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THE STEREOCHEMICAL COURSE OF THE REACTION OF OPTICALLY ACTIVE STYRENE OXIDE WITH ALUMINUM HYDRIDE AND DICHLOROALUMINUM HYDRIDE

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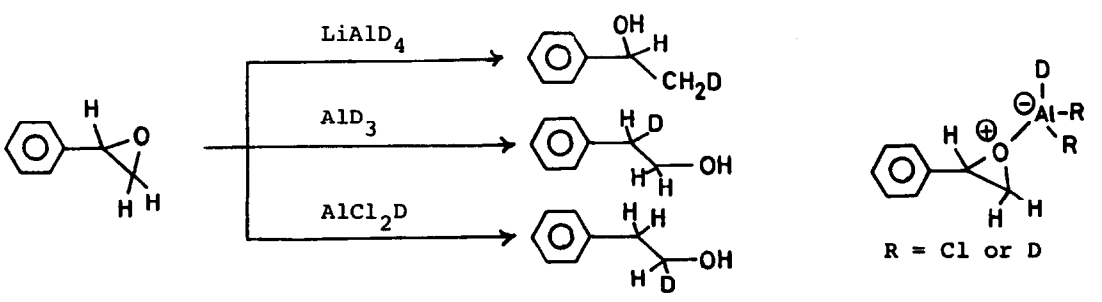
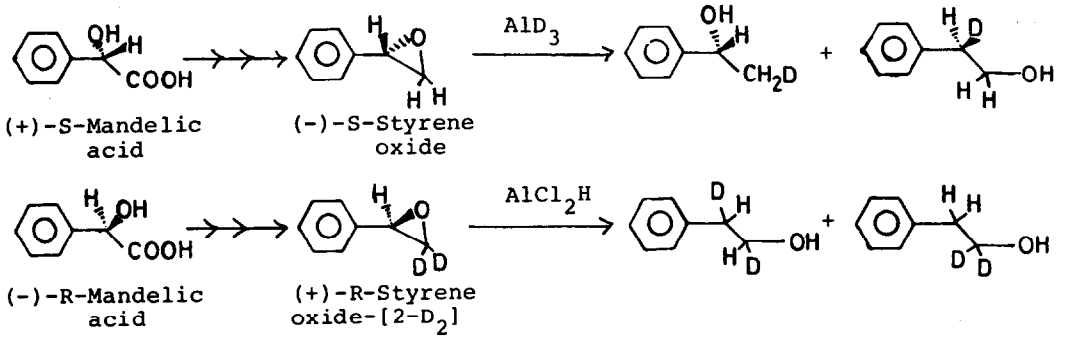
Aluminum hydride(AlH_3) and dichloroaluminum hydride($AlCl_2H$) are reducing reagents conventionally prepared from lithium aluminum hydride($LiAlH_4$) and aluminum chloride, and now widely used for reduction of many functional groups. Eliel has shown that these hydride reagents and $LiAlH_4$ react with unsymmetrical epoxide such as styrene oxide in different ways. In reduction with lithium aluminum deuteride($LiAlD_4$) styrene oxide gave almost exclusively α-phenethyl alcohol carring deuterium at the methyl carbon atom, whereas in reduction with dichloroaluminum deuteride($AlCl_2D$) β-phenethyl alcohol labelled at the carbinol carbon atom was the main product.[1] Contrary to this, reduction of styrene oxide with AlD_3 afforded β-phenethyl alcohol labelled with deuterium at the benzylic methylene.[1] Ashby rationalized these results in terms of initially formed oxide-hydride complex that collapsed with or without prior 1,2-hydride shift.[2] Although the stereochemistry of epoxide reduction with the hydride reagents has



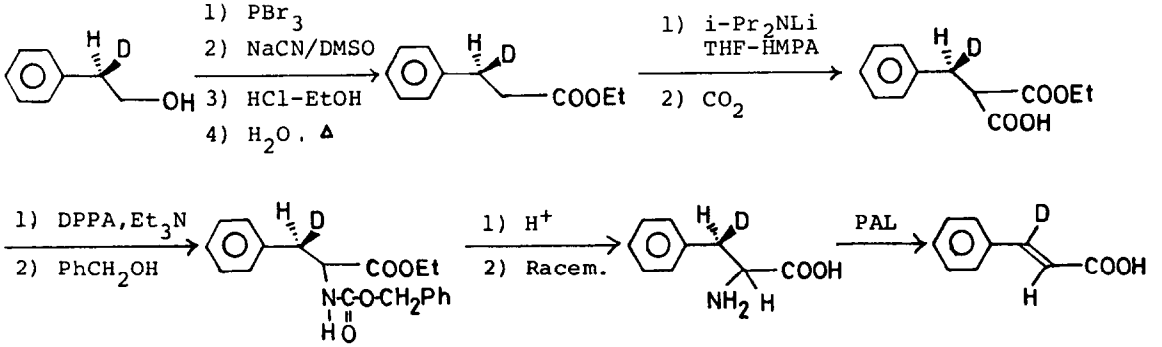
been investigated in cyclopentene and cyclohexene epoxides,[3,4] the results obtained in bicyclic epoxides should inevitably be affected by ring strain and conformational stability. In order to clarify the stereospecificity of the reaction with the hydride reagents in acyclic epoxide and to explore a new method to make chiral labelling at an enantiotopic methylene, we prepared two kinds of optically active styrene oxide from (-)-R- and (+)-S-mandelic acid according to the method of Eliel.[5] (-)-S-Styrene oxide was prepared from (+)-S-mandelic acid. (-)-R-Mandelic acid was converted into (+)-R-styrene oxide-[2-D_2] for the investigation of the reaction involving 1,2-hydride shift. Optical purity of styrene oxide was determined by MTPA(α-methoxy-α-trifluoromethylphenylacetic acid) ester method.[6] α-Phenethyl alcohol obtained on reduction of styrene oxide with $LiAlH_4$ was converted into (-)-MTPA ester and the enantiomeric composition was determined by ^{19}F-NMR[6] and glass capillary GLC. (+)-R-Styrene oxide-[2-D_2] and (-)-S-styrene oxide showed optical purities of 83.6 and 84.0%, respectively and these values are well in accord with that reported.[5]



Reduction of (-)-S-styrene oxide with excess AlD_3 gave a mixture of α-and β-isomers in a ratio of 2:13*, which were separated by preparative GLC and the position and the content of deuterium were determined by NMR and mass spectra. Deuterium was found at the methyl group in α-phenethyl alcohol, whereas β-isomer was labelled at the benzylic methylene. On the other hand, when (+)-R-styrene oxide-[2-D_2] was reduced with $AlCl_2H$, it yielded exclusively β-phenethyl alcohol. The NMR and mass spectral investigation revealed, however, that the product contained 76% of β-phenethyl alcohol-[1-D,2-D] and 24% β-phenethyl alcohol-[1-D_2]. The difference between the results of the experiments with $AlCl_2D$[1] and $AlCl_2H$ may

be attributed to primary isotope effect which effected in lowering the ratio of the 1,2-deuteride shift. The samples of deuterium labelled β-phenethyl alcohol thus obtained were converted into phenylalanine in order to determine the optical purity of chiral methylene group by the action of phenylalanine ammonia lyase(E.4.3.1.5.PAL).[7] Since the enzyme has been known to remove the amino group and 3-*pro* -S hydrogen from L-phenylalanine,[8] the optical purity can be determined from the ratio of deuterium retention in cinnamic acid.

β-Phenethyl alcohol was first converted into ethyl phenylpropionate via bromide and cyanide. Metalation with Li-diisopropylamide and successive carboxylation with CO_2 gave half ester, which was subjected to the modified Curtius reaction with diphenyl phosphorazidate(DPPA).[9] Acid hydrolysis of urethane yielded phenylalanine which was submitted to racemization reaction to remove the deuterium from C-2. The content of deuterium in the samples prepared was determined by the mass-fragmentmetry of N-trifluoroacetyl phenylalanine butyl ester.[10]



(2RS,3R)-Phenylalanine-[3-$^2H_1$]

The samples of phenylalanine were treated with PAL prepared from sweet potatoes.[7] Cinnamic acid extracted from incubation mixture was methylated with diazomethane and analysed by the mass-fragmentmetry. The results summarized in the table clearly demonstrated that AlD_3 reduction of (-)-S-styrene oxide proceeded with the inversion and the stereospecificity was calculated to be 32%, while the reaction of (+)-R-styrene oxide-[2-D_2] with $AlCl_2H$ resulted in complete racemization. A difference in the stereospecificity should be attributed to the nature of the reagents. Since $AlCl_2H$ is a strong Lewis acid and a weak hydride

Reducing Reagent	Optical Purities of Styrene oxide (%)	Deuterium Contents (%) Phenylalanine	Cinnamic acid	Stereospecificity (%)
AlD_3	(-)-S-Styrene oxide 84.0	79	50	32
$AlCl_2H$	(+)-R-Styrene oxide-[2-D_2] 83.4	76	38	≈0

donor,[2,3] ring opening to form a benzylic carbonium ion is very rapid and the ion is quenched by non-stereospecific 1,2-deuterium shift leading to complete racemization. On the other hand, AlD_3 is a less weak Lewis acid and a stronger hydride donor than $AlCl_2H$. Under the condition that excess AlD_3 presents, initially formed oxide-hydride complex is relatively stable and the cleavage of epoxide and the intermolecular attack of the hydride poceed in concerted manner. In reduction of 1-phenylcyclopentene oxide with AlD_3 stereospecificity was 68%,[3] while in our case reduction is less stereospecific. The results so far obtained clearly characterized the two hydride reagents from the point of stereochemistry. Although reduction of the optically active styrene oxide with AlD_3 is not highly stereospecific, it will provide a new method for the preparation of chiral methylene.

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* In this case a part of $LiAlD_4$ used in the experiment seemed to have decomposed and the actual ratio of $LiAlD_4/AlCl_3$ was less than 3:1 resulting in the predominant formation of β-phenethyl alcohol,which contained significant amount of the species labelled at the carbinol carbon.