DIASTEREO ISOMERIC *erythro* AND *threo* FORMS OF 2,3-EPOXY-1-PHENYLPHOSPHOLANE 1-OXIDES SYNTHESIZED BY AN ACTION OF HYDROGEN PEROXIDE WITH BASE ON 1-PHENYL-2-PHOSPHOLENE 1-OXIDE

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Abstract: Diastereo isomeric *erythro* and *threo* forms of 2,3-epoxy-1-phenylphospholane 1-oxides were synthesized from 1-phenyl-2-phospholene 1-oxide using 30% hydrogen peroxide with NaOH. The selectivity of the diastereo isomers was depended on reaction time and concentration of peroxide and base, and kind of solvents, which controlled the selectivity of the *eyrthro* and *threo* forms.

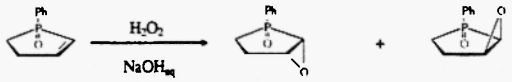
Introduction

Phospha sugar is one of sugar analogs that have a phosphorous atom in place of the ring oxygen atom of normal sugars. Recently, several nucleoside derivatives of sugars, e.g., AZT (1) and Ribavirn (2), are prepared and used as antivirus agents (1,2). In addition to the nucleoside of normal sugars, sugar modified novel nucleoside derivatives of pseudo sugars or hetero sugars such as aza- (3), carba- (4), and thia-sugars (5) have been synthesized and reported. In the present work, we deal with the successful preparative method for formation of the epoxide of 2-phospholene 1-oxide derivatives. 2,3-Epoxy-1-phenylphospholane 1-oxide is an anhydro type phospha sugar derivative and a potential precursor for phospha sugar derivatives. In our laboratory, an efficient method for the stereospecific epoxidation of 2-phospholenes using sodium peroxide as a reagent was developed to make the corresponding epoxide such as 2,3-epoxy-1-phenylphospholane 1-oxide (6). Instead of using sodium peroxide, using 30% hydrogen peroxide and base are less expensive, less harmful to the environment, less dangerous for handling, and more practical than the previous method. The new method of synthesizing diastereo isomeric *erythro* and *threo* forms of 2,3-epoxy-1-phenylphospholane 1-oxides was optimized using hydrogen peroxide with base by different experimental conditions.

Results and Discussion

Scheme 1 shows the epoxidation of 1-phenyl-2-phosopholene 1-oxide (**1**) to prepare 2,3-epoxy-1-phenylphospholane 1-oxide (**2**). The reaction afforded the diastereomeric epoxide mixture of *erythro* **2a**, which was the major product, and *threo* **2b**.

Spectral data of **2a** and **2b** were taken by ^{1}H-NMR and ^{13}C-NMR. The preparation method and NMR data are reported in later experimental section.



1 2a 2b

Scheme 1

Table 1. Synthesis of diastereo isomeric *erythro* and *threo* forms of 2,3-epoxy-1-phenylphospholane 1-oxide under different conditions.

Entry	Reaction Conditions				Products	
	Solvent	H_2O_2 [eq]	NaOH [eq]	Temp. Time	Yield [%]	Ratio of *erythro:threo*
1	Ethanol	40	10	r.t. 1d	8	5 : 3
2	Ethanol	40	10	r.t. 5h	5	2 : 1
3	Ethanol	40	10	r.t. 3d	10	5 : 3
4	Ethanol	40	10	r.t. 6d	40	10 : 7
5	Ethanol	40	10	40°C 1d	45	2 : 1
6	Ethanol	40	0.1	40°C 1d	0	ND[a]
7	Ethanol	40	1	40°C 1d	0	ND[a]
8	Ethanol	40	20	r.t. 1d	1	ND[a]
9	Ethanol	120	10	r.t. 1d	6	2 : 1

a) Not determind

Table 1 shows synthesis of diastereo isomeric *erythro* and *threo* forms of 2,3-epoxy-1-phenylphospholane 1-oxides under different conditions. The selectivity of *erythro* to *threo* was compared and analyzed for each condition. Increased temperature gave a short reaction time and a high selectivity in *erythro* form. The increased concentration on H_2O_2 gave the increased selectivity. The yield was decreased with increasing NaOH concentration. The reaction time was changed from 5 hr to 6 days. The yield was increased with increasing the reaction time, but the selectivity of the *erythro* form was decreased.

Only by using the pure *erythro* form, a further reaction was tested under the same reaction condition for 6 days as shown in Table 1 (entry 4). The results obtained before and after the treatment were shown in Table 2. There was only the *erythro* before the reaction, but the isomerization (by epimerization of *erythro*) was occurred during 6 days. As the result, the selectivity was decreased with increasing of the reaction time, and the reduced *erythro* selectivity was rationalized by epimerization under the reaction conditions.

Table 2. *Erythro* to *threo* ratio of 2,3-epoxy-1-phenylphospholane 1-oxide in the isomerization.

Reaction[a]	Reaction Conditions				Products	
	Solvent	H_2O_2 [eq]	NaOH [eq]	Temp. Time	Yield [%]	Ratio of *erythro:threo*
before	——	——	——	r.t. 0d	——	1 : 0
after	Ethanol	40	10	r.t. 6d	100	10 : 7

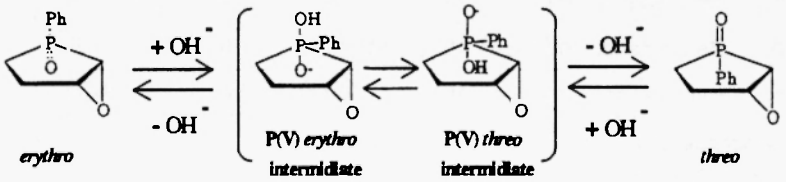
a) Before and after mean the the starting end ending times, respectively, of the treatment.

The condition to suppress the isomerization was determined by changing the reaction medium. Firstly, the relationship of the formed epoxide ratio (*erythro* and *threo*) with epoxidation condition in different alcohol solvents with different polarity was observed. Table 3 shows the results of the product yield and *erythro* to *threo* ratio in the solvent: methanol, ethanol, and isopropanol. The selectivity of *erythro* form in ethanol was higher than the other two. In the order (entry 1, 2, and 3), the molecular size of solvents was increased, and the solvent polarity (7) was decreased; this may attribute the product ratio to facile formation of pentavalent phosphorane P(V)-*erythro* intermediate and also to stabilizing the P(V)-*threo* intermediate to increase *threo* form in highly polarized methanol, which is shown in Scheme 2 (8). As the result, the kind of alcohols have influenced on the result in Table 3.

Table 3. Synthesis of diastereo isomeric *erythro* and *threo* forms of 2,3-epoxy-1-phenylphospholane 1-oxide with changing the alcohol solvent.

		Reaction Conditions					Products	
Entry	Solvent	Formula [a]	ε [b]	NaOH [eq]	Temp.	Time	Yield [%]	Ratio of *erythro*:*threo*
1	Methanol	CH_4O	32.6	10	r.t.	6d	50	10 : 9
2	Ethanol	C_2H_6O	24.3	10	r.t.	6d	41	2 : 1
3	Isopropanol	C_3H_8O	18.3	10	r.t.	6d	23	5 : 3

a) Solvent formula, b) Dielectric constant; see ref. (8)



Scheme 2

Secondly, the relationship with different solvent systems; not only homogeneous but also heterogeneous solution system, were observed: diethylether, tert-butanol, THF, and chloroform. Any of these four solvents, diethylether and tert-butanol gave higher yield and selectivity than the other solvents. In the case of chloroform, *threo* instead of *erythro* became the dominant isomer. The solvent effect is also explained by the less polarity of the solvent causing the predominant formation of *erythro* form and heterogeneous reaction system suppressing the isomerization to *threo* form except chloroform.

Table 4. Synthesis of diastereo isomeric *erythro* and *threo* forms of 2,3-epoxy-1-phenylphospholane 1-oxide with changing the solvent system.

	Reaction conditions						Products	
Entry	Solvent	Formula[a]	ε [b]	Solubility in H_2O[%][c]	NaOH [eq]	Temp. Time	Yield [%]	Ratio of erythro:threo
1	Diethyl ether	$C_4H_{10}O$	4.22	7.5	10	r.t. 6d	47	2 : 1
2	tert-Butanol	$C_4H_{10}O$	12.2	Miscible	10	r.t. 6d	61	2 : 1
3	THF	C_4H_8O	7.4	Solubile	10	r.t. 6d	22	10 : 9
4	Chloroform	$CHCl_3$	4.7	0.82	10	r.t. 6d	26	7 : 10

a) Solvent formula, b) Dielectric constant and c) Solubility in H_2O; see ref. (8)

Thirdly, the effect of different bases on the synthesis of diastereo isomeric *erythro* and *threo* forms was observed and shown in Table 5. The combination of KOH and tert-butanol gave the highest selectivity.

Table 5. Synthesis of diastereo isomeric *erythro* and *threo* forms of 2,3-epoxy-1-phenylphospholane 1-oxide with changing base.

	Reaction conditions				Products	
Entry	Solvent	Base	[eq]	Condition	Yield [%]	Ratio of *erythro:threo*
1	Ethanol	$NaHCO_3$	10	r.t. 6d	0	ND[a]
2	Ethanol	KOH	10	r.t. 6d	70	5 : 3
3	tert-Butanol	KOH	10	r.t. 6d	72	2 : 1
4	tert-Butanol	NaOH	10	r.t. 6d	52	5 : 3
5	tert-Butanol	$NaCO_3$	10	r.t. 6d	0	ND[a]
6	tert-Butanol	$Ca(OH)_2$	10	r.t. 6d	0	ND[a]

a) Not determind

The efficient heterogeneous epoxidation of α,β-unsaturated ketones with hydrogen peroxide using hydrotalcite catalysts under the mild reaction conditions was recommended (9). We tried several hydrotalcite catalysts (1 to 2 equivalents) (10) under the mild reaction condition for the case of preparation of 2,3-epoxy-1-phenylphospholane 1-oxides. However, we did not get any yield of the epoxide product. The catalyst was oxidized by hydrogen peroxide ion, and the formed oxide of the catalyst had no ability to oxidize 2-phospholene **1** because of less oxidizable property caused by less electron density of the C=C double bond with α-phosphoryl group. Therefore, the epoxidation reaction was prevented by the catalyst.

Conclusion

In summary, the present epoxidation procedure was successful in controlling the diasteromer ratio of *erythro* and *threo*

forms of 2,3-epoxy-1-phenylphospholane 1-oxide by convenient and easily handling 30% hydrogen peroxide reagent. To increase the stereospecific epoxidation of 2-phospholenes, we have determined the optimized conditions by changing the epoxidation conditions, i.e., the reaction time, concentration of peroxide and base, and solvent type. The over-all protocol is practical and quite efficient. Further studies on epoxidation, e.g., detailed study on the substituent effect and investigation of the generality of this novel method of epoxidation of 2-phospholenes, as well as nucleophilic substitution reaction of the epoxide to prepare phospha sugar glycosides are currently under investigation in our laboratory (11). By these procedures, *erythro* or *threo* rich epoxide can be produced by changing the experimental conditions.

Experimental

Preparation of 2,3-epoxy-1-phenylphospholane 1-oxide (2) from 1-phenyl-2-phosopholene 1-oxide (1): As our synthetic methods, to 1-phenyl-2-phosopholene 1-oxide (1.0 g , 5.6 mmol) (1) in the mixture of 30 mL of ethanol and 8 mL of 30% hydrogen peroxide was added NaOH aq (15%, 58.5 mmol). The reaction mixture was stirred for 6 days at room temperature. The reaction product was extracted with chloroform from the reaction mixture. Diastereo isomeric *erythro* **2a** and *threo* **2b** forms of 2,3-epoxy-1-phenylphospholane 1-oxide (2) (in scheme 1) were separated by silica gel column chromatography (EtOAc: CH_3OH = 20:1). Tables 6 and 7 show the NMR data of the *erythro* **2a** and *threo* **2b** forms.

Table 6. ^{1}H-NMR data of *erythro* **2a** form of 2,3-epoxy-1-phenylphospholane 1-oxide.

^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
δ (ppm)	δ (ppm)
1.94-2.1 (m, 2H, H-4)	19.49 (d, J=71.35, C-5)
1.94-2.68 (m, 2H, H-5)	24.11 (s, C-4)
3.45 (dd, 1H, J2, P=29.1 Hz,	50.66 (d, J=98.9 Hz, C-2)
J2,3=3.0Hz, H-2)	55.38 (d, J=16.1 Hz, C-3)
3.82-3.86 (m, 1H, H-3)	129.03 (d, J=11.8 Hz, Ph)
7.15-7.76 (m, 5H, Ph)	130.00 (d, J=9.4Hz, Ph)
7.15-7.76 (m, 5H, Ph)	132.61 (d, J=3.1Hz, Ph)

Table 7. ^{1}H-NMR data of *threo* **2b** form of 2,3-epoxy-1-phenylphospholane 1-oxide.

^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
δ (ppm)	δ (ppm)
1.94-2.17 (m, 2H, H-4)	22.48 (d, 70.2Hz, C-5)
1.94-2.68 (m, 2H, H-5)	24.29 (d,2.5Hz, C-4)
3.51(dd, 1H, J2, P=28.7 Hz,	50.60 (d, 102.0Hz, C-2)
J2,3=3.0Hz, H-2)	57.39 (d, J=11.2 Hz, C-3)
3.93-3.96 (m, 1H, H-3)	128.72 (d, JCCP=12.4 Hz, Ph)
8.00-7.51 (m, 5H, Ph)	131.16 (d, JCCCP=10.0Hz, Ph)
	132.60 (d, Jccccp=3.1Hz, Ph)

Rferences and Notes

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(11) For examples, tetrofuranose *N*-glycosides of phospha sugars or 2-amino-3-hydroxy-1-phenylphospholane 1-oxides.

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