CHAPTER V

SUMMARY OF THE THESIS

Asymmetric synthesis implies the De-novo synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other. Out of the several strategies for getting enantiomerically pure compounds, the one using readily available chiral molecules obtained from the chiral pool, as starting point for synthesising molecules with desired stereochemistry gains prominence. Hence during the past two decades there has been a great deal of interest to find cheap and potential chiral molecules from the chiral pool to accomplish synthetic efforts with a high degree of asymmetric induction. Hence any inexpensive new naturally occurring molecules possessing numerous functional groups and stereogenic centres arose recent interest and curiosity. To the organic chemists, chiral pool, which is composed mainly of naturally occurring amino acids, terpines, sugars and carbohydrates is an invaluable source of stereochemically pure molecules. Majority of them are commercially available and many are inexpensive also.

Effort towards the employment of cheap and inexpensive chiral molecules from the chiral pool in the broad area of asymmetric synthesis, recently this laboratory has identified (2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid [(+)-hydroxycitric acid lactone] as a potential chiron for the synthesis of various optically active synthetic intermediates. As the unique structure and stereochemistry of these compounds matches with the chiral \( \gamma \)-butyrolactone moiety of a large number of complex naturally occurring molecules, these molecules can judiciously be used for their synthesis.
As this thesis concerns with the structural and synthetic investigations of chiral (2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid [(+)-hydroxycitric acid lactone]- a molecule with chiral γ-butyrolactone skeleton, Chapter I deals with literature on the strategies for the synthesis of chiral γ-butyrolactone skeleton of naturally occurring molecules which have versatile synthetic as well as pharmaceutical applications. Stereochemically defined γ-butyrolactones serve as key building blocks for the synthesis of alkaloids, macrocyclic antibiotics, pheromones, antileukemics and flavour components. Generally appropriately functionalised γ-butyrolactones are obtained from molecules such as amino acids, hydroxy acids, carbohydrates, chiral sulphoxides or epoxides. Though already few reviews deal with these topics, an exhaustive inventory of chiral γ-butyrolactone bearing natural products and their general synthetic approaches are lacking. In this background an inventory of natural products containing chiral γ-butyrolactone moiety is listed at first followed by the synthesis of chiral γ-butyrolactone moiety.

Garcinia acid, one of the optical isomers of hydroxycitric acid found extensive application in the pharmacological as well as synthetic fronts. However only very little information is available on Hibiscus acid. The potential of the molecule is not yet explored due to the non-availability of the compound in the market. This is due to the lack of any economically viable large-scale isolation procedure and physical data of the compound. In spite of the ready accessibility in the optically pure form from the chiral pool, no effort has been made towards the use of hibiscus acid in the wide area of asymmetric synthesis. In this background, chapter II describes a detailed reinvestigation on the isolation and complete characterisation of the title compound.

The available method for the isolation of hibiscus acid is applicable only in the case of calyxes of Hibiscus sabdariffa. However it is not possible to isolate the free hibiscus acid following this method which is resulted in the isolation of
hibiscus acid as its dimethyl ester. Two independent methods have been developed for the isolation of hibiscus acid from the calyces/leaves of *Hibiscus sabdariffa* and the leaves of *Hibiscus farcatus*. The purity of the title compound has been improved and hence the compound has been isolated in the stable crystalline form. These modified methods are more convenient and economically viable for the isolation of (2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid. The complete characterisation of the compound, using IR, $^1$H NMR, $^{13}$C NMR, HMBC NMR, mass spectra and other analytical methods has been done for the first time.

To confirm the assignment of $^{13}$C NMR values of the carbonyl carbon atom of the lactone, dimethyl ester and methyl thiomethyl ether from the title compound were prepared for the first time. A through analysis of the spectra clearly shows that the esterification of carbonyl groups and protection of hydroxyl group as methyl thiomethyl ether have not altered the $\delta$ values of $^{13}$C NMR signals of the lactone carbonyl carbon atom. Protection of the hydroxyl group as MTM ether offers a change in the $\delta$ value from $\delta$ 78.4 ppm to $\delta$ 81.7 ppm in the $^{13}$C NMR spectrum which confirms presence of tertiary carbon. The assignment of $\delta$ values are further confirmed by the HMBC spectrum also.

An effort towards carrying over the chiral $\gamma$-butyrolactone moiety of (2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid to any chiral $\gamma$-butyrolactone containing target molecule is presented in Chapter III. To overcome the difficulty in obtaining the dimethyl ester of Hibiscus acid in the pure form, following acid catalysed esterification method, diazomethane has been used successfully. This is found to be an efficient method for the exclusive preparation of Hibiscus acid dimethyl ester. Considering the toxicity and hazardous nature of diazomethane an alternative and general method for the formation of diesters avoiding diazomethane is also developed. This involves the preparation of diesters using diacid chloride as an intermediate from disodium salt. In fact this method is
found to be simple and general for the exclusive preparation of any diester of the title compound. The intermediates disodium salt and diacid chloride derived from Hibiscus acid can offer versatile synthetic applications. The disodium salt has been isolated as a stable white powder.

With the objective of preparing useful chiral precursors for the synthesis of natural products, chiral ligands or chiral catalysts, selective reduction of the acid carbonyl of Hibiscus acid and subsequent reactions were designed. Various borane reagents were tried without success. Considering the unique structure of Hibiscus acid having two carboxyl groups along with a hydroxyl group, it is possible to explain the failure of the reduction reaction. It is known that dicarboxylic acids and hydroxy acids occasionally react with borane reagents to give insoluble polymeric intermediates with the inevitable result of incomplete reaction. Lactones arised out of the partial reduction of dicarboxylic acids have also been reported. The laxity of the reaction could also be due to the formation of stable acyloxyborane complexes of the acid.

To overcome the difficulties associated with the reduction of the carbonyl group of hydroxy acids or dicarboxylic acids various strategies were adopted. Though it is known that the polymers formed during borane reductions is highly soluble in presence of trimethyl borate, no desired product was obtained using borane reagents in presence of trimethyl borate. Sodium borohydride – iodine, a system claimed to reduce carbonyl group of hydroxy acids or dicarboxylic acids in presence of several other functional groups is also tried without success. To block the interference of tertiary hydroxyl group, various protection strategies were attempted during reduction reactions.

The attempted acylation of Hibiscus acid was not successful probably the hydroxyl group is tertiary. Conversion of tertiary hydroxyl group to its MTM ether of the free acid was also not successful. However the dimethyl ester smoothly furnished the MTM derivative. Again the MTM ether of hibiscus acid dimethyl
ester, up-on regeneration of the acid, resulted in the decomposition of the product and hence could not be of any use in borane reductions. The use of NBS, the specific reagent recommended for the bromination of tertiary hydroxyl groups, also did not succeed.

Attempts to effect the decarboxylation using concentrated sulphuric acid also was unsuccessful. This could be due to the opening up of the lactone ring followed by exhaustive fragmentation.

Preparation and synthetic applications of novel chiral 1,2-diols from (2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid in asymmetric reactions is presented in Chapter IV. Having two chiral centres and a trans diol moiety, triesters of (+)-hydroxycitric acid are found extensive application in asymmetric synthesis. Attempted esterification of Hibiscus acid in presence of mineral acids like hydrochloric acid failed to give the desired triester as esterification conditions are also suitable for lactonization. Hence a mixture of diester and triester was resulted.

In this background attention was focussed on the preparation of triacid chloride from trisodium salt for the subsequent follow up to the triester. Efforts were made to prepare the trisodium salt of hibiscus acid to carry out the reaction with thionyl chloride and alcohol to get triester. Treatment of the lactone with aqueous sodium hydroxide followed by the under refluxing condition, furnished the trisodium salt. This route leads to the exclusive formation of the triester. This strategy has been generalised for the preparation of different triesters of hibiscus acid and were completely characterised.

It has been observed that a small amount of diester is formed from the triester, upon storage, through transesterification. This could be avoided by protecting the hydroxyl groups of triesters as ketals. Attempts to prepare ketals of triesters following conventional procedures were failed as the molecule is
susceptible to lactonisation. This could be due to the fact that conditions for ketal formation are ideally suited for lactonisation also.

The difficulty encountered in the preparation of acetonides was overcome by following a modified reported procedure.

The endeavours of asymmetric synthesis is linked to asymmetric catalysis. Recently attention has been focussed especially on transition metal based catalysts. Several enantioselective asymmetric reactions between prochiral reagents in presence of chiral alkoxy titanium (IV) reagents of 1,2-diol of diethyl tartrate as catalyst have been reported. With this objective attempts were made to prepare the aryl substituted polyols of hibiscus acid following reported procedures.

A collage of chiral auxiliaries for stereoselective synthesis are in common use. The most successful reagents are prepared from inexpensive chiral precursors such as amino acids, ephedrine, 3-amino-3-phenylpropane-1,3-diol, \( \alpha \)-hydroxybutyric acid, mandelic acid, tartaric acid, chiral terpene, carbohydrates or steroids.

Although large number of asymmetric Diels-Alder reactions are known, greater degree of asymmetric induction can occur with chiral Lewis acids having \( C_2 \)-symmetric diols as chiral ligands. To explore the effect of 1,2-diols of hibiscus acid as chiral ligands, asymmetric Diels-Alder reactions using (+)-hydroxycitric acid lactone derived chiral ligands having no \( C_2 \)-symmetry was considered.

An examination of the structure of triesters show that the molecular topology matches with 1,2-diol ligands of dialkyltartrates except the fact that one of the C-2 hydrogen is substituted with \(-\text{CH}_2\text{COOR}\). Hence it is a curiosity to study the effect of (+)-hydroxycitric acid lactone derived chiral ligands in the place of tartrate derived ligands in asymmetric organic reactions.

Hence a preliminary study was undertaken to assess the influence of (+)-hydroxycitric acid lactone derived chiral ligands on the enantioselectivity in
asymmetric Diels-Alder reactions. Diels-Alder reaction was carried out employing (4S,5R)-4-(2-hydroxy-2,2-diarylethyl)-2,2-dimethyl-\(\alpha,\alpha,\alpha',\alpha'\)-tetraaryl-1,3-dioxolane-4,5-dimethanol as chiral ligand, in place of \(\alpha,\alpha,\alpha',\alpha'\)-Tetraaryl-1,3-Dioxolane-4,5-Dimethanol (TADDOL) following the reported procedure. The reaction proceeded smoothly and the isolated adduct was purified by column chromatography. Optical activity of the adducts reflects the feasibility of using (4S,5R)-4-(2-hydroxy-2,2-diarylethyl)-2,2-dimethyl-\(\alpha,\alpha,\alpha',\alpha'\)-tetraaryl-1,3-dioxolane-4,5-dimethanol as chiral ligands in place of TADDOL.

Though the adduct was found to be optically active, the present study is limited and a detailed investigation on the feasibility of using (4S,5R)-4-(2-hydroxy-2,2-diarylethyl)-2,2-dimethyl-\(\alpha,\alpha,\alpha',\alpha'\)-tetraaryl-1,3-dioxolane-4,5-dimethanol as chiral ligands in various catalytic systems is required.