Chapter 2: Part A
1,3-Addition Reaction of Allylmagnesium Bromide to D-Glucose Derived Nitrone:
Synthesis of Quinolizidine Alkaloids

Introduction:

Azasugars are the compounds in which, a ring oxygen atom in a small or medium ring is replaced by a nitrogen atom and the presence of stereochemically well defined hydroxyl groups, at the carbon centers, resemble sugar like structure. These compounds, also called as iminosugars, are promising glycosidase inhibitors\(^1\) and render interesting medicinal properties for the treatment of various diseases such as cancer,\(^2\) diabetes,\(^3\) viral infection including AIDS,\(^4\) obesity\(^5\) and autoimmune response.\(^6\) Nojirimycin 21 is one of the first naturally occurring carbohydrate mimic azasugar in which a nitrogen atom replaces the oxygen in the D-glucose ring.\(^7\) 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. These compounds thus form a group of azasugars. In general, the azasugars are broadly classified as follows:

1) Polyhydroxylated piperidine alkaloids (six membered) e.g. nojirimycin 21, 1-deoxy-nojirimycin 22,\(^8\) mannonojirimycin 23,\(^9\) 1-deoxy-mannonojirimycin 24,\(^10\) galactostatin 25\(^11\) and their analogues.

\[\text{21} \quad R = \text{OH} \]
\[\text{22} \quad R = \text{H} \]
\[\text{23} \quad R = \text{OH} \]
\[\text{24} \quad R = \text{H} \]
\[\text{25} \]
II) Polyhydroxylated pyrrolidine alkaloids (five membered) such as 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine \( \text{(DMDP)} \) 26.\(^{12} \)

\[
\text{HO} \quad \text{HO} \\
\text{OH} \\
\text{OH} \\
\text{OH} \\
\text{N}
\]

III) Polyhydroxylated bicyclic indolizidine alkaloids (six membered ring fused with the five membered ring) e.g. castanospermine 27,\(^{13} \) swainsonine 28\(^{14} \) and lentiginosine 29.\(^{15} \)

IV) Polyhydroxylated pyrrolizidine alkaloids (five membered ring fused with five membered ring) such as australine 30,\(^{16} \) alexine 31\(^{17} \) and causurine 32.\(^{18} \)

V) Polyhydroxylated quinolizidine alkaloids six membered ring fused to six membered ring, (also known as isosteric homologues of castanospermine) e.g. Nortropanes 33a-c.\(^{19} \) 1,7,8,9-tetrahydroxyquinolizidine 34\(^{20} \) and trihydroxy quinolizidine alkaloid 35.\(^{21} \)
Biological activity:

The iminosugars act as glycosidase enzyme inhibitors by mimicking the normal carbohydrate substrate such as D-glucose and D-mannose. Their ability to act as glycosidase inhibitors, with low cytotoxicity even at relatively high concentration, has stimulated a lot of interest. The basic mechanism in the process namely the glycoprotein processing, glycogenolysis inhibition and saccharide inhibition is to inhibit the cleavage of glycosidic linkages. 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 1.

Step A: The aglycon is activated as a leaving group by co-ordination of the exocyclic glycosidase oxygen atom with an enzymic acidic function (partial protonation by a carboxyl group).

Step B: The next step is more or less concerted attack of the carboxylate group (catalytic nucleophile B\(^-\)), located on the opposite side of the plane of the pyranose ring, at C-1 thus leading to the formation of a glycosyl ester intermediate (II).

Step C: In this step, the aglycone is detached and an oxonium ion (III) thus formed is stabilized by a carboxylate group of the active center. The conformation of the oxonium ion is considered as a half-chair form.
Step D: The water molecule attacks the oxonium ion at the anomeric position. The conjugate base takes up the proton and the newly formed glycosyl ester bond is cleaved to complete the process. The important features of the mechanism are a) the half chair conformation of the transition state of the oxycarbenium ion intermediate III and b) the stabilization of the oxycarbenium species by the nucleophilic base located at the opposite side of the pyranose ring.

However, the shape and charge of III has remained the subject of debate. Pauling had emphasized the importance of shape and explained that an enzyme should bind the transition state.
more strongly than the substrate, in order to effectively catalyze the reaction and thus analogues should be potent inhibitors.

It has been found that various parameters determine the efficiency of good inhibitors. Among the factors that determine the specificity are the chirality and alternation of the hydroxyl groups. The ring structure and the substitution on the nitrogen and conformation of charged species are the factors, which in turn govern the transition state and substrate resemblance. The synthesis of new analogues of azasugars and evaluation of their glycosidase inhibitory activities thus forms a new era at the interface between glycobiology and synthetic organic chemistry. Over the past one decade, our group is actively engaged in the synthesis and evaluation of a number of polyhydroxylated piperidine, indolizidine as well as bicyclic diazasugars. In the continuation of our interest in this area, we were particularly interested in the synthesis of polyhydroxylated quinolizidine alkaloids. Although a plathera of literature is available for azasugars, to begin with, we are confining our discussion related to quinolizidine alkaloids only.

**Quinolizidine Alkaloids: literature survey**

The quinolizidine alkaloids, wherein six membered nitrogen ring is fused with the six membered ring where nitrogen atom is at the fusion are frequently encountered in nature especially in the ant species and in the skin of frog and toads. Although, a variety of structurally complex quinolizidine alkaloids (Figure 2) are known, the synthesis of polyhydroxylated quinolizidine alkaloids and evaluation of their glycosidase inhibitory activity have attracted the
attention of organic chemists only in recent years\textsuperscript{27} and to the best of our knowledge only five synthetic strategies are known so far. A brief account of these, are given below.

**Reported methods for the synthesis of quinolizidine alkaloids**

(i) **Method due to Stutz and coworkers\textsuperscript{27c}**

Stutz and coworkers have reported the first synthesis of tetrahydroxy quinolizidine alkaloids. In this approach, D-glucofuranurono-6,3-lactone was converted to 5-O-tert-butylidemethylsilyl-1,2-O-isopropylidene-$\beta$-L-idohexodialose \textsuperscript{36} in four steps. The compound \textsuperscript{36} was reacted with ten equivalents of freshly prepared Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane in ether, which afforded the mixture of the corresponding nonadialdoses \textsuperscript{37} and \textsuperscript{38}. Separation of the epimers was achieved by protection of C3 and C6 hydroxyl groups with chloromethyl methyl ether, which afforded the compound \textsuperscript{39}. Desilylation was performed using tetrabutylammonium fluoride in THF to give alcohol \textsuperscript{40}, which was converted into 5-azido-5-deoxy-compound \textsuperscript{42} with desired D-$\text{gluco}$ configuration via reaction of unstable triflate \textsuperscript{41} with excess of sodium azide. Azidodeoxy sugar \textsuperscript{42} was deprotected with ion...
exchange resign to give the free nonadialdodifuranose 43. Hydrogenation of 43 afforded the desired tetrahydroxyquinolizidine alkaloid 34.

(ii) Method due to Pearson and coworkers\textsuperscript{27h}

In this approach, authors have utilized double cyclization methodology for the synthesis of four diasteromers of D-mannotetrahydroxyquinolizidine starting from D-arabinose (Scheme 2). D-Arabinose was converted into the 2,3,4-tri-O-benzyl-D-arabinopyranose 44. Wittig reaction with the phosphonium salt 45 gave the Z-alkene 46, which on Mitsunobu reaction with hydrazoic acid afforded the azide 47. Epoxidation of the alkene 47 with m-chloroperbenzoic acid afforded a mixture of diastereomeric epoxides 48α and 48β that was directly subjected to catalytic hydrogenation to generate primary amine, which was cyclized to the separable quinolizidine
alkaloids 49 and 50 upon heating. Hydrogenolysis of the O-benzyl protecting groups under acidic condition afforded the desired quinolizidines 51 and 52.

(iii) For the preparation of the remaining two diasteromers 58 and 60, osmylation of 47 afforded the separable diols 53 and 54 in good yield (Scheme 3). Selective monomesylation of the diol 53 followed by sodium hydride treatment afforded the epoxide 55. A similar sequence on the diol 54 produced the epoxide 56. The reductive cyclization of 55 and 56 gave the quinolizidines 57 and 58, respectively, which on hydrogenolysis afforded the corresponding tetrahydroxy quinolizidines 59 and 60.
In addition, two more known synthetic approaches to trihydroxy and tetrahydroxy quinolizidine alkaloids, involving (iv) ring closing metathesis (RCM) and (v) ruthenium-catalyzed ring rearrangement as key steps, are discussed in part B.

In view of the fact that a limited attention has been focused on the synthesis of polyhydroxylated quinolizidine alkaloid, we have envisioned an altogether different strategy for the synthesis of trihydroxylated quinolizidine alkaloids, 35a and 35b that is depicted below.

Retrosynthetic Analysis:

As shown in the retrosynthetic analysis (Scheme 4), the bicyclic quinolizidine ring skeleton 35 could be built by linking the nitrogen atom of the piperidine ring with the hemiacetal of furanose ring in 62 by reductive amination. The piperidine compound 62 could be obtained from suitably protected α,β-unsaturated-δ-amino ester 63 by hydrogenation followed by cyclization, lactam reduction and deprotection of 1,2-acetonide group. The compound 63 could be obtained by Wittig olefination of the aldehyde 64 that could be achieved by ozonolysis of γ-alkenylamine 65. The compound 65 could be obtained by diastereoselective 1,3-addition of

![Scheme 4](image-url)
allylmagnesium bromide to sugar derived nitrone 61. The nitrone 61 could be easily obtained from D-glucose. It was thought that the diastereoselectivity at the prochiral nitrone carbon atom could be controlled by making use of different Lewis acids wherein metal catalyzed chelation control will afford one diastereomer while the non chelation will provide an access to other diastereomer.

We have already demonstrated the utility of D-glucose derived nitrone 61 in the synthesis of azasugars using 1,3-addition of suitable nucleophiles to sugar nitrone as a key step. In the first approach methylmagnesium bromide was used as a nucleophile. Thus, the 1,3- addition of methylmagnesium bromide to nitrone 61, in the presence of TMSOTf, afforded N-hydroxyamino sugars 69a and 69b in the ratio 87:13 (Scheme 6). The cleavage of N-O bond in the major D-gluco isomer 69a using Zn/Cu-AcOH gave amino compound 70. Hydrogenolysis of 70 followed by treatment with SO$_2$ gas afforded the 6-deoxynojirimycin as a bisulphate adduct 72. The bisulphate
adduct 72 on passing through the basic resin IRA 400 gave the target molecule 6-deoxynojirimycin 73. 251

The second approach makes use of a silyl ketene acetal, as a nucleophile. Thus, the 1,3-addition of silyl ketene acetal to D-glucose derived nitrone afforded D-gluco and L-ido configurated β-amino esters 66a and 66b. The β-amino esters thus obtained were converted to D-glucol-homo-1-deoxynojirimycin 67 and L-ido-homo-1-deoxynojirimycin 68, respectively (Scheme 5). 251

As a continuation of this programme, we are now exploiting the sugar nitrone chemistry in the synthesis of quinolizidine alkaloids 35a and 35b. Although, a few reports are available for the synthesis of polyhydroxylated quinolizidine alkaloids only a single report describes the synthesis of trihydroxy quinolizidine 35b 21 while, the synthesis of 35a is not reported so far.

Present Work:

The required sugar derived nitrone 61 was prepared from easily available D-glucose. Thus, as shown in Scheme 7, α-D-glucose was trapped in the five membered furanose form by reacting
with dry acetone in the presence of catalytic amount of iodine to give 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-\(\beta\)-glucopyranose 74. The C-3 hydroxy functionality in 74 was protected with benzyl group using benzylbromide, sodium hydride in the presence of catalytic amount of TBAI in dry THF to give 3-O-benzyl protected diacetone D-glucose 75. Selective deprotection of 5,6-O-isopropylidene group was carried with 10% \(\text{H}_2\text{SO}_4\) in methanol to give diol 76. Oxidative cleavage of the diol 76 using sodium metaperiodate afforded 1,2-O-isopropylidene-3-0-benzyl-\(\alpha\)-D-\(\beta\)-xylo-pentodialdose 77 in overall 66% yield from D-glucose. Reaction of 77 with \(N\)-benzylhydroxylamine hydrochloride, in

Diastereoselective 1,3-addition of allylmagnesium bromide to D-glucose derived nitrone 61

The 1,3-addition of allylmagnesium bromide to 61 at \(-78\, ^\circ\text{C}\) in dry THF for 2h afforded a mixture of two products in 92% yield. The separation of a mixture by column chromatography and elution first with n-hexane/ethyl acetate = 95/5, afforded a compound with 64% yield.
The IR spectra showed the presence of a broad peak in the region 3300-3000 cm\(^{-1}\), which was assigned to -OH stretching frequency. The analysis was found to be in agreement with the molecular formula C\(_{25}\)H\(_{31}\)NO\(_5\).

The NMR spectrum showed following signals: \(^1\)H NMR (300 MHz, CDCl\(_3\)) (Figure 1) \(\delta\) 1.26 (3H, s, CH\(_3\)), 1.44 (3H, s, CH\(_3\)), 2.49-2.69 (2H, m, H-6), 3.41 (1H, ddd, \(J = 8.3, 7.8, 4.8\) Hz, H-5), 3.76 (1H, d, \(J = 13.6\) Hz, NCH\(_2\)Ph), 3.94 (1H, d, \(J = 13.6\) Hz, NCH\(_2\)Ph) 4.01 (1H, d, \(J = 3.0\) Hz, H-3), 4.37 (1H, d, \(J = 8.3, 3.0\) Hz, H-4), 4.40-4.45 (1H, bs, exchanges with D\(_2\)O, OH), 4.50 (1H, d, \(J = 11.7\) Hz, OCH\(_2\)Ph), 4.54 (1H, d, \(J = 3.9\) Hz, H-2), 4.63 (1H, d, \(J = 11.7\) Hz, OCH\(_2\)Ph), 4.98 (1H, dd, \(J = 11.1, 1.6\) Hz, =CH\(_2\)), 5.10 (1H, dd, \(J = 17.0, 1.6\) Hz, =CH\(_2\)), 5.87 (1H, d, \(J = 3.9\) Hz, H-1), 5.92-6.10 (1H, m, =CH), 7.12-7.28 (10H, m, Ar-H).

The \(^{13}\)C NMR showed the following signals:

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) (Figure 2) \(\delta\) 26.19 (CH\(_3\)), 26.69 (CH\(_3\)), 31.41 (C-6), 60.83 (NCH\(_2\)Ph), 63.36 (C-5), 72.06 (OCH\(_2\)Ph), 79.58, 81.93, 82.55 (C-2, C-3, C-4), 104.54 (C-1), 111.34 (O-C-O), 115.61 (=CH\(_2\)), 127.07, 127.54, 127.76, 128.17, 128.36, 129.07 (Ar-C), 137.61 (=CH), 137.67, 138.31 (Ar-C). Based on the spectral and analytical data, the compound was tentatively assigned the structure 78a.
Figure 1: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 78a
Figure 2: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 78a
Further elution with (n-hexane/ethyl acetate = 90/10) afforded a compound with 28% yield.

$^1$H NMR showed the following signals: $^1$H NMR (300 MHz, CDCl$_3$) (Figure 3) $\delta$ 1.27 (3H, s, CH$_3$), 1.46 (3H, s, CH$_3$), 1.91-2.09 (1H, m, H-6a), 2.21-2.35 (1H, m, H-6b), 3.38 (1H, ddd, $J$ = 9.5, 8.1, 4.3 Hz, H-5), 3.84 (1H, d, $J$ = 3.0 Hz, H-3), 3.92 (1H, d, $J$ = 13.9 Hz, NCH$_2$Ph), 4.09 (1H, d, $J$ = 13.9 Hz, NCH$_2$Ph), 4.39 (1H, d, $J$ = 11.6 Hz, OCH$_2$Ph), 4.44 (1H, dd, $J$ = 3.0, 9.5 Hz, H-4), 4.57 (1H, d, $J$ = 3.8 Hz, H-2), 4.61 (1H, d, $J$ = 11.6 Hz, OCH$_2$Ph), 4.84-4.92 (2H, m, =CH$_2$), 4.93-4.96 (1H, bs, exchanges with D$_2$O, OH), 5.83-6.05 (1H, m, =CH), 5.93 (1H, d, $J$ = 3.8 Hz, H-1), 7.10-7.38 (10H, m, Ar-H).

The $^{13}$C NMR showed the following signals:

$^{13}$C NMR (75 MHz, CDCl$_3$) (Figure 4) $\delta$ 26.47 (CH$_3$), 26.89 (CH$_3$), 34.31 (C-6), 49.45 (C-5), 57.29 (NCH$_2$Ph), 72.03 (OCH$_2$Ph), 81.28, 81.96, 83.57 (C-2, C-3, C-4), 104.92 (C-1), 111.38 (O-C-O), 115.03 (=CH$_2$), 126.25, 127.49, 127.55, 127.73, 128.25, 128.4 (Ar-C), 137.93 (=CH), 138.25, 141.52 (Ar-C). Based on the spectral and analytical data, the compound was tentatively assigned the structure, 78b.

**Assignment of the relative stereochemistry at C5 of 78a and 78b**

The relative stereochemistry at C5 in 78a and 78b was assigned on the basis of $^1$H NMR data. It is known that for a given C5-epimeric pair, derived from the D-gluco-furanose, the $J_{4,5}$ in the L-ido isomer (threo-relationship) is consistently larger than that of the corresponding D-gluco isomer (erythro-relationship)\(^{28}\). The higher value of $J_{4,5}$ observed in the diastereomer 78b (9.5 Hz), as compared to 78a (8.3 Hz) indicated the L-ido configuration for 78b and the D-gluco configuration for 78a. This assignment was further supported by comparison of the chemical shifts of H3 in both the isomers. The chemical shift of H3 is reported to be diagnostic such that in the L-ido isomer, it is significantly upfield ($\delta$ ~3.6) as compared to that in the D-gluco ($\delta$ ~4.0)\(^{28}\). In 78b,
Figure 3: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 78b
Figure 4: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 78b
H3 appeared upfield at $\delta$ 3.84 as compared to 78a at $\delta$ 4.01, further supporting the D-gluco and L-ido configuration at C5 to 78a and 78b, respectively. Thus, the absolute configurations at C-5 in 78a and 78b were assigned as (5R) and (5S), respectively. Thus, the 1,3-addition of allylmagnesium bromide to nitrone 61 afforded D-gluco and L-ido N-hydroxylallyl amines in the ratio 70:30. Attempts were made to achieve the high diastereoselectivity of the 1,3-addition reaction.

**Attempts to improve diastereoselectivity**

To improve the stereoselectivity at the prochiral C5 center, various reaction conditions (e.g. change of solvent, temperature and stoichiometry of reactants) were tried (Table 1). Performing the reaction using ether as solvent had no effect on the stereoselectivity while no product was obtained when dichloromethane was used (entry 2,3). Change in the stoichiometry of the reactants (i.e. decreasing the Grignard to nitrone ratio) lowered the combined yield with no significant change in the stereoselectivity (entry 4,5). In case of nitrones it is known that the presence of an oxygen atom, formally carrying a net negative charge, allows a strong complexation with Lewis acid to occur. The resulting N-oxo-immonium species thus display enhanced reactivity and, in some cases, different stereochemical outcomes in reaction with nucleophiles. In this connection, we have demonstrated the utility of trimethylsilyltriflate (TMSOTf) as a promoter that leads to good stereoselectivity with high yield under kinetic and non-chelation controlled conditions. Inspired with this observation, the reaction of nitrone 61 with allylmagnesium bromide (2.5 equiv.) in the presence of TMSOTf (1 equiv) was performed. The product on desilylation afforded 78a and 78b in the ratio 86:14, respectively, resulting in a significant improvement of the diastereoselectivity in favor of D-gluco isomer with high yield.
Table 1. 1,3-Addition Reaction of Allylmagnesium Bromide to Sugar Derived Nitrone 61

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgBr (equiv)</th>
<th>Solvent</th>
<th>Lewis acid</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R = allyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78a and</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
<td>THF</td>
<td>---</td>
<td>-78</td>
<td>2</td>
<td>70/30</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>Et2O</td>
<td>---</td>
<td>-30</td>
<td>4</td>
<td>65/35</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>CH2Cl2</td>
<td>---</td>
<td>-30</td>
<td>48</td>
<td>No reaction</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>THF</td>
<td>---</td>
<td>-78</td>
<td>2</td>
<td>69/31</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>THF</td>
<td>---</td>
<td>-78</td>
<td>3</td>
<td>65/35</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>THF</td>
<td>TMSOTf</td>
<td>-78</td>
<td>3</td>
<td>86/14</td>
<td>93</td>
</tr>
</tbody>
</table>

* Yields refer to the isolated yields after chromatography.  
  b ratio was calculated by $^1$H NMR data of the crude product.  
  c starting was recovered ~100%.  
  d starting was recovered.

Explanation for the observed stereochemistry

The observed facial selectivity in the 1,3-addition of allylmagnesium bromide to nitrone 61 could be rationalized by Felkin-Anh like transition states (TS) A and B (Figure 3).

According to Felkin-Anh model the large substituent is kept perpendicular to the C=N bond. We believe that the C-O bond will adopt this position; in fact it is known that nucleophilic attack seeks the LUMO of the nitrone which may be stabilized through mixing of the $\pi^*$ C=N orbital with the lowest energy $\sigma^*$ orbital of a substituent, generally associated with the most electronnegative substituent. Amongst the two transition states, the TS A offers the more favorable Burgi-Dunitz trajectory for the incoming nucleophile thus favoring the formation of D-
gluco isomer in a major amount and this effect is magnified in the presence of TMSOTf. Thus, the TMSOTf catalyzed 1,3- addition of allylmagnesium bromide to sugar nitrone 61 afforded D-gluc]

Figure 3

Having both the D-gluco 78a and L-ido N-hydroxyl amines in hand, it was thought to convert them into quinolizidine alkaloids. As per our visualization, it is obvious that D-gluco isomer will lead to the formation of 35a while L-ido isomer will lead to the formation of 35b.

Synthesis of quinolizidine alkaloids 35a and 35b

The next step towards the target molecules was N-O bond reductive cleavage. In the beginning, the reaction sequence was attempted with chiral synthon 78a. Thus, when N-benzyhydroxylamine 78a was treated with zinc-copper acetate in acetic acid-water (85/15) at 70 °C for 1h, the N-O bond reductive cleavage afforded the corresponding γ-alkenyl-N-benzylamine
79a in 76% yield as a thick liquid. The N-benzylamino sugar 79a was purified by column chromatography and was characterized by spectral and analytical data. (Figure 5): \(^1\)H NMR; (Figure 6): \(^{13}\)C NMR.

At this stage, it was imperative to protect the secondary amino functionality with either \(\text{t-butoxycarbonyl}\) or \(\text{benzyloxy carbonyl}\) functionality. As the \(\text{N-Chz}\) group can be easily cleaved under hydrogenation condition, we have decided to protect the secondary amine with \(\text{N-Cbz}\) group. Thus, the amino functionality in 79a was protected with benzyloxy carbonyl chloride in the presence of sodium bicarbonate in aqueous ethanol to a compound in 73% yield.

\[
\text{Bn} \overset{\text{BnHN}}{\rightleftharpoons} \overset{\text{Cbz Cl, NaHCO}_3}{\text{EtOH, rt, 2 h}} \overset{\text{BnO}}{\text{79a}} \rightarrow \overset{\text{Cbz N}}{\text{65a}}
\]

The IR spectrum of the compound showed bands at 1695 and 1601 cm\(^{-1}\), which were assigned to the carbamate carbonyl and double bond frequency, respectively. The analysis was found to be in agreement with the molecular formula \(C_{33}H_{37}NO_6\). The \(^1\)H NMR and \(^{13}\)C NMR spectra of the compound showed doubling of signals. This fact could be accounted to the isomerisation arising due to restricted rotation around C=N bond. An analogous observation was also noticed for \(\text{N-Chz}\) containing compounds by other workers.\(^{33}\) Based on the spectral and analytical data the compound was given the structure 65a. The rational for the doubling of signals in the \(^1\)H NMR could be given as follows.

The rotational barriers about formal single bonds in amides are larger and therefore they become particularly amenable for NMR investigation. Such phenomenon is usually considered separately as involving “partial double bond character”. The most common and thoroughly
Figure 5: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 79a

Figure 6: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 79a
Figure 6: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 79a
investigated examples of this type are amides, where the process (Ia) to (Ib) and vice versa leads to a doubling of signals due to R, R₁ and R₂, when the rate of rotation is slow, and to averaged signals when the rate is fast on the NMR time scale.\(^{34}\)

In the compound 65a, the presence of \(-\text{N-COO-CH}_2\text{-Ph}\) functionality is also expected to show the partial double bond character and therefore, exhibits the doubling of signals.

In the next step, ozonolysis of 65a at \(-40 \, ^\circ\text{C}\) in dry CH\(_2\)Cl\(_2\) for 2h afforded a compound in 91\% yield.

The IR bands at 2731 (weak) and at 1722 (strong) cm\(^{-1}\), characteristic of the C-H stretching and carbonyl frequencies, respectively, indicate the presence of \(-\text{CHO}\) functionality. The other band at 1697 cm\(^{-1}\) was due to carbamate carbonyl group. The analysis was found to be in agreement with the molecular formula C\(_{32}\)H\(_{33}\)N\(_2\)O\(_7\). The \(^1\)H NMR (Figure 7) spectra showed a broad peak at 9.0 \(\delta\). The \(^{13}\)C NMR (Figure 8) showed a signal at 206 \(\delta\) indicating the presence of \(-\text{CHO}\) group. The \(^1\)H NMR and \(^{13}\)C NMR spectrum showed doubling of signals. Based on the spectral and analytical data the compound was assigned the structure 64a.
Figure 7: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 64a
Figure 8: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 64a
At this stage, it was thought to construct the piperidine ring skeleton, for which one requires the δ-amino ester. This could be achieved by Wittig olefination of aldehyde 64a. Thus, Wittig reaction of aldehyde 64a with Ph₃P=CHCOOEt in methanol gave a geometric mixture of α,β-unsaturated-δ-amino esters in 92% yield. The NMR spectrum of the crude compound showed the presence of number of signals arising due to geometrical as well as rotational isomers.

Therefore the compound 63a was directly subjected to hydrogenation with 10% Pd-C in methanol. After 12 h, the isolated product showed single spot on TLC. However, to our surprise, the IR spectrum of the product showed two carbonyl frequencies – one at 1735 cm⁻¹ and other at 1661 cm⁻¹ indicating the presence of an open chain δ-amino ester and the Piperidin-2-one 80a. This fact was further supported by ¹H NMR spectra, which showed the product as a mixture of dihydro-δ-amino ester and 80a. However, when the crude reaction mixture of hydrogenation was treated with sodium acetate in methanol at reflux for 6h, we obtained a crystalline solid in 68% yield.
The appearance of IR carbonyl frequency at 1658 cm\(^{-1}\) indicated the formation of six-membered 5-lactam. As expected the removal of N-Cbz group resulted into the clear appearance of \(^1\)H and \(^{13}\)C NMR spectra. The \(^1\)H and \(^{13}\)C NMR spectra showed following signals:

\(^1\)H NMR (300 MHz, CDCl\(_3\)) (Figure 9) \(\delta 1.32 (3\text{H, s, CH}_3), 1.50 (3\text{H, s, CH}_3), 1.62-2.08 (4\text{H, m, H-6/H-7}), 2.19-2.36 (2\text{H, m, H-8}), 3.64-3.76 (1\text{H, m, H-5}), 3.95 (1\text{H, dd, } J = 2.4, 9.3 \text{ Hz, H-4}), 4.27 (1\text{H, d, } J = 2.4 \text{ Hz, H-3}), 4.55 (1\text{H, d, } J = 3.6 \text{ Hz, H-2}), 4.78-5.11 (1\text{H, bs, exchanges with D}_2\text{O, OH/NH}), 5.91 (1\text{H, d, } J = 3.6 \text{ Hz, H-1}), 8.05-8.22 (1\text{H, bs, exchanges with D}_2\text{O, OH/NH}).

In the \(^1\)H NMR spectrum, the absence of methylene proton signals corresponding to O-Bn and N-Cbz indicated the complete removal of this group in the product. Similarly, the absence of ethyl proton signals and olefinic proton signals suggested the formation of piperidone ring skeleton. This fact was further supported by \(^{13}\)C NMR spectrum, which showed the following signals.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) (Figure 10) \(\delta 17.82 (\text{C-6}), 24.56 (\text{C-7}), 26.16, 26.90 (\text{CH}_3), 31.29 (\text{C-8}), 50.38 (\text{C-5}), 73.42, 82.19, 85.51 (\text{C-2, C-3, C-4}), 104.88 (\text{C-1}), 111.36 (\text{O-C-O}), 174.44 (\text{CO}).

The analysis was found to be in agreement with the molecular formula C\(_{12}\)H\(_{19}\)NO\(_5\). Based on the spectral and analytical data the compound was assigned the structure 80a.

In the subsequent steps, reduction of the lactam functionality in 80a with LAH in THF for 1h and N-protection with benzyloxycarbonyl chloride afforded product in 70% yield.

\[ \text{LAH, dry THF, } 0^\circ\text{C, 1 h} \]

\[ i) \text{Cbz-Cl, NaHCO}_3, \text{EtOH, rt, 2 h} \]

57
Figure 9: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 80a
Figure 10: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 80a
The IR spectrum showed bands at 3475 and 1674 cm\(^{-1}\) each due to \(-\text{OH}\) stretching and carbamate carbonyl stretching frequencies, respectively. The analysis was found to be in agreement with the molecular formula \(\text{C}_{20}\text{H}_{27}\text{NO}_6\). Fortunately, with this compound, the \(^1\text{H}\) NMR spectrum was found to be clean without the doubling of signals (probably the rotation about the formal \(\text{C}=\text{N}\) is sufficiently rapid resulting into an average, well resolved spectra). The \(^1\text{H}\) NMR spectrum showed following signals:

\(^1\text{H}\) NMR (300 MHz, \(\text{CDCl}_3 + \text{D}_2\text{O}\)) (Figure 11) \(\delta\) 1.31 (3H, s, CH\(_3\)), 1.48 (3H, s, CH\(_3\)), 1.88-2.02 (4H, m, H-6, H-7), 2.20-2.35 (2H, m, H-8), 3.38-3.48 (2H, m, H-9), 3.79 (1H, dd, \(J = 9.9, 1.8\) Hz, H-4), 4.02 (1H, d, \(J = 1.8\) Hz, H-3), 4.13 (1H, ddd, \(J = 9.9, 6.6, 2.4\) Hz, H-5), 4.58 (1H, d, \(J = 3.6\) Hz, H-2), 5.12 (2H, ABq, \(J = 12.0\) Hz, OCH\(_2\)Ph), 5.88 (1H, d, \(J = 3.6\) Hz, H-1), 7.22-7.45 (5H, m, Ar-H). The presence of AB quartet at 5.12 \(\delta\) with \(J = 12.0\) Hz indicated the presence of N-COO-CH\(_2\)-Ph functionality. This fact was supported by \(^{13}\text{C}\) NMR spectrum. The \(^{13}\text{C}\) NMR showed the following signals:

\(^{13}\text{C}\) NMR (75 MHz, \(\text{CDCl}_3\)) (Figure 12) \(\delta\) 18.9, 25.1, 25.3, 26.2, 27.0, 41.1, 48.5, 67.8, 73.6, 76.6, 84.5, 104.8, 111.3, 127.8, 128.4, 128.5, 135.9, 156.9. Based on the spectral and analytical data the compound was assigned the structure 62a.

Finally, compound 62a was reacted with TFA-H\(_2\)O at room temperature for 3h (deprotection of 1,2-acetonide group) and the product isolated was immediately subjected to hydrogenation (10% Pd-C at 80 psi in MeOH). The reaction afforded a compound, which on purification by column chromatography gave a semisolid in 85% yield.
Figure 11: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 62a
Figure 12: $^1$H NMR (400 MHz, DMSO) spectrum of compound 62a
The IR spectrum of the compound showed a broad band in the region 3400-3000 cm\(^{-1}\) corresponding to OH stretching frequencies. The \(^1\)H NMR (Figure 13) showed the following signals:

\(^1\)H NMR (300 MHz, D\(_2\)O) \(\delta\) 1.24-1.53 (2H, m), 1.55-1.72 (1H, m), 1.79-1.98 (3H, m), 2.26 (1H, m), 2.60-2.86 (3H, m), 3.22-3.48 (3H, m), 3.62-3.76 (3H, m).

The \(^1\)C NMR (Figure 14) showed following signals:

\(^1\)C NMR (75 MHz, D\(_2\)O) \(\delta\) 21.63, 23.49, 26.93 (C-9, C-8, C-7), 55.37, 56.84 (C-4, C-6), 65.08 (C-9a), 67.09, 72.74, 76.51 (C-1, C-2, C-3). The analysis was found to be in agreement with the molecular formula C\(_9\)H\(_{17}\)NO\(_3\)3H\(_2\)O. Based on the spectral and analytical data the compound was assigned the structure as (1R,2R,3S,9aR)-octahydro-2H-quinolizine-1,2,3-triol 35a (conformational analysis vide supra).

**Synthesis of (1R,2R,3S,9aS)-octahydro-2H-quinolizine-1,2,3-triol 35b.**

Having the success in the synthesis of (1R,2R,3S,9aR)-octahydro-2H-quinolizine-1,2,3-triol 35a from \(\gamma\)-alkenyl-\(\text{N}\)-hydroxylamine 78a we thought of elaborating the same reaction sequence with \(\gamma\)-alkenyl-\(\text{N}\)-hydroxylamine 78b having L-ido configuration. It is obvious that this reaction sequence should lead to the formation of (1R,2R,3S,9aS)-octahydro-2H-quinolizine-1,2,3-triol 35b. Thus, as shown in Scheme 8, \(\gamma\)-alkenyl-\(\text{N}\)-hydroxylamine 78b was converted to \(\delta\)-lactam 80b in overall 35.2% yield. The corresponding C5-epimeric compounds 79b, 65b and 64b were isolated in good yields and were characterized by spectral and analytical data.
Figure 13: $^1$H NMR (300 MHz, D$_2$O) spectrum of compound 35a
Figure 14: $^{13}$C NMR (76 MHz, D$_2$O) spectrum of compound 35a
Reagents and conditions: i) Zn, Cu(OAc)$_2$, AcOH, 70 °C, 1h; ii) Cbz-Cl, NaHCO$_3$, EtOH, rt, 2h; iii) O$_3$, CH$_2$Cl$_2$, DMS, -40 °C, 2h; iv) a) Ph$_3$PCHCOOEt, MeOH, rt, 2h; b) H$_2$, 10 % Pd/C, 80 Psi, MeOH, rt, 12h; c) CH$_3$COONa, MeOH, reflux, 6h.

Scheme 8

The IR spectrum of compound 80b showed bands at 3330 and 1624 cm$^{-1}$ due to –OH and amide carbonyl stretching frequencies, respectively. The $^1$H and $^{13}$C NMR spectra showed following signals:

$^1$H NMR (300 MHz, CDCl$_3$) (Figure 15) δ 1.30 (3H, s, CH$_3$), 1.49 (3H, s, CH$_3$), 1.59-1.81 (2H, m, H-7), 1.82 (2H, m, H-6), 2.21-2.49 (2H, m, H-8), 3.65-3.80 (1H, m, H-5), 3.95 (1H, d, $J = 2.7$ Hz, H-2), 5.01-5.21 (1H bs, exchanges with D$_2$O, OH/NH), 5.95 (1H, d, $J = 3.3$ Hz, H-1), 7.10-7.22 (1H, bs, exchanges with D$_2$O, OH/NH).

$^{13}$C NMR (75 MHz, CDCl$_3$) (Figure 16) δ 19.85 (C-6), 25.94 (C-7), 26.22, 26.86 (CH$_3$), 30.96 (C-8), 52.63 (C-5), 75.78, 81.33, 85.27 (C-2, C-3, C-4), 104.61 (C-1), 111.56 (O-C-O), 173.16 (CO).
Figure 16: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 80b
Figure 16: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 80b
The analysis was found to be in agreement with the molecular formula C\textsubscript{12}H\textsubscript{19}NO\textsubscript{5}. Based on the spectral and analytical data the compound was assigned the structure 80b.

An interesting observation was noticed by comparison of IR and \textsuperscript{1}H NMR spectra of C5-epimeric compound 80a and 80b. In the IR spectrum, compound 80a (D-gluco) showed the amide carbonyl stretching frequency at 1658 cm\textsuperscript{-1} while in compound 80b (L-ido) amide stretching frequency appeared at 1624 cm\textsuperscript{-1}. The decrease in IR carbonyl frequency in 80b could be attributed to the intramolecular hydrogen bonding between C3-OH and amide carbonyl oxygen as shown in figure 4. In general, the relative configuration at C5, for such types of epimeric compounds is revealed by \(J_{4,5}\) and it is known that, for the given C5 epimeric pair, the \(J_{4,5}\) is larger for L-ido isomer than for the corresponding D-gluco isomer.\textsuperscript{39} However, in case of 80a (D-gluco) the observed \(J_{4,5}\) (9.3 Hz) is larger than the \(J_{4,5}\) (4.8 Hz) in 80b. This finding is opposite to that reported and could be attributed to the possible six membered intramolecular hydrogen bonding in 80a and 80b between NH and C3 oxygen by rotation about the C4-C5 bond (Figure 4). In this situation, the molecule is held in such a way that, for the hydrogen bonded D-gluco isomer 80a, the dihedral angle between H4 and H5 is \(-180^\circ\) and that for L-ido isomer 80b is \(-45^\circ\) thus resulting in the observed coupling constants.

![Figure 4](image_url)
In the next step, reduction of lactam functionality in 80b with LAH in THF for 2h and N-protection with benzoxycarbonyl chloride afforded the compound in 69% yield.

\[
\begin{align*}
\text{80b} & \xrightarrow{\text{LAH, dry THF, 0 °C, 1 h}} \text{80b} \\
\text{80b} & \xrightarrow{\text{ii) Cbz-Cl, \ NaHCO}_3} \text{62b}
\end{align*}
\]

The IR spectrum showed bands at 3620 and 1674 cm\(^{-1}\) each due to -OH stretching and carbamate carbonyl frequencies, respectively. The analysis was found to be in agreement with the molecular formula C\(_{20}\)H\(_{27}\)NO\(_6\). The \(^1\)H and \(^{13}\)C NMR spectra showed following signals:

\(^1\)H NMR (300 MHz, CDCl\(_3\) + D\(_2\)O) (Figure 17) \(\delta\) 1.32 (3H, s, CH\(_3\)), 1.51 (3H, s, CH\(_3\)), 1.60-1.80 (2H, m, H-7), 1.81-1.98 (1H, m, H-8), 2.01-2.22 (2H, m, H-6), 3.41-3.60 (2H, m, H-9), 3.98 (1H, dd, \(J = 3.0, 1.8\) Hz, H-4), 4.13 (1H, d, \(J = 1.8\) Hz, H-3), 4.28-4.35 (1H, m, H-5), 4.47 (1H, d, \(J = 3.6\) Hz, H-2), 5.13 (2H, ABq, \(J = 12.3\) Hz, OCH\(_2\)Ph), 5.87 (1H, d, \(J = 3.6\) Hz, H-1), 7.21-7.41 (5H, m, Ar-H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) (Figure 18) \(\delta\) 19.6, 25.2, 26.1, 26.2, 26.8, 40.0, 48.9, 66.9, 74.6, 77.6, 85.4, 104.1, 111.1, 127.3, 127.5, 128.2, 136.8, 156.2. Based on the spectral and analytical data the compound was assigned the structure 62b.

Targeting towards the synthesis of \((1R,2R,3S,9aS)-\)octahydro-2H-quinolizine-1,2,3-triol 35b. The compound 62b was reacted with TFA-H\(_2\)O and the product obtained was subjected to catalytic hydrogenation. The crude product thus obtained was purified by column chromatography to get a semisolid in 91% yield.
Figure 17: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 62b
Figure 18: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 62b
The IR spectrum of the compound showed a broad band in the region 3400-3000 cm\(^{-1}\) corresponding to OH stretching frequencies. The \(^1\)H and \(^13\)C NMR spectrum showed following signals:

\(^1\)H NMR (300 MHz, D\(_2\)O) (Figure 19) \(\delta\) 1.42-1.80 (7H, m), 2.79-2.91 (1H, m), 3.15-3.38 (5H, m), 3.87 (1H, s);

\(^13\)C NMR (75 MHz, D\(_2\)O) (Figure 20) \(\delta\) 21.72, 22.95, 25.76 (C-7, C-8, C-9), 55.74 (C-4, C-6), 61.69 (C-9a), 66.44, 67.20, 70.21 (C-1, C-2, C-3). The analysis was found to be in agreement with the molecular formula C\(_9\)H\(_{17}\)NO\(_3\).2H\(_2\)O. Based on the spectral and analytical data the compound was assigned the structure as (1R,2R,3S,9aS)-octahydro-2H-quinolizine-1,2,3-triol 35b.

We have demonstrated the use of D-glucose derived nitrone in the synthesis of trihydroxy quinolizidine alkaloids 35a and 35b. The compounds, 35a and 35b being analogues to aza-decalin system, it is expected that these compounds could exist in different conformations. Therefore, we have made the attempts to find out the conformations using \(^1\)H NMR spectral data.

**Conformational assignment of 35a and 35b**

Azasugars can exist in different conformations. For example, nojirimycin exists in \(^4C_1\) conformation and the castanospermine and 1-deoxy-castanospermine are present in \(^3C_5\) conformation while we have reported that the 1-deoxy-8a-epi-castanospermine is present in \(^5C_8\)
Figure 19: $^1$H NMR (300 MHz, D$_2$O) spectrum of compound 35b
Figure 20: $^{13}$C NMR (76 MHz, D$_2$O) spectrum of compound 36b
conformation. The quinolizidine alkaloids 35a and 35b have the framework of aza-decaline system wherein one can expect trans or cis ring fusion. In order to know the conformations, we studied the $^1$H NMR spectra of 35a and 35b and the coupling constants information was obtained by decoupling experiments (Table 2). In the $^1$H NMR spectra of 35a the doublet of triplet ($J_{3,4} = 4.4$ and $J_{3,4} = J_{3,2} = 9.5$ Hz), corresponding to H3 proton, indicated the axial orientation of this proton. The triplet ($J_{2,3} = J_{2,1} = 9.5$ Hz), corresponding to H2, requires trans-diaxial relationship with H3 and H1. As the trans aza-decalin is conformationally rigid chair-chair system, the conformation A was assigned to 35a. Since the $^1$H NMR spectrum of 35b is very different from 35a it was thought that 35b could exist in different conformation. Thus, for 35b we considered two conformations - one with cis ring fusion and equatorially oriented OH substituents (conformation B) and the other trans ring fusion with axially oriented OH substituents (conformation C). The initial geometry in the precursor 62b ensures that in the product 35b the substituents at C1, C2 and C3 should be trans. The $^1$H NMR of 35b showed the low coupling constant values ($J_{1,2} = J_{2,3} = 3$ Hz) between the H1-H2 and H2-H3. This indicated the equatorial orientation of these protons at C1/C2/C3. This fact is supported by the noticeable downfield shift

Table 2. Comparison of $^1$H NMR spectra of 35a and 35b

<table>
<thead>
<tr>
<th></th>
<th>H3</th>
<th>H2</th>
<th>H1</th>
<th>H9a</th>
</tr>
</thead>
<tbody>
<tr>
<td>35a</td>
<td>δ 3.69 (dt)</td>
<td>δ 3.41 (t)</td>
<td>δ 3.22-3.36 (m)</td>
<td>δ 3.22-3.36 (m)</td>
</tr>
<tr>
<td>$J_{2,3} = J_{4,3} = 9.5$ Hz, $J_{4,2} = J_{2,3} = 9.5$ Hz</td>
<td>$J_{4,2} = 4.5$ Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35b</td>
<td>δ 3.87 (bs)</td>
<td>δ 3.87 (bs)</td>
<td>δ 3.65 (bs)</td>
<td>δ 3.15-3.38 (m)</td>
</tr>
<tr>
<td>$W_H = 6$ Hz</td>
<td>$W_H = 6$ Hz</td>
<td>$W_H = 6$ Hz</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of H1/H2/H3 as compared to the respective protons in 35a. Based on this observation, we assigned the preferred trans ring fused conformation C, with axial orientation of the OH substituents, for compound 35b.
Conclusions:

1. The 1,3-addition reaction of allylmagnesium bromide with sugar derived nitrone, 61 affording γ-alkenyl-N-hydroxyamines is a high yielding process.

2. The stereocontrol of the 1,3- addition reaction can be improved in favour of D-glucos isomer, 78a by the use of trimethylsilyl triflate at lower temperature.


4. The utility of γ-alkenyl-N-hydroxyamines 78a and 78b was successfully demonstrated in the synthesis of trihydroxy quinolizidine alkaloids such as (1R,2R,3S,9aR)-octahydro-2H-quinolizine-1,2,3-triol 35a and (1R,2R,3S,9aS)-octahydro-2H-quinolizine-1,2,3-triol 35b.
Experimental
Experimental

Expt. No. 2.1.1: Preparation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (74).

\[ \text{D-Glucose} \xrightarrow{\text{Acetone, I}_2} \text{HO} \]

rt, 6h

Expt. No. 2.1.2: Preparation of 1,2:5,6-di-O-isopropylidene-3-O-benzyl-α-D-glucofuranose (75).

\[ \text{NaH, BnBr, TBAI} \xrightarrow{\text{dry THF, 0 °C to rt \ 6h}} \text{BnO} \]

Expt. No. 2.1.3: Preparation of 1,2-O-isopropylidene-3-O-benzyl-α-D-glucofuranose (76).

\[ \text{BnO} \xrightarrow{10 \% \text{ H}_2\text{SO}_4, \text{MeOH}} \text{HO} \]

water, rt, 6h

Expt. No. 2.1.4: Preparation of 1,2-O-isopropylidene-3-O-benzyl-α-D-xylo-pentadialdo-1, 4-furanose (77).

\[ \text{HO} \xrightarrow{\text{NaIO}_4, \text{Acetone-water}} \text{HO} \]

0 °C to rt, 2 h
Expt. No. 2.1.5: Preparation of \((Z)-N-(3-O\text{-}benzyl\text{-}5\text{-}deoxy\text{-}1\text{-}2\text{-}O\text{-}isopropylidene\text{-}\alpha\text{-}D\text{-}xylo\text{-}1\text{-}4\text{-}furanose\text{-}5\text{-}yliden)\text{-}benzylamine\text{ }N\text{-}oxide\ (61)\).

\[
\text{NH(OH)BN.HCl, AcONa, EtOH-H}_2\text{O, rt, 18 h}
\]

Expt. No. 2.1.6: 3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-5-N-(benzylhydroxy-amino)-\(\alpha\text{-}D\text{-}gluco\text{-}7\text{-}eno\text{-}octofuranose\ (78a)\) and 3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-5-N-(benzylhydroxy-amino)-\(\beta\text{-}L\text{-}ido\text{-}7\text{-}eno\text{-}octofuranose\ (78b)\).

\[
\text{AllylMgBr, dry THF, -78 °C, 2 h}
\]

Expt. No. 2.1.7: 3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-5-N-(benzylamino)-\(\alpha\text{-}D\text{-}gluco\text{-}7\text{-}eno\text{-}octofuranose\ (79a)\).

\[
\text{Zn, Cu(OAc)}_2, \text{AcOH, 70 °C, 1 h}
\]

Expt. No. 2.1.8: 3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-5-N-(benzylamino)-\(\beta\text{-}L\text{-}ido\text{-}7\text{-}eno\text{-}octofuranose\ (79b)\).
Expt. No. 2.1.9: 3-O-benzyl-5,6-dideoxy-1,2-0-isopropylidine-5-N-(benzyl-benzoxy carbonylamino)-α-D-gluc-7-eno-octofuranose (65a).

Expt. No. 2.1.10: 3-O-benzyl-5,6-dideoxy-1,2-0-isopropylidine-5-N-(benzyl-benzoxy carbonylamino)-β-L-id-7-eno-octa-1,4-furanose (65b).

Expt. No. 2.1.11: 3-O-benzyl-5,6-dideoxy-1,2-0-isopropylidine-5-N-(benzyl-benzoxy carbonylamino)-α-D-gluco-heptodialdofuranose (64a).

Expt. No. 2.1.12: 3-O-benzyl-5,6-dideoxy-1,2-0-isopropylidine-5-N-(benzyl-benzoxy carbonylamino)-β-L-id-7-eno-octa-1,4-furanose (64b).
Expt. No. 2.1.13: 1,2-0-isopropylidine-5,6,7,8-tetraideoxy-5,9-imino-α-D-glucos-1,4-furan-9-ulos (80a).

Expt. No. 2.1.14: 1,2-0-isopropylidine-5,6,7,8-tetraideoxy-5,9-imino-β-L-idos-1,4-furan-9-ulos (80b).

Expt. No. 2.1.15: 1,2-0-isopropylidine-5,6,7,8,9-pentaideoxy-5,9-N-(benzoxycarbonylimino)-α-D-glucos-1,4-furanos (62a).
Expt. No. 2.1.16: 1,2-O-isopropylidene-5,6,7,8,9-pentadeoxy-5,9-N-(benzoxycarbonylimino)-β-L-idono-1,4-furanose (62b).

Expt. No. 2.1.17: (1R,2R,3S,9aR)-octahydro-2H-quinolizine-1,2,3-triol (35a).

Expt. No. 2.1.18: (1R,2R,3S,9aS)-octahydro-2H-quinolizine-1,2,3-triol (35b).
Expt. No. 2.1.1: Preparation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (44).

To a stirred solution of Iodine (3.0 g, 11.81 mmol) in dry acetone was added D-glucose (1.0 g, 38.46 mmol). The reaction mixture was stirred at room temperature for 6 hours. Iodine was decomposed by addition of saturated solution of sodium thiosulphate. Acetone was evaporated on rotavapour, the residue extracted with chloroform (50 mL x 5). The organic layer was dried and concentrated to afford white solid, which was recrystallised from chloroform-hexane to give 74 in 1.2 g, 77 % yield, mp 108-110 °C. (lit° mp 110-111 °C)

Expt. No. 2.1.2: Preparation of 1,2:5,6-di-O-isopropylidene-3-O-benzyl-α-D-glucofuranose (75).

Sodium Hydride (2.08 g, 51.92 mmol) was added with dry hexane (10 mL). Diacetone D-glucose 74 (9.0 g, 43.62 mmol) in dry THF (30 mL) was added drop-wise to the reaction mixture at 0 °C. After stirring the reaction mixture for 30 min., benzyl bromide (3.98 mL, 34.62 mmol) in dry THF (10 mL) was added drop-wise followed by addition of tetrabutylammonium iodide (0.64 g, 1.731 mmol). The reaction mixture was stirred at room temperature for 6 hours. Reaction poured into ice-water (10 mL), THF layer was evaporated on rotavapour. The residual aqueous layer extracted with ether (25 mL X 3), ethereal layer washed with brine, dried (Na₂SO₄) and concentrated to afford a thick liquid which on purification by column chromatography (hexane/ethyl acetate = 9.5/0.5) gave pure 75 (11.21 g, 93 %) as a thick liquid.

[α]D = -20.2 (c 0.4, CHCl₃) lit.¹⁰ [α]D = -20.8 (c 0.1, MeOH)

Expt. No. 2.1.3: Preparation of 1,2-O-isopropylidene-3-O-benzyl-α-D-glucofuranose (76).
3-O-benzyl protected diacetone D-Glucose 75 (4.0 g 12.90 mmol) was dissolved in methanol (62 mL) and water (12.5 mL and 10% H$_2$SO$_4$ (3.3 mL) and stirred at room temperature. After 6 hours, saturated potassium carbonate was added to neutralize the reaction mixture to pH = 7-8. Methanol was evaporated and the residue extracted with chloroform (20 mL x 4), organic layer dried (Na$_2$SO$_4$) and evaporated to give a thick liquid, which after column purification (hexane/ethyl acetate = 8.5/1.5) gave pure 76 (3.11 g, 88%).

$[\alpha]_D^0 = -34.8$ (c 0.4, CHCl$_3$) lit.$^{[1]} [\alpha]_D^0 = -35$ (c 0.6, CHCl$_3$)

Expt. No. 2.1.4: Preparation of 1,2-O-isopropylidene-3-O-benzyl-α-D-xylo-pentodialdo-1,4-furanose (77).

A solution of 1,2-O-isopropylidene-3-O-benzyl-α-D-xylo-1,4-furanose 76 (2.75g, 8.88 mmol) in acetone-water (12.5 mL-12.5 mL) was cooled to 0 °C. Sodium metaperiodate (2.85g, 13.3 mmol) was added in portions to the cooled solution and stirred for 2 hours. Ethylene glycol (1 mL) was added to the reaction mixture and extracted with chloroform (10 mL x 3). The chloroform layer dried and evaporated to afford a thick liquid which on column purification (hexane/ethyl acetate = 8.5/1.5) afforded the pentadiolose 77 (2.27 g, 92%).

$[\alpha]_D^0 = -90.1$ (c 1.0, CHCl$_3$) lit.$^7 [\alpha]_D^0 = -86.5$ (c 2.7, CHCl$_3$).

Expt. No. 2.1.5: (Z)-N-(3-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-D-xylo-1,4-furanose-5-yliden)-benzylamine N-oxide (61)

A mixture of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose 47 (0.7 g, 2.50 mmol), anhydrous sodium acetate (0.25 g, 3.00 mmol) and N-benzylhydroxylamine hydrochloride (0.50 g, 3.00 mmol) in ethanol-water was stirred at
room temperature for 16h. The reaction mixture was extracted with chloroform and the collected organic layers were washed with saturated solution of NaHCO₃, dried over anhydrous sodium sulphate and evaporated to give a crude solid. Crystallisation (n-hexane/ethyl acetate = 9/1) furnished nitrone 43 (0.75 g, 78%) as a white solid:

\[ R_f = 0.28 \text{ (EtOAc/Hexane} = 3/7); \]

mp = 96-98 °C (lit. mp = 96 °C);

\[ [\alpha]_D = -137.0 \text{ (c 1.0, CHCl}_3 \text{) (lit.} [\alpha]_D = -135.7 \text{ (c 0.4, CHCl}_3 \text{);} \]

\[ \text{IR } \nu_{\max} \text{ (neat)} = 1612, 1496, 1456, 1372, 1210 \text{ cm}^{-1}; \]

Expt. No. 2.1.6: 3-O-benzyI-1,2-O-isopropylidine-5,6,7,8-tetradeoxy-5-N-(benzylhydroxy-amino)-α-D-glucopyranose (78a) and 3-O-benzyI-1,2-O-isopropylidine-5,6,7,8-tetradeoxy-5-N-(benzyl-hydroxy-amino)-β-L-idopyranose (78b).

To a stirred solution of nitrone 61 (1 g, 2.61 mmol) in THF under nitrogen atmosphere, at −78 °C, was added dropwise allylmagnesium bromide (1M in diethylether, 1.4 mL, 6.52 mmol). The mixture was stirred at −78 °C for 2h, then quenched with a saturated solution of NH₄Cl (5 mL) and filtered. The filtrate was concentrated and the residue was dissolved in diethylether (30 mL). The etheral layer was washed with brine, dried with sodium sulphate and evaporated to give oil. The crude oil was subjected to column chromatography (hexane/ethyl acetate 8/2) to give first a fraction containing α-D-glucopyranose isomer 78a (0.710 g, 67%) as thick liquid:

\[ H R_f = 0.52 \text{ (EtOAc/Hexane} = 3/7); \]

\[ [\alpha]_D = -30.0 \text{ (c 2.40, CHCl}_3 \text{);} \]

\[ \text{IR } \nu_{\max} \text{ (neat)} = 3510-3160 \text{ (br), 1639 cm}^{-1}; \]
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.26 (3H, s, CH$_3$), 1.44 (3H, s, CH$_3$), 2.49-2.69 (2H, m, H-6), 3.41 (1H, ddd, $J = 8.3$, 7.8, 4.8 Hz, H-5), 3.76 (1H, d, $J = 13.6$ Hz, NCH$_2$Ph), 3.94 (1H, d, $J = 13.6$ Hz, NCH$_2$Ph) 4.01 (1H, d, $J = 3.0$ Hz, H-3), 4.37 (1H, dd, $J = 8.3$, 3.0 Hz, H-4), 4.40-4.45 (1H, bs, exchanges with D$_2$O, OH), 4.50 (1H, d, $J = 11.7$ Hz, OCH$_3$Ph), 4.54 (1H, d, $J = 3.9$ Hz, H-2), 4.63 (1H, d, $J = 11.7$ Hz, OCH$_3$Ph), 4.98 (1H, dd, $J = 11.1$, 1.6 Hz, =CH$_2$), 5.10 (1H, dd, $J = 17.0$, 1.6 Hz, =CH$_2$), 5.87 (1H, d, $J = 3.9$ Hz, H-1), 5.92-6.10 (1H, m, =CH-), 7.12-7.28 (10H, m, Ar-H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 26.19 (CH$_3$), 26.69 (CH$_3$), 31.41 (C-6), 60.83 (NCH$_2$Ph), 63.36 (C-5), 72.06 (OCH$_3$Ph), 79.58, 81.93, 82.55 (C-2, C-3, C-4), 104.54 (C-1), 111.34 (O-C-O), 115.61 (=CH$_2$), 127.07, 127.54, 127.76, 128.17, 128.36, 129.07 (Ar-C), 137.61 (=CH), 137.67, 138.31 (Ar-C);

Anal. Calcd for C$_{25}$H$_{31}$NO$_5$: C, 70.57; H, 7.34; Found C, 70.51; H, 7.30.

Further elution with (hexane/ethyl acetate 7/3) afforded the second fraction containing the $\beta$-L-ido isomer 78b (0.325 g, 29%) as thick liquid:

LR$_f$ = 0.44 (EtOAc/Hexane = 3/7);

[$\alpha$]$_D$ = -48.0 (c 0.25, CHCl$_3$);

IR $\nu_{max}$ (neat) = 3530-3150 (br), 1639 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.27 (3H, s, CH$_3$), 1.46 (3H, s, CH$_3$), 1.91-2.09 (1H, m, H-6a), 2.21-2.35 (1H, m, H-6b), 3.38 (1H, ddd, $J = 9.5$, 8.1, 4.3Hz, H-5), 3.84 (1H, d, $J = 3.0$ Hz, H-3), 3.92 (1H, d, $J = 13.9$ Hz, NCH$_2$Ph), 4.09 (1H, d, $J = 13.9$ Hz, NCH$_2$Ph), 4.39 (1H, d, $J = 11.6$ Hz, OCH$_3$Ph), 4.44 (1H, dd, $J = 3.0$, 9.5 Hz, H-4), 4.57 (1H, d, $J = 3.8$ Hz, H-2), 4.61 (1H, d, $J = 11.6$ Hz, OCH$_3$Ph), 4.84-4.92 (2H, m, =CH$_2$), 4.93-4.96
(1H, bs, exchanges with D$_2$O, OH), 5.83-6.05 (1H, m, =CH), 5.93 (1H, d, J = 3.8 Hz, H-1), 7.10-7.38 (10H, m, Ar-H);

$^1$C NMR (75 MHz, CDCl$_3$) δ 26.47 (CH$_3$), 26.89 (CH$_3$), 34.31 (C-6), 49.45 (C-5), 57.29 (NCH$_2$Ph), 72.03 (OCH$_2$Ph), 81.28, 81.96, 83.57 (C-2, C-3, C-4), 104.92 (C-1), 111.38 (O-C-O), 115.03 (=CH$_2$), 126.25, 127.49, 127.55, 127.73, 128.25, 128.4 (Ar-C), 137.93 (=CH), 138.25, 141.52 (Ar-C);

Anal. Calcd for C$_{25}$H$_{31}$NO$_5$; C, 70.57; H, 7.34; Found C, 70.29; H, 7.59.

Expt. No. 2.1.7: 3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetraoxy-5-N-(benzylamino)-α-D-glucopyranose (79a).

Zinc dust (0.29 g, 4.50 mmol) was added to a solution of copper(II) acetate (0.015 g) in glacial acetic acid (1 mL) under nitrogen, the mixture was stirred at room temperature for 15 min until the color disappeared. N-benzylhydroxylamine 78a (0.30 g, 0.75 mmol) in glacial acetic acid (0.7 ml) and water (0.3 mL) was successively added, the reaction mixture was heated at 70 °C for 1h and then cooled to room temperature. The sodium salt of EDTA (0.1 g) was added the mixture was stirred for 10 min and then made alkaline to pH 10 by addition of 3N NaOH. The resulting solution was extracted with CHCl$_3$ (10 mL x 3) the combined organic layer was washed with brine dried over Na$_2$SO$_4$ and evaporated to give oil. Purification by column chromatography gave 79a (0.22 g, 77%) as a thick liquid:

$R_f$ = 0.19 (EtOAc/Hexane = 5/5);

$[\alpha]_D$ = −30.97 (c 1.55, CHCl$_3$);

IR $\nu_{\text{max}}$ (neat) = 3640-3310 (br), 1588 cm$^{-1}$;
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.31 (3H, s, CH\(_3\)), 1.47 (3H, s, CH\(_3\)), 1.59-1.62 (1H, bs, exchanges with D\(_2\)O, OH), 2.31-2.42 (1H, m, H-6a), 2.51-2.61 (1H, m, H-6b), 3.20 (1H, ddd, \(J = 9.3, 6.0, 4.0\) Hz, H-5), 3.68 (1H, d, \(J = 12.7\) Hz, NCH\(_2\)Ph), 3.85 (1H, d, \(J = 12.7\) Hz, NCH\(_2\)Ph), 3.99 (1H, dd, \(J = 9.3, 3.1\) Hz, H-4), 4.09 (1H, d, \(J = 3.1\) Hz, H-3), 4.53 (1H, d, \(J = 11.5\) Hz, OCH\(_2\)Ph), 4.60 (1H, d, \(J = 3.8\) Hz, H-2), 4.68 (1H, d, \(J = 11.5\) Hz, OCH\(_2\)Ph), 5.10-5.20 (2H, m, =CH\(_2\)), 5.71-6.00 (1H, m, =CH), 5.92 (1H, d, \(J = 3.8\) Hz, H-1), 7.18-7.38 (10H, m, Ar-H);

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 26.3 (CH\(_3\)), 26.8 (CH\(_3\)), 34.8 (C-6), 51.5 (C-5), 54.0 (NCH\(_2\)Ph), 71.9 (OCH\(_2\)Ph), 81.7, 81.8, 81.9 (C-2, C-3, C-4), 104.7 (C-1), 111.4 (O-C-O), 118.1 (=CH\(_2\)), 126.8, 127.7, 127.8, 128.1, 128.3, 128.4 (Ar-C), 134.5 (=CH), 137.5, 140.7 (Ar-C);

Anal. Calcd for C\(_{25}\)H\(_{31}\)NO\(_4\): C, 73.32; H, 7.63 Found C, 73.26; H, 7.58.

Expt. No. 2.1.8: 3-O-benzyl-1,2-0-isopropylidene-5,6,7,8-tetraideoxy-5-N-(benzylamino)-\(\beta\)-L-ido-7-eno-octofuranose (79b).

The reaction of N-benzylhydroxylamine 78b (0.30 g, 0.75 mmol) with Zn/Cu couple under the same reaction conditions reported for 79a, gave N-benzylamine 79b (0.23 g, 80%) as a thick liquid:

\(R_f = 0.11\) (EtOAc/Hexane = 5/5);

\([\alpha]_D = -60.0\) (c 1.0, CHCl\(_3\));

IR \(\nu_{max}\) (neat) = 3620-3260 (br), 1638.6 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.01 (3H, s, CH\(_3\)), 1.49 (3H, s, CH\(_3\)), 1.80-1.97 (1H, bs, exchanges with D\(_2\)O, OH), 2.01-2.14 (1H, m, H-6a), 2.20-2.32 (1H, m, H-6b), 3.19 (1H, ddd, \(J = 10.0, 9.3, 5.1\) Hz, H-5), 3.83 (2H, ABq, \(J = 12.3\) Hz, NCH\(_2\)Ph), 3.89 (1H, d, \(J = 69\).
3.0 Hz, H-3), 4.08 (1H, dd, J = 9.3, 3.0 Hz, H-4), 4.44 (1H, d, J = 11.7 Hz, OCH2Ph), 4.64 (1H, d, J = 3.9 Hz, H-2), 4.86 (1H, d, J = 11.7 Hz, OCH2Ph), 4.93-5.08 (2H, m, =CH2), 5.81-5.98 (1H, m, =CH), 5.93 (1H, d, J = 3.9 Hz, H-1), 7.19- 7.39 (10H, m, Ar-
H);

13C NMR (75 MHz, CDCl3) δ 26.4 (CH3), 26.7 (CH3), 34.8 (C-6), 51.7 (C-5), 55.3 (NCH2Ph), 71.4 (OCH2Ph), 81.3, 81.7, 82.6 (C-2, C-3, C-4), 104.5 (C-1), 111.4 (O-C-O), 116.7 (=CH2), 126.6, 127.8, 127.9, 128.1, 128.2, 128.3 (Ar-C), 135.1 (=CH), 136.9, 140.5 (Ar-C);

Anal. Calcd for C25H31NO4: C, 73.32; H, 7.63 Found C, 73.22; H, 7.51.

Expt. No. 2.1.9: 3-O-benzyl-5,6-dideoxy-1,2-O-isopropyldine-5-N-(benzyl-
benzoxycarbonylamino)-α-D-gluc-7-eno-octofuranose (65a).

To the stirred solution of N-benzylamine 79a (0.622g, 1.50 mmol) benzoxycarbonyl chloride (0.385 g, 2.25 mmol) and sodium bicarbonate (0.253 g, 3.00 mmol) was added and the reaction mixture was stirred at room temperature for 2h. The solvent was evaporated, water was added and extracted with chloroform, the combined organic layer was washed with brine dried over anhydrous Na2SO4 and evaporated to give an oil which on purification by column chromatography gave 65a (0.610 g, 80%) as a thick liquid:

RF = 0.72 (EtOAc/Hexane = 3/7);

[α]D = −43.79 (c 3.75, CHCl3);

IR νmax (neat) = 1695, 1601 cm⁻¹;

Anal. Calcd for C33H37NO6: C, 72.91; H, 6.86 Found C, 73.11; H, 7.09.
Expt. No. 2.10: 3-0-benzyl-5,6-dideoxy-1,2-0-isopropylidine-5-N-(benzylbenzoxycarbonylamino)-β-L-idoo-7-eno-octa-1,4-furanose (65b).

The reaction of 79b (1.5 g, 3.63 mmol) with benzyloxycarbonyl chloride (0.929 g, 5.45 mmol) and sodium bicarbonate (0.610 g, 7.26 mmol) was performed under the same conditions as reported for 65a. Column chromatography afforded 65b (1.5 g, 76%) as a thick liquid:

- $R_f = 0.59$ (EtOAc/Hexane = 3/7);
- $[\alpha]_D = -8.11$ (c 1.85, CHCl$_3$);
- IR $v_{\text{max}}$ (neat) = 1697, 1598 cm$^{-1}$;
- Anal. Calcd for C$_{33}$H$_{37}$NO$_6$: C, 72.91; H, 6.86; Found C, 72.85; H, 7.13.

Expt. No. 2.1.11: 3-0-benzyl-5,6-dideoxy-1,2-0-isopropylidine-5-N-(benzylbenzoxycarbonylamino)-α-D-glucopyranosylidene-7-eno-octa-1,4-furanose (64a).

Ozone was bubbled through a solution of 65a (0.3 g, 0.55 mmol) in dichloromethane (10 mL) at -40 °C until a blue color persisted. The reaction mixture was purged with O$_2$ until the blue color disappeared, dimethyl sulfide (1 mL, 5.5 mmol) added, the reaction mixture stirred for 2h and evaporated under reduced pressure to give a crude product that was purified by column chromatography to give aldehyde 64a (0.275 g, 89%) as a thick liquid:

- $R_f = 0.65$ (EtOAc/Hexane = 3/7);
- $[\alpha]_D = -28.65$ (c 3.35, CHCl$_3$);
- IR $v_{\text{max}}$ (neat) = 2731, 1722.3, 1697.2 cm$^{-1}$.
\[ ^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 1.34 (3\text{H, s, CH}_3), 1.46 (3\text{H, s, CH}_3), 2.00-2.15 (1\text{H, m, H-6a/6b}), 2.66-2.79 (1\text{H, m, H-6a/6b}), 3.79 (1\text{H, bs}), 4.20-4.89 (6\text{H, m}), 5.05-5.25 (3\text{H, bs}), 5.93 (1\text{H, d, } J = 3.0 \text{ Hz, H-1}), 7.05-7.45 (15\text{H, m, Ar-H}), 9.10 (1\text{H, bs, CHO}); \]

Anal. Calcd for C\(_{32}\)H\(_{35}\)NO\(_7\): C, 70.44; H, 6.47 Found C, 70.31; H, 6.38.

Expt. No. 2.1.12: 3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidine-5-N-(benzylbenzoxycarbonylamino)-\(\beta\)-L-idoo-heptodialdo-1,4-furanose (64b). The reaction of 65b (1.0 g, 1.83 mmol) with ozone and dimethyl sulfide in dichloromethane at -40 °C was performed under the same conditions as reported for 64a. Column chromatography afforded 64b (0.900g, 88%) as a thick liquid:

\[ R_f = 0.61 \text{ (EtOAc/Hexane = 3/7)}; \]
\[ [\alpha]_D = -23.0 \text{ (c 2.0, CHCl}_3); \]

IR \( \nu_{\text{max}} \text{ (neat)} = 3030.0, 2985.6, 1726.2, 1697.2 \text{ cm}^{-1}; \]

Anal. Calcd for C\(_{32}\)H\(_{35}\)NO\(_7\): C, 70.44; H, 6.47 Found C, 70.29; H, 6.32.

Expt. No. 2.1.13: 1,2-O-isopropylidine-5,6,7,8-tetradeoxy-5,9-imino-\(\alpha\)-D-glucopyranosio-1,4-furan-9-ulose (80a). To a solution of aldehyde 64a (1g, 1.83 mmol) in methanol (5 mL), Wittig reagent, triphenylethoxycarbonylmethylene phosphorane (0.957 g, 2.75 mmol) was added and reaction mixture was stirred for 2.5h at room temperature. The methanol was evaporated the thick liquid obtained which on usual work up gave an oil. The crude product was directly subjected to hydrogenation with 10% Pd/C (0.200 g) in methanol (10 mL) at 80 psi for 12h. The solution was filtered through Celite and washed with methanol. To the filtrate anhydrous sodium acetate (0.265 g, 3.18 mmol) was added and refluxed for 6h. The pH of the solution was adjusted to eight by addition of 1M NaOH. Methanol was
removed and the solution was extracted with chloroform (3 x 15 mL). The combined chloroform layer was dried and evaporated to give gummy solid, which was purified by column chromatography (2% MeOH/CHCl₃) to give 80a (0.321 g, 68%) as a white solid: mp = 166-168 °C;

$R_f = 0.61 \ (\text{MeOH/CHCl}_3 = 1/9)$;

$[\alpha]_D = -24.0 \ (c \ 2.0, \ \text{CHCl}_3)$;

IR $\nu_{\text{max}}$ (neat) = 3330- 2880, 1658 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.32 (3H, s, CH$_3$), 1.50 (3H, s, CH$_3$), 1.62-2.08 (4H, m, H-6/H-7), 2.19-2.36 (2H, m, H-8), 3.64-3.76 (1H, m, H-5), 3.95 (1H, dd, $J = 2.4, 9.3$ Hz, H-4), 4.27 (1H, d, $J = 2.4$ Hz, H-3), 4.55 (1H, d, $J = 3.6$ Hz, H-2), 4.78-5.11 (1H, bs, exchanges with D$_2$O, OH/NH), 5.91 (1H, d, $J = 3.6$ Hz, H-1), 8.05-8.22 (1H, bs, exchanges with D$_2$O, OH/NH);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.82 (C-6), 24.56 (C-7), 26.16, 26.90 (CH$_3$), 31.29 (C-8), 50.38 (C-5), 73.42, 82.19, 85.51 (C-2, C-3, C-4), 104.88 (C-1), 111.36 (O-C-O), 174.44 (CO);

Anal. Calcd for C$_{12}$H$_9$NO$_5$: C, 56.02; H, 7.44 Found C, 55.94; H, 7.29.

**Expt. No. 2.1.14: 1,2-0-isopropylidine-5,6,7,8-tetradeoxy-5,9-imino-β-L-idono-1,4-furan-9-ulose (80b).**

The reaction of 64b (0.91 g, 1.67 mmol) with Wittig reagent triphenylethoxycarbonylmethylene phosphorane (0.871 g, 2.50 mmol) and followed by hydrogenation with 10% Pd/C (0.180 g) and sodium acetate (0.242 g, 2.96 mmol) was performed under the same conditions as reported for 80a. Column chromatography (4% MeOH/CHCl$_3$) afforded 80b (0.330 g, 70%) as a white solid:
mp = 156-157 °C;

\( R_f = 0.58 \) (CHCl₃/MeOH = 9/1);

\([\alpha]_D = -11.55 \) (c 2.25, CHCl₃);

IR \( \nu_{max} \) (neat) = 3330-2880, 1624 cm⁻¹;

\(^1\)H NMR (300 MHz, CDCl₃) δ 1.30 (3H, s, CH₃), 1.49 (3H, s, CH₃), 1.59-1.81 (2H, m, H-6), 1.82 (2H, m, H-7), 2.21-2.49 (2H, m, H-8), 3.65-3.80 (1H, m, H-5), 3.95 (1H, dd, \( J = 4.8, 2.7 \) Hz, H-4), 4.22 (1H, d, \( J = 2.7 \) Hz, H-3), 4.51 (1H, d, \( J = 3.6 \) Hz, H-2), 5.01-5.21 (1H, bs, exchanges with D₂O, OH/NH), 5.95 (1H, d, \( J = 3.6 \) Hz, H-1), 7.10-7.22 (1H, bs, exchanges with D₂O, OH/NH);

\(^1^3\)C NMR (75 MHz, CDCl₃) δ 19.85 (C-6), 25.94 (C-7), 26.22, 26.86 (CH₃), 30.96 (C-8), 52.63 (C-5), 75.78, 81.33, 85.27 (C-2, C-3, C-4), 104.61 (C-1), 111.56 (O-C-O), 173.16 (CO);

Anal. Calcd for C₁₂H₁₉NO₅: C, 56.02; H, 7.44% Found C, 55.91; H, 7.25.

Expt. No. 2.1.15: 1,2-O-isopropylidene-5,6,7,8,9-pentadeoxy-5,9-N-(benzoxycarbonylimino)-α-D-glucono-nona-1,4-furanose (62a).

To an ice cooled suspension of LAH (0.223 g, 6.03 mmol) in dry THF (10 mL) was added a solution of 80a (0.310 g, 1.20 mmol) in dry THF (15 mL) over a period of 10 min. The mixture was stirred at room temperature for 2h. Ethyl acetate (10 mL) was added at 0 °C and stirred for 10 min. The reaction was quenched with saturated aq. solution of NH₄Cl (2 mL), filtered and residue rinsed with ethyl acetate (5 mL). Work up, the compound thus obtained was dissolved in ethanol/water (2 mL, 1/1) and sodium bicarbonate (0.299 g, 2.41 mmol), benzzyloxy carbonyl chloride (0.304 g, 1.80 mmol) added at 0 °C. The mixture was stirred at 25 °C for 2h. Work up, extraction with
chloroform (5 mL x 3). The chloroform layer was dried, evaporated to afford a thick liquid, which was purified by column chromatography to give 62a (0.165 g, 74%) as a thick liquid:

\[ R_f = 0.76 \text{ (ethyl acetate/n-hexane = 6/4)}; \]
\[ [\alpha]_D = -43.0 \text{ (2.0 c, CHCl}_3); \]
\[ \text{IR } \nu_{\text{max}} \text{ (neat) } = 3475, 1674 \text{ cm}^{-1}; \]
\[ ^1H \text{ NMR (300 MHz, CDCl}_3+D_2O) \delta 1.31 \text{ (3H, s, CH}_3), 1.48 \text{ (3H, s, CH}_3), 1.88-2.02 \text{ (4H, m, H-6, H-7), 2.20-2.35 \text{ (2H, m, H-8), 3.38-3.48 \text{ (2H, m, H-9), 3.79 \text{ (1H, dd, } J = 9.9, 1.8 Hz, H-4), 4.02 \text{ (1H, d, } J = 1.8 \text{ Hz, H-3), 4.08-4.19 \text{ (1H, m, H-5), 4.58 \text{ (1H, d, } J = 3.6 \text{ Hz, H-2), 5.12 \text{ (2H, ABq, } J = 12.0 \text{ Hz, OCH}_2\text{Ph), 5.88 \text{ (1H, d, } J = 3.6 \text{ Hz, H-1), 7.22-7.41 (5H, m, Ar-H);}}\]
\[ ^13C \text{ NMR (75 MHz, CDCl}_3) \delta 18.94, 25.11, 25.30, 26.20, 27.00, 41.10, 48.50, 67.80, 73.60, 76.60, 84.50, 104.80, 111.30, 127.80, 128.40, 128.50, 135.90, 156.90; \]

Anal. Calcd for C\text{\textsubscript{20}}H\text{\textsubscript{27}}NO\text{\textsubscript{6}}: C, 64.63; H, 7.21 Found C, 63.51; H, 7.09.

Expt. No. 2.1. 16: 1,2-O-isopropylidene-5,6,7,8,9-penta-deoxy-5,9-N-(benzoxycarbonylimino)-\beta-L-idono-1,4-furanose (62b).

The reaction of 80b (0.342 g, 1.33 mmol) with LAH (0.250 g, 6.65 mmol) and sodium bicarbonate (0.223 g, 2.66 mmol), benzylxycarbonyl chloride (0.340 g, 1.99 mmol) was performed under the same conditions as reported for 62a. Column chromatography (pet. ether/ethyl acetate = 92/8) afforded 62b (0.200 g, 78%) as a thick liquid:

\[ R_f = 0.68 \text{ (n-hexane/ethyl acetate = 4/6)}; \]
\[ [\alpha]_D = -72.26 \text{ (1.55 c, CHCl}_3); \]
\[ \text{IR } \nu_{\text{max}} \text{ (neat) } = 3110-3620, 1674 \text{ cm}^{-1}; \]
\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}+D\textsubscript{2}O) \(\delta\) 1.32 (3H, s, CH\textsubscript{3}), 1.51 (3H, s, CH\textsubscript{3}), 1.60-1.80 (2H, m, H-6), 1.81-1.98 (2H, m, H-7), 2.01-2.22 (2H, m, H-8), 3.41-3.60 (2H, m, H-9), 3.98 (1H, dd, \(J = 3.0, 1.8 \text{ Hz}\), H-4), 4.13 (1H, d, \(J = 1.8 \text{ Hz}\), H-3), 4.28-4.35 (1H, m, H-5), 4.47 (1H, d, \(J = 3.6 \text{ Hz}\), H-2), 5.13 (2H, ABq, \(J = 12.3 \text{ Hz}\), OCH\textsubscript{2}Ph), 5.87 (1H, d, \(J = 3.6 \text{ Hz}\), H-1), 7.21-7.41 (5H, m, Ar-H);

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 19.68, 25.22, 26.17, 26.27, 26.85, 39.90, 48.91, 66.90, 74.65, 77.60, 85.45, 104.19, 111.11, 127.34 (Ar-C), 127.57 (Ar-C), 128.17 (Ar-C), 136.82 (Ar-C), 156.21 (CO);

Anal. Calcd for C\textsubscript{20}H\textsubscript{27}NO\textsubscript{6}: C, 64.63; H, 7.21 Found C, 64.49; H, 7.01.

**Expt. No. 2.1.17: (1R,2R,3S,9aR)-octahydro-2H-quinolizine-1,2,3-triol (35a).**

A solution of 62a (0.10 g, 0.29 mmol) in TFA-H\textsubscript{2}O (2 mL, 3/2) was stirred at 25°C for 2h. Trifluoroacetic acid was co-evaporated with benzene to furnish a thick liquid, which was directly used in the next reaction. A solution of above product in methanol (5 mL) was added 10\% Pd/C (0.01 g) and solution was hydrogenated at 80 psi for 12h. The catalyst was filtered, washed with methanol and the filtrate concentrated to get a sticky solid which was purified by column chromatography to give 35a (0.055 g, 90\%) as a thick liquid:

\(R_F = 0.29\) (chloroform/methanol = 7/3);

\([\alpha]_D = -36.0\) (0.2 c, MeOH);

\(\text{IR} = 3676-3250 \text{ cm}^{-1}\);

\textsuperscript{1}H NMR (300 MHz, D\textsubscript{2}O) \(\delta\) 1.24-1.53 (2H, m, H-7), 1.55-1.72 (1H, m, H-9), 1.79-1.98 (3H, m, H-8, H-9), 2.26 (1H, bd, \(J = 13.2 \text{ Hz}\), H-6a), 2.60-2.86 (3H, m, H-6b), 3.22-3.36 (2H, m, H-1, H-9a), 3.41 (1H, t, \(J = 9.5 \text{ Hz}\), H-2), 3.69 (1H, dt, \(J = 9.5, 4.5 \text{ Hz}\), H-3);
$^1$H NMR (300 MHz, D$_2$O) $\delta$ 1.42-1.80 (6H, m, H-7, H-8, H-9), 2.79-2.91 (1H, m, H-6a), 3.15-3.38 (4H, m, H-4, H-6b, H-9a), 3.65 (1H, bs, $W_H$ = 6.0 Hz, H-3), 3.87 (2H, bs, $W_H$ = 6.0 Hz, H-2, H-1); $^13$C NMR (75 MHz, D$_2$O) $\delta$ 21.72, 22.95, 25.76 (C-7, C-8, C-9), 55.74 (C-4, C-6), 61.69 (C-9a), 66.44, 67.20, 70.21 (C-1, C-2, C-3); Anal. Calcd for C$_9$H$_{17}$NO$_3$·2H$_2$O: C, 52.15; H, 10.21; Found C, 51.95; H, 10.30.
References:


Chapter 2:
Part B
Ring Closing Metathesis in the Synthesis of Quinolizidine Alkaloids

In the search for structure-activity relationship, the development of new methodologies towards the synthesis of biological active, natural and unnatural molecules is one of the fascinating area in organic synthesis. Considering this aspect, our group is actively engaged in devising new synthetic strategies towards polyhydroxylated piperidine, indolizidine and quinolizidine alkaloids.

In the previous section (Part A) we have discussed the synthesis of trihydroxy quinolizidine alkaloids 35a and 35b π-facial diastereoselective using stereoselective 1,3-addition reaction of allylmagnesium bromide to d-glucose derived nitrone 61 as a key step. As an alternative, we thought of devising an altogether different synthetic route for the synthesis of these (Figure 1).

![Figure 1](image)

Retrosynthetic analysis:

As shown in the retrosynthetic analysis (Scheme I), the bicyclic quinolizidine ring skeleton could be built by linking the nitrogen atom of the piperidine ring with the hemiacetal of furanose ring in 62 by reductive amination. The N-Cbz protected piperidine compound 62 could be obtained from dihydropiperidine 81 by hydrogenation and hydrolysis of acetonide group. The ring-closing metathesis (RCM) of the diene compound 82 could give an easy access to compound
The compound 82 could be achieved by 1,3 addition of allylmagnesium bromide to sugar-derived nitrore 61 followed by N-allylation. The nitrore 61 was obtained from the D-glucose, as reported in the previous section (part A). Thus, the D-glucose derived nitrore will give an access to A ring skeleton, with required polyhydroxylated functionalites while; the B ring skeleton could be achieved by RCM of diene.

In the present approach, the RCM is the key step in our reaction sequence therefore, it is appropriate to discuss a brief account of the RCM in the synthesis of azasugars.

**Ring Closing Metathesis (RCM) in the synthesis of Azasugars:**

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes, with the advent of efficient catalysts, this reaction has emerged as a powerful tool for the formation of C-C bonds in
chemistry. The number of applications of this reaction has dramatically increased in the past few years. This type metathesis utilizes no additional reagents beyond a catalytic amount of metal carbene and the only other product from the reaction is, in most cases, a volatile olefin such as ethylene. Olefin metathesis can be utilized in three closely related type of reactions as shown Scheme 2: (A)- ring-opening metathesis polymerization (ROMP); (B)- ring-closing metathesis (RCM); and (C)- acyclic cross metathesis, which when carried out on diolefins results in polymers (ADMET). Recently ring-closing olefin metathesis (RCM, type B) has received a great deal of attention for the synthesis of medium or large sized rings from acyclic diene precursors. The scope and limitations of the RCM reaction has been reviewed extensively in recent years. This intensive study is primarily due to the development of well-defined metathesis catalysts which are tolerant to many functional groups as well as reactive towards a diverse range of substrates.

At the present time, there are two main types of catalyst in use (Figure 2). These are (a) molybdenum-based complex (I), developed by Schrock and co-workers (b) ruthenium-based complexes (II) and (III), developed by Grubbs and co-workers. The molybdenum-based
Complex (I) has major disadvantage of being particularly air- and moisture sensitive. In addition, Complex (I) is relatively less tolerant of functionality such as ketones, esters, amides, epoxides, acetals, silyl ethers and sulfides. Whereas ruthenium-based complexes (II) and (III) are not significantly affected by air and moisture and are remarkably tolerant of oxygen. In addition, complexes (II) and (III) more tolerate the substrates containing free alcohols, as well as the functional group listed above for complex (I).

![Schrock Catalyst](attachment://schrock_catalyst.png)  ![Grubbs Catalyst](attachment://grubbs_catalyst.png)

**Figure 2**

**Mechanism:**

The generally accepted mechanism of metathesis reaction consists of a series of alternating [2+2] cycloadditions and cycloreversions between metal alkylidene and metallacyclobutane intermediates. The mechanism of the ring-closing metathesis (RCM) of a diene, is presented in scheme 3. In the first turn of the catalytic cycle, the alkene-byproduct depends on the R group in the original catalyst, while in second and subsequent catalytic cycles it depends on the substrate. For terminal alkene substrates the reaction by-product is ethylene. Alkene substitution in both substrate and product can dramatically influence the reaction rate and outcome. In this particular
case, the forward process is entropically driven because RCM cuts one substrate molecule into two products.

![Scheme 3. Mechanism for Ring Closing Metathesis](image)

Due to high catalytic activity and functional group tolerance, catalysts (II) and (III) are ideally suited to applications involving nitrogen atom in the substrate. The RCM approach has found wide applications in azasugar synthesis. A number of nitrogen heterocycles were easily prepared using RCM approach. The tolerance of catalysts (II) and (III) towards oxygen and alcoholic functionality permits use of RCM with carbohydrate substrates. In the present work, our objective was to synthesize trihydroxy quinolizidine alkaloids 35a and 35b. Therefore, we would like to confine our discussion on the synthetic aspects of indolizidine and quinolizidine alkaloids using RCM. To the best of our knowledge only two RCM strategies are known for quinolizidine alkaloids.

**Method due to Pandit and coworkers**

Pandit and coworkers have reported the first synthesis of trihydroxy quinolizidine alkaloid 35b using RCM as a key step (Scheme 4). In this approach, D-xylose was first converted to lactone 83 in three steps. The first alkene moiety was introduced into lactone 83 via aminolysis with allylamine in methanol. Oxidation of the primary hydroxyl function in 84 gave an equilibrium mixture of aldehyde 85 and hydroxylactam 86. This mixture was treated with methanolic
ammonia to obtain 86 as the sole product. Introduction of the second alkene moiety was subsequently accomplished by transformation of 86 into acetoxylactam 87 followed by reaction with allyltrimethylsilane to afford diene 88. Diene 88 was subjected to the RCM conditions that afforded the perbenzylated compound 89. Reduction of the lactam 89 followed by hydrogenation of the double bond and benzyl deprotection led to the formation of quinolizidine alkaloid 35b.

**Scheme 4**

**Reagents and conditions:**
(i) Allylamine, MeOH;  (ii) Dess Martin Periodinane; (iii) NH$_3$, MeOH;  (iv) Ac$_2$O, Py, DMAP;  (v) Allyltrimethylsilane, BF$_3$:OEt$_2$;  (vi) Grubb’s catalyst, CH$_2$Cl$_2$;  (vii) a) LAH, THF;  b) H$_2$, Pd(OH)$_2$, EtOH.
Method due to Pyne and coworkers.\textsuperscript{11}

Pyne and coworkers have describe the synthesis of Indolizidine alkaloid namely swainsonine 28 (Scheme 5). The key steps in their methodology involve vinyl epoxide aminolysis, ring closing metathesis and intramolecular N-alkylation. The synthesis start with commercially available 4-pentyn-1-ol, which was converted to the trans allylic alcohol 90 in three high yielding steps. Catalytic asymmetric epoxidation of 90 gave the epoxy alcohol 91. Swern oxidation of the primary alcohol 91 gave the aldehyde that was converted to the vinyl epoxide 92 by Wittig olefination. Aminolysis of 92 was achieved by allylamine to afford anti amino alcohol 93.

\[\text{CH}_2\text{OH} \xrightarrow{i} \text{CH}_2\text{OH} \xrightarrow{ii} \text{CH}_2\text{OH} \xrightarrow{iii} \]

Reagents and conditions: i) D-\((-\)-DIPT, Ti(OP\textsubscript{r})\textsubscript{4}, TBHP, CH\textsubscript{2}Cl\textsubscript{2}, 4Å MS, -20 °C; ii) DMSO, (COCl)\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, -60 °C, NEt\textsubscript{3}; iii) MeP(Ph)\textsubscript{3}Br, KHMDS, toluene; iv) allylamine, p-TsOH-H\textsubscript{2}O; v) (Boc)\textsubscript{2}O, NEt\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}; vi) Cl\textsubscript{2}(Cy\textsubscript{3}P)\textsubscript{2}Ru=CHPh, CH\textsubscript{2}Cl\textsubscript{2}, reflux; vii) NaH, BnBr, TBAI, THF, rt; viii) TFA-anisole, 0 °C; ix) Ph\textsubscript{3}P, CBr\textsubscript{4}, NEt\textsubscript{3}, 0 °C; x) AD mix 2,2-dimethoxypropane, p-TsOH, 3h, rt; xi) a) PdCl\textsubscript{2}, H\textsubscript{2}, MeOH, rt, 1h; b) 2M HCl, THF, rt, 20h, basic-ion exchange.

Scheme 5
Protection of amino group in 93 afforded N-Boc derivative 94, which on ring closing metathesis gave the dihydroprrole derivative 95. Protection of secondary alcohol in 95 with benzyl ether afforded the compound 96 that on treatment with TFA gave the amino alcohol 97. The intramolecular N-alkylation gave the indolizidine derivative 98. The asymmetric cis-dihydroxylation of 98 followed by acetonide protection gave the compound 99. Catalytic hydrogenolysis of 99 followed by deprotection of acetonide afforded (-)-swainsonine 28.

Method due to Singh and coworkers

Singh and coworkers have described the total synthesis of indolizidine alkaloid namely, lentiginosine 29 from D-mannitol (Scheme 6). The synthesis starts with diol 100. Reaction of diol

![Chemical Structure Image]

**Reagents and conditions:** a) (i) Pb(OAc)$_4$, CH$_2$Cl$_2$, 3h; (ii) NaBH$_4$, EtOH, 3h; (iii) TsCl, NEt$_3$, CH$_2$Cl$_2$, 12h; (iv) NaN$_3$, DMF, 80 °C, 8h; b) TFA, THF-H$_2$O, 65 °C, 8h; c) (i) Pb(OAc)$_4$, CH$_2$Cl$_2$, 3h; (ii) SnCl$_2$, allyltributyl tin, CH$_2$Cl$_2$, 6h; d) MsCl, NEt$_3$, CH$_2$Cl$_2$, 6h; e) LAH, THF, reflux, 12h; f) acryloyl chloride, NEt$_3$, CH$_2$Cl$_2$, 12h; g) Grubbs catalyst, toluene reflux, 24h; h) (i) 10% Pd-C, H$_2$, 24h; (ii) LAH, THF, reflux, 6h.

**Scheme 6**
with lead tetraacetate gave an aldehyde, which was reduced to primary alcohol that was directly converted to azido compound 101. The acetonide cleavage in 101 to get diol 102, its oxidation and the diastereoselective addition of allyltributylstannane to the crude aldehyde gave homoallylic alchol 103. Its mesylate 104, on treatment with LAH gave the cyclized amine 105. Amine 105 was converted into acrylamide 106. Ring closing metathesis of 106 afforded cyclized product 107, which on hydrogenation followed by lactam reduction gave the target lentiginosine 29.

**Method due to Blechert and coworkers**

In this approach, Blechert and coworkers demonstrated the utility of ruthenium-catalyzed ring rearrangement of cyclopentene derivative in the synthesis of tetrahydroxy quinolizidine alkaloid 108 (Scheme 7). The cis-cyclopentene derivative 110 was obtained by Pd-catalyzed allylation of N-Nosylbutenylamine with 109. Reaction of 110 with TBDMSCl afforded the

Reagents and conditions: Pd(OAc)₂, PPh₃, N-nosylbutenylamine, DMF, rt to 40 °C; b) TBDMSCl, imidazole, DMF, rt; c) 1 mol% [Ru], CH₂Cl₂, rt; d)TBAF, THF, rt; e) OsO₄, NMO, acetone-H₂O, rt; f) PPh₃, DEAD, py, 0 °C; g) OsO₄, NMO, acetone-H₂O, rt.

Scheme 7
TBDMS protected compound 111. The uncommon rearrangement of 111 with 1 mol% [Ru] on CH₂Cl₂ gave the piperidine derivative 112. Deprotection of TBDMS gave alcohol 113 that on dihydroxylation afforded a triol 114. Deprotection and cyclisation under Mitsunobu condition gave 115, which on syn-dihydroxylation afforded the target compound 108.

Thus, ring-closing metathesis is a unique approach that gives an easy access for the formation of a ring with endocyclic double bond from an acyclic diene. The noteworthy features of this approach are (a) the endocyclic double bond is a potential functionality for two hydroxyl groups by syn-dihydroxylation and (b) the approach also provides an entry towards nitrogen heterocyclic compounds provided the N-allyl and an olefin functionality is present in the molecule. For this reason, the D-glucose derived N-benzylamino sugars 79a and 79b were considered to be the true synthons wherein, the required diene for RCM could be easily obtained by N-allylation and presence of well defined hydroxyl group in the sugar part will lead to the construction of polyhydroxylated piperidine ring skeleton.

**Present Work:**

The requisite N-benzylamino sugars 3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-5-N-(benzylamino)-α-D-gluc-7-en-2-eno-octofuranose 79a and 3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-5-N-(benzylamino)-β-L-id-7-en-2-eno-octofuranose 79b were prepared from Grignard reaction of allylmagnesium bromide to sugar derived nitrone 61 followed by reductive cleavage of N-O bond as described earlier in previous Part A. To test the feasibility of our approach, we have performed the reactions first with the readily available D-gluco configurated N-benzylamine 79a.
In the next step, to get diene functionality, the compound 79a was reacted with allyl bromide in the presence of potassium carbonate in dry DMF for 18h. The reaction afforded the product in 75% yield.

The IR spectrum of the compound showed a band at 1639 cm\(^{-1}\) and a strong band at 914 cm\(^{-1}\) due to the olefinic frequency and C-H bending of terminal methylene group, respectively. The analysis was found to be in accordance with the molecular formula C\(_{28}\)H\(_{35}\)NO\(_4\). The \(^1\)H NMR (Figure 1) spectrum showed following signals:

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.30 (3H, s, CH\(_3\)), 1.46 (3H, s, CH\(_3\)), 2.48 (2H, bt, \(J = 7.2\) Hz, H-6), 3.12 (1H, dd, \(J = 14.1, 6.6\) Hz, N-CH\(_2\)C), 3.22 (1H, dd, \(J = 14.1, 6.3\) Hz, N-CH\(_2\)C), 3.34 (1H, q, \(J = 7.2\) Hz, H-5), 3.73 (2H, ABq, \(J = 14.4\) Hz, N-CH\(_2\)Ph), 3.95 (1H, d, \(J = 3.0\) Hz, H-3), 4.22 (1H, dd, \(J = 7.2, 3.0\) Hz, H-4), 4.48 (1H, d, \(J = 11.7\) Hz, O-CH\(_2\)Ph), 4.53 (1H, d, \(J = 3.6\) Hz, H-2), 4.63 (1H, d, \(J = 11.7\) Hz, O-CH\(_2\)Ph), 4.87-5.18 (4H, m, C=CH\(_2\)), 5.63-5.80 (1H, m, HC=C), 5.89 (1H, d, \(J = 3.6\) Hz, H-1), 5.92-6.08 (1H, m, HC=C), 7.16-7.22 (10H, m, Ar-H). The appearance of signals at 5.63-5.80 and at 5.92-6.08 as a multiplet and multiplets at 4.87-5.18 for four hydrogens indicated the presence of two allyl functionalities. This fact was supported by the \(^{13}\)C NMR (Figure 2) spectrum, which shows following signals

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 26.2, 26.8 (CH\(_3\)), 32.9 (C-6), 54.5, 54.7, 57.3 (C-5, N-CH\(_2\)C, N-CH\(_2\)Ph), 71.8 (O-CH\(_2\)Ph), 79.9, 81.6, 82.7 (C-2, C-3, C-4), 104.7 (C-1), 111.4 (O-C-O), 115.4.
Figure 1: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 116a
Figure 2: $^{13}$C NMR (76 MHz, CDCl$_3$) spectrum of compound 116a.
116.6 (C=CH₂), 126.7, 127.6, 127.7, 128.1, 128.3, 128.5 (Ar-C), 137.2 (C=C), 137.6 (Ar-C), 138.28 (C=C), 140.5 (Ar-C). Based on the spectral and analytical data the compound was assigned the structure 116a.

Having the diene compound 116a in hand, it was subjected to ring-closing metathesis using first generation Grubbs catalyst (benzylidene-bis-tricyclohexylphosphone-dichlororuthenium) in dry CH₂Cl₂ for 18h. The TLC of the crude mixture showed two spots, of which one was having same Rf as that of starting compound. The chromatographic purification and elution first with ethyl acetate/hexane = 5/95 afforded a new compound in 70% yield.

In the IR spectrum, the band at 1640 cm⁻¹ indicated the presence of double bond. However, the disappearance of terminal olefinic CH- bending (=CH₂) frequency and appearance of CH-bending at 736 cm⁻¹ indicated the disubstituted cis double bond. ¹H NMR (Figure 3) showed following signals:

¹H NMR (300 MHz, CDCl₃) δ 1.34 (3H, s, CH₃), 1.46 (3H, s, CH₃), 2.30-2.41 (2H, m, H-6), 3.10-3.18 (2H, m, H-9), 3.47-3.56 (1H, m, H-5), 3.77 (2H, ABq, J = 13.8 Hz, N-CH₂Ph), 4.11 (1H, d, J = 2.7 Hz, H-3), 4.35 (1H, dd, J = 9.3, 2.7 Hz, H-4), 4.62 (1H, d, J = 3.9 Hz, H-2), 4.70 (2H, ABq, J = 11.7 Hz, O-CH₂Ph), 5.56-5.64 (1H, m, H-7), 5.87-5.92 (1H, m, H-8), 5.95 (1H, d, J = 3.9 Hz, H-10).
H-1), 7.20-7.38 (10H, m, Ar-H). The disappearance of multiplets at 5.63-5.80 and at 5.92-6.08 and the multiplet at 4.87-5.18 for four hydrogens and presence of the multiplets at 5.56-5.80 and 5.87-5.92 indicated the presence of disubstituted cis double bond. This fact was supported by the $^{13}$C NMR (Figure 4) spectrum, which shows following signals.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 22.4 (C-6), 26.2, 26.8 (CH$_3$), 47.2 (C-9), 54.1, 55.3 (C-5, N-CH$_2$Ph), 72.4 (O-CH$_2$Ph), 79.6, 81.8, 82.4 (C-2, C-3, C-4), 104.5 (C-1), 111.4 (O-C-O), 124.0, 125.3 (C=C), 126.7, 127.6, 127.7, 128.2, 128.4, 128.5, 137.9, 139.9 (Ar-C). The analysis was found to be in agreement with the molecular formula C$_{26}$H$_{31}$NO$_4$. Based on these observations the compound was assigned the structure 117a.

Further elution with ethyl acetate/hexane = 10/90 gave the compound in 30% yield which was found to be the starting compound 116a based on the spectral data.

In order to increase the yield, we tried different solvent, benzene and optimized the reaction conditions. The above RCM reaction when carried out with first generation Grubbs catalyst in dry benzene at reflux for 2h, it afforded exclusively the RCM product 117a in 81% yield.

We have also attempted the use of second generation catalyst namely, benzylimidene[1,3-bis(2,4,6-trimethyl-phenyl)-2-imidazolidinylidene]dichloro-(tricyclohexylphosphine) ruthenium. The reaction of the diene compound 116a with second generation Grubbs catalyst in dry CH$_2$Cl$_2$ at 25 °C for 24h afforded two products. The chromatography on elution first with ethyl...
Figure 3: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 117a
Figure 4: \textsuperscript{13}C NMR (76 MHz, CDCl\textsubscript{3}) spectrum of compound 117a
acetate/hexane = 10/90 afforded the RCM product 117a in 67%. Further elution with ethyl acetate/hexane = 10/90 gave the compound in 33% yield. The spectral and analytical data was found to be consistent with the compound 79a. The cleavage of N-allyl group leading to the formation of 79a, under Grubbs conditions, was surprising. No such observation is known in literature.

In the subsequent step, compound 117a was subjected to hydrogenation using 10%Pd-C in methanol. The crude product was analysed by $^1$H NMR spectra and was found to be the secondary amine with cleavage of N-benzyl and O-benzyl group along with the reduction of double bond. The product was found to be relatively unstable and therefore was directly subjected to the selective N-protection with Cbz group using benzyl chloroformate that afforded in 78% yield.

Based on the spectral and analytical data the compound was assigned the structure 62a. The compound 62a was already reported by us. The specific rotation, spectral and analytical data were found to be in good agreement with that prepared earlier by us (part A).
The conversion of 62a to \((1R,2R,3S,9aR)\)-octahydro-2H-quinolizine-1,2,3-triol 35a by opening of 1,2-acetonide functionality and followed by hydrogenation is discussed in the earlier part. The present strategy thus represents a new formal synthesis of trihydroxy quinolizidine alkaloid 35a.

Having the success in the synthesis of \((1R,2R,3S,9aR)\)-octahydro-2H-quinolizine-1,2,3-triol 35a from \(\text{\textit{N}}\)-benzylamino sugar 79a we thought of elaborating the same reaction sequence with \(L\)-\textit{ido} configurated \(\text{\textit{N}}\)-benzylamino sugar 79b. It is obvious that this reaction sequence should lead to the formation of \((1R,2R,3S,9aS)\)-octahydro-2H-quinolizine-1,2,3-triol 35b. Thus as shown in Scheme 8, the \(\gamma\)-alkenyl-\(\text{\textit{N}}\)-benzylamino sugar 79b was converted to the trihydroxy quinolizidine 35b in overall 23.2% yield. The corresponding C5-epimeric compounds 116b, 117b, 62b and 35b were isolated in good yields and were characterized by spectral and analytical data (Figure 5- Figure 8). The spectral and analytical data of 35b is consistent with that reported earlier by us in the Part A.

![Scheme 8](image)
Figure 6: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 116b
Figure 6: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 116b
Figure 7: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 117b
Figure 8: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 117b
Conclusions:

1. We have successfully synthesized the required diene functionality with nitrogen substituent from D-glucose and utilized the same in a ring-closing metathesis in the synthesis of trihydroxy quinolizidine alkaloids 35a and 35b.

2. The easy availability of the chiral starting materials, mild reaction conditions and good yields make the route attractive and indicate that it could operate on a gram scale required for biological-medicinal study.
Experimental
EXPERIMENTAL

Expt. No. 2.2.1: 3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-5-(N-allyl-N-benzylamino)-α-D-glucopyranosyl-7-eno-octa-1,4-furanose (116a).

Expt. No. 2.2.2: 3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-5-(N-allyl-N-benzylamino)-β-D-idopyranosyl-7-eno-octa-1,4-furanose (116b).

Expt. No. 2.2.3: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzylamino)-α-D-glucopyranosyl-7-eno-nonan-1,4-furanose (117a).

Expt. No. 2.2.4: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzylamino)-β-D-idopyranosyl-7-eno-nonan-1,4-furanose (117b).
Expt. No. 2.2.5: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzyloxycarbonyl-imino)-
α-D-glucono-nona-1,4-furanose (62a).

Expt. No. 2.2.6: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzyloxycarbonyl-imino)-
β-L-ido-nona-1,4-furanose (62b).

Expt. No. 2.2.7: (1R,2R,3S,9aR)-octahydro-2H-quinolizine-1,2,3-triol (35a).

Expt. No. 2.2.8: (1R,2R,3S,9aS)-octahydro-2H-quinolizine-1,2,3-triol (35b).
Expt. No. 2.2.1: 3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-5-(N-allyl-N-benzylamino)-α-D-glucopyranose (116a).

To a stirred solution of 79a (0.45 g, 0.98 mmol) and anhydrous potassium carbonate (0.68 g, 4.07 mmol) in dry DMF (5 mL) was added allyl bromide (0.27 g, 1.62 mmol) in dry DMF (1 mL). The reaction mixture was stirred at room temperature for 30 h, decomposed with cooled water (2 mL) and extracted with chloroform (3 X 10 mL). Work-up followed by chromatography (EtOAc/Pet. ether = 5/95) gave 116a (0.38 g, 71%) as thick liquid:

\[ R_f = 0.65 \text{ (EtOAc/Hexane = 2/8)}; \]
\[ [\alpha]_D = -36.4 (c 0.44, CHCl_3); \]
\[ \text{IR } v_{max} \text{ (neat) } = 1639, 1605 \text{ cm}^{-1}; \]
\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta 1.30 (3H, s, CH}_3 \), 1.46 (3H, s, CH}_3 \), 2.48 (2H, bt, } J = 7.2 \text{ Hz, H-6)}, 3.12 (1H, dd,} J = 14.1, 6.6 \text{ Hz, N-CH}_2\text{C}, 3.22 (1H, dd,} J = 14.1, 6.3 \text{ Hz, N-CH}_2\text{C}, 3.34 (1H, q,} J = 7.2 \text{ Hz, H-5)}, 3.73 (2H, ABq,} J = 14.4 \text{ Hz, N-CH}_2\text{Ph}, 3.95 (1H, d,} J = 3.0 \text{ Hz, H-3)}, 4.22 (1H, dd,} J = 7.2, 3.0 \text{ Hz, H-4)}, 4.48 (1H, d,} J = 11.7 \text{ Hz, O-CH}_2\text{Ph), 4.53 (1H, d,} J = 3.6 \text{ Hz, H-2)}, 4.63 (1H, d,} J = 11.7 \text{ Hz, O-CH}_2\text{Ph), 4.87-5.18 (4H, m, C=CH}_2 \text{), 5.63-5.80 (1H, m, HC= C)}, 5.89 (1H, d,} J = 3.6 \text{ Hz, H-1)}, 5.92-6.08 (1H, m, HC= C), 7.16-7.22 (10H, m, Ar-H); \]
\[ ^13C \text{ NMR (75 MHz, CDCl}_3 \delta 26.2, 26.8 (CH}_3 \), 32.9 (C-6), 54.5, 54.7, 57.3 (C-5, N-CH}_2\text{C, N-CH}_2\text{Ph}, 71.8 (O-CH}_2\text{Ph), 79.9, 81.6, 82.7 (C-2, C-3, C-4), 104.7 (C-1), 111.4 (O-C-O), 115.4, 116.6 (C=CH}_2 \text{), 126.7, 127.6, 127.7, 128.1, 128.3, 128.5 (Ar-C), 137.2 (C=C), 137.6 (Ar-C), 138.28 (C=C), 140.5 (Ar-C)); \]

Anal. Calcd for C_{28}H_{33}NO_4: C, 73.32; H, 7.63 Found C, 73.26; H, 7.58.
The reaction of 79b with anhydrous potassium carbonate (0.72 g, 5.25 mmol) and allyl bromide (0.43 g, 1.05 mmol) in dry DMF (5 mL) under the same conditions reported for 116a gave 116b. Column chromatography (EtOAc/Pet Ether = 10/90) afforded 116b (0.335 g, 71%) as a thick liquid:

\[
R_f = 0.53 \text{ (EtOAc/Hexane = 2/8)};
\]

\[
[a]_D = -38.2 \ (c \ 0.33, \ \text{CHCl}_3);
\]

IR \text{ v}_{\text{max}} (\text{neat}) = 1641, 1601 cm^{-1};

\[1^1 \text{H NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 1.41 \ (3H, s, \text{CH}_3), 1.59 \ (3H, s, \text{CH}_3), 1.80-1.93 \ (1H, m, H-6a/6b), 2.11-2.23 \ (1H, m, H-6a/6b), 3.30-3.47 \ (3H, m, H-5, N-CH_2C), 3.81 \ (1H, d, J = 3.0 Hz, H-3), 3.82 \ (1H, dd, J = 14.1 Hz, N-CH_2Ph), 3.94 \ (1H, d, J = 14.1 Hz, N-CH_2Ph), 4.30 \ (1H, dd, J = 9.6, 3.0 Hz, H-4), 4.45 \ (1H, d, J = 11.7 Hz, O-CH_2Ph), 4.64 \ (1H, d, J = 3.9 Hz, H-2), 4.70 \ (1H, d, J = 11.7 Hz, O-CH_2Ph), 4.90-5.24 \ (4H, m, C=\text{CH}_2), 5.79-5.96 \ (2H, m, HCC= C), 6.02 \ (1H, d, J = 3.9 Hz, H-1), 7.20-7.46 \ (10H, m, Ar-H);
\]

\[1^3 \text{C NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta 26.2, 26.8 \ (\text{CH}_3), 34.5 \ (C-6), 53.3, 54.9, 56.8 \ (C-5, N-CH_2Ph, N-CH_2C), 71.3 \ (O-CH_2Ph), 81.1, 81.9, 82.4 \ (C-2, C-3, C-4), 104.8 \ (C-1), 111.2 \ (O-C-O), 115.1, 115.9 \ (C=\text{CH}_2), 126.3, 127.5, 127.8, 127.9, 128.4, 128.9 \ (Ar-C), 137.2, 137.3 \ (C=\text{C}), 138.3, 141.3 \ (Ar-C);
\]

Anal. Calcd for C_{28}H_{35}NO_4: C, 73.32; H, 7.63 Found C, 73.26; H, 7.58.
The compound 116a (0.180 g, 0.4 mmol) was dissolved in dry benzene (15 mL), and benzylidene-bis-tricyclohexylphosphine-dichlororuthenium (0.006 g, 5 mol%) was added at room temperature, the reaction mixture was refluxed under nitrogen for 18h, solvent was removed in vacuo to give a brown oil. The crude product was subjected to column chromatography (EtOAc/Pet. ether = 5/95), which afforded the compound 117a (0.155 g, 81%) as a thick liquid:

R_f = 0.50 (EtOAc/Hexane = 2/8);
[α]D = -21.8 (c 0.55, CHCl3);
IR νmax (neat) = 1640, 1605 cm⁻¹;

1H NMR (300 MHz, CDCl3) δ 1.34 (3H, s, CH3), 1.46 (3H, s, CH3), 2.30-2.41 (2H, m, H-6), 3.10-3.18 (2H, m, H-9), 3.47-3.56 (1H, m, H-5), 3.77 (2H, ABq, J = 13.8 Hz, N-CH2Ph), 4.11 (1H, d, J = 2.7 Hz, H-3), 4.35 (1H, dd, J = 9.3, 2.7 Hz, H-4), 4.62 (1H, d, J = 3.9 Hz, H-2), 4.70 (2H, ABq, J = 11.7 Hz, O-CH2Ph), 5.56-5.64 (1H, m, H-7), 5.87-5.92 (1H, m, H-8), 5.95 (1H, d, J = 3.9 Hz, H-1), 7.20-7.38 (10H, m, Ar-H);

13C NMR (75 MHz, CDCl3) δ 22.4 (C-6), 26.2, 26.8 (CH2), 47.2 (C-9), 54.1, 55.3 (C-5, N-CH2Ph), 72.4 (O-CH2Ph), 79.6, 81.8, 82.4 (C-2, C-3, C-4), 104.5 (C-1), 111.4 (O-C-O), 124.0, 125.3 (C=C), 126.7, 127.6, 127.7, 128.2, 128.4, 128.5, 137.9, 139.9 (Ar-C);

Anal. Calcd for C26H31NO4: C, 73.32; H, 7.63 Found C, 73.26; H, 7.58.

Expt. No. 2.2.3: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzylamino)-α-D-gluco-7-eno-nona-1,4-furanose (117a).

The reaction of 116a (0.180 g, 0.4 mmol) was dissolved in dry benzene (15 mL), and benzylidene-bis-tricyclohexylphosphine-dichlororuthenium (0.006 g, 5 mol%) was added at room temperature, the reaction mixture was refluxed under nitrogen for 18h, solvent was removed in vacuo to give a brown oil. The crude product was subjected to column chromatography (EtOAc/Pet. ether = 5/95), which afforded the compound 117a (0.155 g, 81%) as a thick liquid:

R_f = 0.50 (EtOAc/Hexane = 2/8);
[α]D = -21.8 (c 0.55, CHCl3);
IR νmax (neat) = 1640, 1605 cm⁻¹;

1H NMR (300 MHz, CDCl3) δ 1.34 (3H, s, CH3), 1.46 (3H, s, CH3), 2.30-2.41 (2H, m, H-6), 3.10-3.18 (2H, m, H-9), 3.47-3.56 (1H, m, H-5), 3.77 (2H, ABq, J = 13.8 Hz, N-CH2Ph), 4.11 (1H, d, J = 2.7 Hz, H-3), 4.35 (1H, dd, J = 9.3, 2.7 Hz, H-4), 4.62 (1H, d, J = 3.9 Hz, H-2), 4.70 (2H, ABq, J = 11.7 Hz, O-CH2Ph), 5.56-5.64 (1H, m, H-7), 5.87-5.92 (1H, m, H-8), 5.95 (1H, d, J = 3.9 Hz, H-1), 7.20-7.38 (10H, m, Ar-H);

13C NMR (75 MHz, CDCl3) δ 22.4 (C-6), 26.2, 26.8 (CH2), 47.2 (C-9), 54.1, 55.3 (C-5, N-CH2Ph), 72.4 (O-CH2Ph), 79.6, 81.8, 82.4 (C-2, C-3, C-4), 104.5 (C-1), 111.4 (O-C-O), 124.0, 125.3 (C=C), 126.7, 127.6, 127.7, 128.2, 128.4, 128.5, 137.9, 139.9 (Ar-C);

Anal. Calcd for C26H31NO4: C, 73.32; H, 7.63 Found C, 73.26; H, 7.58.

Expt. No. 2.2.4: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzylamino)-β-L-ido-7-eno-nona-1,4-furanose (117b).

The reaction of 116b (0.220 g, 0.48 mmol) with benzylidene-bis-tricyclohexylphosphine-dichlororuthenium (0.010 g, 5 mmol) in dry benzene (15 mL) under the same conditions reported
for 117a gave 117b. Column chromatography (EtOAc/Pet. Ether = 10/90) afforded 117b (0.175 g, 78%) as a thick liquid:

$$R_f = 0.46 \text{ (EtOAc/Hexane = 2/8)};$$

$$[\alpha]_D = -19.4 \text{ (c 0.22, CHCl}_3);$$

IR $\nu_{max}$ (neat) = 1650, 1603 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.37 (s, 3H), 1.52 (s, 3H), 1.72-1.79 (m, 1H), 2.29-2.43 (m, 1H), 3.10-3.28 (m, 2H), 3.53 (ddd, $J$ = 9.6, 5.8, 3.8 Hz, 2H), 3.82 (1H, d, $J$ = 3.0 Hz, H-3), 3.94 (2H, ABq, $J$ = 13.8 Hz, N-CH$_2$Ph), 4.46 (1H, d, $J$ = 11.7 Hz, O-CH$_2$Ph), 4.54 (1H, dd, $J$ = 9.6, 3.0 Hz, H-4), 4.64 (1H, d, $J$ = 3.9 Hz, H-2), 4.73 (1H, d, $J$ = 11.7 Hz, O-CH$_2$Ph), 5.60-5.72 (2H, bs, H-7, H-8), 6.05 (1H, d, $J$ = 3.9 Hz, H-1), 7.19-7.45 (10H, m, Ar-H);

$^13$C NMR (75 MHz, CDCl$_3$) $\delta$ 26.3 (CH$_3$), 26.7(C-6), 26.8 (CH$_3$), 47.0 (C-9), 54.4, 58.3 (C-5, N-CH$_2$Ph), 71.5 (O-CH$_2$Ph), 78.4, 81.1, 82.6 (C-2, C-3, C-4), 105.1 (C-1), 111.3 (O-C-O), 123.6, 125.7 (C=C), 126.5, 127.7, 127.9, 128.1, 128.4, 128.8, 137.2, 140.5 (Ar-C);

Anal. Calcd for C$_{26}$H$_{31}$NO$_4$: C, 73.32; H, 7.63 Found C, 73.26; H, 7.58.

Expt. No. 2.2.5: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzyloxy carbonyl-imino)-$\alpha$-D-glucos-ona-1,4-furanose (62a).

A 117a (0.600 g, 1.42 mmol) and 10% Pd/C (0.100 g) in methanol (5 mL) was hydrogenolysed at 80 psi for 12h. The catalyst was filtered through celite and washed with methanol. The usual work up afforded a thick oil that was dissolved in ethanol/water (2 mL, 1/1). The solution was cooled to 0 °C and sodium bicarbonate (0.299 g, 2.41 mmol), benzyloxy carbonyl chloride (0.304 g, 1.80 mmol) was added successively. The mixture was stirred at 25 °C for 2h. Ethanol was evaporated at reduced pressure and the residue was extracted with chloroform (3 X 15 mL). The usual work
up afforded a thick liquid, which was purified by column chromatography (EtOAc/Pet. Ether = 15/85) to give 62a (0.365 g, 80%) as a thick liquid:

\[ R_f = 0.76 \text{ (ethyl acetate/n-hexane = 6/4)}; \]

\[ [\alpha]_D = -43.0 \text{ (c 2.0, CHCl}_3); \]

IR \( \nu_{\text{max}} \) (neat) = 3475, 1674 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)+D\(_2\)O) \( \delta \) 1.31 (3H, s, CH\(_3\)), 1.48 (3H, s, CH\(_3\)), 1.88-2.02 (4H, m, H-6, H-7), 2.20-2.35 (2H, m, H-8), 3.38-3.48 (2H, m, H-9), 3.79 (1H, dd, \( J = 9.9, 1.8 \text{ Hz, H-4} \)), 4.02 (1H, d, \( J = 1.8 \text{ Hz, H-3} \)), 4.13 (1H, ddd, \( J = 9.9, 6.6, 2.4 \text{ Hz, H-5} \)), 4.58 (1H, d, \( J = 3.6 \text{ Hz, H-2} \)), 5.12 (2H, ABq, \( J = 12.0 \text{ Hz, OCH}_2\text{Ph} \)), 5.88 (1H, d, \( J = 3.6 \text{ Hz, H-1} \)), 7.22-7.45 (5H, m, Ar-H);

\(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 18.94, 25.22, 26.17, 26.27, 26.85, 39.90, 49.71, 66.34, 74.65, 77.01, 85.45, 104.19, 111.11, 127.34 (Ar-C), 127.57 (Ar-C), 138.17 (Ar-C), 136.31 (Ar-C), 156.21 (CO).

Anal. Calcd for C\(_{20}\)H\(_{27}\)NO\(_6\): C, 64.63; H, 7.21 Found C, 64.51; H, 7.09.

Expt. No. 2.2.6: 1,2-O-Isopropylidene-5,6,7,8,9-penta-deoxy-5,9-(N-benzoxy carbonyl-imino)-\( \beta \)-L-ido-nona-1,4-furanose (62b).

The reaction of 117b (0.650 g, 1.54 mmol) with 10% Pd/C (0.150 g) in methanol (5 mL) followed by reaction with sodium bicarbonate (0.223 g, 2.66 mmol) and benzyloxycarbonyl chloride (0.340 g, 1.99 mmol) under the same conditions as reported for 62a and column chromatography (EtOAc/Pet. Ether = 15/85) afforded 62b (0.350 g, 69%) as a thick liquid:

\[ R_f = 0.68 \text{ (n-hexane/ethyl acetate = 4/6)}; \]

\[ [\alpha]_D = -72.26 \text{ (c 1.55, CHCl}_3); \]

IR \( \nu_{\text{max}} \) (neat) = 3110-3620, 1674 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)+D\(_2\)O) \( \delta \) 1.32 (3H, s, CH\(_3\)), 1.51 (3H, s, CH\(_3\)), 1.60-1.80 (2H, m, H-7), 1.81-1.98 (1H, m, H-8), 2.01-2.22 (2H, m, H-6), 3.41-3.60 (2H, m, H-9), 3.98 (1H, dd, \( J = 3.0, 1.8 \text{ Hz, H-2} \)).
Hz, H-4), 4.13 (1H, d, J = 1.8 Hz, H-3), 4.28-4.35 (1H, m, H-5), 4.47 (1H, d, J = 3.6 Hz, H-2),
5.13 (2H, ABq, J = 12.3 Hz, OCH₂Ph), 5.87 (1H, d, J = 3.6 Hz, H-1), 7.21-7.41 (5H, m, Ar-H);
¹³C NMR (75 MHz, CDCl₃) δ 19.68, 25.22, 26.17, 26.27, 26.85, 39.90, 49.71, 66.34, 74.65, 77.01,
85.45, 104.19, 111.11, 127.34 (Ar-C), 127.57 (Ar-C), 138.17 (Ar-C), 136.31 (Ar-C), 156.21 (CO);
Anal. Calcd for C₂₀H₂₇NO₆: C, 64.63; H, 7.21 Found C, 64.49; H, 7.01.

Expt. No. 2.2.7: (1R,2R,3S,9aR)-octahydro-2H-quinolizine-1,2,3-triol (35a).
A solution of 62a (0.100 g, 0.26 mmol) in TFA-H₂O (2 mL, 3/2) was stirred at 25°C for 2h.
Trifluoroacetic acid was co-evaporated with benzene to furnish a thick liquid, which was directly
used in the next reaction. To a solution of above product in methanol (5 mL) was added 10% Pd/C
(0.01 g) and solution was hydrogenated at 80 psi for 16h. The solution was filtered through celite
and celite was washed with methanol and the filtrate concentrated to get a sticky solid, which was
purified by column chromatography (MeOH/CHCl₃ = 5/95) to give 35a (0.042 g, 85%) as a thick
liquid:
Rₐ = 0.29 (chloroform/methanol = 7/3);
[α]₀ = −36.0 (c 0.2, MeOH);
IR = 3676-3250 cm⁻¹;
ⁱH NMR (300 MHz, D₂O) δ 1.24-1.53 (2H, m), 1.55-1.72 (1H, m), 1.79-1.98 (3H, m), 2.26 (1H,
m), 2.60-2.86 (3H, m), 3.22-3.48 (3H, m), 3.62-3.76 (3H, m);
¹³C NMR (75 MHz, D₂O) δ 21.63, 23.49, 26.93 (C-9, C-8, C-7), 55.37, 56.84 (C-4, C-6), 65.08
(C-9a), 67.09, 72.74, 76.51 (C-1, C-2, C-3);
Anal. Calcd for C₉H₁₇NO₃: C, 57.73; H, 9.15; Found C, 57.61; H, 9.01.
Expt. No. 2.2.8: \((1R,2R,3S,9aS)\)-octahydro-2H-quinolizine-1,2,3-triol (35b).

The reaction of 62b (0.13 g, 0.34 mmol) with TFA-H\(_2\)O (3 mL, 3/2) followed by hydrogenation with 10% Pd/C (0.02 g) as reported for 35a. Column chromatography (MeOH/CHCl\(_3\) = 10/90) afforded 35b (0.058 g, 91%) as a thick liquid:

- \(R_f = 0.25\) (chloroform/methanol = 7/3);
- \([\alpha]_D = -80.0\) (c 0.1, MeOH);
- IR = 3640-3180 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, D\(_2\)O) \(\delta\) 1.42-1.80 (7H, m), 2.79-2.91 (1H, m), 3.15-3.38 (5H, m), 3.87 (1H, s);

\(^13\)C NMR (75 MHz, D\(_2\)O) \(\delta\) 21.72, 22.95, 25.76 (C-7, C-8, C-9), 55.74 (C-4, C-6), 61.69 (C-9a), 66.44, 67.20, 70.21 (C-1, C-2, C-3);

Anal. Calcd for C\(_9\)H\(_{17}\)NO\(_3\): C, 57.73; H, 9.15; Found C, 57.58; H, 8.97.
References:


