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A Novel Stereocontrolled Preparation of Phospho Sugar Derivatives from Phospholenes

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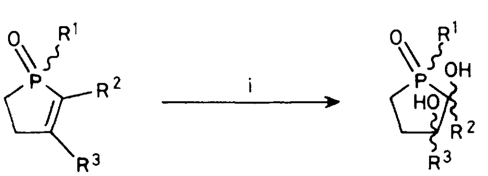
A highly stereospecific oxidation of 2-phospholene 1-oxides gives the first successful preparation of phospho sugars, having phosphorus as the sugar ring hetero atom, the relative configuration being confirmed by *X*-ray crystallography.

Phospho sugars,[1,2] which have a phosphorus atom in the hemiacetal ring, come under the category of heteroatom sugar derivatives. Amino and thio sugars,[3] having a nitrogen and a sulphur atom, respectively, in the ring, are well known, some are naturally occurring, and they play important biological roles. For example, 5-amino-5-deoxy-D-glucose is an antibiotic and 5-deoxy-5-thio-D-glucopyranose is an active substance for increment of blood sugar concentration.[4,5] Phospho sugars have never been found in nature and information about their expected bioactivity[2] has hitherto been sparse, since the amounts obtained were very small. Previous methods for the preparation of phospho sugars used sugar derivatives as starting materials and therefore required many synthetic steps,[6,7] resulting in comparatively low overall yields. The present communication presents a new route to phospho sugars *via* the oxidation of phospholenes which are prepared by the addition of phosphorus halides to 1,3-dienes, as well as the *X*-ray crystallographic analysis of the phospho sugar.

Addition of phosphorus trihalides or phosphonous halides to 1,3-dienes is known to produce cyclic unsaturated phosphorus compounds, phospholenes.[8] Oxidation of the phospholenes to vicinal diols has not been reported so far, and attempts using well known methodologies such as oxidation with permanganates have failed.[9]



(1) (2)

a; R^1 = Ph, R^2 = H, R^3 = Me
b; R^1 = Ph, R^2 = Me, R^3 = H
c; R^1 = OMe, R^2 = H, R^3 = Me

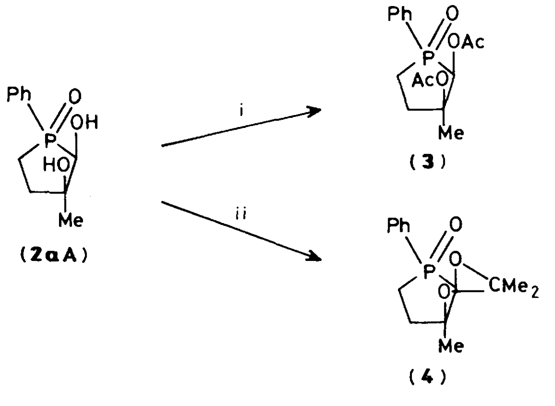
Scheme 1. *Reagents:* i, OsO_4–$MClO_4$.

Oxidation of 3-methyl-1-phenyl-2-phospholene-1-oxide (**1a**) (2.89 g) in aqueous tetrahydrofuran with osmic acid and potassium chlorate (2.63 g) (18 h, 45—50 °C) afforded vicinal diols (**2a**) in 91% yield (Scheme 1). The product was further separated into three components by column chromatography on silica gel. These are the first sugar derivatives prepared

Table 1. Diols (**2**) prepared by oxidation of phospholenes (**1**).

Reaction conditions			Product diol
Reagent	Temperature/°C	Time/h	(Yield/%)
OsO_4–$KClO_3$	45—50	18	(**2a**) [68(91)][a]
OsO_4–$NaClO_3$	45—50	18	(**2a**) (66)
OsO_4–$Ba(ClO_3)_2$	45—50	18	(**2a**) (65)
OsO_4–Bu^tO_2H	40	24	(**2a**) (20)
OsO_4–$KClO_3$	45—50	18	(**2b**) (42)[a]
OsO_4–$KClO_3$	55—60	24	(**2c**) (35)[a]

[a] M.s. for (**2a**): *m/z* 226 (M^+); (**2b**): *m/z* (M^+); (**2c**): *m/z* 178 (M^+).



Scheme 2. *Reagents*: i, Ac_2O–pyridine; ii, H^+, acetone.

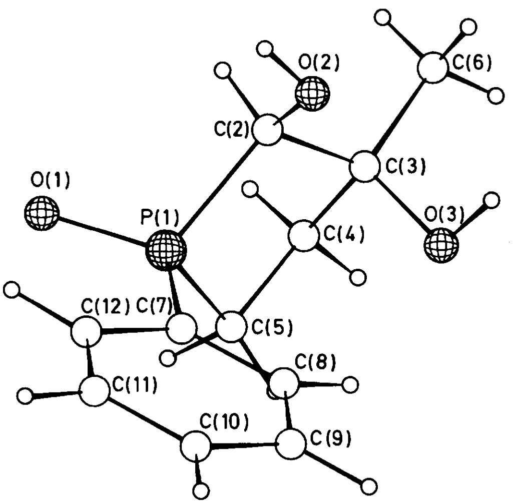


Figure 1. Molecular structure of (**2aA**). Selected bond distances (Å): P(1)–C(2) 1.849(5), C(2)–C(3) 1.532(5), C(3)–C(4) 1.524(6), C(4)–C(5) 1.522(7). C(5)–P(1) 1.811(4), P(1)–O(1) 1.498 (3), P(1)–C(7) 1.784(4). Selected bond angles (°): P(1)–C(2)–C(3) 105.2(3), C(2)–C(3)–C(4) 105.2(3), C(3)–C(4)–C(5) 108.0(3), C(4)–C(5)–P(1) 103.7(3), C(5)–P(1)–C(2) 95.5(2), O(1)–P(1)–C(2) 112.4(2), O(1)–P(1)–C(7) 110.7(2), C(5)–P(1)–C(7) 112.5(2), C(2)–P(1)–C(7) 110.5(2), O(1)–P(1)–C(5) 114.4(2).

from non-sugar precursors, phospholenes. 2-Methyl-1-phenyl-2-phospholene 1-oxide (**1b**) and 1-methoxy-3-methyl-2-phospholene 1-oxide (**1c**) were also oxidized by the osmic acid–chlorate method.[10] These results together those of other oxidation methods[10] are summarized in Table 1.

The three components isolated from (**2a**) consisted of one major compound (**2aA**) and two minor compounds (**2aB**) and (**2aC**) in the ratio (**2aA**) : (**2aB**) : (**2aC**) 13 : 1 : 1. Compound (**2aA**) was further purified by recrystallization from carbon tetrachloride, m.p. 185—188 °C, $[\alpha]_D^{16}$ +3.5° (*c* 1.0, MeOH).† Treatment of (**2aA**) with acetic anhydride in pyridine (Scheme 2) afforded 1,2-di-*O*-acetyl derivative (**3**)‡ in 94% yield.[11] Reaction of (**2aA**) with acetone in the presence of sulphuric acid and copper(II) sulphate gave 1,2-*O*-isopropylidene derivative (**4**)§ in quantitive yield.[12] Addition of dipivaloylmethanatoeuropium(III) (Eu-dpm)[13] to compound (**2aA**) caused a downfield shift of the ^{1}H n.m.r. signals of the methyl (δ_H 1.45 to 2.20) and phenyl (δ_H 7.55 to 7.80) groups. The structure of (**2aA**) was further elucidated by *X*-ray crystallographic analysis of the single crystal,[14] (Figure 1). Compound (**2aA**) was thus proved to be 3-deoxy-2-*C*-methyl-1,4-*C*-(phenylphosphinylidene)-α-L-*glycero*-tetrafuranose whose conformation was ^3E.[15]¶

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† *Spectral data* for (**2aA**): ^{1}H n.m.r. δ_H (60 MHz, $CDCl_3$) 1.45 (3H, d, *J* 2.0 Hz, CH_3), 1.75—2.85 (4H, m, CH_2–CH_2), 3.80 (1H, d, *J* 2.0 Hz, PCH), 4.60 (2H, s, 2 × OH), 7.5—7.9 (5H, m, C_6H_5); i.r., $\nu_{max.}$ (KBr) 3375 (OH), 1450 (P–Ph), 1150 (P=O), 750 cm^{-1} (P–C); *m/z* 226 (M^+).

(**2aB**): M.p. 152—158 °C; ^{1}H n.m.r. δ_H (60 MHz, $CDCl_3$) 1.40 (3H, d, *J* 1.8 Hz, CH_3), 1.9—3.0 (4H, m, CH_2–CH_2), 3.75 (1H, d, *J* 1.3 Hz, PCH), 4.60 (2H, s, 2 × OH), 7.3—7.8 (5H, m, C_6H_5); *m/z* 226 (M^+).

(**2aC**): M.p. 173—175 °C; ^{1}H n.m.r. δ_H (60 MHz, $CDCl_3$) 1.40 (3H, d, *J* 1.2 Hz, CH_3), 1.9—2.8 (4H, m, CH_2–CH_2), 3.75 (1H, br., PCH), 5.00 (2H, br. s, 2 × OH), 7.3—7.9 (5H, m, C_6H_5); *m/z* 226 (M^+).

‡ *Spectral data* for (**3**): ^{1}H n.m.r. δ_H (60 MHz, $CDCl_3$) 1.55 (3H, s, CH_3), 1.75 and 2.10 (6H, 2s, 2Ac), 2.2—3.0 (4H, m, CH_2–CH_2), 5.10 (1H, d, *J* 9.0 Hz, PCH), 7.4—8.2 (5H, m, C_6H_5): i.r., $\nu_{max.}$ (neat) 1740 cm^{-1} (C=O); *m/z* 310 (M^+).

§ *Spectral data* for (**4**): ^{1}H n.m.r. δ_H (60 MHz, $CDCl_3$) 1.40 (3H, s, CH_3), 1.50 and 1.72 (6H, 2d, *J* 4.0 Hz, CMe_2), 2.0—2.9 (4H, m, CH_2–CH_2), 4.40 (1H, d, *J* 11.0 H$_z$, PCH), 7.4—8.0 (5H, m, C_6H_5); i.r. $\nu_{max.}$ (neat) 1215 cm^{-1} (CMe_2); *m/z* 266 (M^+).

¶ *Crystal data* for (**2aA**): $C_{11}H_{15}O_3P$, monoclinic, space group $P2_1/a$, a = 8.105(1), b = 17.029(3), c = 9.080(1) Å, β = 113.38(1)°, U = 1150.32(29) Å^3, Z = 4, D_c = 1.306 g cm^{-3}, μ(Cu-K_α) = 20.1 cm^{-1}, all unique diffraction maxima with $2\theta < 114°$ were collected using graphite monochromated Cu-K_α radiation (λ = 1.54178 Å) and variable speed, 1° ω-scans. 1555 Unique reflections were obtained, of which 954 were considered 'observed' [$I > 3\sigma(I)$ and $I > 100$]. The structure was solved by standard heavy atom and Fourier techniques and refined by block-diagonal least-squares methods to R = 0.039 (R_w = 0.051). Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.