ABSTRACT

This thesis deals with the reactions and synthetic utility of 1,2-cyclopropanated sugars. The thesis consists of three sections, namely, introduction, results and discussion, and experimental. The introduction commences with the advantages offered by glycals for the synthesis of modified sugars and transmits the concept of strained 3-membered strategy towards the synthesis of higher order carbohydrates of biological significance. Finally, it provides an account of recent developments in 1,2-cyclopropanated sugars.

Towards the exploitation of 1,2-cyclopropanated sugars, which is the main thrust of this thesis, we focussed our attention on their synthetic utility and reactions. By nature, 1,2-cyclopropanated sugars are donor-activated by the pyranose oxygen and considering the electronic factors, their electrophilic ring openings provide products resulting from ring opening, rather than ring expansion.

a- and β-Cyclopropanes **106** and **109** respectively, derived from 2,4,6-tri-*O*-benzyl-D-glucal served as suitable substrates in this regard. The ring openings of **106** and **109** were carried out with different electrophiles in methanol as well as with N-bromosuccinimide (NBS) as the activator (source of Br^+) in various solvents.

The proton induced electrophilic ring opening of **106** in methanol at refluxing temperature was found to be sluggish and incomplete even after 15 days. It was even worse with cyclopropane **109** where no reaction occurred. The ring opening of **106** and **109** with Br^+ as electrophile in methanol resulted in the ring opened products in good yields. Although, the iodonium ion, using N-iodosuccinimide (NIS) as source, was able to open α-cyclopropane **106** in good yield, the inertness of β-cyclopropane **109** towards this reagent prompted us to employ iodoniumdi(s-collidine) perchlorate (IDCP). The reaction of α-cyclopropane **106** with IDCP gave the ring opened products in very good yield

and that of 109 resulted in partial conversion to the ring opened product in moderate yield. The reactions of **106** with both Br^+ and *V* resulted in a mixture of both anomers, whereas that of **109** gave only a-anomers.

Later, in order to show the flexibility of this method, the bromonium ion induced ring opening of cyclopropanes **106** and **109** were carried in 2-chloroethanol, 2,2,2-trichloroethanol, benzyl alcohol and water. α-Cyclopropane **106** underwent ring opening in a facile and high yielding manner, resulting always in anomeric mixtures. The ring openings of β-cyclopropane **109** were slow compared to 106 and resulted exclusively in a-anomers.

Towards further elaboration of this methodology, sugar alcohols were used as nucleophiles, leading to branched-chain disaccharides with defined C-2 stereochemistry. After monitoring the reaction conditions with varying concentrations of sugar alcohol and different reaction times (NBS activation), we succeeded in opening 106 and **109** with three sugars alcohols, 1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (72), 1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose **(150)** and 2,3:4,5-di-*O*-isopropylidine-D-arabinitol in acetonitrile in the presence of 4A molecular sieves in moderate to good yields. In a similar fashion as with other alcohols, the ring opening of **106** in all the three cases gave both the anomers and 109 resulted in exclusive a-anomers.

The scope of 1,2-cyclopropanated sugars as suitable precursors for the stereoselective construction of 2-deoxy-2C-methyl pyranose templates was extended by the mercuric ion mediated ring opening of 106 and **109,** as their direct protonation resulted in poor yields. Mercuric trifluoroacetate was found to be convenient in opening both the cyclopropanes. The methyl or n-butyl 2-deoxy-2C-methyl-β-D-glucopyranosides and 2-deoxy-2-C-methyl-α-D-mannopyranosides, resulting from 106 and 109, respectively, were obtained in good yields (when reaction was carried out in methanol and n-butanol). This methodology was further extended to the cyclopropanes **107** and **110, 108** and **111** derived from galactal and

rhamnal, respectively. However, with β-cyclopropanes **110** and **111**, competitive formation of bis(sugar)mercury compounds limits the applicability of this procedure in a more general fashion. It is interesting to note that in contrast to halonium ion mediated ring openings, in all the cases, the ring openings with mercuric ion were found to yield only one anomer with inversion at C-1.

These experiments clearly reveal that the reactions using halonium electrophiles with β-cyclopropane **109** are slower and display higher anomeric selectivity compared to those of the α-cyclopropane 106. The resulting anomeric ratio in the case of ring openings of 106 was found to be solvent dependent. This excludes the participation of either S_N1 or S_N2 alone in these ring openings. The formation of only a-anomers from cyclopropane 109 suggests that its ring openings involve only S_N2 type processes. However, dependence of the rate of the reactions on the nature of solvent in both the cases, as well as the formation of anomeric mixtures in the case of cyclopropane 106 clearly provides enough support for S_N1 participation.

To better understand the processes taking place, we prepared the a- and p-cyclopropanes 185 and 186, with a free 6-OH group, starting with 3,4-di-*O*-benzyl-6-*O*-trityl-D-glucal (182). Dichlorocarbene addition followed by detritylation using 1 : 2 formic acid/ether and dehalogenation with lithium aluminum hydride in THF yielded the corresponding α-cyclopropane 185. Under Simmons-Smith cyclopropanation conditions, 182 directly yielded the required β-cyclopropane 186.

The intramolecular ring opening of a-cyclopropane 185 in acetonitrile with NBS as an activator in the presence of 4A molecular sieves, took place smoothly within 5h, giving the levoglucosan derivative 187 in good yield. On the other hand, under similar conditions, the reaction with p-cyclopropane 186 was incomplete and yielded the levomannosan derivative **188** in poor yield after 36h. These results clearly indicate that the lower reactivity of the p-cyclopropane 186, when compared to 185, is due to steric hindrance to the approach of the electrophile. While

a-cyclopropane 185 reacts cleanly and rapidly by an S_N2 type process to give the levoglucosan derivative 187 in good yield, the β-cyclopropane 186, with no such option available, forms the levomannosan derivative **188** in much lower yield, probably through an S_N1 mechanism.

Towards further elaboration of the scope of 1,2-cyclopropanated sugars, we anticipated that the products derived from the ring openings of cyclopropanated sugars with electrophiles in water, would serve as a suitable starting point for the construction of chiral α-methylene-δ-valerolactones following a two step oxidation and dehydrohalogenation strategy. Initial failure in the attempts in oxidising halolactols with PCC, PDC and I_2 prompted us to search for a appropriate reagent. Gratifyingly, and most surpisingly, the reaction of p-cyclopropane 106 with IDCP in dioxane-water at 60 - 70° gave the desired α-methylene-δ-valerolactone 195 in moderate yield.

Generalisation of this reaction was made using the cyclopropanes 106, 107, 110, **111** and **112**. The corresponding chiral α-methylene-δ-valerolactones 195 - 198 were obtained in moderate to good yields.

All new compounds prepared in the course of this thesis were completely characterised by their analytical and/or spectral data as appropriate.