

**MODULE -1 LEARNING MATERIA**

**Learning Material**

**Course: B. Pharmacy 4<sup>th</sup> Sem**

**MODULE-1: STEREOISOMERISM**



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## STEREOISOMERISM

**1. INTRODUCTION:** Many organic compounds have same molecular formula but are different in their physical and chemical properties. These compounds are known as isomers and this property is known as isomerism.

### 1.1 STRUCTURAL ISOMERISM

- Structural isomers are compounds that have same molecular formula but different structural formulas.

- Types of Structural isomers:

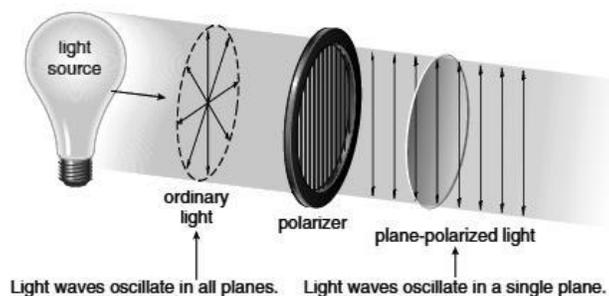
(i) Chain isomerism (ii) Position isomerism (iii) Functional isomerism (iv) Metamerism (v) Tautomerism

**1.2 STEREOISOMERISM:** The isomers have the same structural formula but differ in relative arrangement of atoms or groups in space within the molecule are known as stereoisomers and the phenomenon as stereoisomerism. It can be further classified into three types:-

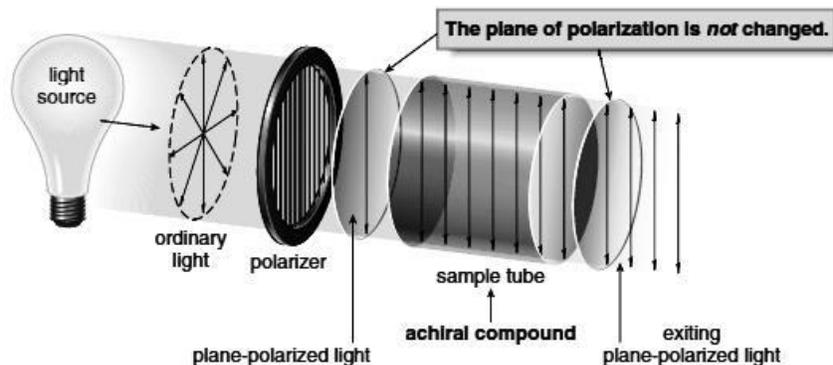
1. Geometrical isomerism
2. Optical isomerism
3. Conformational isomerism

**2. OPTICAL ISOMERISM:-** Any substance that rotates the plane polarized light is optically active and the phenomenon related to it is called optical isomerism.

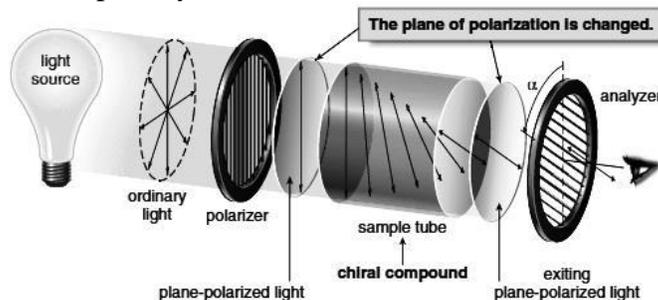
**2.1 Plane polarised light:-** Ordinary light consists of electromagnetic waves that oscillate in all planes perpendicular to the direction in which the light travels. Passing light through a polarizer allows light in only one plane to come through. This is plane-polarized light (or simply polarized light), and it has an electric vector that oscillates in a single plane.



A **POLARIMETER** is an instrument that allows plane-polarized light to travel through a sample tube containing an organic compound. After the light exits the sample tube, an analyzer slit is rotated to determine the direction of the plane of the polarized light exiting the sample tube. There are two possible results. With achiral compounds, the light exits the sample tube unchanged, and the plane of the polarized light is in the same position it was before entering the sample tube. A compound that does not change the plane of polarized light is said to be optically inactive.



With chiral compounds, the plane of the polarized light is rotated through an **angle  $\alpha$** . The **angle  $\alpha$** , measured in **degrees ( $^{\circ}$ )**, is called the observed rotation. A compound that rotates the plane of polarized light is said to be optically active.



The rotation of polarized light can be in the clockwise or counterclockwise direction.

- If the rotation is clockwise (to the right from the noon position), the compound is called **dextrorotatory**. The rotation is labeled ***d*** or (+).
- If the rotation is counterclockwise (to the left from noon), the compound is called **levorotatory**. The rotation is labeled ***l*** or (–).

**3. OPTICAL ACTIVITY:-** Substances which can rotate the plane polarised light through a certain angle are called optically active substances and this property of a substance by virtue of which the organic substances rotate the plane polarised light is called as optical activity. If the plane polarised light shows no change in angle it means that the substance is optically inactive.

**3.1 Angle of rotation:-** The angle through which the plane polarized light is rotated by an optically active substance is called as angle of rotation. It is denoted by  $\alpha$ .

**3.2 SPECIFIC ROTATION:-** The observed rotation depends on the number of chiral molecules that interact with polarized light. This in turn depends on the concentration of the sample and the length of the sample tube. To standardize optical rotation data, the quantity specific rotation ( $[\alpha]_D$ ) is defined using a specific sample tube length (**usually 1 dm**), concentration, temperature (**25 °C**), and wavelength (**589 nm, the D line emitted by a sodium lamp**).

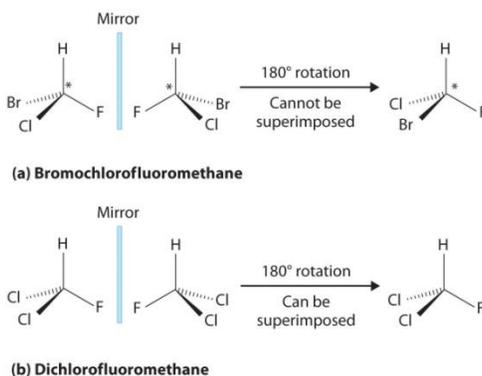
- Specific rotations are physical constants just like melting points or boiling points, and are reported in chemical reference books for a wide variety of compounds.

$$c = \alpha \cdot \frac{1}{[\alpha]_D} \cdot \frac{100}{l}$$

↑ desired quantity    
 ↑ measured value    
 ↑ input values    
 ↑ input values

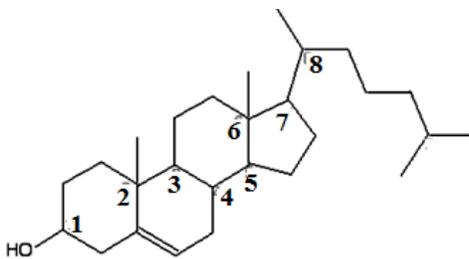
#### 4. CHIRAL AND ACHIRAL MOLECULES

- A molecule (or an object) is said to be chiral or dissymmetric, if it is not superimposable on its mirror image and the property of non-superimposability is called chirality.
- On the other hand, a molecule (or an object) which is superimposable on its mirror image is called achiral (non-dissymmetric or unsymmetrical).
- Chiral carbon atom (chiral centre/stereo centre). Carbon atom bonded to four different atoms or groups is called an asymmetric carbon atom or a chiral atom. A chiral atom is indicated by an asterisk (\*).



If a molecule contains only one chiral centre/atom, then the molecule has to be optically active (i.e. non superimposable on its mirror image) as it will not contain any element of symmetry. Molecules containing two or more chiral centers may or may not be chiral (optically active).

- It is necessary to distinguish chiral and chiral centre. The word chiral is used for molecule as a whole which is optically active, whereas chiral centre is for an atom which is attached to form different atoms/groups.

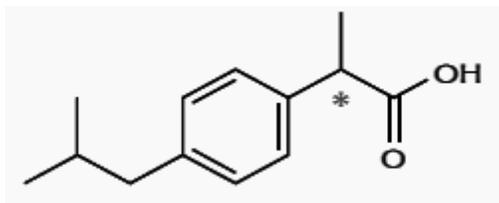


*Cholesterol has eight chiral centres*

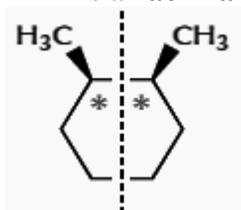
### Relationships between Chiral Centers and Chiral Molecules

- The term **chiral center** refers to an atom in the molecular structure. The term **chiral molecule** refers to the entire molecule.
- The presence of one chiral center renders the entire molecule chiral. The presence of two or more chiral centers may or may not result in the molecule being chiral. In the examples given below the chiral centers are indicated with an asterisk. The vertical broken line represents a plane of symmetry.

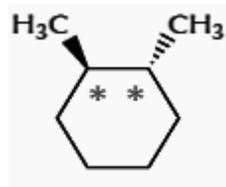
**Ibuprofen:** One chiral center renders the molecule chiral



*cis*-1,2 dimethylcyclohexane is an **achiral molecule**



*trans*-1,2- dimethylcyclohexane is a chiral molecule

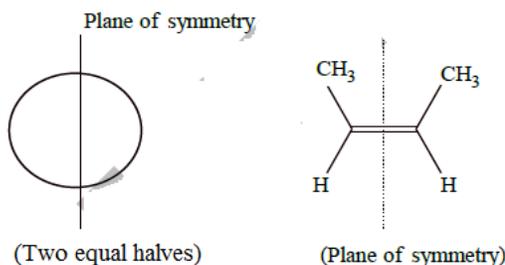


**CHIRALITY:-** The property of **nonsuperimposability** of an object on its mirror image is called **chirality**. Such molecule has no symmetry elements of the second kind. If the molecule is superposable on its mirror image, it is **ACHIRAL**.

### 5. ELEMENT OF SYMMETRY:-

To exhibit optical activity molecule must not have the symmetry elements, (a) plane of symmetry (b) centre of symmetry (c) n-fold alternating axis of symmetry. If these three are absent then only the compounds exhibits optical activity.

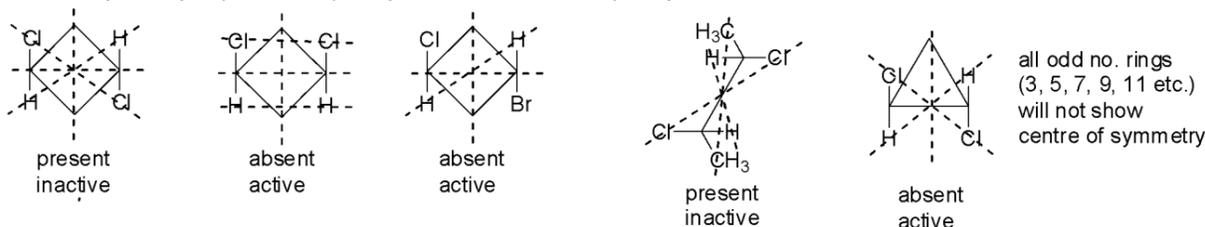
**Plane of symmetry:** A molecule is said to possess a plane of symmetry if the atoms or groups on one side of the plane forms the mirror image of those on the other side. In other words, a plane which bisects a molecule/object in two equal halves.



### Centre of symmetry:

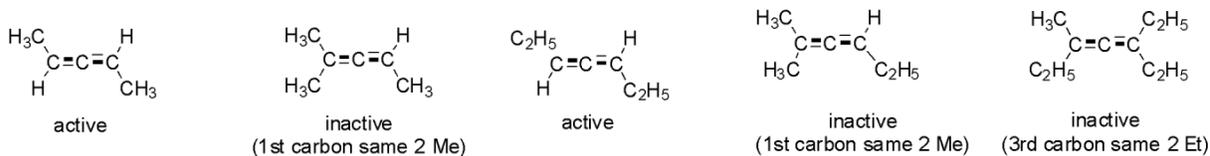
- A centre of symmetry in a molecule is said to exist if a line is drawn from any atom or group to this point and then extended to an equal distance beyond this point meets the identical atom or group. A centre of symmetry is usually present only in an even membered ring.

Centre of symmetry: if present = optically inactive; if absent = optically active



***n*-Fold alternating access of symmetry:** If a rotation by  $360^\circ/n$  degrees ( $n = 1, 2, 3, \dots$ ) followed by reflection in plane perpendicular to the axis taken results in identical molecule the compound said to be possess *n*-fold alternating access of symmetry. If plane of symmetry or centre of symmetry is present then *n*-fold alternative access of symmetry is present. If plane of symmetry or centres of symmetry are absent then *n*-fold alternating access of symmetry will be absent. If the *n*-fold alternating access of symmetry present then the molecule is optically inactive, if absent then optically active.

Allenes are optically active because absence of plane of symmetry. However, if on first or third carbon two same groups present it will be inactive.



## 6. ENANTIOMERS & DIASTEREOMERS

### Enantiomers

An enantiomer is one of two stereoisomers that are non-superimposable complete mirror images of each other.

Molecules must contain atleast one chiral centers.

### Diastereomers

Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers (non-superimposable mirror images of each other).

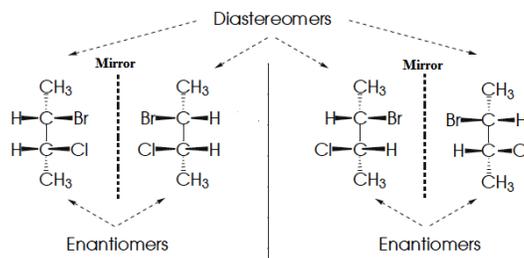
Molecules must contain more than one chiral center.

Enantiomers have, when present in a symmetric environment, identical chemical and physical properties except for their ability to rotate plane polarized light by equal amounts but in opposite directions.

A mixture of equal parts of an optically active isomer and its enantiomer is termed Racemic and has a net rotation of plane polarized light of zero.

Diastereomers can have different physical properties and different reactivity. In another definition diastereomers are pairs of isomers that have opposite configurations at one or more of the chiral centers but are not mirror images of each other.

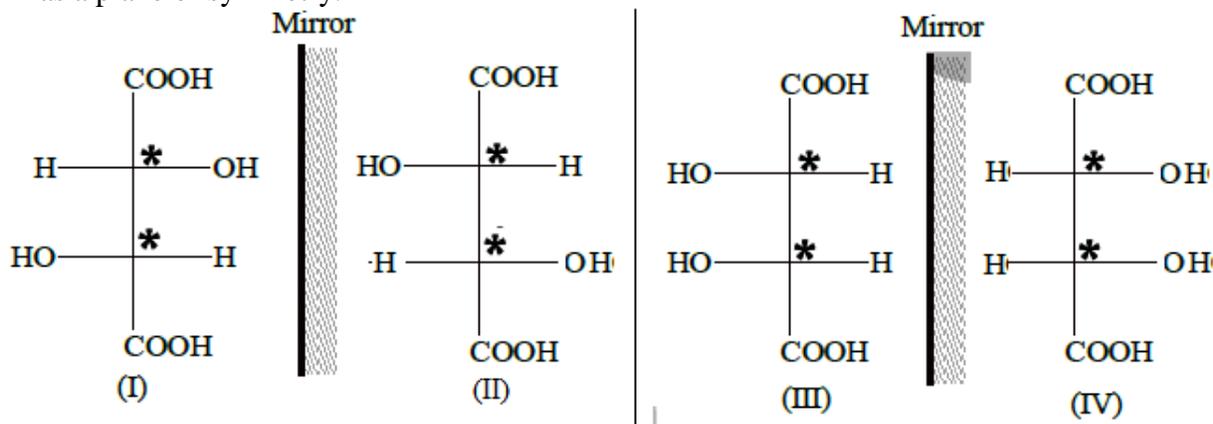
Racemic mixture is not possible.



*2-bromo-3-chlorobutane*

## 7. MESO COMPOUND

- An optically inactive compound whose molecule is superimposable on its mirror image inspite of the presence of chiral carbon atoms is called a meso compound.
- If a molecule has two or more chiral centers, it is usually chiral. The exceptions are meso-molecules, which are not chiral. These are molecules that due to symmetry have chiral centers that 'cancel' each other out.
- Has two or more chiral centers
- Has a plane of symmetry.



I and II are enantiomers (non-superimposable); III and IV are meso form (superimposable).

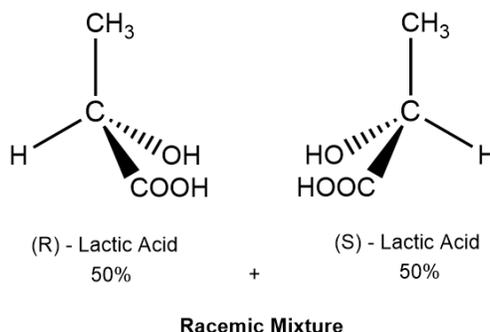
## 8. RACEMIC MIXTURE

- A racemic mixture is a 1:1 mix of two enantiomers (Each of a pair of molecules that are mirror images of each other).

- No matter how many molecules are in a mixture, it is racemic if there are equal numbers of the two enantiomers.

- The racemic mixture produces a net optical rotation - of plane polarized light - of zero degrees. This is because the mixture contains equal amounts - **equimolar mixture** - of both enantiomers that have opposite rotations.

- A **racemic mixture** is a solution containing equal amounts of a **pair of enantiomers**.



A solution containing equal amounts of **(R)-2-butanol** and **(S)-2-butanol** is a **racemic mixture**.

### 8.1 RESOLUTION OF RACEMIC MIXTURES

- The separation of a racemic mixture into the individual enantiomerically pure enantiomers is called resolution.

- Since enantiomers have identical physical properties, such as solubility, boiling point and melting point, they cannot be resolved by common physical techniques such as direct crystallization, distillation or basic chromatography.

- The main difficulty in a process of resolution is that **d** or (+) and **l** or (–) forms have identical physical and chemical properties, so they cannot be separated by ordinary methods. However, the following methods can be used for this purpose.

#### (i) **Mechanical separation:**

If the **d** or (+) and **l** or (–) forms of a substance exists in well-defined crystalline forms, the separation can be done by hand picking with the help of magnifying lens and a pair of tweezers.

For example, the **d** and **l** forms of sodium ammonium tartarate can be separated by this method.

The method has very limited application and applies to only few crystalline constituents having different shape.

#### (ii) **Biochemical separation:**

In this method, the resolution is done by the use of microorganisms.

When certain **bacteria** or **moulds** are added to a solution of a racemic mixture, they decompose one of the optically active forms more rapidly than the other.

For example, when the **mould, racemic ammonium tartarate**, the mould completely decomposes the **d** form while **l** form is left practically unaffected. The main drawback of the

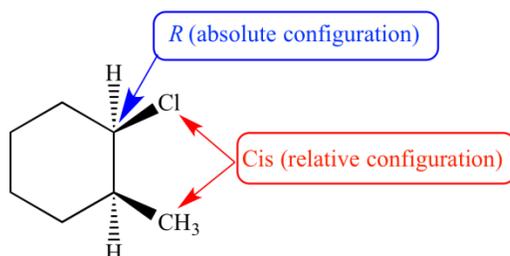
method is that half of the material is destroyed during resolution. The process is very slow and only small amounts of the materials can be separated.

(iii) **Chemical separation:**

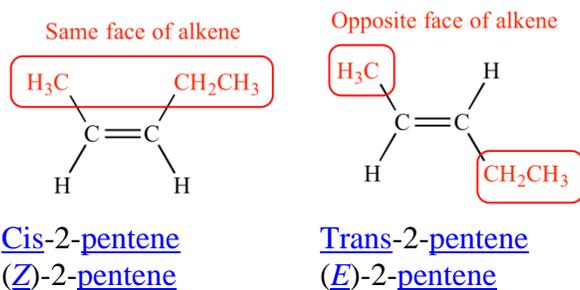
- This is probably the best method of resolution. The racemic mixture is made to combine with another optically active compound and the resulting solubility in various solvents.
- By fractional crystallization from a suitable solvent, they can be separated.
- For example, the racemic mixture of lactic acid is allowed to combine with the optically active base (-) strachnine or (+) brucine.

**9. CONFIGURATION:** The arrangement of atoms that characterizes a particular stereoisomer is called its configuration.

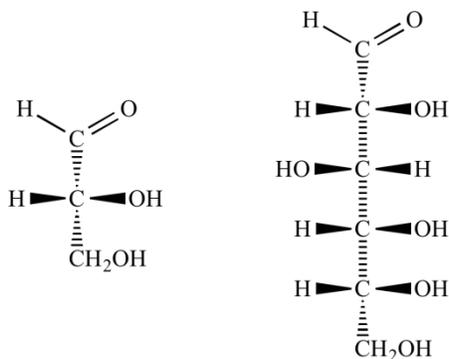
**9.1 Relative configuration:** The position of atoms or groups in space in relation to (i.e., relative to) something else in the molecule. Compare with absolute configuration, which is independent of atoms or groups elsewhere in the molecule.



Relative to the position of the methyl group, the chlorine atom is on the same face of the cyclohexane ring. The stereocenter bearing the chlorine atom has an *R* absolute configuration (this configuration does not involve or depend on positions elsewhere in the molecule). Hence this molecule is *cis*-1-chloro-2-methylcyclohexane or (*1R*, *2S*)-1-chloro-2-methylcyclohexane.



In *cis*-2-pentene, the methyl and ethyl groups are on the same side of the alkene. The groups with highest Cahn-Ingold-Prelog priority are on the same face of the alkene, so this is also (*Z*)-2-pentene. In *trans*-2-pentene, also named (*E*)-2-pentene, the methyl and ethyl groups are on opposite faces of the alkene. *Cis*, *trans*, *E*, and *Z* are all designations of relative configuration.



[D-glyceraldehyde](#)    [D-glucose](#)

At the stereocenter next to the  $\text{CH}_2\text{OH}$  carbon, both of these monosaccharides have the OH group pointing to the right, so they have the same relative configuration. This relative configuration is indicated with the prefix D. D and L are designations of relative configuration.

### 9.2 Absolute configuration: R,S-System

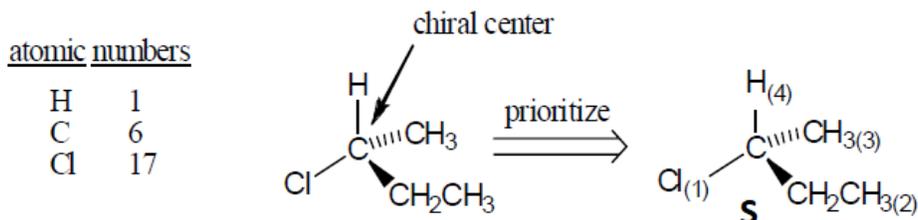
- An absolute configuration refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its Stereochemical description e.g. **R** (*Rectus*) or **S** (*Sinister*).

- The arrangement of atoms in an optically active molecule, based on chemical interconversion from or to a known compound, is a **relative configuration**. Relative, because there is no way of knowing just by looking at a structure whether the assignment of (+) or (-) is correlated to a particular isomer, **R** or **S**.

- **R** and **S** notations are used only to describe asymmetric molecules following **Cahn-Ingold-Prelog (CIP)** sequence rules.

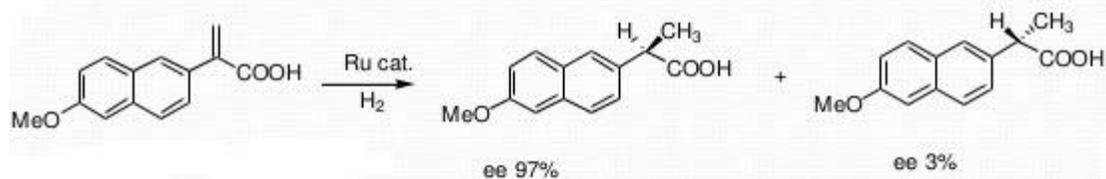
(a) **Rule 1:** first we assign the priority numbers to the four atoms/groups attached to chiral centre according to CIP rules. For example in the case of **CHClBrI**, the four atoms attached to the chiral center are all different and priority will be given based on atomic weight, thus the priority follows as **I, Br, Cl, H**.

**Rule 2:** If two or more of the atoms that are bonded directly to the chiral center are the same, then prioritize these groups based on the next set of atoms (i.e., atoms adjacent to the directly bonded atoms). Continue until priorities can be assigned. Priority is assigned at the first point of difference.



### Asymmetric synthesis or Stereoselective synthesis

A chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts. Traditionally called *asymmetric synthesis*.



What do we mean by asymmetric synthesis – a reaction that creates one configuration of new stereogenic elements by the action of a chiral reagent chiral auxiliary or solvent acting on heterotopic (enantiotopic or diastereotopic) faces, atoms or groups of a substrate.

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