CHAPTER VI

Summary of the Thesis

The thesis describes the successful synthesis of 3,4-disubstituted chiral pyrrolidines starting from (2S,3S)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (Garcinia acid) and (2S,3R)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (Hibiscus acid), two less studied, optically active 2-hydroxy acid lactones obtained from the chiral pool. The study reveals that while Garcinia acid is easily getting converted to novel 3,4-disubstituted pyrrolidinediones, reserve for several pyrrolidine based natural products, its diastereomer Hibiscus acid failed to form 3,4 trans fused five membered ring. The pyrrolidinedione obtained from Garcinia acid [(3aS,6aS)-5[2-(3,4-dimethoxy phenyl)ethyl]-3a-hydroxydihydro-2H-furo[2,3-c]pyrrole-2, 4,6[3H,5H]-trione] has been ultimately identified as an analogue of mescaline isocitrirriide lactone, a psychotropic bioprinciple obtained from an endangered cactus species, Mescal. Novel and rare 3-substituted pyrrolidinediones which forms basic unit of several biologically interesting molecules have been obtained in one pot from the tri and diesters of (-) and (+) 2-hydroxycitric acids. It is envisaged that the 3-substituted pyrrolidinediones obtained by the use of appropriate amines are capable of forming C_2 symmetric chiral supramolecular dimers. Garcinia and Hibiscus acids and related (3aS, 6aS)-3a-(acetyloxy) dihydro-5-(phenylmethyl)-6H-furo[2,3-c] pyrrole-2,4,6 (3H,4H)-trione and Methyl (2S)- [2(3S)-1 p-methoxybenzyl-3-hydroxy-2-5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate synthesized for the first time have been subjected to a systematic VCD analysis for establishing the absolute configuration as it is necessary to understand and fine tune the mechanism of interaction of these molecules in solution state in the fat metabolism pathway. For the first time the absolute configuration of Garcinia and Hibiscus acids and related molecules have been verified with VCD.
Hydroxy acids present an attractive starting point for the preparation of a range of chiral synthons, ligands for catalysts and auxiliaries. However hydroxy acids namely Garcinia acid and Hibiscus acid which are endowed with unique stereostructure have evaded the attention of organic chemists. Though several reports pertaining to the pharmaceutical applications of garcinia acid are available especially in fat metabolism and also as anti-obesity agents, the chemistry of these acids still remains unexplored irrespective of the fact that these compounds can be easily made available from cheap natural sources. In this context, a brief description on the title compounds and chiron prepared from them have been presented in chapter I. This highlights the scope and objective of the present work and the ideal suitability of Garcinia acid and Hibiscus acid for the synthesis of chiral pyrrolidines forms the basis of the thesis.

Chiral pyrrolidines are common structural subunits found in a variety of natural and unnatural bioactive products. Besides a review on the general strategies for the synthesis of 2,5-disubstituted pyrrolidines appeared in 1996, no documentation has been available regarding the synthesis of chiral pyrrolidines since then. Acknowledging the potential of these molecules chapter II presents a systematic account on various aspects on the synthesis of chiral pyrrolidines in general. Attention has been focused on the use of chiral hydroxy acids namely Malic acid and Tartaric acid for the synthesis of chiral pyrrolidines through chiral pyrrolidinedione intermediates.

It is certain that the 3 and 2',4-disubstituted chiral pyrrolidine diones obtained from Garcinia acid and Hibiscus acid would be a versatile entry towards a wide range of natural products. With this background efforts have been made to synthesize chiral pyrrolidinediones from Garcinia acid and Hibiscus acid and the same has been presented chapter III.

Simple condensation of Garcinia acid with alkyl amines furnishes pyrrolidinediones in one pot. The formation of pyrrolidinedione have been generalized by using different amines namely benzyl, 4-methoxy benzyl, 2,(3-4 dimethoxy phenyl) ethyl amines and glycine methyl ester. All these new molecules have been completely characterized. Cyclic imide [(3aS,6aS)-5[2-(3,4-dimethoxyphenyl)ethyl]-3a-hydroxydihydro-2H-furo[2,3-c]pyrrole-2,4,6 [3H,5H]-trione] prepared from 2,(3-4 dimethoxy phenyl) ethyl amine was found to be an
analogue of less known mescaline isocitrimide lactone. The rare availability of this molecule increases the scope of this reaction.

The stereofeature of Hibiscus acid, different from that of Garcinia acid, answers the failure of the formation of cyclic imide which is trans fused. Alternatively the reaction was repeated with its dimethylester (dimethyl (2S,3R)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate) and benzyl amine which resulted in the exclusive formation of 3-substituted pyrrolidinedione Methyl (2R)-, [2(3S)-1 benzyl-3-hydroxy-2-5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate. Initially it was mistakenly reported as monoamide [(methyl(2S,3R)-2[(benzylamino)carbonyl]-3-hydroxy-5-oxotetrahydro-3-furan carboxylate] based on spectral values and the position of the hanging amide group was assigned based on the following. Position of –CONHR group in mono amides obtained from Hibiscus acid dimethylester was confirmed by comparing $^{13}$C δ values of methyl (2S,3R)-2[(benzyl amino) carbonyl]-3-hydroxy-5-oxo tetra hydro-3-furan carboxylate with that of Hibiscus acid and its dimethyl ester. HMBC and $^{13}$C spectra of Hibiscus acid lead to the shift assignment of C-3 acid carbonyl as δ 172.9, C-2 acid carbonyl as 167.8 and C-5 lactone carbonyl as δ 173.2. Analogy to this the δ values assigned for Hibiscus acid diester are 170.8, 166.1 and 172.7 respectively. Based on these values the δ values assigned for methyl (2S, 3R)-2[(benzyl amino) carbonyl]-3-hydroxy-5-oxo tetra hydro-3-furan carboxylate are 171.3 (C-3 ester carbonyl), 176.87 (C-2 amide carbonyl), and 173.4 (C-5 lactone carbonyl). More over a selective reduction of the geminal carbonyl of the ester group of methyl (2S, 3R)-2[(benzyl amino) carbonyl]-3-hydroxy-5-oxo tetra hydro-3-furan carboxylate was also carried out.

Surprisingly it was found that the spectroscopic data of the products obtained from the reactions of di and triesters of Garcinia acid with same amines were identical. Hence a reinvestigation of the structure of monoamides was carried out using HMBC and corrected the structure to be 3-substituted Methyl (2R)-, [2(3S)-1 benzyl-3-hydroxy-2-5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate.

The reaction was generalized by preparing methyl (2S)-, [2(3R)- 1[(4-methoxybenzyl -3-hydroxy-2-5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate and methyl (2S)-, [2(3R)- 1[2-(3,4-dimethoxyphenyl) ethylcarbonyl]-3-hydroxy-2-5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate using methoxy benzyl amine and 2-(3,4-dimethoxy phenyl) ethyl amine respectively. All the hitherto unknown imides obtained were completely
characterized. The structural features of pyrrolidinediones are potentially interesting as the same can be used for preparing biologically active molecules.

Dimethyl ester of Garcinia acid [(dimethyl(2S,3S)-tetrahydro-3hydroxy-5-oxo-2,3-furandicarboxylate] gave Methyl (2S)-, [2(3S)-1 benzyl-3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate with benzyl amine. The structure was again confirmed with HMBC as there are other possibilities by which the reaction can take place. The reaction was generalized by preparing methyl (2S)-, [2(3S)-1[(4-methoxybenzyl -3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate and methyl (2S)-, [2(3S)-1[2-(3,4-dimethoxyphenyl) ethylcarbonyl]-3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate using methoxylaniline and 2-(3,4-dimethoxy phenyl) ethyl amine respectively. All these hitherto unknown imides obtained were completely characterized.

Triesters of (-) and (+) 2-hydroxycitric acid obtained from Garcinia acid and Hibiscus acids have been effectively employed as chiral ligands in asymmetric epoxidation and sulfoxide reactions. Further these chiral esters possess carboxyls at 1, 4 and 1,5 position which are ideally suited for the formation of pyrrolidinedione and piperidinedione skeleton with alkyl amines. Independently, upon reaction of these triesters with benzyl amine lead to the formation of chiral pyrrolidinedione. Out of the three possibilities for the cyclisation open to triesters the possibility of formation of piperidine skeleton can be ruled out on the basis of IR spectrum. Further the formation of methyl (2S)-[2(3S)-1-benzyl-3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate by the condensation of carbethoxy group attached to C_3 and carbethoxy group at C_4 of trimethyl (1S,2S)-1,2-dihydroxy-1,2,3-propanetricarboxylate with benzyl amine was confirmed with the help of long range 'H-'C correlations of the HMBC spectrum. The reaction was generalized by preparing methyl (2S)-, [2(3S)-1[(4-methoxybenzyl -3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate using methoxylaniline. However with 2-(3,4-dimethoxy phenyl) ethyl amine the product obtained was (2S) - N' - ((3, 4 dimethoxy phenyl) ethyl) -2- (3S)-1-[(3, 4 dimethoxy phenyl) ethyl] -3- hydroxy -2,5 -dioxo tetra hydro -1 H-pyrrol -3-yl]-2-hydroxy ethanamide. Though this molecule itself is not C_2 symmetric it is envisaged that the supramolecular dimmer is C_2 symmetric. The reaction was further extended with trimethyl ester of Hibiscus acid and with benzyl amine, (2S) -N'-benzyl -2-(3R) -1- benzyl -3-hydroxy -2, 5 dioxotetrahydro -1 H- pyrrol -3-yl] -2-hydroxy ethanamide was obtained and the structure was confirmed with HMBC.
when the reaction was repeated with methoxy benzyl amine and 2-(3,4-dimethoxy phenyl) ethyl amine, the products obtained were identical with that of the products obtained from diesters.

Synthesis of chiral pyrrolidinediones is the most convenient entry towards the synthesis of diversely functionalised chiral pyrrolidines. With this background pyrrolidinediones prepared from Garcinia acid have been attempted to convert to \( \beta \)-hydroxy lactam and pyrrolidine using NaBH\( _4 \), BH\( _3 \).THF and LiAlH\( _4 \) respectively and has been presented in chapter IV. With NaBH\( _4 \) and BH\( _3 \).THF the isolation of any partially or completely reduced product was unsuccessful. However LiAlH\( _4 \) gave \( (3S,4S)-4-\text{(acytloxy)}-3\text{-(acytloxy)methyl}6\text{-benzyl-5-oxotetrahydro-1H-pyrrol-3-ylacetate} \) from \( (3aS,6aS)-3a\text{-acytloxy})\text{dihydro-5-}-(\text{phenylmethyl})-6\text{-furo[2,3-c]pyrrole-2,4,6(3H,4H)-trione} \), which was a 3,4-disubstituted chiral pyrrolidine.

The understanding of conformational properties of molecules is rather easy when absolute configuration is known. Usually Garcinia and Hibiscus acids have been isolated from different sources from different regions assuming that the conformational status have been identical. Though Boll et al reported the absolute configuration of Garcinia and Hibiscus acids to be \( (2S,3S) \) and \( (2S,3R) \) so far no systematic study on the Absolute Configuration of these molecules have been undertaken. Hence a VCD analysis was necessary. VCD analysis of \( (3aS,6aS)-3a\text{-acytloxy})\text{dihydro-5-}-(\text{phenylmethyl})-6\text{-furo[2,3-c]pyrrole-2,4,6(3H,4H)-trione} \) is necessary to establish the actual Absolute configuration of naturally occurring mescaline isocitrimide lactone and thus the parent Isocitric acid lactone. There is also possibility of forming other diastereomers if epimerisation takes place in triesters. The VCD analysis of Methyl \( (2S)-, \) \( (2S)-1\text{p-methoxybenzyl-3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl-2-hydroxyethanoate} \) is necessary to confirm the AC of Methyl \( (2S)-, \) \( (2S)-1\text{p-methoxybenzyl-3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl-2-hydroxyethanoate} \). Hence Garcinia and Hibiscus acids and related \( (3aS,6aS)-3a\text{-acytloxy})\text{dihydro-5-}-(\text{phenylmethyl})-6\text{-furo[2,3-c]pyrrole-2,4,6(3H,4H)-trione} \) and Methyl \( (2S)-, \) \( (2S)-1\text{p-methoxybenzyl-3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl-2-hydroxyethanoate} \) synthesized for the first time have been subjected to a systematic VCD analysis and it is found that no epimerisation has taken place in the case of Methyl \( (2S)-, \) \( (2S)-1\text{p-methoxybenzyl-3-hydroxy-2,5-dioxotetrahydro-1H-pyrrol-3-yl-2-hydroxyethanoate} \).
The VCD of Garcinia acid in DMSO and acetonitrile are not the same as the carbonyl matrix is not well resolved in DMSO and all conformers show individual peaks for each carbonyl having positive phase leading to an ambiguous assignment of AC. In deuterated acetonitrile the three carbonyl peaks could be resolved and their spectral phases matches with the calculated spectra leading to the assignment as SS, and thus the AC is solvent dependent. In the case of Hibiscus acid the width of IR bands does not match with the positions and the expected VCD is broad and the larger number of conformers affects the S/N ratio of the spectrum. Comparison of VCD with calculation in the carbonyl region reveals the AC as S,R.

Due to the rigidity of the system the VCD of (3aS, 6aS)-3a-(acetyloxy) dihydro-5-(phenylmethyl)-6H-furo[2,3-c] pyrrole-2,4,6 (3H,4H)-trione in CDCl₃ is sharp which is in contrast to the VCD of Hibiscus acid. The carbonyl stretches are distinct differing in phase, position and intensity confusing the arrangement to be S,R. The experimental spectrum in CDCl₃ shows an axially symmetrical pattern with Ø1 > Ø2 > Ø1. The intensity of Ø3 is four times greater than that of Ø1. In contrast to this the calculated spectrum shows a rhombic pattern in the carbonyl stretch Ø1 > Ø2 > Ø3 with the intensity of Ø3 twice as much as Ø1 or Ø2. However the pattern and relative intensities of the calculated S,R spectrum do not match with the experimental pattern on the CO stretching region. The calculated spectrum of SS matches perfectly with the experimental spectrum obtained from CDCl₃, except in the carbonyl region where the phase of one of the carbonyl peaks is reversed in the calculated spectrum. The VCD of (3aS, 6aS)-3a-(acetyloxy) dihydro-5-(phenylmethyl)-6H-furo[2,3-c] pyrrole-2,4,6 (3H,4H)-trione in DMSO-d6 (100 %) reveals the negative phase of carbonyl bands 1 and 2 in alignment with the expectation based on the calculated spectrum for the SS configuration. Also the experimental spectrum in DMSO shows a rhombic symmetric pattern with v₁ > v₂ > v₃. Further, the intensity of v₃ is 4 times greater than that of v₁. This is in agreement with the calculated spectrum which also shows a rhombic pattern in the carbonyl stretch v₁ > v₂ > v₃. The calculated spectrum of (3aS, 6aS)-3a-(acetyloxy) dihydro-5-(phenylmethyl)-6H-furo[2,3-c] pyrrole-2,4,6 (3H,4H)-trione in DMSO matches perfectly with the experimental confirming the AC to be S,S.
Out of all the conformers of Methyl (2S)-[2(3S)-1 p-methoxybenzyl-3-hydroxy-2-5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate the VCD of SR conformer does not match with the expected spectrum in the carbonyl region ruling out the S, R configuration. The phase of the computed spectrum in the carbonyl region for some of the SS conformers agree with the experimental spectrum revealing the existence of multiple conformation in solution. Only those conformers whose phase matches well with the carbonyl region were selected and the corresponding spectra were averaged which produced a good fit to the experimental spectrum indicating their dominance in solution. The shift in the position, arise from the well known over estimation of the gas phase calculation. However, the phase and pattern matches very well. The AC of Methyl (2S)-[2(3S)-1 p-methoxybenzyl-3-hydroxy-2-5-dioxotetrahydro-1H-pyrrol-3-yl]-2-hydroxyethanoate is assigned as SS configuration.