ASYMMETRIC [3+2] CYCLOADDITION OF AZOMETHINE YLIDES: APPLICATION TO THE SYNTHESIS OF NATURAL PRODUCTS

A THESIS

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FOR THE DEGREE OF

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IN

CHEMISTRY

BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Asymmetric [3+2] Cycloaddition of Azomethine Ylides: Application to the synthesis of Natural Products"*** *submitted by Mr. Joydev Kumar Laha 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: June 14, 2001

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Research Guide

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DECLARATION

I hereby declare that the thesis entitled ***"Asymmetric [3+2] Cycloaddition of Azomethine Ylides: Application to the synthesis of Natural Products"*** *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.*

Date: June 14, 2001

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(JOYDEV KUMAR LAHA)

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Joydev Kumar Laha

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 OF THE THESIS

Asymmetric [3+2]-Cycloaddition of Azomethine Ylides: Application to the Synthesis of Natural Products

CHAPTER-1: Introduction

This chapter describes all existing asymmetric approaches for the synthesis of azabicyclic compounds possessing the basic skeleton X-azabicyclo[m.2.1]alkane frameworks.

Many biologically active compounds which display the intriguing structural feature, X-azabicyclo[m.2.1]alkane frameworks, are synthetically challenging target to organic chemists. Epibatidine, an extremely potent agonist of the acetylcholine receptor, represents the only alkaloid of the class 7-azabiclo[2.2.1]heptane. 8-Azabiclo[3.2.1]octane, the basic skeleton of all tropane class of alkaloids, comprises of 200 natural products and several of them have profound behavioral and neuronal reinforcing properties. Anatoxin-a, a highly potent nicotinic acetylcholine receptor, is the only representative member of 9-azabiclo[4.2.1]nonane skeleton.

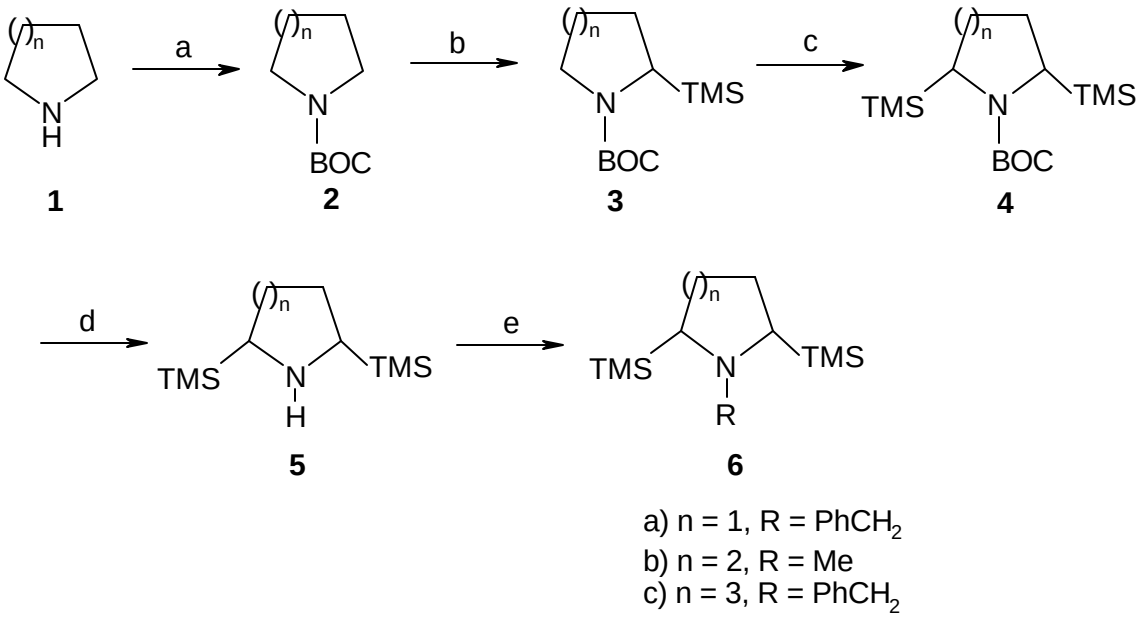
CHAPTER-2: Diastereoselectivity in Asymmetric [3+2]-Cycloaddition Reactions

This chapter reports the diastereoselectivity attained during the asymmetric [3+2]-cycloaddition of cyclic azomethine ylides (AMYs) with Oppolzer's chiral acryloyl dipolarophile.

Previously, our group have reported a conceptually new methodology for the stereoselective construction of X-azabiclo[m.2.1]alkanes by taking advantage of the *exo/endo* selectivity of [3+2]-dipolar cycloaddition of cyclic AMYs with a suitable dipolarophile. The successful execution of this process has stimulated us to explore this chemistry in diastereoselective fashion by performing an asymmetric [3+2]-cycloaddition of cyclic AMYs with Oppolzer's chiral acryloyl dipolarophile (-)-**7**. The cyclic AMYs were generated in situ from precursors **6** by the sequential double desilylation using Ag(I)F as

one electron oxidant. The preparation of synthetic precursors **6** was obtained through the reaction sequences as shown in Scheme 1.

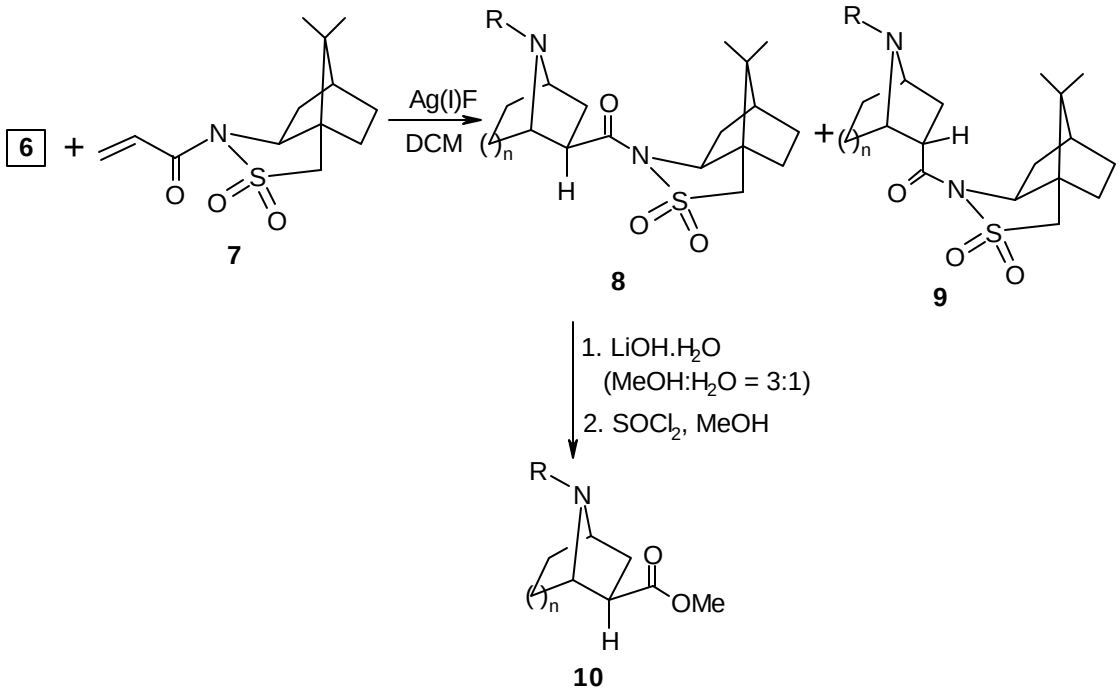
Scheme 1



Reagents and Conditions*: a) Boc-N3, Et3N, dioxan, 92-98 %; b) TMEDA, s-BuLi, TMSCl, -78 °C, 80-90 %; c) TMEDA, s-BuLi, TMSCl, -50 °C to -30 °C, 1 h (for n = 1 & 2), 60-70 %; -40° C, 5 h (for n = 3) 58 %; d) TFA, DCM, quantitative; e) PhCH2Cl, K2CO3, CH3CN (for n = 1 & 3), 80-85 %; HCHO, NaBH3CN, gl.CH3COOH (for n = 2), 68 %.*

The key cycloaddition reaction involved addition of 6 to a stirring mixture of (-)-7 and Ag(I)F in dry DCM. The diastereomeric ratio of cycloadducts (**8:9**) was determined by comparing the integration values of the H-3 from their corresponding ^{1}H NMR spectra. The *endo*-stereochemistry of H-3 in the major diastereomeric cycloadducts **8** was established by ^{1}H NMR decoupling and COSY experiment. The cost effective D-camphor sultam chiral auxiliary has offered stubble benefits in addition to serving as the source of chiral induction. The high diastereoselectivity attained during this asymmetric [3+2]-cycloaddition was explained on the basis of selective attack of cyclic AMYs on to *re*-face of (-)-**7** and the results are summarized below in Scheme-2.

Scheme 2



Substrate (**8**)	R	Yield (isolated)	**8** : **9**	m.p. of **8** (uncorrected)	Optical rotation of **10** $[\alpha_D]^{25}$ obs
A, n = 1	$PhCH_2$	62%	98 : 2	135-137°C	+ 22.38 (c = 0.52, $CHCl_3$)
B, n = 2	Me	58%	80 : 20	165-167°C	- 04.50 (c = 0.64, $CHCl_3$)
C, n = 3	$PhCH_2$	68%	95 : 5	205-207°C	+15.69 (c = 0.54, $CHCl_3$)

The validity of this asymmetric cycloaddition in the chiral synthesis of X-azabicyclo[m.2.1]alkanes was firmly evaluated by the removal of chiral auxiliary from the major diastereomeric cycloadducts. These chiro compounds **10** are amenable to conversion into a range of natural product targets.

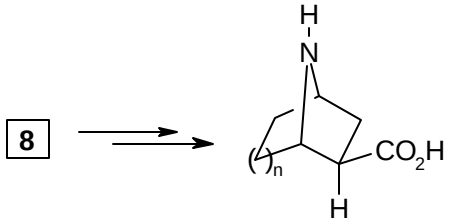
CHAPTER-3: Synthesis of Conformationally Constrained Amino Acids and Synthetic Studies towards the Enantioselective Synthesis of Epibatidine

This chapter presents the applications of our asymmetric [3+2]-cycloaddition reactions in the synthesis of few conformationally constrained amino acids. It also describes the synthetic studies directed towards the enantioselective synthesis of epibatidine.

Section A: Synthesis of Few Conformationally Constrained Cyclic Amino Acids

The conformationally constrained cyclic amino acids hold considerable potential for use in inducing constraint in peptides and polypeptides in peptidomimetics research. Due to apparent structural similarities of the cycloadducts 8 with the constrained cyclic amino acids, we became interested in gaining access to few of these constrained cyclic amino acids to focus on the diverse synthetic applications of these cycloadducts. Towards this goal, the major diastereomeric cycloadducts 8 were converted into constrained amino acids with the anticipation that they would appear as excellent candidates for examining the conformational requirements of peptides in structure activity studies as shown below in Scheme-3.

Scheme-3



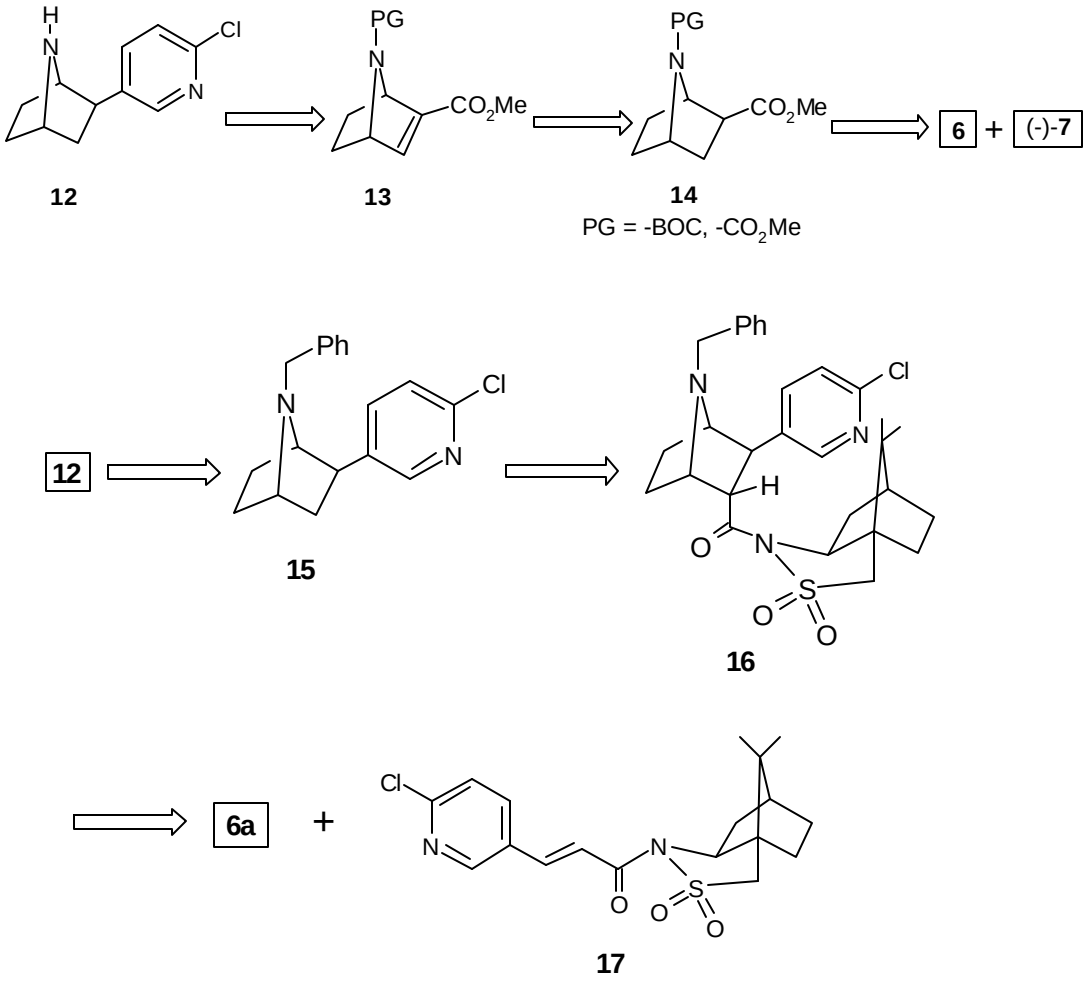
11

Reagents and Conditions: $LiOH.H_2O$, $MeOH:H_2O$ (3:1), 60 ^oC. 45 min. 90-95 % and then Pd/C, H_2 (70-80) psi, rt, 85-90 % for n = 1, 3 and α-chloroethyl chloroformate, N,N,N',N' -tetramethyl-1,8-napthanyl diamine, dichloroethane (for n = 2), 65 %.

Section B: Synthetic studies directed toward the enantioselective synthesis of epibatidine

Having demonstrated the validity of our asymmetric [3 + 2]-cycloaddition reaction in the chiral synthesis of X-azabicyclo[m.2.1]alkanes, we undertook a synthetically challenging target aimed at the enantioselective synthesis of epibatidine. Epibatidine (**12**), a novel alkaloid possessing the 7-azabicyclo[2.2.1]heptane ring system with a 2-chloropyridyl substituent in exo-orientation was isolated by Daly *et al* in 1992 from the skin extracts of Ecuadoran poison frog, Epipedobates tricolor and it has been shown to exhibit non-opioid analgesic activity 200-500 times more potent than that of morphine. The two complementary retrosynthetic approaches of epibatidine were envisaged as shown in **scheme-4.**

Scheme -4



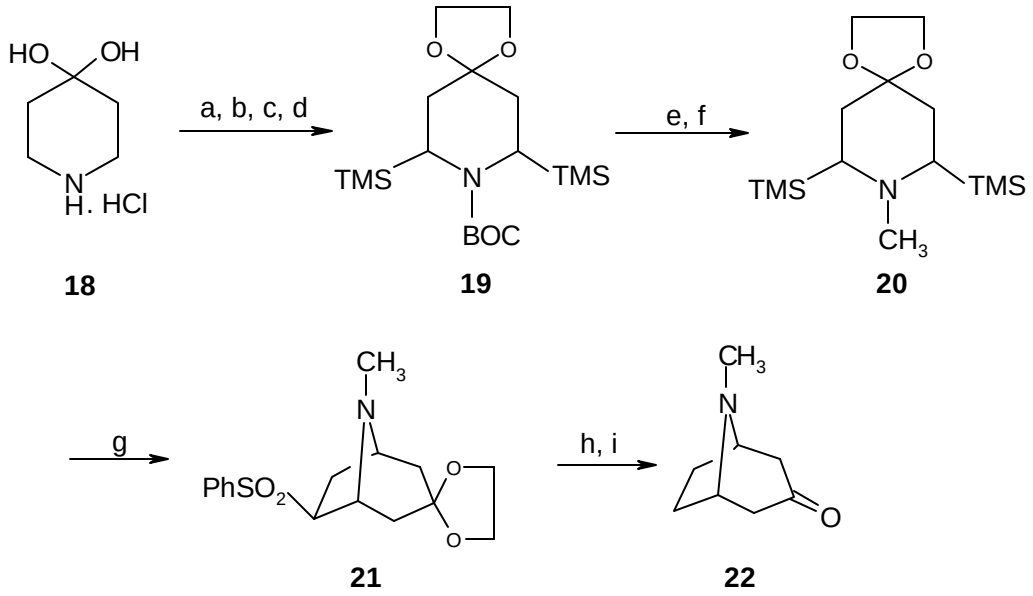
The efforts to create double bond α to ester group in substrate **14,** directed for the installation of 2-choloropyridyl moiety by effecting Michael addition on to substrate **13,** were futile (route I) leading to a change in our synthetic strategy. This surmountable obstacle was greatly circumvented by promoting the cycloaddition of cyclic azomethine ylide (generated from **6a**) with the synthetically designed chiral dipolarophile bearing 2-chloropyridyl moiety **17** whereby this moiety was installed along with the construction of 7-azabiclo[2.2.1]heptane skeleton (Route II). The exclusive formation of desire cycloadduct **16** to which 2-chloropridyl moiety is attached in *exo* orientation was a reasonable prize for us towards this endeavor.

CHAPTER 4: Synthesis of Tropinone and a Synthetic Chiro Tropane Intermediate

This chapter reports another applications of our asymmetric [3+2]-cycloaddition reactions in the development of a new general methodology to make entry into the tropane class of alkaloids by emphasizing the syntheses of tropinone and a synthetic chiro tropane compound **24**.

The quest for the development of a new general methodology to access tropane class of alkaloids has animated us to embark on this research project. Our [3+2]-cycloaddition protocol was successfully evaluated with the synthesis of tropinone, a simple class of tropane alkaloid **22** as shown in Scheme–5.

Scheme 5

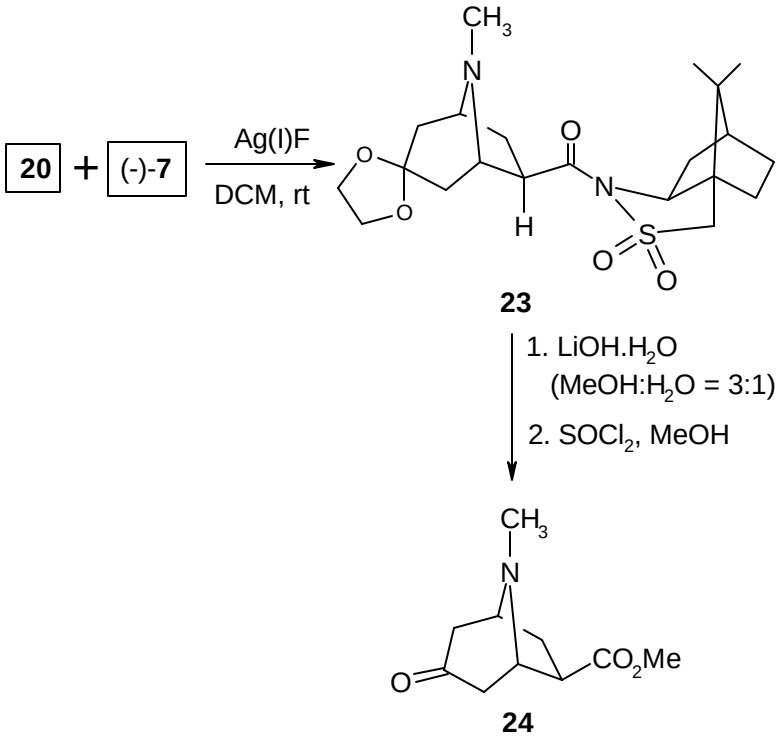


18 **19** **20** **21** **22**

Reagents and Conditions: *a) Boc-N_3, Et_3N, dioxan, 92 %; b) $(CH_2OH)_2$, p-PTS, benzene, 87 % ; c) TMEDA, s-BuLi, TMSCl, -78 ^oC, 86 %; d) TMEDA, s-BuLi, TMSCl, -50 ^oC to –30 ^oC,1 h, 62 %; e) TFA, DCM, quantitative; f) $NaBH_3CN$, HCHO, gl.CH_3COOH, 66 %; g) Phenyl vinylsulfone, Ag(I)F, DCM, 68%; h) Ni-Al Alloy, EtOH, reflux, 65%; i. p-TSA, MeOH,*

The impetus behind this preliminary investigation was to realize a practical route for the asymmetric synthesis of these alkaloids. Thus, asymmetric [3+2]-cycloaddition of **20** with (-)-**7** has provided a chiro tropane compound **24** as in Scheme-6.

Scheme 6

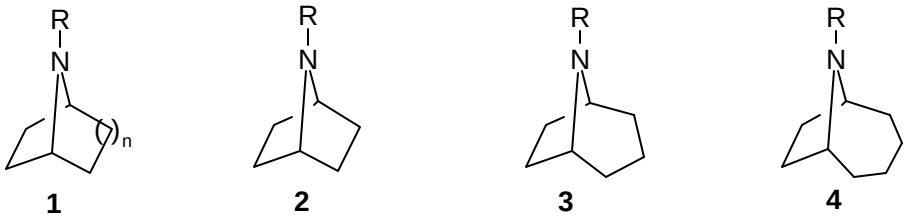


The chiro compound **24** augurs interesting synthetic applications towards the synthesis of various chiral tropane alkaloids.

1. Introduction

The compounds displaying X-azabicyclo[m.2.1]alkane framework (**1**) represent an

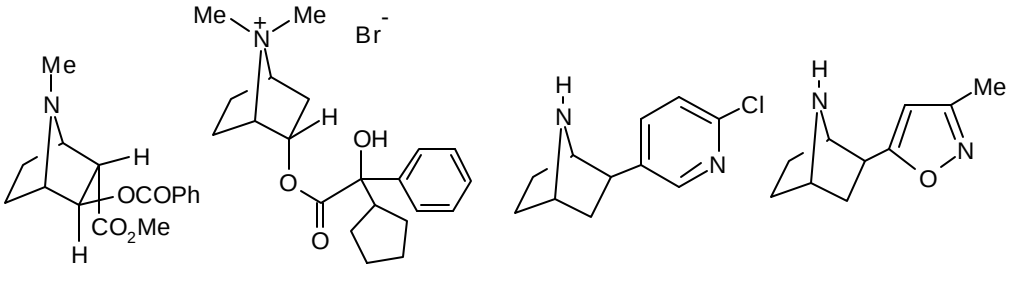
Fig.1



important class of ligands for the nicotinic acetylcholine receptors (nAChRs)[1] since they show accentuated binding affinity towards nAChRs. Therefore, the research activities in this area have led to the registration of several nAChRs ligands of these classes.[2] Some of the useful probes towards the binding with nAChRs are presented as follows:

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 (**5**) was shown to have local anesthetics activity.[3] The *endo*-2-(2-cyclopentyl-2-hydroxy-2-phenyl)-acetoxy-7-methyl-7-azabicyclo[2.2.1]heptane methobromide (**6**) was found to be a potent long acting anticholinergic bronchodilator agent.[4]

Fig.2

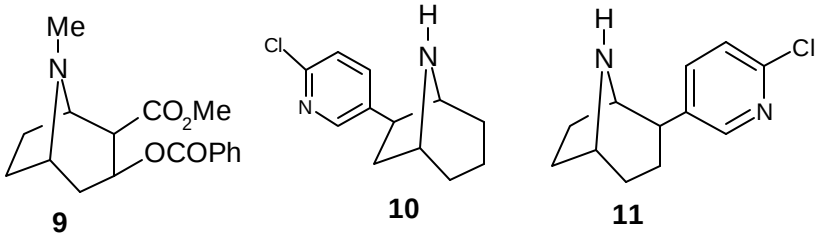


Epibatidine (**7**)[5] {exo-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane} has been found to be 200-500 times more potent than morphine and has been shown to exhibit non-opiod

analgesic activity.[6] Another synthetic analogue of **7**, epiboxidine (**8**)[7] having 7-azabicyclo [2.2.1]heptane framework with an isoxazole moiety attached at 2β-position showed significant binding affinity at nAChRs in comparison to **7**.

8-Azabicyclo[3.2.1]octane skeleton (**3**) is the basic structural feature of all tropane class of alkaloids.[8] Cocaine (**9**) and its synthetic analogues show high binding affinity to serotonin (5HT) and norepinephrine transporters.[9] Homoepibatidine (**10**) has been reported[10] to have comparable analgesic activity in the hot plate assay to that of **7**.[10] Recently, (1R, 2R, 5S)-2β-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane (**11**)[11] was reported to have lower nicotinic receptor binding affinity than **7**.

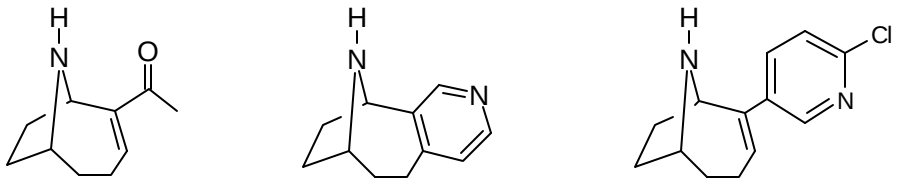
Fig. 3



9 **10** **11**

Anatoxin-a (**12**)[12] is the only representative alkaloid possessing the novel unusual structural feature 9-azabicyclo[4.2.1]nonane skeleton (**4**). It has been shown to have exquisite potency towards nAChR.[13] Few other ligands such as PHT (**13**)[14] and UB-165 (**14**)[15] having 9-azabicyclo[4.2.1]nonane ring systems were identified as potent nicotinic ligands and showed intermediate potency of anatoxin-a and epibatidine.

Fig. 4



12 **13** **14**

In view of the growing importance of these compounds as effective nAChR ligands, considerable synthetic efforts have been directed towards the development of new approaches to synthesize these molecules. As a consequence, diverse array of synthetic approaches have been devised to setup the individual basic skeleton of X-azabicyclo[m.2.1]alkane system.[16,17,18] Although few general synthetic strategies have appeared in literature[19] to build-up this basic skeleton, they are inappropriate to initiate a complex total synthesis.

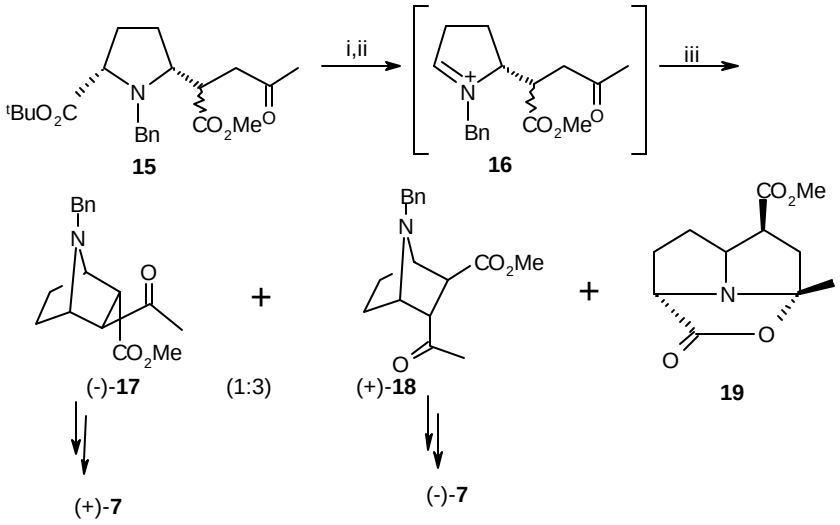
Remarkably, inspite of the growing interest prevailing towards the synthesis of these compounds, there remains a conspicuous absence of a general asymmetric synthetic approach to construct these basic skeletons. Although, this propensity has unveiled few admirable asymmetric approaches to construct the individual basic skeleton, no effort has been made to provide a general strategy for asymmetric construction of these structural frameworks. In this chapter we will highlight all the reported asymmetric approaches for understanding the current status of this research field.

1.1. Methodologies concerning with the asymmetric constructions of 7-azabicyclo[2.2.1] heptane skeleton (2):

Until recently, the construction of 7-azabicyclo[2.2.1]heptane ring system was a matter of academic interest since no naturally occurring compound was known containing this ring system. The synthesis of this particular skeleton (**2**) has seen strong revival since the structural elucidation of epibatidine (**7**). Some of the conceptually attractive asymmetric approaches for the construction of 7-azabicyclo[2.2.1]heptane skeleton are briefed below in this section. It may be noted that the approaches concerning with the construction of enantiopure 7-azabicyclo[2.2.1]heptane skeleton by resolution of racemic[20] compounds are not highlighted here.

Rapoport et al.[21] have introduced a novel "chiron" concept of decarboxylative/ iminium-ion cyclization of **16,** obtained from **15,** for the construction of enantiopure 7-azabicyclo[2.2.1] heptane **18** as shown below in Scheme 1.

Scheme 1

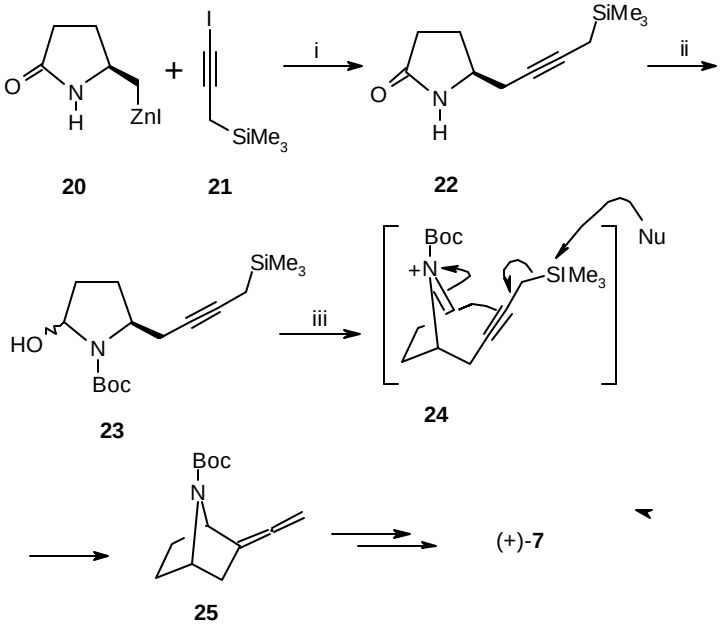


Reagents and conditions*: i) H^+/ H_2O; ii) $(COCl)_2$; iii) Ä, 73 %.*

However, the formation of regio- and diastereomers in the key cyclization step of this approach raises serious limitation of this strategy.

A somewhat similar approach[22] for the construction of enantiopure 7-azabicyclo[2.2.1]heptane (**25**) was described involving intramolecular iminium ion cyclization of **24**. The synthesis of iminium ion precursor **23** and its reaction is detailed in Scheme 2.

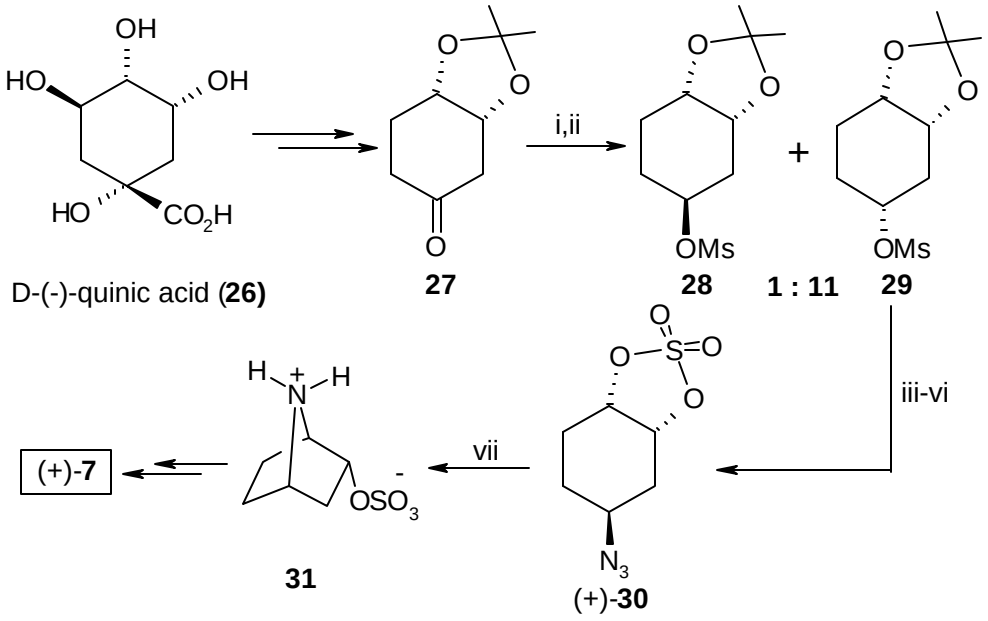
Scheme 2



Reagents and Conditions*: i) CuCN.2LiCl, 49 %; ii) a) $(Boc)_2O$, Et_3N, DAMP; b) DIBAL-H, THF, -78 ^oC, 1 h, 95 %; iii) HCO_2H, O ^oC to rt, 10 min.,74 %.*

Synthesis of optically pure 7-azabicyclo[2.2.1]heptane (**31**)[23] has also been achieved through a facile and regio-selective intramolecular nucleophilic ring opening of a chiral cyclic sulfate, **30,** derived from D-(-)-quinic acid (**26**) in a number of steps as shown in Scheme 3.

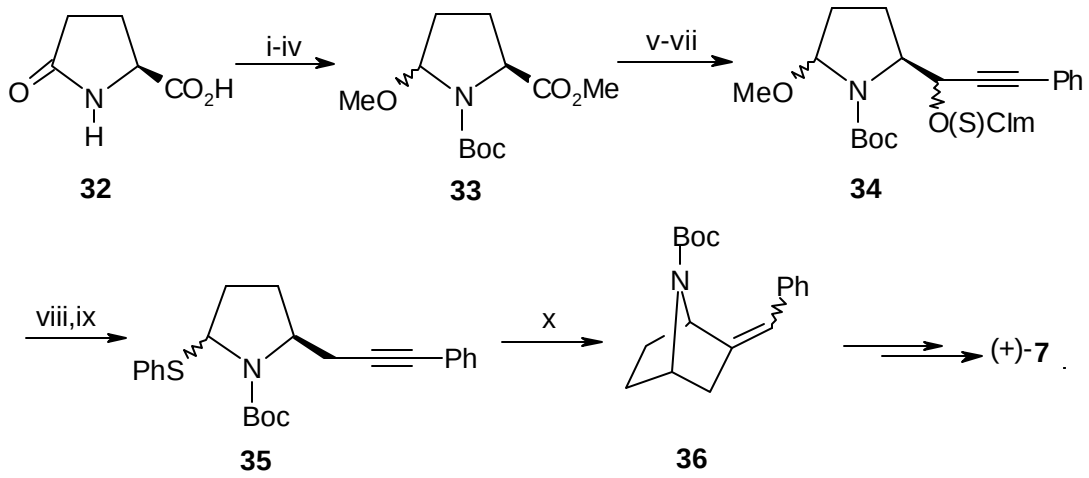
Scheme 3



Reagents and Conditions*: i) $NaBH_4$, 85 %; ii) MsCl, Et_3N, 86 %; iii) NaN_3, DMF; 80 ^oC, 24 h, 81 %; iv) 5 % HCl, 98 %; v) $SOCl_2$, Et_3N, DCM, 10 min, O ^oC, 78 %; vi) $NaIO_4$, $RuCl_3$ (Cat.), CCl_4, CH_3CN, H_2O, 1 h, 20 ^oC, 68 %; vii) H_2, Pd/C, THF / H_2O, 30 psi, 2 h, 92 %; vii) Conc. H_2SO_4 (cat.), H_2O, THF, 1 h, 90 ^oC then Na_2CO_3, 86 %.*

Clive et al[24] have introduced the concept of radical cyclization for the construction of **36** from phenyl thio acetylene **35**, obtained from *S*-pyroglutamic acid (**32**). The α-amino radical is generated by the homolytic cleavage of C-SPh bond using Bu_3SnH as a reagent (Scheme 4).

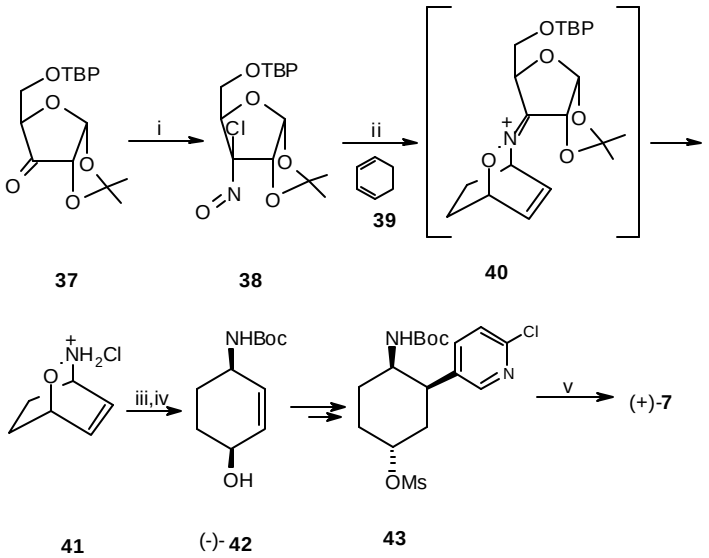
Scheme 4



Reagents and Conditions*: i) CH_2N_2, Et_2O, 98 %; ii) $(Boc)_2O$, DAMP, DCM, 90 %; iii) DIBAL-H, DCM, -78 °C, 89 %; iv) MeOH, $TsOH.H_2O$, 81 %; v) DIBAL-H, DCM, -78 °C, 73 %; vi) PhCCLi, THF, -78 °C, 90 %; vii) $Im_2C(S)$, DMAP, DCM, 77 %; viii) Bu_3SnH , AIBN, toluene, 80 °C, 76 %; ix) PhSH, DCM, TsOH.H2O, 80 %; x) Bu_3SnH, AIBN, toluene, 110 °C, 76 %.*

The intramolecular 1,4-transannular cyclization reaction of **43** has widely been used for the construction of 7-azabicyclo[2.2.1]heptane skeleton.[25] One such report[26]describes the asymmetric synthesis of compound **43** using auxiliary controlled hetero Diels-Alder reaction of an α-nitroso compound **38**, derived from D-xylose, with a cyclic diene **39** (>96 % ee).

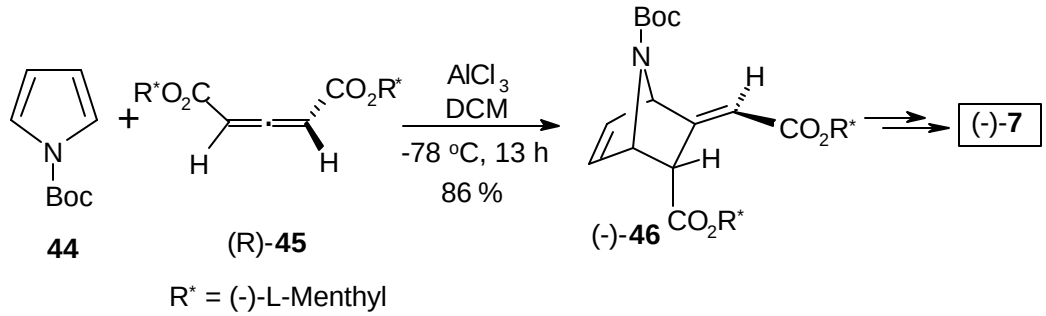
Scheme 5



Reagents and Conditions*: i) a) $NH_2OH.HCl$, $NaHCO_3$, $EtOH$-H_2O; b) Bu^tOCl, DCM, 69 %; ii)* ***39****, $CHCl_3$-Pr^iOH-H_2O (100:100:1), O ^oC, 94 %; iii) a) Zn, AcOH; b) $(Boc)_2O$, Na_2CO_3, acetone-methanol, 67 %; iv) BzCl, DAMP, pyridine, DCM, 87 %; v) a) CF_3CO_2H, H_2O, rt; b) CH_3CN, reflux, 85 %.*

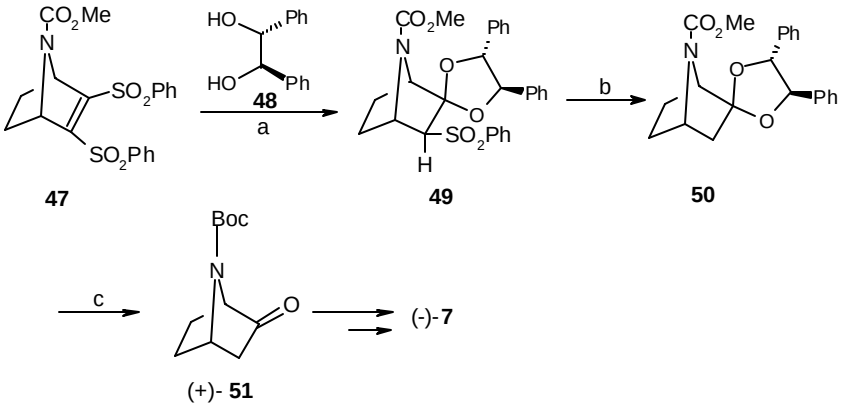
A very interesting approach has been adapted by Node et al[27] for the construction of enantiopure 7-azabicyclo[2.2.1]heptane **46** involving highly *endo*-selective asymmetric Diels-Alder reaction of a chiral allene **45** with N-Boc pyrrole (**44**). Chiral allene **45** (>98 % ee) was obtained by asymmetric transformation of desymmetric allene-1,3-dicarboxylate, through epimerization/crystallization with the assistance of a tertiary amine.

Scheme 6



Very recently, the asymmetric desymmetrization strategy of **47** has been utilized by our group to obtain enantio-pure 7-azabicyclo[2.2.1]hept-2-one **51** in the formal synthesis of epibatidine (**7**).[28] The easy access of starting material, **47**, and high enantioselectivity (>99 % ee) observed in the desymmetrization step have made this approach a unique for initiating a multi-step total synthesis.

Scheme 7



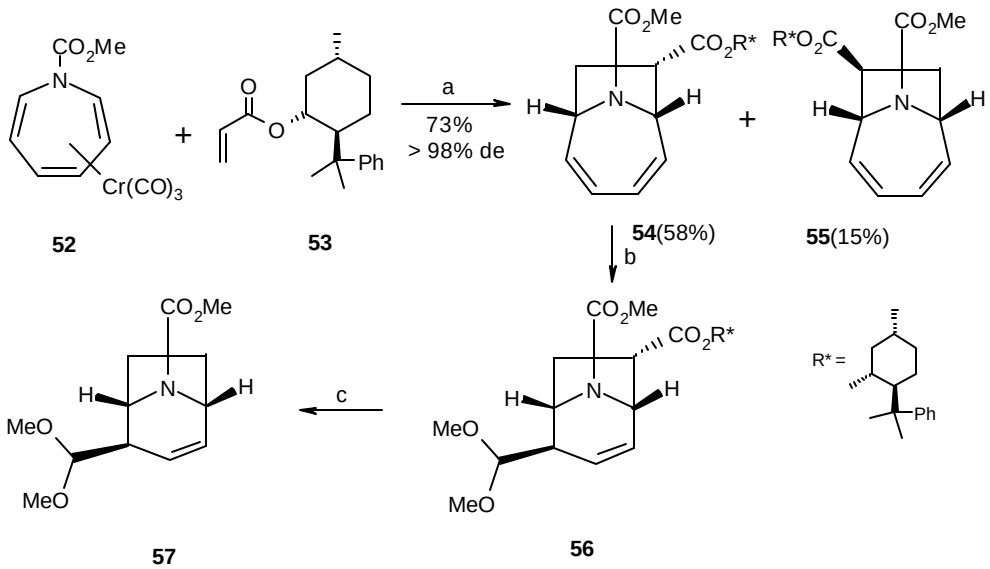
Reagents and Conditions*: a)* ***48****, NaH, THF, 85 %; b) Na-Hg 6 %, $NaH_2PO_4.H_2O$, 95 %; c) I) Pd/C, H_2 (55 psi), EtOAc-EtOH, 10 h; ii) TMSCl, NaI, MeCN; iii) $(Boc)_2O$, Et_3N, DCM, 92 %.*

1.2 Methodologies concerning with the asymmetric construction of 8-azabicyclo[3.2.1] octane skeleton (3):

8-Azabicyclo[3.2.1]octane (**3**), the basic skeleton of all tropane class of alkaloids, comprises of about 200 natural products and several of them have been found to possess potent pharmacological activity. The profound behavioral and neuronal reinforcing properties of these alkaloids have attracted serious attention of synthetic chemists. Below are presented some of the important asymmetric approaches for the construction of 8-azabicyclo[3.2.1]octane framework.

Asymmetric induction during transition metal promoted higher order cycloadditions have represented a potentially effective method for the construction of enantioenriched 8-azabicyclo[3.2.1]octane skeleton. Rigby et al.[29] have shown that auxiliary based induction during Cr(O)-mediated [4π +2π] cycloaddition of azepine derivatives **52** provides direct access to chiral homotropane products **54** which on subsequent ring contraction provides optically active 8-azabicyclo[3.2.1]octane **56.**

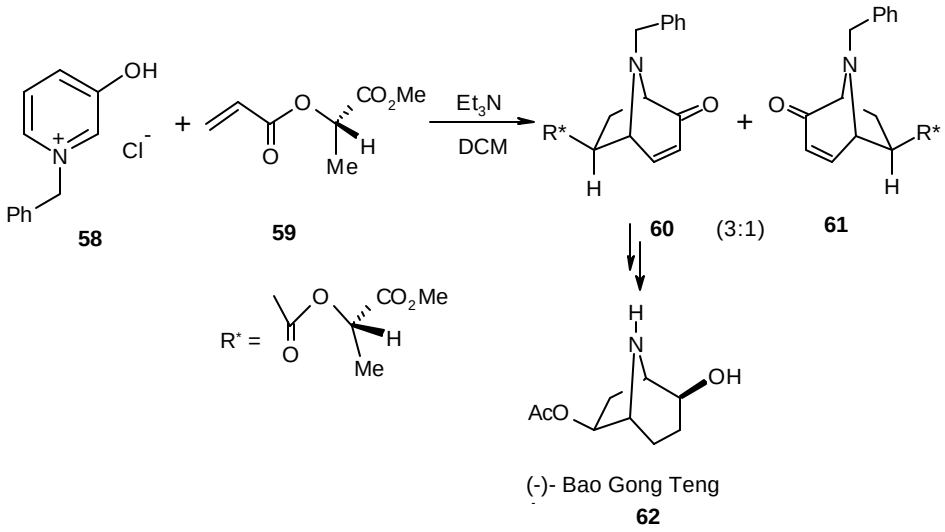
Scheme 8



***Reagents and Conditions**: a) hí, 73 %; b) $Tl(ONO)_2.3H_2O$, MeOH, 85 %; c) i) $LiOH.H_2O$, MeOH / H_2O, 84 %; ii) $ClCO_2Bu^i$, N-Methylmorpholine, Na-Salt of N-hydroxypyridine-2-thione, Et_3N, Bu^tSH, hí, 49 %.*

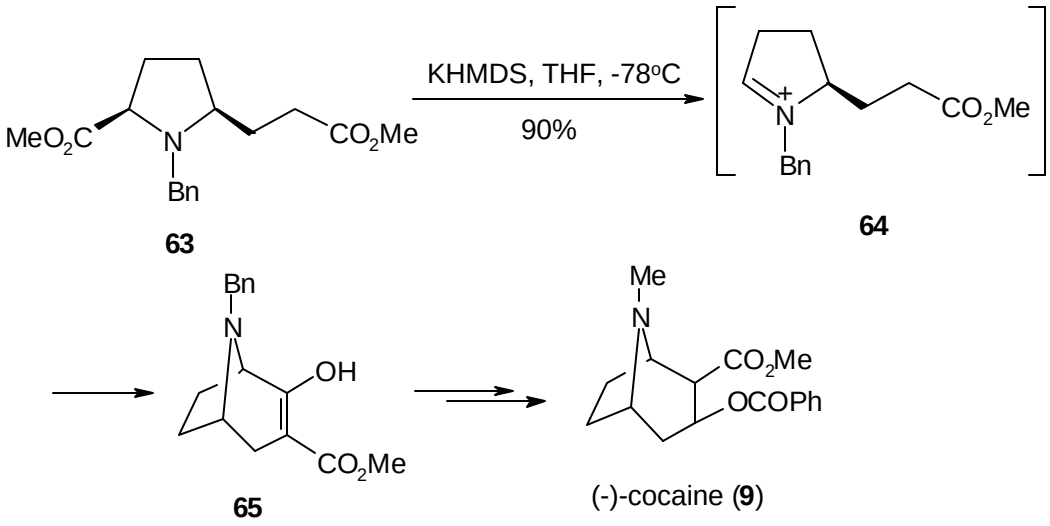
The basic skeleton 8-azabicyclo[3.2.1]octane (**60**) has been constructed by the auxiliary controlled 1,3-dipolar cycloaddition of pyridinium based betaine **58** and **59** in the synthesis of Bao Gong Teng A (**62**).[30] This 1,3-dipolar cycloaddition reaction occurred at the *re*-face of **59** giving rise to a very good *exo*-selectivity (*exo*:*endo* = 98:2). The lack of any appreciable diastereoselectivity (de<76 %) places serious limitation of this approach.

Scheme 9



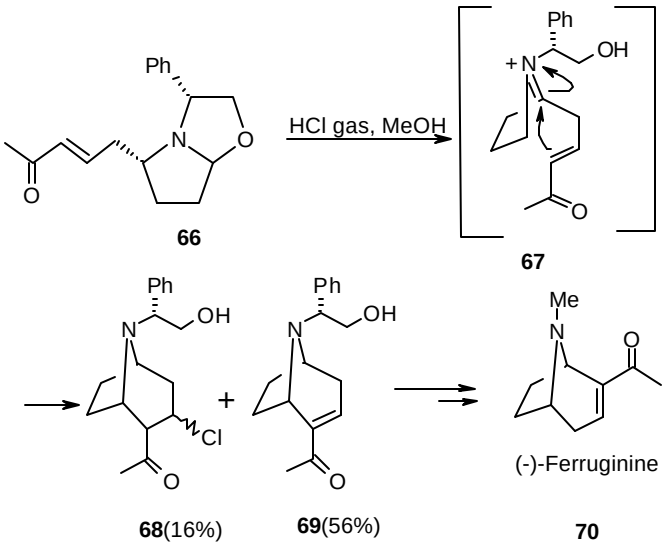
A more classical approach for the construction of 8-azabicyclo[3.2.1]octane skeleton **65,** pioneered by Rapoport[31], involves the transannular cyclization of **64**. However, the formation of regio- and diastereomers inherent with this cyclization places serious limitations of this approach.

Scheme 10



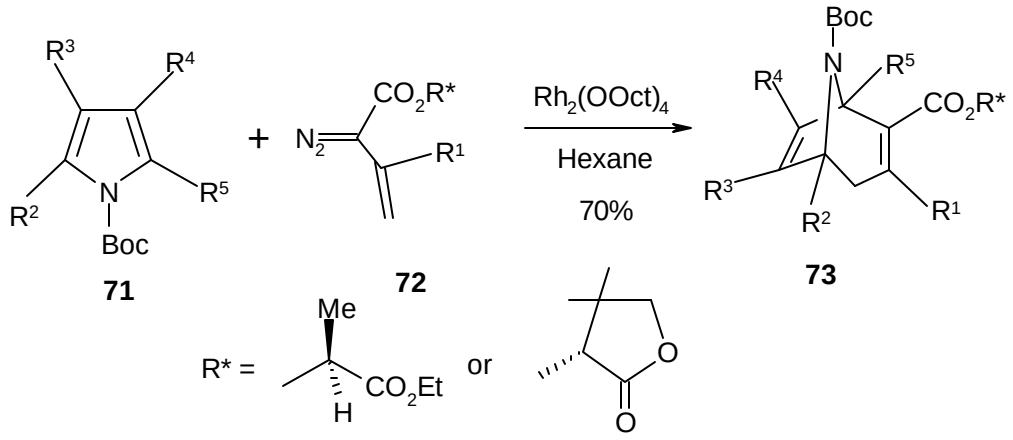
A somewhat similar approach[32] for the construction of enantiopure 8-azabicyclo[3.2.1]octane **69** involves a stereospecific intramolecular cyclization of α,β-unsaturated ketone onto an iminium ion intermediate **67**. The low yield of the product and the formation of side product **68** limits the applicability of this approach.

Scheme 11



Another conceptually attractive approach for the construction of 8-azabicyclo[3.2.1] octane **73** involves auxiliary controlled [4+3]-annulation reaction of vinyl diazomethane and pyrroles.[33] This reaction is believed to occur by tandem cyclopropanation/Cope rearrangement. Despite the obvious advantage of constructing the basic skeleton in single step operation, this approach suffers from low yield (<70 %) and poor diastereoselectivity (<75 %).

Scheme 12



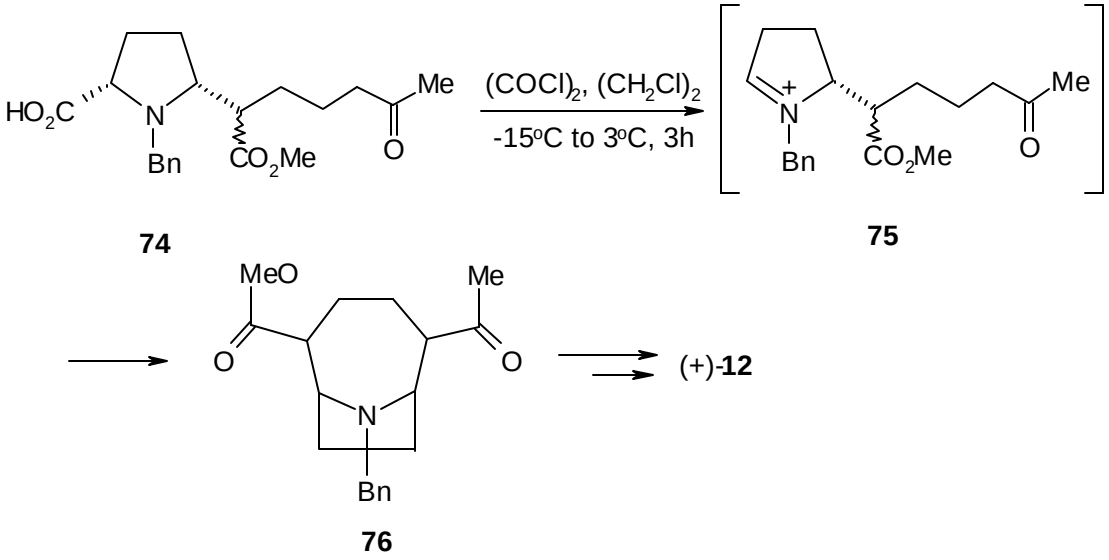
1.3 Methodologies concerning with asymmetric synthesis of 9-azabicyclo[4.2.1]nonane skeleton 4 :

Due to the unusual structural feature, the 9-azabicyclo[4.2.1]skeleton (**4**) is barely found in naturally occurring alkaloids. The only member of this class, Anatoxin-a (**12**), is known until recently. Owing to its important pharmacological probe and the only naturally occurring member of this class, the synthetic approaches developed for the construction of this basic skeleton were aimed at the synthesis of this novel alkaloid, though asymmetric approaches are relatively few**.**

The asymmetric approaches leading to the construction of enantiopure 9-azabicyclo[4.2.1]nonane skeleton are mostly concerned with the intramolecular cyclization of iminium ion. They differ significantly in the preparation of substituted pyrrolidine precursors and in overall yield for the construction of this basic skeleton. Rapoport et al[34] have made significant contribution in this field using the same concept of intramolecular iminium cation cyclization for the construction of enantiopure 9-azabicyclo [4.2.1]nonane

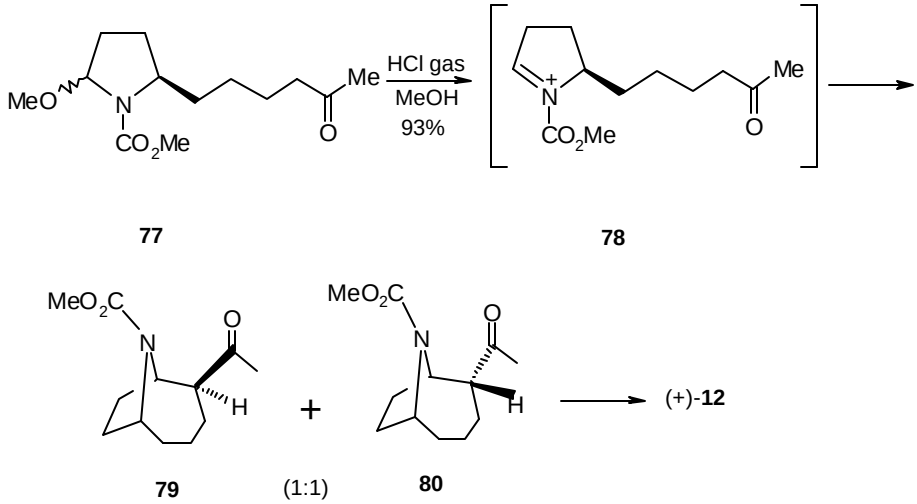
skeleton. The first asymmetric synthesis of anatoxin-a was reported by this group where the intermediate iminium ion **75**, obtained from **74**, undergoes intramolecular cyclization to give enantiopure 9-azabicyclo[4.2.1]nonane **76**.

Scheme 13



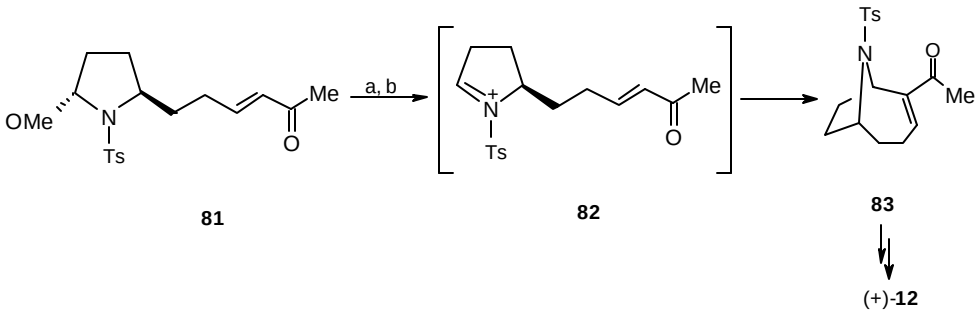
A similar approach for the construction of 9-azabicyclo[4.2.1]nonane (**80**) was forwarded by Skringar et al[35] where the intermediacy of acyl iminium ion **78** for the formation of C-C bonds at both C-2 and C-5 of substituted pyrrolidine precursor **77** was utilized (Scheme 14).

Scheme 14



In another variation, the construction of optically pure 9-azabicyclo[4.2.1]nonane **83** was achieved via a tosyl iminium ion **82**, conceptually similar to that described above.[36]

Scheme 15



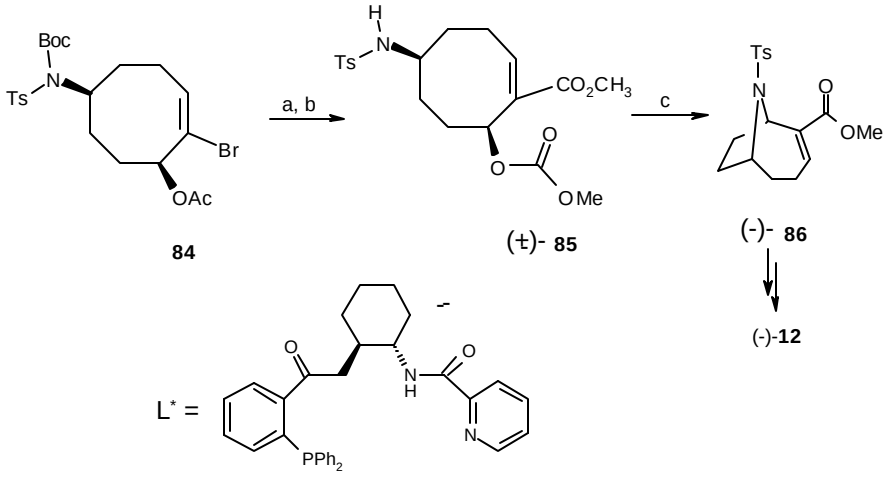
81 **82** **83**

(+)-**12**

Reagents and Conditions*: a) HCl, MeOH, DCM, -78 °C; b) DBU, toluene, reflux, 67 %.*

The synthetic routes that provide optically pure anatoxin-a, almost all utilize a starting material from the "Chiral pool". The introduction of chirality by an asymmetric catalytic process has been recorded for the construction of enantiopure 9-azabicyclo[4.2.1] nonane skeleton.[37] The high enantioselectivity(>98 %) achieved in the palladium-catalyzed asymmetric cyclization of **85** to 9-azabicyclo[4.2.1]nonane **86** was the concept involved in the successful synthesis of (-)-anatoxin-a.

Scheme 16



84 (±)- **85** (-)- **86**

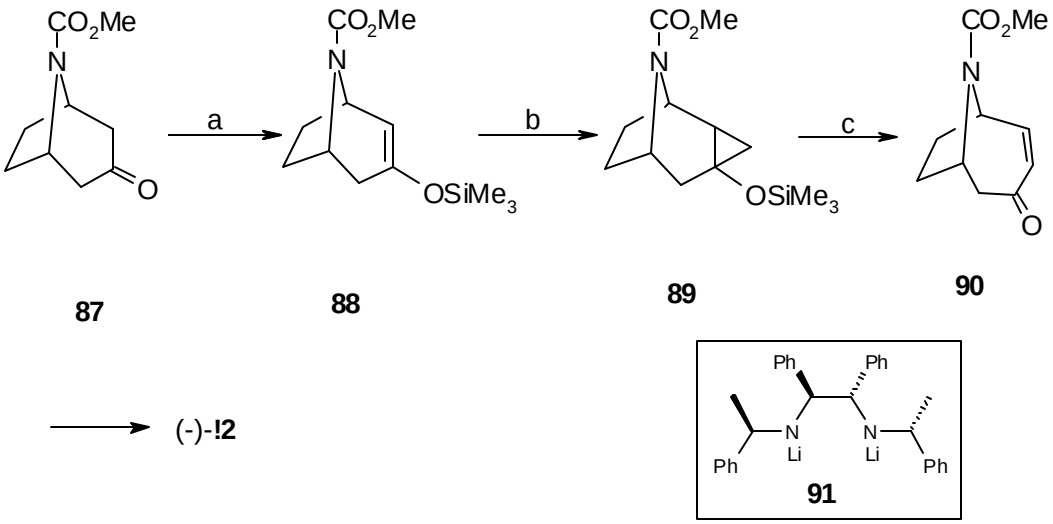
(-)-**12**

***Reagents and Conditions**: a) CO, CH_3OH, 5 % $(PPh_3)_4Pd$, Et_3N, DMPU, 100 ^oC, 70 %; b) i) K_2CO_3, CH_3OH, rt; ii) n-BuLi, $ClCO_2CH_3$, THF, -78 ^oC; iii) CF_3CO_2H, DCM, rt, 70 %; c) 2.5 % (dba)$_3$Pd.$CHCl_3$, 7.5 % L^*, 96 %, 98 % ee.*

A conceptually attractive strategy for the construction of enantiopure 9-azabicyclo[4.2.1]nonane skeleton (**4**) relies on the concept of asymmetric desymmetrization of a meso-ketone by enantioselective enolization using a chiral lithium amide base.

Simpkins et al[38] have first used this concept in the enantioselective enolization of **87** using **91**. Taking advantage of the high enantioselectivity (>85 % ee) associated with this process, compound **88** on subsequent cyclopropanation/ring expansion reaction gave enantiopure 9-azabicyclo[4.2.1]nonane **90**.

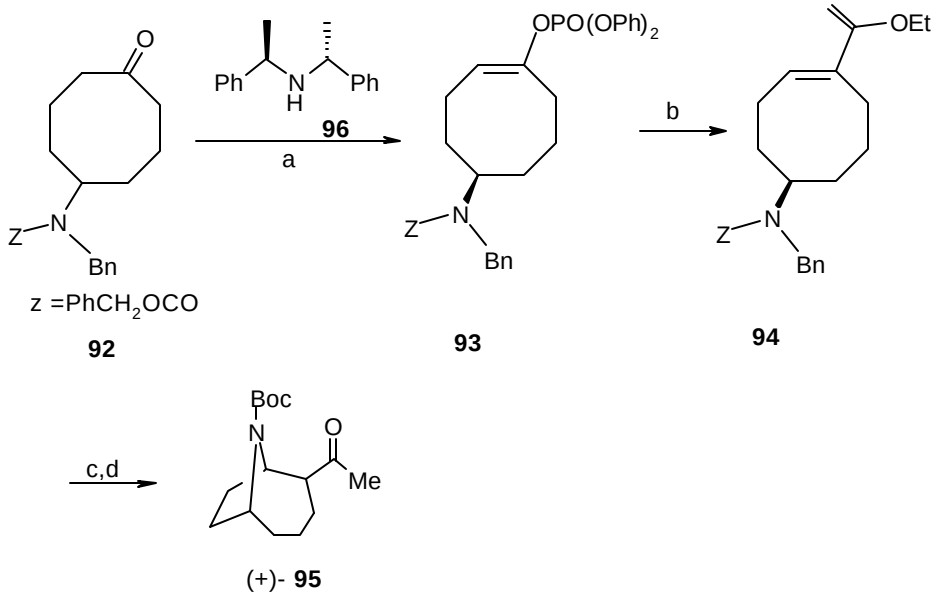
Scheme 17



***Reagents and Conditions**: a) **91**, TMSCl, THF, 90 %, 92 % ee; b) Et_2Zn, ICH_2Cl, $(CH_2Cl)_2$, 99 %; c) $FeCl_3$, DMF, NaOAc, MeOH, 71 %.*

In another example, the high enantioselectivity (89% *ee*) was achieved in the enantioselective enolization of **92** using **96** as a chiral base setting a rare example of asymmetric desymmetrization of an eight membered ring ketone.[39] Compound **94** on subsequent novel cascade reaction entailing unmasking the enone moiety with concomitant nitrogen deprotection and intramolecular conjugate addition gave enantiopure 9-azabicyclo [4.2.1]nonane **95**.

Scheme 18



***Reagents and Conditions**: a) (R,R)-**96** .HCl, n-BuLi (2 equiv), $(PhO)_2POCl$, THF, -100 °C, 89 %, 89 % ee,; b) $[Pd(PPh_3)_4]$, $CH_2=CH(OEt)SnBu_3$, LiCl, THF, Ä, 84 %; c) 45 % HBr in AcOH, 95 %; d) Pd/C, H_2 (50 psi), MeOH, $(Boc)_2O$, 89 %.*

CONCLUSION

From the above literature survey, it is evident that there has been no general asymmetric route for the construction of X-azabicyclo[m.2.1] alkane skeleton. A close look at the structures of these compounds reveals the presence of α,α'-fused pyrrolidine moiety to a cyclic amine. Since [3+2] cycloaddition of azomethine ylides with a suitable dipolarophile is one of the most powerful strategies for the construction of pyrrolidine ring system, the asymmetric version of this concept in the application of natural product synthesis possessing this basic skeleton will be discussed in the proceeding chapters.

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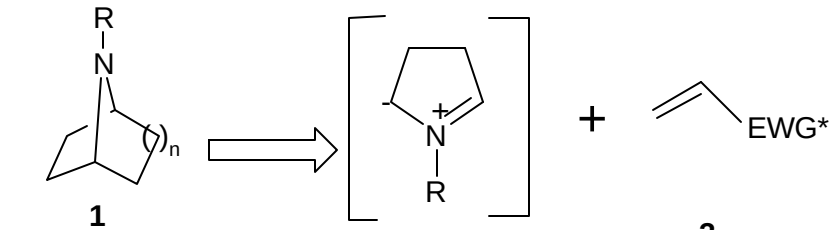
Introduction

Asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides (AMYs) to a variety of alkenes has emerged as one of the most powerful strategy for the construction of enantiopure pyrrolidine ring system.[1] A close look at the structure of the compounds possessing X-azabicyclo[m.2.1]alkane framework **1** reveals the presence of α,α′-fused pyrrolidine ring system.

Scheme 1



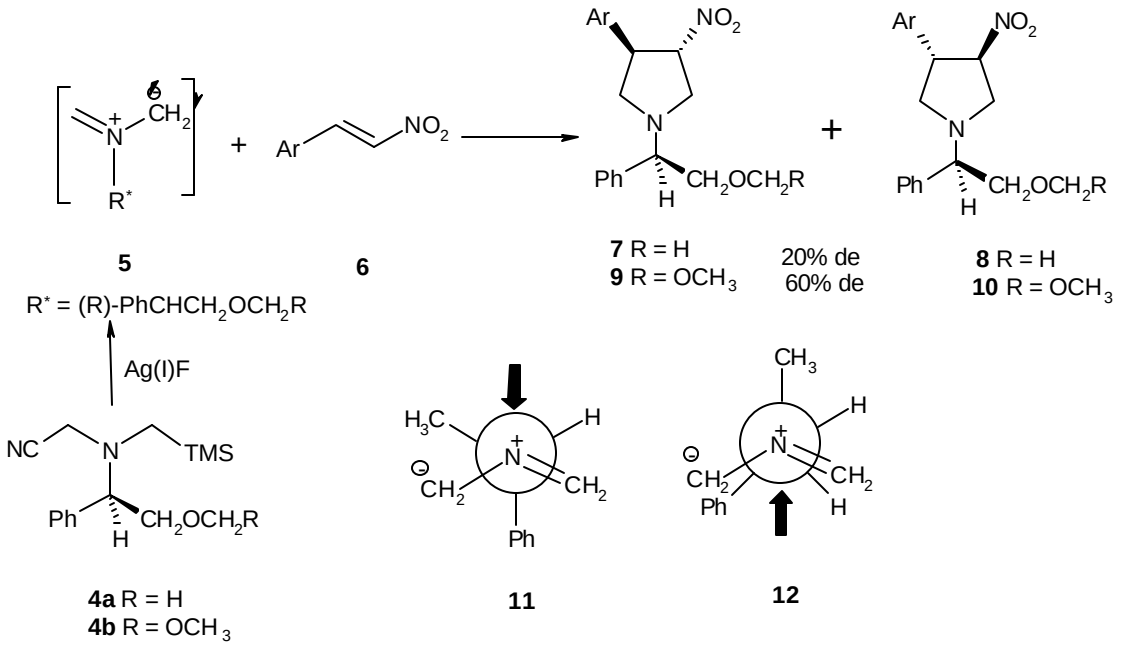
The quest for the development of a new general asymmetric route for the construction of enantiopure X-azabicyclo[m.2.1]alkane skeleton led us to envision an unprecedented asymmetric [3+2]-cycloaddition strategy involving cyclic AMYs and a suitable chiral dipolarophile (Scheme 1). Before going into the details of our own work, it would be appropriate to discuss some of the existing approaches pertaining to the asymmetric [3+2]-cycloaddition of AMYs to alkenes in order to evaluate of our approach.

Despite potentially great utility in the synthesis of alkaloids, asymmetric 1,3-dipolar cycloadditions involving AMYs has been the subject of few reports. There are three decisive factors which need to be considered while evaluating the utility of asymmetric 1,3-dipolar cycloadditions : a) chiral 1,3-dipoles[2] b) chiral dipolarophiles[3] c) chiral catalysts[4].

The asymmetric 1,3-dipolar cycloaddition reactions involving chiral AMYs and chiral dipolarophiles (acyclic and cyclic) have been studied extensively. In 1985, Padwa *et al.*[5] reported the first asymmetric 1,3-dipolar cycloaddition of chiral acyclic non-stabilized AMYs with alkenes leading to optically active pyrrolidines. In the 1,3-dipolar cycloaddition of the AMY precursor **4a** with 1-nitro-2-[3,4-(methylenedioxy)-phenyl]ethylene **(6)** the product **7**

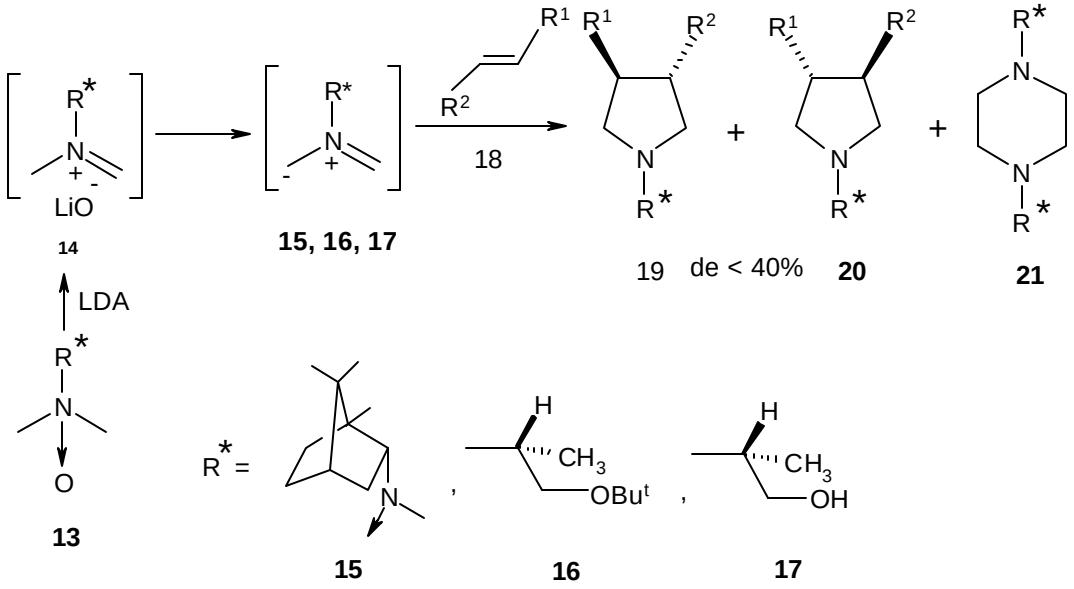
was obtained with 20 % de, while **4b** gave a de of 60 %. To account for the diastereoselectivity, two conformations of the AMY were considered (viz.**11** and **12**). The approach of the alkene towards **11** is from the face of the AMY *anti* to the phenyl group, while *anti* attack in **12** results from an approach of the alkene towards the opposite face of the dipole. It was argued that since the groups bound to the nitrogen atom in the AMY are similar both in size and electronic make-up, the diastereoselectivity excess was small.

Scheme 2



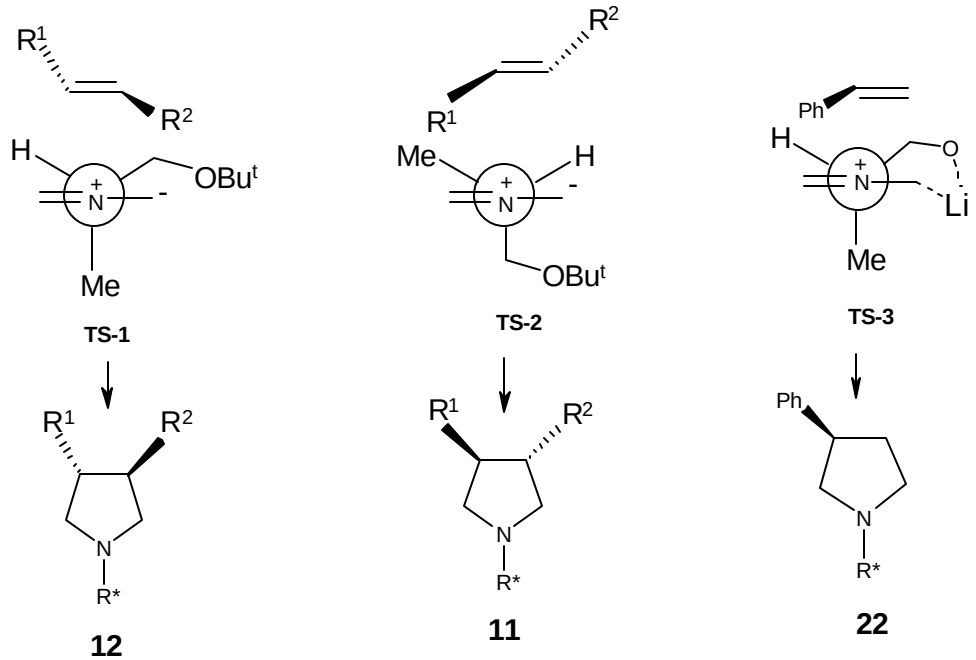
Much later, it was shown that cycloadditions of chiral non-stabilized AMYs (**15,16**,**17**), generated from corresponding amine oxides **13** by treatment with LDA, with olefins **18** gave poor facial selectivity (de<40 %) along with the low yields (35-45 %) of pyrrolidines (**19, 20**). The low chemical yield of pyrrolidines was due to the competitive dimerization of AMYs to the corresponding piperizines **21**.[6]

Scheme 3



The poor diastereoselectivity was explained by considering the fact that the dipolarophile can approach *anti* to two large groups in the ylide (CH_2OBu^t and Me) leading to two diastereomeric transition states **TS-1** and **TS-2** of close energy (Fig.1).

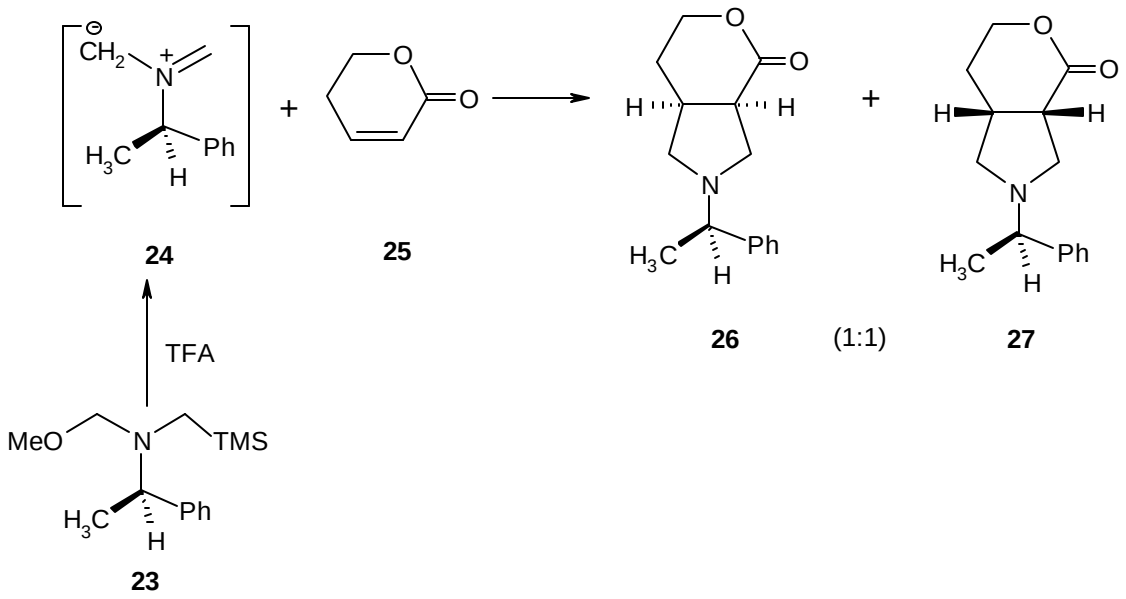
Fig.1



Interestingly, in the reaction between stilbene and AMY **17** good diastereoselectivity (de 60 %) was observed at the cost of yield. The hydroxyl function appears to be of importance in the asymmetric induction. The increased selectivity could be due to a better diastereofacial control resulting from the chelation between lithium alkoxide and dipole terminii, so that the transition state (**TS-3**) in which the preferred configuration holds the largest group *anti* to the dipolarophile is rigid.

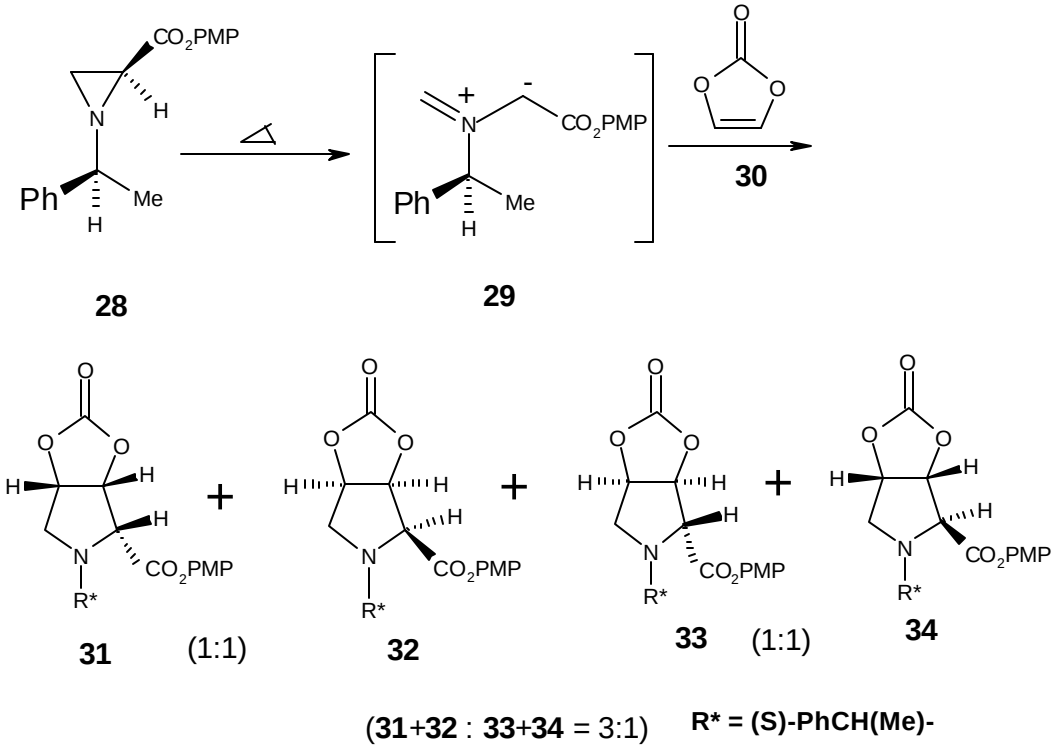
It has also been shown that 1,3-dipolar cycloaddition of chiral non-stabilised AMY **24**, derived from **23**, undergoes cycloaddition with cyclic dipolarophile **25** with no facial selectivity resulting a 1:1 mixture of diastereomers (**26** & **27**).[7]

Scheme-4



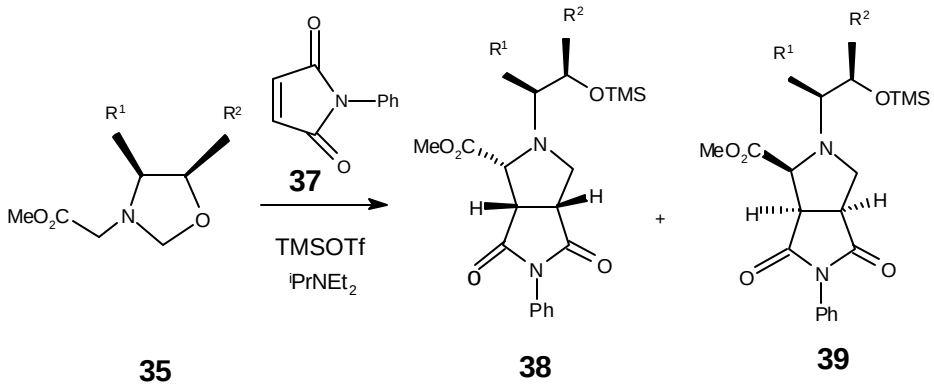
Even chiral stabilized AMY **29**, generated from aziridine **28** under thermal condition, adds to cyclic dipolarophile **30** to give *exo* (**31** & **33)** and *endo* (**32 & 34**) isomers in 3:1 ratio with very poor diastereoselectivity (**31** / **32** $\simeq$ 1 and **33** / **34** $\simeq$ 1).[8]

Scheme 5



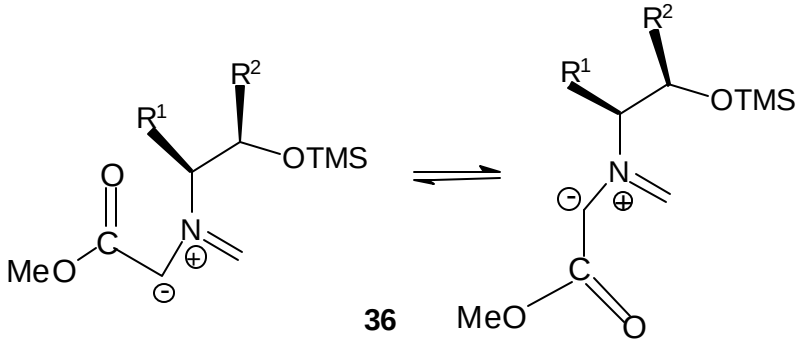
Another type of chiral stabilized AMY **36,** generated from **35**, reacts readily with N-phenyl maleimide (**37**) to give two *exo*- isomers (**38** & **39**) in a (1:1) diastereomeric ratio (Scheme 6).[9]

Scheme 6



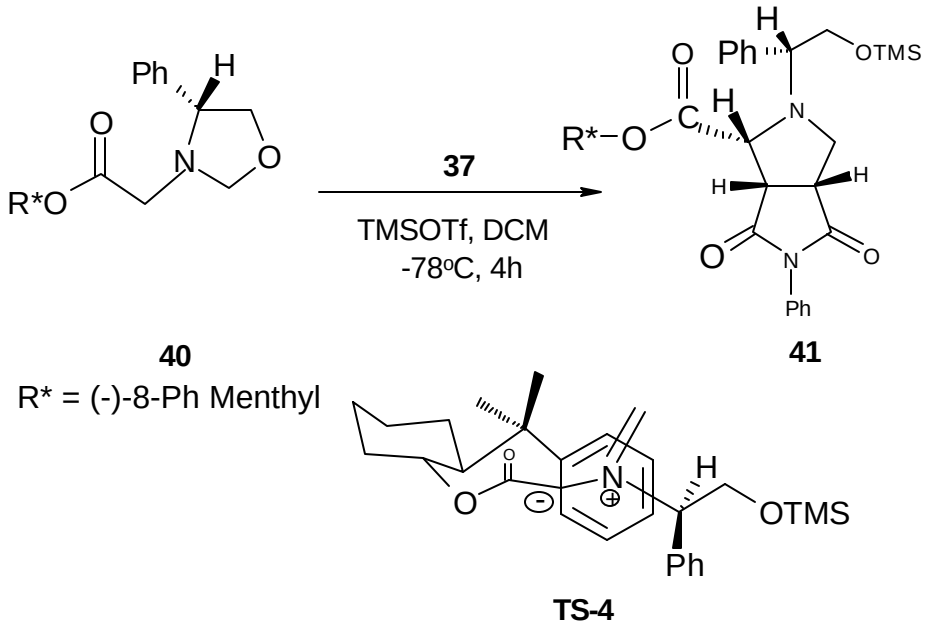
The reason for the poor asymmetric induction is explained due to the equilibrium between two equally probable conformers of the ylide **36** as shown in Fig**.** 2.

Fig. 2



The stereochemistry of the products was explained by an *exo* attack on each side of the U-shaped ylide **36** without facial selectivity. This low diastereofacial selectivity was not improved by the modification of substituents R^1 and R^2 on the oxazolidine ring of **35**. A possible explanation for this observation is that during the *exo* mode of cycloaddition, the chiral center cannot interact with the dipolarophile because of its remote position. The diastereoselectivity was improved by incorporating a chiral group in the ester moiety. Thus, oxazolidine **40**, derived from (-)-8-phenylmenthol, was reacted with *N*-phenylmalimide to give single *exo* cycloadduct (**41**).[9c] The high facial selectivity of this cycloaddition indicates that one face of the ylide is completely masked by the phenyl ring of the 8-phenyl menthyl group and the stereochemistry of the product implicates an *exo* transition state (**TS-4**). To explain the stereochemical course of the reaction, the transition state model **TS-4** was proposed (Scheme 7).

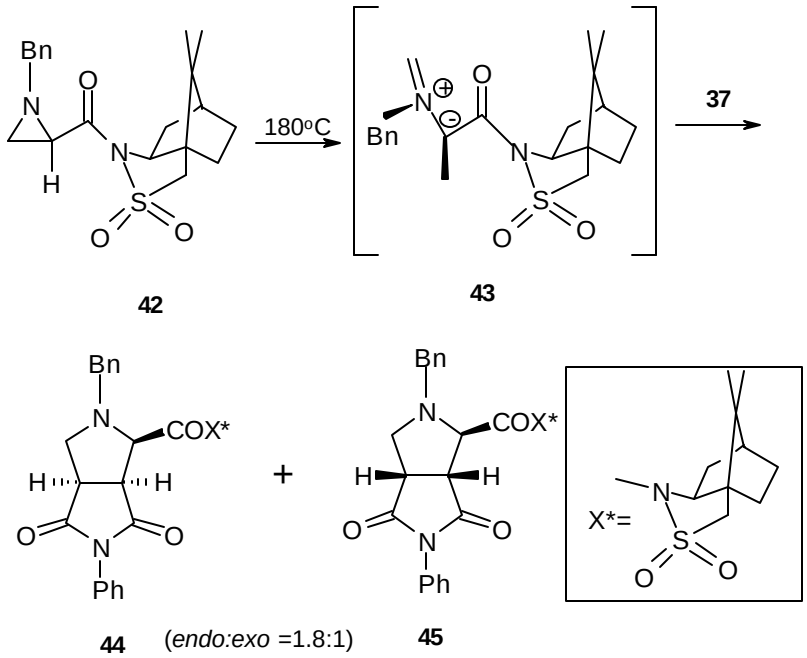
Scheme 7



The first chiral center borne by the nitrogen atom forces the exclusive *exo* addition of the dipolarophile while the second chiral center on the ester group permits diastereofacial selectivity.

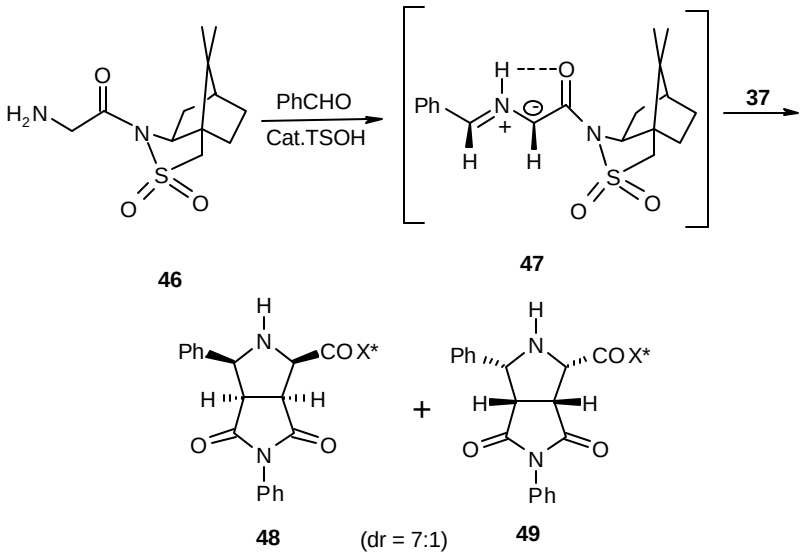
Garner *et al.*[10] have shown that chiral stabilized AMY **43** obtained by thermolysis of aziridines **42**, undergoes 1,3-dipolar cycloaddition with N-phenylmaleimide **37** in good chemical yield (73 %). Though the facial selectivity (*de* 82 %) in this experiment was good but the poor *endo/exo* selectivity (*endo: exo* = 1.8:1) was disappointing.

Scheme 8



They have also shown that the dipolar cycloaddition of the NH-azomethine ylide **47**, generated *via* the "imine tautomerization route", gives only *endo* cycloadducts (**48** & **49**) with decreased facial selectivity (dr = 7:1) (Scheme 9).

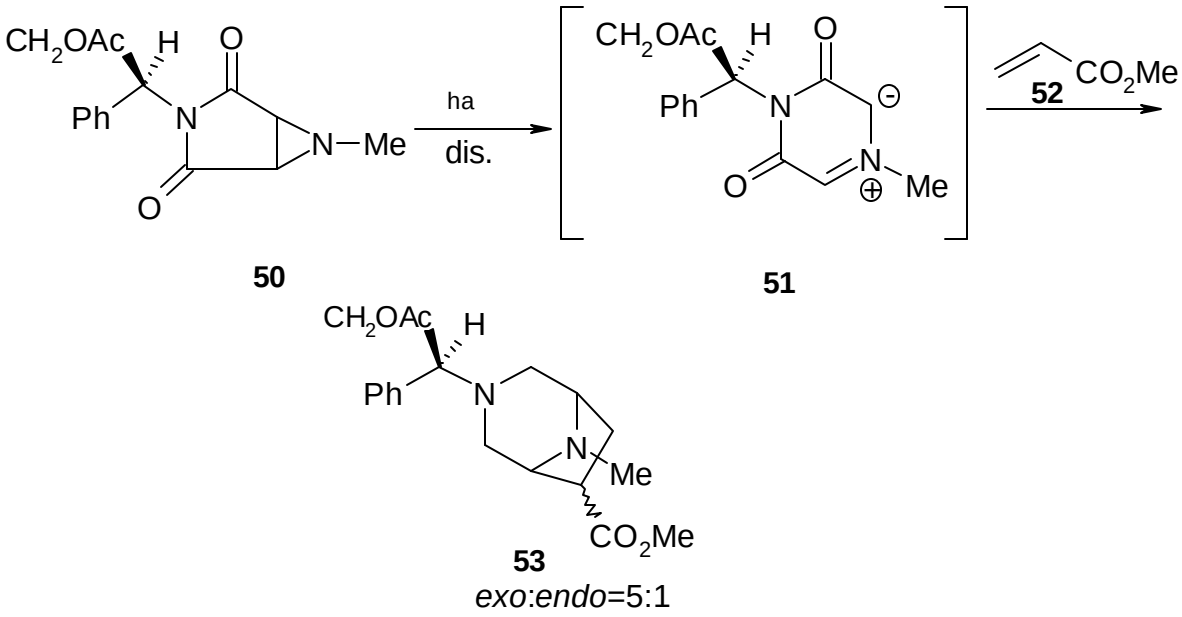
Scheme 9



It should be noted that the facial selectivity of AMYs (**43** & **47**) is controlled by bulky camphor sultam moiety.

Identical to asymmetric 1,3-dipolar cycloaddition reactions involving chiral acyclic AMY and acyclic dipolarophile, the dipolar cycloadditions of chiral cyclic AMYs with acyclic dipolarophile are also attempted. In fact, the later cycloadditions are more encouraging as far as diastereoselectivity is concerned. Chiral aziridines have also been used as precursors for cyclic azomethine ylides in the asymmetric 1,3-dipolar cycloaddition of acyclic dipolarophile. Photolysis of the aziridine **50** produces chiral stabilized AMY **51** which was found to add smoothly to methyl acrylate **52** (Scheme 10).[11] The 1,3-dipolar cycloaddition proceeded with little or no de but this was not really surprising as the chiral center in **51** is somewhat remote from the reacting centers of the AMY.

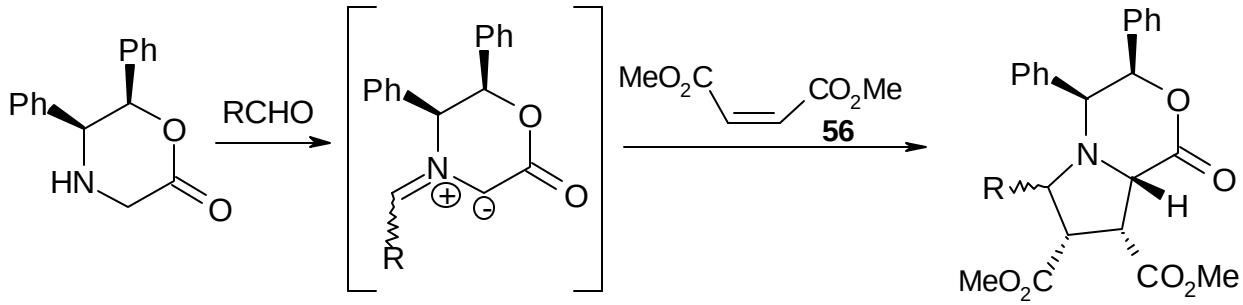
Scheme 10



The selectivity in the cycloadditions of azomethine ylides **55,** derived from (5S, 6R)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxarin-2-one (**54**) and various aldehydes, with dimethyl maleate **56** have been found to depend on the electronic nature of the aldehydes (Scheme 11).[12] For example, in the case of higher aliphatic and aromatic aldehydes the *endo* selectivity

was found to be excellent while the stereoselectivity at the C-7 position of **57,** the carbon to which the aldehyde substituent is bound, was generally low due to the *syn-anti* interconversion of the R substituent in **55**. However, an exception to this observation was found by using isobutyraldehyde where a single diastereomer was obtained.

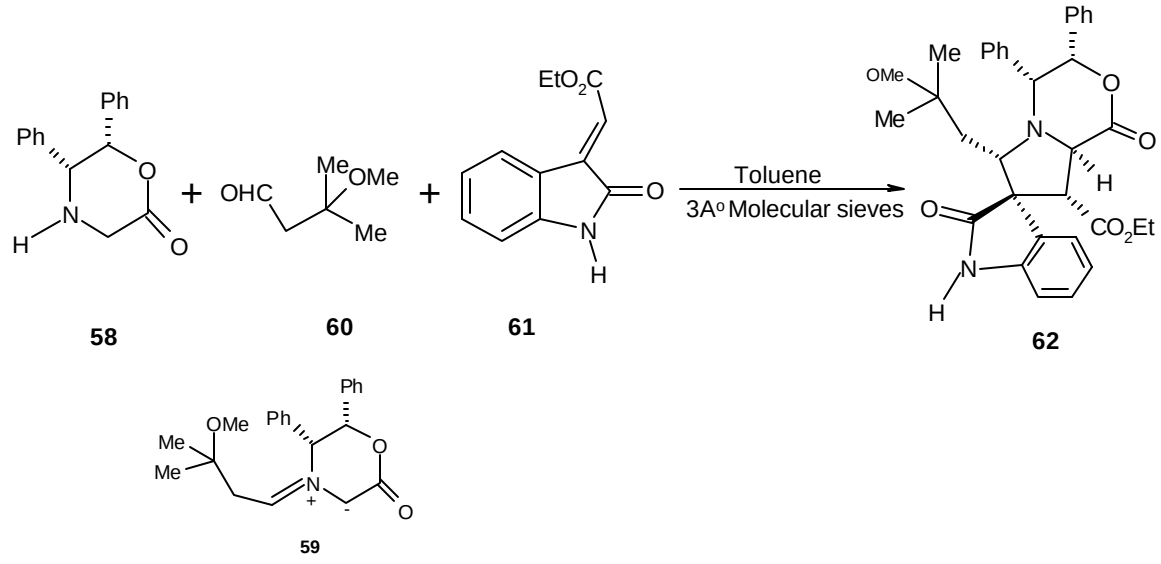
Scheme 11



54 **55** **57**

Williams *et al.*[13] have extended this concept of asymmetric 1,3-dipolar cycloaddition by utilizing AMY **59** with a cyclic dipolarophile **61** to observe a high degree of *endo* specificity to give only one diastereomer **62 (**Scheme 12**)**.

Scheme 12



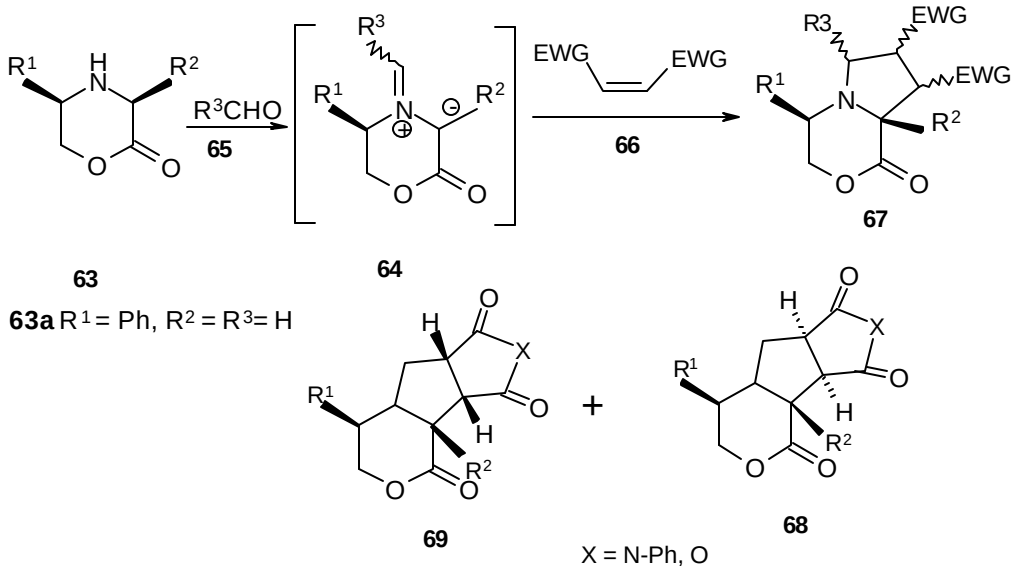
58 **60** **61** **62**

59

The cycloaddition of chiral AMY **64** with maleimides is reported to give both *endo*-cycloadducts **69** as well as *exo* cycloadduct albeit the former being obtained in excess. However, an interesting observation was made during the cycloaddition of **64** with maleic

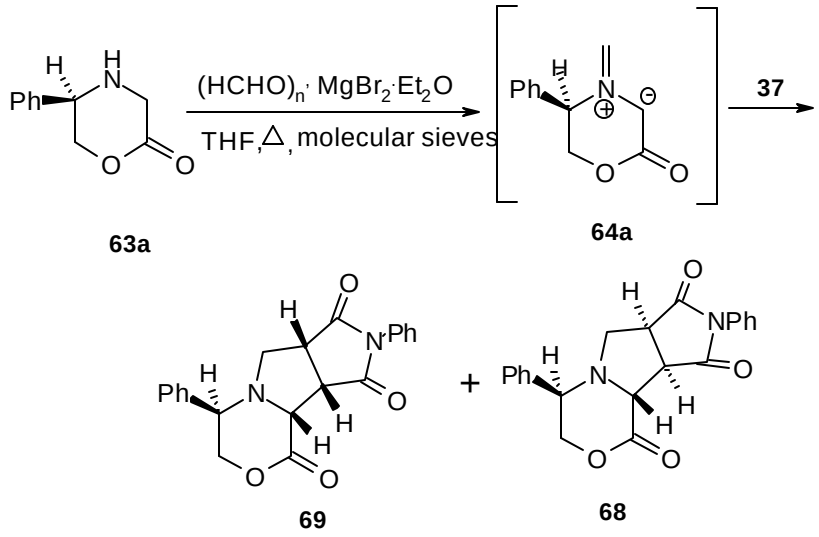
anhydride where the formation of endo isomer was observed. No explanation was provided to this unexpected observation.

Scheme 13



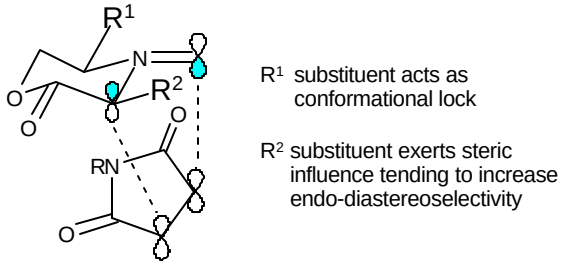
It was also observed that the cycloaddition in the presence of a Lewis acid such as $MgBr_2.Et_2O$ leads to an improvement of the yield of the cycloadduct; however, the diastereo- and regioselectivities are reversed in comparison to the corresponding uncatalyzed reactions (Scheme14).[14]

Scheme 14



The presence of Lewis acid was proposed to change the interaction between the AMY **64a** and the alkene **37** from a dominant HOMO dipole – LUMO alkene interaction to LUMO dipole – HOMO alkene interaction, but no thorough investigations have been performed to support this argument. The suggested FMO interaction between the AMY **64a** and maleimide leading to the *endo* diastereomer **69** is presented in Fig.3**.**

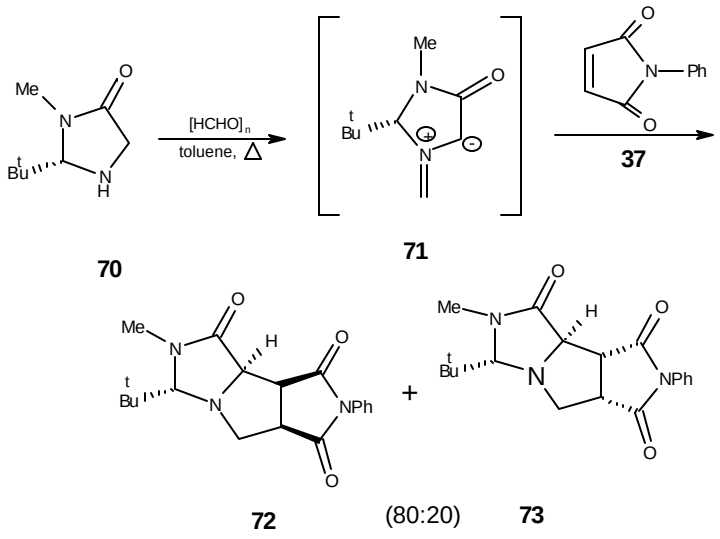
Fig. 3



Molorey *et al.*[15] have extended this observation further by reacting **64** (R^3 = H) with a variety of unactivated alkenes and alkenes having an electron withdrawing group (EWG) to prepare various chiral functionalized protein derivatives.

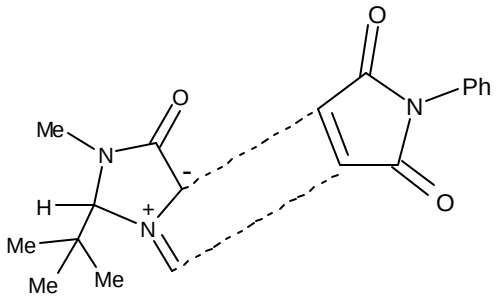
Other cyclic chiral AMYs **71**, derived from 2-(tert-butyl)-3-imidazolidin-4-one (**70**), have also been tested as chiral controller in 1,3-dipolar cycloadditions.

Scheme 15



The cycloaddition of AMY **71** with a series of different electron-deficient alkenes is reported to give cycloadducts **72** and 73 in moderate diastereoselectivity (upto 60 % *de)* (Scheme 15).[16] The stereochemical outcome of this dipolar cycloaddition has been rationalized by envisaging *endo/exo* approaches of the dipolarophile to predominantly one face of the essentially planer ylide **71.** The major cycloadduct **72** results from an *endo* addition of **37** with **71** from the side anti to the Bu^t group (Fig. 4).

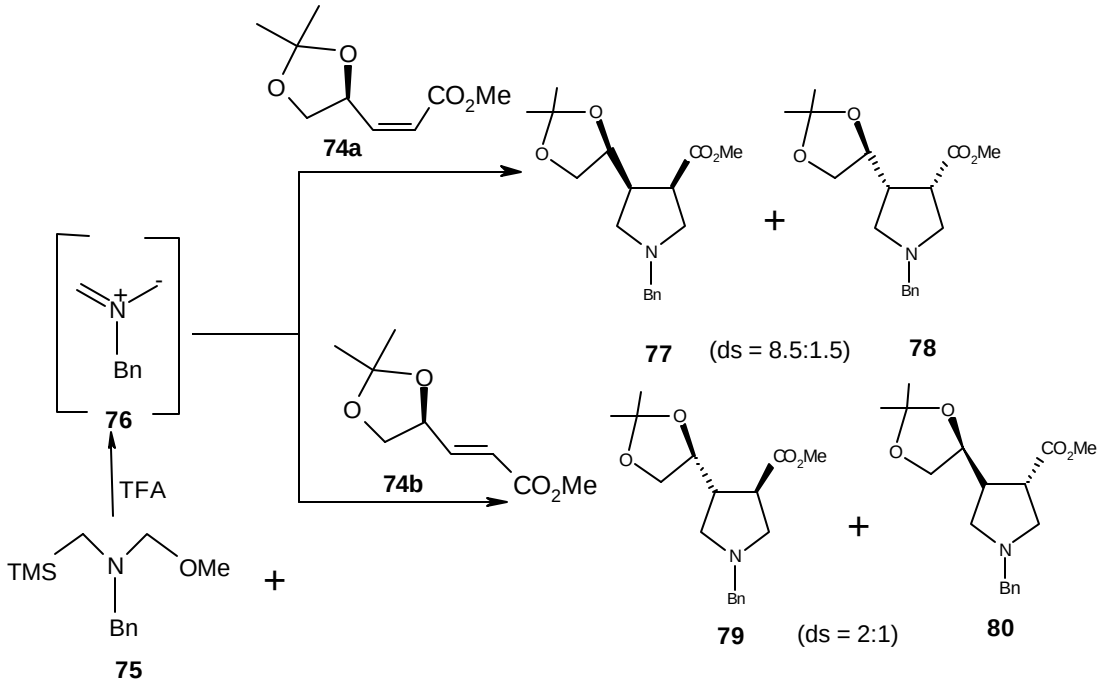
Fig. 4



Sterically and electronically preferred approach of **71** to N-phenylmaleimide

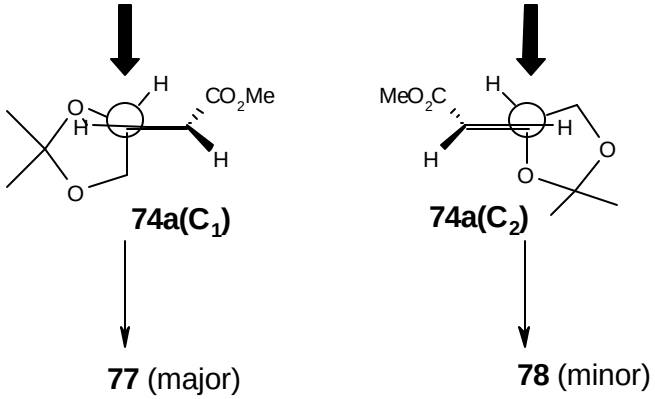
The asymmetric 1,3-dipolar cycloaddition of achiral AMYs with chiral dipolarophiles has seen strong revival since the development of a number of good chiral auxiliaries.[17] The diastereoselectivity of the cycloadditions involving achiral AMYs (acyclic and cyclic) and chiral dipolarophiles (acyclic and cyclic) have been studied exhaustively and in a number of cases good to excellent diastereoselectivity has been achieved. The diastereoselective study of asymmetric dipolar cycloaddition involving acyclic AMYs and chiral acyclic dipolarophile is more interesting. One such report[18] describes an interesting example of the cycloaddition involving reaction of an achiral non-stabilized AMY **76**, obtained from its precursor **75** by treatment with TFA with the two geometrical isomers of a homochiral dipolarophile (**74a** & **74b**). While the reaction of **76** with **74a** proceeded with good π-facial selectivity to give two readily separable products in a diastereomeric ratio of 8.5:1.5, the reaction of **76** with **74b** exhibited lower π-facial selectivity and the two products were formed in diastereomeric ratio of 2:1.

Scheme 16



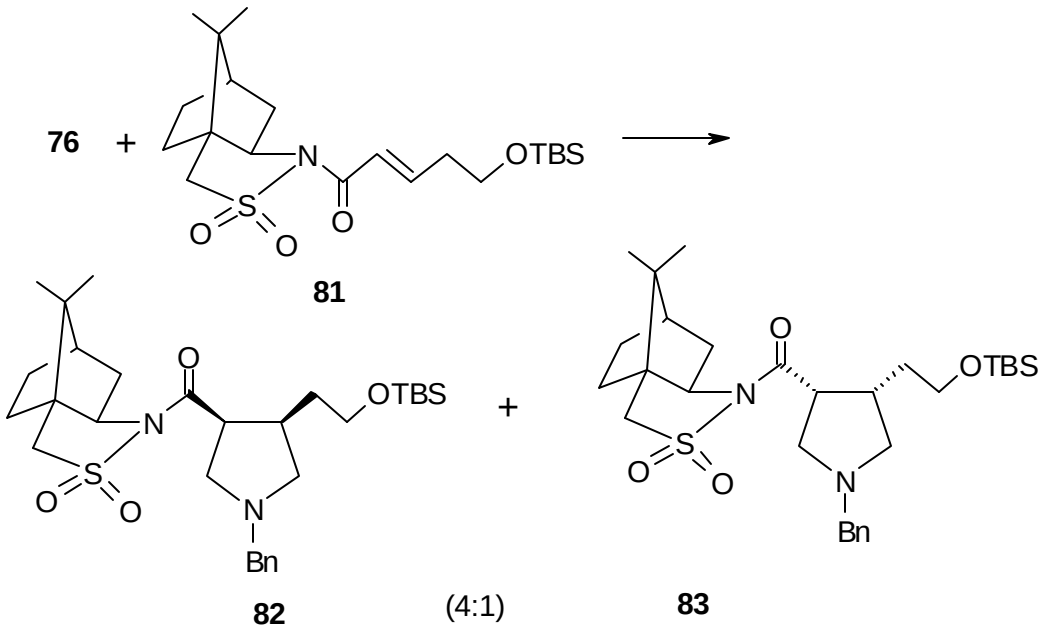
The moderate diastereoselectivity observed with cis-ester **74a** was explained by considering two reactive conformers **74a(C_1)** & **74a(C_2)** of the dipolarophile (Fig. 5). The conformer with the more preferred "inside" alkoxy conformation is unstable due to severe non-bonded interactions between *cis*-methoxycarbonyl group and the dioxalane ring and hence the *cis*-ester **74a** is forced to react via the "outside" alkoxy conformer **74a(C_1)** to give **77** as the major product. The minor product **78**, on the other hand is formed by the conformer **74a(C_1)** in which the allylic C-O bond is perpendicular to the plane of the π-bond. Conformer such as **74a(C_2)** is the least likely to participate in 1,3-dipolar cycloaddition reactions since this would result in an unfavorable π-$\sigma^*_{c\text{-}o}$ interaction in the electron-deficient transition state.

Fig. 5



In another example, the non-stabilized AMY **76** has been shown to undergo cycloaddition with a (Z)-alkene **81** with good facial selectivity giving rise to a 4:1 mixture of diastereomeric cycloadducts **82** & **83**.[19]

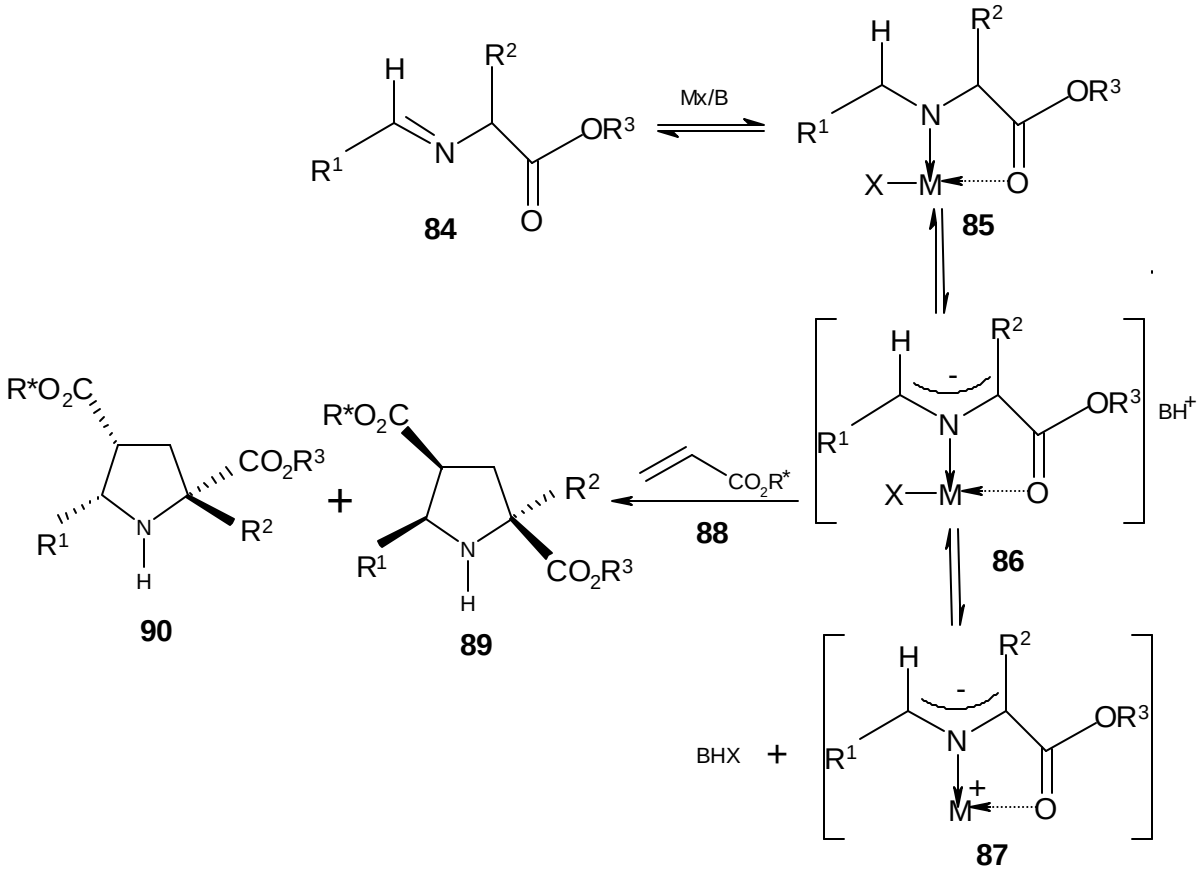
Scheme 17



The asymmetric 1,3-dipolar cycloadditions of stabilized AMYs with chiral dipolarophiles have invariably utilized *N*-metallated AMYs as stable 1,3-dipole. Although

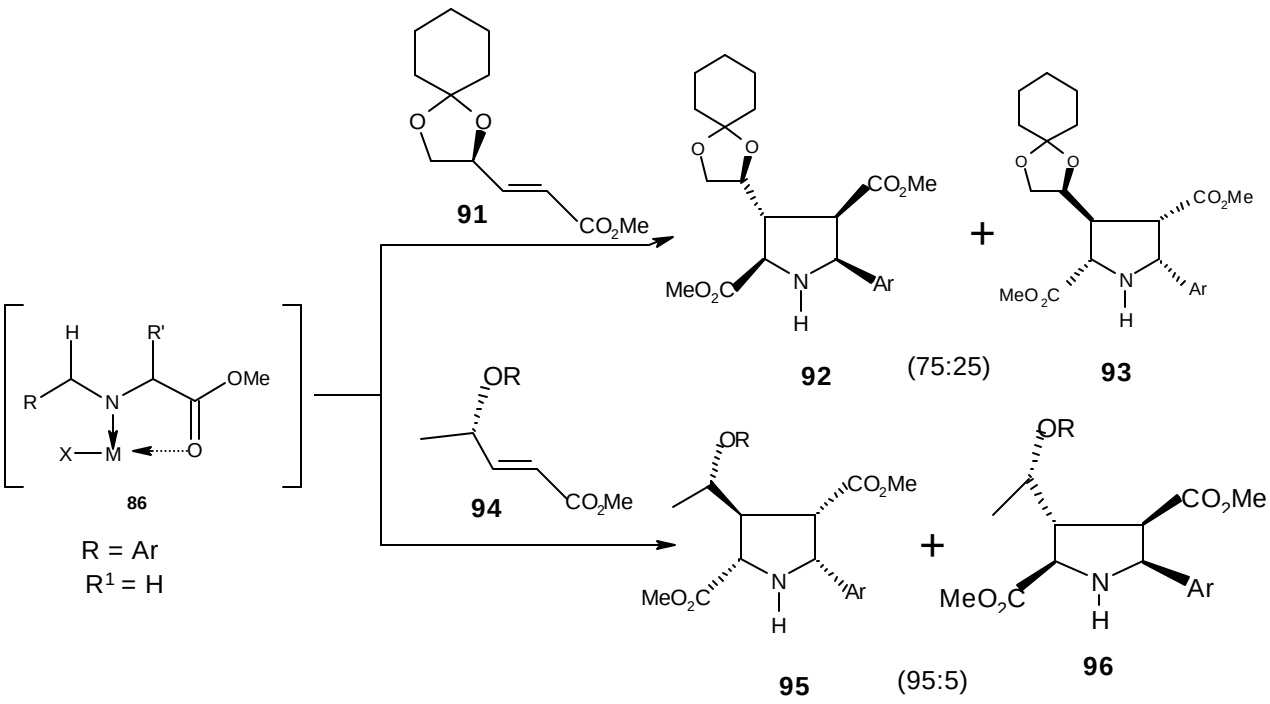
metallo-azomethine ylide cycloadditions with both acyclic and cyclic chiral dipolarophiles are known, the asymmetric cycloadditions of N-metallated azomethine ylides with acyclic chiral dipolarophiles have been studied extensively. Metallo-azomethine ylides **86**, generated from imines **84**, by the action of amine bases in combination with LiBr or AgOAc, undergo cycloaddition with a variety of acyclic chiral dipolarophiles **88** to give homochiral pyrrolidines **89** and **90** in good to excellent yields. It is further reported that these metallo-azomethine ylides generation is specific to either *syn* **86** or *anti* **87** configurations.

Scheme 18



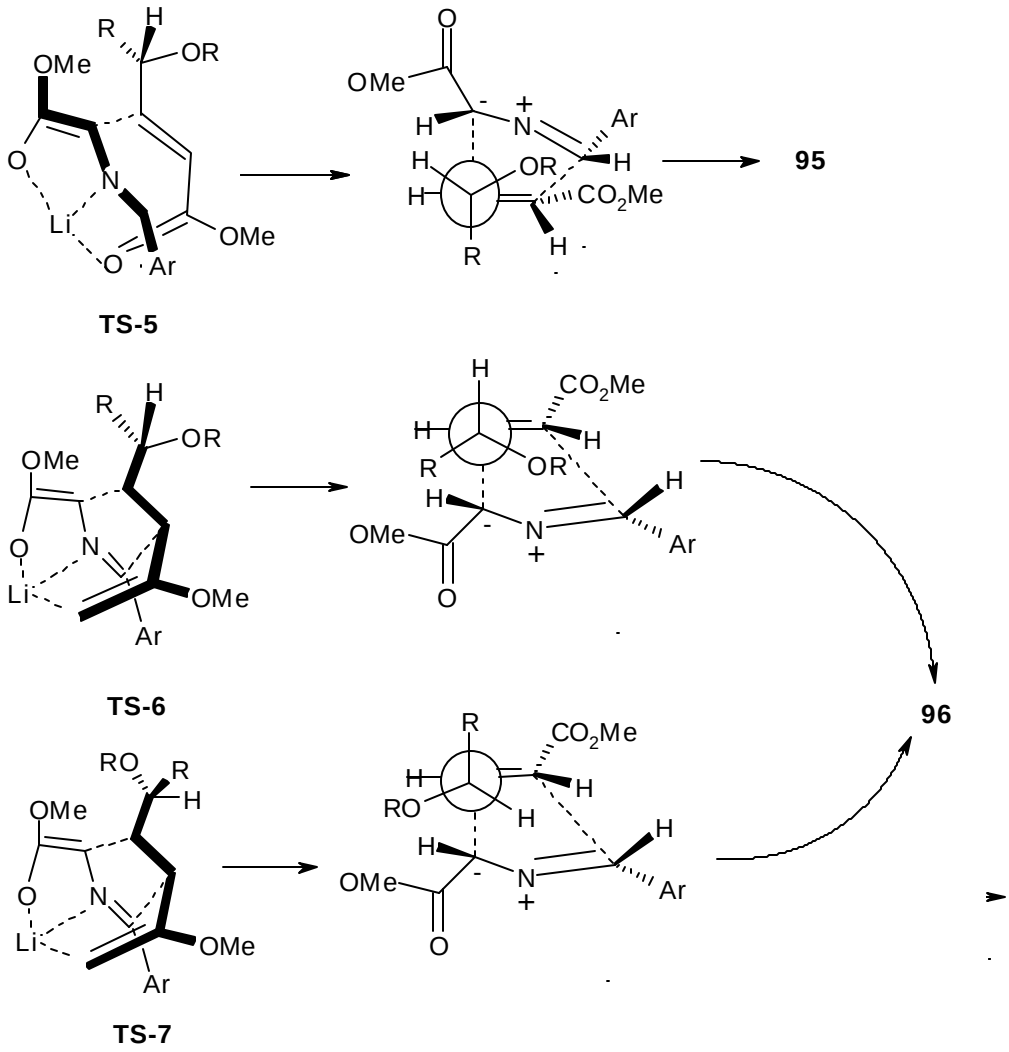
The first report[20] of metallo-azomethine ylide cycloaddition involved the reaction of acyclic chiral dipolarophiles **91** and **94** with glycine-derived AMYs **86**, generated in THF solution from the corresponding imines **84** in the presence of DBU/LiBr. In this case, only two diastereomers (**92** & **93**) / (**95** & **96**) were obtained with a ratio of 75:25 to 95:5 (maximum).

Scheme 19



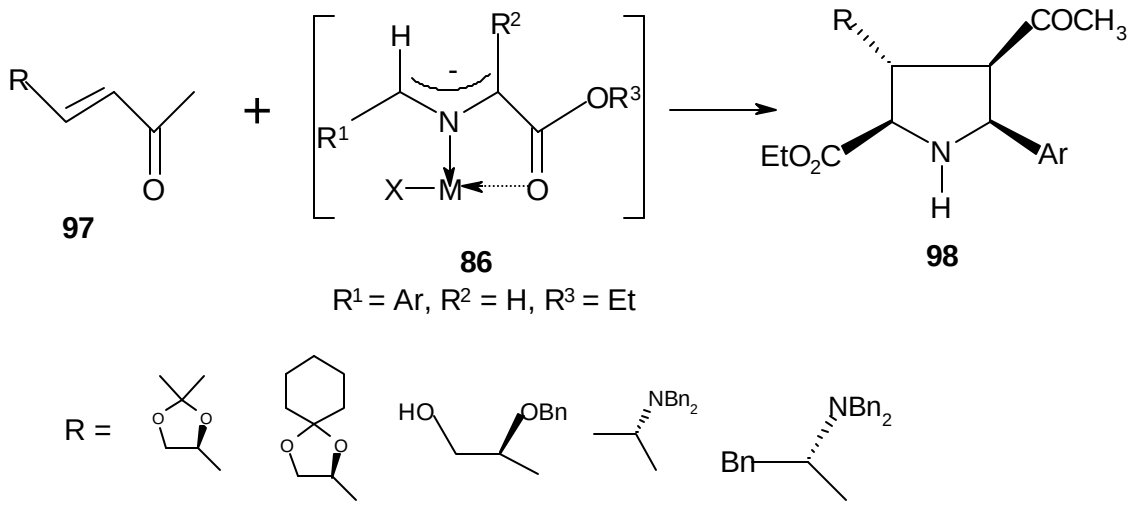
To account for the regio- and stereospcificity of this cycloaddition, three transition state models (**TS-5, TS-6, TS-7**) are proposed as shown in Fig. 6. To explain the formation of 95**,** it is proposed that the ylide attacks the *re*/*re* face of the ester away from the bulky alkyl residue at the stereocentre involving **TS-5**. This attack leads to a transition state where the OR allylic substituent occupies the stereoelectronically favored "inside" position and the small H group the more sterically demanding "outside" position, closer to the incoming dipole. Similarly, for the formation of **96**, transition structure **TS-6** can be invoked, featuring the attack at the *si/si* face antiperiplanar to the small H group with the alkoxy group "inside" and an unfavorable steric interaction between the ylide OMe group and the allylic R group in the "outside" region. The model **TS-7** has been proposed to be energetically less favorable as the steric interaction between the "outside" OR group and the methoxy residue on the ylide destabilizes this transition structure with respect to **TS-5**.

Fig. 6



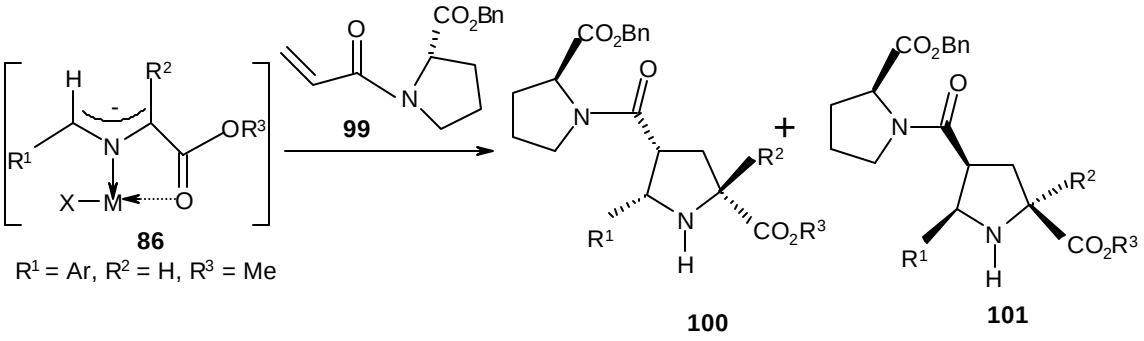
The cycloaddition of **86** with different enones **97** is reported to be regio- as welI as stereospecific (> 95:5) (Scheme 20). The stereochemical outcome is here explained by the (E)-configuration of the dipolarophile and the known W-shape of the dipole.

Scheme 20



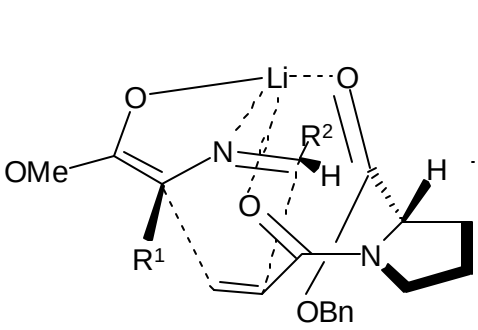
The high facial selectivity (ds >99:1) during 1,3-dipolar cycloaddition of the α,β-unsaturated proline benzyl ester amide **99** with the metallated AMY **86**, generated from their corresponding imines of aliphatic and aromatic amino esters by deprotonation with Et_3N or DBU in the presence of LiBr, was reported by Waldmann *et al*.[22]

Scheme 21

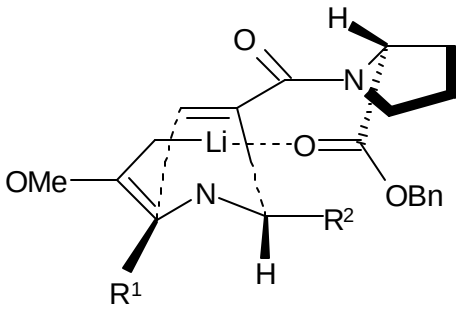


The almost complete *endo/exo* selectivity is explained by considering the highly ordered *endo* transition states **TS-8** and **TS-9** (Fig. 7).

Fig. 7



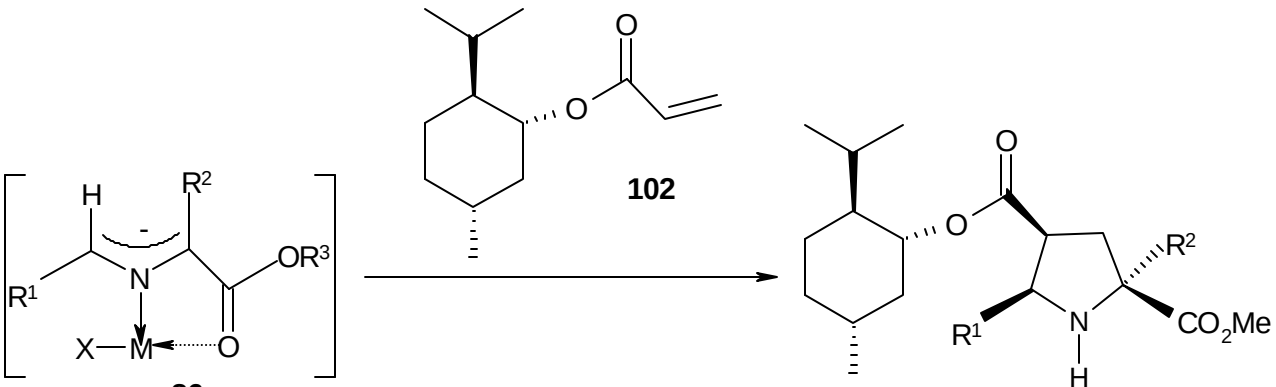
TS-8



TS-9

Complete diastreoselectvity as well *endo*-selectivity have been reported [23] in the cycloaddition of metallated AMYs **86** with menthyl acrylate **102** (Scheme 22).

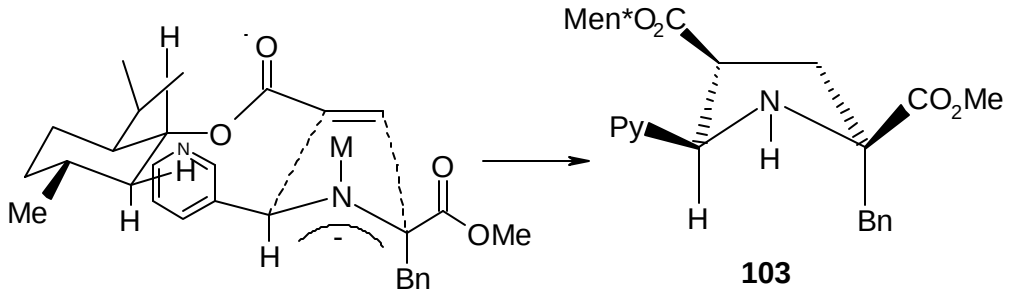
Scheme 22



To explain the regio- and *endo* specificity during the formation of **103,** transition state model **TS-10** was proposed where facial shielding effect of menthyl isopropyl moiety is accommodated. The cycloaddition is reported to involve the addition of the dipole to the *re*-face of the s-*cis* acrylate. The menthyl isopropyl group effectively shields the *si*-face of the s-cis acrylate. The C(6) equatorial hydrogen atom of the menthyl moiety is believed to infringe

slightly on the π-cloud of any C(3)-aryl substituent on the dipole, adding the streospecificity of this cycloaddition.

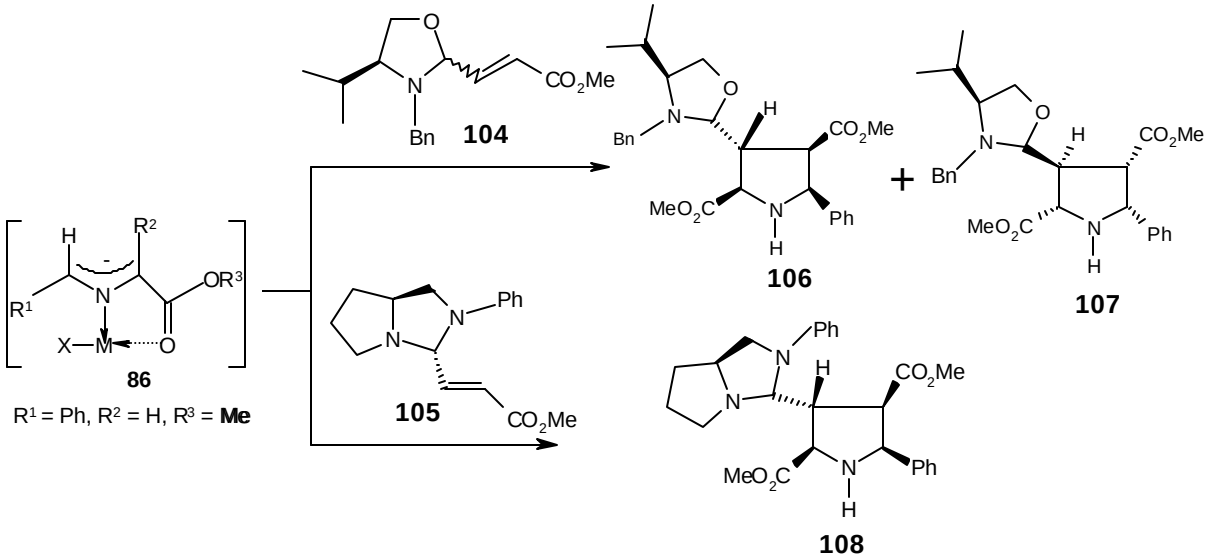
Fig.8



TS-10 **103**

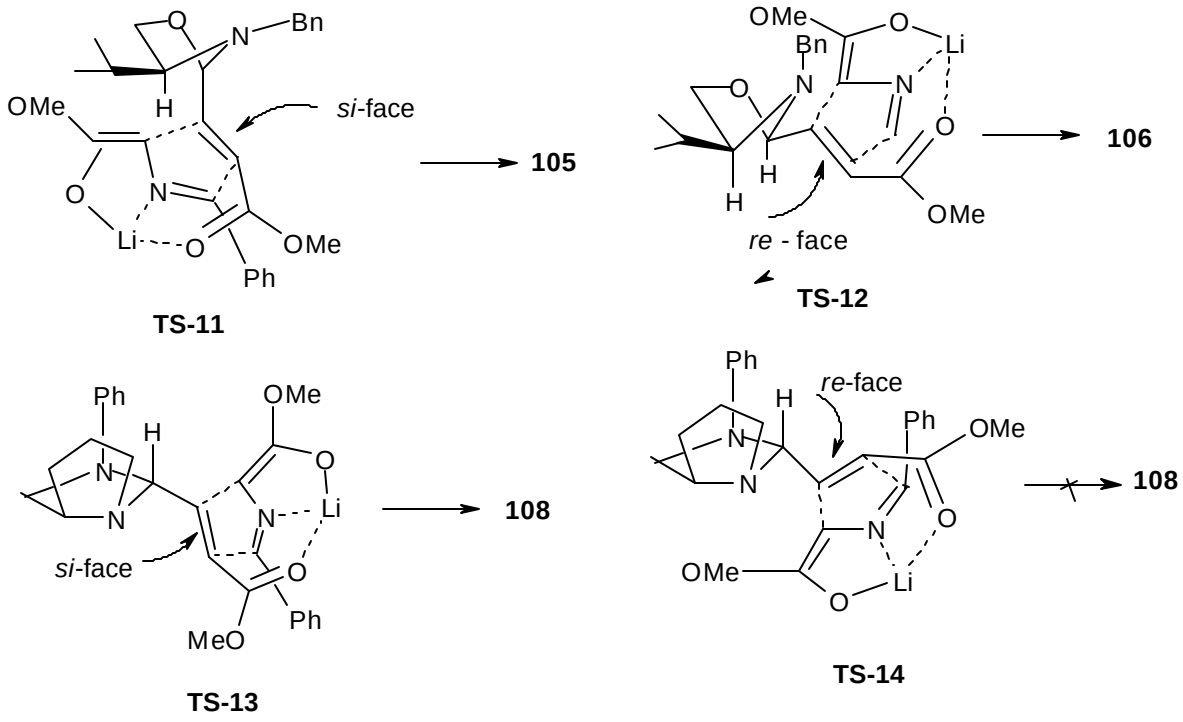
In another related study the cycloaddition of a highly reactive *N*-metallated AMY **86** with an α,β-unsaturated ester bearing a chiral 2-oxazolidinyl unit **104** or a bicyclic aminal type chiral controller at the β-position **105** is reported to produce cycloadducts in excellent yields (80-85 %) as a single diastereomer.[24]

Scheme 23



The *endo*-specificity together with excellent diastereoselectivity for this cycloaddition reaction was explained by considering transition state models **TS-11** to **TS-14** (Fig. 9).

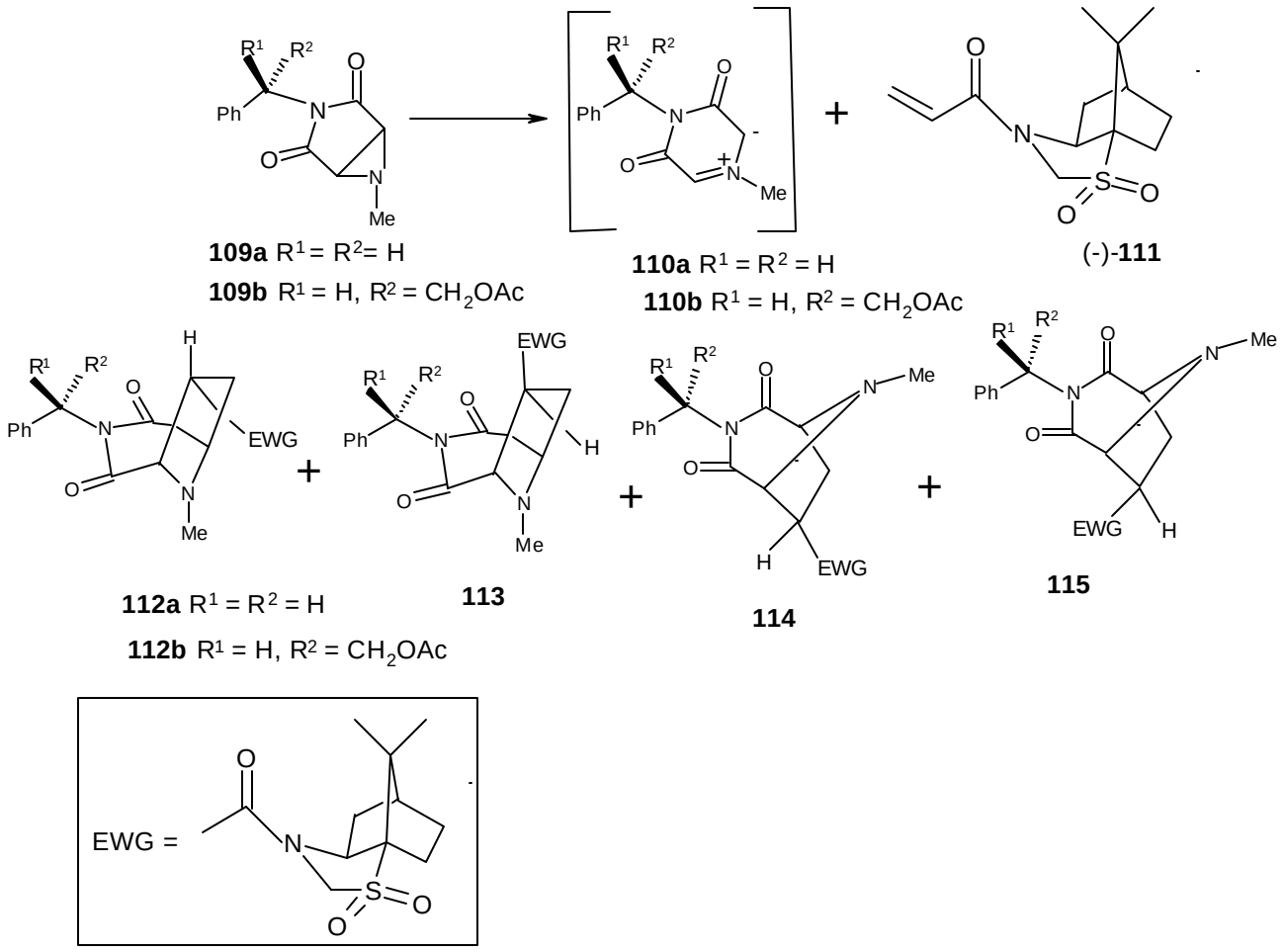
Fig. 9



The diastereoselectivity observed during the formation of **105** is explained by invoking the predominant involvement of thermodynamically more stable C(2)-C(β) antiperiplanar conformer (ap) of **TS-11** instead of synperiplanar conformer (sp) in the cycloaddition reaction as in this situation is expected, so that *si*(C_α)-face would be open to attack by the dipole because of the critical steric hindrance caused by the N-phenyl substituent. Similarly, the exclusive attack of ylide at the *re*(C_α)-face of C(2)-C(β) antiperiplanar conformer of **TS-12** produced cycloadduct **106**. On the other hand, the cycloadduct **108** involved the transition state **TS-13** where ylide **86** attacked the *si*-face (C_2) of thermodynamically less favored 3H/3'-H synperiplanar conformation of **TS-13**. Existence of serious steric hindrance between the ester moiety of **86** and 7a′-H of **107** or between the ester moiety and the bridgehead hydrogen was considered a major stereoselectivity determining factor.

Despite the advantages that would be associated with cyclic AMYs due to its inherent conformational rigidity, the asymmetric 1,3-dipolar cycloaddition of achiral cyclic AMYs with chiral acyclic dipolarophile has been the subject of only few reports. Garner *et al.*[25] have observed disappointingly very poor selectivity (~ 1:1) in the cycloaddition of Oppolzer's chiral acryloyl dipolarophile (-)-**111** with photochemically generated cyclic AMY **110a** though the *exo/endo* selectivity for these intermolecular cycloadditions was good (3:1). Since the *si*-face of (-)-**111** is effectively shielded by bulky camphor moiety, the attack of dipole was reported to occur from the *re*-face of dipolarophile **111,** which clearly explains the *exo/endo* selectivity associated with these cycloadditions.

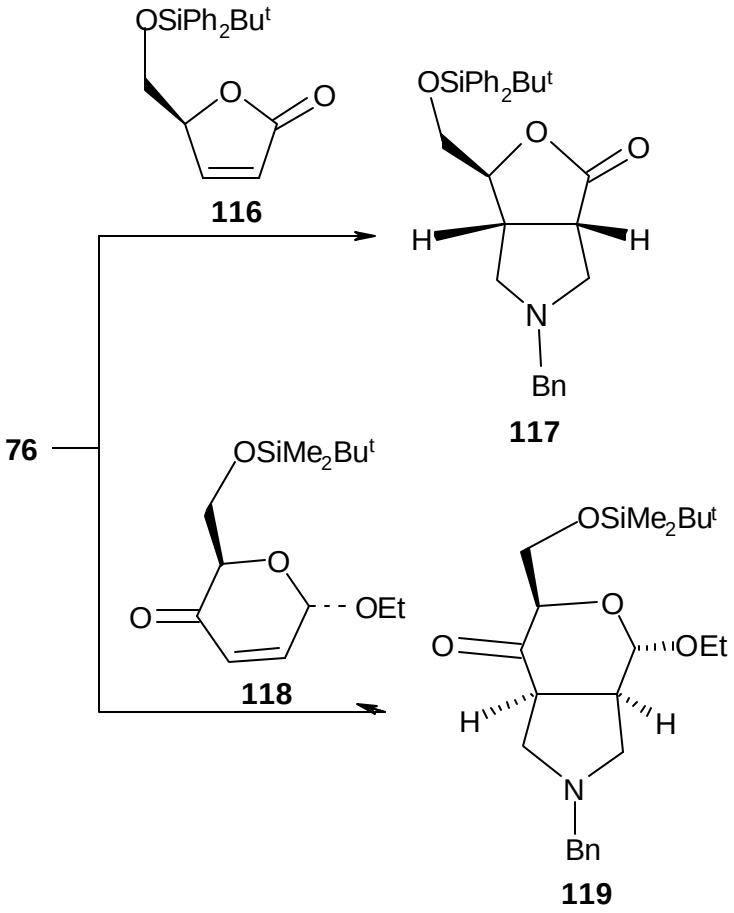
Scheme 24



The diastereoselection (facial selectivity) was amplified by incorporating chiral element to that nitrogen which is not involved in AMY formation. Thus, the cycloaddition of **110** with (-)-**111** showed an excellent facial selectivity where only a single diastereomer (**112b**) was formed. The chiral element borne by nitrogen controls the attack of dipolarophile by discriminating two faces of AMY (**110b**) thereby setting a rare example of 1,4-asymmetric induction.

The non-stabilized AMY **76** is reported[26] to undergo smooth cycloaddition with homochiral cyclic dipolarophile in a more stereoselective manner. The cycloaddition reactions of AMY **76** with chiral cyclic dipolarophiles **116** and **118** have been shown to proceed with excellent facial selectivity to yield only one diastereomer in each case.[26]

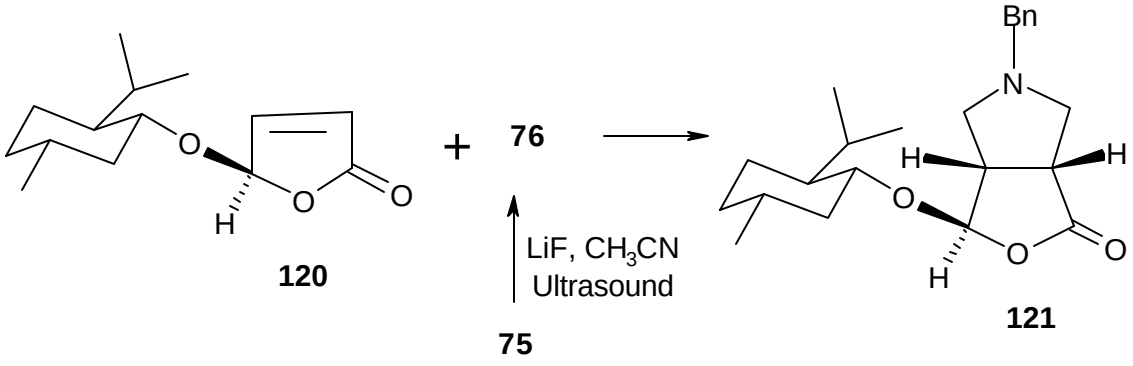
Scheme 25



Cycloaddition of **116** is explained to occur from the side opposite to the bulky silyloxymethyl substituent and in the case of **118**, cycloaddition proceeded from the side opposite to the anomeric ethoxy group.

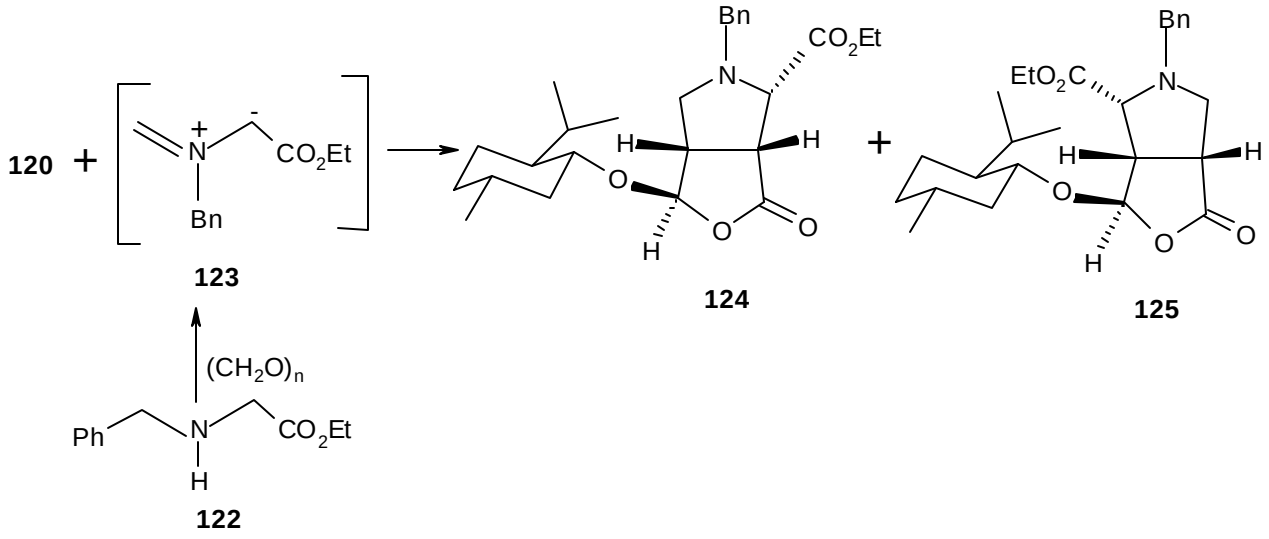
In an another report, the same AMY **76** has been shown to undergo smooth cycloaddition with a different chiral dipolarophile 5--methyloxy-2(5H)-furanone **120** to give diastereomerically pure **121** in 81% yield (Scheme 26).

Scheme 26



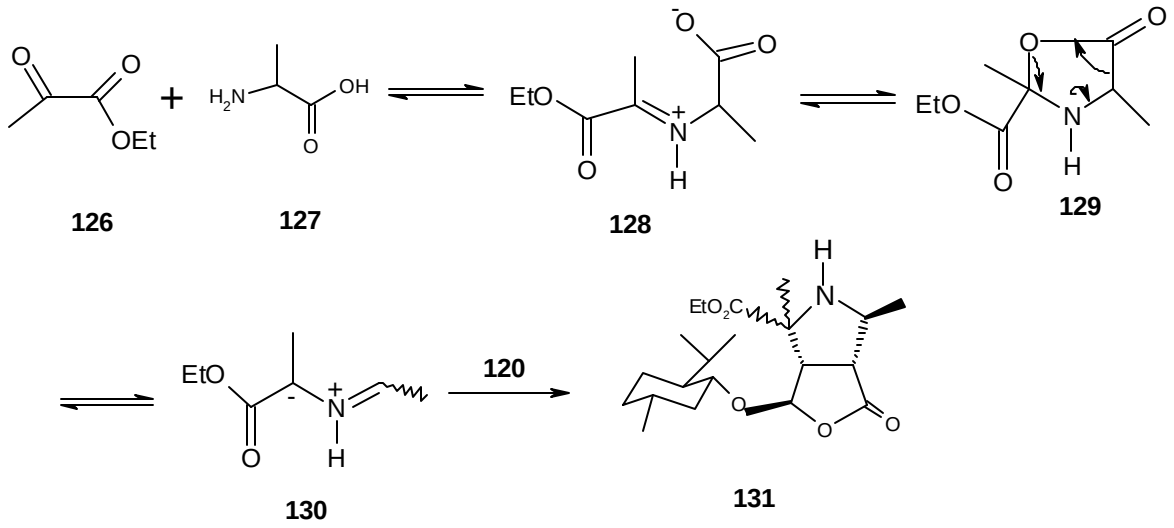
Even the stabilized AMY **123** showed excellent facial selectivity towards this dipolarophile though two regioisomers **124** and **125** were formed in a ratio of 1:2 in this cycloaddition (Scheme 27).[27]

Scheme 27



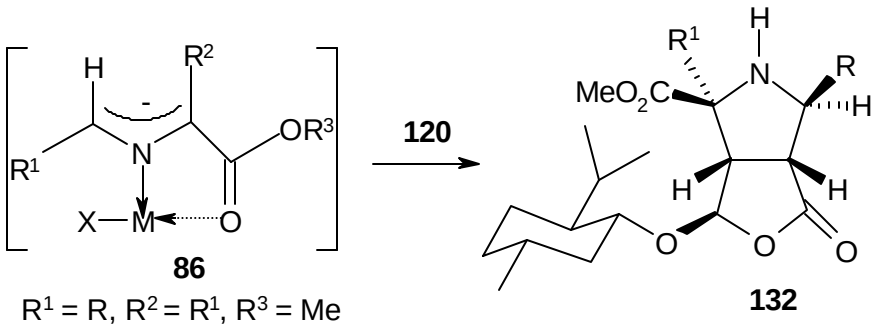
Another stabilized AMY **130**, generated in situ from ethyl pyruvate **126** and alanine **127**, is reported to react with **120** to give **131** (epemeric at C_6) as a diastereomeric mixture (23:2). The pyrrolidines are formed by an *anti*-facial approach of the dipole where the cycloadduct with *endo*-ester orientation is found to be the major product.

Scheme 28



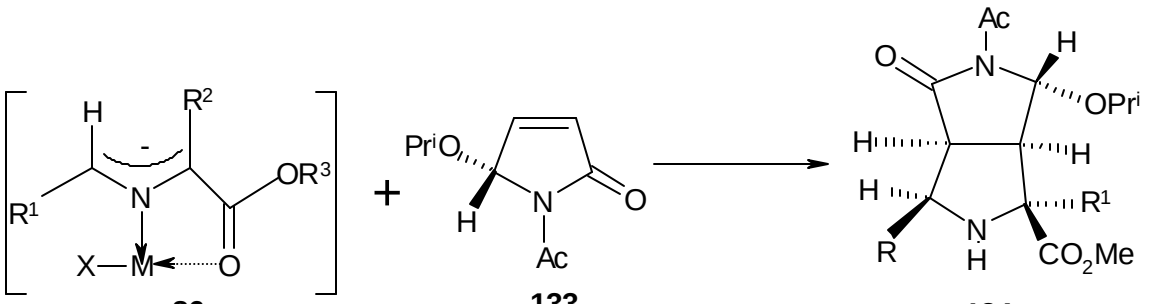
The metallo-azomethine ylide **86** is also reported to exhibit excellent diastereoselectivity with chiral acyclic dipolarophile **120** producing a single *endo* cycloadduct **132**.[28]

Scheme 29



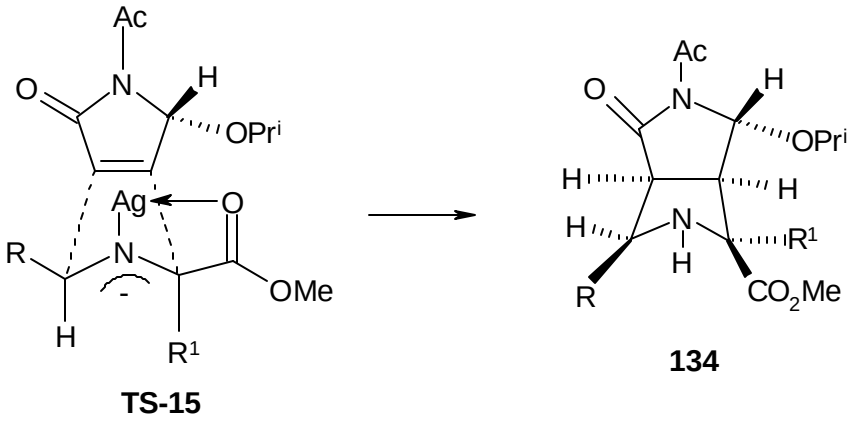
Similarly, the cycloaddition of **86** with **133** is also observed to produce **134** with excellent diastereoselectivity (de>99 %).[29]

Scheme 30



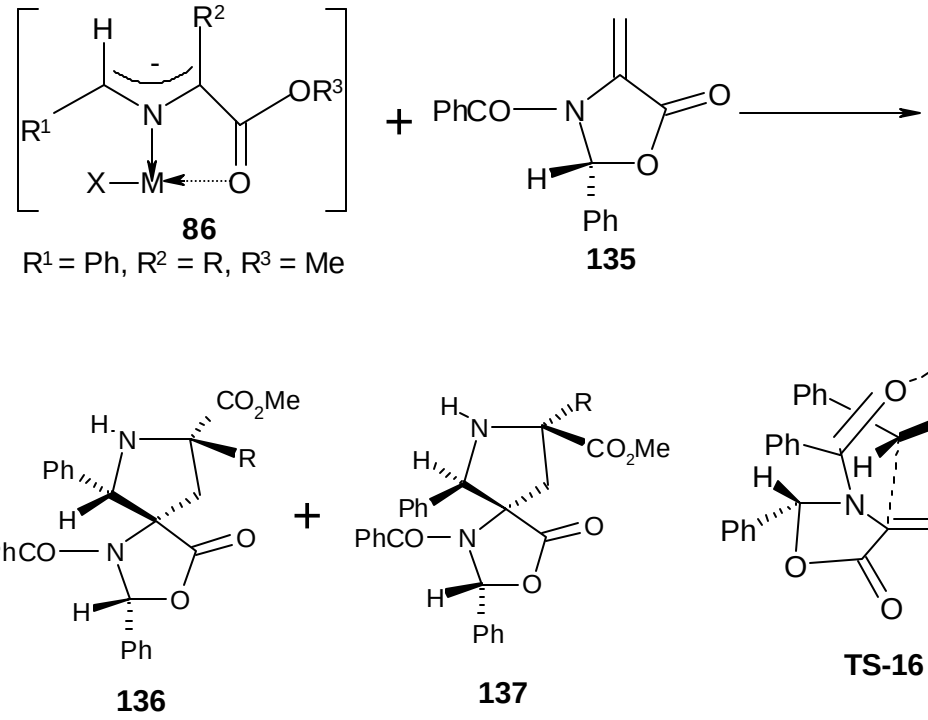
The stereochemical outcome of **134** is explained through the transition state model **TS-15** where the *syn*- or *anti*- dipole (neglecting M) adds *via* its α-*si*/β-*re* face to the lactum 3-*re*/4-*si* face producing syn-*endo* cycloadducts. The cycloaddition occurs on the face of the dipolarophile that is *trans* to the bulky isopropoxy substituent.

Fig 10



In another report[30], the metallo-azomethine ylide cycloadditons of **86** with a chiral lactam **135** has been shown to proceed with good diastereoselectivity (de 60-80 %), though, the yield of the products **136** and **137** was not satisfactory (45-61 %).

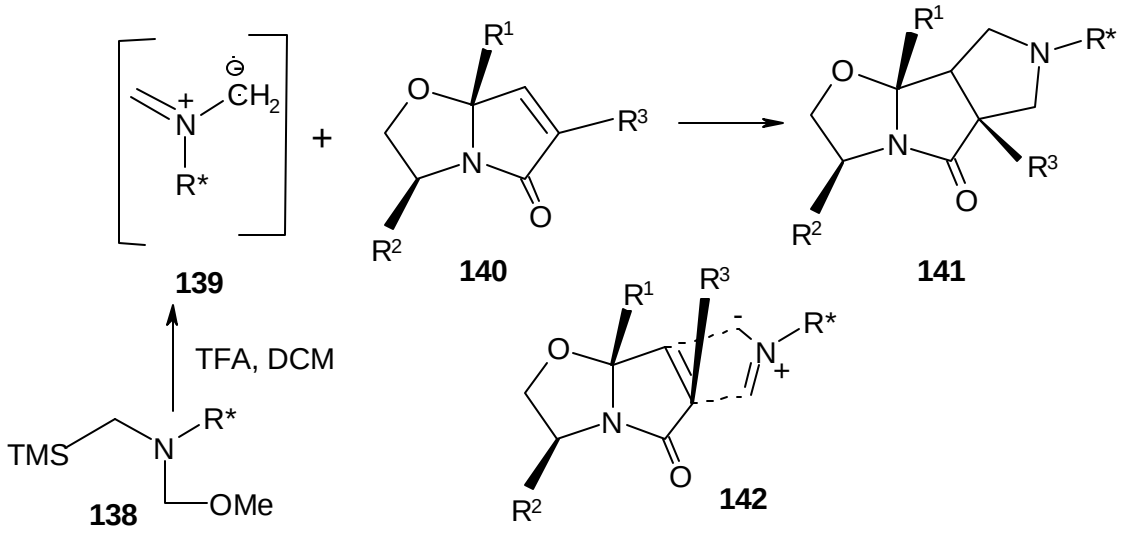
Scheme 31



The preference for *exo*-cycloaddition adducts was rationalized by assuming chelation between the lithium cation and the N-benzoyl carbonyl groups and the AMY as shown in the possible transition state (**TS-16**).

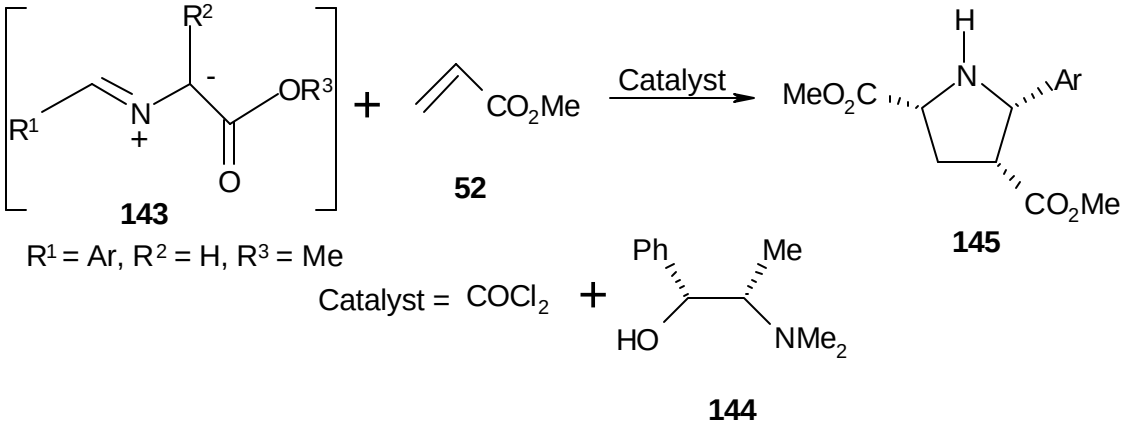
Double asymmetric induction has been explored by Meyers *et al*[31] in the cycloaddition of chiral AMYs **139** with chiral unsaturated bicyclic lactams **140**. The diastereoselectivities are dependent on the various substituents R^1-R^4. For R^1 = Me, Ph, the major stereoisomer obtained is **141**, whereas for R^1= H, the other diastereomer is formed. Furthermore, it was found that for R^3 = H, the π-facial selectivity is insensitive to the chiral substituents of the dipole (R^4 = chiral group) whereas for R^3 = CO_2Me or CO_2Bu^t lower selectivities were observed. On the basis of experimentally observed results the approach of the chiral AMY to the alkene as outlined in **142** was suggested.

Scheme 32



While the asymmetric 1,3-dipolar cycloaddition using either chiral AMY or chiral dipolarophile have been studied exhaustively, the asymmetric dipolar cycloaddition of AMYs with dipolarophiles employing chiral metal catalysts is in infancy. Only one report[32] has appeared where chiral Co(II) and Mn(II) complexes have been shown to be as excellent catalysts for the 1,3-dipolar cycloaddition reaction of AMYs. Reaction of the N-metallated AMY **143** with methyl acrylate (**52**) in the presence of a stoichiometric amount of Co(II) and the chiral ephedrine ligand (**144**) is reported to give the pyrrolidine **145** in 86 % yield (96 % ee).

Scheme 33



It has also been found that Ag(I) salts in combination with chiral ligands can catalyze similar 1,3-dipolar cycloaddition reaction with ee's of about 70%.

From the above discussion, it is accrediated that though diastereofacial control in asymmetric 1,3-dipolar cycloaddition involving either chiral AMYs or chiral dipolarophiles is a subject of much discussion, there has been very less successful results and very limited scope is available for further implementation of this process. Though the aforementioned reports are conceptually attractive and deserve much credit due to their pioneering nature, they are inappropriate to initiate a complex total synthesis.

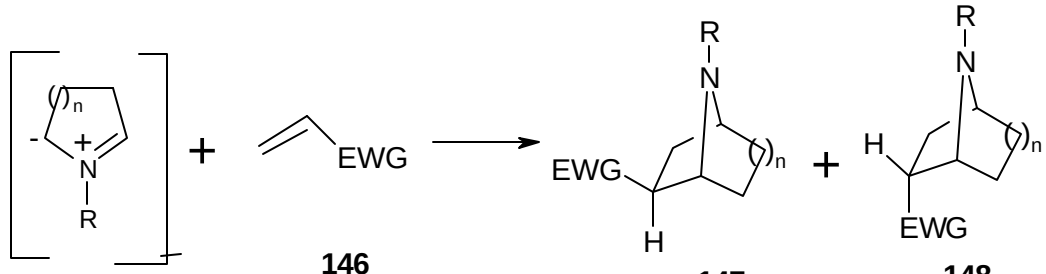
2. Results and Discussion

2.1. Background and Concept:

The foregoing discussion of this chapter will present an attractive strategy of asymmetric [3+2]-cycloaddition utilizing cyclic AMYs and Oppolzer's chiral acryloyl sultam as dipolarophile.

Our group have introduced a new concept for the generation of cyclic AMYs of the type **2** and their trapping with suitable dipolarophiles **146** to produce X-azabicyclo[m.2.1]alkanes (**147** & **148**) with good *exo*/*endo* selectivity.[33]

Scheme 34



2 **146** **147** **148**

n = 1, R = Bn EWG = CO_2Et

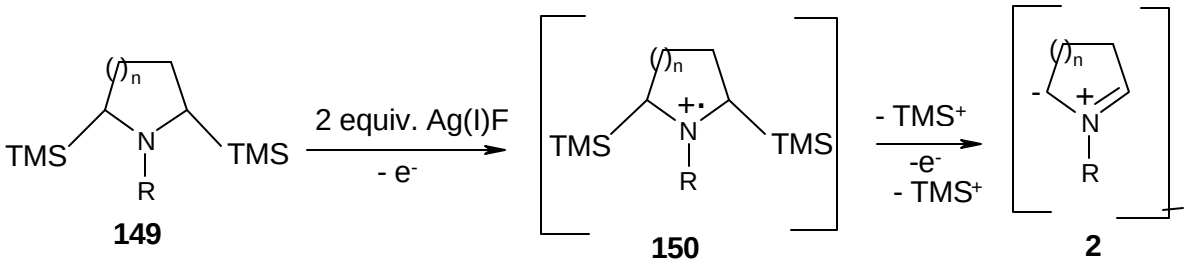
n = 2, R = Me EWG = SO_2Ph

n = 3, R = Bn

No.	R	Isolated Yield %	*Exo : Endo*
1.	Bn	68	90 : 10
2.	Me	72	88 : 12
3.	Bn	62	80 : 20

These cyclic AMYs **2**, where the whole ylide conjugation is in ring, are generated from their synthetic precursors **149** by treating with 2 equiv of Ag(I)F in dry DCM. The following mechanism was proposed for the generation of AMYs **2**.[34]

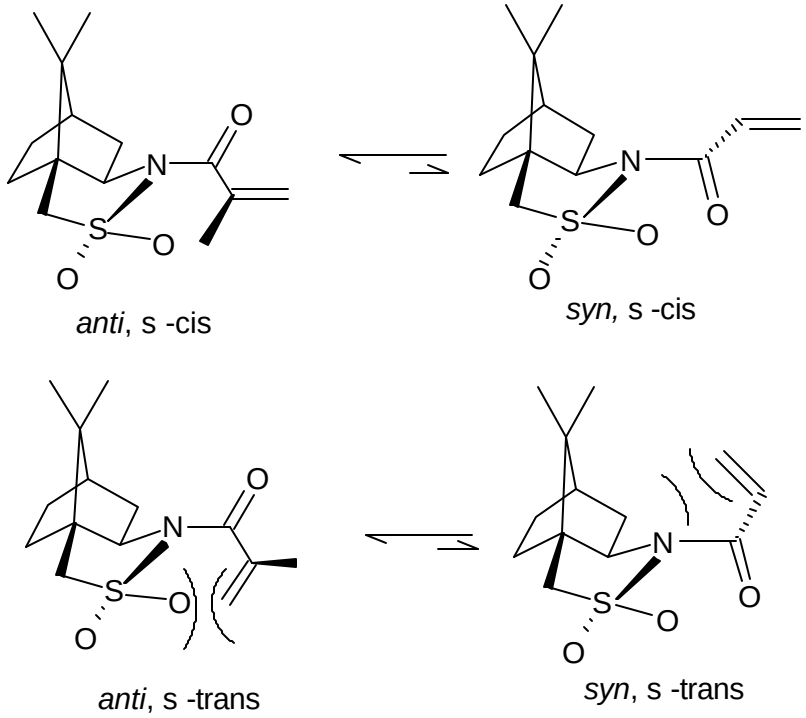
Scheme 35



The basic concept in the generation of **2** from **149** involved sequential one electron oxidation of the lone pair of electrons located on nitrogen and exploitation of the β-silicon effect[35] to induce sequential desilylation process to generate AMY **2** (Scheme 35). The high *exo/endo* selectivity attained during this cycloaddition is explained on the basis of selective attack of dipolarophile **146** on the rigid conformation of cyclic AMYs **2**.

Taking the advantage of high *exo/endo* selectivity, we envisaged the cycloaddition of **2** with a suitable chiral dipolarophile which has excellent facial selectivity by virtue of its unique structural feature with the premise that it would provide an easy and general route for the synthesis of optically pure X-azabicyclo[m.2.1]alkanes. Oppolzer's chiral acryloyl dipolarophile[36] was evaluated as an ideal dipolarophile due to following reasons. This dipolarophile has four possible planar rotamers that are generated by rotating the sulfonamide C-N bond (*syn*, *anti*) and the acryloyl (O)C-C(=C) bond (s-*cis*, s-*trans*) (Fig. 12). s-*trans* rotamers are expected to be quite high in energy due to severe steric interactions and *syn*-rotamers will be disfavored relative to *anti* because of unfavorable dipole interactions. The *anti*, s-*cis* rotamer of the acryloyl sultam then stands alone as the ground state energy minimum. It has been shown[36] that the reagents attack "top face" of the favored rotamer in the thermal reactions of Oppolzer's chiral acryloyl dipolarophile. The three possible factors are responsible for this facial selectivity: a) twisting of the acrylate, (b) pyramidalisation of sulfonamide nitrogen and (c) asymmetric disposition of the two sulfur oxygen. Therefore, the unique structural feature coupled with ease of preparation has resulted enormous use of this dipolarophile in asymmetric 1,3-dipolar cycloadditions. The cost effective camphor sultam can offer stubble benefit in addition to inducing chirality in the cycloaddition.

Fig. 11

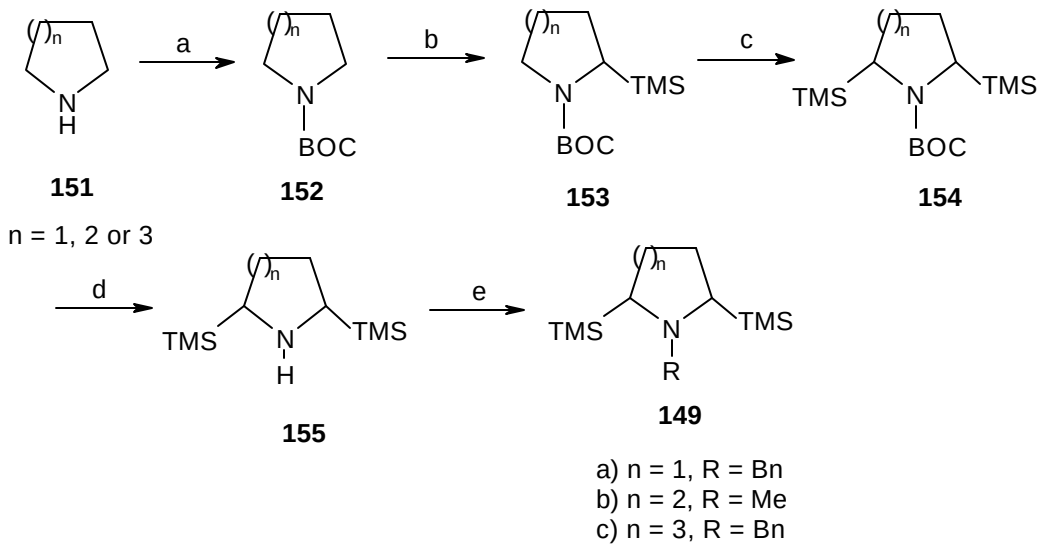


Therefore, the study of diastereoselectivity in asymmetric 1,3-dipolar cycloaddition involving cyclic AMYs **2** with Oppolzer's chiral dipolarophile (-)-**111** was undertaken as our research program. The demonstration of our asymmetric [3+2]-cycloaddition reactions involving cyclic AMYs **2** and Oppolzer's chiral acryloyl dipolarophile (-)-**111** in the asymmetric synthesis few azabicyclic compounds of this general class will be the main focus of this chapter.

2.2 Preparation of Non-stabilized AMY precursor 149:

The synthetic precursor **149,** for the generation of cyclic AMY **2**, was prepared from cyclic amine **151** by following the reaction sequences as shown in Scheme 36:

Scheme 36



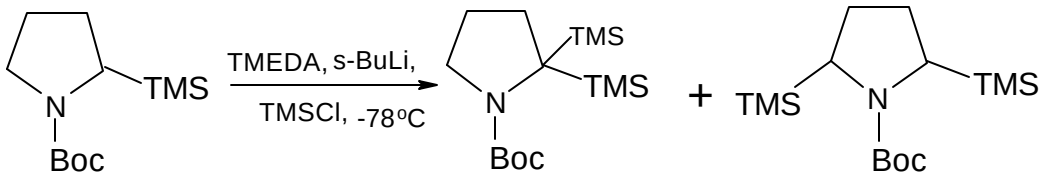
***Reagents and Conditions**: a) Boc-N_3, Et_3N, Dioxan, 90-95 %; b) TMEDA, s-BuLi, TMSCl, -78 ^oC, 80-90 %; c) TMEDA, s-BuLi, TMSCl, -50 to -30 ^oC, 1 h (n = 1 & 2), 70-75 %; -40 ^oC, 5 h (for n = 3), 68 %; d) TFA, DCM, quantitative; e) $PhCH_2Cl$, K_2CO_3,CH_3CN (for n = 1 & 3), 80-85 %; HCHO, $NaBH_3CN$, CH_3CN, gl. CH_3COOH (for n = 2), 80 %.*

The cyclic amines **151** were converted to their corresponding N-Boc derivatives **152** in 90-95 % yield by treating with *tert*-butyl azidoformate and Et_3N in dioxan. α-Silylation of **152** essentially employed the protocol reported by Beak and co-workers.[37] α-Metallation of **152** with s-BuLi in the presence of TMEDA in ether at −78 °C followed by quenching of the lithiated species with TMSCl at −78 °C afforded **153** in 80-90 % yield. Spectral characteristics (IR, ^{1}H NMR, ^{13}C NMR and mass analyses) are in agreement with that reported [38] values and are detailed in experimental section.

2.1 Synthesis of N-Boc-α,α′-bis(trimethylsilyl) derivative of cyclic Amines (149):

Extension of the experimental protocol as described above for the monosilylation of **152a** towards the preparation of **154a** from **153a**, however, resulted in the formation of **156** as the major product (65 %) along with the trace amount of **154a** (<5 %).

Scheme 37



153a **156** (65 %) **154a** (trace)

Compound **156** was characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analyses and the details are given in experimental section.

Formation of *gem* disilylated product **156** upon further silylation of **153a**, could be attributed to the following two factors:

a) Silicon ability to enhance the acidity of the adjacent proton

b) Kinetic stability of α-silyl anion

However, to synthesize required precursor **149a**, we required to introduce the two silyl moieties at C_2 and C_5 position of the pyrrolidine unit, respectively. At this point, it was realized that it would be difficult to alter the ability of silicon moiety to the acidity of the adjacent proton; however, we could certainly play with the kinetic stability of α-silyl carbanions by employing thermodynamic parameters such as temperature variants. Towards this direction, we extensively studied the reactivity pattern and the product ratio of **154a**:**156** by carrying out the metallation reaction using s-BuLi at a range of temperature viz. −60 °C to -30 °C. These studies led us to achieve an optimum reaction condition whereby the thermodynamic product **154a** was obtained as the major one. It was also noted that the use of THF as solvent did not influence the product ratio, however, diethyl ether appeared to be the solvent of choice for these reactions. Optimized reaction condition for the thermodynamic path for the preparation of **154a** involved treatment of **153a** in dry ether with s-BuLi in the presence of TMEDA at −45 °C followed by immediate warming of the reaction mixture to −30 °C and maintaining at this temperature for 30 min. Afterwards, the temperature was lowered once again to −45 °C and quenching with chlorotrimethylsilane afforded **154a** in 70 % yield as a pale yellow oil. Compound **154a** was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analyses and are given in experimental section.

The adaptation of the above optimized method for silylation of **153b** gave compound **154b** in 75 % yield as a colorless oil which was characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral analyses and the same is given in experimental section.

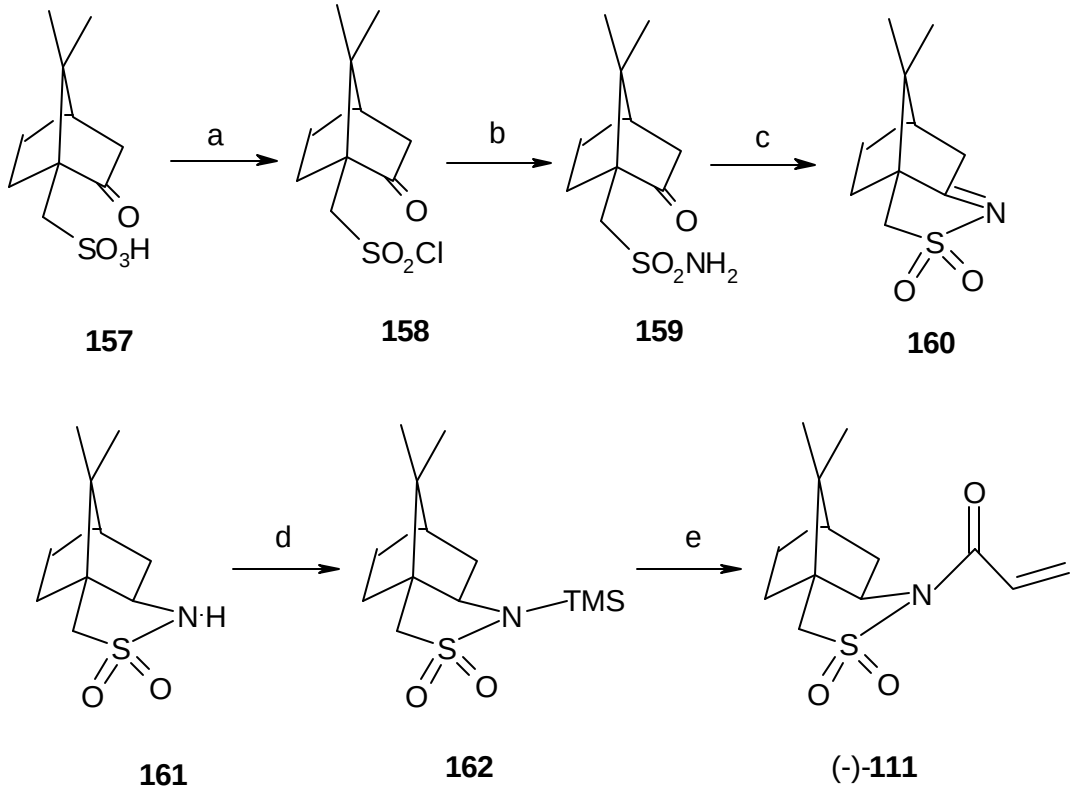
The adaptation of the above protocol for silylation of **153c,** however, gave only trace amount of **154c** (<5 %). After several experimentation, optimum reaction condition for the formation of **154c** in 68 % yield was found which involved the treatment of **153c** with TMEDA followed by s–BuLi at −78 °C. After 15 min., temperature was raised to -40 °C and the anion generation was continued for 5 h at this temperature. The temperature was again lowered down to −78 °C and TMSCl was added to the reaction mixture. Compound **154c** was characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analyses and are detailed in experimental section.

Since Ag(I)F promoted double desilylation (α,α′ to nitrogen) involves electron transfer processes from amine functionality, it was necessary to make N-alkyl compounds from their corresponding N-Boc derivatives (**154**) by deprotection of Boc moiety followed by alkylation reaction. N-Deprotection of Boc-moiety from compound **154** was achieved quantitatively by stirring with TFA in dry DCM at room temperature for 2 h. N-Benzylation of the crude amine (**155a/155c**) was achieved in 80-85 % yield by refluxing with benzyl chloride in the presence of K_2CO_3 in dry CH_3CN. Since N-benzylation of **155b** was found somewhat difficult, the same was converted to N-methyl derivative. This was achieved by reductive methylation of the crude amine **155b** with HCHO in the presence of $NaBH_3CN$ and gl. CH_3COOH gave compound **149b** in 80 % yield. Compound **149** was characterized by IR, ^{1}H NMR, ^{12}C NMR and Mass analyses. ^{1}H NMR, ^{13}C NMR, Mass spectra of compound **149c** are shown in Fig. 12 and 13.

3. Preparation of (-)-N-Propenoylbornane-2,10-sultam (-)-111:

Dipolarophile **(-)-111** was prepared from D-(+)-camphor sulfonic acid **157** by following the reported[39] literature procedure (Scheme 38).

Scheme 38



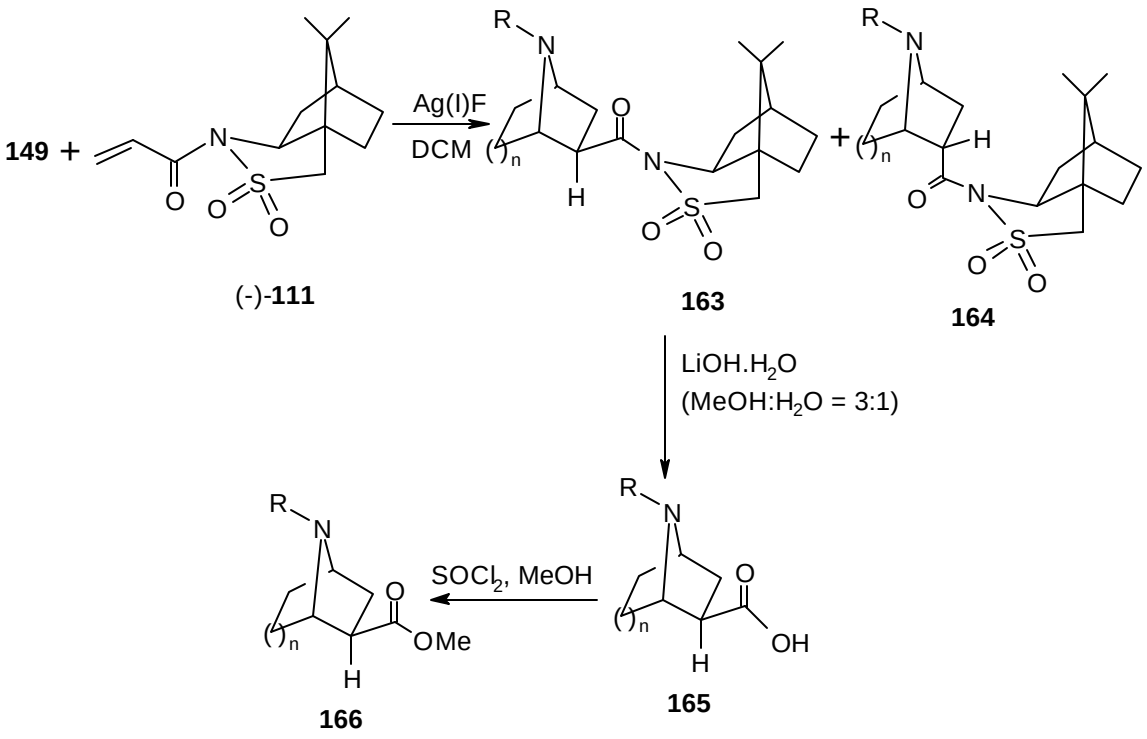
Reagents and Conditions*: a) $SOCl_2$, 85 %; b) NH_4OH, DCM, rt, 90 %; c) Amberlyst 15, benzene, reflux, 91 %; d) LAH, THF, reflux, 85 %; e) TMSCl, MeCN, ET_3N, 91 %; f) propenoyl chloride, 0.1mol $CuCl_2$ (anhyd.), benzene, reflux, 95 %.*

The low yield (42 %) obtained in the conversion of **157** to **158** by the use of PCl_5[39a] was improved up to 85 % using $SOCl_2$. Similarly, the use of 0.1 mole of anhydrous $CuCl_2$ instead of catalytic amount[39c] during the transformation of **162** to **111** reduced reaction time without affecting the yield.

4. Construction of X-azabicyclo[m.2.1]alkanes by asymmetric [3+2]-cycloaddition of cyclic AMYs 2 with (-)-111:

The cyclic AMYs **2**, generated from **149** by the reaction of Ag(I)F in dry DCM, undergo smooth [3+2]-cycloaddition reaction with (-)-**111** giving rise to two cycloadducts (**163** & **164**) with excellent *exo/endo* selectivity (Table 1).

Scheme 39



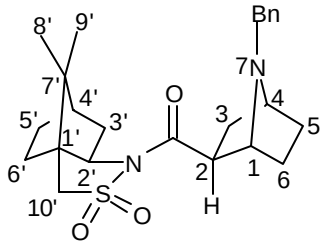
A typical cycloaddition reaction involved the slow addition of a solution of **149** in dry DCM to a stirring mixture of Ag(I)F and (-)-**111** under argon atmosphere. The reaction mixture was allowed to stir for additional 2 h and the progress of the reaction was monitored by TLC. After the considerable consumption of dipolarophile, the reaction mixture was filtered through a plug of Celite. Evaporation of the filtrate gave crude mixture of cycloaddition reaction. Purification of the crude residue by silica-gel (60-120) column chromatography gave mixture of diastereomeric cycloadducts (**163** & **164**) in 58-68 % overall cycloaddition yield. The ratio of diastereomers (*exo/endo*) was determined by comparing the integration values of the proton á to amide functionality from their corresponding ^{1}H NMR spectrum. The two diastereomers were separated carefully by flash column chromatography. The two diastereomers were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass and HRMS analyses. It should be noted here that ^{1}H NMR spectra of cycloadducts in $CDCl_3$ were not very helpful in establishing the relative stereochemistry of diastereomeric cycloadducts due to overlapping of few characteristic protons together. The better resolution of these characteristic proton peaks was obtained by adding varying amounts of C_6D_6 in $CDCl_3$. Only the ^{1}H NMR

spectra with high resolution of all characteristic proton peaks of both diastereomeric cycloadducts are presented here for discussion.

Table-1

Substrate	Overall cycloaddition yield	*Exo*:*Endo* (**163**:**164**)	M.P. of **163**	M.P. of **164**
1. n = 1	62 %	98:2	135-137 ^{o}C	133-135 ^{o}C
2. n = 2	58 %	80:20	165-167 ^{o}C	169-171 ^{o}C
3. n = 3	68 %	95:5	205 207 ^{o}C	210-212 ^{o}C

Characterization of 163a:



IR spectrum displayed a sharp band at 1683 cm^{-1}, characteristic of a carbonyl group of amide functionality.

^{1}H NMR spectrum of the cycloadduct **163a** showed following patterns (Fig. 14).

Two sharp singlets at δ 0.52 and 1.05, integrating for three protons each, are assigned to methyl protons of $C_{8'}$ and $C_{9'}$. The eight different multiplets appearing in between δ 0.70-2.08, accounting for a total of twelve protons, could be assigned to the methylene protons (*exo* and *endo*) present in two bicyclic ring systems. Two doublets appearing at δ 2.30 (*J* = 4.0 Hz) and at ä 2.35 (*J* = 4.4 Hz), integrating for one proton, may be attributed to H_{3exo}. A set of two doublets observed at δ 2.85 and 2.92 (*J* = 13.6 Hz), integrating for one proton each, are characterized to $H_{10'}$ protons. A triplet at δ 3.18 (*J* = 4.4 Hz), integrating for one proton, could be assigned to bridgehead H_1 whereas bridgehead H_4 is found to appear as a broad singlet at δ 4.23. A set of two doublets at δ 3.55 and 3.68 (*J* = 13.5 Hz), equivalent to one proton each, is assigned to the two benzylic protons. A triplet at δ 3.80 (*J* = 5.6 Hz), integrating for one

proton, corresponds to $H_{2'}$. A doublet of doublet appearing at δ 4.30 (J = 5.6, 3.8 Hz), integrating for one proton, could be assigned to H_2. The five aromatic protons have appeared as two triplets at δ 7.20 (J = 7.3 Hz), 7.35 (J = 7.5 Hz) and one doublet at δ 7.55 (J = 7.6 Hz).

Based on the above ^{1}H NMR spectral evaluation tentatively the stereochemistry of the product **163a** is assigned as 7-benzyl-2-*exo*-bornane-2,10-sultam-7-azabicyclo[2.2.1] heptane.

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

Decoupling of H_2 proton appearing at δ 4.30 indicated its coupling only with H_3 (*exo* and *endo*) and no coupling with adjacent bowsprit H_1 at δ 4.23. It is known[40] that in 7-azabicyclo[2.2.1]heptane system, as in the case of norbornane system[41], no coupling between the bridgehead bowsprit and adjacent *endo* hydrogens is observed due to a dihedral angle of 90° between them. Therefore, the assignment of H_2 as *endo* gets confirmed and thereby confirming the *exo*-orientation of amide functionality in the cycloadduct **163a**. This observation is further supported by ^{1}H COSY spectrum (Fig. 15).

^{13}C NMR spectrum displayed a total of seventeen carbon signals in the aliphatic region in between δ 19.01 to 64.77 besides aromatic signals at δ 126.49, 127.90, 128.63, 139.95 and a carbonyl signal at δ 172.48 (Fig. 16). DEPT experiment suggested that the signals at δ 19.01 and 20.12 are methyl (-CH_3) carbons and are assignable to $C_{8'}$ and $C_{9'}$ Methylene carbon signals (-CH_2-) at δ 24.63, 25.91, 28.55, 29.54, 31.80, 38.27, 51.46 and 52.10 are attributed to C_5, C_6, C_3, $C_{5'}$, $C_{6'}$, $C_{3'}$, $C_{10'}$ and N$\underline{C}H_2$Ph carbons, respectively. Methine carbon signals at 44.18, 46.99, 60.22, 63.61, 64.77 are assigned to $C_{4'}$, C_2, C_1, $C_{2'}$ respectively. The two quaternary carbon signals at δ 47.38 and 47.82 are characterized to $C_{7'}$ and $C_{1'}$ respectively.

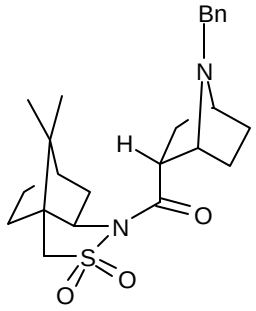
Mass spectrum revealed a molecular ion peak at 428 (M^+, 17) and a base peak at 91 along with other prominent fragmentation peaks at 337 (5), 214 (9), 186 (29), 159 (86) and 68 (9).

Characterization of 164a:

IR spectrum showed a strong absorption band at 1683 cm^{-1} indicating the presence of carbonyl amide functionality.

^{1}H NMR spectrum displayed following signals.

Two sharp singlets at δ 0.42 and 1.23, integrating for three protons each, are assigned to methyl protons of $C_{8'}$ and $C_{9'}$. The six different multiplets appearing in between δ 0.92-2.35



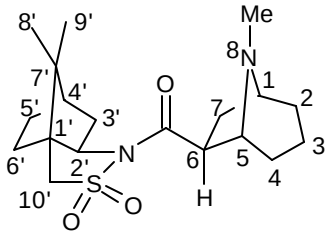
account for the thirteen protons that could be assigned to the methylene protons (*exo* and *endo*) present in two bicyclic ring systems. A set of two doublets appearing at δ 2.95 and 3.08 (J = 13.6 Hz), integrating for one proton each, are characterized to $H_{10'}$ protons. A triplet at δ 3.32 (J = 4.3 Hz), equivalent to one proton, is assigned to bridgehead H_4. Another set of two doublets appearing at δ 3.68 and 3.72 (J = 13.3 Hz), integrating for two protons, may be attributed to two benzylic protons. A triplet observed at δ 3.75 (J = 5.5 Hz), equivalent to one proton, corresponds to $H_{2'}$. A multiplet between δ 4.08-4.15, integrating for one proton, could be assigned to H_{2exo}. Another triplet appearing at δ 4.35 (J = 4.1 Hz), equivalent to one proton, is attributed to bridgehead H_1. The five aromatic protons are observed as a multiplet between δ 7.25 – 7.35 and a doublet at δ 7.55 (J = 7.5 Hz).

Based on the above ^{1}H NMR spectral evaluations the stereochemistry of **164a** is tentatively assigned as 7-benzyl-2-*endo*-bornane-2, 10-sultam-7-azabicyclo[2.2.1]heptane. The stereochemical orientation of amide functionality is further confirmed by ^{1}H NMR decoupling and COSY experiments. H_2 proton at δ 4.12 is found to couple with bridgehead H_1 at δ 4.35 (t, J = 4.1 Hz) and H_3 protons (*exo* and *endo*) at δ 2.20, thus, confirming the *exo* orientation of H_2. Therefore, the *exo*-orientation of H_2 is diagonistic for *endo*-orientation of amide functionality.

^{13}C NMR spectrum revealed a total of seventeen carbon signals in the aliphatic region in between δ 19.90–65.74 besides aromatic signals at δ 126.84, 128.21, 128.76, 140.36 and a carbonyl carbon signal at ä 173.71. DEPT experiment suggested that the signals at δ 19.90 and

20.84 are methyl carbons (CH_3-) and are assignable to $C_{8'}$ and $C_{9'}$. Methylene carbon (CH_2-) signals at δ 24.17, 26.52, 28.63, 29.66, 32.90, 38.79, 51.49, 53.23 are attributed to C_5, C_6, C_3, $C_{5'}$,$C_{6'}$, $C_{3'}$, $C_{10'}$ and N<u>C</u>H_2Ph carbons respectively. Methine carbon signals at δ 44.65, 45.84, 60.40, 63.63, 65.74 are assigned to $C_{4'}$, C_2, C_4, C_1 and $C_{2'}$ respectively. The two quaternary carbon signals at δ 47.37 and 47.88 are characterized to $C_{7'}$ and $C_{1'}$ respectively. Mass spectrum showed molecular ion peak at 428 (M^+, 15) and base peak at 91 along with other similar peaks as observed for major cycloadduct.

Characterization of 163b:



IR spectrum showed a strong absorption band at 1689 cm^{-1},a characteristic of amide functionality along with other bands at 2927, 3018 cm^{-1}.

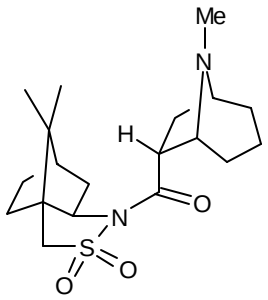
^{1}H NMR spectrum showed following characteristic patterns (Fig.17):

Two sharp singlets at δ 0.70 and 1.05, integrating for three protons each, are characteristic of methyl protons of $C_{8'}$ and $C_{9'}$. The three multiplets in between δ 1.12–1.95, accounting for total fourteen protons are assigned to the aliphatic protons (*exo* and *endo*) present in two bicyclic systems. A sharp singlet appearing at δ 2.30 corresponds to –NCH_3 protons. A distinct multiplet appeared at δ 2.81, equivalent to one proton, could be assigned to H_{7exo}. $H_{10'}$ protons are found to appear as two doublets at δ 3.06 and 3.12 (J = 13.3 Hz). Another multiplet appearing at δ 3.19, integrating for one proton, may be attributed to bridgehead H_1 whereas bridgehead H_5 is found to appear as a broad singlet at δ 3.37. A characteristic doublet of a doublet at δ 3.42 (J = 7.6, 4.3 Hz) is assigned to H_{6endo}. A triplet at δ 3.75 (J = 5.6 Hz), integrating for one proton, is characterized to $H_{2'}$. Thus, the structure of compound **163b** is tentatively assigned as 8-methyl-6-*exo*-bornane-2,10-sultam-8-azabicyclo[3.2.1]octane. This assignment is further confirmed by carrying out ^{1}H NMR decoupling and COSY experiments.

^{13}C NMR spectrum displayed eighteen carbon signals for aliphatic carbons between δ 16.11-67.33 along with a carbonyl carbon signal at δ 174.39 (Fig. 18). DEPT experiment suggested that the methylene carbon signals at ä 16.11, 26.06, 28.35, 28.44, 28.84, 29.10, 32.44, 52.80 can be assigned to C_3, C_2, C_4, C_7, $C_{5'}$, $C_{6'}$, $C_{3'}$ and $C_{10'}$ carbons. The three methyl carbons signaling at δ 19.44, 20.45 and 38.12 may be attributed to $C_{8'}$, $C_{9'}$ and $-N\underline{C}H_3$ respectively. Methine carbon signals at δ 39.09, 44.25, 61.71, 65.34, 67.33 are characteristic of C_6, $C_{4'}$, C_1, $C_{2'}$ and C_5 respectively. The quaternary carbon signals at δ 47.37 and 47.88 are characterized to $C_{7'}$ and $C_{1'}$

Mass spectrum showed molecular ion peak at 366 (M^+, 11), and a base peak at 97 along with other prominent fragmentation peaks at 152 (24), 124 (17), 82 (57).

Characterization of 164b:



IR spectrum showed a strong absorption band at 1690 cm^{-1} characteristic of amide functionality.

^1H NMR spectrum showed following characteristic patterns:

Two sharp singlets at δ 0.72 and 1.05, integrating for three protons each, are characterized to the methyl protons of $C_{8'}$ and $C_{9'}$. The three multiplets between δ 1.20-2.10, accounting for total fourteen protons, are assigned to the methylene protons (*exo* and *endo*) present in the two bicyclic systems. A distinct multiplet at δ 2.12-2.20, integrating for one proton, is assigned to H_{7exo}. A sharp singlet at δ 2.21 corresponds to $-NCH_3$ protons. $H_{10'}$ protons and bridgehead H_1 are observed to appear as multiplet at δ 2.95-3.10. A triplet at δ 3.65 (J = 5.6 Hz), integrating for one proton, could be assigned to bridgehead H_5. Another

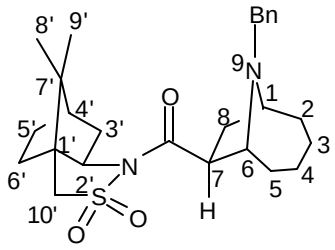
multiplet at δ 3.75, integrating for one proton, is characterized to H_{6exo}. $H_{2'}$ proton appeared as two doublets at δ 4.08 and 4.15 (J = 13.6 Hz).

From the above interpretation of ^{1}H NMR spectrum, the structure of **164b** was tentatively assigned as 8-methyl-6-*endo*-bornane-2,10-sultam-8-azabicyclo[3.2.1]octane. This assignment was further confirmed by carrying out ^{1}H NMR COSY experiment.

^{13}C NMR spectrum displayed a total of eighteen carbon signals in the aliphatic region in between δ 15.11 to 65.74 along with a characteristic carbonyl carbon signal at δ 171.34. DEPT experiment suggested that the signals at δ 19.88 and 20.60 are methyl carbons that could be assigned to $C_{8'}$ and $C_{9'}$. Methylene carbon signals at δ 15.11, 26.48, 26.93, 28.36, 31.42, 32.77, 38.50, 53.06 are assigned to C_3, C_2, C_4, C_7, $C_{5'}$, $C_{6'}$, $C_{3'}$ and $C_{10'}$ respectively. The methyl carbon signal at δ 41.13 corresponds to $-N\underline{C}H_3$. Methine carbon signals at δ 44.57, 46.44, 61.77, 65.49 and 65.74 could be assigned to $C_{4'}$, C_6, C_1, $C_{2'}$, C_5 respectively. The quaternary carbon signals at δ 47.67 and 47.97 are characterized by $C_{7'}$ and $C_{1'}$ respectively.

Mass spectrum showed molecular ion peak at 366 (M^+, 11) and a base peak at 97 along with other similar fragmentation peak as observed in the case of minor isomer.

Characterization of 163c:



IR spectrum showed a strong absorption band at 1669 cm^{-1} for carbonyl group. ^{1}H NMR spectrum showed following characteristic patterns (fig.19):

Two sharp singlets at δ 0.52 and 1.08, corresponding to three protons each, are assigned to methyl protons of $C_{8'}$ and $C_{9'}$. The six bunches of multiplets appearing in between δ 0.68–

2.18, accounting for total fifteen protons, could be assigned to methylene protons (*exo* and *endo*) present in two bicyclic systems. Two distinct multiplets appearing at δ 2.33–2.43 and 2.48–2.57, corresponding to one proton each, may be attributed to H_{8endo} and H_{8exo} respectively. Two doublets at δ 2.87 and 2.92 (J = 13.7 Hz) are assigned to $H_{10'}$ protons. Bridgehead H_1 appeared as a broad singlet at δ 3.22 whereas bridgehead H_6 was found to appear as triplet at δ 4.20 (J = 4.1 Hz). Two benzylic protons are observed as two sets of doublets at δ 3.63 and 3.94 (J = 13.4 Hz). Another triplet at δ 3.80 (J = 4.1 Hz), corresponding to one proton, is characteristic of $H_{2'}$. A doublet of a triplet appeared at δ 4.45 (J = 8.9, 3.6 Hz), equivalent to one proton, could be assigned to H_{7endo}. The five aromatic protons have appeared as two sets of multiplets at δ 7.10-7.30 and 7.50-7.60.

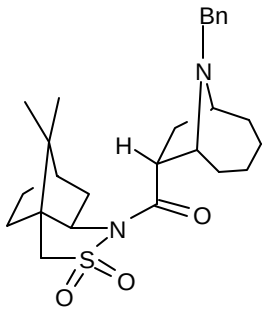
Based on the above ^{1}H NMR spectral evaluation, tentatively the stereochemistry of the product is assigned as 9-benzyl-7-*exo*-bornane-2, 10-sultam-9-azabicyclo[4.2.1]nonane. This assignment was further confirmed by carrying out ^{1}H NMR decoupling and COSY experiments (Fig. 20).

^{13}C NMR spectrum displayed nineteen carbon signals in the aliphatic region in between δ 19.75-66.71 besides aromatic signals at δ 126.44, 127.88, 128.18, 140.89 and a characteristic carbon signal at δ 172.33 for amide group (Fig. 21). DEPT experiment suggested that the methyl carbons signaling at δ 19.75 and 20.65 are characteristic of $C_{8'}$ and $C_{9'}$. Methylene carbon signals at δ 24.67, 26.36, 29.55, 31.52, 32.65, 34.89, 36.10, 38.60, 53.03 and 61.23 could be assigned to C_3, C_2, C_4, C_5, C_8, $C_{5'}$, $C_{6'}$, $C_{3'}$, $C_{10'}$ and –N<u>C</u>H_2Ph respectively. Methine carbon signals at δ 44.37, 48.15, 62.67, 65.51 and 66.71 are characterized by $C_{4'}$, C_7, C_1, $C_{2'}$ and C_6 respectively. The two quaternary carbon signals at δ 47.48, 47.67 are characterized by $C_{7'}$ and $C_{1'}$ respectively.

Mass spectrum revealed the presence of molecular ion peak at 456 (M^+ 7) and a base peak at 214 along with other fragmentation peaks at 242 (6), 186 (11), 91 (66), 81 (49), 69 (98).

Characterization of 164c:

IR spectrum showed a strong absorption band at 1669 cm^{-1} for carbonyl amide functionality.



^{1}H NMR spectrum showed following characteristic pattern:

Two sharp singlets observed at δ 0.46 and 1.10, integrating for three protons each, are assigned to methyl protons of $C_{8'}$ and $C_{9'}$. The four bunches of multiplets in between δ 0.58-2.45, accounting for total seventeen protons, could be assigned to the methylene protons (*exo* and *endo*) present in two bicyclic ring systems. The two $H_{10'}$ methylene protons appeared as two sets of doublets at δ 2.78 and 2.82 (J = 13.5 Hz). A multiplet at δ 3.21 was accorded to bridgehead H_1. A doublet of a doublet at δ 3.65 (J = 5.6, 4.2 Hz) is characterized to $H_{2'}$. Two sets of doublets at δ 3.75 and 3.95 (J = 13.6 Hz) are assigned to two benzylic protons. Another multiplet appearing at δ 4.25-4.45, integrating for two protons, may be attributed to bridgehead H_6 and H_{7exo}. The aromatic protons have appeared as two multiplets between δ 7.15-7.30 and 7.45-7.55. From the above interpretation of ^{1}H NMR spectrum the structure of the compound **164c** was tentatively assigned as 9-benzyl-7-*endo*-bornane-2, 10-sultam-9-azabicyclo[4.2.1]nonane.

Furthermore, this assignment was confirmed by analyzing ^{1}H NMR COSY spectrum in a similar manner as described earlier.

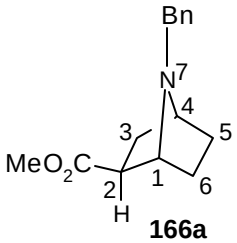
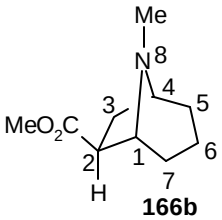
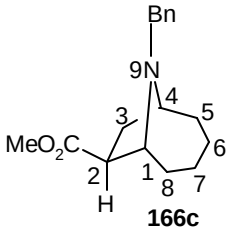
^{13}C NMR spectrum revealed nineteen carbon signals in between δ 19.76-66.46 in the aliphatic region besides aromatic carbon signals at δ 126.42, 127.86, 128.22, 140.94 and a carbonyl carbon signal at δ 171.71. DEPT experiment suggested that the methyl carbon signals at δ 19.76 and 20.50 are assigned to $C_{8'}$ and $C_{9'}$. Methylene carbon signals at δ 24.44, 24.86, 26.40, 31.33, 32.16, 32.74, 34.76, 38.48, 52.97, 61.15 could be assigned to C_3, C_2, C_4, C_5, C_8, $C_{5'}$, $C_{6'}$, $C_{3'}$, $C_{10'}$ and $-N\underline{C}H_2Ph$ respectively. Methine carbon signals at δ 44.61, 48.63, 62.92, 65.30 and 66.46 are assigned to $C_{4'}$, C_7, C_1, C_2 and C_6 respectively. The two quaternary carbon signals at δ 47.60 and 47.97 are characterized to $C_{7'}$ and $C_{1'}$ respectively.

Mass spectrum revealed the presence of molecular ion peak at 456 (M^+, 7) and a base peak at 69 along with other similar fragmentation peaks as observed with compound **164c.**

5. Synthesis of X-azabicyclo[m.2.1]alkanes by removing the chiral auxiliary from 163:

The manifestation of our asymmetric [3+2]-cycloaddition methodology in the chiral synthesis of X-azabicyclo[m.2.1]alkanes was firmly evaluated with the cleavage of chiral auxiliary from the major diastereomeric cycloadducts **163**. The removal of chiral auxiliary from cycloadduct **163** was achieved by hydrolysis carried out by warming **163** with $LiOH.H_2O$ in $MeOH:H_2O$ (3:1) for 45 min. The acids **164**, thus obtained, was isolated as the corresponding methyl ester **166** prepared by the reaction of $SOCl_2$ in dry methanol at 0°C. Compound **166** was characterized by IR, ^1H NMR, ^{13}C NMR and Mass analyses and are shown in Fig. 22, 23, 24. ^1H NMR spectra and optical rotation of **166** is shown in Table 2.

Table-2

Substrate	H_3, H_5, H_6, H_7, H_8 (*exo* and *endo* protons)	H_2	Bridge head H_4	Bridge head H_1	NCH_2Ph / NCH_3	OCH_3	$[á_D]^{25}_{obs}$
 **166a**	1.35-1.42 (m, 2H), 1.60 (dd, *J* = 12.2, 9.2 Hz, 1H), 1.82-1.95 (m, 2H) 2.22-2.36 (m, 1H)	2.45 (dd, *J* = 9.2, 4.9 Hz)	3.42 (t, J = 5.9 Hz)	3.65 (bs)	3.50 (d, *J* = 13.7 Hz, 1H) 3.60 (d, *J* = 13.7 Hz, 1H)	3.70 (s, 3H)	+22.38 (c = 0.52, $CHCl_3$)
 **166b**	1.35-1.60 (m, 4H), 1.75-1.95 (m, 3H), 2.45 (m, 1H)	2.85 (dd, *J* = 9.8, 5.9 Hz)	3.17-3.27 (m)	3.55 (bs)	2.25 (s, 3H)	3.70 (s, 3H)	-04.50° (c = 0.64, $CHCl_3$)
 **166c**	1.30-1.52 (m, 2H), 1.55-1.85 (m, 7H), 2.52-2.65 (m, 1H)	2.83 (dd, *J* = 8.9, 3.6 Hz)	3.45-3.54 (m)	3.55-3.62 (m)	3.85 (s, 2H)	3.70 (s, 3H)	+15.69° (c = 0.54, $CHCl_3$)

It may be worth mentioning at this juncture that the asymmetric synthesis of these representative azabicyclic compounds (**166**) were necessary for gaining advance knowledge prior to launching into the total synthesis of their natural products.

Summary

In summary, we have developed an asymmetric general route for the construction of X-azabicyclo[m.2.1]alkanes. The basic skeleton was constructed by [3+2]-cycloaddition of cyclic AMYs with Oppolzer's chiral dipolarophile. This commending methodology not only holds promise to be extremely useful in the synthesis of natural product targets, but also makes a new entry into the field of asymmetric 1,3-dipolar cycloaddition. Due to its generality coupled with excellent diastereoselection in the cycloaddition step, this methodology should deserve more credit over the existing protocol.

Experimental

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (110°C), which was dried under argon. All organic layers obtained from extractions were dried over anhydrous Na_2SO_4. Solvents for anhydrous reactions were dried according to the procedure outlined in Perrin's book. Benzene, THF, DCM, triethyl amine were distilled from CaH_2. Solvents used for chromatography were distilled at respective boiling points.

All commercial reagents were obtained from Aldrich Chemical Co. Progress of the reaction was monitored by TLC and was visualized by UV absorption, by fluorescence quenching or I_2 staining or by both. Silica gel for column chromatography was 60-120 or 200-430 mesh obtained from S.D. Fine Chemical, India or SRL, India.

All melting points were uncorrected in degree Celsius and were recorded on a Thermonik melting point apparatus. IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^1H NMR spectra were recorded using TMS as internal reference on Bruker AC-200, Bruker MSL-300, DRX-500 instruments using $CDCl_3$ and/or C_6D_6 as solvent. Chemical shifts are reported in δ. ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker MSL-300 instruments operating at 50.32 MHz and 75.3 MHz, respectively. Mass spectra were recorded on Finnigan – Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 ev.

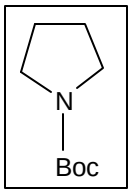
1. Preparation of AMY Precursor 149:

1.1 Preparation of N-(*tert*-butoxycarbonyl) derivatives of cyclic amines 152:

To a solution of cyclic amine **151** (92.3 mmol) and Et_3N (11.6 g, 115.3 mmol) in dioxan (50 mL), tert-butyl azidoformate (11.0 g, 76.9 mmol) was added drop-wise over a period of 15 min. The pH of the reaction mixture was maintained at 12 by the addition of excess Et_3N if required. The reaction mixture was stirred until a clear solution resulted. After the evaporation of dioxan, the residue was taken up in ether, washed twice with water (75 mL)

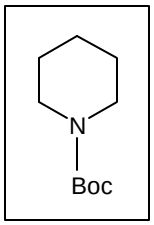
followed by brine (75 mL). Ether was evaporated and the resultant brown oil obtained was purified by vacuum distillation (b.p. 55-60 °C/1 mm) to obtain **152** (90-95 %) as colorless oil. The characteristic data of individual N-(*tert*-butoxycarbonyl) derivatives of cyclic amines **152** are given below:

152a:



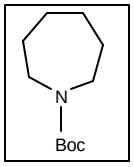
IR (Neat)	:	1700, 1400, 1160, 1110 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 1.45 (s, 9H), 1.80–1.95 (m, 4H), 3.37 (t, *J* = 7.3 Hz, 4H)
Mass (m/z)	:	171 (M^+, 11), 114 (100), 57 (82).

152b :



IR (Neat)	:	2940, 1695, 1420, 1385, 1260, 1170 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 1.45 (s, 9H), 1.58-1.78 (m, 6H), 3.31-3.45 (m, 4H).
Mass (m/z)	:	185 (M^+, 66), 129 (53), 84 (63), 57 (100).

152c:

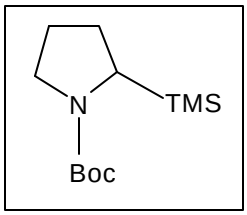


IR (Neat)	:	2929,1693, 1368, 1278 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.45(s, 9H), 1.55-1.65 (m, 4H), 1.68-172 (m, 4H) 3.30-3.45 (m, 4H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	26.66, 27.19, 28.29, 46.39, 46.75,78.58, 155.30

1.2 Preparation of N-*tert*-butoxycarbonyl-2-trimethylsilyl derivatives of cyclic amines 153:

A solution of N-Boc derivative of cyclic amine **152** (20.1 mmol) in 40 mL of dry ether was charged into a 250 mL flask, equipped with a magnetic bar and argon gas balloon and was cooled to −78 °C. TMEDA (2.79 g, 24.12 mmol) followed by s-BuLi (1.5 M solution in cyclohexane, 16.1 mL, 24.12 mmol) were introduced to the stirring mixture dropwise over 15 min. The mixture was further allowed to stir for 2 h at −78 °C. TMSCl (2.61 g, 24.12 mmol) was added dropwise into the flask. The reaction mixture was allowed to warm to room temperature and diluted with 15 mL of saturated aqueous NH_4Cl solution. The organic layer was concentrated and the crude oily residue was purified by fractional distillation (b.p. 55-60 °C/0.5 mm) to give **153** (80-90 %) as colorless oil. The characteristic data of **153** is given below:

153a:



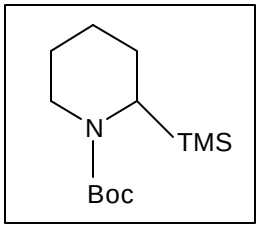
IR (Neat) : 1692, 1478, 1365, 1246, 1170 cm^{-1}

^{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 ($CDCl_3$) (50.32 MHz) : δ -2.30, 27.80, 28.40, 46.70, 47.50, 78.00, 154.50.

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

153b:



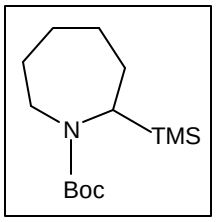
IR (Neat) : 1688, 1415, 1159, 1098, 838 cm^{-1}

^{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 ($CDCl_3$) (50.32 MHz) : δ -1.0, 23.05, 25.70, 28.10, 45.00, 78.40, 154.50.

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

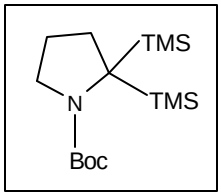
153c:



IR (Neat)	:	2927, 1685, 1406, 1365 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)		δ 0.05 (s, 9H), 1.45(s, 9H), 1.55-1.90 (m, 8H), 2.50- 2.72 (m, 2H), 3.60-3.85 (m, 1H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ -2.58, 27.40, 27.51, 28.52, 28.90, 29.08, 29.20, 29.63, 29.73, 44.10, 18.29, 78.78, 155.56
Mass (m/z)	:	271 (M^+, 1), 214 (55), 200 (78), 170 (100), 73 (95)

1.2 Preparation of N-(*tert*-Butyloxycarbonyl)-2,2-bis(trimethylsilyl)pyrrolidine 156:

Treating a solution of **153a** (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 **152**, followed by quenching with TMSCl (2.61 g, 24 mmol) and usual work-up and purification by silica gel chromatography gave 4.09 g (65 %) of **156** as a pale yellow oil.

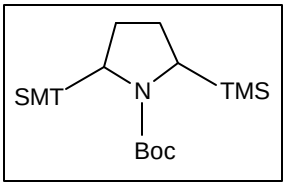


IR (Neat)	:	1690, 1392, 1248, 1169 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	ä 0.1 (s, 18H), 1.45 (s, 9H), 1.75-182 (m, 2H), 1.95 (t, *J* = 6.8 Hz, 2H), 3.35 (t, *J* = 6.8 Hz, 2H).
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	ä 0.18, 25,50, 28.80, 32.20, 46.50, 48.50, 78.10, 154.60.
Mass (m/z)	:	258 (72), 244 (70), 21 (37), 186 (36), 73 (100).

1.4 Preparation of N-Boc- a ,a ¢-bis(trimethylsilyl) derivatives of cyclic amines (154):

A 250 mL two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of **153a/153b** (20 mmol) in 30 mL of dry ether and was cooled to −45 °C. TMEDA (2.79 g, 24 mmol) followed by s-BuLi (1.5 M in cyclohexane, 15.92 mL, 24 mmol) were added to the flask dropwise while stirring. After 15 min of stirring at −45 °C, temperature was raised to −30 °C. After 30 min, it was recooled to −45 °C and TMSCl (2.6 g, 24 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, diluted with 10 mL of saturated aqueous NH_4Cl solution and worked up as mentioned in previous experiment to get an oily residue which was further purified by silica gel column chromatography to give **154a/154b** (70-75 %) as pale yellow oil.

154a:



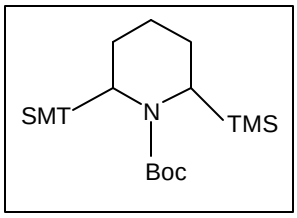
IR (Neat)	:	1684, 1406, 1365, 1171 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 0.05 (s, 18H), 1.45 (s, 9H), 1.75-2.00

(m, 4H), 3.00–3.10 (bs, 1H), 3.20-3.30 (bs, 1H).

^{13}C NMR ($CDCl_3$) (50.32 MHz) : δ -1.03, -0.50, 28.93, 29.00, 49.44, 50.00, 154.82.

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

154b:



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 ($CDCl_3$) (50.32 MHz) : δ -0.70, 0.12, 24.70, 26.20, 26.91, 28.70, 47.70, 48.52, 78.82, 155.80.

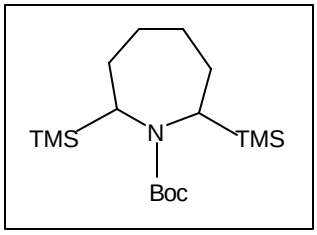
Mass (m/z) : 272 (100), 258 (46), 242 (66), 228 (51), 200 (80), 156 (44), 73 (98).

1.4.1. Preparation of N-Boc-2, 7-bis(trimethylsilyl)hexamethylene imine (154c):

A 250 mL two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of **153c** (4.1 g, 15.0 mmol) in 30 mL of dry ether and was cooled to −78 °C. TMEDA (3.2 g, 18.1 mmol) followed by s-BuLi (1.5 M in cyclohexane,

12.1 mL, 18.1 mmol) were added to the flask drop-wise while stirring. After 15 min of stirring at −78 °C, temperature was raised to −40 °C. The solution was allowed to stir for additional 4 h at this temperature. TMSCl (2.7 g, 18.1 mmol) was added drop-wise and the reaction mixture was allowed to warm to 0 °C. 10 mL of saturated aqueous NH_4Cl solution was added and worked-up as mentioned earlier. The crude oily residue was purified by column chromatography eluting with hexane to give 3.5 g (68 %) of **154c** as a colorless oil.

154c



IR (Neat)	:	1684, 1421, 1175 cm^{-1}
^1H NMR($CDCl_3$): (200 MHz)	:	δ 0.5 (s, 18H), 1.45 (s, 9H), 1.55-1.62 (m, 4H), 1.80-2.0 (m, 4H), 2.15-2.20 (m, 1H) 3.50-3.60 (m, 1H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ -2.28, -0.41, 27.57, 28.86, 29.27, 29.94, 32.00, 47.27, 49.04, 78.64, 155.16
Mass (m/z)	:	328 (M^+, 5), 287 (26), 242 (86), 215 (51), 171 (36), , 98 (78), 73 (98)

1.4. Preparation of N-alkyl-a ,a ¢-bis (trimethylsilyl) derivatives of cyclic Amines 149:

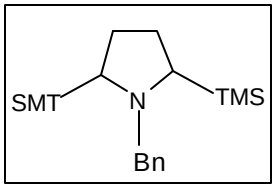
Into a stirring solution of **154** (10.0 mmol) in 40 mL of dry DCM at 0 °C, contained in a 100 mL round bottom flask, equipped with argon gas balloon, was added TFA (5.7 g, 50.0 mmol) drop-wise over 30 min. The mixture was allowed to warm to room temperature and allowed to stir further for 4 h. The reaction mixture was recooled to 0 °C and was basified with 20 % aqueous NaOH solution (pH = 10). The organic layer was separated and the aqueous layer was extracted with DCM (2 x 30 mL). The combined extracts were washed with

brine, dried over Na_2SO_4 and concentrated to give crude amine **155**, which was utilized as such without further purification for the next step.

1.4.1. Preparation of N-Benzyl- a ,a ¢-bis (trimethylsilyl) derivatives of cyclic amines (149a/149c):

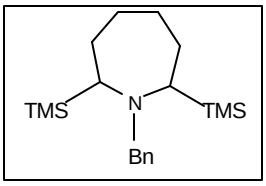
To a solution of the crude amine (**155a**/**155b**) (8.59 mmol) in 40 mL dry CH_3CN, K_2CO_3 (1.49 g, 10.8 mmol) and benzyl chloride (1.08 g, 8.59 mmol) were added. The resultant suspension was refluxed for 5–6 h. Progress of the reaction was monitored by TLC. On completion of the reaction, mixture was cooled, filtered and the solvent was evaporated under vacuum. The crude yellow oil was purified by silica gel column chromatography eluting with hexane/EtOAc (98:2) to obtain **149a**/**149c** as pale yellow oil (80-85 % yield).

149a:



IR (Neat)	:	3028, 2951, 1452, 1248, 935 cm^{-1}
^1H 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* = 12.8 Hz, 1H), 3.8 (d, *J* = 12.8 Hz, 1H), 7.20-735 (m, 5H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ -1.60, 26.81, 56.03, 60.10, 126.80, 128.10, 129.40, 141.70
Mass (m/z)	:	305 (M^+, 3), 290 (17), 233 (100), 91 (90), 73 (54)

149c:

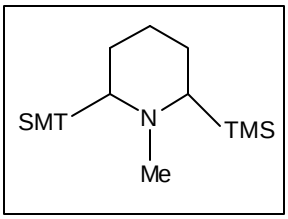


IR (Neat)	:	2921, 2850, 1450, 1245 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 0.05 (s, 18H), 1.58-165 (m, 2H), 1.78-1.98, (m, 6H), 2.38-2.48 (m, 2H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.88 (d, *J* = 13.6 Hz, 1H), 7.30-7.45 (m, 5H).
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ -1.53, 27.83, 29.28, 29.62, 51.96, 58.12, 126.51, 127.79, 127.85, 129.83, 141.18
Mass (m/z)	:	333 (M^+, 1), 318 (6), 260 (100), 188 (38), 91 (32), 73 (29)

1.4.2. Preparation of N-Methyl-2,6-bis(trimethylsilyl)-piperidine (149b):

To a stirring solution of crude amine **155b** (3.1g, 13.67 mmol) in CH_3CN (120 mL), 37 % aqueous solution of HCHO (1.5 mL) and $NaBH_3CN$ (1.71 g, 27.35 mmol) were added. The reaction mixture was stirred for an additional 15 min. Neutralization of the reaction mixture by adding gl. CH_3COOH followed by basification by the slow addition of conc. NH_4OH and extraction with hexane (3 x 50 mL) followed by concentration and purification of the residue by silica chromatography, eluting with EtOAc:hexane (3:97), gave **149b** (2.65 g, 80 % yield) as a colorless viscous liquid.

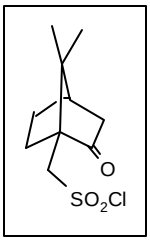
149b:



^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 0.06 (s, 18H), 1.52–1.67 (m, 6H), 2.21 –2.32 (m, 2H), 2.55 (s, 3H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ -1.23, 20.70, 24.33, 42.45, 54.12
Mass (m/z)	:	243 (M^+, <1), 226 (1.3), 184 (100), 96 (4.5), 73 (85).

2. Preparation of Oppolzer's Chiral Acryloyl Dipolarophile, (-)- 111:

2.1 Preparation of (+)-Camphor sulfonyl chloride (158):

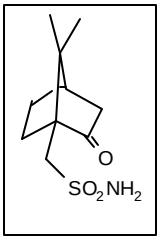


A 250 mL two neck RB flask, containing a magnetic bar, was charged with freshly distilled thionyl chloride (27 mL, excess) with one side neck fitted with an addition tube containing recrystallized D(+)-Camphor sulfonic acid, (21 g, 9.05 mmol) and the other side neck connected to a $CaCl_2$ guard tube. The addition of **157** was initiated in portions at 0 °C with vigorous stirring. The immediate reaction of **157** with $SOCl_2$ was monitored by noting the gas evolved out through the $CaCl_2$ guard tube. The addition was continued at the same temperature for 2 h. After the addition was over, the cooling bath was removed and the

mixture was allowed to stir for 2 h at room temperature. The reaction mixture was essentially left for standing for 3-4 h. The black reaction mixture was then poured into 500 g of crushed ice contained in a 500 mL beaker. The mixture was immediately poured into a second beaker containing a similar quantity of crushed ice. The mixture was poured back and forth between the two beakers until all evidence of reaction had disappeared. The fine white product was collected on a suction filter and washed several times with ice-cold water. The moist sulfonyl chloride was dried under vacuum to give 19.8 g (85 %) of D(+)-Camphor sulfonyl chloride m.p. 65-67 °C (lit.[39] m.p. 67-69 °C).

The crude white solid of (+)-**158** was used in the next step without further purification

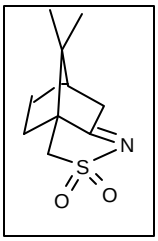
2.2 Preparation of S(+)-10-Camphorsulfonamide (159):



Into a 1 L three-neck round bottom flask, equipped with mechanical stirrer, teflon stirring blade and a 250 mL dropping funnel, was charged 250 mL of reagent grade NH_4OH. The reaction mixture was cooled to 0 °C in an ice bath and stirred vigorously. A solution of 25.0 g (0.1 mol) of (+)-Camphorsulfonyl chloride (**158**) in 250 mL of CH_2Cl_2 was then added drop-wise in two portions over 30 min. The reaction mixture was stirred for an additional 2 h. at this temperature, transferred to a 1000 mL separating funnel and the phases were separated. The aqueous phase was washed with CH_2Cl_2 (2 x 100 mL) and the combined organic extracts were dried for 10-15 min. over anhydrous Na_2SO_4. Filtration and removal of the solvent using a rotary evaporator gave 205 g (90 %) of **159**, m.p. 123-125 °C (lit.[39] 125-128 °C).

^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 0.93 (s, 3H), 1.07 (s, 3H), 1.40–2.50 (m, 7H), 3.14 (AB quartet, *J* = 15.1 Hz, 1H), 3.53 (AB quartet, *J* = 15.1 Hz, 1H), 5.54 (bs, 2H).

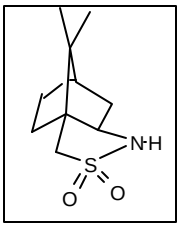
2.3. Preparation of (-)-(Camphorsulfonyl)imine (160) :



Into a 500 mL round bottom flask were charged 20.5 g of the crude sulfonamide and 2 g of Amberlyst 15 ion exchange resin in 250 mL of toluene. The reaction mixture was refluxed for 4 h under Dean-Stark condition. After the reaction flask was cooled, but while it is still warm (40-50 °C), 100 mL of DCM was added to dissolve any camphorsulfonyl imine that crystallized. The solution was filtered through sintered glass funnel and the reaction flask and filter funnel were washed with an additional 100 mL of DCM.

Isolation of the (-)-camphorsulfonyl imine was accomplished by removal of solvent under reduced pressure. The resulting solid was recrystallized from absolute ethanol (200 mL) to give white crystals, 18.5 g (91 %) m.p. 221-223 °C (lit.[39] m.p. 225-228 °C).

2.4. Preparation of (-)-D-2, 10-Camphorsultam (161):

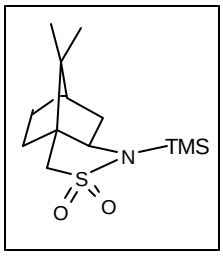


A 250 mL round bottom flask, equipped with a 100 mL Soxhlet extraction apparatus connected to an argon balloon and a magnetic bar, was charged with 120 mL of dry THF and 1.27 g (0.032 mol) of $LiAlH_4$. In the Soxhlet extraction thimble was placed 7.2 g (0.32 mol) of (-)-camphorsulfonyl imine and the reaction mixture was heated at reflux. After all the compound **160** has been siphoned into the reaction flask (3-4 h), the mixture was allowed to

cool to room temperature. The unreacted $LiAlH_4$ was cautiously hydrolyzed by drop-wise addition of 200 mL of 1N HCl. After the hydrolysis was complete the contents of the flask were transferred to a 1 L separating funnel, the lower silver-colored aqueous layer was separated, and the upper layer was placed in another round bottom flask. The aqueous phase was transferred back to the separating funnel and washed with DCM (3 x 100 mL). The combined organic washings were mixed with the THF phase and dried over Na_2SO_4. The removal of solvent under reduced pressure gave 6.8 g (85 %) of the crude (-)-2,10-camphorsultam. The repeated crystallization of crude (-)-2,10-camphorsultam from absolute ethanol gave pure **161** as white crystalline solid, m.p. 181-183 °C (lit.[39] m.p. 183 °C-184 °C, $[á_D]_{obs}$ -29.7° (c = 2, $CHCl_3$,).

^{1}H NMR ($CDCl_3$) (200 MHz)	:	ä 94 (s, 3H), 1.14 (s, 3H), 1.33 (m, 1H), 1.47 (m, 1H), 1.80-2.05 (m, 5H), 3.09 (d, *J* = 14.0 Hz, 1H), 3.14 (d, *J* = 14.0 Hz, 1H), 3.43 (m, 1H), 4.05 (bs, 1H).
^{13}C NMR ($CDCl_3$) (50.32 MHz)		δ 20.17, 26.51, 31.55, 35.72, 44.44, 47.15, 50.08, 54.46, 62.48.

2.5 Preparation of (-)-(1S,5R)-N-Trimethylsilyl) bornane-2,10-Sultam (162) :

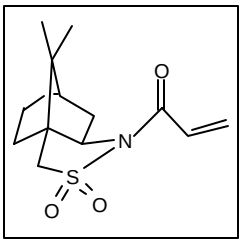


To a stirred solution of (+)-bornane-2,10-sultam **161** (5.0 g, 23 mol) in dry C_6H_6 (60 mL) containing CH_3CN (10 mL) was added TMSCl (14 mL, 0.11 mol). The mixture was then cooled in an ice bath and Et_3N (3.8 mL, 26 mmol) in dry C_6H_6 (20 mL) was added slowly resulting in the immediate formation of a white precipitate (Et_3N.HCl). After the addition was complete the mixture was stirred at room temperature for 15 h. The resultant suspension was concentrated and the white solid mass was triturated with toluene and the salt was removed by

filtration. Most of the solvent was removed at reduced pressure and the residue was allowed to stand and the resulting crystalline product collected by suction filtration to give the title compound **162** (6.0 g, 91 % yield) in sufficient purity for use in the next step, m.p. 89-90 °C (lit.[39] m.p. 91°-93 °C), $[\alpha_D]_{obs}$ – 52 ° (c =1.7, $CHCl_3$) (lit[39]. $[\alpha_D]_{obs}$ = -56° (c = 1.7, $CHCl_3$).

IR (Neat)	:	2922, 1457, 1296, 1138, 1026, 849 cm^{-1}.
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 0.35 (s, 9H), 0.91 (s, 3H), 1.11 (s, 3H), 1.28 (dd, *J* = 9.3, 7.7, Hz, 1H), 1.42 (dd, *J* = 9.3, 7.3 Hz, 1H), 1.77 (dd, *J* = 12.5, 8.0, Hz, 1H), 1.89–1.84 (m, 3H), 2.16-2.06 (m, 1H), 3.40 (s, 2H), 3.51 (dd, *J* = 8.0, 5.0Hz, 1H).
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ 0.35, 20.1, 20.4, 26.8, 32.1, 37.8, 45.0, 47.5, 51.6, 53.0, 66.8

2.6 Preparation of (-)-(1S, 5R)-N-N-Propenoylbornane-2, 10-sultam (111):



(-)-N-(Trimethylsilyl) bornane-2, 10-sultam **162** (5.0 g, 17.4 mmol) in dry benzene (25 mL) containing propenoyl chloride (5.7 mL, 70.2 mmol) and anhydrous $CuCl_2$ (0.234 g, 1.74 mmol) was heated at reflux for 16 h under N_2. The mixture was filtered while still warm and the reaction vessel washed with EtOAc. The combined filtrate and washings were concentrated to give a white solid (4.72 g) which was then recrystallized from toluene to give (3.9 g, 14.7 mmol) of **111** as white needles with 85 % yield. The mother liquors were concentrated and the residue was purified by chromatography on silica gel with 30 % EtOAc-Hexane (pet. ether : ethyl acetate = 70:30) as eluent to give further 0.47 g (total 4.37 g, 16.4

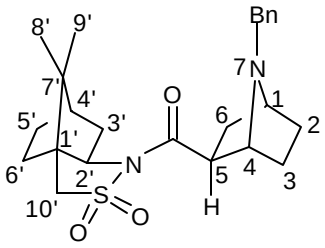
mmol, 95 %); m.p. 102- 105 °C (lit[39]. m.p. 105-107 °C); $[\alpha_D]^{25}_{Obs}$ = - 45° , (c = 5.5, $CHCl_3$) and $[\alpha_D]^{18}_{authentic}$ = - 48° (c = 5.5, $CHCl_3$).

IR (Neat)		2921, 1675, 1462, 1376, 1223, 1133, 879, 769 cm^{-1}.
^1H NMR ($CDCL_3$) (200 MHz)	:	δ 0.96 (s, 3H), 0.99 (s, 3H), 1.30-1.50 (m, 2H), 1.70 (m, 2H), 1.8–2.0 (m, 3H), 3.45 (d, *J* = 13.6 Hz, 2H), 3.8 (t, *J* = 5.6 Hz, 1H), 6.5 (d, *J* = 8.7 Hz, 1H), 6.9 (dd, *J* = 8.7, 7.6 Hz, 1H), 7.2 (d, *J* = 10.1 Hz, 1H)
^{13}C NMR ($CDCL_3$) (50.32MHz)	:	δ 20.08, 20.90, 26.53, 32.95, 38.55, 44.76, 47.90, 48.60, 53.20, 65.21, 127.87, 131.56, 163.90

3.0. [3+2]-Cycloaddition reaction of 149 with (-)-111:

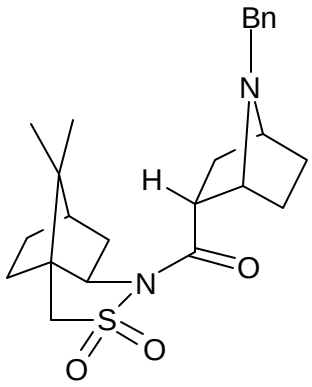
A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (10.20 mmol) (dried previously under vacuum at 40°C) and with a solution of dipolarophile (-)-**111** (1.64 g, 6.10 mmol) in 30 mL of dry DCM. Compound **149** (4.10 mmol) dissolved in 15 mL of dry DCM was introduced into the reaction flask drop-wise over a period of 15 min. The color of the reaction mixture gradually turned dark brown with the concomitant deposition of silver on the surface of the reaction flask in the form of mirror and the progress of the reaction was periodically monitored by TLC. After stirring for 6h, the reaction mixture was filtered through a small plug of Celite and the solvent was evaporated to give a brown residue. Purification of the crude residue by silica gel (60-120) column chromatography gave mixture of stereoisomers (*exo* and *endo*) with 58-68 % overall cycloaddition yield from which the ratio of *exo/endo* isomers were determined from their corresponding ^1H NMR spectra. The two isomers were separated by careful flash column chromatography. The analytical data of both isomers for each system are given below:

163a:



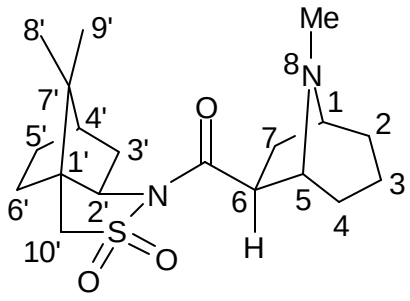
IR ($CHCl_3$)		3018, 1683 cm^{-1}
^1H NMR (C_6D_6) (500 MHz)		δ 0.52 (s, 3H), 0.70-0.78 (m, 1H), 0.88-0.95 (m, 1H), 1.05 (s, 3H), 1.20-1.30 (m, 1H), 1.40-1.45 (m, 2H), 1.55-1.65 (m, 2H), 1.75-1.85 (m, 2H), 1.94-1.98 (m, 1H), 2.01-2.08 (m, 2H) 2.30 and 2.35 (d, *J* = 4.0 Hz, *J* = 4.4 Hz, 1H), 2.85 (d, *J* = 13.6 Hz, 1H), 2.92 (d, *J* = 13.6 Hz, 1H), 3.18 (t, *J* = 4.4 Hz, 1H), 3.55 (d, *J* = 13.5 Hz, 1H), 3.68 (d, *J* = 13.5 Hz, 1H), 3.80 (t, *J* = 5.6 Hz, 1H), 4.23 (bs, 1H) 4.30 (dd, *J* = 5.6, 3.8 Hz, 1H), 7.2 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H)
^{13}C NMR (C_6D_6) (125 MHz)	:	δ 19.01, 20.12, 24.63, 25.91, 28.55, 29.54, 31.80, 38.27, 44.18, 46.99, 47.38, 47.82, 51.46, 52.10, 60.22, 63.61, 64.77, 126.49, 127.90, 128.63, 139.95, 172.48
Mass (m/z)	:	428 (M^+, 17), 337 (5), 214 (9), 186 (29), 159 (86), 91 (!00), 68 (9)
HRMS		Calculated for $C_{24}H_{32}N_2O_3S$: 428.213365 Observed: 428.213456
M.P.	:	135-137 °C

164a:



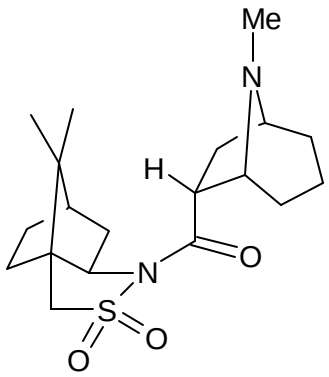
IR (Neat)	:	3019, 1683 $cm^{=1}$
^{1}H NMR (C_6D_6: $CDCl_3$) (500 MHz)	:	δ 0.42 (s, 3H), 0.92-0.99 (m, 1H), 1.02-1.08 (m, 2H), 1.23 (s, 3H), 1.32-1.48 (m, 2H), 1.55-1.70 (m, 1H), 1.85-1.95 (m, 1H, 2.05–2.35 (m, 6H), 2.95 (d, *J* = 13.6 Hz, 1H), 3.08 (d, *J* = 13.6 Hz, 1H), 3.32 (t, *J* = 4.3 Hz, 1H), 3.68 (d, *J* = 13.3 Hz, 1H), 3.72 (d, *J* = 13.3 Hz, 1H), 3.75 (t, *J* = 5.5 Hz, 1H), 4.08-4.15 (m, 1H), 4.35 (t, *J* = 4.1 Hz, 1H), 7.25–7.35 (m, 3H), 7.55 (d, *J* = 7.5 Hz, 2H)
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	δ 19.90, 20.84, 24.17, 26.52, 28.63, 29.66, 32.90, 38.79, 44.65, 45.84, 47.88, 48.37, 51.49, 53.23, 60.40, 63.63, 65.74, 126.84, 128.21, 128.76, 140.36, 173.71
Mass (m/z)	:	428 (M^+, 15), 337 (7), 214 (9), 186 (30), 159 (86), 91(100), 68 (9)
M.P.:	:	133-135 °C

163b:



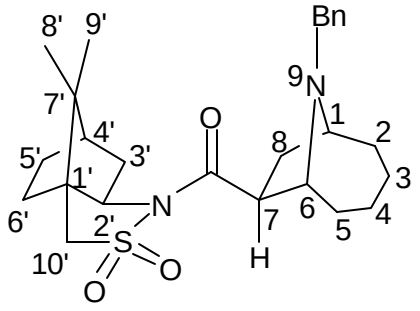
IR (Neat)	:	3018, 2927, 1689 cm^{-1}
^{1}H NMR (C_6D_6: $CDCl_3$= 1:1) (500 MHz)	:	δ 0.70 (s, 3H), 1.05 (s, 3H), 1.12-1.28 (m, 3H), 1.40-1.80 (m, 9H), 1.92-1.95 (m, 2H), 2.30 (s, 3H), 2.78-2.85 (m, 1H), 2.95 (d, *J* = 13.6 Hz, 1H), 3.08 (d, *J* = 13.6 Hz, 1H) 3.17-3.20 (m, 1H), 3.37 (bs, 1H), 3.42 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.75 (t, *J* = 5.6 Hz, 1H).
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	δ 16.11, 19.44, 20.45, 26.06, 28.35, 28.44, 28.84, 29.10, 32.44, 38.12, 39.09, 44.25, 47.37, 47.88, 52.80, 61.71, 65.34, 67.33, 174.39.
Mass (m/z)	:	366 (M^+, 10), 152 (24), 124 (61), 97 (100), 82 (29)
HRMS		Calculated for $C_{19}H_{30}N_2O_3S$: 366.197715 Observed: 366.196762

164b:



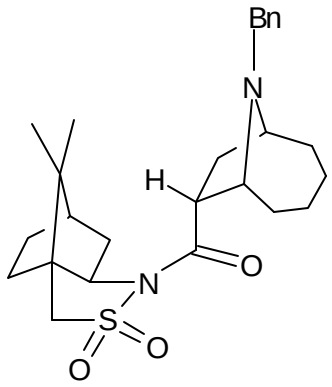
IR (Neat)	:	3018, 2928, 1690 cm^{-1}
^{1}H NMR (C_6D_6: $CDCl_3$ = 1:1)	:	δ 0.72(s, 3H), 1.05 (s, 3H), 1.20-1.30 (m, 3H), 1.40-1.75 (m, 9H), 1.80-2.10 (m, 2H), 2.12-2.20 (m, 1H), 2.21 (m, 3H), 2.95-3.10 (m, 3H), 3.65 (t, *J* = 5.6 Hz, 1H), 3.75 (m, 1H), 4.15 (dd, *J* = 7.9, 5.6 Hz, 1H),
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	δ 15.11, 19.88, 20.60, 26.48, 26.93, 28.36, 31.42, 32.77, 38.50, 41.13, 44.57, 46.44, 47.67, 47.67, 47.97, 53.06, 61.77, 65.49, 65.74, 174.3
Mass (m/z)	:	366 (M^+, 11), 152 (25), 124 (65), 97(100), 82 (30)
M.P.	:	169-171°C

163c



IR (Neat)	:	3028,1669, 1425 cm^{-1}
^{1}H NMR (C_6D_6) (500 MHz)	:	δ 0.52 (s, 3H), 0.68-0.75 (m, 1H), 0.82-0.90 (m, 1H), 1.08 (s, 3H), 1.17-1.25 (m, 1H), 1.37-1.45 (m, 3H), 1.62-1.70 (m, 1H) 1.78–2.18, (m, 8H), 2.33-2.43 (m, 1H), 2.48-2.57 (m, 1H), 2.87 (d, *J* = 13.7 Hz, 1H), 2.92 (d, *J* = 13.7 Hz, 1H), 3.22 (bs, 1H), 3.63 (d, *J* =13.4 Hz, 1H) 3.80 (t, *J* = 5.5 Hz, 1H) 3.94 (d, *J* = 13.4 Hz, 1H), 4.20 (t, *J* = 4.1 Hz, 1H), 4.45 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.10 – 7.30 (m, 3H), 7.50-7.60 (m, 2H)
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	δ 19.75, 20.65, 24.67, 26.36, 29.55, 31.52, 32.65, 34.89, 36.10, 38.60, 44.37, 47.48, 47.67, 48.15, 53.03, 61.23, 62.67, 65.51, 66.71, 126.44, 127.88, 128.18, 140.89, 172.33
Mass (m/z)	:	456 (M^+, 7), 242 (6), 214 (100), 186 (11), 91(66), 81 (49), 69 (98)
HRMS		Calculated for $C_{26}H_{36}N_2O_3S$: 456.244665 Observed: 456.244281
M.P.	:	205-207 °C

164c:



IR ($CHCl_3$)	:	3025, 1669, 1428 cm^{-1}
^1H NMR (C_6D_6: $CDCl_3$ = 1:1) (500 MHz)	:	δ 0.46 (s, 3H), 0.58-0.88 (m, 3H), 1.10 (s, 3H), 1.28-1.45 (m, 4H), 1.75-2.08 (m, 8H), 2.3-2.45, (m, 2H), 2.78 (d, *J* = 13.5 Hz, 1H), 2.82 (d, *J* = 13.5 Hz, 1H), 3.15-3.27 (m, 1H), 3.65 (dd, *J* = 5.6, 4.2 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 3.95 (d, *J* = 13.6 Hz, 1H), 4.25-4.45 (m, 2H), 7.10-7.30 (m, 3H), 7.45-7.55 (m, 2H)
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	δ 19.76, 20.50, 24.44, 24.86, 26.40, 31.33, 32.16, 32.16, 32.74, 34.76, 38.48, 44.61, 47.60, 47.97, 48.63, 52.97, 61.15, 62.92, 65.30, 66.46, 126.42, 127.86, 128.22, 140.94, 171.71.
Mass (m/z)	:	456 (M^+, 7), 242 (6), 214 (100), 186 (12), 91(65), 81 (49), 69 (95)
M.P.	:	210-212 °C

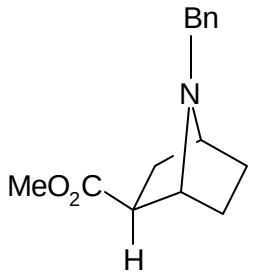
4.0. Preparation of X-Alkyl-2-*exo*-carbomethoxy-X-Azabicyclo[m.2.1] alkanes

(166):

A solution of **163** (1.10 mmol) in 12 mL THF:H_2O (3:1) mixture containing LiOH. H_2O (4.6 mg, 1.10 mmol) was warmed to 45 °C while stirring. After 45 min., mixture was cooled and the resulting solution was extracted with EtOAc (3 x 5 mL) to remove the sultam chiral

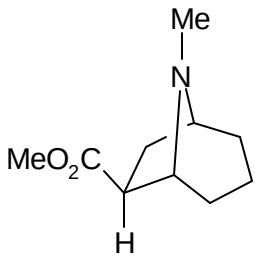
auxiliary **161.** The aqueous layer was acidified to pH 6-7 by careful addition of 3N HCl under ice-cold condition. The crude acid **165** thus obtained by evaporating the aqueous layer was used as such without further purification for the next step reaction. The crude acid **165** was dissolved in 15 mL of dry MeOH and was transferred to a 25 mL flask equipped with argon gas balloon. The freshly distilled $SOCl_2$ (0.7 mL, excess) was added to that solution at 0 °C over a period of 15 min. The solution was allowed to stir at this temperature for 4 h and it was allowed to stir for 6 h at rt. The solution was evaporated to dryness and dry $CHCl_3$ (20 mL) was added to it. The ammonia gas was passed through this suspension until basic (pH ~ 8). The suspension was filtered and evaporation of the solution gave crude methyl ester compound **166**. Purification of the crude mixture by column chromatography afforded optically pure methyl ester compound **166** in 82-85 % yield. Following analytical data are supplied for each methyl ester compound **166.**

166a



IR ($CHCl_3$)	:	2954, 1731, 1215 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 1.35–1.42 (m, 2H), 1.60 (dd, *J* = 12.2, 9.2 Hz, 1H), 1.82-1.95 (m, 2H), 2.22-2.36 (m, 1H), 2.45 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.42 (t, *J* = 5.9 Hz, 1H), 3.50 (d, *J* = 13.7 Hz, 1H), 3.60 (d, *J* = 13.7 Hz, 1H), 3.65 (bs, 1H), 3.7 (s, 3H), 7.20-7.35 (m, 5H).
Mass (m/z)	:	245 (M^+, 54), 230 (2), 216 (10), 186 (31), 158 (84), 91 (100), 65 (26)
HRMS		Calculated for $C_{15}H_{19}NO_2$: 245.141579 Observed: 245.141103

166b



IR ($CHCl_3$) : 2925, 2851, 1712 cm^{-1}

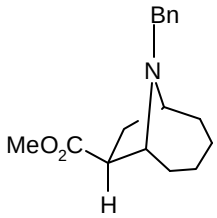
^1H NMR ($CDCl_3$) : δ 1.35–1.6 (m, 4H), 1.75-1.95 (m, 3H), 2.25 (s, 3H), 2.45 (m, 1H), 2.85 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.17-3.27 (m, 1H), 3.55 (bs, 1H), 3.70 (s, 3H).

^{13}C NMR ($CDCl_3$) (75.3 MHz) : ä 16.48, 29.23, 29.81, 30.03, 39.81, 46.62, 51.53, 61.79, 65.33, 176.0

Mass (m/z) : 183 (M^+, 10), 168 (<1), 152 (9), 140 (28), 124 (47), 96 (95), 82 (100).

HRMS Calculated for $C_{10}H_{17}NO_2$: 183.125929
Observed: 183.125856

166c:



IR ($CHCl_3$) : 2927, 1731, 1225 cm^{-1}

^1H NMR ($CDCl_3$) (200 MHz) : ä 1.30-1.45 (m, 2H), 1.55-1.85 (m, 7H), 2.52–2.65 (m, 1H), 2.83 (dt, *J* = 8.9, 3.6 Hz, 1H), 3.45-3.62, (m, 2H), 3.70 (s, 3H), 3.85 (s, 2H), 7.25-7.35 (m, 5H)

^{13}C NMR ($CDCl_3$): (75.3 MHz)	:	ä 24.44, 25.11, 33.05, 34.73, 36.09,51.28, 51.69, 60.18, 64.08, 67.65, 126.66, 128.05, 128.18, 140.64, 177.22
Mass (m/z)	:	273 (M^+, 56), 258 (1), 242 (10), 214 (100), 186 (21), 158 (45), 91 (92), 65 (19).
HRMS		Calculated for $C_{17}H_{23}NO_2$: 273.172879 Observed: 273.172606

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4. See ref. 32
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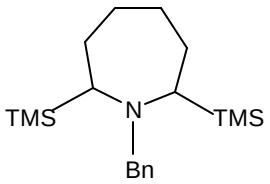
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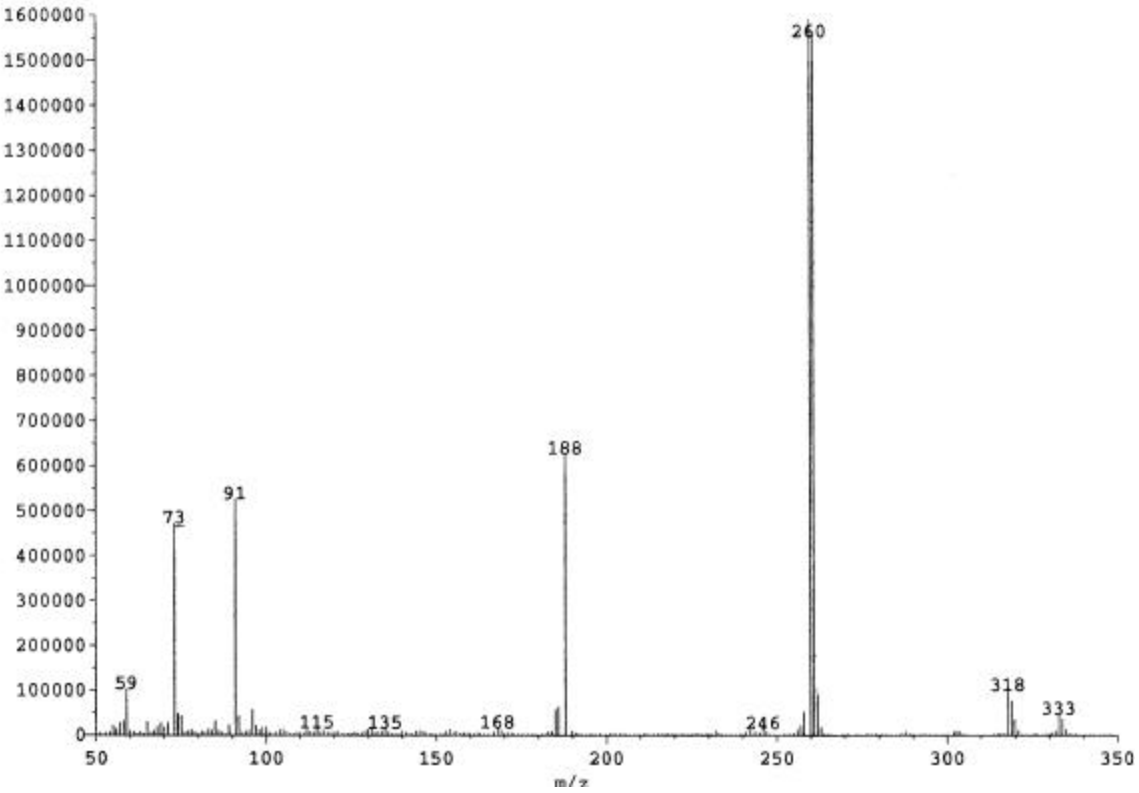
N
TMS
Bn

149c

Fig. 12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100000
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300
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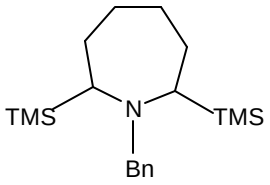
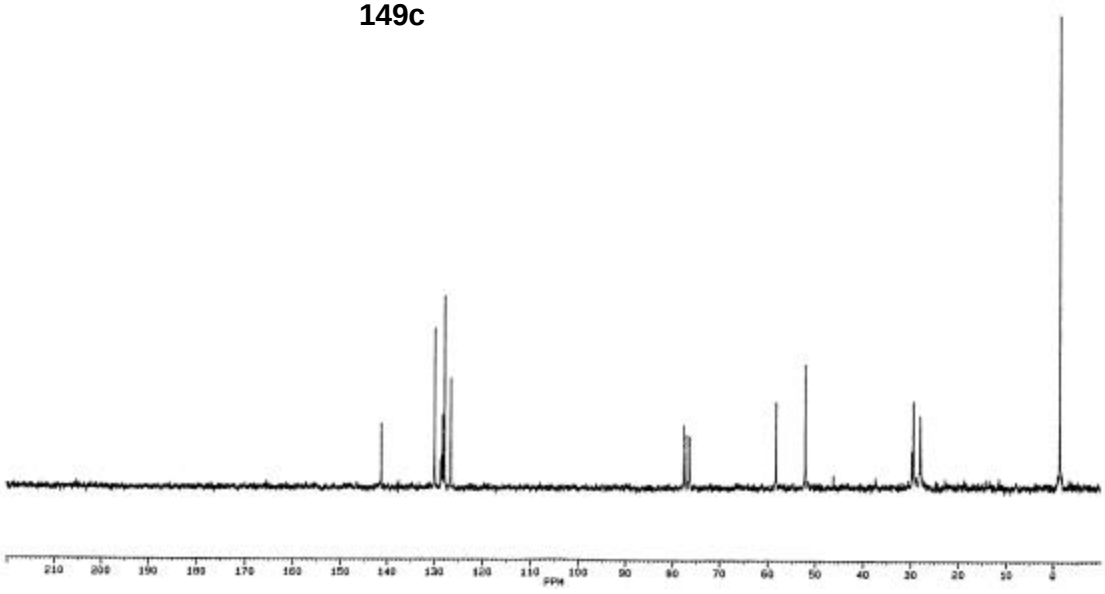
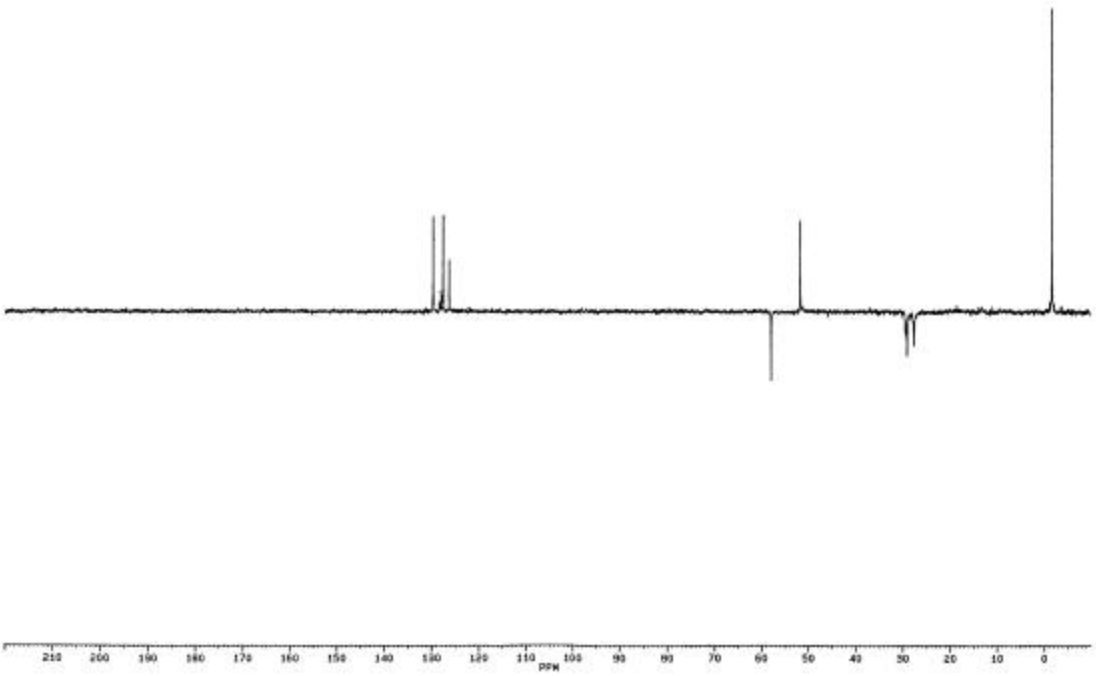
73
91
115
135
168
188
246
260
318
333

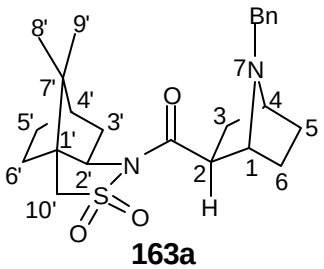


149c

Fig. 13

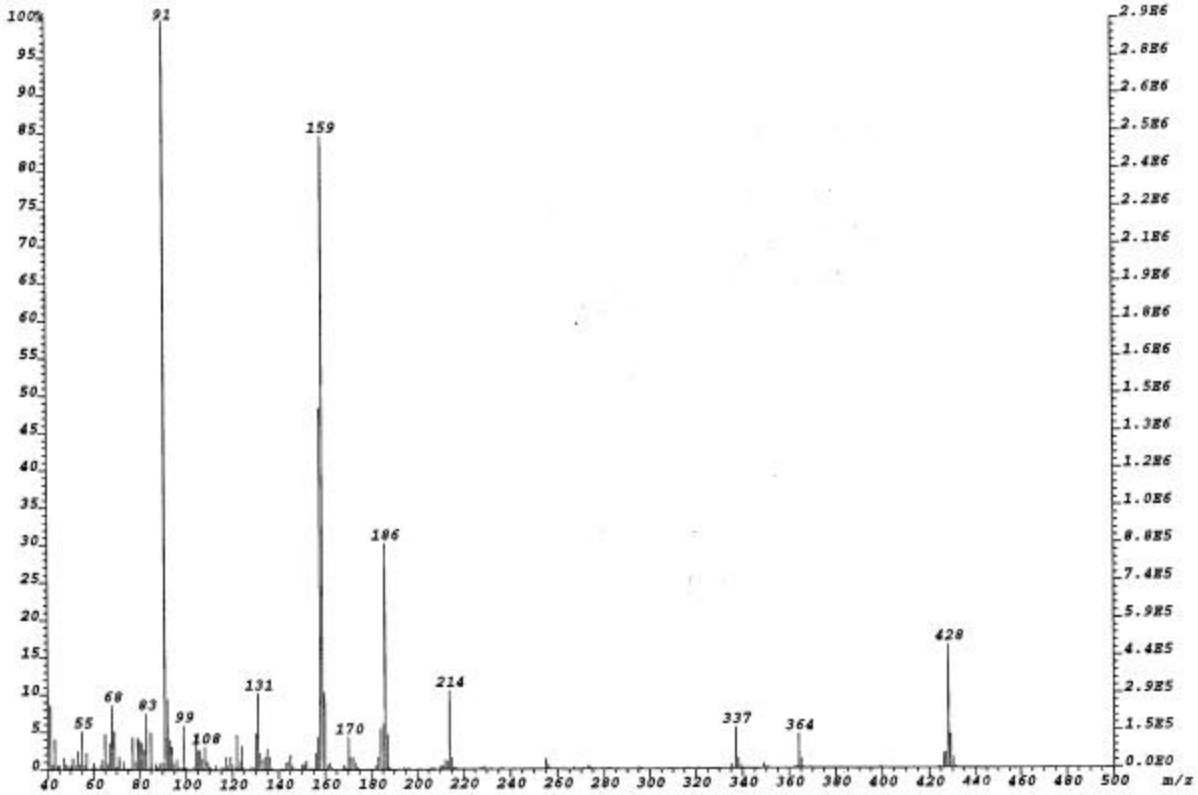





8'
9'
Bn
7'
7N
4'
O
4
5'
3'
3
5
1'
1
6'
2'
N
2
6
S
10'
O
O
H

163a

Fig. 14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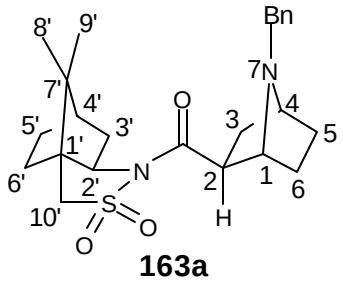
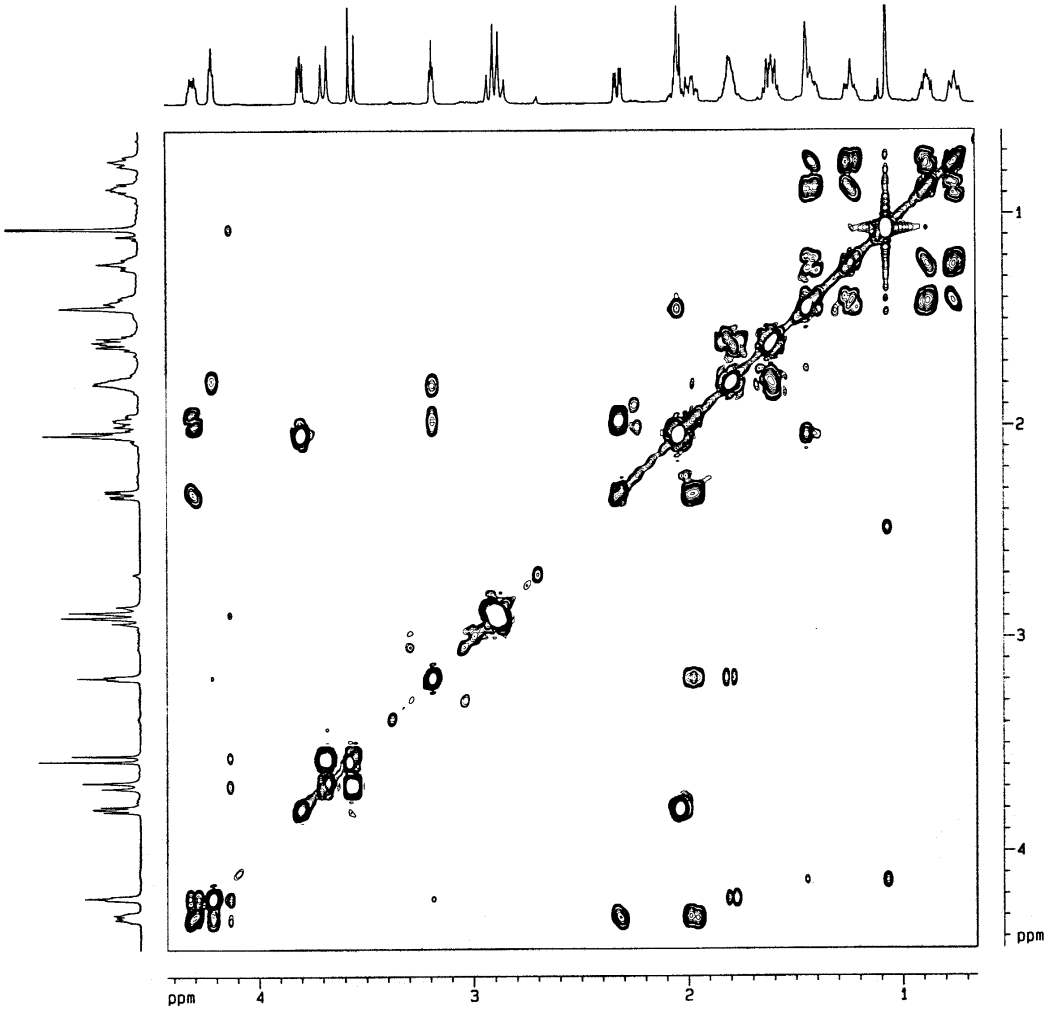
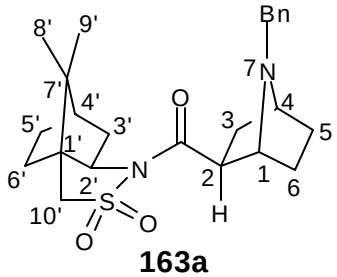
196
214
131
429
337
364
170
m/z



163a

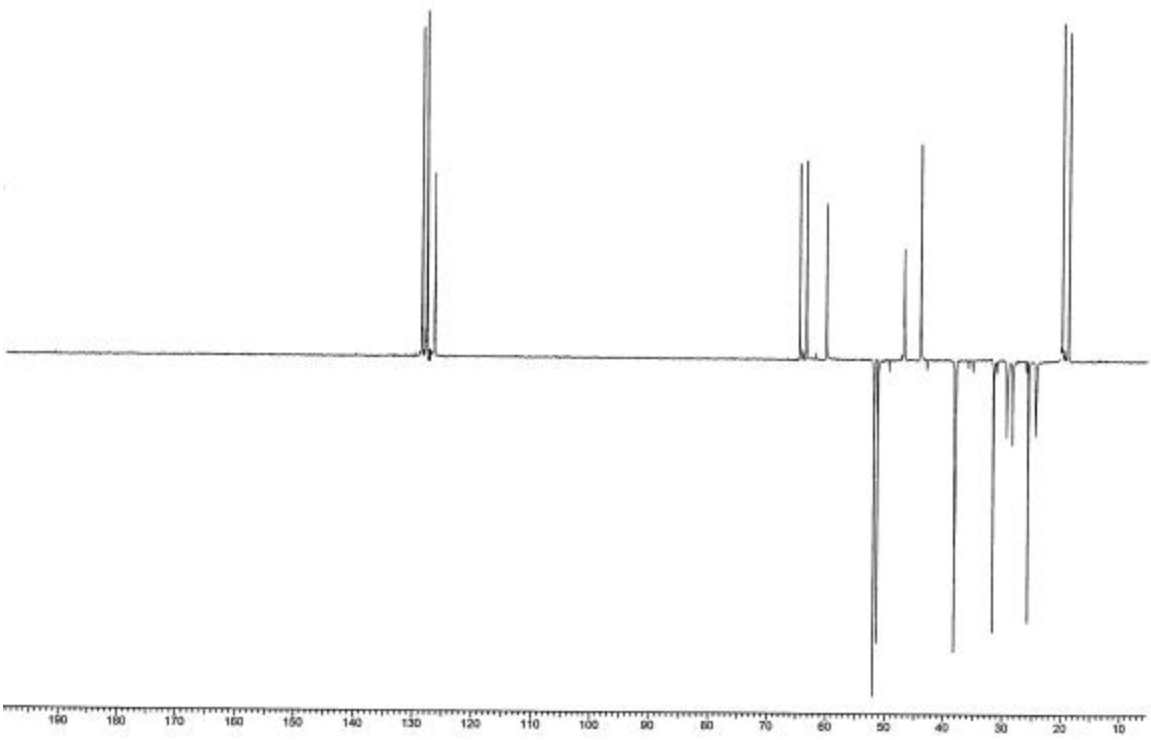
Fig. 15

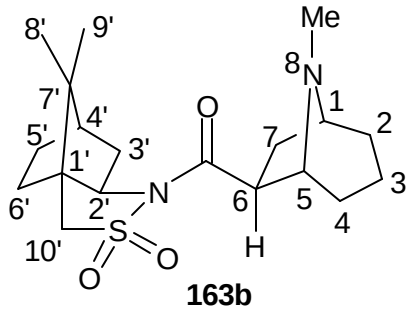




163a

Fig. 16

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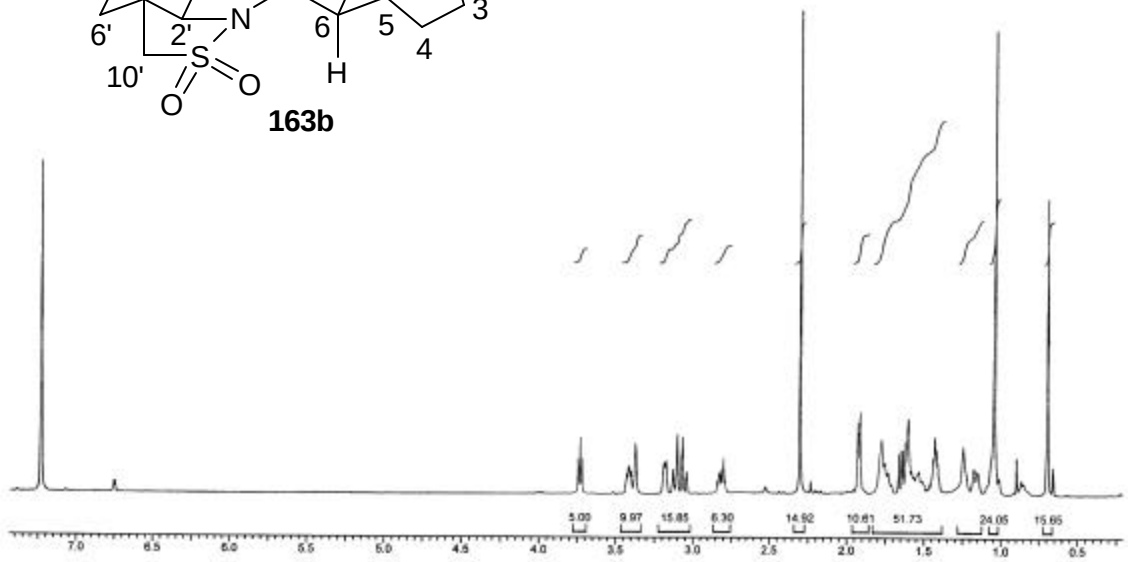
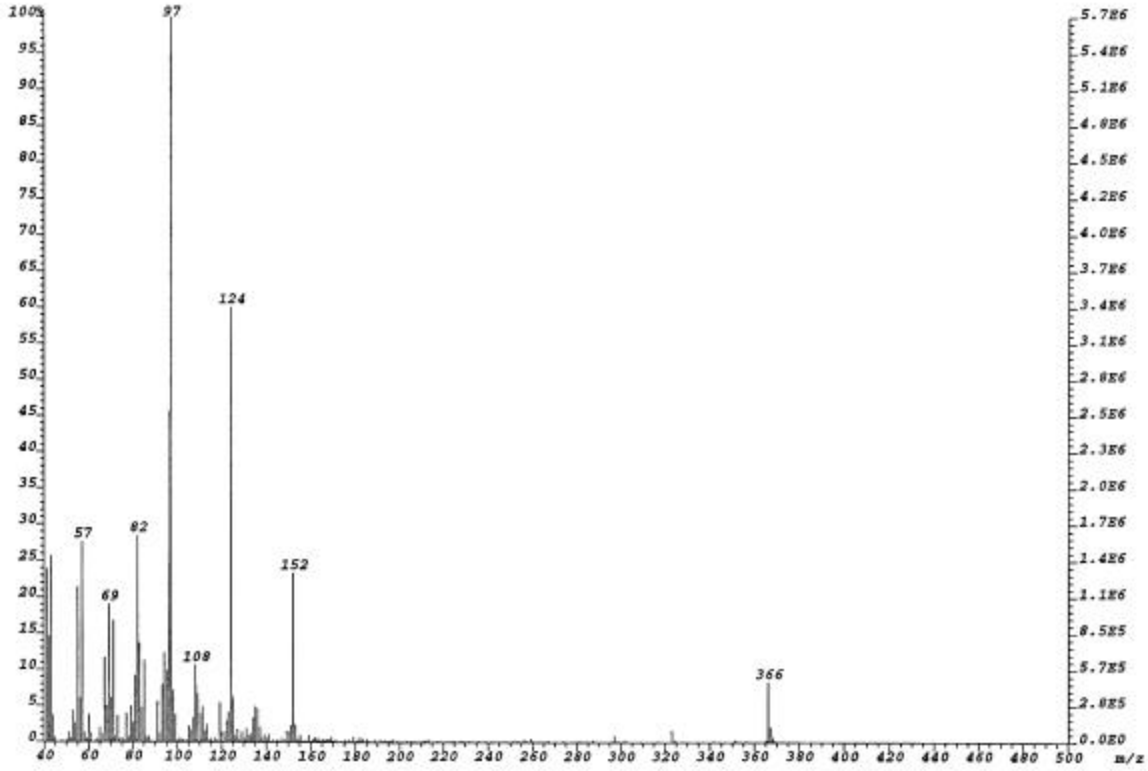
8'
9'
8
N
7'
4'
O
1
2
5'
3'
7
1'
N
6
5
3
6'
2'
4
S
10'
O
O
H

163b

Fig. 17

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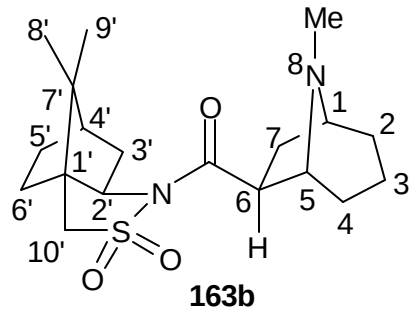
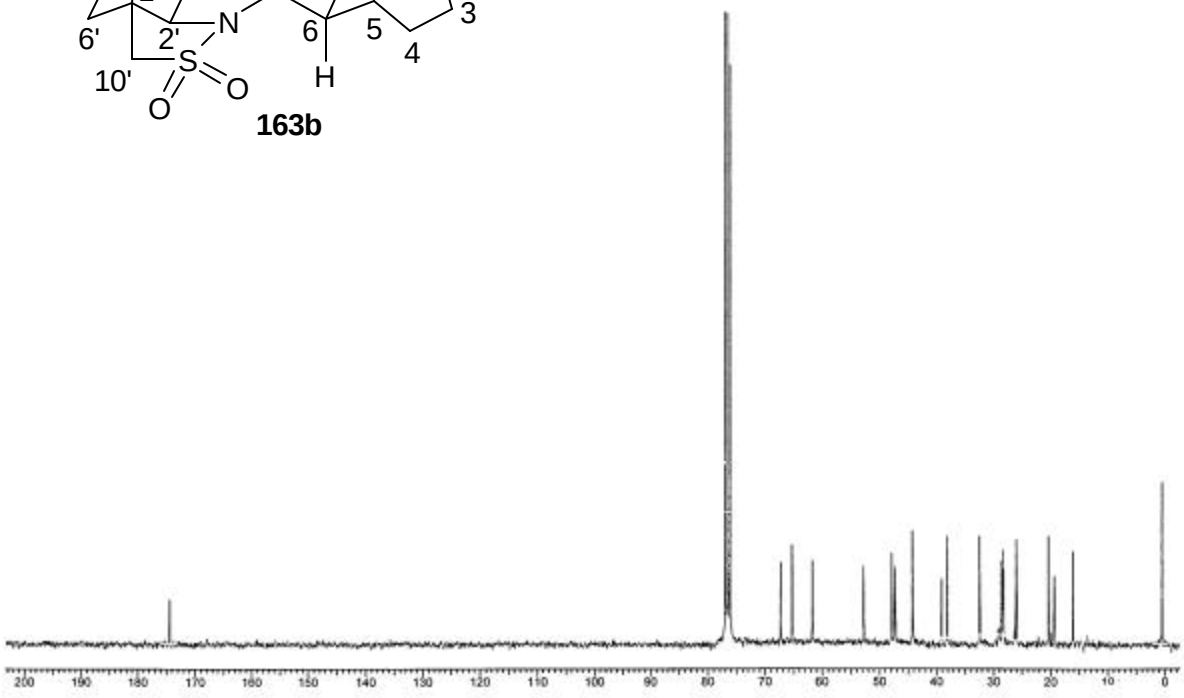
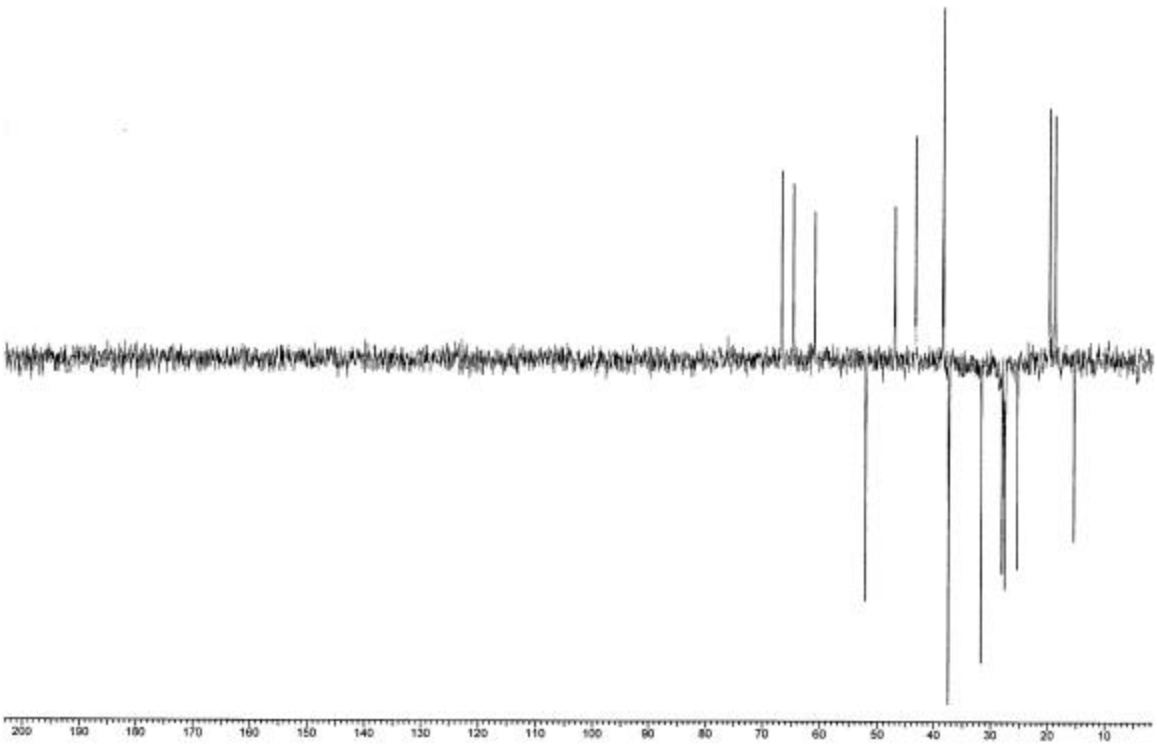
124
57
92
69
152
108
366
m/z

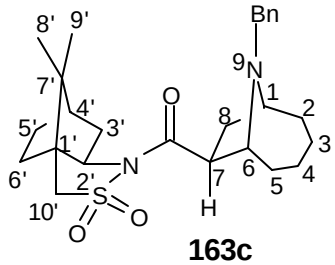


163b

Fig. 18

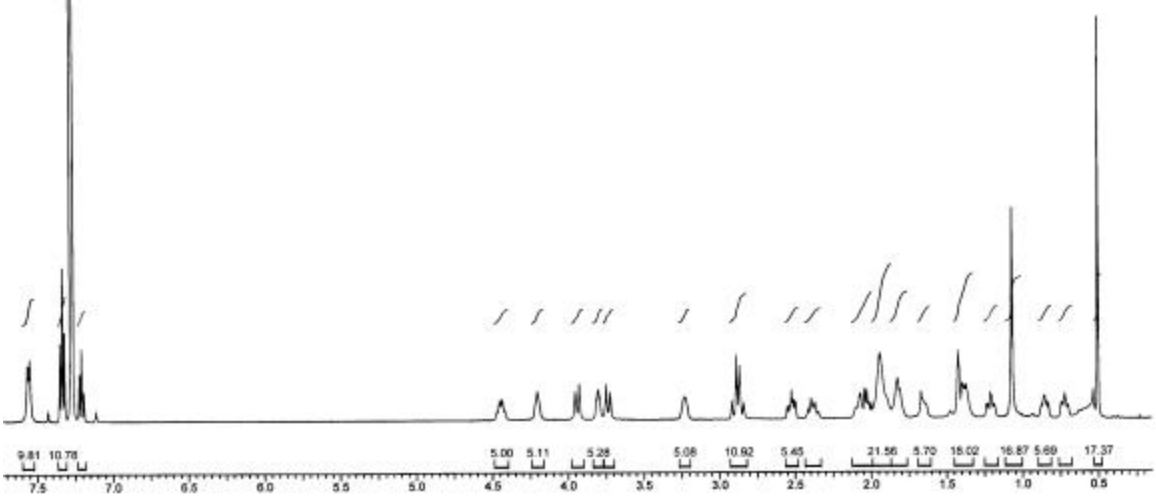


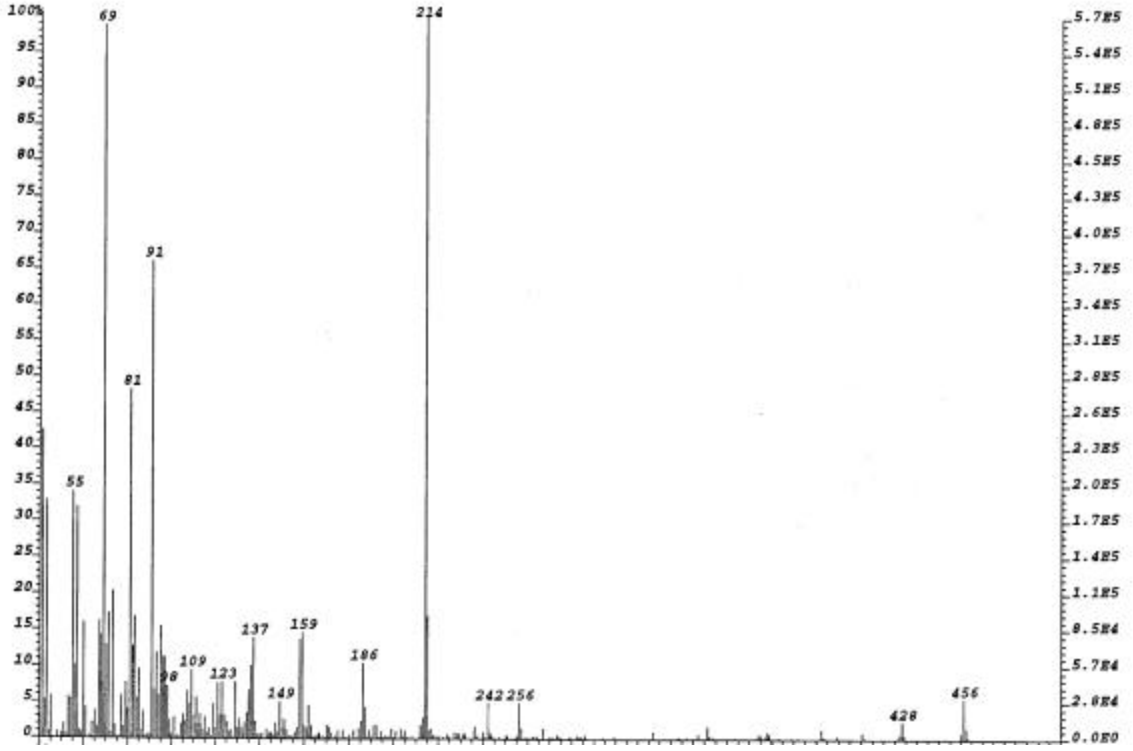



Bn
9
N
1
2
3
4
5
6
7
8
O
H
8' 9'
7'
4'
3'
5'
1'
6'
2'
N
S
O
O
10'

163c

Fig. 19

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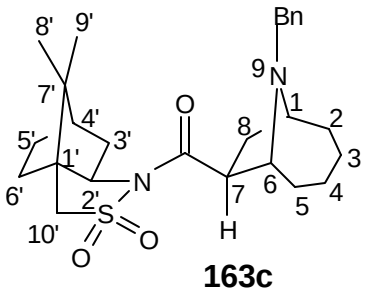
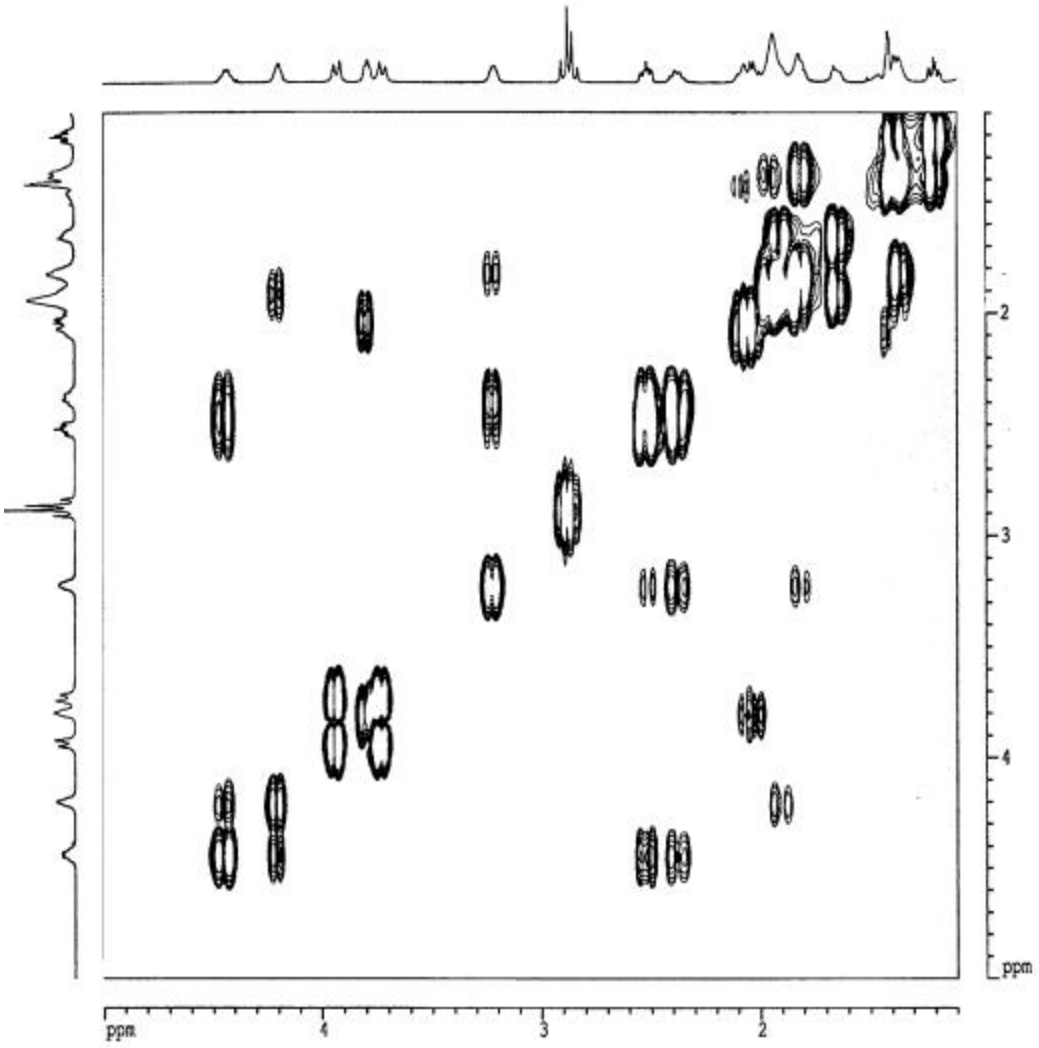
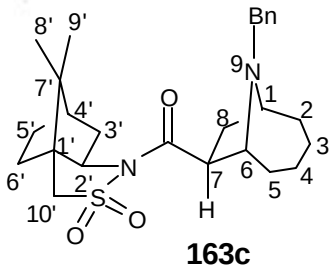
242
256
428
456



163c

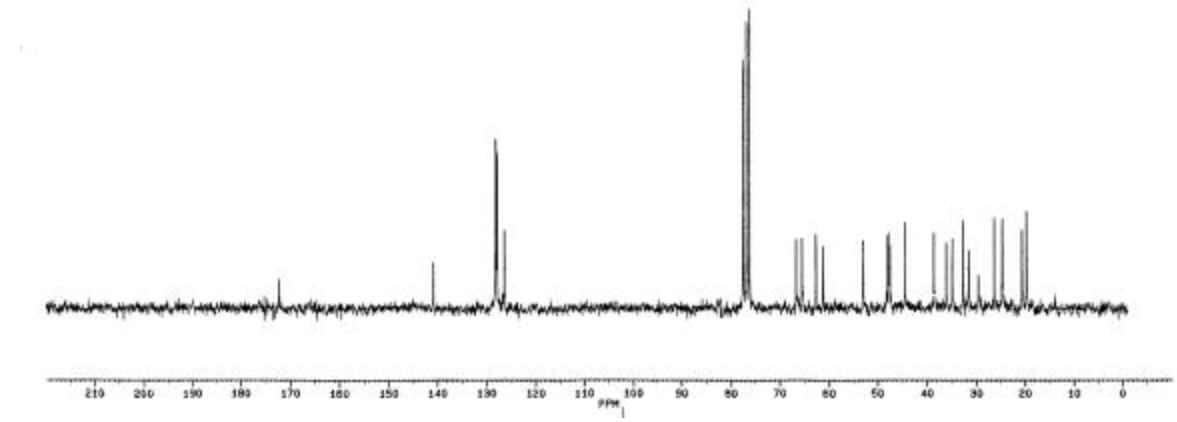
Fig. 20

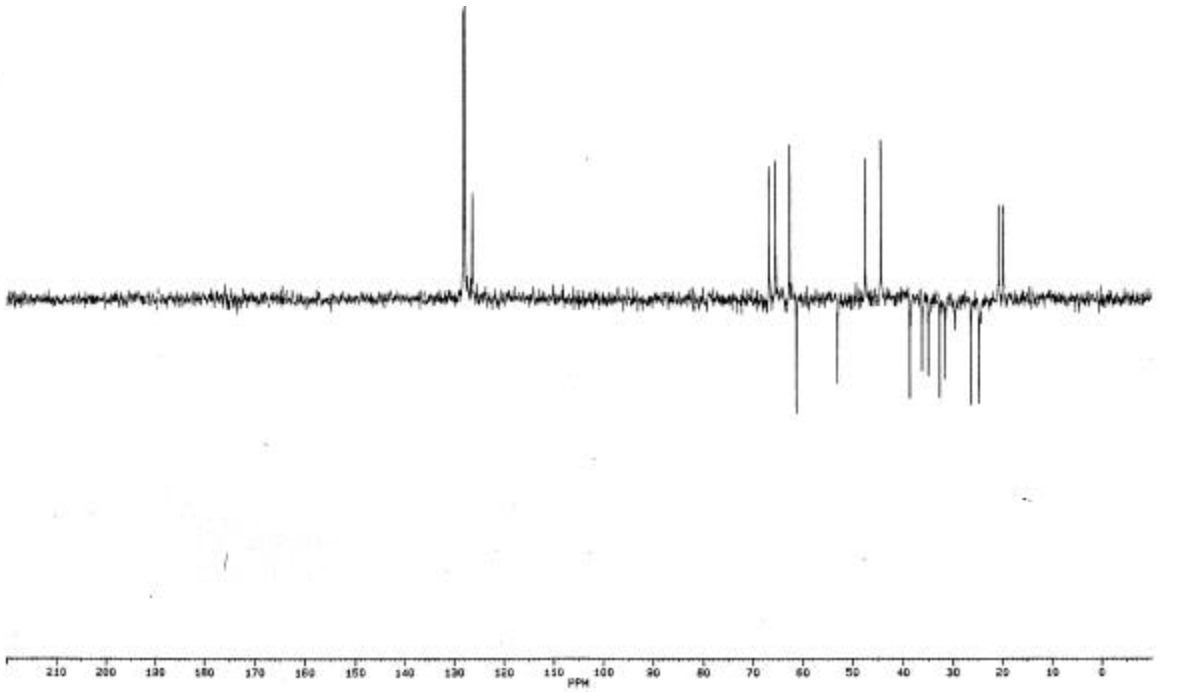


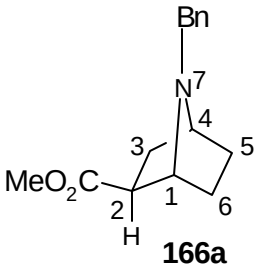


163c

Fig. 21



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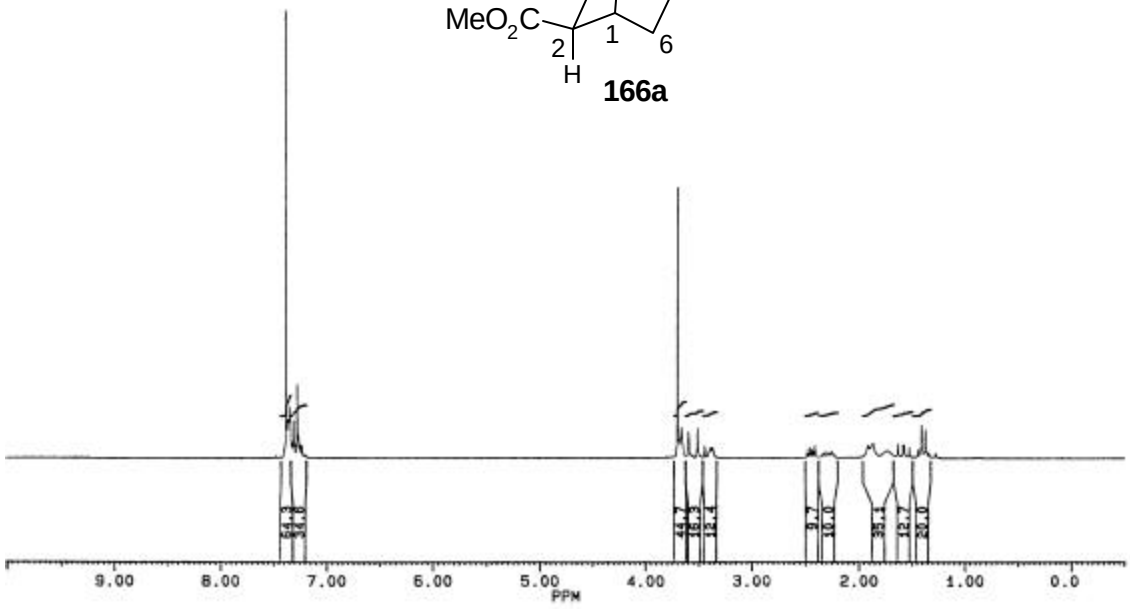
N
7
4
3
5
MeO2C
2
1
6
H

166a

Fig. 22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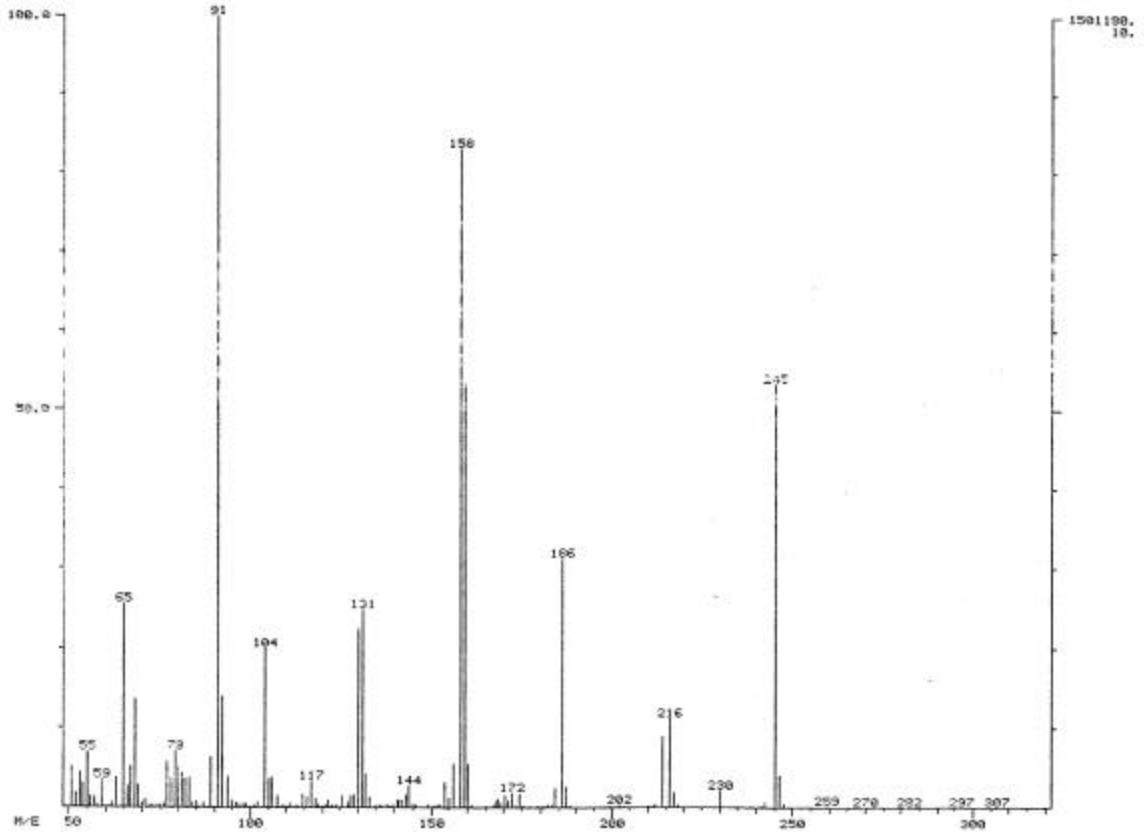
5.00
4.00
3.00
2.00
1.00
0.0
PPM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M/E
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202
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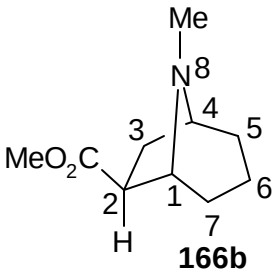
100
150
200
250
300


Me
N
8
4
3
5
MeO2C
1
6
2
7
H

166b

Fig. 23

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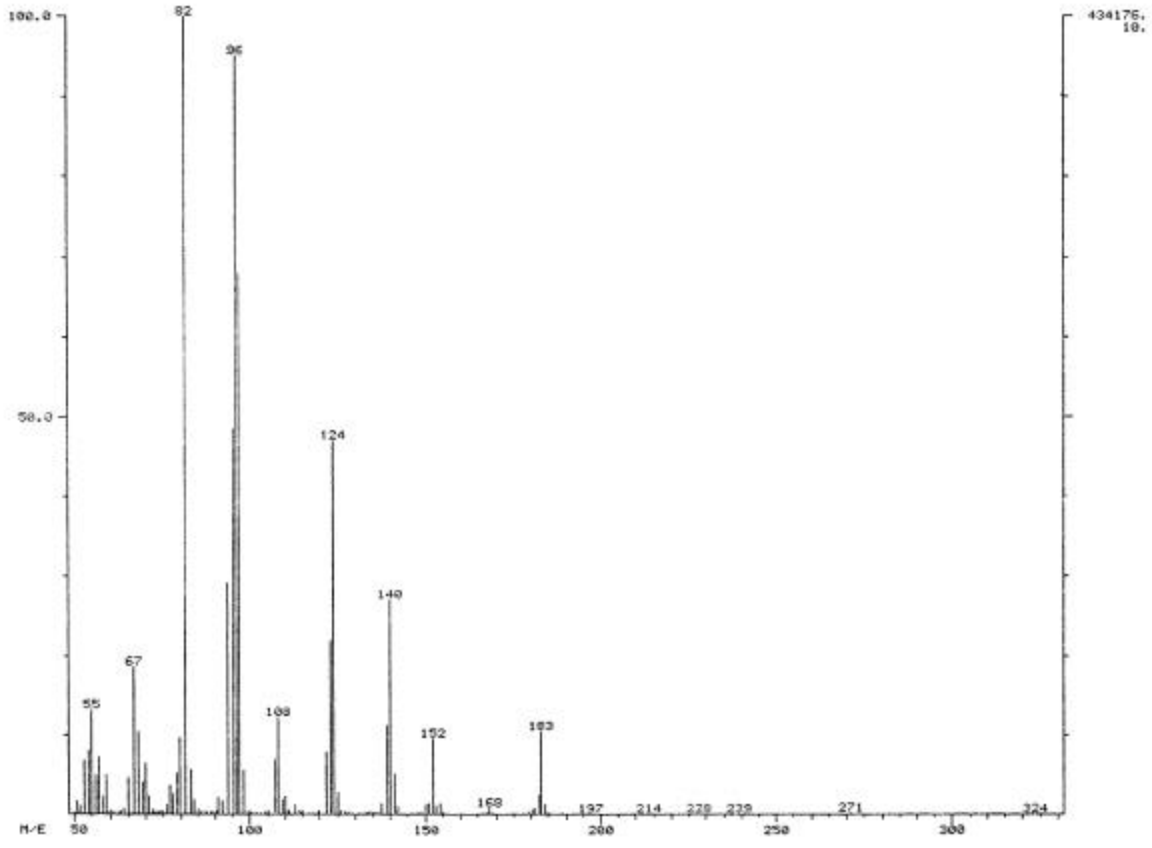
11.12
10.48
32.27
54.59
47.47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M/E
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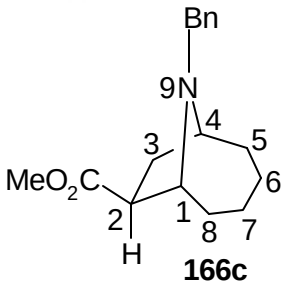
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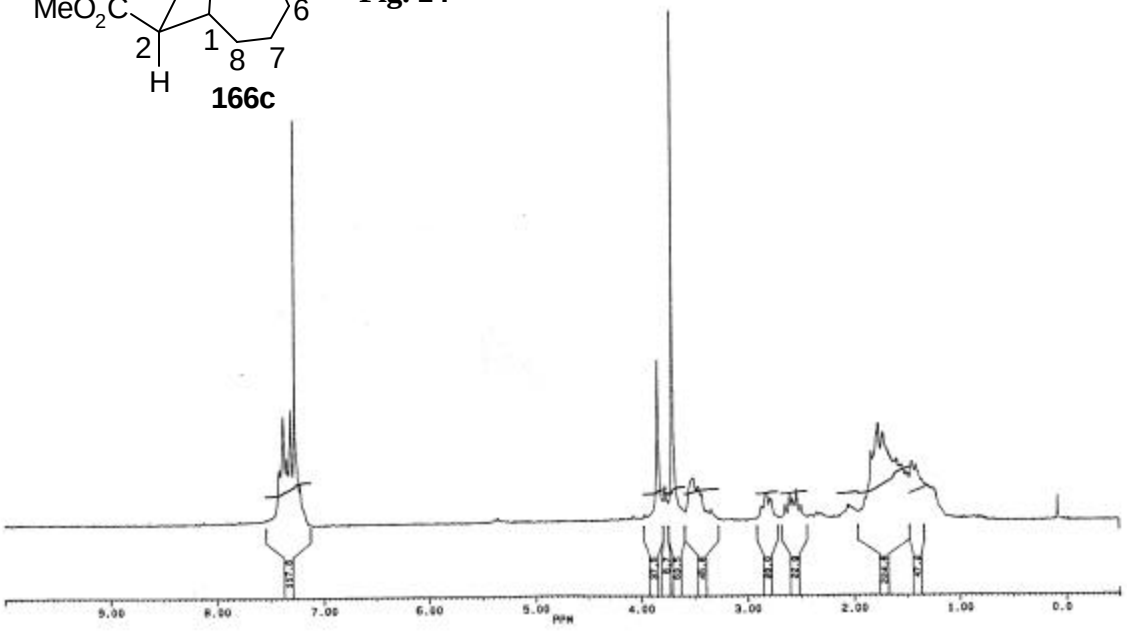
9N
4
5
3
6
MeO2C
1
2
8
7
H

166c

Fig. 24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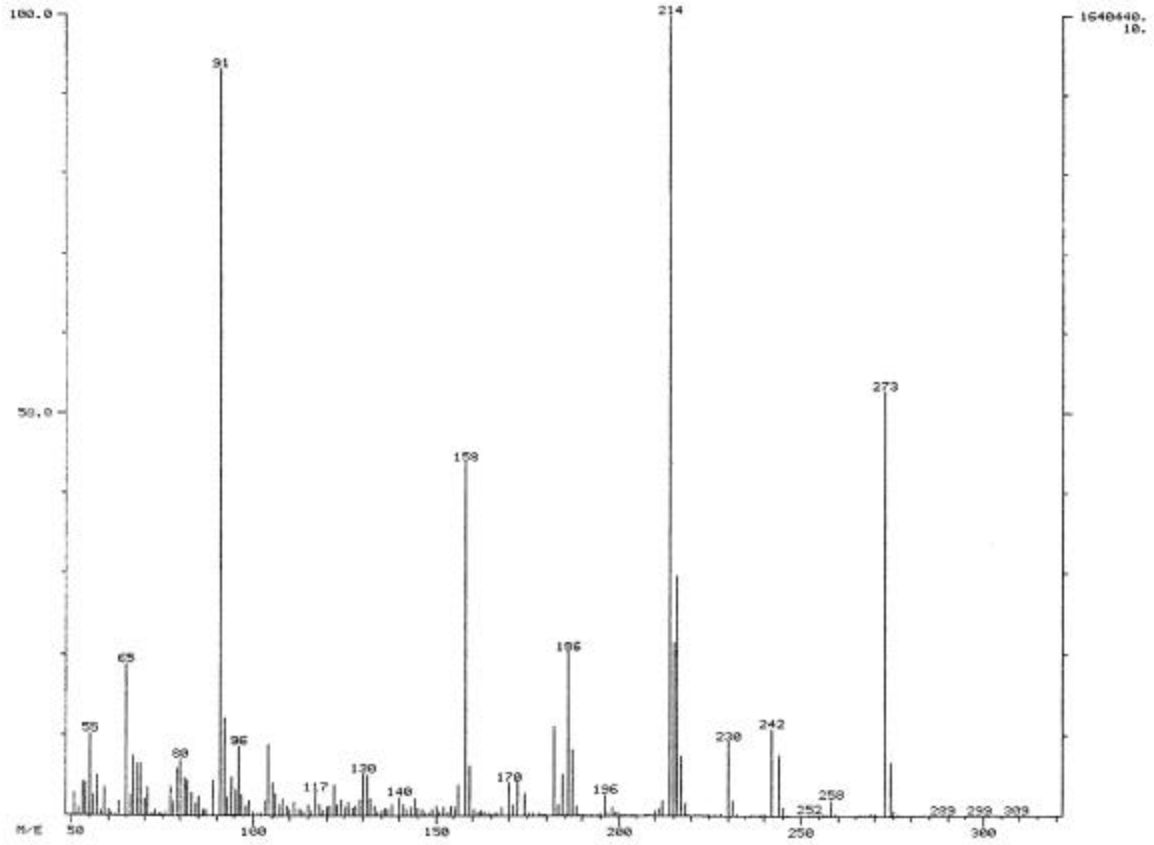
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130
140
170
196
230
242
252
258
288
298
309

1. Introduction

Peptides play a central role in the control and modulation of virtually all biological processes regulating biological functions by acting as hormones, enzymes, receptors and inhibitors.[1] In the past two decades, a wide variety of naturally occurring peptides have been discovered and characterized.[2] Many of these have been found in both neuronal and in non-neuronal tissues. Representative examples include somatostatin, substance P, chloecystokinin, endorphin, enkephalin, angistensin II. After binding to their corresponding receptors or enzymes, they can influence cell-cell communication and control a series of vital functions such as metabolism, immune defense, digestion, respiration, sensitivity to pain, reproduction, behavior and electrolyte levels. Thus, extensive studies have been undertaken in an effort to understand the physiological effects of these peptidic molecules towards the design of new peptide-base therapeutic agents.[3]

It is known from the growing number of three dimensional structures of peptides that there are preferred structural elements that are involved in packing and folding- these include β-sheets, α-helices and β-turns. Of the three types of structural motifs the β-turn offers the significant advantage that it is compact and of such a size that it can readily be mimicked by a small organic molecule. An important structural feature of many biologically active peptides is the β-turn motif. β-turns in proteins are segments between secondary structural elements that reverse the direction of the chains. These turns are often situated on the protein surface and usually consist of polar residues that offer the opportunity of intermolecular interactions with other protein surfaces and hence provide sites for intermolecular recognition. Substantial evidence suggests that smaller peptides also possess β-turns in their biologically active conformations and the resulting compact structures have clustered side chains available for interaction with receptors.

The importance of β-turns in peptides may well be crucial in receptor interactions that ultimately lead to biological activity. In recognition of this fact there have been several efforts to "lock" peptides in β-turn configuration[4] and to synthesize organic molecules that might mimic a β-turn[5] in an otherwise "normal" peptide. It has been suggested that backbone conformations of β-bends are not always critical for activity provided that optimal side chain conformations are preserved. This may explain why several types of β-turns, existing in proteins, different in their backbone configurations with the overall geometry and clustering of side chains are relatively similar. In turn, this

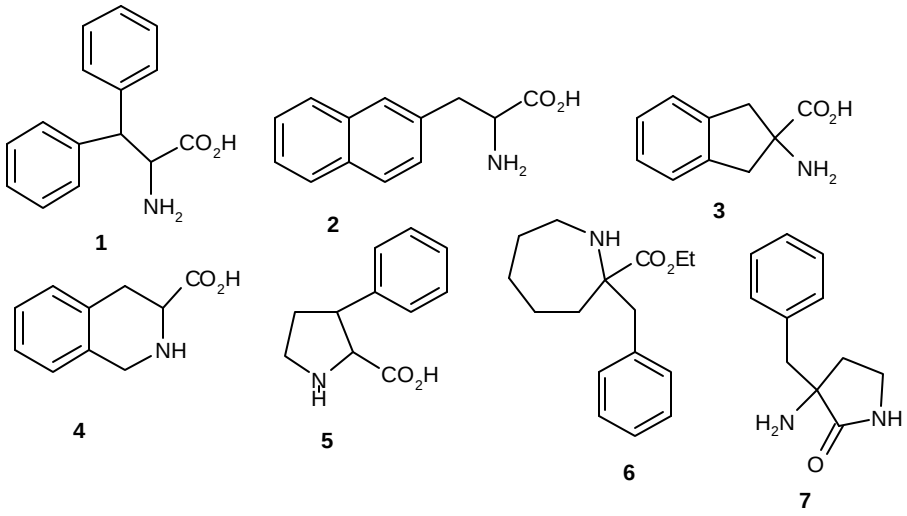
implies many different backbone conformations may be consistent with an active peptide pharmacophore and it is the spatial disposition of the side chain that determines activity.

As a result of major advances in organic chemistry and in molecular biology[6], most bioactive peptides have been prepared in larger quantities and made available for pharmacological and clinical experiments. However, the use of peptides as drugs is limited by the following factors: a) low metabolic stability towards proteolysis in the gastrointestinal tract and in serum; b) poor absorption after oral ingestion, in particular due to their relatively high molecular mass or the lack of specific transport systems or both; c) rapid excretion through liver and kidneys; d) can cause defects in several types of cells and organ systems, since peptide receptors and/or iso-receptors can be widely distributed in an organism; e) conformationally flexible structure and the question that which of the conformations are biologically relevant; f) many biologically active peptides have multiple sites of interaction and hence the question of specificity and its relation to structure and conformation is a central concern.

In an effort to counteract these problems, peptidomimetics drug design has emerged as an important tool for both peptide chemists and medicinal chemists. One successful tactic in overcoming some limitations of peptides as drugs has been the use of conformationally restricted peptidomimetics that mimic the receptor bound conformation of the bioactive peptide. The following requirements exist for the pharmacological properties of a peptidomimetics: a) metabolic stability, b) good bioavailability, c) high receptor affinity and receptor selectivity and d) minimal side effects. For the identification of conformationally restricted peptidomimetics, a number of strategies have been developed which involves i) the use of conformationally constrained amino acids; ii) modification of the peptides backbone; iii) the use of non-peptide analogues.

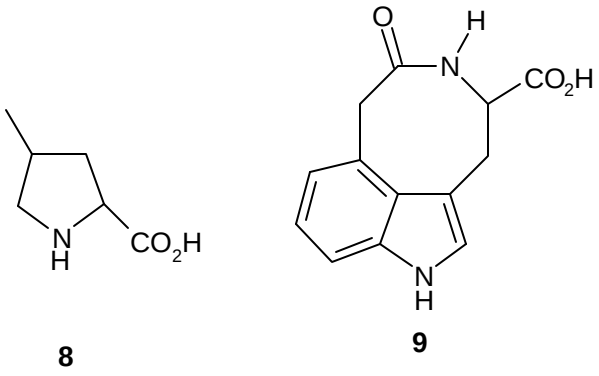
Several possibilities exist for the synthesis of conformationally restricted peptidomimetics at the amino acid level. The systematic exchange of individual amino acids by α-C-alkylated, α-N-alkylated, and D-amino acids is well established. In addition, α,β-unsaturated cyclic and β-amino acids as well as amino acids with sterically demanding side chain may also be employed. The structures of some analogues of the amino acid phenylalanine (Phe) are shown in Fig.1. The number of possible conformations can be limited by the introduction of sterically demanding groups (**1**-**7**)[7] or rigid bridging units (**8**, **9**)[8].

Fig.1



Sterically demanding and conformationally fixed analogues of phenylalamine

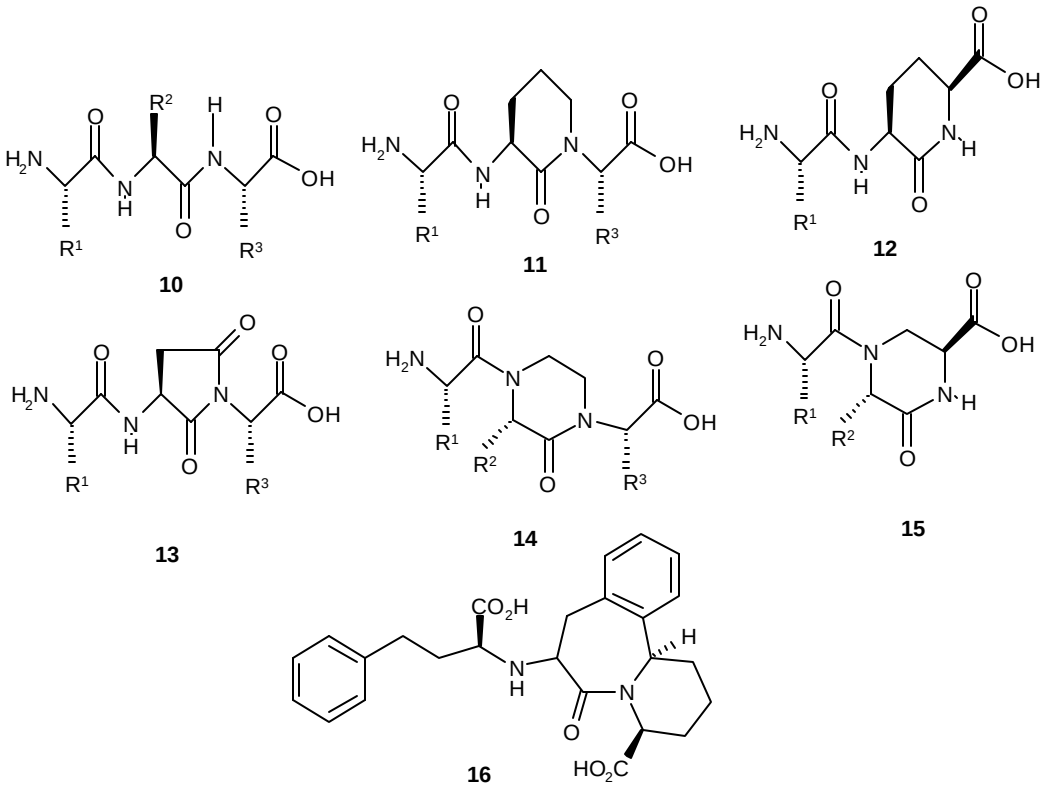
Fig.2



Rigid Bridging Unit

Bridging between two neighboring amino acids in a peptide leads to a dipeptide mimetic, the conformational flexibility of which is limited in comparison with that of regular dipeptides. Some possibilities for forming such bridges are shown by the structural modifications of peptides **10**: incorporation of lactams (**11-13**)[9] and piperazinones (**14**, **15**)[10].

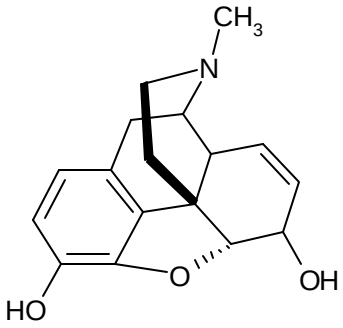
Fig. 3



Modification of the peptide backbone leads primarily to an increase in the biological half-life in comparison with that of parent compounds and only secondarily if at all, the restrictions in conformation. Replacement of an amide bond by a suitable mimetic[11] was particularly important for the development of enzyme inhibitors. In the area of receptor ligands this concept has hitherto been less successful. Examples of ligands that are still biologically active after exchange of an amide group for an isosteric group include the [Tyr[1]-(E)-CH=CH-Gly[2]]-leu-enkephalin analogue[12]. A further approach for changing the peptide backbone is the use of retro-inverso modifications.[13] In this method the L-amino acids of a peptide are exchanged for D-amino acids and simultaneously the direction of the peptide is reversed.

The design of non-peptide ligands is still in its infancy; the discovery of lead structures in large-scale screening is essential. The opioid alkaloids[14] are classic examples of non-peptide ligands (**17**) that were later discovered to be mimetic of endogeneous peptides.

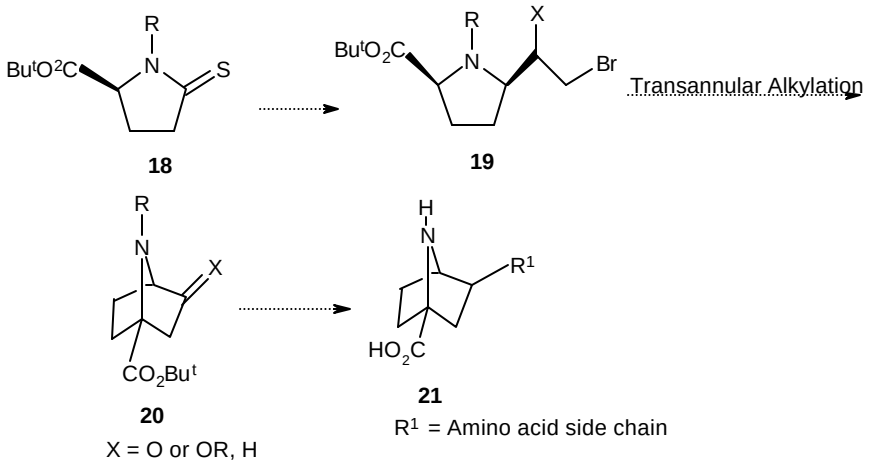
Fig. 4



17

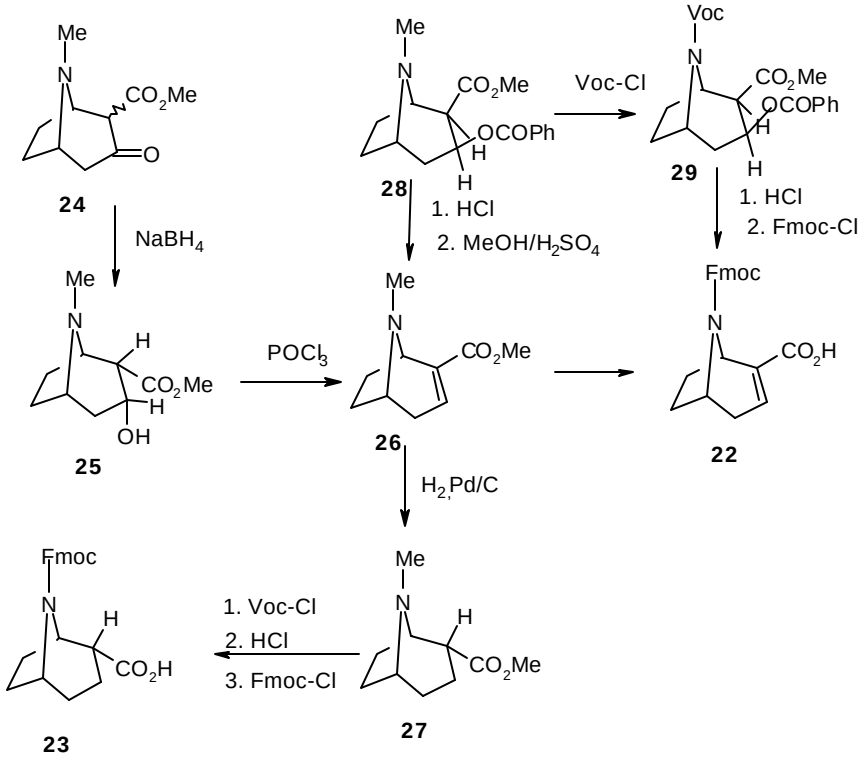
As a result of such endeavors, the advantages of peptidomimetics over the native peptides has been demonstrated by increasing the potency and selectivity decreasing the side effects and improving oral bioavailability. It is also clear that the development of peptidomimetics has mainly involved incorporation of conformationally constrained amino acids. Even if the receptor-bound conformation of the parent peptide is not known, substitution of conformationally constrained amino acids for the natural amino acids in the parent peptide can generate structurally defined peptides, possibly serving a dual role as conformational probes and bioactive peptidomimetics. Therefore, the design of novel, readily available amino acids for use in inducing conformational constraint in peptides and pseudo peptides has been identified as an important goal in peptidomimetics research.[15] Incorporation of conformationally constrained amino acid analogues, such as X-azabicyclo[m.2.1]alkane amino acids, containing the pendant side chain of the parent amino acid into the backbone of a peptide in order to mimic the presumed bioactive conformation, might produce such an effective peptidomimetics. To date, however, only two such type of peptidomimetics are reported. The first such conformational probe for peptidomimetics is 1-carboxy-7-azabicyclo[2.2.1]heptane amino acids [16] (**21**) whose synthesis is outlined below in Scheme 1.

Scheme 1



Another report[17] describes the synthesis of F-moc derivatives of nor-ecgonidine (**22**) and nor-tropan-2α-carboxylic acid (**23**). The synthesis of **22** and **23** are shown below.

Scheme 2



Diversification of such azabicyclo[m.2.1]alkane amino acids by appendage of different pharmacophore onto the amine and carboxylate handles may thus provide a stereodefined library members exhibiting biological activity and thereby it has inspired an intense research activity to synthesize their heterocycle counterparts.

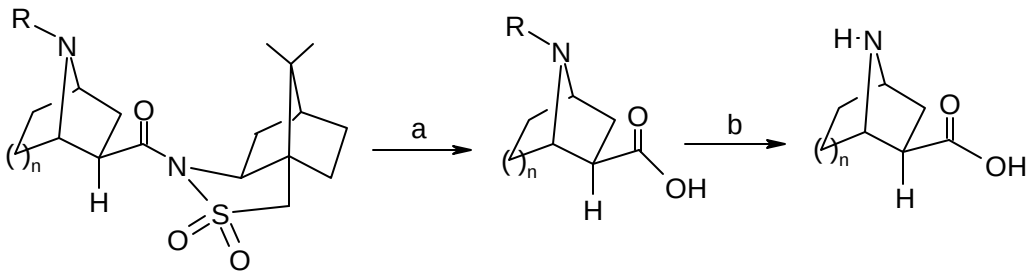
In the light of importance of these amino acids, we have synthesized a variety of X-azabicyclo[m.2.1]alkane amino acids to focus on the applications of our [3+2] cycloaddition strategy.

2. Results and Discussion

From the above discussion, it should be alluded that the conformationally constrained cyclic amino acids can serve as tools for rigidifying peptide structures in order to probe conformation-activity relationships in peptide science. They can also be employed in medicinal chemistry as inputs for targeted library synthesis in which different pharmacophores are systematically displayed for studying recognition events.[18] Azabicyclo[m.2.1]alkane amino acids are particularly attractive scaffolds for functionalization by combinatorial technology. Due to structural homology of these particular class of amino acids with the cycloadducts **30**, we became interested in gaining access to few of these constrained amino acids to show diverse synthetic applications of these cycloadducts. Thus, we approached this problem with a desire to utilize the major diastereomeric cycloadducts to generate few potential peptidomimetics groups which are appropriate in solid phase peptide synthesis by virtue of their rigid and chemically inert structures. The rigidity inherent with these constrained acids should significantly binds the conformation of the resultant peptide and thereby stabilizes specific conformational motifs.

Towards this goal, the major diastereomeric cycloadducts **30** were first hydrolyzed to their corresponding acids which on subsequent N-dealkylation gave constrained amino acids **32** as shown in scheme 3.

Scheme 3



30

n = 1, 2 or 3

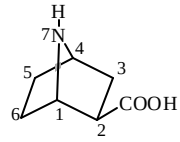
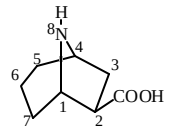
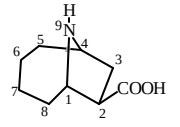
31

32

Reagents and Conditions: a) *LiOH .H_2O, MeOH:H_2O (3:1), 60^oC, 45 min. 90-95%; b) H_2 (80 psi), Pd/C, MeOH, rt, 85-90% for n = 1, 3; α-chloroethyl chloroformate, N,N,N',N'-tetramethyl-1,8-napthalene diamine, 1,2-dichloroethane (for n = 2), then MeOH, reflux, 65% .*

The hydrolysis of amide functionality in the cycloadducts **30** was successfully carried out with LiOH.H_2O in MeOH-H_2O (3:1) mixture, already described in chapter II. N-debenzylation of the corresponding acids **31a** and **31c** were carried out smoothly almost in quantitative yield by hydrogenation using Pd/C and H_2 (70 psi) in MeOH. N-demethylation of the corresponding acid **31b** was carried out in 68% yield by refluxing with α-chloromethyl chloroformate in the presence of N,N,N′,N′-tetramethyl-1,8-naphthalene diamine followed by refluxing with MeOH. The constrained amino acids **32** were characterized by IR, ^{1}H NMR and Mass analyses (Fig. 5 & 6). The characteristic details of ^{1}H NMR of constrained amino acids along with specific rotation and m.p. are summarized below in Table -1.

Table-1

Amino acid	H_3, H_5, H_6, H_7, H_8 (*exo* and *endo* protons)	H_2 *endo* proton	Bridge head H_4	Bridge head H_1	$[á_D]^{25}$	m.p. (uncorrected)
	1.75-1.90 (m, 2H, H_{5endo}, $H_{6\ endo}$), 1.95-2.10 (m, 3H, $H_{3\ endo}$, $H_{5\ endo}$, H_{6exo}), 2.15-2.25 (m, 1H, H_3*exo*)	3.40 (dd, *J* = 8.8, 4.2 Hz, 1H)	4.25-4.35 (m, 1H)	4.45 (t, *J* = 5.6 Hz, 1H)	-5.27°	238°-241°C
	1.25-1.35 (m, 2H, $H_{6\ endo}$, H6 $_{exo}$), 1.35-1.58 (m, 2H, $H_{5\ endo}$, $H_{7\ endo}$), 1.59-1.65 (m, 2H, $H_{5\ exo}$, $H_{7\ exo}$,), 1.95-2.15 (m, 2H, $H_{3\ endo}$, $H_{3\ exo}$)	2.70 (dd, *J* = 7.9, 4.1 Hz, 1H)	3.75-3.82 (m, 1H)	3.87 (t, *J* = 5.2 Hz, 1H)	-4.76	210°-215°C
	1.25-1.55 (m, 4H, $H_{7\ endo}$, H_{7exo}, $H_{6\ endo}$ H_{6exo}), 1.65-1.75 (m, 4H, H_{5endo}, H_{5exo}, H_{5endo}, H_{6exo}), 1.75-1.85 (m, 2H, H_{3endo}, H_{3exo})	2.25 (dt, *J* = 7.6, 3.9 Hz, 1H)	2.90-2.98 (m, 1H)	2.98-3.05 (m, 1H)	-9.18°	225°-227°C

3. Experimental

Preparation of 32 from 30:

The hydrolysis of **30** with $LiOH.H_2O$ in $MeOH/H_2O$ mixture to obtain corresponding acids 3**1** is already described in chapter II.

Synthesis of amino acids 32 from 31:

N-debenzylation of acids **31a** and **31c** was carried out by hydrogenation. To the solution of crude acid (**31a**/**31c**) (8.6 mmol) in MeOH (10 mL) was added Pd/C (20 mg) and the resultant solution was hydrogenated at rt for 24 h. The reaction mixture was filtered, the filtrate was evaporated to give corresponding amino acids (**32a**/**32c**) in almost quantitative yield (90-92%) as white crystalline solid

32a	:	
α_D	:	-5.27^o
m.p.	:	238-241 ^oC
IR (Nujol)	:	3417, 2968, 1635, 1209 cm^{-1}
^1H NMR (D_2O) (200 MHz)	:	1.75-1.90 (m, 2H), 1.95-2.10 (m, 3H), 2.15-2.25 (m, 1H), 3.40 (dd, *J* = 8.8, 4.2 Hz, 1H), 4.25-4.35 (m, 1H), 4.45 (t, *J* = 5.6 Hz, 1H).
Mass (m/z)	:	141 (M^+, 75), 124 (56), 112 (32), 96 (95), 67 (100).

32c

á$_D$		-9.18^o
m.p.	:	225-227 ^oC
IR (Nujol)	:	3423, 1637 cm^{-1}
^1H NMR (D_2O) (200 MHz)	:	δ 1.25-1.55 (m, 4H), 1.65-1.85 (m, 6H), 2.25 (dt, J = 7.6, 3.9 Hz, 1H), 2.90-3.05 (m, 2H).
Mass (m/z)	:	169 (M^+, 65), 96 (65), 87 (100), 65 (82)

Preparation of 32c:

The crude acid **32c** (0.20 g, 3.82 mmol) was treated with α-chloroethyl chloroformate (0.165 g, 7.69 mmol) in presence of proton sponge [N,N,N′,N′-tetramethyl-

1,8-naphthalene diamine (0.365g, 3.82 mmol) in 1,2-dichloroethane (15 mL) and refluxed. After 6h of reflux, dry HCl was bubbled into the reaction mixture, resulting precipitate was filtered off and filtrate was evaporated under reduced pressure. The resulting viscous liquid was dissolved in dry MeOH (10 mL) and refluxed for 1 h. It was then washed with $CHCl_3$ (3 x 5 mL) and the resultant mass was basified to obtain **33b** (0.068 g) in 68% yield.

32c

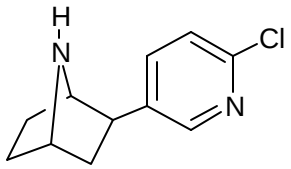
$á_D$		-04.76°
m.p.		210-215 °C
IR (Nujol)	:	3419, 1648 cm^{-1}
^1H NMR (D_2O) (200 MHz)	:	δ 1.25-1.65 (m, 6H), 1.90-2.15 (m, 2H), 2.70 (dd, *J* = 7.9, 4.3 Hz), 3.75-3.82 (m, 1H), 3.87 (t, *J* = 5.2 Hz, 1H).
Mass (m/z)	:	155 (M^+, 65), 140 (25), 126 (12), 110 (27), 82 (100), 68 (17).

CONCLUSION:

In summary, we have synthesized few conformationally constrained cyclic amino acids with the anticipation that the semi-rigid nature of these amino acids may make them excellent candidates for examining the conformational requirements of peptides in structure-activity studies.

1. Introduction

Epibatidine (**33)** is an entirely new class of alkaloid possessing an unusual structural feature, 7-azabicyclo[2.2.1]heptane skeleton to which is attached a 5-(2-chloropyridinyl) substituent in *exo*-orientation.



Epibatidine (**33**)

It was first isolated[19] from the skin extracts of poison frog, *Epipedobates tricolor*, in minute amounts (<5 mg from 750 frogs) by Daly and co-workers in 1992. Epibatidine (**33)** was found to be 200-500 times more potent than morphine as analgesic and its effects are not blocked by the opiate receptor antagonist naloxone, suggesting a non-opioid mode of action.[20] It is also extremely potent agonist of the acetylcholine receptor that is found to be involved in the mediation of several human disorders such as Alzheimer's, Parkinson's diseases.[21] Due to intriguing structural features and important biological activities exhibited by epibatidine, its synthesis has attracted intense research activities. As a result, numerous synthetic approaches towards the synthesis of **33** have been reported which may be classified into the following categories: (a) the carbon skeleton including the single nitrogen atom bridge generated by Diels-Alder reaction of N-(methoxycarbonyl) pyrrole and (phenylsulfonyl)(6-chloro-3-pyridyl) acetylene; (b) the carbon skeleton assembled in the early steps, and the single nitrogen atom bridge was constructed in the last step of the synthesis; (c) a 7-azabicyclo[2.2.1] heptane system synthesized and condensed with a pyridine derivative; (d) the carbon skeleton including the single nitrogen atom bridge generated by 1,3-dipolar cycloaddition of cyclic azomethine ylides with a suitable dipolarophile bearing 5-(2-chloropyridinyl) substituent.

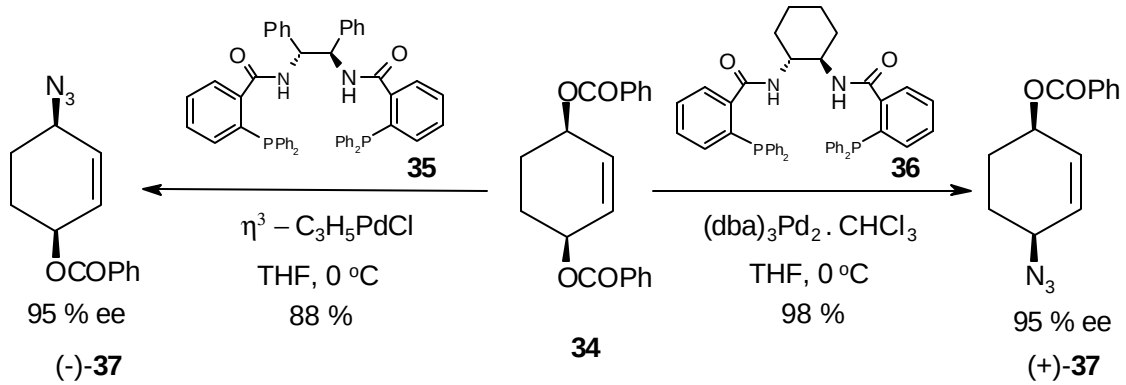
All these synthetic strategies involve the key step of constructing the 7-azabicyclo[2.2.1]heptane framework starting from different precursors. Interesting review articles dealing with the construction of 7-azabicyclo[2.2.1]heptane ring system and synthesis of **33** have been published by Trudell[22] *et al* and Sestanz[23] *et al* respectively.

Remarkably, inspite of the intense research activity, there was no report of asymmetric synthesis of this target until a report published by B.M. Trost *et al.*[24] in 1996.

Its availability in enantiomeric pure form has occurred through resolution at some point in the synthesis of the final product.[25] Several strategies have been directed towards an asymmetric synthesis of epibatidine[26-35] but have not culminated in an enantioselective synthesis before this report.

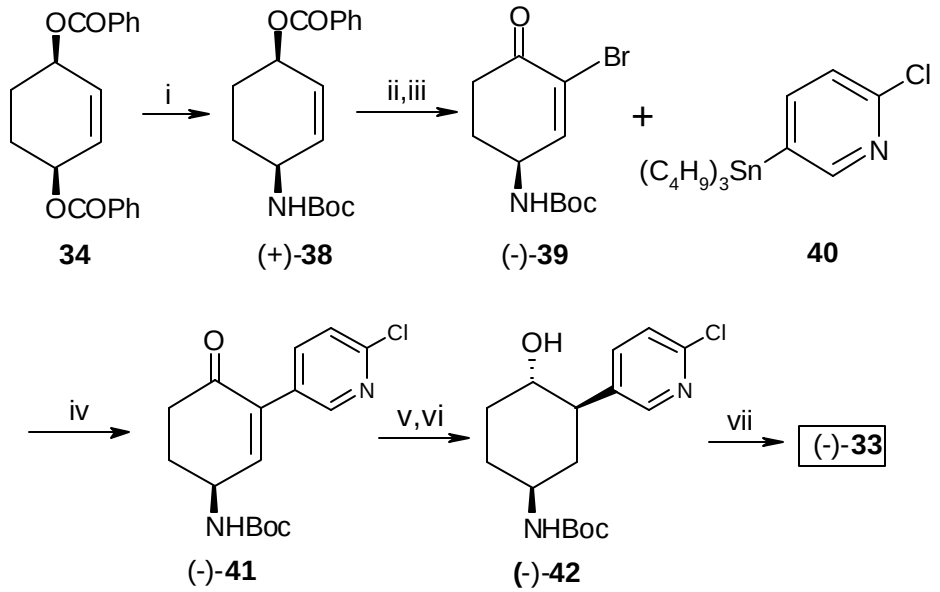
Trost *et al.*[24] first described the total synthesis of (-)-epibatidine **33** and its optical antipode using a Pd-catalyzed desymmetrization of cis-3,6-dibenzoyloxy-2-cyclohexene **34** and a Pd-catalyzed cross coupling reaction as two key steps. A mixture (1:1) of the dibenzoate **34** and trimethyl silylazide was reacted with a catalyst, derived from π-allyl palladium chloride dimer and **35** or **36** to obtain (-)-**37** or ent-**37,** respectively, as shown below in Scheme 1.

Scheme 1



In the later stage, the chloropyridine moiety was installed into the vinyl bromide **39** by Pd(0) catalyzed cross-coupling reaction of stable organostanane **40**. The enone **41** was converted to epibatidine precursor **42** by selective reduction of ketone group by K-selectride followed by saturation of double bond. The precursor **42** was subjected to *trans*-annular cyclization to give (-)-epibatidine **33** in 45 % yield (Scheme 2).

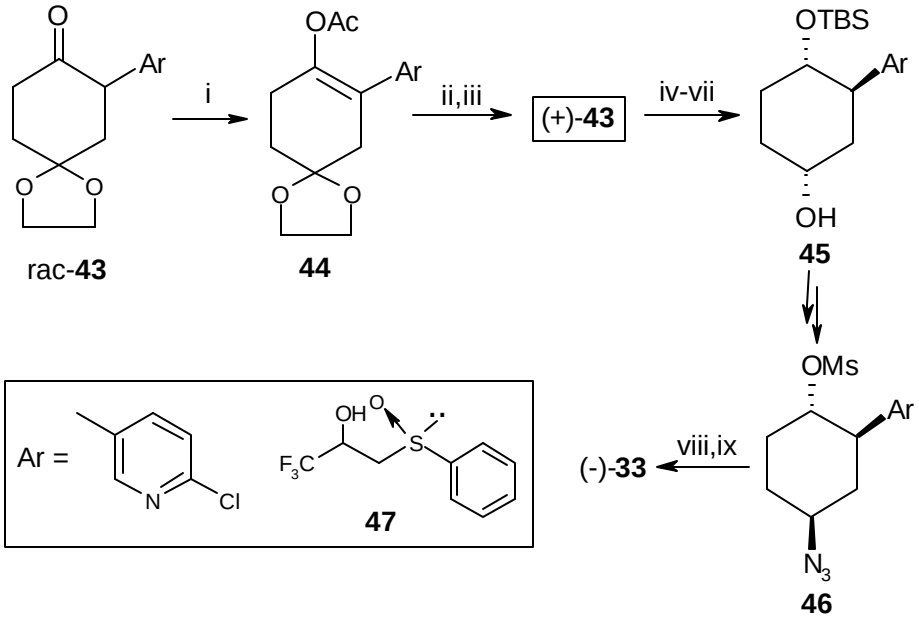
Scheme 2



*Reagents and conditions: i) a) 0.25 mol % [P^3-C_3H_5PdCl]$_2$, 0.75 mol % **36,** 1.2 equiv. $TMSN_3$, THF, 0^0C ; b) $(CH_3)_3P$, 2:1 THF-H_2O, 1.2 equiv. $(CH_3)_3P$, rt. then $(BOC)_2O$, Et_3N; ii) K_2CO_3, CH_3OH, rt., Dess-Martin periodinane, DCM, rt. ; iii) Br_2, Et_3N, DCM, 0 ^oC; iv) 2.5 mol % $(dba)_3Pd.CHCl_3$, 15 mol % Ph_3As, THF, 55 ^0C; v) K-selectride, THF, -78 ^0C to 0 ^oC, then cat. DBU, THF; vi) $NaBH_4$, CH_3OH, 0 ^oC; vii) CH_3SO_2Cl, Et_3N, DCM, 0 ^0C; CF_3COOH, H_2O, rt; CH_3CN, reflux.*

Kosugi *et al.*[36] have reported the asymmetric synthesis of (-)-epibatidine **33** employing the asymmetric protonation of the achiral lithium enolate of cyclohexanone derivative **44** with chiral β-hydroxy sulfoxide **47** as the key step. The racemic **43** was converted to enantioenriched (+)-**43** by regioselective enol acetate formation followed by asymmetric protonation using **47**. In the later stage **45** was converted to **46** by simple chemical manipulation which in turn was subjected to *transannular cyclization* to give (-)-epibatidine **33 (**Scheme 3**)**.

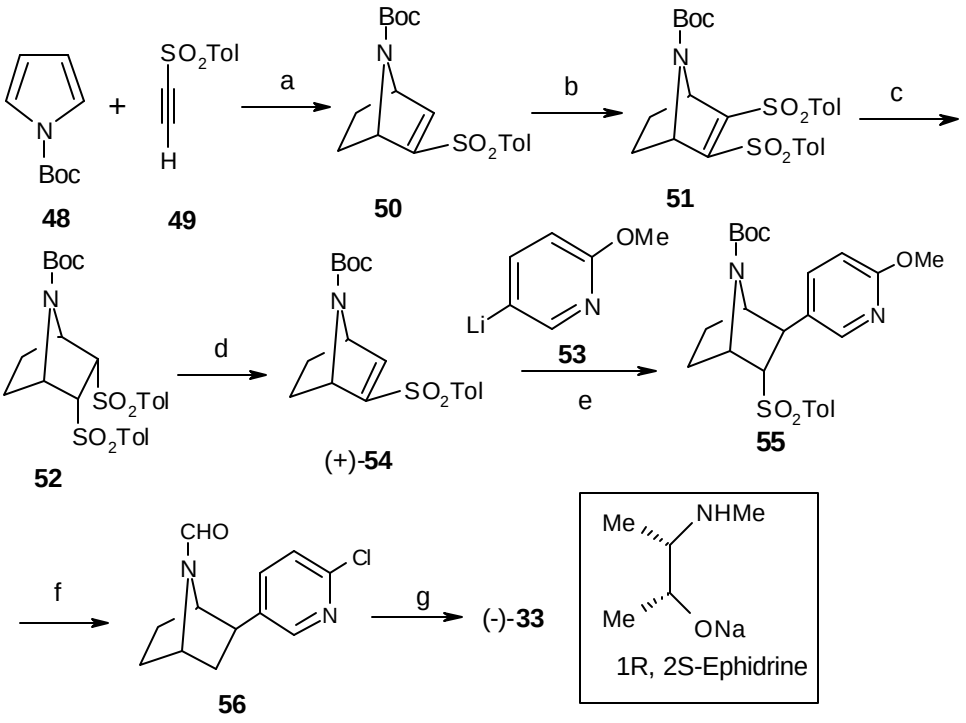
Scheme 3



***Reagents and conditions**: i) Bu^tOK, Ac_2O, THF; ii) MeLi (2 equiv.), Et_2O, 0 ^0C, 15 min.; iii) **47**, (2.5 equiv.), DCM, -90 ^0C to -60 ^0C iv) $NaBH_4$, MeOH; v) 80 % aq. AcOH; vi) $Bu^tMgSiCl_2$, Pr^iNEt_2, DMF; vii) $LiBBu^s_3H$, THF; viii) a) Bu_4NF, THF; b) MsCl, Et_3N, CH_2Cl_2; ix) a) $SnCl_2.2H_2O$, MeOH-THF; b) $CHCl_3$, reflux.*

Simpkins *et al.*[37] have put forwarded an entirely different approach for the total synthesis of (-)-epibatidine **33**. A vicinal bis-sulfone **52**, obtained from **50** which in turn was obtained by the Diels-Alder cycloaddition reaction of N-Boc pyrrole **48** and **49**, was subjected to asymmetric elimination by the treatment with sodium alkoxide derivative of (1R, 2S)-ephidrine to give an alkenyl sulfone **54**, a key intermediate for the synthesis of this alkaloid (Scheme 4).

Scheme 4

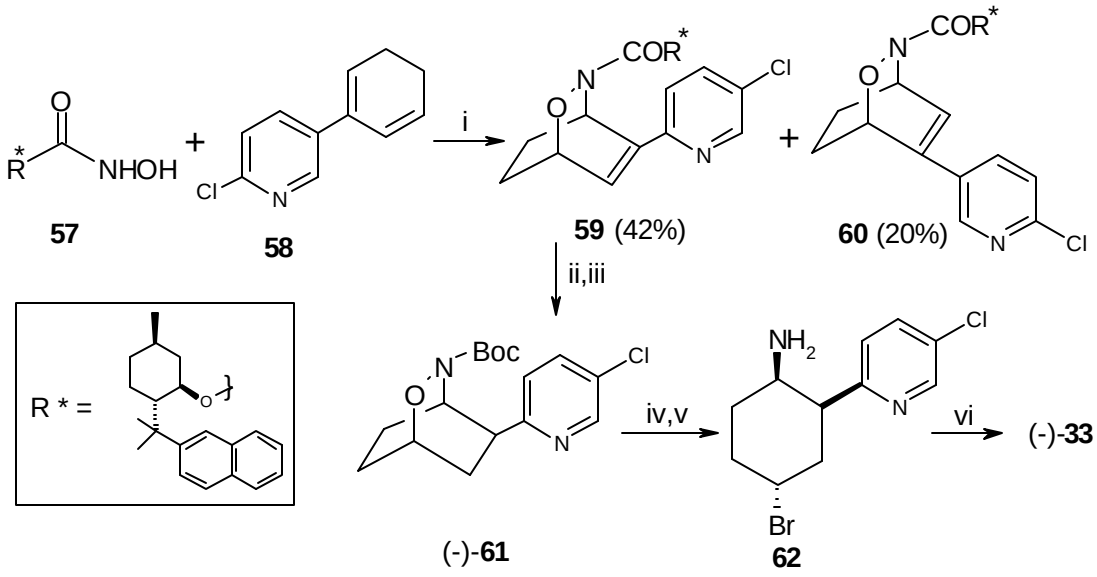


Reagents and conditions: a) I) 85 ^{0}C to 90 ^{0}C; ii) H_2, Pd/C, CH_3CN; b) n-BuLi, THF, $TolSO_2F$; c) H_2, 80 psi, $Pd(OH)_2/C$, CH_2Cl_2, EtOAc; d) Na-alkoxide of 1R,2S-ephedrine, THF, -78 ^{0}C; e) **53**, THF; f) 6 % Na(Hg), THF, MeOH; g) $POCl_3$, DMF, 95 ^{0}C.

The key step of this synthesis suffers from poor yield (34 %) and low *ee* (60 %).

In the same year, another total synthesis of this target was reported by Aoyagi *et al*.[38] This group has synthesized (-)-epibatidine **33** in eight steps involving **62** as a key intermediate. This key intermediate **62** was obtained from **61**, a product derived from an asymmetric hetero Diels-Alder cycloadduct **59,** obtained by the reaction of an acylnitroso dienophile **57** bearing (1S)-8-(2-naphthyl)menthol as a chiral inducer, with a diene **58**.

Scheme 5



***Reagents and conditions**: i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^0C; ii) a) H_2, PtO_2, dioxan (81 %); b) $LiNH_2BH_3$.THF; iii) $(Boc)_2O$, Na_2CO_3 (62 %); iv) a) $Mo(CO)_6$, MeCN-H_2O b) PPh_3, CBr_4, MeCN; v) CF_3COOH, DCM, (40 %); vi) $CHCl_3$, 97 %.*

From the above literature survey, it is evident that only limited number of asymmetric approaches is available for the total synthesis of epibatidine. Having demonstrated the validity of our methodology for the construction of enantiopure X-azabicyclo[m.2.1]alkane framework (as described in Chapter II), the chemistry has matured to a stage where this novel methodology could be exploited for the total synthesis of enantioenriched epibatidine. The synthesis of enantiopure epibatidine using asymmetric [3+2] cycloaddition of a cyclic AMY **65** with a suitable chiral dipolarophile is the focus of this Section.

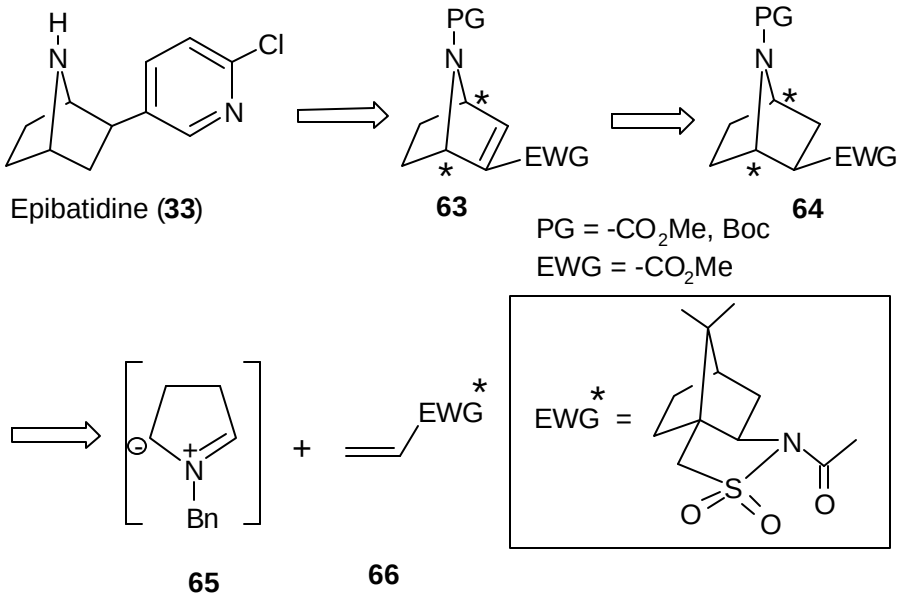
2. Results and Discussion

2.1. Planning of Enantiopure Epibatidine synthesis

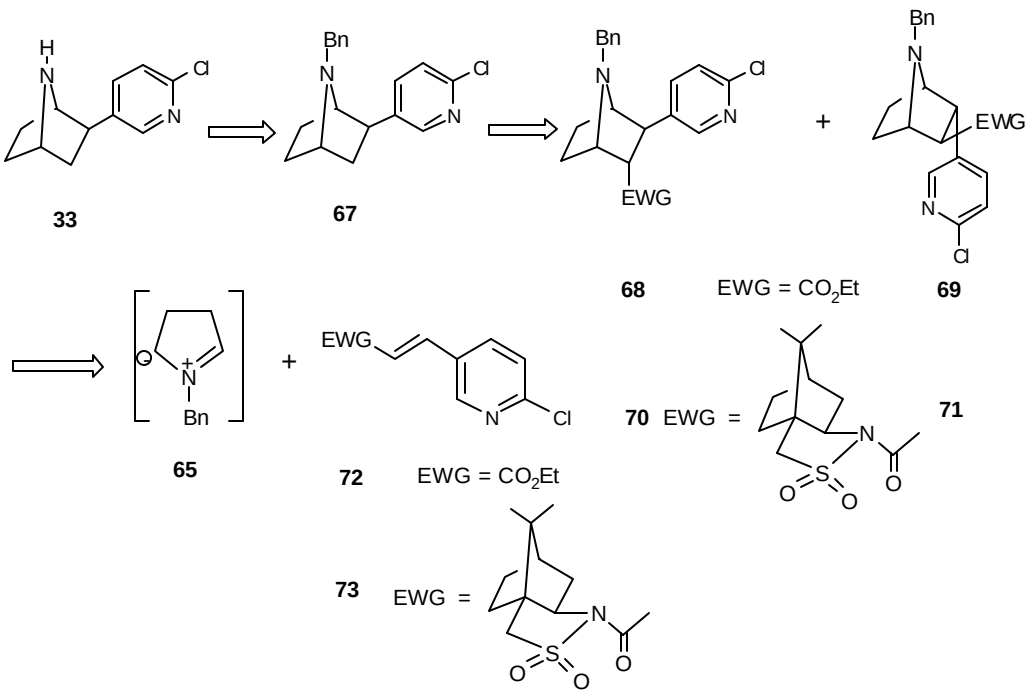
In the previous chapter, we have shown that asymmetric induction during [3+2] cycloaddition of the AMY **65**, with a non-racemic dipolarophile **66** represents a potentially effective method for the rapid assembly of enantioenriched 7-azabicyclo[2.2.1]heptane skeleton that are amenable to conversion into a range of natural product targets. With this advanced knowledge, we envisaged two complementary (asymmetric approaches) retrosynthetic analyses of **33** which are as follows:

Scheme 6

Route I



Route II



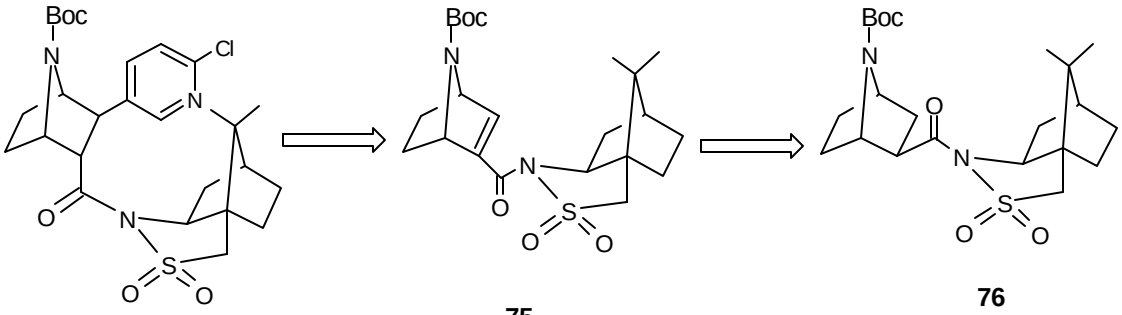
The asymmetric synthesis of epibatidine could be possible by carrying out an asymmetric [3+2]-cycloaddition with a chiral dipolarophile leading to a non-racemic 7-azabicyclo[2.2.1]hept-2-ene system of the type **63** (**Route I**) which on Michael addition with 5-(2-chloro)lithiopyridine would provide an easy access to enantioenriched epibatidine. An alternative way (**Route II**) to accomplish this asymmetric synthesis is to promote our previous protocol with an asymmetric variant whereby the dipolarophile being used in this cycloaddition would be chiral by virtue of its induced chirality. Our previous synthetic approach[39] suffers from two serious limitations: (1) the lack of stereoselectivity in the cycloaddition step, (2) the major isomer being the undesired one with *endo*-orientation of 5-(2-chloropyridinyl) moiety. Taking advantage of the excellent diastereo-selectivity inherent in the cycloaddition and knowledge of the cycloadduct **64** to be useful for diverse synthetic applications, we became more interested in gaining access to epibatidine using Route I.

2. 1.1. Unsuccessful efforts towards the synthesis of epibatidine :

Since the Michael addition of 5-(2-chloroidopyridine) to a substrate of the type **63** is known[40] to give adduct with *exo*-oriented 5-(chloropyridinyl) group, it was reasonable to

effect Michael addition of 2-chloro-5-iodopyridine on to a α,β-unsaturated N-Boc derivative cycloadduct **75** that would lead to epibatidine by simple functional group manipulation as shown in Scheme-7.

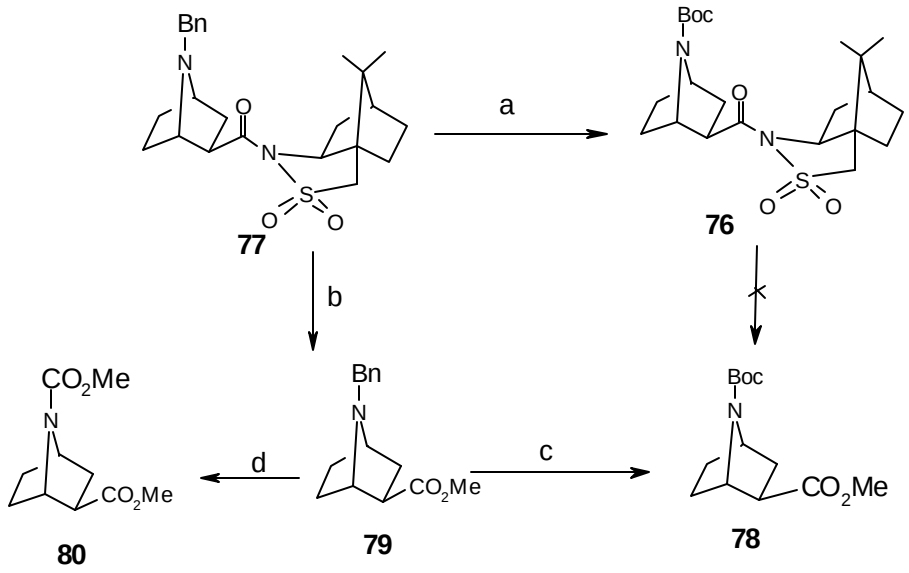
Scheme 7



In the previous chapter, we have described the preparation of the major cycloadduct **77** in details. This cycloadduct was deliberately converted to N-Boc derivative **74** by N-debenzylation followed by treatment with $(Boc)_2O$, Et_3N in dry DCM (Scheme 8). It is noteworthy to mention that N-debenzylation was unsuccessful using common hydrogenation procedure (e.g. H_2, Pd/C, 80-90 psi; H_2, $Pd(OH)_2$/C, 60-70 psi). The less commonly used procedure (5% HCOOH-MeOH, equal wt. of Pd/C) proved successful for this particular case. The above mentioned hydrogenation method finds less applications in synthetic organic chemistry due to its liability towards acid sensitive functional groups present in the substrate. The N-Boc derivative cycloadduct **76** was fully characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass analyses. It was necessary at this stage to create double bond α to carbonyl group in N-Boc cycloadduct **76** using selenium chemistry. The anion generation (α to carbonyl group), directed to create double bond via incorporating SePh group and subsequent oxidative elimination of PhSeH is well known in literature.[41] We wanted to take advantage of the distinctive reactivity of the carbonyl sulfonamide group present in the cycloadduct **76** compared to ordinary carbonyl group. Due to lack of precedence for this type of anion generation, we had to run several experiments on trial basis to generate anion. Initially, the anion generation was tried with LDA using different proportions and in different conditions. Since the anion generation was unsuccessful with LDA, we also evaluated the use of several other strong bases of choice. These operations

were not successful and in each case we recovered starting material. Therefore, our present hypothetical concept to deliver epibatidine in a shortest route was futile.

Scheme 8



Reagents and Conditions*: a) 4.5 % HCOOH-MeOH, equal wt. of Pd/C, rt, 36 h, 82 %; b) i) LiOH.H_2O, MeOH:H_2O (3:1), ii) $SOCl_2$, Dry MeOH, 94 %; c) i) H_2 (70 psi), $Pd(OH)_2$/C, EtOAc; ii) $(Boc)_2O$, Et_3N, DCM, 92 %; d) i) H_2 (70 psi), $Pd(OH)_2$/C, EtOAc; ii) $ClCO_2Me$, K_2CO_3, DCM, 93 %.*

Since the anion generation α to ester group is well documented in literature[41], the conversion of N-Boc CA **76** to N-Boc methyl ester **78** was deemed logical. The hydrolysis of amide functionality using LiOH-H_2O in THF:H_2O (3:1) at 60 °C followed by esterification was inconvenient due to practical difficulties encountered during this operation. While the hydrolysis was carried out smoothly, but even careful acidification with 3 N HCl of the Li-salt of acid was causing complications due to deprotection of Boc group from the substrate. This untoward practical problem was circumvented by changing the sequence of reaction. The sequence involved first the conversion of the cycloadduct **77** to N-Bn methyl ester **79** and secondly the N-Boc protection of methyl ester **79** to give **78**. The preparation of compound **79** from **77** was already described in Chapter II.

Compound **79** was subjected to N-debenzylation by standard hydrogenation procedure (H_2, Pd(OH)/C, 60-70 psi, 2 days) and the crude debenzylated product was treated with $(Boc)_2O$, Et_3N in dry DCM to afford N-Boc methyl ester **78** in 92 % yield.

At this stage, it should be alluded that the enantiopure 7-azabicyclo[2.2.1] heptane skeleton **78** was never used before for the asymmetric synthesis of epibatidine. Therefore, our immediate task was to create a double bond α to ester which would lead to epibatidine by installation of chloropyridine moiety by effecting a Michael addition. The generation of anion was initially tried with LDA at −78 °C in dry THF. Since it was unsuccessful even with several other strong bases of choice, we were greatly disappointed until we found a reported literature procedure[42] where the same protocol was adopted in 7-azabicyclo[2.2.1]heptane system to create double bond α to ester. Intrigued by this report, we made N-CO_2Me methyl ester **80** to be used in the subsequent reaction to create double bond though Boc group virtually does not make any difference with CO_2Me group. Compound **80** was characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analyses (Fig. 7 & 8). With our best effort, we could not generate anion by this method too. At this stage, it was little consolation for us to learn that our previously reported protocol was more efficient and straightforward for epibatidine synthesis.

2.1.2. Synthesis towards enantiopure Epibatidine :

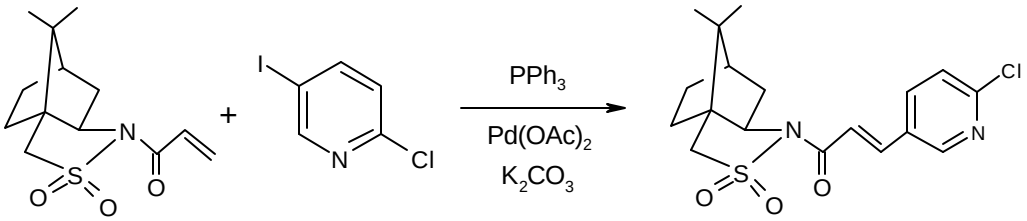
Our previous protocol for the stereoselective synthesis of **33** involves a [3+2] cycloaddition of a cyclic AMY **65** with an activated dipolarophile **72** bearing chloropyridine moiety (**Route II**). The stereochemical outcome of the cycloadduct depends on the type of dipolarophile used in the cycloaddition reaction. The novelty of this cycloaddition is that the four stereo-centers are formed concurrently in a stereoselective manner. In the later stage, the major cycloadduct **69** was transformed into epibatidine by functional group manipulations.

In order to promote this protocol to an asymmetric fashion, a chiral dipolarophile bearing chloropyridine moiety has to be taken. The chiral element should serve dual nature by inducing chirality in the cycloaddition and should easily be removable in the later stage of synthesis. Therefore, we had to design a chiral dipolarophile which is synthetically useful for cycloaddition and can meet the demand of chiral element.

From our previous experience[39], it was apparent that Oppolzer's chiral acryloyl dipolarophile is a bonafide one that can serve dual formalities. To serve this purposes we

designed a chiral dipolarophile **73** bearing chloropyridine moiety where camphor sultam part and chloropyridine moiety maintain *trans*-relationship to each other. This dipolarophile was successfully synthesized by performing a novel Heck-coupling reaction of 2-chloro-5-iodopyridine **81** onto Oppolzer's acryloyl chiral dipolarophile **66** (Scheme 9). Compound **66** was characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analyses (Fig. 9 & 10). To our delight, we found that this dipolarophile was not known earlier.

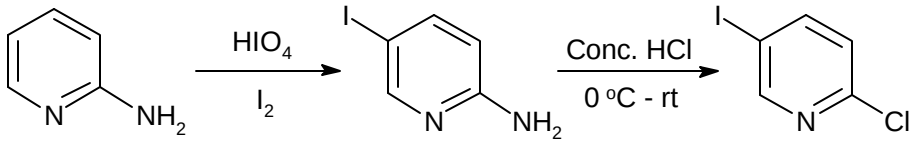
Scheme 9



66 **81** **73**

2-chloro-5-iodopyridine was prepared by following reported literature procedure[43] as shown below:

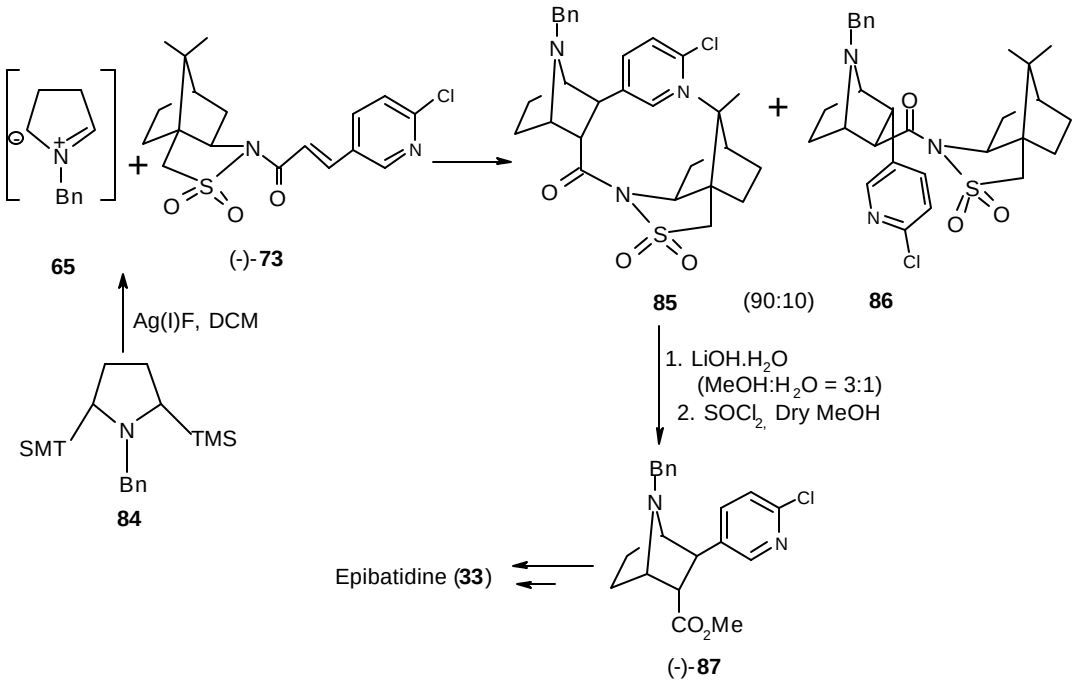
Scheme 10



82 **83** **81**

Therefore, on line with our aim towards the stereoselective synthesis of optically pure epibatidine, a typical cycloaddition reaction of cyclic AMY **65** with the dipolarophile (-)-**73** was performed in a similar way as described in previous chapter. The two diastereomers (**85** and **86**) were formed with excellent *exo*/*endo* selectivity (90:10) as shown in Scheme 11.

Scheme 11



The two diastereomers were separated by careful flash column chromatography. They were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass analyses. The ratio of two diastereomeric cycloadducts was determined from their crude ^{1}H NMR spectrum by comparing the integration values of H_2 and/or H_3. The stereochemical orientation of amide functionality and chloropyridinyl moiety was determined by decoupling experiment and ^{1}H COSY experiment. These characteristic features of two cycloadducts are described below:

Characterization of major cycloadduct, 85:

IR spectrum showed a strong absorption band at 1683 cm^{-1} indicating the presence of carbonyl amide functionality (Fig.).

^{1}H NMR spectrum displayed following signals (Fig. 11):

Two sharp singlets at δ 0.98 and 1.23, integrating for three protons each, are assigned to methyl protons of $C_{8'}$ and $C_{9'}$. The six different multiplets appearing in between δ 1.34-2.15, integrating for a total of eleven protons, may be attributed to methylene protons (*exo* and *endo*) present in two bicyclic ring systems. A doublet appearing at δ 3.22

(J = 4.4 Hz), integrating for one proton, is assignable to bridgehead H_1. H_{2endo} proton, adjacent to the pyridyl moiety, appeared as a doublet at δ 3.37 (J = 4.8 Hz). Two benzylic protons appeared as two sets of doublets at δ 3.41 and 3.72 (J = 13.7 Hz). Two doublets appearing at δ 3.49 and 3.53 (J = 13.1 Hz) is characterized to $H_{10'}$ protons. A triplet appearing at δ 3.61 (J = 4.2Hz), integrating for one proton, is attributed to H_{3exo}. Another triplet at δ 3.90 (J = 5.1 Hz) is characterized to $H_{2'}$. A triplet at δ 4.06 (J = 4.4Hz), integrating for one proton, corresponds to bridgehead H_4. Pyridyl $H_{2'}$ proton is observed as a doublet at δ 7.2 (J = 8.3 Hz) and the five aromatic protons of phenyl moiety are observed as two multiplets at δ 7.21-7.29 and at δ 7.31-7.39. Remaining pyridyl, $H_{4'}$ and $H_{5'}$ protons appeared as a doublet of doublet at δ 7.82 (J = 8.3, 2.4 Hz) and a doublet at ä 8.3 (J = 2.4 Hz) respectively. Based on ^{1}H NMR analysis, the structure of compound **85** is tentatively assigned as 7-benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-bornane 2,10-sultam 7-azabicyclo[2.2.21]heptane.

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

Decoupling of H_3 proton appearing at δ 3.61 indicated its coupling only with H_2 at δ 3.37 and with adjacent bow-spirit H_4 at δ 4.06. Therefore, the assignment of H_3 as *exo* gets confirmed and thereby confirming the *endo*-orientation of amide functionality in the cycloadduct **85**. Proton H_2 is found to couple with H_3 at δ 3.61 but not with bridgehead H_1 at δ 3.22, confirming its *endo*-orientation and therefore, implying an *exo*-orientation for the pyridyl moiety. These studies also showed the relative *trans*-stereochemistry between H_2 and H_3 indicating the retention of olefin geometry of the dipolarophile in the cycloadduct. These observations are further supported by the ^{1}H COSY spectrum (Fig. 12).

^{13}C NMR spectrum displayed a total of seventeen carbon signals in the aliphatic region in between δ 20.23 to 66.17 along with aromatic carbon signals at δ 124.21, 127.45, 128.70, 128.85, 138.41, 139.63, 139.78, 149.39, 149.70 and a carbonyl carbon signal at δ 171.18 (Fig. 13). DEPT experiment characterized the methyl carbonyl signals at δ 20.23 and 21.18 to $C_{8'}$, $C_{9'}$. Methylene carbon signals at δ 22.19, 26.83, 27.19, 33.17, 39.06, 52.00, 53.44 are corresponding to C_5, C_6, $C_{5'}$, $C_{6'}$, $C_{3'}$, $C_{10'}$, -NCH_2Ph respectively. The carbon signals at δ 45.08, 47.03, 58.60, 64.03, 65.86, 66.17 characterized as methine carbons are assigned to $C_{4'}$, C_3, C_2, C_1, $C_{2'}$ and C_4 respectively. The two quaternary carbon signals at δ 48.13 and 48.65 are characterized by $C_{7'}$ and $C_{1'}$ respectively.

Mass spectrum revealed molecular ion peak at 539 and base peak at 91 along with other peaks at 506 (15), 380 (17), 297 (45), 242 (85), 160 (27).

Characterization of minor cycloadduct, 86:

IR spectrum showed strong absorption band at 1683 cm^{-1} for amide functionality. ^1H NMR spectrum showed following characteristic pattern:

A sharp singlet at δ 0.85, integrating for six protons, is characteristic of methyl protons of $C_{8'}$ and $C_{9'}$. The three bunch of multiplets appearing in between δ 1.15 to 2.05, integrating for total eleven protons, are assigned to methylene protons (*exo* and *endo*) present in two bridgehead bicyclic systems. A doublet at 3.05 (J = 4.4 Hz) is assigned to bridgehead H_4. Another doublet at δ 3.12 (J = 4.2 Hz), integrating for one proton, could be assigned to H_{3endo}. The two benzylic protons have appeared as two sets of doublets at δ 3.35 and 3.63 (J *=13.6 Hz*). A singlet at δ 3.22, integrating for two protons, is characteristic of $H_{10'}$ protons. A triplet appearing at δ 3.60 (J = 6.4 Hz), equivalent to one proton, is assigned to bridgehead H_1. A triplet at δ 3.72 (J = 6.2 Hz), integrating for one proton, corresponds to $H_{2'}$. H_{2exo} is observed to appear as a triplet at δ 4.08 (J = 4.5 Hz). The aromatic protons have appeared as multiplets between δ 6.95-7.25, doublet at δ 7.75 (J = 2.6 Hz) and singlet at δ 8.15. This stereochemical assignment was further confirmed by ^1H COSY experiment. Thus, the structure of compound **86** is 7-benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*exo*-bornane 2,10-sultam 7-azabicyclo[2.2.21]heptane.

^{13}C NMR spectrum displayed a total of seventeen carbon signals in the aliphatic region in between δ 20.17-65.99 along with aromatic carbon signals at δ 124.34, 127.39, 128.64, 128.94, 138.22, 139.72, 139.96, 149.09 149.76 and a carbonyl carbon signal at δ 171.52. DEPT experiment suggested that methyl carbon signals of $C_{8'}$ and $C_{9'}$ are observed to appear at δ 20.17 and 21.00. Methylene carbon signals at δ 21.91, 26.83, 27.19, 33.11, 39.00, 51.82, 53.44 are characterized by C_5, C_6, $C_{5'}$, $C_{6'}$, $C_{3'}$, $C_{10'}$ and $-N\underline{CH_2}Ph$ respectively. Methine carbon signals at δ 44.77, 49.99, 57.65, 64.33, 65.96, 65.99 are corresponding to $C_{4'}$, C_3, C_2, C_1, $C_{2'}$ and C_4 respectively. The two quaternary signals at ä 48.16, 48.77 are characterized by $C_{7'}$ and $C_{1'}$ respectively.

Mass spectrum gave molecular ion peak at 539 and base peak at 91 along with other similar fragmentation peaks as observed with major isomer.

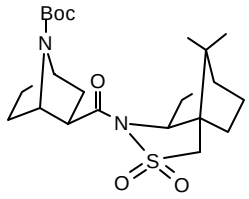
Thus, the results of this cycloaddition are on line with our previous observation which is already explained in chapter II. The excellent *exo*/*endo* selectivity, featuring the novelty of this cycloaddition, paved the way to make a new entry into the enantioselective synthesis of epibatidine. The synthetic potential of the major cycloadduct **85** towards the enantioselective synthesis of epibatidine was visualized by removal of chiral auxiliary followed by simple chemical manipulation of functional groups. The formation of **85** as the major cycloadduct in which chloropyridinyl substituent is in *exo*-orientation was a reasonable prize for us towards this endeavor. Thus, a formal total synthesis of epibatidine was completed by converting the major cycloadduct **85** into methyl ester **87** by a similar protocol as described in earlier section. Compound 87 was characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass analyses (Fig. 14 & 15). The compound **87** is already described to be an useful precursor for the total synthesis of epibatidine by our group.

SUMMARY:

We have developed a conceptually new methodology for the asymmetric synthesis of epibatidine. The excellent diastereoselectivity inherent with the cycloaddition makes this route feasible for the practical synthesis of enantiopure epibatidine. Moreover, this process is sufficiently flexible to permit access to optically pure epibatidine analogues and its higher homologues.

3. Experimental

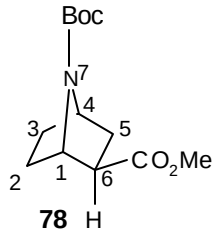
Preparation of 7-(*tert*-butoxycarbonyl)-2-*exo*-bornane-2,10-sultam-7-azabicyclo-[2.2.1]heptane 76 from 77:



To a solution of **77** (0.5 g, 1.16 mmol) in 50 mL of 4.5 % MeOH-HCOOH was added Pd/C (0.5 g) and the resultant suspension was stirred at rt for 36 h. The reaction mixture was filtered, the filtrate was evaporated and the crude amine was dissolved in 30 mL of dry DCM and treated with a solution of $(Boc)_2O$ (0.305 g, 1.40 mmol) in 10 mL DCM followed by Et_3N (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 (7:3) to afford 0.62 g of **76** (82 %) as a white solid, m.p.173-175 ^oC

IR (Nujol)	:	2945, 1679 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 0.95 (s, 3H), 1.12 (s, 3H), 1.32–1.60 (m, 4H), 1.45 (s, 9H), 1.65-1.95 (m, 6H), 2.05-2.15 (m, 3H), 3.40 (d, *J* = 13.6 Hz, 1H), 3.50 (d, *J* = 13.6 Hz, 1H), 3.55 (dd, *J* = 7.9, 4.3 Hz, 1H), 3.90 (t, *J* = 5.6 Hz, 1H), 4.20 (t, *J* = 4.8 Hz, 1H), 4.60–4.70 (m, 1H).
^{13}C NMR ($CDCl_3$) (50.32 MHz)		δ 19.98, 20.08, 24.84, 26.48, 28.01, 29.02, 31.55, 32.98, 34.45, 38.85, 44.86, 47.01, 48.05, 53.55, 57.55, 58.95, 66.25, 79.02, 154.55, 171.23.
Mass (m/z)	:	438 (M^+, 5), 365 (15), 338 (100), 135 (17), 83 (25).

Preparation of 78 from 79:

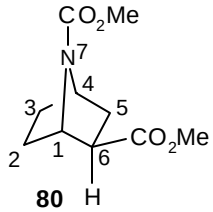


78

To a solution of **79** (0.5 g, 0.4 mmol) in 30 mL of ethanol was added palladium hydroxide (50 mg) and the resultant suspension was hydrogenated (50 psi, rt) for 2 days. The reaction mixture was worked-up as mentioned above and was converted to N-Boc derivative in a similar manner to afford 0.475 g of 7**8** (92 %) as a colorless oil.

$[\alpha_D]^{25}$	:	-12.1° (c =1.06, $CHCl_3$)
IR (Nujol)	:	1770, 1740 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	1.38-1.42 (m, 2H), 1.43 (s, 9H), 1.61 (dd, *J* = 12.4, 8.9, 1H), 1.71-1.82 (m, 2H), 2.25-2.29 (m, 1H), 2.55 (dd, *J* = 8.9, 5.1Hz, 1H), 3.70 (s, 3H), 4.29-4.35 (m, 1H), 4.45 – 4.52 (m, 1H).
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	28.1, 28.7, 29.3, 33.1, 47.3, 51.9, 55.8, 59.1, 99.5, 154.7, 173.6
Mass (m/z)	:	255 (M^+, 0.9), 196 (25), 169 (52), 96 (42), 69 (100).

Preparation of 80 from 78:



80

The crude amine obtained from **79** (0.5 g, 1.96 mmol) by N-debenzylation as described above was dissolved in 30 mL of dry DCM and treated with methyl

chloroformate (0.13 g, 1.96 mmol) under argon atmosphere. The resulting mixture was stirred for 1 h and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/EtOAc (8:2) to afford 0.35 g of **80** (84 %) as a colorless oil. $[\alpha_D]^{25}_{obs}$ = -16.2° (c = 0.92, $CHCl_3$).

IR (Nujol)	:	1737, 1634 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 1.30-1.55 (m, 2H), 1.63 (dd, *J* = 12.5, 8.9 Hz, 1H), 1.75-1.95 (m, 2H), 2.17-2.35 (m, 1H), 2.55 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.63 (s, 3H), 3.67 (s, 3H), 4.35 (t, *J* = 4.2 Hz, 1H), 4.55 (d, *J* = 3.7 Hz, 1H).
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ 28.63, 29.11, 33.29, 47.18, 51.69, 52.0, 55.69, 59.08, 155.53, 173.42
Mass (m/z)	:	213 (M^+, 16), 184 (13), 154 (39), 126 (100), 82 (17)

Preparation of 2-Amino-5-iodo pyridine 83:

A mixture of 2-aminopyridine **82** (5.22 g, 0.05 mol), periodic acid dihydrate (2.53 g, 0.01 mol) and iodine (5.66 g, 0.20 mol) were heated in a mixed solution of gl. CH_3COOH (35 mL), water (6 mL) and conc. H_2SO_4 (1 mL) at 80 °C for 4 h. The mixture was then poured into aq. dil. $Na_2S_2O_3$ solution to remove unreacted iodine and the organic was extracted with ether (3 x 20 mL). The extract was washed with dil. NaOH, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel with $CHCl_3$ as eluent and recrystallization from ethanol to obtain colorless prisms of 2-amino-5-iodopyridine **83** (8.23 g, 67%); m.p. 130-132 °C (lit.[43] 137-139 °C).

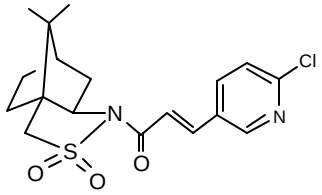
Preparation of 2-chloro-5-iodopyridine 81:

Into a 100 mL RB flask was introduced **83** (4.0 g, 18.1 mol) and 27 mL of conc. HCl was added slowly at 0°C with vigorous stirring. 1.6 g of $NaNO_2$ was added in portions into the stirring solution over 30 minutes maintaining the temperature at 0°C. After the addition was over, it was allowed to stir for another 2 h at the same temperature and then left for overnight stirring at room temperature. The reaction mixture was poured slowly into 100 mL of ice-cold water. The solution was made slightly basic by adding 10% aq. NaOH solution with constant stirring. The whole aqueous solution was extracted with

ether (3 x 50 mL) and the ether layer was washed with water (2 x 50 mL), brine and dried over anhydrous Na_2SO_4.

Evaporation of solvent gave crude **81** which was purified by column chromatography over silica gel affording pure **81** (2.35 g, 54% yield) as a yellow solid; m.p. 65-67 °C (lit.[43] 69-71°C).

Preparation of 73 by Heck-Coupling Reaction:



K_2CO_3 (5.37 g, 0.02 mmol), $Pd(OAc)_2$ (0.25 g, 0.001mmol) and PPh_3(0.59 g, 0.002 mmol) were added to a stirring solution of olefin **66** (3.03 g, 0.01 mmol) and **81** (2.70 g, 0.01 mmol) in 30 mL of dry CH_3CN. The mixture was purged with nitrogen and the mixture was refluxed for 4 h under argon atmosphere. The solvent was removed under reduced pressure and the whole dark-brown mass was taken in $CHCl_3$, the organic layer was washed with 0.1 (N) HCl (3 x 10 mL) followed by water (2 x 10 mL) and brine. The crude residue was purified by column chromatography eluting with EtOAc/$CHCl_3$ (2:8) to afford 3.65 g (85 %) of **73** as a white solid, m.p. 225-227 °C.

IR (Nujol) : 3018, 1679, 1334, 1215 cm^{-1}

^1H NMR ($CDCl_3$) (200 MHz) : δ 0.98 (s, 3H), 1.20 (s, 3H), 1.35-1.52 (m, H), 1.87-2.05 (m, 3H), 2.18 (d, *J* = 7.3 Hz, 1H), 3.45 (d, *J* = 13.6 Hz, 1H), 3.55 (d, *J* = 13.6 Hz, 1H), 3.98 (t, *J* = 6.3, Hz, 1H), 7.20 (d, *J* = 15.6 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 15.6 Hz, 1H), 7.9 (dd, *J* = 8.3, 2.4 Hz, 1H), 8.5 (d, *J* = 2.5 Hz, 1H).

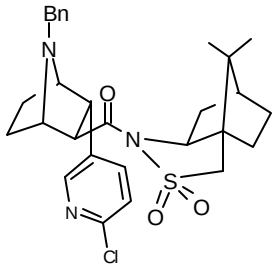
^{13}C NMR ($CDCl_3$) (50.32 MHz) : δ 19.67, 20.62, 26.32, 32.68, 38.23, 44.59, 47.68, 48.49, 52.93, 65.03, 120.27, 124.32, 129.10, 136.60, 139.68, 149.94, 163.10

Mass (m/z) : 381 (M^+, 10), 317 (15), 274 (5), 167 (100), 138 (29), 102 (84), 76 (55).

[3+2] Cycloaddition of 65 with 73:

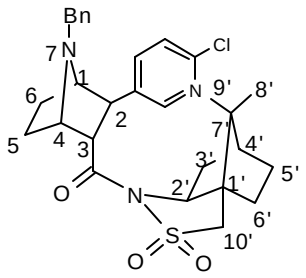
A typical cycloaddition of **84** (1.50 g, 4.91 mmol) with **73** (2.24g, 5.90 mmol) using Ag(I)F (1.54 g, 0.01 mol) was performed as described in the experimental section of the previous chapter. Column purification of crude cycloaddition mixture using (60:120) silica gel gave mixture of diastereomeric cycloadducts (**85**&**86**) in a ratio of 9:1 with 64 % overall yield. The two diastereomers were separated by careful flash column chromatography eluting with acetone/hexane (2.5:7.5) to afford 1.53 g (58 %) of **85** as a white prism shaped solid, m.p. 237- 239 ^{o}C and further elution with the same polarity of solvent gave 0.17 g (7 %) of **86.** The two cycloadducts were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analyses and are given below:

Characterization of **86**:



IR (Nujol)	:	1683 cm^{-1}
^{1}H NMR (C_6D_6 + $CDCl_3$ 1:1) (500 MHz)	:	ä 0.85 (s, 6H), 1.15-1.35 (m, 3H), 1.65-1.82 (m, 5H), 1.95–2.05 (m, 3H), 3.05 (d, *J* = 4.4 Hz, 1H), 3.12 (d, *J* = 4.8 Hz, 1H), 3.22 (s, 2H), 3.35 (d, *J* = 13.6 Hz, 1H), 3.60 (t, *J* = 6.4 Hz, 1H), 3.63 (d, *J* = 13.6 Hz, 1H), 3.72 (t, J = 5.6 Hz, 1H), 4.08 (t, *J* = 4.5 Hz, 1H), 6.95–7.25 (m, 6H), 7.75 (d, *J* = 2.6 Hz, 1H), 8.15 (s, 1H)
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	ä 20.17, 21.00, 21.91, 26.83, 27.19, 33.11, 39.00, 44.77, 48.16, 48.77, 49.99, 51.82, 53.44, 57.65, 64.33, 65.96, 65.99, 124.34, 127.39, 128.64, 128.94, 138.22, 139.72, 139.96, 149.09, 149.76, 171.52.
Mass (m/z)	:	539 (M^{+}, 5), 506 (5), 380 (12), 297 (18), 242 (5), 160 (97), 91 (100)
m.p.		230-232 ^{o}C

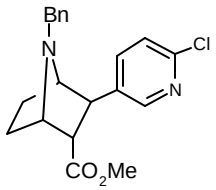
Characterization of **85**:



85

IR (Nujol)	:	1683, 12 15 cm^{-1}
^{1}H NMR ($CDCl_3$, 500 MHz)	:	0.98 (s, 3H), 1.23 (s, 3H), 1.34–1.43 (m, 2H), 1.45-1.51 (m, 1H), 1.62-1.67 (m, 1H), 1.86-1.95 (m, 4H), 2.01-2.08 (m, 2H), 2.09-2.15 (m, 1H), 3.22 (d, *J* =4.4 Hz, 1H), 3.37 (d, *J* = 4.8 Hz, 1H), 3.41 (d, *J* = 13.7 Hz, 1H), 3.49 (d, *J* = 13.1 Hz, 1H), 3.53 (d, *J* = 13.1 Hz, 1H), 3.61 (t, *J* = 4.2 Hz, 1H), 3.72 (d, *J* = 13.7 Hz, 1H), 3.90 (t, *J* = 5.1 Hz, 1H), 4.06 (t, *J* = 4.4 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.21-7.29 (m, 1H), 7.31-7.39 (m, 4H), 7.82 (dd, *J* = 8.3, 2.4 Hz, 1H), 8.3 (d, *J* = 2.4 Hz, 1H)
^{13}C NMR ($CDCl_3$, 75.3 MHz)	:	20.23, 21.18, 22.19, 26.83, 27.19, 33.17, 39.06, 45.08, 47.03, 48.13, 48.65, 52.00, 53.44, 58.60, 64.03, 65.86, 66.17, 124.21, 127.45, 128.70, 128.85, 138.41, 139.63, 139.78, 149.39, 149.70, 171.18
Mass (m/z)	:	539 (M^+, 8), 506 (5), 380 (10), 297 (18), 242 (7), 160 (97), 91 (100).
HRMS		Calculated for $C_{29}H_{34}N_3O3SCl$: 539.200942
		Observed: 539.200469
m.p.		220-222 ^{o}C

Preparation of 87 from 85:



A solution of **85** (0.5 g, 0.92 mmol) in 24 mL THF: H_2O (3.1) containing $LiOH.H_2O$ (37 mg, 0.926 mmol) was warmed to 45° for 1 h. THF was evaporated and the aqueous layer was extracted with EtOAc (3 x 2.0 mL). The aqueous layer was cooled to 0°C, acidified with 1(N) HCl to pH = 6-7, and extracted with $CHCl_3$ (3 x 3.0 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to obtain crude acid. The resultant crude acid was converted into corresponding methyl ester **87** in the similar manner as described in the previous chapter to obtain 0.285 g (90%) of **87**, $[á_D]^{25}_{obs}$ = -16.7° .The methyl ester **87** was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass analyses.

IR ($CHCl_3$)	:	1726, 1458, 1112 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ 1.52-1.70 (m, 2H), 1.90-2.30 (m, 2H), 2.85 (t, *J* = 5.1 Hz, 1H), 3.10 (d, *J* = 5.3 Hz, 1H), 3.30 (d, *J* = 4.2 Hz, 1H), 3.6 (s, 2H), 3.70 (s, 3H), 3.60-3.70 (t, *J* = 4.4 Hz, 1H), 7.15-7.45 (m, 6H), 7.80 (dd, *J* = 8.4, 2.6 Hz, 1H), 8.5 (d, *J* = 2.4 Hz, 1H).
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	21.61, 26.55, 47.30, 51.42, 57.16, 61.31, 66.05, 66.10, 123.39, 126.78, 128.00, 128.24, 137.64, 138.92, 139.72, 148.69, 149.00, 172.25
Mass (m/z)	:	356 (M^+ ,5), 297 (1),159 (56), 131 (14), 91 (100), 65 (12).
HRMS		Calculated for $C_{20}H_{21}N_2O_2Cl$: 356.12915 Observed: 356.129226

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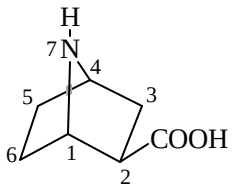
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3
6
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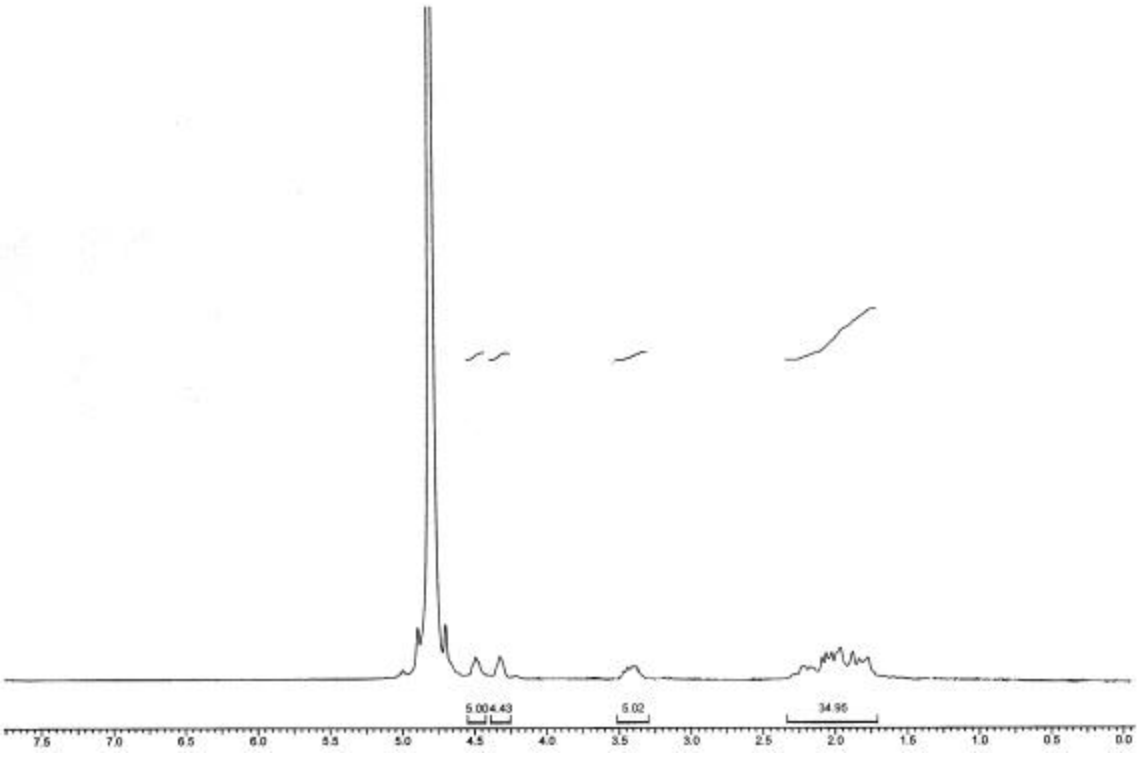
COOH
2

32a

Fig. 5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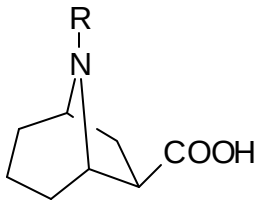
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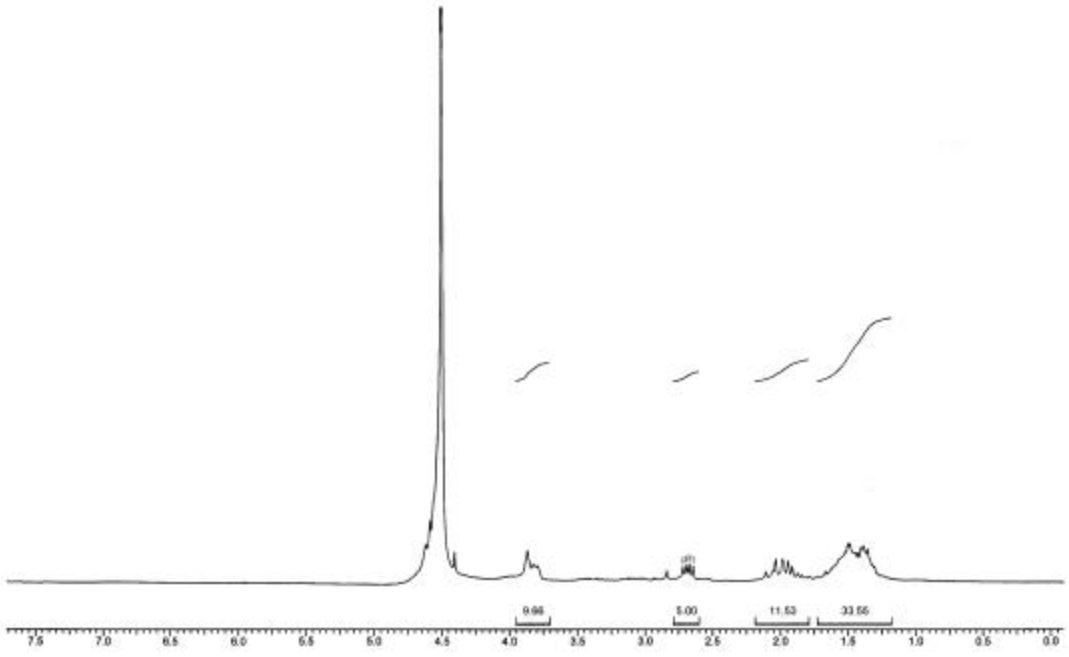
N
COOH

Fig. 6

32b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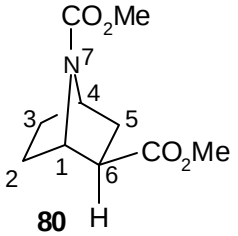
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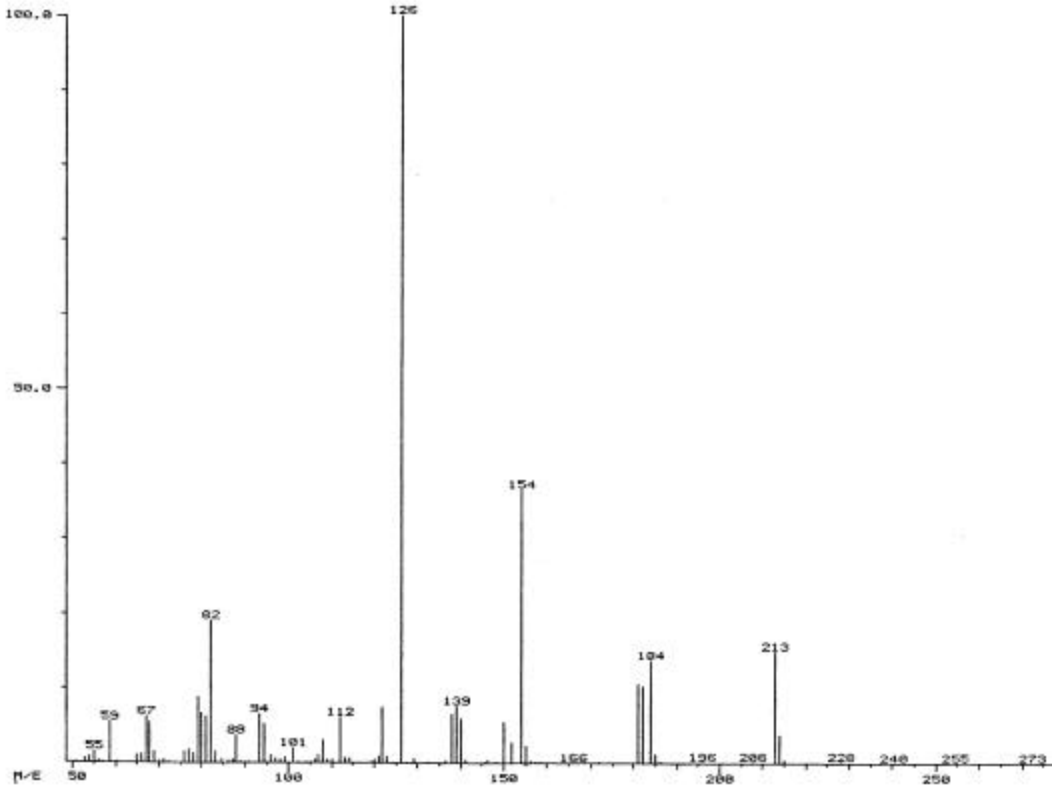
6
H

80

Fig. 7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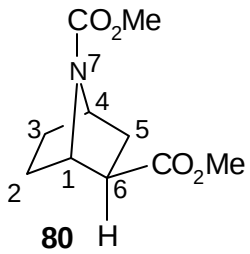
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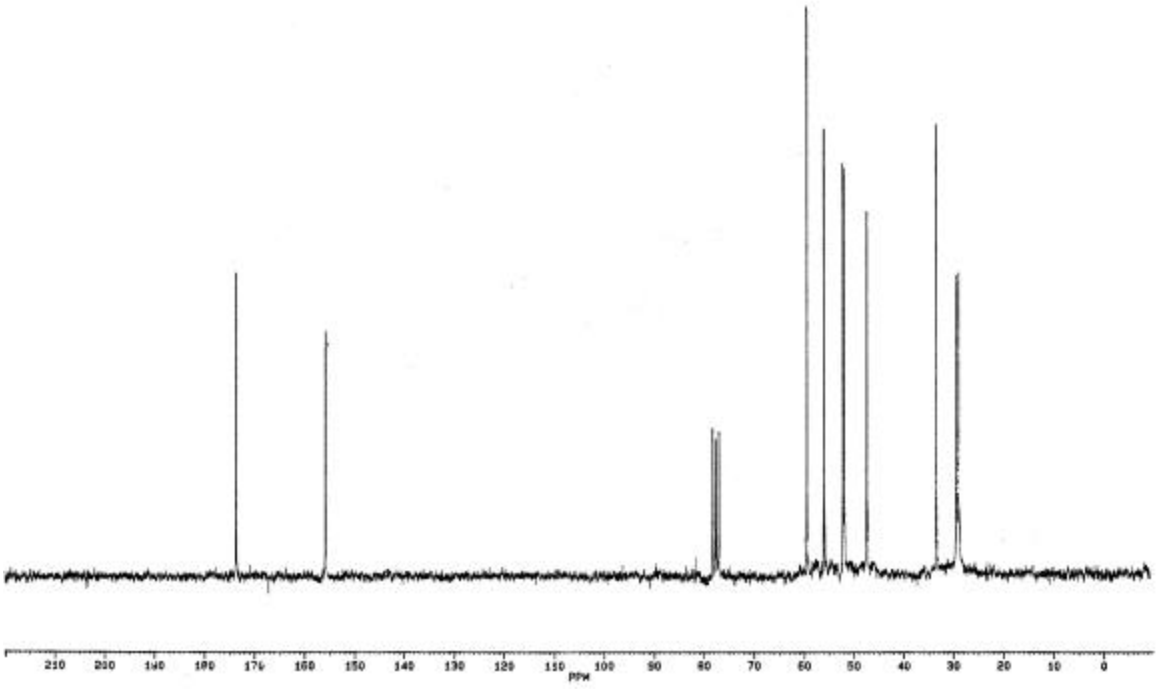
80 **Fig. 8**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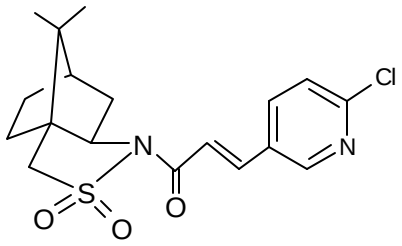
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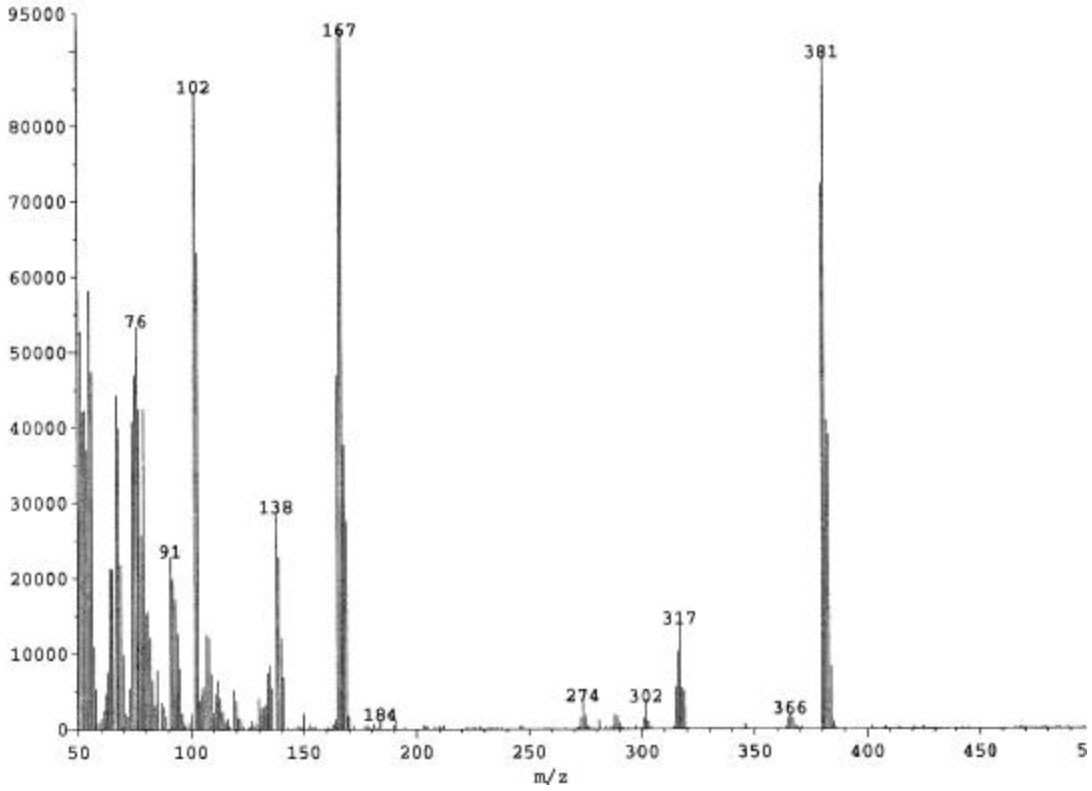
S
O
O
O

(-)-**73**

Fig. 9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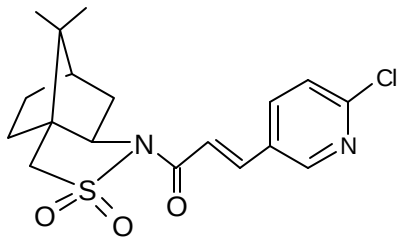
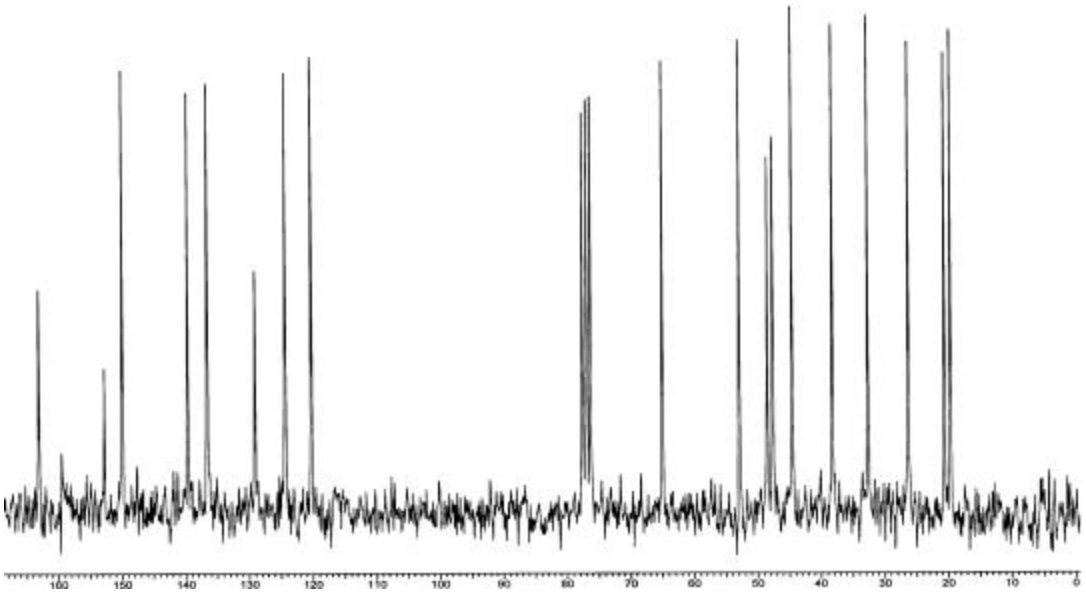
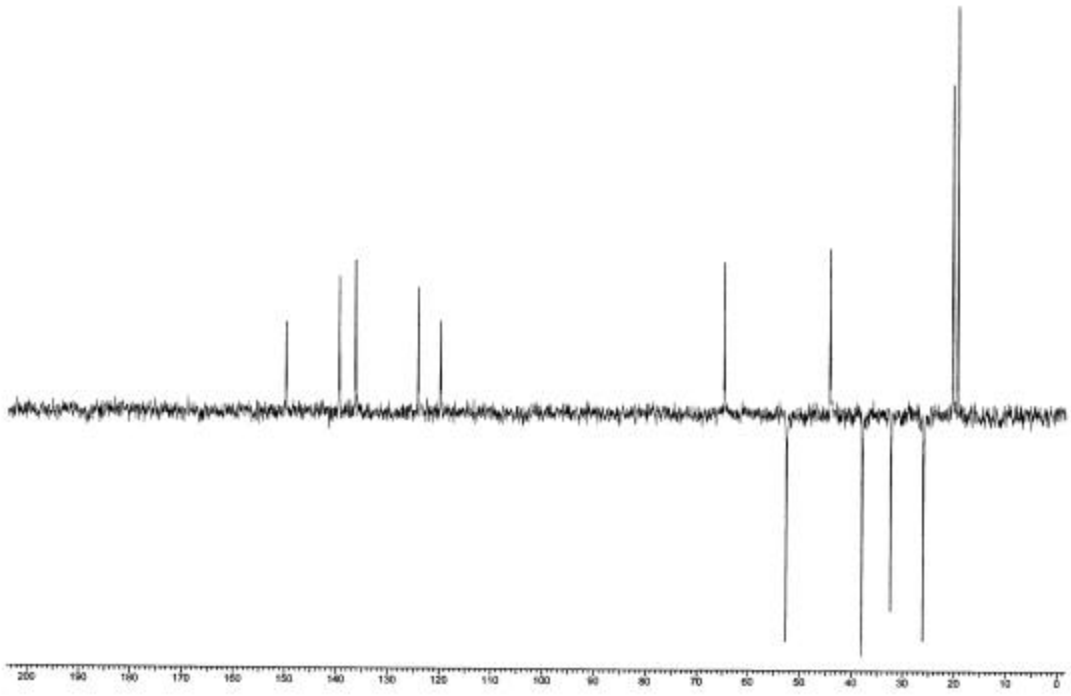
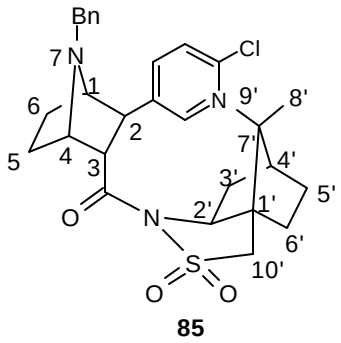


Fig. 10

(-)-**73**



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Cl
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9'
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7'
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2'
1'
6'
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10'
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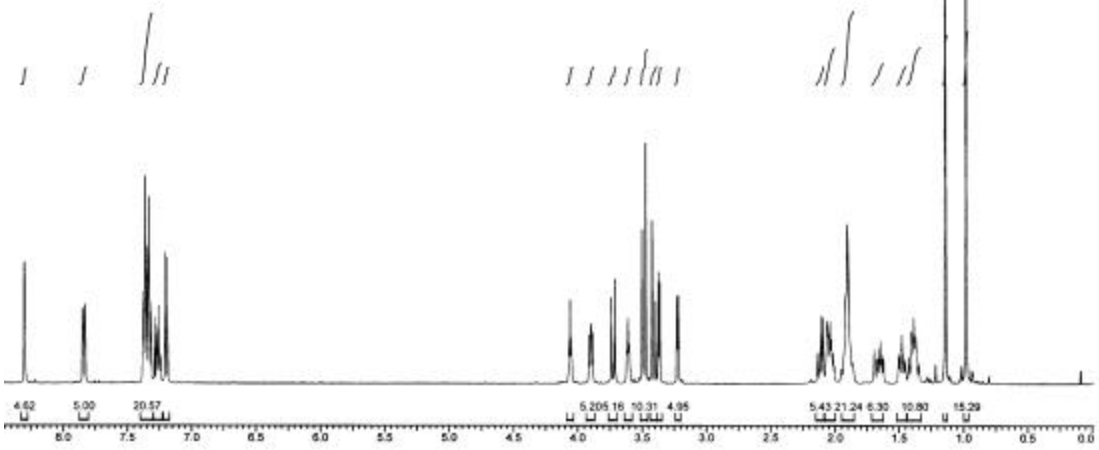
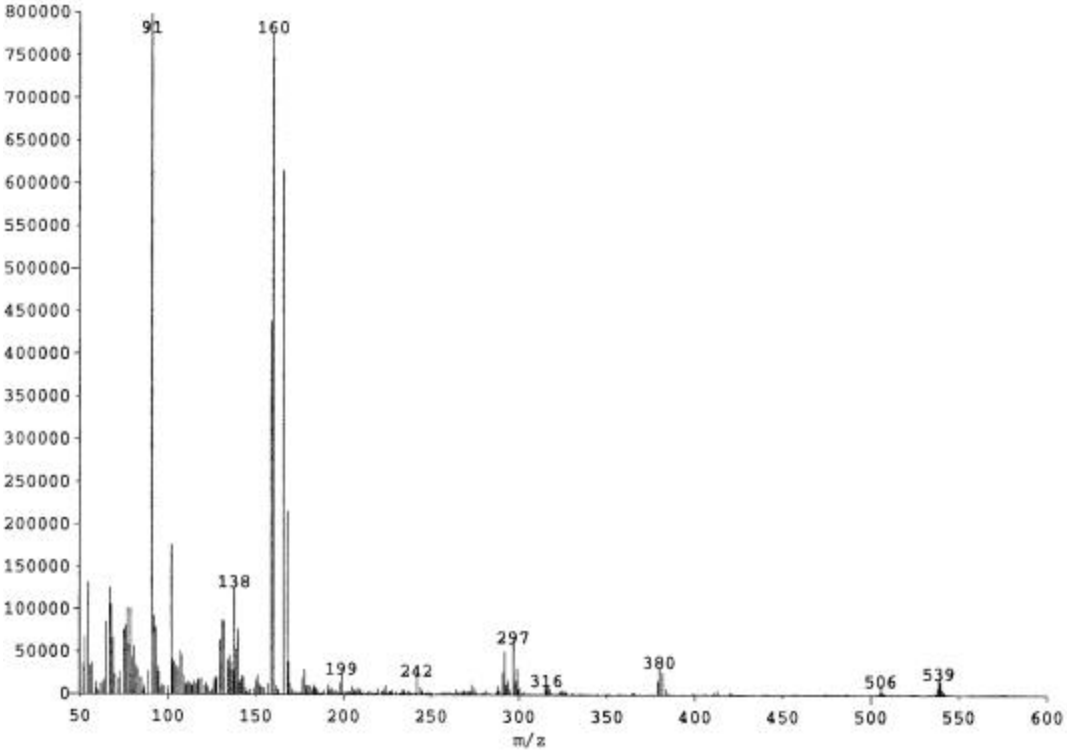
O

85

Fig. 11

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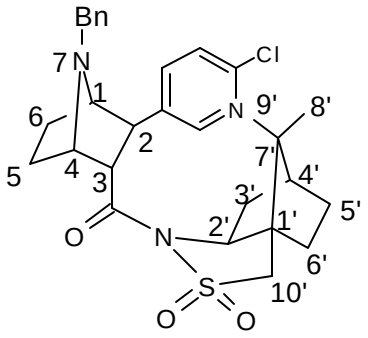
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9'
8'
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4'
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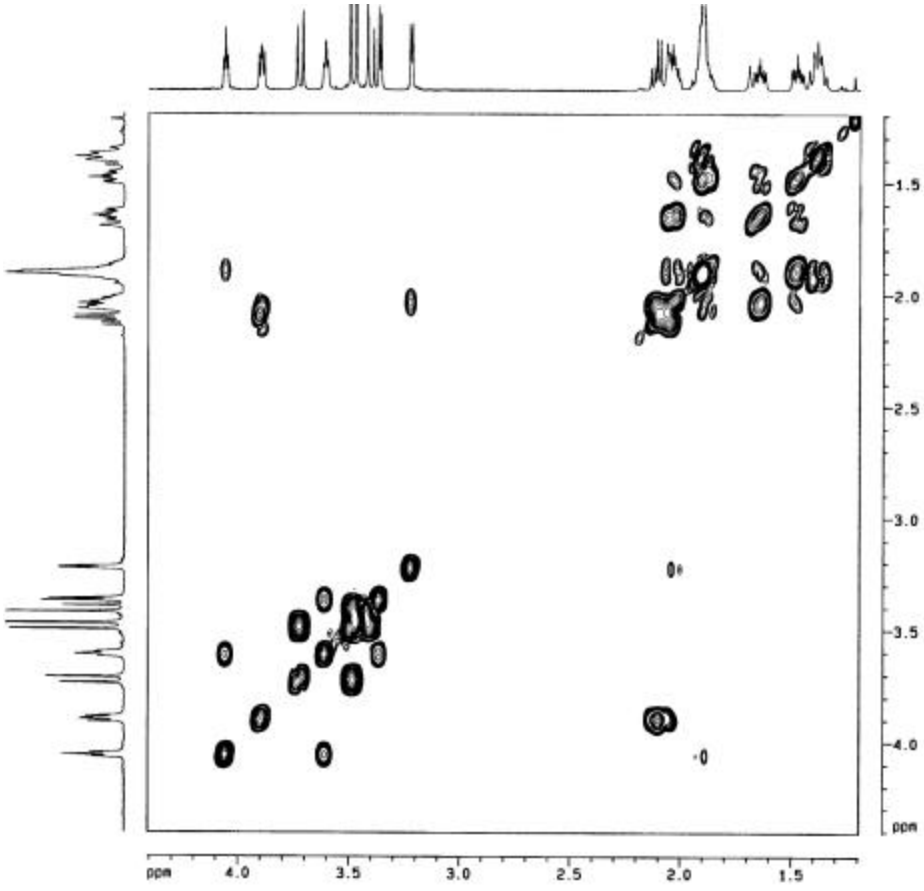
6'
10'
S
O
O

85

Fig. 12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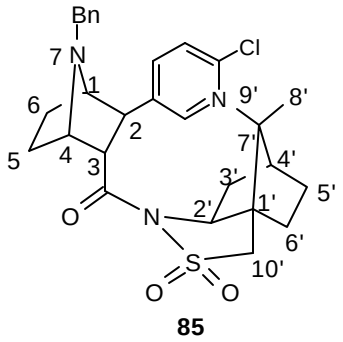

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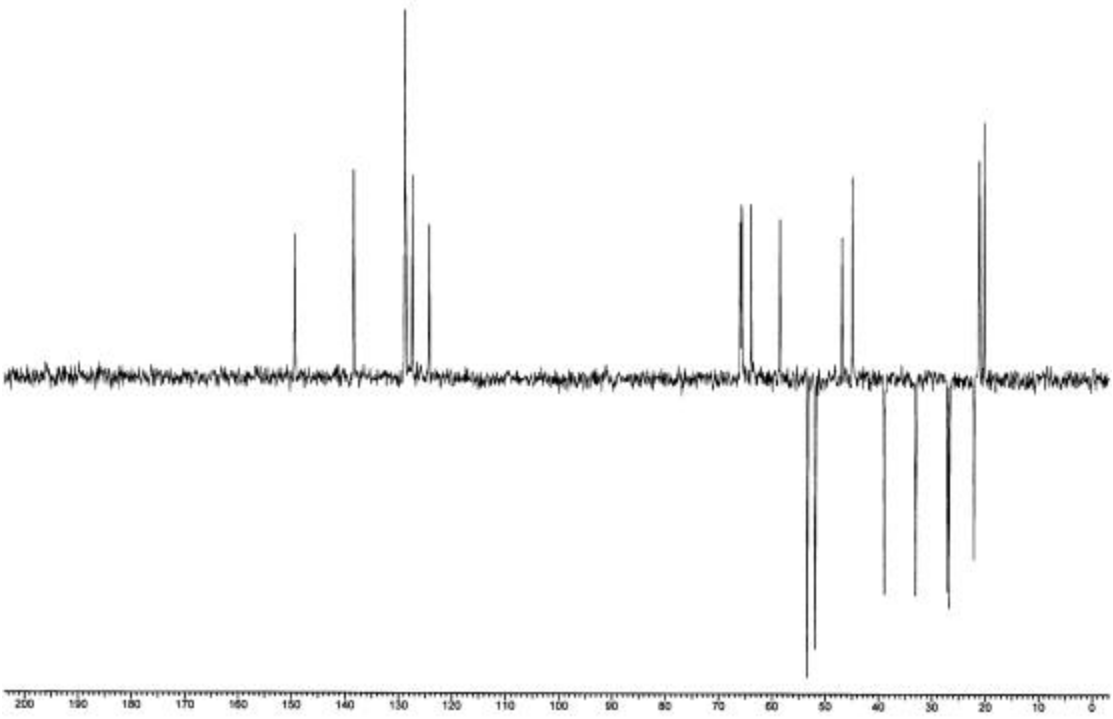
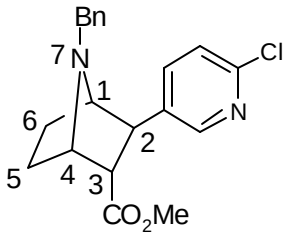
Fig. 13

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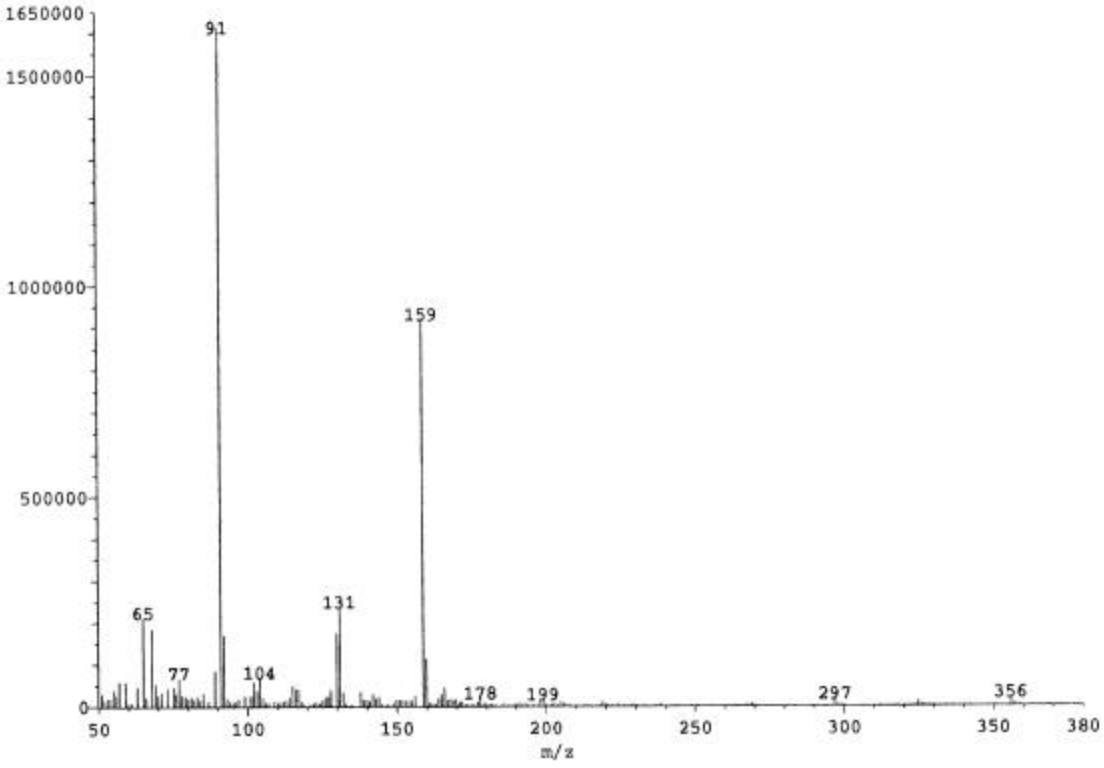
CO2Me

87

Fig. 14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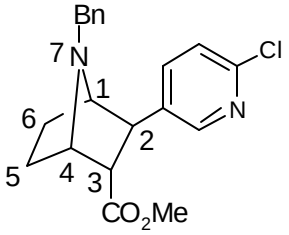
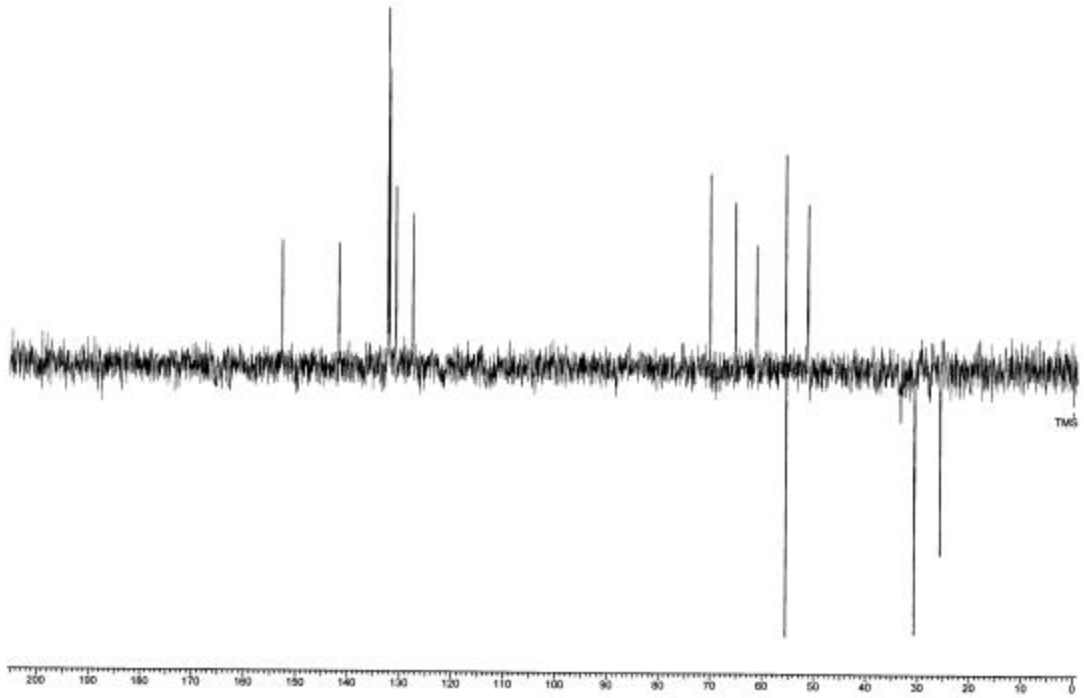
380
m/z



87

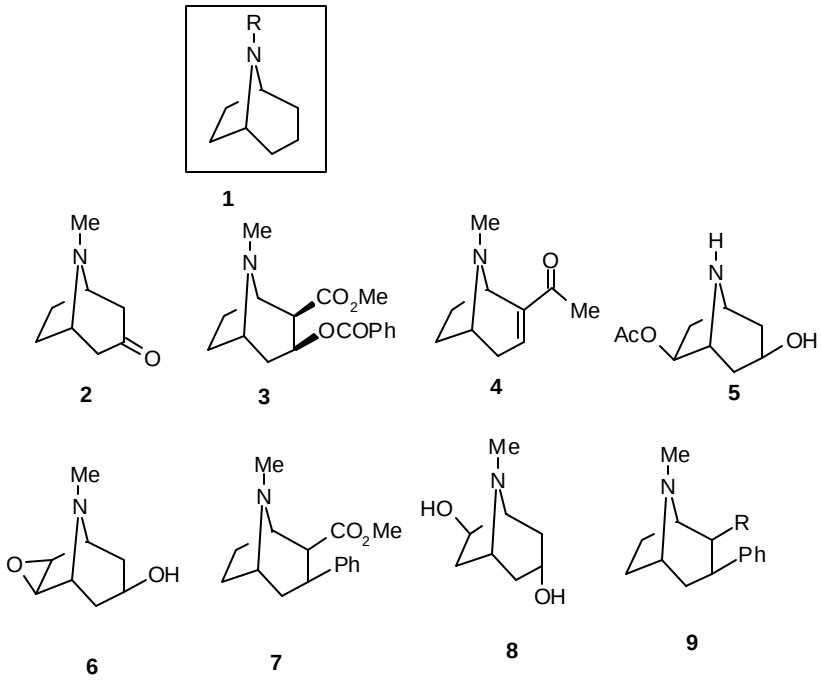
Fig. 15



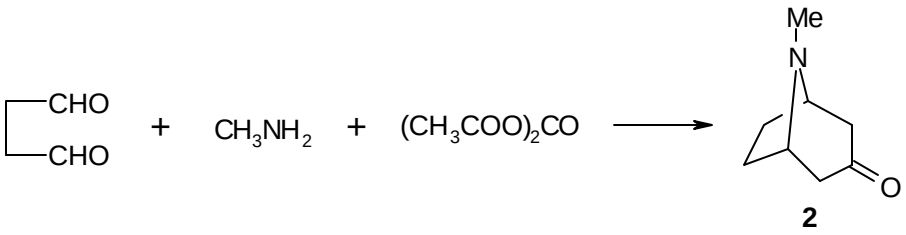
1. Introduction

Tropane alkaloids comprise a group of some 200 natural products which mostly occur in plants of *Solanaceae* family and many of these alkaloids possess potent biological activities.[1] All these classes of alkaloids contain a basic skeleton, 8-azabicyclo[3.2.1]octane framework (**1**).

Fig. 1



Of particular importance are Cocaine (**3**)[2], Ferruginine (**4**)[3], Bao Gong Teng A (**5**)[4] and Scopolamine (**6**)[5] as these compounds are useful probes to study the neurochemistry of drug addiction. For these purposes, a prodigious number of racemic syntheses leading to tropane class of alkaloids have appeared.[6] The first synthesis of tropinone was reported by Willstatter[7] in an extended series of transformations starting from cycloheptanone. Soon thereafter, Robinson[8] devised an efficient, superbly elegant approach involving the condensation of succinaldehyde, methylamine and the calcium salt of 1,3-acetone dicarboxylic acid to afford tropinone in 42 % yield.



2

This yield was increased to 92.5 % by careful control of reaction conditions (i.e. pH, temperature etc).[9] These classical approaches fail to allow incorporation of any functionalities in the two carbon bridge of tropane skeleton and the efforts to extend these approaches to cocaine encountered stereochemical problem.[10] Several methods employ cycloaddition reactions including [4+3]-cycloaddition of iron oxallyl cations to pyrrole[11], nitrone cycloaddition[12], nitroso cycloaddition[13] and pyridinium betaine-based dipolar cycloaddition[14]. Due to profound behavioral and neuronal reinforcing properties associated with cocaine and its abuse in social and health, much synthetic effort has been directed in the search of cocaine antagonist (*viz.***7**)[15] and partial agonists (*viz.***8**, **9**)[16] of cocaine. As a result many asymmetric synthetic routes have been developed over the last few years.[17] Ferruginine (**4**), another prominent member of this class, was found to be good agonist for the nicotinic acetylchlorine receptor (nAChR).[18] Astonishingly, its asymmetric synthesis was not known until 1995.[19] Much less attention has been paid to the synthesis of tropane class of alkaloids having functionalities in the two carbon bridge (e.g. Bao Gong Teng A, Scopolamine etc.).[20] As a consequence, only few asymmetric routes have emerged for the synthesis of this particular class of alkaloids (e.g. Bao Gong Teng A).[21]

From the above precedent, it is conspicuous that different synthetic approaches have been administered for the asymmetric synthesis of various tropane alkaloids. A good synthetic strategy towards tropane alkaloids should be general, *i.e.* it should allow access to several different alkaloids and should be enantioselective with the possibility of synthesizing both enantiomers *via* essentially the same route being a desirable feature. The quest for the development of a general route for the tropane alkaloids has resulted the discovery of few asymmetric routes in recent years, which are discussed below:

The concept of enantioselective enolisation of tropinone (**2**) by chiral lithium amide bases[22] has been used by several groups for the synthesis of chiral tropane alkaloids. Majewski *et al.*[23] have studied the enantioselectivity of enolisation of tropinone using

different chiral lithium amide bases in the presence of LiCl for the construction of the basic skeleton in the synthesis of benzyl tropanes and pyrotropanes (Scheme 1).

Scheme 1

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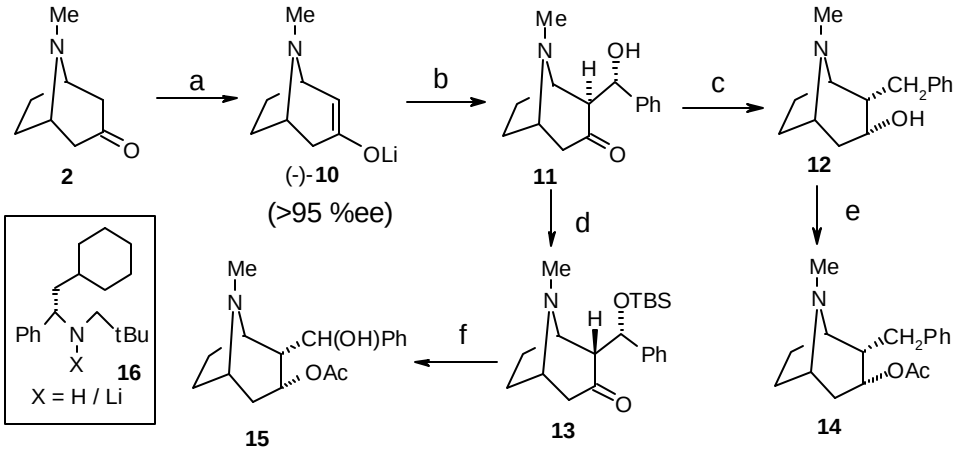
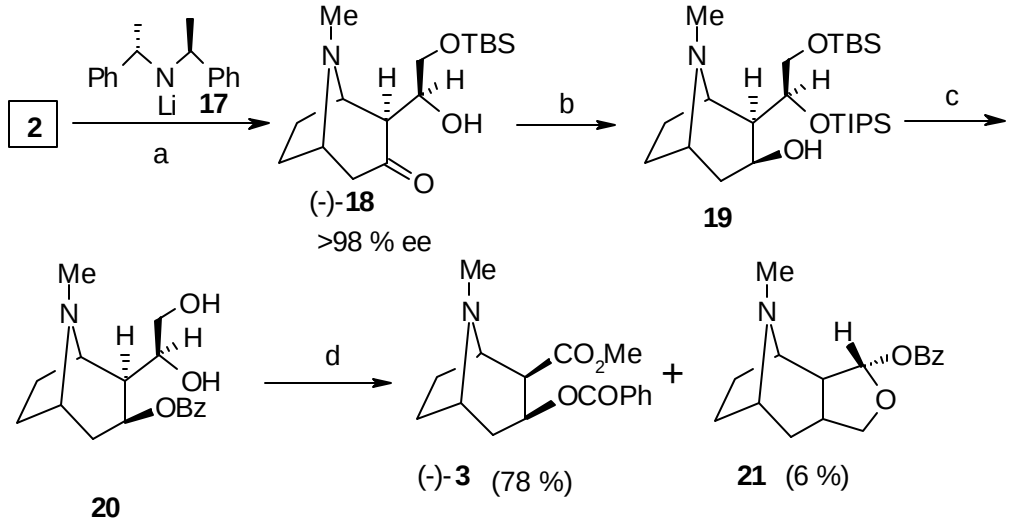


***Reagents and Conditions**: a) n-BuLi, **16**, THF, -78 °C; b) PhCHO; c) i) Ac_2O; ii) SiO_2; iii) H_2/PtO_2; d) i) TBDMSCl, Et_3N, ii) SiO_2; e) Ac_2O; f) i) H_2/PtO_2, ii) Ac_2O, iii) Bu_4N.*

Few other groups have successfully synthesized various tropane alkaloids using the same concept.[24] Very recently, Cha *et al.*[25] have achieved high enantioselectivity in the enolisation of tropinone using **17** as a chiral lithium amide base in the synthesis of (-)-cocaine **3** (Scheme 2).

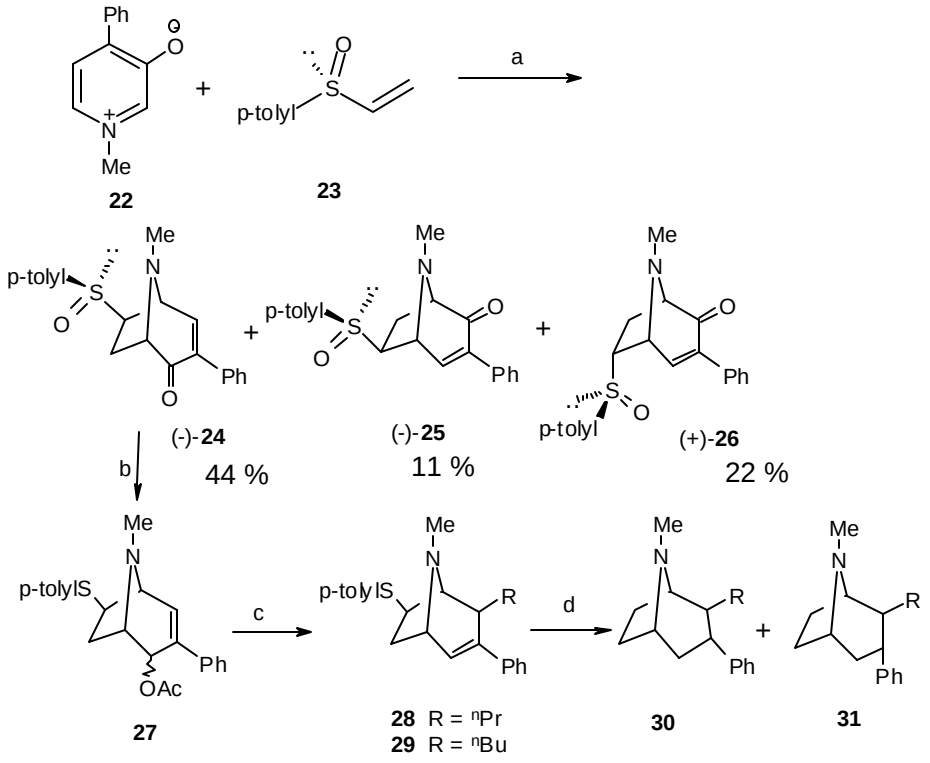
Scheme 2



***Reagents and Conditions**: a) **17**, TBSO-CH_2CHO, LiCl, THF, -78 ^oC, 72 %; b) I) TIPSOTf, 2,6-leutidine, ii) Li/NH_3, 96 %; c) i) PhCOCl, Et_3N, ii) HF, 98%; d) $RuCl_3$-$NaIO_4$, $TMSCHN_2$.*

Another general approach for the construction of tropane skeleton in single step operation involved the use of asymmetric 1,3-dipolar cycloaddition reaction.[26] Kozikowskii *et al.*[27] have described the synthesis of diversely substituted tropanes involving the asymmetric 1,3-dipolar cycloaddition of oxidopyridinium betaine **22** and the chiral sulfoxide **23** as shown below (Scheme 3). The formation of regio- and diastereomers inherent with intermolecular cycloaddition raises serious limitation of this approach.

Scheme 3

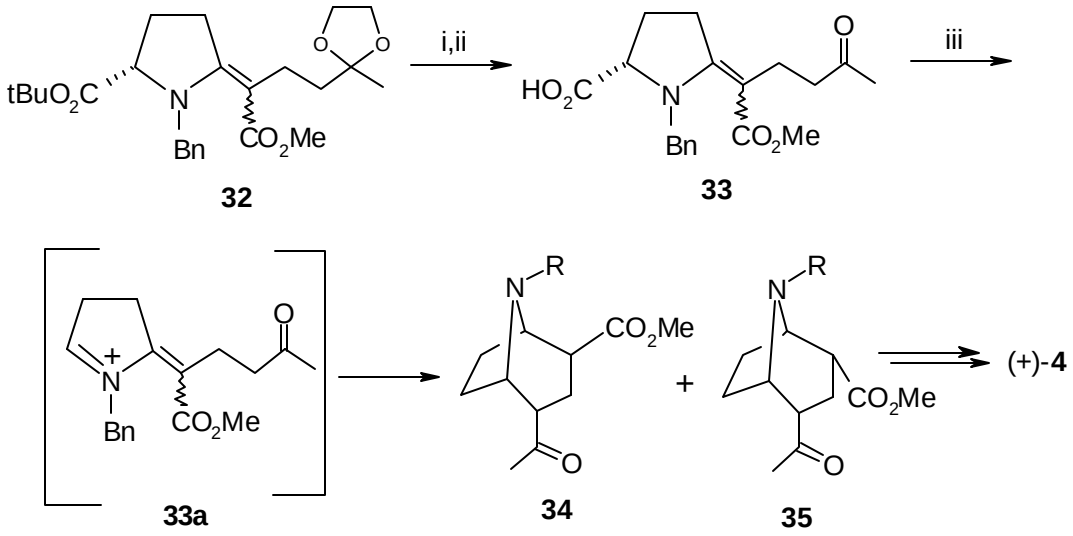


***Reagents and Conditions**: a) 1,4-dioxan, reflux, 24 h, 87 %; b) i) NaBH4, $CeCl_3$, MeOH, rt, ii) Ac_2O, py, rt, iii) PCl_3, DMF, O ^oC, 88 %; c) RMgBr, CuCN, Et_2O, rt, 77 %; d) Raney Ni (W_2), EtOH, reflux, 65 %.*

Rapoport *et al.*[28] have made significant contribution in this field by developing independently a novel "Chiron" concept of decarbonylative/ iminium-ion intramolecular

cyclization for the construction of tropane skeleton. One such report[28a] describes the synthesis of (+)-ferruginine involving intramolecular cyclization of **33a**, obtained from **33** (Scheme 4). However, the formation of regio- and diastereomers in the key cyclization step of this approach places serious limitation of this approach.

Scheme 4

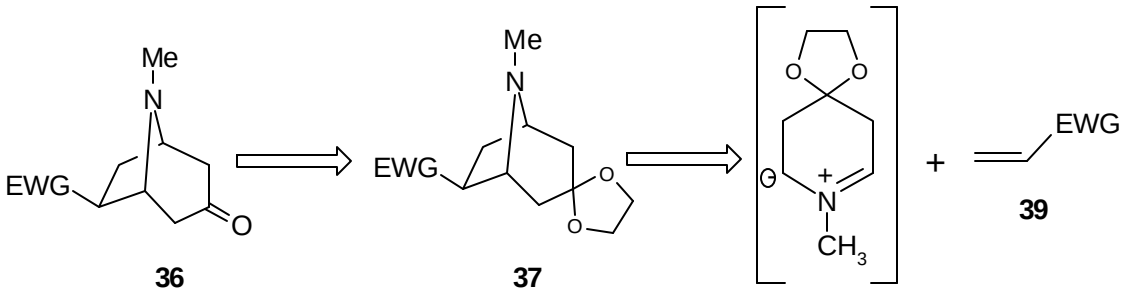


Reagents and Conditions*: i) H+/H2O, ii) (COCl)2; iii) Ä.*

These studies deserve much credit due to their pioneering nature. However, the issues of regio, diastereo- and enantioselectivities are not contented and the yields, for the most part, are low.

As we have already shown the potentiality of our asymmetric [3+2]-cycloaddition methodology in the enantioselective total synthesis of epibatidine, we turned our attention towards building of a strategy for the synthesis of diverse tropane alkaloids. The construction of **1** by our [3+2]-cycloaddition approach has already been demonstrated in Chapter II. To introduce diverse functionalities into **1,** the following retrosynthetic analysis was envisaged (Scheme 5).

Scheme 5



The above retrosynthetic analysis revealed that [3+2]-cycloaddition of AMY **38** with a suitable electron deficient dipolarophile **39** would afford the desired framework of tropane alkaloids. The cycloadduct **37** would be of valuable synthetic intermediate capable of leading to a wide range of tropane class of alkaloids. The application of such an unprecedented asymmetric [3+2]-cycloaddition approach to functionalized tropanes is the main focus of this chapter.

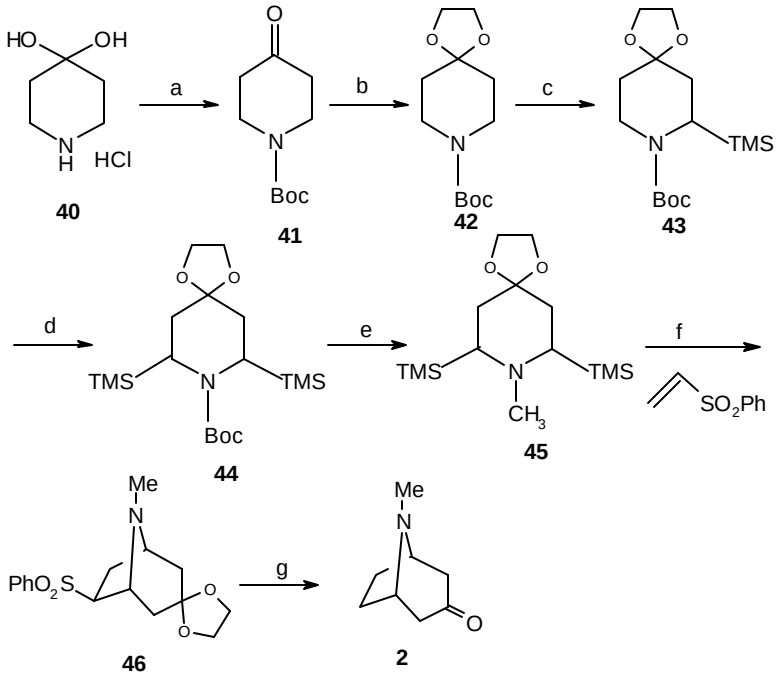
2. Results and Discussion

To evaluate the utility of our methodology in this direction, we embarked upon this research project first by attempting the synthesis of tropinone **2**, a simple tropane alkaloid.

2.1 Synthesis of Tropinone (2):

Synthesis of **2** commenced with the preparation of AMY precursor **45** followed by the construction of tropane skeleton by [3+2]-cycloaddition of cyclic AMY **38** with phenyl vinyl sulfone. The cycloadduct **46** on simple functional group manipulation gave tropinone **2** (Scheme 6).

Scheme 6



Reagents and Conditions*: a) Boc-N_3, Et_3N, Dioxan, H_2O, 92 %; b) $(CH_2OH)_2$, p-PTS, benzene , reflux, 87 %; c) TMEDA, s-BuLi, TMSCl, -78 ^oC, 86 %; d) TMEDA, s-BuLi, TMSCl, -40 ^oC, 1 h, 62 %; e) i) TFA, DCM, ii) HCHO, $NaBH_3CN$, gl. CH_3COOH, 66 %; f) Ag(I)F, DCM, 68 %; g) i) 6 % Na-Hg, $NaH_2PO_4.H_2O$, MeOH, 2 h, 65 %.*

2.1.1 Synthesis of AMY precursor 45:

The synthetic precursor **45** was prepared from an inexpensive commercially available 4-piperidone monohydrate hydrochloride (**40)** by following the reaction sequences as shown in Scheme 6 .

Compound **40** was at first converted to N-(*tert*-butoxycarbonyl)-4-piperidone (**41)** in 92 % yield by treating with Boc-N_3 and Et_3N as described earlier. The ketone group in **41** was protected as ketal for the regioselective α-lithiation of nitrogen. The protection of ketone group was carried out in 87 % yield by refluxing a mixture of **41**, ethylene glycol and p-PTS in benzene under Dean-Stark condition. The first α-lithiation of **42** was achieved in 86 % yield following our previous protocol. By adopting the same protocol for second lithiation of **43**, as described earlier in the case of piperidine mono-TMS

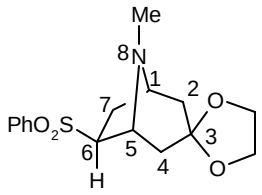
compound, compound **44** was obtained in 34 % yield along with the formation of side products.

Several experiments were carried out to optimize the yield of compound **44** under different conditions using different molar quantities of TMEDA, s-BuLi and TMSCl. The comparatively better yield (62 %) of di-TMS compound **44** was obtained by allowing the anion generation at −40 °C for 1 h. Under this condition the other side products were mostly eliminated though some amount (~20 %) of starting material remained unreacted. The N-Boc di-TMS compound **44** was fully characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analyses. Thus, the synthetic precursor **45** was obtained from **44** in 66 % yield by N-deprotection of Boc-moiety followed by reductive formylation of the resultant crude amine in a similar manner as described earlier. Compound **45** was fully characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analyses (Fig. 2 & 3).

2.1.2 [3+2]-Cycloaddition of 45 with phenyl vinyl sulfone:

The cycloaddition of cyclic AMY **38**, generated from its synthetic precursor **45**, by reaction with Ag(I)F and phenyl vinyl sulfone gave only one cycloadduct **46** in 68 % yield. The cycloadduct was fully characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analyses.

IR spectrum showed strong absorption bands at 1275, 1125 cm^{-1}.



^{1}H NMR spectrum showed following characteristic pattern (fig. 4).

A triplet at δ 1.60 (*J = 5.5 Hz*), integrating for two protons, could be assigned to H_{2endo} and H_{4endo}. Two doublets at δ 2.15 (*J = 9.1 Hz*) and 2.20 (*J = 9.5 Hz*) correspond to H_{2exo} and H_{4exo} respectively. Two multiplets appearing between δ 2.25-2.35 and 2.38-2.45, integrating for one proton each, may be attributed to H_{7endo} and H_{7exo} respectively. -NCH_3 protons appeared as a singlet at δ 2.55. A broad singlet at δ 3.40, integrating for one proton, is assigned to bridgehead H_1. A multiplet at δ 3.65 corresponds to four protons of ethylene glycol moiety. A doublet of doublet appearing at δ 3.90 (*J* = 10.7, 5.9 Hz),

integrating for one proton, is characteristic of H_{6endo}. Bridgehead H_5 has appeared as a triplet at δ 4.2 (*J = 8.0 Hz*). The five aromatic protons have appeared as two triplets at δ 7.55 (*J = 7.8 Hz*) and 7.65 (*J = 7.4 Hz*) and as a doublet at δ 7.90 (*J = 7.2 Hz*).

Thus, the structure of compound **46** was tentatively assigned as 6-*exo*-phenylsulfonyl-3-ethylenedioxy-8-methyl-8-azabicyclo[3.2.1]octane. Furthermore, this assignment was confirmed by ^{1}H COSY experiment (Fig. 5).

^{13}C NMR spectrum displayed a total of ten carbon signals in the aliphatic region in between δ 30.56 to 107.12 along with aromatic carbon signals at δ 128.31, 129.35, 133.76, 139.36 (Fig. 6). DEPT experiment suggested that methylene carbon signals at δ 30.56, 35.86, 36.10 are assigned to C_2, C_4 and C_7, respectively. Another two methylene carbon signals at δ 63.59 and 64.87 are characterized to two carbons present in ethylene glycol moiety. Methine carbon signals at δ 59.56, 60.21 and 67.25 correspond to C_6, C_1 and C_5 respectively. $-N\underline{C}H_3$ carbon is observed to appear at δ 37.12. A quaternary carbon signal at δ 107.12 is characterized to C_3.

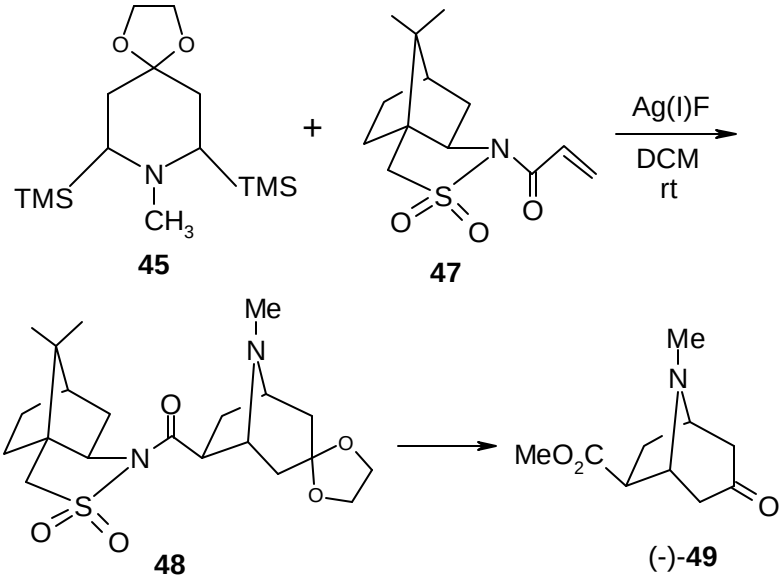
Mass spectrum revealed molecular ion peak at 323 (M^+, 6) and base peak at 87 along with other fragmentation peaks at 293 (1), 264 (2), 237 (6), 182 (33), 155 (30), 96 (73), 67 (13).

The excellent *exo/endo* selectivity inherent with this intermolecular cycloaddition manifested further exploration of this chemical process to the natural product targets. Moreover, this strategy allows introduction of diverse functionalities into the two carbon bridge which deserves much credit due to its pioneering nature. Thus, the synthesis of tropinone (**2**) was completed by taking advantage of the excellent *exo/endo* selectivity of the above cycloaddition. Towards this goal, compound **2** was obtained from **46** in 65% yield by desulfonylation carried out by stirring a buffered solution of **46** in methanol with sodium amalgam followed by *in situ* deprotection of ketal group. Thus, by synthesizing tropinone, it was proved that our [3+2]-cycloaddition strategy made a new entry into the tropane class of alkaloids. The impetus behind this preliminary investigation was to realize a practical asymmetric route for the construction of tropane skeleton using our [3+2]-cycloaddition approach. The successful execution of this preliminary investigation, thus, formed the corner stone for the development of an asymmetric approach. In order to promote this cycloaddition in its asymmetric version, use of Oppolzer's chiral acryloyl dipolarophile[29] as an asymmetric variant would be advantageous since it was proved

successful from our previous experiments. Due to the obvious advantage that would be associated with an asymmetric approach to tropanes using chiral dipolarophile, further study was undertaken to explore the synthetic potential of this chemistry. To demonstrate the utility of such asymmetric [3+2]-cycloaddition strategy in the asymmetric synthesis of tropane alkaloids, we synthesized a chiro tropane compound **49**.

The cycloaddition of AMY **38** with Oppolzer's chiral acryloyl dipolarophile **47** was carried out in a similar manner as described earlier. To our delight, we found that the cycloaddition proceeded in a highly stereoselective manner giving rise to only one cycloadduct **48** in **64** % yield which permitted access to a optically pure tropane compound **49** in a similar manner as described earlier (Scheme 7).

Scheme 7



The cycloadduct **48** was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass analyses. IR spectrum displayed strong absorption band at 1683 cm^{-1} characteristic of amide functionality.

^{1}H NMR spectrum showed following characteristic patterns (Fig. 7):

Two sharp singlets at δ 0.98 and 1.18, integrating for three protons each, are characterized to methyl protons of $C_{8'}$ and $C_{9'}$. The four multiplets appearing in between δ 1.30-2.40, integrating for total twelve protons are assigned to methylene protons (*exo* and *endo*) protons present in two bicyclic systems. -NCH_3 protons are observed as singlet at δ

2.48. A distinct multiplet between δ 2.70-2.85, integrating for one proton, is assigned to H_{7exo}. Another multiplet at δ 3.35, integrating for one proton, could be assigned to bridgehead H_1. Two doublets observed at δ 3.48 and 3.52 (*J = 13.6 Hz*) correspond to $H_{10'}$ protons. H_{6endo} has appeared as a doublet of doublet at δ 3.71 (*J =10.1, 5.1 Hz*). A multiplet at δ 3.82, integrating for four protons, is assigned to four protons present in the ethylene glycol moiety. Bridgehead H_5 and H_2 are found to appear together as multiplet at δ 3.97. Therefore, the structure of compound **5** tentatively assigned as 6-*exo*-bornane-2, 10-sultam-3-mthylenedioxy-8-methyl-8-azabicyclo[3.2.1]octane. Furthermore, this assignment was confirmed by ^{1}H COSY experiment.

^{13}C NMR spectrum displayed a total of twenty carbon signals in between δ 20.08 to 105.85 in the aliphatic region along with a characteristic carbonyl carbon signal at δ 170.75 (Fig. 8). DEPT experiment suggested that the methyl carbon signals at δ 20.08, 21.08 and 39.08 are assigned to $C_{8'}$, $C_{9'}$ and $-N\underline{C}H_3$, respectively. Methylene carbon signals at δ 26.68, 27.26, 33.31, 36.98, 38.77, 40.84, 53.56 are assigned to C_2, C_4, C_7, $C_{5'}$, $C_{6'}$, $C_{3'}$ and $C_{10'}$ respectively. Another two methylene carbons at δ 63.45 and 64.42 are assigned to two carbons of ethylene glycol moiety. Methine carbon signals at δ 45.22, 48.23, 59.67, 63.16 and 66.49 are characteristic of $C_{4'}$, C_6, C_1, C_5 and $C_{2'}$, respectively. Three quaternary carbon signals at δ 47.57, 47.94 and 105.85 are assigned to C_7, $C_{1'}$ and C_3 carbons respectively.

Mass spectrum revealed molecular ion peak at 424 (M^+, 11) and base peak at 55 along with other fragmentation peaks at 409 (1), 210 (12), 182 (11), 155 (63), 82 (60).

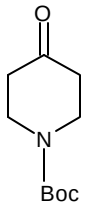
The chiro tropane compound **49** was made from **48** by removal of chiral auxiliary followed by treatment of the resultant acid with $SOCl_2$ at 0°C in dry MeOH in a similar manner as described earlier. Further studies toward the conversion of this chiro intermediate **49** to optically pure ferruginine and Bao Gong Teng A are in progress.

3. CONCLUSION:

We have developed a new and efficient methodology for the construction of tropane skeleton using a novel asymmetric [3+2] cycloaddition reaction. While previous synthetic methodologies have been directed primarily by altering substituents about the three carbon bridge, no asymmetric general strategy that allows introduction of diverse functionalities into the two carbon bridge has been available. Our methodology can offer dual services. Moreover, the simplicity of this process coupled with highly substitution pattern of the cycloadduct augurs interesting synthetic applications of this methodology. Thus, this dipolar cycloaddition strategy can be used to create a stereodefined library of tropane structures for biological assay.

4. Experimental

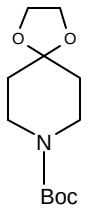
Preparation of N-Boc-piperidine -4-one 41:



To a stirring solution of 4-piperidine monohydrate hydrochloride **40** (25 g, 0.16 mol) and Et_3N (20 mL) in 20 mL water, solution of Boc-N_3 (23.3 g, 0.16 mol) in dioxan (20 mL) was added dropwise over a period of 30 min. After the addition was over, the pH of the reaction mixture was adjusted to 10-12. Usual work-up followed by purification by vacuum distillation (b.p. 70-75°/0.5 mm) afforded 29.8 g of **41** (92 % yield) as a thick liquid.

IR ($CHCl_3$)	:	3018, 1689, 1215 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	δ 1.45 (s, 9H), 2.45 (t, *J* = 5.5 Hz, 4H), 3.75 (t, *J* = 5.8 Hz, 4H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	δ 28.65, 41.42, 43.54, 81.75, 155.59, 208.78
Mass (m/z)	:	199 (M^+, 12), 144 (15), 126 (35), 98 (100), 57 (25).

Preparation of ethylene dioxy- N-Boc-piperidine -4-one 42:

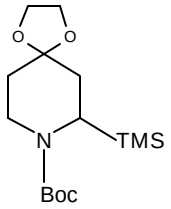


A mixture of **41** (10.0 g, 50.2 mmol), ethylene glycol (3.7 g, 60.3 mmol) and p-PTS (1.2 g, 5.02 mmol) was refluxed in benzene for 8 h under Dean-Stark condition. The solvent was evaporated under reduced pressure and the whole residue was taken in ethylacetate (80 mL). The organic layer was washed with water (2 x 20 mL), brine and

dried over Na_2SO_4. Column chromatography of the crude reaction mixture eluting with EtOAc/Hexane (1.5:2.5) afforded 10.6 g of **42** in 87 % yield.

IR ($CHCl_3$)	:	2974, 1697, 1421 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	ä 1.45 (s, 9H), 1.70 (t, *J* = 5.6 Hz, 4H), 3.50 (t, *J* = 6.2 Hz, 4H), 3.98 (s, 4H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	ä 28.17, 34.70, 41.65, 64.08, 79.07, 106.82, 154.30
Mass (m/z)	:	243 (M^+, 10), 187 (27), 170 (35), 142 (26), 99 (100), 87 (45), 57 (15).

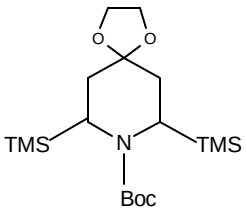
Preparation of ethylene dioxy- N-Boc-2-(Trimethylsilyl)-piperidine -4-one 43:



Compound **43** was made from **42** in a similar manner as described earlier.

IR ($CHCl_3$)	:	2940, 1691, 1423 cm^1
^1H NMR ($CDCl_3$) (200 MHz)	:	ä 0.10 (s, 9H), 1.45 (s, 9H), 1.58-1.62 (m, 2H), 1.70-1.80 (m, 2H), 3.50-3.75 (m, 3H), 4.02 (s, 4H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	ä -0.94, 28.29, 35.41, 35.53, 44.13, 45.23, 64.07, 64.29, 78.96, 107.37, 154.78
Mass (m/z)	:	316 (M^{+1}, 6), 244 (25), 128 (23), 99 (100), 73 (89), 57 (45).

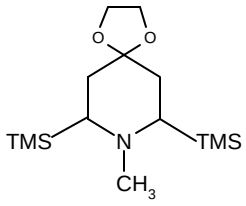
Preparation of ethylene dioxy- N-Boc-2, 6-bis(Trimethylsilyl)-piperidine -4-one 44 :



A 250 mL two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of **43** (3.0 g, 11.6 mmol) in 30 mL of dry ether and was cooled to –78 °C. TMEDA (1.6 .g, 13.9 mmol) followed by s-BuLi (1.5 M in cyclohexane, 9.3 mL) were added to the flask dropwise while stirring. After 15 min of stirring, the temperature was raised to –40 °C. The stirring was continued for 1 h and at this temperature TMSCl (1.5 g, 13.9 mmol) was added. Usual work-up followed by column chromatography gave 2.5 g of **44** (62 % yield) as a colorless liquid.

IR ($CHCl_3$)	:	2973, 1692, 1430 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	ä 0.15 (s, 18H), 1.40 (s, 9H), 1.60-1.80 (m, 4H), 2.50-2.60 (m, 2H), 3.85 (s, 4H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	ä -1.32, -0.68, 28.47, 35.11, 36.07, 45.06, 46.07, 64.26, 79.04, 108.22, 155.86
Mass (m/z)	:	388 (M^{+1}, 15), 330 (100), 316 (25), 300 (35), 244 (27), 171 (28), 147 (11), 128 (15), 73 (85).

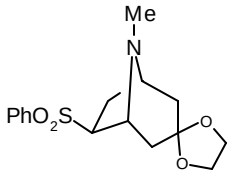
Preparation of ethylene dioxy-N-methyl-2, 6-bis(Trimethylsilyl)-piperidine -4-one 45:



Compound **45** was prepared from compound **44** in a similar manner as described earlier.

IR ($CHCl_3$)	:	2940, 1263 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	0.12 (s, 18H), 1.72 (d, J = 7.2 Hz, 4H), 2.45 (s, 3H), 2.48 (t, J = 5.8 Hz, 2H), 3.92 (s, 4H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	ä -1.46, 28.63, 28.78, 42.14, 52.87, 64.19, 108.48
Mass (m/z).	:	301 (M^+, 2), 286 (6), 228 (53), 142 (100), 73 (55), 59 (49)

[3+2]-Cycloaddition reaction of 45 with phenyl vinyl sulfone:



A typical cycloaddition reaction was performed by adding the solution of **45** (1.5 g, 4.9 mmol) in 30 mL dry DCM to a stirring suspension of phenyl vinyl sulfone (1.0 g, 5.9 mmol) and Ag (I)F (1.5 g, 0.01 mol) in 15 mL dry DCM, as described in chapter II. The cycloadduct **46** was characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analyses.

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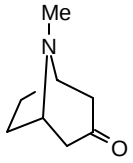
IR ($CHCl_3$)	:	2925, 1275, 1125 cm^{-1}
^{1}H NMR ($CDCl_3$) (500 MHz)	:	ä 1.60 (t, *J* = 5.5 Hz, 2H), 2.15 (d, *J* = 9.1 Hz, 1H), 2.20 (d, *J* = 9.5 Hz, 1H), 2.25-2.35 (m, 1H), 2.38-2.45 (m, 1H), 2.55 (s, 3H), 3.40 (bs, 1H), 3.65 (m, 4H), 3.9 (dd, *J* = 10.7, 5.9 Hz, 1H), 4.2 (t, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 2H)
^{13}C NMR ($CDCl_3$) (75.3 MHz)	:	ä 30.56, 35.86, 36.10, 37.12, 59.56, 60.21, 63.59, 64.87, 67.25, 107.12, 128.31, 129.35, 133.76, 139.36
Mass (m/z)	:	323 (M^{+}, 6), 293 (1) 264 (2), 237 (6), 182 (33), 155 (30), 96 (73), 87 (100), 67 (13).

Synthesis of tropinone 2:



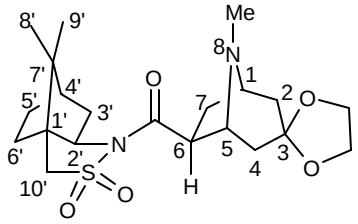
To a stirring solution of **46** (0.5 g, 1.54 mmol) and anhydrous sodium dihydrogen phosphate (0.7 g, 6.19 mmol) in 15 mL dry methanol was added 1.5 g of 6 % Na-Hg and the stirring was continued for 2 h. The reaction mixture was poured into 10 mL of water

and extracted with $CHCl_3$ (3 x 10 mL). Column purification of the crude mixture gave 0.2 g of **2** in 65 % yield.

IR ($CHCl_3$)	:	3018, 2952, 1714 cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	ä 1.50-1.65 (m, 2H), 2.05-2.20 (m, 4H), 2.45 (s, 3H), 2.55-2.70 (m, 2H) 3.35-3.50 (m, 2H)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	ä 27.42, 37.94, 47.24, 60.47, 208.86
Mass (m/z)	:	139 (M^+, 11), 110 (25), 96 (85), 82 (100), 68 (37), 55 (35).

[3+2]-Cycloaddition reaction of 45 with Oppolzer's chiral acryloyl dipolarophile (-)-47:

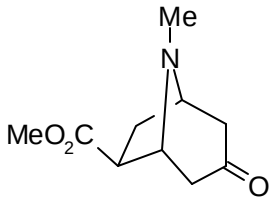
A typical cycloaddition reaction was performed by adding the solution of **45** (1.5 g, 4.9 mmol) in 30 mL dry DCM to a stirring suspension of 47 (1.6 g, 5.9 mmol) and Ag (I)F (1.5 g, 0.01mol) in dry 15 mL DCM, as described in chapter II. The cycloadduct **48** was characterized by IR, ^1H NMR, ^{13}C NMR and Mass analysis.



IR ($CHCl_3$)	:	3015, 2925, 1683, cm^{-1}
^1H NMR ($CDCl_3$) (200 MHz)	:	ä 0.98 (s, 3H), 1.18 (s, 3H), 1.30 (t, *J* = 5.6 Hz, 2H), 1.38-1.52 (m, 2H), 1.80-2.02 (m, 2H), 2.10-2.40 (m, 6H), 2.48 (s, 3H), 2.70-2.85 (m, 1H), 3.25-3.40 (m, 1H), 3.48 (d, *J* = 13.6 Hz, 1H), 3.52 (d, *J* = 13.6 Hz, 1H), 3.71 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.82 (m, 4H), 3.90–4.05 (m, 2H)

^{13}C NMR ($CDCl_3$) (50.32 MHz)	:	ä 20.08, 21.08, 26.68, 27.26, 33.31, 36.98, 38.77, 39.08, 40.84, 45.22, 47.57, 47.94, 48.23, 53.56, 59.67, 63.16, 63.45, 64.42, 66.49, 105.85, 170.75
Mass (m/z)	:	424 (M^+, 11), 409 (1), 210 (12), 182 (11), 155 (63) 82 (60), 55 (100).

Preparation of *exo*-2-carbomethoxy tropinone 49 from 48:



Compound **48** (0.5 g, 1.17 mmol) was hydrolyzed by LiOH-H_2O (47 mg, 1.17 mmol) in 24 mL MeOH/H_2O mixture (3:1) as described in the preceding chapters. The crude acid, thus obtained, was isolated as the corresponding methyl ester **49** in a similar manner as described earlier. $[\alpha_D]^{25}_{obs}$ = -9.63^0 (c = 1.2, $CHCl_3$)

IR ($CHCl_3$)	:	3017, 2958, 1712, 1698 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	:	ä 1.55-1.65 (m, 2H), 2.05-2.20 (m, 2H), 2.50-2.68 (m, 2H), 2.4 (s, 3H), 2.80 (dd *J* = 7.3, 4.4 Hz), 3.20-3.32 (m, 2H), 3.55 (bs, 1H), 3.70 (s, 3H)
Mass (m/z)	:	197 (M^+, 12), 137 (25), 82 (100), 68 (45).

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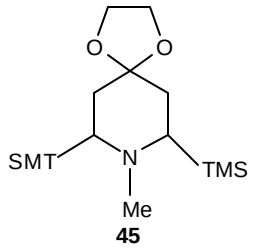
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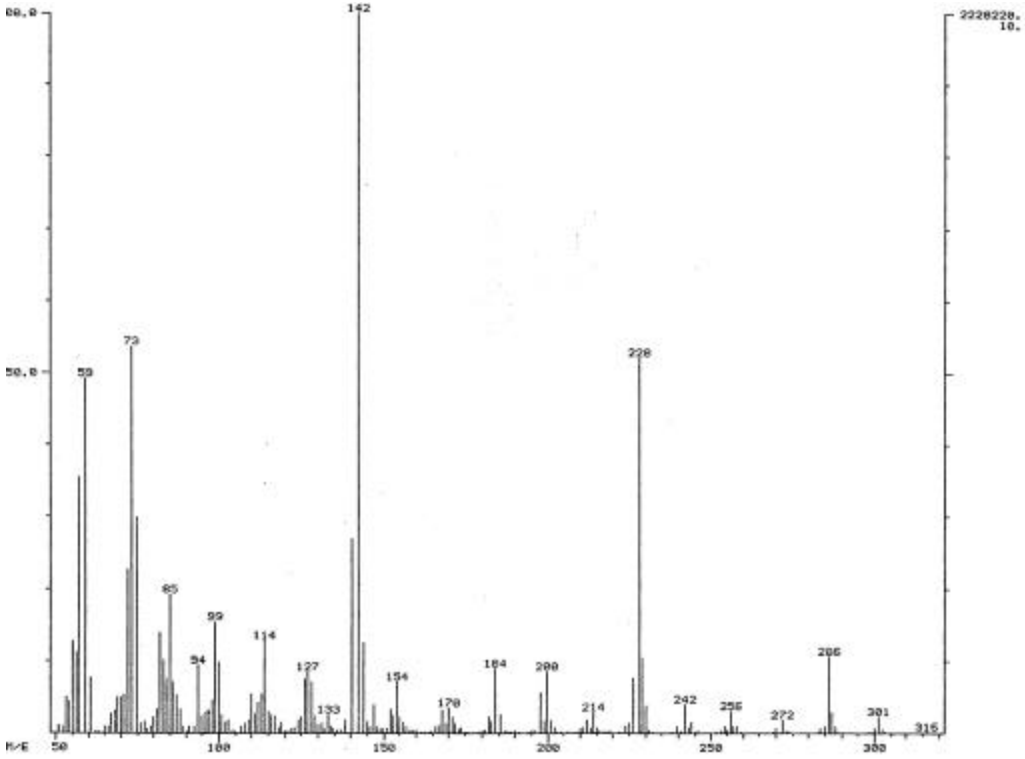
Fig. 2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73
59
228
85
99
114
54
127
154
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200
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242
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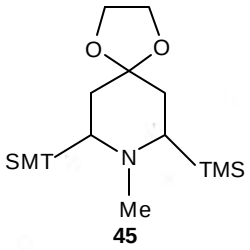
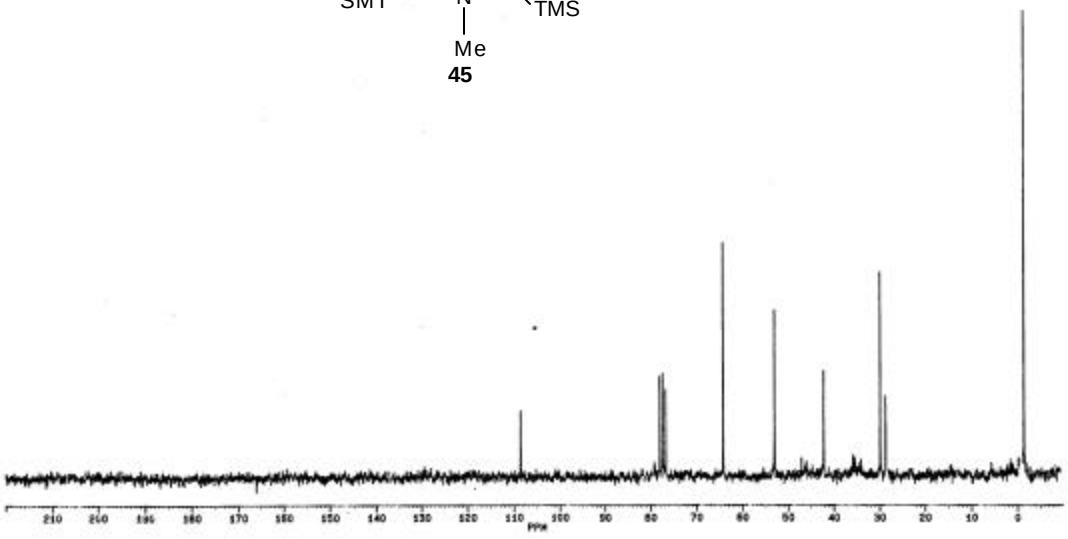
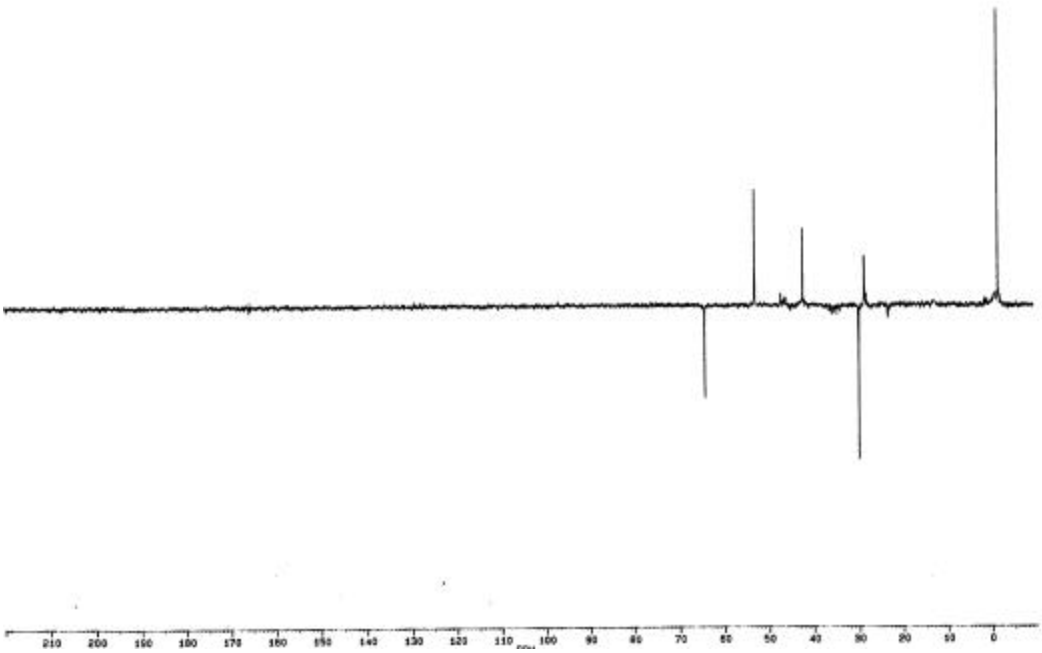
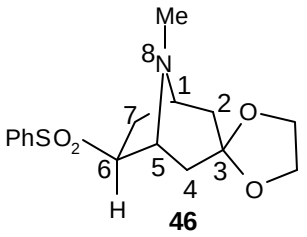


45

Fig. 3

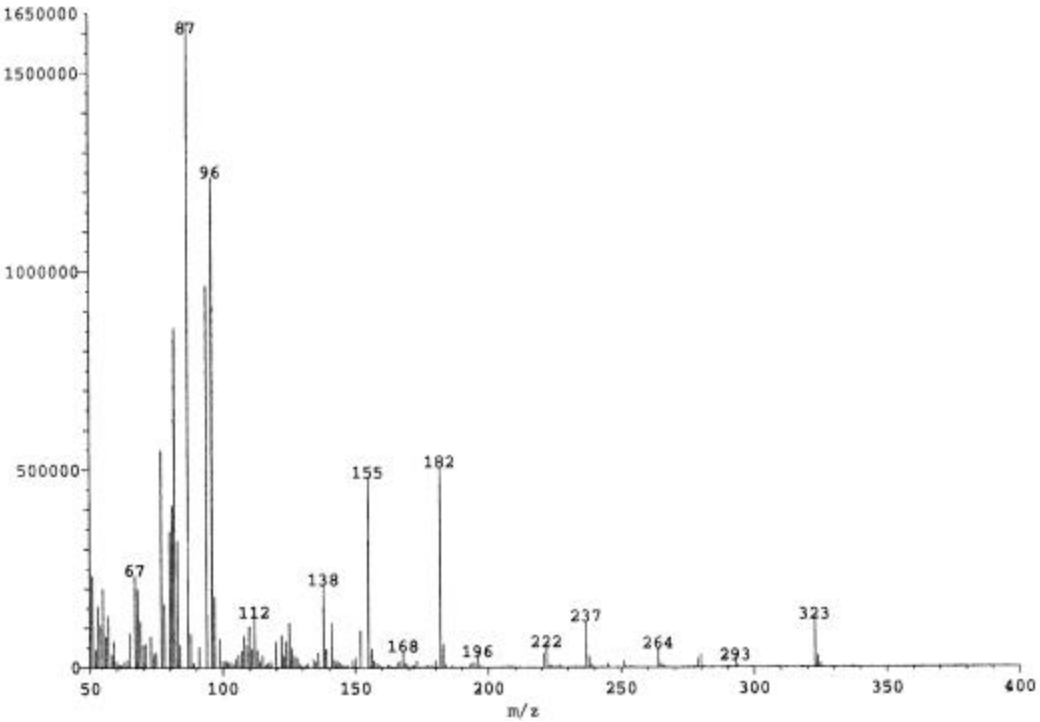


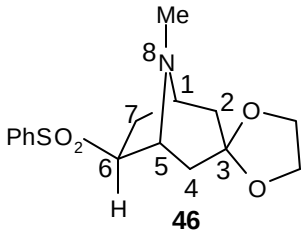



Me
8
N
1
2
O
7
PhSO2
6
5
3
O
4
H

46

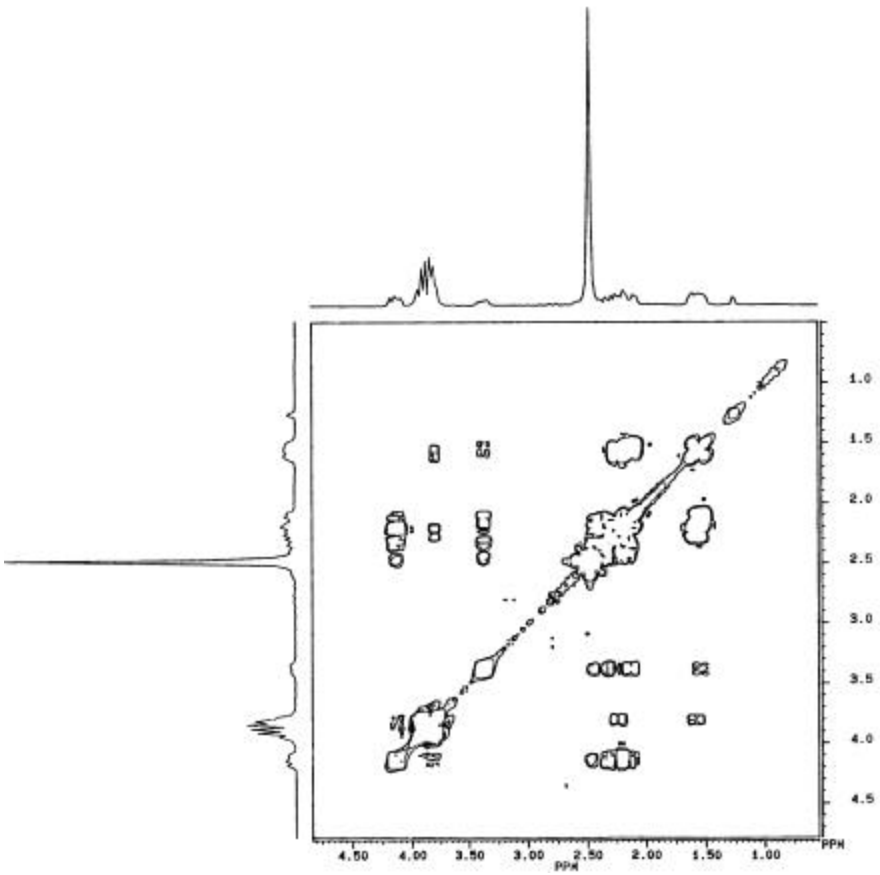
Fig. 4

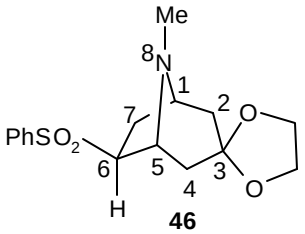

1650000
1500000
1000000
500000
0
87
96
155
182
67
138
112
168
196
222
237
264
293
323
50
100
150
200
250
300
350
400
m/z


Me
8
N
1
2
O
7
PhSO2
6
5
3
O
4
H

46

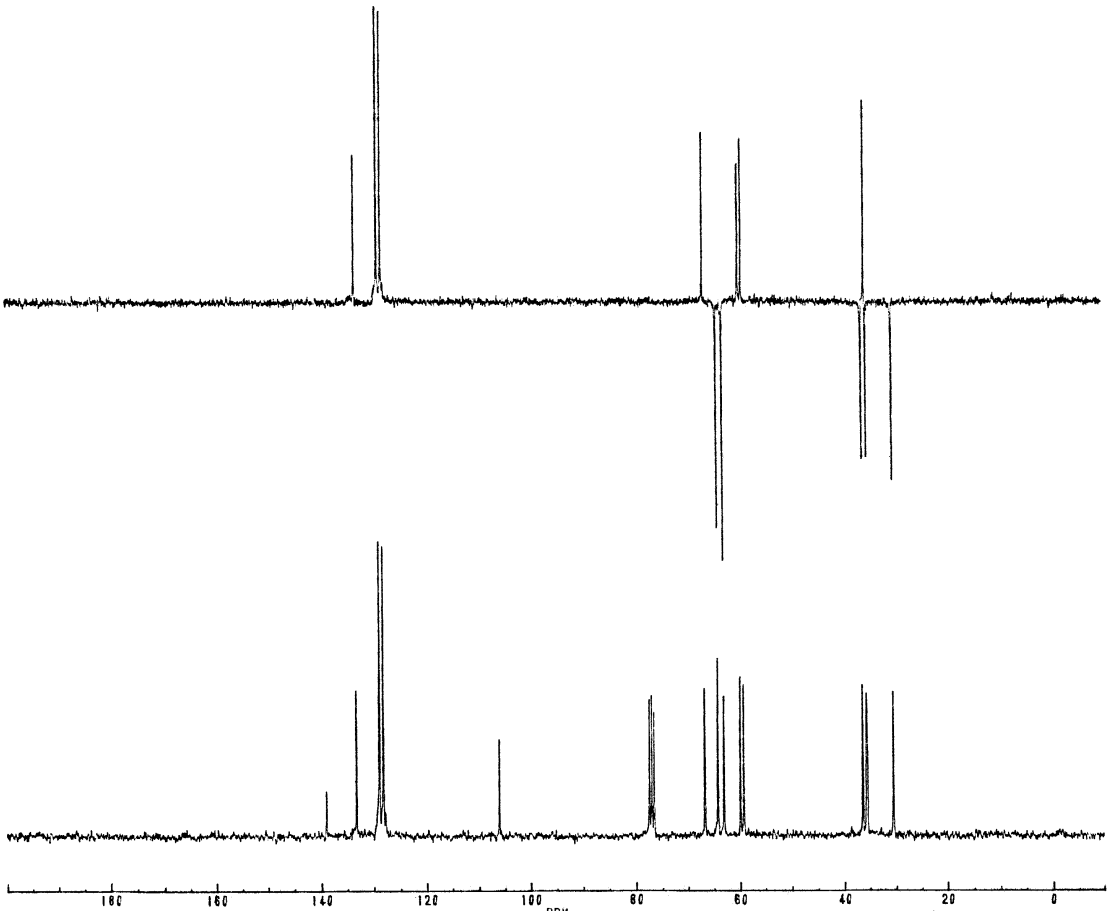
Fig. 5


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
PPM
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
PPM



46

Fig. 6



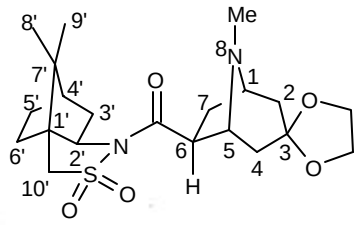
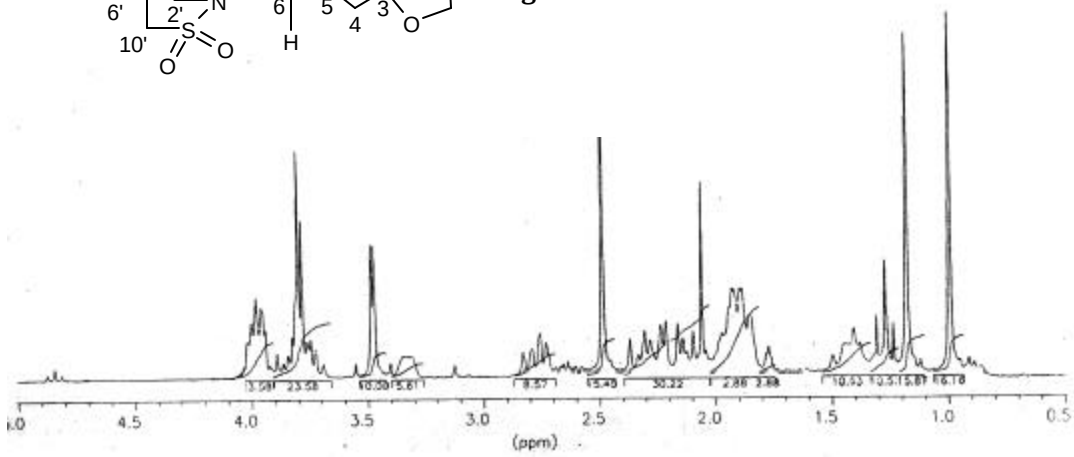
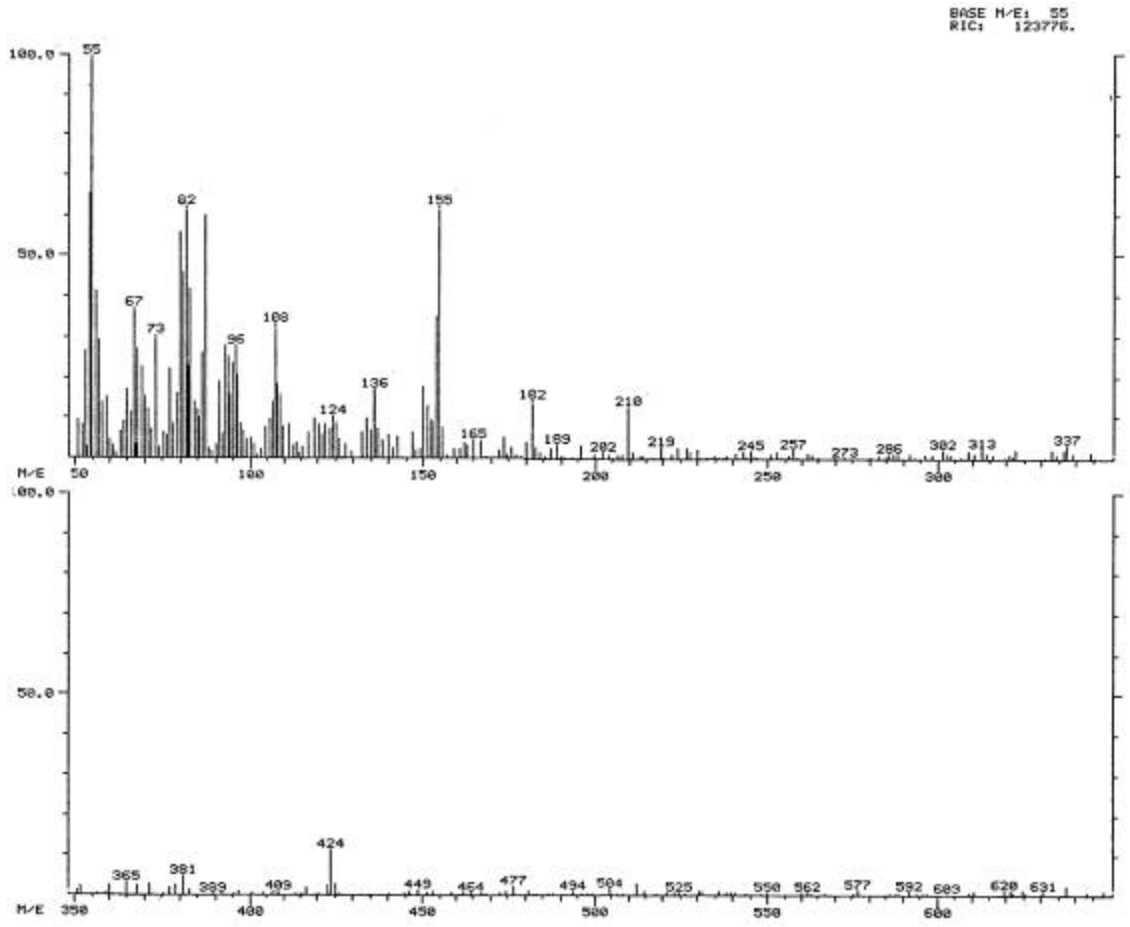

8'
9'
Me
8
N
1
2
O
7'
4'
5'
1'
3'
O
7
6'
2'
N
6
5
4
3
O
10'
S
O
O
H

Fig. 7


4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


BASE M/E: 55
RIC: 123776.
100.0
50.0
55
82
155
67
73
96
108
136
124
182
210
165
189
202
219
245
257
273
286
302
313
337
M/E
50
100
150
200
250
300
100.0
50.0
424
365
381
389
409
449
464
477
494
504
525
550
562
577
592
603
620
631
M/E
350
400
450
500
550
600

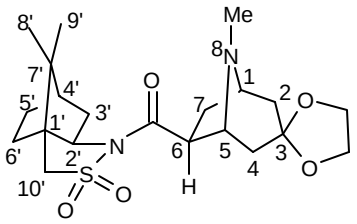
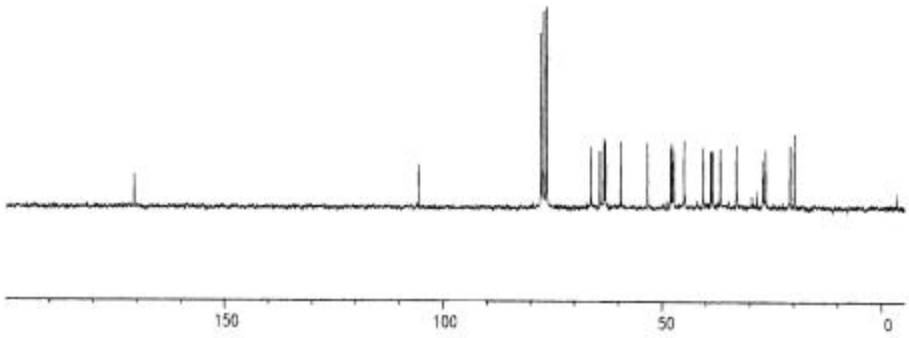
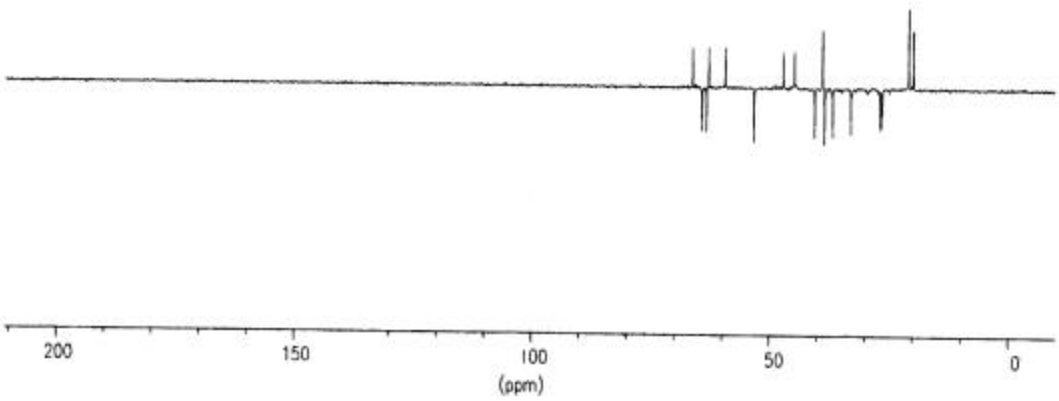

8'
9'
Me
8
N
7'
4'
O
1
2
O
5'
3'
7
1'
6'
2'
N
6
5
4
3
O
10'
S
O
H
O

Fig. 8


150
100
50
0


200
150
100
50
0
(ppm)

List of Publications:

1. [3+2]-Cycloaddition of Nonstabilized Azomethine Ylides, Part 9[#]: A General Approach for the Construction of X-azabicyclo[m.2.1]alkanes in Optically Pure form by Asymmetric 1,3-dipolar Cycloaddition Reactions.
   Ganesh Pandey, **Joydev K. Laha**, and A. K. Mohanakrishnan, *Tetrahedron Lett.* **1999**, 40, 6065.

2. Stereoselective Construction of X-azabicyclo[m.2.1]alkanes by [3+2]-Cycloaddition of Nonstabilized Azomethine Ylides: Synthesis of optically pure Conformationally Constrained Amino Acids and Formal Total Synthesis of Epibatidine.(Communicated to JOC)

3. [3+2]-Cycloaddition of Nonstabilized Azomethine Ylides, Part 12[#]: A General Entry into the Tropane class of Alkaloids by emphasizing total synthesis of ferruginine. (Manuscript under preparation).