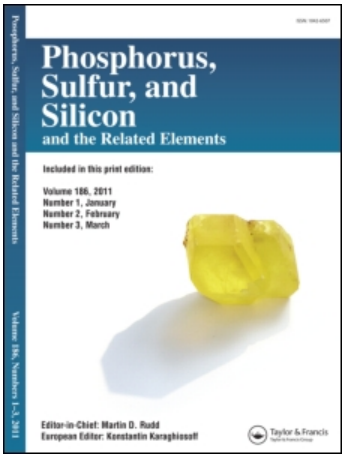



**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# Synthesis and Structure of Novel Glycoside and Nucleoside Derivatives of Phospha Sugar Analogs

Mitsuji Yamashita; Yukihiro Kato; Kazumitsu Suzuki; Tatsuo Oshikawa; Akihito Iida; Putta Mallikarjuna Reddy

**To cite this Article** Yamashita, Mitsuji , Kato, Yukihiro , Suzuki, Kazumitsu , Oshikawa, Tatsuo , Iida, Akihito and Reddy, Putta Mallikarjuna(1999) 'Synthesis and Structure of Novel Glycoside and Nucleoside Derivatives of Phospha Sugar Analogs', Phosphorus, Sulfur, and Silicon and the Related Elements, 144: 1, 641 — 644
**To link to this Article: DOI:** 10.1080/10426509908546326
**URL:** http://dx.doi.org/10.1080/10426509908546326

*Phosphorus, Sulfur and Silicon*, 1999, Vol. 144-146, pp. 641-644
Reprints available directly from the publisher
Photocopying permitted by license only



# Synthesis and Structure of Novel Glycoside and Nucleoside Derivatives of Phospha Sugar Analogs

MITSUJI YAMASHITA, YUKIHIRO KATO, KAZUMITSU SUZUKI, TATSUO OSHIKAWA, AKIHITO IIDA and PUTTA MALLIKARJUNA REDDY

*Department of Materials Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432–8561, Japan*



The synthesis and structure of novel glycoside and nucleoside derivatives of phospha sugar analogs from phospholenes are reported. 1-Phenyl-2-phospholene 1-oxide was regio-and diastereo-selectively converted into a 2-bromo-3-hydroxyphospholane derivative by an action of bromine in aqueous media. The reaction of the 2-bromophospholane derivative with some amines afforded 2-amino derivatives, which were *N*-glycosides of phospha sugar analogs. The 2-bromophospholane derivative was also converted into the corresponding azido derivative by the replacement of the 2-bromo substituent with sodium azide. 1,3-Diploar cycloaddition of the azido derivative with alkynes afforded phospha sugar nucleoside analogs which have a triazole ring as a nitrogen heterocycle.

*Keywords:* Phospha sugar; phospholene; 2-bromophospholane; glycoside; triazole; nucleoside

## INTRODUCTION

Phospha sugars, being one kind of pseudo sugar derivatives having a phosphorus atom in the hemiacetal ring of the sugar. Like aza or thia sugars, whose hemiacetal rings has a nitrogen or a sulfur atom, respectively, phospha sugars have been expected to exert biological activities. Therefore, phospha sugars were of interest in the aspects related to not only syntheses but also structures and biological activities. They were mainly prepared so far from sugar starting materials with suitable protections, functional group interconversions, cyclizations, and deprotections.[1] In our previous paper, we reported the *cis*-dihydroxylation of 2-phospholene 1-oxides with a catalytic amount of osmium(VIII) oxide and co-oxidants.[2] We now report the synthesis and structure of novel glycoside and nucleoside derivatives of phospha sugar analogs from phospholenes.

## RESULTS AND DISCUSSION

Treatment of 1-phenyl- and 1-methoxy-2-phospholene 1-oxides (**1**)[3,4] with bromine or *N*-bromoacetamide (NBA) in aqueous organic solvent afforded regio- and diastereoselectively the *erythro* and *threo* 2-bromo-3-hydroxyphospholane derivatives **2** in good yields. 1-Phenyl-2-phospholene 1-oxide (**1a**) afforded *threo* **2at** (43%, mp 180-183 °C) over *erythro* **2ae** (24%, mp 136-139 °C) diastereoselectively owing to the steric hindrance of phenyl group on the phospholene ring and stability caused by hydrogen bonding of 3-hydroxy group on the phosphoryl oxygen atom.[4]

*threo* 3-Methyl-1-phenyl-2-phospholene 1-oxide (**2bt**, 46%, 150-152 °C) was separated by fractional recrystallization or by column chromatography on silica gel, and the $^{31}$P-NMR ($CDCl_3$) spectrum of *threo* **2bt** showed a single peak at 68.9 ppm. The single crystal prepared from the chloroform solution was analized by X-ray crystallography, whose ORTEP drawing was shown in FIGURE 1(left).

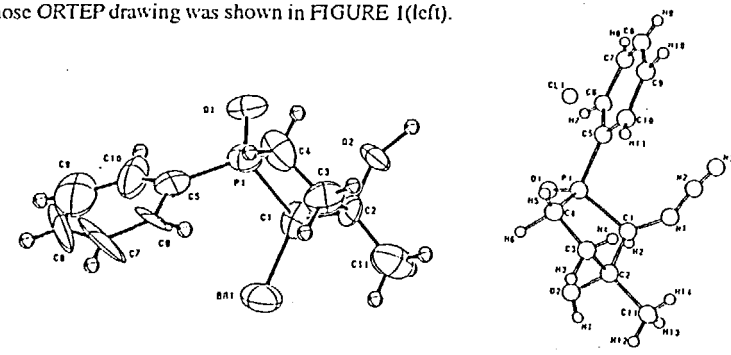


FIGURE 1. ORTEP drawing of *threo* 2-bromo- and 2-azido-3-hydroxy-3-methyl-1-phenyl-2-phospholene 1-oxide (**2bt**, left) and **5bt** (right), respectively).

Reaction of a mixture of *erythro* and *threo* 2-bromo-3-hydroxy-1-phenylphospholane **2ae** and **2at** with triethylamine at room temperature for 1day gave the corresponding *threo* and *erythro* 2,3-epoxyphospholane derivatives **3at** and **3ae**, respectively, in good yields. Treatment of *threo* **2ae** with amines at 40 °C afforded *threo* epoxide **3at** in 84-88% yields, whereas *erythro* **3ae** afforded *erythro* 2-amino-3-hydroxy-1-phenylphospholane 1-oxide (**4ae**) in good yield ($MeNH_2$, 56%; *i*-$PrNH_2$, 75%; *t*-$BuNH_2$, 55%; $Et_2NH$, 80%; $Et_3N$, 100%). $^1$H-NMR ($CDCl_3$) data for **4ae** (tBuNH) are shown in TABLE 1. The coupling constant, $J_{1,2}$=8.3 Hz, shows that the relationship of H-1 and H-2 (carbohydrate numbering) is *trans* diaxial and $J_{1,P}$=4.9 Hz shows that the relationship of H-1 and P=O in the dihedral angle made by H-1-C-1-P=O is *trans*. The conformation of the five membered ring containing the phosphorus ring is $^2$E form, where C-2 atom is out of the plane as shown in FIGURE 2. The configuration of the product, *erythro* 2-*t*-butylaminophospholane **4ae** (*t*-BuNH), sugests that the product was formed via *threo* epoxide **3at**, and the mechanism was confirmed by the reaction of epoxide **3at** with amine giving the same product **4ae**.

*threo* 2-Bromo-3-hydroxy-1-phenylphospholane 1-oxide **2bt** was treated with sodium azide in DMF for 24 h at 70 °C to give colorless crystalline *threo* azido product **5bt**, being *N*-glycoside of phospha sugar derivative. The product analysis was perform-

ed by $^{1}$H-, $^{13}$C-, $^{31}$P-NMR ($CDCl_3$) and IR spectroscopies. $^{1}$H-NMR showed $\delta$ =3.9 ppm for H-1 (carbohydrate numbering) signal being shifted toward higher field than the H-1 signal of the bromo derivative. $^{13}$C-NMR spectrum showed $\delta$ =67.9 ppm for C-1 (carbohydrate numbering) signal being shifted toward lower field. IR spectrum showed typical azido group absorption at 2100 cm$^{-1}$. A single signal at $\delta$ =67.3 ppm was observed by $^{31}$P-NMR. The X-ray single crystallography was successful and the ORTEP drawing was obtained (FIGURE 1, right).

TABLE 1. 500MHz $^{1}$H-NMR ($CDCl_3$) parameters for compound **4ae** (*t*-BuNH).

| Chemical shift ( $\delta$ /ppm) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H-1 | H-2 | H-3 | H-3' | H-4 | H-4' | *t*-Bu | OH | NH | *o*-H | *m*-H | *p*-H |
| 2.82 | 3.97 | 2.47 | 1.78 | 2.33 | 2.05 | 0.92 | 1.86 | 2.98 | 7.75 | 7.50 | 7.53 |
| Coupling constant (*J*/Hz) | | | | | | | | | | | |
| $J_{1,P}$=4.9 | | $J_{2,P}$=5.0 | | $J_{3,P}$=25.0 | | $J_{3',P}$=8 | | $J_{4,P}$=8.0 | | $J_{4',P}$=26 | |
| $J_{1,2}$=8.3 | | $J_{2,3}$=5.0 | | $J_{3,3'}$=13.2 | | $J_{3',4}$=7.8 | | $J_{4,4'}$=16 | | | |
| | | $J_{2,3'}$=9.6 | | $J_{3,4}$=3.6 | | $J_{3',4'}$=11.0 | | | | | |
| | | | | $J_{3,4'}$=8.4 | | | | | | | |

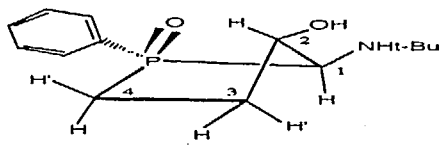
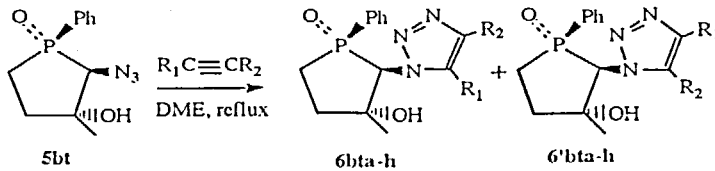



FIGURE 2. Structure of *N*-glycoside **4ae** (*t*-BuNH).

The reaction of *threo* azido derivative **5bt** with alkynes in refluxing DME proceeded to prepare 2-triazoyl derivatives **6bta-h**-**6'bta-h** (SCHEME 1). Symmetrically di-substituted alkynes afforded a single regio isomer, whereas most asymmetrically mono-substituted alkynes gave two regio isomers. Exceptionally asymmetric trimethylsilylacetylene only afforded a sole regio isomer owing to the steric hindrance of the bulky TMS group and the quite large difference of the electron densities between the two acetylenic carbon atoms. The novel triazole derivatives of phospholane 1-oxides correspond to nucleoside analogs of deoxyphospha sugars in their structures. The prepared triazole derivatives are summarized in TABLE 2.




SCHEME 1.

TABLE 2. 1,3-Dipolar cycloaddition of azido derivative **5bt** with alkynes to prepare **6bta-h** and **6'bta-h**.

| $R_1$ | $R_2$ | Reaction time (h) | Product No. | Yield (%) | Ratio of **6** : **6'** |
|---|---|---|---|---|---|
| H | $SiMe_3$ | 12 | **6bta** | 65 | 100 : 0 |
| H | COOMe | 12 | **6btb** + **6'btb** | 67 | 1 : 1 |
| COOMe | COOMe | 18 | **6btc** | 88 | ----- |
| COOEt | COOEt | 24 | **6btd** | 79 | ----- |
| H | $CH_2OH$ | 48 | **6bte** + **6'bte** | 66 | 1 : 1 |
| H | $C(OH)Me_2$ | 96 | **6btf** + **6'btf** | 51 | 3 : 1 |
| $CH_2OH$ | $CH_2OH$ | 72 | **6btg** | 66 | ----- |
| COOH | COOH | 24 | **6bth** | 55 | ----- |

## EXPERIMENTAL

*Synthesis of threo 2-azido-3-hydroxy-3-methyl-1-phenylphospholane 1-oxide (5bt.).* Reaction of *threo* 2-bromo-3-hydroxy-3-methyl-1-phenylphospholane 1-oxide (**2bt**) 1.36 g (4.71 mmol) [5] with sodium azide 0.95 g (12.7 mmol) in DMF (30 ml) for 24 h at 70 °C followed by removal of the solvent under reduced pressure, extraction of the $CHCl_3$ (30 ml) solution of the residue with water (20 ml x 3), and the usual work-up afforded 1.03 g (4.10 mmol) of azido derivative (**5bt**) in 87% yield; mp 174-176 °C. IR (neat) $\nu$ (cm-1), 3150 (OH), 2120 ($N_3$); 31P-NMR ($CDCl_3$) $\delta$ (ppm), 67.29; $^1$H-NMR ($CDCl_3$) $\delta$ (ppm), $J$ (Hz), 1.53 (s, 3H, $CH_3$), 1.6-2.6 (m, 4H, $CH_2$-$CH_2$), 4.00 (d, 1H, $J$=1.98, CH), 5.80 (brs, 1H, OH), 7.4-8.0 (m, 5H, Ph); $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm), $J$ (Hz), 24.24 (d, $J$=7.35, $CH_3$), 26.39 (d, $J$=63.48, C5), 36.23 (d, $J$=4.68, C4), 67.89 (d, $J$=72.84, C2), 78.45 (d, $J$=12.03, C3), 128.60 (d, $J$=11.3, *m*-Ph), 129.24 (d, $J$=93.54, *x*-Ph), 131.54 (d, $J$=9.36, *o*-Ph), 132.61 (d, $J$=2.67, *p*-Ph).

*Synthesis of (1R, 2S, 3R)-3-hydroxy3-methyl-1-phenyl-2-(4'-trimethylsilyl-1'H-1',2',3'-triazo-1'-yl)-phospholane 1-oxide (6bta).* Reaction of *threo* 2-azido compound (**5bt**) 0.300 g (1.19 mmol) with trimethylsilylacetylene 1.17 g (11.9 mmol) in refluxing DME (3 ml) for 24h afforded a precipitation, which was filtrated, washed with DME (5 ml), and dried to give 0.270 g (7.73 mmol) of triazole derivative **6bta** in 65% yield; mp 222 °C. $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm), 70.39; $^1$H-NMR ($CDCl_3$) $\delta$ (ppm), $J$ (Hz), 0.12 (s, 9H, $SiMe_3$), 1.46 (s, 3H, Me), 2.3-3.3 (m, 4H, $CH_2$-$CH_2$), 5.31 (d, 1H, $J$=9.48, CH), 6.36 (brs, 1H, OH), 7.2-7.7 (m, 5H, Ph), 7.34 (s, 1H, triazole-H); $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm), $J$ (Hz), 0.00 (s, $SiMe_3$), 23.98 (d, $J$=6.68, $CH_3$), 25.24 (d, $J$=62.83, C5), 37.98 (d, $J$=4.00, C4), 68.93 (d, $J$=68.84, C2), 79.73 (d, $J$=16.71, C3), 127.88 (d, $J$=92.89, *x*-Ph), 128.00 (d, $J$=11.86, *m*-Ph), 130.85, 145.74 (triazole C4', C5'), 130.93 (d, $J$=10.01, *o*-Ph), 132.37 (d, $J$=2.67, *p*-Ph).

## *References*


[1] M. Yamashita, M. Yamada, M. Sugiura, H. Nomoto, and T. Oshikawa, *Nippon Kagaku Kaishi*, 1207 (1987).

[2] M. Yamashita, M. Uchimura, A. Iida, L. Parkanayi, and J. Clardy, *J. Chem. Soc., Chem. Commun.*, 569 (1988).

[3] O. Korpium, R. A. Lewis, J. Chickos, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4842 (1968).

[4] M. Yamashita, A. Iida, H. Mizuno, Y. Miyamoto, T. Morishita, N. Sata, K. Kiguchi, A. Yabui and T. Oshikawa, *Heteroatom Chem.*, **4**, 553 (1993), and references cited therein.

[5] K. Ikai, A. Iida, and M. Yamashita, *Synthesis*, **595** (1989).