Synthesis and Characterization of the Novel 1-(Substituted phenoxy/phenyl)-2-Phospholene and Phospholane 1-Oxide Derivatives

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The synthesis of the novel 1-(substituted phenoxy/phenyl)-2-phospholene and phospholane 1-oxide derivatives, which are analogs of sugars having a phosphorus atom in place of the ring oxygen of normal sugars, is described. All of the synthesized derivatives are structurally characterized by multi nuclear NMR, mass, and IR spectral data, elemental and X-ray crystallographic analyses.

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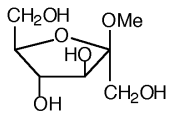
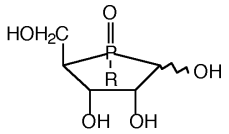
Introduction.

Replacement of the oxygen atom in the hemiacetal ring of normal sugars by a hetero atom or a carbon atom leads to pseudo sugars, some of which have been widely investigated in the fields of synthetic, biological, and medicinal chemistry [1]. In particular, hetero sugars in which the ring oxygen has been replaced by a nitrogen, sulfur, or selenium atom have been extensively studied and widely developed [2]. Aza and thia sugars are known to exist in the nature, but phospha sugar derivatives, having a P atom in place of the ring oxygen of normal sugars, have not yet been found in naturally occurring products.



Methyl β-D-fructofuranoside



An example of pentafuranose analog of phospha sugar, D-ribose analog of phospha sugar

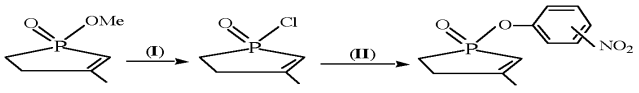
In recent years focus is increased on the synthesis of bioactive phosphorus compounds [3], among those, phospha sugars are interesting due to their potential biological activities in various fields [4]. In view of their characteristic biological activities, nitro- and/or chloro-substituted phenyl phospha sugar derivatives are expected to have heightened bioactivity. Several reports suggested that the molecules containing substituted aromatic groups being mainly nitro- and/or halo-substituted possess potential bioactivity [5]. Moreover chloro- and nitro-substituted aromatic compounds are more toxic [6]. By incorporating these substituted aromatic moieties into a basically bioactive phospha sugar molecule [4] the resulting bioactivity is expected to be enhanced more than that of the normal phospha sugar molecules.

Addition of phosphorus trihalides or phosphonous dihalides to 1,3-alkadienes is known to produce cyclic unsaturated phosphorus compounds, *i.e.*, phospholenes [7,8]. In our earlier papers we reported the synthesis of phospha or phosphanyl sugar derivatives starting from 2-phospholene derivatives, having the unsaturated five membered phosphorus heterocycles. We are further interested in the synthesis of several phospha sugar derivatives which are to be potentially bioactive in various fields. The present paper deals with the synthesis and characterization of the novel 1-(substituted phenoxy/phenyl)-2-phospholene and phospholane 1-oxide derivatives as well as some of their 1-sulfides.

Results and Discussion.

Reaction of 1-chloro-3-methyl-2-phospholene 1-oxide (**1**) with *o*-, *m*-, and *p*-nitrophenols gave products of **2a-c**, *i.e.*, 1-(nitro-substituted phenoxy)-3-methyl-2-phospholene 1-oxides (Scheme 1). Dry triethylamine was used as the base for the reaction of **1** with phenols with dry toluene as the solvent and at a temperature that was varied between 45-50 °C. Isolation of the products **2a-c** was achieved by filtering off the triethylammonium chloride, and evaporating the resulting filtrate under a vacuum. All products are purified by column chromatography on silica gel with $CHCl_3$ and MeOH (20:1) as the mixture of eluent.

Scheme 1



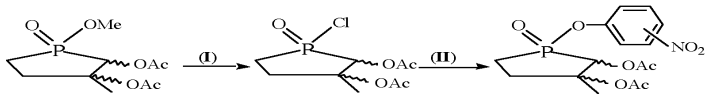
1 **2a-c**

(I) $SOCl_2$, Rt, 24 hrs; (II) dry Toluene, Nitrophenols, Et_3N, 45-50 °C, 6 hrs a) *o*-Nitrophenol; b) *m*-Nitrophenol; c) *p*-Nitrophenol

In an analogous manner as that of **2a-c**, 2,3-diacetoxy-3-methyl-1-(nitro-substituted phenoxy)phospholane 1-oxides (**4a-c**) (Scheme 2) were prepared from 2,3-diacetoxy-1-chloro-3-methylphospholane 1-oxide (**3**). Isolation and purification methods of products **4a-c** were similar to the products **2a-c.** The isomeric ratios of **4a-c** were calculated on the basis of ^{31}P NMR and are reported in Table I. Attempts to prepare phospholanes **4a-c** from 2-phospholenes **2a-c** failed because the P-O-C bond was broken in aqueous medium during *cis*-dihydroxylation with OsO_4. This was due to the strong electron withdrawing nature of the P=O bond [9] and the negative inductive and resonance

effect of nitro group on 1-phenyl substituent. The alternative synthetic method shown in Scheme 2 was followed. The isomeric ratios and preparation of 2,3-diacetoxy-1-methoxy-3-methylphospholane 1-oxide, which is the starting material in the preparation of **4a-c**, were explained precisely in our earlier reported methods [9]. These are the first phospha sugar derivatives which possess phosphorus ester functional moiety (O=P-O-) [10] with a nitrophenyl group prepared from 2-phospholenes as the starting materials. Proton NMR spectra were rather simple for all of these products, while ^{13}C NMR spectra are given in Table II for all of these products cited here. The aromatic carbon atoms bearing a nitro-group (*ipso*-carbons) are found in the low field range of 135-150 ppm, and the carbonyl resonances were observed at 166.5-167.8 ppm.

Scheme 2



3 **4a-c**

(I) $SOCl_2$, Rt, 24 hrs; (II) dry Toluene, Nitrophenols, Et_3N, 45-50 °C, 6 hrs
a) *o*-Nitrophenol; b) *m*-Nitrophenol; c) *p*-Nitrophenol

Table I

Physical Properties , ^{31}P-NMR, and Isomeric Ratios for **2a-c**, and **4a-c**

Product	Yield(%)	^{31}P-NMR(ppm)	Isomeric ratio
2a	80	76.31	
2b	75	76.51	
2c	78	78.25	
4a	70	55.21 (major)	
		62.01 (minor)	7.7:1.0
4b	67	55.15 (major)	
		61.55 (minor)	5.4:1.0
4c	68	56.02 (major)	
		61.26 (minor)	4.9:1.0

In connection with our greater interest in the synthesis of substituted 1-phenyl-2-phospholene 1-oxide derivatives, compounds **5a-g** were synthesized through Grignard reagent formation [11,12]. The essence of our synthetic method by using a Grignard reagent is to generate a P-phenyl bond through metal-halogen exchange and then to trap it by nucleophilic addition (Grignard coupling). The Grignard reagent is therefore used in excess. Addition of a dry THF solution of 1-chloro-3-methyl-2-phospholene 1-oxide to 2 equivalents of substituted phenylmagnesium bromide in the same solvent at room temperature followed by stirring for 6 hours gave, after hydrolysis, a 50-60% yield of **5a-g** (Scheme 3). Isolation of the obtained derivatives was achieved by extraction of the aqueous mixture with chloroform, then the organic layer was dried over anhydrous Na_2SO_4, evaporated under vacuum, and purified by column chromatography on silica gel using EtOAc and MeOH (20:1) as eluent. Except for the first entry, all of the products in Table III are new compounds.

Table III

Physical Properties , and ^{31}P-NMR Shifts of **5a-g**

Compound	*n*-X	Yield(%)	^{31}P-NMR(ppm)
5a	H	60	60.68
5b	*p*-chloro	62	60.39
5c	*m*-chloro	58	60.68
5d	*o*-chloro	52	63.59
5e	*p*-methoxy	71	61.75
5f	*m*-methoxy	69	62.33
5g	*o*-methoxy	66	60.19

Nitration of **5a-g** with nitration mixture, afforded a variety of positional isomeric products (Scheme 3) due to the electrophilic aromatic substitution reaction [13] on mono- and di-substituted benzene rings of **5a-g**. Because the P=O

Table II

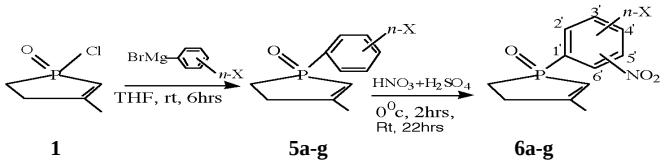
^{13}C-NMR Chemical Shifts of Products **2a-c*** and **4a-c*** (ppm values from TMS)

	Carbon Atom												
Compound	C-2 (J_{PC})	C-3 ($^2J_{PC}$)	C-4 ($^2J_{PC}$)	C-5 (J_{PC})	C-1' ($^2J_{PC}$)	C-2' ($^3J_{PC}$)	C-3'	C-4'	C-5'	C-6'	C-CH_3 ($^3J_{PC}$)	OCH_3	C=O
2a	119.2	166.8	31.2	24.4	156.2	120.4	125.2	143.5			20.5		
	(128.3)	(34.7)	(13.3)	(27.2)	(8.1)	(5.3)					(8.5)		
2b	118.9	166.6	30.9	24.3	151.1	115.2	148.1	127.4	129.7	126.4	21.2		
	(120.2)	(34.1)	(13.4)	(27.2)	(8.2)	(4.4)					(12.1)		
2c	119.6	167.2	31.2	25.2	144.2	134.1	124.7	125.2	137.1	119.9	21.1		
	(128.1)	(35.4)	(13.3)	(27.2)	(8.6)	(1.3)				(6.6)	(8.6)		
4a	67.6	25.9	31.2	26.9	156.6	121.2	125.7	145.1			19.8	15.6	166.5
	(170.1)	(6.1)	(21.1)	(64.1)	(9.1)	(5.3)					(6.1)	16.1	166.6
4b	68.2	25.8	32.1	26.5	152.2	118.2	150.1	127.8	130.8	125.4	19.7	15.5	166.5
	(172.1)	(8.1)	(13.2)	(70.1)	(10.1)	(5.1)				(4.5)	(7.6)	15.9	167.8
4c	67.6	25.9	31.3	26.8	144.9	134.3	125.5	125.3	133.8	124.3	16.1	15.2	165.6
	(180.1)	(7.2)	(12.1)	(66.6)	(10.9)	(6.1)				(6.8))	(6.6)	15.6	166.7

*Data in parantheses are coupling constants (J_{PC}) expressed in Hz.

is *deactivating* group [9], in the first case of compound **5a** mono substitution with electrophile NO_2^+ was oriented *meta* to the directing (P=O) group, giving product 1-(3'-nitrophenyl)-3-methyl-2-phospholene 1-oxide (**6a**). However, it was a somewhat surprising observation that compounds **5b-d**, which are disubstituted with P=O (*meta* directing) and Cl (*ortho-para* directing) groups, nitration

Scheme 3



1 **5a-g** **6a-g**

X=H, Cl, OMe; n=*p, m, o*

occurred and the incoming group (NO_2^+) was oriented to the favourable position, *i.e*., either *ortho* or *para* to the chloro and *meta* to the P=O group, giving products 1-(4'-chloro-3'-nitrophenyl)-3-methyl-2-phospholene 1-oxide (**6b**), and 1-(2'-chloro-5'-nitrophenyl)-3-methyl-2-phospholene 1-oxide (**6d**), while in the case of compound **5c**, *i.e*., when a *meta* directing group (P=O) located *meta* to an *ortho-para* directing group (Cl), NO_2^+ was oriented *ortho* to the P=O group rather than *para* giving 1-(5'-chloro-2'-nitrophenyl)-3-methyl-2-phospholene 1-oxide (**6c**), according to the *ortho effect* [14]. And compounds **5e-g** are also disubstituted with a strong *ortho-para* activating group (OCH_3), the rate of nitration was enhanced and dinitration occurred under the same reaction conditions as those of **5a-d**, and the orientation effect is similar as that observed for products **6a-d**. All of these products (Table IV) were purified by fractional recrystallization from EtOAc and *n*-hexane.

Table IV

Product Structures, Physical and ^{31}P NMR Ddata of **5a-g**

Entry	Substrate	Product	Yield(%)	MP(°C)	^{31}P-NMR(ppm)
1	**5a**	**6a**	80	117-120	59.90
2	**5b**	**6b**	56	ND [a]	77.28
3	**5c**	**6c**	55	ND [a]	76.57
4	**5d**	**6d**	50	ND [a]	77.92
5	**5e**	**6e**	75	170-173	57.96
6	**5f**	**6f**	71	162-166	56.65
7	**5g**	**6g**	70	155-159	58.18

[a] ND=Not determined due to syrupy state.

High resolution ^{1}H-NMR (300 MHz) analyses of all these products were capable of characterizing all positional isomers precisely. A single crystal was developed for product **6e** from EtOAc by slow evaporation method. The X-ray analysis revealed the structure of the product **6e** as shown in the ORTEP drawing in Figure 1 and afforded bond lengths, bond angles, and torsion angles as shown in Table V.

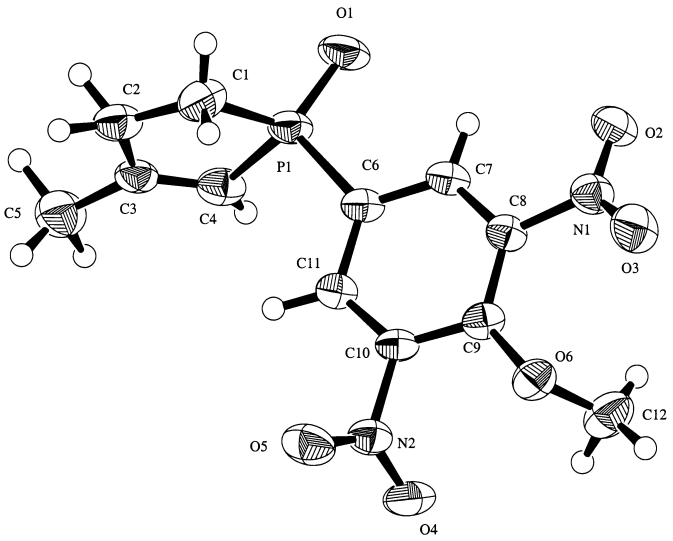


Figure 1. ORTEP drawing of 1-(4'-methoxy-3',5'-dinitrophenyl)-3-methyl-2-phospholene 1-oxide (**6e**) [15].

All proton NMR signals for **6a-g** in the aryl rings were observed at low field (Table VI), and the coupling constants varied in the range between 6-9 Hz for *ortho*, 1-3 Hz for *meta*, and 0-1 Hz for *para* coupling, respectively. PCH coupling was observed for *ortho* ($^2J_{PCH}$) as well as *meta* ($^3J_{PCH}$) oriented protons, and are in between 1-12 Hz. All ^{13}C NMR signals (Table VII) appeared as doublets due to PC coupling. The nitrogen-bearing aromatic ring carbons were observed at low field in the range 130-135 ppm and 145-153 ppm for NO_2 substitution with and without Cl substituent, respectively. The ^{31}P-NMR values of products **6e-g** and **6a** showed an increasing upfield shift of 15-20 ppm. This is due to the electron withdrawing ability of the NO_2 group in the aromatic ring being increased compared with that of products **6b-d** [16], where back donation of electrons from 'O' atom to 'P' atom in P=O bond is reasoned**.**

Table V

Selected Bond Lengths, Bond Angles, and Torsion Angles for Compound **6e** [15].

Selected bond length		Selected bond angle		Selected torsion angle	
Bond	Length(Å)	Bond	Angle(°)	Bond	Angle(°)
P(1)-O(1)	1.489	O(1)-P(1)-C(1)	117.6	P(1)-C(1)-C(2)-C(3)	11.7
P(1)-C(1)	1.801	O(1)-P(1)-C(4)	118.9	P(1)-C(4)-C(3)-C(2)	-3.1
P(1)-C(4)	1.771	O(1)-P(1)-C(6)	108.4	P(1)-C(4)-C(3)-C(5)	177.3
P(1)-C(6)	1.820	C(1)-P(1)-C(4)	93.5	P(1)-C(6)-C(7)-C(8)	178.7
O(2)-N(1)	1.225	C(1)-P(1)-C(6)	108.3	P(1)-C(6)-C(11)-C(10)	178.6
O(3)-N(1)	1.220	C(4)-P(1)-C(6)	109.2	O(1)-P(1)-C(1)-C(2)	113.5
O(4)-N(2)	1.219	C(9)-O(6)-C(12)	116.7	O(1)-P(1)-C(4)-C(3)	-115.4
O(5)-N(2)	1.217	O(2)-N(1)-O(3)	123.9	O(1)-P(1)-C(6)-C(11)	-167.2
O(6)-C(9)	1.349	O(2)-N(1)-C(8)	117.2	O(2)-N(1)-C(8)-C(7)	-18.6
O(6)-C(12)	1.443	O(3)-N(1)-C(8)	118.8	O(2)-N(1)-C(8)-C(9)	163.9
N(1)-C(8)	1.473	O(4)-N(2)-O(5)	125.3	O(4)-N(2)-C(10)-C(9)	-60.7
N(2)-C(10)	1.479	O(4)-N(2)-C(10)	118.0	O(5)-N(2)-C(10)-C(11)	-59.7
C(1)-C(2)	1.498	O(5)-N(2)-C(10)	116.8	O(6)-C(9)-C(8)-C(7)	-178.5
C(2)-C(3)	1.498	P(1)-C(1)-C(2)	107.5	O(6)-C(9)-C(10)-N(2)	-4.4
C(3)-C(4)	1.334	C(1)-C(2)-C(3)	109.6	N(2)-C(10)-C(9)-C(8)	179.9
C(3)-C(5)	1.495	C(2)-C(3)-C(4)	116.2	C(1)-P(1)-C(4)-C(3)	8.9
C(6)-C(7)	1.386	C(2)-C(3)-C(5)	118.0	C(1)-P(1)-C(6)-C(7)	-115.5
C(6)-C(11)	1.395	C(4)-C(3)-C(5)	125.8	C(2)-C(1)-P(1)-C(4)	-11.7
C(7)-C(8)	1.374	P(1)-C(4)-C(3)	111.6	C(2)-C(1)-P(1)-C(6)	-123.3
C(8)-C(9)	1.405	O(6)-C(9)-C(8)	126.5	C(7)-C(8)-C(9)-C(10)	-3.2
C(9)-C(10)	1.392	P(1)-C(6)-C(11)	123.0	C(8)-C(7)-C(6)-C(11)	-1.1
C(10)-C(11)	1.373	O(6)-C(9)-C(10)	118.3	C(10)-C(9)-O(6)-C(12)	114.4

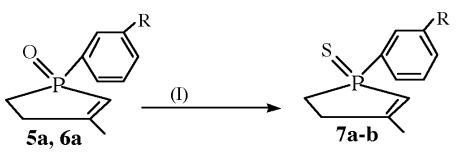
Table VI

^{1}H-NMR Chemical Shifts and Coupling Constant (J) Values for Compounds **6a-g**.

Compound	Phospholene ring protons	Ar-H
6a	2.06(s, 3H, CH_3), 2.34-2.48(m, 2H, H- 4, 4'), 2.62-2.75(m, 2H, H-5, 5'), 5.97(d, 1H, H-2, J_{PCH}=25.5Hz)	7.50-7.85(m, 1H, H-5'), 7.95-8.55(m, 3H, H-2',4',6')
6b	2.05(s, 3H, CH_3), 2.51-2.62(m, 2H, H- 4, 4'), 2.86-2.94(m, 2H, H-5, 5'), 5.91(d, 1H, H-2, J_{PCH}=25.2Hz)	7.66(dd, 1H, H-5', J_{HH}=8.2Hz, $^3J_{PCH}$=1.5Hz), 7.84(td, 1H, H-6', J_{HH}=8.4Hz & 1.5Hz, $^2J_{PCH}$=9.9Hz), 8.02(dd, 1H, H-2', $^2J_{PCH}$ =11.4Hz, J_{HH}=1.5Hz)
6c	2.01(s, 3H, CH_3), 2.44-2.52(m, 2H, H- 4, 4'), 2.71-2.88(m, 2H, H-5, 5'), 5.98(d, 1H, H-2, J_{PCH}=24.1Hz)	7.56(dd, 1H, H-4', J_{HH}=8.7Hz & 1.8Hz), 7.77(dd, 1H, H-6', $^2J_{PCH}$=11.1Hz & J_{HH}=1.9Hz), 8.01(dd, 1H, H-3', J_{HH}=8.5Hz, $^3J_{PCH}$=4.2Hz)
6d	2.03(s, 3H, CH_3), 2.46-2.55(m, 2H, H- 4, 4'), 2.76-2.85(m, 2H, H-5, 5'), 5.97(d, 1H, H-2, J_{PCH}=24.7Hz)	7.48(dd, 1H, H-4', J_{HH}=8.1Hz & 2.1Hz), 7.69(dd, 1H, H-6', $^2J_{PCH}$=12.0Hz, J_{HH}=2.1Hz), 8.22(dd, 1H, H-3', J_{HH}=8.1Hz, $^3J_{PCH}$=4.6Hz)
6e	2.16(s, 3H, CH_3), 2.66-2.78(m, 2H, H- 4, 4'), 2.89-2.97(m, 2H, H-5, 5'), 5.91(d, 1H, H-2, J_{PCH}=25.8Hz)	8.32(d, 2H, H-2', 6', $^2J_{PCH}$=10.9Hz), 3.98(s, 3H, OCH_3)
6f	2.05(s, 3H, CH_3), 2.64-2.72(m, 2H, H- 4, 4'), 2.82-2.92(m, 2H, H-5, 5'), 5.95(d, 1H, H-2, J_{PCH}=25.2Hz)	7.21(d, 1H, H-4', J_{HH}=9.1Hz), 7.99(dd, 1H, H-5', J_{HH}=9.1Hz, &$^3J_{PH}$=3.1Hz), 3.99(s, 3H, OCH_3)
6g	2.03(s, 3H, CH_3), 2.44-2.56(m, 2H, H- 4, 4'), 2.86-2.95(m, 2H, H-5, 5'), 5.99(d, 1H, H-2, J_{PCH}=25.8Hz)	8.86(d, 1H, H-4', J_{HH}=2.7Hz), 8.94(dd, 1H, H-6', J_{HH}=2.8Hz, $^2J_{PCH}$=11.1Hz), 3.98(s, 3H, OCH_3)

In an effort to ascertain the replacement of oxygen atom in the P=O group of substituted 1-phenyl-2-phospholenes by sulfur atom [17], compounds **5a** and **6a** (Scheme 4) were treated with P_4S_{10} in the presence of dry benzene as the solvent medium to give good yields of **7a-b**. The resulting products were mainly characterized by IR spectral analysis, where a strong band was observed at IR frequency 760 cm^{-1} which corresponded to P=S absorption, while the IR band at 1240 cm^{-1} of P=O was not observed. ^{1}H-NMR spectral analyses have shown that the olefinic protons of C=C in the products **7a-b** (Scheme 4) were shifted to higher field than those of compounds **5a** and **6a**. The spectral data confirm that the 'O' atom is replaced by 'S' atom in the products **7a-b**.

Scheme 4



(**5a**) R=H; (**6a**) R=NO_2; (**I**) P_4S_{10}, C_6H_6, 20hrs

Table VII

^{13}C NMR Chemical Shifts for **6a-g*** (ppm values from TMS)

Compound	Carbon Atom											
	C-*CH*$_3$ ($^3J_{PC}$)	C-2 (J_{PC})	C-3 ($^2J_{PC}$	C-4 ($^2J_{PC}$)	C-5 (J_{PC})	C-1' (J_{PC})	C-2' ($^2J_{PC}$)	C-3' ($^3J_{PC}$)	C-4' ($^4J_{PC}$)	C-5' ($^3J_{PC}$)	C-6' ($^2J_{PC}$)	OMe
6a	21.09	119.44	167.00	34.04	27.15	137.01	125.23	148.16	126.23	129.79	136.55	
	(17.4)	(100.9)	(26.07)	(9.4)	(70.9)	(94.2)	(12.7)	(14.7)	(2.7)	(11.4)	(9.4)	
6b	21.07	118.53	167.36	33.97	26.66	134.71	134.85	134.98	130.48	127.44	132.34	
	(18.1)	(101.32)	(26.7)	(9.3)	(70.9)	(84.1)	(9.9)	(9.9)	(3.1)	(13.1)	(11.8)	
6c	21.05	117.32	167.62	33.97	26.82	131.66	133.85	133.26	132.26	130.81	126.48	
	(18.1)	(105.7)	(29.2)	(9.9)	(75.8)	(93.2)	(8.4)	(9.2)	(1.8)	(10.5)	(4.9)	
6d	21.03	117.53	167.82	33.92	26.55	133.18	131.56	133.88	131.11	135.12	129.98	
	(18.2)	(103.6)	(28.6)	(9.5)	(73.5)	(89.9)	(6.2)	(10.6)	(2.1)	(9.6)	(8.1)	
6e	21.20	118.01	168.57	33.95	26.49	131.26	130.75	145.11	149.56			64.82
	(17.4)	(102.6)	(27.3)	(9.3)	(71.5)	(92.6)	(11.8)	(13.6)	(2.4)			
6f	20.49	118.85	169.11	33.88	26.22	132.33	153.33	127.54	126.77	123.42	153.49	65.18
	(18.7)	(104.2)	(30.7)	(11.3)	(74.8)	(90.1)	(7.1)	(5.6)	(2.1)	(6.1)	(6.5)	
6g	21.14	117.63	167.31	34.23	25.58	132.55	158.98	142.28	125.21	141.46	132.63	63.31
	(18.7)	(105.1)	(29.9)	(9.9)	(73.4)	(87.6)	(5.4)	(13.1)	(1.8)	(12.2)	(8.1)	

*Data in parantheses are coupling constants (J_{PC}) expressed in Hz.

Mass spectral analyses (Table VIII) were conducted on a few representative compounds and confirmatory for the molecular ions for **2b, 4a, 5e**, and **6b**. Although the fragmentation patterns were many, major fragmentations were easily identified and reported. ^{31}P NMR spectral analyses were recorded for almost all of the synthesized compounds, elemental analyses were performed for several representative products.

Conclusions.

All of the synthesized products are novel. Synthesis has been through simple and convenient methodologies, and all products are supported by a variety of spectral, elemental, and X-ray crystallographic analyses. The advantages of this technology are that the reactions are performed smoothly, and the products are relatively easy to isolate and purify. Moreover, all of these derivatives are expected to possess novel bioactivity since analogs of these derivatives are reported to have potential utility in the area of agriculture and as antibacterial agents. Further synthesis and bioactive studies of all these products are currently in progress.

Table VIII

Mass Spectral *m/z* Values (% of important ions) for **2b**, **4a**, **5e**, and **6b** [18]

Compound	*m/z Values*
2b	253[9, M^+], 115[100, M^+-$C_6H_4NO_3$], 97[12, (M^+-$C_6H_4NO_3$)-H_2O], 47[60, P=O]
4a	371[12, M^+], 312[20, M^+-$OCOCH_3$], 269[60, M^+-$(CH_3CO)_2O$], 241[30, M^+-$(CH_3CO)_2O$-CO], 233[20, M^+-$C_6H_4NO_3$], 102[100, O=P-$(CH_2)_2$-C-CH_3]
5e	222[100, M^+], 207[12, M^+-CH_3], 194[80, M^+-CO], 115[25, M^+-C_7H_7O], 99[43, M^+-$C_7H_7O_2$], 47[75, P=O]
6b	271[8, 2.7, M^+, (M^++2)], 225[1, M^+-NO_2], 115[57, M^+-$C_6H_3NO_2Cl$], 99[100, M^+-$C_6H_3NO_3Cl$], 75[35, C_6H_3], 47[93, P=O]

EXPERIMENTAL

General.

All melting points were determined on a Mel-Temp apparatus (Gallenkamp) and were uncorrected. Thin-layer chromatography was performed by using 0.2 mm coated silica gel plates. Column chromatography was performed on silica gel Waco gel C-200 by using mixture of ethyl acetate, chloroform, and methanol as eluents. All IR spectra were recorded on Japan Spectroscopic Co. Ltd. (JASCO) FT/IR-8000 and A-3 spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on Japan Electron Optics Laboratory (JEOL) JNM-EX300 or JNM-EX90 (90 MHz) spectrometer operating at 300.40 MHz (^{1}H) and 75.45 MHz (^{13}C) using chloroform-d and TMS as the solvent and the internal standard, respectively. ^{31}P-NMR was recorded on JEOL JNM-EX90 (at 36.18 MHz) spectrometer by using chloroform-d and H_3PO_4 as the solvent and external standard, respectively. Mass spectra were measured on Hitachi RMU7M GC-MS and Shimadzu GCMS-AP5050 gas chromatograph mass spectrometers.

1-Chloro-3-methyl-2-phospholene 1-oxide (**1**) was prepared by reported procedure from the corresponding 1-methoxy-3-methyl-2-phospholene 1-oxide, which was prepared *via* cycloaddition of 2-methyl-1,3-butadiene (isoprene) and phosphorus trichloride according to the reported methods (McCormack reaction) [19].

Preparation of 1-(Nitrosubstituted Phenoxy)-3-methyl-2-phospholene 1-Oxides (**2a-c**).

The general procedure to obtain products **2a-c** is illustrated for the preparation of **2a**. To dry toluene (15 mL), *p*-nitrophenol (0.75 g, 5 mmol) and dry triethylamine (1 mL, 5 mmol) was added 1-chloro-3-methyl-2-phospholene 1-oxide (**1**, 0.75 g, 5 mmol) in dry toluene (15 mL) in a dropwise manner for 30 minutes. The mixture was stirred for 6 hours at 40 °C, filtered and dried over

anhydrous sodium sulfate. Evaporation of the solvent afforded product **2a**, 1.0 g (80% yield) and was purified by column chromatography on silical gel by using $CHCl_3$ and MeOH (20:1) as the mixture of eluent. Physical and spectral data are shown in Tables I, II and VIII. The boiling point of products: **2a**, bp 155-157 °C /0.1 mmHg; **2b**, bp 158-160 °C /0.1 mmHg; and **2c**, bp 160-163 °C /0.1 mmHg. IR (neat)**:** Products **2a-c**: ir: ν (cm^{-1}) 1650 (C=C), 1530 and 1350 (NO_2), and 1245 (P=O). ^{1}H-NMR**:** δ (in ppm) (**2c**) 2.05 (s, 3H, CH_3), 2.13-2.30 (m, 2H, H-4,4'), 2.60-2.67 (m, 2H, H-5,5'), 5.92 (dd, 1H, J_{PCH}=24.4 Hz, J_{HH}=1.3 Hz), 7.31 (dt, 2H, J_{HH}=7.2 Hz, 2.1 Hz and J_{PCH}=1.1 Hz), and 8.22 (dd, 2H, J_{HH}=7.1 Hz and 2.1 Hz).

Anal. Calcd for $C_{11}H_{12}NO_4P$ (**2c**): C, 52.18; H, 4.78; N, 5.53. Found: C, 52.01; H, 4.55; N, 5.41.

Preparation of 2,3-Diacetoxy-3-methyl-1-(nitro-substituted Phenoxy)phospholane 1-Oxides (**4a-c**)**.**

Products **4a-c** were also prepared under similar experimental procedure as for compounds **2a-c** from 1-chloro-2,3-diacetoxy-3-methylphospholane 1-oxide (**3**). Physical and spectral data are found in Tables I, II andVIII. The boiling point of products: **4a**, bp 135-138 °C/0.1 mmHg; **4b**, bp 139-140 °C/0.1 mmHg; and **4c**, bp 140-142 °C/0.1. IR (neat)**:** Products **4a-c**: ν (cm^{-1}) 1740 (C=O), 1532 and 1350 (NO_2), 1380 (O-CO-CH3), 1250 (P=O), and 750 (P-C); ^{1}H-NMR: δ (in ppm): (**4c**) 1.96 and 1.97 (2s, 6H, CH_3), 2.12 (s, 3H, CH_3), 2.21-2.52 (m, 2H, CH_2, H-4,4'), 2.73-3.11 (m, 2H, CH_2, H-5,5'), 4.41-4.92 (m, 1H, H-2), 7.21 (dt, 2H, J_{HH}=7.3 Hz, 2.2 Hz and $J_{PC\ H}$=1.3 Hz), and 8.12 (dd, 2H, J_{HH}=7.1 Hz and 2.2 Hz).

Anal. Calcd for $C_{15}H_{18}NO_8P$ (**4c**): C, 48.53; H, 4.89; N, 3.77. Found: C, 48.67; H, 4.79; N, 3.69.

Preparation of 1-(Substituted Phenyl)-3-methyl-2-phospholene 1-Oxide Derivatives (**5a-g**) *via* Grignard Reaction.

A general procedure for compounds **5a-g** is illustrated with that of **5b**. A suspension of 1-chloro-3-methyl-2-phospholene 1-oxide (**1**, 0.60 g, 4.0 mmol) in (6 mL) of dry THF was added dropwise over 30 minutes to a solution of *p*-chlorophenylmagnesium bromide (which was prepared from 1.0 g (5.2 mmol) of *p*-chlorobromobenzene, 0.13 g (5.2 mmol) of magnesium in 15 mL of dry THF stirred vigorously for 40 minutes at 0 °C) and the mixture was stirred for an additional 6 hours at room temperature. The reaction mixture was quenched with ice and dilute hydrochloric acid, and the aqueous mixture was extracted with chloroform. The organic layer was dried and the solvent was evaporated under vacuum to give an oily mixture. This mixture was purified by column chromatography on silica gel by using ethyl acetate and methanol (20:1) as eluent, gave 0.60 g, 50% of 1-(4'-chlorophenyl)-3-methyl-2-phospholene 1-oxide (**5b**). ^{1}H-NMR: δ (in ppm) 2.08 (s, 3H, CH_3), 2.00-2.40 (m, 2H, H-4,4'), 2.50-3.00 (m, 2H, H-5,5'), 5.92 (d, 1H, J_{PCH}=25.2 Hz, H-2), and 7.35-8.20 (m, 4H, Ph); ^{13}C-NMR: δ (in ppm) 21.00 (d, $^3J_{PC}$=17.3 Hz, CH_3), 27.47 (d, J_{PC}=69.5 Hz, C-5), 34.08 (d, $^2J_{PC}$=8.7 Hz, C-4), 120.32 (d, J_{PC}=100.2 Hz, C-2), 128.8 (d, $^3J_{PC}$=12.1 Hz, C-3'), 131.97 (d, $^2J_{PC}$ =11.3 Hz, C-2'), 132.69 (d, J_{PC}=98.2 Hz, C-1'), 138.15 (d, $^4J_{PC}$=3.4 Hz, C-4'), and 165.31 (d, $^2J_{PC}$ =25.4 Hz, C-3).

Anal. Calcd for $C_{11}H_{12}OPCl$: C, 58.30; H, 5.34. Found: C, 58.12; H, 5.01.

Preparation of 1-(Substituted Nitrophenyl)-3-methyl-2-phospholene 1-Oxide Derivatives (**6a-g**).

A general procedure of the products **6a-g** is illustrated with that of **6e**. To a solution of 1.0 g (4.5 mmol) of **5e**, *i.e.*, 1-(4'-methoxyphenyl)-3-methyl-2-phospholene 1-oxide in 3.5 mL of concentrated H_2SO_4 being cooled to 0 °C, was added dropwise 0.5 mL of fuming HNO_3. The reaction mixture was stirred for 2 hours at 0 °C and allowed to stand for 22 hours at room temperature. The reaction mixture was poured onto 100 g of crushed ice, the aqueous solution was extracted with chlorofrom (20 mL x 3), the organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under a vacuum to give yellow crude solid. The crude product was purified by fractional recrystallization from ethyl acetate and *n*-hexane to give pure **6e** (0.70 g, 50%), mp 168-170 °C. Physical and spectral properties of memebrs **6a-g** are shown in Tables IV, VI, VII and VIII. IR (KBr)**:** Products **6a-g**: ν (cm^{-1}) 1640 (C=C), 1530 and 1350 (NO_2), and 1245 (P=O).

Anal. Calcd for $C_{12}H_{13}O_6N_2P$ (**6e**): C, 46.16; H, 4.20; N, 8.97. Found: C, 46.05; H, 4.15; N, 8.88.

Preparation of 1-(Substituted Phenyl)-3-methyl-2-phospholene 1-Sulfide Derivatives (**7a-b**).

A general procedure of the members of **7a-b** is illustrated with that of **7a**. To a solution of 0.42 g (2.15 mmol) of **5a**, *i.e.*, 1-phenyl-3-methyl-2-phospholene 1-oxide in 20 mL of dry benzene, was added 0.71 g (3.21 mmol) of P_4S_{10}, and then the reaction mixture was refluxed for 20 hours. The resultant mixture was allowed to cool at room temperature, and followed by filtration of the insoluble material, and evaporation of the solvent under a vacuum. The crude product was dissolved in 50 mL of chloroform, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The product was purified by column chromatography on silica gel with chloroform and methanol (10:1) as the eluent to give 0.34 g (1.63 mmol, 75%) of **7a**, mp 86-88 °C. IR (KBr)**:** Product **7a**: ν (cm^{-1}) 1650 (C=C), and 770 (P=S); ^{1}H-NMR: δ (in ppm) 1.80-3.00 (m, 4H, H-4,4', 5,5'), 2.03 (s, 3H, CH_3), 5.78 (d, 1H, J_{PCH}= 29.1 Hz, H-2), and 7.40-7.85 (m, 5H, Ph). Product **7b**: Yield 76.9%, mp 91-93 °C; IR (KBr)**:** ν (cm^{-1}) 1655 (C=C), 1537 and 1355 (NO_2), and 770 (P=S); ^{1}H-NMR: δ (in ppm) 2.13 (s, 3H, CH_3), 2.40-3.00 (m, 4H, H-4,4', 5,5'), 5.86 (d, 1H, J_{PCH}=29.4 Hz, H-2), 7.60-7.80 (m, 1H, H-5' of Ph), and 8.15-8.70 (m, 3H, H-2',4',6' of Ph).

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[15] X-ray data for measurement and analysis of structure of **6e.** Rigaku AFC7R X-ray diffractometer with four-axis goniometer was used. Crystal data: Empirical formula, $C_{12}H_{13}N_2PO_6$; Formula weight, 312.22; Crystal color, Habit, colorless, prismatic; Crystal dimensions, 0.30 x 0.30 x 0.20 mm; Crystal system, triclinic; Lattice type, Primitive; No. of reflections used for unit cell determination (2 θ range), 25 (58.0 - 59.8°); Omega scan peak width at half-height, 0.38°; Lattice parameters a = 8.571(1)Å, b = 9.8094(8)Å, c = 8.1736(8)Å, α = 95.463(7)Å, β= 98.933(10)Å, γ= 91.644(9)Å, V = 675.1(1)Å; Space group, P-1 (#2); Z value, 2; D_{calc}, 1.536 g/cm^3; F_{000}, 324.00; μ (CuK α), 21.18 cm^{-1}. Intensity measurements: Diffractometer, Rigaku AFC7R; Radiation CuK α (λ=1.54178Å), graphite monochromated; Attenuator, Ni foil (factor = 9.18); Take-off angle, 6.0°; Detector aperture, 3.0 mm horizontal, 5.0 mm vertical; Crystal to detector distance, 235 mm; Voltage, Current 40 kV, 30 mA; Temperature, -70.0 °C; Scan type, ω-2θ; Scan rate, 16.0°/minute (in ω)- up to 5 scans; Scan width, (1.89 + 0.30 tanθ)°; $2\theta_{max}$, 120.2°; No. of reflections measured, total 2177; Unique 2013 (Rint = 0.021); Corrections, Lorentz-polarization. Structure solution and refinement: Structure solution, Direct methods (SIR92); Refinement, full-matrix least-squares; Function minimized, $\Sigma w(|Fo|-|Fc|)^2$; p-factor, 0.0020; Anomalous dispersion, all non-hydrogen atoms; No. observations, (I>3.00σ(I)), 1815; No. variables, 243; Reflection/Parameter ratio, 7.47; Residuals: R; Rw, 0.038 ; 0.037; Goodness of fit indicator, 2.33; Max. shift/Error in final cycle, 0.39; Maximum peak in final diff. map, 0.21 e^-/Å^3; Minimum peak in final diff. map, -0.17 e^-/Å^3. Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2IEZ, UK.

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