Heteroatom Chemistry
Volume 14, Number 4, 2003

Chemo- and Regioselective Allylic Oxidation: Oxo-Derivatives of 2-Phospholene Sugar Analogs

Valluru Krishna Reddy, Lakonda Nagaprasada Rao, Motoki Maeda, Buchammagari Haritha, and Mitsuji Yamashita

Department of Materials Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432-8561, Japan

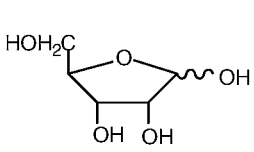
Received 13 March 2002; revised 2 January 2003

ABSTRACT: *A convenient and facile chemo- and regioselective oxidation of the allylic methylene group in a 2-phospholene ring system afforded the novel carbonyl derivatives of 2-phospholenes (***2a–i***). The method gives high conversion and selectivity in the formation of allylic ketones. The advantages of this oxidation method in such a five-membered pseudo sugar 2-phospholene ring are mentioned, and the oxidation is examined on several substituted 2-phospholenes (***1a–i***).* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:320–325, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10154

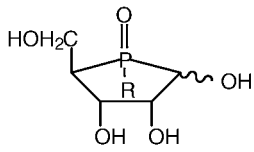
INTRODUCTION

A number of useful carbon–carbon bond forming reactions using aldehydes and ketones have been developed; efficient and reliable methods for preparing various types of aldehydes and ketones are important in organic synthesis. α,β-Unsaturated ketones are extremely versatile reaction intermediates for the preparation of various pentofuranose analogs of phospha sugars.

Replacement of the oxygen atom in the hemiacetal ring of normal sugars by a hetero or carbon atom leads to pseudo sugars (Scheme 1), some of



D-ribofuranose



An example of pentofuranose phospha analog, phospha D-ribofuranose

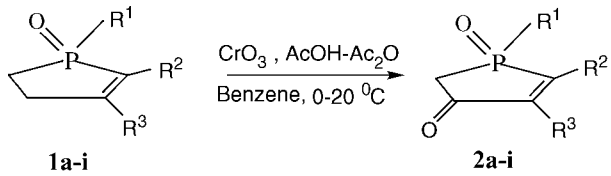
SCHEME 1

Correspondence to: Mitsuji Yamashita; e-mail: tcmyama@ipc.shizuoka.ac.jp.
Contract grant sponsor: Shizuoka Prefecture.
Contract grant sponsor: Shizuoka University.
Contract grant sponsor: Ministry of Education, Culture, Sports, Science, and Technology, Japan.

which have been widely investigated in synthetic, biological, and medicinal chemistry [1]. In particular, hetero sugars in which the ring oxygen has been replaced by nitrogen, sulfur, or selenium atom have been extensively studied and widely developed [2]. Phospha sugars belong to a category of pseudo sugar derivatives having a phosphorus atom instead of the oxygen atom in the hemiacetal ring [3] of normal sugars (Scheme 1) and are of interest in synthesis and structure analysis because of potent bioactivities in various fields [4]. Despite extensive studies on the synthesis, spectrum, and bioactivity of carba [5], aza [6], and thia sugars [7], little research has been done on phospha sugars since they have not been found in naturally occurring sources. Synthesis of phospha sugars is rather difficult because of long reaction sequences and low yields [8], and preparations generally use normal sugars as starting materials [9,10]. Hence, we wished to develop a more general synthetic route to such phospha sugars and have reported the successful synthesis of tetrafuranose analogs [11] of phospha sugars using phospholenes as starting materials [12]. Our interest to develop potential inhibitors of HIV led us to synthesize pentafuranose analogs of phospha sugars, such as Ribavarin [13], AZT [14], etc., in a facile synthetic route using phospholenes as starting materials. Considerable effort has been devoted to the synthesis of keto-derivatives of 2-phospholenes based on allylic oxidation [15], because these are expected to be the active and important precursors in the synthesis of pentafuranose skeleton of phospha sugars. The present paper deals with the improved synthesis and structure analysis of allylic carbonyl derivatives, and determination of selectivity using 2-phospholenes as starting materials.

RESULTS AND DISCUSSION

Recently we reported allylic oxidation of 2-phospholenes using CrO_3 in an AcOH–Ac_2O mixture.



SCHEME 2 Preparation of 4-oxo-2-phospholene 1-oxides **2a–i**.

Many reported reagents failed to oxidize allylic methylene group of 2-phospholenes. For reasons explained in our preliminary communication [16], however, in early stages the conversion was high but the isolated yields were low. This is mainly due to solubility of the products (**2a–i**) in water during isolation. We improved the isolated yields of all products (**2a–i**) and extended our oxidation method to several substituted 2-phospholene derivatives by using less CrO_3 than used previously. Several interesting results have been noticed and are reported. After completion of the oxidation, the reaction mixture was diluted with $CHCl_3$, stirred for 30–40 min at room temperature (during this time the product completely dissolved in $CHCl_3$ improving the isolated yield of **2a–i**), followed by the slow neutralization with saturated $NaHCO_3$ solution. Then the organic layer was extracted with $CHCl_3$. The selectivity is outlined in the oxidation of 3-methyl-substituted 2-phospholenes **1b, 1d, 1e, 1f**, and **1h** (Table 1), where hydrogen atoms are abstracted from the allylic CH_2 group but not from the CH_3 group, and the 4-oxo-2-phospholenes result. This is an example of highly *regio*- and *chemoselective* C—H bond activation. The reaction progress is monitored by TLC every 30 min; the rate of the reaction and the product conversion [characterized from gel permeation chromatography (GPC) analysis] are fairly enhanced by the presence of methyl group at C3 position of 2-phospholenes **1b, 1d, 1e, 1f**, and **1h**. The 2-phospholenes that are substituted at P atom with sterically hindering groups **1d, 1e**, and **1f** (Table 1)

TABLE 1 Allylic Oxidation of 2-Phospholenes **1a–i**

R^1	R^2	R^3	*Product [17]*	*Reac. Time (h)*	*Conv. (%) [18]*	*Isol. Yield (%)*	*Molar Ratio of CrO_3 to Substrate*
Ph	H	H	**2a**	4	85	62	2:1
OMe	H	Me	**2b**	4	90	60	2:1
OMe	H	H	**2c**	4	86	55	2:1
3-ClC_6H_4	H	Me	**2d**	5	80	60	3:1
4-OMe-3,5-$(NO_2)_2C_6H_2$	H	Me	**2e**	6	78	62	3:1
4-$OMeC_6H_4$	H	Me	**2f**	5	82	64	3:1
Ph	Br	H	**2g**	5	70	55	2:1
Ph	Br	Me	**2h**	4	75	60	2:1
Ph	OMe	H	**2i**	5	88	66	2:1

also produced allylic carbonyl derivatives, but the reaction conditions, yields, and molar ratio of CrO_3 slightly differ from those of other substrates given in Table 1. The experimental results show that there is no considerable effect of bulky groups at P atom. But the molecules being substituted with electron-donating groups at C2 and C3 of 2-phospholene afforded high conversions while electron-withdrawing groups lowered the conversion of allylic oxidation.

A single crystal of **2a** was grown from ethyl acetate by slow evaporation. Its X-ray crystallography [19] revealed the structure depicted in Fig. 1 and afforded bond lengths, bond and torsion angles as shown in Table 2. The substitution of O by P in the hemiacetal ring caused several changes in the geometry and conformation of the five-membered ring. The C1—P1—C4 bond angle of **2a** (93.1°) differs considerably from 110° of C1—O—C4 in ribofuranose and 93.5° of C1—S—C4 in thio sugars [20]. The bond angles of C4—P1—C5 and C1—P1—C5 (∼107°) show that the phenyl and phospholenone rings of **2a** lie in different planes (Fig. 1).

The P1—C1 bond is shorter than P1—C4 by 0.029 Å. Also C3—O2 is shorter than P1—O1 by 0.271 Å. The positive C1—P1—C4—C3 torsion angle and the negative P1—C4—C3—C2 torsion angle of **2a** (Table 2) show that the molecule is conformationally of C3-exo and C2-endo type. All other product structures are assigned by analogy and spectral comparison. While the C5 methylene protons of the substrates **1a–i** give a complicated multiplet in the ^{1}H NMR spectrum (300 MHz), those of the products **2a–i** give a clear pair of double doublets (AB part of an ABX spectrum, $\delta_A \sim 2.71$, $\delta_B \sim 2.85$, $J_{AB} = {}^2J_{HH} \sim 18.1$ Hz, $J_{AX} = {}^2J_{PH} \sim 15.2$ Hz, $J_{BX} = {}^2J_{PH} \sim 6.3$ Hz). The ^{31}P NMR signals of all the products are shifted upfield 20–30 ppm from those of the substrates because of the electron-withdrawing nature of carbonyl group in good agreement with earlier results [21].

In summary, a convenient and facile allylic oxidation of 2-phospholenes has been developed with high conversion and selectivity, and in all cases where comparison could be made, the yields were improved and there was no over oxidation, and no by-products. The reaction conditions are mild and the work-up of the reaction mixture is easy. The greatest synthetic use for allylic oxidation is realized for compounds that possess only one allylic methylene group.

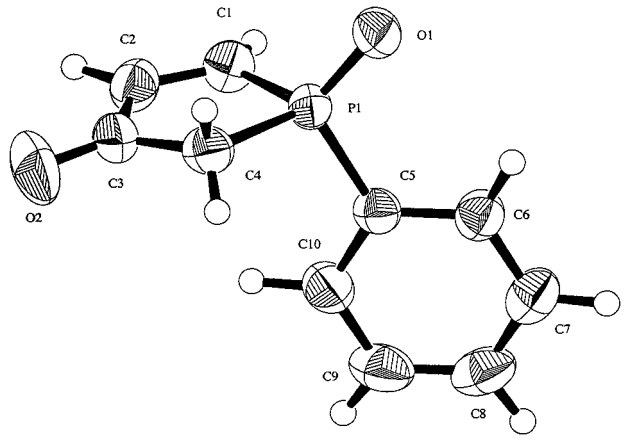


FIGURE 1 ORTEP drawing of compound **2a**.

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus (Gallenkamp) and were uncorrected. TLC 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 $CHCl_3$, EtOAc, and MeOH as the eluents. All IR spectra were recorded on FT/IR-8000 and A-3 spectrophotometer (Japan Spectroscopic Co. Ltd., JASCO). ^{1}H and ^{13}C NMR spectra were recorded on JNM-EX300 or JNM-EX90 (90 MHz) spectrometer (Japan Electron Optics Laboratory, JEOL) 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, and ^{31}P NMR was recorded on JEOL JNM-EX90 (at

TABLE 2 Selected Bond Lengths (Å) and Bond and Torsion Angles (deg) of **2a**

P(1)–O(1)	1.477	O(1)–P(1)–C(1)	117.3	P(1)–C(1)–C(2)–C(3)	−1.5
P(1)–C(1)	1.781	O(1)–P(1)–C(4)	116.9	P(1)–C(4)–C(3)–O(2)	173.0
P(1)–C(4)	1.810	O(1)–P(1)–C(5)	112.4	P(1)–C(4)–C(3)–C(2)	−6.6
P(1)–C(5)	1.799	C(1)–P(1)–C(4)	93.1	P(1)–C(5)–C(6)–C(7)	178.5
O(2)–C(3)	1.206	C(1)–P(1)–C(5)	107.3	P(1)–C(5)–C(10)–C(9)	−177.9
C(1)–C(2)	1.311	C(4)–P(1)–C(5)	107.9	O(1)–P(1)–C(1)–C(2)	−124.8
C(2)–C(3)	1.481	C(1)–C(2)–C(3)	114.4	C(1)–P(1)–C(4)–C(3)	4.9
C(3)–C(4)	1.494	C(2)–C(3)–C(4)	123.6	C(1)–C(2)–C(3)–C(4)	5.6
C(5)–C(10)	1.390	C(6)–C(5)–C(10)	119.4	C(7)–C(6)–C(5)–C(10)	−0.9
C(10)–C(9)	1.381	C(7)–C(8)–C(9)	120.3	C(7)–C(8)–C(9)–C(10)	0.7

36.18 MHz) spectrometer by using chloroform-*d* and 85% 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.

All starting compounds can be prepared by reported methods [22,23].

*General Procedure for the Preparation of 4-Oxo-2-phospholene 1-oxides (**2a–i**)*

The oxidation reagent was prepared by adding CrO_3 (3 g, 30 mmol) in small portions to a mixture of Ac_2O (7.5 ml) and glacial AcOH (15 ml), followed by dilution with benzene or dichloromethane under ice cooling. To this reagent was added slowly the 2-phospholene **1a–i** (6 mmol) in benzene or dichloromethane (5 ml), and the reaction mixture was stirred for 4–5 h at 0–20°C. After complete oxidation, the reaction mixture was diluted with 30 ml of $CHCl_3$, and stirred for 30–40 min at room temperature followed by slow neutralization with saturated $NaHCO_3$ solution. Then the organic layer was extracted with $CHCl_3$ (2×40 ml) and dried over anhydrous Na_2SO_4. Evaporating the solvent in a vacuum afforded products **2a–i** (Scheme 2). They were purified by flash chromatography using EtOAc–MeOH (20:1) as eluent and recycled by GPC.

*1-Phenyl-4-oxo-2-phospholene 1-oxide (**2a**)*

Yield 62%, solid, mp 92–95°C. ^{1}H NMR ($CDCl_3$): δ 2.71 (dd, 1H, H-5,5′, J_{PH} 6.3 Hz, J_{HH} 18.1 Hz), 2.85 (dd, 1H, H-5,5′, J_{PH} 15.2 Hz, J_{HH} 18.1 Hz), 6.91 (d, 1H, H-3, J_{PH} 8.3 Hz), 7.17 (d, 1H, H-2, J_{PH} 8.1 Hz), 7.52–7.65 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 36.8 (d, J_{CP} 75.4 Hz, C-5), 128.2 (d, $^3J_{CP}$ 12.1 Hz, *m*-Ph), 130.1 (d, $^2J_{CP}$ 10.1 Hz, *o*-Ph), 131.3 (d, $^4J_{CP}$ 2.6 Hz, *p*-Ph), 133.1 (d, J_{CP} 97.5 Hz, *x*-Ph), 147.2 (d, $^2J_{CP}$ 8.2 Hz, C-3), 150.3 (d, J_{CP} 76.5 Hz, C-2), 196.5 (d, $^2J_{CP}$ 21.8 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 36.9. MS: $m/z = 192$ (M^+). IR (KBr): υ (cm^{-1}) 1730 (C=O), 1640 (C=C), 1260 (P=O). Anal. Calcd for $C_{10}H_9PO_2$: C, 62.51; H, 4.72. Found: C, 62.66; H, 4.77.

*Crystal Data for **2a***

Rigaku AFC7R X-ray diffractometer with four-axis goniometer was used. Empirical formula, $C_{10}H_9PO_2$; formula weight, 192.15; crystal color and habit, colorless and prismatic; crystal dimensions, $0.50 \times 0.50 \times 0.70$ mm; crystal system, monoclinic; space group, $P2_1/n$(#14); lattice parameters, $a = 6.242(3)$ Å, $b = 6.850(3)$ Å, $c = 22.536(3)$ Å, $\beta = 96.13(2)$ Å, $V = 958.0(5)$ Å^3; Z value, 4; $D_{calc.}$, 1.332 g/cm^3; F_{000}, 400.00; μ(Cu Kα), 22.54 cm^{-1}. Radiation Cu Kα ($\lambda = 1.54178$ Å); temperature, 23.0°C; scan type, ω-2θ; scan rate, 16.0°/min (in ω)-up to 5 scans; scan width, $(1.89 + 0.30 \tan \theta)$°; $2\theta_{max}$, 120.1°; p-factor, 0.0010; anomalous dispersion, all non-hydrogen atoms; no. of observations ($I > 3.00\sigma(I)$), 1342; no. of variables, 155; reflection/parameter ratio, 8.66; residuals: R; Rw, 0.042; 0.050.

*1-Methoxy-3-methyl-4-oxo-2-phospholene 1-oxide (**2b**)*

Yield 60% [24], semisolid. ^{1}H NMR ($CDCl_3$): δ 1.91 (s, 3H, CH_3), 2.52 (dd, 2H, H-5,5′, J_{HH} 17.2 Hz, J_{PH} 6.6 Hz), 3.71 (d, 3H, OCH_3, J_{PH} 16.2 Hz), 6.92–7.12 (dd, 1H, H-2, J_{PH} 15.1 Hz, J_{HH} 1.8 Hz). ^{13}C NMR ($CDCl_3$): δ 13.4 (d, $^3J_{CP}$ 19.2 Hz, CH_3), 32.1 (d, J_{CP} 102.1 Hz, C-5), 52.3 (d, $^3J_{CP}$ 6.1 Hz, OCH_3), 139.1 (d, J_{CP} 113.1 Hz, C-2), 157.3 (d, $^2J_{CP}$ 2.6 Hz, C-3), 194.8 (d, $^2J_{CP}$ 27.3 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 46.1. MS: $m/z = 160$ (M^+). IR (neat): υ (cm^{-1}) 1729 (C=O), 1655 (C=C), 1261 (P=O).

*1-Methoxy-4-oxo-2-phospholene 1-oxide (**2c**)*

Yield 55%, solid, mp 72–75°C. ^{1}H NMR ($CDCl_3$): δ 2.72 (dd, 1H, H-5,5′, J_{HH} 16.6 Hz, J_{PH} 6.1 Hz), 2.88 (dd, 1H, H-5,5′, J_{HH} 16.6 Hz, J_{PH} 12.6 Hz), 3.75 (d, 3H, OCH_3, J_{PH} 17.4 Hz), 6.99–7.11 (dd, 1H, H-2, J_{PH} 12.9 Hz, J_{HH} 1.5 Hz). ^{13}C NMR ($CDCl_3$): δ 32.4 (d, J_{CP} 102.2 Hz, C-5), 52.8 (d, $^3J_{CP}$ 6.9 Hz, OCH_3), 140.6 (d, J_{CP} 112.9 Hz, C-2), 157.4 (d, $^2J_{CP}$ 8.7 Hz, C-3), 195.3 (d, $^2J_{CP}$ 27.4 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 47.7. MS: $m/z = 146$ (M^+). IR (neat): υ (cm^{-1}) 1712 (C=O), 1645 (C=C), 1250 (P=O).

*1-(3-Chlorophenyl)-3-methyl-4-oxo-2-phospholene 1-oxide (**2d**)*

Yield 60%, semisolid. ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H, CH_3), 2.92 (dd, 2H, H-5,5′, J_{HH} 16.1 Hz, J_{PH} 5.5 Hz), 6.92–7.12 (dd, 1H, H-2, J_{PH} 15.1 Hz, J_{HH} 1.8 Hz), 7.2–7.7 (m, 4H of Ph). ^{13}C NMR ($CDCl_3$): δ 13.2 (d, CH_3, $^3J_{CP}$ 16.1 Hz), 37.1 (d, C-5, J_{CP} 75.1 Hz), 142.1 (d, C-2, J_{CP} 85.1 Hz), 158.3 (d, C-3, $^2J_{CP}$ 5.1 Hz), 128.47 (d, *o*-Ph, *p*-Cl, $^2J_{CP}$ 9.3 Hz), 129.85 (d, *o*-Ph, *o*-Cl, $^2J_{CP}$ 12.7 Hz), 130.24 (d, *m*-Ph, *m*-Cl, $^3J_{CP}$ 11.3 Hz), 131.57 (d, *p*-Ph, *o*-Cl, $^4J_{CP}$ 2.7 Hz), 134.78 (d, *x*-Cl, $^3J_{CP}$ 15.3 Hz), 136.51 (d, *x*-Ph, J_{CP} 92.8 Hz), 195.8 (d, $^2J_{CP}$ 19.9 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 29.23. MS: $m/z = 240$ (M^+), 242 ($M^+ + 2$).

*1-(4-Methoxy-3,5-dinitrophenyl)-3-methyl-4-oxo-2-phospholene 1-oxide (**2e**)*

Yield 62%, semisolid. ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 3H, CH_3), 2.42 (dd, 2H, H-5,5′, J_{HH} 16.7 Hz, $J_{PH} = 6.2$ Hz), 4.12 (s, 3H, OCH_3), 7.12 (dd, 1H, H-2, J_{PH} 15.8 Hz, J_{HH} 1.4 Hz), 8.92 (s, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 13.27 (d, $^3J_{CP}$ 16.2 Hz, CH_3), 35.6 (d, J_{CP} 75.0 Hz, C-5), 62.82 (s, OCH_3), 141.1 (d, J_{CP} 84.2 Hz, C-2), 158.5 (d, $^2J_{CP}$ 6.0 Hz, C-3), 152.1 (d, $^3J_{PC}$ 13.6 Hz, *m*-Ph, *o*-OMe), 130.28 (d, $^2J_{PC}$ 11.8 Hz, *o*-Ph, *m*-OMe), 132.26 (d, J_{PC} 92.6 Hz, *x*-Ph, *p*-OMe), 149.56 (d, $^4J_{PC}$ 2.4 Hz, *p*-Ph, *x*-OMe), 195.9 (d, $^2J_{CP}$ 20.9 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 29.22. MS: $m/z = 326$ (M^+). IR (neat): υ (cm^{-1}) 1731 (C=O), 1530 and 1350 (NO_2). Anal. Calcd for $C_{12}H_{11}O_7N_2P$: C, 44.19; H, 3.40; N, 8.59. Found: C, 44.01; H, 3.38; N, 8.61.

*1-(4-Methoxyphenyl)-3-methyl-4-oxo-2-phospholene 1-oxide (**2f**)*

Yield 64%, semisolid. ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H, CH_3), 2.88 (dd, 1H, H-5,5′, J_{PH} 5.2 Hz, J_{HH} 18.7 Hz), 2.95 (dd, 1H, H-5,5′, J_{PH} 15.9 Hz, J_{HH} 18.7 Hz), 4.12 (s, 3H, OCH_3), 7.12 (dd, 1H, H-2, J_{PH} 15.1 Hz, J_{HH} 1.8 Hz), 6.92 (dd, 2H of Ph, J_{HH} 6.7 Hz), 7.54 (dd, 1H of Ph, J_{HH} 6.7 Hz, J_{PH} 12.9 Hz). ^{13}C NMR ($CDCl_3$): δ 13.27 (d, $^3J_{CP}$ 16.8 Hz, CH_3), 37.6 (d, J_{CP} 75.0 Hz, C-5), 62.82 (s, OCH_3), 141.8 (d, J_{CP} 88.2 Hz, C-2), 158.7 (d, $^2J_{CP}$ 6.0 Hz, C-3), 152.11 (d, $^3J_{PC}$ 13.6 Hz, *m*-Ph, *o*-OMe), 130.28 (d, $^2J_{PC}$ 11.8 Hz, *o*-Ph, *m*-OMe), 132.26 (d, J_{PC} 92.6 Hz, *x*-Ph, *p*-OMe), 149.56 (d, $^4J_{PC}$ 2.4 Hz, *p*-Ph, *x*-OMe), 199.9 (d, $^2J_{CP}$ 20.6 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 20.01. MS: $m/z = 236$ (M^+). IR (neat): υ (cm^{-1}) 1729 (C=O).

*1-Phenyl-2-bromo-4-oxo-2-phospholene 1-oxide (**2g**)*

Yield 55%, semisolid. ^{1}H NMR ($CDCl_3$): δ 2.93 (dd, 1H, H-5,5′, J_{PH} 4.5 Hz, J_{HH} 18.6 Hz), 3.08 (dd, 1H, H-5,5′, J_{PH} 16.5 Hz, J_{HH} 18.6 Hz), 7.21 (d, 1H, H-3, J_{PH} 14.1 Hz), 7.47 (m, 5H of Ph). ^{13}C NMR ($CDCl_3$): δ 27.3 (d, J_{CP} 65.0 Hz, C-5), 141.1 (d, J_{CP} 84.2 Hz, C-2), 158.5 (d, $^2J_{CP}$ 6.0 Hz, C-3), 127.2 (d, $^3J_{CP}$ 12.1 Hz, *m*-Ph), 129.1 (d, $^2J_{CP}$ 10.1 Hz, *o*-Ph), 131.3 (d, $^4J_{CP}$ 2.6 Hz, *p*-Ph), 132.1 (d, J_{CP} 97.5 Hz, *x*-Ph), 195.9 (d, $^2J_{CP}$ 20.9 Hz, C—O). ^{31}P NMR ($CDCl_3$): δ 35.5. MS: $m/z = 270$ (M^+), 272 ($M^+ + 2$).

*1-Phenyl-2-bromo-3-methyl-4-oxo-2-phospholene 1-oxide (**2h**)*

Yield 60%, semisolid. ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 3H, CH_3), 2.33 (dd, 1H, H-5,5′, J_{HH} 18.6 Hz, J_{PH} 4.8 Hz), 2.98 (dd, 1H, H-5,5′, J_{HH} 18.6 Hz, J_{PH} 16.5 Hz), 7.47 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 35.6 (d, J_{CP} 74.8 Hz, C-5), 114.4 (d, J_{CP} 94.2 Hz, C-2), 158.4 (d, $^2J_{CP}$ 6.0 Hz, C-3), 128.2 (d, $^3J_{CP}$ 12.1 Hz, *m*-Ph), 130.1 (d, $^2J_{CP}$ 10.1 Hz, *o*-Ph), 131.3 (d, $^4J_{CP}$ 2.6 Hz, *p*-Ph), 133.1 (d, J_{CP} 97.5 Hz, *x*-Ph), 195.9 (d, $^2J_{CP}$ 20.0 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 29.23. MS: $m/z = 284$ (M^+), 286 ($M^+ + 2$).

*1-Phenyl-2-methoxy-4-oxo-2-phospholene 1-oxide (**2i**)*

Yield 66%, semisolid. ^{1}H NMR ($CDCl_3$): δ 2.99 (dd, 1H, H-5,5′, J_{PH} 4.5 Hz, J_{HH} 18.9 Hz), 3.18 (dd, 1H, H-5,5′, J_{PH} 16.1 Hz, J_{HH} 18.9 Hz), 3.79 (d, 3H, OCH_3, J_{PH} 14.6 Hz), 7.11 (d, 1H, H-3, J_{PH} 15.2 Hz), 7.47 (m, 5H of Ph). ^{13}C NMR ($CDCl_3$): δ 35.1 (d, J_{CP} 67.0 Hz, C-5), 114.1 (d, J_{CP} 88.2 Hz, C-2), 158.5 (d, $^2J_{CP}$ 6.0 Hz, C-3), 126.2 (d, $^3J_{CP}$ 11.1 Hz, *m*-Ph), 128.1 (d, $^2J_{CP}$ 10.5 Hz, *o*-Ph), 131.3 (d, $^4J_{CP}$ 2.6 Hz, *p*-Ph), 133.1 (d, J_{CP} 98.5 Hz, *x*-Ph), 201.1 (d, $^2J_{CP}$ 21.1 Hz, C=O). ^{31}P NMR ($CDCl_3$): δ 25.9. MS: $m/z = 222$ (M^+). IR (neat): υ (cm^{-1}) 1732 (C=O).

REFERENCES

[1] McGuigan, C.; Pathirana, R. N.; Balzarini, J.; DeClercq, E. J Med Chem 1993, 36, 1048.

[2] Goto, R.; Inokawa, S.; Sera, A.; Otani, S. Tantorui no Kagaku (Chemistry of Monosaccharides; Maruzen: Tokyo, 1988.

[3] For example: Yamamoto, H.; Hanaya, T.; Kawamoto, H.; Inokawa, S.; Yamashita, M.; Armour, M. A.; Nakashima, T. T. J Org Chem 1985, 50, 3516.

[4] (a) Yamashita, M.; Nakatsukasa, Y.; Yoshikane, M.; Yoshida, H.; Ogata, T.; Inokawa, S. Carbohydr Res 1977, 59, C12; (b) Yamashita, M.; Nakatsukasa, Y.; Yoshida, H.; Ogata, T.; Inokawa, S.; Hirotsu, K.; Clardy, J. Carbohydr Res 1979, 70, 247; (c) Yamada, M.; Yamashita, M. Carbohydr Res 1981, 95, C9; (d) Yamashita, M.; Yamada, M.; Tsunekawa, K.; Oshikawa, T.; Seo, K.; Inokawa, S. Carbohydr Res 1983, 121, C4; (e) Yamashita, M.; Yamada, M.; Sugiura, M.; Nomoto, H.; Oshikawa, T. J Chem Soc Jpn 1987, 1207; (f) Yamamoto, H.; Inokawa, S. Adv Carbohydr Chem Biochem 1984, 42, 135.

[5] (a) Madhavan, G. V. B.; Martin, J. C. J Org Chem 1986, 51, 1287; (b) Maag, H.; Rydzwski, R. M. J Org Chem 1992, 57, 5823; (c) Patil, S. D.; Koga, M.; Schneller, S. W.; Snoeck, R.; De Clercq, E. J Med Chem 1992, 35, 2191; (d) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. J Org Chem 1999, 64, 4173; (e) Cowart, M.; Bennett, M. J.; Kerwin, J. F., Jr. J Org Chem 1999, 64, 2240.

[6] (a) Legler, G.; Julich, E. Carbohydr Res 1984, 128, 61; (b) Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C. H. J Am Chem Soc 1997, 119, 8146; (c) Momotake, A.; Togo, H.; Yokoyama, M. J Chem Soc, Perkin Trans I 1999, 1193.

[7] (a) Branalt, J.; Kvarnstrom, I.; Niklasson, G.; Svensson, S. C. T. J Org Chem 1994, 59, 1783; (b) Secrist, J. A., III; Riggs, R.; Tiwari, K. N.; Montgomery, J. A. J Med Chem 1992, 35, 533;

(c) Dyson, M. R.; Coe, P. L.; Walker, R. T. J Med Chem 1991, 34, 2782.
[8] Yamamoto, H.; Inokawa, S. Adv Carbohydr Chem Biochem 1984, 42, 135.
[9] Yamashita, M.; Yamada, M.; Sugiura, M.; Nomoto, H.; Oshikawa, T. Nippon Kagaku Kaishi 1987, 1207.
[10] Yamamoto, H.; Hanaya, T. In Studies in Natural Products Chemistry; Atta-ur-Rahaman (Ed.); Elsevier: Amsterdam, 1990; Vol. 6, pp. 351–384.
[11] Yamashita, M.; Yabui, A.; Suzuki, K.; Kato, Y.; Uchimura, M.; Iida, A.; Mizuno, H.; Ikai, K.; Oshikawa, T.; Parkanayi, L.; Clardy, J. J Carbohydr Chem 1997, 16, 499.
[12] Yamashita, M.; Uchimura, M.; Iida, A.; Parkanayi, L.; Clardy, J. J Chem Soc, Chem Commun 1988, 569.
[13] McCormick, J. B.; Getchell, J. P.; Mitchel, S. W.; Hicks, D. R. Lancet 1984, 2(8416), 1367.
[14] Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrmann, S. N.; Gallo, R. S.; Bolognes, D.; Barry, D. W.; Broder, S. Proc Natl Acad Sci USA 1985, 82, 7096.
[15] Nakayama, M.; Shinke, S.; Matsushita, Y.; Ohira, S.; Hayashi, S. Bull Chem Soc Jpn 1979, 52, 184.
[16] Reddy, V. K.; Rao, L. N.; Maeda, M.; Oshikawa, T.; Takahashi, M.; Yamashita, M. Synth Commun 2002, 32, 69.
[17] For optical resolution of product **2a**, see: Bodalski, R.; Janacke, T.; Galdecki, Z.; Glowka, M. Phosphorus Sulfur Silicon 1982, 14, 15.
[18] Percentage of conversion was determined from GPC analysis. The unreacted starting material was recovered from column chromatography.
[19] Tables of atomic coordinates, bond lengths, and bond angles have been deposited (deposition number: CCDC 195398) 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; e-mail: deposit@ccdc.cam.ac.uk.
[20] Bobek, M.; Bloch, A.; Parthasarathy, R.; Whistler, R. L. J Med Chem 1975, 18, 784.
[21] Da Silva, J. F. C.; Pedrosa, M. S.; Nakayama, H. T.; Neto, C. C. Phosphorus Sulfur Silicon 1997, 131, 97.
[22] (a) Quin, L. D.; Gratz, J. P.; Barket, T. P. J Org Chem 1968, 33, 1034; (b) Reddy, V. K.; Onogawa, J. I.; Rao, L. N.; Oshikawa, T.; Takahashi, M.; Yamashita, M. J Heterocycl Chem 2002, 39, 69.
[23] Frank Du, C. J.; Hart, H. J Org Chem 1987, 52, 4311.
[24] 1-Methoxy-2-phospholene derivatives are more soluble in water than 1-phenyl-2-phospholenes.