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Selective Epoxidation of Chiral 2-Methyl-3,4-unsaturated Aldehyde Acetals

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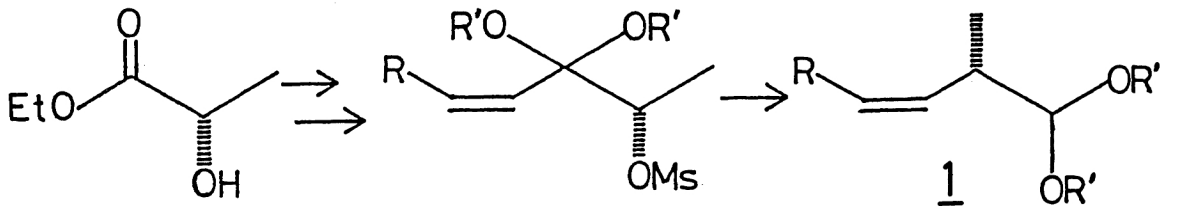
Title compounds were treated with $EtAlCl_2$ or $TiCl_3OPr^i$ and *t*-butyl hydroperoxide (TBHP) at -78 °C, followed by K_2CO_3 to give anti-epoxide, which reacted with $LiAlH_4$ at γ-position.

We have already reported the synthesis of chiral 2-methyl-3,4-unsaturated aldehyde acetals (1) starting from chiral ethyl lactate *via* reductive 1,2-rearrangement mediated by DIBAL and Et_3Al (Eq. 1).[1)]



(1)

The acetals (1) are useful as the bi-functional synthetic blocks utilized widely in stereoselective synthesis of acyclic molecules. Now we wish to report the asymmetric induction in the epoxydation of 1 which will add another entry for the utility of 1. At first, 1 was treated with several known reagents. As the results, both of MCPBA at 0 °C in CH_2Cl_2 and TBHP in the presence of Mo^{6+} under reflux in benzene gave the epoxide as a diastereomeric mixture.

Asymmetric induction in the epoxidation of 2-substituted homoallylic alcohol by V^{5+}/TBHP procedure [2)] has been reported.[3)] The anti selectivity was explained by the steric interactions in a cyclic transition state involving vanadate ester. We assumed that if a metal which activates TBHP coordinates with the oxygen of the acetal without decomposition of 1, anti-epoxide (2) could be obtained *via* a

similar transition state (Fig. 1). Lewis acid has been generally used for activation of the acetal to cause the reductive alkylation or the deprotection. In practice, the treatment of (Z)-acetal (1) with $TiCl_4$ and TBHP in CH_2Cl_2 at -78 °C gave only the chlorohydrin (3) in a 31% yield (Table 1, entry 3). We supposed that it was caused by the decomposition of the oxiran ring of the generated epoxide (2) in the presence of the strong Lewis acid. Thus, the epoxidation of the (Z)-cyclic acetal (1) proceeded by means of decreasing the Lewis acidity of the metal reagents to afford the mixture of the anti-epoxide (2) and the corresponding chlorohydrin (3) (Fig. 2, Table 1). The syn-epoxide could not be detected by HPLC analysis. A typical procedure was as follows: Under an argon atmosphere, TBHP (4-5 equiv.) was added to a 0.1 M solution of 1 (1.0 equiv.) in CH_2Cl_2. Then metal halide was added at -78 °C until 1 disappeared. The reaction mixture was quenched by pyridine, followed by aq. $NaHCO_3$ and Na_2SO_3 (10 equiv.) at 0 °C. The mixture was extracted with diethyl ether and separated by silica gel column chromatography. The chlorohydrin (3) was derived into the epoxide (2) by the treatment with K_2CO_3 (0.3 M) in methanol at room temperature. (E)-Aldehyde cyclic acetals, aldehyde dimethyl acetals, and ketone acetals[4] were decomposed under these conditions.[5] When the substrate had another double bond besides β,γ-double bond, the later was selectively reacted (entries 8,9).

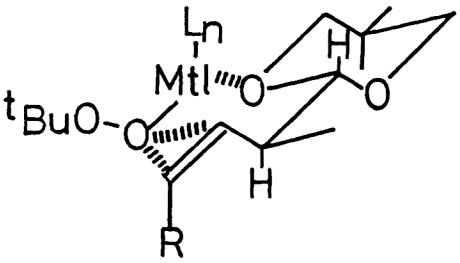


Fig. 1.

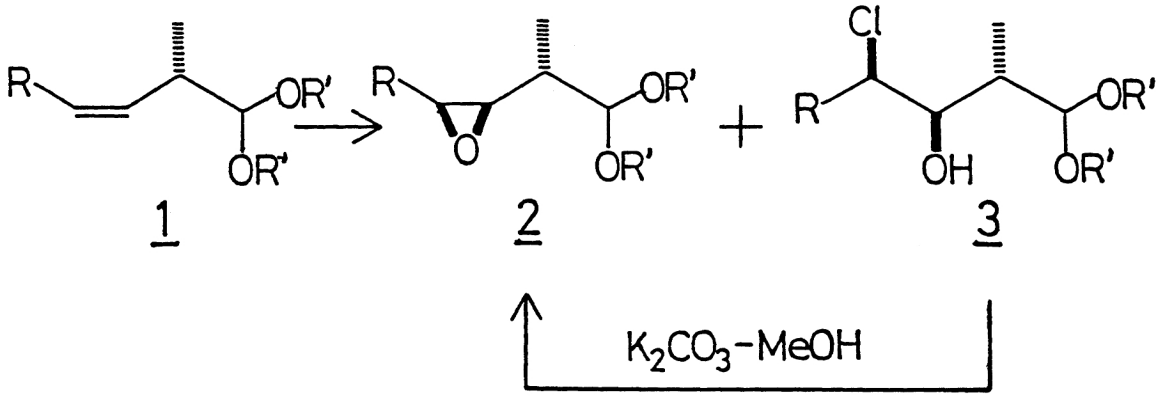


Fig. 2. Epoxidation of the aldehyde acetal (1).

Table 1. Yields of epoxidation of 1 and reduction of 2

Entry	R	R'	Metal halide(equiv.)	2/%	3→2/%	Total/%	4/%
1	Ph		$EtAlCl_2$ (3.0)	63	-	63	94
2	"	"	$TiCl_3OPr^i$ (2.5)[a]	60	-	60	"
3	"		$TiCl_4$ (1.0)	-	(31)[c]	-	-
4	"	"	$EtAlCl_2$ (3.5)	76	-	76	96
5	"	"	$TiCl_4 \cdot OEt_2$ (2.0)[b]	65	15	80	-
6	"	"	$TiCl_3OPr^i$ (2.5)[a]	78	6	84	-
7	Ph	"	" (4.0)[a]	80	4	84	96
8	Ph	"	$EtAlCl_2$ (2.0)	-	-	79	98
9	"	"	$TiCl_{3.25}(OPr^i)_{0.75}$ (2.0)[a]	74	8	82	-

a) $TiCl_n(OPr^i)_{4-n}$ was prepared by mixing $TiCl_4$ (n mol) with $Ti(OPr^i)_4$ (4-n mol) under an argon atmosphere.

b) Diethyl ether was added, and then $TiCl_4$ was added at -78 °C.

c) Yield of the chlorohydrin (3).

The epoxide (2) reacted with $LiAlH_4$ in diethyl ether at γ-position to give the threo aldol equivalent (4) in a quantitative yield (Fig. 3, Table 1). As the applications of these procedures, asymmetric syntheses of natural products are in progress.

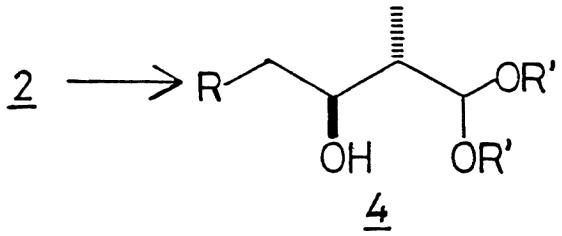


Fig. 3. Reduction of the epoxide (2).

The absolute configuration of anti-epoxide (2) was determined by ^{1}H-NMR[6] of the corresponding cyclic acetal derivative (6), prepared from the acetate (5) by the deprotection, followed by reduction, hydrolysis, and acetalization. The authentic sample was prepared from the homoallyl alcohol (7)[7] by the treatment with V^{5+}/TBHP,[3,8] followed by reduction by DIBAL (4 equiv.) in toluene at room temperature, and acetalization (Fig. 4).

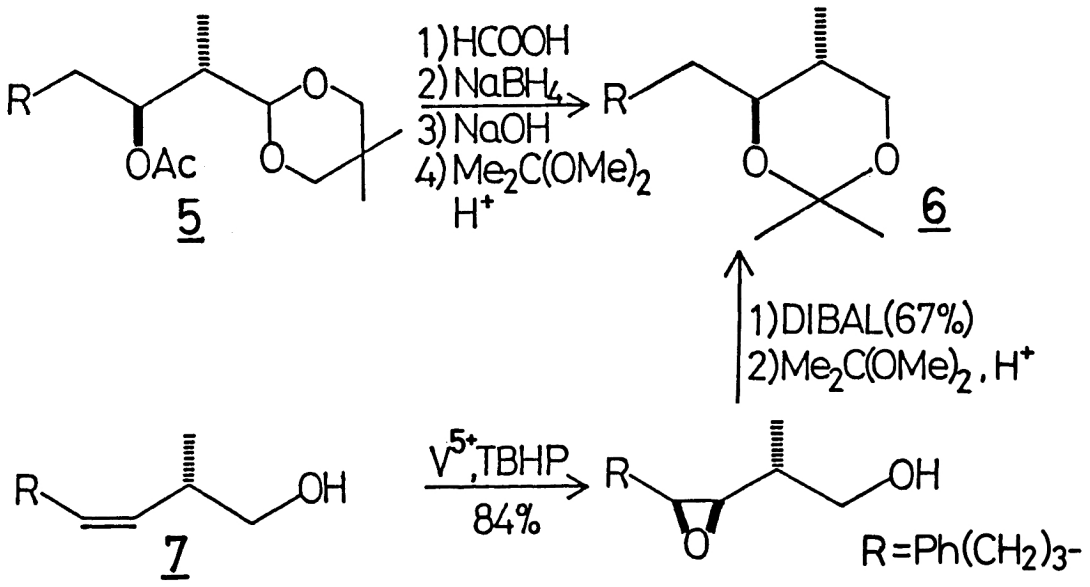


Fig. 4. Determination of the absolute configuretion of the epoxide (2).

References

1) Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, 1985, 1153.

2) K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, 12, 63, (1979).

3) E. D. Miehelich, K. Daniels, and D. J. Eickhoff, *J. Am. Chem. Soc.*, 103, 7690, (1981).

4) Y. Honda, E. Morita, and G. Tsuchihashi, *Chem. Lett.*, 1986, 277.

5) The exchange of the acetal by TBHP mainly occured.

6) 6; ^{1}H-NMR (CCl_4): δ 0.69 (d, 3H, *J*=6.9 Hz), 1.0-1.8 (m, 7H), 1.27 (s, 3H), 1.33 (s, 3H), 2.56 (t, 2H, *J*=7.5 Hz), 3.29 (m, 2H), 3.54 (dd, 1H, *J*=5.6 Hz, *J*=11.3 Hz), 7.08 (s, 5H) ppm.

7) The alcohol (7) was prepared from the corresponding 2-methyl-3,4-unsaturated ester[9] by treatment with $LiAlH_4$ in diethyl ether at room temperature.

8) The corresponding syn-epoxide was not detected by TLC.

9) Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, 1986, 13.

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