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DIASTEREOSELECTIVE SYNTHESIS OF 2,3-EPOXYALKYLPHOSPHONATES AND PHOSPHINATES BY EPOXIDATION

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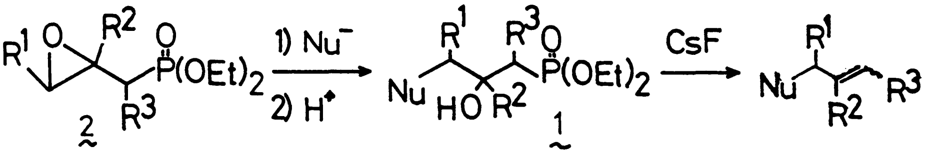
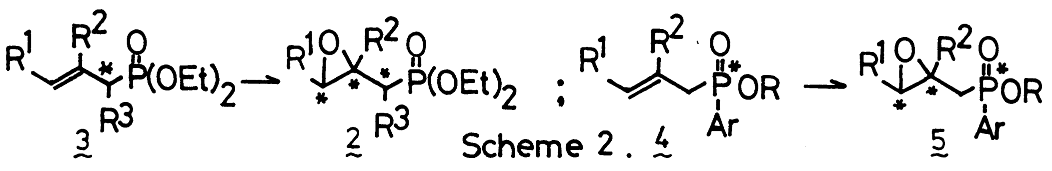
The title compounds were prepared highly diastereoselectively by treatment of 2-alkenylphosphonates and phosphinates with m-chloroperbenzoic acid or MoO_5·HMPA complex in good yields.

In a previous paper,[1)] we have reported new synthetic route to 2-hydroxyalkylphosphoryl compounds (**1**) from 2,3-epoxyalkylphosphoryl derivatives (**2**) and nucleophiles. These 2-hydroxyalkylphosphoryl compounds (**1**) are converted to the corresponding olefins in moderate to good yields by cesium fluoride induced reaction developed by us [1,2)] (Scheme 1). In the case of $R^3 \neq H$, the resulting olefins are usually obtained as a mixture of E- and Z-isomers. When pure E- or Z-olefin is desired, a diastereomer mixture of **1** must be separated by chromatography, recrystallization, and so on. But if **2** can be prepared in a highly diastereoselective manner, it is not necessary to separate diastereomers of **1**.



Scheme 1.

We now report on diastereoselective epoxidation of 2-alkenylphosphonates (**3**) with two oxidizing reagents.[3)] In the process of this investigation, a possibility of 1,3-asymmetric induction controlled by a chiral center on a phosphorus atom was also studied using racemic 2-alkenylarylphosphinates (**4**)(Scheme 2).



Scheme 2.

Diethyl 1-substituted 2-alkenylphosphonates (**3**) were treated with m-chloroperbenzoic acid (MCPBA) in methanol-free dichloromethane to yield a diastereomer mixture of the corresponding 2,3-epoxyalkylphosphonates (erythro- and threo-**2**) in good or high yields. The diastereomer ratio was determined by ^{31}P NMR and ^{13}C NMR spectroscopies. The results are shown in Table 1.

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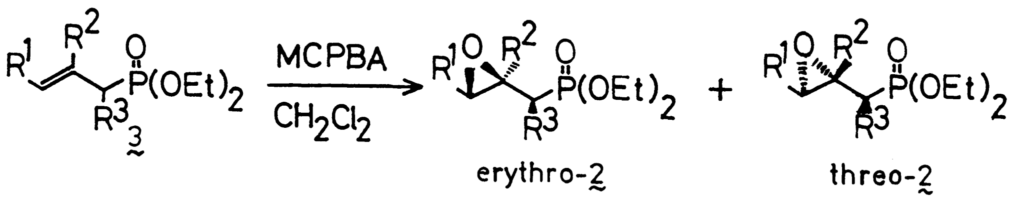
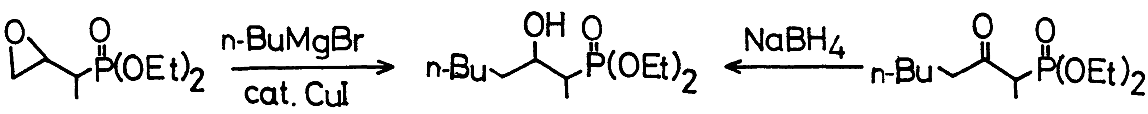


Table 1. Epoxidation of **3** with MCPBA

3	R^1	R^2	R^3	Temp /$^\circ$C	2	Yield/%	Diastereomer Ratio (erythro:threo)
a	H	H	Me	rt	a	94	69:31
b	H	Me	Me	0	b	87	69:31
c	H	Me	Et	rt	c	100	72:28
d	Me	H	Me	rt	d	85	73:27 (from E-**3d**)
							>96: 4 (from Z-**3d**)
e	Me	H	Et	0	e	89	72:28 (from E-**3e**)
							88:12 (from Z-**3e**)
f	Me	H	PhCH$_2$	rt	f	95	76:24 (from E-**3f**)
							77:23 (from Z-**3f**)
g$^{a)}$	H	Me	PhCH(OH)	rt	g	59	84:16
h$^{a)}$	Me	H	PhCH(OH)	rt	h	87	88:12 (from E-**3h**)
							>96: 4 (from Z-**3h**)

a) Diastereomer ratios of these hydroxyphosphonates were >95:5.

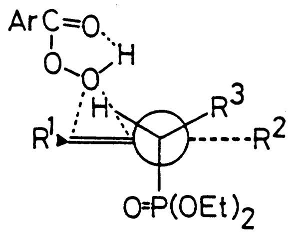
Diastereomer ratio was more than about 70:30 in all cases and the temperature-dependence was observed as usual.$^{4)}$ Especially Z-2-butenyl phosphonates series showed higher diastereoselectivity than others. Z-1-Methyl-2-butenylphosphonate (Z-**3d**) exhibited the highest selectivity and the minor diastereomer from Z-**3d** could not be detected by ^{31}P NMR and ^{13}C NMR spectroscopies, indicating the diastereomer ratio of more than 96:4. The exact stereochemistry of the major epoxide was determined to be erythro by comparison of the diastereomer mixture of diethyl 2-hydroxy-1-methylheptylphosphonate prepared by the reaction of **2a** with butylmagnesium bromide in the presence of a catalytic amount of CuI$^{1)}$ with the threo predominant mixture obtained by reduction of diethyl 1-methyl-2-oxoheptylphosphonate with sodium borohydride.$^{5)}$



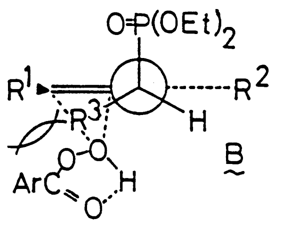
According to these experimental data, the present high diastereoselectivity can be reasonably explained as follows: In the transition state, unexpectedly peracid molecule does not interact with the oxygen atom of phosphoryl group and two transition states **A** and **B** would be imagined. This model is similar to the Felkin's model.$^{6)}$ In the present case peracid molecule approaches to the double bond from the reverse side of the phosphoryl group as shown in **A** and **B**. In the transition state **B**, a large steric repulsion would exist between Z-substituent R^1 and substituent R^3 adjacent to phosphoryl group, but in the transition state **A** this repulsion no longer exists. Consequently epoxidation would proceed predominantly through the transition state **A** to produce mainly erythro isomer. When the bulkiness of both R^1 and R^3 increases at the same time, the steric repulsion between R^2 and R^3 could not be ignored and the decrease of diastereoselectivity would be presumed (see **2e** and **2f** in Table 1). In the case of 2-alkenylphosphonate (**3**) without any Z-substituents, such a higher selectivity would not be observed because of the absence of the steric repulsion between R^1 and R^3 in **B**, which was supported experimentally (**3a-c** and E-**3d-f** in Table 1). Reactions using **3g** and **3h** were more diastereoselective than others, because these compounds are considered as homoallyl alcohols,[7)] which are well known to be oxidized diastereoselectively by treatment with MCPBA or other oxidants.[8)]

Table 2. Epoxidation of **3** with MoO_5·HMPA

3	2	Yield/%	Diastereomer Ratio (erythro:threo)
b	b	61	75:25
d	d	31	95: 5 (from E-**3d**)
			>96: 4 (from Z-**3d**)
e	e	79	93: 7 (from E-**3e**)
			88:12 (from Z-**3e**)
f	f	65	95: 5 (from E-**3f**)
			>96: 4 (from Z-**3f**)



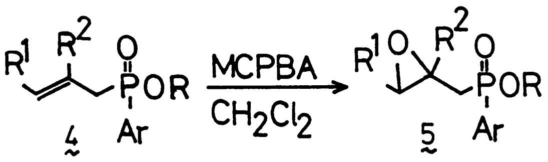
A

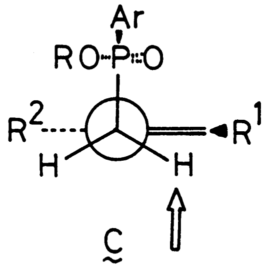


B

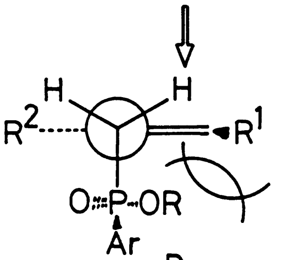
Treatment of **3** with anhydrous molybdenum pentoxide hexamethylphosphoramide complex (MoO_5·HMPA) yielded **2** with a higher diastereoselectivity in refluxing dichloromethane. The major diastereomer was the same as that in the case of MCPBA. The results are summarized in Table 2. Such a high diastereoselectivity appeared in the present system can be illustrated as follows: MoO_5·HMPA complex has HMPA as a ligand on a metal, so that it is reasonable to expect an existence of a strong affinity between this metal and phosphoryl group. Therefore, the phosphonate coordinates instead of HMPA to interact more tightly with oxidant. Thus the transition state would be influenced by steric effect more than in the case of MCPBA. The transition metal-catalyzed epoxidation using t-butyl hydroperoxide was also applied to **3**, but the use of titanium tetraisopropoxide or vanadyloxy acetylacetonate as a catalyst did not afford any epoxides.[7)]

In order to investigate 1,3-asymmetric induction based on chirality on a phosphorus atom, we also treated alkyl 2-alkenylarylphosphinates (**4**) with MCPBA in dichloromethane. The results are summarized in Table 3. Z-Butenyl derivatives afford the corresponding epoxides more diastereoselectively than others. The use of 1-naphthyl group as an aryl moiety gave better results. Although the exact stereochemistry of the major diastereomer has not be determined yet, it can be presumed from consideration by molecular model that the reaction would proceed via the transition state **C** rather than the transition state **D**, which has large steric repulsion between Z-methyl group and an alkoxyl group.





C



D

Table 3. Epoxidation of 2-Alkenylarylphosphinates (**4**)

4	R^1	R^2	R	Ar	**5**	Yield/%	Diastereomer Ratio
a	Me	H	Et	o-Anisyl	a	80	53:47 (from E-**4a**)
							73:27 (from Z-**4a**)
b	Me	H	Et	1-Naphthyl	b	91	72:28 (from E-**4b**)
							77:23 (from Z-**4b**)
c	Me	H	Me	1-Naphthyl	c	62	57:43 (from E-**4c**)
							>96: 4 (from Z-**4c**)

The present investigation seems to be very important in the following points: (1) Through highly diastereoselective formation of epoxyalkylphosphonate pure Z-olefin could be obtained, and (2) 1,3-asymmetric induction based on a chiral center on a phosphorus atom could be shown experimentally.

References

1) T. Nagase, T. Kawashima, and N. Inamoto, Chem. Lett., 1984, 1997.

2) T. Kawashima, T. Ishii, and N. Inamoto, Chem. Lett., 1983, 1375.

3) Very recently, McElroy and Warren reported independently on the diastereoselective synthesis of 2,3-epoxyalkylphosphine oxides by the reaction of the corresponding 2,3-alkenylphosphine oxides with MCPBA; A. B. McElroy and S. Warren, Tetrahedron Lett., 26, 2119 (1985).

4) For example, when the epoxidation of **3e** was carried out at room temperature diastereomer ratios (erythro:threo) were 67:33 (from E-**3e**) and 84:16 (from Z-**3e**).

5) For 2-oxoalkylphosphonic diamides, see: E. J. Corey and G. T. Kwiatkowski, J. Am. Chem. Soc., 88, 5653 (1966). For 2-oxoalkyldiphenylphosphine oxides, see: A. D. Buss, R. Mason, and S. Warren, Tetrahedron Lett., 24, 5293 (1983).

6) M. Chérest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199.

7) Similar results were observed by McElroy and Warren, see: Ref. 3.

8) K. B. Sharpless and T. R. Verhoeven, Aldrichimica Acta, 12, 62 (1979).

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