Synopsis

The thesis entitled **"Synthesis and Application of Spiro-Cyclopropanecarboxylated Sugars"** is divided into four chapters.

Chapter 1

An Introduction to the chemistry of spiro-cyclopropane-carboxylated sugars

This chapter mainly discuss the synthesis of *exo*-glycals from different sugar based scaffolds and its applications in the synthesis of *C*-glycosides and carbasugars. *exo*-glycals are very important synthetic intermediates in both carbohydrate synthesis as well as in total synthesis of natural products. In addition, they have been versatile starting materials for the synthesis of spiro-cyclopropanecarboxylated sugars. This chapter starts with a brief introduction about the glycals followed by synthesis of *exo*-glycals. Different protocols available for the incorporation of an *exo*-olefin on pyranose or furanose moiety are outlined in the chapter. Out of several methods for the synthesis of *exo*-glycals we have chosen two methods which have been used in the current research work are Petasis reagent mediated conversion of lactones to vinyl ether and 1,8- diazabicyclo[5.4.0]undec-7-ene (DBU) mediated dehydrohalogenation reaction.

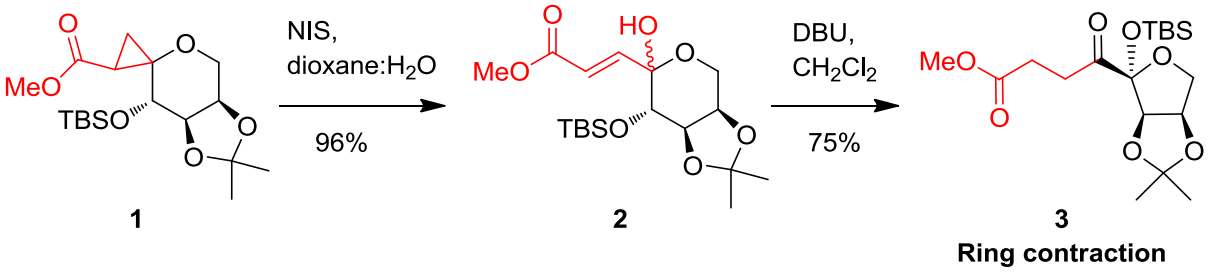
Like 1,2-cyclopropanated sugar derivatives, chemistry of spiro-cyclopropanated carbohydrate moieties are very important in synthetic organic chemistry. Sugar derived spiro-cyclopropanes are synthesized by cyclopropanation of the corresponding *exo*-glycals through metal catalysed reactions. Electrophilic ring opening of these donor-acceptor spiro-cyclopropane carboxylated sugars is a key reaction, applicable to the stereoselective total synthesis of various natural products like asteltoxin, pantolactone homolog, eremantholide A. Due to the ring strain in cyclopropane ring system these spiro-cyclopropanes acts as glycosidase inhibitors, and also useful in the synthesis of spiroketals, bicyclic and tricyclic systems. In comparison with *endo*-glycals, cyclopropanation of *exo*-glycals is not very much explored in the synthetic organic chemistry. To the best of our knowledge, stereoselective cyclopropanation of *exo*-glycals is still an unsolved problem.

Chapter 2

Ring-Contraction *vs* Ring-Expansion Reactions of Spiro-Cyclopropanecarboxylated Sugars

This chapter mainly describes the electrophilic ring-opening of spiro-cyclopropanecarboxylated sugars followed by reaction with 1,8- diazabicyclo[5.4.0]undec-7-ene that revealed an interesting ring-contraction and ring-expansion reactions depending on the substrate and the kind of hydroxyl protective group present adjacent to the spiro centre. A stereoselective method for accessing a new class of carbon chain extended keto-furanoses and *C*-glycosylated bicyclic compounds is reported.

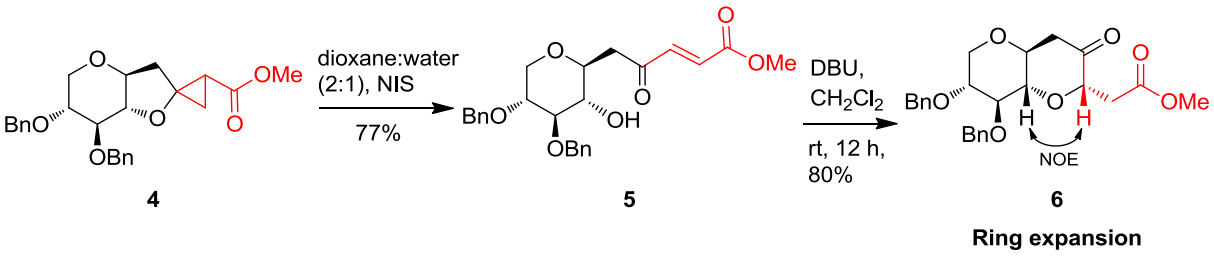
Spiro-cyclopropanecarboxylated sugar derivatives were prepared by cyclopropanation of various sugar derived protected *exo*-glycals with methyl diazoacetate (MDA) and catalytic amount of $Rh_2(OAc)_4$ in moderate yields and with good diastereoselectivity. *N*-Iodosuccinimide (NIS) mediated ring-opening of these spiro-cyclopropanecarboxylated sugar **1** (TBS group adjacent to the spirocenter) in dioxane/water provided the α,β-unsaturated ester **2** in excellent yield. Reaction of **2** with 1,8- diazabicyclo[5.4.0]undec-7-ene in CH_2Cl_2, at 0 °C gave the ring contracted product **3** in good yield as a single diastereomer. This methodology was successfully applied to various sugar derived (pyranose or furanose) spiro-cyclopropanecarboxylates to provide the corresponding hemiacetals in moderate to good yield (Scheme 1).



Scheme 1: Ring contraction reaction of spiro-cyclopropanecarboxylated sugar.

In addition to the ring contraction reaction, ring expansion reaction was also developed using fused bicyclic spiro-cyclopropanecarboxylated sugar derivatives. In this protocol electrophilic ring opening of the spiro-cyclopropane carboxylate **4** with *N*-iodosuccinimide

dioxane/water provided the ring opened α,β-unsaturated ester **5** which upon exposing to 1,8-diazabicyclo[5.4.0]undec-7-ene provided the ring-expanded bicyclic-pyrano[3,2-*b*]pyran derivative **6** as a single diastereomer (Scheme 2). This protocol was also successfully implemented to various fused bicyclic spiro-cyclopropanecarboxylated sugar derivatives to synthesize the corresponding bicyclic compounds.



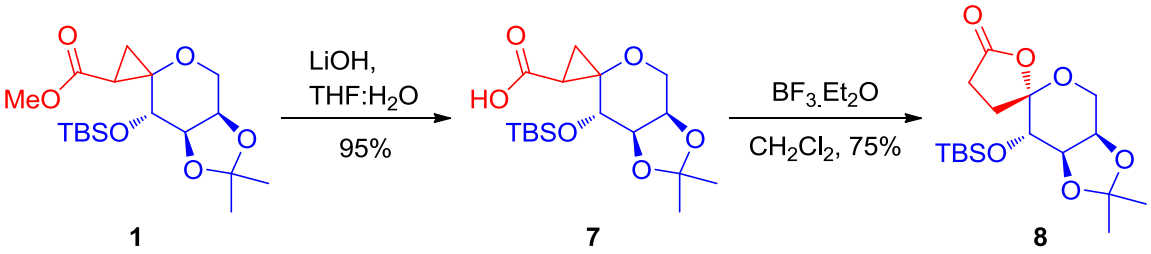
Scheme 2: Ring expansion reaction of fused bicyclic spiro-cyclopropanecarboxylated sugar.

Chapter 3

Stereoselective synthesis of 1,6-dioxaspirolactones from spiro-cyclopropanecarboxylated sugars: Total synthesis of dihydro-pyrenolide D

Chapter 3 mainly address the synthesis of a thermodynamically driven stereoselective synthesis of 1,6-dioxaspiro[4.n]decan-2-one systems (n = 4, 5) from spiro-cyclopropanecarboxylated sugar derivatives. The reaction involves a one-pot cyclopropane ring opening followed by cyclization to form γ-spiroketal γ-lactone moiety. The generality and the stereoselectivity of the reaction are examined by synthesizing a series of spirocyclic systems. A successful approach to the synthesis of saturated analogues of pyrenolide D is also revealed by the application of the current protocol particularly for the formation of crucial quaternary spiro centre of this molecule. These spiro systems are present in number of biologically active natural products like pyrenolide D, crassalactone D, *epi*-crassalactone D, cephalosporolide E and F, papyracillic acid A, B and C.

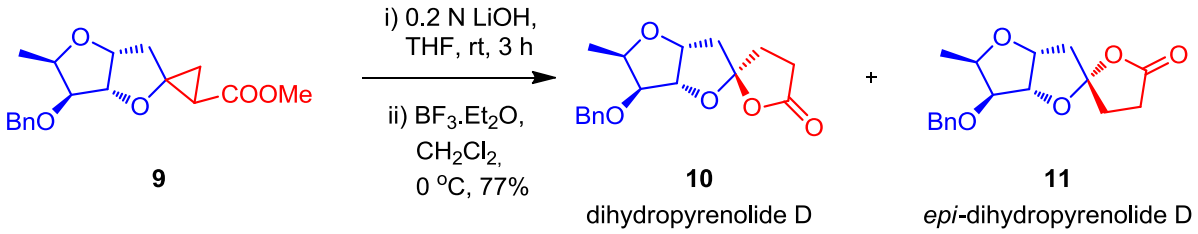
Our synthesis depart from fructose derived spiro-cyclopropanecarboxylated sugar **1** transformed into corresponding carboxylic acid **7** using lithium hydroxide (0.2 N), followed by treatment with boron trifluoride diethyl etherate at 0 ^{o}C to provide the spiro-lactone **8** as single diastereomer in 75% yield respectively (Scheme 3).



1 7 8

Scheme 3: Synthesis of spiro-lactone from spiro-cyclopropanecarboxylated sugar.

The above strategy was applied to various pyranose and furanose derived spiro-cyclopropanecarboxylated sugars to give the corresponding spiro-lactones in good yield. Further the methodology was extended to the synthesis of dihydropyrenolide D and epi-dihydropyrenolide D from xylose derived fused bicyclic spiro-cyclopropanecarboxylate (Scheme 4).



9 10 dihydropyrenolide D 11 *epi*-dihydropyrenolide D

Scheme 4: Synthesis of dihydropyrenolide D and *epi*-dihydropyrenolide D.

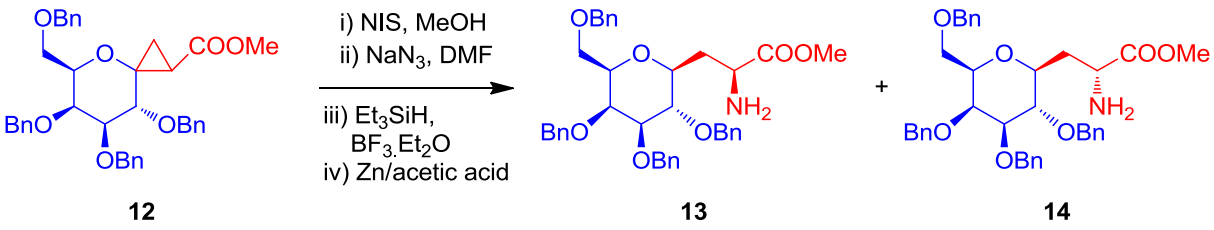
Chapter 4

Synthesis of β-*C*-Glyco Amino-acids from spiro-cyclopropanecarboxylated sugars

Chapter 4 summarizes synthesis of β-*C*-glycosyl α-amino acids from spiro-cyclopropane carboxylated sugars. Stereoselective synthesis of 1-*C*-branched glyco-amino acids involving *N*-iodosuccinimide mediated electrophilic ring opening of spiro-cyclopropane carboxylated sugar, followed by conversion of iodide to azide and then Staudinger reduction/Zn in acetic acid mediated conversion of azide to amine. Interestingly, some of the antibiotics possessing the glyco-amino acid subunit are found to be excellent antibiotics. For

example, furanose derived glyco-amino acids polyoxins, nikkomycins, and pyranose derived glyco-amino acids miharamycins, amipurymicin are some of the anti-biotic molecules isolated from bacterial cultures. In addition β-*C*-glycosidic amino acid structural units are present in the synthesis of β-*C*-galcer, β-*C*-glucer and its new β-aza-*C*-glycoside analogues, glycospingolipids. These are having *in vitro* and *in vivo* natural killer (NK) cell activity.

Electrophilic ring opening of spiro-cyclopropanecarboxylated sugar with *N*-iodosuccinimide in presence of methanol furnished the ring opened iodo-ketal as mixture of diastereomers. Substitution of the iodide with azide followed by removal of OMe with triethylsilane in presence of boron trifluoride diethyl etherate followed by reduction of the azide to amine using Zn/acetic acid provided the β-D-glycosyl α-amino acids **13** and **14** (Scheme 5). Further the developed methodology was extended to glucose and fructose derived spiro-cyclopropanecarboxylated sugars to furnish the corresponding glyco-amino acids in good yield.



Scheme 5: Synthesis of β-*C*-galactosyl alanines.