Int. J. Chem. Sci.: 9(1), 2011, 1-10
ISSN 0972-768X

– CHEMICAL EDUCATION

TEACHING SHARPLESS EPOXIDATION – A NEW APPROACH

SAROJ AGRAWAL[*], VIRENDRA PAL[a] and P. S. KALSI[b]

Department of Chemistry, M. B. Khalsa College, INDORE (Raj.) INDIA
[a]Synthesis Laboratory, IPCA Laboratory, RATLAM (M.P.) INDIA
[b]Indira Gandhi National Open University, DELHI, INDIA

ABSTRACT

Sharpless enantioselective epoxidation of achiral primary allyl alcohols is one of the best reaction discovered during the last about three decades. During teaching programmes, it is observed that generally students lack a sound basic background on which the teaching of such an advanced topic in the class is based. Moreover, in general the students often question the utility of the topic being taught, in every day life in industry/ design of drug/ biochemical aspects etc.

The authors here present the example of Sharpless epoxidation, the way, it should be taught by providing:

- Background knowledge
- The reaction
- Some applications of the reaction

Key words: Sharpless epoxidation, Teaching, New approach.

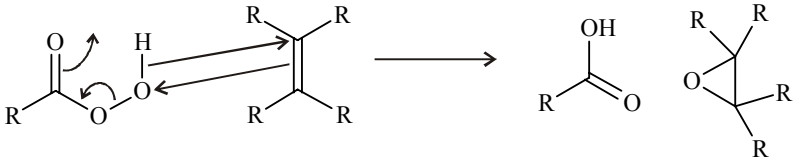
INTRODUCTION

Background knowledge

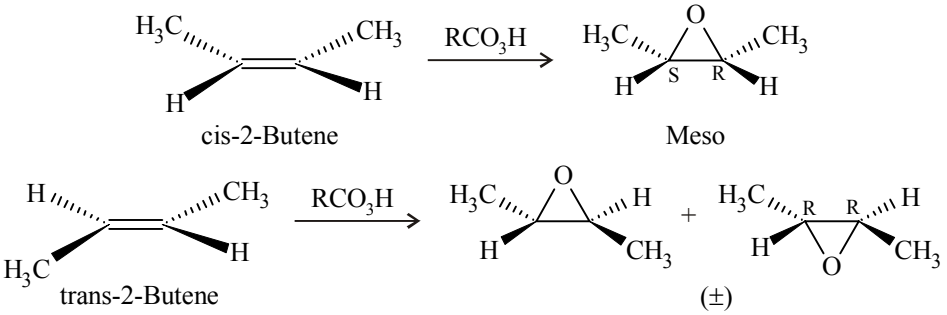
Epoxides are formed by reacting an alkene with a peracid (RCOOOH). The reactive peroxy group transfers its "extra" oxygen atom to the π bond of the alkenes to give an epoxide. The transfer of the oxygen atom from a peracid to alkene π bond is thought to be a concerted process, the actual mechanistic details are not agreed upon; however, using the

[*]Author for correspondence

formalism (**Scheme 1**) allows us to predict the correct product for this type of reaction including the stereochemistry of the epoxide ring. The alkene must present only one face of the π bond to the peracid, the epoxidation is therefore syn-stereospecific and results in the retention of the alkene stereochemistry **(Scheme 2)**.

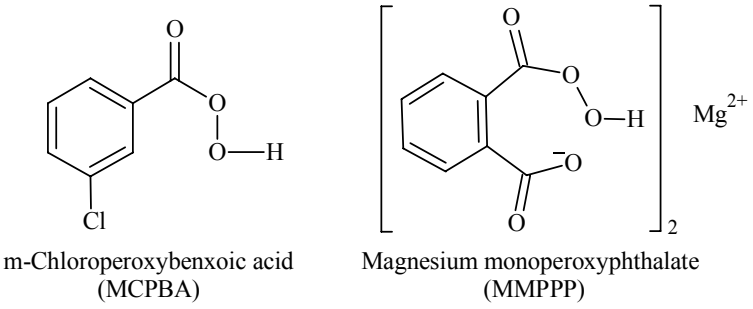


Scheme 1



Scheme 2

Recall that the faces of cis-2-butene are homotopic while the faces of trans-2-butene are enantiotopic. Peracetic acid, CH_3COOOH is the simplest of the stable peracids. The one used most commonly for epoxidation reaction is 3-chlorobenzoic acid, or MCPBA; however, it is shock sensitive and may explode. More recently, magnesium monoperoxyphthalate (MMPP) has been introduced as a safer substitute, which in less prone to thermal decomposition **(Scheme 3)**.

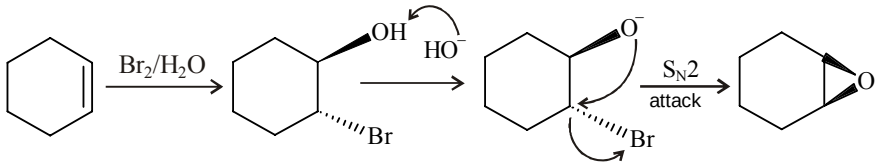


Scheme 3

In general, alkyl substitution on the carbon atoms at the ends of a double bond raises

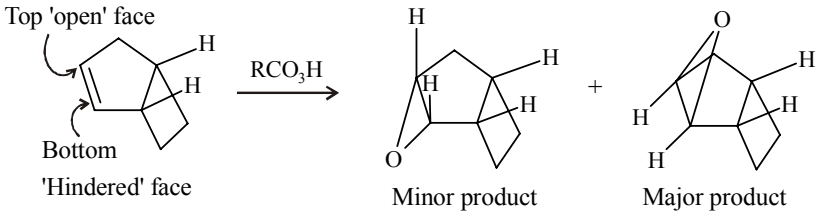
the electron density in the π system because of electron donation by the alkyl substituents and this effect makes the π bond a better nucleophile. The oxygen atom that is transferred from a peracid is considered to be electrophilic and therefore, more highly substituted alkenes react faster with peracids.

Direct epoxidation is a method of choice; however, a halohydrin on treatment with base (OH^-) leads to deprotonation of the OH group and subsequent intramolecular substitution reaction yields an epoxide **(Scheme 4)**.

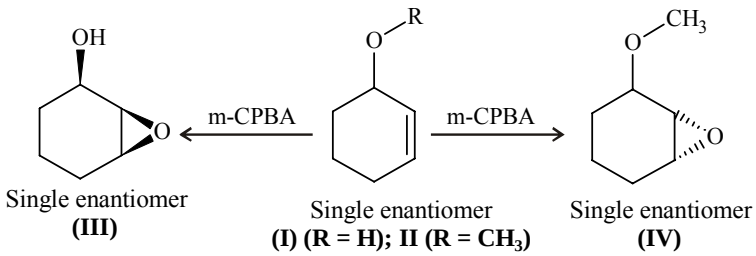


Scheme 4

The approach of the peracid to the alkene unit is influenced by steric and electronic factors. Thus, an unsymmetrical bicycloalkene is epoxidised on the less hindered face **(Scheme 5)**. In keeping with these arguments, epoxidation of II to give IV (**Scheme 6**), occurs on the less hindered face. Epoxidation of (I to give III) is on the more hindered face, to suggest that a prior coordination of the reagent and substrate occurs. The OH group of (I, **Scheme 6)** can act as hydrogen bonding acceptor and donor group but the OCH_3 group of (II) can only be an acceptor. Probably, the OH of (I) forms a hydrogen bonded complex with the incoming peracid, which directs epoxidation on its own (top) face of the double bond.



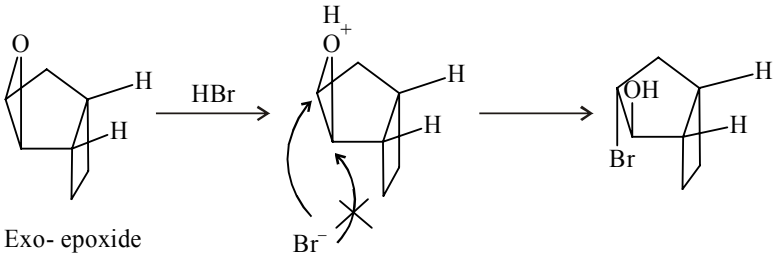
Scheme 5



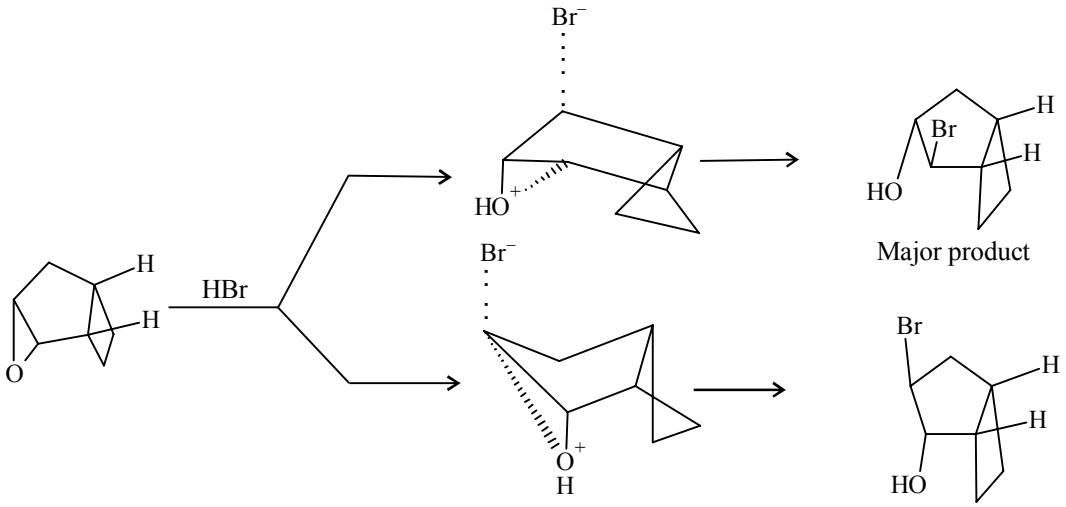
Scheme 6

Prior complexation of reagent and substrate lowers the activation energy as in many enzyme-catalyzed reactions. The faces in (I and II, Scheme 6) are diastereotopic.

Epoxides are highly useful intermediates in organic synthesis, since these undergo ring opening on attack by a wide variety of nucleophiles. The regioselectivity of the ring – opening reaction is controlled by several factors- the nucleophile, the size and electronic nature of the atoms or groups on the carbon atoms of the epoxy ring and also on reaction condition e.g., acid catalysis. The epoxide (**Scheme 7**) reacts after protonation of epoxy oxygen, which undergoes ring opening by Br^- (S_N2 pathway) at the less hindered position (away from the cyclobutane ring). The isomeric epoxide (endo-epoxide) on the other hand seems to prefer a role through protonated form, which involves an axial- axial arrangement of the C-Br and C-O bonds to be formed subsequently (**Scheme 8**).



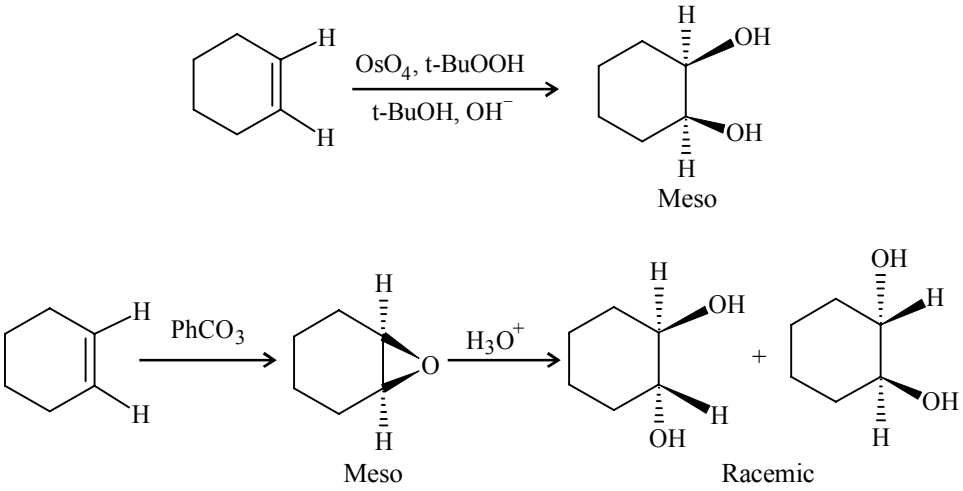
Scheme 7



Scheme 8

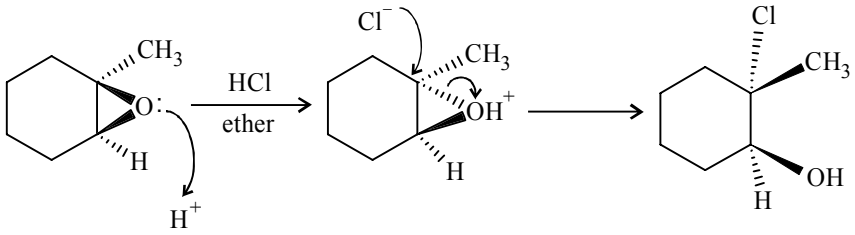
Epoxides undergo ring opening, when they react with nucleophiles. With water as the nucleophile, the product is a vicinal diol. The product stereochemistry from this transfor-

mation is opposite to that from the osmium tetroxide dihydroxylation reaction; so, these two processes provide complementary stereochemical control.



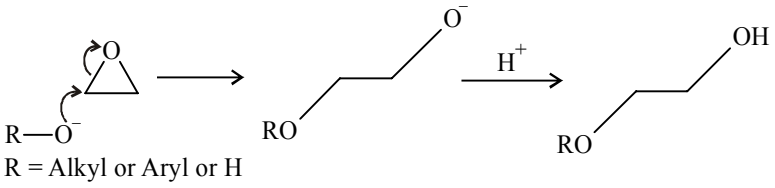
Scheme 9

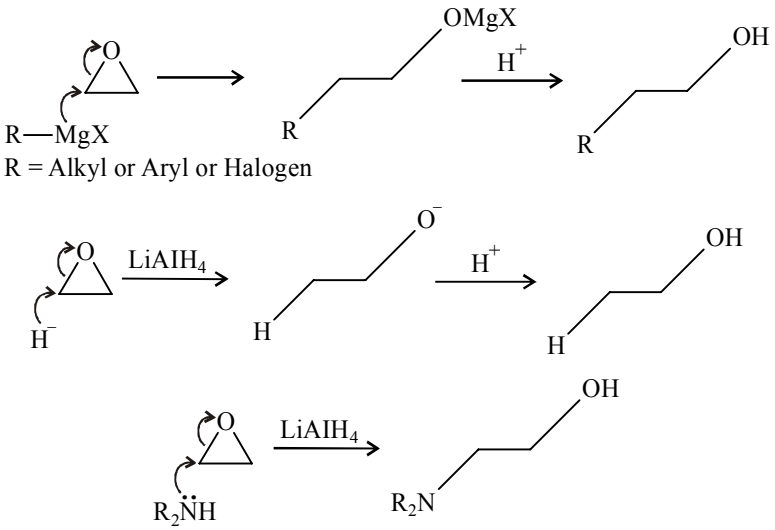
If HCl in dry ether is used to ring-open an epoxide, then the nucleophile attacks at more substituted carbon (carbocation stability, **Scheme 10**).



Scheme 10

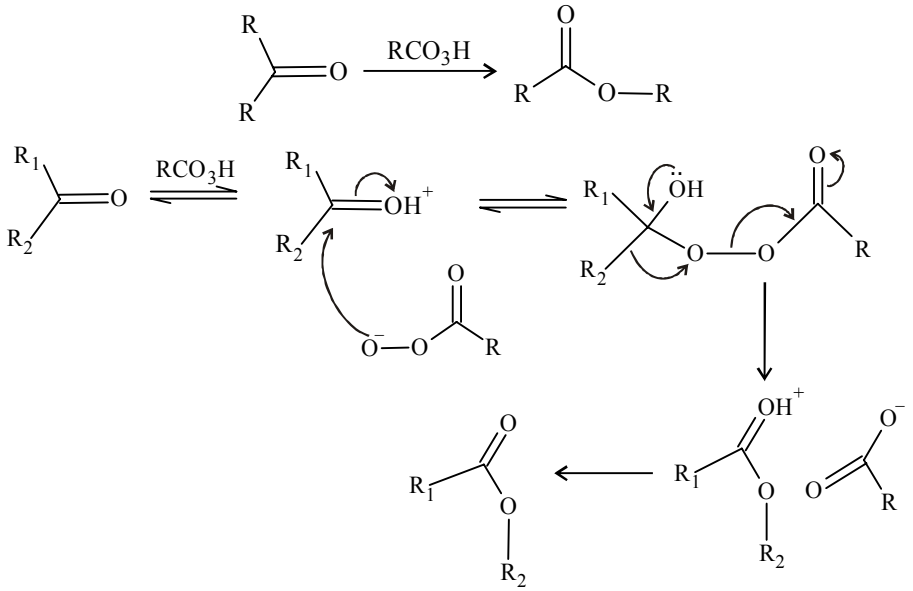
Thus, in the opening of epoxide (**Scheme 10**), tertiary carbocation is formed, as opposed to the secondary carbocation that would be formed at the other carbon. Other epoxide ring opening reaction is given **(Scheme 11)**.





Scheme 11

Lastly, mention may be made of ketones, which can be oxidized to an ester using a peroxy acid. The reaction is a rearrangement, Baeyer- Villiger oxidation, where one of the alkyl/ aryl groups of the ketone migrates to form the ester **(Scheme 12)**.



There is a preference order for the migration of alkyl groups:
Tertiary > Secondary > Primary > Methyl

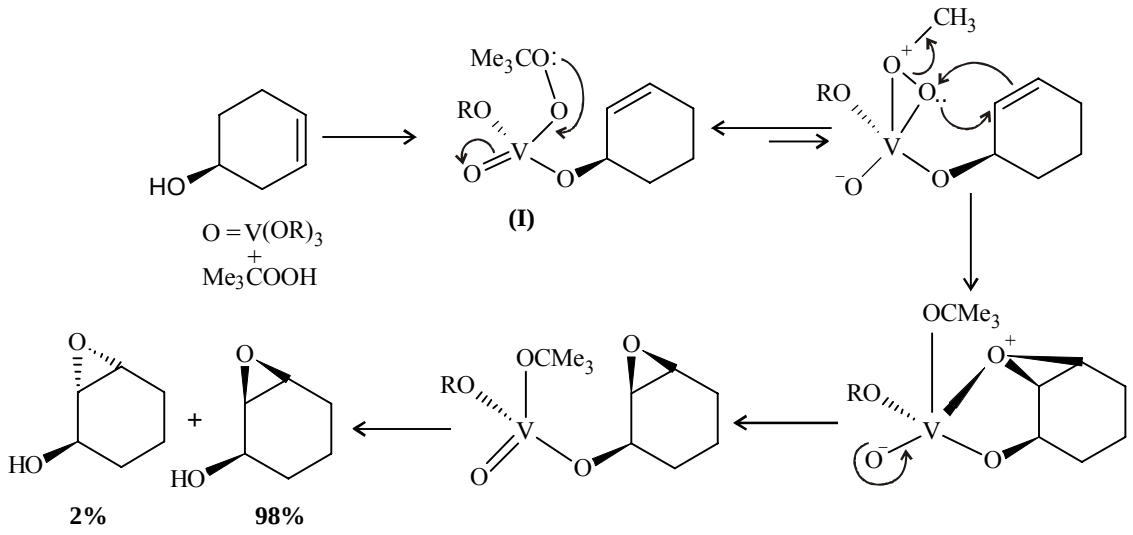
Scheme 12

This background knowledge makes a student aware and more ready to appreciate the enantioselective epoxidation involved in Sharpless epoxidation.

Sharpless epoxidation[1]

Before Sharpless epoxidation reaction is presented in its final form, it is suggested that a proper introduction to the development of this reaction must be discussed first. This discussion may be limited to the following facts:

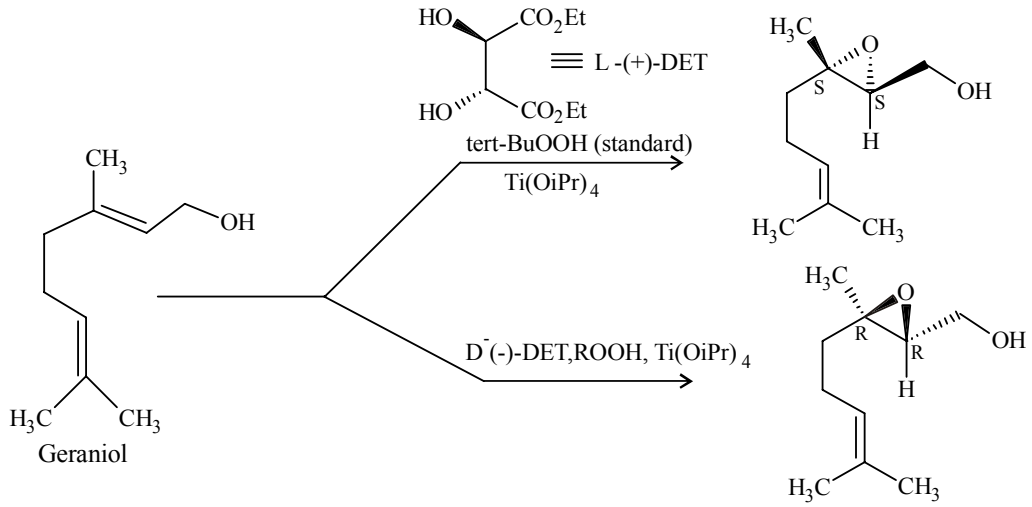
Alkyl hydroperoxides (ROOH) also convert alkenes into epoxides under catalysis by a transition metal and allylic alcohols give epoxy alcohols with the OH group on the same side as the epoxy group **(Scheme 13)** as the almost exclusive product. The mechanism of the reaction involves the initial coordination of the metal with both; the allylic alcohol as well as hydroperoxide and by the subsequent displacement at the peroxy group by the alkene moiety. Thus, as shown **(Scheme 13)**, vanadium (V) species yield a reactive complex (I) by the displacement of two alkoxy ligands.



Scheme 13

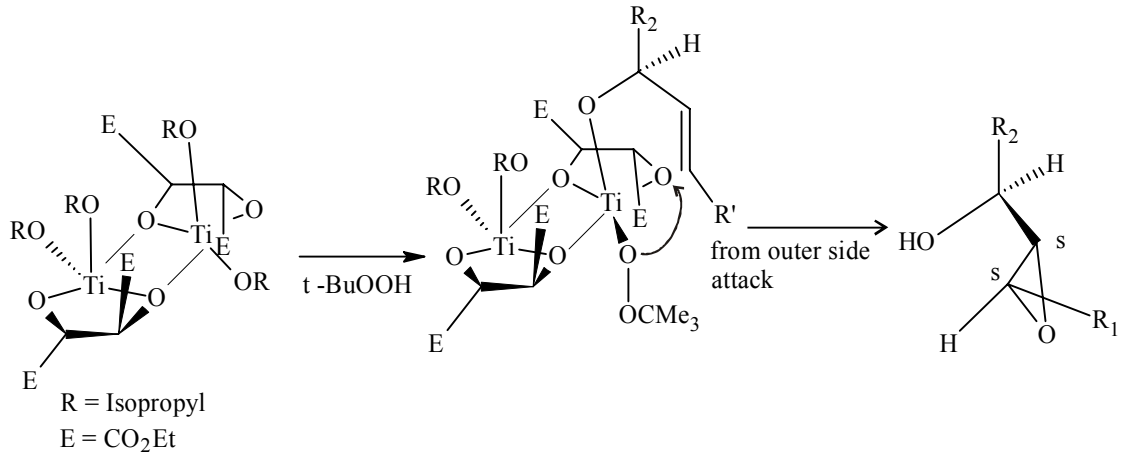
It is here that the students should be impressed that this diastereoselective epoxidation of **(Scheme 13)** was made enantioselective by the incorporation of a chiral ligand on the transition metal. This field was developed by Professor Sharpless. The oxidation reagent is always a hydroperoxide, which is normally tert- BuOOH and the chiral addition is an enantiomerically pure dialkyl ester of tartaric acid, which is usually the diethyl ester (diethyl tartrate, DET). The reaction is catalyzed by titanium (IV) tetraisopropoxide Ti

(*OiPr*)$_4$. Thus, an achiral primary allylic alcohol geraniol gives either of the enatiomeric epoxides **(Scheme 14)**.



Scheme 14

The mechanism of the reaction is not fully understood but the involvement of the binuclear titanium complex **(Scheme 15)** bridged by two tartrate ligands is invoked during this epoxidation reaction.



Scheme 15

Initially, the tartrate e.g., L (+) DET displaces two isopropoxy groups from the tetraisopropoxide. Further displacement of two more isopropoxy groups by the allylic alcohol e.g. $R^1CH{=}CHCH_2OH$ and the peroxide sets up the preferred disposition of the

alkene and oxidant for the formation of only one of the epoxide enantiomers with a specific DET enantiomer.

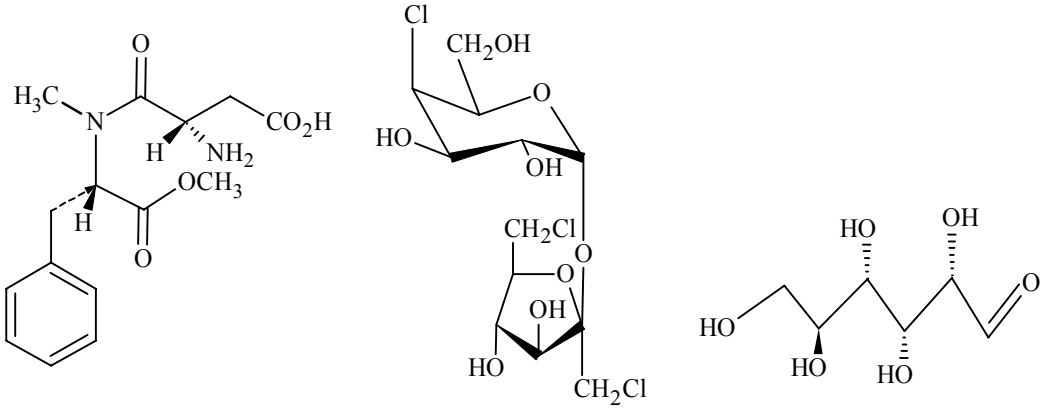
Application of the reagent

After having taught epoxidation of an alkene and the elegant way of enantioselective epoxidation, it becomes necessary to explain to the student the utility of such a reaction. There are vast examples; however, only three are presented here.

(i) Sweeteners

Sucrose (table sugar) and fructose are the most common natural sweeteners, However, they add to our calorie intake and promote tooth decay. Artificial sweeteners thus became an attractive alternative. One of the widely used artificial sweeteners is aspartame, the methyl ester of a dipeptide formed from phenylalanine and aspartic acid. Aspartame is about 100 times sweeter than sucrose. It however, undergoes slow hydrolysis in solution, decomposes with heat and for these reasons, aspartame cannot be used in soft drinks and for baking.

Apart from aspartame, sucralose, the trichloro derivative of sucrose **(Scheme 16)** is about 600 times sweeter than sugar and it looks, feels and tastes like sugar. It is stable to heat, for use in baking and it also does not cause tooth decay or provide calories. However, much is talked about the prolonged use of these sweeteners as health hazards.



Aspartame Sucralose L - Glucose

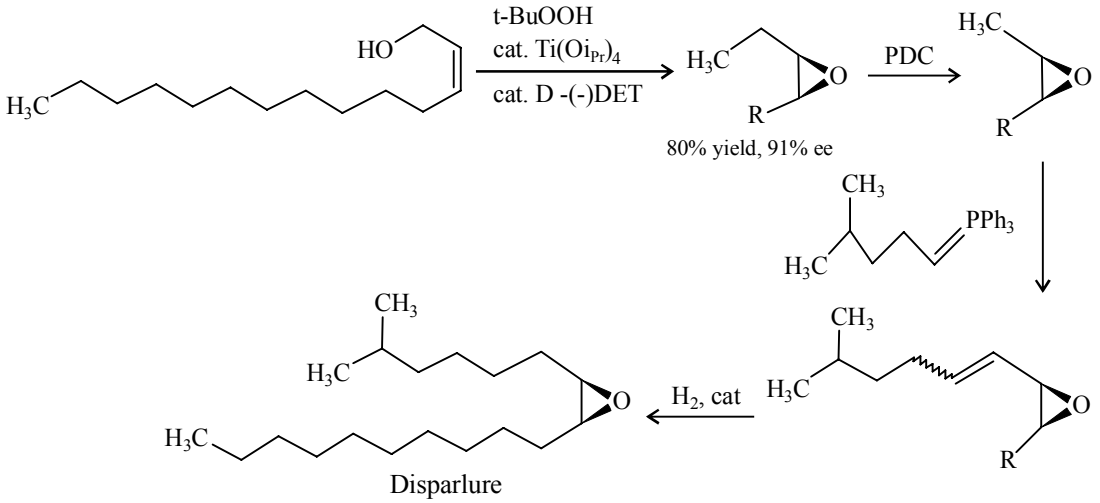
Scheme 16

Many other compounds have promise as artificial sweeteners. L sugars are also sweet and they presumably would provide either zero or very few calories because body enzymes selectively metabolize their enantiomers (the D sugars). Although sources of L

sugars are rare in nature, all eight L-hexoses have been synthesized by Sharpless et al.[1,2] by the application of asymmetric epoxidation and other enantioselective synthetic methods. Thus, the proper stereochemistry of an epoxide on reduction can lead to a hydroxyl group with desired stereochemistry in a L-sugar.

(ii) Synthesis of other sensitive biologically active compounds

In an industrial process, the American Company, J. T. Baker, employs this process to make synthetic disparlure, which is the pheromone of the gypsy moth (**Scheme 17**).



Scheme 17

Direction of epoxidation

During enantioselective Sharpless epoxidation of achiral primary allyl alcohols, the direction of the attack of the complexes derived for L-(+) and D- (-) –DET can be remembered with the following mnemonic: L, from lower face; D, doesn't attack from down face.

REFERENCES

1. R. M. Hanson and K. B. Sharpless, J. Org. Chem., **51**, 1922 (1986).
2. Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, J. Am. Chem. Soc., **109**, 5765 (1987).

Revised : 01.01.2011 *Accepted : 03.01.2011*