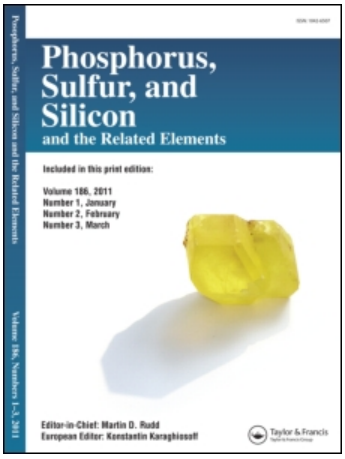

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NOVEL SYNTHESIS OF PHOSPHONO SUGAR DERIVATIVES

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Abstract 2- And 3-phospholenes were used as the starting materials for the syntheses of sugar derivatives having a phosphorus atom in the hemiacetal ring of the sugar derivatives (phosphono sugars). Alkylation or benzyloxymethylation of 3-phospholene 1-oxides afforded phospholene derivatives with more than 5 carbon atoms. Epoxidation followed by epoxide ring opening and *cis*-dihydroxylation of 5-benzyloxymethyl-2-phospholene derivatives afforded four pentofuranose type phosphono sugars (arabinose, lyxose, ribose, and xylose). Some nucleosides and isonucleosides of phosphono sugars were also prepared. Some of these derivatives of phosphono sugars were subjected to structure elucidation and bioassay.

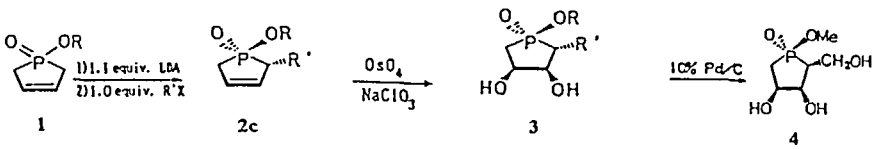
Key Words: Phosphono sugar; phospholene; LDA; Bromohydrin; Nucleoside

INTRODUCTION

Phosphono sugars, being one kind of sugar derivatives having a phosphorus atom in the hemiacetal ring of the sugar, had been expected to excert biological activities.[1] Therefore phosphono sugars were of interest in the aspects related to syntheses, structure, and biological activities. They were mainly prepared from sugar starting materials with suitable protections, functional group interconversions, cyclization, and deprotection.[1] In our previous paper, we reported the *cis*-dihydroxylation of 2-phospholenes with catalytic amount of osmium(VIII) oxide and co-oxidants.[2] The present paper deals with further conversion of 2- and 3-phospholene 1-oxide derivatives to prepare 1-deoxy pentofuranose and pentofuranose type phosphono sugars as well as their nucleosides and isonuleosides and their structural and biological analyses.

RESULTS, DISCUSSION, AND EXPERIMENTAL

1-Alkoxy-3-phospholene 1-oxides **1** were treated with 1.1 equivalents of lithium diisopropylamide (LDA) followed by alkylation with 1.0 equivalent of alkyl halides or (benzyloxy)methyl chloride in tetrahydrofuran (THF) at -78 °C to afford 2-alkyl or 2-(benzyloxy)methyl-3-phospholene 1-oxide, respectively. The alkylation proceeded stereoselectively to provide *syn* alkylated 2-methyl-3-phospholene 1-oxide, and only a little amount of *anti* isomer was obtained as the minor product. 2,5-(Dibenzyloxy)methyl-3-phospholene 1-oxide was also obtained as the minor product for the 2-(benzyloxy)methylation. These results are summarized in TABLE I.



1 2c 3 4

TABLE I Alkylation of 3-phospholene derivatives.

R of phospholene	Alkyl halide R'X		*C*-Alkylated product Yield/%	Diastereomer excess/%
Me	MeI	**2a**	44	95
Me	BnBr	**2b**	69	100
i-Pr	MeI	**2c**	55	100
Me	$BnOCH_2Cl$	**2d**	61	100

1-Alkoxy-2-alkyl-3-phospholene 1-oxides were subjected to *cis*-dihydroxylation with catalytic amount of osmium(VIII) oxide in the presence of sodium chlorate at 40°C to afford 3,4-dihydroxyphospholane 1-oxides **3** (racemate) stereoselectively. This stereoselectivity may be attributable to the steric hindrance and electro-repulsive effect between oxygen atoms of phosphoryl moiety and osmium(VIII) oxide. The structure of (1*S*, 2*R*, 3*R*, 4*S*)-2-benzyl-3,4-dihydroxy-1-methoxyphospholane 1-oxide (**3b**), namely, 1,4,5-trideoxy-4-[(*S*)-methoxyphosphinyl]-5-*C*-phenyl-D-ribofuranose, was established by assignment of all signals and analysis of coupling constants measured by 500 MHz ^{1}H-NMR (FIGURE I), The $J_{3,4}$ value of 9.7 Hz shows the C_3-H_3 and C_4-H_4 bonds are nearly in the *trans* relationship, whereas the small $J_{2,3}$ value of 3.0 Hz indicates the *cis*-relation (C_2-H_2 and C_3-H_3 bonds). The small $J_{3,P}$ value of 3.0 Hz and large $J_{2,P}$ value of 33.7 Hz reveals that the compound exists mainly in $^3T_2$

conformation (FIGURE I). Stereoselectively formed diol **3d** was hydrogenolyzed for 1 d at room temperature to afford 1,4-dideoxy-4-[(*S*)-methoxyphosphinyl]-D-ribofuranose (**4**) and its enatiomer. Structure of **4** was confirmed by ^{1}H-NMR spectroscopy of the peracetate ($^{3}T_{2}$). The structure of the acetonide of compound **4** was established by X-ray crystallographic analysis (FIGURE 2).

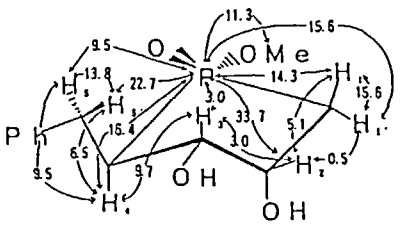


FIGURE 1 Structure of **3b**.

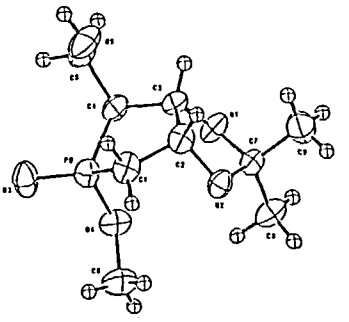
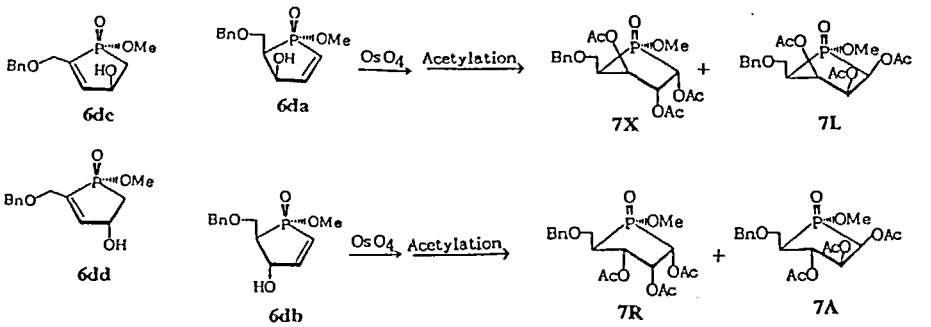


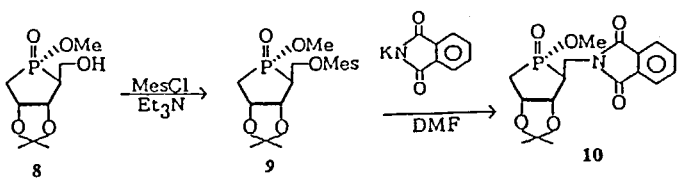
FIGURE 2 Structure of acetonide of **4**.

2-Benzyloxymethyl-1-methoxy-3-phospholene 1-oxide (**3d**) was treated with 1.7 equivalents of 3-chloroperbenzoic acid (mCPBA) in chloroform at 100°C for 2 d to afford (3*R*, 4*S*)- and (3*S*, 4*R*)-2-benzyloxymethyl-3,4-epoxyphospholane 1-oxides (**5da** and **5db**, respectively) in a quantitative yield (**5da** : **5db** = 4 : 7). Treatment of the mixture of **5da** and **5db** with triethylamine (1.0 equivalent) in ethanol at 100 °C for 2 d followed by separation by column chromatography on silica gel gave 2-phospholene derivatives **6da** (18.4%), **6db** (32.0%), **6dc**, and **6dd** (**6dc** + **6dd**, 16.8%). Osmium(VIII) oxide-catalyzed *cis*-dihydroxylation of compounds **6da** at 40 °C followed by treatment with acetic anhydride in pyridine at room temperature afforded racemic (1*R*, 2*S*, 3*R*, 4*R*, 5*R*)- and (1*R*, 2*R*, 3*S*, 4*R*, 5*R*)-2,3,4-triacetyloxy-5-benzyloxymethyl-1-methoxyphospholane 1-oxides and thier enatiomers, namely, 1,2,3-tri-*O*-acetyl-5-*O*-benzyl-4-deoxy-4-[(*R*)-methoxyphosphinyl]-α-D-xylofuranose (**7X**) and β-D-lyxofuranose (**7L**) (74 : 26; 78% total yield from **6da**). The δ values of ^{31}P-NMR in $CDCl_3$ were 51.6 and 50.3 ppm. In contrast to the result, the *cis*-dihydroxylation of acetylated compound of **6da** afforded diastereoselectively a sole product **7X** in 87% yield from **6da**. This stereoselectivity can be explained by steric and electro-repulsive effects of the oxo-substituents of the phospholene towards osmium(VIII) oxide. The same method for compound **6db** gave 1,2,3-tri-*O*-acetyl-5-*O*-benzyl-4-deoxy-4-[(*R*)-methoxyphosphinyl]-α-D-ribofuranose (**7R**, δ ^{31}P = 49.3 ppm) and -β-D-

arabinofuranose (**7A**, δ ^{31}P = 47.9 ppm) (47 : 53; 99% total yield from **6db**). The *cis*-dihydroxylation of acetylated compound of **6db** afforded products **7R** and **7A** (**7R** : **7A** = 59 : 41; **7R** + **7A** 51% yield from **6db**) upon acetylation. The four pentofuranose type phosphono sugar derivatives were first synthesized from 3-phospholenes.



Reaction of acetonide **8** with methanesulfonyl chloride in dichloromethane in the presence of triethylamine at 0 °C for 1 d afforded *O*-mesylated phosphono sugar derivative **9** (69% yield), which was further treated with potassium phthalimide in DMF at 80 °C for 8 h afforded phthalimido derivative **10** (24% yield) upon separation by thin layer chromatography on silica gel. Mitsunobu reaction of compound **8** with phthalimide (triphenylphosphine and diethyl azodicarboxylate in THF at 0°C for 2 d) gave compound **10** in 65% yield. The reaction of 1-phenyl-2-phospholene 1-oxide with bromine in protic media proceeded to give bromohydrin derivative, which was further converted into triazole derivatives via 1,3-dipolar cycloaddition of azido. Some of these phosphono sugar derivatives prepared showed some biological activities.



REFERENCES

1. M. Yamashita, M. Yamada, M. Sugiura, H. Nomoto, and T. Oshikawa, *Nippon Kagaku Kaishi*, 1207 (1987); H. Yamamoto, S. Inokawa, *Adv. Carbohydr. Chem. Biochem.*, **42**, 135 (1984).
2. M. Yamashita, M. Uchimura, A. Iida, L. Parkanayi, and J. Clardy, *J. Chem. Soc., Chem. Commun.*, 569 (1988).