Chapter 2

Aziridine based synthetic strategies
Section 1

Introduction to aziridine


2.1 Introduction of Aziridine

2.1.1 Introduction

Aziridines are saturated three membered heterocycles containing one nitrogen atom and other two methylene bridges, which are also known as ethyleneimines (Fig 1). They theoretically can be obtained from cyclopropane by replacing one of the methylene groups with nitrogen. Aziridine was introduced as the smallest nitrogen containing heterocycle in 1888 by Gabriel. Since its discovery, it has been a synthetic target as well as useful building block in synthesis. The ring strain and unique reactivity of aziridine attracted synthetic chemists and they have extensively explored the various manipulations of aziridine containing compounds. The possible invertomers of aziridines are cis and trans, which are key synthons in the organic synthesis. These smallest heterocycles also exhibit synthetically very useful balance between stability and reactivity. Thus, they are often employed as versatile and selective intermediates.

**Biological properties of aziridines**

As powerful alkylating agents, aziridines have inherent in vivo potency, based on toxicity rather than specific activity. Several classes of aziridine containing natural products display selective potency, the best examples are mitosanes. Mitosanes were isolated from soil extracts of *Streptomyces verticillactus*, which show both anti-tumour and antibiotic activities. The aziridine ring is much essential for such biological activity and thus large amount of work has concentrated on derivatisation of these natural products with increased potency.
Mitosanes represent the first class of bioactive compounds to rely on bio-reductive activation to provide a means for DNA alkylation. FR and FK compound which are analogous to mitosanes show similar anti-cancer activity. Azinomycin, a structurally distinct class, possesses activity against wide range of cancer cells, tumour cells and exert cytotoxicity against human tumour cell lines. PBI class natural products, which contain aziridinyl quinone, represent another group of DNA-alkylating compounds (Fig 2).

![Chemical structures of mitosanes and azinomycin](image)

**Fig 2** Aziridine ring-containing natural products

**Physical properties of aziridines**

The bond angle in the aziridine is approximately 60°, less than hydrocarbons 109.5°, which results in the angle strain as comparable to cyclopropane and epoxides. In general aziridines are less basic compared with acyclic amines (the aziridinium ion has \(pK_a = \))

![Inversion barrier for aziridines](image)

**Scheme 1** Physical properties of aziridines
due to increased ‘s’ character of the nitrogen lone pair. The increased ‘s’ character results into increase in angle strain which is the barrier for the aziridine inversion. This inversion barrier can be enough for the separation of invertomers, for instance the cis and trans invertomers of \( N \)-chloro-2-methylaziridine described in Scheme 1.\(^2\) The large inversion energy for aziridine is due to angle and torsional strains.

### 2.1.2 Synthesis of aziridines

It is certain that the chemistry of aziridine has been hindered by dearth of suitable methods available for aziridination compared with epoxidation. In other words, the methods for the preparation of aziridines are dwarfed by these available for preparation of epoxides, which are traditionally being mainstay from the alkenes. Reason for this incongruity is the inertness of N-O and N-N bonds compared to peroxide bond. Thus,

![Scheme 2 Aziridines synthesis; Overview^3](image)

whereas alkenes react with peroxycids and alkylhydroperoxides (in presence of Lewis acid), a parallel reactivity is not observed when alkenes are treated with the aza-analogues. The methods for aziridines preparation have been usually distinct from those for epoxides synthesis. Asymmetric aziridine formation method is still not generalized while asymmetric epoxidation is much generalized. Thus considering the importance of the smallest heterocycle inspired many organic groups to develop synthetic methodologies for the preparation of aziridines. Due to important features of the
aziridine, chemical communities have established the different ways of $N$-substituted and $N$-unsubstituted aziridine synthesis in achiral and chiral fashion. Also some efforts have been made for synthesis of cis and trans aziridines which is outlined in the Scheme 2.

**Addition of nitrene**

It is the classical method for aziridination, featuring the addition of the nitrene to the unsaturated partner (Scheme 3). The limitations to the method (often involving alkoxy carbonylnitrenes) are well documented, with necessity for harsh reaction conditions and lack of stereoselectivity, which have limited the attractiveness of this methodology.\(^4\)

\[
\begin{align*}
\text{R}_1^1 \underset{\alpha}{\equiv} \text{R}_2^2 & \quad \underset{\text{R}_3^3 \text{N}^1}{\text{R}_3^3 \text{N}^1} \quad \text{R}_1^1 \underset{\text{H}}{\text{N}} \text{R}_2^2 + \quad \text{R}_1^1 \underset{\text{H}}{\text{N}} \text{R}_3^3 \text{R}_2^2 \\
\text{From singlet nitrene} & \quad \text{From triplet nitrene}
\end{align*}
\]

**Scheme 3 Addition of nitrene**

Typically such nitrenes were generated by thermal or photochemical decompositions of the corresponding azides, which led to the mixture of very active singlet nitrenes and more stable triplet nitrenes. The reaction of single nitrenes to 1, 2-disubstituted alkenes partner gives stereospecifically addition, while triplet nitrenes react in two step process with alkenes to furnish stereoselective products, in which N-C bond is formed in each step. The nature of the $N$-substituents in this case exerts powerful effect on exposing under this reaction conditions. When non-acyl azide undergo cycloaddition with alkene partner they furnished substituted triazoline, which is isolated in many instance and separately converted to the aziridine poor in stereoselectivity (Scheme 4).

\[
\begin{align*}
\text{R}_1^1 \underset{\alpha}{\equiv} \text{R}_2^2 & \quad \underset{\text{hv or heat}}{\text{hv or heat}} \quad \text{R}_3^3 \text{N}_3 \quad \text{R}_3^3 \text{N}_3 \quad \text{R}_2^2 \quad \underset{\text{hv or heat}}{\text{hv or heat}} \\
\text{N}^3 \text{N}^2 \text{R}_1^1 \text{R}_2^2 & \quad \text{N}_2 \\
\text{Scheme 4 Addition of azide}
\end{align*}
\]

The useful modification of the method involves in situ generation of nitrene by the oxidation of hydrazine derivatives. This method provides the aziridines in more stereoselective manner than previous reported examples. Atkinson et al demonstrated that using hydrazine derivatives 5 led to the stereospecific addition to alkenes due to formation of $N$-nitrene 6, which reacts only in singlet state. The $N$-amino phthalimide 5 in
presence of Pb(OAc)$_4$ generated singlet nitrene 6, which underwent addition to both cis-alkene 9 and trans-alkenes 7 to provide stereospecific products 10 and 8 respectively. The primary reason was the high inversion barrier of phthalimide group (Scheme 5).\(^5\)

\[ \begin{align*}
\text{Scheme 5 } & \text{ } N\text{-Nitrene addition on cis and trans alkene} \\
\text{In the case of mono-substituted olefin, the above reaction condition provides the diastereoselective addition products 11 and 12 at different temperature (Scheme 6).} \\
\text{Scheme 6 } & \text{ Effect of temperature on } N\text{-nitrene addition} \\
\text{By addition to imines} \\
\text{Carbene and ylide method} \\
\text{The addition of the carbines and ylides with imines provides aziridines through the formation of one C–N bond and one C–C bond as outlined in Scheme 6. The stereochemical outcome of singlet and triplet carbene addition is similar to the nitrene reaction with alkene but the addition of ylide is in stereospecific way via } S_N2 \text{ attack.} \\
\text{Scheme 7 } & \text{ Carbene addition to imine} \\
\text{Jacobsen and Finney reported that metallocarbene derived from ethyl diazoacetate and copper-(I)-hexafluorophosphate added to } N\text{-arylaldimine 14 in presence of catalyst} \\
\end{align*} \]
derived from the Evans chiral bis(oxazoline) ligand 15 to afford acceptable
diastereoselectivities (> 10:1) but enantioselectivity was low. Jorgensen using similar
copper catalyst and 19 reported the better level of enantiocontrol, but falls short of
standards of modern asymmetric transformation. Wulff et al utilized the axially-chiral
boron Lewis acid 22 for asymmetric addition of ethyldiazoacetate to imine 21 and
observed better enantioselective product 23 (Scheme 8).6

![Scheme 8 Asymmetric aziridine synthesis](image)

Huang et al has been recently published the first asymmetric catalytic reaction of diazo-
compound 24 and N-Boc imine 23 in the presence of chiral polyborate as Bronsted acid
(S)-VAPOL 25 gave trisubstituted aziridine 26 (Scheme 9).7

![Scheme 9 Asymmetric synthesis of trisubstituted aziridine 26](image)
From 1, 2-aminoalcohols and 1, 2-aminohalides

**Gabriel’s aziridine synthesis**

This is oldest method used for the aziridines synthesis. Gabriel who introduced aziridine as the three membered heterocyclic synthon in 1888 and demonstrated the synthesis of the aziridine from the ethanoamine in two step protocol. The 1, 2-aminoalcohol when treated with thionyl chloride resulted into halo-intermediate, which on alkali-mediated cyclisation to provide aziridine. The general example is described in Scheme 10.

![Scheme 10 Gabriel’s aziridine synthesis](image)

**Wenker’s synthesis**

In 1935, Wenker synthesized the first pure form of aziridine by heating ethanolamine 27 in presence of conc. sulfuric acid at higher temperature to afford compound 28, which was termed as ‘β-aminoethyl sulfuric acid’ (Scheme 11). The compound 28 was distilled out from aq. base to furnish aziridine, which was represented the first preparation of parent aziridine I in purest form. Afterwards different reaction conditions were utilized for the activation of hydroxy group of 1, 2-ethanolamines, enabling the preparation of aziridines in achiral and enantiomerically pure form as the synthetic point of view.

![Scheme 11 Wenker’s aziridine synthesis](image)

These reaction conditions were not applied to wide range of aminoalcohols, which led to mixture of cyclised and eliminated products if any α-substituents to hydroxy moiety were present. These are major limitations of this synthetic procedure for the preparation of aziridines. But some methods like Mitsunobu reaction by oxyphosphonium activation of
amino alcohols, which is extensively utilized in the organic transformations for aziridines synthesis.

From 1, 2-azidoalcohols

This method generally used for the asymmetric synthesis of aziridines from their readily available enantiopure O-analogs, epoxides. The enantiomerically pure epoxides, which could be obtained using the well documented asymmetric processes of epoxide preparation. The epoxides are the key precursor for the aziridines synthesis in multi-step procedure. Most useful procedure, the phosphine-mediated ring closing of 1, 2-azido alcohol (i.e. Staudinger reaction), which was derived from chiral epoxide 29 opening using azide as N-nucleophile afforded azidoalcohols 30 and 31 as regioproducts. Following the treatments of trialkyl/triarylphosphine furnished the N-unsubstituted aziridine product 32. This is wildly used process for the aziridination, which gives the both asymmetric center smoothly and predictably from the chiral and achiral epoxides (Scheme 12).10

![Scheme 12 Synthesis of aziridine from 1, 2-azidoalcohol](image)

From α-bromoacrylates

Gabriel-Cromwell reaction

This is one of useful procedure for wide range of chiral aziridination. The aziridines were obtained by treatment of α-bromoacrylates with the wide range of amines following the reaction sequences conjugated addition of amines; proton transfer and S_N2 ring closing. The chiral α-bromoacrylates 35 on the similar addition of amine 36 led to aziridine 39 in chiral form (Scheme 13).11 The unsubstituted chiral aziridine can be derived using ammonia as nitrogen source undergoes similar reaction sequences.
Reactions of aziridines

Ring-opening process

One of the most widely encountered reactions of aziridines is the nucleophilic ring opening. Aziridine having the Baeyer strain around 111 kJ mol\(^{-1}\) comparable to oxirane due to smallest cyclic nature and electronegativity of the nitrogen atom, which undergo ring opening under mild conditions with release of ring strain. The compared electronegativity of nitrogen is less compared with oxygen, thus ring-opening reaction of aziridine is less facile than the epoxide. But still there is requirement of an extensive exploration of the aziridine chemistry (Scheme 14). There are several features of these reactions which are worthy of consideration.\(^{12}\)

The nature of the \(N\)-substituents

The presence of the additional valency on the nitrogen atom in aziridines that of epoxides makes its chemistry comparatively complicated. The aziridine ring opening is carried using high basic and carbon-centered nucleophiles. The N-H bond of aziridines should be masked to avoid side reactions. The \(N\)-substituents should be stabilizes the anion
generated by ring opening. On the basis reactivity of the N-substituents aziridines have been devided into two type i.e. activated and unactivated aziridines. The activated aziridines having electron withdrawing groups like acyl, sulfonyl, carbonyl etc as substituents. These groups stabilize the negative charge on the nitrogen during the ring opening and also facilitate the nucleophilic ring opening. The unactivated aziridines are also known as simple aziridines, which having alkyl substituents on the nitrogen. Usually, these aziridines in presence of acid catalysts are prone to facile ring opening (Scheme 15).13

\[ \text{EWG} - \text{SO}_2\text{R, CO}_2\text{R, COR etc} \]

\[ \text{EDG} - \text{H, alkyl, aryl, benzyl etc} \]

**Activated aziridine**

**Unactivated aziridine**

**Scheme 15** Types of aziridines based on N-substituents

The inductive effect of N-substituent is responsible for kinetic activation and led to the polarization of C-N bond. The amide like anion produced after ring-opening is thermodynamically stabilized. If carbonyl is present as substituent the resonance stabilization is highly likely.

**Regeoselectivity in ring-opening processes**

Ring cleavage is most useful process for the 1, 2-functionalization of the aziridines as per design. The nucleophilic aziridine ring opening process provides product selectivity similar to the epoxide ring opening. In the case of the unsymmetrically substituted aziridines were subjected to attack of nucleophiles led to the mixture of regioisomeric

**Scheme 16** Regeoselectivity in aziridine ring opening
ring opened products. Fundamentally the nucleophiles would preferentially direct the
attack from the less crowding arm of aziridine considering the electronic factor as
described in Scheme 16.  

Inconsistent reactivity profiles of aziridines are occasionally observed when nucleophiles
either hindered 43 or a relatively weak Lewis base 41 or weakly activated aziridines. In
this situation, attack at a quaternary ‘C’ atom is preferred over the less substituted ‘C’
atom (Scheme 17)

Scheme 17 Hindered nucleophilic ring opening

Scheme 18 Aziridine ring opening: Overview
The nucleophilic aziridine ring opening provides the regioselective and stereoselective product. It is possible to synthesize the number of the functionalized compounds that show 1, 2-relation of incoming nucleophiles. The wide range of the nucleophiles e. g. carbon, oxygen, sulfur, nitrogen, halogen, hydrogen, phosphorous, silanes, selenols, cobalt, etc. have been utilised to synthesise 1, 2-functionalised compounds. The functionalizations of the aziridines by ring opening as outlined in the Scheme 18.\textsuperscript{15}

**Effect of Lewis acid**

The non-bonding lone pair electrons acts as Lewis base, its mean presence of the Lewis acids enhances the rate of epoxide ring opening process by weakening the already strained C-O bond through coordinating. In aziridines, when alkyl as substituents on the nitrogen atom then it can interact with Lewis acids and since the polar activating $N$-substituent is often required for efficient aziridine ring opening. The ring opening of aziridine is less facile as compared with epoxide by the use of Lewis acid. Nonetheless, the desirability of polar oxygenated $N$-substituent for ring-opening still allow for some use of this type of activation *via* coordination of oxygen lone pair to Lewis acid (Scheme 19).

**Electrocyclic aziridine ring-opening**

Aziridines are considered as the precursor of azidomethane ylide. On heating the aziridines rupture in stereospecifically to generate 1, 3-dipolar azidomethane ylides, which insitu were trapped with dipolarophiles to provide the substituted pyrrolidines
The aziridine stereochemistry is maintained in the stereochemistry of the dipole such that $S$-dipole 46, which is obtained from cis-aziridines 45 leading to trans-2, 5-substituted pyrrolidines 47, where as the $W$-dipole 49 obtained from trans aziridines 48 leading to cis-2, 5-substituted pyrrolidines 50. The $S$-dipoles reacts efficently with wide range of dipolarophiles with retention of geometry whilst $W$-dipoles react smoothly with reactive dipolarophiles such as acetylenedicarboxylates and maleimides (Scheme 21).

**Scheme 21** $S$ and $W$ dipole reactivity

### 2.1.3 Application of aziridines in synthesis

The renewed interest in aziridination has fostered increased application in synthesis of variety of nitrogen containing bioactive natural products. Last 20 years have attracted organic chemists for the synthesis of aziridines and dealing with the preparation of small nitrogen containing heterocyclic compounds and its reactions. Aziridine moiety presents itself, or can serve as intermediates in strategies for the synthesis of natural products. The high strain and inherent potent abilities of aziridines led to stereo- and regioselective ring-opening reactions have been exploited in natural.
The aziridine based synthesis of natural products are categorized in two type *i.e.* synthesis of natural products containing aziridine units and synthesis of natural products involving the transformation of an aziridine moiety.

**Synthesis of natural products containing aziridine units**

Numbers of natural products possessing aziridine ring as unit possesses potent biological activity.

**Synthesis of aziridine-2, 3-dicarboxylic acid**

The C$_2$-symmetry compound 51, which is metabolite of Streptomyces MD 398-A1. The compound 51 was prepared from L-(+)-diethyl tartarate as chiral starting material in enantiopure form is described in Scheme 22.

\[ \text{Scheme 22 Aziridine-2, 3-carboxylic acid} \]

**Synthesis of (Z)-dysidazine**

The first enantioselective synthesis of (Z)-dysidazine 57 reported by Molishki, which was isolated from the marine sponge *Dysidea fragilis* shows antifungal activity. The intermediate 55 was converted into aziridine 56, followed by Lindlar reduction afforded

\[ \text{Scheme 23 (Z)-Dysidazine} \]
(Z)-dysidazine 57 (Scheme 22).

**Synthesis of Mitomycins**

This is the important class of aziridine ring containing natural products show very potent antibacterial and anticancer activities, which were extracted from the genus *Streptomyces*. Most efforts have been put by synthetic chemists for the synthesis of the natural products, which contains aziridine ring.

Scheme 24 Mitomycin A 1a and C 1c

Fukuyama and co-workers synthesized mitomycin A 1a and mitomycin C 1c which is briefly described in the Scheme 24.\(^{18}\) The azide 58 on intramolecular cycloaddition at 110 °C provided aziridine 59, followed by few reaction sequences compound 59 was
converted into target compounds 1a and 1c.

Danishefsky and colleagues reported a short synthesis of mytomycin K 3c. The N-methyl aziridine 63 was obtained from the olefin 1c by 1, 3-dipolar cycloaddition of methylthiophenyl azide provided triazole 61, which on two step sequences afforded compound 62. Compound 62 was irradiated at 254 nm to furnish aziridine 63 as key intermediate, which was converted to Mitomycin K 3c in few steps (Scheme 25).

**Synthesis of FR-900482**

The FR-900482 2a is structurally related with Mitomycin C 1c and show antitumor and antibiotic activities. Fukuyama has reported the first total synthesis of FR-900482 2a, which is outlined in Scheme 26.19

Epoxide 64 was opened with NaN₃, followed by the mesylation afforded azide 65. The azide 65 was transformed to compound 66 using few reaction sequences, which was treated with PPh₃ in presence of base ended aziridine 67 as the key intermediate. The aziridine 67 was advanced to the target compound 2a in few steps.

**Synthesis of natural products involving the transformation of an aziridine moiety**

The aziridines are undergoing nucleophilic ring opening to release ring strain. Unactivated aziridines required acids to catalyze reaction e.g. unsubstituted or alkyl-substituted aziridines while activated aziridines are facile to the attack of nucleophiles.
Thus aziridines are useful and having the good potency in the synthesis of natural products.

**Carbon-centered nucleophiles**

Generally organometallic reagents are used as C-centered nucleophiles in the natural product synthesis through nucleophilic ring opening. Late 1980 have witnessed for its application in natural products synthesis using organocuprate or Grignard reagents to open $N$-alkyl aziridines in Lewis acids or $N$-tosyl aziridines with no need of Lewis acids.

Organocopper reagents mediated ring opening has proved useful in the number of synthesis. First example reported by Tanner and co-workers of an enantioselective synthesis of (+)-PS-5 70 described in Scheme 27.20

The aziridine 68 on LiEt$_2$Cu addition afforded compound 69, which provided target compound 70 in few reaction sequences.

The Grignard reagents have been also used in the natural products synthesis as like organocopper reagents. The allyl magnesium reagent obtained from the allylic alcohol 71 by deprotonation/transmetallation was reacted with $N$-sulfonyl aziridine 72 afforded compound 73. Compound 73 was cyclised to the advanced intermediate piperidine 74, which eventually provided nuphar alkaloids 75, 76 and 77 (Scheme 28).21

![Scheme 27 (+)-PS-5 70](image)

**Scheme 28 Nuphar alkaloids**
Nitrogen-centered nucleophiles

Amines and azides are representative examples of nitrogen nucleophiles for the aziridine ring opening. They have attracted synthetic community for preparation of diamine-containing compounds due to synthetic importance and their utility in pharmaceutical. The limited number of compounds bearing the diamine functionality as structural unit, made it less applicable.

Shiba and co-workers described the synthesis of L-epicapreomycin-HBr 80 from the enantiopure trans-N-tosylaziridine-2-carboxylate 78 (Scheme 29). Aziridine 78 was underwent S_N2 attack of ammonia to provide diamine 79 and followed by few steps derived L-epicapreomycin-HBr 80.  

![Scheme 29 L-epi-Capreomycin-HBr 80](image)

The sodium pipecolinic acid 82 was also found as nucleophile, which was efficiently reacted with mono-substituted enantiopure N-tosyl aziridine 81 to furnish piperidine adduct 83. The adduct 83 was transformed to verruculotoxin 84 in few steps described in Scheme 30.

![Scheme 30 Verruculotoxin 84](image)

Yoshimitsu, Ino and Tanaka disclosed the synthesis of (-)-agelastatin A 87, which involved sodium azide as nucleophile for aziridine opening. The sodium azide selectively opened the aziridine ring of the 85 to afford azide 86, followed by via reaction sequences was transformed to (-)-agelastatin A 87 (Scheme 31).
Oxygen-centered nucleophiles

It provides the method for direct access to amino alcohol unit that is ubiquitous in nature on oxygen nucleophilic aziridine ring opening.

The aziridine ring opening by oxygen nucleophiles are less active reaction compared to with epoxides. It requires aziridines to be activated by electron withdrawing groups as N-substituent or Bronsted or Lewis acids.

Generally water and strong Bronsted acids e.g. TsOH and TFA are used as nucleophiles for aziridine activation. Olofsson and Somfai synthesized D-erythro-sphingosine 91 in enantiomerically pure form. Aziridine 89 was prepared from the enantiopure 1, 2-amino alcohol 88, followed by TFA mediated aziridine opening with water as nucleophile furnished compound 90. Compound 90 was converted to target D-erythro-sphingosine 91 in few steps (Scheme 32).

Scheme 31 (S)-Agelastatin A 87

Scheme 32 D-erythro-Sphingosine 91

Trost and Dong reported the synthesis of the non-natural (+)-agelastatin A 95 utilizing regio- and stereoselective hydrolytic ring opening of enantiopure aziridine 92 to afford alcohol 93, which was oxidized to ketone 94. Ketone 94 was obtained in one step from
the aziridine 92 in DMSO/indium triflate and followed by few reaction steps provided agelastatin A 95 (Scheme 33).\(^{26}\)

![Scheme 33 (+)-Agelastatin A 95](image)

**Halogen nucleophiles**

The uses of halogen as nucleophiles in natural product synthesis have been reported recently. Hydrogen bromide has used to generate vicinal bromo-amine from the aziridine ring opening.

Maycock and co-workers reported synthesis of (+)-bromoxone 98, where they used 0.1 M HBr/MeOH for aziridine opening 96 in presence of epoxide unit to afford vinyl bromide 97. The vinyl bromide 97 on TBS deprotection furnished target compound 98 as described in Scheme 34.\(^{27}\)

![Scheme 34 (+)-Bromoxone 98](image)

**Reductions**

![Scheme 35 L-Ristsosamine methyl glycoside 101](image)

Catalyst mediated reductive opening of aziridines provide high regioselective products. Mendlik et al reported palladium charcoal catalysed C-N bond cleavage of aziridine 99 to
obtain carbamate 100, which on hydrolysis provided L-ristosamine methyl glycoside 101 (Scheme 35).  

**Cycloaddition reactions and rearrangements**

Aziridines have been used as partner for cycloaddition reaction to obtain cyclic adducts in organic synthesis.

**Aziridines in [3+2] cycloaddition**

Aziridinyl esters are used as precursors of azomethine ylide, which react with olefin moiety in a [3+2] cycloaddition reaction to provide cyclic products and this reaction has been used as transformation for the synthesis of acromellic acid A 104 by Takano and co-workers (Scheme 36). The aziridine 102 was underwent thermal conditions afforded cycloadduct 103, which was converted to acromellic acid A 104 following some reaction steps.  

**Aziridines in [2+3]-Wittig rearrangements**

Somfai and co-workers demonstrated the application of the [2, 3]-Wittig rearrangement in enantioselective synthesis of indolizidine 299D 107. Aziridine 105 was treated with LDA and the generated enolate underwent [2, 3]-Wittig rearrangement to furnish
piperidine derivative 106. Compound 106 was converted into target compound 107 using few reaction conditions (Scheme 37).\(^\text{30}\)

**Aziridines in iodide-mediated rearrangement**

This is another method to rearrange the vinyl aziridines into pyrrolines by \(S_N2\) ring opening of vinyl aziridine with iodine. First time this method was recognized by Hudlicky’s and co-workers to accomplish the synthesis of \textit{rac}-suoinidine 110. The aziridine 108 was treated with TMSI to undergo \(S_N2\)’ ring opening which afforded \textit{rac}-suoinidine 110, through intermediate 109 (Scheme 38).\(^\text{31}\)

![Scheme 38 rac-Suoinidine 110](image)

**Aziridines in Miscellaneous rearrangements**

The Lewis acid mediated aziridine rearrangement provide the retention of configuration e.g. \(N\)-acyl aziridine rearranged to oxazolidin-2-one. Tomasini synthesized \textit{threo} phenylserine 113 from \(N\)-acyl aziridine 111 with retention of the configuration is outlined in Scheme 39.\(^\text{32}\)

![Scheme 39 threo-Phenylserine 113](image)

Trost and Fandrick reported total synthesis of (+)-pseudodistomine D 116. They have used palladium (0) catalyst for the insertion of isocyanate to aziridine 114 in the presence of chiral ligand 115 provided enantioselective imidazolidin-2-one 116. Urea 116 was converted to (+)-pseudodistomine D 117 in few steps (Scheme 40).\(^\text{33}\)
Scheme 40 (±)-Pseudodistomine 117
2.1.4 References


Section 2

Lactone based strategy towards Tamiflu and shortest synthesis of major building block of mitomycinoids
2.2.1 Present work

2.2.1.1 Objective

A modern synthetic design demands better yielding sequences coupled with mild reaction conditions, high stereoselectivity as well as versatile template that could be used as platform to achieve the neuraminidase inhibitor from readily available starting materials. With these objectives, in mind an efficient route for tamiflu 1 from D-mannitol as a starting material, which is available in enantiopure form, was undertaken and the results are discussed in this section.

2.2.1.2 Retrosynthetic analysis

It was envisioned that the oseltamivir phosphate (Tamiflu) 1 can be accessed from the key intermediate 2, which could be obtained from the aziridine lactone 3 using appropriate chemical transformations. The aziridine lactone 3 can be derived from the 2-carboxylate aziridine 4, which could be derived from the cheap and abundant chiral source D-mannitol as shown in the Scheme 1.

\[\text{AchN}_2 \text{NH}_2 \cdot \text{H}_3\text{PO}_4 \rightarrow \text{C}_{\text{H}} \text{N} \rightarrow \text{O} \rightarrow \text{C}_{\text{H}} \text{N} \rightarrow \text{O} \rightarrow \text{D-Mannitol}\]

\[\text{Tamiflu 1} \quad \Rightarrow \quad 2 \quad \Rightarrow \quad 3\]

\[\text{Scheme 1 Retrosynthetic analysis for Tamiflu 1}\]

2.2.1.3 Results and discussion

The synthesis began with 2-carboxylate aziridine 4, which can be easily obtained from the D-mannitol using reported procedure.\(^1\) The acetonide deprotection of 4 was carried out using TMSOTf in DCM at 0 °C to afford dihydroxy ester 5 in 90% yield.\(^2\) The IR
spectrum showed bands at 1736, 3588 and 3369 cm\(^{-1}\) for ester and primary and secondary hydroxy functionalities respectively. The \(^1\)H NMR spectrum showed a multiplet at \(\delta\) 3.73-3.63 (m, 1 H) ppm corresponding to one proton of –CHOH while peak at \(\delta\) 3.44-3.28 (m, 1 H) and 3.23-3.06 (m, 1 H) ppm were assigned to two protons of -CH\(_2\)OH group. Also the peaks at \(\delta\) 4.23 (q, \(J = 8\) Hz, 2 H) and 1.30 (t, \(J = 8\) Hz, 3 H) ppm were observed in \(^1\)H NMR spectrum for ethyl ester functionality. The \(^{13}\)C NMR spectrum showed peaks at \(\delta\) 77.4 and 64.7 ppm which were related to carbons of -CHOH and -CH\(_2\)OH groups and peaks in \(^{13}\)C DEPT NMR spectrum at \(\delta\) 61.3 and 14.1 ppm were due to -CH\(_2\) and -CH\(_3\) carbons of ethyl ester functionality. The HRMS spectrum showed the peak at 364.1516 (M+Na)\(^+\) which confirmed the molecular formula C\(_{20}\)H\(_{23}\)NO\(_4\) of dihydroxy aziridine 7.

The dihydroxy aziridine 7 was stirred with K\(_2\)CO\(_3\) in DCM at room temperature for 3 h to furnish the five membered lactone 3 in 85% yield. The IR spectrum of lactone 3 showed the bands at 1773 cm\(^{-1}\) and 3445 cm\(^{-1}\) indicating the presence of the five membered lactone and hydroxy functionality respectively. The \(^1\)H NMR spectrum showed a multiplet at \(\delta\) 4.48-4.46 (m, 1H) ppm for –CHOH proton as well as peaks at \(\delta\) 3.89-3.79 (m, 1H) and 3.67-3.64 (m, 1H) ppm corresponding to the two protons of –CH\(_2\)OH group. The \(^{13}\)C peaks at \(\delta\) 172.3 and 81.1 ppm corresponding with the carbonyl carbon of lactone and carbon of –CHOH group. The \(^{13}\)C DEPT NMR spectrum showed the peak at \(\delta\) 62.2
Chapter 2 Section 2

ppm for the methylene carbon of –CH$_2$OH group. The HRMS peak was observed at 318.1100 (M+Na)$^+$ confirmed the molecular formula C$_{18}$H$_{17}$NO$_3$ of the lactone 3.

The lactone aziridine 3 and its analogous are very important motifs for the pharmaceutical activities and are also used as magical precursors for the synthesis of the bioactive compounds. The lactone aziridine skeletons are ready for desired substitutions using proper chemical tools.$^3$

\[ \text{Scheme 3 Attempt towards synthesis of tamiflu 1 from lactone 3} \]

Further lactone 3 was treated with tosyl chloride, TEA and cat. DMAP in dry DCM at 0 °C to room temperature to furnish tosyl derivative 8 in 87%. The IR spectrum of tosylate 8 showed the disappearance of band at 3445 cm$^{-1}$ indicating the formation of tosyl derivative. The peaks in $^1$H NMR spectrum at $\delta$ 4.28 - 4.05 (m, 2 H) ppm corresponding to methylene protons of –CH$_2$OTs group and peak at $\delta$ 2.46 (s, 3 H) ppm related to the methyl protons of tosyl functionality. The $^{13}$C NMR spectrum showed the peaks at $\delta$ 170.2 and 21.7 ppm corresponding to the lactone carbonyl carbon and methyl group of tosyl functionality respectively. In $^{13}$C NMR DEPT spectrum peak at $\delta$ 68.0 ppm was
assigned to methylene carbon of \(-\text{CH}_2\text{OTs}\) group. The HRMS spectrum showed the peak at 472.1188 (M+Na)\(^+\) which confirmed the molecular formula \(\text{C}_{25}\text{H}_{23}\text{NO}_5\text{S}\) for tosyl derivative.

2.2.1.5 Shortest synthesis of major building block of mitomycins

There are several classes of aziridine-containing natural products, amongst which mitosane and mitosene compounds are best known for their inbuilt powerful alkylating ability.\(^4\) They are isolated from soil extracts of \(\text{Streptomyces lavendulae}\) and show both antitumor and antibacterial activity. Mitomycin C is the most potent of this family and is registered antineoplastic drug supplied by Bristol-Myers Squibb Co.

It can be seen that mitomycins are actually naturally occurring pro-drugs that must be activated in vivo. These extraordinary antitumor activities along with mitomycinoid’s unique structural features have attracted the interest of synthetic community and as a result several approaches and few total syntheses have been published. We have been deeply fascinated by those synthetic programs involving a highly functionalized four-carbon building block.

Aziridine was introduced as the smallest nitrogen containing three membered heterocycle in 1888 by Gabriel.\(^5\) Aziridines are highly useful intermediates for the preparation of nitrogen containing compounds. Their value is reflected by the numerous studies that have been conducted to optimize their preparation and to enhance the scope of their applications in the total synthesis of natural and/or biologically active products.\(^6\) Among the large varieties of substituted aziridines described, aziridine 2-carboxylate holds a prominent position as a synthon for the synthesis of nitrogen containing bioactive molecules.\(^7\)

Thus \(\text{cis-aziridine-2-carboxylate}\ 4\) was chosen as the key synthon for synthesis of mesyl aziridine\(^8\) from D-mannitol as chiral raw material.

2.2.1.6 Results and discussion

The synthesis was started from the \(\text{cis-2-carboxylate aziridine}\ 4\), which was converted into the diol 7 which is already discussed in Scheme 2. The diol 7 was subjected for the
NaIO₄ cleavage in DCM/NaHCO₃ to afford crude aldehyde. The crude aldehyde without purification was subjected for chemoselective reduction using NaBH₄ in MeOH to obtain alcohol 12 in 78% yield over two steps. The IR spectrum of hydroxy compound 12 showed the bands at 3439 and 1733 cm⁻¹ corresponding to hydroxy and ester functionality. The ¹H NMR spectrum showed the peaks at δ 4.20 (q, J = 8 Hz, 2 H) and 1.28 (t, J = 8 Hz, 3 H) ppm for the five protons of ethyl ester while peak at δ 3.70 (d, J = 6 Hz, 2 H) ppm related with two protons of –CH₂OH group. The ¹³C NMR spectrum showed the peak at δ 169.1 ppm corresponding to the ester carbonyl carbon and ¹³C DEPT NMR spectrum showed the peaks at δ 61.1 and 60.2 ppm for the methylene carbons of –CH₂OH and ethyl ester group while peak at δ 14.2 ppm corresponded to methyl carbon of ethyl ester. The LCMS spectrum showed the peak at 334.18 (M+Na)⁺ confirming the molecular formula C₁₉H₂₁NO₃ of the hydroxy compound 12.

Further the hydroxy compound 12 was subjected to mesylation using TEA as base, mesyl chloride and cat. DMAP in dry DCM to afford mesylate 13 in 82% yield. The IR spectrum of mesylate 13 showed the peak at 1734 cm⁻¹ indicating the ester functionality while disappearance of 3439 cm⁻¹ band of hydroxy group indicated the formation of

Scheme 4 Synthesis of mesylate 13
mesyl derivative. The $^1$H NMR showed the peaks at $\delta$ 4.39 - 4.34 (m, 2 H) related with methylene protons of –CH$_2$OMs while $\delta$ 4.20 (q, $J$ = 7.2 Hz, 2 H) and 1.27 (t, $J$ = 8 Hz, 3 H) ppm peaks revealed the presence of methyl and methylene protons of ethyl ester respectively. The peak at $\delta$ 2.76 (s, 3 H) ppm in $^1$H NMR spectrum was assigned for the methyl protons of mesyl functionality. The $^{13}$C NMR spectrum showed the peak at $\delta$ 168.3 ppm for the ester carbonyl and DEPT $^{13}$C NMR showed the peaks at $\delta$ 67.2 and 61.1 ppm assigned for methylene carbon of –CH$_2$OMs and ethyl ester respectively while peak at $\delta$ 37.12 ppm indicated the methyl carbon of mesyl functionality. The peak observed at 412.09 (M+Na)$^+$ in MS (ESI) spectrum confirmed the molecular formula C$_{20}$H$_{23}$NO$_5$S of the mesylate 13.

2.2.2 Conclusion

In conclusion, the successful synthesis of five membered lactone aziridine as key intermediate has been achieved. The lactone can be explored for the tamiflu using suitable chemical transformations. The synthesis of major building block of the mitomycinoid alkaloids has been accomplished in very short and robust way in high yield. The synthesis involved the simple reaction conditions, inexpensive and abundant chiral D-mannitol as raw material.
2.2.3 Experimental Section

**Ethyl (2R, 3S)-1-benzhydryl-3-((S)-1,2-dihydroxyethyl)aziridine-2-carboxylate (7)**

To a stirred, ice-cold solution of the aziridine acetonide 4 (15 gm, 39.37 mmol) in anhydrous DCM (150 mL) under nitrogen atmosphere, was added TMSOTf (8.1 mL, 51.18 mmol) dropwise at 0 °C. The resulting solution was stirred at the same temperature for 3 h and the reaction mixture was quenched with solid NaHCO₃. Water was added and the compound was extracted with DCM (3 X 80 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 30% ethyl acetate in pet. ether as an eluent to afford compound 7 (12.08 gm, 90%) as a white solid.

*Rf*: 0.3 (Pet. ether: ethyl acetate, 40:60).

**MF**: C₂₀H₂₃NO₄, **MW**: 341.41.

**Yield**: 90%.

**[α]₂⁵ᵥ**: +101.6 (c 1.8, CHCl₃).

**IR** (CHCl₃, cm⁻¹): vmax 3588, 3369, 2927, 1736, 1603, 1454, 1371, 1193.

**MP**: 122-124 °C.

**¹H NMR (200 MHz, CDCl₃ + CCl₄)**: δ 7.52 - 7.18 (m, 10H), 4.23 (q, J = 8 Hz, 2H), 3.74 (s, 1H), 3.73 - 3.63 (m, 1H), 3.44 - 3.28 (m, 1 H), 3.23 - 3.06 (m, 1H), 2.64 - 2.52 (m, 1H), 2.44 (d, J = 8 Hz, 1H), 2.21 (t, J = 8 Hz, 1H), 1.30 (t, J = 8 Hz, 3H).

**¹³C NMR (50 MHz, CDCl₃ + CCl₄)**: δ 169.5, 142.1, 141.7, 128.5, 128.3, 127.9, 126.9, 77.3, 64.6, 61.1, 46.8, 42.5, 14.0.
Chapter 2 Section 2

HRMS: Observed- 364.1516 (M+Na)⁺, Calculated-364.1519.

(1R, 4S, 5S)-6-Benzhydryl-4-(hydroxymethyl)-3-oxa-6-azabicyclo-[3.1.0]-hexan-2-one (3)

The diol 7 (4 gm, 11.73 mmol) was dissolved in DCM (40 mL) and K$_3$CO$_3$ (3.2 gm, 23.44 mmol) added at room temperature. Further, the reaction mixture was stirred for 3-4 h and progress of reaction was monitored with TLC. The reaction mixture was filtered through simple filter paper, washed with DCM (3 X 30 mL) and filtrate was concentrated under reduced pressure. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography over silica gel, eluting with 30% ethyl acetate in pet. ether as an eluent to afford compound 3 (2.94 gm, 85%) as colourless syrup.

$R_f$: 0.2 (Pet. ether: ethyl acetate, 40:60).

MF: C$_{18}$H$_{17}$NO$_3$, MW: 295.34.

Yield: 85%.

$[\alpha]^{25}_{D}$: +42.00 (c 1.0, CHCl$_3$).

MP : 112-114 °C.

IR (CHCl$_3$, cm$^{-1}$): v max 3445, 2928, 2850, 1773, 1580, 1150, 1080, 833.

$^1$H NMR (400 MHz, CDCl$_3$ + CCl$_4$): δ 7.46 - 7.22 (m, 10H), 4.47 (t, $J = 3.2$ Hz, 1H), 3.91 - 3.78 (m, 1H), 3.75 (s, 1H), 3.65 (dd, $J = 2.7, 12.5$ Hz, 1H), 3.02 (d, $J = 4.4$ Hz, 1H), 2.94 (bs, 1H), 2.80 (d, $J = 4.4$ Hz, 1H).

$^{13}$C NMR (50 MHz, CDCl$_3$ + CCl$_4$): δ 172.39, 142.0, 141.5, 128.8, 128.6, 127.2, 126.8, 81.12, 74.5, 62.2, 44.3, 40.7.

HRMS: Observed- 318.1100 (M+Na)⁺, Calculated-318.1101.
(1S, 2S, 5R)-6-Benzhydryl-4-oxo-3-oxa-6-azabicyclo-[3.1.0]-hexan-2-yl)-methyl-4-methyl benzenesulphonate (8)

To a stirred solution of lactone 3 (1.5 gm, 5.08 mmol) in dry DCM at 0 °C was added TEA (2.1 mL, 15.25 mmol), tosyl chloride (1.44 gm, 7.62 mmol) and DMAP (62 mg, 0.5 mmol). Reaction mixture was stirred for 2 h at room temperature and completion of the reaction was monitored with TLC. Water was added to the reaction mixture and the compound was extracted with DCM (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound 8 (1.94 gm, 87%) as a colourless syrup.

**Rf:** 0.6 (Pet. ether: ethyl acetate, 75:25).

**MF:** C_{25}H_{23}NO_{5}S, **MW:** 449.52.

**Yield:** 87%.

[α]_{D}^{25} : +36.36 (c 1.1, CHCl_{3}).

**MP:** 146-148 °C.

**IR** (CHCl_{3}, cm^{-1}): v_{max} 3340, 2928, 2850, 1764, 1580, 1150, 1080.

**{^1}H NMR** (200 MHz, CDCl_{3} + CCl_{4}): δ 7.75 (d, J = 8.3 Hz, 2H), 7.43 - 7.22 (m, 12H), 4.55 (t, J = 3.4 Hz, 1H), 4.28 - 4.05 (m, 2H), 3.76 (s, 1H), 3.08 (d, J = 4.3 Hz, 1H), 2.84 (d, J = 4.3 Hz, 1H), 2.46 (s, 3H).

**{^{13}}C NMR** (50 MHz, CDCl_{3} + CCl_{4}): δ 170.2, 141.7, 141.2, 130.0, 128.7, 128.0, 127.1, 126.8, 74.7, 68.0, 43.9, 40.2, 21.7.

**HRMS:** Observed- 472.1188 (M+Na)^{+}, calculated-472.1189.

**Ethyl (2R, 3S)-1-benzhydryl-3-(hydroxymethyl)aziridine-2-carboxylate (12)**
To a solution of diol 7 (2 gm, 5.86 mmol) in DCM (20 mL) was added solid NaHCO₃ (1.5 gm, 17.58 mmol) and sodium metaperiodate (2.51 gm, 11.73 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3-4 h and completion of reaction was monitored by TLC. The reaction mass was quenched using ethylene glycol (0.01 mL), extracted with DCM (3 X 20 mL), washed with brine, dried over anhydrous sodium sulphate and filtered. The combined organic layer was concentrated under reduced pressure to afford crude aldehyde which was used as such for next reaction.

To a solution of crude aldehyde (1.9 gm, 6.11 mmol) obtained above in MeOH (15 mL) was added sodium borohydride (0.24 gm, 7.37 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature then quenched with saturated aq. solution of ammonium chloride (10 mL). The solvent was evaporated under reduced pressure and crude residue obtained was extracted with ethyl acetate (3 X 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated to give a crude residue which was purified by column chromatography over silica gel, eluting with 30% ethyl acetate in pet ether as an eluent to afford compound 12 (1.42 gm, 78% over two steps) as a colourless syrup.


*MF*: C₁₉H₂₁NO₃, *MW*: 311.38.

*Yield*: 78% (over two steps).

*[^{25}D]* : +63.80 (c 0.7, CHCl₃).

*IR* (CHCl₃, cm⁻¹): νmax 3439, 1733, 1599, 1454, 1196.

*¹H NMR* (200 MHz, CDCl₃ + CCl₄): δ 7.50 - 7.18 (m, 10H), 4.20 (q, *J* = 8 Hz, 2H), 3.79 (s, 1H), 3.70 (d, *J* = 6 Hz, 1H), 2.44 - 2.27 (m, 1H), 1.28 (t, *J* = 8 Hz, 3H).
**Ethyl (2R, 3S)-1-benzhydryl-3-(((methylsulfonyl)oxy)methyl)aziridine-2-carboxylate (13)**

To a stirred solution of alcohol 12 (1 gm, 3.21 mmol) in dry DCM (10 ml) at 0 °C was added TEA (1.3 mL, 9.64 mmol), mesyl chloride (0.4 mL, 4.82 mmol) and DMAP cat. (125 gm, 0.32 mmol). Reaction mixture was stirred for 3 h at room temperature and completion of the reaction was monitored with TLC. Water was added to the reaction mixture and the compound was extracted with DCM (3 X 20 ml). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet. ether as an eluent to afford compound 13 (1.02 gm, 82%) as a colourless syrup.

**Rf**: 0.5 (Pet.ether: ethyl acetate, 65:35).

**MF**: C\(_{20}\)H\(_{23}\)NO\(_5\)S, **MW**: 389.47.

**Yield**: 82% (over two steps).

\([\alpha]\)\(_{25}^D\) : +42.00 (c 0.2, CHCl\(_3\)).

**MP**: 77-79 °C.

**IR** (CHCl\(_3\), cm\(^{-1}\)): v\(_{\text{max}}\) 3027, 1734, 1492, 1360, 1201.

\(^1\)H NMR (200 MHz, CDCl\(_3\) + CCl\(_4\)): \(\delta\) 7.50 - 7.19 (m, 10H), 4.39 - 4.34 (m, 2H), 4.20 (q, \(J = 7.2\) Hz, 2H), 3.82 (s, 1H), 2.76 (s, 3H), 2.56 - 2.39 (m, 2H), 1.27 (t, \(J = 8\) Hz, 3H).
$^{13}$C NMR (50 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 168.3, 141.9, 141.5, 128.5, 127.5, 126.9, 67.1, 61.32, 43.1, 41.9, 37.06, 14.1.

2.2.4 Spectral Data

$^1$H NMR spectrum of diol 7 (200 MHz, CDCl$_3$ + CCl$_4$)

$^{13}$C NMR spectrum of diol 7 (50 MHz, CDCl$_3$ + CCl$_4$)
DEPT spectrum of diol 7 (50MHz, CDCl₃ + CCl₄)

1H NMR spectrum of lactone 3 (400 MHz, CDCl₃ + CCl₄)
**Chapter 2 Section 2**

**$^{13}$C NMR spectrum of lactone 3 (50 MHz, CDCl$_3$ + CCl$_4$)**

**DEPT spectrum of lactone 3 (50 MHz, CDCl$_3$ + CCl$_4$)**
Chapter 2 Section 2

$^1$H NMR spectrum of tosylate 8 (200 MHz, CDCl$_3$ + CCl$_4$)

$^{13}$C NMR spectrum of tosylate 8 (50 MHz, CDCl$_3$ + CCl$_4$)
DEPT spectrum of tosylate 8 (50MHz, CDCl₃ + CCl₄)

FRI1AV2#066 TFLP-LACTONE TOSYL DEPT.001.001.1R.ESP

1H NMR spectrum of aziridine 12 (200 MHz, CDCl₃ + CCl₄)

MON5AV2#090 TFLP-HYDROXY ESTER 1H.001.001.1R.esp
Chapter 2 Section 2

$^{13}$C NMR spectrum of aziridine 12 (125 MHz, CDCl$_3$ + CCl$_4$)

DEPT spectrum of aziridine 12 (125MHz, CDCl$_3$ + CCl$_4$)


**Chapter 2 Section 2**

**$^1$H NMR spectrum of mesylate 13 (200 MHz, CDCl$_3$ + CCl$_4$)**

![H NMR spectrum of mesylate 13](image)

**$^{13}$C NMR spectrum of mesylate 13 (50 MHz, CDCl$_3$ + CCl$_4$)**

![C NMR spectrum of mesylate 13](image)
DEPT spectrum of mesylate 13 (50 MHz, CDCl$_3$ + CCl$_4$)

Chemical Shift (ppm)

128.64
127.79
127.65
127.45
126.96
67.24
61.41
43.20
42.01
37.12
14.19
2.2.5 References


Section 3

Formal synthesis of Tamiflu using cis-aziridine as the key precursor and RCM
2.3.1 Present work

2.3.1.1 Objective

The literature study revealed that there is always considerable mortality and morbidity rates due to influenza infection and it continues to be a threat to the health of human as well as other animals and birds. Last decade’s drug designing and development studies on the neuraminidase inhibitors led to discovery of Oseltamivir phosphate (Tamiflu®) and Zanamivir (Relenza®) as effective drugs. Tamiflu is widely used for the treatment and prevention of both human influenza (H1N1) as well as avian influenza (H5N1) infections. It is available as a capsule or powder for liquid suspension with good bioavailability, which is well absorbed by gastrointestinal track and hydrolyzed to its carboxylate active form.

Aziridine has been extensively explored for the construction of stereogenic centers containing nitrogen compounds. The literature reports revealed that aziridines are less explored for the synthesis for oseltamivir phosphate. There is only one report of synthesis of tamiflu, which involved the chiral aziridine as chiral building block. Enantiomerically pure aziridines have been considered to be prominent precursors in the synthesis of natural and unnatural biologically active compounds due to their inherent ability to undergo regio and chemoselective nucleophilic ring opening reactions as well as cycloaddition pathways.

Our group is engaged in the synthesis of the natural products from the aziridine chiral synthon and development of synthetic methodologies based on the aziridine chemistry. The present work was undertaken in the view of the exploration of the aziridine chemistry for the synthesis of the neuraminidase inhibitor drug. The reported chiral pool approaches for tamiflu are associated with low yields and lengthy routes or involve usage of potentially hazardous chemicals such as azides. In this context, there is a need of convenient and efficient route for its enantiopure synthesis.

In the present section an alternative approach based on chiral pool strategy is described. The current novel route for oseltamivir phosphate (Tamiflu) synthesis involved the use of aziridine-2-carboxylate as chiral synthon derived from D-mannitol which is abundant and inexpensive starting material.
2.3.1.2 Retrosynthetic analysis

Owing to their ring strain, aziridines are very prone to nucleophilic ring opening reactions with various nucleophiles with predictable chemo and regio selectivity to trans-diamine compounds.

The aziridine ring can be used to access the diamine as per the existing stereochemistry in tamiflu by proper chemical tools. Taking account of this, as shown in Scheme 1, it was thought that trans-vicinal diamine skeleton of the tamiflu 1 can be obtained from aziridine 2, a key precursor, which could be obtained by intramolecular RCM of bis olefin 3. Compound 3 in turn could be obtained from the aziridine 4 by DIBAL-H reduction, one carbon Wittig olefination, acetonide deprotection, diol cleavage and Barbier addition. The aziridine 4 is the key synthon readily available from D-mannitol (Scheme 1).

![Scheme 1 Retrosynthetic analysis for tamiflu 1](image)

2.3.1.3 Results and discussion

The present section describes the total synthesis of oseltamivir phosphate 1 (Scheme 2). The cis-aziridine ester 4 can be synthesized from D-mannitol diacetonide and was converted to 6 in two steps using the reported procedure. The cis-aziridine ester 4 was subjected to the DIBAL-H reduction at -78 °C in DCM to furnish the aldehyde 5. The crude aldehyde without purification was subjected for the one carbon homologation using
the Wittig conditions\(^6\) wherein to the one carbon Wittig salt dissolved in dry toluene was added potassium \(t\)-butoxide at room temperature and after 1 h compound 5 in dry THF was added to afford the olefin 6. The band in IR spectrum at 1636 cm\(^{-1}\) indicates the presence of double bond functionality. The \(^1\)H NMR spectrum showed the peaks at \(\delta\) 7.42-7.12 (m, 10 H) for aromatic protons while peaks at \(\delta\) 5.91-5.74 (m, 1 H) and 5.43-5.22 (m, 2 H) ppm were assigned to three protons of terminal olefin. The \(^{13}\)C NMR spectrum showed the peaks at \(\delta\) 26.7 and 25.3 ppm for two methyl carbons of acetonide protecting group and \(^{13}\)C DEPT NMR spectrum showed the peak at \(\delta\) 118.5 for the methylene of terminal olefin. The peak observed at 336.1957 (M+H)+ in HRMS spectrum confirmed the molecular formula C\(_{22}\)H\(_{25}\)NO\(_2\) of olefin compound 6.

![Scheme 2 Synthesis of RCM precursor 3](image)

The next task was to obtain the diene 3. Accordingly, the olefin 6 was treated with TMSOTf in DCM at 0 \(^\circ\)C to furnish the diol 7 in 85% yield\(^7\). The strong bands at 3640, 3451 cm\(^{-1}\) in IR spectrum indicated the presence of two hydroxy groups and 1638 cm\(^{-1}\) for olefin functionality. The disappearance of the peaks for two methyl groups at \(\delta\) 1.31
(s, 3 H) and 1.23 (s, 3 H) ppm in $^1$H NMR supported the formation of diol 7. The $^{13}$C NMR spectrum showed the peaks at $\delta$ 118.8 and 64.9 ppm for the methylene carbon of terminal olefin and –CH$_2$OH group. The HRMS spectrum showed the peak at 296.1643 (M+H)$^+$ which confirmed the molecular formula C$_{19}$H$_{21}$NO$_2$ of the dihydroxy olefin 7.

The diol 7 was treated with NaIO$_4$ and NaHCO$_3$ in DCM at room temperature to afford aldehyde 8, which was directly subjected for the addition of ethyl 2-(bromomethyl)-acrylate 9 in presence of Zn powder in THF/NH$_4$Cl to furnish the diastereomers 3a:3 in ratio 3:2 with 92% yield (Scheme 2). The isomer 3a was inverted to desired isomer 3 using Mitsunobu reaction conditions, $p$-nitrobenzoic acid and DEAD in toluene at room temperature for 1 h, to provide ester which on basic hydrolysis with NaOEt/EtOH gave 3 in 69% over two steps.

The IR spectrum showed the bands at 3451 and 1638 cm$^{-1}$ indicating the presence of the hydroxy and olefin functionalities. The peaks in $^1$H NMR spectrum at $\delta$ 6.16 (d, $J$ = 1 Hz, 1 H) and 5.49 (s, 1 H) ppm were assigned to two protons of unsaturated ester while the peaks at $\delta$ 4.18 (q, $J$ = 8 Hz, 2 H) and 1.30 (t, $J$ = 8 Hz, 3 H) ppm corresponded to the five protons of ethyl ester. The peak at $\delta$ 166.7 in $^{13}$C NMR spectrum indicated carbonyl carbon of ester and DEPT NMR spectrum showed the peaks at $\delta$ 127.1 and 118.8 ppm for the two methylene carbons of unsaturated ester and terminal olefin respectively, while the peaks $\delta$ 60.5 and 14.2 ppm related to methylene and methyl carbons of ethyl ester. The peak observed at 378.2065 (M+H)$^+$ in HRMS spectrum confirmed the molecular formula C$_{24}$H$_{27}$NO$_3$ of the diene 3.

Further the diene 3 on RCM using the Grubbs’ II gen catalyst in presence of Ti(iPrO)$_4$ under reflux in dry DCM furnished the cyclohexene aziridine 10 in 74% yield. The IR spectrum showed the bands at 1710 and 1637 cm$^{-1}$ for carbonyl of ester functionality. The $^1$H NMR spectrum exhibited peaks at $\delta$ 7.44-7.20 (m, 11H) ppm for the ten aromatic protons and one $\beta$-proton of unsaturated ester. The $^{13}$C NMR spectrum showed the peak at $\delta$ 166.5 ppm for carbonyl carbon of ester and peak at 136.4 ppm for carbon of unsaturated ester. The disappearance of the peaks at $\delta$ 127.1 and 118.8 ppm in $^{13}$C DEPT spectrum confirmed the formation of cyclic compound 10. The HRMS spectrum showed the peak at 350.1748 (M+H)$^+$ which confirmed the molecular formula C$_{22}$H$_{23}$NO$_3$ of cyclohexene aziridine 10.
The next step of mesylation of hydroxy aziridine 10 was carried out using mesyl chloride, TEA and cat. DMAP in DCM at 0 °C to afford the mesylate derivative 11 in 79% yield. The IR bands at 1709 and 1645 cm\(^{-1}\) indicated presence of ester and double bond functionality. \(^1\)H NMR spectrum showed the peak at \(\delta\) 2.94 (s, 3H) ppm for the methyl protons of mesyl group. The \(^{13}\)C NMR spectrum exhibited peak at \(\delta\) 165.9 ppm corresponding to carbonyl carbon of ester while peaks at \(\delta\) 139.3, 128.7, 128.5, 127.6, 127.3, 127.1 and 126.9 ppm for aromatic carbons. The \(^{13}\)C DEPT NMR spectrum showed the peak at \(\delta\) 38.8 for the methyl carbon of mesyl functionality. The peak at 428.1524 (M+H)\(^+\) in HRMS spectrum corresponded to the molecular formula C\(_{23}\)H\(_{25}\)NO\(_5\)S of the mesylate 11. The characterization data of mesyl 11 was in full agreement with the data reported by Ishiwata and coworkers.\(^{10}\)

Further, the mesylate 11 was treated with 3-pentanol in DCM at room temperature in presence of BF\(_3\).Et\(_2\)O followed by addition of TEA after 3 h to afford the reaziridination product 2 in 80% yield. The IR spectrum of 2 showed the band at 1712 cm\(^{-1}\) for the ester carbonyl. \(^1\)H NMR spectrum showed the peak at \(\delta\) 6.78-6.76 (m, 1H) ppm for \(\beta\)-proton of unsaturated ester while peaks at \(\delta\) 1.46-1.32 (m, 4 H), and 0.86-0.80 (m, 6 H) ppm were assigned to the four methylene protons and six protons of two methyl groups respectively of pentyl group. The peaks at \(\delta\) 166.9 and 134.2 ppm in \(^{13}\)C NMR spectrum were present for the carbonyl and olefinic –CH carbon and \(^{13}\)C DEPT NMR spectrum showed the peaks at \(\delta\) 26.5 and 24.3 ppm for two methylene carbons while peaks at \(\delta\) 9.8 and 9.6
ppm corresponding to methyl carbons supported the iso-pentyl group. The peak observed at 420.2535 \((M+H)^+\) in HRMS spectrum confirmed the molecular formula \(C_{27}H_{33}NO_3\) of the aziridine 2. The spectral data of aziridine 2 was in agreement with the data reported by Ishiwata and coworkers.

2.3.2 Conclusion

In conclusion, a very short and practical formal synthesis of the tamiflu has been accomplished starting from the economical and abundant chiral material D-mannitol. Cis-aziridine as a key building block is utilized in the synthesis to fix the desired stereocenter of the neuraminidase inhibitor drug oseltamivir phosphate. In the strategy, we had advantages of the Wittig olefination and Barbier reaction for acyclic diene precursor for RCM, which was converted to cyclohexene core of tamiflu by means of well-organized ring closing metathesis (RCM). The undesired stereoisomer of Barbier reaction was converted into desired isomer using Mitsunobu conditions. The synthetic route is concise, uses inexpensive reagents throughout the synthesis and involves high yielding reaction steps.
2.3.3 Experimental section

(2S, 3S)-1-Benzhydryl-2-((S)-2, 2-dimethyl-1, 3-dioxolan-4-yl)-3-vinylaziridine (6)

To a stirred solution of cis aziridine 2-carboxylate 4 (10 gm, 26.24 mmol) in dry DCM (100 mL) was added DIBAL-H (33.65 mL, 26.24 mmol, 1M solution in toluene) at -78 °C slowly over period of 15 min and the reaction mixture was stirred at same temperature for 20 min. Reaction was quenched by careful addition of pre-cooled (-78 °C) MeOH (25 mL) and allowed to warm to 0 °C. Roche’s salt (saturated solution of sodium potassium tartarate, 30 mL) was added and stirred for 0.5 h. The compound was extracted with DCM (3 x 80 mL) and combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude aldehyde 5, which was used as such for next reaction.

To a stirred solution of methyltriphenylphosphonium bromide (28.5 gm, 79.88 mmol) in dry toluene (90 mL) was added KtOBu (7.54 gm, 66.57 mmol) portion wise and stirred at room temperature for 1 h. The crude aldehyde 5 (9.4 gm, 26.62 mmol) in dry THF (50 mL) was added dropwise to the reaction mixture and stirred at room temperature for 1.5 h. Reaction mixture was quenched by addition of saturated aq. solution of NH₄Cl and the compound was extracted with DCM (3 x 80 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford olefin 6 (5.71 gm, 65%) as a yellow syrup.

Rf: 0.7 (Pet. ether: ethyl acetate, 80:20).

MF: C₂₂H₂₅NO₂, MW: 335.45.

Yield: 65%.

[α]²⁵_D: +41.33 (c 1.5, CHCl₃).

IR (CHCl₃, cm⁻¹): νmax 2970, 1638, 1598, 1453, 1370, 1213, 1054.
$^1$H NMR (200 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 7.42 - 7.12 (m, 10H), 5.91 - 5.74 (m, 1H), 5.43 - 5.22 (m, 2H), 3.80 - 3.59 (m, 3H), 2.85 (dd, $J$ = 6, 8.0 Hz, 1H), 2.32 (t, $J$ = 6 Hz, 1H), 1.87 (dd, $J$ = 6, 8 Hz, 1H), 1.31 (s, 3H), 1.23 (s, 3H).

$^{13}$C NMR (50 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 143.2, 142.5, 133.3, 128.4, 128.1, 128.0, 127.0, 126.8, 118.5, 109.1, 77.9, 68.1, 46.7, 45.9, 26.7, 25.3.


(S)-1-((2S, 3S)-1-Benzhydryl-3-vinylaziridin-2-yl)-ethane-1, 2-diol (7)

To a stirred, ice-cold solution of the aziridine acetonide 6 (6 gm 14.92 mmol) in anhydrous DCM (70 mL) under nitrogen atmosphere, was added TMSOTf (4.8 mL, 29.85 mmol) dropwise at 0 °C. The resulting solution was stirred at the same temperature for 2 h and the reaction mixture was quenched by addition of solid NaHCO$_3$. Water (50 mL) was added and the compound was extracted with DCM (3 X 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound 7 (4.4 gm, 85%) as colourless syrup.

$R_f$: 0.3 (Pet. ether: ethyl acetate, 50:50)

MF: C$_{19}$H$_{21}$NO$_2$, MW: 295.38.

Yield: 85%.

$[\alpha]^{25}_D$: +112.0 (c 1.0, CHCl$_3$).

IR (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3451, 2927, 1638, 1453, 1096.

$^1$H NMR (500 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 7.40 - 7.20 (m, 10H), 5.85-5.92 (m, 1H), 5.43 - 5.39 (m, 1H), 5.29 (dd, $J$ = 1, 10 Hz, 1 H), 3.73 (s, 1H), 3.52 - 3.47 (m, 1H), 3.27 (d, $J$ =
10 Hz, 1H), 3.13 (dd, J = 5, 10 Hz, 1H), 2.38 - 2.35 (m, 1H), 2.16 (bs, 1H), 1.97 (dd, J = 5, 10 Hz, 1H).

$^13$C NMR (125 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 143.0, 142.2, 133.9, 128.6, 128.2, 128.1, 127.9, 127.1, 127.0, 118.8, 78.0, 69.8, 64.9, 46.3, 46.2.

HRMS: Calculated- 296.1645, Observed- 296.1643 (M+H)$^+$. 

**Ethyl-(S)-4-((2S,3S)-1-benzhydryl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (3)**

To the solution of diol 7 (3.3 gm, 11.18 mmol) in DCM (40 mL) was added sodium metaperiodate (5.4 gm, 22.37 mmol). The reaction mixture was stirred at room temperature for 1.5 h and completion of reaction was monitored by TLC. The reaction mass was quenched using ethylene glycol (0.01 mL), extracted with DCM (3 X 30 mL), washed with brine, dried over anhydrous sodium sulphate and filtered. The combined organics were concentrated under reduced pressure to afford crude aldehyde 8 which was used as such for next reaction.

To the solution of crude aldehyde 8 (3.1 gm, 11.78 mmol) from above reaction in THF (40 mL) was added ethyl 2-(bromomethyl) acrylate 9 (1.8 mL, 12.96 mmol), activated zinc powder (3 gm, 47.14 mmol) and saturated aq. solution of NH$_4$Cl (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for additional 10 min. The reaction mixture was filtered through a simple filter paper and thoroughly washed with ethyl acetate (3 X 30 mL). Water was added to the filtrate and the organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated to give a crude residue that was purified by flash chromatography (pet. ether-ethyl acetate, 9:1) to afford 3a:3 in 3:2 ratio (2.76 gm, 94%) as colourless syrup.

To the solution of 3a (500 mg, 1.326 mmol) in toluene (10 mL) was added triphenyl phosphine (870 mg, 3.315 mmol), p-nitrobenzoic acid (560 mg, 3.315) and DEAD (0.6 mL, 3.315 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at same temperature for 2.5 h and progress of reaction was monitored by
TLC. To the reaction mass, water (20 mL) was added and the compound was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude product, which was as such subjected for next reaction.

The crude product (570 mg, 1.08 mmol) was dissolved in absolute ethanol (10 mL) and to the solution was added NaOEt (81 mg, 1.19 mmol) at -20 °C. The reaction mixture was stirred further for 0.5 h at same temperature. Several drops of CH₃COOH were added to the reaction mixture to adjust the pH to 7. The solution was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 15% ethyl acetate in pet. ether to provide the product 3 (345 mg, 69% yield over two steps) as colourless syrup.

**Ethyl 2-((S)-(2S, 3S)-1-benzhydryl-3-vinylaziridin-2yl)-4-hydroxy)methyl)acrylate (3)**

**Rf**: 0.6 (Pet. ether: ethyl acetate, 70:30)

**MF**: C₂₄H₂₇NO₃, **MW**: 377.48.

**[α]²⁵**: +32.0 (c 1.5, CHCl₃).

**IR (CHCl₃, cm⁻¹)**: \(ν_{\text{max}}\) 3434, 2925, 1715, 1626, 1153.

**¹H NMR (400 MHz, CDCl₃ + CCl₄)**: \(δ\) 7.41-7.21 (m, 10H), 6.16 (d, \(J = 1\) Hz, 1H), 5.85-5.76 (m, 1H), 5.49 (s, 1H), 5.36 - 5.18 (m, 2H), 4.18 (q, \(J = 8\) Hz, 2H), 3.77 (s, 1H), 3.65 - 3.60 (m, 1H), 2.36 - 2.29 (m, 2H), 2.24 - 2.19 (m, 1H), 1.92 (t, \(J = 8\) Hz, 1H), 1.81 (bs, 1H), 1.30 (t, \(J = 8\) Hz, 3H).

**¹³C NMR (100 MHz, CDCl₃ + CCl₄)**: \(δ\) 166.7, 143.5, 142.3, 136.7, 134.2, 128.8, 128.2, 127.8, 127.7, 127.4, 127.1, 126.9, 118.8, 77.7, 67.6, 60.6, 49.6, 47.1, 37.8, 14.2.

**HRMS**: Observed- 378.2065 (M+H)⁺, calculated- 378.2064.

**Ethyl(R)-4-((2S,3S)-1-benzhydryl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylene butanoate (3a)**
Rf: 0.5 (Pet. ether: ethyl acetate, 70:30).

\[ \alpha \]_D^{25} : +13.33 (c 1.5, CHCl₃).

\(^1\)H NMR (200 MHz, CDCl₃ + CCl₄): \( \delta 7.42 - 7.16 \) (m, 10H), \( 6.11 \) (d, \( J = 2 \) Hz, 1H), \( 6.01 - 5.84 \) (m, 1H), \( 5.41 - 5.21 \) (m, 3H), \( 4.34 - 4.11 \) (m, 3H), \( 3.76 \) (s, 1H), \( 3.64-3.54 \) (m, 1H), \( 2.92 \) (bs, 1H), \( 2.32 \) (t, \( J = 6 \) Hz, 1H), \( 2.22 - 2.10 \) (m, 2H), \( 1.93 \) (t, \( J = 6 \) Hz, 1H), \( 1.34 \) (t, \( J = 6 \) Hz, 3H).

\(^13\)C NMR (50 MHz, CDCl₃ + CCl₄): \( \delta 167.9, 143.3, 142.6, 137.3, 134.4, 128.4, 128.2, 128.0, 127.6, 127.5, 127.0, 126.8, 118.2, 77.9, 69.0, 60.9, 49.1, 46.3, 37.6, 14.1.

Ethyl(1S,5S,6S)-7-benzhydryl-5-hydroxy-7-azabicyclo-[4.1.0]hept-2-ene-3-carboxylate (10)

To the solution of the olefin compound 3 (500 mg, 1.32 mmol) in dry DCM (400 mL) was added titanium tetraisopropoxide (0.23 mL, 0.66 mmol) and Grubbs’ 2nd generation catalyst (45 mg, 0.05 mmol). The reaction mixture was refluxed for 12 h and the completion of the reaction was monitored with TLC. The reaction mixture was filtered through celite bed and thoroughly washed with DCM (3 X 50 mL). The solvent was evaporated under reduced pressure to furnish the crude product, which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound 10 (342 mg, 74%) as colourless syrup.

Rf: 0.3 (Pet ether: ethyl acetate, 70:30)

MF: C_{22}H_{23}NO_{3}, MW: 349.43.

MF: C_{27}H_{33}NO_{3}, MW: 419.57.

Yield: 74%.

\[ \alpha \]_D^{25} : - 128.75 (c 1.6, CHCl₃).
IR (CHCl₃, cm⁻¹): νₓₘₙₐₓ 3428, 2925, 1710, 1637, 1495, 1249, 1249.

¹H NMR (500 MHz, CDCl₃ + CCl₄): δ 7.44-7.20 (m, 11H), 4.35 (t, J = 5 Hz, 1H), 4.26-4.18 (m, 2H), 4.18 – 4.43 (m, 1H), 3.79 (s, 1H), 2.79 (d, J = 20 Hz, 1H), 2.56-2.51 (m, 1H), 2.42-2.51 (m, 1H), 2.24 (t, J = 5 Hz, 1H), 1.32 (t, J = 10 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃ + CCl₄): δ 166.5, 143.0, 142.8, 136.4, 128.5, 128.4, 127.3, 127.2, 127.1, 76.5, 63.9, 60.6, 46.7, 35.8, 30.2, 14.3.

HRMS: Calculated- 350.1751, Observed- 350.1748 (M+H)+.

Ethyl (1S,5S,6S)-7-benzhydryl-5-((methylsulfonyl)oxy)-7-azabicyclo[4.1.0]hept-2-ene-3-car boxylate (11)

To a solution of alcohol 10 (150 gm, 0.42 mmol) in DCM (3 mL) was added triethylamine (0.3 mL, 2.15 mmol) followed by mesyl chloride (0.04 mL, 0.47 mmol) and DMAP (cat.) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h under nitrogen atmosphere. The completion of reaction was monitored by TLC and reaction mixture was poured in cold ice water. The compound was extracted with DCM (3 X 5 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound 11 (144 mg, 79%) as colourless syrup.

Rᶠ: 0.4 (Pet. ether: ethyl acetate, 70:30).

MF: C₂₃H₂₅NO₅S, MW: 427.51.

Yield: 79%.

[α]ᴰ²⁵ : - 4.44 (c 0.9, CHCl₃).

IR (CHCl₃, cm⁻¹): νₓₘₙₐₓ 3026, 2925, 1709, 1645, 1359, 1263.
\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3} + CCl\textsubscript{4}): \( \delta 7.30\text{-}7.20 \) (s, 11H), 5.28\text{-}5.27 (m, 1H), 4.24\text{-}4.17 (m, 2H), 3.81 (s, 1H), 3.02 (d, \( J = 20 \) Hz, 1H\textsubscript{1}), 2.94 (s, 3H), 2.64\text{-}2.57 (m, 2H), 2.35 (t, \( J = 5 \) Hz, 1H\textsubscript{1}), 1.31 (t, \( J = 5 \) Hz, 3H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3} + CCl\textsubscript{4}): \( \delta 165.9, 142.3, 139.3, 128.7, 128.5, 127.6, 127.3, 127.1, 126.9, 76.3, 73.4, 60.8, 44.2, 38.8, 36.1, 27.7, 14.3 \).

HRMS: Observed- 428.1524, calculated- 428.1526 (M+H\textsuperscript{+}).

Ethyl (1\textit{R},5\textit{R},6\textit{R})-7-benzhydryl-5-(pentan-3-yloxy)-7-azabicyclo[4.1.0]hept-3-ene-3-carboxylate (2)

Mesyl compound 11 (0.05 gm, 0.11 mmol) was dissolved in 3-pentanol (2 mL) and dry DCM (1 mL). To the reaction mixture was added BF\textsubscript{3}.Et\textsubscript{2}O (0.083 mL, 0.58 mmol) dropwise and stirred at room temperature for 3 h. Then TEA (0.25 mL, 1.75 mmol) was added to the reaction mixture and stirred for 1 h at room temperature. Reaction mixture was concentrated under reduced pressure to remove low boiling impurities. To the remaining residue, water (3 mL) was added. The compound was extracted with DCM (3 X 5 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude product, which was purified by column chromatography over silica gel, eluting with 10\% ethyl acetate in pet. ether as an eluent to afford compound 2 (49 mg, 80\%) as a colourless syrup.

\textbf{Rf}: 0.6 (Pet. ether: ethyl acetate, 80:20).

\textbf{MF}: C\textsubscript{27}H\textsubscript{33}NO\textsubscript{3}, \textbf{MW}: 419.57.

\textbf{Yield}: 80\%.

\([\alpha]_{D}^{25}\text{:} -4.0 \quad (c \text{ 1.0, CHCl}_3)\).

\textbf{IR} (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 2968, 2876, 1712, 1660, 1493, 1302, 1248, 1080.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3} + CCl\textsubscript{4}): \( \delta 7.40\text{-}7.20 \) (m, 10H), 6.78\text{-}6.76 (m, 1H), 4.19 (q, \( J = 5 \) Hz, 2H), 4.05 (bs, 1H\textsubscript{1}), 3.70 (s, 1H\textsubscript{1}), 3.13\text{-}3.10 (m, 1H\textsubscript{1}), 2.72 \text{-}2.68 (m, 1H\textsubscript{1}), 2.61 \text{-}2.55 (m, 1H\textsubscript{1}), 2.14 \text{-}2.12 (m, 1H\textsubscript{1}), 1.96 (d, \( J = 5 \) Hz, 1H\textsubscript{1}), 1.46 \text{-}1.32 (m, 4H\textsubscript{1}), 1.31 (t, \( J = 5 \) Hz, 3H\textsubscript{1}), 0.86\text{-}0.80 (m, 6H)
$^{13}$C NMR (125 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 166.9, 143.4, 143.0, 134.2, 128.3, 127.6, 127.2, 127.0, 82.1, 77.7, 69.8, 60.6, 39.8, 38.2, 26.5, 26.4, 14.3, 9.8, 9.7.

HRMS: Observed- 420.2535, calculated- 420.2533 (M+H)$^+$. 
2.3.4 Spectral Data

**1H NMR spectrum of olefin 6 (200 MHz, CDCl$_3$ + CCl$_4$)**

![1H NMR spectrum of olefin 6](image)

**13C NMR spectrum of olefin 6 (50 MHz, CDCl$_3$ + CCl$_4$)**

![13C NMR spectrum of olefin 6](image)
\textbf{\textsuperscript{13}C NMR spectrum of olefin 6 (50 MHz, CDCl}_3 + CCl}_4

\textbf{\textsuperscript{1}H NMR spectrum of diol 7 (500 MHz, CDCl}_3 + CCl}_4
$^{13}$C NMR spectrum of diol 7 (125 MHz, CDCl$_3$ + CCl$_4$)
**Chapter 2 Section 3**

**$^1$H NMR spectrum of compound 3 (400 MHz, CDCl$_3$ + CCl$_4$)**

![$^1$H NMR spectrum](image)

**$^{13}$C NMR spectrum of compound 3 (100 MHz, CDCl$_3$ + CCl$_4$)**

![$^{13}$C NMR spectrum](image)
$^{13}$C NMR spectrum of compound 3 (100 MHz, CDCl$_3$ + CCl$_4$)

$^1$H NMR spectrum of compound 3a (200 MHz, CDCl$_3$ + CCl$_4$)
$^{13}$C NMR spectrum of compound 3a (50 MHz, CDCl$_3$ + CCl$_4$)
$^1$H NMR spectrum of cyclohexene 10 (500 MHz, CDCl$_3$ + CCl$_4$)

$^{13}$C NMR spectrum of cyclohexene 10 (125 MHz, CDCl$_3$ + CCl$_4$)
\[ ^{13}C \text{ NMR spectrum of cyclohexene 10 (125 MHz, CDCl}_3 + \text{CCl}_4) \]

\[ ^1H \text{ NMR spectrum of mesylate 11 (500 MHz, CDCl}_3 + \text{CCl}_4) \]
$^13$C NMR spectrum of mesylate 11 (125 MHz, CDCl$_3$ + CCl$_4$)
$^1$H NMR spectrum of pentanide 2 (500 MHz, CDCl$_3$ + CCl$_4$)

$^{13}$C NMR spectrum of pentanide 2 (125 MHz, CDCl$_3$ + CCl$_4$)
$^{13}$C NMR spectrum of pentanide 2 (125 MHz, CDCl$_3$ + CCl$_4$)

SUN4AV500#003 TLFP-PENTANOIDE.002.001.1R.ESP

Chemical Shift (ppm)

134.22
128.34
127.57
127.21
127.02
82.08
77.69
69.81
60.56
39.83
38.22
26.50
24.39
14.30
9.83
9.68
2.3.5 References


4) Khairnar, L. B. *Ph.D. Thesis*, **2012**, Pune University, INDIA.


