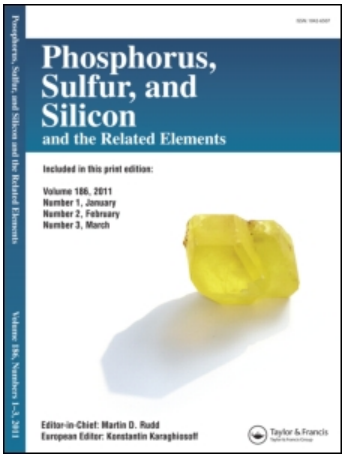


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

PREPARATION OF A NOVEL NON-NATURAL PHOSPHONO SUGAR NUCLEOSIDE DERIVATIVE

Mitsuji Yamashita[a]; Koichi Ikai[a]; Chihiro Takahashi[a]; Tatsuo Oshikawa[a]
[a] Department of Applied Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu, Japan

To cite this Article Yamashita, Mitsuji , Ikai, Koichi , Takahashi, Chihiro and Oshikawa, Tatsuo(1993) 'PREPARATION OF A NOVEL NON-NATURAL PHOSPHONO SUGAR NUCLEOSIDE DERIVATIVE', Phosphorus, Sulfur, and Silicon and the Related Elements, 79: 1, 293 — 296
To link to this Article: DOI: 10.1080/10426509308034421
URL: http://dx.doi.org/10.1080/10426509308034421

Phosphorus, Sulfur, and Silicon, 1993, Vol. 79, pp. 293–296
Reprints available directly from the publisher
Photocopying permitted by license only

Communication

PREPARATION OF A NOVEL NON-NATURAL PHOSPHONO SUGAR NUCLEOSIDE DERIVATIVE

MITSUJI YAMASHITA,† KOICHI IKAI, CHIHIRO TAKAHASHI, and TATSUO OSHIKAWA

Department of Applied Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432, Japan

(Received February 19, 1992; in final form January 16, 1993)

Reaction of 2-bromo-3-hydroxy-1-methoxy-3-methylphospholane 1-oxide with silylated 2-hydroxypyridine gave a novel non-natural phosphono sugar nucleoside derivative.

Key words: Phosphono sugar; 2-phospholene 1-oxide; phospholane 1-oxide; 2-trimethylsilyloxypyridine; nucleoside.

INTRODUCTION

Hetero sugar nucleosides are important, because they are expected to have biological and physiological activities as do sugar nucleosides such as AZT, puromycin, breomycin, and 2′,3′-dideoxycytidine.[1,2] Hetero sugar nucleosides synthesized thus far, such as 1-(2-deoxy-4-thio-α-D-*erythro*-pentofuranosyl)-5-fluorouracil and (±)-aristeromycin, show interesting biological properties.[3,4]

On the other hand, the syntheses of phosphono sugar nucleosides have not been reported possibly because the phosphono sugars prepared until now employed as starting materials carbohydrates which are difficult to transform into the phosphono sugar nucleosides. We previously reported the preparation of phosphono sugar derivatives from 2-bromo-3-hydroxy-1-phenylphospholane 1-oxide.[5] In this paper, we describe the novel synthesis of a phosphono sugar nucleoside from a phospholane derivative by a nucleophilic substitution reaction with silylated 2-hydroxypyridine.

RESULTS AND DISCUSSION

The starting material, 1-methoxy-3-methyl-2-phospholene 1-oxide (**1**), was prepared as described earlier.[6] Reaction of compound **1** with *N*-bromoacetamide (NBA) gave pure 2-bromo-3-hydroxy-1-methoxy-3-methylphospholane 1-oxide (**2**) (25%) after recrystallization from chloroform-carbon tetrachloride (the ratio of diastereomers was 3:10). 2(1*H*)-Pyridinone was silylated using hexamethyldisilazane as trimethylsilylating (TMS) reagent to afford 2-trimethylsilyloxypyridine (**3**) in 98% yield.[7]

The reaction of bromohydrin **2** with silylated compound **3** in the presence of a

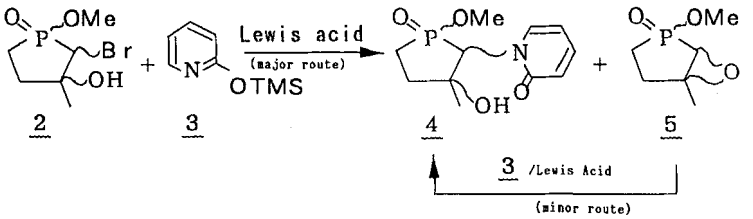
Lewis acid such as tin(IV) chloride or boron trifluoride ether complex afforded the phosphono sugar nucleoside **4**, 1-(3-hydroxy-1-methoxy-3-methylphospholane 1-oxido)-1,2-dihydroxypyridine-2-one, in a yield of 4.4–62% depending on the solvent and the catalyst used (Table I) with simultaneous formation of epoxide **5** (Scheme 1).

Epoxide **5** was also prepared by treatment of 2-phospholene **1** with m-chloroperbenzoic acid (mCPBA) in 30% yield. Opening of the epoxide ring of compound **5** with silylated compound **3** in the presence of 0.5 eq. of boron trifluoride ether complex in refluxing acetonitrile for 48 h gave the same product **4** in 15% yield (Scheme 2). This shows that major route to nucleoside **4** is the direct substitution reaction of bromohydrin **2** with nucleophile **3** and the minor one is opening the ring of epoxide **5** with **3** (Scheme 1).

TABLE I

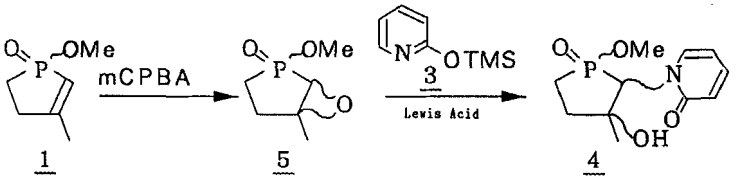
Preparation of phosphono sugar nucleoside **4** by reaction of **2** with **3** in acetonitrile for 24 h in the presence of Lewis acid

Solvent	Lewis acid/eq.	Yield (%)
$ClCH_2CH_2Cl$	$SnCl_4$/0.1	4.4
DMF	$SnCl_4$/0.1	11.0
CH_3CN	$SnCl_4$/0.1	21.5
CH_3CN	$SnCl_4$/0.5	28.0
CH_3CN	$BF_3 \cdot OEt_2$/0.5	62.0



2 3 4 5

SCHEME 1 Preparation of phosphono sugar nucleoside **4** from bromohydrin **2**.



1 5 4

SCHEME 2 Preparation of phosphono sugar nucleoside **4** via epoxide **5**.

EXPERIMENTAL

^{1}H-NMR spectra were recorded with a Hitachi R-24B (60 MHz) and/or a JEOL EX-90 (89.45 MHz) spectrometers using TMS as an internal standard (δ = 0). ^{31}P-NMR spectra were measured on a JEOL EX-90 (36.10 MHz) spectrometer, and IR spectra on a Japan Spectroscopic Co., Ltd. A-3 IR spectrophotometer.

2-Bromo-3-hydroxy-1-methoxy-3-methylphospholane 1-oxide (**2**). NBA[8] (13.3 g, 69.6 mmol) was added to a solution of 1-methoxy-3-methyl-2-phospholene 1-oxide (**1**, 10.2 g, 69.6 mmol) in THF (15 ml) and water (60 ml). The mixture was stirred for 24–36 h at room temperature. The solvent was evaporated *in vacuo*, and the residue was taken up in $CHCl_3$ (45 ml); the $CHCl_3$ layer was dried (Na_2SO_4) and evaporated. Addition of CCl_4 to the residue gave crystals, which upon recrystallization from $CHCl_3$-CCl_4, afforded pure **2** (4.29 g, 25% yield); mp 108.5–111.5°C; ^{1}H-NMR ($CDCl_3$/TMS/δ): 1.50 (s, 3 H, CH_3), 1.7–2.5 (m, 4 H, P—CH_2—CH_2), 3.7–4.0 (m, 4 H, P—OCH_3, P—CHBr), 3.85–4.5 (bs, 1 H, OH); ^{31}P-NMR ($CDCl_3$/P(C_6H_5)$_3$ = 5.60/δ): 74.19, 81.81 (two diastereomers in a ratio of 3:10).

$C_6H_{12}BrO_3P$ calc.: C, 29.65; H, 4.98; P, 12.74%.
(243.0) found: C, 29.38; H, 4.89; P, 12.53%.

Phosphono sugar nucleoside **4** *from bromohydrin* **2**. To a solution of compound **2** (1.46 g, 3.88 mmol) and 2-trimethylsilyloxypyridine (**3**, 1.05 g, 6.28 mmol) in freshly distilled acetonitrile (20 ml) was added a solution of 1.0 M of $SnCl_4$ (2.5 ml, 0.5 eq.) in 1,2-dichloroethane under nitrogen atmosphere at 0°C. The mixture was refluxed for 24 h. The cooled reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and the resulting emulsion was filtered over a layer of Celite. The filtrate was extracted with $CHCl_3$ (20 ml) and the extract was dried and evaporated. The residue was separated by thin layer chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.24) to give compound **4** (0.432 g, 28% yield); syrup; IR (neat/ν/cm^{-1}): 3400 (OH), 1650 (2-pyridone), 1220 (P=O), 1040 (P—O—C); ^{1}H-NMR ($CDCl_3$/TMS/δ): 1.43 (s, 3 H, CH_3), 1.6–2.55 (m, 4 H, P—CH_2—CH_2), 3.68, 3.74 (2 × *d*, 3 H, J_{HCOP} = 10.8 Hz, P—OCH_3), 3.87 (d, 1 H, J_{HCP} = 4.4 Hz, P—CH), 6.1–7.7 (m, 4 H, 2-pyridone); ^{31}P-NMR ($CDCl_3$/P(OCH_3)$_3$ = 140.0/δ): 50.8, 60.8 (two diastereomers).

$C_{11}H_{16}NO_4P$ calc.: C, 51,36; H, 6.27; N, 5.45; P, 12.04%.
(257.2) found: C, 57.07; H, 6.14; N, 4.29; P, 11.95%.

2,3-Epoxy-1-methoxy-3-methylphospholane 1-oxide (**5**). A mixture of phospholene **1** (3.56 g, 24.4 mmol) and mCPBA (5.5 g, 1.3 eq.) in $CHCl_3$ was refluxed for 2 d. The reaction mixture was cooled and insoluble material was filtered off. The filtrate was treated with 10% aqueous $NaHSO_3$ solution (15 ml), neutralized with $NaHCO_3$, and successively the solvent was evaporated. The residue was dissolved in $CHCl_3$ (20 ml), insoluble material was filtered off, and then the solvent was evaporated. The crude product was subjected to silica gel chromatography ($CH_3CO_2C_2H_4$, R_f = 0.32) affording epoxide **5** (1.43 g, 30%); syrup; ^{1}H-NMR ($CDCl_3$/TMS/δ): 1.38 (s, 3 H, CH_3), 1.1–2.8 (m, 4 H, P—CH_2—CH_2), 2.92 (d, 1 H, J_{HCP} = 27.0 Hz, P—CH), 3.70 (d, 3 H, J_{HCOP} = 10.8 Hz, $POCH_3$).

$C_6H_{11}O_3P$ calc.: C, 44.45; H, 6.84; P, 19.10%.
(162.1) found: C, 44.19; H, 6.73; P, 10.01%.

Phosphono sugar nucleoside **4** *from epoxide* **5**. To an anhydrous acetonitrile (15 ml) solution of epoxide **5** (0.496 g, 3.09 mmol) and nucleophile **3** (0.52 g, 3.11 mmol) was added boron trifluoride ether complex (0.2 ml, 0.5 eq.), and the mixture was refluxed under nitrogen atmosphere for 48 h. The same work-up as that of the reaction of **2** with **3** gave the same product **4** (0.12 g, 15% yield).

ACKNOWLEDGMENTS

This work was partially supported by Grants-in-Aid for Scientific Research (No. 04304049) from the Japanese Ministry of Education, Science and Culture.

REFERENCES AND NOTES

1. J. F. Kennedy and C. A. White, *Biocative Carbohydrates: in Chemistry, Biochemistry and Biology* (John Wiley & Sons, New York, 1983), Chap. 12.

2. C. Kibayashi and M. Akiba, *Organic Chemistry for Life Science* (Sankyou Shuppan, Tokyo, 1988), pp. 162–169.
3. Y.-L. Fu and M. Bobek, *Nucleic Acid Chemistry*, Part 1 (John Wiley & Sons, New York, 1978), p. 317.
4. Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, **88,** 3885 (1966).
5. K. Ikai, A. Iida, and M. Yamashita, *Synthesis*, 595 (1989).
6. L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33,** 1034 (1968).
7. H. Aoyama, Y. Kusayanagi, M. Yotsuji, I. Kitayama, T. Yamaguchi, and T. Kodama, *Nippon Kagaku Kai Shi*, 1765 (1986).
8. D. G. Smith and D. J. H. Smith, *Tetrahedron Lett.*, 1249 (1973).