounds **1b**, **1c**, **2a**, **2b**, **2c**, and **2d**, respectively.

REFERENCES

1. T. R. Burke, Jr., Z. H. Li, J. B. Bolen, and V. E. Marquez, *J. Med. Chem.*, **34,** 1577 (1991).
2. B. Stowasser, K. H. Budt, Q. L. Jian, A. Peyman, and D. Ruppert, *Tetrahedron Lett.*, **33,** 6625 (1992).
3. M. L. Moore and G. B. Dreyer, *Perspect. Drug Discovery Des.*, **1,** 85 (1993).
4. D. L. Pomplianno, E. Rands, M. D. Schaber, S. D. Mosser, N. J. Anthony, and J. B. Gibbs, *Biochemistry*, **31,** 3800 (1992).
5. R. Y. Chen, L. Z. Liu, and Z. B. Zhang, *Heteroatom Chem.*, **6,** 503 (1995).
6. D. M. Pogatchnik and D. F. Wiemer, *Tetrahedron Lett.*, **38,** 3495 (1997).
7. M. S. Kharasch, R. A. Mosher, and I. S. Bengelsdorf, *J. Org. Chem.*, **25,** 1000 (1960).
8. A. F. Janzen and R. Pollitt, *Can. J. Chem.*, **48,** 1987 (1970).
9. O. Pamies and J. E. Backvall, *J. Org. Chem.*, **68,** 4815 (2003).
10. T. Tatsuoka, K. Imao, and K. Suzuki, *Hetercycles*, **24,** 617 (1986).
11. J. X. Cai, Z. G. Zhou, G. F. Zhao, and C. C. Tang, *Heteroatom Chem.*, **14,** 312 (2003).
12. T. B. Francoise and A. Foucaud, *Synthesis*, **7,** 165 (1982).
13. A. N. Pudovik and I. V. Konovalova, *Synthesis*, **7,** 81 (1979).
14. H. Fang, M. J. Fang, Z. P. Zeng, Z. B. Wei, and Y. F. Zhao, *Acta Cryst.* **E62,** o1378 (2006).
15. S. X. Cao, J. C. Zhang, J. Xu, X. C. Liao, and Y. F. Zhao, *Rapid Commun. Mass Spectrom.*, **17,** 2237 (2003).

16. Y. W. Yin, Y. Ma, and Y. F. Zhao, *Org. Mass. Spectrom.*, **29,** 201 (1994).
17. Y. F. Zhao, D. Q. Zhang, C. B. Xue, J. N. Zeng, and G. J. Ji, *Org. Mass. Spectrom.*, **26,** 510 (1991).
18. G. M. Sheldrick, SHELXL97 (University of Gottingen, Gottingen, Germany, 1997).
19. E. Prince, *Mathematical Techniques in Crystallography* (Springer-Verlag, Berlin, 1982).
20. SAINT (V6.22), SMART (V5.625), and SADABS (V2.03) (Bruker AXS Inc., Madison, Wisconsin, USA, 2001).
21. L. J. Farrugia, *J. Appl. Cryst.*, **30,** 565 (1997).
22. T. M. Lane, S. M. Levsen, M. K. Tasz, and S. E. Cremer, *Heteroatom Chem.*, **7,** 9 (1996).
23. H. Fang, M. J. Fang, X. X. Liu, G. Tang, and Y. F. Zhao, *Heteroatom Chem.*, **18**(1), 9 (2007).
24. H. Fang, Z. P. Zeng, M. J. Fang, T. Ji, and Y. F. Zhao, *Acta Cryst.*, **E62,** 3797 (2006).
25. T. J. Mosmann, *Immunol. Methods*, **65,** 55 (1983).
26. M. Drescher, F. Hammerschmidt, and H. Kahlig, *Synthesis*, **10,** 1267 (1995).
27. (a) F. Texier-Boullet and A. Foucaud, *Synthesis*, **11,** 916 (1982); (b) J. Jacques, M. Leclerq, and M.-J. Brienne, *Tetrahedron*, **37,** 1727 (1981); (c) A. S. Remizov, T. I. Koroleva, V. K. Promonenkov, and A. F. Grapov, *Zh. Obshch. Khim.*, **51,** 341 (1981).
28. (a) A. R. Sardarian and B. Kaboudin, *Synth. Commun.*, **27,** 543 (1997); (b) A. Kamyar, R. W. Charles, and J. I. Cadogan, *Tetrahedron*, **46,** 7175 (1990).