Phospho Sugars; Novel Preparation and Their Glycosyl Compounds

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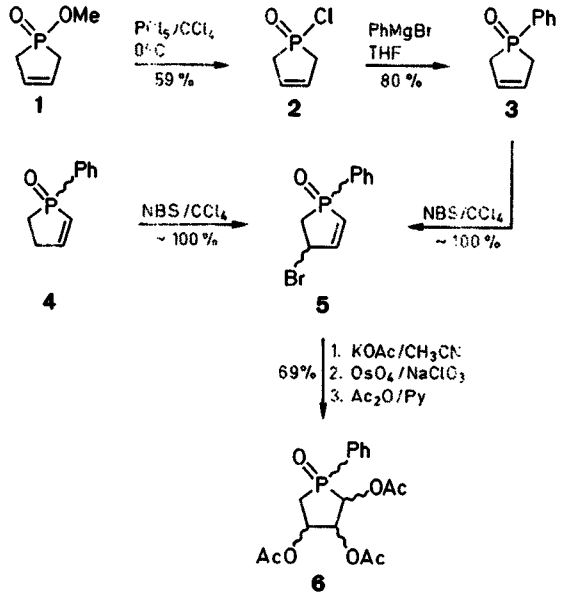
Treatment of 1-phenyl-2-, and -3-phospholene 1-oxides with *N*-bromosuccinimide affords 4-bromo-1-phenyl-2-phospholene 1-oxide. Substitution of the bromide with acetate, followed by stereoselective oxidation with osmium tetroxide and peracetylation with acetic anhydride/pyridine affords phospho sugar derivatives of tetrafuranose. Furthermore, *N*-, *O*-, and *S*-glycosyl compounds of phospho sugars can be prepared from 3-methyl-1-phenyl-2-phospholene 1-oxide by bromination and nucleophilic substitution reactions. This is a novel and excellent route to prepare phospho sugar derivatives.

Phospho sugars, having a phosphorus atom in the hemiacetal ring instead of the oxygen atom, are one of the sugar analogs containing a hetero atom in the hemiacetal ring.[1,2] The synthesis of phospho sugars reported so far used carbohydrates as the starting material. The overall yield of phospho sugars starting from carbohydrates is low owing to the long sequence of synthetic steps. In a previous paper,[3] we described the conversion of 2-phospholene 1-oxide to 2,3-dihydroxy-phospholane 1-oxide by stereoselective oxidation with osmium tetroxide. It is thus expected that oxidation of 4-oxosubstituted 2-phospholenes with osmium tetroxide may lead to phospho sugars of tetrafuranose type.

A large number of nucleosides, containing *N*- or *C*-glycosyl bonds,[4] have been prepared by the known procedure so far. On the other hand, synthesis of phospho sugar nucleosides has never been reported. Biological and physiological activities of phospho sugars[3] as well as their nucleosides are of interest, however, they are unknown. In this paper, we describe the synthesis of 4-oxosubstituted 2-phospholene 1-oxides using allylic oxidation of phospho sugar derivatives and the successive reaction of the 1-bromo-1-deoxy derivative of phospho sugars with some nucleophiles to give phospho sugar *N*-, *O*-, and *S*-glycosyl compounds.

The starting material, 1-phenyl-2-phospholene 1-oxide (**4**) is prepared by the known method.[5] 1-Phenyl-3-phospholene 1-oxide (**3**) is synthesized from 1-methoxy-3-phospholene 1-oxide (**1**)[6] as follows (Scheme A).

Reaction of **1** with phosphorus pentachloride gives phosphinyl chloride **2** in 59% yield,[7] which is treated with phenylmagnesium bromide to afford 1-phenyl-3-phospholene 1-oxide **3** in 80% yield.[7] Direct treatment of **1** with phenylmagnesium bromide[7] leads to a complex mixture containing only a small amount of **3**. 2-Phospholene **4** is treated with *N*-bromosuccinimide (NBS)[8] to afford 4-bromo-2-phospholene **5** in



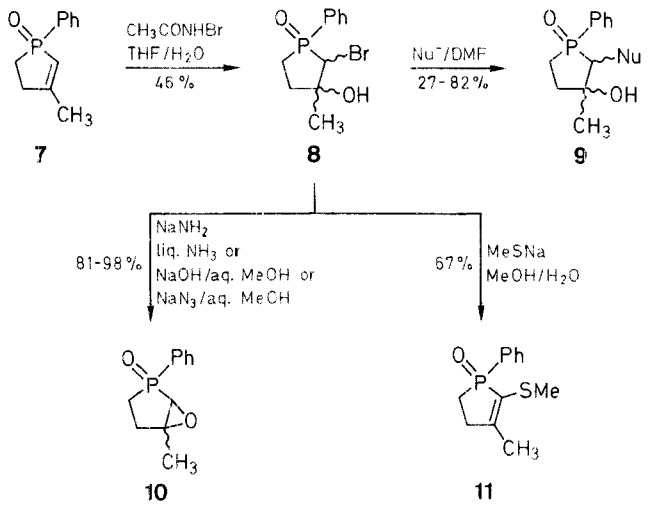
Scheme A

quantitative yield. In the case of 3-phospholene **3**, the double bond isomerizes so as to conjugate with P=O group, and hence 4-bromo-2-phospholene **5** is formed during the treatment with NBS (Scheme **A**).

Treatment of 4-bromo derivative **5** with potassium acetate affords the 4-acetate, which is oxidized with osmium tetroxide[3] and subsequently peracetylated with acetic anhydride/pyridine. The crude end product obtained from these sequence of reactions is subjected to column chromatography on silica gel. The fractions are carefully monitored by HPLC and the main fraction, consisting of the triacetate **6**, is obtained in 69% yield (Scheme **A**).

It is considered that stereoselectivity of the oxidation reaction has occurred in the same way as reported,[3] and that osmic acid attacks the substrate from the reverse side of allylic oxygen.[9] Therefore, phospho sugar **6** should take exclusively the following relative configuration: C 1-OAc and C 2-OAc are *cis*, C 2-OAc and C 3-OAc are *trans*, and C 1-OAc and P-Ph are *cis*. ^{1}H-NMR (500 MHz) measurement confirms that the relative configuration agrees well with the above consideration.[10]

2-Bromo-3-methyl-1-phenylphospholane 1-oxide (**8**) is prepared by the reaction of 3-methyl-1-phenyl-2-phospholene 1-oxide (**7**) with *N*-bromoacetamide in aqueous tetrahydrofuran at room temperature. Reaction of **8** with nucleophiles (Scheme **B**) gives various glycosyl compounds **9** of the phospho sugar (Table).



Scheme **B**

Epoxide **10** is solely produced from **8**, when basic nucleophiles such as sodium amide and sodium hydroxide are used, and the same product is obtained, when sodium azide is used in methanol/water.

Reaction of **8** with sodium methanethiolate gives 2-phospholene **11** by dehydration of the intermediate sulfide. This reason may be attributable to the strong nucleophilicity and basicity of the methylthiolate anion.

In summary, the present reactions provide not only novel and convenient preparative ways for phospho sugars but also for a variety of glycosyl compounds depending on the nucleophilicity and basicity of the used nucleophiles. We are currently working on the synthesis of nucleosides of phospho sugars via conversion of *N*-glycosyl compounds thus prepared.

1-Chloro-3-phospholene 1-Oxide (2):
To a solution of 1-methoxy-3-phospholene 1-oxide (**1**; 1.64 g, 12.4 mmol) in CCl_4 (10 mL) is added PCl_5 (3.00 g) at 0°C under a N_2 atmosphere. The mixture is allowed to warm up to room temperature and is stirred for an additional day. The solvent is removed under reduced pressure and the residue is distilled to give **2**; yield: 1.10 g (59%); bp 125–126°C/12 mbar (Lit.[12] bp 100–105°C/0.13 mbar).

IR (neat): ν = 1615 (C=C), 1220 cm^{-1} (P=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.90 (d, 4H, $J_{H,C}$ = 12 Hz, H-2,2',5,5'); 5.74 (d, 2H, $J_{H,P}$ = 36 Hz, H-3,4).

1-Phenyl-3-phospholene 1-Oxide (3):
To a solution of **2** (1.10 g, 7.32 mmol) in freshly distilled THF (8 mL) is added a solution of 1.2 equiv of phenylmagnesium bromide (9 mL) using a syringe during 10 min at 0°C under a N_2 atmosphere. The mixture is allowed to warm up to room temperature and stirred for 22 h, and then quenched by adding sat. NH_4Cl (10 mL). The separated aqueous layer is extracted with $CHCl_3$ (4×6 mL) and the combined organic layer is washed with H_2O (10 mL), and dried (Na_2SO_4). Evaporation of the solvent, followed by column chromatography of the crude product on silica gel ($CHCl_3$/MeOH, 30:1, R_f = 0.35) affords **3**; yield: 1.04 g (80%); oil.

$C_{10}H_{11}OP$	calc.	C 67.40	H 6.22	P 17.23
(178.2)	found	67.27	6.45	17.12

IR (neat): ν = 1440 (P–C), 1220 cm^{-1} (P=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.73, 1.82 (2 br s, 4H, H-2,2',5,5'); 6.39 (d, 2H, $J_{H,P}$ = 39 Hz, H-3,4); 7.1–7.9 (m, 5H, C_6H_5).

4-Bromo-1-phenyl-2-phospholene 1-Oxide (5):
A mixture of NBS (1.74 g, 9.79 mmol), 2-phospholene **4** (1.70 g, 9.57 mmol) [or 3-phospholene **3** (0.239 g, 1.34 mmol)] and a catalytic amount of benzoyl peroxide in CCl_4 (20 mL) is refluxed for 3 h under a N_2 atmosphere. The mixture is cooled to 0°C, and the insoluble materials are filtered. The filtrate is diluted with $CHCl_3$ (50 mL), the $CHCl_3$ layer is washed with sat. $NaHCO_3$ (3×15 mL), water (3×10 mL), and dried with (Na_2SO_4). Evaporation of the solvent affords the crude bromide **5**; yield: 2.34 g (~100%); oil.

Table. Compounds **9** Prepared

Product	Nu	Reagent/ solvent	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (*m/z*)
9a	I	NaI/acetone	82[b]	161–163	$C_{11}H_{13}IO_2P$ (335.1)	1.6 (s, 3H, CH_3); 1.8–2.8 (m, 4H, CH_2CH_2); 4.2 (d, 1H, J = 4, CHI); 6.15 (br s, 1H, OH); 7.33–8.03 (m, 5H, C_6H_5)	336
9b	OAc	NaOAc/AcOH	66[b]	131–135	$C_{13}H_{16}O_4P$ (267.2)	1.7 (s, 3H, CH_3); 1.89 (s, 3H, $COCH_3$); 1.15–3.0 (m, 4H, CH_2CH_2); 4.11 (d, 1H, CHOAc); 6.21 (br s, 1H, OH); 7.22–7.91 (m, 5H, C_6H_5)	268
9c	SCN	KSCN/EtOH	27[b,c]	120–125	$C_{12}H_{13}NO_2PS$ (266.3)	1.2 (s, 3H, CH_3); 1.8–3.0 (m, 4H, CH_2CH_2); 4.23, 4.30 (2d, 1H, CHSCN); 6.10 (bs, 1H, OH); 7.40–7.93 (m, 5H, C_6H_5)	267
9d	N_3	NaN_3/DMF	58[d]	183	$C_{11}H_{13}N_3O_2P$ (250.2)	1.5 (s, 3H, CH_3); 1.7–2.9 (m, 4H, CH_2CH_2); 4.0 (d, 1H, CHN_3); 4.6 (br s, 1H, OH); 7.3–8.0 (m, 5H, C_6H_5)	251

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.23, N ±0.30.
[b] Yield determined by HPLC.
[c] IR (KBr.): ν = 3300 (OH), 2250 cm^{-1} (C≡N).
[d] Yield of isolated product. IR (KBr.): ν = 3300 (OH), 2100 cm^{-1} (N_3).

$C_{10}H_{10}BrOP$	calc.	C 46.72	H 3.92	Br 31.07	P 12.05
(257.1)	found	46.90	3.88	30.91	12.13

IR (neat): ν = 1440 (P–C), 1210 cm^{-1} (P=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.0–3.0 (m, 2H, H-5,5'); 4.7–5.5 (m, 1H, H-4); 5.9–6.8 (m, 1.5H + 0.5H, H-2 + H-3); 7.2–8.0 (m, 5.5H, C_6H_5 + H-3).

2,3,4-Tri-*O*-acetyl-1-phenylphospholane 1-Oxide (6):

A solution of the bromide **5** (1.7 g, 4.14 mmol) and KOAc (0.69 g, 7 mmol) in CH_3CN (10 mL) is refluxed for 2 d. After removal of the insoluble material by filtration, the solvent is evaporated, and the residue is taken up in $CHCl_3$ (50 mL). The solution is washed with water (2 × 10 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude product is chromatographed on silica gel ($CHCl_3$/MeOH, 20:1, R_f = 0.25) to give the 4-acetate; yield: 0.595 g (61%). This is dissolved in THF (3 mL) and water (6 mL) and treated with $NaClO_3$ (0.491 g, 4.63 mmol) and OsO_4 (19.2 mg, 3 mol%) at room temperature. The mixture is then heated for 4 d at 45 °C. After evaporation of the solvent, the residue is taken up into 30 mL of $CHCl_3$, and the solution is dried (Na_2SO_4). Removal of the solvent gives the crude product, which is chromatographed on silica gel ($CHCl_3$/MeOH, 10:1, R_f = 0.12) to give the triol monoacetate in 45% yield. The triol monoacetate (0.297 g, 1.1 mmol) is dissolved in pyridine (1 mL) and treated with Ac_2O (0.216 g, 2.12 mmol) and the mixture is stirred for 2.5 d at room temperature. After aqueous workup and extraction with $CHCl_3$, the product is purified by chromatography on silica gel ($CHCl_3$/MeOH, 30:1, R_f = 0.33); yield: 0.267 g (69%).

$C_{16}H_{19}O_7P$	calc.	C 54.24	H 5.41	P 8.74
(354.3)	found	54.09	5.33	8.84

IR (neat): ν = 1775 (C=O), 1440 (P–C), 1230 cm^{-1} (P=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.3–3.0 (m, 11H, 3 × $COCH_3$ + H-5,5'); 5.2–5.8 (m, 3H, H-2,3,4); 7.3–8.0 (m, 5H, C_6H_5).

MS: m/z = 354 (M^+).

3-Methyl-1-phenyl-2-phospholene 1-Oxide (7):[11,13]

A mixture of isoprene (6.0 g, 88.1 mmol) and phenylphosphonous dichloride (15.8 g, 88.1 mmol) is stirred for about a week at room temperature, and the resulting solid is dissolved in $CHCl_3$ (50 mL). The $CHCl_3$ solution is poured into ice-water (50 mL) in small portions with vigorous stirring. After neutralization of the solution with $NaHCO_3$, the insoluble material is filtered, and the filtrate is extracted with $CHCl_3$ (3 × 15 mL). The extract is washed with water (25 mL), dried (Na_2SO_4), and evaporated to afford **7**; yield: 9.47 g (56%); bp 150 °C/2 mbar (Lit.[12] bp 156–157 °C/0.7 mbar).

IR (neat): ν = 1620 (C=C), 1440 (P–C), 1250 (P=O), 750 cm^{-1} (P–C)

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.05 (s, 3H, CH_3); 2.15–2.80 (m, 4H, CH_2CH_2); 5.88 (d, 1H, $J_{H,P}$ = 25.1 Hz, =CH); 7.35–7.85 (m, 5H, C_6H_5).

MS: m/z = 192 (M^+).

2-Bromo-3-hydroxy-3-methyl-1-phenylphospholane 1-Oxide (8):[14]

N-Bromoacetamide (2.01 g, 10.5 mmol) is added to a solution of **7** (1.45 g, 10.5 mmol) in THF (5 mL) and water (20 mL). The mixture is stirred for 24–36 h at room temperature. The solvent is evaporated, and the residue is taken up in $CHCl_3$ (15 mL), the $CHCl_3$ layer dried (Na_2SO_4) and evaporated. The residue is recrystallized from $CHCl_3$/CCl_4 to afford the product; yield: 1.39 g (46%); mp 161 °C.

$C_{11}H_{24}BrO_2P$	calc.	C 45.70	H 4.88	P 10.71
(289.1)	found	44.91	4.79	10.14

IR (KBr): ν = 3200 (OH), 1445 (P–C), 1150 (P=O), 750 (P–C), 550 cm^{-1} (C–Br).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.61 (s, 3H, CH_3); 1.92–2.95 (m, 4H, CH_2CH_2); 4.21 (d, 1H, $J_{H,P}$ = 5 Hz, CHBr); 5.05–5.85 (br s, 1H, OH); 7.30–7.96 (m, 5H, C_6H_5).

MS: m/z = 289 (M^+), 291 (M^+ + 2).

2-Azido-3-hydroxy-3-methyl-1-phenylphospholane 1-Oxide (9d); Typical Procedure:

NaN_3 (1.38 g, 20 mmol) is added to a solution of **8** (5.0 g, 14 mmol) in DMF (20–30 mL). The solution is stirred overnight under reflux. The solvent is removed and the residue is dissolved in CHCl (30 mL). The solution is washed with water, dried (Na_2SO_4), and evaporated. Phospho sugar *N*-glycoside derivative **9d** is isolated from the residue by column chromatography on silica gel ($CHCl_3$/MeOH, 15:1); yield: 2.04 g (58%) (Table).

2,3-Epoxy-3-methyl-1-phenylphospholane 1-Oxide (10):

Using $NaNH_2$ in liquid NH_3:

A mixture of bromide **8** (0.25 g, 0.87 mmol) and sodium amide (0.040 g, 1.0 mmol) are stirred in liq. NH_3 (20–30 mL) for 5 h at –78 °C. After NH_3 is vaporized, the residue is dissolved in 0.1 M aq. NaOH (10 mL, 1 mmol). The solvent is removed and the residue is dissolved in $CHCl_3$ (20 mL). After insoluble materials are filtered off, the filtrate is dried (Na_2SO_4) and evaporated to afford **10**; yield: 0.192 g (98%); oil.

$C_{11}H_{13}O_2P$	calc.	C 63.46	H 6.29	P 14.88
(208.2)	found	63.34	6.21	14.56

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.5 (s, 3H, CH_3); 1.7–2.8 (m, 4H, CH_2CH_2); 3.12 (d, 1H, J_{PH} = 30 Hz, CH); 7.0–7.95 (m, 5H, C_6H_5).

MS: m/z = 208 (M^+).

Using $NaOH/CH_3OH/H_2O$:

A 0.09 M aq. solution of NaOH (15 mL, 1.3 mmol) is added to a solution of **8** (0.30 g, 1.04 mmol) in MeOH (15 mL). The solution is stirred overnight under reflux. The solvent is removed and the residue is dissolved in $CHCl_3$ (20 mL). The solution is washed with water (2 × 15 mL), dried (Na_2SO_4), and evaporated; yield: 0.175 g (81%).

Using $NaN_3/MeOH/H_2O$:

To a solution of **8** (0.50 g, 1.4 mmol) in H_2O/MeOH (1:1 in v/v, 20 mL) is added NaN_3 (0.13 g, 2.0 mmol). The solution is stirred overnight under reflux. The solvent is removed and the residue is dissolved in $CHCl_3$ (20 mL). The solution is washed with water (2 × 15 mL), dried (Na_2SO_4), and evaporated; yield: 0.277 g (95%).

3-Methyl-2-methylthio-1-phenyl-2-phospholene 1-Oxide (11):

Aq. solution (0.98 g) of NaSMe is added to a solution of **8** (0.50 g, 1.73 mmol) in MeOH (20 mL). The solution is stirred for 24 h under reflux. The solvent is removed and the residue is dissolved in $CHCl_3$ (20 mL), which is washed with water (2 × 15 mL), dried (Na_2SO_4), and evaporated; yield: 0.31 g (67%).

$C_{12}H_{15}OPS$	calc.	C 60.48	H 6.35	P 13.00	S 13.45
(238.3)	found	60.19	6.34	12.87	13.35

IR (neat): ν = 1660 cm^{-1} (C=C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.0 (s, 3H, CH_3); 2.18 (s, 3H, SCH_3); 2.26–3.0 (m, 4H, CH_2CH_2); 7.4–7.93 (m, 5H, C_6H_5).

MS: m/z = 238 (M^+).

Received: 6 September 1988; revised: 24 February 1989

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