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1. Learning Outcomes

After studying this module, you shall be able to

- Know about helicity and the chirality due to the helical shape of some molecules.
- Understand the Cram's and the Prelog's rule.
- Learn about correlation of the configuration of the newly created chiral centre in the preponderant diastereomer with that of the existing one.
- Analyse various cases of helicity.

2. Introduction

Dear students, in this paper we have different and varying concepts relating to stereochemistry like conformational analysis, stereospecific and stereoselective synthesis and chirality of many interesting molecular species etc. Now we are at stage where we are aptly equipped in our knowledge base to start topics of higher understanding like chirality due to helical shape and Cram's and Prelog's rule. These topics provide deeper insights into the understanding of stereochemical aspects of molecules.

Helicity presents a special case of chirality axis in molecules with a helical shape. Correlation of the configuration of the newly created chiral centre in the preponderant diastereomer with that of the existing one takes into account some rules known as Cram's and Prelog's rule which are to discussed at length in this module.

2.1 Helicity:

A special case of chirality axis appears in molecules with a helical shape. A helix is inherently chiral and is non-superimposable on its mirror image. Helices are chiral objects that look like screws and can therefore be right- or left-handed respectively.

In nature, this type of chirality is frequently found, for example, in mussel or snail shells. A helically shaped molecule, that is of great interest for chemists and biologists, is deoxyribonucleic acid (DNA), which appears in two right-handed (A- and B-helix) and one left-handed (Z-helix) types of helices. The DNA backbone is winded around the chirality axis. A helix's rotational sense, or helicity, can be ascertained by following the chirality axis from the end of the helix. It does not matter from which end of the helix the molecule is viewed, because the result of ascertaining the helicity of a particular molecule is always the same. Optical rotatory dispersion and circular dichroism provide interesting experimental study of polypeptide helicity.

A helix may, in fact, be considered as manifesting axial chirality, its axis serving as the chiral axis, although it is more convenient to discuss chirality of this type under the heading of helicity. If it has a C_2 axis perpendicular to the axis of the cylinder, the helix is called palindromic. For assigning the chiral designation to the helix, if moving from one end to the other along the axis, the helix describes a clockwise direction, it is designated ***P*** (plus) and if it describes an anticlockwise direction, it is designated as ***M*** (minus).

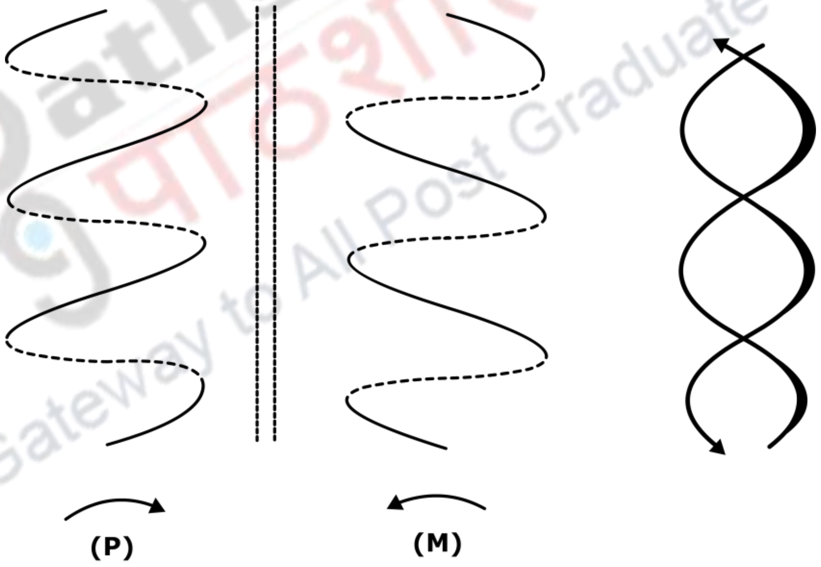
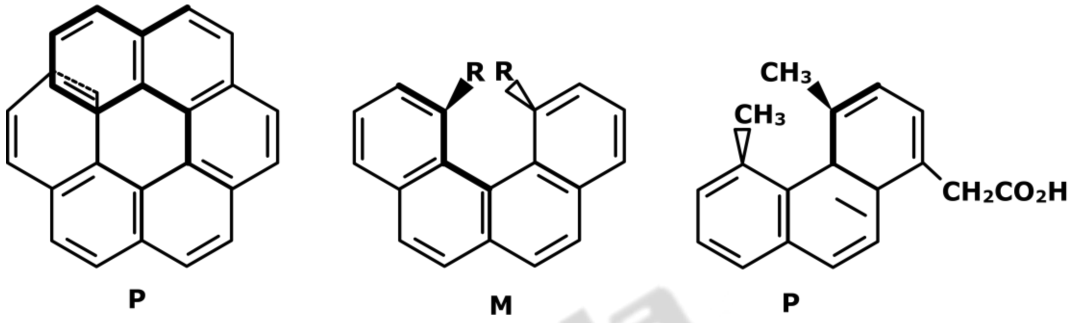


Fig. 1: Helical structures

Helicity in a molecule may also result from molecular overcrowding. This is manifested in molecules such as helicenes, benzphenanthrenes or even phenanthrenes (Figure 2). These molecules are normally expected to be planar but, due to molecular overcrowding, the ring structures assume a helical shape; the terminal rings and the substituents are in different planes and the molecules exist as two helical enantiomers. Hexahelicene (Structure A, Figure 2) is a classic example of a stable helical molecule with exceptionally high optical rotation,

$[\alpha]_D$ being 6200°. Higher helicenes (e.g., hepta- and octa- etc.) are also known. The chiral designations of the molecules (A, B, C) are *P*, *M* and *P* respectively. The first two have a C_2 axis passing through the central ring junction of the molecules with the two planes of the terminal rings symmetrically oriented around it and belong to the C_2 point group.



Structure A **Structure B** **Structure C**

Fig. 2: Molecular overcrowding

It is often very convenient to specify the chiral descriptor of the conformational or atropisomeric enantiomers such as substituted ethanes and biphenyl derivatives with axial chirality by helical nomenclature (*P* and *M*). Some rules are listed below:

- The substituents are ordered in three in the case of ethanes and two in case of the biphenyls (Figure 3).
- The highest priority group (CIP) is selected in front (fiducal group) and related to the highest priority group at the rear. If, in doing so, a clockwise turn is described the configuration is *P*, an anticlockwise turn on the other hand is *M*. This is clearly illustrated in the two enantiomeric conformers of *meso* tartaric acid (Figure 3).
- For studying the specific case of biphenyls, we can consider the case of *S*-dinitrodiphenic acid (Figure 3). The two fiducal groups are NO_2 in the front and NO_2 in the rear. Movement from the former to the latter takes place in the clockwise direction and so is represented as a *P* helix. The enantiomer is an *M* helix. In the biphenyls, *R* corresponds to *M* and *S* to *P*.

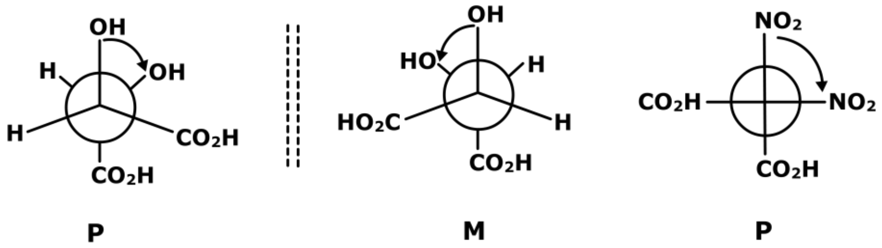


Figure 3: *P* and *M* nomenclature of acyclic conformers

2.2 Cram's Rule and Prelog's Rule

2.2.1 Correlation based on asymmetric synthesis:

When a new chiral centre is formed in a molecule which already contains one or more, two diastereomers are formed in unequal amounts. The reaction is known as asymmetric synthesis and the existing chiral centre (or centres) brings about asymmetric induction. A few empirical rules have been proposed, depending on the substrates, which correlate the configuration of the newly created chiral centre in the preponderant diastereomer with that of the existing one.

1. Cram's rule: When a ketonic group attached to a chiral centre (e.g., $RCOCR_LR_MR_S$ where, L, M, and S stand for large, medium, and small respectively) undergoes nucleophilic addition with organometallic or metal hydride reagents, two diastereomeric products are formed, erythro and threo, one of which predominates. The relative configuration of the predominant isomer can be predicted by 'Cram's rule' based on some arbitrary models (Cram and Elhafez 1952). In the *open chain* model (Structure I, Figure 4), the C=O group is flanked by two smaller groups (R_S and R_M) with the large group (R_L) nearly eclipsed with R (Figure 4). The metallic part of the reagent gets complexed with C=O and the

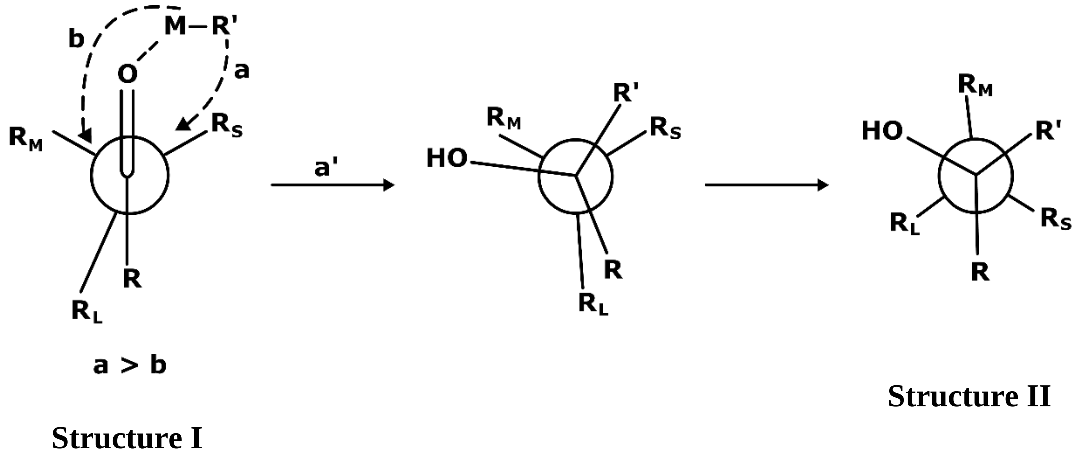


Figure 4: Cram's open chain model

carbanion equivalent of alkyl group (R′) or H is transferred to the trigonal carbon from the side of R_S (Route a) in preference to that of R_M (Route b) to give (Structure II, Figure 4). Although no mechanistic rationalisation has been claimed, it is reasoned that C=O being complexed with the reagent becomes effectively the bulkiest group and is thus better placed between R_S and R_M . Two examples are given in Figure 5 which illustrate the rule and are self-explanatory. It may be noted that

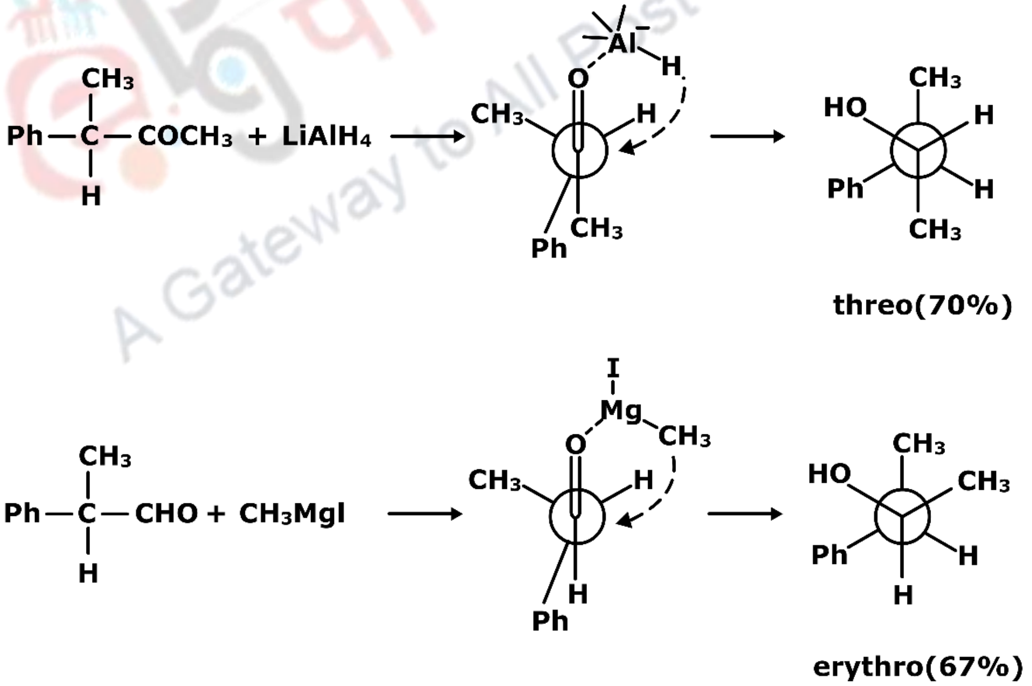
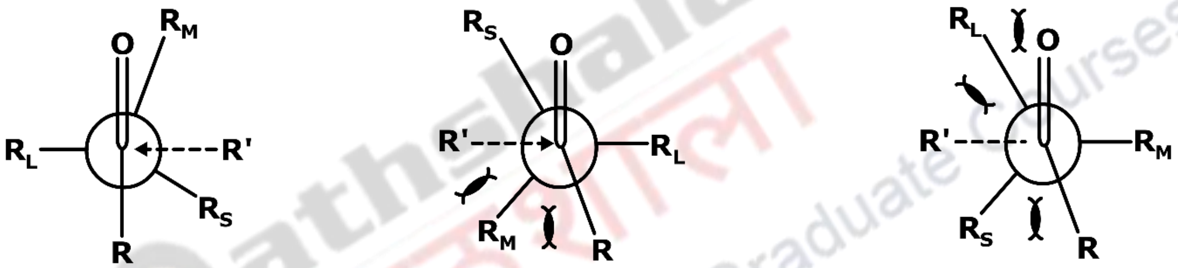


Figure 5: Application of Cram's rule; examples

although only one enantiomer of the substrate is shown, the rule is equally applicable to racemic substrate in which case, the products are also racemic.

Although, the model correctly predicts the stereochemical course of the reactions, it often fails to give quantitative assessment of the asymmetric induction in terms of steric interactions. From mechanistic consideration, a few alternative models have been suggested of which the Felkin-Anh model (Anh 1980) has gained consensus. In this model, two reactive conformations (Structure III) and (Structure IV) (Figure 6) have been considered in which either the largest (R_L) or

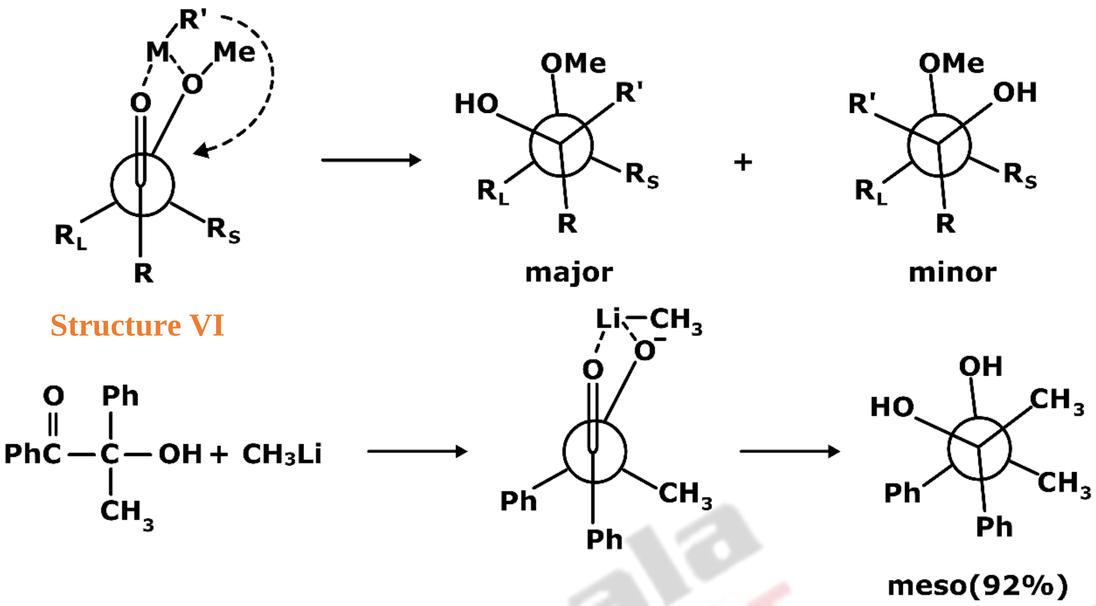


Structure III **Structure IV** **Structure V**

Figure 6: Felkin-Anh model-an alternative to Cram's model

the most electron-withdrawing group (which provides the greatest σ^*-π^* overlap with the carbonyl π^* orbital) at $C\alpha$ is placed at right angle to the C=O double bond. Between the two, the first with R_M opposing C=O and R_S gauche to R is usually preferred. The non-bonded interactions which involve R' and R_S (rather than R' and R_M as in Structure IV) are thus minimised. The model predicts the same stereochemistry as Cram's but provides a more quantitative assessment of 1,2-asymmetric induction. A third conformation (Structure V) may make some contribution but is generally ignored (unfavourable steric interactions).

If the chiral centre in the ketone contains an α-group such as OH, NH_2, and OMe which is capable of coordinating with the reagents, the stereochemistry of the product is predicted by Cram's rule based on a rigid (chelate) *cyclic model* (Structure VI) (Figure 7) in which the metallic part of the reagent is doubly coordinated to



Structure VI

Figure 7: Cram's cyclic (chelate) model

form a five-membered ring. The nucleophile preferentially approaches the electrophilic carbon from the side of R_S (an example follows). If the chelating group is R_M (which is often the case), the cyclic model predicts the same stereochemistry (qualitatively) as the open chain model: but if it is R_S or R_L opposite stereochemistry follows. Asymmetric induction through chelate model is usually high.

If a strongly electronegative group, e.g., a halogen atom is present at Cα, yet another model, a *dipolar* one is suggested for prediction of the stereochemistry. The dipoles of the carbonyl bond and the C-X bond oppose each other and so they are placed anti as in the model (Structure VII) (Figure 8). The dipole repulsion is thus minimised, the electrophilic character of the carbonyl carbon increases, and

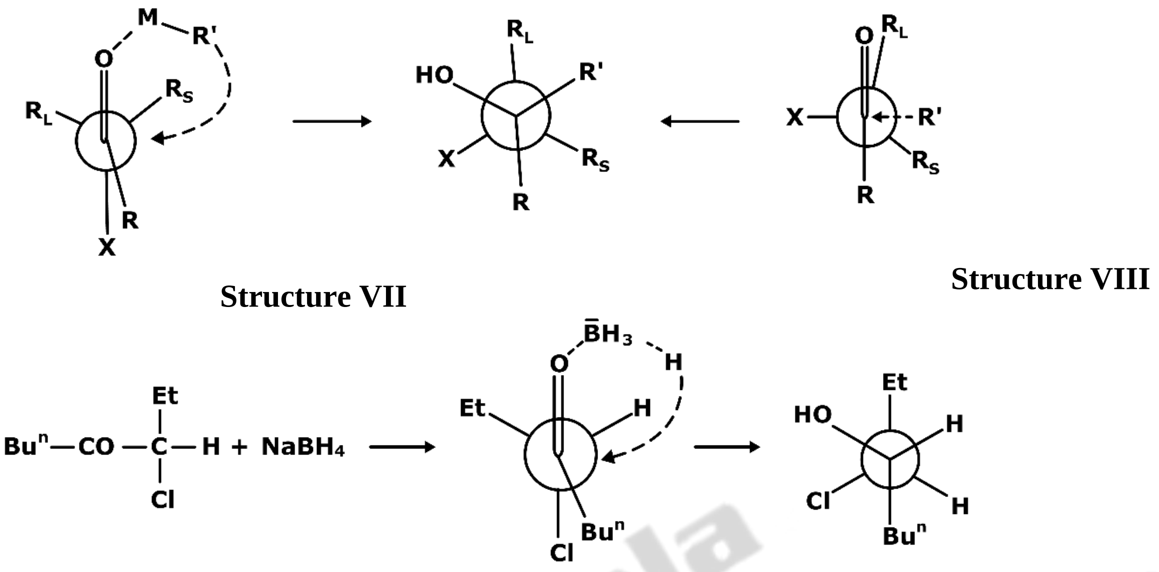


Figure 8: Cram's dipolar model

the nucleophile adds from the side of R_S giving the major product as shown. The Felkin-Anh model (Sturcture VIII) in which the electron-withdrawing X is placed perpendicular to C=O bond also predicts the same stereochemistry.

2. Prelog's rule. Prelog's rule which correlates the configurations of chiral alcohols with those of α-hydroxyacids, especially mandelic acid and atrolactic acid is the outcome of generalisation of the results of asymmetric synthesis carried out by McKenzie group in the early part of the century. When phenylglyoxylic acid is esterified with an optically active alcohol, e.g., (–)-menthol and the ester is reduced with sodium amalgam (or with sodium borohydride), mandelic acid enriched in one of its enantiomers, in this case, *R*-(–), is obtained after complete hydrolysis of the product. The reduction step has now been replaced by Grignard addition of methylmagnesium halide so that configurationally stable atrolactic acid is produced. Prelog's rule correlates the configuration of the hydroxyacid, i.e., atrolactic acid with that of the alcohol as follows. The ester of phenylglyoxylic acid is so written that the two carbonyl groups are antiperiplanar as in Structure IX (Figure 9) and the large group R_L (C-4) at

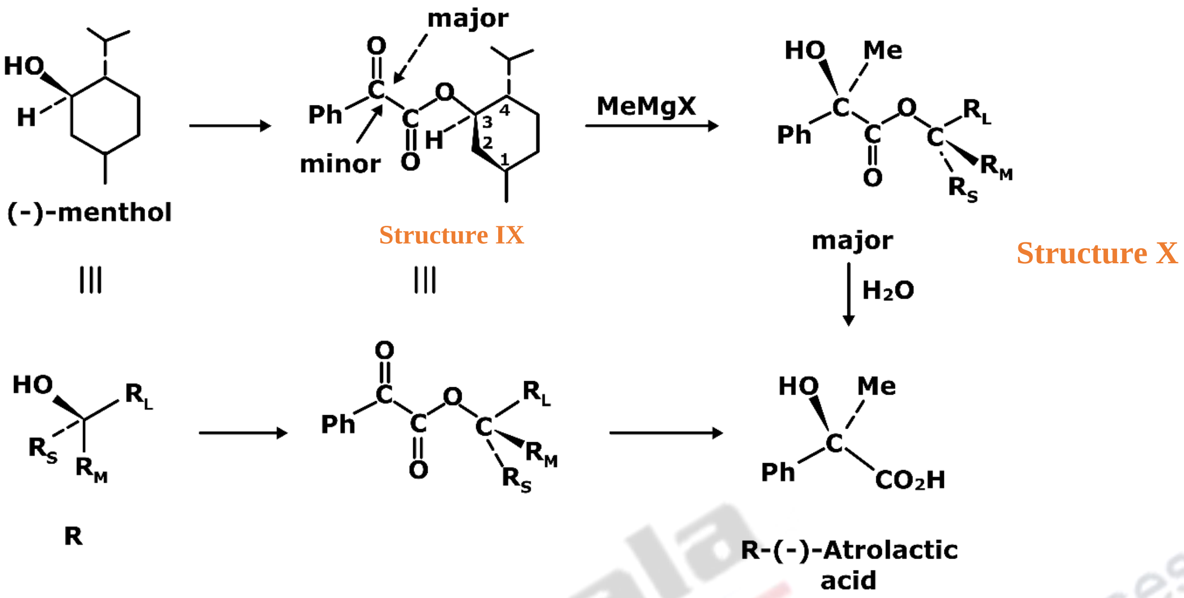


Figure 9: Prelog's model and the atrolactic acid rule

the chiral centre of the alcohol moiety is on the same side of the ketonic carbonyl (PhCOCOOC*-L lies in a plane)*. R_S(H) and R_M (C-2) are in the back and front of the plane respectively†. Methylmagnesium bromide approaches the electrophilic carbon (of the ketonic C=O) from the side of R_S more easily than from the side of R_M. The preferred diastereorner is thus XLV which on complete hydrolysis affords atrolactic acid enriched in *R*-(–)-enantiomer. The carbonyl carbon in menthol has *R* configuration and it follows that obtention of *R*-(–)-atrolactic acid from the above sequence of reactions (esterification of an alcohol with phenylglyoxylic acid, Grignard addition of MeMgX, and subsequent complete hydrolysis of the product) settles the configuration of the chiral alcohol as *R*. Similarly, if *S*-(+)-atrolactic acid is obtained, the configuration of the alcohol is *S**. This is illustrated with two steroidal alcohols, 7α- and 7β-hydroxycholestane (Figure 10). The asymmetric induction is usually moderate (10-30%) but is sufficient for the correlation of configuration. Since the configuration of atrolactic acid is known, the method gives the absolute configuration of the chiral alcohols.

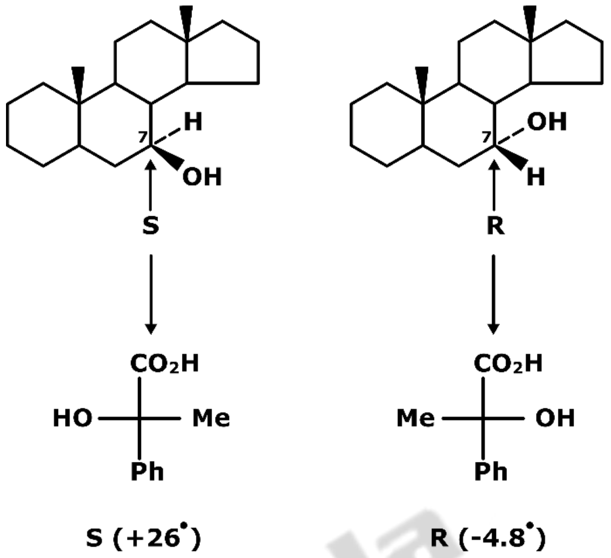


Figure 10: Configuration at C-7 of steroids (Prelog's rule)

As in Cram's rule, this is a formal and not a mechanistic assumption. Alternative conformation with R_S in place of R_L may also be considered in which case,-it is a choice between the approaches from R_M side versus that from the R_L side. The former is preferred and the same stereochemistry results.

3. Summary

- A special case of chirality axis appears in molecules with a helical shape. A helix is inherently chiral and is non-superimposable on its mirror image. Helices are chiral objects that look like screws and can therefore be right- or left-handed respectively.
- Helicity in a molecule may also result from molecular overcrowding. This is manifested in molecules such as helicenes, benzphenanthrenes or even phenanthrenes.
- When a new chiral centre is formed in a molecule which already contains one or more, two diastereomers are formed in unequal amounts. The reaction is known as asymmetric synthesis and the existing chiral centre (or centres) brings about asymmetric induction.
- Cram's rule and Prelog's rules can be used to predict the relative configuration of the predominant isomer.