

1,2-Cyclopropanated Sugars: Reactions and Synthetic Utility

A Thesis
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Doctor of Philosophy

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*To My
Parents
Teachers and Almighty*


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DECLARATION

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad under the supervision of Professor M. Nagarajan.

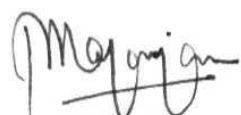

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.



C.V. RAMANA

CERTIFICATE

This is to certify that the work described in this thesis entitled *1,2-Cyclopropanated Sugars: Reactions and Synthetic Utility* has **been** carried out by Mr. **C. V. Ramana** under my supervision and the same has not been submitted elsewhere for any degree.

**M. NAGARAJAN****(THESIS SUPERVISOR)**
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IV

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ABBREVIATIONS

A	Angstrom
Ac	acetyl
AcOH	acetic acid
AIBN	2,2'-azobisisobutyronitrile
aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
CSA	camphorsulfonic acid
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
E	electrophile
Et	ethyl
h	hour(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LTMP	lithium tetramethylpiperidide
MCPBA	m-chloroperbenzoic acid
Me	methyl
min	minute(s)
ml	millilitre(s)
mmol	millimole(s)
Ms	methanesulfonyl (mesyl)
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide

Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichlorochromate
Ph	phenyl
Piv	pivaloyl
Pr	propyl
PTSA	p-toluenesulphonic acid
rt	room temperature
TBDMS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
TBS	tributylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPHB	triphenylphosphinehydrogen bromide
Tr	triphenylmethyl (trityl)
Ts	p-toluenesulfonyl (tosyl)

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 glycols 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.

α - 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 α -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 α -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-isopropylidene- α -D-galactopyranose (72)**, **1,2-O-isopropylidene-3-O-benzyl- α -D-xylofuranose (150)** and **2,3:4,5-di-O-isopropylidene-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 α -anomers.

The scope of **1,2-cyclopropanated** sugars as suitable precursors for the stereoselective construction of **2-deoxy-2-C-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

rhannal, 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

α -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 surprisingly, 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.