Chapter 1

Polyhydroxylated Pyrrolidine Iminosugars: Synthesis and Biological Activity
Chapter 1

Polyhydroxylated Pyrrolidine Iminosugars: Synthesis and Biological Activity

1.1. Introduction

Glycosyltransferases and glycosidases are important classes of enzymes involved in the biosynthesis of oligosaccharides with diverse structures. Development of specific inhibitors of such enzymes has been considered to be a useful strategy for the control of cellular functions, especially those related to metabolic disorders and diseases. Some inhibitors of glycosidases and glycosyltransferases have shown promising chemotherapeutic applications against cancer, diabetes, viral infections including AIDS, obesity, and Gaucher's disease. Enzymatic hydrolysis of the glycosidic bonds generally takes place via general acid-base catalyses that requires two critical residues, a proton donor and a nucleophile. Five- or six-membered nitrogen heterocycles carrying hydroxyl groups with specific orientation, commonly known as iminosugars, have been used to mimic the shape and charge of the transition state of the reaction and have been shown to be potent inhibitors of such enzymes. Thus, polyhydroxylated alkaloids isolated from plants and micro-organisms are arousing considerable interest as potential therapeutic agents and as tools used to understand biological recognition processes. The first natural polyhydroxylated alkaloid was the piperidine alkaloid nojirimycin which can be considered as nitrogen analogue of D-glucose in which the ring oxygen has been replaced by nitrogen. Over the years, a large number of polyhydroxylated mono- or bicyclic ring compounds, with nitrogen atom in the ring, have been either isolated from the nature or
synthesized in the laboratory and form a group of iminosugars, which are also known as azasugars. Thus, synthesis of structurally different iminosugars and study of their glycosidase inhibitory activities have been established as an area of active research at the interface of organic chemistry and glycobiology. In general, azasugars are broadly classified as (a) monocyclic azasugars, (b) bicyclic azasugars and (c) bicyclic diazasugars.

1.1.1. Monocyclic azasugars:

(a) The first polyhydroxylated piperidine alkaloid namely nojirimycin (NJ 1) was isolated from a fermentation broth of *Streptomyces roseochromogenes* R-468 in 1967. The more stable analogue of NJ is the 1-deoxynojirimycin (DNJ 2) also called as moranoline which was first prepared by catalytic hydrogenation of NJ and later on isolated from different species of the plant *Morus*. Other examples are mannonojirimycin 3, 1-deoxymannonojirimycin 4, 1-deoxyaltronojirimycin 5 and galactostatin 6. The dideoxy analogues of NJ are fagomine 7, isofagomine 8 and their analogues (Figure 1).

(b) The five-membered polyhydroxylated nitrogen atom containing ring compounds are considered as polyhydroxylated pyrrolidine iminosugar. A few examples of this class are...
3,4-dihydroxy-5-hydroxymethyl-1pyrroline (Nectrisine)\textsuperscript{9,14} 2R,5R dihydroxymethyl 3R,4R dihyroxyprrolidine (DMDP) \textsuperscript{10,15} 2,5-dideoxy-2,5-imino-D-glycero-D-manno-heptitol (homoDMDP) \textsuperscript{11,16} 1,4-dideoxy-1,4-iminopentitol \textsuperscript{12,17} and their analogues. Among these, DMDP shows potent glycosidase inhibitory activity against \(\alpha\)-glycosidases.

(c) The seven-membered analogues of iminosugars, commonly known as polyhydroxy azepanes are little late to be recognized as glycosidase inhibitors. These are di-substituted azepane \textsuperscript{13,18} tri-substituted azepane \textsuperscript{14,19} tetrahydroxyazepane \textsuperscript{15,20} pentahydroxyazepane \textsuperscript{16,21} aminotetrahydroxyazepanes \textsuperscript{17,18,22} In addition, they are potentially useful as DNA minor groove binding ligands (MGBL) due to the flexibility of the seven membered ring.

1.1.2. Bicyclic azasugars:

(a) Polyhydroxylated bicyclic indolizidine alkaloids (six-membered ring fused with the five-membered ring with the nitrogen atom at the ring junction) include castanospermine \textsuperscript{19,23} swainsonine \textsuperscript{20,24} lentiginosine \textsuperscript{21,25} uniflorine-A \textsuperscript{22,26} and their analogues.
(b) Polyhydroxylated pyrrolizidine alkaloids (five-membered ring fused with five-membered ring with the nitrogen atom at the ring junction) are australine 23, alexine 24, causurine 25, hyacinthacine A, 26 and their analogues.

(c) Polyhydroxylated quinolizidine iminosugars (six-membered ring fused to the six-membered ring with the nitrogen atom at the ring junction) are isosteric homologues of castanospermine. For example, 1,7,8,9-tetrahydroxyquinolizidine 27 and trihydroxy quinolizidine iminosugars 28.

(d) Polyhydroxylated perhydro-azaazulene system (five- and seven-membered ring fused with the nitrogen atom at the ring junction) includes trihydroxy-4-azabicyclo-[5.3.0]-decane 29 and pentahydroxy-4-azabicyclo-[5.3.0]-decane 30.
Miscellaneous examples of bicyclic azasugars are noratropanes 31a-c,\textsuperscript{35} and aziridines 32,\textsuperscript{36} 33,\textsuperscript{37} 34.\textsuperscript{38}

\begin{align*}
31a &: R_1 = R_2 = H \\
31b &: R_1 = \text{OH}, R_2 = H \\
31c &: R_1 = H, R_2 = \text{OH}
\end{align*}

1.1.3. Bicyclic diazasugars:

The six- and five-membered ring fused skeleton having one nitrogen atom at the ring junction and another at the anomeric position with hydroxy substituents in either of the rings, are bicyclic diazasugars. For example, kifunensine 35,\textsuperscript{39} nagstatin 36\textsuperscript{40} which are known to act as selective glycosidase inhibitors.

\begin{align*}
35 &: \text{HO}_2\text{C} - \text{N} - \text{C} - \text{O} \\
36 &: \text{HO}_2\text{CH} - \text{N} - \text{C} - \text{CH}_2\text{COOH}
\end{align*}

The search for selective and effective inhibitors of oligosaccharide processing enzymes has promoted intense research for the past 25 years in the synthesis and isolation of stereochemically well-defined polyhydroxylated pyrrolidine alkaloids. This resulted into a number of review articles in the literature.\textsuperscript{41}
**Glycosidase mechanism:**

Enzymes are one of the four major classes of nature’s biopolymers playing a fundamental role in the life processes. In particular, glycosidases and glycosyl transferases are ubiquitous macromolecules, which catalyze glycosyl group transfer reactions that assemble, trim and shape bioactive glycoprotein and glycolipid conjugates. Overall, these processes involve cleavage of the glycosidic bond linking anomic carbon of the sugar with an oligo- or polysaccharide or a nucleoside diphosphate group. The liberated glycosyl group is further transferred to water (by glycosidases) or to some other nucleophilic acceptor (by transferases).

The basic mechanism in the process namely the glycoprotein processing, glycogenolysis inhibition and saccharide-glycolysis inhibition, is to inhibit the cleavage of glycosidic linkages.

**Figure 2. Glycosidase mechanism**
The mechanism was proposed by Koshland in 1953 and was subsequently refined by many workers. The currently accepted form of this mechanism is shown in Figure 2. α-Glycosidase mechanism is generally believed to occur through an E2 type elimination process in which a positively charged aglycon (the leaving group) and the lone pair of the ring oxygen are positioned antiperiplanar, cooperatively facilitating the glycosidic bond cleavage reaction. In the case of the β-glycosidase reaction, the enzyme proceeds via an E2 type mechanism, similar to that of the α-glycosidases, and the protonated substrate II has to go through sterically congested intermediate B that may not favour further reaction. Therefore, it is considered that in the case of a β-glycosidase reaction, the positively charged aglycon leaves via an E1 like mechanism involving the glycosyl cation C that is further rearranged by the lone pair of electrons on the ring oxygen to D. Although, the final reaction intermediate in both the reaction mechanisms is the same flattened, half chair oxocarbonium ion D, the first intermediate in the case of β-glycosidase reaction differs with respect to the position of charge development.

Glycosidases are classified on the basis of stereochemistry of the anomeric glycosidic bond that they cleave. Enzymes catalyzing the cleavage of an α-glycosidic bond are termed as α-glycosidases while those cleaving a β-glycosidic bond are termed as β-glycosidases. Furthermore depending on the sugar residue cleaved, they are called as α-glucosidase, β-glucosidase, α-mannosidase or β-galactosidase.

Glycosidases are also classified on the basis of the stereochemical outcome of the newly formed anomeric bond. The enzymatic cleavage of the glycosidic bond liberates a sugar hemiacetal with either the same configuration as the substrate (retention) or less commonly, the opposite configuration (inversion) and based on this criterion, glycosidases are classified as retaining or inverting glycosidases. The chemical entity that is capable of mimicking either the charge or shape (or both) of the substrate or that of any of the transition states, can act as a
reversible inhibitor of that particular glycosidase. These entities are termed as *glycosidase inhibitors*.

The biological activity of azasugars—the glycomimetics come from the conformational resemblance to natural sugar. The protonation of the ring nitrogen at physiological pH, mimics the developing charge of an intermediate oxocarbonium ion during glycosidic bond cleavage.

\[ \text{OH} \quad \text{HO} \quad \text{HO} \quad \text{H} \]
\[ \text{Physiological} \quad \text{pH} \]
\[ \text{Si} \quad \text{OH} \quad \text{OH} \]

It has been found that various parameters determine the efficiency of good inhibitor. Among the factors that determine the specificity are (i) the chirality and alternation of the hydroxyl groups (ii) the ring structure (iii) the substitution on the nitrogen and (iv) the conformation of the charged species. The synthesis of new analogues of azasugars and evaluation of their glycosidase inhibitory activities thus gained a lot of mutual interest between glycobiology and synthetic organic chemistry. Thus, the presence of azasugar moiety inhibits the process of glycosyl bond cleavage and this inherent capability of azasugars makes them to be recognized as potential therapeutic agents for the treatment of various human disorders.

Over the past one decade, our group is actively engaged in the synthesis and evaluation of a number of polyhydroxylated piperidine, pyrrolidine as well as bicyclic azasugars. Our present work, in the forthcoming chapters, is related to the syntheses of polyhydroxylated pyrrolidine, and indolizidine alkaloids. The reported methods for these compounds are given in the respective chapters whereas, a detailed account of the biological activities and synthetic methodologies for the polyhydroxylated pyrrolidine is given below.
Polyhydroxylated pyrrolidines:

Polyhydroxylated pyrrolidines have been found in a large number of biologically active natural and artificial compounds. Among them, a certain class of polyhydroxylated pyrrolidines (as shown in Figure 3,4) has drawn considerable interest in recent years, primarily due to their ability to inhibit glycosidases. However, the strong inhibitory activity of pyrrolidine glycomimetics is frequently accompanied by low enzyme specificity. This class of inhibitors are considered to mimic the high energy intermediate in the cleavage of glycosidic bond that presumably proceeds through a transition state with substantial sp2 character and positive charge at anomeric center. In general, the five membered azasugars are more flexible and adopts conformation that resembles well with the twisted half-chair conformation of the incipient oxocarbenium cation postulated as the transition state of enzymatic glycoside hydrolysis.

Different stereoisomers may exhibit the same degree of inhibition toward one enzyme, and one stereoisomer may inhibit several glycosidases equally well. It was postulated that the shape recognition and electrostatic interaction between enzyme and the inhibitor play important roles than the stereochemical differentiation in the stabilization of the transition state. Considering the implication of glycosidases in many serious diseases like diabetes, cancers, and viral infections including HIV, such compounds and their derivatives may find useful therapeutic applications for treating these medical conditions. Furthermore, chiral polyhydroxylated pyrrolidines have been used as catalysts, chiral ligands for asymmetric catalysis and chiral auxiliaries.43

In particular, there are two stereochemical motifs that are common to several of these natural products of pyrrolidine alkaloids that includes either cis- or trans- hydroxymethyl substituents at C-2 and C-5 (Figure 3), combined with either a cis- or trans- array of hydroxy...
groups at C-3 and C-4. A brief account of natural occurrence, synthetic aspects and biological activity of pyrrolidine and homopyrrolidine is described in this section.

![Figure 3.](image)

1.2. Natural Occurrence of polyhydroxylated pyrrolidines:

Polyhydroxylated pyrrolidine alkaloids mimicking sugar furanoses in size and shape are now believed to be widespread in plants and microorganisms. In 1976, 2R,5R-dihydroxymethyl-3R,4R-dihydroxypyrrrolidine (DMDP, 2,5-dideoxy-2,5-imino-D-mannitol) 10 (Figure 4), a mimic of β-D-fructofuranose, was found in leaves of the legume *derris elliptica*. DMDP has been reported from many disparate species of plants and has more recently been isolated from the cultured broth of streptomyces species. Sometimes, it co-occurs with DMJ 4, suggesting that it is a common precursor in the biosynthetic pathway.41a
Figure 4. Polyhydroxylated pyrrolidine alkaloids

6-Deoxy derivative of DMDP, namely 1,2,5-trideoxy-2,5-imino-D-mannitol 37, was isolated from the seeds of *Angylocalyx pynaertii* and its isomers 1,2,5-trideoxy-2,5-imino-L-glucitol 38, 1,2,5-trideoxy-2,5-imino-D-altitol 39 and 2,5-dideoxy-2,5-imino-D-fucitol 40 from the bark of *Angylocalyx pynaertii*. Removal of one hydroxymethyl group from DMDP leads to 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1) 41, which was first found in the fruits of *Angylocalyx boutiqueanus*. The acid analogue of D-AB1 L-2,3-trans-3,4-trans-dihydroxyproline (DHP) (42), was isolated from the acid hydrolysates of the toxic mushroom *Amanita virosa*.

In recent years, a number of 6-C-alkylated derivatives of DMDP (or 1-C-alkylated D-AB1) are being discovered more frequently. As shown in figure 4, the first naturally occurring
2,5-dideoxy-2,5-iminoheptitol, namely 2,5-dideoxy-2,5-imino-D-glycero-D-manno-heptitol (homoDMDP) 11, which can be regarded as a ring-contracted form of α-homonojirimycin, was found in the leaves of bluebell *Hyacinthoides non-scripta* 16. Hyacinths (*Hyacinthus orientalis*) further co-produced 2,5,6-trideoxy-2,5-imino-D-mannoheptitol (6-deoxy-homoDMDP) 43 and 2,5,6-trideoxy-2,5-imino-D-gulo-heptitol 44. DMDP derivatives with a longer side chain than homoDMDP and 6-deoxyhomoDMDP have been isolated that include 6-C-butyl-DMDP 45 from *Adenophora triphylla* var. *japonica* (Campanulaceae) 50 and 6-deoxy-6-C-(2,5-dihydroxyhexyl)-DMDP 46 from *Hyacinthoides non-scripta*. A variety of DMDP derivatives with very long side chain such as broussonetine C 47 was isolated from *Broussonetia kajinoki* (Moraceae). 52 The species *Broussonetia kajinoki* is distributed throughout China, Taiwan, Korea, and Japan, and its cortex is known as a raw material of the Japanese paper "washi".

**N-Alkylated naturally occurring pyrrolidine iminosugars:**

The *N*-alkylated polyhydroxylated pyrrolidines are relatively rare in nature (Figure 5). For example, *N*-hydroxyethyl-2-hydroxymethyl-3-hydroxypyrrolidine 48 was isolated from *Castanospermum australe*, a large leguminous tree native to northeastern Australia 53a and the *N*-methyl-1,4-dideoxy-1,4-imino-D-arabinitol 49 and *N*-hydroxyethyl-DAB (1,4-dideoxy-1,4-imino-(hydroxyethyliminiumyl)-D-arabinitol) 50 was isolated from the pods of *A. pynaerti*. 10a,53b

![Figure 5. N-Alkylated pyrrolidine alkaloids](image-url)
1.3. Reported methods for pyrrolidine iminosugars:

Over the past two decades, many studies aimed at stereocontrolled syntheses of these alkaloids have been carried out. Most common strategies for the synthesis of pyrrolidine iminosugar involves (i) intra- and inter-molecular cyclization by $S_N2$ nucleophilic substitution (ii) double reductive amination (iii) nitrore approach (iv) ring closing metathesis and (v) enzyme catalyzed synthesis. A few illustrative examples are described herein.

(i) Intra- and inter-molecular cycloamination by $S_N2$ nucleophilic substitution:

(a) Many examples of synthesis of pyrrolidine homoazasugars by intramolecular $S_N2$ nucleophilic substitution of amino alcohol derivatives are described in the literature. The general strategy is to obtain the amino alcohol derivative through a stereofacial conjugate addition of amine equivalent, like ammonia, to $\alpha,\beta$-unsaturated ester. The *insitu* generated aminol undergoes $S_N2$ displacement to give pyrrolidine azasugar (Scheme 1). A few examples of cyclization of this category are summarized in Table 1.

![Scheme 1](image)
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Products</th>
<th>Yield (%)</th>
<th>De (%)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBSO</td>
<td>H₂, Pd/C</td>
<td>A</td>
<td>62</td>
<td>100</td>
<td>62, 1, 4 cis, 54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bn</td>
<td>Tf₂O, Py</td>
<td></td>
<td>72</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>R = CH₂Ph or alkyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R' = OCH₃ or alkyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaOAc,</td>
<td></td>
<td></td>
<td>78</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>Pd/C,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methanol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = MOM</td>
<td>r-BuOK</td>
<td></td>
<td>83</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>R = TES</td>
<td>r-BuOK</td>
<td></td>
<td>71</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>R = C₂H₅</td>
<td>r-BuOK</td>
<td></td>
<td>71</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>R = TES</td>
<td>r-BuOK</td>
<td></td>
<td>94</td>
<td>100</td>
<td>58</td>
</tr>
<tr>
<td>R = C₂H₅</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NH₃, EtOH</td>
<td></td>
<td>38</td>
<td>cis</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>NH₃, EtOH</td>
<td></td>
<td>88</td>
<td>-</td>
<td>59, 60</td>
</tr>
<tr>
<td></td>
<td>NH₃, EtOH</td>
<td></td>
<td>79</td>
<td>cis</td>
<td>59, 60</td>
</tr>
</tbody>
</table>
(b) Fleet and co-workers\textsuperscript{61} have described one pot azide reduction-cyclization strategy of the γ-azidoepoxide for the construction of the pyrrolidine ring. Thus, epoxides 51 and 53 on separate hydrogenation with palladium black in ethyl acetate undergo reduction of the azide to the corresponding amine and concomitant intramolecular epoxide ring opening to give homopyrrolidine nitriles 52 and 54, respectively (Scheme 2).

(c) Dureault and co-workers\textsuperscript{62} have reported nucleophilic opening of bis-aziridine 55 by thiophenolate or azide ion, followed by cyclization leading to homopyrrolidines (Scheme 3). A mixture of pyrrolidine 56 (major, 5 \textit{exo-tet} cyclization) and piperidine 57 (7\%, 6 \textit{endo-tet} cyclization) was thus obtained.

(d) Sequential nucleophilic attack of primary amine on mesyl/tosyl/ triflate is a well-known reaction and directly provides the aminocyclization.\textsuperscript{63} Thus, gluconolactone 58 was converted to dimesylate derivative 59, which on reaction with benzylamine at 120 °C gave initial nucleophilic displacement of the primary mesylate followed by intramolecular \textit{Sn2}
displacement with inversion of configuration of the secondary mesylate to give protected pyrrolidine 60 (Scheme 4). Hydrogenolysis of the N-benzyl group followed by de-protection of TBDMS functionality afforded 1,4-dideoxy-1,4-imino-galactitol 61.

Scheme 4. Reagents and conditions: (a) acetone, p-TSA; (b) TBDMSCI, imidazole, DMF; (c) LiBH₄, THF, then MsCl, imidazole, pyridine; (d) BnNH₂, 120 °C; (e) H₂, Pd black, EtOH; (f) HCl, MeOH, basic resin.

(e) Y. H. Jung and co-workers reported synthesis of DAB₁ using D-lyxose as a starting material (Scheme 5). The Wittig olefination of 62 with DMSO anion in THF at 45 °C afforded 63 as a ca. 3.1:1 mixture of cis/trans isomers. The hydroxyl moiety of 63 was converted to bromide 64 using appel reaction. The chlorosulphonyl isocyanate (CSI) reaction was carried out on cinnamyl tribenzyl ether 64 followed by desulfonylation using an aqueous solution of 25% aq. sodium sulfite to give allylic amine 65 with a high diastereoselectivity (syn/anti 1:26, 96% ds). Treatment of 65 with potassium tert-butoxide provided the pyrrolidine 66. Ozonolysis of 66 and subsequent reduction of the resulting aldehyde gave the alcohol 67. Finally, hydrogenolysis of O-benzyl and N-Cbz afforded DAB₁ 41.
Scheme 5. Reagents and conditions: (a) NaH, DMSO, BnPPh3Cl, THF, 45 °C; (b) CBr3, PPh3, Et3N, CH2Cl2, 0 °C; (c) (i) CSI, Na2CO3, toluene 0 °C; (ii) 25% Na2SO3; (d) KO'Bu, THF, 0 °C; (e) (i) O3, −78 °C, then NaBH4; (ii) 10% Pd/C, H2, 6 N HCl, EtOH

(f) J-B. Behr reported a short and practical procedure for the preparation homoDMDP 11 and DMDP 10 (Scheme 6). Thus, addition of vinylmagnesium bromide to 2,3,5-tri-O-benzyl-L-xylose 68 gave a desired epimer 69a as a major product (70% de). Activation of the secondary hydroxyl groups with mesyl chloride and base gave bis-mesylate product 70 that on reaction with benzylamine (or azide), gave 71 as the product by SN2' displacement (rather than vinyl pyrrolidine by sequential SN2 displacement). Alternatively, a reaction of 70 with OsO4 in the presence of NMO gave a mixture of the two possible diols 72a,b (20% de) which were separated as the corresponding acetonides 73a and 73b. Nucleophilic displacement of mesyloxy groups in 73a and 73b with benzylamine at 135 °C afforded protected pyrrolidines 74a,b. Acetonide deprotection and hydrogenolysis of 74a afforded homoDMDP 11. Similarly, acetonide deprotection, NaIO4 mediated oxidative cleavage of 74b followed by reduction of gave 75 which on debenzylation afforded DMDP 10.
Scheme 6. Reagents and conditions: (a) vinylMgBr, THF, 0 °C, 91%; (b) MsCl, NEt,

b, CH₂Cl₂, 91%; (c) OsO₄, NMO, acetone/water, 80%; (d) acetone, TsOH, 89%; (e) BnNH₂, 120 °C; (f) 80% HCOOH then H₂, Pd(OH)₂/C, 70%; (g) 5% TFA in CH₂Cl₂, 100%; (h) NaO₄ in EtOH/water, then NaBH₄, 66%; (i) HCOONH₄, 10% Pd/C, MeOH, reflux, 67%.

(g) Singh and Han (Scheme 7) utilized regioselective asymmetric aminohydroxylation (RAA) and aminomercuration protocol as key steps for the synthesis of 84. Thus, RAA reaction of α,β-unsaturated ester 76 using (DHQD)₂PHAL and N-bromoacetamide afforded syn-

aminoalcohol 77 with an excellent regio- (>20:1) and enantio-selectivity (>99%). Protection of secondary hydroxyl group of 77 with p-methoxybenzyl, and -NHAc group with tert-butyl carbamate (Boc) followed by a hydrazinolysis (to cleave acetyl group) afforded 78. Partial reduction of 78 with DIBAL afforded aldehyde which on the Grignard reaction using vinylmagnesium bromide at -50 °C afforded allylic alcohols 80a and 80b in a 7:3 diastereoselectivity. Epoxidation of allylic alcohol 80b with VO(acac)₂/t-BuOOH (TBHP) system at 60 °C gave epoxide 81. Cyclization of epoxide 81 with 2.5 equiv. of TFA and
deprotection of Boc afforded cyclized amine 82 which was purified by column by making its triacetate derivative 83. Finally, deprotection of PMP groups and acidic hydrolysis of acetates afforded polyhydroxylated pyrrolidine 84 as HCl salt. A similar protocol was followed by Chikkanna and Han to get 46a (OBn protection instead of PMB) using intramolecular aminomercuration as a key step to build pyrrolidine ring.67

Scheme 7. Reagents and conditions: (a) K2OsO4,2H2O (5 mol %), (DHQD)2PHAL (6 mol %), LiOH, N-bromosuccinimide, t-BuOH/H2O 2:1, 4 °C, 8 h; (b) (i) NaH, PMBCl, DMF, 0 °C, 10 h, (ii) (Boc)2O, DMAP, THF, reflux, 4 h; (c) DIBAL, CH2Cl2, -78 °C, 3 h; (d) vinylmagnesium bromide, THF, 50 °C, 1 h, then room temp. 1 h; (e) VO(acac)5 (4 mol %), TBHP (2.0 equiv), toluene, 60 °C, 32 h, 38% for 18 and 42% for 22; (f) TFA (2.5 equiv), CH2Cl2, rt, 32 h; (g) Ac2O, Et3N, CH2Cl2; (h) (i) CAN, CH3CN-H2O 4:1, 4 °C, 10 min, (ii) 3N HCl, 3 h.

(h) Izquierdo and co-workers reported68 a chiron approach for the synthesis of 84 using D-fructose as a substrate (Scheme 8). Thus, D-Fructose was converted to 3-O-benzoyl-4-O-benzyl-1,2-O-isopropylidene-β-D-fructopyranose 85 by known synthetic method. Compound 85 was transformed into the corresponding 5-O-methanesulphonyl derivative 8615a which was de-O-benzoylated to the corresponding alcohol 87 (by standard Zemplen conditions without
observing any substitution or elimination of the mesyloxy group at C-5. Oxidation of 87 with the Dess–Martin reagent gave 2,3-diulose 88, which was reduced and benzylated to give 4-O-benzyl-1,2-O-isopropylidene-5-O-methanesulfonyl-β-D-psicosanose 89. S\textsubscript{2} \text{Displacement} of -OMs with lithium azide in DMF gave 90, which was finally benzylated to the required 91. Acetonide deprotection of 91 in acid medium afforded the corresponding diol 94. Reaction of 74 with pivaloyl chloride gave in a highly regioselective manner 5-azido-3,4-di-O-benzyl-5-deoxy-1-O-pivaloyl-α-L-tagatopyranose 93. Hydrogenation of 93 under the presence of Raney nickel catalyst occurred in moderate yield but with high stereoselectivity affording (2R,3S,4R,5S)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)20-O-pivaloylpyrrolidine 94. Deprotection of pivaloyl with NaOMe/MeOH afforded 95 which on hydrogenation gave 84 as its hydrochloride salt.

**Scheme 8. Reagents and conditions:** (a) Ref. 3; (b) Ref. 4; (c) MeOH/NaOMe (cat.), rt; (d) Dess–Martin/Cl\textsubscript{2}CH\textsubscript{2}, rt; (e) NaBH\textsubscript{4}/MeOH, 0 °C; (f) Li\textsubscript{2}N\textsubscript{2}/ DMF, 100 °C; (g) NaH/DMF/BnBr, rt; (h) H\textsubscript{2}O\textsubscript{2} \text{OMs} (i) PivCl/TEA/Cl\textsubscript{2}CH\textsubscript{2}, rt; (j) Raney Ni/H\textsubscript{2}/MeOH; (k) NaMeO/ MeOH; (l) 10\% Pd–O/H\textsubscript{2}/MeOH/HCl.
(ii) Double reductive amination strategy:

Baxter and Reitz⁹⁹ have synthesized three stereoisomeric homopyrrolidine derivatives (97, 98 and 10) by double reductive amination of dicarbonyl sugars using primary amines in conjunction with NaBH₃CN (Scheme 9). Thus, 5-keto-D-fructose 96 on double reductive amination with a variety of primary amines furnished three stereoisomeric pyrrolidine azasugars 97 (related to D-glucitol), 98 (related to L-iditol) and 10 (related to D-mannitol) with varying selectivity (60:30:10 to 92:8:0).

![Scheme 9. Reagents and conditions: (a) microbial oxidation; (b) RNH₂, NaBH₃CN, MeOH, 20-75%](image)

(iii) Nitrone approach:

(a) Dondoni and co-workers⁷⁸ have reported the synthesis of pyrrolidines 106, 107, 108 and 10 by 1,3-addition of formyl anion equivalent to a sugar nitrone (Scheme 10). Thus, 2,3,5-tri-(9-benzyl-D-arabino-furanose 99 on treatment with N-benzylhydroxylamine resulted in the formation of the corresponding arabinosyl hydroxylamine 100 (α-anomer only), which is in equilibrium with the open chain nitrone 101. Subsequently, 1,3-addition of 2-lithiothiazole 102 to nitrone 101 afforded formal adduct (A), which by reductive N-O bond cleavage furnished the δ-hydroxy amine 103. The activation of the free hydroxyl group as O-triflate gives an easy access to an intramolecular substitution reaction leading to the 2-thiazolylpyrrolidine 104. Finally, unveiling of the formyl group from the thiazole ring gave the 2-formyl pyrrolidine 105 as a stable compound. Reduction of the formyl and removal of the benzyl groups afforded the
target pyrrolidine homoazasugar 106. The scope of this methodology was demonstrated by synthesizing other homoazasugars 107, 108 and 10.

Scheme 10. Reagents and conditions: (a) BnNHOH, 88%; (b) 101, Zn, Cu(OAc)$_2$, (102, 58%) $\text{dr} = 9:1$; (c) Ti$_2$O, Py, 65%; (d) TIOMe, then NaBH$_4$, then AgNO$_3$ in MeCN-H$_2$O, 73%; (e) H$_2$, 20% Pd(OH)$_2$/C, then Dowex (OH$^-$), 86%.

(b) In the approach of Lombardo and co-workers$^{71}$ the key reaction involves 1,3-addition of vinylmagnesium chloride to (3S,4S)-3,4-bis-(benzyloxy)-3,4-dihydro-2H-pyrrole-1-oxide a cyclic nitrone 109 easily available from L-tartaric acid (Scheme 11). The major diastereoisomer 110 thus obtained was converted to the intermediate 111, which on oxidative manipulation followed by hydrogenolysis gave 1,4-dideoxy-1,4-imino-D-galactitol 61.
(c) Jager et al.\textsuperscript{72} synthesized homopyrrolidine 118 from D-ribose using the nitrene approach (Scheme 12). Thus, D-ribose on successive treatment with 2,2-dimethoxy propane, PPh\textsubscript{3}/I\textsubscript{2} followed by n-butyllithium was converted to protected pentenose 112. Condensation of 112 with N-benzylhydroxylamine and MgSO\textsubscript{4} afforded nitrene 113, which on vinylation and Cope-House cyclization gave 114 as the major diastereomer. Reduction of 114 to 2-vinyl pyrrolidine 115 followed by dihydroxylation and lead tetraacetate cleavage of the diol 116 gave aldehyde 117. Reduction of the formyl group, de-protection of Cbz and acetonide removal furnished homoazasugar 118.

\begin{center}
\textbf{Scheme 11.} Reagents and conditions: (a) vinylmagnesium chloride; (b) Zn/Cu, AcOH, H\textsubscript{2}O\textsubscript{2}; (c) CbzCl, Et\textsubscript{3}N; (d) AD-mix α, t-BuOH/H\textsubscript{2}O\textsubscript{2}; (e) H\textsubscript{2}, Pd/C, 2 N HCl in EtOH, 1 atm.
\end{center}
Scheme 12. Reagents and conditions: (a) 2,2-DMP, MeOH, HCl, acetone; (b) PPh₃, imidazole, I₂, toluene; (c) n-BuLi, THF, -80 °C; (d) BnNH₂OH, MgSO₄, CH₂Cl₂; (e) vinyl magnesium bromide, THF; (f) CHCl₃, rt; (g) Zn, AcOH, rt; (h) OsO₄, NMO, acetone/H₂O; (i) H₂, Pd(OH)₂/C, MeOH; (j) CbzCl, Na₂CO₃; (k) Pb(OAc)₄, K₂CO₃, CH₂Cl₂, (l) NaBH₄, EtOH; (m) H₂, Pd/C, MeOH; (n) MeOH, HCl (1.5 N), then Dowex 50 W x 8 (H⁺).

(d) M. K. Gurjar et al. reported⁷ the synthesis of cyclic nitrones with L-arabino configuration and its application in the total synthesis of radicamine B 125 (Scheme 13). Thus, L-arabinose was converted to 2,3,5-tri-O-benzyl-L-arabinose 119 using the reported procedure.⁷b The reaction of lactol 119 with hydroxylamine hydrochloride afforded an inseparable mixture (7:3) of E/Z-oximes 120. Selective O-silylation with TBDMSCl, followed by iodination with inversion of the configuration at C-4 afforded E/Z-oxime derivatives 121. Desilylation of 121E and intramolecular nucleophilic displacement of iodine with anhydrous TBAF gave the required cyclic nitrene 122 as a crystalline solid. The reaction of 122 with the Grignard reagent (p-benzyloxyphenylmagnesium bromide) at -78 °C afforded N-hydroxypyrrolidine derivative.
123. Reductive N–O bond cleavage using Zn in aq. NH₄Cl gave the pyrrolidine derivative 124.

Finally, hydrogenolysis of 124 using PdCl₂ in ethanol gave radicamine B 125.

![Scheme 13. Reagents and conditions:](image)

**Scheme 13. Reagents and conditions:**
(a) NH₄OH·HCl, NaHCO₃, EtOH, reflux, 2 h; (b) (i) TBDMSOT, pyridine, rt, 36 h; (ii) I₂, TPP, imidazole, toluene, reflux, 3 h; (c) TBAF, toluene, reflux, 3 h; (d) 4-benzylxylophenyl MgBr, Et₂O–THF (1:2), –78 °C, 2 h; (e) Zn, aq NH₄Cl, reflux, 3 h; (f) H₂, PdCl₂, EtOH, rt, 20 h.

(iv) Ring closing metathesis (RCM):

Ring closing metathesis of diene-substrate containing nitrogen functionality followed by asymmetric dihydroxylation (Figure 6) has found wide applicability in the synthesis of pyrrolidine alkaloids.

![Figure 6](image)
M. D. Diaz-de-Villegas and co-workers reported the synthesis of 1,4-dideoxy-1,4-imino-D-mannitol and D-altritol using RCM approach (Scheme 14). Thus, allylation of 126 derived from glyceraldehydes, with allyl bromide using NaH and DMF gave 1,6-dine 127. Treatment of 127 with first generation Grubbs catalyst A afforded dehydropyrrolidine 128. The yield of the reaction was increased up to 98% when the RCM was carried out using the more active second generation Grubbs’ catalyst B. Reaction of 128 with AD-mix-β (Sharpless asymmetric epoxidation) gave desired diol 129 in high diastereoselectivity (dr 10/1). Finally, N-debenzylation and acetonide deprotection in 129 was achieved in one step by catalytic hydrogenolysis with Pd(OH)$_2$/C in the presence of HCl to give 1,4-dideoxy-1,4-imino-D-mannitol 130 as its HCl salt.

Alternatively N-acrylation of 126 with acryloyl chloride followed by RCM of the resulting amide 131 gave intermediate 132. Treatment of 132 with a catalytic amount of OsO$_4$ in the presence of NMO led to a dihydroxylated product 133 in high de. Finally, reduction of the carbonyl group in 133 followed by one step acetonide and benzyl deprotection provided 1,4-dideoxy-1,4-imino-D-allitol 134 as its HCl salt.
Scheme 14. Reagents and conditions: (a) allyl bromide, NaH, DMF, 0 °C to rt, 12 h; (b) (i) 8% Grubbs’ catalyst A, CH₂Cl₂, rt, 12 h, 85%; (ii) 5% Grubbs’ catalyst B, CH₂Cl₂, reflux, 24 h, 97%; (c) AD-mix-β, MeSO₂-NH₂, tert-butanol/H₂O (1:1), 0 °C to rt, 24 h; (d) H₂ Pd(OH)₂/C, MeOH/HCl (100:1), rt, 12 h; (e) acryloyl chloride, Et₃N, CH₂Cl₂, 0 °C to rt, 3 h; (f) (i) 8% Grubbs’s catalyst A, CH₂Cl₂, reflux, 36 h, 85%; (ii) 5% Grubbs’ catalyst B, CH₂Cl₂, reflux, 36 h; (g) 10% OsO₄, NMO, acetone/H₂O, rt, 48 h; (h) LiAlH₄, THF, reflux, 3 h; (i) H₂, Pd(OH)₂/C, MeOH/HCl (100:1).

(b) Blechert and co-workers reported the synthesis of polyhydroxylated pyrrolidines 144, 142, and 143 using RCM as a key step (Scheme 15). Thus, Vinyl glycine methyl ester 135 on N-Cbz protection followed by chemoselective reduction gave carbamate aminol 136 that on allylation gave N-allyl-4-vinyl-oxazolidine-2-one 137. Hydrolysis, decarboxylation and Boc protection of 137 gave metathesis precursor 139. The RCM of 140 with 4 mol % Cl₂(PCy₃)₂Ru=CH-CH=CPh₂ (Grubbs catalyst) in benzene gave dihydroprolinol derivative 140 which was subsequently protected with trityl chloride. Tritylated product 133 on dihydroxylation with catalytic osmium tetroxide, followed by removal of Boc and trityl protection gave pyrrolidine 141. While, epoxidation of 140 and regioselective epoxide ring
opening with LiBH$_4$ and removal of protecting groups gave 142. Similarly, 143 was obtained by epoxide ring opening using KOH and deprotection of protecting groups.

Scheme 15. Reagents and conditions (a) (i) CbzCl, NaHCO$_3$, CH$_2$Cl$_2$, H$_2$O, rt, 30 min; (ii) LiBH$_4$, CH$_2$OH, Et$_2$O, rt, 2 h; (b) NaH, DMF, allyl bromide, rt, 24 h; (c) (i) NaOH, EtOH, H$_2$O, 80 °C, 4 h; (ii) Boc$_2$O, Et$_3$N, CH$_2$Cl$_2$, rt, 6 h; (d) (i) 4 mol % C$_2$(Pcy$_3$)$_2$Ru=CHCH=CPh, PhH, rt, 32 h; (ii) TrCl, Et$_3$N; (e) (i) OsO$_4$, Me$_3$NO; (ii) HCl, MeOH; (f) (i) MCPBA, Et$_2$O; (ii) LiBH$_4$, MeOH; (iii) HCl, MeOH; (g) (i) MCPBA, Et$_2$O; (ii) KOH, H$_2$O; (iii) HCl, MeOH.

(v) Enzyme catalyzed strategy:

Use of aldolase for the synthesis of a number of chiral α,β-dihydroxy-γ-azido-ketosugars and elaboration of this chiral synthon to a number of pyrrolidine homoazasugars have been described by Paulsen et al.$^{26}$ and C.-H. Wong et al.$^{77}$ This pathway involves aldol condensation of α-diazo aldehyde with DHAP using aldolase enzyme that led to enantioselective formation of α,β-dihydroxy-γ-azido keto sugar which on treatment under hydrogenation gave enantiomerically pure homoazasugars.
This sequence was exploited in the synthesis of a variety of pyrrolidine iminosugars that are described in Table 2.

**Table 2. Pyrrolidine homoazasugars from azido keto sugar**

<table>
<thead>
<tr>
<th>azido keto sugar</th>
<th>Yield %</th>
<th>de %</th>
<th>pyrrolidine homoazasugars</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO(\text{N}_3)(\text{O}_2)(\text{H}_2)</td>
<td>97</td>
<td>100</td>
<td>HO(\text{N} = \beta)(\text{O}_2)(\text{H}_2)</td>
<td>78</td>
</tr>
<tr>
<td>HO(\text{N}_3)(\text{O}_2)(\text{OH}_2)</td>
<td>67</td>
<td>100</td>
<td>HO(\text{N} = \alpha)(\text{O}_2)(\text{H}_2)</td>
<td>79</td>
</tr>
<tr>
<td>HO(\text{N}_3)(\text{O}_2)(\text{OH}_2)</td>
<td>100</td>
<td>100</td>
<td>HO(\text{N} = \beta)(\text{O}_2)(\text{H}_2)</td>
<td>80</td>
</tr>
<tr>
<td>HO(\text{N}_3)(\text{O}_2)(\text{OH}_2)</td>
<td>80</td>
<td>100</td>
<td>HO(\text{N} = \beta)(\text{O}_2)(\text{H}_2)</td>
<td>81</td>
</tr>
<tr>
<td>HO(\text{N}_3)(\text{O}_2)(\text{OH}_2)</td>
<td>80</td>
<td>100</td>
<td>HO(\text{N} = \beta)(\text{O}_2)(\text{H}_2)</td>
<td>81</td>
</tr>
<tr>
<td>HO(\text{N}_3)(\text{O}_2)(\text{OH}_2)</td>
<td>76</td>
<td>100</td>
<td>HO(\text{N} = \beta)(\text{O}_2)(\text{H}_2)</td>
<td>82</td>
</tr>
<tr>
<td>HO(\text{N}_3)(\text{O}_2)(\text{OH}_2)</td>
<td>76</td>
<td>100</td>
<td>HO(\text{N} = \beta)(\text{O}_2)(\text{H}_2)</td>
<td>82</td>
</tr>
</tbody>
</table>

Recently, our group has reported two different chiron approaches for the synthesis of pyrrolidine iminosugar. First approach involves intermolecular conjugate addition reaction on
sugar derived α,β-unsaturated ester for the synthesis of N-alkylated iminosugar. Thus, compound 144a,b (Scheme 16) on intermolecular conjugate addition and N-alkylation with ethyl bromoacetate followed by reduction gave 145. Protection of primary hydroxyl with acetate in 145 afforded diacetate derivative 146. Debenzylation followed by N-Cbz and 3-O-acetate protection afforded 147 that on acetonide deprotection, metaperiodate cleavage (to chop C-1) and hydrogenation afforded the target molecules 148a,b.

The second approach involves intermolecular addition of amine to D-glucose derived α,β-unsaturated ester as a key step. Thus, α,β-unsaturated ester 144a (Scheme 17) on acetonide deprotection, chopping anomeric carbon and intramolecular conjugate addition gave pyrrolidine 149 and 150 which on LAH reduction followed by benzyl deprotection afforded pyrrolidine 151 and 152, respectively.
Scheme 17. Reagents and conditions: (a) (i) TFA-H₂O (3:2), 0-25°C, 3 h; (ii) NaI, acetone–water, 0-25°C, 40 min; (iii) BnNH₂ (1.0 equiv), cat. CH₃COOH, NaCNBH₃ (1.5 equiv) dry MeOH, -20°C, 3 h then 25°C, 8 h; (b) LiAlH₄, THF, 0-25°C, 75 min; (c) H₂, Pd/C, 80 psi, MeOH, 18 h.

1.4. Biological activity

Glycosidase inhibition:

Most of the polyhydroxylated alkaloids that are listed in Table 3 show moderate to high glycosidase inhibitory activity in a reversible and competitive manner. Although the type of the glycosidases that will be inhibited by certain polyhydroxylated alkaloids can be predicted to some extent from the number, position and configuration of the hydroxyl groups there can be marked differences in the inhibition of isoenzymes of a given glycosidase in different species and even within the same cell. Large number of iminosugars are studied for glycosidase inhibition but only few of them are developed as drug. N-hydroxyethyl-DNJ (miglitol) proved to be a potent inhibitor of the glycogenolysis induced by glucagon, Ca²⁺ ionophores or anoxia and now commercially available (GLYSET™ in USA and Canada) for the treatment of type II diabetes.⁵⁵ N-Butyl-1-DNJ (zavesca) has also successfully completed clinical trials for type I Gauchers disease and lysosomal storage disorder.⁵⁶ Mulberry tree additionally occur 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) (41), which was found to be a potent inhibitor of mammalian glycosidases, such as ER α-glucosidase II, Golgi α-mannosidases I and II, and
digestive α-glucosidases. In 1976, 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) (10) mimicking β-D-fructofuranose was found to be a more potent inhibitor of yeast α-glucosidase than mammalian α-glucosidases. Recently, the L-enantiomer of DMDP was synthesized from D-gulonolactone and found to be a more powerful and more specific α-glucosidase inhibitor than the natural product DMDP. More interestingly, the natural D-enantiomer is a competitive inhibitor of α-D-glucohydrolases but its synthetic L-enantiomer is a noncompetitive inhibitor. Similarly, the L-enantiomer of DAB was found to be a more potent inhibitor of mammalian digestive α-glucosidases than the enantiomeric natural product DAB. The IC₅₀ values of polyhydroxylated pyrrolidines are summarized in Table 3. Watson et al. reported that 11 is a more potent inhibitor (Kᵢ = 1.5 μM) of almond β-glucosidase than DMDP (10) (Kᵢ = 10 μM). A similar type of result was obtained by Asano and co-workers that 11 was a potent inhibitor of bacterial (Caldocellum saccharolyticum) β-glucosidase (IC₅₀ = 3.8 μM) and mammalian trehalase (IC₅₀ = 5 μM). The 6-deoxy derivative of 8, as in 37, 38, 40 showed very weak inhibition towards the glycosidases tested except α-L-fucosidase. The deoxygenation at C-6 of 11 relative to 43 significantly suppressed its inhibitory activity toward β-glucosidase, β-galactosidase and trehalase whereas its potency toward rice and rat α-glucosidases was greatly enhanced (Table 3). Thus, the presence of C-6 OH is essential in DMDP (8) for inhibitory activity and the introduction of CHOH functionality to 8 (as in 45) enhances the potency toward glycosidase inhibition. All cis substituted compound 84 showed remarkable selectivity in the inhibition of α-galactosidase (Kᵢ = 0.05 μM). The N-hydroxy ethyl residue (50) of DAB markedly lowered or abolished its inhibition toward all enzymes tested.
Table 3. IC$_{50}$ of pyrrolidine iminosugars

<table>
<thead>
<tr>
<th>enzyme</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>a-glucosidase</td>
<td></td>
</tr>
<tr>
<td>rice</td>
<td>300</td>
</tr>
<tr>
<td>rat intestinal maltase</td>
<td>290</td>
</tr>
<tr>
<td>rat intestinal sucrase</td>
<td>NI*</td>
</tr>
<tr>
<td>rat liver lysosomal</td>
<td>92</td>
</tr>
<tr>
<td>Yeast</td>
<td></td>
</tr>
<tr>
<td>rat intestinal isomaltase</td>
<td>91</td>
</tr>
<tr>
<td>trehalase (porcine kidney)</td>
<td>200</td>
</tr>
<tr>
<td>a-galactosidase (coffee bean)</td>
<td></td>
</tr>
<tr>
<td>b-galactosidase</td>
<td></td>
</tr>
<tr>
<td>bovine liver</td>
<td>3.3</td>
</tr>
<tr>
<td>a-L-fucosidase</td>
<td></td>
</tr>
<tr>
<td>bovine epididymis</td>
<td>NI</td>
</tr>
<tr>
<td>b-glucosidase (Caldocellum saccharolyticum)</td>
<td>11</td>
</tr>
<tr>
<td>b-Xylosidase</td>
<td>2.5</td>
</tr>
<tr>
<td>Invertase</td>
<td>5.25</td>
</tr>
<tr>
<td>a-mannosidase</td>
<td></td>
</tr>
<tr>
<td>rat epididymis</td>
<td>NI</td>
</tr>
<tr>
<td>b-mannosidase</td>
<td></td>
</tr>
<tr>
<td>rat epididymis</td>
<td>14</td>
</tr>
</tbody>
</table>

*a NI = less than 50% inhibition at 1000 µM.
1.5. Conclusion

In conclusion, we have described a brief account of synthetic methods for polyhydroxylated pyrrolidines. The literature survey indicated a wide interest in the synthesis and evaluation of biological activities of these compounds. As a part of our continuing interest in the synthesis and evaluation of glycosidase inhibitory activity and immunomodulatory activity of azasugars, we have developed new strategies for the synthesis of five-membered as well as bicyclic azasugars. Our results in this direction are discussed in forthcoming chapters.
1.6. References


35
Niida, T.; Nobe, M.; Ogawa, Y. J. Antibiot. 1984, 37, 1579. (b) Fellows, L. E.; Bell, E.
Commun. 1979, 977.
35, 2788. (b) Jespersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols,
Antibiot. 1988, 41, 296. (b) Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T.
15. Welte, A.; Jadot, J.; Dardenne, G.; Martier, M.; Casimir, J. Phytochemistry 1976, 15,
747.
Phytochemistry 1997, 46, 255.


33. Lindsay, K. B.; Pyne, S. G. Tetraedron 2004, 60, 4173.


47. Nash, R. J.; Bell, E. A.; Williams, J. M. *Phytochemistry* 1985, 24, 1620.


57. Dhavale, D. D; Matin, M. M. Arkivoc 2005, iii, 110.


1995, 34, 412.