Novel Synthesis of 2-Phosphinoylphospholane 1-Oxide Derivatives

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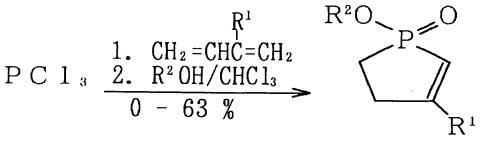
Synopsis. Reactions of 2-phospholene 1-oxides with *N*-bromoacetamide in aqueous organic solvent produced 2-bromo-3-hydroxyphospholane 1-oxides, which reacted with sodium salts of dialkyl phosphonates to afford novel 2-phosphinoylphospholane 1-oxide derivatives. A 4-phosphinoyl-2-phospholene derivative was also prepared.

Phosphorus-in-ring sugar analogs[1] (phosphono sugars),[2-4] in which an oxygen atom in the hemiacetal ring is substituted by a phosphorus atom,[5,6] such as 5-deoxy-5-phosphinylaldopyranoses[7] and 4-deoxy-4-phosphinylaldofuranoses,[8] are expected to excert some biological activities, as observed in hetero sugars.[3,6] In the previous synthesis of sugar analogs having a phosphorus atom in the hemiacetal ring,[9] the oxygen atom in the hemiacetal ring of the starting sugar materials was replaced by a phosphorus atom via successive reactions of carbon–phosphorus bond formation and a ring-closure reaction with the phosphorus atom.[1,5] On the contrary, we have reported a new method which starts from 2-phospholenes: 3-Phosphacyclopentene derivatives were prepared by a Diels–Alder reaction of 1,3-dienes with phosphorus halides, followed by conversion of the carbon-carbon double bond into a *cis* glycol.[10] The introduction of a substituent which included a hetero atom, such as oxygen, nitrogen, sulfur, or phosphorus, into the 2-position of the phospholene, i.e., *O*-, *N*-, *S*-, and *P*-glycoside analogs, respectively, was interesting on the basis of the biological activities of sugar glycosides.[11-14] The present note concerns novel chemical conversion of phospholene 1-oxides into new 2- and 4-phosphinoyl derivatives of phospholane and phospholene 1-oxides.

Results and Discussion

2-Phospholenes **1a**—**c** were prepared by a Diels–Alder reaction of phosphorus trichloride with 1,3-dienes, and the successive alcoholysis of the adducts [Eq. (I)].[15] The alcoholysis of the adduct, i.e., 1-chloro-3-phospholenium chloride, with 2-methyl-2-propanol, however, was unsuccessful; this was probably because of the unstability of 1-(2-methyl-2-propanoxy)-2-phospholene 1-oxide, as well as the fact that di-*t*-butyl phosphonate was spontaneously hydrolized at room temperature, and that triethyl phosphite and di-*t*-butyl peroxide gave triethyl phosphate while triethyl phosphite and diethyl peroxide gave a pentavalent adduct, pentaethoxyphosphorane.[16,17] These results are summarized in Table 1.

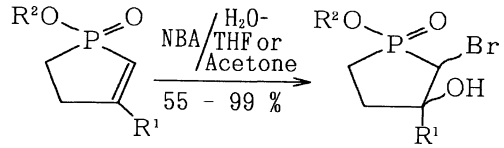


(I)

1a—d

a: $R^1=R^2=Me$
b: $R^1=H$, $R^2=Me$
c: $R^1=H$, $R^2=Et$
d: $R^1=H$, $R^2={}^t$Bu

Treatment of 2-phospholenes **1a**—**c** with *N*-bromoacetamide (NBA) introduced bromo and hydroxyl groups at the 2- and the 3-positions, respectively, of the phospholene to afford bromohydrins **2a**—**c** (Eq. (II) and Table 2).[18]



(II)

1a—c **2a—c**

a: $R^1=R^2=Me$
b: $R^1=H$, $R^2=Me$
c: $R^1=H$, $R^2=Et$

The reaction of bromohydrins **2a**—**c** with trimethyl phosphite did not proceed to afford 2-phosphinoylphos-

Table 1. Preparation of 2-Phospholene 1-Oxides **1**

Product[a]	R^1	R^2	Reaction conditions		Yield/%[b]	Bp/°C (mmHg)
			Temp/°C	Time/d		
1a	Me	Me	r.t.	8	38	90 (0.25)
1b	H	Me	35	20	54	79 (0.40)
1c	H	Et	35	30	63	78 (0.20)
1d	H	^{t}Bu	35	25	ca. 0	—

a) All products gave satisfactory IR, ^{1}H and ^{13}C NMR spectral data. b) Yield of isolated product based on phosphorus trichloride.

Table 2. Preparation of Bromohydrins **2**

Bromohydrins[a]	R^1	R^2	Reaction conditions		Yield/%[b]	Mp/°C
			Solvent	Time/h or d		
2a	Me	Me	Acetone–H_2O	18 h	84	137—139
2b	H	Me	THF–H_2O	3 d	55	oil
2c	H	Et	THF–H_2O	4 d	99	oil

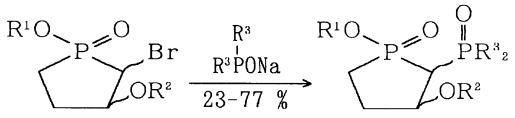
a) All products gave satisfactory IR, ^1H and ^{13}C NMR spectral data. b) Yield of isolated product based on 2-phospholene 1-oxide.

Table 3. Becker Reaction of 2-Bromophospholane 1-Oxides **3**—**5** to Afford 2-Phosphinoyl Derivatives **6**—**8**

Substrate	Base/Solvent	R^1	R^2	R^3	Product[a]	Yield/%[b]
3	NaH/THF	Et	Ac	OMe	**6a**	23
3	NaH/Toluene	Et	Ac	Ph	**6b**	77
4	NaH/THF	Et	THP	OMe	**7a**	49
4	NaH/Toluene	Et	THP	Ph	**7b**	61
5	NaH/Toluene	Me	Bz	OEt	**8**	29

a) All products gave satisfactory IR, ^1H and ^{13}C NMR spectral data. b) Yield of isolated product based on **3**—**5**.

pholane 1-oxide derivatives; however, the ^1H NMR spectra of the reaction mixture showed a disappearance of the OH signal due to an unanalyzable reaction. The hydroxyl group of phospholanes **2a**—**c** was thus protected as the acetyl, tetrahydropyranyl, and benzoyl derivatives **3**—**5** by the usual method.[19] The protected 2-bromophospholanes **3**—**5** were treated with sodium salts of dialkyl phosphonates or diphenylphosphine oxide to afford 2-phosphinoylphospholane 1-oxide derivatives **6**—**8** [Eq. (III)]. The result is shown in Table 3.



(III)

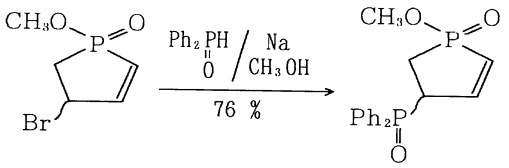
3—**5** **6**—**8**

3: R^1=Et, R^2=Ac
4: R^1=Et, R^2=THP
5: R^1=Me, R^2=Bz

6: R^1=Et, R^2=Ac
7: R^1=Et, R^2=THP
a: R^3=OMe; **b**: R^3=Ph
8: R^1=Et, R^2=Bz, R^3=OEt

Although diphenylphosphinoyl derivatives **6b** and **7b** were obtained in good yield, dimethoxyphosphinoyl and diethoxyphosphinoyl derivatives **6a**, **7a**, and **8** were obtained in low yield. The ^1H NMR spectra of 2-(dialkoxyphosphinoyl)phospholane derivatives **6a** and **7a** showed the methoxyl protons as one pair of a doublet, suggesting the presence of diastereomers.

4-Bromo-1-methoxy-2-phospholene (**9**) afforded the expected 4-diphenylphosphinoyl-1-methoxy-2-phospholene 1-oxide (**10**) in 76% yield by a treatment of diphenylphosphine oxide under similar reaction conditions to those for the preparation of 2-phosphinoyl derivatives **6b** and **7b** [Eq. (IV)].



(IV)

9 **10**

Experimental

All bp's and mp's were uncorrected. The ^1H NMR spectra were measured on Hitachi R-24B (60 MHz) and R-40 (90 MHz) spectrometers with TMS used as an internal standard, ^{13}C NMR spectra were measured on a JEOL EX-90 (22.4 MHz) spectrometer with proton decoupling, and IR spectra on a Japan Spectroscopic Co., Ltd. A-3 IR spectrophotometer.

1-Ethoxy-2-phospholene 1-Oxide (1c). Phosphorus trichloride (45 cm³, 500 mmol) reacted with excess 1,3-butadiene (60 cm³, 720 mmol) for 30 d at 35°C. The resulting material was dissolved in $CHCl_3$ (250 cm³), and then slowly added into excess ethanol (200 cm³) at −20°C. After neutralization of the mixture with solid $NaHCO_3$, the insoluble material was filtered off, the filtrate was evaporated, and the residue was distilled in vacuo to afford **1c** (47.3 g, 63% yield); bp 78°C/0.20 mmHg;[20] ^1H NMR ($CDCl_3$) δ=1.34 (t, 3H, J_{HCCH}=7.0 Hz, P–O–CH_2–CH_3), 1.7—2.1 (m, 2H, P–CH_2–CH_2–), 2.5—2.9 (m, 2H, P–CH_2–CH_2–), 4.10 (dq, 2H, J_{HCCH}=7.4 Hz, J_{HCOP}=7.4 Hz, P–O–CH_2–), 6.20 (ddt, 1H, $J_{HC=CH}$=8.4 Hz, $J_{HC=CP}$=23.7 Hz, J_{HCCH}=8.6 Hz, P–CH=CH–), and 7.02 (ddt, 1H, $J_{HC=CH}$=8.4 Hz, J_{HCP}=48.7 Hz, $J_{HC=CCH}$=2.6 Hz, P–CH=CH–); ^{13}C NMR ($CDCl_3$) δ=14.7 (d, J_{CCOP}=6.0 Hz, P–O–CH_2–CH_3), 18.5 (d, J_{CP}=96 Hz, P–CH_2–), 25.3 (d, J_{CCP}=15.4 Hz, P–CH_2–CH_2–), 58.9 (d, J_{COP}=6.7 Hz, P–O–CH_2–), 121.9 (d, J_{CP}=120.2 Hz, P–CH=CH–), and 150.0 (d, $J_{C=CP}$=32.2 Hz, P–CH=CH–).

Similarly, **1a** and **1b** were prepared. **1a**: ^1H NMR ($CDCl_3$) δ=1.7—2.2 (m, 2H, –CH_2–C=), 2.00 (s, 3H, C–CH_3), 2.3—2.8 (m, 2H, P–CH_2–), 3.69 (d, 3H, J_{HCOP}=11.1 Hz, P–O–CH_3), and 5.84 (dm, 1H, J_{HCP}=23.5 Hz, P–CH=C–); ^{13}C NMR ($CDCl_3$) δ=19.6 (d, $J_{CC=CP}$=36.9 Hz, P–CH=C–CH_3), 21.3 (d, J_{CP}=75.2 Hz, P–CH_2–), 30.1 (d, J_{CCP}=12.8 Hz, P–CH_2–CH_2–), 50.1 (d, J_{COP}=6.0 Hz, P–O–CH_3), 116.1 (d, J=127.6 Hz, P–CH=), and 162.8 (d, J_{CCP}=33.6 Hz, P–CH=C–). **1b**: ^1H NMR

($CDCl_3$) δ=1.7—2.1 (m, 2H, -C<u>H</u>$_2$-CH=), 2.5—3.0 (m, 2H, P-C<u>H</u>$_2$-), 3.73 (d, 3H, J_{HCOP}=11.1 Hz, P-O-C<u>H</u>$_3$), 6.21 (ddm, 1H, $J_{HC=CH}$=8.6 Hz, $J_{HC=CP}$=23.7 Hz, P-CH=C<u>H</u>-), and 7.05 (ddm, 1H, $J_{HC=CH}$=8.6 Hz, J_{HCP}=49.0 Hz, P-C<u>H</u>=CH-); ^{13}C NMR ($CDCl_3$) δ=18.3 (d, J_{CP}=95.4 Hz, P-<u>C</u>H$_2$-), 25.8 (d, J_{CCP}=15.4 Hz, P-CH$_2$-<u>C</u>H$_2$-), 50.4 (d, J_{COP}=6.0 Hz, P-O-<u>C</u>H$_3$), 121.9 (d, J_{CP}=120.9 Hz, P-<u>C</u>H=), and 151.4 (d, J_{CCP}=31.6 Hz, P-CH=<u>C</u>H-).

2-Bromo-3-hydroxy-1-methoxyphospholane 1-Oxide (2b). NBA (12.6 g, 90 mmol) was added to a solution of **1b** (9.27 g, 70 mmol) in THF (20 cm^3) and water (80 cm^3). The mixture was stirred for 3 d at room temperature. The solvent was evaporated, and the residue was extracted with $CHCl_3$ (40 cm^3×5); the $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to afford product **2b** (9.05 g, 55% yield); oil; ^{1}H NMR ($CDCl_3$) δ=1.4—2.6 (m, 4H, P-CH$_2$-CH$_2$-), 3.3—3.7 (m, 1H, P-CHBr), 3.71, 3.80 (d×2, 3H, J_{HCOP}=11.2 Hz, P-O-CH$_3$), 3.9—4.4 (m, 1H, C<u>H</u>OH), and 5.30 (bs, 1H, OH); IR (KBr) 3500 (OH) and 1240 cm^{-1} (P=O).

Similarly, **2a** and **2c** were prepared. **2a**: ^{1}H NMR ($CDCl_3$) δ=1.46 (s, 3H, =C-CH$_3$), 1.7—2.3 (m, 4H, P-CH$_2$-CH$_2$-), 3.74, 3.79 (d×2, 3H, J_{HCP}=11.2 Hz, P-O-CH$_3$), 3.9—4.0 (m, 1H, P-CHBr), and 4.74 (bs, 1H, OH). **2c**: ^{1}H NMR ($CDCl_3$) δ=1.34 (t, 3H, J_{HCCH}=7.4 Hz, P-O-CH$_2$-C<u>H</u>$_3$), 1.4—2.6 (m, 4H, P-CH$_2$-CH$_2$-), 3.5—4.4 (m, 2H, P-C<u>H</u>Br-C<u>H</u>OH), 4.17 (dq, 2H, J_{HCCH}=7.4 Hz, J_{HCOP}=7.5 Hz, P-O-C<u>H</u>$_2$-), and 5.29 (s, 1H, OH).

2-Bromo-1-ethoxy-3-(tetrahydropyranyloxy)phospholane 1-Oxide (4). To an ice-cooled solution of **2c** (1.01 g, 4.1 mmol) and 3,4-dihydro-2*H*-pyran (1.45 cm^3, 16 mmol) in dry dichloromethane (20 cm^3) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate. The mixture was stirred for 10 min at 0°C, and then stirred for additional 2 h at room temperature. The mixture was diluted with $CHCl_3$ (12 cm^3), washed successively with saturated brine, saturated $NaHCO_3$, water, and saturated brine. The organic layer was dried with Na_2SO_4, and evaporated to afford product **4** (1.13 g, 83% yield); oil; ^{1}H NMR ($CDCl_3$) δ=1.38 (t, 3H, J_{HCCH}=7.0 Hz, P-O-CH$_2$-C<u>H</u>$_3$), 1.4—2.9 (m, 10H, P-C<u>H</u>$_2$-C<u>H</u>$_2$-, O-CH$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.4—3.7 (m, 1H, P-C<u>H</u>Br), 3.8—4.0 (m, 1H, C<u>H</u>OTHP), 4.1—4.3 (m, 2H, O-C<u>H</u>$_2$-CH$_2$-), 4.25 (dq, 2H, J_{HCCH}=7.4 Hz, J_{HCOP}=8.0 Hz, P-O-C<u>H</u>$_2$-), and 4.7—4.9 (m, 1H, O-C<u>H</u>-O).

Similarly, **3** and **5** were prepared.[19] **3** (82% yield): ^{1}H NMR ($CDCl_3$) δ=1.36 (t, 3H, J_{HCCH}=6.9 Hz, P-O-CH$_2$-C<u>H</u>$_3$), 1.8—2.8 (m, 4H, P-CH$_2$-CH$_2$-), 2.04 (s, 3H, Ac), 3.84 (m, 1H, P-CHBr), 4.25 (dq, J_{HCCH}=6.9 Hz, J_{HCOP}=7.0 Hz, P-O-C<u>H</u>$_2$-CH$_3$), and 5.15 (m, 1H, C<u>H</u>OAc). **5** (52% yield): ^{1}H NMR ($CDCl_3$) δ=1.5—2.9 (m, 4H, P-CH$_2$-CH$_2$-), 3.75, 3.85 (d×2, 3H, J_{HCOP}=11.2 Hz, P-O-CH$_3$), 3.9—4.3 (m, 1H, P-CHBr), 5.1—5.6 (m, 1H, C<u>H</u>OBz), and 7.1—8.1 (m, 5H, Ph).

2-(Dimethoxyphosphinoyl)-1-ethoxy-3-(tetrahydropyranyloxy)phospholane 1-Oxide (7a). To a toluene (25 cm^3) solution of dimethyl phosphonate (121 mg, 1.1 mmol) was slowly added NaH (60% oil, 44.0 mg, 1.1 mmol); the mixture was then stirred for 1 h. To the mixture, 2-bromo-1-ethoxy-3-(tetrahydropyranyloxy)phospholane 1-oxide (**4**, 294.0 mg, 0.90 mmol) in toluene (30 cm^3) was slowly added and refluxed for 3 h. An insoluble material was filtered off, and the filtrate was washed with water, and dried (Na_2SO_4). The solvent was evaporated to afford product **7a** (155.4 mg, 49% yield); oil; ^{1}H NMR ($CDCl_3$) δ=1.15 (t, 3H, J_{HCCH}=7.0 Hz, P-O-CH$_2$-C<u>H</u>$_3$), 1.2—2.5 (m, 10H, P-C<u>H</u>$_2$-C<u>H</u>$_2$, O-CH$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.4—4.4 (m, 6H, O-C<u>H</u>$_2$-CH$_2$-, P-O-C<u>H</u>$_2$-CH$_3$, P-C<u>H</u>-C<u>H</u>OTHP), 3.55, 3.60 (d×2, 6H, J_{HCOP}=12.0 Hz, 2×POCH$_3$), and 4.5—4.8 (m, 1H, O-C<u>H</u>-O).

Similarly, **6a**, **6b**, **7b**, **8**, and **10** (sodium metal/methanol was used as the base/solvent) were prepared. **6a**: ^{1}H NMR ($CDCl_3$) δ=1.33 (t, 3H, J_{HCCH}=7.4 Hz, P-O-CH$_2$-C<u>H</u>$_3$), 1.3—2.8 (m, 4H, P-CH$_2$-CH$_2$-), 2.04 (bs, 3H, Ac), 3.69 (d, 6H, J_{HCOP}=12.0 Hz, P-O-CH$_3$), and 3.7—4.4 (m, 4H, P-O-C<u>H</u>$_2$-CH$_3$, P-C<u>H</u>-C<u>H</u>OAc). **6b**: ^{1}H NMR ($CDCl_3$) δ=1.40 (t, 3H, J_{HCCH}=7.0 Hz, P-O-CH$_2$-C<u>H</u>$_3$), 1.7—2.4 (m, 4H, P-CH$_2$-CH$_2$-), 2.05 (s, 3H, Ac), 3.8—4.4 (m, 1H, P-CH-P), 4.11 (dq, 2H, J_{HCOP}=8.0 Hz, J_{HCCH}=7.0 Hz, P-O-C<u>H</u>$_2$-CH$_3$), 5.0—5.5 (m, 1H, C<u>H</u>OAc), and 6.8—7.9 (m, 10H, 2×Ph). **7b**: ^{1}H NMR ($CDCl_3$) δ=1.49 (t, 3H, J_{HCCH}=7.4 Hz, P-O-CH$_2$-C<u>H</u>$_3$), 1.4—2.7 (m, 10H, P-C<u>H</u>$_2$-C<u>H</u>$_2$-, O-CH-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.4—4.6 (m, 6H, P-C<u>H</u>-C<u>H</u>-OTHP, O-C<u>H</u>$_2$-, P-O-C<u>H</u>$_2$-CH$_3$), 4.8—5.0 (m, 1H, O-C<u>H</u>-O), and 7.0—8.0 (m, 10H, 2×Ph). **8**: ^{1}H NMR ($CDCl_3$) δ=1.22 (t, 6H, J_{HCCH}=7.0 Hz, 2×P-O-CH$_2$-C<u>H</u>$_3$), 1.3—2.4 (m, 4H, P-CH$_2$-CH$_2$-), 3.5—4.3 (m, 8H, 2×P-O-C<u>H</u>$_2$-CH$_3$, P-O-CH$_3$, P-CH-P), 5.1—5.5 (m, 1H, C<u>H</u>-OBz), and 7.1—8.1 (m, 5H, Ph). **10**: ^{1}H NMR ($CDCl_3$) δ=2.0—2.8 (m, 2H, P-CH$_2$-), 3.2—3.5 (m, 1H, P-CH-), 3.59 (d, 3H, J_{HCOP}=10.8 Hz, P-O-CH$_3$), and 6.0—8.0 (m, 12H, 2×Ph, P-CH=CH-).

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