STEREOSELECTIVE SYNTHESIS OF EPIBATIDINE AND RELATED COMPOUNDS EMPLOYING [3+2] CYCLOADDITION OF NON-STABILIZED AZO-METHINE YLIDE AS A KEY STEP

A THESIS

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BY

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DECLARATION

I hereby declare that the thesis entitled "**Stereoselective Synthesis of Epibatidine and Related Compounds Employing [3+2] Cycloaddition of Non-Stabilized Azo-Methine Ylide as a Key Step**" submitted for Ph. D. degree to the University of Poona has been carried out at National Chemical Laboratory, under the supervision of Dr. Ganesh Pandey. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Stereoselective Synthesis of Epibatidine and Related Compounds Employing [3+2] Cycloaddition of Non-Stabilized Azo-Methine Ylide as a Key Step**" submitted by Trusar. D. Bagul was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

Date 14th March 1998

(Ganesh Pandey)
Research Guide

To

My Three

Affectionate and Beloved

Sisters

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Trusar. D. Bagul

Contents

List of Abbreviatons

Ac	Acetyl
aq	aqueous
Bn	benzyl
bp.	boiling point
Bu	butyl
DCM	dichloromethane
DMF	N, N-dimethyl formamide
Et	ethyl
EtOAc	ethyl acetate
g	gram
h	hour
IR	infrared
M	molar
mL	millilitre
mmol	millimole
mp.	melting point
rt	room temp
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilane
TMSCl	chlorotrimethylsilane

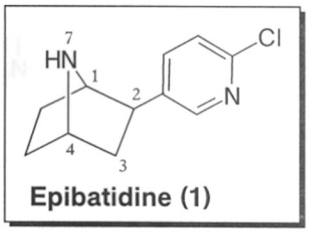
Abstract

Epibatidine (**1**) is an alkaloid possessing the 7-azabicyclo(2.2.1)heptane skeleton, first isolated from the skin extracts of poison frog, *Epipedobates tricolor*, in minute amounts (<5 mg) by Daly and co-workers in 1992. Epibatidine was found to be unusual for three reasons:

a) A member of an entirely new class of alkaloid.

b) Possesses an organochlorine compound, rarely found in animals.

c) Powerful painkiller.



Epibatidine (1)

Epibatidine (**1**) is found to be 200-500 times more potent than morphine as analgesic and its effects are not blocked by the opiate receptor antagonist naloxone, suggesting a non-opioid mode of action. Subsequent studies have revealed that **1** is an extremely potent agonist of the acetyl choline receptor that is found to be involved in the mediation of several human disorders such as Alzheimer's and Parkinson's diseases.

The proposed dissertation describes in detail a novel synthesis of **1** and its analogue utilizing [3+2] cycloaddition of an nonstabilized azo-methine ylide as key step. The study has been presented in three chapters.

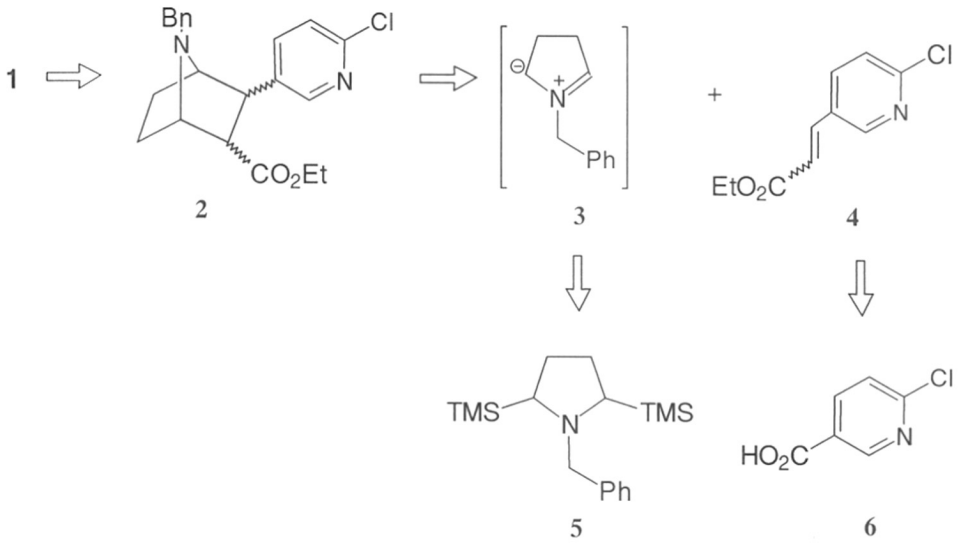
Chapter-1: A Brief History of Epibatidine

Chapter-1 begins with an introduction on the significance of Epibatidine: its isolation, structural elucidation and biological activity. It also provides an exhaustive account of the synthetic approaches developed towards this alkaloid.

Chapter-2 : Stereoselective Synthesis of Epibatidine

Chapter-2 begins with a brief discussion on our disconnection approach involved in designing the synthetic route for the synthesis of **1**, employing [3+2] cycloaddition of non-stabilized azomethine ylide as key step (Scheme-1).

Scheme-1

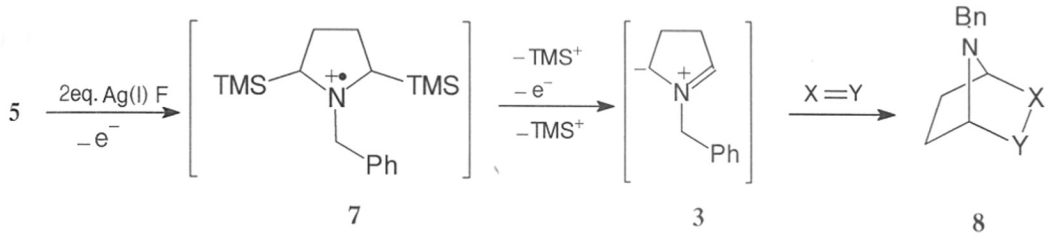


A brief introduction on 1,3-dipolar cycloaddition of azomethine ylide and various methods available in literature for their generation has also been provided.

In designing the synthesis of **1**, through the retrosynthetic route as depicted in Scheme-1, we were guided by an earlier investigation from our group on the construction

of 7-azabicyclo (2.2.1) heptane skeleton **8** by the [3+2] cycloaddition of azomethine ylide **3** with electron deficient alkenes (Scheme-2).

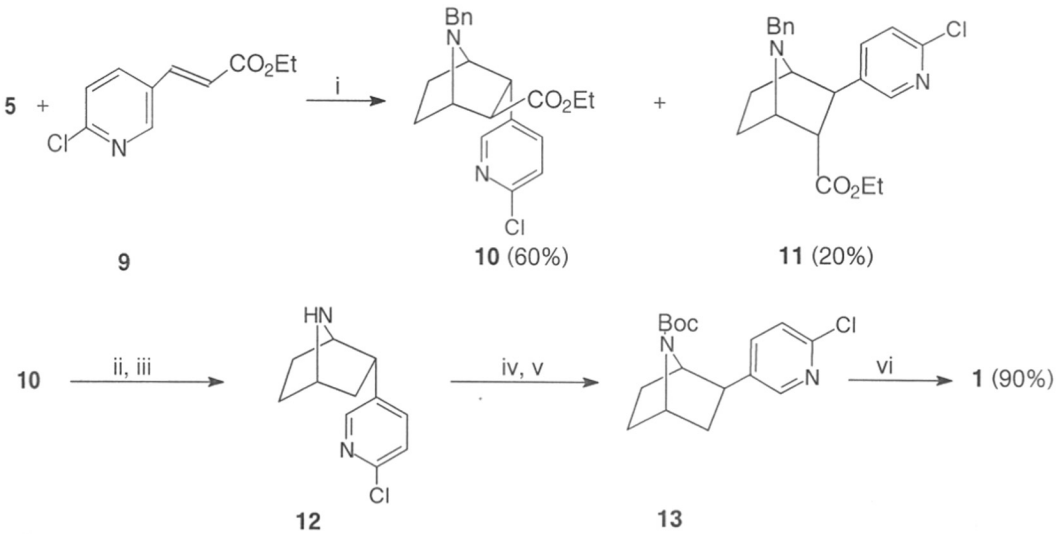
Scheme-2



The generation of **3** has involved sequential double desilylation of **5** by electron transfer initiation using Ag(I)F as one electron oxidant.

Cycloaddition of **5** with *trans*-ethyl-3-(6-chloro-3-pyridyl) propen-2-oate (**9**) gave stereoisomeric cycloadducts **10** (60%) and **11** (20%) in 3:1 ratio (Scheme-3). The

Scheme-3



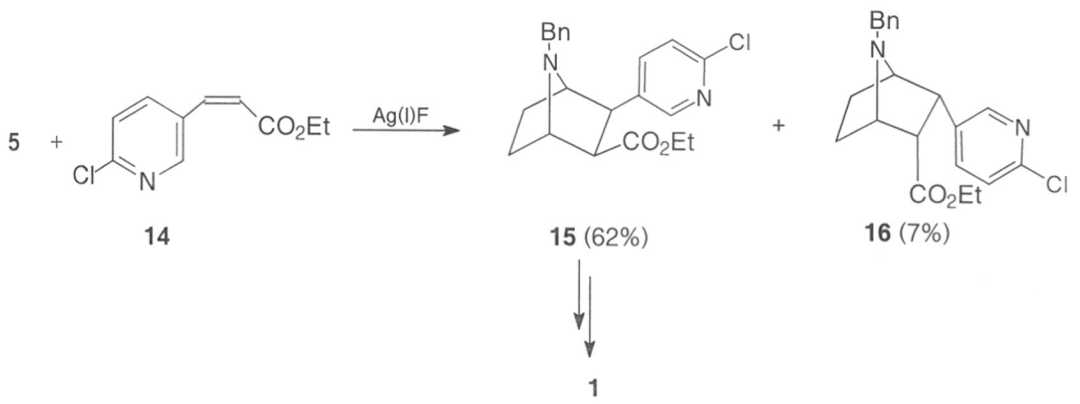
***Conditions**: i) Ag(I)F, ii) Decarboxylation, iii) Debenzylation, iv) Boc-protection, v) Epimerization, vi) Boc-deprotection.*

stereochemistry of the cycloadducts **10** and **11** have been determined by detailed ^{1}H NMR decoupling and ^{1}H COSY experiments.

6-Chloro-3-pyridyl moiety in the major cycloadduct **10** being *endo*-oriented, decarboxylation of **10** employing Barton's radical decarboxylation protocol followed by debenzylation with α-chloroethyl chloroformate in refluxing 1,2-dichloroethane afforded the unnatural isomer **12** of Epibatidine. However, **12** could be epimerized (45%) to **1** using KO^{t}Bu as base in refluxing ^{t}BuOH.

Although, we could synthesize **1** through the above route, the poor yield of epimerization and multiple steps involved guided us to use *cis*-ethyl-3-(6-chloro-3-pyridyl)propen-2-oate (**14**) as dipolarophile for the cycloaddition reaction. Cycloaddition of 5 with *cis*-pyridyl acrylate **14** gave cycloadducts **15** (62 %) and **16** (7 %) respectively as shown in Scheme-4. The stereochemistry of 6-chloro-3-pyridyl and carbethoxy moieties were assigned as *exo* for the major cycloadduct **15** and *endo* for the minor cycloadduct **16** by detailed ^{1}H NMR studies. The cycloadduct **15** is converted to **1** *via* decarboxylation and debenzylation.

Scheme-4



14

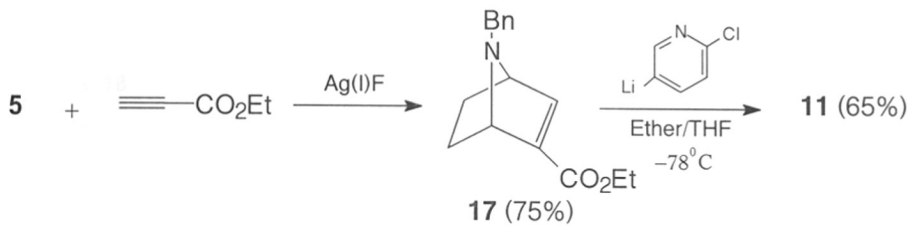
15 (62%)

16 (7%)

1

Stereoselective synthesis of **1** is also described through an alternative route involving the conjugate addition of 6-chloro-3-lithio pyridine to α,β-unsaturated ester **17** at -78°C (Scheme-5). Addition was found to be stereoselective favoring *exo*-orientation of 6-chloro-3-pyridyl moiety. The precursor **17** is obtained through the cycloaddition of **5** with ethyl propiolate.

Scheme-5



Adduct **17** is further synthetically transformed to Epibatidine in an identical fashion as described in Scheme-3.

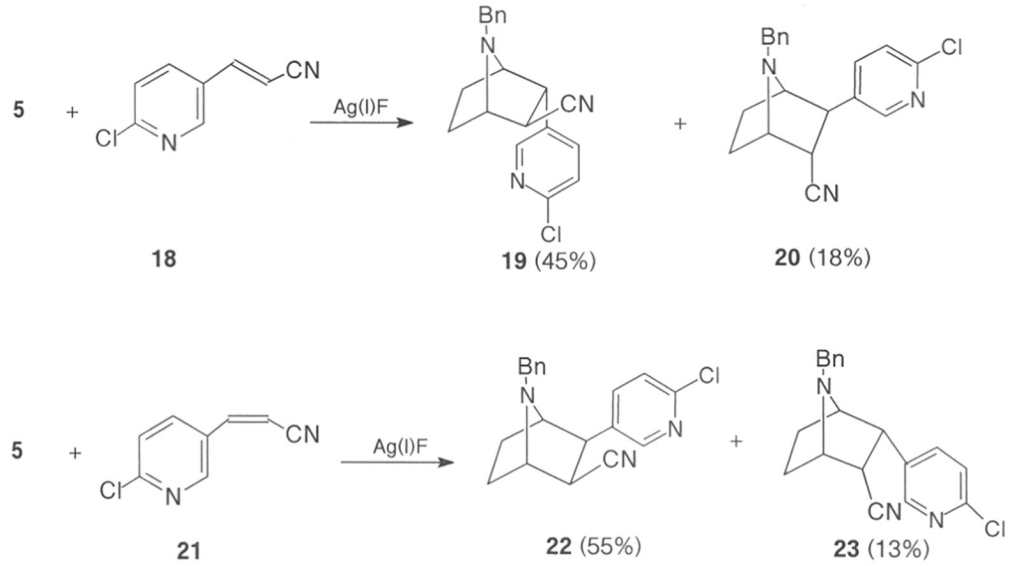
Chapter-3: Synthesis of Epibatidine Analogues

Chapter-3 deals with the application of [3+2] cycloaddition of azomethine ylide **3** towards the synthesis of substituted Epibatidine and other analogues.

Due to the structural resemblance of Epibatidine to nicotine, Epibatidine, its derivatives and isomers have found to exhibit a very high affinity in the picomolar range for [^{3}H] nicotine and [^{3}H] cystine binding sites in brain. Therefore, there is growing interest in devising methodologies to synthesize various derivatives and structural analogues of Epibatidine. In this context, the cycloaddition reactions with different dipolarophiles having 6-chloro-3-pyridyl group have been studied.

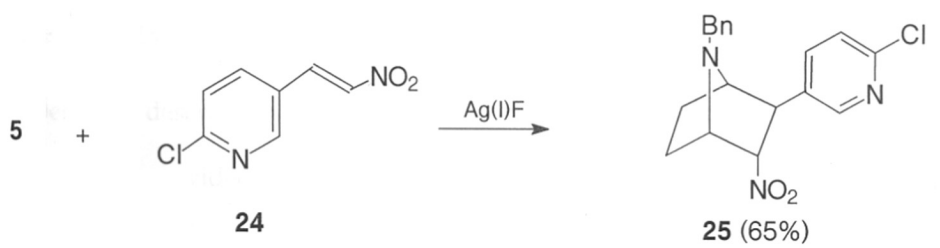
Cycloaddition of **5** with *trans*-3-(6-chloro-3-pyridyl)-2-propionitrile (**18**) as well as *cis*-3-(6-chloro-3-pyridyl)-2-propionitrile (**21**) gave corresponding cycloadducts **19** (45%) & **20** (18%) and **22** (55%) & **23** (13%) respectively (Scheme 6).

Scheme-6



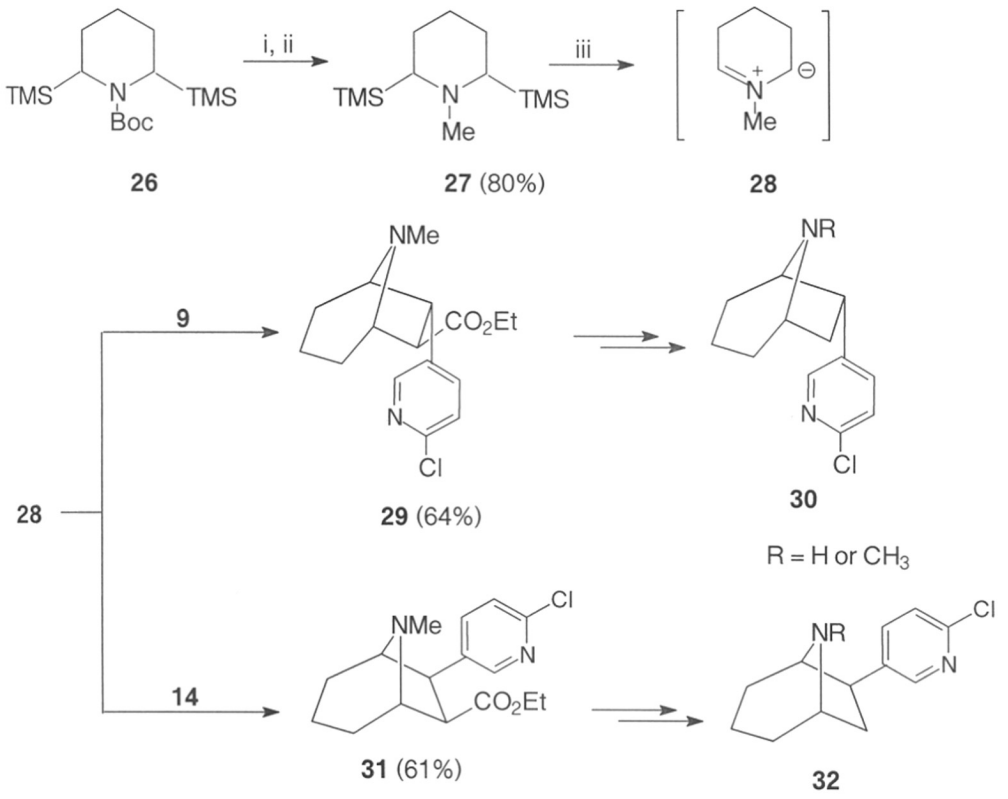
Similarly, cycloaddition of **5** with *trans*-3-(6-chloro-3-pyridyl)-1-nitro ethylene (**24**) afforded cycloadduct **25** with a reversal of stereoselectivity, in sharp contrast to that observed for *trans*-dipolarophiles ester (**9**) and nitrile (**18**) (Scheme 7).

Scheme-7



Formal synthesis of Homo-epibatidine, its N-methyl derivative and its epimers have also been described *via* the cycloaddition of homologous azomethine ylide **28**, derived from piperidine (Scheme 8).

Scheme-8



Reagents: *i) TFA, DCM, RT; ii) Na(BH4)CN, HCHO, CH3CN; iii)Ag(I)F, DCM.*

Detailed description regarding stereochemistry assignments and appropriate explanations are provided wherever found necessary.

Chapter. 1

A Brief History of Epibatidine

"Natural product synthesis poses the challange to consider and develop new pathways of structural transformation. Natural products as targets for synthetic research possess a special fertility in this regard, because the structural channels of biosynthesis are not neccessarily the conduits of organic synthesis."

A. Eschenmoser.

Science 1977, 196, 1410.

1. Introduction

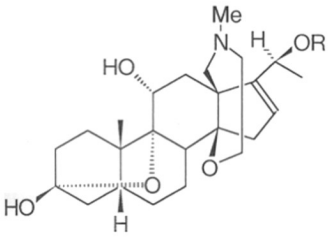
"Nature continues to be exceedingly generous to the synthetic chemist in providing ample opportunity for discovery and creative endeavour of highest magnitude and in surrounding him with an incredible variety of fascinating and complicated structures"

- E. J. Corey

The above quote from Prof. Corey[1] is best reflected in Daly, Albuquerque and others epitomic endeavors (1960-1992) towards the isolation of various alkaloids (more than hundread in number) having complex structural features and diverse pharmacological properties[2,3] from the skin extracts of a single species of Panamian poison frog of *Epipedobates* family. These amphibians are vividly pigmented to have warning coloration and produce irritating and unpleasant skin secretions to provide partial protection against predation. The skin secretions of these species have been used by Cholo Indians of Choco rain forests in western Columbia for poisoning the tips of their blow darts for hunting.

Daly *et al* systematically pursued their studies[2, 3] by collecting the skin extracts of these *Epipedobates* frogs from the northwestern Panama. The skin extracts of these species caused a straub-tail reaction (STR), a characteristic of opiate alkaloid[4], when injected in mice[5,6]. Isolation process displayed presence of the broad spectrum of alkaloids with diverse structural and pharmacological features[2,3]. The alkaloids isolated from these extracts are listed below with their structural frameworks and pharmacological activity (Fig. 1).

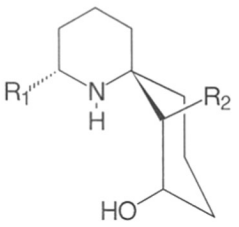
Fig. 1



1

Batrachotoxin Class of Alkaloids: Constitutes three major alkaloids.

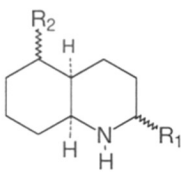
Activity: Potent neurotoxin and sodium ion channel activator.



2

Histrionicotoxin Class of Alkaloids: Constitues a group of ten alkaloids, three major and seven minor.

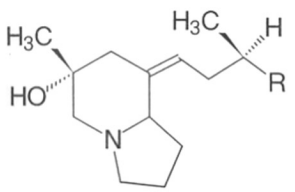
Activity: Nicotinic Acetyl Choline Receptor.



3

Pumiliotoxin C Class of Alkaloids: Constitutes a group of 42 alkaloids, three major.

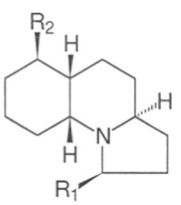
Activity: Neuromuscular Blocking Agent.



4

Pumiliotoxin A, B & D Class of Alkaloids: Constitues a group of 24 Alkaloids.

Activity: Cardioactive Inotropic Agents and Specific Inhibitors of Calcium-Dependent ATPase.



5

Gephyrotoxin Class of Alkaloids: Constitues a group of six alkaloids.

Activity: Muscarinic Agonist.

Of all the above class of alkaloids identified, none showed the STR response. As a result Daly *et al*[7] continued their pursuit in search of STR causing alkaloid from the various fractions obtained during the purification of skin extract that were stored over the years. Thus, the fractions showing positive response towards STR were purified by chromatography on a prepacked silica-gel 60 column (Merck 1.0×24 cm) with chloroform-methanol-aqueous ammonia (6 N) (500 mL of 800 : 10 : 0.1 followed by 1000 : 100 : 2) yielding only 1 mg of STR active alkaloid, which was further acetylated to remove the other contaminating pumiliotoxin alkaloids and characterised as its N-acetyl derivative[7].

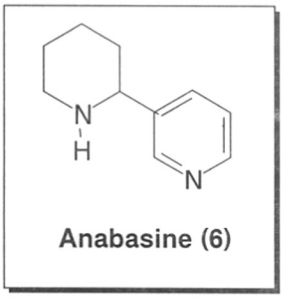
GC/MS analysis of chromatographic fractions of the skin extracts of *Epipedobates tricolor* indicated that the trace alkaloid causing STR had a molecular ion 208, 210 and several pairs of fragments all in 3:1 ratio indicating the presence of chlorine. High resolution mass measurements established the formula for the m/z 208 ion as $C_{11}H_{13}N_2{}^{35}Cl$, indicating the presence of six membered rings or double bonds. The major ^{35}Cl-containing fragments were $C_9H_8N_2Cl^+$ (m/z 179, M^+- C_2H_5) and $C_7H_7N^+$ (m/z 69).

The properties of alkaloid with 208/210 molecular weight fraction were found to be basic, relatively polar with one exchangeable and acetylable NH having *uv* spectrum at 210 nm with a broad shoulder at 250-280 nm (absorbance ratio 2:1), a chromophore suggesting a pyridine moiety among other possibilities. It gave negative Ehrlich test on TLC for pyrroles and indoles.

The GC-FTIR spectrum showed similarities with the IR spectrum of the tobacco alkaloid Anabasine [**6**, 2-(3-pyridyl) piperidine, Fig. 2], which has significant

absorbance at 1428 and 1112 cm^{-1}, suggesting the presence of a pyridine moiety and in particular a 2-chloropyridyl moiety since the IR spectrum of 2-chloropyridine has absorbance at 1423 and 1132 cm^{-1}. The mass spectrum and the GC-FTIR spectrum of N-acetyl derivative of the alkaloid indicated one acetyl unit and a similarity to that of N-acetyl pyrrolidine.

Fig. 2



Anabasine (6)

Daly *et al* could assign[7] the structure and stereochemistry of this STR active alkaloid as *exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo(2.2.1)heptane from the analysis of the 500 MHz ^1H NMR spectrum of the N-acetyl derivative 7 (Fig. 3) in $CDCl_3$, which revealed a series of double signals originating from the equimolar N-acetyl rotamers

Fig. 3

7a **7b**

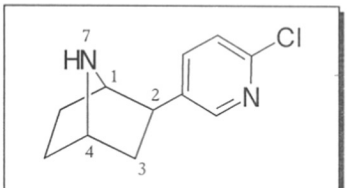
due to the constrain to the planarity between C_1-N_7 and C_4-N_7 bonds caused by amide group. Interconversion between rotamers is very slow due to the partial

double bond character of N-acetyl bond. In rotamer **7a**, a large deshielding of H_4 relative to H_1 by the anisotropy of the acetamido carbonyl group was observed. However, in rotamer **7b** H_1 was relatively shielded to H_4.

Signals between δ 7.2-8.3 were assigned to a 6-chloro pyridine substituted at 3-position. Only one structure was compatible with the remaining ^1H NMR signals and mass spectral fragmentation, and that structure neccessitated a number of vicinal coupling of $J \cong 0$ Hz. This suggested a cyclohexane type ring in the boat conformation for a portion of the structure since it is well known that the coupling between the bowspirt hydrogens and adjacent *trans* axial hydrogens is small or zero[8]. This moiety is implicit in a 7-azabicyclo(2.2.1)heptane and it has been reported[9] for the parent heterobicyclic compound that no coupling at 100 MHz could be detected between bridgehead and adjacent *endo* hydrogens. Thus, the chloropyridyl group must occupy 2-*exo* position in the bicyclic compound to account for the signal of the 2-proton (*endo*) to show no coupling with adjacent bridgehead hydrogen.

The electron impact mass spectral fragmentation pathways also confirmed the structure, earlier deduced by ^1H NMR spectroscopy, as 2-*exo*-(6-chloro-3-pyridyl)-7-azabicyclo (2.2.1) heptane (**8**, Fig. 4) for the STR active alkaloid and was dubbed as **Epibatidine** after the frog, *Epipedobates Tricolor*.

Fig. 4



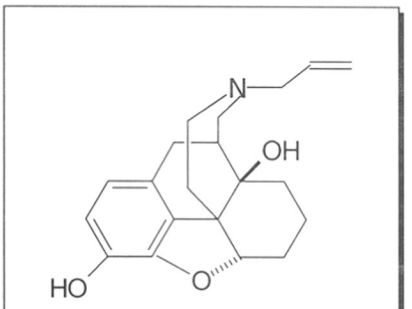
Epibatidine (8)

Daly and coworkers' all attempt towards retrieving Epibatidine in pure form from **7** for complete characterization after the removal of the N-acetyl moiety failed due to the poor yield (less than 5 %), however, the unambigous assignment of the structure and stereochemistry was confirmed by its first synthesis reported[10] by Broka, C. A.

2. Biological Activity of Epibatidine

A straub-tail reaction is characteristic of opiate alkaloids and has been used as an assay for opiate agonists and antagonists[4]. Preliminary biological tests indicated that in hot plate and straub tail assays **8** was active at 10-50 μg/kg and calculated to be 200-500 times more potent than morphine. Moreover, its *in vivo* analgesic effect was not antagonized by naloxone (**9**, Fig. 5) and other opiates, thus, suggesting a

Fig. 5



Naloxone (9)

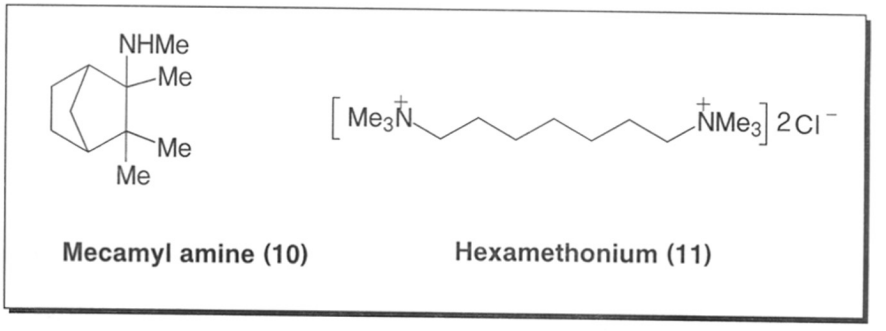
non - opioid mode of action for its analgesic effect[11-16]. Nevertheless, **8** has also very low affinity for opioid receptors, since it is nearly 9000-fold less potent at such receptors.

A detailed pharmacological study by Shen *et al*[13] have confirmed the potent analgesic properties of natural **8** and have also shown that all the three forms of **8** such as racemic, *d* and *l* have comparable potency and no enantioselectivity for analgesia in tail flick model is observed. In short, both the enantiomers *d*-**8** and *l*-**8** of this rigid bicyclic alkaloid are active at the same level.

The *exo* orientation of 6-chloro-3-pyridyl moiety is critical for its high potency as the corresponding *endo* isomer is not active even at 1 mg/kg. The good activity of *exo*-7-N-methyl derivative and the lack of potency for *endo*-7-N-acetyl derivative suggests that a basic centre at the apical 7-position is essential or preferred for the biological activity.

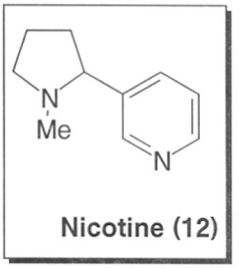
The analgesic activity of **8** is antagonised by the neuronal nicotinic acetyl choline receptor channel blocker such as mecamyl amine (**10**, Fig. 6) but remains unaffected by the nicotinic acetyl choline receptor antagonist hexamethonium (**11**, Fig. 6)[4, 11, 5]. Since, **11** has been shown to be incapable of crossing the blood-brain barrier, it is believed that the primary mechanism of action of epibatidine is mediated

Fig. 6



through the occupation of nicotinic acetyl choline receptors in the brain. Either enantiomers of epibatidine equally displaced bound [^{3}H] nicotine (**12**, Fig. 7) from rat brain (K_i = 55 pM) making **8** one of the most potent acetyl choline receptor ligands known till date[10]. (±) [^{3}H] epibatidine binds to two sites in rat brain with affinities of 15 and 360 pM (IC) [10, 13, 15].

Fig. 7



Nicotine (12)

Subsequent studies showed that epibatidine is an extremely potent agonist of nicotinic acetyl choline receptors[10, 12, 17] that is found to be involved in the mediation of several human disorders such as Alzheimers and Parkinsons diseases[18]. Its *in vivo* studies have further confirmed the involvement of nicotinic acetyl choline receptors in the central and autonomic nervous systems[11, 12]. It has little or no activity at a variety of other central receptors including muscarinic, adrenergic, dopamine, serotonin, and GABA receptors.

Epibatidine (**8**) has also been shown to be an extremely potent toxin, producing convulsions and death at doses of 50-86 μg / kg in mice[19, 20]. [^{3}H] Epibatidine has been employed as chemical probe for the study of nicotinic receptors in chick retina and in rodent and human brains[21-23]. The 4′-substituted ^{18}F and ^{123}I analogues are currently being developed as useful imaging agents for emission tomography[24].

3. Synthetic approaches to Epibatidine

Due to intriguing structural features and important biological activity[11-27] exhibited by **8**, several synthetic approaches have been reported for its synthesis. As the main structural feature of **8** is the 7-aza-bicyclo(2.2.1)heptane ring system, most of the strategies reported have devoted their attempt in constructing this bicyclic framework. Interesting review articles dealing with the construction of 7-azabicyclo(2.2.1)heptane ring systems and synthesis of **8** have been published by Chen and Trudel[28] and Sestanj *et al*[29], respectively recently.

Synthetic approaches developed towards **8** may be classified into the following three categories, which is based upon the key reaction utilized towards the construction of 7-azabicyclo(2.2.1)heptane framework.

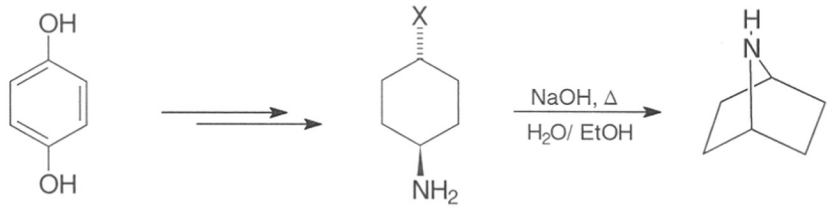
- *Trans*-annular nucleophilic intramolecular cyclization of cyclohexyl amine derivative.
- [4+2] Cycloaddition of pyrrole with acetylenic equivalents.
- Miscellaneous.

3.1. *Trans*-annular Nucleophilic Intramolecular Cyclization of Cyclohexyl amine derivatives:

The first report on the synthesis of the basic 7-azabicyclo(.2.2.1)heptane skeleton (**15**) was published by Von Braun and Schwartz[30] in 1929 by the intramolecular cyclization of **14** under hot alkaline conditions in only 1% yield. Substrate **14** was obtained from hydroquinone (**13**) in four steps. Fraser and Swingle[9]

in 1970 improved the overall yield of **15** to 18-36% by using X= OTs instead of Br (Scheme 1).

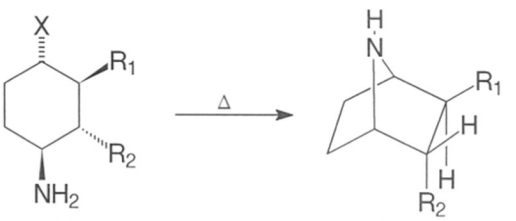
Scheme 1



13 **14** (X = Br / OTs) **15**

Several groups have later employed the intramolecular 1,4-*trans*-annular cyclization protocol for the construction of cyclohexyl amine derivatives in order to synthesize **8**. An important feature of this cylization was the *exo* orientation of *cis*-substituent (R_1) in relation to -NH_2 present in **16** in the resultant 7-azabicyclo(2.2.1)heptanes (**17**) and *endo* orientation for a *trans*-substituent (R_2) with respect to -NH_2 in **17** (Scheme 2). However, the synthesis of the required 1,4-cyclohexyl amine precursors have often involved multiple steps.

Scheme 2

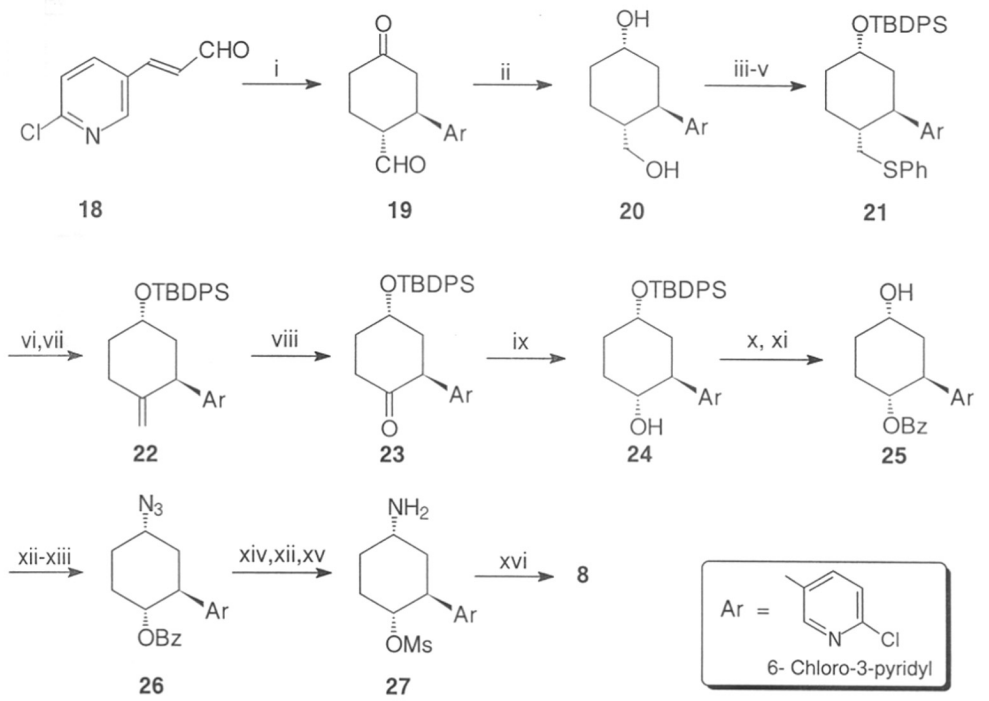


16 (X = Br / Ms) **17**

Broka *et al*[10], during the synthesis of **8**, employed [4+2] cycloaddition reaction of 3-(6-chloro-3-pyridyl)prop-2-en-1-al (**18**) and 2-(trimethylsilyloxy)-1,3-butadiene for the constuction of cyclohexyl amine derivative **27**. Both the carbonyl groups in **19**

were reduced with L-selectride to obtain diol **20**. Unwanted carbon atom from the **20** was removed by converting the primary alcohol to phenyl sulfide followed by the elimination *via* its sulfoxide to generate **22**, which was further ozonolyzed and reduced to afford 1,4-*cis* cyclohexane diol derivative (**24**). Aminomesylate **27** was prepared from **24** in four steps and subjected to intramolecular cyclisation by heating in choroform for three days to obtain **8** (Scheme 3). This was the first report for the total synthesis of **8** confirming the structural assignments given by Daly and co-workers[7].

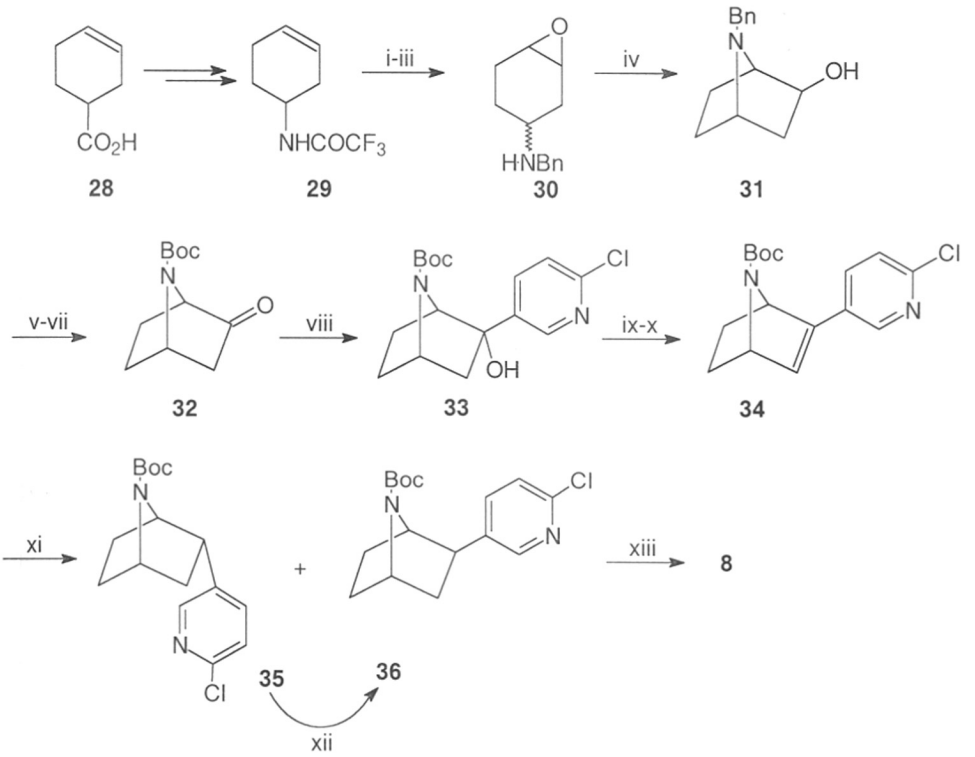
Scheme 3.



Reagents and conditions: i) 150° C, 10 h; ii) L-selectride (3eq), -78° C → 20°C; iii) TsCl (1.1 eq), pyr., 20°, 1d; iv) PhSK, DMF/THF (1:1), 20°, 30 mi; v) TBDMSCl, imidazole, DMF, 20°, 1d; vi) MCPBA, CH_2Cl_2, 20°, 15 min; vii) Xylene, 200°, 2h; viii) OsO_4 (cat), NMMO, acetone/H_2O (9:1), $Pb(OAc)_4$; ix) $NaBH_4$, MeOH; x) BzCl, pyr.; xi) TBAF, THF; xii) MsCl, TEA, DCM, 0°C, 45min. xiii) LiN_3, DMF, 55°C, 12h; xiv) 0.5 M NaOH in H_2O/THF/MeOH (1:2:4), 20°C, 3.5h; xv) $SnCl_2$, MeOH/THF (1:1), 20°C, 1h. xvi) $CHCl_3$, Δ, 4d, (84 %)

Fletcher *et al*[31] utilised intramolecular cyclization of 4-amino-1,2-epoxy cyclohexane (**30**) for the construction of 7-benzyl-7-azabicyclo(2.2.1)heptan-2-ol (**31**), which was further elaborated to **34** employing multiple steps as shown in Scheme 4.

Scheme 4



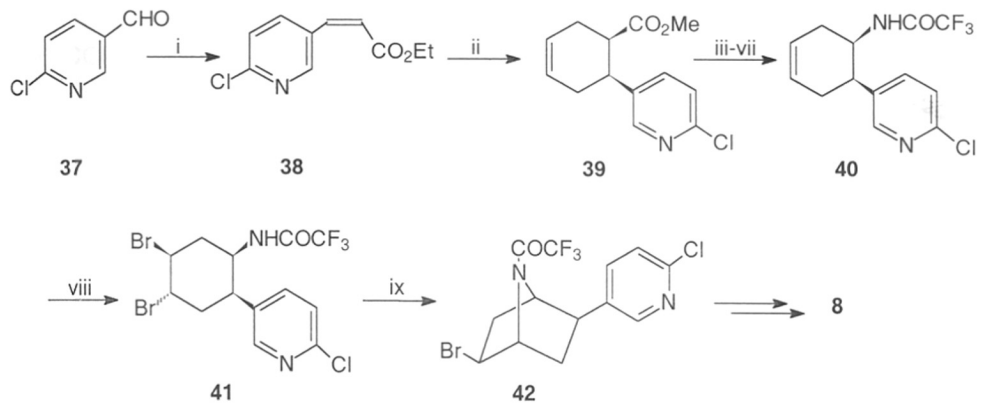
Reagent and conditions: *i)BnBr, Cs_2CO_3, DMF, 70°C, 40 h; ii) m-CPBA, CH_2Cl_2, 0°→ 20°C, 4 h; iii) K_2CO_3, MeOH, 3 d; iv) 1-Methyl-2-pyrrolidinone, 180°, 16 h; v) $Pd(OH)_2$, EtOH, HCl, 40°C, H_2 (40 psi); vi) $(BOC)_2O$, dioxan, 1 N NaOH, 18 h; vii) $(COCl)_2$, CH_2Cl_2, -70°, TEA; viii) n-BuLi, Et_2O/THF, -70°C; ix) KH, THF, 0°C, CS_2, MeI; x) toluene, 110°C, 2 h; xi) PtO_2, EtOAc, H_2, (40 psi); xii) t-BuOH, K'BuO, 100°C, 30 h; xii) HCl, EtOAc.*

Hydrogenolysis of **34** using Adams catalyst produced a 4:1 mixture of *endo:exo* isomeric mixture of **35** and **36**. The undesired *endo* isomer **35** was epimerized using potassium *tert*-butoxide in *tert*-butyl alcohol at reflux for 30 h to *exo* isomer. The deprotection of the N-Boc moiety from the *exo*-isomer **36** with trifluoroacetic acid gave **8** in good yields.

Synthesis of the (+) and (-) enantiomers of **8** was also accomplished by the resolution of alcohol **31** through its R-(-)-Moshers esters. The two diastereomers separated by crystalization and chromatographic purification were hydrolysed to afford (+) and (-)-**31**. Each enantiomer with absolute configuration fixed at the bridgehead protons were subjected to the reaction sequence as developed for the racemate (Scheme 3) to give the (+) and (-) enantiomers of **8**.

Corey *et al*[32], employed thermal Diels-Alder cycloaddition of 1,3-butadiene with *cis*-methyl-3-(6-chloro-3-pyridyl)-2-propenoate (**38**) to obtain *cis*-ester **39**, which was further converted to dibromide **41** through a series of steps (Scheme 5). Dibromide **41** was transformed to **8** by intramolecular ring closure using KO^{t}Bu as base followed by the reductive radical debromination employing Bu_3SnH and hydrolysis of the amide group.

Scheme 5

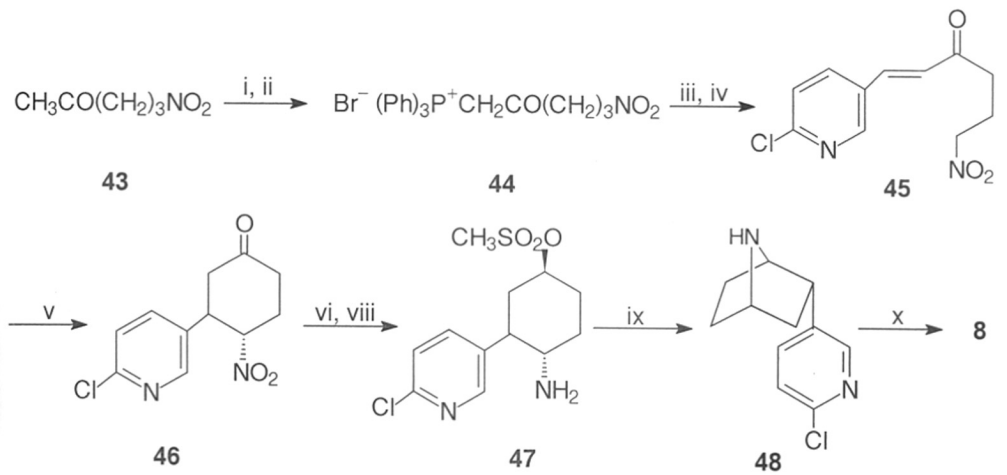


Reagents and conditions: *i) $(F_3CH_2CO)_2P(O)CH_2CO_2Me$, KHMDS, 18- crown- 6- CH_3CN complex, THF -78°C, 1 h; ii) 1,3-butadiene, toluene, 190°C, 24 h; iii) LiOH, THF, 23°C, 5 h; iv) TEA, $(PhO)_2P(O)N_3$, toluene, 85°, 12 h; v) $TMSCH_2CH_2OH$, 85°C, 12 h; vi) TBAF, THF, 55°C, 4 h; vii) $(CF_3CO)_2O$, TEA, CH_2Cl_2, 23°C, 30 min; viii) $Et_4N^+Br^-$ (10 eq), Br_2, -78°C, 30 min, CH_2Cl_2; ix) KOt-Bu, THF, -78°- 4°C, 18 h.*

The same group[32] also synthesized the enantiomerically pure **8** by separating the enantiomers from N-(trifluroacetyl)epibatidine using chiral HPLC (Daicel OD column).

Intramolecular conjugate addition of nitro alkane **45** was utilized to construct the cyclohexylamine precursor **47** by Szantay *et al*[33] during the synthesis of **8**. Cyclization of **45** on treatment with KF/AL_2O_3 resulted cyclohexanone **46** in which the pyridyl moiety and nitro moiety were *trans* to each other. Reduction of the keto group followed by the mesylation and subsequent reduction of nitro group afforded amino cyclohexanol derivative **47** which on heating in toluene resulted *endo* epimer (**48**) of **8**. Compound **48** was epimerized to **8** by heating with KO^tBu in ^{t}BuOH (Scheme 6).

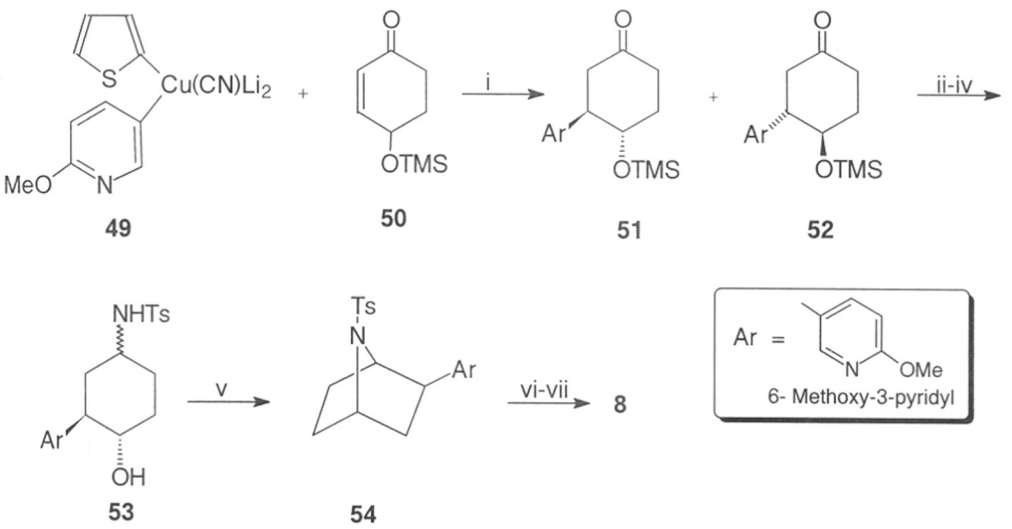
Scheme 6



Reagents and conditions: *i) Br_2 (1eq.), MeOH, rt, 4 h; ii) Ph_3P (1.2 eq), benzene, rt, 24 h (89 %); iii) CH_2Cl_2, 1 % NaOH, rt, 0.5 h (72 %); iv)* ***31*** *(0.6 eq), CH_2Cl_2, reflux, 8 h (84 %); v) KF/alumina (1.4 eq), THF, rt, 12 h (56 %); vi) $NaBH_4$ (3 eq), EtOH, 0°C, 1.5 h (67 %); vii) CH_3SO_2Cl (1.2 eq), CH_2Cl_2, pyr., rt, 12 h (91 %); viii) $SnCl_2.2H_2O$ (1.4 eq), EtOH, reflux, 24 h (80 %); ix) toluene reflux, 24 h (80 %); x) KO^tBu (1.0 eq), Bu^tOH, reflux, 30 h (50 %).*

Sestanj *et al*[34] employed conjugate addition of a "higher order" lithio cuprate **49**, derived from known 2-methoxy-5-lithio pyridine, to 4-trimethylsilyloxy-2-cyclohexenone (**50**) to afford **51** and **52** in 9 : 1 ratio (Scheme 7). Cyclohexanone derivative **51** having *trans* stereochemistry between the pyridyl and the hydroxyl moeity was converted to tosyl amine derivative **53** *via* its oxime which on subjecting to Mitsunobu reaction (DEAD, PPh_3) gave the required 7-azabicyclic ring system **54** with *exo* stereochemistry of the pyridyl moiety. Tosyl group from **54** was removed by the treatment of sodium amalgam and the resulting free amine was converted to its dihydrochloride salt. Finally, the methoxy group of pyridyl moiety was transformed to the required chloro derivative using $POCl_3/PCl_5$.

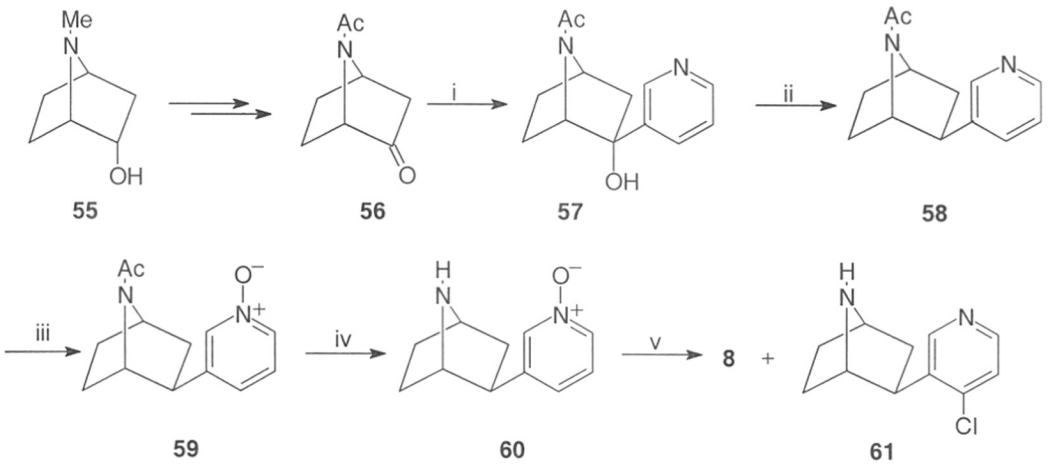
Scheme 7



Reagents and conditions: *i) -35°C to 20°C, Et_2O/THF, NH_4Cl; ii) NH_2OH, NaOAc, MeOH; iii) Ni/Al, NaOH, EtOH; iv) TsCl, $NaHCO_3$, THF/H_2O; v) DEAD, PPh_3, THF; vi) Na/Hg, Na_2HPO_4, Et_2O/HCl; vii) $POCl_3/PCl_5$, Et_2O/HCl.*

An approach similar to that of Fletcher *et al*[31] was adopted by Nakai *et al*[35] for the construction of 2-oxo-7-azabicyclo(2.2.1)heptane (**56**). Stereoselective *exo*-addition of 3-lithio pyridine to **56** led to the formation of **57** from which the hydroxyl group was reductively removed with the retention of configuration. In order to chlorinate the pyridyl moiety a series of reactions as shown in the Scheme 7 were performed. Finally, preparative HPLC was utilized to separate pure **8**.

Scheme 8



Reagents and conditions: *i) 3-bromopyridine, n-BuLi, Et_2O-THF, -78°, 1 h; ii) Ra-Ni (W-7), EtOH-H_2O (5:1), reflux, 12 h; iii) m-CPBA, $CHCl_3$, 5°C-25° C, 45 min; iv) 2N HCl, reflux, 8 h; v) $POCl_3$, reflux, 2.5 h.*

Bicyclic peroxide **63** and **64** were utilized by Ko *et al*[36] for the construction of cyclohexyl amine derivative **66**. Compound **63** was obtained in 40 % yield by the [4+2] cycloaddition reaction of **62** with singlet oxygen. The required precursor **66** was obtained by the hydrogenolysis of **63** over Rhodium followed by the reduction of the double bond to obtain 1,4-*cis*-cyclohexanediol derivative **65** which on further transformation to cyclohexyl amino-mesylate **66** and cyclisation by heating at higher dilution in chloroform yielded **8** in 78 % yield (Scheme 9).

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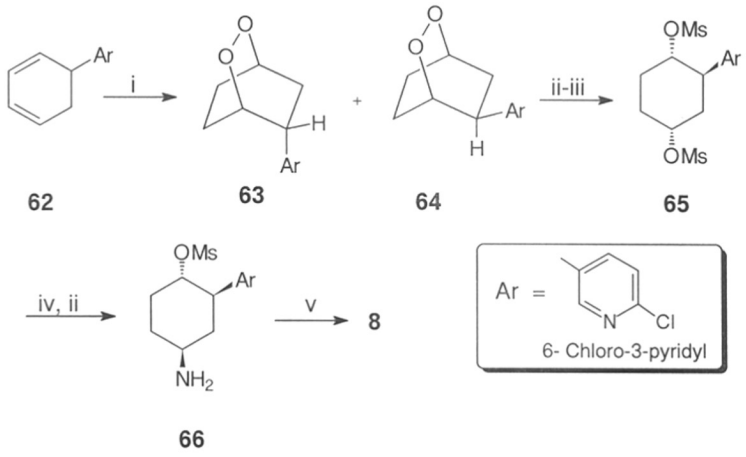
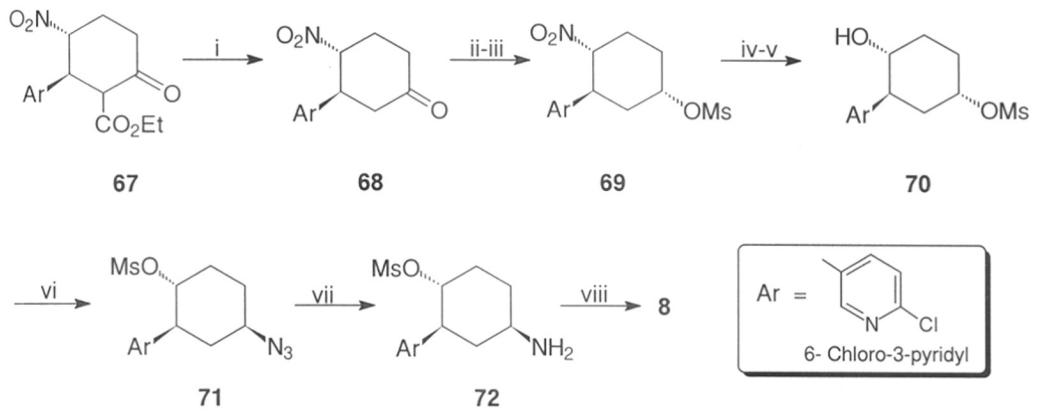
Scheme 9



Reagents and conditions: *i) Oxygen, 5,10,15,20-tetraphenyl-21H,23H-porphine, CCl_4, Hg lamp, rt (80 %); ii) H2, Rh/Al_2O_3, MeOH, rt (70 %); iii) MsCl, TEA, dioxan, 0°C (93 %); iv) NaN_3, DMF, 60°C; v) $CHCl_3$, 0.01 mol dm^{-1}, 55°C (78 %).*

Albertini *et al*[37] utilized *rac*-1α-2β-[3-(6-chloropyridyl)]-cyclohexanone (**67**), prepared from 5-(2-nitrovinyl)-2-chloropyridine either by Diels-Alder reaction or tandem Michael reaction using 2-trimethylsilyloxy-1,3-butadiene as diene or methyl 3-oxo-4-pentenoate as Michael acceptor as the key intermediate for the construction of required precursor. Though the transformation of **68** to **8** was reported by Szantay and co-workers[33], *anti*-stereochemistry of pyridyl moiety relative to the amino functionality led to unnatural *endo* isomer of **8** and had to be epimerised. In another related synthetic strategy, epimerisation step was avoided by stereoselective reduction of the carbonyl group of **68** using L-Selectride. Mesylation and transformation of the nitro moiety to hydroxyl functionality with the retention of stereochemistry afforded the mesyl alcohol **70**. Further synthetic manipulation by following the known synthetic protocol gave **8** (Scheme 10).

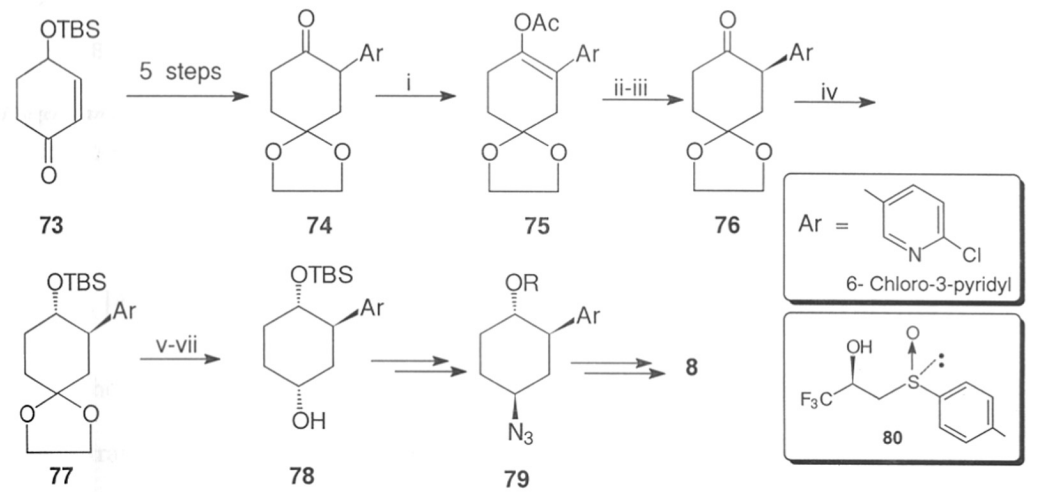
Scheme 10



Reagents and conditions: *i) DMSO, H_2O, LiCl (48%); ii) L-selectride; iii) MsCl, TEA (53%); iv) MeONa, O_3, -78°C, Me_2S, $NaBH_4$ (80%); v) NaN_3, DMF; vi) MsCl, TEA (63%); vii) $SnCl_2$, MeOH:THF (1:1), 25°C; viii) $CHCl_3$, 55°C.*

Asymmetric synthesis of (-)-**8** was accomplished by Kosugi *et al*[38] by employing the asymmetric protonation of the achiral lithium enolate of cyclohexanone derivative **74** (Scheme 11). Sequential transformation of the two keto

Scheme 11

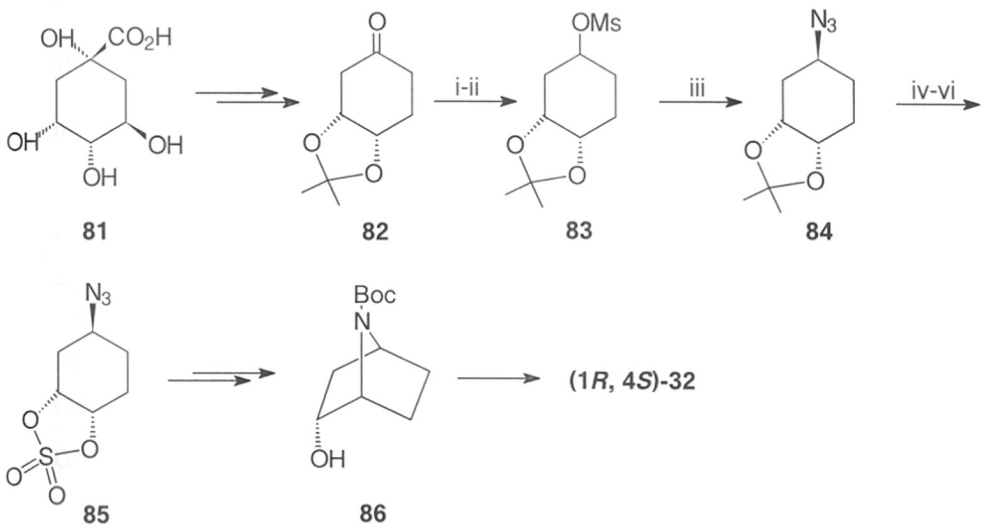


Reagents and conditions: *i)^{t}BuOK,Ac_2O, THF; ii) MeLi (2 eq), Et_2O, O°C, 15 min; iii)* ***80****, CH_2Cl_2, -90°C to -60°C; iv) $NaBH_4$, MeOH; v) 80 % aq. AcOH; vi) TBDMSCl, $^i Pr_2EtN$, DMF; vii) LiB^sBu_3H, THF.*

groups to hydroxyl and amino functionality, *trans* to each other, led to a common synthetic intermediate **78** for the construction of 7-azabicyclo[2.2.1]heptane system of **8** as developed originally by Broka *et al*[10].

A formal asymmetric synthesis of (–)-**8**, have been reported *via* **86** utilizing 3,4-O-isopropylidene -3(*R*), 4(*S*)-dihydroxy cyclohexanone (**82**), prepared from D(-)-Quinic acid in five steps[39] (Scheme 12).

Scheme 12



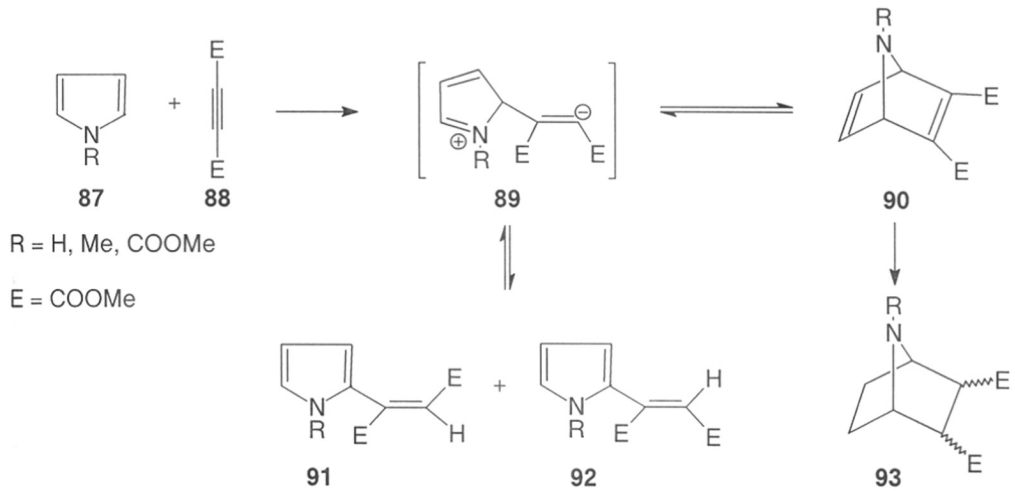
Reagents and conditions: *i) $NaBH_4$; ii) MsCl, TEA (86 %); iii) NaN_3, DMF, 80°, 24 h (81 %); iv) H_3O^+ (98 %); v) $SOCl_2$, TEA; vi) $NaIO_4$, $RuCl_3$.*

3.2. [4+2] Cycloaddition of pyrroles with acetylenic equivalents

The [4+2] cycloaddition reaction between pyrroles and dienophiles has been demonstrated to be the general method for the synthesis of 7-azabicyclo(2.2.1)heptane derivatives **93** *via* the hydrogenation of the cycloadduct 7-

azabicylo(2.2.1)hept-2-ene or 7-azabicyclo(.2.2.1)hept-2,5-diene derivatives **90**. Pyrrole (**87**, R = H) being a poor diene undergoes competing Michael addition reaction in addition to cycloaddition reaction with alkenyl and acetylenic dicarboxylic acid derivatives **88** (Scheme 13)[40]. However, when an electron withdrawing group (R = CO_2Me or SO_2Ph) is placed on the nitrogen atom of pyrrole, the aromatic ring is found to be more reactive as a diene towards acetylenic dienophiles (**88**)[41]. A number of successful [4+2]-cycloaddition reactions using of N-protected pyrroles and acetylenic derivatives are reported[28]. This protocol has formed the basis of various synthetic strategies for **8** (Scheme 13).

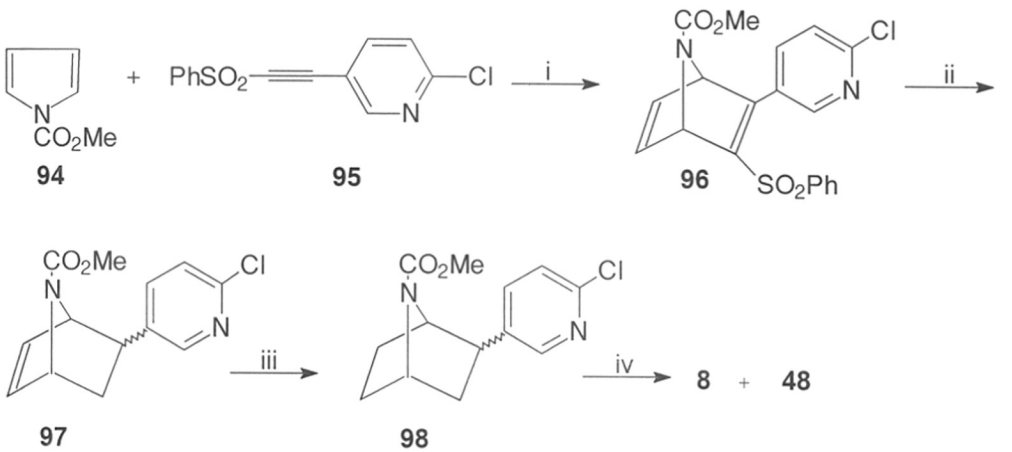
Scheme 13



Shen T.Y. *et al*[42] employed [4+2] cycloaddition of N-carbomethoxy pyrroles **94** and phenyl sulfonyl 6-chloro-3-pyridyl acetylene **95** for the synthesis of **8**. Required acetylenic precursor **95** was prepared from methyl phenyl sulfone and 6-chloro-nicotinyl chloride in two steps[43, 44]. [4+2]-Cycloaddition was carried out by heating **95** at 85°C for 24 h with the excess of N-carbomethoxy pyrrole (**94**). Treatment of the

resultant 7-azanorbornadiene derivative **96** with 4 eq of 6 % sodium amalgam resulted in the desulfonation as well as reduction of the conjugate double bond in one pot to yield a 1:2 mixture of *exo* and *endo* isomers of N-carbomethoxy dehydroepibatidine **97**. Reduction of the remaining double bond by hydrogenation over 10 % Pd-C and deprotection of N-carbomethoxy group with hydrobromic acid afforded a 1:2 mixture of **8** and its *endo* isomer **48** (Scheme 14).

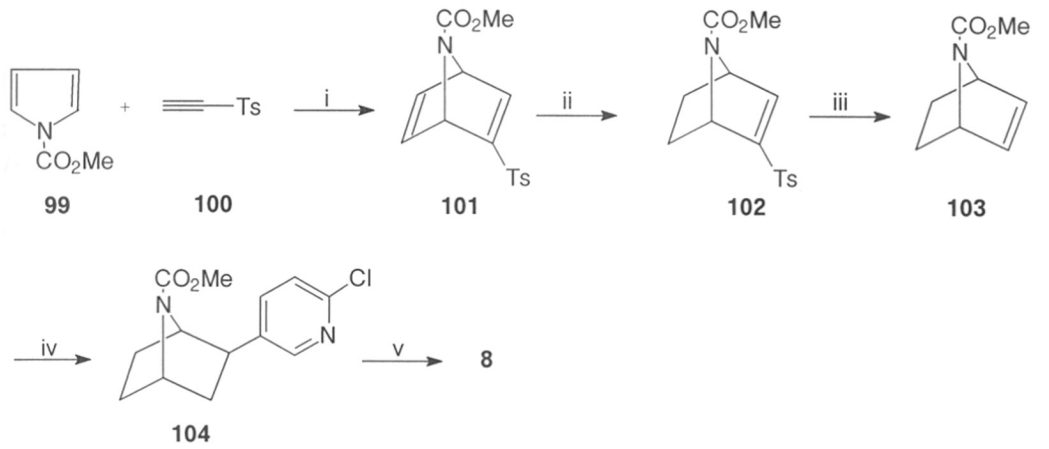
Scheme 14



***Reagents and condition:** i) 80-85°C, 24 h (50-70 %); ii) 6 % Na(Hg), -20°C- rt, 3 h (36-42 %); iii) H_2/10 % Pd-C, 5 min (92 %); iv) 33% HBr/HOAc, 20 h.*

N-Carbomethoxy-7-azabicyclo(2.2.1)hept-2-ene (**103**), prepared by employing the [4+2] Diels-Alder cycloaddition of N-carbomethoxy pyrrole (**99**) with *para*-toluene sulfonyl acetylene (**100**) by following the route reported by Altenbach *et al*[45], have been utilized as a precursor during the synthesis[46] of **8**. Cycloaddition of **99** and **100** afforded N-carbomethoxy-7-azabicyclo(2.2.1)hepta-2,5-diene (**101**) in 36 % yield. Catalytic hydrogenation followed by the treatment of **102** with 6 % sodium amalgam in methanol-THF affords the alkene **103** (Scheme 15).

Scheme 15

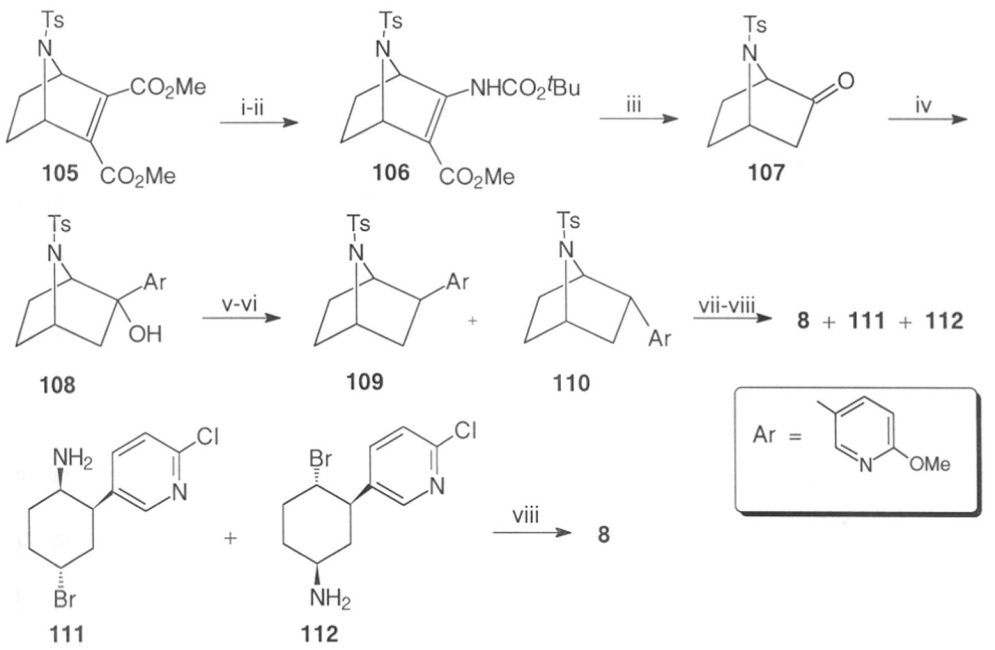


Reagents and coonditions: *i) 80-85°C, 24 h (36%); ii) H2, Pd/C, rt (99%); iii) 6% Na/Hg, MeOH-THF, Na_2HPO_4, -78°C-rt ; iv) $(Ph_3P)_2Pd(OAc)_2$, DMF, piperidine, HCO_2H, 70°, 6.5 h (35%); v) HBr-AcOH, rt, 22 h.*

6-Chloro-3-pyridyl moiety was stereoselectively introduced to alkene **103** in *exo* orientation utilizing reductive palladium catalysed Heck coupling protocol. N-carbomethoxy epibatidine (**104**) obtained from the coupling reaction (35% yield) was further treated with hydrogen bromide in acetic acid to yield **8** in 74% yield (Scheme 15).

Okabe and Natsume[47] utilized [4+2]-cycloaddition strategy to prepare **105** as a precursor during the synthesis of **8**. Hydrolysis of **105** to corresponding monoester followed by Curtius rearrangement afforded enamine **106** which on heating with 2% HCl containing 1,4-dioxan and water (3:2) at 80°C for 14 h provides **107**. Addition of 3-lithio-pyridyl derivative to **108** followed by dehydration and catalytic hydrogenation over 10% Pd-C in 1% HCl solution of methanol and water (11:1) at room temperature for 4 h gave a mixture of *endo* and *exo* isomers of N-tosyl derivatives **109** and **110** in 1:3 ratio (Scheme 16).

Scheme 16



Reagents and conditions: *i) LiOH, DME:H_2O (2:1) (70%); ii) DPPA, t-BuOH (75 %); iii) 2 % HCl Dioxan-H_2O (68 %); iv) 5-bromo-2-methoxypyridine, n-BuLi, Et_2O, 80°C (88 %); v) $MeOOCNSO_2NEt_3^+$, benzene (68 %); v) H_2, Pd/C, HCl, ^iPrOH (95 %); vi)DMF-$POCl_3$ (89 %); vii) 30 % HBr-AcOH, PhOH.; viii) LiOH, DME-H_2O.*

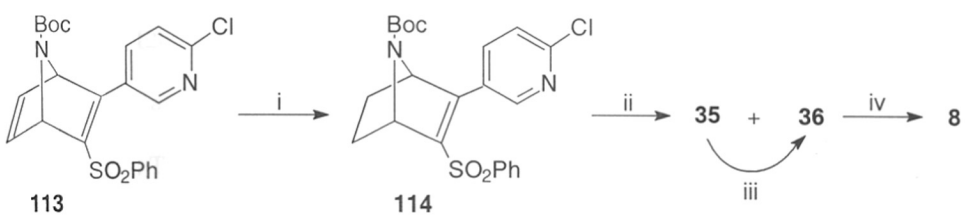
Hydrogenation in acidic medium dramatically reversed the ratio of *endo*:*exo*. The plausible explanation for the observed reversal is based on the assumption that protonic cation associated with an alcohol molecule interacts with electron rich double bond at the more reactive *exo* face of the bicyclo framework which is partly assisted by slightly basic tosyl nitrogen , thus, regulating the approach of the palladium catalyst from the *endo* side favouring the formation of *exo* product **109**. The *exo* selectivity for the palladium catalyzed hydrogenation was further improved

(3.5:1) by using 2-propanol which being bulkier than methanol further assisted in blocking the *exo* face of the double bond.

The methoxy group in the pyridyl moiety was converted to chloro substituent by employing Vilsmeier reagent. The final step involving the removal of tosyl group required forcing conditions by heating a chloroform solution of **109** with 30 % HBr-acetic acid and phenol in a sealed tube at 55°C for 18 h which resulted complicated reaction products consisting of **8** and bromoamines **111** and **112**.

Carroll and Kotian[48] essentially modified the approach of Shen *et al*[42] for the synthesis of **8**. They observed that the use of N- ^{t}Boc group instead of N- CO_2Me facilitates the synthesis. The selective reduction of the least substituted double bond of the cycloadduct **113**, carried out using Ni_2B prior to desulfonation, followed by the treatment with sodium amalgam led to the desulfonation with concomitant reduction of the olefin yielding a mixture of *endo* and *exo* isomers **35** and **36** with improved yields. *Endo* isomer **35** was further epimerised to *exo* isomer **36** using KO^{t}Bu as base. Deprotection of Boc moiety with trifluoroacetic acid afforded **8** in 40% overall yield (Scheme 17).

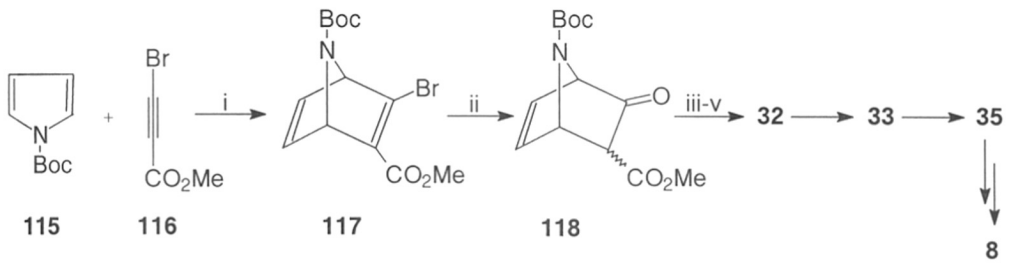
Scheme 17



Reagents and conditions: *i) Ni_2B, EtOH-H_20 (96 %); ii) 6 % Na/Hg, Na_2HPO_4, -20°C, THF/CH_3OH (1:1); iii) KO^{t}Bu, ^{t}BuOH, reflux, 18 h (46 %).; iv) TFA, CH_2Cl_2, 3 H (97 %).*

Zhang and Trudell[49] have synthesized 7-azabicyclo(2.2.1)heptan-2-one (**32**)by the cycloaddition reaction of methyl 3-bromopropiolate (**116**) as dipolarophile with N-Boc pyrrole (**115**).

Scheme 18

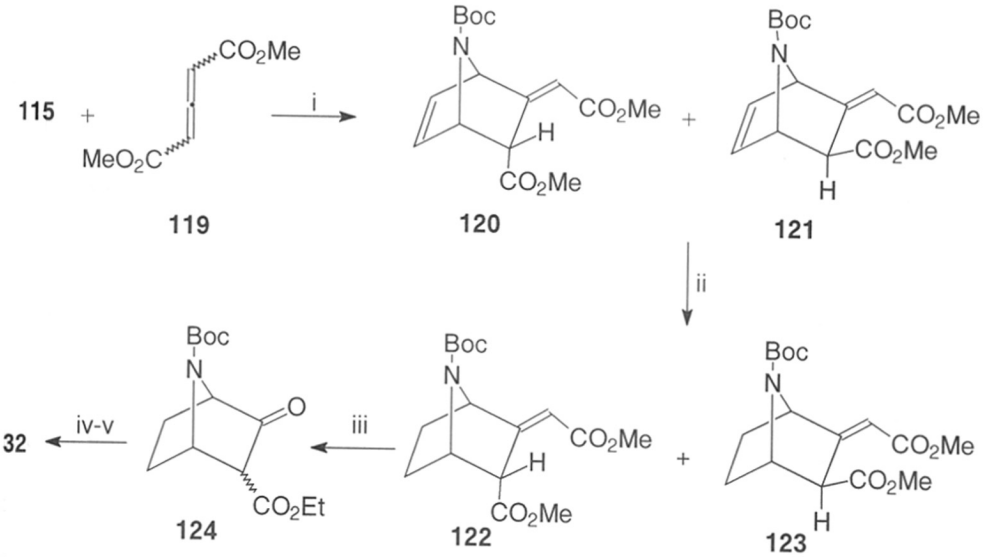


Reagents and conditions: *i)90°C, 30 h (60 %); ii) Et_2NH, TEA, 1.5 h, 10 % HCl,4 h (87 %); iii) H_2, Pd/C , 10 h (99 %); iv) 10 % HCl reflux, 3 h ; v) $(Boc)_2O$, TEA, CH_2Cl_2, 24 h (77 %).*

Bicyclic azanorbornadiene **117** was converted to β-keto ester **118** by treating with diethyl amine in acetonitrile in the presence of triethylamine at room temperature followed by the hydrolysis at room temperature. Transformation of β-keto ester **118** to **8** utilized a series of known reactions as depicted in Scheme 18.

Trudell and Pavri[50] employed (4+2) cycloadition reaction of allenic esters **119** and N-acyl pyrrole **115** towards the synthesis of ketone **32**, a key intermediate utilized by many workers for the synthesis of **8**. Cycloaddition reaction afforded only two isomers (**120** and **121**) of the possible four isomers, which were regioselectively hydrogenated at the least substituted site to give the alkylidenes **122** and **123** quantitatively. The *endo* isomer **122** was subjected to ozonolysis to obtain the β-keto ester **124** which upon decarboxylation afforded ketone **32** (Scheme 19).

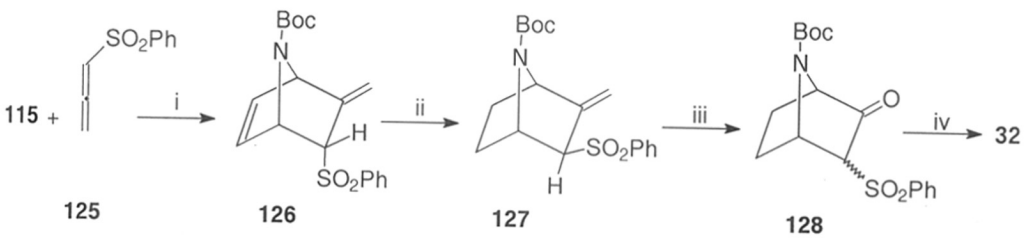
Scheme 19



Reagent and conditions: *i) 85-90°C, 14-16 h (65 %); ii) H_2, 5 % Pd/C, EtOH (98 %); iii) O_3, -78°C, CH_2Cl_2, Me_2S (70 %); iv) 10 % HCl, reflux. v) $(Boc)_2O$*

As an alternative to the allenic ester **119**, the N-acyl pyrrole **115** was also reacted with 1-(bezene sulfonyl)-1,2-propadiene **125** to get the cycloadduct **126** in 45% yield. Hydrogenation followed by ozonolysis of **126** gave **128**. Reductive cleavage of benzene sulfonyl moiety from **128** using Al(Hg) gives ketone **32** in 60 % yield (Scheme 20).

Scheme 20

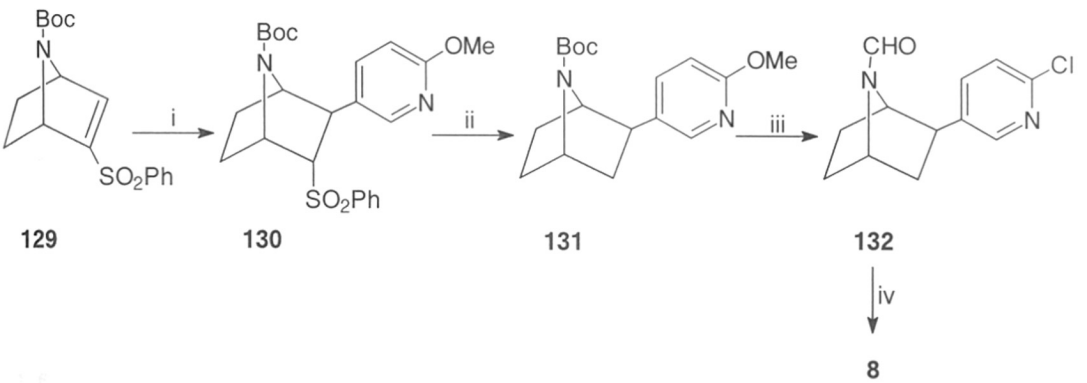


Reagent and conditions: *I) 85-90°C, 14-16 h (65 %); ii) H_2, 5 % Pd/C, EtOH (98 %); iii) O_3, -78°C, CH_2Cl_2, Me_2S (70 %); iv) Al(Hg), THF, H_2O (60 %).*

The later approach with allenic sulfones was found to be more efficient and high yielding than the former allenic ester sequence.

Simpkins *et al*[51] have utilized the alkenyl sulfone intermediate **129,** obtained by the [4+2]-cycloaddition of N-Boc pyrrole (**115**) with acetylenic sulfone **100**, in their synthesis of **8**. Conjugate addition of 3-lithio-6-methoxy pyridine gave the desired adduct **130** as a single diastereomer with *exo*-orientation of pyridyl moiety. Desulfonation with sodium amalgam followed by the treatment with $POCl_3$ in DMF and hydrolysis using HCl afforded target molecule (Scheme 21). However, it may be noted that the authors have opted for 3-lithio-6-methoxy pyridine instead of 6-chloro-3-lithio pyridine due to the concomitant loss of chlorine substituent from the chloropyridyl moiety during the reductive removal of sulfonyl moiety from the resultant product.

Scheme 21



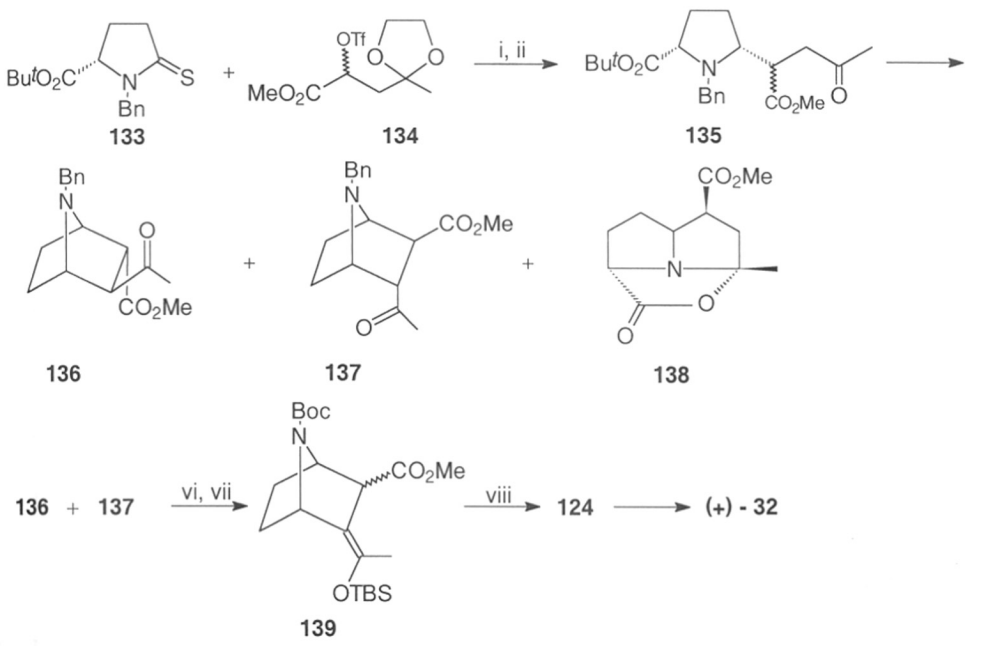
Reagents and conditions: *i) 6-methoxy-3-lithiopyridine, THF, -78°C (85 %); ii) 6 % Na(Hg), THF, MeOH (58 %); iii) $POCl_3$, DMF, 95° C (78 %); iv) HCl, THF, 55-60°C (79 %).*

3.3. Miscellaneous

Rapoport *et al*[52] employed intramolecular Mannich cycilsation protocol of iminium ion derived from substituted proline derivatives for the synthesis of (+) and (–)- N - Boc - 7- azabicyclo (2.2.1) hetan -2-one (**32**), a versatile intermediate which could be utilized for the synthesis of the either of enantiomer of **8**.

N-benzyl-5-(1′-methoxy carbonyl-3′-oxo butyl)-proline (**135**), prepared from pyroglutamic acid, was converted to *trans*-2,3-disubstituted-7-azabicyclo(2.2.1) heptane derivative **136** and **137** *via* a decarboxylation-iminium ion cyclization reaction sequence. The mixture of **136** and **137** was converted to **32** by transforming to silyl enol ether **139**, followed by ozonolysis and decarboxylation of the resultant substrate **124** (Scheme 22).

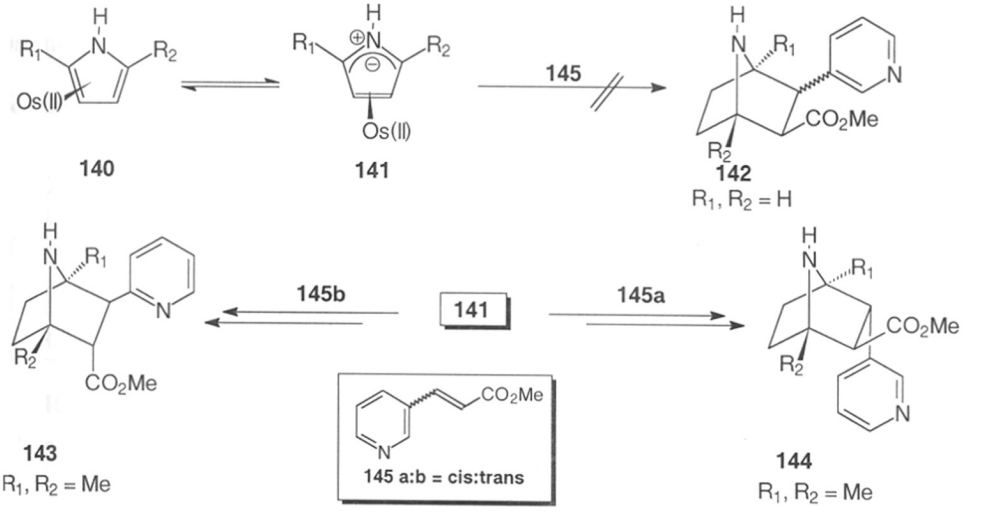
Scheme 22



Reagents and conditions: *i) NMP, ii) H_2, Pt/C iii) H^+/H_2O, iv) $(COCl)_2$, v) Δ, vi) H2, Pd/C, vii) $(Boc)_2O$ viii) NaH, TBSCl, ix) O_3, DMS x) H^+/H_2O, $(Boc)_2O$.*

Harman and co-workers[53] in their synthetic endeavour towards 7-azabicyclo(2.2.1)heptane derivatives have demonstrated that the complexation of pyrrole by the π-base pentaammine osmium (II) across C3 and C4 transforms the uncoordinated portion of the aromatic pyrrole nucleus into an azomethine ylide **141** and there by dramatically enhancing its tendency to unergo 1,3-dipolar cycloaddition reaction with electron deficient alkenes (Scheme 23).

Scheme 23



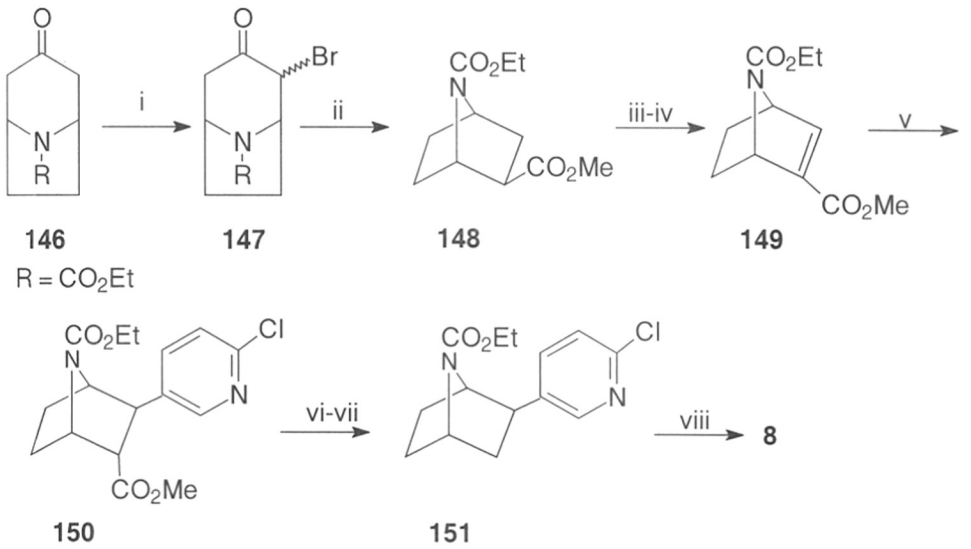
It has been further observed by these workers that when the pyrrole nitrogen is unsubstituted, the cycloaddition proceeds with *exo*-orientation for the electron withdrawing substituent and *endo*-selectivity when nitrogen is either alkylated or silylated.

The complexed cycloadduct was highly stabilized by metal co-ordination in sharp contrast to 7-azanorbornene derivatives obtained from Diels Alder cycloaddition reaction. Cycloadducts were decomplexed by using DDQ as oxidant in

acetonitrile and subsequently hydrogenated over 10% Pd-C to yield 7-azanorbornanes. However, author's all attempts to synthesize **8** using cycloadduct **142** as precursor have failed due to lack of reactivity of pyrrole complex **140** (R_1, R_2 = H) towards pyridyl acrylate **145** in sharp contrast to moderate reactivity exhibited by **140** (R_1, R_2 = Me) which yielded cycloadducts **143** and **144** .

Bai *et al*[54] have employed a distinctly different route for the construction of 7-azabicyclo(2.2.1)heptane structural framework of **8** by ring contraction of the commercially available tropionone utililizing Favorskii rearrangement (Scheme 24).

Scheme 24



Reagent and conditions: *i) $CuBr_2$ (2 eq), $CHCl_3$, EtOAc, reflux, 1 h; ii) NaOMe (3 eq), DME, rt, 0.5 h (56 %); iii) LDA, THF, -78°, 20 min, then PhSeBr; iv) 30% H_2O_2, CH_2Cl_2, rt, 15 min (68%); v) 6-chloro-3-iodopyridine, $(Ph_3P)_2Pd(OAc)_2$ (cat), TEA, HCO_2H, DMF, rt, 4 d (56 %); vi) $LiOH.H_2O$, MeOH-H_2O (3:2); vii) $(COCl)_2$, 2-mercatopyridine-N-oxide sodium salt, t-BuSH, benzene, reflux, 3 h (75%); viii) TMSI (1.1 eq), $CHCl_3$, reflux,4 h.*

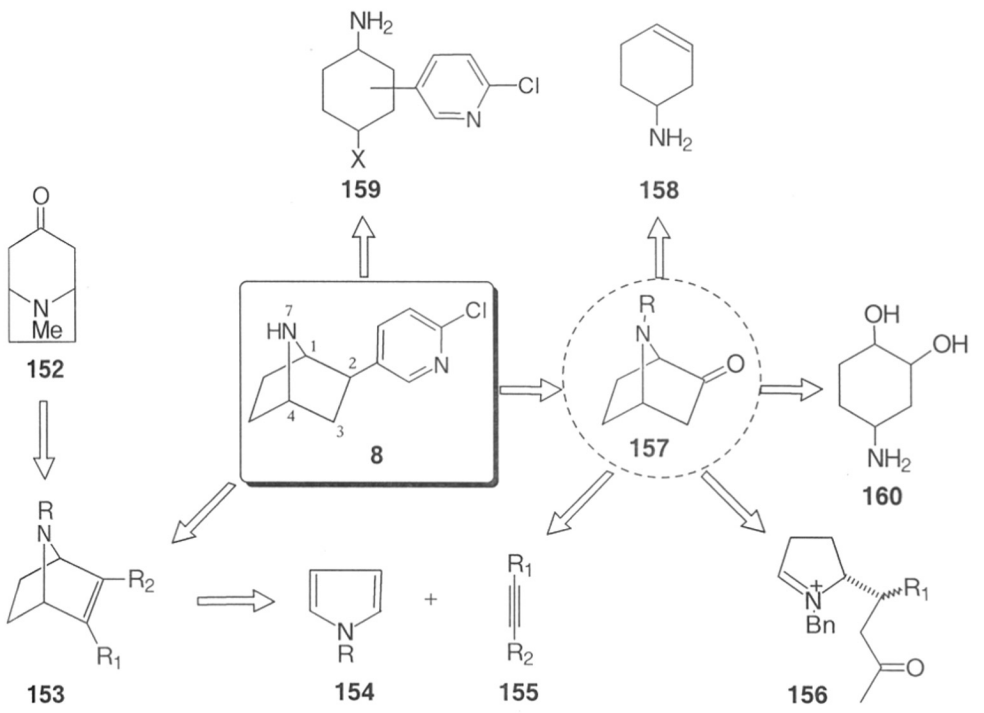
N-Carboethoxy tropinone (**146**) was brominated using cupric bromide in a mixed solvent of $CHCl_3$ and EtOAc to obtain monobromide **147**. Favorskii rearrangement of **147** was affected stereoselectively by using sodium methoxide as base in DME to obtain 7-azabicyclic ester **148** with *exo*-orientation of carbomethoxy moiety. Unsaturated ester **149** was obtained by α-selenation of **148** followed by selenoxide elimination using H_2O_2. Attempted conjugate addition of 5-pyridyl cuprate to **149** have failed under various conditions. However, reductive palladium catalyzed Heck coupling reaction of **149** with 6-chloro-3-iodo pyridine by stirring in DMF containing triethyl amine, formic acid and 8 mol % $(PPh_3)_2$ $Pd(OAc)_2$ at room temperature for 4 days afforded coupling product **150** stereoselectively (Scheme 24). However the same reaction failed at higher temperature probably due to competing retro-Diels Alder cycloaddition.

Compound **150** is converted to **8** by decarboxylating the carboxyl group employing the Barton's radical decarboxylation protocol[55] followed by deprotection of carboethoxy group with iodo trimethylsilane.

4. Summary

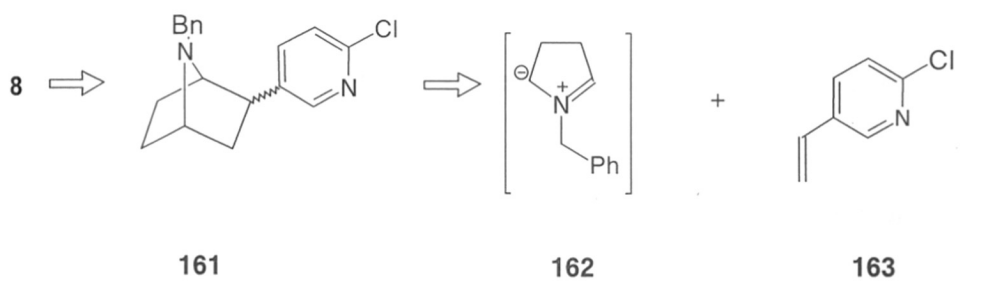
From the above survey of of literature precedent, it is evident that there are only two major routes: i) Transannular cyclisation of 1,4-cyclohexyl amine derivatives and ii) [4+2]-Cycloaddition of pyrroles with acetylenic equivalents, and few miscellaneous approaches involving Favorskii rearrangement and intramolecular iminium ion Mannich cyclisation towards the synthesis of **8**, which can be briefly summarised retrosynthetically as shown in Scheme 25.

Scheme 25



Preceding chapters would describe in detail our approach[56, 57] towards **8**, involving the [3+2]-cycloaddition of pyrrolidine based non-stabilized azomethine ylide with vinyl pyridine derivative as shown retrosynthetically in Scheme 26.

Scheme 26



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Chapter. 2

Stereoselective Synthesis of Epibatidine

"When we have been faced with a problem of effecting a chemical synthesis we have sought known methods. We have not paused to think why we do not invent a new method every time. If we adopt this philosophy we are going to be extremely busy till the end of the century (a) trying to equal the enzymes and (b) thinking of new ways of synthesis."

Sir. Derek. H. R. Barton.
Chem. Br. 1973, 9, 149.

1. Introduction

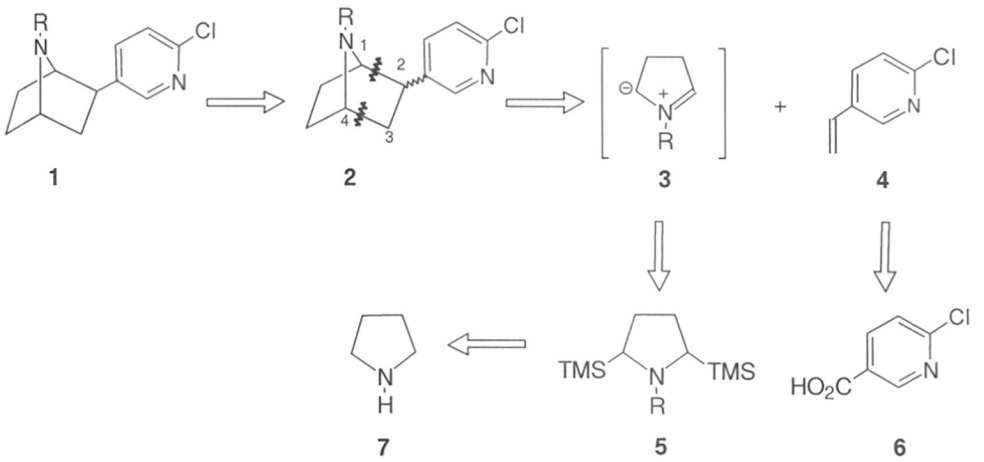
Due to the intriguing pharmacological activity, interesting structural features and scarcity in nature (less than 5 mg was isolated from 750 frogs)[1], Epibatidine (**1**) has been the subject of many biological[2-17] and synthetic studies[18-41]. Basically, the strategies adopted for the synthesis of this novel alkaloid, involved the construction of 7-azabicyclo(2.2.1)heptane skeleton as described in the previous chapter. Intramolecular transannular cyclisation of cyclohexylamine derivatives, originally developed[42] for the construction of 7-azanorbornane system, employs multiple steps even to reach the crucial *trans*-1,4-amino cyclohexanol derivatives. The [4+2]-cycloaddition strategy, utilizing N-protected pyrroles and activated dienophiles, developed for assembling the 7-azanorbornadienes[18] and its further elaboration to **1** have involved many steps with overall poor yields. Elaboration of tropinone skeleton into **1** *via* Favorskii rearrangement, recently reported by Bai *et al*[39], though is elegant, yet suffers from low yield. Intramolecular iminium-ion Mannich cyclisation protocol, developed by Rapoport *et al*[37] utilizes a long reaction sequence even to reach the key intermediate originally developed by Fletcher *et al*[21].

2. Retrosynthetic Analysis and Design

For an elegant design of synthetic route to **1**, retrosynthetic scission of 7-azabicyclo(2.2.1)heptane framework of **1** at C_1-C_2 and C_3-C_4 bond led us to visualize pyrrolidine and 6-chloro-3-vinyl pyridine as potential precursors. It was envisaged that the only way this synthetic design can be realised is by a [3+2]-dipolar cycloaddition of cyclic azomethine ylide **3**, derivable from pyrrolidine (**7**), with 6-chloro-3-vinyl pyridine (**4**). The corresponding pyrrolidine based azomethine ylide **3**

could be easily generated from N-alkyl-2,5-bis(trimethylsilyl)pyrrolidine (**5**) by a protocol developed in our laboratory[43-47]. The synthesis of dipolarophile **4**, can be achieved *via* Horner-Wordsworth-Emmons or a Wittig olefination reaction of 6-chloro-3-pyridyl carboxaldehyde, easily obtainable from commercially available 6-chloro-3-pyridine carboxylic acid (**6**) (Scheme 1).

Scheme 1

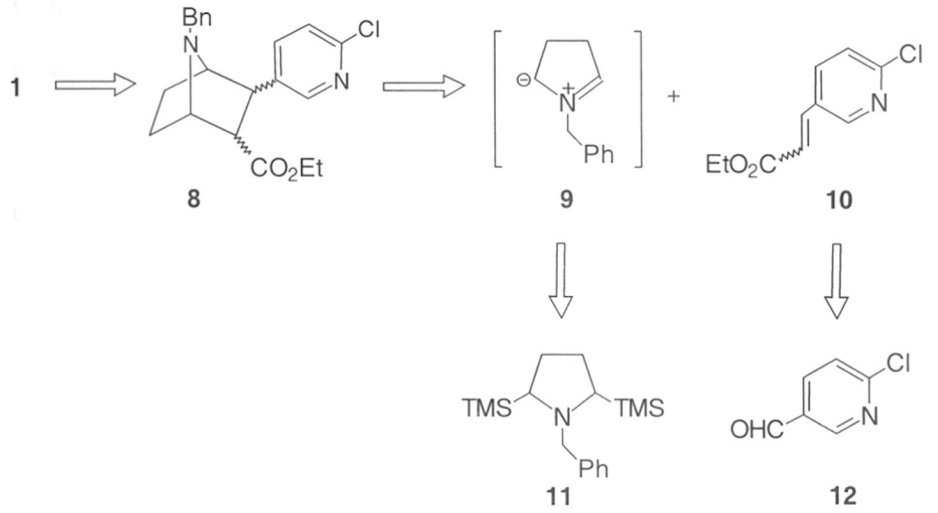


1 **2** **3** **4** **5** **6** **7**

It is evident from the above retrosynthetic analysis that [3+2]-cycloaddition of cyclic azomethine ylide **3**, where the 4π-electron conjugation is inside the pyrrolidine ring, with vinyl pyridine would directly provide an access to N-alkyl-2-(6-chloro-3-pyridyl)-7-azabicyclo(2.2.1)heptane (**2**). However, it is precedented in the literature[48] that non-polarised alkenes are unreactive towards the non-stabilised [3+2]-azomethine ylide cycloaddition reaction. Keeping this fact in mind, it was envisaged to employ vinyl pyridine conjugated with an electron withdrawing functionality *viz.* carboalkoxy moiety, which can easily be removed at a later stage of the synthesis. Thus, the cycloadduct **8** that would result from the cycloaddition of **9** and ethyl-(6-

chloro-3-pyridyl)propen-2-oate (**10**) was expected to be a simple and elegant precursor towards the synthesis of **1**. N-Debenzylation and reductive decarboxylation of the intermediate **8** would finally lead to **1** (Scheme 2).

Scheme 2.



It would be worthy of mention, since the chloropyridyl moiety in naturally occurring **1** is *exo*-oriented it becomes essential to monitor the stereochemical course of the reaction employed. Non-stabilized azomethine cycloaddition reaction are known[48-52] to be highly stereoselective towards the electron withdrawing group of the dipolarophile and hence the stereoselectivity of the chloropyridyl moiety could be governed by introducing proper variation in the olefin geometry (*E*/*Z*) of **10**.

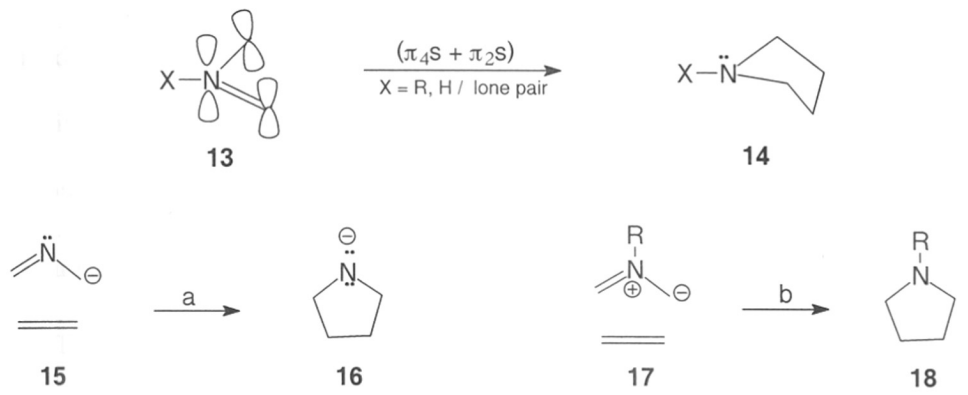
Since our synthetic endeavor towards **1** involves [3+2]-cycloaddition of azomethine ylide as a key step, it would be appropriate to highlight the salient features of azomethine ylide as 1,3-dipole and the protocol developed in our laboratory for its generation and trapping.

3. Azo-methine Ylide

3.1. Background

Azomethine ylides are planar intermediate composed of one nitrogen and two terminal sp^2 carbons. At the most, four geometrical isomers are possible for these transient intermediates. Their cycloadditions to olefin or acetylene dipolarophiles give rise to the formation of two sets of carbon-carbon bond in a single step (Figure 1).

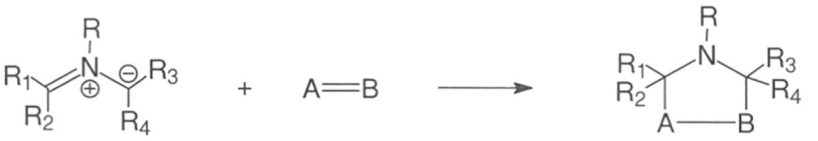
Figure 1



The [3+2]-cycloaddition of azomethine ylide requires an olefin as the 2π-electron component and a 2-azaallylic anion system as the 4π-electron fragment. When X is a lone pair, the cycloaddition is that of a 2-azaallyl anion leading to a pyrrolidine anion **16** as the product (reaction a). When X is a substituent H or R, the reaction is that of a neutral 1,3-dipole (most commonly known as azomethine ylide), leading to a neutral pyrrolidine **18** (reaction b). In both the cases, a 2-azaallylic orbital is participating in the reaction.

These 1,3-dipolar cycloaddition of azomethine ylides with an olefin (Scheme 3) has been identified as one of the most attractive strategy for the construction of pyrrolidine ring system, a frequently encountered structural unit of many synthetically challenging alkaloids[50]. The strong preference for this reaction in the

Scheme 3



19 **20** **21**

alkaloid synthesis have stemmed due to its chemo-, stereo- and regio-selectivity and reactivity[48-52]. Usually these cycloadditions have shown preference towards *endo*-addition similar to the *iso*-electronic Diels Alder reaction[51].

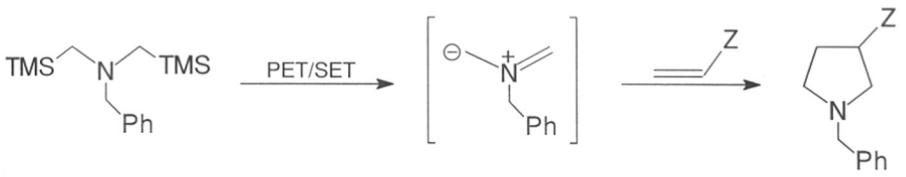
3.2. Our Concept And Protocol

Though there are several methods available[48-52] for the generation of acyclic azomethine ylide, to the best of our knowledge, there is no method for the generation of cyclic azomethine ylide; where whole of the ylide conjugation is included in the N-heterocyclic ring.

In order to overcome the limitations involved and to provide a general and versatile method for the generation of cyclic and acyclic azomethine ylide, our research group have previously demonstrated the generation and trapping of non-stabilised azomethine ylide **23** from N,N'-bis(trimethylsilyl methyl)benzyl amines

initiated by one electron transfer processes promoted either by PET or Ag(I)F[43, 44] (Scheme 4).

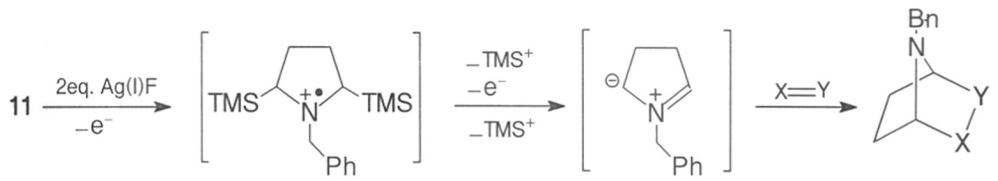
Scheme 4



22 **23** **24**

The basic concept in the generation of **23** from **22** involved sequential one electron oxidation of the lone pair of electrons located on nitrogen and exploitation of the β-silicon effect[53] to induce sequential desilylation processes to generate azomethine ylide (1,3-dipole) (Scheme 4). Thus, one electron oxidation of N-benzyl-2,5-bis(trimethylsilyl)pyrrolidine (**11**) using Ag(I)F as one electron oxidant leads to the formation of radical cation **25**, which loses silyl cation (TMS^+) and subsequent one electron oxidation results in the iminium cation. Elimination of the second silyl cation (super acid group) leads to the formation of non-stabilized azomethine ylide **9** (Scheme 5)[45].

Scheme 5



25 **9** **26**

The above proposed sequential one electron oxidative mechanistic pathway for the generation of azomethine ylide (**9**) is supported by the fact that only N,N'-bis(trimethylsilyl methyl)alkyl amines affords the cycloadducts and not the corresponding carbamates. This mechanistic route finds further confirmation in a

report published by Torii *et al*[54] where bis(trimethylsilyl methyl)benzyl amine, introduced from our laboratory as a precursor, is transformed to azomethine ylide *via* two electron oxidation effected electrochemically or by using one electron oxidative reagent $VO(acac)_2$ in combination with N-oxyl.

Isolation and characterization of Epibatidine (**1**) in 1992 by Daly and co-workers[1] gave further impetus to our research interest in this area, thus offering a synthetically challenging target and an opportunity to prove the synthetic potential of our methodology towards the construction of this alkaloid.

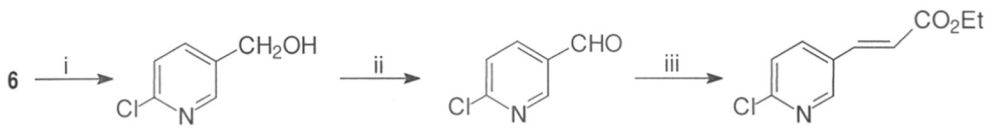
4. Stereoselective Synthesis of Epibatidine : Path I

Synthesis of **1** , as perceived through the retrosynthetic strategy described in the previous section, was initiated with the preparation of dipolarophile **28** and the azomethine ylide precursor **11** followed by the crucial cycloaddition reaction.

4.1. Synthesis of *trans*- Ethyl- 3- (6- Chloro-3-Pyridyl)- 2- Propenoate (28):

Dipolarophile **28** is prepared in three steps starting from commercially available 6-chloro-3-nicotinic acid (**6**). Reaction sequence comprises of reduction, oxidation and Wittig olefination as shown in Scheme 6.

Scheme 6



27 (44%) **12** (80%) **28** (80%)

Reagents and conditions: *i) THF, $LiAlH_4$, 0°C. ii) PCC, Celite, DCM, 3h. iii) Ph_3PCHCO_2Et, CH_3CN, Δ, 3h.*

Lithium aluminium hydride reduction of **6** in THF at 0°C afforded 6-chloro-3-pyridyl carbinol (**27**) in 45% yield. Oxidation of **27** with pyridinium chlorochromate in dichloromethane at room temperature gave 6-chloro-3-pyridyl carboxyaldehyde **12** in 80% yield as a white crystalline solid mp. 80-82 °C. Wittig olefination of **12** by refluxing with ethyl triphenyl phosphoranylidene acetate in acetonitrile for 6 h afforded *trans*-ethyl-3-(6-chloro-3-pyridyl)-propen-2-oate (**28**) in 80 % yield as a white crystalline solid mp. 81-83 °C.

IR spectrum of compound **28** showed a strong band at 1711 cm^{-1} indicating the presence of a carboxylate group.

^1H NMR spectrum displayed a triplet and a quartet at δ 1.25 (J = 7.30 Hz, 3H) and δ 4.2 (J = 7.30 Hz, 2H), respectively, for the ethyl group of carboethoxy moiety. A set of two doublets observed at δ 6.5 and δ 7.65 with a coupling constant, J = 14.45 Hz, suggests the presence of vicinal olefinic protons with *trans*-stereochemistry. Signals at δ 7.35 (d, J = 8.4 Hz), 7.8 (dd, J = 8.42, 2.10 Hz) and 8.5 (d, J = 2.23 Hz) corresponds to $H_{5'}$, $H_{4'}$ and $H_{2'}$ protons of pyridyl moiety, respectively.

^{13}C NMR spectrum displayed a total of ten signals at δ 14.3, 60.9, 121.3, 124.6, 129.3, 136.7, 139.3, 149.5, 152.7 and 166.0. ^{13}C NMR INEPT experiment exhibited the presence of methyl and methylene carbons of ethyl group in carboethoxy moiety at δ 14.3 and 60.9, respectively. The two vinylic C_2 and C_3 carbons are observed at δ 121.3 and δ 124.6, respectively. Three methine aromatic carbons at δ 136.7, 139.3 and 149.5 are attributed to C_4, $C_{5'}$ and $C_{2'}$ respectively. The two quarternary aromatic carbons at

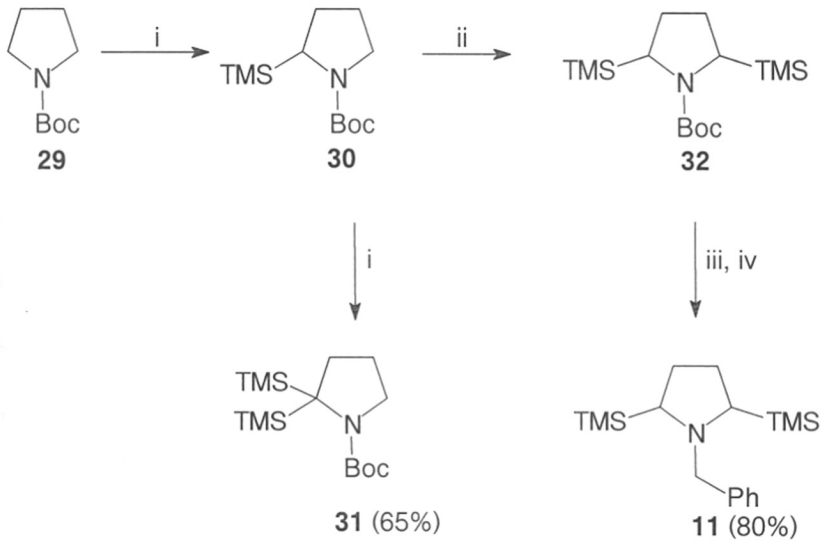
δ 129.3 and 152.7 are attributed to $C_{3'}$ and $C_{6'}$ respectively, and a signal at δ 166.0 to the carbonyl moeity of carboethoxy group.

Mass spectrum exhibited a molecular ion peak at 211 (30) along with other major fragments at 142 (42), 166 (100) and 138 (53).

4.2. Preparation of N-benzyl-2,5-bis(trimethyl silyl) pyrrolidine (11):

The key precursor **11,** required for the generation of azomethine ylide, is prepared in five steps starting from commercially available pyrrolidine by following the steps as shown in Scheme 7.

Scheme 7



Reagents and conditions: *i) Ether, TMEDA, -78 °C, s-BuLi, 2 h, TMSCl. ii) Ether, TMEDA, -45 °C, s-BuLi, -35 °C (15 min), -45 °C, TMSCl. iii) DCM, TFA, rt, 4 h. v) BnCl, CH_3CN, Δ, 4h.*

α-Silylation of **29** essentially employed the protocol reported by Beak and co-workers[55]. Treatment of **29** in ether at -78 °C with *s*-BuLi in the presence of tetramethyl ethylene diamine (TMEDA) followed by quenching with TMSCl at -78 °C afforded **30** in 90% yield upon purification by vacuum distillation (bp. 55°C/0.5

mm). Spectral characteristics (IR, ^{1}H NMR, ^{13}C NMR and mass analysis) are in agreement to that reported in literature[56] and are detailed in experimental section.

4.2.1. Silylation of N-Boc-2(trimethyl silyl) pyrrolidine (30):

Extension of the same protocol as described above for the monosilylation of **29** towards the preparation of **32** from **30**, however, resulted in the formation of **31** as a major product (65 %) alongwith the trace amount of **32** (< 5%).

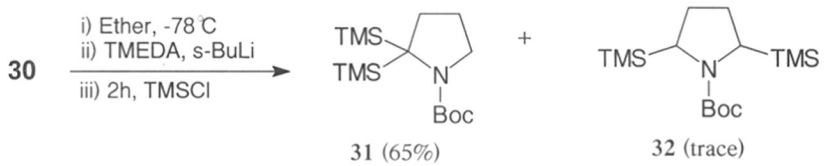
Compound **31** was characterised by IR, ^{1}H NMR , ^{13}C NMR and mass spectral analysis.

^{1}H NMR of **31** revealed a set of two singlets at δ 0.1 and δ 1.45, integrating for eighteen and nine protons, assignable to the six methyls of two trimethyl silyl group and three methyls of Boc moiety, respectively. A multiplet at δ 1.75, equivalent to two protons, is attributed to H_{2a} and H_{2b}. Protons corresponding to $H_{3a/b}$ and $H_{4a/b}$ appeared as triplets at δ 1.95 (J = 6.8 Hz) and δ 3.35 (J = 6.8 Hz), integrating for two protons each.

These spectral characteristics suggests the presence of geminal α, α-bis(trimethylsilyl) moiety on the pyrrolidine ring (Scheme 8).

^{13}C NMR spectrum displayed the presence of a total of eight cabon signals at δ 0.18, 25.5, 28.8, 32.2, 46.5, 48.5, 78.1 and 154.6. INEPT ^{13}C NMR spectrum revealed the presence of methyls of two TMS and one Boc moieties at δ 0.18 and 28.8, respectively. Three methylene carbons, characterized for C_2, C_3 and C_4 are observed at δ 25.2, 32.2 and 46.5, respectively. The quarternary C_1 carbon appeared at δ 48.5 and the *t*-butyl and carbonyl carbons at δ 78.1 and δ 154.6, respectively.

Scheme 8



31 (65%) 32 (trace)

Formation of gem disilylated product **31** upon further silylation of **30**, could be attributed to the following two factors :

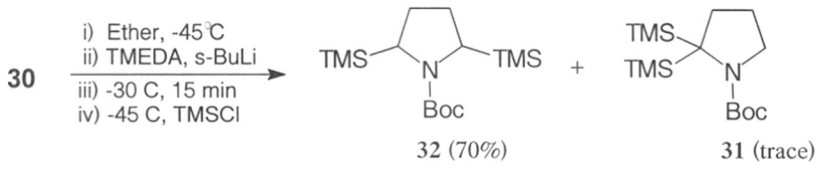
1) Silicon ability to enhance the acidity of the adjacent protons.

2) Kinetic stability of α-silyl anion.

However, to synthesize required precursor **11**, we required to introduce the two silyl moieties at C_2 and C_5 position of the pyrrolidine unit, respectively. At this point, it was realised that it would be difficult to alter the ability of silicon moiety to acidify the adjacent proton, however, we could certainly play with the kinetic stability of α-silyl carbanions by employing thermodynamic parameters such as temperature variants. Towards this direction, we studied the reactivity pattern and the product ratio of **31** : **32** by carrying out the metalation reaction using *s*-BuLi at a range of temperature *viz.* -60 °C to -30 °C. These studies led us to achieve an optimum reaction condition whereby the thermodynamic product **32** was obtained as the major one. It was also noted that the use of THF as solvent did not influence the product ratio, however, diethyl ether appeared to be the solvent of choice for these reactions. Optimized reaction condition for the thermodynamic path for the preparation of **32** involved treatment of **30** in dry ether with s-BuLi in the presence of TMEDA at -45 °C followed by immediate warming of the reaction mixture to -30 °C

and maintaing at this temperature for 30 min. Afterwards the temperature was lowered once again to -45 °C and quenching with chlorotrimethylsilane afforded **32** in 70% yield as a pale yellow oil (Scheme 9).

Scheme 9



32 (70%) **31** (trace)

Compound **32** was characterised by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analyses.

^{1}H NMR spectrum of compound **32** displayed two singlets at δ 0.05 and δ 1.45, corresponding to the eighteen and nine protons each, attributable to the methyl groups of the TMS and Boc moieties, respectively. A multiplet between δ 1.75-2.0, integrating for four protons, corresponds to H_3 and H_4 protons. Two broad singlets at δ 3.1 and δ 3.3, integrating for one proton each, corresponds to H_1 and H_5 α-silyl protons, respectively.

^{13}C NMR spectrum displayed total of eight carbon signals at δ -1.0, -0.5, 28.9, 29.0, 49.4, 50.0, 78.9 and 154.8. INEPT ^{13}C NMR spectrum revealed the presence of methyl groups of two trimethylsilyl moieties at δ -1.0 and -0.5, and Boc moiety at δ 28.9. Carbon signal at δ 29.0 corresponds to C_3 and C_4 methylene carbons. Two methine carbons at δ 49.4 and δ 50.0 corresponds to either of C_1 and C_4. Quarternary

carbons of *t*-butoxy and carbonyl group of Boc moiety appeared at δ 78.9 and 154.8, respectively.

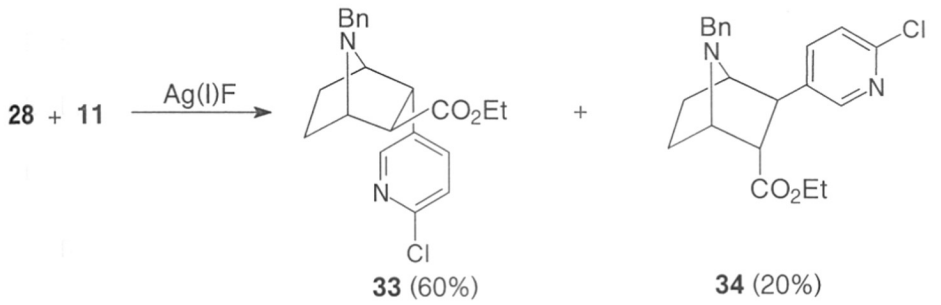
Compound **11** was prepared from **32** in two steps (Scheme 7) involving the deprotection of the Boc moiety followed by N-benzylation. *Tert*-Boc moiety of **32** was deprotected (90%) by stirring with trifluoro acetic acid in dry dichloromethane at rt for 4 h and was utilized as such without further purification. N-benzylation was achieved by refluxing with a mixture of benzyl chloride and potassium carbonate in dry acetonitrile for 5 h. Purification by silica gel column chromatography afforded compound **11** as yellow oil in 80% yield. Compound **11** was characterised by ^{1}H NMR, ^{13}C NMR and mass spectral analyses (Fig. 2, Fig. 3 and Fig. 4).

4.3. Cycloaddition Reaction:

To a stirring mixture of Ag(I)F (12.5 mmol) and *trans*-ethyl-3-(6-chloro-3-pyridyl)-propen-2-oate (**28**) (6.26 mmol) in dry DCM (40 mL) was added N-benzyl-2,5-bis(trimethylsilyl)pyrrolidine (**11**) (5.69 mmol) dropwise under argon atmosphere. The reaction mixture was allowed to stir for additional 10-12 h and the progress of the reaction was monitored by TLC. After the considerable consumption of dipolarophile, the reaction mixture was filtered through a plug of celite. Evaporation of the filtrate gave brownish oily residue. HPLC analysis of the crude reaction mixture indicated it to be a mixture of two stereoisomers in a 3:1 ratio. Purification by silica gel column chromatography, eluting with pet ether:ethyl acetate (9:1) afforded the minor cycloadduct **34** in 20 % yield. Further elution using the same solvent system gave the major isomer **33** in 60 % yield as a pale yellow oil. Both stereoisomeric cycloadducts are fully characterised by IR, ^{1}H NMR, ^{13}C NMR and

Mass spectral analyses and their stereochemistries are assigned and confirmed by ^1H NMR decoupling and COSY experiments.

Scheme 10



4.3.1 Spectral analysis and stereochemical assignment of the major cycloadduct 33:

IR spectrum displayed a sharp band at 1728 cm $^{-1}$; characteristic of a carbonyl group of a carboxylate functioality (Fig. 6).

^1H NMR spectrum of the cycloadduct **33** showed following patterns (Fig. 5).

A multiplet at δ 1.35, integrating for two protons, could be assigned to H_{5endo} and H_{6endo}. Another two multiplets appearing at δ 1.7 and δ 1.98, integrating for one proton each, may be attributed to H_{5exo} and H_{6exo}, respectively. A doublet at δ 2.55 (J = 6.5 Hz) integrating to one proton is assigned to H_{3endo}. Another doublet appearing at δ 3.60 (J = 4.48 Hz), equivalent to one proton, corresponds to bridgehead H_4. A set of two doublets at δ 3.72 and δ 3.61 (J = 13.71 Hz), integrating to one proton each, is assigned to the two benzylic protons. Another doublet of doublet at δ 3.80 (J = 4.78, 0.83 Hz) corresponding to one proton, is assigned to bridgehead H_1 and a triplet at δ

3.90 (J = 4.55 Hz), integrating for one proton, corresponds to H_{2exo}. Signals corresponding to methyl and methylene moieties of carboethoxy group are observed as triplet at δ 1.25 (J = 7.1 Hz, 3H) and a quartet at δ 4.2 (J = 7.3 Hz, 2H), respectively. A bunch of multiplets between δ 7.52-7.25, integrating for seven protons, are attributed to the five aromatic protons of benzylic group and $H_{4'}$ and $H_{5'}$ of the pyridyl moiety. A doublet at δ 8.25 integrating for one proton is assigned to pyridyl proton $H_{2'}$.

Based on the above ^1H NMR spectral evaluation, tentatively the stereochemistry of the product **33** is assigned as 7-benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*exo*-carboethoxy-7-azabicyclo(2.2.1)heptane.

This assignment is further confirmed by carrying out ^1H NMR decoupling and COSY experiments.

Decoupling of H_3 proton appearing at δ 2.55 indicated its coupling only with H_2 at δ 3.90 and no coupling with adjacent bowsprit H_4 at δ 3.60. It is known in the literature[42] that in 7-azabicyclo(2.2.1)heptane system, as in the case of norbornane system[56], no coupling between the bridgehead bowsprit and adjacent *endo* hydrogen's is observed due to a dihedral angle of 90 ° between them. Therefore, the assignment of H_3 as *endo* gets confirmed and thereby confirming the *exo*-orientation of carboethoxy moiety in the cycloadduct **33**. Proton H_2 is found to couple with H_3 and H_1 at δ 3.80, confirming its *exo*-orientation and therefore, implying an *endo*-orientation for the pyridyl moiety. These studies also showed the relative *trans* stereochemistry between H_2 and H_3 indicating the retention of olefin geometry of the

dipolarophile in the cycloadduct. These observations are further supported by the ^1H COSY spectrum.

^{13}C NMR spectrum displayed a total of nine signals at δ 14.01, 20.99, 27.26, 47.16, 51.37, 52.49, 60.70, 63.31 and 63.96 besides aromatic signals at δ 123.6, 126.7, 128.0, 134.7, 139.4, 149.2 and carbonyl signal at δ 173.1 (Fig. 5). INEPT experiment suggested the signals at δ 20.99, 27.26, 51.37 and 60.70 as methylene (-CH_2-) carbons which are assignable to C_5, C_6, -O$\underline{C}H_2CH_3$ and N$\underline{C}H_2$Ph carbons, respectively. Methyl carbon signal corresponding to $OCH_2\underline{C}H_3$ is observed at δ 14.01. Four methine carbon signals at δ 47.16, 52.49, 63.31 and 63.96 can be assigned to C_2, C_3, C_1 and/or C_4, respectively.

Mass spectrum revealed a molecular ion peak at 370 (3). Retro fragmentation of 7-azabicyclo(2.2.1)hetane ring system gave base peak at 159, corresponding to N-benzyl pyrrolidine, alongwith other prominent fragments at 131 (26) and 91 (81), (Fig. 6).

4.3.2. Spectral analysis and stereochemical assignment of the minor cycloadduct 34:

IR spectrum showed a strong absorption band at 1728 cm^{-1} indicating the presence of carboethoxy functionality (Fig. 8).

^1H NMR spectrum displayed following signals (Fig. 7):

A multiplet at δ 1.55, corresponding to two protons is assigned to H_{5exo} and H_{6exo}. A multiplet at δ 2.0, integrating for two protons is, attributed to H_{5endo} and H_{6endo}. A triplet at δ 2.85 (J =5.07 Hz), integrating for one proton, corresponds to H_{3exo}. H_{2endo} proton, adjacent to the pyridyl moiety, appeared as doublet at δ 3.06 (J = 5.39

Hz). A doublet appearing at δ 3.24 (J = 3.76 Hz), integrating for one proton, is assignable to bridgehead proton H_1. A singlet at δ 3.54 (2H) is assigned to the two benzylic protons. A triplet signal appearing at δ 3.65 (J = 4.07, 4.43 Hz), integrating for one proton, is attributed to bridgehead H_4 proton. Signals corresponding to methyl and methylene moieties of caboethoxy group are observed as triplet at δ 1.20 (3H, J = 7.05 Hz, 3H) and a quartet at δ 4.1 (2H, J = 7.09 Hz, 2H). Pyridyl $H_{2'}$ proton is observed as a doublet at δ 7.2 (J = 2.41 Hz) and the five aromatic protons of phenyl moiety are observed as a bunch of multiplet between δ 7.23-7.35. Remaining pyridyl, $H_{4'}$ and $H_{5'}$ protons appeared as doublet at δ 7.84 (J = 8.35 Hz) and doublet of doublet at δ 8.42 (J = 2.47, 8.26 Hz), respectively.

Based on the above ^{1}H NMR spectral evaluations the stereochemistry of **34** is tentatively assigned as 2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-carboethoxy-7-azabicyclo (2.2.1)heptane.

The stereochemical orientation for the 6-chloro-3-pyridyl and carboethoxy moieties in **34** are further confirmed by ^{1}H NMR decoupling and COSY experiments. H_3 proton at δ 2.85 (t, J = 4.43, Hz) is found to couple with H_4 at δ 3.65 (t, J = 4.43, Hz) and H_2 at δ 3.06 (d, J = 5.39 Hz) , thus, confirming the *exo*-orientation of H_3 thus, implying the *endo*-orientation of the carboethoxy group. Similarly, H_2 at δ 3.06 is found to couple only with H_3 ascertaining its *endo*-orientation and *exo*-orientation for the 6-chloro-3-pyridyl moiety.

^{13}C NMR spectrum revealed a total of nine signals at δ 14.13, 21.83, 26.86, 47.49, 52.71, 57.58, 60.65, 66.15, and 66.44, in the aliphatic region alongwith aromatic

signals at δ 123.66, 127.03, 128.26, 128.54, 137.96, 139.25 and 148.95 and a carbonyl carbon signal at δ 172.05 (Fig. 7). INEPT ^{13}C NMR experiment characterised the methylene carbons at δ 21.83 and 26.86 to either of C_5 and/or C_6 and at δ 51.71 and 60.65 to methylene of carboethoxy ($O\underline{C}H_2CH_3$) and benzylic ($N\underline{C}H_2Ph$) moieties, respectively. The methine carbons at δ 47.49 and 57.58 are attributed to C_3 and C_2, respectively, and C_1 and C_4 signals are characterised at δ 61.59 and 66.44, respectively. Signal at δ 14.13 is attributed to methyl carbon of carboethoxy moiety ($(C(O)OCH_2\underline{C}H_3$).

Mass spectrum gave molecular ion peak at 370 (20) and a base peak at 159 alongwith identical fragments as observed for major cycloadduct **33** (Fig. 8).

4.4. Chemistry Following Cycloaddition Reaction:

Since the major stereoisomer **33**, obtained by the cycloaddition of **11** and **28**, has the chloropyridyl moiety in *endo*-orientation instead of the required *exo*-orientation, we decided to carryout further synthetic transformations to procure unnatural *endo*-epimer of **1.**

Towards this endeavor, the decarboxylation of the carboethoxy moiety from **33** was initiated prior to the N-debenzylation due to the anticipated difficulties in carryingout the N-debenzylation by reductive methods utilizing metal catalysts in the presence of chloro substituent on the pyridyl moiety and the acid/base sensitive carboethoxy moiety. Aryl halides are known to undergo dehalogenation under various metal catalysed reductive hydrogenation *viz.* $PdCl_2/H_2$, Pd-C/H_2, Raney-Ni/H_2 etc. The use of dissolving metal reduction protocol (Na/liq.NH3) could also

be ruled out due to the susceptibility of pyridyl moiety and the carboethoxy group. Non-reductive methods employing chloroformates for N-debenzylation was, thus, selected.

4.4.1 Decarboxylation of major cycloadduct 33:

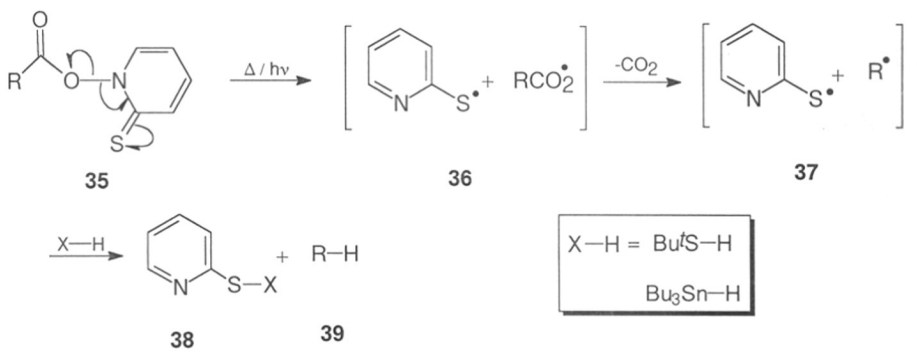
There are three general methods available in literature for carrying out the decarboxylation of a non activated carboxylic acid : 1) the decomposition *via* peracids or peresters[57] , 2) the Hunsdiecker reaction[58] and 3) Bartons protocol[59] *via* thiohydroxamic esters. However, the photochemical or thermal reaction of hydroxamic esters obtained from N-hydroxy -2-thiopyridone, developed by Barton and co-workers[59], appears most flexible and best adopted method for the transformation of a -COOH group into many other functionalities. The intermediate radical, R·, resulting from the decarboxylation can be oriented in various ways *viz.* substitution, addition etc. (Scheme 11). The overall reaction process is driven by three thermodynamic parameters:

i) the passage from thiocarbonyl to carbonyl,

ii) aromatization of the pyridine nucleus and

iii) the overall increase in the entropy upon fragmentation .

Scheme 11

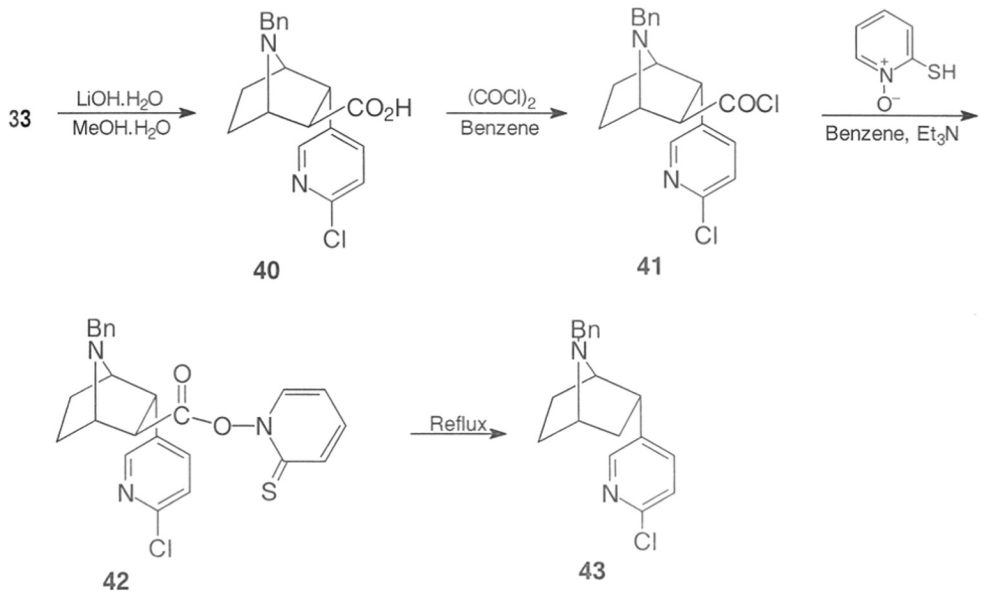


35 36 37 38 39

Thus alkyl carboxylic acid is converted to nor alkane by using stannanes (Bu_3SnH) or mercaptams (tert-butyl mercaptam) as a hydrogen source.

Due to the above advantages of Barton's radical decarboxylation protocol, decarboxylation of cycloadduct **33** was carried out in three steps involving i) Hydrolysis of ester **33** to acid **40**; ii) Conversion of acid **40** to acid chloride **41** and iii) Preparation and pyrolysis of thio-hydroxamate ester **42** as shown in Scheme 12.

Scheme 12



Ester **33** was hydrolyzed by warming with LiOH in MeOH:H_2O (3:1). The crude acid **40**, thus obtained was used as such for the next step. Treatment of the acid **40** in benzene with oxalyl chloride (5eq) in the presence of catalytic amount of DMF (one drop) at room temperature afforded acid chloride **41** as a brownish solid. Compound **41** was converted to thiohydroxamate ester **42**, by esterification with N-hydroxy-pyridine-2-thione in benzene in the presence of pyridine (1.2 eq) and catalytic amount of DMAP at room temperature. Pyrrolysis of **42** in the presence of

tert-butyl mercaptan (5 eq) by refluxing in benzene under argon atmosphere for 2.5-3 h followed by normal workup and purification by silica gel column chromatography afforded the decarboxylated product **43** in 55% yield.

4.4.2. Spectral Analysis of the Decarboxylated Product 43:

IR spectrum displayed a strong signal at 1460 cm^{-1} and 1105 cm^{-1} indicating that the phenyl and pyridyl substituent are intact in the product. The striking difference from the starting ester **33** was the absence of carbonyl band at 1720 cm^{-1} (Fig. 10).

^1H NMR spectrum of **43** revealed the absence of the ester group and a drastic change in the splitting pattern for the most of the protons compared to the starting ester **33** (Fig. 9). A multiplet at δ 1.35, equivalent to two protons, is attributed to H_{5endo} and H_{6endo}. H_{3endo} appeared as a doublet of doublet at δ 1.50 (J = 5.36, 7.92 Hz). A set of two multiplets appearing at δ 1.65 and δ 1.95, integrating for one proton each, corresponds to either of H_{5exo} and/or H_{6exo}. Another multiplet at δ 2.3, which on expanding horizontally appears to be a triplet of triplet is attributed to H_{3exo}. Two bowsprit bridgehead H_1 and H_4 protons appeared as a triplet at δ 3.45 (J = 4.7 Hz). A multiplet corresponding to one proton at δ 3.55 is assigned to H_{2exo} proton. A singlet appearing at δ 3.70, equivalent to two protons, is assigned to the benzylic protons. A bunch of multiplets integrating for seven protons between δ 7.25-7.50 is attributed to five phenyl group protons and $H_{4'}$ and $H_{5'}$ of the pyridyl substituent. A doublet appearing at δ 8.25 (J = 2.51 Hz) is characterised as $H_{2'}$.

Based upon the above ^1H NMR spectral analysis, the strucure of the decarboxylated product **43** is tentatively assigned as 7-benzyl-2-*endo*-(6-chloro-3-pyridyl)-7-azabicyclo(2.2.1)heptane. Although the stereochemical orientation for 6-chloro-3-pyridyl moiety is already fixed as *endo* in the starting ester **33**, nevertheless, the retention of stereochemistry is once again acertained by ^1H NMR decoupling experiments.

^{13}C NMR spectrum of decarboxylated product **43** displayed a total of seven signals in the upfield region at δ 21.6, 28.3, 33.7, 42.7, 51.7, 60.2 and 63.9 alongwith the requisite signals for the aromatic moieties in the downfield region at δ 123.5, 126.8, 128.2, 128.3, 136.1, 138.3,139.6, 148.9 and 149.5 (Fig. 9). INEPT experiment revealed the presence of four methylene carbons at δ 21.6, 28.3, 33.7 and 51.7, characterised for C_5, C_6, C_3 and benzylic carbon ($N\underline{C}H_2Ph$), respectively and three methine carbons at δ 42.7, 60.2 and 63.9 attributed to C_2, C_1 and C_4, respectively.

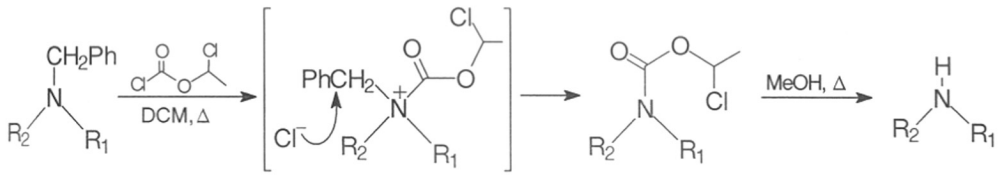
Mass spectrum of **43** showed the molecular ion peak at 298 (9) and a base peak at 91 alongwith other prominent fragments at 187 (9), 159 (70) and 131 (30) (Fig. 10).

4.4.3. Debenzylation of compound 43:

N-Debenzylation of **43** employing the metal-mediated reductive methods *viz.* hydrogenolysis and dissolving metal reductions could be ruled out due to the non-compatibility of the chlorine atom in the pyridyl substituent. In search of a mild and an efficient non-reductive N-debenzylation strategy, protocol reported by Yang and co-workers[60] employing α-chloroethyl chloroformate was found suitable. In this approach N-debenzylation reaction proceeds through the formation of α-chloroethyl

carbamate *via* its N-acyl quarternary ammonium salt, which on refluxing with methanol affords the debenzylated amine hydrochloride salt as shown in Scheme 13.

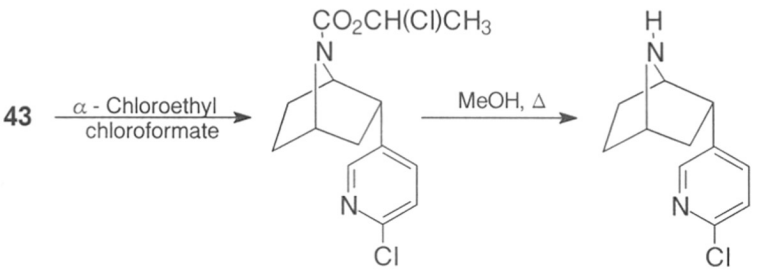
Scheme 13



44 **45** **46** **47**

Compound **43** in 1, 2-dichloroethane on refluxing with α-chloroethyl chloroforomate (1.2 eq) for 1.5 h afforded the crude α-chloroethyl carbamate **48** which on heating in MeOH for 0.5 h gave **49** in 52 % yield (Scheme 14).

Scheme 14



48 **49** (52%)

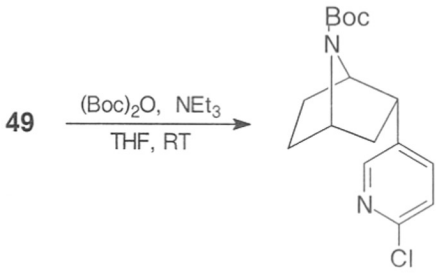
The free base **49** was characterized by IR and ^{1}H NMR and the values were found to be in accordance to the literature values[23] reported for 2-*endo*-(6-chloro-3-pyridyl)-7-azabicyclo(2.2.1)heptane, the unnatural *endo* epimer of Epibatidine (**1**).

4.4.4. Transformation of 49 to Natural Epibatidine (1):

Since the above cycloaddition resulted *endo*-epimer **49**, it was envisaged that the epimerization of **49** would result natural **1**. In this context, the NH moiety of **49**

was protected to Boc derivative **50** (90 %) by treating it with $(Boc)_2O$ and triethyl amine in THF at room temperature (Scheme 15).

Scheme 15



50 (89%)

Compund **50** was fully characterized by IR, ^1H NMR, ^{13}C NMR and Mass spectroscopy as N-*tert*-butoxy carbonyl-2-*endo*-(6-chloro-3-pyridyl)-7-azabicyclo (2.2.1)heptane.

IR spectrum showed a strong characteristic absorption band for Boc moiety at 1693 cm^{-1}, alongwith other prominent bands for chloropyridyl moiety at 1582, 1460, 1367, 1250 and 1158 cm^{-1} (Fig. 12).

^1H NMR spectrum of **50** (Fig. 11) revealed the presence of Boc moiety by displaying a sharp singlet at δ 1.48 (nine protons). A multiplet appearing at δ 1.40, integrating for two protons, can be attributed to H_{5endo} and H_{6endo}. Another multiplet at δ 1.55, corresponding to two protons, is attributable to H_{6exo} and H_{3endo}. Another two multiplets appearing at δ 1.90 and δ 2.3, integrating for one proton each, could be assigned to H_{5exo} and H_{3exo}, respectively. H_{2exo} appeared as a doublet of doublet of doublet (ddd) at δ 3.45 (J = 11.5, 5.4, 5.4 Hz). A broad singlet at δ 4.35, integrating for two protons, corresponds to the two bowsprit bridgehead protons H_1 and H_4.

Pyridyl ring protons $H_{5'}$, $H_{4'}$ and $H_{2'}$ are observed at δ 7.30 (d, J = 8.67 Hz), 7.50 (dd, J = 2.63, 8.69 Hz) and 8.26 (d, J = 2.46 Hz), respectively.

^{13}C NMR spectrum of **50** displayed total number of eight signals upfield at δ 23.1, 28.1, 30.0, 34.2, 43.4, 57.1, 60.1 and 79.8 along with requisite number of signals for pyridyl moiety downfield at δ 123.7, 134.6, 138.3, 149.3(2 C) and a carbonyl signal at δ 155.3 (Fig. 11). INEPT experiment characterised three methylene carbons at δ 23.1, 30.1 and 34.2 for C_3, C_5 and C_6, respectively and three methine carbons at δ 43.4, 57.1 and 60.1 for C_2, C_1 and C_4. One signal for three methyls of the Boc moiety appeared at δ 28.1. Two quarternary carbons at δ 79.8 and 155.3 corresponds to *t*-butyl and carbonyl carbon of Boc moiety.

Mass spectrum displayed molecular ion peak at 308 (2) and base peak at 57 alongwith prominent fragments at 208 (37), 140 (72) and 69 (51) (Fig. 12).

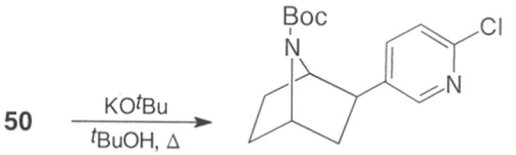
The above spectral analysis confirms the compound **50** as N-Boc-2-*endo*-(6chloro-3-pyridyl)-7-azabicyclo(2.2.1)heptane which is in complete agreement with the values reported in literature[21, 33, 34].

4.4.5. Epimerization of Unnatural *endo*-isomer 50 to 51:

Stereochemistry of the 6-chloro-3-pyridyl moiety in **50** being *endo* instead of the required *exo*-orientation, it was essential to transform the stereochemistry of 6-chloro-3-pyridyl moiety towards *exo*-orientation in order to obtain the targeted naturally occurring **1**. This was made possible by epimerization reaction brought about in 45 % yield by refluxing for three days in the presence of KO^{t}Bu in *t*-BuOH (Scheme 16). Epimerised product **51** was purified from the unreacted *endo*-epimer **50**

by careful silica gel column chromatography eluting with ethyl acetate : pet ether (1:9) and was fully characterised by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Scheme 16



51 (45%)

^{1}H NMR spectrum of **51** revealed following notable changes from the *endo*-epimer **50** (Fig. 13). H_2 Proton was observed as a doublet of doublet at δ 2.87 (J = 5.04, 8.93 Hz), in sharp contradiction to that observed for the same proton in **50** at δ 3.45 (ddd, J = 11.5, 5.4, 5.4 Hz), thus, suggesting the inversion of stereochemistry at C_2. Moreover, H_2 showed no coupling with the bridgehead H_1 and H_4 protons appearing separately as broad singlets at δ 4.16 and δ 4.37, unlike in the case of **50** both appeared together as multiplet at δ 4.35, confirming the epimerisation of chloropyridyl moiety from *endo* to *exo*-orientation.

^{13}C NMR spectrum of **51** revealed downfield shift of 1 ppm for the epimerized carbon C_2 compared to its *endo* isomer **50** (Fig. 13). INEPT experiment showed the presence of three methine carbons corresponding to C_2, C_1 and C_4 at δ 44.7, 55.9 and 61.8, respectively and three methylene carbons corresponding to C_3, C_5 and C_6 at δ 28.1, 29.5 and 40.2, respectively, alongwith other signals corresponding to Boc and pyridyl moieties.

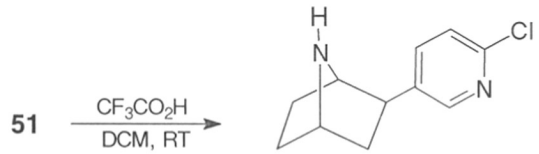
The mass spectrum of **51** was almost identical to that observed for **50**.

The above spectral characteristics and analyses are in conformity with the reported[21, 33, 34] values of 7-*tert*-butoxycarbonyl-7-azabicyclo(2.2.1)heptane.

4.4.6. Deprotection of N-Boc Epibatidine :

Synthesis of Epibatidine (**1**) was completed by deprotecting the N-Boc moiety of **51** by stirring with trifluroacetic acid in DCM for 3 h (Scheme 17). Normal workup and purification by silica gel column chromatography using $CHCl_3$: MeOH: NH_4OH as eluent gave **1** in 90 % yield.

Scheme 17



Epibatidine (**1**)

IR spectrum displayed broad absorption bands at 2960 and 2850 cm^{-1} alongwith other absorption bands at 1574, 1457, and 1324 cm^{-1}.

^1H NMR spectrum revealed the presence of a characteristic H_{2endo} proton as a doublet of doublet (J = 5.1, 8.9 Hz) at δ 2.77 and two bridgehead protons H_1 and H_4 as broad singlets at δ 3.8 and δ 3.57, respectively. Two sets of multiplets appearing at δ 1.60 and δ 1.91, integrating for five and one protons, respectively, corresponds to the remaining six protons of the 7-azabicyclic ring. The 6-chloro-3-pyridyl moiety was observed by the presence of a series of doublet signals at δ 7.45 (d, J = 8.3 Hz, 1H), 7.62 (dd, J = 8.3, 2.6 Hz, 1H) and 8.26 (d, J = 2.6 Hz, 1H).

The above IR, ^1H NMR and mass spectral analyses values are found in perfect agreement with those reported in literature[21, 33, 34].

4.5. Formal Synthesis of 1 from Minor Diastereomeric Cycloadduct (34):

The minor diastereomeric cycloadduct **34** has the desired *exo*-stereochemistry for the 6-chloro-3-pyridyl moiety and hence would formally lead to **1** stereoselectively which would avoid the tedious and lengthy low yielding epimerization process. In this context **34** was transformed to *tert*- butyl carbamate

Scheme 18

52 (55%)

derivative **52** (Scheme 18), a key precursor known to lead to **1**. Substrate **52** was obtained by affecting the N-debenzylation using α-chloroethyl chloroformate as reagent followed by Boc protection with $(Boc)_2O$ employing the identical protocols as described in the previous section.

Boc-derivative **52** is fully characterized by IR, ^1H NMR, ^{13}C NMR and mass spectral analyses (Fig. 14 and Fig. 15) and the structure is assigned as 7-*tert*-butoxy carbonyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-carboethoxy--7-azabicyclo(2.2.1)heptane (**52**) which is in agreement with the spectral characteristics reported by Bai *et al*[39] for the corresponding ethoxy carbamate derivative.

Though, further synthetic elaboration of **52** would obviously lead to **1** it could not be pursued due to the availability of **34** in minor quantity by the cycloaddtion process as described in Scheme 10.

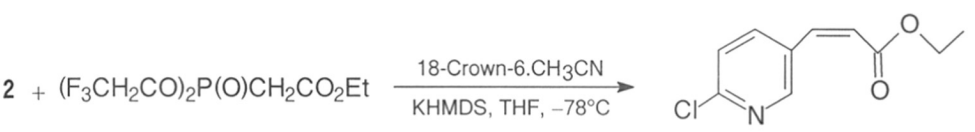
5. Stereoselective Synthesis of Epibatidine (1) : Path. II

Although, we could achieve the synthesis of **1** through the route described above, the employment of the poor yielding epimerization step coupled with multiple step led us to envision the use of *cis*-dipolarophile **54** for the cycloaddition reaction where *exo*-orientation of 6-chloro-3-pyridyl moiety was expected in the resultant cycloadduct. It was evident from the cycloaddition results with *trans*-pyridyl acrylate **28**, that the reaction with *cis*-pyridyl acrylate **54** would proceed with *exo*-selectivity towards the electron withdrawing component of the dipolarophile and therefore, governing the stereochemistry of the other substituent, as 1,3-dipolar cycloaddition reaction is a concerted process which would retain the geometry of the dipolarophile in the resultant cycloadduct completely. Keeping this logic in mind *cis*-dipolarophile **54** was prepared from the aldehyde **12** employing Still and Ginnaris protocol[61] and subjected to the identical azomethine cycloaddition reaction, which is described briefly in the following section.

5.1. Preparation of *cis*-Dipolarophile 54:

Cis-dipolarophile **54** was prepared by treating bis(2,2,2-trifluoroethyl) (ethoxy carbonyl methyl) phosphonate (**53**) with KHMDS (1M solution in THF) in THF at -78°C in the presence of 5 eq of 18-crown-6.CH_3CN complex followed by the addition of aldehyde **12** in 75 % yield as a thick yellow oil.

Scheme 19



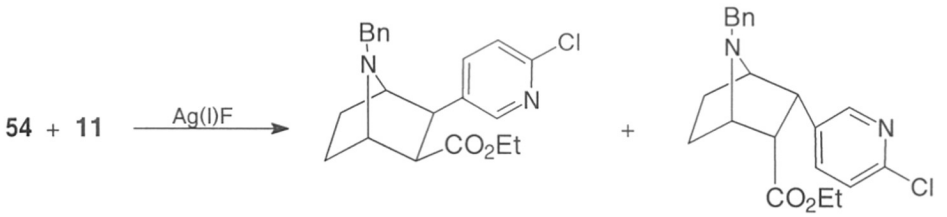
53 54

54 is characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

5.2. [3+2]-Cycloaddition of 54 with 11 :

Cycloaddition of **54** with **11** was carried out by following the same experimental protocol as described previously with *trans*-dipolarophile **27** (Scheme 10). The silica gel column chromatographic purification of the cycloadducts afforded **55** (62%, major) and **56** (7%, minor) (Scheme 20). Both cycloadducts **55** and **56** are characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses and their respective stereochemistries are assigned on the basis as described below.

Scheme 20



55 (62%) **56** (7%)

5.2.1. Spectral Analysis of Major Cycloadduct 55 :

IR spectrum showed prominent absorption bands at 1731, 1455 and 1106 cm^{-1} indicating the presence of ester and aromatic moieties (Fig.17).

^{1}H NMR spectrum of compound **55** showed following patterns (Fig. 16):

Two multiplets at δ 1.45-1.60 and δ 2.1-2.2, integrating for two protons each, is attributed to H_{5endo} and H_{6endo}, and H_{5exo} and H_{6exo}, respectively. A set of two doublets at δ 2.9 and δ 3.1, with J = 10.13 Hz and integrating for one proton each, is attributed to H_{3endo} and H_{2endo},respectively. Due to the absence of coupling of *endo* protons with the bridgehead, the H_1 and H_4 protons appeared as doublets (J = 4.03 Hz) at δ 3.25 and δ 3.75, respectively. Two benzylic protons appeared as a singlet at δ 3.70. Signals corresponding to methyl and methylene groups of carboethoxy moiety appeared as a triplet and mixed quartet at δ 0.8 (J = 6.95 Hz) and δ 3.65 (J = 7.0 Hz). A bunch of multiplets appearing between δ 7.25-7.50 corresponds to five aromatic protons of phenyl moiety. Pyridyl protons $H_{5'}$, $H_{4'}$ and $H_{2'}$ appeared at δ 7.20 (d, J = 8.38 Hz), 8.05 (dd, J = 8.35, 2.70 Hz) and 8.35 (d, J = 2.70 Hz), respectively.

From the above spectral analysis the stereochemistry for the **55** could be assigned as 7-benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*exo*-carboethoxy-7-azabicyclo (2.2.1) heptane.

^{13}C NMR spectrum revealed a total of eighteen signals (Fig. 16). INEPT experiment suggested the presence of a methyl carbon signal at δ 13.3 ($OCH_2\underline{C}H_3$), four methylene carbons C_5, C_6, $O\underline{C}H_2CH_3$ and $N\underline{C}H_2Ph$ at δ 25.3, 26.2, 51.4 and 59.5, respectively and four methine C_2, C_3, C_4 and C_1 carbons at δ 49.1, 54.8, 59.7 and 65.3, respectively. Signals pertaining to the phenyl and pyridyl moieties appeared downfield. The eight aromatic methine carbons appeared at δ 122.9, 126.6, 127.9 (2C),

128.2 (2C), 138.5 and 150.2 while three tertiary carbons appeared at δ 146.7, 139.0 and 149.0. Quarternary carbon corresponding to carbonyl carbon was observed at δ 170.6.

Mass spectrum displayed a molecular ion peak at 308 (8) and a base peak at 159 alongwith other fragments at 130 (15), 91 (87) and 68 (18) (Fig. 17).

5.2.2. Spectral Analyses of Minor Cycloadduct 56 :

IR spectrum displayed carboethoxy moiety at 1720 cm^{-1} alongwith other requisite bands corresponding to aromatic moieties (Fig. 19).

^1H NMR spectrum revealed a series of multiplets (Fig. 18). Methyl protons of carboethoxy moiety appeared as a triplet at δ 1.0 (J = 7.1 Hz). A multiplet appearing between δ 1.60-1.80, integrating for two protons, is attributed to H_{5endo} and H_{6endo}. Another two multiplets between δ 1.85-2.0 and δ 2.0-2.1, corresponding to one proton each, are attributed to H_{5exo} and/or H_{6exo}. A multiplet at δ 3.45, integrating for two proton, is assigned to H_{2exo} and H_{3exo}. A triplet at δ 3.60 (J = 4.45 Hz) is characterized to H_1 and a multiplet at δ 3.75 (3H) corresponds to the two benzylic ($NC\underline{H}_2Ph$) protons and H_4. Methylene group protons of the carboethoxy moiety are observed as a mixed quartet at δ 3.80-4.06 (J = 7.0 Hz). Aromatic protons of the phenyl and pyridyl moiety are observed as a multiplet at δ 7.25-7.42 (7H) and a doublet at δ 8.10 (1H, J = 2.19 Hz).

From the above spectral analyses, it is evident that there is a prominent coupling (J = 4.5 Hz) between H_2 and H_3 with the bowsprit bridgehead H_1 and H_4, respectively, confirming the *endo*-orientation of both 6-chloro-3-pyridyl and carboethoxy moieties in **56**. Therefore, the stereochemistry of compound **56** could be

assigned as 7-benzyl-2-*end0*-(6-chloro-3-pyridyl)-3-*exo*-carboethoxy-7azabicyclo(2.2.1) heptane.

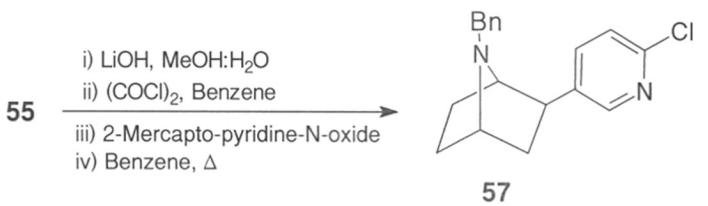
^{13}C NMR (Fig. 18) and mass spectral analyses were in perfect agreement with the above assigned structure and has been detailed in experimental section.

5.3. Chemistry After Cycloaddition :

Since the major cycloadduct **55** has the required *exo*-stereochemistry of the 6-chloro-3-pyridyl moiety, it would obviously lead to the naturally occurring **1** in a short reaction sequence avoiding a tedious and lengthy epimerization process as encountered in the previous synthetic approach.

The carboethoxy moiety, as in the earlier approach (Scheme 12), was first decarboxylated employing Bartons protocol[59] to give the decarboxylated product **57** in 55 % yield (Scheme 21). The IR, ^1H NMR, ^{13}C NMR and mass spectral analysis (given in the experimental section) confirmed the product **57** as 7-benzyl-2-*exo*-(6-chloro-3-pyridyl)-7-azabicyclo(2.2.1)heptane.

Scheme 21



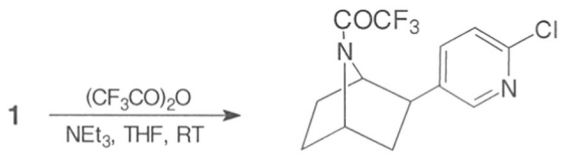
57

Finally, the target molecule **1** was achieved by cleaving the N-benzylic moiety using α-chloroethyl chloroformate, as described in the previous synthesis, in 52 %

yield. IR and ^1H NMR of **1** was found in perfect agreement with the **1** obtained from the previous approach (Scheme 17).

Due to the high polar nature of **1** and the presence of probably minor ring scission products formed during N-debenzylation process, it was found difficult to get **1** in very pure form for proper characterization and hence **1** was derivatised as N-Boc (**51**) and N-trifloroacetyl (**58**) derivative by stirring with either $(Boc)_2O$ or trifloroacetic anhydride in THF and triethyl amine at rt for 4-5 h.

Scheme 22



58

Spectral analysis of N-Boc derivative **51** is found to be in perfect agreement with the one obtained by epimerization reaction and with the literature values[21, 33, 34]. N-trifloro acetyl derivative **58** was fully characterized by ^1H, ^{13}C NMR and mass spectral analysis.

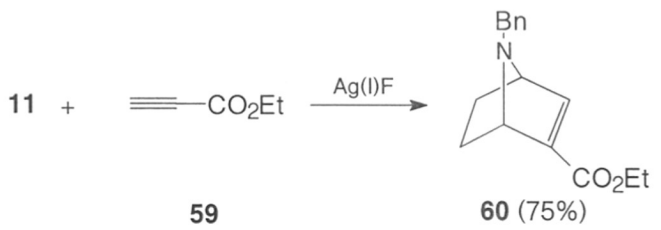
^1H NMR of **58** displayed a series of double signals originating due to the equimolar N-trifloro acetyl rotamers as observed by Daly *et al*[1] and was in conformity to the related N-acetyl derivative.

6.Alternative Approach For the Synthesis of 1:

Although the synthesis of **1** has been achieved by governing the stereochemical course of the reaction through the geometry of the olefin of the

dipolarophile as a stereochemical handle, yet it was difficult to avoid the formation of minor diastereomeric cycloadduct during the cycloaddition processes. It was, therefore, envisioned that this could be avoided if we could synthesize the α,β-unsaturated ester **60** by [3+2]-cycloaddition process and later introduce 6-chloro-3-pyridyl moiety stereoselectively. It was expected on the basis of the addition stereochemistry known on the related norbornene substrate[62] that this type of approach would be stereoselective towards the *exo*-isomer. The crucial precursor **60** was visualized to be obtained by the cycloaddition of **11** and ethyl propiolate (**59**) (Scheme 23).

Scheme 23



59 **60** (75%)

Towards this end, the cycloaddition was performed by following the experimental protocol as described earlier, utilizing **11** (1 eq) and ethyl propiolate (1.2 eq) in the presence of Ag(I)F (2.2 eq) which gave **60** in 75 % yield. Cycloadduct **60** is characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses.

IR spectrum of **60** revealed strong absorption bands at 1714 , 1600 and 1456 cm^{-1} indicating the presence of carboxylate and unsaturated functionalities (Fig. 21).

^{1}H NMR spectrum (Fig. 20) exhibited a doublet of doublet at δ 1.10 (J = 10.20, 0.5 Hz), equivalent to two protons, for the H_{5endo} and H_{6endo} protons. A triplet

appearing at δ 1.30 (J = 7.10 Hz, 3H) corresponds to methyl group protons of carboethoxy moiety. A broad doublet of doublet at δ 1.98 (J = 10.45, 3.0 Hz), integrating to two protons, can be attributed to H_{5exo} and H_{6exo}. A sharp singlet appearing at δ 3.42, equivalent to two protons, is assigned to the benzylic protons (N-$\underline{CH_2}$Ph). H_4 appeared as a broad singlet at δ 3.89 and a doublet at δ 4.10 (J = 2.49 Hz) is assigned to H_1. Methylene protons of carboethoxy moiety appeared as aquartet at δ 4.25 (J = 7.10 Hz, 2H). H_3 olefinic proton appeared downfield as doublet at δ 6.95 (J = 2.1 Hz). Further downfield, a multiplet between δ 7.25-7.40, integrating to five protons, is attributed to the phenyl protons.

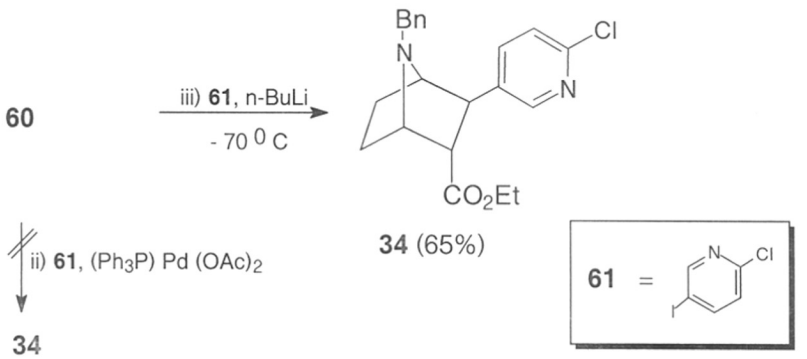
Based upon the above ^{1}H NMR spectral analysis the structure of compound **60** was tentatively assigned as 7-benzyl-2-carboethoxy-7-azabicyclo(2.2.1)hept-2-ene.

The structural assignment was further confirmed by ^{13}C NMR spectrum which displayed a total of six signals in the upfield aliphatic region at δ 14.1, 23.5, 51.8, 60.1, 64.0 and 65.1 and eight signals in the downfield aromatic region at δ 126.7, 127.1, 128.1, 128.5, 128.7, 139.1, 142.9 and 164.5 (Fig. 14). INEPT experiment revealed presence of methyl group of carboethoxy moiety at δ 14.0. Both C_5 and C_6 appeared at δ 23.5. Methylene carbons of carboethoxy (O$\underline{C}H_2CH_3$) and benzylic (N$\underline{C}H_2$Ph) moieties appeared at δ 51.8 and 60.1, respectively. Two methine carbon signals at δ 64.0 and 65.1 were attributed to C_4 and C_1, respectively. Two vinylic carbons, C_2 and C_3 of the azabicycloheptene ring, appeared downfield at δ 142.9 and 139.1, respectively. The tertiary carbon of carbonyl group of carboethoxy moiety appeared at δ 164.5. Rest of the signals accounted for the aromatic carbons of the phenyl moiety.

6.1. Synthesis of Key Precursor 34 for the Synthesis of 1 *via* Conjugate addition of 6-Chloro-3-Iodopyridine:

Our attempts to introduce the 6-chloro-3-pyridyl moiety to **60** through the reductive palladium catalyzed coupling (Heck reaction) of 6-chloro-3-iodo pyridine (**61**) were not successful. Therefore, we decided to solve this problem by carrying out conjugate addition of **61** *via* its lithio derivative to **60** (Scheme 24).

Scheme 24



Addition of **60** (1 eq) to a stirring mixture of **61** (0.95 eq) and *n*-BuLi (0.95 eq) in THF at -78°C followed by work-up and purification by silica gel column chromatography, gave **34** in 65% yield as pale yellow oil. The characterization and stereochemical assignment of the product **34**, thus, obtained was ascertained by comparing its spectral characteristics with the product realized through the cycloaddition reaction sequence as delineated in Scheme 10.

7. Summary

In summary, we have accomplished an efficient and stereoselective synthesis of Epibatidine (**1**) through a distinctly different approach employing [3+2]-cycloaddition of pyrrolidine based non-stabilized azomethine ylide with 6-chloro-3-vinyl-pyridine derivative. Additionally, an alternative approach towards the synthesis of **1** is also suggested *via* the [3+2]-cycloaddition with ethyl propiolate in order to overcome the loss in overall yield due to the formation of minor undesired diasteromeric cycloadducts.

These synthetic efforts have also confirmed the *exo*-selectivity for the electron withdrawing component of the dipolarophile in the [3+2]-cycloaddition processes of azomethine ylide. Thus, the [3+2]-cycloaddition protocol developed in our laboratory has been demonstrated as a powerful synthetic tool.

8. EXPERIMENTAL

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C) which was dried under argon. All organic layers obtained from extractions were dried over anhydrous Na_2SO_4. Solvents for anhydrous reactions were dried according to Perrin *et al*[63]. Benzene, THF, DCM, triethyl amine were distilled from CaH_2. Solvents used for chromatography were distilled at respective boiling points.

All commercial reagents were obtained from Aldrich Chemical Co. Progress of the reaction was monitored by TLC and was visualized by UV absorption by fluoroscence quenching or I_2 staining or by both. Silica gel for column chromatography was 60-120 mesh obtained from S. D. Fine Chemical Co. India or SRL India.

All melting points were uncorrected in degrees celsius and were recorded on a Thermonik melting point apparatus. IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^1H NMR spectra were recorded using TMS as internal reference on Bruker AC-200 and Bruker MSL-300 instruments using $CDCl_3$ as solvent. Chemical shifts are reported in δ. ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker MSL-300 instruments operating at 50.32 MHz and 75.3 MHZ, respectively. Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and are obtained at an ionization potential of 70 eV.

8.1. Preparation of 6-chloro-3-pyridylcarbinol (27):

A 250 mL R.B flask, equipped with a magnetic stirring bar and argon gas balloon, containing a solution of 6-chloro nicotinic acid (**6**) (5.12 g, 32.5 mmol) in THF (50 mL) was cooled to 0 °C. 1.0 M solution of lithium aluminium hydride (32.5 mL, 32.5 mmol) in THF was introduced to the flask dropwise while stirring. The resultant red slurry was allowed to stir for 3 h at 0°C. The reaction mixture was quenched at 0 °C itself by the addition of NaF (5.46g, 130 mmol) followed by H_2O (3.50 mL). The resulting slurry was washed with ethyl acetate (5×100 mL). The crude product obtained after concentration was purified by silica gel column chromatography, eluting with EtOAc:hexane (1:3) to afford 2.09 g (45 %) of alcohol **27** as a white solid mp. 40-42 °C.

IR ($CHCl_3$) : 3356, 1681, 1593, 1456, 1137 cm^{-1};

^{1}H NMR (200 MHz) : δ 3.7 (bs, 1H), 4.75 (s, 2H), 7.3 (d, *J* = 8.2 Hz, 1H), 7.7 (dd, *J* = 2.1, 8.1 Hz, 1H), 8.35 (d, *J* = 1.9 Hz, 1H).

^{13}CNMR (50.32 MHz) : δ 61.0, 124.0, 135.7, 137.8, 147.6, 149.7.

Mass : 142 (98), 114 (100), 78 (60).

8.2. Preparation of 6-chloro-3-pyridylcarboxyaldehyde (12):

A solution of compound **27** (2.09 g, 14.61 mmol) in CH_2Cl_2 (20 mL) was introduced dropwise to a stirring mixture of celite (4.8 g) and pyridinium chlorochromate (4.72 g, 21.89 mmol) in a 40 mL of dry CH_2Cl_2 at 0 ^{0}C. The resultant black slurry was allowed to stir for additional 2 h at rt and finally diluted with dry ether (80 mL). The reaction mixutre was filtered and its black residue was thoroughly

washed with dry ether (2×50 mL). The combined washings were evaporated under vacuum and the brown residue was purified by silica-gel column chromatography eluting with EtOAc:hexane (2:8) to afford 1.65 g (80 %) of **12** as a white solid. mp. 80-82°C.

IR : 2870, 1746, 1587, 1137 cm^{-1}.

^{1}H NMR (200MHz) : δ 7.5 (d, *J*= 8.2 Hz,1H), 8.15 (dd, *J* = 2.4, 8.2 Hz, 1H), 8.9 (d, *J* = 2.4 Hz, 1H), 10.1 (s, 1H).

^{13}C NMR (50.32 MHz) : δ 123.9, 130.3, 137.9, 152.3, 156.8, 189.1.

Mass : 140 (100), 112 (27).

8.3. Preparation of *trans*-ethyl-(6-chloro-3-pyridyl)-2-propenoate (28):

To a stirring solution of **12** (1.69 g, 12 mmol) in 20 mL of acetonitrile was added ethyl triphenyl phosphoranylidine acetate (4.18 g, 12 mmol) dissolved in 30 mL of acetonitrile. The reaction mixture was refluxed for 10 h. After the completion of the reaction, solvent was removed under vacuum. The crude solid obtained was repeatedly triturated with 20 % ethyl acetate in hexane (5×50 mL) to remove triphenyl phosphine oxide formed in the reaction. The combined hexane fractions were evaporated to afford a solid residue which was purified by silica gel column chromatography eluting with hexane:EtOAc (9:1) to give 2.03 g (80%) of **28** as a white crystalline solid. mp. 81-83 °C.

IR : 1711, 1464, 1215 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.25 (t, *J* = 7.30 Hz, 3H), 4.25 (q, *J* = 7.30 Hz, 2H), 6.5 (d, *J* = 14.45 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 14.45Hz, 1H), 7.8 (dd, *J* = 2.10, 8.42 Hz, 1H), 8.5 (d, *J* = 2.23 Hz, 1H).

^{13}C NMR (50.32 MHz) : 14.3, 60.9, 121.3, 124.6, 129.3, 136.7, 139.3, 149.5, 152.7, 166.0.

Mass : 211(M^+, 30), 183 (42), 166 (100), 138 (53).

8.4. Preparation of N-(*tert*-butoxycarbonyl) pyrrolidine (29):

To a solution of pyrrolidine (6.5 g, 92.3 mmol) and triethylamine (11.6 g, 115.3 mmol) in dioxane (50 mL), *tert*-butyl azidoformate (11 g, 76.9 mmol) was added dropwise over 15 min. The pH of the reaction mixture was maintained at 12 by the addition of excess triethylamine if required. The reaction mixture was stirred untill a clear solution resulted. After the evaporation of dioxan, the residue was taken up in ether, washed twice with water (75 mL) followed by brine (75 mL). Ether was evaporated and the resultant brown oil obtained was purified by vacuum distillation (bp. 55-57°C/1mm) to obtain 11.84 g (90 %) of **29** as a clear colorless oil.

IR : 1700, 1400, 1160, 1110 cm^{-1}.

^{1}H NMR (200MHz) : 1.45 (s, 9H), 1.8-1.95 (m, 4H), 3.37 (t, J = 7.3 Hz, 4 H).

Mass : 171 (M^+, 11%), 114 (100%), 57 (82%).

8.5. Preparation of N-(*tert*-butoxy carbonyl)-2-trimethylsily pyrrolidine (30):

A solution of N-Boc pyrrolidine (**29**) (6.84 g, 39.99 mmol) in 40 mL of dry ether charged into a 250 mL flask, equipped with a magnetic stirring bar and argon gas balloon, was cooled to -78 °C. TMEDA (5.57 g, 47.99 mmol) followed by *s*-BuLi (1.5 M solution in cyclohexane, 31.99 mL, 47.99 mmol) were introduced to the stirring mixture dropwise over 15 min. The mixture was further allowed to stir for 2 h at -

78°C. Chlorotrimethylsilane (5.21g, 47.99 mmol) was added dropwise into the flask. The reaction mixture was allowed to warm to rt and diluted with 15 mL of saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ether (2×30 mL). The combined extracts were washed with water (80 mL), brine (80 mL) and dried over Na_2SO_4. The organic extract was concentrated and the crude oily residue obtained was purified by fractional distillation (bp 55-57°C/0.5 mm) to give 8.74 g (90%) of **30** as a colorless oil .

IR : 1692, 1478, 1365, 1246, 1170 cm^{-1}

^{1}H NMR (200MHz) : δ 0.05 (s, 9H), 1.45 (s, 9H), 1.75-1.95 9 (m, 3H),1.95-2.05 (m, 1H), 3.15-3.3 (m, 2H), 3.35-3.6 (m, 1H).

^{13}C NMR (50.32 MHz) : δ -2.3, 27.8, 28.4, 46.7, 47.5, 78.0, 154.5.

Mass : 243 (M^+, 1), 186 (43), 172 (100), 142 (94).

8.6. Preparation of N-(*tert*-butoxy carbonyl)-2,2-bis(trimethylsilyl)pyrrolidine (31) :

Treating the solution of **30** (4.86 g, 20 mmol) in ether with s-BuLi (24 mmol, 16 ml of 1M solution in cyclohexane) in the presence of TMEDA (2.78 g, 24 mmol), in the identical manner as described for **30**, followed by quenching with TMSCl (2.60 g, 24 mmol) and usual workup and purification by silica gel column chromatography, eluting with hexane/ethyl acetate (99/1), afforded 4.09 g (65 %) of **31** as a pale yellow oil. Further elution with same solvent system gave a trace amount of **32** (in <5% yield).

IR (Neat) : 1690, 1392, 1248, 1169 cm^{-1}

^{1}H NMR (200MHz) : δ 0.1 (s, 18H), 1.45 (s, 9H), 1.75 (m, 2H), 1.95 (t, J = 6.8 Hz, 2H), 3.35 (t, J = 6.8 Hz, 2H).

^{13}C NMR (50.32 MHz) : δ 0.18, 25.5, 28.8, 32.2, 46.5, 48.5, 78.1, 154.6.

Mass : 258 (72), 244 (70), 214 (37), 186 (36), 73 (100 %).

8.7. Preparation of N-(*tert*-butoxycarbonyl)-2,5-bis(trimethylsilyl)pyrrolidine (32):

A 250 mL two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of **30** (4.86 g, 20 mmol) in 30 mL of ether and was cooled to - 45°C. TMEDA (2.79 g, 24 mmol) followed by *s*-BuLi (1.5 M in cyclohexane, 15.92 mL, 24 mmol) were added to the flask dropwise while stirring. After 15 min of stirring at -45°C, temperature was raised to -30°C. After 30 min, it was recooled to -45°C and chlorotrimethylsilane (2.6 g, 24 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, diluted with 10 mL of saturated aqueous NH_4Cl solution and worked up as mentioned in previous experiment, to get an oily residue which was purified by silica gel column chromatography eluting with hexane:EtOAc (99:1) to give 4.41g (70 %) of **32** as a pale yellow oil. Only trace amount of **31** was isolated in this case.

IR : 1684, 1406, 1365, 1171 cm^{-1}

^{1}H NMR (200MHz) : δ 0.05 (s, 18H), 1.45 (s, 9H), 1.75-2.00 (m, 4H), 3.00-3.10 (bs, 1H), 3.20-3.30 (bs, 1H).

^{13}C NMR (50.32 MHz) : δ -1.03, -0.50, 28.93, 29.0, 49.44, 50.0, 78.96, 154.82

Mass : 315 (M^+, 1), 258 (83), 244 (41), 228 (45), 214 (71), 186 (33), 73 (100).

8.8. Preparation of N-benzyl-2,5-bis(trimethylsilyl)pyrrolidine (11):

To a stirring solution of **32** (3.15 g, 10 mmol) in 40 mL of dry CH_2Cl_2 at 0 °C contained in a 100 mL round bottom flask equipped with argon gas balloon, was added trifluroacetic acid (5.70 g, 50 mmol) dropwise over 15 mins. The mixture was allowed to warm to rt and allowed to stir further for 4 h. The reaction mixture was recooled to 0°C and basified with 20% aqueous NaOH solution (pH =10). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give 1.93 g of crude amine which was utilised as such without further purification for the next step.

To a 40 mL solution of the crude amine (1.93 g, 8.97 mmol) in acetonitrile, K_2CO_3 (1.49 g, 10.8 mmol) and benzyl chloride (1.08 g, 8.55 mmol) were added. The resultant suspension was refluxed for 5-6 h. Progress of the reaction was monitored by TLC. On completion of the reaction, mixture was cooled, filtered and the solvent was evaporated under vacuum. The crude yellow oil was purified by silica gel column chromatography, eluting with hexane: EtOAc (98:2), to obtain 2.44 g (80 %) of **11** as a pale yellow oil.

IR : 3028, 2951, 1452, 1248, 935 cm^{-1}.

^{1}H NMR (200MHz) : δ 0.1 (s, 18H), 1.65-1.80 (m, 2H), 1.90-1.95 (m, 2H), 2.25-2.30 (m, 2H), 3.35 (d, *J* = 12.85 Hz, 1H), 3.8 (d, *J*= 12.87 Hz, 1H), 7.20-7.35 (m, 5H);

^{13}C NMR (50.32 MHz) : δ -1.6, 26.8, 56.0, 60.1, 126.8, 128.1, 129.4, 141.7.

Mass : 305 (M^+, 3), 290 (17), 233 (100), 91 (90), 73 (54).

8.9. [3+2]-Cycloaddition reaction of 28 with 11 :

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (1.58 g, 12.5 mmol) (dried previously under vaccum at 40 ^{0}C) and with a solution of dipolarophile **28** (1.32 g, 6.26 mmol) in 40 mL of dry dichloromethane. Compound **11** (1.73 g, 5.69 mmol), dissolved in 30 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. The color of the reaction mixture gradually turned dark brown with concomitant deposition of silver on the surface of the flask in the form of mirror and the progress of the reaction was periodically monitored by TLC. After stirring for 8-10 h, the reaction mixture was filtered through a small plug of celite and the solvent was evaporated to give a crude brown residue. Purification of the crude residue by silica gel column chromatography, eluting with hexane:EtOAc (9:1), afforded 0.42 g (20 %) of **34** yield. Further elution with hexane:EtOAc (9:2) afforded 1.26 g (60 %) of **33** as a thick yellow oil.

7- Benzyl- 2- *endo*-(6- chloro- 3- pyridyl)-3- *exo*- carbethoxy- 7- azabicyclo [2.2.1] heptane (33):

IR (Neat) : 1728, 1462, 1142, 1052 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.35-1.45 (m, 2H), 1.60-1.80 (m, 1H), 1.95-2.05 (m, 1H), 2.55 (d, *J* = 6.16 Hz, 1H), 3.60 (d, *J* = 4.48 Hz, 1H), 3.61 (d, *J* = 13.71 Hz, 1H), 3.72 (d, *J* = 13.70 Hz, 1H), 3.81 (dd, *J* = 4.78, 0.84 Hz, 1H), 3.90 (t, *J* = 4.55 Hz, 1H), 4.20 (q, *J* = 7.21 Hz, 2H), 7.25-7.52 (m, 7H), 8.25 (d, *J* = 2.7 Hz, 1H).

^{13}C NMR (50.32 MHz) : δ 14.0, 20.9, 27.2, 47.1, 51.3, 52.4, 60.7, 63.3, 63.9, 123.6, 126.7, 128.0, 134.7, 138.2, 139.4, 149.2, 173.1.

Mass : 370 (M^+, 3), 159 (100), 131 (26), 91 (81 %).

7- Benzyl- 2- *exo*- (6- chloro- 3- pyridyl)- 3- *endo*- carbethoxy- 7- azabicyclo [2,2,1] heptane (34):

IR : 1728, 1457, 1101 cm^{-1}.

^{1}H NMR (300MHz) : δ 1.20 (t, *J*= 7.05 Hz, 3H), 1.55 (dt, *J* = 2.32, 7.93 Hz, 2H), 2.0 (m, 2H), 2.85 (dt, *J* = 1.83, 5.07 Hz, 1H), 3.06 (d, *J*= 5.39 Hz, 1H), 3.24 (d, *J* = 3.76 Hz, 1H), 3.54 (s, 2H), 3.65 (t, *J* = 4.07, 4.43 Hz, 1H), 4.10 (q, *J* = 7.09 Hz, 2H), 7.20 (d, *J* = 8.35 Hz, 1H), 7.23-7.35 (m, 5H), 7.84 (dd, *J* = 2.47, 8.26, 1H), 8.42 (d, *J* = 2.41 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 14.1, 21.8, 26.8, 47.4, 51.7, 57.5, 60.6, 66.6, 66.4, 123.6, 127.0, 128.2, 128.5, 137.9, 139.2, 140.2, 148.9, 172.0.

Mass : 370 (M^+, 20), 211 (22), 184 (140, 166 (72), 159 (100), 138 (30), 91 (90).

8.10. Synthesis of 43 *via* Bartons Decarboxylation of Major Diastereomer 33:

A solution of **33** (1.0 g, 2.7 mmol) in MeOH:H_2O (3:1, 20 mL) containing LiOH:H_2O (0.17 g, 4.04 mmol) was warmed to 45 ^{0}C while stirring. After 1.5 h, mixture was cooled and washed with CH_2Cl_2 (3×20 mL). The aqueous layer was cooled to 0°C, acidified with 6 N HCl to pH = 5 and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate. Evaporation of the organic layer gave crude acid **40** as a white solid. Compound **40** was dissolved in 30 mL of dry benzene and was transferred to a 50 mL flask equipped with argon gas balloon. Oxalyl chloride (1.18 mL, 13.52 mmol) and DMF (one drop) were added to the flask at rt and stirred for 2 h. Evaporation of the solvent under vacuum gave acid chloride **41** as brown solid. The crude acid chloride **41** was dissolved in dry benzene (30 mL)

and to the resultant solution, DMAP (0.033 g, 0.26 mmol), N-hydroxy-2-mercaptopyridine (0.41 g, 3.24 mmol) and 1.2 mL pyridine were added maintaining the argon atmosphere. The reaction mixture was stirred for 1.5-2 h at rt. Solid suspension was allowed to settle and the supernatant solution containing thiohydroxamic ester **42** was syringed out and added to a refluxing solution of *t*-BuSH (1.5 mL) in 40 mL of dry benzene. The mixture was refluxed for 2.5-3 h, cooled and washed with aqueous 1N NaOH solution, water, brine, and dried over Na_2SO_4. Concentration gave a black brownish residue which upon silica gel column chromatographic purification eluting with EtOAc:hexane (2:8) afforded 0.442 g (55 %)of **43** as a thick yellow oil.

IR (Neat) : 2960, 1460, 1105 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.30-1.40 (m, 2H), 1.45-1.60 (dd, *J* = 5.36, 17.92 Hz, 1H), 1.60-1.85 (m, 1H), 1.90-2.0 (m, 1H), 2.35 (m, 1H), 3.45 (t, *J* = 4.7 Hz, 2H), 3.55 (m, 1H), 3.70 (s, 2H), 7.25-7.50 (m, 7H), 8.25 (d, *J* = 2.51 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 21.6, 28.3, 33.7, 42.7, 51.7, 60.2, 63.9, 123.5, 126.8, 128.2, 128.3, 136.1, 138.3, 139.6, 148.9, 149.5.

Mass : 298 (M^+, 9), 159 (70), 91 (100), 83 (36).

8.11. Debenzylation of 43 to *endo*-2-(6-chloro-3-pyridyl)-7-aza-bicyclo[2.2.1]heptane (49) :

α-Chloroethyl chloroformate (0.18 g, 1.26 mmol) was added at rt to a 20 mL solution of **43** (0.3 g, 0.99 mmol) in dry 1,2-dichloroethane. The reaction mixture was refluxed for 2 h, cooled and concentrated under vacuum. The residue was dissolved in 15 mL of methanol and further refluxed for 3 h. The reaction mixture was

evaporated to dryness and the solid residue was dissolved in chloroform (20 mL) and basified with aqueous 1 N NaOH solution to pH = 8. The chloroform layer was separated and the aqueous layer was further extracted with (2×10 mL) chloroform. Combined extracts were dried over anhydrous $CaCl_2$ and concentrated to give brown oily residue. Column chromatographic purification eluting with hexane: EtOAc (8:2) gave 0.025 g of unreacted **43**. Further elution using (9:0.5:0.1 / $CHCl_3$:MeOH:NH_4OH) as eluent gave **49** (0.107 g) in 52 % yield.

IR : 3250, 1570, 1230, 1105 cm^{-1}.

H NMR (200MHz) : δ 1.4-1.5 (m, 6H), 2.25 (m, 1H), 3.55 (m, 1H), 3.9 (bs, 2H), 7.3 (d, *J* = 8.30 Hz, 1H), 7.5 (dd, *J* = 8.28, 2.47 Hz, 1H), 8.24 (d, *J* = 2.45 Hz, 1H).

8.12.Preparation of N-(*tert*-butoxy carbonyl)-2-endo-(6-chloro-3-pyridyl)-7-azabicyclo [2.2.1]heptane (50):

To a stirring solution of **49** (0.10 g, 0.48 mmol) in 15 mL of THF, $(Boc)_2O$ (0.126 g, 0.576 mmol) followed by triethyl amine (0.06 g, 0.576 mmol) were added under argon atmosphere. The resulting mixture was stirred for 6-8 h, concentrated and residue was purified by silica gel column chromatography eluting with hexane: EtOAc (9:1) to afford 0.132 g of **50** (**89**%) as a pale yellow oil.

IR (Neat) : 1693, 1582, 1460, 1104 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.37-1.45 (m, 2H), 1.5 (s, 9H), 1.55 (m, 2H), 1.85-1.95 (m, 1H), 2.30 (m, 1H), 3.45 (ddd, *J* = 11.5, 5.4, 5.4 Hz, 1H), 4.30 (bs, 2H), 7.30 (d, *J* = 8.67 Hz, 1H), 7.50 (dd, *J* = 2.63, 8.69 Hz, 1H), 8.26 (d, *J* = 2.46 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 23.1, 28.1, 30.0, 34.2, 43.4, 57.1, 60.1, 79.8, 123.7, 134.6, 138.3, 149.3, 155.3.

Mass : 308 (M^+, 2), 208 (37), 140 (72), 126 (11), 69 (51), 57 (100).

8.13. Epimerisation of 50 to 51:

A mixture containing **50** (0.10 g, 0.32 mmol) and *t*-BuOK (0.182 g, 1.62 mmol) in *tert*-butyl alcohol (5 mL) was refluxed for 40 h under argon atmosphere. Removal of the solvent and the purification of the residue by silica gel column chromatogrphy eluting with hexane:EtOAc (9:1) afforded 0.045 g (45%) of **51**. Further elution with the same solvent system gave unreacted **50** (0.03 g, 30%).

N-(*tert*-butoxy carbonyl)-2-*exo*-(6-chloro-3-pyridyl)-7-azabicyclo [2.2.1]heptane (51):

IR ($CHCl_3$) : 1693, 1582, 1460, 1155 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.45 (s, 9H), 1.55-1.65 (m, 2H), 1.75-1.85 (m, 3H), 1.95 (dd, *J* =8.93, 12.3 Hz, 1H), 2.87 (dd, *J* =5.04, 8.93 Hz, 1H), 4.16 (bs, 1H), 4.38 (bs, 1H), 7.25 (d, *J* = 8.35 Hz, 1H), 7.65 (dd, *J* = 2.42, 8.32 Hz, 1H), 8.25 (d, *J* = 2.46 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 28.1, 28.6, 29.5, 40.2, 44.7, 55.9, 61.8, 79.8, 124.0, 137.1, 139.9, 148.5, 155.1.

Mass : 308 (M^+, 3), 208 (37), 140 (72), 69 (51), 57 (100).

8.14. Deprotection of Boc moiety from 51: Synthesis of 1

Trifluoroacetic acid (0.1 mL, 1.16 mmol) was added to a stirring solution of **51** (0.045 g, 0.15 mmol) in DCM (5 mL) at 0 ^{0}C under argon atmosphere. Contents were

further stirred for additonal 4 h at room temperature.The reaction mixture was basified with saturated aqueous Na_2CO_3 solution. The organic layer was separated and the aqueous layer was extracted with DCM (3×5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with $CHCl_3$:MeOH: NH_4OH (98:2:1), to give 0.028 g (90 %) of **1** as a thick pale yellow paste.

IR : 2960, 2850, 1574, 1457, 1324 cm^{-1}.

^1H NMR (200MHz) : δ 1.5-1.65 (m, 5H), 1.91 (dd, *J* = 12.1, 8.8 Hz, 1H), 2.77 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.57 (bs, 1H), 3.8 (bs, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.75 (dd, *J* = 8.3, 2.5 Hz, 1H), 8.26 (d, *J* = 2.6 Hz, 1H).

8.15. Synthesis of 7-*tert*- Butoxycarbonyl- 2-*exo*- (6-chloro-3-pyridyl)-3-*endo*-carbethoxy -7-azabicyclo [2.2.1] heptane (52) :

α-Chloroethyl chloroformate (0.18 g, 1.26 mmol) was added at rt to a 20 mL solution of **34** (0.3 g, 0.81 mmol) in dry 1,2-dichloroethane (20 mL). The reaction mixture was refluxed for 2 h, cooled and concentrated under vacuum. The residue was dissolved in 15 mL of methanol and further refluxed for 3 h. The reaction mixture was evaporated to dryness and the solid residue was dissolved in chloroform (20 mL) and basified with aqueous 1 N NaOH solution to pH = 8. The chloroform layer was separated and the aqueous layer was further extracted with (2×10 mL) chloroform. Combined extracts were dried over anhydrous $CaCl_2$ and concentrated to give brown oily residue which was taken up in dry THF. The mixture was treated with triethyl amine and DMAP (10 mg, 0.16 mmol) followed by dropwise addition of di-*tert*-butyl dicarbonate (0.23 g, 1.05 mmol) in THF. Reaction

mixture was allowed to stir for 3-4 h. The solvent was evaporated and the residue was purified by silica gel column chromatography eluting with hexane:EtOAc (9:1) to afford 0.17 g (55 %) of **52** as a yellow viscous oil.

IR (Neat) : 1727, 1708, 1460, 1227, 1056 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.25 (t, *J* = 7.21 Hz, 3H), 1.42 (s, 9H), 1.50-1.55 (m, 1H), 1.55-1.70 (m, 1H), 1.70-1.95 (m, 2H), 3.0 (t, *J*= 4.89 Hz, 1H), 3.30 (d, *J* =5.46 Hz, 1H), 4.2 (q, *J* =7.31 Hz, 2H), 4.30 (bs, 1H), 4.60 (bs, 1H), 7.25 (d, *J* = 8.44 Hz, 1H), 7.65 (dd, *J* = 2.43, 8.27 Hz, 1H), 8.30 (d, *J* = 2.44 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 14.0, 24.5, 28.0, 29.3, 47.0, 56.8, 58.1, 61.0, 62.3, 80.2, 124.0, 137.0, 138.4, 148.4, 154.57, 170.9.

Mass : 380 (M^+, 3), 280 (25), 212 (60), 142 (10), 69 (100).

8.16. Preparation of *cis*-Ethyl-(6-chloro-3-pyridyl)-2-propenoate (54):

18-Crown-6 acetonitrile complex (10.83 g, 35.46 mmol) and bis (2,2,2-trifluoroethyl) (ethoxy carbonyl methyl) phosphonate (5.8 g, 15.60 mmol) dissolved in THF (400 mL) were charged into a two neck flask equipped with a magnetic stirring bar and argon gas balloon. The mixture was cooled to -78°C and potassium bis (trimethyl silyl) amide (1.0 M solution in THF, 15.60 mL, 15.60 mmol) was introduced into the flask while stirring. Compound **12** (2.0 g, 14.13 mmol) dissolved in 10 mL of THF was added to the reaction mixture and the whole contents were allowed to stir for 30 min. Contents were poured on a 120 mL of saturated aqueous solution of NH_4Cl and the aqueous layer was extracted with ether (3×50 mL). Combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give crude oil which was purified by silica gel column chromatography, eluting with EtOAc:hexane (2:8), to afford 2.24 g (75 %) of **54** as a pale yellow oil.

IR (Neat) : 1721, 1636, 1555, 1462 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.25 (t, *J* =7.12 Hz, 3H), 4.15 (q, *J* = 7.22 Hz, 2H), 6.1 (d, *J* = 12.49 Hz, 1H), 6.85 (d, *J* =12.33 Hz, 1H), 7.30 (d, *J* = 8.30 Hz, 1H), 8.10 (dd, *J* = 2.44, 8.29 Hz, 1H), 8.45 (d, *J* = 2.45 Hz, 1H).

^{13}C NMR (50.32 MHz) : δ 14.0, 60.6, 122.7, 123.4, 129.6, 138.2, 139.5, 150.7, 151.3, 165.3.

Mass : 211 (M^+, 28), 182 (42), 166 (100), 138 (53).

8.17. [3+2]-Cycloaddition of 54 with 11:

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (1.58 g, 12.5 mmol) (dried previously under vaccum at 40 ^{0}C) and solution of dipolarophile **54** (1.32 g, 6.26 mmol) in 40 mL of dry dichloromethane. Compound **11** (1.73 g, 5.69 mmol), dissolved in 30 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 1.26 g (62%) of 55. Further elution with hexane:EtOAc (9:2) afforded 0.15 g (7 %) of **56** as a thick yellow oil.

7- Benzyl- 2- *exo*- (6-chloro- 3-pyridyl)-3-*exo*-carbethoxy-7-azabicyclo [2.2.1] heptane (55):

IR : 1731, 1455, 1215, 1106 cm^{-1}.

^{1}H NMR (200MHz) : δ 0.8 (t, *J* = 6.95 Hz, 3H), 1.45-1.60 (m, 2H), 2.1-2.2 (m, 2H), 2.90 (d, *J* = 10.12 Hz, 1H), 3.1 (d, *J* = 10.13 Hz, 1H), 3.25 (d, *J* = 4.03 Hz, 1H), 3.65 (q, *J* = 7.0 Hz, 2H), 3.70 (s, 2H), 3.75 (d, *J* = 4.03 Hz, 1H), 7.20 (d, *J* = 8.38 Hz, 1H), 7.25-7.45 (m, 4H), 7.5 (m, 1H), 8.05 (dd, *J* = 8.35 Hz, 1H), 8.35 (d, *J* = 2.7 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 13.3, 25.3, 26.2, 49.1, 51.4, 54.8, 59.5, 59.7, 65.3, 122.9, 126.6, 127.9, 128.2, 136.7, 138.5, 139.0, 149.0, 170.6.

Mass : 370 (M^+, 8), 159 (100), 130 (15), 91 (87), 68 (18).

7- Benzyl- 2- *endo*- (6- chloro- 3- pyridyl)- 3- *endo*- carbethoxy- 7-azabicyclo [2.2.1] heptane (56):

IR : 1720, 1216, 1108 cm^{-1}.

^{1}H NMR (300MHz) : δ 1.00 (t, *J*= 7.1 Hz, 3H), 1.60-1.80 (m, 2H), 1.85-2.0 (m, 1H), 2.10-2.20 (m, 1H), 3.45 (m, 2H), 3.60 (t, *J* = 4.45 Hz, 1H), 3.75 (m, 3H), 3.80-4.06 (q, *J* = 7.1 Hz, 2H), 7.25-7.42 (m, 7H), 8.10 (d, *J* = 2.19 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 13.7, 21.3, 22.7, 29.4, 44.6, 47.9, 51.1, 60.0, 62.2, 64.5, 122.9, 126.9, 128.2, 133.5, 138.7, 139.1, 149.0, 150.0, 171.6;

Mass : 370 (M^+, 3.5), 159 (100), 131 (13.5), 91 (89).

8.18. Synthesis of 7- Benzyl- 2- *exo*- (6-chloro- 3- pyridyl)- 7- azabicyclo [2.2.1] heptane (57) :

Compound **55** (1.0 g, 2.70 mmol) was hydrolysed to the corresponding acid and converted to its thiohydroxamate ester by following the same protocol as mentioned in this section 8.10. Usual work up, gave brownish residue which on purification by silica gel column chromatography eluting with hexane:EtOAc (8:2) afforded 0.44 g (55 %) of **57** as a thick yellow oil.

^{1}H NMR (200MHz) : δ 1.60-1.80 (m, 2H), 1.85-2.00 (m, 2H), 2.10-2.20 (m, 2H), 3.15 (dd, *J* = 4.53, 5.60 Hz, 1H), 3.45 (m, 1H), 3.65 (d, *J* = 16.8 Hz, 2H), 4.15 (m, 1H), 7.25-7.42 (m, 6H), 8.10 (dd, *J* = 2.19, 8.0 Hz, 1H), 8.40 (d, *J* = 2.30 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 17.3, 26.9, 29.1, 51.5, 54.4, 63.7, 66.6, 79.9, 123.3, 127.8, 128.2, 137.4, 148.2.

Mass : 298 (M^+, 10), 159 (70), 91 (100), 83 (36).

8.19. Synthesis of 1 from 57 *via* debenzylation:

α-Chloroethyl chloroformate (0.18 g, 1.26 mmol) was added at rt to a 20 mL solution of **57** (0.3 g, 0.99 mmol) in dry 1,2-dichloroethane. The reaction mixture was refluxed for 2 h, cooled and concentrated under vacuum. The residue was dissolved in 15 mL of methanol and further refluxed for 3 h. The reaction mixture was worked up as mentioned previously to give brown oily residue which on silica gel column chromatographic purification, eluting with hexane: EtOAc (8:2), gave 0.025 g (8.3%) of unreacted **57**. Further elution using (9:0.5:0.1 / $CHCl_3$:MeOH:NH_4OH) as eluent gave 0.107 g (52 %) of **1**.

8.20. Derivatization of 1 to N-trifloroacetyl-2-*exo*-(6-chloro-3-pyridyl)-7-azabicyclo [2..2.1] heptane (58):

A stirring solution of **1** (0.03 g, 0.14 mmol) and triethylamine (0.17g, 0.18 mmol) in dry THF (5 mL) at rt were treated with trifloroacetic anhydride (0.33 g, 0.16 mmol) in THF. The resulting solution was further stirred at rt for additional 5 h and the solvent was evaporated to obtain the browinsh residue which was purified by silica gel column chromatography eluting with hexane:EtOAc (2.5:7.5) to afford 0.035 g (80 %) of **58** as a colorless oil.

IR : 1694, 1429, 1144 cm^{-1}.

^{1}H NMR (300MHz) : δ 1.50-2.25 (m, 12H), 3.05 (m, 2H), 4.30(s, 1H), 4.65 (s, 1H), 4.78 (s, !H), 4.95 (s, 1H), 7.11 (dd, *J* = 2.5, 8.2 Hz, 2H), 7.65 (dd, *J* = 3.4, 8.3 Hz, 2H), 8.20 (m, 2H).

^{13}C NMR (75.3 MHz) : δ 27.7, 28.7, 29.9, 30.7, 37.7, 40.9, 43.7, 45.7, 55.4, 57.3, 60.4, 63.7, 115.6 (q), 116.0 (q), 134.8, 135.7, 136.1, 138.6, 139.0, 148.5, 148.7, 149.6, 149.9, 152.3 (q), 153.2 (q).

Mass : 304 (60), 165 (100), 140 (70), 68 (48).

8.21. Preparation of 7-Benzyl-2-carbethoxy-7-azabicyclo[2.2.1]heptane-2-ene (60):

Compound **60** was prepared by the reaction of **11** (0.50 g, 1.64 mmol) and ethyl propiolate (**59**) (0.178 g, 1.8 mmol) using Ag(I)F (0.458 g, 3.6 mmol) in DCM (30 mL) in an identical manner as described for the preparation of compounds **33** and **34**. The crude residue was purified by silica gel column chromatography, eluting with EtOAc:hexane (1.5:8.5), to obtain 0.29 g (75 %) of **60** as a pale yellow oil.

IR (Neat) : 1714, 1606, 1456 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.10 (dd, *J* = 10.2, 2.9 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.98 (dd, *J* = 3.0 Hz, 10.45 Hz, 2H), 3.42 (s, 2H), 3.89 (bs, 1H), 4.10 (d, *J* = 2.49 Hz, 1H), 4.25 (q, *J* = 7.15 Hz, 2H), 6.95 (d, *J* = 2.1 Hz, 1H), 7.25-7.40 (m, 5H).

^{13}C NMR (75.3 MHz) : δ 14.1, 23.5, 51.8, 60.1, 64.0, 65.1, 126.7, 127.1, 128.1, 128.5, 128.7, 139.1, 142.9, 164.5.

Mass : 257 (M^+, 2), 228 (80), 183 (68), 91 (100).

8.22.7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-carbethoxy-7-azabicyclo[2.2.1] heptane (34):

To a stirring solution of **61** (0.233 g, 0.97 mmol) into a mixture of ether (8 mL) and THF (4 mL) at -70°C, *n*-BuLi (1.6 M in hexane, 0.61 mL, 0.97 mmol) was introduced dropwise. The mixture was stirred at -70°C for 20 min before a solution of **60** (0.25 g, 0.97 mmol) dissolved in ether (4 mL) was introduced. The reaction mixture was allowed to stir additionally for 2 h at -70°C before warming to -50°C. After stirring for 30 min at -50°C, saturated aqueous NH_4Cl (2 mL) was added and the

mixture was warmed to rt. The aqueous phase was extracted with EtOAc (15 mL) and the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography eluting with hexane: EtOAc (8.5:1.5) to give **34** (0.215 g, 60%).

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Spectra

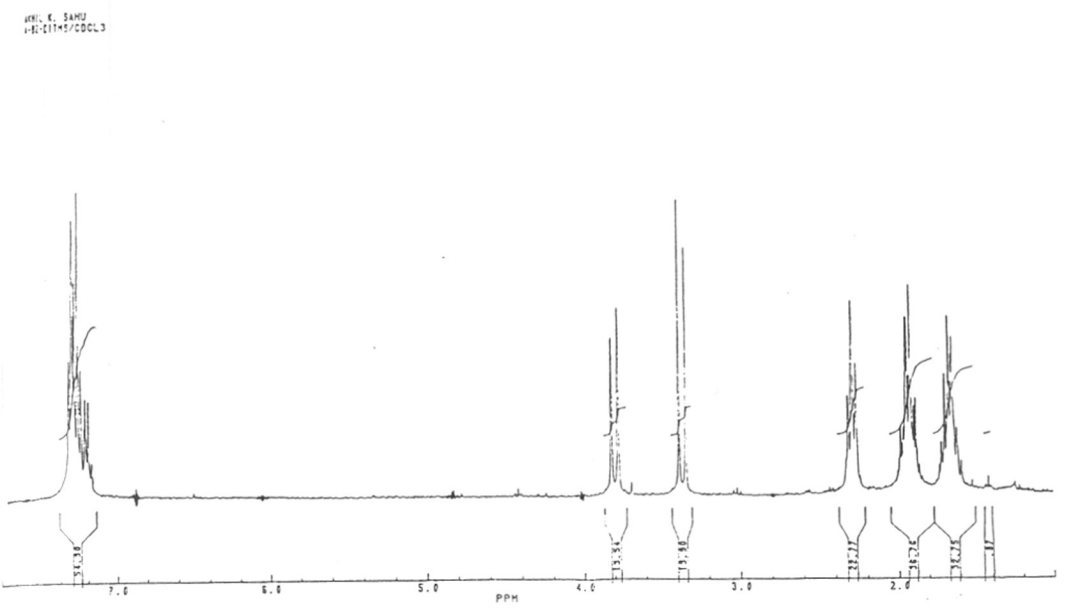
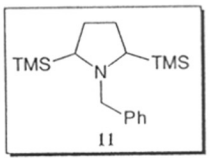


Fig. 2



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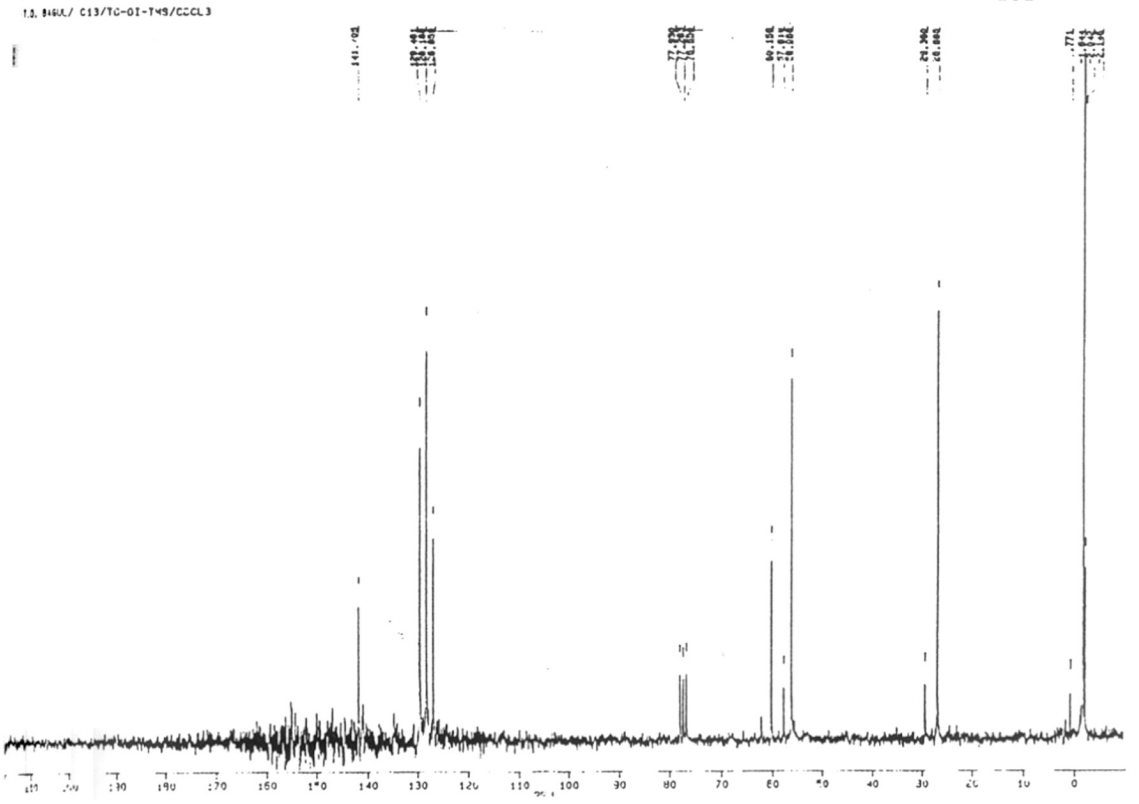
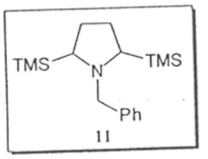
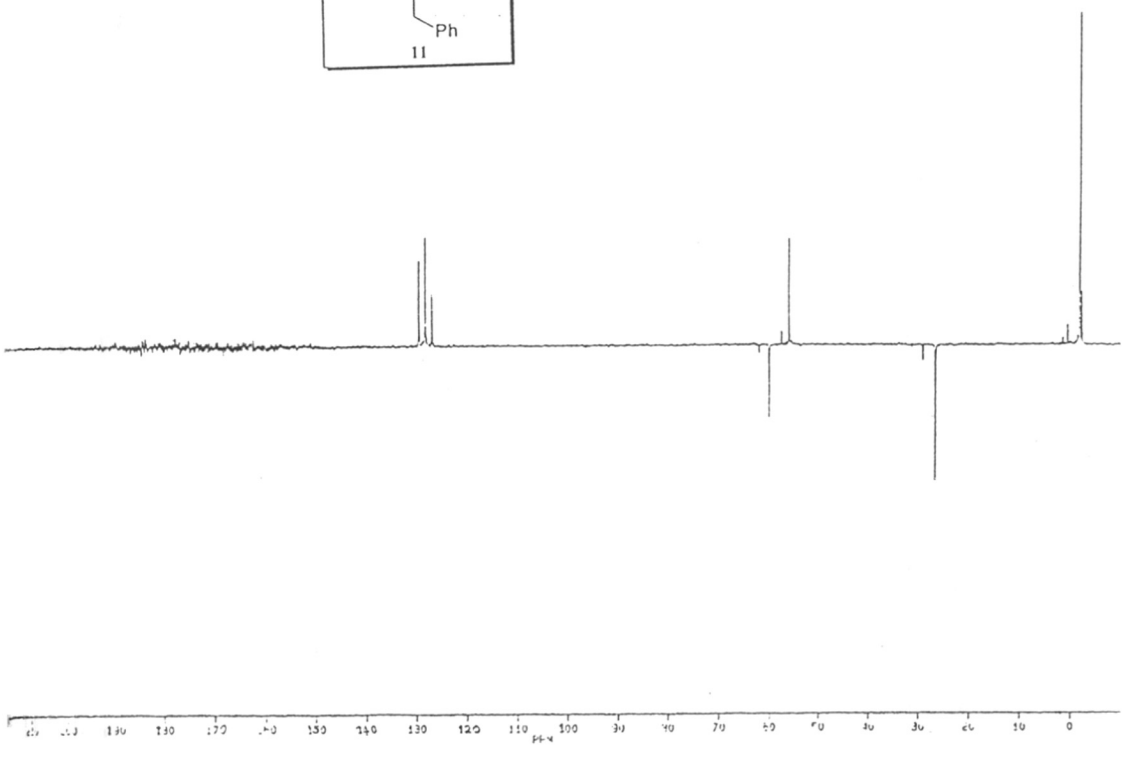


Fig. 3



11



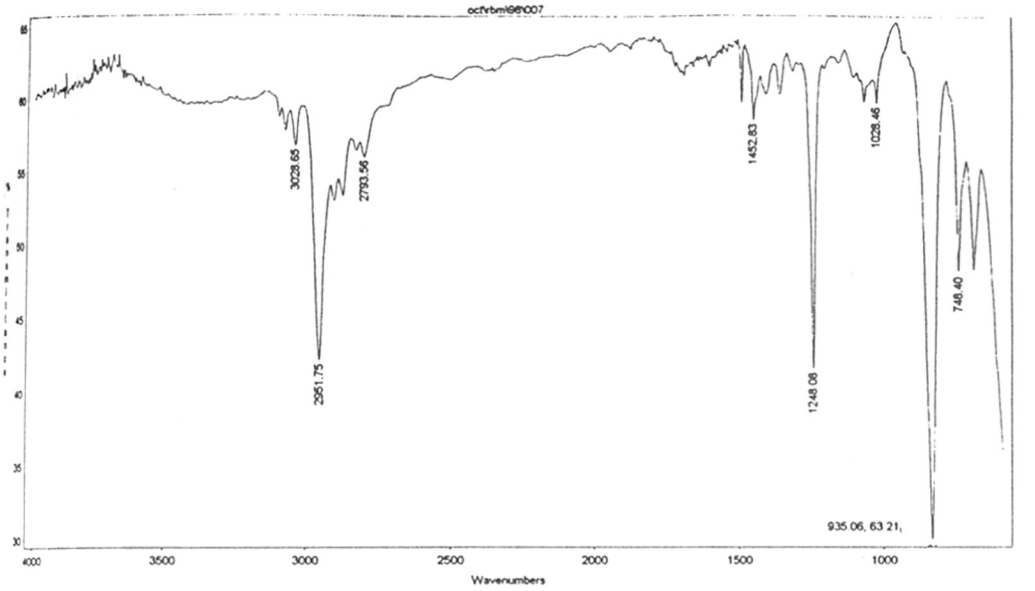
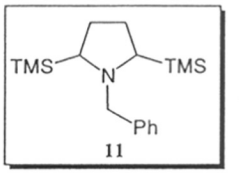
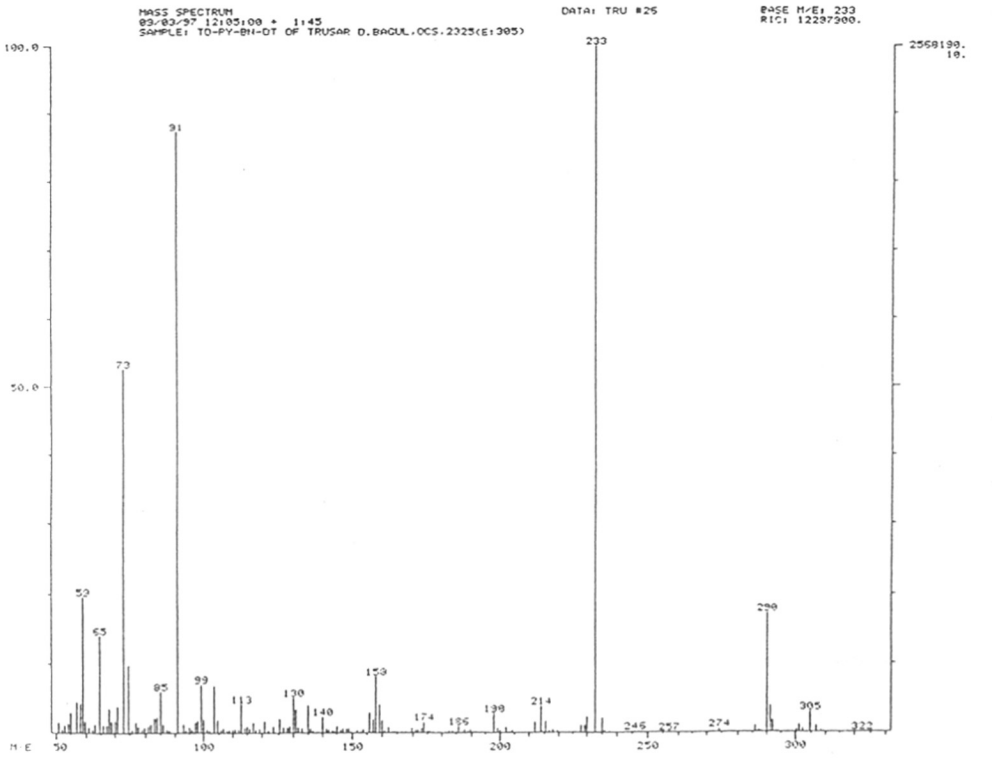


Fig. 4



11

Mr. Akhil Sahoo ; A-1 ; Neat ,04 / 03 / 98



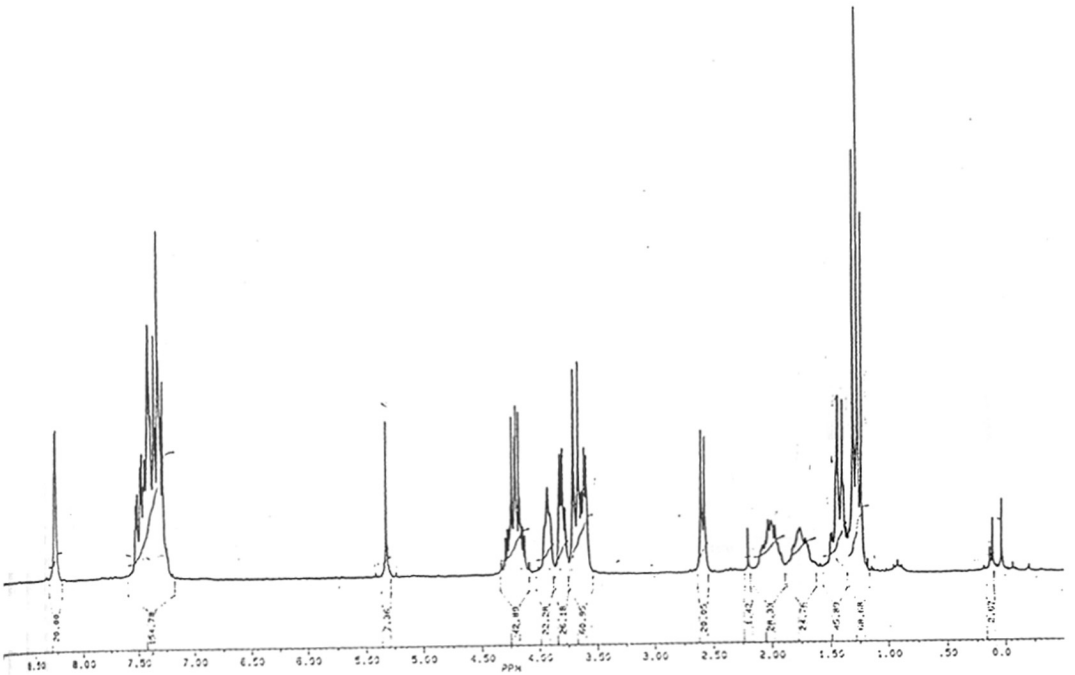
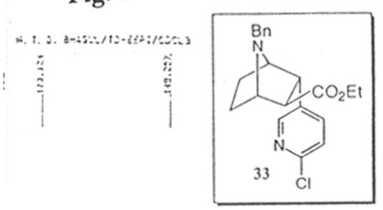
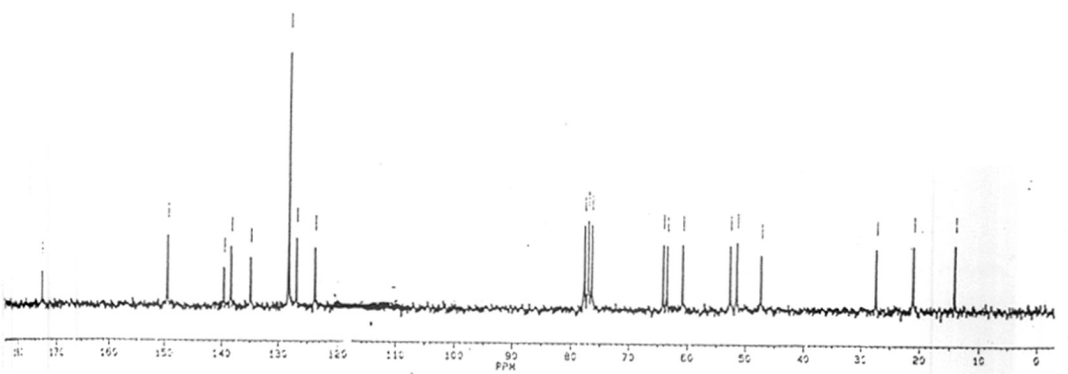
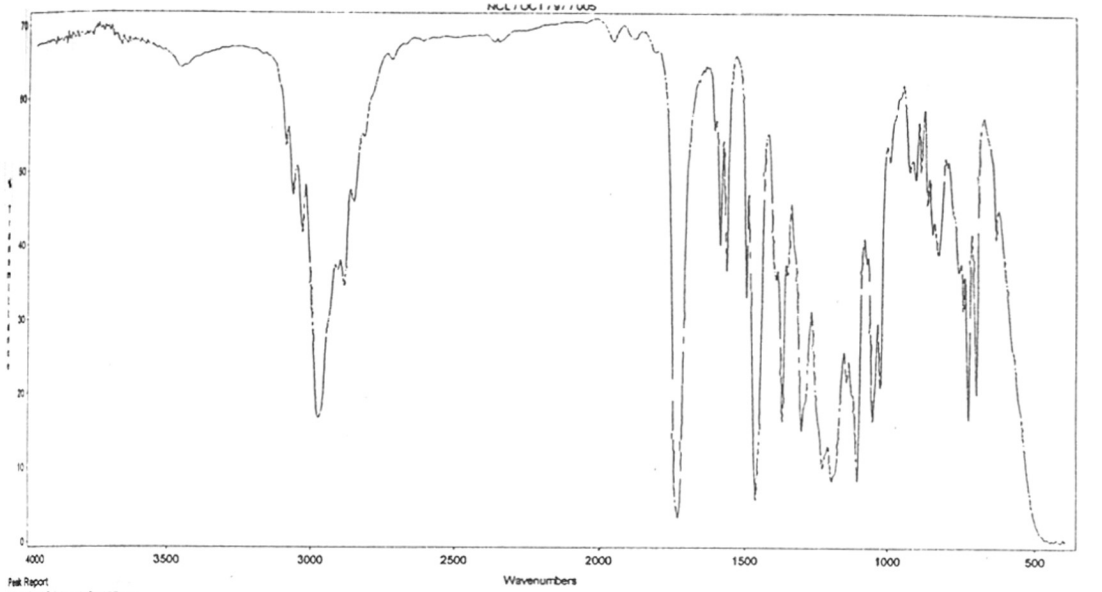


Fig. 5



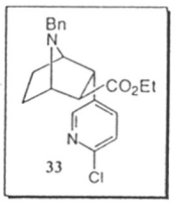




Peak Report
File: c:\fm\data\tmp\cfirst55.ras
Title: NCL / OCT / 97 / 005
Filter: Three Point Center of Gravity

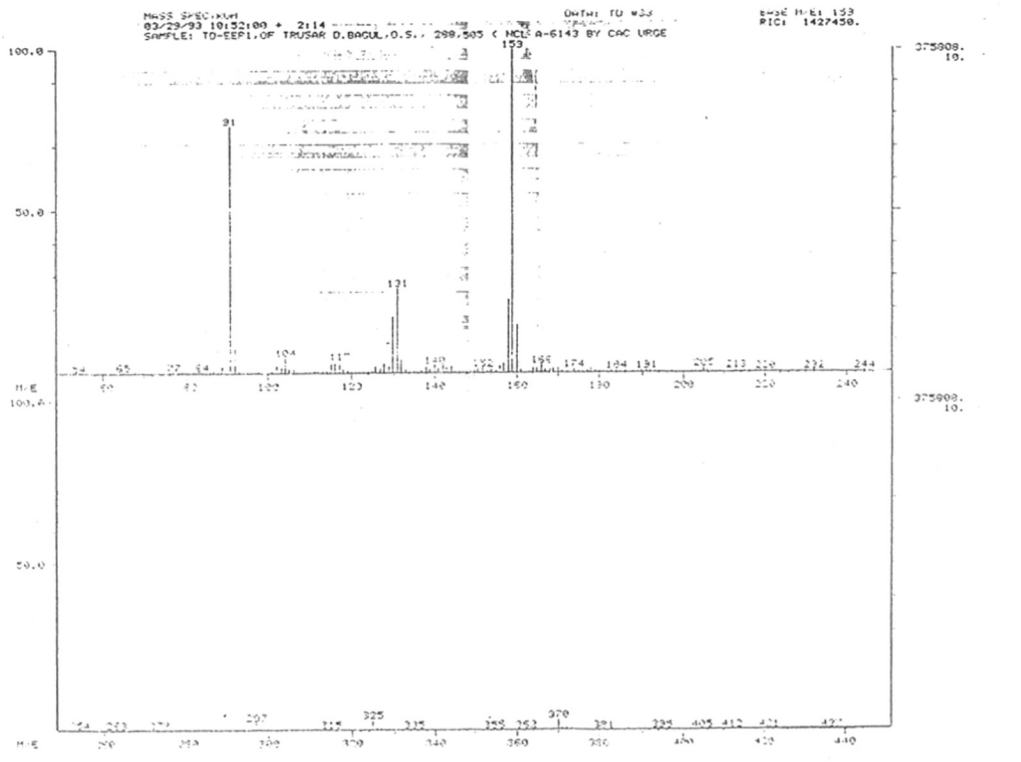
cm-1	%T	cm-1	%T	cm-1	%T	cm-1	%T
413.10	0.11	436.84	0.22	449.40	0.24	487.32	0.48
698.87	19.96	725.82	16.51	1025.02	20.65	1052.12	16.34
1105.82	8.23	1142.96	21.67	1195.29	8.13	1227.90	9.95
1301.88	14.97	1368.48	16.29	1462.74	5.76	1728.33	3.31
2851.91	34.64	2904.61	36.72	2972.80	16.72		

Fig. 6



WinFIRST Report

Name: Mr. T. D. Bagul
Date: 27 / 05 / 97
Sample: TD - END - Bn - Est
Comments: Neat



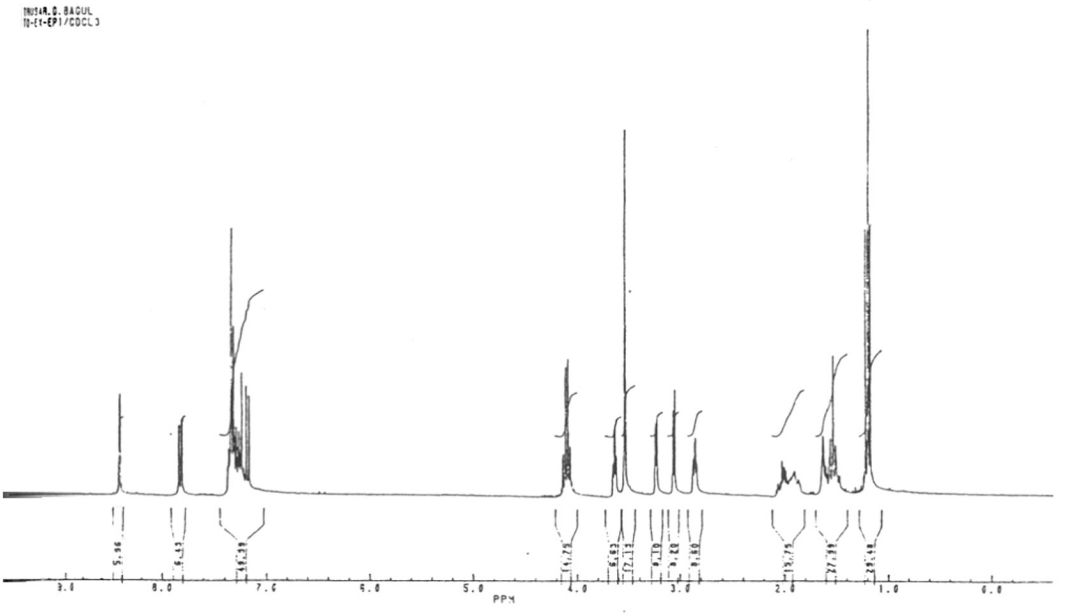
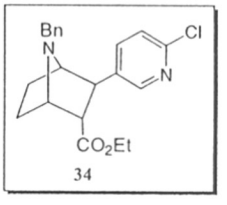
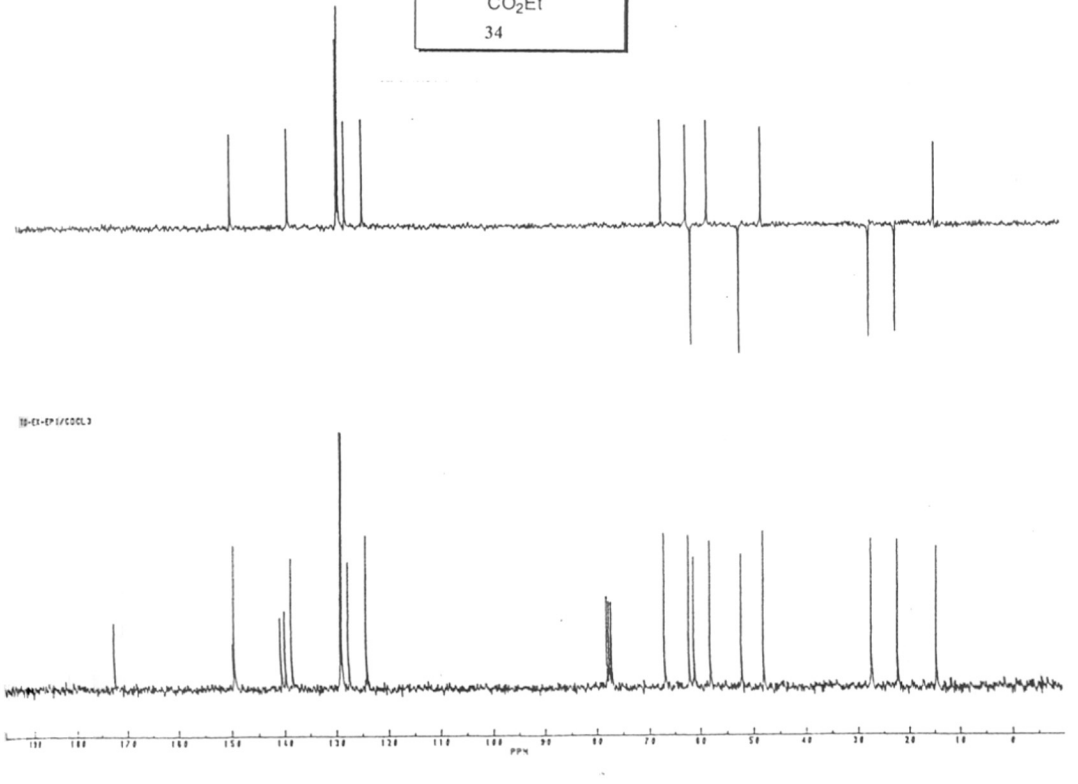
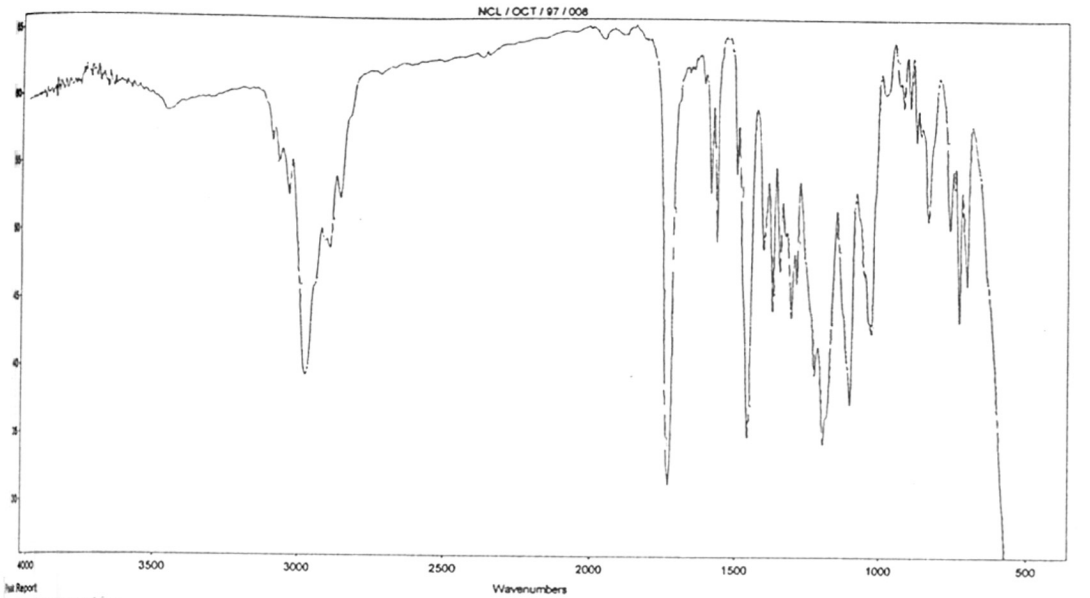


Fig. 7



34

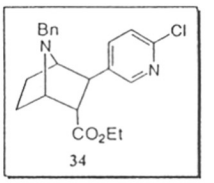




Fat Report
File c:\first\data\tmp\cfirst58.ras
File NCL / OCT / 97 / 008
Filter Three Point Center of Gravity

pk	%T	cm-1	%T	cm-1	%T	cm-1	%T
1078	0.00	427.13	0.47	436.96	0.32	446.49	0.28
1722	0.37	472.09	0.66	1101.73	37.23	1194.72	34.26
1650	34.76	1728.34	31.29	2972.42	39.27		

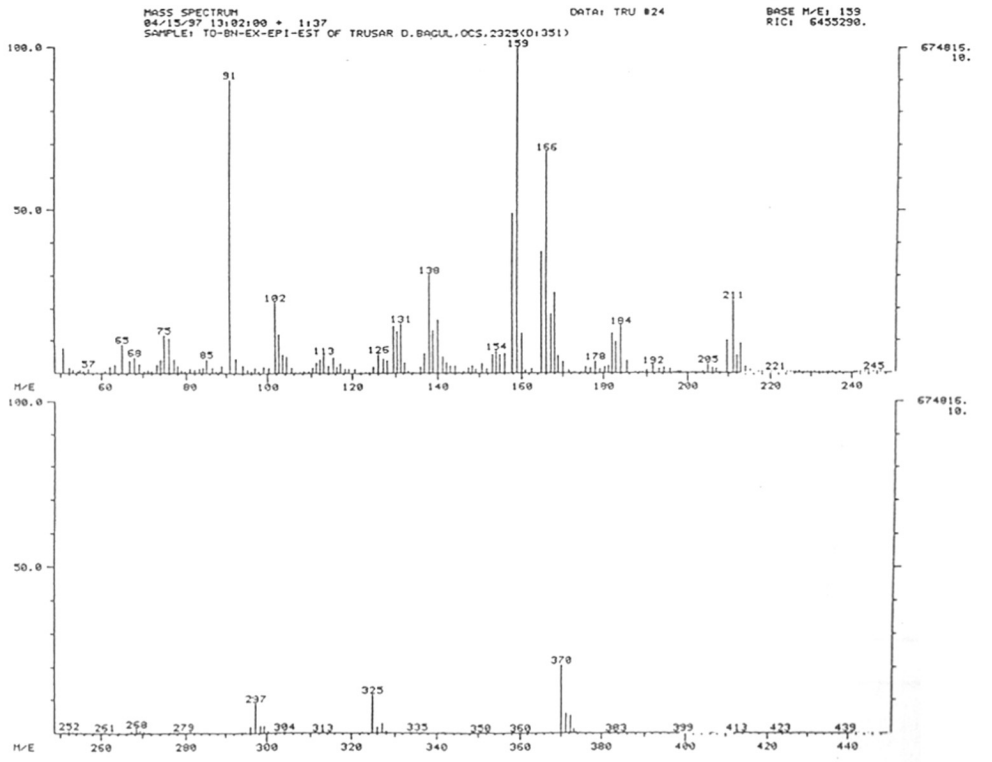
Fig. 8



34

WinFIRST Report

Name: Mr. T. D. Bagul
Date: 28 / 05 / 97
Sample: TD - Exo - Bn - Est
Comments: Neat



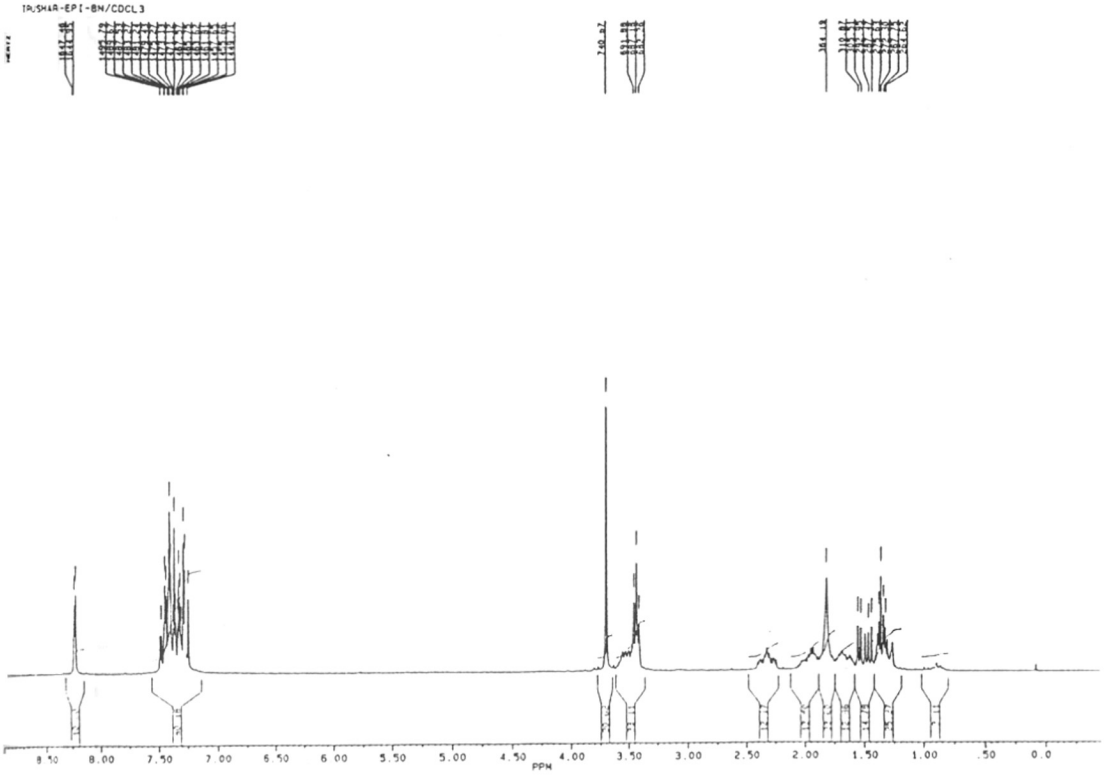
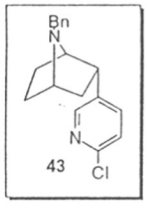
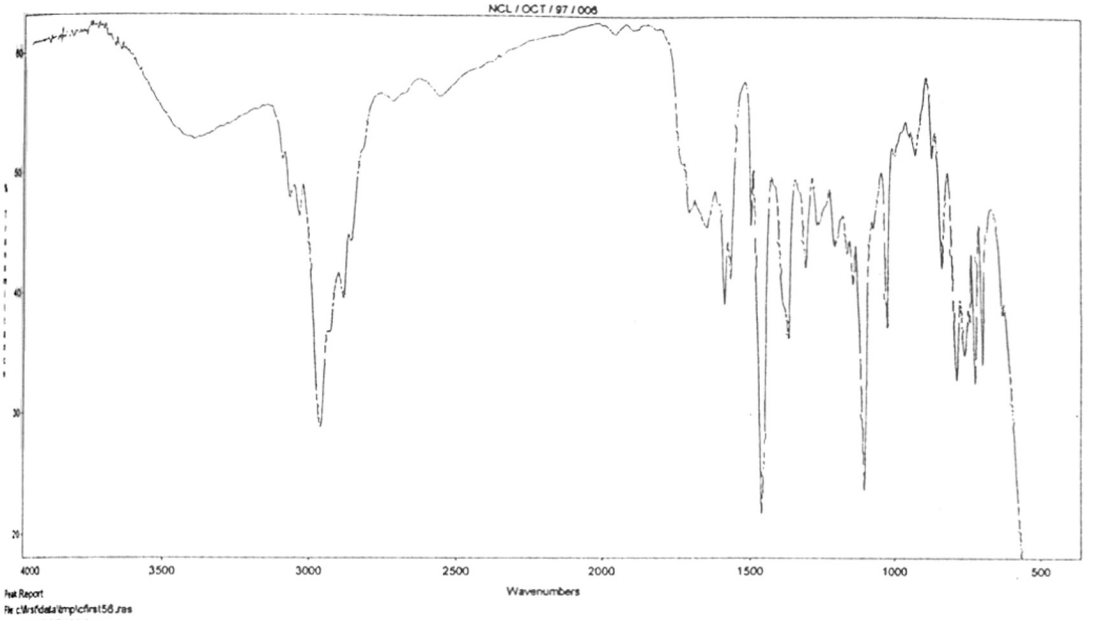

IRISHAR-EPI-BN/CDCL3
8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 .50 0.0
PPM

Fig. 9

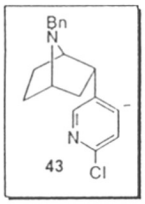

Bn
N
N
Cl
43



Peak Report
File: c:\first\data\dmplc\first56.ras
Title: NCL / OCT / 97 / 006
Filter: Three Point Center of Gravity

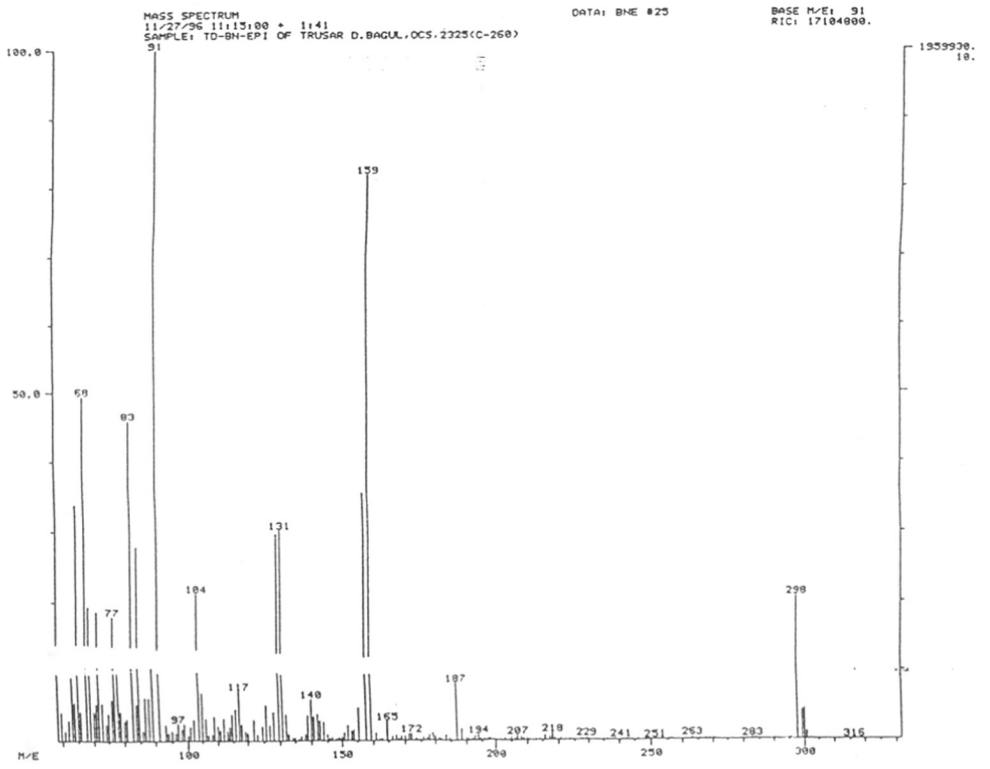
cm-1	%T	cm-1	%T	cm-1	%T	cm-1	%T
411.80	0.10	433.25	0.24	448.39	0.17	456.97	0.29
1105.87	23.62	1460.98	21.62	2879.09	39.54	2928.25	36.72
2960.82	28.80						

Fig. 10



WinFIRST Report

Name: Mr. T. D. Bagul
Date: 28 / 05 / 97
Sample: TD - Bn - Epi
Comments: Neat



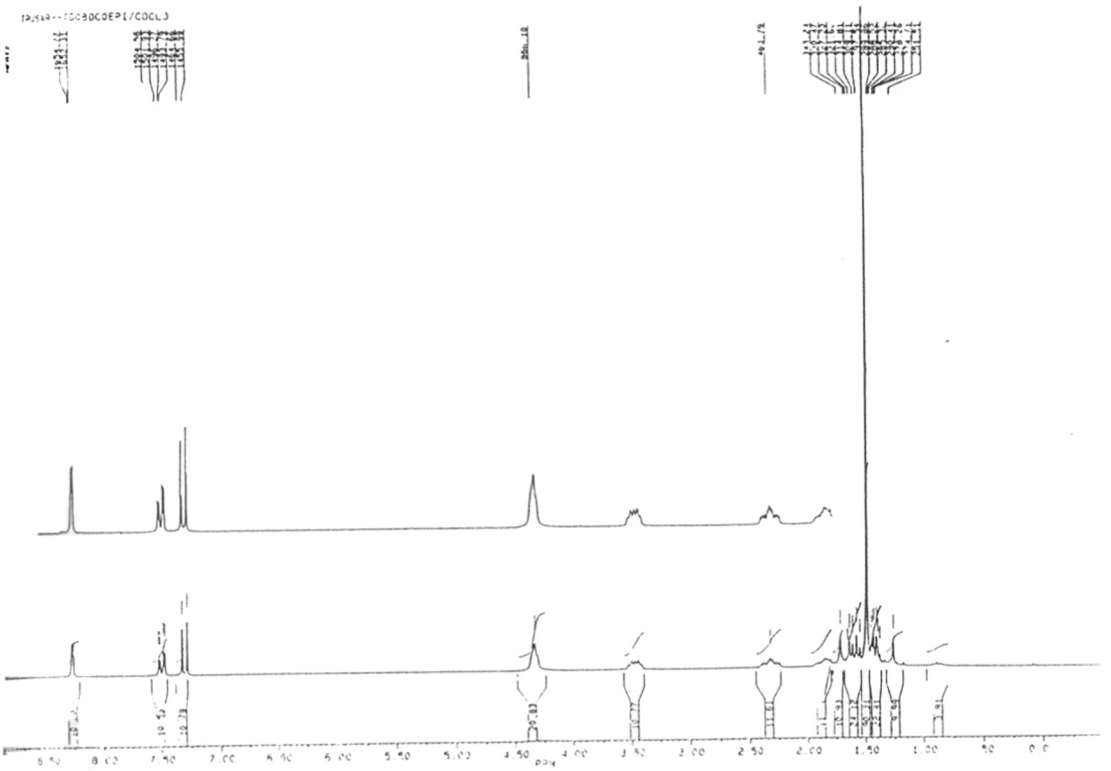
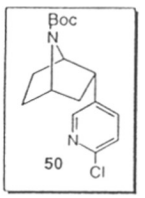
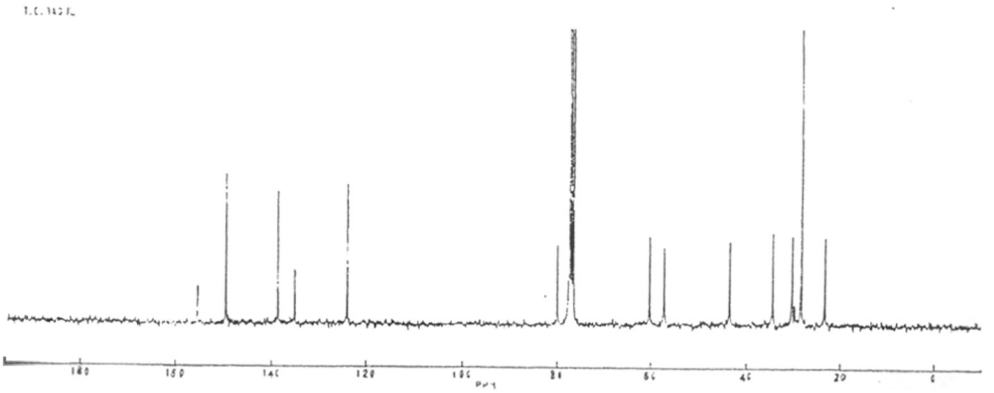


Fig. 11





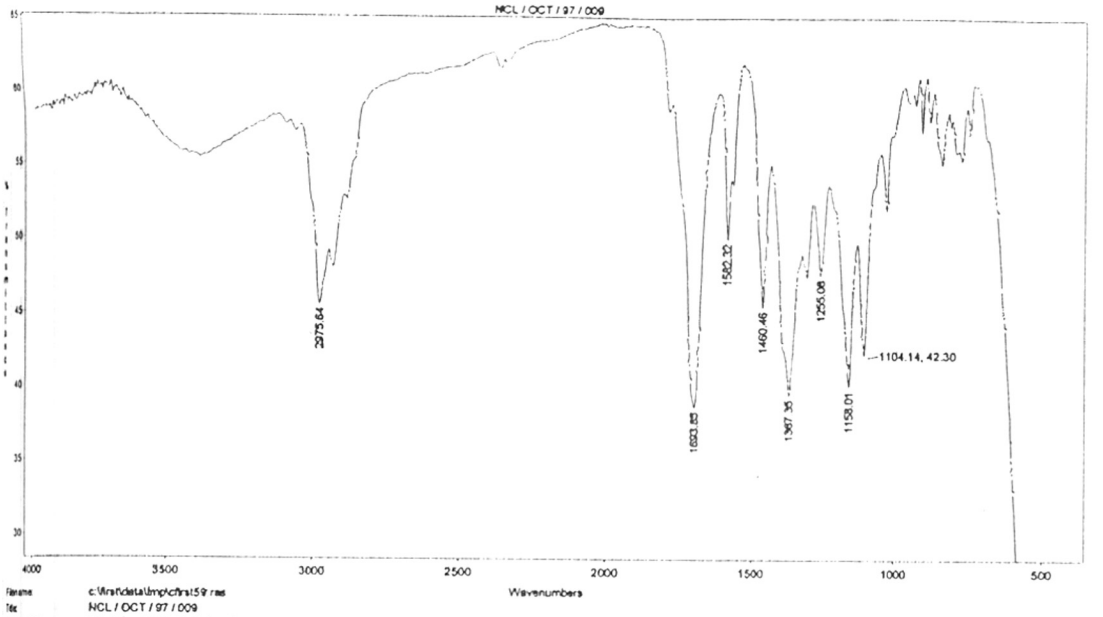
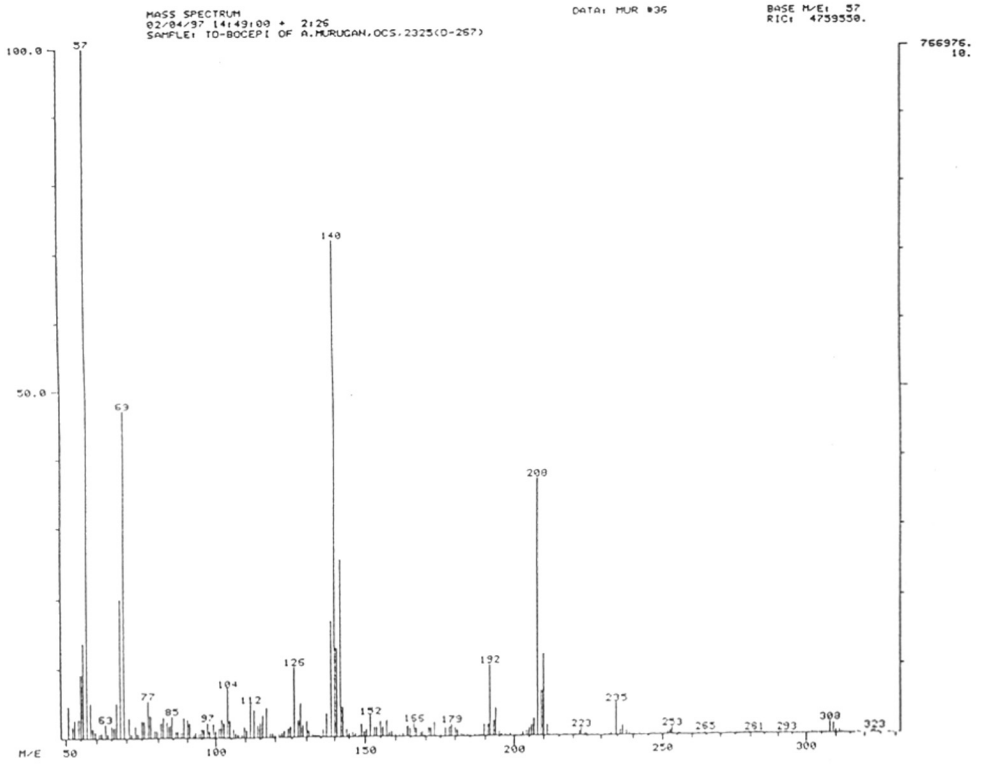

NCL / OCT / 97 / 009
2975.64
1693.85
1580.32
1460.46
1367.35
1255.08
1158.01
1104.14, 42.30
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers
Filename c:\first\data\lmp\cf\first59.ras
Title NCL / OCT / 97 / 009
Collected On: Wed May 28 16:18:23:24 1997
Starting wavenumber: 399.19
Ending wavenumber: 3999.66
Resolution: 4.0
Scans: 32
Gain Detector Iris
1 Standard 0
Mirror Velocity Optical Filter Apodization
10.0 kHz 10.0 kHz Auto Triangle
WinFIRST Report
Name: Mr T. D. Bagul
Date: 28 / 05 / 97
Sample: TD - Boc - Epi
Comments: Neat
Boc
N
N
Cl
50

Fig. 12


MASS SPECTRUM
02/04/97 14:49:00 + 2:25
SAMPLE: TD-BOCEPI OF A.MURUGAN.OCS.2325(0-267)
DATA: MUR #36
BASE M/E: 57
RIC: 4759550.
766976.
10.
100.0
50.0
M/E
57
140
63
200
126
192
104
77
112
85
97
152
166
179
205
223
253
265
281
293
300
329
50
100
150
200
250
300

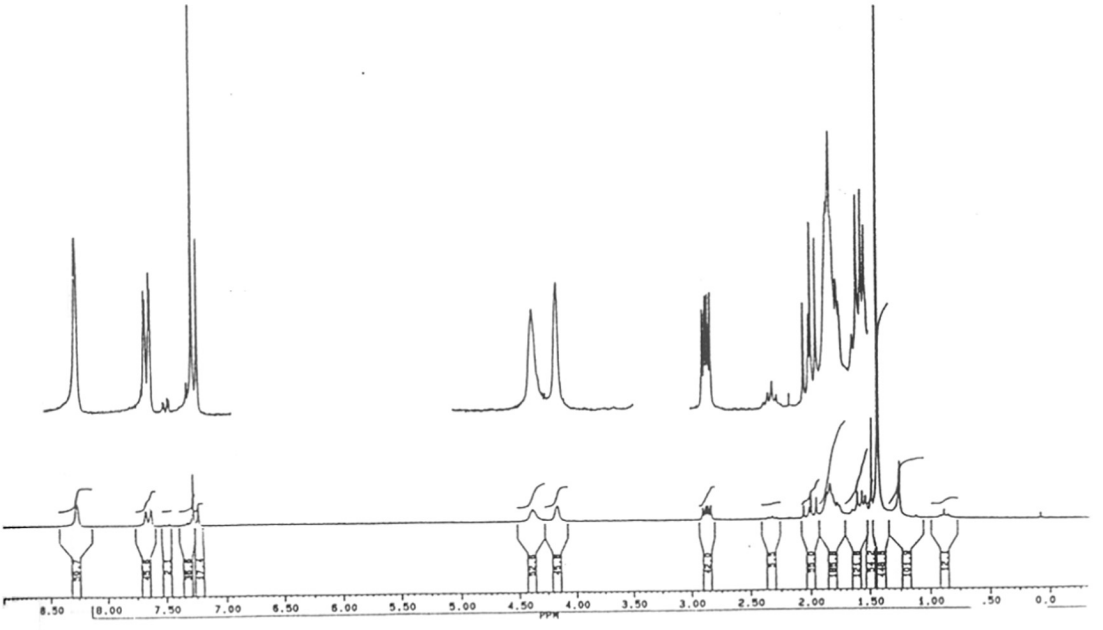
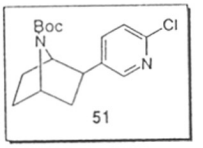


Fig. 13



51

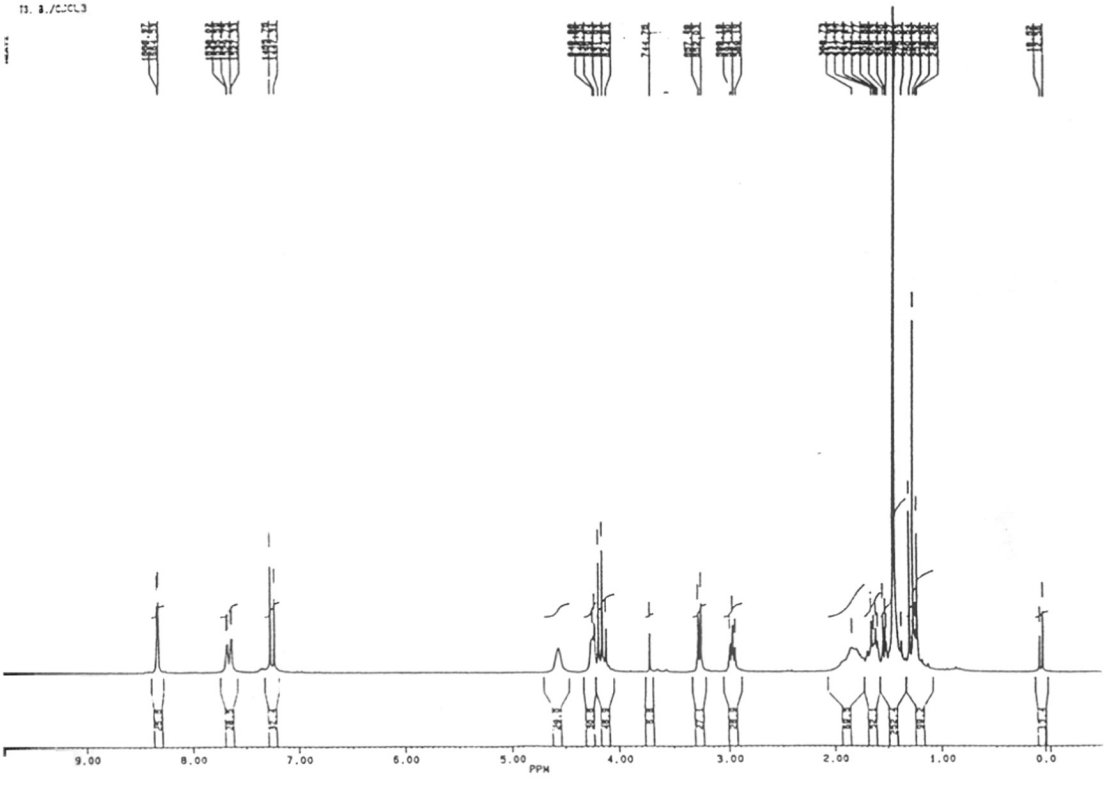
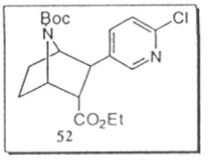
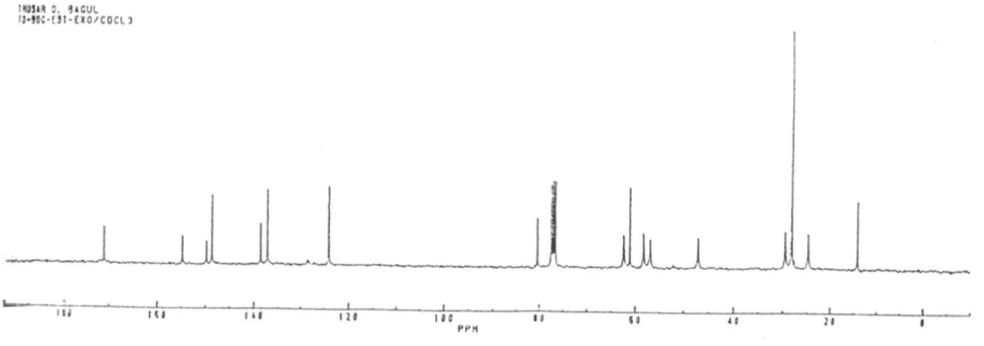
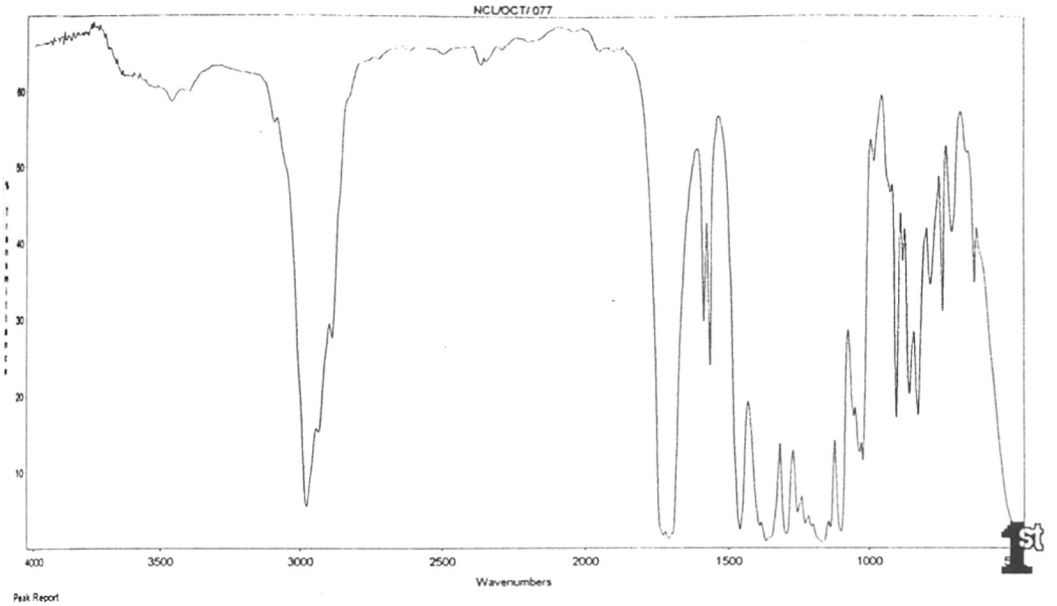


Fig. 14



52





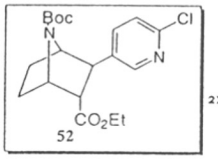
Peak Report
File c:\ifs\data\tmp\cifirs164.ras
Title NCL/OCT/077
Filter Three Point Center of Gravity

cm-1	%T	cm-1	%T	cm-1	%T	cm-1	%T
829.10	17.28	905.24	16.99	1023.24	11.37	1035.83	12.42
1058.26	17.11	1102.79	2.21	1138.98	2.70	1167.19	0.87
1206.15	2.84	1227.66	3.16	1254.49	4.61	1293.48	1.89
1352.24	1.43	1367.82	0.98	1391.50	2.86	1460.93	2.41
1694.09	1.86	1708.91	1.32	1727.03	1.71	2884.69	27.40
2934.18	15.14	2977.82	5.45				

Name : Mr T. D. Bagul
Sample : TD - Boc - Exo - EST
Date : 23/07/97
Comment : Neat

Organic Tech

Fig. 15



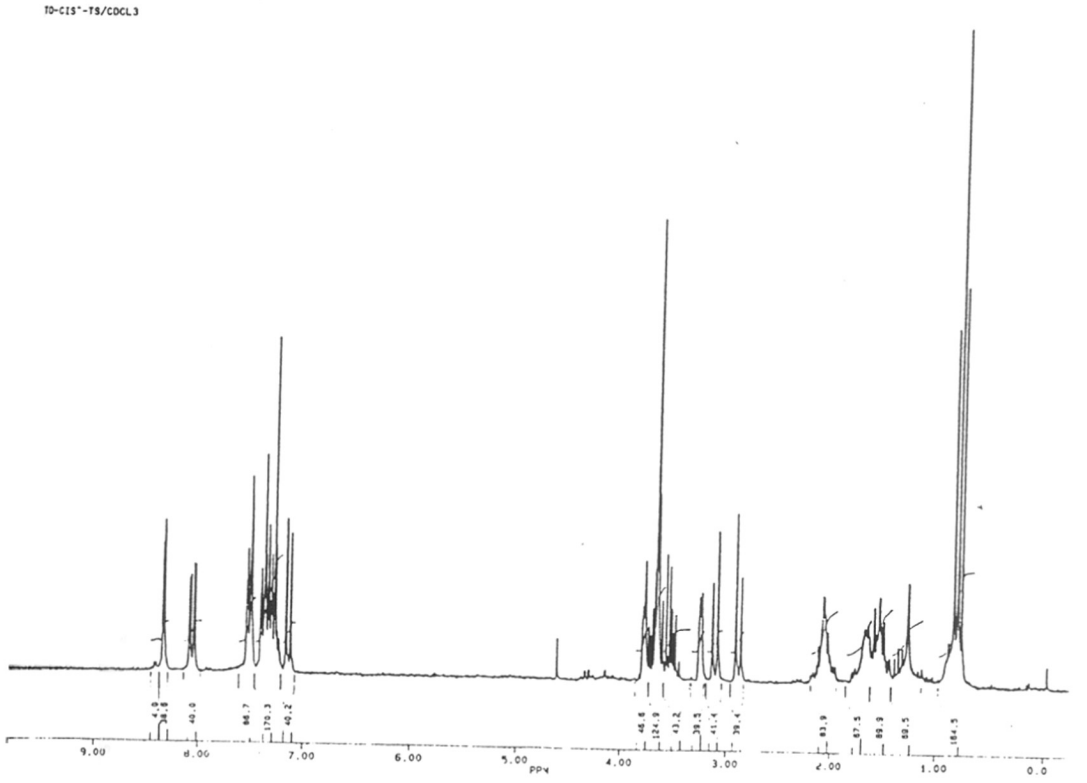
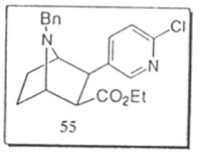
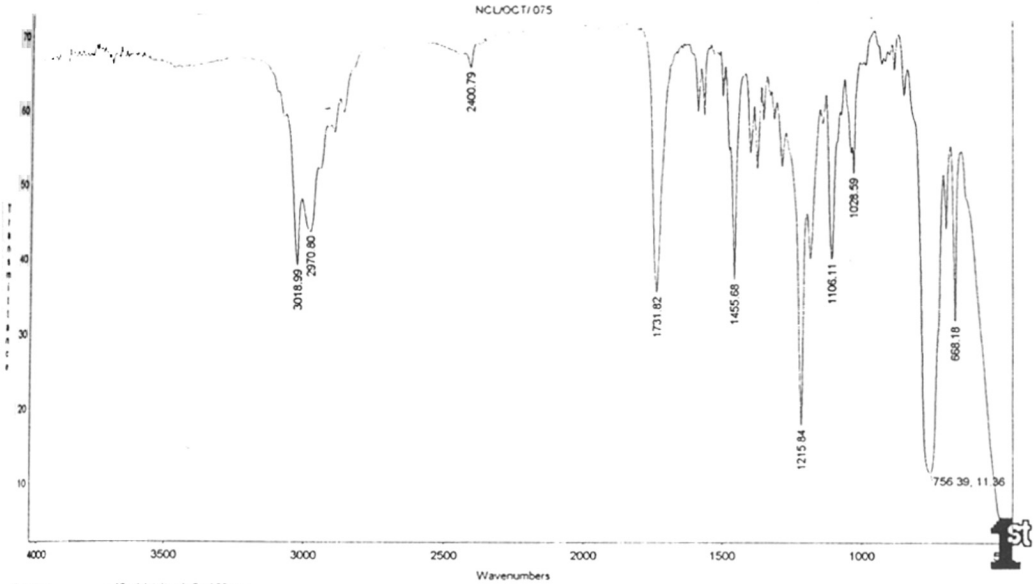

TD-CIS"-TS/CDCL3
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM

Fig. 16


Bn
N
Cl
N
CO2Et

55

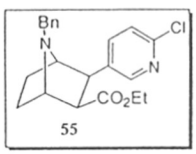
T.D.BAGUL
PPM



Filename c:\first\data\tmp\cfirs162.ras
Title NCL/OCT/075
Collected On Wed Jul 23 14:35:24:47 1997
Starting wavenumber 499.47
Ending wavenumber 3999.66
Resolution 4.0
Scans 32

Gain Detector Iris
1 Standard 0

Mel n-ml lpf apod

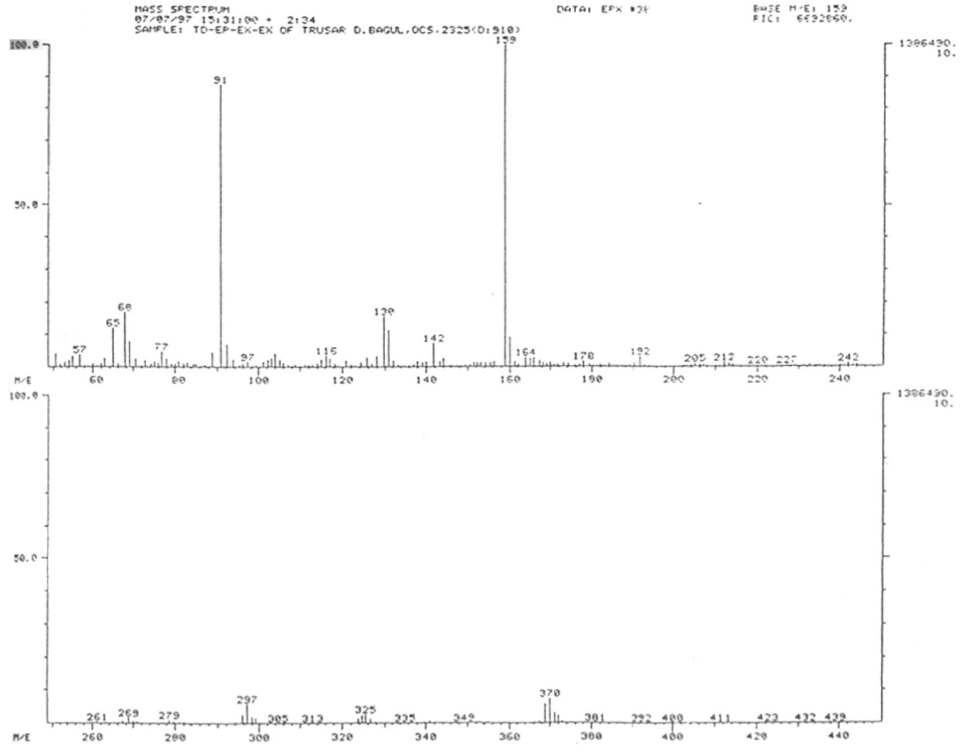


55

Name : Mr T. D. Bagul
Sample : TD - EP - Ex -Ex
Date : 23 / 07 / 97
Comment : In Choroform

N.C.L. Tech

Fig. 17



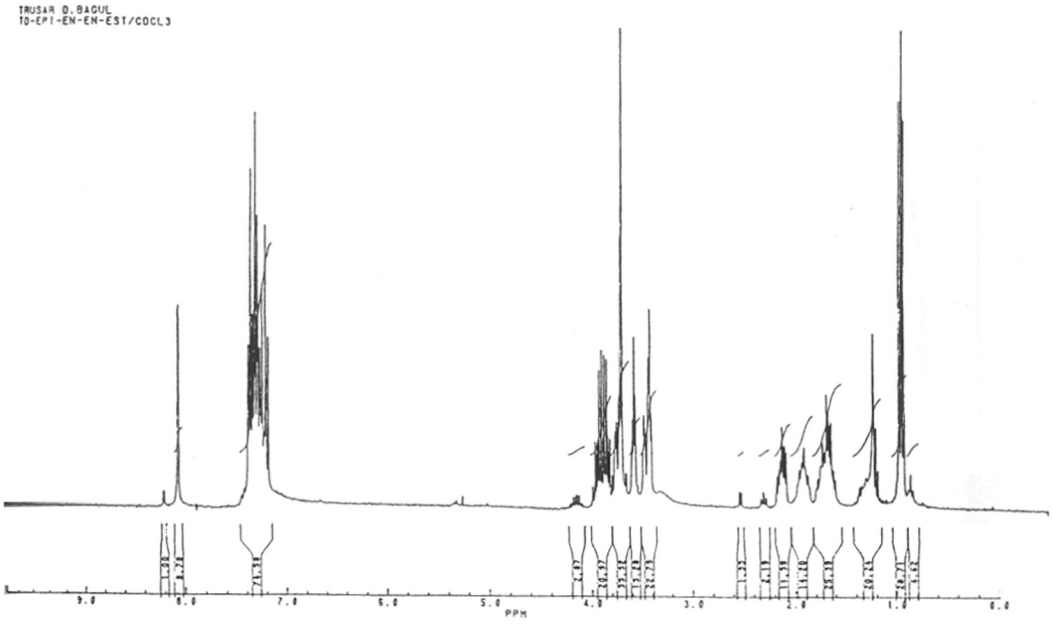
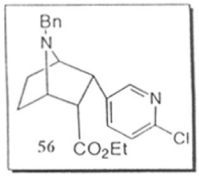
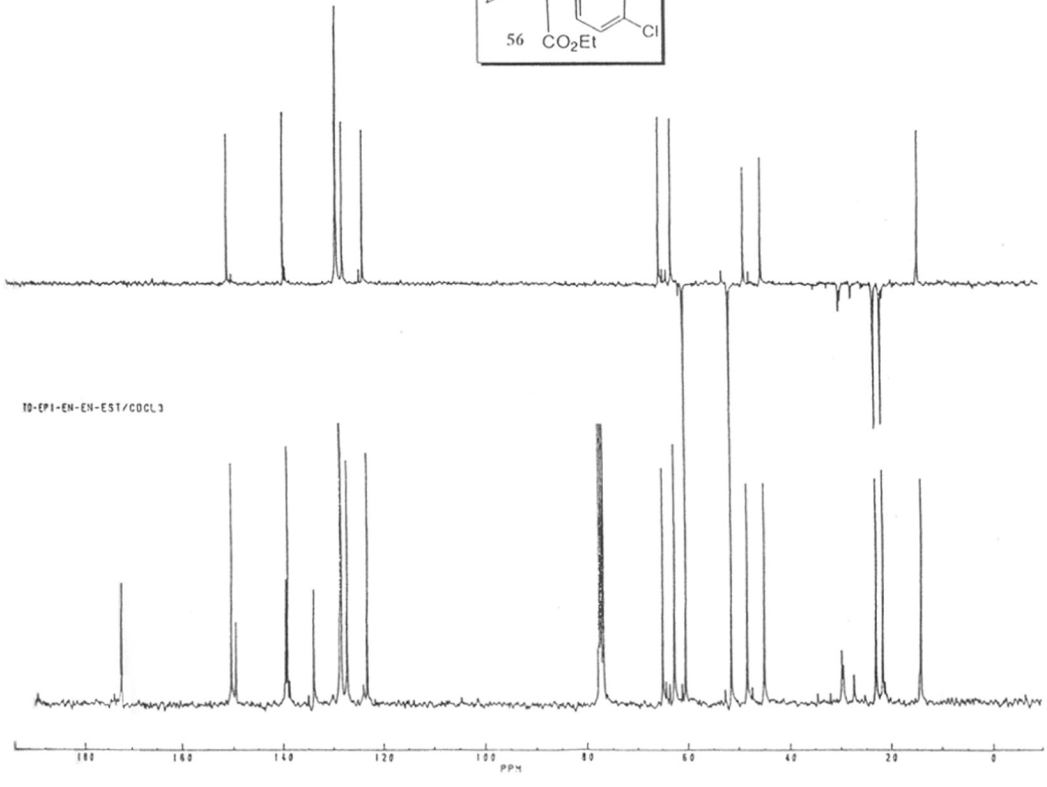

TRUSAR D.BAGUL
TD-EPI-EN-EN-EST/CDCL3
PPM

Fig. 18


Bn
N
N
Cl
56
CO2Et


TD-EPI-EN-EN-EST/CDCL3
PPM

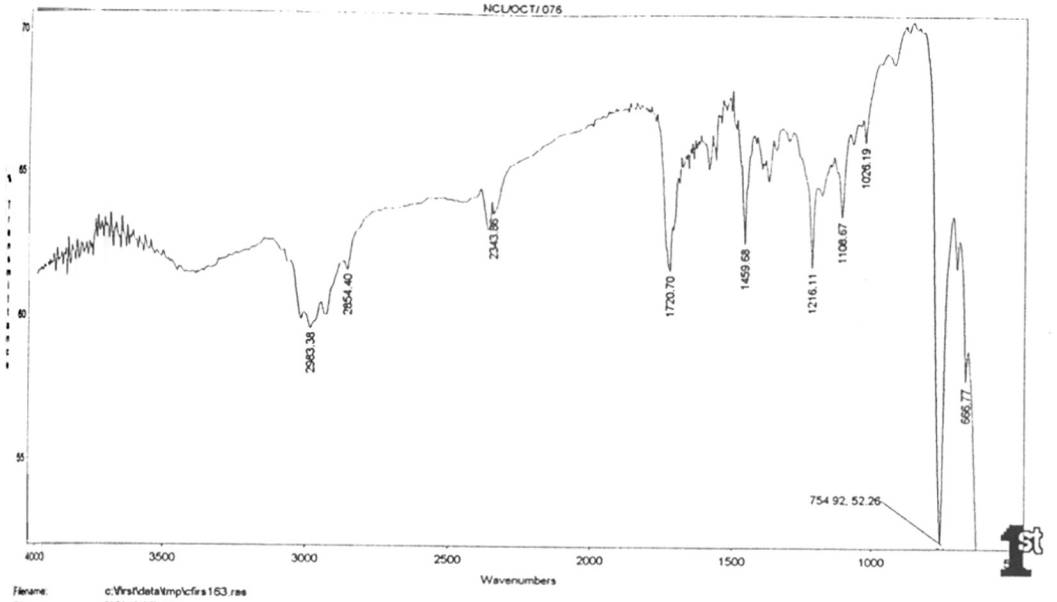
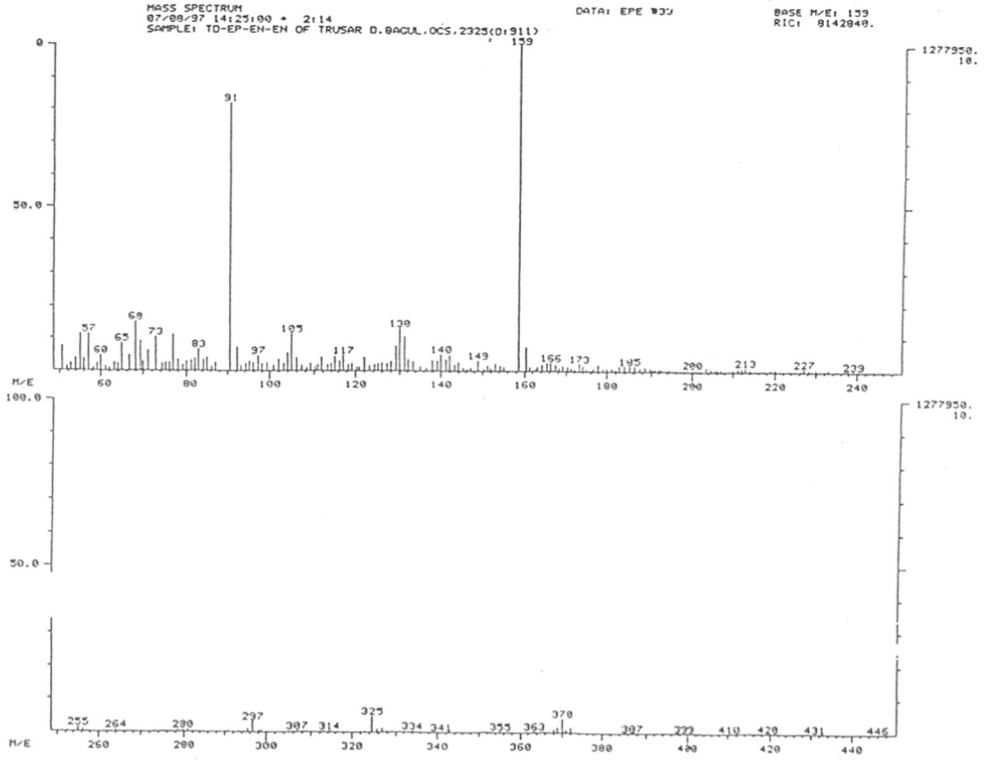

NCL/OCT/076
2963.38
2854.40
2343.86
1720.70
1459.68
1216.11
1106.67
1026.19
754.92, 52.26
666.77
Wavenumbers
Filename: c:\firs\data\tmp\cfirs163.ras
Title: NCL/OCT/076
Collected On: Wed Jul 23 14:45:17 07 1997
Starting wavenumber: 499.47
Ending wavenumber: 3999.66
Resolution: 4.0
Scans: 32
Name : Mr. T. D. Bagul
Sample : TD - EP - EN - EN
Date : 23/07/97
Comment : In Chloroform
Bn
N
N
Cl
56 CO2Et
Organic Tech

Fig. 19


MASS SPECTRUM
07/08/97 14:25:00 + 2:14
SAMPLE: TD-EP-EN-EN OF TRUSAR D.BAGUL.OCS.2325(0:911)
DATA: EPE 80U
BASE M/E: 159
RIC: 8142840.
1277950.
10.
M/E

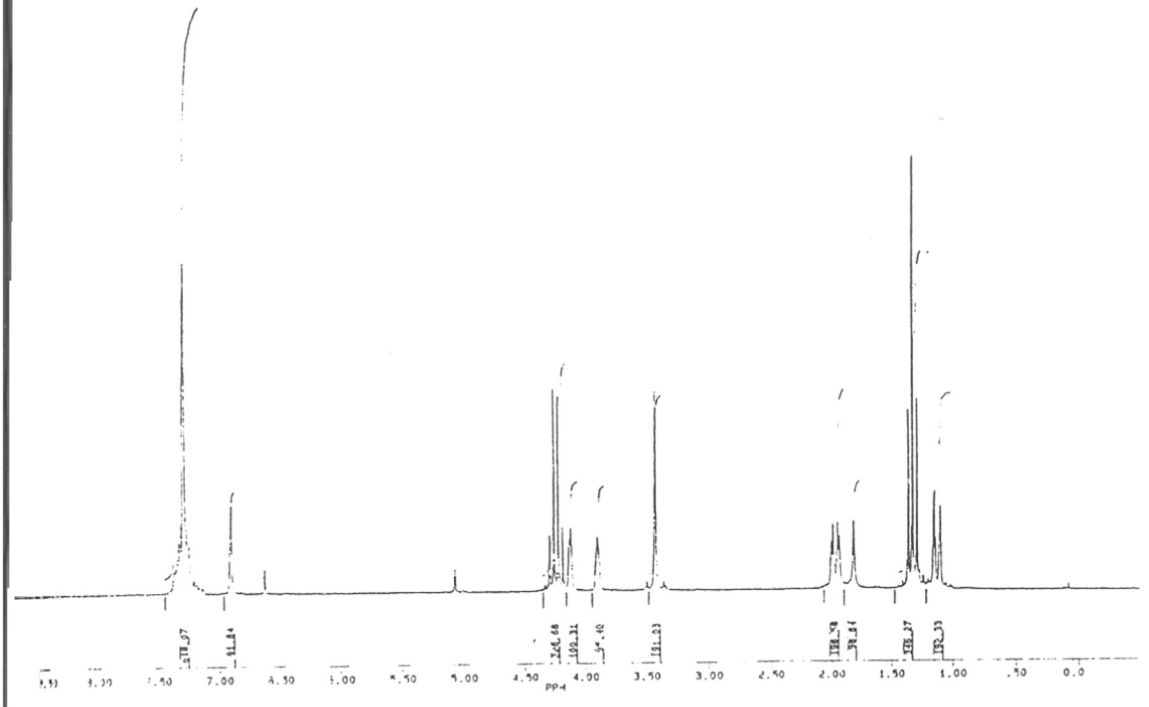
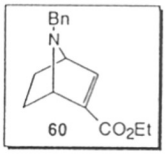
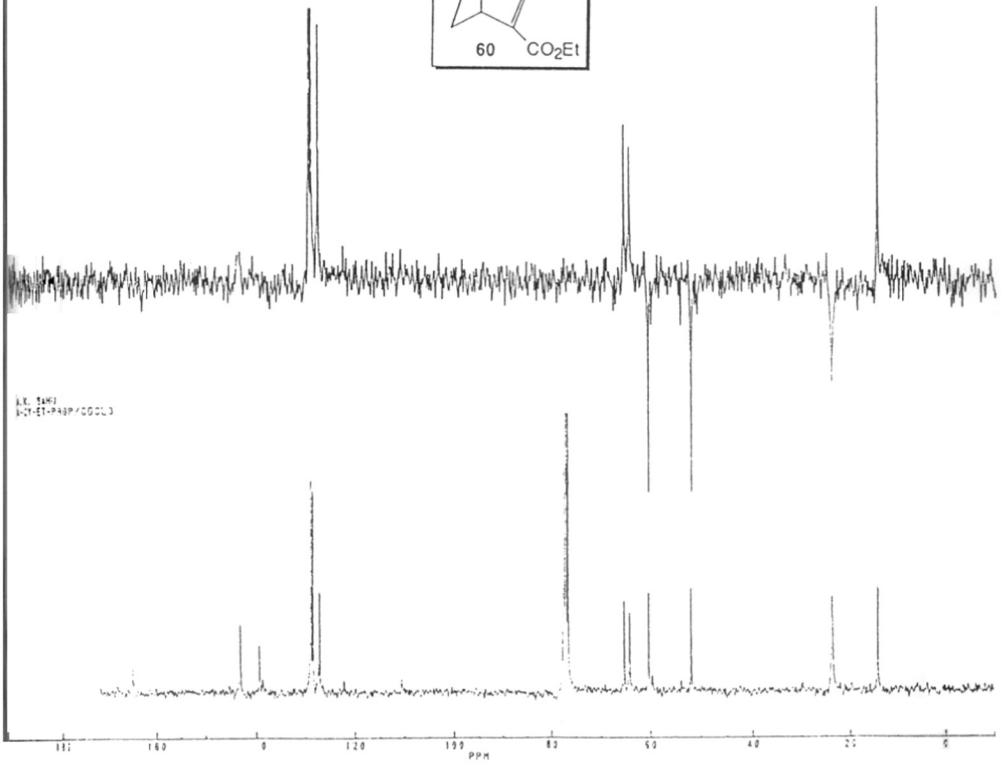
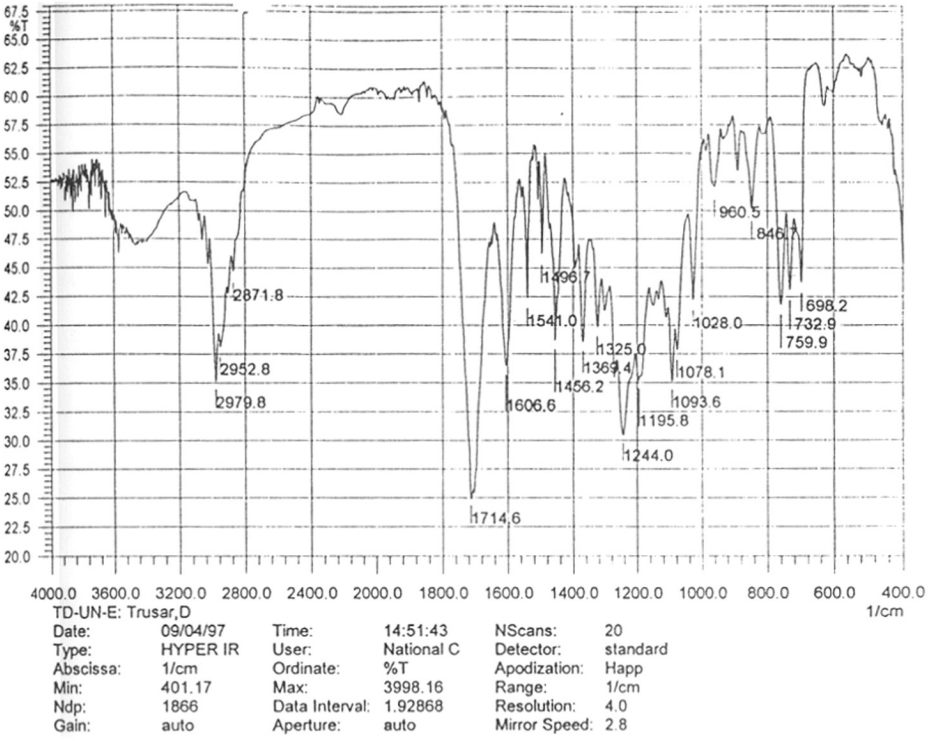


Fig. 20



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4000.0 3600.0 3200.0 2800.0 2400.0 2000.0 1800.0 1600.0 1400.0 1200.0 1000.0 800.0 600.0 400.0
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Abscissa: 1/cm Ordinate: %T Apodization: Happ
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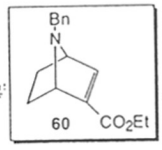
Gain: auto Aperture: auto Mirror Speed: 2.8

Fig. 21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DATA: SAH #17
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RIC: 7061500.
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133
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200
156
65
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140
170
212
242
257
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277
291
301
320
50
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150
200
250
300

Chapter. 3

Synthesis of Analogues of Epibatidine

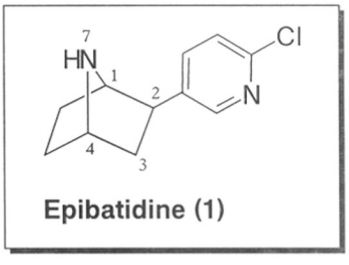
"Where nature finishes producing its own species man begins, using natural things and in harmony with this very nature, to create an infinity of species."

J. -M. Lehn.

Angew. Chem. Int. Ed. Eng. 1990, 29, 1304.

1. Introduction

(±)-Epibatidine (**1**), isolated from the skin extracts of poison frog, Epipedobates Tricolor, is found to be a potent analgesic[1] about 200-500 times more potent than that of morphine, whose mode of action is suggested to involve non-opiod mechanism due to its indifference towards naloxone[1]. Further studies[2-17] have found **1** to have potent antinociceptive activity due to activation of central nicotinic receptors. Both the antipodes [(+) as well as (-)] of **1** showed selectivity for central neuronal $\alpha_2\beta_2$ and ganglionic $\alpha_3\beta_4$ nicotinic recetors[2,10,11,18, 19], unlike other nicotinic receptors *viz.* Anatoxin-a. These pharmacological properties[1-19] have led to recognise Epibatidine as a therapeutically important drug target.



Epibatidine (1)

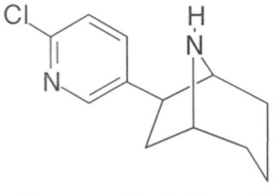
However, Epibatidine is found to be highly toxic causing death in mice (six out of six) when injected at 10 μl/kg scale[2,6]. This high toxicity of **1** has become major concern towards the therapeutic developement of **1**. Thus, the high affinity of **1** towards central nicotinic receptors and its non-compliance with current nicotine receptor pharmacophore model suggests that a new nicotine receptor pharmacophore needs to be developed[20]. As a result there is a renewed interest towards searching a pharmacophore related to the structure of **1**, that would exhibit

pharmacological properties similar to **1** but with better ratios of pharmacological to toxicological activity. In this direction, chemist and pharmacologist have begun perceiving compounds analogous to **1** by

- altering, extending or cleaving the 7-azabicyclo(2.21)heptane framework of **1**, keeping the pyridyl moiety intact;
- adding extra functionalities in the original framework of **1** alongwith the features described above or
- keeping in view the earlier known alkaloids having high affinity towards nicotinic receptors and then designing a molecule having a combination of stuctural features of both the earlier known alkaloid and **1**, and study their activity.

Utilizing the above mentioned parameters few groups have synthesized a variety of new pharmacophore (Fig.1) analogous to **1** and have studied their pharmacological properties in comparison to **1**, also evaluating their toxicity at the same time.

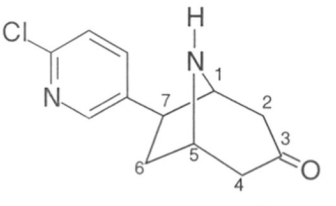
Fig. **1**



Homoepibatidine (2)

Activity: Weaker Analgesic than 1.

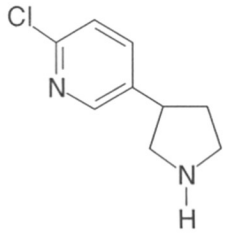
Toxicity: Not reported.



3-Oxo-Homoepibatidine (3)

Activity: Inactive.

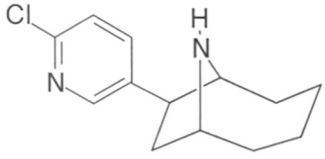
Toxicity: Not reported.



Desethyl Epibatidine (4)

Activity: Inactive.

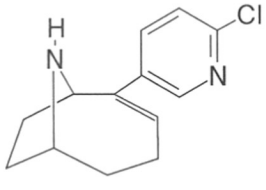
Toxicity: Not reported.



Bis-Homoepibatidine (5)

Activity: Inactive.

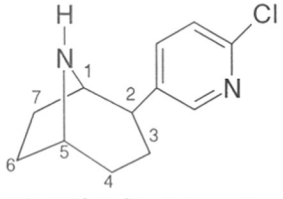
Toxicity: Not reported.



UB-165 (6)

Activity: Potent nicotinic receptor ligand.

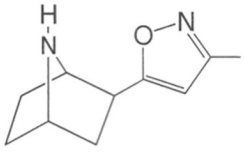
Toxicity: Not reported



***(1R, 2S, 5S)*-2-(2-chloro-5-pyridinyl) -8-azabicyclo(3.2.1)octane (7)**

Activity: Nicotinic receptor and stimulant.

Toxicity: Not reported.



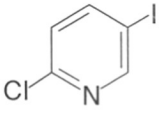
Epiboxidine (8)

Activity: Potent nicotinic receptor agonist and ten fold less potent than 1 as antinociceptive agent.

Toxicity: Twenty fold less toxic than 1.

2. Synthetic Approaches towards Epibatidine Analogues.

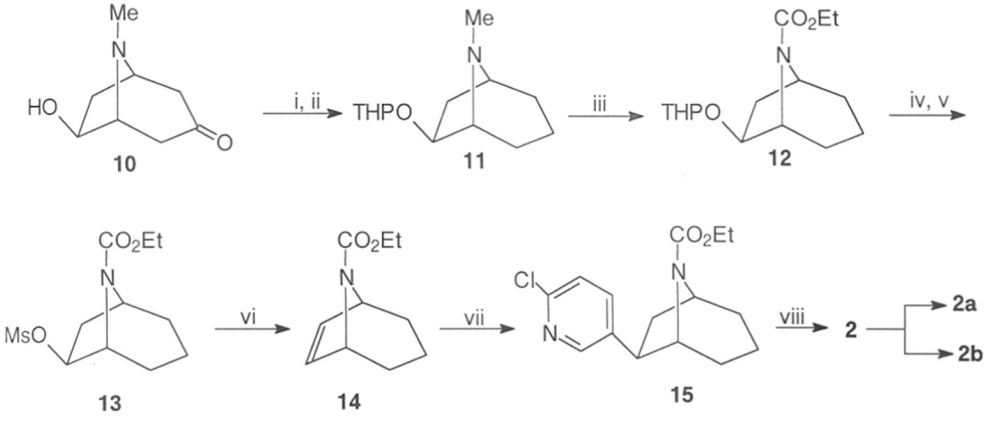
Synthetic approaches reported so far towards analogues of Epibatidine have utilized the reductive coupling of 6-chloro-3-iodo-pyridine (**9**) or its metalated derivatives with the corresponding X-azabicyclo(m.2.1)alkene ring system.



9

Bai *et al*[21] have synthesized Homoepibatidine (**2**) and its 3-oxo derivative **3** alongwith its nicotine related analogue (Scheme 1), Desethyl epibatidine (**4**), in their pursuit for a better pharmacophore and evaluated its activity.

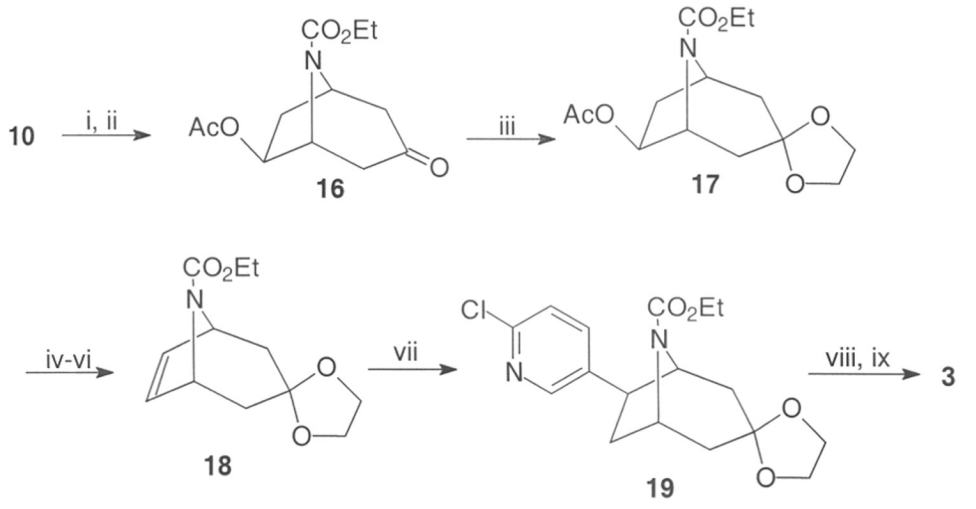
Scheme 1



*Reagents and conditions: i) $NH_2NH_2.H_2O$, Ethanol, KOH, 100 °C, 3h.; ii) DHP, p-TsOH, DCM (90%); iii) $ClCO_2Et$, $CHCl_3$, Δ, 2h; iv) PPTs, ehanol, Δ, 5h (97%); v) MsCl, pyridine, 24h, (93%); vi) DBU, Collidine, Δ, 8h (79%); vii) $(PPh_3P)_2Pd(OAc)_2$, **9**, piperidine, DMF, 70 °C, 5h (75%); viii) TMSI, DCM, 0 °C (95%).*

Homoepibatidine (**2**) was synthesized starting from commercially available 6β-hydroxy tropionone (**10**). Wolff-Kisner reduction of **10** followed by the protection of the hydroxyl group and demethylation with ethyl chloroformate afforded carbamate **12**. Deprotection of the hydroxyl group and its elimination *via* mesylate **13**, in refluxing collidine gave the crucial precursor **14** in 79 % yield (Scheme 1). Usual stereoselective reductive palladium catalysed coupling of **14** with **9** followed by cleavage of the carbamate moiety with TMSI yielded **2**, which has also been converted to its N-Methyl and N-iPropyl derivatives **2a** and **2b**, respectively, by reductive amination of formaldehyde and acetone, respectively.

Scheme 2

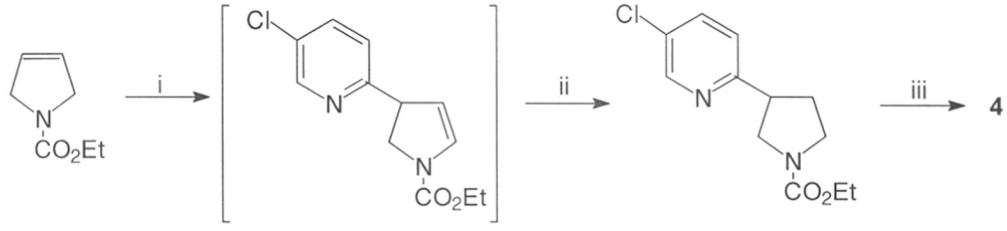


Reagents and conditions: *i) Ac_2O, Et_3N, THF; ii) $ClCO_2Et$, $CHCl_3$, Δ, 2 h (90%); iii) $(CH_2OH)_2$, p-TsOH, benzene, Δ, 12h (92%); iv) 3N NaOH, MeOH, 6 h (96%); v) MsCl, Et_3N, DCM, 0 °C, 1 h (97%); vi) DBU, toluene, Δ, 56 h (67%); vii) $(Ph_3P)_2Pd(OAc)_2$, **9**, DMF, piperidine, 70 °C, 5h (70%); viii) HBr, AcOH, 60 h (70%).*

3-Oxohomoepibatidine (**3**) is also prepared[21] from **10** by protecting the keto group as 1,3-dioxalan after acetylation and demethylation. Further synthetic transformation as described for **2**, by the same authors, afforded **3** as shown in Scheme 2.

Desethyl epibatidine (**4**), nicotine related analogue, is prepared[21] from N-carboethoxy-3-pyrroline (**20**) by reductive coupling with **9** followed by the hydrogenation over Pd/C and the cleavage of carbamate moiety (Scheme 3).

Scheme 3



20 **21** **22**

Reagents and conditions: *i)* **9**, *$Pd(OAc)_2$, n-Bu_4Br, KOAc, DMF, 40 °C, 4 d (62%); ii) Pd/C, H_2; iii) TMSI, CH_2Cl_2*

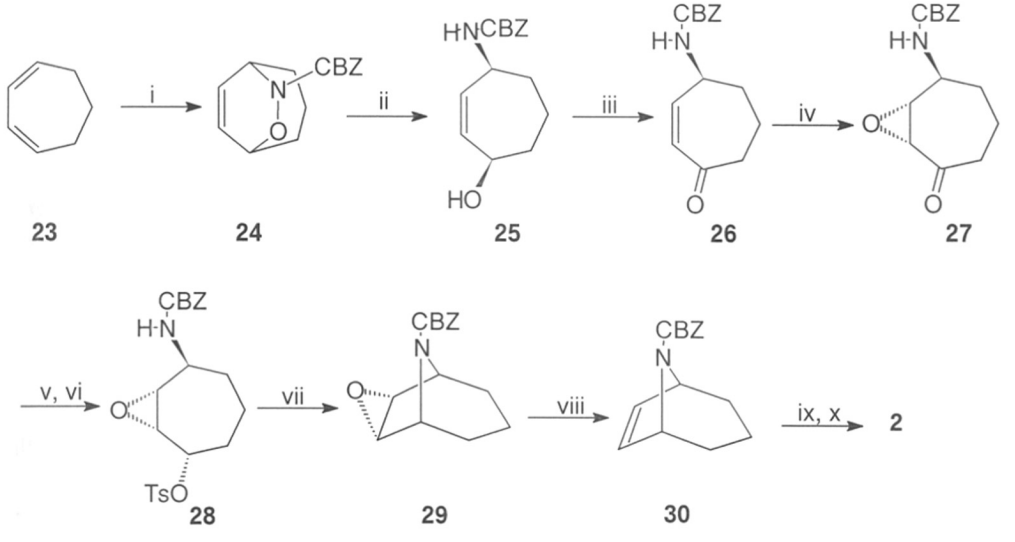
Pharmacological studies[21] with **2**, **3** and **5**, showed marked analgesic effect with **2** at a dose of 40 μg/kg comparable to that exhibited by **1** at 10 μg/kg . N-Methyl derivative **2a** showed similar analgesic activity to that of **2**, whereas N-^{i}Pr derivative **2b** was less active and imparted analgesia at a higher dose of 190 μg/kg . However the 3-oxo derivative **3** and nicotinic analogue exhibited no activity even at a dose of 4 mg/kg. Toxicity data of these molecules, however, are not reported.

Malpass *et al*[22] have also synthesized Homoepibatidine (**2**) and Bis-homoepibatine (**5**) by a protocol earlier developed in their laboratory for the

construction of azabicyclic ring system. Crucial precursors **30** and **35** are prepared from cyclohepta-1,3-diene (**23**) and cycloocta-1,3-diene (**31**) by [4+2]-cycloaddition with nitroso derivatives followed by further synthetic manipulations as shown in Scheme 4 and Scheme 5.

The overall yields during the synthesis of **2** were improved by transforming the olefin functionality in **25** to epoxide before carrying out intramolecular *trans*-annular nucleophilic ring closure reaction. Regeneration of the olefin was achieved by deoxygenating the epoxide in **29** using Zn-Cu couple (Scheme 4).

Scheme 4

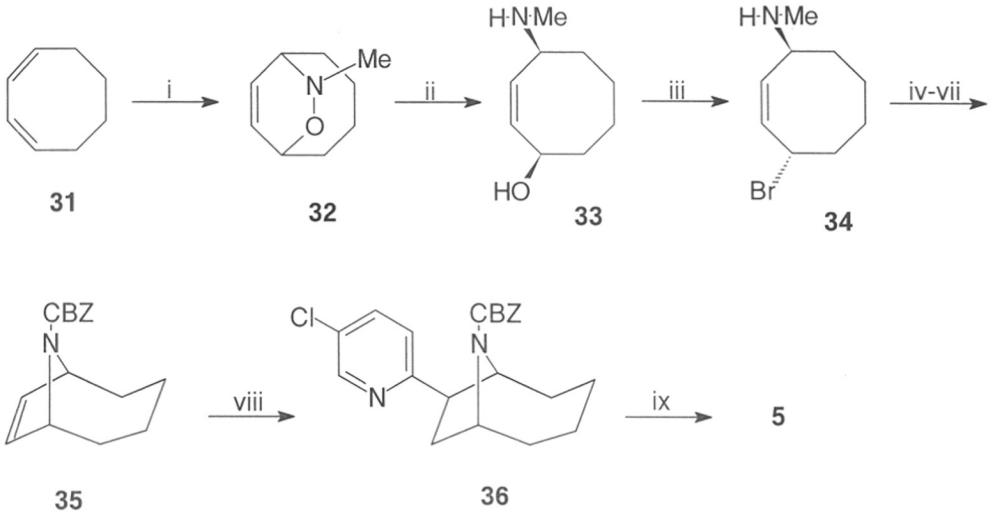


Reagents and conditions: *i) CBZN=O, Δ; ii) Na/Hg, MeOH (95%); iii) CrO_3.pyridine iv) m-CPBA, DCM, O °C; v) $NaBH_4$, MeOH; vi) n-BuLi, p-TsCl, THF; vii) NaH, THF (93%); viii) Zn/Cu, EtOH, 150 °C, 48 h (77%); ix)***9***, $Pd(PPh_3)_4$, DMF, piperidine, HCO_2H, 75 °C, 24 h (63%); x) TMSI, CH_2Cl_2, rt.*

However, the synthesis of **5** did not require epoxidation of the olefinic moiety in **33** and instead, involved the bromination of hydroxyl group in **33** with thionyl

bromide followed by intramolecular *trans*-annular nucleophilic ring closure in refluxing collidine (Scheme 5).

Scheme 5



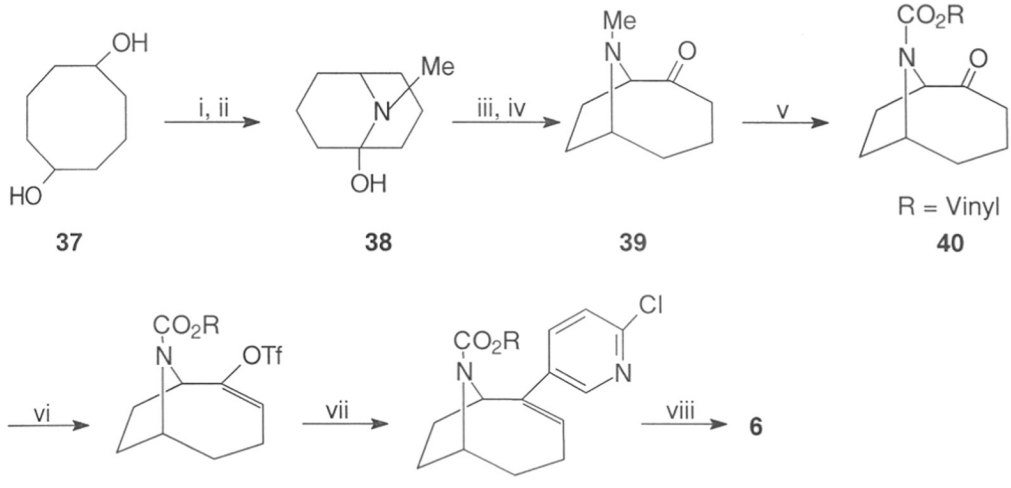
Reagents and conditions: *i) MeN=O, Δ; ii) Na/Hg, MeOH; iii) $SOBr_2$; iv) TMP, Δ; v) α-Chloroethyl chloroformate, EDC, Δ; vi) MeOH, Δ (99%); vii) CBZCl, NEt_3 (57%); viii)* **9**, *$Pd(PPh_3)_4$, DMF, piperidine, HCO_2H, 75 °C, 24 h (53%); ix) TMSI.*

Activity and toxicity of **5** is hitherto not reported.

UB-165 (**6**) a hybrid analogue of Anatoxin-a and **1**, has been synthesized by Gallgher *et al*[23] by combining the bulky 8-azabicyclo(4.2.1)nonane moiety of anatoxin-a with the pyridyl unit, a known hydrogen bond acceptor component in the general pharmacophore model, of epibatidine and possessing absolute configuration of natural Anatoxin-a. Synthesis of UB-165 utilized a protocol reported by Wiseman and Lee[24] for the preparation of precursor azabicyclic ketone **39** from *cis*-1,5-cyclooctanediol (**37**) (Scheme 6). Racemic **39** was resolved using (-)-dibenzoyl

tartarate to obtain pure enantiomers. Both (+) - and (-) - **39** were independently transformed to UB-165 by employing a sequence of synthetic transformation.

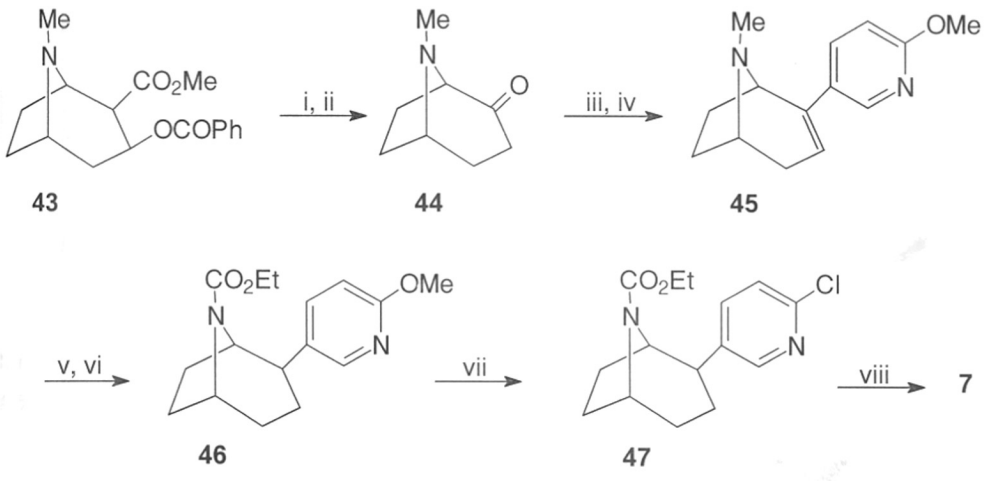
Scheme 6



Reagents and conditions: *i) CrO_3 (1 eq), H_2SO_4, acetone; ii) 40% aq. CH_3NH_2, TsOH, 100 °C, 2 d; iii) Pyr.HBr.Br_2, AcOH, 115 °C, 15 h; iv) (-)-Dibenzoyl tartarate, EtOH, Δ; v) Vinyl chloroformate, K_2CO_3, CH_2Cl_2; vi) KHMDS, 2-NTf_2-5-chloro-pyridine, THF, -78°C; vii) 9, n-BuLi, THF, $ZnCl_2$, $Pd(PPh_3)_4$; viii) HCl, aq. dioxan, Δ.*

Trudell and co-workers[25] have synthesized both 2α- and 2β-isomers of **7** in enantiomerically pure forms using (1*R*)-2-tropionone **44** as a starting precursor (Scheme 7). **44** is transformed to **45** by reductive palladium catalyzed coupling of its enol triflate to 2-methoxy-pyridinyl zinc chloride. Demethylation followed by hydrogenation yielded **46** as a 10:1 mixture of α- and β-isomers. Methoxy group in **46** is converted to chloro substituent using Vilsmeier conditions and later the carbamate moiety cleaved with trimethylsilyl iodide to give **7**.

Scheme 7

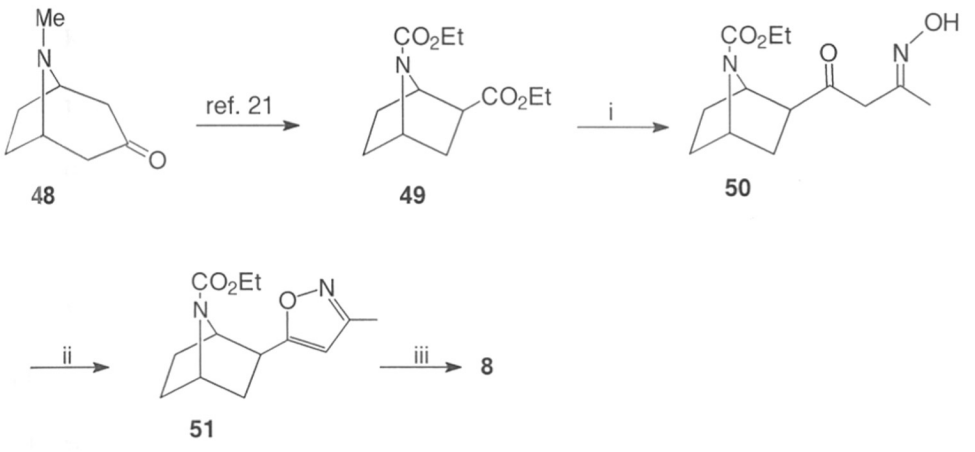


Reagents and conditions: *i) HCl, Δ; ii) $(PhO)_2PON_3$, DMAP, 10% HCl (78%); iii) NaHMDS, THF, -78 °C, $PhNTf_2$ (96%); iv) 2-methoxy-5-pyridinyl zinc chloride, $Pd(OAc)_2$, dppb, THF, Δ (93%); v) $ClCO_2Et$, K_2CO_3, benzene, Δ (76%); vi) 10% Pd/C, H_2, ^iPrOH:10% HCl (10:1) (96%); vii) $POCl_3$, DMF, 100 °C (48%); viii) TMSI, CH_2Cl_2 (90%).*

Stimulant activity (arterial pressure response) *in vivo* for both α and β-**7** is found to be 30-100 fold less potent than (±)-**1**. The nicotinic receptor binding ability of **7** to displace [^{3}H]-**1** is significantly lower than that of (±)-**1**.

Epiboxidine (**8**), a methyl isoxazole analogue (where the pyridyl unit is replaced by methyl isoxazole ring), was devised and synthesized by Daly *et al*[20] by taking a clue from ABT 418 , well known nicotinic receptor agonist. The key 7-aza bicyclic precursor **49** was prepared by employing a protocol developed by Bai *et al*[21] *via* Favorskii rearrangement of tropinone. Isoxazole ring was constructed from the ester moiety *via* the acetone oxime, by a reported procedure[26] (Scheme 8).

Scheme 8



Reagents and conditions: *i) $(CH_3)_2C$=N-OH (1 eq), n-BuLi (2 eq), THF, -78 °C; ii) Conc. Hcl; iii) 100 °C (47%).*

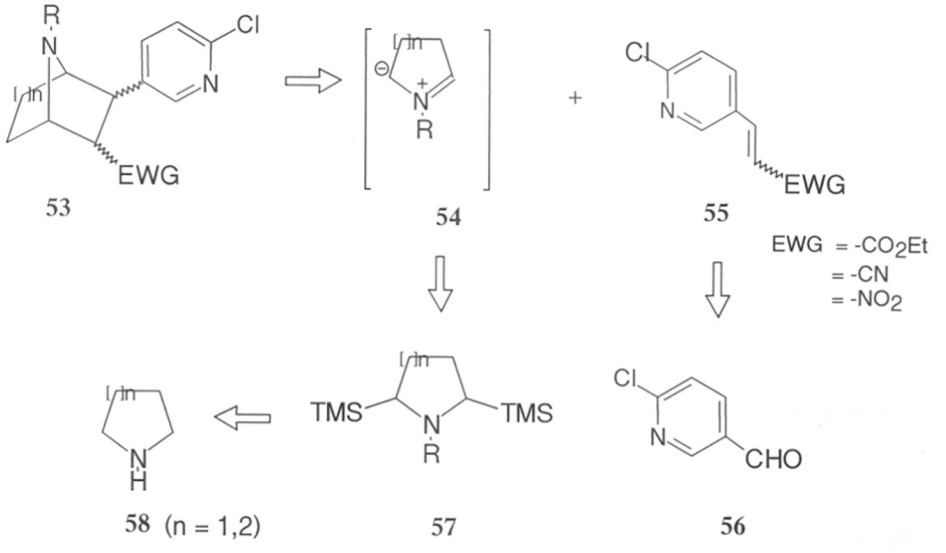
Epiboxidine (**8**) is found to be five fold less potent than **1** and 30 fold more potent than ABT 418 in TE671 cells with $\alpha_1\beta_1\gamma\delta$ nicotinic receptors. In a hot plate antinociceptive assay with mice, **8** was about 10 fold less potent than **1**. However, **8** was much less toxic than **1** in mice.

3. Results and Discussion

Keeping in pace with the above mentioned recent upsurge in designing a novel pharmacophore, related to **1**, having a better ratio of pharmacological to toxicological activity, we have also extended the scope of our methodology for the synthesis of X-azabicyclo(m.2.1)alkane framework towards this purpose.

Earlier results, described in Chapter 2, have demonstrated the retention of olefin geometry of the dipolarophile and the *exo*-selectivity for the electron withdrawing substituent in the [3+2] cycloaddition processes. These salient feature of the cycloaddition processes are utilized towards the synthesis of various *endo/exo* analogues of **1**. Thus, in this direction, we chose to introduce various functionality in the 7-azabicyclic framework in addition to 6-chloro-3-pyridyl moiety by tethering vinyl pyridine **55** to various electron withdrawing moieties (Scheme 9) and

Scheme 9



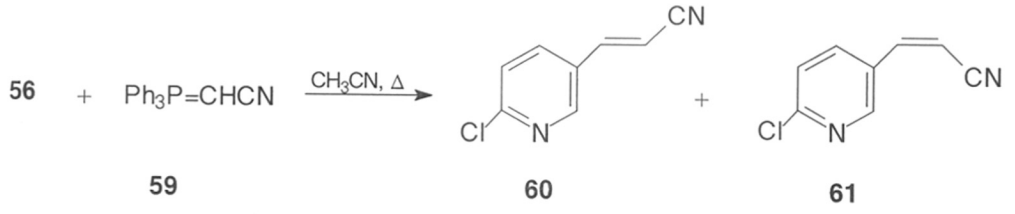
performing their cycloaddition with pyrrolidine or piperidine based azomethine ylide **54** towards the synthesis of analogues of Epibatidine.

Thus, the synthesis of substituted epibatidines and Homoepibatidine was undertaken.

3.1. Synthesis of Cyano Substituted Epibatidine: 7-Benzyl-2-(6-choro-3-pyridyl)-3-cyano-7-azabicyclo(2..2.1)heptane

For the synthesis of **63, 64, 65** and **66,** 3-(6-chloro-3-pyridyl)-propionitrile (**60** and **61**) was required. Wittig olefination of **56** with cyanomethylene triphenyl phosphorane in acetonitrile at reflux for 11 h (Scheme 10) afforded a 1:1 mixture of

Scheme 10



trans-**60** and *cis*-**61**. The synthesis of azomethine ylide precursor **62** is already described in detail in Chapter 2.

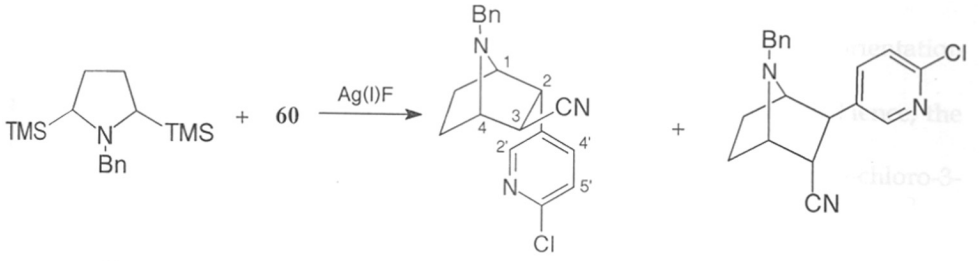
Towards the synthesis of nitrile substituted epibatidines the cycloadditions of *trans*-**60** and *cis*-**61** with **62** were carried out as follows:

3.1.1. Cycloaddition of 60 and 62:

The cycloaddition was carried out by the addition of **62** to the stirring solution of Ag(I)F and **60** in dichloromethane, in the identical manner as described in Chapter II, Section 4.3. After the completion of the reaction, mixture was filtered through a plug of celite and the residue obtained was purified by silica gel column

chromatography, eluting with hexane:EtOAc (8:2) to afford minor diastereomer **64** (18%) as a yellow oil. Further elution with the same eluent gave major diastereomer **63** (45%) as a yellow oil (Scheme 11). Both diastereomers are characterised by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses and their respective stereochemistries are assigned on the similar basis as mentioned in Chapter 2 for the corresponding ester analogues.

Scheme 11



62 **63** (45%) **64** (18%)

3.1.1.1. Spectral Analysis of Major Cycloadduct 63:

IR spectrum indicated the presence of nitrile moiety as a weak absorption band at 2221 cm^{-1} alongwith other bands at 1462 and 1107 cm^{-1} (Fig 3).

^{1}H NMR spectrum displayed a multiplet between δ 1.40-1.52, integrating for two protons, corresponds to H_{5endo} and H_{6endo}. Two multiplets appearing between δ 1.70-1.90 and 1.95-2.15, integrating for one proton each, could be attributed to either of H_{5exo} and/or H_{6exo}. Two diagnostic signals at δ 2.65 and δ 3.65, equivalent to one proton each, as a doublet (J = 5.94 Hz) and a triplet (J = 4.15 Hz) corresponds to H_{3endo} and H_{2exo}, respectively. A multiplet overlapping with singlet at δ 3.75, integrating for four protons, is attributed to the two benzylic protons and bridgehead

H_1 and H_4 protons together. A broad multiplet appearing between δ 7.25-7.5, integrating for seven protons, is characterized to five aromatic protons of phenyl moiety and $H_{4'}$ and $H_{5'}$ of pyridyl moiety. A doublet at δ 8.25 (J = 2.46 Hz) corresponds to $H_{2'}$ of pyridyl moiety (Fig 2).

The above ^{1}H NMR spectral analyses clearly indicates that the coupling of H_3 proton at δ 2.65 (d, J = 5.94 Hz) is observed only with the adjacent H_2 proton at δ 3.65 (t, J = 4.15, 5.58 Hz) and not with the bridgehead H_4. H_2 is found to couple with bridgehead H_1 proton at δ 3.75. This pattern of coupling suggested *exo*-orientation for the nitrile moiety and *endo*-orientation for the chloro pyridyl moiety. Hence, the structure and stereochemistry of **63** is assigned as 7-benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*exo*-cyano-7-azabicyclo(2.2.1)heptane.

^{13}C NMR spectrum revealed the presence of a total seven signals upfield at δ 20.5, 27.2, 36.6. 49.9, 51.2, 63.5 and 64.4 for the azabicyclic part and ten signals downfield at δ 121.4, 124.0, 127.1, 128.1, 128.3, 132.2, 137.9, 138.5, 148.7 and 150.1 for the aromatic and nitrile moieties (Fig. 2). INEPT experiment revealed the existence of C_5 and C_6 methylene carbons at δ 20.5 and 27.2 and methylene carbon of benzylic moiety (N$\underline{C}$H2Ph) at δ 51.2. C_3, C_2, C_1 and C_4 methine carbons are observed at δ 36.6, 49.9, 63.5 and 64.4, respectively. Quarternary carbon of nitrile moiety was observed at δ 150.1 and rest of the downfield signals are accountable to the aromatic carbons of phenyl and pyridyl moieties.

Mass spectrum revealed the molecular ion peak at 323 (1) and a base peak at 91 alongwith other prominent fragments at 159 (34), 140 (55), 126 (54), 105 (39) and 83 (55) (Fig 3).

3.1.1.2. Spectral Analysis of Minor Cycloadduct 64:

IR spectrum of **64** revealed the presence of nitrile group at 2400 cm^{-1}.

^1H NMR spectrum displayed two multiplets between δ 1.55-1.70 and δ 2.00-2.15 , integrating for one and three protons, respectively, attributable to H_{5exo}, H_{5endo}, H_{6exo} and H_{6endo} protons, respectively. A doublet of doublet appearing at δ 2.85 (J = 4.76, 9.73 Hz), equivalent to two protons, is characterised to H_{2endo} and H_{3exo}. Two singlets observed at δ 3.30 and δ 3.65, corresponding to one proton each, is assigned to bridgehead H_1 and H_4 protons, respectively. Another singlet at δ 3.55, integrating for two protons, corresponds to the two benzylic protons. A broad multiplet between δ 7.25-7.45, integrating for six protons, corresponds to the five aromatic protons of the phenyl moiety and $H_{5'}$ proton of pyridyl moiety. A doublet of doublet at δ 7.58 (J = 2.45, 8.24 Hz, 1H) and a doublet at δ 8.45 (J = 2.45 Hz, 1H) corresponds to $H_{4'}$ and $H_{2'}$ protons, respectively.

Based on the above spectral analysis the structure and stereochemistry for compound **64** can be assigned as 7-benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-cyano-7-azabicyclo(2.2.1)heptane.

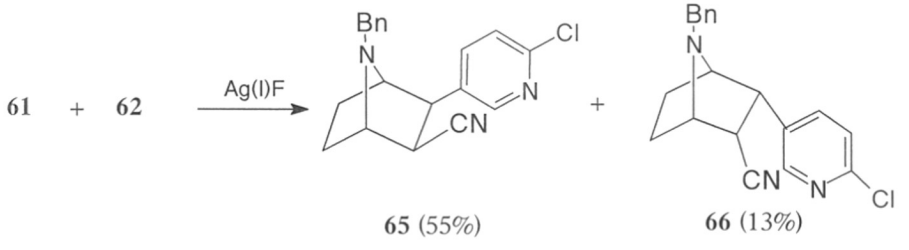
^{13}C NMR revealed seven carbon signals upfield at δ 22.0, 26.8, 41.4, 51.2, 51.7, 61.59 and 65.7 and nine signals downfield at δ 119.9, 124.0, 127.3, 128.4, 128.5, 137.5, 138.4, 148.5 and 150.2. INEPT experiment revealed the presence of C_5 and C_6

methylene carbons at δ 22.0 and δ 26.8 while C_2 and C_3 methine carbons appeared at δ 41.4 and δ 51.2, respectively. The benzylic carbon was observed at δ 51.7 and the two bridgehead carbons C_1 and C_4 at δ 61.59 and δ 65.7. Rest of the downfield carbon signals corresponds to pyridyl and phenyl ring carbons alongwith a quarternary nitrile carbon signal at δ 150.2.

3.1.2.Cycloaddition of 61 with 62 :

Cycloaddition of **61** with **62** was carried out by following the same experimental protocol as described previously with **60** (Scheme 11). Silica gel column chromatographic purification afforded the major diastereomer **65** (55%) and the minor diastereomer **66** (13%) as a pale yellow oil (Scheme 12).

Scheme 12



65 (55%) **66** (13%)

Both the diastereomeric cycloadducts **65** and **66** were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis and their stereochemistries ascertained by ^{1}H NMR COSY experiment.

3.1.2.1. Spectral Analysis of Major Cycloadduct 65:

IR spectrum displayed the nitrile moiety at 2400 cm^{-1} as medium absorption band alongwith other absorption bands at 1398, 1461, 1271 and 1105 cm^{-1} (Fig. 5)

^{1}H NMR spectrum of **65** displayed sets of two multiplet at δ 1.55-1.75 and δ 2.05-2.15, each integrating to two protons, assignable to H_{5endo}, H_{6endo} and H_{5exo}, H_{6exo}, respectively. A singlet observed at δ 3.0, integrating for two protons, could be attributed to *endo* protons of H_2 and H_3. Two sharp doublets at δ 3.38 and 3.8 with coupling constant, J = 4.17 Hz, equivalent to one proton each, is attributed to bridgehead H_1 and H_4 protons. A singlet, equivalent to two protons, at δ 3.67 is attributed to the two benzylic protons. Downfield multiplet between δ 7.25-7.50, integrating for six protons, corresponds to the five aromatic protons of phenyl ring and $H_{5'}$ of the pyridyl moiety, while $H_{4'}$ and $H_{2'}$ of pyridyl moiety appeared at δ 8.05 (dd, J = 2.45, 8.30 Hz, 1H) and δ 8.26 (d, J = 2.45 Hz), respectively (Fig 4).

From the above ^{1}H NMR spectral analysis, the stereochemistry and the structure for **65** is assigned as 7-benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*exo*-cyano-7-azabicyclo(2.2.1)heptane, however, ambiguity arising due to the appearance of H_{2endo} and H_{3endo} together as a singlet at δ 3.0 is clarified by carrying out the ^{1}H NMR COSY experiment and recording the spectrum in deuterated benzene (C_6D_6). ^{1}H COSY spectrum revealed the absence of coupling for the assigned H_{2endo} and H_{3endo} with any of the other protons, including bridgehead H_1 and H_4.

^{1}H NMR spectrum of **65** in C_6D_6 resolved and separated signals for the two H_2 and H_3 protons. H_{2endo} appeared as doublet at δ 2.60 (J = 5.6 Hz) and H_{3endo} merged with the two benzylic and bridgehead (H_1 and H_4) protons at δ 3.0-3.2 and appeared as a part of multiplet. Though the spectrum in C_6D_6 could not define the stereochemistry of H_3 as *endo* due to overlapping of signals, it is possible to suggest

that H_3 must be *endo* oriented considering the retention of dipolarophile geometry in the cycloadducts.

^{13}C NMR displayed total seven signals upfield at δ 21.3, 24.0, 34.9, 44.7, 51.5, 63.0 and 63.9, and ten signals downfield at δ 119.3, 123.7, 127.4, 128.3, 128.5, 130.9, 138.4, 139.4, 150.4 and 150.5 (Fig. 4). INEPT experiment revealed the presence of C_5 and C_6 methylene carbon at δ 21.3 and 24.0, while C_2 and C_3 methine carbons at δ 34.9 and 44.7, respectively. The benzylic methylene carbon was observed at δ 51.5. The two bridgehead C_1 and C_4 methine carbons appeared at δ 63.0 and 63.9, respectively. The quarternary nitrile carbon is assigned to the signal appearing at δ 150.4. The rest of the downfield signals are accountable for the aromatic carbons from the phenyl and pyridyl moieties.

3.1.2.2. Spectral Analysis of the Minor Cycloadduct 66:

IR spectrum of **66** displayed nitrile functionality at 2400 cm^{-1} alongwith other absorption bands at 1522, 1463, 1217 and 1046 cm^{-1} (Fig. 7).

^1H NMR spectrum displayed sets of two multiplets, integrating for two protons each, between δ 1.80-1.95 and 2.05-2.15, assignable to H_{5endo}, H_{6endo} and H_{5exo}, H_{6exo}, respectively. Another set of two multiplets appearing at δ 3.55 and δ 3.75, integrating for two and four protons each, is attributed to H_{2exo}, H_{3exo} and the two benzylic and bridgehead H_1 and H_4, respectively. Downfield multiplet observed between δ 7.30-7.45, equivalent to six protons, corresponds to the five aromatic protons of phenyl ring and $H_{5'}$ of the pyridyl moiety. $H_{4'}$ and $H_{2'}$ of pyridyl moiety

are observed at δ 7.70 (J = 2.45, 8.23 Hz) and δ 8.26 (d, J = 2.44 Hz), respectively (Fig. 6).

Based on the above spectral analyses the stereochemistry of **66** is tentatively assigned as 7-benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*endo*-cyano-7-azabicyclo (2.2.1) heptane which is further confirmed by studying the ^{1}H NMR spectrum in deuterated benzene (C_6D_6) and recording its ^{1}H NMR COSY spectrum.

The ^{1}H NMR was well resolved in C_6D_6 and the individual protons could be characterized properly. Characteristic H_{2exo} proton appeared as a multiplet at δ 2.6 and H_1 as a multiplet at δ 2.75. H_{3exo} appeared as a doublet of doublet at δ 2.85 (J = 4.2, 8.5 Hz). The bridgehead H_4 appeared as a triplet at δ 2.96 (J = 4.35 Hz) and the two benzylic protons at δ 3.15 as singlet (Fig 6).

Above stereochemical assignment finds further support from the observed coupling between the two bridgehead H_1 and H_4 with the adjacent H_2 and H_3 *exo* protons, respectively, in the ^{1}H NMR COSY spectrum.

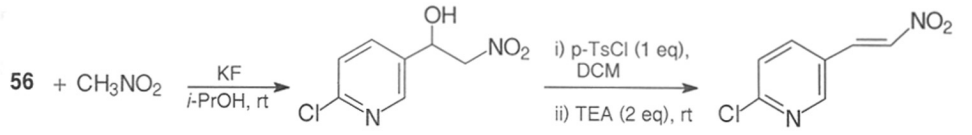
^{13}C NMR spectrum displayed a total of seven carbon signals upfield at δ 21.3, 24.0, 34.9, 44.7, 51.4, 63.0 and 63.9, and ten carbon signals downfield at δ 119.3, 123.7, 127.4, 128.3, 128.5, 128.8, 130.9, 138.4, 139.4, 150.4 and 150.5 (Fig. 7). INEPT experiment revealed the presence of C_5 and C_6 methylene carbons at δ 21.3 and δ 24.0. Methine carbons C_2 and C_3 appeared at δ 34.9 and δ 44.7, respectively, while the benzylic carbon appeared at δ 51.4. The bridgehead methine carbons C_1 and C_4 are observed at δ 63.0 and δ 63.9, respectively. Rest of the downfield signals were

assignable to the aromatic carbons of pyridyl and phenyl moieties. The quarternary carbon signal for the nitrile moiety appeared at δ 150.4.

3.2. Synthesis of Nitro-substituted Epibatidine derivative: 7-benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-nitro-7-azabicyclo(2.2.1)heptane (70).

In order to synthesize **70**, the required dipolarophile **69** was prepared in three steps starting from 6-chloro-3-pyridyl carboxaldehyde (**56**) as shown in Scheme 13.

Scheme 13



67 **68** **69**

Nitroaldol condensation of **56** (1 eq) with nitromethane (**67**, 1.2 eq) in ^{i}PrOH using catalytic amount of potassium fluoride (0.5 eq) afforded 2-(6-chloro-3-pyridyl)-1-nitro-ethan-2-ol (**68**, 90%). Tosylation of **68** (1 eq) by using p-TsCl (1.1 eq) followed by elimination in the presence of triethyl amine (2.2 eq) gave **69** (75 %). Compound **69** is fully characterised by IR, ^{1}H NMR and mass spectral analyses.

IR spectrum displayed strong absorption bands at 1637, 1583 and 1506 cm^{-1} indicating the presence of nitro moiety conjugated to vinyl pyridine along with other absorption bands at 1340 and 1099 cm^{-1}.

^{1}H NMR spectrum exhibited a doublet at δ 7.45 (J = 8.30 Hz) corresponding to pyridyl $H_{5'}$ proton. The two vinylic H_1 and H_2 protons appeared as doublets, each integrating for one proton, at δ 7.65 (J = 12.25 Hz) and δ 8.0 (J =12.25 Hz),

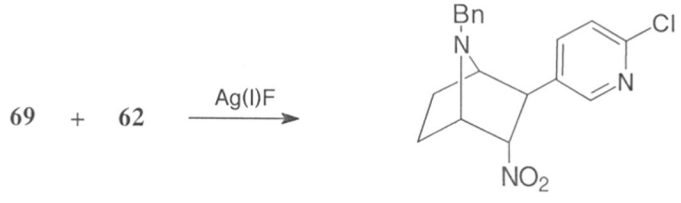
respectively. Remaining pyridyl $H_{4'}$ and $H_{2'}$ protons appeared at δ 7.85 (dd, J = 2.38, 8.30 Hz) and δ 8.55 (d, J = 2.38 Hz).

Mass spectrum indicated molecular ion peak at 184 (41) and a base peak at 102 alongwith other prominent fragments at 137 (91), 126 (19) and 75 (79).

3.2.1. Cycloaddition of 69 with 62 : Synthesis of 70.

The cycloaddition of dipolarophile **69** with **62** by following the identical protocol as mentioned in previous section gave cycloadduct **70** (65%) as the only product as a pale yellow thick oil (Scheme 14).

Scheme 14



70 (65%)

IR spectrum of **70** indicated the presence of nitro moiety by displaying a strong absorption band at 1550 cm^{-1} alongwith other absorption bands at 1470, 1230 and 1120 cm^{-1} (Fig. 9)

^1H NMR spectrum of **70** revealed H_{5endo} and H_{6endo} protons as a multiplet between δ 1.60-1.75, and H_{5exo} and H_{6exo} as multiplet between δ 2.0-2.2. A doublet at δ 3.35 (J = 4.5 Hz), equivalent to one proton, is attributed to H_1 and another doublet at δ 3.45 (J = 5.36 Hz) corresponding to one proton is assigned to H_{2endo}. A singlet, equivalent to two protons, appearing at δ 3.63 corresponds to the two benzylic protons. A set of two multiplets observed at δ 4.02 and δ 4.75, integrating for one

proton each, is attributed to bridgehead H_4 and H_{3exo} protons, respectively. A doublet observed at δ 7.28 (J = 8.45 Hz, 1H) is attributed to $H_{5'}$ of pyridyl moiety while the multiplet between δ 7.35-7.45(5H) corresponds to the five aromatic protons of the phenyl ring. $H_{4'}$ and $H_{2'}$ of pyridyl moiety were observed at δ 7.78 (dd, J = 2.45, 8.3 Hz) and δ 8.5 (d, J = 2.46 Hz), respectively (Fig 8).

Based on the coupling pattern and chemical shifts observed for the diagnostic H_1, H_2, H_3 and H_4 , the structure and stereochemistry for **70** is assigned as 7-benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-nitro-7-azabicyclo(2.2.1)heptane.

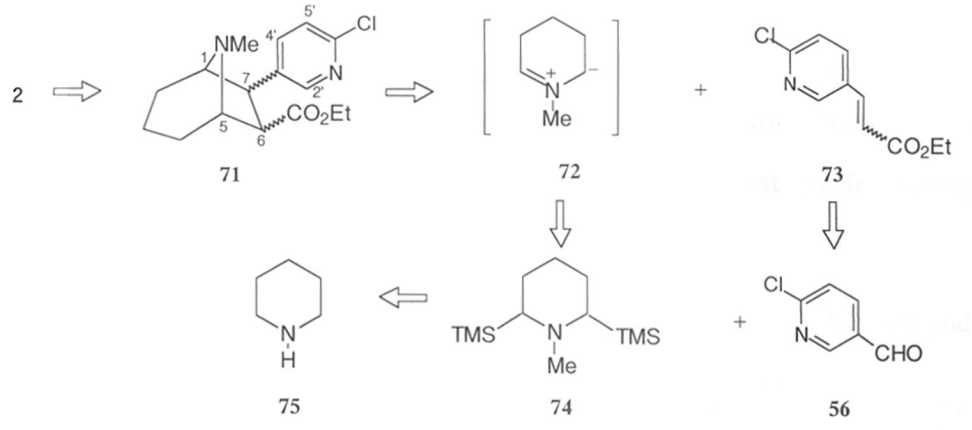
^{13}C NMR spectrum revealed a total of seven signals upfield at δ 20.3, 26.5, 48.4, 51.8, 62.8, 66.9 and 93.0, and nine signals downfield at δ 124.0, 127.5, 128.5, 128.6, 137.2, 137.9, 138.1, 148.9 and 150.1 (Fig. 8). INEPT experiment revealed the presence of C_5 and C_6 methylene carbons at δ 20.3 and 26.5, respectively. C_2 methine carbon, bearing the pyridyl moiety, was observed at δ 48.5 while the benzylic carbon at δ 51.8. The two bridgehead methine carbons C_1 and C_4 were observed at δ 62.8 and δ 66.9, respectively. A characteristic signal for C_3 methine carbon, bearing nitro moiety, was observed at δ 93.0. Rest of the signals were characterised as aromatic carbons.

The *exo*-selectivity for 6-chloro-3-pyridyl moiety observed in the cycloaddition reaction using **69** as dipolarophile appears to be in contrast to the cycladdition stereochemistries observed with dipolarophiles **60** as well as **61**. Although, at present we do not have explanations for the reversal of stereochemistry in **70**, difference in the orbital coefficients of nitro olefin than ester or cyano may be considered for this observation.

3.3. Formal Synthesis of Homoepibatidine (2):

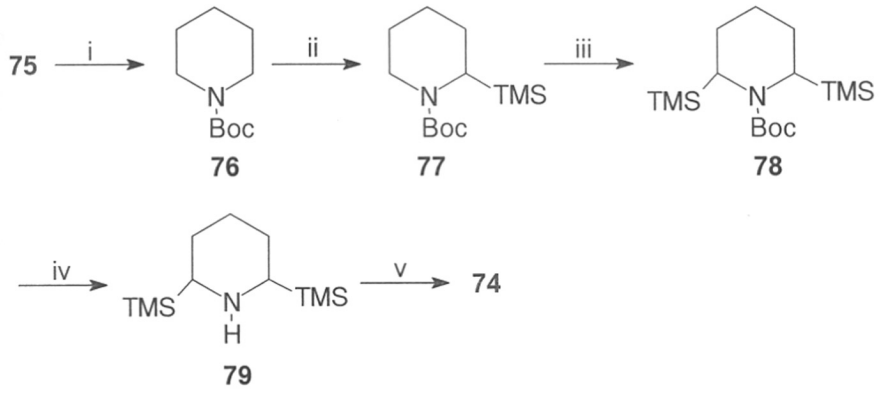
The two synthetic strategies reported so far towards the synthesis of Homoepibatidine have employed Heck-coupling of iodo-pyridyl derivative with 8-azabicyclo(3.2.1)oct-6-ene with overall poor yields due to the involvement of multiple steps. In this context, it was envisaged that the cycloaddition of piperidine based azomethine ylide **72** with pyridyl acrylates **73** would provide an easy access to a shorter and stereoselective synthetic route towards the synthesis of Homoepibatidine (Scheme 15).

Scheme 15



Synthesis of **2** commenced with the preparation of both **80** and **83** as described for their preparation in Chapter 2. Azomethine ylide precursor **74** was prepared in five steps starting from commercially available piperidine (**75**) as shown in Scheme 16.

Scheme 16



Reagents and conditions: *i) Tert-butyl azidoformate, TEA, rt (90%); ii) Ether, TMED, -78 °C, s-BuLi, 2h, TMSCl (90%); iii) Ether, TMEDA, -45 °C, s-BuLi, -30 °C, 30 min, -45 °C, TMSCl (70%); iv) TFA, DCM; v) 37% HCHO, CH_3CN, $NaCNBH_4$.*

N-Boc piperidine **76** was disilylated to **78** and later the Boc moiety was deprotected to obtain the free base **79** by following the expermental protocol as described in Chapter 2 for the corresponding pyrrolidine analogue. Reductive amination of formaldehyde with **79** using sodium cyanoborohydride in acetonitrile after usual workup and purification by silica gel column chromatography, eluting with hexane:EtOAc (4:96), afforded **74** (80%) as a thick yellow oil.

Azomethine ylide precursor **74** is characterised by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses as N-methyl-2,6-bis(trimethyl silyl)piperidine.

^{1}H NMR spectrum displayed the two trimethylsilyl moieties at δ 0.06 as a singlet integrating for eighteen protons. A multiplet corresponding to the six *axial* and *equatorial* H_3, H_4 and H_5 protons is observed between δ 1.52-1.67. H_2 and H_6 protons adjacent to two silyl moieties appeared as a multiplet between δ 2.20-2.30. Singlet at δ 2.55, equivalent to three protons, corresponds to the methyl group on nitrogen (Fig 10).

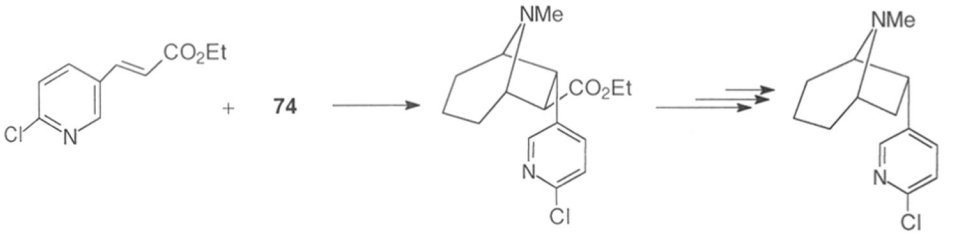
^{13}C NMR spectrum displayed a total of five signals upfield at δ -1.2, 20.7, 24.3, 42.4 and 54.1 (Fig. 10). INEPT experiment showed the presence of methyl carbons of two TMS moieties at δ -1.2. C_3, C_4 and C_5 methylene carbons appeared at δ 20.7 and 24.3. Methyl on nitrogen was observed at δ 42.4 and the two C_2 and C_6 methine carbons appeared at δ 54.1.

Mass spectrum displayed the presence of a molecular ion peak at 243 (<1) and a base peak at 170 alongwith other prominent fragments at 228 (4.3) and 96 (4.5). (5.2).

3.3.1.Cycloaddition Reaction of 74 with 80 :

Cycloaddition of **74** with **80**, carried out by following the protocol analogous to that employed for the pyrrolidine based azomethine ylide, afforded cycloadduct **81** (64%) as the only isolable product as a yellow thick oil (Scheme 17).

Scheme 17



80 **81** (64%) **82**

Compound **81** is characterised by IR, ^1H NMR, ^{13}C NMR and mass spectral analyses as described below.

IR spectrum showed a strong absorption band corresponding to carboethoxy moiety at 1724 cm^{-1} alongwith other absorption bands at 1582, 1241 and 1103 cm^{-1} (Fig 12).

^1H NMR spectrum displayed six H_2, H_3 and H_4, *axial* and *equatorial* hydrogens as a set of two multiplets, each integrating for three protons, between δ 1.5-1.75 and δ 1.85-2.05. The methyl group on nitrogen was observed as a singlet at δ 2.5. H_{7exo} and H_{6endo} appeared together as a multiplet at δ 3.17. Another multiplet observed between δ 3.50-3.55, equivalent to one proton, is attributed to bridgehead H_1 proton. Bridgehead H_5 proton was observed as doublet at δ 3.65 (J = 6.65 Hz). Methyl and methylene groups of carboethoxy moiety appeared as a triplet and quartet at δ 1.25 (J = 7.21 Hz) and δ 4.20 (J = 7.20 Hz, 2H), respectively. Pyridyl ring protons $H_{5'}$, $H_{4'}$ and $H_{2'}$ were observed at δ 7.27 (d, J = 8.24 Hz, 1H), 7.88 (dd, J = 2.73, 8.25 Hz, 1H) and 8.42 (d, J = 2.75 Hz, 1H), respectively (Fig 11).

Based on the above ^1H NMR spectral analyses, the structure and stereochemistry for the cycloadduct **81** is assigned as 8-methyl-6-*exo*-carboethoxy-7-*endo*-(6-chloro-3-pyridyl)-8-azabicyclo(3.2.1)octane.

^{13}C NMR displayed a total of ten carbon signals upfield at δ 14.1, 16.7, 19.5, 23.21, 34.6, 45.9, 57.1, 60.5, 62.0 and 66.1 and six signals downfield at δ 123.9, 137.2, 142.2, 148.4, 149.1 and 171.9 (Fig. 11). INEPT experiment revealed the presence C_2, C_3 and C_4 methylene carbons of azabicyclic ring systems at δ 16.7, 19.5 and 23.2, respectively. N-Methyl carbon signal appeared at δ 34.6. C_7 and C_6 methine carbon signals were observed at δ 45.99 and δ 57.11, respectively. Methyl and methylene

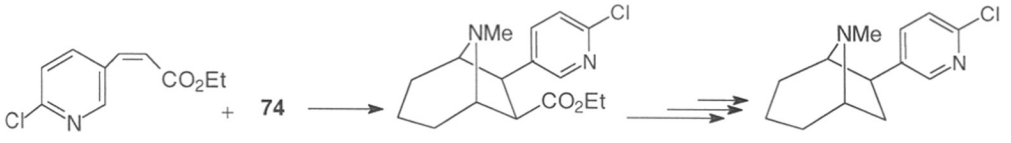
carbons of carboethoxy moiety were observed at δ 14.1 and δ 60.59, respectively. The two bridgehead C_1 and C_5 methine carbons appeared at δ 62.04 and δ 66.19, respectively. Quarternary carbonyl carbon of carboethoxy moiety was observed at δ 171.9. The rest of the downfield signal were assignable to the aromatic carbons of pyridyl moiety.

Mass spectrum indicated the molecular ion peak at 308 (3) and a base peak at 97 alongwith other prominent fragments at 235 (6), 166 (10) and 83 (73) (Fig 12).

3.3.2. Cycloaddition of 74 with *Cis*-pyridyl acrylate 83:

Cycloaddition of **74** with **83**, carried out as described for the preparation of **81**, afforded cycloadduct **84** (61%) as the only isolable diastereomer (Scheme 18).

Scheme 18



83 **84** (61%) **85**

The cycloadduct **84** is characterised by IR, ^1H NMR, ^{13}C NMR and mass spectral analyses as follows.

IR spectrum displayed the presence of carboethoxy moiety as a strong absorption band at 1728 cm^{-1} (Fig 14)

^1H NMR spectrum displayed the six H_2, H_3 and H_4 axial and equatorial protons as a set of three multiplets, each integrating for two protons, at δ 1.10-1.22, 1.62-1.75 and 1.92-2.05, repectively. A singlet at δ 2.58 equivalent to three protons

corresponds to N-methyl group. H_1 was observed as a broad singlet at δ 3.08, whereas H_{7endo} was identified as a doublet at δ 3.25 (J = 10.2 Hz). A multiplet, appearing as a broad singlet and a doublet signals, between δ 3.60-3.65, corresponding to two protons, is attributed to the H_{6endo} and bridgehead H_5. Methyl and methylene protons of carboethoxy moiety are observed as a triplet and mixed quartet at δ 0.8 (J = 7.21 Hz, 3H) and δ 3.42 (J = 7.21 Hz, 2H), respectively. Pyridyl ring protons were observed at δ 7.12 (d, J = 3.37 Hz, 1H), 7.92 (dd, J = 2.76, 8.34 Hz, 1H) and 8.24 (d, J = 2.78 Hz, 1H) (Fig 13).

Thus, the appearance of H_6 and H_7 protons as doublets and the retention of olefin geometry observed confirms the structure and stereochemisty of **84** as 8-methyl-6-*exo*-carboethoxy-7-*exo*-(6-chloro-3-pyridyl)-8-azabicyclo(3.2.1)octane.

^{13}C NMR spectrum revealed total sixteen carbon signals (Fig. 13). INEPT experiment revealed the presence of the three methylene carbons C_3, C_4 and C_2 of azabicyclic ring at δ 17.4, 20.5 and 21.2, respectively. Methyl on nitrogen was observed at δ 32.6. The two methine carbons C_6 and C_7, bearing carboethoxy and pyridyl moiety, were observed at δ 47.7 and δ 53.5, respectively. Methylene and methyl group ($O\underline{C}H_2\underline{C}H_3$) of carboethoxy moiety was observed at δ 13.4 and δ 59.5, respectively. The two bridigehead C_1 and C_5 methine carbons appeared at δ 60.0 and 66.2, respectively. Pyridyl moiety was observed as a set of three methine carbon signals downfield at δ 123.5, 138.1 and 149.7, and two quartenary carbon at δ 138.5 and 149.2. Quarternary carbonyl carbon of carboethoxy moiety appeared at δ 171.8.

*Cycloadducts **81** and **84** would obviously lead to both the endo and exo isomers* of Homoepibatidine on further synthetic transformations as already described for Epibatidine in Chapter 2.

4. Summary

In summary, we have successfully demonstrated the synthesis of various substituted epibatidine derivatives and a formal synthetic approach for both the stereoisomers of Homoepibatidine by utilizing [3+2]-cycloaddition of non stabilized azomethine ylide derived from cyclic amines.

5. Experimental

General experimental techniques which have been described in the experimental section of Chapter 2 were followed.

5.1. Preparation of 3-(6-Chloro-3-pyridyl)propionitriles (60 and 61):

To a stirring solution of **56** (1.69 g, 12 mmol) in 20 mL of acetonitrile was added cyanomethyl triphenyl phosphoranylidine (3.62 g, 12 mmol) dissolved in 40 mL of acetonitrile. The reaction mixture was refluxed for 10 h. After the completion of the reaction, solvent was removed under vacuum. The crude solid obtained was repeatedly triturated with 20 % ethyl acetate in hexane (5×50 mL) to remove triphenyl phosphine oxide formed in the reaction. The combined hexane fractions were evaporated to afford a solid residue which was purified by silica gel column chromatography eluting with hexane:EtOAc (9:1) to give 0.78 g of **60** (40%) and 0.59 g of **61** (30%) as a 1:1 mixture.

***Trans*-3-(6-chloro-3-pyridyl)-propionitrile (60):** mp. 167-168 °C.

IR (Nujol) : 2120, 1580, 1460 cm^{-1}.

^{1}H NMR (200MHz) : δ 6.00 (d, *J* = 16.67 Hz, 1H), 7.40 (d, *J* = 16.67 Hz, 1H), 7.45 (d, *J* = 8.36 Hz, 1H), 7.45 (d, *J* = 8.36 Hz, 1H), 7.80 (dd, *J* = 2.55, 8.34 Hz, 1H), 8.50 (d, *J* = 2.49 Hz, 1H).

^{13}C NMR (50.32 MHz) : δ 98.6, 116.3, 123.5, 127.6, 135.4, 144.5, 148.0, 151.9.

Mass : 164 (M^+, 100), 137 (29), 129 (82), 102 (59).

***Cis*-3-(6-chloro-pyridyl)-propionitrile (61):** mp. 97-98 °C.

IR (Nujol) : 2120, 1580, 1460 cm^{-1}.

^{1}H NMR (200MHz) : δ 5.65 (d, *J* = 12.00 Hz, 1H), 7.10 (d, *J* = 12.00 Hz, 1H), 7.45 (d, *J* = 8.50 Hz, 1H), 8.40 (dd, *J* = 2.40, 8.49 Hz, 1H), 8.60 (d, *J* = 2.40 Hz, 1H).

^{13}C NMR (50.32 MHz) : δ 98.3, 116.2, 124.4, 128.2, 137.0, 143.5, 150.5, 153.1.

Mass : 164 (M^+, 100), 129 (82), 102 (59).

5.2. Cycloaddition reaction of 60 and 62:

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.77 g, 4.72 mmol) (dried previously under vaccum at 40 ^{0}C) and with a solution of dipolarophile **60** (0.95 g, 6.26 mmol) in 30 mL of dry dichloromethane. Compound **62** (1.20 g, 3.93 mmol), dissolved in 25 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. The color of the reaction mixture gradually turned dark brown with concomitant deposition of silver on the surface of the flask in the form of mirror and the progress of the reaction was periodically monitored by TLC. After stirring for 8-10 h, the reaction mixture was filtered through a small plug of celite and the solvent was evaporated to give a crude brown residue. Purification of the crude residue by silica gel column chromatography, eluting with hexane:EtOAc (9:1), afforded 0.22 g (18 %) of **64** yield. Further elution with hexane:EtOAc (9:2) afforded 0.56 g (45 %) of **63** as a thick yellow oil.

7-Benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*exo*-cyano-7-azabicyclo[2.2.1]heptane (63) :

IR ($CHCl_3$) : 2221, 1462, 1107 cm^{-1};

^1H **NMR (200MHz)** : δ 1.40-1.52 (m, 2H), 1.70-1.90 (m, 1H), 1.95-2.12 (m, 1H), 2.65 (d, *J* = 5.94 Hz, 1H), 3.65 (t, *J* = 4.15 Hz, 1H), 3.75 (m, 4H), 7.25-7.50 (m, 7H), 8.25 (d, *J* = 2.46 Hz, 1H).

^{13}C **NMR (75.3 MHz)** : δ 20.5, 27.2, 36.6, 49.9, 51.2, 63.5, 64.4, 121.4, 124.0, 127.1, 128.1, 128.3, 132.2, 137.9, 138.5, 148.7, 150.1.

Mass : 323 (M^+, 1), 159 (34), 140 (55), 126 (54), 105 (39), 91 (100), 83 (55).

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-cyano-7-azabicyclo[2.2.1]heptane (64):

IR ($CHCl_3$) : 2400, 1461, 1217, 1046 cm^{-1};

^1H **NMR (200MHz)** : δ 1.55-1.70 (m, 1H), 2.00-2.15 (m, 3H), 2.85 (dd, *J* = 4.76, 9.73 Hz, 2H), 3.30 (s, 1H), 3.55 (s, 2H), 3.65 (s, 1H), 7.25-7.45 (m, 6H), 7.58 (dd, *J* = 2.45, 8.24 Hz, 1H), 8.45 (d, *J* = 2.45 Hz, 1H).

^{13}C **NMR (75.3 MHz)** : δ 22.0, ,26.8, 41.4, 51.2, 51.7, 61.59, 65.7, 119.9, 124.0, 127.3, 128.4, 128.5, 137.5, 138.4, 148.5, 150.2.

5.3. Cycloaddition of 61 and 62:

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.54 g, 4.29 mmol) (dried previously under vaccum at 40 ^0C) and solution of dipolarophile **61** (0.47 g, 2.92 mmol) in 20 mL of dry dichloromethane. Compound **62** (0.59 g, 1.96 mmol), dissolved in 15 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous

experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.34 g (55%) of **65**. Further elution with hexane:EtOAc (9:2) afforded 0.08 g (13 %) of **66** as a thick yellow oil.

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*exo*-cyano-7-azabicyclo[2.2.1]heptane (65):

IR (Nujol) : 2400, 1461, 1271, 1105 cm^{-1}.

^{1}H NMR (200 MHz) ($CDCl_3$) : δ 1.55-1.75 (m, 2H), 2.05-2.15 (m, 2H), 3.0 (s, 2H), 3.38 (d, *J* = 4.17 Hz, 1H), 3.67 (s, 2H), 3.8 (d, *J* = 4.17 Hz, 1H), 7.25-7.50 (m, 6H), 8.05 (dd, *J* = 2.45, 8.30 Hz, 1H), 8.26 (d, *J* = 2.45 Hz, 1H).

^{1}H NMR ($C6D_6$, 300 MHz) δ 1.35-1.40 (m, 2H), 1.95 (d, *J* = 8.5 Hz, 2H), 2.60 (d, *J* = 5.6 Hz, 1H), 3.0-3.15 (m, 5H), 6.92 (d, *J* = 8.03 Hz, 1H), 7.15-7.22 (m, 5H), 7.55 (d, *J* = 2.03, 8.05 Hz, 1H), 8.12 (d, *J* = 2.03 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 21.3, 24.0, 34.9, 44.7, 51.5, 63.0, 63.9, 119.3, 123.7, 127.4, 128.3, 128.5, 130.9, 138.4, 139.4, 150.4, 150.5.

Mass : 323 (M^+, <1), 159 (61), 131 (25), 91 (100).

7-Benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*endo*-cyano-7-azabicyclo[2.2.1]heptane (66):

IR ($CHCl_3$) : 2400, 1522, 1463, 1217, 1046 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.80-1.95 (m, 2H), 2.05-2.15 (m, 2H), 3.55 (m, 2H), 3.75 (m, 4H), 7.30-7.45 (m, 6H), 7.70 (dd, *J* = 2.45Hz, 8.23 Hz, 1H), 8.26 (d, *J* = 2.44 Hz, 1H).

^{1}H NMR ($C6D_6$, 300 MHz) δ 1.08-1.25 (m, 2H), 1.30-1.42 (m, 1H), 1.65 -1.85 (m, 1H), 2.6 (m, 1H), 2.75 (m, 1H), 2.85 (dd, *J* = 4.2 Hz, 8.5, 1H), 2.96 (t, *J* = 4.35 Hz, 1H), 3.15 (s, 2H), 6.82 (d, *J* = 8.35 Hz, 1H), 7.1-7.25 (m, 6H), 7.95 (d, *J* = 2.5Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 21.3, 24.0, 34.9, 44.7, 51.4, 63.0, 63.9, 119.3, 123.7, 127.4, 128.3, 128.5, 128.8, 130.9, 138.4, 139.4, 150.4, 150.5.

Mass : 323 (M^+, 1), 189 (26), 159 (73), 91 (100).

5.4. Preparation of 2-(6-Chloro-3-pyridyl)-1-nitro ethan-2-ol (68):

A 10 mL *i*-PrOH solution of **56** (1.41g, 10 mmol) was treated with KF (0.03 g, 0.5 mmol) and nitromethane (0.65 mL, 12 mmol). After stirring for 6 h at rt, solvent was evaporated to dryness and the residue was purified by silica gel column chromatography eluting with hexane:EtOAc (8:2) to obtain 2-hydroxy-2-(6-chloro-3-pyridyl)nitroethane (**68**) (1.81 g, 90 %) as thick dark yellow oil.

^{1}H NMR (200MHz) : δ 4.6 (d, *J* = 4.36 Hz, 2H), 5.6 (dd, *J* = 9.72, 4.32 Hz, 1H), 7.3 (d, *J* = 8.40 Hz, 1H), 7.80 (dd, *J* = 2.6, 8.41 Hz, 1H), 8.40 (d, *J* = 8.35 Hz, 1H).

^{13}C NMR (50.32 MHz) : δ 67.9, 80.7, 124.7, 134.0, 137.3, 147.2, 151.2;

Mass : 202 (M^+, 4), 155 (82), 140 (100), 128 (20).

5.5. Preparation of 2-(6-Chloro-3-pyridyl)-1-nitroethylene (69):

Compound **68** (1 g, 4.94 mmol) dissolved in 50 mL of dry DCM was cooled to 0 ^{0}C and was treated with TEA (1.0 g, 9.89 mmol) followed by *p*-toluene sulfonyl chloride (0.59 g, 5.43 mmol). After the completion of the reaction, the reaction mixture was stirred at rt overnight. The mixture was successively washed with aqueous 1 M $NaHCO_3$ solution (2×25 mL), water, brine and finally dried over Na_2SO_4. Evaporation of the solvent gave crude solid which was purified by silica gel column chromatography eluting with hexane:EtOAc (9:1) to get **69** (0.68 g, 75 %) as a white solid, mp. 138-140 °C.

IR (Nujol) : 1637, 1583, 1506, 1340, 1099 cm^{-1}.

^{1}H NMR (200MHz) : δ 7.45 (d, *J* = 8.30 Hz, 1H), 7.65 (d, *J* = 12.25 Hz, 1H), 7.85 (dd, *J* = 2.38, 8.30 Hz, 1H), 8.0 (d, *J* = 12.25 Hz, 1H), 8.55 (d, *J* = 2.38 Hz, 1H).

^{13}C NMR (50.32 MHz) : 124.4, 125.6, 134.2, 138.6, 139.4, 150.8, 152.9.

Mass : 184 (M^+, 41), 137 (91), 126 (19), 102 (100 %), 75 (79 %).

5.6. Cycloaddition of 69 and 62: Synthesis of 7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-nitro-7-azabicyclo[2.2.1]heptane (70):

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.36 g, 2.82 mmol) (dried previously under vaccum at 40 ^{0}C) and solution of dipolarophile **69** (0.28 g, 1.57 mmol) in 30 mL of dry dichloromethane. Compound **62** (0.40 g, 1.31 mmol), dissolved in 20 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.19 g (65%) of **70** as yellow oil.

IR ($CHCl_3$) : 1550, 1470, 1230, 1120, 770 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.60-1.75 (m, 2H), 2.0-2.2 (m, 2H), 3.35 (d, *J* = 4.5 Hz, 1H), 3.45 (d, *J* = 5.36 Hz, 1H), 3.63 (s, 2H), 4.02 (m, 1H), 4.75 (m, 1H), 7.28 (d, *J* = 8.45 Hz, 1H), 7.35-7.45 (m, 5H), 7.78 (dd, *J* = 2.45, 8.3 Hz, 1H), 8.5 (d, *J* = 2.46 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 20.3, 26.5, 48.4, 51.8, 62.8, 66.9, 93.0, 124.0, 127.5, 128.5, 128.6, 137.2, 137.9, 138.1, 148.9, 150.1.

Mass : 221 (6), 191 (14), 140 (9), 83 (100).

5.7. Preparation of N-(*tert*-butoxycarbonyl) piperidine (76):

To a solution of piperidine (8.76 g, 92.3 mmol) and triethylamine (11.6 g, 115.3 mmol) in dioxane (50 mL), *tert*-butyl azidoformate (11 g, 76.9 mmol) was added dropwise over 15 min. The pH of the reaction mixture was maintained at 12 by the

addition of excess triethylamine if required. The reaction mixture was stirred untill a clear solution resulted. After the evaporation of dioxan, the residue was taken up in ether, washed twice with water (75 mL) followed by brine (75 mL). Ether was evaporated and the resultant brown oil obtained was purified by vacuum distillation (bp. 55-57°C/1mm) to obtain 15.3 g (90 %) of **76** as a clear colorless oil.

IR : 2940, 1695, 1420, 1385, 1260, 1170 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.45 (s, 9H),1.58 (m, 6H), 3.31-3.45 (m, 4H).

Mass : 185 (M+, 66), 129 (53), 84 (63), 57 (100).

5.8. Preparation of N-(*tert*-butoxy carbonyl)-2-trimethylsily piperidine(77):

A solution of N-Boc piperidine (**76**) (5.55 g, 30.0 mmol) in 40 mL of dry ether charged into a 250 mL flask, equipped with a magnetic stirring bar and argon gas balloon, was cooled to -78 °C. TMEDA (4.18 g, 36.0 mmol) followed by *s*-BuLi (1.5 M solution in cyclohexane, 23.93 mL, 36.0 mmol) were introduced to the stirring mixture dropwise over 15 min. The mixture was further allowed to stir for 2 h at -78°C. Chlorotrimethylsilane (3.91g, 36.0 mmol) was added dropwise into the flask. The reaction mixture was allowed to warm to rt and diluted with 15 mL of saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ether (2×30 mL). The combined extracts were washed with water (80 mL), brine (80 mL) and dried over Na_2SO_4. The organic extract was concentrated and the crude oily residue obtained was purified by fractional distillation (bp 55-57°C/0.5 mm) to give 6.96 g (90%) of **77** as a colorless oil .

IR (neat) : 1688, 1415, 1159, 1098, 838 cm^{-1}.

^{1}H NMR (200MHz) : δ 0.06 (s, 9H), 1.43 (s, 9H), 1.55-1.75 (m, 6H), 2.15-2.30 (m, 2H), 3.60-3.75 (bs, 1H).

^{13}C NMR (50.32 MHz) : δ -1.0, 23.0, 25.7, 28.1, 45.0, 78.4, 154.5.

Mass : 257 (M^+, <1), 156 (84), 128 (54), 84 (75), 73 (100).

5.9. Preparation of N-Boc-2,6-bis(trimethylsilyl)piperidine (78):

A 250 mL two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of **77** (5.14 g, 20 mmol) in 30 mL of ether and was cooled to - 45°C. TMEDA (2.79 g, 24 mmol) followed by *s*-BuLi (1.5 M in cyclohexane, 16.0 mL, 24 mmol) were added to the flask dropwise while stirring. After 15 min of stirring at -45°C, temperature was raised to -30°C. After 30 min, it was recooled to -45°C and chlorotrimethylsilane (2.60 g, 24 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, diluted with 10 mL of saturated aqueous NH_4Cl solution and worked up as mentioned in previous experiment, to get an oily residue which was purified by silica gel column chromatography eluting with hexane:EtOAc (99:1) to give 4.93 g (75 %) of **78** as a pale yellow oil.

IR : 1684, 1421, 1175, cm^{-1}.

^{1}H NMR (200MHz) : δ 0.08 (s, 18H), 1.45 (s, 9H), 1.55-1.75 (m, 6H), 2.15 (m, 1H), 3.60-3.75 (bs, 1H).

^{13}C NMR (50.32 MHz) : δ -0.7, 0.1, 24.7, 26.2, 26.9, 28.7, 47.7, 48.5, 78.8, 155.8.

Mass : 272 (100), 258 (46), 242 (66), 228 (51), 200 (80), 156 (44), 73 (98).

5.10. Preparation of N-Methyl-2,6-bis(trimethylsilyl)piperidine (74):

To a stirring solution of **78** (5.0 g, 15.2 mmol) in 40 mL of dry CH_2Cl_2 at 0 °C contained in a 100 mL round bottom flask equipped with argon gas balloon, was added trifluroacetic acid (8.66 g, 76 mmol) dropwise over 15 mins. The mixture was

allowed to warm to rt and allowed to stir further for 4 h. The reaction mixture was recooled to 0°C and basified with 20% aqueous NaOH solution (pH =10). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give 3.12 g of crude **79** which was utilised as such without further purification.

To a stirring solution of crude amine **79** (3.1 g, 13.67 mmol) in CH_3CN (120 ml), 37 % aqueous solution of HCHO (1.5 mL) and $NaBH_3CN$ (1.71 g, 27.35 mmol) were added. The reaction mixture was stirred for an additional 15 min. Neutralisation of the reaction mixture by adding glacial acetic acid followed by basification by the slow addition of conc. NH_4OH and extraction with hexane (3×50 mL) followed by concentration and purification of the residue by silica gel column chromatography, eluting with EtOAc:hexane (3:97), gave **74** (2.65 g, 80 % yield) as a colorless viscous liquid.

^{1}H NMR (200MHz) : δ 0.06 (s, 18H), 1.52-1.67 (m, 6H), 2.2-2.3 (m, 2H), 2.55 (s, 3H)

^{13}C NMR (50.32 MHz) : δ -1.2, 20.7, 24.3, 42.4, 54.1.

Mass : 243 (M^+, <1), 228 (4.3), 170 (100), 96 (4.5), 73 (5.2).

5.11. Synthesis of 8-Methyl-6-*exo*-carbethoxy-7-*endo*-(6-chloro-3-pyridyl)-8-azabicyclo [3.2.1]octane (81): Cycloaddition of 74 with 80

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.57 g, 4.51 mmol) (dried previously under vaccum at 40 ^{0}C) and solution of dipolarophile **80** (0.52 g, 2.47 mmol) in 40 mL of dry dichloromethane. Compound **74** (0.50 g, 2.05 mmol), dissolved in 20 mL of dry DCM,

was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.40 g (65%) of **81** as yellow oil.

IR (Neat) : 1724, 1582, 1241, 1103 cm^{-1}.

^{1}H NMR (200MHz) : δ 1.25 (t, *J* = 7.21 Hz, 3H), 1.50-1.75 (m, 3H), 1.85-2.05 (m, 3H), 2.52 (s, 3H), 3.17 (m, 2H), 3.50-3.55 (m, 1H), 3.65 (d, *J* = 6.65 Hz, 1H), 4.2 (q, *J* = 7.2 Hz, 2H), 7.27 (d, *J*=8.24 Hz, 1H), 7.88 (dd, *J* = 2.73, 8.25 Hz, 1H), 8.42 (d, *J* = 2.75 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 14.1, 16.7, 19.5, 23.2, 34.6, 45.9, 57.1, 60.5, 62.0, 66.1, 123.9, 137.2, 142.2, 148.4, 149.1, 171.9.

Mass : 308 (M^+, 3), 166 (10), 97(100), 83 (72).

5.12. Synthesis of 8-Methyl-6-*exo*-carbethoxy-7-*exo*-(6-choro-3-pyridyl)-8-azabicyclo [3.2.1] octane (84): Cycloaddition of 74 with 83

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.57 g, 4.51 mmol) (dried previously under vaccum at 40°C) and solution of dipolarophile **83** (0.52 g, 2.47 mmol) in 40 mL of dry dichloromethane. Compound **74** (0.50 g, 2.05 mmol), dissolved in 20 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.40 g (65%) of **84** as yellow oil.

IR ($CHCl_3$) : 1728, 1106 cm^{-1}.

^1H NMR (200MHz) : δ 0.80 (t, *J* = 7.21 Hz, 3H), 1.10-1.22 (m, 2H), 1.62-1.75 (m, 2H), 1.92-2.05 (m, 2H), 2.58 (s, 3H), 3.08 (bs, 1H), 3.25 (d, *J* = 10.2 Hz ,1H), 3.42 (m, 2H), 3.60-3.65 (q, 2H), 7.12 (d, *J*= 3.37 Hz, 1H), 7.92 (dd, *J* = 2.76, 8.34 Hz, 1H), 8.24 (d, *J* = 2.78 Hz, 1H).

^{13}C NMR (75.3 MHz) : δ 13.4, 17.4, 20.5, 21.2, 32.6, 47.7, 53.5, 59.5, 60.0, 66.2, 123.5, 138.1, 138.5, 149.2, 149.7, 171.8.

Mass : 308 (M^+, 16), 235 (37), 194 (18), 97 (100), 82 (14).

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Spectra

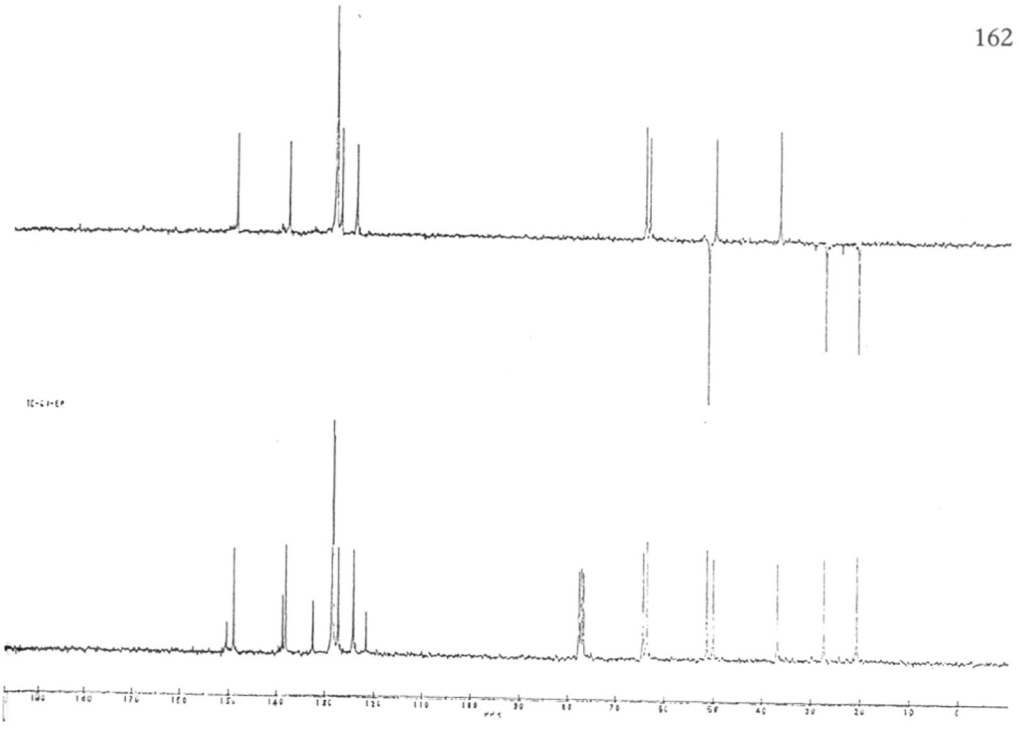
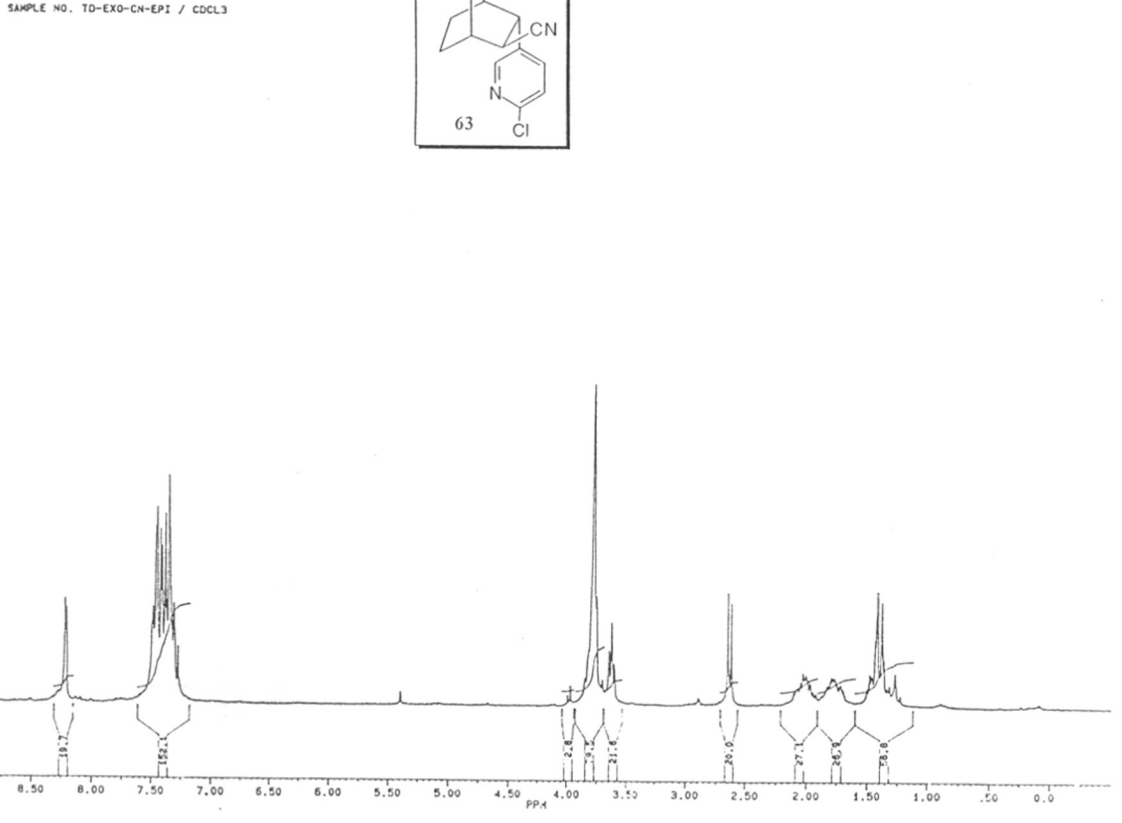


Fig. 2


SAMPLE NO. TD-EXO-CN-EPI / CDCL3
Bn
N
CN
N
63
Cl
19.7
152.1
2.8
3.4
21.6
20.0
27.1
26.8
38.8
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

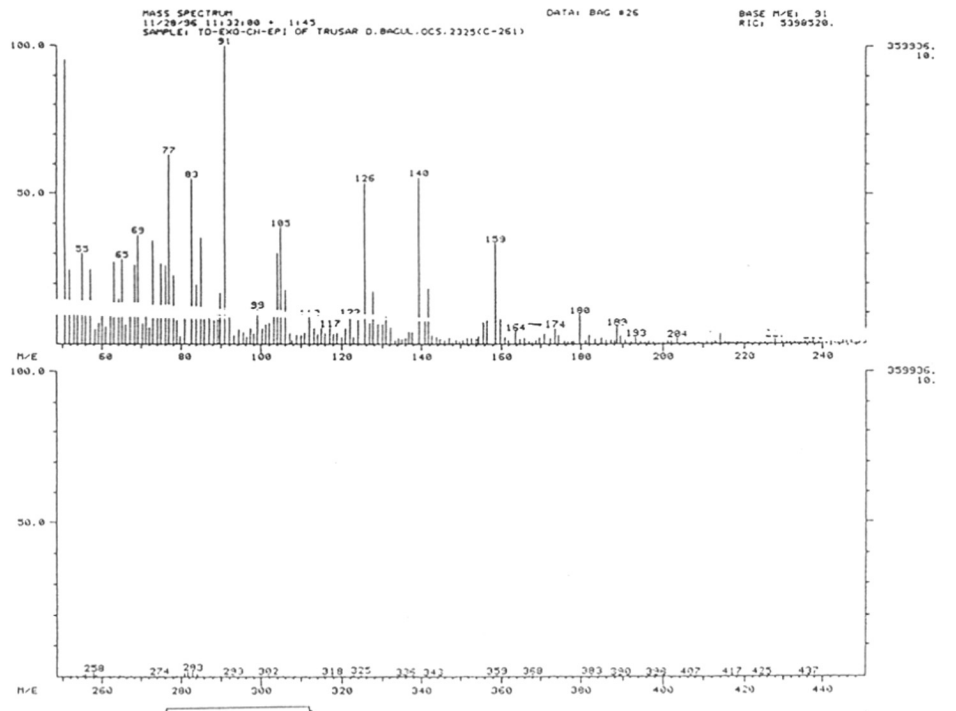
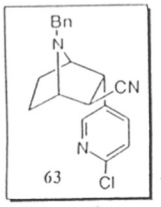


Fig. 3



Peak Report
File: c:\first\data\tmp\cfirst57.ras
Title: NCL / OCT / 97 / 007
Filter: Three Point Center of Gravity

cm-1	%T	cm-1	%T	cm-1	%T	cm-1	%T
404.80	0.25	435.80	0.00	462.88	0.43	479.81	0.71
754.80	15.48	1107.46	14.51	1462.83	13.16	2885.76	32.73
2932.28	31.75	2971.34	25.56	3026.84	33.74		

WinFIRST Report

Name: Mr. T. D. Bagul
Date: 28 / 05 / 97
Sample: TD - Exo - CN - Epi
Comments: In Choroform

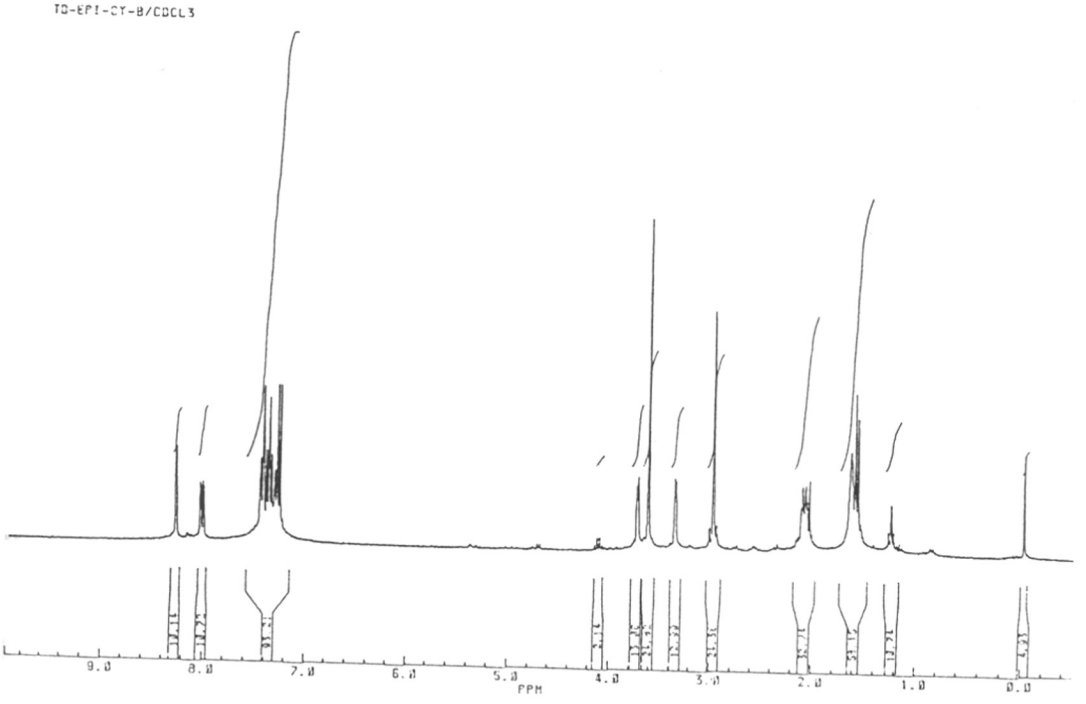
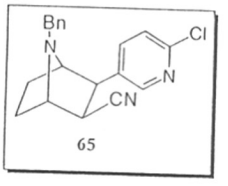
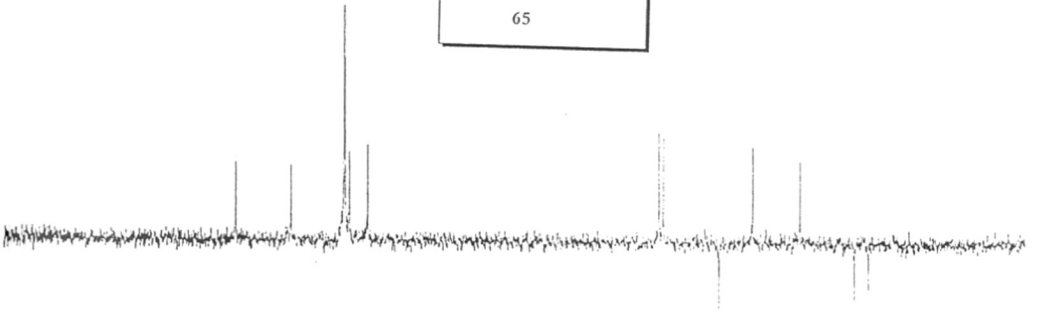
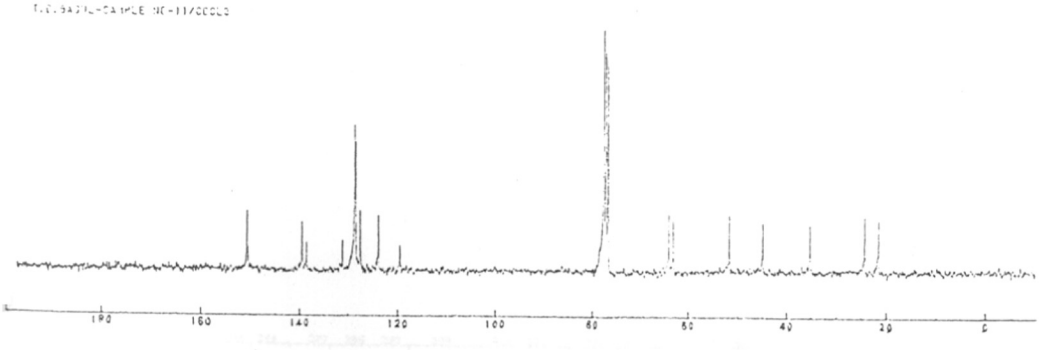

TQ-EPI-CY-B/CDCL3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

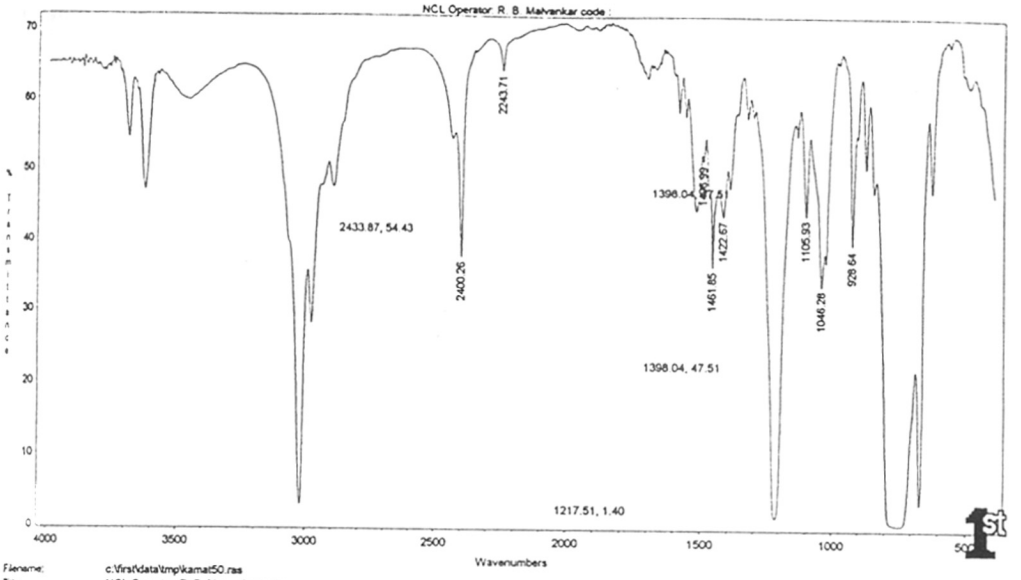
Fig. 4


Bn
N
Cl
N
CN

65




190
160
140
120
100
80
60
40
20
0



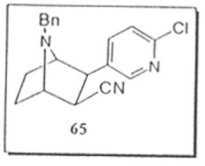
Filename: c:\first\data\tmp\kamat50.ras
Title: NCL Operator: R. B. Malvankar code :
Collected On: Wed Apr 17 15:11:13:77 1996
Starting wavenumber: 399.19
Ending wavenumber: 3999.66
Resolution: 4.0
Scans: 32

Gain	Detector	Iris
1	Standard	0

WinFIRST Report

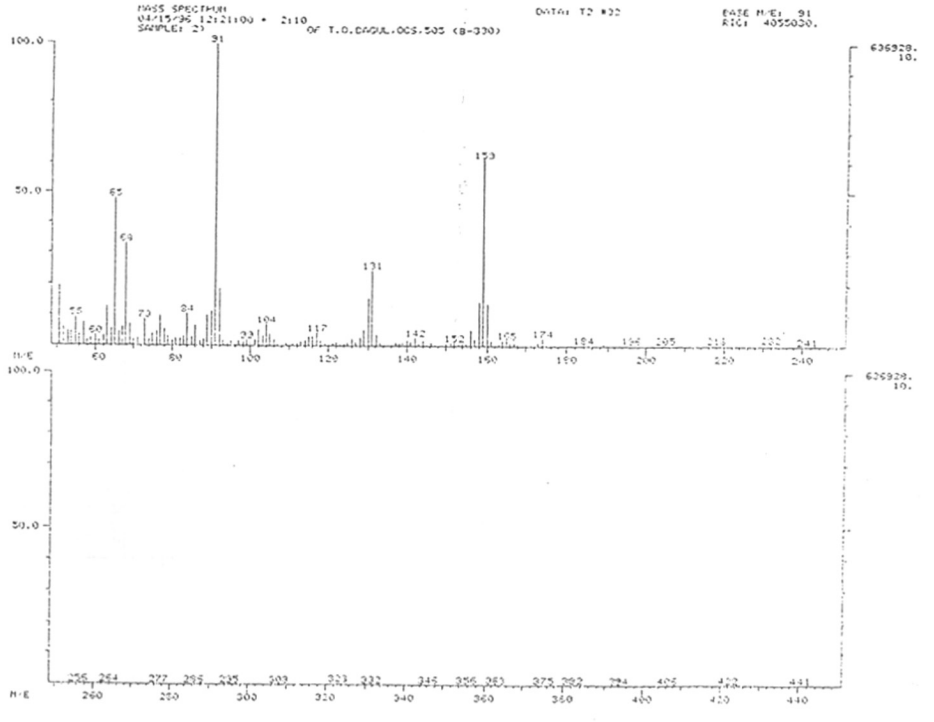
Name: Mr. T. D. Bagul
Date: 17 / 04 / 96
Sample: Epi - cn - 85
Comments: In Nujol

NCL Organic Tech



65

Fig. 5



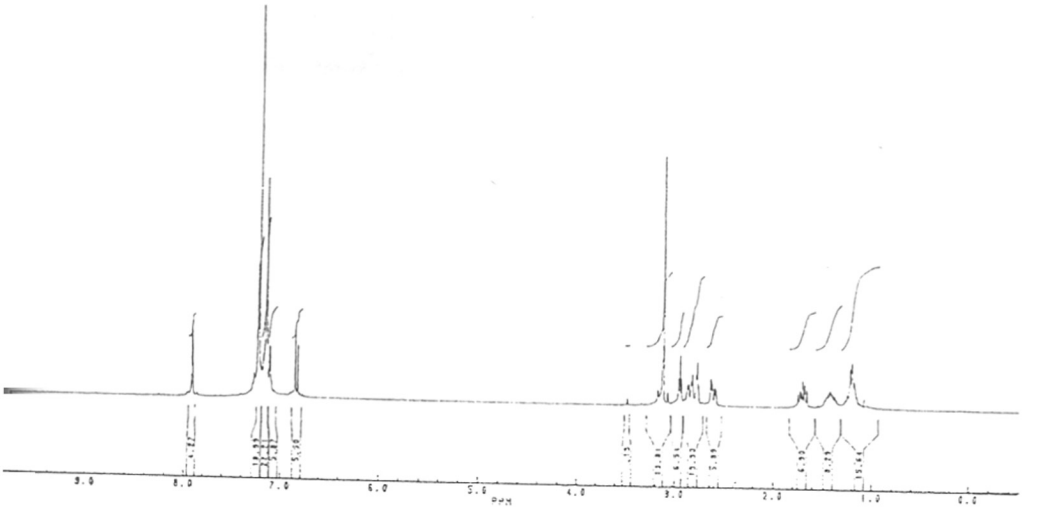
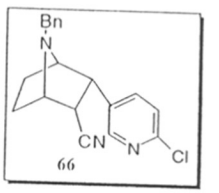
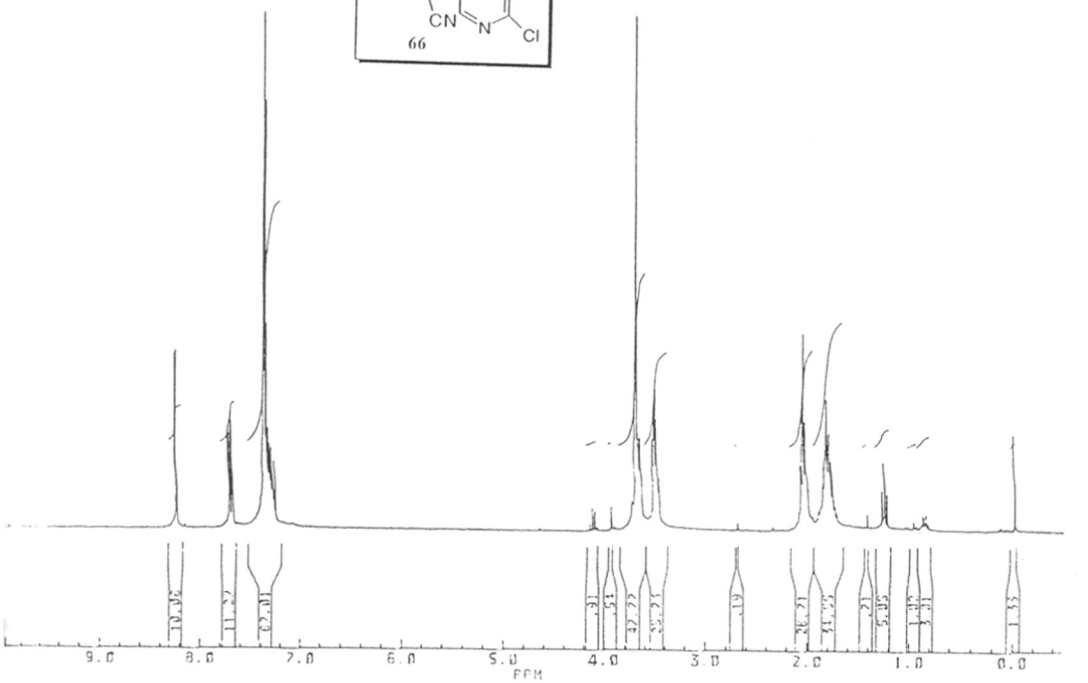


Fig. 6



66



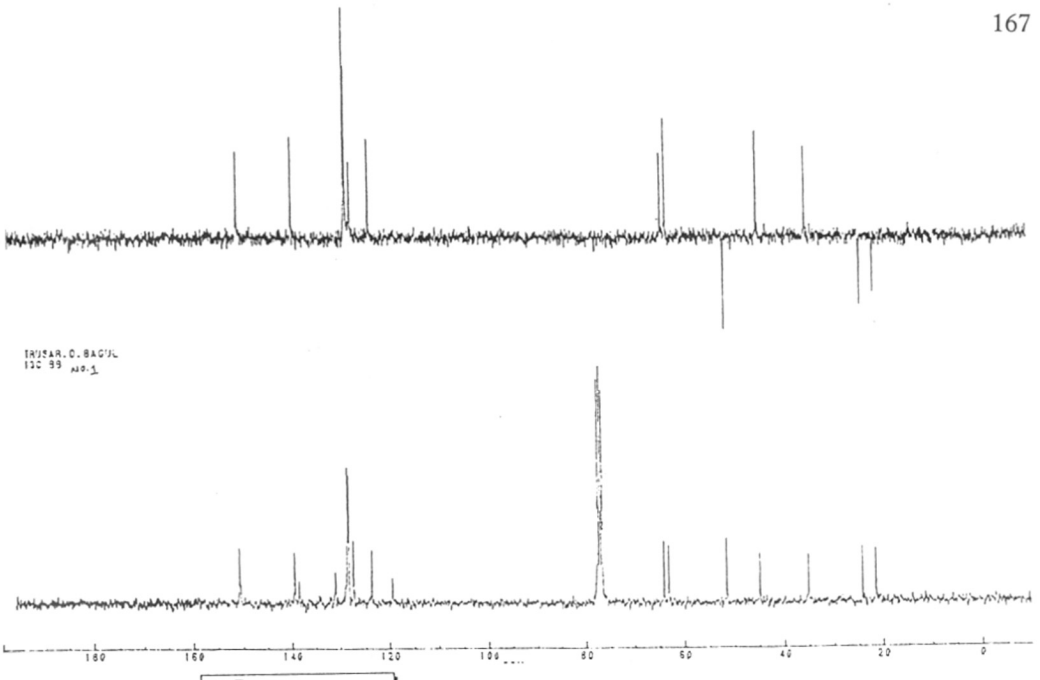
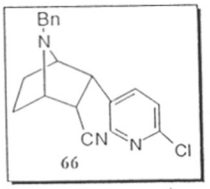
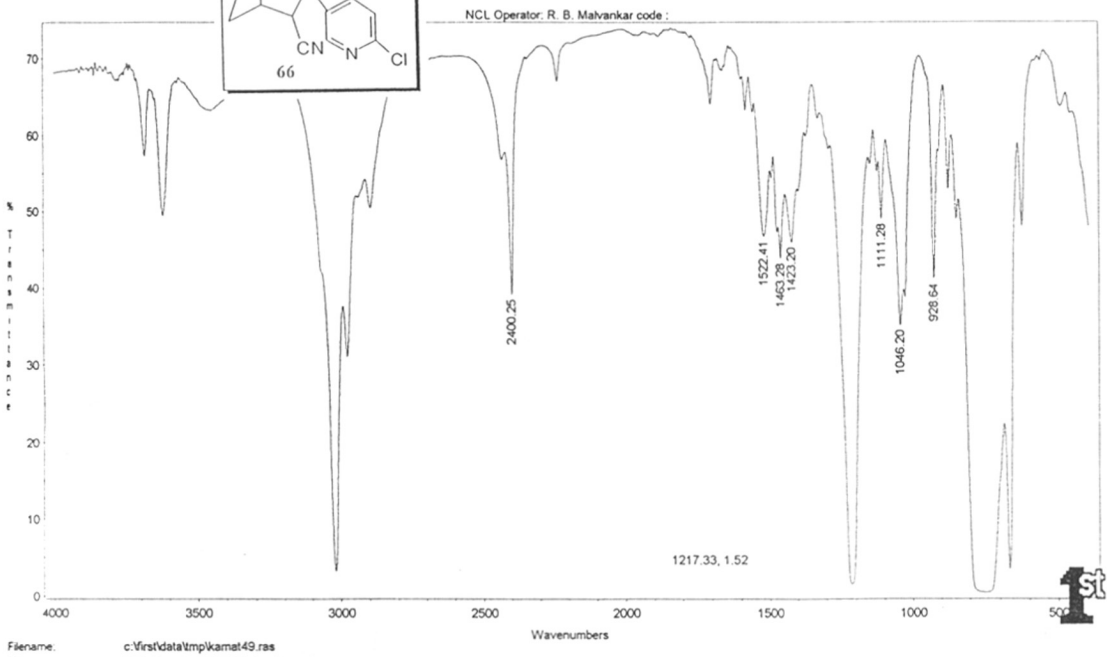


Fig. 7





Filename: c:\first\data\tmp\kamat49.ras
Title: NCL Operator: R. B. Malvankar code :
Collected On: Wed Apr 17 14:49:24:28 1996
Starting wavenumber: 399.19
Ending wavenumber: 3999.66
Resolution: 4.0
Scans: 32

Gain 1 Detector Standard Iris 0

WinFIRST Report

Name: Mr. T. D. Bagul
Date: 17 / 04 / 96
Sample: Epi - cn - TPS
Comments: in Choroform

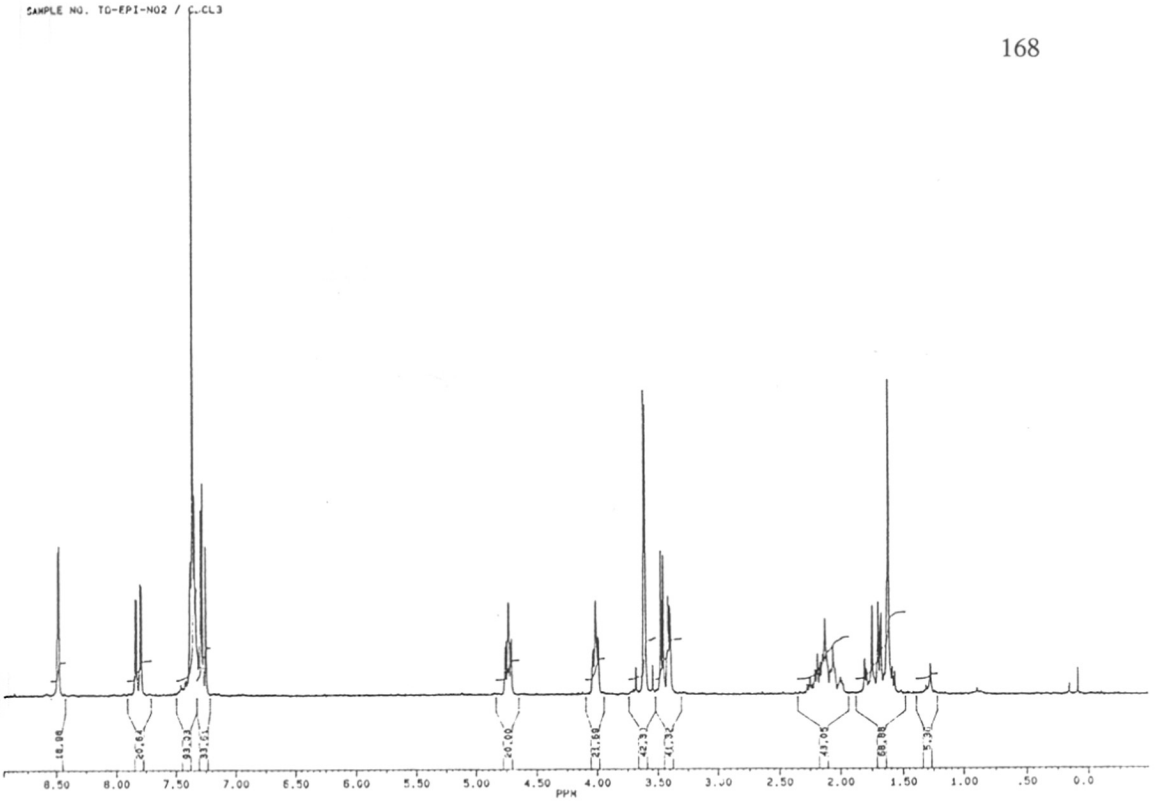
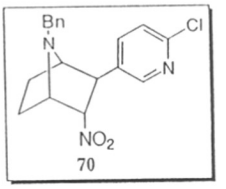
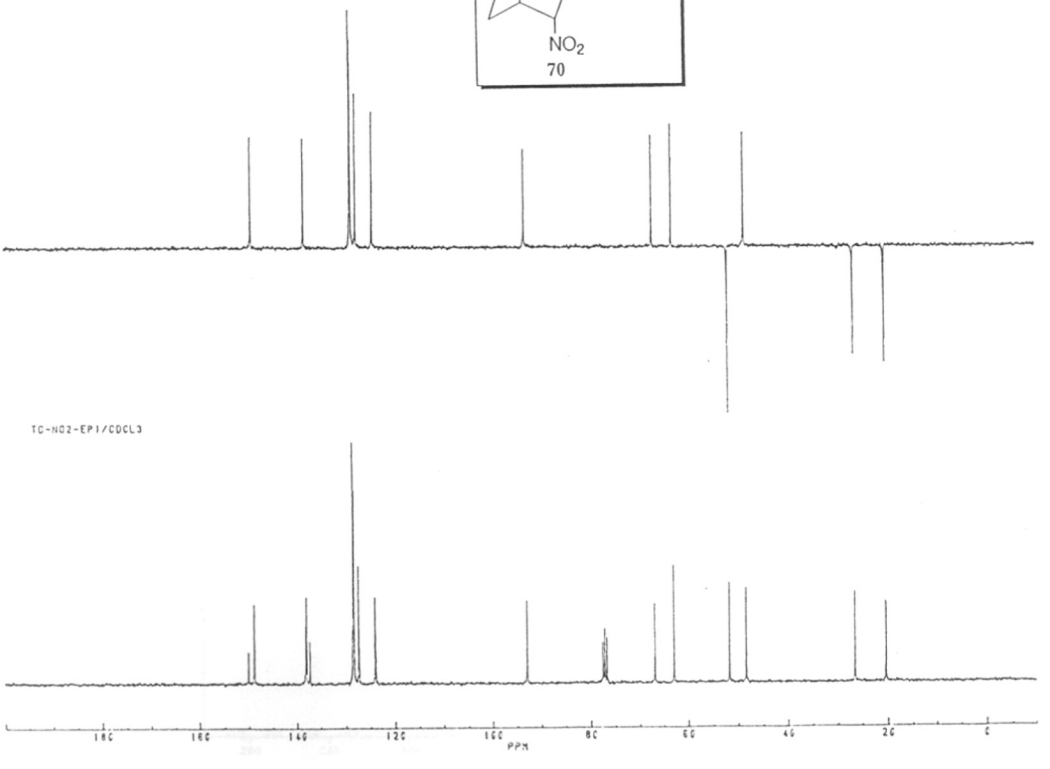

SAMPLE NO. TG-EPI-NO2 / C.CL3
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

Fig. 8


Bn
N
Cl
N
NO2

70


TG-NO2-EPI/CDCL3
160
140
120
100
80
60
40
20
0
PPM

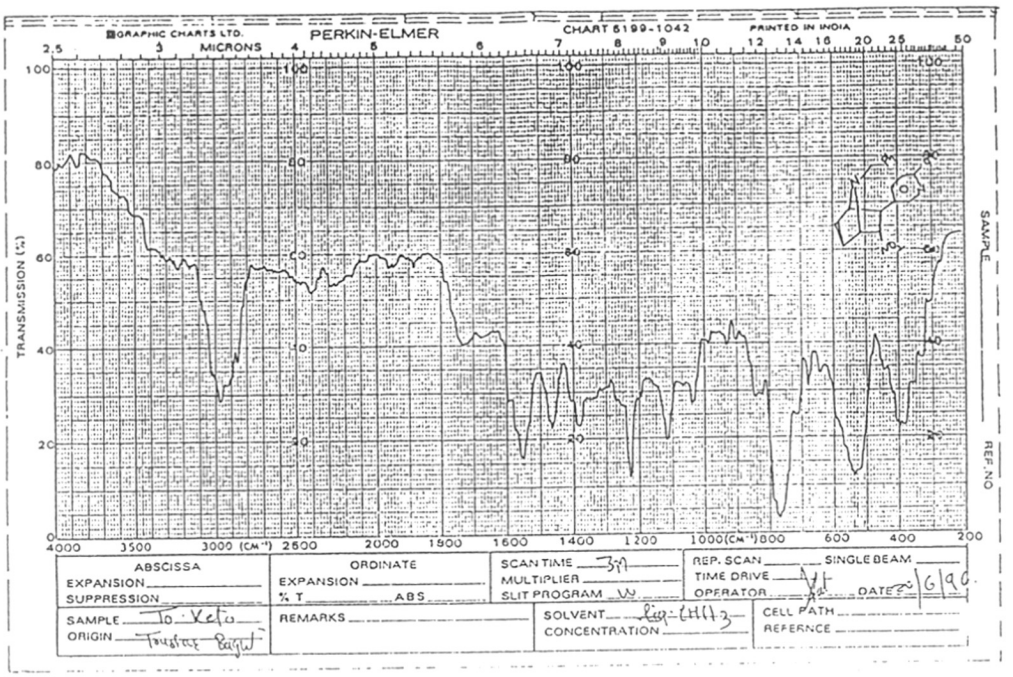
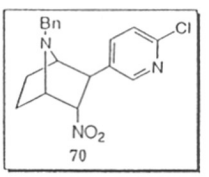
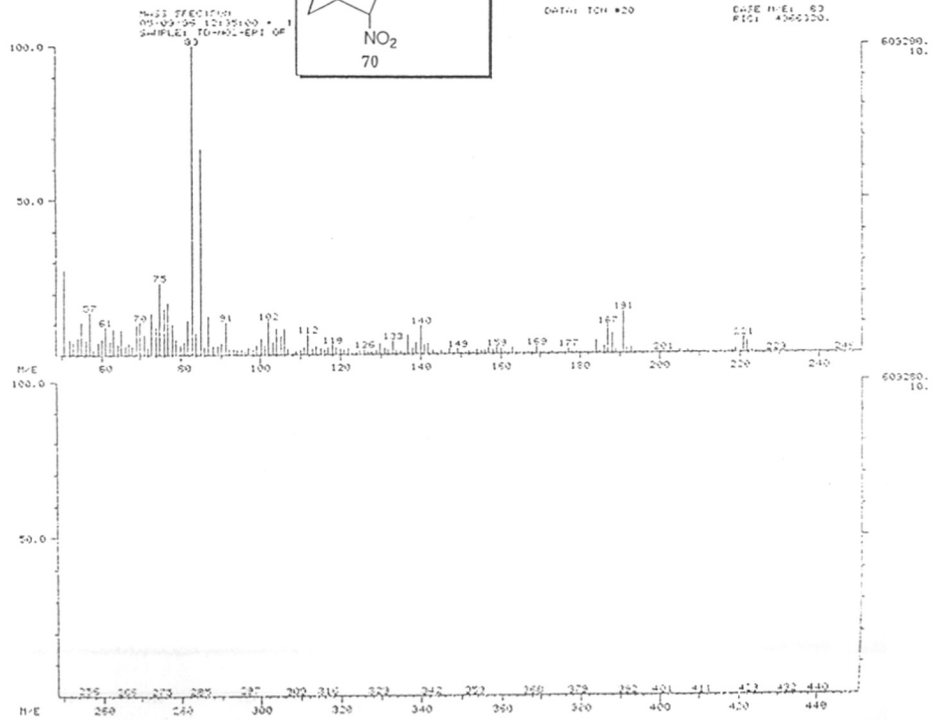

PERKIN-ELMER
CHART 5199-1042
PRINTED IN INDIA
MICRONS
TRANSMISSION (%)
SAMPLE
REF.NO
4000 3500 3000 (CM⁻¹) 2500 2000 1900 1600 1400 1200 1000(CM⁻¹)800 600 400 200
ABSCISSA
EXPANSION
SUPPRESSION
ORDINATE
EXPANSION
% T ABS
SCAN TIME 3m
MULTIPLIER
SLIT PROGRAM W
REP. SCAN SINGLE BEAM
TIME DRIVE
OPERATOR
DATE 2/6/96
SAMPLE To Keto
ORIGIN Toulouse Paget
REMARKS
SOLVENT liq-CHCl3
CONCENTRATION
CELL PATH
REFERNCE

Fig. 9


Bn
N
Cl
N
NO2
70


100.0
50.0
M/E
603280.
10.

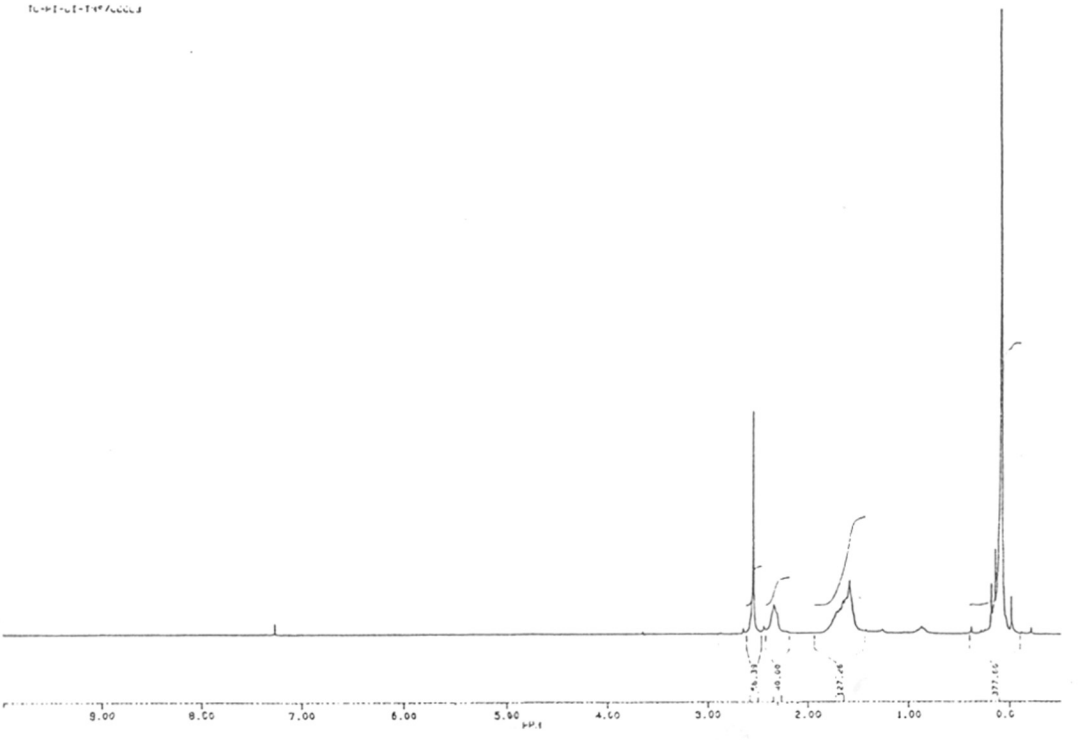
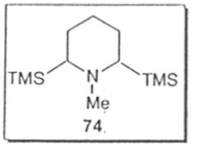
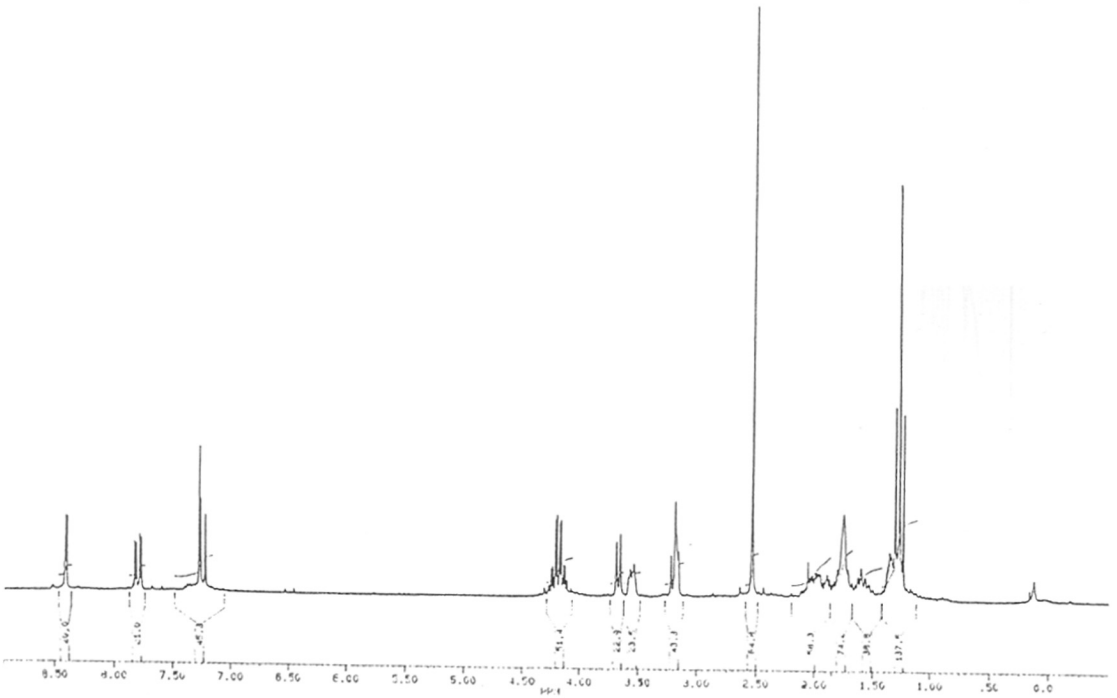

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM

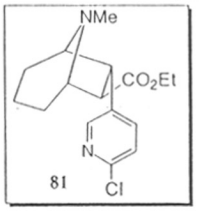
Fig. 10


TMS
N
TMS
Me

74

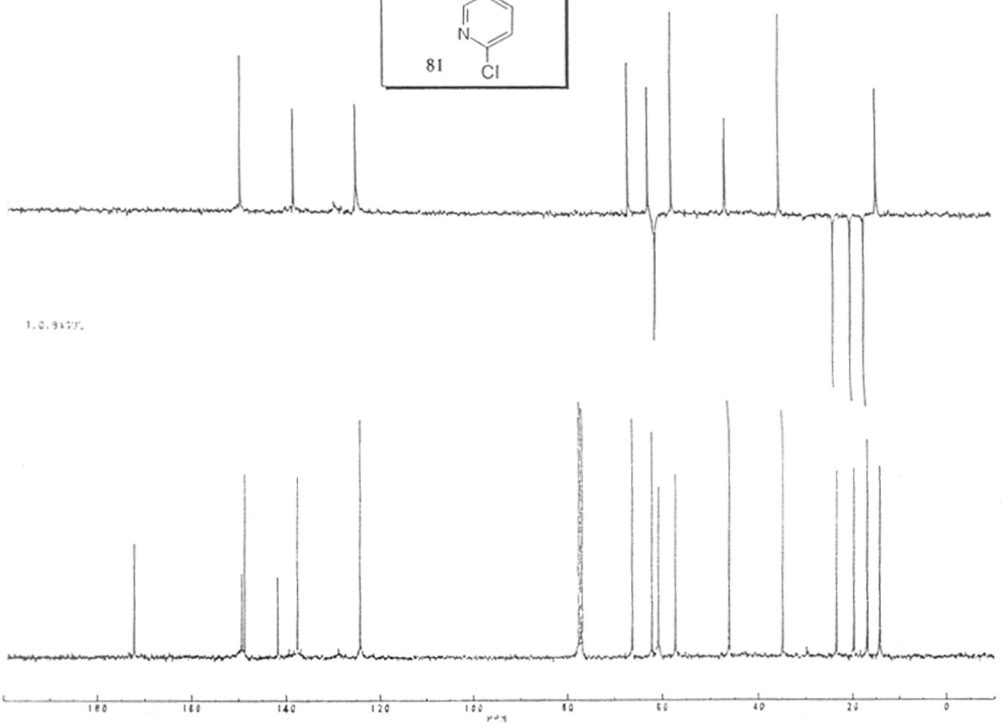
160
140
120
100
80
60
40
20
0
PPM

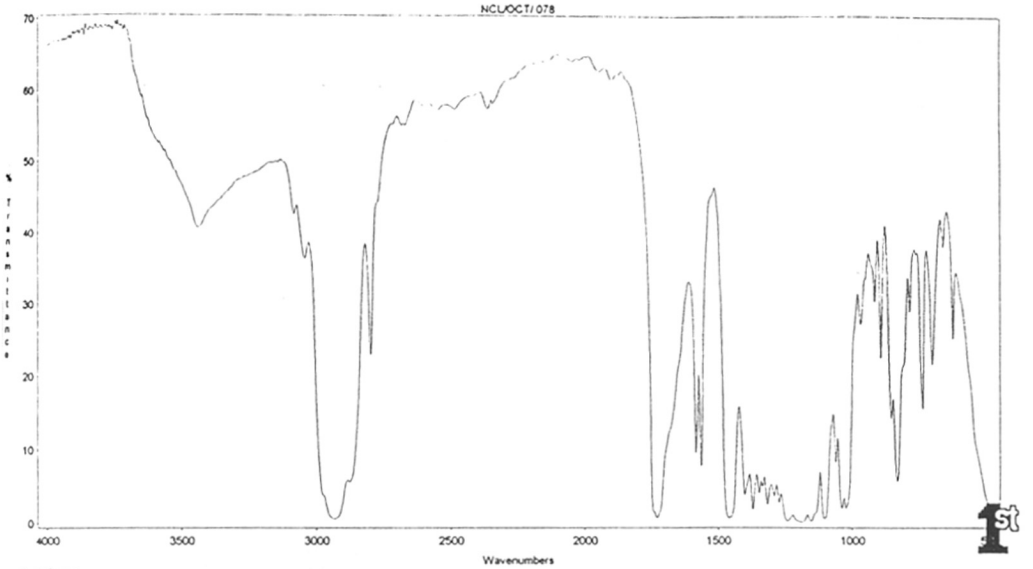




81

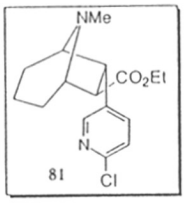
Fig. 11





Peak Report
File: c:\Firs\data\tmp\cfirs166.ras
Title: NCL/OCT/078
Filter: Three Point Center of Gravity

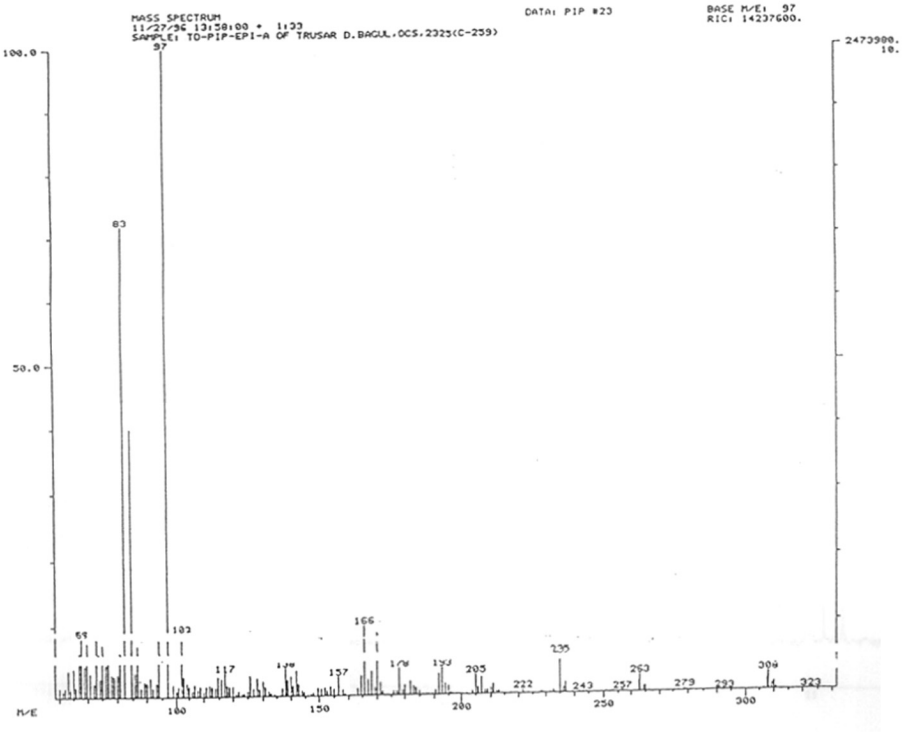
cm-1	%T	cm-1	%T	cm-1	%T	cm-1	%T
835.28	5.82	1024.53	2.07	1040.51	2.05	1063.80	8.36
1105.58	0.62	1154.76	0.29	1189.61	0.17	1241.02	0.29
1272.66	2.79	1290.68	3.73	1315.28	2.56	1333.89	5.05
1346.78	4.13	1370.25	1.90	1401.19	3.93	1461.02	0.70
1563.46	7.82	1582.87	9.54	1724.41	0.81	2878.56	5.68
2935.84	0.61						



Name : Mr. T. D. Bagul
Sample : TD - Pip - Epi
Date : 23 / 07 / 97
Comment : Neat

NCL Organic Tech

Fig. 12



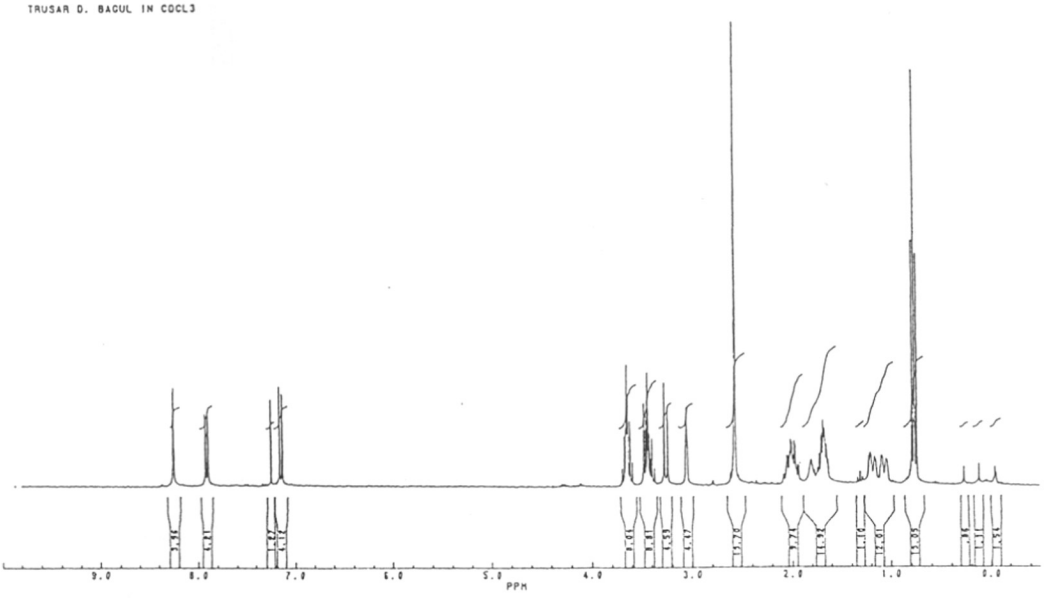
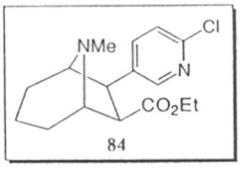
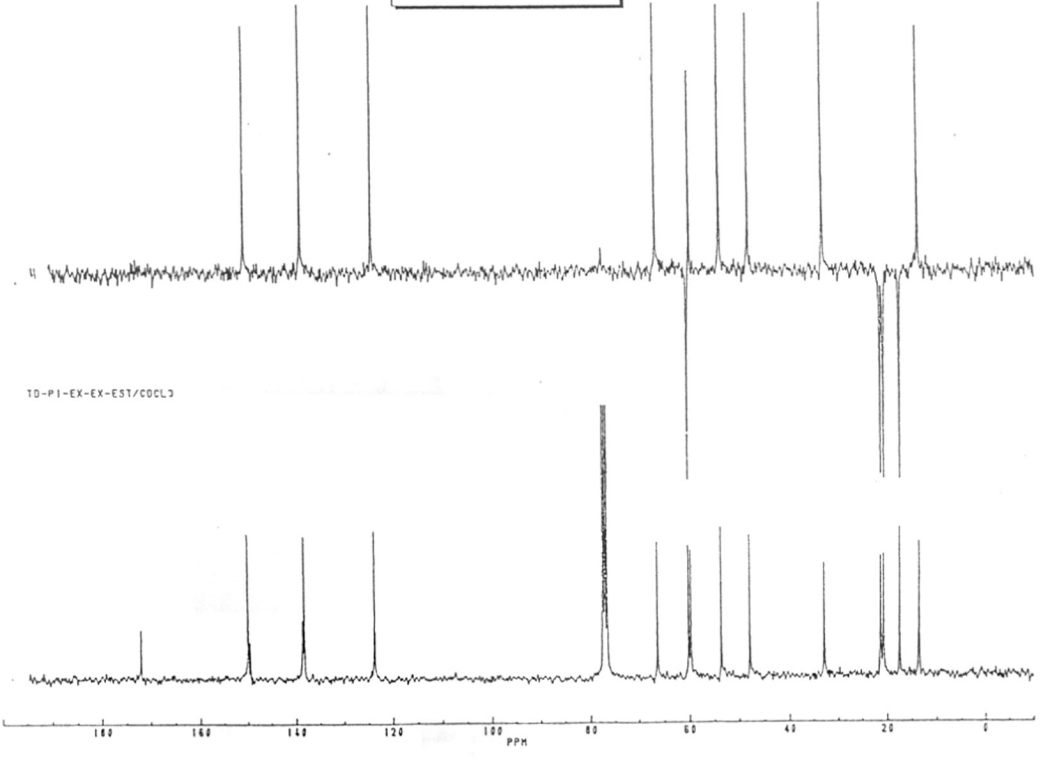
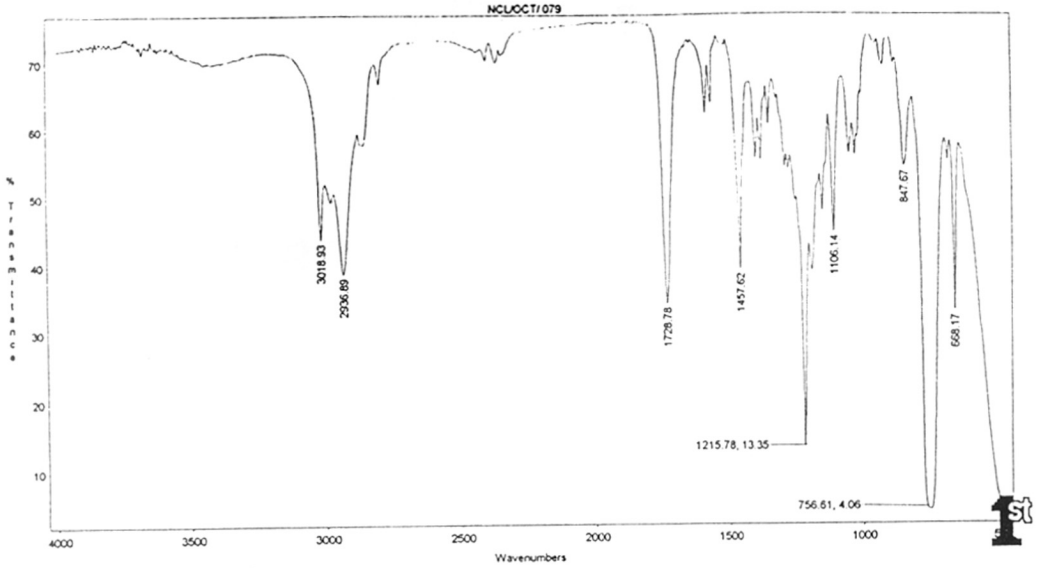

TRUSAR D. BAGUL IN CDCL3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

Fig. 13


NMe
Cl
N
CO2Et

84

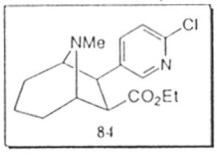

TD-PI-EX-EX-EST/CDCL3
160
140
120
100
80
60
40
20
0
PPM



Filename: c:\irsf\data\tmp\cfirs167.ras
Title: NCL/OCT/079
Collected On: Wed Jul 23 15:12:45:75 1997
Starting wavenumber: 499.47
Ending wavenumber: 3999.66
Resolution: 4.0
Scans: 32

Gain: Detector: Iris
1 Standard: 0

fvel fvel lpf apod



8.4

Name : Mr. T. D. BAGUL
Sample : TD - Pip - Ex - Ex
Date : 23 / 07 / 97
Comment : In Chloroform

NCL Tech

Fig. 14