

COOPERATIVE EFFECT BY A HYDROXY AND ETHER OXYGEN
IN EPOXIDATION WITH A PERACID

Mark R. Johnson and Yoshito Kishi*

Department of Chemistry, Harvard University
12 Oxford Street, Cambridge, MA 02138

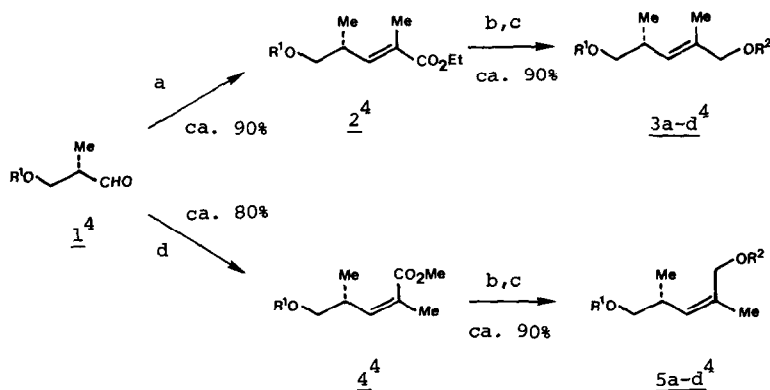
Abstract: Examples are given for a cooperative effect by a hydroxy group and ether oxygen in directing the steric course of epoxidation with m-chloroperbenzoic acid.

In 1957 Henbest and Wilson¹ reported their studies on epoxidation with perbenzoic acid of cyclohexene derivatives bearing various allylic substituents. Although 3-methoxy- and 3-acetoxycyclohexene gave predominantly the trans epoxide, 3-hydroxycyclohexene yielded mainly the cis epoxide at a significantly faster rate. In 1973 Sharpless and Michaelson² published a useful, highly stereoselective method to epoxidize allylic and homoallylic alcohols using transition metal catalysts. Related to the synthesis of various antibiotics,³ we have recently observed a unique cooperative effect by a hydroxyl group and ether oxygen in directing the steric course of epoxidation with a peracid.

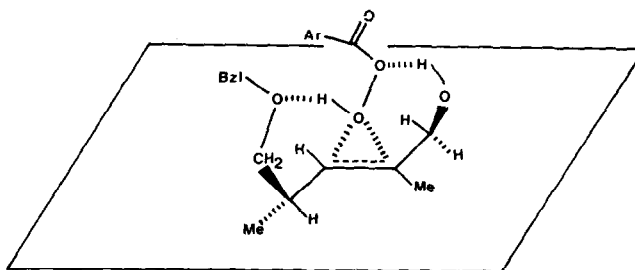
Trans and cis allylic alcohol derivatives 3a-d⁴ and 5a-d⁴ were stereoselectively synthesized from the suitably protected aldehyde 1, which is readily available in racemic and optically active forms.⁵ Geometric purity of 3a-d and 5a-d was insured by carefully removing the minor cis and trans esters produced in the Wittig processes, i.e., steps a and d⁶, by silica gel chromatography.⁷

The results of epoxidation of the trans allylic alcohol derivatives 3a-d are summarized in the following table. The stereoselectivity observed for 3a and 3b and non-stereoselectivity for 3d are expected, judging from the known examples.⁸ Again, the low degree of stereoselectivity for 3c under the Sharpless procedure is anticipated based on the proposed mechanism for the oxidation.⁹ Epoxidation of 3c with m-chloroperbenzoic acid (MCPBA) in methylene chloride at 0°C gave the epoxide 6c as the only observed product, the stereochemistry of which corresponds to that of the major product from 3a and 3b.¹⁰ The observed stereoselective epoxidation of 3c is unique, for superficially the ether oxygen near the asymmetric center directs the steric course of the incoming peracid. This result is not consistent with the previous observations made by Henbest¹ and others.⁸ One possible rationalization for this might be the cooperative effect by the hydroxy group and ether oxygen; namely the most preferred conformation of 3c in the transition state would be A,^{3, 11} with which m-chloroperbenzoic acid could be complexed nicely by two hydrogen bonds as indicated.¹² In preliminary experiments it was noticed that the rate of epoxidation of 3c with MCPBA is faster than that of 3d, but similar to that of 3b.

Scheme



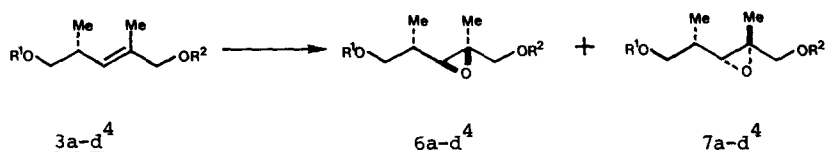
Reagents: a. $\text{CH}_3\text{C}(\text{P}(\text{C}_6\text{H}_5)_3)\text{CO}_2\text{Et}/\text{C}_6\text{H}_6/\text{reflux}$, b. $\text{LiAlH}_4/\text{Et}_2\text{O}/0^\circ\text{C}$, c. protection or deprotection if necessary, d. $\text{CH}_3\text{C}(\text{PO}(\text{OMe})_2)\text{CO}_2\text{Me}/\text{NaH}/\text{THF}/-78 \rightarrow 0^\circ\text{C}$.⁶

A

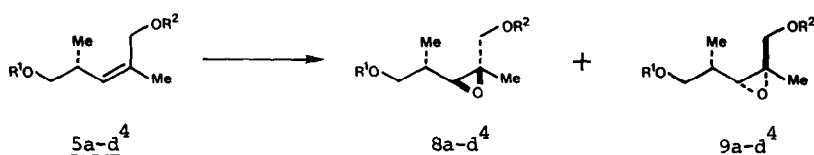
The results of epoxidation of the corresponding cis allylic alcohol derivatives **5a-d** are summarized in the following table. These data are parallel with those observed for the trans series.

These results together with those reported in the previous paper³ and others from our laboratories indicate this cooperative effect seems to be general, and useful in solving many synthetic problems.

Table



	R^1	R^2	Ratios* (6 : 7)	
			MCPBA/ $\text{CH}_2\text{Cl}_2/0^\circ\text{C}$	$t\text{-BuO}_2\text{H}/\text{VO}(\text{acac})_2/\text{C}_6\text{H}_6/\text{RT}$
<u>a</u>	H	H	>25 : 1	>25 : 1
<u>b</u>	H	$\text{C}_6\text{H}_5\text{CH}_2$	6 : 1	>25 : 1
<u>c</u>	$\text{C}_6\text{H}_5\text{CH}_2$	H	>25 : 1	4 : 3
<u>d</u>	$\text{C}_6\text{H}_5\text{CH}_2$	$\text{C}_6\text{H}_5\text{CH}_2$	1 : 1***	**



	R^1	R^2	Ratios* (8 : 9)	
			MCPBA/ $\text{CH}_2\text{Cl}_2/0^\circ\text{C}$	$t\text{-BuO}_2\text{H}/\text{VO}(\text{acac})_2/\text{C}_6\text{H}_6/\text{RT}$
<u>a</u>	H	H	4 : 1	5 : 1
<u>b</u>	H	$\text{C}_6\text{H}_5\text{CH}_2$	7 : 1	>25 : 1
<u>c</u>	$\text{C}_6\text{H}_5\text{CH}_2$	H	15 : 1	2 : 3
<u>d</u>	$\text{C}_6\text{H}_5\text{CH}_2$	$\text{C}_6\text{H}_5\text{CH}_2$	1 : 1***	**

* Ratios determined from the nmr spectrum of the total reaction mixture.

** The reaction was too slow to measure the ratio.

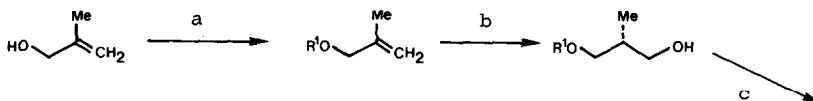
*** The oxidation was achieved at room temperature because of its slowness at 0°C .

Acknowledgment Financial assistance from the National Institutes of Health, National Science Foundation, and the Hoffmann-La Roche Company is gratefully acknowledged.

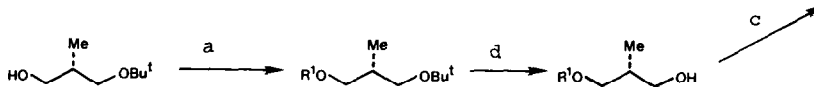
References and Footnotes

1. H. B. Henbest and R. A. L. Wilson, J. Chem. Soc., 1958 (1957).
2. K. B. Sharpless and R. C. Michaelson, J. Am. Chem. Soc., **95**, 6136 (1973).
3. M. R. Johnson, T. Nakata, and Y. Kishi, Tetrahedron Lett., 0000 (1979).
4. Satisfactory spectroscopic data (ms, nmr, ir) were obtained for this substance.
5. Racemic and optically active forms of 1 were synthesized as shown below. For starting material of the optically active series, see N. Cohen, W. F. Eichel, R. J. Lopresti, C. Newkom, and G. Saucy, J. Org. Chem., **41**, 3505 (1976).

Racemic series



Optically active series



Reagents: a. protection of the alcoholic group, for example, $\text{C}_6\text{H}_5\text{CH}_2\text{Br/KH/THF-DMF/RT}$;

b. $\text{B}_2\text{H}_6/\text{THF}/0^\circ\text{C}$, followed by $\text{H}_2\text{O}_2/\text{aq. NaOH/RT}$;

c. $(\text{COCl})_2/\text{DMSO}/\text{CH}_2\text{Cl}_2/-60^\circ\text{C}$, followed by Et_3N (see A. J. Mancuso, S.-L. Huang, and D. Swern, J. Org. Chem., **43**, 2480 (1978)).

d. $\text{TFA}/0^\circ\text{C}$.

6. See footnote 14 in G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, J. Am. Chem. Soc., **101**, 259 (1979).
7. Stereoselectivity for steps a and d was in the range of 20 : 1.
8. For example, see G. Berti, Topics in Stereochem., **7**, 93 (1975), ed. N. L. A. Allinger and E. L. Eliel.
9. A. O. Chong and K. B. Sharpless, J. Org. Chem., **42**, 1587 (1977).
10. Benzylation ($\text{C}_6\text{H}_5\text{CH}_2\text{Br/KH/THF-DMF}/0^\circ\text{C}$) of 6b and 6c yielded 6d, and debenylation ($\text{H}_2/\text{Pd-C/MeOH}$) gave 6a, which established the correlation of the epoxides 6a-d. Aluminum hydride reduction ($\text{AlH}_3/\text{THF/RT}$) of 6b afforded a mixture of the expected single secondary and tertiary alcohols. The same procedures were applied for the correlation and structure elucidation of the epoxides 8a-d and 9a-d.
11. Picture A corresponds to the enantiomer of 3c.
12. There is an alternative transition state with two hydrogen bonds, one of which is between the hydrogen of the allylic alcohol group and the carbonyl oxygen of the peracid.

(Received in USA 30 July 1979)