SYNOPSIS

Synthesis, Conformation and Glycosidic Bond Stabilities of Septanoside Sugars

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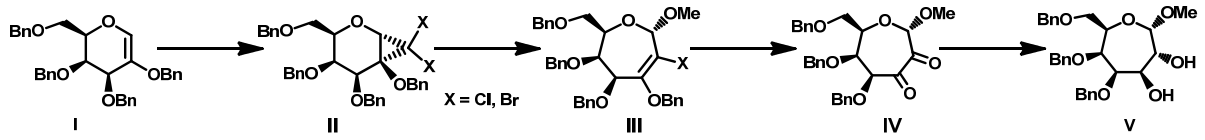
Seven-membered cyclic sugars, namely, septanoses and septanosides, are less commonly known sugar homologues. Synthesis of septanoses arise an interest due to their configurational and conformational features and the attendant possibilities to explore their chemical and biological properties. Septanosides derivatives, mostly, deoxy-septanosides were synthesized, by many synthetic methodologies, such as, Knoevengal condensation, ring-closing metathesis, Bayer-Villeger oxidation and ring-expansion of 1,2-cyclopropanted glycals as key steps. Apart from septanosyl monosaccharides, septanoside containing di- and tri-saccharides were also performed using glycosylation and ring expansions.

Another area of sustained interest is the studies of the stabilities of glycosidic bonds. Acid- and enzyme-catalyzed hydrolysis of glycosidic bond were investigated intensely in the case of pyranosides and furanosides. The explanation of the hydrolysis of such stereomeric sugars were rationalized on the basis of stereoelectronic effects, such as, (i) antiperiplanarity; (ii) synperiplanarity of lone-pair of electrons involed in the hydrolysis process; (iii) steric effects; (iv) field and hyperconjugative effects; (v) conformational effects; (vi) disarming torsional effects and (vii) substituent effects. **Chapter 1** of the thesis describes a survey of (i) synthesis of deoxy-septanosides and septanoside-containing di-and tri-saccharides and (ii) acid-catalyzed hydrolysis of glycopyranosides.

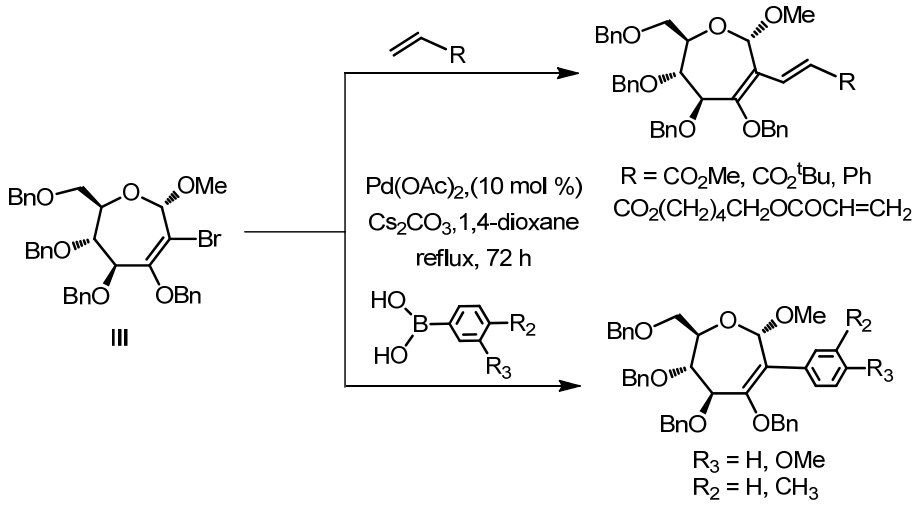
In a programme, it was desired to identify a new methodology for the synthesis of 2-deoxy-2-*C*-septanosides. Synthesis of various septanosides from 2-hydroxy glycals, namely, oxyglycals, involves intermediates, such as, vinyl halide (**III**) and diketone (**IV**) (**Scheme 1**). These intermediates were identified as precursors for the synthesis of desired 2-deoxy-2-*C*-septanosides.

Scheme 1



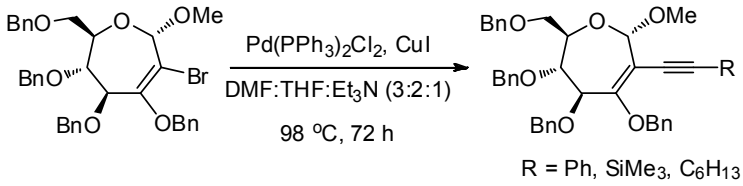
In this context, bromo-oxepine **III** was examined using Pd-catalyzed C-C bond forming reactions, namely, Heck, Suzuki and Sonogashira reaction for the formation of hither-to unknown septanoside, branching out at C-2. Heck coupling and Suzuki coupling reaction of bromo-oxepine was performed using activated alkenes, acrylates and substituted boronic acid, respectively, in presence of $Pd(OAc)_2$, to furnish 2-deoxy-2-*C*-alkyl/aryl septanoside derivatives (**Scheme 2**).

Scheme 2

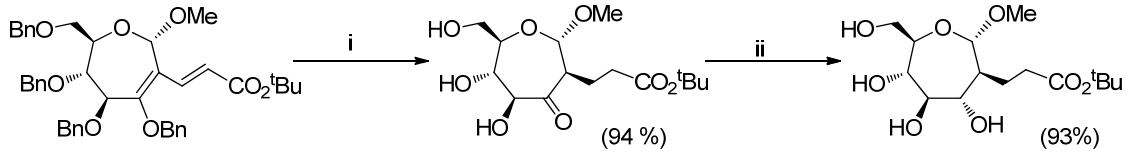


Sonogashira reaction of bromo-oxepine was performed using acetylenes in presence of $Pd(PPh_3)_2Cl_2$ as catalyst and CuI as co-catalyst in DMF:THF:Et_3N (5:3:2) solvent mixture to furnish 2-deoxy-2-*C*-alkynyl septanoside derivatives (**Scheme 3**).

Scheme 3



One of the 2-deoxy-2-*C*-alkyl septanoside derivative was converted to the corresponding protecting-group free 2-deoxy-2-*C*-alkyl septanoside, using hydrogenolysis (Pd/C, H_2) and $NaBH_4$-mediated reduction.

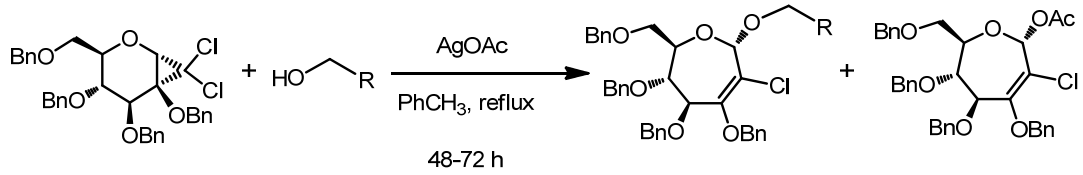


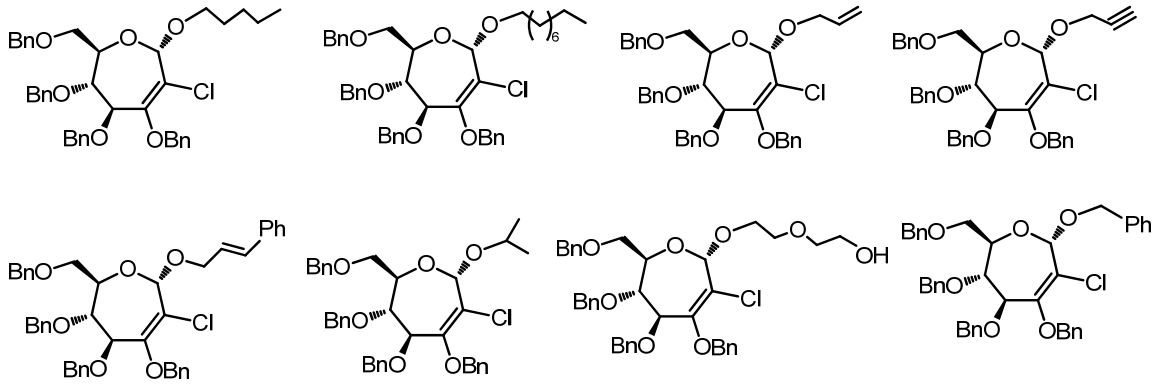
Scheme 4. Reaction conditions: (i) Pd-C (10 %), H_2, MeOH, 24 h; (ii) $NaBH_4$, MeOH, 0 ^oC-rt, 3 h.

Chapter 2 presents details of the synthesis of 2-deoxy-2-*C*-alkyl/aryl/alkynyl septanoside derivatives from a bromo-oxepine.

Continuing the efforts to extend the ring-opening of oxyglycal derived *gem*-dihalo-1,2-cyclopropanted sugar, a Lewis acid-catalyzed ring-opening was considered important. The presence of an additional substituent in C-2 of oxyglycal switches reactivity as compared to glycals. For example, ring-opening of glycal derived *gem*-dihalo-1,2-cyclopropane generates 2-*C*-branched pyranoside, whereas corresponding oxyglycal generates oxepines even when both the reactions were performed under a mild basic condition, illustrating a sufficient reactivity difference between a glycal and an oxyglycal. Thus, ring-opening reaction of *gem*-dichloro-1,2-cyclopropanted oxyglycal in the presence of a Lewis acid, hither-to unknown, was examined. In this event, it was found that ring-opening reaction led to chloro-oxepine derivatives in the presence of AgOAc, using alcohol as nucleophiles. Primary, secondary, unsaturated and aromatic alcohols were used in the ring-opening reaction. The ring-opening reaction was stereoselective and only α-anomer was obtained in a good yield in each case (**Scheme 5**). The counter-anion also reacted in an instance, so as to furnish *O*-acetyl chloro-oxepine during the ring-opening reaction.

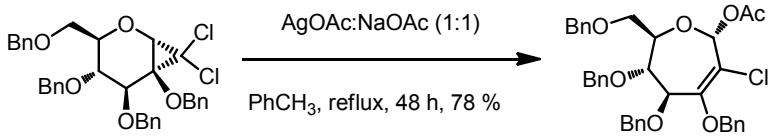
Scheme 5





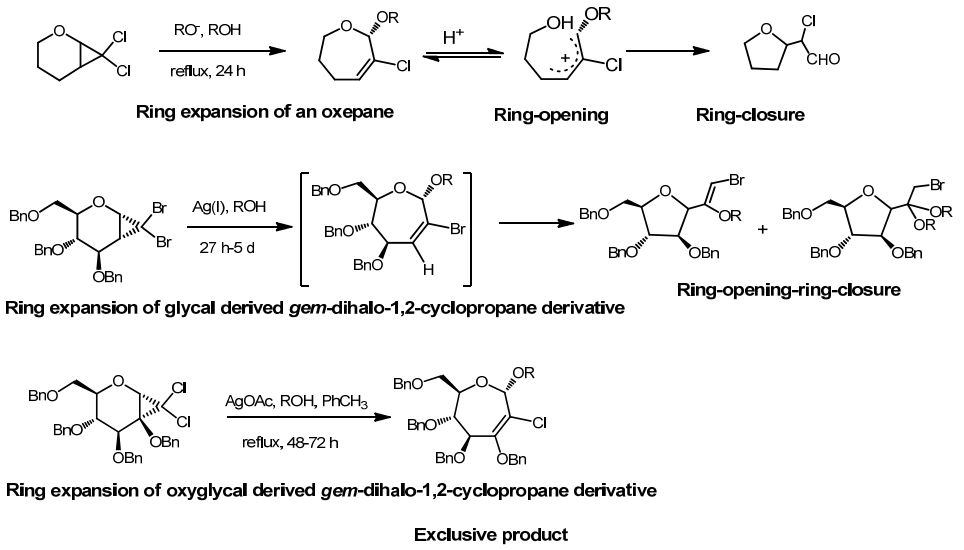
The course of the reaction in the absence of alcohol led to afford only the *O*-acetyl chloro-oxepine (**Scheme 6**).

Scheme 6



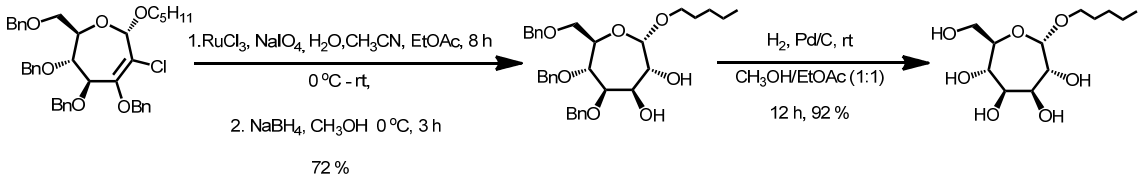
It became pertinent to compare the result this work with that of AgOAc-catalyzed ring-opening of glycal derived *gem*-dihalo-1,2-cyclopropanated sugar, which led to *C*-furanoside derivative, as reported by Harvey and co-workers. The sequence of reactions involved were protonation of the *endo*-cyclic oxygen, followed by ring-opening to generate resonance stabilized allylic ion, which rearranged to *C*-furanoside. In contrast, oxyglycal derived *gem*-dihalo-1,2-cyclopropane studied herein led to chloro-oxepine exclusively, without subsequent rearrangement. Ring-opening of glucal derived *gem*-dihalo-1,2-cyclopropanated sugars, followed by cyclization to *C*-furanoside were likely to have occurred, due to isomerisation of less-substituted *endo*-cyclic double bond at *C*2-*C*3 of oxepine to *C*1-*C*2 unsaturated vinyl ether. Such a reaction was related closely to the acid-catalyzed rearrangement in less-substituted oxepine systems. On the other hand, *gem*-dichloro-1,2-cyclopropanated oxyglycal derived chloro-oxepine did not undergo such an isomerisation, possibly due to unsaturation being present at highly substituted *C*2-*C*3 carbons (**Scheme 7**). Thus, the presence of an additional oxy-substituent at C-2 in oxyglycal derived cyclopropane derivative plays a major role to control the reactivity, as compared to glycal derived cyclopropane derivatives.

Scheme 7



The observation that D-oxyglycal derived cyclopropanes afforded only halo-oxepines, without undergoing further reactions, was confirmed further by the following reactions: (i) $RuCl_3$-$NaIO_4$ mediated oxidation; (ii) $NaBH_4$ reduction and (iii) Pd/C mediated hydrogenolysis (**Scheme 8**).

Scheme 8

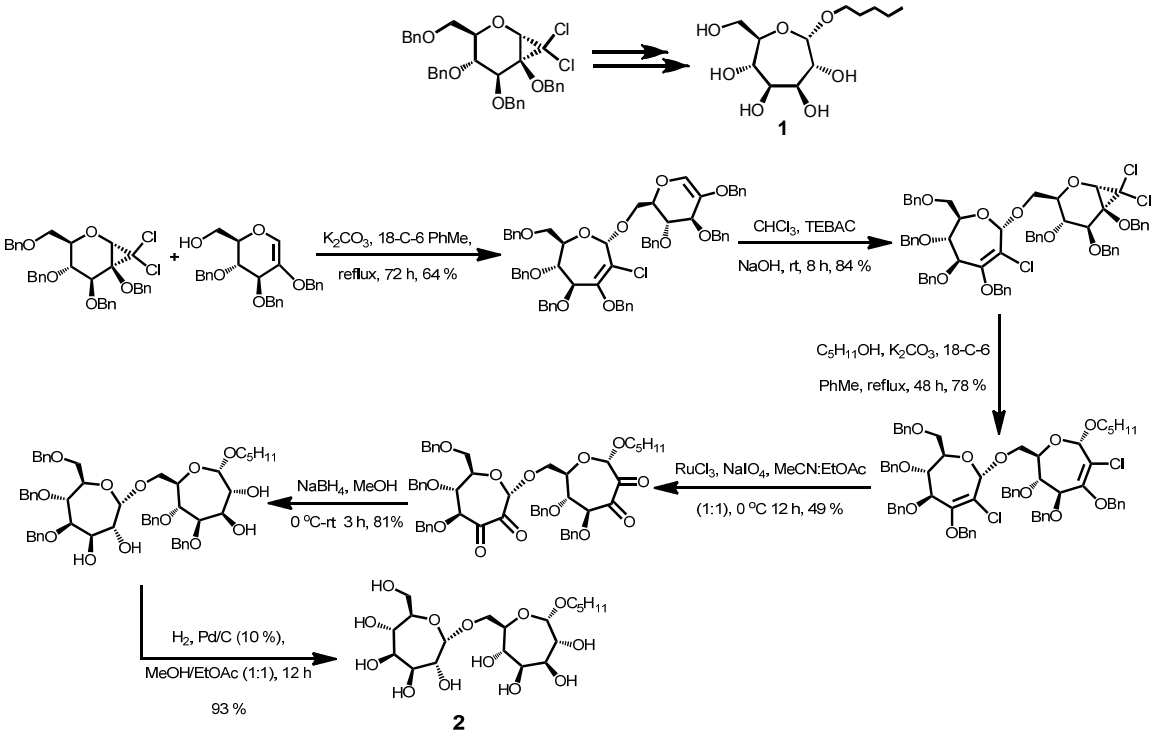


Chapter 3 describes details of the ring-opening reactions of oxyglycal derived *gem*-dihalo-1,2-cyclopropane to exclusive formation of chloro-oxepine in the presence of AgOAc.

It was planned further to synthesize a 1,7-linked-α-D-diseptanoside, through the oxyglycal route. Ring-opening of oxyglycal derived *gem*-dihalo-1,2-cyclopropanated derivative with 6-hydroxy glycal led to 1,7-α-linked disaccharide unit. The following reactions were performed in order to synthesize 1,7-linked-α-diseptanoside **2**: (i) cyclopropanation of the glycal double bond; (ii) ring opening of the *gem*-dihalo cyclopropane; (iii) RuO_4 mediated oxidation; (iv) $NaBH_4$ reduction

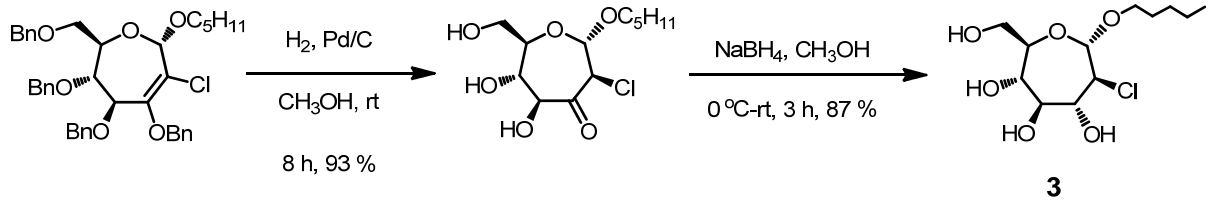
and (v) hydrogenolysis using Pd/C, H_2 (**Scheme 9**). Similar methodology was used for the synthesis of monoseptanoside, namely, *n*-pentyl-D-*glycero*-D-*galacto*-septanoside.

Scheme 9



Oxyglycal route was also used for the synthesis of 2-chloro-2-deoxy septanoside **3**, using hydrogenolysis (Pd/C, H_2) and $NaBH_4$ mediated reduction of chloro-oxepine (**Scheme 10**).

Scheme 10



A kinetic study of the hydrolytic stabilities of mono-and diseptanoside was undertaken using an acid-catalysis, in a subsequent investigation. In the course of studies, it was observed that glycosidic bond in the reducing-end hydrolyzed twice faster than that at the non-reducing end, whereas glycosidic bond in monosaccharide **1** hydrolyzed 1.5 times faster than of reducing-end glycosidic bond in diseptanoside **2**. Further, it was found that the replacement of the C-2 hydroxyl group by a chloride group reduced the rate of hydrolysis (**Table 1**).

Table 1. First order rate constants and thermodynamic parameters for the acid-catalyzed hydrolysis of glycosidic bond in septanosides **1**, **2** and **3**.

Compound	Rate of hydrolysis (k_{obs}) (10^4 s^{-1})				$\Delta H^{\#}$ (kcal/mol)	$\Delta S^{\#}$ (cal/mol K)	$\Delta G^{\#}$ (kcal/mol)
	35 °C	45 °C	85 °C	90 °C			
1	2.34	5.61	-	-	12.95	−32.88	23.26
2	1.54	3.31	-	-	13.18	−33.17	23.56
	-	1.36[a]					
3	-	-	0.418	2.12	72.44	−123.60	27.90

[a] non-reducing end of **2**.

A computational study was conducted, in order to gain further insight into the hydrolysis, using B3LYP/6-311G* level theory in the Gaussian 09 program packages. Calculations using the PCM solvent model with water as the solvent showed that the orientation of hydroxylmethyl group plays an important role. In the case of **1**, the *gg* conformer was calculated stable by 2.12 kcal/mol, as compared, to *tg*-conformer. In the *gg* conformation, the optimal positioning of the dipole C7-O7 stabilized the oxo-carbonium ion in the transition state (**Figure 1**). Also, hydroxyl group at C4 stabilized the transition state, through non-covalent interaction (**Figure 1**). The transition state for the hydrolysis of **1** was found to present activation barrier ($\Delta G^{\#}$) of 19.9 kcal/mol, which was in good agreement with value for **1** ($\Delta G^{\#}$ = 23.26 kcal/mol), as calculated from Erying plot (**Table 1**). On the other hand, inductive effect of the chloride group, as well as, the *tg*-orientation of the hydroxymethyl group appeared to contribute to the slower rate of the hydrolysis.

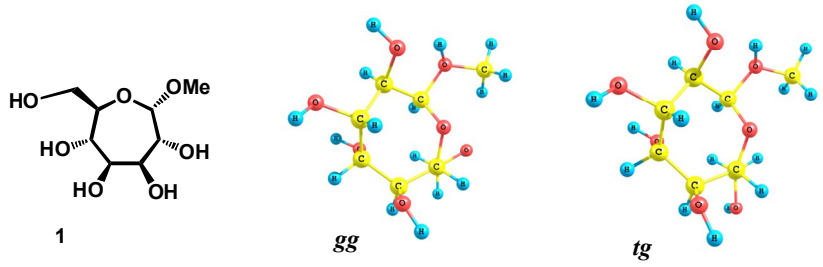
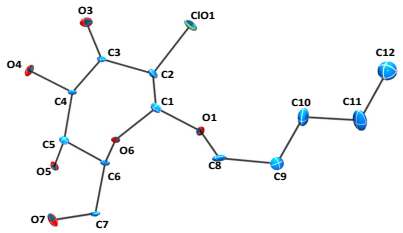


Figure 1. *gg*- and *tg*-conformations in the ground state of **1**.

Chapter 4 describes synthesis of 1,7-linked-α-D-diseptanoside, 2-chloro-2-deoxy septanoside and their acid-catalyzed hydrolysis studies.

Solid-state and solution phase conformation of septanosides are rare at present even when solid-state structures of pyranoside and furanosides are known commonly, that provide rich information of covalent and non-covalent interactions. In this context, single crystal X-ray structural analysis of septanosides, namely, *n*-pentyl-2-chloro-2-deoxy-α-D-*manno*-sept-3-uloside **4** and *p*-bromo phenyl 4,5,7-tri-*O*-benzyl-β-D-*glycero*-D-*talo*-septanoside **5** were analyzed. It was observed that the solid-state structure of **4** adopted twist-chair conformation, namely, $^{5,6}TC_{3,4}$, whereas **5** adopted $^{O,1}TC_{2,3}$ conformation (**Figure 2**). An analysis of non-covalent interactions revealed that a dense network of O−H···O and C−H···O stabilized the crystal lattice of **4**, whereas O−H···O and C−H···π stabilized the crystal lattice of **5**. **Chapter 5** describes the detailed analysis of X-ray crystal structure of two septanoside derivatives including non-covalent interactions responsible for the stabilization of crystal lattice.



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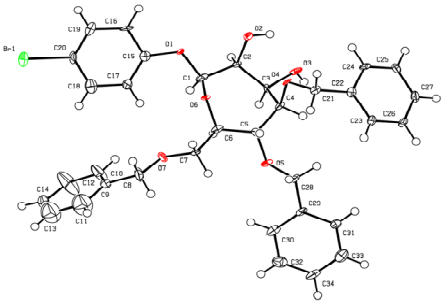

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Figure 2. ORTEP of **4** and **5** with displacement ellipsoids, at a 10 % and 50 % probability level.

In summary, the thesis established the following major results: (i) synthesis of 2-deoxy-2-*C*-alkyl/aryl septanoside from a bromo-oxepine, using organometallic C-C bond forming reactions; (ii) the ring-opening reaction of oxyglycal derived *gem*-dihalo-1,2-cyclopropane in the presence of AgOAc and the effect of additional C-2 oxy-substituent in the reactivity, in comparison to glycal; (iii) an oxyglycal route for the synthesis of 1,7-linked-α-D-diseptanoside, 2-chloro-2-deoxy septanoside and their acid-catalyzed hydrolysis studies and (iv) solid-state X-ray crystal structural analysis and computational analysis of the conformation and non-covalent interactions associated with the stabilization of crystal lattice.

Overall, the studies presented in the thesis provide a new insight into the synthesis, acid-catalyzed hydrolysis and solid-state structural analysis of septanoside derivatives.

The following publications and presentations were based on the Thesis work:

1. **Dey, S**.; Jayaraman, N. "Branching out at *C*-2 of Septanosides. Synthesis of 2-deoxy-2-*C*-alkyl/aryl septanosides from a bromo-oxepine", *Beilstein J. Org. Chem.* **2012**, *8*, 522-527.

2. **Dey, S**.; Jayaraman, N. "Exclusive Ring Opening of *gem*-dihalo-1,2-Cyclopropanated Oxyglycal to Oxepines in AgOAc", *Carbohydr. Res*. **2014**, *389*, 66-71.

3. **Dey, S**.; Jayaraman, N. "Dense Network of O−H···O and C−H···O Interactions in the Solid-state Structure of *n*-Pentyl-2-Chloro-2-Deoxy-α-D-*manno*-Sept-3-Uloside", *Carbohydr. Res*. **2014**, Revised manuscript submitted.

4. **Dey, S**.; Jayaraman, N. "Glycosidic Bond Hydrolysis in Septanosides: A Comparison of Mono-, Di- and 2-Chloro-2-Deoxy-Septanosides", Manuscript submitted.

5. **Dey, S**.; Jayaraman, N. "Solid-state Structure of *p*-Bromo Phenyl 4,5,7-Tri-*O*-benzyl-β-D-*glycero*-D-*talo*-septanoside: Stabilization of the crystal lattice by a network of O−H···O, C−H···O and C−H··· π interactions", Manuscript to be submitted.

6. **Dey, S**.; Jayaraman, N. "Studies of 1,2-Unsaturated Sugars Through Expansion, Shifts and Rearrangements", Oral presentation in 26th International Carbohydrate Symposium, July 2012, Madrid, Spain.

7. **Dey, S**.; Jayaraman, N. "Studies of 1,2-unsaturated sugars through expansions and rearrangements", Poster presentation in International Meeting on Chemical Biology, May 2013, IISER-Pune, India.

8. **Dey, S**.; Jayaraman, N. "Branching out at C-2 of septanosides. Synthesis of 2-deoxy-2-*C*-alkyl/aryl septanosides from a bromo-oxepine", Oral presentation in 27th International Carbohydrate Symposium, Jan 2014, IISc, Bangalore, India.

9. **Dey, S**.; Jayaraman, N. "Ring Opening of Cyclopropanated Oxyglycals: (i) Branching out at *C*-2 of Septanosides and (ii) Studies of Ring Opening Reactions", Oral presentation on Pfizer Symposium on Organic Chemistry, Prof. D.K. Banerjee and Prof. A. Srikrishna Memorial Award Lectures, Jan 2012, IISc-Bangalore, India.