[3+2] CYCLOADDITION OF NONSTABILIZED AZOMETHINE YLIDES: SYNTHESIS OF EPIBOXIDINE AND VARIOUS X-AZATRICYCLO[m.n.0.0 ^{a,b}]ALKANES

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BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"[3+2] Cycloaddition of Non-Stabilized Azomethine Ylides: Synthesis of Epiboxidine and Various X-Azatricyclo[m.n.0.0^{a,b}]Alkanes"*** *submitted by Mr. Akhila Kumar Sahoo was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources has been duly acknowledged in the thesis.*

Date: April 16, 2001

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DECLARATION

I hereby declare that the thesis entitled ***"[3+2] Cycloaddition of Non-Stabilized Azomethine Ylides: Synthesis of Epiboxidine and Various X-Azatricyclo[m.n.0.0$^{a,\ b}$]Alkanes"*** *submitted for Ph. D. degree to the University of Pune 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.*

Akhila Ku. Sahoo.

(AKHILA KUMAR SAHOO)

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Akhila Kumar Sahoo

TO

MY BELOVED PARENTS

AND

ALMIGHTY

CONTENTS

ABBREVIATIONS

Ac	acetyl
Ar	aryl
aq	aqueous
Bn	benzyl
bp	boiling point
Bu	butyl
t-Bu	*tert*-butyl
n-BuLi	n-butyllithium
s-BuLi	s-butyllithium
$(Boc)_2O$	di-*tert*-butyldicarbonate
t-Boc	*tert*-butyloxycarbonyl
CBZ	benzyloxycarbonyl
CH_3CN	acetonitrile
$CHCl_3$	chloroform
DCM	dichloromethane
DMF	N,N-dimethyl formamide
Et	ethyl
Et_3N	triethyl amine
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
h	hour
IR	infrared
K_2CO_3	potassium carbonate
KOH	potassium hydroxide
LDA	lithium diisopropylamide

LAH	lithium aluminium hydride
m	molar
MeOH	methanol
mL	millilitre
mmol	millimole
mp	melting point
$NaBH_4$	sodium borohydride
$NaBH_3CN$	sodium cyanoborohydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate
rt	room temperature
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilane
TMSCl	chlorotrimethylsilane

Abstract

[3+2] Cycloaddition of NonStabilized Azomethine Ylides: Synthesis of Epiboxidine and Various X-Azatricyclo[m.n.0.0$^{a,\ b}$]Alkanes

Chapter I

Introduction

This chapter presents a concise reports from literature on the synthesis of biologically relevant molecules possessing 7-azabicyclo[2.2.1]heptane skeleton. The synthesis of epibatidine, a potent nicotinic acetylcholine receptor, by the [3+2] cycloaddition reaction of cyclic non-stabilized azomethine ylide with appropriate dipolarophile is highlighted.

Chapter II

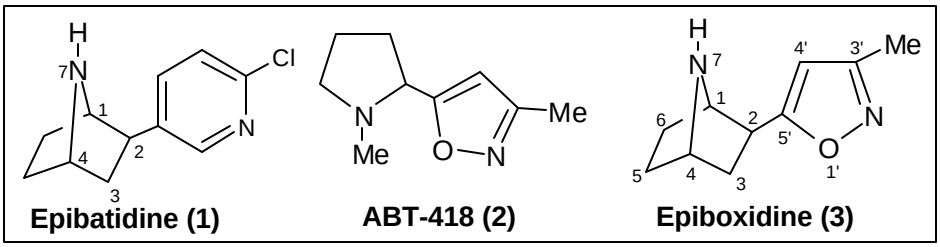
Synthesis of Epiboxidine

This chapter describes the synthesis of epiboxidine {exo-2-(3-methyl-5-isoxazolyl)-7-azabicyclo[2.2.1]heptane} as a synthetic analog of the alkaloid epibatidine. Biological and pharmacological studies exhibited epibatidine to be an extremely potent agonist of the acetylcholine receptor with antinociceptive activity. However, due to high toxicity of epibatidine (causing death in mice at 10 μL/Kg scale), the development of a pharmacophore related to the structure of **1,** exhibiting better ratios of pharmacological to toxicological activity was considered of great interest.

In this context, Badio *et al.* [*Eur. J. Pharmacol.* 1997, 321, 189.] designed a pharmacophore by combining the structural features of the known nicotinic receptor antagonist ABT-418 (**2**) and **1** and named it as epiboxidine (**3)** (Fig. 1). Epiboxidine was shown to be a potent nicotinic receptor agonist, proved to be equipotent at the ganglionic type receptor in PC12 cells and about 5-fold less potent in TE671 cells than epibatidine. In hot-plate antinociceptive assay with mice, **3** showed 10-fold less potency with 20-fold less

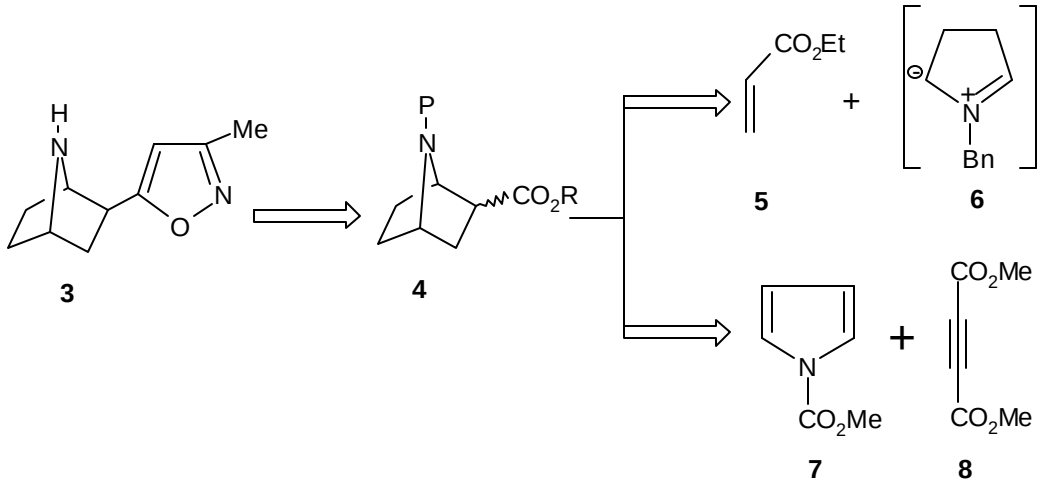
toxicity than **1**. Owing to the promising pharmacological properties, epiboxidine drew a great deal of attention in context of its synthetic and biological studies.

Fig. 1



We opted two protocols either by employing [3+2] cycloaddition approach or by [4+2] cycloaddition approach towards the preparation of common precursor **4**, for the synthesis of epiboxidine as shown retrosynthetically in Scheme 1.

Scheme 1

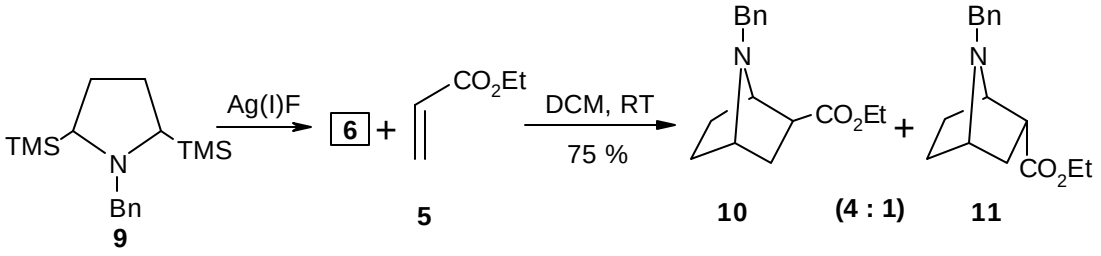


[3 + 2] Cycloaddition approach:

The *in situ* generation of **6** from the precursor **9** was achieved, utilizing the known protocol developed in our laboratory, by the sequential one electron oxidation of **9** employing Ag(I)F as one electron oxidant. The key [3+2] cycloaddition reaction of **9** with ethyl acrylate gave stereoisomeric cycloadducts **10** (60 %) and **11** (15 %) in 4 : 1 ratio

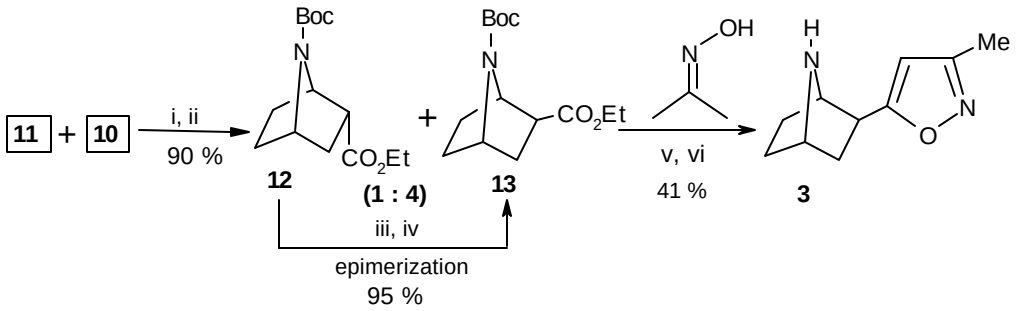
(Scheme- 2). The stereochemistry of cycloadducts **10** and **11** were determined by detailed ^{1}H NMR decoupling and ^{1}H COSY experiments.

Scheme 2



It was felt necessary to cleave the *N*-benzyl moiety from **10** and **11** prior to the construction of oxazolidine moiety to avoid the complication at the later stage of the synthesis of **3**. In this context, *N*-debenzylation of the cycloadducts were carried out by hydrogenation using 10 % $Pd(OH)_2$ at 40 psi of hydrogen. After Boc protection of crude amine, the undesired *endo* isomer **12** was epimerized quantitatively to **13** by treating with K_2CO_3 in MeOH at 80 ^oC. The carboethoxy moiety of **13**, was transformed to 2-methyloxazolidine by treating with the dianion of acetone oxime at 0 ^oC, followed by reacting the mixture with 11 M HCl at 80 ^oC to afford product **3** in 41 % yield (Scheme- 3). Compound **3** was confirmed as epiboxidine by ^{1}H and ^{13}C NMR and mass spectral analysis and was found to be in complete agreement with the data reported by Badio *et al*. [*Eur. J. Pharmacol*. 1997, 321, 189.].

Scheme 3

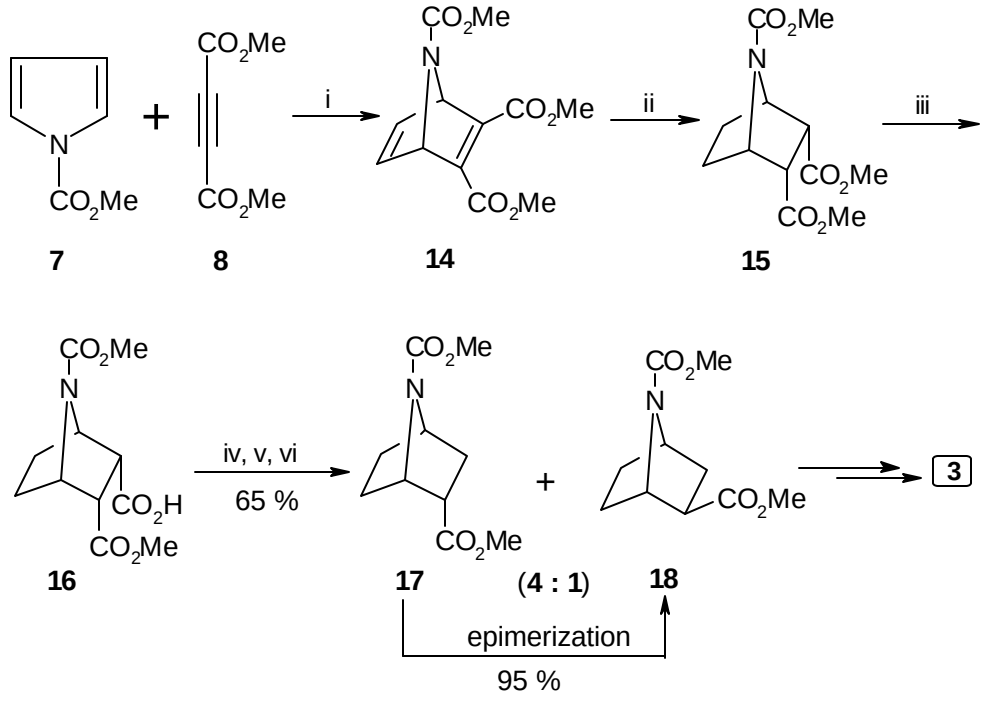


Reagents and conditions: *i) 10 % $Pd(OH)_2/H_2$, 50 psi; ii) $(Boc)_2O$, THF, TEA, rt; iii) K_2CO_3, MeOH, 80 ^oC, 1 h; iv) $SOCl_2$, EtOH, rt, 3 h; v) n-BuLi (2 eq.), THF, 0 ^oC; vi) 11M HCl, 80 ^oC, 4 h.*

[4 + 2] Cycloaddition Strategy:

The azanorbornadiene **14** was obtained by the [4+2]-cycloaddition of *N*-carbomethoxy pyrrole (**7**) with dimethyl acetylene dicarboxylate (**8**) in DCM in the presence of $AlCl_3$. Compound **14** was hydrogenated using 10 % Pd/C at 45 psi to afford **15.** The hydrolysis of **15** gave **16** in 90 % yield. Reductive radical monodecarboxylation of compound **16** was carried out by following Barton's procedure [*Tetrahedron*. 1985, 41, 3901] *via* the pyrrolysis of the corresponding thiohydroximate ester in presence of radical scavenger *tert*-butyl mercaptan, which gave stereoisomeric products **17** (52 %) and **18** (13 %) in 4 : 1 ratio (Scheme - 4).

Scheme 4

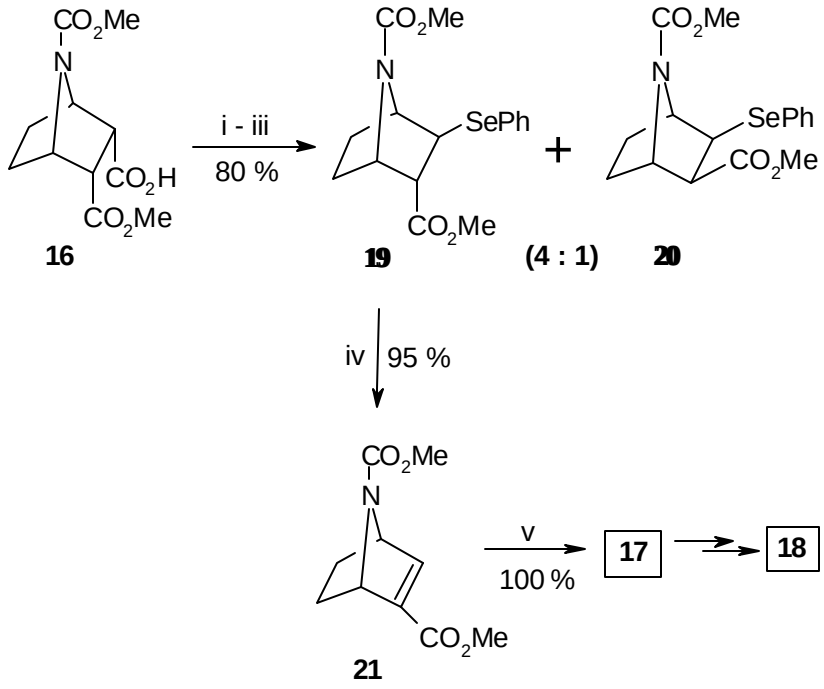


Reagents and conditions: *i) $AlCl_3$, DCM, 40 ^oC, 1 h, 90 %; ii) 10 % Pd/C, H_2, 40 psi, 6 h, 95 %; iii) LiOH (1 eq.), MeOH/H_2O (3:1), rt, 3 h, 90 %; iv) $(COCl)_2$, DCM, rt, 2 h; v) 2-Mercaptopyridine-N-Oxide, PhH, TEA, rt, 6 h; vi) PhH, t-BuSH, D, rt, 4 h.*

Although, we could synthesize **18**, the moderate yield encountered in the reductive radical decarboxylation step using *t*-BuSH as radical trap, encouraged us the use of

PhSeSePh as a better and efficient radical trapping agent. Thus, the photolysis of thiohydroximate ester in the presence of PhSeSePh gave selenylated products **19** and **20** in a 4 : 1 ratio in 80 % yield. Compound **19** was deselenylated by the reaction of H_2O_2 and the resultant product upon hydrogenation gave **17** exclusively. Epimerization of **17** gave key precursor **18** as depicted in Scheme- 5.

Scheme 5



Reagents and conditions: *i) $(COCl)_2$, DCM, rt, 2 h; ii) 2-Mercaptopyridine-N-Oxide, TEA, rt, 6 h; iii) PhH, hν, PhSeSePh, 4 h; iv) H_2O_2, DCM, 0 °c; v) H_2, Pd/C, MeOH, 40 psi.*

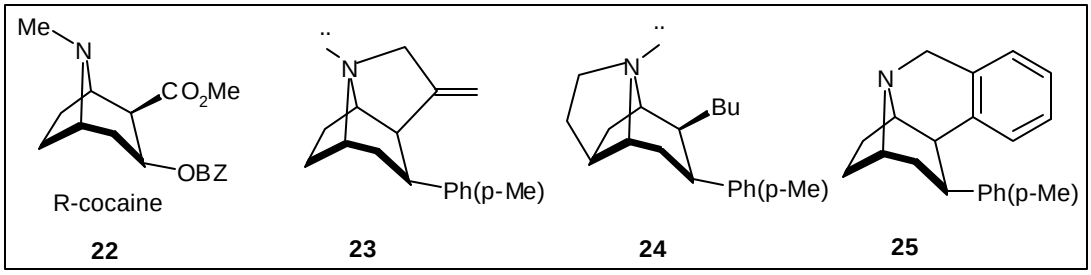
Based upon the results, it was concluded that [3+2] cycloaddition approach for the synthesis of **3** was shorter and high yielding in comparison with the related [4+2] cycloaddition strategy.

Chapter III

Construction of X-azatricyclo[m.n.0.0^{a,b}]alkanes by Intramolecular Cycloaddition of Cyclic Azomethine Ylides

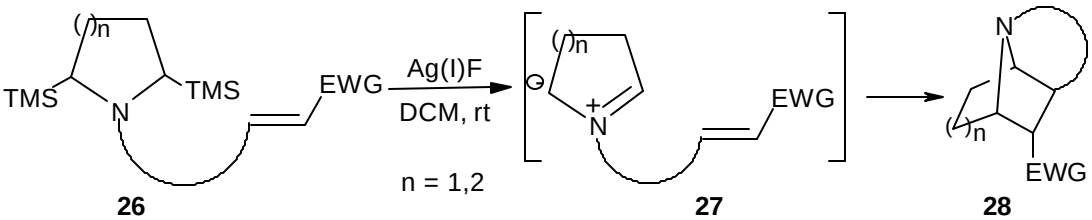
Chapter-3 deals with the application of [3+2] cycloaddition of cyclic non-stabilized azomethine ylides towards the construction of various new structural entities related to X-azatricyclo[m.n.0.0 ^{a,b}]alkanes through intramolecular cycloadditions.

Fig. 2



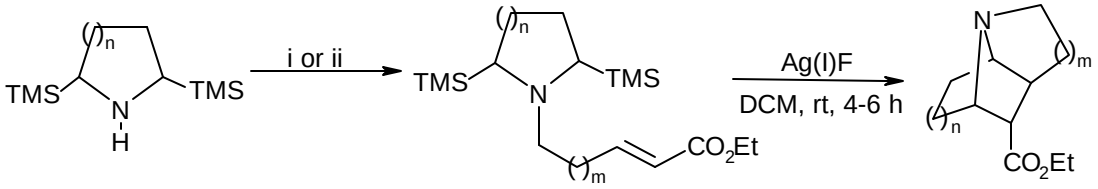
Recently Kozikowski *et al.* [*J. Am. Chem. Soc.* 1998, 120, 9072] reported the synthesis of a series of rigid azatricyclo cocaine analogues (Fig. 2). It was observed that these azatricyclo cocaine analogues showed high binding affinity at the dopamine transporter with about 2.5 to 104 fold greater potency than cocaine, resulting tremendous implications for the design of such structures for treatment of wide range of neurological disorders. We were encouraged with these observations and therefore, began to construct the structural entities related to skeleton **28** through the strategy as shown in Scheme - 6.

Scheme 6



The precursors **30a** and **30b** were prepared by refluxing a mixture of 2,5-di(trimethylsilyl)pyrrolidine (**29a)** with 6-iodo-(E)-2-hexenoate (**32a**) and 7-iodo-(E)-2-heptenoate (**32b**), respectively, with K_2CO_3 in dry CH_3CN. Similarly, the substrates **30c** and **30d** were synthesized by the reductive amination of 6-oxo-(E)-2-hexenoate (**33a**) and 7-oxo-(E)-2-heptenoate (**33b**), respectively, with 2,6-di(trimethylsilyl)piperidine (**29b**). Intramolecular [3 + 2]-cycloaddition reaction of these precursors were carried out in dry DCM in the presence of Ag(I)F at room temperature (Scheme 7). ^{1}H NMR, ^{13}C NMR and mass spectral data characterized the cycloadducts and their stereochemistries were confirmed by ^{1}H decoupling and ^{1}H COSY experiments.

Scheme 7



29a n = 1
29b n = 2

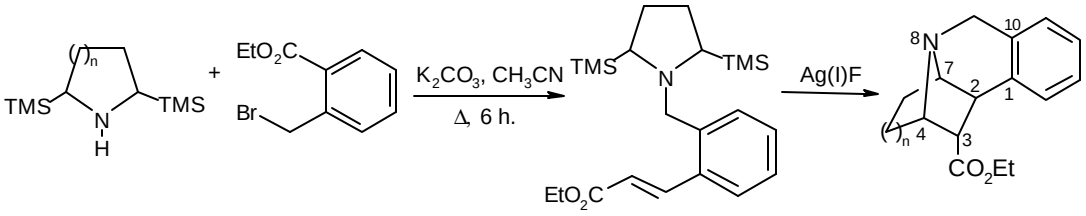
30a n = 1, m = 2 65 %
30b n = 1, m = 3 67 %
30c n = 2, m = 2 73 %
30d n = 2, m = 3 75 %

31a 61 %
31b 41 %
31c 69 %
31d 64 %

i) $ICH_2(CH_2)_mCH{=}CHCO_2Et$, (**32**), K_2CO_3, CH_3CN, 80 ^{o}C, 24-30 h.
ii) $OHC(CH_2)_mCH{=}CHCO_2Et$, (**33**), ethanol, $NaBH_3CN$, rt, 6-8 h.

In order to synthesize more rigid structures related to skeleton **28**, cycloaddition of **35a-b,** synthesized by refluxing **29** with **34** in acetonitrile in the presence of K_2CO_3, were studied. Reaction of **35** with Ag(I)F gave cycloadducts **36a-b** in 73-75 % yield (Scheme 8). ^{1}HNMR, ^{13}CNMR and mass spectral data characterized these cycloadducts and stereochemical assignments were established by ^{1}H COSY experiment.

Scheme 8



29a n = 1
29b n = 2

34

35a 81 %
35b 84 %

36a 73 %
36b 75 %

In summary a number of polycyclic azatricyclo[m.n.0.0 ^{a,b}]alkanes are synthesized by employing intramolecular [3+2]-dipolar cycloaddition of nonstabilized cyclic azomethine ylides with a hope that some of these structures would be of interest in natural product synthesis and medicinal chemistry.

1. Introduction

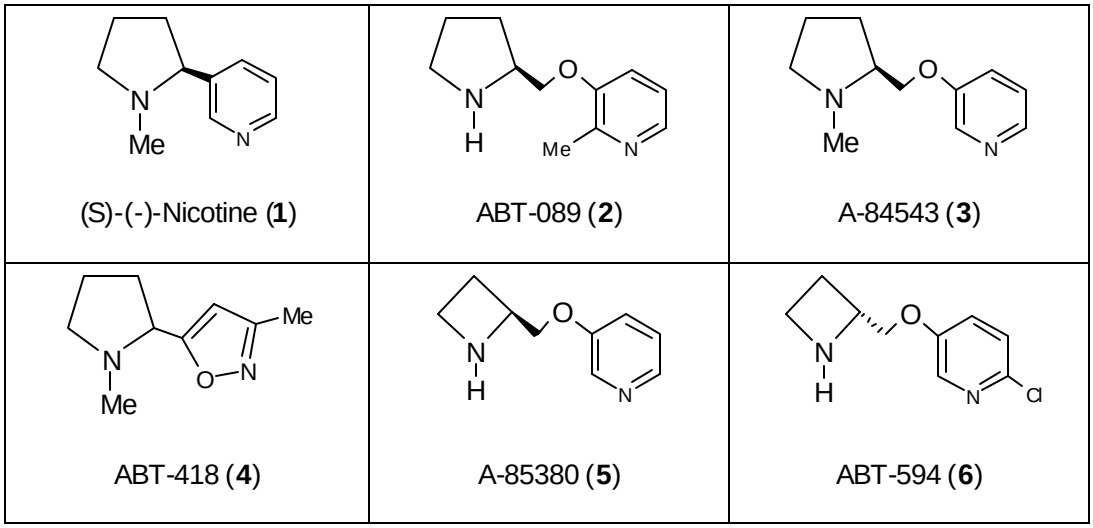
The sensation of pain is at one and the same time the salvation and bane of all sentient living organisms. The remedy to relieve pain has, therefore, figured prominently in many mythologies as one of mankind's aspirations. Towards fifth century B. C., Hippocrates used a bitter powder obtained from willow bark to relieve aches and pains and also to reduce fever, which is now referred to as aspirin. It has recently become recognized that the pain that accompanies inflammation and related conditions is actually triggered by the local synthesis of high levels of prostaglandins. Cyclooxygenase inhibitors such as aspirin and other nonsteroid anti-inflammatory agents have been used for the treatment of mild to moderate pain associated with elevated prostaglandin synthesis. Opium, the crude dried sap of the immature fruit of the poppy, *Papaver somniferum*, had some folkloric use as an analgesic, sedative and euphoriant. The major alkaloid contained in opium, morphine is identified as one of the extremely effective analgesic agent and is capable of relieving pain *e.g.,* traumatic pain, chronic pain of cancer, obstetrical pain and post-operative pain. Despite the broad spectrum analgesic action of opioids, their clinical use is limited by side effects such as respiratory depression, induction of constipation and its propensity to cause physical addiction. In 1932, scientists first realized the possibility of blocking pain by targeting the acetylcholine receptors. At first, nicotine was found to bind to one variant receptor dampening the pain but causes serious side effects such as lung cancer and heart diseases.

Nicotinic acetylcholine receptors are a group of ion channel receptors[1] that play an important role in many biological processes related not only with the pain but also with a number of nervous system disorders such as Alzheimer's and Parkinson's[2] diseases, attention deficit/hyperactivity disorder,[3] Tourette's syndrome,[4] and depression.[5] Over the years, considerable efforts have been directed towards the identification and characterization of ligands for nicotinic acetylcholine receptors (nAChRs). Nicotine (**1**) has been known for a longtime, as an effective antinociceptive agent to nAChRs but without

significant specific binding affinity.[6] Although, several promising tracers for nAChRs have been developed, none have been found diagnostic for human objectives. Therefore, an intense current interest prevails in the search for potent nAChR ligands with a high binding selectivity with central nervous system (CNS) receptors.

The research activities in this area has led to the development of a novel series of compounds possessing pyridine substituents attached either to a pyrrolidine or to an azetidine ring and some of these derivatives have shown subnanomolar affinity for central neuronal nicotinic acetylcholine receptors (nAChRs).[7] For example, ABT-089 (**2**), an orally bioavailable pyrrolidine nAChR ligand has been shown to possess neuroprotective and cognition-enhancing properties.[8] Another pyrrolidine based ligand, A-84543 (**3**), showed moderate specific binding to nAChRs *in vivo* in mice.[9] Recently, a novel cholinergic channel activator ABT-418 (**4**) have been shown to be very potent and selective ligand for neuronal nAChR.[10] A-85380 (**5**)[7] and ABT-594 (**6**),[11] the azetidine based ligands, have shown exceptionally high affinity for central nAChRs.

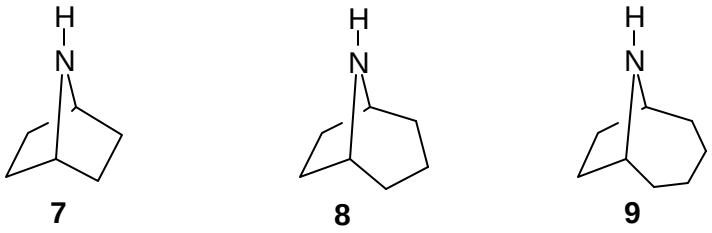
Fig. 1



Apart from pyridine based nAChR ligands, compounds possessing constrained X-azabicyclo[m.2.1]alkane framework as a basic architectural feature (**7**, **8**, and **9**) (Fig. 2)

are also known for a longtime to represent an important class of ligands for the nicotinic acetylcholine receptors.[12]

Fig. 2

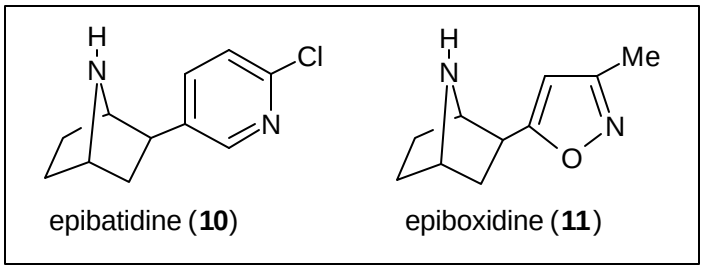


7 **8** **9**

Since, the subject of this thesis concerns only with the synthesis of compounds possessing 7-azabicyclo[2.2.1]heptane skeleton, we would restrict our introduction in this chapter to the compounds related to the 7-azabicyclo[2.2.1]heptane skeletons only.

Recently, the isolation of new alkaloid epibatidine (**10**) {*exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane} by Daly *et al.*,[13] found in trace amounts from the skin extracts of an Ecuadorian poison frog, *Epipedobates tricolor*, has generated considerable interest in the 7-azanorbornane framework.[14,15] This molecule has been shown to exhibit non-opioid analgesic activity (about 200-500 times more potent than morphine).[16-19] Recent studies have also shown that **10** is an extremely potent naturally occurring nicotinic acetylcholine receptor known to date.[20-23] Another synthetic analogue of **10**, epiboxidine (**11**),[24] having 7-azabicyclo[2.2.1]heptane framework with methylisoxazole moiety attached at 2β-position, showed significant binding affinity in comparison to **10**.

Fig. 3

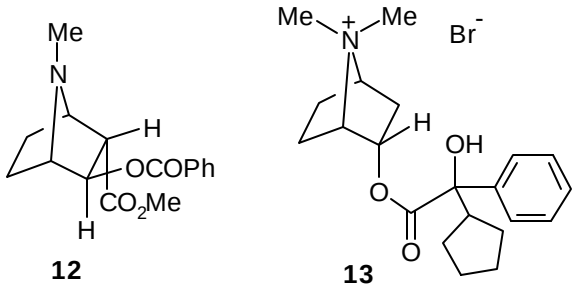


epibatidine (**10**) epiboxidine (**11**)

Apart from the epibatidine, several other molecules bearing 7-azabicyclo[2.2.1]heptane framework have also been synthesized and are known to possess some other biological activities.

For example, the first 7-azabicyclo[2.2.1]heptane derivative such as 2-*exo*-(benzyloxy)-3-*endo*-carbomethoxy-7-methyl-7-azabicyclo[2.2.1]heptane (**12**, *pseudo*-norcocaine) was shown to have local anesthetics activity.[25] The *endo*-2-(2-cyclopentyl-2-hydroxy-2-phenyl)acetoxy-7-methyl-7-azabicyclo[2.2.1]heptane methobromide (**13**) (Fig. 4) was found to be a potent long acting anticholinergic bronchodilator agent.[26]

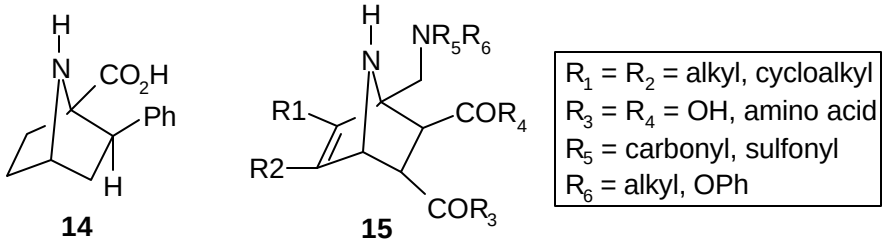
Fig. 4



12 **13**

Recently, 2-*exo*-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid (**14**) (Fig. 5), a conformationally constrained proline analogue, was employed for the synthesis of structurally defined peptides.[27] These conformationally constrained peptides were utilized for the generation of bioactive peptidomimetics. They have also been shown to possess more protease resistance as well as increased selectivity towards various neurotransmitter and neuromodulator receptor activity.[27] The 1-(aminomethyl)-7-azabicyclo[2.2.1]heptane-2,3-dicarboxylates (**15**) (Fig. 5) were reported to act as a neoplasm inhibitors.[28]

Fig. 5



14 **15**

The presence of 2β-(6-chloropyridinyl) group to the rigid carbon skeleton of 7-azabicyclo[2.2.1]heptane ring system in naturally occurring epibatidine (**10**) has been found to bring dramatic change in binding affinity with nAChRs.[21-23] However, the high toxicity associated with it prevents its use in therapeutic development. The synthetic analogue epiboxidine (**11**) was developed and has been found to be a potent nAChR agonist.[24] The biological and pharmacological studies of epiboxidine have shown that it possesses better ratio of pharmacological to toxicological activity than epibatidine.

In view of the growing interest of these class of compounds in general and epiboxidine (**11**) in particular, we have undertaken the synthesis of these synthetically challenging targets. The major hurdle in the synthesis of this class of molecules has been the stereoselective construction of 7-azabicyclo[2.2.1]heptane skeleton. The quest for the development of new methodology for the construction of this basic skeleton has resulted several admirable approaches. However, before discussing our own approach in this field, it would be pertinent to summarize some of the approaches reported in literature on the construction of 7-azabicyclo[2.2.1]heptane skeleton.

2. Strategies towards the construction of basic 7-azabicyclo[2.2.1]heptane skeleton

Synthesis of the 7-azabicyclo[2.2.1]heptane system has been the subject of numerous synthetic studies. Recently, Chen and Trudell[29] and Szantay *et al.*[30] have published interesting review articles summarizing the methodologies related to the construction of structures related to **7**. The key reaction utilized towards the construction of this framework can be classified into the following categories.

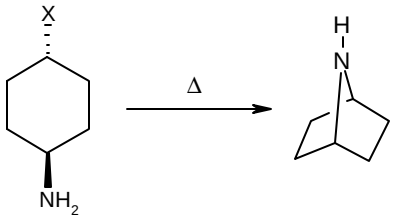
- Transannular nucleophilic intramolecular cyclization of cyclohexylamine derivatives.
- Reduction of 7-azabicyclo[2.2.1]hept-2,5-dienes and 7-azabicyclo-[2.2.1]hept-2-enes.

- Intramolecular cyclization of substituted proline derivatives.
- Miscellaneous reactions.
- [3+2] cycloaddition reactions of azomethine ylide (AMY).

2.1. Transannular nucleophilic intramolecular cyclization of cyclohexylamine derivatives:

Generally, there are three different types of cyclohexylamine derivatives known to undergo transannular nucleophilic intramolecular cyclization reactions to give 7-azabicyclo[2.2.1]heptane skeleton. The most fundamental approach utilized for the synthesis of basic skeleton **7** was reported by the intramolecular cyclization of *trans*-4-substituted cyclohexylamine derivative **16** *via* SN_2 displacement as shown in Scheme 1. At first Von Braun and Schwarz in 1929 reported intramolecular cyclization of *trans*-4-bromocyclohexylamine derivative **16** under hot alkaline condition to afford **7** in 1 % overall yield.[31] Later, Fraser and Swingle[32] in 1970 improved the overall yield of **7** to 18-36 % by using tosylate derivative of **16** (Scheme 1). The yield of **7** was further improved to 44 % by the cyclodehydration of *trans*-4-hydroxycyclohexylamine with diethoxy triphenylphosphorane.[33]

Scheme 1



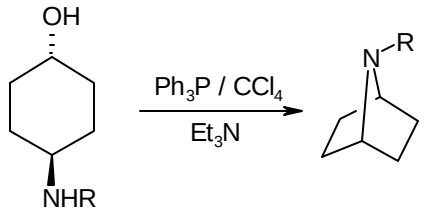
16 **7**

X = Leaving Group
-Br / -OTs / -OMs

Recently, Hassner and Belostotskii[34] have reported the construction of 7-alkyl-7-azabicyclo[2.2.1]heptane skeleton **18** in 42-70 % yield by *in situ* activation and

cyclization of *trans*-4-alkylaminocyclohexanols (**17**) with triphenylphosphine-carbon tetrachloride in the presence of triethylamine (Scheme 2).

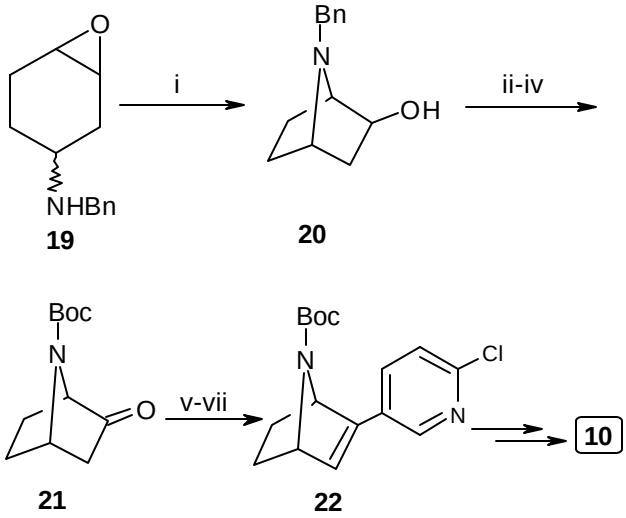
Scheme 2



17 R = Bn, i-Pr, t-Bu **18**

Intramolecular epoxide ring opening-cyclization strategy of 4-amino-1,2-epoxycyclohexane (**19**) is another strategy that has been utilized for the construction of 7-benzyl-7-azabicyclo[2.2.1]heptane-2-ol (**20**) derivative.[35] Fletcher *et al.*[36] have extended the same strategy for the synthesis of epibatidine (**10**) as shown in Scheme 3. They have also accomplished the synthesis of (+) and (-) enantiomers of **20** by resolution *via* its *R*-(-)-Moshers esters.

Scheme 3



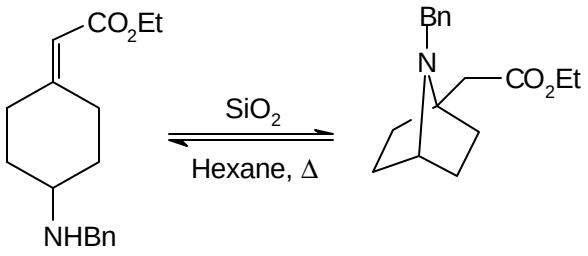
19 **20**

21 **22**

Reagents and conditions: *i) 1-Methyl-2-pyrrolidinone, 180 ^{o}C, 16 h; ii) Pd(OH)$_2$, EtOH, HCl, 40 ^{o}C, H$_2$ (40 psi); iii) (Boc)$_2$O, dioxane, 1 N NaOH, 18 h, 79 %; iv) DMSO, (COCl)$_2$, DCM, -70 ^{o}C, TEA, 89 %; v) 2-Chloro-5-iodopyridine, n-BuLi, Et$_2$O/THF, -70 ^{o}C; vi) KH, THF, 0 ^{o}C, CS$_2$, MeI; vii) Toluene, 110 ^{o}C, 24 h.*

Recently, 7-benzyl-7-azabicyclo[2.2.1]heptane-1-acetic acid ethyl ester (**24**) has been prepared in 61 % yield by Johnson[37] *via* silica gel catalyzed transannular amine Michael addition reaction from the unsaturated ester of **23** (Scheme 4).

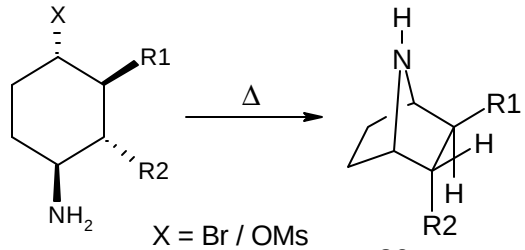
Scheme 4



23 **24**

An important stereochemical feature of such cyclizations has also been established during the intramolecular 1,4-transannular ring-closure reactions of cyclohexylamine derivatives of type **25** and it has been found that the substituents *cis* to the amino group adopt an *exo* orientation in the resultant 7-azabicyclo[2.2.1]heptanes (**26**) while the *trans* group finds an *endo* orientation (Scheme 5). These observed stereochemical orientations have been utilized in the synthesis of epibatidine and other related compounds.

Scheme 5

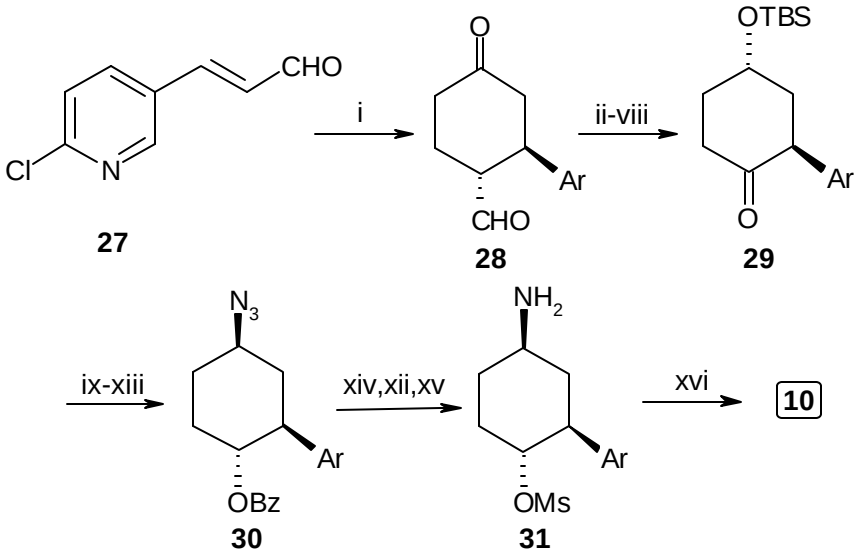


25 **26**

From above discussion, it is apparent that *trans*-4-substituted cyclohexylamine derivatives are most suitable precursor for the construction of 7-azabicyclo[2.2.1]heptane skeleton in general. Since, compounds of type **25** have mainly been used for the synthesis of epibatidine by many researchers, it would be relevant to highlight important approaches schematically for the preparation of **25**.

2.1.1. Broka's approach:[38]

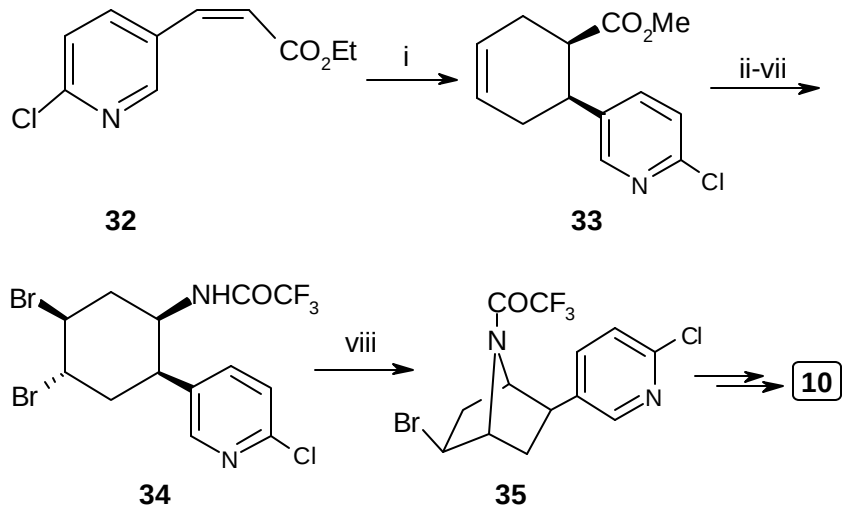
Scheme 6



Reagents and conditions: *i) 2-(Trimethylsilyloxy)-1,3-butadiene, 150 °C, 10 h; ii) L-Selectride (3eq.), -78 °C to 20 °C, iii) TsCl (1.1 eq.), pyr., 20 °C, 1 d; iv) PhSK, DMF/THF (1:1), 20 °C, 30 min.; v) TBDMSCl, imidazole, DMF, rt, 1 d; vi) mCPBA, DCM, rt, 15 min.; vii) Xylene, 200 °C, 2 h; 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, 45 min.; xiii) LiN_3, DMF, 55 °C, 12 h; xiv) 0.5 M NaOH in H_2O,/THF/MeOH (1:2:4), rt, 3.5 h; xv) $SnCl_2$, MeOH/THF (1:1), 20 °C, 1 h. xvi) $CHCl_3$, D, 4 d, (84 %).*

2.1.2. Corey's approach:[39]

Scheme 7

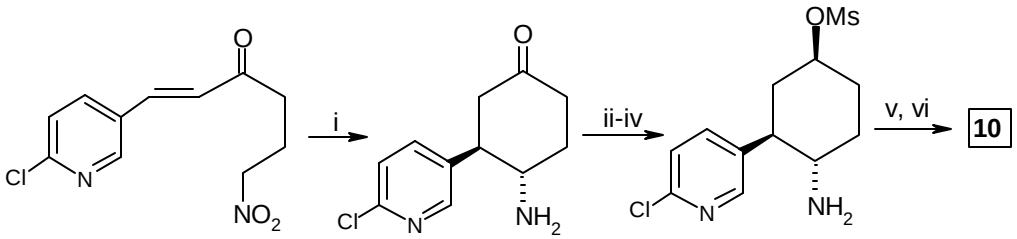


Reagents and conditions: *i) 1,3-Butadiene, toluene, 190 ^{o}C, 24 h; ii) LiOH, THF, rt, 5 h; iii) TEA, $(PhO)_2P(O)N_3$, toluene, 85 ^{o}C, 12 h; iv) $TMSCH_2CH_2OH$, 85 ^{o}C, 12 h; v) TBAF, THF, 55 ^{o}C, 4 h; vi) $(CF_3CO)_2O$, TEA, DCM, rt, 30 min.; vii) $Et_4N^+Br^-$ (10 eq.), Br_2, -78 ^{o}C, 30 min, DCM; viii) KO^{t}Bu, THF.*

The same group[39] has also resolved the *N*-(trifluroacetyl)epibatidine using chiral HPLC, for the synthesis of enantiomarically pure **10**.

2.1.3. Szantay's approach:[40]

Scheme 8

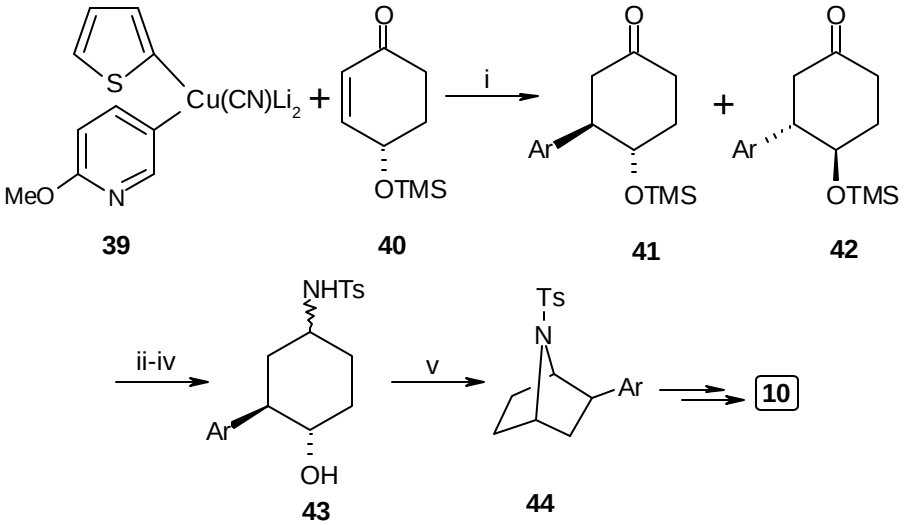


36 **37** **38**

Reagents and conditions: *i) KF/alumina (1.4 eq), THF, rt, 12 h, 59 %; ii) $NaBH_4$ (3 eq.), EtOH, 0 ^{o}C, 1.5 h, 67 %; iii) CH_3SO_2Cl (1.2 eq), DCM, pyr., rt, 12 h, 91 %; iv) $SnCl_2.2H_2O$ (1.4 eq), EtOH, reflux, 24 h, 80 %; v) Toluene, reflux, 24 h 46 %; vi) KO^{t}Bu (1 eq.), Bu^{t}OH, reflux, 30 h, 50 %.*

2.1.4. Sestanj's approach:[41]

Scheme 9

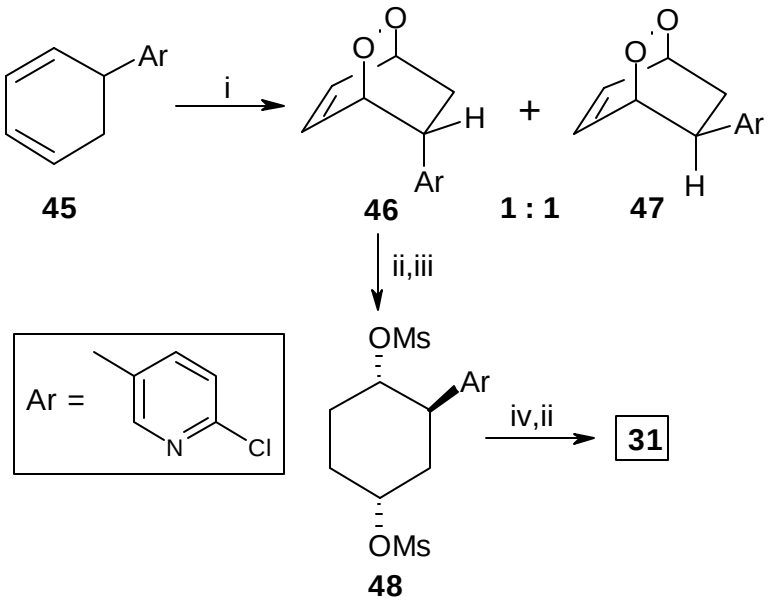


39 **40** **41** **42** **43** **44**

Reagents and conditions: *i) –35 ^{o}C to 20 ^{o}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.*

2.1.5. Ko's approach:[42]

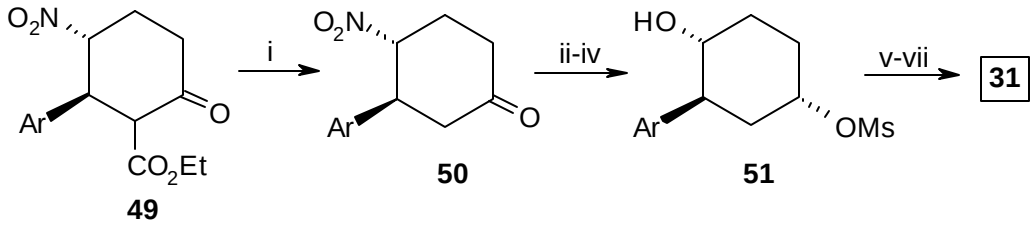
Scheme 10



Reagents and conditions: *i) Oxygen, 5,10,15,20-tetraphenyl-21H,23H-porphine, CCl_4, Hg lamp, rt, 80 %; ii) H_2, Rh/Al_2O_3, MeOH, rt, 70 %; iii) MsCl, TEA, dioxane, 0 ^oC, 93 %; iv) NaN_3, DMF, 60 ^oC; v) $CHCl_3$, 0.01 $mol.dm^{-1}$, 55 ^oC, 78 %.*

2.1.6. Albertini's approach:[43]

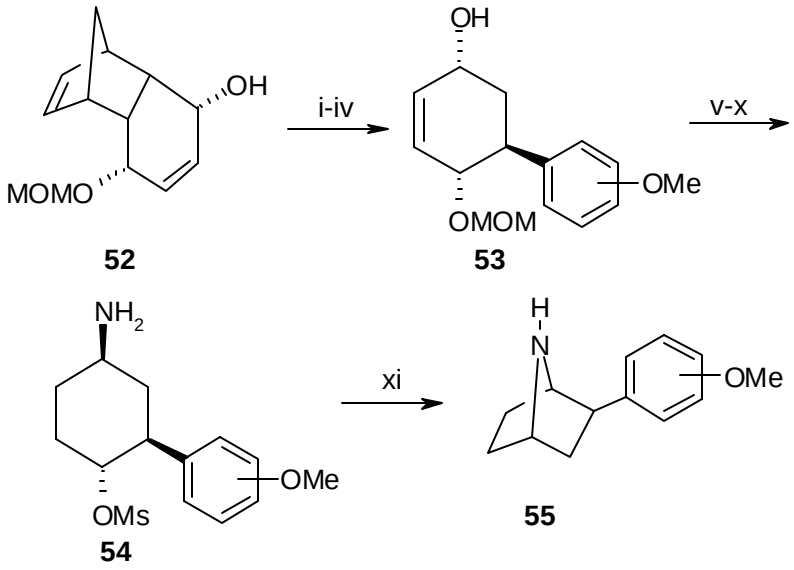
Scheme 11



Reagents and conditions: *i) DMSO, H_2O, LiCl, 48 %; ii) L-Selectride; iii) MsCl, TEA, 53 %; iv) MeONa, O_3, -78 ^oC, Me_2S, $NaBH_4$, 80 %; v) NaN_3, DMF; vi) MsCl, TEA, 63 % vii) $SnCl_2$, MeOH:THF, 1:1, rt.*

2.1.7. Hiroya's approach:[44]

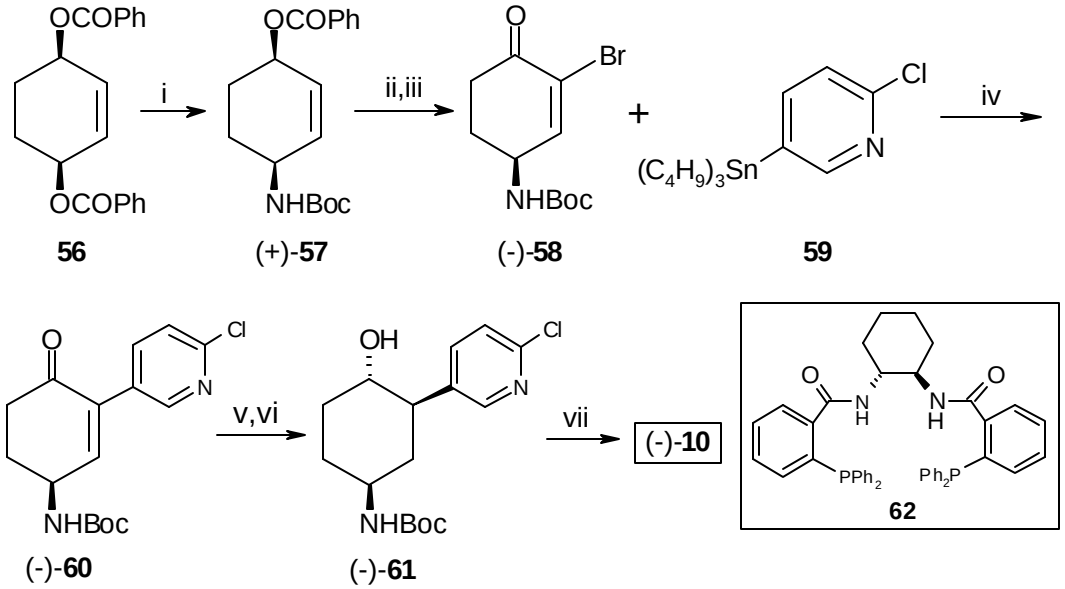
Scheme 12



Reagents and conditions: *i) PDC, DMF, rt, 84 %; ii) ArMgBr, CuBr.Me$_2$S, HMPA, THF, -78 ^{o}C; iii) NaBH$_4$, MeOH, -12 ^{o}C; iv) Diphenyl ether, reflux, 3 h; v) H$_2$, 10% Pd/C, EtOH, rt; vi) MsCl, TEA, DMAP, DCM, 0 ^{o}C, 1 h; vii) NaN$_3$, DMF, 60 ^{o}C, 12 h; viii) AcCl (cat), MeOH, rt, 12 h; ix) MsCl, TEA, DMAP (cat), DCM, 0 ^{o}C, 1 h; x) H$_2$, 10% Pd/C, EtOH, rt; xi) CHCl$_3$, reflux, 4 d.*

2.1.8. Trost's approach:[45]

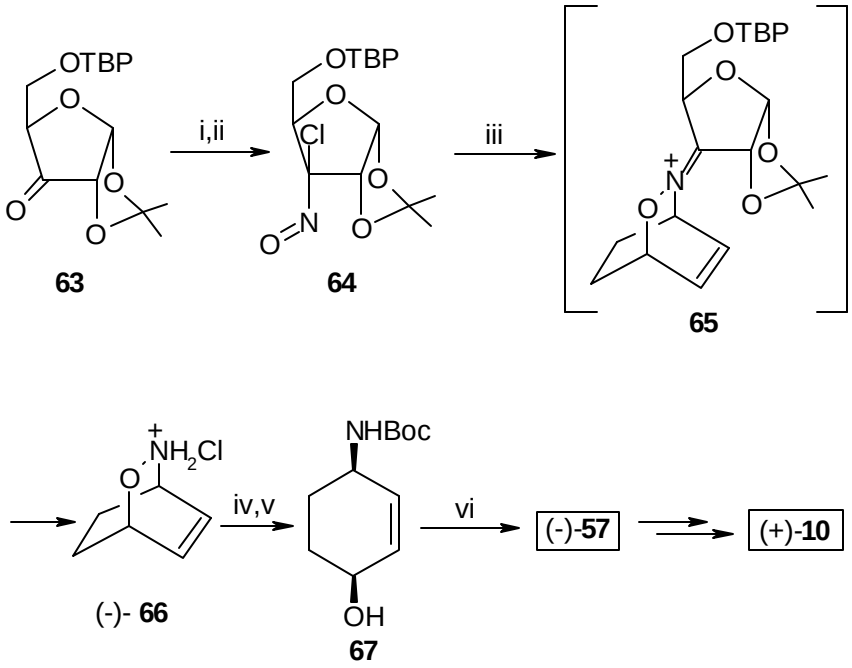
Scheme 13



Reagents and conditions: *i) a) 0.25 mol% [η^3-$C_3H_5PdCl]_2$, 0.75 mol%* ***62****, 1.2 equiv. $TMSN_3$, THF, 0 ^oC; b) PPh_3, 2:1 THF-H_2O, PPh_3 (1.2 eq.), rt, $(Boc)_2O$, TEA, 81 %; ii) K_2CO_3, MeOH, rt, then Dess-Martin periodinane, DCM, rt; iii) Br_2, TEA, DCM, 0 ^oC, 85 %; iv) 2.5 mol% $(dba)_3Pd.CHCl_3$, 15 mol% Ph_3As, THF, 55 ^oC; v) K-Selectride, THF, -78 ^oC to 0 ^oC, DBU, THF; vi) $NaBH_4$, MeOH, 0 ^oC, 70 %; vii) MsCl, TEA, DCM, 0 ^oC; TFA, H_2O, rt, MeCN, reflux, 45 %.*

2.1.9. Hall's approach:[46]

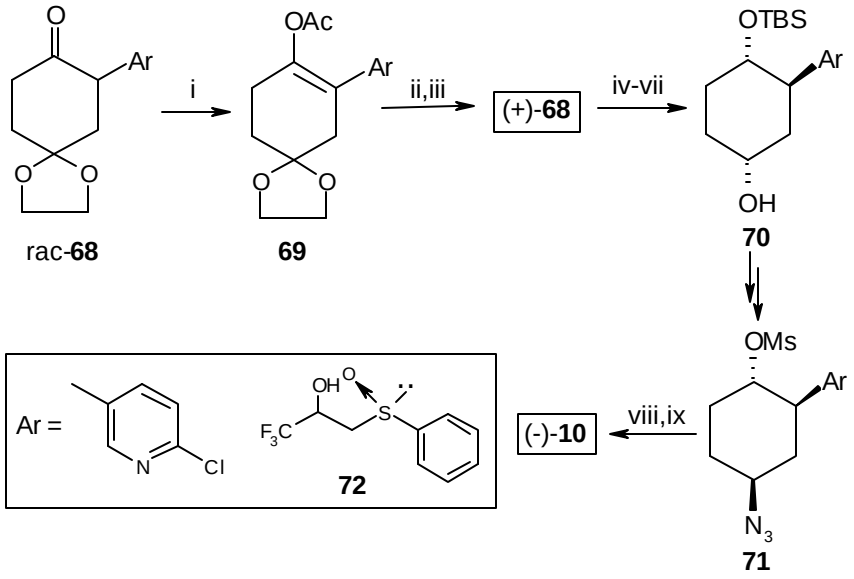
Scheme 14



Reagents and conditions: *i) $NH_2OH.HCl$, $NaHCO_3$, EtOH-H_2O; ii) ^tBuOCl, DCM; iii) cyclohexa-1,3-diene, $CHCl_3$-^{i}PrOH-H_2O (100:100:1), 0 ^oC; iv) Zn, AcOH; v) $(Boc)_2O$, Na_2CO_3, acetone-MeOH; vi) BzCl, DMAP, pyridine, DCM.*

2.1.10. Kosugi's approach:[47]

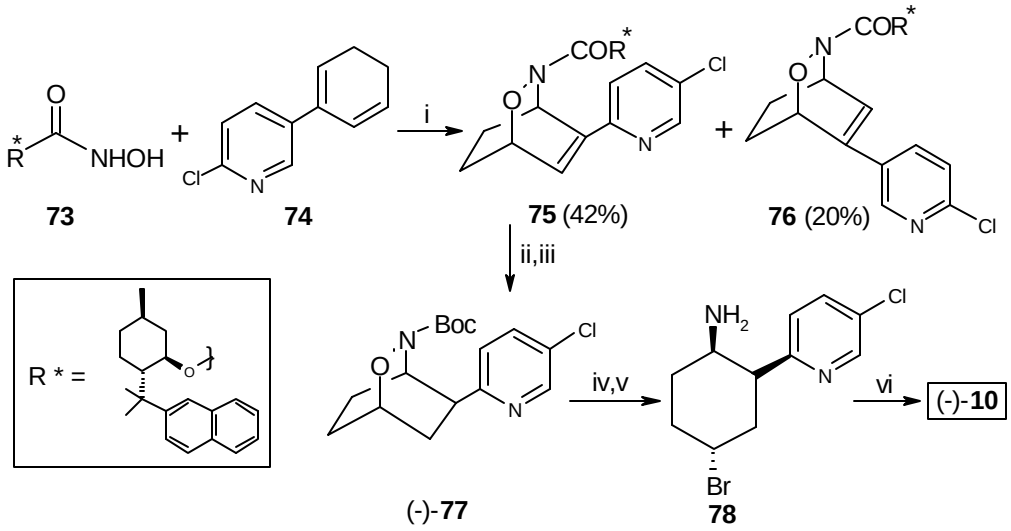
Scheme 15



Reagents and conditions: *i) ^{t}BuOK, Ac_2O, THF; ii) MeLi, (2 eq.), Et_2O, 0 ^{o}C, 15 min; iii)* ***72****, DCM, -90 ^{o}C to –60 ^{o}C; iv) $NaBH_4$, MeOH; v) 80 %aq. AcOH; vi) TBDMSCl, $^{i}Pr_2EtN$, DMF; vii) $LiB^{s}Bu_3H$, THF; viii) $SnCl_2 2H_2O$, MeOH-THF; ix) $CHCl_3$, reflux.*

2.1.11. Aoyagi's approach:[48]

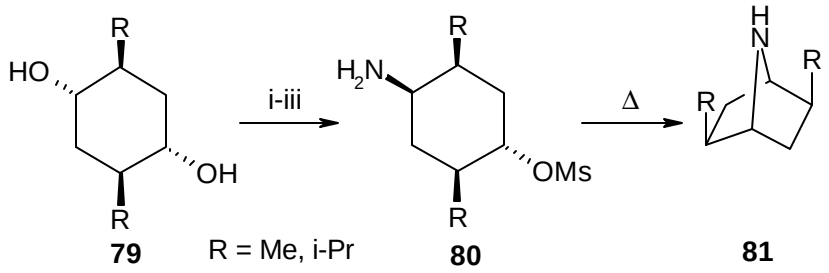
Scheme 16



Reagents and conditions: *i) $(COCl)_2$, DMSO, TEA, DCM, -78 ^{o}C; ii) H_2, PtO_2, dioxane, 81 %; iii) a) $LiNH_2BH_3$, THF; b) $(Boc)_2O$, Na_2CO_3, 58 %; iv) $Mo(CO)_6$, MeCN-H_2O, reflux, 85 %; v) a) PPh_3, CBr_4, MeCN; b) CF_3CO_2H, DCM, 40 %; vi) $CHCl_3$, reflux, 3 d, 97 %.*

2.1.12. Xiao's approach:[49]

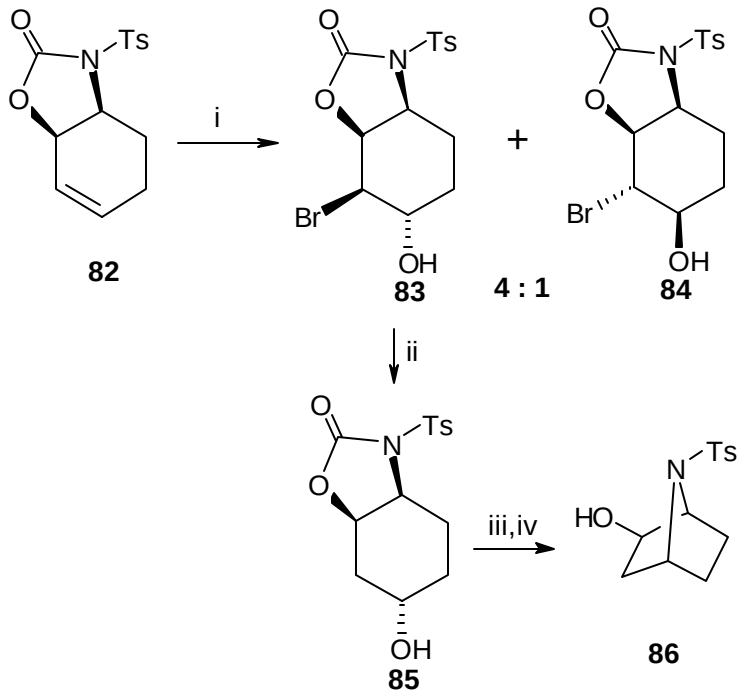
Scheme 17



Reagents and conditions: *i) TEA, MsCl, DCM, 0 ^{o}C; ii) NaN_3, DMF, 55 ^{o}C, 24 h; iii) H_2, Pd/C (5 %) in MeOH.*

2.1.13. Cabanal-Duvillard's approach:[50]

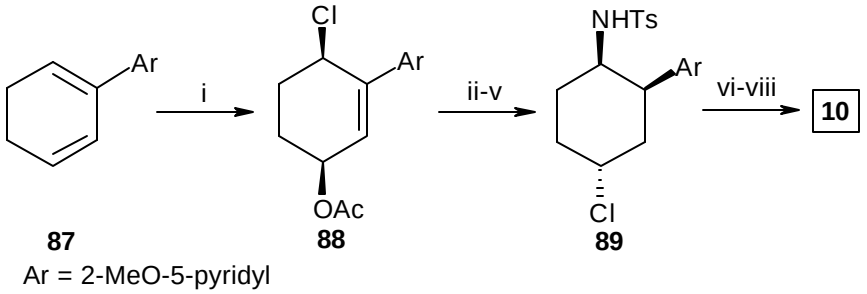
Scheme 18



Reagents and conditions: *i) Br_2 (2 eq.), DME/H_2, rt, 75 %; ii) AIBN, Bu_3SnH, 70 ^{o}C; iii) LiOH, MeOH, rt; iv) PPh_3, DEAD, THF, rt.*

2.1.14. Palmgren's approach:[51]

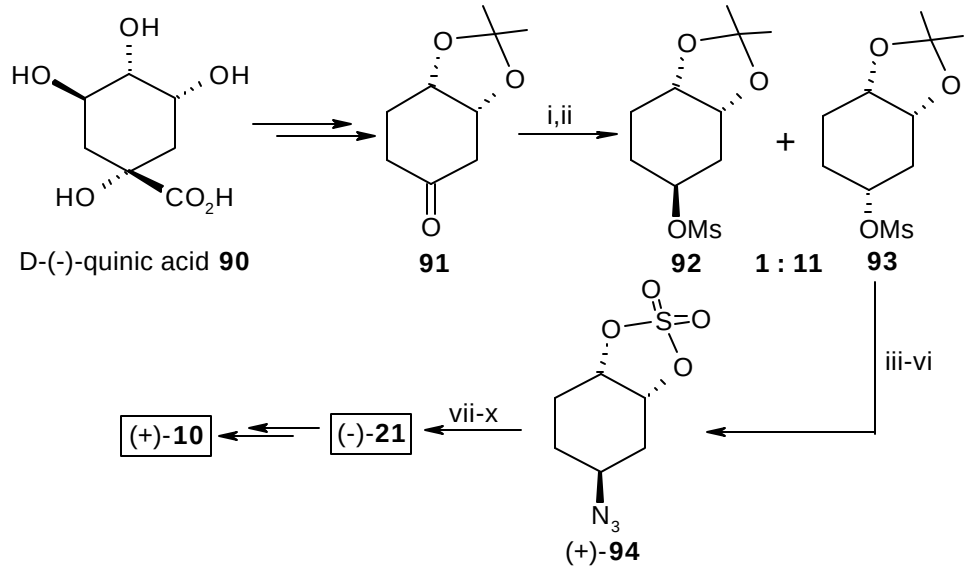
Scheme 19



Reagents and conditions: *i) $Pd(OAc)_2$, p-benzoquinone, LiCl, LiOAc, HOAc, acetone; ii) Pd(0), NaNHTs; iii) K_2CO_3; iv) PtO_2/H_2; v) $SOCl_2$; v) K_2CO_3; vi) K_2CO_3, MeOH; vii) Na, $C_{10}H_8$; viii) ref. 41.*

Albertini *et al.*[52] have reported an unified asymmetric route for the construction of optically pure 7-azabicyclo[2.2.1]heptane skeleton by employing regioselective intramolecular nucleophilic ring opening of the vicinal diol cyclic sulfate (+)-**94,** obtained from D-(-)-quinic acid (**90**) by following the steps as depicted in Scheme 20.

Scheme 20

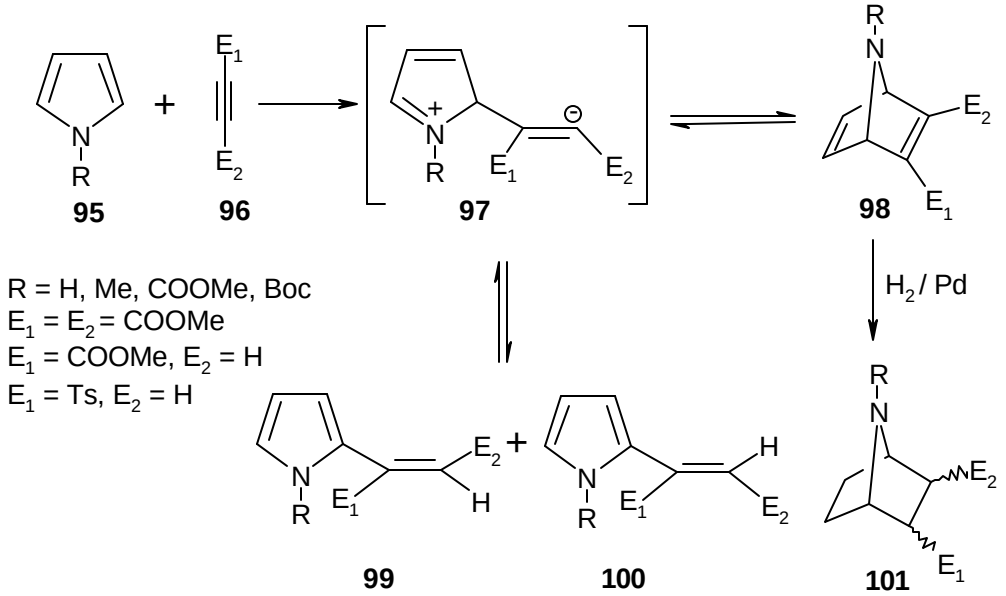


Reagents and conditions: *i) $NaBH_4$; ii) MsCl, TEA, 86 %; iii) NaN_3, DMF, 80 ^oC, 24 h, 81 %; iv) H_3O^+, 98 %; v) $SOCl_2$, TEA; vi) $NaIO_4$, $RuCl_3$ (cat.), CCl_4, MeCN, H_2O, 1 h, rt; vii) H_2, Pd/C, THF/H_2O, 30 psi, 2 h; viii) Conc. H_2SO_4 (cat.), H_2O, THF, 1 h, 90 ^oC then Na_2CO_3; ix) $(Boc)_2O$, DCM, 1 h, 25 ^oC; x) $(COCl)_2$, DMSO, TEA, -78 ^oC to 25 ^oC, 30 min.*

2.2. Reduction of 7-azabicyclo[2.2.1]hept-2,5-dienes and 7-azabicyclo-[2.2.1]-hept-2-enes:

The catalytic hydrogenation of the 7-azabicyclo[2.2.1]hept-2,5-dienes (**98**), obtained by the [4+2] cycloaddition reaction between pyrrole and dienophiles (olefins/acetylenic equivalents) have also been demonstrated to be the general method for the synthesis of 7-azabicyclo[2.2.1]heptane derivatives **101** (Scheme 21). Although, pyrrole (**95**, R = H) is a poor diene,[53] and it does not easily participate in cycloaddition reaction as such, but introduction of an electron withdrawing group (R = CO_2Me, Boc or SO_2Ph) at nitrogen atom is found to activate it towards [4+2] cycloaddition reaction with very reactive acetylenic dienophiles.[54,55,29]

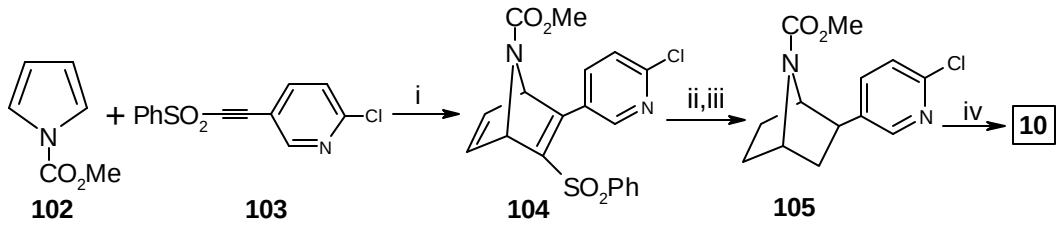
Scheme 21



The above protocol have been utilized by several workers for the synthesis of epibatidine and related 7-azabicyclo[2.2.1]heptane skeleton which are represented schematically as follows:

2.2.1. Huang's approach:[56]

Scheme 22

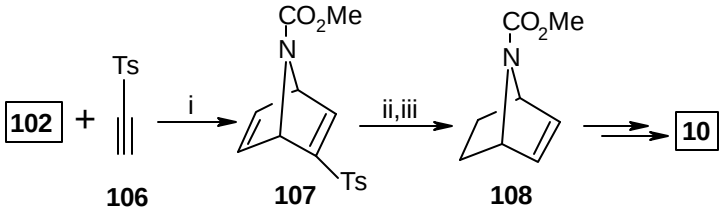


Reagents and conditions: *i) 80-85 ^{o}C, 24 h, (50-70 %); ii) 6 % Na/Hg, -20 ^{o}C to rt, 3 h (36-42 %); iii) H_2, 10 % Pd/C, 5 min, 92 %; iv) 33 % HBr/HOAc, 20 h.*

Later, Kotian and Carrole[57] have modified the same approach by using *N*-Boc group instead of *N*-CO_2Me moiety.

2.2.2. Clayton's approach:[58]

Scheme 23

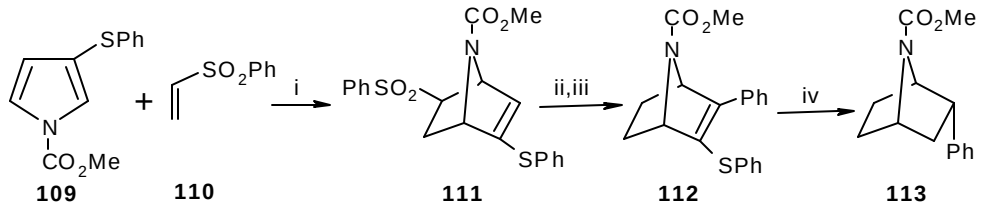


Reagents and conditions: *i) 80-85 ^{o}C, 24 h, 36 %; ii) H_2, Pd/C, rt, 99 %; iii) 6% Na/Hg, MeOH-THF, Na_2HPO_4, -78 ^{o}C to rt.*

The reductive removal of tosyl group from **107** has been modified by Otten *et al.*[59] to obtain **108** in better yield. The same strategy has been utilized later in the synthesis of various analogues of epibatidine.[60,61]

2.2.3. Aben's approach:[62]

Scheme 24

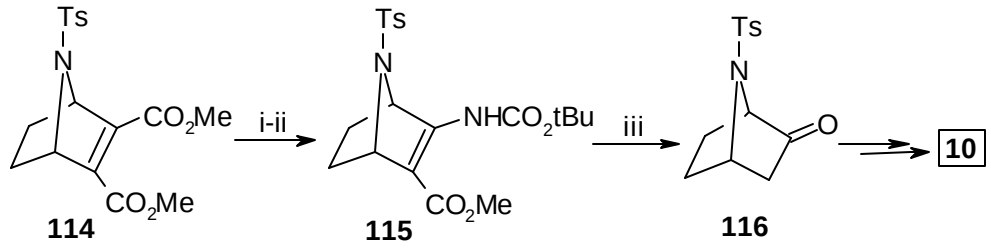


Reagents and conditions: *i) 12 Kbar; ii) 6% Na/Hg; iii) $Pd(OAc)_2$, PPh_3, PhBr, TMEDA; iv) Ra-Ni.*

Since, it was demonstrated by Fletcher *et al.*[36] that *N*-Boc-7-azabicyclo[2.2.1]heptane-2-one (**21**) is an attractive precursor for the synthesis of epibatidine, many research groups have developed different routes utilizing Diels-Alder reaction for the synthesis of **21**. All these approaches are summarized schematically as follows.

2.2.4. Okabe and Natsume approach:[63]

Scheme 25

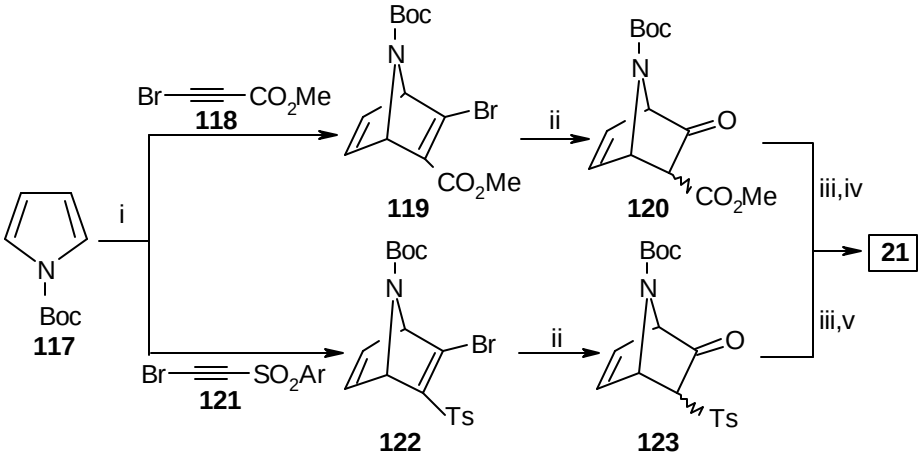


Reagents and conditions: *i) LiOH, DME:H_2O (2:1), 70 %; ii) DPPA, tBuOH, 75 %; iii) 2% HCl, dioxane-H_2O, 68 %.*

.

2.2.5. Zhang and Trudell's approach:[64,65]

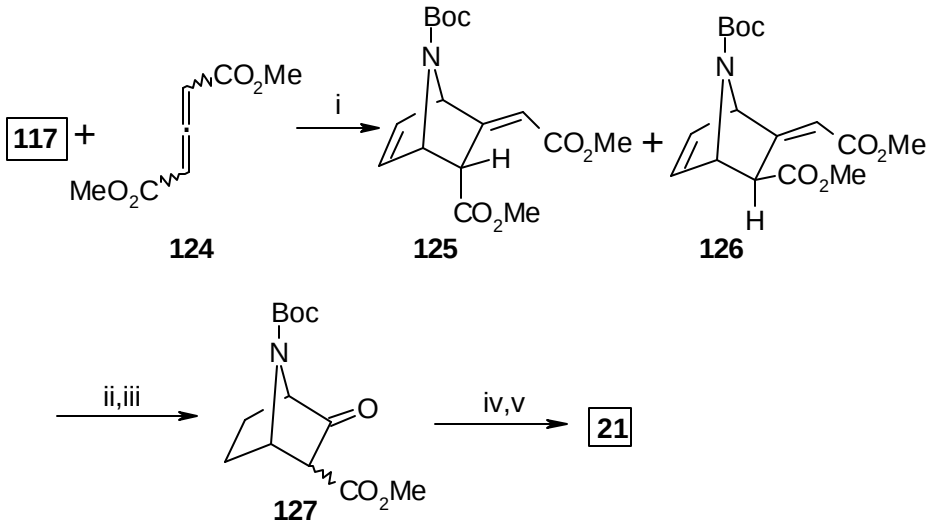
Scheme 26



Reagents and conditions: *i) 90 ^{o}C, 30 h, 60 %; ii) Et_2NH, TEA, 1.5 h, 10% HCl, 4 h, 87 %; iii) H_2, 10% Pd/C, MeOH; iv) 10 % HCl, reflux, 3 h, then $(Boc)_2O$, TEA, 24 h, 77 %; v) Al(Hg), MeOH.*

2.2.6. Pavri and Trudell's approach:[66]

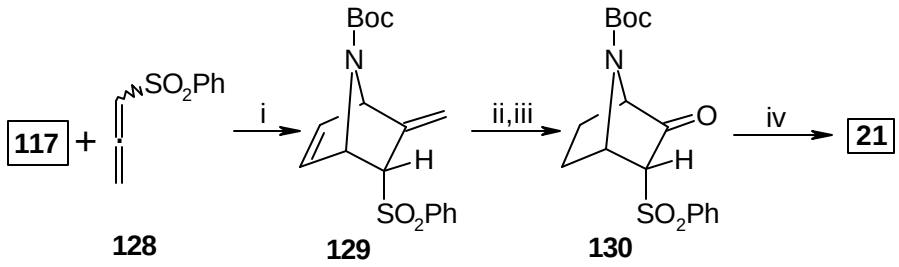
Scheme 27



Reagents and conditions: *i) 85-90 ^{o}C, 14-16 h, 65 %; ii) H_2, 5% Pd/C, EtOH, 98 %; iii) O_3, -78 ^{o}C, DCM, Me_2S, 70 %; iv) 10 % HCl, reflux; v) $(Boc)_2O$, TEA, DCM.*

A minor alteration has been also reported by the same group[66] to obtain **129** as a precursor for **21**, by the cycloaddition of **117** with allenic 1-(benzene sulfonyl)-1,2-propadiene (**128**) as shown in Scheme 28. This approach was found to be more efficient and high yielding than the former sequence.[66]

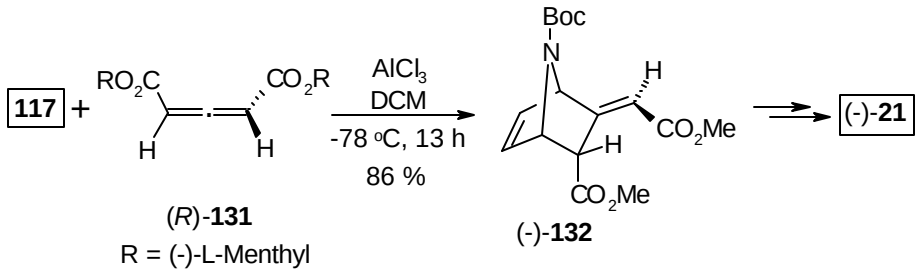
Scheme 28



Reagents and conditions: *i) 85-90 ^{o}C, 14-16 h, 65 %; ii) H_2, 5% Pd/C, EtOH, 98 %; iii) O_3, -78 ^{o}C, DCM, Me_2S, 70 %.*

Node *et al.*[67] have demonstrated the application of highly *endo*-selective asymmetric Diels-Alder reaction between chiral allene (*R*)-**131** and **117** for the construction of enantiopure 7-azabicyclo[2.2.1]heptane skeleton (Scheme 29).

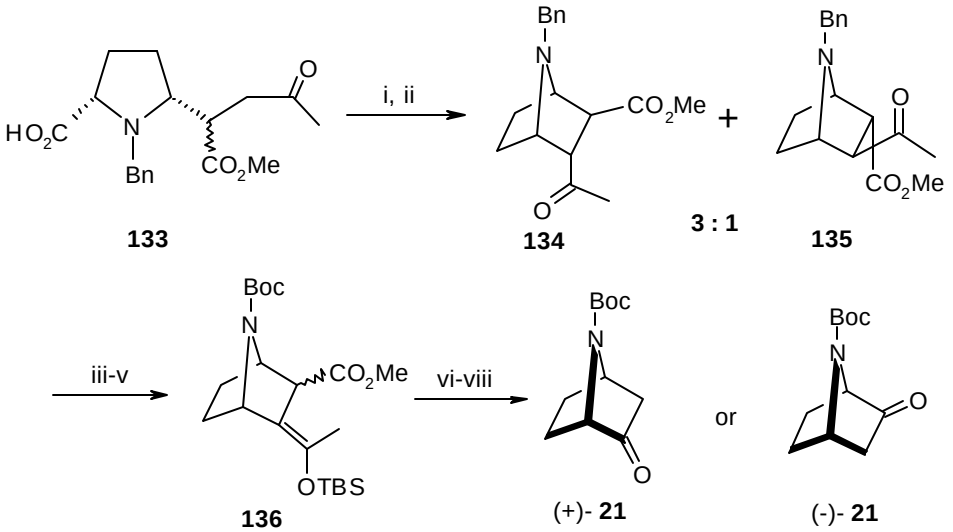
Scheme 29



2.3. Intramolecular cyclization of substituted proline derivatives:

Rapoport *et al.*[68] have reported decarbonylative iminium ion intramolecular cyclization of *N*-benzyl-5-(1′-methoxycarbonyl-3′-oxobutyl)proline (**133**) strategy for the construction of optically active *trans*-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes (**134**) and (**135**) in 3:1 ratio. The mixture of **134** and **135** were ultimately converted into (+)-**21** and (-)-**21,** respectively *via* corresponding silyl enol ether **136** as depicted in Scheme 30.

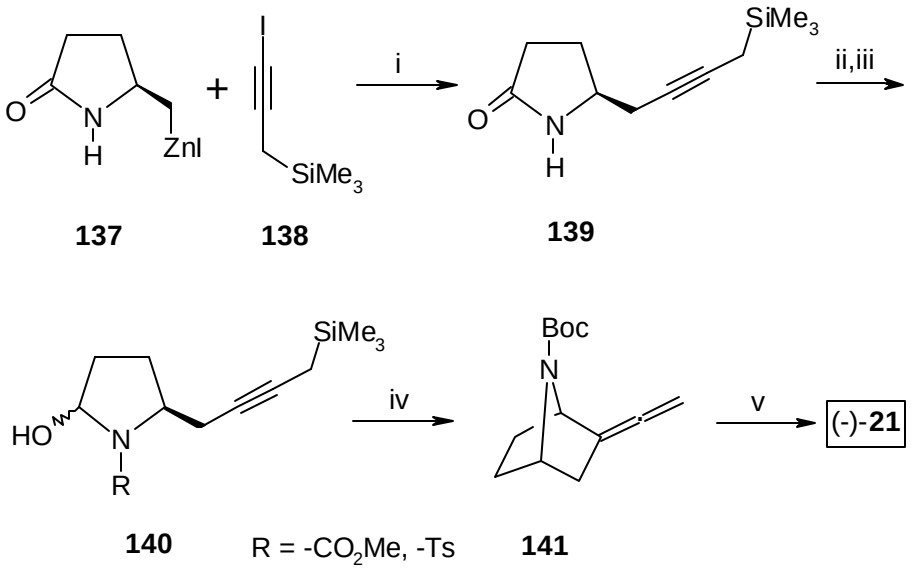
Scheme 30



Reagents and conditions: *i) H^+/H_2O; ii) $(COCl)_2$, D; iii) H_2, Pd/C; iv) $(Boc)_2O$; v) NaH, TMSCl; vi) O_3, Me_2S; vii) 10 % HCl, reflux; viii) $(Boc)_2O$.*

A similar strategy of intramolecular *N*-acyl or *N*-sulfonyliminium ion cyclization of **140** led to the construction of enantiopure 7-azabicyclo[2.2.1]heptane skeleton (**141**).[69] The precursor **140** was prepared by the coupling of copper(I)-mediated (*S*)-pyroglutamic acid-derived organozinc reagent **137** with 1-iodo-3-trimethylsilyl-1-propyne (**138**) followed by DIBAL reduction of **139** (Scheme 31). Ozonolysis of **141** produced (-)-**21** in overall good yield.

Scheme 31

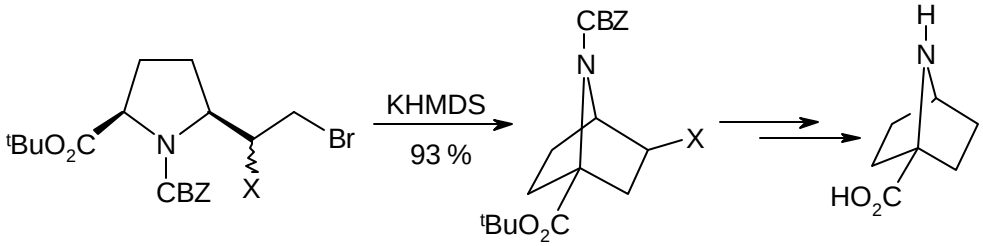


137 **138** **139** **140** **141**

Reagents and conditions: *i) CuCN.2LiCl, 49 %; ii) a) LDA, -78 ^{o}C, NCCOOMe, 89 %; b) n-BuLi, THF, -78 ^{o}C, TsCl, 94 %; iii) DIBAL-H (2 eq.), THF, -78 ^{o}C, 1 h, 95 %; iv) HCO_2H, 0 ^{o}C to rt, 10 min, 74 %; v) O_3, -78 ^{o}C, DCM, Me_2S, 96 %.*

Campbell and Rapoport[70] have also reported a chirospecific route for the synthesis of conformationally constrained 1-carboalkoxy-7-azabicyclo[2.2.1]heptane amino acids (**144**) by employing transannular alkylation of **142** as shown in Scheme 32.

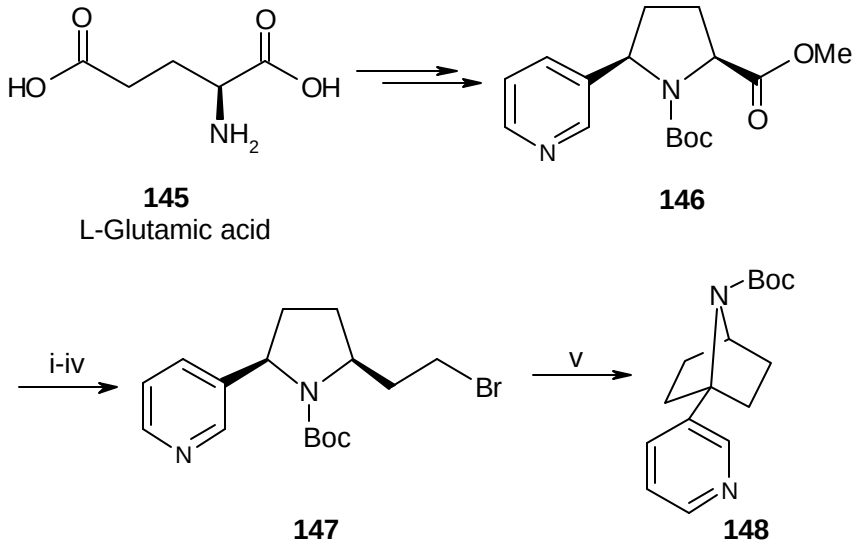
Scheme 32



142 **143** **144**

Later, the same group have also published the construction of 1-pyridinyl-7-azabicyclo[2.2.1]heptane analogue **148** by the intramolecular anionic cyclization of **147** as depicted in Scheme 33.[71]

Scheme 33



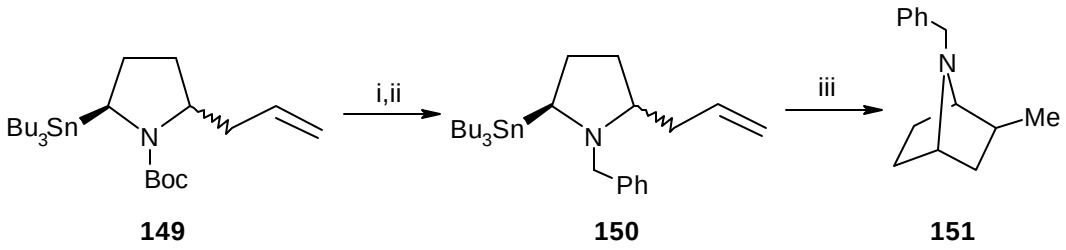
145
L-Glutamic acid

146 **147** **148**

Reagents and conditions: *i) EtOCOCl, TEA, CH_2N_2; ii) $PhCO_2Ag$, TEA, MeOH, 70 %; iii) $CaCl_2$, $NaBH_4$, 71 %; iv) 2-Mesyl-5-methylimidazolediazonium triflate, LiBr, 73 %; v) n-BuLi, THF, 64 %.*

trans-Metallation of either *cis* or *trans* isomer of 5-allyl-2-tri-n-butylstannyl-*N*-benzyl pyrrolidine (**150**) is also utilized to initiate an intramolecular anionic cyclization to obtain 7-azabicyclo[2.2.1]heptane skeleton **151** in good yield (Scheme 34).[72]

Scheme 34

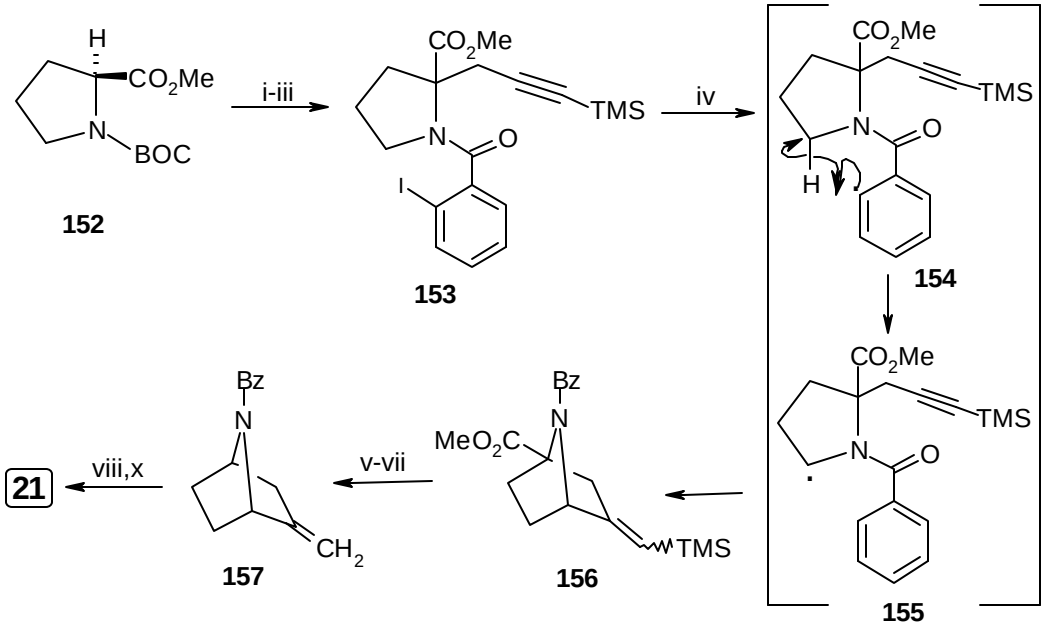


149 **150** **151**

Reagents and conditions: *i) 9-Bromocatecholborane, DCM, NaOH (aq.), PhCOCl, 70 %; ii) AlH_3, Et_2O, 79 %; iii) n-BuLi, hexane/Et_2O/THF (4:1:1), -78 ^oC to rt, 6 h, 60-83 %.*

Ikeda *et al.*[73] have described Bu_3SnH-mediated radical translocation/cyclization from methyl-2-[3-(trimethylsilyl)prop-2-ynyl]-1-(o-iodobenzoyl)pyrrolidine-2-carboxylate (**153**) to construct the 7-azabicyclo[2.2.1]heptane skeleton **156** as shown in Scheme 35.

Scheme 35

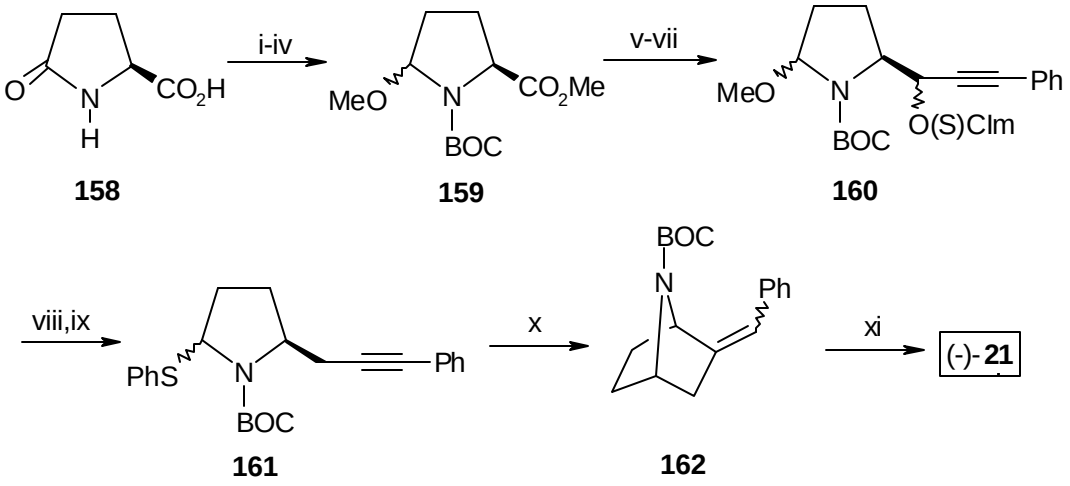


152 **153** **154** **155** **156** **157**

Reagents and conditions: *i) $(TMS)_2NLi$, THF, -78 ^oC, $TMSC^oCCHCH_2I$, 62 %; ii) TMSI; iii) o-Iodobenzoyl chloride, Et_3NPh, DMAP, 77 %; iv) Bu_3SnH, AIBN, toluene, reflux, 78 %; v) TsOH-H_2O, CH_3CN, 69 %; vi) DIBAL-H, Et_2O, -50 ^oC; vii) $Rh(PPh_3)_3Cl$, xylene, 49 %; viii) OsO_4, $NaIO_4$, 65 %; ix) 5 % HCl, Et_3N, $(Boc)_2O$, 54 %.*

An elegant intramolecular radical cyclization approach has also been reported by Clive and Yeh[74] for the construction of enantiopure 7-azabicyclo[2.2.1]heptane skeleton (**162**) from **161**. Ozonolysis of **162** gave (-)-**21**, a precursor used in the synthesis of (-)-epibatidine. The synthesis of **161** and details of the reactions are depicted in Scheme 36.

Scheme 36

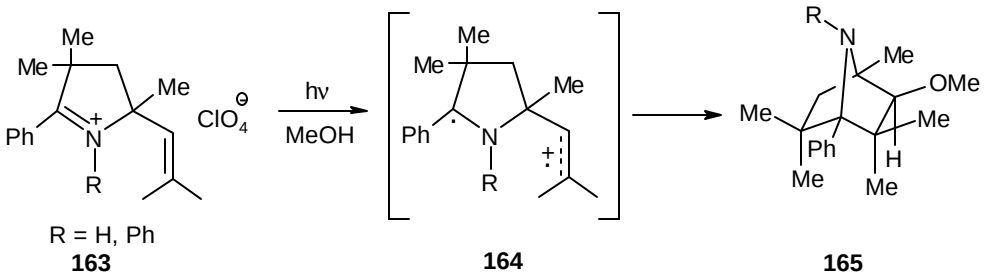


Reagents and conditions: *i) CH_2N_2, Et_2O, 100 %; ii) $(Boc)_2O$, DMAP, DCM, 90 %; iii) DIBAL-H, DCM-THF, -78 ^oC, 89 %; iv) MeOH, TsOH.H_2O, 81 %; v) DIBAL-H, DCM, -78 ^oC, 73 %; vi) PhC≡CLi, THF, -78 ^oC, 90 %; vii) $Im_2C(S)$, DMAP, DCM, 77 %; viii) Bu_3SnH, AIBN, PhMe, 80 ^oC, 76 %; ix) PhSH, DCM, TsOH.H_2O, 80 %; x) Bu_3SnH, AIBN, PhMe, 110 ^oC, 76 %; xi) O_3, DCM-MeOH, Me_2S, -78 ^oC, 95 %.*

2.4. Miscellaneous Reactions:

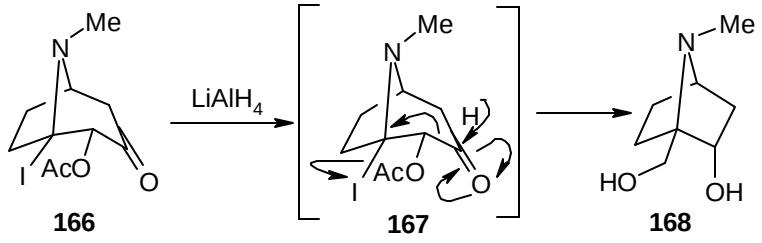
Mariano *et al.*[75] have described the construction of 7-azabicyclo[2.2.1]heptane (**165**) *via* intramolecular photocyclization of 2-phenyl-5-isobutenyl-1-pyrrolinium perchlorate (**163**), as shown in Scheme 37. Mechanistically, electron transfer from olefin to excited iminium salt followed by nucleophilic reaction of methanol on the radical cation **164** and subsequent radical-radical coupling provides azabicyclic system **165**.

Scheme 37



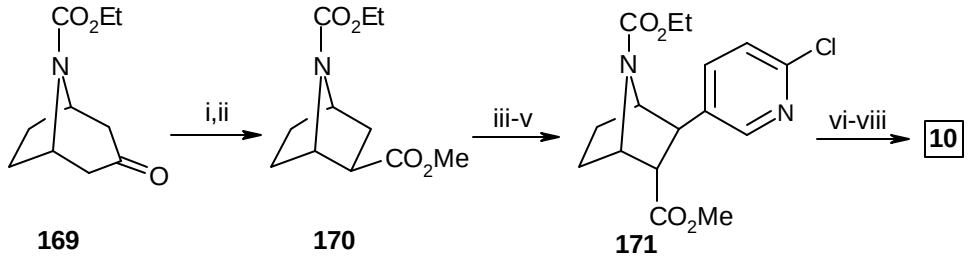
Sarel and Dykman[76] have described a reductive ring contraction strategy for synthesizing 7-azabicyclo[2.2.1]heptane skeleton (**168**) (Scheme 38). The reaction is proposed to involve β-elimination of iodo group from the intermediate (**167**) by the lithium aluminium hydride reduction of 1-iodo-2-acetoxy-8-methyl-8-azabicyclo[3.2.1]octane-3-one (**166**).

Scheme 38



Recently, Bai *et al.*[77] have employed a distinctly different approach for the construction of 7-azabicyclo[2.2.1]heptane framework **170** by ring contraction of the tropinone skeleton **169** *via* Favorskii rearrangement. Substrate **170** has further been converted to **10** in seven steps as shown in Scheme 39.

Scheme 39

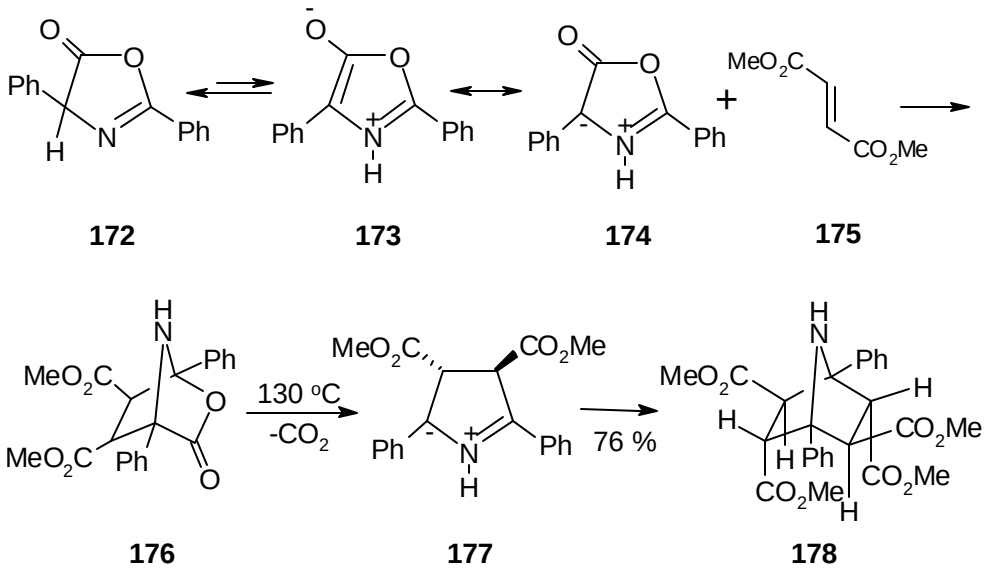


Reagents and conditions: *i) $CuBr_2$ (2 eq.), $CHCl_3$, EtOAc, reflux, 1h; ii) NaOMe (3 eq.), DME, rt, 0.5 h, (56 %); iii) LDA, THF, -78 ^oC, 20 min, then PhSeBr; iv) 30 % H_2O_2, DCM, rt, 15 min (68 %); v) 6-Chloro-3-iodopyridine, $(Ph_3P)_2Pd(OAc)_2$ (cat.), TEA, HCO_2H, DMF, rt, 4d, (56 %); vi) $LiOH.H_2O$,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

2.5. [3+2] cycloaddition Approach:

Huisgen *et al.*[78] have described the synthesis of polysubstituted 7-azabicyclo[2.2.1]heptane skeleton **178** in 76 % yield by the 1,3-dipolar cycloaddition reaction of azalactones **172** with dimethyl fumarate (**175)**. The cycloaddition reaction is shown to involve two successive dipoles **174** and **177**, as shown in Scheme 40.

Scheme 40

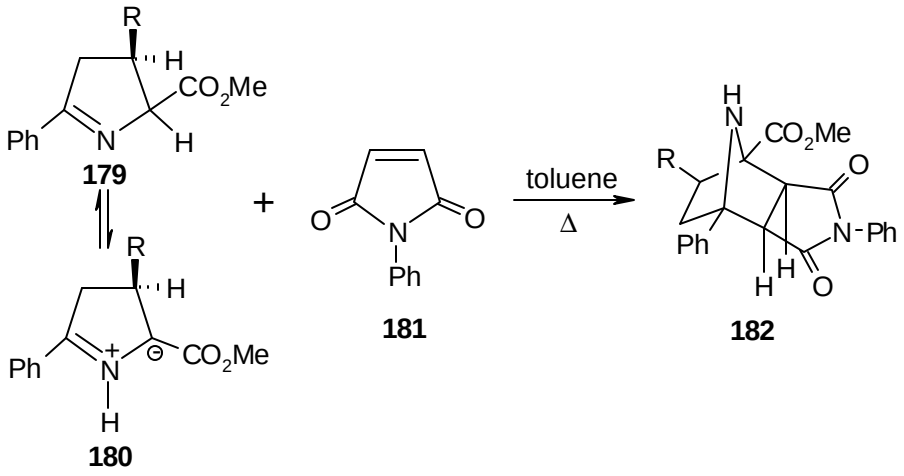


172 **173** **174** **175**

176 **177** **178**

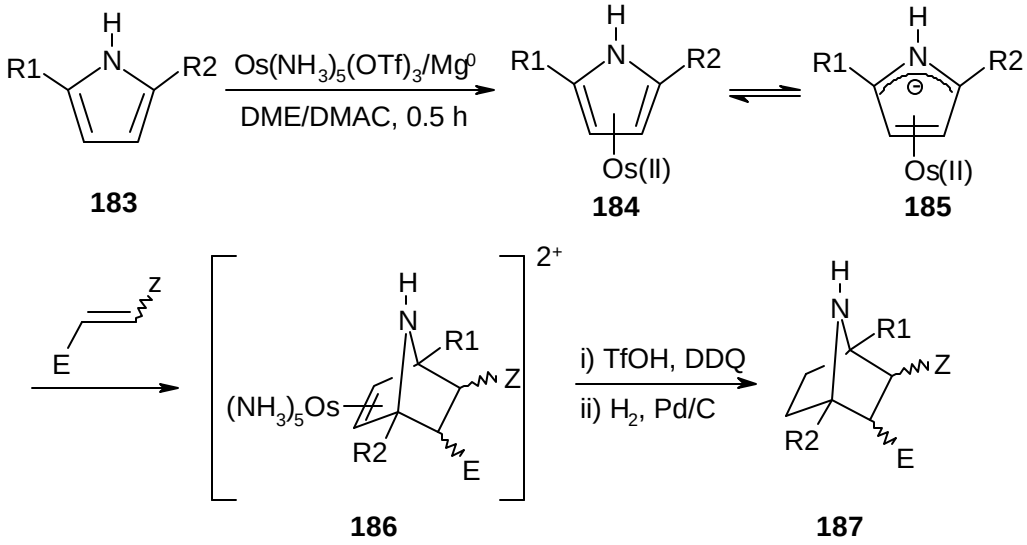
The synthesis of substituted 7-azabicyclo[2.2.1]heptane skeleton **182** in 70 % yield is also reported by the reaction of **179** with *N*-phenylmalemide (**181**). The reaction is supposed to involve 1,3-dipolar cycloaddition of **181** with tautomerized azomethine ylide **180** (Scheme 41).[79]

Scheme 41



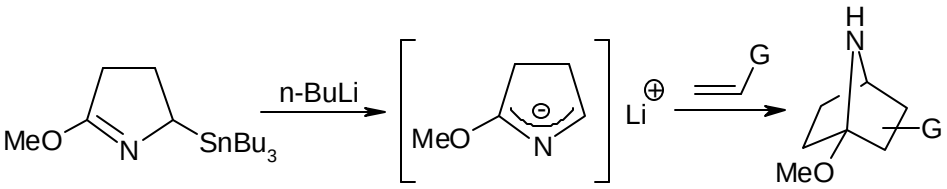
Harman and co-workers[80] have demonstrated that the complexation of pyrrole by pentaamineosmium(II) moiety across C(3) and C(4), transforms aromatic pyrrole into an azomethine ylide **185**, which on 1,3-dipolar cycloaddition reaction with a variety of dipolarophiles produces 7-azabicyclo[2.2.1]heptane skeleton **187** efficiently (Scheme 42).

Scheme 42



Recently, Pearson and Stevens[81] have reported an elegant approach for the construction of 1-methoxy-7-azabicyclo[2.2.1]heptane framework **190** in 60-80 % yield by the [3+2] cycloaddition of methoxy-substituted 2-azaallyl anions **189** (Scheme 43).

Scheme 43

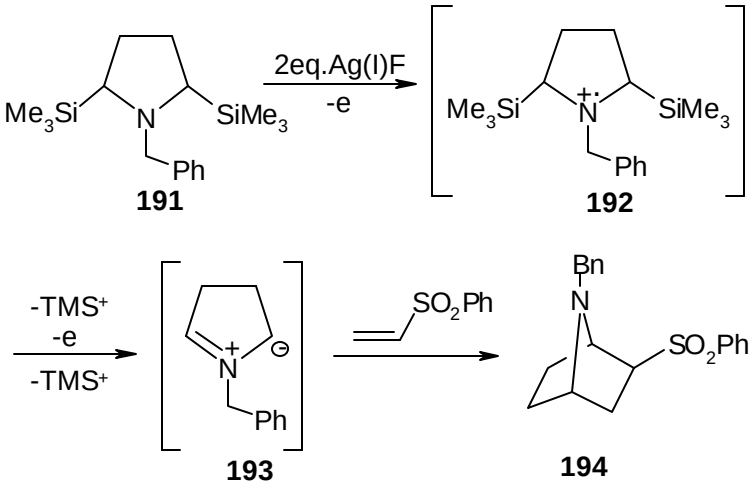


188 **189** **190**

G = -$SiMe_3$, -SePh, -SPh

Our own group have reported the stereoselective construction of 7-azabicyclo[2.2.1]heptane skeleton **194** by the [3+2]-cycloaddition of cyclic non-stabilized azomethine ylide **193** with dipolarophile vinyl sulfone. The *in situ* generation of **193** was achieved by the sequential double desilylation of **191** employing Ag(I)F as one electron oxidant (Scheme 44).[82-89]

Scheme 44



191 **192** **193** **194**

Epiboxidine, a synthetic analogue of epibatidine, possessing the basic skeleton 7-azabicyclo[2.2.1]heptane, is found to be less toxic than epibatidine but with comparable pharmacological activities. Due to lack of good synthetic strategy for the synthesis of epiboxidine, we undertook the synthesis of epiboxidine utilizing [3+2]-cycloaddition approach. The proceeding chapter of this thesis presents a concise account of the synthesis of epiboxidine.

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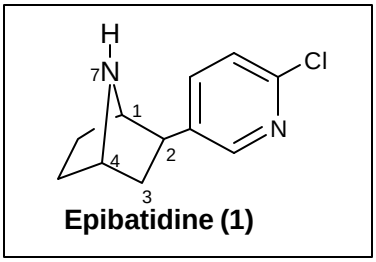
1. Introduction

The construction of 7-azabicyclo[2.2.1]heptane framework has seen strong revival immediately after the structural elucidation of epibatidine (**1**) {*exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane}.[1] Epibatidine (**1**); the only prominent member of this class, as introduced in the previous chapter, has been shown to be a highly potent non-opioid analgesic agent[2-5] and a novel nicotinic acetylcholine receptors (nAChRs)[3-5] agonist.

Fig. 1



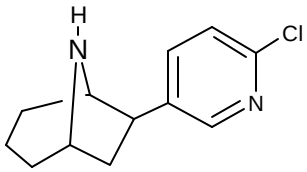
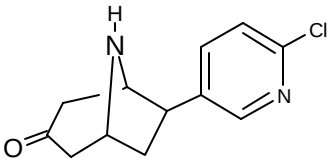
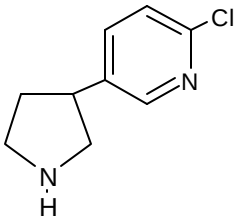
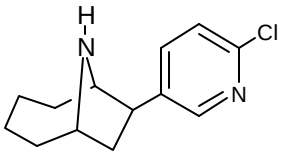
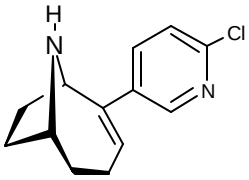
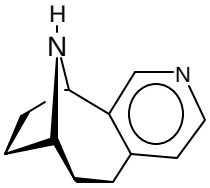
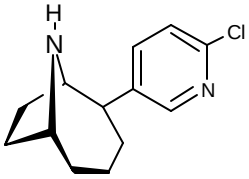
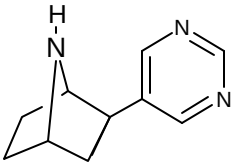
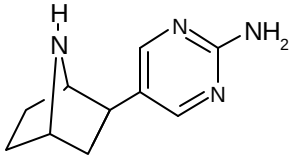
Epibatidine (1)

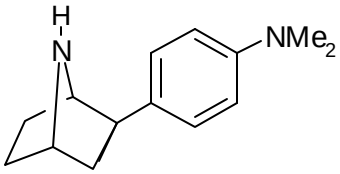
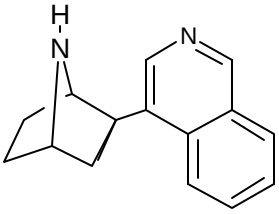
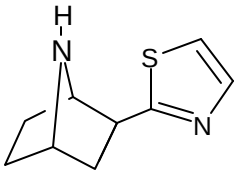
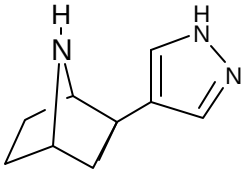
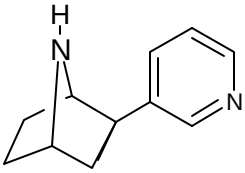
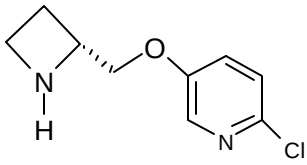
Although these outstanding pharmacological activities of **1** have kindled interest to recognize this molecule as an useful therapeutically important drug, its high toxicity, causing death in mice (six out of six) when injected at 10 μL/ Kg scale, has become a major impediment in developing this molecule as a drug.[6] Therefore, there has been continuing research interest towards an alternate pharmacophore related to the structure **1** capable of exhibiting comparable pharmacological properties but with an enhanced ratio of pharmacological to toxicological activity. In this context, chemists and phamacologists have begun synthesizing compounds analogous to **1** by

- altering, extending or cleaving the 7-azabicyclo[2.2.1]heptane framework of **1**, keeping the pyridyl ring intact,
- adding extra functionalities in the original framework of **1** along with the features described above or,
- by combining structural features of the known alkaloids having high affinity towards nicotinic receptors and **1**.

By exploring the above-mentioned parameters, many groups have synthesized various synthetic analogues of **1** and have studied their pharmacological activity as well as toxicity in comparison to **1**. The details are summarized in Fig. 2.

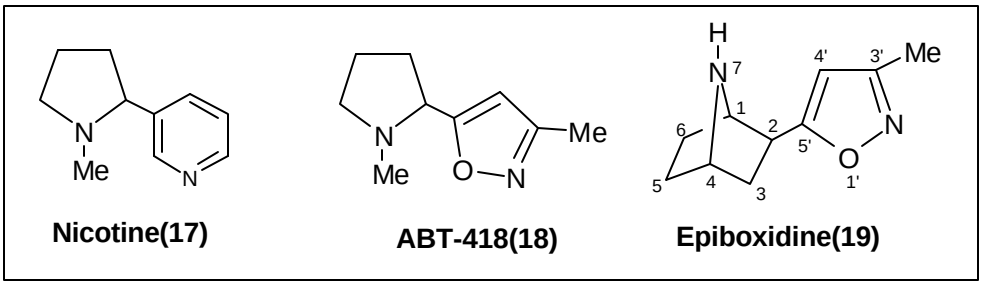
Fig. 2

		
Homoepibatidine (2)[7,8]	**3-Oxo-Homoepibatidine (3)**[7]	**Desethyl Epibatidine (4)**[9]
Activity: Weaker analgesic than **1** **Toxicity:** Not reported	**Activity:** Inactive **Toxicity:** Not reported	**Activity:** Inactive **Toxicity:** Not reported
		
Bis-Homoepibatidine (5)[8]	**UB-165 (6)**[10]	**PHT (7)**[11]
Activity: Inactive **Toxicity:** Not reported	**Activity:** Potent nicotinic receptor ligand **Toxicity:** Not reported	**Activity:** Potent nicotinic receptor **Toxicity:** Not reported
		
(8)[12]	**(9)**[13]	**(10)**[13]
Activity: Nicotinic receptor and stimulant **Toxicity:** Not reported`	**Activity:** 5-fold less binding affinity to nAChRs than **1** **Toxicity:** Not reported	**Activity:**16-fold less binding affinity to nAChRs than **1** **Toxicity:** Not reported

 **(11)**[13] **Activity:** Inactive **Toxicity:** Not reported	 **(12)**[13] **Activity:** Less active **Toxicity:** Not reported	 **(13)**[13] **Activity:** Inactive **Toxicity:** Not reported
 **(14)**[13] **Activity:** Moderately active **Toxicity:** Not reported	 **(15)**[13] **Activity:** Similar to that **1** **Toxicity:** Not reported	 **ABT – 594 (16)**[14] **Activity:** Potent nicotinic receptor & comparable to **1** **Toxicity:** Less toxic than **1**

It has been shown that (*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole (ABT-418), (**18**) another nicotinic receptor agonist, in which the pyridyl ring of nicotine **17** is replaced by methyl-isoxazolyl ring, is found to show a better anxiolytic and potent antinociceptive effect in mice[15a,b] than **17**. Because of the enhanced antinociceptive and anxiolytic activity of **18**, Badio *et al.*[6] designed a pharmacophore by combining the structural features of the known nicotinic receptor agonist **18** and **1**, by replacing the chloropyridyl moiety of **1** to methylisoxazole moiety and named it as epiboxidine (**19**), {exo-2-(3-methyl-5-isoxazolyl)-7-azabicyclo[2.2.1]heptane}. It showed similar nAChR binding affinity and drastic reduction of toxicity behavior compared to **1**. Out of all the synthetic analogue of epibatidine in Fig. 2, epiboxidine (**19**) was found to be not only a less toxic but also a selective ganglionic nicotinic receptor.

Fig. 3



The nicotinic receptor agonist and antinociceptive activities of epiboxidine is evaluated and further compared with the activities of epibatidine along with ABT-418 and the results are summarized as follows:

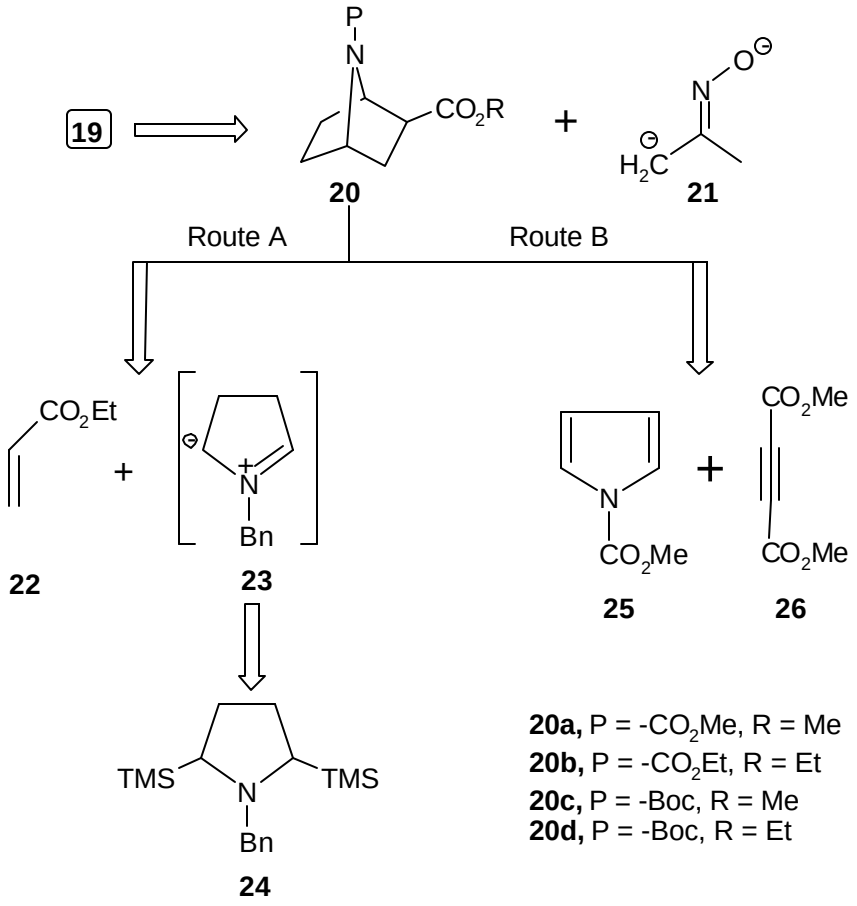
1) Epiboxidine is about 10-fold less potent than epibatidine and about 17-fold more potent than ABT-418 in inhibiting [^{3}H] nicotinic binding to $\alpha_4\beta_2$ nicotinic receptors in rat cerebral cortical membranes.
2) In cultured cells with functional ion flux assays, epiboxidine is nearly equipotent to epibatidine and 200-fold more potent than ABT-418 at $\alpha_3\beta_{4(5)}$ and at ganglionic-type PC12 cell nicotinic receptors.
3) Epiboxidine is about 5-fold less potent than epibatidine and about 30-fold more potent than ABT-418 in neuromuscular-type TE671 cells with $\alpha_1\beta_1\gamma\delta$, nicotinic receptors.
4) In a hot-plate antinociceptive assay with mice, epiboxidine is about 10-fold less potent than epibatidine.
5) The *in vivo* profile, study showed epiboxidine as about 10-fold less potent than epibatidine as an antinociceptive agent, but it appeared to be much less toxic (around 20-fold less) in comparison to **1**.

Therefore, it was concluded that epiboxidine (**19**) represents a novel and potent antinociceptive agent with better ratio of pharmacological to toxicological activity than **1**. Thus, epiboxidine has been presumed to be a better therapeutic target. However, owing to

the lack of good viable synthetic strategy by which epiboxidine could be accessed in multigram scale to carry out the detailed pharmacological evaluations, a short and efficient strategy was planned.

Retrosynthetic analysis (Scheme 1) of the target suggested that *N*-protected-2-exo-(carboalkoxy)-7-azabicyclo[2.2.1]heptane (**20**) could be a valuable synthetic precursor for the synthesis of **19**. Synthesis of methylisoxazole moiety[15a] of epiboxidine (**19**) was visualized to be achieved by reacting the dianion of acetone oxime (**21**) to the ester moiety of (**20**). For the synthesis of **20,** we envisaged two complementary cycloaddition approaches such as [3+2]-cycloaddition (Route A) and [4+2]-cycloaddition (Route B).

Scheme 1



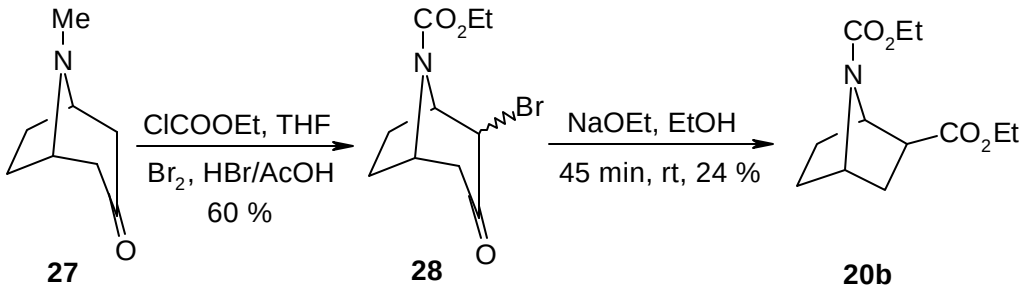
The above retrosynthetic analysis suggested that the [3+2]-dipolar cycloaddition reaction of cyclic azomethine ylide **23**, where whole of the ylide conjugation is inside the ring of pyrrolidine, with ethyl acrylate (**22**) will lead to an efficient assembling of 7-azabicyclo[2.2.1]heptane skeleton **20**. The *in situ* generation of azomethine ylide **23** could be achieved by the sequential one electron oxidation of *N*-benzyl-2,5-bis(trimethylsilyl)pyrrolidine (**24**) employing Ag(I)F as one electron oxidant, a methodology previously developed by our group.[16-19] Construction of **20** was also envisaged by utilizing an alternate [4+2] cycloaddition approach of *N*-carbomethoxypyrrole (**25**) with dimethyl acetylenedicarboxylate (DMAD) (**26**).

However, before going into the details of our work, a brief introduction on the reported methods for the synthesis of the novel precursor **20**, for the synthesis of **19** would be appropriate to understand the current status of this research field.

2. Reported approaches for the synthesis of *N*-protected-2-*exo*-(carboalkoxy)-7-azabicyclo[2.2.1]heptane (20)

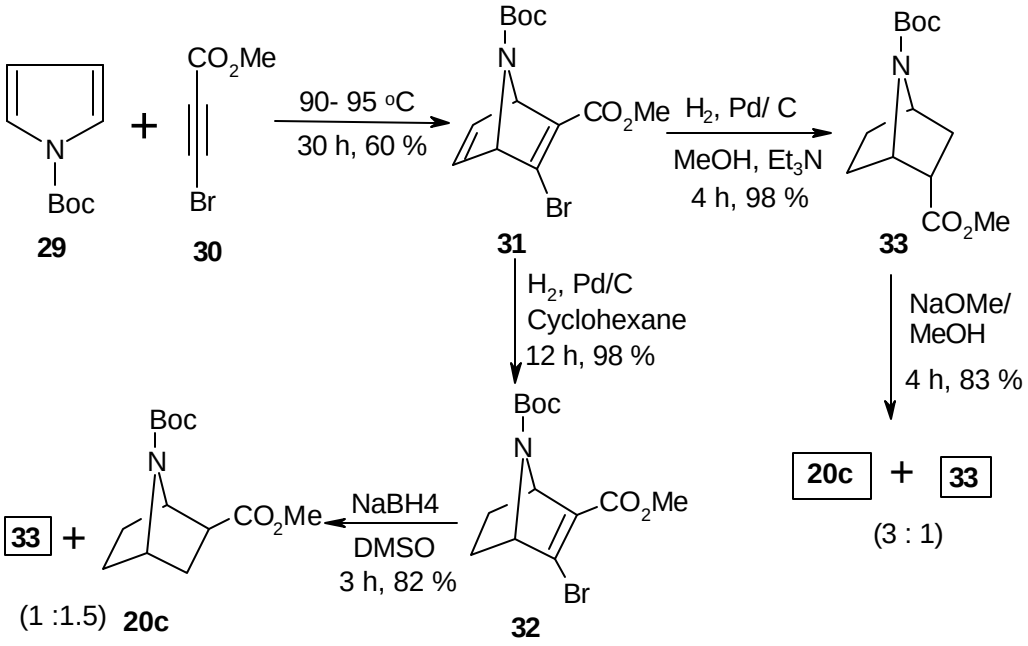
The precursor 7-carboethoxy-2-*exo*-(carboethoxy)-7-azabicyclo[2.2.1]heptane (**20b**) was prepared by Bai *et al.*[7] employing ring contraction of the 2-bromotropinone derivative **28** *via* Favorskii rearrangement (Scheme 2). However, the yield of **20b** was very poor.

Scheme 2



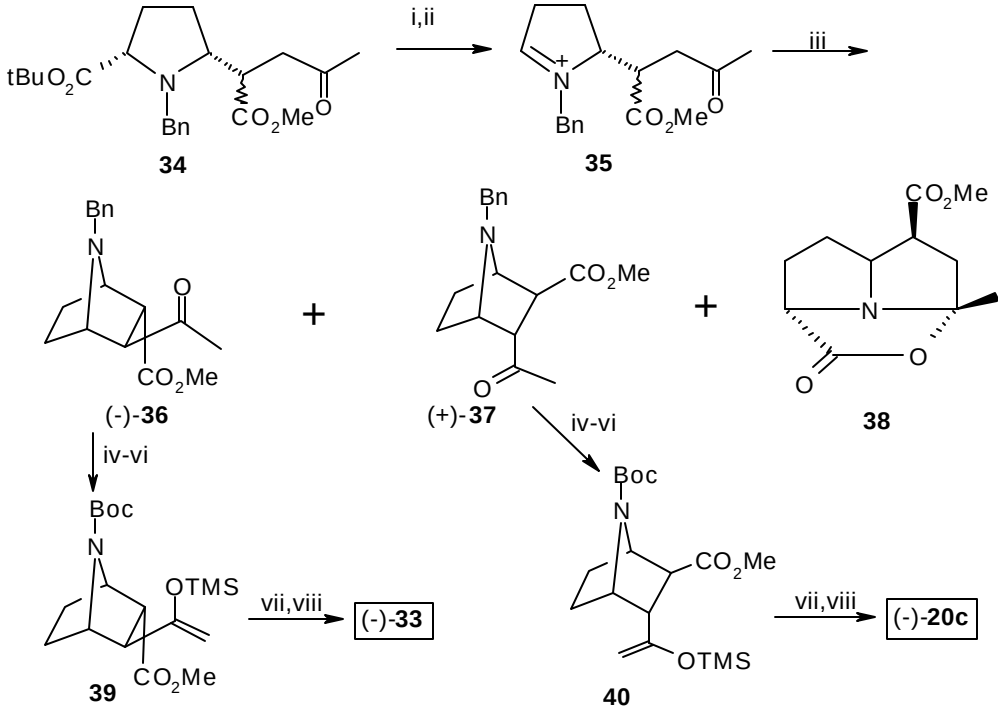
Recently, Singh *et al.*[20] have reported the synthesis of **20c** from **31** either *via* hydrogenation followed by reductive dehalogenation or *via* hydrodehalogenation followed by epimerization (Scheme 3). The diene **31** was obtained (60 % yield) by Diels-Alder reaction of *N*-Boc pyrrole (**29**) and methyl-3-bromopropiolate (**30**).

Scheme 3



Rapoport *et al.*[21] have reported the intramolecular Mannich cyclization of iminium ion intermediate **35**, derived by the decarbonylation of the substituted proline derivatives **34**, for the preparation of optically active (-)-**20c** and (-)-**33** as shown in Scheme 4. However, overall processes were cumbersome with resulting poor yield.

Scheme 4



Reagents and conditions: *i) H^+ / H_2O; ii) $(COCl)_2$; iii) Δ, 73 %; iv) H_2, Pd/C; v) $(Boc)_2O$, TEA, DCM, rt, 82 %; vi) KHMDS, TMSCl; vii) O_3, Me_2S; viii) i-BuO_2CCl, N-hydroxy-2-thiopyridone, hν*

The demerits of above-mentioned approaches may thus be summarized as follows: The ring contraction of tropinone skeleton into **20b** *via* Favorskii rearrangement suffers from poor yield. The [4+2]-cycloaddition strategy involves many steps with poor diastereoselectivity. Intramolecular iminium-ion Mannich cyclization protocol has involved a long reaction sequence. Therefore, we evaluated to utilize our [3+2]-cycloaddition strategy for the stereoselective construction of 7-azabicyclo[2.2.1]heptane skeleton, as the validity of this approach was fully established by the synthesis of epibatidine.[17,18] In the proceeding section the synthesis of epiboxidine using [3+2]-cycloaddition approach is described.

3. Results and Discussion

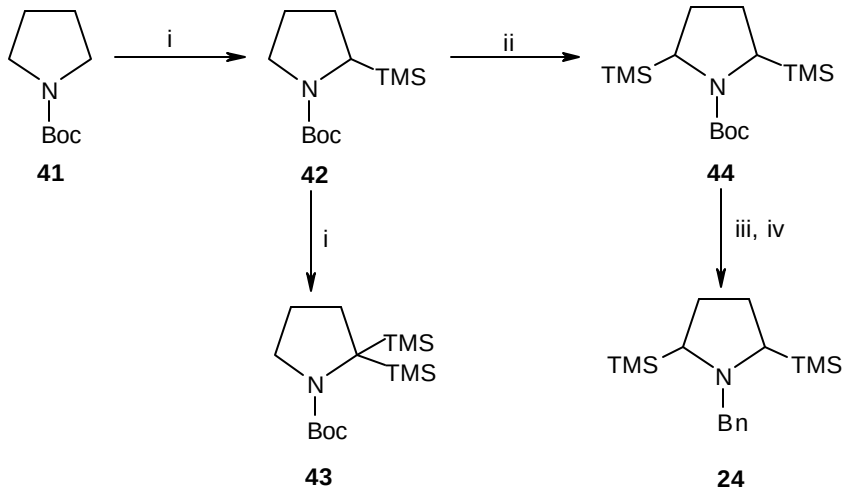
Towards the fulfillment of our planned synthetic strategy for the synthesis of epiboxidine (**19**) through the retrosynthetic route as shown in Scheme 1, we first initiated the stereoselective synthesis of azabicyclic precursor **20** by the [3+2]-cycloaddition strategy.

3.1. [3 + 2]-cycloaddition approach for the synthesis of 20:

3.1.1. Preparation of *N*-Benzyl-2,5-bis(trimethylsilyl)pyrrolidine (24):

The key precursor **24**, required for the generation of non-stabilized azomethine ylide, was prepared in 51 % overall yield from commercially available pyrrolidine in five steps, as depicted in Scheme 5.

Scheme 5



Reagents and conditions: *i) Ether, TMEDA, -78 °C, s-BuLi, 2 h, TMSCl, 90 %; ii) Ether, TMEDA, -45 °C, s-BuLi, -30 °C (15 min), then -45 °C, TMSCl, 70 %; iii) DCM, TFA, rt, 4 h; iv) BnCl, CH3CN, D, 4 h, 80 %.*

α-Silylation of **41** was carried out employing the protocol reported by Beak and coworkers.[22] Metallation of **41** in ether at –78 °C using s-BuLi in the presence of

tetramethylethylenediamine (TMEDA) followed by quenching with TMSCl at –78 ^{o}C afforded **42** in 90 % yield, (bp 55 ^{o}C/ 0.5 mm). Spectral characteristics (^{1}H NMR, ^{13}C NMR, IR and mass analysis) are in agreement to that reported in the literature[23] and are detailed in the experimental section.

3.1.1.1. Silylation of *N*-Boc-2-(trimethylsilyl)pyrrolidine (42):

The same protocol, as described above for the monosilylation of **41**, was extended towards the preparation of **44** from **42.** However, it resulted in the formation of **43** as the major product (65 %) along with trace amount of **44** (< 5 %).

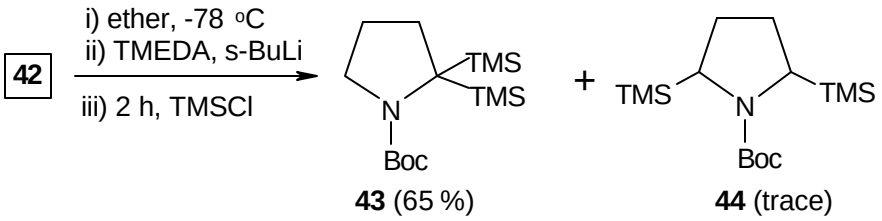
Compound **43** was characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis.

^{1}H NMR of **43** revealed a set of two singlets at δ 0.1 and δ 1.45, integrating for eighteen and nine protons each, assignable to the six methyls of two trimethylsilyl groups and three methyls of –Boc moiety, respectively. A multiplet at δ 1.75 (2H) was 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.

^{13}C NMR spectrum displayed a total of eight carbon signals at δ 0.18, 25.5, 28.8, 32.2, 46.5, 48.5, 78.1 and 154.6. DEPT experiment 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 were observed at δ 25.5, 32.2 and 46.5, respectively. The quaternary C_1 appeared at δ 48.5 and the *t*-butyl and carbonyl carbons appeared at δ 78.1 and 154.6, respectively.

These spectral characteristics suggests the presence of geminal α,α-bis(trimethylsilyl) moiety on the pyrrolidine ring (Scheme 6).

Scheme 6



43 (65 %) **44** (trace)

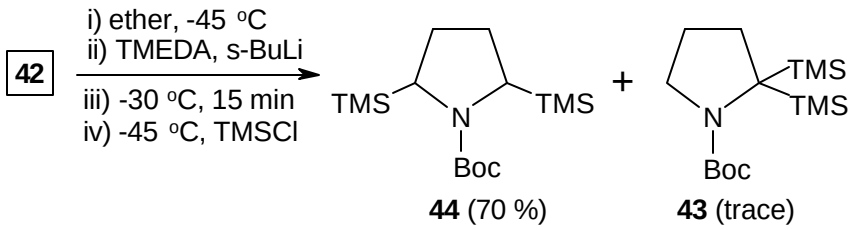
Formation of *gem* disilylated product **43** could be attributed to the following two factors:

(i) Silicon ability to enhance the acidity of the adjacent proton.

(ii) Kinetic stability of α-silyl anion.

However, our requirement was to introduce the two silyl moieties at C_2 and C_5 position of the pyrrolidine unit, respectively. Although, it was clear to us that it would be difficult to alter the ability of silicon moiety to enhance the acidity of the adjacent proton, we envisioned that playing with the kinetic stability of α-silyl carbanions by employing thermodynamic parameters such as temperature variant might alter the regioselectivity of the second silylation reaction. Towards this direction, we extensively studied the reactivity pattern and the product ratio of **43** and **44**, by carrying out the metallation reaction using s-BuLi at a range of temperatures *viz.,* –50 °C to –30 °C. These studies led us to achieve an optimum reaction condition where the thermodynamic product **44** was obtained as a 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. The optimized reaction condition for the preparation of **44** involved treatment of **42** in dry ether at –45 °C with s-BuLi in the presence of TMEDA followed by warming the reaction mixture to –30 °C immediately. After stirring for additional 30 min at –30 °C, the temperature was again lowered to –45 °C and the reaction mixture was quenched with TMSCl to afford **44** in 70 % yield as a pale yellow liquid with a trace amount of **43** (< 3 %) (Scheme 7).

Scheme 7



44 (70 %) **43** (trace)

Compound **44** was characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis.

^{1}H NMR spectrum of compound **44** displayed two singlets at δ 0.05 and 1.45, corresponding to the eighteen and nine protons each, attributable to the methyl group of the TMS and Boc moieties, respectively. A multiplet between δ 1.75-2.0, integrating for four protons, correspond to H_3 and H_4 protons. Two broad singlets at δ 3.1 and 3.3, integrating for one proton each, correspond 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, 28.93, 29.0, 49.44, 50.0, 78.96 and 154.82. DEPT experiment showed 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 50.0 correspond to either of C_1 or C_4. Quaternary carbons of *t*-butoxy and carbonyl group of -Boc moiety appeared at δ 78.9 and 154.8, respectively.

Compound **24** was prepared from **44** in two steps (Scheme 5) involving the deprotection of the -Boc moiety followed by *N*-benzylation. The *N*-Boc deprotection was carried out quantitatively using TFA in dry DCM and the crude amine was benzylated using benzyl chloride in the presence of K_2CO_3 in dry acetonitrile. Compound **24** was characterized by the ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis.

^{1}H NMR spectrum of compound **24** showed a singlet at δ 0.1 corresponding to eighteen protons of the methyl groups of the TMS moiety. Two multiplets between

δ 1.65-1.80 and δ 1.90-1.95, integrating for two protons each, were attributed to H_{3a}, H_{4a} and H_{3b}, H_{4b}, respectively. Another multiplet between δ 2.25-2.30, integrating for two protons, corresponds to H_2 and H_5. A set of two doublets at δ 3.35 and δ 3.80 (d, J = 12.9 Hz), integrating for one proton each, were assigned to the two benzylic protons. The five aromatic protons of phenyl moiety were observed as a multiplet between δ 7.20-7.35.

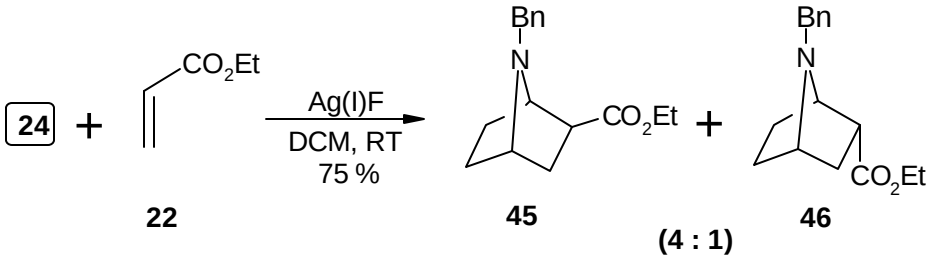
^{13}C NMR spectrum displayed a total of four signals at δ –1.6, 26.8, 56.0 and 60.1 in aliphatic region along with aromatic signals at δ 126.8, 128.1, 129.4 and 141.7. Based on DEPT experiment, the signal at δ –1.6 was assigned to the methyl groups of trimethylsilyl moiety. The signal at δ 26.8 was assigned to C_3 and C_4 methylene carbons. A methine carbon signal at δ 56.0 was assigned to C_2 and C_5. A signal appearing at δ 60.1 corresponds to the methylene carbon of benzylic (-N-CH_2Ph) moiety.

Mass spectrum gave molecular ion peak at 305 (3) and a base peak at 233 (M^+- TMS), along with other prominent fragmentation peaks at 290 (17), 91 (90) and 73 (54).

3.1.2. [3 + 2] Cycloaddition Reaction:

To a stirring mixture of Ag(I)F (1.87 g, 14.75 mmol) (dried previously under vacuum at 40 ^{o}C) and **22** (0.78 g, 7.86 mmol) in dry DCM (30 mL) was added **24** (2.0 g, 6.56 mmol) in 10 mL dry DCM under argon atmosphere. The reaction mixture was allowed to stir for additional 8-10 h and the progress of the reaction was monitored by TLC. After the considerable consumption of compound **24**, the reaction mixture was filtered through a plug of celite. The mother liquor was evaporated and the crude residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (9 : 1) to afford the minor cycloadduct **46** (15 %) as a pale yellow liquid. Further elution with the same solvent system gave the major isomer **45** (60 %) as a pale yellow liquid (Scheme 8).

Scheme 8



22 **45** **(4 : 1)** **46**

Both these diastereoisomeric cycloadducts were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis and their stereochemistry was confirmed by ^{1}H NMR decoupling and COSY experiments.

3.1.2.1. Spectral analysis and stereochemical assignment of major cycloadduct 45:

IR spectrum of **45** displayed a sharp band at 1732 cm^{-1}, characteristic of an ester carbonyl group besides other bands at 2958, 2361, 1451, 1180 cm^{-1}.

^{1}H NMR spectrum of cycloadduct **45** showed following pattern (Fig. 4).

A multiplet at δ 1.35, integrating for two protons, was assigned to H_{3endo} and H_{6endo}. The H_{3endo} proton appeared as a doublet of doublet at δ 1.50 (J = 12.2, 9.3 Hz, 1H) due to coupling with H_{3exo} and H_{2endo} protons. Both H_{5exo} and H_{6exo} protons resonated at δ 1.85 (2H) as a multiplet. Another multiplet at δ 2.25 (1H) was assigned to H_{3exo}. H_{2endo} proton appeared as a doublet of doublet at δ 2.40 (J = 9.3, 4.9 Hz) due to its coupling with H_{3exo} and H_{3endo} protons. The broad singlet appearing at δ 3.35, equivalent to one proton corresponds to bridgehead H_4. A set of two doublets at δ 3.40 and δ 3.60 (J = 13.7 Hz), integrating to one proton each, were assigned to the two benzylic protons. The broad singlet at δ 3.63, integrating for one proton, was assigned to bridgehead H_1. The signals corresponding to methyl and methylene moieties of carbethoxy group were observed as a triplet at δ 1.25 (J = 7.1 Hz, 3H) and a quartet at δ 4.1 (J = 7.1 Hz, 2H), respectively. A multiplet between δ 7.15-7.40, integrating for five protons, was attributed to the five aromatic protons of benzylic group.

This stereochemical assignment of the respective protons of **45** was confirmed by carrying out ^{1}H NMR decoupling experiment.

The H_2 proton at δ 2.40 (J = 9.3, 4.9 Hz, 1H) was found to couple only with the adjacent two H_{3exo} and H_{3endo} hydrogens at δ 2.25 (m, 1H) and δ 1.50 (J = 12.9, 9.3 Hz, 1H), respectively, but not with the bridgehead proton H_1 at δ 3.63 (bs, 1H). This observation was found to be in conformity with the ^{1}H NMR patterns of the 7-azabicyclo[2.2.1]heptane system,[24] where no coupling was observed between the bridgehead bowsprit and adjacent *endo* hydrogen due to a dihedral angle of 90° between them. Therefore, the assignment of H_2 as *endo* was confirmed and that confirms the *exo* orientation of the carbethoxy moiety in major diastereomeric cycloadduct.

In ^{13}C NMR spectrum (Fig. 5) a total of nine signals appeared at δ 13.98, 26.65, 26.82, 33.2, 47.69, 51.24, 59.2, 60.1 and 62.98 besides aromatic signals at δ 126.36, 127.8, 127.93, 140.0 and carbonyl signal at δ 174.12. DEPT experiment showed the methylene carbons at δ 26.65, 26.82, 33.2, 51.24, 60.1, which were assigned to be C_5, C_6, C_3, -O$\underline{C}H_2CH_3$ and -N$\underline{C}H_2$Ph carbons, respectively. Methyl carbon signal corresponding to ester (–$CO_2CH_2\underline{C}H_3$) moiety was observed at δ 14.01. Three methine carbon signals at δ 47.69, 59.2, and 62.98 were assigned to C_2, C_4, and C_1, respectively.

The above spectral analyses confirmed the compound **45** as 7-benzyl-2-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane.

Mass spectrum (Fig. 4) revealed a molecular ion peak at 259 (6), along with base peak at 91, corresponding to benzyl group. The other prominent fragmentation peaks were found at 158 (24, M^+- 101), 131 (11) and 104 (10).

3.1.2.2. Spectral analysis and stereochemical assignment of the minor cycloadduct 46:

IR spectrum showed a strong absorption band at 1724 cm^{-1}, indicating the presence of carbethoxy functionality.

^{1}H NMR spectrum of **46** (Fig. 6) displayed signals corresponding to H_{6endo} and H_{6endo} between δ 1.40-1.50 (2H) as a multiplet. A multiplet between δ 1.65-1.90, integrating for three protons, was attributed to H_{3endo}, H_{5exo} and H_{6exo}. Another multiplet between δ 1.90-2.10 (1H) was assigned to H_{3exo}. H_{2exo} proton appeared as a multiplet at δ 3.10. Two triplets at δ 3.32 (J = 4.5 Hz) and δ 3.55 (J = 4.3 Hz), integrating for one proton each, were assigned to bridgehead H_4 and H_1, respectively. The signal corresponding to two benzylic protons appeared as a broad singlet at δ 3.60 (2H). Signals corresponding to methyl and methylene moieties of carbethoxy group were observed as a triplet at δ 1.25 (J = 7.9 Hz, 3H), and a quartet at δ 4.15 (J = 7.9 Hz, 2H), respectively. The five aromatic protons of benzyl group were observed as a multiplet between δ 7.20-7.45.

The H_2 proton at δ 3.10 was found to couple with both H_3 hydrogen between δ 1.90-2.10 (m, 1H) and 1.65 (m, 1H), respectively and also with H_1 at δ 3.55 (t, J = 4.3 Hz, 1H), confirming the *exo*-orientation of H_2. The correlation implied the *endo*-orientation of carbethoxy group. Therefore, compound **46** was assigned as 7-benzyl-2-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane.

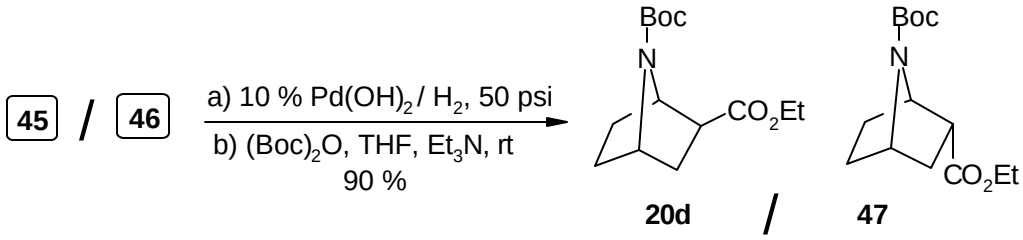
^{13}C NMR spectrum (Fig. 7) revealed a total of nine signals at δ 14.16, 24.09, 28.11, 30.99, 45.66, 51.66, 60.13, 60.21 and 62.05, in aliphatic region along with aromatic signals at δ 126.7, 128.12, 128.31, 139.79 and carbonyl carbon signal at δ 173.89. DEPT experiment characterized the methylene carbon signals at δ 24.09 and 28.11 to either C_5 and/or C_6 while the signals at δ 30.99, 51.66 and 60.21 could be assigned to C_3, methylene of carbethoxy (-O$\underline{C}H_2CH_3$) and benzylic (-N$\underline{C}H_2$Ph) moieties, respectively. The methine carbons at δ 45.66, 60.21 and 62.05 were characterized for C_2, C_4 and C_1, respectively. The signal at δ 14.16 was attributed to methyl carbon of carbethoxy moiety (-OCH$_2\underline{C}H_3$).

Mass spectrum (Fig. 6) gave molecular ion peak at 259 (6) and a base peak at 91, along with the identical fragments as those were observed for the major cycloadduct **45**.

3.1.3. Conversion of 45 and 46 to corresponding *N*-Boc derivatives 20d and 47:

To avoid the complications at the later stage of the synthesis, it was mandatory to cleave the *N*-benzyl moiety of the cycloadducts **45** / **46**, prior to the construction of oxazolidine moiety. *N*-Debenzylation of the cycloadducts were carried out by performing hydrogenation over Pearlman's catalyst [10 % $Pd(OH)_2$] at 40 psi of hydrogen for two days. After filtration of catalyst and concentration, the crude reaction mixture was subjected as such for the *N*-Boc protection. The *N*-Boc protection was carried out by treating the crude amine with $(Boc)_2O$ in the presence of triethylamine in DCM at room temperature (Scheme 9).

Scheme 9



Both compounds **20d** and **47** were fully characterized by ^1H NMR, ^{13}C NMR, IR and mass spectral analysis and their stereochemistry was assigned by ^1H NMR decoupling experiment.

3.1.3.1. Characterization of compound 20d:

IR spectrum of **20d** displayed strong absorption bands at 1738 cm^{-1} and 1706 cm^{-1} for an ester carbonyl group and –Boc carbonyl group, respectively, along with other prominent bands at 2979, 1368, 1156 cm^{-1}.

^1H NMR spectrum of **20d** (Fig. 8) revealed the presence of -Boc moiety by displaying a sharp singlet at δ 1.45 (nine protons). A multiplet appearing between δ 1.50-1.70, integrating for two protons was attributed to H_{5endo} and H_{6endo}. Another multiplet between δ 1.70-1.90, corresponding to three protons, was assigned to H_{6exo},

H_{6exo} and H_{3endo}. H_{3exo} appeared as a multiplet between δ 2.20-2.35 (1H). H_{2endo} resonated as a doublet of doublet at δ 2.57 (J = 8.6, 3.9 Hz, 1H). A triplet at δ 4.30 (J = 4.3 Hz), integrating for one proton, was assigned to bridgehead proton H_4. Due to the absence of coupling of H_{2endo} proton with the bridgehead, the H_1 proton appeared as a doublet at δ 4.55 (J = 4.1 Hz, 1H). A triplet and quartet at δ 1.25 (J = 7.1 Hz, 3H) and δ 4.15 (J = 7.1 Hz, 2H) corresponds to methyl and methylene groups of the carbethoxy moiety, respectively.

From the above spectral analysis the stereochemistry of **20d** was assigned as 7-(*tert*-butyloxycarbonyl)-2-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane.

In the ^{13}C NMR spectrum of **20d** (Fig. 9) a total of twelve signals appeared at δ 13.79, 27.81 28.46, 29.12, 32.84, 47.17, 55.45, 58.89, 60.27, 79.03, 154.3 and 172.73. DEPT experiment suggested that two methyl carbons at δ 13.79 and 27.81, correspond to methyl carbon of carbethoxy moiety and three methyls of -Boc moieties, respectively. The methylene carbon signals at δ 28.46 and 29.12 could be attributed to either C_5 and/or C_6 while signals at δ 32.84 and 60.27 were assigned to C_3 and methylene of carbethoxy ($-O\underline{C}H_2CH_3$) moieties, respectively. Three methine carbons C_2, C_4, and C_1 signals were observed at δ 47.17, 55.45 and 58.89, respectively. Two quaternary carbons at δ 79.03 and 154.3 were characterized to *t*-butyl and carbonyl carbon of Boc moiety, respectively. Another quaternary carbon at δ 172.73 corresponds to carbonyl carbon of carbethoxy moiety ($-\underline{C}OOC_2H_5$).

Mass spectrum (Fig. 8) gave a molecular ion peak at 269 (1) and a base peak at 69 along with the other fragments at 196 (23), 169 (52) and 96 (42).

3.1.3.2. Characterization of compound 47:

The IR spectrum of **47** was found almost identical to that of **20d**.

^1H NMR spectrum of **47** (Fig. 10) displayed a sharp singlet at δ 1.40 (nine protons), revealing the presence of Boc moiety. The signals corresponding to H_{5endo} and H_{6endo}

appeared as a multiplet between δ 1.45-1.55 (2H). Another multiplet between δ 1.60-1.95, integrating for four protons, was attributed to H_{3exo}, H_{6exo}, H_{3endo} and H_{3exo}. H_{2exo} proton was observed as a multiplet between δ 2.90-3.05, in sharp contrast to that observed for the same proton in **20d** at δ 2.57 (J = 8.6, 3.9 Hz). Two methylene protons of carbethoxy moiety (-OC$\underline{H}_2$CH$_3$) along with bridgehead H_4 appeared as a multiplet between δ 4.05-4.25 (3H). Another bridgehead proton H_1 appeared as a triplet at δ 4.35 (J = 4.4 Hz, 1H). The signal corresponding to methyl group of carbethoxy moiety appeared as a triplet at δ 1.25 (J = 7.1 Hz, 3H).

The H_2 proton between δ 2.90-3.05 (m, 1H) was found to couple with both H_3 hydrogens between δ 1.60-1.95 (m, 4H) and H_1 at δ 4.35, confirming the *exo*-orientation of H_2. Thus, the stereochemistry of **47** was assigned as 7-(*tert*-butyloxycarbonyl)-2-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane.

^{13}C NMR spectrum (Fig. 11) showed total of twelve signals at δ 14.09, 25.22, 28.12, 29.08, 32.28, 46.35, 57.04, 58.19, 60.46, 79.63, 155.18, and 172.42. DEPT experiment revealed the presence of two methyl carbons at δ 14.09 and 28.12 corresponding to methyl group of carbethoxy moiety and Boc moiety, respectively. The methylene carbon signals at δ 25.22 and 29.08 could be assigned to C_5 and/or C_6 while other methylene signals at δ 32.28 and 60.46 are assigned to C_8 and ester (-O$\underline{C}$H$_2$CH$_3$) moiety, respectively. Three methine carbons at δ 46.35, 57.04 and 58.19 correspond to C_2, C_4 and C_1, respectively. The three quaternary carbons at δ 79.63, 155.18 and 172.42 were assigned to *t*-butyl, and carbonyl carbon of Boc moiety, and carbonyl carbon of carbethoxy moiety (-$\underline{C}$OO-), respectively.

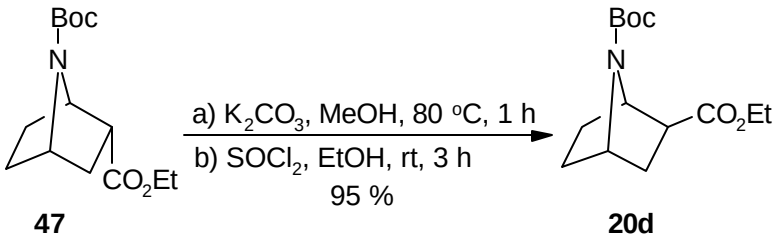
The mass spectrum of **47** was almost identical to that of **20d**.

3.1.4. Epimerization of *endo* isomer 47 to 20d:

Since our cycloaddition gave a mixture of diastereomers **45** and **46**, it was felt imperative to convert **47** into **20d** to improve upon our synthetic strategy. Taking the

advantage of the acidity of H_{exo} proton, its epimerization was effected by refluxing **47** with anhydrous K_2CO_3 in dry methanol for 1 h.[25] We observed that along with the epimerization of **47** to **20d**, hydrolysis of the ester moiety also occurred. Therefore, the crude epimerized acid was again re-esterified (95 % yield) by treating the acid with $SOCl_2$ at 0 °C in ethanol (Scheme 10).

Scheme 10

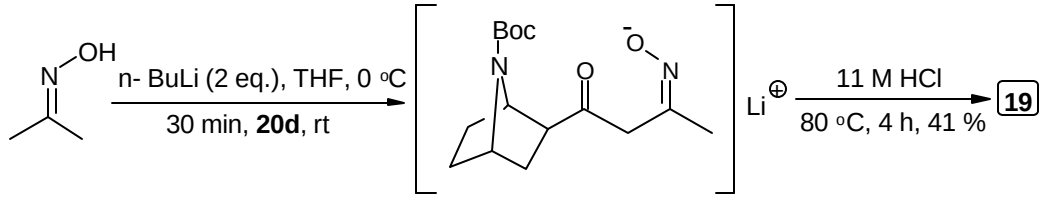


47 **20d**

3.1.5. Transformation of 20d into epiboxidine (19):

With the key precursor **20d** in hand, we transformed its carbethoxy moiety into 2-methyloxazolidine by treating with the dianion of acetone oxime **21**, obtained by reacting acetone oxime (**48**) with 2 eq. of n-BuLi in THF at 0 °C, followed by heating the reaction mixture for 4 h with 11M HCl at 80 °C. After usual workup, the residue was purified by silica gel column chromatography eluting with ($CHCl_3$/MeOH/NH_3 = 97:2:1) to afford **19** in 41 % yield as a pale yellow liquid[6] (Scheme 11).

Scheme 11



48 **49**

Compound **19** was fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis.

IR spectrum showed strong bands at 1711, 1600, 1419, 1366 cm^{-1}, the characteristic absorption bands for oxazolidine moiety.[6] The other prominent bands were observed at 3275, 2967, 1088, 1059, 922 cm^{-1}.

^1H NMR spectrum of **19** (Fig. 12) displayed following pattern. A multiplet between δ 1.30-1.45, integrating for two protons, was assigned to H_{5endo} and H_{6endo}. Another multiplet between δ 1.55-1.75, corresponding to four protons, was attributed to H_{5exo}, H_{6exo}, H_{3endo} and H_7. A doublet of doublet at δ 1.90 (J = 12.4, 8.7 Hz), integrating for one proton, was assigned to H_{3exo}. H_3-Methyl appeared as a singlet at δ 2.21. H_{2endo} proton was found resonating as doublet of doublet at δ 2.95 (J = 8.7, 4.8 Hz, 1H). A doublet at δ 3.68 (J = 4.1 Hz) and a triplet at δ 3.75 (J = 4.4 Hz), integrating for one proton each, were characterized to two bridgehead protons H_1 and H_4, respectively. The oxazolidine ring proton $H_{4'}$ appeared as a singlet at δ 5.77.

The retention of *exo*-stereochemistry in **19** was once again ascertained by detailed ^1H NMR decoupling experiment. The H_2 proton at δ 2.95 was found to couple with H_{3endo} at δ 1.65 and H_{3exo} at δ 1.90 but not with H_1 at δ 3.68. This correlation of protons confirmed the *endo*-orientation of H_2 and thus, implying the retainment of *exo*-orientation for oxazolidine moiety.

^{13}C NMR spectrum (Fig. 13) revealed a total of ten signals at δ 11.21, 29.14, 29.57, 38.02, 41.07, 56.03, 61.34, 100.58, 159.45, and 176.07 (fig 10). DEPT experiment characterized the signal appearing at δ 11.21 for the 3′-methyl group of oxazolidine moiety. The methylene carbon signals at δ 29.14 and 29.57 could be assigned to either C_5 and/or C_6, while the signal at δ 38.02 is assigned to C_8. The methine carbon signals at δ 41.07, 56.03, 61.34 and 100.58 were assigned to C_2, C_4, C_1, and C_7, respectively. Two downfield signals appearing at δ 159.45 and 176.07 were characterized to the quaternary carbons ($C_{3'}$ and $C_{5'}$) of the oxazolidine ring, respectively.

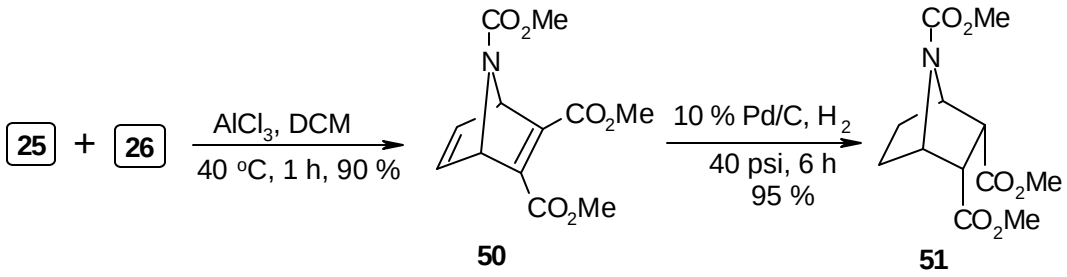
Mass spectrum (Fig. 12) gave a molecular ion peak at 179 (23) with base peak at 69. The other fragments were observed at 149 (10), 110 (M^+ - 69, 24), 94 (13) and 82 (19).

The above spectral analysis confirmed the structure of compound **19** which was further supported by comparing it with the data reported by Badio *et al.*[6]

3.2. [4 + 2]-Cycloaddition Approach for the Construction of 20:

Although we have demonstrated the synthesis of epiboxidine by [3+2]-cycloaddition approach, an alternate strategy was also considered for the preparation of precursor **20a** through [4+2]-cycloaddition of *N*-carbomethoxy pyrrole (**25**) with dimethyl acetylenedicarboxylate (**26**) in order to compare the efficiency of our [3+2]-cycloaddition approach. The known cycloaddition protocol by heating a neat mixture of **25** and **26** afforded **50** in poor yield[26] (42 %), due to the competing Michael addition[27] and retro Diels-Alder reaction.[27] Therefore, it was decided to carry out this cycloaddition reaction at a lower temperature (40 ^{o}C) using Lewis acid as a catalyst[28a,b]. Stirring of a mixture containing **25** and **26** in DCM at 40 ^{o}C in the presence of $AlCl_3$ (3 eq.) afforded **50** in 90 % yield. The cycloadduct **50** was hydrogenated at 40 psi over 10 % Pd/C to afford azanorbornane **51** in 95 % yield (Scheme 12).

Scheme 12

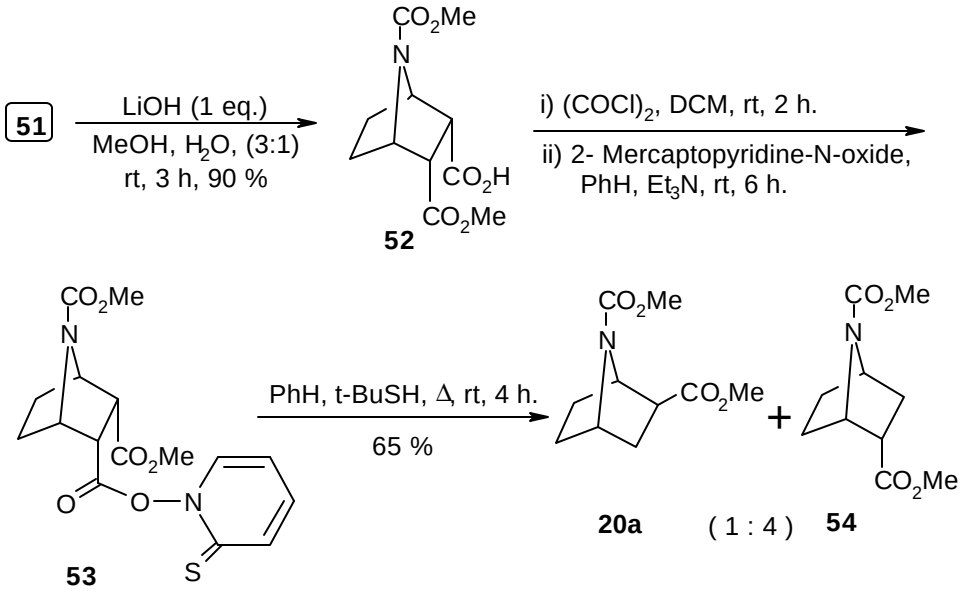


3.2.1. Decarboxylation of 51 in the presence of *t*-BuSH:

At this stage, the removal of one of the carboxylate moiety from **51** was essential to obtain the required compound **20**. The reductive radical decarboxylation route either by photochemical or thermal reaction of the corresponding thiohydroximate ester, obtained from *N*-hydroxy-2-thiopyridone in the presence of radical scavengers, developed by

Barton and co-workers,[29] was adopted to achieve the monodecarboxylation of azanorbornane diester.

Scheme 13



To this end, the diester **51** was hydrolyzed with 1 equiv. of LiOH in MeOH/H_2O (3:1) to obtain monoacid ester **52** in 90 % yield. The crude **52** was converted into its corresponding acid chloride by treating with 5 equiv. of oxalyl chloride which was subsequently transformed into the thiohydroximate ester (**53**) by stirring with 2-mercaptopyridine *N*-oxide in the presence of triethylamine. Pyrrolysis of the resultant **53** in the presence of *tert*-butyl mercaptan under argon atmosphere afforded **20a** (13 %) and **54** (52 %) as colorless liquids (Scheme 13). The formation of *exo*-isomer **20a** was possible by the epimerization caused by the reaction of **52** with triethylamine. However, epimerization of **54** could transform once again it to *exo*-isomer **20a** quantitatively.

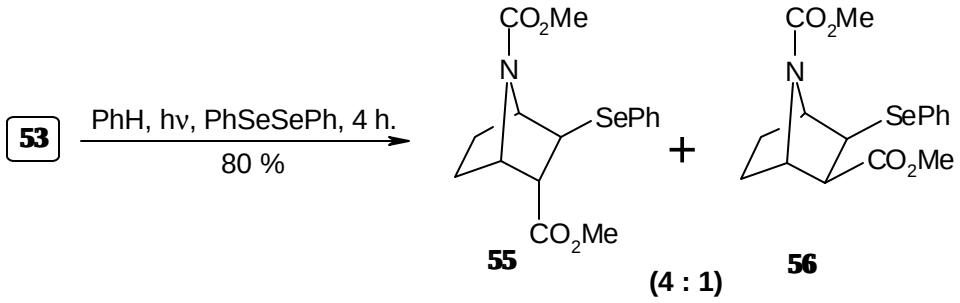
Both diastereomers **20a** and **54** were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis and by analogy with compounds **20d** and **47**, respectively. The details have been given in experimental section.

3.2.2. Decarboxylation of 51 in the presence of PhSeSePh:

Although we could synthesize **20a**, the moderate yield encountered in the reductive radical decarboxylation step using *tert*-butyl mercaptan as radical trap prompted us to develop an indirect route. We envisaged the use of PhSeSePh, known to be a better and efficient radical trapping agent than *tert*-butyl mercaptan.[30] It was expected that the stereoselective incorporation of –SePh group in the reductive radical decarboxylation step followed by selenoxide elimination and hydrogenation would generate the precursor **20**.

Towards this goal, the photolysis (400 W tungsten lamp) of thiohydroximate ester (**53**) was carried out in the presence of PhSeSePh under argon atmosphere for 4-6 h, which afforded selenylated products **55** and **56** in (4:1) ratio in 80 % yield as a pale yellow liquids (Scheme 14).

Scheme 14



3.2.2.1. Characterization of 55:

IR spectrum displayed sharp absorption bands at 1712 and 1707 cm^{-1}, characteristic of ester carbonyl and *N*-carbomethoxy moieties, respectively, along with other prominent bands at 2952, 1577, 1361, 1193 cm^{-1}.

^1H NMR spectrum (Fig. 14) revealed H_{5endo} and H_{6endo} protons as a multiplet between δ 1.35-1.60. Another two multiplets appearing between δ 1.65-1.80 and 1.80-1.95, integrating for one proton each, could be assigned to either H_{5exo} and/or H_{6exo}, respectively. The signal corresponding to H_{2exo} proton appeared as a triplet at δ 3.05 (J = 6.5 Hz, 1H). Two singlets appearing at δ 3.65 and 3.70, equivalents to three protons

each, were assigned to methyl protons of ester carbomethoxy and *N*-carbomethoxy moieties, respectively. Due to the absence of coupling between *endo* proton and bridgehead, the H_{3endo} appeared as a doublet at δ 3.75 (J = 7.1 Hz, 1H). The signals appearing at δ 4.25 (bs) and 4.55 (t, J = 5.1 Hz), integrating for one proton each, were shown to correspond to bowsprit bridgehead H_4 and/or H_1, respectively. The five aromatic protons of –SePh group were observed as a two bunch of multiplets between δ 7.20-7.30 (three protons) and 7.50- 7.60 (two protons).

From the above spectral analysis the stereochemistry of **55** was assigned as 7-carbomethoxy-2-*endo*-(carbomethoxy)-3-*exo*-(phenylseleno)-7- azabicyclo[2.2.1]heptane.

In ^{13}C NMR (Fig. 15) a total of eight signals appeared at δ 24.94, 29.65, 45.98, 52.19, 52.55, 55.48, 58.85, and 62.76, in the aliphatic region along with aromatic signals at δ 127.91, 129.24, 129.49, and 134.48 and carbonyl carbon signals at δ 155.94, 171.39. DEPT experiment suggested that two methylene carbons at δ 24.94 and 29.65 correspond to either C_5 and/or C_6. The signals at δ 52.19 and 52.55 correspond to methyl carbon of carbomethoxy and *N*-carbomethoxy moieties, respectively. The methine C_2 and C_3 carbons appeared at δ 45.98, 55.48 while other methine C_1 and/or C_4 carbons appeared at δ 58.85 and 62.76, respectively.

Mass spectrum (Fig. 14) displayed a molecular ion peak at 369 (12) with base peak at 127. Other fragments were observed at 220 (15), 212 (71), 157 (31).

3.2.2.2. Characterization of 56:

The IR spectrum of **56** was found almost identical to that of **55**.

In the ^1H NMR spectrum (Fig. 16) two multiplets appearing between δ 1.40-1.55 and 1.65-1.95, integrating for two protons each, were assigned to H_5, and H_6 protons, respectively. Due to the absence of coupling between *endo* hydrogen with the bridgehead hydrogen, the H_{2endo} and H_{3endo} appeared as a set of two doublets at δ 3.05 (J = 10.2 Hz, 1H) and 3.50 (J = 10.2 Hz, 1H), respectively. The methyl protons of ester carbomethoxy

and *N*-carbomethoxy group appeared as singlets at δ 3.70 (3H) and 3.73 (3H), respectively. Two bridgehead protons H_1 and H_4 appeared at δ 4.45 (bs, 1H) and 4.65 (bs, 1H), respectively. The phenyl protons of –SePh was observed as two sets of multiplets between δ 7.25-7.35 (3H) and δ 7.50-7.65 (2H).

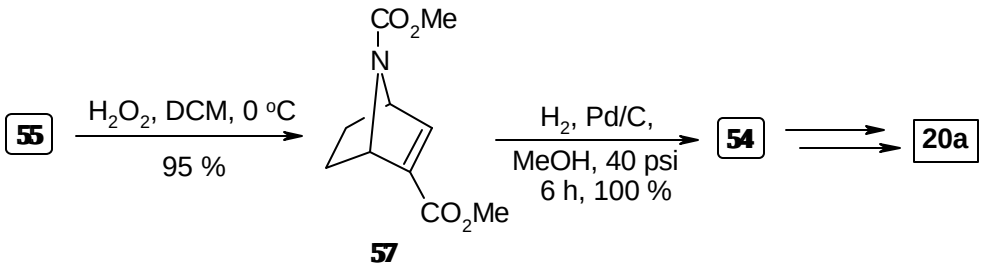
From the above spectral analyses, it is evident that there is no coupling observed between H_2 and H_3 with the bowsprit bridgehead H_1 and H_4, respectively, confirming the *exo* orientation of both ester and –SePh moieties in **56**. Therefore, the stereochemistry of compound **56** could be assigned as 7-carbomethoxy-2-*exo*-(carbomethoxy)-3-*exo*-(phenylseleno)-7- azabicyclo[2.2.1]heptane.

^{13}C NMR (Fig. 17) and mass spectral (Fig. 16) analyses were found in perfect agreement with the above assigned structure and have been detailed in experimental section.

3.2.3. Preparation of 7-Carbomethoxy-2-(carbomethoxy)-7-azabicyclo-[2.2.1]hept-2-ene (57).

The selenide **55** was oxidized with H_2O_2 at 0 ^{o}C to afford **57** in 95 % yield as a colorless liquid. Hydrogenation of **57** yielded **54** exclusively which upon epimerization gave key precursor **20a** (Scheme 15).

Scheme 15



IR spectrum of **57** showed a sharp band at 1721 and 1708 cm^{-1}, characteristic for ester carbonyl and *N*-carbomethoxy moieties, respectively along with other prominent bands at 2955, 2879, 1603, 1284, 1080 cm^{-1}.

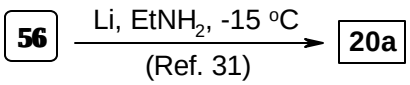
^{1}H NMR spectrum (Fig. 18) displayed two singlets at δ 3.65 and 3.78, equivalents to three protons each, assignable to methyl protons of carbomethoxy and *N*-carbomethoxy moieties, respectively. Two sets of multiplets appearing between δ 1.15-1.35 (2H) and 1.90-2.15 (2H) were assigned to H_5 and H_6 protons, respectively. The signals corresponding to two bowsprit bridgehead protons H_4 and H_1 appeared as broad singlet at δ 4.75 (1H) and 5.05 (1H), respectively. A broad singlet at δ 7.03 (1H) was assigned to H_3 olefinic proton.

^{13}C NMR spectrum (Fig. 19) showed a total of five signals in aliphatic region at δ 23.96, 51.43, 52.36, 59.67 and 61.01 along with four downfield signals at δ 140.63, 144.12, 155.49 and 163.11. DEPT experiment revealed that both methylene C_5 and C_6 appeared at δ 23.96. Methyl carbons of carbomethoxy (-$CO_2\underline{C}H_3$) and (-N-$CO_2\underline{C}H_3$) moieties appeared at δ 51.53 and 52.36, respectively. The methine carbon signals appearing at δ 59.67 and 61.01 were assigned to C_4 and C_1, respectively. Two vinylic carbons C_2 and C_3 of the azabicyclo heptane ring appeared at δ 140.63 and 144.12, respectively. The signals at δ 155.49 and 163.11 correspond to the carbonyl carbons of carbomethoxy and *N*-carbomethoxy moieties, respectively.

Mass spectrum (Fig. 18) showed the molecular ion peak at 212 (1) with a base peak at 152. The other fragments were observed at 183 (77), 108 (56) and 93 (22).

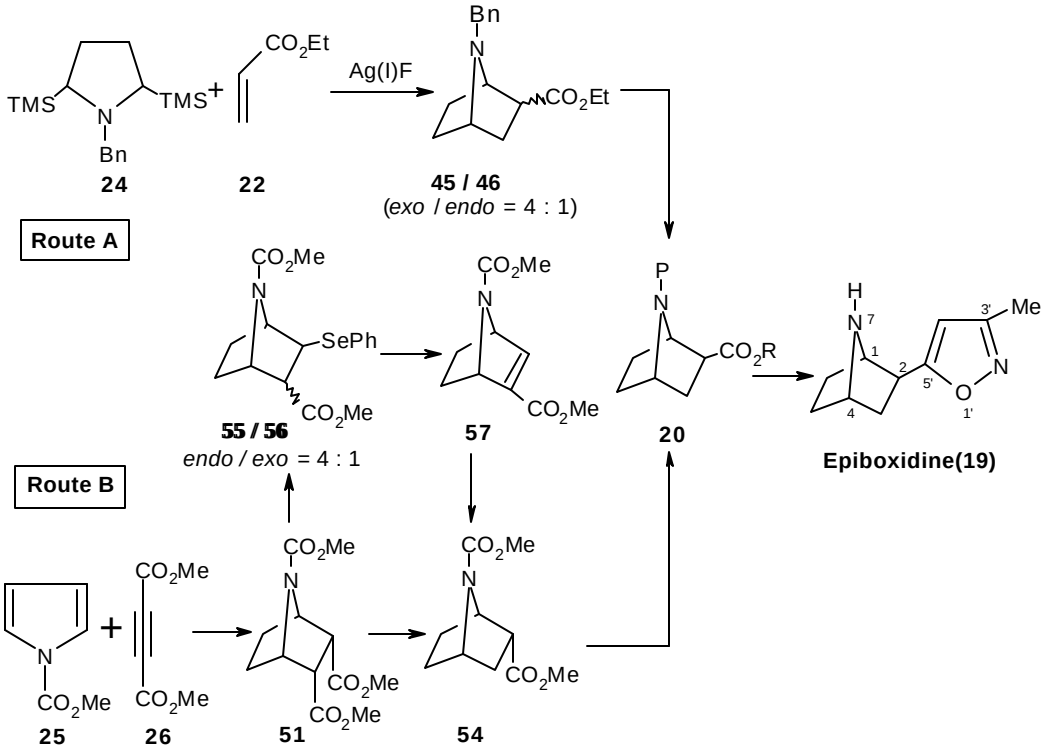
However, reductive removal of the phenylselenyl moiety from **56** by the known protocol[31] afforded **20a** directly (Scheme 16).

Scheme 16



4. Conclusion

In summary, synthesis of epiboxi dine (**19**) was accomplished by employing [3+2] cycloaddition reaction of pyrrolidine based azomethine ylide with ethyl acrylate. Additionally, an alternate approach for the construction of the precursor **20** for the synthesis of **19** is also suggested *via* [4+2] cycloaddition of *N*-carbomethoxy pyrrole (**25**) with dimethyl acetylenedicarboxylate (**26**). Comparatively, the [3+2] cycloaddition approach is found to be more efficient, shorter, economically viable and high yielding than the conventional [4+2] cycloaddition strategy. The synthetic scheme presented in this chapter can be summarized schematically as follows.



Route A, P = -Boc, R = Et

Route B, P = -CO_2Me, R = Me

Route A, [3 + 2] cycloaddition strategy

Route B, [4 + 2] cycloaddition strategy

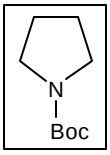
5. Experimental

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which were cooled 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*.[32] Benzene, DCM, triethyl amine were distilled from CaH_2 and stored over molecular sieves and KOH, respectively. Solvents used for chromatography were distilled at respective boiling points.

All commercial reagents are obtained from Aldrich Chemical Co. and Lancaster Chemical Co (UK). Progress of the reaction was monitored by TLC. Column chromatography was performed on Silica gel 60-120 / 100-200 / 230-400 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. ^{1}H NMR spectra were recorded using TMS as internal reference on Bruker AC-200, Bruker MSL-300 and Bruker DRX-500 instruments using $CDCl_3$ as solvent. Chemical shifts are reported in δ. ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker MSL-300 and Bruker DRX-500 instruments operating at 50.32 MHz, 75.3 MHz and 125.3 MHz respectively. Mass spectra were recorded on Finnigan-Mat 102 °C mass spectrometer and are obtained at an ionization potential of 70 eV.

5.1. Preparation of *N*-(*tert*-Butyloxycarbonyl) pyrrolidine (41):



To a solution of pyrrolidine (13.0 g, 182.79 mmol) and triethylamine (23.2 g, 229.3 mmol) in dioxan (100 mL), *tert*-butyl azidoformate (22 g, 153.85 mmol) was added dropwise over 15 min. The pH of the reaction mixture was maintained at 12 by the addition of excess triethylamine. The reaction mixture was stirred overnight. After the

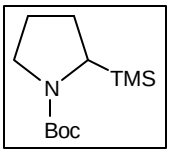
evaporation of dioxan, the residue was extracted in ether, washed with water (3×50 mL) followed by brine (50 mL). Ether layer was dried over Na_2SO_4, concentrated and the resultant brown oil was purified by vacuum distillation (bp. 55-57 °C/ 1mm) to obtain 23.7 g (90 %) of **41** as a colorless liquid.

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

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.45 (s, 9H), 1.80-1.95 (m, 4H), 3.37 (t, J = 7.3 Hz, 4H).

MS (m/ z) : 171 (M^+, 11 %), 114 (100 %), 57 (82 %).

5.2. Preparation of *N*-(*tert*-Butyloxycarbonyl)-2-trimethylsilyl pyrrolidine (42):



A 250 mL two neck flask equipped with a magnetic stirring bar and argon balloon was charged with *N*-Boc pyrrolidine (**41**) (5.0 g, 29.24 mmol) in 30 mL of dry ether and the flask was cooled to –78 °C. TMEDA (4.08 g, 35.09 mmol) followed by sBuLi (1.5 M in cyclohexane, 23.4 mL, 35.09 mmol) were added to the stirring mixture dropwise over 15 min. The mixture was further allowed to stir for 2 h at –78 °C. Chlorotrimethylsilane (3.81 g, 35.09 mmol) was added dropwise into the flask. The reaction mixture was allowed to warm to rt and treated with 10 mL of saturated 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 (50 mL) and dried over Na_2SO_4. The organic extract was concentrated and the crude residue was purified by fractional distillation (bp 55- 57 °C/ 0.5 mm) to give 6.39 g (90 %) of **42** as a colorless liquid.

IR (neat) : 1692, 1478, 1365, 1246, 1170 cm^{-1}.

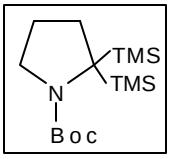
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 9H), 1.45 (s, 9H), 1.75-1.95 (m, 3H), 1.95-2.05 (m, 1H), 3.15-3.30 (m, 2H), 3.35-3.60

(m, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ -2.30, 27.80, 28.40, 46.70, 47.50, 78.0, 154.50.

MS (m/ z) : 243(M^+, 1), 186 (43), 172 (100), 142 (94).

5.3. Preparation of *N*-(*tert*-Butyloxycarbonyl)-2,2-bis(trimethylsilyl)pyrrolidine (43):



Treating a solution of **42** (4.86 g, 20 mmol) in ether with s-BuLi (24 mmol, 16 mL of 1M solution in cyclohexane) in the presence of TMEDA (2.79 g, 24 mmol), in the identical manner as described for **42**, followed by quenching with TMSCl (2.61 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 **43** as a pale yellow liquid. Further elution with same solvent system gave a trace amount of **43** (in < 5 % yield).

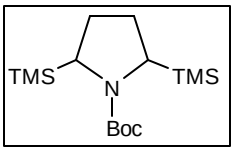
IR (neat) : 1690, 1392, 1248, 1169 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : 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 ($CDCl_3$, 50.3 MHz) : δ 0.18, 25.50, 28.80, 32.20, 46.50, 48.50, 78.10, 154.60.

MS (m/ z) : 258 (72), 244 (70), 214 (37), 186 (36), 73 (100).

5.4. Preparation of *N*-(*tert*-Butyloxycarbonyl)-2,5-bis(trimethylsilyl) pyrrolidine (44):



A 250 mL two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of **42** (5 g, 20.57 mmol) in 30 mL of dry ether and was cooled to –45 °C. TMEDA (2.87 g, 24.69 mmol) followed by s-BuLi (1.5 M in cyclohexane, 16.5 mL, 24.69 mmol) were added dropwise at the same temperature. 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 (2.68 g, 24.69 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, diluted with 10 mL of saturated NH_4Cl solution and worked up as mentioned in previous experiment. The crude residue was purified by silica gel column chromatography eluting with hexane/EtOAc (99:1) to afford 4.54 g (70 %) of **44** as a pale yellow liquid.

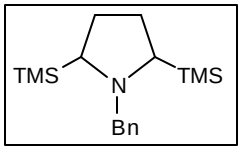
IR (neat) : 1684, 1406, 1365, 1171 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : 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 ($CDCl_3$, 50.3 MHz) : δ -1.03, -0.50, 28.93, 29.0, 49.44, 50.0, 78.96, 154.82.

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

5.5. Preparation of *N*-Benzyl-2,5-bis(trimethylsilyl) Pyrrolidine (24):



To a stirring solution of **44** (3.15 g, 10.0 mmol) in 40 mL of dry DCM at 0 °C contained in a 100 mL two neck round bottom flask equipped with argon gas balloon was added trifluoroacetic acid (5.70 g, 50.0 mmol) dropwise over a period of 15 min. The reaction mixture was allowed to warm to rt and stirring was continued further for 3 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 DCM (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 that was utilized 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 dry acetonitrile, K_2CO_3 (1.49 g, 10.8 mmol) and benzyl chloride (1.08 g, 8.53 mmol) were added. The

resultant suspension was refluxed for 7-8 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled, filtered and the solvent was evaporated under vacuum. The crude yellow liquid was purified by silica gel column chromatography eluting with hexane/EtOAc (98:2), to obtain 2.08 g (80 %) of **24** as pale yellow liquid.

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

^{1}H NMR ($CDCl_3$, 200 MHz) : 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 = 12.9 Hz, 1H), 3.80 (d, J = 12.9 Hz, 1H), 7.20-7.35 (m, 5H).

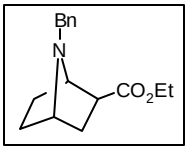
^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ -1.6, 26.80, 56.0, 60.10, 126.80, 128.10, 129.40, 141.70.

MS (m/ z) : 305 (M^+, 3), 290 (17), 233 (100), 91 (90), 73 (54).

5.6. [3+2]-Cycloaddition of *N*-Benzyl-2,5-bis(trimethylsilyl)pyrrolidine (24) with ethyl acrylate :

An argon flushed two-neck flask equipped with a magnetic bar was charged with Ag(I)F (1.87 g, 14.74 mmol) (dried previously under vacuum at 40 °C) and ethyl acrylate(0.78 g, 7.79 mmol) in 30 mL of dry dichloromethane. Compound **24** (2.0 g, 6.56 mmol) in 30 mL dry DCM was introduced into the flask dropwise over a period of 15 min. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the surface of the flask in the form of mirror. The reaction mixture was periodically monitored by TLC. After stirring for 8-10 h, the reaction mixture was filtered through a small plug of celite and solvent was evaporated to give a crude brown residue. The crude residue was purified by silica gel column chromatography eluting with hexane/ethylacetate (9:1) to afford 0.25 g of **46** (15%) as a pale yellow liquid and further elution with same solvent system yielded 1.02 g of **45** (60%), as a pale yellow liquid.

5.6.1. 7-Benzyl-2-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane (major diastereomer) (45):



IR (neat) : 2958, 2361, 1732, 1451, 1180 cm^{-1}.

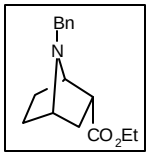
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.35 (m, 2H), 1.50 (dd, *J* = 12.2, 9.3 Hz, 1H), 1.85 (m, 2H), 2.25 (m, 1H), 2.40 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.35 (bs, 1H), 3.40 (d, *J* = 13.7 Hz, 1H), 3.60 (d, *J* = 13.7 Hz, 1H), 3.63 (bs, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 7.15-7.40 (m, 5H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 13.98, 26.65, 26.82, 33.2, 47.69, 51.24, 59.2, 60.1, 62.98, 126.36, 127.8, 127.93, 140.0, 174.12.

MS (m/ z) : 259 (M^+, 6), 158 (24), 131 (11), 104 (10), 91 (100).

HRMS : calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1569.

5.6.2. 7-Benzyl-2-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (minor diastereomer) (46):



IR (neat) : 2961, 2361, 1724, 1442, 1171 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.25 (t, *J* = 7.9 Hz, 3H), 1.40-1.50 (m, 2H), 1.65-1.90 (m, 3H), 1.90-2.10 (m, 1H), 3.10 (m, 1H), 3.32 (t, *J* = 4.5 Hz, 1H), 3.55 (t, *J* = 4.3 Hz, 1H), 3.60 (bs, 2H), 4.15 (q, *J* = 7.9 Hz, 2H), 7.20-7.45 (m, 5H).

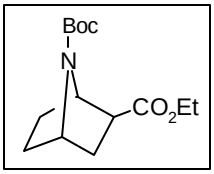
^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 14.16, 24.09, 28.11, 30.99, 45.66, 51.66, 60.13,

60.21, 62.05, 126.7, 128.12, 128.31, 139.79, 173.89.

MS (m/ z) : 259 (M^+, 6), 158 (27), 130 (14), 91 (100).

Anal. : calcd for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16; N, 5.40. Found: C, 74.26; H, 8.39; N, 5.52.

5.7. Preparation of 7-(*tert*-Butyloxycarbonyl)-2-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane (20d):



To a solution of **45** (0.5 g, 1.93 mmol) in 30 mL of ethanol was added palladium hydroxide (0.1 g) and the resultant suspension was hydrogenated (50 *psi*, rt) for 2 days. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The resultant crude amine dissolved in 30 mL of DCM was exposed with a solution of $(Boc)_2O$ (0.5 g, 2.3 mmol) in DCM followed by triethylamine (0.8 mL) under argon atmosphere. The resulting mixture was stirred for 18 h and concentrated. The residue was purified by silica gel column chromatography eluting with hexane/EtOAc (9:1), to afford 0.47 g of **20d** (90 %) as a colorless liquid.

IR (neat) : 2979, 1738, 1706, 1368, 1156 cm^{-1}.

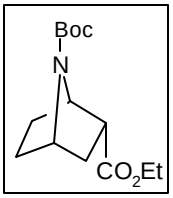
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.25 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 1.50-1.70 (m, 2H), 1.70-1.90 (m, 3H), 2.20-2.35 (m, 1H), 2.57 (dd, J = 8.6, 3.9 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.30 (t, J = 4.3 Hz, 1H), 4.55 (d, J = 4.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 13.79, 27.81 28.46, 29.12, 32.84, 47.17, 55.45, 58.89, 60.27, 79.03, 154.3, 172.73.

MS (m/ z) : 269 (M^+, 1), 196 (23), 169 (52), 96 (42), 69 (100).

Anal. : calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20.
Found: C, 62.34; H, 8.85; N, 5.52.

5.8. Preparation of 7-(*tert*-Butyloxycarbonyl)-2-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (47):



A similar reaction sequence as described above for the preparation of **20d** (Section 5.7) was followed from **46** to obtain **47** in (90 %) yield as a colorless liquid.

IR (neat) : 2978, 1734, 1703, 1366, 1156 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.25 (t, J = 7.1 Hz, 3H), 1.40 (s, 9H), 1.45-1.55 (m, 2H), 1.60-1.95 (m, 4H), 2.90-3.05 (m, 1H), 4.05-4.25 (m, 3H), 4.35 (t, J = 4.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 14.09, 25.22, 28.12, 29.08, 32.28, 46.35, 57.04, 58.19, 60.46, 79.63, 155.18, 172.42.

MS (m/ z) : 169 (95), 124 (85), 96 (58), 69 (100).

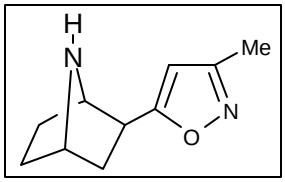
Anal. : calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20.
Found: C, 62.24; H, 8.79; N, 5.44.

5.9. Epimerization of *endo* isomer 47 to 20d:

A mixture of **47** (0.25 g, 0.93 mmol) and anhydrous K_2CO_3 (0.26 g, 1.88 mmol) in dry methanol (15 mL) was refluxed for 1 h. The reaction mixture was cooled to 0 ^oC, quenched by adding saturated NH_4Cl solution, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The aqueous layer was acidified (pH = 2) by adding 6 N HCl at 0 ^oC, extracted with DCM, dried over Na_2SO_4, and the solvent was evaporated. The crude acid was dissolved in methanol and the solution was treated with $SOCl_2$ (0.12 g, 1.01 mmol) at 0 ^oC. After stirring for 10 h, the reaction mixture was washed with $NaHCO_3$ solution,

extracted with DCM, dried over Na_2SO_4 and concentrated. The combined crude product was purified by silica gel column chromatography to afford **20d** (0.24 g, 95 %) as a colorless liquid.

5.10. Transformation of 20d in to Epiboxidine (19):



A solution of acetone oxime (0.19 g, 2.6 mmol) in 10 mL of dry THF at 0 ^{0}C was treated dropwise with n-butyllithium (2.1 M in hexane, 2.70 mL, 5.67 mmol), and the reaction mixture was allowed to warm to room temperature over 30 min. A solution of **20d** (0.5 g, 1.86 mmol) in 10 mL of THF was introduced dropwise at room temperature. The reaction mixture was refluxed for 45 min and the solvent was removed under argon atmosphere. The crude obtained was dissolved in 8 mL of concentrated HCl and heated at 80 ^{0}C for 4 h. The mixture was cooled, diluted with water, and washed with ethyl acetate (2 $\times$ 10 mL). The aqueous layer was basified with saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2 (3 $\times$ 30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with ($CHCl_3$/MeOH/NH_3 = 97:2:1), to afford **19** (0.135 g) in 41% yield as a pale yellow liquid.

IR (neat) : 3275, 2967, 2875, 1711, 1600, 1419, 1366, 1059, 1008, 922 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.30-1.45 (m, 2H, H_{5endo}, H_{6endo}), 1.55-1.75 (m, 4H, H_{5exo}, H_{6exo}, H_{3exo}, H-7), 1.90 (dd, J = 12.4, 8.7 Hz, 1H, H_{3endo}), 2.21 (s, 3H, 3′-Methyl), 2.95 (dd, J = 8.7, 4.8 Hz, 1H, H_{2endo}), 3.68 (d, J = 4.1 Hz, 1H, H-1), 3.75 (t, J = 4.4 Hz, 1H, H-4), 5.77 (s, 1H,

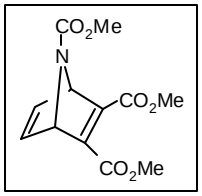
H-4′).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 11.21, 29.14, 29.57, 38.02, 41.07, 56.03, 61.34, 100.58, 159.45, 176.07.

MS (m/ z) : 179 (M^+, 23), 149 (10), 110 (24), 94 (13), 82 (19), 69 (100).

HRMS : calcd for $C_{10}H_{14}N_2O$ 178.1106, found 178.1103.

5.11. Synthesis of 7-Carbomethoxy-2,3-di(carbomethoxy)-2,5-diene-7-azabicyclo[2.2.1]heptane (50):

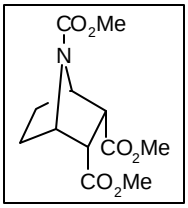


To a stirring solution of **25** (7.0 g, 56 mmol) and DMAD (**26**) (7.95 g, 56 mmol) in 100 mL of dry DCM at 0 °C in a 250 mL two neck flask equipped with argon balloon was added $AlCl_3$ (22.4 g, 168 mmol) portion wise over a period of 15 min at 0 °C. The reaction mixture was heated up to 40 °C and stirred for an additional 2 h at this temperature. The reaction mixture was cooled to rt, diluted with DCM, washed with water, dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography eluting with hexane/EtOAc (7:3), to obtain 13.45 g (90 %) of **50** as a colorless liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.65 (s, 3H), 3.83 (s, 6H), 5.52 (s, 2H), 7.15 (s, 2H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 24.90, 47.50, 51.80, 52.60, 59.30, 155.90, 171.00.

5.12. Preparation of 7-Carbomethoxy-2-*endo*-3-*endo*-di(carbomethoxy)-7-azabicyclo[2.2.1]heptane (51).



A solution of **50** (10.0 g, 37.45 mmol) in 70 mL ethanol containing 10% Pd/C (0.8 g, 20 mole %) was hydrogenated (40 *psi,* rt) for 8 h. The reaction mixture was filtered and the filtrate was evaporated and chromatographed over silica gel, eluting with hexane/EtOAc (8:2) to afford 9.67 g (95%) of **51** as a colorless liquid.

IR (neat) : 2954, 1716, 1605, 1441, 1078 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.65-1.80 (m, 2H), 1.90-2.05 (m, 2H), 2.25 (bs, 2H), 3.65 (s, 6H), 3.68 (s, 3H), 4.45 (bs, 2H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 24.95, 47.26, 51.58, 52.56, 59.13, 155.65, 170.83.

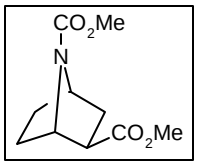
MS (m/z) : 272 (M^+, 2), 146 (80), 127 (100), 114(57).

5.13. Decarboxylation of 51 in the presence of *t*-BuSH:

A solution of **51** (5.0 g, 18.38 mmol) in methanol-water (3:1, 80 mL) containing LiOH-H_2O (0.77 g, 18.38 mmol) was stirred for 3 h at room temperature. The solvent was evaporated, diluted with water, and washed with CH_2Cl_2 (2 × 10 mL). The aqueous layer was cooled to 0 ^{o}C, acidified (pH = 2) with 6N HCl, and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and evaporated to give **52** as a foamy white solid (4.27 g) in 90 % yield. The resultant crude acid was dissolved in 100 mL dry DCM was treated with oxalyl chloride (4.34 mL, 49.8 mmol) and DMF (0.1 mL) and the contents were stirred at rt for 2 h under argon atmosphere. The solvent was evaporated under vacuum to give the corresponding acid chloride as a brown solid. The crude acid

chloride was dissolved in dry benzene (100 mL) and to the resultant solution were added DMAP (0.2 g, 1.6 mmol), *N*-hydroxy-2-mercaptopyridine (2.53 g, 19.9 mmol) and triethylamine (4.6 mL, 33.2 mmol) under argon atmosphere. After stirring for 4 h at room temperature the solid suspension was allowed to settle and the supernatant solution was added through syringe to a refluxing solution of *tert*-butyl mercaptan (7.5 mL) in 100 mL of dry benzene. The resultant mixture was refluxed for 4 h, cooled, washed successively with aqueous 1N NaOH solution, water and brine and dried over Na_2SO_4. The benzene layer was concentrated and the crude residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (8:2), to afford **20a** (0.51 g, 13%) and **54** (2.03 g, 52%) as a colorless liquids.

5.13.1. 7-Carbomethoxy-2-*exo*-(carbomethoxy)-7-azabicyclo[2.2.1]heptane (20a).



IR (neat) : 2954, 2879, 1737, 1704, 1634, 1367, 1161 cm^{-1}.

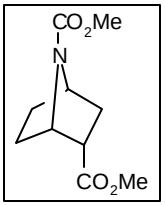
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30-1.55 (m, 2H, H_{5endo}, H_{6endo}), 1.63 (dd, J = 12.5, 8.9 Hz, 1H, H_{3endo}), 1.75-1.95 (m, 2H, H_{5exo}, H_{6exo}), 2.17-2.35 (m, 1H, H_{3exo}), 2.55 (dd, J = 8.9, 4.9 Hz, 1H, H_{2endo}), 3.63 (s, 3H), 3.67 (s, 3H), 4.35 (t, J = 4.2 Hz, 1H, H_4), 4.55 (d, J = 3.7 Hz, 1H, H_1).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 28.63, 29.11, 33.29, 47.18, 51.69, 52.0, 55.69, 59.08, 155.53, 173.42.

MS (m/ z) : 213 (M^+, 16), 184 (13), 154 (39), 126 (100), 82 (17).

HRMS : calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.0999.

5.13.2. 7-Carbomethoxy-2-*endo*-(carbomethoxy) -7-azabicyclo[2.2.1]heptane (54).



IR (neat) : 2954, 1708, 1737, 1633, 1444 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.40-1.55 (m, 2H, H_{5endo}, H_{6endo}), 1.70-2.10 (m, 4H, H_{5exo}, H_{6exo}, H_3), 2.95-3.15 (m, 1H, H_{2exo}), 3.71 (s, 3H), 3.74 (s, 3H), 4.28 (t, J = 5.5 Hz, 1H, H_4), 4.50 (t, J = 5.5 Hz, 1H, H_1).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 25.49, 29.24, 32.48, 46.35, 51.77, 52.36, 57.08, 58.16, 155.84, 172.72.

MS (m/ z) : 213 (M^+, 15), 184 (12), 154 (37), 126 (100), 82 (19).

Anal. : calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.65; H, 7.21; N, 6.42.

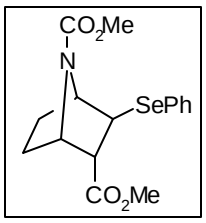
5.14. Epimerization of 54 to 20a:

A similar reaction procedure was adopted, as described above (Section 5.9) for the epimerization of **47** to **20d**, to epimerize **54** to **20a**.

5.15. Decarboxylation of 53 in the presence of PhSeSePh:

An identical decarboxylation (Section 5.13) procedure was carried out in the presence of PhSeSePh instead of *tert*-butyl mercaptan. The crude residue was purified by silica gel column chromatography, eluting with hexane/ethylacetate (7:3) to afford **55** (64%) and **56** (16%) as a pale yellow liquids.

5.15.1. 7-Carbomethoxy-2-*endo*-(carbomethoxy)-3-*exo*-(phenylseleno)-7-azabicyclo[2.2.1]heptane (55):



IR (neat) : 2952, 1712, 1707, 1577, 1361, 1193 cm^{-1}.

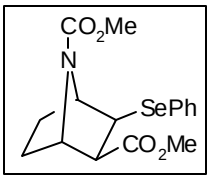
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35-1.60 (m, 2H), 1.65-1.80 (m, 1H), 1.80-1.95 (m, 1H), 3.05 (t, J = 6.5 Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.75 (d, J = 7.1 Hz, 1H), 4.25 (bs, 1H), 4.55 (t, J = 5.1 Hz, 1H), 7.20-7.30 (m, 3H), 7.50-7.60 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 24.94, 29.65, 45.98, 52.19, 52.55, 55.48, 58.85, 62.76, 127.91, 129.24, 129.49, 134.48, 155.94, 171.39.

MS (m/ z) : 369 (M^+, 12), 220 (15), 212 (71), 157 (31), 127 (100).

HRMS : calcd for $C_{16}H_{19}NO_4Se$ 369.0479, found 369.0487.

5.15.2. 7-Carbomethoxy-2-*exo*-(carbomethoxy)-3-*exo*-(phenylseleno)-7-azabicyclo[2.2.1]heptane (56):



IR (neat) : 2952, 1707, 1578, 1359, 1105 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.40-1.55 (m, 2H), 1.65-1.95 (m, 2H), 3.05 (d, J = 10.2 Hz, 1H), 3.50 (d, J = 10.2 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 4.45 (bs, 1H), 4.65 (bs, 1H),

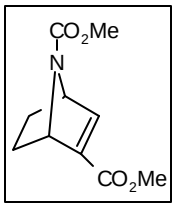
7.25-7.35 (m, 3H), 7.50-7.65 (m, 2H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 28.46, 28.77, 48.36, 51.07, 52.06, 53.34, 58.52, 62.67, 127.19, 128.85, 130.79, 133.4, 155.16, 170.55.

MS (m/ z) : 369 (M^+, 2), 212 (37), 157 (24), 126 (100).

Anal. : calcd for $C_{16}H_{19}NO_4Se$: C, 52.18; H, 5.20; N, 3.80. Found: C, 52.34; H, 5.37; N, 3.61.

5.16. Preparation of 7-Carbomethoxy-2-(carbomethoxy)-7-azabicyclo[2.2.1]hept-2-ene (57):



To a stirring solution of **55** (2.0 g, 5.42 mmol) in 20 mL of CH_2Cl_2 was added H_2O_2 (30%, 2 mL) dropwise at 0 °C. The resulting reaction mixture was allowed to stir at room temperature for 30 min, washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. The organic layer was concentrated and chromatographed on silica gel, eluting with hexane/EtOAc (9:1) to afford 1.09 g (95%) of **57** as a colorless liquid.

IR (neat) : 2955, 2879, 1721, 1708, 1603, 1284, 1080 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15-1.35 (m, 2H), 1.90-2.15 (m, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 4.75 (bs, 1H), 5.05 (bs, 1H), 7.03 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 23.96, 51.43, 52.36, 59.67, 61.01, 140.63, 144.12, 155.49, 163.11.

MS (m/ z) : 212 (M^+, 1), 183 (77), 152 (100), 108 (56), 93 (22), 59 (32).

Anal. **:** calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63.
Found: C, 56.55; H, 6.35; N, 6.93.

5.17. Preparation of 7-Carbomethoxy-2-*endo*-(carbomethoxy)-7-azabicyclo-[2.2.1]heptane (54).

A suspension of **57** (1.0 g, 4.72 mmol) and 0.2 g of 10% Pd/C in 15 mL ethanol was hydrogenated (40 *psi*, rt) for 6 h. The reaction mixture was filtered, concentrated, and chromatographed over silica gel, eluting with hexane/EtOAc (9:1), to afford 1.0 g, (100%) of **54** as a colorless liquid.

6. References

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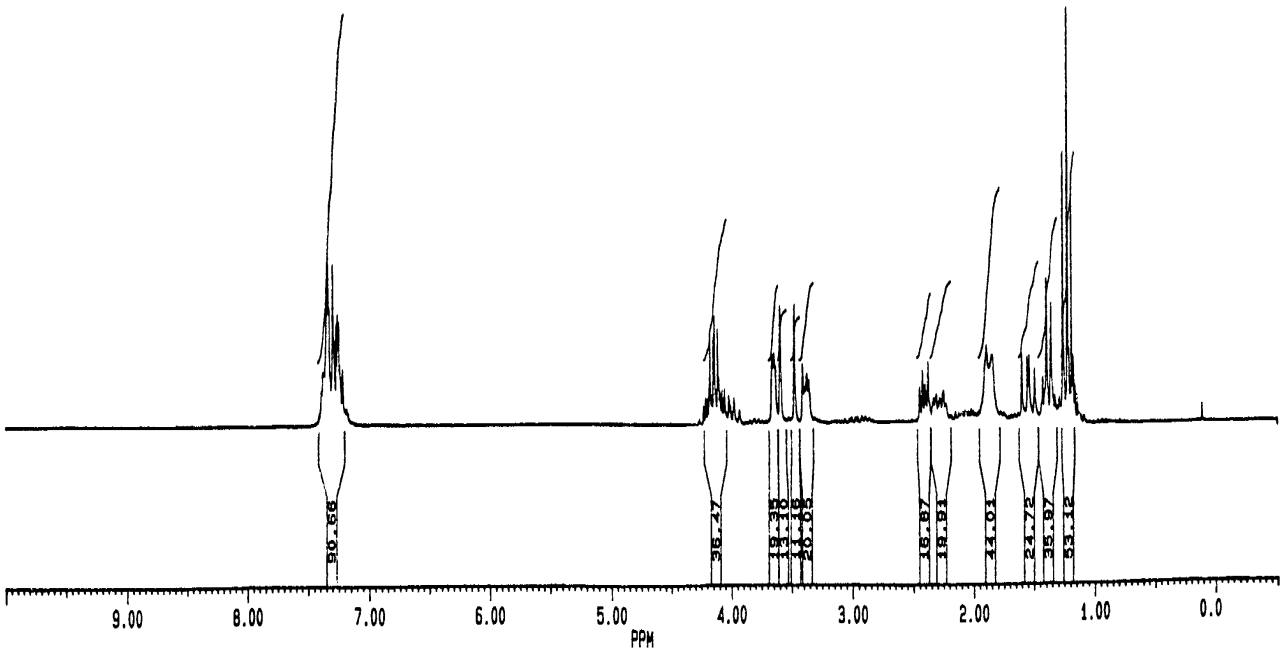
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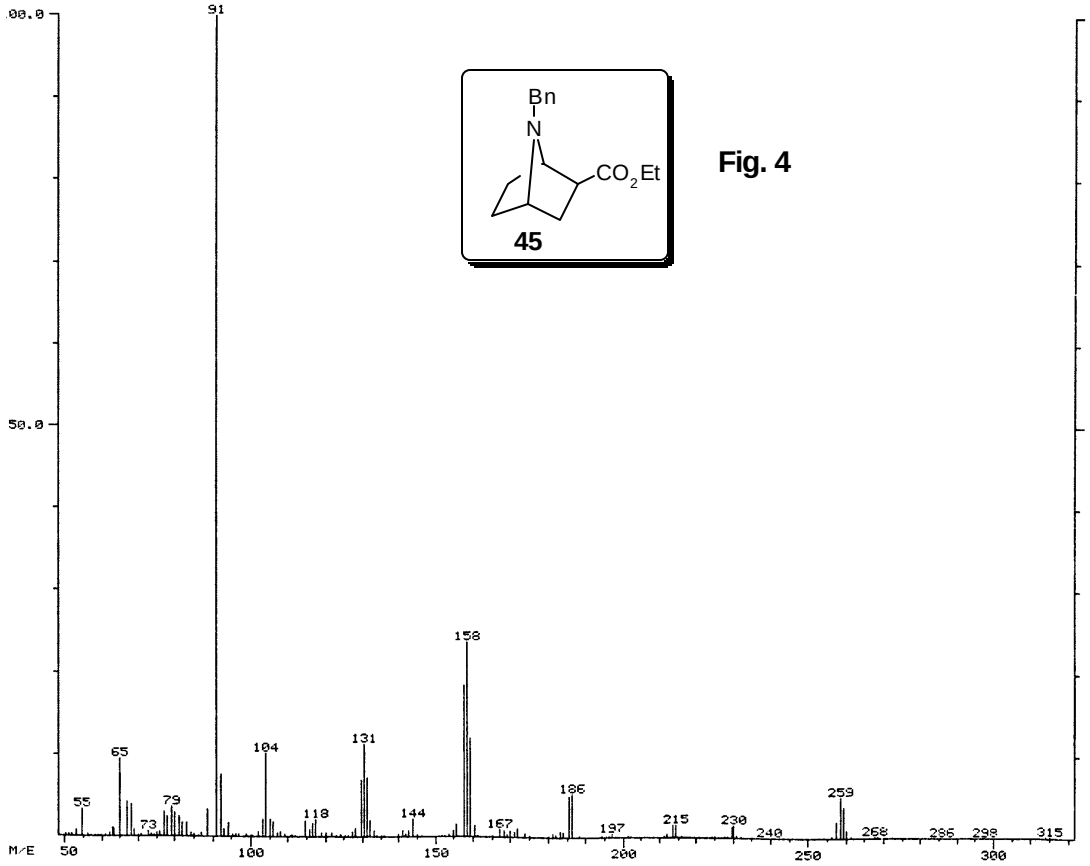
36.47
13.35
13.10
11.46
20.05
16.87
18.81
44.01
24.75
35.87
53.12
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM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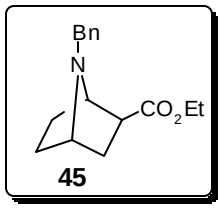
50.0
M/E
91
65
55
79
73
104
118
131
144
158
167
186
197
215
230
240
259
268
285
298
315
50
100
150
200
250
300

Bn
N
CO2Et

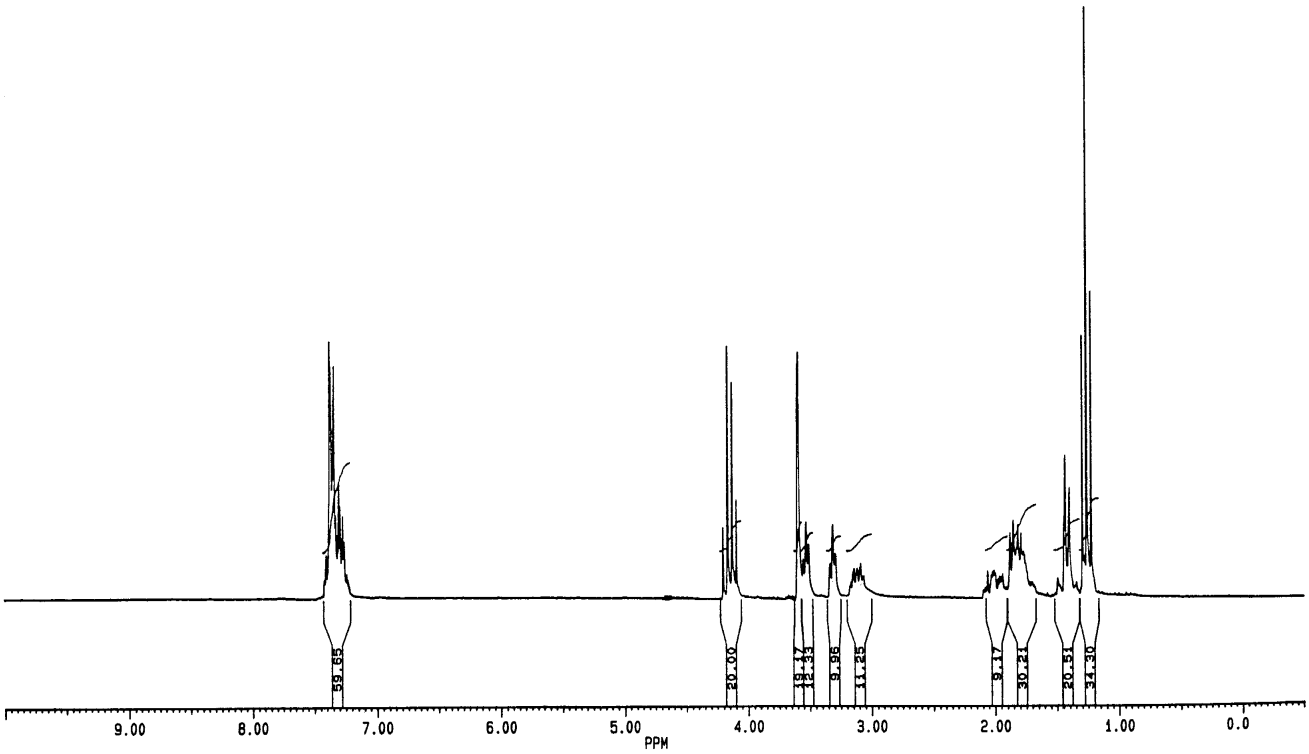
45

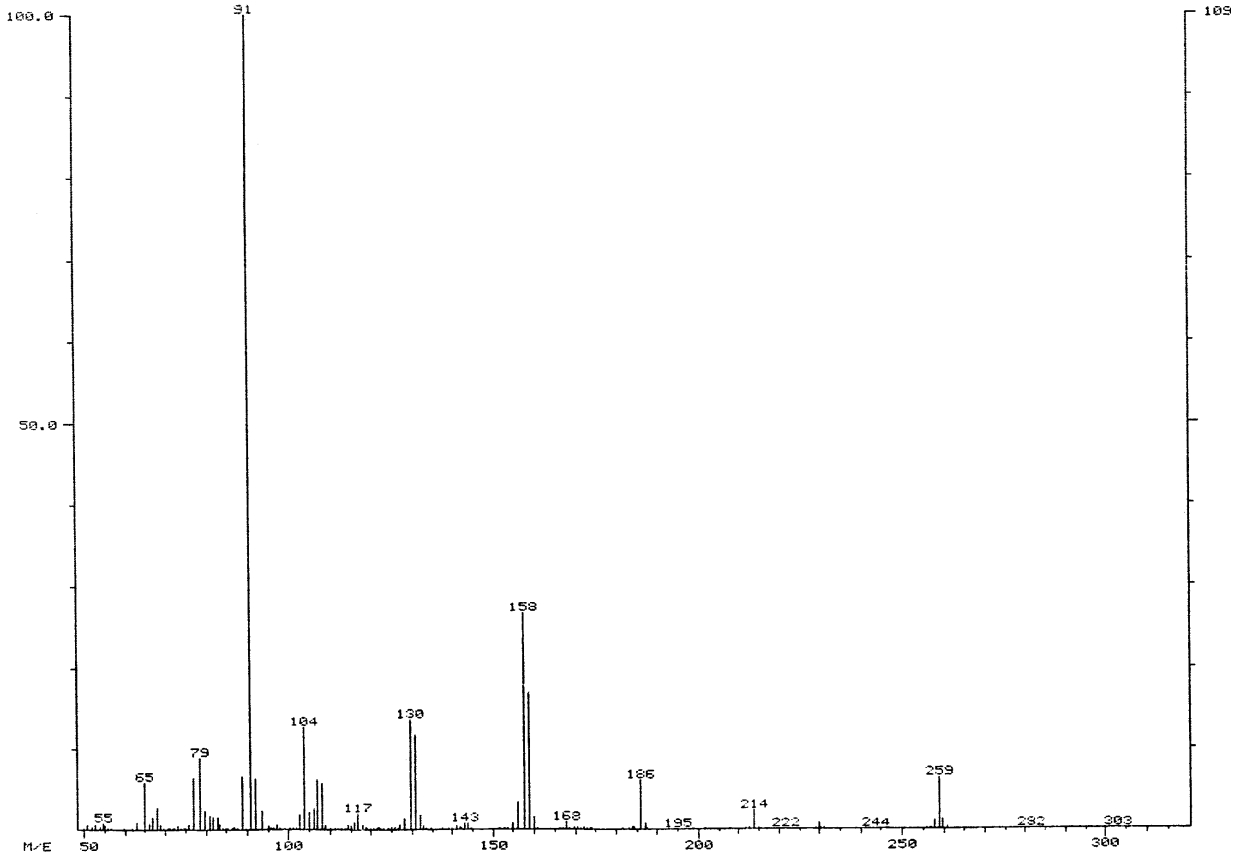
Fig. 4



45

Fig. 5


9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM
59.65
20.00
18.47
12.33
9.86
11.25
9.17
30.21
20.81
34.30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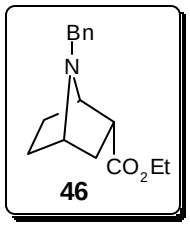
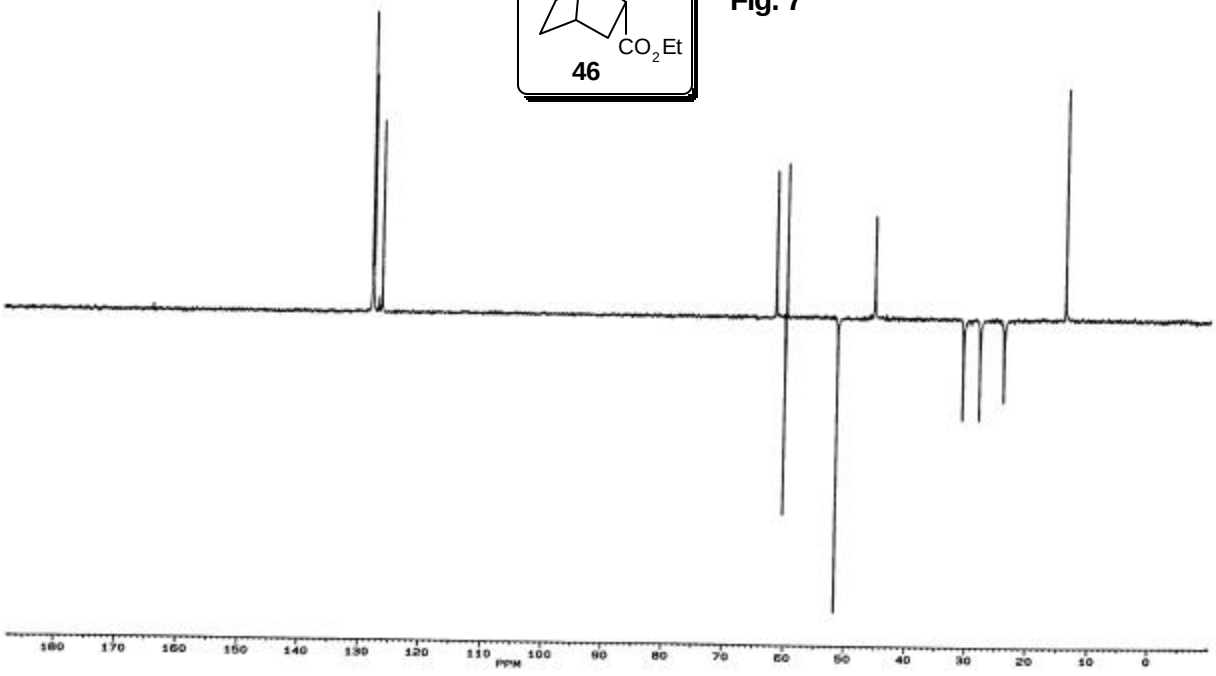
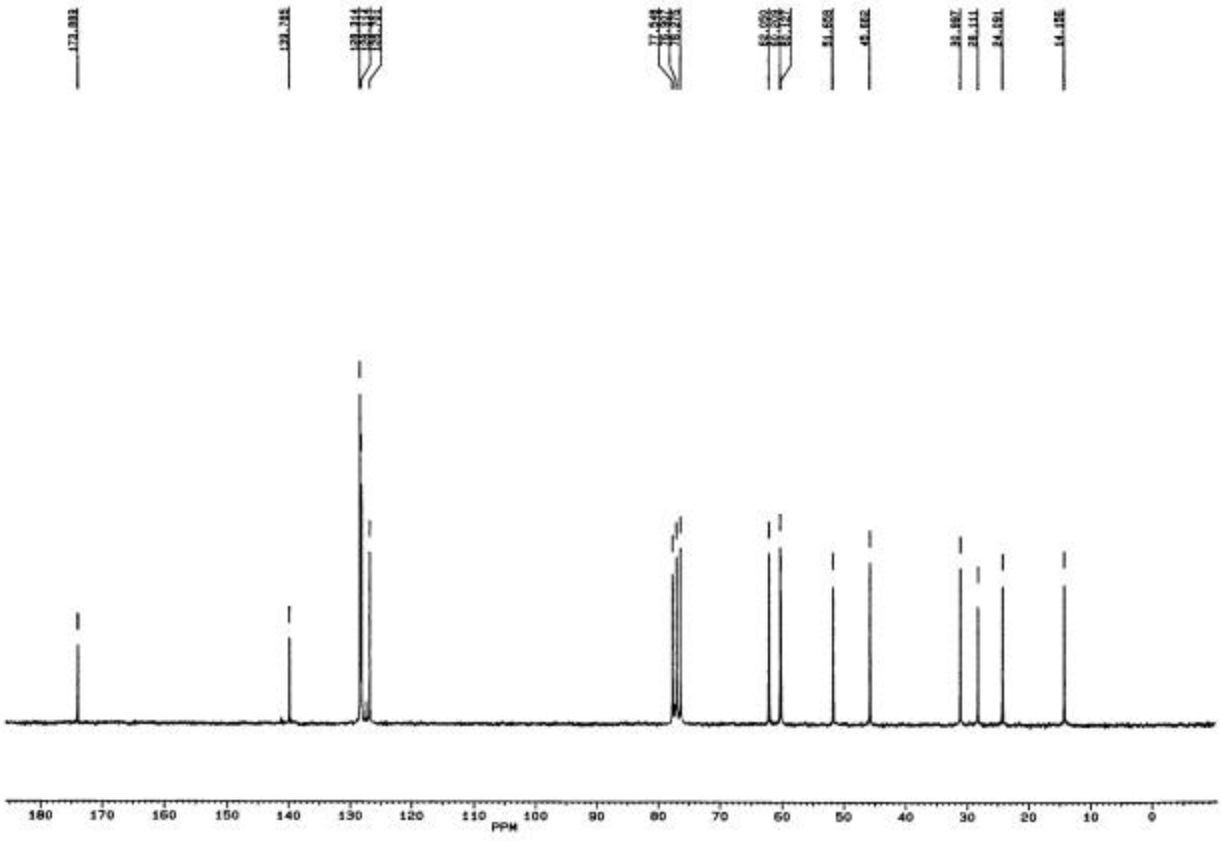
109
M/E
50
100
150
200
250
300
31
55
65
79
104
117
130
143
158
168
186
195
214
222
244
259
282
303

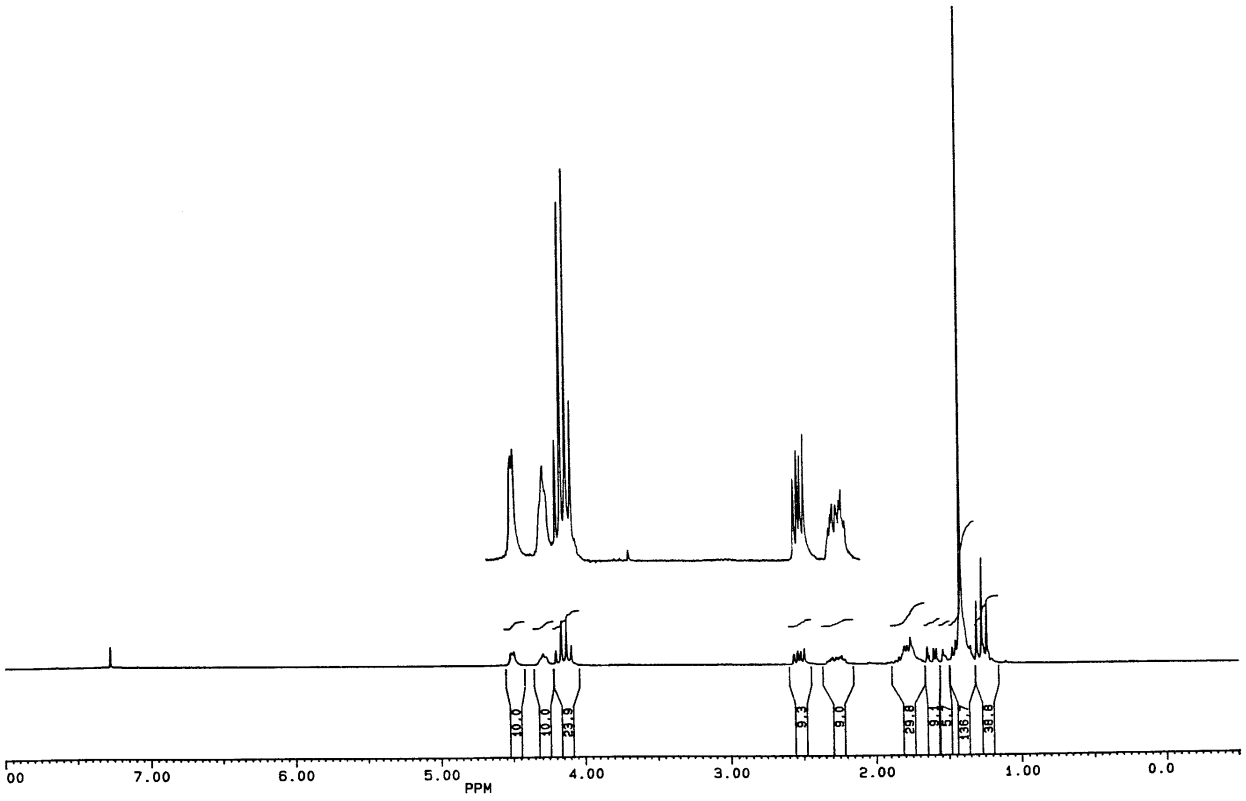


46

Fig. 7



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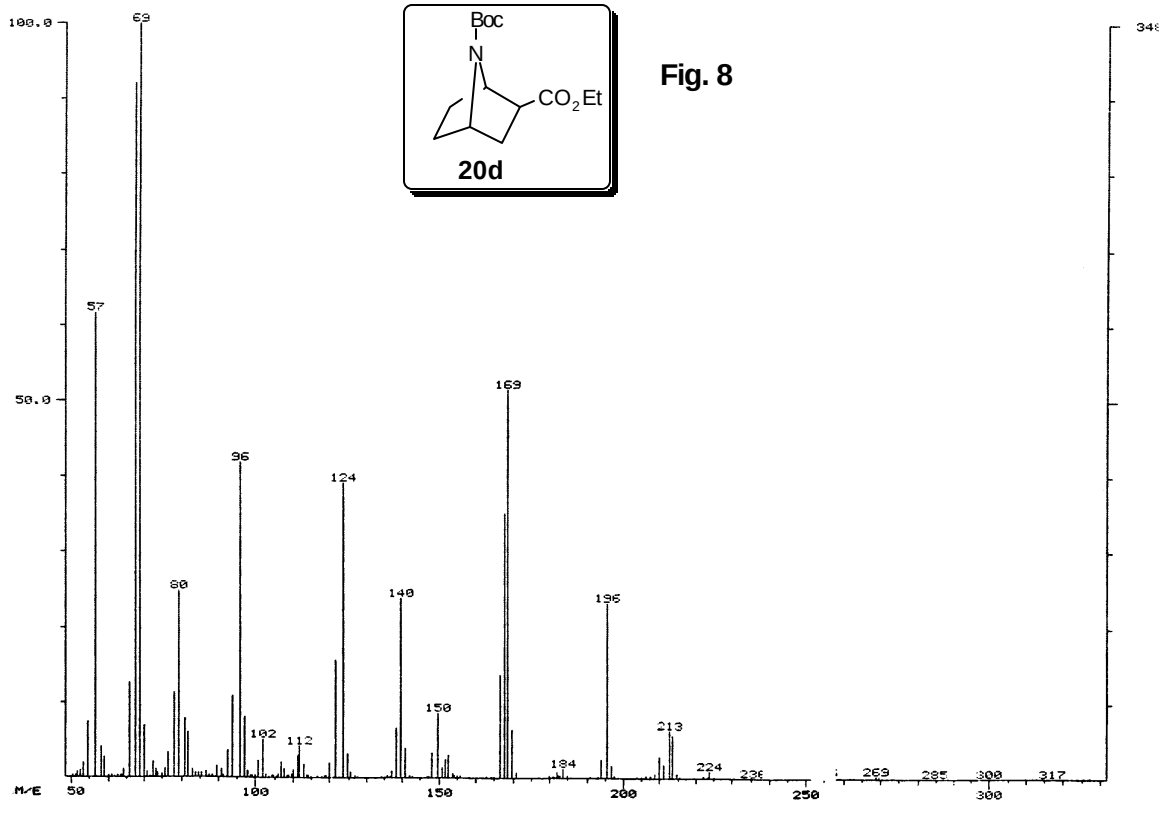
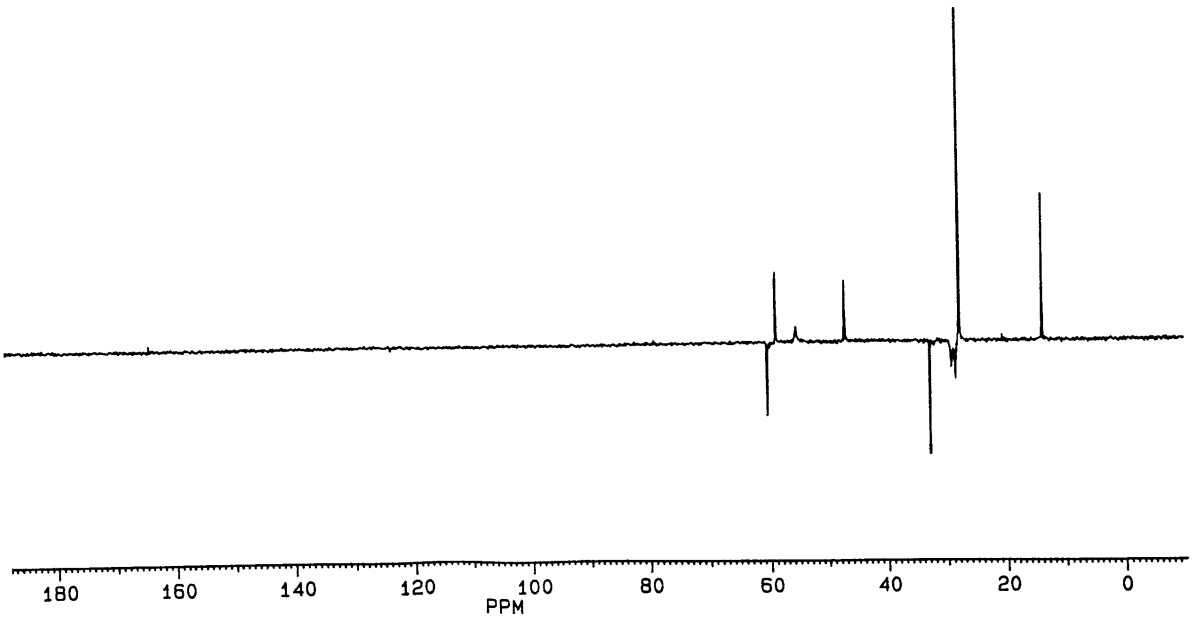
10.0
23.9
9.3
9.0
29.8
9.1
5.4
136.7
38.8
00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


100.0
50.0
M/E
69
57
80
96
124
140
150
169
184
196
213
224
50
100
150
200
250
300

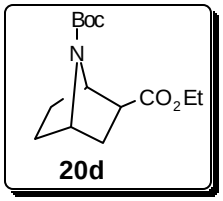
Boc
N
CO2Et

20d

Fig. 8


180
160
140
120
100
80
60
40
20
0
PPM

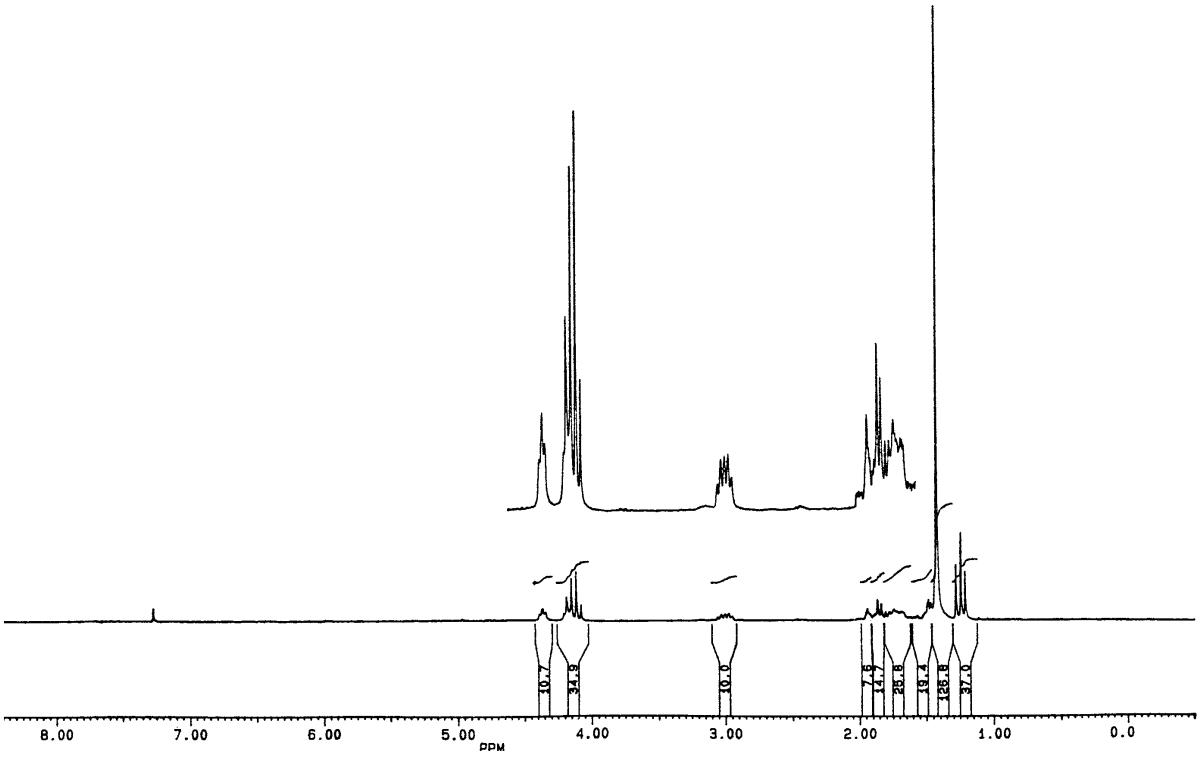

172.730
154.309
79.032
77.317
77.000
76.683
76.231
60.268
59.998
55.445
47.172
32.835
29.121
28.451
27.611
13.792


Boc
N
CO2Et

20d

Fig. 9

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM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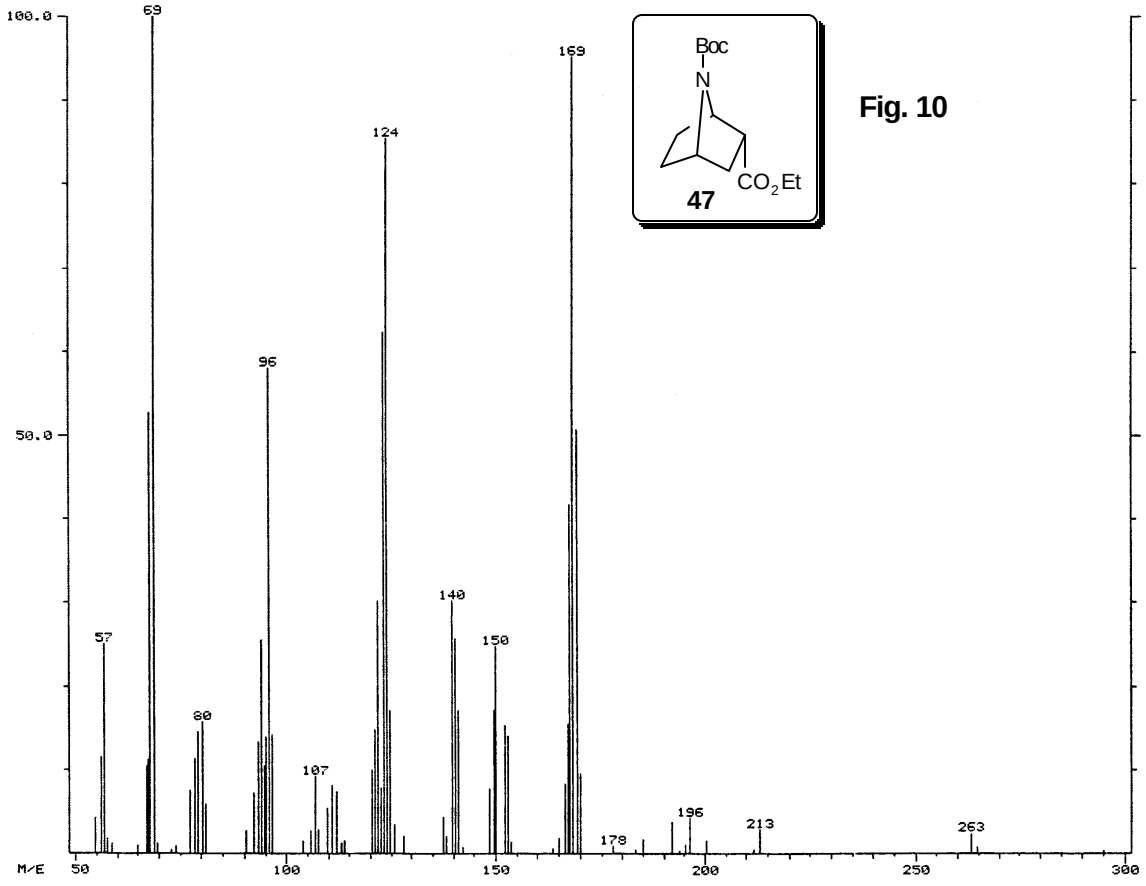
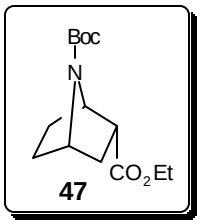
34.8
10.0
7.8
14.7
25.8
19.4
128.8
37.0
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


100.0
50.0
M/E
69
96
124
169
57
80
107
140
150
178
196
213
263
50
100
150
200
250
300

Boc
N
CO2Et

47

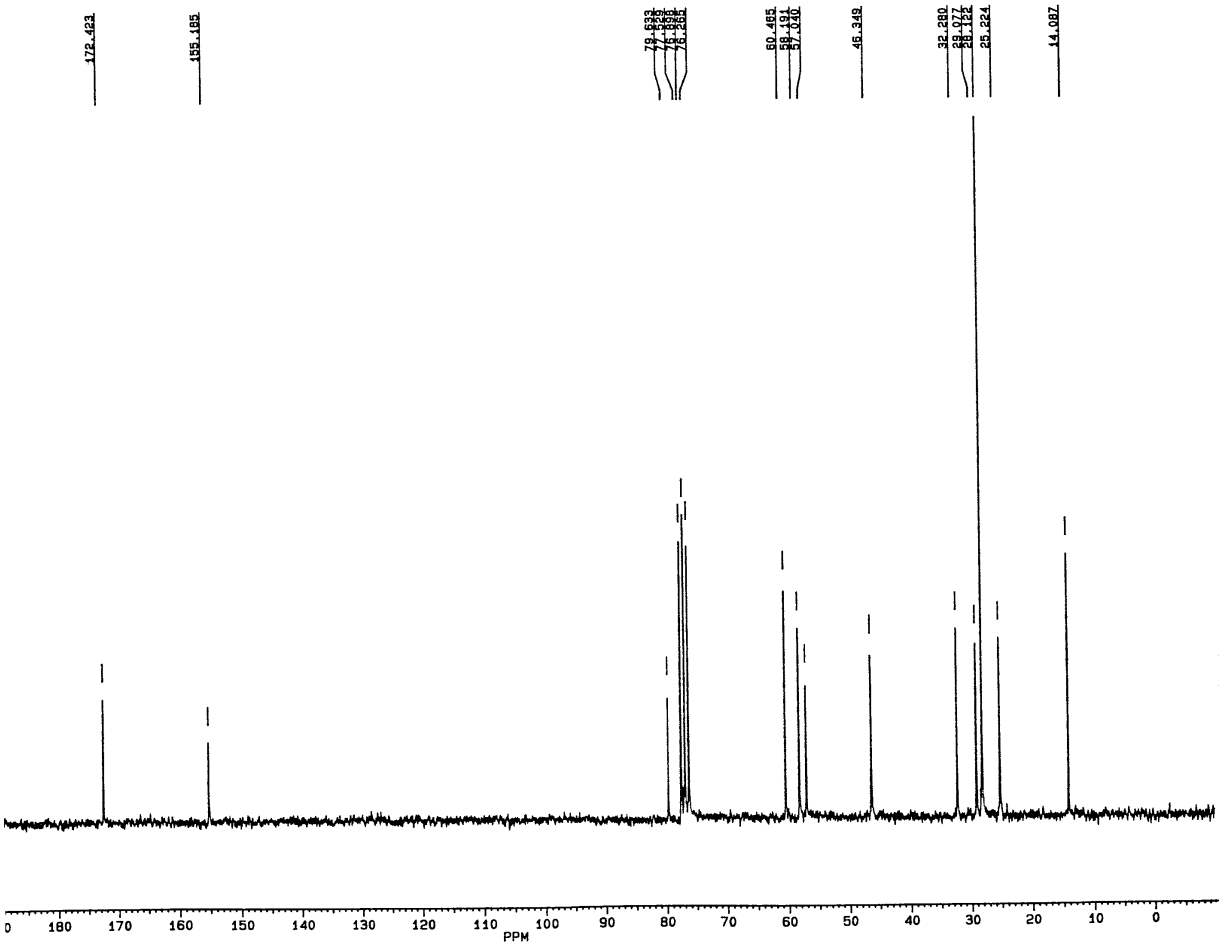
Fig. 10


Boc
N
CO2Et

47

Fig. 11

0 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM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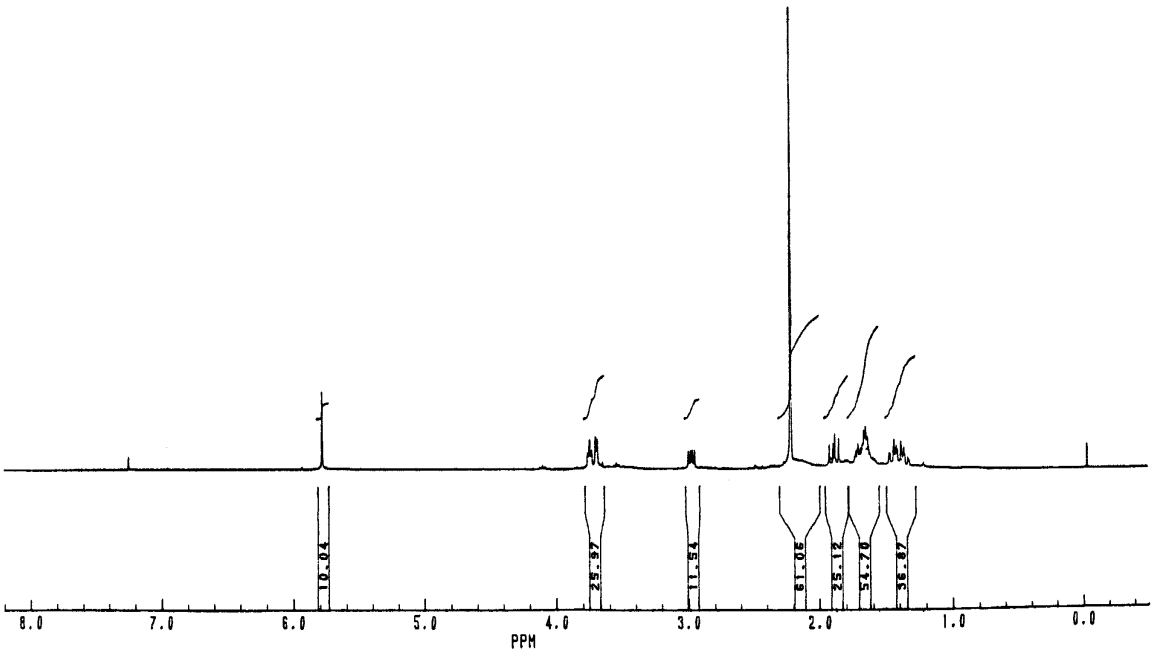
155.185
79.633
77.316
77.000
76.686
76.281
60.465
58.191
57.040
46.349
32.280
28.077
28.122
25.224
14.087
0 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


10.04
25.97
11.54
61.06
25.12
54.70
36.87
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

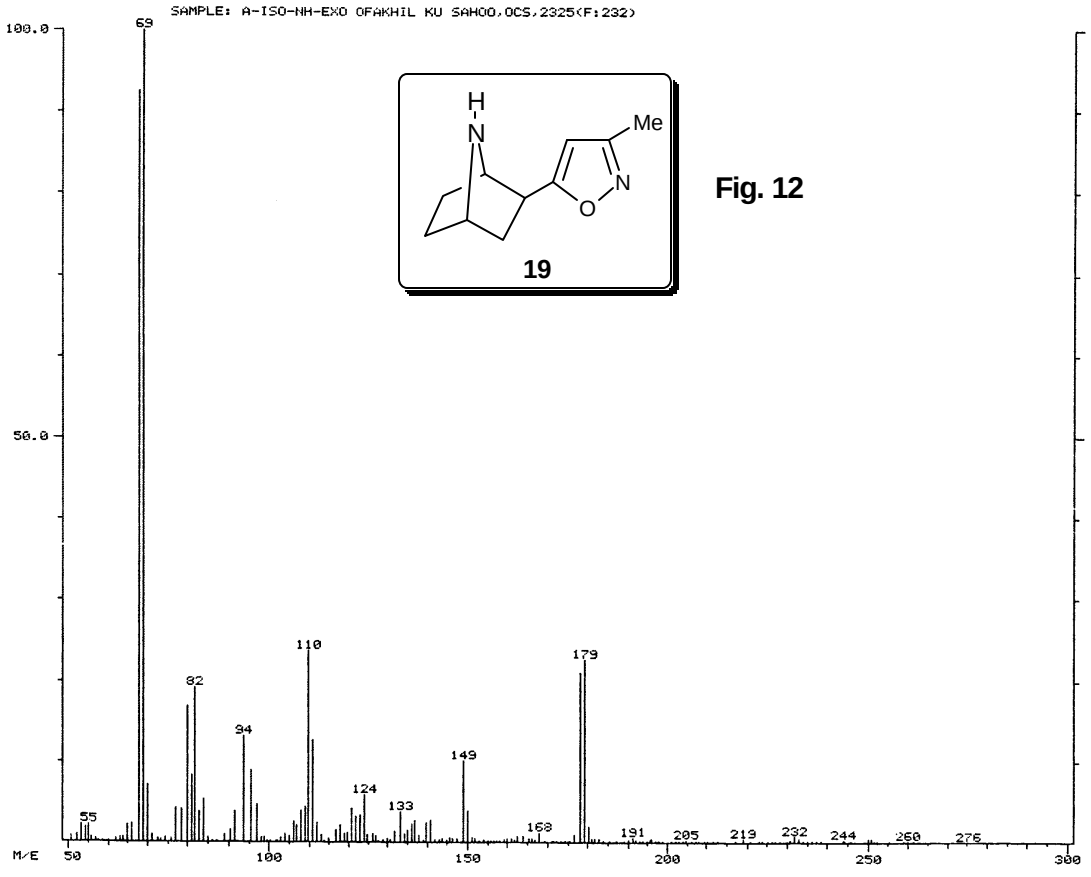
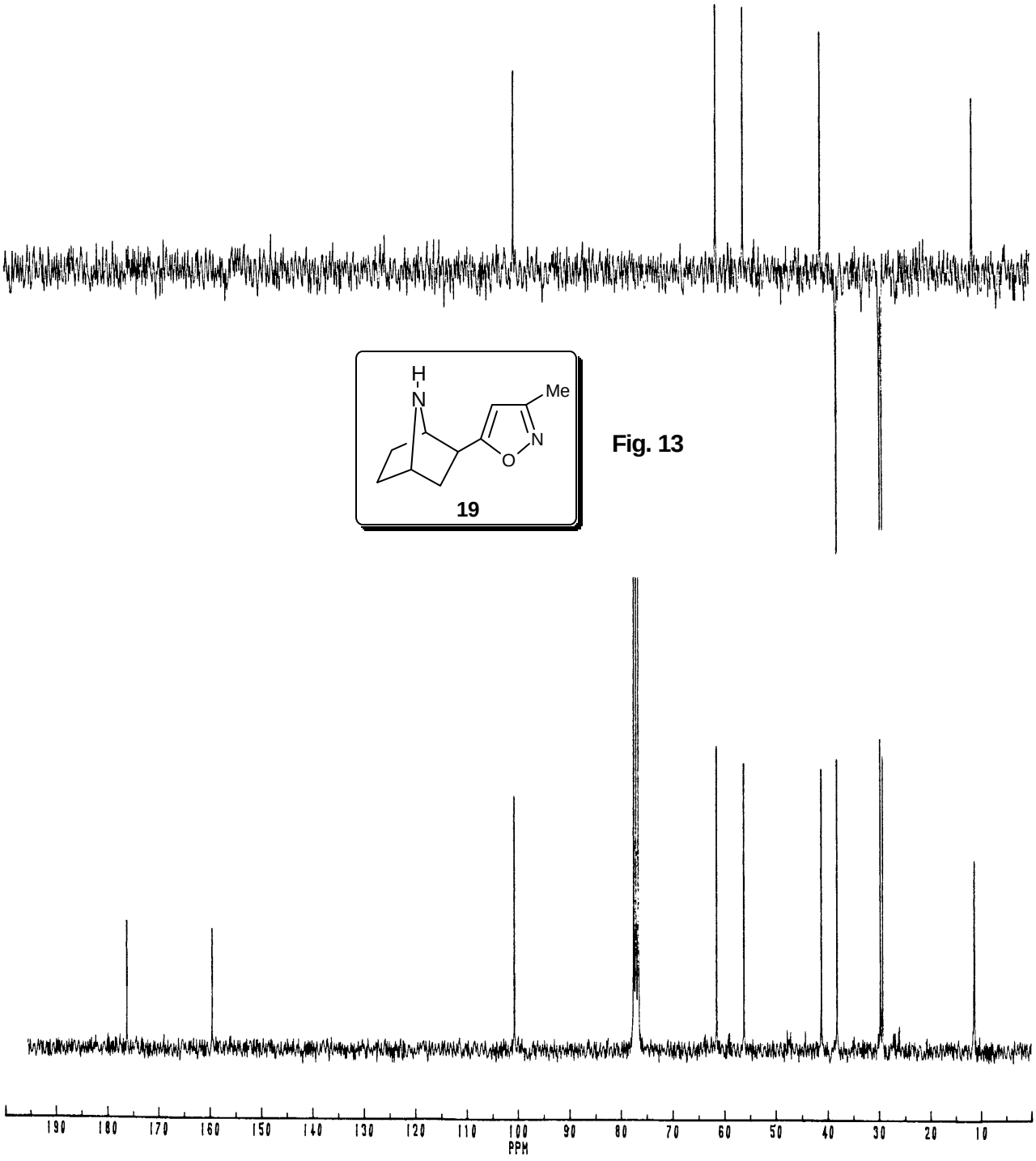
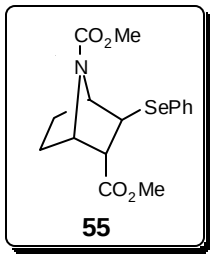

SAMPLE: A-ISO-NH-EXO OFAKHIL KU SAHOO.OCS,2325(F:232)
100.0
50.0
M/E
69
110
82
94
179
149
124
133
55
168
191
205
213
232
244
260
276
50
100
150
200
250
300
H
N
Me
N
O
19

Fig. 12


H
N
Me
N
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
PPM

19

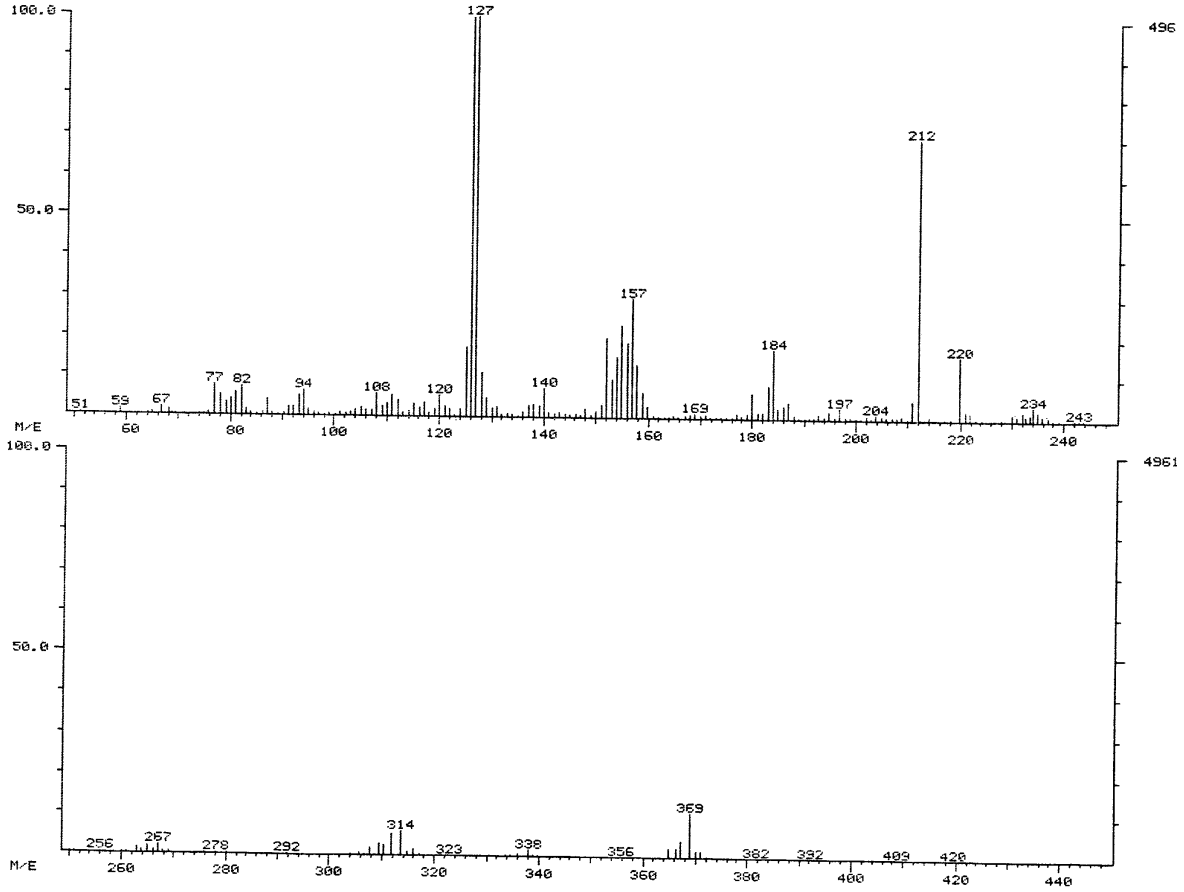
Fig. 13

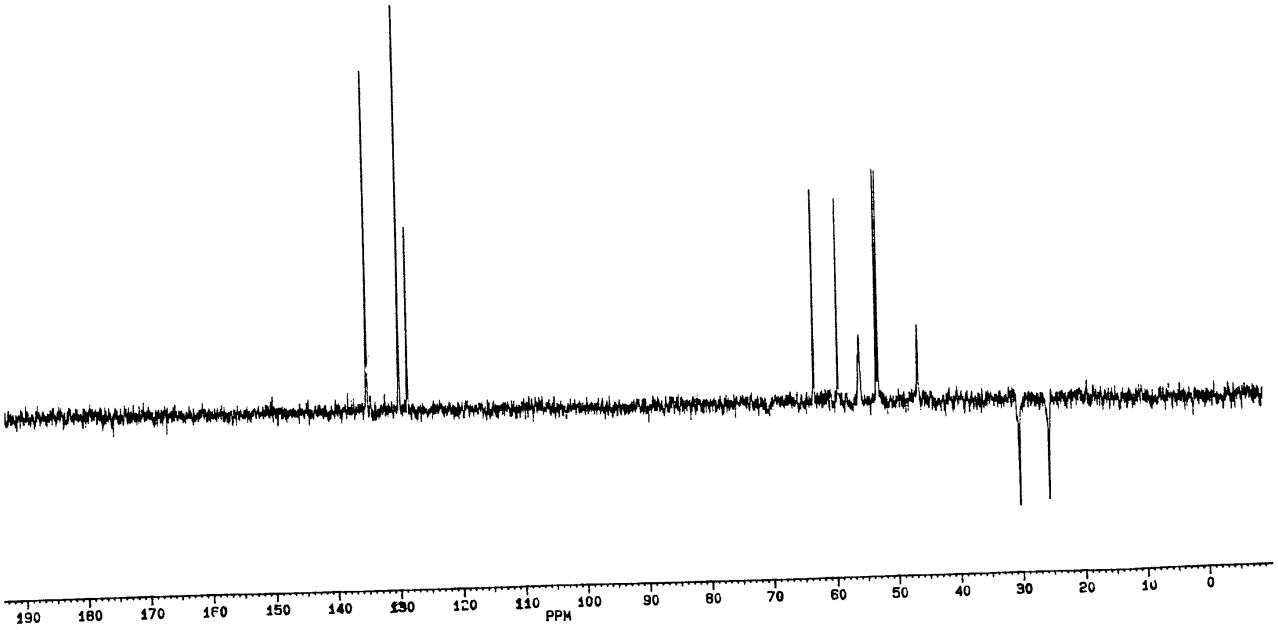

CO2Me
N
SePh
CO2Me

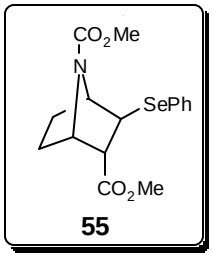
55

Fig. 14

5.40
8.09
2.40
3.49
20.52
2.54
3.81
5.75
7.40
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


100.0
50.0
M/E
127
157
212
184
220
77
82
94
108
120
140
51
59
67
169
197
204
234
243
496
4961
256
257
278
292
314
323
338
356
369
382
392
409
420

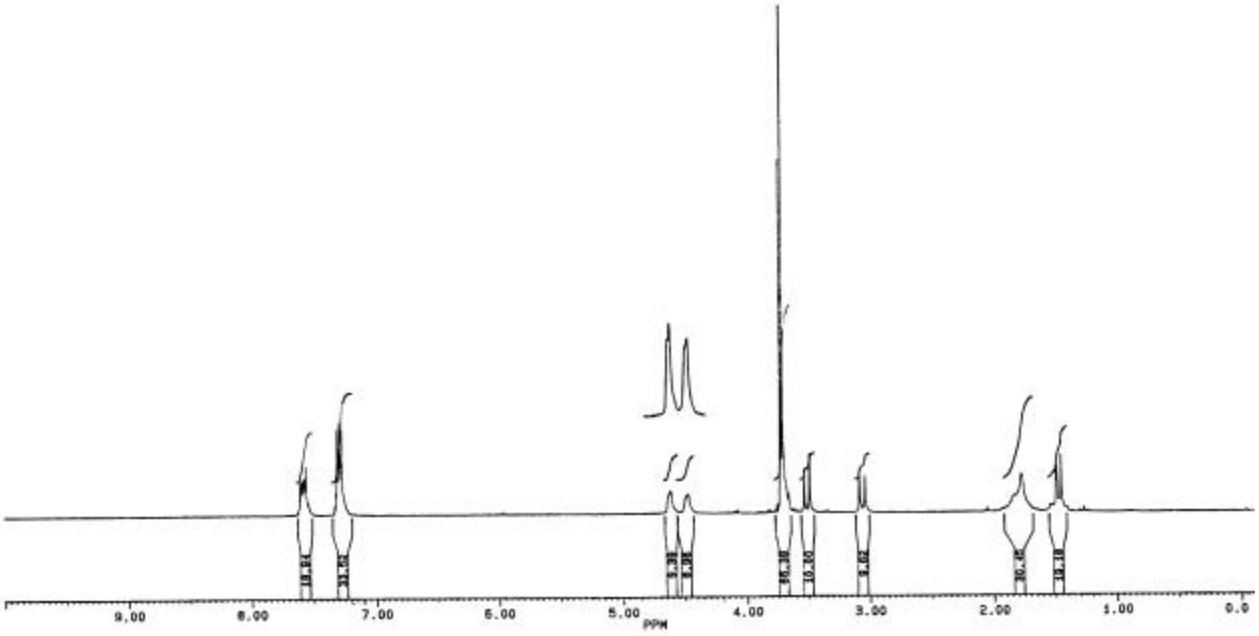

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

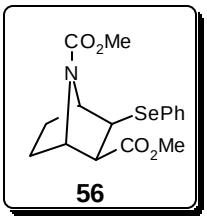

CO2Me
N
SePh
CO2Me

55

Fig. 15

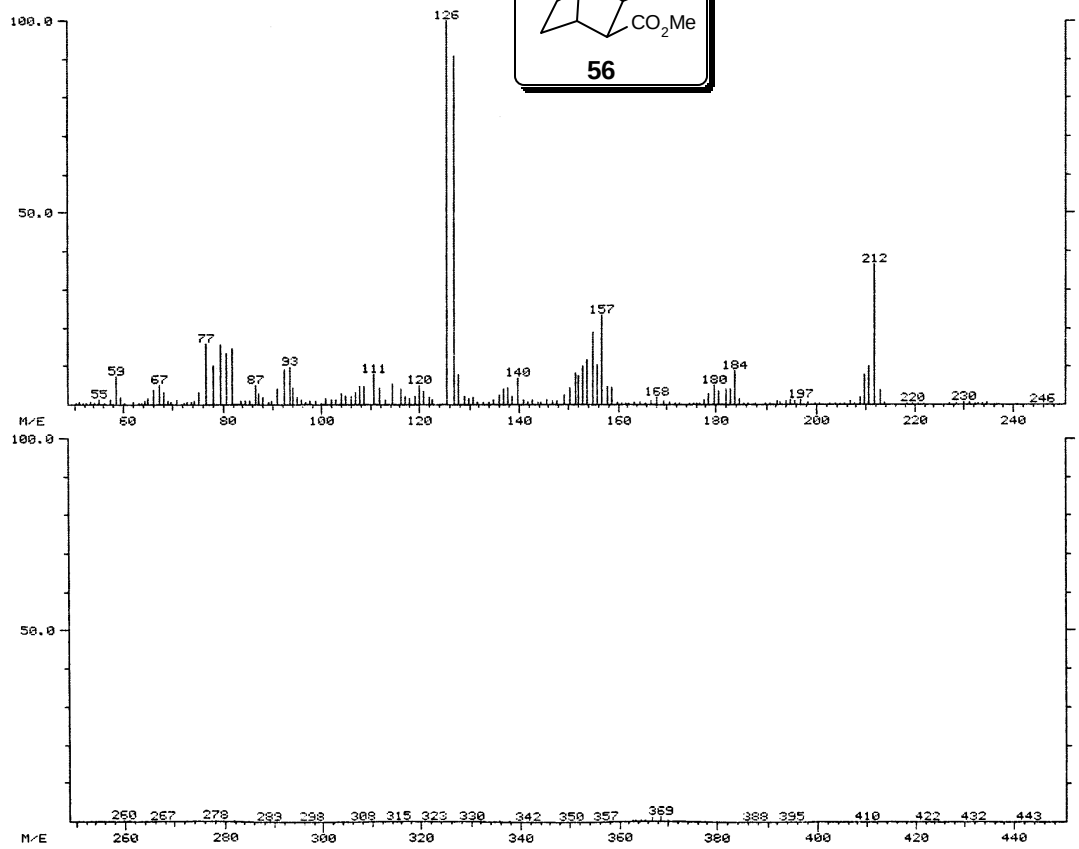
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM


9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


CO2Me
N
SePh
CO2Me

56

Fig. 16


100.0
50.0
M/E
55
59
67
77
87
93
111
120
126
140
157
158
180
184
197
212
220
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342
350
357
369
388
395
410
422
432
443

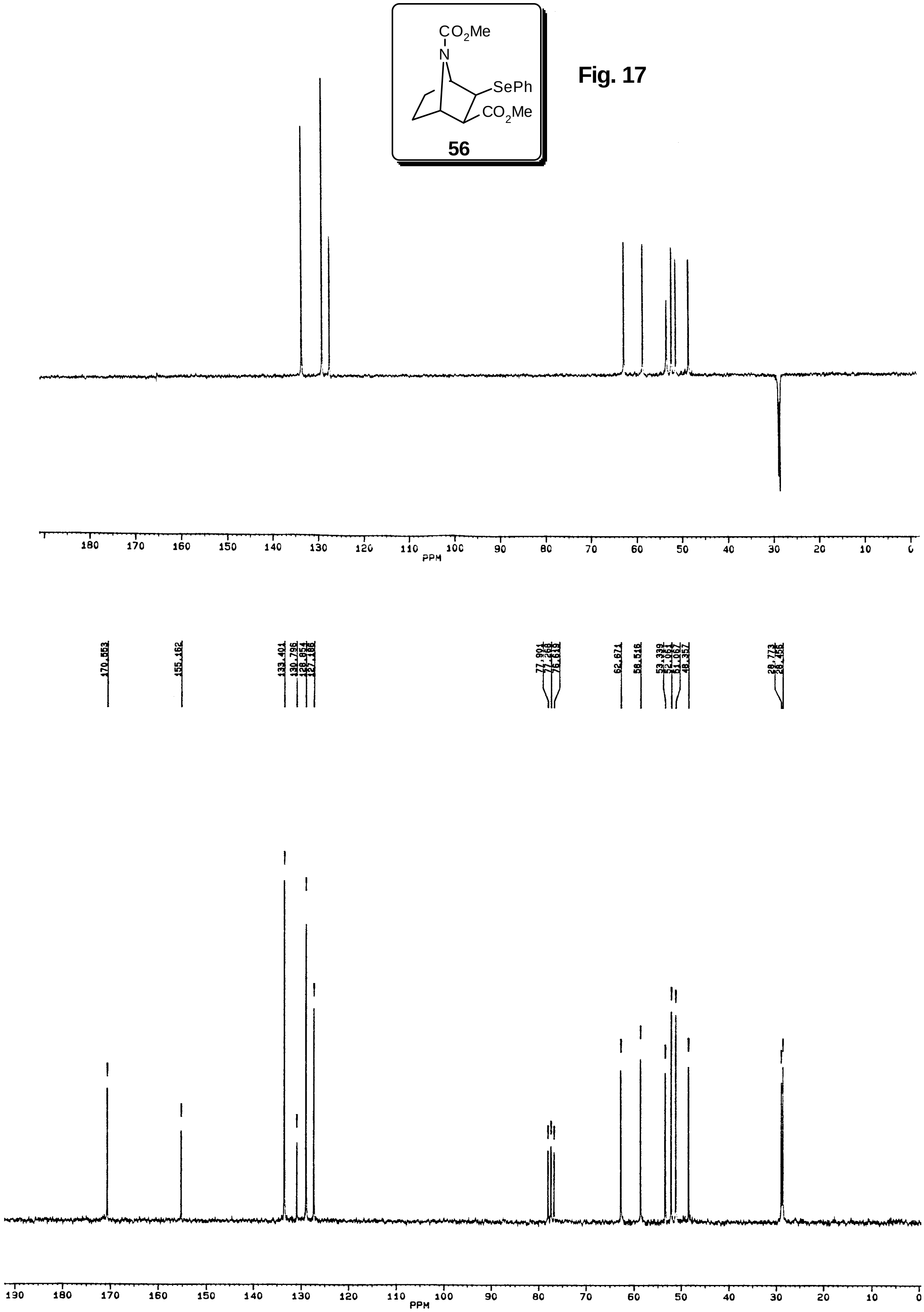


Fig. 17

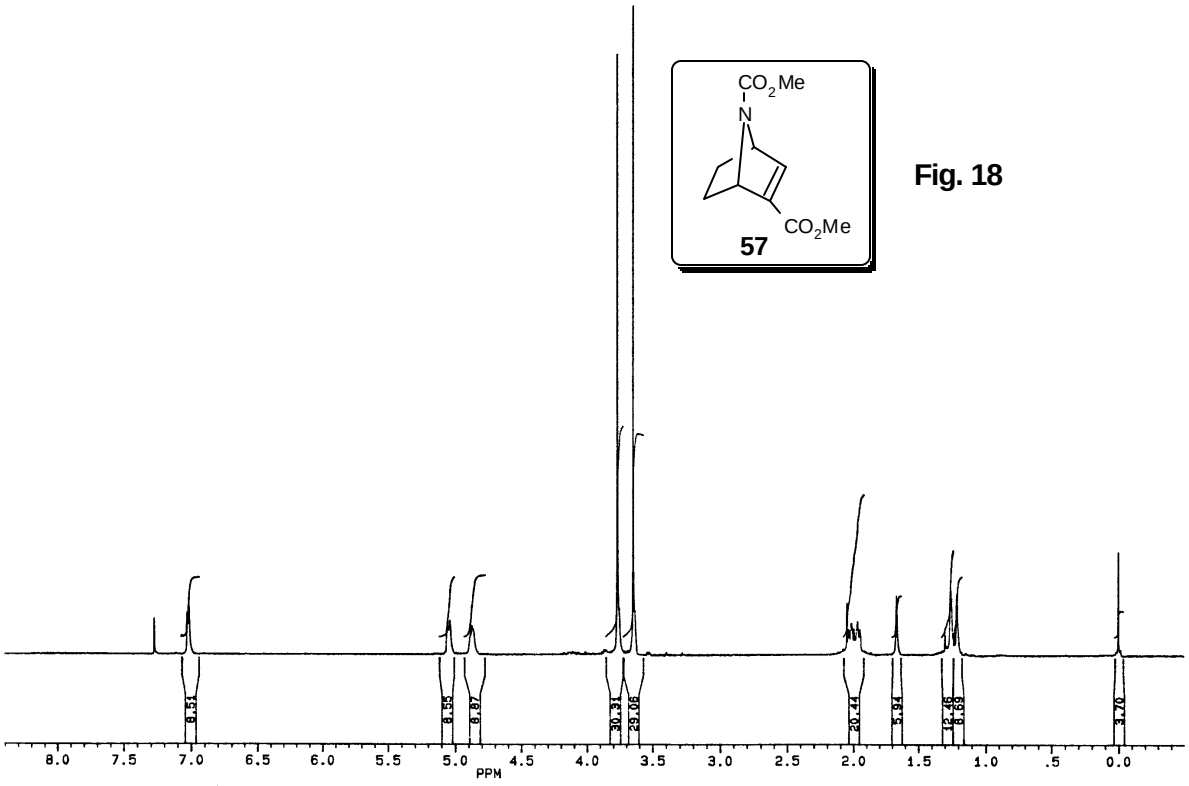
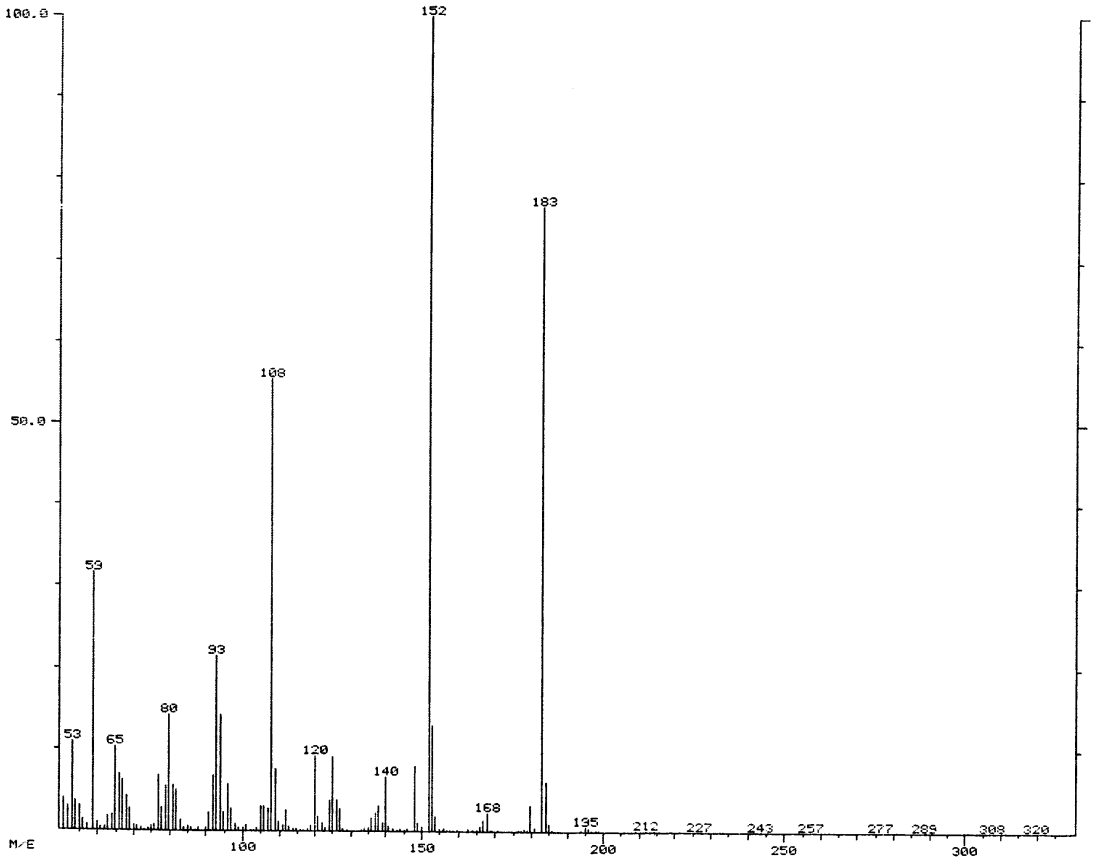
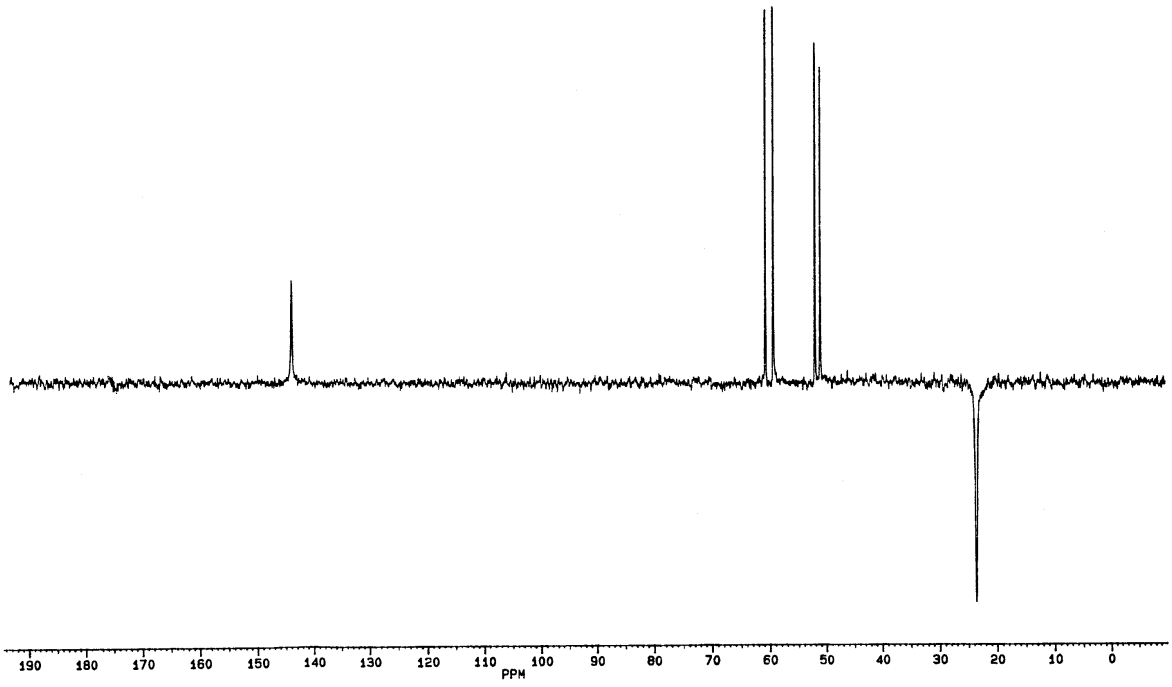
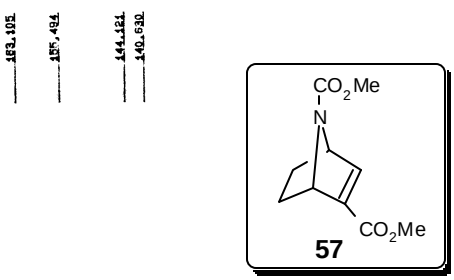

CO2Me
N
CO2Me
57
8.51
8.35
8.87
30.31
29.06
20.44
5.84
12.46
8.69
3.70
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

Fig. 18

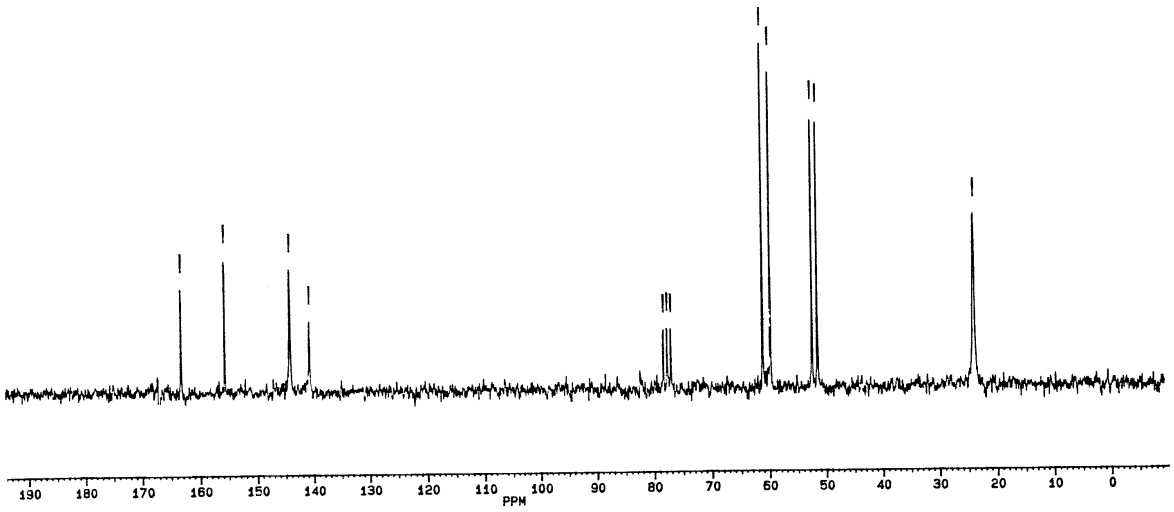

100.0
50.0
M/E
152
183
108
53
93
80
65
120
140
168
135
212
227
243
257
277
288
303
320
100
150
200
250
300


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


CO2Me
N
CO2Me

57

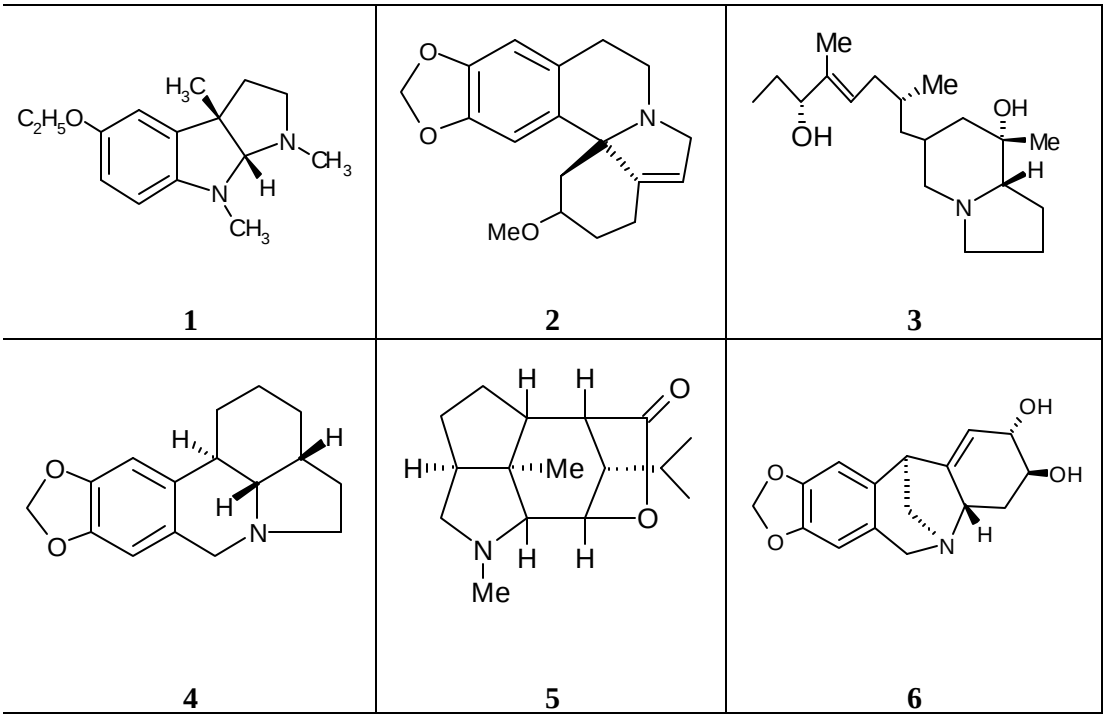
Fig. 19


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

1. Introduction

The fused pyrrolidine ring systems are frequently encountered structural unit in many synthetically challenging and biologically active alkaloids[1] such as eserethole (**1**),[2] erythramine (**2**),[3] pumiliotoxin A (**3**),[4] α-lycorane (**4**),[5] dendrobine (**5**),[6] (-)-pancracine (**6**)[7] *etc*. As a consequence, the construction of polycyclic fused pyrrolidine ring system has emerged as an important and challenging synthetic endeavor. Since the 1,3-dipolar cycloaddition of azomethine ylides with olefins is identified as one of the most attractive strategy for the construction of heterocyclic pyrrolidine ring systems,[8] the intramolecular version[9] of such cyclization has provided an easy entry into the construction of complex structures possessing fused pyrrolidine moiety.

Fig. 1



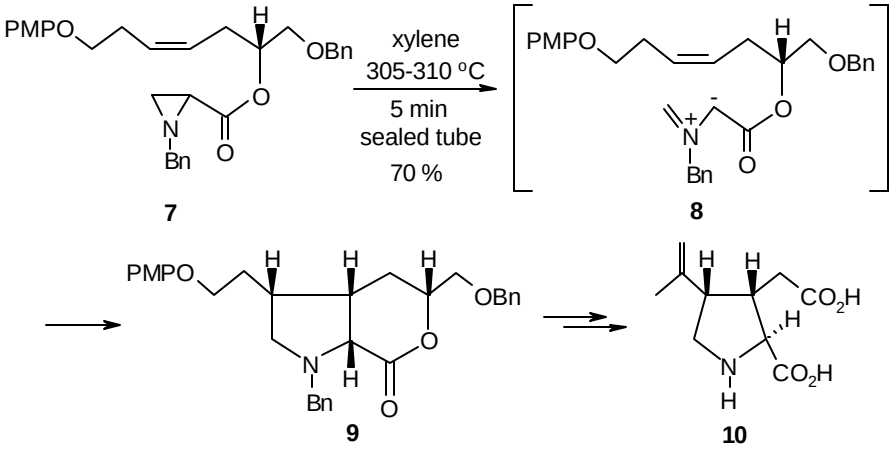
1 **2** **3**

4 **5** **6**

Takano *et al.*[10] have reported the synthesis of (-)-α-kainic acid (**10**), the representative member of the kainoid family of neuroexcitatory amino acids, by an intramolecular 1,3-dipolar cycloaddition of azomethine ylide from an intermediate **8** as

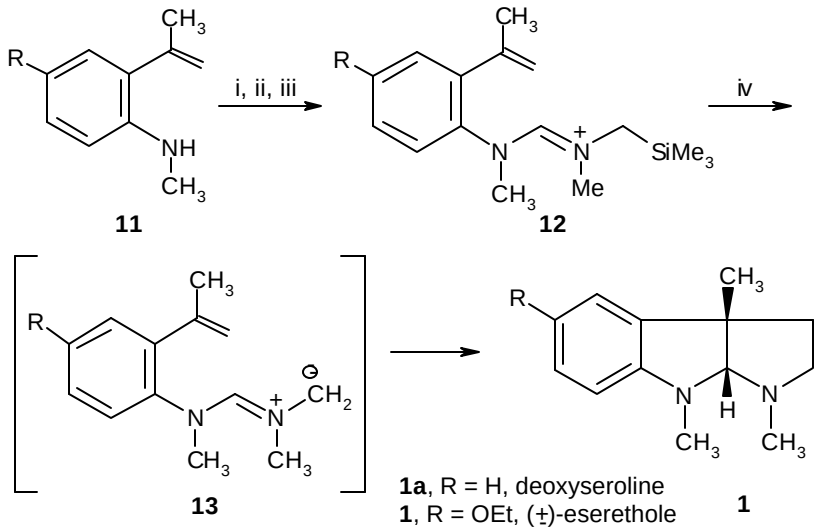
shown in Scheme 1. The same strategy was also utilized for the synthesis of various other fused pyrrolidines,[11] and the synthesis of allokainic acid[12] and acromelic acid.[13]

Scheme 1



Stereospecific syntheses of physostigmine alkaloids (**1**) have been achieved[14] through intramolecular dipolar cycloaddition of an unactivated olefin to an imidate methylide intermediate **13**. The intermediate **13** was readily generated by the CsF or TBAF induced desilylation of immonium salt **12** (Scheme 2).

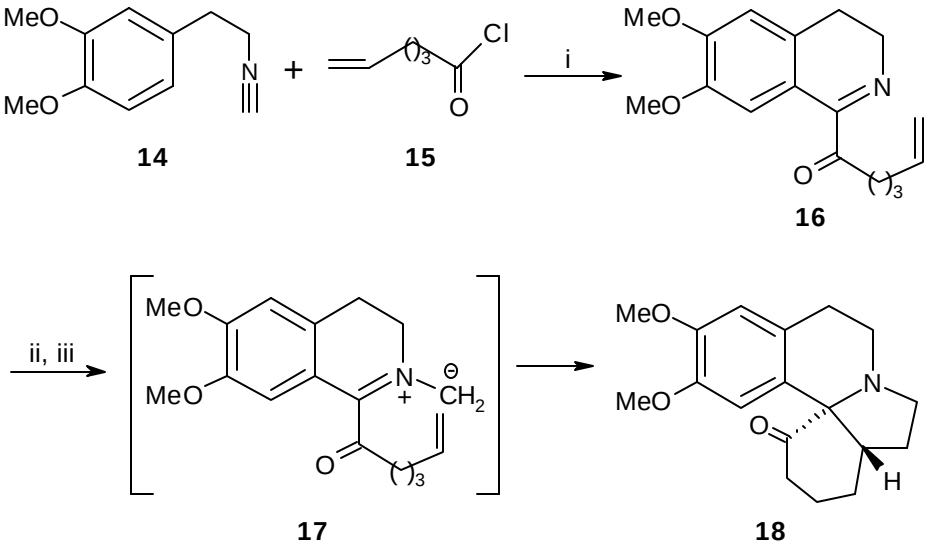
Scheme 2



Reagents and conditions: *i) n-BuOCHO, 108 °C; ii) MeOTf, rt, $Me_3SiCH_2NH_2$, 0 °C; iii) MeOTf, DCM, rt; iv) CsF, DMF, 50 °C, or TBAF in THF, 45 °C, 70 %.*

Livinghouse *et al.*[15] have reported the construction of 4-oxo-15,16-dimethoxyerythrinane (**18**) in 70 % yield by the intramolecular [3+2] cycloaddition of nonstabilized α-ketoiminium ylides (**17**). The generation of azomethine ylide **17** was accomplished by reacting imine **16** with $TMSCH_2OTf$ followed by the desilylation with CsF (Scheme 3).

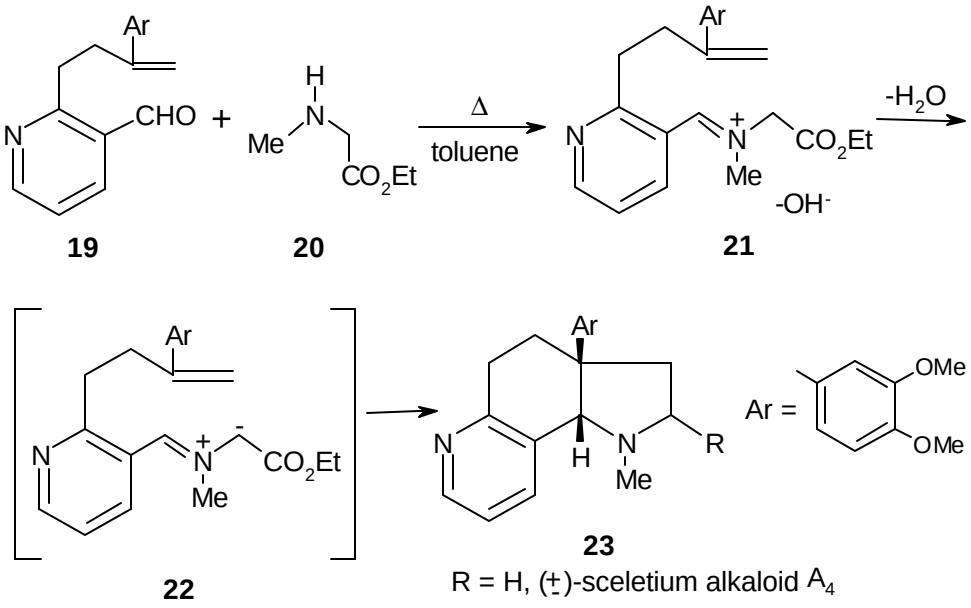
Scheme 3



Reagents and conditions: *i) AgOTf, -20 °C, TEA; ii) $TMSCH_2OTf$, DCM, rt; iii) CsF, DME, 65 °C, 70 %.*

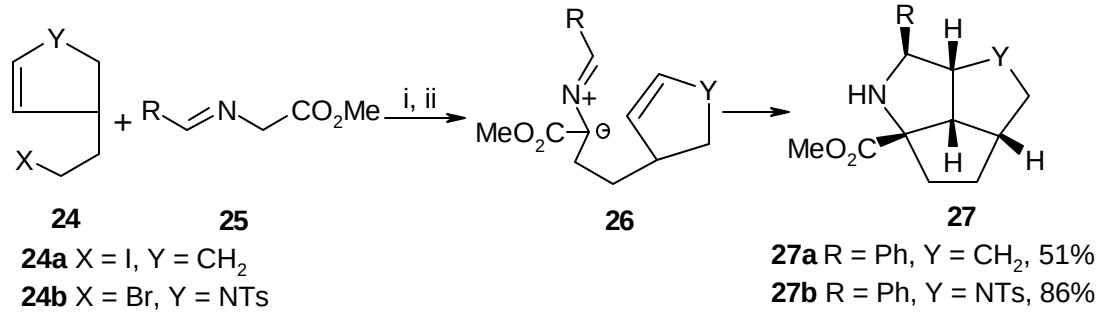
Synthesis of sceletium alkaloid A_4 (**23**) has also been demonstrated[16] by utilizing the intramolecular [3+2] cycloaddition of azomethine ylide from **22**, generated by heating aryl aldehyde (**19**) with ethyl sarcosinate (**20**) (Scheme 4).

Scheme 4



A convenient synthesis of the rare 2-azatricyclo[5.2.1.0^{4,10}]decane (**27a**) and 2,5-azatricyclo[5.2.1.0^{4,10}]decane (**27b**) was accomplished by the intramolecular cycloaddition of azomethine ylide moiety of intermediate **26** (Scheme 5).[17]

Scheme 5



24 **25** **26** **27**

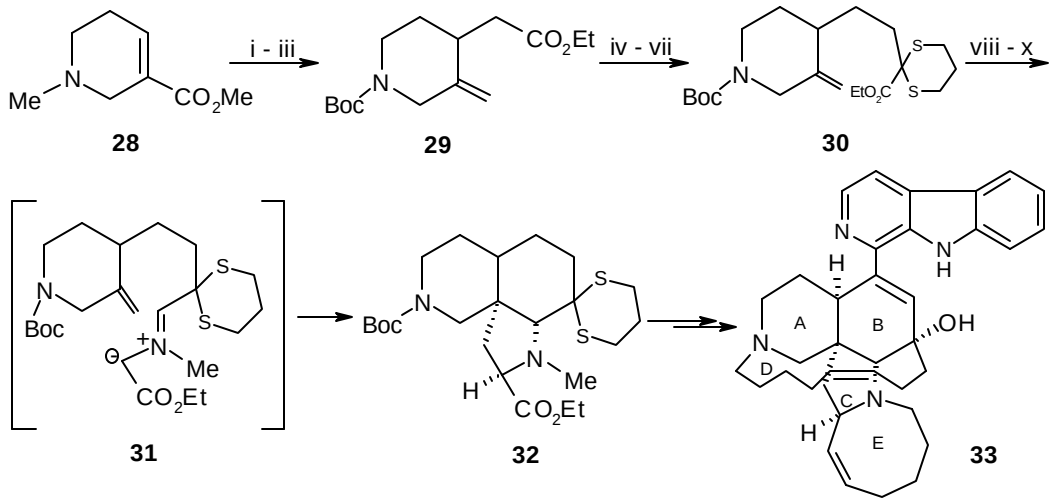
24a X = I, Y = CH_2
24b X = Br, Y = NTs

27a R = Ph, Y = CH_2, 51%
27b R = Ph, Y = NTs, 86%

Reagents and conditions: *i) ^{t}BuOK, THF, -78 ^{o}C to rt; ii) xylene, reflux.*

The construction of the ABC ring system (**32**) of the menzamine alkaloids (**33**) have been reported by Coldham *et al.*[18] involving an intramolecular cycloaddition reaction of azomethine ylide moiety **31**. This strategy has provided a direct route to the formation of three new chiral centers with simultaneous formation of B and C rings of **33** (Scheme 6).

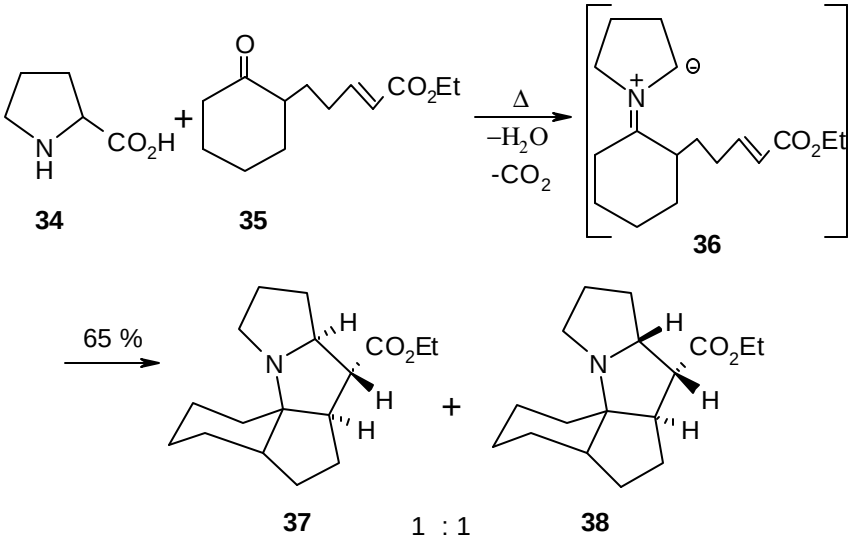
Scheme 6



Reagents and conditions: *i) $LiAlH_4$, THF, 0 ^oC, 95 %; ii) $MeC(OEt)_3$, xylene, 2,4-dinitrophenol, D, 71 %; iii) MeCH(Cl)OCOCl, D, MeOH, $(Boc)_2O$, DCM, TEA, 81 %; iv) $LiAlH_4$, THF, 0 ^oC, 85 %; v) CBr_4, Ph_3P, DCM; vi) NaI, acetone, 96 %; vii) n-BuLi, THF, HMPA, -78 ^oC, TEA, 70 %; viii) $LiAlH_4$, THF, 0 ^oC, 92 %; ix) DMSO, $(COCl)_2$, DCM, -78 ^oC, TEA, 70 %; x) 2^o amine sarcosine ethyl ester, $^iPr_2NEt$, toluene, D, 24 h, 45 %.*

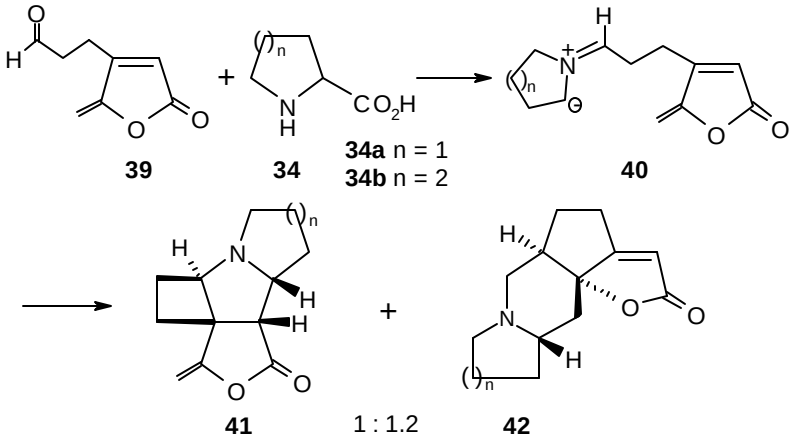
The intramolecular [3+2] cycloaddition of non-stabilized azomethine ylide moiety of **36** has been reported to give a diastereomeric mixture of polycyclic nitrogen heterocyclic compounds **37** and **38** (1:1 ratio) in 65 % yield as shown in Scheme 7.[19]

Scheme 7



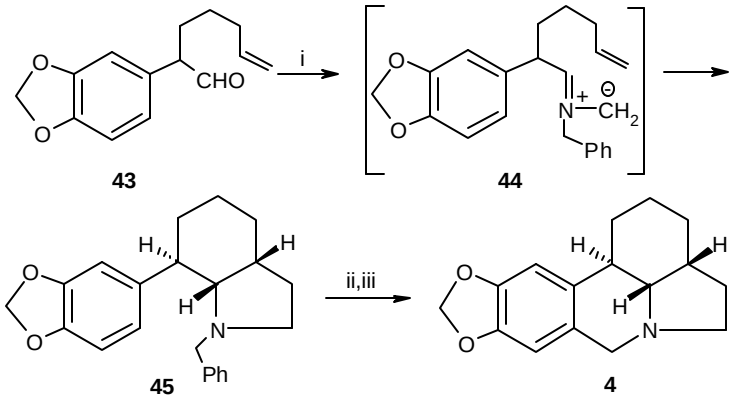
Two different cycloaddition products (**41** & **42**) in 1:1.2 ratio were obtained by the intramolecular cycloaddition of intermediate **40**, generated by the reaction of **34** with 4-(3-propanalyl)-5-methylene-2(5H)furanone (**39**). These cycloaddition products have resulted involving both the α,β-double bond as well as γ,δ-double bond moiety of **40** as shown in Scheme 8.[20]

Scheme 8



A key precursor **45** utilized in the synthesis of (±)-α-Lycorane (**4**) has also been obtained by the intramolecular cycloaddition of the tethered olefin with the azomethine ylide intermediate of **44**.[3] Intermediate **44** was produced by the reaction of **43** with *N*-benzyl glycine as depicted in Scheme 9.

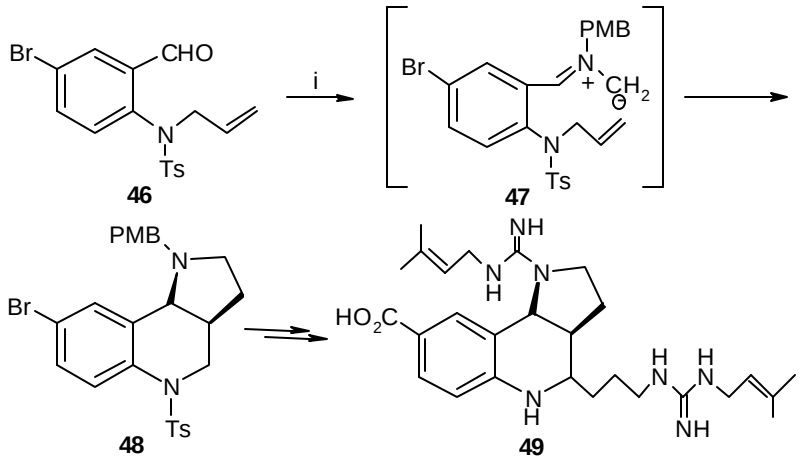
Scheme 9



Reagents and conditions: *i) N-Benzyl glycine + $HN(SiMe_3)_2$, toluene, reflux; ii) HCOOH, MeOH, 10 % Pd/C; iii) HCHO.*

The pyrroloquinoline skeleton **48**, found in the Martinelline alkaloids (**49**) has been synthesized using the intramolecular [3+2] cycloaddition from intermediate **47** (Scheme 10).[21]

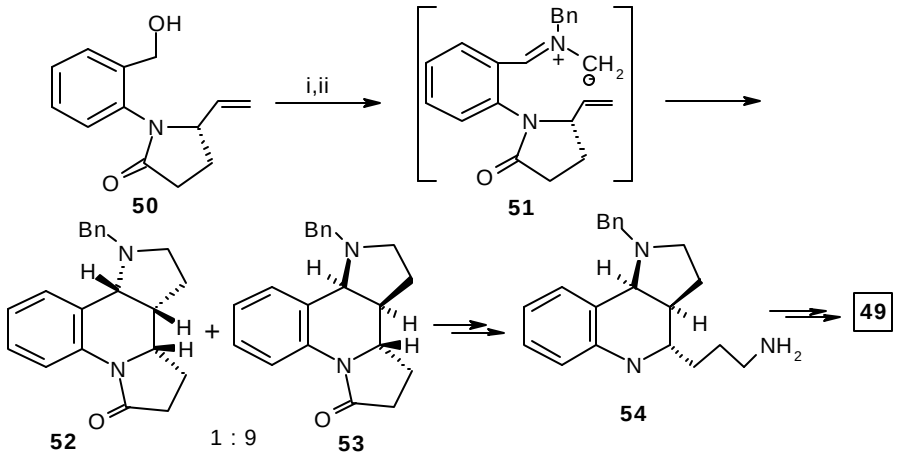
Scheme 10



Reagents and conditions: *i) $PMBHNCH_2CO_2H.HCl$, TEA, DMF, reflux, 83 %.*

An intramolecular [3+2] cycloaddition reaction of nonstabilized azomethine ylide moiety of **51** has given a diastereomeric mixture of **52** and **53** (1:9 ratio) in 75 % yield. The major substrate **53** has been **t**ransformed to tricyclic triamine core unit **54**, found in the martinellic acid (**49**) in overall 11 % yield (Scheme 11).[22]

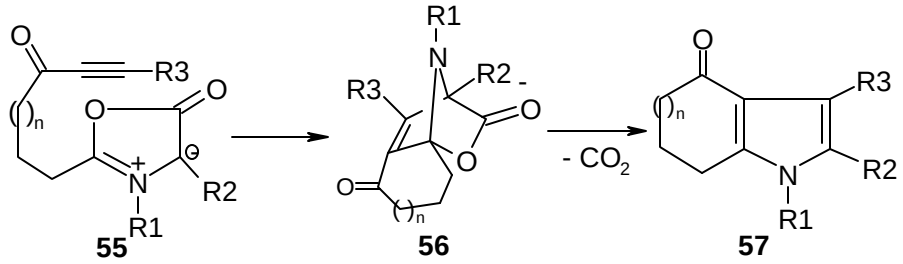
Scheme 11



Reagents and conditions: *i) MnO_2, DCM, rt, 12 h; ii) excess $PhCH_2NHCH_2CO_2H$, toluene, reflux, 12 h, 75 %.*

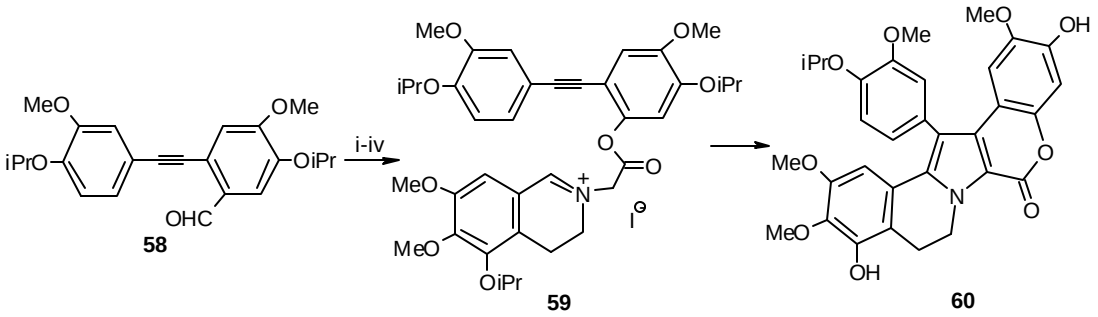
A new and efficient approach for the general synthesis of oxotetrahydroindoles **57**, found as a core unit in mitomycin skeleton and other medicinally important polycyclic heterocyclic compounds, have been reported[23] by involving the intramolecular cycloaddition of an ylide moiety from **55** with tethered alkynes (Scheme 12).

Scheme 12



Marine alkaloid lamellarin K4 (**60**) skeleton have also been constructed[24] by the intramolecular [3+2] cycloaddition of an ylide structure **59** as shown in Scheme 13.

Scheme 13

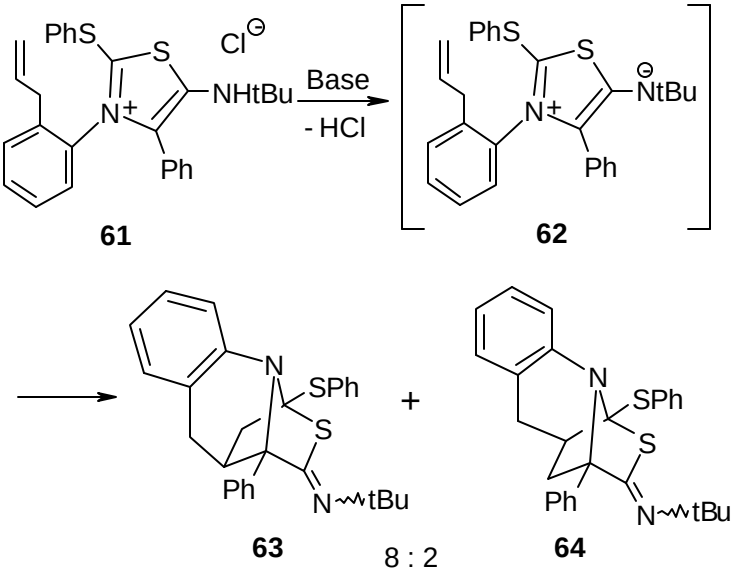


Reagents and conditions: *i) mCPBA, (1.5 equiv.), $KHCO_3$ (3 equiv.), DCM, rt, 1 h; ii) NH_3 in MeOH (sat.), rt, 1 h; iii) ICH_2CO_2H (1.05 eq.), DCC (1.05 equiv.), DMAP (5 mol %), DCM, rt, 3 h; iv) 3,4-Dihydro-6,7-dimethoxy-5-isopropoxyisoquinoline (1.1 equiv.), $ClCH_2CH_2Cl$, rt, 7 h, then Hunig base (1.0 equiv.), 83 ^oC, 32 h.*

The 5-aminothiazolium salt **61** was reported[25] to undergo base induced intramolecular [3+2] cycloaddition reaction to provide ring-annulated multicyclic compounds **63** and **64** (8:2 ratio) in 65 % yield. This cyclization is understood to involve

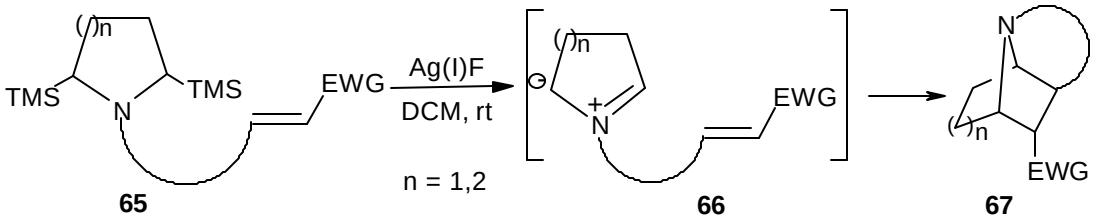
the intramolecular cyclization of the olefinic part of **61** to the cyclic azomethine ylide intermediate **62** as shown in scheme 14.

Scheme 14



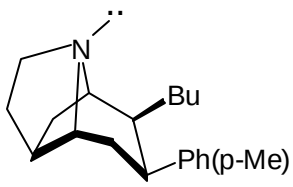
Until recently, intramolecular cycloaddition reactions of a non-stabilized, especially, cyclic azomethine ylides, for the construction of polycyclic fused pyrrolidine ring systems, was not much explored in literature due to the non-availability of methodologies for cyclic azomethine ylides generation. Considering the importance of the fused pyrrolidine ring systems, we envisaged the construction of X-azatricyclo[m.n.0.0^{a,b}]alkanes, **67**, a new azatricyclic structural entities by the intramolecular [3+2]-dipolar cycloaddition reaction of a nonstabilized cyclic azomethine ylide **66**, generated by sequential double desilylation of **65** using Ag(I)F as one electron oxidant[26,27] as shown in Scheme 15.

Scheme 15

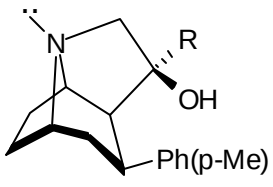


Our interest of constructing skeletons of type **67** was further enlightened by the recent disclosure of Smith *et al.*[28,29] that the rigid cocaine analogues (**68-70**) having azatricyclo ring show high binding affinity to the site of the monoamine transporters. The enhanced selectivity of these rigid tropane analogues for the monoamine transporter inhibitors was influenced by the fixed orientation of the nitrogen lone pair due to tethered carbon bridge of the tropane moiety.

Fig. 2

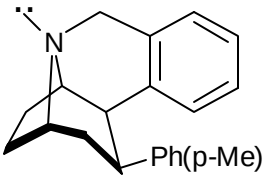


68



R = Me, Pr, Ph

69



70

With this brief introduction, we present herein the details of our approach and results on the construction of X-azatricyclo[m.n.0.0^{a,b}]alkanes skeleton in the proceeding section.

2. Results and Discussion

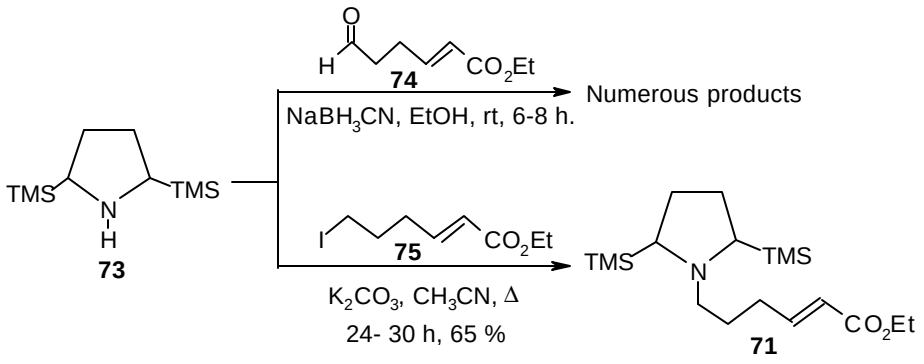
2.1. Synthesis of Ethyl-2-azatricyclo[4.4.0.0^{2,8}]decane-7-carboxylate (72):

Our study initially started with the possible construction of ethyl-2-azatricyclo[4.4.0.0^{2,8}]decane-7-carboxylate (**72**) through intramolecular [3+2]-dipolar cycloaddition of the azomethine ylide generated from the precursor ethyl-6-[2,5-di(trimethylsilyl)tetrahydro-1*H*-1-pyrrolyl]-(*E*)-2-hexenoate (**71**).

2.1.1. Preparation of Ethyl-6-[2,5-di(trimethylsilyl)tetrahydro-1*H*-1-pyrrolyl]-(*E*)-2-hexenoate (71):

In an attempt to obtain **71** easily, we initially tried the reductive amination of 2,5-di(trimethylsilyl)pyrrolidine (**73**, preparation described in the previous chapter) with 6-oxo-(*E*)-2-hexenoate (**74**) in the presence of $NaBH_3CN$ in ethanol. However, this approach failed due to the formation of many uncharacterized products. Therefore, we modified our approach by refluxing a solution of **73** with 6-iodo-(*E*)-2-hexenoate (**75**) in dry acetonitrile in the presence of K_2CO_3 for 24-30 h which afforded **71** in 65 % yield as a pale yellow liquid (Scheme 16).

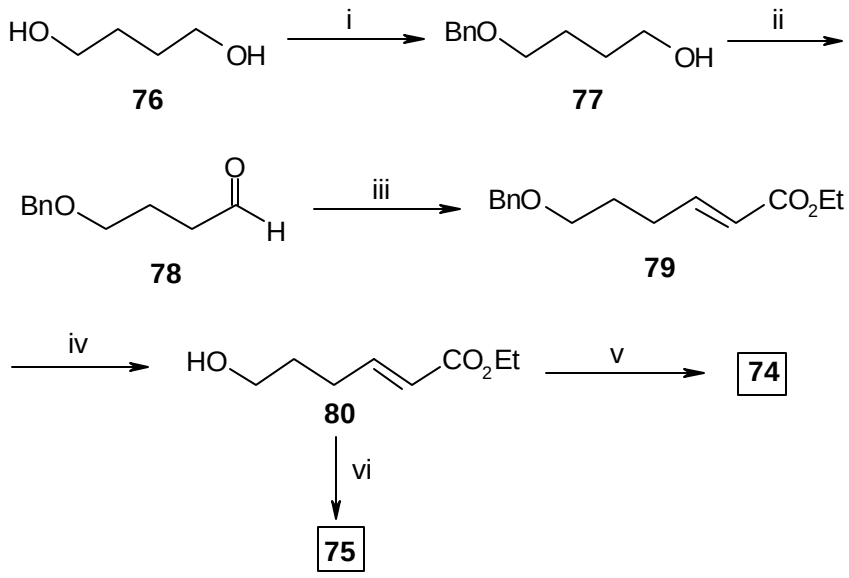
Scheme 16



The aldehyde **74** was prepared in 93 % yield by the Swern oxidation[30] of ethyl-6-hydroxy-(*E*)-2-hexenoate (**80**), whereas the iodo compound (**75**) was synthesized in 91 % yield from **80** by stirring with triphenylphosphine, iodine and imidazole[31] in DCM for 12 h at

room temperature. The common alcohol precursor **80** was prepared in four steps from commercially available 1,4-butanediol (**76**). The mono-benzyl protection of **76** was carried out[32] using benzyl chloride instead of benzyl bromide reagent. PCC oxidation of **77** gave **78** which was subjected to Wittig olefination with ethoxycarbonylmethylene triphenylphosphorane to give **79** (92 % yield) as a colorless liquid. Debenzylation[33] of **79** by stirring with TMSCl and NaI in acetonitrile gave **80** as a pale yellow liquid (Scheme 17). Detailed procedure and spectral data are given in experimental section.

Scheme 17



Reagents and conditions: *i) BnCl, KOH, rt, 5 h, 87 %; ii) PCC/Celite, DCM, rt, 3 h, 83 %; iii) Ph_3PCHCO_2Et, DCM, rt, 24 h, 92 %; iv) TMSCl, NaI, CH_3CN, rt, 4 h, 66 %; v) $(COCl)_2$, DMSO, Et_3N, - 78^o C, 93 %; vi) Ph_3P, I_2, imidazole, DCM, rt, 6 h, 91 %.*

2.1.1.1. Characterization of 71:

IR spectrum of **71** showed an absorption band at 1722 cm^{-1} suggesting the presence of an ester carbonyl group. The other bands were observed at 3381, 2952, 1367 and 1249 cm^{-1}.

^{1}H NMR spectrum of **71** (Fig. 3) displayed a singlet at δ 0.05 corresponding to the eighteen protons of the methyl groups of the –TMS moiety. A triplet at δ 1.27 (J = 7.3 Hz,

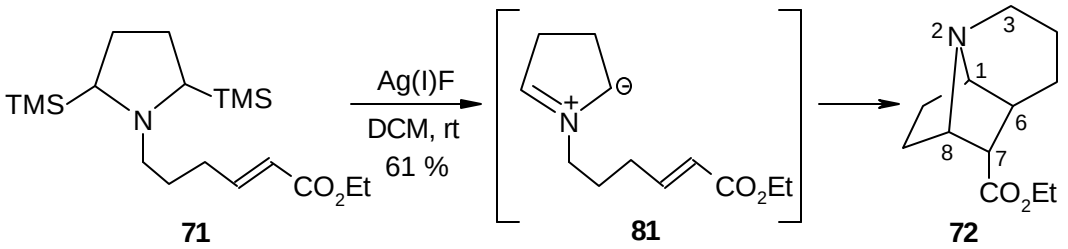
3H) and a quartet at δ 4.18 (*J* = 7.3 Hz, 2H) were assigned to the methyl and methylene protons of ester $-CO_2CH_2CH_3$ moiety, respectively. Two multiplets appearing between δ 1.35-2.03 and 2.05-2.62, integrating for six protons each, were attributed to the protons of pyrrolidine ring and methylene protons of the *N*-alkyl chain moiety. The two olefinic 3-C<u>H</u> and 2-C<u>H</u> protons appeared as a doublet of triplet at δ 5.83 (*J* = 15.2, 1.4 Hz, 1H) and δ 6.97 (*J* = 15.2, 6.9 Hz, 1H), respectively.

Mass spectrum (Fig. 3) showed a molecular ion peak at 355 (1) and a base peak at 282 (M^+ - TMS). The other fragmentation peaks were found at 340 (9), 73 (53).

2.1.2. [3 + 2]-cycloaddition reaction of 71:

The intramolecular [3+2]-dipolar cycloaddition reaction of **71** was carried out by the slow addition of a solution of **71** (1.0 g, 2.82 mmol) in dry DCM to a stirred suspension of vacuum dried Ag(I)F (0.89 g, 7.02 mmol) at room temperature. The color of the reaction mixture gradually turned dark brown and the reaction was completed within 4-6 h with the concomitant formation of silver mirror on the surface of the reaction flask. The reaction mixture was passed through a Celite pad and the residue was purified by silica gel column chromatography using chloroform / methanol (7:3) to afford a single product **72** in 61 % yield, characterized by ^{1}H NMR, ^{13}C NMR and mass spectral data (Scheme 18). The stereochemistry of **72** was assigned and confirmed by ^{1}H COSY experiment.

Scheme 18



71 **81** **72**

IR spectrum of **72** displayed a sharp band at 1723 cm^{-1}, confirming the presence of ester group. The other bands were observed at 3145, 2927 and 1395 cm^{-1}.

^{1}H NMR spectrum of compound **72** (Fig. 4) showed a multiplet between δ 1.22-1.25 (1H) corresponding to H_{10endo}. A triplet at δ 1.27 (J = 7.3 Hz, 3H) and a multiplet at δ 4.15 (2H) were attributed to the methyl and methylene protons of the ester (-$CO_2\underline{C}H_2\underline{C}H_3$) moiety, respectively. A multiplet between δ 1.31-1.43, integrating for two protons, was assigned to H_{4endo} and H_{9endo}. Another multiplet between δ 1.51-1.64, corresponding to three protons, is suggested to relate to the H_{5endo}, H_{9exo} and H_{10exo}. A multiplet between δ 1.65-1.78, equivalent to two protons, corresponds to H_{4exo} and H_{5exo}. H_{6endo} appeared as a multiplet at δ 2.53. A doublet at δ 2.95 (J = 5.7 Hz, 1H) could be attributed to H_{7exo}.A multiplet between δ 3.05-3.17, integrating for three protons, was assigned to H_{3endo}, H_{3exo} and H_1. Another, bridgehead H_8 appeared as a triplet at δ 3.73 (J = 4.6 Hz, 1H).

The stereochemistry of **72** was confirmed by detailed ^{1}H COSY experiment (Fig. 6). The H_6 proton at δ 2.53 (m, 1H) was found to couple with H_7 at δ 2.95 (d, J = 5.7 Hz, 1H), H_{5endo} at δ 1.51-1.64 (m, 3H) and H_{5exo} at δ 1.65-1.78 (m, 2H), but not with H_1 at δ 3.05-3.17 (m, 3H). This observation was found to be in conformity with the ^{1}H NMR patterns of the 7-azabicyclo[m.2.1]alkane skeletons[34,35] where no coupling is observed between bridgehead bowsprit and the adjacent *endo*-hydrogen due to the dihedral angle of 90° between them. Therefore, H_6 can be assigned with an *endo*-orientation. In contrast, H_7 coupled with H_6 and H_8 at δ 3.73 (t, J = 4.6 Hz, 1H), confirming the *endo*-orientation of the carboethoxy moiety.

^{13}C NMR spectrum (Fig. 5) displayed total of eleven signals at δ 14.06, 17.45, 25.49, 26.73, 28.07, 39.79, 46.17, 48.69, 60.42, 64.22 and 65.31 along with a carbonyl signal at δ 172.77. The assignments of carbon signals were confirmed by DEPT (Fig. 5) and Het COSY (Fig. 6) experiments. It was observed that the signals related to methyl and methylene carbons of ester (-$CO_2\underline{C}H_2\underline{C}H_3$) moiety appeared at δ 14.06 and 60.42, respectively. Five methylene signals at δ 17.45, 25.49, 26.73, 28.07 and 46.17 were assigned to C_9, C_4, C_{10}, C_5 and C_3 (-N-$\underline{C}H_2$-) carbons, respectively. The methine carbon

signals at δ 39.79 and 48.69 correspond to C_6 and C_7, respectively. Two bridgehead carbons C_8 and C_1 were characterized at δ 64.22 and 65.31, respectively.

Mass spectrum (Fig. 4) revealed a molecular ion peak at 209 (56) and a base peak at 136. The other prominent fragmentation peaks were found at 180 (26), 164 (28) and 83 (68).

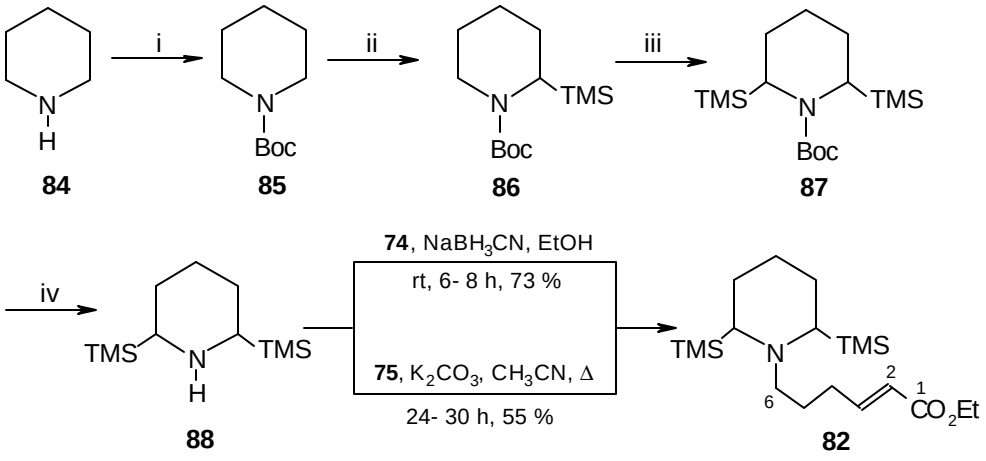
The above spectral analyses confirmed the compound **72** as ethyl-2-azatricyclo[4.4.0.0 ^{2,8}]decane-7-carboxylate.

The successful construction of azatricyclo skeleton **72** by the intramolecular cycloaddition of the non-stabilized azomethine ylide (**81**) generated from **71** encouraged us to evaluate the generality of this reaction. Following part of this thesis presents the construction of several X-azatricyclo[m.n.0.0^{a,b}]alkane skeleton.

2.2. Synthesis of Ethyl-7–azatricyclo[5.4.0.0^{3,8}]undecane–2–carboxylate (83):

The designed precursor **82**, for the construction of **83**, was obtained either by the reductive amination of 2,6-di(trimethylsilyl)piperidines (**88**) with 6-oxo-(*E*)-2-hexenoate (**74**) (73 % yield) in the presence of $NaBH_3CN$ or by the *N*-alkylation of **88** with **75** (yield 55 %) as shown in Scheme 19.

Scheme 19



Reagents and conditions: *I) tert-Butyl azidoformate, TEA, rt (90 %); ii) Ether, TMEDA, -78 ^{o}C, s-BuLi, 2 h, TMSCl, (90 %); iii) Ether, TMEDA, -45 ^{o}C, s-BuLi, -30 ^{o}C, 30 min, -45 ^{o}C, TMSCl (75 %); iv) TFA, DCM.*

The amine **88** was obtained in 60 % overall yield from commercially available piperidine (**84**) in 4 steps through the sequence, by adopting the identical experimental protocol as described in Chapter-II for the corresponding pyrrolidine analogue, as shown in Scheme 19.

2.2.1. Characterization of 82:

IR spectrum of **82** showed a strong absorption band at 1723 cm^{-1} indicating the presence of α,β-unsaturated ester group along with other bands at 2951, 1655, 1402, 1248 and 1044 cm^{-1}.

^{1}H NMR spectrum of **82** (Fig. 7) displayed a singlet at δ 0.05 (18 H) corresponding to the methyl protons of trimethylsilyl moiety. A triplet at δ 1.30 (J = 7.3 Hz, 3H) was assigned to the methyl protons of ester (-$CO_2CH_2C\underline{H}_3$) moiety. A multiplet between δ 1.35-1.70, integrating for eight protons, can be assigned to six –CH_2 protons of the piperidine ring along with two 5-C$\underline{H}_2$ protons of *N*-alkyl chain. Another multiplet between δ 2.03-2.42, equivalent to five protons, can be attributed to two –N-C$\underline{H}$- protons of piperidine ring, two 4-C$\underline{H}_2$ protons and one 6-C$\underline{H}_2$ proton of *N*-alkyl chain. Another 6-C$\underline{H}_2$ proton appeared as a multiplet at δ 2.83-2.95 (1H). A quartet at δ 4.17 (J = 7.3 Hz, 2H) corresponds to methylene protons of -$CO_2C\underline{H}_2CH_3$ moiety. Two doublets of triplet resonating at δ 5.78 (J = 15.4, 1.4 Hz, 1H) and 6.97 (J = 15.4, 6.9 Hz, 1H) were assigned to two olefinic 3-C$\underline{H}$ and 2-C$\underline{H}$ protons, respectively.

^{13}C NMR spectrum of **82** (Fig. 8) showed total of eleven signals at δ -1.45, 14.12, 19.65, 25.06, 28.25, 29.85, 50.34, 51.53, 59.82, 121.25 and 149.06 along with a carbonyl signal at δ 166.36. DEPT experiment suggested that the methyl carbon signals at δ -1.45 and 14.12 correspond to –$\underline{C}H_3$ carbons of –TMS and ester (-$CO_2CH_2\underline{C}H_3$) moieties, respectively. The signal at δ 19.65 was attributed to C_3 and C_5 methylene carbons while

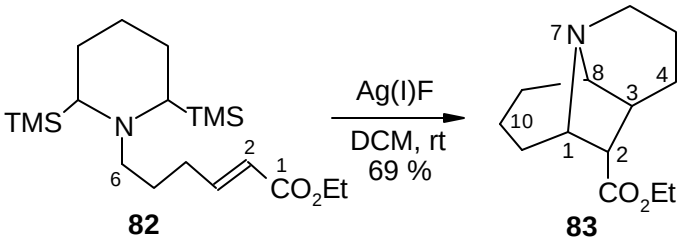
the other signal at δ 25.06 was assigned to C_4 methylene carbon of the piperidine ring. The other methylene signals at δ 28.25, 29.85, 50.34 and 59.82 were assigned to C_5, C_4 (-$\underline{C}H_2$-CH=CH-), C_6 (-N-$\underline{C}H_2$-) and –CO_2-$\underline{C}H_2CH_3$ carbons, respectively. The signal at δ 51.53 was attributed to two methine carbons (-N-$\underline{C}$H-) of piperidine ring. Two olefinic carbons C_3 and C_2 appeared at δ 121.25 and 149.06, respectively.

Mass spectrum of **82** (Fig. 7) gave a molecular ion peak at 369 and a base peak at 296 (M^+ - CO_2Et, 1) along with other peaks at 354 (4) and 73 (81).

2.2.2. [3 + 2]-cycloaddition reaction of 82:

Intramolecular [3+2]-dipolar cycloaddition reaction of **82** carried out by adopting the identical experimental procedure as described previously (section 2.1.2) afforded cycloadduct **83** in 69 % yield as a thick yellow liquid (Scheme 20). IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses characterized the product.

Scheme 20



82 **83**

IR spectrum of compound **83** showed a strong absorption band at 1723 cm^{-1}, indicating the presence of ester group. The other bands appeared at 3147, 2930, 1400, 1181 and 1048 cm^{-1}.

^{1}H NMR spectrum of **83** (Fig. 9) showed a triplet at δ 1.27 (J = 7.3 Hz) equivalent to three protons corresponding to the methyl protons of ester (-$CO_2CH_2\underline{C}H_3$) moiety. Three multiplets appearing between δ 1.35-1.48 (2H), δ 1.53-1.84 (6H) and δ 1.85-2.13 (2H) could be assigned to ten –CH_2 protons related to H_4, H_5, H_9, H_{10}, and H_{11}. Another multiplet

at δ 2.78, equivalent to one proton, was assigned as H_{3endo}. The bowsprit bridgehead H_8 appeared as a broad singlet at δ 2.87. One more multiplet between δ 2.93-3.07 (2H) belongs to the methylene protons of H_{3endo} and H_{6exo} of –N-C<u>H</u>$_2$- group. H_{2exo} appeared as a broad doublet at δ 3.10 (J = 6.3 Hz, 1H). Another bridgehead H_1 appeared as a multiplet between δ 3.58-3.69 (1H). Two methylene protons of ester (-CO_2C<u>H</u>$_2$CH_3) moiety appeared as a multiplet between δ 4.04-4.32 (2H).

The stereochemistry of the cycloadduct as shown in structure **83** was confirmed by detailed ^{1}H COSY (Fig. 10) experiment. The H_3 hydrogen was found to couple only with H_{2exo} at δ 3.07-3.14 (bd, J = 6.3 Hz, 1H) and H_4 at δ 1.53-1.84 (m, 6H) but not with the bridgehead proton H_8 at δ 2.87 (bs, 1H) confirming its *endo*-orientation. The H_2 proton was found to couple with H_{3endo} and H_1 at δ 3.58-3.69 (m, 1H) confirming the *endo*-orientation of the carbethoxy moiety.

In ^{13}C NMR spectrum of compound **83** (Fig. 11) total of twelve signals appeared at δ 14.11, 15.97, 18.47, 29.41, 29.74, 32.04, 39.51, 50.32, 53.96, 60.19, 64.08 and 67.80 along with a signal at δ 173.53 for carbonyl carbon. DEPT experiment revealed the presence of methyl and methylene carbons of ester (-CO_2C<u>H</u>$_2$C<u>H</u>$_3$) moiety at δ 14.11 and 60.19, respectively. Six methylene signals at δ 15.97, 18.47, 29.41, 29.74, 32.04 and 53.96 can be assigned to C_{10}, C_{11}, C_9, C_5, C_4 and C_6 (-N-C<u>H</u>$_2$-) carbons, respectively. The methine carbon signals at δ 39.51 and 50.32 were assigned to C_3 and C_2, respectively. Two bridgehead methine carbons C_1 and C_8 were characterized at δ 64.08 and 67.80, respectively.

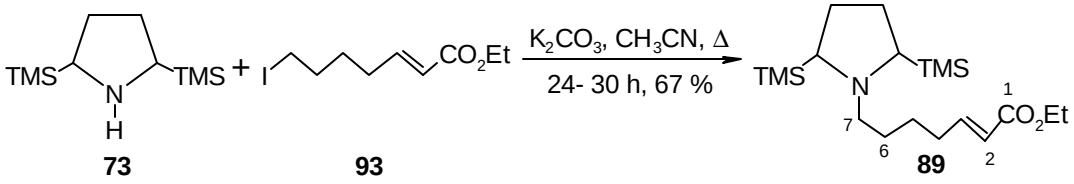
Mass spectrum of **83** (Fig. 9) showed a molecular ion peak at 223 (M^+, 77) and a base peak at 97, corresponding to *N*-methyl piperidine moiety. The other fragmentation peaks were found at 194 (M^+- C_2H_5, 55), 178 (M^+-OC_2H_5, 38), 150 (M^+- $CO_2C_2H_5$, 78) and 136 (43).

The above spectral analyses confirmed the structure of **83** as ethyl-7–azatricyclo[5.4.0.0^{3,8}]undecane–2–carboxylate.

2.3. Synthesis of Ethyl-2–azatricyclo[5.4.0.0^{2,9}]undecane–8–carboxylate (90):

The designed precursor **89**, for the synthesis of **90**, was prepared in the similar manner as described in section 2.1.1 by heating **73** with 7-iodo-(*E*)-2-heptenoate (**93**) in dry acetonitrile in the presence of K_2CO_3 in 67 % yield as a viscous yellow liquid (Scheme 21).

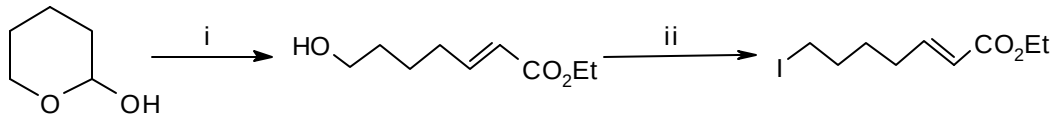
Scheme 21



73 **93** **89**

The iodo derivative **93** was prepared in 91 % yield from the corresponding ethyl-7-hydroxy-(*E*)-2-heptenoate (**92**) by stirring with of triphenylphosphine, iodine and imidazole[31] in DCM for a period of 12 h at rt (Scheme 22). The alcohol **92** was obtained by the reaction of 2-hydroxypyran (**91**)[36] with ethoxycarbonylmethylene triphenylphosphorane. Detailed procedures and spectral data are given in the experimental section.

Scheme 22



91 **92** **93**

Reagents and conditions: *I) Ph_3PCHCO_2Et, DCM, rt, 2 d, 83 %; ii) Ph_3P, imidazole, DCM, rt, 6 h, 91 %.*

2.3.1. Characterization of 89:

IR spectrum of **89** showed a strong absorption band at 1717 cm^{-1} confirming the presence of α,β-unsaturated ester group. Other prominent bands were observed at 3429, 2952, 1654, 1368, 1254, 1042 cm^{-1}.

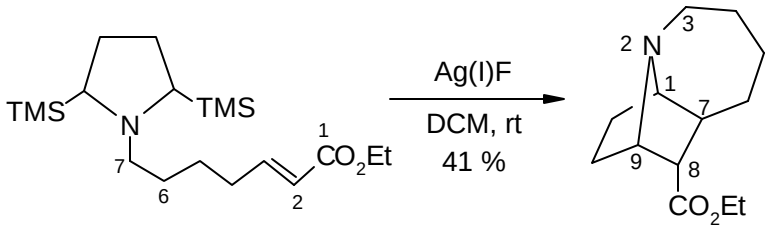
In the ^{1}H NMR spectrum of **89** (Fig. 12), a singlet at δ 0.05 (18H) corresponds to methyl protons of –TMS moiety. A triplet at δ 1.27 (J = 7.2 Hz, 3H) and a quartet at δ 4.18 (J = 7.2 Hz, 2H) were assigned to methyl and methylene protons of ester (-$CO_2CH_2CH_3$) moiety, respectively. Two multiplets between δ 1.35-1.73 (5H) and δ 1.76-1.98 (3H) could be assigned to the four –CH_2 protons of pyrrolidine ring along with two 5-CH_2 and two 6-CH_2 protons of *N*-alkyl chain. Another multiplet between δ 2.11-2.59, integrating for six protons could be attributed to two –N-CH- protons of pyrrolidine ring along with two allylic 4-CH_2 (-CH_2CH=CH-) and two –N-CH_2- protons of *N*-alkyl chain moiety. Two doublets of triplet appearing at δ 5.83 (J = 15.6, 1.4 Hz, 1H) and δ 6.95 (J = 15.6, 6.9 Hz, 1H) were assigned to both olefinic 3-CH- and 2-CH- protons, respectively.

^{13}C NMR (Fig. 13) and mass spectral (Fig. 12) analyses were in perfect agreement with the above assigned structure and have been detailed in the experimental section.

2.3.2. [3 + 2]-cycloaddition reaction of 89:

With the key precursor **89** in hand, we carried out the [3+2]-dipolar cycloaddition reaction of **89** adopting the similar experimental protocol as described previously in Section 2.1.2. The crude residue was purified by column chromatography eluting with $CHCl_3$/MeOH (9:1) to afford **90** in 41 % yield as a thick yellow liquid (Scheme 23). IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis characterized the compound **90**.

Scheme 23



89 **90**

IR spectrum of compound **90** showed a strong absorption band 1725 cm^{-1}, confirming the presence of ester group. The other bands were found at 2937, 1451, 1385 and 1231 cm^{-1}.

^{1}H NMR spectrum of **90** (Fig. 14) displayed a triplet at δ 1.27 (J = 7.3 Hz, 3H) for the methyl group of ester (-$CO_2CH_2C\underline{H}_3$) moiety. A multiplet between δ 1.32-1.87 integrating for ten protons could be assigned to the methylene (–$C\underline{H}_2$) protons related to H_4, H_5, H_6, H_{10} and H_{11}. Another multiplet between δ 2.53-2.62 (1H) could be attributed to H_{7endo}. Two methylene H_{8endo} and H_{8exo} protons of (-N-$C\underline{H}_2$-) moiety appeared as a multiplet between δ 2.62-2.68 (1H) and δ 3.23-3.37 (1H), respectively. H_{8exo} appeared as a triplet at δ 2.88 (J = 5.1 Hz, 1H). A doublet at δ 3.40 (J = 3.6 Hz) corresponding to one proton was assigned to bridgehead H_1. The other bridgehead H_9 appeared as a triplet at δ 3.55 (J = 4.3 Hz, 1H). The signal corresponding to the methylene protons of ester (-$CO_2C\underline{H}_2CH_3$) moiety was observed as a quartet at δ 4.15 (J = 7.3 Hz, 2H).

The ^{1}H NMR decoupling experiment suggested that H_7 at δ 2.53-2.62 (m, 1H) coupled with H_8 at δ 2.88 (t, J = 5.1 Hz, 1H) as well as with H_6 protons at δ 1.32-1.87 (m, 10H) but not with the bridgehead proton H_1 at δ 3.40 (d, J = 3.6 Hz, 1H). This confirms the *endo*-orientation of H_7 proton. However, H_8 proton was found to couple with H_{7endo} and bridgehead H_9 at δ 3.55 (t, J = 4.3 Hz, 1H) confirming the *endo*-orientation of the carbethoxy moiety.

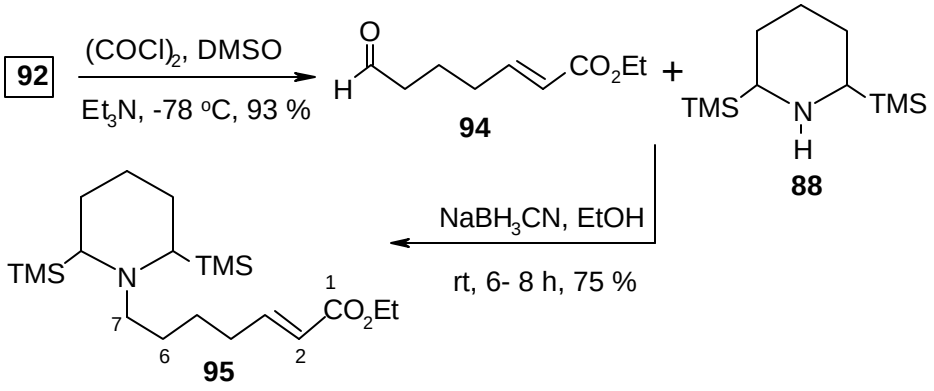
^{13}C NMR spectrum (Fig. 14) displayed total of twelve signals at δ 14.11, 24.59, 25.82, 27.39, 29.26, 29.52, 45.52, 49.56, 50.29, 60.52, 63.72 and 66.54 along with carbonyl signal at δ 172.89. DEPT experiment characterized the signals at δ 14.11 and 60.52 as methyl and methylene carbons of ester (-$CO_2\underline{C}H_2\underline{C}H_3$) moiety, respectively. Six methylene signals at δ 24.59, 25.82, 27.39, 29.26, 29.52 and 49.56 can be assigned to C_5, C_{10}, C_{11}, C_4, C_6 and C_8 carbons, respectively. The signals appearing at δ 45.52 and 50.29 as methine carbons correspond to C_7 and C_8, respectively. The bridgehead carbons C_9 and C_1 were characterized at δ 63.72 and 66.54, respectively.

The above spectral analyses confirmed the compound **90** as ethyl-2–azatricyclo[5.4.0.0^{2,9}]undecane–8–carboxylate.

2.4. Synthesis of Ethyl-2–azatricyclo[5.5.0.0^{2,9}]dodecane–8–carboxylate (96):

The designed cycloaddition precursor **95** for the construction of **96** was obtained following the identical procedure as described for the preparation of **82** in Section 2.2.1. The reductive amination of **88** in ethanol with 7-oxo-(*E*)-2-heptenoate (**94**), obtained by Swern oxidation[30] of ethyl-7-hydroxy-(*E*)-2-heptenoate (**92**), in the presence of $NaBH_3CN$ afforded **95** in 75 % yield as a viscous yellow liquid (Scheme 24). IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses characterized the compound **95**.

Scheme 24



IR spectrum of **95** showed a strong absorption band at 1723 cm^{-1}, indicating the presence of ester group along with other bands at 3442, 2949, 1655, 1445, 1368, 1248, 1044 cm^{-1}.

^{1}H NMR spectrum of compound **95** (Fig. 15) showed a singlet at δ 0.05, corresponding to eighteen protons of the methyl groups of –TMS moiety. A triplet at δ 1.29 (J = 7.3 Hz, 3H) and a quartet at δ 4.19 (J = 7.3 Hz, 2H) were assigned to methyl and methylene protons of ester (-$CO_2C\underline{H}_2C\underline{H}_3$) moiety, respectively. A multiplet between δ 1.33-1.72, integrating for ten protons can be assigned to the six –$C\underline{H}_2$ protons of piperidine ring along with two 5-$C\underline{H}_2$ and two 6-$C\underline{H}_2$ protons of *N*-alkyl chain. Another multiplet between δ 2.12-2.43 (5H) can be attributed to two –N-C$\underline{H}$- protons of piperidine ring along with two allylic 4-$C\underline{H}_2$ (-$C\underline{H}_2$CH=CH-) protons and one of the 7-$C\underline{H}_2$ (-N-$C\underline{H}_2$-)

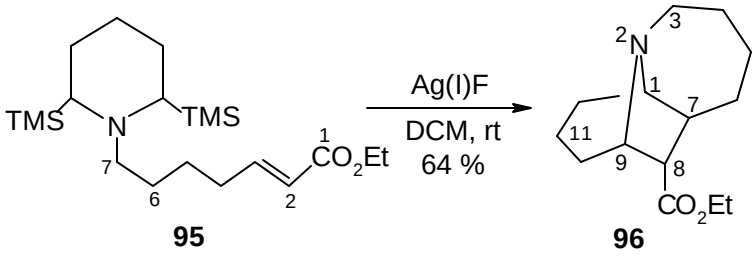
proton of *N*-alkyl chain. The other 7-C<u>H</u>$_2$ proton appeared as a multiplet between δ 2.76-2.95 (1H). Two doublets of triplet at δ 5.83 (J = 15.2, 1.4 Hz, 1H) and δ 6.97 (J = 15.2, 6.9 Hz, 1H) were assigned to both olefinic 3-C<u>H</u> and 2-C<u>H</u> protons respectively.

^{13}C NMR (Fig. 16) and mass spectral (Fig. 15) analysis were in perfect agreement with the above assigned structure and are detailed in the experimental section.

2.4.1. [3 + 2]-cycloaddition reaction of 95:

The [3+2] cycloaddition reaction of **95** was carried out following the same experimental protocol as described in Section 2.1.2. The crude residue was purified by silica gel column chromatography eluting with CHCl$_3$/MeOH (9:1) to afford **96** in 64 % yield as a thick yellow liquid (Scheme 25).

Scheme 25



IR spectrum of compound **96** showed a strong absorption band 1726 cm^{-1}, confirming the presence of ester group. The other prominent bands were observed at 2929, 1453, 1398 1233 and 1180 cm^{-1}.

^{1}H NMR spectrum of **96** showed following pattern (Fig 17). A triplet at δ 1.28 (J = 7.2 Hz) equivalent to three protons corresponds to methyl group of ester (-CO$_2$CH$_2$C<u>H</u>$_3$) moiety. A multiplet between δ 1.33-1.92 integrating for twelve protons could be assigned to the methylene (–C<u>H</u>$_2$) protons related to H$_4$, H$_5$, H$_6$, H$_{10}$, H$_{11}$ and H$_{12}$. A doublet of triplet at δ 2.61 (J = 14.8, 5.4 Hz) corresponding to one proton can be attributed for H$_{3endo}$. H$_{7endo}$ appeared as a multiplet between δ 2.81-2.94 (1H). A triplet at

δ 3.01 (J = 7.2 Hz, 1H) could be assigned to H_{8exo}. Other multiplet at δ 3.06-3.16 (1H) attributed to H_{3exo}. The signals resonating at δ 3.22 (bs) and at δ 3.32-3.45 (m), integrating for one proton each, can be assigned to two bridgehead protons H_1 and H_9, respectively. Two methylene protons of ester (-$CO_2C\underline{H}_2CH_3$) moiety appeared as a multiplet between δ 4.04-4.31.

The ^{1}H COSY (Fig. 18) experiment suggested that H_7 between δ 2.81-2.94 (m, 1H) coupled with H_8 at δ 3.01 (t, J = 7.2 Hz, 1H) along with H_6 protons between 1.33-1.92 (m, 12H) but not with the bridgehead proton H_1 at δ 3.22 (bs, 1H). This confirms the *endo*-orientation of H_7 proton. In contrast, H_8 was found to couple with H_{7endo} and the bridgehead H_9 between δ 3.32-3.45 (m, 1H) confirming the *endo*-orientation of carbethoxy moiety.

In ^{13}C NMR spectrum of compound **96** (Fig. 19) total of thirteen signals appeared at δ 14.08, 16.75, 25.49, 27.53, 29.50, 30.43, 32.0, 43.95, 54.98, 55.97, 59.99, 62.43 and 66.06, along with a signal at δ 173.0 for the carbonyl carbon. DEPT experiment suggested the signals at δ 14.06 and 62.43 to be methyl and methylene carbons of ester (-$CO_2\underline{C}H_2\underline{C}H_3$) moiety, respectively. Seven methylene signals at δ 16.75, 25.49, 27.53, 29.50, 30.43, 32.0 and 55.97 can be assigned to C_{11}, C_5, C_{10}, C_{12}, C_6, C_4 and C_3 carbons, respectively. The methine carbon signals appearing at δ 43.95 and 54.98 is attributed to C_7 and C_8, respectively. Two bridgehead carbons C_9 and C_1 were characterized at δ 62.43 and 66.06, respectively.

Mass spectrum (Fig. 17) showed a molecular ion peak at 237 (27) and a base peak at 97, corresponding to *N*-methyl piperidine moiety. The other prominent fragmentation peaks were found at 208 (M^+- C_2H_5, 42), 192 (M^+- OC_2H_5, 27), 164 (M^+- $CO_2C_2H_5$, 54), 136 (M^+- $C_5H_9O_2$, 45), 123 (M^+- $C_6H_{10}O_2$, 87) and 83(53).

The above spectral analyses confirmed the compound **96**, as ethyl-2–azatricyclo[5.5.0.0^{2,9}]dodecane–8–carboxylate.

We have synthesized a number of azatricyclo compounds by employing intramolecular [3+2]-cycloaddition of non-stabilized cyclic azomethine ylides. A recent report by Smith *et al.*[28] that the azatricyclo analogue bearing a benzo-tether group to the 2β-position of tropane moiety showed high binding affinity at the dopamine transporter. Keeping the above observation in mind, we have further extended our effort towards the synthesis of a more rigid azatetracyclo compounds having a benzene-tether ring in *N*-alkyl chain moiety.

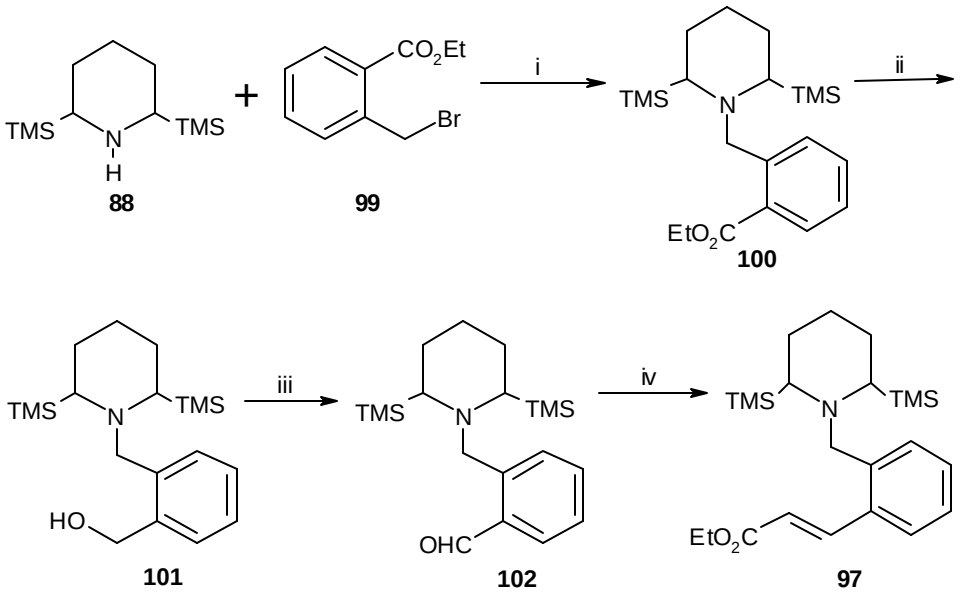
2.5. Synthesis of Ethyl-9-azatetracyclo[8.5.0.0^{2,7}.0^{9,14}]pentadeca-2(7),3,5-triene-15-carboxylate (98):

The designed precursor ethyl-3–{2-[2,6–di(trimethylsilyl)hexahydro–1–pyridinyl methyl]phenyl}–(*E*)–2–propenoate (**97**) is subjected to undergo intramolecular [3+2] cycloaddition reaction to give rigid ethyl-9-azatetracyclo[8.5.0.0^{2,7}.0^{9,14}]pentadeca-2(7),3,5-triene-15-carboxylate (**98**).

2.5.1. Preparation of Ethyl-3–{2-[2,6–di(trimethylsilyl)hexahydro–1–pyridinyl methyl]phenyl}–(*E*)–2–propenoate (97):

Synthesis of the precursor **97** was accomplished from 2-[2,6-di(trimethylsilyl)hexahydro-1-pyridinylmethyl]phenylmethanol (**101**) in 85 % yield by performing Swern oxidation followed by Wittig olefination using ethoxycarbonylmethylene triphenylphosphorane. $LiAlH_4$ reduction of ester **100** gave **101** in 91 % yield. *N*-Alkylation of **88** with ethyl 2-(bromomethyl)benzoate (**99**)[37] afforded **100** in 83 % yield (Scheme 26). Detailed procedure and spectral data are given in experimental section. IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses characterized the compound **97**.

Scheme 26



Reagents and conditions: *I) K_2CO_3, CH_3CN, D, 6 h, 83 %; ii) $LiAlH_4$, rt, 12 h, 91 %; iii) $(COCl)_2$, DMSO, Et_3N, -78° C, 95 %; iv) Ph_3PCHCO_2Et, DCM, rt, 24 h, 89 %.*

IR spectrum of **97** showed a strong absorption band at 1716 cm^{-1}, indicating the presence of α,β-unsaturated ester group. Other bands appeared at 2920, 1631, 1500 (aromatic -CH=CH-), 1441, 1312 and 1244 cm^{-1}.

^{1}H NMR spectrum of **97** (Fig. 20) displayed a singlet at δ 0.05 (18H) characterizable as methyl protons of –TMS moiety. A triplet at δ 1.32 (J = 7.3 Hz, 3H) and a quartet at δ 4.28 (J = 7.3 Hz, 2H) were assigned to methyl and methylene protons of ester (-$CO_2CH_2CH_3$) moiety, respectively. A multiplet between δ 1.47-1.77, integrating for six protons could be attributed to the six –CH_2 protons of piperidine ring. Another multiplet between δ 2.22-2.40 (2H) corresponds to two methine –N-CH- protons of piperidine ring. A set of two doublets at δ 3.63 and δ 4.34 (J = 13.7 Hz), equivalent to one proton each were assigned to the two benzylic protons. Two olefinic 2-CH and 3-CH protons appeared as a doublet at δ 6.34 (J = 15.6 Hz, 1H) and δ 8.27 (J = 15.6 Hz, 1H), respectively. Besides these, four aromatic protons appeared in two bunches of multiplets between δ 7.21-7.45 (2H) and δ 7.50-7.67 (2H).

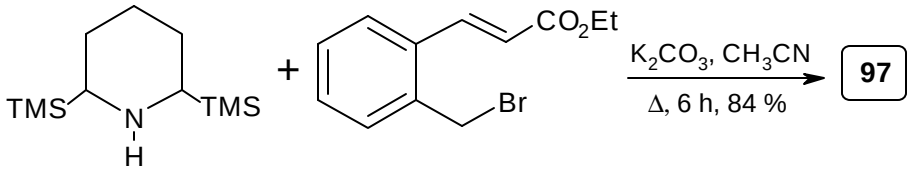
^{13}C NMR of **97** (Fig. 21) showed total of seven signals at δ -1.23, 14.19, 19.68, 24.76, 50.87, 51.57 and 60.06 in aliphatic region. DEPT experiment suggested that the signals at δ -1.23 and 14.19 corresponding to the methyl carbons of –TMS and ester (-$CO_2CH_2\underline{C}H_3$) moieties, respectively. The signal at δ 19.68 could be assigned to both C_3 and C_5 methylene carbons of piperidine ring while the signal at δ 24.76 is assigned to C_4 carbon of piperidine ring. The signal at δ 50.87 was attributed to both methine (-N-$\underline{C}$H-) carbons of piperidine ring. Another two methylene signals at δ 51.57 and 60.06 were attributed to benzylic (-N-$\underline{C}H_2$-) and ester (-$CO_2\underline{C}H_2CH_3$) carbons, respectively. Two olefinic carbons C_2 and C_8 appeared at δ 119.52 and 142.41, respectively. Besides these, aromatic signals appeared at δ 126.12, 126.85, 129.44, 130.39, 134.08, 139.61, and carbonyl signal appeared at δ 166.58.

Mass spectrum (Fig. 20) revealed the molecular ion peak at 417 (2) and a base peak at 345 (M^+-$CO_2C_2H_5$). Other prominent peaks were observed at 131 (16), 117 (43) and 73 (81).

2.5.1.1. Alternate method for the preparation of 97:

Although, we could synthesize **97** in four steps (Scheme 26) with 64 % over all yield, the multistep reaction sequences and relatively moderate yield, led us to visualize an alternate one step strategy towards the preparation of **97**. This procedure involved refluxing of a solution of **88** in acetonitrile with ethyl-3-(2-bromomethyl phenyl)-(*E*)-2-propenoate (**103**)[38] in the presence of K_2CO_3 which gave **97** in 84 % yield as a thick yellow liquid (Scheme 27).

Scheme 27

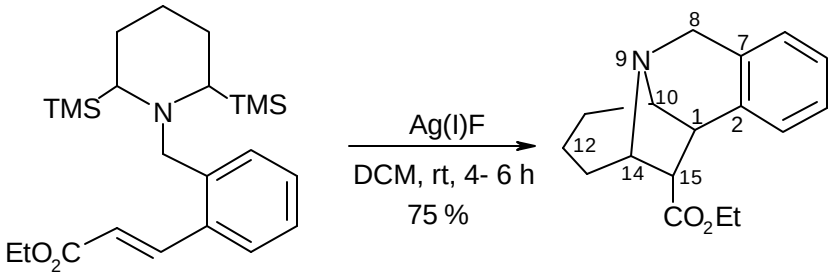


88 **103**

2.5.2. [3 + 2]-cycloaddition reaction of 97:

The [3+2]-dipolar cycloaddition reaction of **97** was carried out following similar experimental protocol (Section 2.1.2), by stirring a mixture containing **97** and Ag(I)F in dry DCM at room temperature for a period of 6-8 h. After usual workup, the crude residue was purified by column chromatography eluting with pet ether/acetone (7:3) to afford **98** in 75 % yield as a viscous yellow liquid (Scheme 28). IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses characterized the compound **98**.

Scheme 28



97 **98**

IR spectrum of **98** showed a strong absorption band 1730 cm^{-1}, confirming the presence of ester group. The other bands were observed at 2937, 1581, 1457 and 1190 cm^{-1}.

^{1}H NMR spectrum of **98** showed the following pattern (Fig. 22). A triplet at δ 1.27 (J = 7.3 Hz), integrating for three protons, corresponds to methyl protons of ester (-$CO_2CH_2CH_3$) moiety. Both H_{12} methylene protons appeared as a multiplet between δ 1.37-1.67 (2H). Another multiplet between δ 1.72-2.0 integrating for four protons can be attributed to H_{11} and H_{13} methylene protons. A doublet of doublet at δ 3.03 (J = 7.8, 2.0 Hz, 1H) was assigned to H_{15exo}. A broad singlet at δ 3.16 (1H) corresponds to bridgehead H_{10}. H_{1endo} appeared as a doublet at δ 3.59 (J = 2.0 Hz, 1H). Another bridgehead H_{14} appeared as a triplet at δ 3.68 (J = 3.9 Hz, 1H). Two doublets appearing at δ 3.77 (J = 18.0 Hz) and δ 4.55 (J = 18.0 Hz), equivalent to one proton each were characterized to two

benzylic protons H_{8endo} and H_{8exo}, respectively. A multiplet between δ 4.05-4.31 (2H) could be attributed to both the methylene protons of carbethoxy (-$CO_2CH_2CH_3$) moiety. The remaining four protons of aromatic ring appeared as a multiplet between δ 6.82-7.20.

The stereochemistry of the cycloadduct **98** was confirmed by detailed ^{1}H COSY (Fig. 23) experiment. The H_1 at δ 3.59 (d, J = 2.0 Hz, 1H) was found to couple only with H_{15exo} at δ 3.03 (dd, J = 7.8, 2.0 Hz, 1H) but not with the bridgehead proton H_{10} at δ 3.16 (bs, 1H). This confirms the *endo*-orientation of H_1 proton. However, H_{15} was found to couple with both H_{1endo} and bridgehead H_{14} at δ 3.68 (t, J = 3.9 Hz, 1H), confirming the *endo*-orientation of carbethoxy moiety.

^{13}C NMR spectrum (Fig. 24) showed total of nine signals in aliphatic region at δ 14.03, 15.79, 29.20, 43.84, 58.40, 58.68, 60.21, 65.27 and 67.74 along with aromatic signals at δ 123.77, 125.17, 125.93, 126.24, 132.8, 147.9 and carbonyl signal at δ 172.05. DEPT experiment suggested that the signal at δ 14.03 attributable to methyl carbon of ester (-$CO_2CH_2\underline{C}H_3$) moiety. The methylene carbon signal at δ 15.79 can be assigned to C_{12}. Both C_{11} and C_{13} resonated at δ 29.20. Other two methylene signals at δ 58.68 and 60.21 were attributed to C_8 (benzylic –*N*-$\underline{C}H_2$-) and ester (-$CO_2\underline{C}H_2CH_3$) carbons respectively. The signals appearing at δ 43.84 and 58.40 were methine carbons corresponding to C_1 and C_{15}, respectively. Other two methine carbon signals at δ 65.27 and 67.74 could be assigned to either of the two bridgehead C_{10} and/or C_{14} carbons.

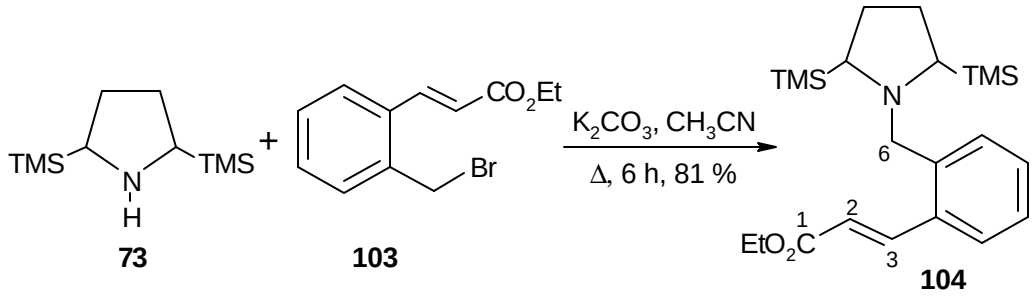
Mass spectrum of **98** (Fig. 22) revealed a molecular ion peak at 271 (62) and a base peak at 198 (M^+-$CO_2C_2H_5$). The other prominent fragmentation peaks were found at 184 (37), 156 (24), 117 (45) and 82 (22).

The above spectral analyses confirmed the compound **98** as ethyl-9-azatetracyclo[8.5.0.0^{2,7}.0^{9,14}]pentadeca-2(7),3,5-triene-15-carboxylate.

2.6. Synthesis of Ethyl-8-azatetracyclo[8.4.0.0^{2,7}.0^{4,8}]tetradeca-1(10),11,13-triene-3-carboxylate (105):

The designed precursor **104**, for the synthesis of **105**, was obtained in 81 % yield as a viscous yellow liquid by heating the mixture of **73** with **103** in acetonitrile in the presence of K_2CO_3 for 6-8 h (Scheme 29). IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses characterized the compound **104**.

Scheme 29



73 **103** **104**

IR spectrum of **104** was found to be almost identical to that observed for **97**.

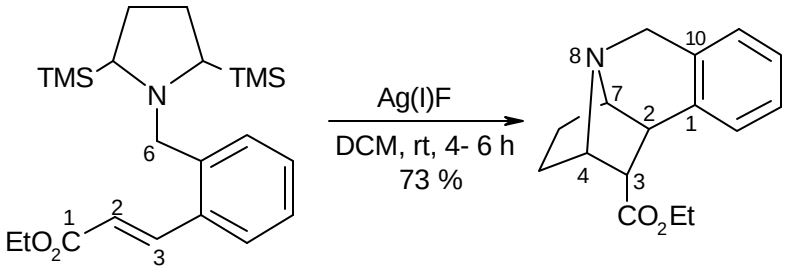
In ^{1}H NMR spectrum of **104** (Fig. 25), a sharp singlet appearing at δ -0.1, equivalent to eighteen protons correspond to methyl protons of –TMS moiety. A triplet at δ 1.35 (J = 7.3 Hz, 3H) and a multiplet between δ 4.14-4.35 (2H) could be attributed to methyl and methylene protons of ester (-$CO_2CH_2CH_3$) moiety, respectively. Two multiplets between δ 1.55-1.77 and δ 1.83-2.04, integrating for two protons each, could be assigned to four methylene (-CH_2-) protons of pyrrolidine ring. A triplet at δ 2.33 (J = 4.8 Hz), equivalent to two protons, was attributed to both the methine –N-CH- protons of pyrrolidine ring. A set of two doublets at δ 3.43 and δ 3.98 (J = 13.7 Hz), equivalent to one proton each, were assigned to the two benzylic (-N-CH_2-) protons. Another set of two doublets at δ 6.33 (J = 15.6 Hz, 1H) and δ 8.48 (J = 15.6 Hz, 1H) correspond to two olefinic 2-CH and 3-CH protons, respectively. The four aromatic protons appeared as a bunch of two multiplets between δ 7.17-7.36 (3H) and δ 7.48-7.72 (1H).

^{13}C NMR (Fig. 26) and mass spectral (Fig. 25) analyses were in perfect agreement with the above assigned structure and have been detailed in the experimental section.

2.6.1. [3 + 2]-cycloaddition reaction of 104:

The [3+2] cycloaddition reaction of **104** was carried out by adopting same experimental protocol as described earlier in Section 2.5.2. The crude residue was purified by silica gel column chromatography eluting with pet ether/acetone (6:4) to afford **105** in 73 % yield as a viscous yellow liquid (Scheme 30). IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses characterized the compound **105**.

Scheme 30



104 **105**

IR spectrum of **105** was found almost identical to that observed for **102**.

^{1}H NMR spectrum of **105** (Fig. 27) showed a triplet at δ 1.27 (J = 7.3 Hz, 3H), corresponding to the methyl group of ester (-$CO_2CH_2CH_3$) moiety. Two multiplets appearing between δ 1.28-1.43 (1H) and δ 1.55-1.97 (3H) can be assigned to four methylene protons of H_5 and H_6. Three doublets at δ 2.77 (J = 6.3 Hz), δ 3.18 (J = 5.4 Hz) and δ 3.36 (J = 1.8 Hz), integrating for one proton each, could be assigned to H_{3exo}, bridgehead H_7 and H_{2endo} protons respectively. Other bridgehead H_4 appeared as a triplet at δ 3.74 (J = 4.9 Hz, 1H). A set of two doublets at δ 4.04 (J = 18.5 Hz) and δ 4.42 (J = 18.5 Hz), corresponding to one proton each were assigned to two benzylic H_{9endo} and H_{9exo} protons, respectively. A quartet at δ 4.14 (J = 7.3 Hz, 2H) belongs to both the

methylene protons of carbethoxy (-$CO_2C\underline{H}_2CH_3$) moiety. Another multiplet between δ 6.95-7.20 corresponds to four aromatic protons.

^{1}H COSY experiment (Fig. 28) showed that H_2 at δ 3.36 (d, J = 1.8 Hz, 1H) was coupling only with H_3 at δ 2.77 (d, J = 6.3 Hz, 1H) but not with the bridgehead proton H_7 at δ 3.18 (J = 5.4 Hz) confirming the *endo*-orientation of H_2 proton. However, H_3 proton was found to couple with both H_{2endo} and bridgehead H_4 at δ 3.74 (J = 4.9 Hz, 1H), confirming the *endo*-orientation of carbethoxy moiety.

^{13}C NMR spectrum of **105** (Fig. 29) showed a total of nine signals in aliphatic region at δ 13.93, 25.43, 25.7, 45.33, 50.67, 56.31, 60.1, 62.32 and 66.78 along with aromatic signals at δ 124.63, 125.19, 125.62, 125.98, 132.88, 143.98 and carbonyl carbon at δ 172.03. DEPT experiment revealed that the signal at δ 13.93 corresponds to methyl carbon of ester (-$CO_2CH_2\underline{C}H_3$) moiety. Two methylene signals at δ 25.43 and 25.7 can be assigned to either of C_5 and/or C_6 carbons. Other two methylene signals at δ 50.67 and 60.1 were attributed to benzylic (-N-$\underline{C}H_2$-) and ester (-$CO_2\underline{C}H_2CH_3$) carbons, respectively. The methine carbon signals at δ 45.33 and 56.31 can be attributed to C_2 and C_3 carbons, respectively. Two methine carbons at δ 62.32 and 66.78 belong to either of the two bridgehead C_4 and/or C_7 carbons.

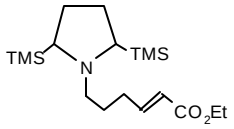
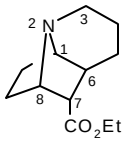
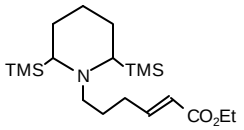
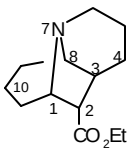
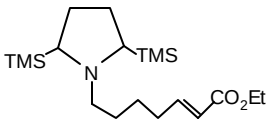
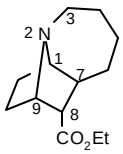
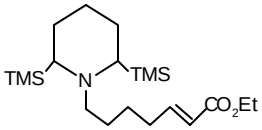
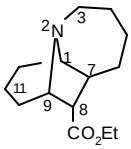
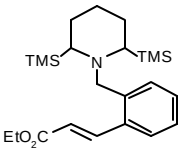
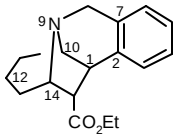
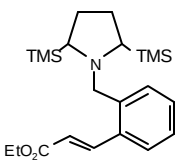
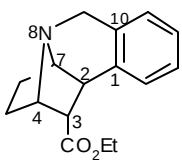
Mass spectrum of **105** (Fig. 27) showed a molecular ion peak at 257 (42) and a base peak at 184 (M^+-$CO_2C_2H_5$). The other prominent fragmentation peaks were found at 169 (47), 115 (77), 91 (40) and 68 (76).

The above spectral analyses confirmed the compound **105** as ethyl-8-azatetracyclo[8.4.0.0^{2,7}.0^{4,8}]tetradeca-1(10),11,13-triene-3-carboxylate.

3. Summary

In summary, we have successfully demonstrated the synthesis of a number of polycyclic x-azatricyclo[m.n.0.0^{a,b}]alkanes by employing the intramolecular [3+2]-dipolar cycloaddition of nonstabilized cyclic azomethine ylides as shown in Table 1. The study related to the biological activities of these products is in progress and will be reported appropriately.

Table 1

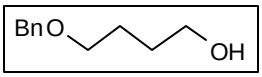
Sr. No.	Cycloaddition Precursor	Product	Yield
1	 **71**	 **72**	61 %
2	 **82**	 **83**	69 %
3	 **89**	 **90**	41 %
4	 **95**	 **96**	64 %
5	 **97**	 **98**	75 %
6	 **104**	 **105**	73 %

4. Experimental

Since, the experimental part of this chapter involves a series of similar starting materials, the experimental section has been divided into three parts. The preparation of the substrates for the synthesis of cycloaddition precursors is presented in Section-I. Section-II involves general approach for the [3+2] cycloaddition reaction and the detail spectral data of cycloadducts. Section-III deals with the preparation of rigid azatricyclo compounds having tethered benzene unit.

Section - I

4.1. Preparation of 4–Benzyloxy–1–butanol (77):



Powdered KOH (19.91 g, 355.5 mmol) and benzyl chloride (25.0 g, 197.48 mmol) were added in four equal portions over 1 h to 1,4–butanediol (**76**) (44.5 g, 493.7 mmol) at rt with stirring. After stirring for an additional 4-5 h at rt, 100 mL of water was added and the reaction mixture was extracted with diethyl ether (3 $\times$ 50 mL). The combined extracts were washed with water (2 $\times$ 30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated under vacuo. The crude residue was purified by fractional distillation (bp 80 ^oC / 1mm) to afford 30.9 g (87 %) of **77** as a colorless liquid.

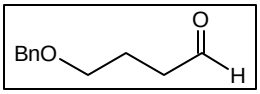
IR (neat) : 3393, 2864, 1363 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.60-1.85 (m, 4H), 2.55 (s, -OH), 3.55 (t, J = 7.9 Hz, 2H), 3.65 (t, J = 7.9 Hz, 2H), 4.55 (s, 2H), 7.25-7.45 (m, 5H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 25.61, 28.86, 61.28, 69.58, 72.1, 126.78, 126.85, 127.58, 137.84.

MS (m/ z) : 180 (M^+, 3), 107 (45), 91 (100), 77 (31).

4.2. Preparation of 4-Benzyloxy–1–butanal (78):



In to a stirring mixture of pyridinium chlorochromate (18 g, 83.5 mmol) and Celite (9 g) in 100 mL of dry CH_2Cl_2 at 0 °C was added dropwise a solution of **77** (10 g, 55.55 mmol) in dry CH_2Cl_2 (20 mL). The resulting black slurry was stirred for an additional 2.5 h at rt and diluted with dry ether (100 mL). The supernatant solution was filtered from the black residue and washed with dry ether (2 × 30ml). The combined filtrate was evaporated under vacuum and the brown residue was chromatographed on silica gel, eluting with hexane/EtOAc (8:2), to afford 8.21 g (83%) of **78** as a colorless liquid.

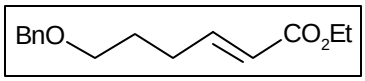
IR (neat) : 2935, 1711, 1364 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.85-2.05 (m, 2H), 2.55 (t, J = 8.1 Hz, 2H), 3.55 (t, J = 7.9 Hz, 2H), 4.50 (s, 2H), 7.25-7.45 (m, 5H), 9.80 (s, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 21.77, 39.82, 68.38, 71.82, 126.59, 127.43, 137.91, 200.55.

MS (m/ z) : 178 (M^+, 1), 107 (78), 91 (100).

4.3. Preparation of Ethyl-6-benzyloxy-(*E*)-2-hexenoate (79):



To a solution of ethoxycarbonylmethylene triphenylphosphorane (19.27 g, 55.34 mmol) in 50 mL CH_2Cl_2 was added a solution of **78** (8.21 g, 46.12 mmol) in 15 mL of dry CH_2Cl_2 at rt. The reaction mixture was further allowed to stir for another 24 h at rt. The solvent was removed under vacuum and the residue was chromatographed on silica gel, eluting with hexane/EtOAc (9:1) to afford 10.52 g (92 %) of **79** as a colorless liquid.

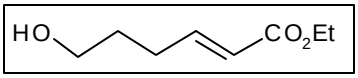
IR (neat) : 2928, 1718, 1366, 1168 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.70-1.90 (m, 2H), 2.32 (dt, *J* = 7.9, 1.4 Hz 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.52 (s, 2H), 5.85 (dt, *J* = 15.6, 1.4 Hz, 1H), 6.97 (dt, *J* = 15.6, 6.9 Hz 1H), 7.20-7.45 (m, 5H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 13.86, 27.94, 28.53, 59.59, 68.94, 72.56, 121.47, 127.16, 127.95, 138.28, 147.92, 165.2.

MS (m/ z) : 248 (M^+, 1), 202 (9), 114 (39), 91 (100).

4.4. Preparation of Ethyl-6-hydroxy-(*E*)–2-hexenoate (80):



To a solution of **79** (10 g, 40.32 mmol) and sodium iodide (6.05 g, 40.32 mmol) in 45 mL of acetonitrile was added dropwise trimethylsilyl chloride (4.38 g, 40.32 mmol) at 0 °C. The resulting reaction mixture was allowed to stir at rt for 5-6 h untill the completion of reaction as monitored by TLC. The reaction mixture was quenched with water (25 mL) and extracted with diethyl ether (2 × 30 mL), washed with sodium thiosulphate, brine and dried over Na_2SO_4. The ether layer was concentrated and the crude residue was chromatographed on silica gel, eluting with hexane/EtOAc (7:3) to afford 4.2 g, (66 %) of **80** as a colorless liquid.

IR (neat) : 3421, 2876, 1717, 1370 cm^{-1}.

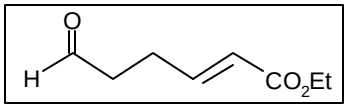
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.60-1.80 (m, 2H), 2.28 (q, *J* = 6.3, Hz, 2H and -OH, 1H), 3.65 (q, *J* = 6.3 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 5.83 (dt, *J* = 15.6, 1.4 Hz, 1H), 6.94 (dt, *J* = 15.6, 6.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 13.39, 27.77, 30.22, 59.39, 60.57, 120.82, 148.13,

165.98.

MS (m/ z) : 158 (M^+, 2), 127 (20), 112 (100), 99 (55), 84 (84).

4.5. Preparation of Ethyl-6-oxo-(*E*)–2-hexenoate (74):



A solution of oxalyl chloride (3.25 g, 25.6 mmol) in 30 mL dry CH_2Cl_2, charged into 100 mL two neck argon-flushed flask, was cooled to –78 °C. DMSO (3.34 g, 42.75 mmol) in 10 mL CH_2Cl_2, followed by **80** (2.7 g, 17.1 mmol) in 10 mL CH_2Cl_2 was introduced dropwise into the flask over 5 min. The mixture was allowed to stir for 1.5 h at –78 °C and then Et_3N (6.92 g, 68.51 mmol) in 10 mL CH_2Cl_2 was introduced dropwise. The reaction mixture was allowed to warm to rt and quenched with 30 mL of water. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), the combined extracts were washed with water (4 × 20 mL), brine, dried over Na_2SO_4, and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography, eluting with hexane/EtOAc (8:2) to afford 2.48 g (93 %) of **74** as a colorless liquid.

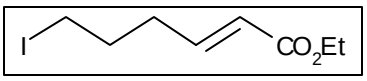
IR (neat) : 3446, 1719, 1401 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, J = 7.1 Hz, 3H), 2.45-2.75 (m, 4H), 4.15 (q, J = 7.1 Hz, 2H), 5.83 (dt, J = 15.6, 1.4 Hz, 1H), 6.93 (dt, J = 15.6, 6.9 Hz, 1H), 9.75 (t, J = 1.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 13.65, 23.89, 41.22, 59.61, 121.88, 145.91, 165.53, 199.76.

MS (m/ z) : 156 (M^+, 1), 126 (39), 108 (100), 99 (71).

4.6. Preparation of Ethyl-6-iodo-(*E*)–2-hexenoate (75):



To a stirring solution of triphenylphosphine (4.97 g, 18.95 mmol) and imidazole (1.29 g, 18.95 mmol) in 40 mL of dry CH_2Cl_2 at 0 °C, was added iodine (4.81 g, 18.95 mmol) portion wise over a period of 30 min. A solution of **80** (2.3 g, 14.56 mmol) in 10 mL of CH_2Cl_2 was introduced dropwise at 0 °C and the reaction was further allowed to stir for 6 h at rt. The reaction mixture was diluted with 50 mL of CH_2Cl_2, washed with 20 % sodium thiosulphate solution, water, brine, and dried over Na_2SO_4. The organic layer was concentrated and the crude residue was chromatographed on silica gel, eluting with hexane/EtOAc (9:1) to afford 3.55 g (91 %) of **75** as a colorless liquid which changed slowly to a brownish color on keeping for a longer time at room temperature.

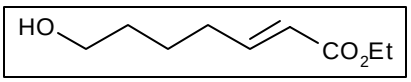
IR (neat) : 2979, 1720, 1367 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.28 (t, *J* = 7.3 Hz, 3H), 1.85-2.05 (m, 2H), 2.32 (q, *J* = 6.6 Hz, 2H), 3.18 (t, *J* = 6.6 Hz, 2H), 4.17 (q, *J* = 7.3 Hz, 2H), 5.85 (dt, *J* = 15.4, 1.4 Hz, 1H), 6.88 (dt, *J* = 15.4, 6.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 5.13, 13.84, 31.0, 32.23, 59.68, 122.13, 145.98, 165.61.

MS (m/ z) : 268 (M^+, 6), 223 (32), 155 (39), 141 (100), 113 (56), 99 (23).

4.7. Preparation of Ethyl-7-hydroxy-(*E*)–2-heptenoate (92):



A solution of ethoxycarbonylmethylene triphenylphosphorane (22.4 g, 64.3 mmol) in 100 mL CH_2Cl_2 was treated with 2-hydroxypyran **91** (4.8 g, 47.1 mmol) under argon atmosphere. The reaction mixture was stirred at rt for 36 h and concentrated. The solid residue obtained was stirred with 40 mL of diethyl ether/hexane (7:3) mixture for 30 min and filtered. The filtrate was

evaporated under vacuum and purified by silica gel column chromatography, eluting with hexane/EtOAc (7:3) to afford 6.72 g (83 %) of **92** as a colorless liquid.

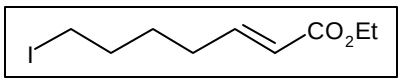
IR (neat) : 3421, 2933, 1719, 1401 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, *J* = 7.3 Hz, 3H), 1.45-1.70 (m, 5H), 2.20- 2.35 (m, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 4.17 (q,*J* = 7.3 Hz, 2H), 5.83 (dt, *J* = 15.4, 1.4 Hz, 1H), 6.95 (dt, *J* = 15.4, 6.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 13.34, 23.61, 31.03, 31.22, 59.31, 60.98, 120.67, 148.35, 165.92.

MS (m/ z) : 172 (M^+, 1), 126 (74), 97 (54), 81 (100).

4.8. Preparation of Ethyl-7-iodo-(*E*)–2-heptenoate (93):



The alcohol **92** (2.1 g, 12.21 mmol) was converted to its corresponding iodo compound **93** following the similar experimental protocol as described in Section 4.6. The crude residue was purified by silica gel column chromatography, eluting with hexane/EtOAc (9:1) to provide 3.13 g (91 %) of **93** as a colorless liquid.

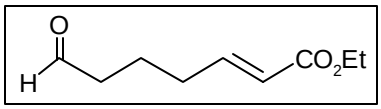
IR (neat) : 2935, 1716, 1367 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, *J* = 7.3 Hz, 3H), 1.48-1.63 (m, 2H), 1.72-1.92 (m, 2H), 2.23 (q, *J* = 7.3 Hz, 2H), 3.16 (t, *J* = 6.6 Hz, 2H), 4.13 (q, *J* = 7.3 Hz, 2H), 5.78 (dt, *J* = 16.1, 1.4 Hz, 1H), 6.90 (dt, *J* = 16.1, 6.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 5.58, 13.89, 28.48, 30.50, 32.34, 59.60, 121.54, 147.44, 165.78.

MS (m/ z) : 282 (M^+, 21), 237 (22), 155 (100), 127 (78), 81 (90).

4.9. Preparation of Ethyl-7-oxo-(*E*)–2-heptenoate (94):



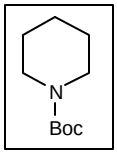
Swern oxidation of alcohol **92** (1.2 g, 6.98 mmol) was carried out by adopting the similar reaction procedure as described earlier in Section 4.5. After usual work up, the crude residue was purified by silica gel column chromatography, eluting with hexane/EtOAc (8:2) to afford 1.1 g (93 %) of **94** as a colorless liquid.

IR (neat) : 2955, 1728, 1441 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, J = 7.2 Hz, 3H), 1.60-1.90 (m, 2H), 2.25 (q, J = 6.9 Hz, 2H), 2.48 (t, J = 6.9 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 5.85 (dt, J = 15.6, 1.4 Hz, 1H), 6.94 (dt, J = 15.6, 6.9 Hz 1H), 9.8 (t, J = 1.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 14.23, 20.38, 31.24, 42.91, 60.11, 122.19, 147.69, 166.22, 201.55.

4.10. Preparation of *N*-(*tert*-Butyloxycarbonyl)piperidine (85):



Identical reaction condition was adopted for the preparation of **85** by following the experimental protocol as described in Chapter-II (Section 5.1) for the preparation of corresponding pyrrolidine analogue **41**.

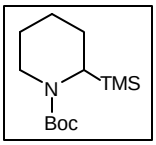
Yield : 90 % (bp. 55-57 ^oC / 1mm), colorless liquid.

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

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.45 (s, 9H), 1.58 (m, 6H), 3.31-3.45 (m, 4H).

MS (m/ z) **:** 185 (M^+, 66), 129 (53), 84 (63), 57 (100).

4.11. Preparation of *N*-(*tert*-Butyloxycarbonyl)-2-trimethylsilyl piperidine (86):



Monosilylation of *N*-Boc piperidine (**85**) was carried out following the exact experimental protocol as described for the preparation of pyrrolidine analogue **42** in chapter-II (Section 5.2).

Yield : 90 %, colorless liquid.

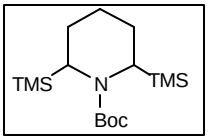
IR (neat) **:** 1688, 1415, 1159, 1098, 838 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** 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 ($CDCl_3$, 50.3 MHz) **:** δ -1.0, 23.0, 25.7, 28.1, 45.0, 78.4, 154.5.

MS (m/ z) **:** 257 (M^+, 1), 156 (84), 128 (54), 84 (75), 73 (100).

4.12. Preparation of *N*-(*tert*-Butyloxycarbonyl)-2,6-bis(trimethylsilyl)piperidine (87):



Further silylation of **86** was carried out following the exact experimental condition as described for the preparation of **44** in chapter-II (Section 5.4).

Yield : 75 %, pale yellow liquid.

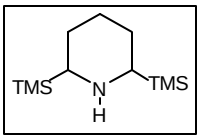
IR (neat) **:** 1684, 1421, 1175 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** 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 ($CDCl_3$, 50.3 MHz) **:** δ -0.7, 0.1, 24.7, 26.2, 26.9, 28.7, 47.7, 48.5, 78.8, 155.8.

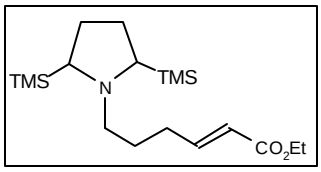
MS (m/ z) : 272(100), 258 (46), 242 (66), 228 (51), 200 (80), 156 (44), 73 (98).

4.13. Preparation of 2,6-bis(Trimethylsilyl)piperidine (88):



The *N*-Boc deprotection of **87** was carried out quantitatively following the exact procedure as described for the deprotection of the *N*-Boc moiety of pyrrolidine analogue (**44**) in chapter-II (Section 5.5). The crude amine was utilized as such without further purification.

4.14. Preparation of Ethyl-6–[2,5–di(trimethylsilyl)tetrahydro–1*H*–1-pyrrolyl]–(*E*)–2-hexenoate (71):



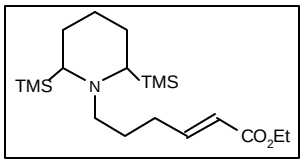
To a suspension of **73** (1.9 g, 8.83 mmol) and K_2CO_3 (2.47 g, 17.9 mmol) in 30 mL of acetonitrile was added a solution of **75** (1.6 g, 5.97 mmol) in 10 mL of acetonitrile under argon atmosphere at rt. The resultant suspension was refluxed for 24-30 h. The reaction mixture was cooled, filtered, diluted with EtOAc, washed with water, brine and dried over Na_2SO_4. The organic layer was evaporated under vacuum and the brownish oily residue was purified over silica gel column chromatography using hexane/EtOAc (8:2) to give 1.38 g (65 %) of **71** as a pale yellow liquid.

IR (neat) : 3381, 2952, 1722, 1367, 1249 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 18H), 1.27 (t, J = 7.3 Hz, 3H), 1.35-2.03 (m, 6H), 2.05-2.62 (m, 6H), 4.18 (q, J = 7.3 Hz, 2H), 5.83 (dt, J = 15.2, 1.4 Hz, 1H), 6.97 (dt, J = 15.2, 6.9 Hz, 1H).

MS (m/ z) : 355(M^+, 1), 340 (9), 282 (100), 73 (53).

4.15. Preparation of Ethyl-6–[2,6–di(trimethylsilyl)hexahydro–1–pyridinyl]–(*E*)–2-hexenoate (82):



To a stirred solution of **88** (1.5 g, 6.55 mmol) in 50 mL of ethanol was added a solution of **74** (0.72 g, 4.61 mmol) in 10 mL of ethanol at rt. After stirring for 3 h, $NaBH_3CN$ (0.29 g, 4.61 mmol) followed by glacial acetic acid (1.0 mL) was added and contents were further allowed to stir for another 3 h at rt. The reaction mixture was basified by slow addition of concentrated NH_4OH solution. The reaction mixture was diluted with water (10 mL), extracted with chloroform (3 $\times$ 25 mL), washed with brine and dried over Na_2SO_4. The organic layer was concentrated and the crude residue was purified by silica gel chromatography using hexane/EtOAc (9:1) to afford 1.24 g (73 %) of **82** as a pale yellow liquid.

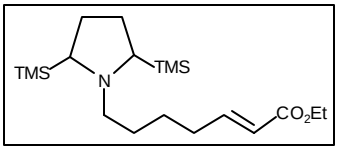
IR (neat) : 2951, 1723, 1655, 1402, 1248, 1044 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 18H), 1.30 (t, J = 7.3 Hz, 3H), 1.35-1.70 (m, 8H), 2.03-2.42 (m, 5H), 2.83-2.95 (m, 1H), 4.17 (q, J = 7.3 Hz, 2H), 5.78 (dt, J = 15.4, 1.4, Hz, 1H), 6.97 (dt, J = 15.4, 6.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ - 1.45, 14.12, 19.65, 25.06, 28.25, 29.85, 50.34, 51.53, 59.82, 121.25, 149.06, 166.36.

MS (m/ z) : 369 (M^+, 1), 354 (4), 296 (100), 73 (81).

4.16. Preparation of Ethyl-7–[2,5–di(trimethylsilyl)tetrahydro–1*H*–1-pyrrolyl]–(*E*)–2-heptenoate (89):



The *N*-alkylation reaction of **73** (1.5 g, 6.97 mmol) with **94** (1.31 g, 4.65 mmol) was carried out by adopting the procedure detailed in Section 4.14 to obtain 1.15 g (67 %) of **89** as a viscous yellow liquid.

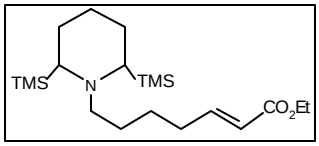
IR (neat) : 3429, 2952, 1717, 1654, 1368, 1254, 1042 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 18H), 1.27 (t, J = 7.2 Hz, 3H), 1.35-1.73 (m, 5H), 1.76-1.98 (m, 3H), 2.11-2.59 (m, 6H), 4.18 (q, J = 7.2 Hz, 2H), 5.83 (dt, J = 15.6, 1.4 Hz, 1H), 6.95 (dt, J = 15.6, 6.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ - 2.12, 13.88, 25.60, 26.36, 29.66, 31.88, 55.29, 55.57, 59.38, 121.18, 148.32, 165.80.

MS (m/ z) : 369 (M^+,1), 354 (6), 296 (100), 73 (53).

4.17. Preparation of Ethyl-7–[2,6–di(trimethylsilyl)hexahydro–1–pyridinyl]–(*E*)–2-heptenoate (95):



The reductive amination of **88** (1.5 g, 6.55 mmol) with **94** (0.79 g, 4.65 mmol) in the presence of $NaBH_3CN$ (0.29 g, 4.62 mmol) was carried out by adopting the procedure as detailed in Section 4.15 to obtain 1.34 g (75 %) of **95** as a viscous yellow liquid.

IR (neat) : 3442, 2949, 1723, 1655, 1445, 1368, 1248, 1044 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 18H), 1.29 (t, J = 7.3 Hz, 3H), 1.33-1.72 (m, 10H), 2.12-2.43 (m, 5H), 2.76-2.95 (m, 1H), 4.19 (q, J = 7.3 Hz, 2H), 5.83 (dt, J = 15.2, 1.4 Hz, 1H), 6.97 (dt, J = 15.2, 6.9 Hz, 1H).

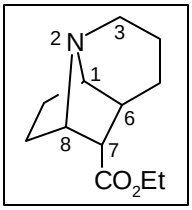
^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ - 1.49, 14.05, 19.62, 25.06, 25.74, 29.25, 32.10, 50.57, 51.45, 59.69, 121.33, 148.65, 166.22.

MS (m/ z) : 383 (M^+, 1), 310 (58), 156 (49), 73 (100).

4.18. Section-II: General Intramolecular [3 + 2]-Cycloaddition Procedure:

This is illustrated by taking the example of the synthesis of ethyl-2-azatricyclo[4.4.0.0^{2,8}]decane-7-carboxylate (**72**).

4.18.1. Ethyl-2-azatricyclo[4.4.0.0^{2,8}]decane-7-carboxylate (72).



A solution of **71** (1.0 g, 2.82 mmol) in 10 mL of dry CH_2Cl_2 was introduced dropwise to an argon flushed 50 mL two neck flask containing a suspension of vacuum dried Ag(I)F (0.89 g, 7.02 mmol) in CH_2Cl_2 (30 mL). The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the surface of the flask in the form of a mirror. The reaction mixture was periodically monitored through TLC. After stirring for another 4-6 h, the reaction mixture was filtered through a small plug of Celite and the solvent was evaporated to give a brown residue. The crude residue was purified by silica gel column chromatography using ($CHCl_3$: MeOH: NH_3 = 97: 2: 1) to afford **72** (0.36 g) in 61 % yield as a thick yellow liquid.

IR (neat) : 3145, 2927, 1723, 1395 cm^{-1}.

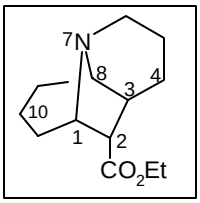
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.22-1.25 (m, 1H, H_{10endo}), 1.27 (t, J = 7.3 Hz, 3H), 1.31-1.43 (m, 2H, H_{4endo}, H_{9endo}), 1.51-1.64 (m, 3H, H_{5endo}, H_{9exo}, H_{10exo}), 1.65-1.78 (m, 2H, H_{4exo}, H_{5exo}), 2.53 (m, 1H, H_{6endo}), 2.95 (d, J = 5.7 Hz, 1H, H_{7exo}), 3.05-3.17 (m, 3H, H_{3exo}, H_{3endo}, H_1), 3.73 (t, J = 4.6 Hz, 1H, H_8), 4.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 125.3 MHz) : δ 14.06, 17.45, 25.49, 26.73, 28.07, 39.79, 46.17, 48.69, 60.42, 64.22, 65.31, 172.77.

MS (m/ z) : 209 (M^+, 56), 180 (26), 164 (28), 136 (100), 83 (68).

HRMS : calcd for $C_{12}H_{19}O_2N$ 209.1415 found 209.1410.

4.18.2. Ethyl-7-azatricyclo[5.4.0.0^{3,8}]undecane-2-carboxylate (83):



Thick yellow liquid. Yield 69 %.

IR (neat) : 3147, 2930, 1723, 1400, 1181, 1048 cm^{-1}.

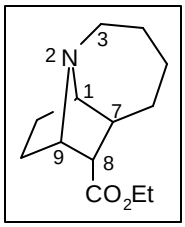
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, J = 7.3 Hz, 3H), 1.35-1.48 (m, 2H), 1.53-1.84 (m, 6H), 1.85-2.13 (m, 2H), 2.78 (m, 1H, H_{3endo}), 2.87 (bs, 1H, H_8), 2.93-3.07 (m, 2H, H_{6endo}, H_{6exo}), 3.10 (d, J = 6.3 Hz, 1H, H_{2exo}), 3.58-3.69 (m, 1H, H_1), 4.04-4.32 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 14.11, 15.97, 18.47, 29.41, 29.74, 32.04, 39.51, 50.32, 53.96, 60.19, 64.08, 67.80, 173.53.

MS (m/ z) : 223 (M^+, 77), 194 (55), 178 (38), 150 (78), 136 (43), 97 (100).

HRMS : calcd for $C_{13}H_{21}O_2N$ 223.1572 found 223.1563.

4.18.3. Ethyl-2–azatricyclo[5.4.0.0^{2,9}]undecane–8–carboxylate (90):



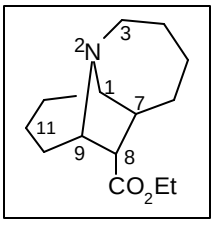
Thick yellow liquid. Yield 41 %.

IR (neat) : 2937, 1725, 1451, 1385, 1231 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, J = 7.3 Hz, 3H), 1.32-1.87 (m, 10H), 2.53-2.62 (m, 1H, H_{7endo}), 2.62-2.68 (m, 1H, H_{3endo}), 2.88 (t, J = 5.1 Hz, 1H, H_{9exo}), 3.23-3.37 (m, 1H, H_{3exo}), 3.40 (d, J = 3.6 Hz, 1H, H_1), 3.55 (t, J = 4.3 Hz, 1H, H_9), 4.15 (q, J = 7.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125.3 MHz) : δ 14.11, 24.59, 25.82, 27.39, 29.26, 29.52, 45.52, 49.56, 50.29, 60.52, 63.72, 66.54, 172.89.

4.18.4. Ethyl-2-azatricyclo[5.5.0.0^{2,9}]dodecane-8-carboxylate (96):



Thick yellow liquid. Yield 64 %.

IR (neat) : 2929, 1726, 1453, 1398, 1233, 1180 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.28 (t, J = 7.2 Hz, 3H), 1.33-1.92 (m, 12H), 2.61

(dt, J = 14.8, 5.4 Hz, 1H, H_{8endo}), 2.81-2.94 (m, 1H, H_{7endo}), 3.01 (t, J = 7.2 Hz, 1H, H_{8exo}), 3.06-3.16 (m, 1H, H_{3exo}), 3.22 (bs, 1H, H_1), 3.32-3.45 (m, 1H, H_9), 4.04-4.31 (m, 2H).

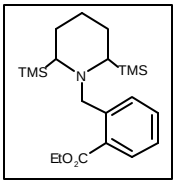
^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 14.08, 16.75, 25.49, 27.53, 29.50, 30.43, 32.0, 43.95, 54.98, 55.97, 59.99, 62.43, 66.06, 173.0.

MS (m/ z) : 237 (M^+, 27), 208 (42), 192 (27), 164 (54), 136 (45), 123 (87), 97 (100), 83 (53).

HRMS : calcd for $C_{14}H_{23}O_2N$ 237.1728 found 237.1747.

Section-III: Synthesis of rigid azatricyclo compounds having benzene tethered ring.

4.19. Preparation of Ethyl-2-[2,6-di(trimethylsilyl)hexahydro-1-pyridinylmethyl]benzoate (100):



To a stirring mixture of **88** (2.5 g, 10.91 mmol) in 50 mL acetonitrile containing K_2CO_3 (3.0 g, 21.71 mmol) was added a solution of ethyl-2-(bromomethyl)benzoate (**99)** (2.12 g, 8.72 mmol) in 10 mL of acetonitrile dropwise under argon atmosphere at rt. The resulting suspension was refluxed for 8-10 h. The reaction mixture was cooled, filtered, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. The organic layer was evaporated under vacuum and the crude residue was chromatographed over silica gel using hexane/EtOAc (9:1) as eluent to afford 2.83 g (83 %) of **100** as a pale yellow liquid.

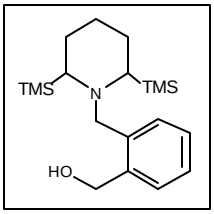
IR (neat) : 2920, 1717, 1442, 1244, 1092, 833 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.04 (s, 18H), 1.42 (t, J = 7.3 Hz, 3H), 1.45-1.85 (m, 6H), 2.29 (t, J = 3.9 Hz, 2H), 3.77 (d, J = 16.6 Hz, 1H), 4.26-4.47 (m, 2H), 4.63 (d, J = 16.6 Hz, 1H), 7.18-7.30 (m, 1H), 7.48 (ddd, J =7.8, 6.3, 1.5 Hz, 1H), 7.78 (dd, J = 7.8, 1.5 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ -1.22, 14.25, 19.99, 24.81, 51.69, 51.87, 60.54, 125.72, 129.54, 130.3, 131.28, 142.6, 167.77.

MS (m/z) : 391 (M^+, 1), 318 (100), 163 (19), 135 (56), 73 (34).

4.20. Preparation of 2-[2,6-di(Trimethylsilyl)hexahydro-1-pyridinylmethyl]phenylmethanol (101):



$LiAlH_4$ (0.23 g, 6.06 mmol) was charged into a 250 mL two neck RB flask, equipped with magnetic stirring bar and argon gas balloon containing 70 mL of dry ether. The flask was cooled to 0 °C. A solution of **100** (2.0 g, 5.11 mmol) in 100 mL dry ether was added dropwise into the flask. The reaction mixture was allowed to stir overnight at rt. The reaction mixture was quenched at 0 °C by the addition of 5 % NaOH solution. The organic layer was extracted with ether (2 × 30 mL) and dried over Na_2SO_4. The crude residue was evaporated under vacuum and purification through column chromatography using hexane/EtOAc (7:3) gave **101** (1.62 g) in 91 % yield as a colorless thick liquid.

IR (neat) : 3380, 2950, 1441, 1249, 1027, 832 cm^{-1}.

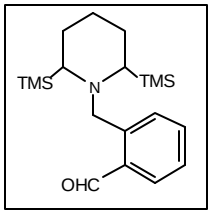
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.12 (s, 18H), 1.45-1.89 (m, 6H), 2.23-2.50 (m, 2H), 3.83 (d, J = 12.5 Hz, 1H), 4.22 (d, J = 11.8

Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 4.82 (d, J = 12.5 Hz, 1H), 6.46 (bs, -OH), 7.12-7.45 (m, 4H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ -0.95, 19.74, 24.19, 50.34, 50.49, 52.76, 64.32, 127.18, 127.58, 128.86, 130.75, 137.38, 141.40.

MS (m/z) : 349 (M^+, 8.5), 277 (100), 156 (31), 121 (39), 93 (46), 73 (54).

4.21. Preparation of 2-[2,6-di(Trimethylsilyl)hexahydro-1-pyridinylmethyl]benzaldehyde (102):



Swern oxidation of alcohol **101** (1.5 g, 4.29 mmol) was carried out following exact reaction procedure as described in Section 4.5. After usual work up the crude residue was chromatographed eluting with hexane/EtOAc (8:2) to afford 1.41 g (95 %) of **102** as a thick yellow liquid.

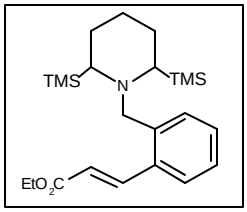
IR (neat) : 2955, 1697, 1449 (-C=C-), 1248, 1092, 834 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 18H), 1.45-1.83 (m, 6H), 2.20-2.40 (m, 2H), 3.87 (d, J = 14.6 Hz, 1H), 4.65 (d, J = 14.6 Hz, 1H), 7.40 (t, J = 6.8 Hz, 1H), 7.55 (ddd, J = 7.3, 6.1, 1.8 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.85 (dd, J = 7.9, 1.9 Hz, 1H), 10.45 (s, 1H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ -1.32, 19.65, 24.59, 50.64, 51.26, 126.64, 130.17, 132.95, 134.59, 143.24, 191.82.

MS (m/z) : 347 (M^+, 2), 275 (100), 156 (34), 119 (76), 91(40), 73 (52).

4.22. Preparation of Ethyl-3-{2-[2,6-di(trimethylsilyl)hexahydro-1-pyridinylmethyl]phenyl}-(*E*)-2-propenoate (97):



To a solution of ethoxycarbonylmethylene triphenylphosphorane (1.84 g, 5.28 mmol) in 40 mL of dry CH_2Cl_2 was added a solution of **102** (1.41, 4.06 mmol) in 10 mL of CH_2Cl_2 at rt. The reaction mixture was further stirred for another 24 h at rt. The solvent was removed under vacuum and the solid compound was purified by silica gel column chromatography eluting with hexane/EtOAc (9:1) to give **97** (1.51 g) in 89 % yield as a thick yellow liquid.

IR (neat) : 2920, 1716, 1631, 1500, 1441, 1312, 1244 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 18H), 1.32 (t, J = 7.3 Hz, 3H), 1.47-1.77 (m, 6H), 2.22-2.40 (m, 2H), 3.63 (d, J = 13.7 Hz, 1H), 4.28 (q, J = 7.3Hz, 2H), 4.34 (d, J = 13.7 Hz, 1H), 6.34 (d, J = 15.6 Hz, 1H), 7.21-7.45 (m, 2H), 7.50-7.67 (m, 2H), 8.27 (d, J = 15.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ -1.23, 14.19, 19.68, 24.76, 50.87, 51.57, 60.06, 119.52, 126.12, 126.85, 129.44, 130.39, 134.08, 139.61, 142.41, 166.58.

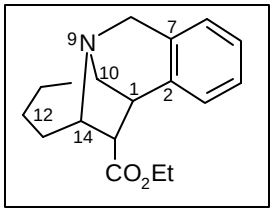
MS (m/z) : 417 (M^+, 2), 345 (100), 131 (16), 117 (43), 73 (81).

4.23. Alternate method for the Preparation of Ethyl-3–{2-[2,6–di(trimethylsilyl)hexahydro–1–pyridinylmethyl]phenyl}–(*E*)–2–propenoate (97).

To a slurry of **88** (1.5 g, 6.55 mmol) and K_2CO_3 (1.5 g, 10.87 mmol) in 30 mL of dry acetonitrile was added a solution of ethyl-3-(2-bromomethyl phenyl)-(*E*)-2-propenoate

(**103**) (1.46 g, 5.45 mmol) through syringe under argon atmosphere at rt. The resultant suspension was refluxed for 6-8 h and then allowed to cool to rt. The reaction mixture was filtered, diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. The organic layer was evaporated and the crude residue was chromatographed using hexane/EtOAc (9:1) to afford 1.91 g (84 %) of **97** as a thick yellow liquid.

4.24. Synthesis of Ethyl-9-azatetracyclo[8.5.0.0^{2,7}.0^{9,14}]pentadeca-2(7),3,5-triene-15-carboxylate (98):



The intramolecular [3+2] cycloaddition reaction of **97** (1.5 g, 3.59 mmol) was carried out by adopting the identical procedure as described in section 4.18.1. After usual workup, the residue was purified over silica gel column chromatography eluting with pet ether/acetone (7:3) to afford **98** (0.73 g) in 75 % yield as a viscous yellow liquid.

IR (neat) : 2937, 1730, 1581, 1457, 1190 cm^{-1}.

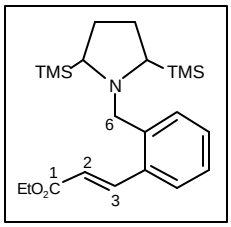
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.27 (t, J = 7.3 Hz, 3H), 1.37-1.67 (m, 2H), 1.72-2.00 (m, 4H), 3.03 (dd, J = 7.8, 2.0 Hz, 1H, H_{15exo}), 3.16 (bs, 1H, H_{10}), 3.59 (d, J = 2.0 Hz, 1H, H_{1endo}), 3.68 (t, J = 3.9 Hz, 1H, H_{14}), 3.77 (d, J = 18.0 Hz, 1H, H_{8endo}), 4.05-4.31 (m, 2H), 4.55 (d, J = 18.0 Hz, 1H, H_{8exo}), 6.82-7.20 (m, 4H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 14.03, 15.79, 29.20, 43.84, 58.40, 58.68, 60.21, 65.27, 67.74, 123.77, 125.17, 125.93, 126.24, 132.8, 147.9, 172.05.

MS (m/z) : 271 (M^+, 62), 198 (100), 184 (37), 156 (24), 117 (45), 82 (22).

HRMS : calcd for $C_{17}H_{21}O_2N$ 271.1572 found 271.1567.

4.25. Preparation of Ehtyl-3-{2-[2,5-di(trimethylsilyl)tetrahydro-1*H*-pyrrolylmethyl]phenyl}-(*E*)-2-propenoate (104):



The *N*-benzylation of **73** (1.5 g, 6.97 mmol) with **103** (1.4 g, 5.22 mmol) was carried out, utilizing the similar experimental procedure as described earlier for the preparation of **97** (Section 4.23.), which afforded **104** (1.7 g) in 81 % yield as a viscous yellow liquid.

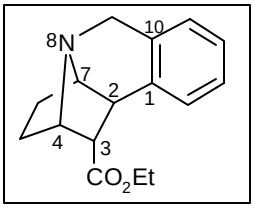
IR (neat) : 2935, 1695, 1428 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ -0.1 (s, 18H), 1.35 (t, J = 7.3 Hz, 3H), 1.55-1.77 (m, 2H), 1.83-2.04 (m, 2H), 2.33 (t, J = 4.8 Hz, 2H), 3.43 (d, J = 13.7 Hz, 1H), 3.98 (d, J = 13.7 Hz, 1H), 4.14-4.35 (m, 2H), 6.33 (d, J = 15.6 Hz, 1H), 7.17-7.36 (m, 3H), 7.48-7.72 (m, 1H), 8.48 (d, J = 15.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ -2.26, 14.06, 26.36, 55.38, 57.48, 59.84, 119.19, 126.2, 127.19, 129.14, 131.15, 134.7, 138.99, 142.77, 166.43.

MS (m/z) : 403 (M^+, 2), 330 (100), 117 (35), 73 (39).

4.26. Synthesis of Ethyl-8-azatetracyclo[8.4.0.0^{2,7}.0^{4,8}]tetradeca-1(10),11,13-trine-3-carboxylate (105):



Intramolecular [3+2] cycloaddition reaction of substrate **104** (1.5 g, 3.72 mmol) was carried out adopting the similar reaction procedure as described earlier for the cycloaddition reaction of **97** (section 4.24.). After usual workup, the crude residue was purified over silica gel column chromatography eluting with pet ether/acetone (6:4) to afford **105** (0.70 g) in 73 % yield as a viscous yellow liquid.

IR (neat) : 2975, 1729, 1455,1177 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (t, J = 7.3 Hz, 3H), 1.28-1.43 (m, 1H), 1.55-1.97 (m, 3H), 2.77 (d, J = 6.3 Hz, 1H, H_{3exo}), 3.18 (d, J = 5.4 Hz, 1H, H_1), 3.36 (d, J = 1.8 Hz, 1H, H_{2endo}), 3.74 (t, J = 4.9 Hz, 1H, H_4), 4.04 (d, J = 18.5 Hz, 1H, H_{9endo}), 4.14 (q, J = 7.3 Hz, 2H), 4.42 (d, J = 18.5 Hz, 1H, H_{9exo}), 6.95- 7.20 (m, 4H).

^{13}C NMR ($CDCl_3$, 75.3 MHz) : δ 13.93, 25.43, 25.7, 45.33, 50.67, 56.31, 60.1, 62.32, 66.78, 124.63, 125.19, 125.62, 125.98, 132.88, 143.98, 172.03.

MS (m/z) : 257 (M^+, 42), 184 (100), 169 (47), 115 (77), 91 (40), 68 (76).

HRMS : calcd for $C_{16}H_{19}O_2N$ 257.1415, found 257.1426.

5. References

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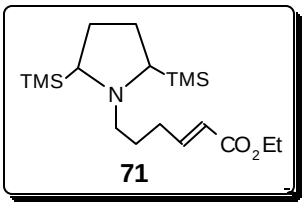
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TMS
CO2Et

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Fig. 3

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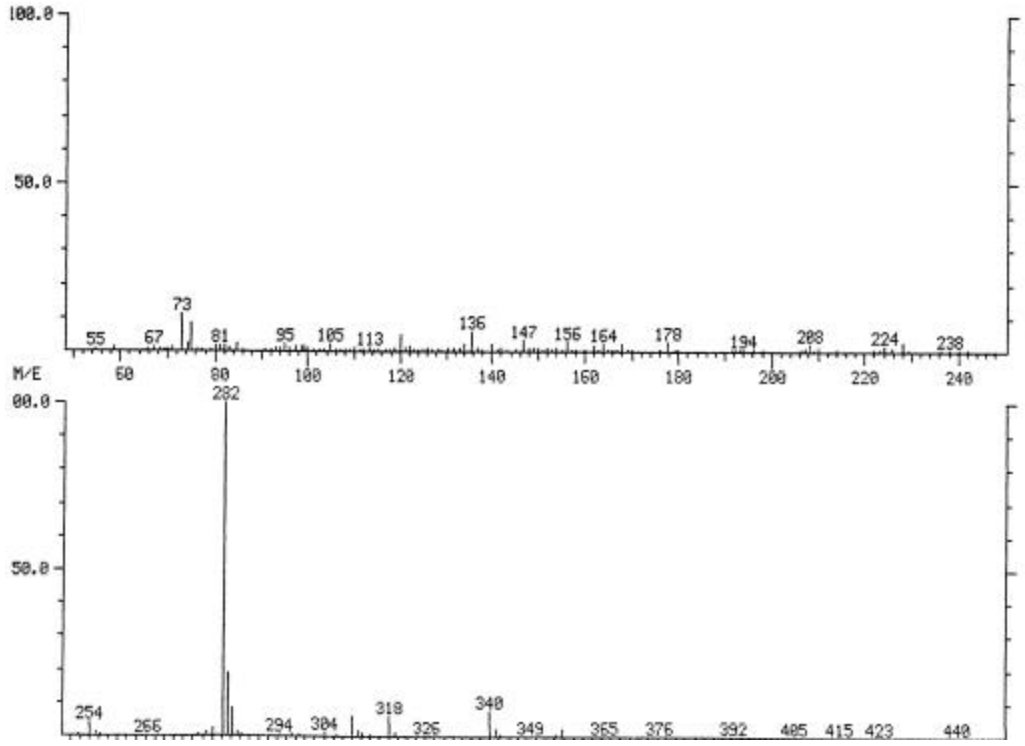
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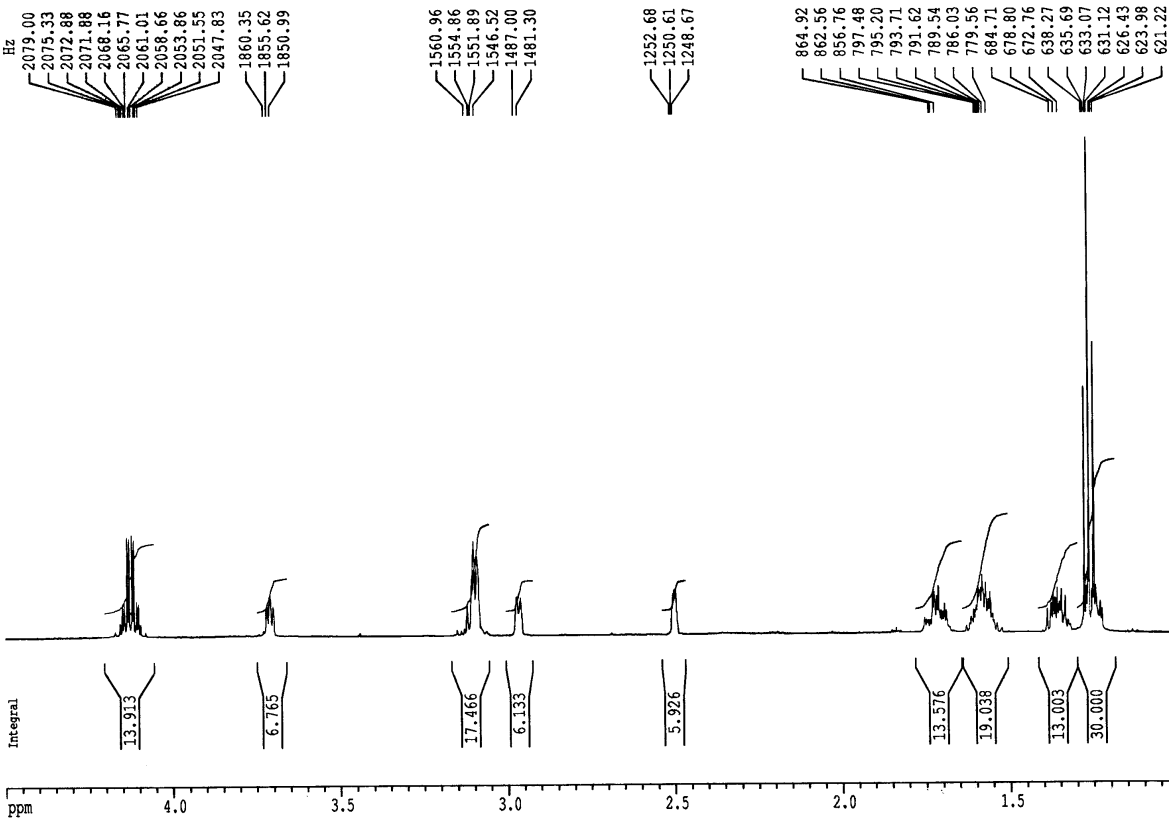
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626.43
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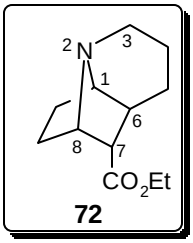
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CO2Et

72

Fig. 4

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180
122
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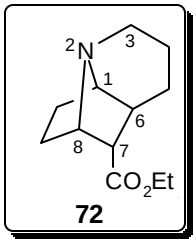
94
55
68
m/z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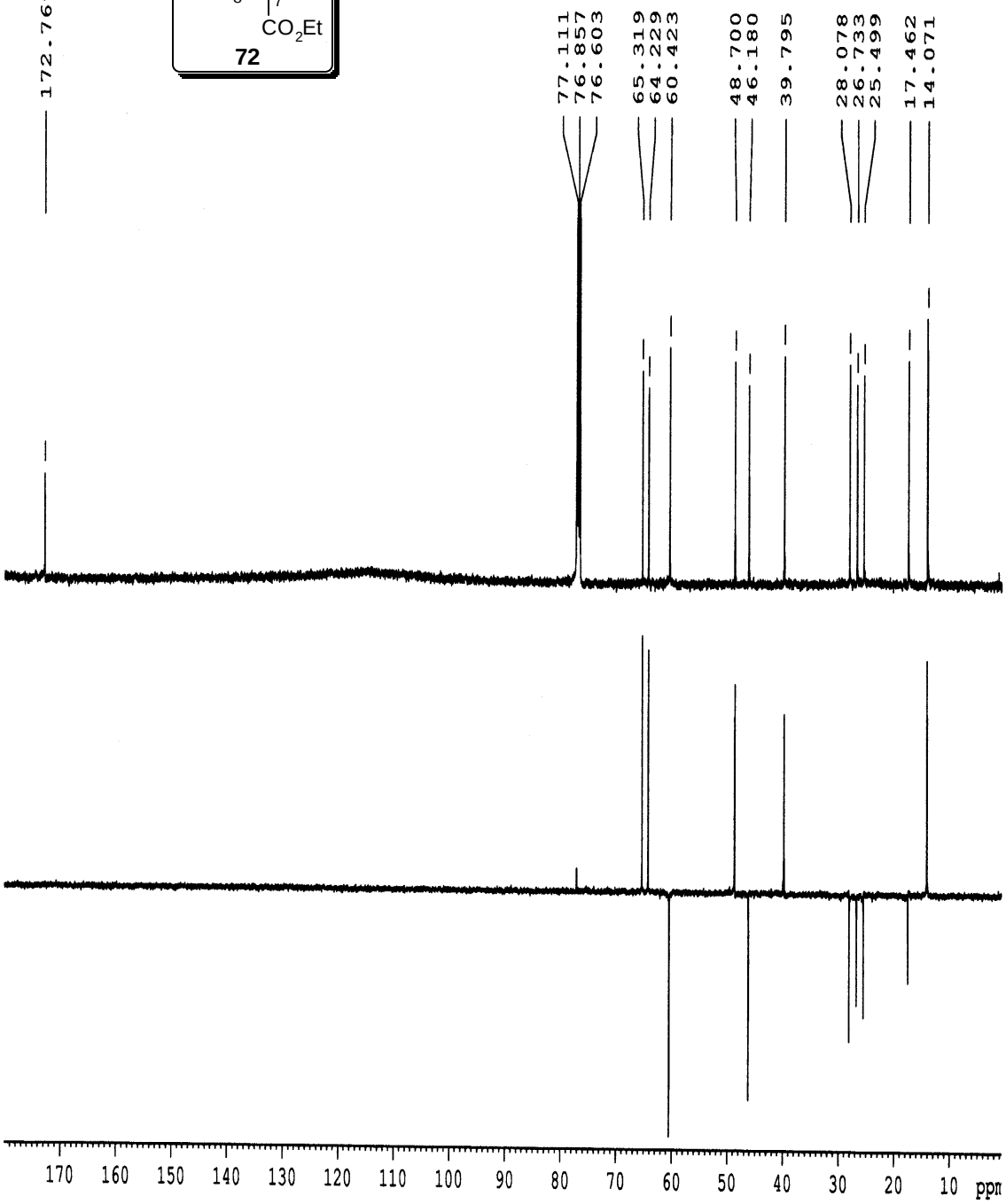
CO2Et

72

Fig. 5


172.769
77.111
76.857
76.603
65.319
64.229
60.423
48.700
46.180
39.795
28.078
26.733
25.499
17.462
14.071
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

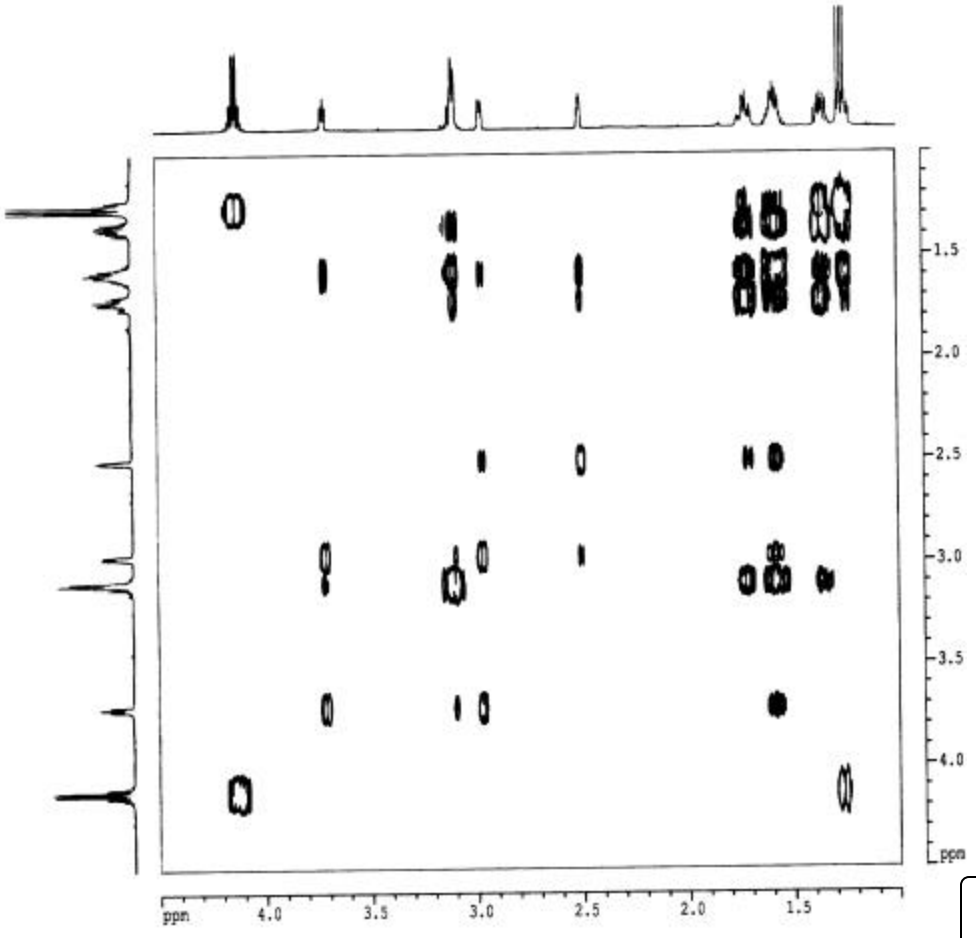
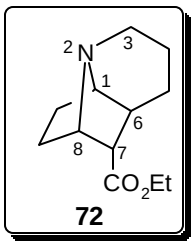
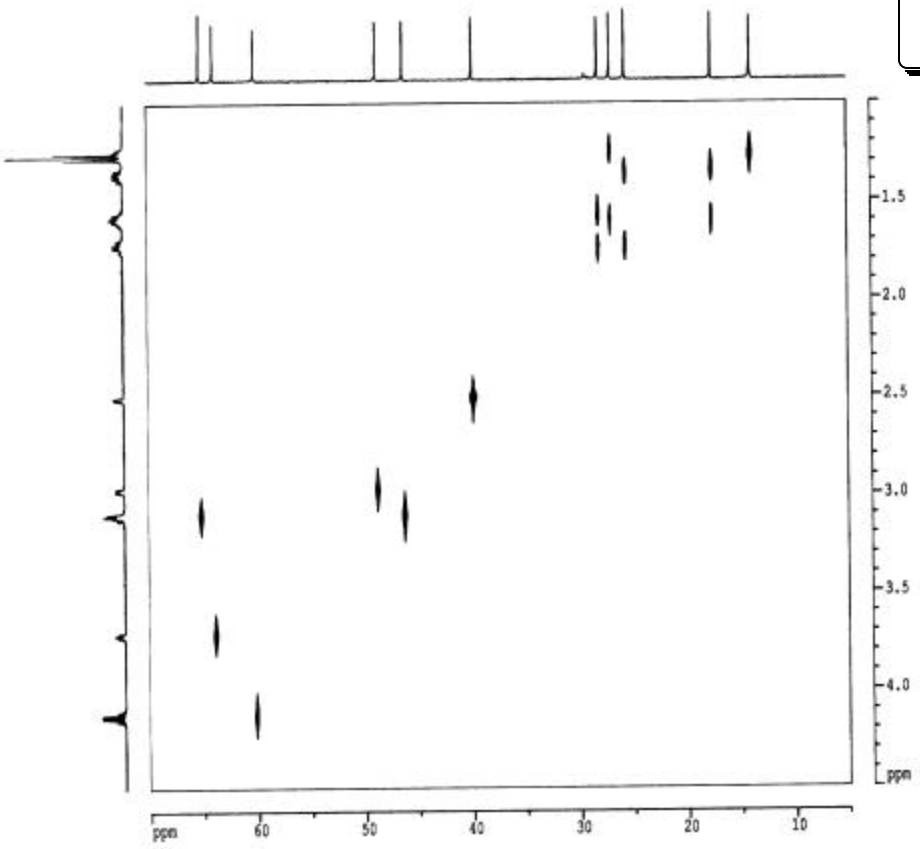
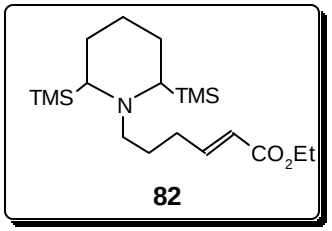

1.5
2.0
2.5
3.0
3.5
4.0
ppm
ppm
4.0
3.5
3.0
2.5
2.0
1.5

Fig. 6


2
N
3
1
6
8
7
CO2Et

72

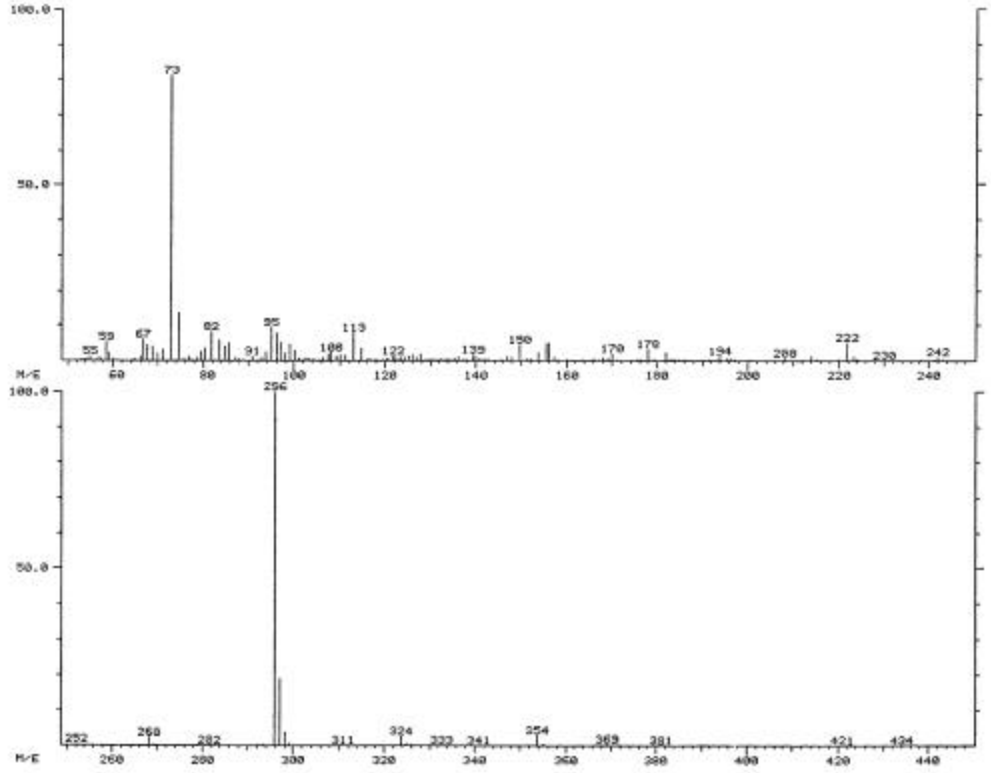

1.5
2.0
2.5
3.0
3.5
4.0
ppm
ppm
60
50
40
30
20
10

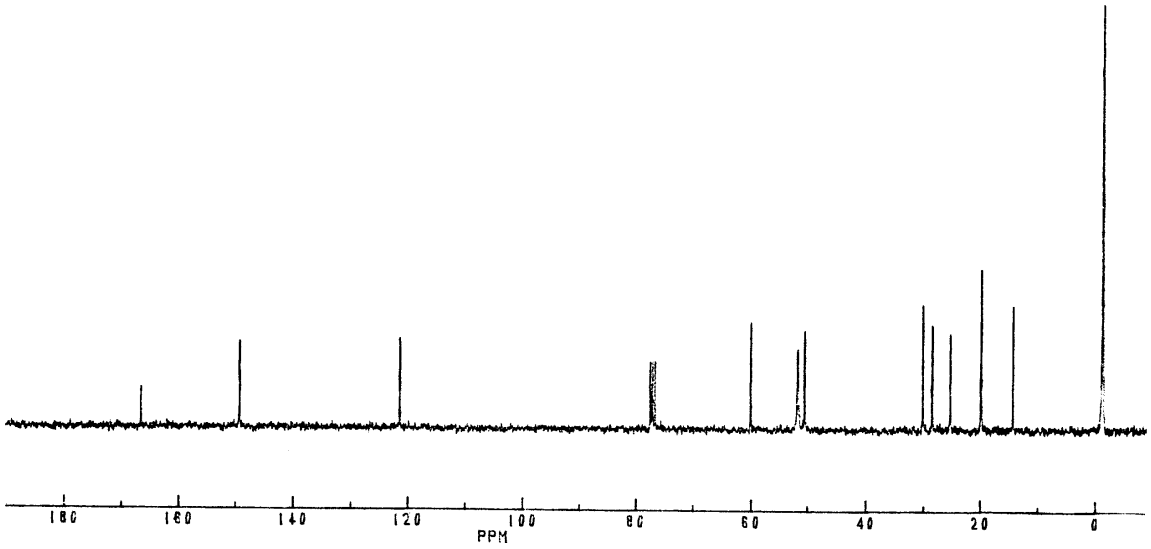

TMS
N
TMS
CO2Et

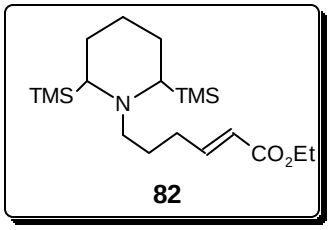
82

Fig. 7

4.53
5.20
15.18
4.13
40.48
4.47
72.84
30.11
165.79
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM

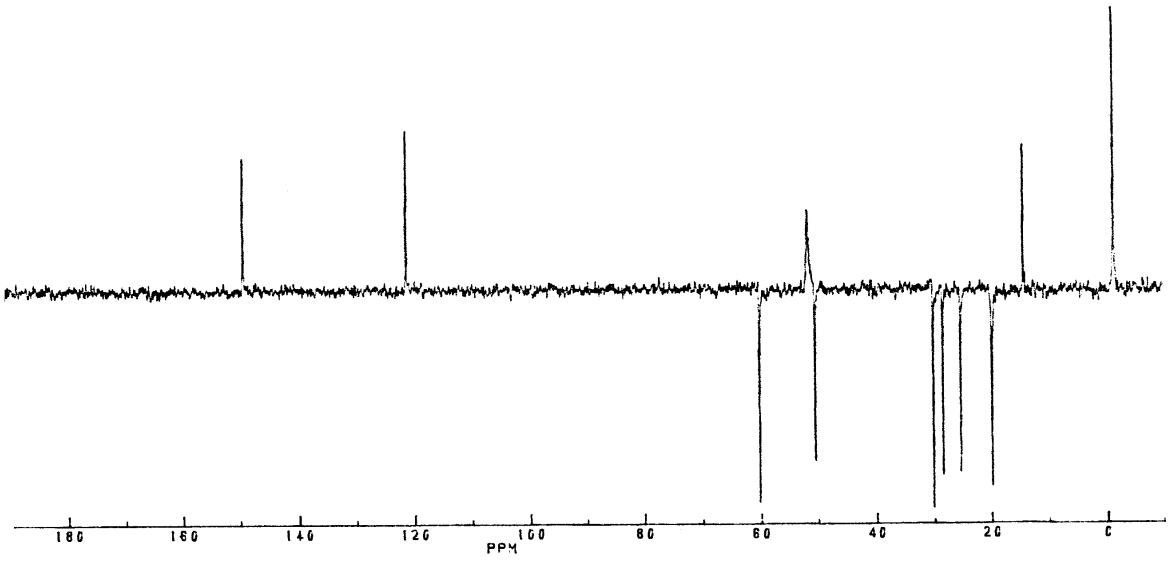

100.0
50.0
73
M/E
296

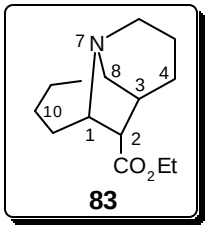

180
160
140
120
100
80
60
40
20
0
PPM


TMS
N
TMS
CO2Et

82

Fig. 8

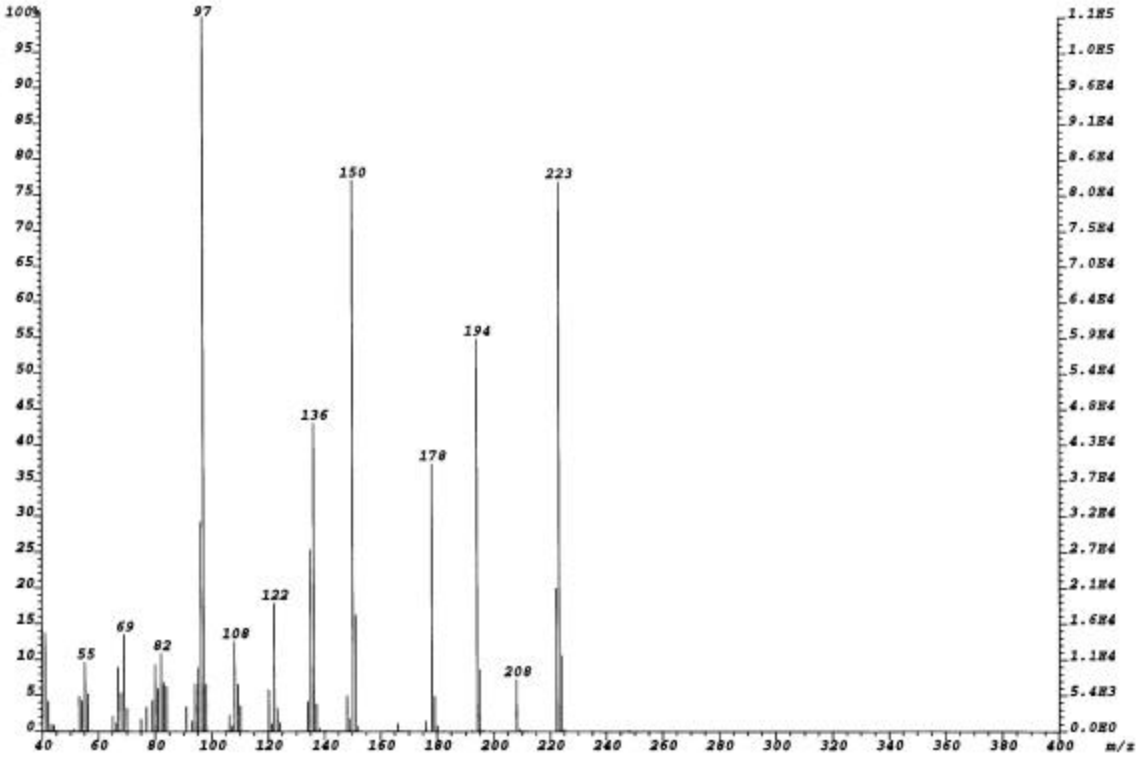

180
160
140
120
100
80
60
40
20
0
PPM

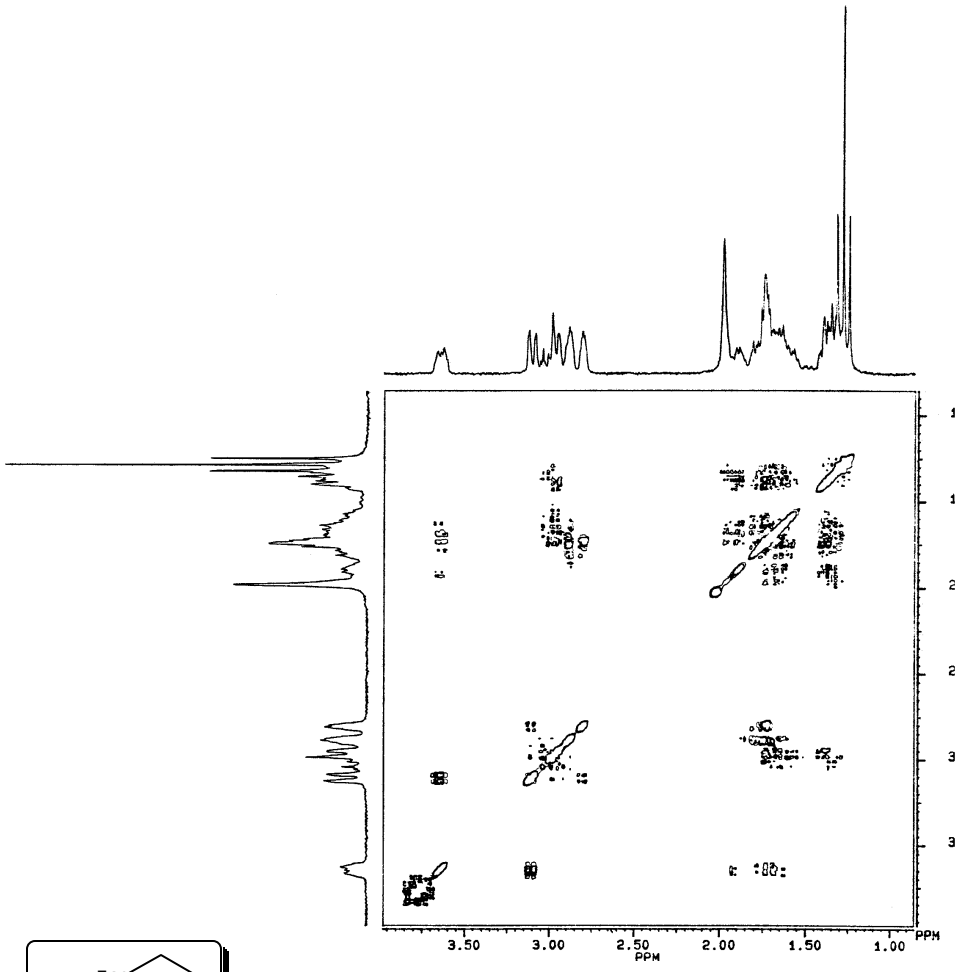

7 N
8
3
4
10
1
2
CO2Et

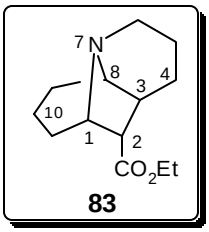
83

Fig. 9

8.00
7.00
6.00
5.00
PPM
4.00
3.00
2.00
1.00
0.0

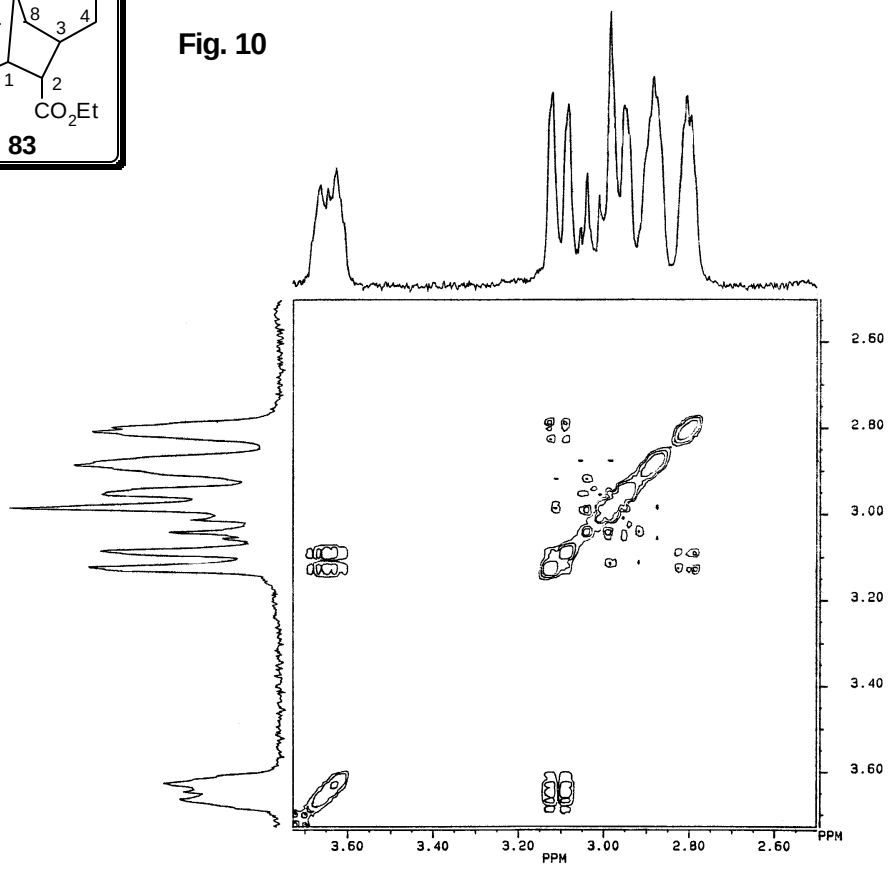

97
150
223
194
136
178
122
108
69
82
55
208
m/z

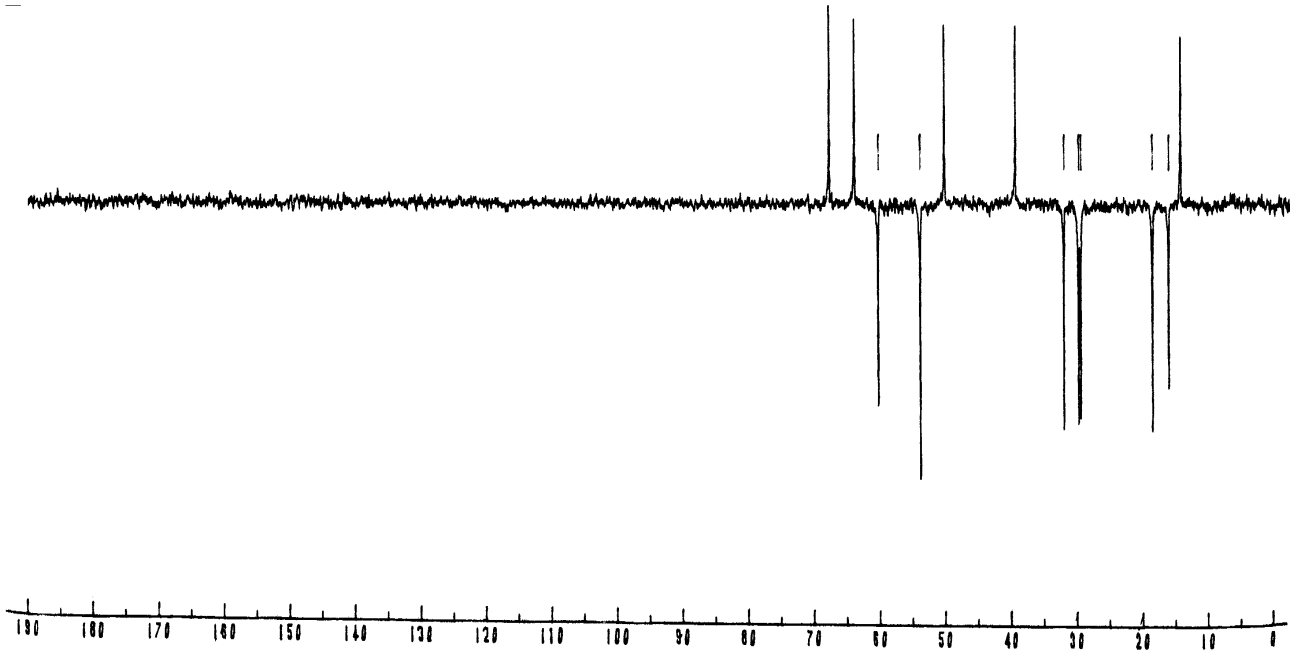

3.50
3.00
2.50
2.00
1.50
1.00
PPM

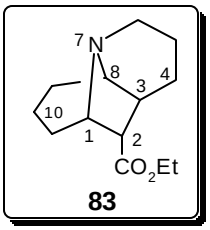

7
N
8
3
4
10
1
2
CO2Et

83

Fig. 10

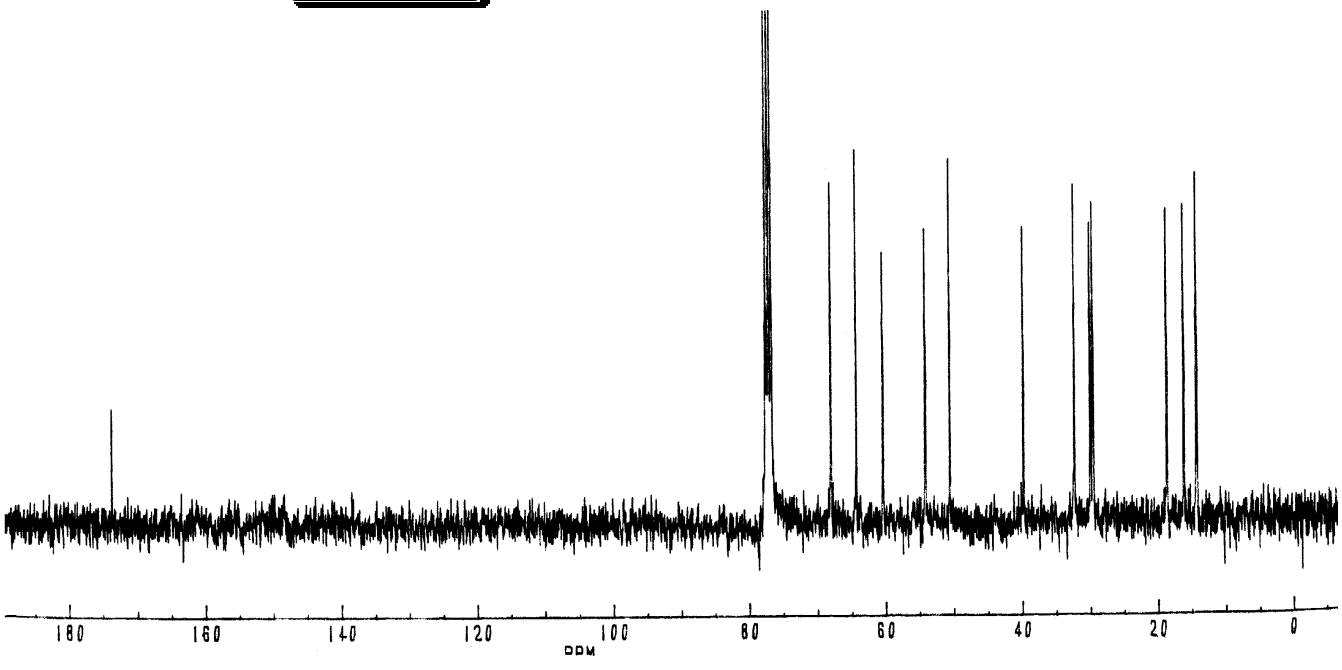

2.60
2.80
3.00
3.20
3.40
3.60
3.60
3.40
3.20
3.00
2.80
2.60
PPM

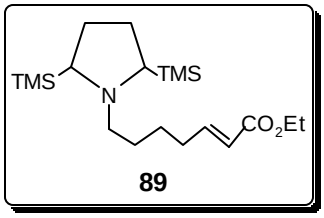

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7
N
8
3
4
10
1
2
CO2Et

83

Fig. 11

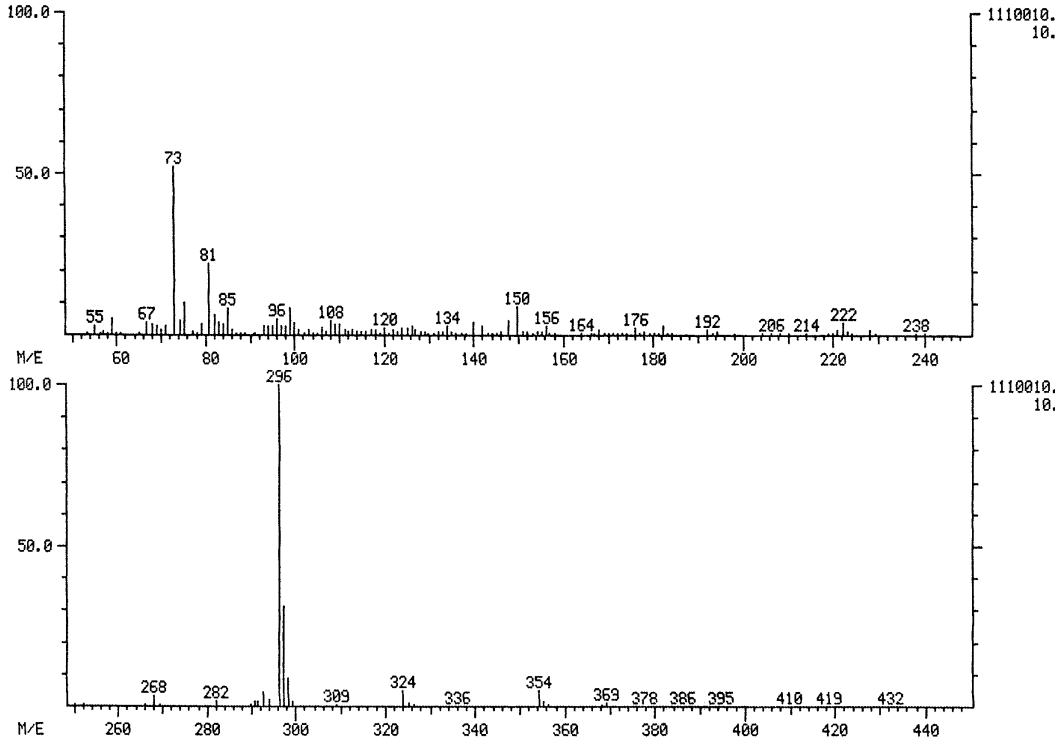

180
160
140
120
100
80
60
40
20
0
PPM

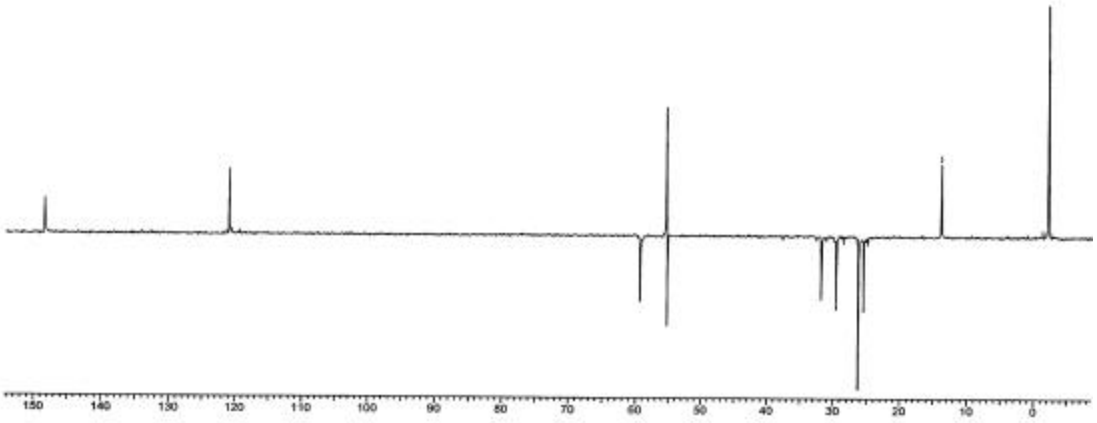

TMS
N
TMS
CO2Et

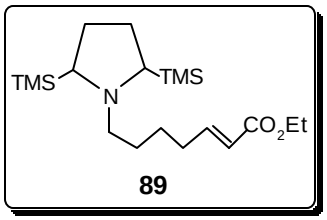
89

Fig. 12

7.00
6.00
5.00
PPM
4.00
3.00
2.00
1.00
0.0

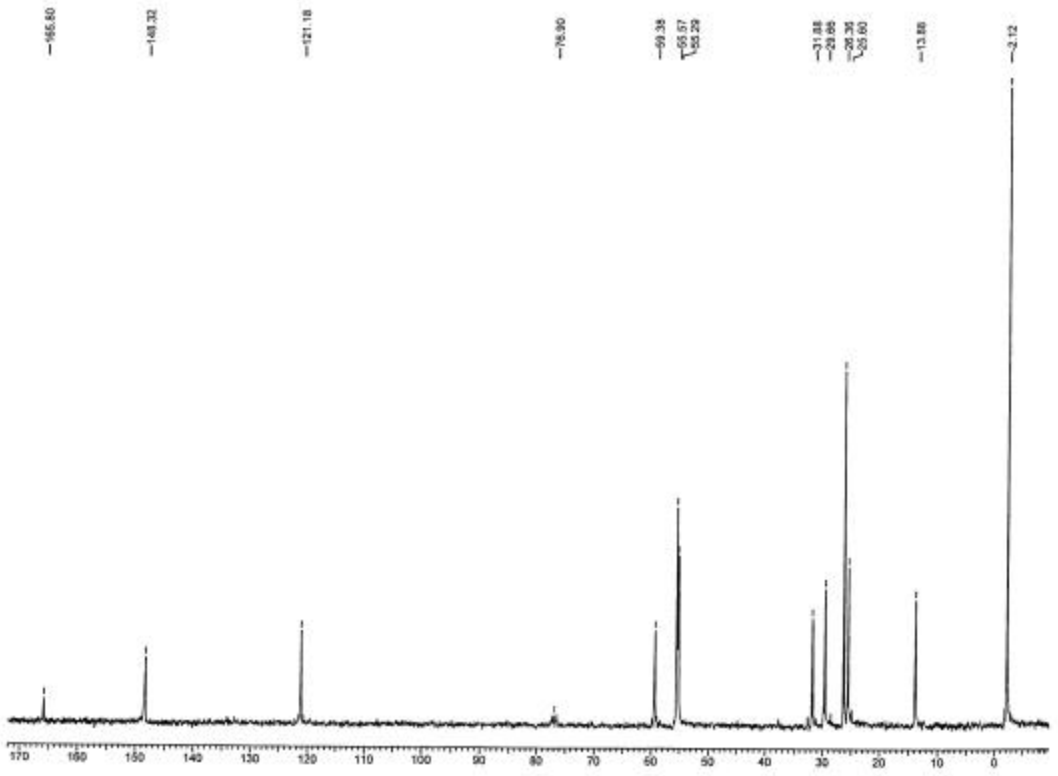

100.0
50.0
1110010.
10.
73
81
85
55
67
96
108
120
134
150
156
164
176
192
206
214
222
238
M/E
60
80
100
120
140
160
180
200
220
240
100.0
50.0
1110010.
10.
296
268
282
309
324
336
354
369
378
386
395
410
419
432
M/E
260
280
300
320
340
360
380
400
420
440

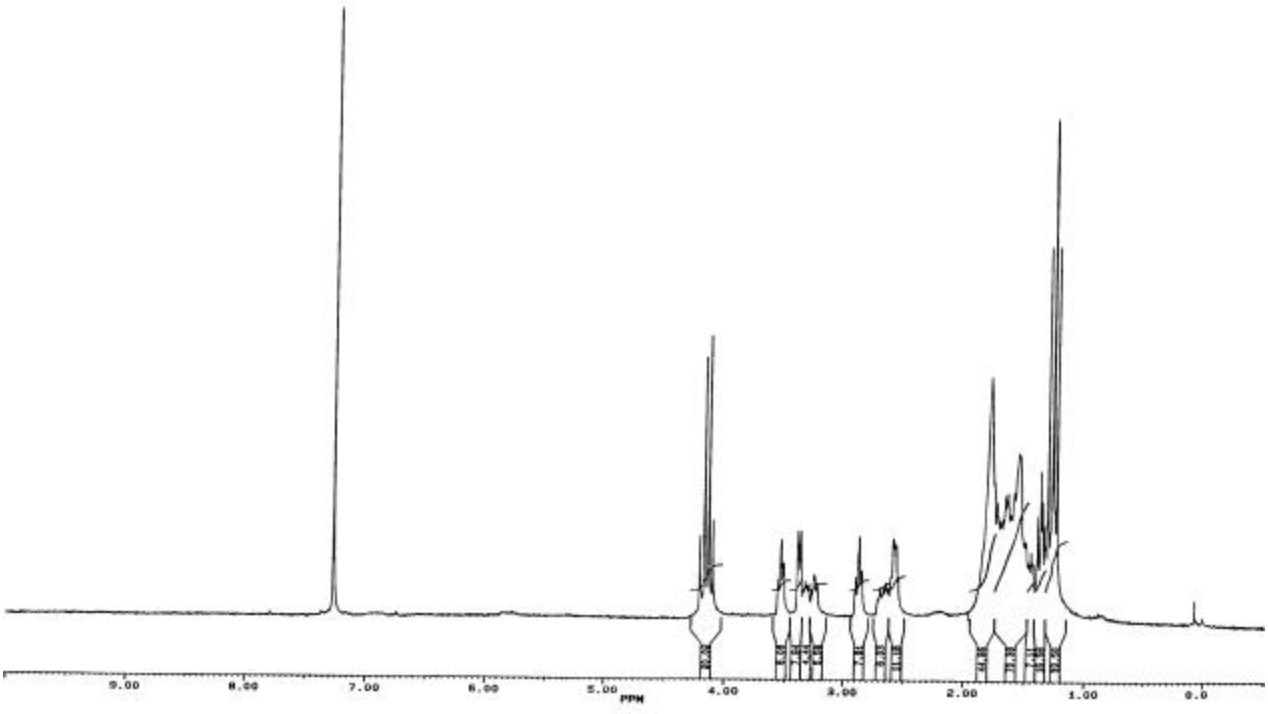


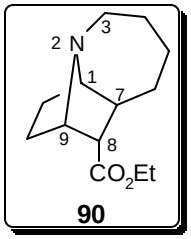


89

Fig. 13



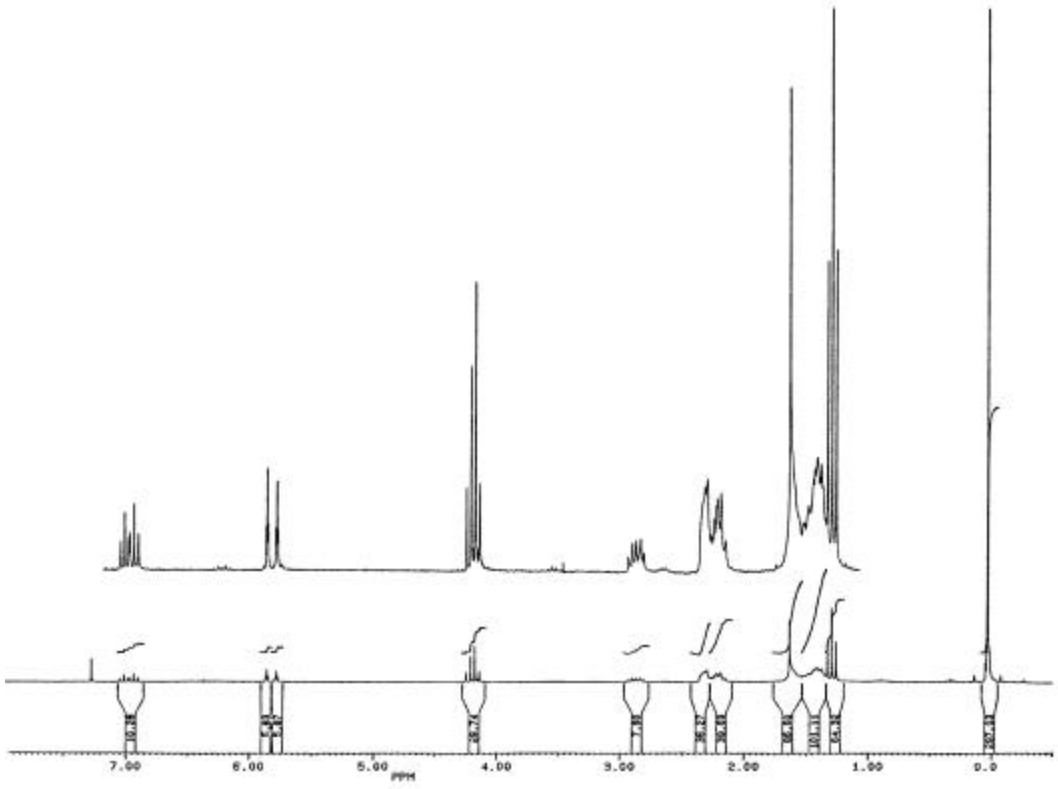

9.00
8.00
7.00
6.00
5.00
PPM
4.00
3.00
2.00
1.00
0.0

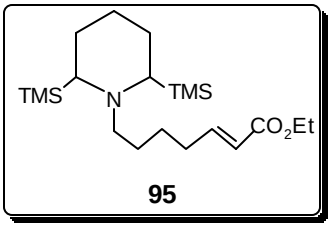

2
N
3
1
7
9
8
CO_2Et

90

Fig. 14

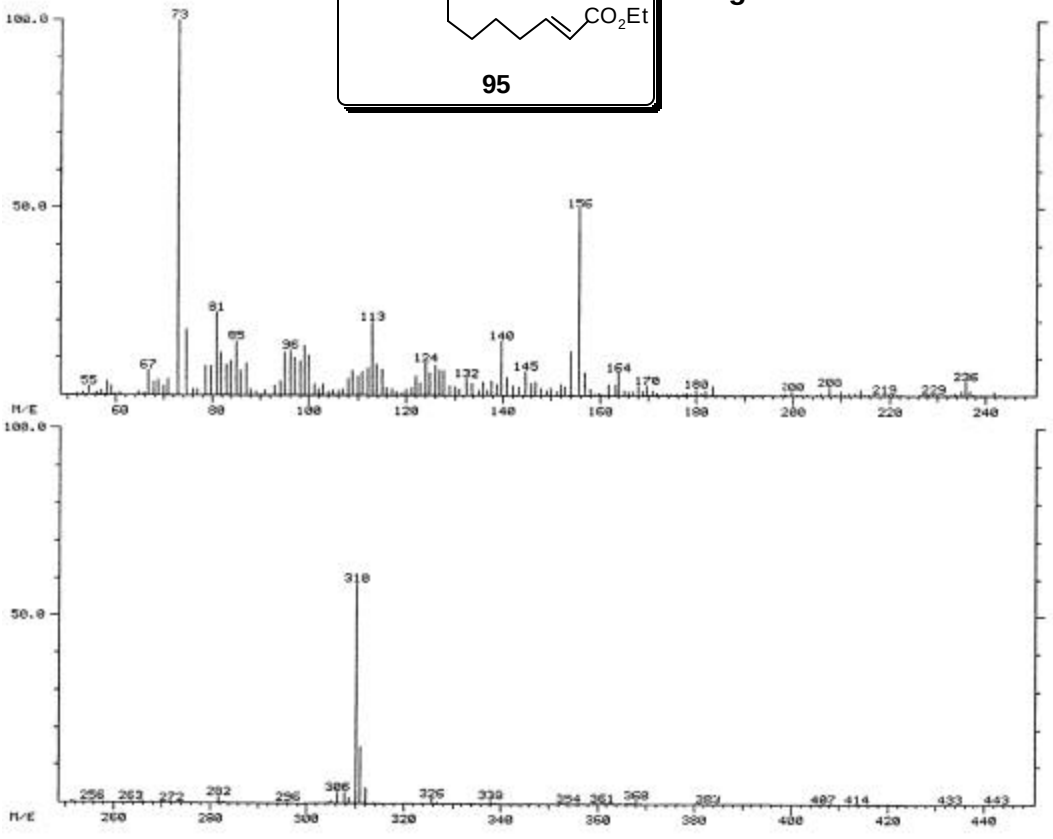
172.887
77.098
76.844
76.590
66.541
63.721
60.525
50.295
49.561
45.522
29.518
29.258
27.395
25.820
24.587
14.114
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

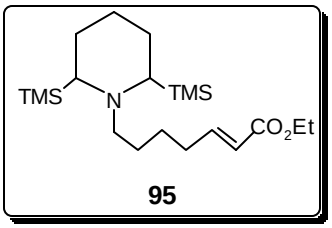

7.00
6.00
5.00
PPM
4.00
3.00
2.00
1.00
0.0


TMS
N
TMS
CO2Et

95

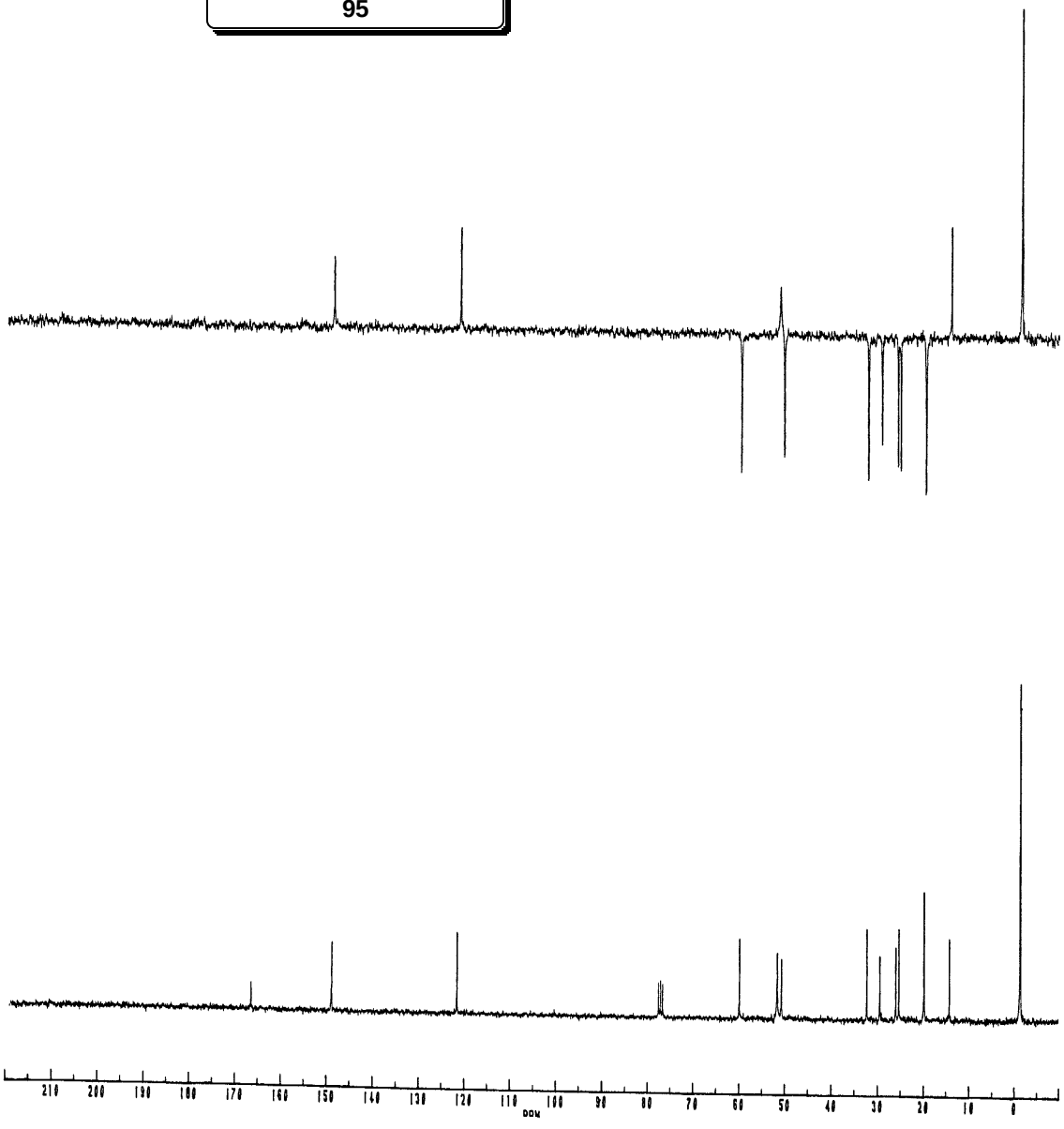
Fig. 15

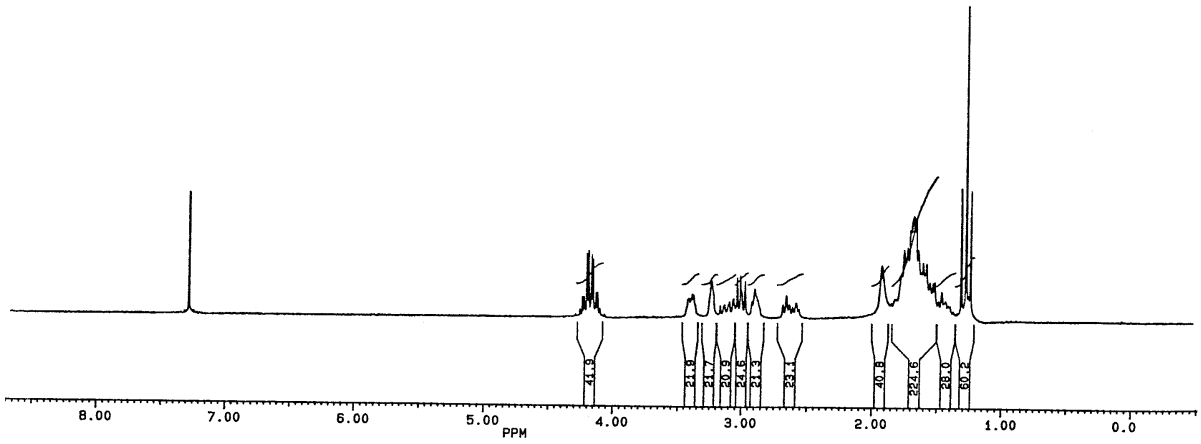

100.0
50.0
73
156
81
113
140
55
67
85
96
124
132
145
164
178
M/E
60
80
100
120
140
160
180
200
220
240
100.0
50.0
310
M/E
260
280
300
320
340
360
380
400
420
440

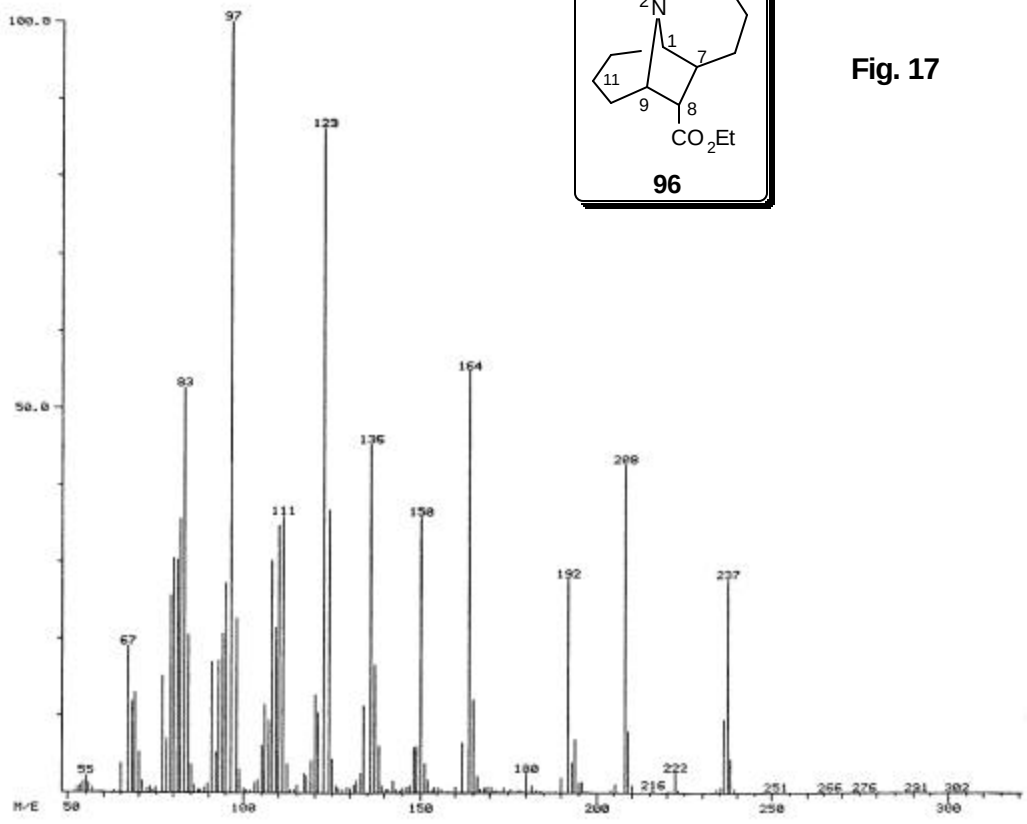


95

Fig. 16



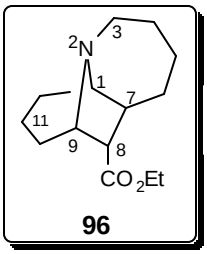

41.9
21.9
21.7
20.9
24.6
21.3
23.1
40.8
224.6
28.0
60.2
8.00
7.00
6.00
5.00
PPM
4.00
3.00
2.00
1.00
0.0


100.0
50.0
M/E
97
123
83
164
136
200
111
158
192
237
67
55
180
222
216
251
256
276
281
302
50
100
150
200
250
300

2N
3
1
7
11
9
8
CO2Et

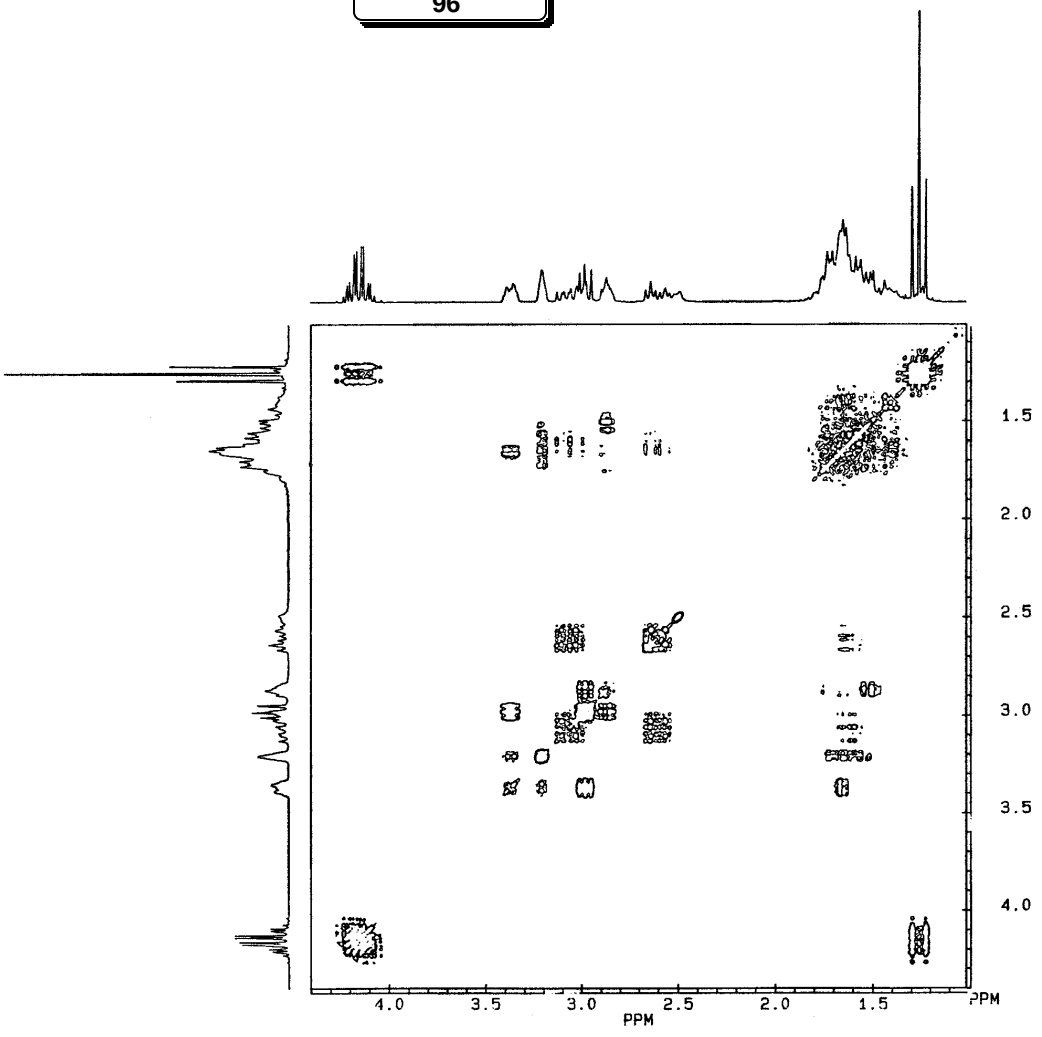
96

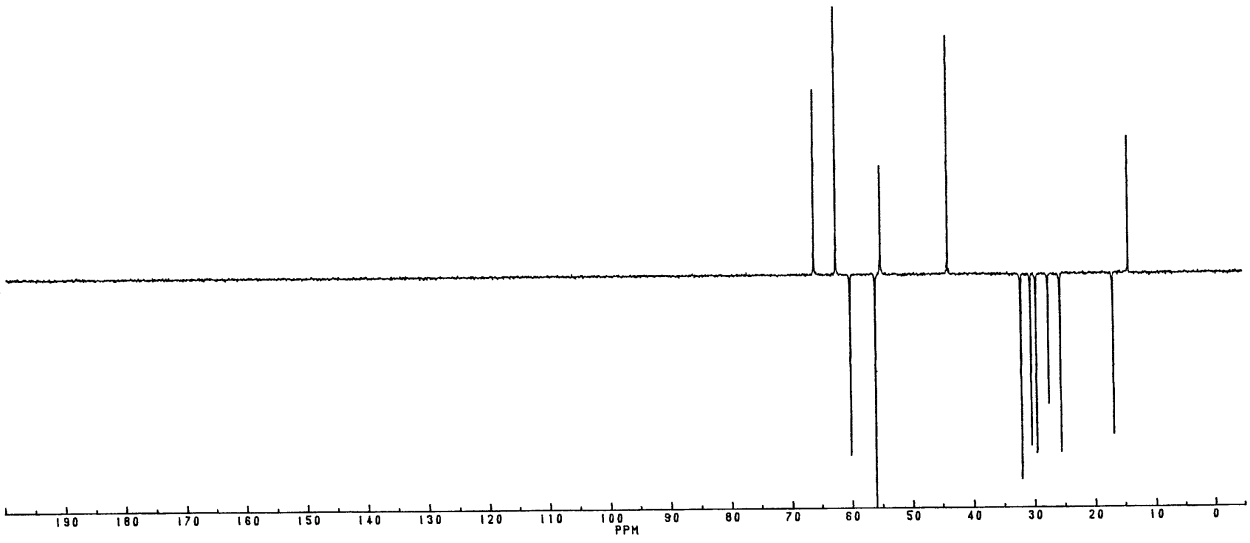
Fig. 17

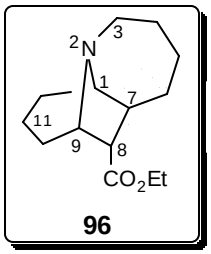


96

Fig. 18

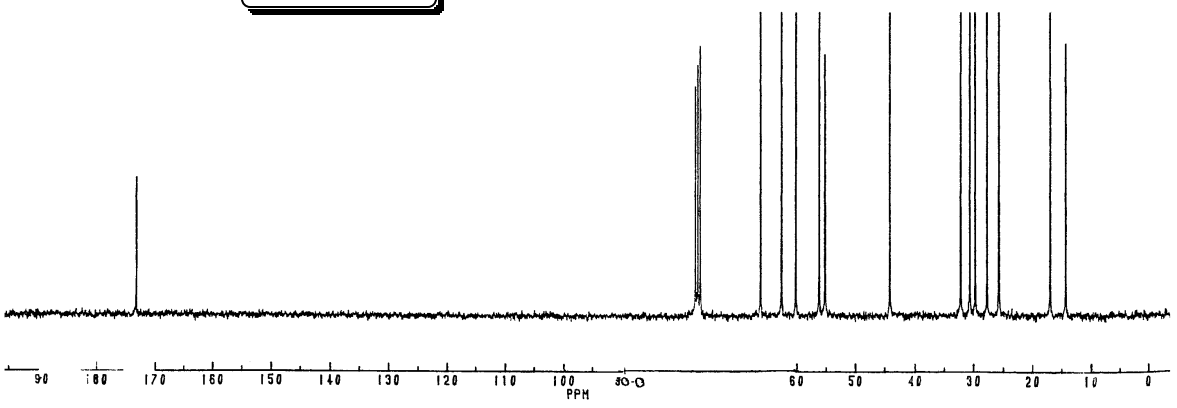


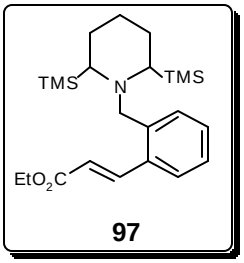

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


2N
3
1
7
11
9
8
CO2Et

96

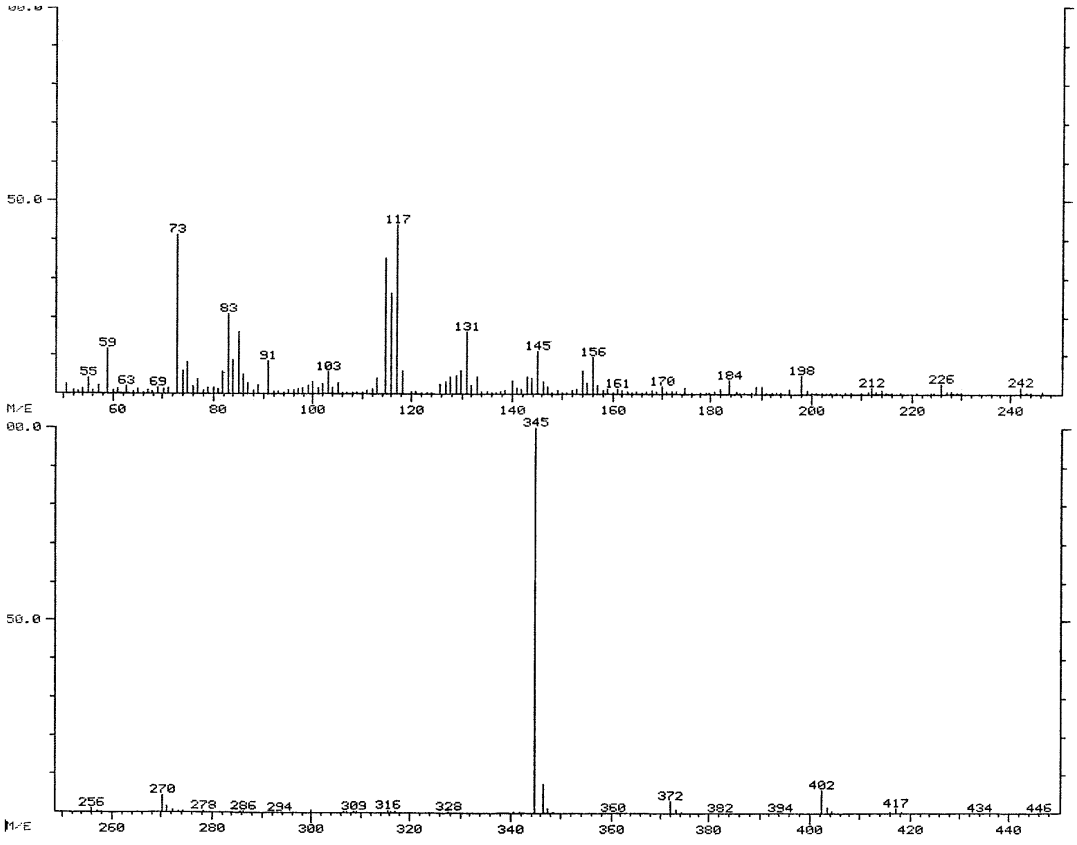
Fig. 19

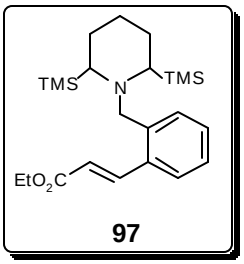

90 180 170 160 150 140 130 120 110 100 90 80 60 50 40 30 20 10 0
PPM


TMS
N
TMS
EtO2C

97

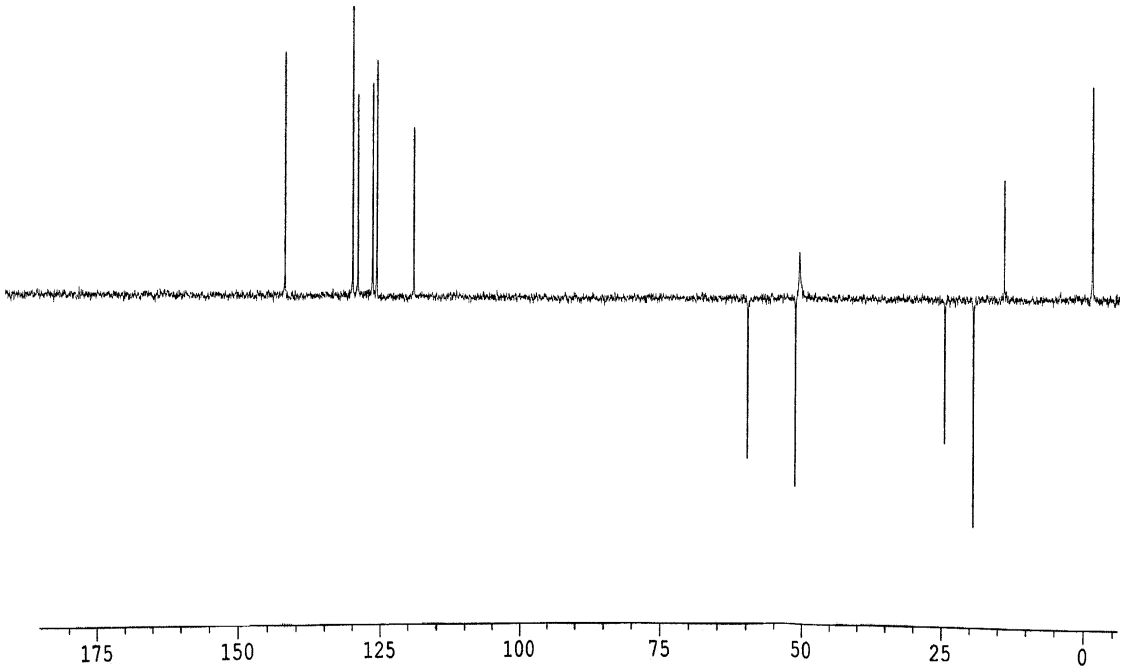
Fig. 20

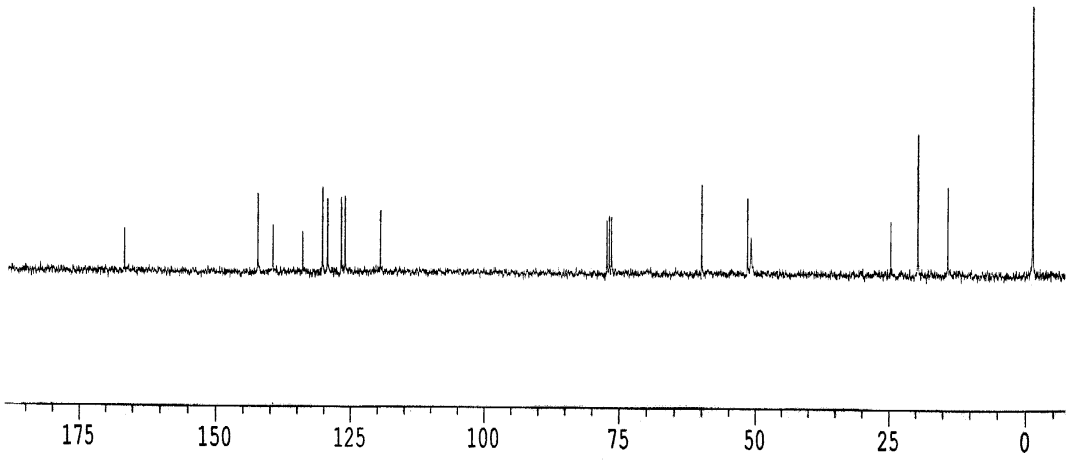

100.0
50.0
M/E
73
117
83
131
59
145
91
156
103
55
63
69
161
170
184
198
212
226
242
60
80
100
120
140
160
180
200
220
240
100.0
50.0
M/E
345
270
402
256
278
286
294
309
316
328
350
372
382
394
417
434
445
260
280
300
320
340
360
380
400
420
440

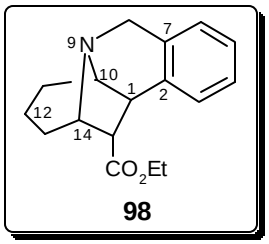

TMS
N
TMS
EtO2C

97

Fig. 21


175
150
125
100
75
50
25
0

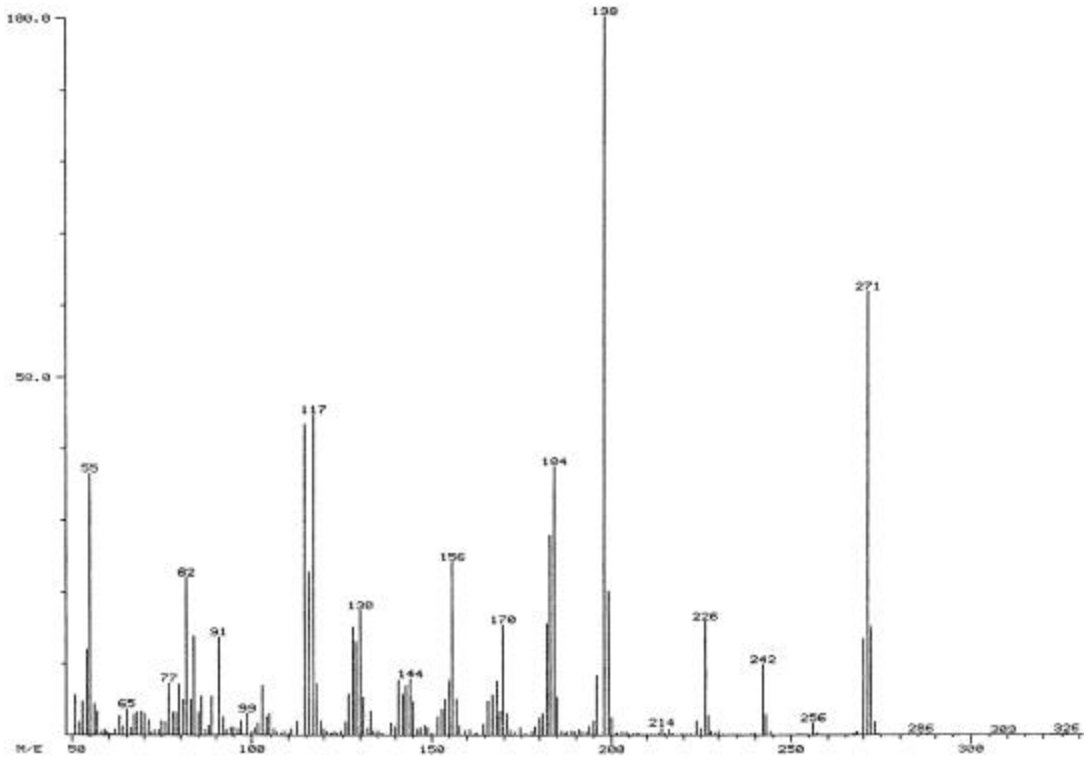

175
150
125
100
75
50
25
0

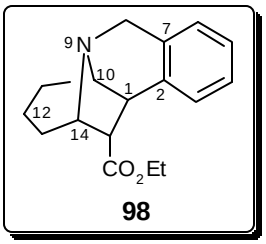

9
N
7
10
1
2
12
14
CO_2Et

98

Fig. 22

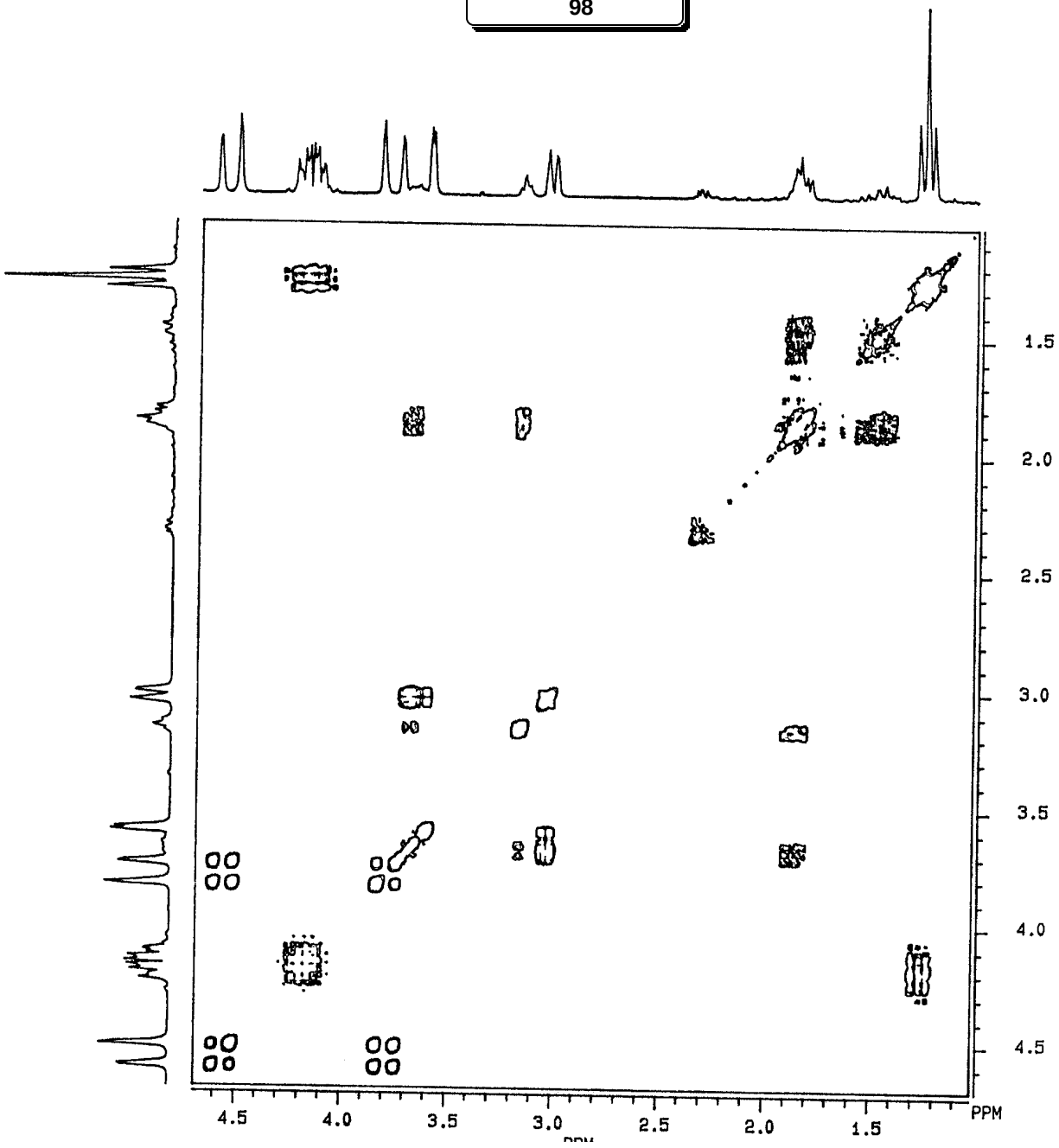
37.43
10.00
20.57
29.14
10.19
38.63
22.61
33.05

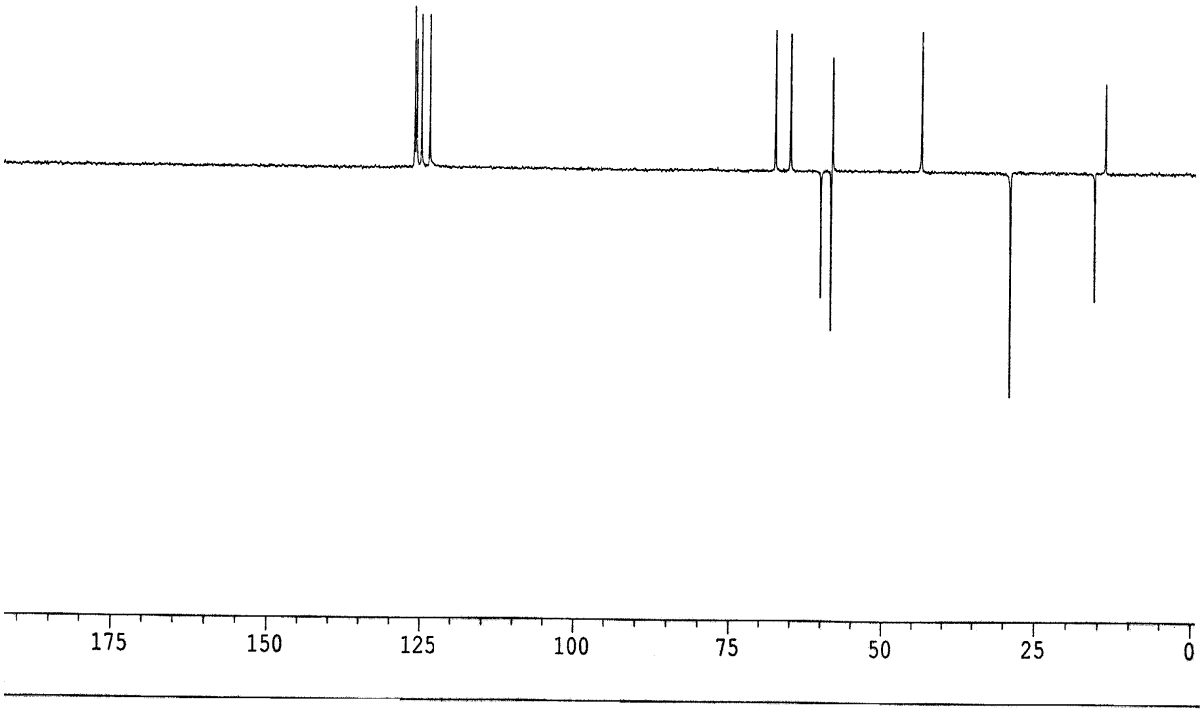

100.0
50.0
M/E
55
62
65
77
91
99
117
120
130
144
156
170
184
214
226
242
256
271
285
302
326

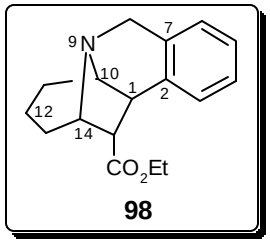


98

Fig. 23

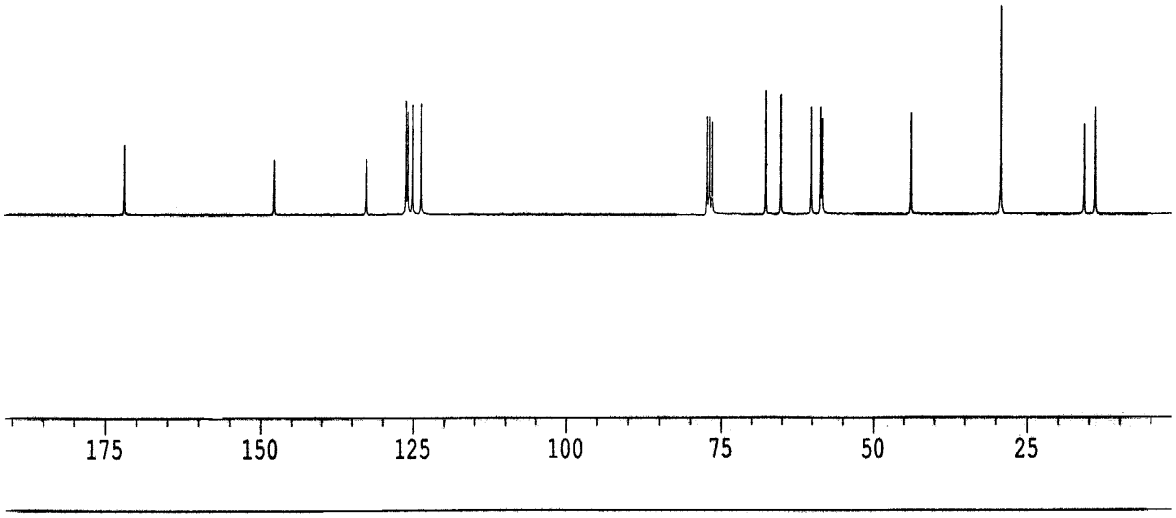


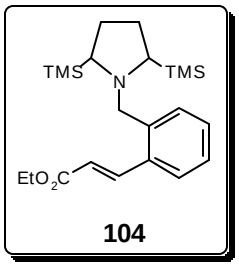

175
150
125
100
75
50
25
0


9N
7
10
1
2
12
14
CO2Et

98

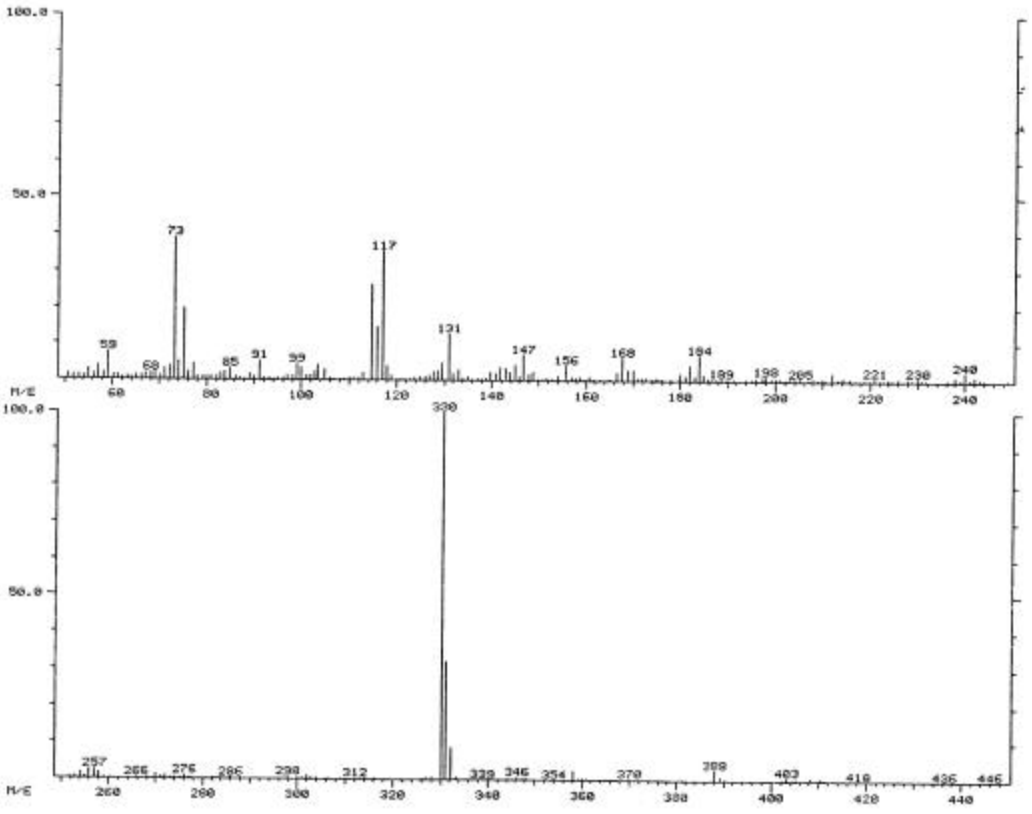
Fig. 24

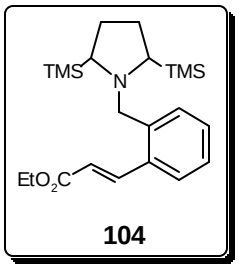

175
150
125
100
75
50
25



104

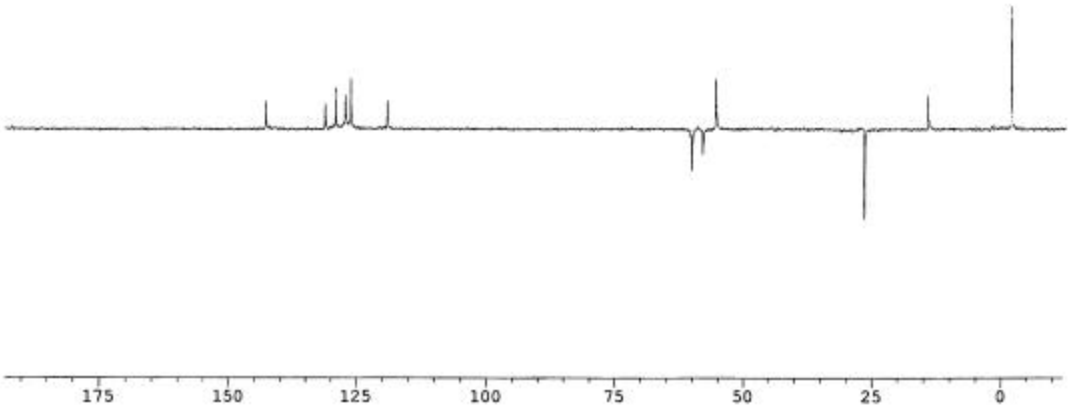
Fig. 25




TMS
N
TMS
EtO2C

104

Fig. 26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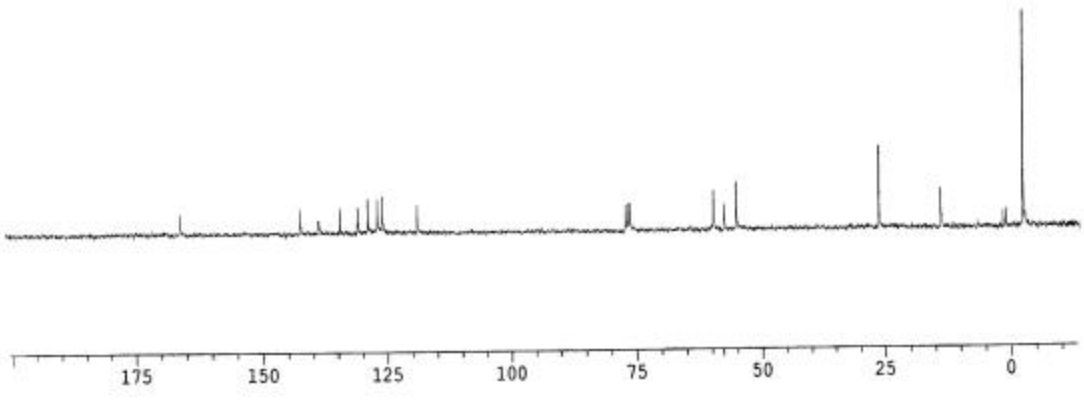
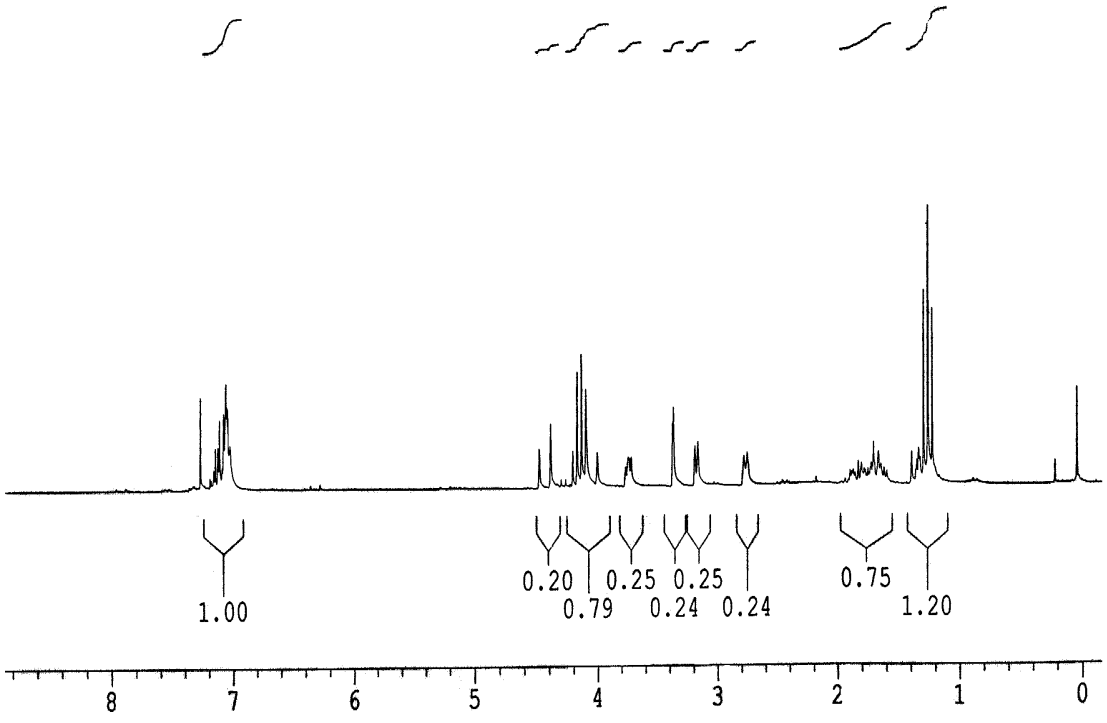
125
100
75
50
25
0


175
150
125
100
75
50
25
0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0.79
0.25
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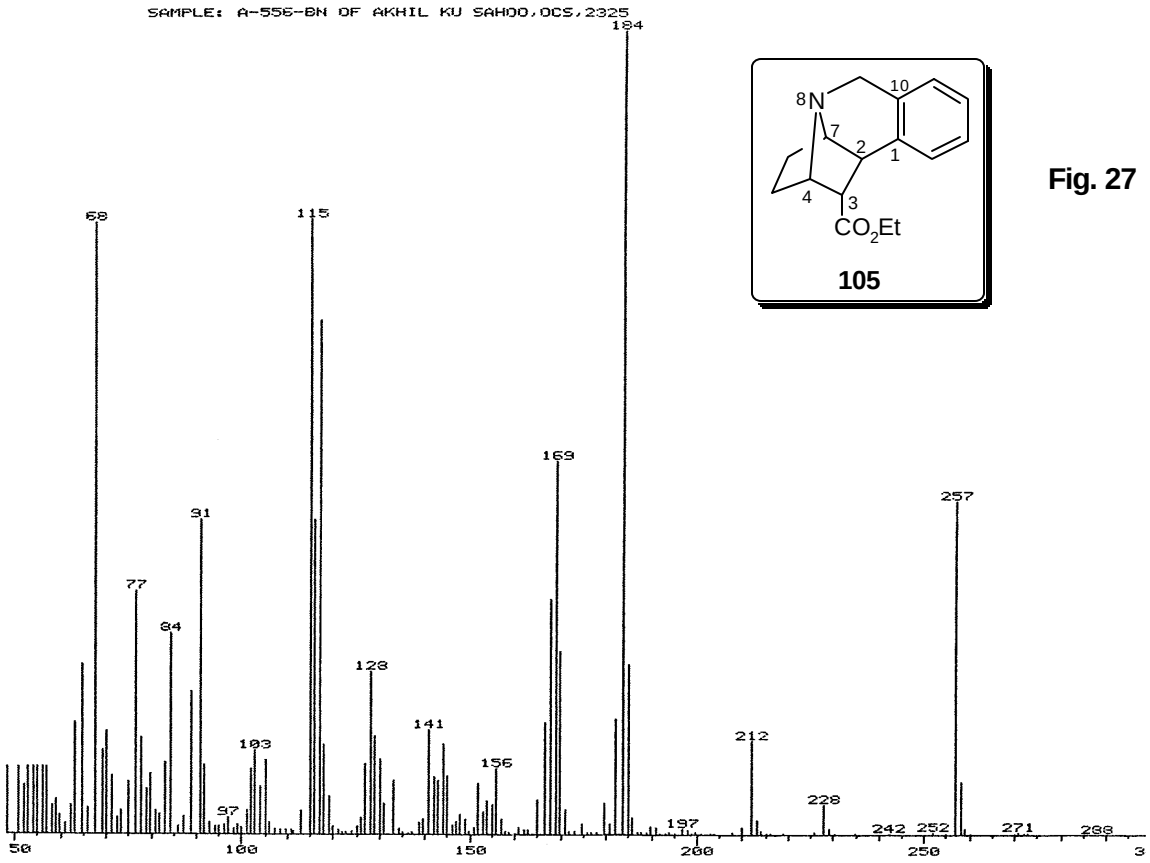
0.25
0.24
0.75
1.20
8
7
6
5
4
3
2
1
0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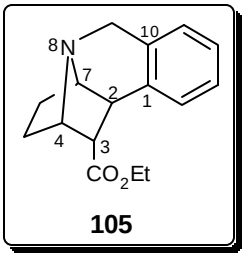
184
115
58
169
91
257
77
84
128
141
103
156
212
228
97
197
242 252
271
288
50
100
150
200
250
3

8N
10
7
2
1
4
3
CO2Et

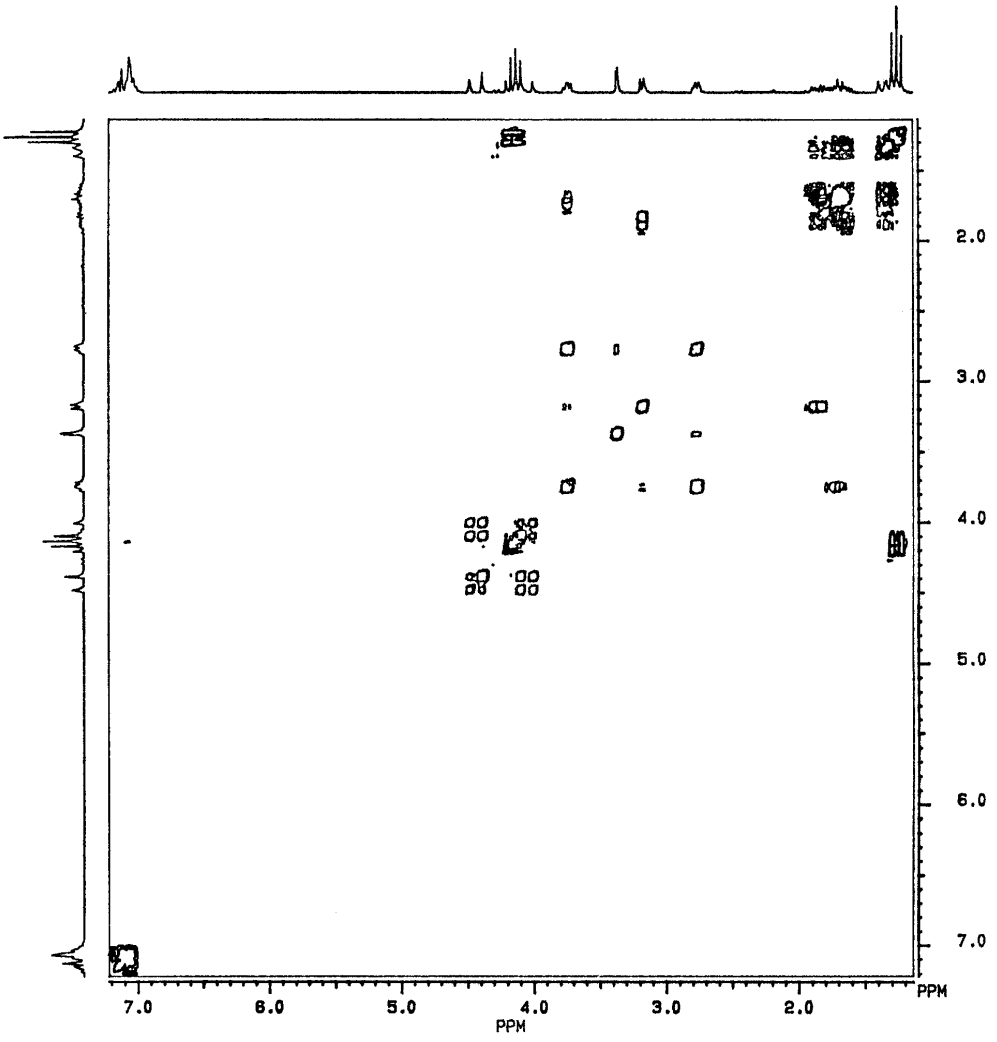
105

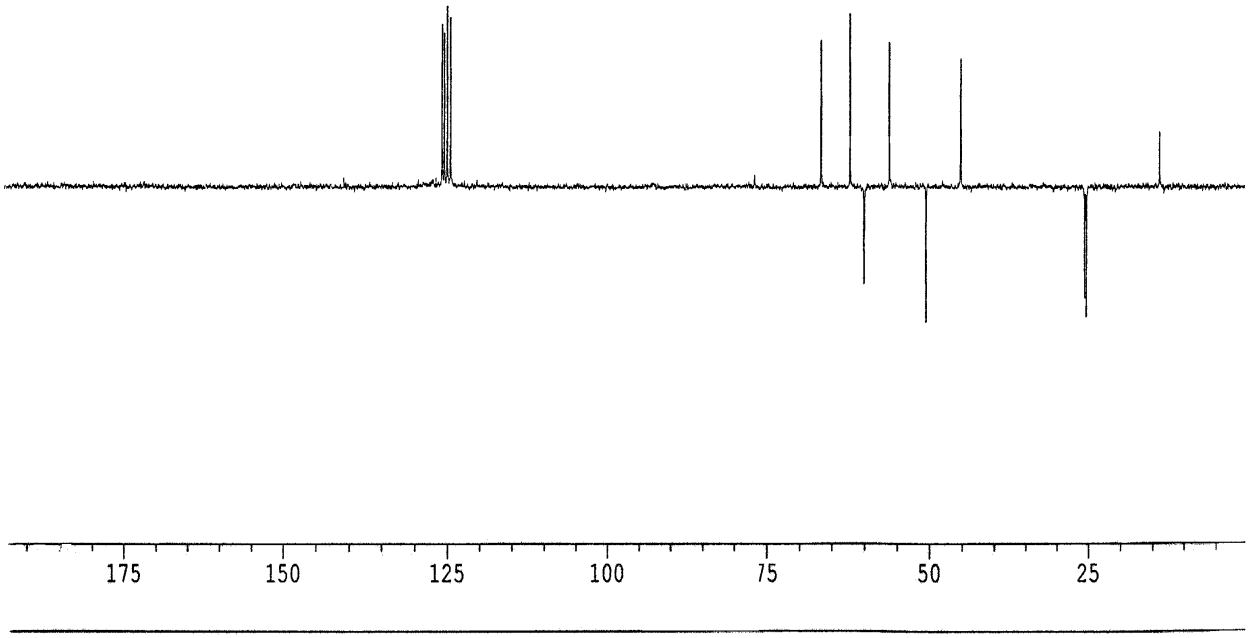
Fig. 27



105

Fig. 28

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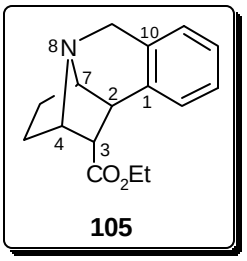
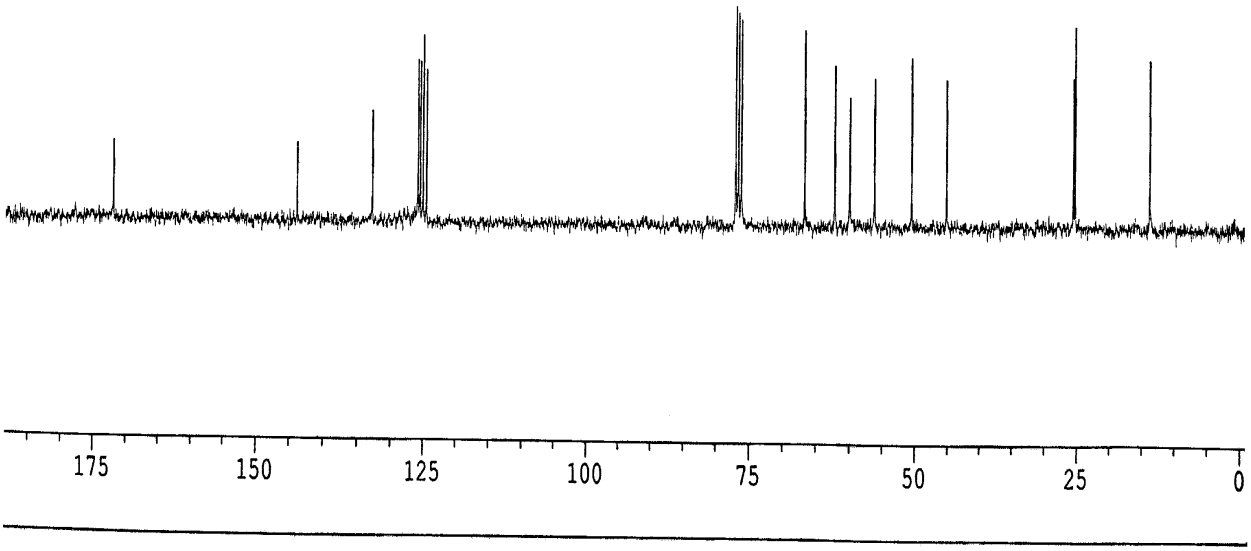
125
100
75
50
25


8N
10
7
2
1
4
3
CO2Et

105

Fig. 29


175
150
125
100
75
50
25
0

List of Publications

1. [3+2] Cycloaddition of Nonstabilized Azomethine Ylides. 7. Stereoselective Synthesis of Epibatidine and Analogues.

   Ganesh Pandey, Trusar D. Bagul and **Akhila K. Sahoo.**
   J. Org. Chem. 1998, *63*, 760.

2. **[3+2] Cycloaddition of Nonstabilized Azomethine Ylides. 8. An Efficient Synthetic Strategy for Epiboxidine.**

   Ganesh Pandey, **Akhila K. Sahoo**, Smita R. Gadre, Trusar D. Bagul and Usha D. Phalgune.
   J. Org. Chem. 1999, *64*, 4990.

3. [3+2] Cycloaddition of Nonstabilized Azomethine Ylides. 10. An Efficient Strategy for the Construction of Various X-azatricyclo[m.n.0.$0^{a,b}$]alkanes by Intramolecular Cycloaddition of Cyclic Azomethine Ylide

   Ganesh Pandey, **Akhila K. Sahoo** and Trusar D. Bagul.
   Org. Lett. 2000, *2*, 2299.