Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2339–2341

TETRAHEDRON LETTERS

# An efficient approach towards the stereospecific synthesis of epoxides from phospholene oxides

Mitsuji Yamashita,[a,*] Valluru Krishna Reddy,[b] Lakonda Nagaprasada Rao,[b] Buchammagari Haritha,[c] Motoki Maeda,[c] Keiji Suzuki,[c] Hirono Totsuka,[c] Masaki Takahashi[a] and Tatsuo Oshikawa[d]

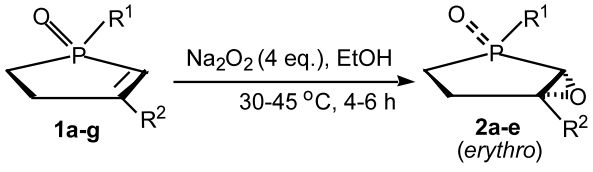
[a]*Department of Materials Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432-8561, Japan*
[b]*Satellite Venture Business Laboratory, Shizuoka University, Hamamatsu 432-8561, Japan*
[c]*Graduate School of Science and Engineering, Shizuoka University, Hamamatsu 432-8561, Japan*
[d]*Department of Chemistry and Biochemistry, Numazu College of Technology (NCT), Numazu 410-8501, Japan*

Received 8 December 2002; revised 24 January 2003; accepted 24 January 2003

**Abstract**—A novel method has been developed for stereospecific conversion of 2-phospholene 1-oxides into their corresponding 2,3-epoxides in high yields using sodium peroxide as a reagent. 

Methods for the epoxidation of olefins are indispensable tools in organic synthesis, in view of the fact that the epoxide obtained can be transformed further into a variety of synthetically useful reactions.[1] Many classical reagents have been reported to date for the epoxidation. However, intensive efforts to develop efficient and reliable protocols for preparing epoxides are required important in organic synthesis. We describe herein an efficient method for the stereospecific epoxidation of 2-phospholenes using sodium peroxide as a reagent. To the best of our knowledge, no method of epoxidation has hitherto been described in the literature using a sodium peroxide reagent, particularly on 2- (or 3-)-phospholene 1-oxides. 2,3-Epoxides of 2-phospholenes are extremely versatile reactive intermediates in the synthesis of various nucleoside analogs of phospha sugar† derivatives that structurally resemble bioactive normal sugar nucleosides, for example AZT,[2] 4′-thio-ddC,[3] aristeromycin,[4] and ribavarin.[5] Our interest in developing potential inhibitors of HIV led us to the synthesis of AZT analogs of phospha sugar derivatives. The epoxidation of 2-phospholene derivatives has been a key step reaction in the synthesis of AZT analogs of phospha sugar derivatives from 2-phospholenes.

Epoxidation using *m*-chloroperbenzoic acid (Prilezhaev reaction) was reported in 1980 by Quin et al.[6] on 2-phospholene oxides which are joined to cycloalkano groups at the *b* face. However, 2-phospholene 1-oxides **1a**–**g** were found to be inert to react with *m*-chloroperbenzoic acid even if the reaction was conducted in a basic medium (2N $NaHCO_3$ solution) at reflux temperature for 3 days. In our previous synthetic methods, the reaction of 1-phenyl-2-phospholene 1-oxide (**1a**) with bromine or *N*-bromoacetamide (NBA) in chloroform–water or acetone–water at room temperature afforded 2-bromo-3-hydroxy-1-phenylphospholane 1-oxide as a diastereomeric mixture. Subsequent treatment of the bromohydrin derivative mixture with aqueous potassium hydroxide at 40–50°C for 1 h afforded a diastereomeric mixture of *erythro* and *threo* 2,3-epoxides.[7,8] We tried the next step of the reaction to synthesize the desired molecule, but the diastereomeric epoxide mixture impeded the stereospecific formation of epoxide. Hence, it is indeed essential to prepare a single 2,3-epoxide isomer of 2-phospholene in order to




**Scheme 1.** Epoxidation of phospholene oxides.

* Corresponding author. Tel./fax: (81)-53-478-1144; e-mail: tcmayama@ipc.shizuoka.ac.jp

† The term 'phospha sugar' strictly denotes either replacement of hemiacetal oxygen, or of C(1), of normal sugar by a phosphorus moiety.

0040-4039/03/$ - see front matter 
doi:10.1016/S0040-4039(03)00255-7

obtain the target AZT analogue of the phospha sugar. To access the formation of a single isomeric 2,3-epoxides from 2-phospholenes in high yields, we treated 2-phospholenes **1a**–**g** with sodium peroxide‡ in ethanol for 4–6 h at 30–45°C.[9] The stereospecifically formed epoxides **2a**–**e** were fairly and exclusively produced in 70–80% yields as outlined in Scheme 1. The best results were obtained using 4 equiv. of the sodium peroxide reagent.

The 2,3-epoxides **2a**–**e** obtained via sodium peroxide oxidation showed only a single peak on the HPLC chromatogram and also in the $^{31}P$ NMR spectrum, revealing the formation of only one isomer, whereas the 2,3-epoxides prepared previously via the bromohydrin pathway showed two peaks on HPLC and in the $^{31}P$ NMR spectrum. On HPLC analysis the major one [i.e. the *erythro*] of these two isomers fit exactly with the single peak that was prepared by sodium peroxide route. Addition of 10% $Eu(DPM)_3$ complex[10] caused a downfield shift of the $^1H$ NMR signals of compounds **2a**–**e**. The stereochemistry of product **2a** was precisely determined from X-ray crystallographic analysis. A single crystal of compound **2a** was developed by recrystallization from ethyl acetate and *n*-hexane; X-ray crystallographic study[11] of compound **2a** afforded its structure as depicted in Figure 1. From the X-ray analysis of compound **2a**, the torsion angles revealed the phosphoryl group (P=O) and epoxide oxygen lie in parallel planes, i.e. the P=O group is in *syn* fashion to the epoxide group of C-1, C-2 and thus it proved to be *erythro* 2,3-epoxy-1-phenylphospholane 1-oxide (**2a**). This protocol was then applied to several substituted 2-phospholenes,[12] and the results are summarized in Table 1.[13,14] The yield of the products is slightly enhanced by the presence of strong electron-withdrawing groups on the phenyl group of substrate **1b**; however, there was no appreciable effect on epoxidation with electron-donating groups on the phenyl ring. From the results obtained in Table 1, it should be pointed out that the epoxidation on substrate **1e** produced 2,3-epoxy-1-hydroxyphospholane 1-oxide **2e** by the conversion of P–OMe to P–OH; however, the selectivity of the reaction remained the same as that of other products obtained. Surprisingly, the 2-phospholenes **1f** and **1g** were not reacted with $Na_2O_2$ to give the corresponding epoxides. The reasons for the substituent effect are being examined after proposing the reaction mechanism and will be reported in due course.

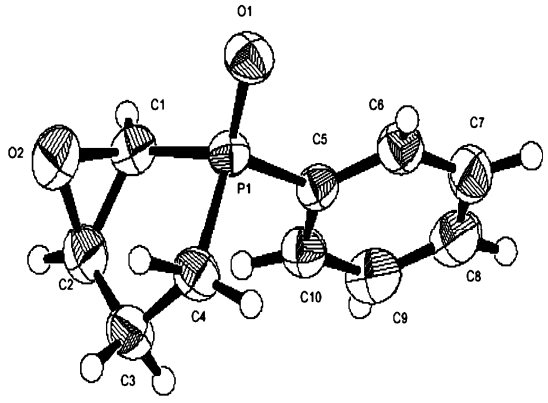



**Figure 1.** The crystal structure of compound **2a**.

In summary, we have found a moderate reagent for stereospecific epoxidation of 2-phospholenes. The overall 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, are currently under investigation in our laboratory.

## Acknowledgements

One of the authors (V.K.R.) is thankful to Satellite Venture Business Laboratory (SVBL), Shizuoka University for financial support.

**Table 1.** Epoxidation of 2-phospholene 1-oxides **1a**–**g** produced in Scheme 1

| Entry | Substrate | $R^1$ | $R^2$ | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **1a** | Ph | H | 5 | 76 |
| 2 | **1b** | $C_6H_4$–$NO_2$ (*m*) | H | 6 | 80 |
| 3 | **1c** | $C_6H_4$–OMe (*p*) | H | 6 | 75 |
| 4 | **1d** | $C_6H_4$–Cl (*m*) | H | 6 | 77 |
| 5 | **1e** | OMe | H | 4 | 70[b,c] |
| 6 | **1f** | Ph | Me | 6 | No epoxidation |
| 7 | **1g** | OMe | Me | 6 | No epoxidation |

[a] Only product **2a** is solid, and other products (**2b**–**e**) are in a syrupy state.[15]
[b] Yield is comparatively low, because nearly 10% of the formed epoxide was converted to enol (1,3-dihydroxy-2-phospholene 1-oxide) formation as a side product.
[c] P–OMe was converted as P–OH during epoxidation.

‡ $Na_2O_2$ is an explosive reagent; therefore, it is noteworthy to comment on the safety of sodium peroxide reagent. It is a precautionary advice to open the reagent container in moisture free conditions since it is a moisture sensitive reagent. However, we have not had any unpleasant events associated with this reagent in our laboratory, although we used a large amount of sodium peroxide for our reactions.

## References


1. For a recent review on epoxide chemistry and reactivity, see: Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149–1163 and references cited therein.
2. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrmann, S. N.; Gallo, R. S.; Bolognes, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 7096–7100.
3. Secrist, J. A., III; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med. Chem.* **1992**, *35*, 533–538.
4. Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885–3887.
5. McCormack, J. B.; Getchell, J. P.; Mitchel, S. W.; Hicks, D. R. *Lancet ii* **1984**, 1367–1369.
6. Quin, L. D.; Symmes, C.; Middlemas, E. D., Jr.; Lawson, H. F. *J. Org. Chem.* **1980**, *45*, 4688–4694.
7. Yamashita, M.; Suzuki, K.; Iida, A.; Ikai, K.; Reddy, P. M.; Oshikawa, T. *J. Carbohydr. Chem.* **1999**, *18*, 915–935.
8. Epoxidation on phospholene oxides using a mixture of hydrogen peroxide and various catalysts is currently under way in our laboratory and the results will be published elsewhere.
9. Monitoring the progression of the reactions by TLC showed that the reactions were proceeding very slowly at below 30°C.
10. For example, see: Yamashita, M.; Uchimura, M.; Iida, A.; Parkayani, L.; Clardy, J. *J. Chem. Soc., Chem. Commun.* **1988**, 569–570.
11. Crystal data for **2a**: $C_{10}H_{11}PO_2$, $M=194.17$, colorless, prismatic, 0.40×0.20×0.70 mm, monoclinic, $P2_1/n$ (#14), $a=9.779(2)$, $b=9.502(2)$, $c=10.703(2)$ Å, $\beta=110.98(1)°$, $V=928.5(3)$ Å$^3$, $Z=4$, $D_{calcd}=1.389$ g/cm$^3$, $F_{000}$, 408.00; $\mu$(CuKα), 23.26 cm$^{-1}$, radiation CuKα ($\lambda=1.54178$ Å), $T=23.0$°C, no. observations = ($I>3.00\sigma(I)$), 1218, no. of variables = 163, reflection/parameter ratio = 7.47, *R*, *Rw*, 0.063, 0.068. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 201197. 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].
12. Phospholene oxides **1a**–**g** were prepared from the reported synthetic methods, see: Krishna Reddy, V.; Onogawa, J. I.; Rao, L. N.; Oshikawa, T.; Takahashi, M.; Yamashita, M. *J. Heterocyclic Chem.* **2002**, *39*, 69–75.
13. The general experimental procedure is as follows for the preparation of compounds **2a**–**e**. Preparation of *erythro* 2,3-epoxy-1-phenylphospholane 1-oxide (**2a**): To a stirred mixture of 1-phenyl-2-phospholene 1-oxide (**1a**, 0.45 g, 2.5 mmol) in EtOH (25 mL) was added sodium peroxide (0.78 g, 10 mmol), then the resulting suspension was allowed to warm up to 45°C, stirred vigorously for 30–40 min at 45°C until the sodium peroxide was dissolved in ethanol, and stirred for an additional 4–5 h 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 0.01N HCl. The solvents were evaporated under reduced pressure. The solid residue was dissolved in $CHCl_3$ (40 mL), and the insoluble material was filtered. The filtrate was dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel using 20:1:1 EtOAc, *n*-hexane and methanol as the eluent, to give product **2a** as a colorless solid. Mp: 113–115°C.
14. Spectral data and chemical shift reagent studies of compounds **2a**, **2b**: Chemical shift reagent studies were carried out using 10, 20, 30, and 40% Eu(DPM)$_3$ [dipivaloylmethanatoeuropium (III)] complex. The best results have been obtained by adding 10 mol% of Eu(DPM)$_3$ complex. The NMR signals were clearly broadened and shifted to down field.
*erythro*-2,3-Epoxy-1-phenylphospholane 1-oxide (**2a**). $^1$H NMR ($CDCl_3$): $\delta$ 7.68–7.43 (m, 5H, Ph), 3.79–3.76 (m, 1H, H-3), 3.37 (dd, 1H, $J_{HH}=3.2$ Hz and $J_{PH}=29.3$ Hz, H-2), 2.60–1.87 (m, 4H, H-4,5); $^{13}$C NMR ($CDCl_3$): $\delta$ 132.65 (d, $J=3.3$ Hz, C-2,6 of P-Ph), 129.58 (d, $J=11.4$ Hz, C-3,5 of P-Ph), 130.25 (C-4 of P-Ph), 128.82 (d, $J=92.1$ Hz, C-1 of P-Ph), 55.4 (d, $J=16.1$ Hz, C-3), 50.68 (d, $J=99.4$ Hz, C-2), 24.16 (s, C-4), 19.49 (d, $J=71.8$ Hz, C-5); $^{31}$P NMR ($CDCl_3$, $H_3PO_4$): $\delta$ 49.23. MS (*m*/*z*): 195 ($M^+$+H). IR (KBr): $\nu$ (cm$^{-1}$) 2962 (C–H of epoxide), 1271 and 828 (epoxide), 1185 (P=O). $^1$H NMR ($CDCl_3$) of **2a** with 10% Eu(DPM)$_3$ complex: $\delta$ 7.89–7.50 (2br s, 5H, Ph), 3.90 (br s, 1H, H-3), 3.61 (d, 1H, $J=29.7$ Hz, H-2), 2.66–2.16 (m, 4H, H-4,5).
*erythro*-2,3-Epoxy-1-*m*-nitrophenylphospholane 1-oxide (**2b**): $^1$H NMR ($CDCl_3$): $\delta$ 8.88–7.63 (m, 4H, Ph), 4.26 (dd, 1H, $J_{HH}=2.4$ Hz and $J_{PH}=25.2$ Hz, H-2), 3.62–3.40 (m, 1H, H-3), 2.40–1.23 (m, 4H, H-4,5); $^{13}$C NMR ($CDCl_3$): $\delta$ 137.65 (d, $J=91.3$ Hz, *x*-Ph), 126.28 (d, $J=12.4$ Hz, *o*-Ph, *o*-$NO_2$), 148.25 (d, $J=14.3$ Hz, *x*-$NO_2$), 127.82 (s, *p*-Ph, *o*-$NO_2$), 129.29 (d, $J=11.3$ Hz, *m*-Ph, *m*-$NO_2$), 136.52 (d, $J=9.4$ Hz, *o*-Ph, *p*-$NO_2$), 54.41 (d, $J=14.1$ Hz, C-3), 50.68 (d, $J=99.4$ Hz, C-2), 28.45 (s, C-4), 20.87 (d, $J=66.8$ Hz, C-5); $^{31}$P NMR ($CDCl_3$, $H_3PO_4$): $\delta$ 63.69; MS (*m*/*z*): 240 ($M^+$+H); IR (neat): $\nu$ (cm$^{-1}$) 2974 (C–H of epoxide), 1529 and 1349 ($NO_2$), 1261 and 813 (epoxide), 1178 (P=O). $^1$H NMR ($CDCl_3$) of **2b** with 10% Eu(DPM)$_3$ complex: $\delta$ 9.85–8.22 (3br s, 4H, Ph), 5.01 (d, 1H, $J=25.7$ Hz, H-2), 4.00 (br s, 1H, H-3), 2.86–2.20 (m, 4H, H-4,5).
15. All compounds **2a**–**e** were fully characterized by $^1$H, $^{13}$C NMR (300 MHz), $^{31}$P NMR (90 MHz), mass, and IR spectral analyses. The stereochemistry of other products **2b**–**e** was assigned by chemical shift reagent studies, crystallographic analogy of compound **2a** and also based on other similar compounds reported in the literature: see, Ref. 6.