CHAPTER 3

Synthesis of Pentahydroxy Indolizidine Alkaloids Using

Ring Closing Metathesis:

Attempts to Find the Correct Structure of Uniflorine A
3.1. Introduction

M. Arisawa and co-workers have isolated uniflorine A 7b and uniflorine B 7c from leaves of the tree *Eugenia uniflora* L. and demonstrated that 7b is a promising inhibitors of maltase and sucrase, with IC\textsubscript{50} values of 12 and 3.1 µM, respectively; while compound 7c is also a promising inhibitor of maltase (4.0 µM) and sucrase (1.8 µM). The structures for 7b and 7c were assigned with the help of spectral and analytical methods. The IR spectrum of 7b and 7c showed strong absorption for hydroxyl groups at 3500 cm\textsuperscript{-1}. The ion spray mass spectrum (ISMS) of both 7b and 7c showed a quasimolecular ion peak at \textit{m/z} 206 (M + 1). The \textsuperscript{13}C NMR of 7b and 7c showed eight carbon signals that were assigned to two methylene (δ 60.0 and 65.3) and six methine (δ 72.5, 73.6, 74.2, 78.1, 79.9, and 81.2) by heteronuclear multiple quantum coherence (HMQC) spectral data. Based on these findings, the molecular formula of 7b and 7c was estimated as C\textsubscript{8}H\textsubscript{15}NO\textsubscript{5}. Each of eight carbon signals from high to low magnetic fields were labeled and their connection was analyzed based on HMQC data and the results of \textsuperscript{1}H-\textsuperscript{1}H correlation spectroscopy (COSY). Additionally, heteronuclear multiple bond connectivity (HMBC) confirmed that in 7b and 7c the C-3, C-5 and C-8a were linked with N-atom, and thus the planar structure was identified for 7b as 1,2,6,7,8-pentahydroxyindolizine and compound 7c was identified as 1,2,5,7,8-pentahydroxyindolizidine.

![Figure 32](image)
In addition, in case of 7b a nuclear Overhauser effect (Figure 32) was observed between (H-6 and H-3), (H-1 and H-8) and (H-5 and H-7) confirms the cis ring fusion. In the $^1$H NMR of 7c, H-7 coupled with H-8 with $J = 8.1$ Hz and H-6 with $J = 6.8$ Hz, but the $J$ value was found to be zero with H-6. Since nOe was observed between H-6 and H-8a, the six-member ring was in the boat form, closely resembling the twist form on this compound. The nOe was observed between H-3 and H-5. In addition, the nOe was observed between H-1 and H-3. In the subsequent years, different pentahydroxy indolizidine analogues have been synthesized. In the chapter 2, we have carried out the synthesis of castanospermine 7a and its analogues. Uniflorine A 7b, Uniflorine B 7c and other pentahydroxy indolizidine alkaloids 15a and 174a-d are 2-hydroxy substituted analogues of castanospermine (Figure 33).

In 2004, Pyne and co-workers have first attempted the total synthesis of uniflorine A 7b by using Petasis borono-Mannich reaction and ring closing metathesis reactions as key steps (Scheme 23). Thus, L-xylose was reacted with (E) styrene boronic acid and allyl amine under Petasis reaction conditions that afforded aminotetraol 175 as a single diastereomer. The aminotetraol 175 was converted to its N-Boc derivative and the primary alcohol was protected as its O-trityl derivative to give 176. The ring closing metathesis of 176 using Grubbs catalyst followed by syn dihydroxylation furnished dihydroxy pyrrolidine ring skeleton 177 as a single diastereomer. The pentahydroxy compound 177 on perbenzylation gave penta-O-benzyl
derivative, which on selective removal of N-Boc group to give secondary amine and displacement of -OTf group with TFA in presence of anisole as cation scavenger at room temperature gave indolizidine 178. Debenzylation of 178 under hydrogenolysis conditions afforded uniflorine A 7b. Compound 7b under standard acetylation conditions gave pentaacetate derivative 179 the structure of which was assigned on the basis of the X-ray data. However, $^1$H and $^{13}$C NMR data of synthetic 7b was found to be different from that reported by M. Arisawa for isolated uniflorine A.

![Scheme 23](image)

This fact, thus raised a controversy about the structure of uniflorine A. In another report in 2005, Mariano and co-workers have reported photochemical ring rearrangement reaction for the synthesis of castanospermine 7a and pentahydroxy indolizidine alkaloids and attempted to match the data with natural uniflorine A. Thus as shown in scheme 24, the tetrabenzyl ether 68b was prepared from cis-trans-N-allylacetamidocyclopentenediol derivative 65 (Chapter 1, Scheme 9, page no. 19). The stereocontrolled asymmetric dihydroxylation of 68b afforded the corresponding diols 180a and 180b. Amide hydrolysis and Mitsunobu cyclization were employed to get pentahydroxy indolizidine derivative, which on hydrogenation afforded 2(S)-
hydroxy-castanospermine 15a and 2(R)-hydroxy-castanospermine 174c, respectively. The pentahydroxy indolizidines 15a and 174c also showed deviation in the spectral data from that of the isolated uniflorine A.

In another report, Fleet and co-workers\(^{4b}\) have reported synthesis of 2(5)-hydroxy-castanospermine 15a (Scheme 25). Thus, mild acid hydrolysis of easily available octonolactone 181 with aqueous acetic acid followed by selective silylation of primary alcohol and

\[
\begin{align*}
&\text{180a} \\
&\text{180b} \\
&\text{181} \\
&\text{182} \\
&\text{183} \\
&\text{184} \\
&\text{185}
\end{align*}
\]

Scheme 24

Scheme 25
esterification of alcohol with triflic anhydride gave silyltriflate, which on treatment with TBAF gave epoxide 182. Regioselective opening of epoxide ring by sodium azide and protection of hydroxyl group with tert-butyldimethyl triflate gave azidolactone 183. Reduction of lactone with lithiumborohydride afforded compound, which on mesylation gave azidomesylate 184. Hydrogenation of 184 yielded amine that in situ undergoes double S$_2$N$_2$ displacement to give indolizidine 185. Deprotection of silyl and acetonide functionality afforded 2(S)-hydroxy-castanospermine 15a.

Thus, attempts made by Pyne et al. and Mariano et al. were unsuccessful to deduce the correct structure of uniflorine A. As a part of our interest in the synthesis of bicyclic azasugars, we thought of resolving this conflict. In this direction, the RCM of dienes to provide sugar substituted dihydropyrrolidine ring systems was elaborated to provide 1,2,6,7,8-pentahydroxylated indolizidine alkaloids to decide whether the naturally isolated product was one of these isomers. Our visualization relies on the fact that the trihydroxylated piperidine ring skeleton of naturally isolated and synthetic uniflorine A is identical. We assume that the same piperidine ring skeleton could be obtained from D-glucose derived nitrone 153 by the $\pi$-facial stereoselective 1,3-addition of vinylmagnesium bromide. This would give an access for the bicyclic skeleton with different stereochemistry at the ring junction while; syn/anti dihydroxylation in the pyrrolidine ring would afford the dihydroxylated pyrrolidines and all the isomers, if obtained, could be converted to the compounds with structures analogous to uniflorine A. Thus, if one finds an approach to synthesize differently oriented dihydroxylated pyrrolidine ring as well as possibility to modify ring junction 8a, keeping hydroxylated piperidine intact, then one may get the correct structure of uniflorine A.
3.2. Present work

3.2.1. Retrosynthetic analysis

As shown in scheme 26, we envisioned that, the requisite bicyclic ring skeleton of polyhydroxylated indolizidine alkaloids 7a and 174a,b could be built by joining C-5 amino group with C-1 hemiacetal (obtained by 1,2-acetonide cleavage) using reductive amination of N-Cbz protected triol 186. The dihydroxylated pyrrolidine ring in triol 186 could be obtained by asymmetric dihydroxylation (AD) or by epoxidation followed by hydrolysis of dihydropyrrolidine 187. The key intermediate dihydropyrrolidine 187, with double bond at the desired position is a product of ring closing metathesis of sugar-derived diene 188 that could be derived from N-allylation of 169a,b. The synthesis of 169a,b is reported in chapter 2 by 1,3-addition of vinylmagnesium bromide to nitrone 153 wherein the stereochemical outcome at C-5 will decide the configuration at the fused ring junction in bicyclic indolizidine, while the substrate directed asymmetric dihydroxylation of the double bond in 187 would give an access for 1,2-diol functionality with different stereochemistry. Our efforts towards the synthesis of penta hydroxy indolizidine alkaloids are presented herein.

![Scheme 26](image)
3.2.2. Synthesis of 2(R)-hydroxy-1-epi-castanospermine

The requisite substrate namely 3-O-benzyl-1,2-O-isopropylidene-5,6,7-trideoxy-5-N-(benzylamino)-α-D-gluco-6-eno-heptofuranose 169a and 3-O-benzyl-1,2-O-isopropylidene-5,6,7-trideoxy-5-N-(benzylamino)-β-L-ido-6-eno-heptofuranose 169b were prepared from Grignard reaction of vinylmagnesium bromide to D-glucose derived nitrone 153 followed by reductive cleavage of N-O bond as described earlier in chapter 2 (Page no. 48).

First, we have attempted the reactions with D-gluco configurated N-benzylamine 169a. Thus compound 169a was treated with allyl bromide and potassium carbonate in dry DMF for 12 h. Purification using silica gel column chromatography afforded thick liquid in 92% yield.

The IR spectrum of the compound showed bands at 1639 cm⁻¹ due to C=C functionality.

In the ¹H NMR spectrum (Figure 34), appearance of a doublet at δ 3.01 with J = 14.0 Hz for H-8a and a doublet of doublet at δ 3.22 with J = 14.0 and 7.5 Hz for H-8b, a doublet of doublet at δ 4.99 with J = 10.2 and 1.1 Hz for H-10a and a doublet of doublet at δ 5.11 with J = 17.7 and 1.1 Hz for H-10b; a multiplet at δ 5.68–5.84 for H-9 showed the formation of N-allylated compound. This was confirmed by the ¹³C NMR spectrum (Figure 35) by the presence of
olifinic signals, confirm the formation of $N$-allyl derivative. The analysis was found to be in agreement with the molecular formula $C_{27}H_{33}NO_4$. Based on the spectral and analytical data, the structure 188a was assigned to the compound.

Having the diene compound 188a in hand, we thought of ring closing metathesis (RCM) approach to get dihydropyrrolidine ring skeleton. Being RCM is a key step we have studied the mechanistic aspects and related features of RCM and are described below.

**Ring Closing Metathesis (RCM)**

Ring closing metathesis (RCM) of diene-substrate containing nitrogen functionality followed by asymmetric dihydroxylation has found wide applicability in the synthesis of nitrogen heterocycles, alkaloids, peptides and peptidomimetics. The utility of this approach with sugar substrates, wherein the presence of the hydroxylated carbon framework and feasibility to manipulate the functional groups into the required diene-functionality, containing a nitrogen atom give an easy access towards 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. A number of applications of this reaction have increased dramatically in the past few years. This type of 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. Olefin metathesis can be utilized in three closely related type of reactions as shown in figure 36: (A) ring-opening metathesis polymerization (ROMP); (B) ring-closing metathesis (RCM); and (C) acyclic cross metathesis, which when carried out on two different olefin substrates gives an olifinic compound with exclusive "E" geometry. In the present work, our objective is to
synthesize pentahydroxy indolizidine alkaloids. Therefore, we would like to confine our discussion to the synthetic aspects of pentahydroxy indolizidine alkaloids using RCM.

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 limitation of the RCM reaction have 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 catalysts in use. These are (a) a molybdenum-based complex (I) developed by Schrock and co-workers and (b) ruthenium-based complexes (II) and (III) developed by Grubbs and co-workers (Figure 37).

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. On the other hand, ruthenium-based complexes (II) and (III) are not significantly affected by air and moisture and are remarkably tolerant to oxygen. In addition, complexes (II) and (III) are more tolerant to the substrates containing functional groups listed above for complex (I).

**Mechanism:**

A generally accepted mechanism of metathesis reaction consists of a series of alternating [2+2] cycloadditions and cycloreversions between metal alkylidene and metallocyclobutane intermediates. The mechanism of one such application, the ring-closing metathesis (RCM) of a diene, is presented in figure 38. In the first turn of the catalytic cycle, the alkene by-product 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 ethene. 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.

![Figure 38](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 allows the use of RCM with carbohydrate substrates.

Inspired with these facts, we have attempted the RCM of compound 188a. Thus, the reaction of 188a with first generation Grubbs catalyst (benzylidene-bis-tricyclohexylphosphine-dichlororuthenium) in dry CH$_2$Cl$_2$ for 12 h gave thick liquid. The chromatographic purification and elution with ethyl acetate/hexane = 5/95 afforded thick liquid in 82% yield.

![Diagram of 188a and 187a]

In the IR spectrum, the band at 1607 cm$^{-1}$ indicated the presence of C=C bond.

The $^1$H NMR (Figure 39) spectrum showed a doublet of doublets at $\delta$ 3.25 and 3.76 with $J = 15.0, 1.1$ Hz each for H-8a and H-8b, respectively. Another doublet of doublet at $\delta$ 5.82 with $J = 6.3$ and $1.8$ Hz for H-6 and a multiplet at 5.95–6.20 for H-7 indicated the formation of dihydropyrrolidine ring. The $^{13}$C NMR spectrum (Figure 40) showed peaks at $\delta$ 126.7, 126.8 for olifinic carbons C-6 and C-7 confirming the formation of dihydropyrrolidine ring skeleton.

The analysis was found to be in agreement with the molecular formula C$_{25}$H$_{29}$NO$_4$. Based on these observations, structure 187a was assigned to the compound. Dihydropyrrolidine 187a is a true intermediate that can be transformed into syn and anti diol functionalities using different reaction conditions. First we thought of exploiting syn asymmetric dihydroxylation with compound 187a.
Figure 39: 1H NMR (300 MHz, CDCl3) spectrum of compound 187a
General Principles of Asymmetric Dihydroxylation (AD)

During the last two decades a number of powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetry inducing agents. A number of processes have gained wide acceptance and some of them are even used on an industrial scale. Asymmetric epoxidation reaction requires the presence of a directing functional group in the substrate (allylic alcohols), whereas the dihydroxylation process is much less limited in the choice of substrate as it does not require any directing functional group.

Both the processes crucially depend on the ligand acceleration effect (LAE) which ensures that the reaction is funneled through a pathway involving the chiral catalyst. The principle of ligand acceleration is illustrated in figure 41 for the AD reaction. In his pioneering work on the stoichiometric reaction of OsO₄ with olefins, Criegee showed that pyridine accelerates the rate of reaction considerably. However, cost considerations make the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the reoxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility. Inorganic co-oxidants, such as sodium or potassium chlorate, hydrogen peroxide or I₂ were the first to be introduced, but in some cases, these reagents lead to diminished yields due to overoxidation. Much better results were obtained with alkaline tert-butyl hydroperoxide, introduced by Sharpless and N-methyl morpholine N-oxide by Upjohn. Recently, Minato et al demonstrated that K₃Fe(CN)₆ in the presence of K₂CO₃ provides a powerful system for the osmium-catalyzed dihydroxylation of olefins (Figure 41). The use of K₂OsO₂(OH)₄ as a nonvolatile osmium source in combination with an inorganic cooxidant [K₃Fe(CN)₆] has allowed us to formulate a premix containing all
reagents, including the ligand. With this premix, which is commercially available under the name of “AD-mix”, the reaction is extremely easy to carry out. The second key discovery was made by Amberg and Xu who found that the hydrolysis of the osmium (VI) glycolate product can be accelerated considerably by MeSO₂NH₂. Due to this “sulfonamide effect”, most AD reactions can be carried out at 0 °C rather than at room temperature which normally has a beneficial influence on the selectivity.

![Figure 41. The Osmylation of Olefins](image)

The investigations have further shown that the reaction rates are influenced chiefly by the nature of the O9 substituent of the cinchona alkaloid with certain aromatic appendages giving especially large rate accelerations for aromatic olefins. Further evidence from binding data suggests that the rate enhancement is not a ground state effect, but rather caused by a stabilization of the transition state due to aromatic stacking interactions. Although, this kind of stabilization is operative even in monomeric first generation ligands, it is most effective in the dimeric second-generation ligands due to the presence of a binding pocket or cleft. Thus, the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by an especially good transition state stabilization resulting from offset parallel interactions between the aromatic substituent of the
olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the "bystander" methoxyquinoline ring. Corey and Noe\(^2\) proved this, which invoke sandwich-like stacking of the olefin between the methoxyquinolines of the ligand.

\[
\text{AD-mix-} \alpha = 10 \text{ mol\%}, (\text{DHQD})_2\text{PHAL}, 1 \text{ mol\% } \text{K}_2\text{OsO}_2(\text{OH})_4, 3 \text{ eq. } \text{K}_3\text{Fe(CN)}_6, 3 \text{ eq. } \text{K}_2\text{CO}_3, 1 \text{ eq. MeSO}_2\text{NH}_2.
\]

\[
\text{AD-mix-} \beta = 10 \text{ mol\%}, (\text{DHQD})_2\text{PHAL}, 1 \text{ mol\% } \text{K}_2\text{OsO}_2(\text{OH})_4, 3 \text{ eq. } \text{K}_3\text{Fe(CN)}_6, 3 \text{ eq. } \text{K}_2\text{CO}_3, 1 \text{ eq. MeSO}_2\text{NH}_2.
\]

The above observations have led to a revised mnemonic device for predicting the enantiofacial selectivity in the reaction (Figure 42).\(^2\) The southeast quadrant and to a much lesser extent the northwest quadrant of this device present steric barriers, whereas the northeast quadrant is relatively open for olefin substituents of moderate size. The southwest quadrant is special in that it is regarded as being an attractive area, especially well suited to accommodate flat, aromatic substituents or in their absence, "large" aliphatic groups. An olefin positioned according to these constraints will be attacked either from the top face (i.e., the \( \beta \)-face), in the case of dihydroquinidine (DHQD) derivatives, or from the bottom face (i.e., the \( \alpha \)-face), in the case of dihydroquinine (DHQ) derived ligands. However, recent studies have shown that the northwest quadrant, which is normally considered to present a modest steric barrier (vide supra), also can play an attractive role for certain allylic and homoallylic alcohols.
In the light of above developments in AD, the dihydroxylation of 187a using Upjohn's\textsuperscript{19} procedure (potassium osmate, \textit{N}-methylmorpholine \textit{N}-oxide in acetone-water 8:1) was attempted. However, the reaction was found to be unsuccessful. In the next modification the dihydroxylation of 187a using potassium osmate (catalytic), potassium ferricyanide, methane sulfonamide and potassium carbonate in \textit{t}ert-butanol-water (1:1) at 0 \textdegree C for 12 h afforded a single diastereomer as evident from \textsuperscript{1}H NMR analysis of the crude product. Purification using column chromatography afforded thick liquid in 60\% yield.

In the IR spectrum, disappearance of the olefin stretching frequency and appearance of the band at 3550-3200 indicated the presence of hydroxyl groups. The \textsuperscript{1}H NMR spectrum showed the absence of the olefinic protons and appearance of broad singlet at $\delta$ 1.60–2.10 corresponding two protons, exchanges with D$_2$O, a multiplet at $\delta$ 4.12–4.32 for H-6 and H-7. In the \textsuperscript{13}C NMR appearance of signals at $\delta$ 70.7, 73.9 (C-6, C-7), showed formation of diol functionality. The analysis was found to be in agreement with the molecular formula.

\[136\]
C$_{25}$H$_{31}$NO$_6$. Based on these observations, the structure 189a or 189a' were considered to the compound.

To assign a stereochemical outcome of the dihydroxylation reaction, the diol 189a or 189a' was further converted to its peracetate derivative. Thus, the reaction of diol 189a with acetic anhydride in presence of pyridine afforded a thick liquid in 89% yield.

The IR spectrum showed strong peak at 1743 cm$^{-1}$ due to ester carbonyl group. The $^1$H NMR spectrum (Figure 43) showed the following signals: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.35 (s, 3H, CH$_3$), 1.51 (s, 3H, CH$_3$), 1.99 (s, 3H, COCH$_3$), 2.00 (s, 3H, COCH$_3$), 2.56 (t, $J = 9.0$ Hz, 1H, H-8a), 3.19 (dd, $J = 9.0$, 8.0 Hz, 1H, H-8b), 3.34 (bd, $J = 6.0$ Hz, 1H, H-5), 3.70 (d, $J = 13.2$ Hz, 1H, H-6), 3.94-4.08 (m, 3H, H-3, H-4 and N-CH$_2$Ph), 4.38 (d, $J = 11.7$ Hz, 1H, O-C$_2$Ph), 4.64 (d, $J = 3.9$ Hz, 1H, H-2), 4.67 (d, $J = 11.7$ Hz, 1H, O-C$_2$Ph), 5.34 (ddd, $J = 8.7$, 8.0, 4.2 Hz, 1H, H-7), 5.60 (dd, $J = 4.2$, 1.2 Hz, 1H, H-6), 5.97 (d, $J = 3.9$ Hz, 1H, H-1), 7.18-7.40 (m, 10H, Ar-H);

The $^{13}$C NMR spectrum (Figure 44) showed the following signals: $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 20.7, 20.8 (2 x CH$_3$), 26.2, 26.8 (2 x COCH$_3$), 53.9, 60.3, 66.1 (C-5, C-8 and N-CH$_2$Ph), 70.9, 71.4, 74.7 (C-6, C-7 and O-C$_2$Ph), 81.2, 81.4, 82.0 (C-2, C-3, C-4), 104.9 (C-1), 111.6 (O-C-O), 127.1, 127.7(s), 127.9, 128.3(s), 128.4(s), 137.0, 138.9 (Ar-C), 169.5, 169.9 (2 x CO);

The analysis was found to be in agreement with the molecular formula C$_{29}$H$_{35}$NO$_8$. Based on these observations, the structure 190a/a' was assigned to the compound.
The absolute configuration at the newly generated C-6 and C-7 stereocenters in \textbf{190a/a'} was assigned on the basis of the coupling constant information obtained by decoupling experiments. The appearance of a doublet of doublet at 8 5.60 for H-6 \((J_{6,7} = 4.2\text{ Hz})\) and small coupling with H-5, \(J_{6,5} = 1.2\text{ Hz}\) indicated \textit{anti} relationship of H-6 with H-5. This observation was further confirmed with nOe experiments (Figure 45). Thus, irradiation of H-6 showed strong nOe with H-7 showing their \textit{cis} relationship. Weak nOe was also observed between the H-6 and the H-5.\textsuperscript{24} This experiment indicated the relationship of H-6 with H-5 as anti and syn with H-7. Therefore, the relative stereochemistry \((6S, 7R)\) was assigned to \textbf{190a}.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure45.png}
\caption{Figure 45}
\end{figure}

The stereochemical outcome of the dihydroxylation reaction could be explained by the fact that, in \textbf{187a} the addition of bulky osmium reagent from the \(\alpha\)-face of the molecule is preferred over the \(\beta\)-face attack, since the \(\beta\)-face attack is sterically hindered by furanose ring and C-3-OBn functionality (Figure 46).\textsuperscript{25} As \textbf{190a} is a acetyl derivative of \textbf{189a} the same absolute configuration \((6S, 7R)\) was assigned to dihydroxylated product \textbf{189a}.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure46.png}
\caption{Figure 46 preferred attack from \(\alpha\)-face}
\end{figure}

In the subsequent step, compound \textbf{189a} was subjected to hydrogenolysis using 10\% Pd/C and ammonium formate in methanol. The crude product thus obtained showed absence of aromatic protons in \(^1\text{H} \text{NMR} \) spectrum indicating the deprotection of \(-\text{OBn}\) and \(-\text{NBn}\) groups.
The product was further subjected to the selective N-protection with Cbz group using benzyl chloroformate that afforded white solid in 78% yield. The IR spectrum of the compound showed broad peak at 3400-3200 due to hydroxyl groups and a peak at 1688 cm\(^{-1}\) due to carbamate carbonyl group. In the \(^1H\) NMR spectrum (Figure 47), reduction in the number of aromatic protons and appearance of a AB quartet at \(\delta\) 5.14 with \(J = 12.3\) Hz corresponding to benzylic protons of benzyloxy carbonyl group and in \(^13C\) NMR (Figure 48) appearance of a peak at \(\delta 157.2\) for benzyloxy carbonyl group confirmed the debenzylation and N-Cbz protection. The analysis was found to be in agreement with the molecular formula C\(_{19}\)H\(_{25}\)NO\(_8\).

Based on these observations, the structure 186a was assigned to the compound.

In the final step, 1,2-acetonide cleavage in 186a with TFA-H\(_2\)O (3:2) followed by cyclic reductive amination using H\(_2\), 10% Pd/C afforded white solid in 91% yield.

Based on the spectral and analytical data structure 7b was assigned to the compound. The \(^1H\) and \(^13C\) NMR data (Table 2), melting point and specific rotation of 7b were found to be in consonance with that of synthetically reported putative uniflorine A\(^3\) [mp 171–173 °C; lit.\(^3\) mp 170–172° C; [\(\alpha\)]\(_D\) = –5.2 (c 0.40, H\(_2\)O), lit.\(^1\) [\(\alpha\)]\(_D\) = –6.0 (c 5.0, H\(_2\)O), lit.\(^3\) [\(\alpha\)]\(_D\) = –4.4 (c 1.2, H\(_2\)O)]. Based on these observations, the structure 7b was confirmed to the compound.
<table>
<thead>
<tr>
<th>Isolated uniflorine A (500 MHz, D$_2$O) δ</th>
<th>Synthetic uniflorine A (500 MHz, D$_2$O) δ</th>
<th>Our $^1$H NMR (Figure 49 and 50) data (300 MHz, D$_2$O) δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.76 (m, $J = 6.4$, 3.8, 1H Hz, H-6)</td>
<td>2.08 (dd, $J = 9.3$, 7.5 Hz, 1H, H-8a)</td>
<td>2.18–2.41 (m, 2H, H-8a, H-5α)</td>
</tr>
<tr>
<td>2.98 (m, $J = 12.1$, 5.1 Hz, 1H, H-3β)</td>
<td>2.09 (t, $J = 10.8$ Hz, 1H, H-5α)</td>
<td></td>
</tr>
<tr>
<td>3.04 (dd, $J = 12.1$, 5.1 Hz, 1H, H-3α)</td>
<td>2.20 (dd, $J = 10.5$, 6.5 Hz, 1H, H-3β)</td>
<td>2.35 (dd, $J = 10.5$, 6.3 Hz, 1H, H-3β)</td>
</tr>
<tr>
<td>3.14 (dd, $J = 7.7$, 4.5 Hz, 1H, H-8a)</td>
<td>3.01 (dd, $J = 10.5$, 5.5 Hz, 1H, H-5β)</td>
<td>3.14 (dd, $J = 10.8$, 5.3 Hz, 1H, H-5β)</td>
</tr>
<tr>
<td>3.61 (dd, $J = 11.8$, 6.4 Hz, 1H, H-5α)</td>
<td>3.20 (t, $J = 9.0$ Hz, 1H, H-7)</td>
<td>3.32 (t, $J = 9.3$ Hz, 1H, H-7)</td>
</tr>
<tr>
<td>3.76 (dd, $J = 11.8$, 3.8 Hz, 1H, H-5β)</td>
<td>3.25 (t, $J = 9.0$ Hz, 1H, H-8)</td>
<td>3.38 (t, $J = 9.3$ Hz, 1H, H-8)</td>
</tr>
<tr>
<td>3.81 (dd, $J = 9.0$, 7.7 Hz, 1H, H-7)</td>
<td>3.26 (dd, $J = 10.5$, 6.5 Hz, 1H, H-3α)</td>
<td>3.40 (dd, $J = 10.5$, 6.6 Hz, 1H, H-3α)</td>
</tr>
<tr>
<td>3.94 (t, $J = 7.7$ Hz, 1H, H-8)</td>
<td>3.46 (ddd, $J = 11.0$, 9.0, 5.5 Hz, 1H, H-6)</td>
<td>3.58 (ddd, $J = 10.8$, 9.6, 5.1 Hz, 1H, H-6)</td>
</tr>
<tr>
<td>4.18 (t, $J = 4.5$ Hz, 1H, H-1)</td>
<td>3.82 (t, $J = 7.5$ Hz, 1H, H-1)</td>
<td>3.95 (t, $J = 7.6$ Hz, 1H, H-1)</td>
</tr>
<tr>
<td>4.35 (m, 1H, H-2)</td>
<td>4.11 (q, $J = 7.0$ Hz, 1H, H-2)</td>
<td>4.24 (q, $J = 6.6$ Hz, 1H, H-2)</td>
</tr>
</tbody>
</table>

$^1$C NMR data (δ)

| 60.0 (CH$_2$) | 55.4 (CH$_2$) | 54.6(CH$_2$) |
| 65.3 (CH$_2$) | 59.2 (CH$_2$) | 58.5(CH$_2$) |
| 72.5 (CH)     | 68.6 (CH)     | 68.0 (CH)    |
| 73.6 (CH)     | 70.4 (CH)     | 69.6 (CH)    |
| 74.2 (CH)     | 70.5 (CH)     | 69.8 (CH)    |
| 78.1 (CH)     | 73.9 (CH)     | 73.2 (CH)    |
| 79.9 (CH)     | 74.1 (CH)     | 73.3 (CH)    |
| 81.2 (CH)     | 79.1 (CH)     | 78.3 (CH)    |

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The assignment of structure 7b was further confirmed by converting 7b into its penta-acetate derivative (acetic anhydride, pyridine) 173 which showed identical spectral and analytical data with that reported\(^3\) [mp 141-142 °C; lit.\(^3\) mp 142 °C; \([\alpha]_D = -17 (c 0.90, CHCl_3), \text{lit.}\(^3\) [\alpha]_D = -15 (c 1.56, CHCl_3)].

Thus, D-gluco configurated N-Benzyl-allylamine 169a afforded putative uniflorine A 7b, whose \(^1\)H and \(^13\)C NMR data was found to be different to that of isolated one.

Since, the \(^1\)H and \(^13\)C NMR data of known 7b were found to be different from that of the naturally isolated uniflorine A, it was thought that the naturally occurring uniflorine A might be having trans relative stereochemistry at C-1 and C-2 hydroxy functionality. Therefore we made attempts to synthesize dihydroxy pyrrolidine ring skeleton with trans relative stereochemistry with D-gluco isomer. In this direction, first we thought of Woodward-Prevost\(^26\) syn- and/or anti-dihydroxylation of the dihydropyrrolidine ring system of 187a in an effort for stereoselective hydroxylation from the more hindered β-face to afford 15a as well as anti dihydroxylation to yield 174c and 174d (Scheme 27). It was envisaged that treatment of olefin 187a with iodine and silver (I) acetate in aqueous acetic acid would effect iodination from the less hindered α-face followed by opening of the iodonium ion by attack of acetate at C-6 to afford iodo-acetate which would then form a cyclic acetoxonium intermediate due to anchimeric assistance from the acetate group combined with the powerful affinity of the silver ion for iodide. Addition of water will cleave the five-membered ring to the hydroxyl acetates resulting in overall hydroxylation of the more hindered β-face as required for compound 15a. If
water is not added then the acetoxonium intermediate can be opened by the nucleophilic attack of the acetoxy group resulting in to trans diacetates, which could be further converted to 174c,d. However, our attempts towards the synthesis of 15a, 174c and 174d were unsuccessful. The epoxidation of 187a with metachloroperbenzoic acid was also unsuccessful.

3.2.3: Synthesis of (1R,2S,6S,7R,8R,8aS)-1,2,6,7,8-Pentahydroxy-indolizidine (174a) and (1S,2R,6S,7R,8R,8aS)-1,2,6,7,8-Pentahydroxy-indolizidine (174b)

It was then thought of exploiting the L-ido configurated N-benzylallylamine 169b to the synthesis of pentahydroxy indolizidines 174a,b and compare the data obtained with isolated ubiflorine A. It was expected that this reaction sequence should lead to the formation of pentahydroxy indolizidines with different configuration at the ring junction.

Thus, as shown in scheme 32, the similar sequence of reactions with compound 169b namely N-allylation and RCM afforded dihydropyrrolidine 187b. The spectral and analytical data was found to be in good agreement with the structures 188b and 187b.
In the crucial step, dihydroxylation of \(187b\) under similar reaction conditions as described for \(187a\) afforded an inseparable mixture of diols in the ratio 1:9 as evident from \(^1\)H NMR analysis of the crude reaction mixture. The mixture of diols was therefore further subjected to acetylation to give mixture of acetate derivatives. The appreciable difference in R\(_f\) values allowed us to separate the mixture by silica gel column chromatography. Thus, elution first with (n-hexane/ethyl acetate = 90/10) afforded high R\(_f\) compound as thick liquid in 9% yield.

The IR spectrum showed the band at 1750 cm\(^{-1}\) indicating the presence acetate carbonyl group.

The \(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum (Figure 51) showed following signals: \(\delta\) 1.29 (s, 3H, CH\(_3\)), 1.50 (s, 3H, CH\(_3\)), 1.88 (s, 3H, COCH\(_3\)), 1.98 (s, 3H, COCH\(_3\)), 2.54 (t, \(J = 9.0\) Hz, 1H, H-8a), 3.11 (dd, \(J = 9.0, 8.5\) Hz, 1H, H-8b), 3.39 (dd, \(J = 8.3, 2.2\) Hz, 1H, H-5), 3.57 (d, \(J = 13.2\) Hz, 1H, N-CH\(_2\)Ph), 4.01 (d, \(J = 3.3\) Hz, 1H, H-3), 4.17 (dd, \(J = 8.3, 3.3\) Hz, 1H, H-4), 4.26 (d, \(J = 12.9\) Hz, 1H, N-CH\(_2\)Ph), 4.46 (d, \(J = 11.8\) Hz, 1H, O-CH\(_2\)Ph), 4.60 (d, \(J = 3.9\) Hz, 1H, H-2), 4.67 (d, \(J = 11.8\) Hz, 1H, O-CH\(_2\)Ph), 5.21 (dt, \(J = 9.4, 5.8\) Hz, 1H, H-7), 5.33 (dd, \(J = 5.8, 2.7\) Hz, 1H, H-6), 5.97 (d, \(J = 3.9\) Hz, 1H, H-1), 7.10–7.32 (m, 10H, Ar-H);

The \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) spectrum (Figure 52) showed the following signals: \(\delta\) 20.5, 20.6 (2 \(\times\) CH\(_3\)), 26.2, 26.7 (2 \(\times\) COCH\(_3\)), 54.2, 59.9 (N-CH\(_2\)Ph, C-8), 66.3 (C-5), 70.1, 71.5,
73.2 (C-6, C-7, O-CH$_2$Ph), 77.2, 81.2, 82.6 (C-2, C-3, C-4), 105.1 (C-1), 111.6 (O-C-O), 127.1,
127.3(s), 127.7, 128.2, 128.4(s), 129.1, 137.3, 138.6 (Ar-C), 169.6, 169.7 (2 x CO). The
analysis was found to be in agreement with the molecular formula C$_{29}$H$_{35}$NO$_8$. Based on these
observations, the structure 190b/c was assigned to the minor isomer.

Further elution with (n-hexane/ethyl acetate = 90/10) afforded a thick liquid in 75% yield. The IR spectrum showed the band at 1743 cm$^{-1}$ was assigned to the acetate carbonyl group. The $^1$H NMR (300 MHz, CDCl$_3$) spectrum (Figure 53) showed the following signals: δ
1.34 (s, 3H, CH$_3$), 1.54 (s, 3H, CH$_3$), 1.98 (s, 3H, COCH$_3$), 2.08 (s, 3H, COCH$_3$), 2.77 (dd, J =
10.5, 2.0 Hz, 1H, H-8a), 2.98 (dd, J = 10.5, 5.4 Hz, 1H, H-8b), 3.34 (dd, J = 7.7, 5.2 Hz, 1H, H-
5), 3.56 (d, J = 13.0 Hz, 1H, N-CH$_2$Ph), 3.88 (d, J = 3.0 Hz, 1H, H-3), 4.39 (d, J = 13.0 Hz, 1H,
N-CH$_2$Ph), 4.45 (d, J = 11.0 Hz, 1H, O-CH$_2$Ph), 4.45–4.55 (m, 1H, H-4), 4.60 (d, J = 3.9 Hz,
1H, H-2), 4.61 (d, J = 11.0 Hz, 1H, O-CH$_2$Ph), 5.17 (bdd, J = 12.0, 5.4 Hz, 1H, H-7), 5.51 (t, J =
5.2 Hz, 1H, H-6), 5.99 (d, J = 3.9 Hz, 1H, H-1), 7.18–7.40 (m, 10H, Ar-H).

The $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum (Figure 54) showed the following signals: δ 20.6,
20.7 (2 x CH$_3$), 26.3, 26.7(2 x COCH$_3$), 55.1, 59.1 (C-8, N-CH$_2$Ph), 62.9 (C-5), 70.3, 71.8, 72.9
(C-6, C-7, O-CH$_2$Ph), 81.1, 81.8, 83.2 (C-2, C-3, C-4), 104.7 (C-1), 111.4 (O-C-O), 126.9,
127.8(s), 128.0, 128.1(s), 128.5(s), 129.3, 137.0, 138.4 (Ar-C), 170.0, 170.1 (2 x CH$_3$).
The analysis was found to be in agreement with the molecular formula C$_{29}$H$_{35}$NO$_8$. Based on
these observations, the structure 190b/c was assigned to the major isomer.

The absolute configurations at the newly generated C-6 and C-7 stereo centers in 190b,c
were assigned on the basis of coupling constant information. The appearance of doublet of
doublet at δ 5.33 for H-6 in minor isomer with one large coupling with H-7 ($J_{6,7} = 5.8$ Hz) and
small coupling with H-5 ($J_{6,5} = 1.7$ Hz) confirmed anti relationship of H-6 with H-5. This
observation was further confirmed by nOe experiments (Figure 55). Thus, irradiation of H-6 in
minor isomer showed strong nOe with H-7. Therefore, the absolute configuration \((6R, 7S)\) was assigned to minor isomer 190b. Similarly, the appearance of a triplet at 8 5.51 for H-6 in major isomer with large coupling with H-7 and H-5 \((J_{6,7} = J_{6,5} = 5.2 \text{ Hz})\) confirmed syn relationship of H-6 with H-5 and H-7. This observation was further confirmed by nOe experiments (Figure 56). Thus, irradiation at H-6 in major isomer showed strong nOe with H-7 and H-5. The close proximity of H-6 with H-7 and H-5 confirmed their syn relative orientation. Therefore, the absolute configuration \((6S, 7R)\) was assigned to the compound 190c.

The stereochemical outcome of the reaction was supported by the fact that in 187b, the addition of bulky osmium reagent from the \(\alpha\)-face of the molecule is preferred over the \(\beta\)-face attack, since the \(\beta\)-face attack is sterically hindered by C-3-OBn and pseudoaxial H-5 (Figure 56).

The diastereoselectivity of dihydroxylation reaction with 187b was studied by using cinchona alkaloids (Table 3). Thus, the syn-dihydroxylation of 187b in absence of cinchona alkaloids afforded diol that on acetylation gave 190b and 190c in the ratio of 1:9. However, the dihydroxylation of 187b using AD-mix-\(\alpha\) followed by acetylation afforded 190b/190c in the ratio 2:8 (entry 2). The use of AD-mix-\(\beta\) in the presence of methanesulfonamide gave 190c in very high diastereoselectivity (de > 99%) as a single diastereomer in an overall purified yield of 62% (entry 3).
TABLE 3: Dihydroxylation of 182b

<table>
<thead>
<tr>
<th>No.</th>
<th>Ligand</th>
<th>Product</th>
<th>$dr^a$</th>
<th>% yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>190b/190c</td>
<td>20:80</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>(DHQ)$_2$PHAL</td>
<td>190b/190c</td>
<td>20:80</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>(DHQD)$_2$PHAL</td>
<td>190b/190c</td>
<td>0:100$^c$</td>
<td>62</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR of the crude product. $^b$ After purification. $^c$ No corresponding peak for minor isomer was observed.

In the next step, the reaction of diacetate 190b with sodium methoxide in methanol afforded thick liquid in 92% yield. The IR spectrum showed a broad band at 3600-3200 cm$^{-1}$ indicated the formation of free hydroxyl groups.

\[
\begin{align*}
\text{AcO} & \overset{\text{NaOMe, MeOH, 0 °C, 2 h.}}{\longrightarrow} \text{HO-K} \\
190b & \overset{\text{XOBn}}{\longrightarrow} 189b
\end{align*}
\]

The $^1$H NMR spectrum showed the absence of methyl singlets of acetate group and appearance of a broad singlet corresponding to two protons at $\delta$ 1.65-2.30, exchangeable with D$_2$O, for hydroxyl groups and in $^{13}$C NMR spectrum the up field shift for peaks at $\delta$ 69.8 and 73.2 for C-6 and C-7 showed formation of diol functionality. The analysis was found to be in agreement with the molecular formula C$_{25}$H$_{31}$NO$_6$ indicating the structure 189b to the compound.

In the subsequent step, compound 189b was subjected to hydrogenolysis using 10% Pd/C and ammonium formate in methanol. The product was directly subjected to the selective N-protection with Cbz group using benzyl chloroformate to afford thick liquid in 78% yield.

\[
\begin{align*}
\text{HO} & \overset{\text{1. 10% Pd/C, HCOONH$_4$, MeOH, 80 °C, 1 h.}}{\longrightarrow} \text{HO} \\
189b & \overset{\text{2. NaHCO$_3$, CbzCl, MeOH-H$_2$O, 0 °C, 2 h.}}{\longrightarrow} \text{HO}
\end{align*}
\]
The IR spectrum showed a broad peak at 3500-3200 cm$^{-1}$ due to hydroxyl groups and a peak at 1666 cm$^{-1}$ due to carbamate carbonyl group. The $^1$H and $^{13}$C NMR data as well as analytical data is agreed with the structure 186b.

In the final step, cleavage of 1,2-acetonide group in 186b with TFA-H$_2$O (3:2) followed by cyclic reductive amination using H$_2$, 10% Pd/C afforded a thick liquid in 83% yield.

The IR spectrum showed a band at 3600-3200 cm$^{-1}$ indicating the presence of hydroxyl groups. The $^1$H NMR spectrum (Figure 57) showed the following signals: $^1$H NMR (300 MHz, D$_2$O) δ 2.67 (dd, $J$ = 11.3, 3.6 Hz, 1H, $H$-3a), 2.90-3.07 (m, 2H, $H$-5a, $H$-8a), 3.21 (dd, $J$ = 12.6, 2.0 Hz, 1H, $H$-5a), 3.68 (dd, $J$ = 11.3, 6.3 Hz, 1H, $H$-3b), 3.95 (bs, 1H, $H$-8), 4.02 (t, $J$ = 3.0 Hz, 1H, $H$-7), 4.05 (bd, $J$ = 3.0 Hz, 1H, $H$-6), 4.17 (dd, $J$ = 9.4, 6.4 Hz, 1H, $H$-1), 4.29 (dt, $J$ = 6.4, 4.7 Hz, 1H, $H$-2);

The $^{13}$C NMR spectrum (Figure 58) showed following signals: $^{13}$C NMR (50 MHz, D$_2$O) δ 54.1, 60.1, 64.6 (C-3, C-5, C-8a), 66.6, 67.4, 68.5, 68.6(s) (C-2, C-2, C-6, C-7, C-8);

The analysis was found to be in agreement with the molecular formula C$_8$H$_{15}$NO$_5$. Based on these observations, the structure 174a was assigned to the compound. However, it was found that compound 174a also showed $^1$H and $^{13}$C NMR spectra different from that of the naturally isolated uniflorine A.
The pentahydroxy indolizidine 174a was further converted to its penta-acetate derivative. Thus, treatment of 174a with acetic anhydride in pyridine afforded thick liquid in 91% yield.

\[
\text{HO-} \quad \text{174a} \quad \text{Ac}_2\text{O, pyridine, rt, 12 h} \quad \text{HO-} \quad \text{191a}
\]

The IR spectrum showed the band at 1735 cm\(^{-1}\) indicating the presence of acetate carbonyl groups. The \(^1\text{H}\) NMR spectrum showed singlets at \(\delta\) 2.05, 2.07, 2.13, 2.14 and 2.16 for methyl protons of acetate groups. The \(^13\text{C}\) NMR spectrum showed signals at \(\delta\) 20.8, 21.1, 21.2, 21.3, 21.6 for methyl carbons of the acetate group and peaks at \(\delta\) 168.5, 169.8, 170.0, 170.1, 170.2 for ester carbonyl groups. The analysis was found to be in agreement with the molecular formula \(\text{C}_{13}\text{H}_{13}\text{NO}_5\) indicating structure 191a to the compound.

The same sequence of reactions with diacetate 190c afforded 2(R)-hydroxy-8a-epi-castanospermine 174b as shown in scheme 29. The diol 189c, N-Cbz protected compound 186c, target molecule 174b and penta-acetate derivative 191b were characterized by spectral and analytical techniques and the data was found to be in agreement with the structures.
The $^1$H NMR spectrum (Figure 59) of 174b showed the following signals: $^1$H NMR (300 MHz, D$_2$O) δ 3.20 (dd, $J = 12.4$, 3.0 Hz, 1H, H-5a), 3.25 (dd, $J = 13.5$, 2.7 Hz, 1H, H-3a), 3.31–3.48 (m, 3H, H-5b, H-3b, H-8a), 3.80–3.90 (m, 1H, H-6), 4.01 (t, $J = 4.9$ Hz, 1H, H-7), 4.25 (t, $J = 4.9$ Hz, 1H, H-8), 4.50–4.58 (m, 2H, H-1, H-2);

The $^{13}$C NMR spectrum (Figure 60) of 174b showed the following signals: $^{13}$C NMR (75 MHz, D$_2$O) δ 54.6, 58.9, 63.9 (C-3, C-5, C-8a), 67.9, 68.8, 69.2, 69.6, 71.1 (C-1, C-2, C-6, C-7, C-8);

The analysis was found to be in agreement with the molecular formula C$_8$H$_{13}$NO$_5$. Based on these observations, the structure 174b was assigned to the compound.
3.3. Conclusions

1. In conclusion, RCM methodology with aminosugar derived diene coupled with the substrate directed asymmetric dihydroxylation gave an easy access to the synthesis of three analogues of pentahydroxy indolizidine alkaloids $7b$ and $174a,b$.

2. The $^1H$ and $^{13}C$ NMR data of known $7b$ and newly synthesized $174a,b$ were found to be different from that of the naturally isolated uniflorine A.

3. Our results are helpful for further study to determine the correct structure of natural uniflorine A.
3.4. Experimental

Expt. No. 3.4.1: Preparation of 5,6,7-Trideoxy-5-(N-allyl-N-benzylamino)-1,2-O-isopropylidene-3-O-benzyl-α-D-glucopyranos-6-eno-hepta-1,4-furanose (188a).

\[
\text{allyl bromide, } K_2CO_3, \text{ DMF, rt, 12 h}
\]

To a stirred solution of 169a (1.5 g, 3.8 mmol) and anhydrous potassium carbonate (2.6 g, 18.9 mmol) in dry DMF (10 mL) was added allyl bromide (0.55 g, 4.5 mmol) in dry DMF (2 mL). The reaction mixture was stirred at room temperature for 12 h, decomposed with cooled water (10 mL) and extracted with chloroform (3 × 20 mL). The combined organic layer was repeatedly washed with water (30 mL) followed by usual workup and purification by column chromatography (n-hexane/ethyl acetate = 90/10) gave 188a (1.52 g, 92%) as thick liquid; 

\[ R_f 0.65 \text{ (n-hexane/ethyl acetate = 9/1)}; \]

\[ [\alpha]_D^{25} = -17.1 \text{ (c 0.70, CHCl}_3); \]

IR (Neat) 1639, 1600, 1452 cm\(^{-1}\); 

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 1.31 \text{ (s, 3H, } CH_3), 1.48 \text{ (s, 3H, } CH_3), 3.01 \text{ (dd, } J = 14.0, 7.5 \text{ Hz, } 1H, H-8a), 3.22 \text{ (dd, } J = 14.0, 4.8 \text{ Hz, } 1H, H-8b), 3.43 \text{ (d, } J = 14.1 \text{ Hz, } 1H, N-CH}_2\text{Ph), 3.80 \text{ (t, } J = 9.0 \text{ Hz, } 1H, H-5), 3.90 \text{ (d, } J = 14.1 \text{ Hz, } 1H, N-CH}_2\text{Ph), 4.11 \text{ (d, } J = 3.0 \text{ Hz, } 1H, H-3), 4.35 \text{ (dd, } J = 9.0, 3.0 \text{ Hz, } 1H, H-4), 4.56 \text{ (d, } J = 3.9 \text{ Hz, } 1H, H-2), 4.65 \text{ (ABq, } J = 12.0 \text{ Hz, } 2H, O-CH}_2\text{Ph), 4.99 \text{ (bd, } J = 10.2 \text{ Hz, } 1H, H-10a), 5.11 \text{ (bd, } J = 17.7 \text{ Hz, } 1H, H-10b), 5.27 \text{ (dd, } J = 17.4, 1.8 \text{ Hz, } 1H, H-7a), 5.43 \text{ (dd, } J = 10.8, 1.8 \text{ Hz, } 1H, H-7b), 5.68-5.84 \text{ (m, } 1H, H-9), 5.92 \text{ (d, } J = 3.9 \text{ Hz, } 1H, H-1), 5.90-6.06 \text{ (m, } 1H, H-6), 7.18-7.43 \text{ (m, } 10H, \text{ Ar-H}); \]
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \& 26.1, 26.7 (2 \times \text{CH}_3), 54.3, 54.7 (C-8, N-\text{CH}_2\text{Ph}), 59.8 (C-5), 71.9 (O-\text{CH}_2\text{Ph}), 80.2, 81.6, 81.8 (C-2, C-3, C-4), 104.8 (C-1), 111.2 (O-C-O), 116.9, 119.9 (C-7, C-10), 126.7, 127.5, 127.6, 128.2, 128.3, 128.5, 132.9, 136.9, 137.7, 140.0 (C-6, C-9, Ar-C);  
Anal. Calcd. For C\(_{27}\)H\(_{33}\)NO\(_4\): C, 74.45; H, 7.64; Found: C, 74.52; H, 7.80.

**Expt. No. 3.4.2: Preparation of 5,6,7-Trideoxy-5-(N-allyl-N-benzylamino)-1,2-O-isopropylidene-3-O-benzyl-\(\beta\)-L-ido-6-eno-hepta-1,4-furanose (188b).**

The reaction of 169b (1.9 g, 4.7 mmol) with anhydrous potassium carbonate (3.3 g, 23.9 mmol) and allyl bromide (0.68 g, 5.6 mmol) in dry DMF (15 mL) under the same reaction conditions described for synthesis of 188a followed by purification by column chromatography (n-hexane/ethyl acetate = 95/5) afforded compound 188b (1.9 g, 91%) as a thick liquid;  
\(R_f\) 0.62 (n-hexane/ethyl acetate = 9/1);  
\([\alpha]_D^{25} = -51.2\) (c 0.63, CHCl\(_3\));  
IR (Neat) 1641, 1602 cm\(^{-1}\);  
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \& 1.36 (s, 3H, Ch\(_3\)), 1.64 (s, 3H, CH\(_3\)), 3.18 (dd, \(J = 14.0, 6.4\) Hz, 1H, H-8a), 3.37 (dd, \(J = 14.0, 6.1\) Hz, 1H, H-8b), 3.63 (d, \(J = 14.0\) Hz, 1H, N-\text{CH}_2\text{Ph}), 3.82 (d, \(J = 3.0\) Hz, 1H, H-3), 3.89 (dd, \(J = 9.2, 8.0\) Hz, 1H, H-5), 3.98 (d, \(J = 14.0\) Hz, 1H, N-\text{CH}_2\text{Ph}), 4.42 (d, \(J = 11.4\) Hz, 1H, O-\text{CH}_2\text{Ph}), 4.38–4.46 (m, 1H, H-4), 4.59 (d, \(J = 3.9\) Hz, 1H, H-2), 4.62 (d, \(J = 11.4\) Hz, 1H, o-\text{CH}_2\text{Ph}), 5.09 (bd, \(J = 10.2\) Hz, 1H, H-10a/H-7a), 5.17–5.28 (m, 3H, H-10b and H-7), 5.62–5.68 (m, 1H, H-6), 5.82–6.00 (m, 1H, H-9), 6.03 (d, \(J = 3.9\) Hz, 1H, H-1), 7.10–7.50 (m, 10H, Ar-\text{H});
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 26.3, 26.8 (2 x CH\(_3\)), 53.5, 54.2 (C-8, N-CH\(_2\)Ph), 59.8 (C-5), 71.6 (O-CH\(_2\)Ph), 79.7, 81.4, 82.5 (C-2, C-3, C-4), 105.1 (C-1), 111.3 (O-C-O), 116.4, 118.6 (C-C-7, C-10), 126.5, 127.3(s), 127.6, 128.0, 128.3(s), 128.8,133.6, 137.5, 140.6 (C-6, C-9, Ar-C);

Anal. Calcd. For C\(_{27}\)H\(_{33}\)NO\(_4\): C, 74.45; H, 7.64; Found: C, 74.58; H, 7.74.

**Expt. No. 3.4.3: Preparation of 5,6,7,8-Tetra-deoxy-5,8-(N-benzylamino)-1,2-0-isopropylidine-3-O-benzyl-\(\alpha\)-D-gluc-6-eno-octa-1,4-furanose (187a).**

![Chemical Structure](image)

The compound 188a (1.4 g, 3.2 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (20 mL), and benzylidene-bis-tricyclohexylphosphine-dichlororuthenium (0.26 g, 0.32 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. Solvent was removed in vacuo to give oil which on purification by column chromatography (n-hexane/ethyl acetate = 90/10) afforded 187a (1.10 g, 82%) as a thick liquid;

\[ R_f 0.63 \text{(n-hexane/ethyl acetate = 8/2);} \]

\[ [\alpha]_D^{25} = -3.3 \text{ (c 0.60, CHCl}_3\text{);} \]

IR (Neat) 1607, 1454 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.36 (s, 3H, C-3), 1.64 (s, 3H, CH\(_3\)), 3.25 (bd, \(J = 15.0\) Hz, 1H, H-8a), 3.62 (d, \(J = 14.1\) Hz, 1H, N-CH\(_2\)Ph), 3.76 (bd, \(J = 15.0\) Hz, 1H, H-8b), 4.03 (dd, \(J = 7.5, 3.0\) Hz, 1H, H-4), 4.10 (d, \(J = 14.1\) Hz, 1H, N-CH\(_2\)Ph), 4.14 (d, \(J = 3.0\) Hz, 1H, H-3), 4.17–4.26 (m, 1H, H-5), 4.45 (d, \(J = 11.7\) Hz, 1H, O-CH\(_2\)Ph), 4.67 (d, \(J = 4.2\) Hz, 1H, H-2), 5.69 (d, \(J = 11.7\) Hz, 1H, o-CH\(_2\)Ph), 5.82 (bd, \(J = 6.3, 1.8\) Hz, 1H, H-6), 5.97 (d, \(J = 4.2\) Hz, 1H, H-1), 5.95–6.20 (m, 1H, H-7), 7.20–7.40 (m, 10H, Ar-H);
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 26.2, 26.7 (2 x CH$_3$), 60.2, 61.0 (C-8, N-CH$_2$Ph), 68.8 (C-5), 71.3 (O-CH$_2$Ph), 81.3, 82.0, 84.5 (C-2, C-3, C-4), 104.8 (C-1), 111.5 (O-C-O), 126.7, 126.8 (C-6, C-7), 127.5(s), 127.6, 127.8(s), 128.1(s), 128.2(s), 128.4(s), 129.8, 137.2 (Ar-C);

Anal. Calcd. For C$_{25}$H$_{29}$NO$_4$: C, 73.68; H, 7.17; Found: C, 73.60; H, 7.25.

Expt. No. 3.4.4: Preparation of 5,6,7,8-Tetra-deoxy-5,8-(N-benzylamino)-1,2-O-isopropylidine-3-O-benzyl-β-L-idoo-6-eno-octa-1,4-furanose (187b).

The reaction of 188b (2.1 g, 4.8 mmol) with benzylidene-bis-tricyclohexylphosphine-dichlororuthenium (0.39 g, 0.48 mmol) in dry CH$_2$Cl$_2$ (25 mL) under the same reaction conditions described for synthesis of 187a, followed by purification by column chromatography (n-hexane/ethyl acetate = 90/10) afforded 187b (1.65 g, 84%) as a thick liquid; $R_f$ 0.56 (n-hexane/ethyl acetate = 8/2);

$[\alpha]_D^{25} = -51.2$ (c 0.63, CHCl$_3$);

IR (Neat) 1606, 1452 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) δ 1.38 (s, 3H, CH$_3$), 1.56 (s, 3H, CH$_3$), 3.32 (bd, $J = 15.2$ Hz, 1H, H-8a), 3.55–3.78 (m, 2H, H-8b and N-CH$_2$Ph), 3.97 (d, $J = 2.1$ Hz, 1H, H-3), 4.60–4.27 (m, 2H, H-4 and H-5), 4.47 (d, $J = 13.2$ Hz, 1H, N-CH$_2$Ph), 4.51 (d, $J = 11.7$ Hz, 1H, O-CH$_2$Ph), 4.68 (d, $J = 3.9$ Hz, 1H, H-2), 4.75 (d, $J = 11.7$ Hz, 1H, O-CH$_2$Ph), 5.41 (bd, $J = 6.0$ Hz, 1H, H-6), 5.80 (bd, $J = 6.0$ Hz, 1H, H-7), 6.05 (d, $J = 3.9$ Hz, 1H, H-1), 7.20–7.52 (m, 10H, Ar-$H$);
Expt. No. 3.4.5: Preparation of 5,8-Dideoxy-5,8-(N-benzylamino)-1,2-O-isopropylidene-3-O-benzyl-β-D-erythro-D-gluco-oct-1,4-furanose (189a).

K₃Fe(CN)₆ (1.94 g, 5.8 mmol) and K₂CO₃ (0.80 g, 5.8 mmol) were dissolved in water (6 mL) and tert-butyl alcohol (2 mL), and then the mixture was cooled to 0 °C. Methanesulfonamide (0.18 g, 1.9 mmol), catalytic potassium osmate were added and then alkene 187a (0.8 g, 1.9 mmol) dissolved in tert-butyl alcohol (4 mL) were added and the mixture was stirred at 0 °C for 10 h. Sodium sulphite (2 g) was added and the mixture was stirred at room temperature for 1 h. All volatiles were removed in vacuo, and then the residue was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with 2N KOH (5 mL), followed by water (10 mL), and dried over Na₂SO₄, filtered, and evaporated in vacuo to give oil. Purification by column chromatography (n-hexane/ethyl acetate = 60/40) gave 189a (0.52 g, 60%) as a thick liquid:

Rf 0.44 (n-hexane/ethyl acetate = 1/1);

[α]²⁵D = -7.4 (c 0.27, CHCl₃);

IR (Neat) 3550-3200, 1632, 1458 cm⁻¹;
**H NMR (300 MHz, CDCl₃) δ 1.36 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.60–2.10 (bs, 2H, exchanges with D₂O, -OH), 2.56 (dd, J = 10.8, 2.0 Hz, 1H, H-8a), 3.18 (dd, J = 10.8, 4.8 Hz, 1H, H-8b), 3.18–3.30 (m, 1H, H-5), 3.62 (d, J = 13.2 Hz, 1H, N-CH₂Ph), 3.94 (d, J = 13.2 Hz, 1H, N-CH₂Ph), 3.97 (d, J = 3.0 Hz, 1H, H-3), 4.12–4.32 (m, 3H, H-4, H-6 and H-7), 4.45 (d, J = 11.4 Hz, 1H, O-CH₂Ph), 4.67 (d, J = 3.9 Hz, 1H, H-2), 4.70 (d, J = 11.4 Hz, 1H, O-CH₂Ph), 5.94 (d, J = 3.9 Hz, 1H, H-1), 7.20–7.42 (m, 10 H, Ar-H);

**C NMR (75 MHz, CDCl₃) δ 26.3, 26.8 (2 x CH₃), 58.0, 60.5 (N-CH₂Ph, C-8), 66.8 (C-5), 70.7, 71.7, 73.9 (C-6, C-7, O-CH₂Ph), 81.4, 81.7, 82.5 (C-2, C-3, C-4), 104.5 (C-1), 111.8 (O-C-O), 127.0, 128.0(s), 128.3(s), 128.6(s), 128.7(s) 136.5, 139.1 (Ar-C);

Anal. Calcd. For C₂₅H₃₁NO₆: C, 68.01; H, 7.08; Found: C, 68.15; H, 7.20.

**Expt. No. 3.4.6: Preparation of 6,7-Di-acetoxy-5,8-dideoxy-5,8-(N-benzylimino)-1,2-O-isopropylidene-3-O-benzyl-β-D-erythro-D-gluco-oct-1,4-furanose (190a).**

To an ice cooled solution of 189a (0.05 g, 0.11 mmol) in dry pyridine (0.13 g, 1.6 mmol) was added acetic anhydride (0.39 g, 3.8 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 6 h. Ice water (5 mL) was added and extracted with chloroform (3 x 10 mL). Usual workup and chromatographic purification (n-hexane/ethyl acetate = 80/20) afforded di-acetate 190a (0.048 g, 89%) as a thick liquid.

Rf 0.54 (n-hexane/ethyl acetate = 7/3);

[α]D²⁵ = −10.5 (c 0.57, CHCl₃);

The IR, **H and **C NMR data is given on page number 137.
Expt. No. 3.4.7: Preparation of 6,7-Di-acetoxy-5,8-dideoxy-5,8-(N-benzylimino)-1,2-O-isopropyldiene-3-O-benzyl-α-L-erythro-L-idooct-1,4-furanose (190b) and 6,7-Di-acetoxy-5,8-dideoxy-5,8-(N-benzylimino)-1,2-O-isopropyldiene-3-O-benzyl-α-D-erythro-L-idooct-1,4-furanose (190c).

AD-mix-α (5.0 g) and (DHQ)₂PHAL (0.17 g, 0.06 mmol) were dissolved in water (15 mL) and tert-butyl alcohol (5 mL) and cooled to 0 °C. Methanesulfonamide (0.96 g, 2.5 mmol) and then the compound 187b (1.65 g, 4.0 mmol) dissolved in tert-butyl alcohol (10 mL) were added, and the mixture was stirred at 0 °C for 12 h. Sodium sulfite (2.0 g) was added and the mixture was stirred at room temperature for 1 h. All volatiles were removed in vacuo, usual workup as described for 190a and purification by column chromatography (n-hexane/ethyl acetate = 60/40) gave mixture of 189b,c (1.1 g, 62%) as a thick liquid. The reaction of 189b,c (1.0 g, 2.26 mmol) with pyridine (2.93 g, 36.2 mmol), acetic anhydride (8.2 g, 81.3 mmol) and catalytic DMAP was performed under similar reaction conditions as described for the synthesis of 189a followed by separation by column chromatography (n-hexane/ethyl acetate = 90/10) afforded diacetate 190b (0.33 g, 28%) as a thick liquid.

Rᶠ 0.61 (n-hexane/ethyl acetate 3/1);

[α]⁰₂⁵ = -19.0 (c 0.52, CHCl₃);

The IR, ¹H and ¹³C NMR data is given on page number 149.
Further elution with (n-hexane/ethyl acetate = 90/10) afforded 190c (0.67 g, 56 %) as a thick liquid;
Rf 0.58 (n-hexane/ethyl acetate 3/1);
$\left[\alpha\right]_{D}^{25} = -28.5 \, (c \, 0.35, \text{CHCl}_3)$;
The IR, $^1$H and $^{13}$C NMR data is given on page number 150.

Anal. Calcd. For C$_{29}$H$_{35}$NO$_8$: C, 66.27; H, 6.71; Found: C, 66.38; H, 6.79.

**Expt. No. 3.4.8: Preparation of 5,8-Dideoxy-5,8-(N-benzylimino)-1,2-O-isopropylidene-3-O-benzyl-$\alpha$-L-erythro-$\beta$-ido-oct-1,4-furanose (189b).**

Sodium metal (5 mg) was dissolved in dry methanol (3 mL) and diacetate 180b (0.29 g, 0.55 mmol) in methanol was added slowly at 0 °C. The mixture was stirred for 2 h and saturated solution of NH$_4$Cl (1 mL) was added. Methanol was removed under reduced pressure and residue was extracted with chloroform (3 x 15 mL). Usual workup followed by purification with column chromatography (n-hexane/ethyl acetate = 60/40) gave 189b as a thick liquid (0.28 g, 92%);
Rf 0.25 (n-hexane/ethyl acetate = 1/1);
$\left[\alpha\right]_{D}^{25} = -33.3 \, (c \, 0.30, \text{CHCl}_3)$;
IR (Neat) 3600-3200 cm$^{-1}$;
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.33 (s, 3H, CH$_3$), 1.49 (s, 3H, CH$_3$), 1.65-2.30 (bs, 2H, exchanges with D$_2$O, 2 x -OH), 2.42 (dd, $J = 10.2, 5.5$ Hz, 1H, H-8a), 2.80-3.21 (m, 2H, H-5 and H-8a), 3.51 (d, $J = 12.9$ Hz, 1H, N-C$_2$H$_2$Ph), 4.00-4.08 (m, 2H, H-6, H-7), 4.11 (d, $J = 3.0$ Hz, 1H, N-C$_2$H$_2$Ph).
Hz, 1H, H-3), 4.24 (dd, J = 8.1, 3.0 Hz, 1H, H-4), 4.28 (d, J = 12.9 Hz, 1H, N-CH\textsubscript{2}Ph), 4.53 (d, J = 11.7 Hz, 1H, O-CH\textsubscript{2}Ph), 4.65 (d, J = 3.9 Hz, 1H, H-2), 4.72 (d, J = 11.7 Hz, 1H, O-CH\textsubscript{2}Ph), 5.98 (d, J = 3.9 Hz, 1H, H-1), 7.00–7.50 (m, 10H, Ar-C);

\(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 26.3, 26.7 (2 \(\times\) CH\textsubscript{3}), 58.5, 60.1 (C-8, N-CH\textsubscript{2}Ph), 68.8, 69.8, 71.7, 73.2 (C-5, C-6, C-7, N-CH\textsubscript{2}Ph), 81.1, 82.7, 83.4 (C-2, C-3, C-4), 104.9 (C-1), 111.5 (O-C-O), 126.8, 127.8(s), 128.0(s), 128.5(s), 129.0(s), 136.7, 138.8 (Ar-C);

Anal. Calcd. For C\textsubscript{25}H\textsubscript{31}NO\textsubscript{6}: C, 68.01; H, 7.08; Found: C, 68.16; H, 7.21.

Expt. No. 3.4.9: Preparation of 5,8-Dideoxy-5,8-(N-benzylimino)-1,2-O-isopropylidene-3-O-benzyl-\(\alpha\)-D-erythro-L-ido-oct-1,4-furanose (189c).

The reaction of sodium metal (10 mg), compound 190e (0.60 g, 1.14 mmol) in methanol was performed under similar conditions as described for 189b. Purification by column chromatography (n-hexane/ethyl acetate = 60/40) gave 189c (0.45 g, 89%) as a thick liquid; 

R\textsubscript{f} 0.25 (n-hexane/ethyl acetate = 1/1);

\([\alpha]\)\textsubscript{D}\textsuperscript{25} = -33.3 (c 0.30, CHCl\textsubscript{3});

IR (Neat) 3600-3200, 1456, 1379 cm\(^{-1}\);

\(^{1}\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.27 (s, 3H, CH\textsubscript{3}), 1.47 (s, 3H, CH\textsubscript{3}), 1.70-2.20 (m, 2H, exchanges with D\textsubscript{2}O, 2 \(\times\) -OH), 2.35 (dd, J = 11.3, 5.5 Hz, 1H, H-8a), 2.85 (dd, J = 11.3, 2.0 Hz, 1H, H-8b), 2.94 (dd, J = 8.0, 5.5 Hz, 1H, H-5), 3.30 (d, J = 13.2 Hz, 1H, N-CH\textsubscript{2}Ph), 4.07 (dt, J = 5.5, 2.0 Hz, 1H, H-7), 4.13 (t, J = 5.5 Hz, 1H, H-6), 4.40-4.30 (m, 2H, H-3 and H-4), 4.52 (d, J = 13.2 Hz, 1H, N-CH\textsubscript{2}Ph), 4.57 (d, J = 11.5 Hz, 1H, O-CH\textsubscript{2}Ph), 4.62 (d, J = 3.9 Hz,
$^1$H, $H$-2), 4.71 (d, $J = 11.5$ Hz, 1H, O-CH$_2$Ph), 6.00 (d, $J = 3.9$ Hz, 1H, $H$-1), 7.20–7.40 (m, 10H, Ar-$H$);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 26.3, 26.7 (2 x C-3), 58.5, 58.7 (C-8, N-C$_2$H$_2$Ph), 65.8 (C-5), 69.5, 71.9, 72.0 (C-6, C-7, O-C$_2$H$_2$Ph), 81.5, 81.6, 83.2 (C-2, C-3, C-4), 104.7 (C-1), 111.5 (O-C-O), 127.2, 127.6(s), 127.9, 128.2(s), 128.4(s), 129.6(s), 137.3, 137.5 (Ar-C);

Anal. Calcd. For C$_{25}$H$_{31}$NO$_6$: C, 68.01; H, 7.08; Found: C, 68.18; H, 7.16.

Expt. No. 3.4.10: Preparation of 5,8-dideoxy-5,8-(N-benzoxycarbonylimino)-1,2-O-isopropylidene-6(S),7(/f)-dihydroxy-$\alpha$-D-glycero-D-gluco-oct-1,4-furanose (186a).

A solution of compound 189a (0.50 g, 1.13 mmol), 10 % Pd/C (0.10 g) and ammonium formate (0.43 g, 6.80 mmol), in methanol (10 mL) was stirred at 80 °C for 1 h. The reaction mixture was filtered through the pad of celite and the filtrate was evaporated to give thick oil. To a solution of amino alcohol (0.25 g, 1.13 mmol), in methanol-water (15 mL, 9:1) and sodium bicarbonate (0.28 g, 3.3 mmol) cooled to 0 °C was added benzylchloroformate (0.23 g, 1.33 mmol) and the solution was stirred at room temperature for 2 h. Methanol was evaporated under reduced pressure and the aqueous layer was extracted with chloroform (3 x 15 mL). After usual work and purification by column chromatography (n-hexane/ethyl acetate = 60/40) gave 186a (0.35 g, 78% overall) as a thick liquid;

R$_f$ 0.62 (ethyl acetate);

$[\alpha]_D^{25} = +48.2$ (c 0.29, CHCl$_3$);

IR (Neat) 3400-3200, 1688, 1427 cm$^{-1}$;
The reaction of compound 189b (0.17 g, 0.38 mmol) with ammonium formate (0.14 g, 2.3 mmol) and 10% Pd/C (0.08 g) in methanol (5 mL) and further reaction of aminotriol (0.10 g, 0.38 mmol), in methanol-water (6 mL, 9:1) with sodium bicarbonate (0.1 g, 1.14 mmol) and benzylchloroformate (0.10 g, 0.57 mmol) was performed under similar reaction conditions as described for 186a. Purification by column chromatography (n-hexane/ethyl acetate = 60/40) afforded 186b (0.11 g, 73%) as a white solid; mp 131-132 °C; 

\[ [\alpha]_D^{25} = -57.1 \text{ (c 0.35, CHCl}_3) \]
IR (KBr) 3500-3200, 1666, 1421 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.29 (s, 3H, CH\(_3\)), 1.45 (s, 3H, CH\(_3\)), 2.40-3.50 (bs, exchanges with D\(_2\)O, 3H, 3 x OH), 3.48-3.68 (m, 2H, H-8), 4.01-4.23 (m, 4H, H-5, H-3, H-4, H-7), 4.33-4.46 (m, 1H, H-6), 4.47 (d, \(J = 3.6\) Hz, 1H), 5.09 (ABq, \(J = 12.4\) Hz, 2H, O-CH\(_2\)Ph), 5.89 (d, \(J = 3.6\) Hz, 1H, H-1), 7.20-7.38 (m, 5H, Ar-H);

\(^13\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\) 26.6 (CH\(_3\)), 27.3 (CH\(_3\)), 52.1, 62.5 (C-5, C-8), 68.2, 70.3, 75.8 (C-6, C-7, O-CH\(_2\)Ph), 75.9, 81.0, 85.3 (C-2, C-3, C-4), 104.9 (C-1), 111.8 (O-C-O), 128.0(s), 128.3, 128.7(s), 136.2 (Ar-C), 157.4 (C=O);

Anal. Calcd. For C\(_{19}\)H\(_{23}\)NO\(_6\): C, 57.71; H, 6.37; Found: C, 57.84; H, 6.50.

Expt. No. 3.4.12: Preparation of 5,8-dideoxy-5,8-(N-benzoxy carbonylimino)-1,2-O-isopropylidene-6(R),7(S)-dihydroxy-\(\alpha\)-D-glycero-L-idono-1,4-furanose (186c).

The reaction of compound 189c (0.28 g, 0.65 mmol) with ammonium formate (0.25 g, 3.9 mmol) and 10% Pd/C (0.06 g) in methanol (8 mL) and further reaction of aminotriol (0.15 g, 0.65 mmol), in methanol-water (10 mL, 9:1) with sodium bicarbonate (0.17 g, 2.0 mmol) and benzylchloroformate (0.13 g, 0.78 mmol) was performed under similar reaction conditions as described for 186a. Purification by column chromatography (n-hexane/ethyl acetate = 60/40) afforded 186c (0.20 g, 79%) as a white solid;

mp 132-134 °C;

R\(_f\) 0.44 (ethyl acetate);

\([\alpha]_{D}^{25} = -45.2\) (c 0.35, CHCl\(_3\));
IR (Nujol) 3400-3150, 1687 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 1.32 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 3.27 (d, J = 6.9 Hz, exchanges with D₂O, 1H, -OH), 3.47 (d, J = 13.4 Hz, 1H, H-8a), 3.98 (dd, J = 13.4, 6.3 Hz, 1H, H-8b), 4.16–4.38 (m, 4H, H-4, H-5, H-6, H-7), 4.43 (d, J = 12.0 Hz, exchanges with D₂O, 1H, -OH), 4.56 (d, J = 3.6 Hz, 1H, H-2), 4.58 (d, J = 2.1 Hz, 1H, H-3), 4.87 (bs, exchanges with D₂O, 1H, -OH), 5.17 (Abq, J = 12.0 Hz, 2H, O-CH₂Ph), 5.96 (d, J = 3.6 Hz, 1H, H-1), 7.32–7.46 (m, 5H, Ar-H);

¹³C NMR (75 MHz, CDCl₃) δ 26.3, 26.9 (2 x CH₃), 53.4, 56.8 (C-5, C-8), 68.2, 69.6, 70.1 (C-6, C-7, O-CH₂Ph), 75.2, 76.2, 84.6 (C-2, C-3, C-4), 104.4 (C-1), 112.4 (O-C-O), 128.2(s), 128.4, 128.6(s), 135.5 (Ar-C), 157.5 (C=O);

Anal. Calcd. For C₁₉H₂₅NO₅: C, 57.71; H, 6.37; Found: C, 57.79; H, 6.48.

Expt. No. 3.4.13: Preparation of (1S,2R,6S,7R,8aR)-1,2,6,7,8-Pentahydroxy-indolizidine (7b).

Compound 186a (0.30 g, 0.76 mmol) in TFA-H₂O (6.0 mL, 2:1) was stirred at 25 °C for 2.5 h.

Trifluoroacetic acid was co-evaporated with benzene to furnish thick liquid. To a solution of above product in methanol (10 mL) was added 10% Pd/C (0.05 g) and the solution was hydrogenated at 80 psi for 12 h. The catalyst was filtered, washed with methanol and the filtrate was concentrated to afford thick liquid. Purification by column chromatography (chloroform/methanol = 50/50) afforded 7b (0.14 g, 91%) as a white solid;

mp 171-173 °C (lit.¹⁸ 174–178 °C);
$R_f = 0.44 \text{ (MeOH);}$

$[\alpha]_{D}^{25} = -5.2 \text{ (c 0.40, H}_2\text{O)} \text{ [lit.}\ {\text{[a]}}\text{$_{D}^{25} = -4.4 \text{ (c 1.2, H}_2\text{O)}$;}}$

The IR, $^1\text{H}$ and $^{13}\text{C}$ NMR data is given on page number 144.

Anal. Calcd. For C$_8$H$_{15}$NO$_3$: C, 46.82; H, 7.37; Found: C, 46.84; H, 7.49.

Expt. No. 3.4.14: Preparation of (1R,2S,6S,7R,8R,8aS)-1,2,6,7,8-Pentahydroxy-indolizidine (174a).

The reaction of 186b (0.07 g, 0.16 mmol) with TFA-$\text{H}_2\text{O}$ (2 mL, 2:1) followed by 10% Pd/C (0.02 g) in methanol (4 mL) is performed under similar reaction conditions as described for 7b. Purification by column chromatography (chloroform/methanol = 40/60) afforded 174a (0.03 g, 83%) as a thick liquid;

$R_f 0.25 \text{ (methanol);}$

$[\alpha]_{D}^{25} = +217.0 \text{ (c 0.35, H}_2\text{O);}$

The IR, $^1\text{H}$ and $^{13}\text{C}$ NMR data is given on page number 157.

Anal. Calcd. For C$_8$H$_{15}$NO$_3$: C, 46.82; H, 7.37; Found: C, 46.989; H, 7.48.

Expt. No. 3.4.15: Preparation of (1S,2R,6S,7R,8R,8aS)-1,2,6,7,8-Pentahydroxy-indolizidine (174b)
The reaction of 186c (0.16 g, 0.40 mmol) with TFA-H₂O (3 mL, 2:1) followed by 10% Pd/C (0.03 g) in methanol (5 mL) is performed under similar reaction conditions as described for 7b. Purification by column chromatography (chloroform/methanol = 20/80) afforded 165b (0.07 g, 84%) as a thick liquid;

Rf 0.20 (methanol);

[α]D²⁵ = -12.0 (c 0.50, H₂O);

The IR, ¹H and ¹³C NMR data is given on page number 161.

Anal. Calcd. For C₈H₁₅NO₃: C, 46.82; H, 7.37; Found: C, 46.96; H, 7.44.

Expt. No. 3.4.16: Preparation of (1S,2R,6S,7R,8R,8aR)-1,2,6,7,8-Penta-acetoxyindolizidine (173).

The reaction of 7b (0.05 g, 0.24 mmol), pyridine (0.67 g, 8.4 mmol), acetic anhydride (2.0 g, 20.4 mmol) and catalytic N-N-(dimethyl amino) pyridine was carried out under similar reaction conditions as described for synthesis of 190a. Purification by column chromatography (n-hexane/ethyl acetate = 70/30) afforded penta-acetate 173 (0.09 g, 90%) as a white solid,

mp 142 °C (lit.² 142° C);

Rf = 0.40 (n-hexane/ethyl acetate 1/1);

[α]D²⁵ = -17 (c 0.90, CHCl₃) [lit.² [α]D = -15 (c 1.36, CHCl₃)];

IR (Nujol) 1735 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 2.04 (s, 3H, C/H₃), 2.05 (s, 3H, CH₃), 2.06 (s, 3H, 2 x CH₃), 2.07 (s, 3H, CH₃), 2.33 (t, J = 10.2 Hz, 1H, H-5a), 2.48 (dd, J = 9.9, 4.8 Hz, 1H, H-3a), 2.66 (t, J =
8.5 Hz, 1H, H-8a), 3.31 (dd, J = 10.5, 5.4 Hz, 1H, H-5b), 3.60 (dd, J = 9.9, 6.6 Hz, 1H, H-3b),
4.94-4.99 (m, 1H, H-8), 5.01 (dd, J = 9.9, 5.1 Hz, 1H, H-6), 5.06 (t, J = 7.2 Hz, 1H, H-1), 5.15
t, J = 9.3 Hz, 1H, H-7), 5.29 (ddd, J = 12.0, 6.9, 5.4 Hz, 1H, H-2);
$^{13}$C NMR (75 MHz, D$_2$O) δ 20.2, 20.5 (s), 20.6 (s), 20.7 (5 x COCH$_3$), 51.6, 57.1, 65.2 (C-3, C-5,
C-8a), 69.2, 69.6, 71.6, 73.4, 73.5 (C-1, C-2, C-6, C-7, C-8), 169.1, 169.8, 169.9, 170.0, 170.2
(5 x C=O);
Anal. Calcd. For C$_{15}$H$_{25}$NO$_{10}$: C, 52.05; H, 6.07; Found: C, 52.18; H, 6.21.

Expt. No. 3.4.17: Preparation of (1R,2S,6S,7R,8aS)-1,2,6,7,8-Penta-acetoxy-
indolizidine (191a).

The reaction of compound 174a (0.02 g, 0.10 mmol), pyridine (0.27 g, 3.4 mmol), acetic
anhydride (0.82 g, 8.2 mmol) and catalytic N-N-(dimethyl amino) pyridine was performed
under similar reaction conditions as described for 173. Purification by column chromatography
(n-hexane/ethyl acetate = 50/50) afforded penta-acetate 191a (0.035 g, 91%) as a thick liquid;
Rf 0.65 (ethyl acetate);
$[\alpha]_D^{25} = [\alpha]_D = + 37.3$ ($c$ 0.70, CHCl$_3$);
IR (Neat) 1735 cm$^{-1}$;
$^1$H NMR (300 MHz, CDCl$_3$) δ 2.05 (s, 3H, COCH$_3$), 2.07 (s, 3H, COCH$_3$), 2.13 (s, 3H,
COCH$_3$), 2.14 (s, 3H, COCH$_3$), 2.16 (s, 3H, COCH$_3$); 2.32 (dd, J = 10.7, 4.7 Hz, 1H, H-3a),
2.62 (dd, J = 12.9, 2.5 Hz, 1H, H-5a), 2.76 (dd, J = 9.1, 3.5 Hz, 1H, H-8a), 3.15 (bd, J = 12.9
Hz, 1H, H-5b), 3.68 (dd, J = 10.7, 6.9 Hz, 1H, H-3b), 4.86-4.94 (m, 1H, H-6), 4.97-5.03 (m,
2H, H-7, H-8), 5.07 (dd, J = 9.1, 6.9 Hz, 1H, H-1), 5.27 (dt, J = 6.9, 4.7 Hz, 1H, H-2);
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 20.8 (COCH$_3$), 21.1 (COCH$_3$), 21.2 (COCH$_3$), 21.3 (COCH$_3$), 21.6 (COCH$_3$), 52.3, 59.4, 61.8 (C-3, C-5, C-8a), 65.9, 66.7, 67.8, 68.1, 69.6 (C-1, C-2, C-6, C-7, C-8), 168.5, 169.8, 170.0, 170.1, 170.2 (5 x CO);

Anal. Calcd. For C$_{18}$H$_{25}$NO$_{10}$: C, 52.05; H, 6.07; Found: C, 52.00; H, 6.11.

**Expt. No. 3.4.18: Preparation of (1S,2R,6S,7R,8aS)-1,2,6,7,8-Penta-acetoxy-indolizidine (191b).**

The reaction of compound 174b (0.03 g, 0.15 mmol), pyridine (0.40 g, 5.1 mmol), acetic anhydride (1.25 g, 12.3 mmol) and catalytic N,N-(dimethyl amino) pyridine was performed under similar reaction conditions as described for 173. Purification by column chromatography (n-hexane/ethyl acetate = 50/50) afforded penta-acetate 191b (0.055 g, 91%) as a thick liquid;

R$_f$ 0.65 (ethyl acetate);

[α]$^D_{25}$ = + 8.5 (c 1.17, CHCl$_3$);

IR (Neat) 1745, 1656 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) δ 2.08 (s, 3H, CH$_3$), 2.10 (s, 6H, 2 x CH$_3$), 2.12 (s, 3H, CH$_3$), 2.16 (s, 3H, CH$_3$), 2.92 (dd, $J = 12.0$, 3.8 Hz, 1H, H-5a), 3.04 (dd, $J = 12.3$, 7.0 Hz, 1H, H-3a), 3.16-3.30 (m, 3H, H-3b, H-5b, H-8a), 4.92-5.02 (m, 1H, H-6), 5.20-5.28 (m, 2H, H-7, H-8), 5.31 (dt, $J = 7.0$, 2.7 Hz, 1H, H-2), 5.56 (dd, $J = 7.0$, 5.8 Hz, 1H, H-1),

$^{13}$C NMR (75 MHz, D$_2$O) δ 20.4, 20.5, 20.7, 20.8, 20.9 (5 x CH$_3$), 51.9, 58.2, 61.5 (C-3, C-5, C-8a), 67.2, 68.0, 68.7, 70.8(s) (C-1, C-2, C-6, C-7, C-8), 169.1, 169.2, 169.5, 169.7, 169.8 (5 x C=O);

Anal. Calcd. For C$_{18}$H$_{25}$NO$_{10}$: C, 52.05; H, 6.07; Found: C, 52.22; H, 6.16.
3.5. References


15. (a) Jacobsen, E. N.; Mark6, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. J. Am. Chem. Soc. 1989, 111, 737. (b) Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.;


