Towards Developing Novel Strategy for the Syntheses of *Aspidosperma* Class of Alkaloids

THESIS SUBMITTED TO

SAVITRIBAI PHULE PUNE UNIVERSITY

FOR AWARD OF DEGREE OF

DOCTOR OF PHILOSOPHY (PH.D.)
IN CHEMISTRY

SUBMITTED BY

SHIVA KUMAR BURUGU

UNDER THE GUIDANCE OF

DR. GANESH PANDEY

DIVISION OF ORGANIC CHEMISTRY
CSIR-NATIONAL CHMICAL LABORATORY
PUNE – 411008

JULY 2016

Dedicated

To

My Parents

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Towards Developing Novel Strategy for the Syntheses of *Aspidosperma* Class of Alkaloids"** which is being submitted to the **Savitribai Phule Pune University** for the award of **Doctor of Philosophy in Chemistry** by **Mr. Shiva Kumar Burugu** was carried out by him under my supervision at the CSIR-National Chemical Laboratory, Pune. A material that has been obtained from other sources has been duly acknowledged in the thesis.

Date:

Dr. Ganesh Pandey
(Research Guide)

DECLARATION

I declare that the thesis entitled "**Towards Developing Novel Strategy for the Syntheses of *Aspidosperma* Class of Alkaloids**" submitted by me for the degree of Doctor of Philosophy is the record of work carried out by me during the period from 06/11/2010 to 15/07/2016 under the guidance of Dr. Ganesh Pandey and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning

I further declare that the material obtained from other sources has been duly acknowledged in the thesis.

Date: **Shiva Kumar Burugu**

Division of Organic Chemistry,
CSIR-National Chemical Laboratory
Pune – 411008.

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Shiva Kumar Burugu.

CONTENTS

"Towards Developing Novel Strategy for the Syntheses of *Aspidosperma* Class of Alkaloids"

LIST OF ABBREVIATIONS

aq.	aqueous	NMR	Nuclear magnetic resonance
bp	Boling point	NOE	Nuclear Overhauser Effect
Bn	Benzyl	NOESY	Nuclear Overhauser
COSY	Correlated spectroscopy		Enhancement Spectroscopy
DCM	Dichloromethane	ORTEP	Oak Ridge Thermal-Ellipsoid
DEPT	Distortionless Enhancement		Plot Program
	by Polarization transfer	PDC	Pyridinium dichromate
DMF	N,N-dimethyl formamide	*p*-TSA	*p*-Toluenesulfonic acid
DMSO	Dimethylsulfoxide	py	Pyridine
EtOAc	Ethyl Acetate	rt	Room temperature
g	Gram	THF	Tetrahydrofuran
h	hour	TFA	Trifluoroacetic acid
Hz	Hertz	TLC	Thin layer chromatography
mp	Melting point	TMS	Trimethylsily.
mL	Mililiter		
MeOH	Methanol		

General Remarks

- All the solvents were purified according to the literature procedure
- Petroleum ether used in the experiment was of 60-80 °C
- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60-120/ 100-200 or 230-400 mesh size).
- Reaction progress was monitored by TLC. TLC was performed on Merk precoated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, $KMnO_4$, ninhydrin, phosphomolibdic acid solution.
- IR spectra were recorded on FTIR instrument in KBr.
- NMR spectra were recorded on Burker AV 400 (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR).
- Mass spectra were recorded on PE SCIEX API QSTAR pulser (LC-MS), Agilent LC-MS/HRMS instrument.
- All melting points were recorded using electrothermal melting point apparatus (Buchi, B540).
- **Numbering of compounds, schemes, tables, referencing and figures in abstract and chapters are independent.**

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1) Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, 4th ed., Butterworth Heinemann, **1999**

Research Student	**Shiva Kumar Burugu**
Research Guide	Dr. Ganesh Pandey
Title of Thesis	**"Towards Developing Novel Strategy for the Syntheses of *Aspidosperma* Class of Alkaloids"**
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Place of Work	Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune- 411008 INDIA

Thesis Abstract

The present dissertation is divided into three chapters. Chapter one deals with the overview of *Aspidosperma* alkaloids and literature survey towards the total synthesis of Aspidospermidine alkaloid. Chapter two presents our approach using intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide generated from a designed bicyclic aminal for synthesis of (-)-and (+)-Tricyclic core of *Aspidosperma* class of alkaloids. The efficacy of this method was demonstrated by the total synthesis of (+)-aspidospermidine. The experimental section (Chapter-3) describes the detailed reaction procedures used to carry out the reactions along with the spectral data of all the synthesized compounds.

Chapter-1: Introduction to *Aspidosperma* class of alkaloids.

Structurally complex *Aspidosperma* alkaloids (**1**–**4**) which are present in many natural sources, constitute one structurally unique class having pentacyclic {[6.5.6.6.5] ABCDE ring system} frameworks with contiguous *cis*-stereo centers at C-7, C-21 and C-20 (all carbon quaternary) as a common structural feature (Figure 1).

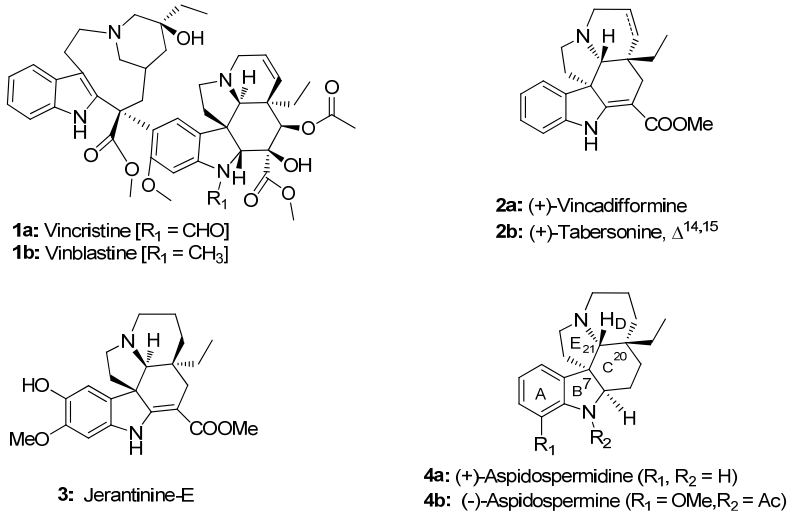


Figure 1. Representative structures of *Aspidosperma* class of alkaloids.

Some of these classes of alkaloids such as vincristine (**1a**) and vinblastine (**1b)**, which has the most complex architecture of this family, have been widely used as a drug for cancer chemotherapy. Other important members are vincadifformine (**2a,** cytotoxic), tabersonine (**2b,** pronounced inhibitory effect against SK-BR-3 human cancer cell lines,

better than cisplatin) and jerantinine-E (**3**, stronger *in vitro* cytotoxicity against human KB cells, IC_{50} <1 μg/mL) known to be pharmacologically important alkaloids. The basic pentacyclic framework of **4**, common to most of these pharmacologically active alkaloids has, thus, been an attractive target for the showcasing of any new synthetic methodologies.

This section represents various important literature reports towards the total synthesis of racemic and enantioselective **4a** as well as structurally similar **4b**. Over the last five decades, number of racemic and few asymmetric syntheses have been reported wherein most of the synthesis towards aspidospermidine (**4a**) follows one of the following five strategies (Figure-2).

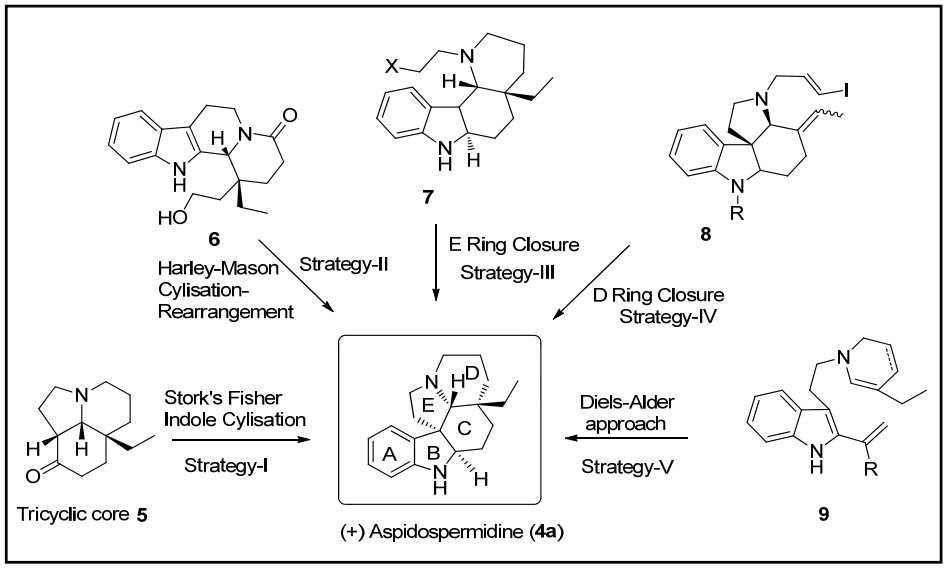


Figure 2. Summary of literature reports

<u>Chapter-2</u>: Studies towards development of novel strategy for synthesis of *Aspidosperma* Class of alkaloids.

This chapter describes the synthesis of (-)- and (+)-tricyclic core of *Aspidosperma* class of alkaloids using intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide. The efficacy of this method was demonstrated by the total synthesis of (+)-Aspidospermidine.

Synthesis of (-)-and (+)-Tricyclic core of *Aspidosperma* class of alkaloids: Total Synthesis of (+)-Aspidospermine:

Interestingly, *Aspidosperma* class of alkaloids are naturally available in both the enantiomeric forms (*i.e.*, as C_7, C_{21} and C_{22} centers are converse), but there are only few articulated methods that can access both the enantiomers of this alkaloids. Since **49** represents the basic skeleton of most of these alkaloids, construction of this highly versatile, in either of enantiomeric forms can efficiently lead to the various alkaloids (Figure 2). This imagination of advancing **5** to several natural products, prompted us to envisage the synthesis of both enantiomers of **5**.

Although, significant development has taken place since Stork's indolization of tricyclic core **5** for constructing *aspidosperma* class of alkaloids**,** this methodology still remains the hallmark in this field.

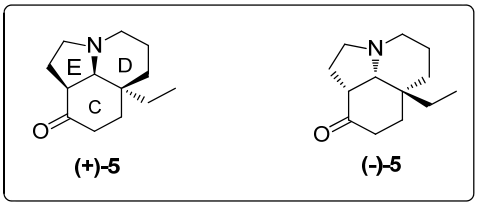


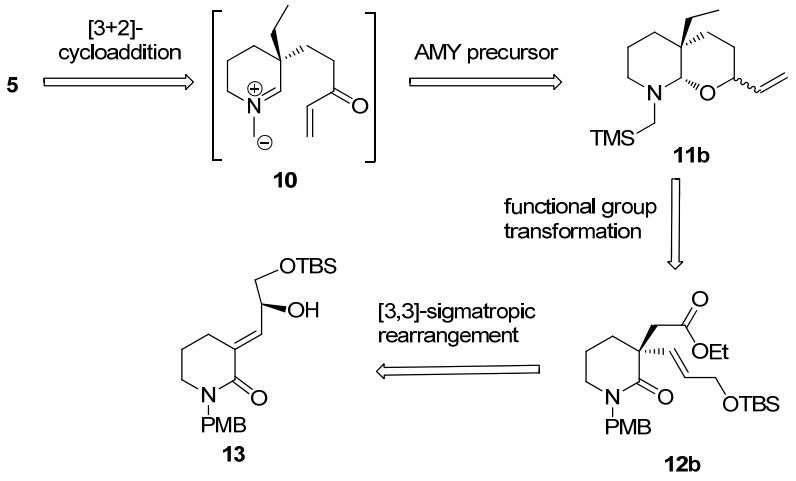
Figure-3

Our continuing research interest in exploring the application of intramolecular 1,3-dipole cycloaddition reaction of non-stabilized azomethine ylide in the total synthesis of fused pyrrolidine containing alkaloids with complex architecture, led us to envisage the synthesis of *aspidosperma* class of alkaloids through intramolecular [3+2] cycloaddition of nonstabilized azomethine ylide (AMY) as shown in the retrosynthetic analysis.

Therefore, from synthetic point of view, how to expeditiously establish such a privileged core **5** with the crucial C-20 all carbon quaternary stereocenter would be an important issue in developing asymmetric synthesis of **4a** and structurally related bisindole alkaloids. Furthermore, if the strategy provides both enantiomers (most of these alkaloids are produced naturally in both enantiomers) it would be an added advantage.

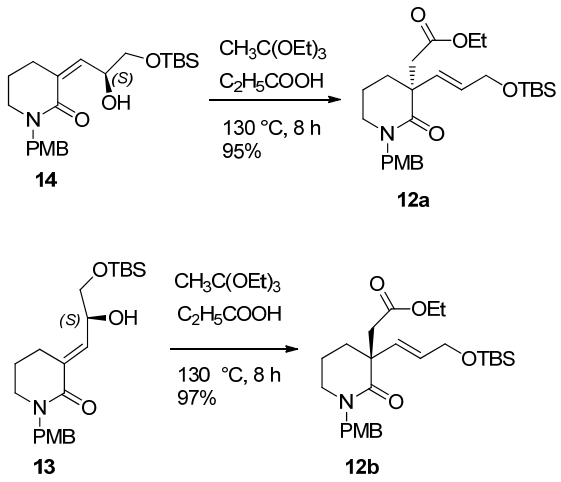
The lack of efficient strategy for the synthesis of tricyclic core, kindled our interest to develop a novel synthetic route for the synthesis of both enantiomers of tricyclic core and *Aspidospema* class of alkaloids. Thus, we developed the synthesis of tricyclic core from a totally different pathway as shown in Scheme-1 retrosynthetically, by employing intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide.

Scheme 1. Retrosynthetic Analysis of (-)-Tricyclic core



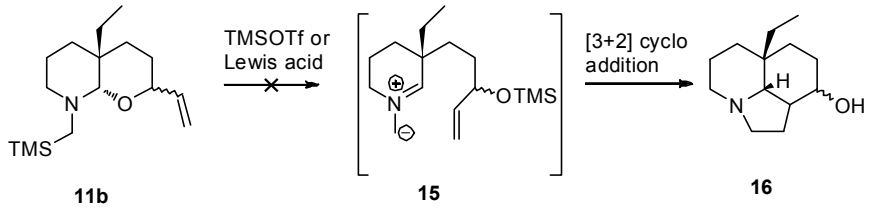
This chapter also includes our strategy of constructing 3,3-dialkylpiperidinones **12a** and **12b** in enantiomerically pure (>99% *ee*) form by [3,3]-sigmatropic rearrangement of **14** and **13**, respectively (as shown in Scheme-2).

Scheme-2: Synthesis of 3,3-Dialkylpiperidinone



As per our planning, **11b** on reaction with different Lewis acids did not result any product and only starting material was isolated as such (Scheme-3).

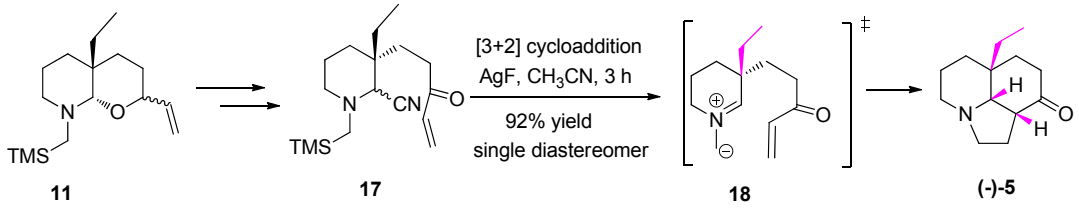
Scheme-3



11b **15** **16**

With this unanticipated hurdles in obtaining **16** through Lewis acid mediated intramolecular [3+2]-cycloaddition, an alternative strategy for azomethine ylide generation from **17** was evaluated as described in scheme-4. Synthesis of **17** was achieved from **11** by simple transformations. At this stage, **(-)-5** was smoothly achieved from **17** by the reaction of AgF in acetonitrile at room temperature (Scheme-4).

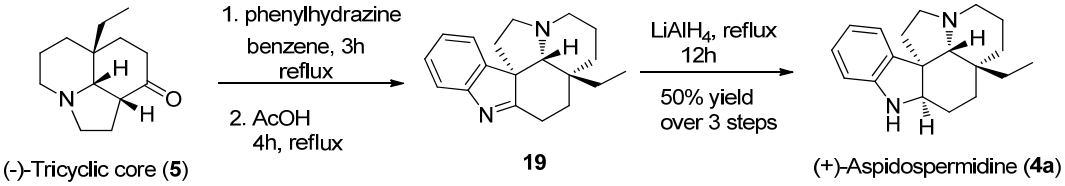
Scheme-4: synthesis of (-)-5



11 **17** **18** **(-)-5**

Total synthesis of (+)-aspidospermidine (**4a**) from **(-)-5** using Fisher Indole synthesis was accomplished as shown in Scheme-5.

Scheme-5: Total synthesis of (+)-aspidospermidine

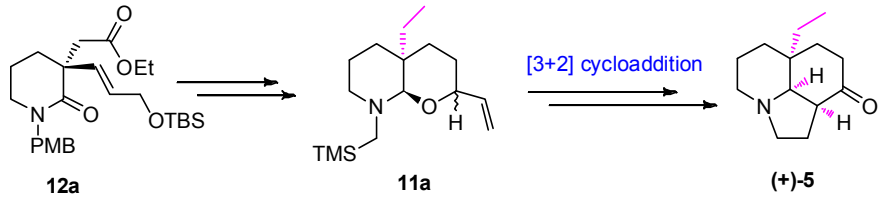


(-)-Tricyclic core (**5**) **19** (+)-Aspidospermidine (**4a**)

Synthesis of (+)-tricyclic core of *Aspidosperma* class of alkaloids.

Synthesis of **(+)-5** was also accomplished starting from **12a** by using same strategy.

Scheme-6: synthesis of (+)-5



Chapter-3: Experimental

This chapter illustrates the detailed experimental procedures and spectral charectarization of the all synthesized compounds.

In summary, we have successfully developed an enantioselective route for the synthesis of both (-)- and (+)-tricyclic core ***5*** *using an efficient and highly stereoselective intramolecular [3+2] cycloaddition of non-stabilized azomethine ylide from a designed precursor. Total synthesis of (+)-aspidospermidine was also accomplished by indolization of* ***5****.*

Chapter-1
Introduction

Alkaloids: General Introduction

Alkaloids are naturally occurring organic compounds that contains mostly one or more nitrogen atoms. These are found primarily in plants, animals and to a lesser degree in microorganisms. Alkaloid containing plants have been used by human since ancient times for therapeutic and recreational purposes. The nitrogen atom in alkaloids originated from amino acids. They are classified based on the nitrogen containing heterocyclic ring system: for example, pyrrolidines, piperidine, pyrrolizidine, indole, quinoline, isoquinolines. Among these, the alkaloids that contain indole nucleus are called indole alkaloids.

The indole alkaloids are mostly derived from the condensation of secologanin **1** and tryptamine **2**, these are classified into several types based on the structural features of their skeletons. Among these, the main three structural types are *Corynanthe* (e.g. akuammicine **3**), *Aspidosperma* (e.g. tabersonine **4**) and *Iboga* (e.g. catharanthine **5**, Figure 1).[1] The secologanin is nine / ten membered carbon fragment and it is of terpenoid origin which on combination with tryptamine followed by skeletal rearrangement of the terpenoid residue leads to three main alkaloid frameworks as shown in Figure 1.

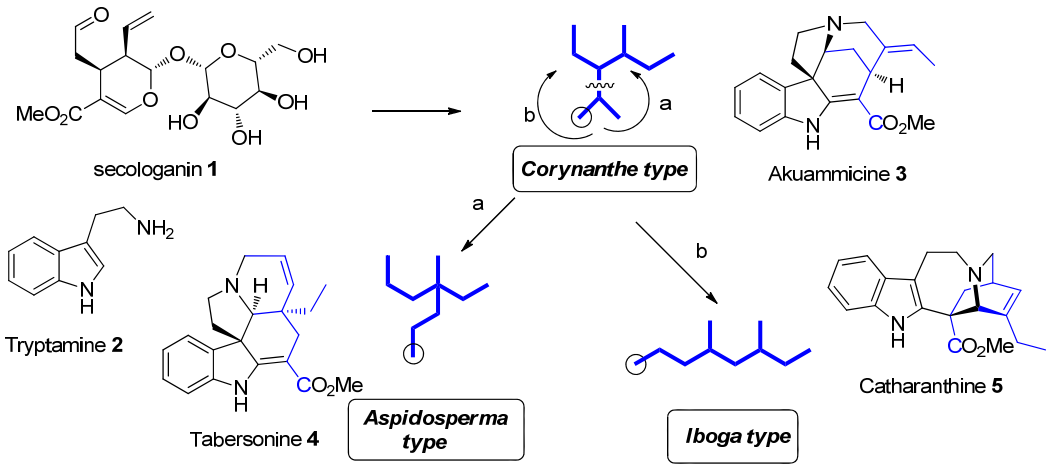
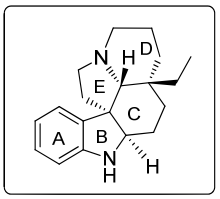


Figure 1: The indole alkaloids

1.1. Introduction to *Aspidosperma* class of alkaloids:



(+)-Aspidospermidine **6**

Structurally complex *Aspidosperma* alkaloids, which are present in many natural sources,[2] constitutes one structurally unique class having pentacyclic {[6.5.6.6.5] ABCDE ring system} frameworks with contiguous *cis*-stereo centers at C-7, C-21 and C-20 (all carbon quaternary) as a common structural feature. The construction of the quaternary carbon center and C/E ring junction are particular challenge toward the synthesis of this family of natural products.

The *Aspidosperma* class is one of the largest group of the indole alkaloids, comprising over 250 compounds, isolated from various biological sources with unique structural complexity shown throughout the family. This class of alkaloids has inspired many research groups to develop new strategies for the construction of this pentacyclic framework, in particular, aspidospermidine. Aspidospermidine (**6)** was isolated from the bark of the *Aspidosperma quebracho-blanco* tree by Biemann and co-workers in 1961.[2b,c] The basic pentacyclic core of **6**, which is common in most of these classes of alkaloids, makes it an attractive target for the showcasing of new synthetic methodologies.

The interesting pharmacological activity and unprecedented structural complexity shown within this class of alkaloids have aroused inspiration for the research groups for over 50 years and they remain an interest of extensive research activity in the present days.

Classification based on structural arrangement:

The *Aspidosperma* class is one of the largest group of indole alkaloids with diverse structural complexities. These alkaloids were classified into seven distinct subgroups based on skeletal architectural features. In each type, the subgroup is diversified by representative parent molecular architectures, namely aspidospermidine (**6)**, vincadifformine (**7)**, quebrachamine (**8)**, aspidofractinine (**9)**, vindolinine (**10)**, meloscine (**11)** and kopsine (**12)** (Figure 2).[3] Interestingly, most of the aspidosperma class of the alkaloids are 6.5.6.6.5 fused complex ring system.

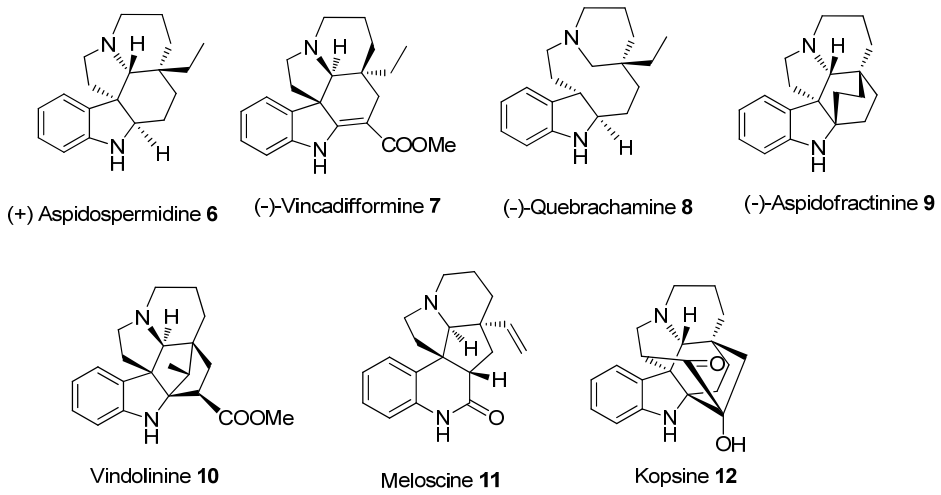


Figure 2: Aspidosperma alkoloid sub-groups

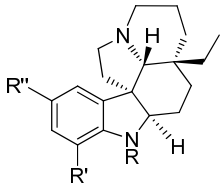
For all the attempts towards synthesis of these alkaloids, the parent molecule **6** was considered as a primary target due to its basic common skeleton. As a result many new synthetic routes were developed for the construction of these alkaloids.

1.2.Biological Activity

1.2.A. Aspidospermidine and structurally related alkaloids:

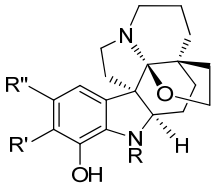
A number of *Aspidosperma* species were used as folk medicines to treat general fever, while some others were used specifically against malaria. Many members of this aspidosperma family such as aspidospermine **16**, aspidospermidine **6**, Tabersonine **4**, Vallesine **15**, Haplosine **19**, Fendlarine **20**, Aspidoalbidine **21**, Aspidolimidine **22** display interesting biological activity including antiplasmoidal activity (Figure 3).[4]

Antiplasmodial activity[4] of several *Aspidosperma* class of alkaloids were also reported in 2002. Several members of this class of alkaloids were tested positive *in vitro* for their activity against *Plasmodium falciparum* (responsible parasite for several forms of malaria).[4]



(+) Aspidospermidine

	Biological Activity
R=H,R'=H,R''=H, Aspidospermidine **6**	Antiplasmodial
R=H,R'=H,R''=OMe, 10-methoxy-Aspidospermidine **13**	Antiplasmodial
R=HCO,R'=H,R''=H, 1N-formyl-Aspidospermidine **14**	Antiplasmodial
R=CHO,R'=H,R''=H, Vallesine **15**	Antiplasmodial
R=CH_3CO,R'=OCH_3,R''=H, Aspidospermine **16**	Antiplasmodial & cytotoxic
R=CH_3CO,R'=OH, R''=H, demethyl-aspidospermine **17**	Antiplasmodial
R=CH_3CO,R'=H, R''=H, demethoxy-aspidospermine **18**	Antiplasmodial



R=C_2H_5CO,R'=H,R''=H, Haplosine **19**	Antiplasmodial
R=C_2H_5CO,R'=OCH_3,R''=H, Fendlarine **20**	Antiplasmodial
R=C_2H_5CO,R'=OCH_3,R''=OCH_3, Aspidoalbidine **21**	Antiplasmodial
R=CH_3CO,R'=OCH_3,R''=H, Aspidolimidine **22**	Antiplasmodial & cytotoxic

Figure-3

These alkaloids were tested against *P. falciparum* and chloroquine - resistant stain for two different time intervals (24 and 72 hours) of incubation of the parasite culture. The results were summarized in Table 1.[4] The pentacyclic alkaloids possessing ethyl chain at quaternary center (**6** and **13-18**) showed IC_{50} = 3.2 – 15.4 µM (after incubation for 72 h), whereas tetrahydrofuran fused hexacyclic alkaloids (**19-22**) showed a reduced activity (IC_{50} = 22.6 – 52.6 µM).

Some of these alkaloids have also shown cytotoxic activity[4] against NIH 3T3 human cancer cell lines, notably aspidospermine **16** and aspidolimidine **22**.

S.No	Alkaloid	Chloroquine-resistant (445 nM) IC_{50} µM ± sd		Chloroquine-sensitive (79 nM) IC_{50} µM ±sd	
		24 h	72 h	24 h	72 h
1	**6**	16.3 ± 2.9	3.8±0.7	11.0±1.7	4.6±0.5
2	**13**	19.5 ± 7.2	3.2±0.9	13.1	5.1
3	**14**	16.1 ± 3.0	5.6±0.7	22.0±7.1	5.9±1.5
4	**15**	11.8 ± 0.9	4.1±0.6	9.3±2.4	6.6±1.4
5	**16**	22.3 ± 11.6	5.6±1.3	nd[a]	nd[a]
6	**17**	15.1 ± 1.9	12.2±5.2	21.5±6.5	20.3±6.2
7	**18**	7.4	6.2	34.0	15.4
8	**19**	15.4 ± 4.2	12.7±4.2	27.2	8.7
9	**20**	17.7 ± 4.9	28.5±13.0	40.8±3.8	22.6±2.5
10	**21**	52.8 ± 7.1	25.6±2.7	113.1	55.3
11	**22**	90.4 ± 43.7	59.2±5.4	44.4	28.0
12	**23**	149.7 ±27.6	49.5±3.7	169.3	57.3

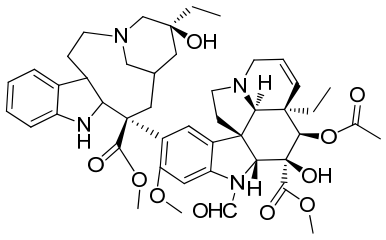
[a]Not derermined; [b]Hemisynthesis

Table-1: Antimalarial activity of some Aspidosperma alkaloids.

Recently, this family of alkaloids have gained interest due to their potent anti-cancer activity exhibited by some of the members.

1.2.B. Vincristine and Vinblastin:

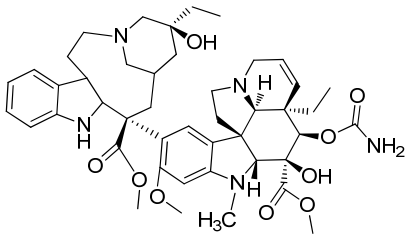
The dimeric *Catharanthus* alkaloids vincristine (**24**) and vinblastin (**25**) have been utilized for cancer chemotherapy[5] in various cancer diseases. These two dimeric indole alkaloids are formed by the dimerization of two *Aspidosperma* class of monoterpenoid indole alkaloids. Although, these two alkaloids are structurally little different, the types of cancer that respond to each of them vary significantly.



24

Vincristine (Oncovin) IC50(nm) 6.0 (L1210)

Breast cancer, Testicular cancer, Hodgkin's disease



25

Vinblastin (velbin) IC50(nm) 5.6 (L1210)

Acute Leukemia, neuroblastoma, Hodgkin's disease

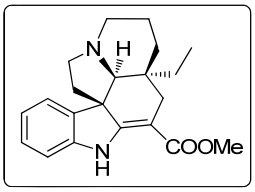
Figure-4

Vinblastine (**25**) is used to treat Hodgkins disease, neuroblastoma and acute leukemia whereas vincristine (**24**) can be used against a much wider range of cancers including breast cancer, cervical cancer, small cell lung cancer and lymphomas. They function by inhibiting cell mitosis by binding to the protein tubulin in the mitotic spindle which prevents polymerization into microtubules and stops cell mitosis.[5]

These two bisindole alkaloids (**24** and **25**) are comprised of two monomeric alkaloids that are analogues of aspidospermidine (**6**) and quebrachamine (**8**) which highlights the importance of both monomeric alkaloids as individual targets.

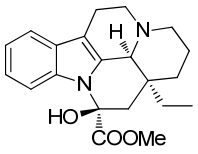
Some of the important pharmacologically important monomeric alkaloids of *Aspidosperma* class are:

1.2.C. Vincadifformine:

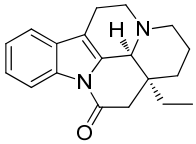


(-)-Vincadifformine (**7**)

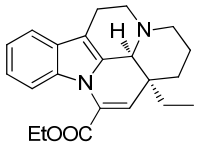
Vincadifformine (**7)** has been isolated from *Vinca difformis* in 1962 by Djerassi and Janot and co-workers.[2d] It exhibits cytotoxic activity against KB and Jurkat cells cancer cell lines.[6] In particular, **7** serves as a valuable precursor for the preparation of pharmaceutically important cerebral vasodilator vincamine **26**, vincamone **27** and carvinton **28**.[7] In addition, it is also suggested to be a possible biogenetic and synthetic precursor for the cytotoxic leucophyllidine **29** and rhazinilam **30** alkaloids respectively.[8]



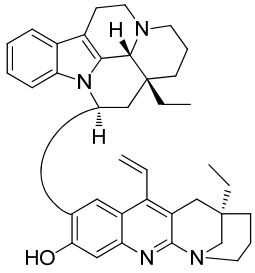
(+)- Vincamine (**26**)



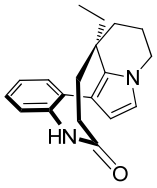
(-)- Eburnamonine (**27**)
(Vincamone)



Ethyl apovincaminate (**28**)
(vinpocetine, Cavinton)



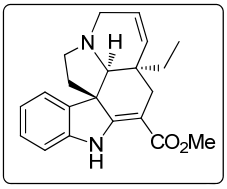
Leucophyllidine (**29**)



(+) Rhazinilam (**30**)

Figure-5

1.2.D. Tabersonine:

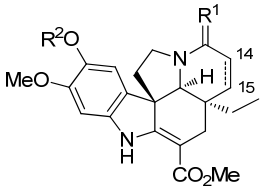


Tabersonine (**4**)

Tabersonine (**4**) shows pronounced inhibitory effect against SK-BR-3, SMMC-7721, HL-60, PANC-1, A-549 (IC_{50} = 5.4 – 25.9 μg/mL) human cancer cell lines.[9]

1.2.E. Jerantinine A-E:

In 2007, Toh-Seok Kam and coworkers had isolated seven *aspidosperma* class of alkaloids (jerantinine A-E, Figure 6) from Malayan *Tabernaemontana corymbosa*. These alkaloids exhibit stronger *in vitro* cytotoxicity against human KB cells (IC_{50} <1 μg/mL).[10] The pharmacological activities of these alkaloids and its derivatives against human KB cells are summarized in Table-2.[10] Among these, jerantinine-E (**35**) is structurally less complex alkaloid with pronounced cytotoxic activity (IC_{50} <1 μg/mL).



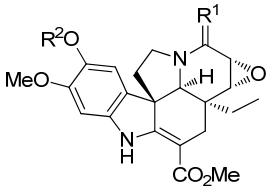
31 $R^1 = H_2$, R^2 = H, $\Delta^{14,15}$

33 R^1 = O, R^2 = H, $\Delta^{14,15}$

35 $R^1 = H_2$, R^2 = H

38 $R^1 = H_2$, R^2 = OAc, $\Delta^{14,15}$

40 $R^1 = H_2$, R^2 = OMe, $\Delta^{14,15}$

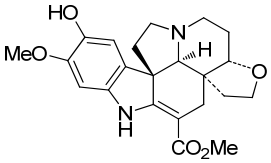


32 $R^1 = H_2$, R^2 = H

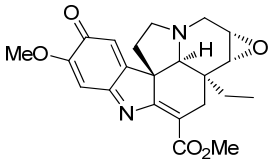
34 R^1 =O, R^2 = H

39 $R^1 = H_2$, R^2 = OAc

41 $R^1 = H_2$, R^2 = OMe



36



37

Figure-6

Table 2: [10] Cytotoxic Effects of Compounds **27-32** and **34-37**

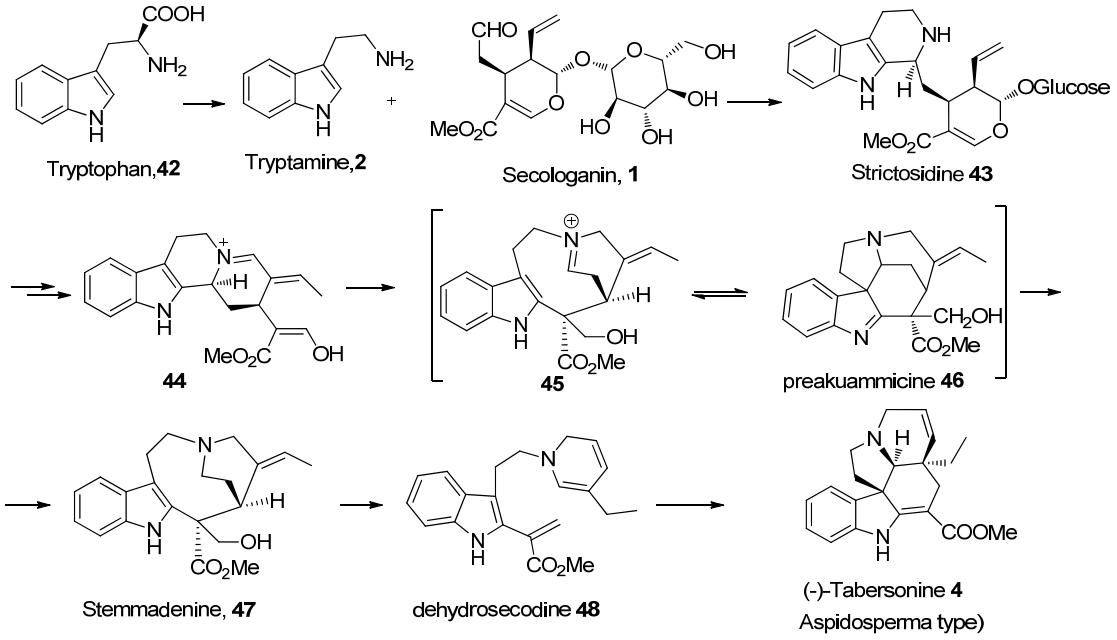
Compound name	IC50, μg/mL, (μM)	
	KB/S [a]	KB/VJ300[a]
Jerantinine A (**31**)	0.76(1.99)	0.66(1.73)
Jerantinine B (**32**)	0.44(1.11)	0.38(0.95)
Jerantinine C (**33**)	0.32(0.81)	0.61(1.54)
Jerantinine D (**34**)	0.28(0.68)	0.39(0.95)
Jerantinine E (**35**)	0.98(2.55)	0.78(2.03)
Jerantinine F (**36**)	5.1(12.8)	4.9(12.3)
Jerantinine A acetate (**38**)	0.44(1.04)	0.35(0.83)
Jerantinine B acetate (**39**)	0.30(0.70)	0.33(0.75)
10-*O*-methyljerantinine A (**40**)	4.77(12.0)	5.40(13.6)
10-*O*-methyljerantinine B (**41**)	2.93(7.36)	4.25(10.7)
Vincristine (**24**)	0.0044(0.0054)	1.0(1.2)

[a]KB/S and KB/VJ300 are vincristine-sensitive and resistant human oral epidermoid carcinoma cell lines, respectively.

1.3. Biosynthesis:

During 1960-1970, studies carried out by a number of research groups have resulted many biosynthetic pathways[11-12] for the several classes of indole alkaloids. Most of the indole alkaloids are derived from the condensation of tryptamine **2** with an aliphatic aldehyde (the iridoid secologanin **1**) having nine or ten carbons. The biosynthesis of the major three classes of alkaloids (*Corynanthe*, *Aspidosperma, iboga class)* begins with the enzymatic conversion of tryptophan **31** to tryptamine **2** in the presence of tryptophan decarboxylase (Scheme 1).[11-12] Tryptamine undergoes Pictet-Spengler condensation with secologanin **1** in the presence of strictosidine synthase to produce strictosidine **43** which is considered a general intermediate for all the three aforementioned indole alkaloids.[12] Furthermore, on deglycosylation by strictosidine deglucosidase it forms a hemiacetal that isomerizes to give a reactive dialdehyde intermediate. This dialdehyde intermediate further undergoes condensation with free amine followed by an allylic rearrangement to afford **44**. The mechanism for transformation of intermediate **44** to preakuammicine **46** is still unknown, despite several proposed pathways. Reduction of **46** gives stemmadenine **47** which on further rearrangement followed by intramolecular cycloaddition presumably forms the *Aspidosperma* skeleton.

Scheme 1: Proposed biosynthetic pathway for synthesis of Aspidosperma-type alkaloids



1.4. Literature reports:

This section represents various important literature reports towards the total synthesis of racemic and optically active **6** and structurally similar **16**. Over last five decades, number of racemic and few asymmetric syntheses have been reported wherein most of the synthesis towards aspidospermidine follows one of the following six strategies (Figure-7).

I. Storks Fisher indole cyclization approach.

II. Harley-Mason's Cyclization-Rearrangement approach.

III. E-ring closure approach.

IV. D-ring closure approach.

V. Diels-Alder approach

VI. Miscellaneous approaches

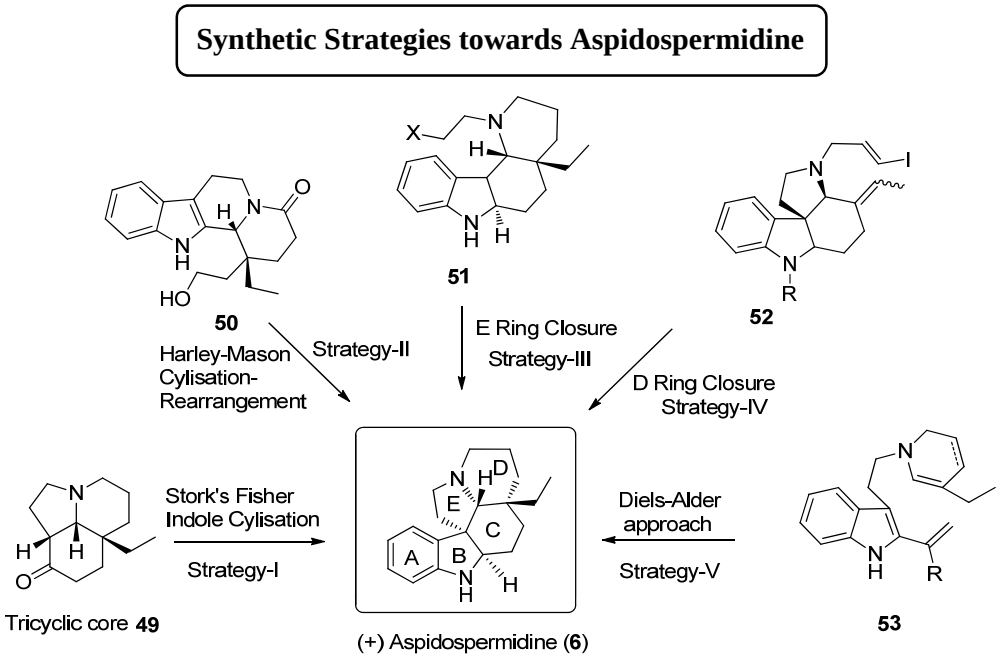


Figure-7

I. Stork's Fischer-Indole cyclization approach

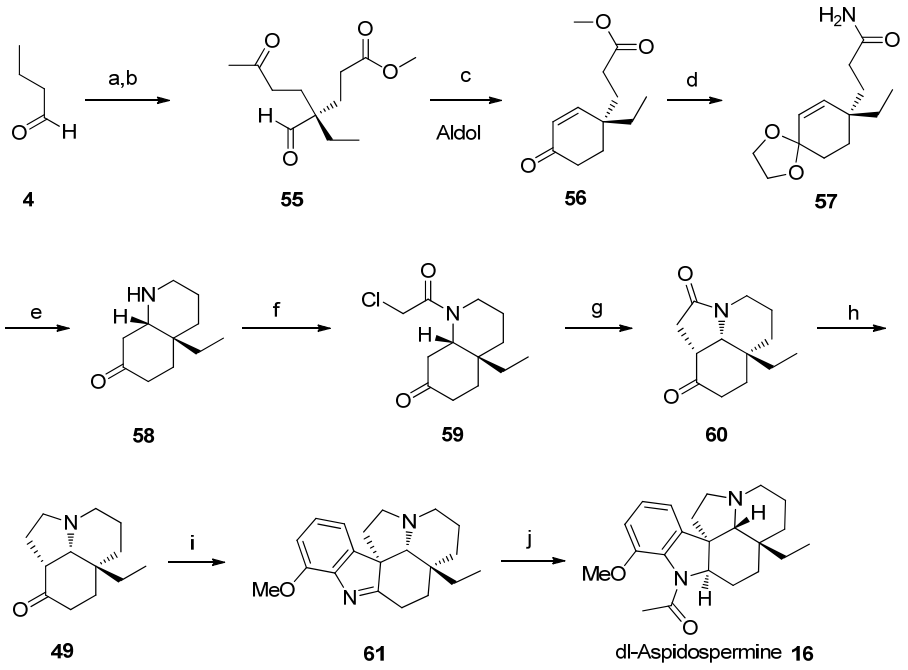
I.a. Stork's approach: (*J. Am. Chem. Soc.* **1963***, 85,* 2872)[13] (Racemic synthesis)

Stork *et al.* reported first total synthesis of this pentacyclic alkaloid through Fisher indolisation of a tricyclic core intermediate **49**. The late stage installation of indole ring on **49** in a stereoselective manner was utilized to fix the required spiroindoline quaternary center. Stork's approach paved the way to many research groups to plan their synthesis through **49**. As a result, many new methods were developed and successfully implemented to obtain **49**.

The synthetic route for the synthesis of **49** was described as shown in Scheme-2. Sequential dialkylation of butyraldehyde enamine with ethylacrylate and methylvinyl ketone respectively, followed by aldol reaction in hot acetic acid produced 4,4-dialkyl cyclohexenone **56**. Ketalization of cyclohexenone followed by functional group transformation of ester moiety to amide gave **57** which on reduction with $LiAlH_4$ followed by deprotection of ketal group underwent intramolecuclar Michael addition to produce

bicyclic ketone **58**. *N*-Acetylation of **58** with chloroacetyl chloride followed by cyclisation produced tricyclic keto-amide core **59**. Further, ketalization of **60** followed by reduction of amide with $LiAlH_4$ and deprotection of ketone gave desired tricyclic core **49** (Scheme-2).

Scheme 2: Stork's approach



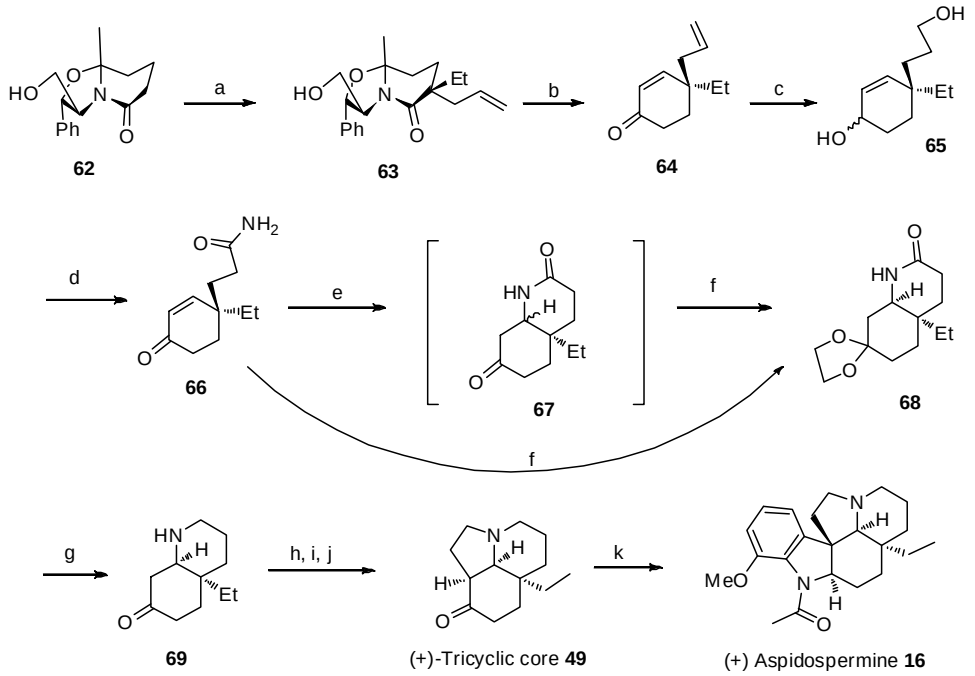
Reagents and conditions: *(a) (i) pyrrolidine, methyl acrylate, aq. AcOH (b) pyrrolidine, methyl vinyl ketone, aq.AcOH (c) aq.AcOH, reflux (d) (i) H^+,ethelene glycol (ii) aq. NH_3 (e) (i) $LiAlH_4$ (ii) aq. acid. (ii) base (f) chloro acetyl chloride, TEA, Benzene (g) K^tOBu, benzene (h) (i) H^+,ethelene glycol (ii) $LiAlH_4$ (iii) Acid (i)o-methoxy phenyl hydrazine, acetic acid, reflux (j) (i) $LiAlH_4$ (ii) $(Ac)_2O$.*

I.b. Meyer's approach: (*J. Org. Chem.* **1989**, *54*, 4673)[14]

(Enantioselective synthesis)

Meyer *et al.* reported first enantioselective synthesis of **49** from enantiomerically enriched 4,4-dialkyl cyclohexanone intermediate **64**. The key quaternary center was generated by the dialkylation of the chiral lactam **62**. Further, functional group transformations followed by sequential annulation using aza Michael and *N*-alkylation/cyclization sequence gave (+)-**49** (Scheme-3).

Scheme 3: Meyer's approach

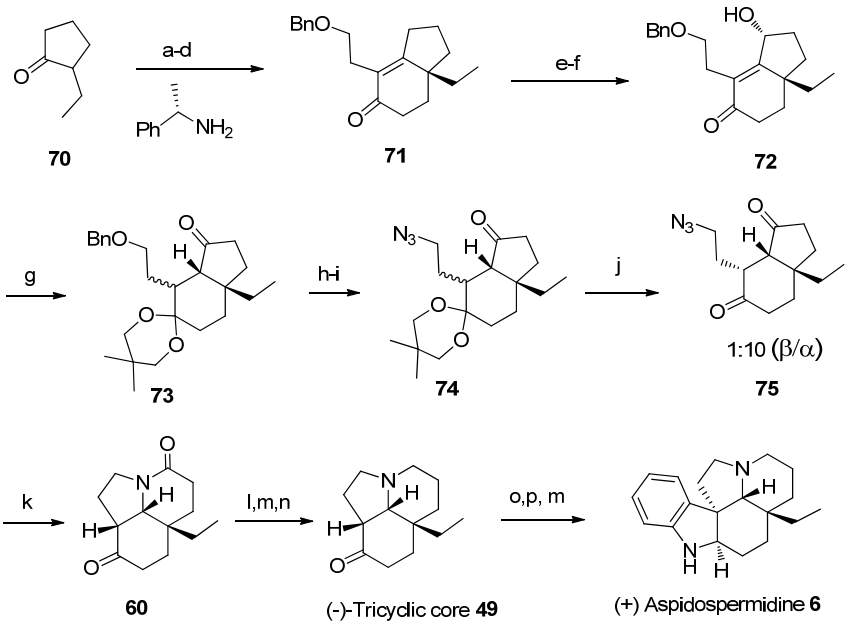


Reagents and conditions: *(a) (i) LDA, EtI (ii) LDA, Ally bromide (b) (i) Red-Al (ii) H^+ (c) 9-BBN (d) (i) Jones Oxidation (ii) Oxalyl chloride (iii) NH_3 (e) p-*TSA*, Benzene (f) PTSA, Benzene, Ethylene glycol, Reflux (g) (i) $LiAlH_4$ Reduction (ii) 1 N HCl, reflux (h) Chloroacetyl chloride, TEA, Benzene (i) K^tOBu, Benzene (j)(i) keto protection.(ii) BH_3.THF, reflux (iii) 1N HCl (k)(i) o-methoxy phenyl hydrazine, acetic acid, reflux (ii) LAH reduction. (iii) Ac_2O, Pyridine.*

I.c. Aube's approach: (*Org. Lett.* **2000,** *2***,** 1625**)**[15] (Enantioselective synthesis)

Aube used an intramolecular Schmidt reaction from **75** for the construction of fused pyrrolidine ring of **60** from which **49** was prepared. The synthesis of **75** from **71** with a quaternary center is shown in Scheme-4.

Scheme 4: Aube's approach

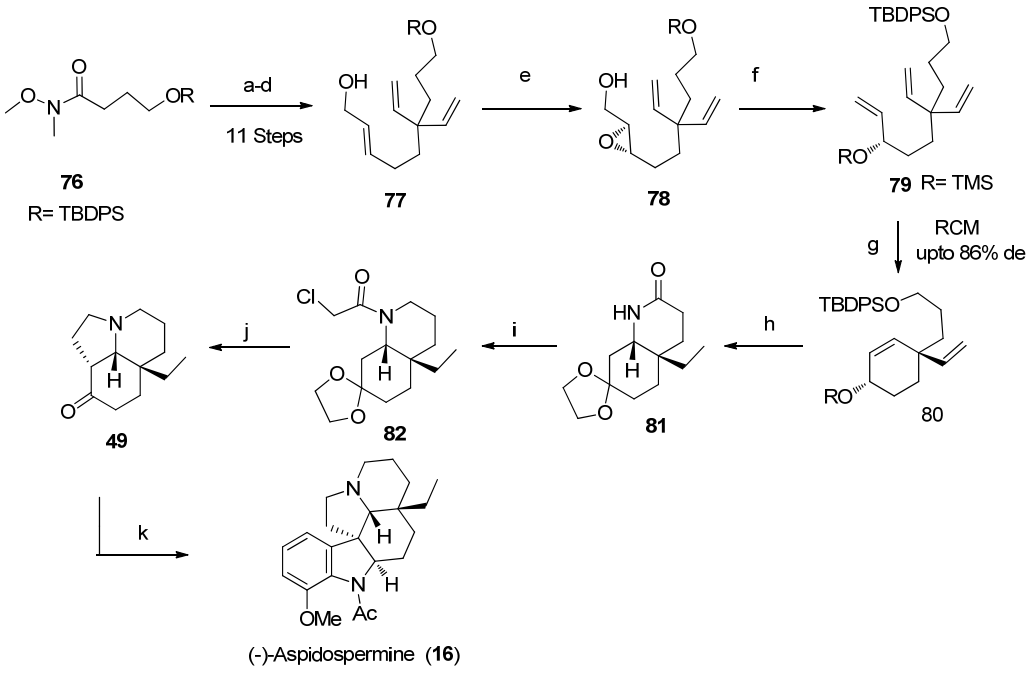


Reagents and conditions: *(a) (s)-α- methylbenzylamine; (b) 6-(benzyloxy)hex-1en-3-one, $ZnCl_2$, Et_2O, reflux; (c) 10% Aq. AcOH (d) NaOMe, MeOH,reflux; (e) isopropenyl acetate; (f) Oxone, Acetone; (g) bis (trimethylsilyl)neopentyl glycol, TMSOTf, DCM, ,0^0C – rt; (h) H_2, Pd/C (i) HN_3, PPh_3, DEAD, PhH, 0^0C – rt; (j) $LiBF_4$;(k) $TiCl_4$; (l) bis (trimethylsilyl)neopentyl glycol, TMSOTf, DCM, 0^0C-rt; (m) LAH, THF, reflux; (n) $LiBF_4$, aq.CH_3CN, reflux; (o) $PhNHNH_2$; (p) AcOH, reflux.*

I.d. Shishido's approach: (*Org. Lett.* **2003**, *5*, 749)[16] (Enantioselective synthesis)

Shishido *et al.* have utilized diastereoselective Ring Closing Metathesis (RCM) from optically pure **79** for the construction of cyclohexenol **80** with a quaternary stereocenter (*de*=84%) which was converted into corresponding **81** using simple protocol. Further transformation of **81** to **49** is shown in Scheme-5.

Scheme 5: Shishido's approach

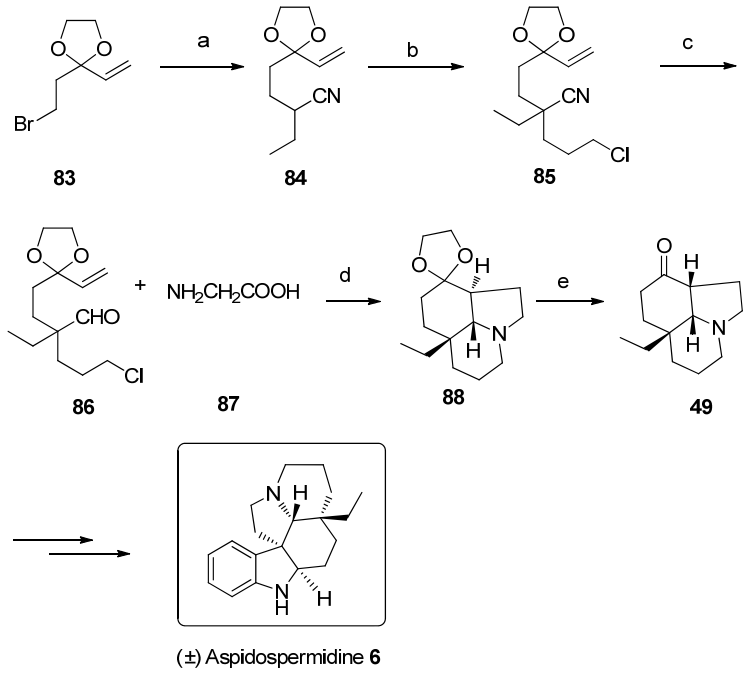


Reagents and conditions: *(a) (i) $TBSO(CH_2)_3Br$, t-BuLi; (ii)$(EtO)_2P(O)CH_2CO_2Et$, NaH, DME; (iii) DIBAL-H, 0 °C; (iv) $EtOCH=CH_2$, $Hg(OAc)_2$, reflux; (b) $^iBu_3Al$, DCM, rt; (c) (i) o-Nitrophenyl selenocyanate, Bu_3P, THF, rt; (ii) H_2O_2, THF, rt; (iii) 1% HCl, MeOH, reflux; (d)(i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt; (ii) $Ph_3P=CHCO_2Et$, benzene, reflux; (iii) DIBAL-H, 0 °C; (e) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, DCM; (f) (i) I_2, PPh_3, Imidazole, benzene, rt; (ii) Zn, AcOH, 50 °C; (g) Grubbs I st Generation Catalyst; (h) (i) TBAF; (ii) Jones oxidation; (iii) NH_3, THF; (iv) keto protection; (v)H_2, PtO_2, EtOH; (i) (i) $LiAlH_4$; (ii) $ClCOCH_2Cl$, TEA, DCM; (j) (i) 1N HCl, THF, reflux; (ii) KO^tBu, Benzene , reflux; (iii) keto protection; (iv) BH_3.THF, reflux; (v) 1N HCl; (k) (i) Fisher indole synthesis; (ii) ACOH, 95 °C; (iii) $LiAlH_4$; (iv) Ac_2O, Pyridine.*

I.e. Coldham's approach: (*J. Org. Chem.* **2009**, *74*, 2290)[17] (Racemic synthesis)

Reaction of **86** with **87** produces corresponding imine which on *in situ N*-alkylation followed by decarboxylation generated an azomethine ylide. An intramolecular [3+2] cycloaddition of azomethane ylide (AMY) with tethered unactivated olefin produced **88** which on hydrolysis gave **49** (Scheme-6).

Scheme 6: Coldham's approach

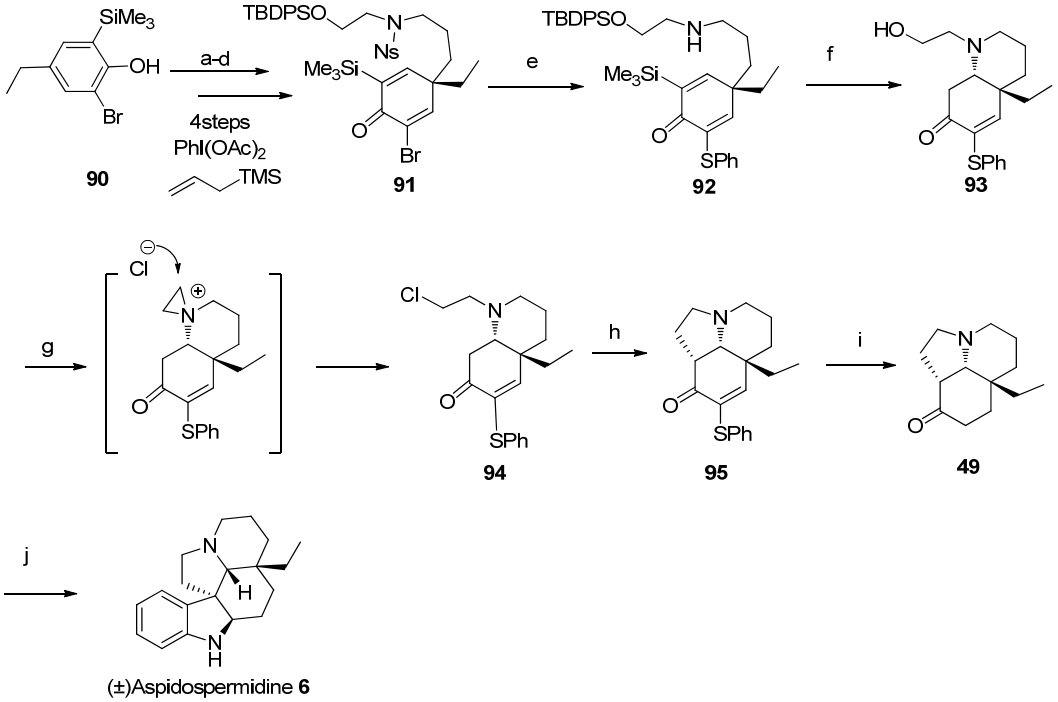


Reagents and conditions: *(a) LDA, $EtCH_2CN$, THF, -78 ˚C, 88 %; (b) LDA, 1-bromo-3-chloro-propane, THF, -78 ˚C; (c) DIBAL-H, DCM, -78 °C then oxalic acid (0.5M), 82%; (d) CSA (10 mol %), Toluene, reflux, 18 h, 79%; (e) 5% aq. HCl, THF, 80 ˚C, 1h, 89%.*

I.f. Canesi's approach: (*Chem. Commun.* **2009**, 2941)[18] (Racemic synthesis)

Hosomi-Sakurai allylation reaction of phenolic compound **90** was exploited to produce **92**, having all carbon quaternary stereocentre, which was further used to construct another two rings to accomplish (±)-**49** (Scheme-7).

Scheme 7: Canesi's approach

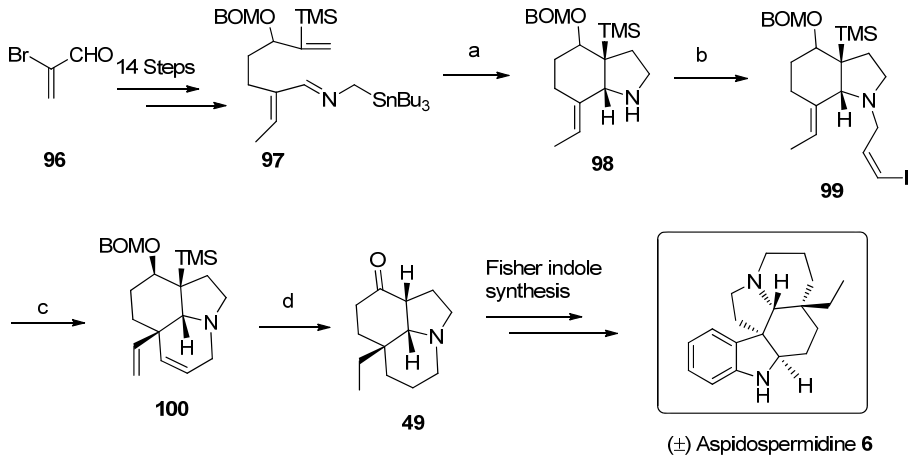


Reagents and conditions: *(a) $PhI(OAc)_2$, HFIP, Allylsilane; (b) 9-BBN, H_2O_2, K_2CO_3; (c) MsCl, Lutidine; (d) NaH, DMF, 65 °C; (e) PhSH, K_2CO_3; (f) TBAF, THF; (g) MsCl, TEA; (h) t-BuOK; (i) Raney-Ni, EtOH; (j) (i) Fisher-indole synthesis; (ii) $LiAlH_4$ reduction.*

I.g. Pearson approach: (*Org. Lett.* **2006,** *8***,** 1661)[19] (Racemic synthesis)

The reactive 2-azapentadienenyl aninons, generated by the reaction of *n*-BuLi reaction of **97,** followed by intramolecular cycloaddition reaction was used to install C and E rings **98** (Scheme-8). Furthermore, a simple allylation followed by an intramolecular Heck cyclisation of **99** was employed for the construction of D-ring **100** which was transformed to (±)-**49**.

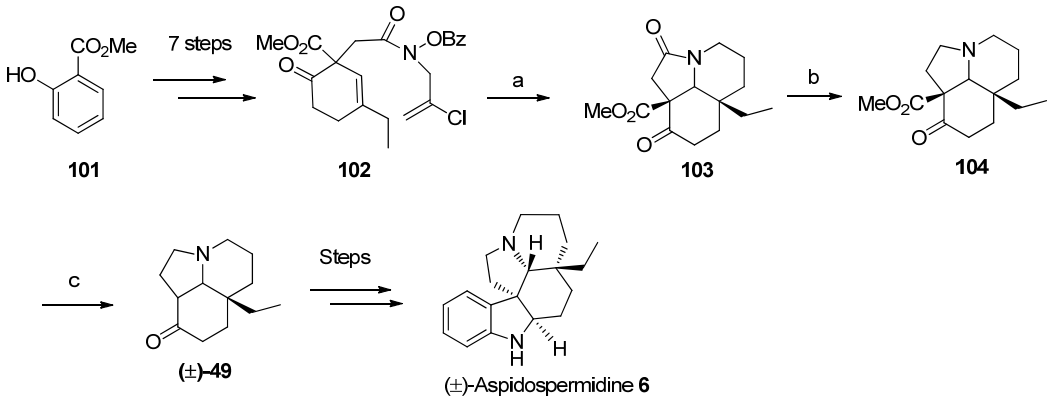
Scheme 8: Pearson approach



Reagents and conditions: *(a) n-BuLi (2 eq), THF, -78 ˚C; (b) K_2CO_3, (Z)-3-bromo-1-iodoprop-1-ene, THF, 59% (over two steps); (c) $Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF, 43 %; (d) H_2, Pd/C, MeOH, TFA, 98%; (ii) Li, THF, NH_3, NH_4Cl then HCl, H_2O/MeOH/THF; (iii) Dessmatin periodinane oxidation, then HCl, Et_2O/H_2O (54% over 2 steps).*

I.h. Zard radical cyclisation approach: (*Org. Lett.* **2006**, *8*, 831)[20] (Racemic synthesis) In this approach **49** was synthesized by using a cascade reaction of amidyl radical (Scheme 8) **102** to produce the tricyclic system **103** which on simple functional group transformations gave **49** as shown in Scheme-9.

Scheme 9: Zard's radical cyclisation approach



Reagents and conditions: *(a) Bu_3SnH, ACCN, α,α,α-trifluorotoluene, 53%; (b) 9-BBN, THF, reflux, 93%; (c) LiCl, DMF, 140 ˚C, 88%.*

II. Harley-Mason's rearrangement/cyclisation Strategy

II.a. Harley-Mason's approach: (*Chem. Commun.* ***1967***, 915)[21] (Racemic synthesis)

Dimethyl acetal **105** on treatment with tryptamine in acetic acid produced tetracyclic skeleton **50** which on reflux with aq. H_2SO_4 underwent C-2 alkylation of indole followed by a skeletal rearrangement to give indolinine **108** (*Aspidosperma* skeleton). Reduction of **108** with $LiAlH_4$ produced **6** (Scheme-10).

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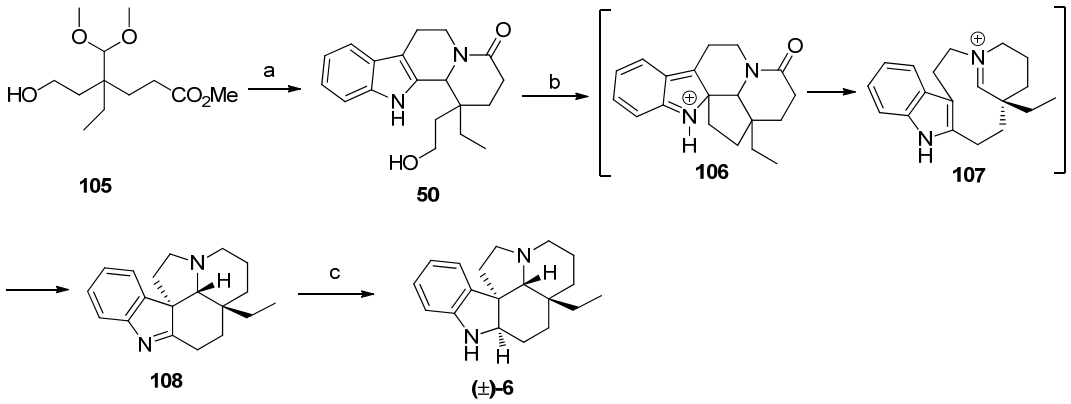
Scheme 10: Harley-Mason's approach

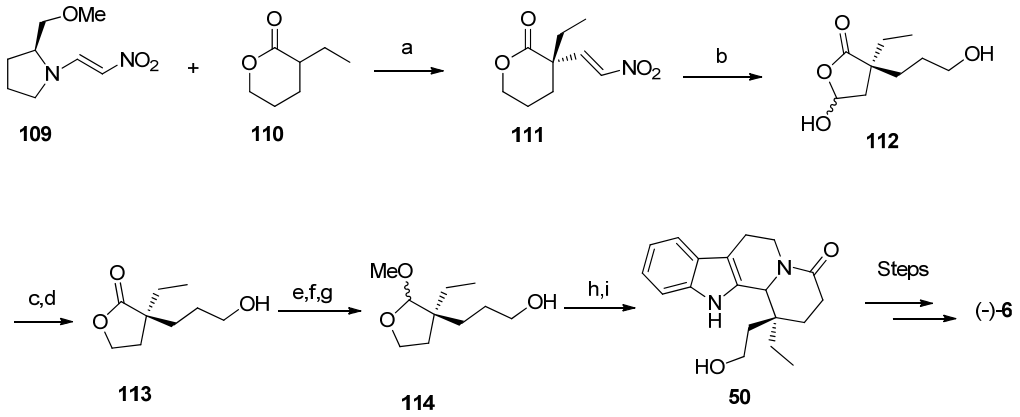


Reagents and conditions: *(a) Tryptamine, AcOH, reflux; (b) 40% H_2SO_4, reflux; (c) $LiAlH_4$,* THF*, reflux.*

II.b. Fuji's asymmetric approach: (*J. Am. Chem. Soc.* **1987**, *109*, 7901)[22]

In this strategy, an efficient preparation of the key tetracyclic hydroxyl lactam **50** was prepared from **111** in 48% overall yield, which on Harley-Mason cyclisation and rearrangement under acidic condition followed by $LiAlH_4$ reduction produced (-)-**6** (Scheme-11).

Scheme 11: Fuji's asymmetric approach

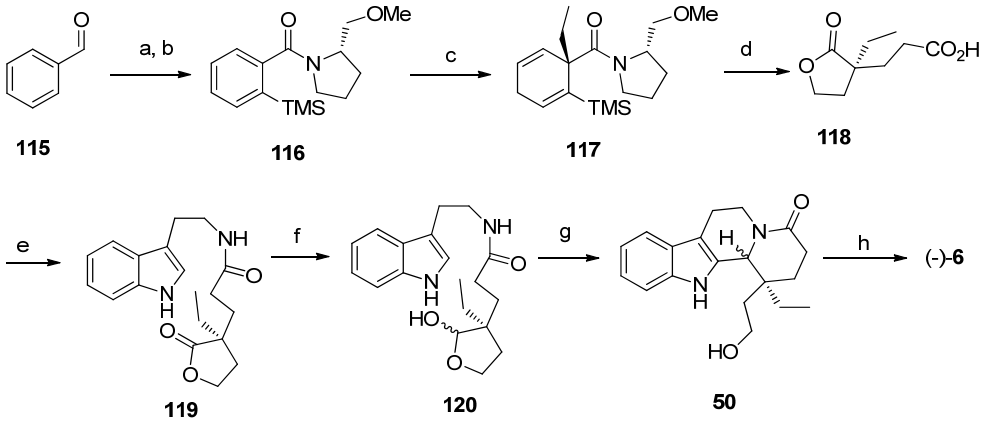


Reagents and conditions: *(a) n-BuLi, Et_2O/DME, –78 °C, 99%; (b) $TiCl_3$, DME; (c) $NaBH_4$; (d) HCl, MeOH, reflux, 75%; (e) CrO_3, H_2SO_4, acetone; (f) DIBAL-H, Et_2O; (g) TsOH, MeOH, reflux, 76%; (h) tryptamine, AcOH, reflux; (i) NaOH, MeOH, 84%, (over 2 steps).*

II.c. Schultz's strategy: (*J. Org. Chem.* **1997**, *62*, 6855)[23] (Enantioselective synthesis)

This route involved a diastereoselective Birch reduction alkylation of proline derived benzamide for the asymmetric construction of lactone **118** with a quaternary center. The condensation of **118** with tryptamine **2** produced **119** (Scheme-12). The intermediate **119** was reduced with DIBAL-H to obtain lactol **120.** Further, cyclisation of **120** in acetic acid produced tetracyclic isoquinazolidine **50** as 1:1 mixture of diasteromeric mixture. Finally, cyclisation-rearrangement sequence from **50** in acidic medium followed by $LiAlH_4$ reduction produced (-)-**6** (Scheme-12).

Scheme 12: Schultz's strategy



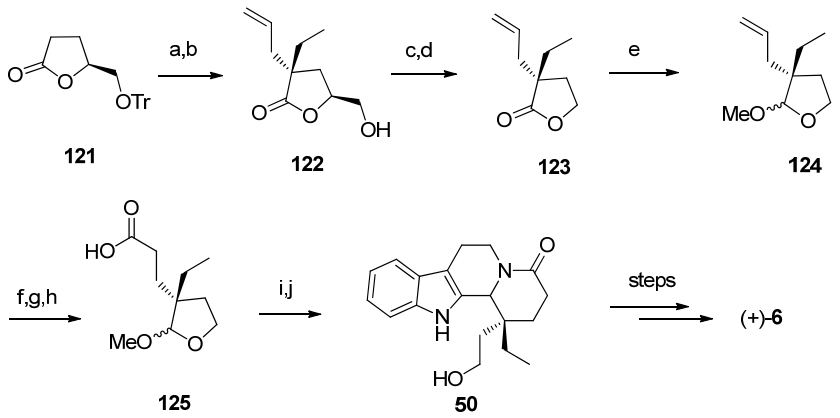
Reagents and conditions: *(a) $MeHN(CH_2)_2NMe_2$, n-BuLi, TMSCl, −20 °C, 24 h, then H_3O^+, 87%; (b) (i) $KMnO_4$, acetone, H_2O, 94%; (ii) $(COCl)_2$, CH_2Cl_2, DMF, rt, 5 h, S-prolinol, CH_2Cl_2, -40 °C then Et_3N; (iii) NaH, THF, 0 °C, MeI, 5h, 88% (2 steps); (c) K, NH_3, t-BuOH, THF, −78 °C, LiBr, piperylene, EtI, −78 °C, 97%; (d)(i) H_2, 10% Pd/C, EtOAc (63 psi); (ii) $CuCl_2$, DMF, 60 °C; (iii) TFAA, UHP,Na_2HPO_4, CH_2Cl_2; (iv) H_2, 5%*

Rh/C, THF (v) TsOH, PhH/H_2O, reflux; (e) tryptamine, $(PhO)_2P(O)N_3$, Et_3N, THF, 84%; (f) DIBAL-H, CH_2Cl_2, −78 °C, 93%; (g) AcOH, reflux, 20% NaOH/MeOH, 65 %.

II.d. Okada's Strategy: (*Tetrahedron* **2004**, *60*, 3273)[24] (Enantioselective synthesis)

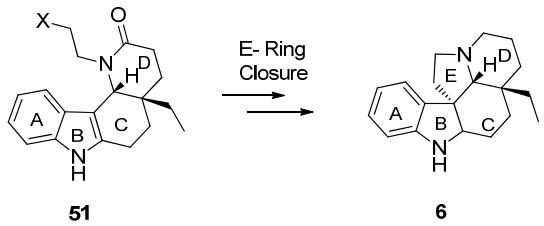
The sequential alkylation of **121** followed by removal of the hydroxyl bearing side chain produced enantiomerically pure lactone **123** which on reduction with DIBAL-H followed by lactol protection gave **124** (Scheme-13). Further, condensation of **124** with tryptamine **2** produced tetracyclic hydroxyl-lactam **5** as mixture of diastereomers which on Harley-Mason cyclisation-rearrangement produced (+)-**6**.

Scheme 13: Okada's Strategy



Reagents and conditions: *(a) LDA, HMPA, EtI then, LDA, HMPA, allyl bromide, THF, −78 ˚C, 93%; (b) 80% AcOH, 80 ˚C, 1 h, 98%; (c) 4 M aq. NaOH, dioxane, 100 ˚C, 1 h, CO_2, aq. $NaIO_4$, rt, 3 h, 1 M HCl, 95%; (d) $NaBH_4$, MeOH, rt, 1 h then, 4 M HCl-MeOH, 70 °C, 1 h, 92%; (e) DIBAL-H, Et_2O, −78 ˚C, 1 h then, $CH(OMe)_3$, p-TsOH, MeOH, 80 ˚C, 40 min, 84%; (f) 9-BBN, THF, rt, 16 h then, 30% H_2O_2, 3 M aq. NaOH, THF, rt, 1 h, 87%; (g) SO_3-Py, DMSO, NEt_3, CH_2Cl_2, rt, 0.5 h; (h) $NaClO_2$, t-BuOH, aq. NaH_2PO_4, Me_2C=CHMe, rt, 1 h, 95% (2 steps); (i) tryptamine, AcOH, 125 ˚C, 6 days, 87%; (j) 20% aq. NaOH, MeOH, rt, 1 h, 72%.*

III. E-ring closure strategy



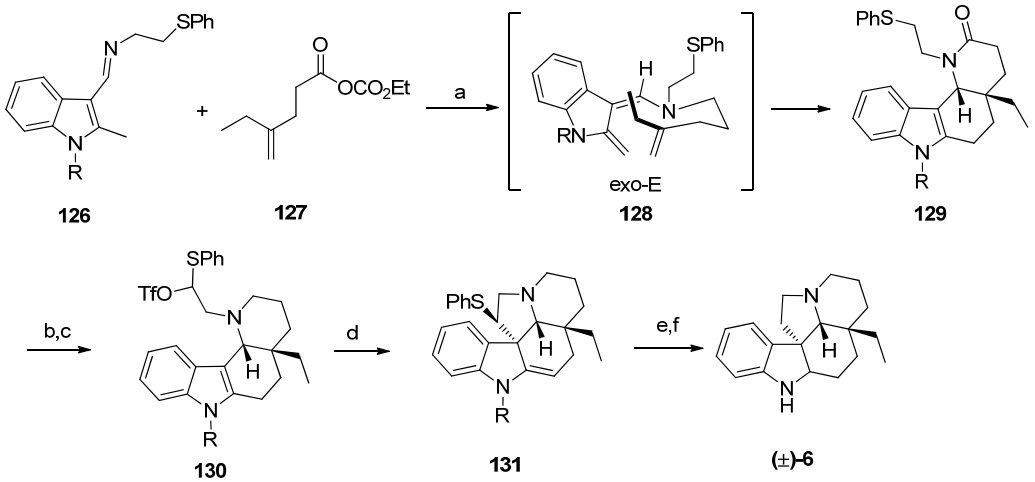
51 **6**

In 1982, Magnus *et al.* reported a new synthetic approach based on late stage construction of pyrrolidine ring (E-ring) by C-3 alkylation of the indole. This approach is called as E-ring closure approach and in this strategy first ABCD tetracyclic core is constructed. Further, E-ring closure of ABCD core **51** gives pentacyclic skeleton **6** (ABCDE ring system).

III.a. Magnus Stategy: (*J. Am. Chem. Soc.* **1982**, *104*, 1140)[25] (Racemic synthesis)

Magnus and coworkers prepared the ABCD tetracyclic core **130** by cyclisation of imine **126** by reacting with **127**, which by intramolecular Pummerer reaction (E-ring closure) gave pentacyclic core **131** (Scheme-14). Desulfurisation with Raney Ni followed by $LiAlH_4$ reduction produced (±)-**6**.

Scheme 14: Magnus Stategy



126 **127** **128** **129**

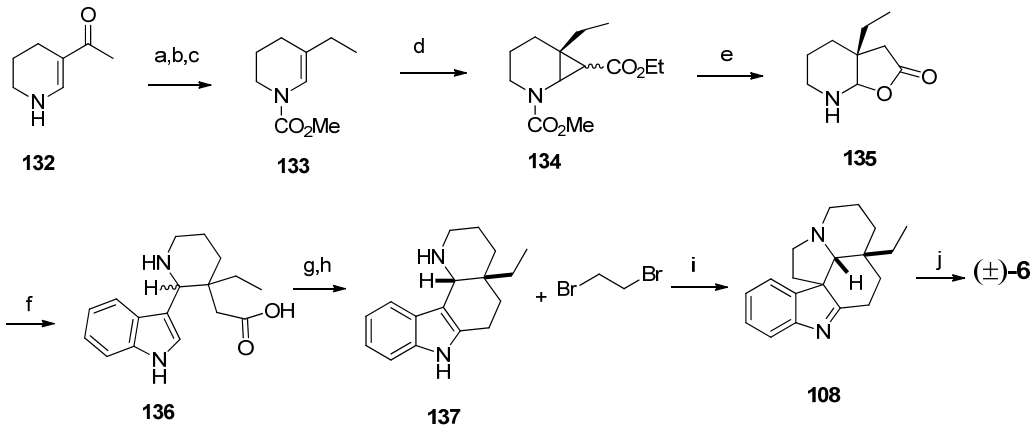
130 **131** **(±)-6**

Reagents and conditions: *(a) chlorobenzene, 140 ˚C, 3 h, 33%; (b) (i) MCPBA, CH_2Cl_2, $NaHCO_3$, 0 ˚C, 97%; (ii) Trifluoroacetic anhydride, CH_2Cl_2, 0 ˚C, 10 min; (c) chlorobenzene, 130 ˚C, 2.5 h, 81% (over 2 steps); (d) Raney Ni, EtOH, rt, 1 h, 81%; (e) $LiAlH_4$, THF, rt, 48 h, 54%.*

III.b. Wenkert's approach: (*J. Org. Chem*., **1988**, *53*, 1953**)**[26] (Racemic synthesis)

The hexahydrofuro[2,3-b]pyridin-2(3H)-one **135**, prepared by the alkaline hydrolysis of cyclopropane carboxylate **134**, on nucleophilic ring by indole in acetic acid produced indolyl amino acid **136**. Freidel-crafts cyclisation followed by reduction produced tetracyclic core **137** which on E-ring closure with 1,2-dibromoethane followed by $LiAlH_4$ reduction produced (±)-**6** (Scheme-15).

Scheme 15: Wenkert's approach

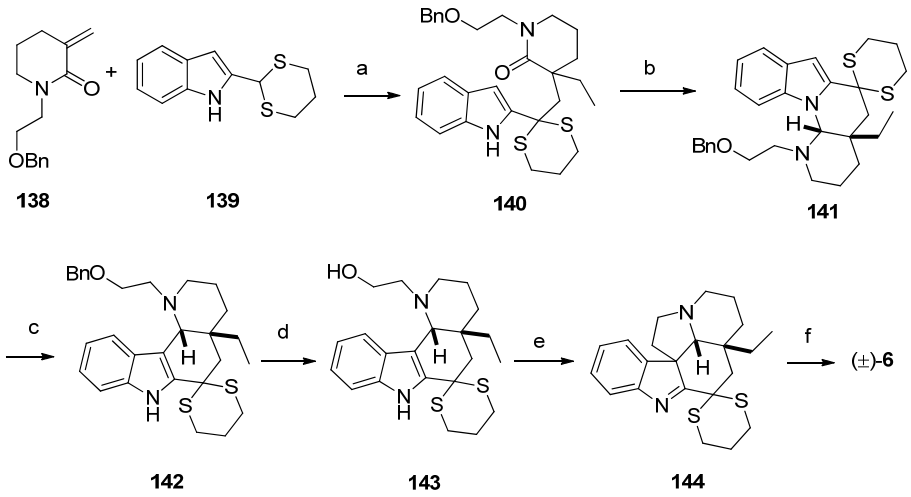


Reagents and conditions: *(a) Methyl chlorocarbonate, NEt_3, THF, 0 ˚C, 4 h, then HCl, 91%; (b) HBr, Et_2O, 0 ˚C, 10 min, 1,3-propanedithiol, rt, 4 h, 48%; (c) W-2 Raney nickel, EtOH, reflux, 12 h, 93%; (d) Ethyl diazoacetate, copper bronze, 135 ˚C, 0.5 h, 95%; (e) KOH, H_2O, diethylene glycol, 110 ˚C, 12 h, then HCl to pH 7, 88%; (f) indole, dioxane, HCl, 10% aq. AcOH, 80 ˚C, 18 h, 89%; (g) PPA, 90 ˚C, 45 min, 61%; (h) $LiAlH_4$, dioxane, reflux, 18 h, 97%; (i) K_2CO_3, 1,2-dibromoethane, 140 °C, 20 min, 32%; (j) $LiAlH_4$, Et_2O, rt, 2 h, 70%.*

III.c. Rubiralta's approach: (*J. Org. Chem.* **1996**, *61*, 7882)[27] (Racemic synthesis)

Rubiralta *et al.* reported a new synthetic method to synthesize **6** by E-ring closure of ABCD core **143** which was prepared in several steps (Scheme-16). Tandem Michael addition-alkylation of **139** with **138** and ethyl iodide produces **140**, which on treatment with DIBAL-H produced **141**. Skeletal isomerization of **141** in the presence of an acid produces **142** which on E-ring closure followed by dithiane reduction produced (±)-**6**.

Scheme 16: Rubiralta's approach



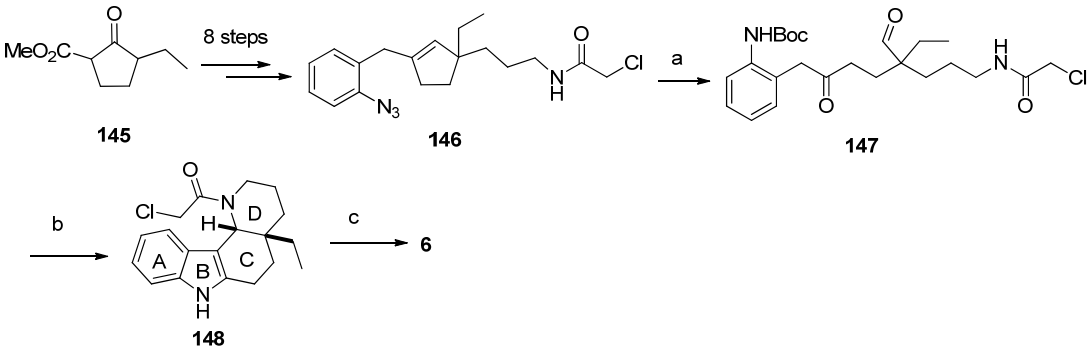
Reagents and conditions: (a) n-BuLi, THF, HMPA, EtI, −78 °C, 2 h, 52%; (b) DIBAL-H, THF, 0 °C, 73%; (c) 50% aq. AcOH, reflux, 2 h, 90%; (d) Me_2S, CH_2Cl_2, $BF_3.Et_2O$, 35 °C, 2 h, 86%; (e) t-BuOK, TsCl, THF, 1 h, rt, 77%; (f) W-2 Raney nickel, dioxane, reflux, 30 min, 65%.

III.d. Heathcock's total synthesis of (±)-6: (*J. Org. Chem.* **2000**, *65*, 2642)[28]

Heathcock and coworkers reported a short and efficient synthesis of (±)-**6** in 13 steps with 5.9% overall yield. The key reactions of this strategy are: (i) An acid mediated cascade reaction to construct B, C, D rings in a single transformation. (ii) Indole ring construction during cascade reaction. (iii) E-ring closure approach as end game to accomplish target molecule. The functionalised cyclopentene derivative **146** was prepared from commercially available **145**, in 8 steps. The intermediate **146** upon ozonolysis produced **147** which on treatment with triflouro acetic acid sets in a cascade cyclisation

reaction to form B, C, D rings in a single transformation. E-ring closure and functional group transformations gave (±)-**6**.

Scheme 17: Heathcock's approach



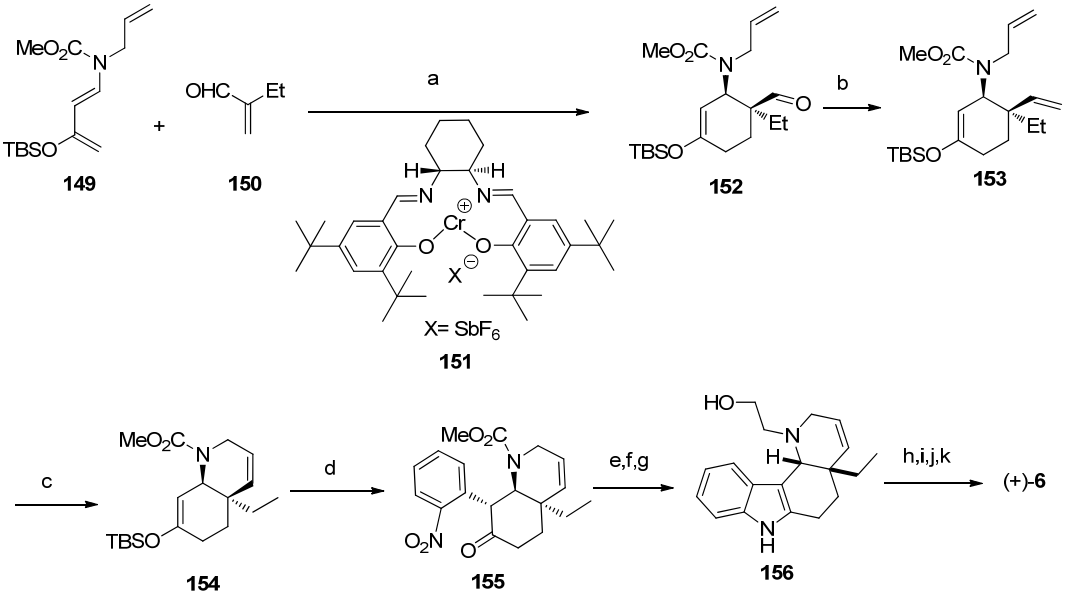
Reagents and conditions: *(a) O_3, −78 °C, Me_2S; (b) TFA : CH_2Cl_2 (1:1), 37% (2 steps); (c) (i) NaI, acetone; (ii) CF_3SO_3Ag, 86%; (iii) $LiAlH_4$, THF, 82%.*

III.e. Rawal's total synthesis of (+)-aspidospermidine using organo catalytic approach:

(*J. Am. Chem. Soc.* **2002**, *124*, 4628)[29] (Enantioselective synthesis)

A concise and stereo controlled strategy for the synthesis of *Aspidosperma* class of alkaloids in enantiomerically enriched form was reported by E-ring construction on ABCD core **156**. The core structure **156** was obtained by a catalytic enantioselective Diels-Alder reaction of 1-amino-3-siloxydiene **149** with ethylacrolein **150** using Jacobsen's chiral Cr(III)-salen complex **151** to construct cyclohexene **152** (C-ring) with C-21 quaternary sterocenter in high yields and enantioselectivity (97% *ee*). Ring closing metathesis reaction of **153** for the construction of D-ring followed by *o*-nitrophenyl group introduction by the reaction of **154** with (*o*-Nitrophenyl)phenyliodonium fluoride (NPIF)and reduction of nitro group produced key tetracyclic core **156** which on E-ring closure furnished (+)-**6**.

Scheme 18: Rawal's organo catalytic approach

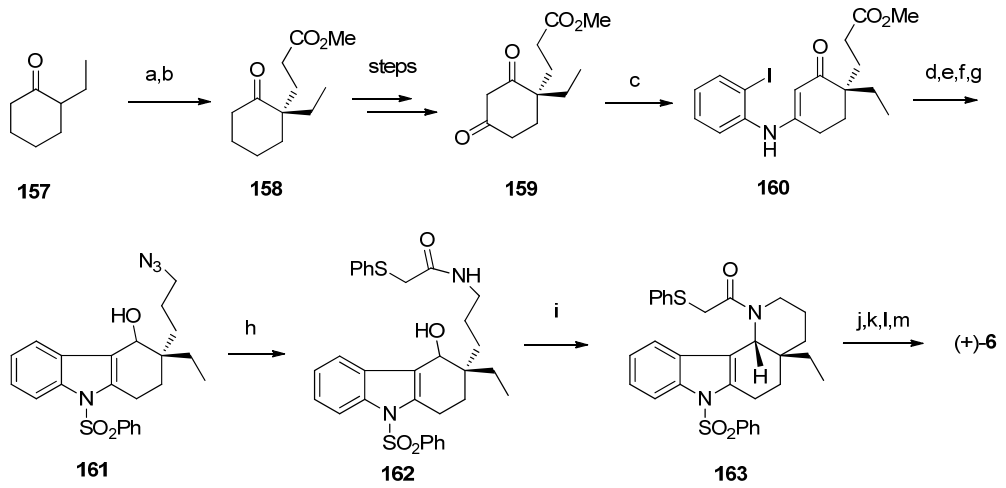


Reagents and conditions: *(a) 5 mol% of* **151***, CH_2Cl_2, -40 ˚C, 2 d, 91%; (b) Ph_3PCH_3Br, n-BuLi, THF, −78 ˚C, 85%; (c) Schrock's molybdenum catalyst (5 mol%), PhH, 60 ˚C, 1 h, 88%; (d) NPIF, DMSO,THF, 94%; (e) $TiCl_3$, NH_4OAc, THF, H_2O, 89%; (f) TMSI (2 equiv.), CH_2Cl_2, MeOH, reflux, 90%; (g) $BrCH_2CH_2OH$ (10 equiv), Na_2CO_3, EtOH, reflux, 18 h, 100%; (h) MsCl, NEt_3, CH_2Cl_2, 90%; (i) t-BuOK, THF, 87%; (j) $NaBH_4$, EtOH; (k) H_2, PtO_2, EtOH, 73% (2 steps).*

III.f. D'Angelo's approach: (*J. Org. Chem.* **1994**, *59*, 2292)[30] (Enantioselective synthesis)

The chiral quaternary center containing cyclohexane-1,3-dione **159** was prepared by enanine Michel addition which on condensation with 2-Iodoanilne followed by indolization gave carbazole **161** intermediate. Further transformation of azide group to an amide followed by cyclization produced tetracyclic **163**, which by E-ring closure followed by desulfurization produced (+)-**6**.

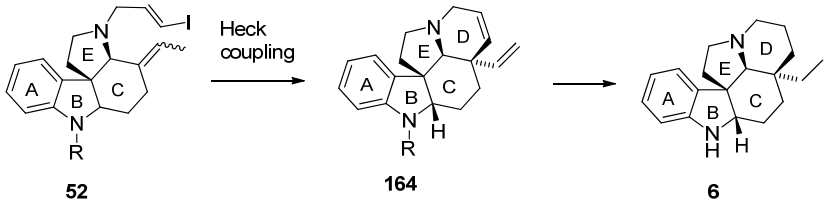
Scheme 19: D'Angelo's approach



Reagents and conditions: *(a) (R)-(+)-phenylethylamine, toluene, p-TsOH, Dean-Stark, reflux, 12 h; (b) methyl acrylate, hydroquinone, 65 °C, 3 d, then AcOH, THF, rt, 3 h, 83%; (c) 2-iodoaniline, p-TsOH, toluene, Dean-Stark, reflux, 5 h, 94%; (d) NaH, HMPA, CuI, 120 ˚C, 2 h, 84%; (e) $LiEt_3BH$, THF, −40 ˚C, 1 h, then EtOH, 6 N NaOH, 0 ˚C, then 30% H_2O_2, rt, 15 h, 88%; (f) (i) NEt_3, DMAP, CH_2Cl_2, THF, MsCl, 2 h, (ii) DMF, NaN_3, 80 °C, 2 h, (iii) tetrabutylammonium hydrogensulfate, (4-methoxyphenyl) sulfonyl chloride, CH_2Cl_2, 50 % aq. NaOH, 2 h, rt, 74%; (g) $NaBH_4$, EtOH, reflux, 30 min, 92%; (h) PPh_3, THF, 18 h, H_2O, rt, 12 h, CH_2Cl_2, 0 ˚C, (phenylthio)acetyl chloride, NaOH, 30 min, 62%; (i) TFA, CH_2Cl_2, 0 ˚C, 15 min, 94%; (j) NaIO4, THF, MeOH, H_2O, rt, 72 h, 88%; (k) trifluoroacetic anhydride, CH_2Cl_2, 0 °C, 15 min, chlorobenzene, 135 °C, 2 h, 89%; (l) W-2, Raney nickel, EtOH, DMF, 20 min, rt, 56%; (m) LiAlH4, THF, 0 °C, rt, 48 h, 68%.*

IV. D-ring closure approach

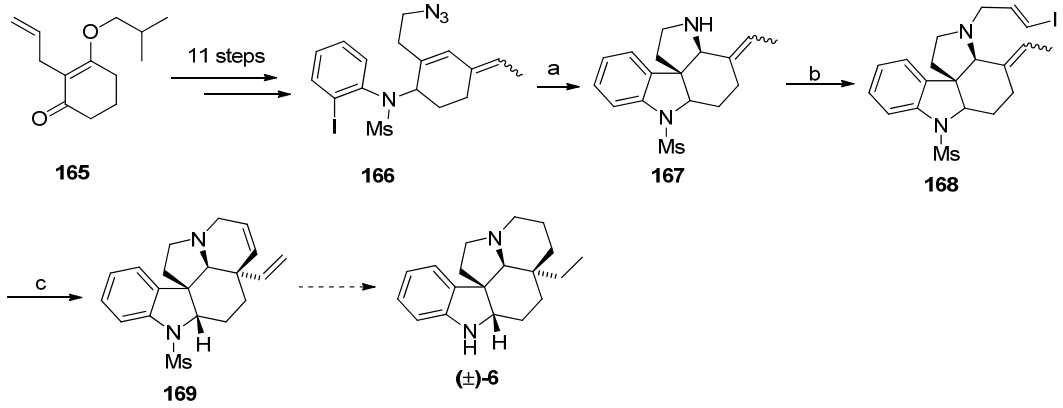
A new synthetic approach based on late stage construction of D-ring by intramolecular Heck-coupling of the vinyl iodide. In this strategy, first ABCE tetracyclic core is constructed on which D-ring is built to give pentacyclic skeleton (ABCDE ring system).



IV.a. Murphy approach: (*Org. Lett.* **2000**, *2*, 3599)[31] (Racemic synthesis)

Murphy and co-workers reported a radical cascade reaction of an iodoazide **166** for the construction of tetracycle core (ABCE) of aspidospermidine. This method is used to construct B and E rings of the tetracycle **167** in a single transformation (Scheme-20). The *N*-alkylation **167** with (*Z*)-3-bromo-1-iodopropane followed by intramolecular Heck coupling produces known pentacycle **169**.

Scheme 20: Murphy approach

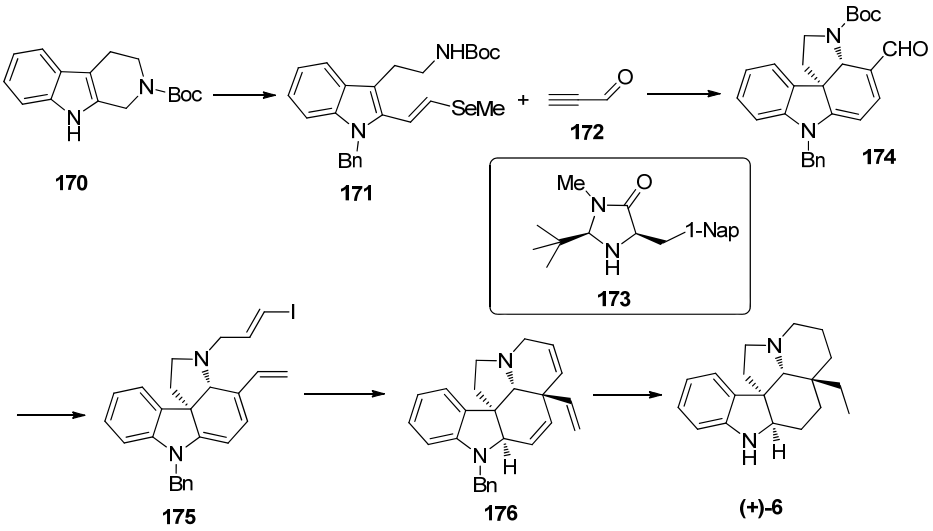


Reagents and conditions: *(a) TTMSS, AIBN, benzene, reflux, 40%; (b) K_2CO_3, ICH=CH–CH_2Br, THF, 63%; (c) $Pd(OAc)_2$, NEt_3, PPh_3, CH_3CN, 32%.*

IV.b MacMillan's approach: (*Nature.* **2011**, *475*, 183)[32] (Enantioselective synthesis)

In 2011, Macmillan and coworkers reported an organo catalytic asymmetric total synthesis several alkaloids employing a cascade Diels-Alder/cyclization sequence. For example, 2-(vinyl-1-selenomethyl) tryptamine **171** on reacting with propynal **172** in presence of imidazolidinone catalyst **173** undergoes an *endo*-selective asymmetric Diels-Alder cycloaddition which on further an elimination/conjugate addition sequence produced **174** (ABCE ring system). The tetracyclic core **174** was converted into **175** in three steps which on D-ring closure by Heck cyclization followed by reduction produced (+)-**6**.

Scheme 21: MacMillan's approach



Reagents and conditions: *(a) NaH, DMF, BnBr, rt; (b) SeO_2, dioxane, H_2O, 100 °C; (c) $(EtO)_2P(O)CH_2SeMe$, 18-crown-6, KHMDS, THF, –78 °C to rt; (d) Ph_3PCH_3I, n-butyllithium, THF, 0 °C, then AcOH, $NaCNBH_3$, 0 °C; (e) TFA, CH_2Cl_2, rt; (f) K_2CO_3, DMF, rt; (g) $(Ph_3P)_4Pd$, Et_3N, toluene, 80 °C; (h) $Pd(OH)_2$, H_2, 200 p.s.i., MeOH, EtOAc, rt; (i) CH_2Cl_2, DMSO, $(COCl)_2$; (j) n-butyllithium, $NCCO_2Me$, THF, –78 °C to rt.*

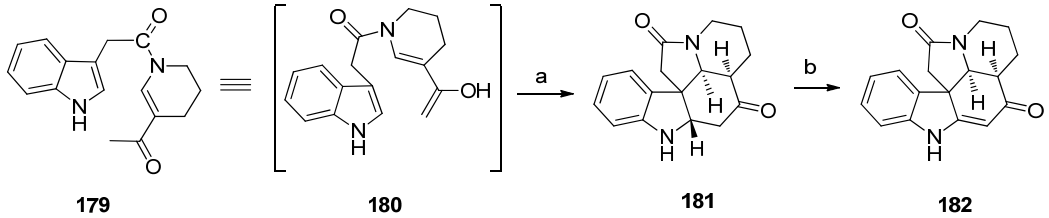
V. Diels-Alder approach

V.a. Wenkert and Kunesh approaches: (Racemic synthesis)

(*Tetrahedron* **1983**, *39*, 3719–3724; *J. Org. Chem*., **1991**, *56*, 2915)[33]

Ernest Wenkert *et al.* reported[33a] a formal [4+2] cycloaddition reaction for the construction of pentacyclic core of aspidospermidine. For example, the vinylogous imide **180** on treatment with $BF_3.OEt_2$ underwent a formal [4+2] cycloaddition reaction and produced pentacycle **181** which on Oppenauer oxidation gave **182** (Scheme-20).

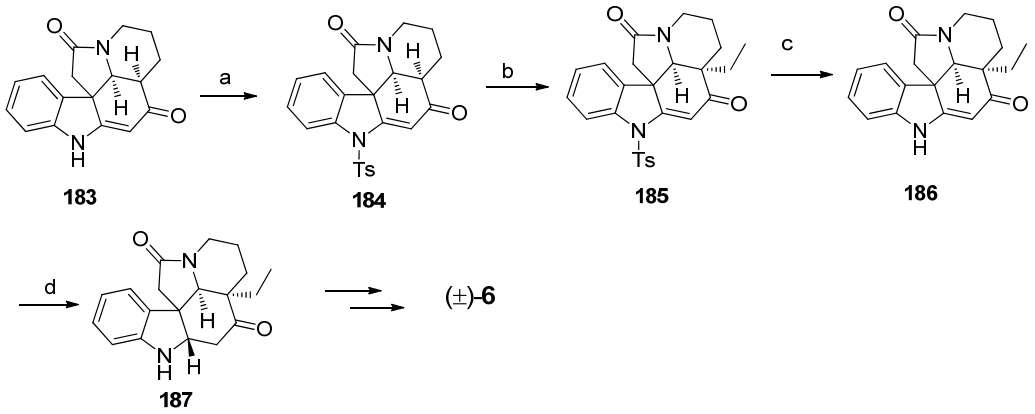
Scheme 22: Wenkert's approach



Reagents and conditions: *(a) $BF_3.O(Et)_2$, 62%; (b) Oppenauer oxidation.*

Subsequently, Kunesch *et al.* synthesized **184** using Wenkert protocol and generated quaternary center by alkylation with ethyl iodide to obtain **185**. Further functional group transformation gave (±)-**6** (Scheme-21).[33b]

Scheme 23: Kunesh's approach

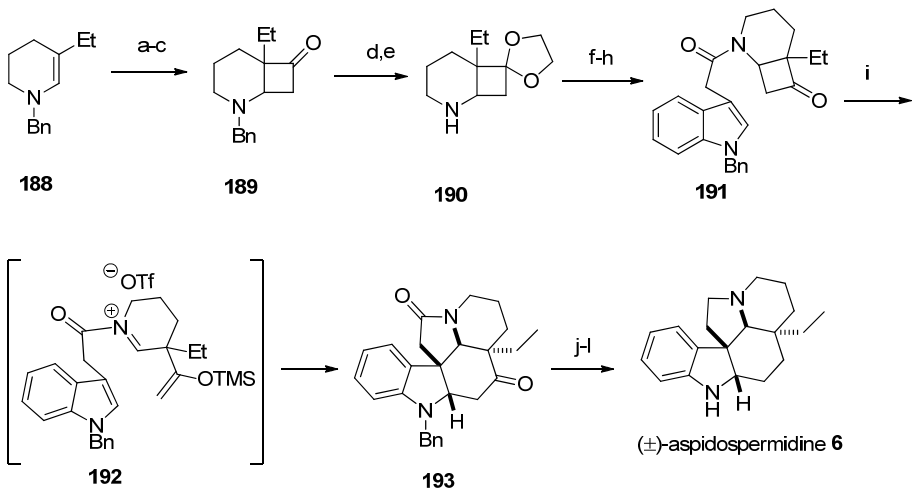


Reagents and conditions: *(a) n-BuLi, p-MeC$_6$H$_4$SO$_2$Cl, THF; (b) KH, LiI, EtI, THF; (c)LiAlH$_4$, THF, reflux; (d) H$_2$, Pt/C, THF, 40 psi.*

V.b. Matsuo Approach: (*Angew. Chem., Int. Ed*. **2013**, *52*, 906)[34] (Racemic synthesis)

Pentacyclic skeleton of aspidospermidine (Scheme-22) **193** was obtained by Lewis acid promoted formal intramolecular [4+2] cycloaddition of cyclobutanones with tethered *N*-benzyl indole **191** for the construction of the **193** by following Wolf-Kishner reduction, $LiAlH_4$ reduction and debenzylation sequence gave (±)-**6**.

Scheme 24: Matsuo's approach



Reagents and conditions: *(a) CbzCl, CH_2Cl_2, rt, 15 h, 99%; (b) Zn/Cu, $Cl_3C(C=O)Cl$, Et_2O, sonication, 0 °C, 0.5 h, then rt, 14 h; (c) Zn/Cu, NH4Cl, MeOH, rt, 2 h, 85% (for two steps); (d) ethylene glycol, TsOH/H2O, benzene, reflux, 12 h, 95%; (e) H_2, Pd/C, EtOH, rt, 3 h, quantitative; (f) 3-indoleacetic acid, EDC, 0 °C, 5 h, 89%; (g) BnBr, NaH, DMF, rt, 2.5 h, 95%; (h) 1N HCl, EtOH, reflux, 3 h, 93%; (i) Me_3SiOTf, toluene, reflux, 10 min, 46%; (j) $N_2H_4 \cdot H_2O$, Na, $(CH_2OH)_2$, 160–210 °C, 18 h; (k) $LiAlH_4$, THF, rt, 1 h, 71% (for 2 steps); (l) H_2, $Pd(OH)_2$, EtOH, rt, 46 h, 93%.*

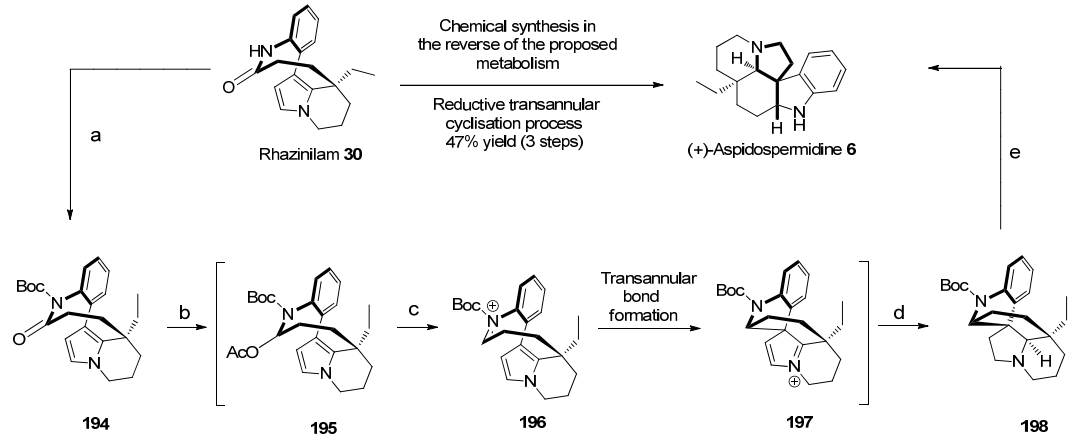
VI. Miscellaneous approaches

VI.a. Matthew J. Gaunt's approach: (*Angew. Chem., Int. Ed.* **2012**, *51*, 9288)[35]

(Enantioselective synthesis)

The conversion of one class of alkaloids into structurally different other class of alkaloids is a natural process through biosynthetic pathways.[36] Gaunt *et al*. designed a chemical process for the conversion of rhazinilam (**30**) to Aspidospermidine (**6**) (Scheme-25) [35] by carrying out the reverse of a proposed biosynthesis of conversion of aspidosperma alkaloid to rhazinilam.[36] In this process two new stereocenters, one new sigma bond and two new rings were formed.

Scheme 25: Matthew J. Gaunt's Strategy



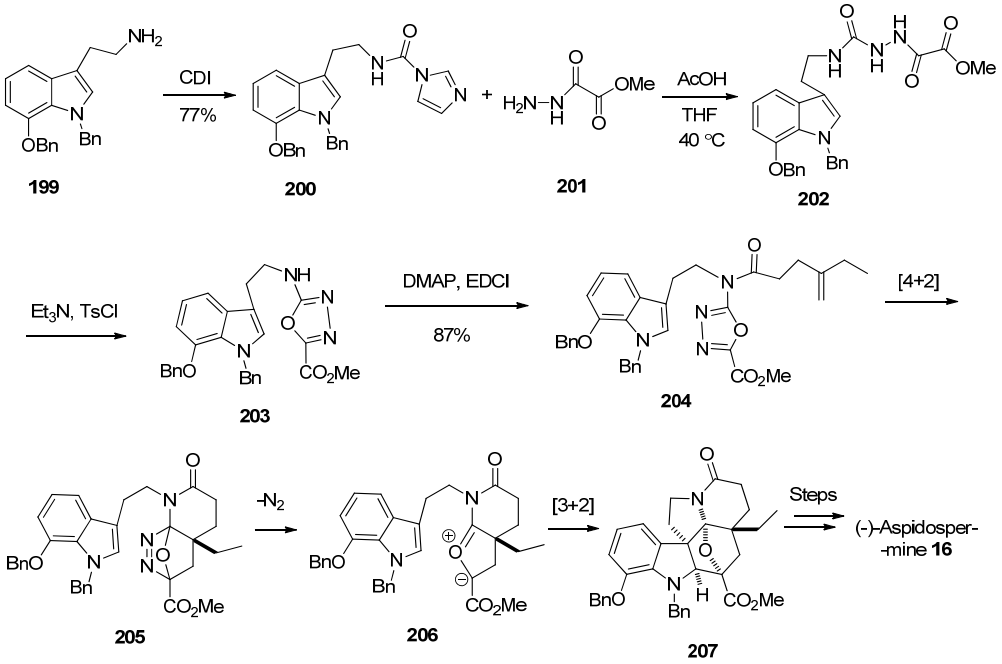
Reagents and conditions: *(a) $(Boc)_2O$, DMAP, THF, 75%; (b) $LiBHEt_3$, THF, then Ac_2O; (c) TFA, CH_2Cl_2; (d) $NaCNBH_3$, CH_2Cl_2, 0 °C to rt; (e) TFA, CH_2Cl_2, 90%.*

VI.b. Boger's approach: intramolecular [4+2] / [3+2] cycloaddition cascade strategy

(Enantioselective synthesis) (*Org. Lett.,* **2012**, *14*, 2078-2081)[37]

Boger and co-workers have reported an efficient intramolecular [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazole **204** for the construction of aspidosperma skeleton.[37] The key intermediate **204** was prepared as described in Scheme-23, which on heating in *o*-dichloro benzene (*o*-DCB) at 180 °C produced the hexacyclic Aspidosperma core **207** in 71% yield. In this cascade reaction, first an intramolecular [4+2] cycloaddition reaction of 1,3,4-oxadiazole **204** with tethered dienophile takes place where loss of N_2 molecule produces 1,3-dipole **206**, which on an endocyclic [3+2]-cycloaddition produces six membered ring skeleton **207** as single diastereomer (Scheme-24). In this reaction, four C-C bonds, three rings and five stereo centres are generated in a single transformation with the complete requisite stereochemistry of aspidosperma skeleton. This cascade reaction is one of the powerful method for the construction of aspidosperma skeleton.

Scheme 26: Boger's approach



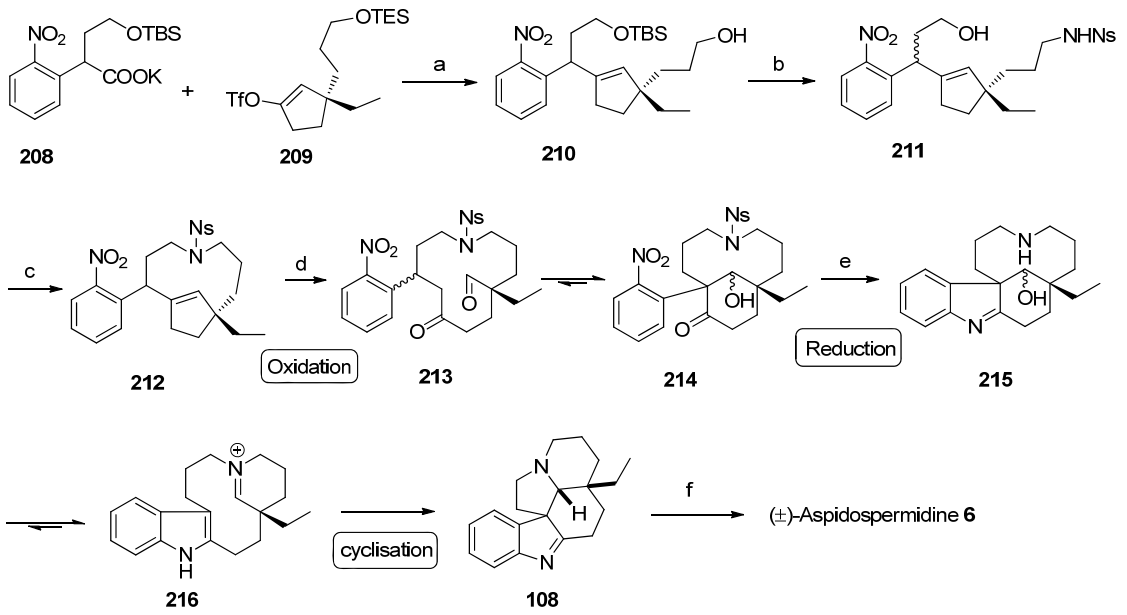
Reagents and conditions: *(a) CDI, 77%; (b) AcOH, THF, 40 °C; (c) TEA, TsCl, 70% (for 2 steps); (d) DMAP, EDCI, 87 %; (d) o-DCB, 180 °C, 71%.*

VI.c. Jieping Zhu's approach: an Integrated Oxidation/ Reduction / Cyclization Cascade Sequence

(Racemic synthesis) (*J. Am. Chem. Soc*. **2014**, *136*, 15102)[38]

Zhu and coworkers reported an integrated oxidation/reduction/cyclization sequence (*i*ORC) for the construction of (±)-**6 (**scheme-27**)**.[38] The key intermediate **210** was accessed by a palladium catalyzed decarboxylative vinylation. The *i*ORC process is described in Scheme-1. The intermediate **210** on ozonolysis gives **213**, which upon deprotection of nosyl group followed by reduction of the nitro group produced **215**. The transannular cyclisation of **215** through iminium ion produces (±)-**6**.

Scheme 27: Jieping Zhu's approach



Reagents and conditions: *(a) [Pd(allyl)Cl]$_2$ (5.0 mol%), X-Phos (15.0 mol%), diglyme, 100 °C, then TBAF, 0 °C, 57%; (b) PPh$_3$, DEAD, NsNH$_2$, neopentyl alcohol (40 %), toluene, rt, then TBAF, rt, 75%; (c) PPh$_3$, DEAD, neopentyl alcohol (40 mol%), toluene,*

rt, 81%; (d) O_3, CH_2Cl_2, Me_2S, then PhSH, Cs_2CO_3; (e) $TiCl_3$, NH_4OAc, MeOH, 51%; (f) aq.$NaHCO_3$, $NaBH_4$, 50%.

1.5. Summary of literature reports:

From the above review, it is evident that there are mainly six major routes known for the construction of pentacyclic skeleton of *Aspidosperma* class of alkaloids: (1) Storks Fisher indolisation of a tricyclic ketone (2) Harley-Mason's cyclization-rearrangement (3) E-ring closure as an end game (4) D-ring closure as an end game (5) Diels-Alder approach (6) miscellaneous approaches.

From the above detailed survey, it can be emphasized that there are only few enantioselective approaches known for the synthesis of aspidospermidine and related alkaloids among the six routes already known in literature, Storks approach through tricyclic core still remains hallmark in this area. Most of the enantioselective approaches for tricyclic core are designed through Stork's 4,4-dialkyl cyclohexenone intermediates. Most of these methods are limited to only one enantiomer of natural product.

1.6. Our concept and protocol:

The lack of efficient strategy for the synthesis of tricyclic core, kindled our interest to develop a novel synthetic route for the synthesis of both enantiomers of tricyclic core and *Aspidospema* class of alkaloids. Thus, we visualized the synthesis of tricyclic core from a totally different pathway as shown in Figure-8 by employing intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide.

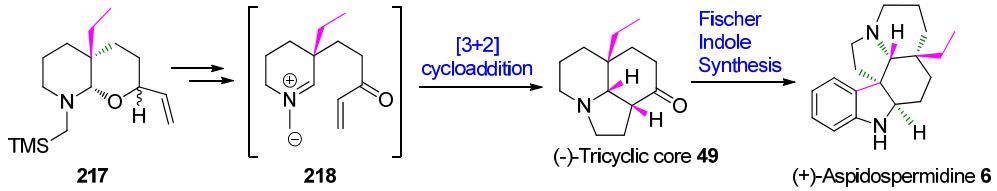


Figure-8

Our approach for the synthesis of (+) and (-)-tricyclic core and total synthesis of (+)-Aspidospermidine is described in the next chapter in detail.

1.7.References:

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Chapter-2

Studies towards development of

Novel strategy for syntheses of *Aspidosperma*

Class of alkaloids

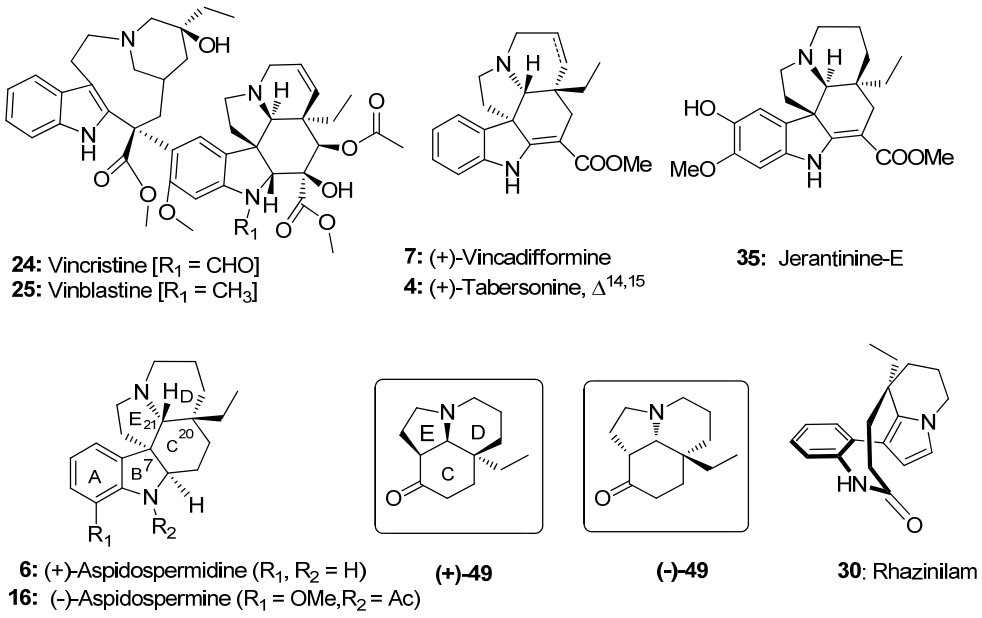
Section A

2.1. Introduction:

Aspidosperma alkaloids (Figure-8), isolated from various biological sources, comprises of more than 250 structurally complex compounds.[1] The unique pentacyclic framework with contiguous *cis*-stereo centers at C-7, C-21 and C-20 (all carbon quaternary) is a common structural feature found among all the alkaloids of this family. The basic pentacyclic framework of a*spidospermidine* (**6**) is common to the most of these pharmacologically active alkaloids (Figure-9) which has been an attractive target for the showcasing of any new synthetic methodologies.[2] Therefore, development of an efficient strategy for the construction of **6** still invites great interest.[3]

One of the most utilized approach for the construction of this pentacyclic alkaloid **6** in racemic[4-6] as well as enatioselective[7,8] form have been the late stage installation of indole moiety on to the 6*a*-ethyloctahydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-9(2*H*)-one (tricyclic core **49**, Figure-9) initially prepared by Stork and Dolfini.[4]

Figure 9. Some of the representative structures of Aspidosperma class of alkaloids and tricyclic cores.



Although remarkable development has taken place since Stork's Fischer indolization[4] of tricyclic core **49** approach for constructing aspidosperma class of alkaloids**,** this

methodology still remains the hallmark in this field. The lack of efficient and novel strategies to the enantioselective construction of **49**, dragged our attention to develop an efficient strategy. Therefore, from synthetic point of view, how to expeditiously establish such a privileged core **49** with the crucial C-20 all carbon quaternary stereocenter would be an important issue in developing asymmetric synthesis of **6** and structurally related bisindole alkaloids. Furthermore, if the strategy provides both enantiomers[9] (most of these alkaloids are produced naturally in both enantiomers)[1] it would be an added advantage.

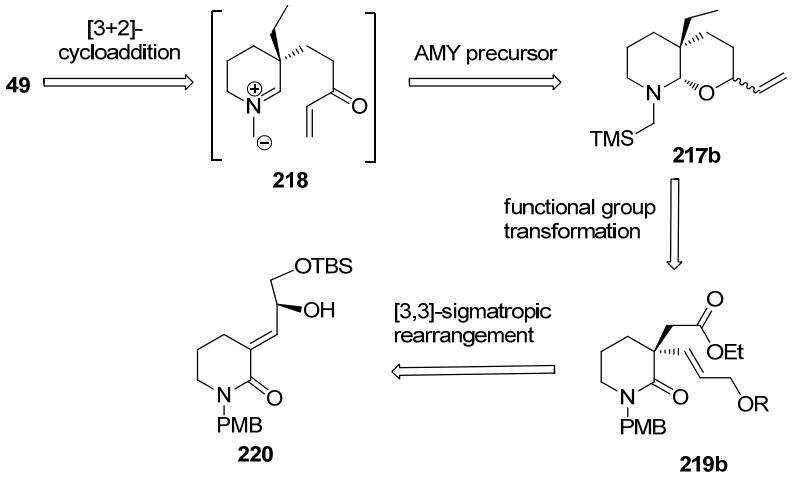
Interestingly, *Aspidosperma* class of alkaloids are naturally available in both the enantiomeric forms[1] (*i.e.*, as C_7, C_{21} and C_{22} centers are converse), but there are only few articulated methods that can access both[9] the enantiomers of this alkaloids. Since **49** represents the basic skeleton of most of these alkaloids, construction of this highly versatile[6,8] in either of enantiomeric forms can efficiently lead to the various alkaloids (Figure 9). This imagination of advancing **49** to several natural products, prompted us to envisage the synthesis of both enantiomers of **49**.

Our continuing research interest in exploring the application of intramolecular 1,3-dipole cycloaddition reaction of non-stabilized azomethine ylide in the total synthesis of fused pyrrolidine containing alkaloids[10-21] with complex architecture, led us to envisage the synthesis of *aspidosperma* class of alkaloids through intramolecular [3+2] cycloaddition of nonstabilized azomethine ylide (AMY) as shown in the retrosynthetic analysis.

2.2. Retrosynthetic plan and design:

The synthesis of (+)-**6** was planned through the indolization[4] of **49** which itself was envisioned *via* intramolecular [3+2] cycloaddition **217.** The synthesis of **217** was visualized from **219** by simple functional group transformations. The synthesis of **219** in enantiomerically pure form was planned to be accessed by [3,3]-sigmatropic rearrangement of **220**. Herein, we disclose our successful effort of accomplishing the construction of both (+)-**49** as well as (-)-**49** and utilization of (-)-**49** for the total synthesis of (+)-aspidospermidine **6** (Scheme-28).

Scheme 28. Retrosynthetic Analysis of (-)-Tricyclic core

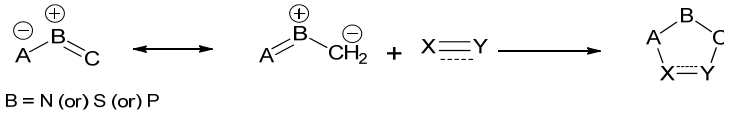


Since the present synthetic route involves intramolecular 1,3-dipolar cycloaddition of non-stabilized azomethine ylide as a key step, it would be important to highlight the salient features of azomethine ylide[22-23] as 1,3-dipole and the protocol developed in our laboratory[10-21] or its generation and application.

2.3. Azomethine Ylide:

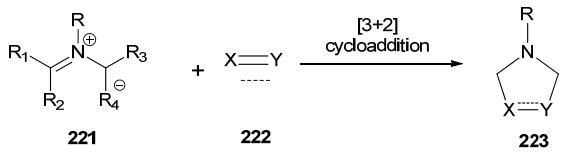
An ylide is a hetero atom containing (usually N, S or P) neutral dipolar intermediate. Ylide is a reactive species which on cycloaddition[24-31] with a variety of unsaturated substrates (dipolarophiles) give a five membered hetrocyclic ring systems (Figure-10).

Figure-10



Azomethine ylides are nitrogen based diplolar intermediates, containing an iminium ion next to the carbanion. These azomethine ylides **221** are used in cycloaddition reactions with olefin or alkyne **222** to form five membered pyrrolidine ring systems **223** (Figure-11).

Figure-11



2.3.a. Intramolecular [3+2] cycloaddition of azomethine ylide:

1,3-Dipolar cycloaddition of azomethine ylide to a dipolarophile (unsaturated olefin or alkyne) is the most fundamental and reliable process to synthesize five-membered heterocyclic compounds in *regio* and stereocontrolled fashion. Intermolecular cycloadditions result in the formation of only one new pyrrolidine ring, whereas intramolecular 1,3-dipole cycloaddition reaction can lead to formation of bicyclic or polycyclic ring systems with fused pyrrolidine ring. The intramolecular 1,3-dipole cycloaddition reactions are employed as a powerful tool to construct polycyclic complex natural products in a simple way.

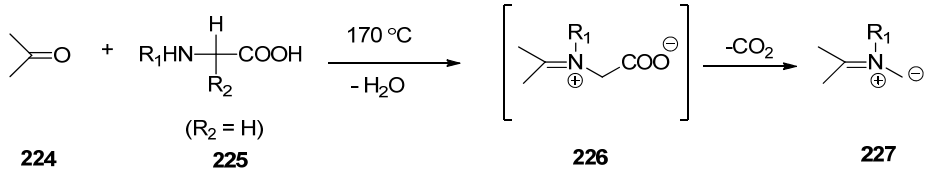
2.3.b. Generation of nonstabilized AMY:

Since last six decades, impressive development has been done for the generation of azomethine ylide. However, most of these methods are known for the generation of stabilized ylide. The generation of non-stabilized AMY is still challenging, requires a strong base or heating conditions and most importantly their generation lacks versatility. Some of the important methods to generate nonstabilized AMY are given below:

1. **George P. Rizzi *et al*. approach:**[32] (*J. Org. Chem.,* **1970**, *56*, 2069-2072)

N-Alkyl amino acid **225** on reaction with carbonyl compounds at high temperature underwent dehydration and decarboxylation reactions to produce azomethine ylide intermediate **227**. The formation of **227** was evidenced by trapping with dipolarophile. This report is the first evidence of nonazomethine ylide intermediate (Scheme-29) generation.

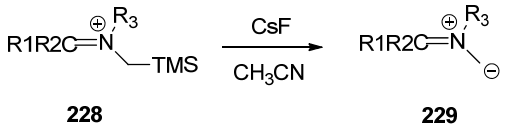
Scheme-29



2. **E. Vedejs *et al.* approach:**[33] (*J. Am. Chem. Soc.* **1979**, *101*, 6452)

Vedejs and coworkers reported a CsF induced desilylation of trimethylsilyl ammonium salts **228** for the generation of **229** which reacted with dipolarophiles to form five memberd heterocyclic ring system (Scheme-28).

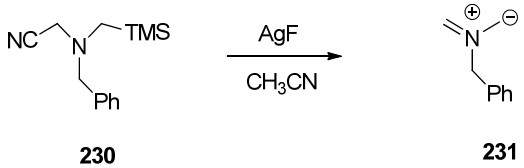
Scheme-28



3. **Albert Padwa *et al.* approach:**[34] *(Tetrahedron Lett.* **1983**, *24*, 3447)

Padwa *et al*. reported α-cyanoaminosilane **230** as a potential precursor for the generation of nonstabilized azomethine ylide by reacting with AgF which was trapped by olefins to give pyrrolidine derivatives in high yields (Scheme-29).

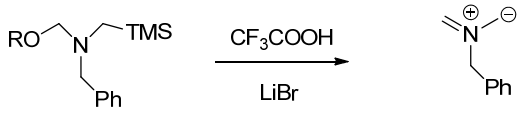
Scheme-29



4. **Albert padwa *et al.* approach:**[35] (*J. Org. Chem.* **1987**, *52*, 235)

In 1987, padwa and coworkers have found that the *N*- [(Trimethylsilyl)methyl]amino ethers **232** are azomethine ylide equivalents. These compounds on treatment with LiF in the presence of reactive unsaturated olefins gave pyrrolidine derivatives as cycloadducts in high yields (Scheme-30).

Scheme-30

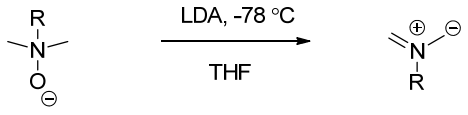


232 **233**

5. **Roussi *et al*. approach:**[36] (*J. Chem. Soc., Chem. Commun.* **1983**, 31).

Roussi and co-workers reported non-stabilized azomethine ylide generation from triethylamine-*N*-oxide **234** by the reaction of lithium di-isopropyl amide (LDA) which on cycloaddition with different olefins produced five membered pyrrolidine derivatives in high yields (Scheme-31).

Scheme-31



234 **235**

From above discussion, it is clearly understood that these methods have certain drawbacks:

(i) require high temperatures or strong base for the generation

(ii) generally suitable for intermolecular cycloaddition reactions.

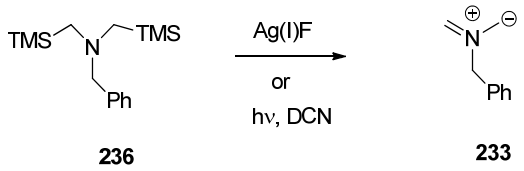
(iii) generate acyclic azomethine ylide, however, scope for cyclic azomethine ylides are not well demonstrated.

To overcome these pitfalls, in 1992 our group developed mild conditions for generation of cyclic and acyclic AMY for intra and intermolecular cycloaddition reactions.

6. Pandey *et al*. approach: [37, 38] **(***J. Chem. Soc., Chem. Commun.* **1992**, 1313)

N,N'-bis(trimethylsilyl)benzyl amine **236** on treatment with Ag(I)F, **233** is generated which on trapping with olefins produced *N*-benzyl pyrrolidine derivatives.

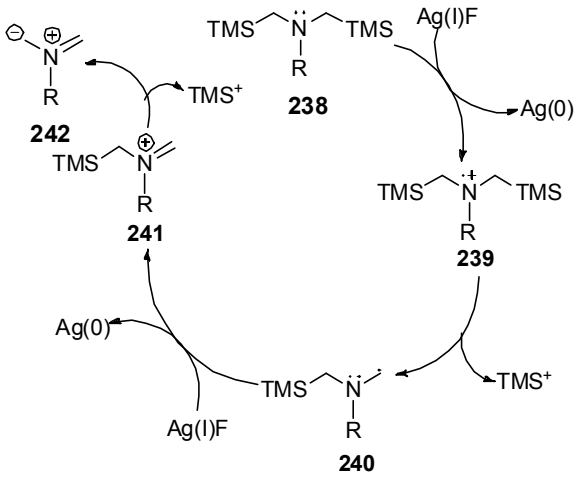
Scheme-32



236 **233**

The basic concept of azomethine ylide generation from *N,N'*-bis(trimethylsilyl methyl)alkyl amine **238** involved sequential one electron oxidation of the lone pair of electrons of nitrogen followed by desilylation due to β-silicon effect[13] (Scheme-33).

Scheme-33

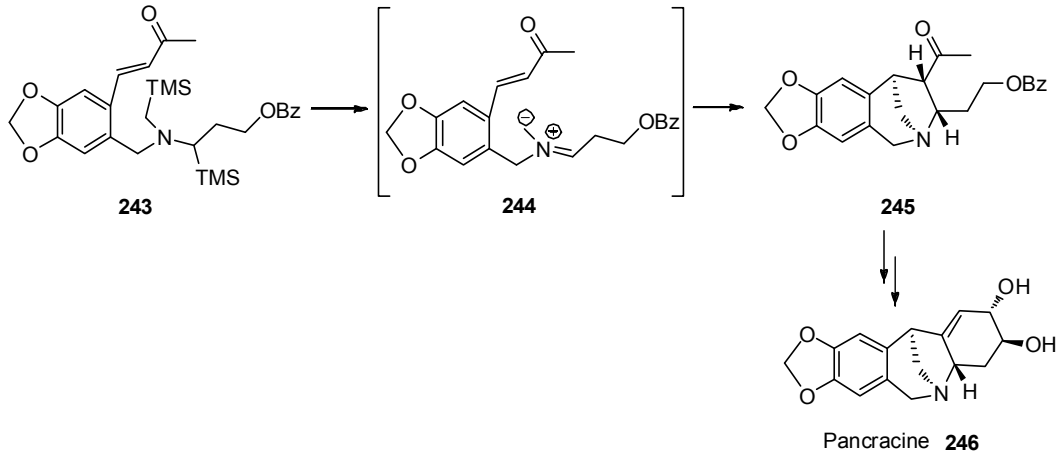


A variety of alkaloids[7,8] and various azabicyclo alkanes [X-azabicyclo (m.2.1) alkane] have been synthesized using this methodology.

2.3.c. Intramolecular [3+2] cycloaddition of nonstabilized AMY for synthesis of Alkaloids:

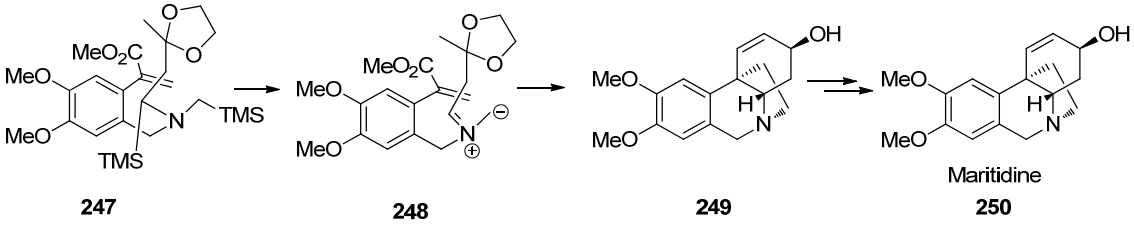
Our group have explored intramolecular [3+2]-cycloaddition strategy of non-stabilized AMY for the total syntheses[18-21] of bioactive *Amaryllidaceae* alkaloids (Scheme-34).

Scheme-34



Pandey *et al*. *Org. Lett*. **2005**, *7*, 3713–3716.

Pandey *et al*. *Eur. J. Org. Chem*. **2011**, 4571–4587.



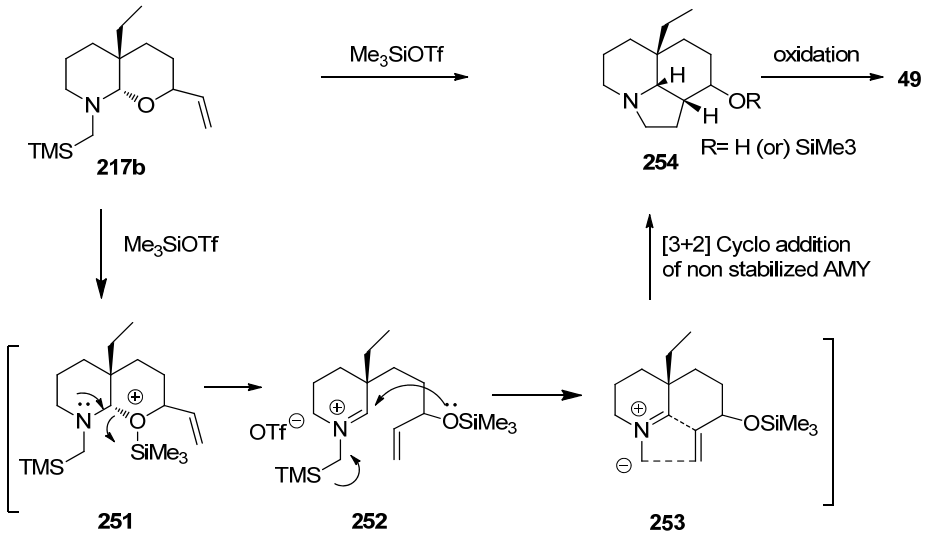
Pandey *et al*. *Org. Lett.* **2009**, *11*, 2547–2550.

Encouraged by these successes, we have planned to develop an intramolecular [3+2]-cycloaddition strategy for the construction of key precursor **49** in a single step for the synthesis of aspidosperma class of alkaloids.

2.4. Our concept: Intramolecular [3+2] cycloaddition for the construction of Tricyclic core *Aspidosperma* class of alkaloids.

The expeditious construction of **49** was visualized by the [3+2] cycloaddition of an AMY generated from **217b** which is shown in Scheme-36. It was planned that **217b** on treatment with a Lewis acid will lead to the generation of iminium ion **252** by the opening of the corresponding aminal ring and subsequent desilylation will give azomethine yilde intermediate **253** which on cycloaddition may give **254**. Oxidation of alcohol will give required tricyclic core **49** (Scheme-35).

Scheme 35



The details of synthesis along with experimental results are discussed below.

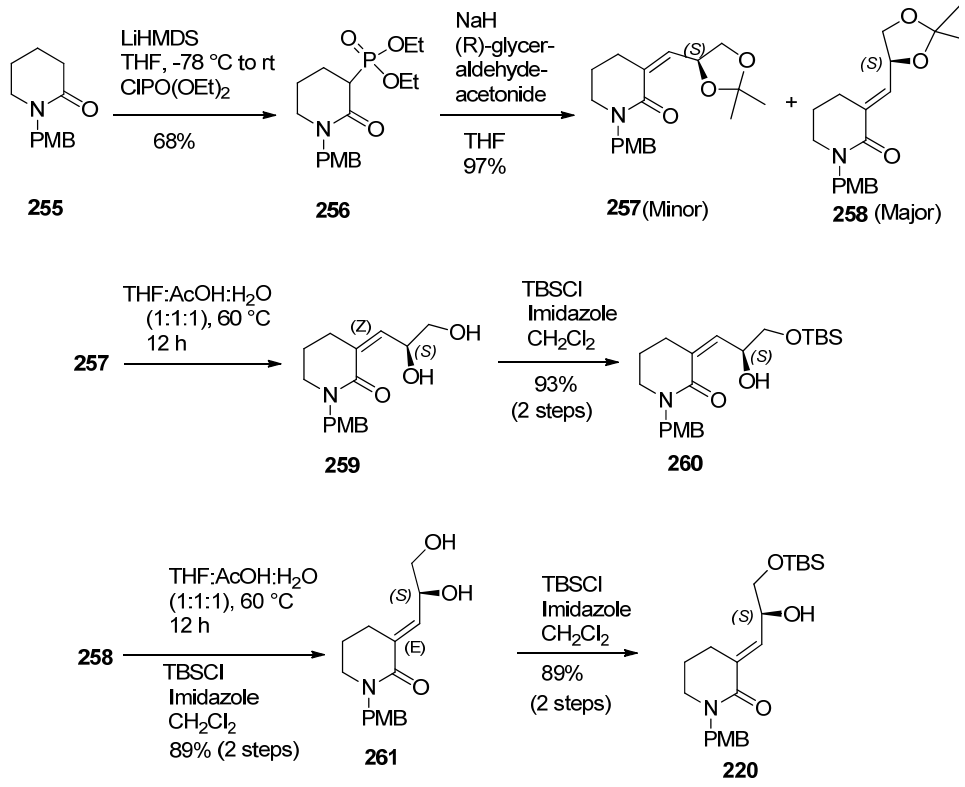
2.5. Synthesis of (-)-tricyclic core of *Aspidosperma* class of alkaloids: Total Synthesis of (+)-Aspidospermine Results and discussion:

Results and discussion:

2.5.a. Synthesis of both enantiomers of ethyl 2-(3-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-(4-methoxybenzyl)-2-oxopiperidin-3-yl)acetate (219a and 219b):

The phosphonate **256** was prepared in 68% yield from commercially available **255** by the reaction of corresponding enolate (LIHMDS, -78 °C) with chlorodiethylphosphate. Wittig-Horner olefination of **256** with (*R*)-(+)-glyceraldehyde acetonide in the presence of NaH at 0 ºC gave a mixture of **257** and **258** (2:3 ratio, 97% yield) which was purified by flash column chromotography. Both the diastereomers were separately subjected for acetonide deprotection in acidic condition (CH_3COOH:THF:H_2O = 1:1:1, 60 ºC) to obtain **259** and **261** in 95% and 92% yields, respectively (Scheme-36).

Scheme 36



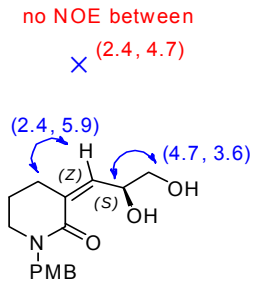
The two diastereomers **259** and **261** were characterized by detailed ^{1}H, ^{13}C, DEPT, HSQC spectral analysis.

The ^{1}H NMR spectrum of **259** showed a doublet at δ 5.96 (J = 6 Hz), integrating for one proton, which was assigned to olefinic proton (C=C-H). The multiplet at δ 4.7, integrating for one proton was assigned to (C=CH-CHOH-) proton. The (-CH-CH_2OH) proton appeared as multiplet at δ 3.65. The triplet appeared at δ 2.45 (J = 6 Hz) integrating for two protons. The PMB group characteristic protons appeared at δ 7.18 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.57 (s, 2H), 3.79 (s, 3H).

The ^{13}C NMR spectrum of **259** displayed a total of fourteen signals at δ 165.3, 159.0, 139.8, 132.3, 129.4, 128.7, 114.0, 68.8, 66.0, 55.2, 49.9, 47.3, 32.2 and 23.0. The most downfield signal δ 165.3 was assigned to lactam carbonyl carbon. The signals present at δ 139.8 (-C=CH), 132.3 (-C=CH) were assigned to olefinic carbons. The other downfield signals at δ 159.0, 129.4, 128.7, 114.0 were assigned to aromatic carbons of PMB group.

After identifying the respective protons by combined ^{1}H and ^{13}C analysis, the NOESY spectra of **259** was interpreted to confirm the geometry of the double bond. Based on the correlation of olefinic proton at δ 5.9 with allylic proton of lactam ring at δ 2.4 as shown in Figure-12 geometry of **259** was assigned as *Z*.

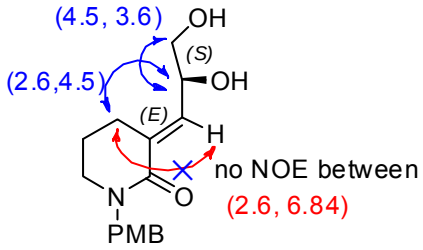
Figure-12



259

Expectedly, **261** did not show any correlation of proton appearing at 6.84 and 2.6 (Figure-13), therefore, in this molecule the olefin geometry is *E*.

Figure-13



261

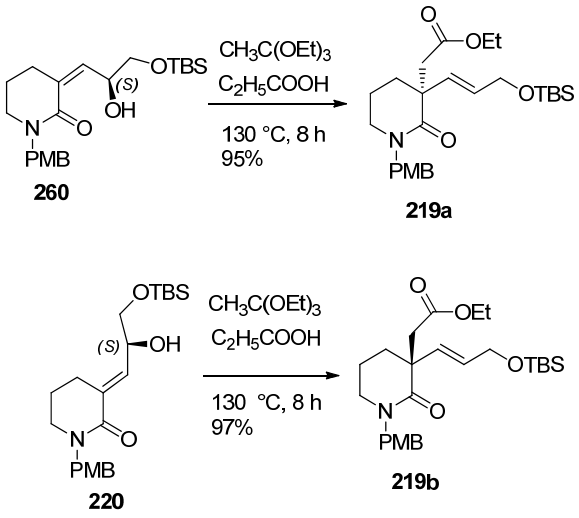
After successfully determining the olefin geometry, the primary free –OH group of these diastereoisomers **259** and **261** were protectected as –O-TBS ethers (**260** and **220)** in quantitative yields (Scheme-36).

2.5.b. 3,3-Sigmatropic Rearrangement of 260: Creation of All Carbon Quaternary Centre

Johnson- Claisen rearrangement reaction (triethyl orthoacetate, cat. propionic acid, 130 $^{\circ}C$) of **260** was successfully carried out in multi gram scale (10 gram scale, 95% yield)) to obtain **219a** (Scheme-37) in high enantiomeric excess (>99% *ee*). The enantiomeric excess was determined by chiral stationary phase HPLC using Chiralcel OD-

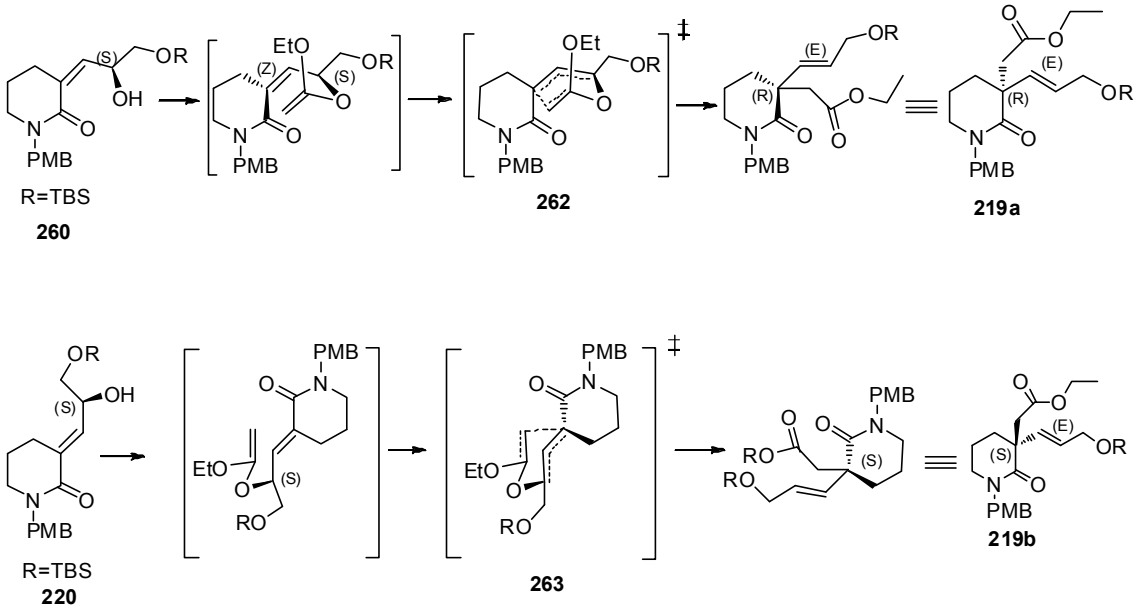
H column, and IPA: n-Hexane (10:90) as eluent (1.0 mL/min, λ = 210 nm, 25 °C). Similarly, **220** was also subjected to rearrangement to afford **219b** in 97% yield (*ee* >99% Scheme-38). The optical rotation of **219a** was measured as $[\alpha]_D^{24}$ = + 12.19 (*c* = 0.31, $CHCl_3$) whereas **219b** shows $[\alpha]_D^{24}$ = - 15.38 (*c* = 0.84, $CHCl_3$), indicating that **219a** and **219b** are enantiomers.

Scheme-37



To explain this stereoselective rearrangement, a plausible transition state (TS, **262-263**) is depicted as shown in Figure-13. It shows that the **219a** is formed by involving **262-TS** where due to the Z-geometry of the olefinic bond, the C_3−C_4 bond is formed from below the plane whereas, in **263-TS** it is clearly visualized that suprafacial attack of the incoming group forces the C_3−C_2 bond below the plane for the formation of **219b** (Figure-14). The detailed study of the role of alcohol stereochemistry and its transition states are described in our group earlier report.[39]

Figure-14



In the ^{1}H NMR spectrum of **219b**, a broad singlet at δ 5.66, integrating for two protons, was attributed to olefinic protons. The signals appeared at δ 4.1 and δ 1.24 represents ethyl group of ester. The ^{13}C NMR spectrum of **219b** displayed signals at δ 171.7 and 171.4 representing ester and lactam carbonyl carbon, respectively. IR spectrum of **219b** showed a strong absorption band at 1734 cm^{-1}, suggesting the presence of ester moiety. The mass spectrum displayed a peak at 498.2656 $[M + Na]^{+}$.

After successful synthesis of both enantiomers of chiral lactam (**219a** and **219b**), we turned our attention for the use of these compounds for the construction of **49**.

2.5.c. Synthesis of (*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-ethylpiperidin-2-one (267b):

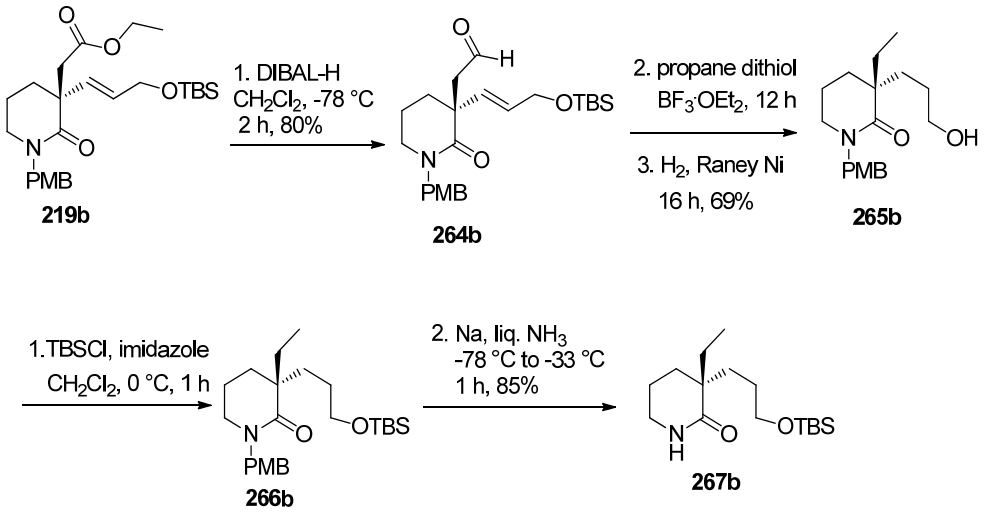
The chiral lactam **219b** in hand, we have proceeded for the formation of **267b** by simple functional group transformation as shown in Scheme-38.

219b was first reduced to its corresponding aldehyde (80% yield) by DIBAL-H at -78 ºC (Scheme-38). Dithioacetalization of the aldehyde moiety followed by reductive desulfurization (Raney Nickel, H_2, EtOH, and reflux) afforded **265b** in 69% yield.

In the ^{1}H NMR spectra of **265b**, a triplet at δ 0.87 (J = 7.4 Hz), integrating for three proton represents methyl group which was also confirmed by the DEPT NMR showing methyl peak at δ 9.08. The mass spectrum displayed a peak at 306.2066 $[M + H]^+$.

The protection of **265b** as -OTBS followed by PMB deprotection[40] using (Na/liq.NH_3) produced **267b** in 85% yield over 2 steps (Scheme-38).

Scheme-38



The ^{1}H NMR spectrum of **267b** showed a characteristic peak at δ 6.04 for (CH_2-N<u>H</u>-C=O) proton as broad singlet. The mass spectrum of **267b** displayed m/z 300.2349 ($M+H^+$).

Having **267b** in hand, we have proceeded for the synthesis of key cycloaddition precursor **217b** by following the steps as described below.

2.5.d. Synthesis of Bicyclic aminal 217b:

First generation approach for synthesis of Bicyclic aminal:

N-alkylation of **267b** with $TMSCH_2Cl$ in presence of NaH and TBAB produced **268** in 80% yield which on stirring in methanol under acidic conditions (PTSA, MeOH, 0 °C) gave the corresponding alcohol. Dess-Martin Periodinane oxidation of this alcohol in dichloromethane gave **269** in 77% overall yield (Scheme-39). Vinylation of **269** using vinyl magnesium bromide in diethylether at -78 °C afforded **270** as a mixture of two diastereomers (1:1) in 85% yield.

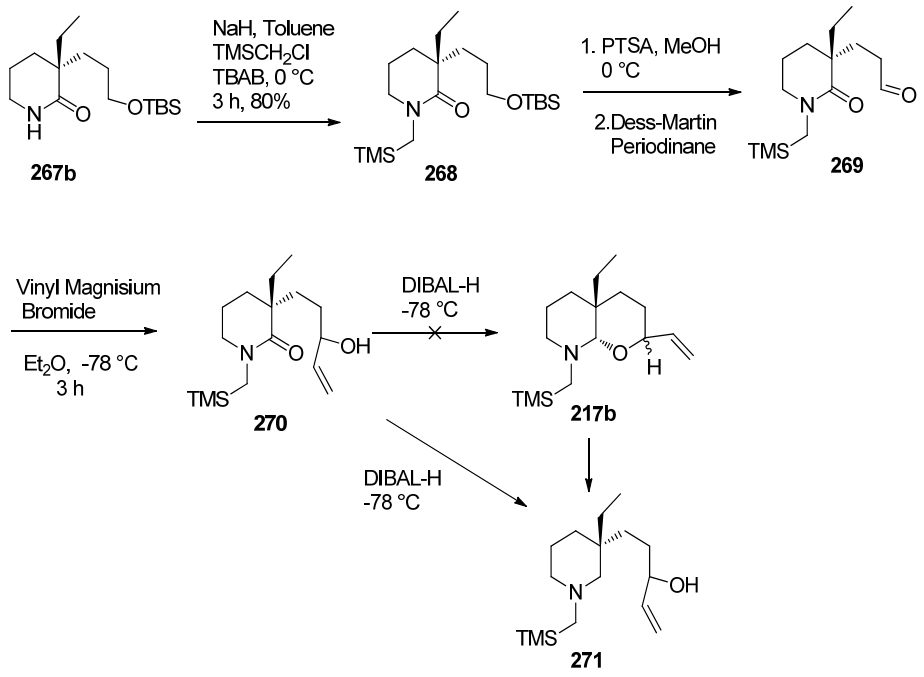
The ^{1}H NMR spectrum of **270** showed three newly generated olefinic protons at δ 5.82, 5.2 and 5.06 as multiplets which were assigned to (CH-CH=C<u>H</u>$_2$), (CH-CH=C<u>H</u>$_2$) and (CH-CH=C<u>H</u>$_2$), respectively. The signal at δ 4.0, integrating for one proton, was assigned to allylic proton (HO-C<u>H</u>-CH=CH$_2$). The methyl protons of TMS group shifted up field and appeared as a sharp singlet at δ 0.05.

The signals at δ 173.6, 173.5 in ^{13}C NMR spectrum of the **270** (diastereomeric mixture) were attributed to the lactam carbonyl. In this spectrum the characteristic olefinic carbons were observed as set of two signals at (δ 141.3, δ 141.1) and (δ 114.3, δ 114.2).

The mass spectrum of **270** displayed m/z 270.1884 ($M+H^+$).

It was presumed beforehand that partial reduction of the lactam carbonyl group of **270** to iminium ion followed by subsequent cyclisation with tethered alcohol will produce bicyclic aminal intermediate. However, to our dismay it underwent over reduction to form **271**. Evaluation of different reaction conditions with DIBAL-H remained unfruitful. Even reduction using $LiAlH_4$ in ether at -40 - 0 °C also gave the same unexpected product **271** (Scheme-39).

Scheme-39



The undesired product **271** was characterized by ^{13}C NMR studies which showed disappearance of lactam carbonyl peaks at δ 173.6, 173.5 (diasteromeric peaks) and appearance of peaks at δ 67.34, 67.14 and δ 59.23 indicating the presence of (-$\underline{C}H_2$-N-$\underline{C}H_2$-) and (-N$\underline{C}H_2$-TMS).

The mass spectrum (m/z 298.2201 ($M+H^+$)) confirmed complete reduction of amide group.

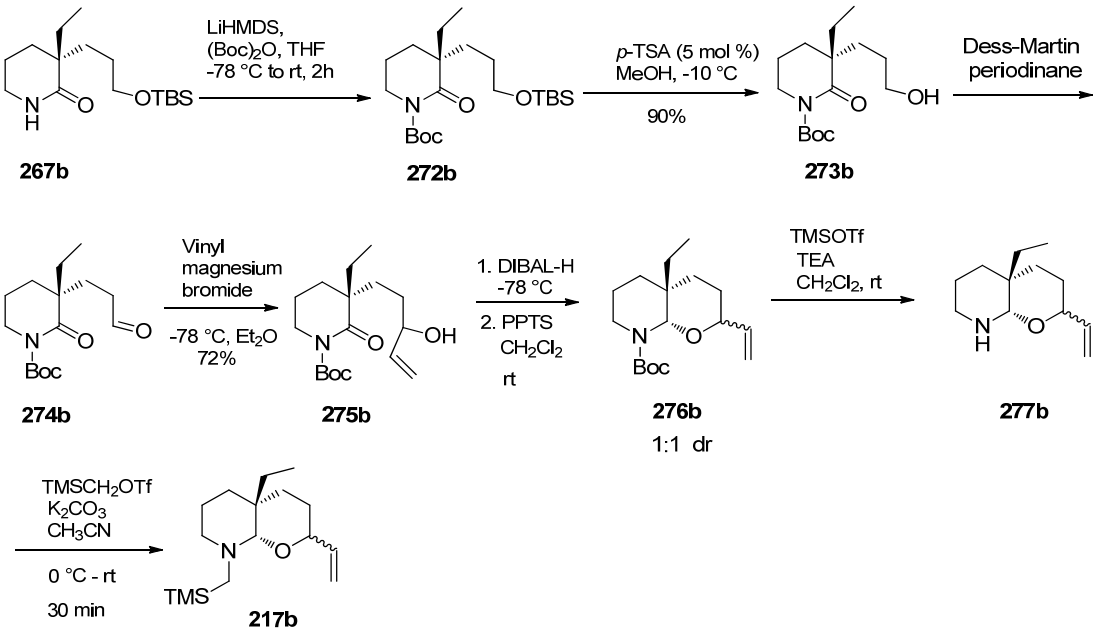
These unexpected results, led us to investigate new synthetic route to access **217b** which is described as follows.

Second Generation approach for synthesis of Bicyclic aminal:

An alternative strategy for the transformation of **267b** to **217b** was worked out as shown in Scheme-41. *N*-Boc protection of **267b** with $(Boc)_2O$ using LiHMDS afforded **272b** from which -OTBS ether group was deprotected using catalytic amount of *p*-TSA in MeOH at -10 ºC (90% yield). Oxidation of **273b** using Dess-Martin periodinane in CH_2Cl_2 at 0 ºC for 30 min produced **274b** (96 % yield) Scheme-41.

Vinylation **274b** by treating it with vinyl magnesium bromide afforded **275b** in 72% yield (Scheme-40) which on reduction with DIBAL-H at -78 ºC resulted into corresponding hemiaminal. Treatment of **275b** with PPTS in dichloromethane at room temperature furnished **276b** as a mixture of diastereomers (1:1). Careful *N*-Boc-deprotection of **276b,** using TMSOTf and trimethylamine, gave bicyclic amine **277b** (Scheme-40).

Scheme-40



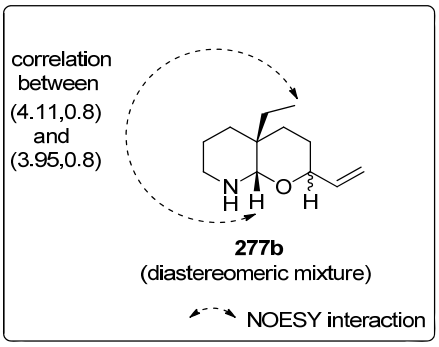
The ^{1}H NMR spectrum of **277b** (diastereomeric mixture) showed three multiplets at δ 5.9, 5.25 and 5.1, integrating for one proton each, were assigned to the olefinic protons. A set of singlet protons at δ 4.11, 3.95, each with 0.5 proton integration value in 1:1 ratio, were attributed to the (-HN-C<u>H</u>-O-) proton. Another set of multiplets at δ 4.56, 3.82, each with 0.5 proton integrating value in 1:1 ratio, were assigned to (-O-C<u>H</u>-CH=CH$_2$) proton. The signal as a multiplet at δ 0.8 integrating for three protons was assigned to (-CH$_2$-C<u>H</u>$_3$).

The ^{13}C NMR spectrum of **277b** (diastereomeric mixture) displayed a set of two carbon signals at (δ 139.4, 139.3) and (δ 115.2, 114.5) which were attributed to olefinic carbons (O-<u>C</u>H=CH$_2$, O-CH-<u>C</u>H$_2$), respectively. The two downfield signals at δ 90.03 and δ 70.72 were assigned to (-HN-<u>C</u>H-O-) and (-O-<u>C</u>H-CH=CH$_2$) carbons, respectively.

The mass spectrum of **277b** displayed the peak at m/z 196.1708 $[M + H]^+$.

The stereochemical assignments of **277b** (diastereomeric mixture), as shown in Figure-14, are based on NOESY NMR spectral studies. The NOSEY cross peaks were observed between (δ 4.11, 0.8) and (δ 3.95, 0.8) which are corresponding to the interaction of (-HN-C<u>H</u>-O-) proton with (-CH$_2$-C<u>H</u>$_3$). These observations revealed the stereochemistry of **277b** as shown in Figure-15. (See page no. 164 for NOESY spectrum of **277b**).

Figure-15



N-Alkylation of **277b** with $TMSCH_2OTf$ in the presence of anhydrous K_2CO_3 resulted in the formation of *N*-(trimethylsilyl methyl) aminal **217b** (Scheme-41) which was characterized by mass spectrum (m/z 282.2246 $[M + H]^+$).

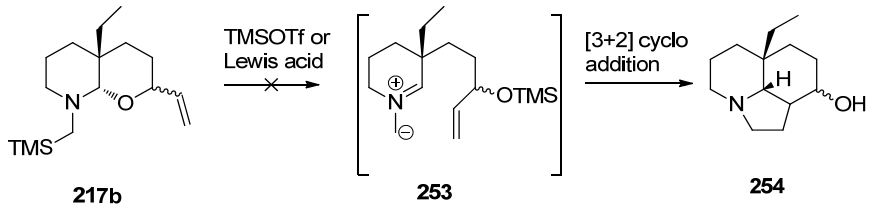
2.5.e. Synthesis of Tricyclic core (-)-49:

First generation approach for [3+2] cycloaddition:

Once **217b** in hand, it was presumed that if this bicyclic aminal is treated with a Lewis acid, the aminal ring would open to give iminium ion that subsequently would undergo desilylation to give an azomethane yilde **253**. Subsequent, intramolecular cycloaddition of this with tethered dipolarophile may give tricyclic core **254** (Scheme-41).

Excited with this planning, we carried out an initial study of intramolecular [3+2] cycloaddition **217b** which began in the presence of different Lewis acids (Scheme-41). Initial reaction with the treatment of TMSOTf at various temperatures (-78 ˚C to rt) in DCM (entries 1-2, Table-3) unfortunately, did not result any product albeit only starting material remained as such. The addition of CsF to accelerate desilylation process for azomethine ylide generation also did not succeed. Surprisingly, the reaction in the presence of TFA as well as TfOH led to the decomposition of reaction mixture. Furthermore, even in the presence of $BF_3{\cdot}OEt_2$ at different reaction conditions did not lead to any product formation. Unfortunately, all our attempts to generate azomethine ylide from aminal **217b** failed (Table-3).

Scheme-41



217b **253** **254**

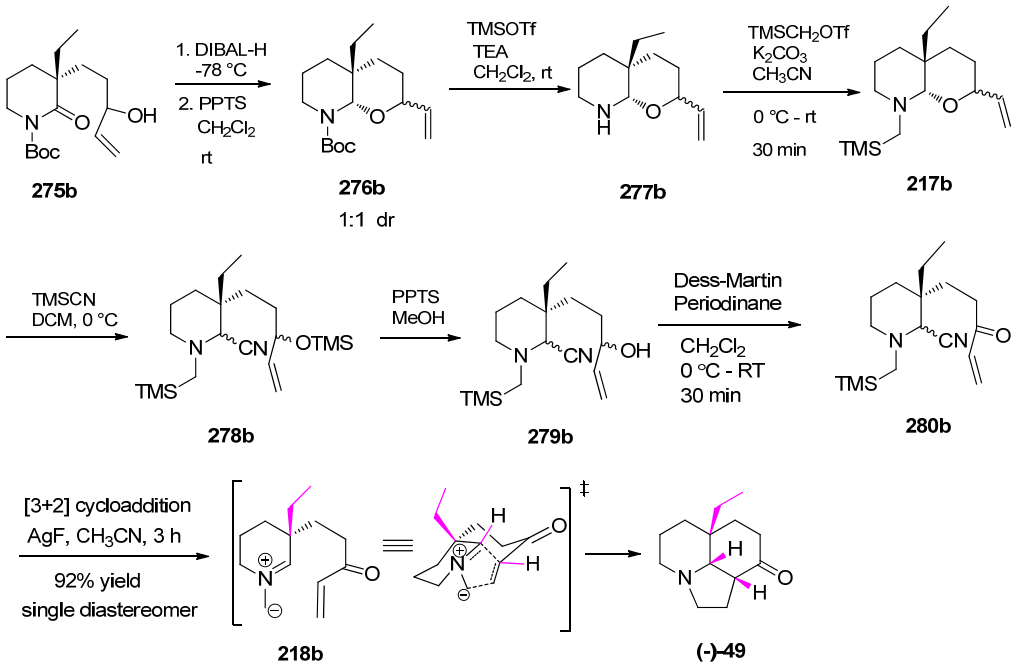
Table-3

S.No	Reaction Conditions	**Inference**
1.	TMSOTf, DCM, -78 ˚C	SM recovered
2.	TMSOTf, DCM, -78 ˚C to rt	SM recovered
3.	TMSOTf, CsF, -78 ˚C to rt	SM recovered
4.	TFA, DCM, -20 ˚C	Decomposed
5.	TfOH, DCM, -78 ˚C to rt	Decomposed
6.	$BF_3{\cdot}OEt_2$, DCM, -78 ˚C	SM recovered
7.	$BF_3{\cdot}OEt_2$, DCM, -78 ˚C to rt	SM recovered

Second generation approach for [3+2] cycloaddition:

This unanticipated setback led us to explore an alternative strategy for generating non stabilized azomethane ylide from **280b** as shown in Scheme-42. The transformation of **275b** to **280b** was carried out without any purification and obtained overall 73% yield over seven steps.[41] (Scheme-42).

Scheme-42



Treatment of **217b** with TMSCN at 0 ºC in dichloromethane followed by subsequent -OTMS ether deprotection and oxidation produced **280b** (Scheme-42).

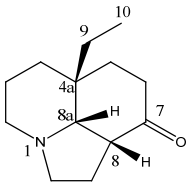
The ^{1}H NMR spectrum of **280b** (diastereomeric mixture) displayed three olefinic protons of enone (O=C-C<u>H</u>=C<u>H</u>$_2$) moiety as multiplets at δ 6.4, 6.3 and 5.8, respectively. The singlets appearing at δ 3.41, 3.38, each integrating for 0.5 proton in 1:1 ratio, were attributed to the (-HN-C<u>H</u>-CN) proton.

The most downfield signals in the ^{13}C NMR spectrum at δ 200.0, 199.8 were assigned to the carbonyl carbon of enone (O=<u>C</u>-CH=CH$_2$). The signals at (δ 136.2, 136.1) and (δ 128.4, 128.1) were assigned to the olefin carbons (O=C-<u>C</u>H=<u>C</u>H$_2$), respectively. The nitrile carbon signals (-HN-CH-<u>C</u>N) appeared at δ 115.5, 115.3.

The IR spectrum displayed a strong absorption peak at 1682 cm^{-1}, indicating the presence of α,β-unsaturated carbonyl functional group.

The mass spectrum showed m/z at 307.2199 (M+H^{+}).

Stirring of this compound with AgF in acetonitrile at room temperature (3 h) which, to our delight, produced (-)-**49** as a single diastereomer in 92% isolated yield (Scheme 42). The formation of **(-)-49** obviously involved the [3+2] cycloaddition[42-43] of non-stabilized azomethine ylide **218b** with tethered enone.

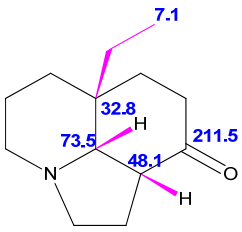


This product was characterized by detailed spectral analyses. For example, in proton NMR, methyl protons (-CH_2-$C\underline{H}_3$, H_{10}) appeared as a triplet at δ 0.94 (J = 7.6 Hz). The proton signal appeared at δ 1.32 (J = 7.4, app sextet) was assigned to (-$C\underline{H}_2$-CH_3, H_9) proton. The protons signal appeared at 2.67 (ddd, J = 7.4, 5.5 Hz, 1H) was attributed to (-$C\underline{H}$-C=O, H_8) proton.

The ^{13}C NMR displayed a total of thirteen signals at δ 211.5, 73.5, 53.2, 52.9, 48.1, 36.8, 34.7, 32.8, 30.1, 26.0, 21.3, 21.2 and 7.1. The signal at δ 211.5 was assigned to the carbonyl moiety (-$\underline{C}$=O, C_7), and the most up field signal at δ 7.1 was assigned to the methyl carbon (-CH_2-$\underline{C}H_3$, C_{10}).

From the combined ^{13}C NMR and DEPT analysis it was revealed that the two methine (-$\underline{C}$H-) carbon signals appeared at δ 73.5 and δ 48.1 which were attributed to the (-N-$\underline{C}$H-, C_{8a}) and (-$\underline{C}$H-C=O, C_8), respectively. The absence of signal at δ 32.8 in DEPT NMR indicates this signal belonging to the quaternary carbon (C_{4a}) whereas, the remaining eight methylenic peaks were observed at δ 53.2, 52.9, 36.8, 34.7, 30.1, 26.0, 21.3 and 21.2.

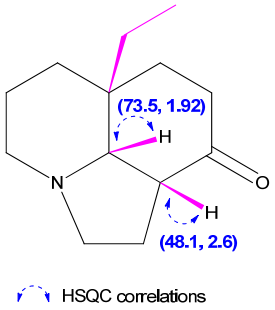
Figure-16



Assignment of carbon δ values based on combined ^{13}C and DEPT NMR analysis

The HSQC spectrum reveals that (i) the carbon signal δ 73.5 (-N-CH-, C_{8a}) having correlation with the proton appearing at δ 1.92. (ii) another carbon signal at δ 48.1 (-CH-C=O, C_8) correlates with the proton appearing at δ 2.6. From these two HSQC correlations, protons appearing at δ 1.92 was assigned to (-N-CH-, H_{8a}) and proton at δ 2.6 to (-CH-C=O, H_8) (Figure-17).

Figure-17



After assigning key protons chemical shifts, the NOESY spectrum correlations were also analysed which are as follows:

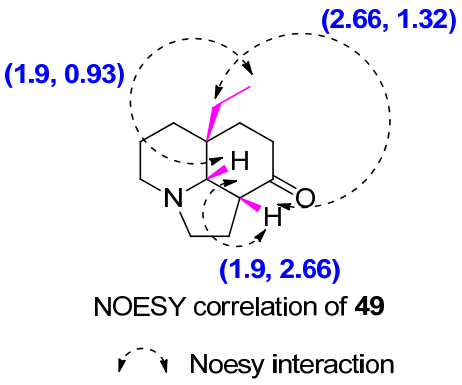
(i) the proton signal at δ 1.9 (H_{8a}) having strong correlation with δ 2.66 (H_8)

(ii) the proton signal at δ 1.9 (H_{8a}) also displayed strong correlation with δ 0.93 (H_{10})

(iii) proton at δ 2.66 (H_8) showed a weak correlation with δ 1.32 (H_9)

Based on these correlations, it can be suggested that H_8, H_{8a}, H_9 and H_{10} protons are in *cis*- relation and the stereochemistry of **(-)-49** is as per the structure shown in Figure-18 {see page no 174-175 for NOESY spectrum of **(-)-49**}.

Figure-18

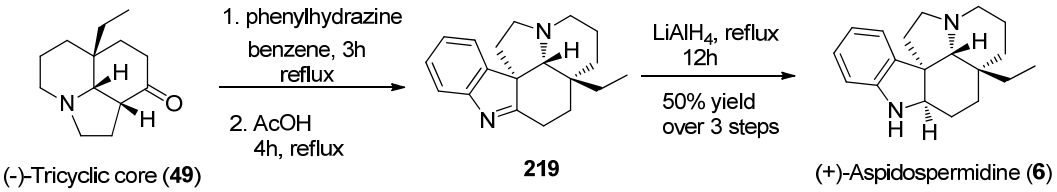


The IR spectrum displayed a strong absorption peak at 1709 cm^{-1}, indicating the presence of ketone carbonyl functional group. The assigned structure was confirmed by the mass spectrum molecular ion peak at [m/z 208.1693 ($M+H^+$)]. The optical rotation was found to be: $[\alpha]_D^{24}$ = -23.81 (*c* 0.5, $CHCl_3$) which is in agreement with the reported values [Lit[8b] value $[\alpha]_D^{29}$ = -24.4 (*c* 0.88, $CHCl_3$)].

2.5.f. Synthesis of (+)-Aspidospermidine through Fischer indole synthesis:

The successful construction of (-)-**49** by the steps as discussed above led us to confirm its structure beyond doubt by converting to (+)-**6** by following the known procedure.[7a] In this context, (-)-**49** (0.035 g, 0.168 mmol) was heated to reflux with phenylhydrazine (0.022 g, 0.202 mmol) in benzene for 3 h form corresponding phenyl hydrazine. Crude hydrazone was dissolved in 5 mL glacial acetic acid and refluxed for 4 h, concentrated to dryness to obtain crude **219** as a brown color liquid. Reduction of **219** by with $LiAlH_4$ (0.059 g, 1.68 mmol) in THF (5 mL) produced (+)-**6** (Scheme 44).

Scheme-44



The structure of (+)-**6** was fully characterized by detailed NMR analysis (800 MHz, $CDCl_3$) and also by comparing its optical rotation $[\alpha]_D^{24}$ = +20.14 (*c* = 0.5, EtOH) with the reported value.[7c] {see page no. 175-182 for all spectral data of (+)-**6**}.

In the ^1H NMR spectrum, the four aromatic protons appeared at δ 7.09 (d, *J* = 7.5 Hz, 1H), δ 7.02 (td, *J* = 7.5, 0.95 Hz, 1H), δ 6.74 (t, *J* = 7.3 Hz, 1H), δ 6.65 (d, *J* = 7.5 Hz, 1H), respectively. The key characteristic H_{21} proton appeared as singlet at 2.23 (s, 1H), whereas the other characteristic H_2 proton appeared as doublet of a doublet at δ 3.52 (dd, *J* = 11.3, 6.3 Hz, 1H). The most up field methyl protons ($-CH_2C\underline{H}_3$) appeared as a triplet at 0.64 (t, *J* =7.5 Hz, 3H).

In ^{13}C NMR, the carbon signals appearing at δ 149.8, 136.1, 127.5, 123.3, 119.4 and 110.7 corresponds to the aromatic carbons. The combined ^{13}C and DEPT NMR analysis revealed that the two methylinic carbon signals appeared at δ 71.3, 65.7 which

were corresponding to the C_{21} and C_2 carbons, respectively. The carbon signal δ 6.8 was assigned to methyl carbon (-$CH_2\underline{C}H_3$).

The spectral data of (+)-**6** was found to be in excellent agreement with the values in literature.[7a,7c] The comparative spectral data for (+)-**6** with reported values[7a,7c] are given in Table-4.

Table 4: Comparative data for compound (+)-6

Compound **(+)-6** (Observed)	Literature data[7a,7c] for Compound **(+)-6**
^{1}H NMR (800MHz ,$CDCl_3$): δ 7.09 (d, *J* = 7.5 Hz, 1H), 7.02 (td, *J* = 7.5, 0.95 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 3.52 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.15 - 3.11 (m, 1H), 3.08 - 3.04 (m, 1H), 2.33 - 2.28 (m, 1H), 2.28 - 2.24 (m, 1H), 2.23 (s, 1H), 1.99 - 1.92 (m, 2H), 1.74 (qt, *J* = 13.04, 4.06 Hz, 1H), 1.67 - 1.62 (m, 2H), 1.54 - 1.46 (m, 3H), 1.43 - 1.36 (m, 1H), 1.12 (td, *J* = 13.7, 4.8 Hz, 1H), 1.06 (dt, *J* = 13.6, 3.8 Hz, 1H), 0.90 - 0.85 (m, 1H), 0.64 (t, *J* =7.5 Hz, 3H).	**^{1}H NMR (400 MHz, $CDCl_3$) :** δ 7.10 (d, *J* =7.3 Hz, 1H), 7.04 (td, *J* = 7.6, 0.9 Hz, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 3.53 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.14 (m, 1H), 3.08 (m, 1H), 2.37-2.22 (m, 2H), 2.24 (s, 1H), 1.97 (m, 2H), 1.76 (qt, *J*= 12.8, 3.9 Hz, 1H), 1.66 (m, 2H), 1.57-1.36 (m, 4H), 1.13 (td, *J* =13.5, 4.6 Hz, 1H), 1.07 (m, 1H), 0.88 (m, 1H), 0.66 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (201 MHz, $CDCl_3$): δ 149.4, 135.7, 127.0, 122.8, 119.0, 110.3, 71.3, 65.7, 53.9, 53.3, 53.0, 38.8, 35.6, 34.4, 30.0, 28.1, 23.0, 21.7, 6.8.	**^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.8, 136.1, 127.5, 123.3, 119.4, 110.7, 71.7, 66.1, 54.3, 53.8, 53.5, 39.2, 36.0, 34.9, 30.4, 28.5, 23.4, 22.2, 7.2.
HRMS (ESI): *m/z* found: 283.2167 $[M + H]^+$	**HRMS** (ESI): Calculated for $[M + H]^+$ $C_{19}H_{27}N_2$: 283.2174,
Melting Point: 118-120 °C. (observed)	**Melting Point [7c]:** 117-119 °C. (Literature)
Optical Rotation: $[\alpha]^{D}_{24}$ = +20.14 (*c* = 0.5, EtOH).	Lit[7a] **$[\alpha]^{D}_{29}$** = +20.6 (*c* = 0.64, EtOH).

2.6. Synthesis of (+)-tricyclic core of *Aspidosperma* class of alkaloids.

Introduction:

Aspidosperma class of alkaloids are naturally available in the both enantiomeric forms[1] (*i.e.*, as C_7, C_{21} and C_{22} centers are converse). However, there are only few articulated methods that can access both[44] the enantiomers of these alkaloids. Since tricyclic ketone **49** represents the basic skeleton from which either of its enantiomers can be synthesized (Figure 19). Therefore, constructing another optical isomer of **(+)-49** was considered from **219a**. This was envisioned that such types of exercise would also serve as paramount importance for the synthesis of a large number of aspidosperma class of alkaloids as shown in Figure.19 and 20.

Figure-19

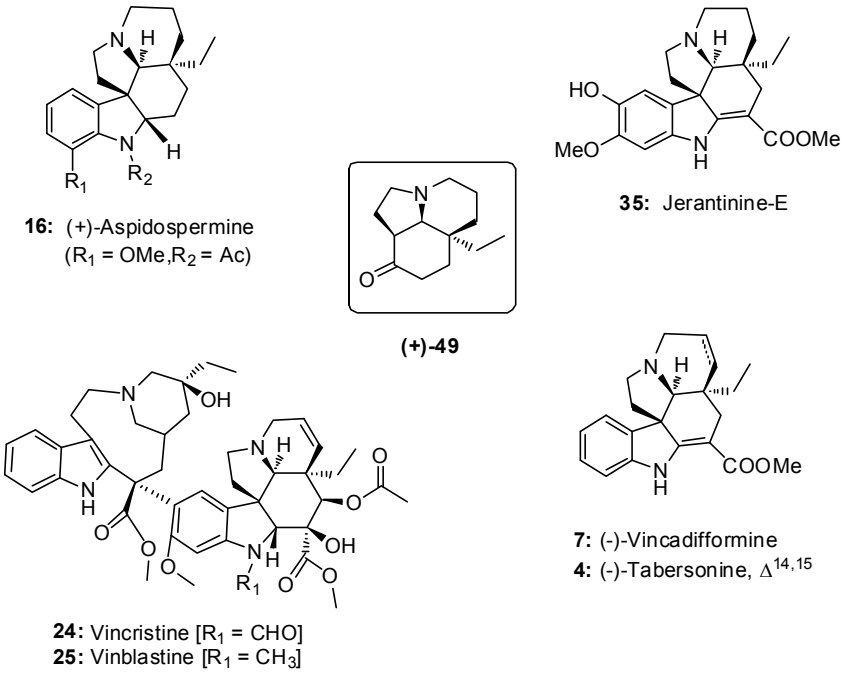
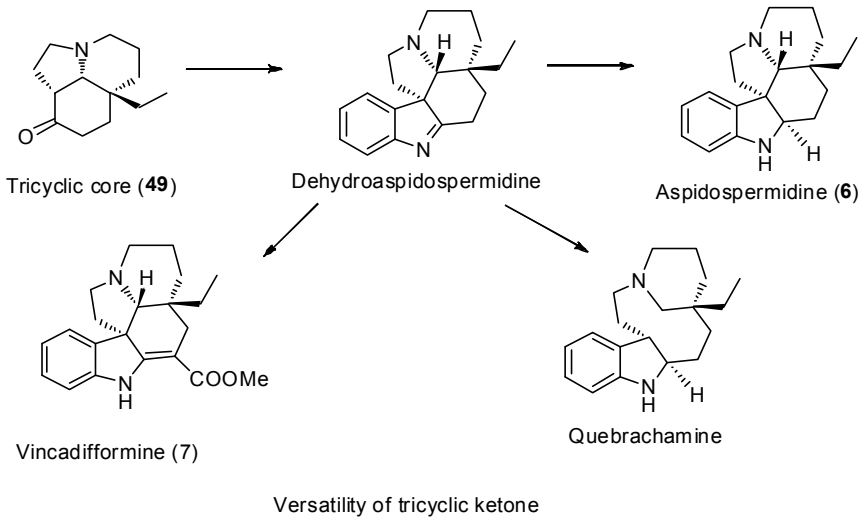
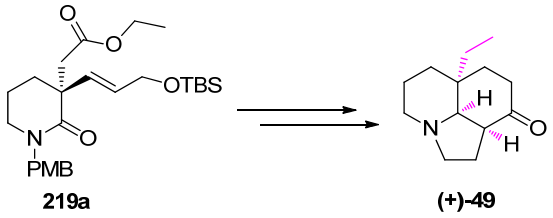


Figure-20

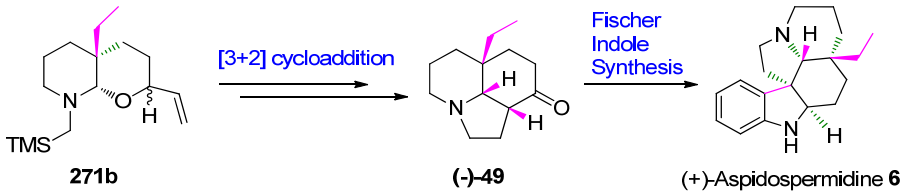


Identical reaction was carried out, as described in Section-A, starting from **219a** to accomplish the synthesis of **(+)-49** (Figure-21). The optical rotation of (+)-**49** was found to be $\{[\alpha]_D^{24} = +21.62$ (*c* 0.5, $CHCl_3)\}$. The NMR spectral data and analytical data of **(+)-49** are in good agreement with the reported values.

Figure-21



2.7. Summary:



In conclusion, we have successfully developed an efficient and conceptually new synthetic route for the construction of (-)-**49** utilizing intramolecular [3+2]-cycloaddition of non-stabilized azomethine ylide. The azomethine ylide was generated from a designed bicyclic aminal **271b**. Synthesis of (+)-**49** was also accomplished by using same strategy. The success of this strategy was demonstrated by carrying out the total synthesis of (+)-aspidospermidine using Fischer indole synthesis.

2.8. REFERENCES

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CHAPTER-3

EXPERIMENTAL

General Experimental Methods:

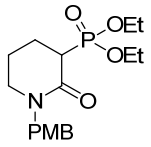
All anhydrous reactions were performed under argon atmosphere and hot air oven dried glassware (110 ºC) were used. Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns and was dried by distillation over sodium / benzophenone. Benzene, toluene, acetonitrile and dichloromethane (DCM) were distilled over calcium hydride and stored over 4Å molecular sieves. Triethylamine (TEA) was distilled over potassium hydroxide. All the solvents used for chromatography were distilled at respective boiling points using known procedures.

All commercial reagents were obtained from Sigma-Aldrich and Spectrochem, India. Progress of the reactions was monitored by thin layer chromatography (0.25 mm Merck 60F254 silica gel plates) and visualized by using UV light, ethanolic solution of phosphomolybdic acid, iodine and $KMnO_4$ solution. Column chromatography was performed on silica gel 60-120/100-200/ 230-400 mesh obtained from Spectrochem Fine Chemical Co. India or LOBA India. Typical syringe and cannula techniques were used to transfer air and moisture sensitive reagents.

All melting points were recorded on a BUCHI melting point M-560 apparatus and were uncorrected in degree Celsius. IR spectra were recorded on a Perkin-Elmer FT-Infrared Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on BRUKER 800 UltraShield PLUS and BRUKER 400 ULTRA SHIELD instruments operating at 800 MHz, 400 MHz and 201 MHz, 101 MHz respectively using deuteriated solvent. Chemical shifts are reported in δ ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, doublet; t, triplet; dd, doublet of doublet; dt, doublet of triplet; td, triplet of doublet; m, multiplet). ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.00). Electro spray ionization (ESI) mass spectrometry (MS) experiments were performed on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. Optical rotations were measured on a Digipol 781 M6U Automatic Polarimeter. HPLC were performed on Agilent Technologies 1260 Infinity.

3.1 EXPERIMENTAL PROCEDURES AND SPECTRAL DATA

1. Synthesis of Diethyl (1-(4-methoxybenzyl)-2-oxopiperidin-3-yl)phosphonate (256) :



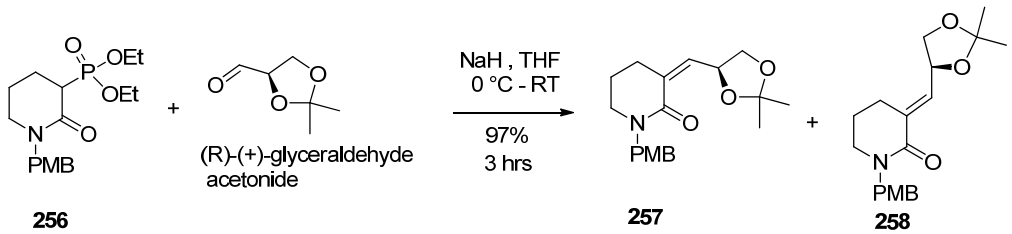
256

To a cooled (- 78 °C) stirring solution of 1-(4-methoxybenzyl) piperidin-2-one (**255**) (15.0 g, 0.068 mol) in THF (200 mL), LiHMDS (75 mL, 1M) solution was added. After 1 h of stirring, diethyl chlorophosphate (10.9 mL, 0.075 mol) was added drop wise to the reaction mixture. The reaction mixture was slowly allowed to warm to room temperature and was continued for overnight. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride, extracted with EtOAc (3×200 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated. The crude compound was purified by column chromatography (SiO_2, ethylacetate - hexane, 3:7→10:0) to obtain **256** (16.6 g, 68%) as a light yellow oil.

Yield	**:**	68%
IR υ_{max} cm^{-1} (KBr)	**:**	2981, 2935, 2910, 1636, 1512, 1491, 1443, 1296, 1246, 1175, 1028, 967
^{1}H NMR ($CDCl_3$, 800 MHz) δ	**:**	7.21 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.64 (d, *J* = 14.9 Hz, 1H), 4.49 (d, *J* = 14.5 Hz, 1H), 4.29 - 4.09 (m, 4H), 3.79 (s, 3H), 3.28-3.24 (m, 1H), 3.21 - 3.15 (m, 1H), 3.10 - 3.02 (m, 1H), 2.24 - 2.16 (m, 1H), 2.13 - 2.01 (m, 2H), 1.72 - 1.66 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	164.9, 158.9, 129.3, 129.0, 114.0, 63.0, 62.0, 55.2, 49.8, 46.9, 42.5, 41.1, 23.2, 21.4, 16.4, 16.3.

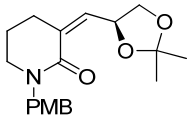
HRMS (m/z)	**:**	378.1457 [(M + Na)$^+$; calcd for ($C_{17}H_{26}NO_5PNa)^+$ 378.1446]

2. Synthesis of (*S,Z*)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-1-(4-methoxybenzyl) piperidin-2-one (257):



256 **257** **258**

To a stirred solution of NaH (2.48 g, 61.91 mmol, 60% dispersion in oil) in THF (75 mL) at 0 ºC, was added diethyl (1-(4-methoxybenzyl)-2-oxopiperidin-3-yl)phosphonate (**256**) (20.0 g, 56.28 mmol) in THF (75 mL). After 15 min, a solution of (*R*)-(+)-glyceraldehyde acetonide (7.69 g, 59.09 mmol) in THF (50 mL) was added drop wise into the flask. The reaction mixture was allowed to warm to room temperature and further stirred for 3 hours and quenched with saturated NH_4Cl solution. The mixture was extracted with ethylacetate (150 mL × 3), dried over Na_2SO_4 and concentrated. The crude on purification by column chromatography (using ethylacetate – hexane 1:9→3:7 gradient) afforded pure **257** and **258** in 4:6 ratio with combined yield of 97 % (18.1 g).



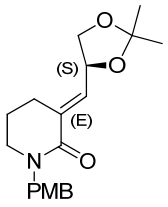
257

Yield	**:**	39 %
TLC	**:**	R_f = 0.6 (ethylacetate : hexane = 3 : 7)
Optical rotation	**:**	$[\alpha]_D^{26}$ = + 104.94 ($CHCl_3$, *c* = 0.79)
IR υ_{max} cm^{-1}	**:**	3439, 3008, 2936, 1733, 1662, 1613, 1512, 1247
^{1}H NMR ($CDCl_3$, 800 MHz) δ	**:**	7.17 (d, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 7.4 Hz, 2H), 5.93 (d, *J* = 6.3 Hz, 1H), 5.59-5.56 (m, 1H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.64 (t, *J* = 7.7 Hz, 1H), 4.42 (d, *J* = 14.5 Hz, 1H), 3.79 (s, 3H), 3.68 - 3.63 (m, 1H), 3.23 (t, *J* = 5.9 Hz, 2H), 2.54 - 2.43 (m, 2H),

		1.90 - 1.84 (m, 1H), 1.83 - 1.75 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H)
^{13}C NMR (CDCl$_3$, 101 MHz) δ	**:**	164.0, 158.9, 140.4, 130.3, 129.2, 129.1, 113.9, 109.0, 74.4, 70.2, 55.2, 49.4, 47.1, 31.6, 26.7, 25.3, 23.2
HRMS (m/z)	**:**	354.1675 [(M + Na)$^+$ calcd for $(C_{19}H_{25}NO_4Na)^+$: 354.1681]

3. Synthesis of (*S,E*)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-1-(4-methoxy benzyl) piperidin-2-one (258):

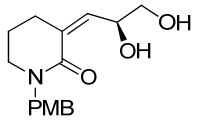
Above mentioned procedure used for the synthesis of **258**.



258

Yield	**:**	58%
TLC	**:**	R_f = 0.4 (ethylacetate : hexane = 3 : 7)
Optical rotation	**:**	$[\alpha]_D^{26}$ = -9.58 ($CHCl_3$, *c* = 1)
IR υ_{max} cm^{-1}	**:**	3440, 2986, 2935, 1665, 1613, 1512, 1246
^{1}H NMR (CDCl$_3$, 800 MHz) δ	**:**	δ 7.20 (d, *J* = 7.4 Hz, 2H), 6.88 - 6.82 (m, 3H), 4.85 - 4.78 (m, 1H), 4.63 (d, *J* = 14.1 Hz, 1H), 4.56 (d, *J* = 14.5 Hz, 1H), 4.12 (t, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.69 (t, *J* = 7.9 Hz, 1H), 3.29 - 3.23 (m, 2H), 2.73 - 2.65 (m, 1H), 2.46 - 2.37 (m, 1H), 1.81-1.78 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H)
^{13}C NMR (CDCl$_3$, 101 MHz) δ	**:**	163.8, 158.9, 134.3, 132.6, 129.4, 129.2, 113.9, 109.6, 72.2, 68.7, 55.2, 50.4, 46.7, 26.5, 25.9, 25.0, 22.5
HRMS (m/z)	**:**	354.1676 [(M + Na)$^+$ calcd for $(C_{19}H_{25}NO_4Na)^+$: 354.1681]

4. Synthesis of (*S, Z*)-3-(2,3-dihydroxypropylidene)-1-(4-methoxybenzyl)piperidin-2-one (259):



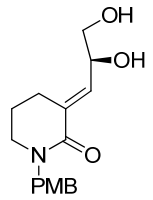
259

To a stirred solution of acetonide protected compounds (15 g, 45.26 mmol) in THF (75 mL) was added glacial acetic acid (75 mL) followed by water (75 mL) at room temperature. The resulting mixture was heated at 60 ºC for overnight. The reaction mixture was allowed to cool to room temperature, concentrated to dryness and crude was neutralized with minimum amount of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate (3×200 mL), dried over Na_2SO_4 and concentrated. Purification by column chromatography (using ethyl acetate - hexane 2:8→10:0 gradient) resulted corresponding diol in excellent Yield.

Yield	**:**	95 %
TLC	**:**	R_f =0.4 (ethyl acetate : hexane = 8 : 2)
Optical rotation	**:**	$[\alpha]_D^{23}$ = - 61.38 ($CHCl_3$, c = 1.03)
Melting point	**:**	95-96 ºC
IR υ_{max} cm^{-1}	**:**	3380, 2932, 1610, 1511, 1490, 1246
^{1}H NMR ($CDCl_3$, 800 MHz) δ	**:**	δ 7.18 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.96 (d, *J* = 6.0 Hz, 1H), 5.60 (br s, 1H), 4.78 - 4.70 (m, 1H), 4.57 (s, 2H), 3.79 (s, 3H), 3.76 - 3.61 (m, 2H), 3.30 - 3.22 (t, *J* = 6.2 Hz, 2H), 3.25 (br s, 1H), 2.52 - 2.48 (t, *J* = 6.0 Hz, 2H), 1.89 - 1.77 (m, 2H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	165.3, 159.0, 139.8, 132.3, 129.4, 128.7, 114.0, 68.8, 66.0, 55.2, 49.9, 47.3, 32.2, 23.0
HRMS (m/z)	**:**	314.1361 [$(M + Na)^+$ calcd for $(C_{16}H_{21}NNaO_4)^+$: 314.1368]

5. Synthesis of (*S, E*)-3-(2,3-dihydroxypropylidene)-1-(4-methoxybenzyl)piperidin-2-one (261):

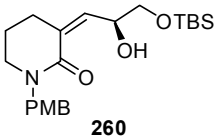
Above mentioned procedure used for the synthesis of **261**.



261

Yield	**:**	92%
TLC	**:**	R_f = 0.25 (ethyl acetate)
Optical rotation	**:**	$[\alpha]_D^{23}$ = + 11.31 ($CHCl_3$, c = 0.7)
Melting point	**:**	85-87 ºC
IR υ_{max} cm^{-1}	**:**	3374, 2930, 1659, 1600, 1511, 1488, 1246
^{1}H NMR ($CDCl_3$, 800 MHz) δ	**:**	7.19 (d, J = 7.6 Hz, 2H), 6.89-6.81 (m, 3H), 4.64 - 4.47 (m, 3H), 3.79 (s, 3H), 3.65 - 3.58 (m, 2H), 3.39 (br s, 1H), 3.29-3.23 (m, 2H), 2.99 (br s, 1H), 2.72-2.58 (m, 1H), 2.54 - 2.39 (m, 1H), 1.82 - 1.78 (m, 2H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	164.5, 159.0, 136.4, 131.5, 129.4, 129.0, 114.0, 69.2, 65.7, 55.2, 50.5, 46.9, 25.0, 22.4
HRMS (m/z)	**:**	314.1358 [$(M + Na)^+$ calcd for $(C_{16}H_{21}NNaO_4)^+$: 314.1368]

6. Synthesis of (*S,Z*)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxypropylidene)-1-(4-methoxybenzyl)piperidin-2-one (260):



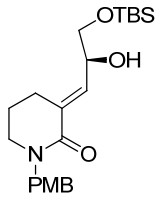
260

To a stirred solution of above mentioned diol (10 g, 34.32 mmol) and imidazole (2.80 g, 41.19 mmol) in dichloromethane (200 mL), a solution of TBSCl (5.43 g, 36.04 mmol) in dichloromethane was added over 15 min at -15 °C and stirring was continued for 2 h. Progress of the reaction was monitored by TLC. On consumption of starting material, the reaction mixture was quenched with water, extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by column chromatography using ethylacetate in hexane which resulted respective silylether in excellent yield.

Yield	**:**	98%
TLC	**:**	R_f = 0.4 (ethyl acetate: hexane = 3:7)
Optical rotation	**:**	$[\alpha]_D^{25}$ = - 10.59 ($CHCl_3$, *c* = 1.02)
IR υ_{max} cm^{-1}	**:**	3369, 3016, 2954, 1610, 1512, 1459, 1246
Melting point	**:**	102-104 ºC
^{1}H NMR ($CDCl_3$, 800 MHz) δ	**:**	7.19 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 6.00 (d, *J* = 5.3 Hz, 1H), 5.05 (br s, 1H), 4.84-4.75 (m, 1H), 4.62 (d, *J* = 14.4 Hz, 1H), 4.52 (d, *J* = 14.4 Hz, 1H), 3.79 (s, 3H), 3.77 - 3.67 (m, 2H), 3.25 (t, *J* = 5.5 Hz, 2H), 2.52-2.45 (m, 2H), 1.92 - 1.76 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	165.0, 159.0, 141.2, 131.2, 129.4, 129.0, 114.0, 68.8, 66.3, 55.2, 49.7, 47.3, 32.3, 25.9, 23.1, 18.3, -5.3, -5.2
HRMS (m/z)	**:**	428.2236 [$(M + Na)^+$ calcd for $(C_{22}H_{35}NO_4SiNa)^+$: 428.2233]

7. Synthesis of (*S,E*)-3-(3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxypropylidene)-1-(4-methoxybenzyl)piperidin-2-one (220):

Above mentioned procedure used for the synthesis of **220**.

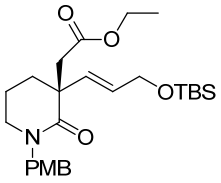


220

Yield	**:**	97%
TLC	**:**	R_f = 0.4 (ethyl acetate: hexane = 1:1)
Optical rotation	**:**	$[\alpha]_D^{25}$ = - 4.97 ($CHCl_3$, *c* = 1.17)
IR υ_{max} cm^{-1}	**:**	3416, 2928, 2856, 1601, 1494, 1253
Melting point	**:**	105-106 ºC
^{1}H NMR	**:**	7.20 (d, *J* = 8.1 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H),
($CDCl_3$, 800 MHz) δ		6.79 (d, *J* = 7.8 Hz, 1H), 4.63 (d, *J* = 14.5 Hz 1H), 4.56 (d, *J* = 14.5 Hz, 1H), 4.43 - 4.52 (m, 1H), 3.79 (s, 3H), 3.65 - 3.52 (m, 2H), 3.26 (t, *J* = 5.4 Hz, 2H), 2.76 - 2.65 (m, 1H), 2.62 (br s, 1H), 2.52 - 2.38 (m, 1H), 1.76 - 1.87 (m, 2H), 1.68 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H)
^{13}C NMR	**:**	164.1, 158.9, 134.9, 132.4, 129.4, 129.3, 113.9,
($CDCl_3$, 101 MHz) δ		69.0, 66.0, 55.2, 50.4, 46.8, 25.9, 25.3, 22.6, 18.3, -5.4

8. Synthesis of *S, E*)-ethyl 2-(3-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-(4-methoxybenzyl)-2-oxopiperidin-3-yl)acetate (219b):

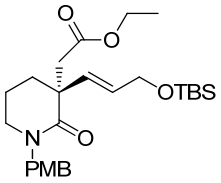
To a solution of **220** (10 g, 24.65 mmol) in triethyl orthoacetate (150 mL), was added catalytic amount of propionic acid (0.2 mL, 2.71 mmol) under argon atmosphere. The resulting mixture was heated at 130 °C for 8 h. The reaction was monitored by TLC. After complete consumption of starting material, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by column chromatography using ethyl acetate and hexane (1:9→2:8 gradient) to obtain **219b** as a colorless liquid.



219b

Yield	**:**	97%
TLC	**:**	R_f = 0.55 (ethyl acetate: hexane = 3:7)
Optical rotation	**:**	$[\alpha]_D^{24}$ = - 15.38 (*c* = 0.84, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	2953, 2931, 2856, 1734, 1640, 1512, 1462, 1249
^{1}H NMR **($CDCl_3$, 400 MHz) δ**	**:**	7.22 (m, *J* = 7.8 Hz, 2H), 6.85 (m, *J* = 7.8 Hz, 2H), 5.66 (br s, 2H), 4.72 (d, *J* = 14.4 Hz, 1H), 4.39 (d, *J* = 14.4 Hz, 1H), 4.21 - 4.15 (m, 2H), 4.15 - 4.06 (m, 2H), 3.80 (s, 3H), 3.29 (td, *J* = 11.2, 3.9 Hz, 1H), 3.20 (d, *J* = 16.5 Hz, 1H), 3.18 - 3.09 (m, 1H), 2.38 (d, *J* = 16.4 Hz, 1H), 2.19 (t, *J* = 13.2 Hz, 1H), 1.97 - 1.75 (m, 2H), 1.68 (m, 1H), 1.24 (t, *J* = 7.3 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H)
^{13}C NMR **($CDCl_3$, 101 MHz) δ**	**:**	171.7, 171.4, 158.8, 133.2, 130.0, 129.6, 129.4, 113.8, 63.5, 60.2, 55.2, 49.9, 47.3, 46.2, 43.2, 31.1, 25.9, 19.4, 18.3, 14.2, -5.2
HPLC data		Chiralcel OD-H Column; 1 mL/min flow rate; IPA: n-Hexane 10:90; λ= 210nm, >99% ee; retention time 7.2 min.
HRMS (m/z)	**:**	498.2656 [$(M + Na)^+$ calcd for $(C_{26}H_{41}NNaO_5Si)^+$: 498.2652]

9. Synthesis of (*R, E*)-ethyl 2-(3-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-(4-methoxybenzyl)-2-oxopiperidin-3-yl)acetate (219a):

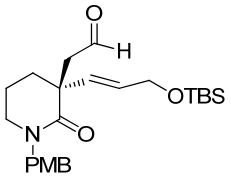


219a

Yield	**:**	95%
TLC	**:**	R_f = 0.55 (ethyl acetate: hexane = 3:7)
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 12.19 (*c* = 0.31, $CHCl_3$)
HPLC data		Chiralcel OD-H Column; 1 mL/min flow rate; IPA: n-Hexane 10:90; λ= 210nm, >99% ee; retention time 6.0 min.
HRMS (m/z)	**:**	498.2655 [$(M + Na)^+$ calcd for $(C_{26}H_{41}NNaO_5Si)^+$: 498.2652]

10. Synthesis of (*S,E*)-2-(3-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-(4-methoxybenzyl)-2-oxopiperidin-3-yl)acetaldehyde: (264b):

To a solution of **219b** (1.0 g, 2.1 mmol) in anhydrous dichloromethane (15 mL), DIBAL-H (3.1 mL, 3.1 mmol, 1 M solution in hexane) was added at -78 °C. After 2 h, the reaction was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (15 mL). The reaction mixture was stirred at room temperature for 1 h. The aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography which afforded corresponding aldehyde.

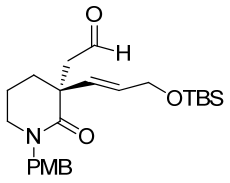


264b

Yield	**:**	(0.72 g, 80%)

TLC	**:**	R_f = 0.5 (SiO_2, ethylacetate : hexane= 3 : 7)
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 3.78 (*c* = 1, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	2952, 2931, 2856, 2897, 1718, 1633, 1512, 1462, 1442, 1357, 1249
^{1}H NMR ($CDCl_3$, 400 MHz) δ	**:**	9.75 (s., 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 2H), 5.68 (br s, 2H), 4.64 (d, *J* = 14.4 Hz, 1H), 4.40 (d, *J* = 14.4 Hz, 1H), 4.19 (s, 2H), 3.78 (s, 3H), 3.28 - 3.12 (m, 2H), 2.86 (d, *J* = 16.9 Hz, 1H), 2.52 (d, *J* = 16.9 Hz, 1H), 1.93 - 1.75 (m, 3H), 1.73-1.64 (m, 1H), 0.90 (s, 9H), 0.05 (s, 6H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	200.7, 171.3, 158.9, 132.3, 131.1, 129.4, 129.2, 113.9, 63.1, 55.1, 52.3, 49.8, 47.2, 46.3, 32.3, 25.8, 18.8, 18.3, -5.3
HRMS (m/z)	**:**	454.2389 [$(M + Na)^+$ calcd for $(C_{24}H_{37}NO_4SiNa)^+$: 454.2390]

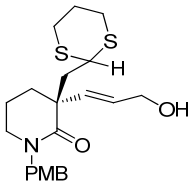
11. Synthesis of (*R,E*)-2-(3-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-(4-methoxy benzyl)-2-oxopiperidin-3-yl)acetaldehyde (264a):



264a

Yield	**:**	(0.7 g, 77 %)
TLC	**:**	R_f = 0.5 (SiO_2, ethylacetate : hexane= 3 : 7)
Optical rotation	**:**	$[\alpha]_D^{24}$ = -3.31 (*c* = 0.8, $CHCl_3$)

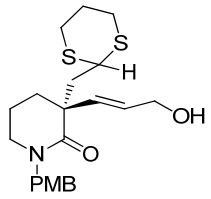
12. Synthesis of (*S,E*)-3-((1,3-dithian-2-yl)methyl)-3-(3-hydroxyprop-1-en-1-yl)-1-(4-methoxybenzyl)piperidin-2-one:



To a solution of above mentioned aldehyde **264b** (1 g, 2.32 mmol) in anhydrous CH_2Cl_2 (20 mL), 1,3-propanedithiol (0.3 mL, 0.3 mmol) and boron trifluoride etherate (1.14 mL, 9.27 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ (15 mL) and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude reaction mixture was purified on neutral silica gel using ethyl acetate: hexane (1:1→1:0 gradient) to afford dithiane as viscous liquid.

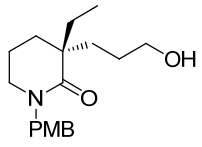
Yield	**:**	(0.77 g, 82%)
TLC	**:**	R_f = 0.5 (SiO_2, ethylacetate : hexane= 3 : 7)
Optical rotation	**:**	$[\alpha]_D^{24}$ = - 1.69 (*c* = 0.64, $CHCl_3$).
IR υ_{max} cm^{-1}	**:**	3410, 2932, 2860, 1614, 1511, 1245.
^{1}H NMR	**:**	δ 7.20 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H),
($CDCl_3$, 400 MHz) δ		5.92 - 5.68 (m, 2H), 4.50 (s, 2H), 4.15 (br s., 2H), 4.12 - 3.98 (m, 1H), 3.79 (s, 3H), 3.37 - 3.07 (m, 2H), 2.95 - 2.66 (m, 4H), 2.43 (dd, *J* = 7.3, 14.6 Hz, 1H), 2.20 - 1.97 (m, 3H), 1.95-1.82 (m, 4H), 1.70 (br s, 1H).
^{13}C NMR	**:**	δ 171.5, 158.8, 135.6, 129.6, 129.5, 129.4, 113.8,
($CDCl_3$, 101 MHz) δ		63.4, 55.2, 50.1, 47.9, 47.3, 44.3, 42.9, 30.3, 30.2, 30.1, 25.3, 19.2.
HRMS (m/z)	**:**	430.1478 [$(M + Na)^+$ calcd for $(C_{21}H_{29}NNaO_3S_2)^+$: 430.1487]

13. Synthesis of (*R,E*)-3-((1,3-dithian-2-yl)methyl)-3-(3-hydroxyprop-1-en-1-yl)-1-(4-methoxybenzyl)piperidin-2-one:



Yield	**:**	(0.79 g, 84%)
TLC	**:**	R_f = 0.5 (SiO_2, ethylacetate : hexane= 3 : 7)
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 1.92 (c = 0.79, $CHCl_3$)
HRMS (m/z)	**:**	408.1658 [$(M + H)^+$ calcd for $(C_{21}H_{30}NO_3S_2)^+$: 408.1667]

14. Synthesis of (*R*)-3-ethyl-3-(3-hydroxypropyl)-1-(4-methoxybenzyl)piperidin-2-one (265b):



265b

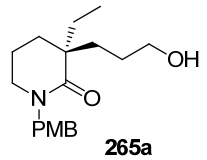
Raney Ni (3 g, W-2) was added to a solution of dithiane (0.77 g, 1.89 mmol) in absolute ethanol (15 mL). The reaction mixture was refluxed for 16 h under hydrogen atmosphere (1 atm). The reaction mixture was filtered through celite, washed with ethyl acetate. The combined filtrate was concentrated and purified by column chromatography using ethyl acetate and hexane (4:6) mixture to obtain alcohol **265b** as colorless liquid.

Yield	**:**	(490 mg, 85%)
TLC	**:**	R_f = 0.4 (SiO_2, ethyl acetate: hexane= 7:3).
Optical rotation	**:**	$[\alpha]_D^{24}$ = -9.319 (*c* = 0.91, $CHCl_3$).
IR υ_{max} cm^{-1}	**:**	3403, 2942, 2873, 1612, 1512, 1460, 1246 cm^{-1}.
^{1}H NMR ($CDCl_3$, 800 MHz) δ	**:**	δ 7.18 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.58 (d, *J* = 14.5 Hz, 1 H), 4.43 (d, *J* = 14.5 Hz,

		1 H), 3.79 (s, 3 H), 3.63 - 3.56 (m, 2 H), 3.17 (t, *J* = 6.1 Hz, 2 H), 2.35 (br s, 1 H), 1.88 - 1.84 (m, 1 H), 1.79 - 1.69 (m, 5 H), 1.66 - 1.62 (m, 1 H), 1.59 – 1.54 (m, 1 H), 1.51 - 1.47 (m, 2 H), 0.87 (t, *J* = 7.4 Hz, 3 H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	175.1, 158.7, 129.6, 129.3, 113.8, 62.7, 55.1, 49.8, 47.4, 44.7, 34.2, 31.7, 28.9, 27.7, 19.6, 8.6.
HRMS (m/z)	**:**	306.2066 [(M + H)$^+$ calcd for $(C_{18}H_{28}NO_3)^+$: 306.2069]

15. Synthesis of (*S*)-3-ethyl-3-(3-hydroxypropyl)-1-(4 methoxybenzyl)piperidin-2-one (265a):

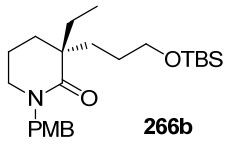
Above mentioned procedure used for the synthesis of **265a**.



265a

Yield	**:**	(325 mg, 85%)
TLC	**:**	R_f = 0.4 (SiO_2, ethyl acetate: hexane= 7:3)
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 10.216 (*c* = 0.8, $CHCl_3$)
HRMS (m/z)	**:**	306.2060 [(M + H)$^+$ calcd for $(C_{18}H_{28}NO_3)^+$: 306.2069]

16. Sythesis of (*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-ethyl-1-(4-methoxybenzyl) piperidin-2-one (266b):



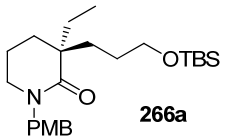
266b

To a solution of compound **265b** (1 g, 3.27 mmol) in dichloromethane (25 mL), imidazole (0.165 g, 7.15 mmol) and TBSCl (0.543 g, 3.6 mmol) were added at 0 °C. After stirring for 1h, the reaction mixture was quenched with water. The aqueous layer was extracted with DCM (3×20 mL) and the combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography to afford corresponding silyl ether.

Yield	**:**	1.37 g, quantitative.
TLC	**:**	R_f = 0.55 (SiO_2, ethyl acetate: hexane= 1.5:8.5)
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 6.62 (*c* = 1.58, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	2952, 2932, 2857, 1633, 1512, 1463, 1352, 1248
^{1}H NMR (800MHz ,$CDCl_3$)		δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.53 (d, *J* = 14.5 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 3.79 (s, 3H), 3.65 - 3.52 (m, 2H), 3.16 (t, *J* = 5.9 Hz, 2H), 1.83-1.76 (m, 1H), 1.75 - 1.66 (m, 5H), 1.59 - 1.44 (m, 4H), 0.91 - 0.88 (m, 9H), 0.87 (t, *J* = 7.6 Hz, 3H), 0.05 (s, 6H).
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	174.7, 158.7, 129.9, 129.3, 113.8, 63.6, 55.1, 49.8, 47.4, 44.7, 34.7, 31.5, 29.1, 27.8, 25.9, 19.8, 18.3, 8.7, -5.3.
HRMS (m/z)	**:**	420.2931 [$(M + H)^+$ calcd for $(C_{24}H_{42}NO_3Si)^+$: 420.2934]

17. Synthesis of (*S*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-ethyl-1-(4-methoxybenzyl) piperidin-2-one (266a):

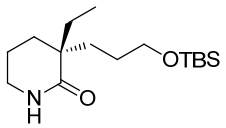
Above mentioned procedure used for the synthesis of **266a**.



266a

Yield	**:**	1.37 g, quantitative.
TLC	**:**	R_f = 0.55 (SiO_2, ethyl acetate: hexane= 1.5:8.5)
Optical rotation	**:**	$[\alpha]_D^{23}$ = - 5.7 (*c* = 0.8, $CHCl_3$)
HRMS (m/z)	**:**	420.2929 [$(M + H)^+$ calcd for $(C_{24}H_{42}NO_3Si)^+$: 420.2934]

18. Synthesis of (*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-ethylpiperidin-2-one (267b):



267b

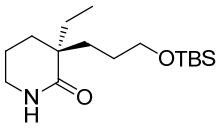
A solution of *N*-PMB lactam **266b** (1 g, 2.38 mmol) in anhydrous THF (15 mL) was charged into 100 mL two neck round bottom flask equipped with a magnetic stirring bar, cold finger condenser and argon balloon was cooled to -78 °C. Ammonia gas was condensed (through KOH column) to the reaction flask at -78 °C from ammonia cylinder, and a small sodium piece was added to the stirred mixture till blue coloration persisted. The resulting blue color solution was warmed to -33 °C and stirring was continued for 1 h (temperature in the cold finger condenser was maintained -78 °C till reaction completed). The reaction mixture was quenched by adding solid ammonium chloride in small portions till blue coloration disappeared, ammonia in the reaction mixture was evaporated at room temperature for overnight. The reaction mixture was filtered and the solid residues were washed with ethyl acetate. The filtrate was concentrated and purified by column chromatography to obtained desired compound.

Yield	**:**	(0.61 g, 85%)
TLC	**:**	R_f = 0.4 (SiO_2, ethyl acetate: hexane= 6:4)

Optical rotation	**:**	$[\alpha]_D^{24}$ = + 19.67 (*c* = 0.36, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	3289, 3212, 2951, 2858, 1658, 1469, 1254 cm^{-1}.
^{1}H NMR (800MHz ,$CDCl_3$)		δ 6.04 (br s, 1H), 3.63 - 3.49 (m, 2H), 3.26 (t, *J* = 5.9 Hz, 2H), 1.81 - 1.76 (m, 2H), 1.75 - 1.62 (m, 4H), 1.57 - 1.44 (m, 4H), 0.89 - 0.86 (m, 12H), 0.03 (s, 6H).
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	177.2, 63.6, 44.5, 42.6, 34.3, 31.0, 29.0, 27.7, 25.9, 19.8, 18.3, 8.6, -5.3.
HRMS (m/z)	**:**	300.2349 [$(M + H)^+$ calcd for $(C_{16}H_{34}NO_2Si)^+$: 300.2359]

19. Synthesis of (*S*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-ethylpiperidin-2-one (267a):

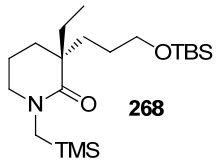
Above mentioned procedure used for the synthesis of **267a**.



267a

Yield	**:**	(0.62 g, 87 %)
TLC	**:**	R_f = 0.4 (SiO_2, ethyl acetate: hexane= 6:4)
Optical rotation	**:**	$[\alpha]_D^{24}$ = - 20.442 (*c* = 0.80, $CHCl_3$).
HRMS (m/z)	**:**	300.2350 [$(M + H)^+$ calcd for $(C_{16}H_{34}NO_2Si)^+$: 300.2359]

20. Synthesis of (*R*)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethyl-1-((trimethyl silyl)methyl) piperidin-2-one (268):

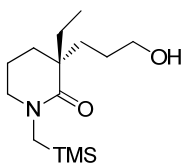


268

To a stirred solution of NaH (0.08 g, 2 mmol, 60% dispersion in oil) in THF (5 mL) at 0 ºC, was added (R)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethylpiperidin-2-one (**267b**) (0.5 g, 1.67 mmol) in THF (5 mL). After 20 min, tetrabutyl ammonium bromide (53 mg, 0.166 mmol) and a solution of chloromethyl(trimethylsilane) (0.25 mL, 1.84 mmol) in THF (3 mL) were added drop wise into the flask. The reaction mixture was allowed to warm to room temperature and further stirred for 1 hours, and quenched with saturated NH_4Cl solution. The mixture was extracted with ethylacetate (30 mL × 3), dried over Na_2SO_4 and concentrated. The crude was purification by column chromatography (using ethylacetate – hexane 1:9→2:8 gradient) afforded pure **268** with yield of 81 % (0.52 g).

Yield	**:**	(0.52 g, 81 %)
TLC	**:**	R_f = 0.5 (SiO_2, ethyl acetate: hexane= 2:8)
IR υ_{max} cm^{-1}	**:**	2954, 2895, 2858, 1617, 1251, 1099
^{1}H NMR (400MHz ,$CDCl_3$)		3.73 - 3.49 (m, 2H), 3.22 (t, *J* = 5.6 Hz, 2H), 2.92 - 2.80 (m, 2H), 1.86 - 1.62 (m, 6H), 1.59 - 1.33 (m, 4H), 0.87 (s, 9H), 0.85 - 0.80 (m, 3H), 0.05 (s, 9H), 0.02 (s, 6H).
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	173.3, 63.7, 50.9, 44.5, 39.8, 34.5, 31.2, 29.2, 27.8, 25.9, 19.9, 18.3, 8.7, -1.3, -5.3.
HRMS (m/z)	**:**	386.2905 [$(M + H)^+$ calcd for $(C_{20}H_{44}NO_2Si_2)^+$: 386.2911]

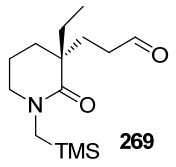
21. Synthesis of (*R*)-3-ethyl-3-(3-hydroxypropyl)-1-((trimethylsilyl)methyl)piperidin-2-one (269):



To a solution of (*R*)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethyl-1-((trimethylsilyl)methyl) piperidin-2-one (**268)** (0.5 g, 1.3 mmol) in methanol, *p*-toluene sulfonic acid (0.022 g, 0.13 mmol) was added at -10 ºC. The solution was stirred for 30 min and quenched with saturated aqueous $NaHCO_3$ solution at -10 ºC. The solution was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated NaCl solution, separated the layers and concentrated, quick purification using Flash chromatography using ethyl acetate and hexane (2:8) mixture to provided corresponding alcohol.

Yield	**:**	(0.31 g, 88 %)
TLC	**:**	R_f = 0.45 (SiO_2, ethyl acetate: hexane= 3:7)
IR υ_{max} cm^{-1}	**:**	3402, 2949, 2873, 1608, 1492, 1247, 1060
^{1}H NMR (400MHz ,$CDCl_3$)		3.57-3.52 (m, *J* = 4.7 Hz, 2H), 3.22 (t, *J* = 5.7 Hz, 2H), 3.02 (d, *J* = 14.8 Hz, 1H), 2.70 (d, *J* = 14.7 Hz, 1H), 1.87 - 1.35 (m, 10H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.08 - 0.02 (m, 9H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	173.7, 62.7, 50.9, 44.5, 39.9, 33.9, 31.6, 29.0, 27.7, 19.8, 8.5, -1.3.
HRMS (m/z)	**:**	272.2036 [$(M + H)^+$ calcd for $(C_{14}H_{30}NO_2Si)^+$: 272.2046]

22. Synthesis of (*R*)-3-(3-ethyl-2-oxo-1-((trimethylsilyl)methyl)piperidin-3-yl)propanal (269):



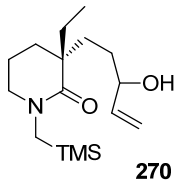
269

To a solution of above crude (0.3 g, 1.11 mmol) in anhydrous dichloromethane (10 mL), Dess-Martin periodinane (0.56 g, 1.3 mmol) was added at 0 ˚C. The reaction temperature was slowly raised to room temperature by removing ice tub and stirring was continued for 30 min. The reaction was quenched successively with a saturated aqueous $Na_2S_2O_3$ solution (5 ml) and saturated aqueous $NaHCO_3$ solution (5 ml), stirred for 30 min. The aqueous layer was extracted with dichloromethane (3×30 mL). The combined

dichloromethane layer was dried over Na_2SO_4 and evaporated and residue was purified by column chromatography using ethyl acetate and hexane (1:9→1.5:8.5 gradient) to afford corresponding aldehyde **269**.

Yield	**:**	(0.25 g, 84 %)
TLC	**:**	R_f = 0.55 (SiO_2, ethyl acetate: hexane= 3:7)
IR υ_{max} cm^{-1}	**:**	3399, 2950, 2897, 2719, 1722, 1621, 1492, 1247, 919, 849
^{1}H NMR (400MHz ,$CDCl_3$)		9.74 (s, 1H), 3.25 (t, *J* = 6.0 Hz, 2H), 2.98 (d, *J* = 14.9 Hz, 1H), 2.76 (d, *J* = 14.9 Hz, 1H), 2.63 - 2.33 (m, 2H), 1.89 - 1.67 (m, 6H), 1.66 - 1.46 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.06 (s, 9H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	202.5, 172.4, 50.8, 43.9, 39.8, 39.7, 30.7, 29.9, 29.8, 19.6, 8.4, -1.4
HRMS (m/z)	**:**	270.1884 [$(M + H)^+$ calcd for $(C_{14}H_{30}NO_2Si)^+$: 270.1889]

23. Synthesis of (3*R*)-3-ethyl-3-(3-hydroxypent-4-en-1-yl)-1-((trimethylsilyl) methyl)piperidin-2-one (270):



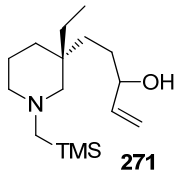
270

To a stirred solution of aldehyde **269** (0.25 g, 0.927 mmol) in anhydrous ether, vinyl magnisium bromide (1.1 mL, 1.1 mmol) was added at -78 °C. After 2 h stirring at -78 °C, it was quenched with saturated aqueous ammonium chloride solution and warmed to room temperature. The solution was extracted with ethyl acetate and concentrated. The crude residue was purified by flash column chromatography using ethyl acetate and hexane (1:9) mixture to obtain allyl alcohol **270** as pale yellow color liquid.

Yield	**:**	(0.22 g, 80 %)
TLC	**:**	R_f = 0.50 (SiO_2, ethyl acetate: hexane= 3:7)

IR υ_{max} cm^{-1}	**:**	3400, 2949, 2872, 1608, 1491, 1248, 917, 849
^{1}H NMR (400MHz ,$CDCl_3$)		5.91 - 5.70 (m, 1H), 5.26 - 5.15 (m, 1H), 5.05 (dd, *J* = 1.2, 10.4 Hz, 1H), 4.02-3.99 (m, 1H), 3.24-3.20 (m, 2H), 3.01 (t, *J* = 14.9 Hz, 1H), 2.81 - 2.66 (m, 1H), 2.59 (br. s., 1H), 1.81 - 1.42 (m, 10H), 0.83 (m, 3H), 0.05 (s, 9H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	173.6, 173.5, 141.3, 141.1, 114.3, 114.2, 73.3, 72.6, 50.9, 44.7, 44.4, 39.8, 39.8, 33.6, 33.2, 32.1, 32.0, 31.7, 31.2, 29.1, 29.0, 19.8, 19.7, 8.6, 8.5, -1.3
HRMS (m/z)	**:**	298.2201 [$(M + H)^+$ calcd for $(C_{16}H_{32}NO_2Si)^+$: 298.2202]

24. Synthesis of 5-((*R*)-3-ethyl-1-((trimethylsilyl)methyl)piperidin-3-yl)pent-1-en-3-ol (271):



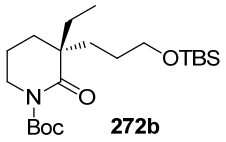
271

DIBAL-H (0.66 mmol, 0.66 mL, 1 M solution in hexane) was added to a solution of **270** (0.1 g, 0.33 mmol) in dry THF (10 mL) at -78 ˚C and stirred for 2 h. The reaction was quenched with saturated aqueous sodium potassium tartrate solution (10 mL) and warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3× 15 mL), dried and purified by column chromatography to obtain crude tertiary amine **271** as colourless liquid.

Yield	**:**	(0.22 g, 80 %)
TLC	**:**	R_f = 0.50 (SiO_2, ethyl acetate: hexane= 3:7)
IR υ_{max} cm^{-1}	**:**	3400, 2949, 2872, 1608, 1491, 1248, 917, 849
^{1}H NMR (400MHz ,$CDCl_3$)		5.92-5.83 (m, 1H), 5.27-5.19 (m, 1H), 5.13-5.08 (m, 1H), 4.18 - 3.95 (m, 1H), 2.22-1.98 (m, 6H), 1.82 - 1.78 (m, 2H), 1.44-1.23 (m, 9H), 0.78 - 0.74 (m, 3H), 0.05 (s, 9H)

^{13}C NMR (CDCl$_3$, 101 MHz) δ	**:**	141.4, 114.6, 114.5, 74.0, 73.7, 66.9, 66.7, 58.8, 51.4, 35.6, 33.2, 33.1, 30.5, 30.3, 29.7, 22.1, 7.3, -1.1, -1.0
HRMS (m/z)	**:**	284.2398 [$(M + H)^+$ calcd for $(C_{16}H_{34}NOSi)^+$: 284.2410]

25. Synthesis of (*R*)-*tert*-butyl 3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-ethyl-2-oxopiperidine-1-carboxylate (272b):



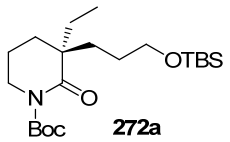
272b

To a solution of **267b** (1 g, 3.34 mmol) in dry THF, LiHMDS solution (1M in THF, 3.67 mL, 3.67 mmol) was added at -78 °C. After stirring for 30 min, di-*tert*-butyl dicarbonate (0.85 mL, 3.67 mmol) was added. The reaction temperature was brought to room temperature and stirring continued for additional 2 h before being quenched with saturated aqueous NH_4Cl Solution (15 mL). The aqueous layer was separated and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography using ethyl acetate and hexane (0.5:9.5) mixture to afforded *N*-Boc-Lactam **272b**.

Yield	**:**	(1.3 g, 97%)
TLC	**:**	R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:9)
Optical rotation	**:**	$[\alpha]_D^{24}$ = - 2.53 (*c* = 1.55, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	2954, 2933, 2884, 2858, 1766, 1716, 1462, 1389, 1367, 1278, 1298, 1254
^{1}H NMR (800MHz ,CDCl$_3$)		δ 3.62 - 3.52 (m, 4H), 1.84 - 1.77 (m, 2H), 1.75 - 1.66 (m, 3H), 1.65 - 1.52 (m, 3H), 1.51 - 1.43 (m, 11H), 0.87 (s, 9H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.02 (s, 6H)

^{13}C NMR	**:**	177.0, 153.8, 82.2, 63.4, 47.8, 47.1, 33.9, 30.8,
($CDCl_3$, 101 MHz) δ		30.6, 28.0, 27.4, 25.9, 20.1, 18.3, 8.4, -5.3.
HRMS (m/z)	**:**	422.2693 [$(M + H)^+$ calcd for $(C_{21}H_{41}NO_4SiNa)^+$: 422.2703]

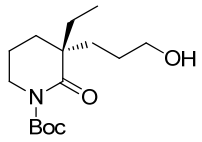
26. Synthesis of (*S*)-*tert*-butyl 3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-ethyl-2-oxopiperidine-1-carboxylate (272a):



272a

Yield	**:**	(1.26 g, 95 %)
TLC	**:**	R_f = 0.5 (SiO_2, ethyl acetate: hexane= 1:9)
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 3.12 (*c* = 1, $CHCl_3$)
HRMS (m/z)	**:**	422.2689 [$(M + H)^+$ calcd for $(C_{21}H_{41}NO_4SiNa)^+$: 422.2703]

27. Synthesis of (*R*)-*tert*-butyl 3-ethyl-3-(3-hydroxypropyl)-2-oxopiperidine-1-carboxylate (273b):

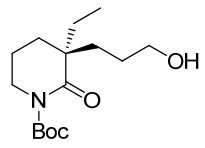


273b

To a solution of **272b** (0.3 g, 0.75 mmol) in methanol, *p*-toluene sulfonic acid (0.006 g, 0.04 mmol) was added at -10 ºC. The solution was stirred for 30 min and quenched with saturated aqueous $NaHCO_3$ solution at -10 ºC. The solution was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated NaCl solution, separated the layers and concentrated, quick purification using flash chromatography using ethyl acetate and hexane (3:7) mixture provided **273b**.

Yield	**:**	(0.2 g, 92%)
TLC	**:**	R_f = 0.5 (SiO_2, ethylacetate : hexane= 4 : 6).
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 3.76 (*c* = 0.5, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	2935, 2877, 1760, 1714, 1458, 1391, 1368, 1297, 1277, 1254
^{1}H NMR (800MHz ,$CDCl_3$)		δ 3.68 - 3.55 (m, 4H), 1.87 - 1.80 (m, 2H), 1.77 - 1.69 (m, 4H), 1.64 - 1.54 (m, 4H), 1.51 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	177.1, 153.8, 82.5, 63.0, 47.8, 47.2, 33.7, 31.1, 30.6, 28.0, 27.5, 20.1, 8.4
HRMS (m/z)	**:**	308.1832 [(M + H)$^+$ calcd for $(C_{15}H_{27}NO_4Na)^+$: 308.1838]

28. Synthesis of (S)-*tert*-butyl 3-ethyl-3-(3-hydroxypropyl)-2-oxopiperidine-1-carboxylate (273a):



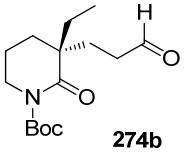
273a

Yield	**:**	(0.2 g, 92%)
TLC	**:**	R_f = 0.5 (SiO_2, ethylacetate : hexane= 4 : 6).
Optical rotation	**:**	$[\alpha]_D^{24}$ = - 3.25 ($CHCl_3$, *c* = 0.35)
HRMS (m/z)	**:**	308.1834 [(M + H)$^+$ calcd for $(C_{15}H_{27}NO_4Na)^+$: 308.1838]

29. Synthesis of (*R*)-*tert*-butyl 3-ethyl-2-oxo-3-(3-oxopropyl)piperidine-1-carboxylate (274b):

To a solution of **273b** (1 g, 3.5 mmol) in anhydrous dichloromethane (30 mL), Dess-Martin periodinane (1.78 g, 4.2 mmol) was added at 0 ˚C. The reaction temperature was slowly raised to room temperature by removing ice tub and stirring was continued for 30 min. The

reaction was quenched successively with a saturated aqueous $Na_2S_2O_3$ solution (5 ml) and saturated aqueous $NaHCO_3$ solution (10 ml) and stirred for additional 30 min. The aqueous layer was extracted with dichloromethane (3×30 mL). The combined dichloromethane layer was dried over Na_2SO_4 and evaporated and residue was purified by column chromatography using ethyl acetate and hexane (1:9→2:8 gradient) to afford corresponding aldehyde **274b**.

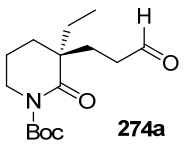


274b

Yield	**:**	(0.95 g, 96%)
TLC	**:**	R_f = 0.6 (SiO_2, ethyl acetate: hexane= 3:7
Optical rotation	**:**	$[\alpha]_D^{24}$ = + 2.13 (*c* = 0.5, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	3206, 2974, 2940, 1759, 1712, 1456, 1392, 1280, 1297
^{1}H NMR (800MHz ,$CDCl_3$)		δ 9.77 (s, 1H), 3.61 (t, *J* = 5.9 Hz, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 1.98 - 1.62 (m, 8H), 1.51 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	δ 201.9, 176.3, 153.6, 82.6, 47.2, 39.3, 30.9, 30.4, 29.2, 27.9, 19.8, 8.2
HRMS (m/z)	**:**	306.1676 [$(M + H)^+$ calcd for $(C_{15}H_{25}NO_4Na)^+$: 306.1681]

30. Synthesis of (*S*)-*tert*-butyl 3-ethyl-2-oxo-3-(3-oxopropyl)piperidine-1-carboxylate (274a):

Above mentioned procedure used for the synthesis of **274a**.

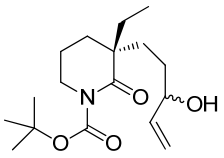


274a

Yield	**:**	(0.95 g, 96%)
TLC	**:**	R_f = 0.6 (SiO_2, ethyl acetate: hexane= 3:7
Optical rotation	**:**	$[\alpha]_D^{24}$ = - 2.72 ($CHCl_3$, *c* = 0.8)
HRMS (m/z)	**:**	306.1674 [$(M + H)^+$ calcd for $(C_{15}H_{25}NO_4Na)^+$: 306.1681]

31. Synthesis of (3*R*)-*tert*-butyl 3-ethyl-3-(3-hydroxypent-4-en-1-yl)-2-oxopiperidine-1-carboxylate (275b):

To a stirred solution of **274b** (0.5 g, 1.76 mmol) in anhydrous ether, vinyl magnisium bromide (2.12 mL, 2.12 mmol) was added at -78 °C. After 6 h of stirring at -78 °C, it was quenched with saturated aqueous ammonium chloride solution and warmed to room temperature. The solution was extracted with ethyl acetate and concentrated. The crude residue was purified by flash column chromatography using ethyl acetate and hexane (1.5:8.5) mixture to obtain allyl alcohol **275b** as pale yellow color liquid.



275b

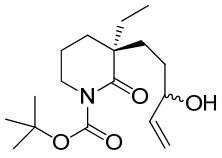
Yield	**:**	(0.42 g, 75%)
TLC	**:**	R_f =0.5 (SiO_2, ethyl acetate: hexane= 3:7)
IR υ_{max} cm^{-1}	**:**	3379, 2971, 2939, 2879, 1761, 1712, 1522, 1459, 1367, 1275, 1252
^{1}H NMR (400MHz ,$CDCl_3$)		mixture of two diasteromers δ 5.92 - 5.77 (m, 1H), 5.38-5.06 (m, 2H), 4.84 - 4.72 (m, 0.5H), 4.60 (br s, 1H), 4.09 - 4.01 (m, 0.5H), 3.65 - 3.53 (m, 1H), 3.08 (d, *J* = 5.8 Hz, 1H), 2.00 - 1.90 (m, 1H), 1.84 - 1.54 (m, 9H), 1.49 (s, 4.5H), 1.42 (s, 4.5H), 0.93 - 0.84 (m, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	mixture of two diasteromers δ 177.0, 175.6, 156.0, 153.7, 140.9, 136.4, 116.7, 114.6, 82.4, 80.5, 73.1,

47.8, 47.1, 45.3, 36.1, 33.2, 31.8, 31.5, 31.1, 30.6, 28.4, 28.0, 27.8, 26.5, 25.0, 20.1, 8.6, 8.3.

HRMS (m/z) : 334.1990 [(M + H)$^+$ calcd for $(C_{17}H_{29}NO_4Na)^+$: 334.1994]

32. Synthesis of (3*S*)-*tert*-butyl 3-ethyl-3-(3-hydroxypent-4-en-1-yl)-2-oxopiperidine-1-carboxylate (275a):

Above mentioned procedure used for the synthesis of **275a**.



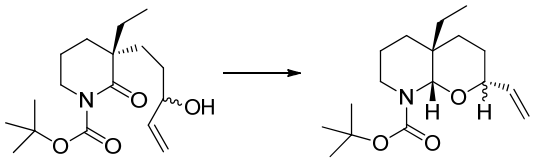
275a

Yield : (0.34 g, 77%)

TLC : R_f =0.5 (SiO_2, ethyl acetate: hexane= 3:7)

HRMS (m/z) : 334.1987 [(M + H)$^+$ calcd for $(C_{17}H_{29}NO_4Na)^+$: 334.1994]

33. Synthesis of (4a*R*, 8a*S*)-*tert*-butyl 4a-ethyl-2-vinylhexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (276b):



275b **276b**

DIBAL-H (2.89 mmol, 2.89 mL, 1 M solution in hexane) was added to a solution of **275b** (0.3 g, 0.96 mmol) in dry THF (10 mL) at -78 ˚C and stirred for 2 h. The reaction was quenched with saturated aqueous sodium potassium tartrate solution (20 mL) and warmed

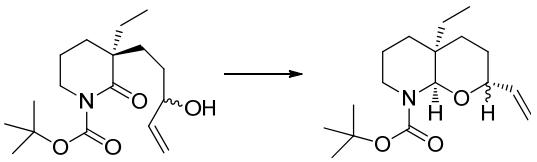
to room temperature. The reaction mixture was extracted with ethyl acetate (3× 25 mL), dried and concentrated to obtain crude hemiaminal as a white foam.

The crude hemiaminal was dried under high vacuum pump and dissolved in dry dichloromethane, charged with pyridinium *p*-toluene sulphonate (0.045 g, 0.192 mmol) at room temperature under Ar atmosphere and stirred for 2 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with dichloromethane (3×25 ml). The combined organic layer was concentrated under reduced pressure and the crude was dissolved in hexane, filtered and concentrated. The crude product was dried under high vacuum which resulted pure **276b** as a pale yellow color liquid (0.27 g). This crude was obtained as a mixture of two diasteromers, and the same was used for further reaction without any column chromatography purification (small quantity was purified for taking NMR and other analytical data).

Yield	**:**	0.27 g
TLC	**:**	R_f = 0.45 (SiO_2, ethyl acetate: hexane= 0.5:9.5).
IR υ_{max} cm^{-1}	**:**	3377, 2967, 2941, 2871, 1700, 1417, 1367, 1157
^{1}H NMR (400MHz ,$CDCl_3$)		6.01 - 5.76 (m, 1H), 5.42 - 5.20 (m, 2H), 5.14 - 5.00 (m, 1H), 4.58 (m, 0.5H), 4.07 - 3.83 (m, 1.5H), 3.15 - 2.88 (m, 1H), 2.11 - 1.81 (m, 2H), 1.73 - 1.47 (m, 6H), 1.47 - 1.41 (m, 9H), 1.23 - 1.10 (m, 2H), 0.86 - 0.69 (m, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	δ 155.1, 138.7, 137.4, 116.7, 114.8, 114.5, 86.8, 85.6, 79.9, 79.6, 77.8, 77.7, , 73.3, 39.3, 38.3, 38.2, 34.5, 34.2, 33.1, 33.0, 28.5, 28.3, 27.8, 27.6, 27.5, 27.0, 26.9, 24.0, 23.6, 23.5, 23.0, 20.3, 20.0, 19.9, 6.7, 6.6, 6.4
HRMS (m/z)	**:**	318.2039 [$(M + H)^+$ calcd for $(C_{17}H_{29}NO_3Na)^+$: 318.2045]

34. Synthesis of (4a*S*,8a*R*)-*tert*-butyl4a-ethyl-2-vinylhexahydro-2*H*-pyrano[2,3-*b*]pyridine-8(8a*H*)-carboxylate (276a):

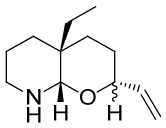
Above mentioned procedure used for the synthesis of **276a**.



275a **276a**

Yield	**:**	0.21 g
TLC	**:**	R_f = 0.45 (SiO_2, ethyl acetate: hexane= 0.5:9.5).
HRMS (m/z)	**:**	318.2036 [$(M + H)^+$ calcd for $(C_{17}H_{29}NNaO_3)^+$: 318.2045]

35. Synthesis of (4a*R*, 8a*S*)-4a-ethyl-2-vinyloctahydro-2*H*-pyrano[2,3-*b*]pyridine (277b):



277b

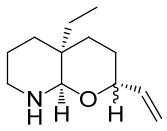
Triethylamine (0.26 mL, 1.83 mmol) and TMSOTf (0.25 mL, 1.37 mmol) were added to a stirred solution of **276b** (0.27 g, 0.914 mmol) in dry dichloromethane (10 mL) at 0 ˚C. After 1 h of stirring at room temperature, the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with dichloromethane (3×25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was dissolved in hexane and filtered. The filtrate was concentrated by rotavapour and dried under moderate vacuum for 15 min which resulted pure bicyclic amine **277b** (small quantity was purified for taking NMR and other analytical data).

Yield	**:**	0.17 g
TLC	**:**	0.5 (SiO_2, ethylacetate : hexane= 3 : 7)

IR υ_{max} cm^{-1}	**:**	3341, 2937, 2861, 1466, 1445, 1310 cm^{-1}.
^{1}H NMR **(400MHz ,$CDCl_3$)**	**:**	5.97 - 5.84 (m, 1H), 5.26 (d, *J* = 17.2 Hz, 0.5H), 5.21 (d, *J* = 17.6 Hz, 0.5H), 5.13 - 5.08 (m, 1H), 4.54 – 4.49 (m, 0.5H), 4.11 (s, 0.5H), 3.95 (s, 0.5H), 3.85 - 3.79 (m, 0.5H), 3.12 - 3.06 (m, 1H), 2.67 - 2.61 (m, 1H), 2.07 (br s, 1H), 1.93 - 1.84 (m, 1H), 1.78-1.72 (m, 1H), 1.65 - 1.52 (m, 3H), 1.47 - 1.22 (m, 4H), 1.18 - 1.12 (m, 1H), 0.82-0.77 (m, 3H)
^{13}C NMR **($CDCl_3$, 101 MHz) δ**	**:**	139.4, 139.3, 115.2, 114.5, 90.0, 70.7, 39.3, 34.1, 33.8, 33.4, 28.9, 28.8, 27.4, 26.1, 24.5, 21.1, 20.9, 6.9, 6.8
HRMS (m/z)	**:**	196.1708 [$(M + H)^+$ calcd for $(C_{12}H_{22}NO)^+$: 196.1701]

36. Synthesis of (4a*S*,8a*R*)-4a-ethyl-2-vinyloctahydro-2*H*-pyrano[2,3-*b*]pyridine (277a):

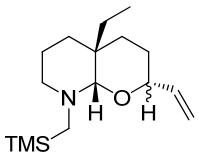
Above mentioned procedure used for the synthesis of **277a**.



277a

Yield	**:**	0.136 g
TLC	**:**	0.5 (SiO_2, ethylacetate : hexane= 3 : 7)
HRMS (m/z)	**:**	196.1694 [$(M + H)^+$ calcd for $(C_{12}H_{22}NO)^+$: 196.1701]

37. Synthesis of (4a*R*, 8a*S*)-4a-ethyl-8-((trimethylsilyl)methyl)-2-vinyloctahydro-2*H*-pyrano[2,3-*b*]pyridine (217b) :



217b

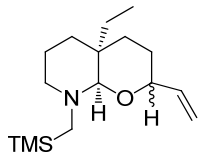
To a stirred solution of bicyclic amine **277b** (0.17 g, 0.87 mmol) in dry acetonitrile (10 mL), anhydrous K_2CO_3 (0.36 g, 2.61 mmol) and $TMSCH_2OTf$ (0.18 mL, 0.914 mmol) were added at 0 ºC. The resulting solution was slowly warmed to room temperature and stirred for 1 h at room temperature. The resulting slurry was filtered and the residue was washed with EtOAc and concentrated the filtrate under reduced pressure. The crude compound was dissolved in hexane, filtered and dried under high vacuum which gave pure (by ^1H and ^{13}C-NMR) **217b** (mixture of two diastereomers) as a pale yellow color liquid, (small quantity was purified for taking NMR and other analytical data).

Yield	**:**	0.24 g
TLC	**:**	0.5 (SiO_2, ethyl acetate : hexane= 0.5:9.5)
IR υ_{max} cm^{-1}	**:**	3434, 2940, 2861, 1645, 1445, 1298, 1247
^{1}H NMR (400MHz ,$CDCl_3$)	**:**	5.94 - 5.83 (m, 1H), 5.28 - 5.16 (m, 1H), 5.12 - 5.05 (m, 1H), 4.37 - 4.27 (m, 0.5H), 3.70 (s, 0.5H), 3.68 - 3.64 (m, 0.5H), 3.28 (m, 0.5H), 2.89 - 2.82 (m, 0.5H), 2.76-2.68 (m, 0.5H), 2.56-2.42 (m, 0.5H), 2.39 - 2.34 (m, 0.5H), 2.33 (d, *J* = 14.6 Hz, 0.5H), 2.02 - 1.87 (m, 2.5 H), 1.75 - 1.69 (m, 2 H), 1.64 - 1.56 (m, 2 H), 1.49 - 1.36 (m, 3 H), 1.33 - 1.27 (m, 1 H), 1.11 - 1.05 (m, 1 H), 0.77 (t, *J* = 7.6 Hz, 3 H), 0.04 (m, 9 H)

^{13}C NMR **($CDCl_3$, 101 MHz) δ**	**:**	139.7, 139.6, 114.9, 113.8, 95.9, 76.5, 69.7, 49.2, 46.1, 43.3, 35.1, 34.9, 33.9, 29.3, 28.7, 27.4, 26.1, 25.7, 23.1, 21.4, 21.1, 7.0, 6.9, -1.1, -1.5
HRMS (m/z)	**:**	282.2246 [$(M + H)^+$ calcd for $(C_{16}H_{32}NOSi)^+$: 282.2253]

38. Synthesis of (4a*S*,8a*R*)-4a-ethyl-8-((trimethylsilyl)methyl)-2-vinyloctahydro-2*H*-pyrano[2,3-*b*]pyridine (217a):

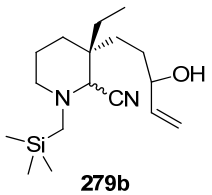
Above mentioned procedure used for the synthesis of **217a**.



217a

Yield	**:**	0.19 g
TLC	**:**	0.5 (SiO_2, ethyl acetate : hexane= 0.5:9.5)
HRMS (m/z)	**:**	282.2249 [$(M + H)^+$ calcd for $(C_{16}H_{32}NOSi)^+$: 282.2253]

39. Synthesis of (3*R*)-3-ethyl-3-(3-hydroxypent-4-en-1-yl)-1-((trimethylsilyl)methyl) piperidine -2-carbonitrile (279 b):



279b

TMSCN (0.22 mL, 1.71 mmol) was added to a stirred solution of **217b** (0.24 g, 0.852 mmol) in anhydrous dichloromethane at 0 ºC and stirred for 15 min. The reaction mixture was quenched with a saturated $NaHCO_3$ solution, both the layers were separated and the organic layer was extracted with dichloromethane. The combined organic layer was

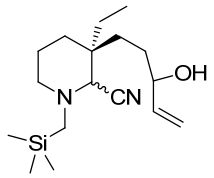
concentrated, dried under high vacuum. The crude was dissolved in hexane and filtered. The filtrate was concentrated to obtain pure TMS-ether compound **278b** (0.32 g).

This compound was dissolved in methanol (20 mL), PPTS (0.02 g, 0.082 mmol) was added to this solution and stirred at room temperature for 12 h. On consumption of starting material, the reaction mixture was concentrated and quenched with saturated $NaHCO_3$ solution (5 mL), extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. This crude compound was dissolved in hexane and filtered. The filtrate was concentrated and dried under vacuum to obtain pure compound **279b** (0.24 g) (small quantity was purified for taking NMR and other analytical data).

Yield	**:**	0.24 g
TLC	**:**	0.5 (SiO_2, ethyl acetate : hexane= 1:9)
IR υ_{max} cm^{-1}	**:**	3435, 3019, 2944, 2863, 2399, 1422, 1216
^{1}H NMR (400MHz ,$CDCl_3$)	**:**	δ 6.00-5.70 (m, 1H), 5.32 - 4.98 (m, 1H), 4.14 - 3.93 (m , 1H), 3.45 - 3.28 (m, 1H), 2.76 - 2.54 (m, 1H), 2.33 - 2.16 (m, 1H), 2.09 - 1.99 (m, 1H), 1.94 - 1.74 (m, 3H), 1.68 - 1.59 (m, 1H), 1.52 - 1.36 (m, 6H), 1.32 - 1.14 (m, 2H), 0.85 - 0.73 (m, 3H), 0.06 (s, 9H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	140.9, 140.7, 140.6, 115.5, 115.3, 115.1, 73.7, 73.6, 73.4, 65.8, 65.7, 65.6, 52.0, 51.9, 51.8, 48.5, 38.3, 38.2, 32.2, 32.0, 30.2, 30.1, 29.5, 29.3, 29.3, 25.5, 23.0, 20.9, 7.2, 6.6, -1.6, -1.5
HRMS (m/z)	**:**	309.2357 [$(M + H)^+$ calcd for $(C_{17}H_{33}N_2OSi)^+$: 309.2362]

40. Synthesis of (3*S*)-3-ethyl-3-(3-hydroxypent-4-en-1-yl)-1-((trimethylsilyl)methyl) piperidine-2-carbonitrile (279a):

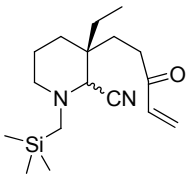
Above mentioned procedure used for the synthesis of **279a.**



279a

Yield	**:**	0.19 g
TLC	**:**	0.5 (SiO_2, ethyl acetate : hexane= 1:9)
HRMS (m/z)	**:**	309.2356 [$(M + H)^+$ calcd for $(C_{17}H_{33}N_2OSi)^+$: 309.2362]

41. Synthesis of (3*R*)-3-ethyl-3-(3-oxopent-4-en-1-yl)-1-((trimethylsilyl)methyl) piperidine-2-carbonitrile (280b) :



280b

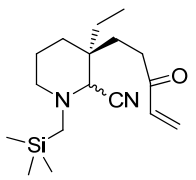
To a solution of **279b** (0.24 g, 0.78 mmol) in dry DCM (5 mL), Dess-Martin periodinane (0.4 g, 0.94 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched successively with saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) solution which was stirred additionally for 15 min. The mixture was extracted with dichloromethane (3×15 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated. This crude compound was dissolved in hexane and filtered. The filtrate was concentrated and dried under vacuum to obtain pure compound **280b** (small quantity was purified for taking NMR and other analytical data).

Yield	**:**	0.22 g
TLC	**:**	0.4 (SiO_2, ethylacetate : hexane= 1 : 9)

IR υ_{max} cm^{-1}	**:**	3019, 2949, 2794, 1682, 1617, 1464, 1402, 1249, 1157
^{1}H NMR (400MHz ,$CDCl_3$) δ	**:**	6.43 - 6.30 (m, 1H), 6.28 - 6.19 (m, 1H), 5.88 - 5.81 (m, 1H), 3.41 (s, 0.5H), 3.38 (s, 0.5H), 2.72 - 2.61 (m, 1H), 2.58 - 2.38 (m, 2H), 2.29-2.19 (m, , 1H), 2.05 (d, *J* = 14.6 Hz, 1H), 1.90 (d, *J* = 14.6 Hz, 1H), 1.85 - 1.63 (m, 3H), 1.56 - 1.39 (m, 4H), 1.29 - 1.18 (m, 1H), 0.88 - 0.74 (m, 3H), 0.07 (s, 4.5H), 0.06 (s, 4.5H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	δ 200.0, 199.8, 136.2, 136.1, 128.4, 128.1, 115.5, 115.3, 65.7, 65.6, 51.8, 51.7, 48.6, 48.5, 38.3, 38.2, 33.6, 32.9, 30.5, 29.6, 29.5, 29.1, 24.1, 23.1, 20.9, 20.8, 7.2, 6.6, -1.6, -1.5
HRMS (m/z)	**:**	307.2199 [$(M + H)^+$ calcd for $(C_{17}H_{31}N_2OSi)^+$: 307.2206]

42. Synthesis of (3*S*)-3-ethyl-3-(3-oxopent-4-en-1-yl)-1-((trimethylsilyl)methyl) piperidine-2-carbonitrile (280a) :

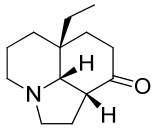
Above mentioned procedure used for the synthesis of **280a**.



280a

Yield	**:**	0.17 g
TLC	**:**	0.4 (SiO_2, ethylacetate : hexane= 1 : 9)
HRMS (m/z)	**:**	307.2200 [$(M + H)^+$ calcd for $(C_{17}H_{31}N_2OSi)^+$: 307.2206]

43. Synthesis of (3[1]*S*,6a*R*,9a*R*)-6a-ethyloctahydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-9(2*H*)-one:



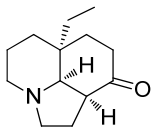
(-)-49

To a stirred solution of **280b** (0.12 g, 0.391 mmol) in anhydrous acetonitrile, Ag(I)F (0.06 g, 0.47 mmol) was added at room temperature and stirred for 3 h (protect reaction mixture from light). On completion of reaction (TLC analysis), the reaction mixture was filtered through celite and washed with EtOAc. The combined organic layer was concentrated and purification by column chromatography resulted **49** as colorless liquid.

Yield	**:**	0.075 g, 92%.
TLC	**:**	0.4 (SiO_2, ethylacetate : hexane= 6 : 4)
Optical rotation	**:**	$[\alpha]^{24}{}_D$ = -23.81 (*c* = 0.5, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	3438, 2934, 2786, 2725, 1709, 1448, 1345
^{1}H NMR (400MHz ,$CDCl_3$) δ	**:**	3.05 - 2.97 (m, 2H), 2.67 (ddd, *J* = 7.4 , 5.5 Hz, 1H), 2.44 - 2.36 (m, 2H), 2.33 - 2.29 (m, 1H), 2.25 (td, *J* = 13.7, 4.3 Hz, 1H), 1.96 - 1.92 (m, 1H), 1.92 - 1.87 (m, 2H), 1.82 - 1.79 (m, 1H), 1.74 - 1.67 (m, 1H), 1.67 - 1.60 (m, 2H), 1.52 - 1.47 (m, 2H), 1.32 (app sextet, *J* = 7.4, 1H), 1.10 (td, *J* = 13.5, 4.7 Hz, 1 H), 0.94 (t, *J* = 7.6 Hz, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	δ 211.5, 73.5, 53.2, 52.9, 48.1, 36.8, 34.7, 32.8, 30.1, 26.0, 21.3, 21.2, 7.1
HRMS (m/z)	**:**	208.1693 [$(M + H)^+$ calcd for $(C_{13}H_{22}NO)^+$: 208.1701]

44. Synthesis of (3[1]*R*,6a*S*,9a*S*)-6a-ethyloctahydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-9(2*H*)-one:

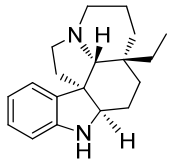
Above mentioned procedure used for the synthesis of **(+)-49**.



(+)-49

Yield	**:**	0.045 g, 91%
TLC	**:**	0.4 (SiO_2, ethylacetate : hexane= 6 : 4)
Optical rotation	**:**	$[\alpha]^{24}{}_D$ = +21.62 (*c* =0.5, $CHCl_3$)
IR υ_{max} cm^{-1}	**:**	3438, 2934, 2786, 2725, 1709, 1448, 1345
^{1}H NMR (400MHz ,$CDCl_3$) δ	**:**	3.07 - 2.96 (m, 2H), 2.67 (ddd, *J* = 7.3 , 5.3 Hz, 1H), 2.47 - 2.19 (m, 4H), 1.98 - 1.62 (m, 7H), 1.54 - 1.44 (m, 2H), 1.37 - 1.28 (app sextet, 7.4 Hz, 1H), 1.10 (td, *J* = 13.3 , 4.5 Hz, 1H), 0.94 (t, *J* = 7.6 Hz, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	δ 211.5, 73.6, 53.2, 52.9, 48.2, 36.8, 34.7, 32.9, 30.1, 26.1, 21.3, 21.2, 7.1
HRMS (m/z)	**:**	208.1694 [$(M + H)^+$ calcd for $(C_{13}H_{22}NO)^+$: 208.1701]

45. Synthesis of (+)-Aspidospermidine (6):



(+) Aspidospermidine (**6**)

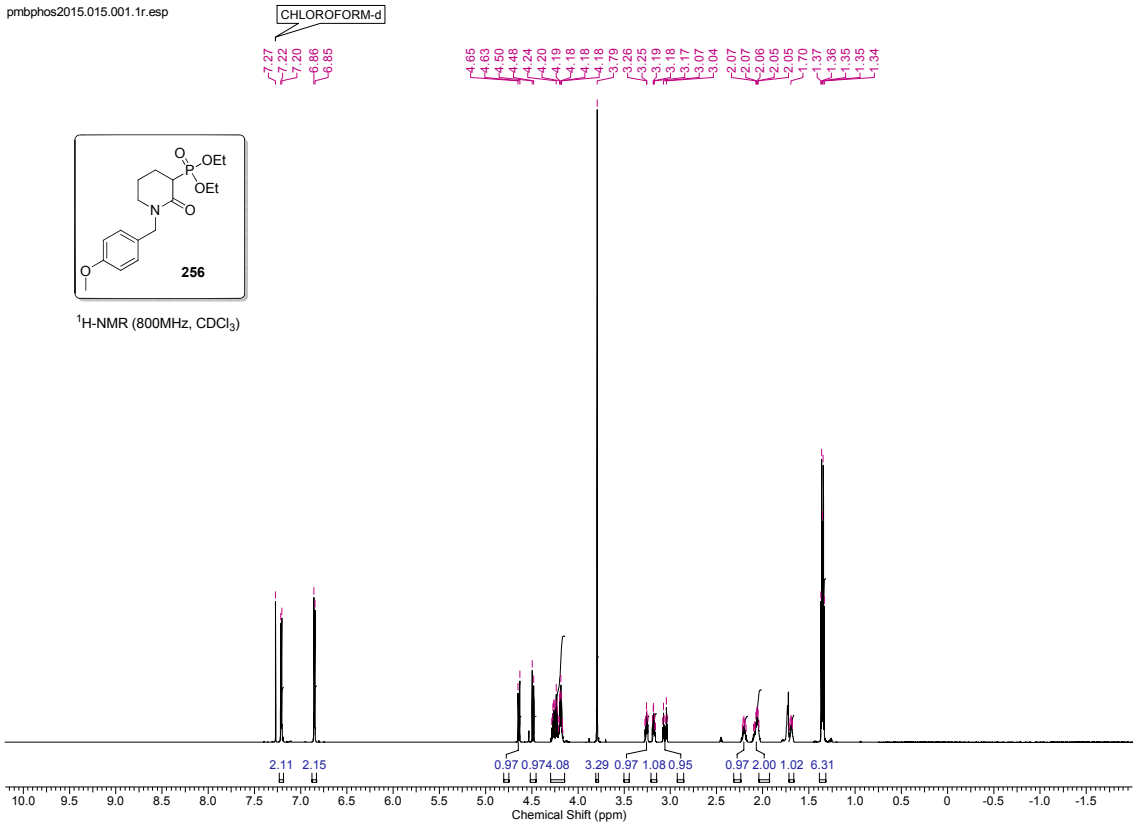
Phenyl hydrazine (0.022 g, 0.202 mmol) was added to a stirred solution of **49** (0.035 g, 0.168 mmol) in benzene (5 mL) and refluxed for 3 h. The reaction mixture was cooled to room temperature and concentrated to obtain crude phenyl hydrazone, which was dissolved in 5 mL glacial acetic acid and refluxed for 4 h, concentrated to dryness to obtain crude indolene (dehydroaspidospermidine) as a brown color liquid.

This crude indolene was dissolved in anhydrous THF (5 mL), added $LiAlH_4$ (0.059 g, 1.68 mmol) and refluxed for 12 h. The reaction mixture was cooled to 0 ˚C, and quenched with H_2O (2 mL) and stirred for 15 min. The suspension was filtered through a plug of celite and the filtrate was dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography using ethylacetate to give aspidospermidine **6** (0.024 g, 50%**)** as a pale yellow oil. This compound **6** on standing long time gave pale yellow color solid.

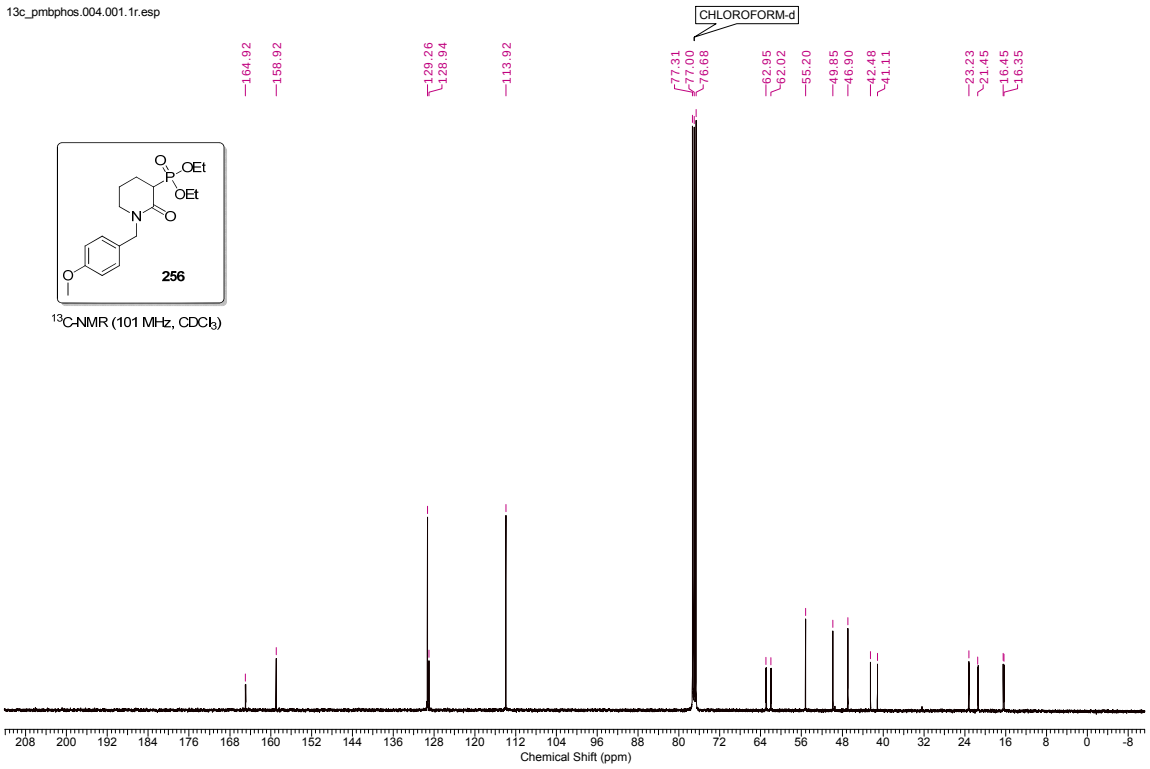
Yield	**:**	50%
TLC	**:**	0.4 (SiO_2, DCM: MeOH = 9:1)
Optical rotation	**:**	$[\alpha]_D^{29}$ +20.14 (*c* = 0.5, EtOH); Lit[8a] $[\alpha]_D^{29}$ = +20.6 (*c* = 0.64, EtOH).
IR υ_{max} cm^{-1}	**:**	3363, 2932, 2860, 2779, 2722, 1606, 1480, 1462, 1332
Melting Point	**:**	118-120 °C
^{1}H NMR (400MHz ,$CDCl_3$) δ	**:**	7.09 (d, *J* = 7.5 Hz, 1H), 7.02 (td, *J* = 7.5, 0.95 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 3.52 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.15 - 3.11 (m, 1H), 3.08 - 3.04 (m, 1H), 2.33 - 2.28 (m, 1H), 2.28 - 2.24 (m, 1H), 2.23 (s, 1H), 1.99 - 1.92 (m, 2H), 1.74 (qt, *J* = 13.04, 4.06 Hz, 1H), 1.67 - 1.62 (m, 2H), 1.54 - 1.46 (m, 3H), 1.43 - 1.36 (m, 1H), 1.12

		(td, *J* = 13.7, 4.8 Hz, 1H), 1.06 (dt, *J* = 13.6, 3.8 Hz, 1H), 0.90 - 0.85 (m, 1H), 0.64 (t, *J* = 7.5 Hz, 3H)
^{13}C NMR ($CDCl_3$, 101 MHz) δ	**:**	δ 149.4, 135.7, 127.0, 122.8, 119.0, 110.3, 71.3, 65.7, 53.9, 53.3, 53.0, 38.8, 35.6, 34.4, 30.0, 28.1, 23.0, 21.7, 6.8
HRMS (m/z)	**:**	283.2167 [$(M + H)^+$ calcd for $(C_{19}H_{27}N_2)^+$: 283.2174]

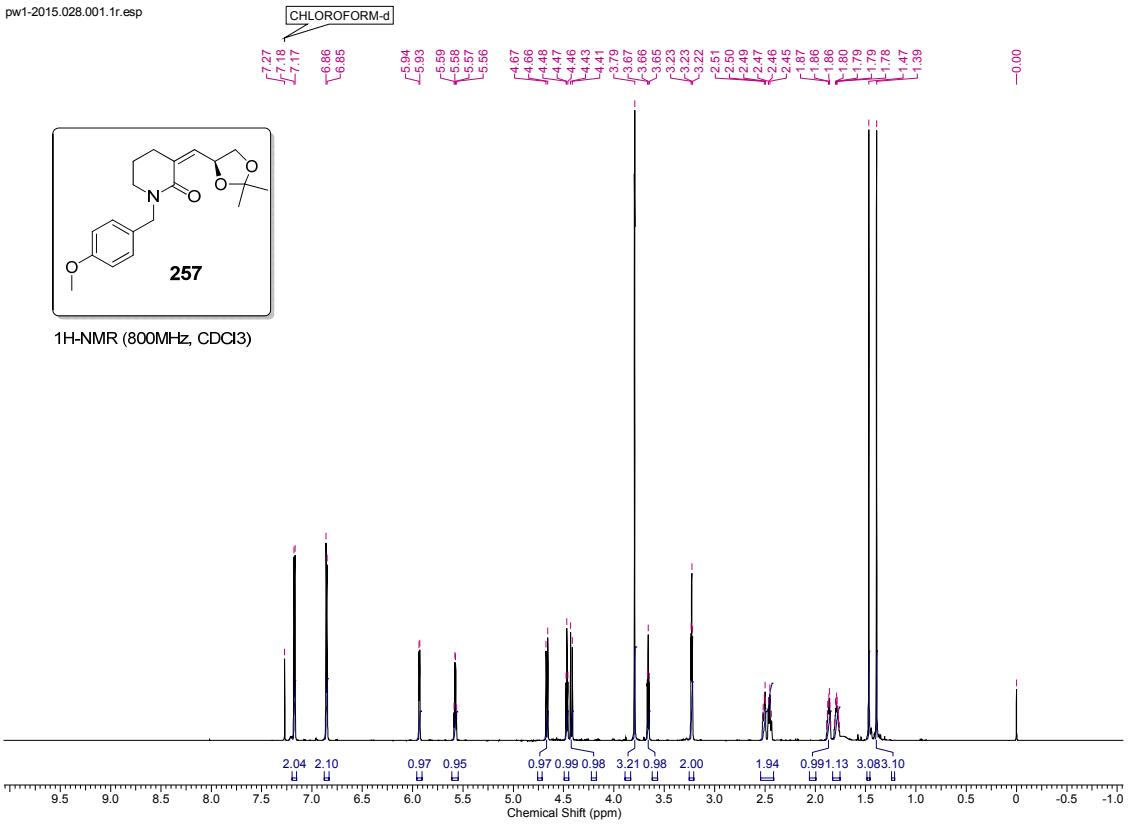
3.2 SPECTRAS

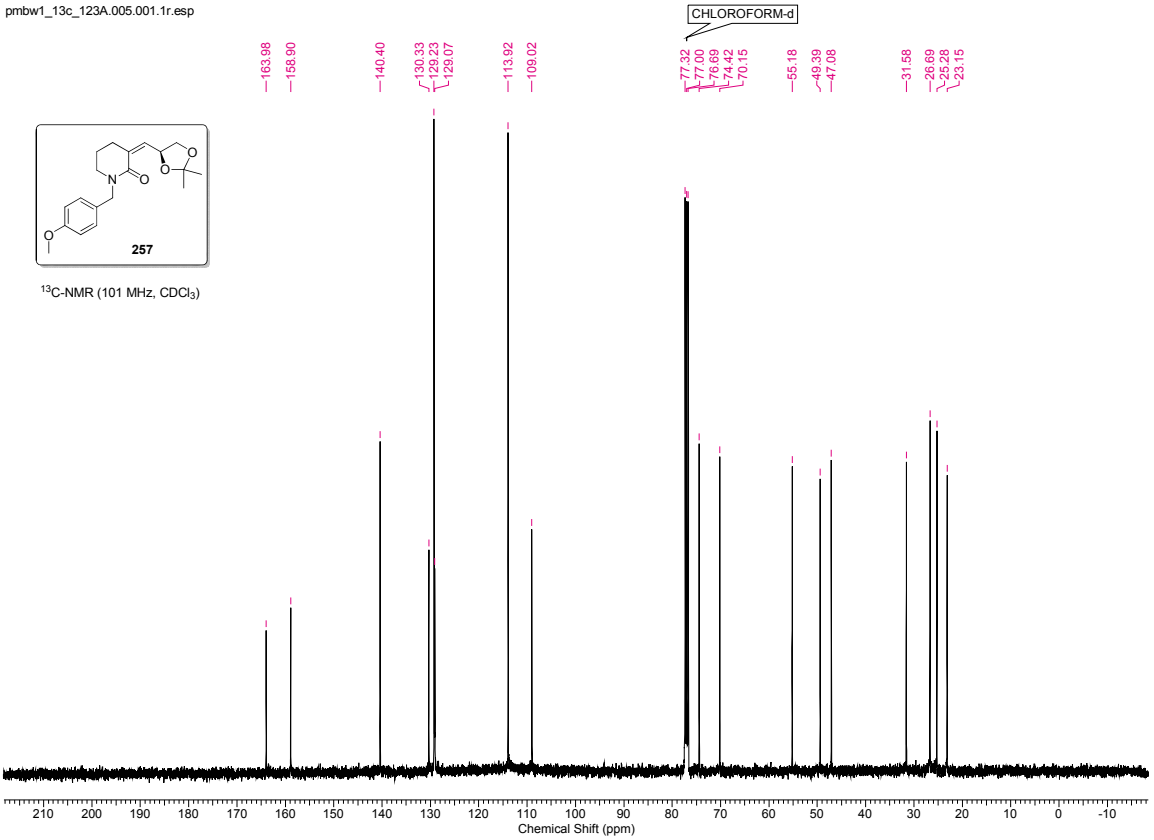


^{1}H-NMR (800MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)


pw1-2015.028.001.1r.esp
CHLOROFORM-d
257
1H-NMR (800MHz, CDCl3)
Chemical Shift (ppm)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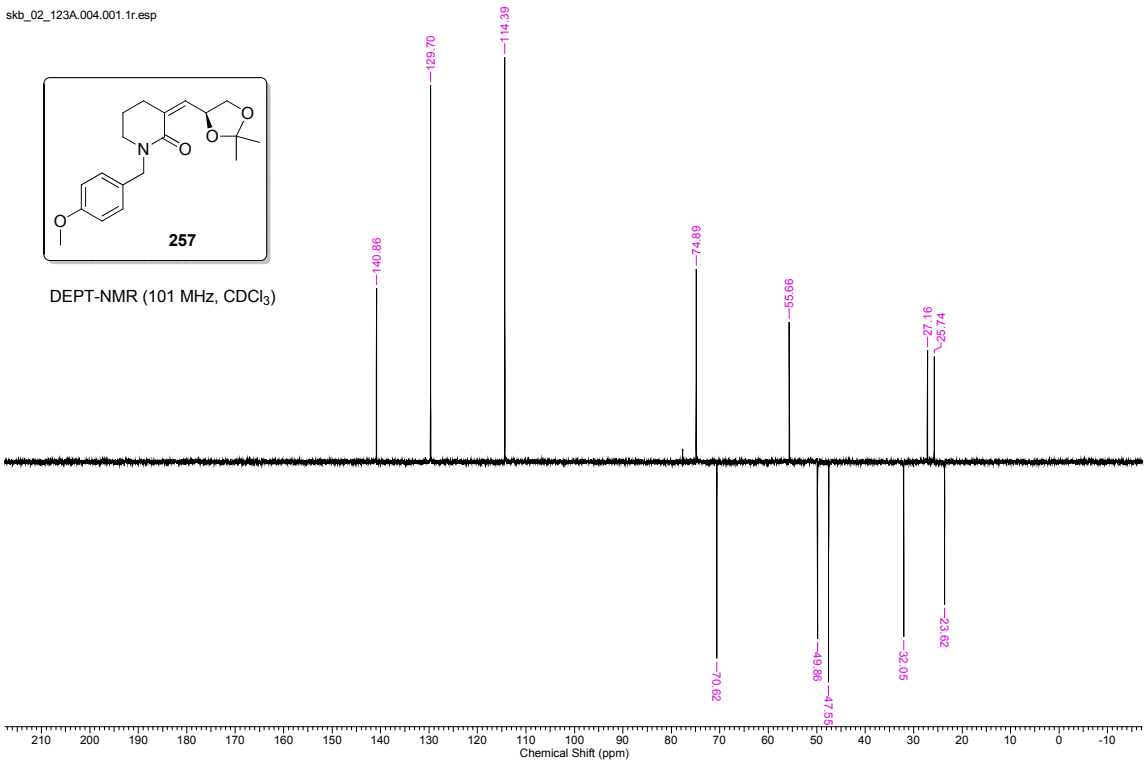
CHLOROFORM-d
257
13C-NMR (101 MHz, CDCl3)
Chemical Shift (ppm)


skb_02_123A.004.001.1r.esp
257
DEPT-NMR (101 MHz, CDCl3)
140.86
129.70
114.39
74.89
55.66
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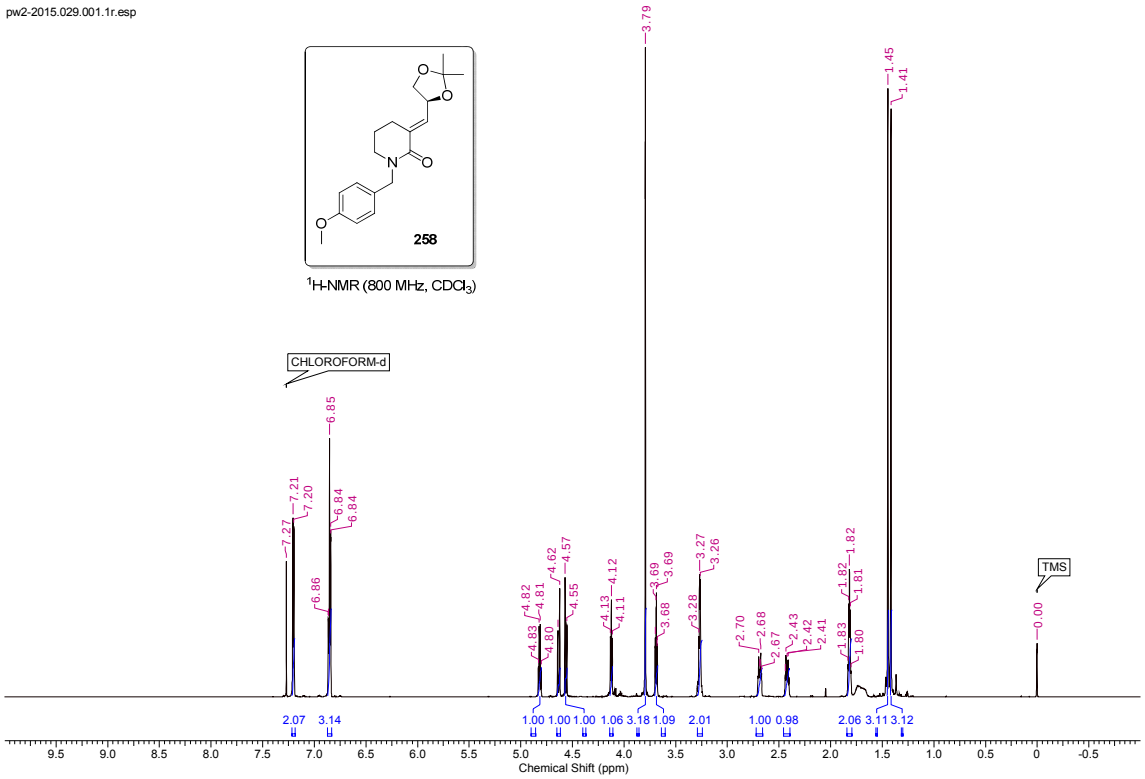
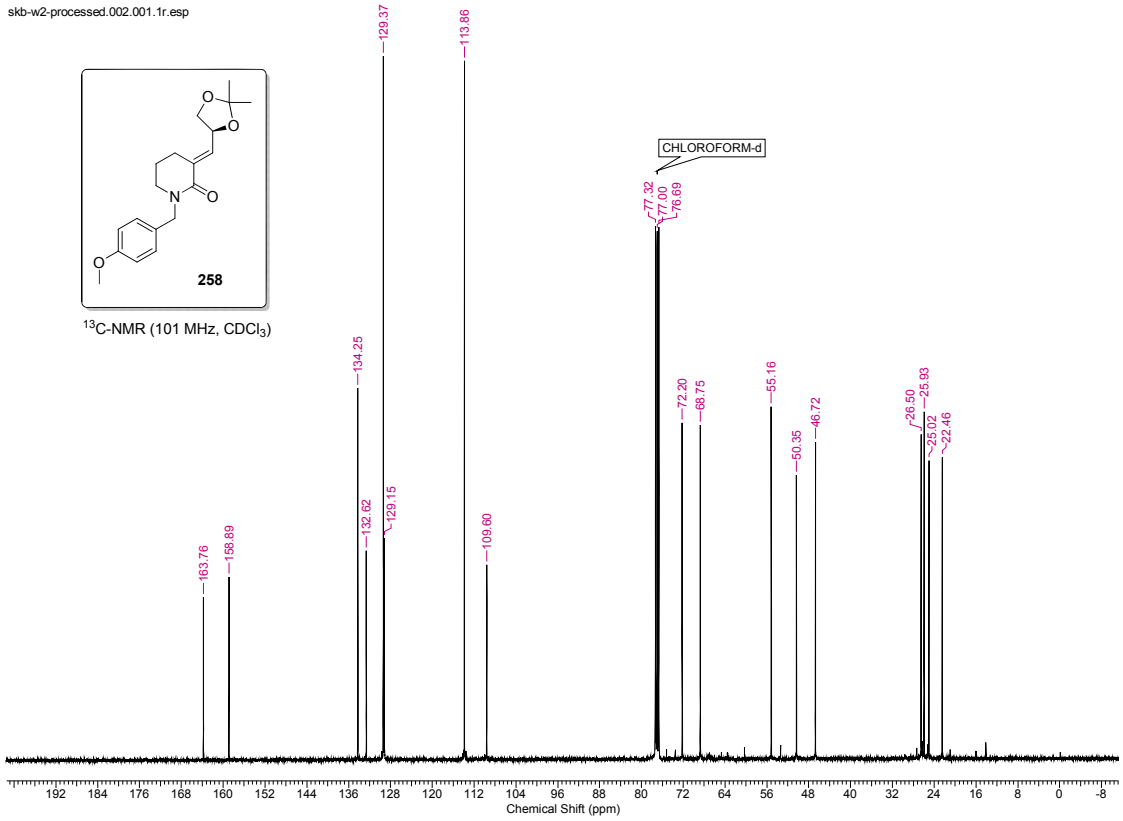
25.74
70.62
49.86
47.55
32.05
23.62
Chemical Shift (ppm)


pw2-2015.029.001.1r.esp
258
1H-NMR (800 MHz, CDCl3)
CHLOROFORM-d
TMS
Chemical Shift (ppm)



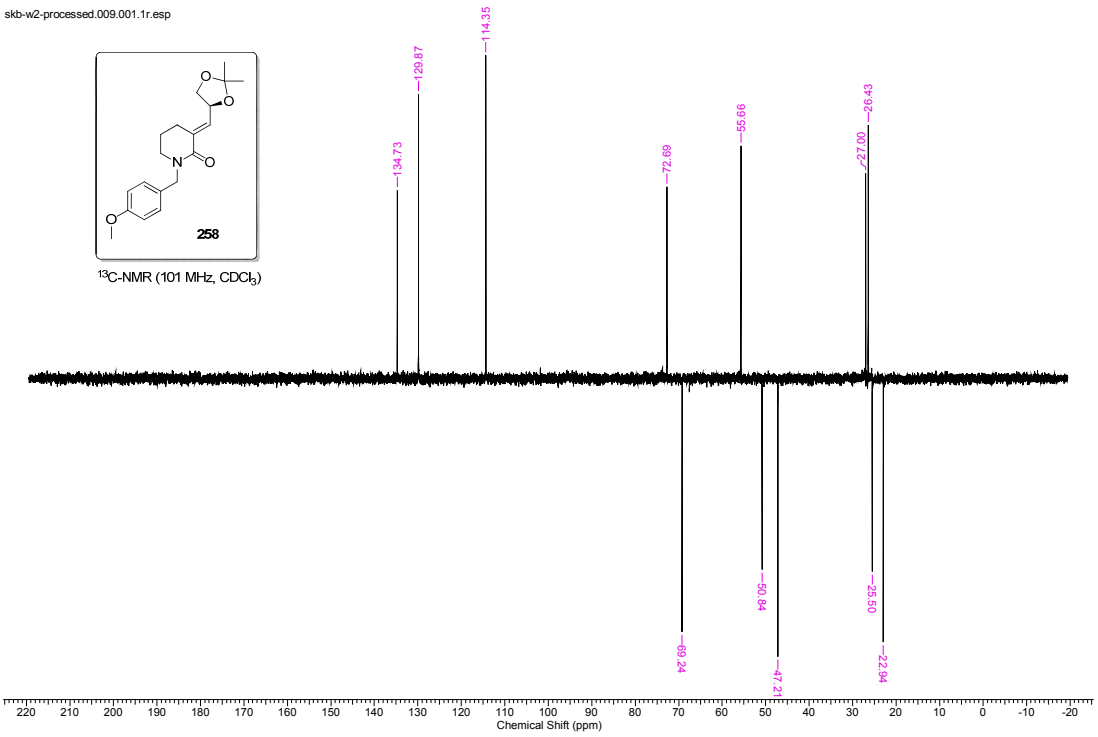
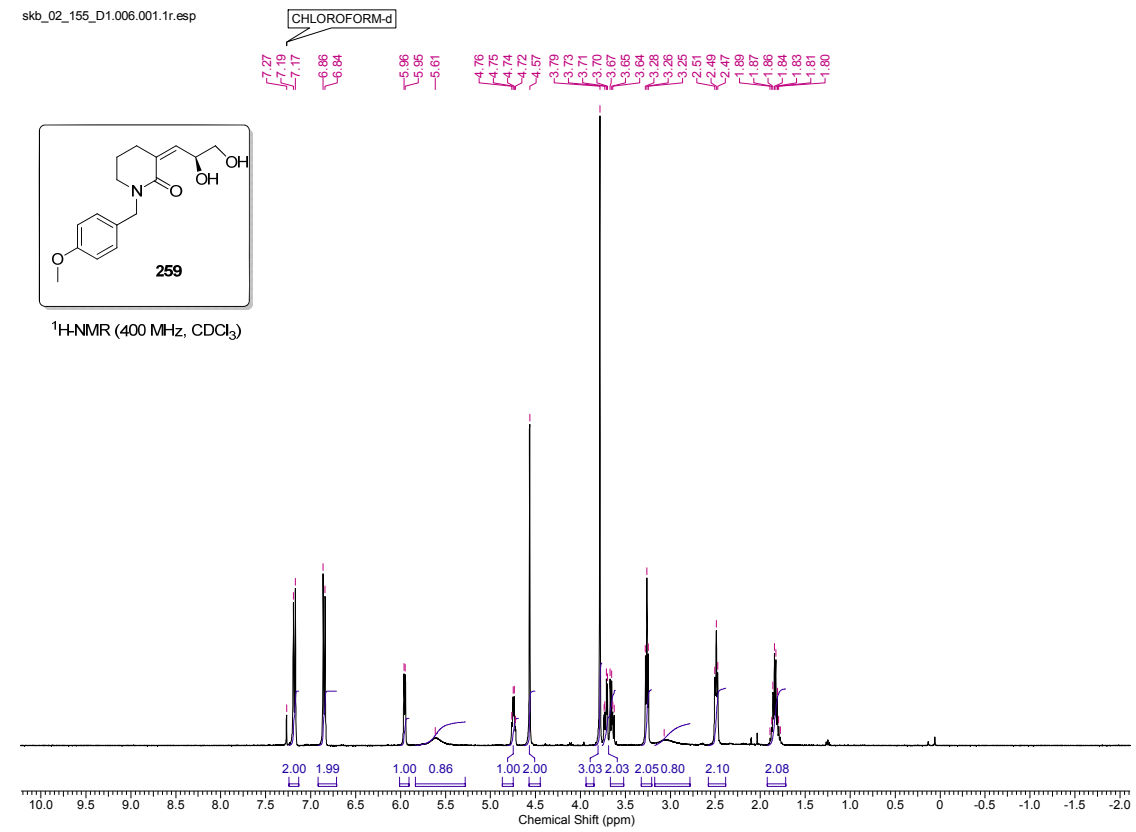
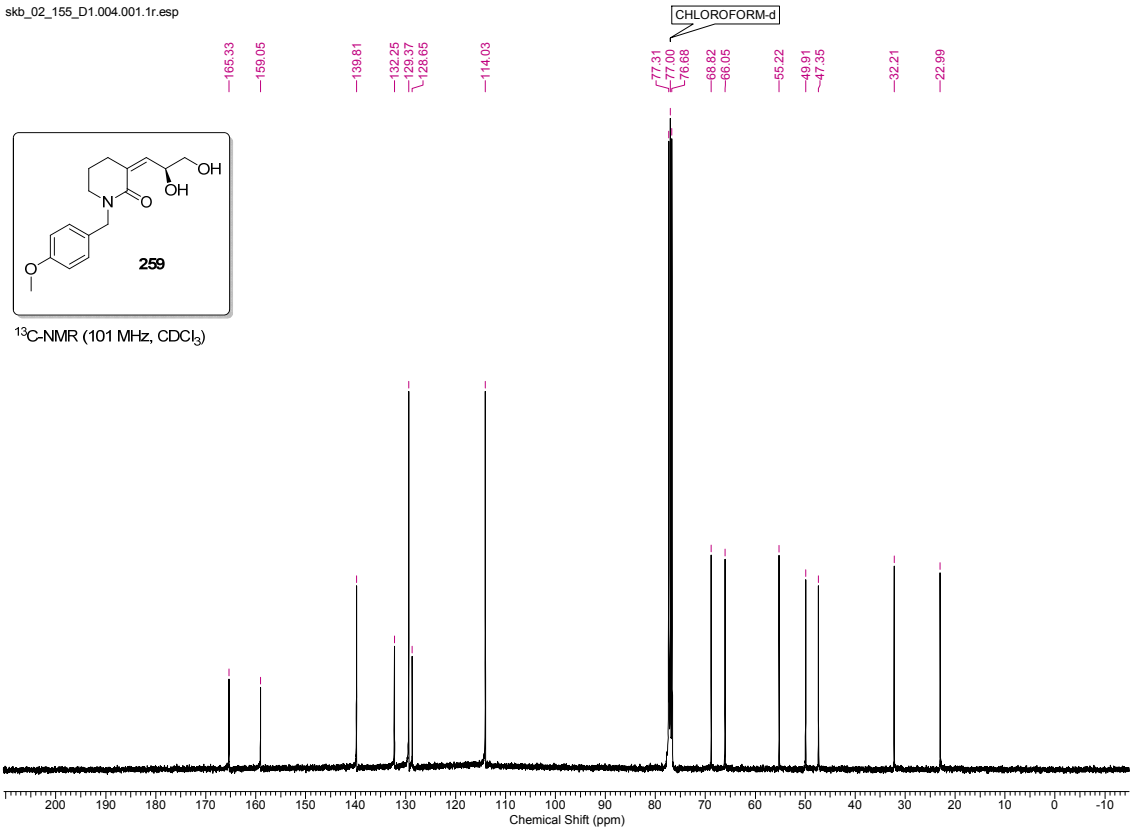


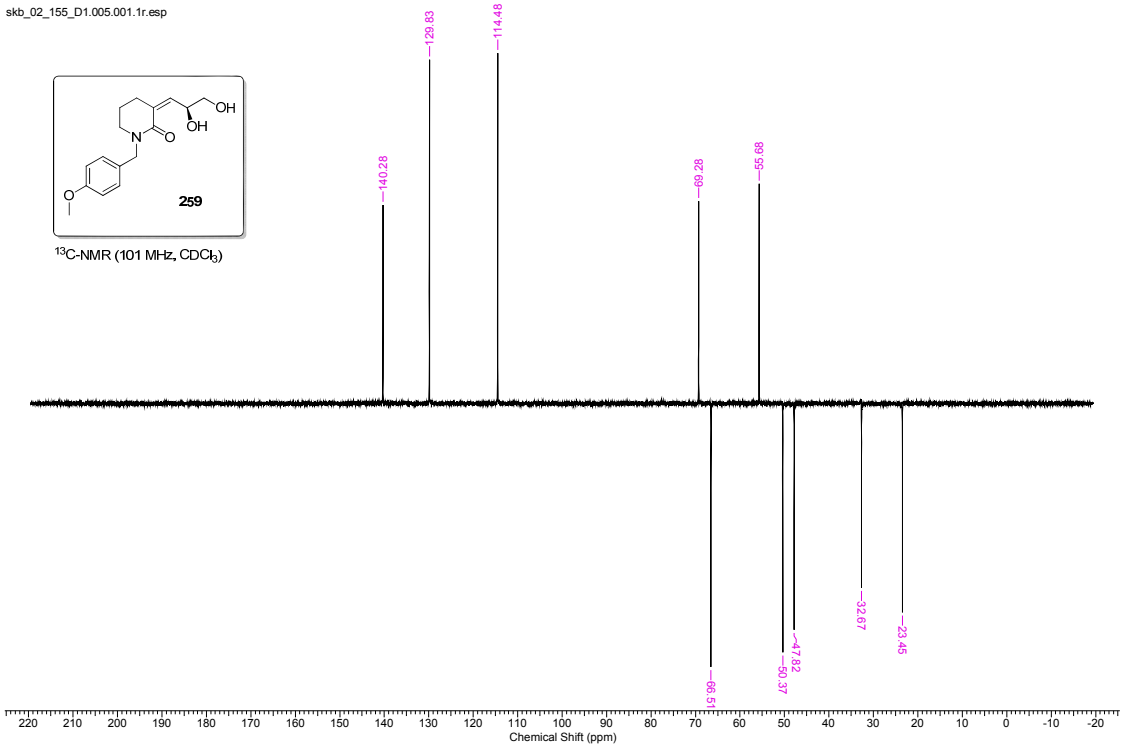
Figure ^{13}C NMR Spectrum (100 MHz, CDCl$_3$)

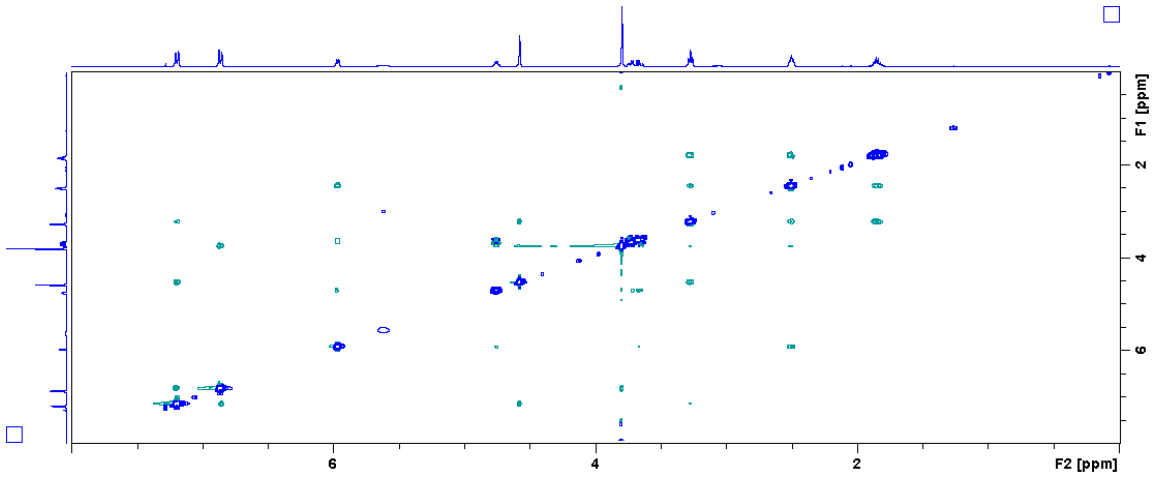


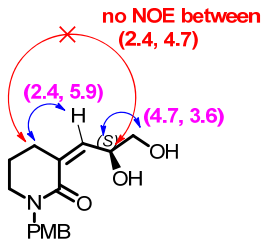
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

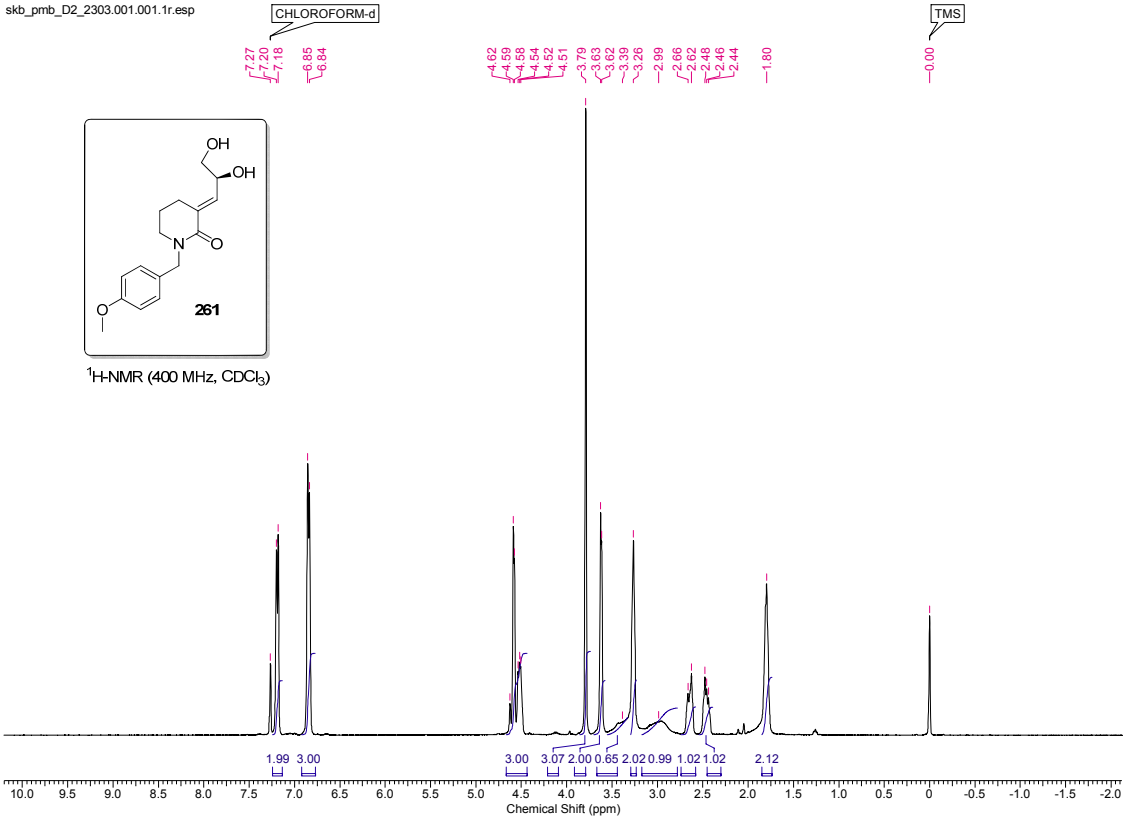




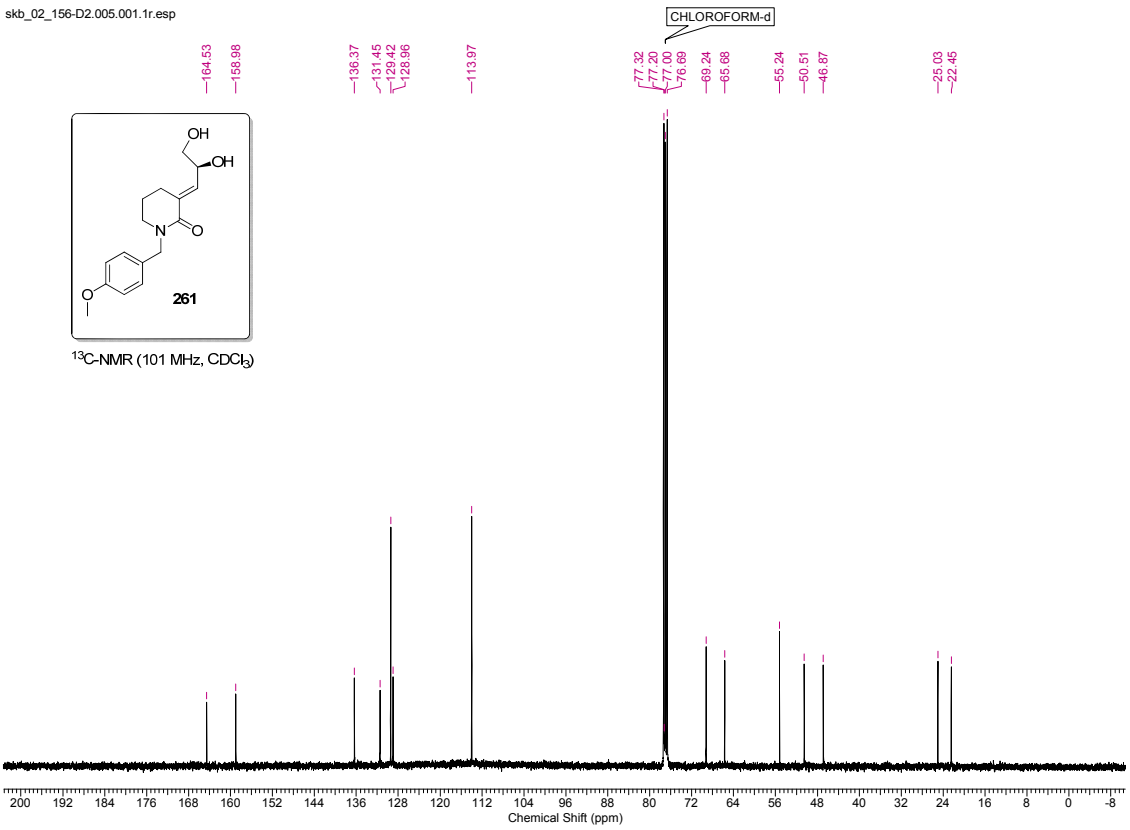


NOE observed between δ (2.4, 5.9 ppm)

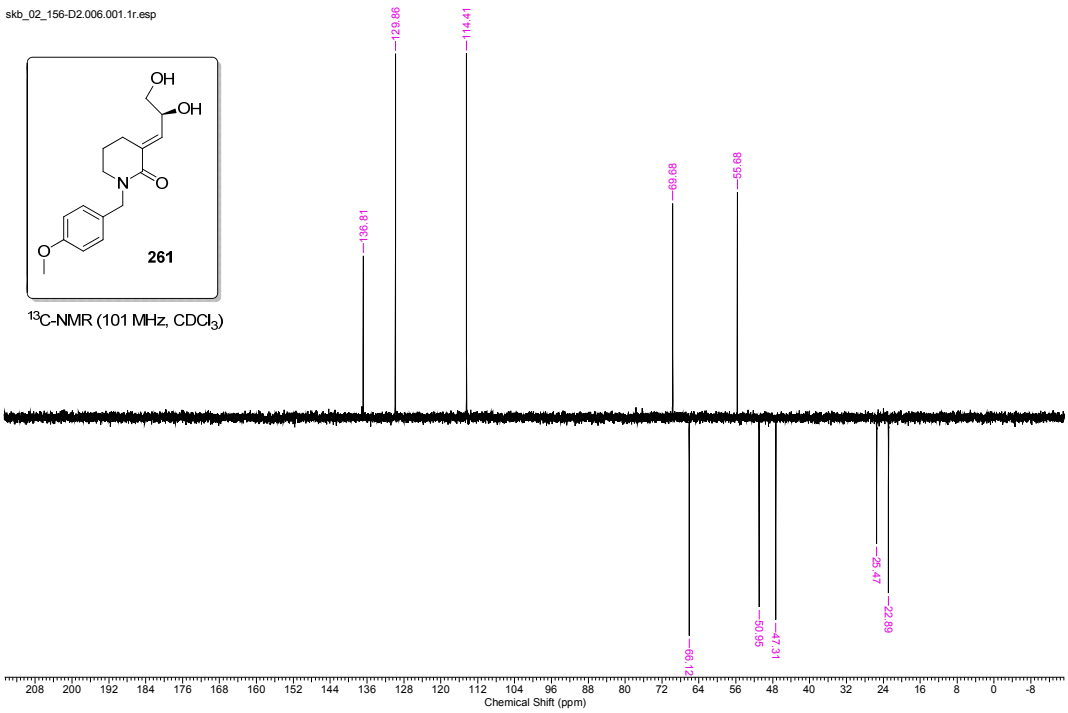
From Noesy spectrum, it is clear that the olefinic proton (δ 5.9 ppm) is in close proximate with allylic protons (2.4ppm)



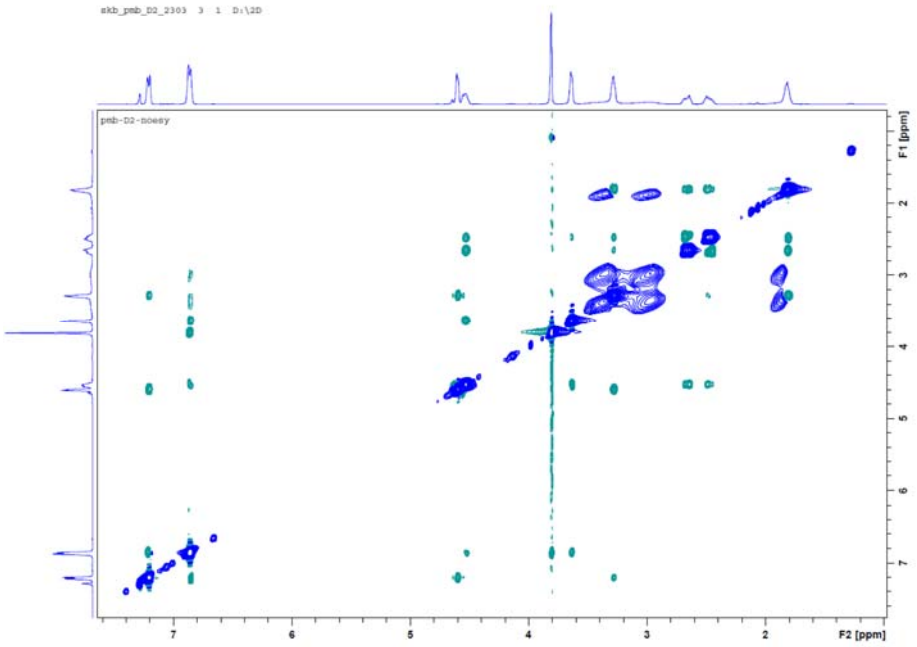
^{1}H-NMR (400 MHz, $CDCl_3$)

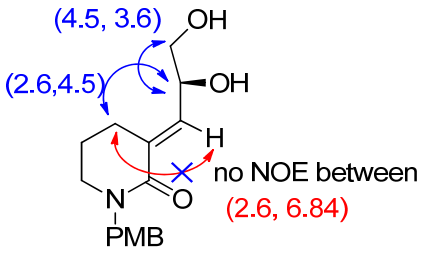


^{13}C-NMR (101 MHz, $CDCl_3$)



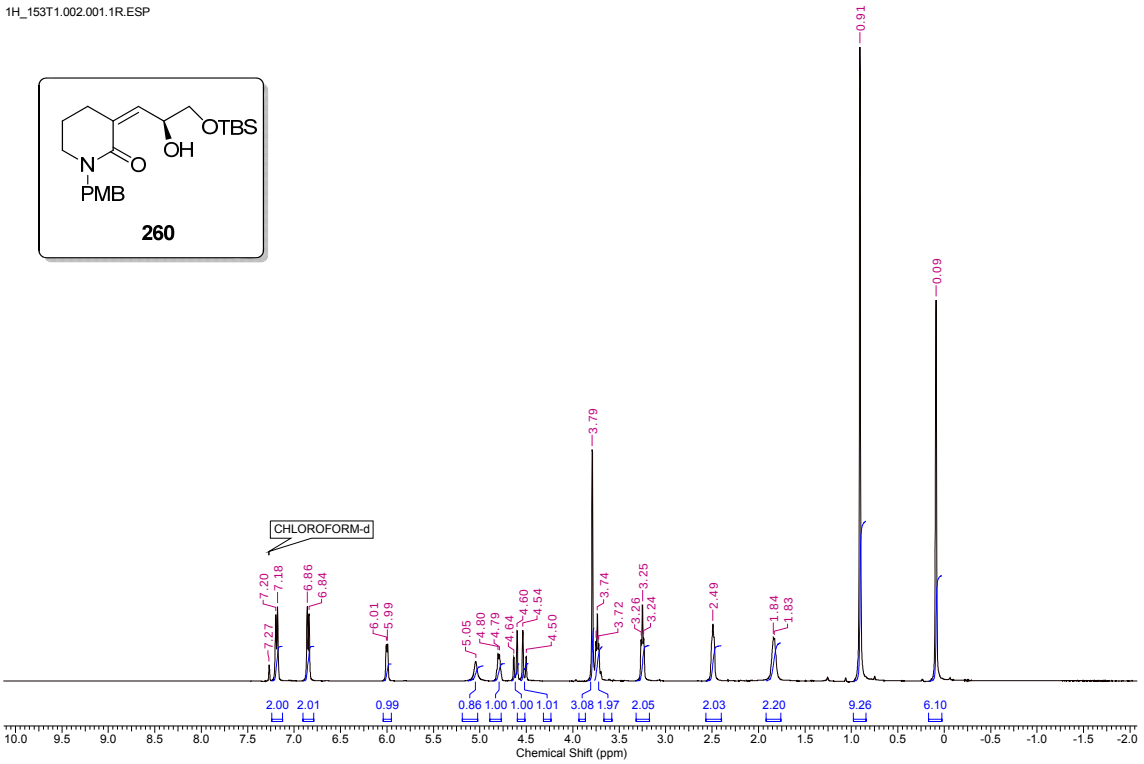
NOESY spectrum

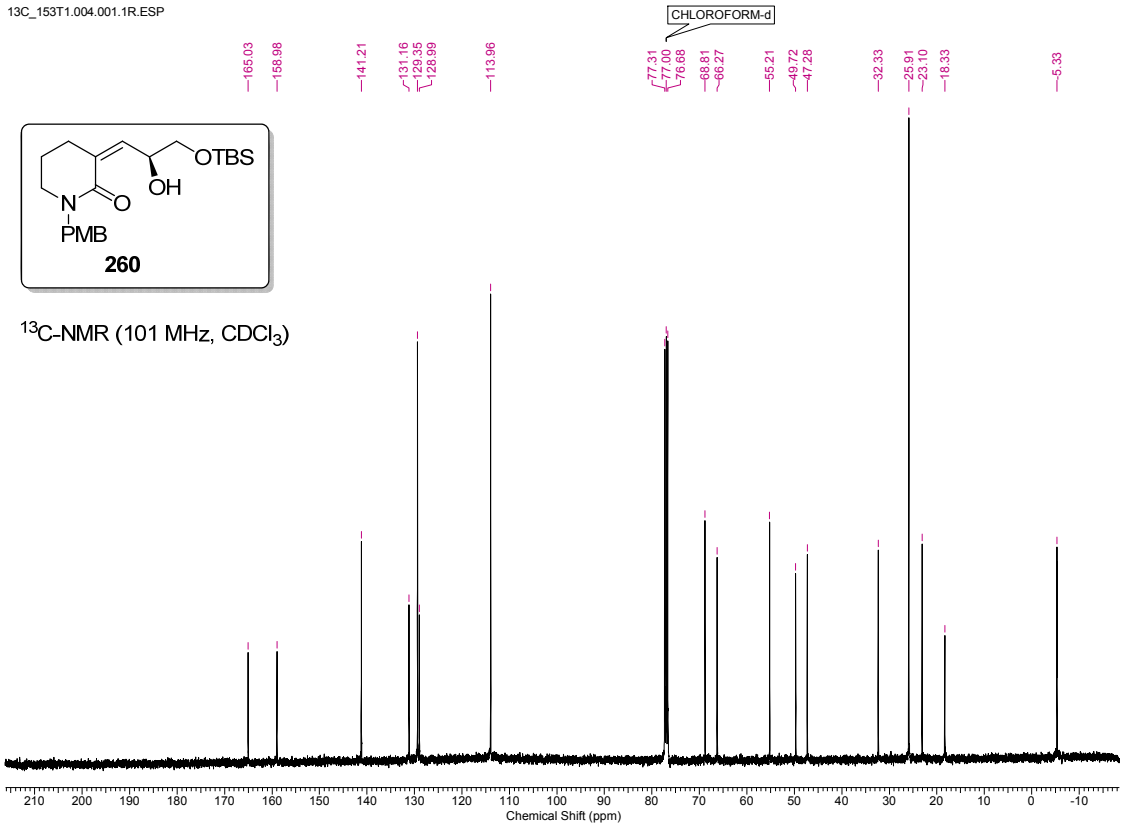




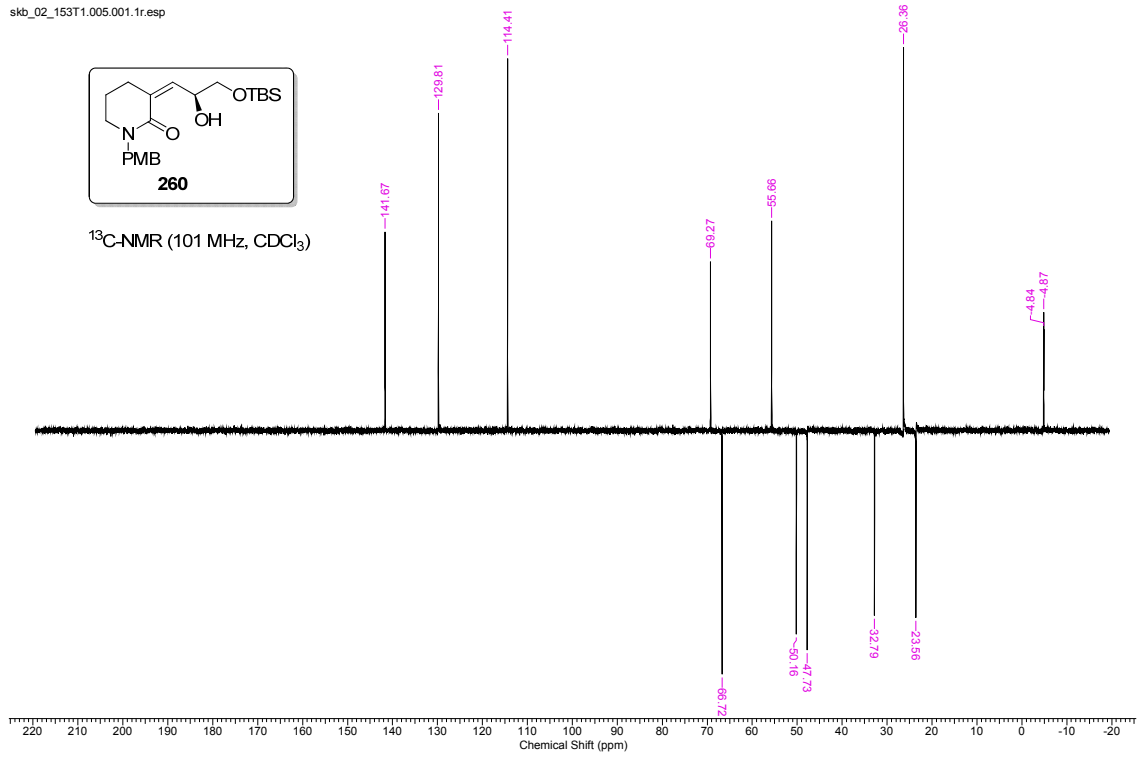
261

NO correlation between protons appearing at δ 6.84 and δ 2.6.

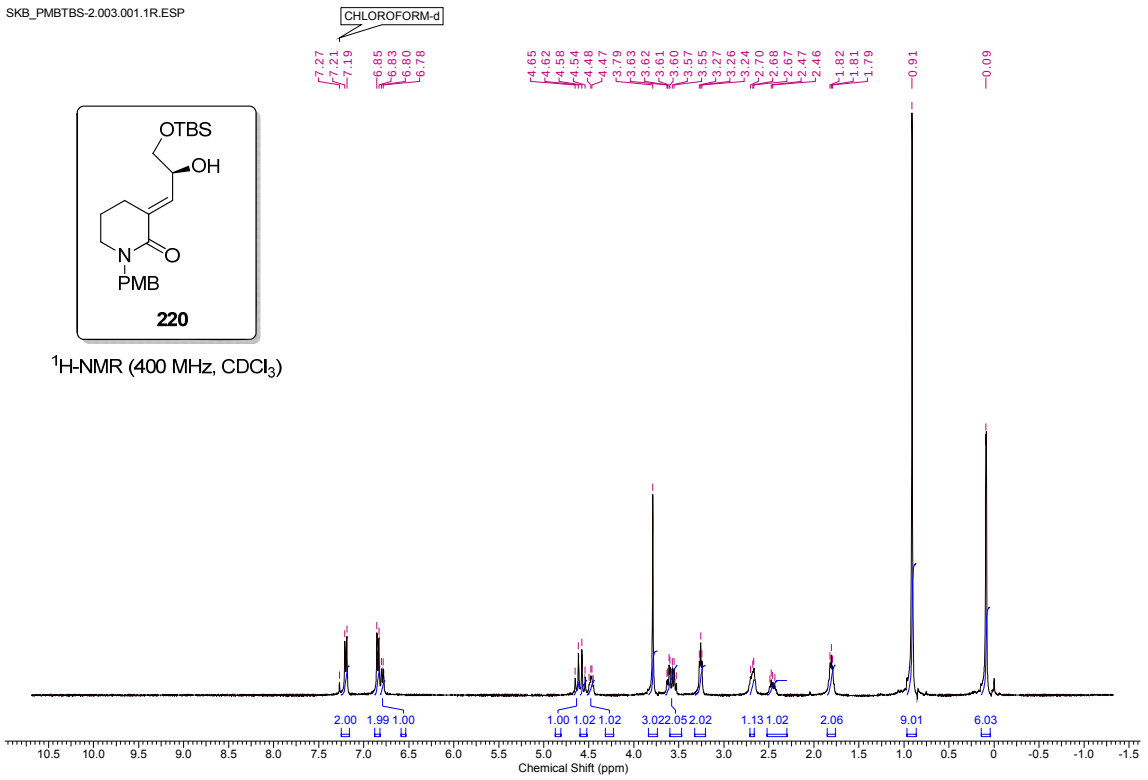




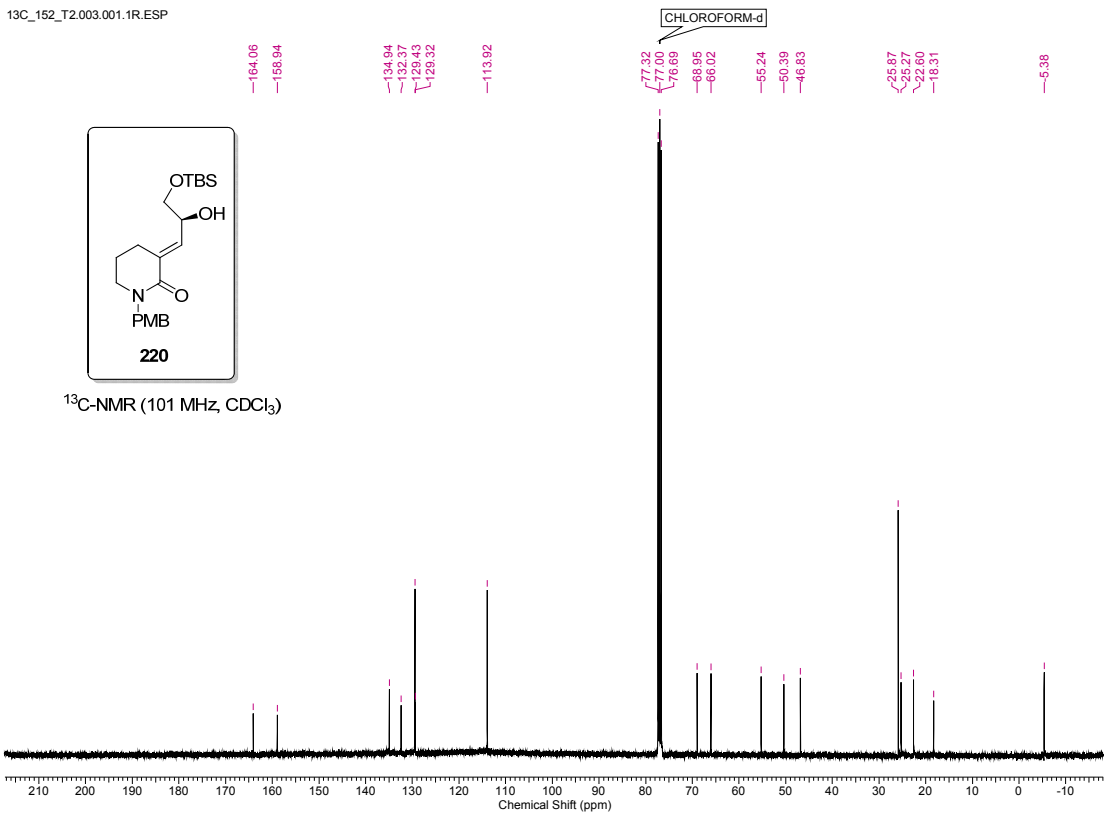
^{13}C-NMR (101 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, $CDCl_3$)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134.94
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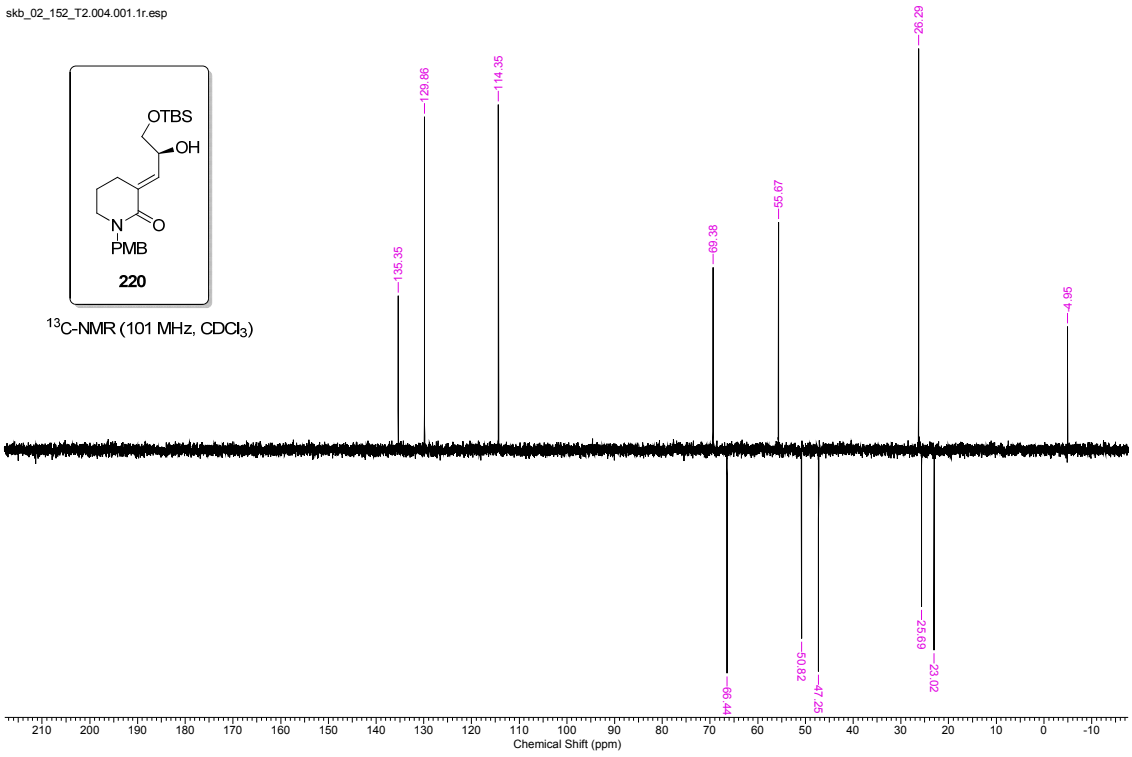
129.32
113.92
77.32
77.00
76.69
68.95
66.02
55.24
50.39
46.83
25.87
25.27
22.60
18.31
-5.38
OTBS
OH
N
O
PMB
220
^{13}C-NMR (101 MHz, $CDCl_3$)
Chemical Shift (ppm)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OTBS
OH
N
O
PMB
220
^{13}C-NMR (101 MHz, $CDCl_3$)
135.35
129.86
114.35
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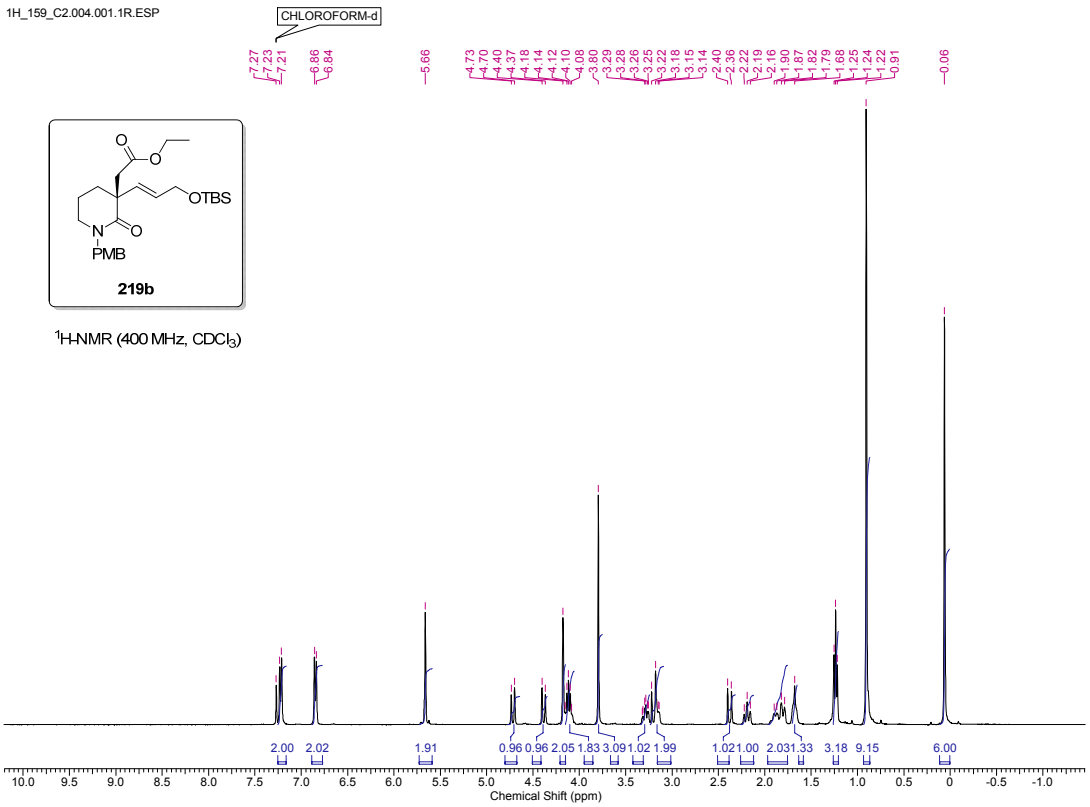
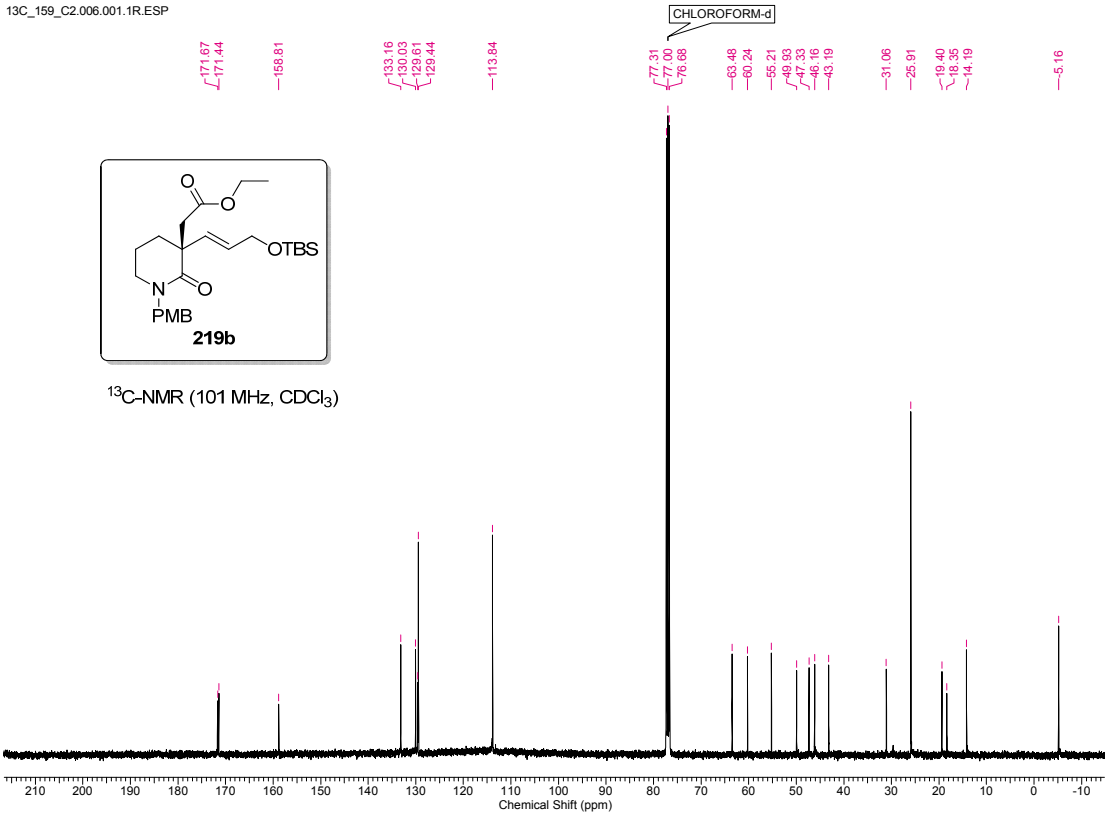
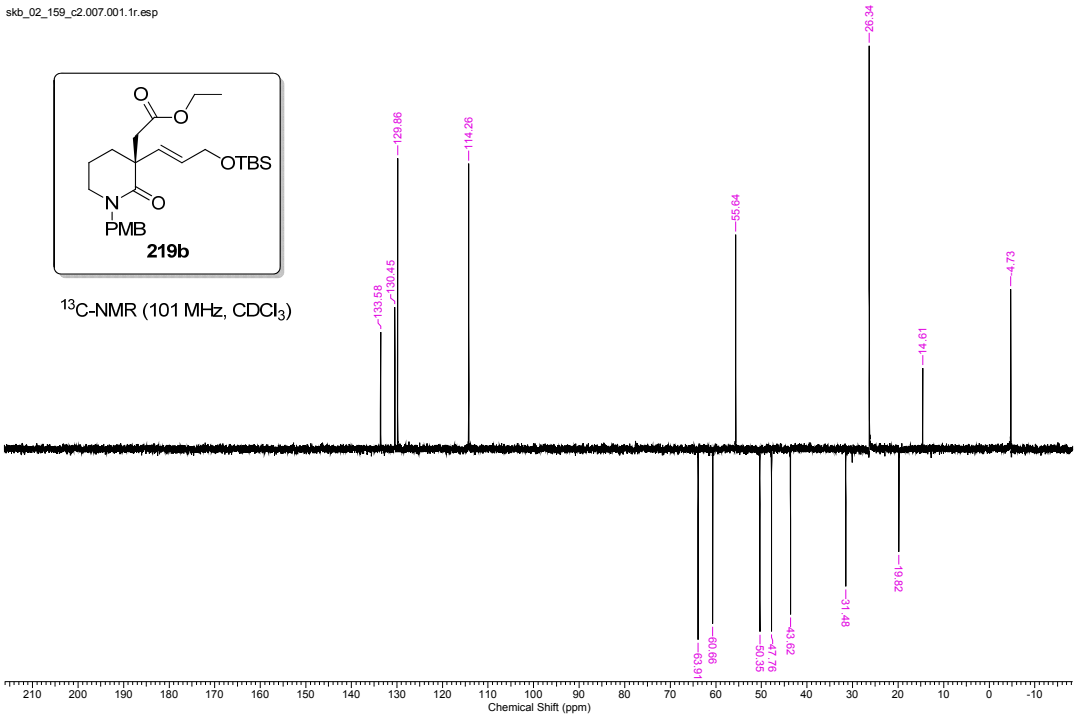
66.44
55.67
50.82
47.25
26.29
25.69
23.02
-4.95
Chemical Shift (ppm)

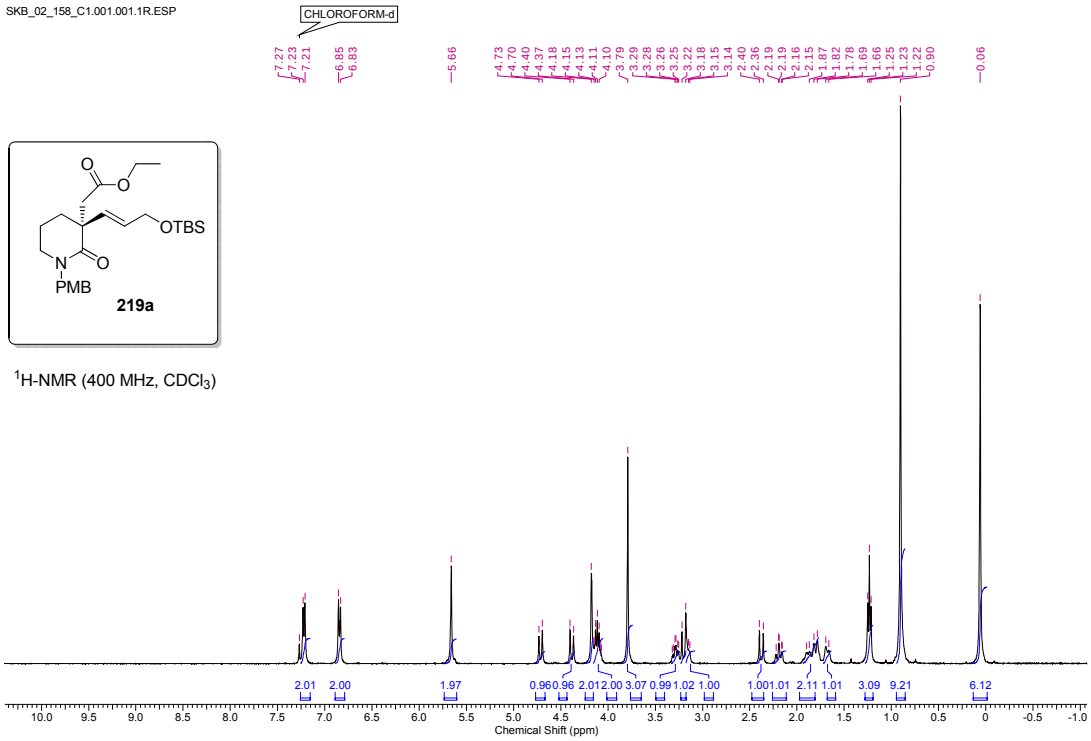


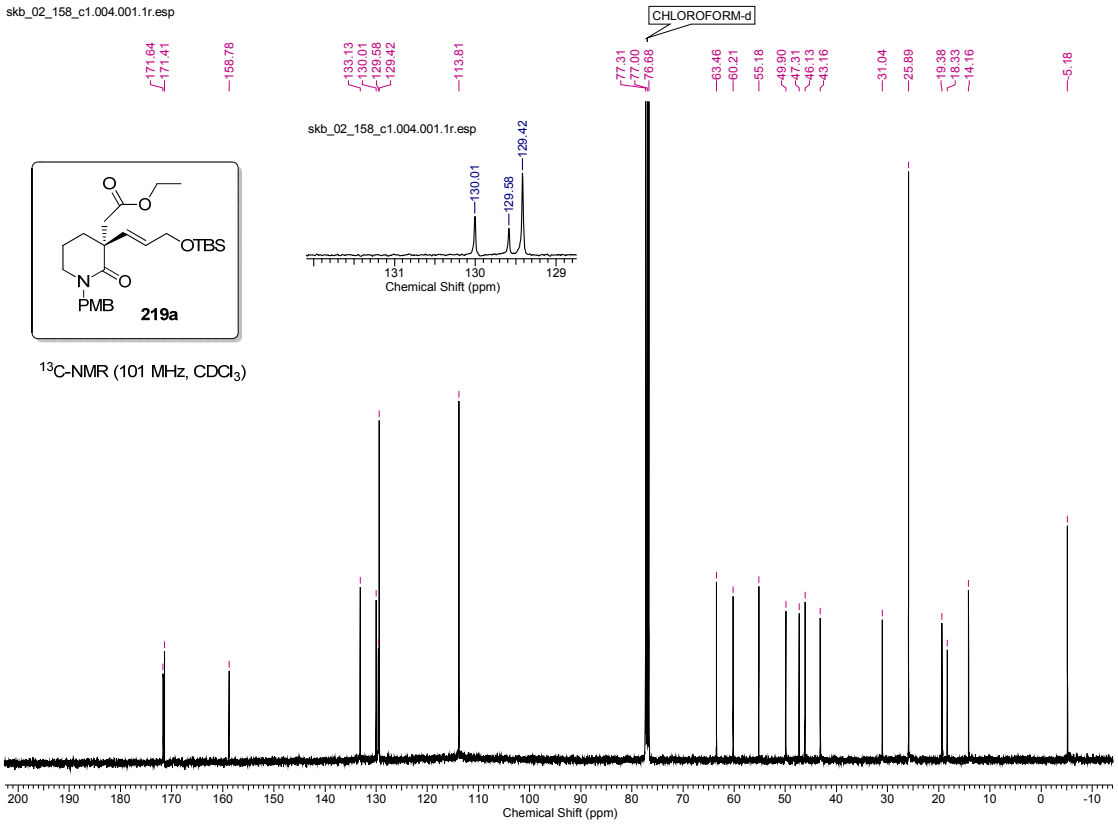
^{1}H-NMR (400 MHz, $CDCl_3$)

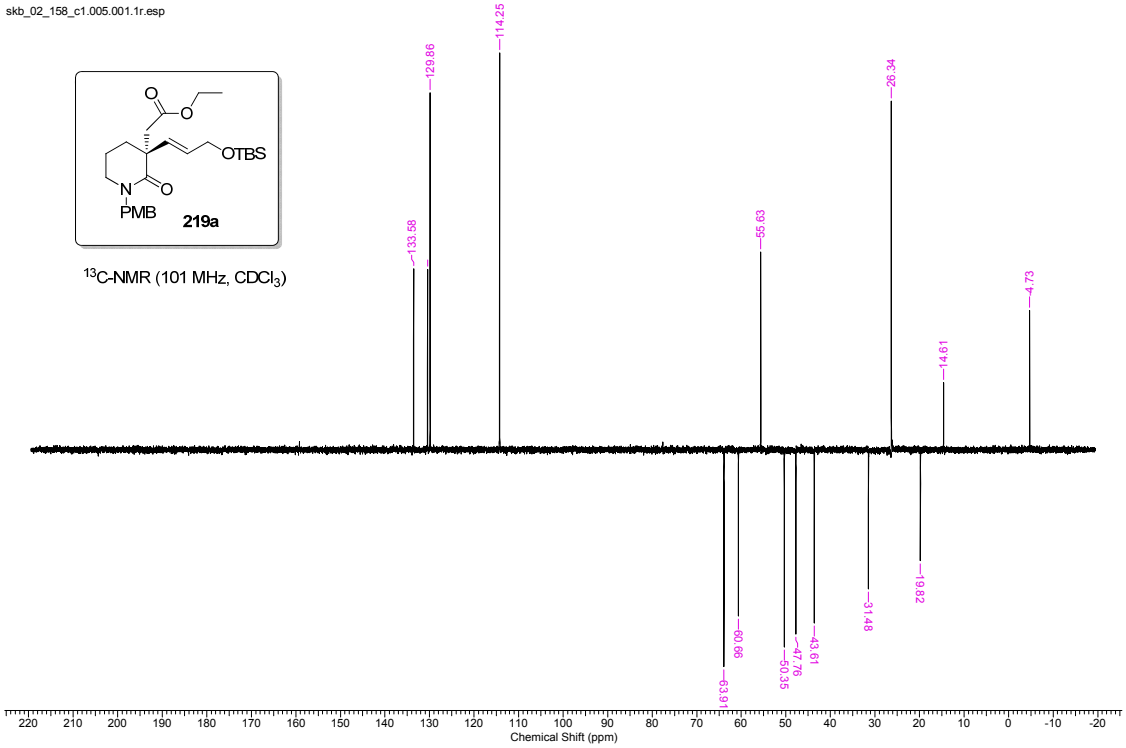


^{13}C-NMR (101 MHz, $CDCl_3$)

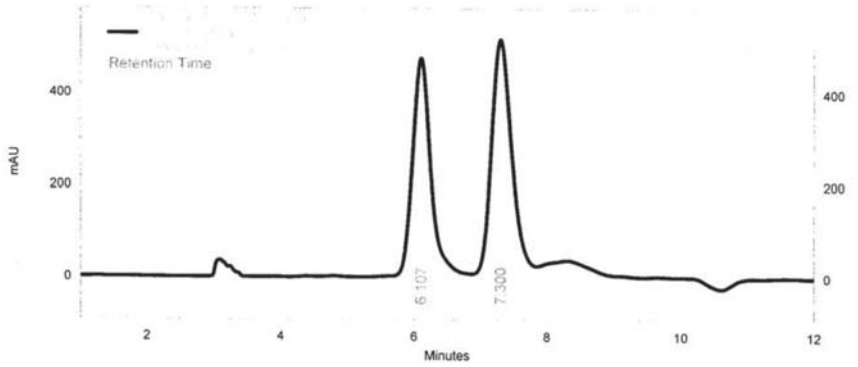

skb_02_159_c2.007.001.1r.esp
OTBS
N
O
PMB
219b
^{13}C-NMR (101 MHz, $CDCl_3$)
133.58
130.45
129.86
114.26
55.64
26.34
14.61
4.73
63.9
60.66
50.35
47.76
43.62
31.48
19.82
Chemical Shift (ppm)

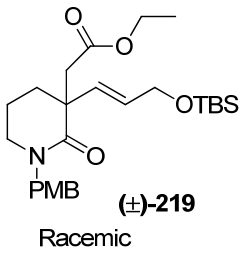

SKB_02_158_C1.001.001.1R.ESP
CHLOROFORM-d
OTBS
N
O
PMB
219a
^{1}H-NMR (400 MHz, $CDCl_3$)
7.27
7.23
7.21
6.85
6.83
5.66
4.73
4.70
4.40
4.37
4.18
4.15
4.13
4.11
4.10
3.79
3.29
3.28
3.26
3.25
3.22
3.18
3.15
3.14
2.40
2.36
2.19
2.19
2.16
2.15
1.87
1.82
1.78
1.68
1.66
1.25
1.23
1.22
0.90
0.06
2.01
2.00
1.97
0.96
0.96
2.01
2.00
3.07
0.99
1.02
1.00
1.00
1.01
2.11
1.01
3.09
9.21
6.12
Chemical Shift (ppm)


skb_02_158_c1.004.001.1r.esp
CHLOROFORM-d
171.64
171.41
158.78
133.13
130.01
129.58
129.42
113.81
77.31
77.00
76.68
63.46
60.21
55.18
49.90
47.31
46.13
43.16
31.04
25.89
19.38
18.33
14.16
5.18
skb_02_158_c1.004.001.1r.esp
130.01
129.58
129.42
131
130
129
Chemical Shift (ppm)
OTBS
N
O
PMB
219a
^{13}C-NMR (101 MHz, $CDCl_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


skb_02_158_c1.005.001.1r.esp
114.25
129.86
133.58
26.34
55.63
4.73
14.61
19.82
31.48
43.61
47.76
50.35
60.86
63.94
OTBS
N
O
PMB
219a
^{13}C-NMR (101 MHz, $CDCl_3$)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
Chemical Shift (ppm)

HPLC reports:



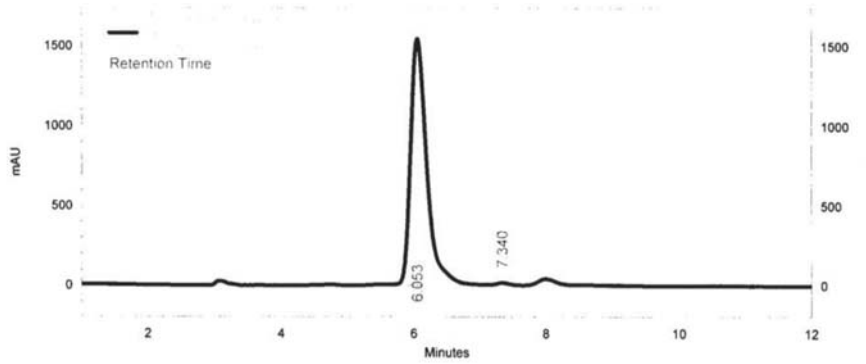


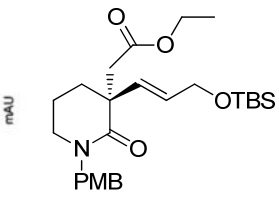
(±)-219
Racemic

DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
6.107	18526906	46.47	988626	48.45
7.300	21338234	53.53	1052056	51.55
Totals	39865140	100.00	2040682	100.00

Column: CHIRALCELOD-H
Solvent: Hexane:Isopropanol (90:10)
Wavelength-210nm
Flow Rate-1ML/min
Pressure:43 bar
Operator :SHIVA



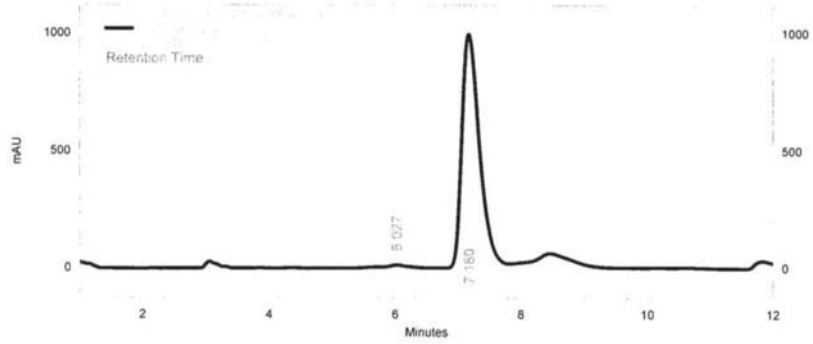


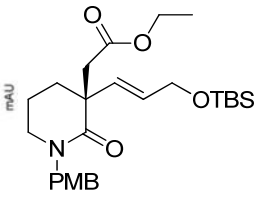
219a

DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
6.053	55266628	99.80	3236296	99.54
7.340	110081	0.20	14921	0.46
Totals	55376709	100.00	3251217	100.00

Column: CHIRALCELOD-H
Solvent: Hexane:Isopropanol (90:10)
Wavelength-210nm
Flow Rate-1ML/min
Pressure:43 bar
Operator :SHIVA



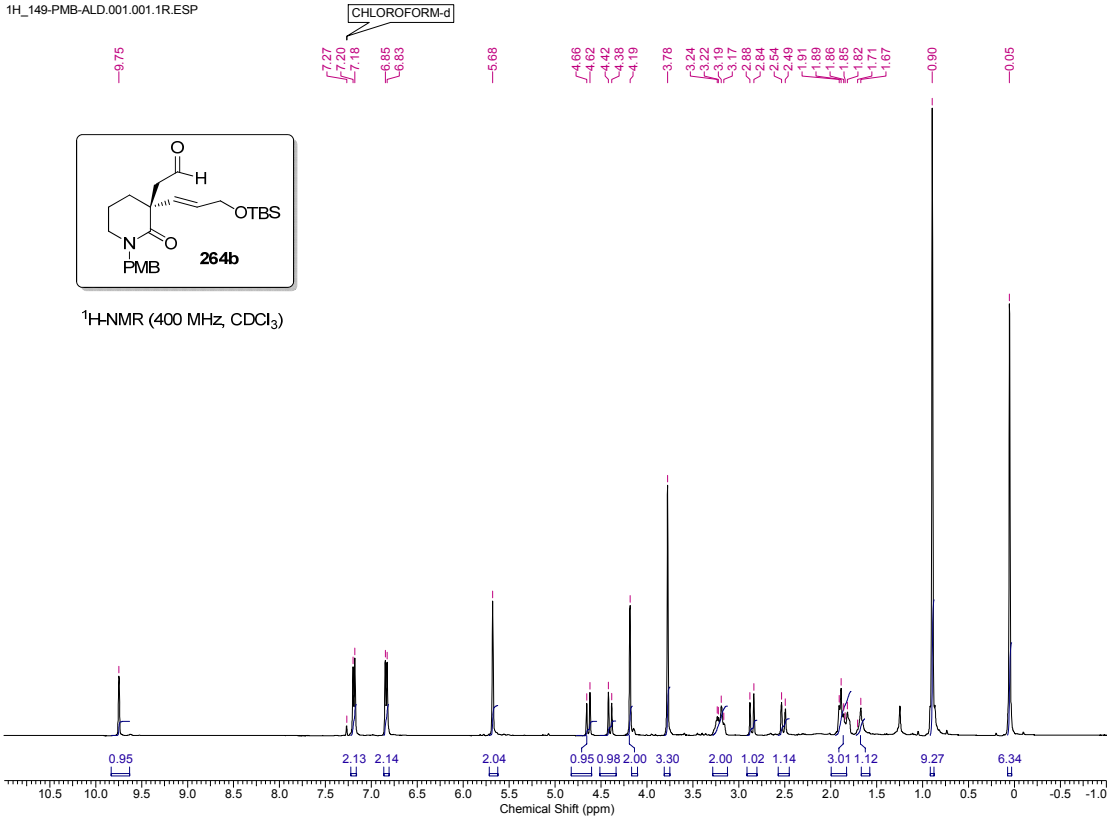


219b

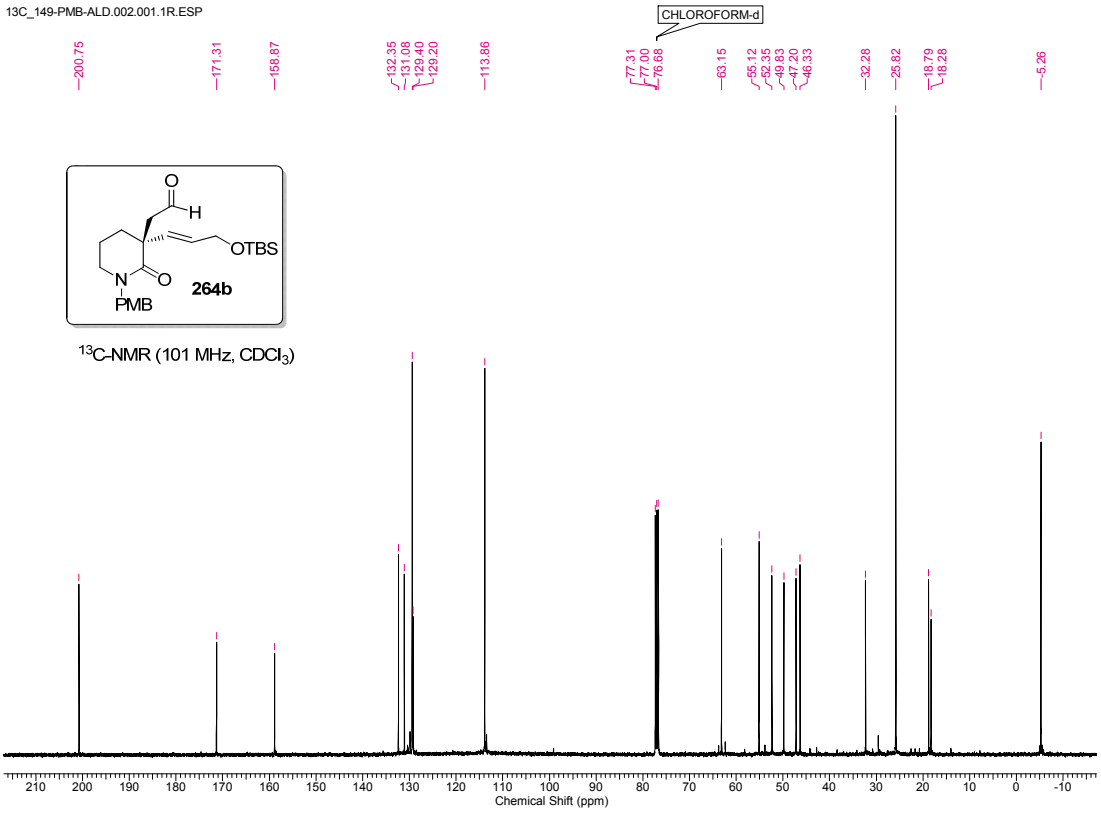
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
6.027	72404	0.18	8120	0.39
7.180	39846816	99.82	2074459	99.61
Totals	39919220	100.00	2082579	100.00

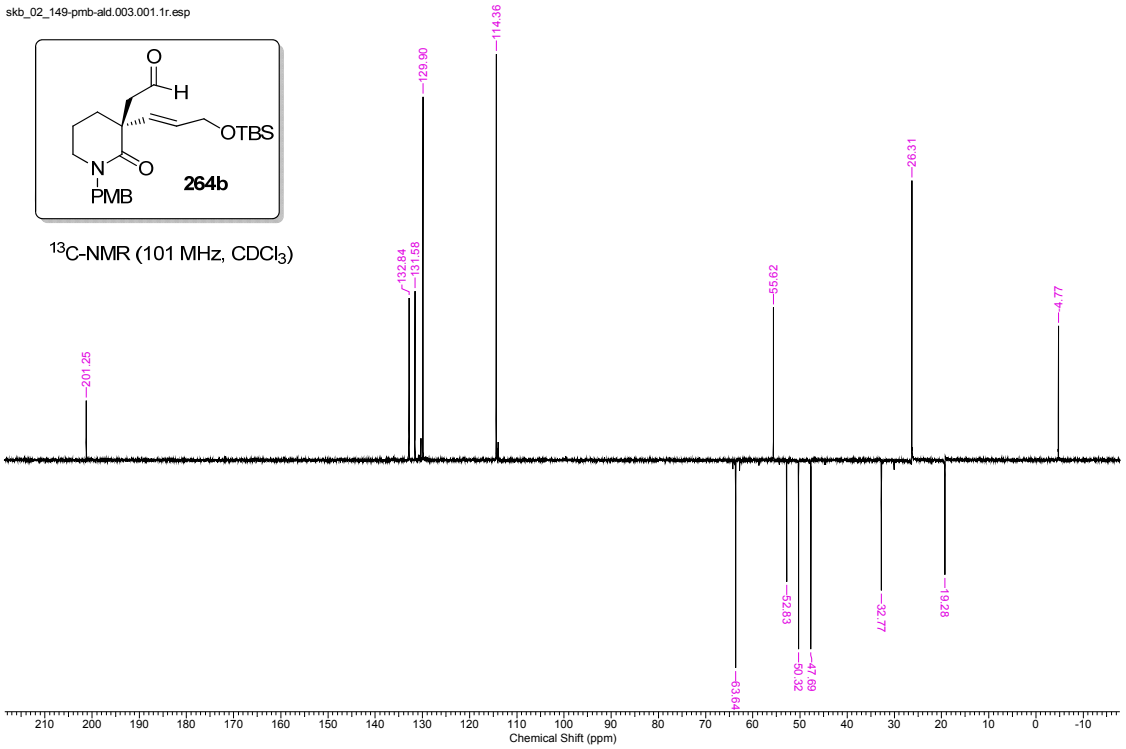
Column: CHIRALCELOD-H
Solvent: Hexane:Isopropanol (90:10)
Wavelength-210nm
Flow Rate-1ML/min
Pressure:43 bar
Operator :SHIVA

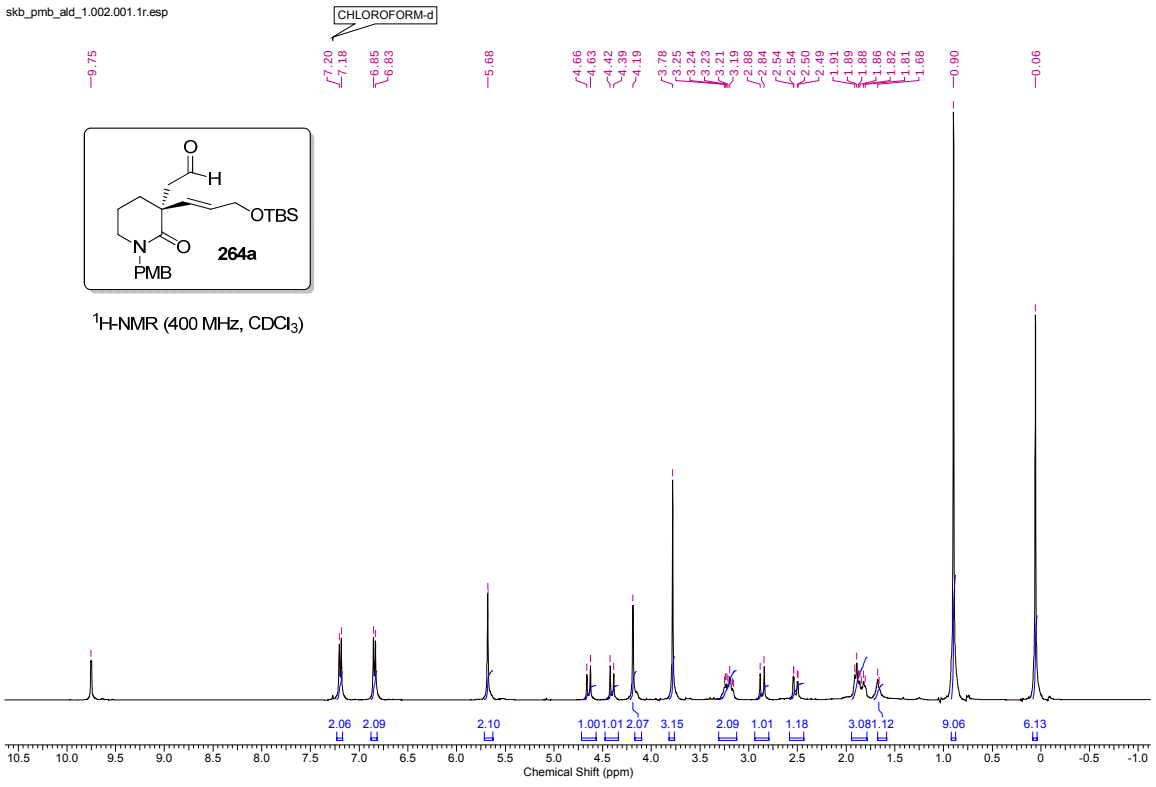


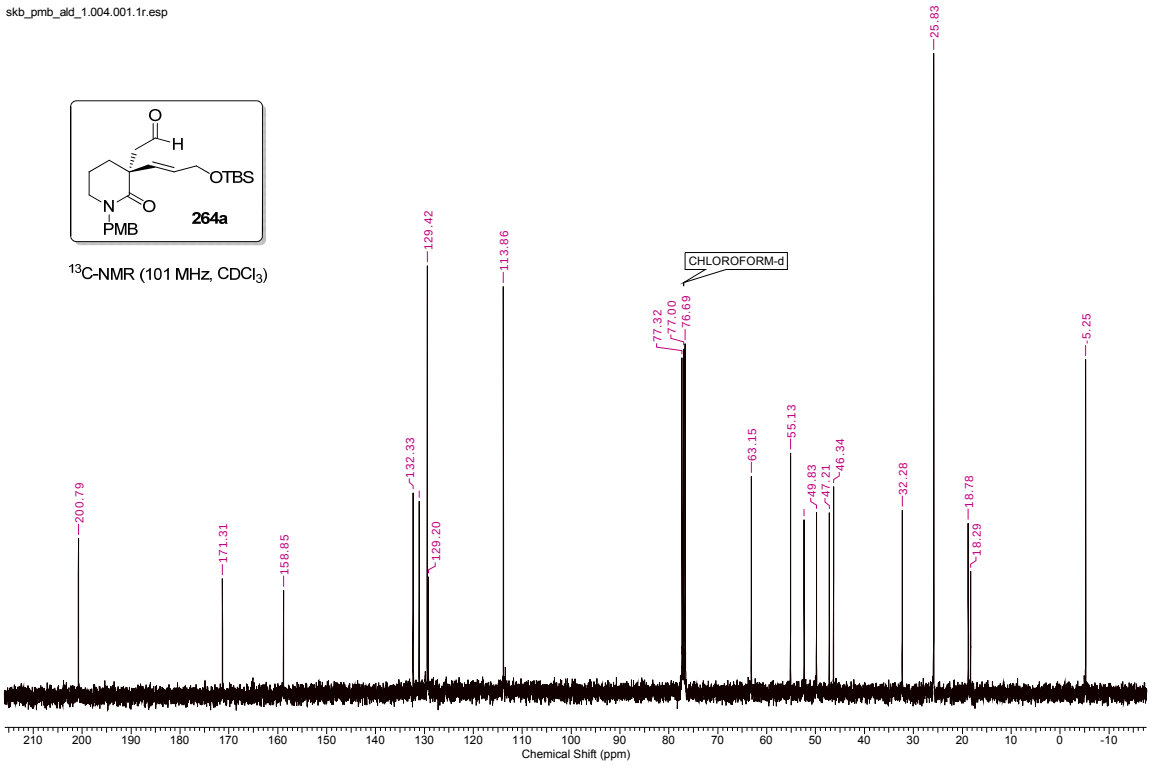
^{1}H-NMR (400 MHz, $CDCl_3$)

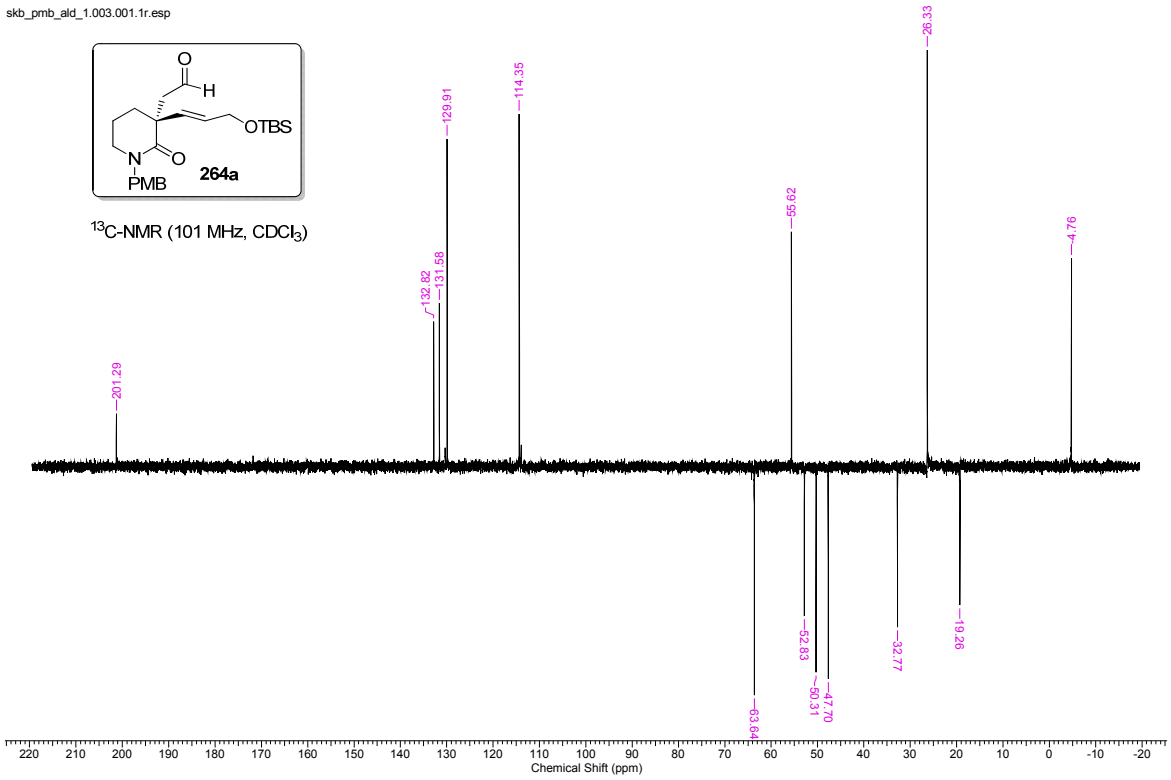


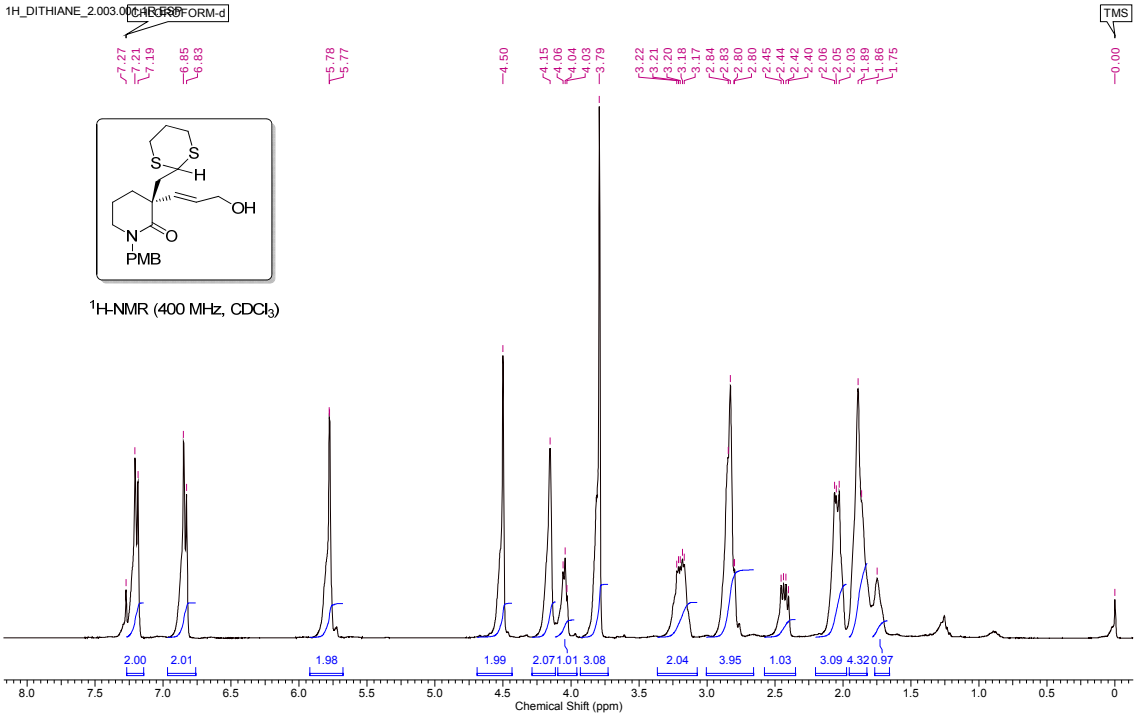
^{13}C-NMR (101 MHz, $CDCl_3$)


skb_02_149-pmb-ald.003.001.1r.esp
O
H
OTBS
N
O
PMB
264b
^{13}C-NMR (101 MHz, $CDCl_3$)
201.25
132.84
131.58
129.90
114.36
63.64
55.62
52.83
50.32
47.69
32.77
26.31
19.28
4.77
Chemical Shift (ppm)

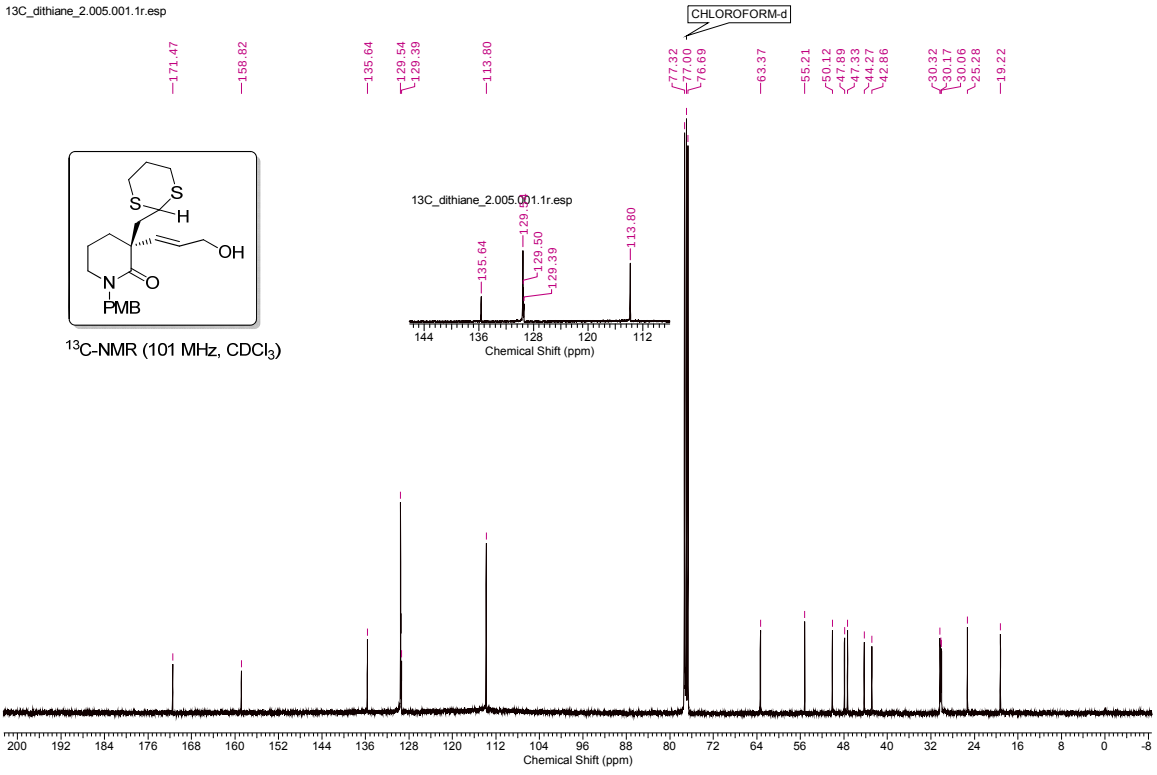

skb_pmb_ald_1.002.001.1r.esp
CHLOROFORM-d
9.75
7.20
7.18
6.85
6.83
5.68
4.66
4.63
4.42
4.39
4.19
3.78
3.25
3.24
3.23
3.21
3.19
2.88
2.84
2.54
2.54
2.50
2.49
1.91
1.89
1.88
1.86
1.82
1.81
1.68
0.90
0.06
O
H
OTBS
N
O
PMB
264a
^{1}H-NMR (400 MHz, $CDCl_3$)
2.06
2.09
2.10
1.00
1.01
2.07
3.15
2.09
1.01
1.18
3.08
1.12
9.06
6.13
Chemical Shift (ppm)


skb_pmb_ald_1.004.001.1r.esp
O
H
OTBS
N
O
PMB
264a
^{13}C-NMR (101 MHz, CDCl$_3$)
CHLOROFORM-d
200.79
171.31
158.85
132.33
129.42
129.20
113.86
77.32
77.00
76.69
63.15
55.13
49.83
47.21
46.34
32.28
25.83
18.78
18.29
-5.25
Chemical Shift (ppm)

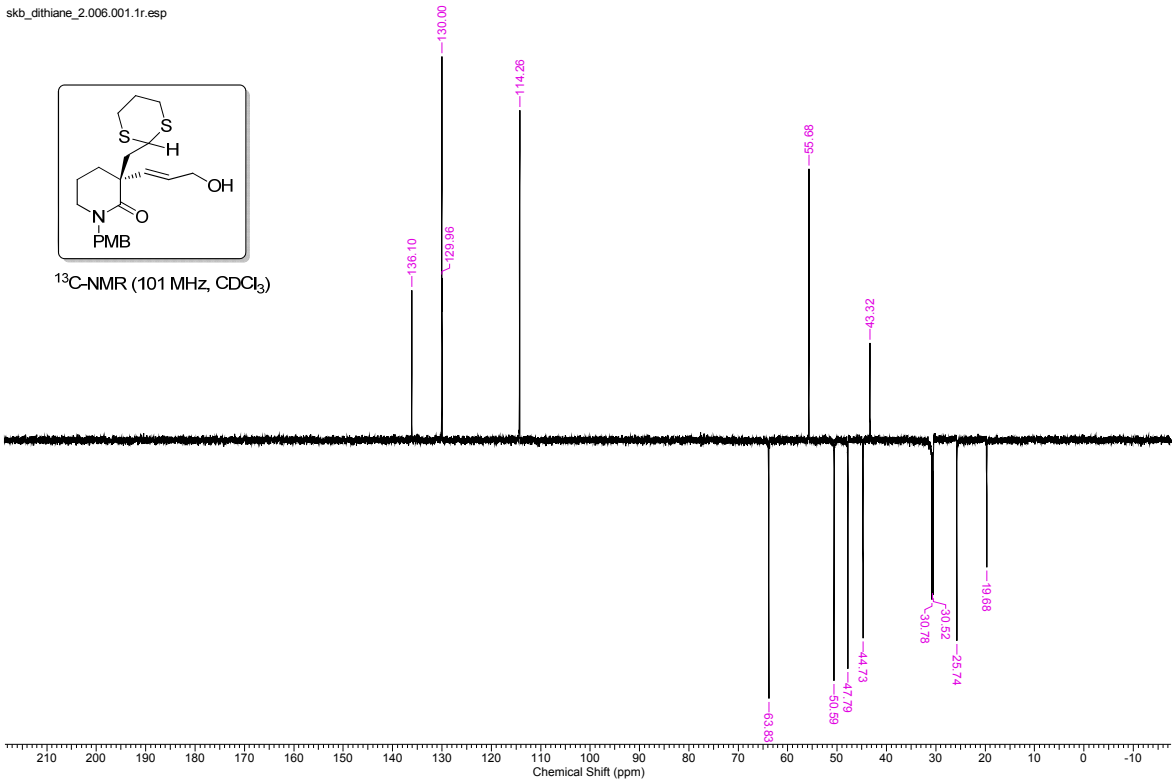

skb_pmb_ald_1.003.001.1r.esp
O
H
OTBS
N
O
PMB
264a
^{13}C-NMR (101 MHz, CDCl$_3$)
201.29
132.82
131.58
129.91
114.35
63.64
55.62
52.83
50.31
47.70
32.77
26.33
19.26
4.76
Chemical Shift (ppm)

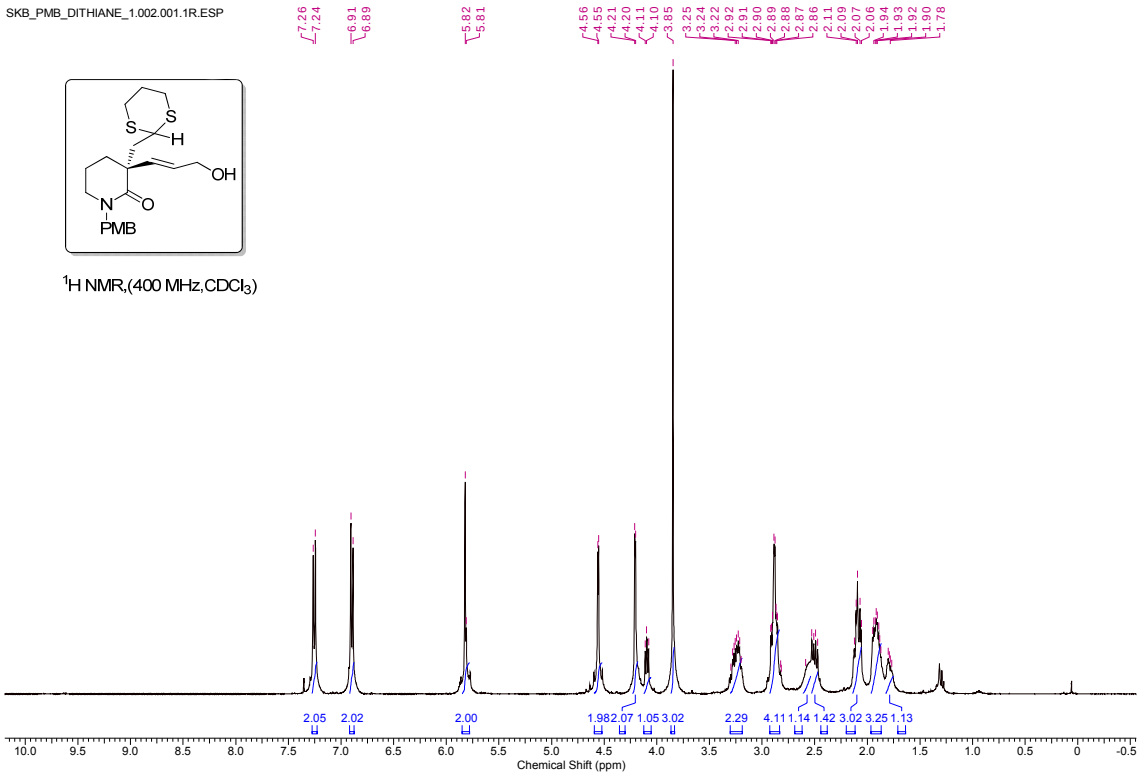


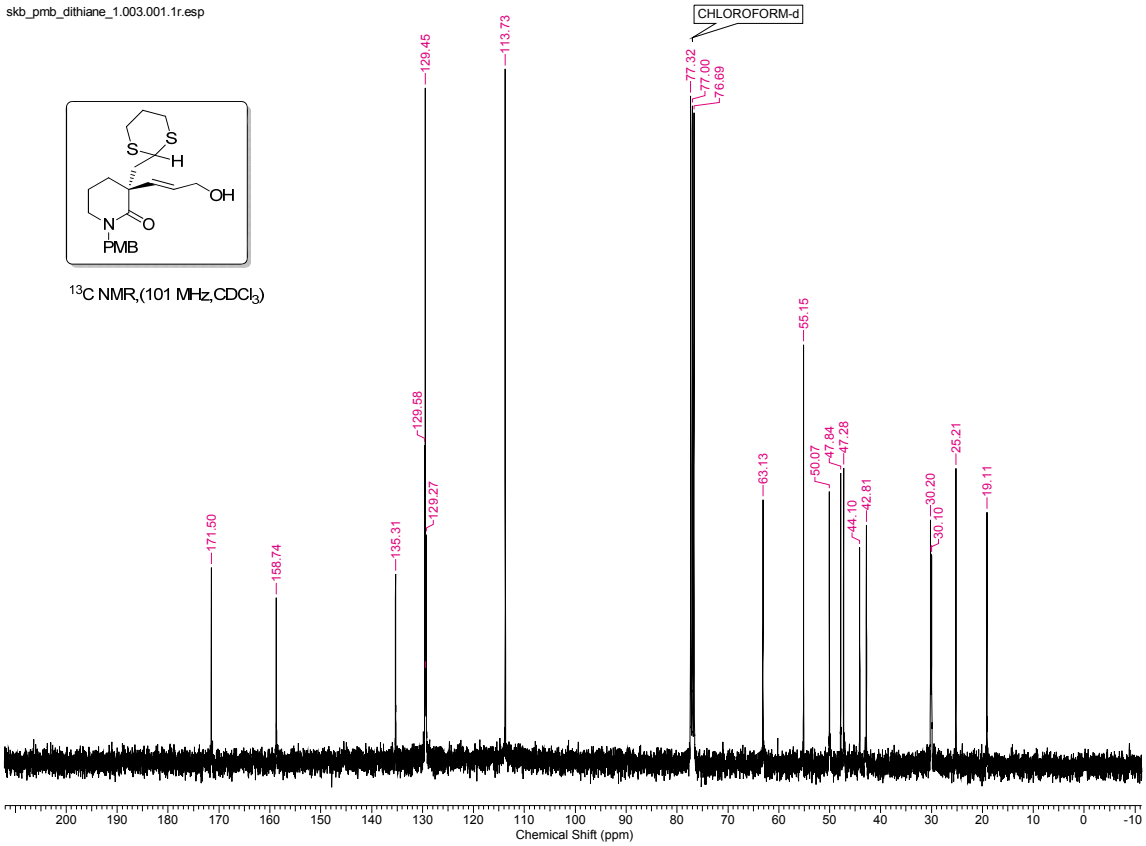
^{1}H-NMR (400 MHz, $CDCl_3$)

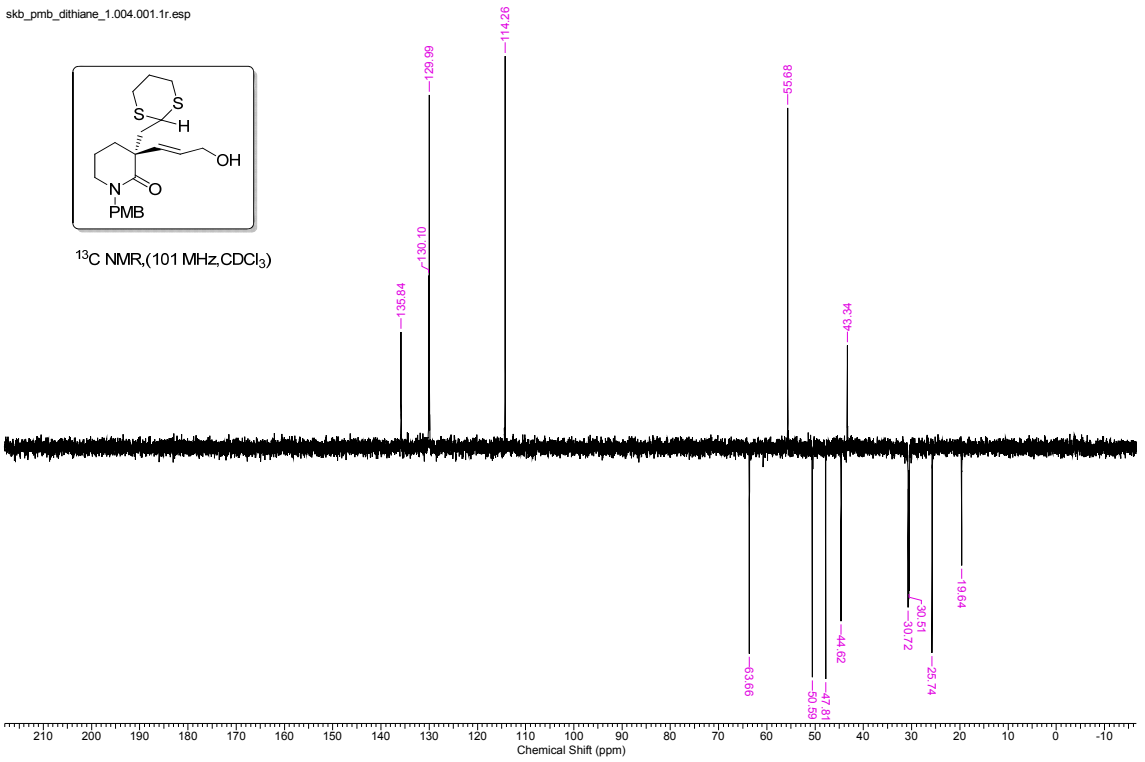


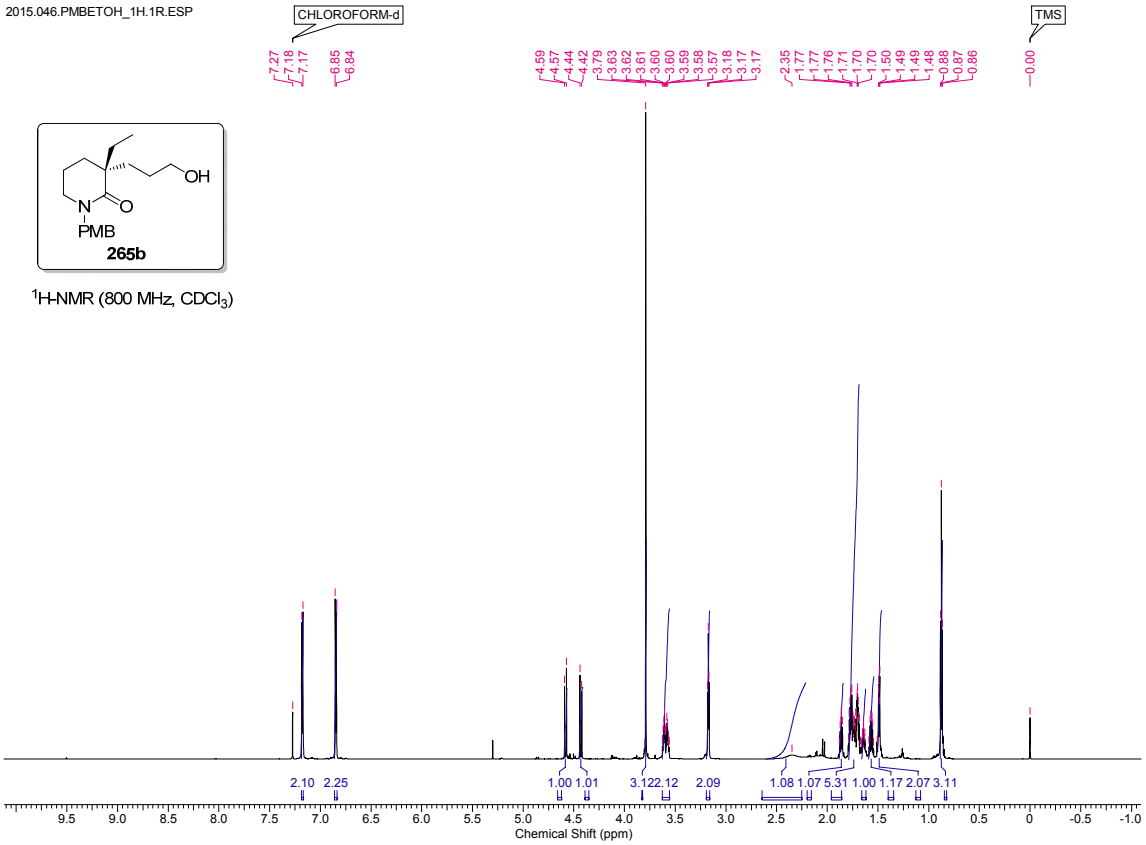
^{13}C-NMR (101 MHz, $CDCl_3$)


skb_dithiane_2.006.001.1r.esp
PMB
^{13}C-NMR (101 MHz, CDCl$_3$)
Chemical Shift (ppm)

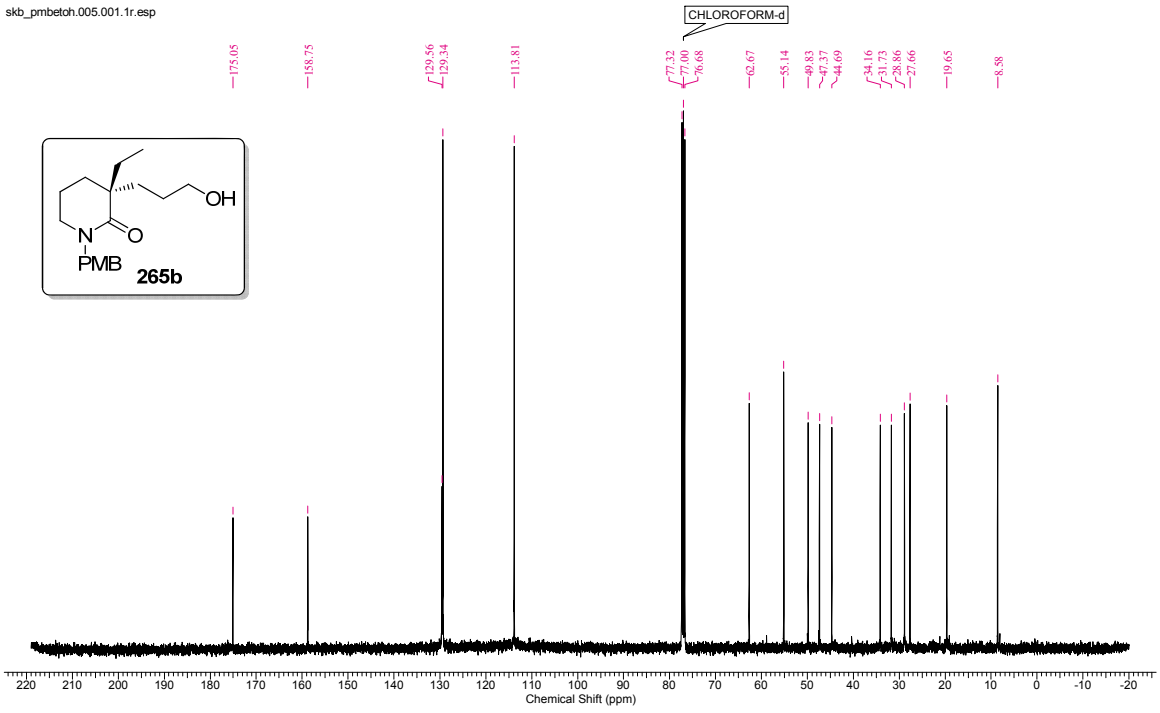

SKB_PMB_DITHIANE_1.002.001.1R.ESP
PMB
^{1}H NMR,(400 MHz,CDCl$_3$)
Chemical Shift (ppm)

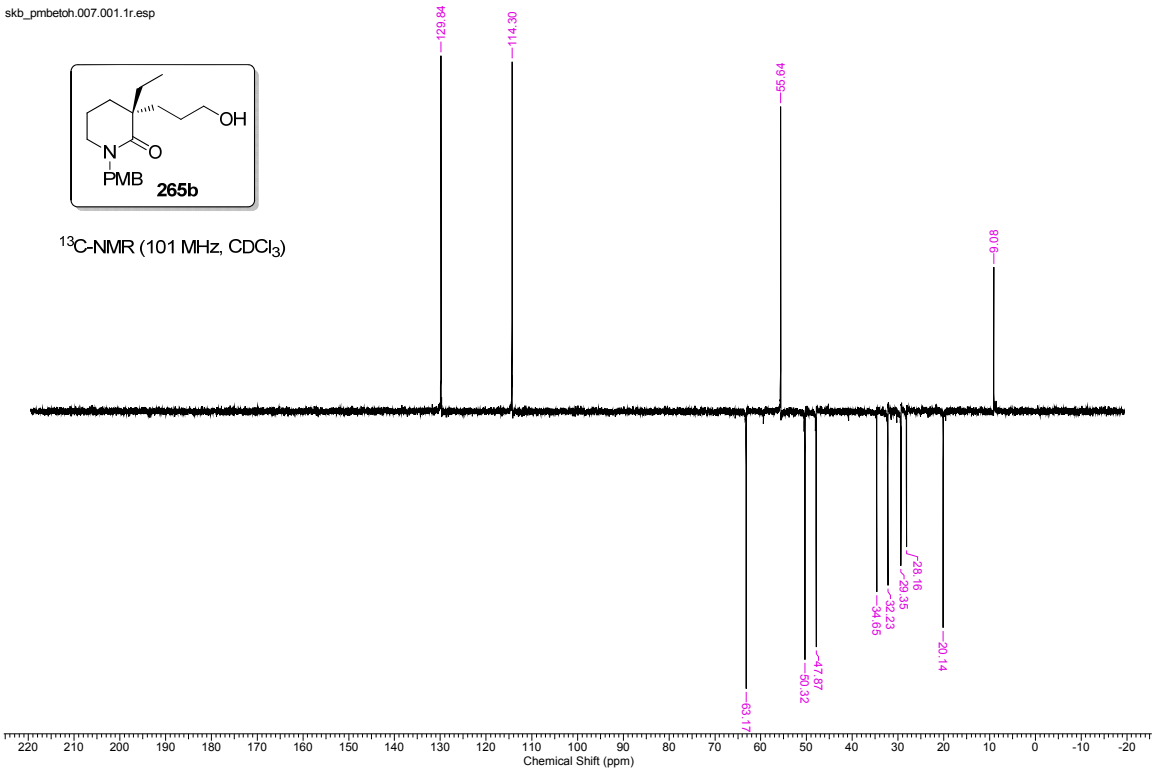

skb_pmb_dithiane_1.003.001.1r.esp
CHLOROFORM-d
129.45
113.73
77.32
77.00
76.69
55.15
129.58
129.27
63.13
50.07
47.84
47.28
42.81
44.10
25.21
19.11
30.20
30.10
171.50
158.74
135.31
OH
N
O
PMB
^{13}C NMR,(101 MHz,CDCl$_3$)
Chemical Shift (ppm)


skb_pmb_dithiane_1.004.001.1r.esp
114.26
129.99
55.68
130.10
135.84
43.34
63.66
50.59
47.81
44.62
30.72
30.51
25.74
19.64
OH
N
O
PMB
^{13}C NMR,(101 MHz,CDCl$_3$)
Chemical Shift (ppm)

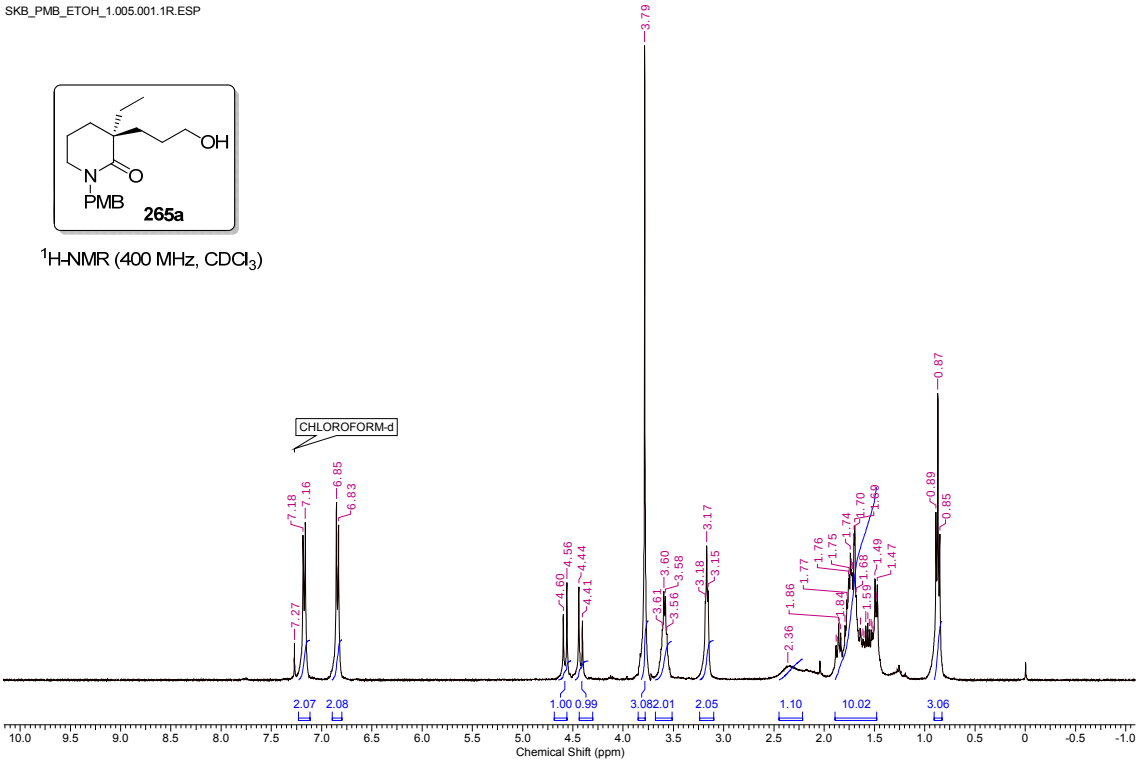


^{1}H-NMR (800 MHz, $CDCl_3$)



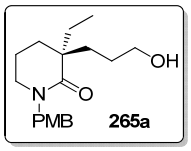


^{13}C-NMR (101 MHz, $CDCl_3$)



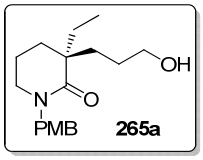
^{1}H-NMR (400 MHz, $CDCl_3$)

skb_pmb_etoh_1.007.001.1r.esp

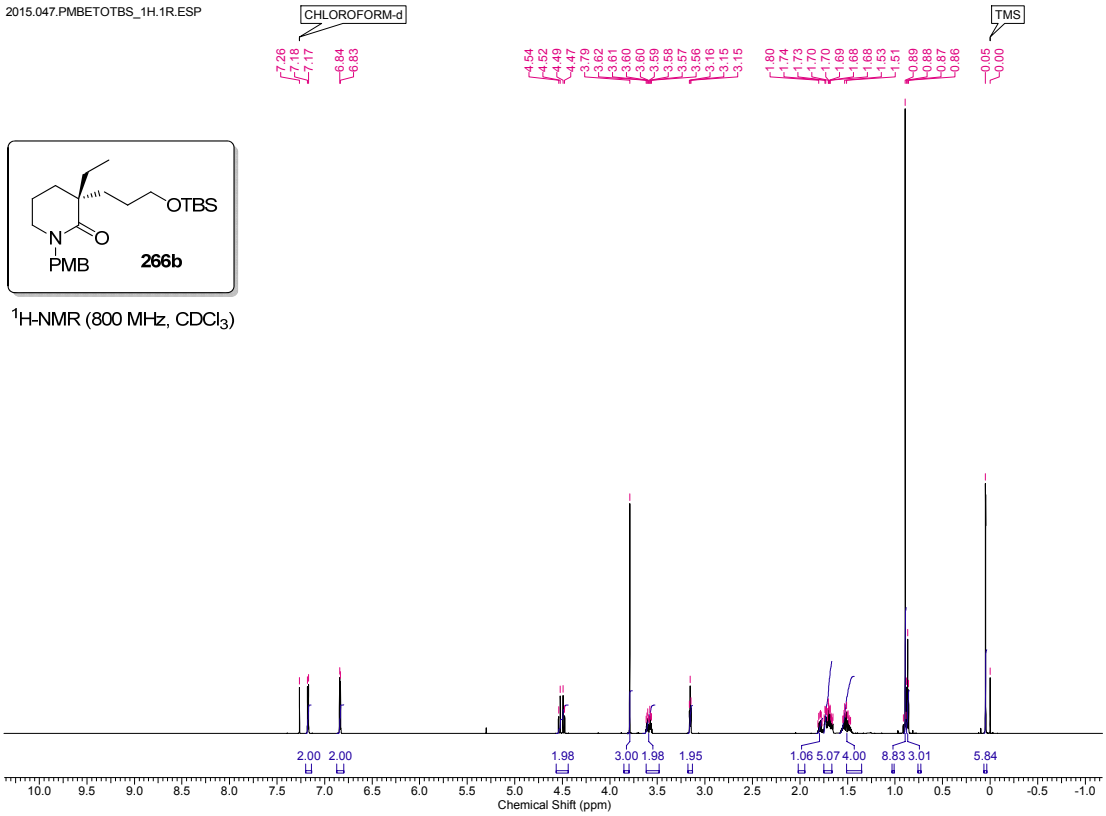


^{13}C-NMR (101 MHz, $CDCl_3$)

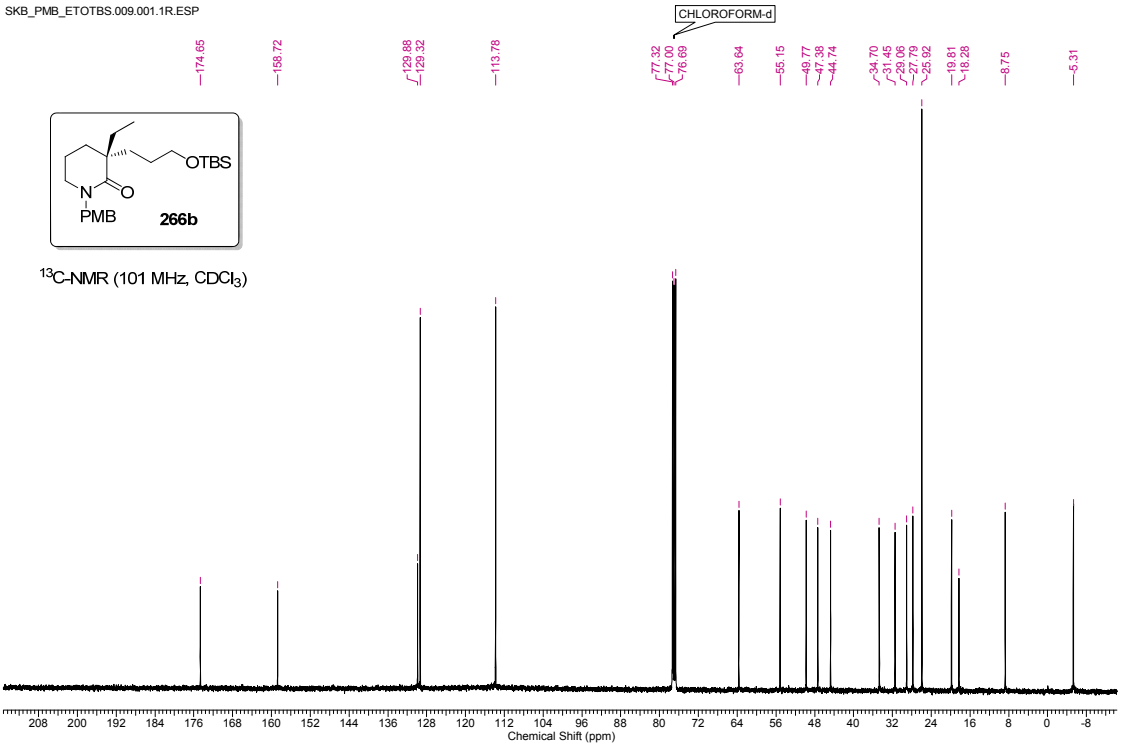
skb_pmb_etoh_1.006.001.1r.esp



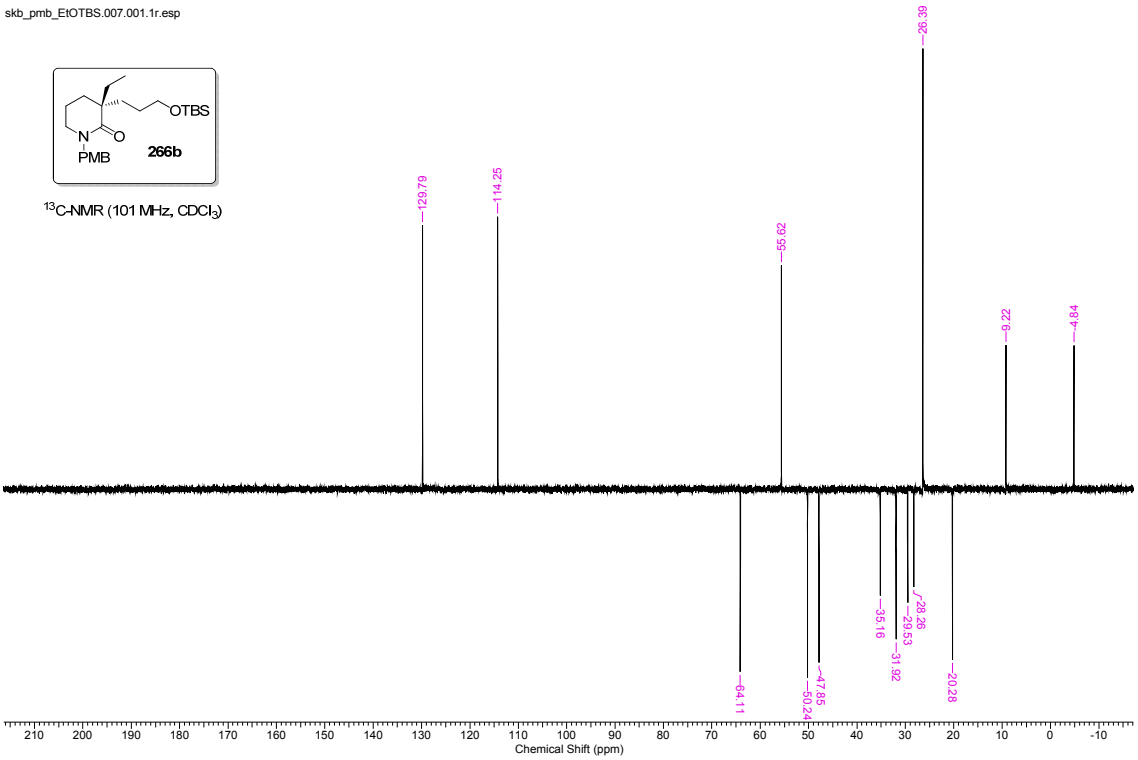
^{13}C-NMR (101 MHz, $CDCl_3$)

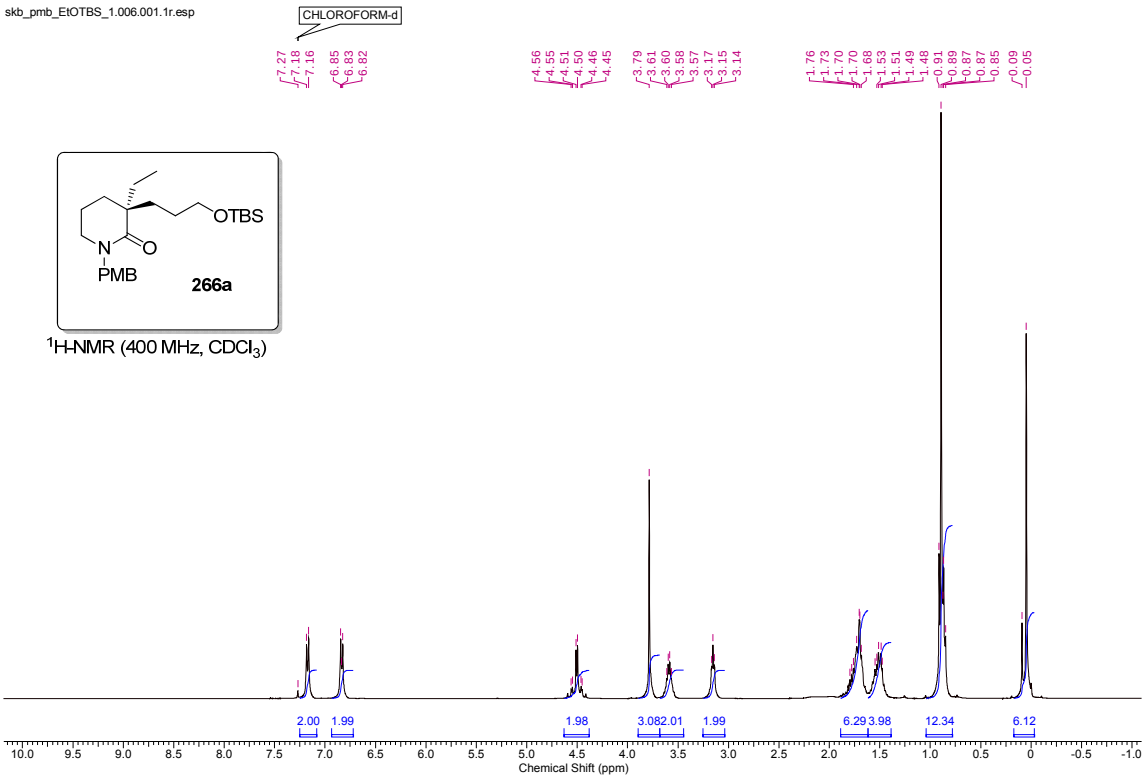


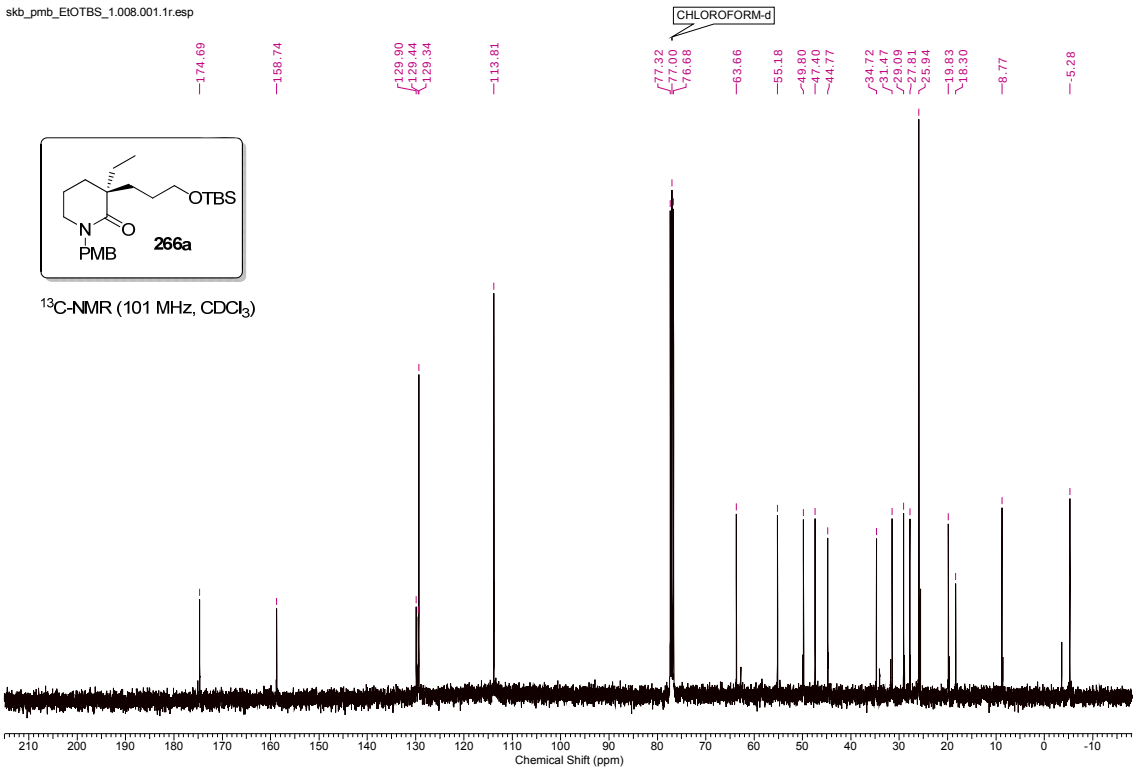
^{1}H-NMR (800 MHz, $CDCl_3$)



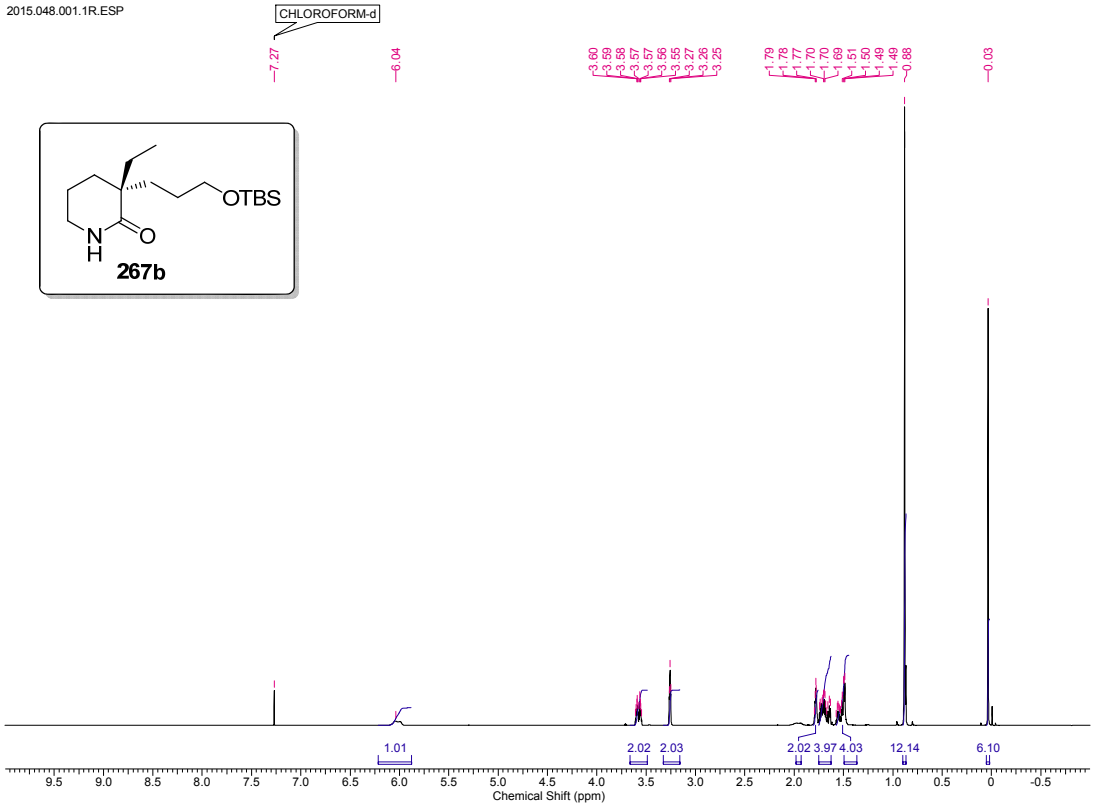
^{13}C-NMR (101 MHz, $CDCl_3$)


skb_pmb_EtOTBS.007.001.1r.esp
OTBS
N
O
PMB
266b
^{13}C-NMR (101 MHz, CDCl$_3$)
129.79
114.25
55.62
26.39
9.22
4.84
64.11
47.85
50.24
35.16
31.92
29.53
28.26
20.28
Chemical Shift (ppm)

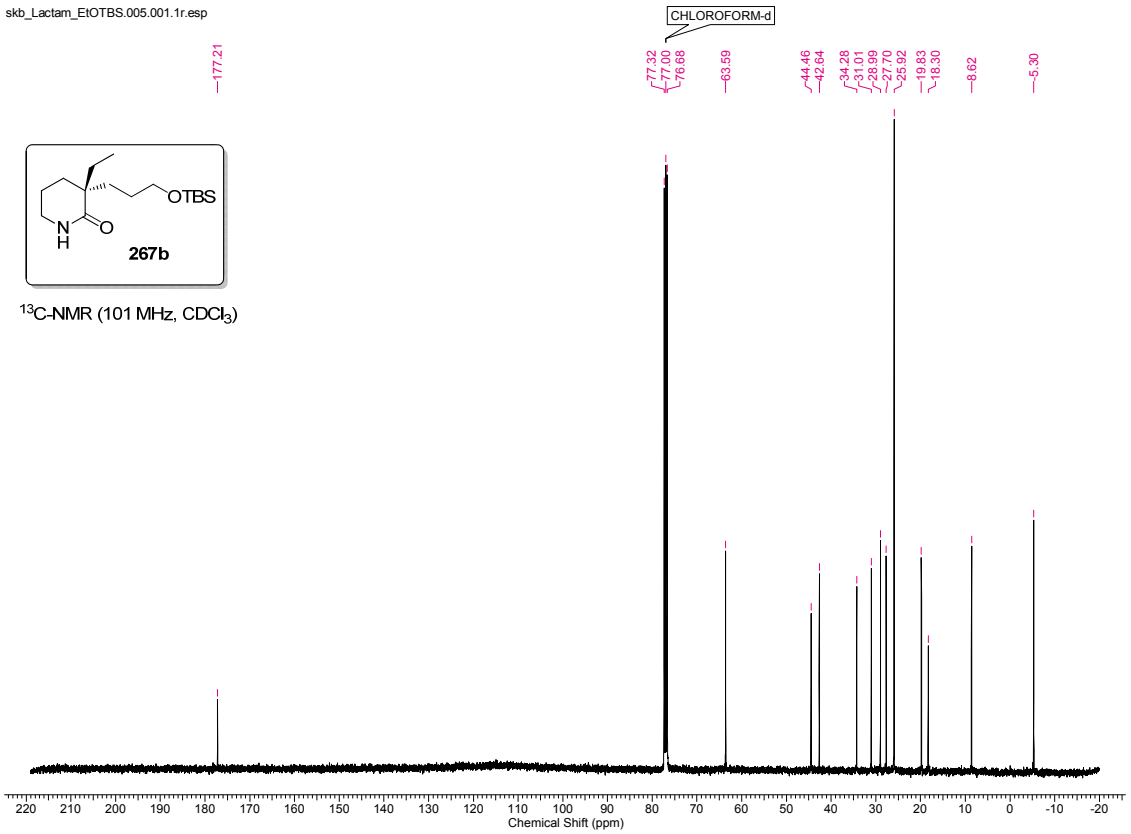

skb_pmb_EtOTBS_1.006.001.1r.esp
CHLOROFORM-d
OTBS
N
O
PMB
266a
^{1}H-NMR (400 MHz, CDCl$_3$)
2.00
1.99
1.98
3.08
2.01
1.99
6.29
3.98
12.34
6.12
Chemical Shift (ppm)



^{13}C-NMR (101 MHz, $CDCl_3$)

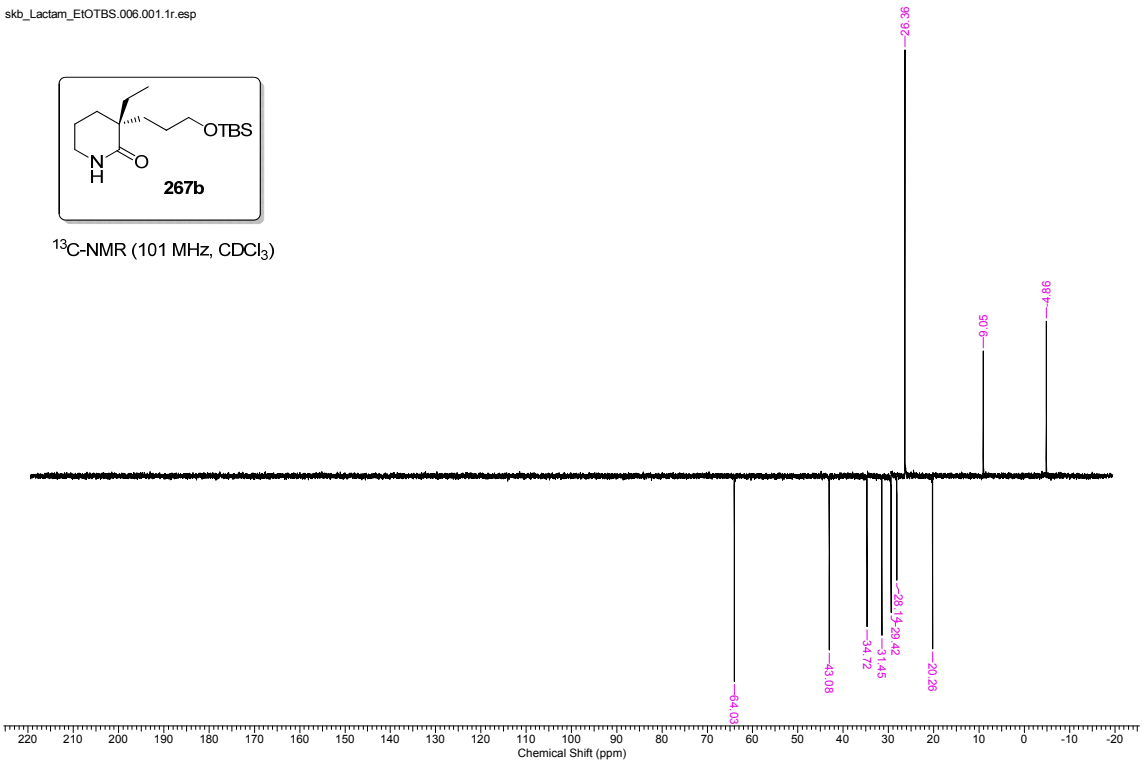


skb_Lactam_EtOTBS.005.001.1r.esp

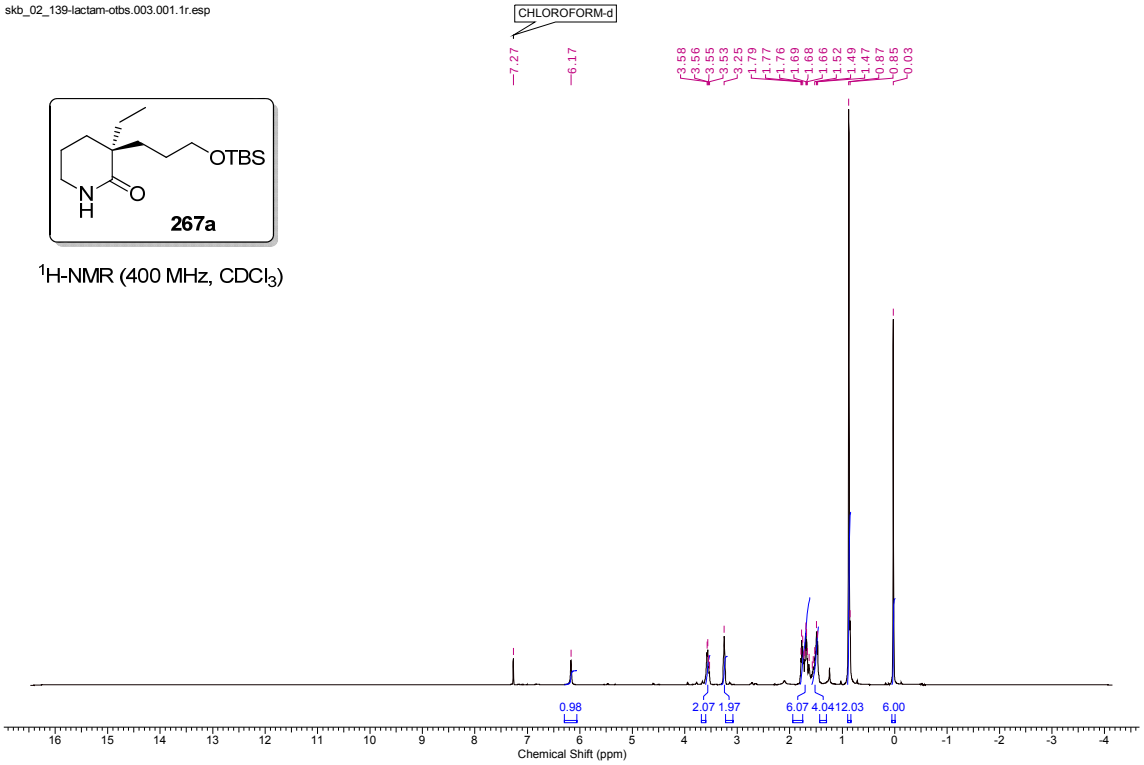


^{13}C-NMR (101 MHz, $CDCl_3$)

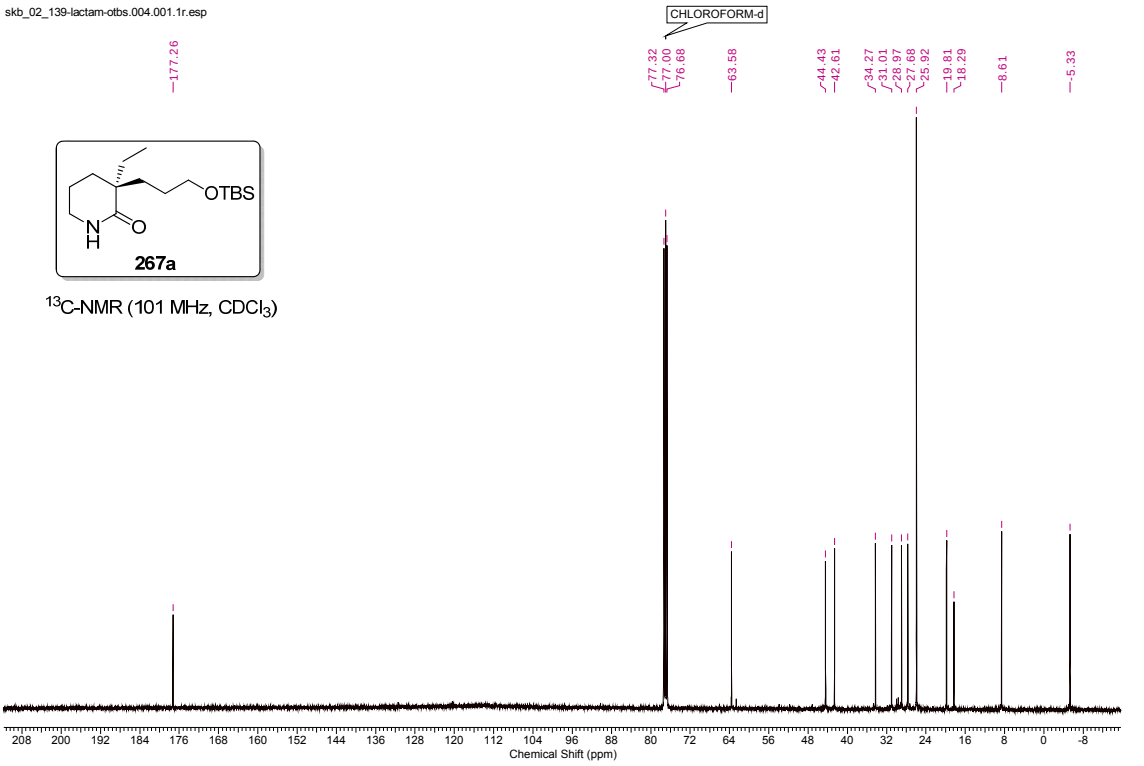
skb_Lactam_EtOTBS.006.001.1r.esp



^{13}C-NMR (101 MHz, $CDCl_3$)

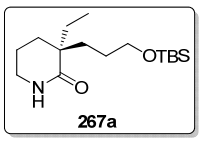


^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

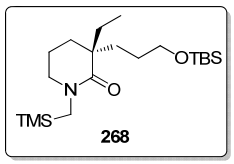
skb_02_139-lactam-otbs.005.001.1r.esp



267a

^{13}C-NMR (101 MHz, $CDCl_3$)

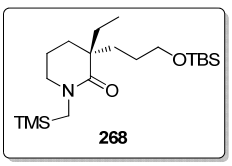
skb_tmsotbs.001.001.1r.esp



268

^{1}H-NMR (400 MHz, $CDCl_3$)

skb_tmsotbs.005.001.1r.esp



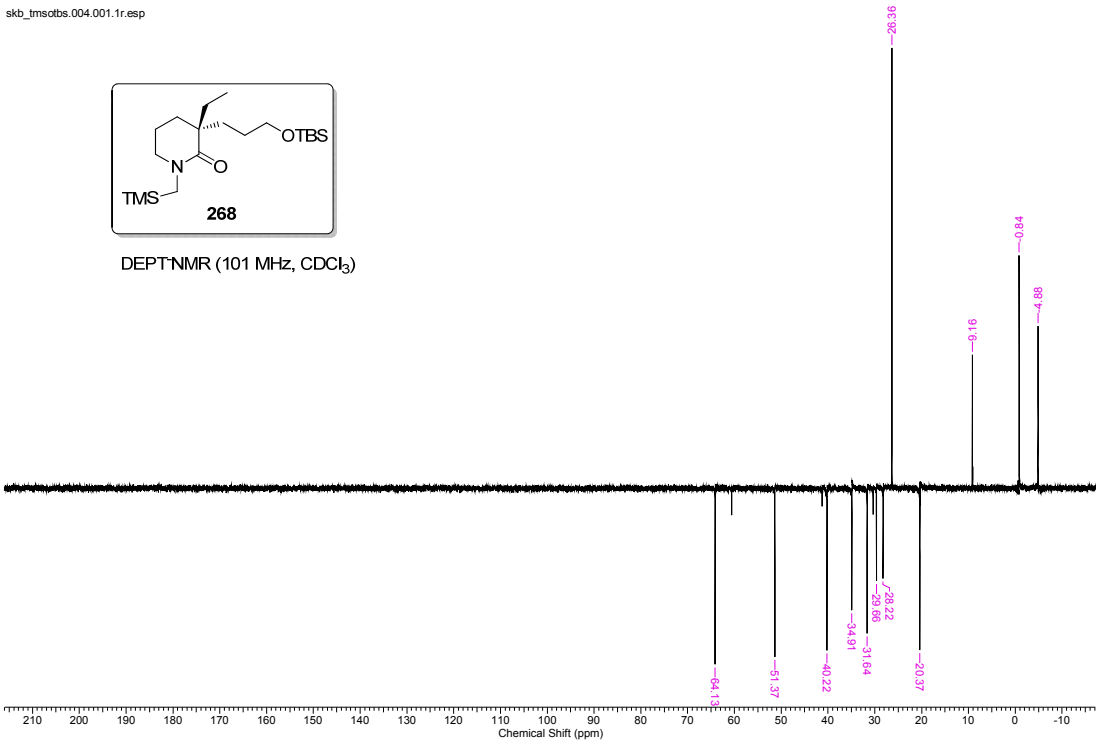
268

^{13}C-NMR (101 MHz, $CDCl_3$)

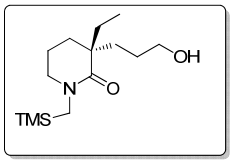
skb_tmsotbs.004.001.1r.esp

268

DEPT-NMR (101 MHz, $CDCl_3$)

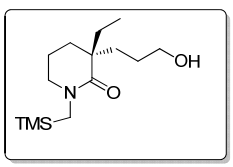


skb_tms_etoh.003.001.1r.esp



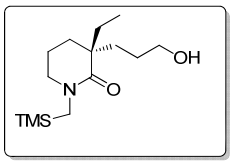
^{1}H-NMR (400 MHz, $CDCl_3$)

skb_tms_etoh.007.001.1r.esp



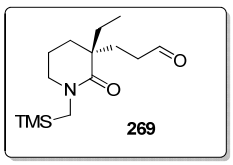
^{13}C-NMR (400 MHz, $CDCl_3$)

skb_tms_etoh.005.001.1r.esp



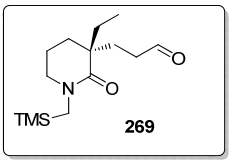
DEPT-NMR (400 MHz, $CDCl_3$)

skb_tmsald.005.001.1r.esp



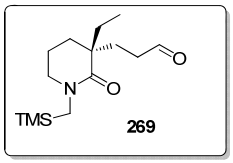
^{1}H-NMR (400 MHz, $CDCl_3$)

skb_tmsald.004.001.1r.esp



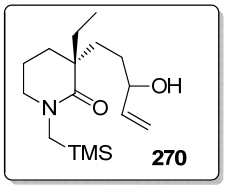
^{13}C-NMR (101 MHz, $CDCl_3$)

skb_tmsald.003.001.1r.esp



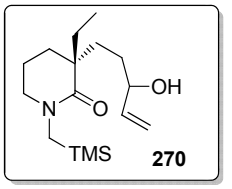
DEPT-NMR (101 MHz, $CDCl_3$)

skb_tms_vin.002.001.1r.esp

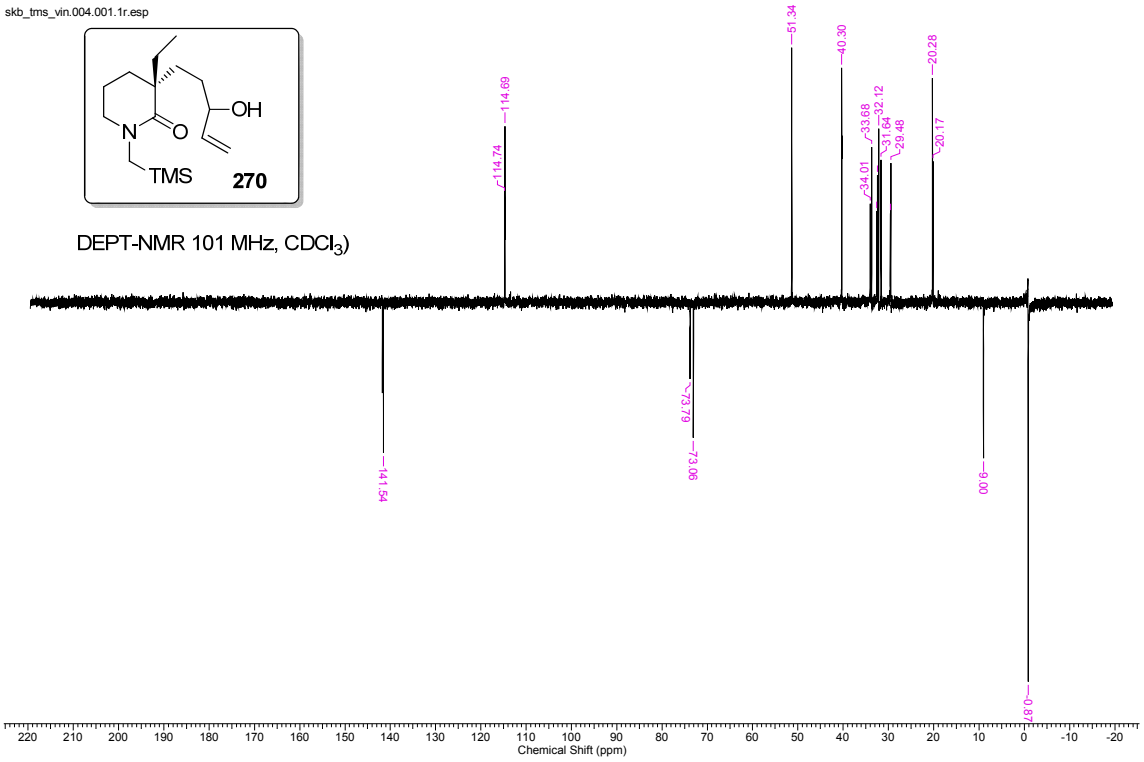


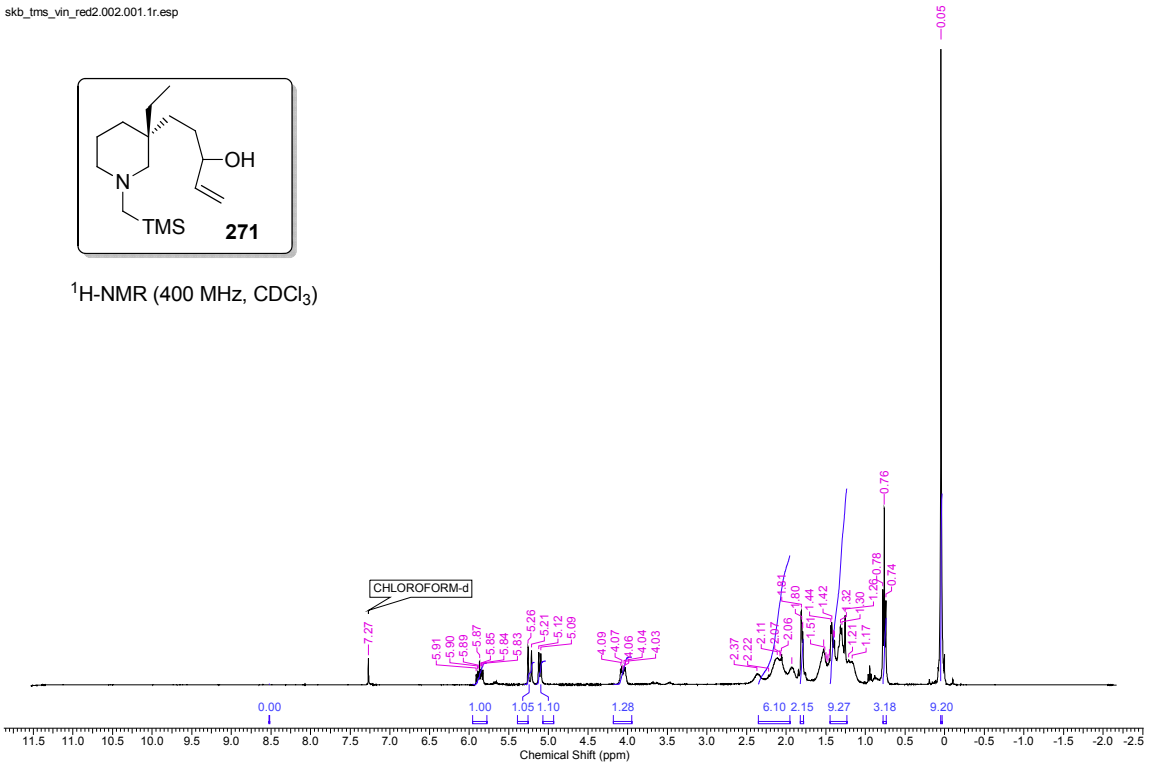
^{1}H-NMR (400 MHz, $CDCl_3$)

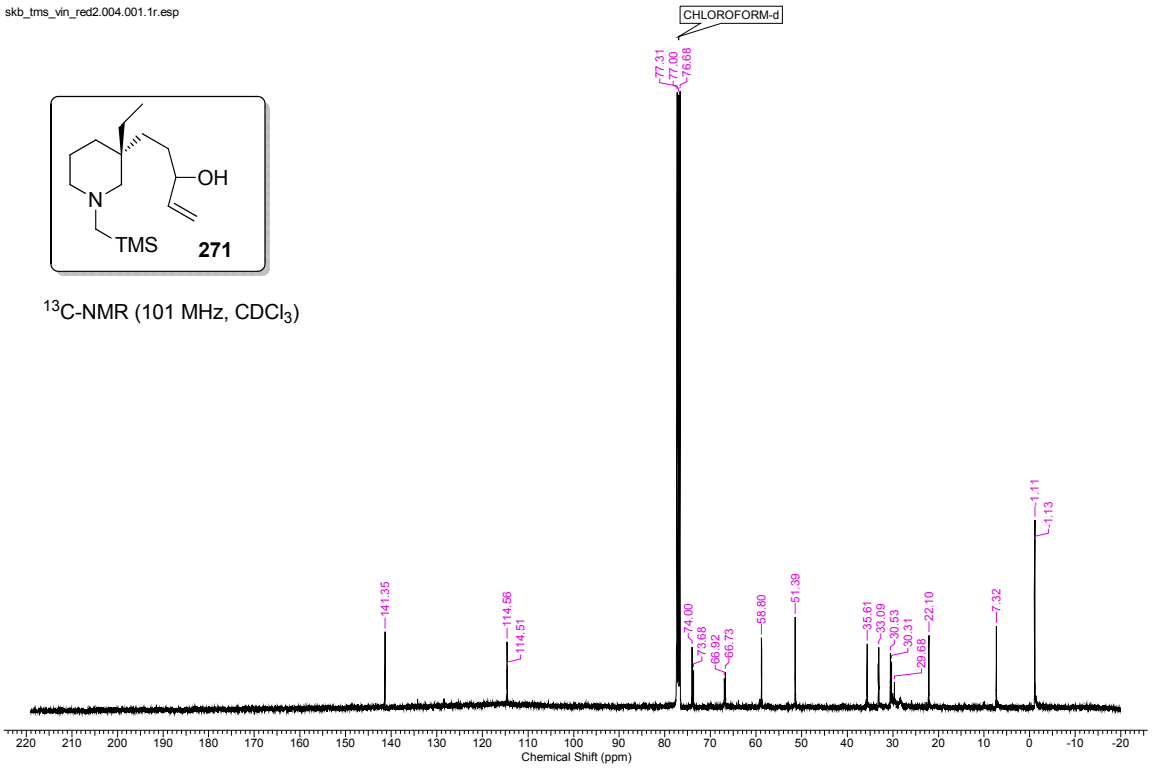
skb_tms_vin.005.001.1r.esp



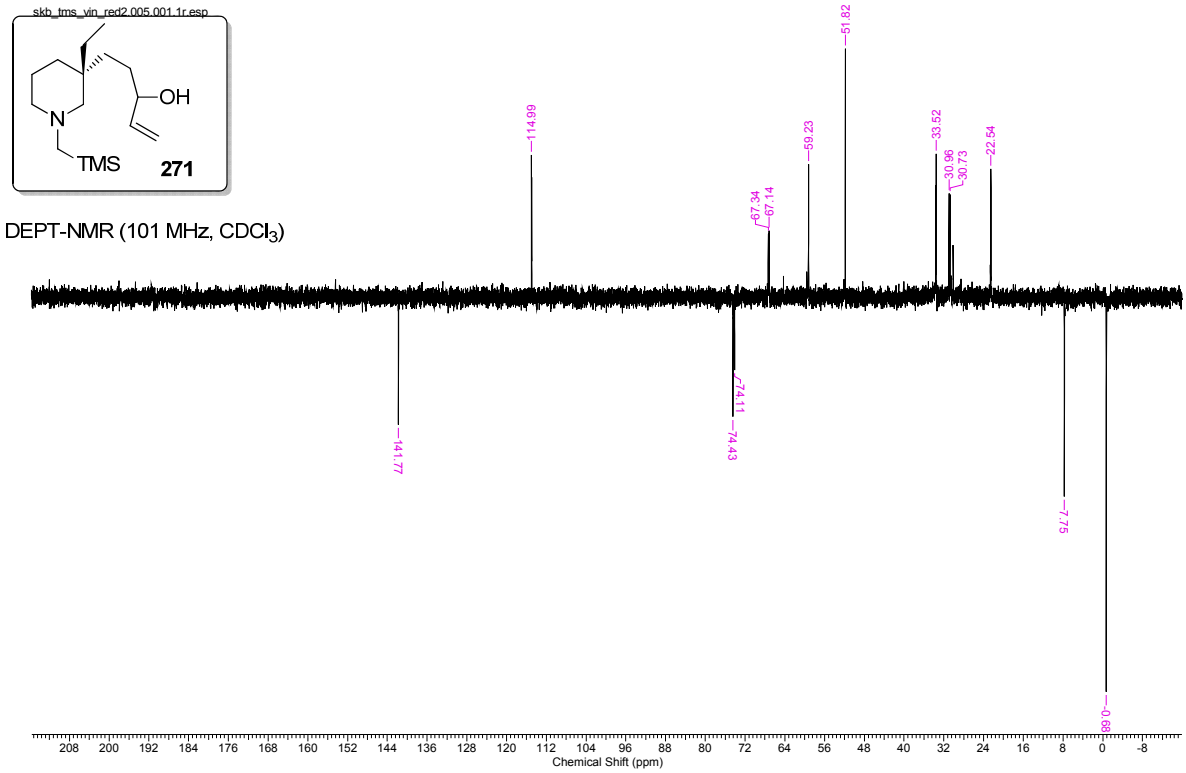
^{13}C-NMR (101 MHz, $CDCl_3$)


skb_tms_vin.004.001.1r.esp
OH
N
O
TMS
270
DEPT-NMR 101 MHz, CDCl3)
51.34
40.30
20.28
114.69
114.74
33.68
32.12
31.64
29.48
20.17
34.01
73.79
73.06
141.54
9.00
0.87
Chemical Shift (ppm)

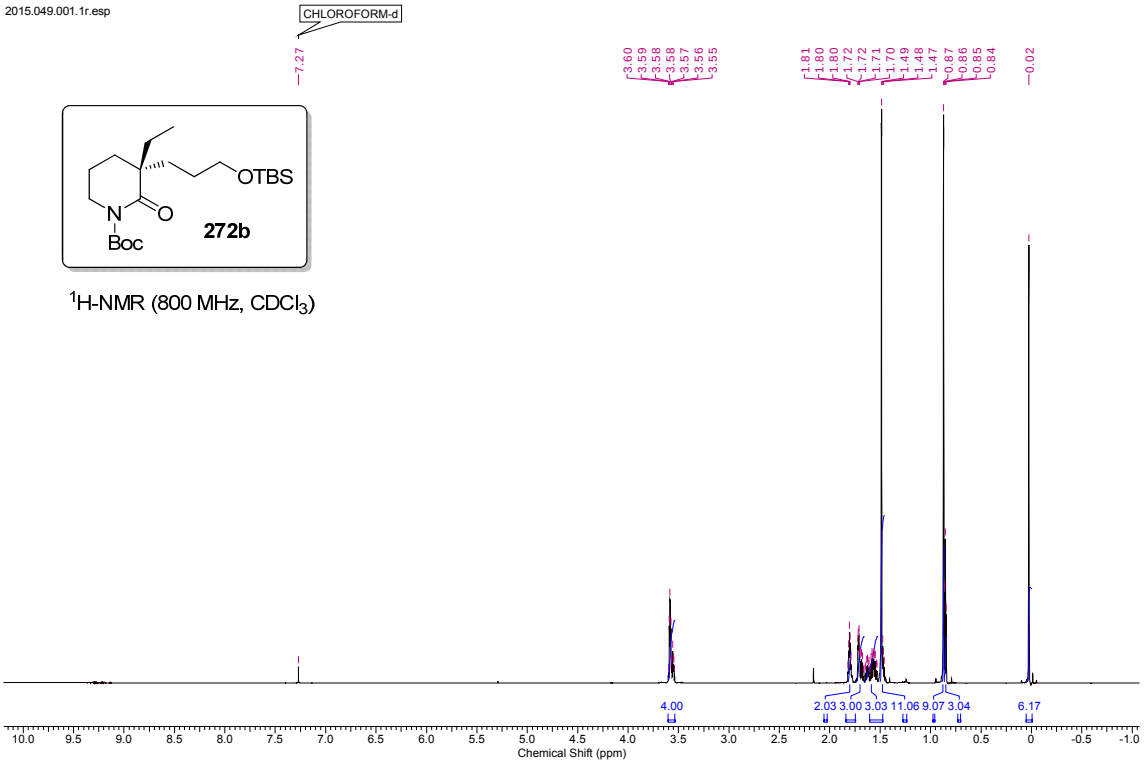

skb_tms_vin_red2.002.001.1r.esp
OH
N
TMS
271
1H-NMR (400 MHz, CDCl3)
0.05
0.76
0.78
0.74
CHLOROFORM-d
7.27
5.91
5.90
5.89
5.87
5.85
5.84
5.83
5.26
5.21
5.12
5.09
4.09
4.07
4.06
4.04
4.03
2.37
2.22
2.11
2.07
2.06
1.80
1.51
1.44
1.42
1.32
1.30
1.21
1.17
0.00
1.00
1.05
1.10
1.28
6.10
2.15
9.27
3.18
9.20
Chemical Shift (ppm)



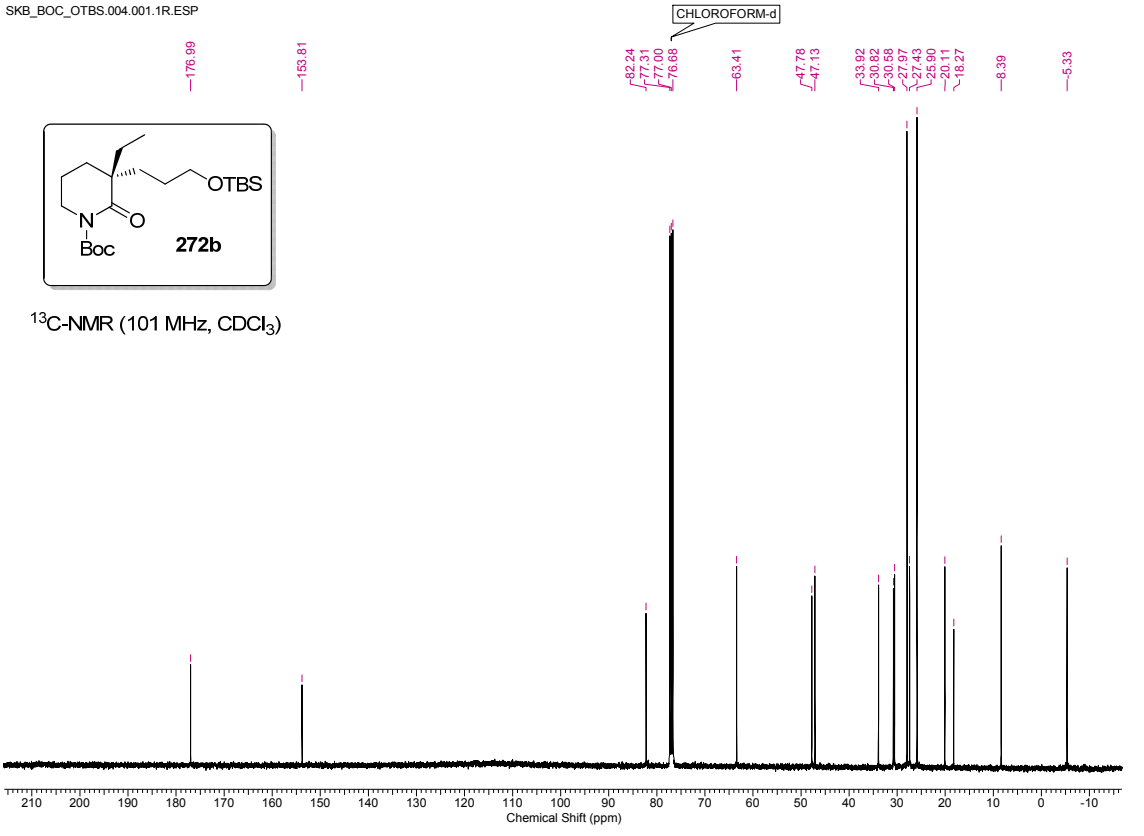
^{13}C-NMR (101 MHz, $CDCl_3$)



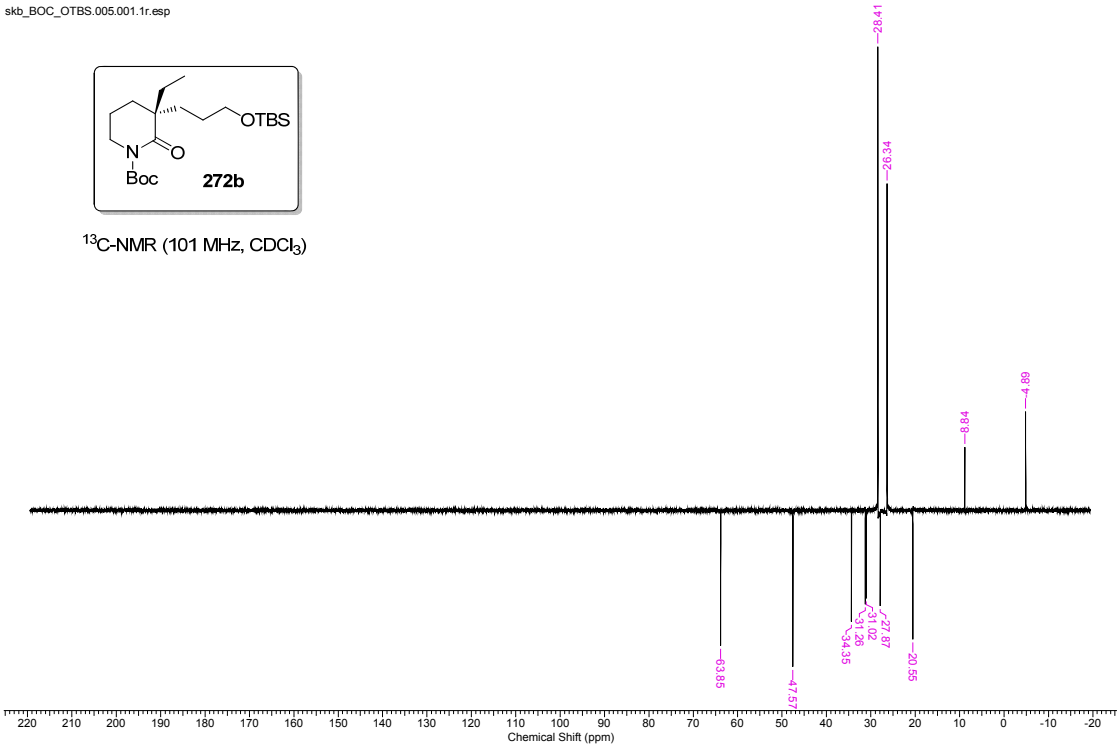
DEPT-NMR (101 MHz, $CDCl_3$)



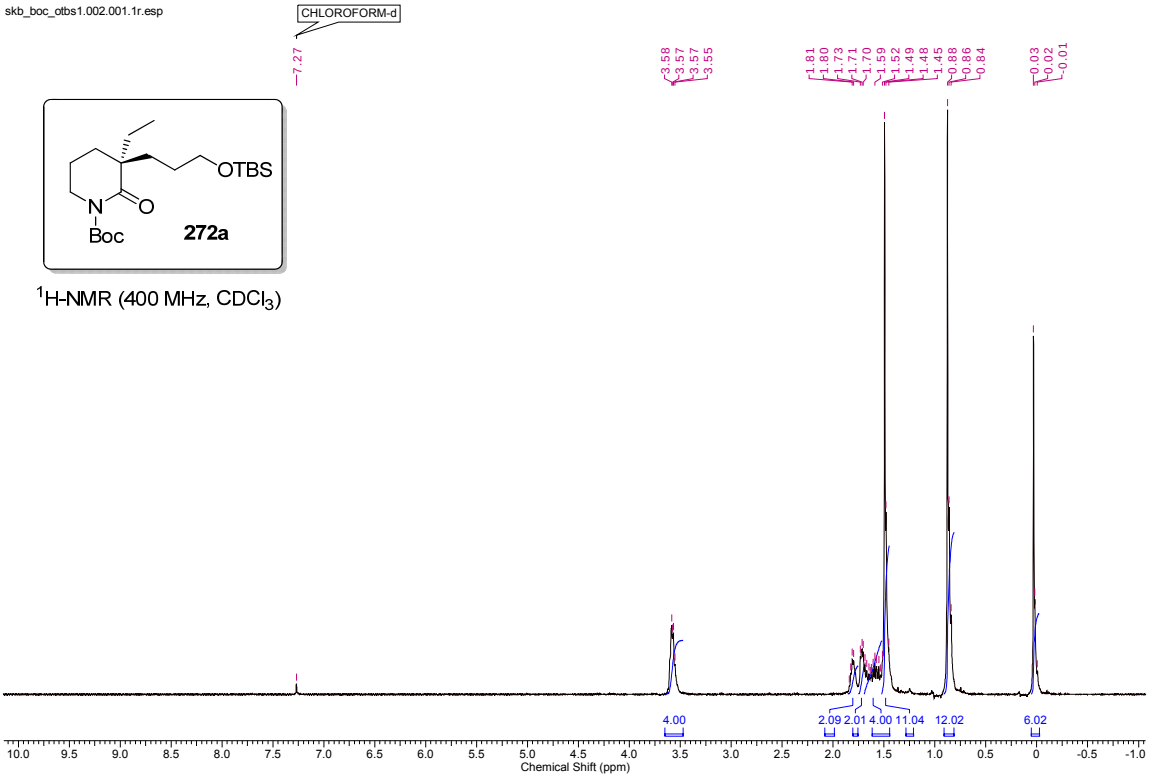
^{1}H-NMR (800 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

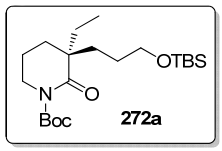


^{13}C-NMR (101 MHz, $CDCl_3$)



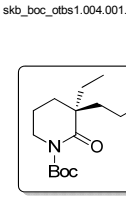
^{1}H-NMR (400 MHz, $CDCl_3$)

skb_boc_otbs1.003.001.1r.esp

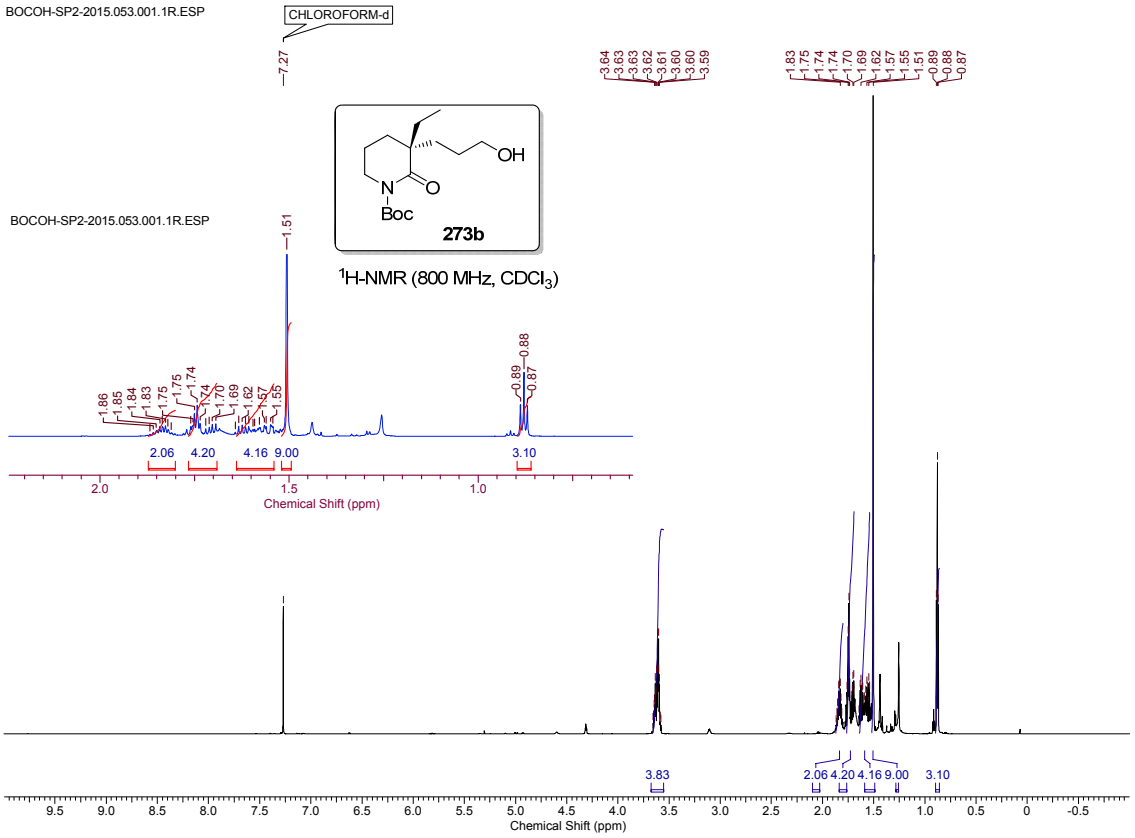


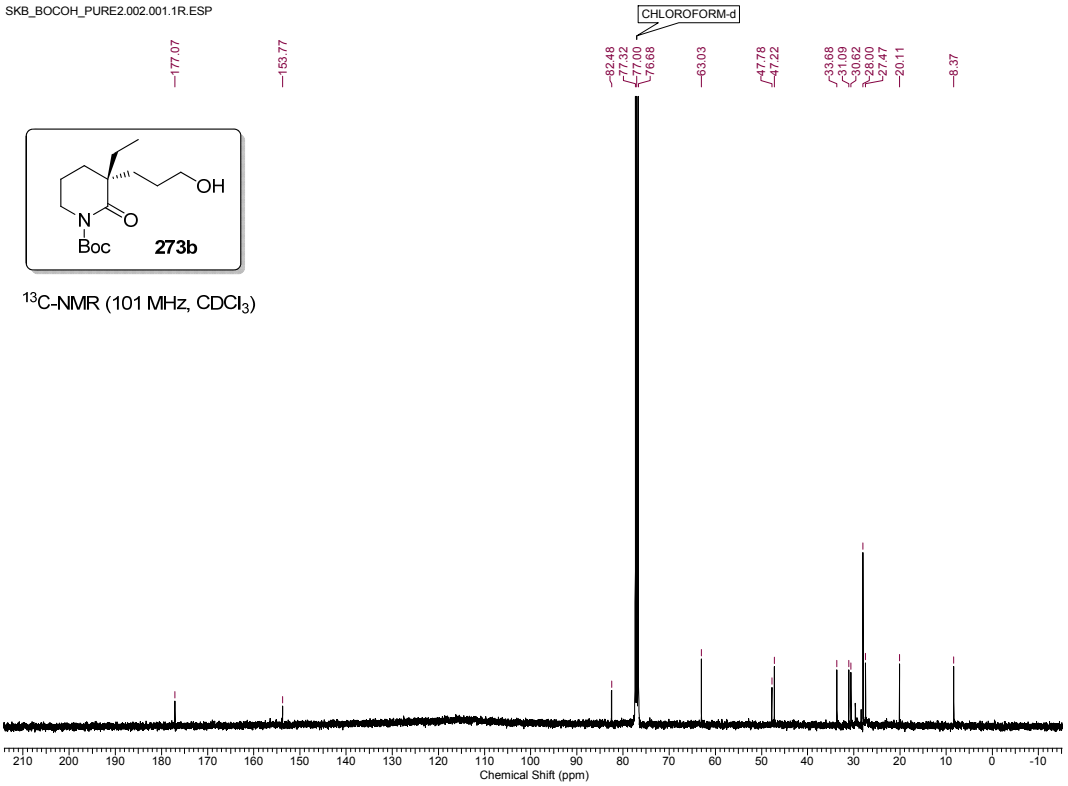
^{13}C-NMR (101 MHz, $CDCl_3$)

skb_boc_otbs1.004.001.1r.esp

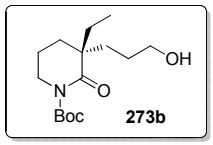


^{13}C-NMR (101 MHz, $CDCl_3$)


BOCOH-SP2-2015.053.001.1R.ESP
CHLOROFORM-d
OH
N
O
Boc
273b
^{1}H-NMR (800 MHz, CDCl$_3$)
Chemical Shift (ppm)


SKB_BOCOH_PURE2.002.001.1R.ESP
CHLOROFORM-d
OH
N
O
Boc
273b
^{13}C-NMR (101 MHz, CDCl$_3$)
Chemical Shift (ppm)

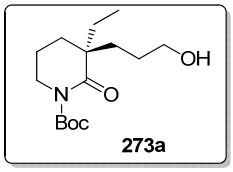
skb_bocoh_Pure2.003.001.1r.esp



273b

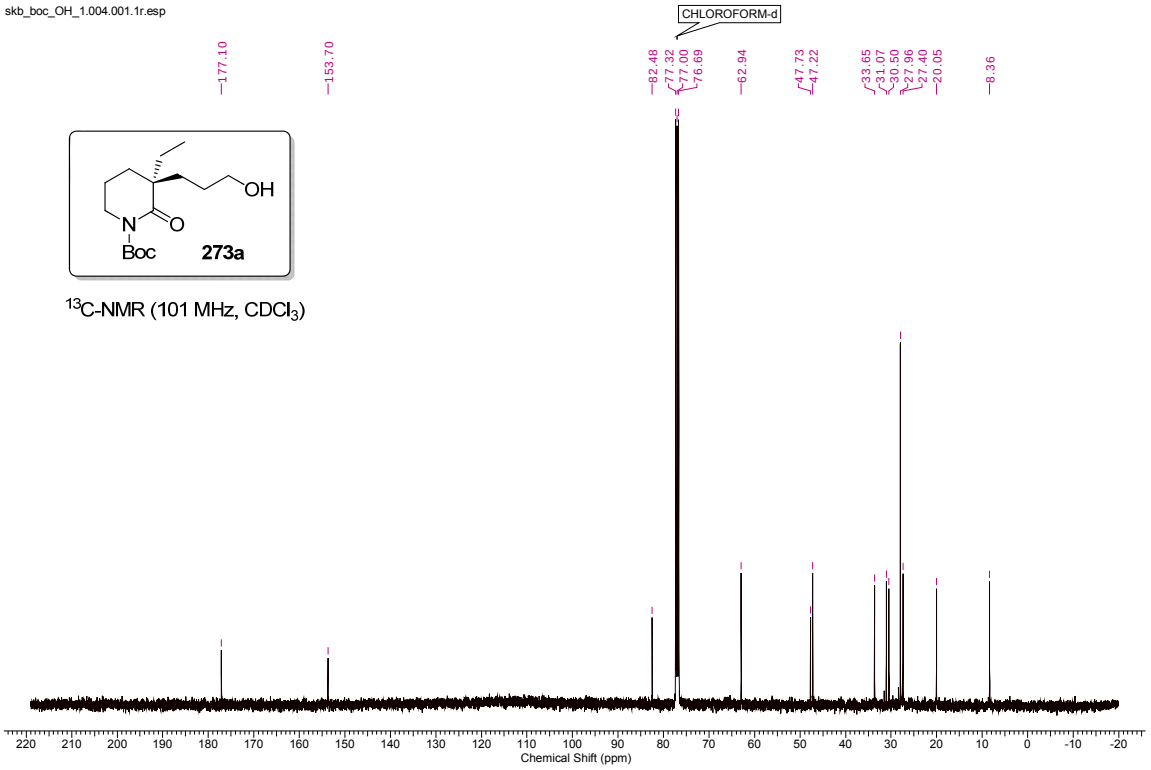
^{13}C-NMR (101 MHz, $CDCl_3$)

skb_boc_OH_1.003.001.1r.esp

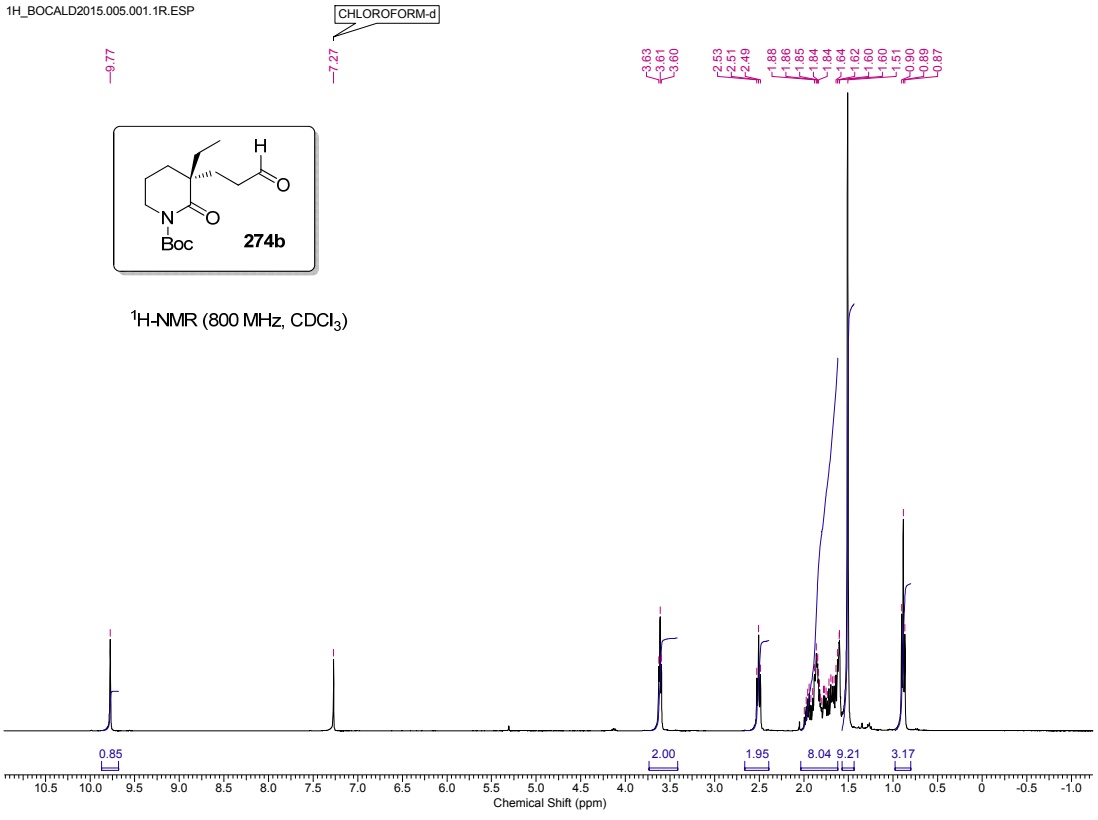


273a

^{1}H-NMR (400 MHz, $CDCl_3$)

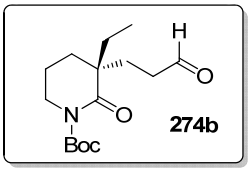


^{13}C-NMR (101 MHz, $CDCl_3$)



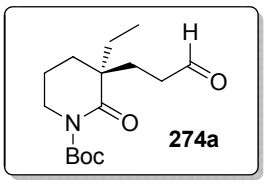
^{1}H-NMR (800 MHz, $CDCl_3$)

SKB-NMR-31122015.082.001.1r.esp

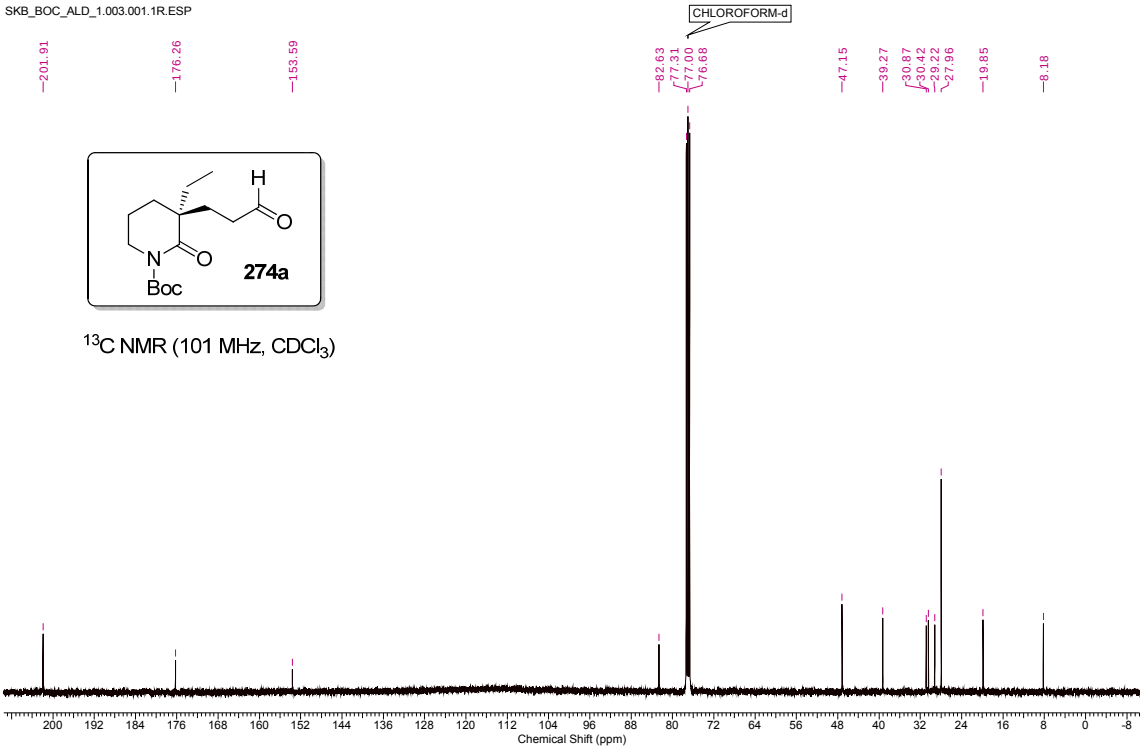


^{13}C-NMR (201 MHz, $CDCl_3$)

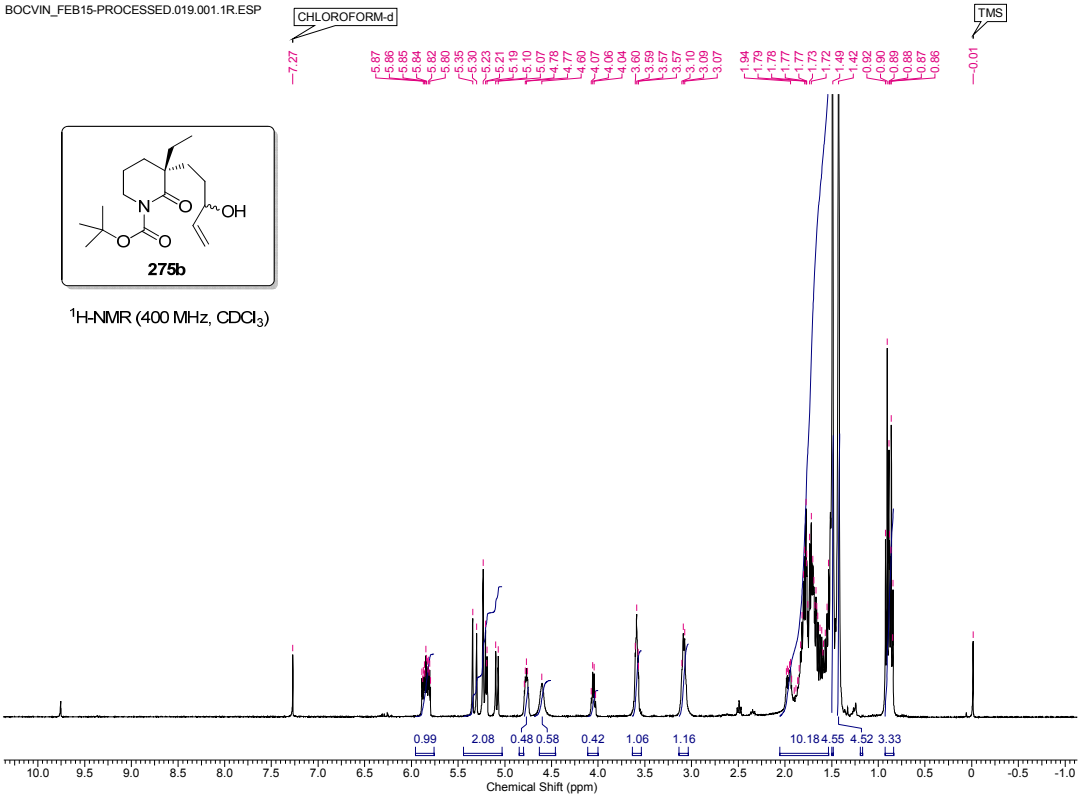
skb_boc_ald_1.002.001.1r.esp



^{1}H-NMR (400 MHz, CDCl3)

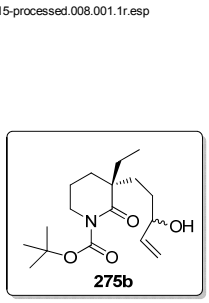


^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, $CDCl_3$)

shiva_feb15-processed.008.001.1r.esp

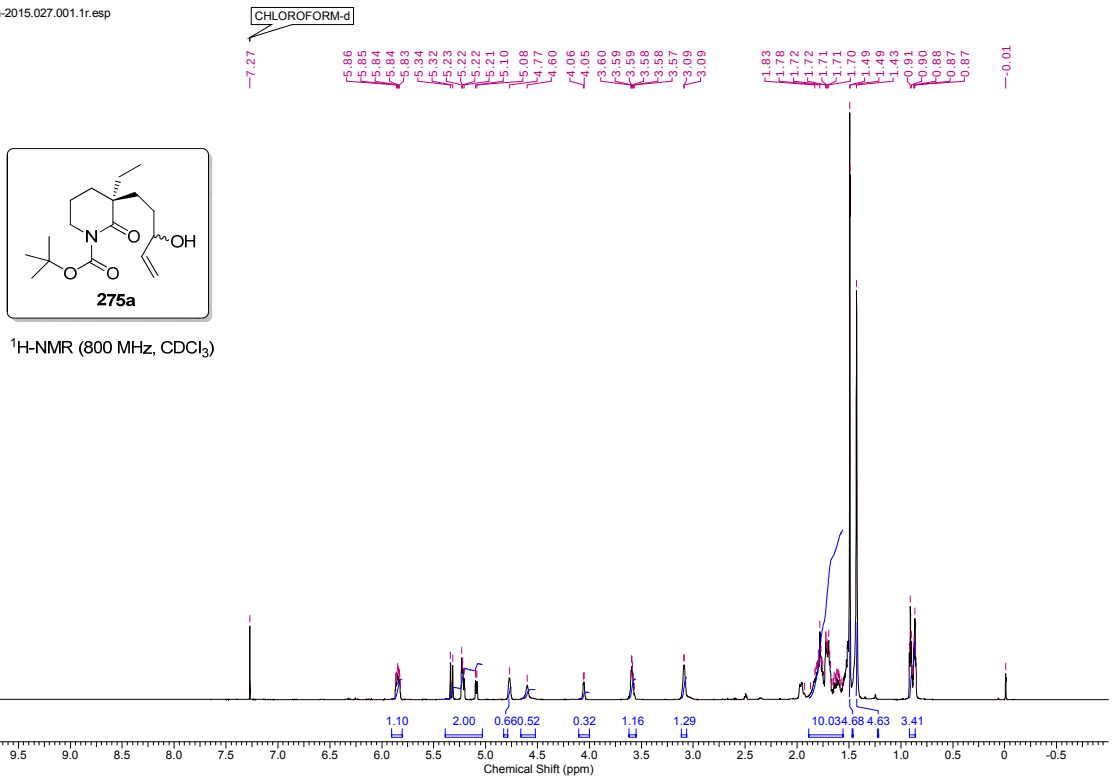


275b

^{13}C-NMR (101 MHz, $CDCl_3$)

Low intensity peaks are rotamers

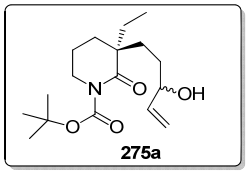
bocvin-2015.027.001.1r.esp



275a

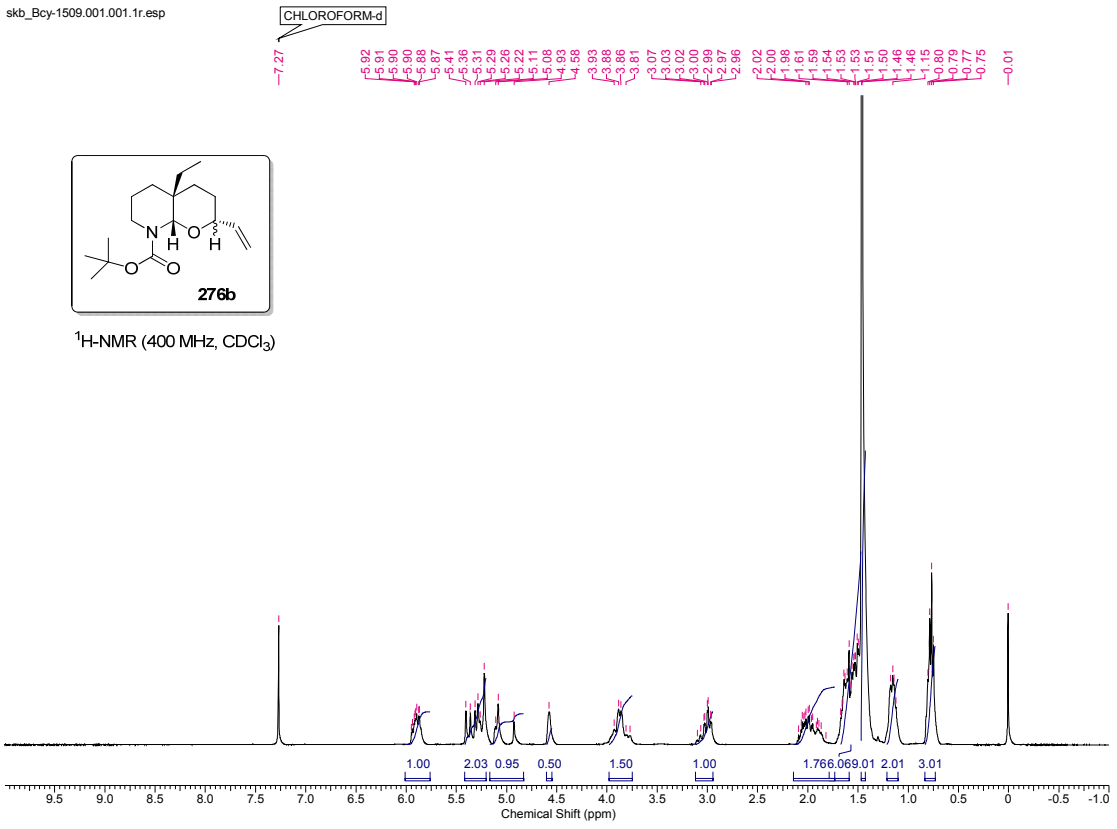
^{1}H-NMR (800 MHz, $CDCl_3$)

skb_boc-vin-1.005.001.1r.esp

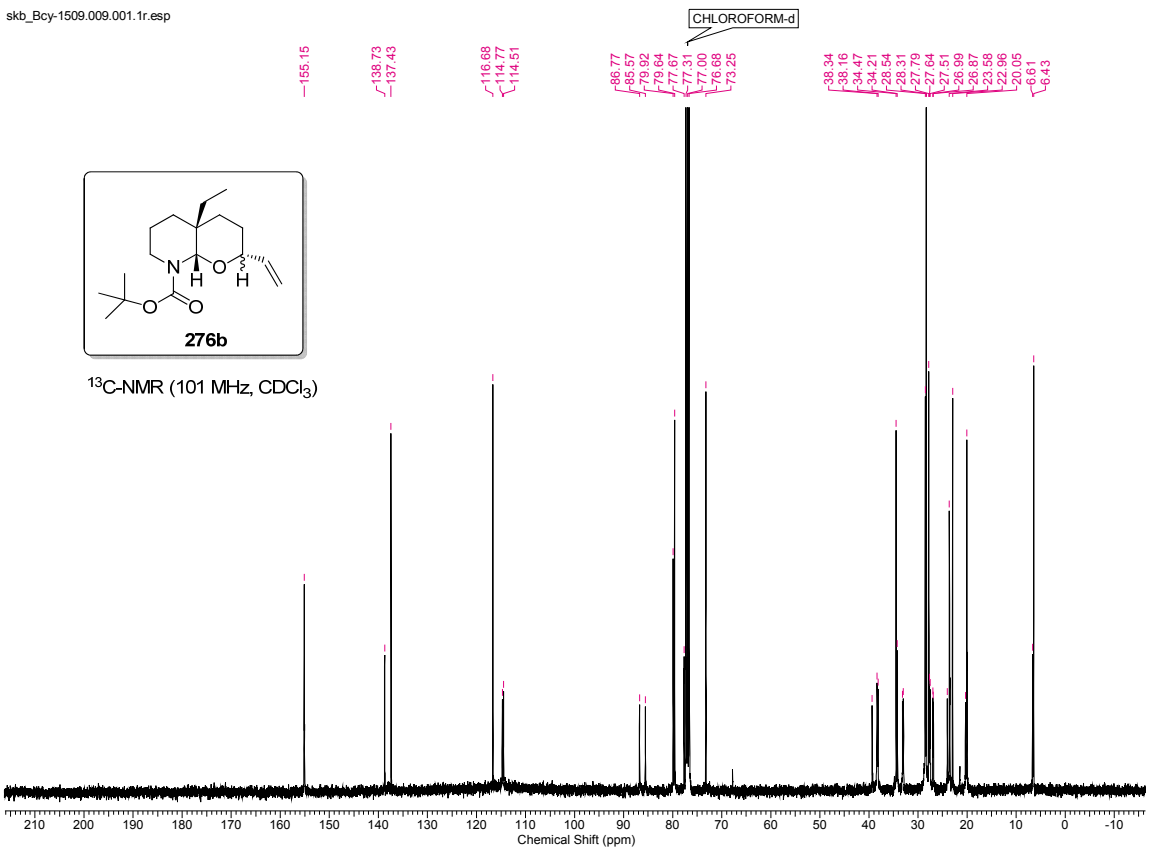


^{13}C-NMR (101 MHz, $CDCl_3$)

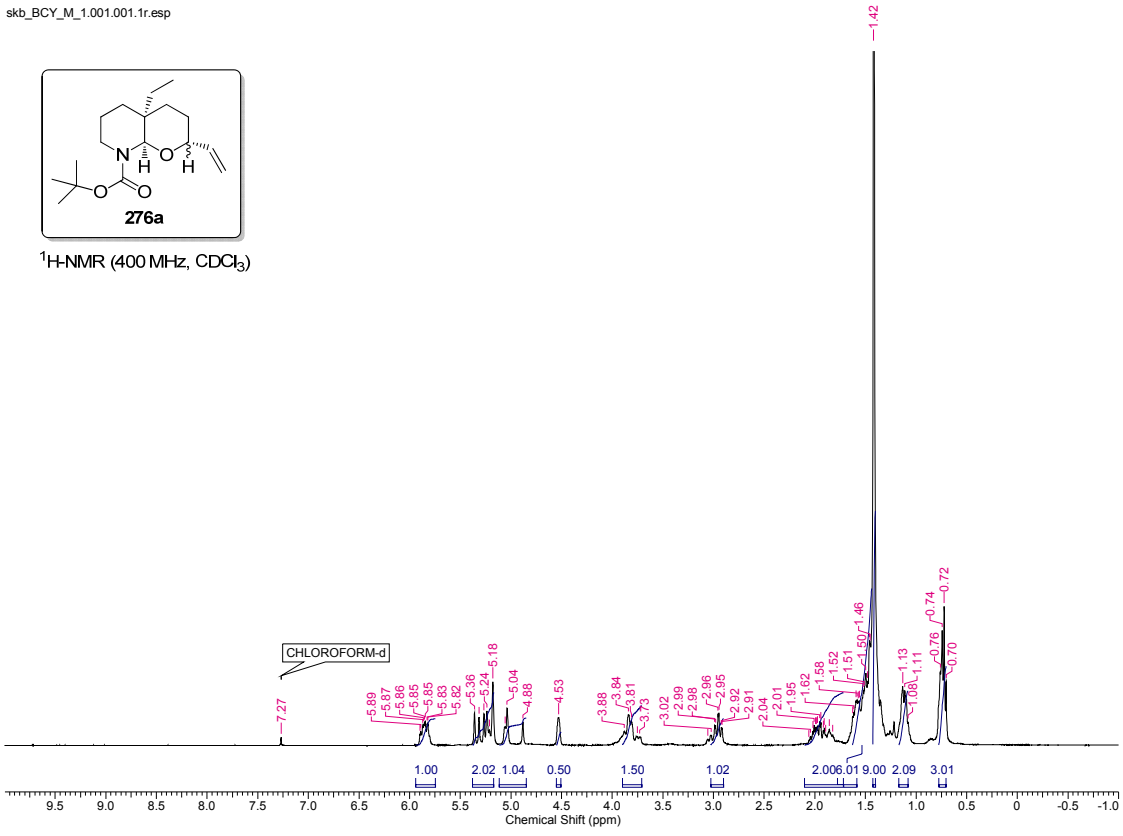
skb_Bcy-1509.001.001.1r.esp



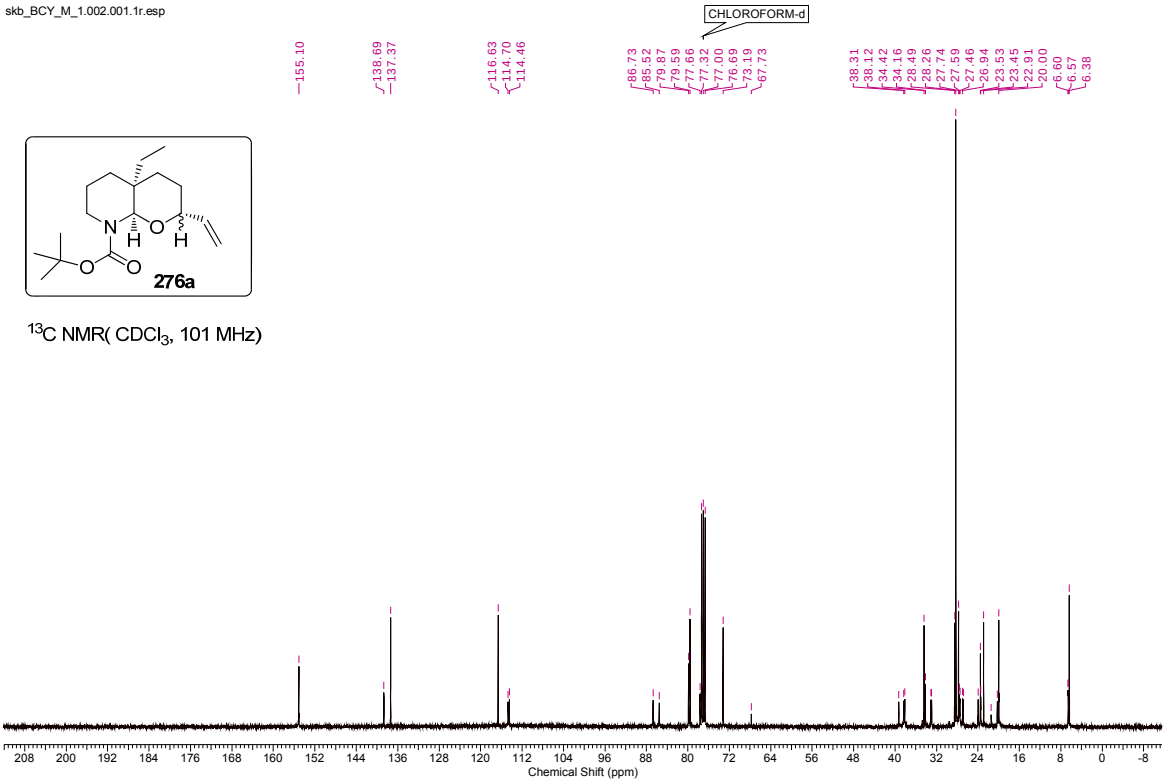
^{1}H-NMR (400 MHz, $CDCl_3$)



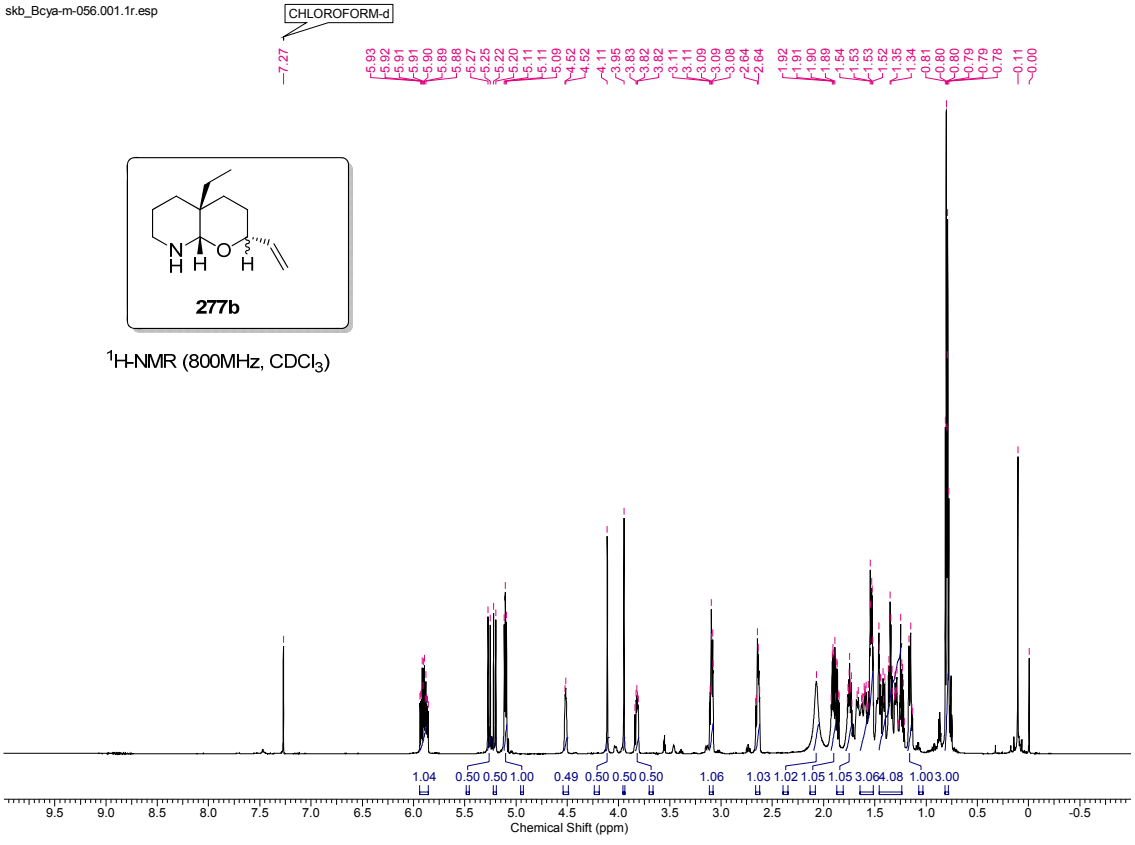
^{13}C-NMR (101 MHz, $CDCl_3$)



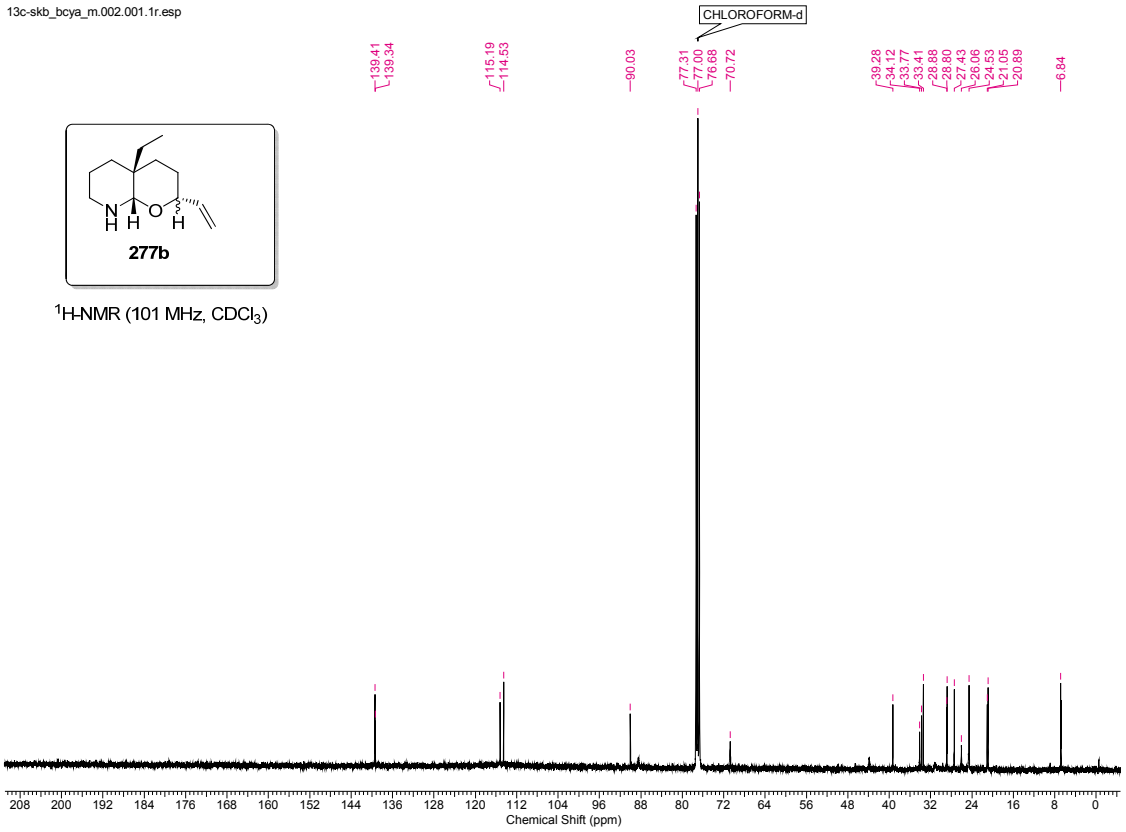
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C NMR($CDCl_3$, 101 MHz)

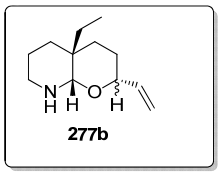


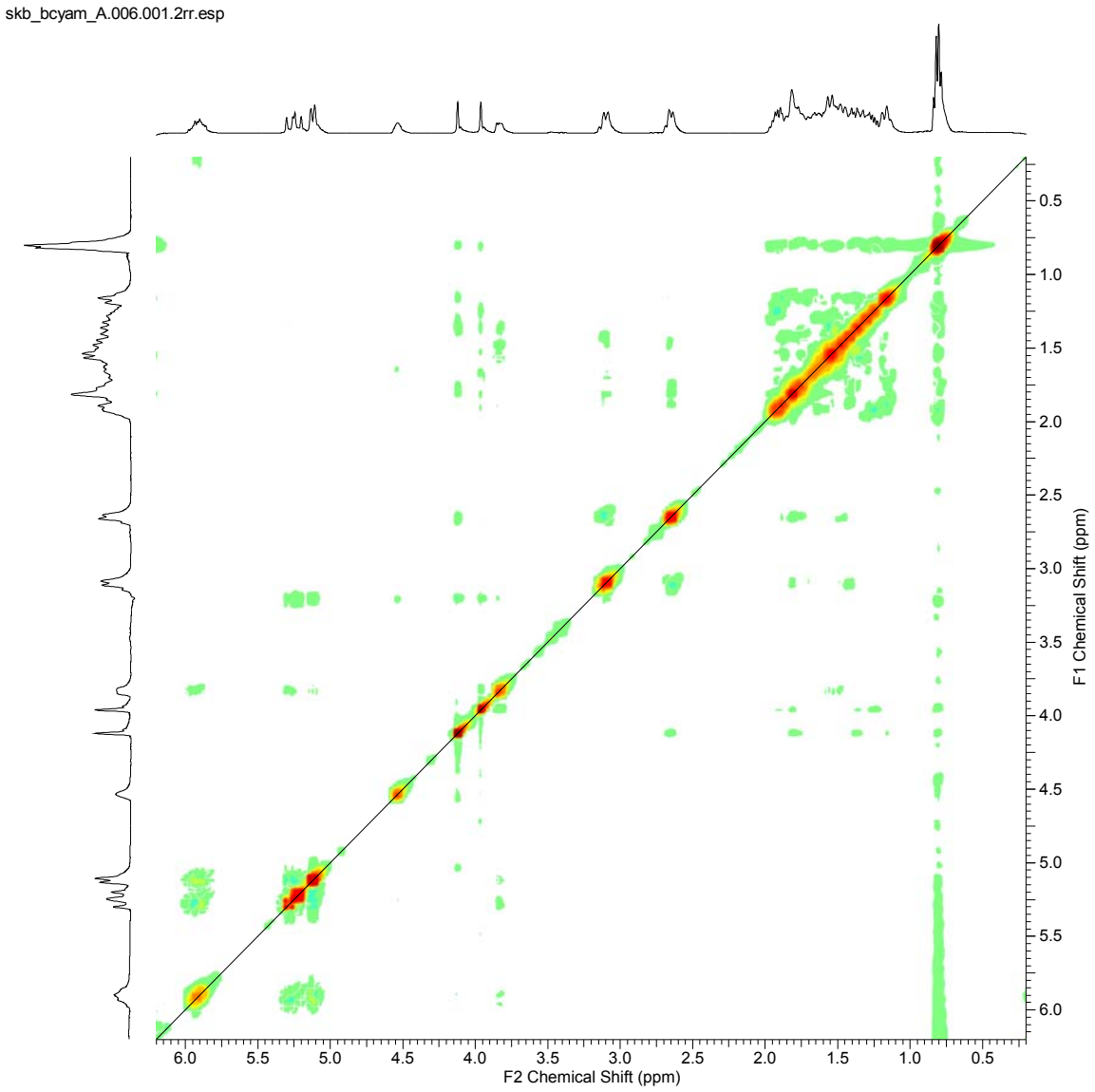
^{1}H-NMR (800MHz, $CDCl_3$)



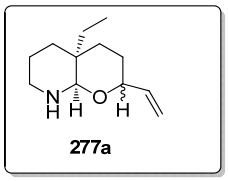
^{1}H-NMR (101 MHz, $CDCl_3$)

NOESY


277b


skb_bcyam_A.006.001.2rr.esp
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

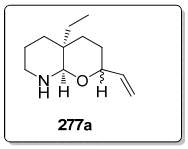
skb_bcyam_A.001.001.1r.esp



277a

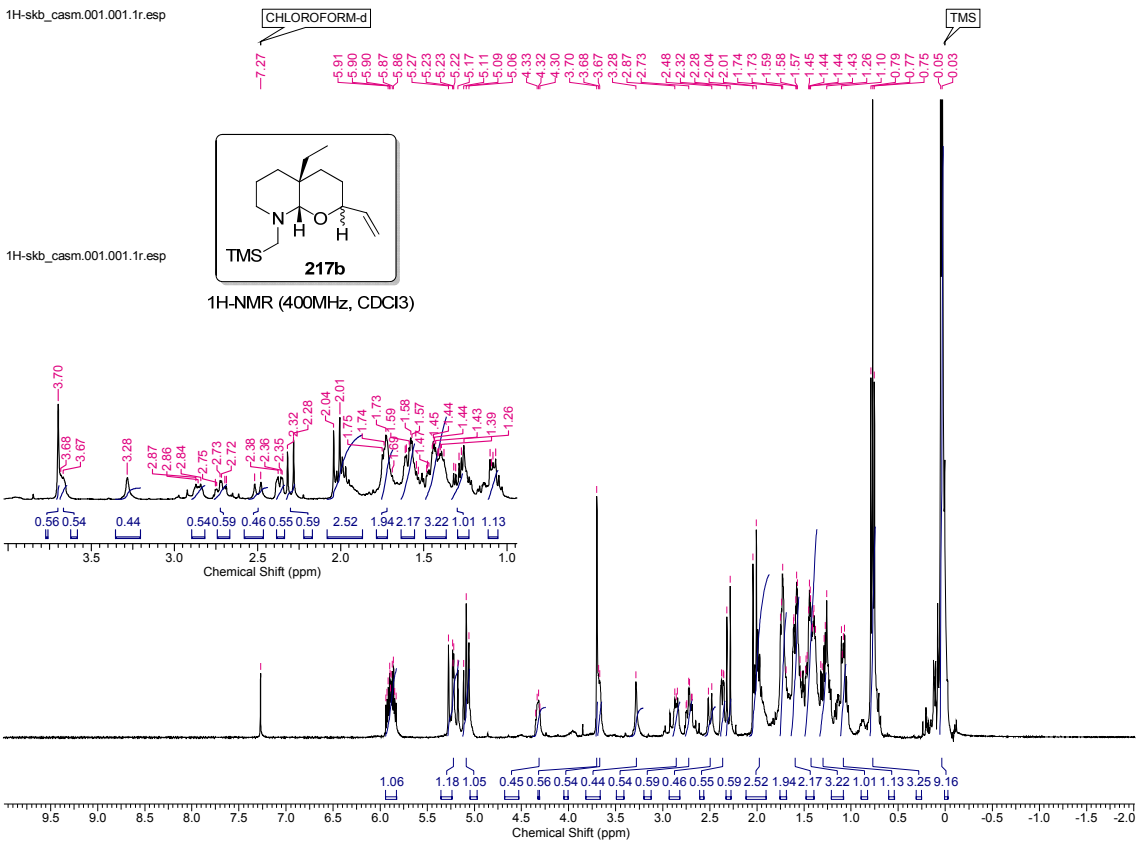
^{1}H-NMR (400MHz, $CDCl_3$)

SKB_BCYAM_A.007.001.1R.ESP

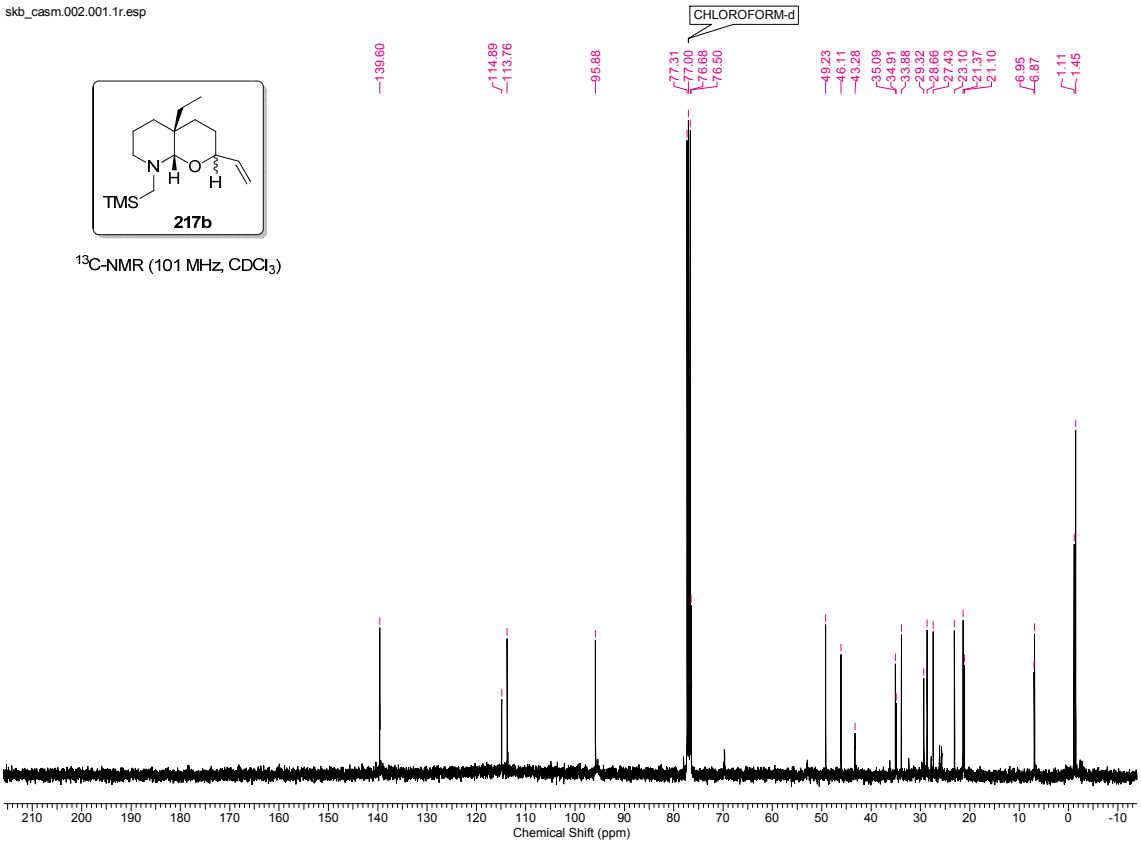


277a

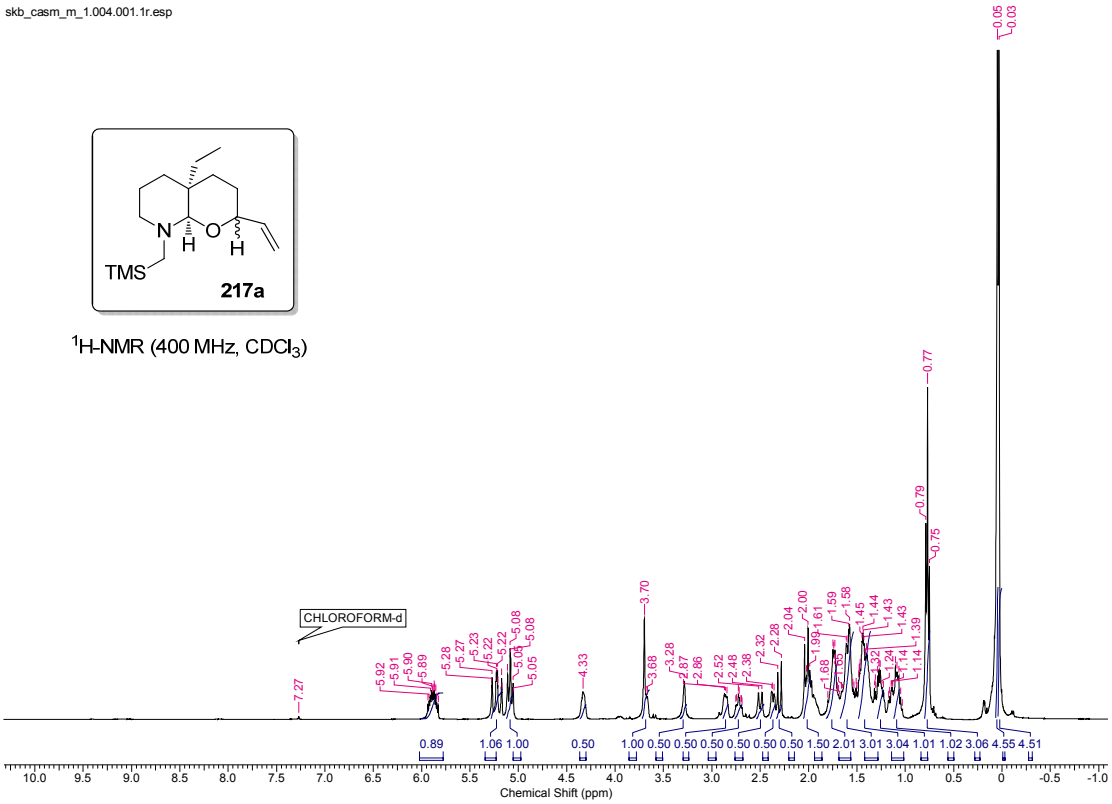
^{13}C-NMR (101 MHz, $CDCl_3$)



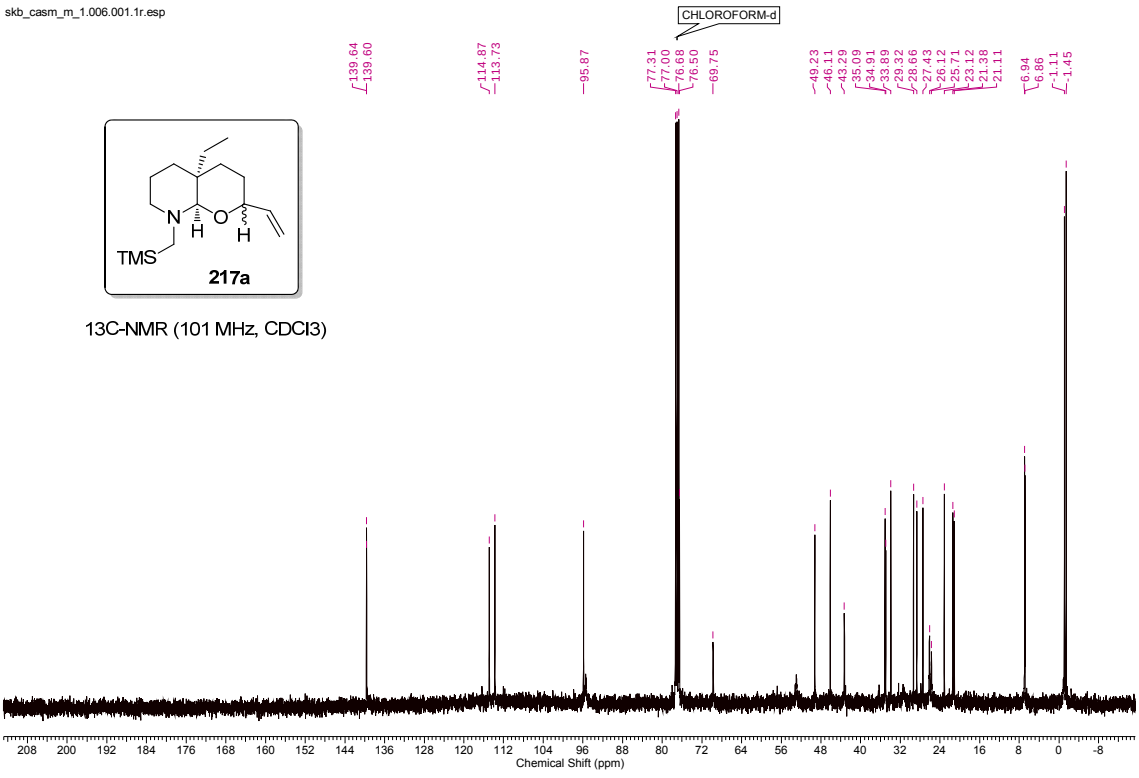
1H-NMR (400MHz, CDCl3)



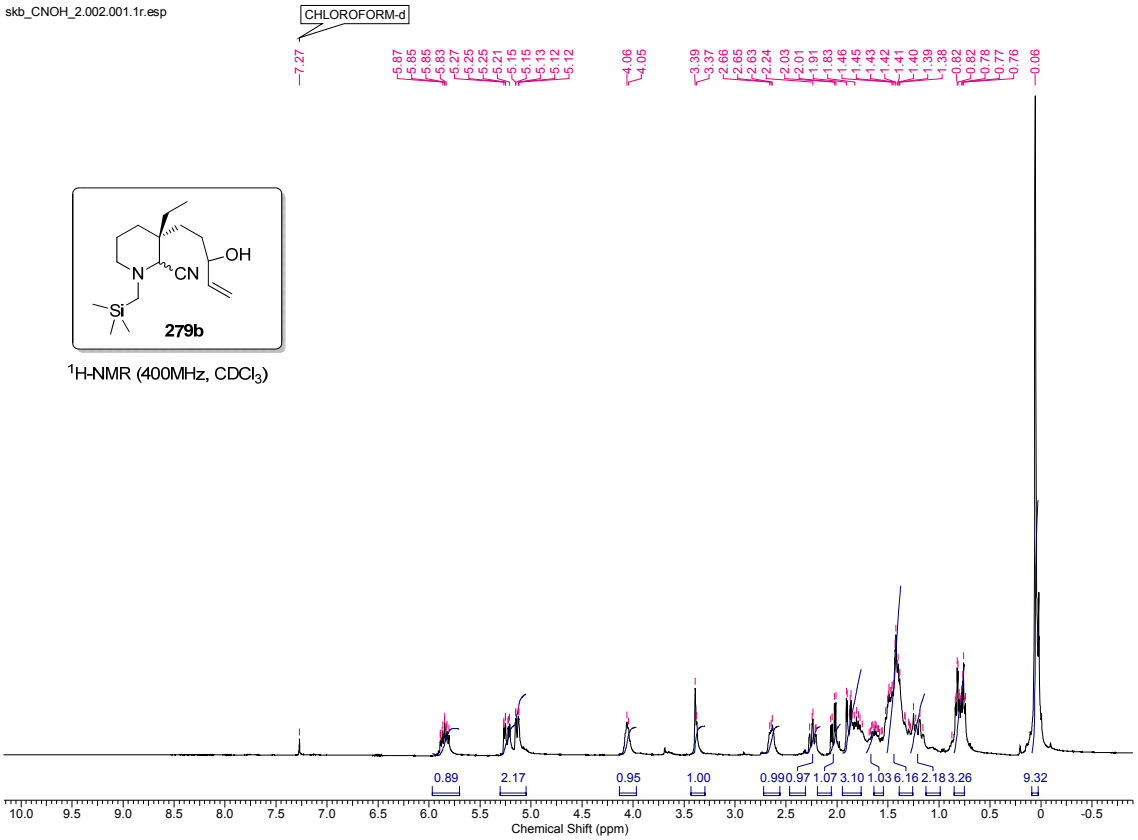
^{13}C-NMR (101 MHz, $CDCl_3$)



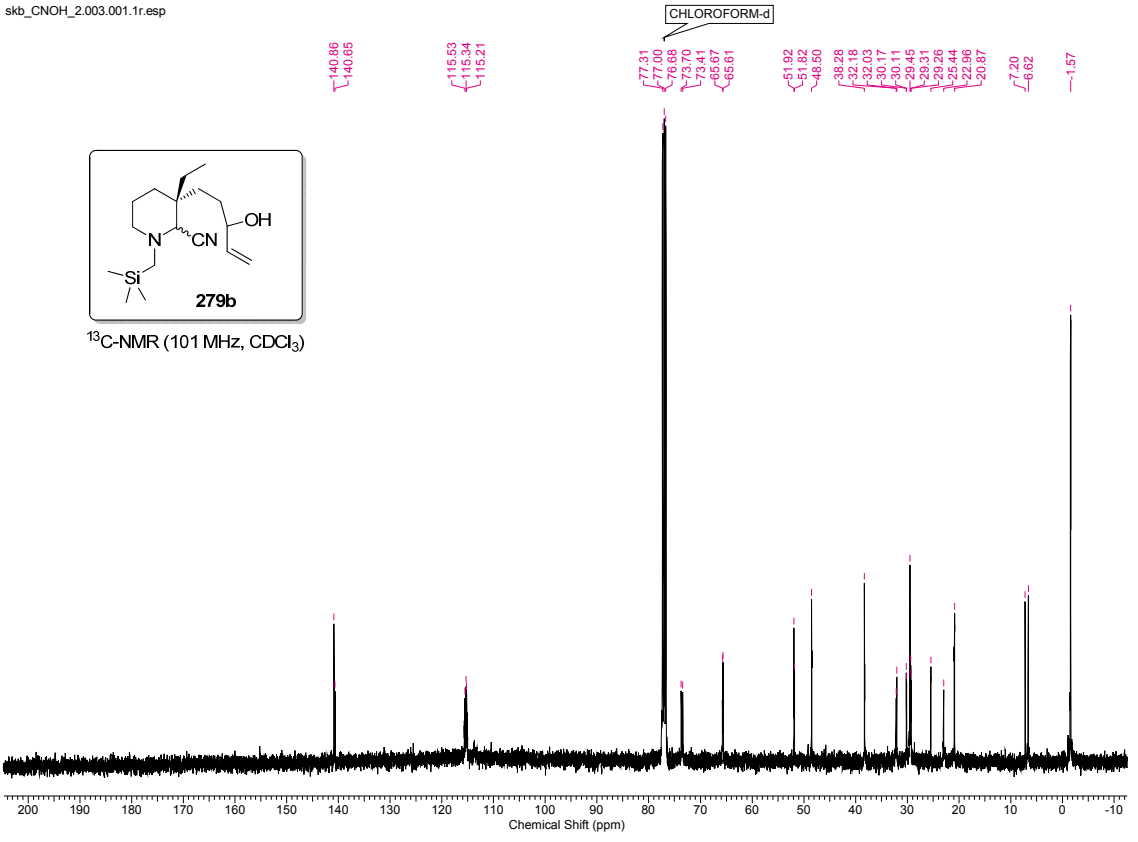
^{1}H-NMR (400 MHz, $CDCl_3$)



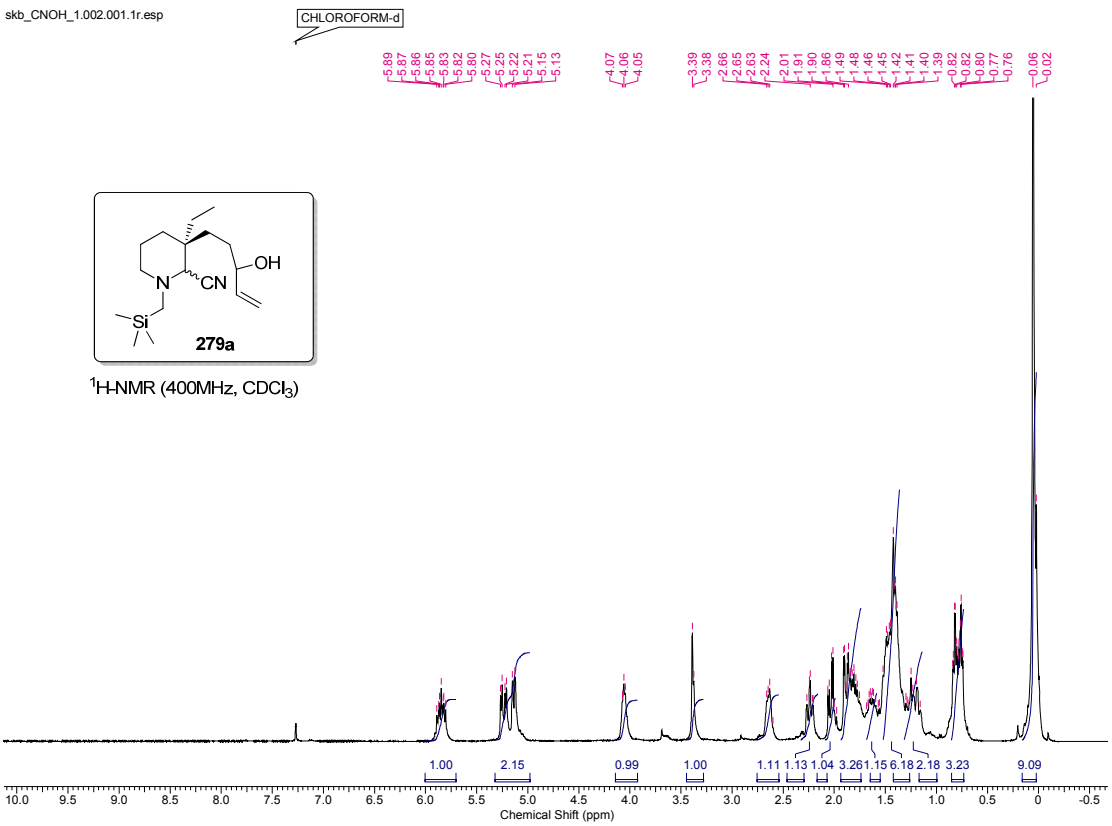
13C-NMR (101 MHz, CDCl3)



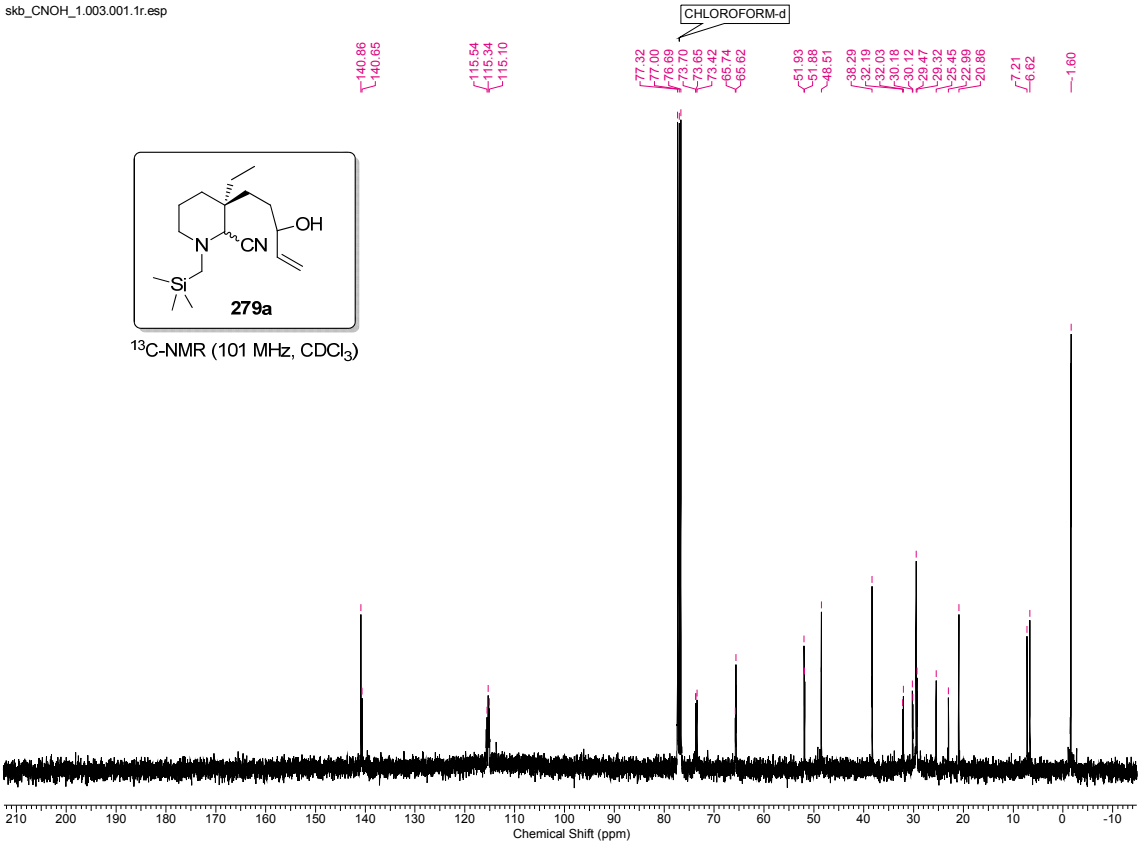
^{1}H-NMR (400MHz, $CDCl_3$)



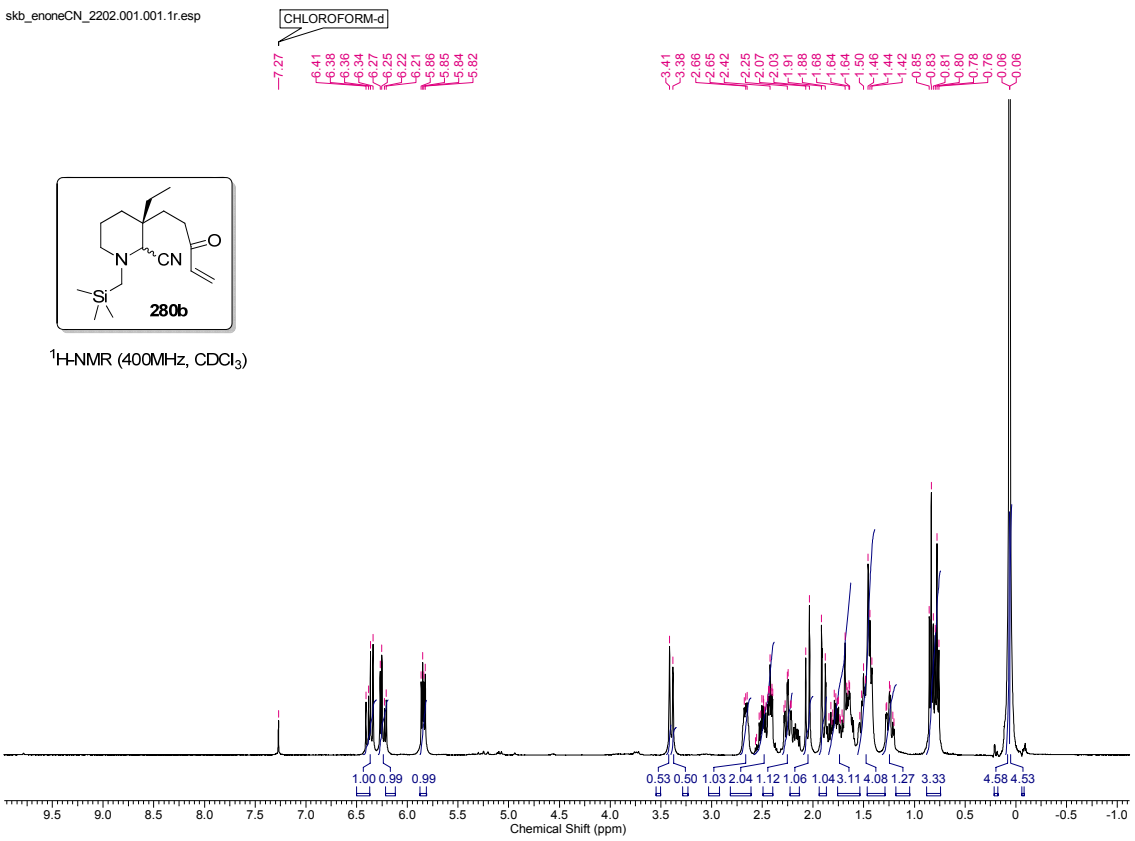
^{13}C-NMR (101 MHz, $CDCl_3$)



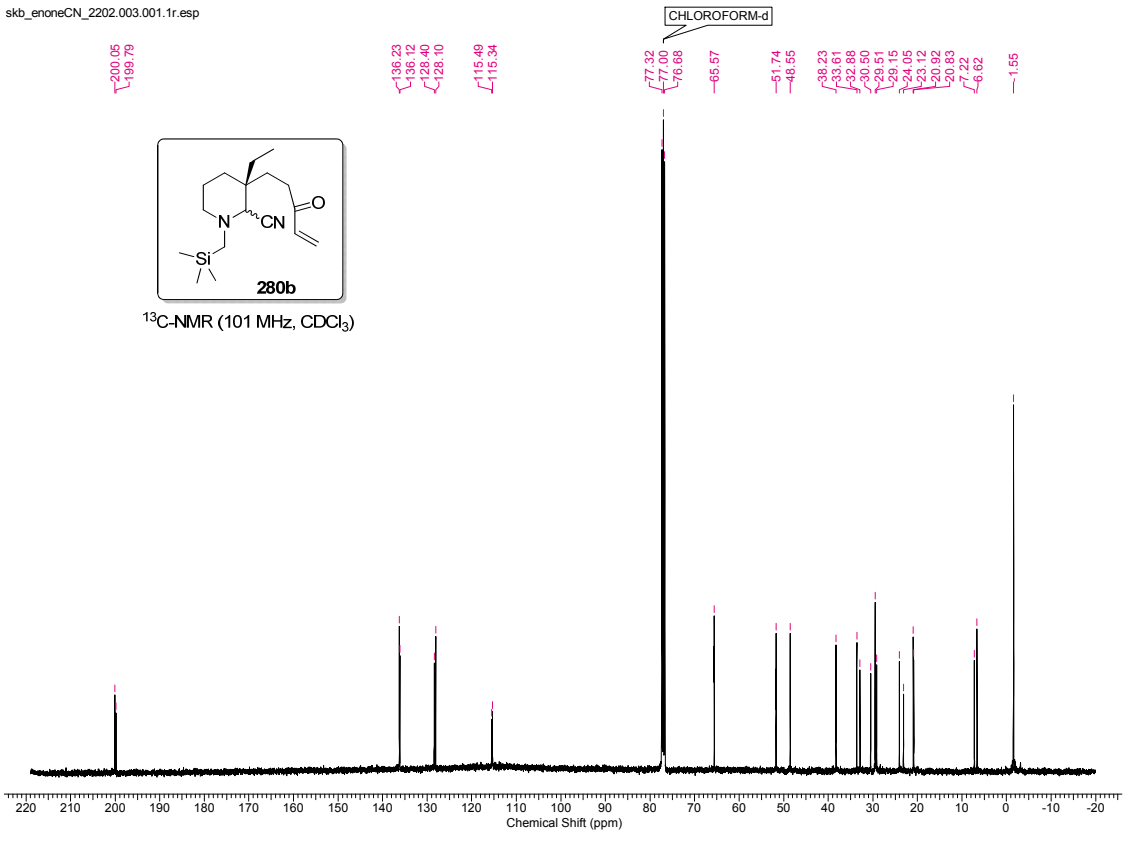
^{1}H-NMR (400MHz, $CDCl_3$)



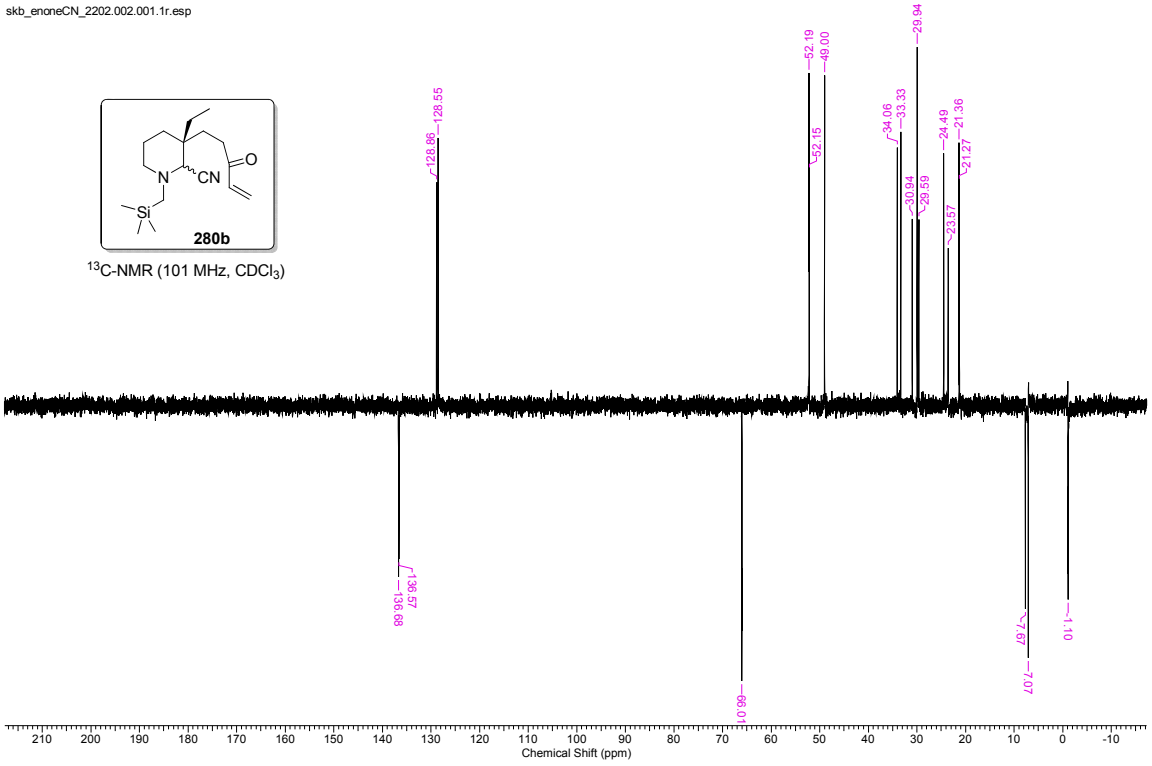
^{13}C-NMR (101 MHz, $CDCl_3$)



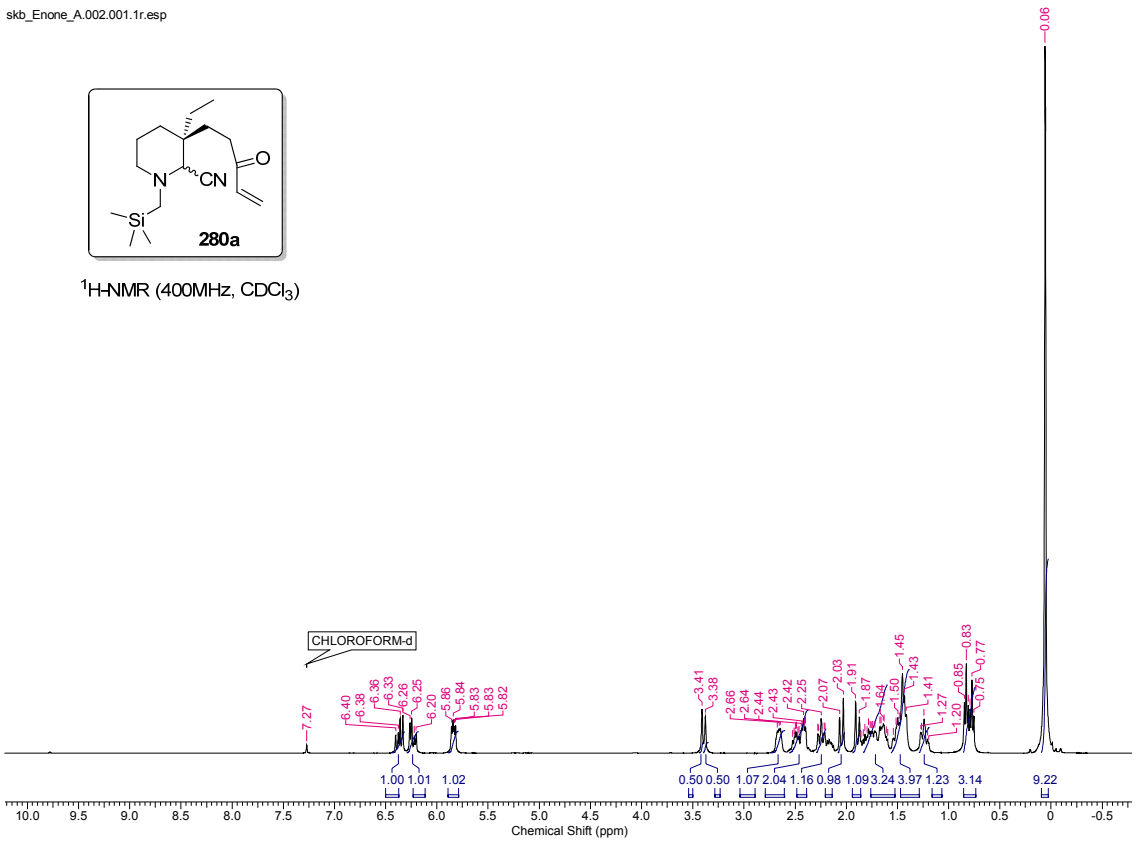
^{1}H-NMR (400MHz, $CDCl_3$)



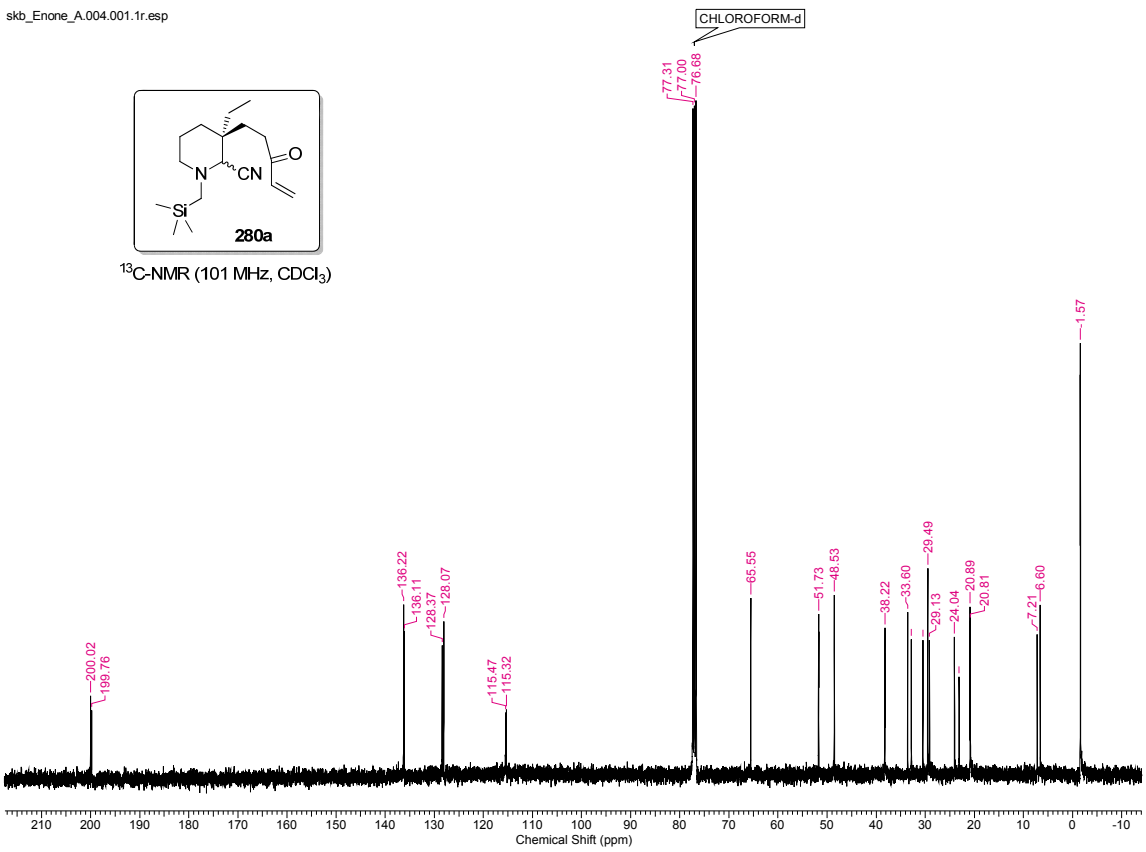
^{13}C-NMR (101 MHz, $CDCl_3$)

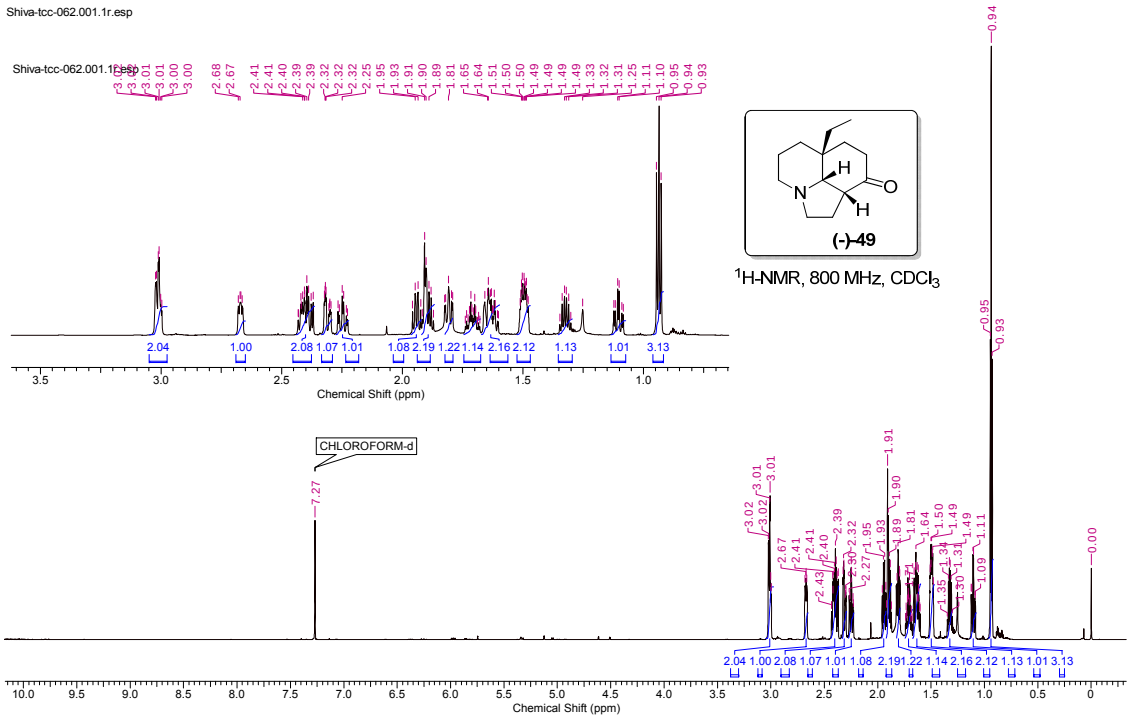


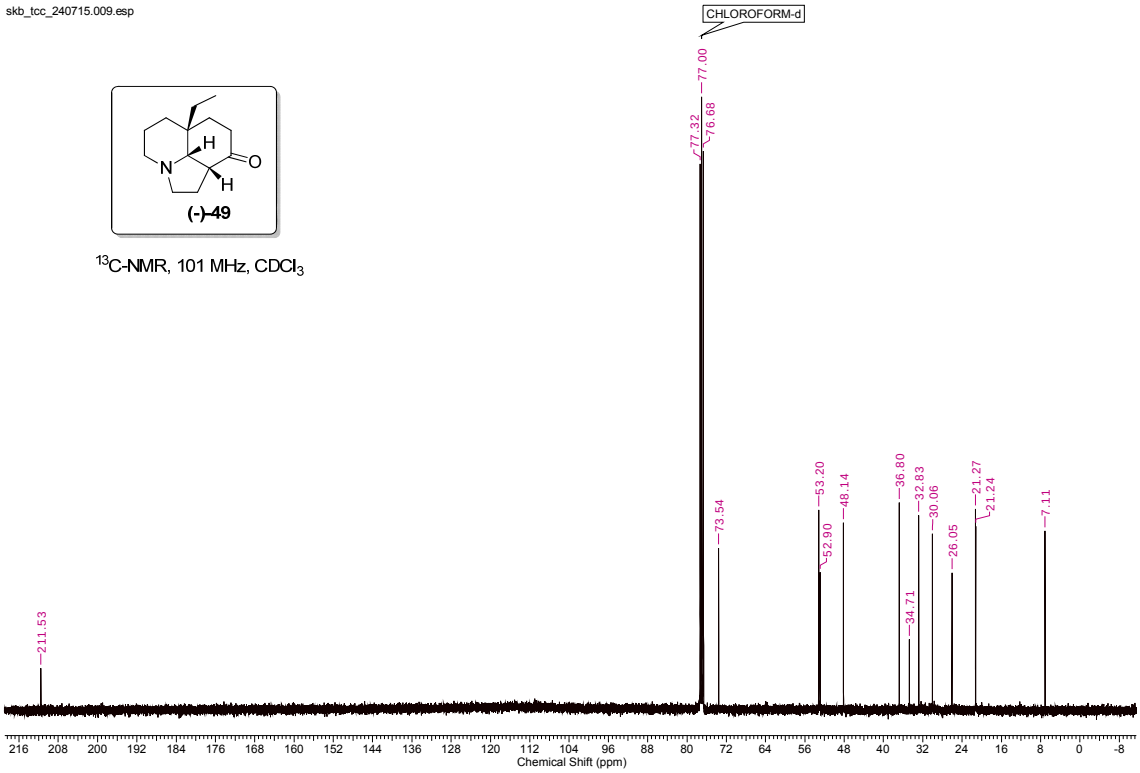
^{13}C-NMR (101 MHz, $CDCl_3$)



^{1}H-NMR (400MHz, $CDCl_3$)

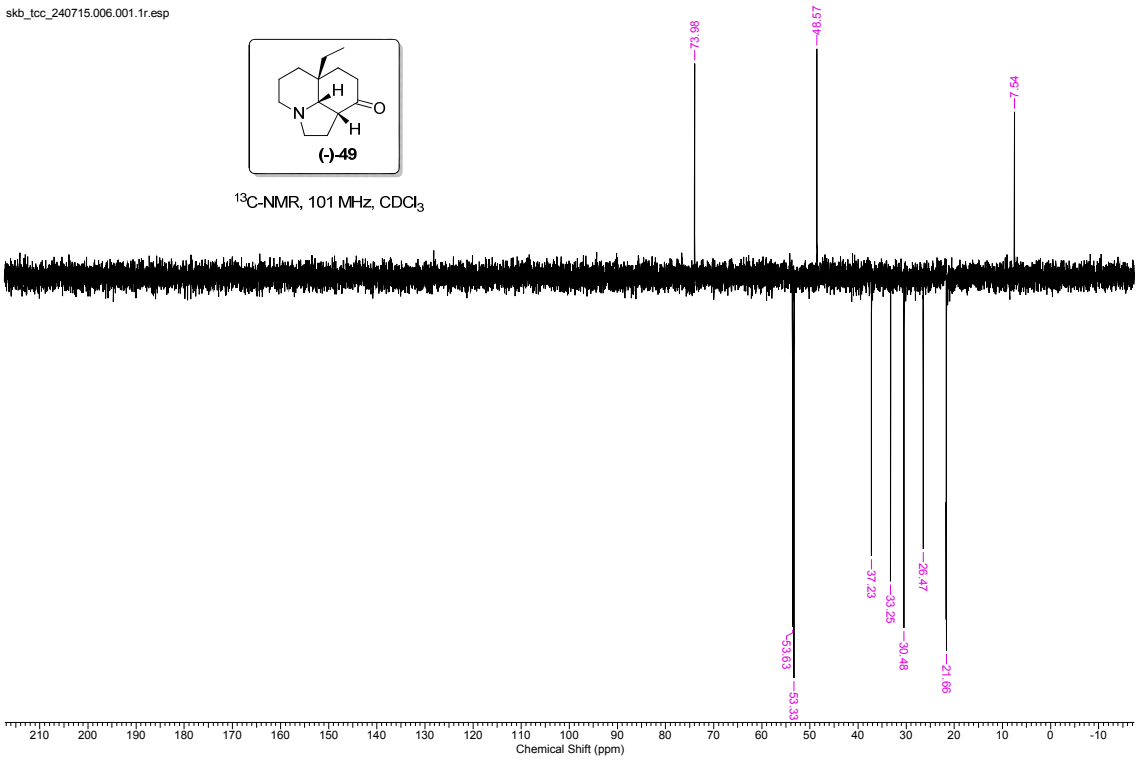

skb_Enone_A.004.001.1r.esp
CHLOROFORM-d
280a
^{13}C-NMR (101 MHz, $CDCl_3$)
Chemical Shift (ppm)


Shiva-tcc-062.001.1r.esp
(-)-49
^{1}H-NMR, 800 MHz, $CDCl_3$
CHLOROFORM-d
Chemical Shift (ppm)



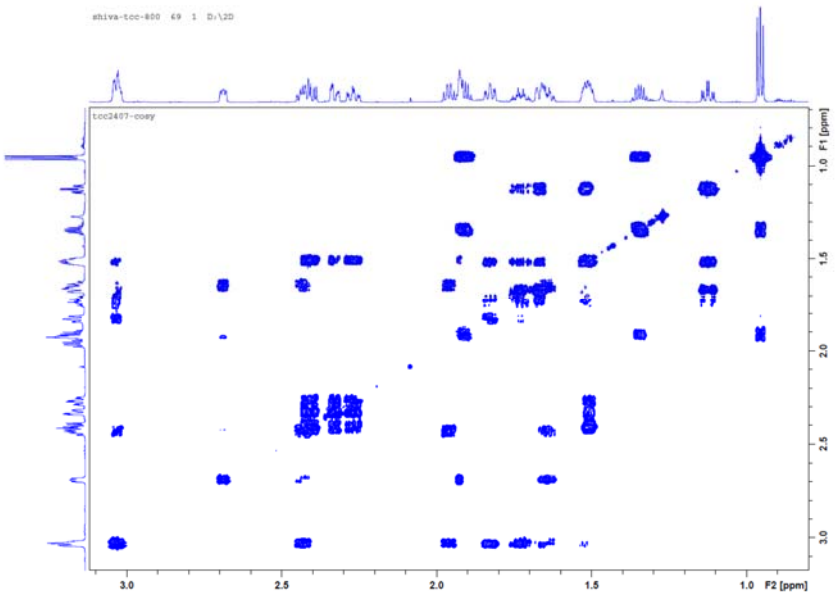
(-)-49

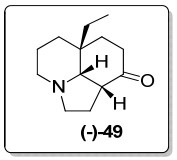
^{13}C-NMR, 101 MHz, $CDCl_3$



(-)-49

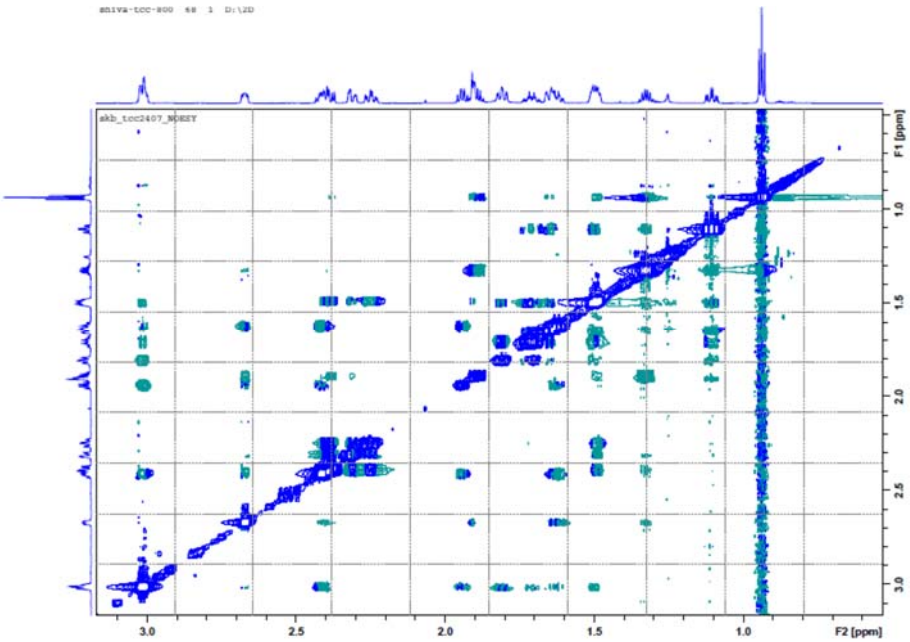
^{13}C-NMR, 101 MHz, $CDCl_3$

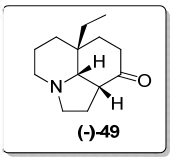




(-)-49

COSY, 101 MHz, $CDCl_3$

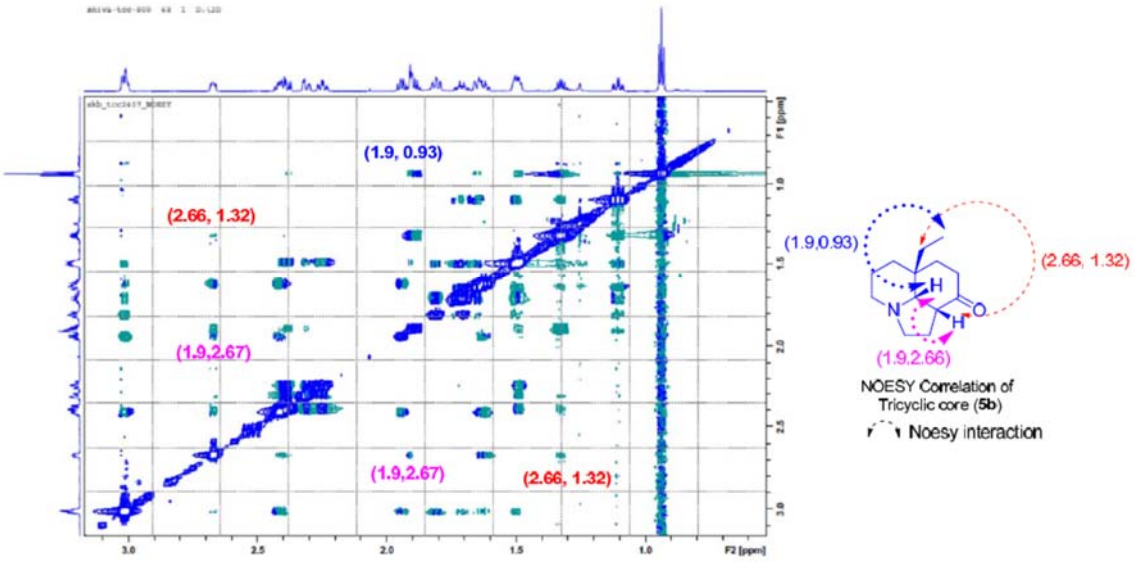




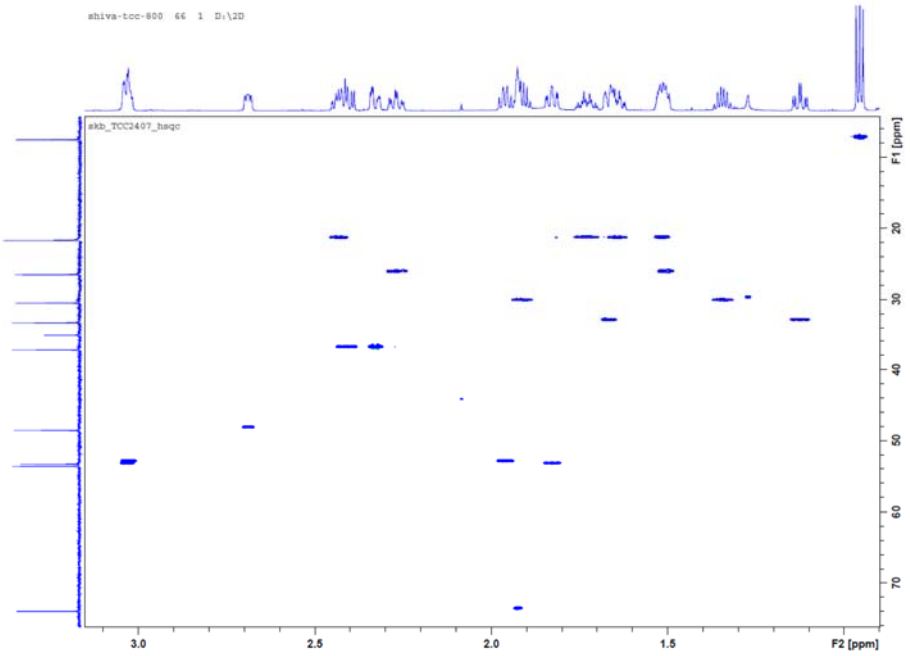
(-)-49

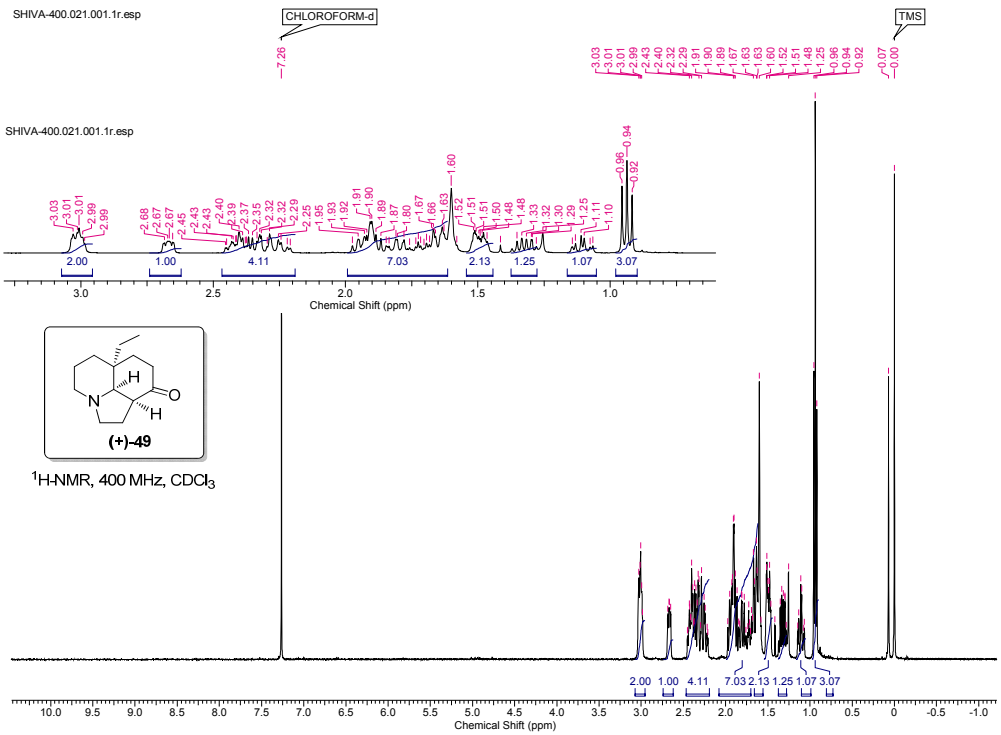
)ESY, 101 MHz, $CDCl_3$

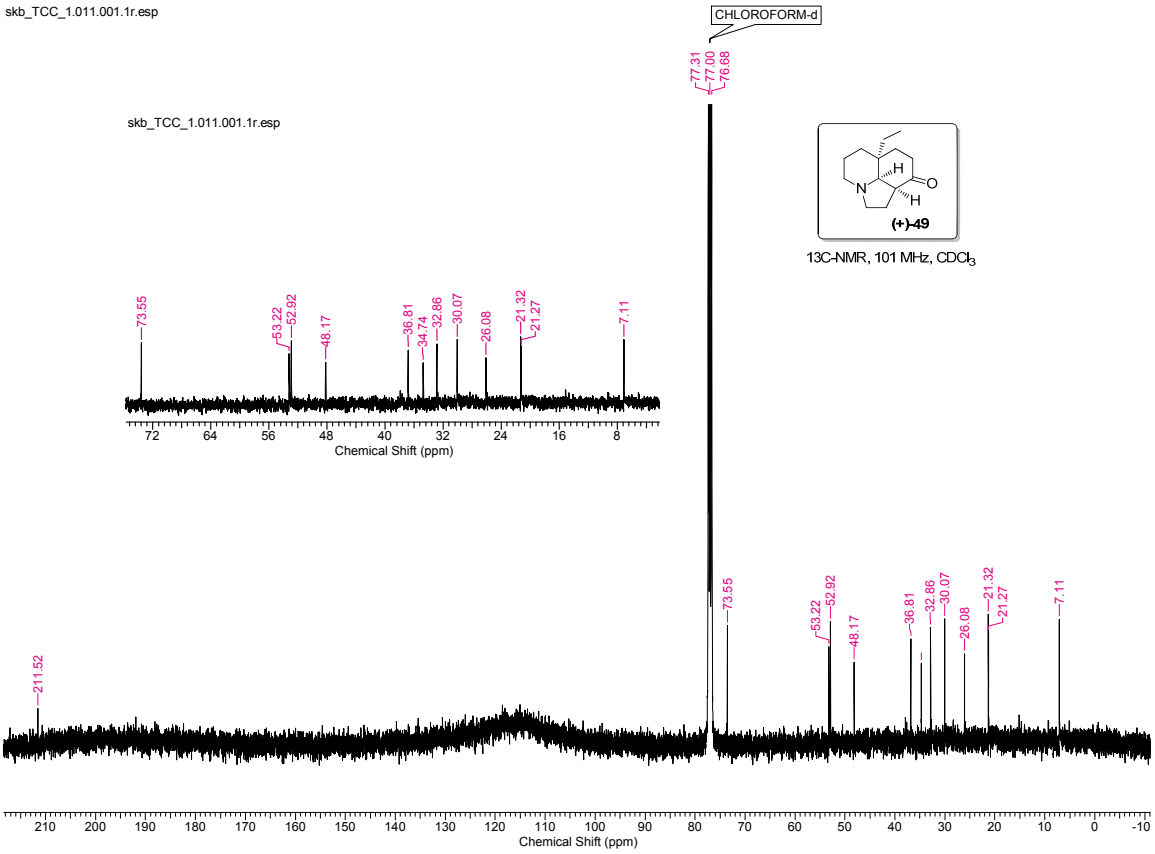
NOESY:

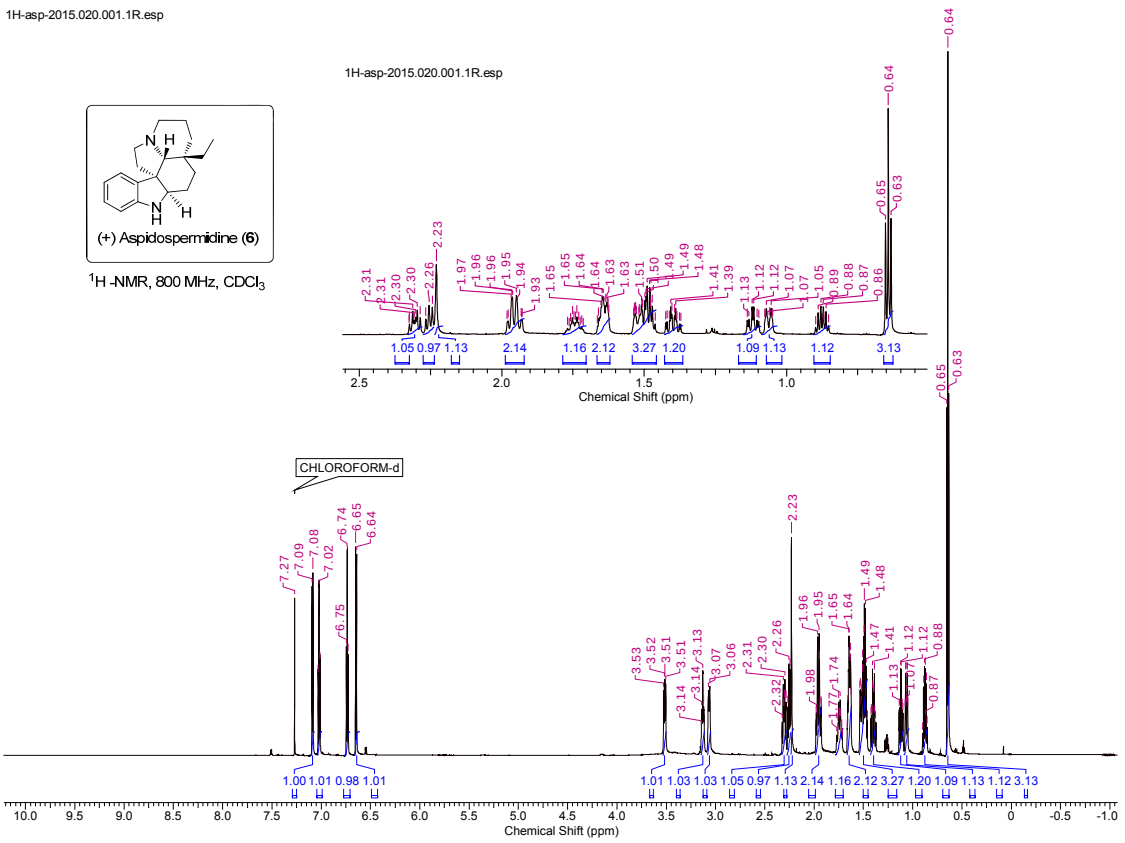

(1.9, 0.93)
(2.66, 1.32)
(1.9,2.67)
(1.9,2.67)
(2.66, 1.32)
F2 [ppm]
F1 [ppm]
(1.9,0.93)
(2.66, 1.32)
(1.9,2.66)
NOESY Correlation of
Tricyclic core (5b)
Noesy interaction

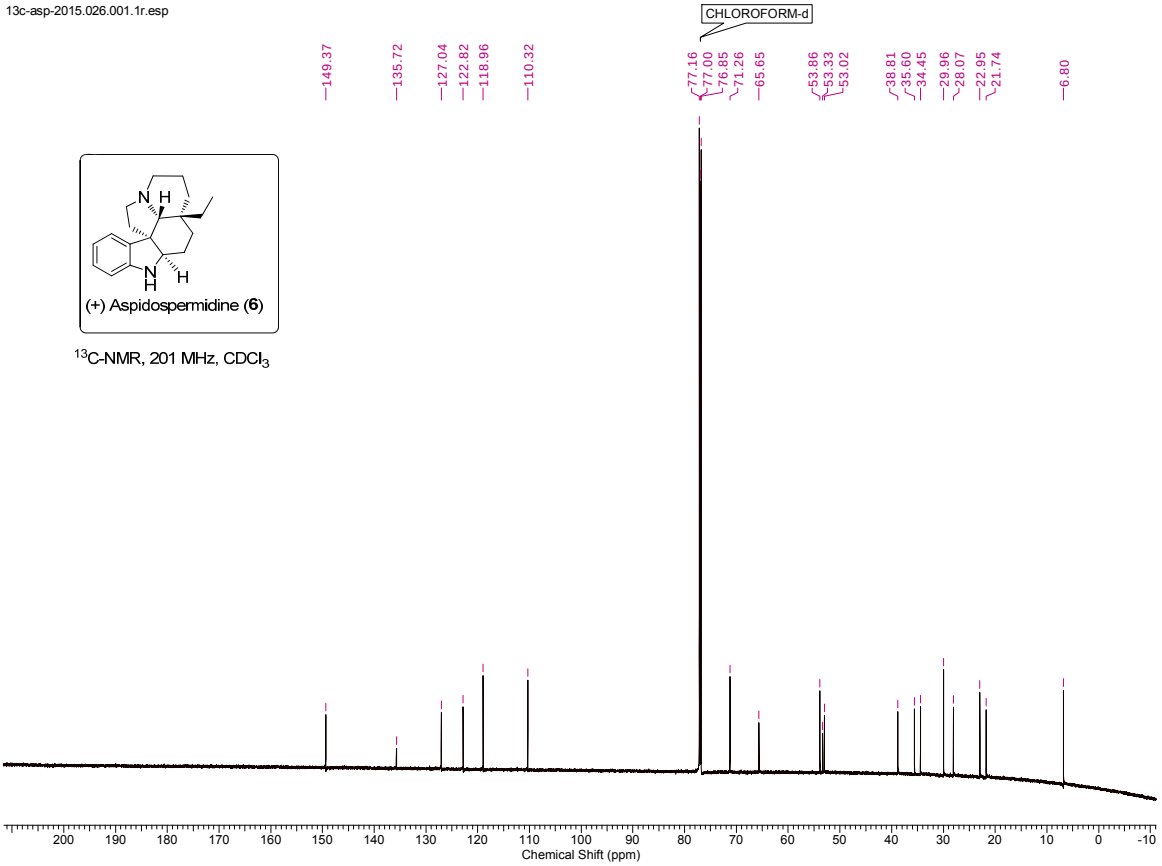
HSQC:

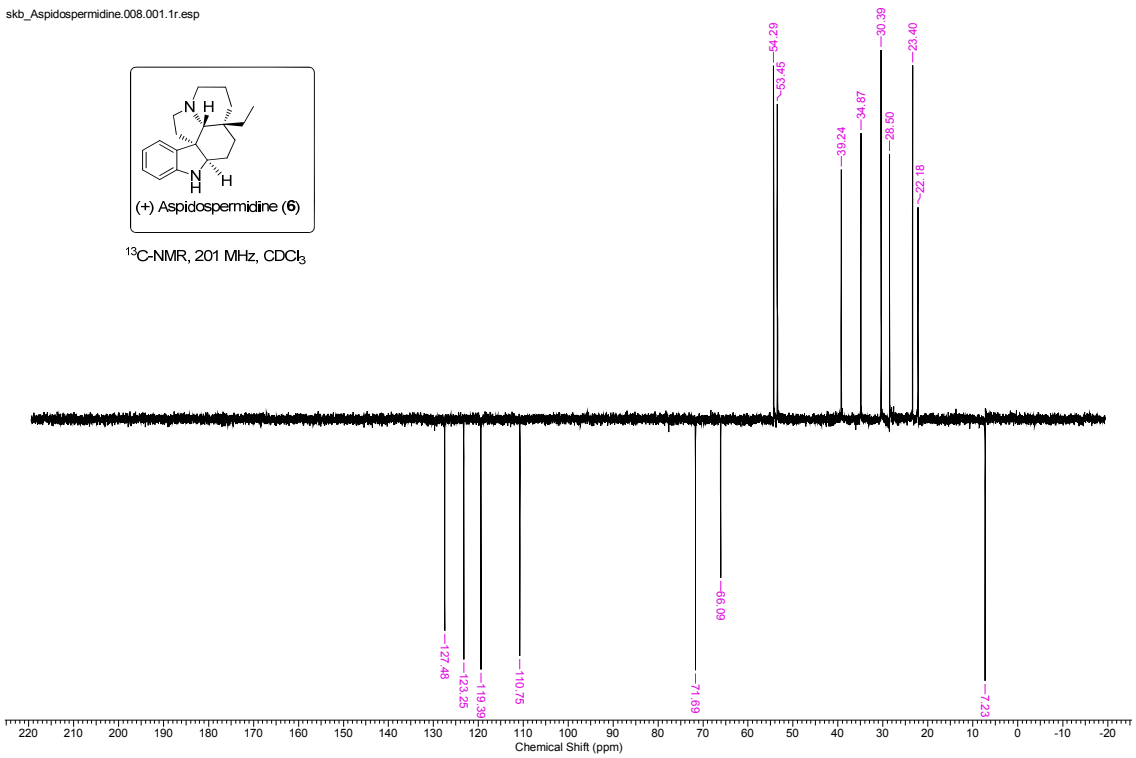

F2 [ppm]
F1 [ppm]


SHIVA-400.021.001.1r.esp
CHLOROFORM-d
TMS
7.26
0.00
SHIVA-400.021.001.1r.esp
2.00
1.00
4.11
7.03
2.13
1.25
1.07
3.07
Chemical Shift (ppm)
(+)-49
1H-NMR, 400 MHz, CDCl3
Chemical Shift (ppm)

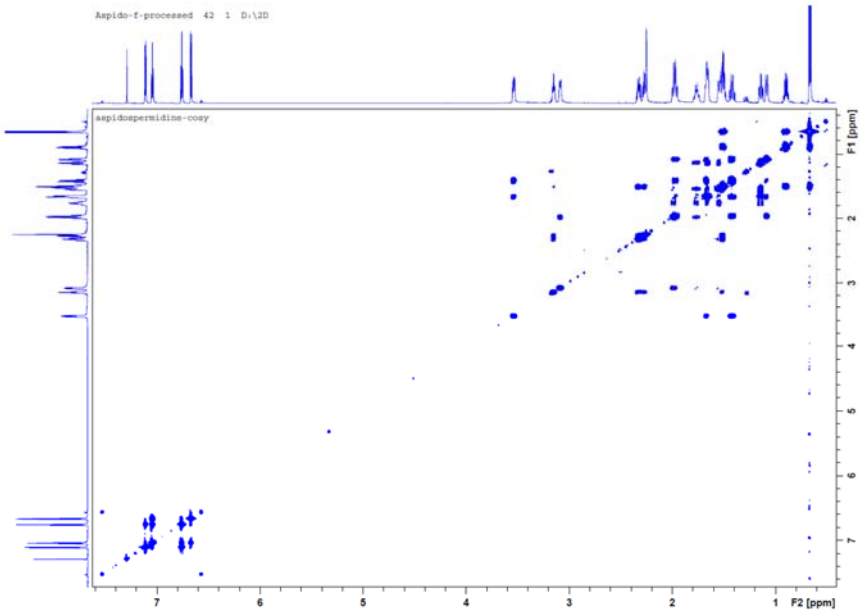

skb_TCC_1.011.001.1r.esp
CHLOROFORM-d
77.31
77.00
76.68
skb_TCC_1.011.001.1r.esp
(+)-49
13C-NMR, 101 MHz, CDCl3
73.55
53.22
52.92
48.17
36.81
34.74
32.86
30.07
26.08
21.32
21.27
7.11
211.52
Chemical Shift (ppm)


1H-asp-2015.020.001.1R.esp
(+) Aspidospermidine (6)
^{1}H -NMR, 800 MHz, CDCl$_3$
CHLOROFORM-d
Chemical Shift (ppm)

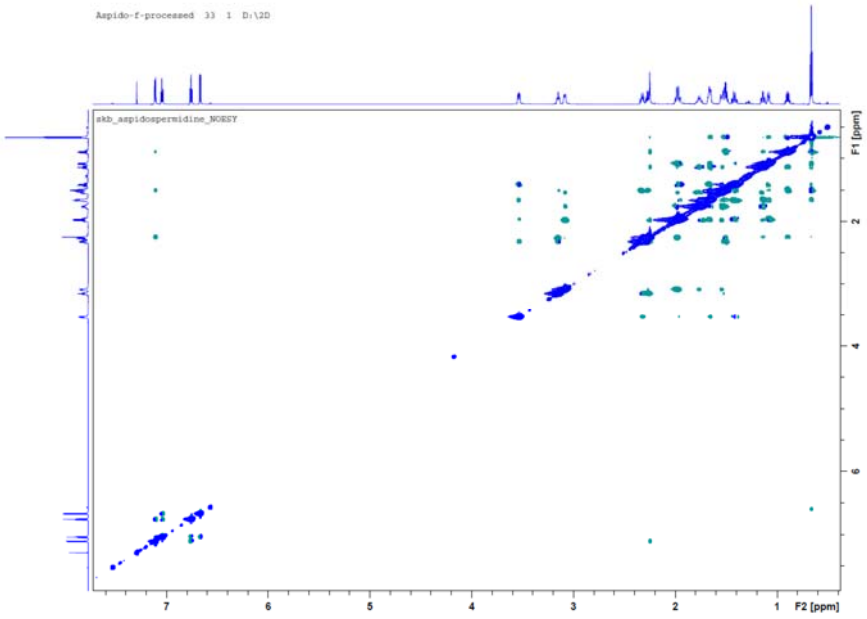

13c-asp-2015.026.001.1r.esp
CHLOROFORM-d
(+) Aspidospermidine (6)
^{13}C-NMR, 201 MHz, CDCl$_3$
Chemical Shift (ppm)

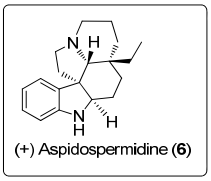


COSY of (+)- Aspidospermidine (**6**)



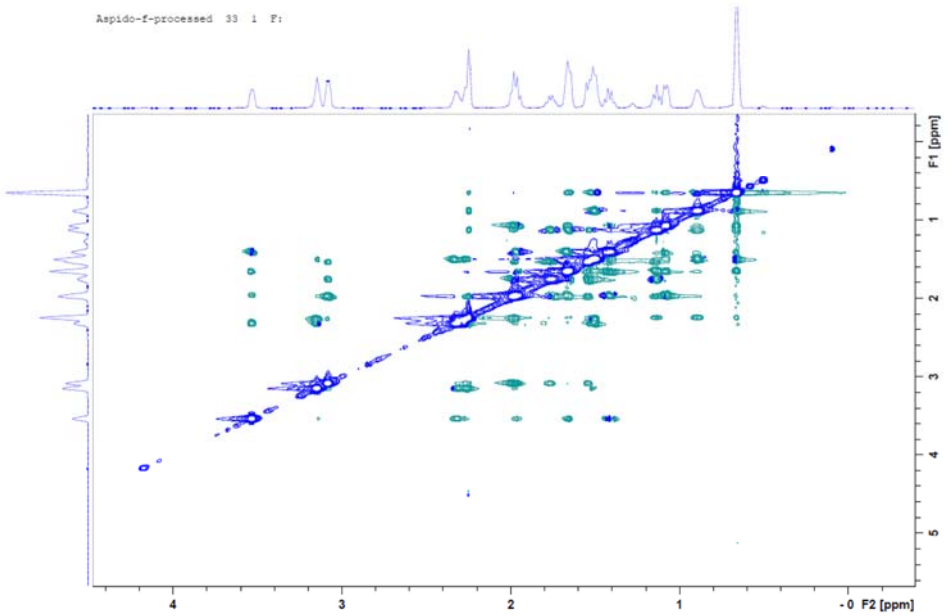
NOESY of (+)- Aspidospermidine(**6**)

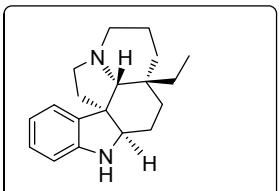




(+) Aspidospermidine (**6**)

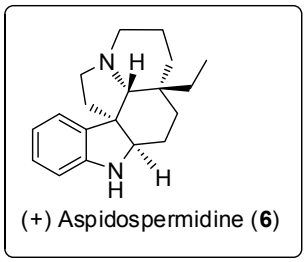
NOESY of (+)- Aspidospermidine (Zoomed spectra)



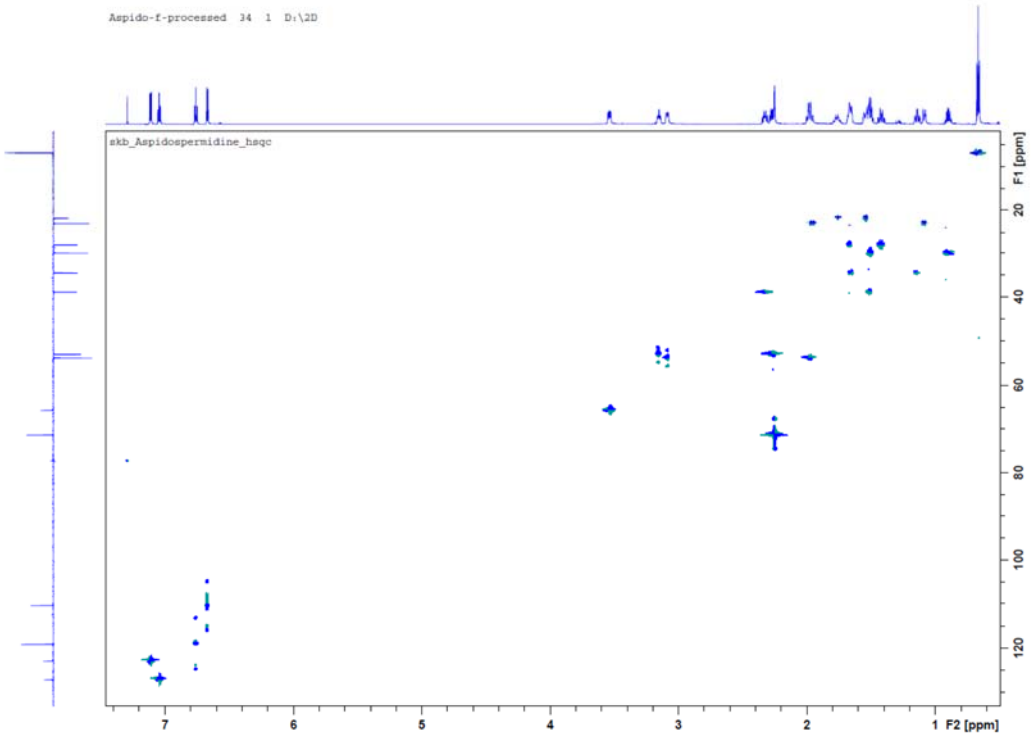


(+) Aspidospermidine (**6**)

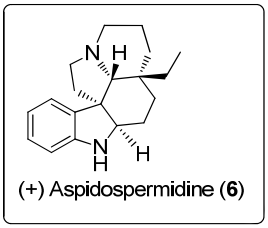
HSQC of (+)- Aspidospermidine(6) (800 MHz):

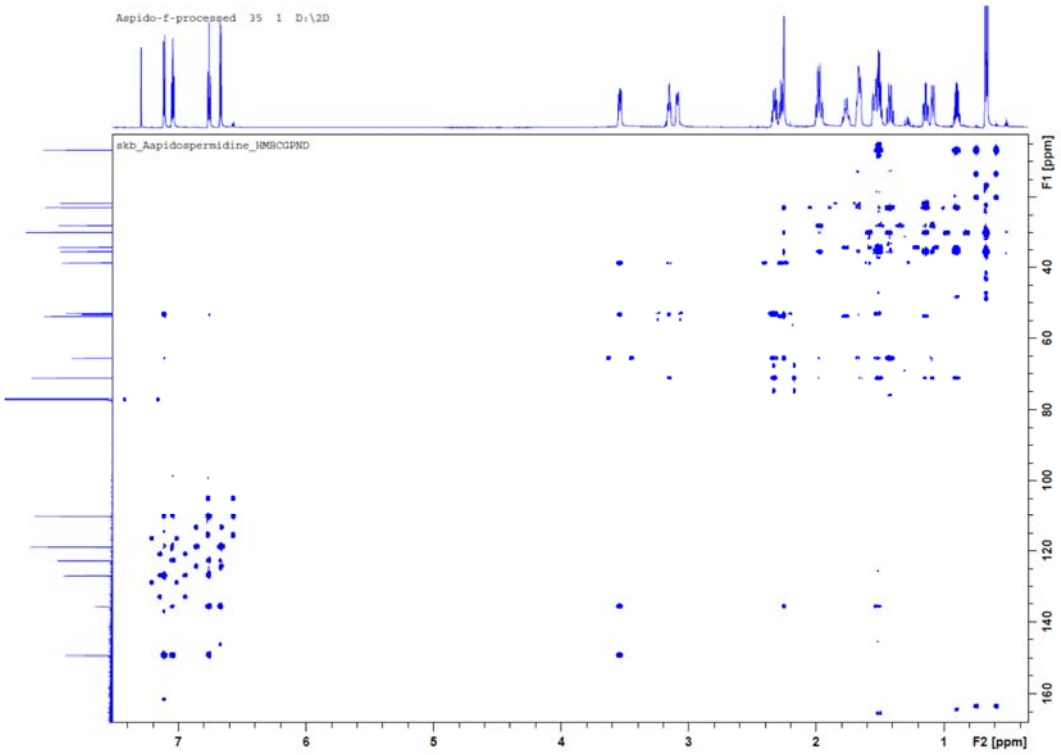


(+) Aspidospermidine (**6**)



HMBC of (+)-Aspidospermidine (6) (800 MHz):





List of Publications

1. Efficient Strategy for the Construction of Both Enantiomers of the Octahydropyrroloquinolinone Ring System: Total Synthesis of (+)-

   Aspidospermidine

   ***Org.Lett*., 2016, 18, 1558-1561.**
   Ganesh Pandey*, **Shiva Kumar Burugu** and Pushpendra Singh.

2. Enantioselective Total Syntheses of (–)-Isonitramine, (–)-Sibirine, and (+)-Nitramine by Ring-Closing Metathesis.
   ***Eur. J. Org. Chem*. 2011, 7372-7377**

   Ganesh Pandey*, C. Prasanna Kumara, **Shiva Kumar Burugu** and Vedavati G. Puranik

Erratum