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Preparation and Structure of Phosphono Sugar *N*-Glycosides

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Treatment of 1-phenyl-2-phospholene 1-oxide with *N*-bromoacetamide or bromine afforded *threo* and *erythro* bromohydrins, the latter being converted into novel *N*-glycosides by reaction with amines. The *N*-*t*-butyl phosphono sugar glycoside exists in the ^{2}E conformation.

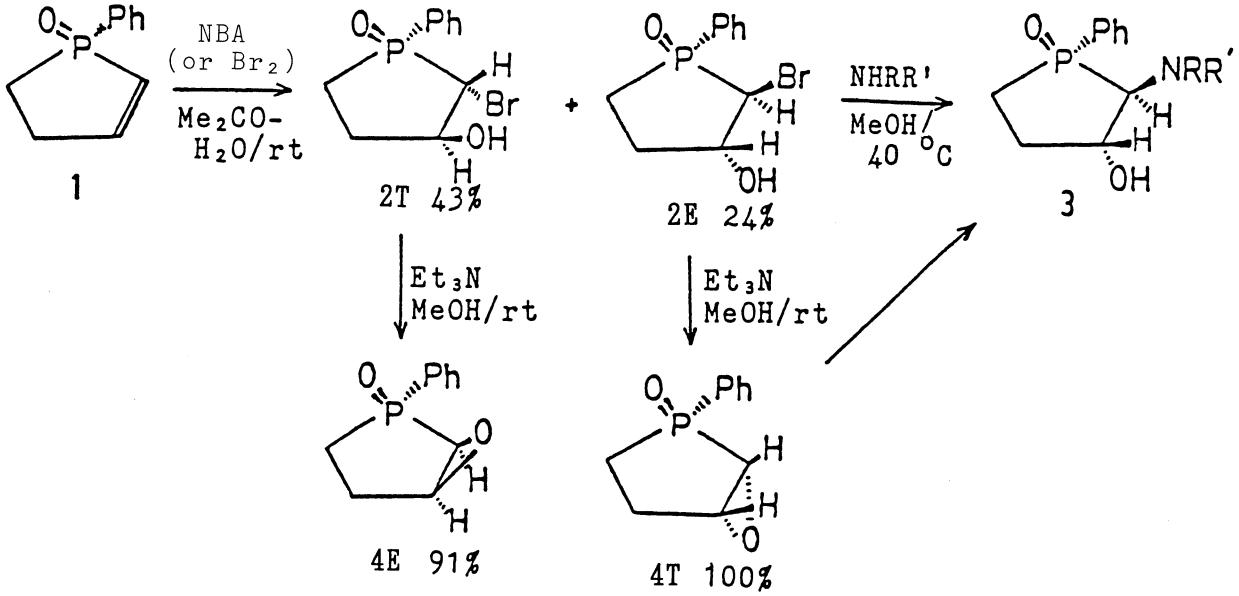
Among a class of hetero sugars, sugar derivatives having a hetero atom in the hemiacetal ring, phosphono sugars are of interest in the aspects related not only to syntheses but also biological activities.[1-4] Most phosphono sugars so far reported have been prepared by starting with sugar materials, whose transformation usually requires many synthetic steps.[2-5] In our preceding paper, we reported synthesis of 3-deoxy-2-*C*-methyl-1,4-*C*-(phenylphosphinylidene)-α-L-*glycero*-tetrofuranose from 3-methyl-1-phenyl-2-phospholene 1-oxide and revealed that phospholenes are potentially useful starting materials for the purpose of preparation of phosphono sugars.[6] It is known that *O*- and *N*-glycosides exist widely and play important biological roles in nature.[7] Nucleosides such as azidothimidine (AZT), which is a useful anti HIV agent with an N_3 substituent on the sugar moiety of the nucleoside,[8] are also biologically important substances. Thus, preparations of sugar derivatives such as glycosides and nucleosides are an interesting field in the hetero sugar chemistry as in the carbohydrate chemistry.[9] This letter deals with a novel synthesis and the structure of phosphono sugar *N*-glycosides.

1-Phenyl-2-phospholene 1-oxide (1) was converted into *threo* and *erythro* 2-bromo-3-hydroxy-1-phenylphospholane 1-oxides (2T and 2E, respectively)[10] by treatment with *N*-bromoacetamide (NBA) or bromine in aqueous

acetone (or oxolane) at room temperature. Fractional recrystallization of the reaction products from chloroform-carbon tetrachloride afforded 2T (mp 180-183℃, 43% yield) and 2E (mp 136-139℃, 24%).[11]

Reaction of compound 2E with some primary and secondary amines at 40℃ afforded phosphono sugar *N*-glycosides, 2-amino-3-hydroxy-1-phenylphospholane 1-oxides (3a-d) (see Table 1). Upon treatment with triethylamine as well as primary and secondary amines for 2 d at room temperature, compounds 2T and 2E gave the *erythro* and *threo* 2,3-epoxy-1-phenylphospholanes (4E and 4T), respectively (Table 1). Compound 4T was smoothly converted into *erythro* *N*-glycosides 3a-d by the reaction with the primary or secondary amine for 2 d at 40℃ (Scheme 1).

These results indicates that during the direct *N*-glycosilation of 2E double inversions of the configuration took place at the reacting carbon atom center of the phospholane *via* 4T. On the other hand compound 2T afforded 4E, which remained unreacted under the similar reaction conditions. The difference of the reactivity may be attributed to the steric hindrance caused by the phenyl group.



Scheme 1. Preparation of phosphono sugar *N*-glycosides 3a-d.

The structure of 1-*N*-*t*-butyl-3,4-dideoxy-1,4-*C*-((*S*)-phenylphosphinylidene)-β-D-*glycero*-tetrofuranosylamine and its enantiomer was established for phosphono sugar *N*-glycoside 3c by the analysis of its 500 MHz ^{1}H NMR spectrum; see Table 2 for the assignments of all signals. The $J_{1,2}$ (8.3 Hz) shows that C-1—H-1 and C-2—H-2 bonds are diaxial, whereas the small $J_{1,P}$ value (4.9 Hz) indicates a *trans* relationship of C-1—H-1 and P=O

bonds.[12,13] The NMR analysis revealed that *N*-glycoside 3c exists predominantly in the ^2E conformation in solution (Fig. 1).

Table 1. Preparation and properties of compounds 3 and 4

Starting material	Amine	Reaction conditn.[a] Solv.	Temp/℃	Product	R	R'	Mp/℃	Yield/%	NMR[b]	MS[c]
2E	$MeNH_2$	MeOH-H_2O	40	3a	Me	H	Syrup	56	2.76	225
2E	*i*-$PrNH_2$	MeOH	40	3b	*i*-Pr	H	138.5-140	75	2.78	253
2E	*t*-$BuNH_2$	MeOH	40	3c	*t*-Bu	H	184-185	55	2.82	267
2E	Et_2NH	MeOH	40	3d	Et	Et	Syrup	84	2.88	267
2E	Et_3N	Et_3N	Room temp	4T	—	—	Syrup	100	3.36	194
2T	Et_3N	Et_3N	Room temp	4E	—	—	116-118	91	3.39	194

a) The reaction was carried out for 2 d. b) ^1H NMR (60 MHz, TMS, $CDCl_3$): δ value for H-1. c) MS datum (in m/z observed) for molecular ion (M^+).

Table 2. Observed 500 MHz ^1H NMR parameters for compound 3c in $CDCl_3$[a]

Chemical shift (δ)											
H1	H2	H3	H3'	H4	H4'	*t*-Bu	OH	NH	*o*-	*m*-	*p*-
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/Hz			
$J_{1,2}$ = 8.3	$J_{1,P}$ = 4.9		
$J_{2,3'}$ = 9.6	$J_{2,3}$ = 5.0	$J_{2,P}$ = 5.0	
$J_{3,P}$ = 25.0	$J_{3,3'}$ = 13.2	$J_{3,4'}$ = 8.4	$J_{3,4}$ = 3.6
$J_{3',4}$ = 7.8	$J_{3',P} \fallingdotseq$ 8	$J_{3',4'}$ = 11.0	$J_{4,4'} \fallingdotseq$ 16
			$J_{4,P}$ = 8.0
			$J_{4',P} \fallingdotseq$ 26

a) Measured with a Varian VXR-500 instrument (the SC-NMR Lab., Okayama Univ.) at 21 ℃.

Compounds 3a-d are the first derivatives of phosphono sugar *N*-glycosides. We are currently working on the synthesis of phosphono sugar nucleosides.

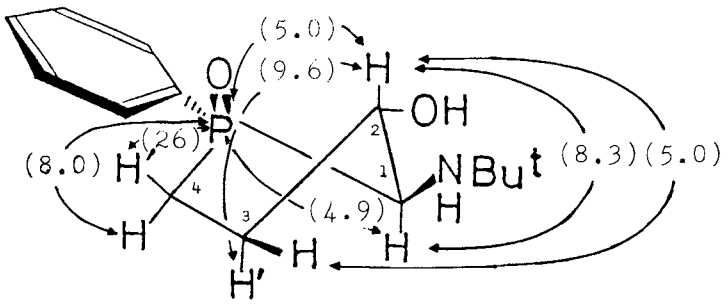


Fig. 1. Structure and favorable conformation of compound 3c. The numerical value in parenthesis shows the coupling constants in Hz.

References

1) H. Yamamoto and S. Inokawa, *Adv. Carbohydr. Chem. Biochem.*, 42, 135 (1984).

2) M. Yamashita, M. Yamada, M. Sugiura, H. Nomoto, and T. Oshikawa, *Nippon Kagaku Kaishi*, 1987, 1207.

3) T. Hanaya, N. Shigetoh, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 61, 2499 (1988).

4) H. Yamamoto, T. Hanaya, H. Kawamoto, and S. Inokawa, *Chem. Lett.*, 1989, 121 and 349.

5) H. Yamamoto and T. Hanaya, "Sugar Analogs Containing Carbon-Phosphorus Bonds," in "Studies in Natural Products Chemistry," ed by Atta-ur-Rahman, Elsevier, Amsterdam (1990), Vol. 6, pp. 351-384.

6) M. Yamashita, M. Uchimura, A. Iida, L. Parkanayi, and J. Clardy, *J. Chem. Soc., Chem. Commun.*, 1988, 569.

7) R. Goto, S. Inokawa, A. Sera, and S. Otani, "Tantourui No Kagaku (Chemistry of Monosaccharides)," Maruzen, Tokyo (1988), pp. 165-182.

8) C. Kibayashi and M. Akiba, "Raifu Saiensu No Yukikagaku (Organic Chemistry for Life Science)," Sankyo Shuppan, Tokyo (1988), p. 168.

9) A. F. Bochkov and G. E. Zaikov, "Chemistry of the O-Glycosidic Bond," Pargamon Press, Oxford (1979), Chap. 2.

10) *Erythro* and *threo* forms are defined on the basis of relative configuration concerning P=O and C-1—Br or C-1—O bonds.

11) The reaction of compound 1 with bromine afforded bromohydrins 2T and 2E in a total yield of 78% [ratio of 2T:2E = 2:1 (HPLC analysis)].

12) H. Yamamoto, Y. Nakamura, H. Kawamoto, S. Inokawa, M. Yamashita, M. A. Armour, and T. T. Nakashima, *Carbohydr. Res.*, 102, 185 (1982).

13) W. R. Purudum and K. D. Berlin, *J. Org. Chem.*, 39, 2904 (1974).

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