Abstract of the thesis entitled “D-Glucose Derived Nitrone in the Synthesis of Quinolizidine, Indolizidine Alkaloids and Aminocyclopentitol: Promising Glucosidase Inhibitors” to be submitted to the University of Pune for the Degree of Doctor of Philosophy in Chemistry by Mr. Santosh M. Jachak under the guidance of Dr. Dilip D. Dhavale, Department of Chemistry, University of Pune, Pune.

The Thesis is divided into four chapters:

Chapter 1: Nitrones in the Organic Synthesis.

Nitrones are becoming increasingly important in providing intermediates for the synthesis of complex molecules, including natural products and bioactive compounds. In general, nitrones are employed in the 1,3-dipolar-cycloaddition pathways with different olefinic compounds both in inter- and intra-molecular version. These particular dipolar cycloaddition reactions can be considered as concerted but asynchronous [4p + 2P] suprafacial processes and the reactions allow creation of up to three contiguous carbon stereocenters in a single step. In any nitrone-alkene cycloaddition reaction, two pairs of regioisomeric and diastereomeric products can result and these arise from the nitrone and alkene approaching each other in either of two regiochemical senses, and in either an endo- or an exo-fashion. Therefore much effort has focused on the development of regioselective and stereo-selective inter- and intramolecular nitrone-alkene cycloaddition reactions. Alternatively, the reactions of nitrones as electrophiles with organometallic reagents (1,3-addition) are gaining interest in recent years. Easy availability of organometallic compounds as nucleophiles, high electrophilicity of nitrones and feasibility to manipulate the stereo-selectivity at the prochiral nitrone-carbon, under different chelation and non-chelation conditions by the use of suitable Lewis acids, made this approach versatile in organic synthesis. This approach has now found applications in carbohydrate chemistry especially in the synthesis of polyhydroxylated indolizidine, pyrrolidine, piperidine and quinolizidine alkaloids. A brief account of cycloaddition and 1,3-addition reactions will be described.

Chapter 2:

Part A: 1,3-Addition reaction of Allylmagnesium bromide to D-Glucose Derived Nitrone.

The quinolizidine alkaloids are frequently encountered in nature especially in ant species and in the skin of frog and toads. Although, a variety of structurally complex quinolizidine alkaloids are known, the synthesis of polyhydroxylated quinolizidine alkaloids and evaluation of their glucosidase inhibitory activity is a topic of current interest. As a part of our continuing efforts in the synthesis of azasugars, we are now describing a synthesis of trihydroxy quinolizidine alkaloids 1a and 1b using 1,3-addition reaction of allylmagnesium bromide to D-glucose derived nitrone 2 as a key step. Although, a few reports are available for the synthesis of polyhydroxylated quinolizidine alkaloids only a single report describes the synthesis of 1b while, the synthesis of 1a is not reported so far. Our results are depicted in Scheme I and discussed in details in this chapter.
Reagents and conditions: i) Ref. 4a; ii) Allyl Magnesiumbromide (2.5 equiv), THF, -78 °C, 2h, 92%; iii) Zn (2 equiv), Cu(OAc)$_2$, AcOH, 70 °C, 1h, 77%; iv) Cbz-Cl (1.5 equiv), NaHCO$_3$, aq. EtOH, 2h, 76%; v) O$_3$, DCM, DMS, -40 °C, 1h, 91%; vi) a) Ph$_2$P=CHCOOEt (1.5 equiv), MeOH, rt, 2h, 92%; b) H$_2$, 10% Pd-C, MeOH, 25 °C, 12h; c) CH$_3$COONa (4 equiv), MeOH, reflux, 6h, 89%; vii) a) LAH (5 equiv), THF, 0 °C, 1h; b) Cbz-Cl (1.5 equiv), NaHCO$_3$, aq. EtOH, 2h, 82%; viii) a) TFA/H$_2$O (3:2), 0 °C to rt, 2.5h; b) H$_2$, 10% Pd-C, MeOH, 25 °C, 12h, 89%

Scheme 1

Part B: Ring Closing Metathesis in the Synthesis of Quinolizidine Alkaloids.

Olefin metathesis is a process by which alkylidene groups on alkenes are exchanged using Grubb’s catalyst. The functional group tolerance and reasonable stability of Grubb’s catalyst has allowed widespread use in the synthesis of peptides, peptidomimetics and azasugars. We have utilized the ring closing metathesis methodology in the synthesis of trihydroxy quinolizidine alkaloids 1a and 1b. (Scheme 2). The individual allylation of homoallylamines 4a and 4b afforded N-alkylated products 11a and 11b respectively. RCM of 11a and 11b and further cyclisation of nitrogen at C5 to C1 afforded 1a and 1b respectively. Our results are presented in details in this chapter.
Intramolecular aminomercuration reaction constitutes a useful approach to a number of heterocyclic compounds. The use of appropriate mercury salt and solvent can control the regio and stereo-selectivity. In general, the 5-exo-trig cyclisation is preferred over 5-endo-trig. Number of attempts were made to cyclize the homoallylamine 4a to

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\text{Scheme 2}
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**Chapter 3: Intramolecular Aminomercuration in Synthesis of 1-deoxy castanospermine and its 8a-epi analogue.**

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\text{Scheme 3}
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pyrrolidine rings. However, we have noticed an unusual observation that aminomercuration of homoallylamines 4a and 4b underwent by 5-endo-trig cyclisation. The pyrrolidines 13a and 13b utilized in the synthesis of 1-deoxy-castanospermine 16a and 1-deoxy-8a-epi-castanospermine 16b. Our results are depicted in Scheme 3 and are described in details in this chapter.

Chapter 4 1,3-Dipolar Intramolecular Nitrone Olefin Cycloaddition Reaction in the Synthesis of Aminocyclopentitol.

Glycosides inhibitors can be used for treating diabetes, cancer, and viral (HIV, influenza) and bacterial infections and also as insecticides. Aminocyclopentitols such as mannostatin are also powerful inhibitors of glycosidases. Recently it has shown that aminocyclopentitols designed as mimics of α- or β-configured protonated glycosides are potent anomeric and selective inhibitors of glycosidase. In the search for structure-activity relationship, the synthesis and evaluation of the glycosidase inhibitory activities of the aminocyclopentitols is a subject of current interest. Recently, we have reported the preparation and utility of ethyl-3-O-benzy-5,6-dideoxy-1,2-isopropylidene-α-D-xylo-5(£)-eno-heptofuranonooate in the synthesis of polyhydroxylated piperidine and indolizidine alkaloids. The utility of sugar α,β-unsaturated ester 18 in the synthesis of aminocyclopentitol 17 is shown in the Scheme 4 and is described in details in this chapter.

Reagents : (i) Ph$_2$PCHCOOEt, CH$_3$CN, reflux, 92% (ii) TFA-H$_2$O (3 : 2), 0 - 30 °C, 2.5 h, 80%, (iii) HN(OH)Bn.HCl, CH$_3$COONa, aq. EtOH, 30 °C, 8 h, reflux, 4.0, 65%, (iv) Ac$_2$O, Pyridine, DMAP, 30 °C, 18 h, 92-95%, (v) LAH, THF, 0 °C, 1 h, 83%, (vi) 10% Pd/C, HCOONH$_4$, MeOH, reflux, 45 min. 84%, (vii) Methanol- 2N HCl, 30 °C, 40 h, 90%.

Scheme 4 natural and unnatural analogues of aminocyclopentitols is a subject of current interest. Recently, we have reported the preparation and utility of ethyl-3-O-benzyl-5,6-dideoxy-1,2-isopropylidene-α-D-xylo-5(£)-eno-heptofuranonooate in the synthesis of polyhydroxylated piperidine and indolizidine alkaloids. The utility of sugar α,β-unsaturated ester 18 in the synthesis of aminocyclopentitol 17 is shown in the Scheme 4 and is described in details in this chapter.