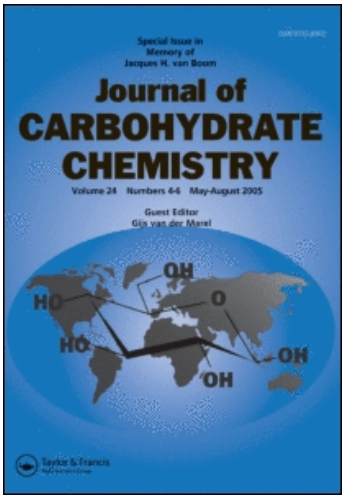

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Diastereoselective Preparation of a New Class of Deoxy λ^5 Phospha Sugar Derivatives

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CONTENTS

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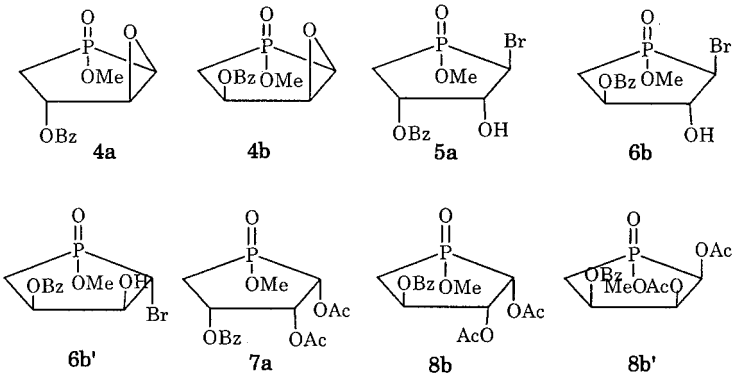
ABSTRACT

Several new classes of deoxy phospha sugar derivatives, analogs of normal sugar derivatives, were conveniently synthesized using 1-methoxy-2-phospholene 1-oxide as a starting material. All compounds were structurally characterized by their spectral data, and stereochemistry was determined by spectral and X-ray crystallographic analyses.

Key Words: Diastereoselectivity; Phospha sugars; Epoxides; Hetero sugars; Phospholane oxides; Absolute configuration.

INTRODUCTION

Hetero sugars, having the hetero atom, like nitrogen, sulfur, or selenium in place of the oxygen atom in the hemiacetal ring of normal sugar are extensively studied and reported as highly interesting substances because of their wide range of potential biological effects in living systems.[1] The term "phospha sugar" belongs to the category of hetero sugars.[2] It has been well-focused on the synthesis (either racemic or enantiomerically pure form) and bioactivity of hetero sugars; for example, 5-amino-5-deoxy-D-glucose is an antibiotic[3] and 5-deoxy-5-thio-D-glucopyranose[4] is an active substance for increment of blood sugar concentration. However, phospha sugars have never been found in nature, and information about their expected bioactivity[5] has hitherto been sparse, since the amounts and kinds of phospha sugars obtained were very small. Previous methods using sugars as starting materials required many and tedious synthetic steps,[6,7] and resulted in low overall yields. Hence, development of general methods for easy preparation of such compounds would undoubtedly lead more detailed studies of their chemistry in view of their physicochemical properties as well as potential biological activity.[2a] We now report the stereoselective preparation of a new class of deoxy phospha sugar molecules, shown in Scheme 1, in good to high yields as racemates.



Scheme 1.

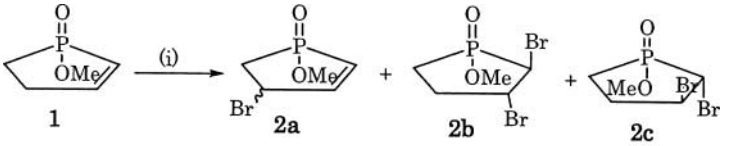
RESULTS AND DISCUSSION

As part of our ongoing program devoted in the facile preparation of phospha sugar molecules, we have synthesized several deoxy phospha sugar molecules. Initially, allylic bromination of 1-methoxy-2-phospholene 1-oxide **1**[8] using *N*-bromosuccinimide and AIBN (2,2′-azobisisobutyronitrile) as a catalyst produced 4-bromo-1-methoxy-2-phospholene 1-oxide (**2a**) as a major compound (48%), together with the minor diastereomeric mixture (*erythro*- and *threo*-) of 2,3-dibromophospholane 1-oxides **2b**, **2c** in 22% and 26%, yields, respectively, as oily liquids, shown in Scheme 2. Compound **2a** is a good intermediate to prepare several new tetrofuranose analogs of phospha sugar derivatives. Further spectral analysis of compound **2a** revealed that it consists of two diastereomers possessing closer R_f values and were unable to separate by column chromatography on silica gel.

Compound **2a** was treated with sodium benzoate in dry CH_3CN, and it afforded a diastereomeric mixture of 4-benzoyloxy phospholene oxides in 98% overall yield and successfully separated by column chromatography on silica gel using ethyl acetate-*n*-hexane (10 : 1) as an eluent, and the diastereomeric ratio was found to be 1 : 2 (**3a** : **3b**). The configurations of these two individual isomers **3a** and **3b**, outlined in Scheme 3 ascertained from ^{1}H-NMR spectroscopy (recorded on 400 MHz). The H-4 (allylic proton) of the minor isomer **3a** clearly shifted to down field (by 0.08 ppm) from the major isomer **3b**, because H-4 of **3a** is deshielded due to the shielding effect exerted by P=O,[9] and thus represents that C-4-H and P=O are coplanar and possess an *anti* relationship between P=O and C-4-OBz (i.e., C-4-H is *syn* to P=O), whereas the major isomer **3b** has the opposite relationship.

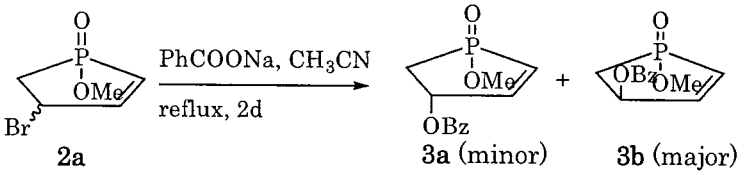
Interestingly, individual treatment of **3a** and **3b** with 2.0 equiv of sodium peroxide in ethanol diastereospecifically afforded *erythro* epoxides (**4a,b**) in 52% and 55% isolated yields, respectively (Scheme 4). The configurations of **4a** and **4b** were determined by ^{1}H-NMR spectroscopy. In ^{1}H-NMR spectrum of **4a** and **4b**, H-2 protons resonated as double doublets (dd) due to the existence of P-C-H and H-H coupling. Addition of 10% $Eu(DPM)_3$ complex caused a downfield shift of ^{1}H-NMR signals of **4a** and **4b**. Therefore, the down field shift of H-2, H-3, and larger $^2J_{PH}$ coupling constants (25–26 Hz) attributed to the *anti* relationship of H-2,3 with P=O.[10]

On the other hand, bromohydrination of compounds **3a** and **3b** afforded their derivatives **5a**, **6b**, and **6b′**, shown in Scheme 5. Significantly, the major 1,4-*cis*-isomer (**3b**) produced diastereomeric mixture of bromohydrin derivatives **6b** and **6b′** in 82% overall yield, whereas the minor isomer **3a** afforded single bromohydrin derivative (**5a**) in 66% pure form. The difference in the reactivity and diastereoselectivity did occur due to the steric hindrance exerted by the bulkier benzoyloxy group at C-4 position. The two



(i) *N*-Bromosuccinimide, AIBN, $CHCl_3$, reflux, N_2, 8 h

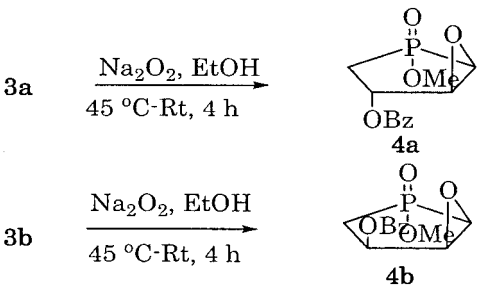
Scheme 2.



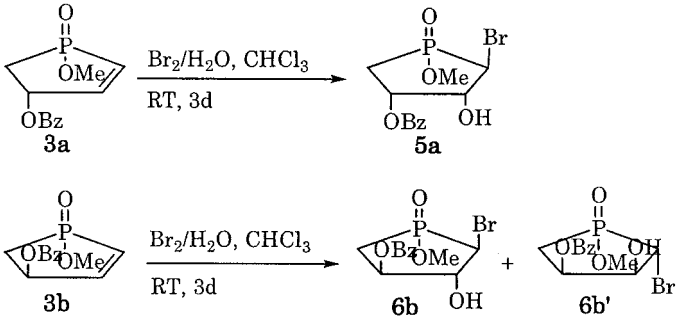
Scheme 3.

diastereomers, **6b** and **6b′** were easily separated by column chromatography on silica gel using a mixture of chloroform and methanol (50 : 1) as an eluent, and the isomeric ratio was found to be 1 : 2 (**6b** : **6b′**). Furthermore, the stereochemistry of all the isomers (**5a**, **6b**, and **6b′**) was confirmed from their spectral studies, and also X-ray crystallographic analysis of compound **5a**.[11] The crystal structure of **5a** depicted in Figure 1 paved the way to determine the absolute configuration of phospholane ring as (*1S*$_P$, *2S*, *3R*, *4R*), and (*1R*$_P$, *2R*, *3S*, *4S*) for its enantiomer. Recrystallization of other products from chloroform-*n*-hexane (1 : 1) produced crystals, but only compound **5a** gave a single crystal suitable for X-ray studies.

In addition, osmium tetroxide (catalytic amount) oxidation of **3a**, **3b** produced corresponding vicinal *cis*-diols (**7**,**8**) in 78% and 75% yields, respectively, as oily liquids outlined in Scheme 6. HPLC analysis of **7** and **8** showed two peaks, and thus each compound is a mixture of two isomers. The isomeric ratio of the crude compounds was determined by HPLC to be 9 : 1 (for **7**) and 1.2 : 1 (for **8**). Nevertheless, attempts were unsuccessful to separate the diastereomers of **7** and **8** due to their closer R_f values. The difference in the isomeric ratio and selectivity did occur mainly due to the variation in the reactivity of OsO_4 toward 2-phospholene oxides, **3a** and **3b**. The reagent may suffer from an electron-repulsive effect, more effectively by P = O than 4-OBz, and hence it prefers to attack from either the rear side of P = O bond or 4-OBz group.[12] Subsequent treatment of **7** and **8** with acetic anhydride in pyridine afforded corresponding 2,3-diacetoxy derivatives, **7a** in 65% yield (since the other isomer quantity was very low it did not find after isolation) as an oily liquid, and diastereomeric mixture of **8b** and **8b′** in 69% overall yield. The two diastereomers **8b** and **8b′** were separated by column chromatography on silica gel using chloroform-methanol (20 : 1) as an eluent and obtained as pure oily liquids. The isomeric ratio of **8b** and **8b′** was found to be 1 : 1. The structure of the three racemic compounds obtained have the configurations shown in Scheme 6. The *syn*



Scheme 4.



Scheme 5.

or *anti* relationship between P = O and 2,3-acetoxy groups of **7a**, **8b**, and **8b′** have been determined unambiguously by their ^{1}H-NMR spectral analyses. The down field chemical shift values of H-2, H-3, P-C-H, and H-H_{vic} coupling constants ($J_{2,3} = 4.95$ and $J_{3,4} = 3.11$) of **8b** represented the co-planarity of P = O, H-2, and H-3, and thus the absolute configuration of the phospholane ring of **8b** was determined as (*1S$_P$*, *2S*, *3S*, *4R*) and (*1R$_P$*, *2R*, *3R*, *4S*) for its enantiomer. The absolute configurations of other compounds **7a** and **8b′** were determined by the spectral analogy of **8b**.

Interestingly, ^{1}H-NMR spectrum of all compounds showed that the C-5 methylene protons resonated as a pair of triple doublets (td) with different δ values, because the two protons are magnetically nonequivalent due to the presence of adjacent chiral

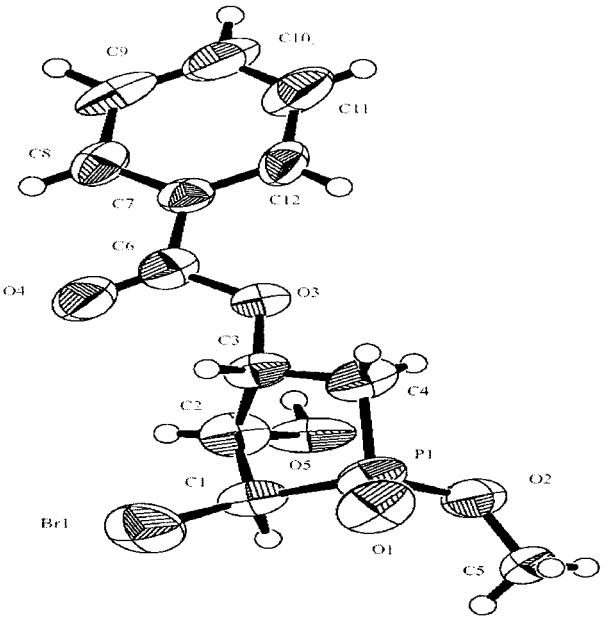
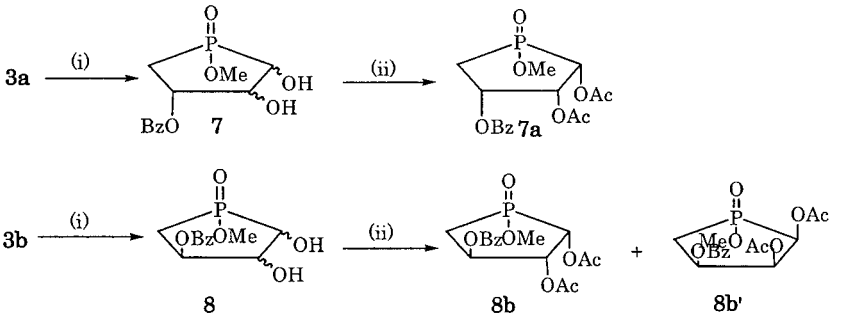


Figure 1. ORTEP drawing of compound **5a**.



(i) OsO_4, $KClO_3$, THF-H_2O (1:2), 40 °C, 24 h (ii) Ac_2O, Pyridine, RT, 24 h

Scheme 6.

centers. Each proton was split by the other (J_{HHgem}) unequally with adjacent C-4-H (J_{HHvic}) and also with P atom ($^2J_{PH}$). Similarly, H-2 protons resonated as double doublets (dd) due to P-C-H and H-H*vic* coupling, and H-3 protons resonated as triple doublets (td) due to P-C-H, H-H*vic* couplings, while H-4 protons resonated as a pair of double doublets (dd) due to P-C-H, H-H*vic* couplings.

Interestingly, the crystal structure of **5a** (Fig. 1) revealed that the positive torsion angle of C-1-P-1-C-4-C-3 (9°) and negative torsion angle of P-1-C-4-C-3-C-2 (−38°) in the phospholane ring show the ring puckers C-3-*exo* (above the plane) and as C-2-*endo* (below the plane). The C-3 atom is displaced by +0.427Å from the best possible four-atom mean square plane of C-4-P-1-C-1-C-2, and C-2 is displaced by −0.421 Å from the best possible four-atom mean square plane of C-1-P-1-C-4-C-3, supporting the existence of $^3T_2$ (C-3-*exo* and C-2-*endo*) *twist envelope conformer* for phospholane ring in the solid state (Fig. 2). On the other hand, the substitution of O by P in the hemiacetal ring caused several changes in the geometry and conformation of the five-membered ring. The C-1-P-1-C-4 bond angle of the phospha sugar was observed as 93°, as compared to the 110° of C-1-O-C-4 in ribofuranose and 93.5° of C-1-S-C-4 in thia sugar.

In conclusion, we have successfully prepared several tetrofuranose analogs of phospha sugars in good to high yields via simple reaction methods for the first time. Preliminary studies on some of these compounds revealed considerable bioactivity. Detailed bioactive studies are currently under investigation and will be reported in due course.

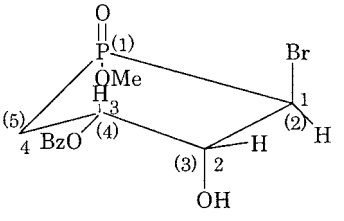


Figure 2. Favoured conformer $^3T_2$) of the phospholane ring of **5a**, based on crystal structure analysis. Numbers correspond to carbohydrate nomenclature while those within the parentheses correspond to heterocyclic nomenclature.

EXPERIMENTAL

General methods

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography was performed by using 0.2 mm coated silica gel plates. Column chromatography was performed on silica gel Wako gel C-200 using appropriate mixture of solvents as an eluent. ^{1}H and ^{13}C-NMR spectral data were recorded on JEOL JNM-300 MHz Spectrometer at 300.40 MHz (^{1}H) at 75.0 MHz (^{13}C) and JEOL JNM-400 at 399.65 MHz (^{1}H). ^{31}P-NMR spectra were recorded on JEOL JNM EX-90 at 36.16 MHz and mass spectral data on Kompact MALDI-TOF MS, using α-cyano-4-hydroxycinnamic acid as a matrix. NMR sample solutions were prepared in $CDCL_3$ using TMS as an internal standard and H_3PO_4 as an external standard for ^{31}P-NMR. Chemical shift value (δ) is expressed in ppm. X-ray crystallographic studies were measured on a Rigaku AFC7R diffractometer with graphite monochromated CuKα radiation and a rotating anode generator.

1-Methoxy-2-phospholene 1-oxide (**1**) was prepared by the reported procedure via the cycloaddition of PCl_3 and 1,3-butadiene.[8]

Typical Experimental Procedures

4-Bromo-1-methoxy-2-phospholene 1-oxide (**2a**): 1-Methoxy-2-phospholene 1-oxide **1** (6.61 g, 0.05 mol) was dissolved in chloroform (20 mL), suspended *N*-bromosuccinimide (10.74 g, 0.06 mol), and catalytic amount of AIBN and refluxed under nitrogen atmosphere for 8 hr. The reaction mixture was left overnight at room temperature and insoluble material was filtered off. The organic layer was washed with saturated sodium hydrogencarbonate solution (2 × 10 mL), followed by water and dried; solvent was evaporated. The crude product was purified on silica gel column chromatography using ethyl acetate-*n*-hexane (10 : 1) as an eluent to give 4-bromo-1-methoxy-2-phospholene 1-oxide (**2a**) a 5.05 g, 48% yield.

^{1}H-NMR ($CDCl_3$, 300.40 MHz): δ 2.27–2.41 (m, 2H, H-5), 2.57–2.78 (m, 2H, H-5′), 3.77 (d, $^2J_{PH}$ = 17 Hz, 3H, OCH_3), 3.81 (d, $^2J_{PH}$ = 17 Hz, 3H, OCH_3′), 4.90–5.09 (m, 2H, H-4, 4′), 6.30 (ddt, $^3J_{PH}$ = 20, 9 and 2 Hz, 2H, H-3, 3′), 7.03 (ddt, $^2J_{PH}$ = 57, 8 and 2 Hz, 2H, H-2, 2′); ^{13}C-NMR ($CDCl_3$, 75.0 MHz): δ 31.88, 32.67, 41.21, 41.48, 52.10, 52.19, 125.15, 125.38, 151.70, 152.05; ^{31}P-NMR ($CDCl_3$, H_3PO_4, 36.18 MHz): δ 65.9 and 67.8; MS (m/z): 209.72 (M^+) for $C_5H_8BrO_2P$.

4-Benzoyloxy-1-methoxy-2-phospholene 1-oxides (**3a**,**b**): 4-Bromo-1-methoxy-2-phospholene 1-oxide (**2a**, 2.11 g, 0.01 mol) was dissolved in dry CH_3CN (25 mL), and sodium benzoate (1.72 g, 0.012 mol) was suspended and refluxed for 2 days. The insoluble material was filtered off and the solvent was evaporated. The residue was taken into chloroform (50 mL), washed with water (2 × 10 mL), and dried over anhydrous sodium sulfate. The solvent was removed and purified on silica gel column chromatography using ethyl acetate-*n*-hexane (10 : 1) as an eluent.

Compound **3a**: mp 131–133°C. ^{1}H-NMR ($CDCl_3$, 399.65 MHz): δ 1.97–2.06 (td, J_{HH}, $^2J_{PH}$ = 15.9, 3.6 and 2.8 Hz, 1H, H-5), 2.56–2.65 (ddd, J_{HH}, $^2J_{PH}$ = 15.9, 7.6 and 3.5 Hz, 1H, H-5), 3.81 (d, $^2J_{PH}$ = 11.6 Hz, 3H, OCH_3), 6.02–6.08 (m, 1H, H-4), 6.43–6.50 (ddd, $^3J_{PH}$ = 20.4, 8.8 and 1.2 Hz, 1H, H-3), 6.97–7.13 (dd, $^2J_{PH}$ = 50.8, 8.8 and

2.8 Hz, 1H, H-2), 7.43–8.03 (m, 5H, Ph); ^{31}P-NMR ($CDCl_3$, H_3PO_4, 36.18 MHz): δ 67.28; MS (m/z): 252.01 (M^+) for $C_{12}H_{13}O_4P$.

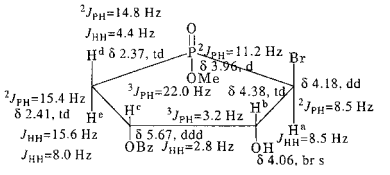
Compound **3b**: mp 102–104°C. ^{1}H-NMR ($CDCl_3$, 399.65 MHz): δ 1.99–2.08 (td, $^2J_{PH} = 15.7$, 3.4 and 2.9 Hz, 1H, H-5), 2.65–2.74 (ddd, $^2J_{PH} = 15.8$, 7.9 and 3.2 Hz, 1H, H-5), 3.77 (d, $^2J_{PH} = 11.6$ Hz, 3H, OCH_3), 5.93–5.99 (m, 1H, H-4), 6.42–6.50 (ddd, $^3J_{PH} = 20$, 8.8 and 2.0 Hz, 1H, H-3), 6.97–7.13 (dd, $^2J_{PH} = 51.6$, 8.8 and 2.0 Hz, 1H, H-2), 7.44–8.04 (m, 5H, Ph); ^{31}P-NMR ($CDCl_3$, H_3PO_4, 36.18 MHz): δ 66.12; MS (m/z): 252.03 (M^+) for $C_{12}H_{13}O_4P$.

1,2-Anhydro-3-*O*-benzoyl-4-deoxy-1,4-*C*-(methoxyphosphinylidene)-β-D-*glycero*-tetrofuranose (or) 4-Benzoyloxy-2,3-epoxy-1-methoxyphospholane 1-oxides (**4a**,**b**): To a stirred solution of 4-benzoyloxy-2-phospholene oxide (0.552 g, 2.0 mmol) in EtOH (20 mL) was added sodium peroxide (0.32 g, 4 mmol). The resulting suspension was allowed to warm up to 45°C and stirred vigorously for 30–40 min at 45°C until the sodium peroxide was dissolved in ethanol; stirring was continued for an additional 4 hr at 30–40°C. The progress of the reaction was monitored by TLC analysis. Then the reaction mixture was cooled to room temperature and neutralized with 0.01 N HCl. The solvents were evaporated under vacuum. The solid residue was dissolved in $CHCl_3$ (20 mL), and the insoluble material was filtered off. The filtrate was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using ethyl acetate-*n*-hexane-methanol (20 : 1 : 1) as an eluent to give pure compounds **5a** and **5b** as a colorless solids. Mp of **4a**: 142–144°C and **4b**: 156–158°C.

Compound **4a**: ^{1}H NMR ($CDCl_3$, 300.40 MHz): δ 2.66 (dt, $^2J_{PH} = 19.1$ Hz, $J_{HH} = 15.1$ Hz and 9.0 Hz, 1H, H-5), 2.86 (dt, $^2J_{PH} = 6.2$, $J_{HH} = 15.2$ Hz and 6.3 Hz, 1H, H-5′), 3.79–3.72 (m, 1H, H-3), 3.84 (d, $^2J_{PH} = 11.4$ Hz, 3H, OCH_3), 4.22 (dd, $^2J_{PH} = 25.1$, $J_{HH} = 2.2$ Hz, H-2), 5.62 (ddd, $^3J_{PH} = 9.1$ Hz, $J_{HH} = 3.1$, 6.5 and 9.0 Hz, 1H, H-4), 7.48–8.10 (m, 5H, Ph); MS (m/z): 269.07 ($M^+ + H$) for $C_{12}H_{14}O_5P$.

1-Bromo-3-*O*-benzoyl-1,4-dideoxy-1,4-*C*-[(*R,S*)-methoxyphosphinylidene]-α,β-D-*glycero*-tetrofuranose (or) 4-Benzoyloxy-2-bromo-3-hydroxy-1-methoxyphospholane 1-oxides (**5a**, **6b**, and **6b**′): 4-Benzoyloxy-1-methoxy-2-phospholene 1-oxide (0.552 g, 2.0 mmol) was dissolved in 20 mL of water-chloroform (4 : 1) mixture, and 2.0 mL of bromine was added at room temperature and stirred for 3 days. To the stirred solution, saturated solution of Na_2SO_3 (20 mL) was added and stirred for a few minutes. After disappearance of bromine color, chloroform layer was separated and water layer was extracted with chloroform (20 mL × 3); the combined chloroform extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified on silica gel column chromatography using chloroform-methanol (50 : 1) as an eluent. Mp of **5a**: 131–132°C; **6b**: 170–172°C; **6b**′: 164-166°C.

^{1}H NMR ($CDCl_3$, 300.40 MHz) of **5a**.

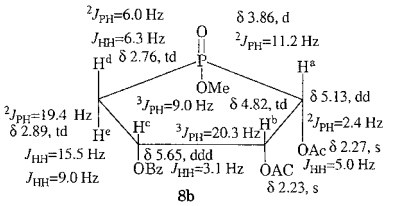


5a

MS of **5a** (m/z): 347.84 (M^+) for $C_{12}H_{14}BrO_5P$.

1,2-*O*-Diacetyl-3-*O*-benzoyl-4-deoxy-1,4-*C*-[(*R*,*S*)-methoxyphosphinylidene]-α,β-D-*glycero*-tetrofuranose (or) 2,3-Diacetoxy-4-benzoyloxy-3-hydroxy-1-methoxy-phospholane 1-oxides (**7a**, **8b** and **8b′**): 4-Benzoyloxy-1-methoxy-2-phospholene 1-oxide (0.552 g, 2.0 mmol), OsO_4 (0.01 g, 0.05 mmol), and $KClO_3$ (0.9 g, 8 mmol) were dissolved in THF (7 mL) and water (15 mL), and the solution was stirred for 24 hr at 40°C. The solvent was removed under vacuum, followed by extraction of the residue with chloroform (20 mL × 2), drying over sodium sulfate, filtering, and concentrating. The resultant crude product was dissolved in dry pyridine (10–15 mL) and acetic anhydride (10 mL) was added. The reaction mixture was stirred at room temperature for 24 hr. Then, chloroform (20 mL) was added to the reaction mixture and the organic phase was washed with water (10 mL × 2). It was dried over sodium sulfate, filtered, and concentrated. The crude products were purified by column chromatography on silica gel using chloroform-methanol (20 : 1) as an eluent to give pure compounds **7a**, **8b**, and **8b′**.

^{1}H NMR ($CDCl_3$, 300.40 MHz) of **8b**.



^{13}C-NMR ($CDCl_3$, 75.0 MHz): δ 20.13, 20.67, 32.52, 52.04, 68.82, 70.31, 71.52, 127.04, 127.72, 148.56, 149.65, 165.41, 169.98, 170.08; MS (m/z): 370.11 (M^+) for $C_{16}H_{19}O_8P$.

Compound **8b′**: ^{1}H-NMR ($CDCl_3$, 300.40 MHz): δ 1.71, 2.08 (2 s, 6H, CH_3CO), 2.37 (td, J_{HH} = 16.12 Hz, 7.33 Hz and $^2J_{PH}$ = 18.78 Hz, 1H, H-5), 3.15 (td,, J_{HH} = 16.12 Hz, 7.82 Hz and $^2J_{PH}$ = 5.37 Hz, 1H, H-5′), 3.79 (d, $^2J_{PH}$ = 12.1 Hz, 3H, OCH_3), 5.66 (dd, J_{HH} = 5.86 Hz and $^2J_{PH}$ = 5.87 Hz, 1H, H-2), 5.74 (ddd, J_{HH} = 8.90 Hz, 7.82 Hz, 7.33 Hz and $^3J_{PH}$ = 7.93 Hz, 1H, H-4), 5.94 (td, J_{HH} = 8.90 Hz, 5.86 Hz and $^3J_{PH}$ = 4.88 Hz, 1H, H-3), 7.46–8.22 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$, 75.0 MHz): δ 19.89, 20.45, 31.80, 53.01, 70.83, 72.19, 72.85, 128.01, 128.79, 148.55, 149.75, 165.67, 168.42, 168.38; MS (m/z): 370.02 (M^+) for $C_{16}H_{19}O_8P$.

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11. Crystal data of **6a**: $C_{12}H_{14}O_5PBr$, $M = 349.12$, colorless, prismatic, $0.30 \times 0.30 \times 0.20$ mm, orthorhombic, $Pna2_1$ (no. 33), $a = 7.016(4)$ Å, $b = 18.560(5)$ Å, $c = 11.003(4)$ Å, $T = 296$ K, Observations $[I > 3.00\sigma(I)] = 847$, Variables = 193, Reflection/Parameter ratio = 4.39, R, $Rw = 0.067$, 0.049. Full crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center. Copies may be requested free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033, or e-mail: deposit@ccdc.cam.ac.uk].
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