Studies Towards the Total Syntheses of *Aspidosperma* and *Nitraria* class of Alkaloids: Syntheses of Vincadifformine, Isonitramine and Sibirine

THESIS

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By

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Dedicated

To My

Parents

NCL

National Chemical Laboratory

Division of Organic Chemistry
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Dr. Ganesh Pandey
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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Studies Towards the Total Syntheses of *Aspidosperma* and *Nitraria* class of Alkaloids: Syntheses of Vincadifformine, Isonitramine and Sibirine**" which is being submitted to the **University of Pune** for the award of **Doctor of Philosophy in Chemistry** by **Mr. Prasanna Kumara C** was carried out by him under my supervision at the **National Chemical Laboratory**, **Pune**. A material that has been obtained from other sources has been duly acknowledged in the thesis.

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"Studies Towards the Total Syntheses of *Aspidosperma* and *Nitraria* class of Alkaloids: Syntheses of Vincadifformine, Isonitramine and Sibirine"** submitted for Ph. D. Degree to the **University of Pune**, has been carried out by me at the **National Chemical Laboratory**, **Pune**, under the supervision of **Dr. Ganesh Pandey**. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University/Institute.

Date: (**Prasanna Kumara C**)

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Prasanna K. C

CONTENTS

LIST OF ABBREVIATIONS

Ac	Acetyl
AcOH	Acetic acid
aq	aqueous
Ar	Aryl
BF_3:OEt_2	Boron trifluride diethyl ether complex
Bn	benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
n-BuLi	*n*-Butyl lithium
Cbz-	benzyloxycarbonyl
COSY	Correlation spectroscopy
$Cu(OTf)_2$	Copper (II) triflate
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	N, N-dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Et_3N	Triethyl amine
EtOAc	Ethyl acetate
EtOH	Ethanol
g	gram
h	hour
HRMS(EI)	High resolution mass spectrometry-Electron ionization
Hz	Hertz
ImH	Imidazole

IBX	Iodoxybenzoic acid
LAH	Lithium aluminium hydride
LDA	Lithiumdiisopropylamide
Me	Methyl
MeOH	Methanol
min	Minute(s)
mL	millilitre
mmol	Millimole
mp	Melting point
MS(ESI)	Electrospray ionization Mass spectrometry
MsCl	Methanesulfonyl chloride
m/z	Mass-to-charge ratio
NMR	Nuclear magnestic resonance
NOESY	Nuclear Overhauser Enhancement spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid plot
Pd/C	Palladium on carbon
py	pyridine
rt	Room temperature
TBS	*tert*-butyldimethylsilyl
TEA	Triethyl amine
TFA	Trifluroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsCl	*p*-Toluene sulfonyl chloride

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Thesis Abstract

The present dissertation is divided into three chapters

<u>Chapter one:</u> Indole alkaloids: An overview

This chapter portrays an introduction to indole alkaloids, their biogenesis, and biological activities.

The indole alkaloids possess good pharmacological activities; among them dimeric *Catharanthus* alkaloids vinblastin (**1**) and vincristine (**2**) are routinely used for the treatment of various human cancers and marketed by Eli Lilly as Velban® and Oncovin® respectively. Vincadifformine (**3**), Tabersonine (**4**) and Jerantinines (**5**) belong to the *Aspidosperma* family exhibited potential inhibition against human cancer cell lines (Figure-1).

The structural complexity posed by these alkaloids in conjunction with interesting pharmacological properties stimulated considerable effort directed toward their synthesis.

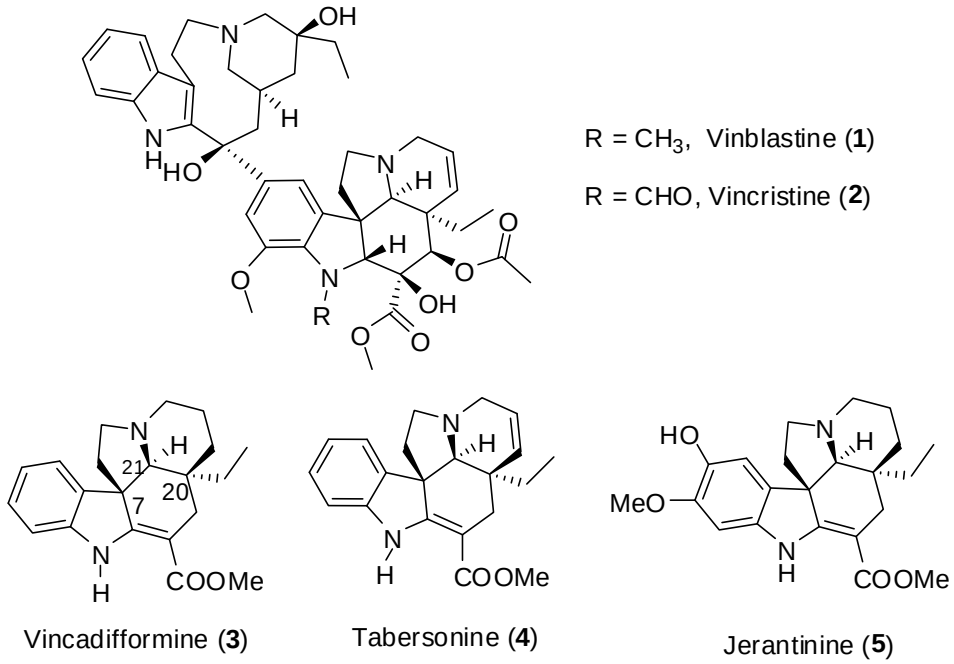


Figure: 1 some of the representative biologically active indole alkaloids.

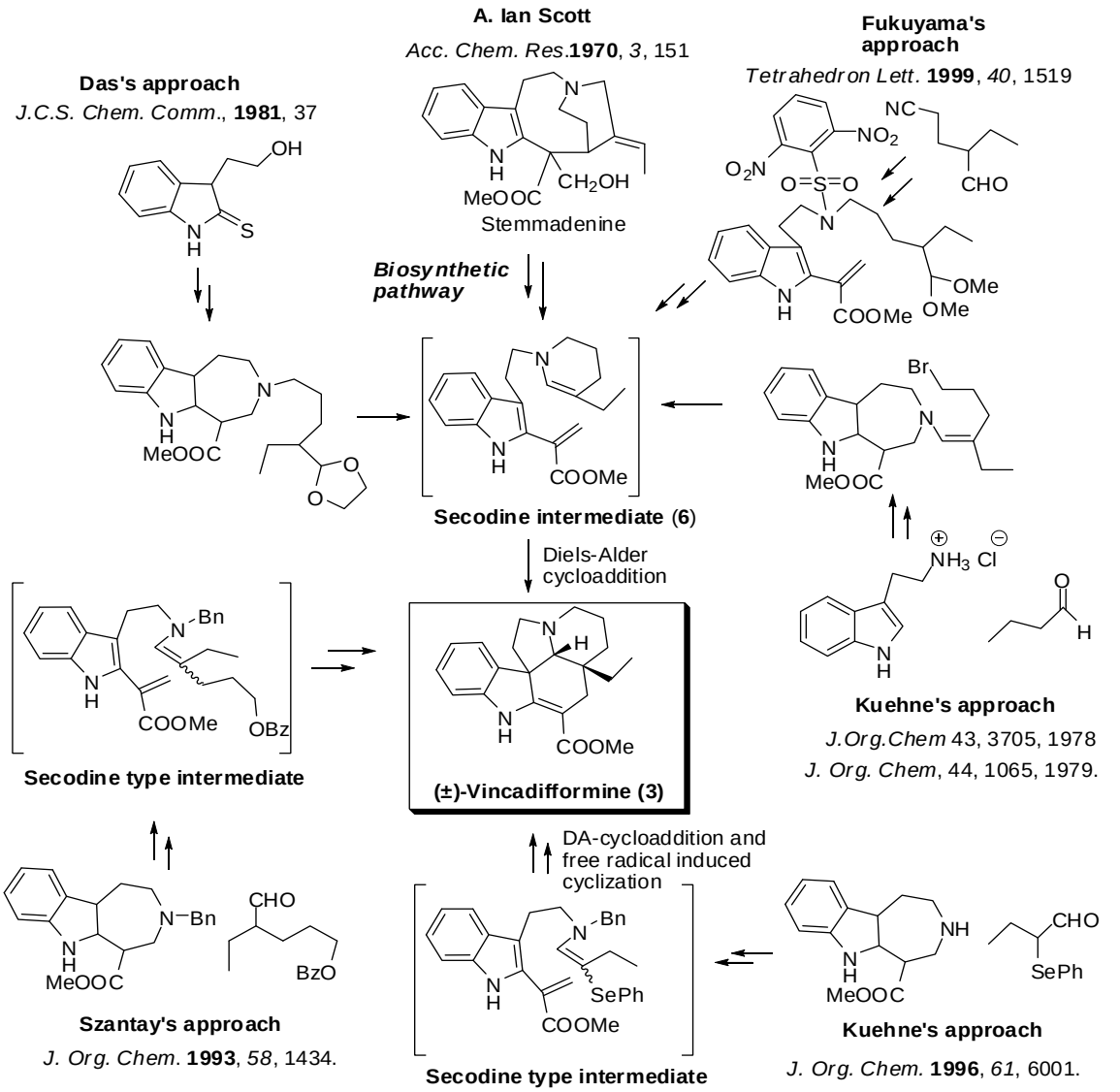
Virtually there is no much information on the structural requirement for the antitumour activity, specific mechanism of action and metabolism. Another unanswered question is to what extent the structure can be modified either stereo chemically or by changing functional groups to provide novel drugs with increased pharmacological activity without side effects. The critical separation, low abundance in the nature and pharmaceutical value of these alkaloids prompted many synthetic chemists to seek laboratory synthesis. It is clear that the solutions for these problems require a laboratory synthesis. So there is a need to develop a conceptually new route to synthesize these molecules and its analogues.

In this regard we have choosen a prime representative of aspidosperma alkaloid vincadifformine (**3**) as a preliminary synthetic target and we discuss our endeavors towards its synthesis in the second chapter comprehensively.

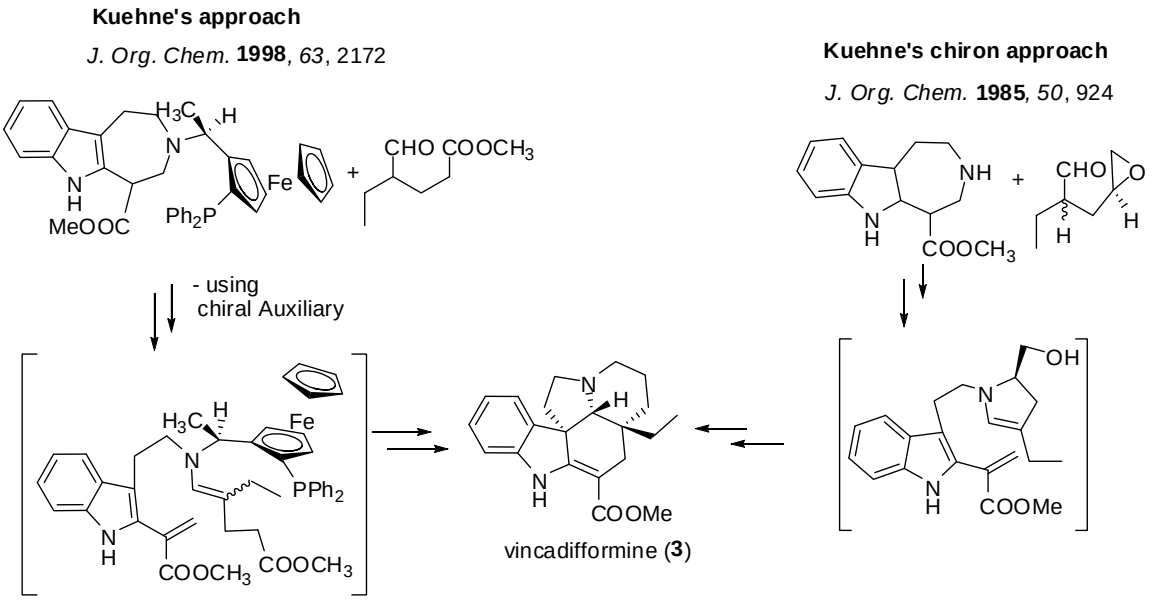
Chapter –two: Total synthesis of (±) and (+)-vincadifformine through an iminium ion cascade reaction

Section –A: Literature reports

This section illustrates various literature reports towards the total synthesis of racemic and optically active vincadifformine. Over the three decades, number of racemic syntheses and two enantioselective synthetic approaches to vincadifformine has been reported, while the majority of approaches proceed by way of the biogenetically postulated secodine intermediate (**6**) via intramolecular Diels-Alder type reactions (Scheme-1 and 2).



Scheme-1: Summary of the literature reports towards the total synthesis of racemic vincadifformine

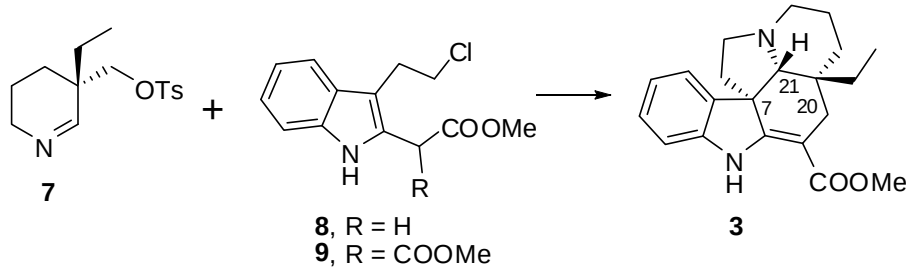


Scheme-2: Summary of the literature reports towards the total synthesis of optically active vincadifformine

Section – B:

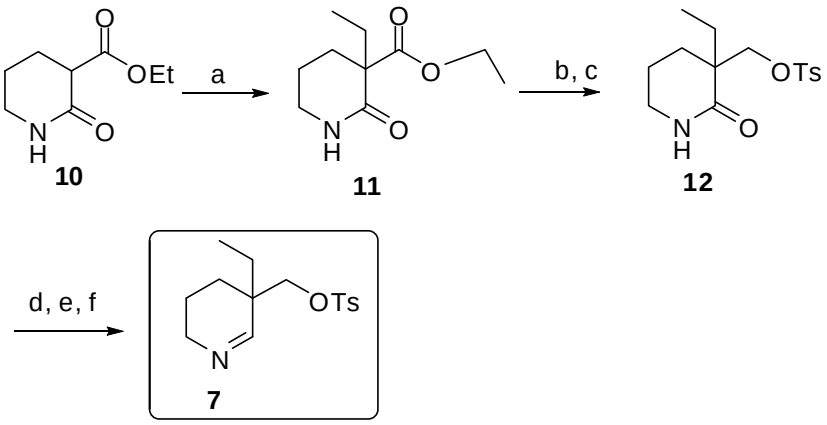
Total synthesis of (±)-vincadifformine through an iminium ion cascade reaction

This section illustrates concise approach for the total synthesis vincadifformine in racemic fashion. Here we have disclosed a short and convergent approach to access aspidosperma skeleton by coupling of imine fragment **7** and indole fragment **8** or **9** through an iminium ion cascade reaction as outlined below (scheme-3).



Scheme-3: Iminium ion triggered cascade cyclization in the synthesis of (±)-**3**

The synthesis of imine (±)-**7** commenced with the commercially available ethyl 2-oxopiperidine 3-carboxylate (**10**) by following the steps as shown in Scheme-4.



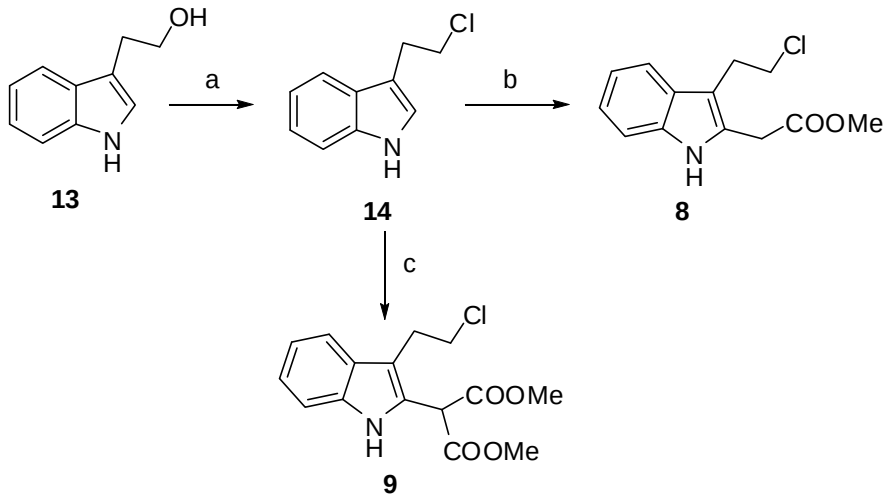
Scheme -4 Synthesis of (±)-**7**

Reagents and conditions (a) n-BuLi, THF, EtI, -78 °C → rt → reflux, 69% (b) $NaBH_4$, $CeCl_3$ $7H_2O$, EtOH, rt, 2 days, 87% (c) pyridine, p-TsCl, rt, 48 h, 84% (d) $(Boc)_2O$, DMAP, TEA, rt, 12 h, 95% (e) DIBAL-H, THF, -78 °C, 4 h, 97% (f) TFA, DCM, rt, 4 h, 90%.

Construction of quaternary stereo centre in lactam **10** was carried out by enolate generation using *n*-BuLi followed by quenching with ethyl iodide afforded **11**. The ester of **11** was reduced to corresponding primary alcohol using Luche conditions which upon tosylation using *p*-TsCl in pyridine afforded **12** as a white solid. The conversion of amide functionality of the **12** to imine function was easily achieved by simple N-Boc protection followed by DIBAL-H reduction and treatment of trifluroacetic acid afforded **7**.

With the racemic imine segment in hand we focused to synthesize indole fragments **8** and **9**. The indole fragment **8** obtained in single step from 3-(2-chloroethyl) indole (**14**), which was synthesized from commercially available tryptophol (**13**) by chlorination using N-chlorosuccinimide and triphenyl phosphine in anhydrous THF.

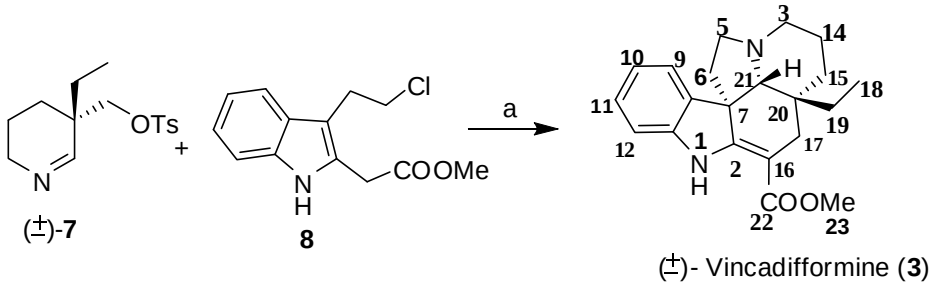
Reaction of **14** with *tert*-butyl hypochlorite followed by the addition of 1-[*tert*-butyl dimethylsilyloxy]-1-methoxy ethene (**15**) in the presence of BF_3:OEt_2 afforded the desired **8**. Compound **9** was also synthesized by utilizing the same protocol by using lithium dimethyl malonate as a nucleophile in the presence of either BF_3:OEt_2 or $ZnCl_2$ (anhydrous) as a Lewis acid (Scheme-5).



Scheme-5 Synthesis of indole segments **8** and **9**.

*Reagents and conditions: (a) NCS, PPh_3, THF, 85% (b) t-BuOCl, BF_3:OEt_2, 1-[tert-butyl dimethylsilyloxy]-1-methoxy ethene (**15**), THF, -78 °C → rt, 61% (c) t -BuOCl, BF_3:OEt_2, $ZnCl_2$, Lithium dimethyl malonate, THF, -78 °C → rt, 86%.*

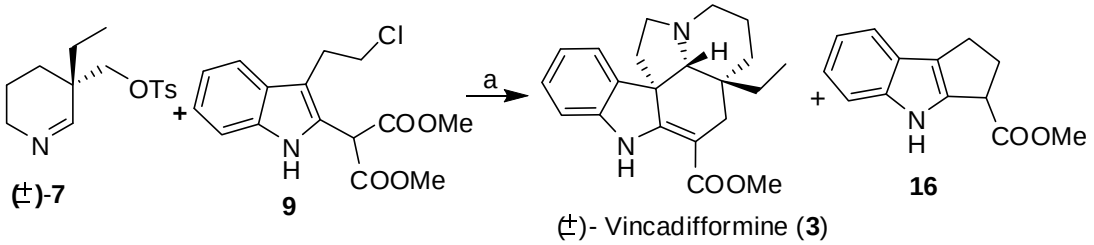
The central feature of our proposed synthetic strategy rests upon the stereoselective formation of the *Aspidosperma* skeleton by coupling of the racemic imine and the indole segments through cascade reaction. The coupling of imine (±)-**7** and indole fragment **8** in refluxing DMF in the presence of potassium iodide producing vincadifformine (±)-**3** as a single diastereomer in 35% yield (Scheme-6).



Scheme-6: Final coupling reaction: Synthesis of (±)-vincadifformine

Reagents and conditions: (a) KI, DMF, 150 °C, 3 h

The coupling of racemic imine (±)-**7** with indole fragment **9** in DMF in presence of potassium iodide resulted minor amount of the vincadifformine (**3**) with the undesired indole compound **16** (Scheme-7).



Scheme-7: Final coupling reaction: Synthesis of vincadifformine.
Reagents and conditions: (a) KI, DMF, 150 °C, 3 h

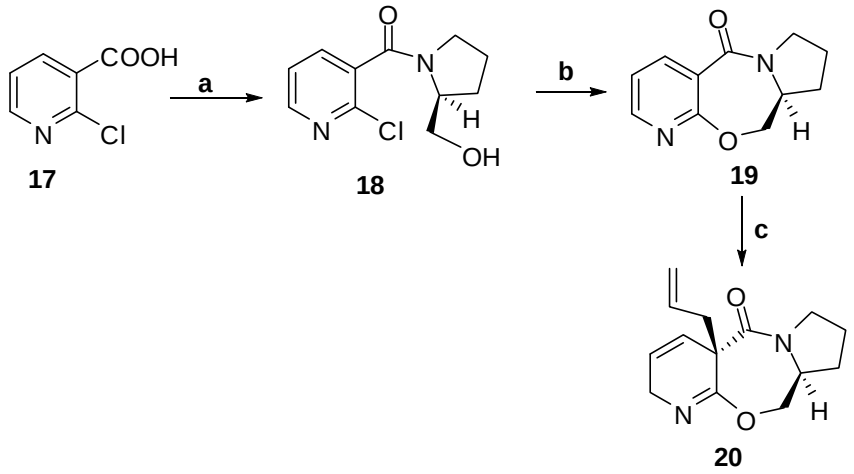
Section – C

Total synthesis of (+)-vincadifformine:

This section describes journey towards the total synthesis of optically active vincadifformine comprehensively.

Attracted by the success of total synthesis of racemic vincadifformine with the desired stereoselectivity, we focus to synthesize optically active vincadifformine and tried to investigate the exact mechanistic path of the final iminium ion cascade cyclization. The enantioselective synthesis of the deceptively simple looking imine fragment **7** was commenced with 2-chloronicotininc acid (**17**) and proceeded as summarized in scheme-8. Thus the amide formation of **17** with chiral auxiliary (*S*) - Prolinol through mixed anhydride method furnished amide **18**, which upon treatment with NaH in THF at reflux condition provided the cyclic ether **19** through an addition-elimination reaction. The stereoselective Birch reduction-allylation of **19** afforded **20** in moderate yield (98% de) (scheme-8).

Crystallization of **20** in a mixture of dichloromethane and *n*-pentane afforded colorless crystals as a single diastereomer. The structure of **20** was confirmed unambiguously by x-ray crystallographic analysis.

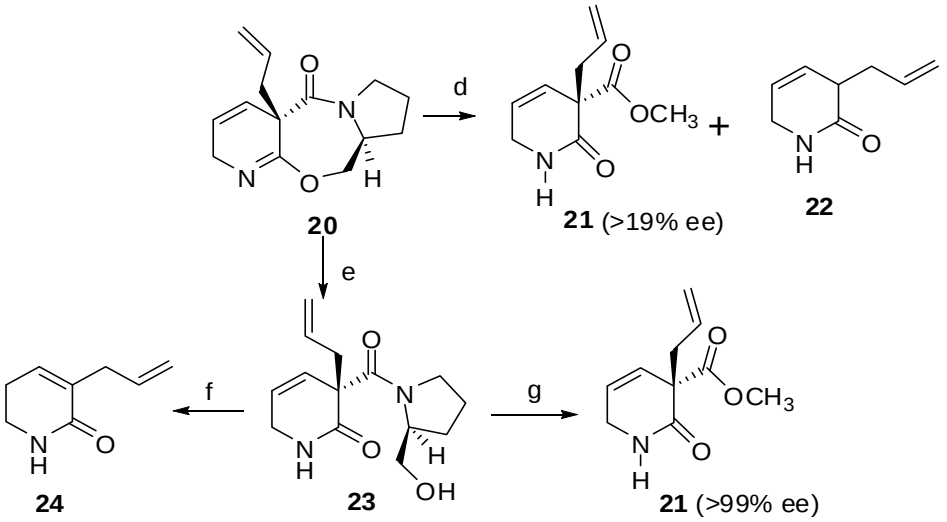


Scheme-8: *Reagents and conditions: (a) ClCOOMe, TEA, (S)-Prolinol, CH_2Cl_2, 0°C→rt, 98% (b) NaH, THF, reflux, 99% (c) Na, THF, Liq NH_3, allyl bromide, -78 °C, 46%.*

The cleavage of chiral auxiliary in an acidic medium using 80% H_2SO_4: MeOH (1:8) underwent ether and amide cleavage in single pot gave some inferior results of partially racemized ester **21** (19%ee) in low yield along with decarboxylated product **22**.

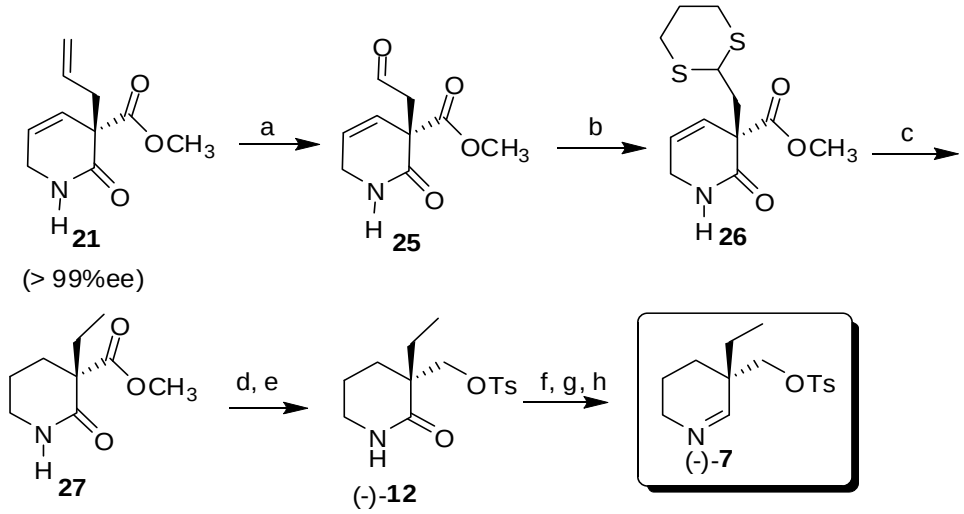
At this stage, we realize that it was necessary to cleave the ether and amide linkage sequentially, thus the compound **21** was treated with CH_3COOH:H_2O: THF at ambient temperature afforded alcohol **23**, which upon methanolysis using sodium methoxide gave undesired decarbonylated product **24**.

Pleasingly, chemoselective cleavage of tertiary amide of **23** was just successful on treatment with copper (II) triflate and methanol at ambient temperature led smoothly ester **21** in excellent yield as a single enantiomer (scheme-9).



Scheme-9 *Reagents and conditions: (d) MeOH, H_2SO_4 (80%), 45% (e) CH_3COOH:THF:H_2O, rt, 89% (f) NaOMe, THF or MeOH, rt, 65% (g) $Cu(OTf)_2$, MeOH, rt, 87%*

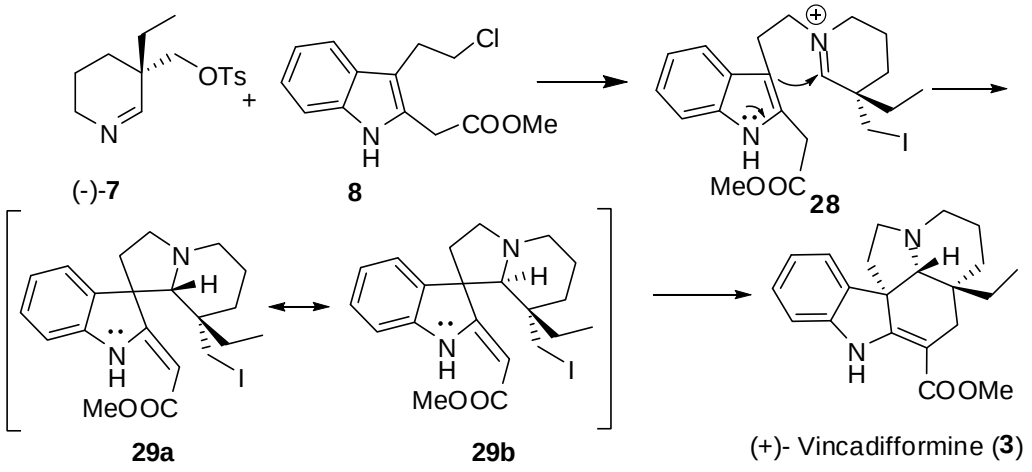
Having synthesized desired optically active ester **21**, we turned our attention towards its conversion to chiral imine **7** (Scheme-10). Oxidative cleavage of terminal olefin of **21** with OsO_4, and $NaIO_4$, followed by dithioketalization with 1, 3 -propanedithiol in presence of BF_3:OEt_2 furnished the dithiane **26**, which upon reductive desulfurization using Raney Nickel and hydrogen at reflux condition afforded **27** in good yield. We adopted the same procedure as described earlier to transform (-)-**27** to **7** (ee > 99%).



Scheme-10 Synthesis of chiral imine **7** from ester **21**

Reagents and conditions: (a) OsO_4, $NaIO_4$, 2, 6- lutidine, Dioxane: H_2O, rt, 4 h, 70% (b) 1,3-propane dithiol, BF_3:OEt_2, DCM, reflux, 12 h, 81% (c)Raney-Ni, Ethanol, reflux, 7 h, 94% (d) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, rt, 2 days, 87% (e) p-TsCl, Pyridine, CH_2Cl_2, rt, 48 h, 84% (f) $(Boc)_2O$, DMAP, TEA, DCM, rt, 12 h, 95% (g) DIBAL-H, THF, -78 °C, 4 h, 97% (h) TFA, DCM, rt, 4 h, 90%.

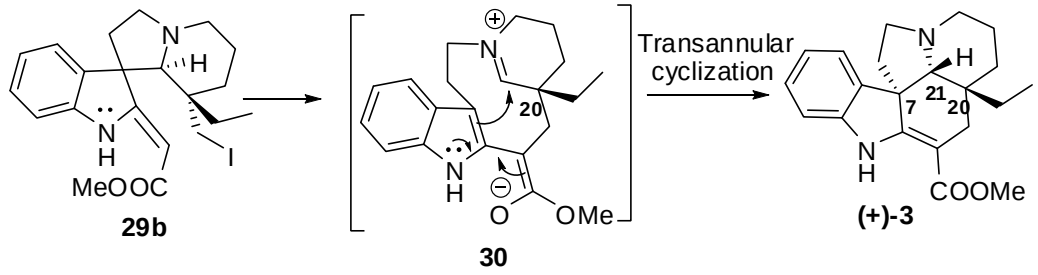
Coupling of chiral imine (-)-**7** with indole fragment **8** in DMF in presence of potassium iodide at 140-150 °C resulted vincadifformine (+)-**3** (>99 % ee) (Scheme-11).



Scheme-11 Plausible mechanism of this iminium ion triggered cascade reaction

We carried out HPLC-Mass spectroscopic analysis to provide support to the intermediacy of **29** and its transformation to (+)-vincadifformine (**3**), involving iminium ion cascade sequence. Analysis of the reaction mixture after short reaction interval showed the formation of **29** as a diastereomeric mixture (88.6:11.3). The exact diastereomeric ratio of **29** could not be determined as its formation was always accompanied with some amount of **3**. This observation revealed that according to Curtin-Hammett principle possibly the **29a** and **29b** were interconvertable and one isomer was converted faster to **3** compared to other. This observation could possibly be visualized through the molecular models of **29a** in which nucleophilic carbon centre of enamine and electrophilic carbon centre of iodomethylene group appears to be in close proximity compared to **29b**.

The conversion of **29b** to vincadifformine (**3**) can also be explained by considering the transannular cyclization involving the intermediate **30** as shown below. In which the emergence of required stereochemistries at C_7 and C_{21} were controlled by C_{20} (Scheme-12).



Scheme-12 Plausible mode of transannular cyclization in conversion of **29b** to (+)-**3**

Section: D

This section illustrates the detailed experimental procedures and spectral characterizations of the new compounds synthesized to achieve the vincadifformine in racemic and asymmetric fashion.

Chapter-3

Enantioselective total syntheses of (-) isonitramine and (-)-sibirine *via* ring closing olefin metathesis

Section –A:

This section illustrates a brief account of Nitraria alkaloids and literature reports towards the asymmetric synthesis of nitramine, isonitramine and sibirine.

The spiro skeleton is common in natural products and appears in a number of alkaloids. Three structurally related sirocyclic alkaloids nitramine (**31**), isonitramine (**32**) and sibirine (**33**) were isolated from *Nitraria Schoberi* and *Nitraria Sibrica* respectively. All three of these alkaloids have received considerable synthetic attention because of their peculiar 2-azaspiro [5, 5] undecane skeleton and their structure resemble closely to the neurotoxic alkaloid histrionicotoxin (**34**). The nitrabirine (**35**), nitrabirine N-oxide (**36**) and sibirinine (**37**) are the analogues of isonitramine isolated from *Nitraria Sibrica* have also been the attractive synthetic targets (Figure-2).

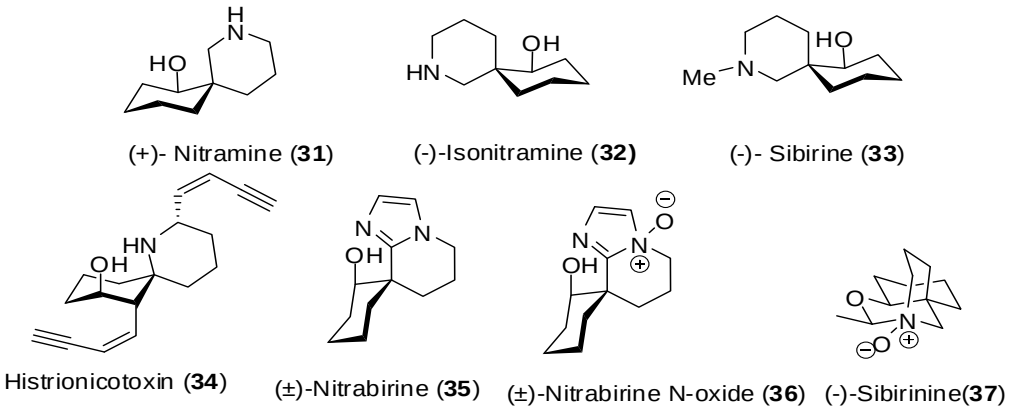
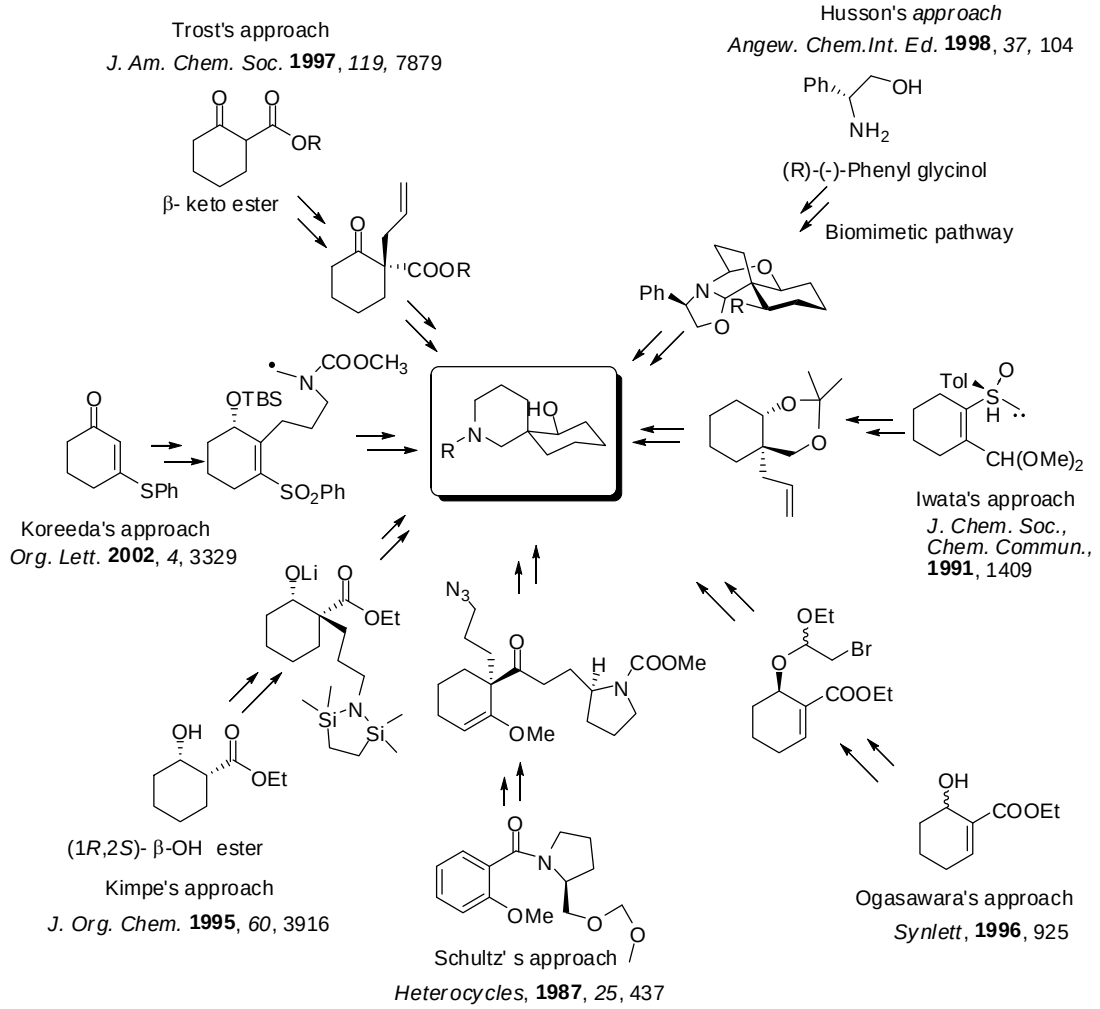


Figure-2 Some of the representative *Nitraria* alkaloids

Literature reports:



Scheme-13: Some of the conceptually designed synthetic routes for optially active sibirine/ isonitramine/Nitramine reported in the literature are summarized above.

Although a considerable number of synthetic routes toward the nitraria alkaloids can be found in literature, only a less number of them deal with enantioselective or enantiospecific synthesis, so still there is necessary to find a versatile asymmetric protocol to synthesize these alkaloids.

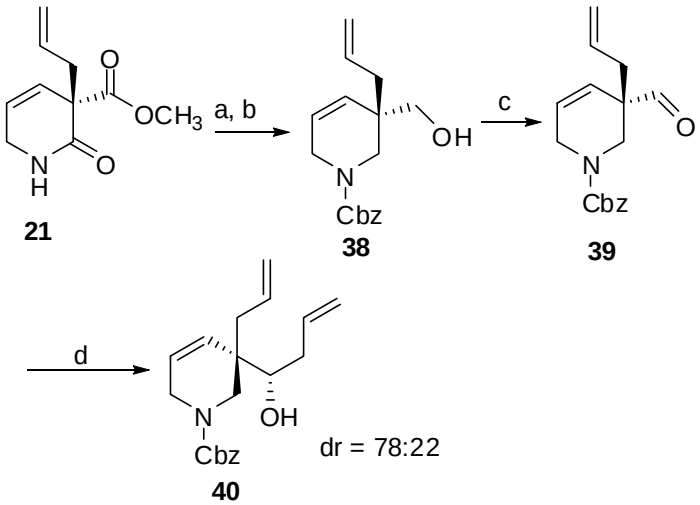
Section –B:-

Total synthesis of (-)-Isonitramine and (-)-Sibirine *via* ring closing olefin metathesis reaction:

This section illustrates the concise syntheses of (-)-Isonitramine and (-)-Sibirine.

We viewed the molecular complexity of these alkaloids from totally different angle and envisaged a conceptually new synthetic route from a key precursor **21** (>99% ee) utilizing ring closing metathesis reaction as a key step.

The syntheses of sibirine (**33**) and isonitramine (**32**) commenced with the transformation of enantio pure **21** (ee>99%) to **38** by LAH reduction and N-Cbz protection. Compound **38** upon oxidation using 2-iodoxy benzoic acid (IBX) afforded aldehyde **39**, which upon allylation using allyl magnesium bromide resulted in several side reactions and obtained desired **40** albeit in low yield. Thus we modified our allylation protocol and carried out the reaction under mild Hosomi-Sakurai conditions using allyltrimethyl silane and boron triflouride-etherate gave desired **40** in excellent yield (*dr*: 78:22) (Scheme-14).

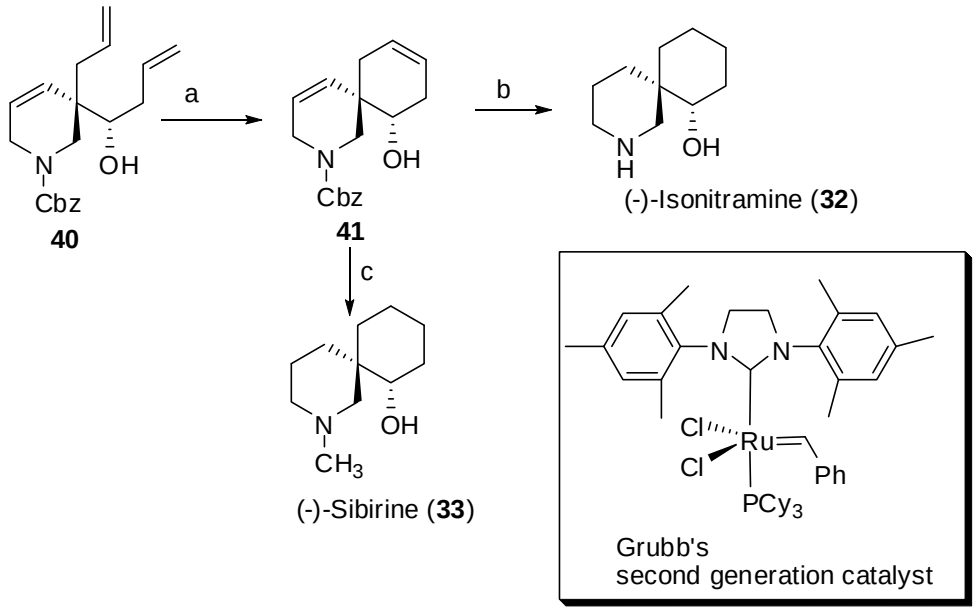


Scheme-14 Synthesis of homoallylic alcohol **40**

Reagents and conditions: (a) LAH, THF, reflux, 8 h (b) CbzCl, dioxane-water, $NaHCO_3$, rt, 5 h, 81% (c) IBX, EtOAc, reflux, 8 h, 95% (d) allyl trimethyl silane, BF_3:OEt_2, DCM, -78 °C, 92%.

Both the isomers were separated pure through flash column chromatography. This set the stage for crucial ring closing metathesis reaction.

Our initial attempt of ring closing metathesis reaction of major isomer **40** with Grubb's first generation catalyst failed to give expected product **41** in satisfactory yield. Therefore, RCM was attempted using Grubb's second generation catalyst which, pleasingly, afforded **41** in good yield. Hydrogenation of **41** with palladium-carbon in anhydrous methanol gave (-)-isonitramine. Reduction of **41** under the same reaction condition but in the presence of aqueous formaldehyde afforded (-)-sibirine (Scheme-15).



Scheme: 15 Synthesis of (-)-isonitramine and (-)-sibirine

Regents and conditions: (a) Grubb's II generation catalyst (7 mol%), DCM, reflux, 6 h, 85% (b) H_2 (1 atm), Pd/C, MeOH, rt, 5 h 90% (c) H_2 (1 atm), Pd/C, HCHO, MeOH, rt, 30 h, 82%.

The structure of (-)-isonitramine was confirmed unambiguously by X-ray crystallographic analysis and (-)-sibirine with ^{1}H, ^{13}C, spectroscopic data.

Section –C: Experimental

This section illustrates the detailed experimental procedures, spectral characterizations of the new compounds synthesized to achieve *Nitraria* alkaloids isonitramine and sibirine and references.

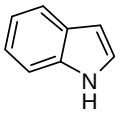
Note: Compound numbers in the abstract are different from those present in the thesis

CHAPTER I

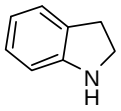
INDOLE ALKALOIDS: An Overview

1.1 INTRODUCTION:

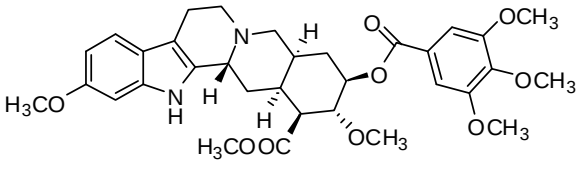
The indole alkaloids constitute a large and complex group of naturally occurring organic compounds possessing the indole (**1**) or dihydroindole (indoline) (**2**) moiety. The distribution of indole alkaloids in plant species has been quite well investigated. The number of structurally known alkaloids is nearly 1200 isolated from more than 400 different plant species. They occur predominantly and frequently in the family *Apocynaceae* and to a lesser extent in the *Asclepiadaceae*, *Rubiaceae* and *Loganiaceae* plant families. After considerable research works many physiologically active indole alkaloids have been isolated from these plant species. Some important alkaloids are reserpine (**3**) (hypotensive sedative agent), strychnine (**4**) (convulsant poison) and lysergic acid diethylamide (LSD) (**5**) (powerful hallucinogen). Vincamine (**6**) and eburnamonine (**7**) alkaloids isolated from *vincaminor* have gained importance as drugs in the treatment of cerebral, vascular and metabolic diseases. Semisynthetic derivative of vincamine, the (+)-apovincaminic acid ethyl ester (vinpocetine) (**8**) is produced in Hungary under the trade name CAVINTON® and CALAN® in Japan as successful drugs in the treatment of aphasia, apraxia, hypertensive encephalopathy, angiospastic and ischemic cerebrovascular disorders. The dimeric *Catharanthus* alkaloids vinblastin (**9**) and vincristine (**10**) are routinely used for the treatment of various human cancers and marketed by Eli Lilly as Velban® and Oncovin® respectively (Fig **-1**).[1-3]



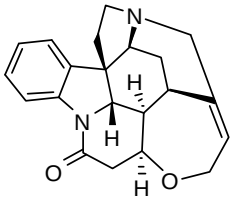
Indole (**1**)



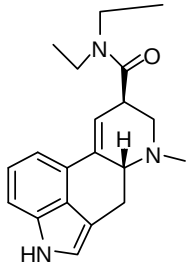
Indoline (**2**)
or Dihydro indole



Reserpine (**3**)



Strychnine (**4**)



Lysergic acid diethylamide (**5**)

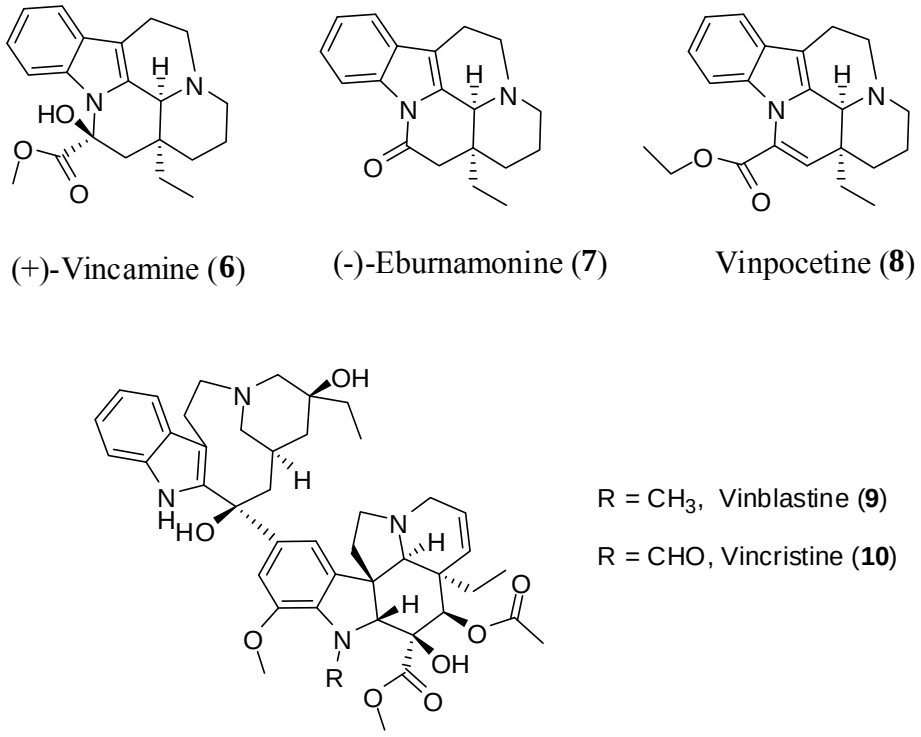


Figure-1 Some of the representative biologically active indole alkaloids.

The natural paucity and difficult separation of many of the biologically active alkaloids of this class has hindered their in depth biological evaluations. Moreover, not much information exists on exact structural requirements for understanding the therapeutic effect and specific mechanism of action and metabolism. Another unanswered question about these alkaloids is to understand the extent of structural modification required in terms of stereochemistry and change of functionalities to obtain novel drugs with increased pharmacological activity without side effects. Therefore, the solutions for these problems require laboratory synthesis and thus, there is a need to develop a general and versatile synthetic route for monomeric and dihydro indole units and their analogues.

The biological importance and architectural complexity of these molecules has stimulated, over the years, many synthetic chemists to choose these molecules as synthetic targets. Therefore, it is not astonishing that the search for efficient synthesis of these molecules and its derivatives has been the goal and a problem in organic synthesis.

1.2 Classification of indole alkaloids:

Majority of indole alkaloids are formally derived from a Mannich condensation of tryptamine (indolylethyl amine) with an aliphatic aldehyde having nine or ten carbons. Despite the perplexing variety of structures, the majority of indole alkaloids may be included under essentially three broad classes which differ in the skeleton of the C_{9-10} unit (non-tryptophan derived portion).

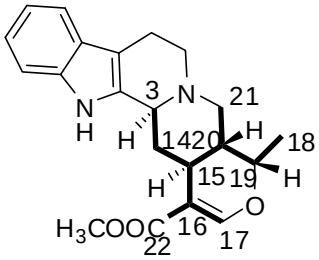
Class I : *Corynanthe – Strychnos* type e.g. Ajmalicine and strychnine
Class II : *Aspidosperma - Hunteria* type e.g. Vincamine and vindoline
Class III : *Iboga* type e.g. Catharanthine.

Besides, the simpler alkaloids e.g. Carbazole alkaloids may be included in class IV while the binary indole alkaloids considered as class V.

All three main classes have a different skeleton of the non-tryptamine unit (C_9 or C_{10}),[4] described comprehensively below:

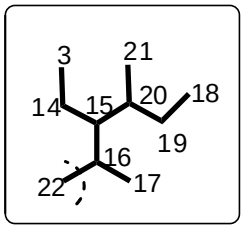
Class I - Corynanthe-Strychnos type:

Corynanthe and strychnos alkaloids were considered to be the products of α- and β-condensation products of tryptamine and hypothetical aldehyde C_{9-10} unit (**11**) (Figure-2).

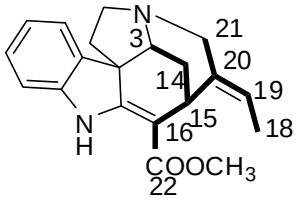


Ajmalicine (**12**)

Corynanthe alkaloid

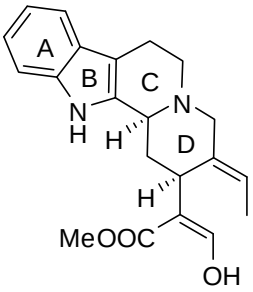


C9-10 unit (**11**)

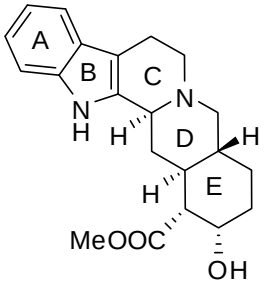


Akuammicine (**13**)

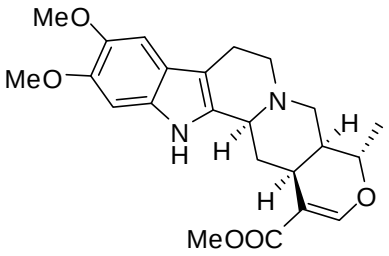
Strychnos alkaloid



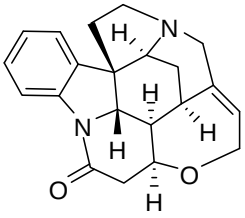
Geissoschizine (**14**)



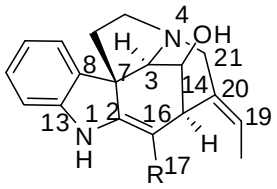
Yohimbine **(15)**



Reserpiline (**16**)

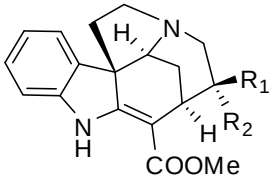


Strychnine (**4**)



Norfluorocurarine, R=CHO (**17**)

Mossambine, R=COOMe(14*S*-OH) (**18**)



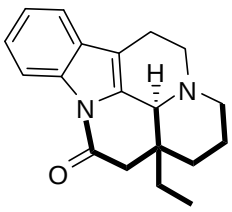
Echitamidine R_1= (*S*)-$CHOHCH_3$; R_2=H (**19**)

20-Epilochneridine R_1= Et; R_2=OH (**20**)

Figure 2: *Corynanthe* and *Strychnos* type alkaloids.

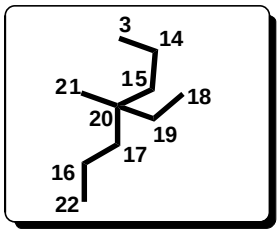
Class-II Aspidosperma- Hunteria type:

The non-tryptomine moieties of the *Aspidosperma* and *Hunteria* alkaloids are identical, though, the mode of linkage in the two groups is very different. Hunteria and Aspidosperma alkaloids were considered to be α- and β- condensation of tryptamine with the hypothetical aldehyde of $C_{9\text{-}10}$ carbon unit (**21**) respectively (Figure-3).

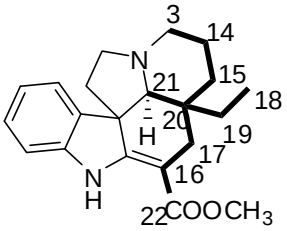


Eburnamonine (**7**)

Hunteria- alkaloid

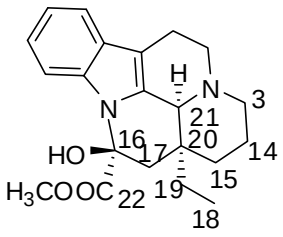


$C_{9\text{-}10}$ non-tryptomine unit (**21**)

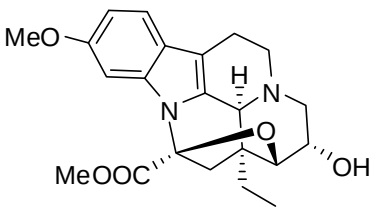


Vincadifformine (**22**)

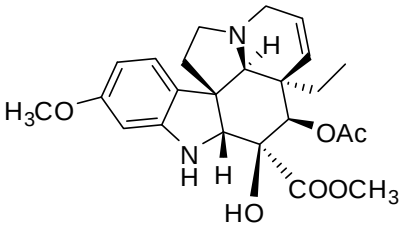
Aspidosperma - alkaloid



Vincamine (**6**)



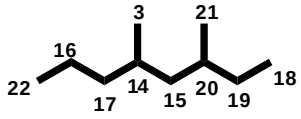
Vincarodine (**23**)



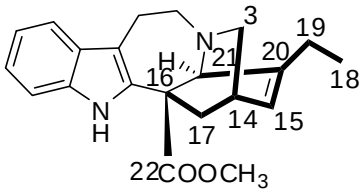
Vindoline (**24**)

Figure-3: Some of the representative examples of ***Hunteria*** and ***Aspidosperma*** alkaloids.

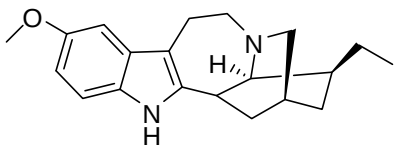
Class III Iboga type:



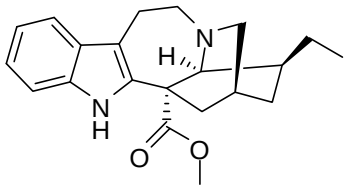
$C_{9\text{-}10}$ non-tryptomine unit (**25**)



Catharinthine (**26**)



Ibogaine (**27**)



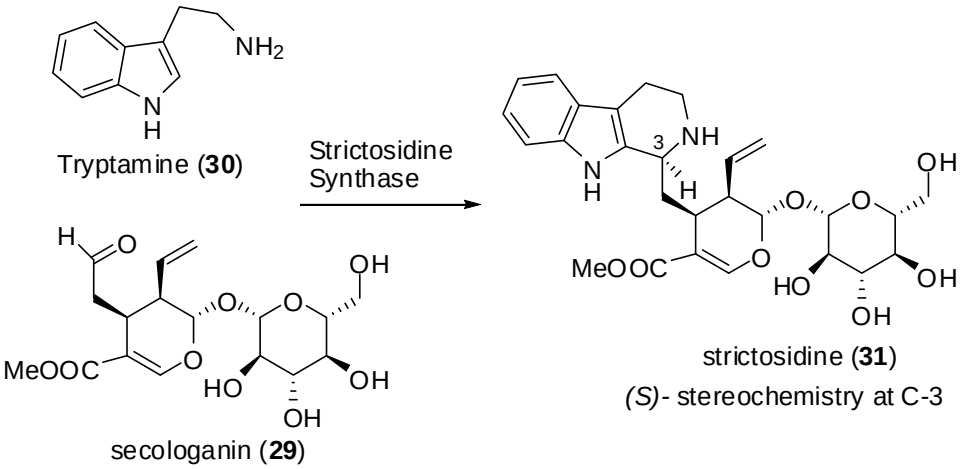
Coronaridine (**28**)

Figure: 4 some of the representative members of the ***Iboga*** alkaloids

1.3 Biosynthesis of Indole alkaloids:

The monoterpenoid indole alkaloids form a uniform group of natural products and many researchers have worked on their isolation, structure determination, chemical transformations and synthesis. Much effort has also gone into elucidating their biogenesis and as a consequence the main pathways of their formation are already known. The fact that more than 2500 indole alkaloids were isolated mainly from three plant families *Apocynaceae* (APO), *Loganiaceae* (LOG) and *Rubiaceae* (RUB) from two building blocks iridoid terpene secologanin (**29**) and tryptamine (**30**) through a single precursor strictosidine (**31**) suggests a strong coherence in this collection of alkaloids.[5] Earlier studies of plant alkaloid biosynthesis relied on administration of isotopically labeled

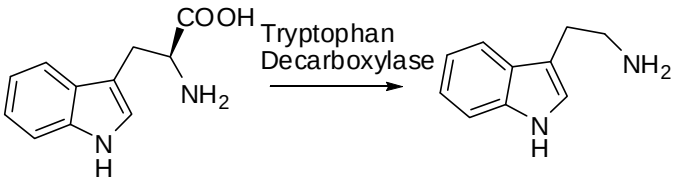
starting materials to different plants or plant cell cultures, followed by isolation and structural characterization of the labeled products. Additionally, chemical reactions with isolated biosynthetic intermediates allowed predictions of chemically reasonable transformations. However, with recent advances in molecular biology, the biosynthetic pathways of plant alkaloid natural products have been subject to study at the enzymatic level. A number of enzymes involved in plant alkaloid biosynthesis have been successfully cloned and many more enzymes have been purified from alkaloid producing plants or cell lines (Scheme-1). [6-10]



Scheme-1: Biosynthesis of Strictosidine

1. Tryptamine portion:

The radioactive tracer studies on the biosynthesis of indole alkaloids revealed that tryptamine moiety of indole alkaloids has been derived from the amino acid tryptophan (**32**).[11-13] Tryptophan decarboxylase, a pyridoxal dependant enzyme converts tryptophan (**32**) to tryptamine (**30**) (Scheme-2).[6]



Tryptophan (**32**) Tryptamine (**30**)

Scheme-2: Biosynthesis of tryptamine

2. Non-tryptamine portion (C_9-C_{10} unit):

The biogenetic origin of the "non-tryptophan" or C_9-C_{10} unit has been the subject of much controversy. Several theories have been proposed over the years. The Barger-Hahn-Robinson-Woodward hypothesis,[14-16] Wenkert's prephenic acid hypothesis,[17-18] and Schittler-Taylor-Leete hypothesis[19-20] did not standup to experimental tests and radioactive tracer studies as well as other studies apparently excluded these hypotheses. The first correct speculation was presented independently by Thomas[21] and Wenkert[18] about the non-tryptophan portion of indole alkaloids (i.e., its monoterpenoid origin). The structural similarity between the non-tryptophan moiety of the indole alkaloids with several co-existed non-nitrogenous cyclopentanoid monoterpenes such as oleuropeine (**33**), gentiopicrin (**34**), bakankosin (**35**), verbenalin (**36**), genepin (**37**) and asperuloside (**38**) led to the suggestion that they may have their structures based on the monoterpene unit (**39**) (Figure-5).

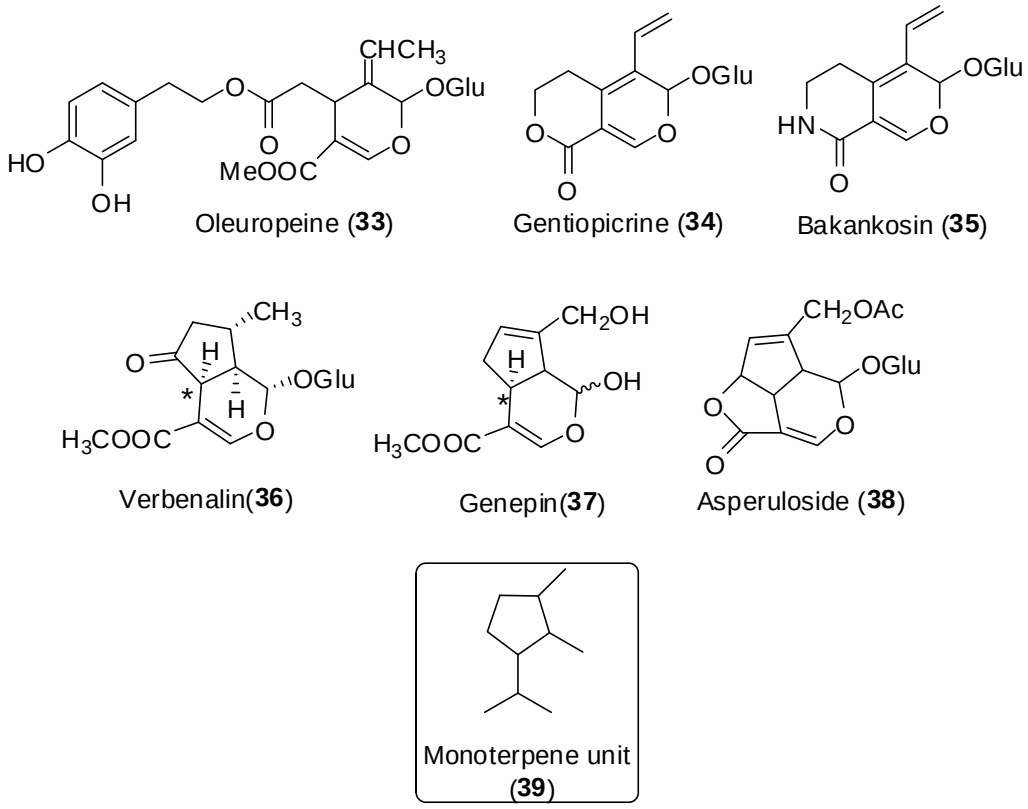


Figure: 5 Non-nitrogenious cyclopentanoid monoterpenes

Thomas[21] and Wenkert[18] suggest that non-tryptophan portion of these alkaloids formed from two mevalonate units **40**, which could combine to afford cyclopentane monoterpene (Iridoid) **39**. This could consequently cleave and incorporate into tryptamine to generate the indole alkaloids of class **I** (*Corynanthe* skeleton) and the ring closure via C_{17}-C_{18} bond formation leads to the *Yohimbe* class. Loss of one carbon rationalizes the *Strychnos* (C_9 unit as found in akuamicine) skeleton. It was further recognized that class **I** alkaloids (*Corynanthe*, e.g. Ajmalicine) are structurally related to class **II** (aspidosperma, eg. Vindoline) and class **III** (*iboga*, e.g. catharanthine) alkaloids and they could in principle be converted into one another by bond fission or bond formation at "a" or "b" (Figure-6).

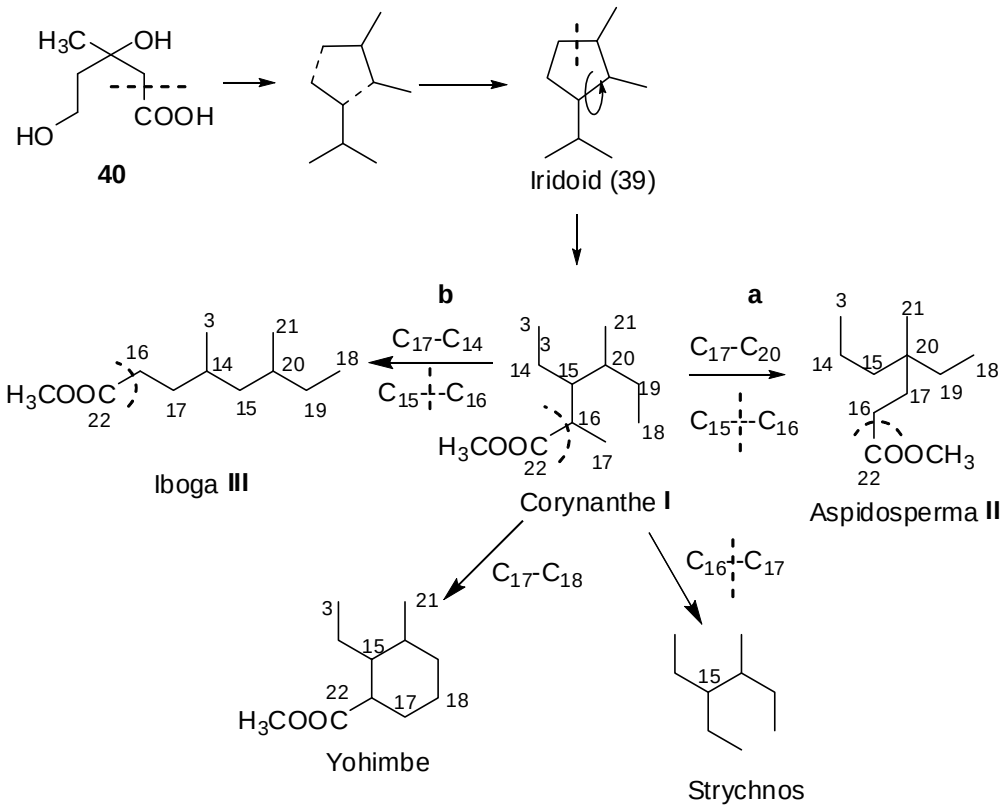
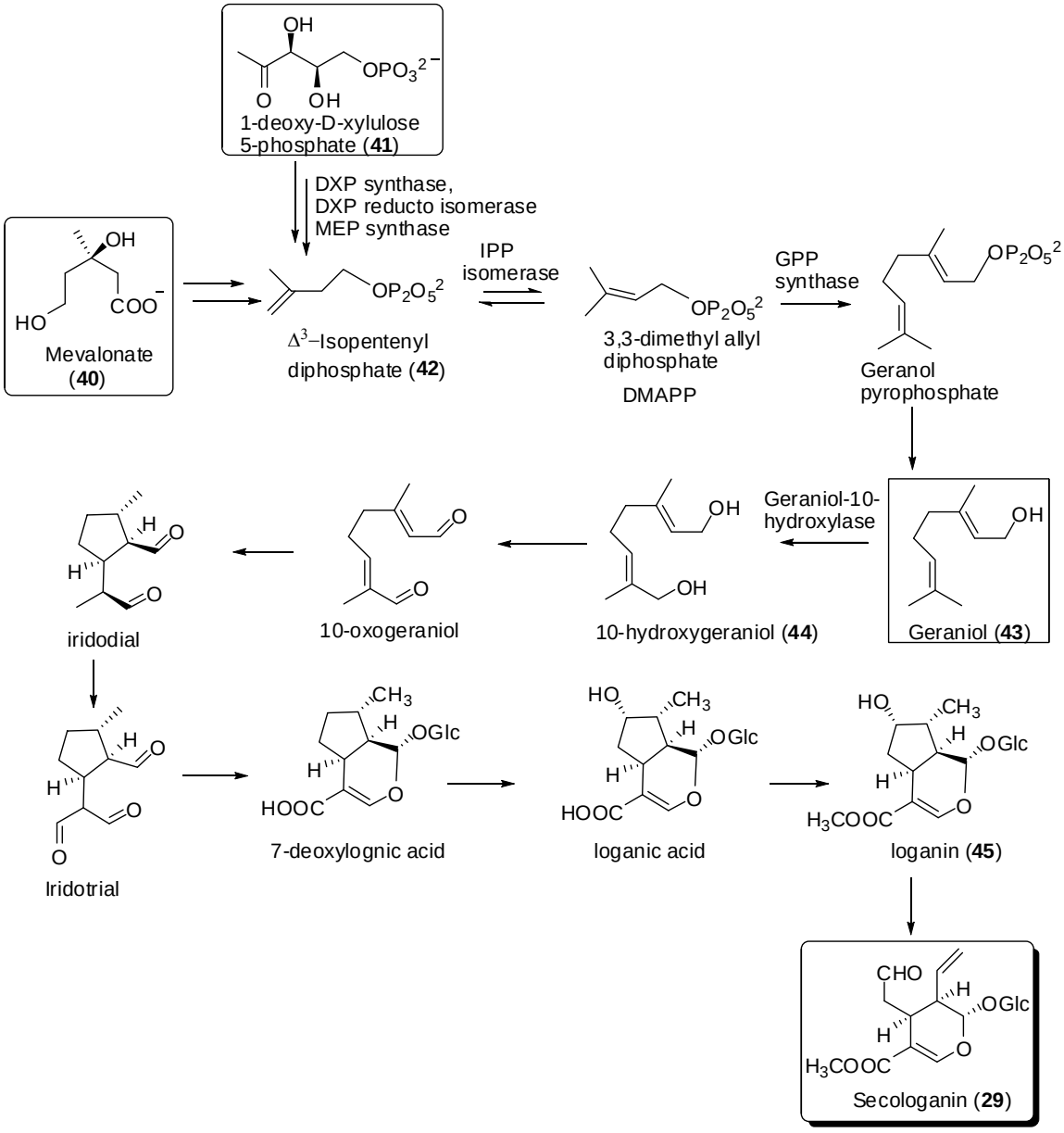


Fig: 6 Thomas – Wenkert hypothesis

This Thomas-Wenkert hypothesis was much disputed when first presented, but it has been shown by radioactive labeling studies to be a correct representation of the events.

Scott[9] has proved beyond doubt that the monoterpenoid hypothesis of Thomas and Wenkert[18, 21] are in accordance with their findings. It was also shown that all three types of the C_9-C_{10} unit (**I**), (**II**) and (**III**) are monoterpenoid in origin. The head-to-tail combination of two mevalonate(C_5) units (**40**) lead to geraniol (**43**), followed by the formation of hydroxygeraniol (**44**), loganin (**45**), secologanin (**29**). Recent literature precedents reveal that secologanin (**29**) itself is a natural product and feeding studies with *Catharanthus roseus* cell suspension cultures and ^{13}C-glucose strongly suggest that secologanin is ultimately derived from the triose phosphate/pyruvate pathway through isopentenyl diphosphate(IPP) (**42**) (Scheme-3).[6]

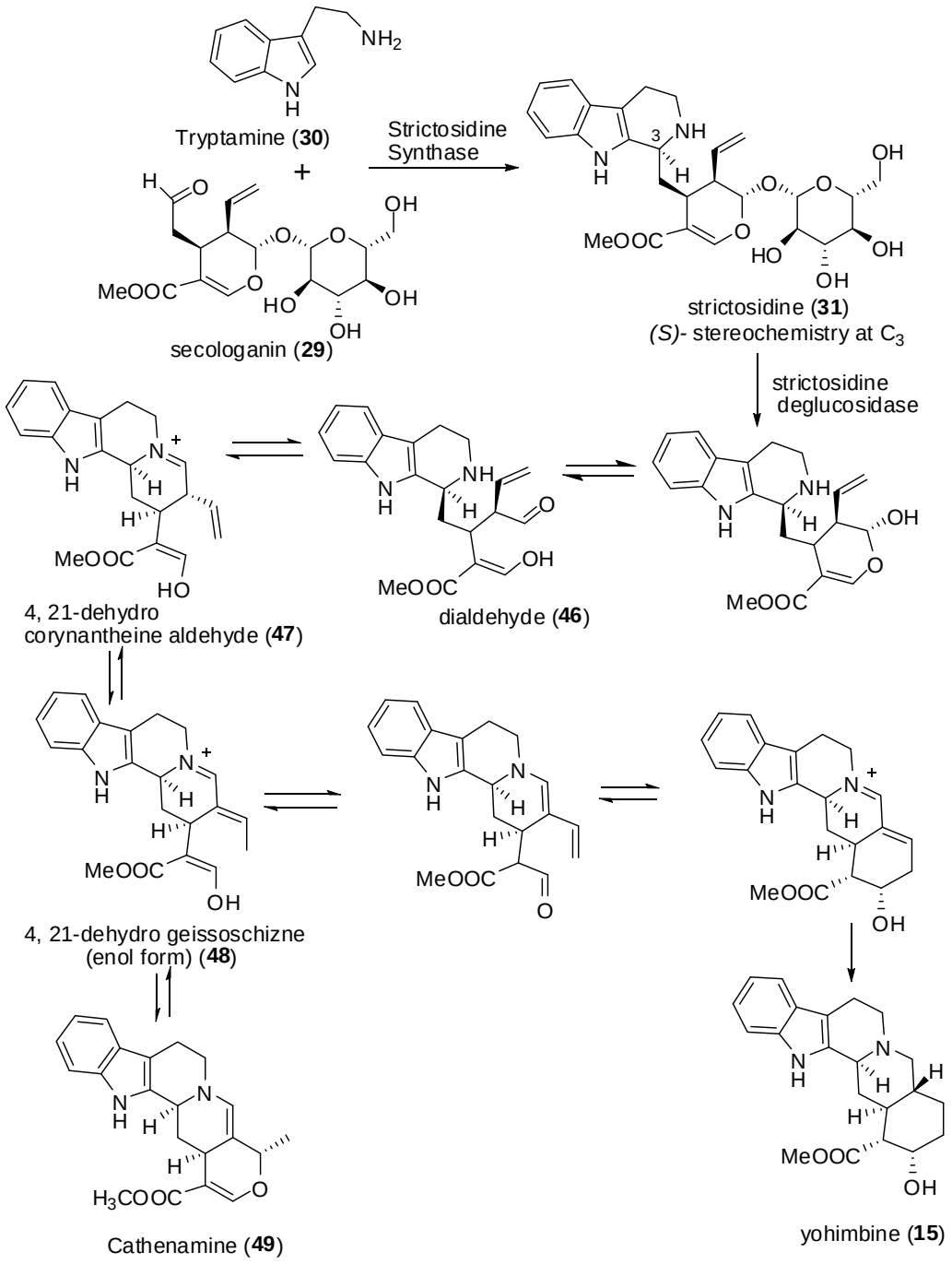


Scheme: 3 Biosynthesis of secolaganin from mevalonate/ triose phosphate

Condensation of tryptamine (**30**) with secologanine (**29**) opened the way to study the later stages of the biogenesis, as discussed below.[6]

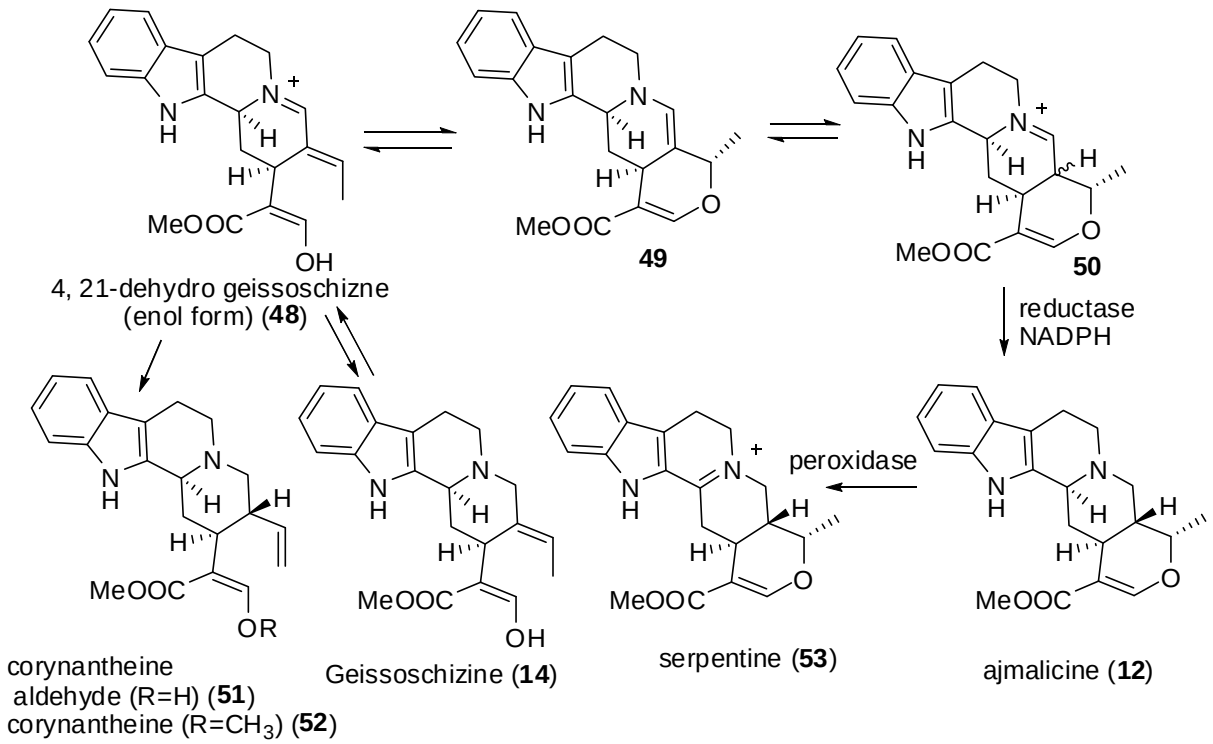
1.3.1Biosynthesis of Corynanthe alkaloids:

Tryptamine (**30**) and secologanine (**29**) condense to form strictosidine (**31**) having *S*-configuration at C-3 position catalyzed by the enzyme strictosidine synthase. The conversion of strictosidine (**31**) into *corynanthe*-type alkaloids requires no skeletal rearrangements, proceeds through the enzymatic (strictosidine deglucosidase) cleavage of the glucosidic residue to form a dialdehyde intermediate (**46**), which later reacts with the secondary amine of the strictosidine frame work to yield 4, 21-dehydrocorynantheine aldehyde (**47**). Dehydrocorynantheine aldehyde (**47**) undergoes allylic isomerization and enolization to produce either the enol or keto forms of dehydrogeissoschizine (**48**). The enol form of dehydrogeissoschizine undergoes 1, 4-conjugate addition to produce the heteroyohimbine cathenamine (**49**). The yohimbine biosynthetic route may involve homoallylic isomerization of the keto dehydrogeissoschizine (**48**) followed by 1, 4 – conjugate addition (Scheme-4).



Scheme: 4 Biosynthesis of *corynanthe* alkaloids

Enzyme catalyzed subsequent rearrangements of the 4, 21-dehydrogeissoschizine (**48**) could result to ajmalicine (**12**), geissoschizine (**14**) serpentine (**53**) and corynantheine (**52**) (Scheme-5).

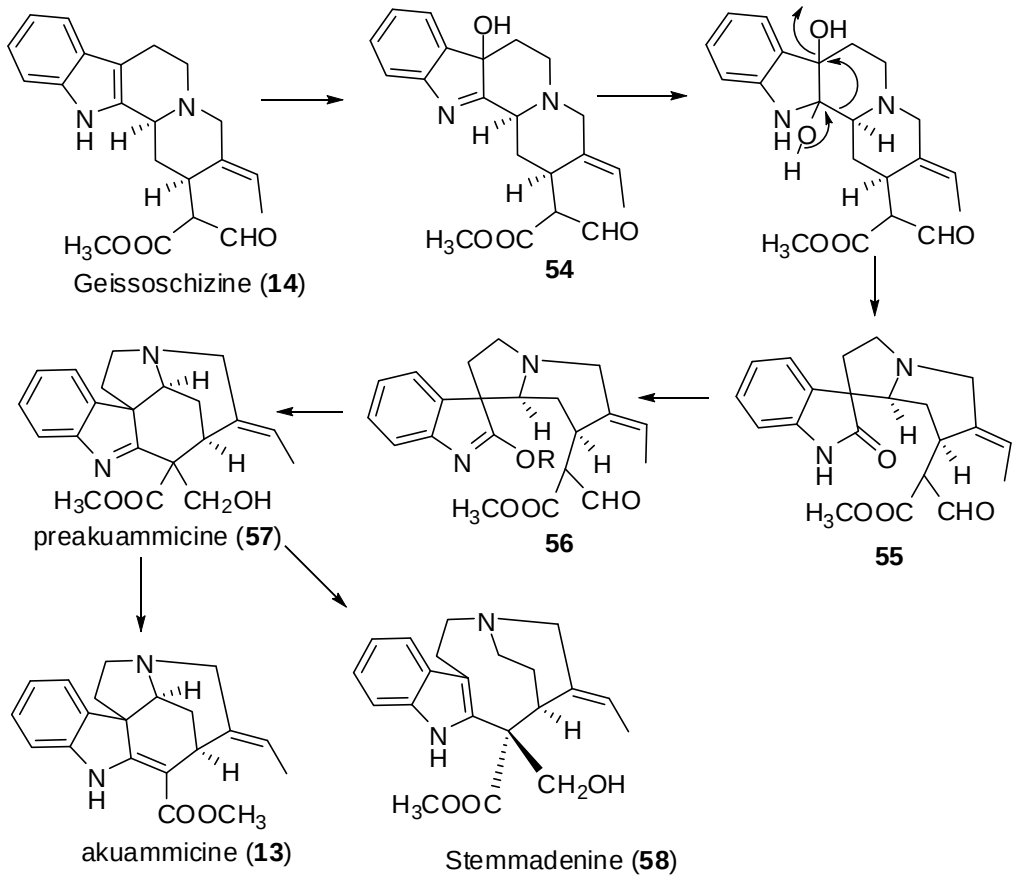


Scheme: 5 Biosynthesis of *corynanthe* alkaloids

1.3.2 Biosynthesis of *Strychnos, Aspidosperma* and *Iboga* type:

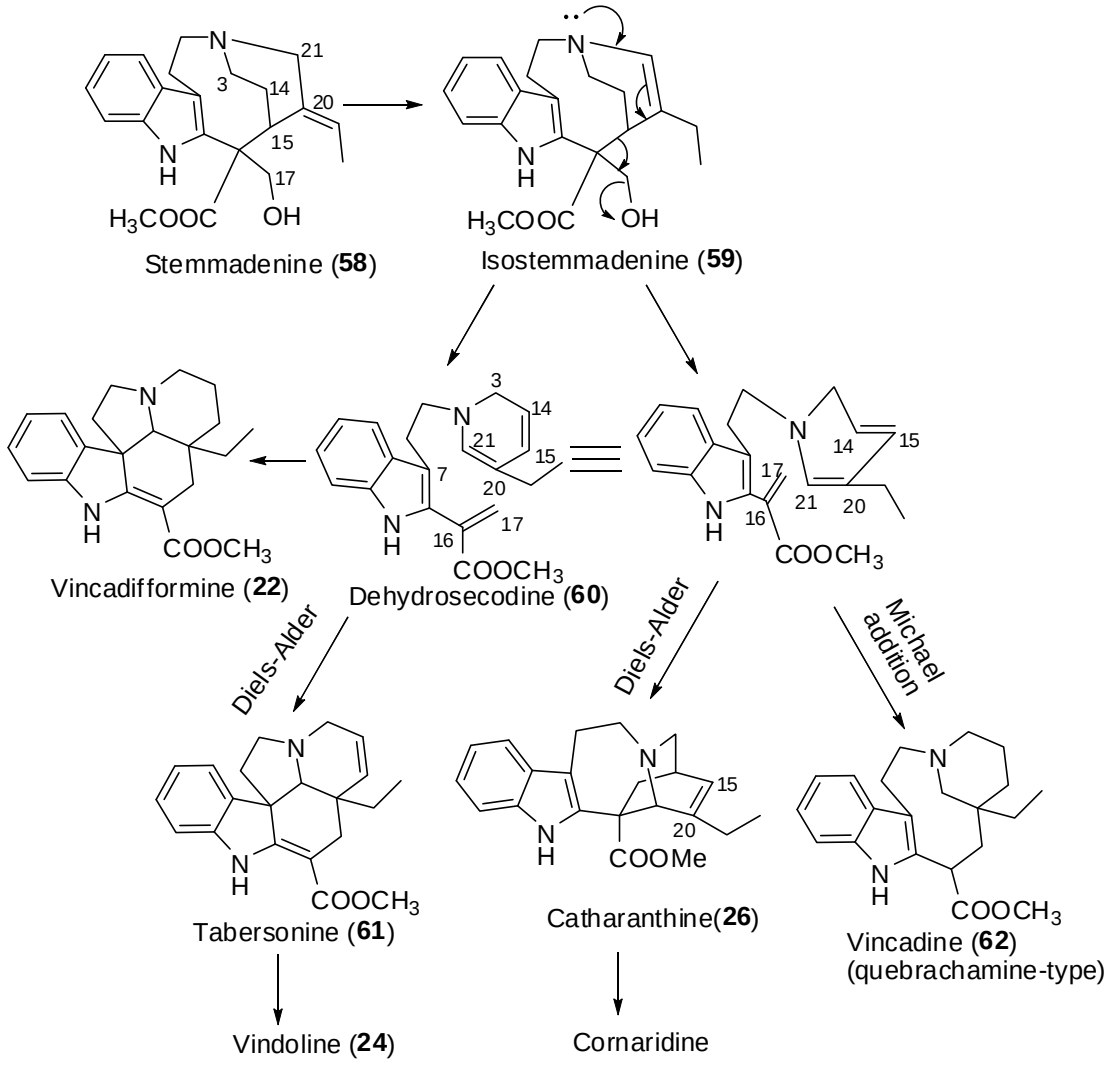
It is believed that the structurally more complex *Aspidosperma*, *Iboga* and *Strychnos* alkaloids are derivatives of the *Corynanthe* alkaloids.[22-23] This hypothesis is indirectly supported by observation that the *corynanthe* alkaloids are produced early in the lifetime of the *Catharanthus roseus* plant, while the *aspidosperma* and *iboga* alkaloids appear mainly in older plants. Studies by numerous groups in the 1960's and 1970 have enabled detailed proposals of the interrelationships and biosynthetic pathways for the *strychnos*, *iboga* and *aspidosperma* type alkaloids in *C. roseus.* Scott and Quershi in 1969 suggested[24] a most favored mechanism for connecting *corynanthe* alkaloids geissoschizine (**14**) with the strychnos series involving the formation of geissoschizine oxindole (**55**) through the β-hydroxy indolenine (**54**). The corresponding imino-ether **56**

could be formed by an intramolecular cyclization affording preakuammicine (**57**), which finally undergo loss of formaldehyde to give akuammicine (**13**) (Scheme-6).



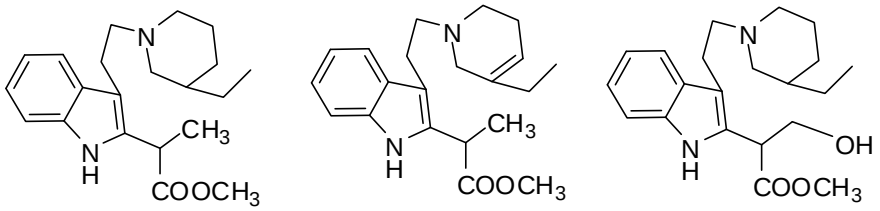
Scheme: 6 Scott hypotheses for the biosynthesis of the *Strychnos* alkaloids.

The very interesting mechanism has been independently proposed by Scott[25] and Kutney[26] for biosynthesis of *aspidosperma* and *iboga* alkaloids which involves strychnos skeletal fission and new bond formation as outlined below in Scheme-7. The transformation involves the isomerization of exocyclic double bond of stemmadenine (**58**) to give isostemmadenine (**59**) which could allow the fragmentation to dehydrosecodine intermediate (**60**) followed by intramolecular cyclization in three different modes leads the formation of tabersonine (**61**) (*aspidosperma*), catharanthine(**26**) (*iboga*) and vincadine(**62**) (*quebrachamine* type) alkaloids.

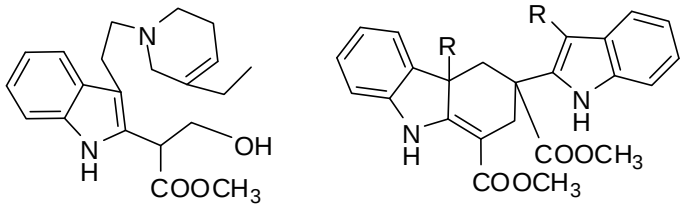


Scheme: 7 Biosynthesis of *Aspidosperma* and *Iboga* alkaloids from the *Strychnos* family *via* dehydrosecodine

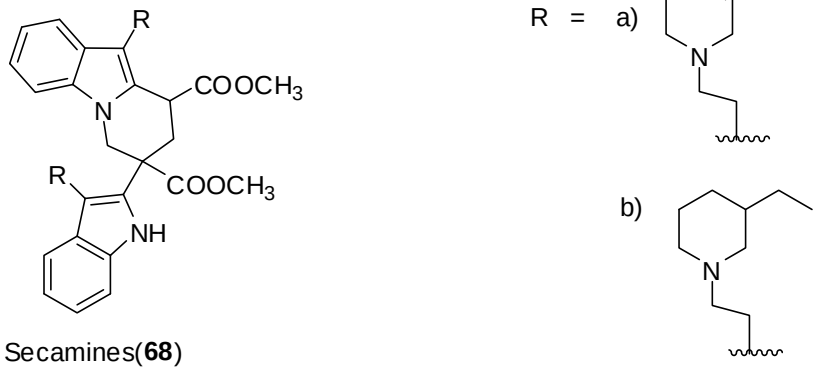
The instability of dihydropyridine and the reactivity of the acrylic ester moiety make the dehydrosecodine (**60**) almost impossible to isolate from the plant system. However, support for the formation of the dehydrosecodine (**60**) intermediate in the biological cleavage process came from the isolation of compounds having same skeleton as secodine intermediate from *Razya orientalis* by Smith[27-28] and from *C. roseus* shoots by Battersby (Figure-7). [29]



Tetrahydrosecodine (**63**) 15, 16-dihydrosecodine (**64**) Tetrahydrosecodinol (**65**)



16, 17-dihydrosecodine-17-ol (**66**) Presecamines (**67**)



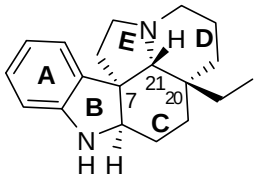
Secamines(**68**)

Figure: 7 Secodine-type compounds isolated from natural sources

Since the detailed discussion on all the above mentioned class of alkaloids is beyond the scope of the present dissertation, only the *Aspidosperma* class of alkaloids in particular vincadifformine has been focused in the further sections.

1.4 An overview of Aspidosperma alkaloids

The *Aspidosperma* family represents one of the largest groups of indole alkaloids[30] with more than 250 compounds isolated from various biological sources and display interesting biological activities. *Aspidosperma* species are widely applied in folk medicine as potential antimalarial agents and contraceptives and they are also employed in the treatment of leishmaniosis, uterine, ovary inflammation, diabetes, cancer, fever and rheumatism.[31] These alkaloids possess a basic framework as complex pentacyclic skeleton that is conformationally rigid due to the *cis*-relationship of the three contiguous stereo centers at C_7, C_{21} and C_{20} in the cyclohexyl ring (Figure-8).



Aspidospermidine (**69**)

Figure: 8 Basic framework of Aspidosperma alkaloids

The pharmacological significance of these alkaloids along with the challenge posed by their diverse and intricate structures has inspired considerable interest since the early days of complex synthetic organic chemistry research and provides a fertile ground for innovation. Dealing with these alkaloids is not only important in order to gain more knowledge about their nature, but some members are also of commercial value, e.g. the transformation of vincadifformine (**22**) to the pharmaceuticals vincamine (**6**), vincamone (**7**) and cavinton® (**8**). Vindoline (**24**) is a characteristic part of the anti-cancer bis-indole alkaloids vincristine (**9**) and vinblastine (**10**).[2] Tabersonine (**61**) isolated from the source of *Melodins tenuicaudatus* showed stronger inhibitory effect against five human cancer cell lines than that of cisplatin.[32] Five indole alkaloids Jerantinine A-E isolated from a leaf extract of the Malayan *Tabernaemontana corymbosa* displayed pronounced *in vitro* cytotoxicity against human KB cells (IC_{50}<1µg/mL).[33] Some of the aspidosperma

alkaloids, mentioned below, show antiplasmodial activity[34] and cytotoxic activity (Figure-9).

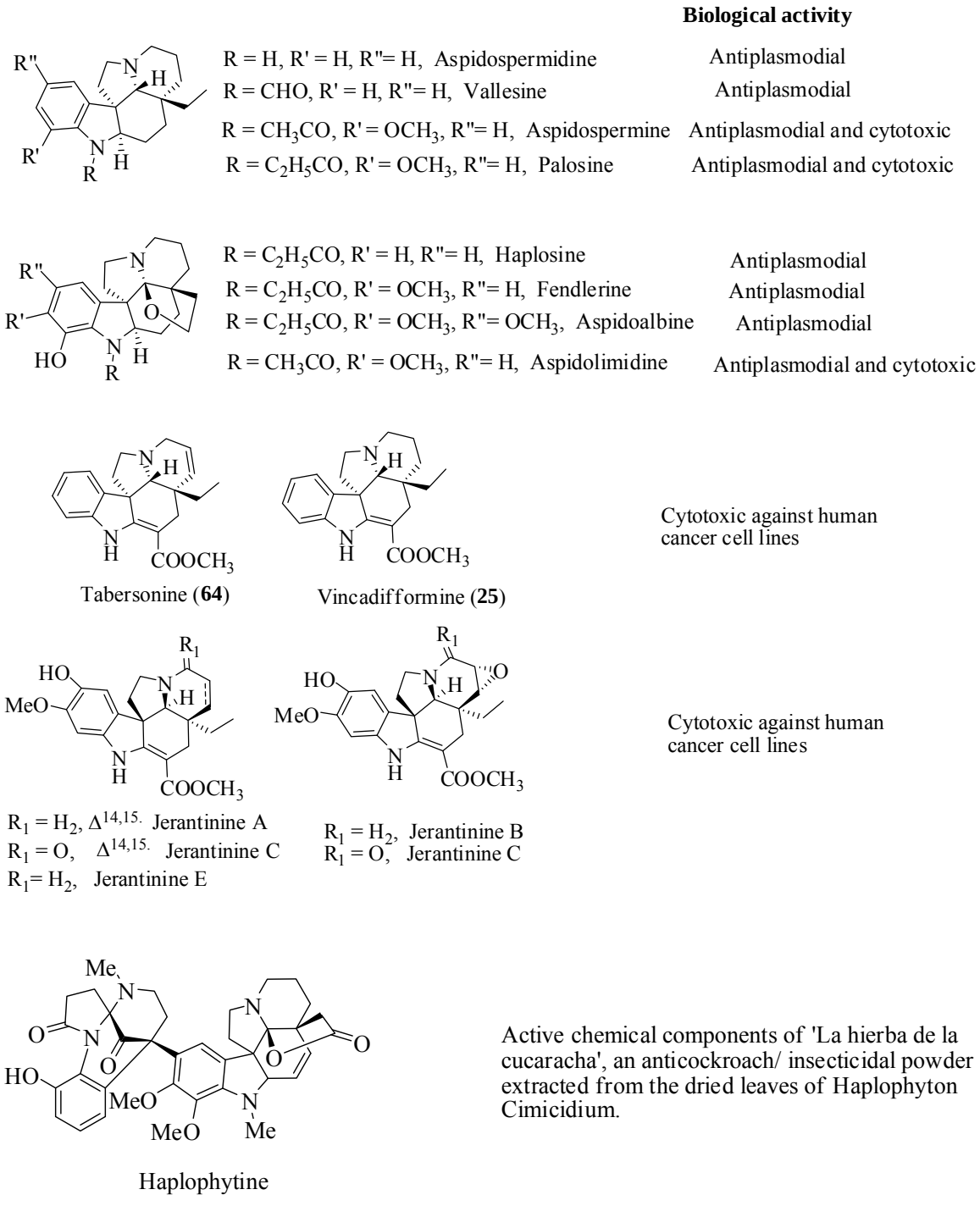


Figure: 9 Some of the important biologically active *Aspidosperma* alkaloids.

The natural paucity of these medicinally important molecules, difficult separation from the natural source and their intricate structure stimulated many synthetic chemists to develop new protocol for the syntheses of aspidosperma alkaloids and their derivatives. In this regard we chose a prime representative of aspidosperma alkaloid vincadifformine (**22**) as a preliminary synthetic target and we discuss our endeavor in the next chapter comprehensively.

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CHAPTER II

Total synthesis of (±) and (+)-vincadifformine through an iminium ion cascade reaction

Section –A

2A.1 Introduction:

Vincadifformine (**1**) is an indole alkaloid of the Plumeran type, isolated from many species of the *Apocynaceae* family. It was isolated in 1963 by Smith and Wahid from the dried leaves of *Rhazya stricta*,[1] which possesses two quaternary stereocentres in a complex pentacyclic skeleton that is conformationally rigid due to the *cis*-relationship of the three contiguous stereocenters in the cyclohexyl ring at C_7, C_{21} and C_{20}. Depending on its origin, the alkaloid may exist in the (+)-, (-)-, or (±)-form. (+)-vincadifformine has the (7*S*, 20*R*, 21*R*) absolute configuration (biogenetic atom numbering; *vide infra*) (Figure- 1).

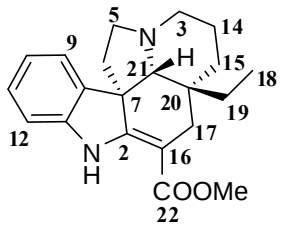


Figure: 1 (+)-Vincadifformine (**1**)

Vincadifformine largely occurs in racemic or partially racemic form[2a] and only the sample obtained from *Amsonia tabernaemontana* seem to have been optically pure (Table-1).

Table1. *Specific rotation of vincadifformine samples of different origin*

Origin	Solvent	$[\alpha]_D$
Aspidosperma album	EtOH	(+)[a]
Amsonia taberaemontana	EtOH	+ 600
Melodinus aeneus	EtOH	+535
Melodinus scandens	EtOH	+526
Rhazya stricta	EtOH	+402
Tabernaemontana riedelii	EtOH	+185
Vincadifformis, V.minor	MeOH	0
Vinca minor	EtOH	-540
Hunteria elliotii	EtOH	(-)[a]

[a]only the sign of rotation was determined

2A.2 Biological activity:

Aspidosperma alkaloids have attracted the attention of many synthetic chemists due to their manifold biological activity. The prime representative of aspidosperma alkaloid vincadifformine (**1**) shows pronounced cytotoxic effects against KB and Jurkat cells[2b] (Table-2). In particular, **1** serves as a valuable precursor for pharmaceutically important cerebral vasodilator vincamine (**2**), vincamone (**3**) and Cavinton® (**4**). In addition it is also suggested to be a possible biogenetic and synthetic precursor for the cytotoxic leucophyllidine (**5**) and rhazinilam (**6**) alkaloids respectively[3] (Figure -2).

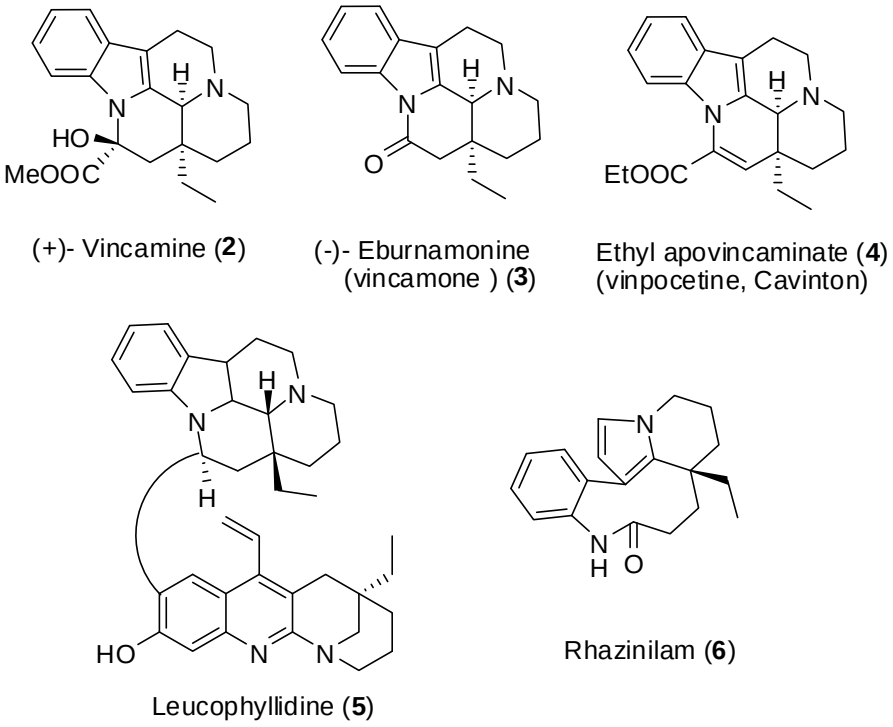


Figure 2: Biologically active Indole alkaloids.

Table-2 Cytotoxic effect of vincadifformine.

Compound	IC_{50}, µg/mL (µM)			
	KB/S[a]	KB/VJ300[a]	KB/VJ300[b]	Jurkat[c]
Vincadifformine (**1**)	10.2 (30.2)	6.3 (18.6)	4.5 (13.3)	21.8 (64.5)

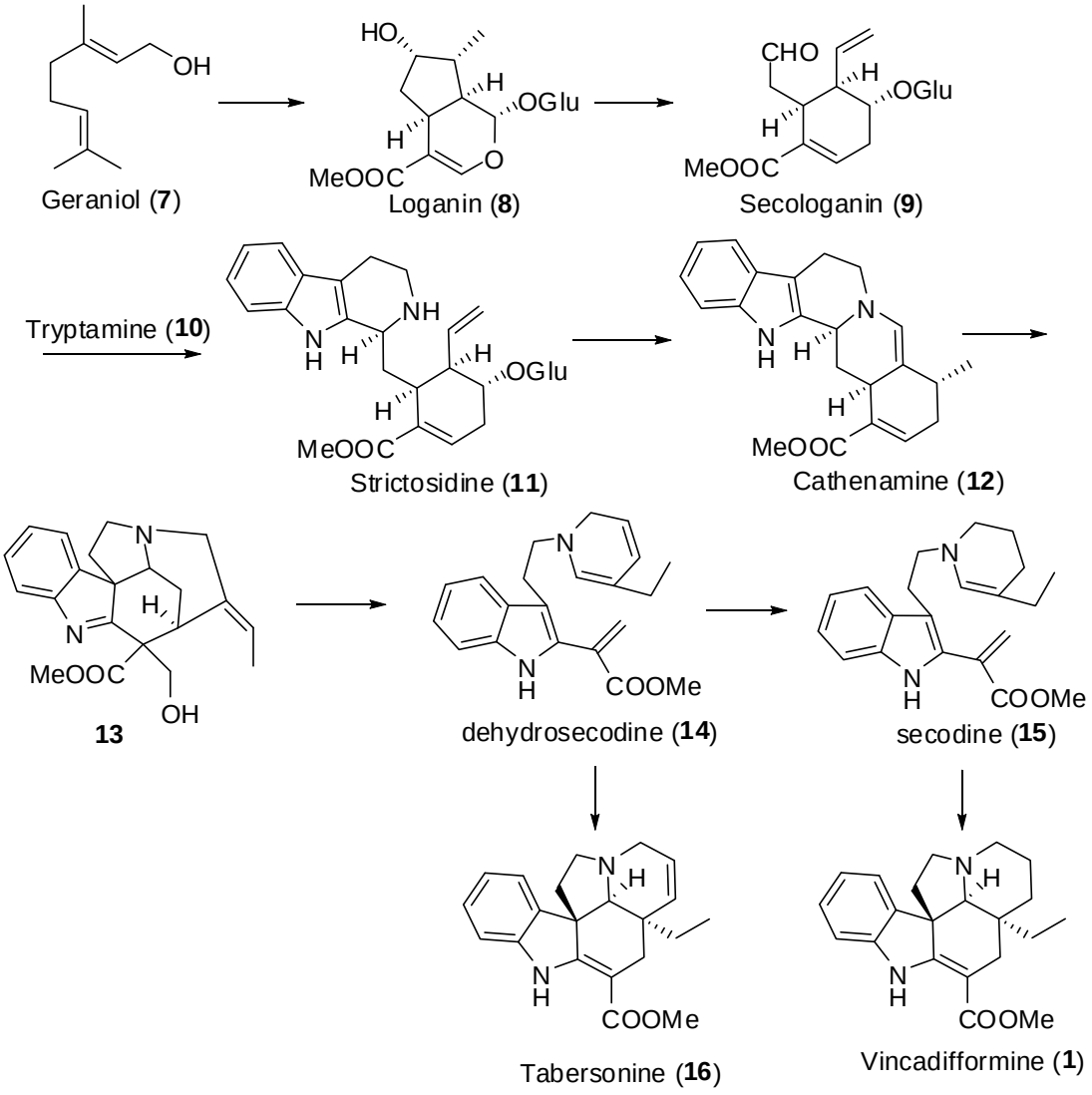
[a]KB/S and KB/VJ300 are vincristine-sensitive and resistant human oral epidermoid carcinoma cell lines, respectively. [b]With added vincristine, 0.1µg/mL(0.121µM), which did not affect the growth of the KB/VJ300 cells. [c]Jurkat is a human leukemic T-cell line.

The intricate structure in conjunction with the biological activity of vincadifformine stimulated many synthetic chemists to elucidate its biogenesis, as a consequence the main pathways of its formation is already known as described schematically below.

2A.3 Biosynthetic Pathway of vincadifformine:

The biosynthetic origin of vincadifformine has been traced to loganin (**8**) and tryptamine (**10**), as shown in the simplified biosynthetic Scheme–1. Its biogenesis has been elucidated through the combined efforts of many research groups and excellent literature reports exist on this subject.[4]

Dehydro secodine (**14**) and secodine (**15**) are the pivotal precursors to aspidosperma alkaloids tabersonine (**16**) and vincadifformine (**1**), respectively.



Scheme-1: Biosynthetic pathway of vincadifformine

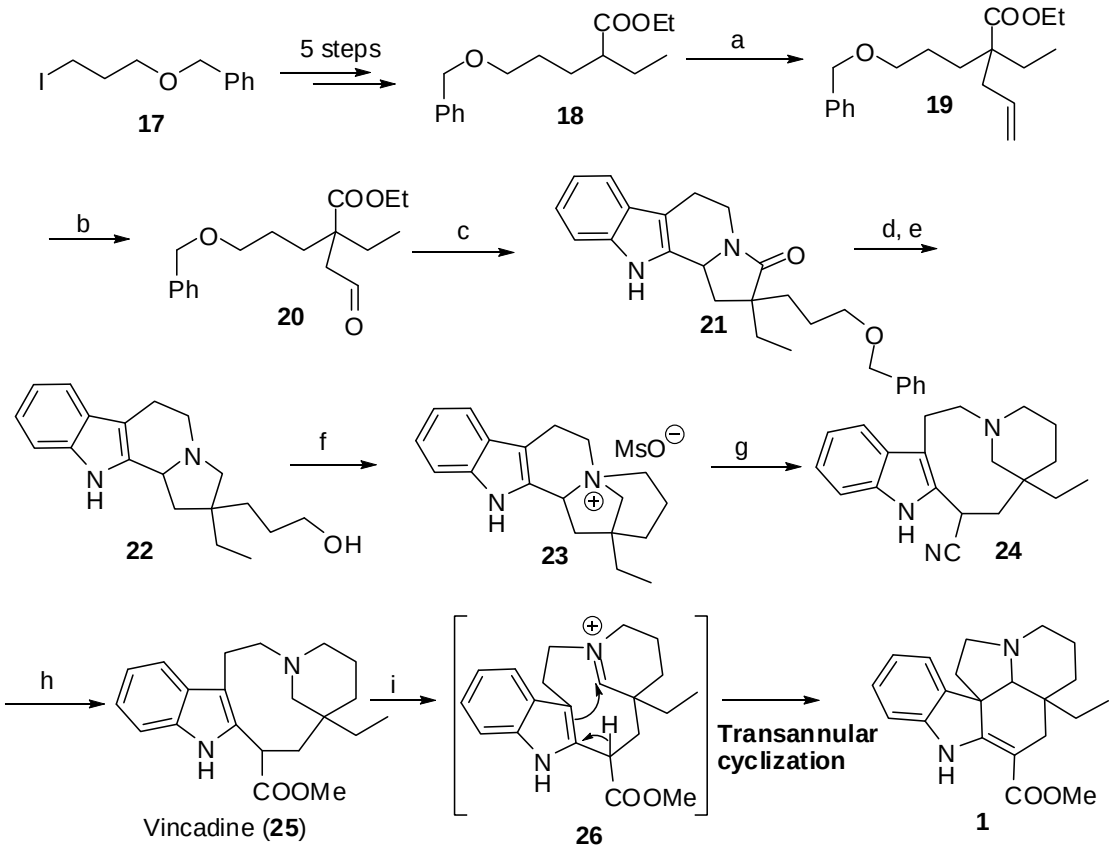
2A.4 Synthetic approaches towards racemic and optically active vincadifformine

Natural products containing one or more quaternary centers in their molecular architecture have always served as challenging targets for synthetic organic chemistry. Vincadifformine (**1**) possess a complex pentacyclic skeleton with two quaternary stereocenteres that is conformationally rigid due to the *cis* relationship of the three contiguous stereocenteres at C_7, C_{21}, and C_{20} in the cyclohexyl ring. The structural complexity posed by this alkaloid in conjunction with interesting pharmacological properties exhibited and its low abundance in nature stimulated considerable effort directed toward its synthesis. Over the last three decades, number of racemic syntheses and two enantioselective synthetic approaches to vincadifformine has been reported, while majority of the approaches were designed to proceed by way of involving biogenetically postulated secodine intermediate **15** *via* intramolecular Diels-Alder type reactions.

(I) Racemic Syntheses:

1. **Kutney's approach:** (*J. Am. Chem. Soc*. **1968**, *90*, 3891; *J. Am. Chem. Soc*.**1966**, *88*, 3656)[5]
   (14 steps)

The first total synthesis of vincadifformine was published in 1968 by Kutney *et al*. using transannular cyclization as a key step, which provided a synthetic entry into the aspidosperma, vinca and iboga classes of alkaloids. Reaction of vincadine (**25**) with either mercuric acetate or oxygen in the presence of a catalyst (5% platinum on charcoal) led to vincadifformine (**1**) *via* transannular cyclization (Scheme-2).



Scheme-2 Kutney's approach

*Reagents and conditions: (a) Triphenylmethyl sodium, allyl bromide, 98% (b) OsO_4, $NaIO_4$, 65% (c) Tryptamine (**10**), 90% (d) LAH (e) Pd/C, CH_3COOH, 84% (f) $MeSO_2Cl$, TEA (g) KCN, DMF (h) (i) $OH^{(-)}$/hydrolysis (ii) CH_2N_2, diethyl ether (i) Mercuric acetate or oxygen in presence of catalyst 5%Pt/C.*

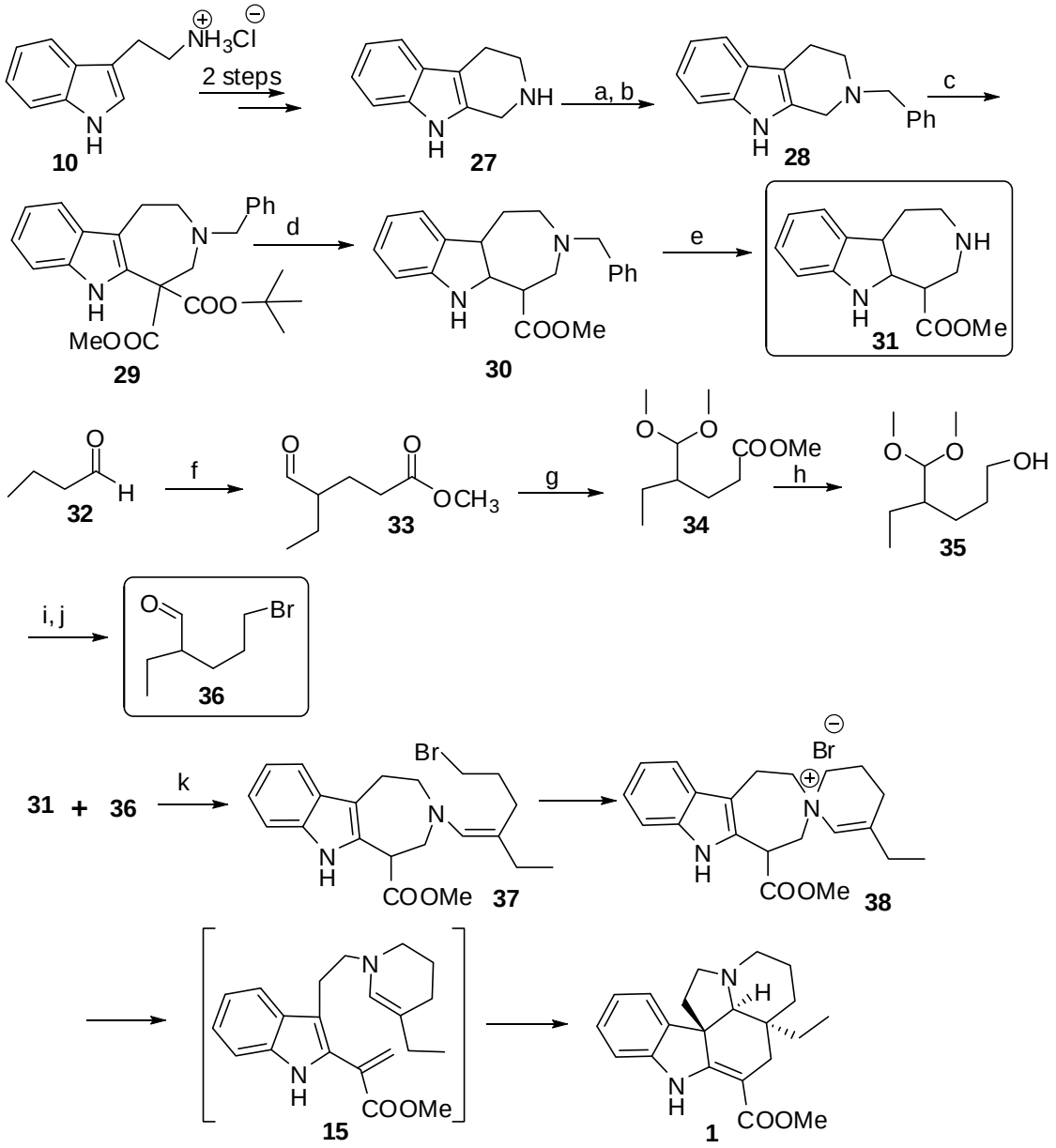
2. Kuehne's approaches:

a) First approach : (*J. Org. Chem*. **1978**, *43*, 3705)[6]

(11steps, 8.8% overall yield)

The pioneering work on the biomimetic synthesis of vincadiffromine was carried out by Kuehne *et al.* in 1978 starting from tryptamine (**10**) and butyraldehyde (**32**)**.** *N*-Benzyltetrahydro-*β*-carboline (**28**) on reaction with *tert*-butyl hypochlorite gave corresponding chloroindolenines which on treatment with thallium dialkyl malonates led to the formation of respective indoleazepine **29**. Monodecarboxylation and

debenzylation of the **29** provided **31**, which was converted to vincadifformine by reaction with 5-bromo-2-ethylpentanal (**36**), proceeding through the biogenetically postulated secodine intermediate **15** as shown in Scheme-3.



Scheme-3 Kuehne's first approach

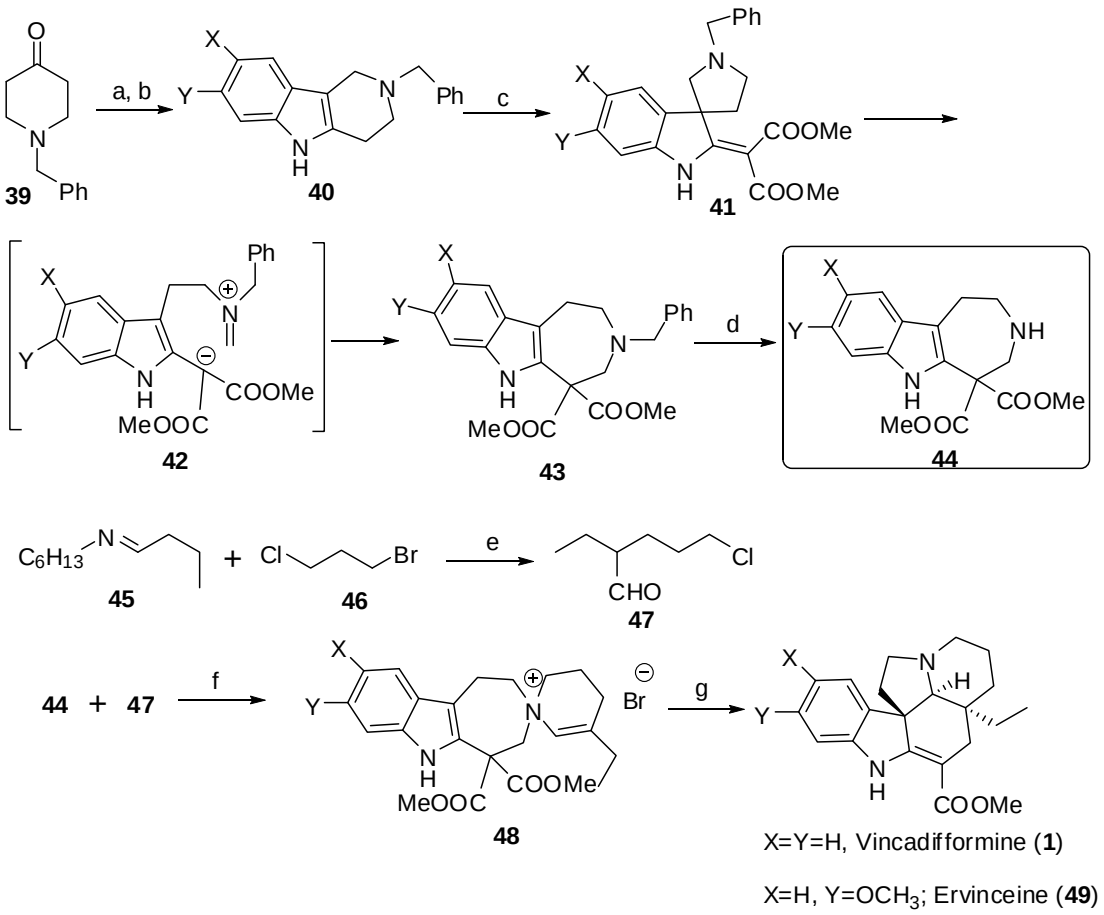
Reagents and conditions: (a) Dry pyridine, C_6H_5COCl, Benzene, reflux, 30 min, 94% (b) LAH, THF, reflux, 6 h, 91% (c) Dry benzene, TEA, t-BuOCl, thallium tert-butyl methyl malonate, reflux, 36 h, 63% (d) 1,2-dichloro ethane, TFA, 84% (e) 5% Pd/C, dry CH_3COOH, H_2, 1 atm, 97% (f) methyl acrylate, piperidine, CH_3CN, 67% (g) MeOH

(anhy), H_2SO_4 (conc), 93% (h) LAH, THF, reflux, 90% (i) TEA, $MeSO_2Cl$, DCM, -20 °C, 99% (j) LiBr, DMF, 40 °C, 1N HCl, 84% (k) Benzene (anhy), 40 °C, 51 h, 26%.

(b) Second approach: (*J. Org. Chem.* **1979**, *44*, 1063)[7]

(8 steps, 20% overall yield)

The author has executed the convergent synthesis of vincadifformine (**1**) and its aryl substituted analogue ervinceine (**49**) through biogenetically postulated secodine intermediate by reaction of indoloazepine (**44**) and chloro aldehyde **47** as shown in Scheme-4.



Scheme-4 Kuehne's second approach

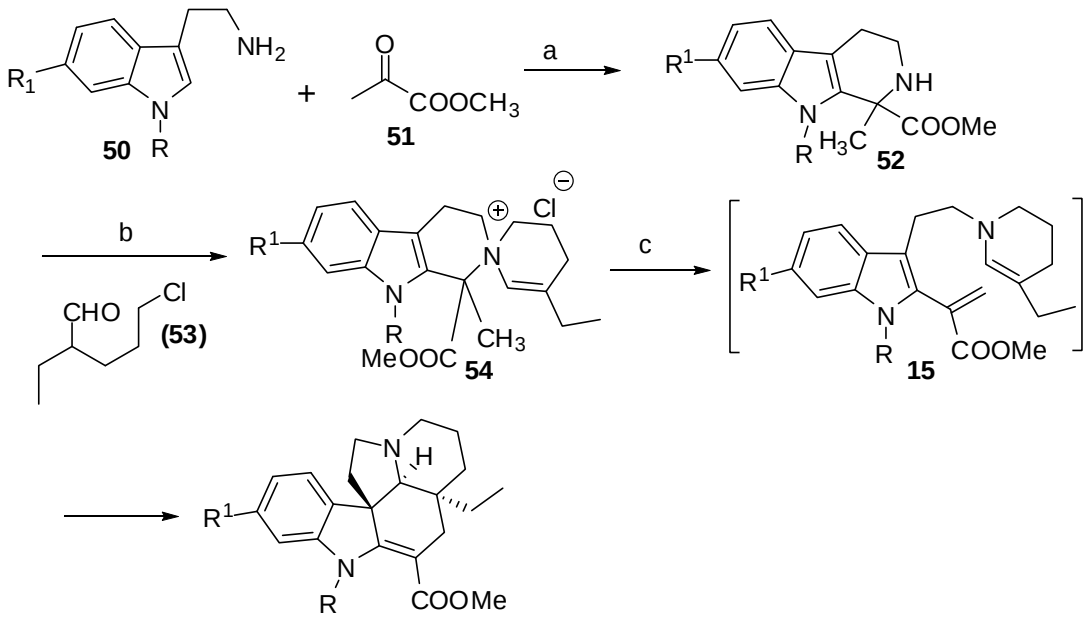
Reagents and conditions: (a) Phenyl hydrazine hydrochloride, H_2O: EtOH, K_2CO_3, rt, 48 h, 87% (b) CH_3COOH (glacial), 6% HCl, rt, 20 min, 87% (c) t-BuOCl, DCM, 18 °C,

Thallium dimethylmalonate, benzene, rt→reflux, 70% (d) CH_3COOH, Pd/C, H_2, 3 h, 71% (e) LDA, THF, -78 °C→rt, 3% HCl, 54% (f) MeOH (anhy), 18 h, rt (g) TEA, 40 °C, 20 h, 55%.

(c) Third approach: (*J. Org. Chem*. **1979**, *44*, 2477)[8]

(8 steps, 38% over yield)

Kuehne *et al.* presented their third approach for the total synthesis of vincadifformine (**1**), minovine (**55**), ervinceine (**49**) through a biogenetically postulated secodine intermediate (**15**). The indole fragment tetrahydro *β*-carbolines **52** obtained through slightly modified way by condensation of tryptamine (**50**) with methyl pyruvate (**51**) as shown in (Scheme-5).



R = H, R^1=H, vincadifformine (**1**)

R=CH_3, R1= H, Minovine (**55**)

R = H, R^1=OCH_3, Ervinceine (**49**)

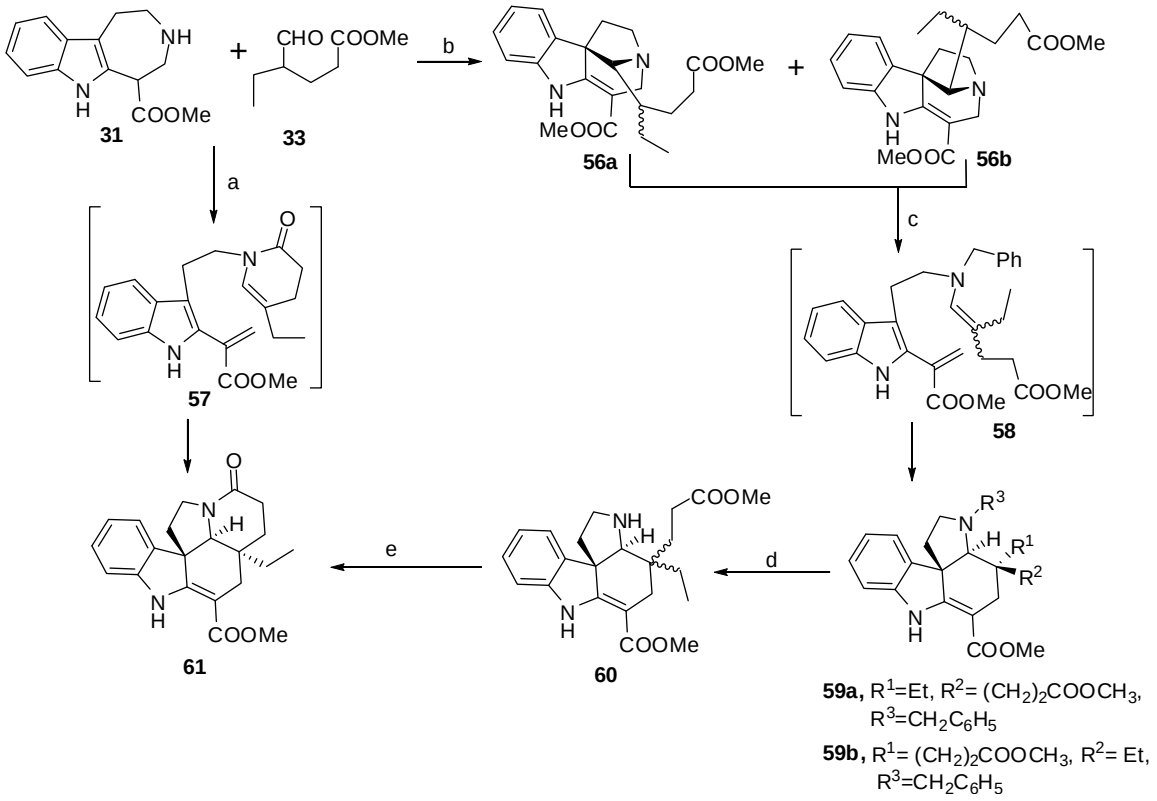
Scheme-5 Kuehne's third approach

Reagents and conditions: (a) MeOH (anhy), reflux, 21 h, 72% (b) p-TsOH (cat), toluene, reflux, 100 h (c) DBU, toluene, reflux, 84%.

(d) Fourth approach: (*J. Org. Chem*.**1981**, *46*, 2002)[9]

(Formal synthesis, 8 steps, 28% overall yield to procure **61**)

Kuehne *et al.* investigated that methyl 4-formyl hexanoate (**33**) on reaction with indoloazepine **31** in toluene gave 3-oxo vincadifformine (**61**) through a biogenetically postulated secodine type intermediates **57** or **58**. The important key observation in this strategy was *N*-benzylation of the bridged indoloazepine esters **56** and reaction of the resultant quaternary salts with base leading to C_{20} epimeric mixture of the rearranged products **59a** and **59b**. The lack of diastereoselectivity in **59** was due to the less *E/Z* selectivity of enamine **58**. The diastereomeric mixture **59** were converted to a single diastereomer 3-oxovincadifformine (**61**) upon debenzylation and heating in toluene with acid catalysis (Scheme-6).



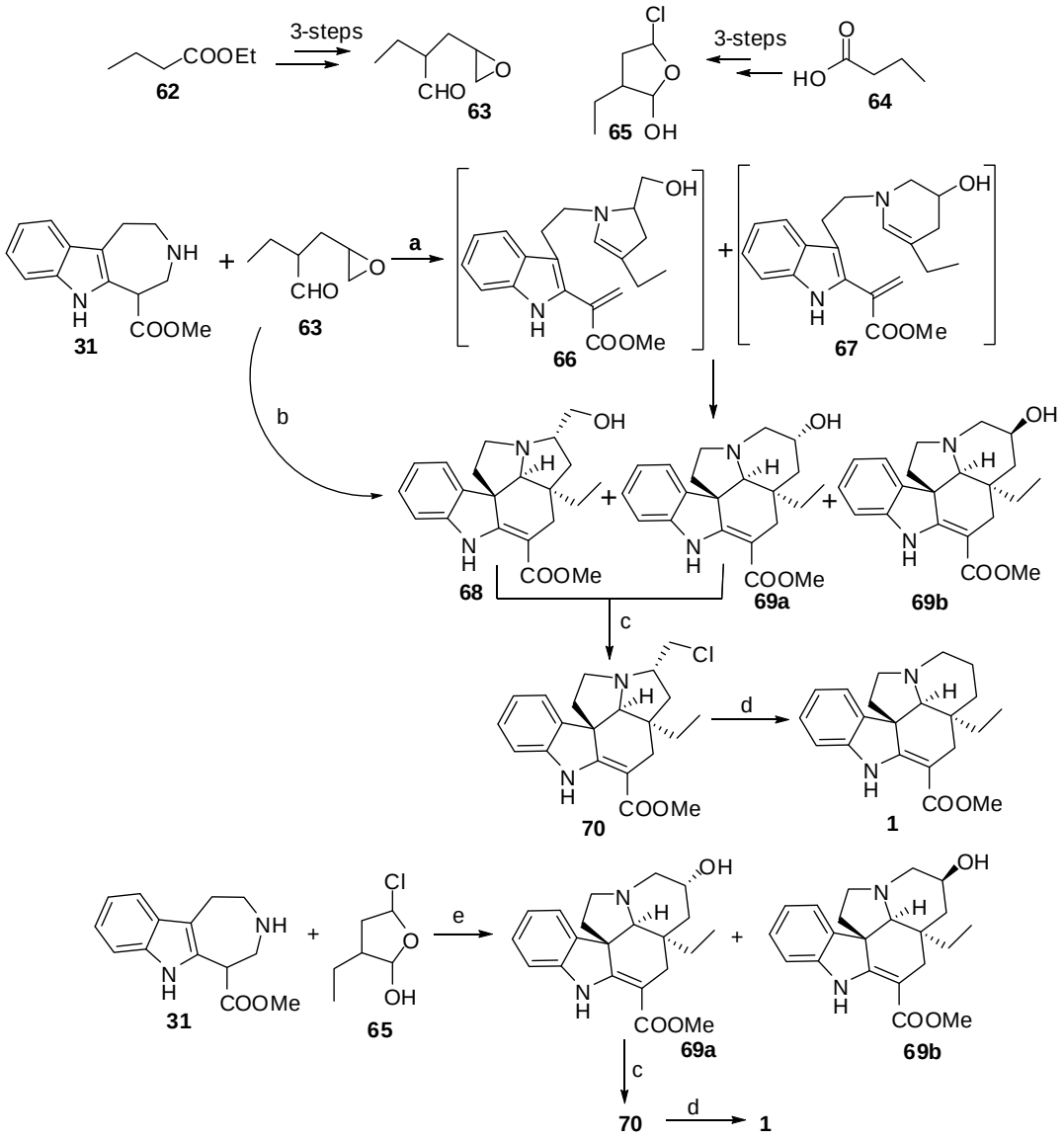
Scheme-6 Kuehne's fourth approach

Reagents and conditions: (a) Toluene, reflux, 18 h, 85% (b) $CHCl_3$, 4Å molecular sieves, 40 °C, 20 h, 80% (c) $C_6H_5CH_2Br$, $CHCl_3$, reflux, 24 h, N,N-diisopropyl amine, reflux, 6 days, 60% (d) CH_3COOH, Pd/C, H_2, 4 h (e) toluene, p-TsOH (cat), reflux, 18 h.

(e) Fifth approach: (*J.Org.Chem*. **1982**, *47*, 1335)[10]

(12 steps, 8.9% overall yield)

The authors demonstrated that the condensation of 4, 5-epoxy-2-ethylpentanal (**63**) with indoloazepine (**31**) leads to a mixture of (hydroxymethyl)-D-norvincadifformine (**68**) and 14-hydroxyvincadifformine (**69a, 69b**) which upon further functional group transformations yield vincadifformine. In the similar way, indoloazepine (**31**) coupled with 5-chloro-2-ethyl-4-hydroxypentanal lactol (**65**) leads to a mixture of diastereomers **69a** and **69b**, where **69a** was converted to vincadifformine by chlorination followed by reduction with sodium borohydride (Scheme-7).



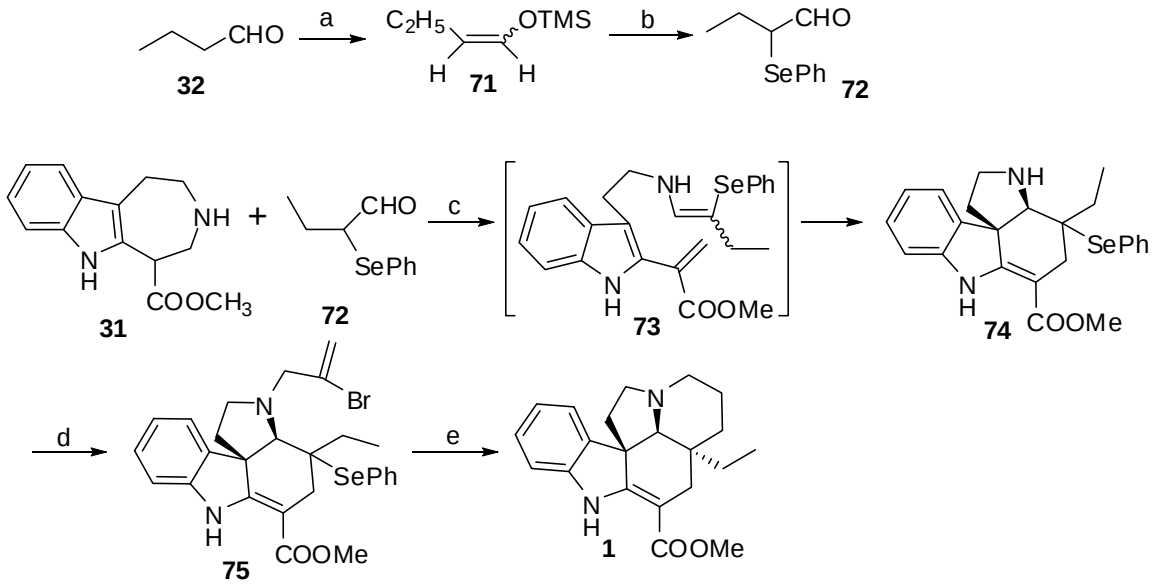
Scheme-7 Kuehne's fifth approach

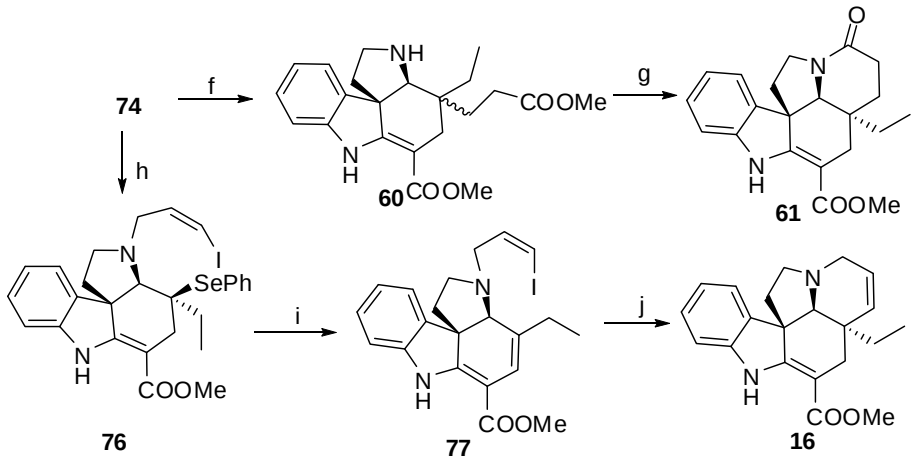
Reagents and conditions: (a) p-TsOH, benzene, 24 h, reflux, TEA, reflux, 8 h; ***68*** *(56%),* ***69a*** *(22%),* ***69b*** *(18%) (b) MeOH, 2 h, reflux;* ***68*** *(68%) (c) PPh_3, CCl_4, $CHCl_3$, heat, 45 min, 68% (d) TEA, $NaBH_4$, DMF, 80 °C, 4 h, 57% (e) Benzoic acid, benzene, reflux, 24 h TEA, reflux, 12 h:* ***69a*** *(47%),* ***69b*** *(34%).*

(f) Sixth approach (*J. Org. Chem*. **1996**, *61*, 6001)[11]

(8 steps, 19% overall yield)

Kuehne and co-authors explored further the synthesis of vincadifformine and tabersonine by employing intramolecular Diels-Alder reaction (through secodine type intermediate) and free radical induced cyclizations as key steps. The coupling of indoloazepine (**31**) with 2-(phenylselenyl) butyraldehyde (**72**) gave tetracyclic core **74** through secodine type intermediate **73** which on *N*-alkylation followed by free-radical induced cyclization led to the formation of vincadifformine (**1**) (Scheme-8).





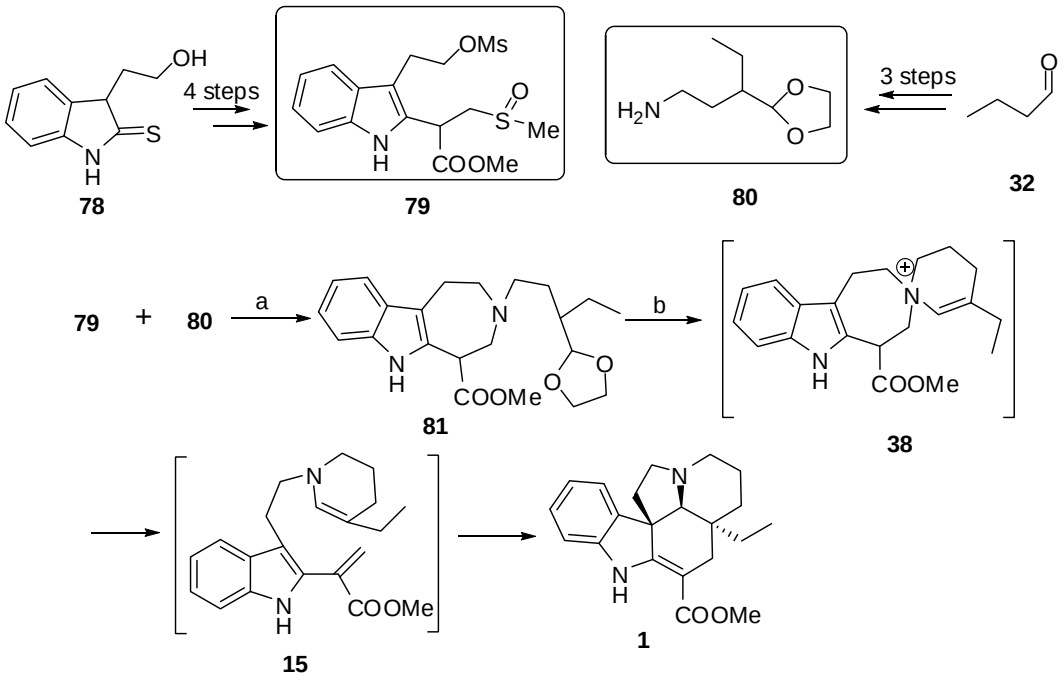
Scheme-8 Kuehne's sixth approach

Reagents and conditions: (a) TMSCl, TEA, DMF, 59% (b) PhSeBr, Ether, -78°C, 73% (c) toluene, reflux, 18 h, 70%, (N, Se-cis 49%; N, Se-trans 20%) (d) 2, 3-dibromo propene, K_2CO_3, THF, reflux, 2 days, 77% (e) Bu_3SnH, AIBN, benzene, 85 °C, 2 h, TEA, 85 °C, 1 h, 85% (f) methyl acrylate, AIBN, Bu_4SnH, benzene, 85 °C, 7 h (g) p-TsOH, toluene, reflux, 18 h, 34% (h) (Z)-1,3-diiodopropene, K_2CO_3, THF, reflux, 6 h, 81% (i) m-CPBA, DCM, -40 °C→rt, 89% (j) $Pd(OAC)_2$, PPh_3, CH_3COONa, CH_3CN, 43%.

3. Das's approach: (*J. Chem. Soc., Chem. Commun***. 1985,** 88)[12]

(9 steps)

Das *et al.* have synthesized vincadifformine based on the coupling of indole fragment **79** and amine fragment **80** proceeding through the biogenetically postulated secodine intermediate **15**. This pathway is conceptually akin to an elegant biomimetic route earlier designed and explored with great success by Kuehne *et al.* (Scheme-9).



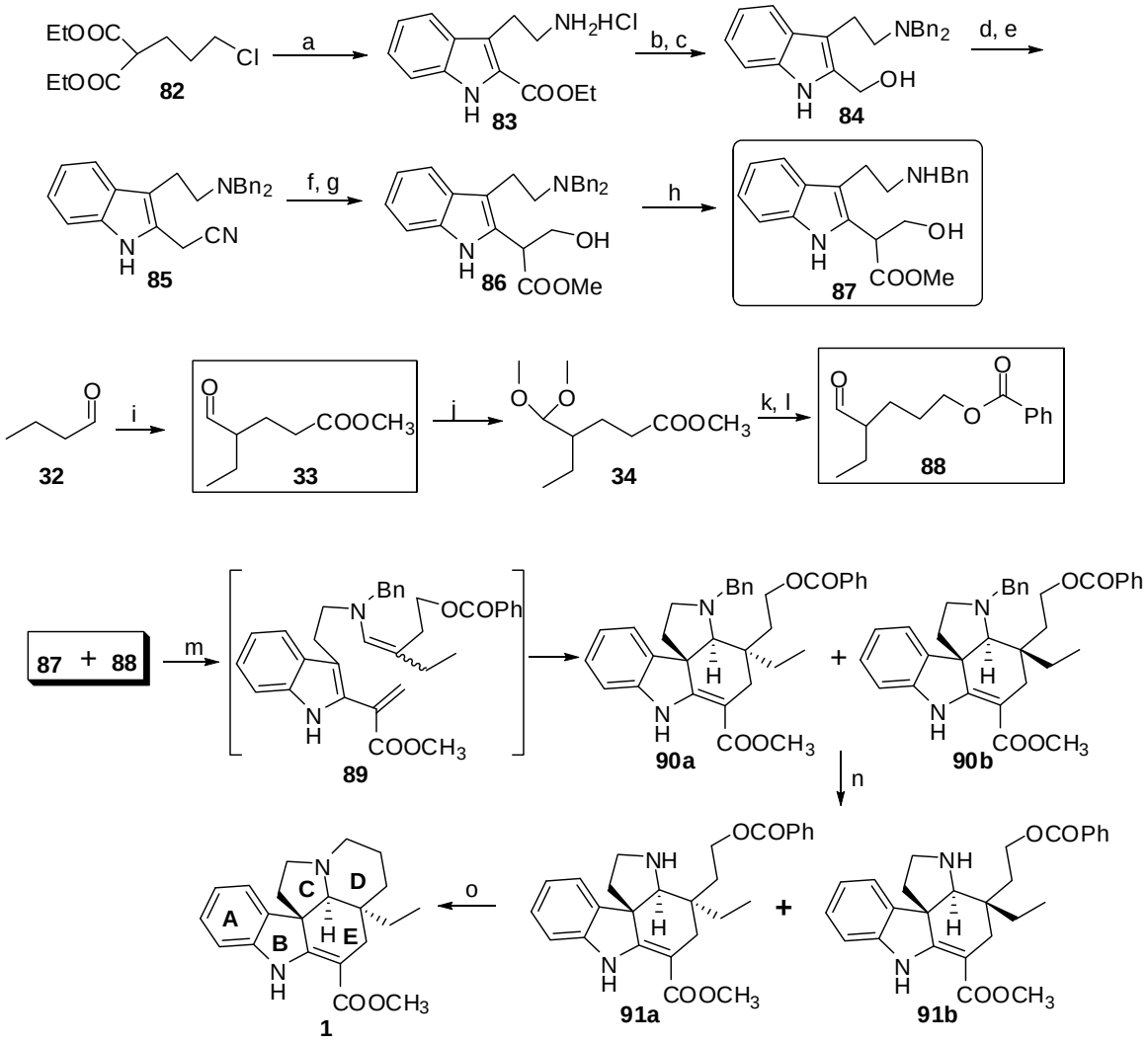
Scheme-9 Das's approach

Reagents and conditions: (a) pyridine, NaI, rt, overnight (b) 1M HCl, H_2O: THF (1:9), 50%.

4. **Szantay's approach** (*J. Org. Chem*. **1993**, *58*, 1434)[13]

(15 steps, 2.5% overall yield)

Another approach to the synthesis of racemic vincadifformine was reported by Szantay *et al.* employing almost Kuehne's approaches. On condensation of indole fragment **87**, containing a masked acryl ester function with 5-(benzyloxy)-2-ethylpentanal (**88**) afforded diastereomeric mixture of **90** through a secodine type intermediate **89**. The important key observation in this strategy was the conversion of diasteromeric mixture of **91** to vincadifformine (**1**) as a single diastereomer by refluxing in dimethylformamide and potassium iodide which proceeded through the internal *N*-alkylation followed by thermal CE-ring cleavage and transannular cyclization (Scheme-10).



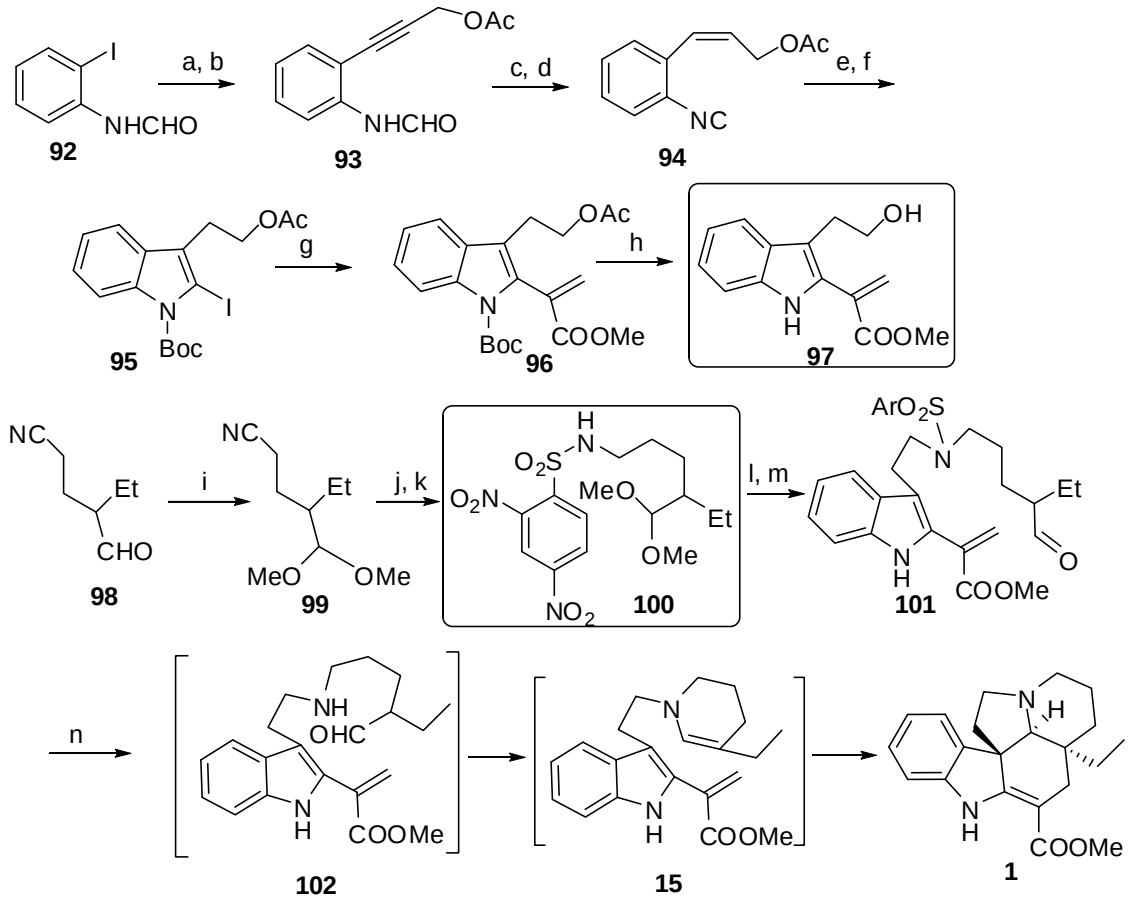
Scheme-10 Szantay's approach

Reagents and conditions: (a) KOH, C_2H_5OH, $C_6H_5N_2Cl$, 17% (b)C_6H_5Cl, KI, K_2CO_3, DMF, rt, 4 h, 75% (c) LAH, THF, 3.5 h, 97% (d) C_6H_5COCl, DMAP, pyridine, rt, 4.5 h, 93% (e) KCN, DMSO, 70 °C, 1 h, 74% (f) MeOH (anhy), HCl (gas), 24 h, 54% (g) HCOOMe, NaH, reflux, 1.5 h, MeOH, CH_3COOH (glacial), $NaBH_4$, -20 °C, 1 h, 62% (h) Pd/C (10%), CH_3COOH (glacial), 1.5 h, 88% (i) methyl acrylate, piperidine, CH_3CN, 67% (j) MeOH (anhy), H_2SO_4 (cat), 93% (k) LAH, THF, reflux, 90% (l) C_6H_5COCl, TEA, DCM, 0 °C→rt, 0.5 h, 83% (m) p-TsOH (cat), toluene (anhyd), reflux, 24 h, 26% (n) Pd/C (10%), CH_3COOH (glacial), 40 min, 43% (o) KI, DMF, reflux, 1h, 58%.

5. Fukuyama's approach (*Tetrahedron. Lett.* **1999,** *40***,** 1519)[14a]

(15 steps, 18% overall yield)

The author described the biomimetic synthesis of vincadifformine by coupling the indole fragment **97** with sulphonamide **100** employing Mitsunobu condition[14b] affording **101** which through a functional group transformations involving secodine intermediate **15** produced vincadifformine (Scheme-11).



Scheme-11 Fukuyama's approach

Reagents and conditions: (a) propargylic alcohol, $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, rt, 1 h (b) Ac_2O, pyridine, rt, 30 min, 88% from **92** *(c) H_2, Lindlar cat, MeOH, rt, 5 h, 93% (d) $POCl_3$, pyridine, CH_2Cl_2, 40 min, 93% (e) n-Bu_3SnH, AIBN, MeCN, 80 °C, then NIS, rt, 20 min. (f) $(Boc)_2O$, TEA, DMAP, MeCN, rt, 1 h, 71% (g) methyl 2-tri-n-butylstannylacrylate, $BnPd(PPh_3)_2Cl$, Ph_3As, CuI, HMPA/DMF, 85 °C, 3.5 h, 62% (h)*

Na_2CO_3, H_2O/MeOH, rt, 2 h, 90% (i) $CH(OMe)_3$, CSA, MeOH, rt, 20 min, 95% (j) H_2 (1500 psi), Raney-Ni (W-2), NH_3-EtOH, 80 °C, 4 h (k) 2, 4-dinitrobenzenesulfonyl chloride, pyridine, CH_2Cl_2, rt, 30 min, 82% (l) ***97****, diethyl azodicarboxylate (40% in toluene), PPh_3, benzene, rt, 40 min, 91% (m) TFA, CH_2Cl_2, rt, 15 min (n) PhOK, MeCN, rt, 4 h, 67%*

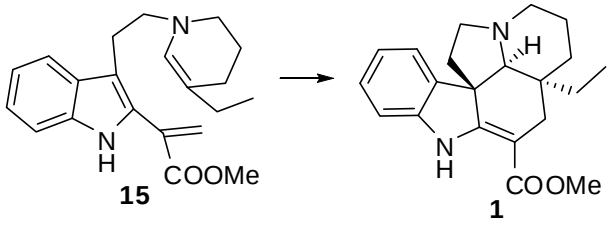
(II) Asymmetric syntheses:

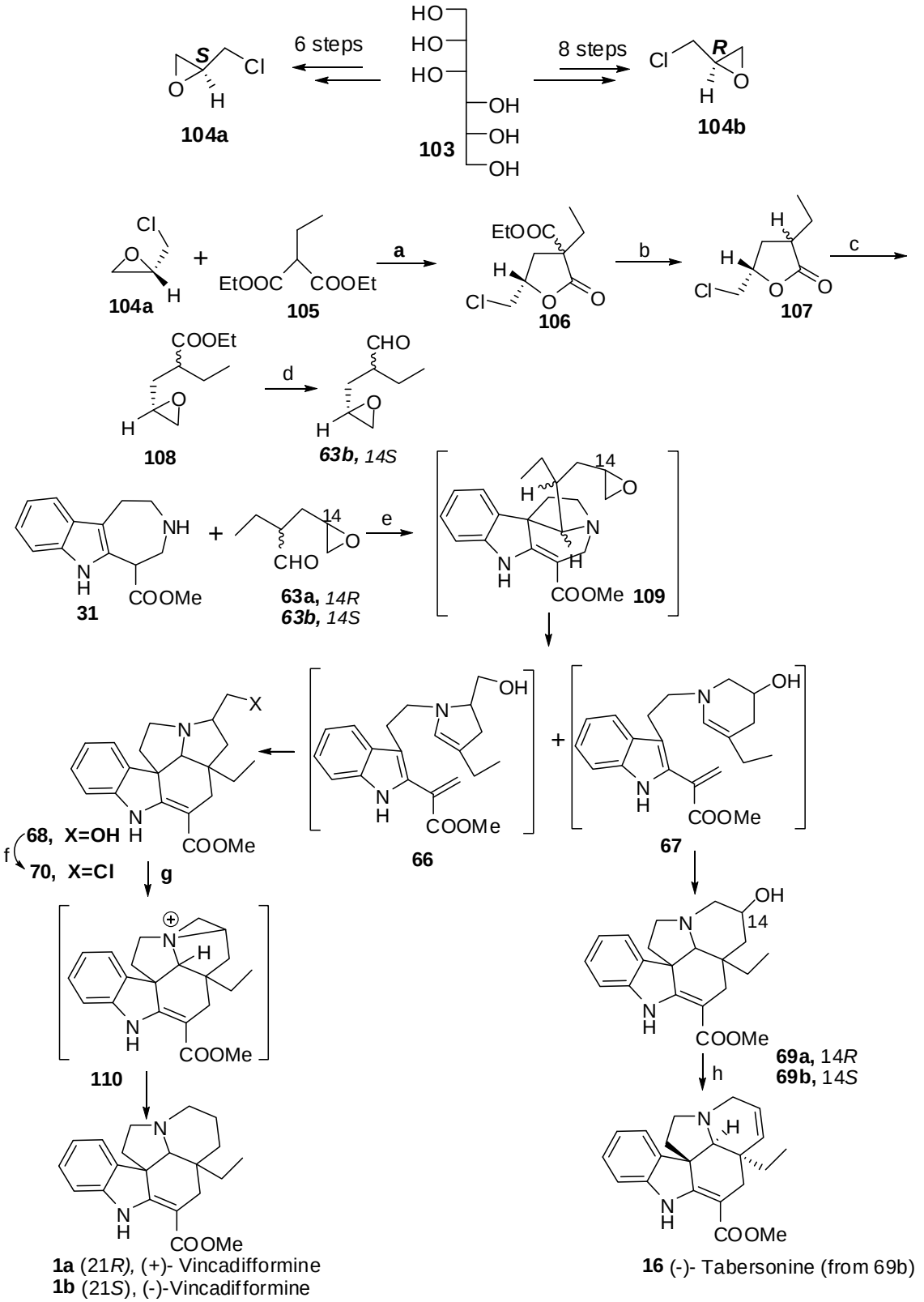
Till date only two approaches, demonstrated by Kuehne *et al.,* are known for the synthesis of optically active vincadifformine.

1. Chiron approach: (**Kuehne *et al***. *J. Org. Chem*. **1985,** *50*, 924)[15]

(10 steps from **104**, overall yield 2.7%)

Kuehne and coworkers envisioned that in order to form the vincadifformine with high enantioselectivity, enamine moiety of secodine reactant **15** should have an inherent stereodirecting substituent to undergo intramolecular Diels-Alder reaction with acrylate moiety for high diastereoselectivity. The authors have executed the total synthesis of (-)- and (+) - vincadifformine with ≥ 98% ee and ≥ 97% ee respectively, from the two enantiomers of epichlorohydrin (**104**) as a starting material. This synthetic scheme is based on the generation and cyclization of the enantiomeric (hydroxymethyl) norsecodine intermediates **66**. By an alternative synthetic route involving (14*S*)-14-hydroxy-$\Delta^{20,21}$-secodine intermediate **67**, tabersonine (**16**) was obtained in ≥ 99% ee. This strategy is almost akin to the earlier racemic synthesis represented in Scheme-7 (Scheme-12).





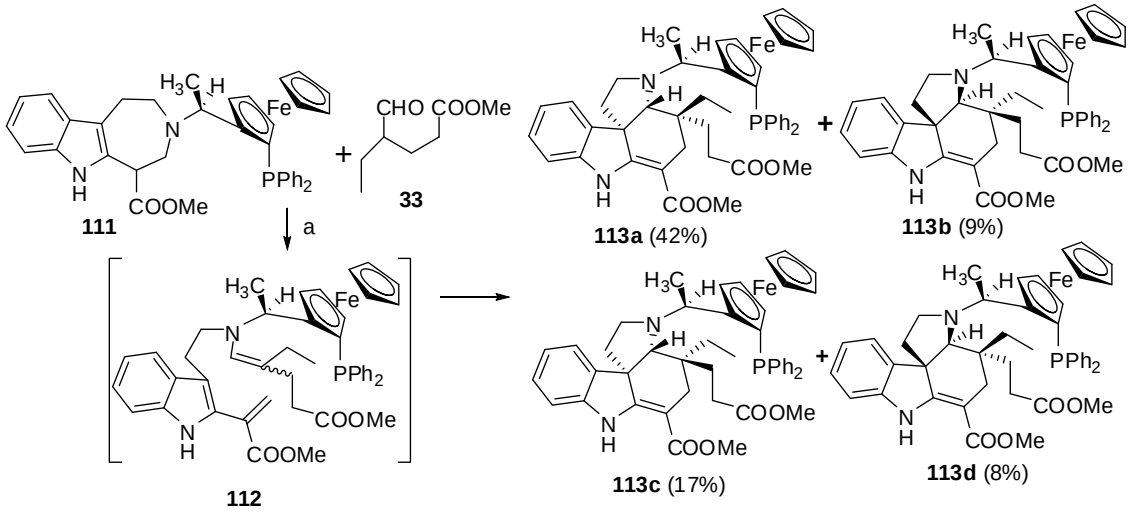
Scheme-12 Kuehne's approach (chiral pool)

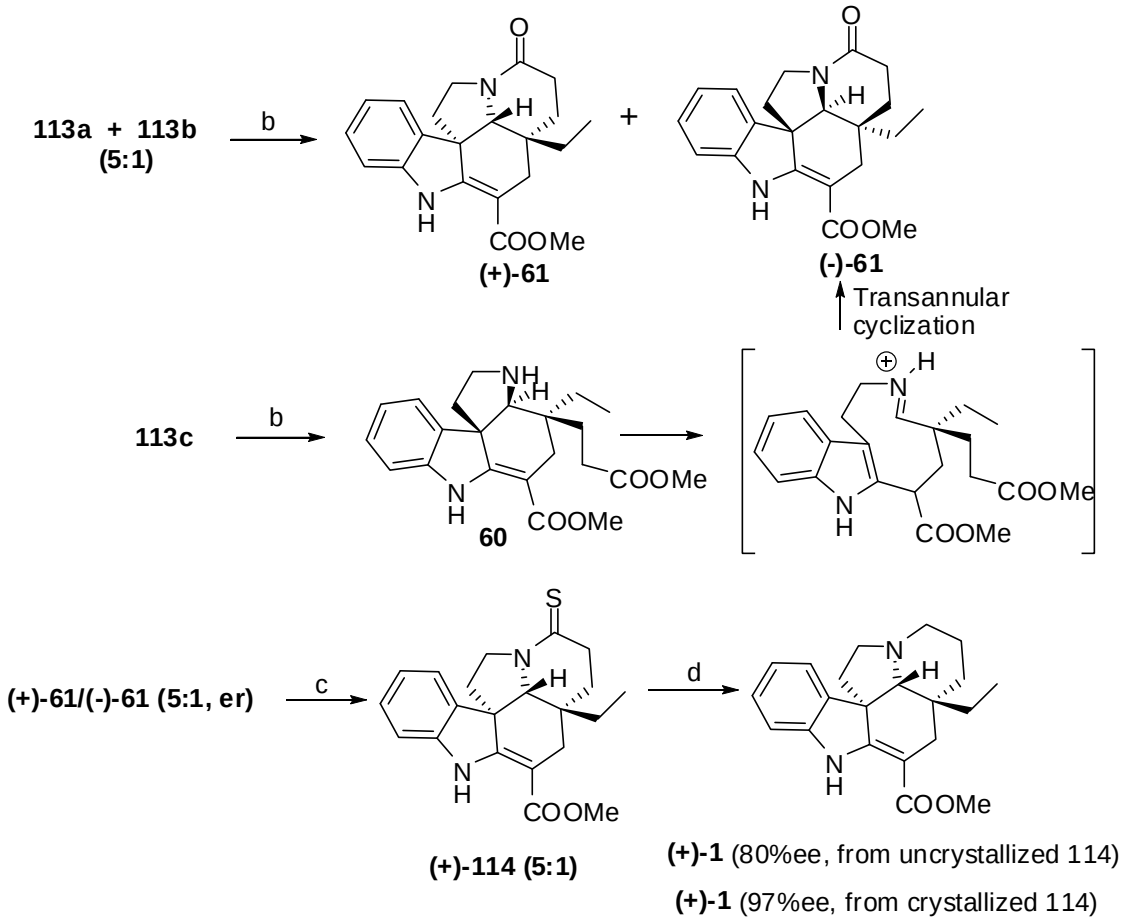
Reagents and conditions: (a) K, t-BuOH, Reflux, 12 h, EtOH-HCl, 97% (b) CH_3COOH, HCl (conc), reflux, 4 h, 80% (c) Na, EtOH, rt, 15 min, 74% (d) DIBAL-H, DCM, -78 °C, 90 min, 31% (e) $B(OH)_3$, MeOH, 20 °C, 2 days, ***68*** *(48%),* ***69*** *(14%) (f) CCl_4, PPh_3, $CHCl_3$, 3 h, 70 °C, 81% (g) pyridine, $NaBH_4$, 70 °C, 2.5 h, 55% (h) PPh_3, CCl_4, CH_3CN, 68%.*

2. Chiral auxiliary approach: (Kuehne *et al*. *J. Org. Chem*. 1998, *63*, 2172)[16]

(10 steps, 13.6% overall yield)

Indoloazepines have been extensively studied and utilized by Kuehne as central precursors to many families of indole alkaloids. Condensation of indoloazepine **111** bearing the chiral *N*-substituents [1-(*R*)-[(*S*)-(diphenylphosphino)-ferrocenyl]-ethyl] with 2-ethyl-4-(methoxy-carbonyl) butanal (**33**) gave diastereomeric mixture of tetracyclic intermediates **113** through an intramolecular Diels-Alder reaction (reverse electron demand) of a secodine type intermediate **112** which upon functional group transformation gave vincadifformine (**1**) (Scheme-13).





Scheme-13 Kuehne's approach (chiral auxiliary)

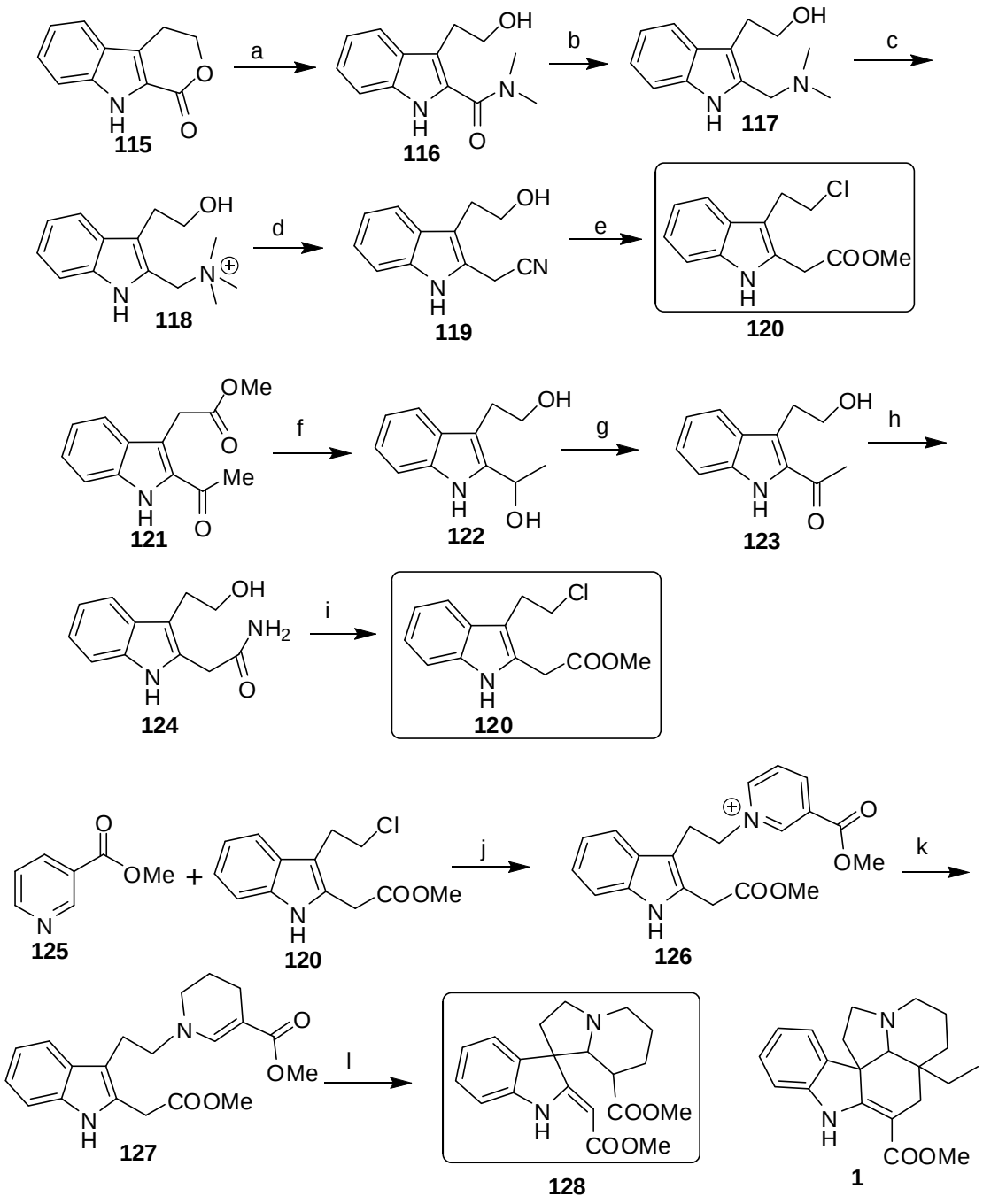
Reagents and conditions: (a) Benzene (anhy), reflux, 24 h (b) CH_3COOH (glacial), 100 °C, 10 min, 97% (c) P_4S_{10}, THF (dry), rt, 19 h, 88% (d) Raney-Ni, EtOH, rt, 16 h, 87%.

III. Miscellaneous approaches:

1. **Ernest Wenkert' s approach for the synthesis of Aspidosperma and Strychnos alkaloid models:** (*J. Am. Chem. Soc*. **1968**, *90*, 5251)[17]

The author executed synthesis of some of aspidosperma model compounds by coupling of indole ester **120** with the methyl nicotinate (**125**). The intermediate **126** upon hydrogenation and treatment of acid led to the formation of tetracyclic compound **128**,

which ideally suited for conversion into pentacyclic systems characteristic of aspidosperma alkaloids, e.g., vincadifformine (**1**) (Scheme-14).

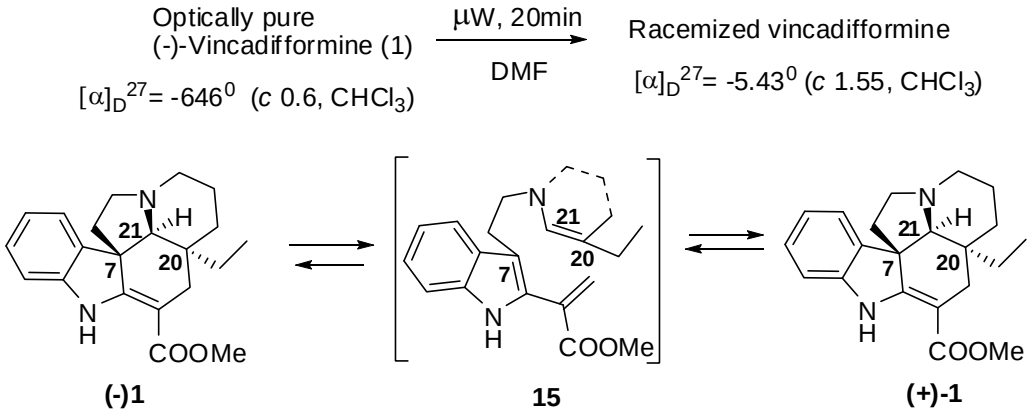


Scheme-14 Wenkert's approach for the synthesis of aspidosperma model compounds

Reagents and conditions: (a) MeOH (absolute), Dimethyl amine (gas), rt, 7 days (b) LAH, THF, reflux, 12 h (c) MeI, EtOAc, 50 °C, 1 h (d) KCN, MeCN, reflux, 18 h (e) MeOH:H_2O (100:1), HCl gas (sat), rt, 48 h (f) LAH, THF, reflux, 3 h (g) MnO_2, $CHCl_3$, rt, 18 h (h) Sulfur, NH_4OH, dioxane, sealed tube, 120 °C, 18 h (i) CH_3COONa, Ac_2O, rt, 12 h, $POCl_3$, $CHCl_3$, reflux, 18 h (j) MeOH, 18 h, reflux (k) TEA, Pd/C, H_2, rt (l) MeOH, HCl (gas), rt, 4 h.

2. Racemization of (-)-vincadifformine (**Takano *et al.*** *Chemistry Letters*, **1989**, 87)[18]

The author has observed the inversion or racemization of the (-)-**1** to (+)-**1** in DMF by heating under microwave oven where inversion is shown to proceed through secodine intermediate **15** involving retro as well as Diels-Alder reaction (Scheme-15).

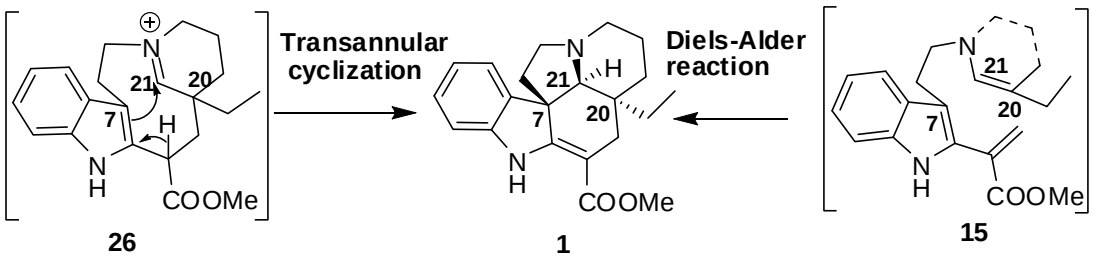


Scheme-15: Racemization of optically active vincadifformine in Microwave condition

2A.5 Summary:

From the above discussions, it is evident that there are only two major routes to construct the vincadifformine stereoselectively (Scheme-16).

1. Transannular cyclization: The relative stereochemistry of C_7 and C_{21} were controlled relative to C_{20}.
2. Diels-Alder reaction: Stereospecific construction of vincadifformine skeleton with the formation of 2 new rings, 3 new stereogenic centres through a biomimetic secodine type intermediate.



Scheme-16: possible mode of cyclization to obtain vincadifformine.

The auxiliary or chiral substrate controlled cycloaddition of secodine type intermediates to optically active vincadifformine limits the further usage of this method due to the poor diastereoselectivity in the key step.

Proceeding sections discuss comprehensively the development of a novel strategy to synthesize racemic and optically active vincadifformine through iminium ion cascade reaction.

Section – B

Total synthesis of (±)-vincadifformine through an iminium ion cascade reaction

2B.1 Introduction:

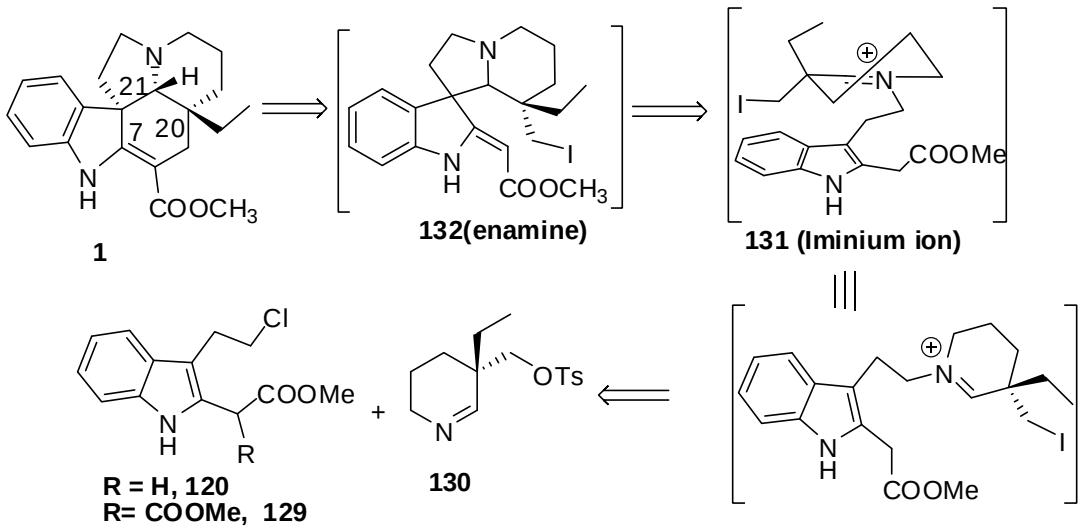
Total synthesis of biologically active complex natural products involving cascade reactions with the formation of multiple bonds or multiple rings has been the subject of intense research in recent years.[19] The design of cascades to obtain specific biologically active structurally complex natural product poses significant intellectual challenge and can be one of the most impressive activities in natural product synthesis. Moreover cascade reactions are more advantageous in the total synthesis of structurally complex natural products owing to their intrinsic superb synthetic efficacies manifested by the formation of two or more rings within one operational step.

Particularly, for the synthesis of vinacadifformine literature scrutiny indicates that the majority of the approaches proceed via intramolecular Diels-Alder (DA) type cycloaddition reaction of biogenetically postulated secodine intermediates. Poor diastereoselectivity in the key step discouraged further usage of this protocol. Therefore, in a quest to overcome the synthetic challenge posed by this molecule and to develop a non-biogenetic route for the synthesis of vincadifformine (**1**), we looked the problem entirely from a different angle and devised a cascade strategy as outlined retrosynthetically in Scheme-17.

2B.2 Retrosynthetic analysis:

We envisioned the cascade protocol for the construction of vincadifformine and its structural analogous by coupling of indole fragment **120** or **129** with imine fragment **130**

constructing two new rings, two new stereogenic centers and three new sigma bonds in a single operation through the sequential involvement of reactive intermediates **131** and **132**.

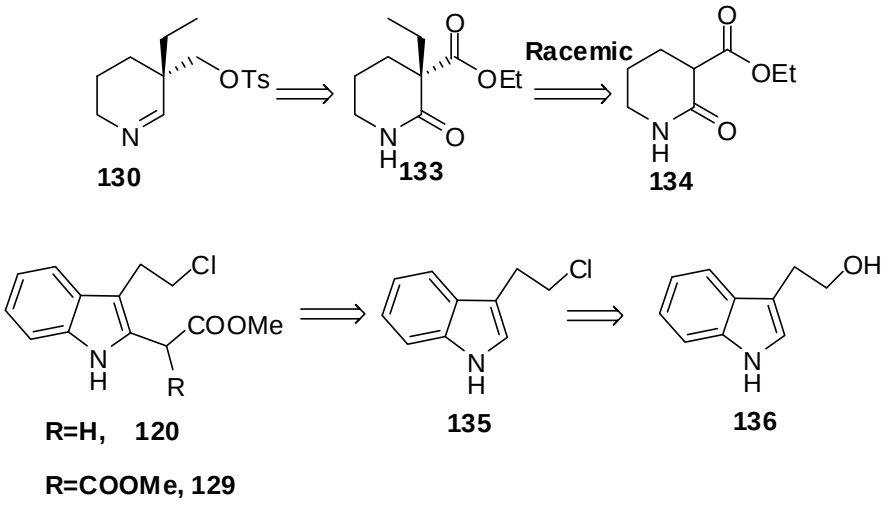


Scheme-17 Retrosynthetic analysis of vincadifformine (**1**)

Having worked out the cascade route towards **1** as charted out retrosynthetically in Scheme-17, we embarked upon the synthesis of key building blocks required for the total synthesis.

The requisite key precursor imine **130** could be obtained from the ester **133** by simple functional group transformation. The construction of quaternary stereo centre to obtain (±)-**133** could be easily envisioned from commercially available ethyl 2-oxo 3- piperidine carboxylate (**134**).[20, 21]

The indole fragment **120**, although, reported in several steps, could be achieved in single step from 3-(2-chloro ethyl) indole (**135**) using Kuehne's protocol,[22] which could in turn be obtained by chlorination of tryptophol (**136**) (Scheme-18).



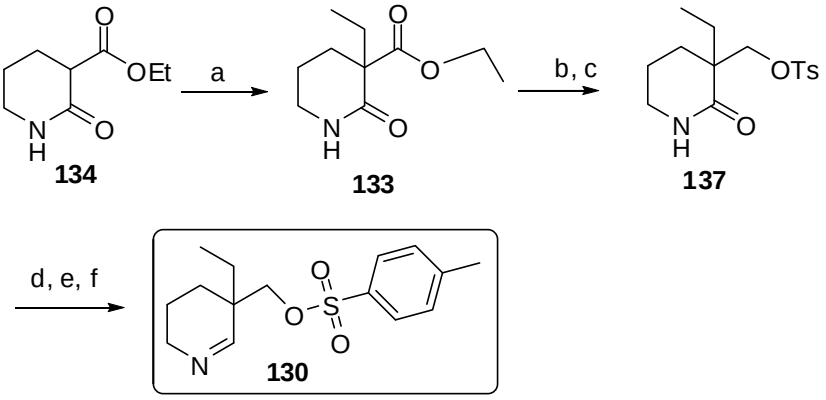
Scheme-18: Retrosynthetic analysis of racemic imine **130** and indole fragments **120/129**

2B.3 Results and Discussion:

Our synthesis started with the assembling of key precursors imine **130** and indole fragments **120/129**.

Synthesis of (3-ethyl-3, 4, 5, 6-tetrahydropyridin-3-yl) methyl 4-methyl benzene sulfonate: (±)-130 (Scheme-19).

The synthesis of imine (±)-**130** commenced with the commercially available ethyl 2-oxopiperidine 3-carboxylate (**134**) by following the steps as shown in Scheme-19.



Scheme-19 Synthesis of (±)-**130**

Reagents and conditions (a) n-BuLi, THF, EtI, -78 °C→ rt→ reflux, 69% (b) $NaBH_4$, $CeCl_3$ $7H_2O$, EtOH, rt, 2 days, 87% (c) pyridine, p-TsCl, rt, 48 h, 84% (d) $(Boc)_2O$, DMAP, TEA, rt, 12 h, 95% (e) DIBAL-H, THF, -78 °C, 4 h, 97% (f) TFA, DCM, rt, 4 h, 90%.

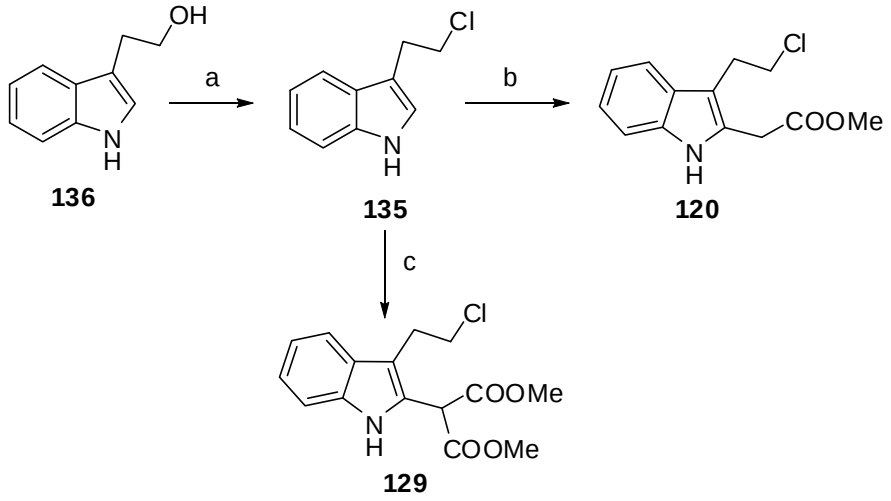
Construction of quaternary stereo centre in lactam **134** was carried out by enolate generation using *n*-BuLi in anhydrous THF at -78 °C, followed by quenching with ethyl iodide which afforded **133** in 69% yield. The ester of **133** was reduced to corresponding primary alcohol using Luche conditions[23] which upon tosylation[24] using *p*-TsCl in pyridine afforded **137** as a white solid in 84% yield. The conversion of amide functionality of the **137** to imine function was easily achieved by simple *N*-Boc protection followed by DIBAL-H reduction[25] and treatment of trifluroacetic acid afforded **130** in 77% yield.

In the ^{1}H NMR spectrum of (±)-**130,** singlets at δ 7.37 and 2.43 were attributed to imine (-N=C<u>H</u>-C-) and (Ar-C<u>H</u>$_3$) protons, respectively. The ^{13}C NMR spectrum displayed most down field signal at δ 164.7, assigned to imine carbon (-N=<u>C</u>H-C-). In addition, ESI-Mass spectrum confirmed the structure of product (±)-**130** by exhibiting two adduct ions at 296.4600 $(M+H)^+$, 318.4808 $(M+Na)^+$**.**

Syntheses of methyl 2-(3-(2-chloroethyl)-1H-indol-2-yl) acetate (120) and dimethyl 2-(3-(2-chloroethyl)-1H-indol-2-yl) malonate (129).

With the racemic imine segment in hand we focused to synthesize indole fragments **120** and **129**. The indole fragment **120,** although, reported in several steps,[17,26] we were able to obtain it in single step from 3-(2-chloroethyl) indole (**135**), synthesized from commercially available tryptophol (**136**)[27] by chlorination using *N*-chlorosuccinimide and triphenyl phosphine in anhydrous THF. Reaction of **135** with *tert*-butyl hypochlorite followed by the addition of 1-[*tert*-butyl dimethylsilyloxy]-1-methoxy ethene (**139**)[28] in the presence of BF_3:OEt_2 afforded the desired **120** in 61% yield by following the mechanistic pathway as shown in Scheme 21. Compound **129** was also synthesized in

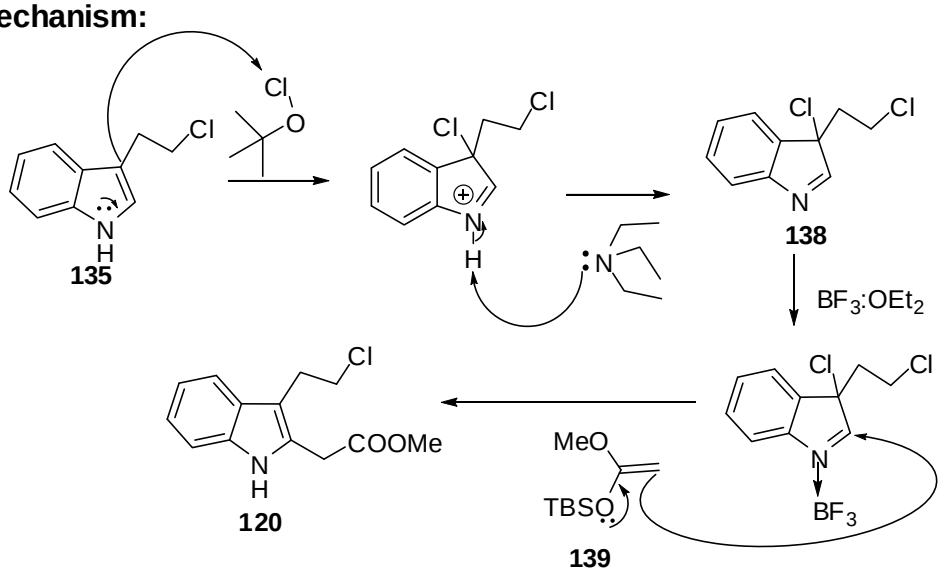
86% yield by utilizing the same protocol by using lithium dimethyl malonate as a nucleophile in the presence of either BF_3:OEt_2 or $ZnCl_2$ (anhydrous) as a Lewis acid (Scheme-20).



Scheme-20 Synthesis of indole segments **120** and **129**

*Reagents and conditions:- (a) NCS, PPh_3, THF, 85%; (b) t-BuOCl, BF_3:OEt_2, 1-[tert-butyl dimethylsilyloxy]-1-methoxy ethene (**139**), THF, -78 °C → rt, 61%.(c) t -BuOCl, BF_3:OEt_2, $ZnCl_2$, Lithium dimethyl malonate, THF, -78 °C → rt, 86%.*

Mechanism:



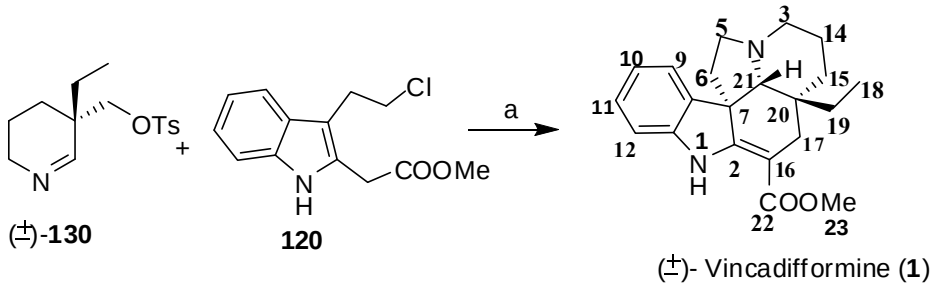
Scheme - 21: Plausible mechanistic path involved in the syntheses of **120** and **129.**

The ^{1}H NMR spectrum of **120** showed broad singlet at δ 8.64 and sharp singlets at δ 3.83, 3.75, integrating for one proton, two protons and three protons, respectively, were attributed to (-NH-), (-C-CH$_2$-COO) and (-COOCH$_3$) protons. The DEPT experiment confirmed total three methylene carbons at δ 27.8, 44.5 and 31.6, assigned to (-C-CH$_2$-CH$_2$-Cl) and (-C-CH$_2$-COO-), respectively. In addition, the exact molecular mass ($C_{12}H_{14}O_2NCl$, *m/z:* 251.05374) obtained by HRMS (EI, 70 eV) corroborated the structure of **120**. Similarly, ^{1}H NMR spectrum of **129** showed sharp singlets at δ 5.0 (-C-CH-COO-) and 3.79 COOCH$_3$), integrating for one proton and six protons, respectively. The exact molecular mass $C_{15}H_{16}O_4NCl$ *m/z* 309.07453 obtained by HRMS (EI, 70 eV) further supported the structure of **129**.

Synthesis of (±)-vincadifformine by coupling of imine fragment 130 and indole fragment 120/129:

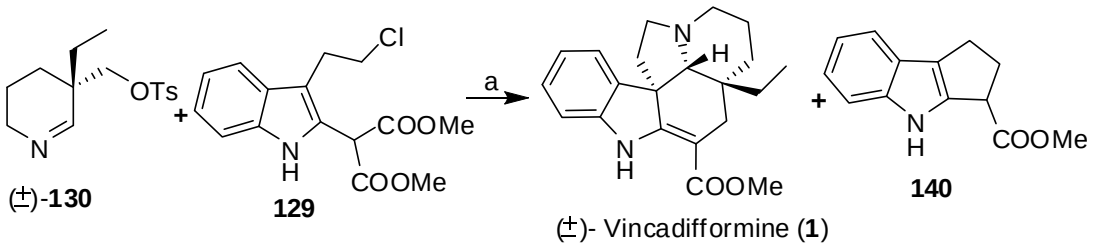
The central feature of our proposed synthetic strategy rests upon the stereoselective formation of the aspidosperma skeleton by coupling of the racemic imine and the indole segments through cascade reaction. The coupling of imine (±)**-130** and indole fragment **120** in dry acetonitrile afforded trace amount of vincadifformine after refluxing for 24 h. Several optimization experiments using solvents such as HMPA and NMP including additives like sodium bicarbonate, DMAP, TBAI etc. also failed to improve the yield. After much experimentation, we found that reaction did proceed in refluxing DMF in the presence of potassium iodide producing vincadifformine **(±)-1** as a single diastereomer in 35% yield (Scheme-22). In a bid to improve the yield of **(±)-1,** we also tried coupling of **(±)-130** with **129** in DMF in presence of potassium iodide, however, yield of **1** could not be improved. Further attempt, by adding triethylamine hydrochloride or p-toluene sulfonic acid to the reaction mixture didn't help either, albeit, decarboxylation (Krapcho decarboxylation) followed by intramolecular cyclization producing **140** appears to be faster than the imine *N*-alkylation (Scheme-23) resulting poor yield of **1**.

The moderate yield of (±)-**1** through this cascade reaction possibly results due to the decomposition of imine fragment during the reaction as evidenced by recovery of indole fragment and increase in the yield of (±)-**1** when imine fragment **130** was used in excess.



Scheme-22: Final coupling reaction: Synthesis of (±)-vincadifformine

Reagents and conditions:- (a) KI, DMF, 150 °C, 3 h



Scheme-23: Final coupling reaction: Synthesis of vincadifformine.

Reagents and conditions: (a) KI, DMF, 150 °C, 3 h

The structural assignments of **1** were based on the detailed spectral analyses. For example**,** the IR spectrum showed absorption bands at 3368 and 1674 $cm^{-1}$are characteristic N-H stretching and C=O stretching of the ester. The ^1H NMR spectrum displayed aromatic protons as a multiplet between δ 7.18-6.78, H_{21} at δ 2.45 as a singlet and H_{18} at 0.56 as a triplet (J = 6.8 Hz) were assigned for three protons respectively. The broad singlet at δ 8.89 and sharp singlet at 3.75 integrating for one and three protons were attributed to (-NH-) and (-COOC$\underline{H}_3$). The multiplets between δ 2.08-1.2 integrating for totally six protons attributed to H_6 (2H), H_{14} (2H) and H_{15} (2H) protons. The H_5 (2H) and H_3 (2H) protons appeared as multiplets at δ 3.12, 2.4, 2.91 and 2.53.

^{13}C NMR spectrum showed a total of twenty one peaks at δ 169.3, 167.9, 143.4, 138.1, 127.5, 121.1, 120.6, 109.4, 92.7, 72.8, 55.6, 51.8, 51.1, 50.8, 45.4, 38.3, 33.0, 29.4, 25.6, 22.3, 7.2 (two methyl, seven methylene, five methine, seven quaternary carbons).

The ESI-Mass spectrum of (±)-**1** showed one adduct ion at 339.4159 $(M+H)^+$.

All the spectroscopic data were in accord with the literature report.[17]

2B.4 Summary:

We have successfully achieved the synthesis of (±)-vincadifformine in total nine steps with 14.6% overall yield *via* iminium ion triggered cascade reaction involving the coupling of 3, 3-substituted tetrahydropyridine **130** and indole derivative **120/129** which allows simultaneous construction of two new rings, two new stereogenic centers and three new sigma bonds in one pot with complete stereochemical control.

This encouraging result prompted us to attempt the synthesis of (+)-**1** utilizing optically pure **130**. The synthesis of enantiomerically pure **130** and its successful coupling with **120** to obtain enantiomerically pure vincadifformine is described in the next section.

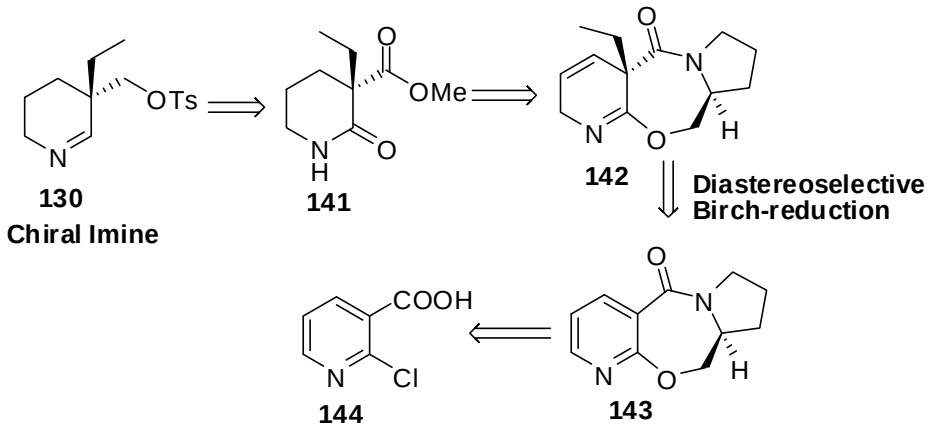
Section – C

Total synthesis of (+)-vincadifformine

2C.1 Introduction:

As described in the introduction part of the previous section, till date only two strategies for asymmetric synthesis of optically active **1** is reported[15, 16] which proceed involving intramolecular Diels-Alder (DA) cycloaddition reaction via biogenetically postulated secodine type intermediate. However, auxiliary controlled or chiral substrate controlled cycloaddition of secodine intermediate have generally led to the formation of mixture of diastereomers which limits further usage of these biomimetic approaches. In a quest to overcome the synthetic challenge and to develop a non-biogenetic route for the synthesis of optically active (+)-**1**, we visualized that if **130** can be obtained in optically pure form and the coupling involves the iminium ion cascade, the reaction would produce optically pure **1.**

The important part of this strategy would be the effective preparation of deceptively simple looking chiral imine fragment **130** in excellent enantiomeric excess. Interestingly, survey of literature revealed that the asymmetric synthesis of this type of skeleton having quaternary stereocenter is not known so far. Therefore, we designed an innovative strategy for chiral **130** through Birch reduction- alkylation of the chiral nicotinic acid derivative **143** as depicted retrosynthetically in Scheme –24.



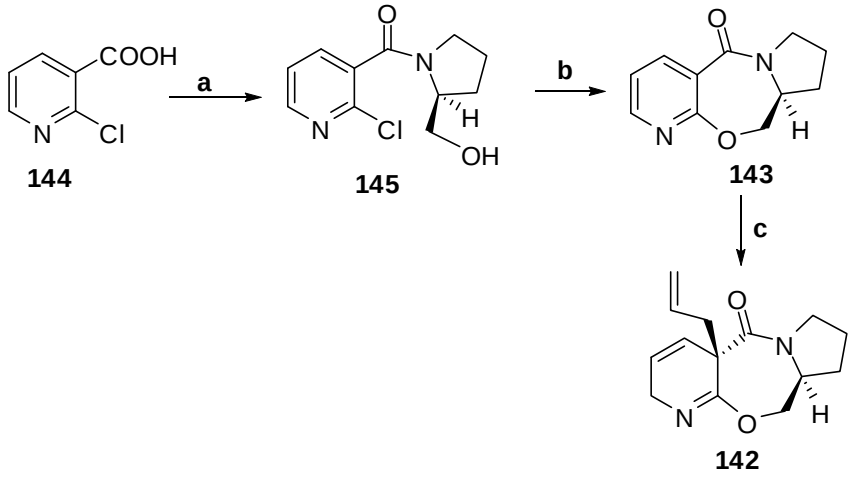
Scheme: 24 Retrosynthetic analysis of chiral imine segment **130**

2C.2 Results and Discussion:

The synthetic efforts and important observations during the synthesis of deceptively simple looking chiral **130** are explained comprehensively below:

Synthesis of (4a*S*, 9a*S*)-4a-Allyl-4a, 7, 8, 9, 9a, 10-hexahydropyrido [3, 2-*f*] pyrrolo [2, 1-*c*] [1, 4] oxazepin-5(2H)-one (142):

The reaction of **144** with (*S*)-prolinol[29] in presence of ethylchloroformate and triethyl amine furnished **145** (98%) which on treating with sodium hydride in THF at reflux underwent addition –elimination sequence to provide cyclic ether **143** in excellent yield.



Scheme-25 Synthesis of **142**

Reagents and conditions:- (a) ClCOOMe, TEA, (S)-prolinol, CH_2Cl_2, 0 °C→rt, 98% (b) NaH, THF, reflux, 99% (c) Na, THF, Liq NH_3, allyl bromide, -78 °C, 46%

In the ^{1}H NMR spectrum of **143** three doublet of doublet at δ 8.61 (*J* = 7.8, 2.0 Hz), 8.36 (*J* = 4.5, 2.0 Hz) and 7.10 (*J* = 7.8, 4.6 Hz), integrating for one proton each, were attributed to three aromatic pyridine protons. The two sets of doublet at δ 4.6 (*J* = 11.5 Hz) and 4.07 (*J* = 11.7 Hz), integrating to one proton each, were assigned to diastereotopic -O-C$\underline{H}_2$-CH-. High resolution mass spectrum (HRMS-EI, 70 eV) confirmed the exact mass (204.08954) and molecular formula ($C_{11}H_{12}O_2N_2$)**.**

As per our synthetic planning, **143** was subjected to Birch reduction-alkylation at -78 °C using ethyl iodide, however, to our utter surprise the expected product was obtained only in ≈6% yield. We attributed the low yield of the alkylation product to the lower electrophilicity of ethyl iodide. Therefore, the same reaction was attempted using allyl bromide for the allylation of Birch reduction intermediate from **143** and succeeded in producing **142** in 46% yield and high diastereomeric ratio (99:1) (Scheme-25), determined by HPLC analysis (Atlantis RP-18 (250 × 4.6mm) column, acetonitrile-water (40:60) as an eluent 1.0 mL/min, λ = 224nm, 25 °C). Crystallization of **142** using a mixture of dichloromethane - *n*-pentane produced single diastereomer as a colorless solid (m.p. 105.5-106.5°C).

Although, enantioselective construction of all carbon quaternary stereocenter in the cyclohexane ring employing Birch-reduction alkylation of benzoic acid derivatives is known,[30] to the best of our knowledge, this is the first report of its kind for generating substituted piperidine system.[31] The excellent diastereoselectivity in the formation of **142**, presumably, results from the rigid molecular architecture of enolate intermediate where proline stereocentre directs the alkylation preferentially at *β*-face.

IR spectrum of **142** showed characteristic -C=O stretching and -N=C- stretching absorption bands at 1627 and 1689 cm^{-1}, respectively. ^{1}H NMR spectrum showed three multiplets at δ 5.81, 5.58 and 5.04, integrating for two protons, one proton and two protons, respectively, which were assigned to ($-CH_2-C\underline{H}=C\underline{H}-C-$), ($-CH_2-C\underline{H}=CH_2$) and ($C\underline{H_2}=CH-CH_2$) protons, respectively. The doublet appearing at δ 2.66 (J = 7.5 Hz), integrating for two protons, was attributed to ($-C-C\underline{H_2}-CH=CH_2$) protons. The ^{13}C NMR and DEPT experiments confirmed three quaternary carbon resonances at δ 169.6, 161.6 and 52.2 and were assigned to amide carbonyl (-<u>C</u>=O), imine carbon (N=<u>C</u>-) and quaternary carbon stereocentre (N=C-<u>C</u>-), respectively. The carbon signals appearing at 132.2, 126.9, 125.17 and 119.3 were assigned to methine and methylene carbons of alkene moiety, respectively. High resolution mass spectrum (HRMS-EI, 70 eV) confirmed the exact mass (*m/z*: 246.13783) and molecular formula ($C_{14}H_{18}O_2N_2$)**.**

Based on the extensive NMR 2D-techniques such as HETCOR, COSY and NOESY, the stereochemical assignments of **142** were made as shown in the Figure- 3.

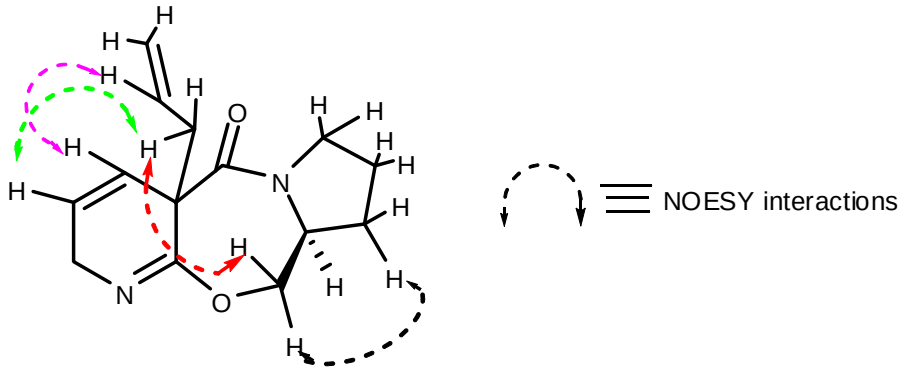


Figure: 3 Selected NOESY cross peaks in **142**

Finally, the structure of **142** was also confirmed unambiguously through x-ray crystallographic analysis (see ORTEP drawing Figure-4)

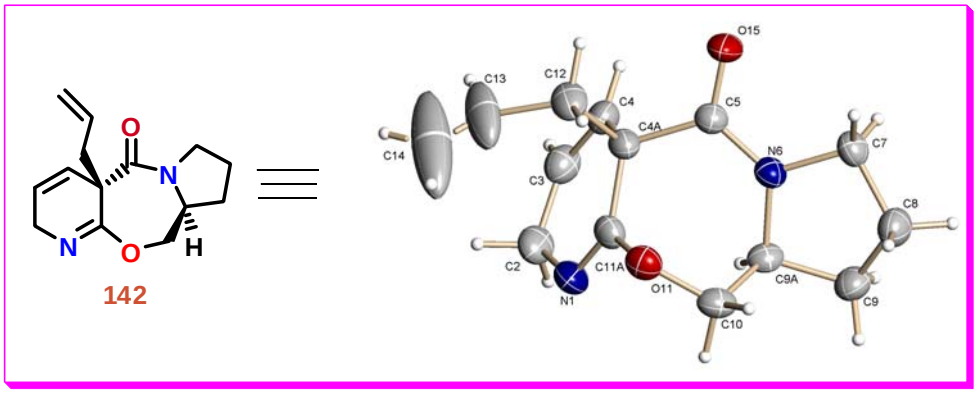


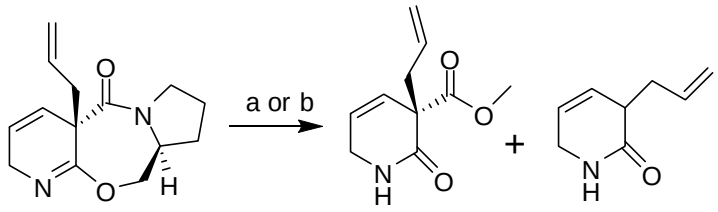
Figure –4 *ORTEP diagram of* ***142.*** *Ellipsoids are drawn at 50% probability.*

(*S*)-Methyl 3-allyl-2-oxo-1, 2, 3, 6-tetrahydropyridine-3-carboxylate (146):

After complete structural elucidation of **142**, we decided to remove the chiral auxiliary to obtain corresponding lactone **146.** Towards this end, we attempted first[30] its hydrolytic cleavage by stirring with H_2SO_4: MeOH (1:8) which led to the cleavage of both ether as well as amide functionalities producing **146** (19% *ee*, 45% yield) and achiral decarboxylated **147** (40% yield). Enantiomeric purity of **146** was determined by HPLC

analysis {Chiralcel OD-H (250 × 4.6mm) column, isopropanol–pet ether (10:90) as an eluent}, 0.5 mL/min (265psi), λ = 220nm, 25 °C, the retention times of isomers being 27.36 and 52.35 minutes.

The efforts to optimize this reaction by changing the percentage of acid or changing reaction temperature didn't provide the desired product in satisfactory yield as well as enantioselectivity (Scheme-26).

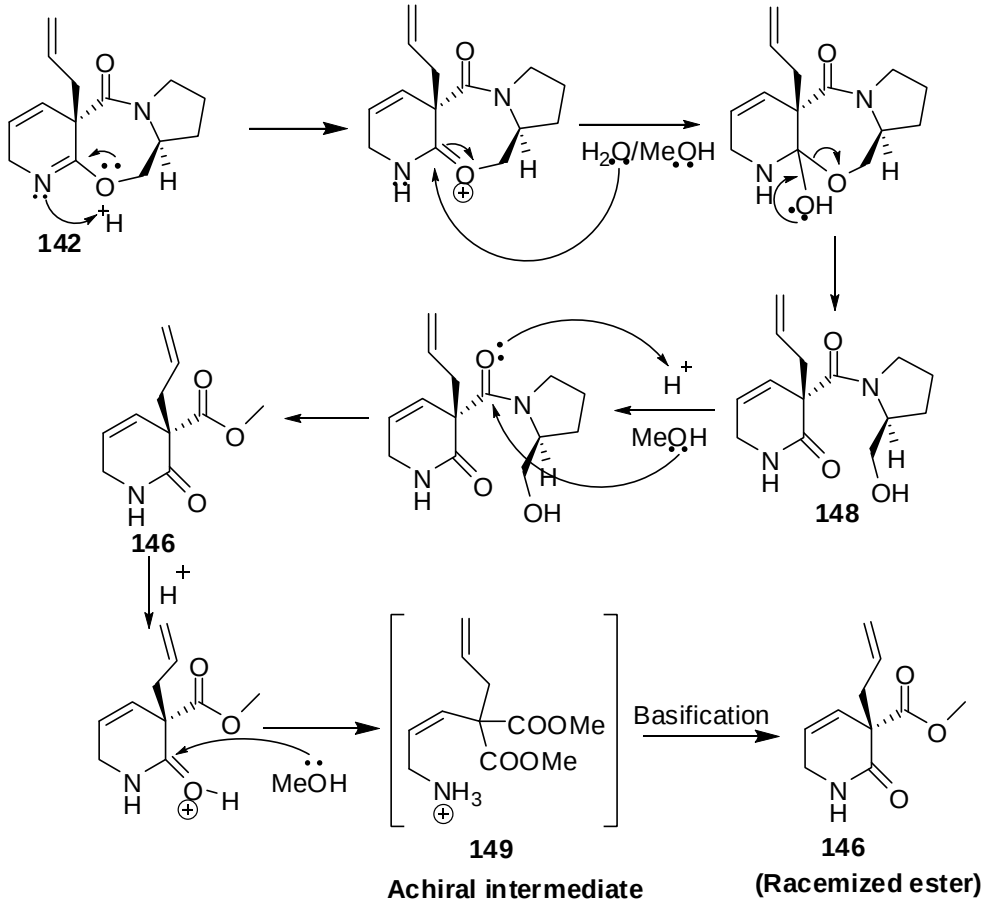


142 (>99%de) → **146** (19%ee) + **147**

Scheme: 26 Acid mediated cleavage of chiral auxiliary in compound **142.**

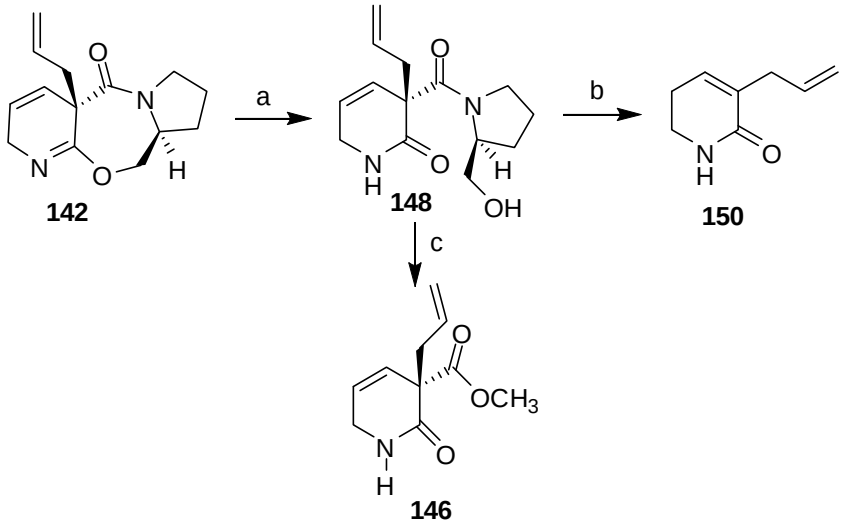
Reagents and conditions: (a) 80% H_2SO_4: MeOH (1:8), rt, 75 h, 45% (b) Conc HCl: MeOH (1.5:8.5), rt, 4 days 40% yield.

The loss of chirality presumably resulted by the involvement of achiral diester **149**, formed by further methanolysis of **146** and re-cyclization (Scheme-27).



Scheme-27: Loss of chirality: plausible mechanism for racemization of ester (**146**)

Due to above mentioned difficulties in the removal of chiral auxiliary in single step, we decided to adopt a two step procedure for conversion of **142** to **146**. This required the cleavage of the ether moiety of **142** first which was achieved (**148**, 85% yield) by stirring with CH_3COOH: H_2O: THF (8:1:1) at ambient temperature. Subsequently, methanolysis of **148** was attempted using sodium methoxide in methanol which gave undesired achiral decarbonylated product **150**. Ultimately, **148** on treatment with copper (II) triflate and methanol at ambient temperature successfully led to the formation of **146** in excellent yield (87%) as well as enantioselectivity (>99% *ee*) $[\alpha]^{23}_{D}$= + 82.81 (*c* = 1.1, $CHCl_3$). The enantiomeric excess was measured by HPLC analysis and compared with the racemized ester **146** (Scheme-28).



Scheme 28: Transition metal mediated cleavage of chiral auxillary in **148**

Reagents and conditions: (a) CH_3COOH: THF: H_2O, rt, 20 h, 89% (b) NaOMe, THF or MeOH, rt, 50 h, 65% (c) $Cu(OTf)_2$, MeOH (anhy), rt, 48 h, 87%.

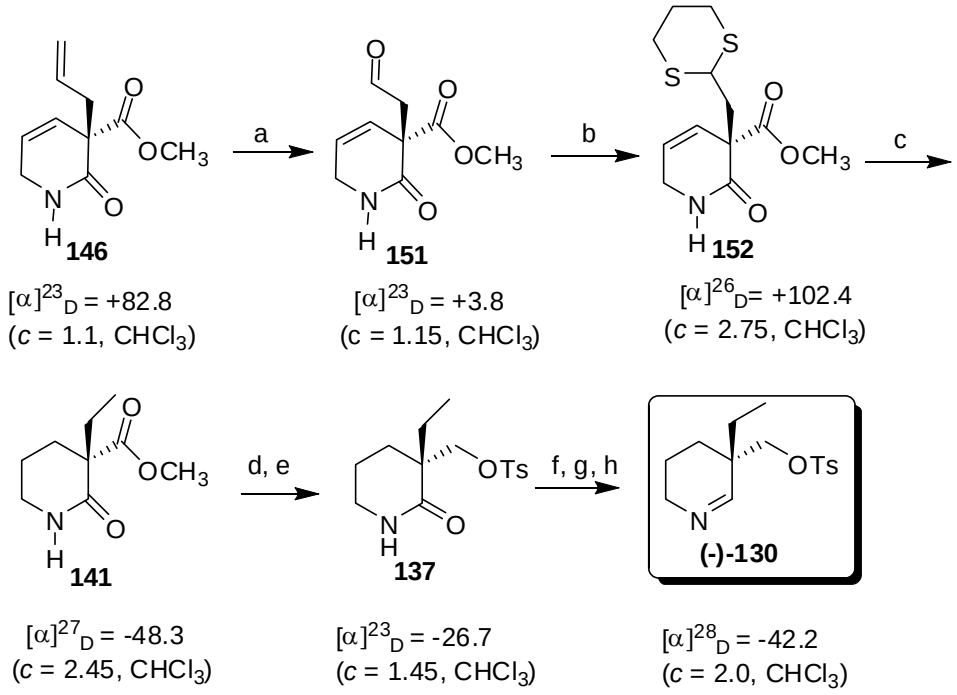
Mechanistically it may be rationalized copper (II) likely chelates with the nitrogen of the amide moiety increasing the electophilicity of the carbonyl group (by deconjugation of the nitrogen) which assists in the departure of amino group from the tetrahedral intermediate.[32]

The IR spectrum of **146** displayed strong absorption bands at 3220 cm^{-1} (N-H), 1677 cm^{-1} (lactam C=O) and 1735 cm^{-1} (ester C=O). In the ^1H NMR spectrum alkene protons appeared as three multiplets at δ 5.94 (1H), 5.63 (2H) and 5.08 (2H). The broad signal at δ 6.66 was attributed for (-N<u>H</u>) proton of lactam moiety. A multiplet at δ 3.97 (2H) and a singlet at 3.71 (3H) were attributed to (-NH-C<u>H</u>$_2$-) and (-COOC<u>H</u>$_3$) respectively. The other two sets of doublet of doublet appeared at δ 2.95 (dd, J = 7.3, 13.7 Hz) and 2.60 (dd, J = 7.2, 13.7 Hz) were assigned for diastereotopic allylic methylene protons (-C-C<u>H</u>$_2$-CH=CH$_2$). The ^{13}C NMR and DEPT experiments confirmed quaternary carbon resonances at δ 171.0, 168.8 and 54.1 for amide carbonyl carbon (-NH-<u>C</u>=O), ester carbonyl (-<u>C</u>OO) and (CO-<u>C</u>-COO), respectively. The signals appearing at δ 132.5, 125.6, 123.2 and 119.2 were attributed to alkene carbons (<u>C</u>H$_2$=CH), (C-<u>C</u>H=CH), (C-

CH=CH) and (CH_2-CH=CH_2). The signals at δ 52.8, 43.4 and 39.5 were assigned to (-$COOCH_3$), (-NH-CH_2-CH-) and (CH_2=CH-CH_2-C) carbons. High resolution mass spectrum (HRMS-EI, 70 eV) confirmed its exact mass (*m/z*: 195.08821) and molecular formula ($C_{10}H_{13}NO_3$).

Synthesis of chiral imine (-)-130:

Having synthesized desired optically active ester **146**, we turned our attention towards its conversion to chiral imine **130** (Scheme-29). Towards this end, the terminal olefin was one carbon degraded reductively following the sequence of olefinic oxidation using (OsO_4/$NaIO_4$, Lemieux-Johnson),[33] dithioketalization of the resultant aldehyde and reductive desulfurization[34] (Raney-Nickel, H_2, EtOH, reflux) afforded **141** in 53% yield. We adopted the same procedure as described earlier to transform **(-)-141** to **130** $[\alpha]^{28}_D$= -42.22 (*c* = 2.0, $CHCl_3$) (ee > 99%), determined by HPLC analysis [(Chiralcel OJ-H (250×4.6 mm) column, isopropanol–pet ether (15:85) as an eluent), 0.7 mL/min (33 kgf), λ=254nm, 25 °C.

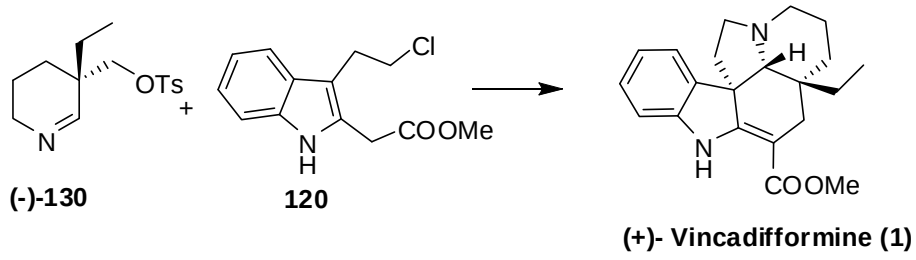


Scheme: 29 Synthesis of chiral imine **130** from ester **146**

Reagents and conditions: (a) OsO_4, $NaIO_4$, 2, 6- lutidine, Dioxane: H_2O, rt, 4 h, 70% (b) 1,3-propane dithiol, BF_3:OEt_2, DCM, reflux, 12 h, 81% (c) Raney-Ni, Ethanol, reflux, 7 h, 94% (d) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, rt, 2 days, 87% (e) p-TsCl, Pyridine, CH_2Cl_2, rt, 48 h, 84% (f) $(Boc)_2O$, DMAP, TEA, DCM, rt, 12 h, 95% (g) DIBAL-H, THF, -78 °C, 4 h, 97% (h) TFA, DCM, rt, 4 h, 90%.

Synthesis of (+)-Vincadifformine (1)

With the advanced chiral imine (-)-**130** in hand, we turned our attention of testing our hypothesis of imminium ion triggered cascade reaction to achieve optically active vincadiffromine. Coupling of chiral imine (-)-**130** with indole fragment **120** in DMF in presence of potassium iodide at 140-150 °C resulted vincadifformine (+)-**1** $\{[\alpha]^{28}_D$ = +550 (*c* 0.2, EtOH) ; lit $\{[\alpha]^{28}_D$ = +542 (*c* 0.04, EtOH)$\}$ in 35% yield (>99 % ee) (Scheme-30).



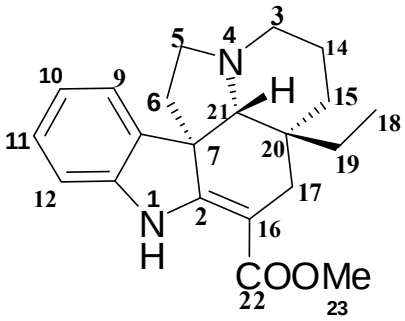
Scheme-30 Synthesis of (+)-vincadifformine

Reagents and conditions: (a) KI, DMF, 150 °C, 3 h

The moderate yield of (+)-**1** possibly results from the decomposition of (-)-**130** during the reaction as evidenced by the recovery of indole fragment and increase in the yield of (+)-**1** when chiral imine (-)-**130** was used in excess.

Based on the extensive spectral studies by NMR 2D-techniques HETCOR, COSY and NOESY, complete structure of (+)-**1** was confirmed. The chemical shift values for each proton and carbon is presented below in the tabular (Table-3) for clarity.

Table: 3 ^{1}H and ^{13}C NMR spectroscopic data for (+)-vincadifformine (1)



Position	δ_H (obtained)	δ_C (obtained)
1	8.89 (bs, 1H)	-
2	-	166.71
3a	3.12 (br d, *J* = 9.3 Hz, 1H)	50.66
3b	2.43-2.35 (m, 1H)	
5a	2.91(t, *J* = 7.2 Hz, 1H),	51.71
5b	2.58-2.52 (m, 1H)	
6a	2.08-2.01 (m, 1H)	45.25
6b	1.69 (dd, *J* = 11.5, 4.5 Hz, 1H)	
7	-	55.45
8	-	137.94
9	6.78 (d, *J* = 7.7Hz, 1H)	121.0
10	7.11 (dt, *J* = 7.5, 1.0 Hz, 1H)	120.45
11	6.84 (dt, *J* = 7.3, 0.75 Hz, 1H)	127.40
12	7.18 (d, *J* = 7.2 Hz, 1H)	109.29
13	-	143.27
14a	1.88-1.81 (m, 1H)	22.14
14b	1.56-1.50 (m, 1H)	
15a	1.80-1.75 (m, 1H)	32.86
15b	1.27-1.20 (m, 1H)	
16	-	92.62

17a	2.71 (d, J = 15.1 Hz, 1H)	25.52
17b	2.26 (dd, J = 15.1, 1.7 Hz, 1H)	
18	0.56 (t, J = 6.8 Hz, 3H)	7.14
19a	0.62 (m, 1H)	29.29
19b	0.96 (m, 1H)	
20	-	38.15
21	2.45 (s, 1H)	72.66
22	-	169.19
23	3.75 (s, 3H)	50.98

High resolution mass spectrum (HRMS-EI) confirmed the exact mass (338.20066) and molecular formula ($C_{21}H_{26}O_2N_2$) of the compound (+)-**1**. The stereochemical assignments for (+)-**1** are based on correlating NOESY cross peaks (Figure-5)

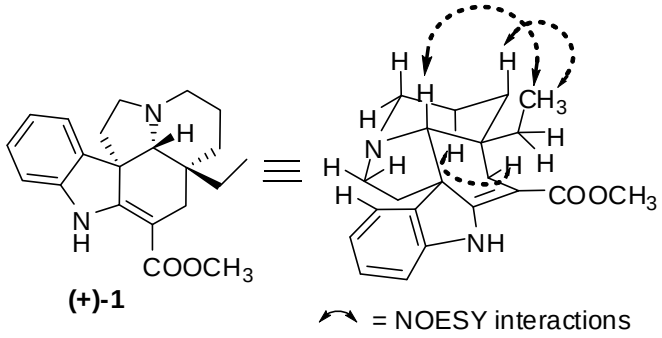
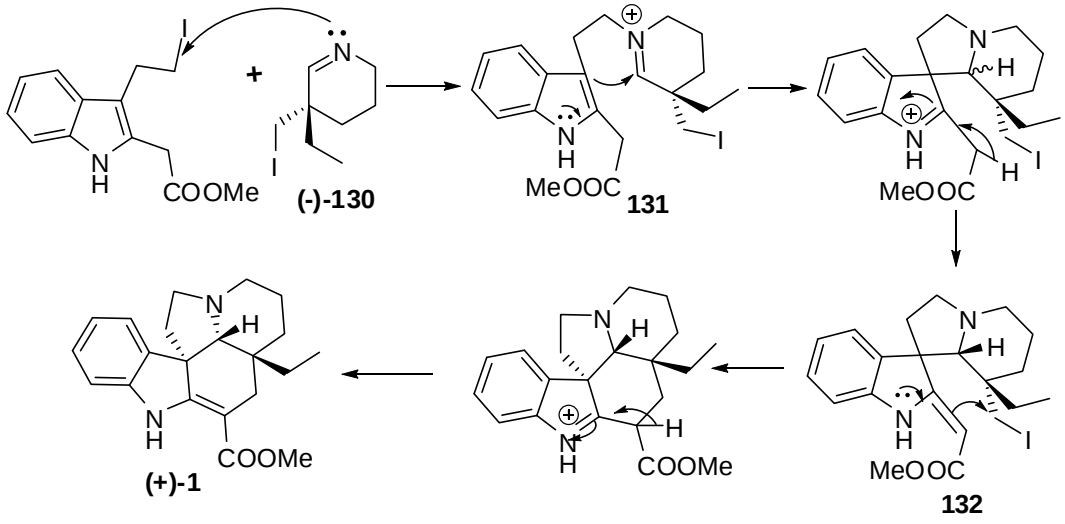


Figure-5 Selected NOESY cross peaks in (+)-**1**

All our spectral data of (+)-**1** were found in complete agreement with the data reported in literature.[17] Chiral HPLC analysis using Chiralcel OD-H column (250×4.6mm), ethanol: petroleum ether: TFA (15:85:0.1), λ=220nm ensured the 99 % enantiomeric purity.

Since, there was no loss of enantiopurity in the formation of (+)-**1,** it was pleasing to note that the reaction underwent as per our synthetic design rather than sequential retro Diels-Alder-Diels-Alder cycloaddition reaction[18] (Scheme-31).



Scheme: 31 plausible mechanism of this iminium ion triggered cascade reaction

In order to provide support to the intermediacy of **132** and its transformation to (+)-vincadifformine (**1**), involving iminium ion cascade sequence, the HPLC-Mass spectroscopic analysis was carried out. Analysis of the reaction mixture after short reaction interval (90 °C, 3 h) by HPLC using Kromasil RP-18 (150×4.6mm) column, methanol: acetonitrile: triethyl ammonium acetate (0.1M. pH-7) (40:40:20) as an eluent, 1.0 mL/min (1140psi), λ=254nm, 25 °C, the retention time of diastereomers being at 8.31 and 9.19 minutes, showed the formation of **132** as a diastereomeric mixture (88.6:11.3). The exact diastereomeric ratio of **132** could not be determined as its formation was always accompanied with some amount of **1**. This observation revealed that according to Curtin-Hammett principle possibly the **132a** and **132b** were interconvertable and one isomer was converted faster to **1** compared to another one. This observation could possibly be visualized through the molecular models of **132a** in which nucleophilic carbon centre of enamine and electrophilic carbon centre of iodomethylene group appears to be in close proximity compared to **132b** (Figure-6).

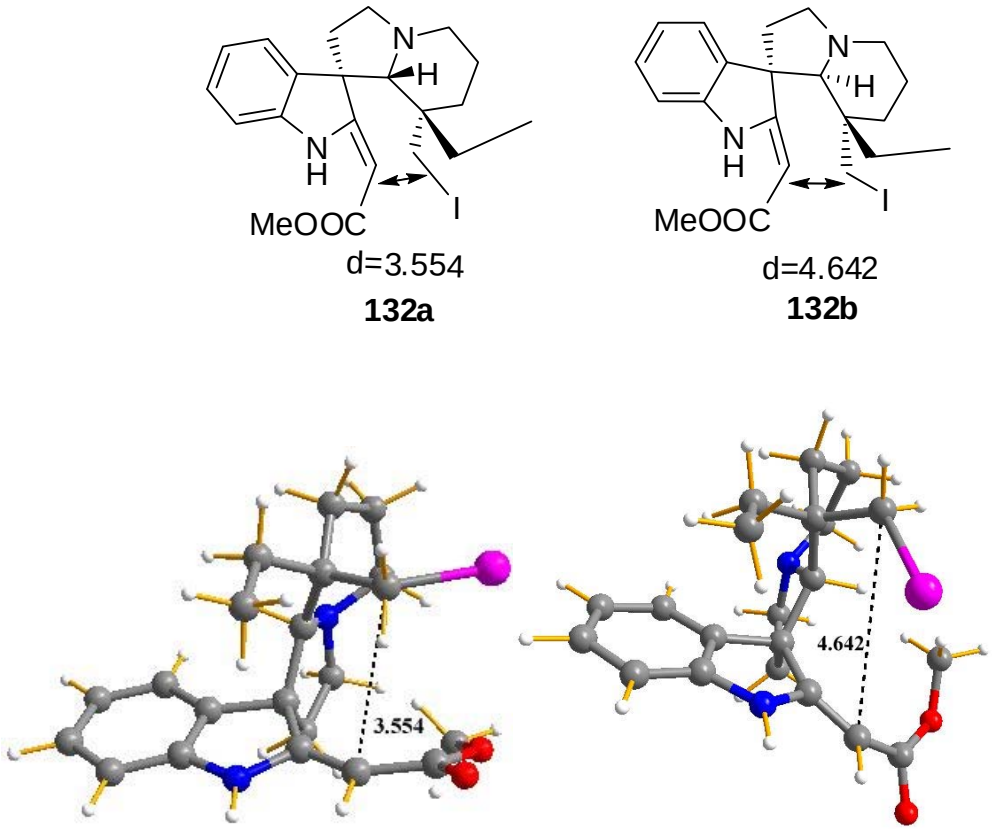
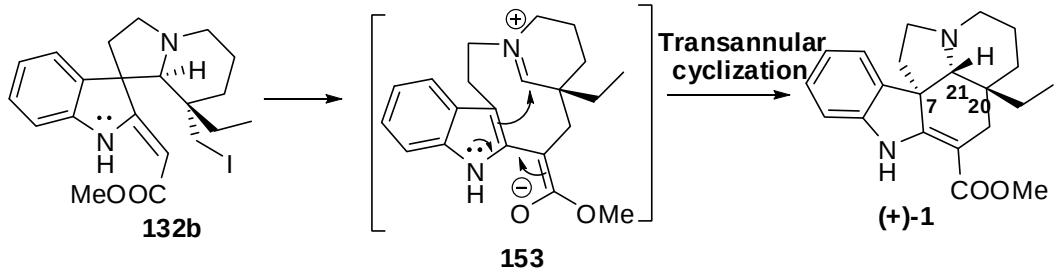


Figure 6: Molecular models of **132a** and **132b**.

The conversion of **132b** to vincadifformine (**1**) can also be explained by considering the transannular cyclization involving the intermediate **153** as shown below. In which the emergence of required stereochemistries at C_7 and C_{21} were controlled by C_{20} (Scheme-32).



Scheme: 32 plausible mode of conversion of **132b** to (+)**-1**.

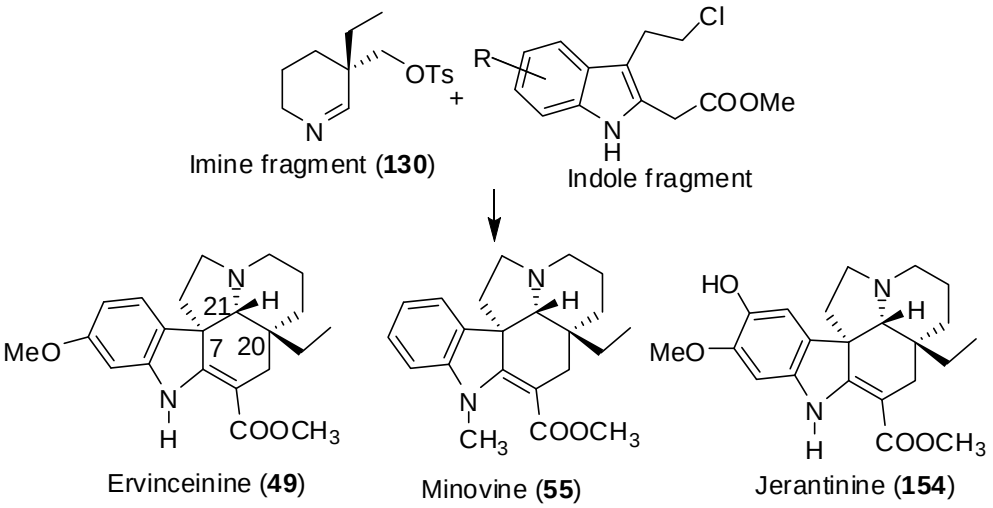
2C.3 Summary:

We have successfully developed a new protocol for the synthesis of optically active vincadifformine through iminium ion triggered cascade reaction. This strategy allows simultaneous construction of two new rings, three new sigma bonds and two new stereogenic centers in one pot with complete stereochemical control. The (+)-vincadifformine was achieved in 15 steps with 4% overall yield.

2C.4 Future prospective……..

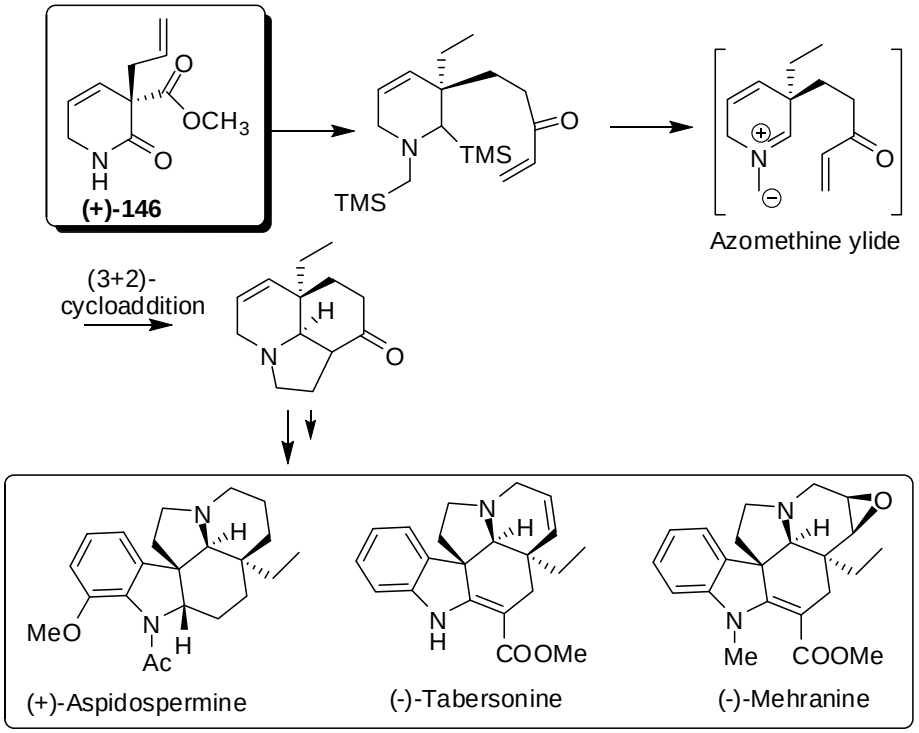
The intermediates, **146**, **141**, **137** and **130** involved in the synthesis of vincadifformine could be utilized to synthesize many biologically active compounds as shown below.

1. This iminium ion triggered cascade reaction can be utilized to synthesize many biologically active complex natural products like jerantinine (**154**), ervinceine (**49**), minovine (**55**), simply by changing the substituted indole fragments (Scheme-33).



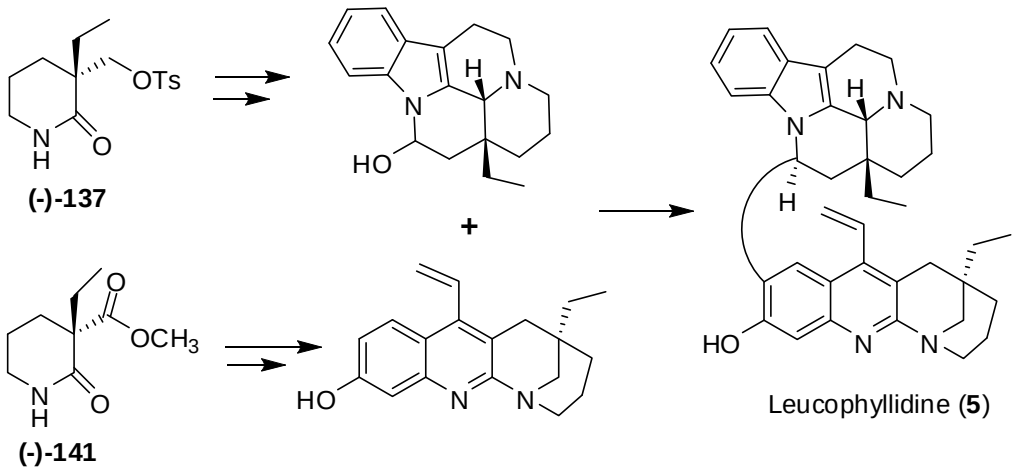
Scheme-33

2. Compound (+)-**146** may be exploited for the synthesis of aspidospermidine, mehranine and tabersonine through (3+2)-cycloaddition of non-stabilized azomethine ylide (Scheme-34).



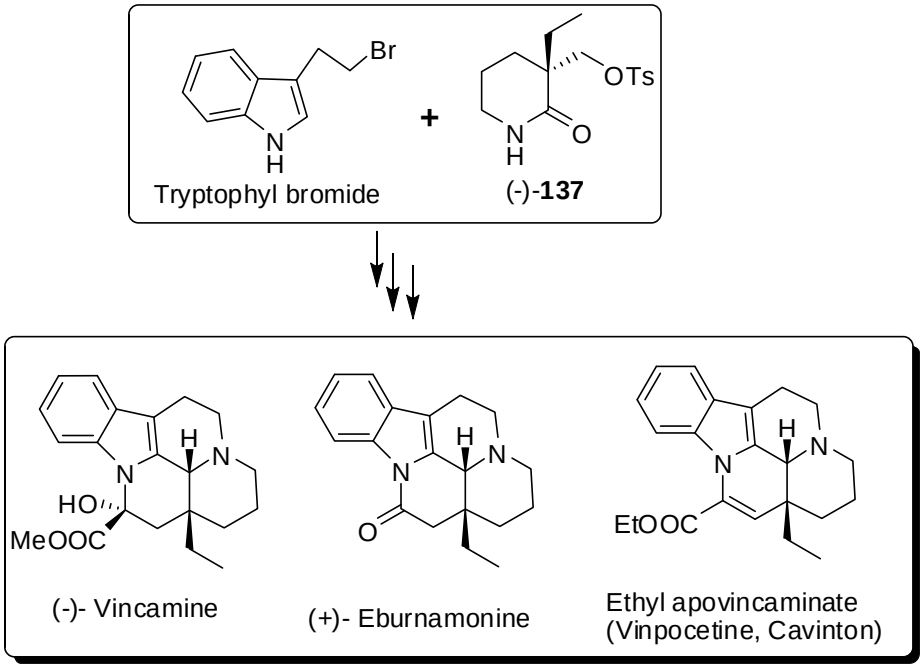
Scheme-34

3. The key intermediates (-)-**137** and (-)-**141** can be used to synthesize recently isolated cytotoxic alkaloid Leucophyllidine (Scheme-35).



Scheme-35

4. Compound (-)-**137** can be utilized to synthesize many pharmaceutically valued products vincamine, eburnamonine and cavinton (Scheme-36).



Scheme-36

Section – D

Experimental Section:

2D.1 General Remarks: All moisture-sensitive reactions were performed under an atmosphere of argon and glass wares were dried in an oven at 125 °C prior to use. Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns and dried by distillation over sodium/benzophenone. Toluene, dimethylformamide (DMF) and dichloromethane (DCM) were distilled from calcium hydride and stored over 4Å molecular sieves. Pyridine and triethyl amine (TEA) were distilled over potassium hydroxide. Solvents used for chromatography were distilled at respective boiling points using known procedures.[35]

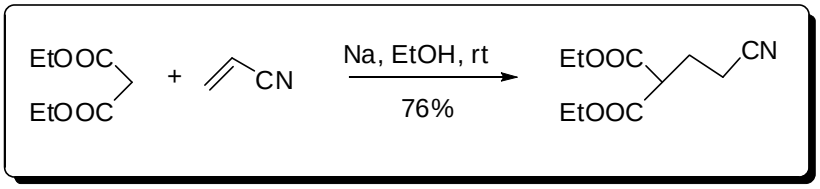
All commercial reagents were obtained from Sigma-Aldrich Chemical Co and S. D. Fine Chemical Co. India. Reactions were monitored by thin layer chromatography (TLC, 0.25 mm E.Merck silica gel plates, $60F_{254}$) and visualized by using UV light, ethanolic solution of phosphomolybdic acid and iodine. Column chromatography was performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or SRL India. Typical syringe and cannula techniques were used to transfer air and moisture sensitive reagents.

All melting points were uncorrected in degree Celsius and were recorded on a Thermonik melting point apparatus. IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX500 instruments using deuteriated solvents. Chemical shifts are reported in 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 spectra were recorded on Bruker AC-200, AV-400 and Bruker DRX500 instruments operating at 50MHz, 100MHz and 125MHz respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Finnigan Mat-1020

spectrometer. High resolution mass spectrometric data were obtained using MSI Concept through direct insertion probe. Optical rotations were measured on a JASCO P-1030 polarimeter.

2D.2 Experimental procedures and spectral data:

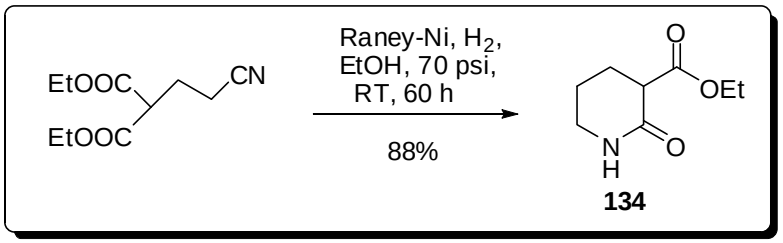
1. Diethyl 2-(2-cyanoethyl) malonate :



Diethylmalonate (88.2 g, 84 mL, 550.6 mmol) was added to a solution of sodium (0.65 g, 27.53 mmol) in absolute ethanol (290 mL). After 25 minutes, acrylonitrile (14.6 g, 18.3 mL, 275.3 mmol) was added drop by drop at such a rate that the temperature did not rise above 35 °C. The product distilled at 104-110 °C at 0.6 mm obtained 45.5 g. R_f = 0.27 (SiO_2, EtOAc: petether 2:8).

Yield	:	76%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	2985, 2248, 1732, 1447, 1371
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	4.21(q, *J* = 7.2 Hz, 4H), 3.48 (t, *J* = 7.2 Hz, 1H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.22 (q, *J* = 7.2 Hz, 2H), 1.26(t, *J* = 7.2 Hz, 6H)
^{13}C NMR (50MHz, $CDCl_3$) δ	:	167.9, 118.3, 61.7, 49.9, 24.2, 41.8, 13.7
MS (ESI): *m/z*	:	236.2638 $(M+Na)^+$

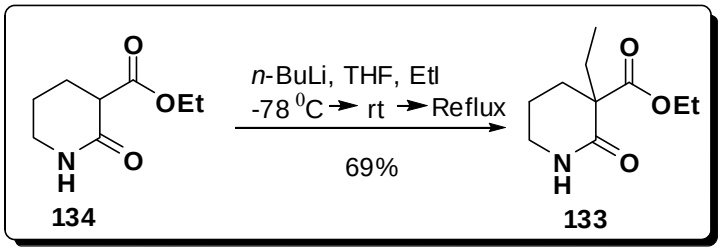
2. Ethyl 2-Oxopiperidine-3-carboxylate (134):



To a solution containing the Diethyl 2-(2-cyanoethyl) malonate (1.55 g, 7.26 mmol) in absolute ethanol (50 mL) was added Raney Nickel (3 g) and the suspension was hydrogenated (70 psi, rt, 60 h) in a Paar reactor. Filtered through a celite, concentrated, subjected to column chromatography (SiO_2, EtOAc: hexane 8:2)) afforded **134** (1.09 g, 88%) as a white solid. (R_f= 0.32, EtOAc).

Yield	:	88%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3234, 2949, 1735, 1668, 1172, 1035.
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	6.72 (brs, 1H), 4.20 (q, *J* = 7.15 Hz, 2H), 3.37-3.33(m, 2H), 3.32-3.27(m, 1H), 2.13-2.01(m, 2H), 1.94-1.87 (m, 1H), 1.76-1.68(m, 1H), 1.26(t, *J* = 7.15 Hz, 3H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	170.6, 168.2, 61.0, 48.2, 41.7, 24.5, 19.9, 13.8
MS (ESI): *m/z*	:	194.2205 $(M+Na)^+$, 210.2027 $(M+K)^+$

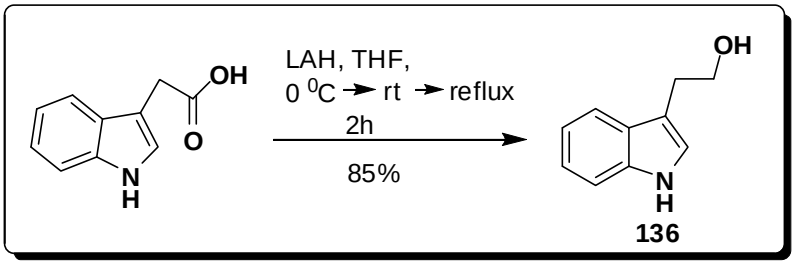
3. Ethyl 3-ethyl-2-oxopiperidine -3-carboxylate (133):



To a stirred solution of 2-oxopiperidine-3-carboxylic acid ethyl ester (**134**) (2.096 g, 12.24 mmol) in 30 mL of anhydrous THF at -78 °C was added *n*-Butyl lithium (5.88 mL, 12.24 mmol, 2.08 M in hexane). The resulting solution was allowed to warm to 0 °C for 10 min, cooled to -78 °C to which ethyl iodide (1 mL, 12.24 mmol) was added. The cooling bath was removed and the solution was heated at reflux for 6 h. The solution was allowed to cool to room temperature, solvent was removed under reduced pressure and the residue was subjected to column chromatography (SiO_2, EtOAc: Petether 6:4) afforded **133** as a liquid (1.68 g, 69%) (R_f= 0.35, EtOAc: petether 8:2)

Yield	:	69%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3217, 2977, 1729, 1666, 1464, 1245.
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	4.18 (q, *J* = 7.20 Hz, 2H), 3.36-3.23 (m, 2H), 2.17-1.90 (m, 3H), 1.87-1.70 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.45 Hz, 3H)
^{13}C NMR (50MHz, $CDCl_3$) δ	:	172.8, 171.1, 61.0, 53.8, 42.0, 28.7, 28.1, 19.4, 13.9, 8.76.
MS (ESI): *m/z*	:	200.0768 $(M + H)^+$, 222.0720 $(M+Na)^+$, 238.0418 $(M+K)^+$

4. Tryptophol (136):

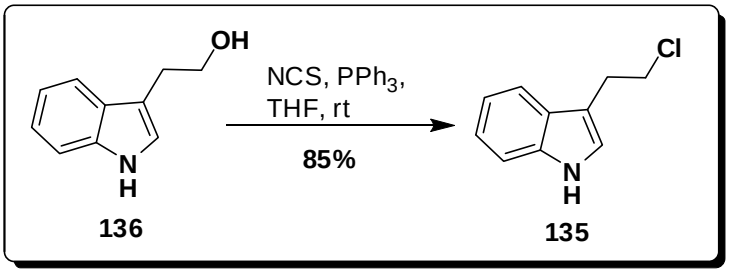


To icecooled stirred slurry of lithium aluminium hydride (3.46 g, 91.33 mmol) in anhydrous THF (200 mL) was added a solution of 3-indole acetic acid (8 g, 45.66 mmol) in THF (60 mL). The reaction mixture was allowed to warm to room temperature and refluxed for 2 h. The reaction mixture was cooled to 0 °C and successively treated with water (7 mL), 10% NaOH solution (12 mL). The solid was removed by filtration and

repeatedly washed with THF. The filtrate was dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography (SiO_2, EtOAc-petether 1:4) afforded tryptophol (6.25 g, 85%) as a pale yellow solid (mp 58-59 °C). R_f = 0.25 (SiO_2, EtOAC: petether 1:4).

Yield	:	85%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3547, 3407, 3010, 1618, 1456, 1216, 1043.
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	8.09 (brs, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.45 Hz, 1H), 7.21 (td, *J* = 7.0, 1.2 Hz, 1H), 7.13 (td, *J* = 7.0, 1.2 Hz, 1H), 7.06 (s, 1H), 3.91 (t, *J* = 6.3 Hz, 2H), 3.03 (t, *J* = 6.3 Hz, 2H), 1.63 (s, 1H)
^{13}C NMR (50MHz, $CDCl_3$) δ	:	136.2, 127.2, 122.5, 121.9, 119.2, 118.6, 111.21, 62.4, 28.51.
MS (ESI): *m/z*	:	184.1475 $(M+Na)^+$, 200.1269 $(M+K)^+$

5. 3-(2-chloroethyl)-1H-indole (135):

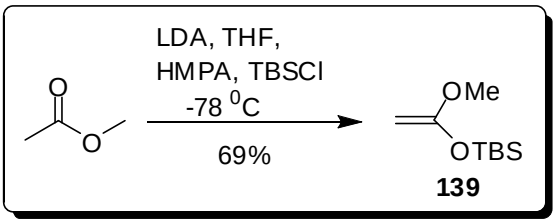


To a stirred solution of *N*-chlorosuccinimide (5.36 g, 40.18 mmol) in THF (40 mL), a solution of triphenylphosphine (10.53 g, 40.18 mmol) in 25 mL dry THF was added dropwise upon which an exothermic reaction occurred with the separation of a solid. To this suspension a solution of tryptophol (**136**) (6.47 g, 40.18 mmol) in THF (35 mL) was added and the mixture was stirred at room temperature for 2 h. The solvent was evaporated, water was added to the resulting residue and the mixture was extracted with dichlromethane. The collected organic phase were washed with brine, dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography (SiO_2, EtOAc-

petether 1:4) afforded 3-(2-chloroethyl) indole (**135**) (5.76 g, 80%) as a pale yellow solid (mp 79-81 °C). R_f = 0.5 (SiO_2, EtOAC: petether 1:4)

Yield	:	80%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3398, 1456, 1351, 1092.
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	8.00 (brs, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.22 (td, *J* = 7.0, 1.2 Hz, 1H), 7.13 (td, *J* = 7.0, 1.2 Hz, 1H), 7.06 (d, *J* = 2.4 Hz) 3.78 (t, *J* = 7.3 Hz, 2H), 3.24 (t, *J* = 7.4 Hz, 2H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	136.0, 126.9, 122.5, 122.0, 119.4, 118.4, 112.3, 111.2, 44.5, 28.9
HR-MS (EI)	:	calcd for $C_{10}H_{10}ClN$: 179.05018. Found:179.05002

6. 1-(*tert*-butyldiethylsilyloxy)-1-methoxyethylene (139):

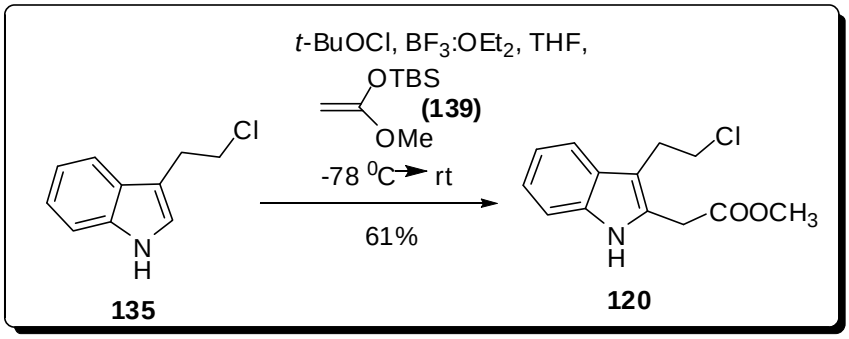


n-Butyllithium (2.24 M in hexanes: 29.7 mL, 66.67 mmol, 1.06 equiv) was added dropwise to a solution of dry diisopropylamine (9.34 mL, 66.60 mmol, 1.06 equiv) in anhydrous THF (70 mL) at 0 °C. The stirring was continued at the same temperature for 30 minutes then cooled to -78 °C. Methyl acetate (5 mL, 62.9 mmol) was added drop wise to a freshly prepared LDA solution over a period of 25 minutes, stirred for 50 minutes and then hexamethylphosphorictriamide (HMPA) (6.6 mL) was added. After 5 minutes, solution of *tert*-butyldimethyl silylchloride in THF (20 mL) was added dropwise over 10 min, stirring was continued for 1 h at -78 °C and quenched with cold water. The reaction mixture was extracted with diethyl ether, dried over sodium sulfate and

concentrated under reduced pressure. The residual oil was distilled to give silyl ketene acetal **139** as a colorless liquid (8.24g, 69%), b.p: 75 °C at 24 mmHg.

Yield	:	69%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	2957, 2859, 1654(C=C), 1446, 1281
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	3.51(s, 3H), 3.21(d, *J* = 2.6, 1H), 3.09 (d, *J* = 2.6, 1H), 0.91 (s, 9H), 0.51 (s, 6H)
^{13}C NMR (50MHz, $CDCl_3$) δ	:	162.2, 60.0, 54.8, 25.5, 18.0, 4.8

6. Methyl 2-(3-(2-chloroethyl)-1H-indol-2-yl) acetate (120):

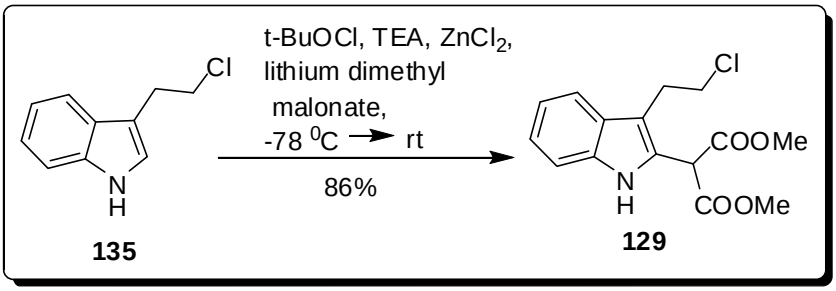


To a stirred solution of 3-(2-chloroethyl)indole (**135**) (0.8 g, 4.46 mmol) and triethyl amine (0.74 mL, 5.35 mmol) in anhydrous THF (20 mL) was added drop wise *t*-BuOCl (0.63 mL, 5.35 mmol) dissolved in dry THF (2 mL) over a period of 10 minutes at-78 °C. After 40 minutes, the silylenol ether **139** (1.9 mL, 8.92 mmol) was added followed by BF_3:OEt_2 (1.1 mL, 8.92 mmol). The solution was warmed to ambient temperature over 15 h, quenched with aqueous $NaHCO_3$ (10 mL), extracted with dichloromethane, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, ethyl acetate-pet ether, 1.5:8.5) to obtain **120** (0.685 g, 61%) as a thick liquid. This compound upon crystallization with cyclohexane-ethyl

acetate gave colorless crystalline solid. m.p = 59-60 °C; R_f = 0.42 (SiO_2, ethyl acetate-pet ether 2.5: 7.5, iodine/PMA);

Yield	:	61%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3457, 3019, 1735, 1438, 1460, 1216.
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	8.65 (brs, 1H), 7.53-7.51 (m, 1H), 7.37-7.33 (m, 1H), 7.23-7.08 (m, 2H), 3.84 (s, 2H), 3.76 (s, 3H), 3.72 (t, *J* = 7.4 Hz, 2H), 3.2 (t, *J* = 7.4 Hz, 2H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	170.8, 135.5, 127.7, 127.4, 122.0, 119.5, 117.9, 110.9, 109.6, 52.3, 44.5, 31.6, 27.8
HR-MS (EI)	:	calcd for $C_{13}H_{14}ClNO_2$:251.07131. Found: 251.05374

7. Dimethyl 2-(3-(2-chloroethyl)-1H-indol-2-yl) malonate (129):

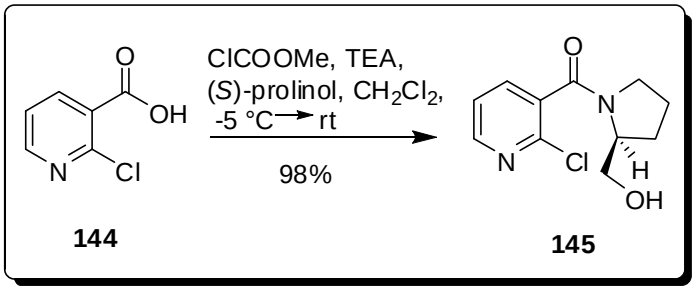


To a stirred solution of 3-(2-chloroethyl) indole **(135)** (0.25 g, 1.39 mmol) and triethylamine (0.21 mL, 1.53 mmol) in 10 mL of anhydrous THF at -78 °C was added 0.2 mL (1.77 mmol) of *tert*-butylhypochlorite drop wise. After 20min, a solution of $ZnCl_2$ (36 mg, 0.27 mmol, fused by flame drying under reduced pressure) in anhydrous THF (2 mL) was added drop wise. The reaction mixture was stirred for 5 min then a solution of lithium dimethylmalonate (1.67 mmol) was added drop wise, the solution was stirred for 1 h at -78 °C and for 1 h at room temperature. Water was added and the aqueous layer was extracted with dichloromethane. The product **129** was obtained in 86% yield after column chromatography, which crystallized from ethyl acetate-pet ether, mp 114.5 °C – 116.4 °C.: R_f: 0.3 (SiO_2, 1:5 ethyl acetate:pet ether)

Yield	:	86%
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3406, 2955, 1736, 1435
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	9.0 (brs, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.5Hz, 1H), 7.26-7.09 (m, 2H), 5.0 (s, 1H), 3.79 (s, 6H), 3.71 (t, *J* = 7.5 Hz, 2H), 3.23 (t, *J* = 7.5 Hz, 2H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	167.4, 135.8, 126.9, 125.6, 122.6, 119.6, 118.3, 111.3, 111.1, 53.1, 48.8, 44.1, 27.8.
HR-MS (EI)	:	calcd for $C_{15}H_{16}ClNO_4$:309.07679. Found: 309.07453.

[Note*: Racemic 137, 130 and 1 were synthesized by using the procedure as same as used for chiral entities shown below]

8. (*S*)- 2-Chloropyridin-3-yl) (2-(hydroxymethyl) pyrrolidin-1-yl)nicotinamide (145):

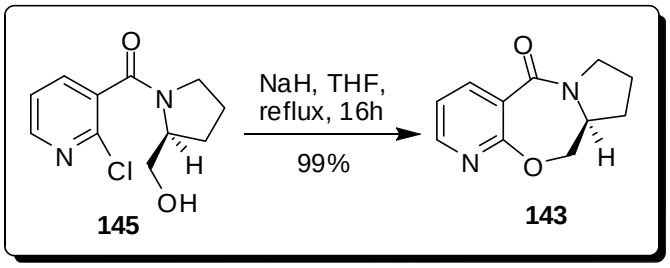


144 **145**

To a stirred solution of 2-chloronicotinic acid (**144**) (2.15 g, 13.66 mmol) and triethylamine (2.1 mL, 15.04 mmol) in anhydrous dichloromethane (65 mL) at –5 °C was added ethyl chloroformate (1.3 mL, 13.66 mmol). The resulting mixture was stirred at -5 °C for 45 minutes and 1.52 g (15.04 mmol) of (*S*) - Prolinol was added into it. The reaction mixture was allowed to warm to room temperature and stirred for additional 4 h, concentrated, purified by column chromatography (SiO_2, acetone-petether,1:5→2:5) to afford **145** (3.22 g, 98%) as a colorless viscous oil which got crystallized from ethyl acetate/pet ether as a colorless solid (m.p. 61-62 °C); R_f = 0.3 (SiO_2, acetone-pet ether, 3:7).

Yield	:	98%
$[\alpha]^{26}_D$	:	-78 (*c* = 0.85, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3397, 2977, 1622, 1074
^1H NMR (500 MHz, $CDCl_3/D_2O$) δ	:	8.44 (dd, *J* = 1.9, 4.9 Hz, 1H), 7.69 (dd, *J* = 1.9, 7.4 Hz, 1H), 7.32 (dd, *J* = 4.9, 7.7 Hz, 1H), 4.52-4.35 (m, 2H), 3.83-3.72 (m, 2H), 3.33-3.27 (m, 2H), 2.21-2.15 (m, 1H), 1.94-1.89 (m,1H), 1.85-1.81 (m,1H), 1.75-1.68 (m, 1H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	166.7, 150.1, 146.4, 136.4, 132.9, 122.7, 65.3, 61.1, 49.1, 28.1 24.2
HR-MS (EI)	:	Calcd for $C_{11}H_{13}ClN_2O_2$:240.06656. Found: 240.06084.

9. 1, 2, 3, 10, 11, 11a, (*S*)-Hexahydro-5H-pyrrolo[2,1-*c*]pyrido-[3,2-*f*][1,4]oxazepin-5-one (143):

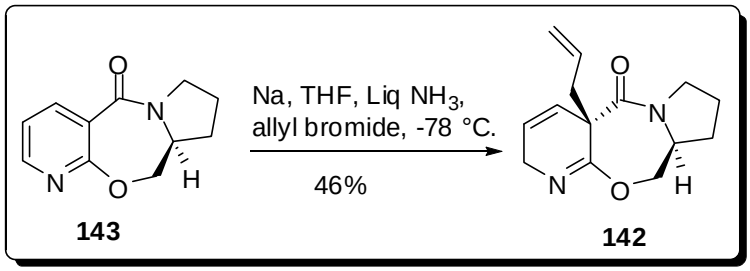


A mixture of **145** (1.2 g, 4.98 mmol) and sodium hydride (0.13 g, 5.48 mmol) in 60 mL of anhydrous THF was refluxed under nitrogen for 16 h. Sodium chloride and unreacted NaH were removed by filtration, solvent evaporation and crystallization (ethyl acetate) afford analytically pure **143** as white crystals (1.0 g, 99%); mp 146-147 °C.

Yield	:	99%
$[\alpha]^{25.7}_D$	:	+230.96 (*c* = 1.55, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3003, 1624, 1590, 1463, 1433, 1383, 1215.

^{1}H NMR (200 MHz, $CDCl_3$) δ	:	8.61 (dd, *J* = 2.0, 7.8 Hz, 1H), 8.36 (dd, *J* = 2.0, 4.5 Hz, 1H), 7.10 (dd, *J* = 4.6, 7.8 Hz, 1H), 4.6 (d, *J* = 11.5 Hz, 1H), 4.16-3.93 (m, 2H), 3.85-3.63 (m, 2H), 2.33-2.19 (m, 1H), 2.09-1.81 (m, 2H), 1.76-1.57 (m, 1H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	162.5, 160.4, 151.2, 143.5, 118.1, 115.8, 73.2, 57.2, 48.1, 29.2, 23.3
HR-MS (EI)	:	calcd for $C_{11}H_{12}N_2O_2$: 204.08988. Found: 204.08954.

10. (4a*S*, 9a*S*)-4a-Allyl-4a, 7, 8, 9, 9a, 10-hexahydropyrido [3, 2-*f*] pyrrolo [2, 1-*c*] [1, 4] oxazepin-5(2H)-one (142):



To a stirred solution of finely powdered **143** (0.25 g, 1.23 mmol) and *tert*-butyl alcohol (0.09 g, 0.11 mL, 1.23 mmol) in THF (2.5 mL) and ammonia (30 mL) was added sodium (0.1 g, 4.56 mmol) in small pieces at -78 °C. After 50 minutes, isoprene (few drops) was added until the blue coloration dissipated and a dark yellow solution resulted. Allyl bromide (3.2 mL, 36.99 mmol) was added into the flask in one portion. The resulting solution was vigorously stirred at -78 °C for 3 h, quenched with water (5 mL). The reaction mixture was allowed to warm to room temperature while ammonia got evaporated. Extracted with dichloromethane (30 mL x 3), dried over Na_2SO_4 and concentrated. Purification by column chromatography (acetone-pet ether 2:8→3:7) afforded **142** as brown colored thick liquid (0.139 g, 46% yield and 97.9% de). Diastereomeric ratio was determined by HPLC analysis using (Atlantis RP-18 (250 × 4.6mm) column, acetonitrile-water (40:60) as an eluent, 1.0 mL/min, λ = 224nm, 25 °C). The retention times of major isomer and minor isomer were 5.33 and 6.19 minutes, respectively. This compound upon crystallization with dichloromethane - *n*-pentane gave single diastereomer as colorless crystals.

(R_f = 0.3 acetone: pet ether 3:7) mp = 105.5-106.5°C;

Yield	:	46%
$[\alpha]^{25.7}_D$	:	+ 133.746° (*c* = 2.6, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	1688, 1630, 1412, 1352.
^1H NMR (400 MHz, $CDCl_3$) δ	:	5.87-5.79 (m, 2H), 5.66-5.55 (m, 1H), 5.1-5.02 (2d, *J* = 17, 11 Hz, 2H), 4.28 (dd, *J* = 10.8, 2.2 Hz, 1H), 4.2-4.07 (m, 3H), 3.9 (t, *J* = 10.5 Hz, 1H), 3.62-3.48 (m, 2H), 2.66 (d, *J* = 7.5 Hz, 2H), 2.11-2.03 (m, 1H), 1.90-1.73 (m, 2H), 1.6-1.51 (m, 1H).
^{13}C NMR (100MHz, $CDCl_3$) δ	:	169.5, 161.6 132.1, 126.9, 125.1, 119.2, 72.7, 54.9, 52.1, 49.5, 48.1, 42.0, 29.2, 22.3.
HR-MS (EI)	:	calcd for $C_{14}H_{18}N_2O_2$: 246.13683. Found: 246.13783.

X-ray Crystal Structure Analysis For $C_{14}H_{18}N_2O_2$ (142): (CCDC 783953)

Crystal Data: Single crystals of the compound **142** were grown by slow evaporation of the solution in dichloromethane and *n*-pentane. Colourless crystal of approximate size 0.30 x 0.26 x 0.14 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, hemisphere data acquisition. Total frames = 1271, Oscillation / frame -0.3º, exposure / frame = 5.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.09 to 25.0 º, completeness to θ of 25.0 º is 100.0 %. SADABS correction applied, $C_{14}H_{18}N_2O_2$, *M* = 246.30. Crystals belong to Tetragonal, space group $P4_32_12$, a = 11.0581(5), *b* = 11.0581(5), *c* = 20.481(4) Å, *V* = 2504.5(5) $Å^3$, *Z* = 8, D_c = 1.306 g /cc, μ (MoK_α) = 0.088 mm^{-1}, *T* = 150(2) K, 12587 reflections measured, 2210 unique [I>2σ(I)], R value 0.0507, wR2 = 0.1281. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)[36] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in Table- 4.

X-ray analysis revealed the relative configuration of the molecule **142** at C_{4A} and C_{9A} as *S* and *S* (Figure-4).

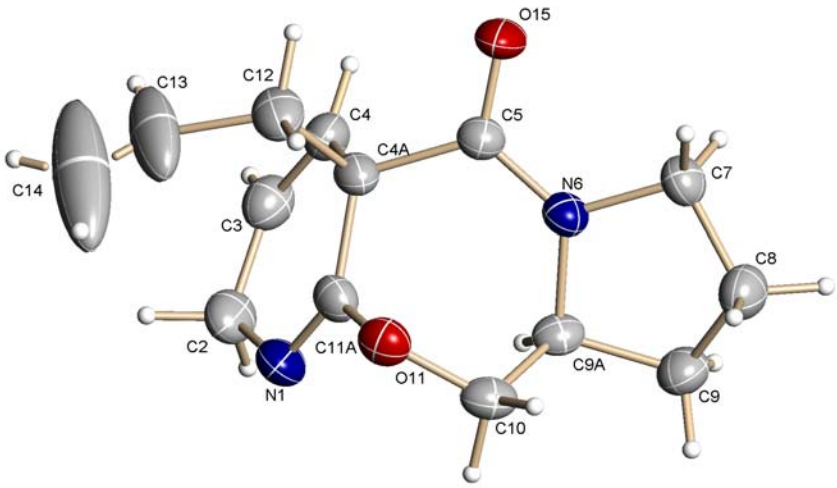


Figure-4: *ORTEP diagram of the molecule **142**. Ellipsoids are drawn at 50% probability.*

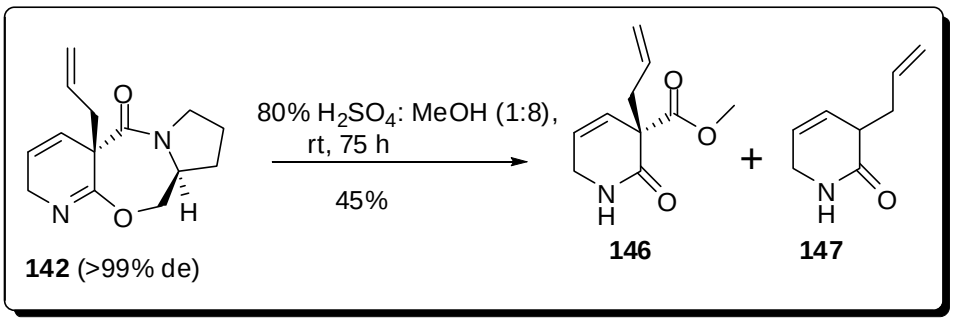
Table-4 Crystal data and structure refinement for **142**

Identification code	$C_{14}H_{18}N_2O_2$compound	
Empirical formula	$C_{14}H_{18}N_2O_2$	
Formula weight	246.30	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P43 21 2	
Unit cell dimensions	a = 11.0581(5) Å	α= 90°.
	b = 11.0581(5) Å	β= 90°.
	c = 20.481(4) Å	γ = 90°.
Volume	2504.5(5) $Å^3$	
Z	8	
Density (calculated)	1.306 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	

F(000)	1056
Crystal size	0.30 x 0.26 x 0.14 mm^3
Theta range for data collection	2.09 to 25.00°
Index ranges	-13<=h<=11, -13<=k<=12, -24<=l<=21
Reflections collected	12587
Independent reflections	2210 [R (int) = 0.0500]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9881 and 0.9742
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2210 / 0 / 163
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0507, wR2 = 0.1281
R indices (all data)	R1 = 0.0523, wR2 = 0.1299
Absolute structure parameter	0(2)
Largest diff. peak and hole	0.454 and -0.375 e.$Å^{-3}$

11. Auxiliary Cleavage:

a) Method-A:



A solution of **142** (0.39 g, 1.59 mmol) in methanol (8 mL) and 80% sulfuric acid (1 mL) was stirred at room temperature for 75 h. The methanol was evaporated under reduced pressure and the residue was basified with the saturated sodium bicarbonate solution, stirred for ten minutes. The mixture was extracted with dichloromethane (3×20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo.

Purification by column chromatography (SiO_2, ethyl acetate:petether, 2:3→3:2) afforded **146** (0.14 g) as a white solid (45% yield and 19% enantiomeric excess) and 40% of undesired achiral decarboxylated **147**.

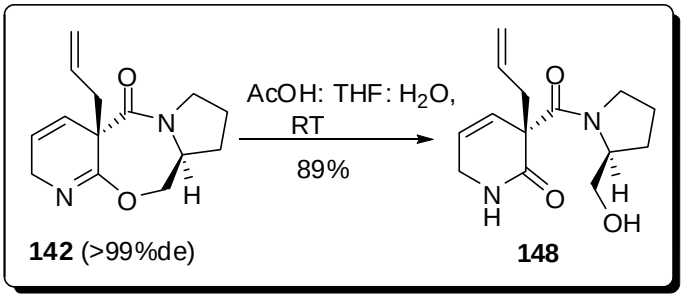
Enantiomeric excess of **146** was determined by HPLC analysis {Chiralcel OD-H (250 × 4.6mm) column, isopropanol–pet ether (10:90) as an eluent}, 0.5 mL/min (265psi), λ = 220nm, 25 °C, the retention times of (+) - isomer and (-) - isomer being 27.36 and 52.35 minutes, respectively.

*^1H and ^{13}C data for achiral **147** as shown below*

Yield	:	40%
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	6.84 (brs, 1H), 5.86-5.65 (m, 3H), 5.12-5.02 (m, 2H), 3.92-3.85 (m, 2H), 3.0-2.91 (m, 1H), 2.55-2.38 (m, 2H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	172.2, 134.5, 126.1, 120.7, 117.6, 43.5, 40.2, 37.0.
MS (ESI): (*m/z*)	:	138.2013 $(M+H)^+$, 160.1948 $(M+Na)^+$

b) Method B:

12. (S)-3-allyl-3-((S)-2-(hydroxymethyl) pyrrolidine-1-carbonyl)-1, 6-dihydropyridin-2(3H)-one (148):

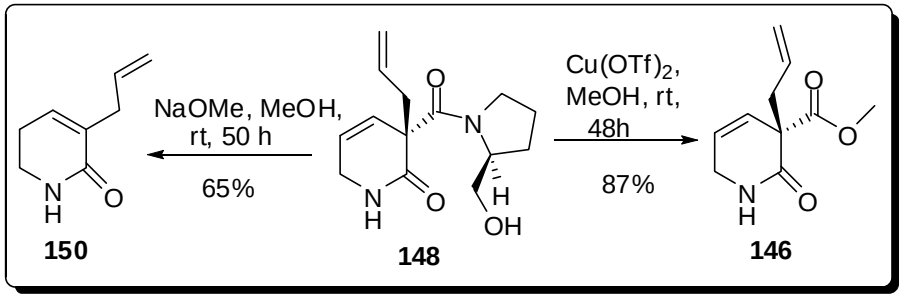


To a stirred solution of **142** (0.5 g, 2.03 mmol) in THF (8 mL) was added glacial acetic acid (1 mL) and water (1 mL) at room temperature. After stirring for 20 h, it was neutralized with saturated $NaHCO_3$ solution, extracted with dichloromethane (3 × 25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue

was purified by silica gel column chromatography (acetone-pet ether 1:1) to afford pure **148** (0.47 g, 89%). mp = 141-142 °C, (R_f = 0.34 acetone: pet ether 7:3).

Yield	:	89%
$[\alpha]^{26.6}_D$	:	+28.82° (*c* 3.254, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3401, 1679, 1658, 1412.
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	7.13 (brs, 1H), 5.96 (td, *J* = 2.9, 9.9 Hz, 1H), 5.82-5.58 (m, 2H), 5.12-5.01 (m, 2H), 4.52 (brs, 1H), 3.96 (brs, 2H), 3.59-3.5 (m, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.9(dd, *J* = 7.8, 13.7 Hz, 1H), 2.6 (dd, *J* = 7, 13.8 Hz, 1H), 2.02-1.74 (m, 3H), 1.62-1.49 (m, 1H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	170.3, 169.9, 132.4, 125.4, 122.2, 119.0, 65.8, 61.7 54.4, 46.7, 43.6, 41.9, 27.1, 24.5.
HR-MS (EI)	:	calcd for $C_{14}H_{20}N_2O_3$: 264.14739. Found: 264.13514.

13. (*S*)-Methyl 3-allyl-2-oxo-1, 2, 3, 6-tetrahydropyridine-3-carboxylate (146):



(a) Sodium methoxide (0.93 g, 17.4 mmol) was added to a solution of amide **148** (0.23 g, 0.87 mmol) in 20 mL of anhydrous methanol, stirred for 50 h at ambient temperature and quenched with 1N HCl. The aqueous layer was extracted with dichloromethane, dried over sodium sulfate, concentrated and purified by column chromatography (SiO_2, ethyl acetate: petether, 2:3→3:2) to afford **150** (0.07 g, 65%). R_f = 0.2 (SiO_2, ethyl acetate: pet ether 4:1)

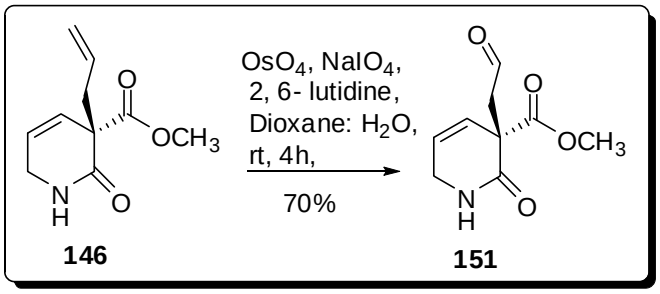
*^{1}H and ^{13}C data for achiral **150** as shown below*

Yield	:	65%
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	6.36 (t, *J* = 4.0 Hz, 1H), 5.95-5.75 (m, 2H), 5.11-5.02 (m, 2H), 3.38 (t, *J* = 6.94 Hz, 2H), 3.04-3.0 (m, 2H).

b) To a stirred solution of **148** (0.21 g, 0.8 mmol) in anhydrous methanol (20 mL) was added copper (II) triflate (0.29 g, 0.8 mmol) at room temperature, stirred for 48 h, concentrated and basified with saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane, dried over sodium sulfate, concentrated and purified by column chromatography (SiO_2, ethyl acetate: petether, 2:3→3:2) to afford **146** as a white solid (0.136 g, 87% yield as single enantiomer). Enantiomeric excess was determined by HPLC analysis and compared with racemized ester **153** by using (Chiralcel OD-H (250×4.6mm) column, isopropanol- pet ether (10:90) as an eluent), 0.5 mL/min (265psi), λ=220nm, 25 °C. The retention time of (+)-isomer showed at 27.89 minutes. (m.p 88-91 °C). R_f = 0.4 (SiO_2, ethyl acetate:pet ether 4:1).

Yield	:	87%
$[\alpha]^{23}_D$	:	+ 82.8 (*c* = 1.1, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3226, 3078, 2952, 1731, 1660, 1236, 923
^{1}H NMR (200 MHz, $CDCl_3$) δ	:	6.67 (brs, 1H), 6.0-5.92 (m, 1H), 5.76-5.55 (m, 2H), 5.18-5.04 (m, 2H), 4.12-3.85 (m, 2H), 3.71 (s, 3H), 2.98(dd, *J* = 7.3, 13.7 Hz, 1H), 2.61 (dd, *J* = 7.2, 13.7 Hz, 1H), 2.0 (brs, 1H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	171.0, 168.8, 132.4, 125.5, 123.1, 119.1, 54.1, 52.8, 43.4, 39.5.
HR-MS (EI)	:	calcd for $C_{10}H_{13}NO_3$: 195.08954. Found: 195.08821.

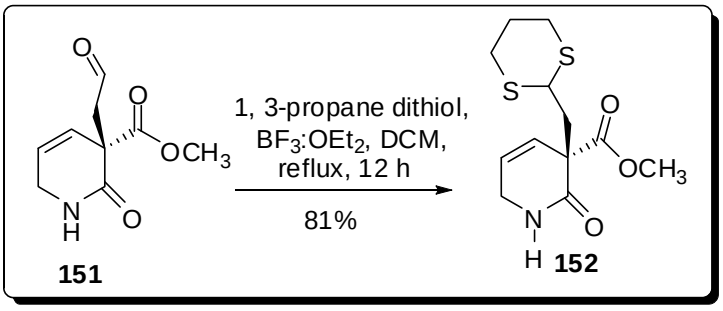
14. (*S*)-Methyl-2-oxo-3-(2-oxoethyl)-1, 2, 3, 6-tetrahydropyridine-3-carboxylate (151):



To a solution of **146** (0.15 g, 0.79 mmol) in dioxane-water (3:1, 8 mL) was added 2, 6-lutidine (0.27 mL, 2.39 mmol), OsO_4 (2.14% in 2-methyl-2-propanol, 4 mg, 0.016 mmol), and $NaIO_4$ (0.68 g, 3.19 mmol). The reaction was stirred at 25 °C for 4 h and diluted with water (20 mL), extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4, concentrated and purification by column chromatography (SiO_2, ethyl acetate- petether, 8:2→10:0) to obtain **151** (0.11 g, 70%) as a colorless liquid. R_f = 0.3 (SiO_2, ethyl acetate-pet ether 6:4).

Yield	:	70%
$[\alpha]^{23}_D$	:	+ 3.884 (*c* = 1.15, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3319, 2955, 1726, 1682, 1660, 1487, 1334, 1235
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	9.72 (d, *J* = 1.6 Hz, 1H), 6.72 (brs, 1H), 6.01-5.97 (m, 1H), 5.68 (dt, *J* = 2.1, 9.9 Hz, 1H), 4.13-4.0 (m, 2H), 3.75 (s, 3H), 3.24 (d, *J* = 17.7 Hz, 1H), 3.02 (dd, *J* = 2.0, 17.7 Hz).
^{13}C NMR (100MHz, $CDCl_3$) δ	:	198.7, 170.1, 168.4, 124.6, 124.0, 53.14, 51.2, 48.1, 43.29
MS (ESI): (*m/z*)	:	220.100 $(M + Na)^+$

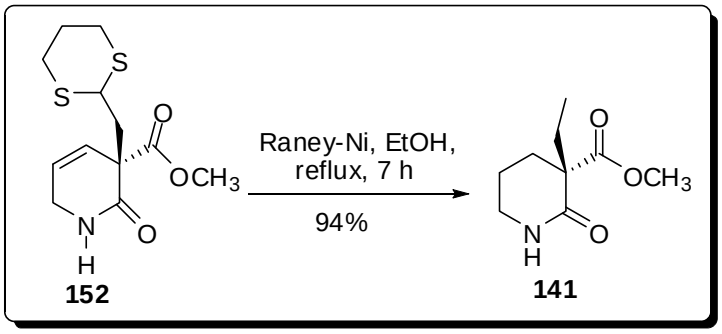
15. (*S*)-Methyl 3-((1,3-dithian-2-yl)-2-oxo-1,2,3,6-tetrahydropyridine-3-carboxylate (152):



To a solution containing **151** (0.21 g, 1.08 mmol) in anhydrous CH_2Cl_2 (25 mL) were added 1,3-propanedithiol (0.15 g, 0.14 mL, 1.41 mmol) and boron trifluoride etherate (1.23 g, 1.1 mL, 8.68 mmol). The mixture was refluxed for 12 h, cooled to room temperature and quenched with aqueous $NaHCO_3$ (10 mL) . The aqueous layer was extracted with CH_2Cl_2, washed with water and dried over sodium sulfate, concentrated and purified by column chromatography (SiO_2, ethyl acetate-pet ether, 6:4→7:3) to afford **152** (0.25 g, 81%) as a gummy compound. (R_f = 0.45, SiO_2, EtOAc)

Yield	:	81%
$[\alpha]^{26}_D$	:	+ 102.4 (*c* = 2.75, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3213, 2902, 1738, 1682, 1662, 1488, 1433, 1229
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	6.87 (brs, 1H), 6.02- 5.97 (m, 1H), 5.67 (dt, *J* = 10.0, 2.1 Hz, 1H), 4.10-3.97 (m, 2H), 3.85 (dd *J* = 9.2, 5.5 Hz, 1H), 3.71 (s, 3H), 2.98 (dd, *J* = 14.6, 9.2 Hz, 1H), 2.95-2.84 (m, 2H), 2.67-2.61 (m, 1H), 2.46 (dd, *J* = 14.56, 5.40 Hz, 1H), 2.01-1.95 (m, 1H), 1.94-1.84 (m, 1H), 1.75 (s, 1H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	170.5, 168.7, 124.2, 123.8, 53.2, 52.8, 43.3, 41.7, 38.9, 28.5, 28.1, 25.1
HR-MS (EI)	:	calcd for $C_{12}H_{17}NO_3S_2$: 287.06498. Found: 287.05690.

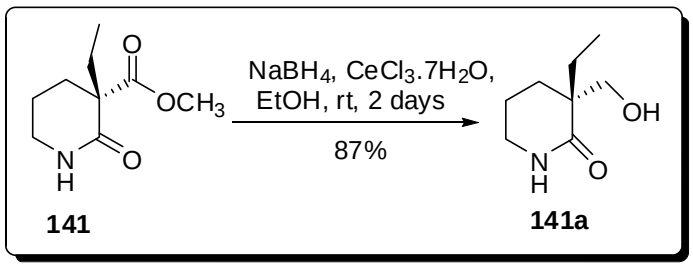
16. (*S*)- Methyl 3-ethyl-2-oxopiperidine-3-carboxylate: (-)-141



To a solution of **152** (0.42 g, 1.47 mmol) in absolute ethanol (65 mL) was added Raney-Ni (W-2, 2 g, prewashed with absolute ethanol) followed by refluxing under a hydrogen atmosphere (1 atm) for 7 h. The reaction mixture was filtrated through celite and the filtrate was concentrated under reduced pressure, purified by column chromatography (silica gel, eluting with EtOAc) to obtain **141** (0.25 g, 94%) as a colorless liquid. (R_f = 0.33, SiO_2, EtOAc).

Yield	:	94%
$[\alpha]^{27.4}_D$	:	- 48.3 (*c* = 2.45, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3300, 2953, 2880, 1732, 1666, 1491, 1449, 1247, 1199.
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	6.0 (brs, 1H), 3.74 (s, 3H), 3.37-3.28 (m, 2H), 2.2-2.16 (1H, m), 2.07-1.99 (m, 1H), 1.97-1.92 (m, 1H), 1.9-1.78 (m, 3H), 1.66 (s, 1H), 0.94 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	173.4, 171.1, 53.9, 52.3, 42.1, 28.8, 28.3, 19.4, 8.8.
HR-MS (EI)	:	calcd for $C_9H_{15}NO_3$: 185.10519. Found: 185.10635

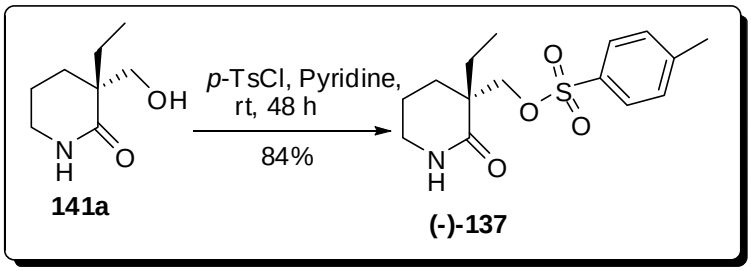
17. (*R*)-3-Ethyl-3-(hydroxymethyl) piperidin-2-one (+)-141a :



To a suspension of $NaBH_4$ (0.18 g, 4.92 mmol) and cerium chloride heptahydrate (0.25 g, 0.67 mmol) in ethanol (4 mL) was added drop wise the solution of **141** (0.08 g, 0.464 mmol) in ethanol (3 mL) for 1 h. The reaction mixture was stirred for 2 days at room temperature and poured into saturated aqueous NH_4Cl solution, extracted with dichloromethane (15 mL x 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, purified by column chromatography (SiO_2 acetone: petether 1:1) to afford alcohol **141a** (0.06 g, 87%) as colorless sticky liquid. (R_f = 0.23, SiO_2, acetone-pet.ether 1:1)

Yield	:	87%
$[\alpha]^{27.5}_D$	:	+ 13.4 (*c* = 1.05, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3297, 2940, 2875, 1644, 1492, 1054.
^1H NMR (400 MHz, $CDCl_3$) δ	:	6.38 (brs, 1H), 3.88 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.57-3.47 (m, 2H), 3.29-3.25 (m, 2H), 1.9-1.68 (m, 5H), 1.49-1.43 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (125MHz, $CDCl_3$) δ	:	178.2, 67.2, 45.1, 41.9, 26.6, 26.4, 19.1, 7.7
HR-MS (EI)	:	calcd for $C_8H_{15}NO_2$: 157.11028. Found: 157.11074.

18. (*R*)– (3-ethyl-2-oxopiperidin-3-yl)methyl 4-methylbenzenesulfonate (-)-137:

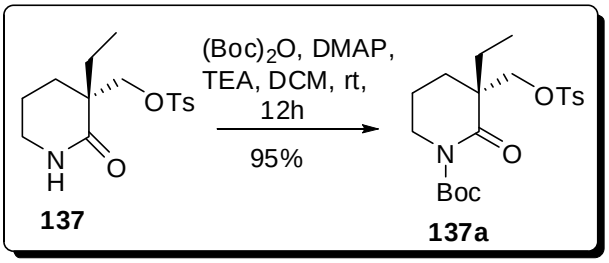


p-Toluenesulfonyl chloride (0.11 g, 0.6 mmol) was added in small portions to a stirred and ice-cooled solution of (+)-**141a** (0.06 g, 0.4 mmol) in anhydrous pyridine (4 mL). The reaction mixture was stirred for 48 h at ambient temperature and poured into ice water. The aqueous layer was extracted with dichloromethane, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, concentrated and purified by column

chromatography (SiO_2, 6:4→10:0 ethyl acetate- pet ether) to afford (-)-**137** as white solid (0.138 g (84%), which got crystallized from ethyl acetate–pet ether as colorless crystals. m.p = 166-168 °C; R_f = 0.45 (SiO_2, EtOAc);

Yield	:	84%
$[\alpha]^{23.7}_D$	:	- 26.7(*c* = 1.45, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3020, 1661, 1359, 1215, 1176.
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	7.76 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.03 (brs, 1H), 4.18 (d, *J* = 8.9 Hz, 1H), 3.91 (d, *J* = 9.0 Hz, 1H), 3.3-3.21 (m, 2H), 2.43 (s, 3H), 1.98-1.89 (m, 1H), 1.86-1.74 (m, 3H), 1.68-1.59 (m, 1H), 1.52-1.45 (m, 1H) 0.84 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100MHz, $CDCl_3$) δ	:	173.2, 144.7, 132.4, 129.7, 127.8, 75.0, 45.3, 42.3, 28.2, 27.2, 21.5, 19.6, 8.3.
HR-MS (EI)	:	calcd for $C_{15}H_{21}NO_4S$: 311.11913. Found: 311.11887.

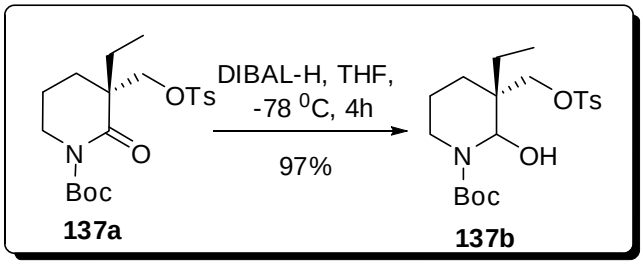
19. (*R*)-*tert*-Butyl 3-ethyl-2-oxo-3-(tosyloxymethyl)piperidine-1-carboxylate (-)-137a:



To a solution of **137** (0.64 g, 2.07 mmol) in dry dichloromethane (15 mL) was added triethylamine (0.72 mL, 5.17 mmol) and DMAP (0.025 g, 0.2 mmol). To this stirred mixture was added drop wise di-tertbutyl dicarbonate (0.7 mL, 3.1 mmol) over a period of 15 min and the mixture was stirred at ambient temperature for 12 h. The reaction mixture was concentrated under reduced pressure, purified by column chromatography (SiO_2, ethylacetate-pet.ether 2:8) to furnish **137a** as a colorless liquid (0.81 g, 95%). (R_f = 0.27, 2:8 ethyl acetate:pet.ether).

Yield	:	95%
$[\alpha]^{26}_D$	:	- 62.8(*c*= 1.05, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	2976, 1765, 1717, 1367, 1177, 1150
^1H NMR (200 MHz, $CDCl_3$) δ	:	7.75 (d, *J* = 8.28 Hz, 2H), 7.33 (d, *J* = 8.03 Hz, 2H), 4.16 (d, *J* = 9.29 Hz, 1H), 3.97 (d, *J* = 9.28 Hz, 1H), 3.65-3.54 (m, 2H), 2.43 (s, 3H), 1.98-1.89 (m, 1H), 1.88-1.75 (m, 3H), 1.64-1.54 (m, 2H), 1.48(s, 9H), 0.81 (t, *J* = 7.53 Hz, 3H).
^{13}C NMR (50MHz, $CDCl_3$) δ	:	173.2, 152.8, 144.8, 132.3, 129.8, 127.8, 82.7, 74.2, 48.3, 46.9, 28.7, 28.5, 27.8, 21.5, 19.7, 8.1.
MS (ESI): *m/z*	:	412.1523 $(M+H)^+$, 434.1089 $(M+Na)^+$, 450.0987 $(M+K)^+$.

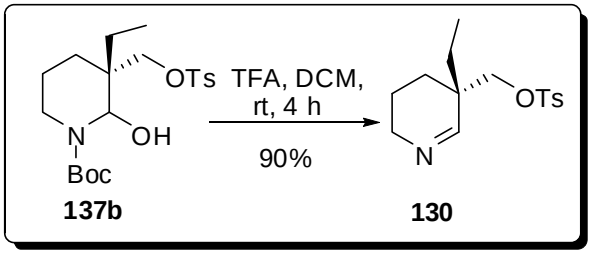
20. (3*R*)-*tert*-Butyl 3-ethyl-2-hydroxy-3-(tosyloxymethyl)piperidine-1-carboxylate: (-)-137b



To a stirred solution of **137a** (0.137 g, 0.33 mmol) in anhydrous THF (4 mL) at -78 °C was added a solution of DIBAL-H (20 wt % solution in toluene, 0.8 mL, 0.99 mmol). After 4 h, the reaction was quenched by successive addition of saturated aqueous solution of NH_4Cl (3.5 mL) and an aqueous solution of Na_2CO_3 (10% wt/v, 2.5 mL). The mixture was extracted with dichloromethane, dried over Na_2SO_4, concentrated and purified by column chromatography (SiO_2, ethyl acetate-pet.ether 2.5:7.5) to afford **137b** as colorless gum (0.133 g, 97%). (R_f= 0.37, 2.5:7.5 ethyl acetate-pet ether).

Yield	:	97%
$[\alpha]^{26}_D$	:	- 5.3(*c* = 1.85, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3414, 2972, 1673, 1366, 1176
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	7.77 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 5.3 (brs, 1H), 4.01-3.73 (m, 3H), 3.06-2.99 (m, 1H), 2.44 (s, 3H), 1.78 (s, 1H), 1.49-1.34 (m, 15H), 0.66 (t, *J* = 7.5 Hz, 3H)
^{13}C NMR (100MHz, $CDCl_3$) δ	:	155.5, 144.7, 132.4, 129.7, 127.8, 80.5, 75.4 71.8, 68.5, 40.4, 28.2, 26.2, 25.3, 21.5, 20.0, 6.4
MS (ESI): *m/z*	:	436.0946 $(M+Na)^+$, 452.0846 $(M+K)^+$

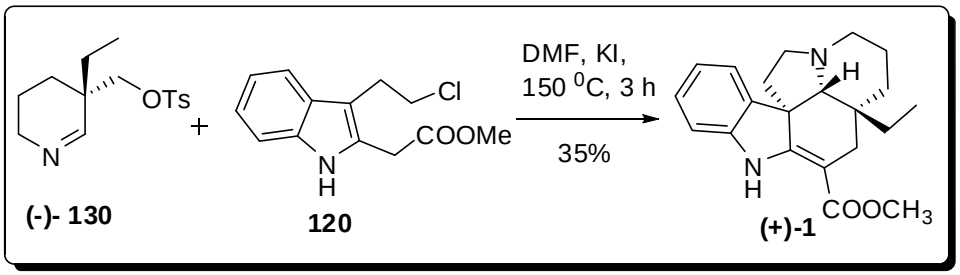
21. (3-Ethyl-3, 4, 5, 6-tetrahydropyridin-3-yl) methyl 4-methylbenzenesulfonate: (-)-130:



To a stirred solution of **139b** (0.11 g, 0.28 mmol) in 5 mL of dry dichloromethane was added trifluoroacetic acid (0.2 mL, 2.78 mmol) drop by drop, stirred at ambient temperature for 4 h, concentrated, neutralized with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was separated, dried over sodium sulfate, concentrated under reduced pressure and purified by column chromatography (SiO_2, EtOAc) to afford pure imine **130** as a colorless liquid (0.07 g, 90% yield, single enantiomer). Enantiomeric excess was determined by HPLC analysis and compared with the racemic imine by using (Chiralcel OJ-H (250×4.6mm) column, Isopropanol–pet ether (15:85) as an eluent), 0.7 mL/min (33 kgf), λ=254nm, 25 °C, the retention times of (-)-isomer and (+)-isomer being 21.408 and 23.867 minutes, respectively. (R_f: 0.4, ethyl acetate)

Yield	:	90%
$[\alpha]^{28}_D$	:	- 42.2 (*c* = 2.0, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	2941, 1654, 1363, 1176.
^{1}H NMR (500 MHz, $CDCl_3$) δ	:	7.77 (d, *J* = 8.0 Hz, 2H), 7.38 (brs, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.85, 3.81 (2 sets of doublet, *J* = 9.3 Hz, 2H), 3.53-3.42 (m, 2H), 2.44 (s, 3H), 1.56-1.39 (m, 6H), 0.81 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (125MHz, $CDCl_3$) δ	:	164.7, 145.0, 132.3, 129.8, 127.8, 127.8, 72.9, 49.1, 39.9, 27.2, 25.3, 21.6, 18.7, 7.6.
HR-MS (EI)	:	calcd for $C_{15}H_{21}NO_3S$: 295.12421. Found: 295.11549

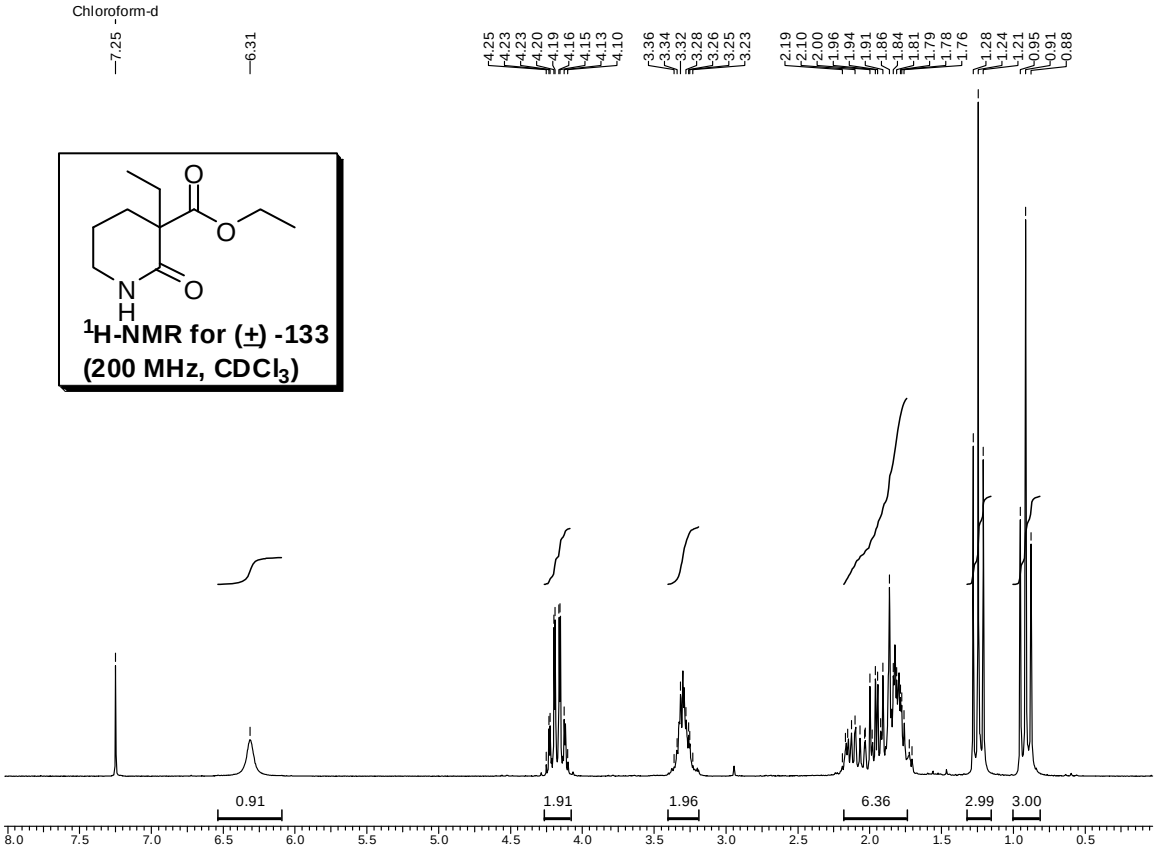
22. (+)-Vincadifformine (1):

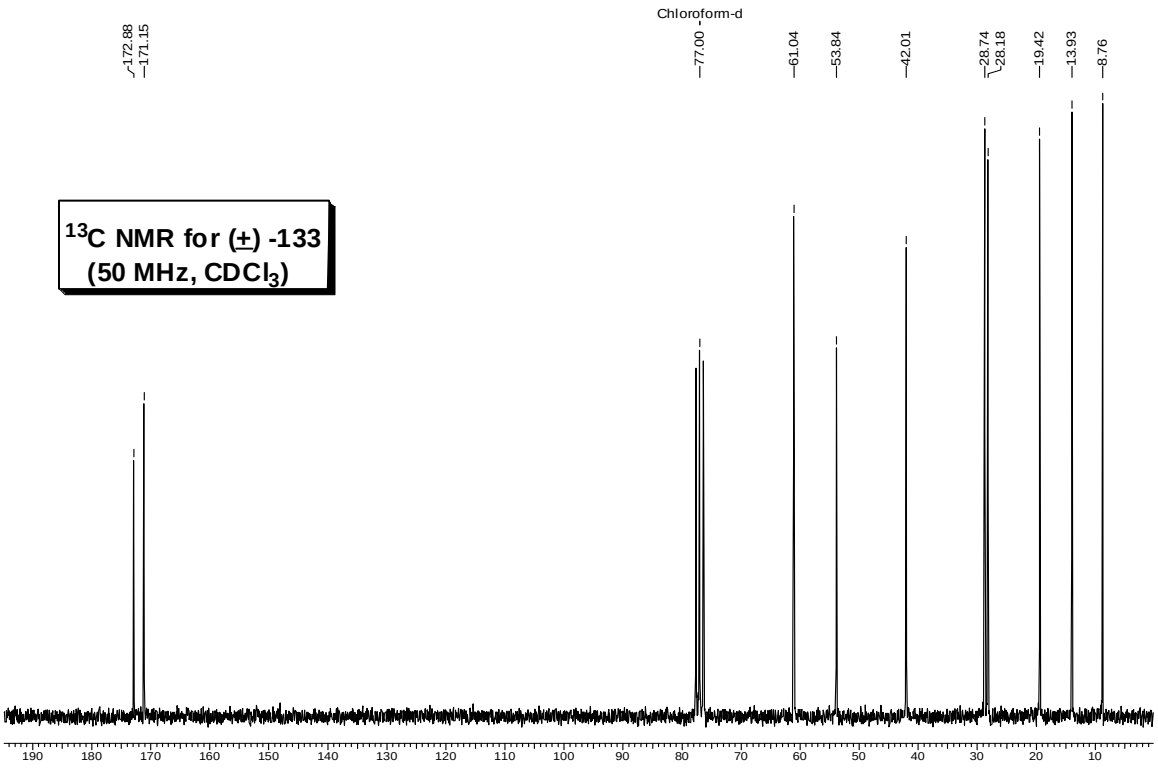


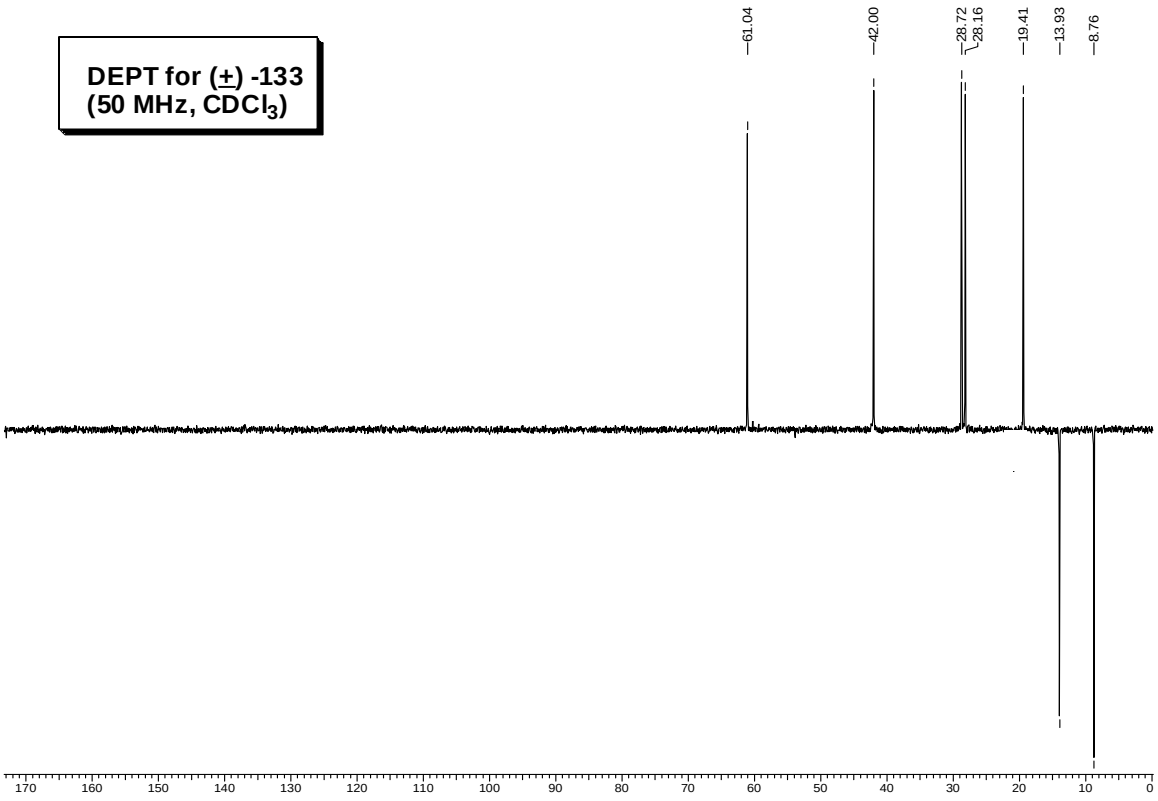
The stirred solution of methyl-2-(3-(2-chloroethyl)-1H-indol-2-yl)acetate (**120**) (0.101g, 0.40 mmol) and potassium iodide (0.467 g, 2.8 mmol) in 4 mL of anhydrous DMF was degassed three to four times in presence of argon and heated at 80 °C for 2 h, cooled to room temperature. Imine **(-)-130** (0.12 g, 0.4 mmol) dissolved in 2 mL anhydrous DMF was added to the flask. After heating at 150 °C to 155 °C for 3 h, it was cooled to rt, diluted with ethyl acetate, quenched with ice water. The organic layer was separated, dried over Na_2SO_4, concentrated, purified by column chromatography (SiO_2, ethyl acetate- pet ether 15:85) to afford vincadifformine (+)-**1** (0.04g, 35%, >99%ee). Enantiomeric excess was determined by HPLC analysis by comparing with the racemic **1**(Chiralcel OD-H (250×4.6mm) column, ethanol: petether:TFA (15:85:0.1) as an eluent), 0.5mL/min (26kgf), λ=220nm, 25°C, the retention times of (+)-isomer and (-)-isomer being 14.94 and 18.98 minutes, respectively. R_f: 0.37(1.5:8.5 ethyl acetate: pet ether).

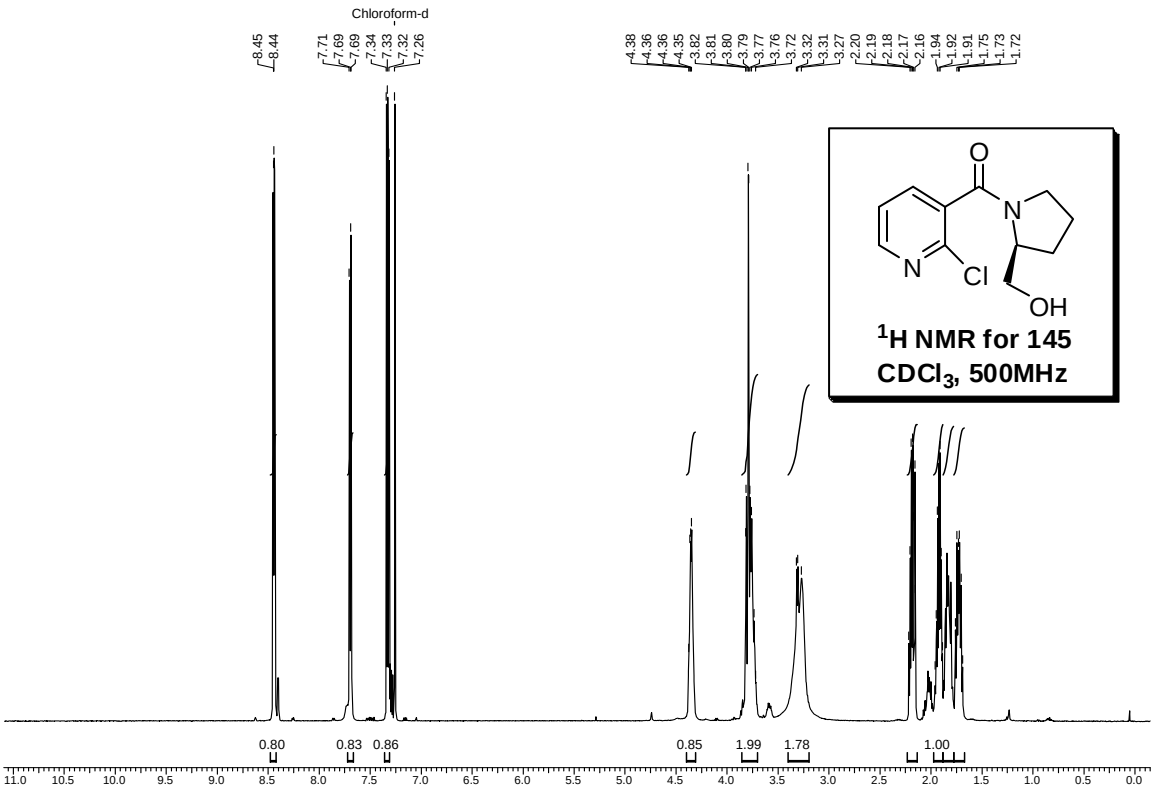
Yield	:	35%
$[\alpha]^{28.3}_{D}$	:	+ 550.76 (*c* = 0.2, EtOH)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	:	3368, 2934, 2774, 1674, 1608, 1463, 908, 733
^{1}H NMR (400 MHz, $CDCl_3$) δ	:	8.89 (brs, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.11 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.84 (dt, *J* = 7.3, 0.75 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 3.75 (s, 3H), 3.12 (brd, *J* = 9.3 Hz 1H), 2.91 (t, *J* = 7.2 Hz, 1H), 2.71 (d, J = 15.1 Hz, 1H), 2.58-2.52 (m, 1H), 2.45 (s, 1H), 2.43-2.35 (m, 1H), 2.26 (dd, *J* = 15.1, 1.7 Hz, 1H), 2.08-2.01 (m, 1H), 1.88-1.81 (m, 1H), 1.80-1.75 (m, 1H), 1.69 (dd, *J* = 11.5, 4.5 Hz, 1H), 1.56-1.50 (m, 1H), 1.27-1.20 (m, 1H), 0.96 (m, 1H), 0.62 (m, 1H), 0.56 (t, *J* = 6.8 Hz, 3H)
^{13}C NMR (100MHz, $CDCl_3$) δ	:	169.3, 167.9, 143.4, 138.1, 127.5, 121.1, 120.6, 109.4, 92.7, 72.8, 55.6, 51.8, 51.1, 50.8, 45.4, 38.3, 33.0, 29.4, 25.6, 22.3, 7.2.
HR-MS (EI)	:	calcd for $C_{21}H_{26}N_2O_2$: 338.19943. Found: 338.20066.

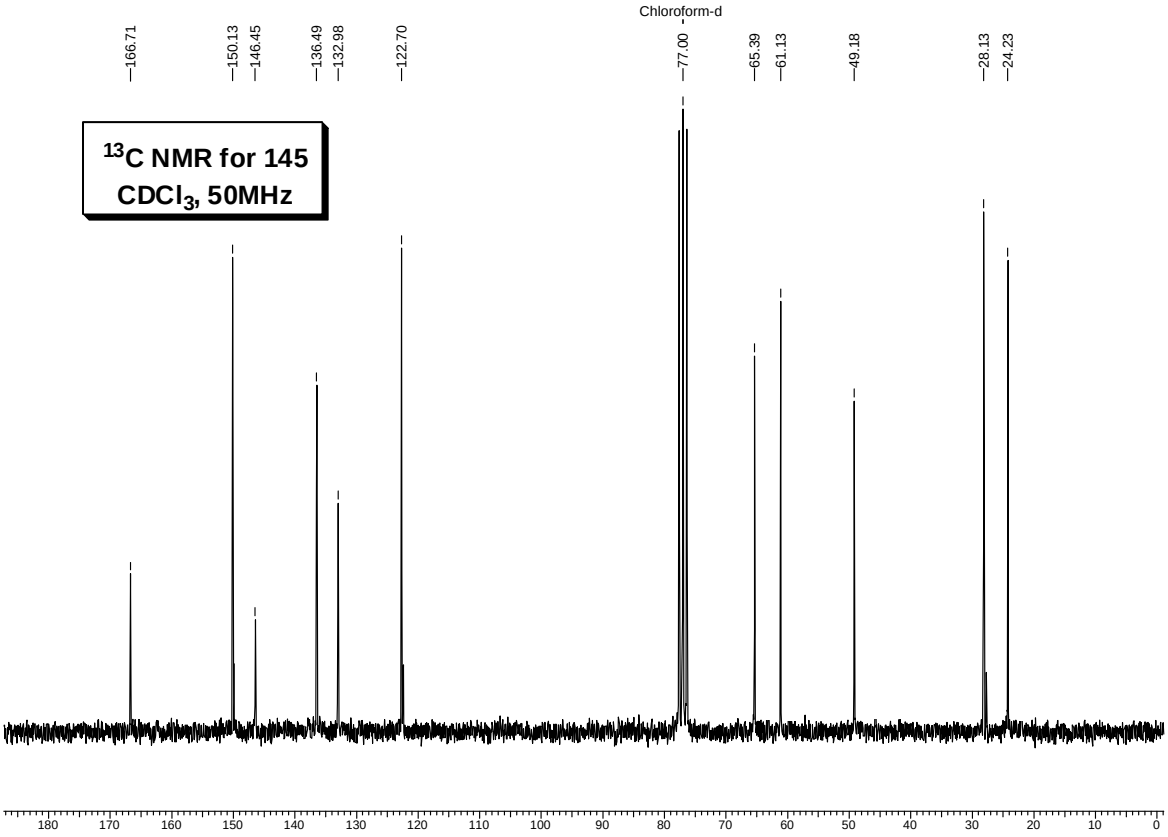
2D.3 Spectra

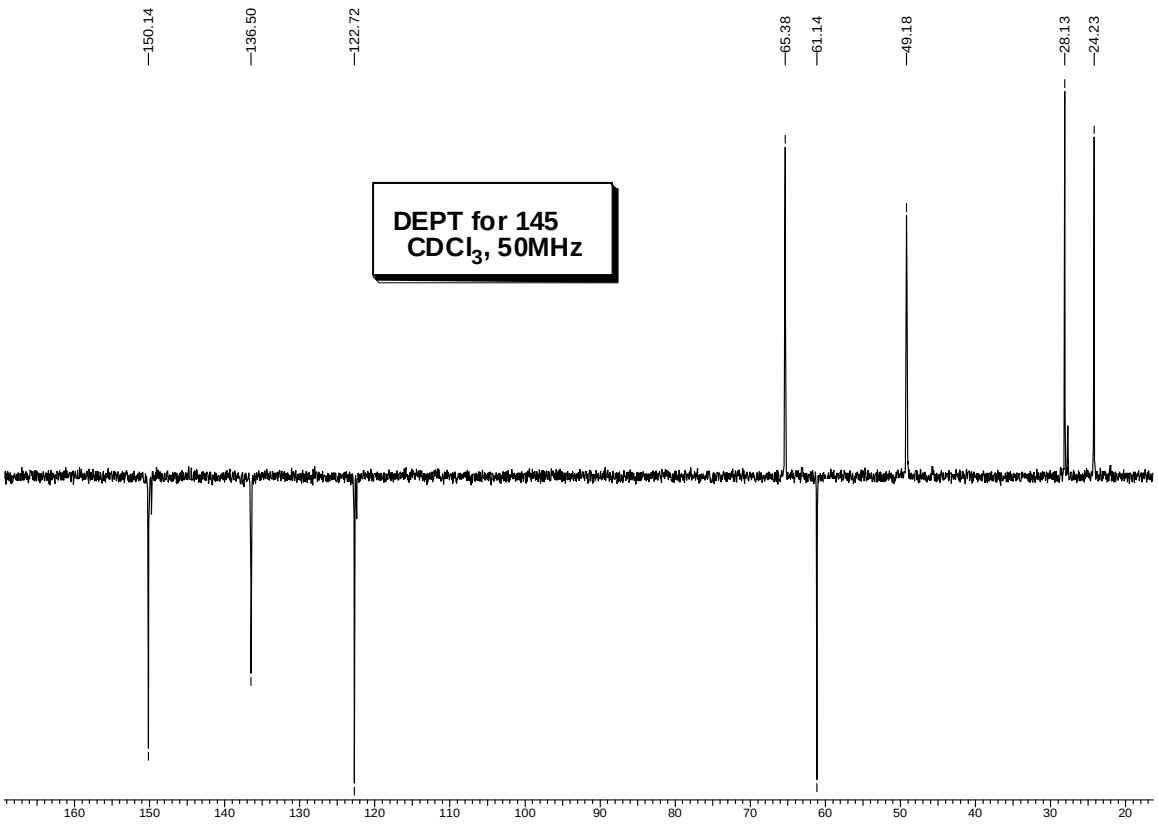

Chloroform-d
7.25
6.31
4.25
4.23
4.23
4.20
4.19
4.16
4.15
4.13
4.10
3.36
3.34
3.32
3.28
3.26
3.25
3.23
2.19
2.10
2.00
1.96
1.94
1.91
1.86
1.84
1.81
1.79
1.78
1.76
1.28
1.24
1.21
0.95
0.91
0.88
O
O
N
H
O
^{1}H-NMR for (±) -133
(200 MHz, $CDCl_3$)
0.91
1.91
1.96
6.36
2.99
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

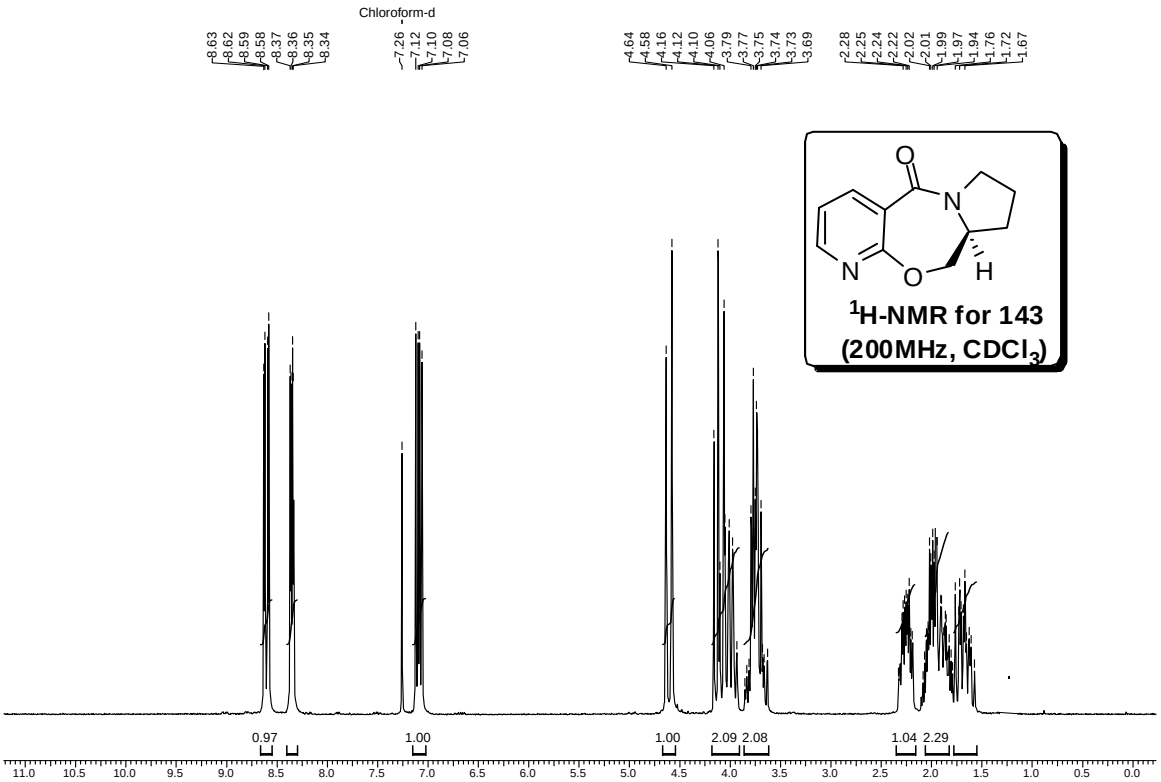

172.88
171.15
Chloroform-d
77.00
61.04
53.84
42.01
28.74
28.18
19.42
13.93
8.76
^{13}C NMR for (±) -133
(50 MHz, $CDCl_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

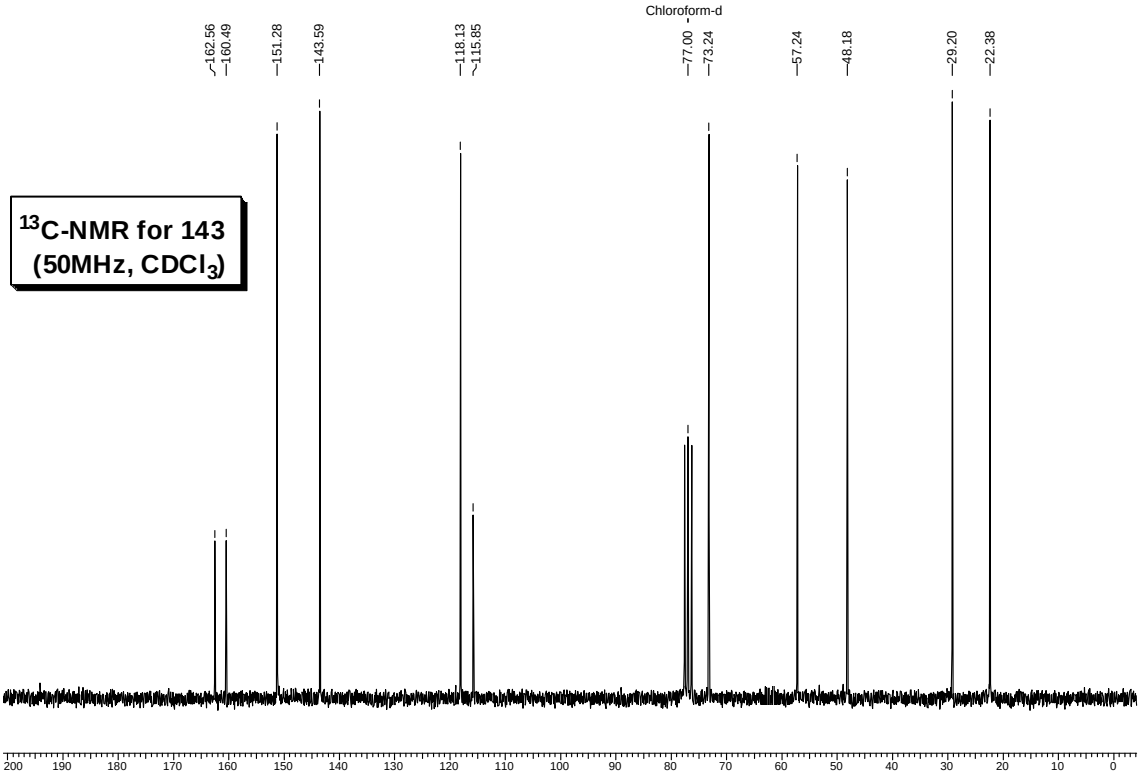

DEPT for (±) -133
(50 MHz, CDCl3)
61.04
42.00
28.72
28.16
19.41
13.93
8.76

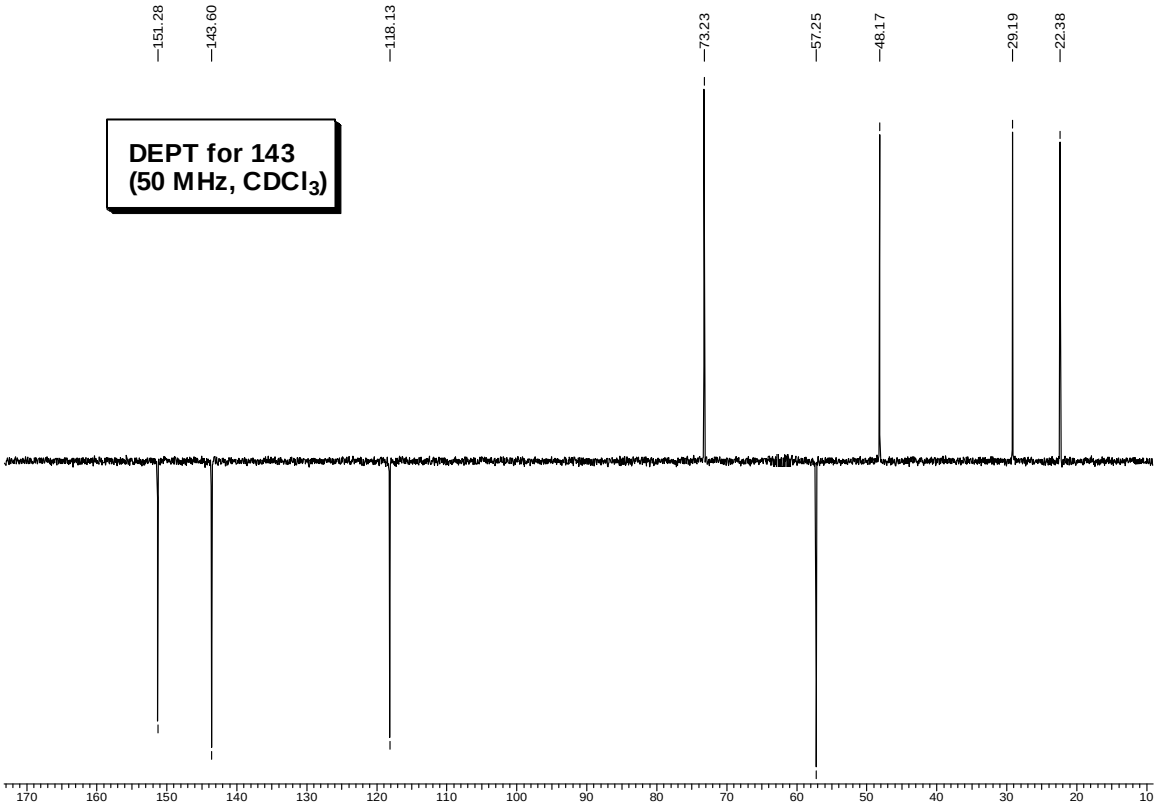

Chloroform-d
8.45
8.44
7.71
7.69
7.69
7.34
7.33
7.32
7.26
4.38
4.36
4.36
4.35
3.82
3.81
3.80
3.79
3.77
3.76
3.72
3.32
3.31
3.27
2.20
2.19
2.18
2.17
2.16
1.94
1.92
1.91
1.75
1.73
1.72
O
N
N
Cl
OH
1H NMR for 145
CDCl3, 500MHz
0.80
0.83
0.86
0.85
1.99
1.78
1.00

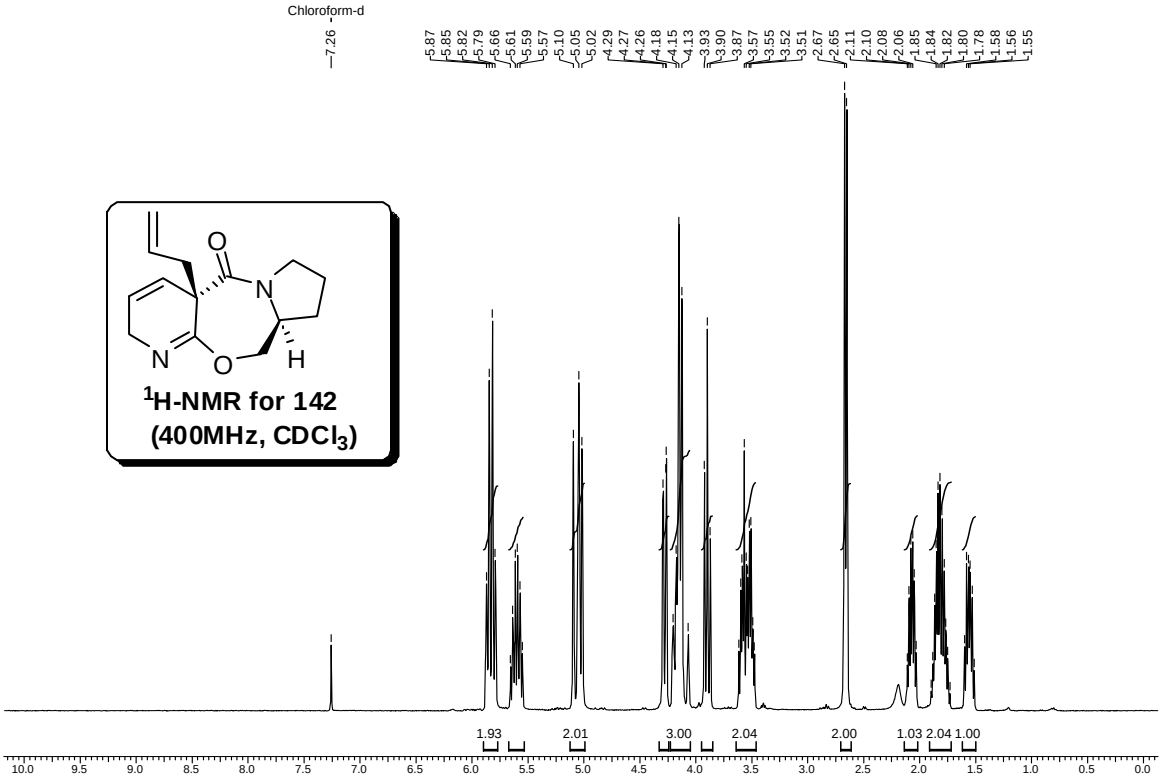

Chloroform-d
166.71
150.13
146.45
136.49
132.98
122.70
77.00
65.39
61.13
49.18
28.13
24.23
13C NMR for 145
CDCl3, 50MHz
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

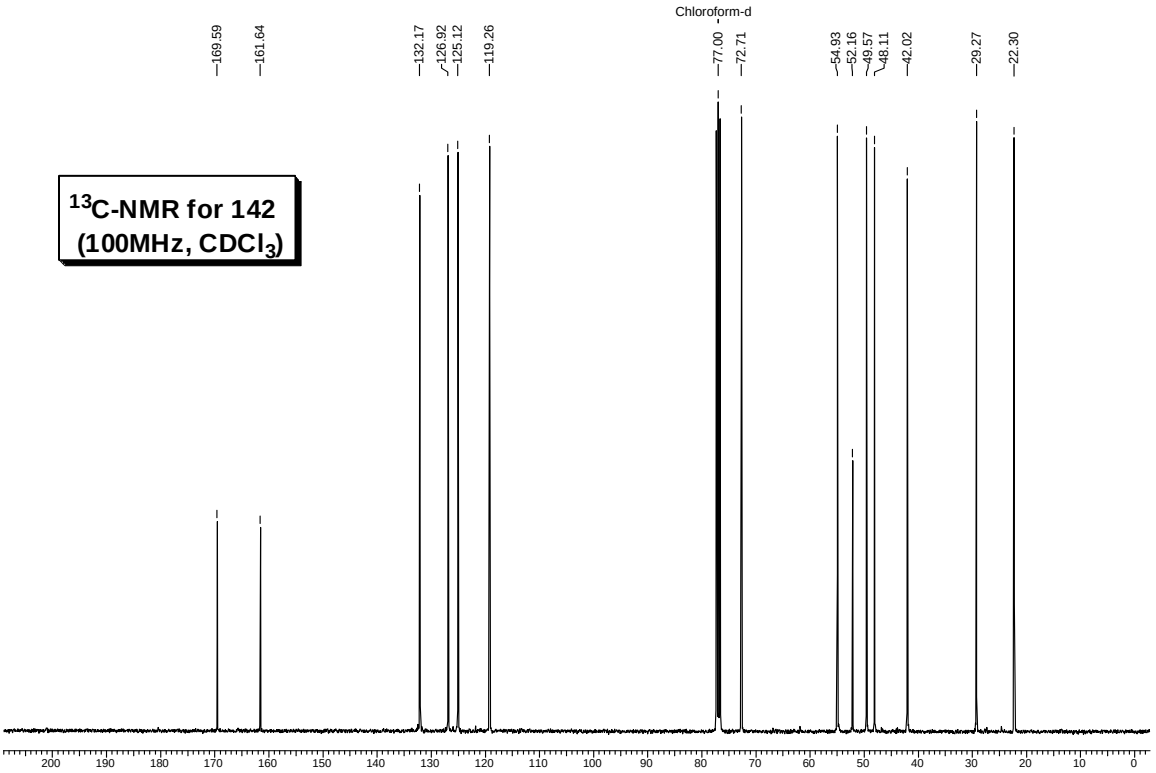

150.14
136.50
122.72
65.38
61.14
49.18
28.13
24.23
DEPT for 145
CDCl3, 50MHz
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20

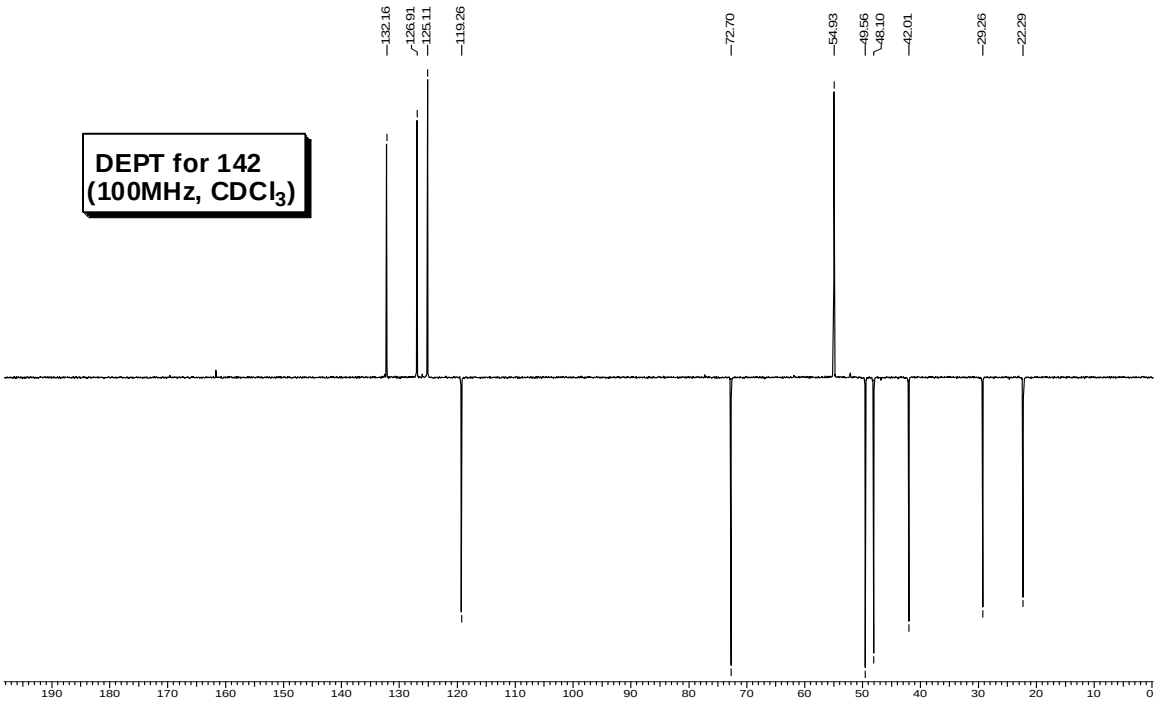

Chloroform-d
8.63
8.62
8.59
8.58
8.37
8.36
8.35
8.34
7.26
7.12
7.10
7.08
7.06
4.64
4.58
4.16
4.12
4.10
4.06
3.79
3.77
3.75
3.74
3.73
3.69
2.28
2.25
2.24
2.22
2.02
2.01
1.99
1.97
1.94
1.76
1.72
1.67
O
N
N
O
H
1H-NMR for 143
(200MHz, CDCl3)
0.97
1.00
1.00
2.09
2.08
1.04
2.29


Chloroform-d
162.56
160.49
151.28
143.59
118.13
115.85
77.00
73.24
57.24
48.18
29.20
22.38
13C-NMR for 143
(50MHz, CDCl3)

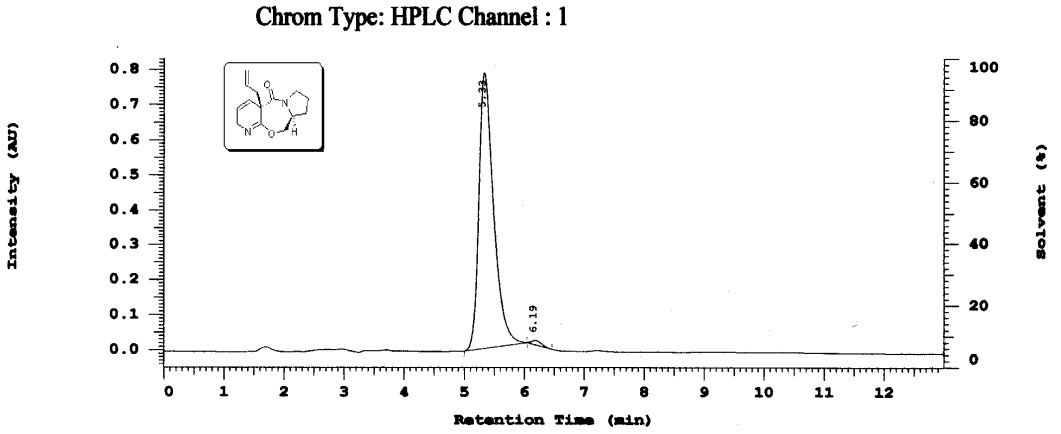

151.28
143.60
118.13
73.23
57.25
48.17
29.19
22.38
DEPT for 143
(50 MHz, CDCl3)


Chloroform-d
7.26
1.93
2.01
3.00
2.04
2.00
1.03
2.04
1.00
1H-NMR for 142
(400MHz, CDCl3)


Chloroform-d
169.59
161.64
132.17
126.92
125.12
119.26
77.00
72.71
54.93
52.16
49.57
48.11
42.02
29.27
22.30
^{13}C-NMR for 142
(100MHz, CDCl$_3$)


132.16
126.91
125.11
119.26
72.70
54.93
49.56
48.10
42.01
29.26
22.29
DEPT for 142
(100MHz, CDCl$_3$)

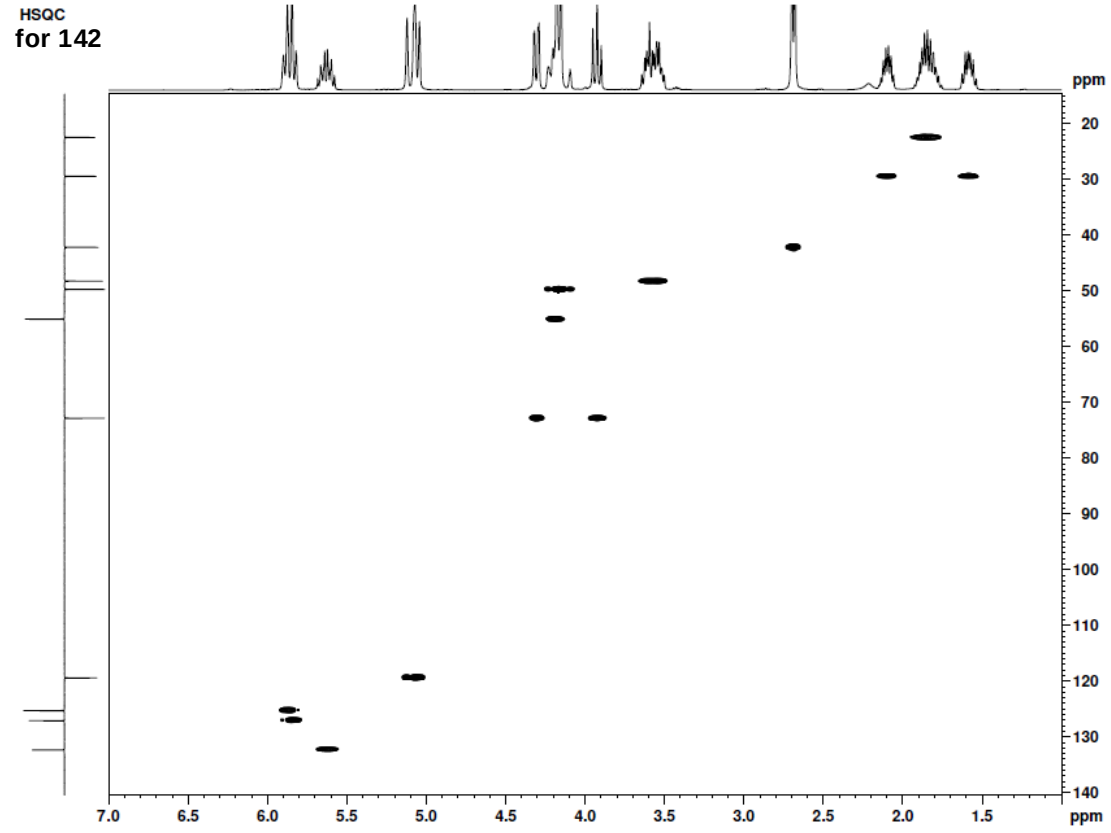
HPLC resolution of diastereomers of 142:



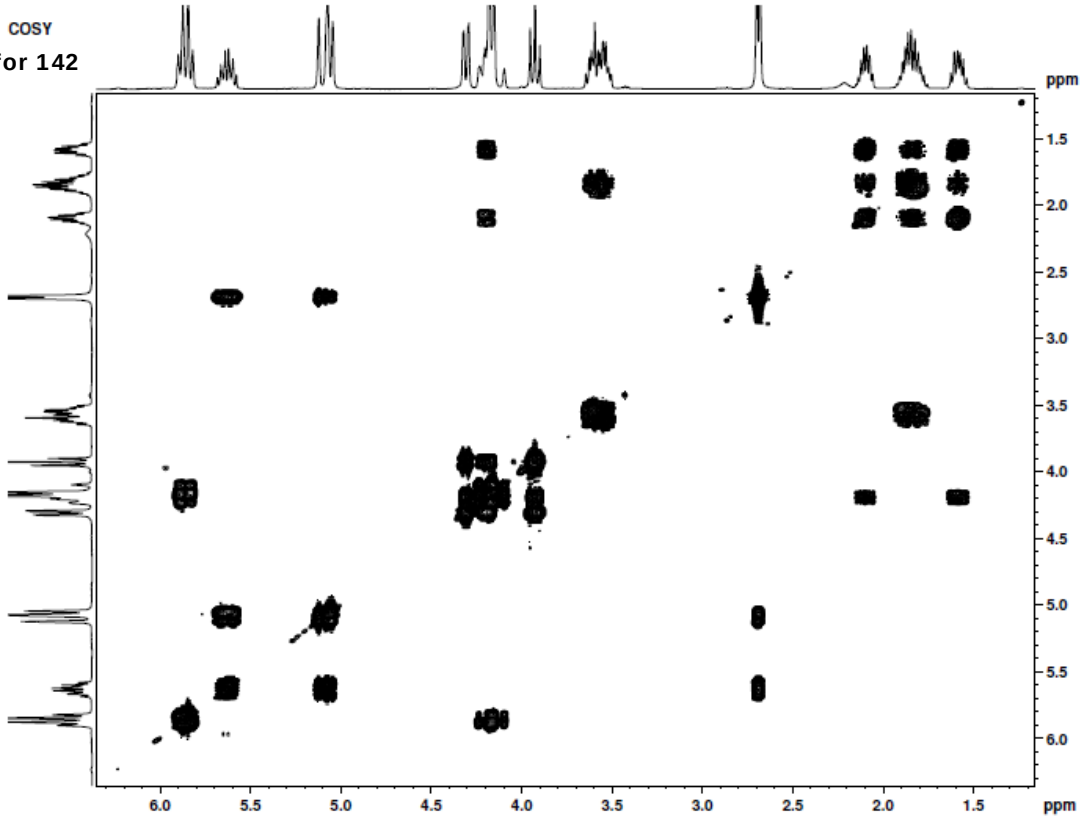
No.	RT	Height	Area	Area %
1	5.33	392937	6709760	98.938
2	6.19	6155	72044	1.062
		399092	6781804	100.000

HPLC Conditions	:	*Column*	:	*Atlantis RP-18 (250×4.6mm)*
		Mobile Phase	:	*Acetonitrile: Water (40:60)*
		Wavelength	:	*224 nm*
		Flow rate	:	*1.0 mL/min (1200psi)*
		Sample Concentration	:	*2 mg/1 mL (Inj vol-5 µL)*

HSQC
for 142

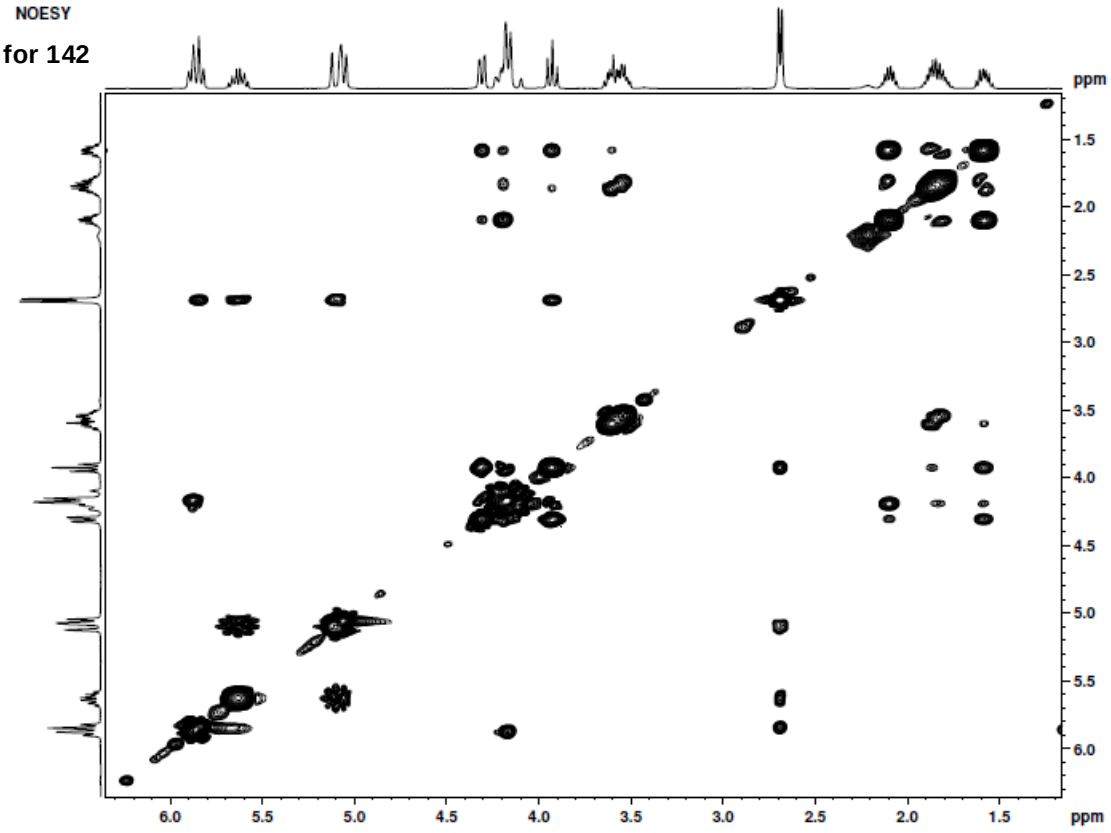


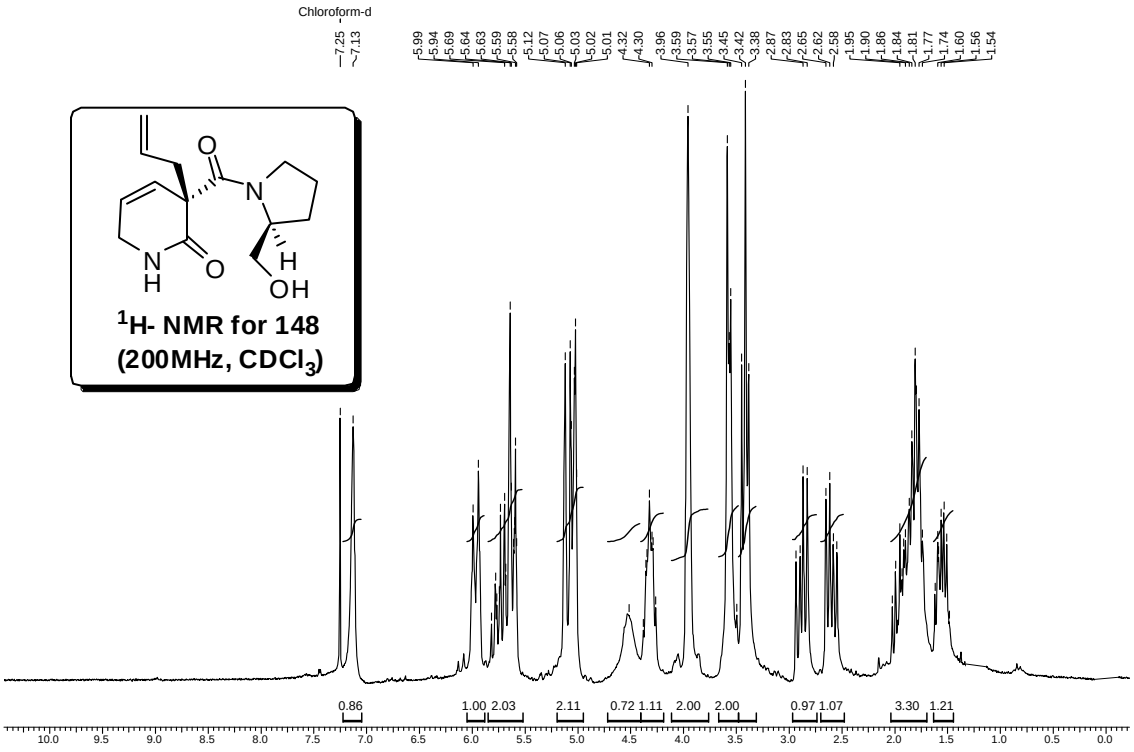
COSY
for 142



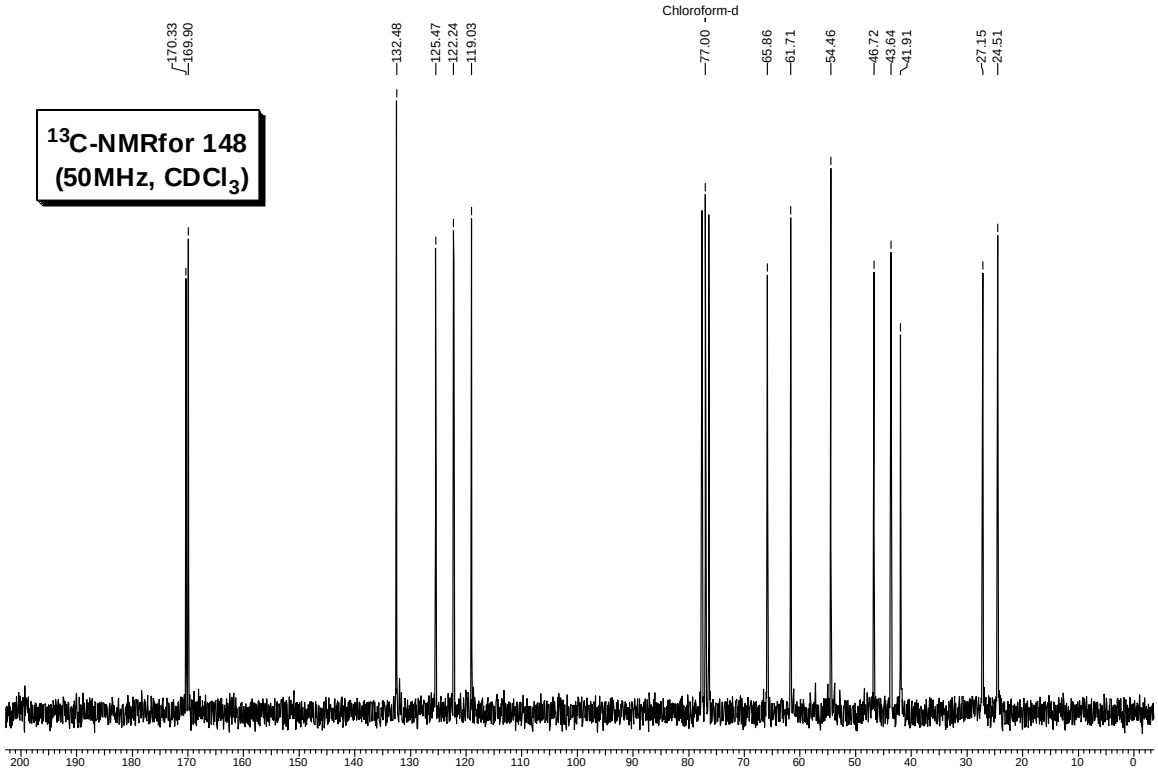
NOESY

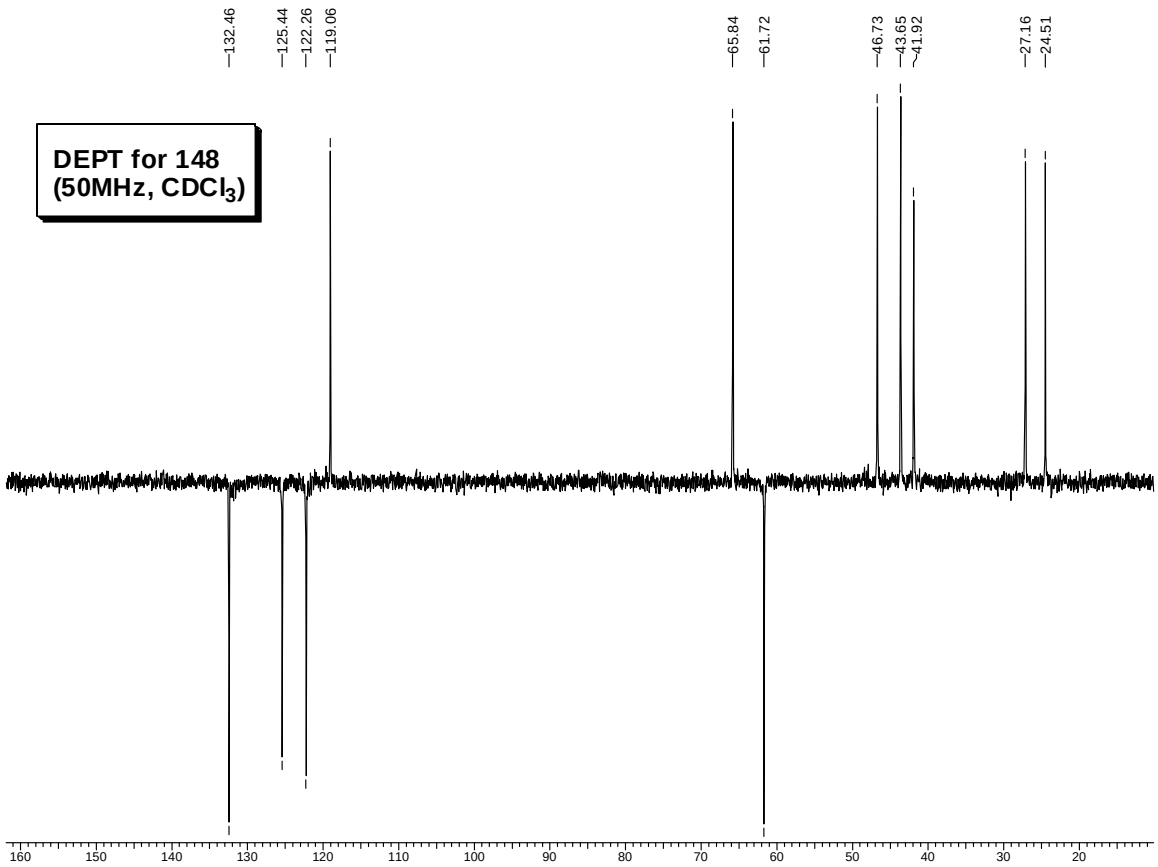
for 142

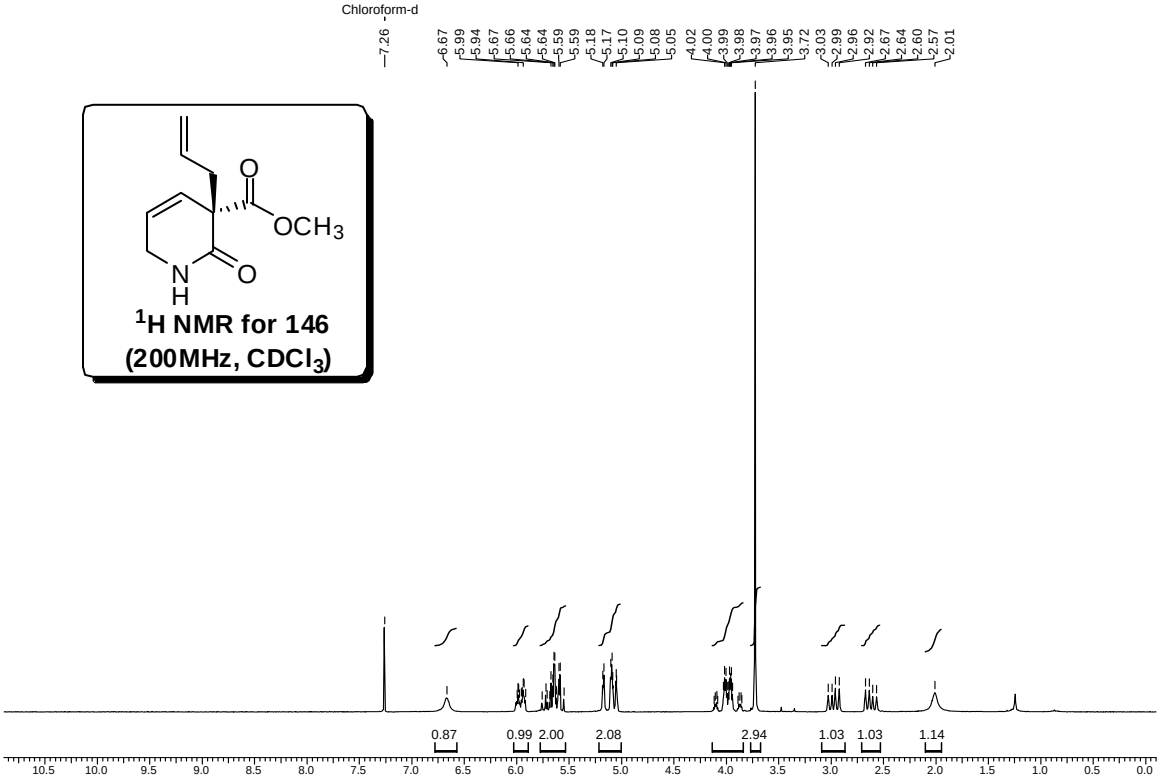




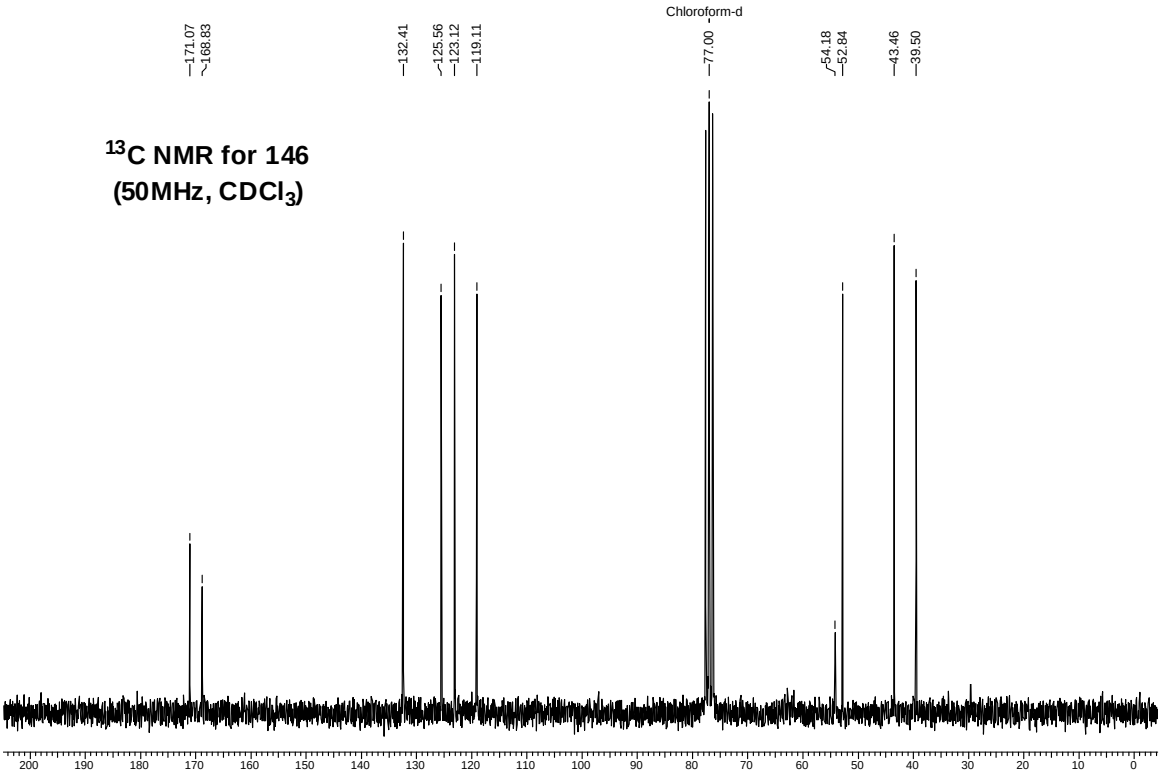
^{1}H- NMR for 148 (200MHz, $CDCl_3$)


Chloroform-d
170.33
169.90
132.48
125.47
122.24
119.03
77.00
65.86
61.71
54.46
46.72
43.64
41.91
27.15
24.51
^{13}C-NMRfor 148
(50MHz, CDCl$_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

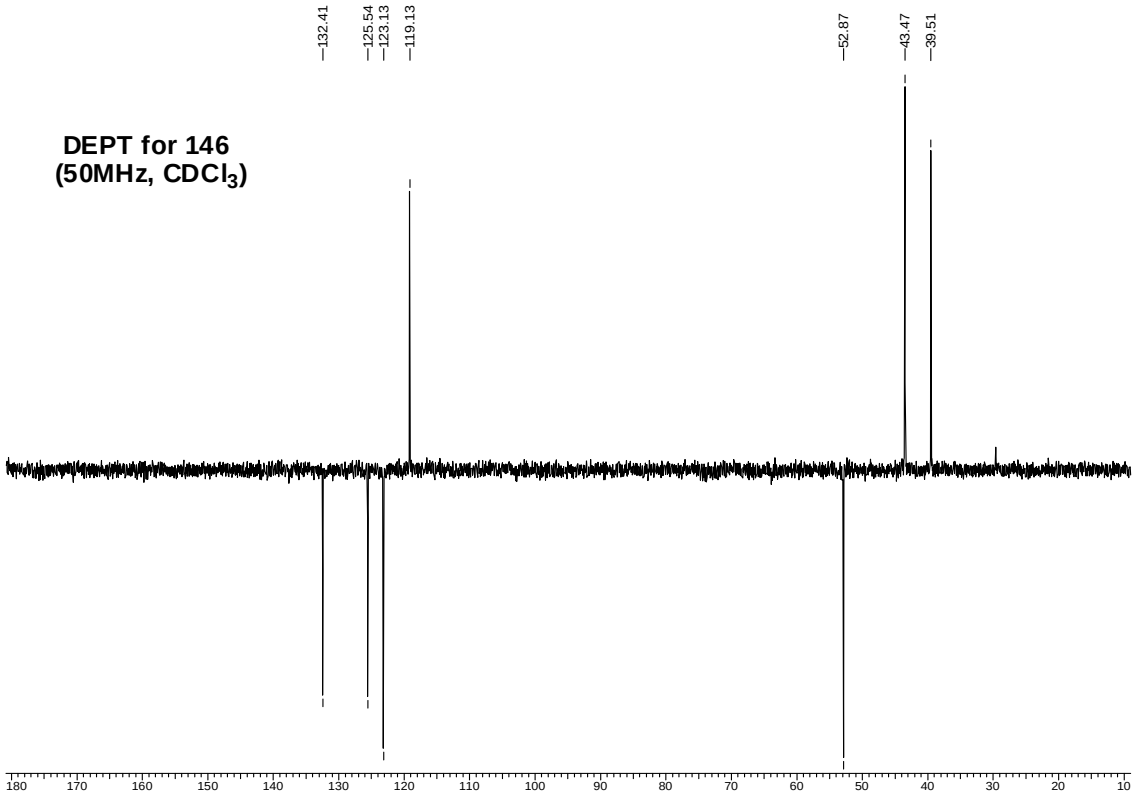

132.46
125.44
122.26
119.06
65.84
61.72
46.73
43.65
41.92
27.16
24.51
DEPT for 148
(50MHz, CDCl$_3$)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20



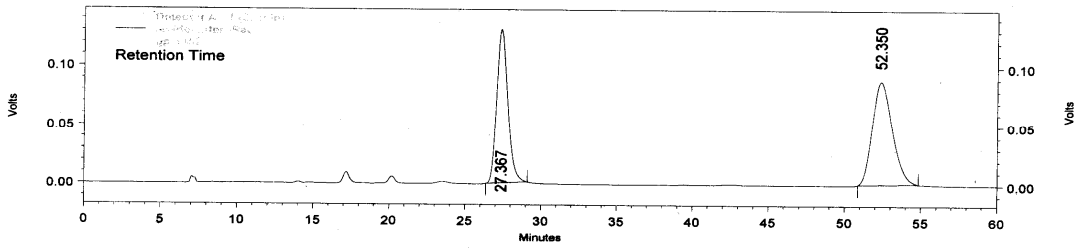
^{1}H NMR for 146 (200MHz, $CDCl_3$)



^{13}C NMR for 146 (50MHz, $CDCl_3$)



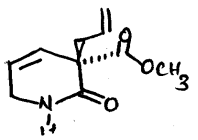
HPLC resolution of enantiomers of 146:



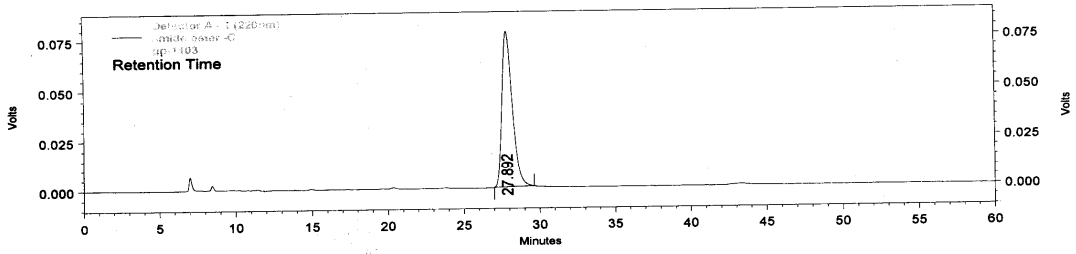
Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	27.367	6676591	45.529	130267	59.72
2	52.350	7987913	54.471	87868	40.28
Totals		14664504	100.000	218135	100.00

Column :-Chiralcel OD- H(250x4.6mm)
M.P. :IPA:P.E.(10:90)
Wavelength :- 220 nm
Flow :- 0.5ml/min(265psi)
conc. :- 2mg/2 ml
Injection vol : Inj Vol- 5ul



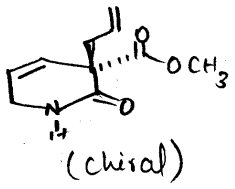
(Racemized product)

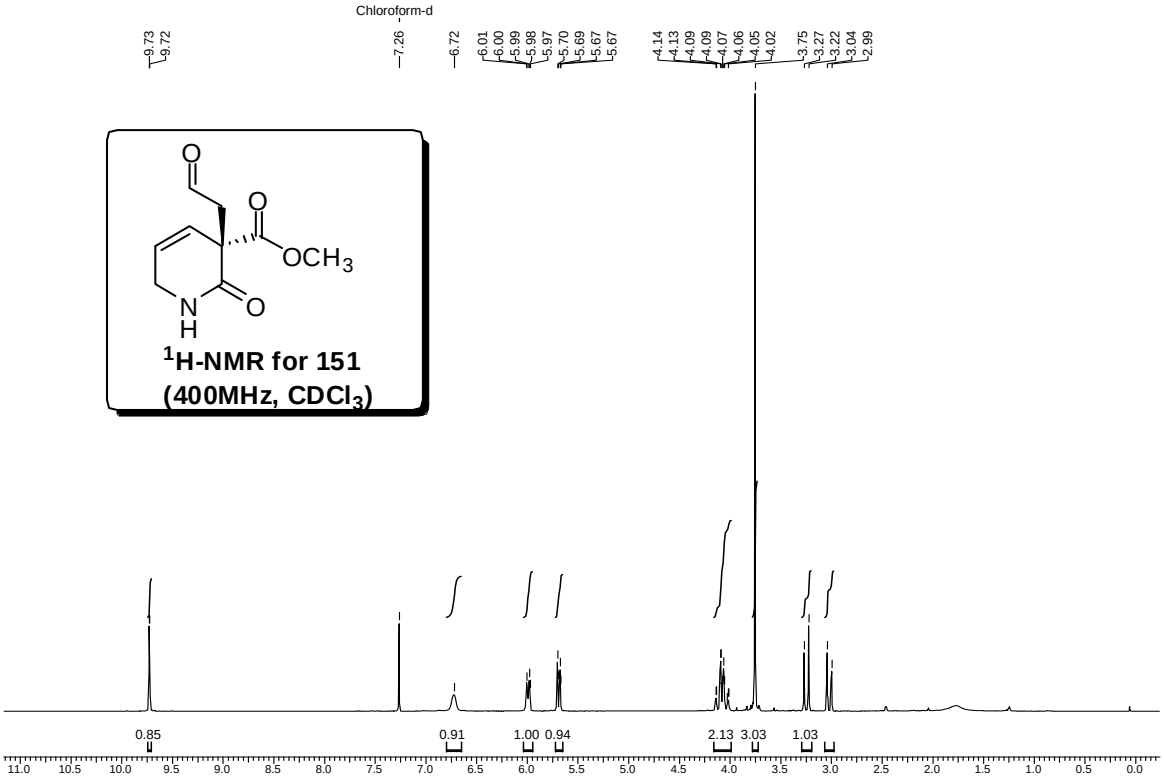


Detector A - 1 (220nm)

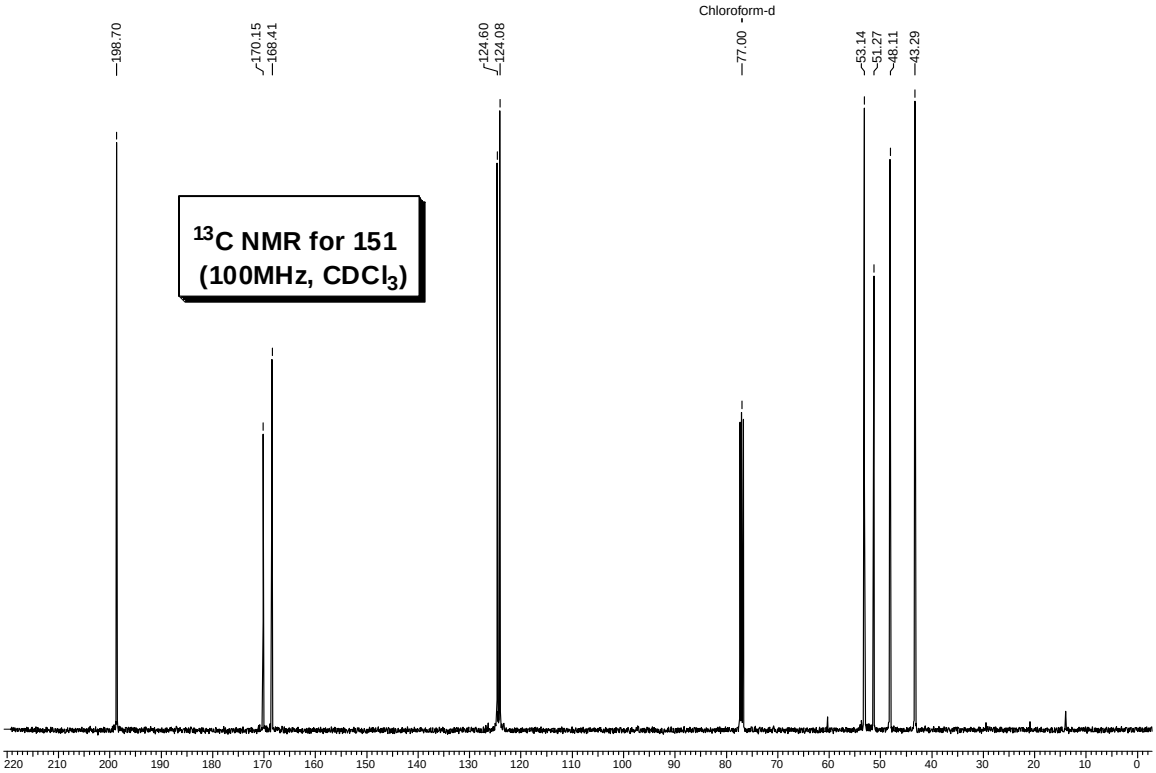
Pk #	Retention Time	Area	Area %	Height	Height Percent
1	27.892	3708490	100.000	78021	100.00
Totals		3708490	100.000	78021	100.00

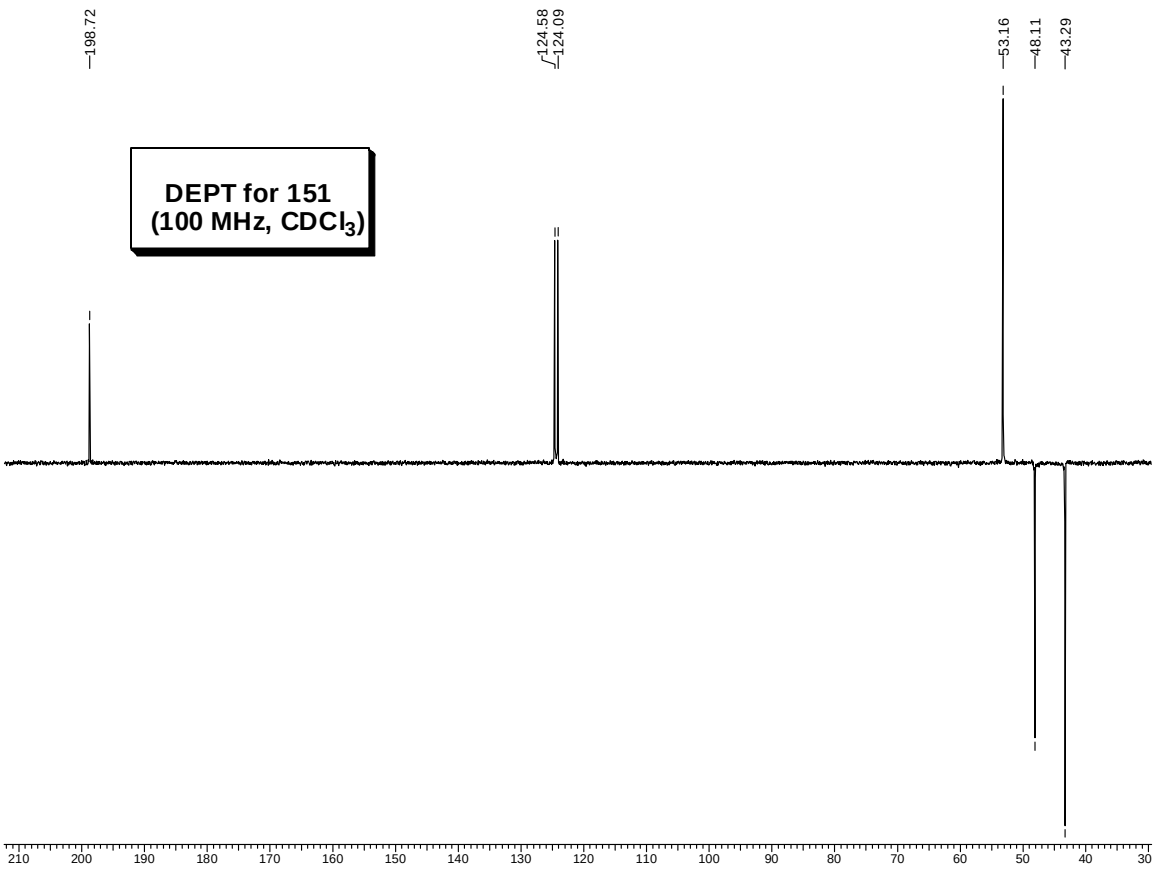
Column :-Chiralcel OD- H(250x4.6mm)
M.P. :IPA:P.E.(10:90)
Wavelength :- 220 nm
Flow :- 0.5ml/min(265psi)
conc. :- 2mg/2 ml
Injection vol : Inj Vol- 5ul

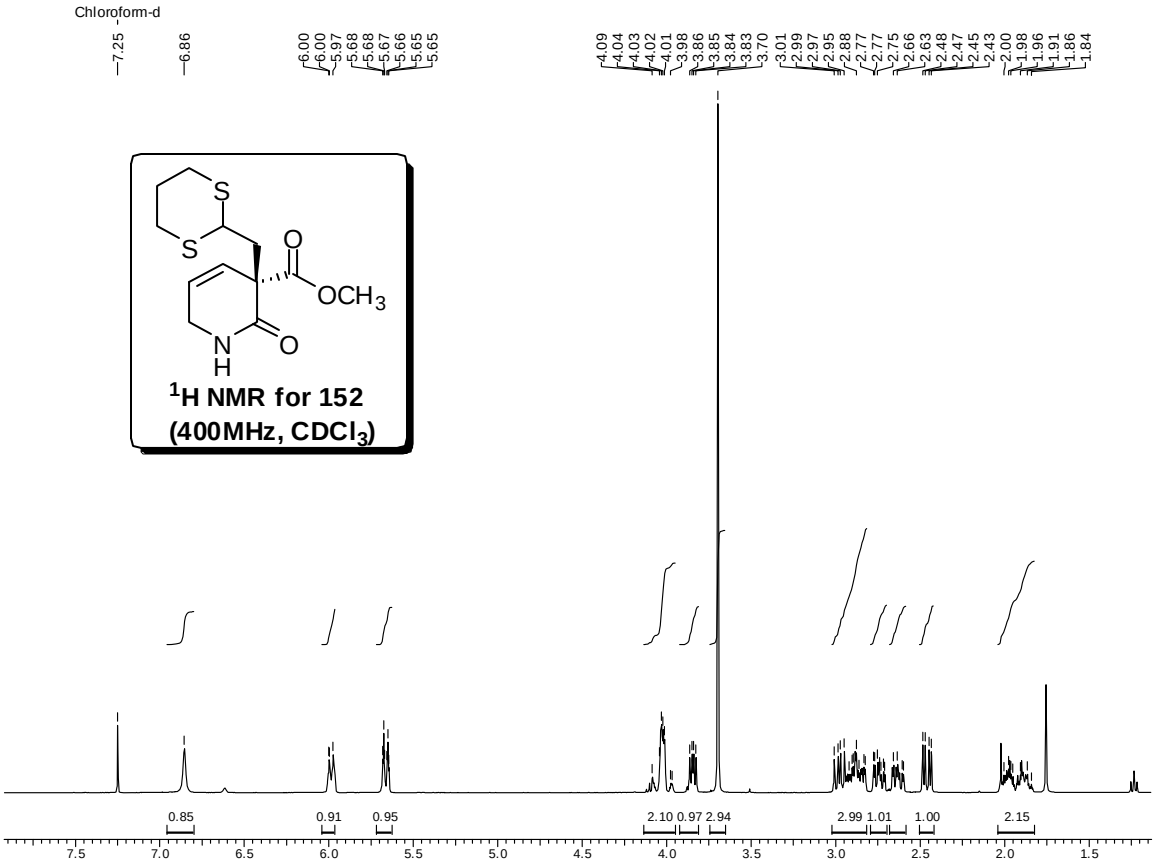


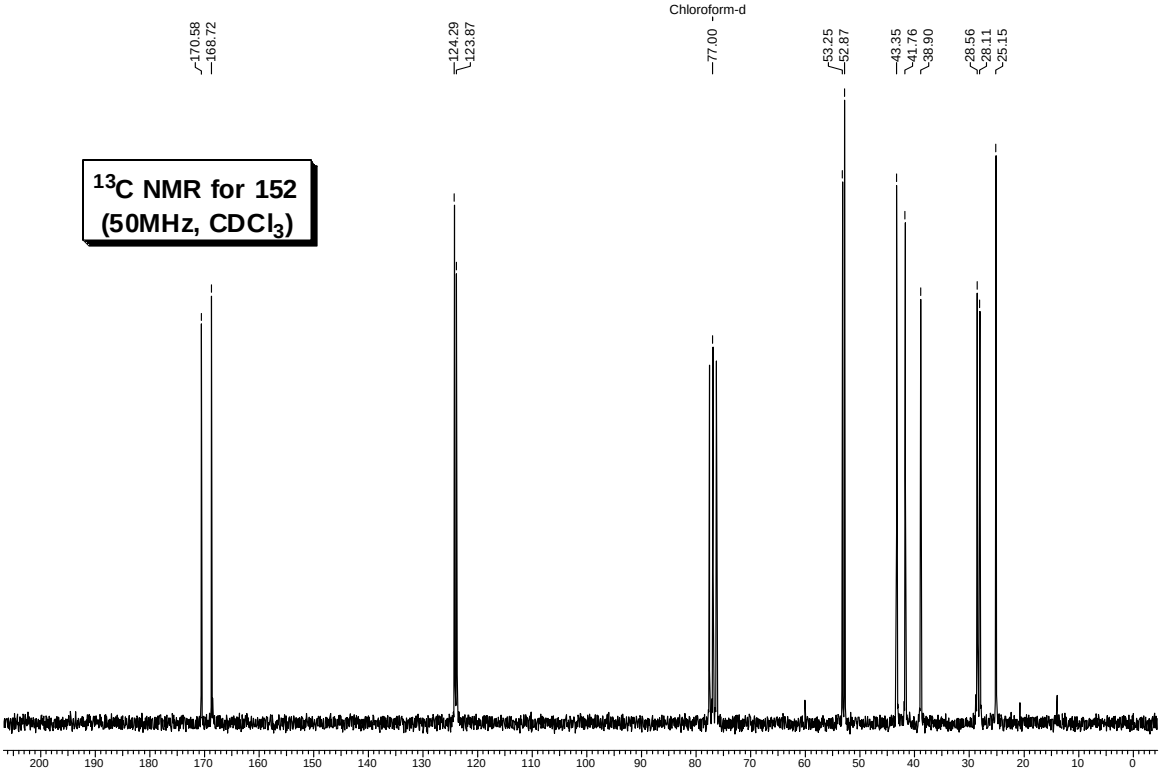


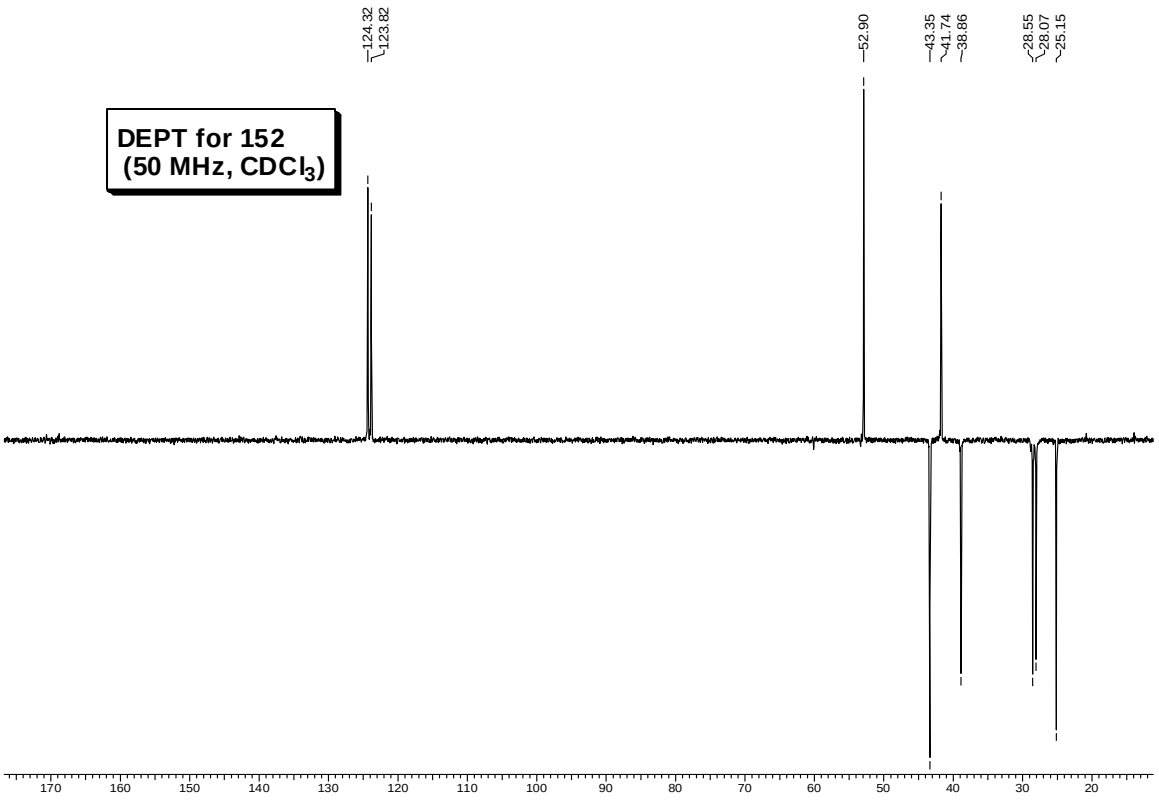
^{1}H-NMR for 151 (400MHz, $CDCl_3$)

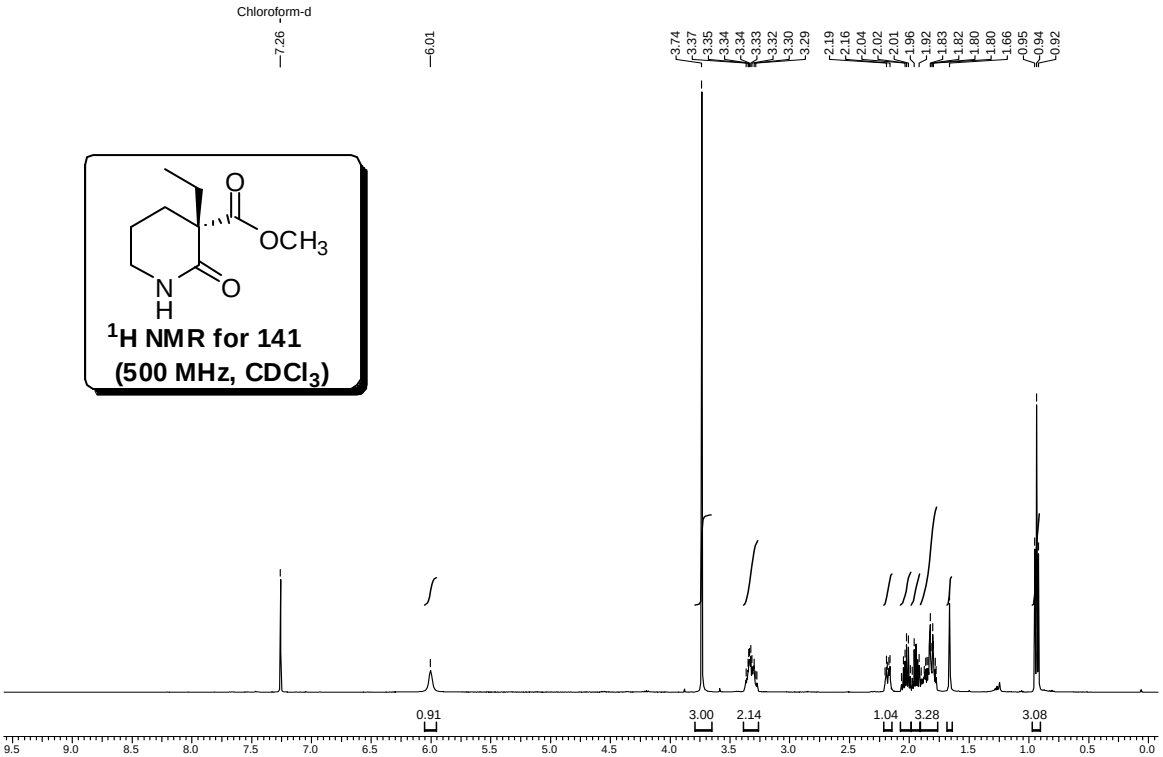

198.70
170.15
168.41
124.60
124.08
Chloroform-d
77.00
53.14
51.27
48.11
43.29
^{13}C NMR for 151
(100MHz, CDCl$_3$)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

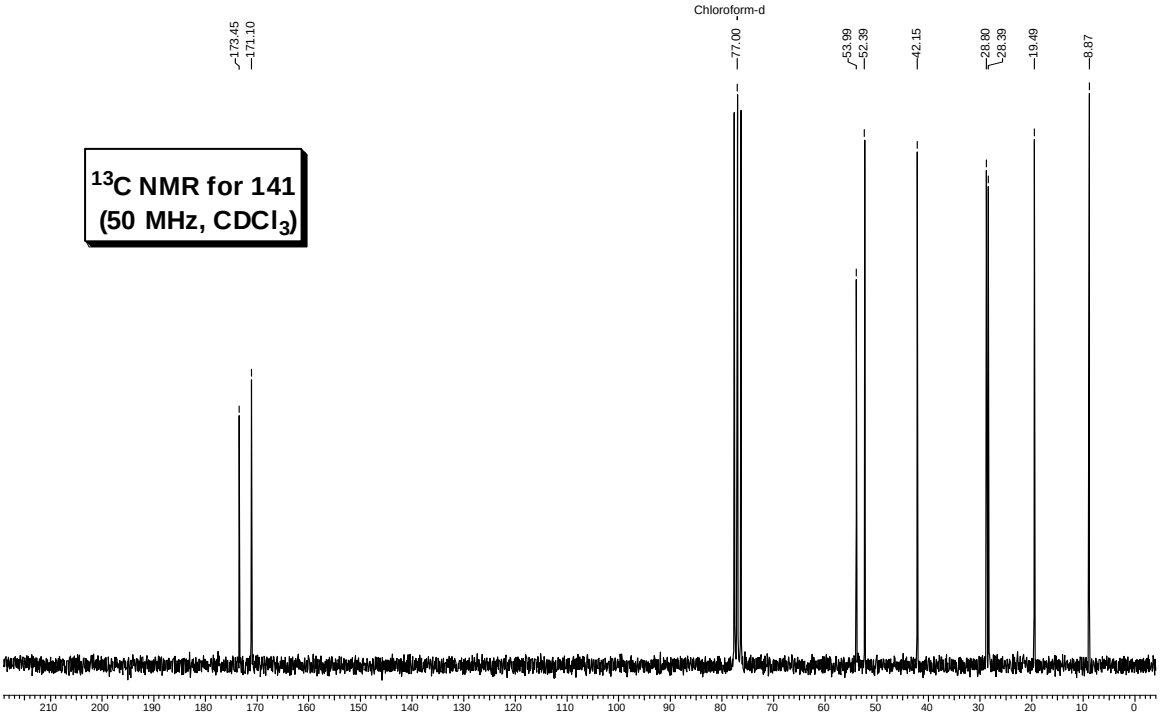

198.72
124.58
124.09
53.16
48.11
43.29
DEPT for 151
(100 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30

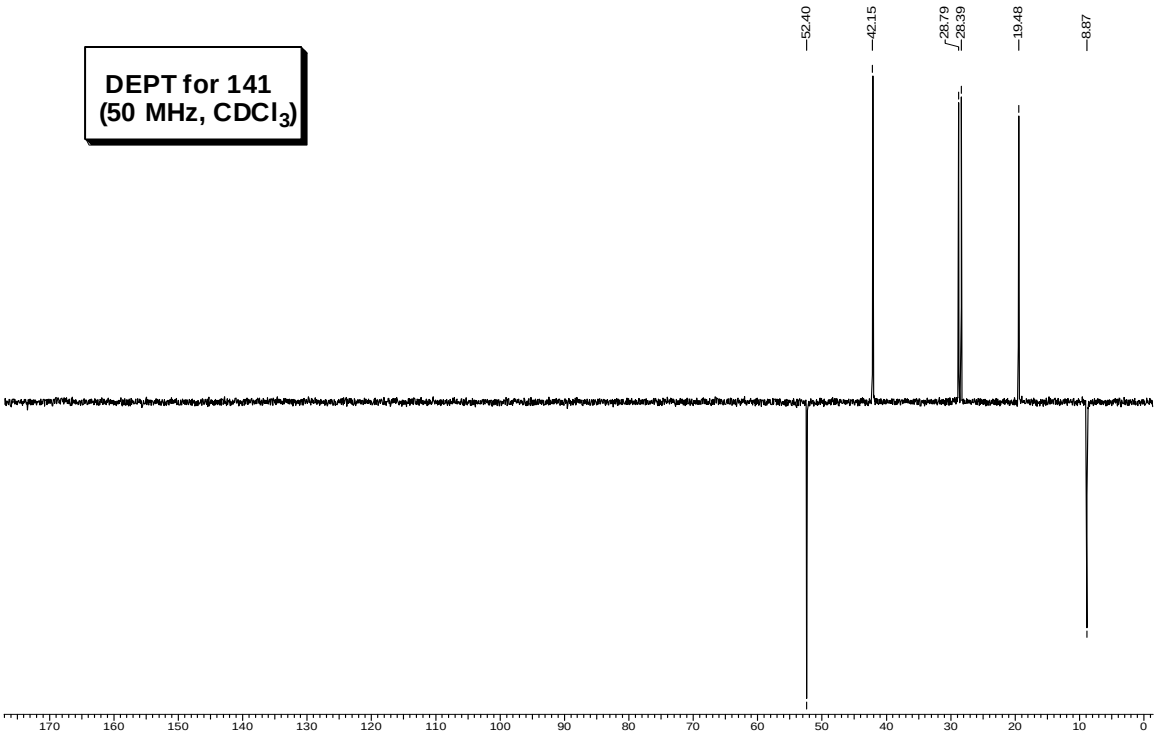

Chloroform-d
7.25
6.86
6.00
6.00
5.97
5.68
5.68
5.67
5.66
5.65
5.65
4.09
4.04
4.03
4.02
4.01
3.98
3.86
3.85
3.84
3.83
3.70
3.01
2.99
2.97
2.95
2.88
2.77
2.77
2.75
2.66
2.63
2.48
2.47
2.45
2.43
2.00
1.98
1.96
1.91
1.86
1.84
S
S
O
OCH3
N
H
O
1H NMR for 152
(400MHz, CDCl3)
0.85
0.91
0.95
2.10
0.97
2.94
2.99
1.01
1.00
2.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

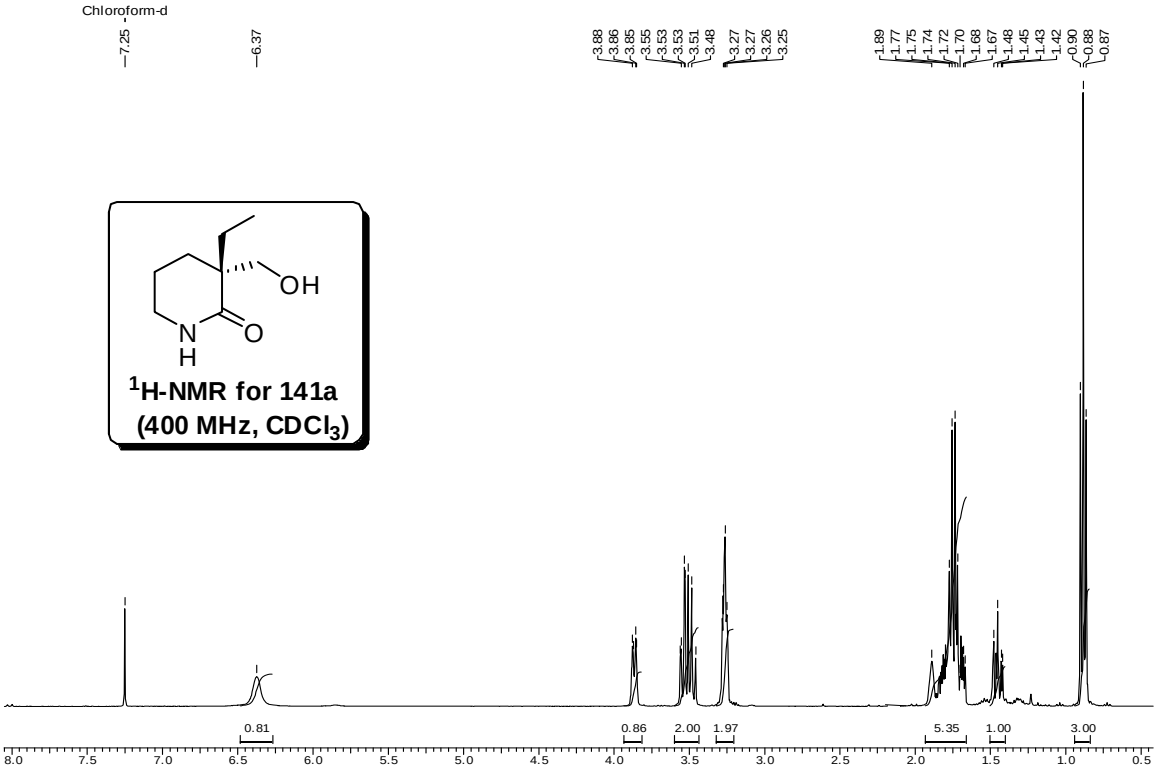

Chloroform-d
170.58
168.72
124.29
123.87
77.00
53.25
52.87
43.35
41.76
38.90
28.56
28.11
25.15
13C NMR for 152
(50MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


124.32
123.82
52.90
43.35
41.74
38.86
28.55
28.07
25.15
DEPT for 152
(50 MHz, CDCl3)

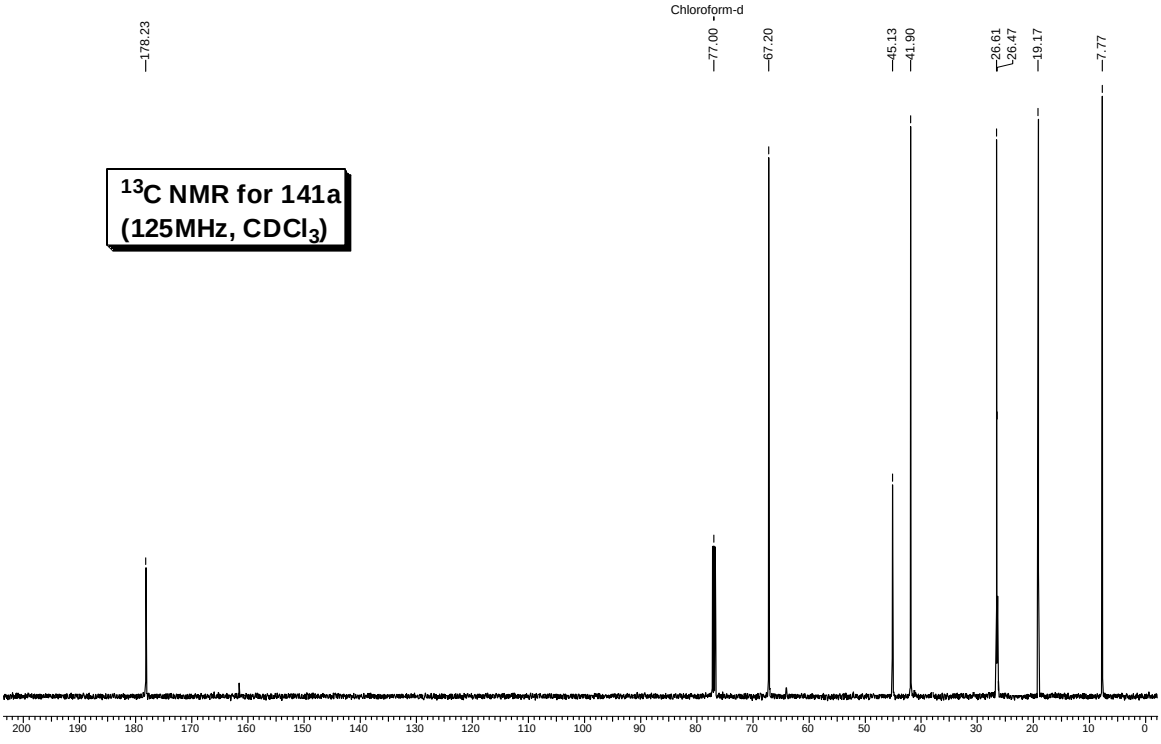

Chloroform-d
7.26
6.01
3.74
3.37
3.35
3.34
3.34
3.33
3.32
3.30
3.29
2.19
2.16
2.04
2.02
2.01
1.96
1.92
1.83
1.82
1.80
1.80
1.66
0.95
0.94
0.92
OCH3
O
N
H
O
1H NMR for 141
(500 MHz, CDCl3)
0.91
3.00
2.14
1.04
3.28
3.08


Chloroform-d
173.45
171.10
77.00
53.99
52.39
42.15
28.80
28.39
19.49
8.87
^{13}C NMR for 141
(50 MHz, CDCl$_3$)

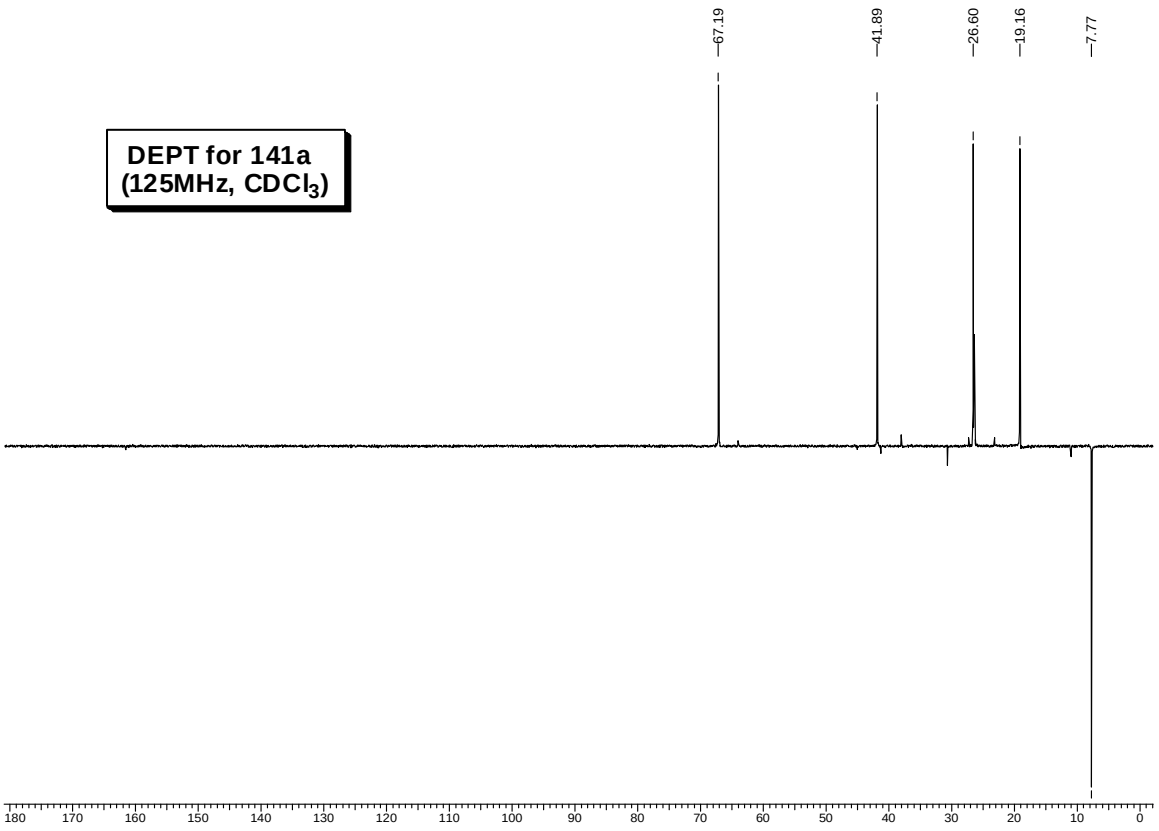

52.40
42.15
28.79
28.39
19.48
8.87
DEPT for 141
(50 MHz, CDCl$_3$)

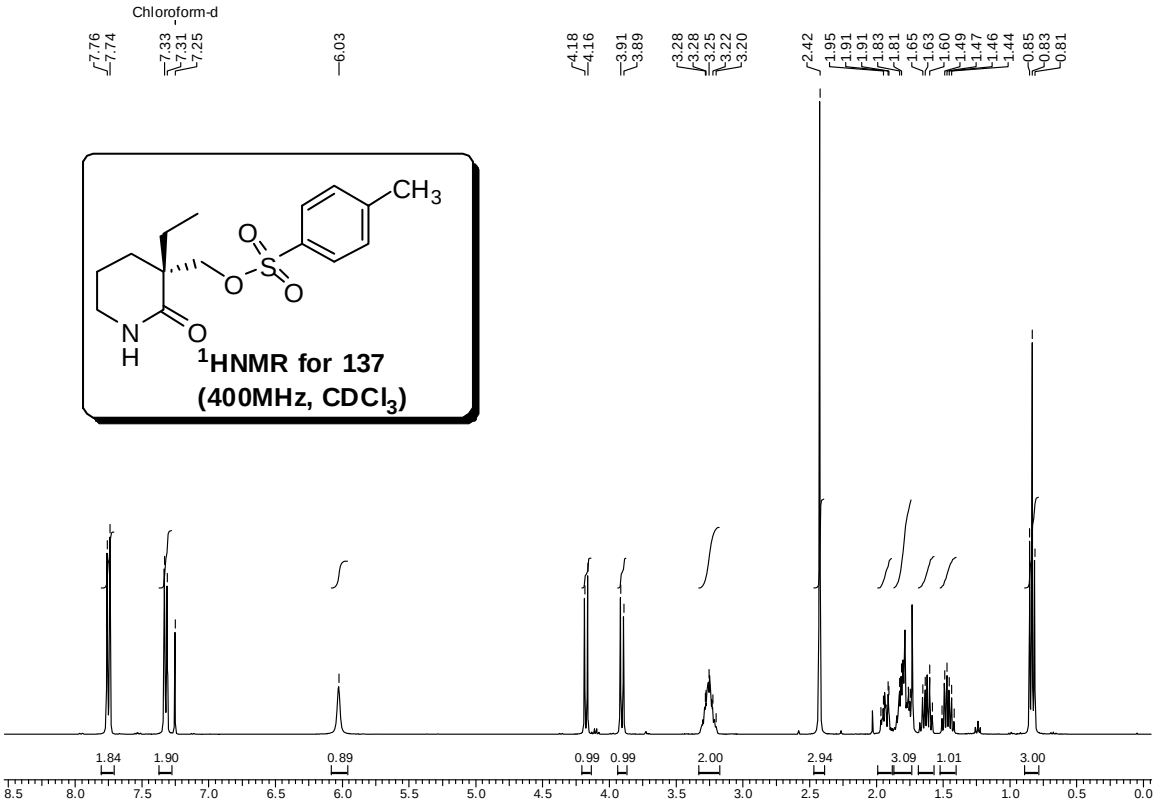


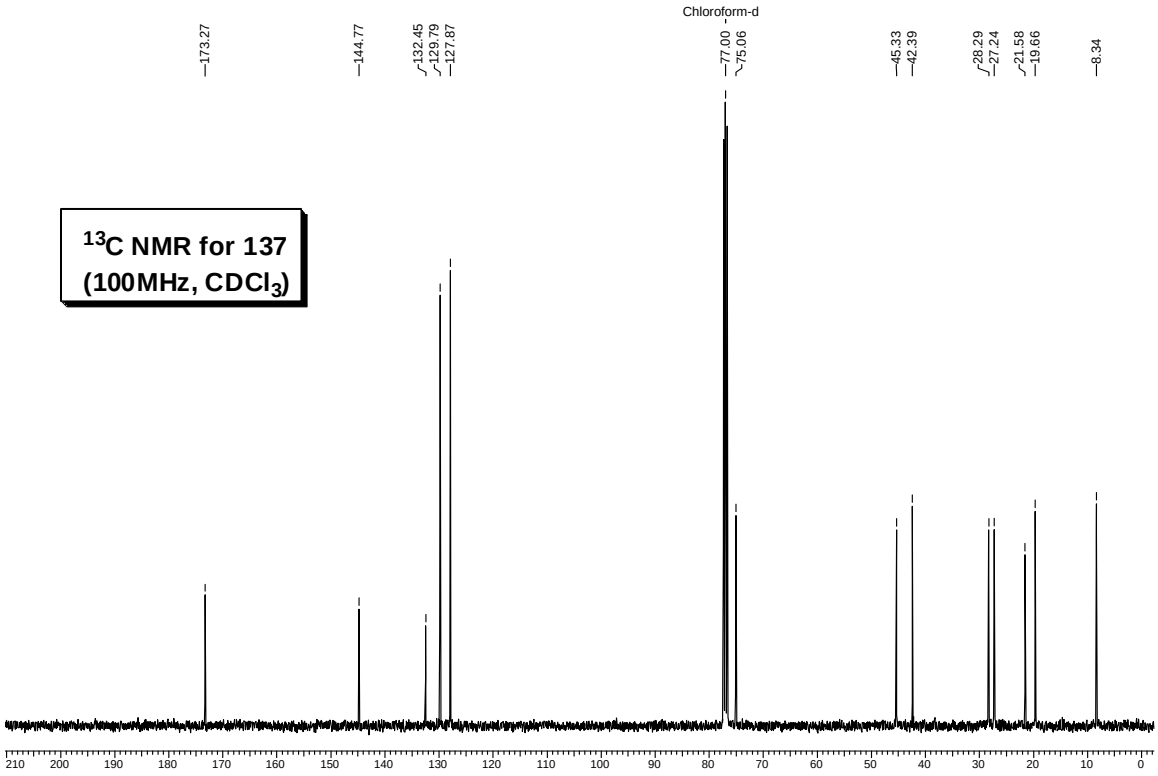
^{1}H-NMR for 141a (400 MHz, $CDCl_3$)

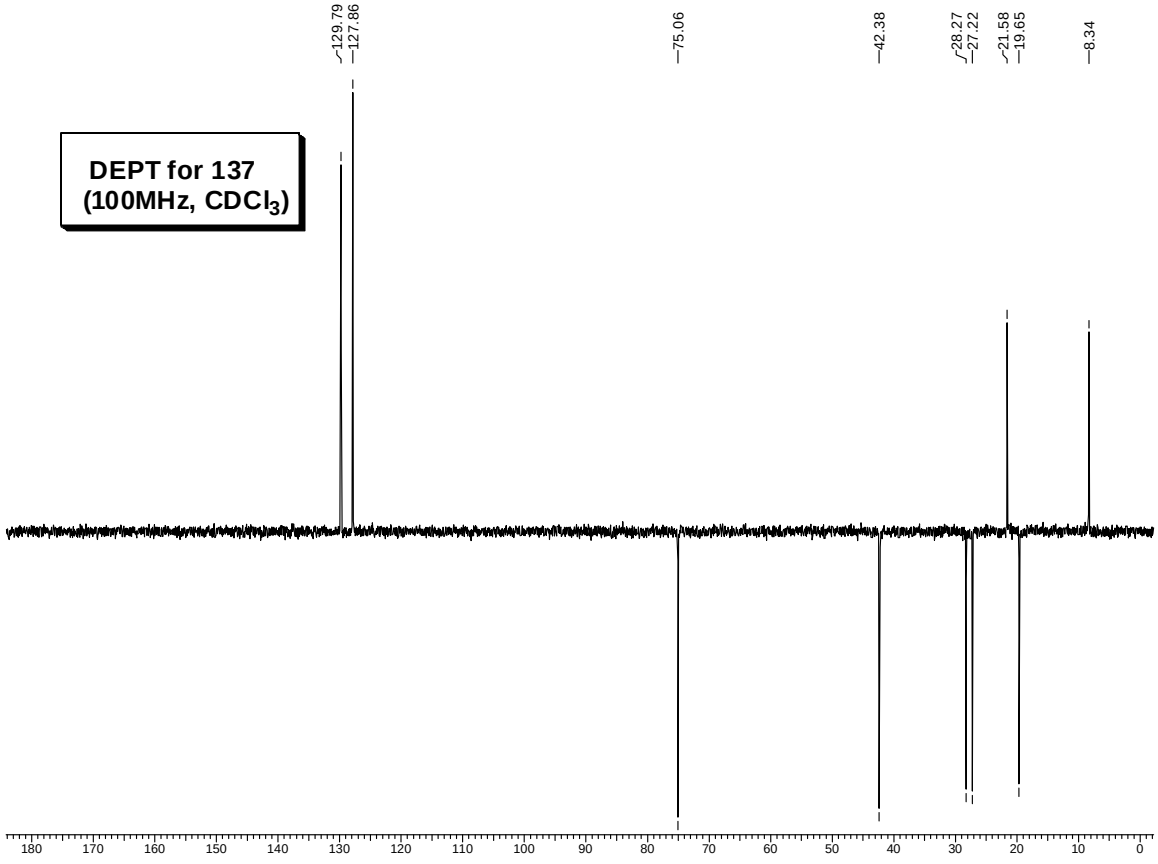


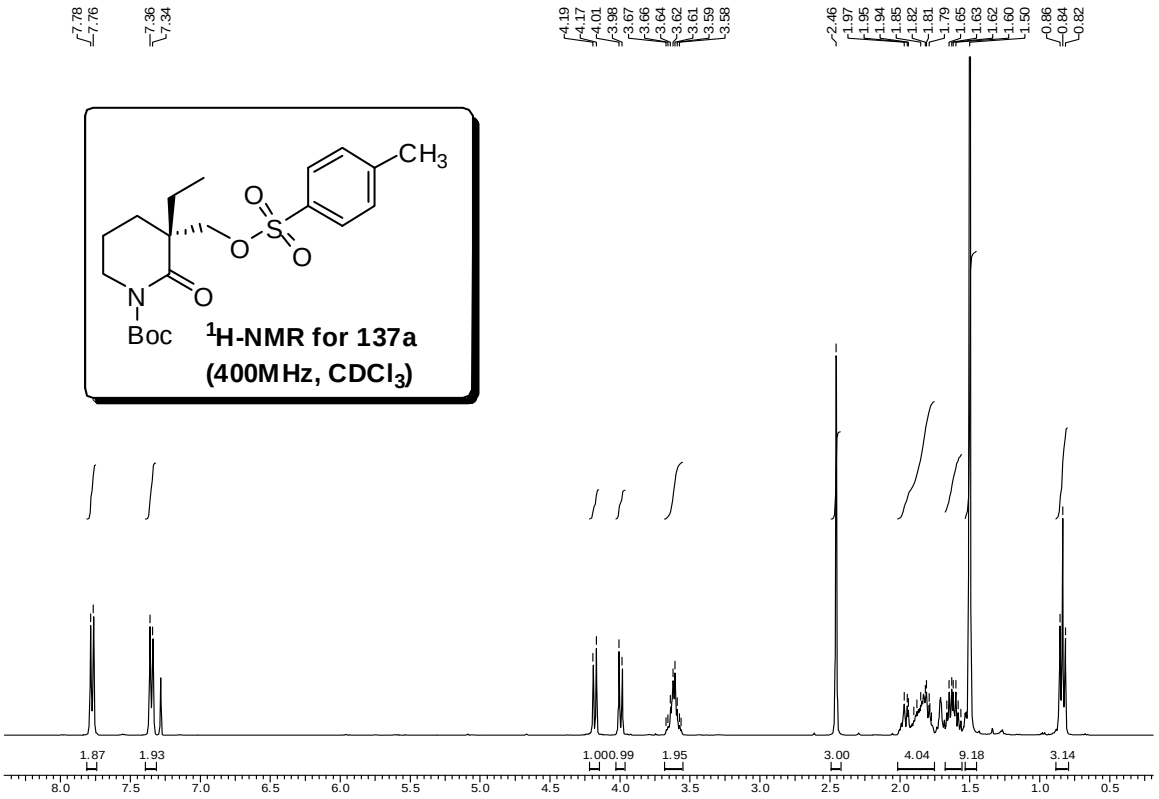
^{13}C NMR for 141a (125MHz, $CDCl_3$)

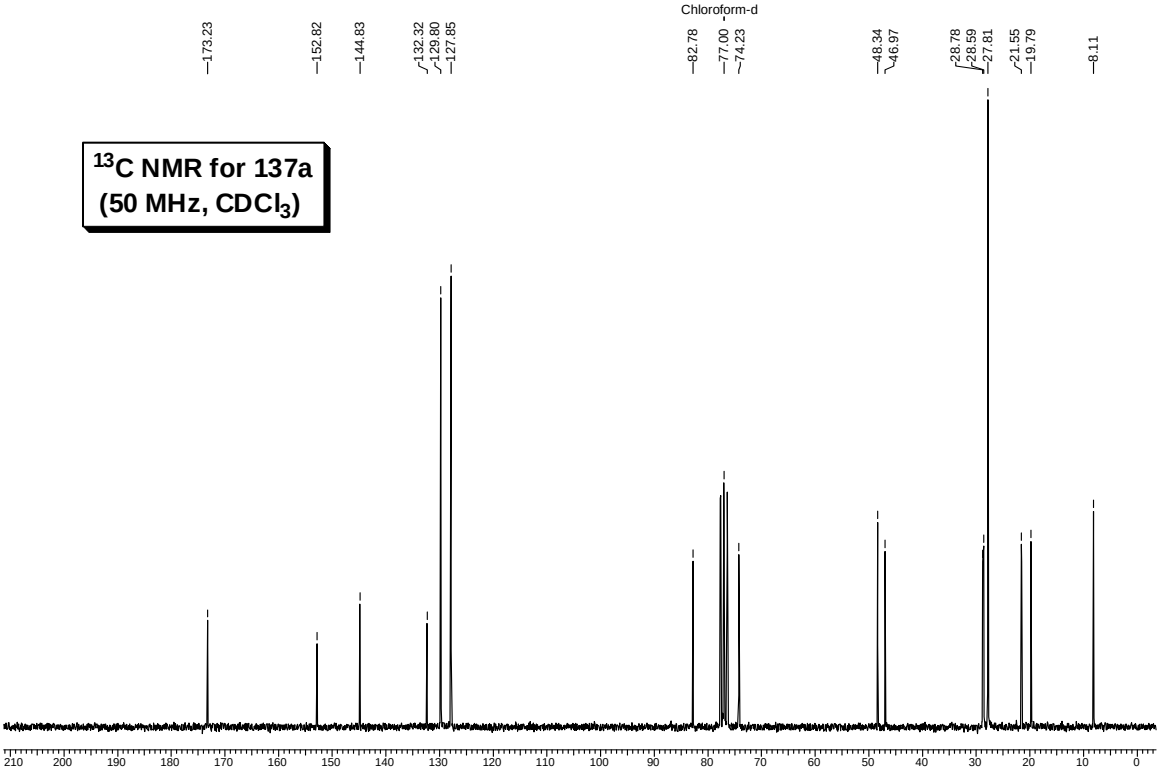

67.19
41.89
26.60
19.16
7.77
DEPT for 141a
(125MHz, CDCl3)

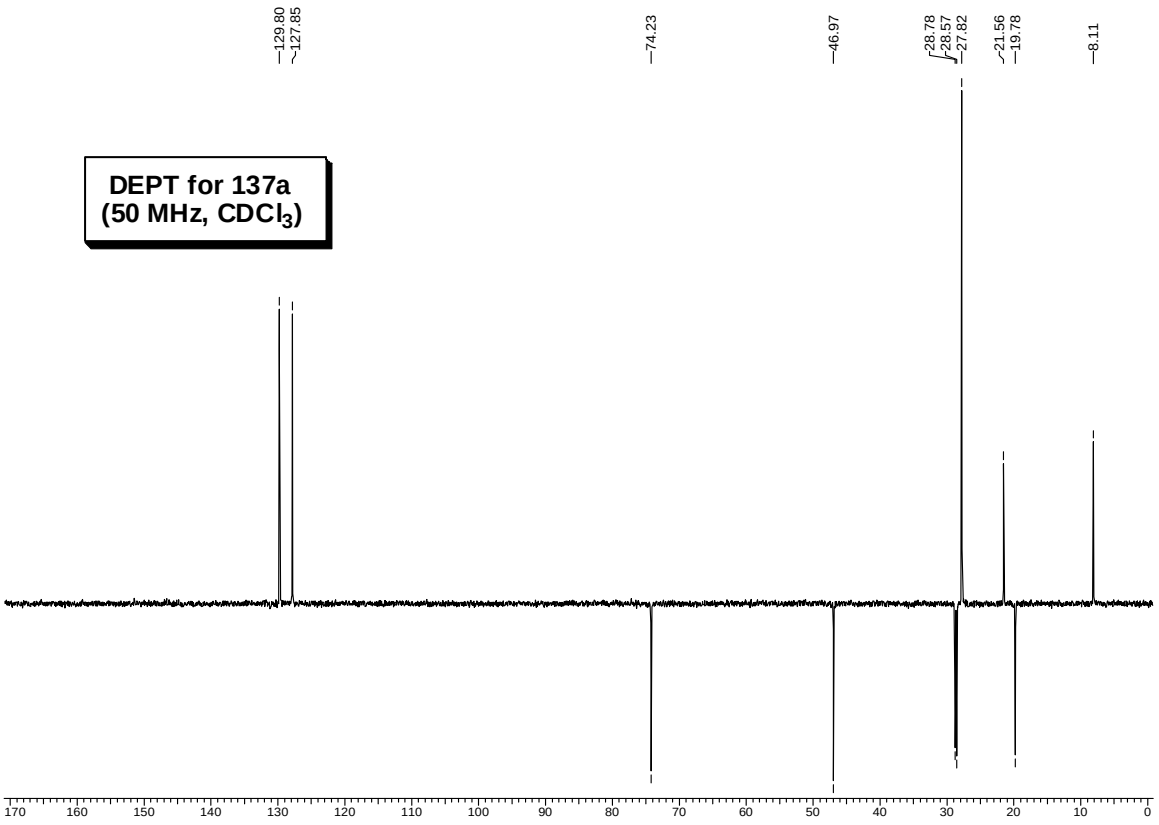

Chloroform-d
7.76
7.74
7.33
7.31
7.25
6.03
4.18
4.16
3.91
3.89
3.28
3.28
3.25
3.22
3.20
2.42
1.95
1.91
1.91
1.83
1.81
1.65
1.63
1.60
1.49
1.47
1.46
1.44
0.85
0.83
0.81
CH3
O
S
O
O
N
H
O
1HNMR for 137
(400MHz, CDCl3)
1.84
1.90
0.89
0.99
0.99
2.00
2.94
3.09
1.01
3.00

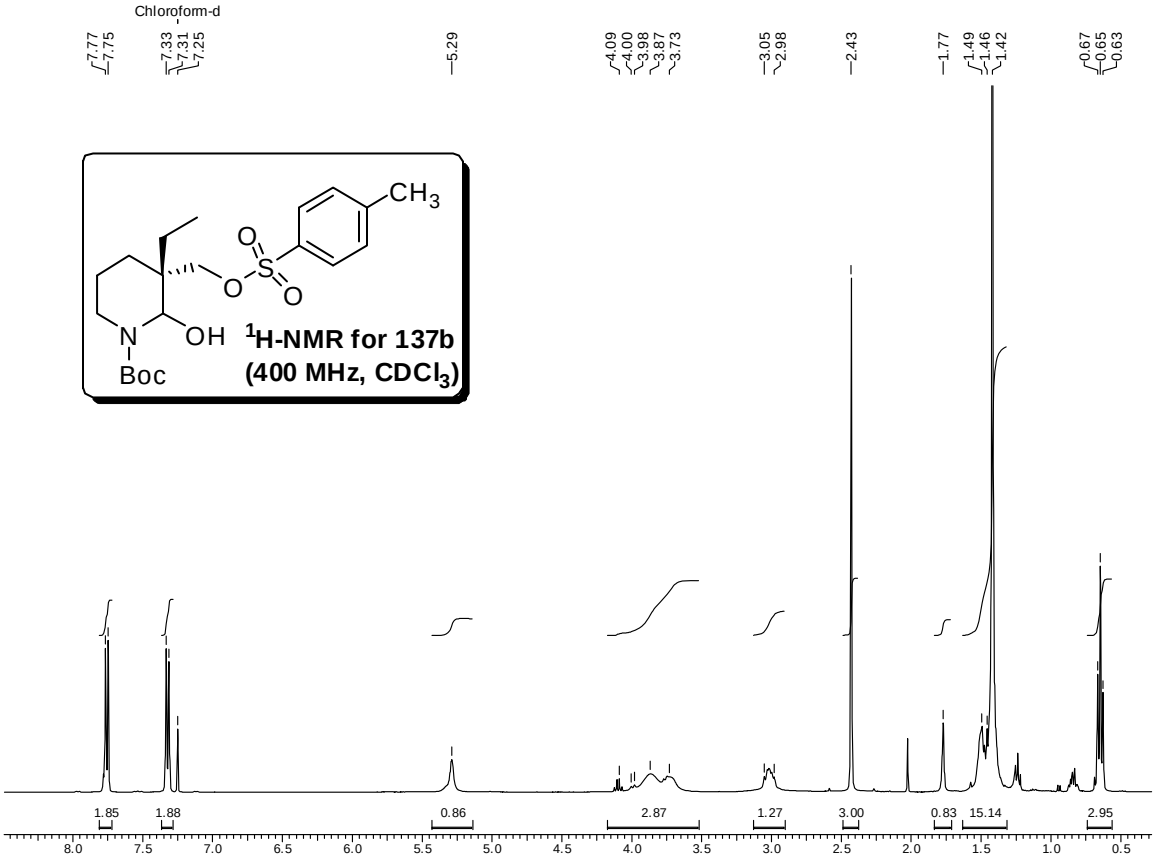

Chloroform-d
173.27
144.77
132.45
129.79
127.87
77.00
75.06
45.33
42.39
28.29
27.24
21.58
19.66
8.34
^{13}C NMR for 137
(100MHz, CDCl$_3$)

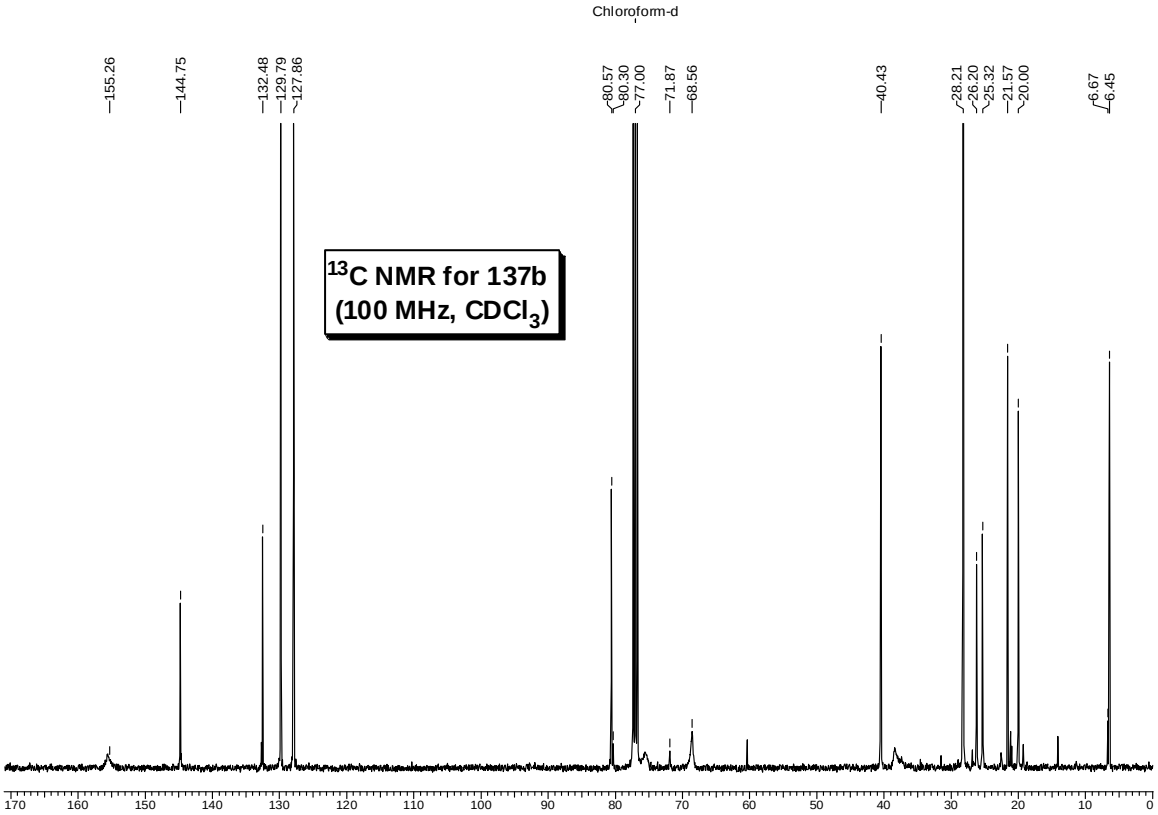

129.79
127.86
75.06
42.38
28.27
27.22
21.58
19.65
8.34
DEPT for 137
(100MHz, CDCl$_3$)

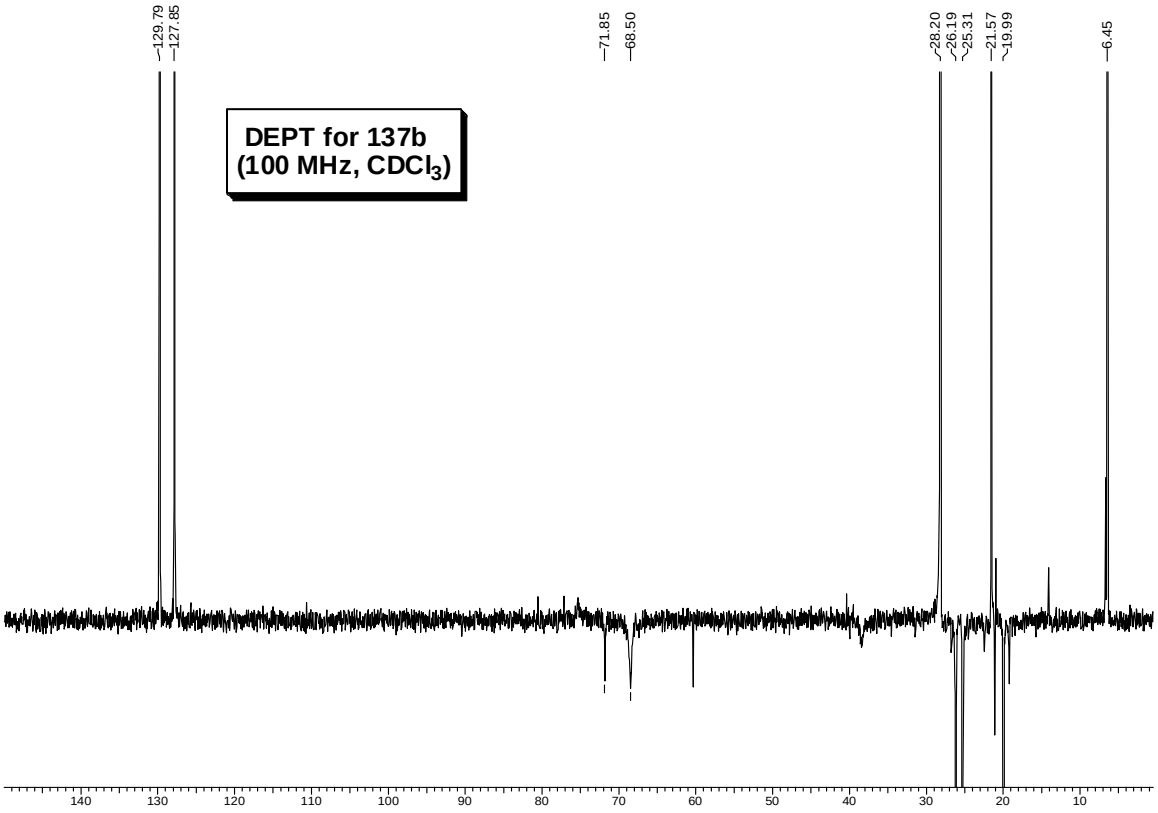

7.78
7.76
7.36
7.34
4.19
4.17
4.01
3.98
3.67
3.66
3.64
3.62
3.61
3.59
3.58
2.46
1.97
1.95
1.94
1.85
1.82
1.81
1.79
1.65
1.63
1.62
1.60
1.50
0.86
0.84
0.82
CH3
O
S
O
O
O
N
Boc
1H-NMR for 137a
(400MHz, CDCl3)
1.87
1.93
1.00
0.99
1.95
3.00
4.04
9.18
3.14

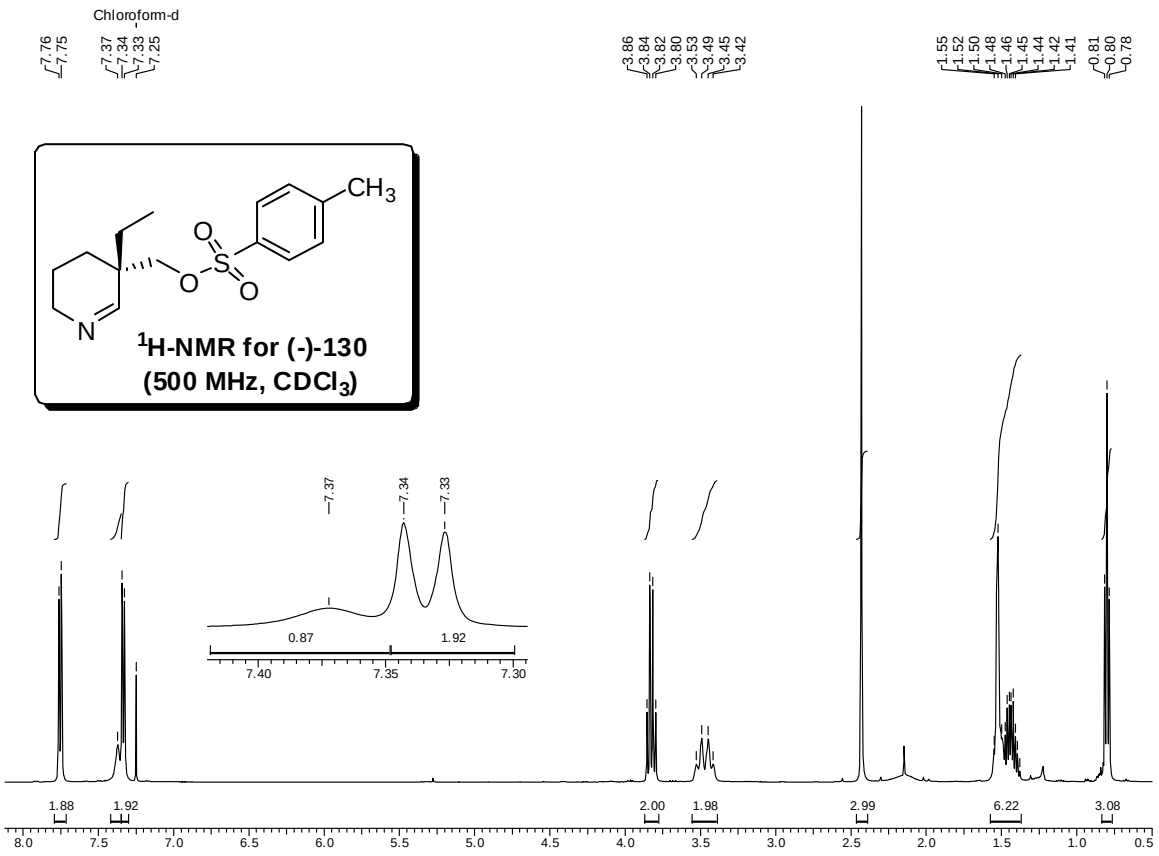

173.23
152.82
144.83
132.32
129.80
127.85
Chloroform-d
82.78
77.00
74.23
48.34
46.97
28.78
28.59
27.81
21.55
19.79
8.11
13C NMR for 137a
(50 MHz, CDCl3)

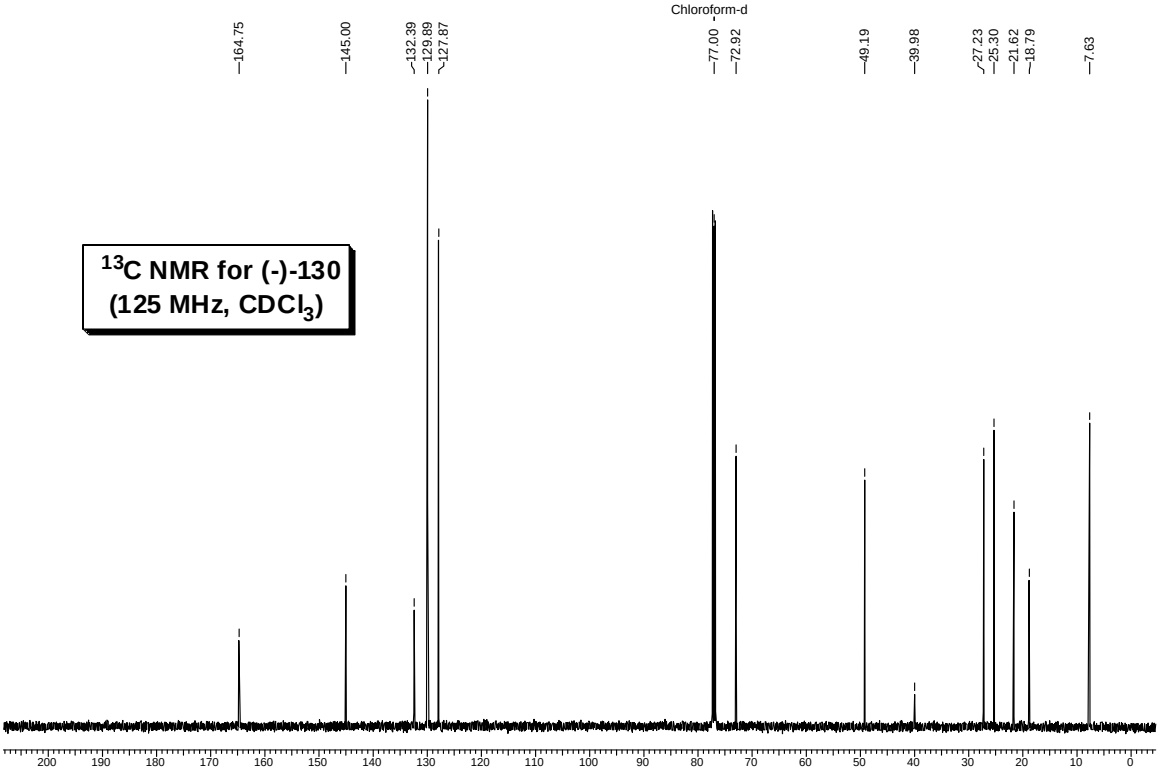

129.80
127.85
74.23
46.97
28.78
28.57
27.82
21.56
19.78
8.11
DEPT for 137a
(50 MHz, CDCl3)

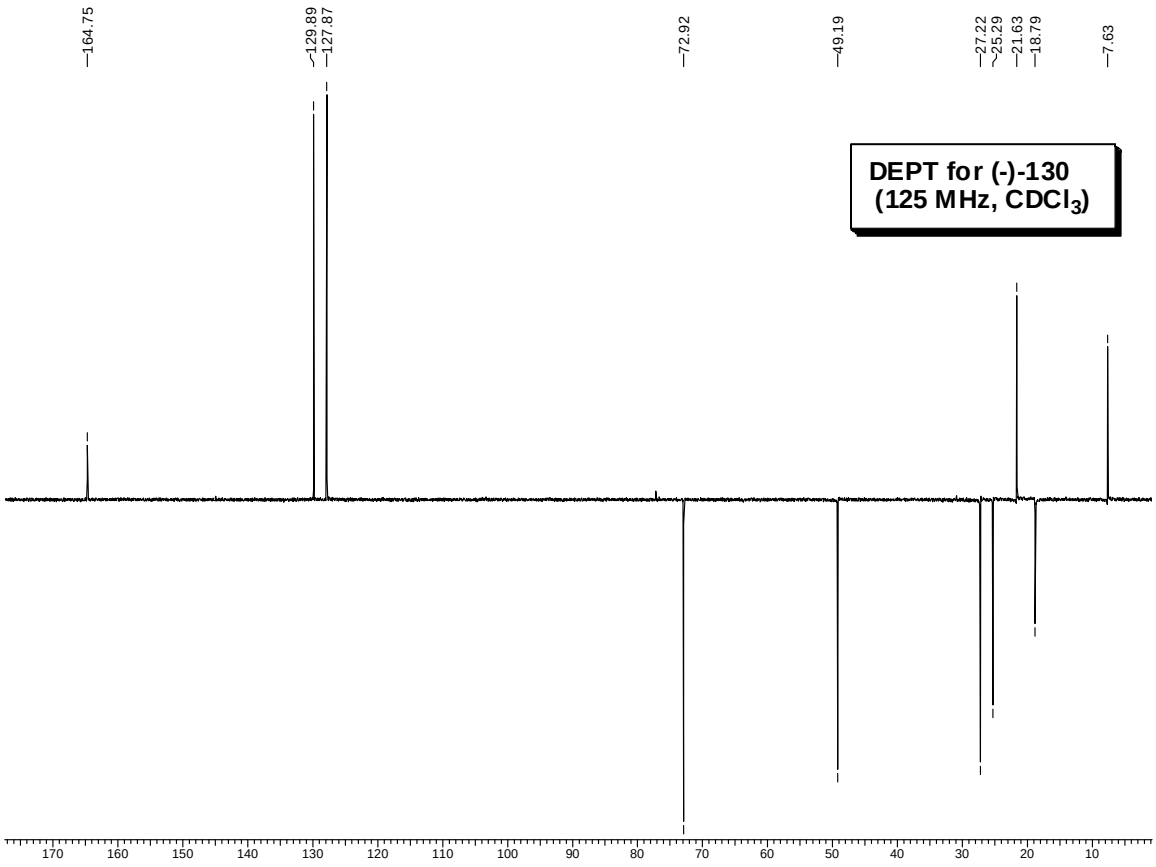

Chloroform-d
7.77
7.75
7.33
7.31
7.25
5.29
4.09
4.00
3.98
3.87
3.73
3.05
2.98
2.43
1.77
1.49
1.46
1.42
0.67
0.65
0.63
CH3
O
S
O
O
N
OH
Boc
1H-NMR for 137b
(400 MHz, CDCl3)
1.85
1.88
0.86
2.87
1.27
3.00
0.83
15.14
2.95


Chloroform-d
155.26
144.75
132.48
129.79
127.86
80.57
80.30
77.00
71.87
68.56
40.43
28.21
26.20
25.32
21.57
20.00
6.67
6.45
13C NMR for 137b
(100 MHz, CDCl3)

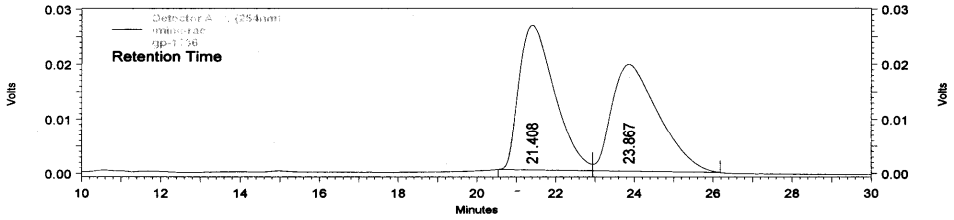

129.79
127.85
71.85
68.50
28.20
26.19
25.31
21.57
19.99
6.45
DEPT for 137b
(100 MHz, CDCl3)


Chloroform-d
7.76
7.75
7.37
7.34
7.33
7.25
3.86
3.84
3.82
3.80
3.53
3.49
3.45
3.42
1.55
1.52
1.50
1.48
1.46
1.45
1.44
1.42
1.41
0.81
0.80
0.78
CH3
O
S
O
O
N
1H-NMR for (-)-130
(500 MHz, CDCl3)
0.87
1.92
1.88
1.92
2.00
1.98
2.99
6.22
3.08


Chloroform-d
164.75
145.00
132.39
129.89
127.87
77.00
72.92
49.19
39.98
27.23
25.30
21.62
18.79
7.63
13C NMR for (-)-130
(125 MHz, CDCl3)



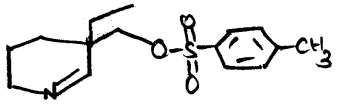
HPLC resolution of enantiomers of 130:



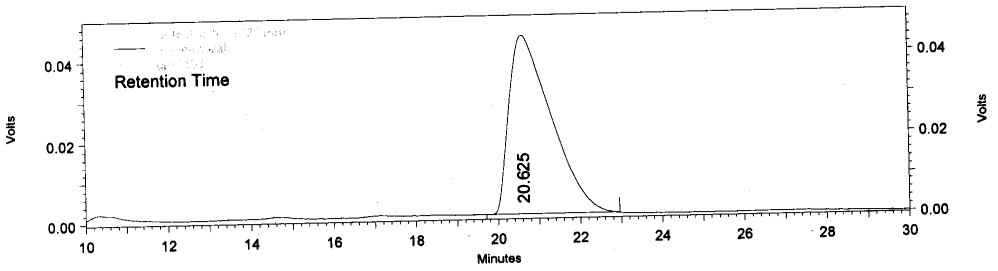
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	21.408	1674827	50.688
2	23.867	1629348	49.312
Totals		3304175	100.000

Column :Chiralcel OJ-H- (4.6x250mm)
Mobile Phase : IPA:Pet ether (15:85)
Wavelength : 254nm
Flow Rate : 0.7ml/min 33kgf
Sample Con :2.3mg/0.5ml Inj vol-10ul

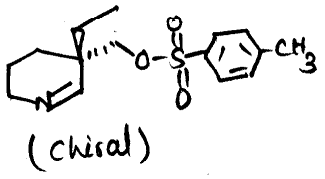


(Racemic)

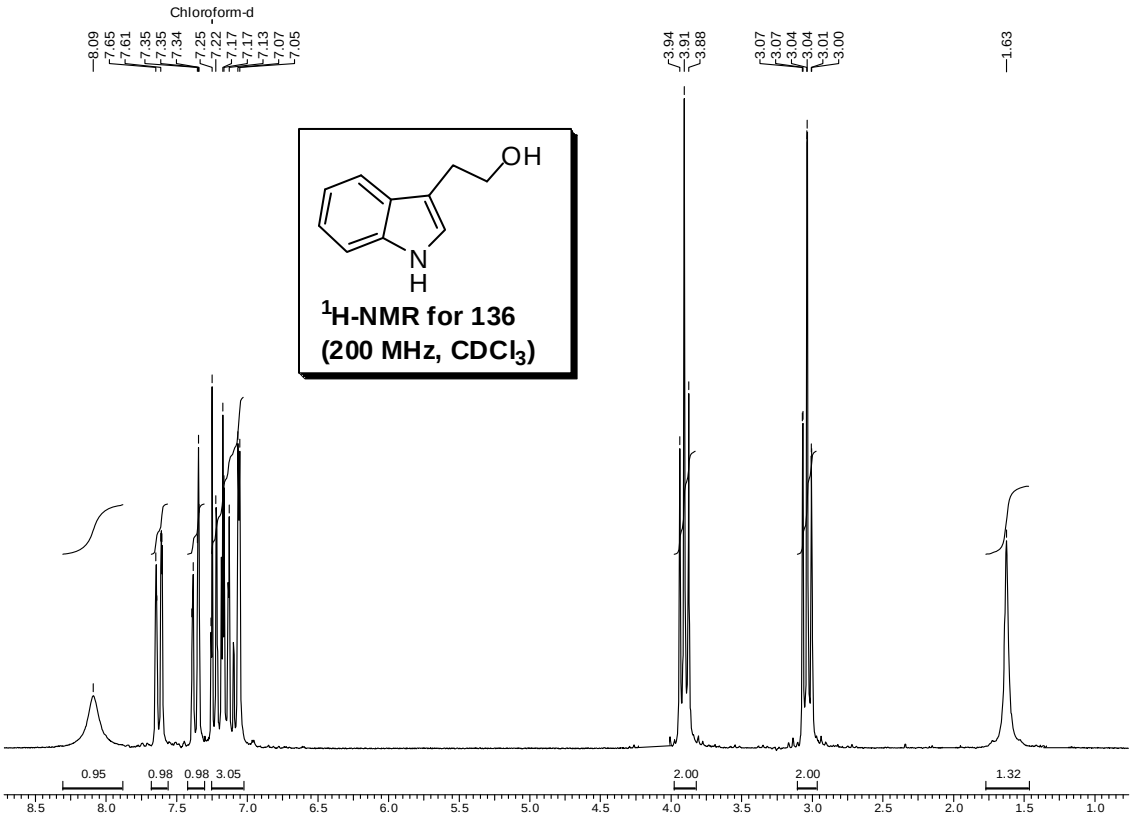


Detector A - 1 (254nm) Pk #	Retention Time	Area	Area %
1	20.625	3155145	100.000
Totals		3155145	100.000

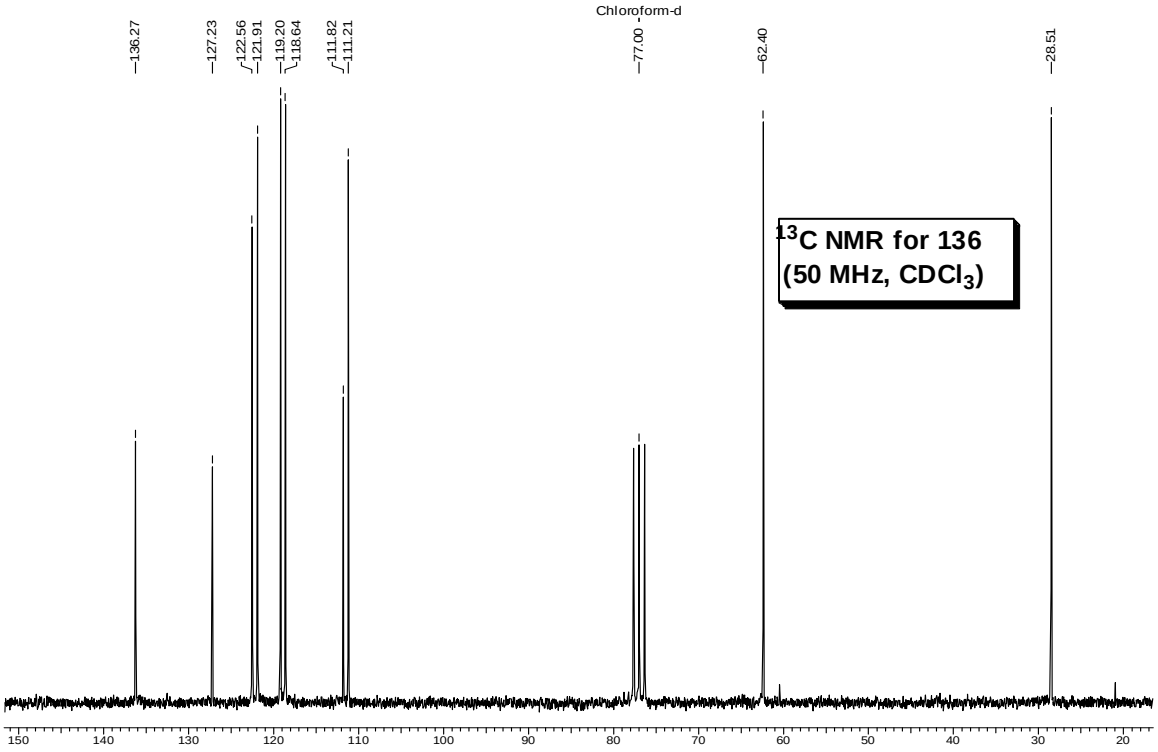
Column :Chiralcel OJ-H- (4.6x250mm)
Mobile Phase : IPA:Pet ether (15:85)
Wavelength : 254nm
Flow Rate : 0.7ml/min 33kgf
Sample Con :2.3mg/0.5ml Inj vol-10ul

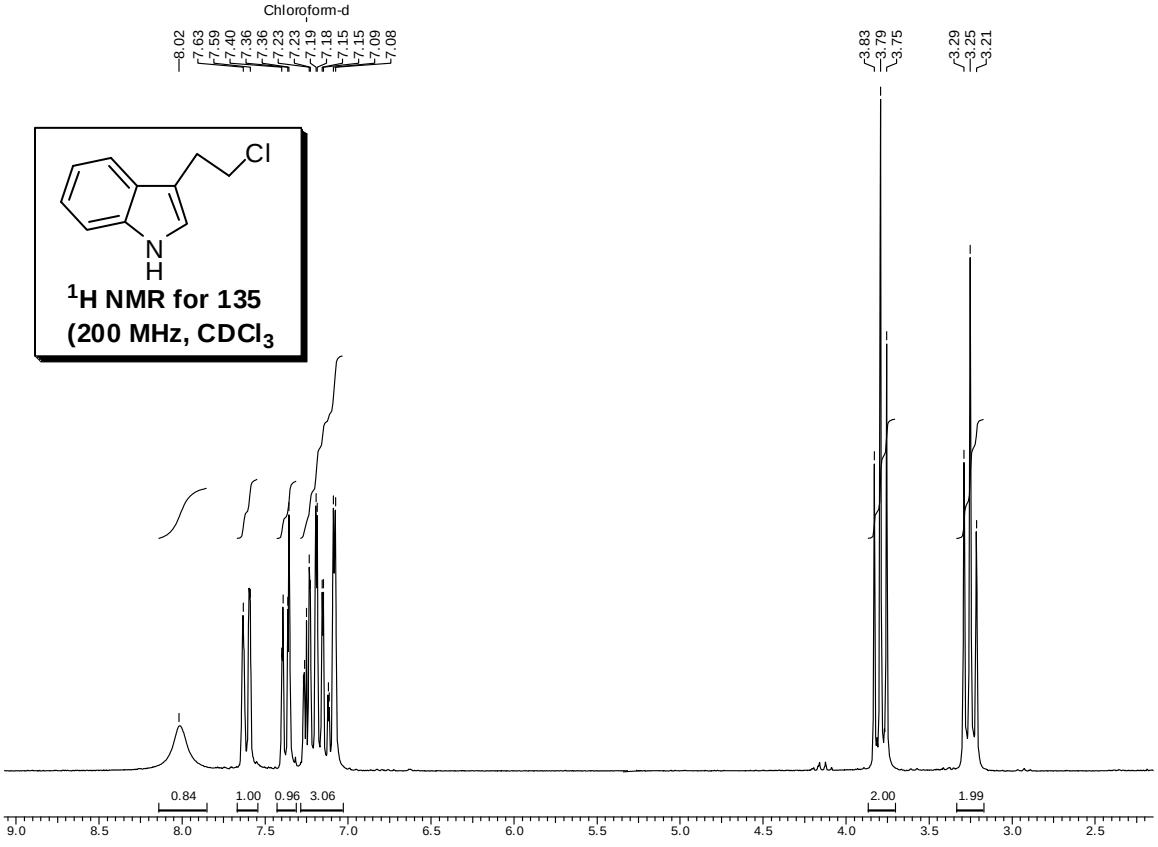


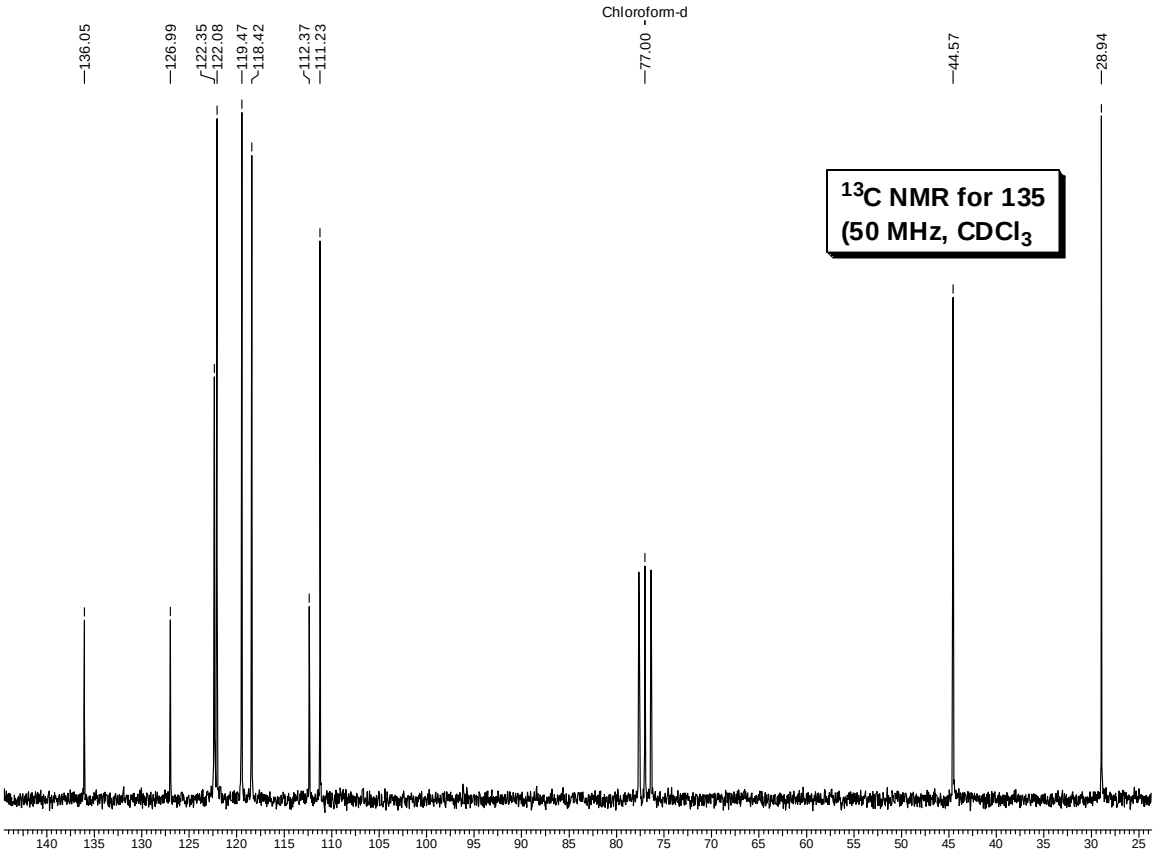
(chiral)

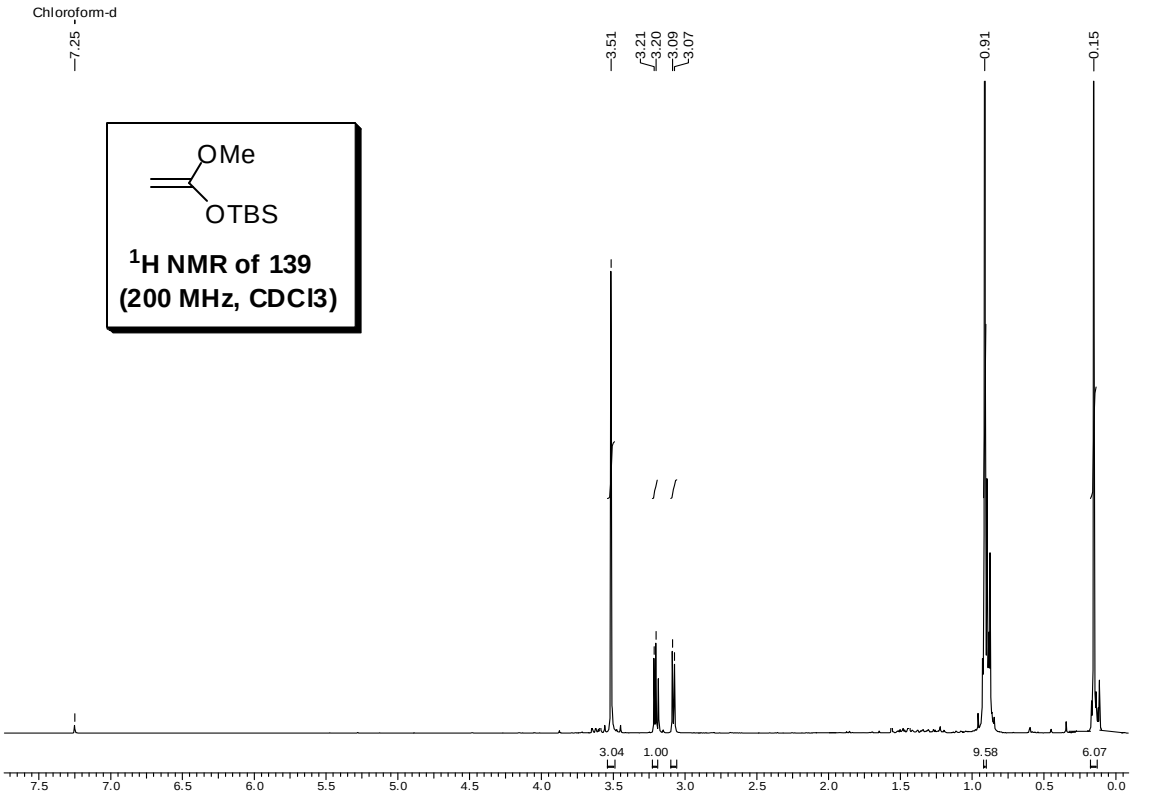


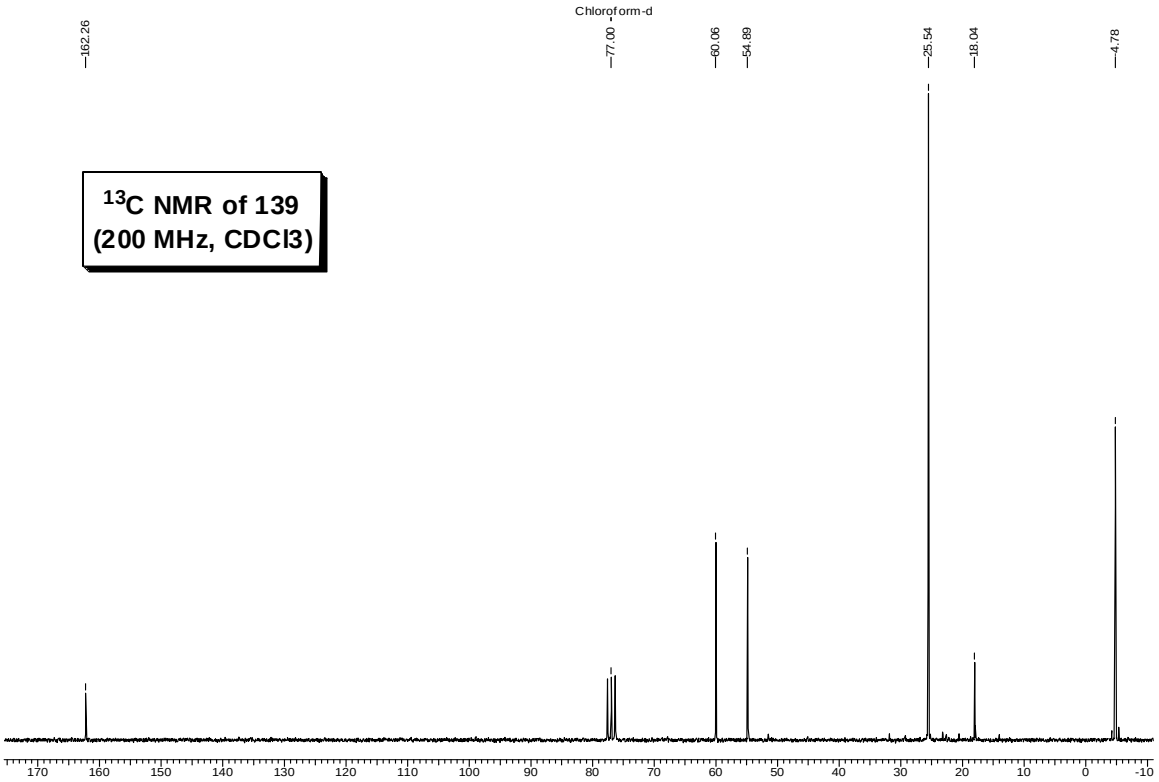
^{1}H-NMR for 136 (200 MHz, $CDCl_3$)

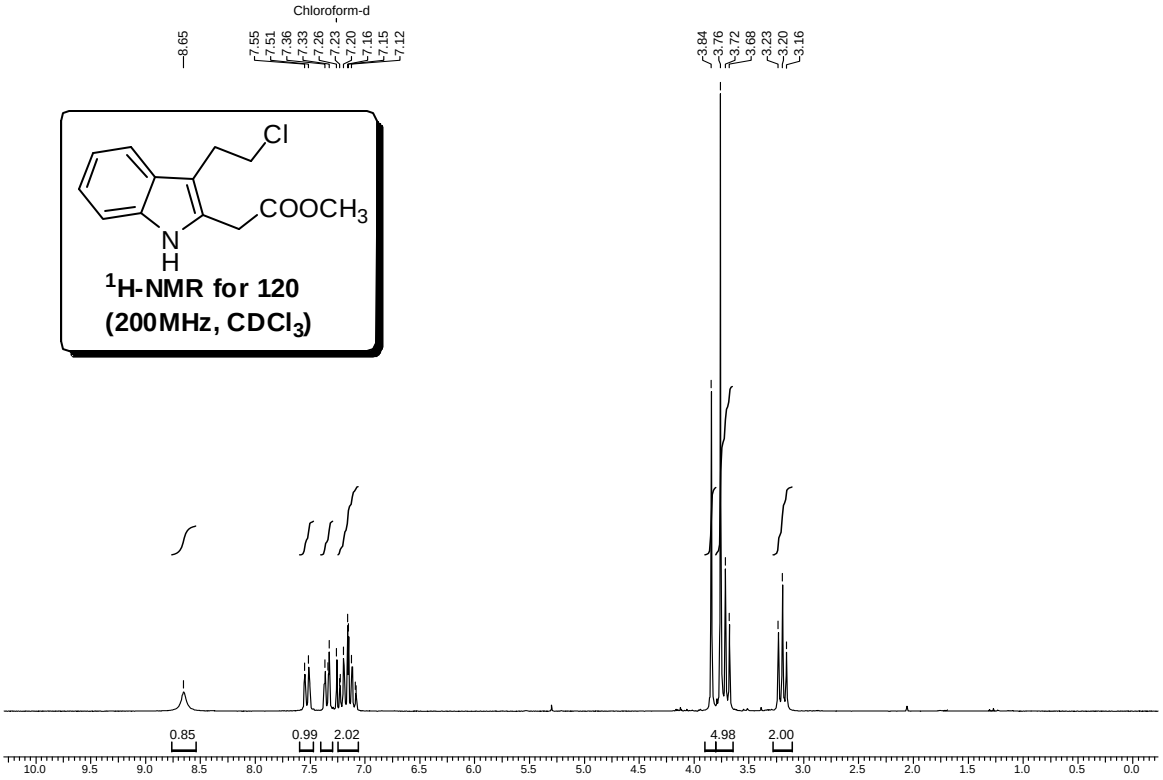

Chloroform-d
136.27
127.23
122.56
121.91
119.20
118.64
111.82
111.21
77.00
62.40
28.51
^{13}C NMR for 136
(50 MHz, CDCl$_3$)

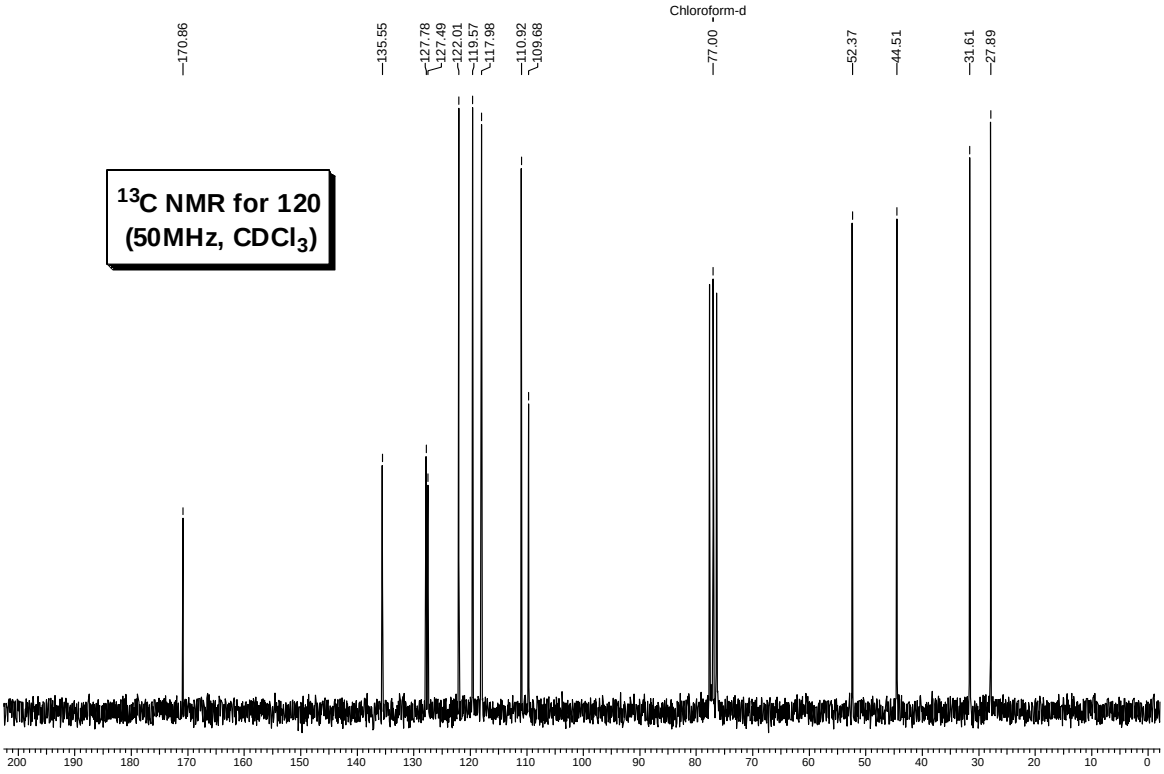

Chloroform-d
8.02
7.63
7.59
7.40
7.36
7.36
7.23
7.23
7.19
7.18
7.15
7.15
7.09
7.08
3.83
3.79
3.75
3.29
3.25
3.21
Cl
N
H
^{1}H NMR for 135
(200 MHz, CDCl$_3$
0.84
1.00
0.96
3.06
2.00
1.99

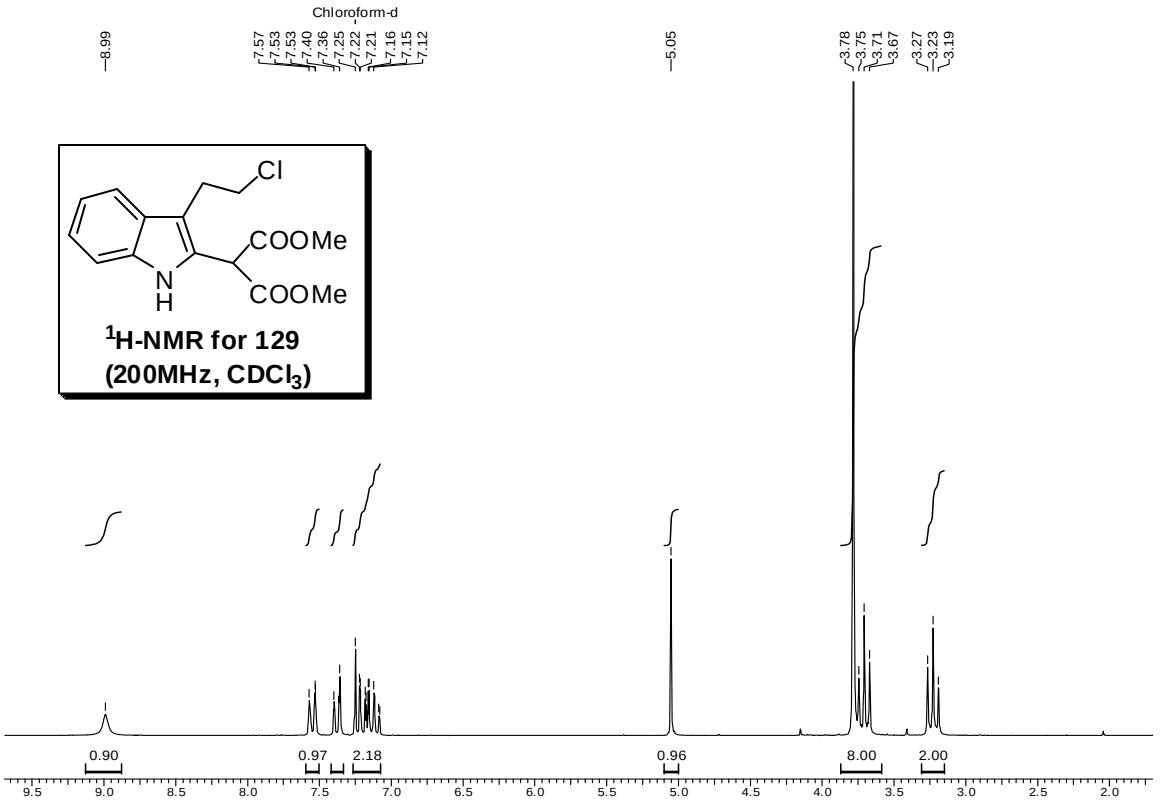

Chloroform-d
136.05
126.99
122.35
122.08
119.47
118.42
112.37
111.23
77.00
44.57
28.94
^{13}C NMR for 135
(50 MHz, CDCl$_3$

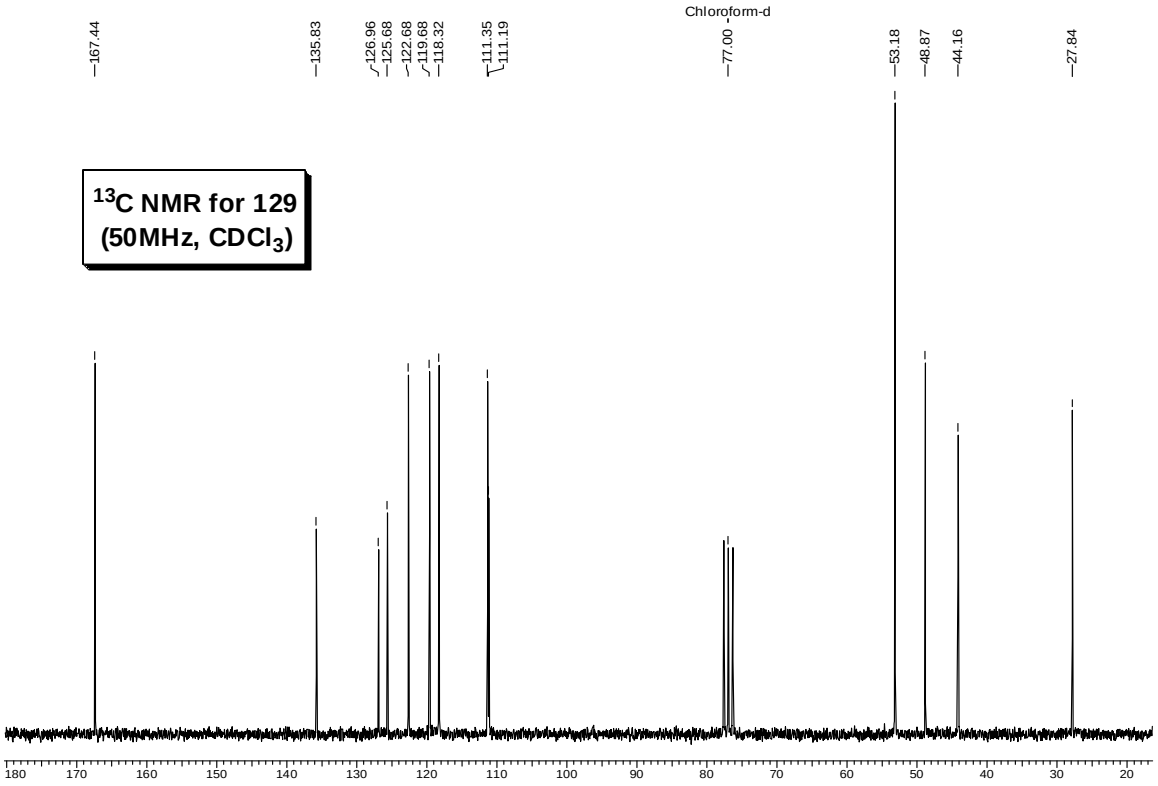

Chloroform-d
7.25
3.51
3.21
3.20
3.09
3.07
0.91
0.15
OMe
OTBS
^{1}H NMR of 139
(200 MHz, CDCl3)
3.04
1.00
9.58
6.07


Chloroform-d
162.26
77.00
60.06
54.89
25.54
18.04
4.78
^{13}C NMR of 139
(200 MHz, CDCl3)

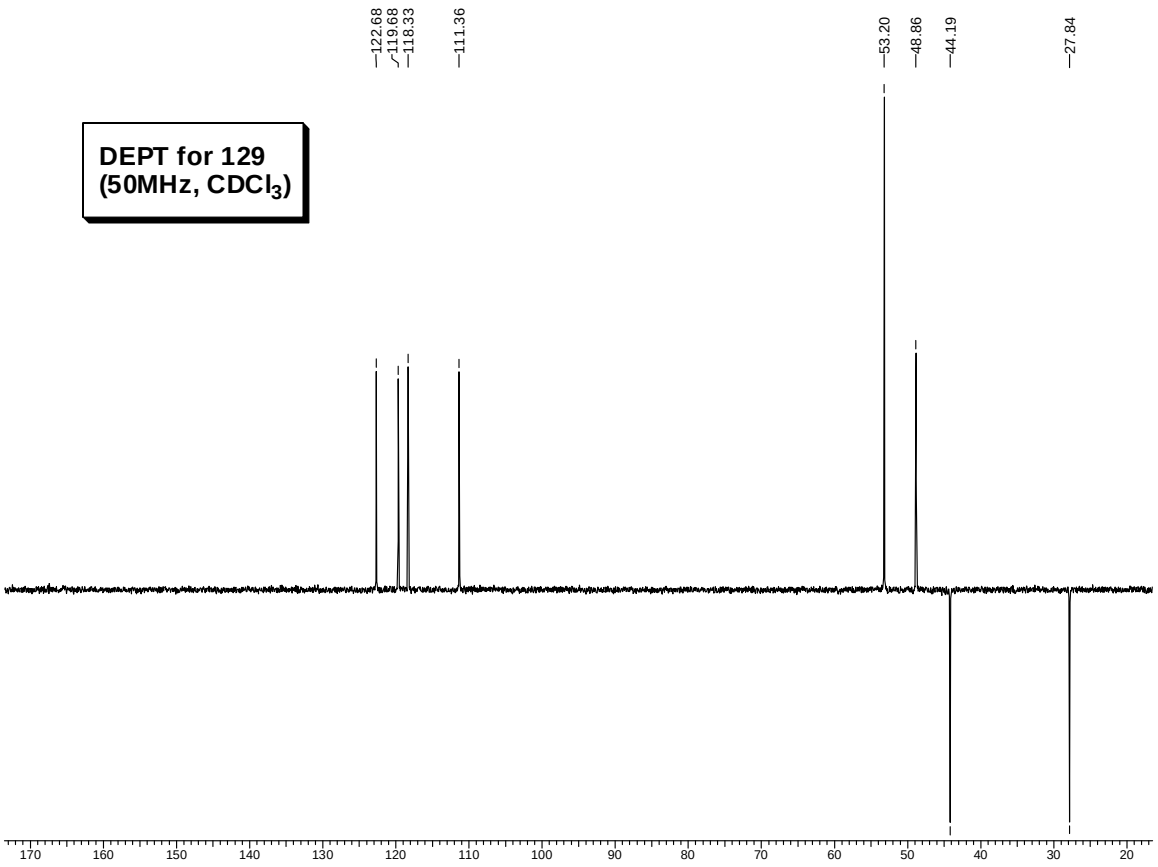

Chloroform-d
8.65
7.55
7.51
7.36
7.33
7.26
7.23
7.20
7.16
7.15
7.12
3.84
3.76
3.72
3.68
3.23
3.20
3.16
Cl
COOCH3
N
H
^{1}H-NMR for 120
(200MHz, CDCl$_3$)
0.85
0.99
2.02
4.98
2.00


Chloroform-d
170.86
135.55
127.78
127.49
122.01
119.57
117.98
110.92
109.68
77.00
52.37
44.51
31.61
27.89
^{13}C NMR for 120
(50MHz, CDCl$_3$)

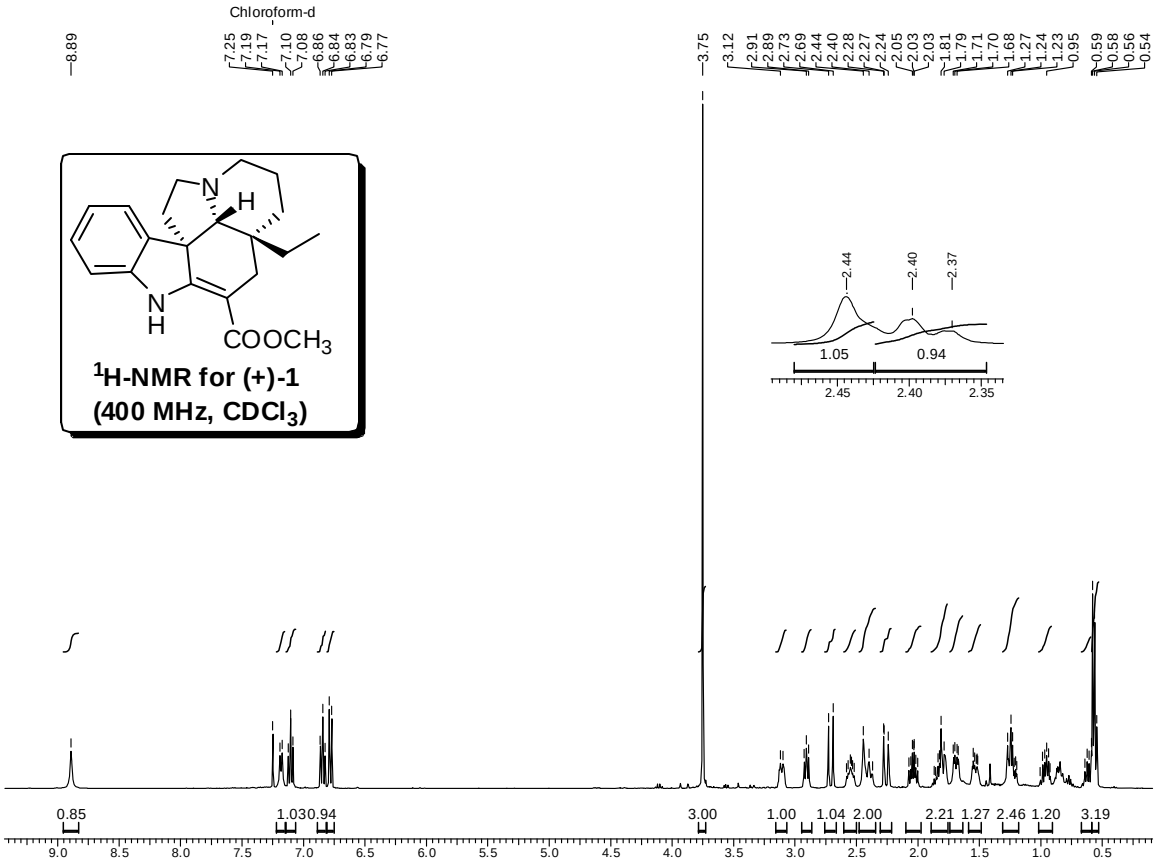

Chloroform-d
8.99
7.57
7.53
7.53
7.40
7.36
7.25
7.22
7.21
7.16
7.15
7.12
5.05
3.78
3.75
3.71
3.67
3.27
3.23
3.19
Cl
COOMe
COOMe
N
H
^{1}H-NMR for 129
(200MHz, CDCl$_3$)
0.90
0.97
2.18
0.96
8.00
2.00

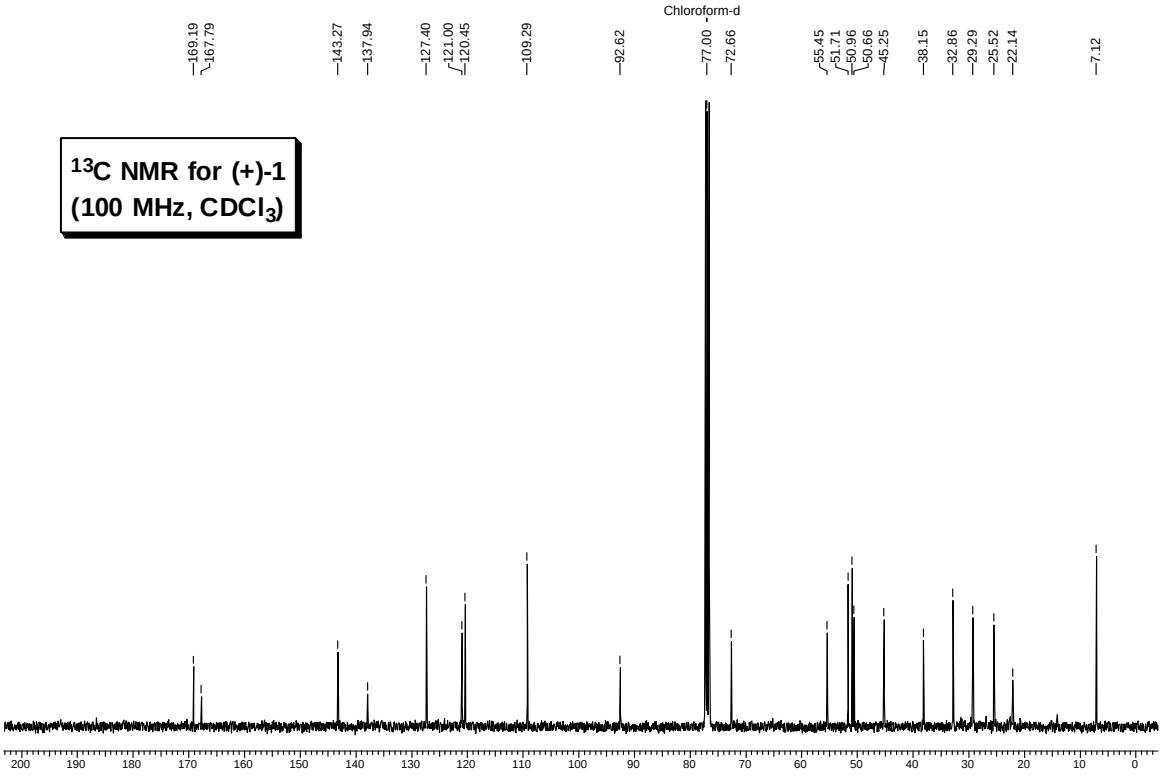


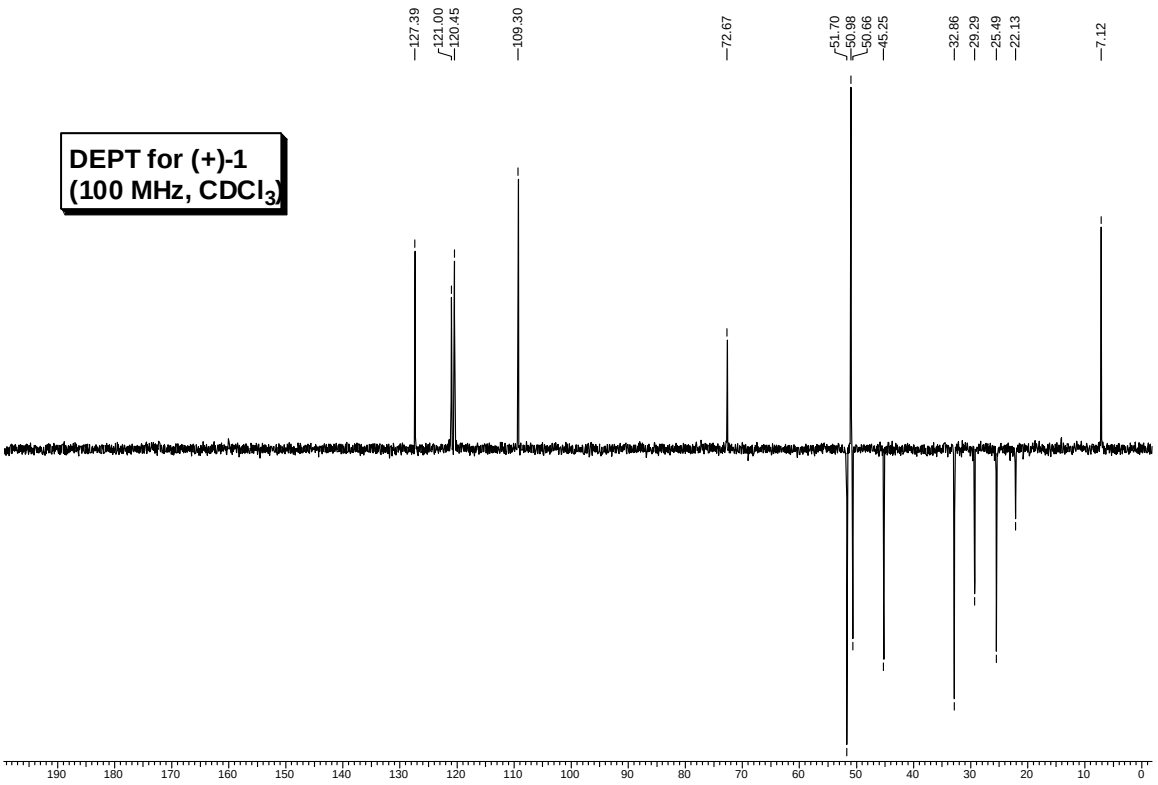
^{13}C NMR for 129 (50MHz, $CDCl_3$)

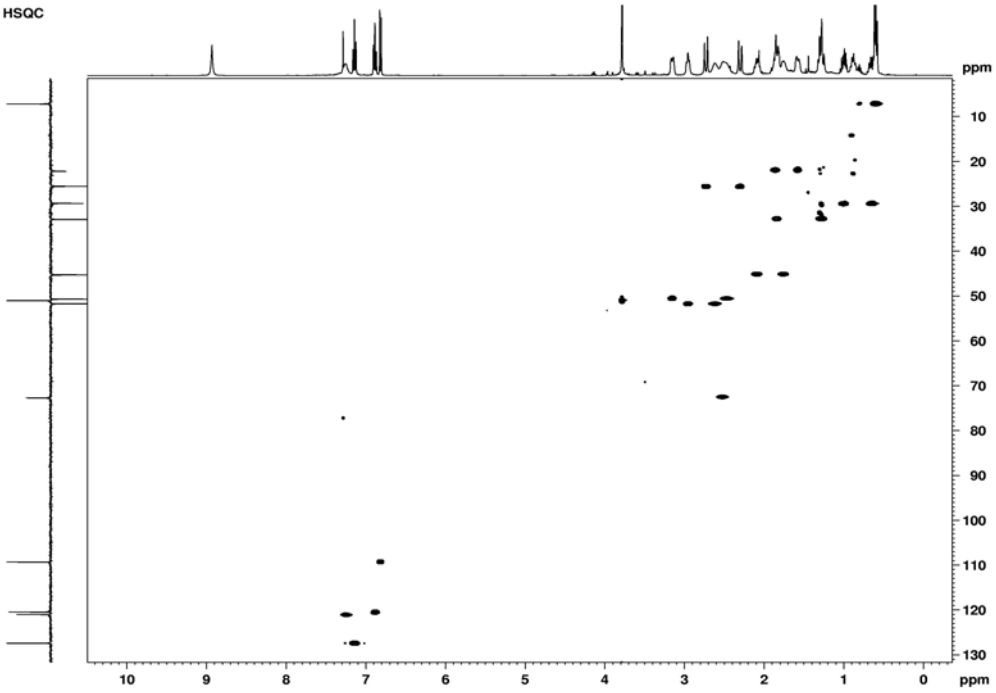


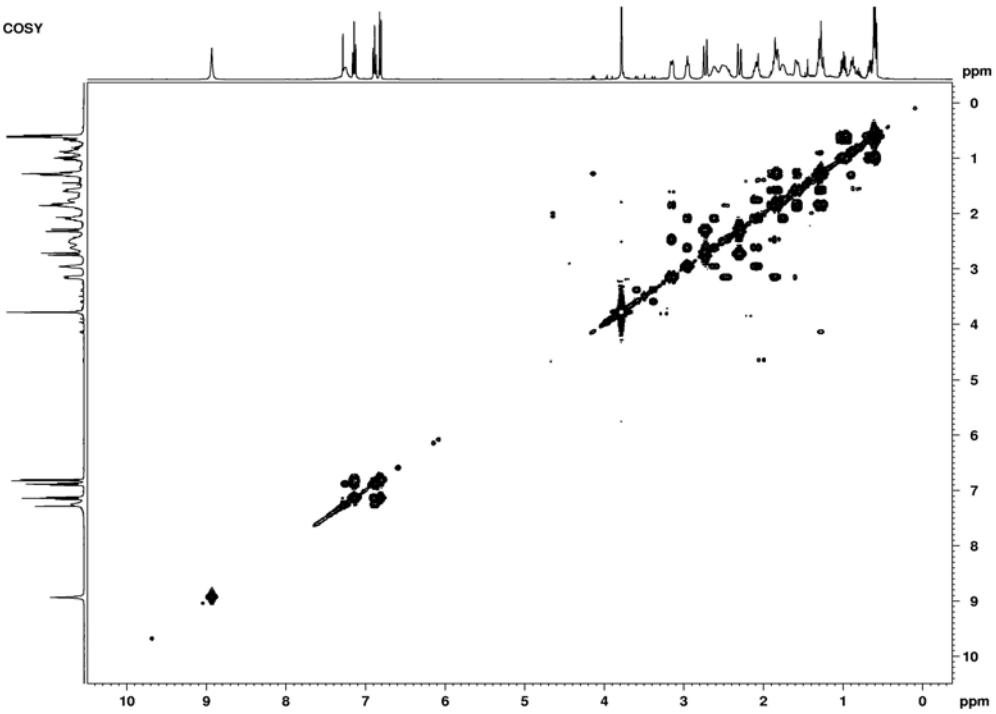
DEPT for 129 (50MHz, $CDCl_3$)

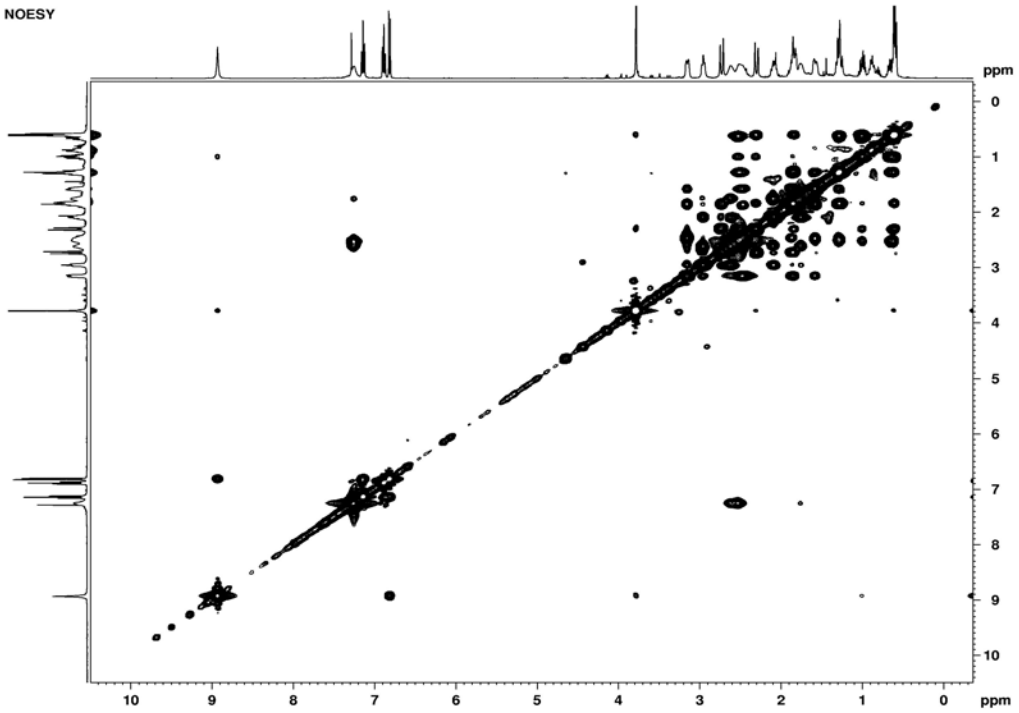

Chloroform-d
8.89
7.25
7.19
7.17
7.10
7.08
6.86
6.84
6.83
6.79
6.77
3.75
3.12
2.91
2.89
2.73
2.69
2.44
2.40
2.28
2.27
2.24
2.05
2.03
2.03
1.81
1.79
1.71
1.70
1.68
1.27
1.24
1.23
0.95
0.59
0.58
0.56
0.54
N
H
N
H
COOCH3
1H-NMR for (+)-1
(400 MHz, CDCl3)
2.44
2.40
2.37
1.05
0.94
2.45
2.40
2.35
0.85
1.03
0.94
3.00
1.00
1.04
2.00
2.21
1.27
2.46
1.20
3.19


Chloroform-d
169.19
167.79
143.27
137.94
127.40
121.00
120.45
109.29
92.62
77.00
72.66
55.45
51.71
50.96
50.66
45.25
38.15
32.86
29.29
25.52
22.14
7.12
13C NMR for (+)-1
(100 MHz, CDCl3)

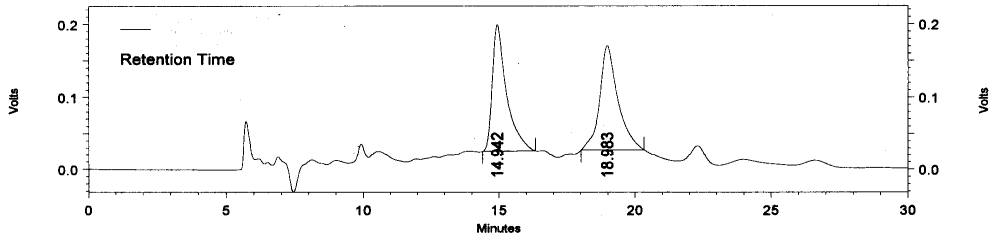

127.39
121.00
120.45
109.30
72.67
51.70
50.98
50.66
45.25
32.86
29.29
25.49
22.13
7.12
DEPT for (+)-1
(100 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


HSQC
ppm
10 20 30 40 50 60 70 80 90 100 110 120 130
10 9 8 7 6 5 4 3 2 1 0 ppm


COSY
ppm
0
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
0
ppm


NOESY
ppm
0
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
0
ppm

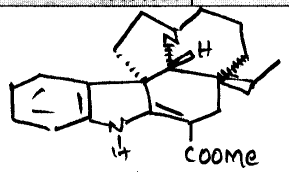
HPLC resolution of enantiomers of 1:



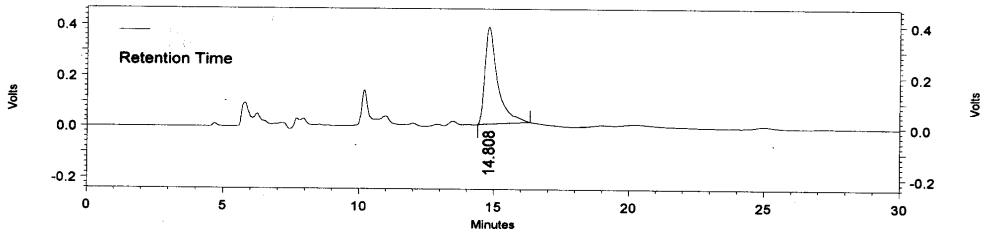
Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	14.942	6337602	48.540
2	18.983	6718724	51.460
Totals		13056326	100.000

Column : Chiralcel OD-H (250x4.6mm)
Mobile Phase :Ethanol:Petether:TFA (15:85:0.1)
Wavelength : 220nm
Flow Rate : 0.5ml/min (26kgf)
Sample Con :1mg/0.5ml Inj vol-5ul



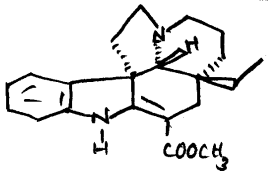
(±)- Vincadifformine.



Detector A - 1 (220nm)

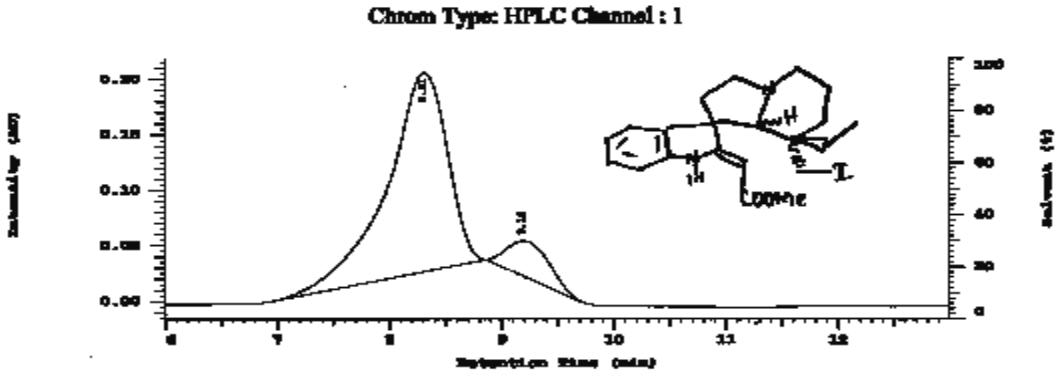
Pk #	Retention Time	Area	Area %
1	14.808	12586161	100.000
Totals		12586161	100.000

Column : Chiralcel OD-H (250x4.6mm)
Mobile Phase :Ethanol:Petether:TFA (15:85:0.1)
Wavelength : 220nm
Flow Rate : 0.5ml/min (26kgf)
Sample Con :1mg/0.5ml Inj vol-5ul



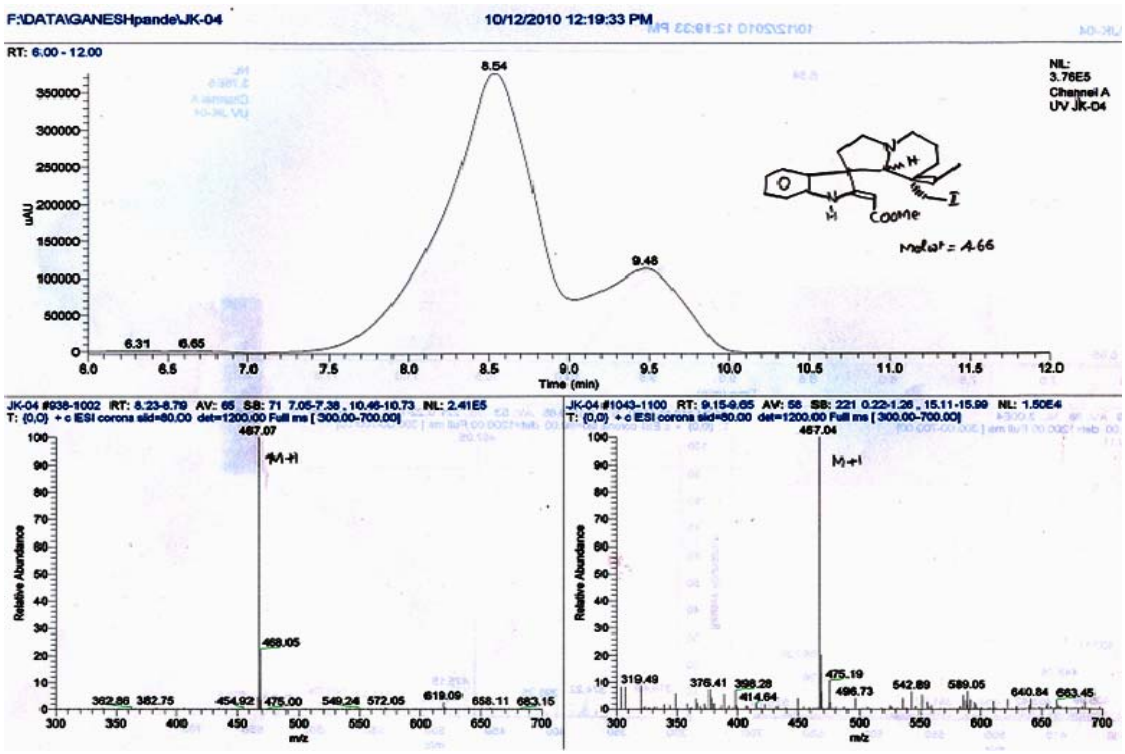
(+)- Vincadifformine.

HPLC-Mass analysis of diastereomeric mixture of 132:

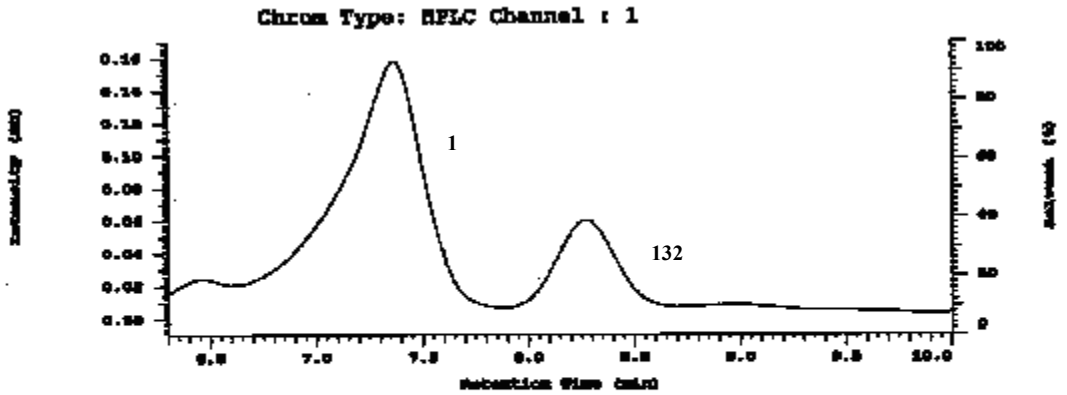


No.	RT	Height	Area	Area %
1	8.31	89724	3356300	88.617
2	9.19	15882	431127	11.383
		105606	3787427	100.000

COLUMN :-Kromasil RP-18(150 x 4.6mm)
MOBILE PHASE :- MeOH:ACN:TEAA(PH-7)(40:40:20)
WAVELENGTH :- 254nm
FLOW RATE :- 1.0 ml/min (1140psi)
SAMPLE CONC :-1mg/1ml (Inj vol-10ul)

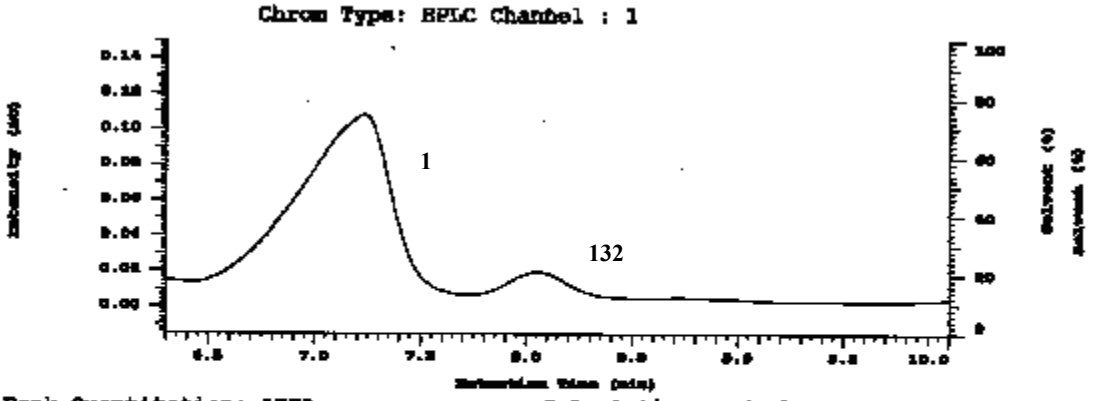


Conversion of spiro compound 132 to Vincadifformine (1) monitored by HPLC and Mass spectrometric analysis



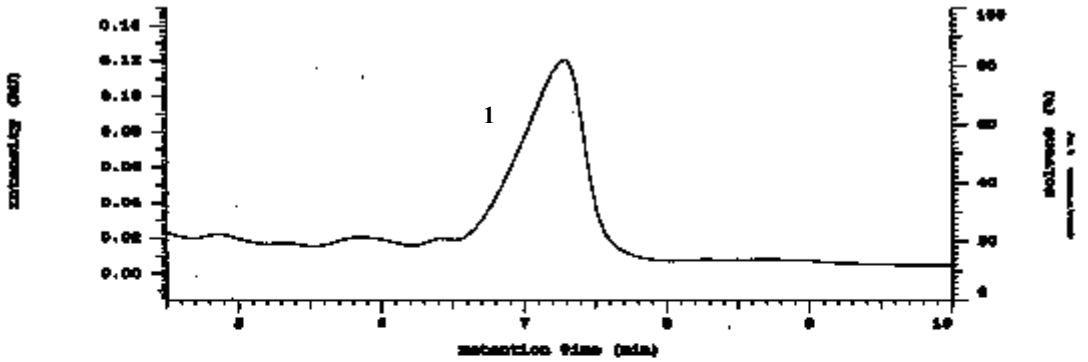
Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	7.37	71759	1770272	79.151
2	8.27	25605	466311	20.849
		97364	2236583	100.000



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	7.24	49011	1437454	96.315
2	8.05	4336	54996	3.685
		53347	1492450	100.000



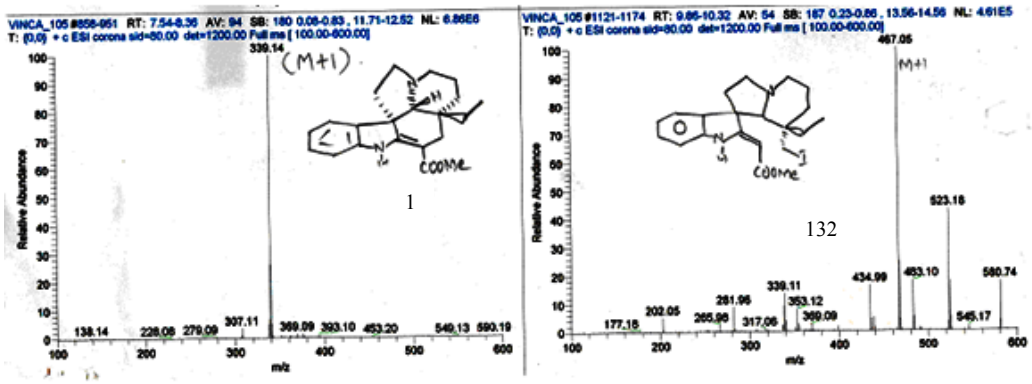
Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	7.29	52165	1561137	100.000
		52165	1561137	100.000

COlumn :Kromasil RP-18(150 X 4.6mm)
M.P. :A)MEOH:H2O(85:15)

Flow Rate :-1.0ml/min (1260psi)
Sample conc :x mg/0.5 ml
Inj vol-10ul

WAVELENGTH :254nm



2D.4 References:

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CHAPTER III

Enantoselective total syntheses of (-)-Isonitramine and (-)-Sibirine *via* Ring closing metathesis reaction

3A.1 INTRODUCTION:

The spiropiperidine structural unit is found in a variety of natural alkaloids which display interesting biological properties. For example, polyzonimine (**155**), a 2-azaspiro [4, 4] non-1-ene alkaloid is produced by the millipede *Polyzonium rosalbum* acts as a insect repellent.[1] Two novel polyketides containing 6-azaspiro [4, 5] decane unit such as pinnaic acid (**156**), tauropinnaic acid (**157**) were isolated from Okinawan bivalve *Pinna muricata*, have shown phospholipase A_2 (PLA_2) inhibitory activity.[2] Both histrionicotoxin (HTX, **158**) and perhydrohistrionicotoxin (pHTX, **159**) having 1-azaspiro [5, 5] undecane-8-ol skeleton are noncompetitive inhibitors of the neuromuscular, ganglionic and central neuronal nicotinic acetylcholine receptors and therefore, these are used as important neurophysiological research tools.[3] Other 2-azaspiro piperidine alkaloids *viz.* nitramine (**160**), isonitramine (**161**) and sibirine (**162**) were isolated[4] from *Nitraria* plants *Nitraria Schoberi* and *Nitraria Sibrica,* respectively, and they have received considerable synthetic attention due to their peculiar 2-azaspiro[5, 5] undecane skeleton and close resemblance to the neurotoxic histrionicotoxin (**158**) (Figure-1).

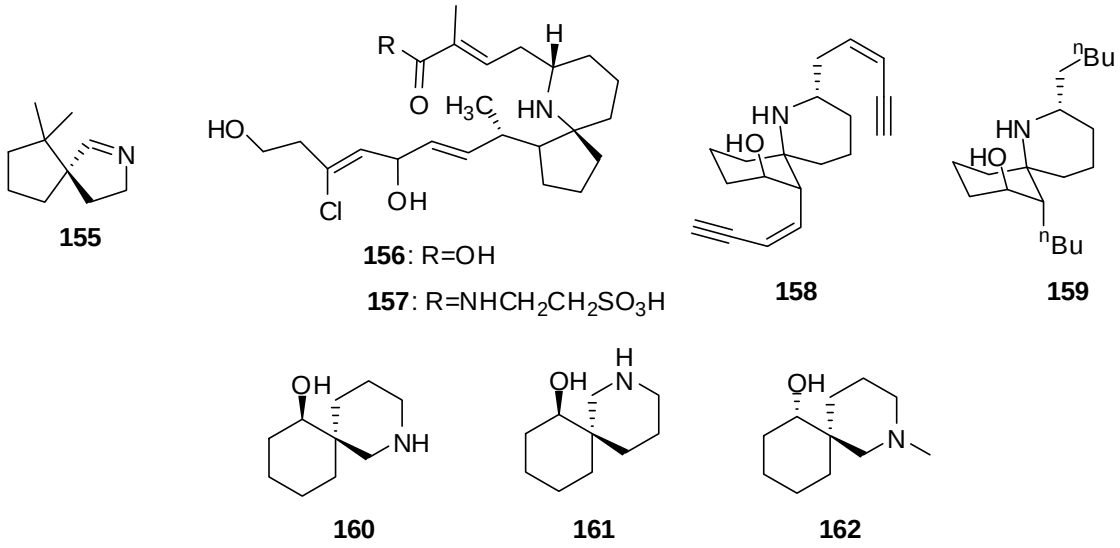


Figure-1 Some of the biologically active spiro alkaloids

3A.2 *Nitraria* alkaloids isolation and classification:

Plants of the *Nitraria* genus (Nitrariaceae) are shrubs that grow up to 2 meters high. They have fleshy leaves and small flowers, with five petals and fifteen stamens, arranged in scorpioid inflorescence. *Nitraria* species are found in the desert regions of south–east Europe (*Nitraria komarovii, Nitraria sibrica*) and middle-east (*Nitraria schoberi* = *Nitraria billardieri*), also in Australia and northen Africa (*Nitraria tridentate* = *Nitraria retusa*). *Nitraria* alkaloids isolated from aerial parts of the *Nitraria* genus are classified[5] into three major groups:

1. Spiro alkaloids: (i) Simple spiro alkaloids: Isonitramine (**161**)
   (ii) Complex spiro alkaloids: Nitraramine (**163**)
2. Tripiperidine alkaloids: Schoberine (**164**)
3. Indole alkaloids: Tangutorine (**165**)

The biosynthesis of alkaloids belonging to the first two groups is explained by the assembly of C_5 units derived from L-lysine (**166**) and for the indole group an additional unit derived from L-tryptophan is required (Figure-2).

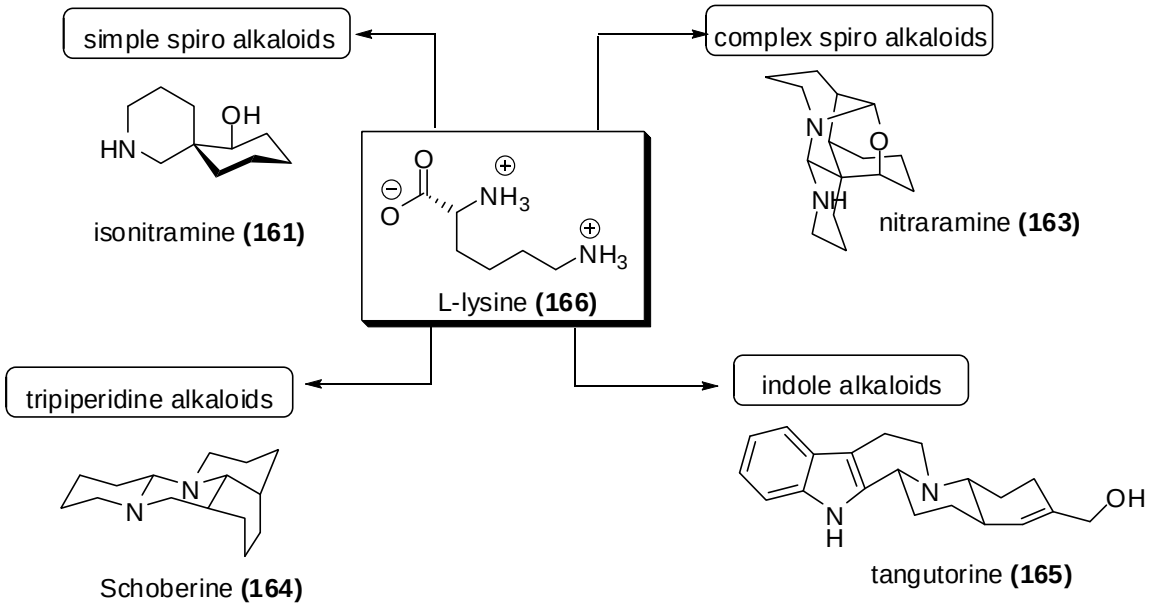
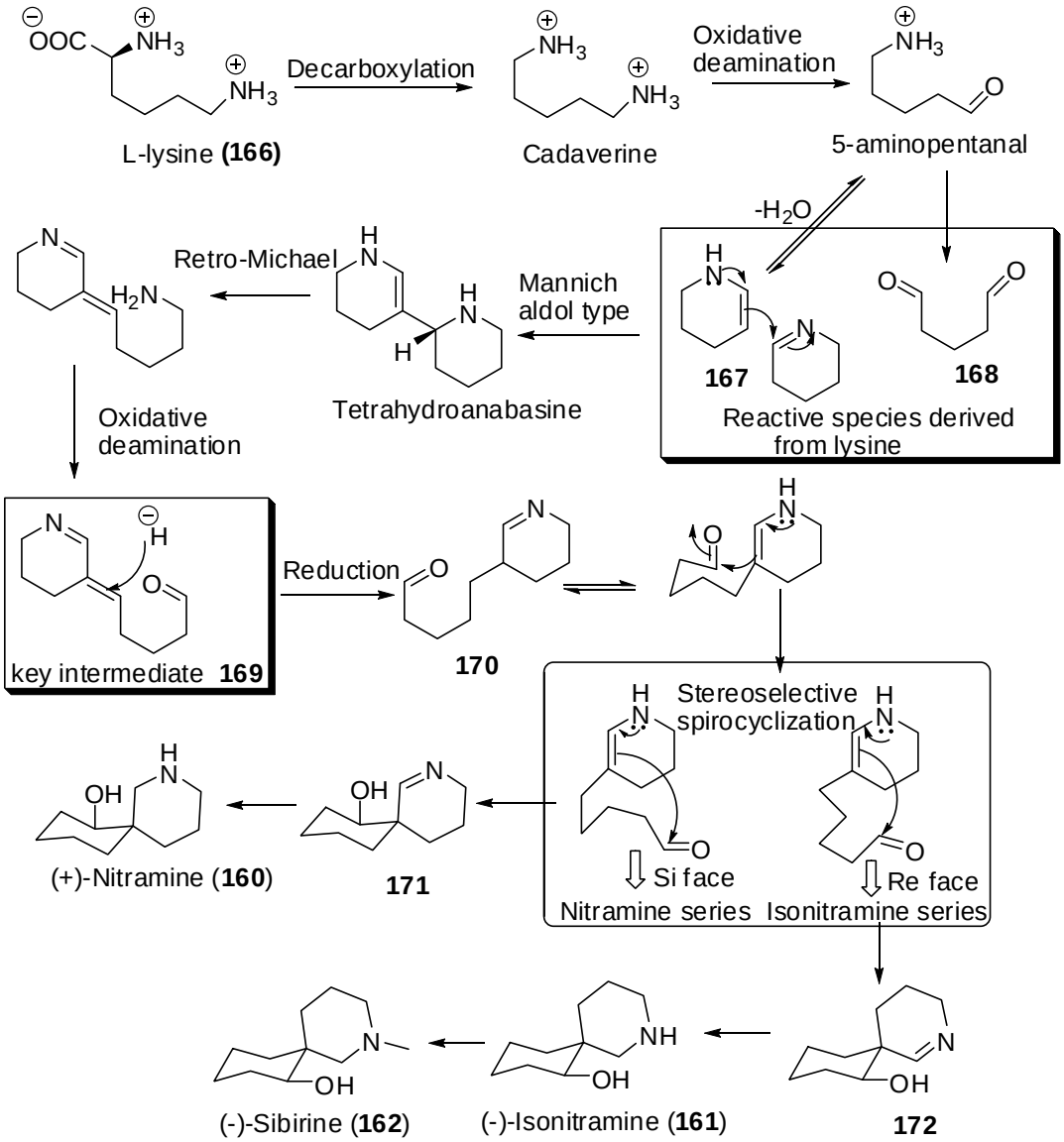


Figure-2 classification of *Nitraria* alkaloids

3A.3 Biosynthetic hypothesis of simple spiranic alkaloids:

In the biosyntheses[5] of *Nitraria* alkaloids, L-lysine (**166**) first undergoes decarboxylation and yields cadaverine which on oxidative deamination gives 5-aminopentanal. This unstable intermediate cyclizes to Δ^2-piperidine (**167**) that can exist either as an enamine (Δ^2-piperidine) or as an imine (Δ^1-piperidine) depending on the acidity of the medium.



Scheme-1 Biosynthetic hypothesis for spiro alkaloids

Another oxidative deamination of 5-aminopentanal in principle could give rise to glutaraldehyde (**168**). Δ^2-Piperidine can dimerize into tetrahydroanabasine which undergoes retro-Michael followed by an oxidative deamination to form **169**. This key intermediate on reduction to produce **170** which via spirocyclization leads to nitramine or isonitramine skeletons. A second reduction of the remaining imines **171** and **172** gives rise to nitramine (**160**) or isonitramine (**161**) depending on the stereochemical outcome of the reaction. A single *N*-methylation to isonitramine provides (-)-sibirine (**162**) (Scheme 1).

3A.4 Synthetic approaches towards optically active *Nitraria* alkaloids: Nitramine, Isonitramine and Sibirine

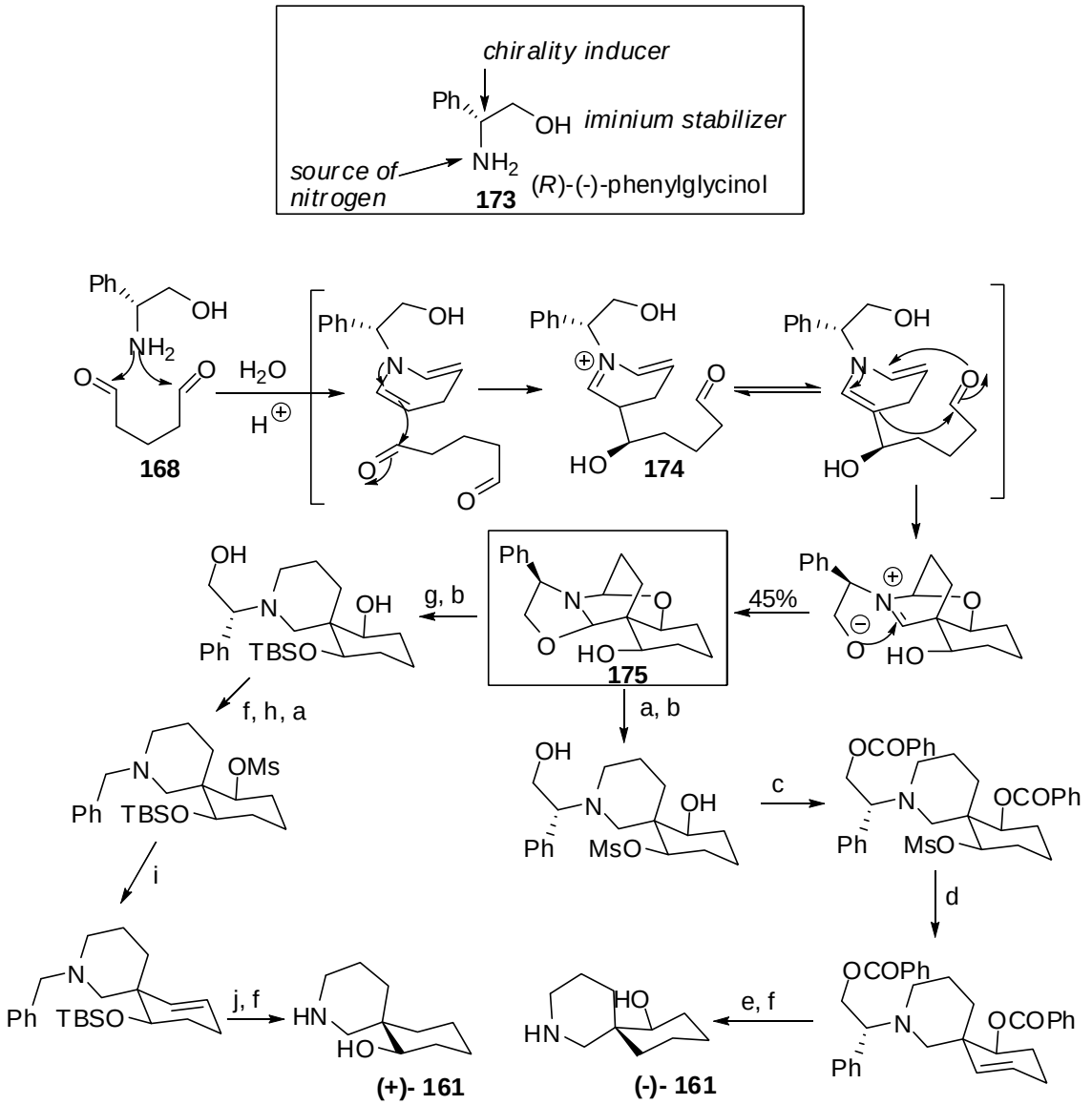
The spiro piperidine alkaloids nitramine, isonitramine and sibirine have received considerable synthetic attention since their isolation from *Nitraria schoberi* L. and *Nitraria sibrica* Pall. The stereoselective construction of the quaternary carbon centre and hydroxyl functionality is a particular challenge towards the synthesis of this family of natural products. Several racemic and enantioselective syntheses of these alkaloids have appeared since their isolation. Some of the conceptually designed asymmetric approaches are discussed below:

1. **Husson's biomimetic first approach:** (*Tetrhedron. Lett*. **1988**, *29*, 3311)[6]

   7 steps for (-)-**161** from **173**: overall yield 8%

   9 steps for (+)-**161** from **173**: overall yield 9%

The pioneering work of the Husson's group in 1980s was significant for the establishment of absolute configurations of simple spiro alkaloids. The key reaction in this strategy was the formation of **175** from (*R*)-(-)-phenylglycinol (**173**) and glutaraldehyde (**168**) through an efficient one-pot three component reaction. The pivotal intermediate **175** was converted to (-) and (+)-isonitramine in 7 and 9 steps, respectively.



Scheme-2 Husson's biomimetic first approach for (+)- and (-)-isonitramine.

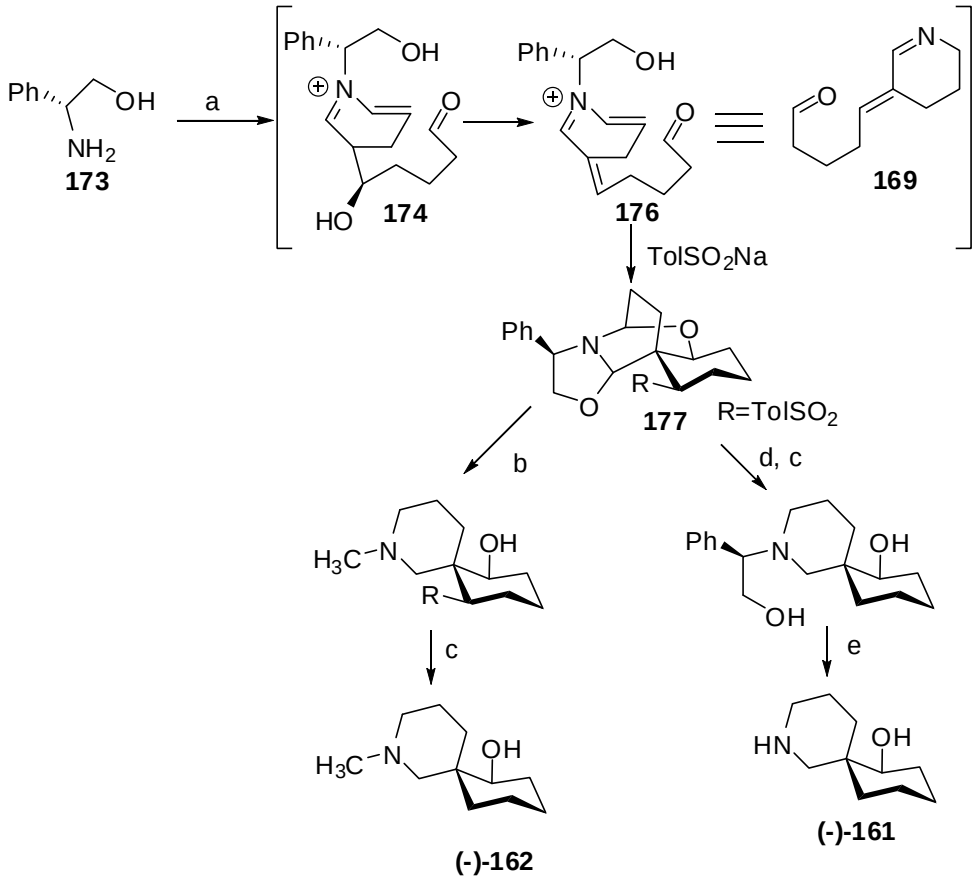
Reagents and conditions: (a) MsCl, DMAP, CH_2Cl_2, 60% (b) $LiAlH_4$, Et_2O, 0 °C, 20 min, 100% (c) C_6H_5COCl, DMAP, CH_2Cl_2, 50% (d) DBU, DMSO, 80 °C, 96 h, 75% (e) LAH, THF, 20 °C, 15 min, 100% (f) H_2, $Pd(OH)_2$/C, MeOH, 18 h, 81% (g) TBSCl, ImH, DMF, 60% (h) $C_6H_5CH_2Br$, $NaHCO_3$, DMF, 60 °C, 87% (i) DBU, C_6H_6, reflux, 96 h, 75% (j) HF, H_2O-CH_3CN

2. Husson's biomimetic second approach: (*Angew. Chem. Int. Ed*. **1998**, *37*, 104)[7]

4 steps for (-)-**161** from **173**: overall yield 33%.

3 steps for (-)-**162** from **173**: overall yield 44%

According to biosynthetic hypotheses, reduction of intermediate **176** (equivalent to biosynthetic precursor **169)** with *p*-toluene sodium sulfinate to produce **177**, further reactions as shown in Scheme-3 gives spirocyclic alkaloids.



Scheme-3 Husson's biomimetic second approach for (-)-isonitramine and (-)-sibirine.

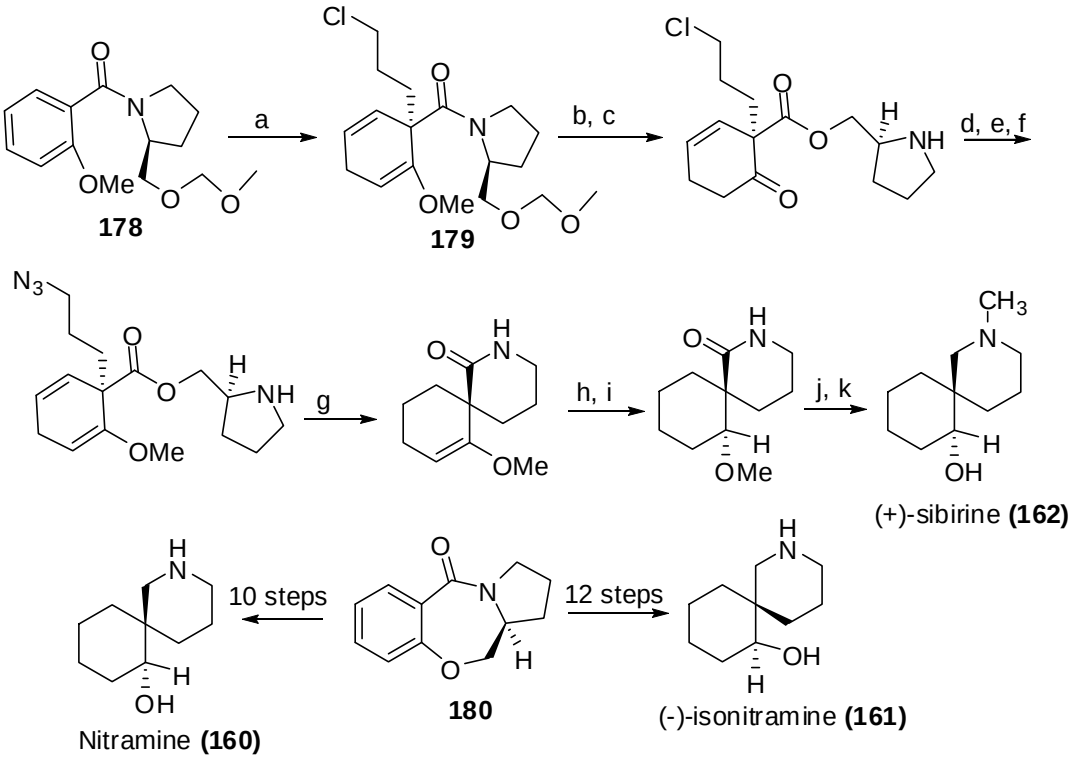
Reagents and conditions: (a) Aqueous glutaraldehyde (2.5 eq), pH 3.5, $NaSO_2Tol$ (2.2 eq), $ZnBr_2$, 3 h, 51% (b) W-2 Raney Ni, MeOH (reflux), 2 h, 91% (c) Na(Hg), anhydrous Na_2HPO_4, 24 h, -20 °C, 95% (d) $LiAlH_4$, Et_2O, 82% (e) $H_2/Pd(OH)_2/C$ 20%, MeOH, 24 h, 85%.

3. Schultz's approach (*Heterocycles,* **1987**, *25*, 437)[8]

12 steps from **178** to (+)-**162**: overall yield 37%

12 steps from **180** to (-)-**161**: overall yield 20%

The author has executed the total synthesis of optically active nitramine, isonitramine and sibirine through stereoselective Birch reduction alkylation of anisic acid derivatives **178** and **180**. This strategy brought a clear answer to the confusion concerning the absolute stereochemistry of **160**, **161** and **162** (Scheme-4).



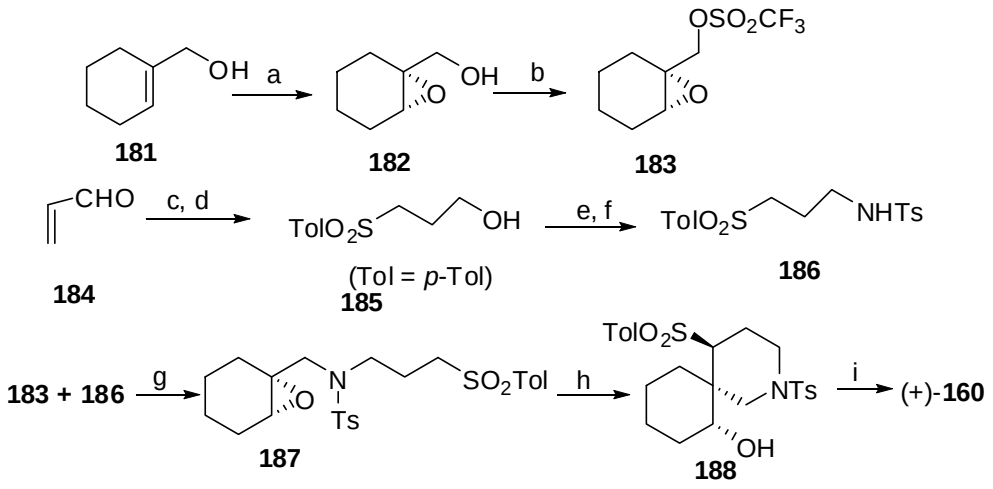
Scheme: 4 Schultz's approach

Reagents and conditions: (a) K, NH_3, t-BuOH, 1-bromo-3-chloro propane, 78% (b) Conc HCl, MeOH, reflux, 4 h (c) ClCOOMe, CH_2Cl_2, 87% (d) H_2, Pd/C, EtOAc, 97% (e) $HC(OMe)_3$, H_2SO_4, MeOH, 93% (f) NaN_3, PTC (hexadecyl tri-n-butyl phosphonium bromide), H_2O (g) $NaBH_4$, PTC, H_2O, 70% (h) NaH, THF, MeI, quant (i) H_2, $[Ir(COD)PyPCy_3]PF_6$, CH_2Cl_2, quant (j) EtSH, $AlCl_3$, CH_2Cl_2, 91% (k) LAH, THF, 95%

4. Tanner's approach (*Tetrahedron,* **1989,** *45***,** 4309, *Tetrahedron Lett*. **1988**, *29*, 6493)[9]

9 steps, overall yield 15%

Tanner *et al*. described convergent enantioselective synthesis of nitramine in 9 steps. The intramolecular ring-opening of chiral epoxy sulfone **187** led to azaspiro ring system **188** which upon further functional group transformation gave (+)- nitramine (**160)** (Scheme-5).



Scheme: 5 Tanner's approach to (+)-nitramine

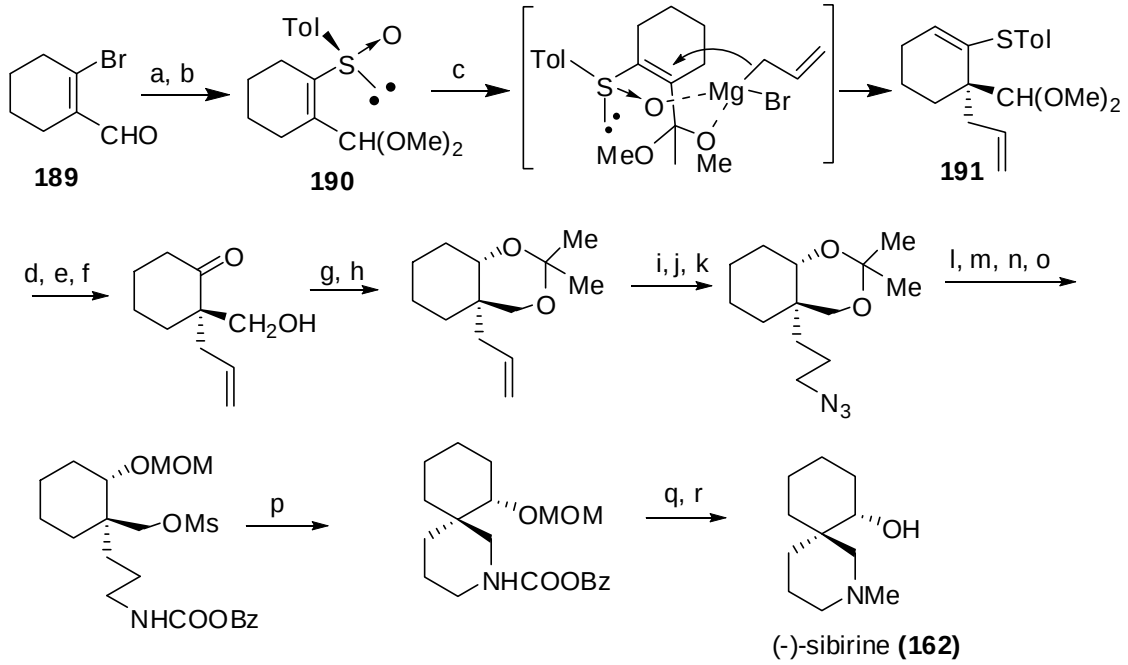
*Reagents and conditions: (a) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, (-)-diethyl tartarate, CH_2Cl_2, -40 °C, 70% (b) $(CF_3SO_2)_2O$, Et_3N, THF, -20 °C (c) 4-thiocresol, Na, EtOH, then $NaBH_4$, 86% (d) H_2O_2, HOAc, 89% (e) CH_3SO_2Cl, Et_3N, THF, 97% (f) H_2NTs, NaH, DMF, 0 °C→60 °C, 81% (g) NaH, DMF, 0 °C, then add **183**→50 °C, 71% (h) n-BuLi, THF/HMPA, -20 °C→rt, then quench at -78 °C, 69% (i) Na(Hg), Na_2HPO_4, MeOH, 0 °C, 74%.*

5. Iwata's approach (*J. Chem. Soc., Chem. Commun*. **1991**, 1409)[10]

18 steps, overall yield 4.5%

Iwata *et al.* demonstrated the total synthesis of (-)-sibirine (**162**) through highly enantioselective construction of quaternary stereocenter by Pummerer-type reaction of a chiral vinylsulfoxide **190** with allyl magnesium bromide leading to the formation

of **191** in 96% ee. Further functional group transformation resulted (-)-**162** in 4.5% overall yield (Scheme-6).



Scheme: 6 Iwata's approach for the synthesis of (-)-sibirine

Reagents and conditions: a) $CH(OMe)_3$, p-$MeC_6H_4SO_3H$, rt, 86% (b) n-BuLi, (-)-menthyl (S)-p-toluenesulphinate, THF, -78 °C, 91% (c) allylmagnesium bromide, THF, -78 °C→rt, 60% (d) p-$MeC_6H_4SO_3H$, acetone, rt, 92% (e) $NaBH_4$, MeOH, 0 °C, 83 % (f) 10% HCl, MeCN, reflux, 62% (g) $Zn(BH_4)_2$, Et_2O-THF, -78 °C (h) dimethoxypropane, p-$MeC_6H_4SO_3H$, rt, 87% (i) $BH_3.SMe_2$, 0 °C, then H_2O_2, NaOH, 75% (j) $MeSO_2Cl$, pyridine, 0 °C, 87% (k) NaN_3, tetra-n-butylammonium iodide, benzene, reflux, 90% (l) H_2, Pd/C (m) $ClCOOCH_2Ph$, K_2CO_3 (aq), CH_2Cl_2, 0 °C→rt (n) $MeSO_2Cl$, pyridine, 0 °C (o) MOMCl, Pr^i_2NEt, CH_2Cl_2, rt, 62% (p) KH, THF, 0 °C→rt, 92% (q) $LiAlH_4$, THF, 0 °C→rt (r) 10% HCl, rt, 70%.

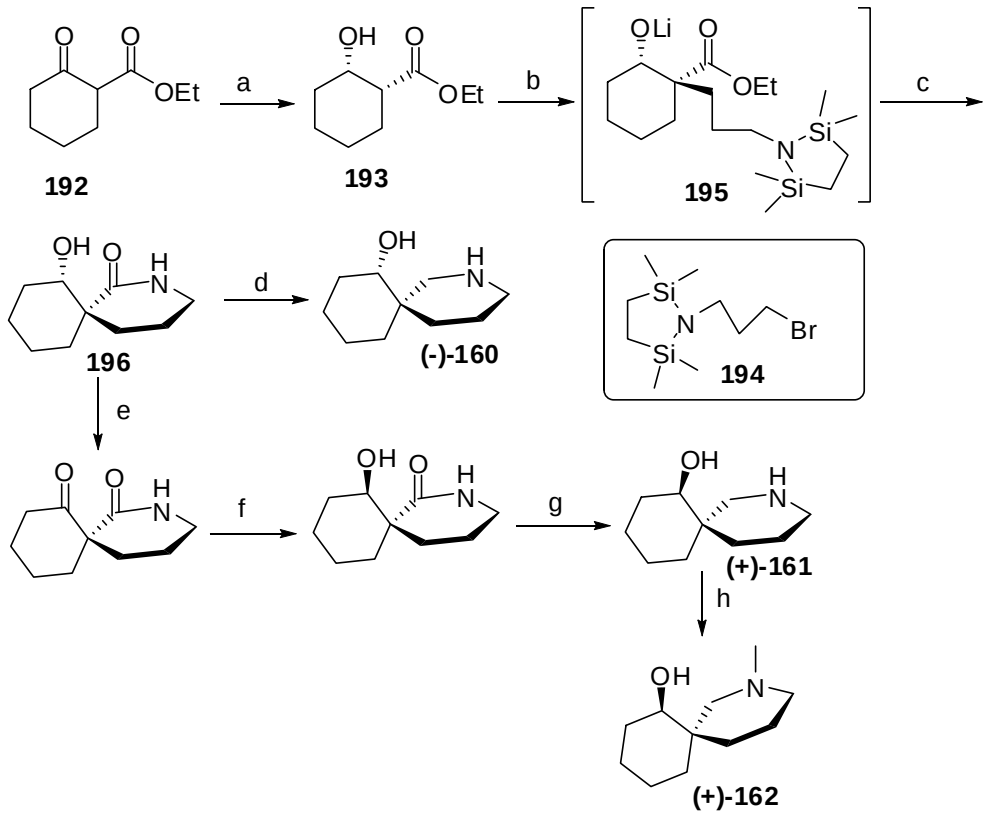
6. Kimpe's approach (*J. Org. Chem*. **1995**, *60*, 3916)[11]

4 steps for (-)-**160**: overall yield 26%

7 steps for (+)-**161**: overall yield 17.7%

Enantioselective synthesis of nitraria alkaloids (**160** and **161**) were achieved by Kimpe *et al*. by alkylation of **193**, achieved by baker's yeast reduction of **192**, using **194** followed

by cyclization under basic conditions led to lactam **196** which upon usual oxidation and reduction sequence gave (-)-nitramine and (+)-isonitramine, respectively (Scheme-7).



Scheme-7: Kimpe's enantioselective approach for (-)-nitramine and (+)-isonitramine

Reagents and conditions (a) Baker's yeast, 65% (b) LDA, THF, -60 ^{0}C, -15 ^{0}C, 30 min, ***194****, THF, -15 °C, 2 h, 3 h→rt (c) K_2CO_3, MeOH, Δ, 3 h, 64% (d) $LiAlH_4$, THF, rt, 72 h, 63% (e) PCC, NaOAc, CH_2Cl_2, rt, 15 h, 83% (f) DIBAL-H, THF, -78 °C, 3 h, 79% (g) $LiAlH_4$, THF, rt, 72 h, 65% (h) MeI, EtOH*

7. **Ogasawara's approach** (*Synlett*, **1996**, 925)[12]

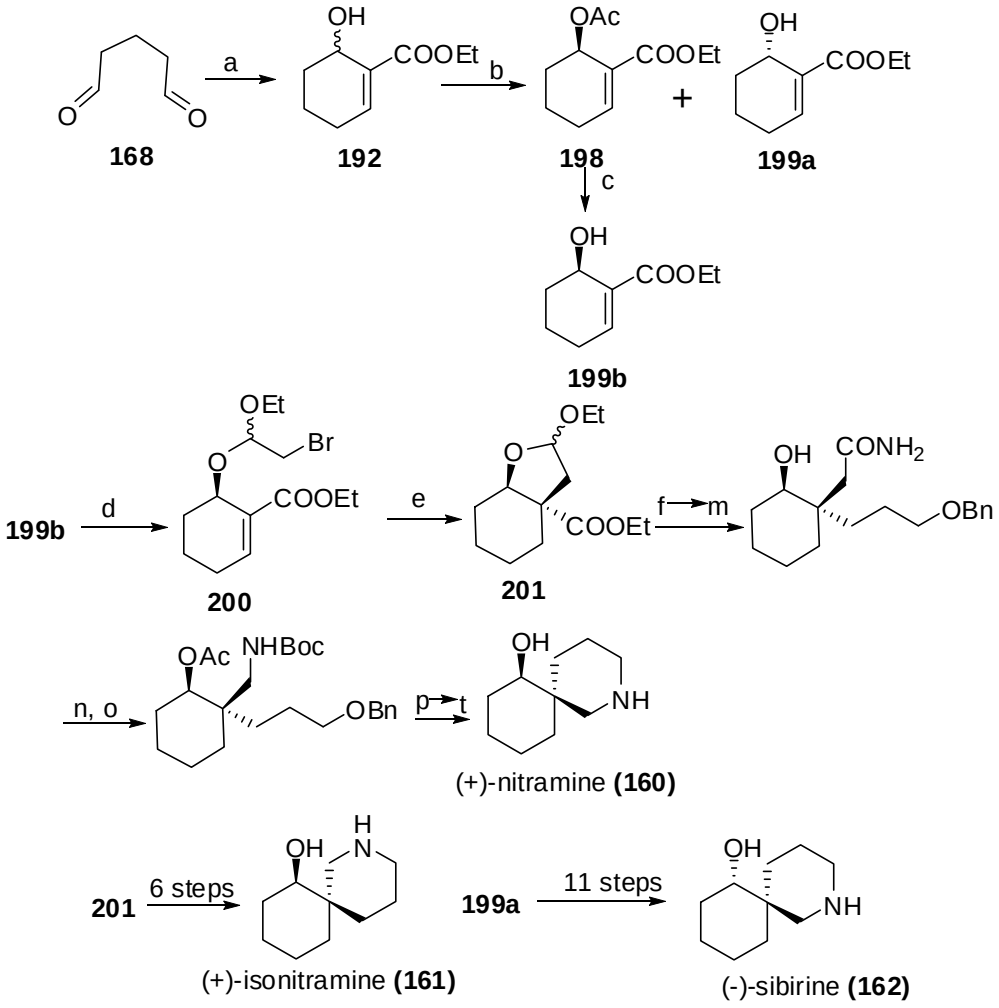
   20 steps for nitramine: overall yield 8%

   13 steps for (+)-isonitramine: overall yield 9%

   14 steps for (-)-sibirine: overall yield 9%

The author has executed stereocontrolled synthesis of all the three alkaloids in natural configurations by utilizing lipase mediated kinetic resolution of **192** and radical

cyclization from **200** to construct all carbon quaternary stetreocentre in **201**. Usual sequences from here (Scheme-8) led to the syntheses of spirocyclic alkaloids.



Scheme: 8 Ogasawara's approach for the synthesis of nitraria alkaloids

Regents and conditions: (a) $(EtO)_2P(O)CH_2COOEt$, aq. K_2CO_3, 60% (b) vinyl acetate, lipase PS, ^tBuOMe, 40% (c) lipase PS, phosphate buffer-acetone (9:1), 93% (d) NBS, ethyl vinyl ether, Et_2O, 0 °C→rt, 86% (e) Bu_3SnH, AIBN, benzene, 70 °C, 97% (f) LAH, THF, 0 °C, 96% (g) Swern oxidation, 93% (h) $(EtO)_2P(O)CH_2COOEt$, NaH, 0 °C, 100% (i) H_2, PtO_2, EtOH, 99% (j) LAH, THF, 0 °C, 100% (k) BnBr, NaH, THF, 70 °C, 98% (l) CrO_3, H_2SO_4, acetone, 95% (m) NH_4Cl, Me_3Al, CH_2Cl_2, 40 °C, 95% (n) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 100% (o) I,I-bis(trifluroacetoxy)iodobenzene, ^tBuOH, 70 °C, 85% (p)

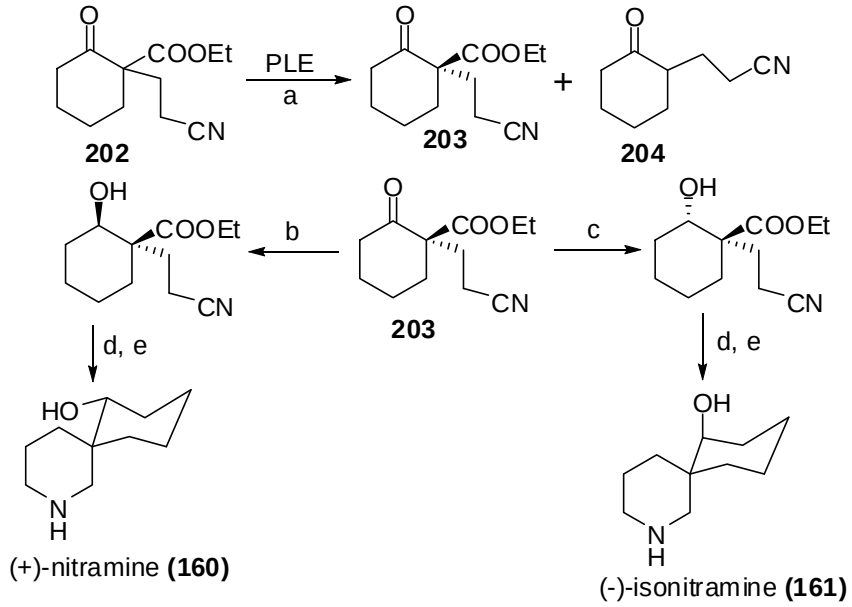
H_2, Pd-C, MeOH, 100% (q) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 99% (r) NaH, THF, 80% (s) K_2CO_3, MeOH, 100% (t) 10% HCl, MeOH, 83%

8. Westermann's approach: (*Tetrahedron Asymmetry*, **1993**, *4*, 2119)[13]

4 steps from **202** for (+)-nitramine: overall yield 13.8%

4 steps from **202** for (-)-isonitramine: overall yield 13.8%

The author has presented the total synthesis of (+)-nitramine and (-)-isonitramine by preparing substituted *β*-ketoesters **203** in enantiomerically pure form by pig liver esterase catalyzed hydrolysis of their racemic precursor **202.** The enzymatic digestion of one enantiomer of **202** leads to a *β*-ketoacid which is decarboxylated to yield **204** during work up. The remaining *β*-ketoester **203** (99%ee) was recovered very easily and was converted to (+)-nitramine and (-)-isonitramine as shown in Scheme-9.



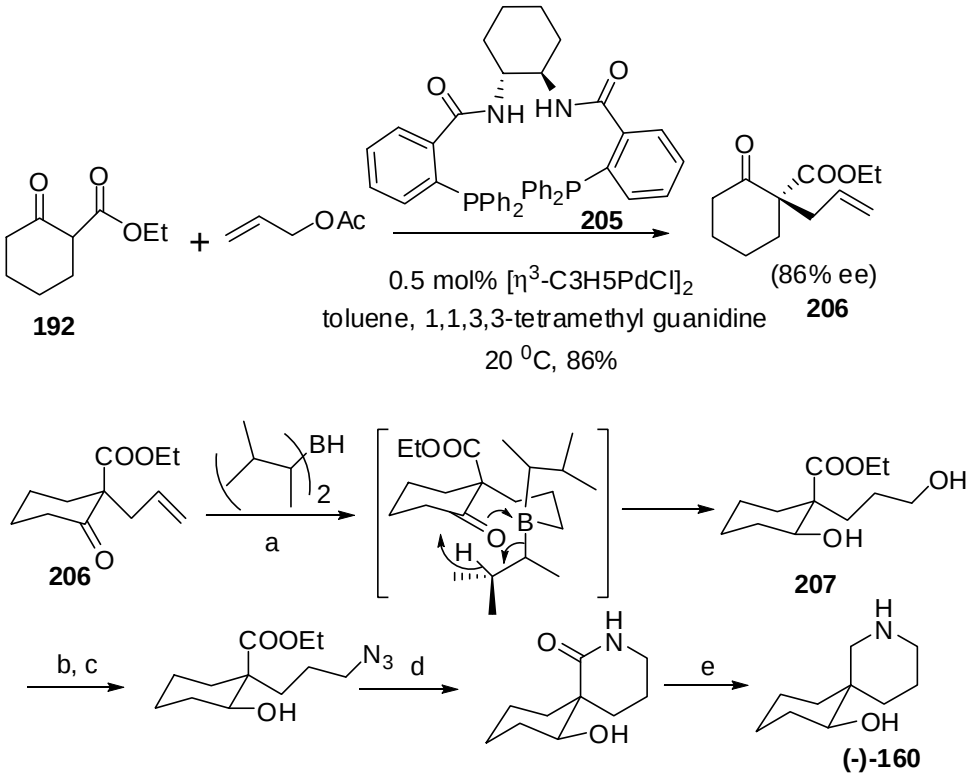
Scheme: 9 Westermann's approach

(a) PLE, pH 8, phosphate buffer, 20 °C, acidic work up, 35% (b) $NaBH_4$, CH_3OH, 2 h, 82% (c) $Al(O^iPr)_3$, ^iPrOH, 3 h, 82% (d) H_2/PtO_2, EtOH, 60 °C, 65% (e) LAH, THF, 15 h, 74%

9. Trost's approach (*J. Am. Chem. Soc*. **1997**, *119*, 7879)[14]

6 steps from **38**: overall yield 37%

The enantioselective construction of quaternary stereocenter by the reaction of 2-carboalkoxycyclohexanone (**192**) with allyl acetate using the chiral ligand **205** in a palladium catalyzed reaction was examined by the author and methodology was used to synthesize optically active spiro alkaloid nitramine as summarized in Scheme-10.



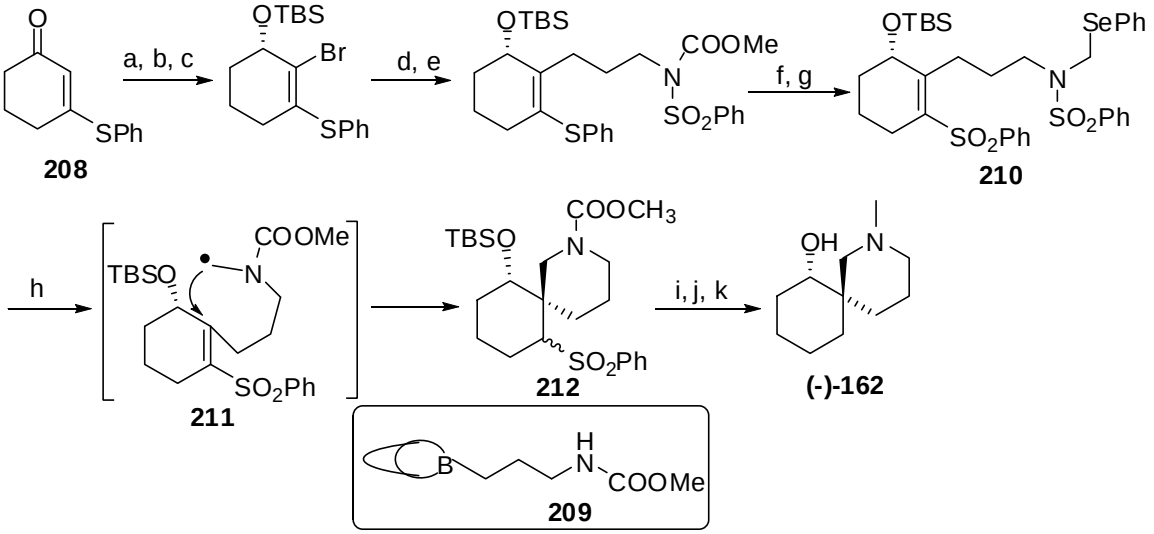
Scheme-10 Trost's approach for the synthesis of (-)-nitramine

Reagents and conditions: (a) THF, -15 °C→rt then $NaBO_3.4H_2O$, H_2O, 80% (b) TEA, CH_3SO_2Cl, -60 °C→0 °C, CH_2Cl_2 (c) NaN_3, DMF, 40 °C, 72% (d) H_2 (1 atm), $Pd(OH)_2/C$, K_2CO_3, C_2H_5OH, rt→reflux, 83% (e) LAH, THF, rt, 90%

10. Koreeda's approach (*Org. Lett*. **2002**, *4*, 3329)[15]

14 steps, overall yield 10.9%

Koreeda *et al.* demonstrated the preferential 6-*exo*-spiro cyclization of (methoxy carbonyl amino) methyl radical **211** to the distal alkene attached to $PhSO_2$ to synthesize optically active spirocyclic alkaloid sibirine as depicted in Scheme-11.



Scheme: 11 Koreeda's approach for (-)-sibirine

Reagents and conditions: (a) NBS, CCl_4, rt, 24 h, 81% (b) $NaBH_4$, $CeCl_3$, MeOH, rt, 0.5 h, 97% (c) TBSCl, ImH, DMF, rt, 95% (d) ***209****, $Pd(PPh_3)_4$, NaOH, THF, H_2O, reflux, 3 h (e) m-CPBA, CH_2Cl_2, rt, 2.5 h (f) t-BuOK, HCHO, t-BuOH, rt, 1 h, 75% (g) PhSeH, p-TsOH, rt, 2 h, 71% (h) $(n\text{-}Bu)_3SnH$, AIBN, toluene, reflux, 7 h (i) Na, ethanol, -20 °C→rt, 2 h, 92% (j) LAH, THF, rt, 30 min (k) CH_3CN, 45% aq HF, rt, 1.5 h, 85%*

3A.5 Summary:

From the above brief introduction on the syntheses of *Nitraria* alkaloids, it is clear that the majority approaches endeavor to create heterocyclic ring either by the formation of C_1-N or C_3-N bond or formation of the C-C bonds of the spiro carbon, i.e. C_1-C_6 or C_5-C_6 (Figure-3).

In the foregoing discussion we wish to present a new protocol for the synthesis of nitraria alkaloids (-)-isonitramine and (-)-sibirine by joining C_9-C_{10} *via* ring closing olefin metathesis.

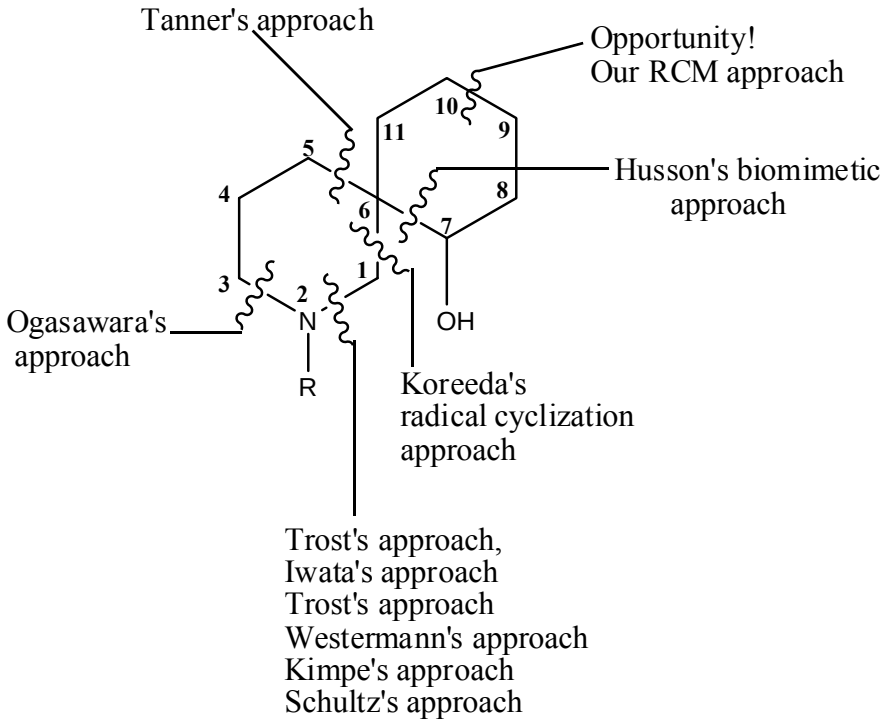


Figure: 3 Various strategies for construction of heterocyclic ring.

Section-B

Total syntheses of (-) Isonitramine and (-)-Sibirine *via* ring closing olefin metathesis reaction

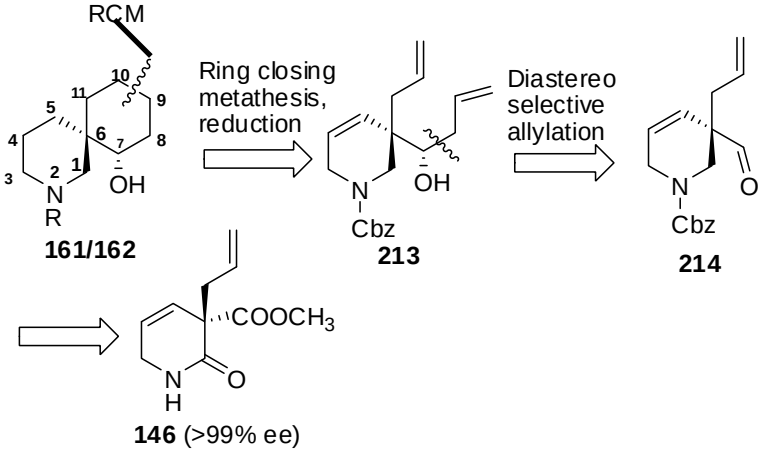
Natural products containing quaternary carbon centres are the target of many current synthetic accomplishments. Since the isolation and structural elucidation of *Nitraria* alkaloids, several synthetic strategies have been published. The interest in these natural compounds stems from the structural similarity with the neurotoxic histrionicotoxin **158** and perhydrohistrionicotoxin **159** and also due to their suitability for biological testing.

Despite the fact that a number of syntheses of *Nitrari*a alkaloids have appeared in literature, only a few of them are enantioselective. Moreover, only few of them are focused on constructing piperidine ring by C-C bond formation or C-N bond formation.

We analyzed the molecular complexity of these *Nitraria* alkaloids in different manner and designed a conceptually new strategy as shown retrosynthetically in Scheme-12

3B.1 Retrosynthetic analysis:

We envisioned that the alkaloids **161** or **162** could be obtained from **213** *via* sequential ring closing olefin metathesis and reduction of the double bond. Precursor **213** can be accessed from the diastereoselective alkylation of **214**. The synthesis of **214** would involve sequential reduction and oxidation reactions from **146** (>99% ee).

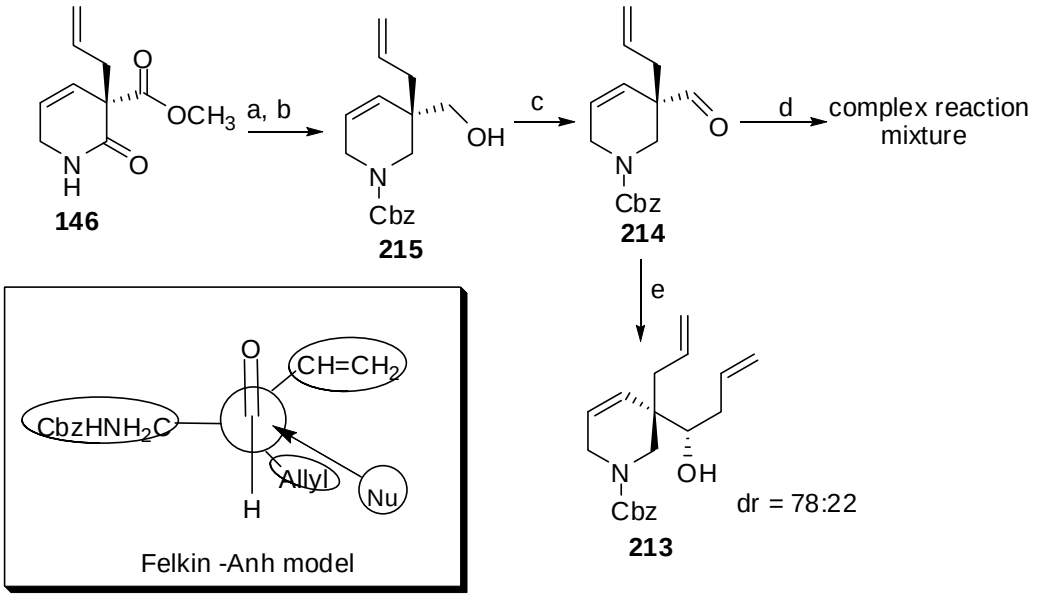


Scheme-12 Retrosynthetic analysis of Sibirine and Isonitramine

3B.2 Results and discussion:

The syntheses of sibirine (**162**) and isonitramine (**161**) commenced with the transformation of enantio pure **146** (ee>99%) to **215** in 81% yield $[\alpha]^{26}_{D}$= + 1.16 (*c* = 1.21, $CHCl_3$) by LAH reduction and *N*-Cbz protection. Compound **215** upon oxidation using 2-iodoxy benzoic acid (IBX)[16] afforded **214** in 95% yield $[\alpha]^{26}_{D}$= +166.83 (*c* = 1.01, $CHCl_3$). The characteristic aldehydic peak was confirmed by observing a signal for δ_H 9.5 in ^{1}H NMR and ^{13}C signal at δ_C 200.0. The diastereoselective allylation of **214**, the important part of our synthetic strategy, was carried out using allyl magnesium bromide and obtained desired **213** albeit in low yield. Thus we modified our allylation protocol and carried out the reaction under mild Hosomi-Sakurai conditions[17] using allyltrimethyl silane and boron triflouride-etherate in DCM at -78 °C which gave desired **213** in 92% yield (*dr*: 78:22) (Scheme-13).

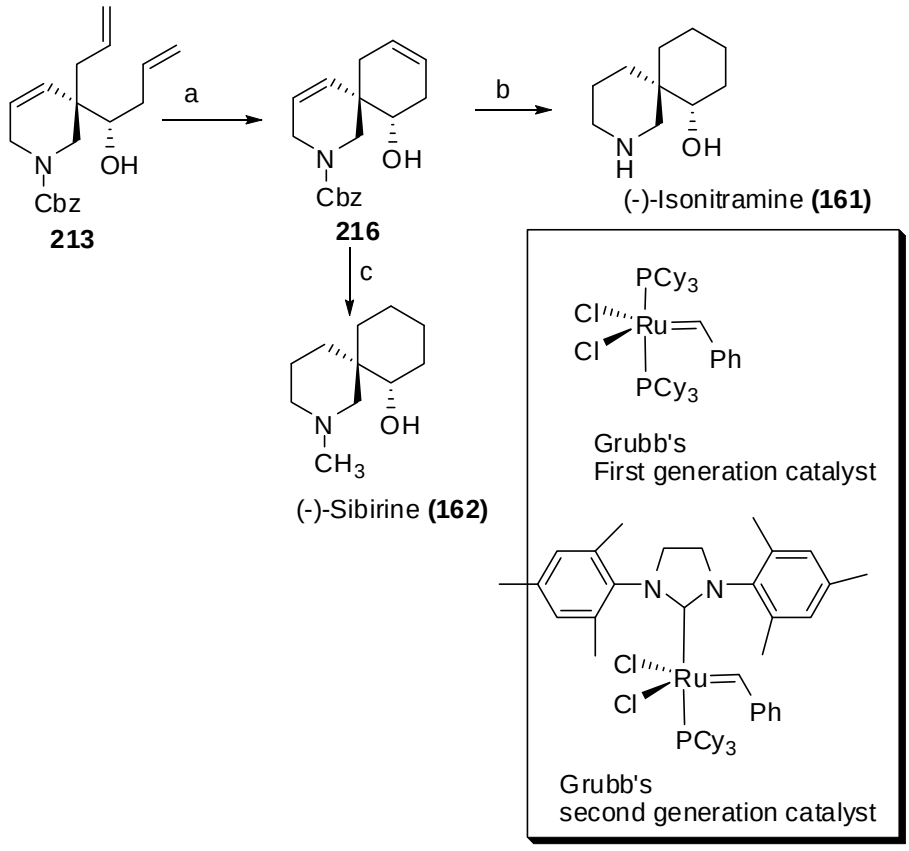
Both the diastereomers of **213** were separated pure through flash column chromatography.



Scheme-13 Synthesis of homoallylic alcohol **213**

Reagents and conditions: (a) LAH, THF, reflux, 8 h (b) CbzCl, dioxane-water, $NaHCO_3$, rt, 5 h, 81% (c) IBX, EtOAc, reflux, 8 h, 95% (d) allyl magnesium bromide, THF, 0 °C (d) allyl trimethyl silane, BF_3:OEt_2, DCM, -78 °C, 92%.

Our initial attempt of ring closing metathesis reaction[18] of major isomer **213** with Grubb's first generation catalyst failed to give expected product **216** in satisfactory yield. Therefore, RCM was attempted using Grubb's second generation catalyst which, pleasingly, afforded **216** in 85% yield. Hydrogenation of **216** with palladium-carbon in anhydrous methanol gave (-)-isonitramine in 90% yield $[\alpha]^{25}_{D}$= -5.1 (*c* = $CHCl_3$). Reduction of **216** under the same reaction condition but in the presence of aqueous formaldehyde[19] gave (-)-sibirine in 82% yield $[\alpha]^{25}_{D}$= - 23.1 (*c* = 0.76, $CHCl_3$) (Scheme-14).



Scheme: 14 Synthesis of (-)-isonitramine and (-)-sibirine

Regents and conditions: (a) Grubb's II generation catalyst (7 mol%), DCM, reflux, 6 h, 85% (b) H_2 (1 atm), Pd/C, MeOH, rt, 5 h 90% (c) H_2 (1 atm), Pd/C, HCHO, MeOH, rt, 30 h, 82%.

The structure of (-)-isonitramine was confirmed unambiguously by X-ray crystallographic analysis (Figure-4) and (-)-sibirine with ^{1}H, ^{13}C, spectroscopic data. The spectroscopic data of (-)-isonitramine and (-)-sibirine are in accord with the literature report.[15, 20]

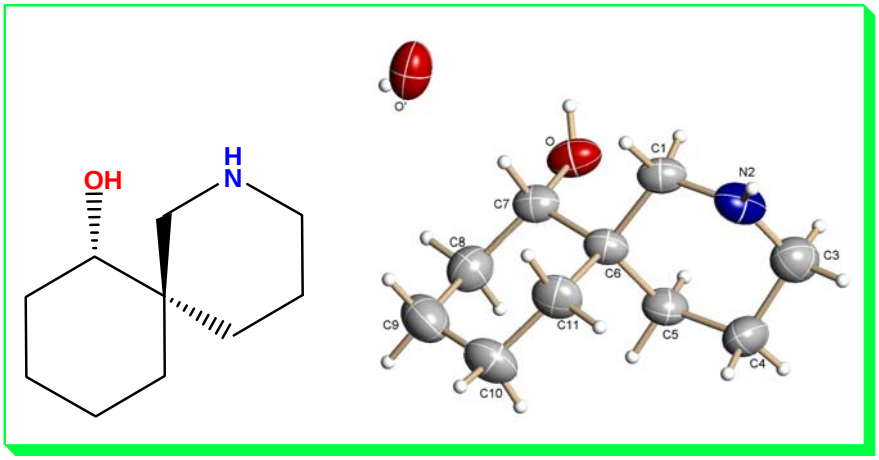


Figure –4 *ORTEP diagram of* ***Isonitramine (161).*** *Ellipsoids are drawn at 50% probability.*

The chemical shifts values of ^{1}H and ^{13}C NMR for (-)-sibirine is presented below in the tabular (Table-1) for clarity

Table: 1 ^{1}H and ^{13}C NMR spectroscopic data for (-)-sibirine (162)

^{1}H ppm ($CDCl_3$)		**^{13}C ppm ($CDCl_3$)**	
Reported[R] (500MHz)	**Obtained (400Mz)**	**Reported (100MHz)**	**Obtained (100 MHz)**
0.85-1.01 (m, 2H)	0.84-1.0 (m, 2H)	20.41	20.32
1.16-1.29 (m, 2H)	1.16-1.27 (m, 2H)	23.13	23.01
1.36-1.43 (m, 24)	1.33-1.40 (m, 2H)	24.44	24.36
1.47-1.56 (m, 2H)	1.44-1.54 (m, 2H)	27.71	27.53
1.68-1.76(m, 2H)	1.68-1.74 (m, 2H)	29.59	29.46
1.87-1.96 (m, 2H)	1.85-1.95 (m, 2H)	37.16	37.04
2.07-2.22 (m, 2H)	2.07-2.17 (m, 2H)	37.26	37.18
2.24 (s, 3H)	2.21 (s, 3H)	46.53	46.45
2.61 (d, 1H, J = 10.9 Hz)	2.60 (d, 1H, J = 11.3 Hz)	56.45	56.31
2.82 (brd, 1H, J = 6.9Hz)	2.79 (brd, 1H, J = 7 Hz)	69.99	69.85
3.61 (dd, 1H, J = 11.2, 3.4 Hz)	3.58 (dd, 1H, J = 11.2, 3.2 Hz)	80.56	80.42
5.40-6.40 (extreamly broadened peak, 1H, OH)	3.21-3.86 (extreamly broadened peak, 1H, OH)		

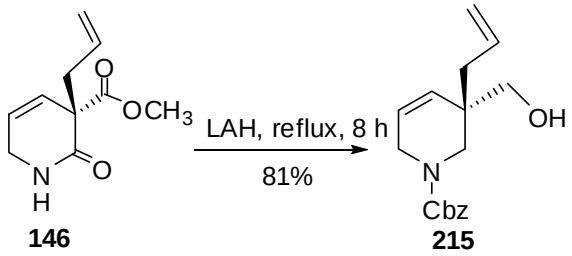
3B.3 Summary:

We have successfully developed a new protocol for the syntheses of optically pure sibirine and isonitramine *via* ring closing olefin metathesis reaction. The (-)-sibirine and (-)-isonitramine was achieved in 42% and 38% overall yield from **146**.

Section-C

3C.1 Experimental procedures and spectral data:

(*S*)-benzyl 5-allyl-5-(hydroxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate (215) :



146 **215**

To an ice cooled stirred slurry of Lithium aluminium hydride (0.47 g, 12.41 mmol) in anhydrous THF (12 mL) was added a solution of **146** (0.2 g, 1.03 mmol) in anhydrous THF (4 mL). The reaction mixture was allowed to warm to room temperature and refluxed for 8 h. The reaction was cooled to room temperature, quenched carefully with moist Na_2SO_4, filtered and the residue was washed with ethylacetate & concentrated.

The resulting crude amino alcohol was dissolved in dioxane -water mixture (1:1, 6 mL), sodium hydrogen carbonate (0.17 g, 2.06 mmol) was added followed by the slow addition of benzyl chloroformate (0.16 mL, 1.13 mmol in 1mL dioxane) under vigorous stirring at 0 °C. The reaction mixture was stirred for another 5 h at ambient temperature, dioxane was evaporated and water (20 mL) was poured to the residue, extracted with ethylacetate (20 mL ×3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (SiO_2, EtOAc: Petether 2:8), afforded **215** as a colourless oil (0.24 g, 81%), (R_f: 0.28, 3:7 EtOAc : Petether)

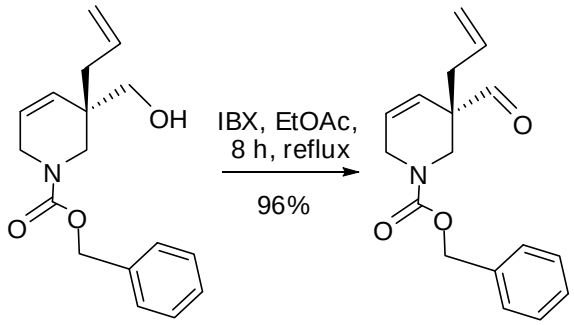
Yield : 81%

$[\alpha]^{26}_D$: + 1.16 (*c* 1.21, $CHCl_3$)

IR (film) γ_{max} cm^{-1} ($CHCl_3$) : 3434, 2925, 1683, 1434, 1237

^{1}H NMR (400 MHz, $CDCl_3$) δ	**:**	7.35-7.30 (m, 5H), 5.81-5.59 (m, 3H), 5.15-5.06 (m, 4H), 4.20-4.09 (m, 1H), 3.93-3.68 (m, 2H), 3.33 (apparent s, 2H), 3.12, 2.87 (2 sets of doublet, *J* = 13.0 Hz, 1H), 2.26-2.11 (m, 2H), 1.87 (brs,1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	**:**	156.3, 136.4, 133.5, 130.5 (129.7), 128.5, 128.0, 127.8 125.5 (125.0), 118.2, 67.3, 65.7 (65.5), 46.2 (46.0) 43.8 (43.6), 41.2, 38.7.
HR-MS (EI)	**:**	calcd for $C_{17}H_{21}NO_3$: 287.15214. Found: 287.14669.

(*S*)-benzyl 5-allyl-5-formyl-5,6-dihydropyridine-1(2H)-carboxylate (214):

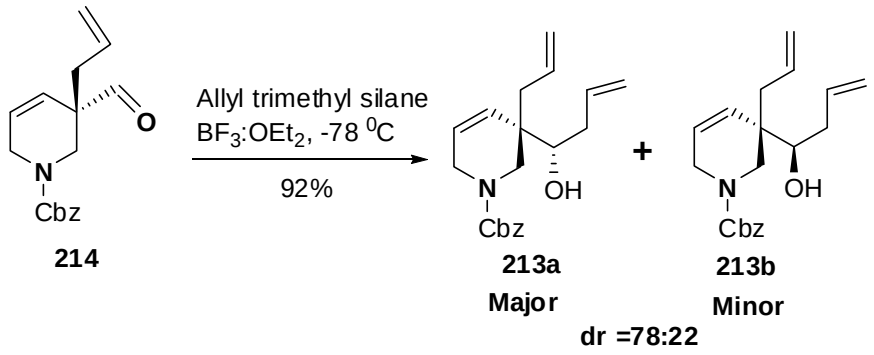


The compound **215** (0.1 g, 0.34 mmol) was dissolved in ethylacetate (5 mL) and IBX (0.19 g, 0.68 mmol) was added. The resulting suspension was refluxed for 8 h and cooled to room temperature, filtered through a celitepad. The filtrate cake was washed with ethylacetate (2×4 mL) and the combined filtrates were concentrated to gave aldehyde **214** as a colorless sticky liquid (0.095 g, 96%); (R_f 0.38, EtOAc:Petether 2:8)

Yield	**:**	96%
$[\alpha]^{26}_D$	**:**	+166.83 (*c* 1.01, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	**:**	3017, 2849, 1722, 1702, 1431, 1238.

^{1}H NMR (400 MHz, $CDCl_3$) δ	**:**	9.52 (apparent doublet, 1H, *J* = 11.79), 7.35-7.29 (m, 5H), 5.99, 5.91 (2 sets of apparent doublet, 1H, *J* = 9.5 Hz), 5.74-5.65 (m, 2H), 5.15-5.09 (m, 4H), 4.18-3.99 (m, 2H), 3.85-3.78 (m, 1H), 3.28,3.17 (2 sets of doublet, 1H, *J* = 13.3 Hz), 2.37-2.33 (m, 2H).
^{13}C NMR (100MHz, $CDCl_3$) δ	**:**	200.7, 155.6 (155.2), 141.7, 136.3, 133.1, 131.7 (131.5), 128.4, 128.1, 127.9, 119.5, 67.4, 51.3, 44.7 (44.6), 43.2, 37.7
MS(ESI): *m/z*	**:**	308.3490 $(M+Na)^+$, 324.3493 $(M+K)^+$.

(*S*)-benzyl5-allyl-5-((*S*)-1-hydroxybut-3-enyl)-5,6-dihydropyridine-1(2H)-carboxylate (213):



A solution of aldehyde **214** (0.287 g, 1.mmol) in 34 mL of anhydrous CH_2Cl_2 at -78 °C under argon was treated with BF_3:OEt_2 (0.31 mL, 2.51 mmol). After 15 min allyltrimethyl silane (0.31 mL, 2 mmol) was added and the resulting solution was stirred for 6 h at -78 °C, the reaction was poured into saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with dichloromethane (3×30 mL). The extracts were combined, washed with brine (25 mL) and dried over Na_2SO_4, concentrated under reduced pressure. The crude residue upon flash column chromatographic separation afforded major isomer **213a** (0.23 g) and minor isomer **213b** (0.067 g), (0.3 g, 92%) as a colorless oil.

(R_f: 0.5 - minor isomer, R_f: 0.42 - major isomer, Acetone : Dichloromethane 0.2:9.8, *p*-anisaldehyde staining solution)

Major isomer 213a :-

$[\alpha]^{26}_D$	**:**	+ 20.49 (*c* = 1.18, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	**:**	3454, 2912, 1698, 1435, 1240.
^1H NMR (500 MHz, $CDCl_3$) δ	**:**	7.35-7.28 (m, 5H), 5.78-5.65 (m, 4H), 5.13-5.03 (m, 6H), 4.01-3.86 (m, 2H), 3.75-3.65 (m, 1H), 3.52 (d, *J* = 10.45 Hz, 1H), 3.35-3.26 (m, 1H), 2.34 (dd, *J* = 6.6, 13.75 Hz, 2H), 2.11-2.03 (m, 2H), 1.73 (brs, 1H)
^{13}C NMR (rotamers) (125MHz, $CDCl_3$) δ	**:**	155.6 (155.52), 136.68, 135.8 (135.7), 134.0, 130.2 (129.94), 128.4, 127.9, 124.8 (124.3), 118.0, 74.4 (73.8), 67.1, 45.3, 43.3, 42.4, 39.4, 36.6.
MS(ESI) *(m/z)*	**:**	328.2168 $(M + H)^+$, 345.1997 $(M + NH_4)^+$, 350.2030 $(M + Na)^+$, 366.1828 $(M + K)^+$

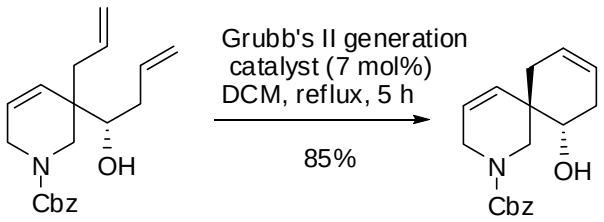
Minor isomer 213b :-

$[\alpha]^{26}_D$	**:**	+19.56 (*c* = 0.77, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	**:**	3454, 2912, 1698, 1435, 1240
^1H NMR (500 MHz, $CDCl_3$) δ	**:**	7.35-7.31 (m, 5H), 5.89-5.59 (m, 4H), 5.15-5.02 (m, 6H), 4.19-4.10 (m, 1H), 4.00 (3.85) (2 sets of doublet, 1H, *J* = 13.48 Hz), 3.77-3.70 (m, 1H), 3.46-3.40 (m, 1H), 3.10 (2.93) (2 sets of doublet, *J* = 13.48 Hz, 1H), 2.34-2.16 (m, 4H), 1.82 (1.76) (apparent brs, 1H).
^{13}C NMR (rotamers) (125MHz, $CDCl_3$) δ	**:**	156.4 (155.41), 136.52 (135.85), 134.15 (134.09), 131.72 (130.46), 128.58 (128.50), 128.17 (128.07), 127.85, 125.39 (124.85), 117.85 (117.79), 116.78, 73.87 (73.26), 67.39 (67.19), 45.88 (45.73), 43.74

(43.48), 43.15 (43.07), 36.94 (36.47), 35.74 (35.43).

MS(ESI): *m/z* : 328.1300 $(M + H)^+$, 350.1170 $(M + Na)^+$, 366.1166 $(M + K)^+$

(6*S*,11*S*)- benzyl 11-hydroxy-2-azaspiro[5,5]undeca-4,8-diene-2-carboxylate (216):



213a **216**

To a degassed solution of **213a** (0.119 g, 0.36 mmol) in anhydrous CH_2Cl_2 (10 mL) under argon atmosphere at 20 °C was added Grubb's II generation catalyst (21 mg, 7 mol%). The solution was heated to reflux for 5 h, at which point the TLC analysis indicated the reaction was completed, concentrated the reaction mixture. Purification by flash column chromatography (10:0→9.8:0.2, DCM:Acetone), afforded **216** (0.09 g, 85%) (R_f = 0.3, acetone: DCM 0.3:9.7)

$[\alpha]^{25}_D$: +57.61 (*c* = 1.07, $CHCl_3$)

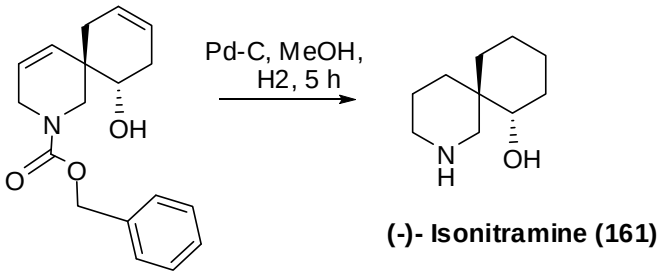
IR (film) γ_{max} cm^{-1} ($CHCl_3$) : 3450, 3029, 2898, 1686, 1432, 1238

^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.34-7.28 (m, 5H), 5.87 (apparent dt, *J* = 2.46, 10.24 Hz, 1H), 5.76 (d, *J* = 8.53 Hz, 1H), 5.59 (brs, 2H), 5.13 (brs, 2H), 3.95 (m, 2H), 3.71 (brs, 1H), 3.56-3.25 (m, 2H), 2.39-2.28 (m, 1H), 2.08-1.93 (m, 4H).

^{13}C NMR (rotamers) (125MHz, $CDCl_3$) δ : 155.8, 136.5 130.0, 128.3, 127.9, 127.7, 124.6, 123.5 (122.9), 71.7 (71.0), 67.1, 48.6, 43.5, 38.8, 32.6, 31.4.

HR-MS (EI) : calcd for $C_{18}H_{21}NO_3$: 299.15214. Found: 299.15306.

(-)- Isonitramine (161):



216 **(-)- Isonitramine (161)**

To a solution of **216** (0.108 g, 0.36 mmol) in anhydrous MeOH (10 mL) was added Pd/C (0.075 g). The suspension was allowed to stir for 5 h at room temperature under an atmosphere of hydrogen. The suspension was filtered over celite and concentrated under reduced pressure. Purification by flash column chromatography ($CHCl_3$: MeOH: aq NH_3, 46: 50: 4, R_f = 0.3) afforded solid **161**, which upon crystallization with ethylacetate-petether gave colorless crystals.

$[\alpha]^{25}_D$	**:**	-5.1 (*c* = 1.1, $CHCl_3$)
IR (film) γ_{max} cm^{-1} ($CHCl_3$)	**:**	3407, 2933, 1215
^{1}H NMR (400Mz, $CDCl_3$)δ	**:**	3.78-3.44 (brs, 2H), 3.62 (dd, *J* = 3.51, 11.29 Hz, 1H), 3.01 (brd, *J* = 10.8Hz, 1H), 2.91 (d, *J* = 11.29 Hz, 1H), 2.57 (td, *J* = 3.26, 11.55 Hz, 1H), 2.49 (d, *J* = 11.3 Hz, 1H), 2.22 (d, *J* = 14 Hz, 1H), 2.08-1.97 (m, 1H), 1.72-1.66 (m, 2H), 1.56-1.43 (m, 2H), 1.39-1.32 (m, 2H), 1.27-1.15 (m, 2H), 1.08-1.03 (m, 1H), 0.97-0.90 (m, 1H).
^{13}C NMR (100MHz, $CDCl_3$) δ	**:**	80.4, 60.6, 47.1, 36.6, 36.1, 29.6, 28.6, 24.2, 23.0, 20.2.
HR-MS (EI)	**:**	calcd for $C_{10}H_{19}NO$: 169.14666. Found: 169.14445.

X-ray Crystal Structure Analysis of *Isonitramine (161)*

Crystal Data: Single crystals of the compound **161** were grown by slow evaporation of the solution in ethyl acetate-petroleum ether. Colourless crystal of approximate size 0.16 x 0.05 x 0.03 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, hemisphere data acquisition. Total frames = 1271, Oscillation / frame -0.3º, exposure / frame = 7.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 3.1 to 25.00 º, completeness to θ of 25.0 º is 99.4 %. SADABS correction applied $C_{10}H_{19}NO$ 0.25(H_2O), M = 173.77. Crystals belong to Monoclinic, space group C_2, a = 11.0145(14), b = 8.5956(11) c = 11.6496(15) Å, V = 1023.6(2) $Å^3$, Z = 4, D_c = 1.128 g /cc, μ (MoK_α) = 0.073 mm^{-1}, T = 296(2) K, 2531 reflections measured, 1683 unique [I > 2σ (I)], R value 0.0615, wR_2 = 0.1416. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)[21] was used for structure solution and full matrix least squares refinement on F^2. The molecule crystallizes along with ¼ water molecule as solvent of crystallization. Hydrogen atoms were included in the refinement as per the riding model however the hydrogen of the solvent water molecule is refined. Data collection and refinement parameters are listed in Table 2.

X-ray analysis revealed the conformation of the molecule with C_6 and C_7 having *S* and *S* configuration.

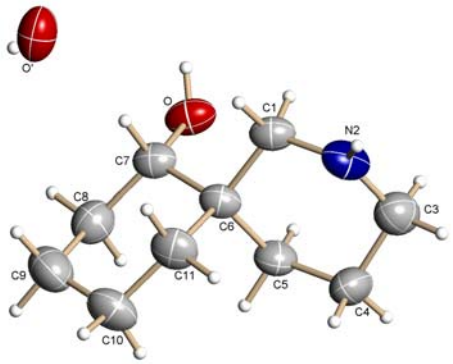
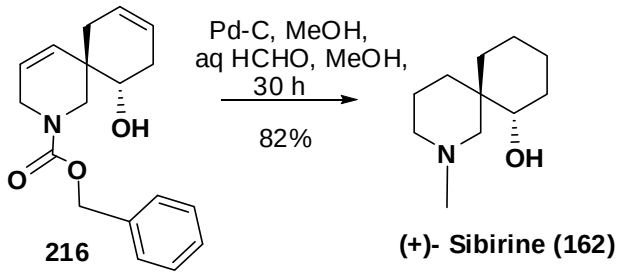


Figure: 4 *ORTEP diagram of the Isonitramine* ***(161)****. Ellipsoids are drawn at 50% probability.*

Table-2 Crystal data and structure refinement of isonitramine (**161**):

Empirical formula	$C_{10}\ H_{19\text{-}50}\ N\ O_{1.25}$	
Formula weight	173.77	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 11.0145(14) Å	α= 90°.
	b = 8.5956(11) Å	β= 111.863(2)°.
	c = 11.6496(15) Å	γ = 90°.
Volume	1023.6(2) $Å^3$	
Z	4	
Density (calculated)	1.128 g/cc	
Absorption coefficient	0.073 mm^{-1}	
F(000)	386	
Crystal size	0.16 x 0.05 x 0.03 mm^3	
Theta range for data collection	3.10 to 25.00°.	
Index ranges	-9<=h<=13, -10<=k<=10, -13<=l<=13	
Reflections collected	2531	
Independent reflections	1683 [R(int) = 0.0252]	
Completeness to theta = 25.00°	99.4 %	
Max. and min. transmission	0.9975 and 0.9887	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1683 / 1 / 119	
Goodness-of-fit on F^2	1.169	
Final R indices [I>2sigma(I)]	R1 = 0.0615, wR2 = 0.1416	
R indices (all data)	R1 = 0.0741, wR2 = 0.1495	
Absolute structure parameter	2(3)	
Largest diff. peak and hole	0.268 and -0.203 e.$Å^{-3}$	

(-)-Sibirine (162):

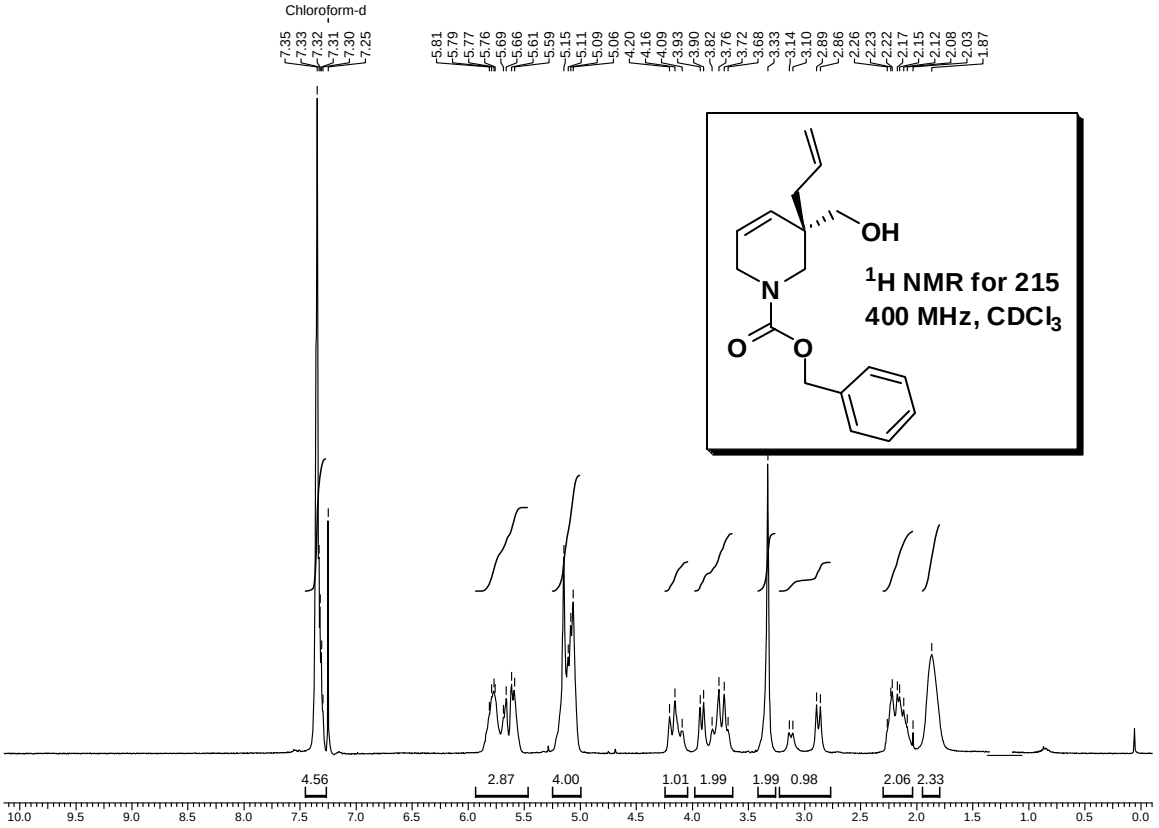


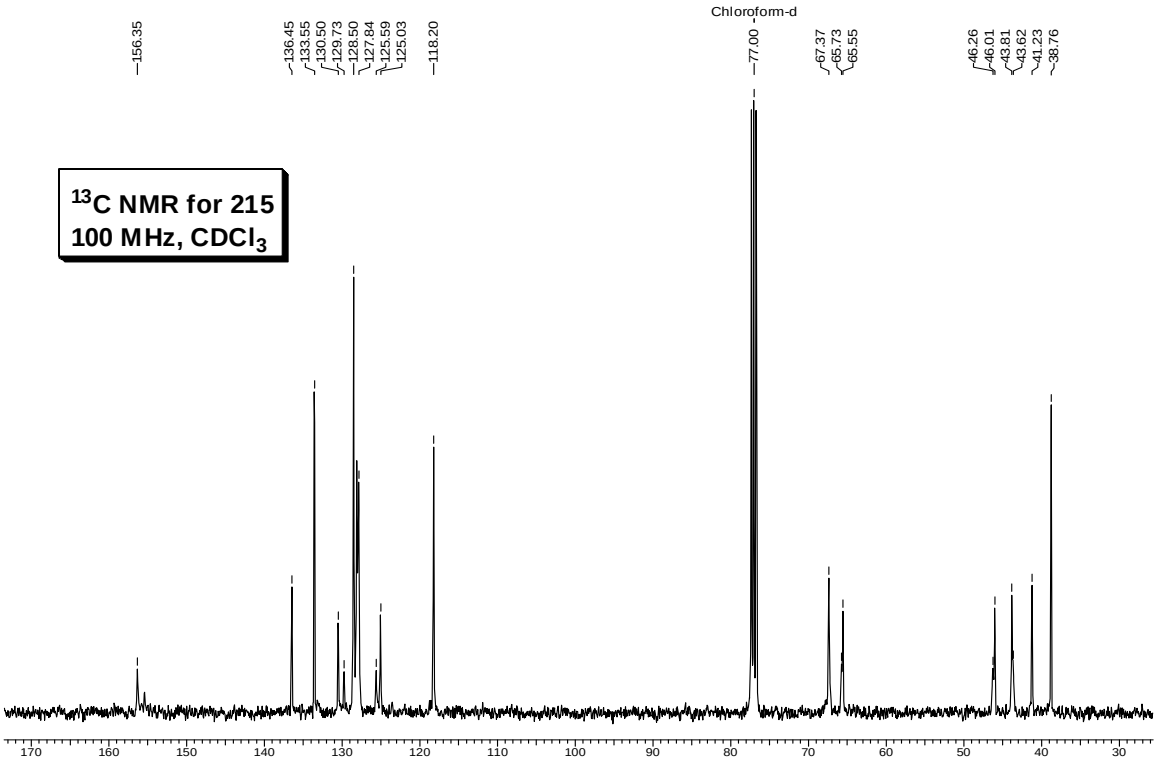
216 **(+)- Sibirine (162)**

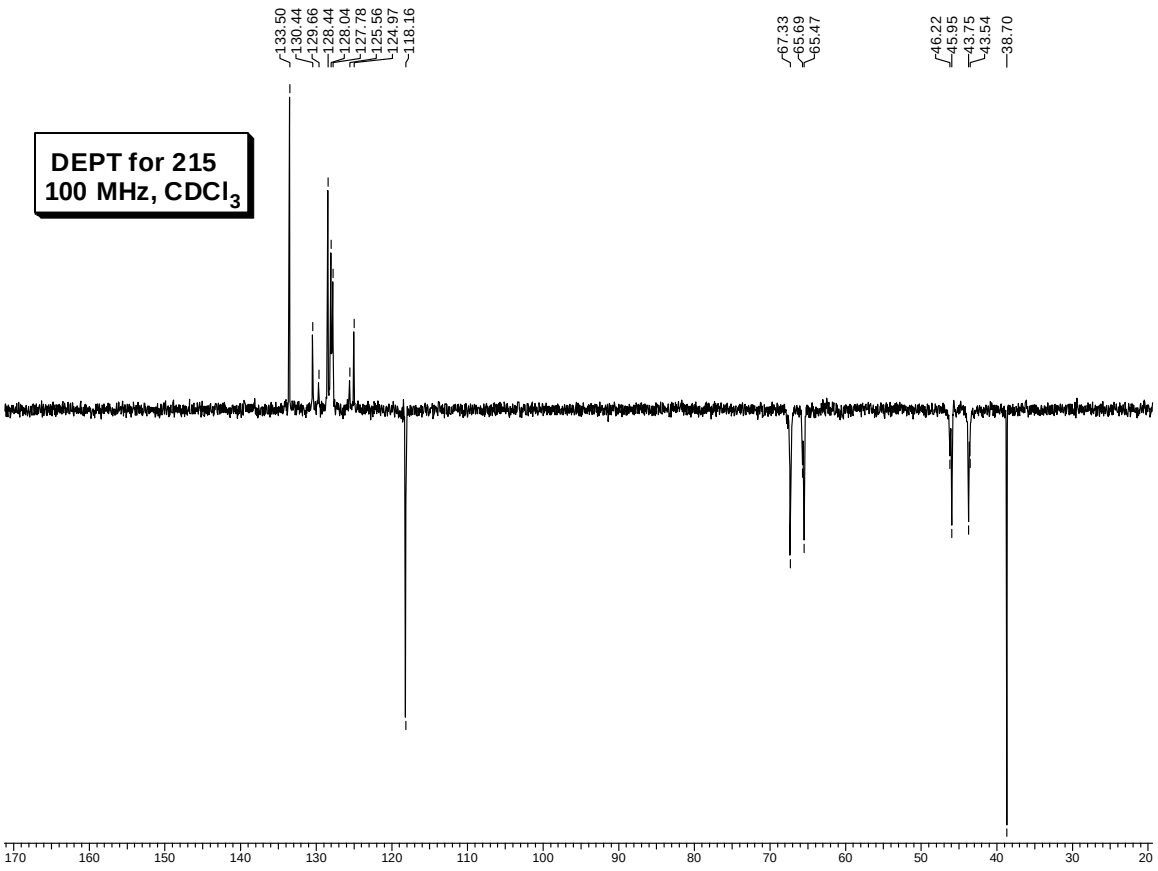
Aqueous formaldehyde (37% solution, 0.1 mL, 1.1 mmol), was added to a stirred solution of the carbamate **216** (0.033 g, 0.11 mmol) in distilled methanol (5 mL). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen in the presence of a catalytic amount of palladium carbon (0.02 g) for 30 h. After completion of the reaction, the reaction mixture was filtered through a pad of celite, concentrated and subjected to column chromatography afforded as colorless oil (0.016g, 82%).

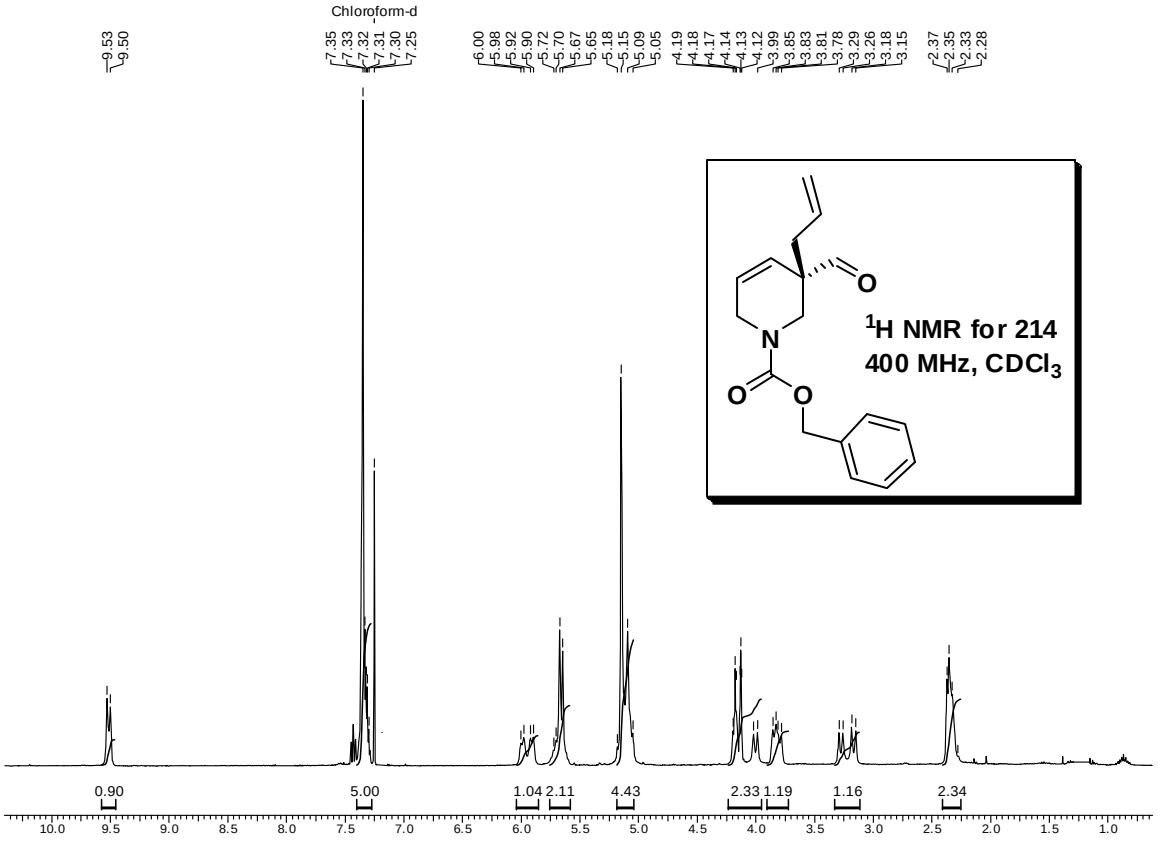
$[\alpha]^{25}_D$	**:**	-23.1 (*c* = 0.76, $CHCl_3$)
^{1}H NMR (400 MHz, CDCl3) δ	**:**	0.84-1.0 (m, 2H), 1.16-1.27 (m, 2H), 1.33-1.40 (m, 2H), 1.44-1.54 (m, 2H), 1.68-1.74 (m, 2H), 1.85-1.95 (m, 2H), 2.07-2.17 (m, 2H), 2.21 (s, 3H), 2.60 (d, 1H, *J* = 11.3 Hz), 2.79 (brd, 1H, *J* = 7 Hz), 3.58 (dd, 1H, *J* = 11.2, 3.2 Hz), 3.21-3.86 (extreamly broadened peak, 1H, OH)
^{13}C NMR (100MHz. $CDCl_3$) δ	**:**	20.32, 23.01, 24.06, 27.53, 29.46, 37.04, 37.18, 46.45, 56.31, 69.85, 80.42
HR-MS (EI)	**:**	calcd for $C_{11}H_{21}NO$:183.16231. Found: 183.16196.

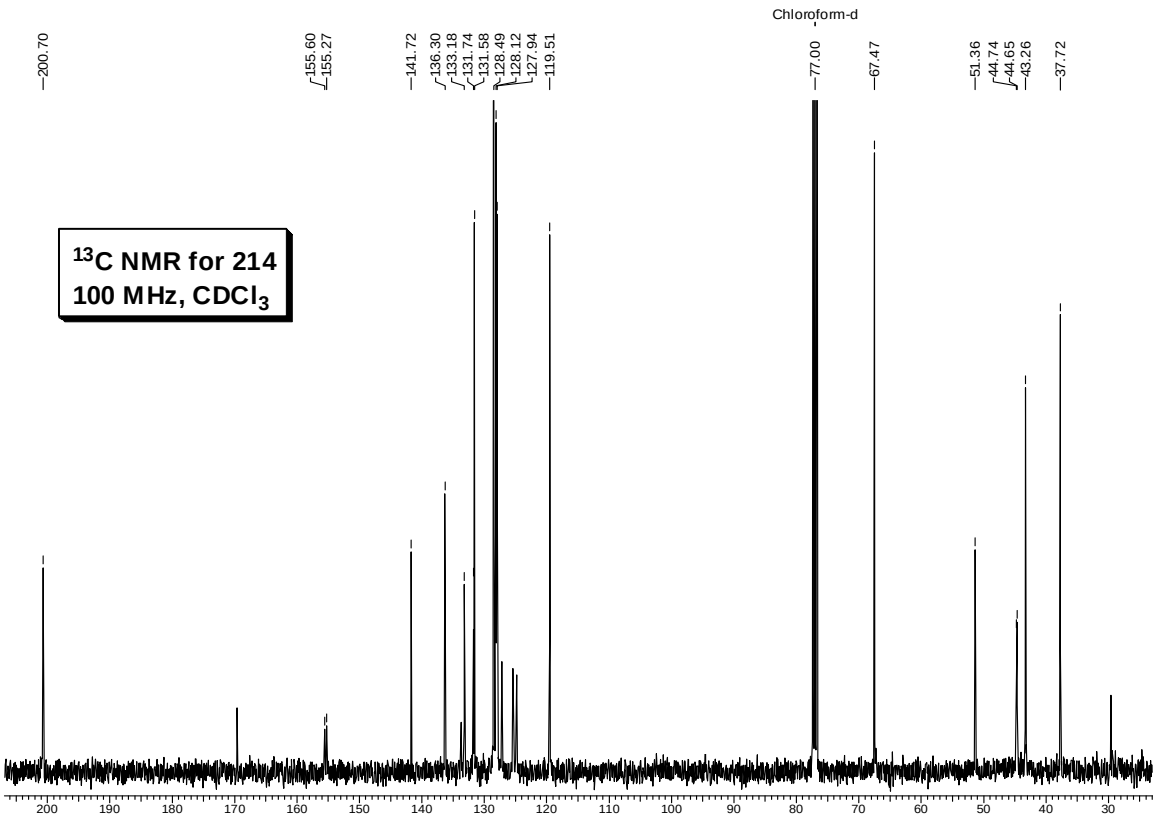
3C.2 Spectra:

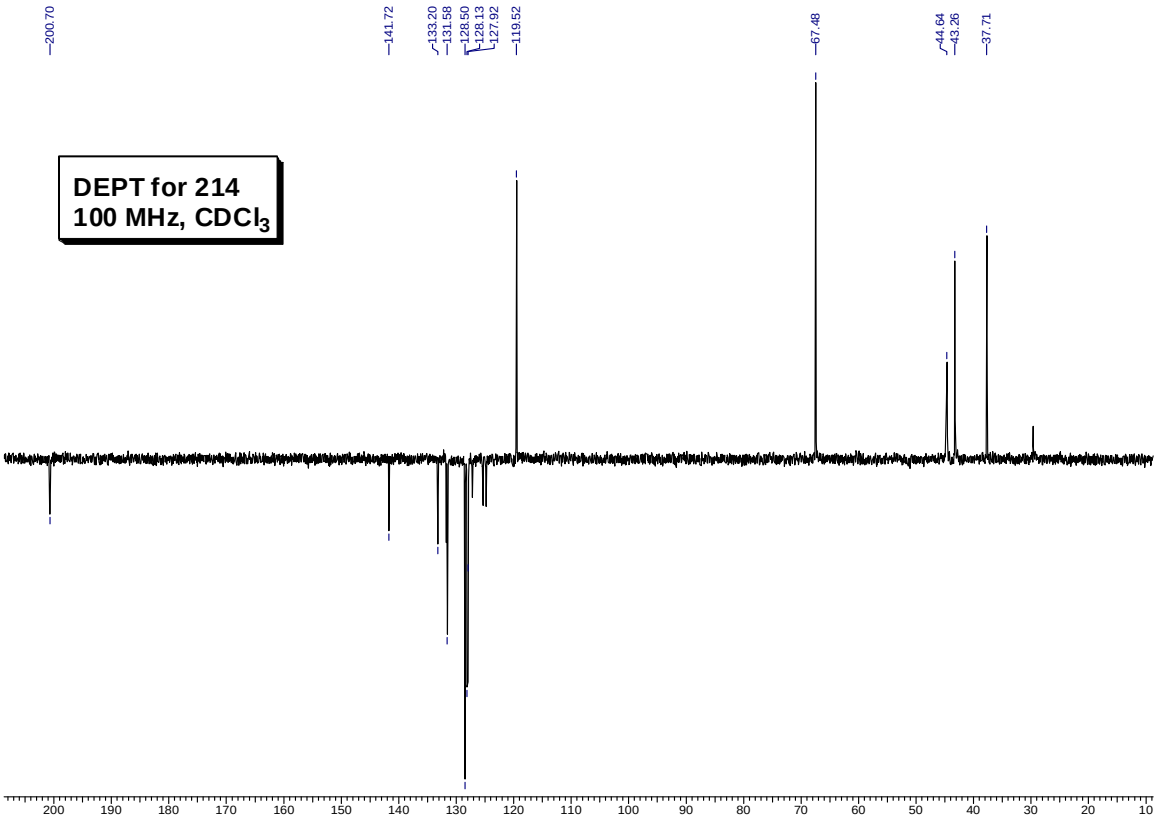

Chloroform-d
7.35 7.33 7.32 7.31 7.30 7.25
5.81 5.79 5.77 5.76 5.69 5.66 5.61 5.59 5.15 5.11 5.09 5.06 4.20 4.16 4.09 3.93 3.90 3.82 3.76 3.72 3.68 3.33 3.14 3.10 2.89 2.86 2.26 2.23 2.22 2.17 2.15 2.12 2.08 2.03 1.87
OH
N
O
O
^{1}H NMR for 215
400 MHz, CDCl$_3$
4.56 2.87 4.00 1.01 1.99 1.99 0.98 2.06 2.33
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

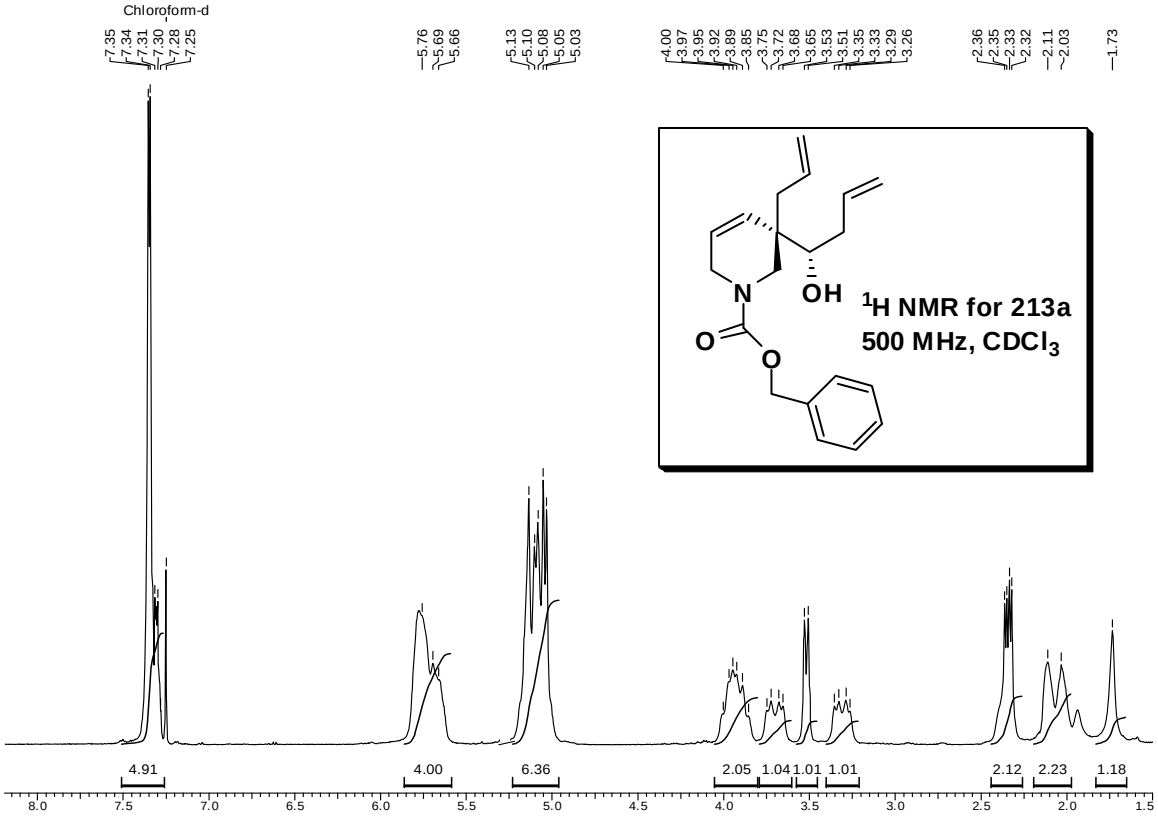

156.35
136.45 133.55 130.50 129.73 128.50 127.84 125.59 125.03
118.20
Chloroform-d
77.00
67.37 65.73 65.55
46.26 46.01 43.81 43.62 41.23 38.76
^{13}C NMR for 215
100 MHz, CDCl$_3$
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30

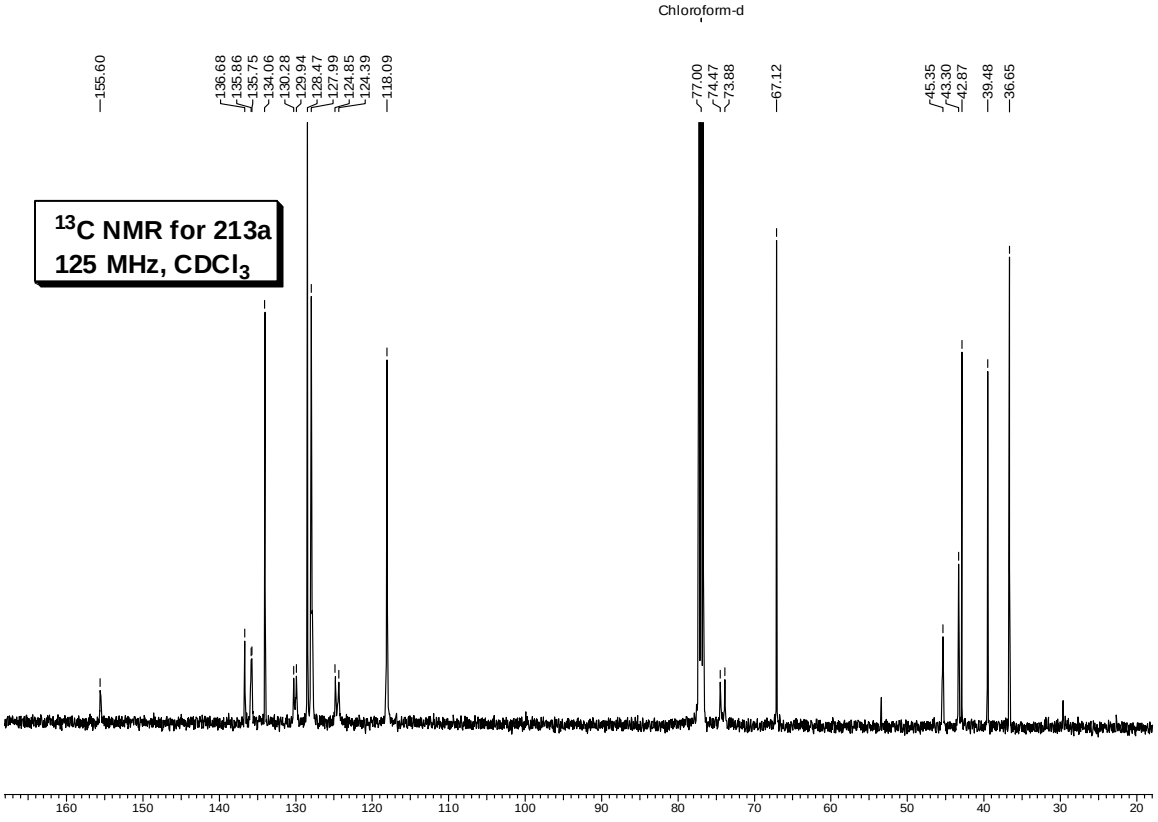

133.50
130.44
129.66
128.44
128.04
127.78
125.56
124.97
118.16
67.33
65.69
65.47
46.22
45.95
43.75
43.54
38.70
DEPT for 215
100 MHz, CDCl3

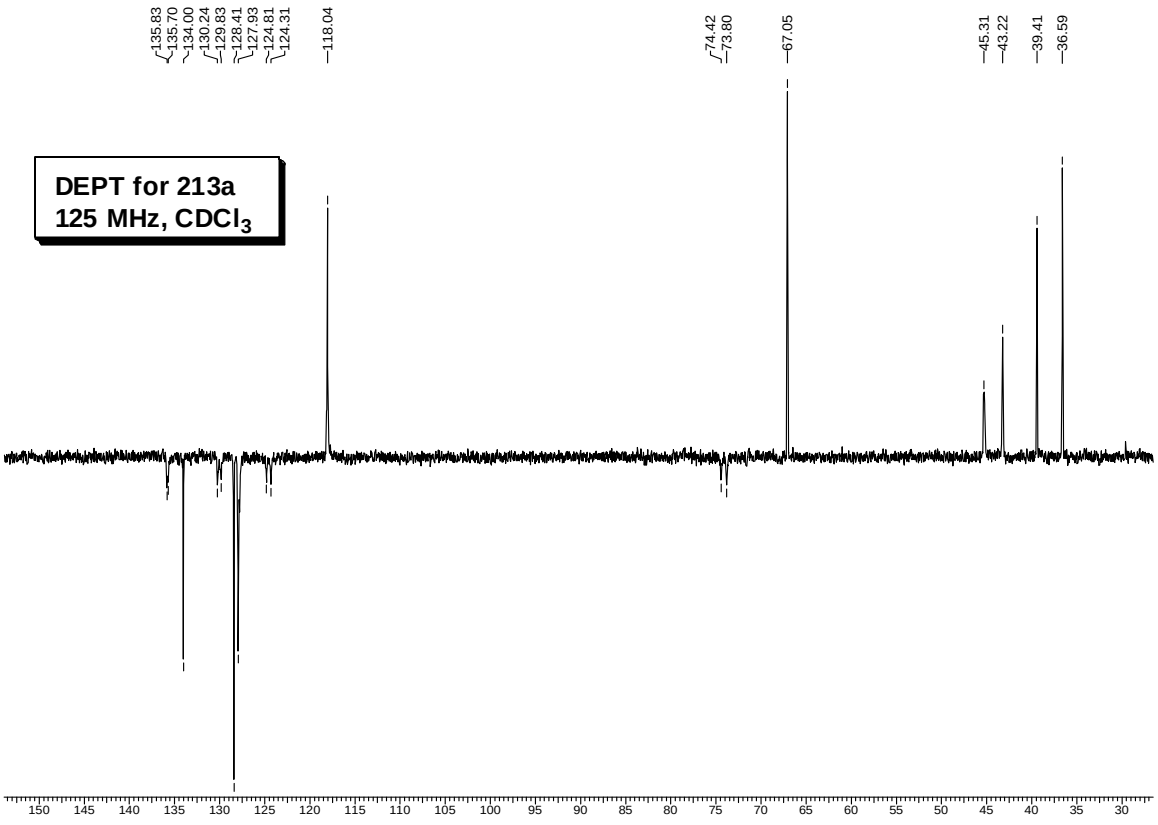

Chloroform-d
9.53
9.50
7.35
7.33
7.32
7.31
7.30
7.25
6.00
5.98
5.92
5.90
5.72
5.70
5.67
5.65
5.18
5.15
5.09
5.05
4.19
4.18
4.17
4.14
4.13
4.12
3.99
3.85
3.83
3.81
3.78
3.29
3.26
3.18
3.15
2.37
2.35
2.33
2.28
O
N
O
O
1H NMR for 214
400 MHz, CDCl3
0.90
5.00
1.04
2.11
4.43
2.33
1.19
1.16
2.34

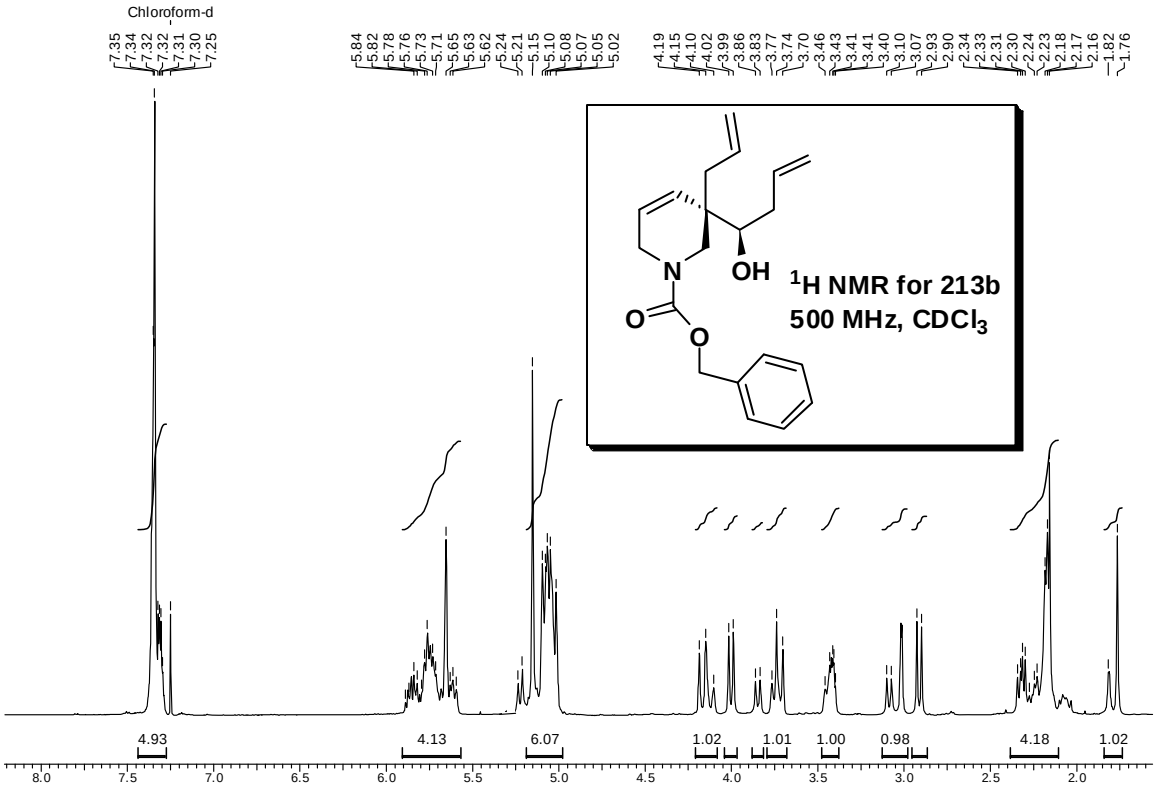

Chloroform-d
200.70
155.60
155.27
141.72
136.30
133.18
131.74
131.58
128.49
128.12
127.94
119.51
77.00
67.47
51.36
44.74
44.65
43.26
37.72
^{13}C NMR for 214
100 MHz, CDCl$_3$

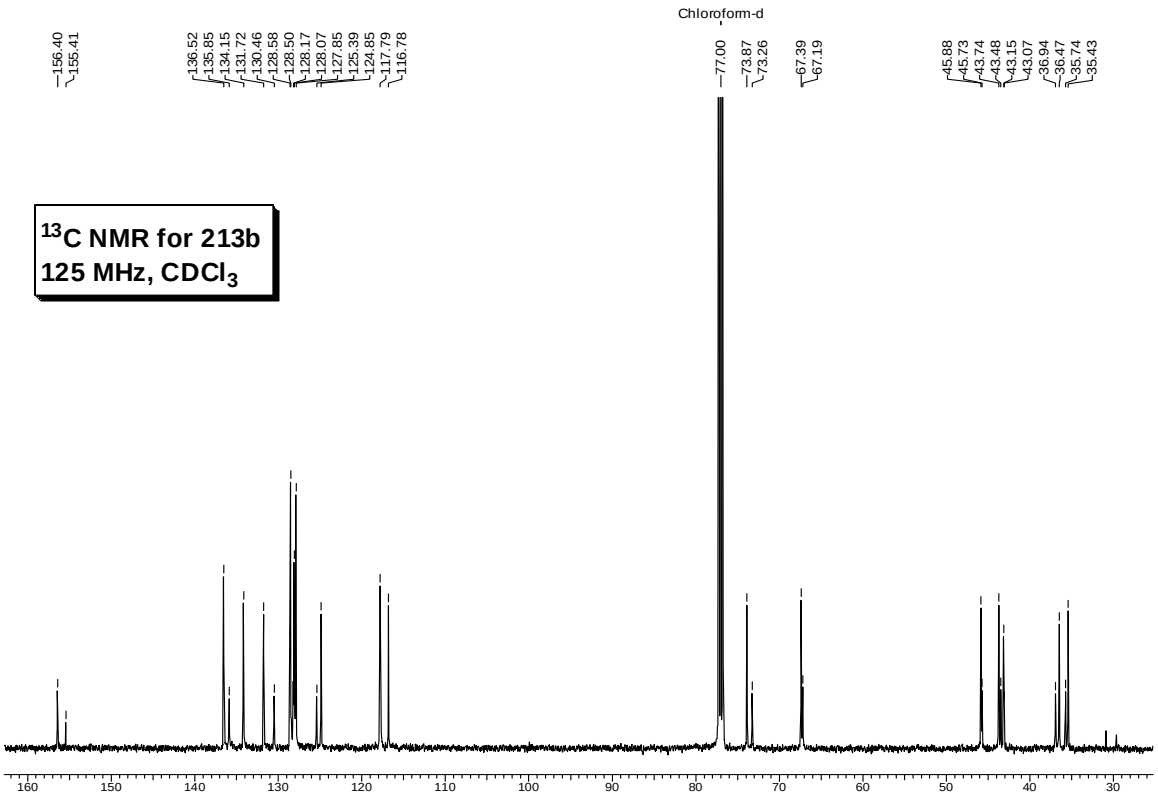

200.70
141.72
133.20
131.58
128.50
128.13
127.92
119.52
67.48
44.64
43.26
37.71
DEPT for 214
100 MHz, CDCl$_3$

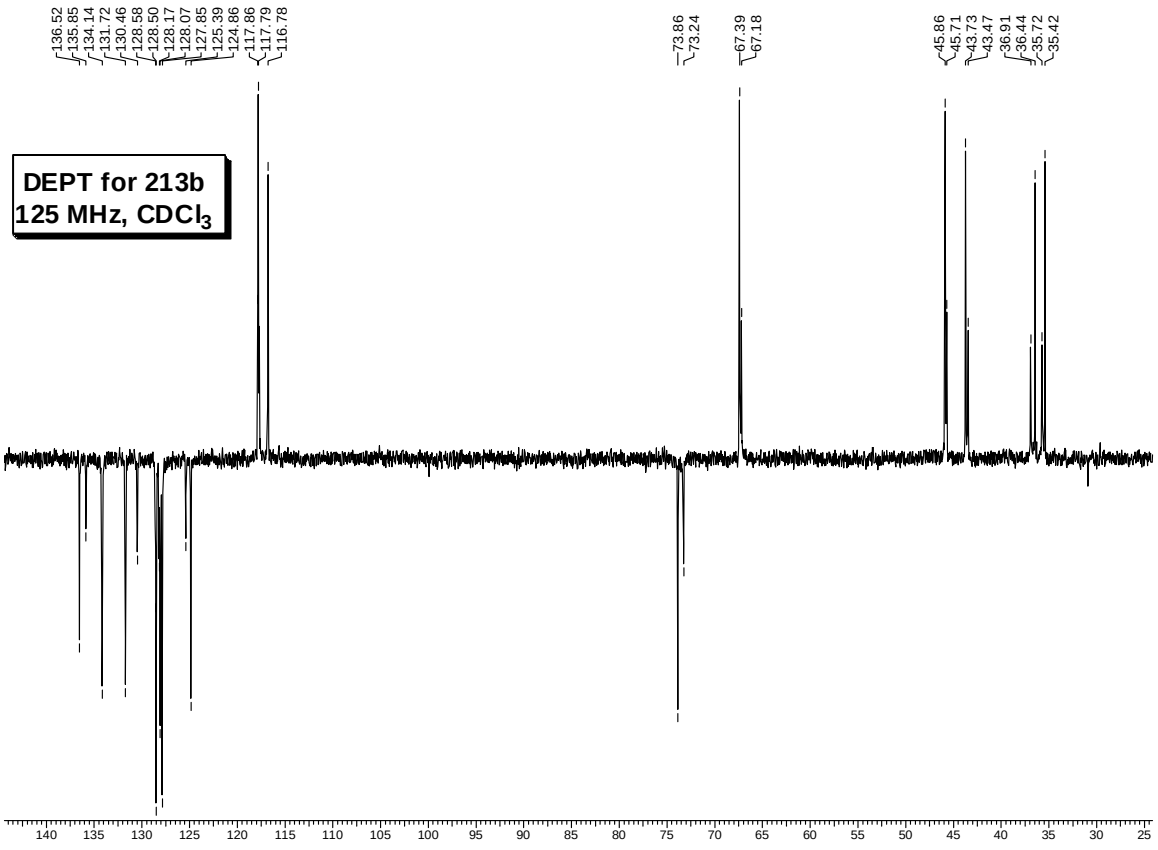

Chloroform-d
7.35
7.34
7.31
7.30
7.28
7.25
5.76
5.69
5.66
5.13
5.10
5.08
5.05
5.03
4.00
3.97
3.95
3.92
3.89
3.85
3.75
3.72
3.68
3.65
3.53
3.51
3.35
3.33
3.29
3.26
2.36
2.35
2.33
2.32
2.11
2.03
1.73
N
OH
O
O
1H NMR for 213a
500 MHz, CDCl3
4.91
4.00
6.36
2.05
1.04
1.01
1.01
2.12
2.23
1.18

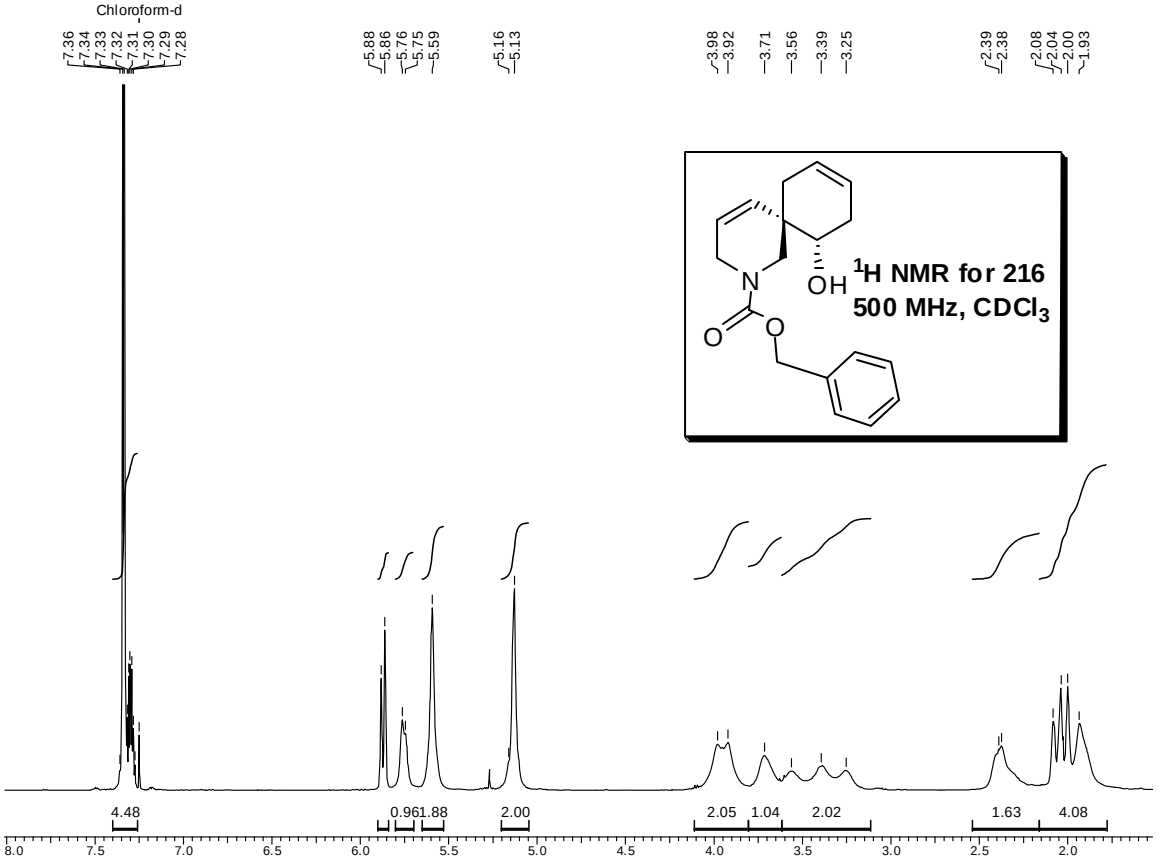

Chloroform-d
155.60
136.68
135.86
135.75
134.06
130.28
129.94
128.47
127.99
124.85
124.39
118.09
77.00
74.47
73.88
67.12
45.35
43.30
42.87
39.48
36.65
13C NMR for 213a
125 MHz, CDCl3

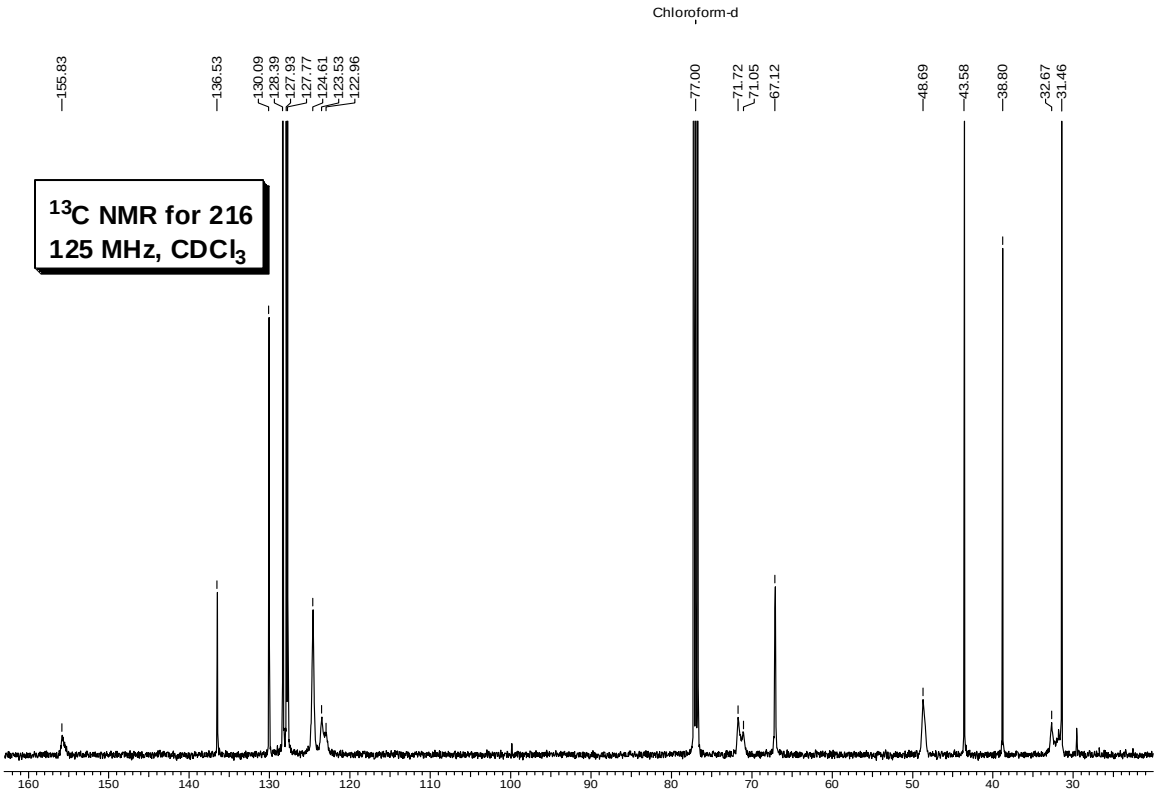

135.83
135.70
134.00
130.24
129.83
128.41
127.93
124.81
124.31
118.04
74.42
73.80
67.05
45.31
43.22
39.41
36.59
DEPT for 213a
125 MHz, CDCl3

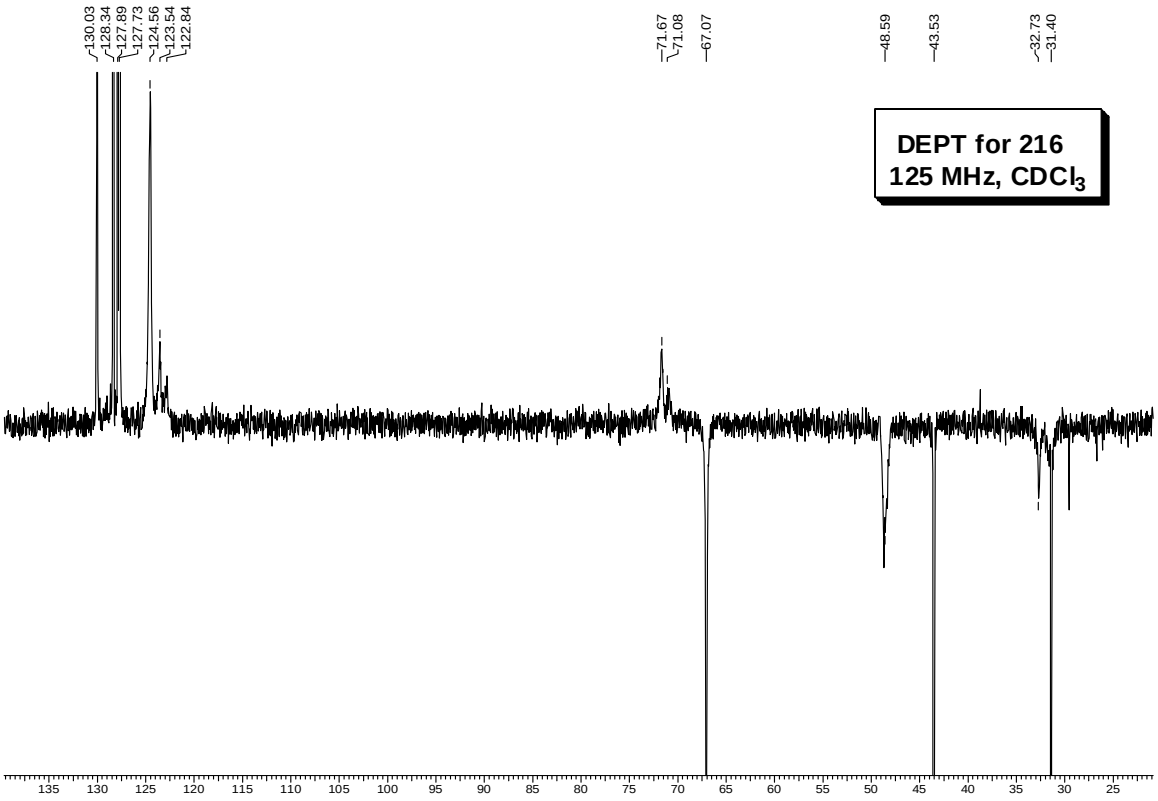

Chloroform-d
7.35
7.34
7.32
7.32
7.31
7.30
7.25
5.84
5.82
5.78
5.76
5.73
5.71
5.65
5.63
5.62
5.24
5.21
5.15
5.10
5.08
5.07
5.05
5.02
4.19
4.15
4.10
4.02
3.99
3.86
3.83
3.77
3.74
3.70
3.46
3.43
3.41
3.41
3.40
3.10
3.07
2.93
2.90
2.34
2.33
2.31
2.30
2.24
2.23
2.18
2.17
2.16
1.82
1.76
N
OH
O
O
1H NMR for 213b
500 MHz, CDCl3
4.93
4.13
6.07
1.02
1.01
1.00
0.98
4.18
1.02

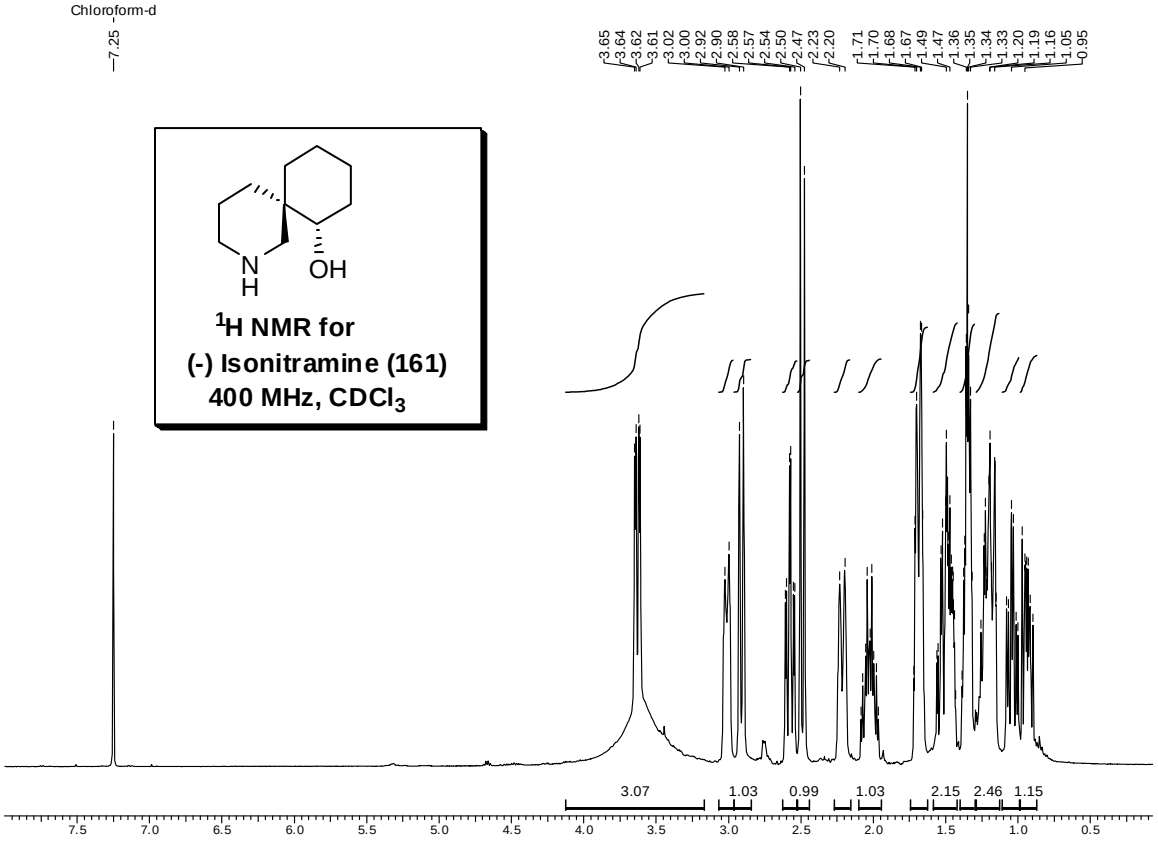

Chloroform-d
156.40
155.41
136.52
135.85
134.15
131.72
130.46
128.58
128.50
128.17
128.07
127.85
125.39
124.85
117.79
116.78
77.00
73.87
73.26
67.39
67.19
45.88
45.73
43.74
43.48
43.15
43.07
36.94
36.47
35.74
35.43
13C NMR for 213b
125 MHz, CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30

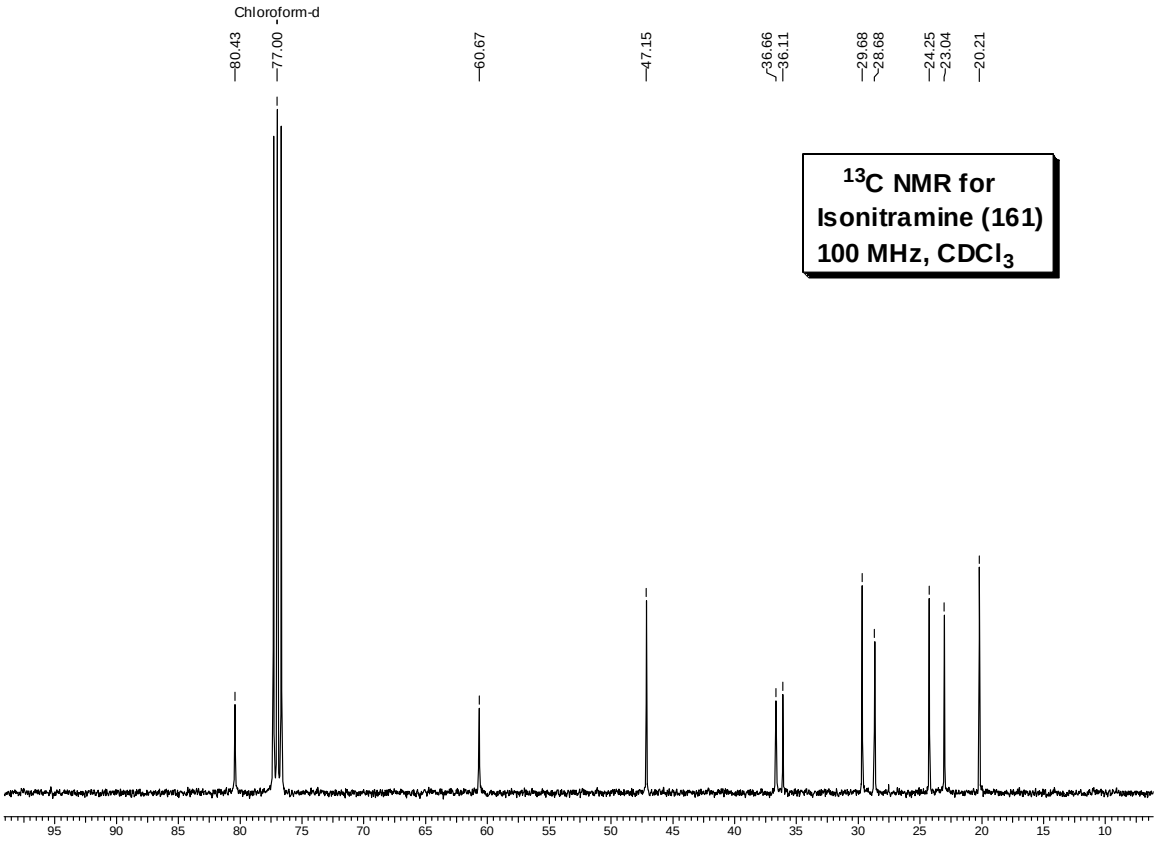

136.52
135.85
134.14
131.72
130.46
128.58
128.50
128.17
128.07
127.85
125.39
124.86
117.86
117.79
116.78
73.86
73.24
67.39
67.18
45.86
45.71
43.73
43.47
36.91
36.44
35.72
35.42
DEPT for 213b
125 MHz, CDCl3
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25

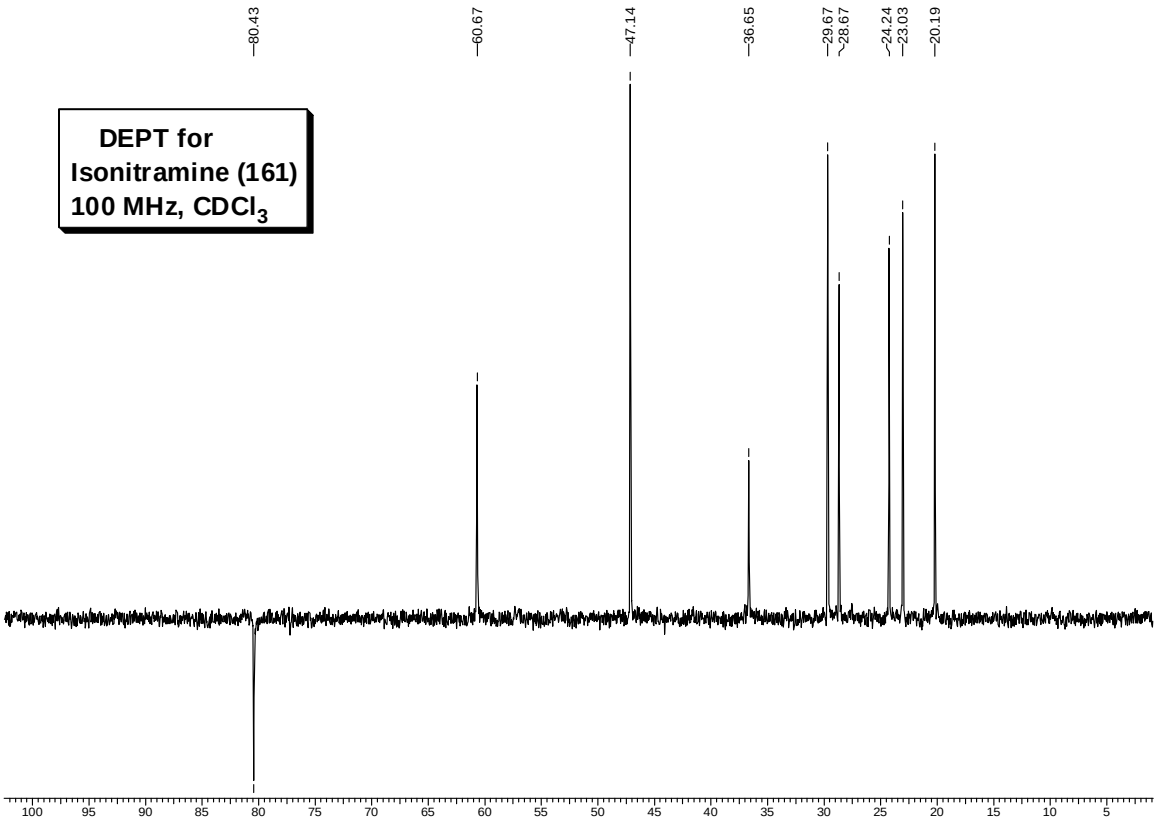

Chloroform-d
7.36
7.34
7.33
7.32
7.31
7.30
7.29
7.28
5.88
5.86
5.76
5.75
5.59
5.16
5.13
3.98
3.92
3.71
3.56
3.39
3.25
2.39
2.38
2.08
2.04
2.00
1.93
OH
N
O
O
1H NMR for 216
500 MHz, CDCl3
4.48
0.96
1.88
2.00
2.05
1.04
2.02
1.63
4.08

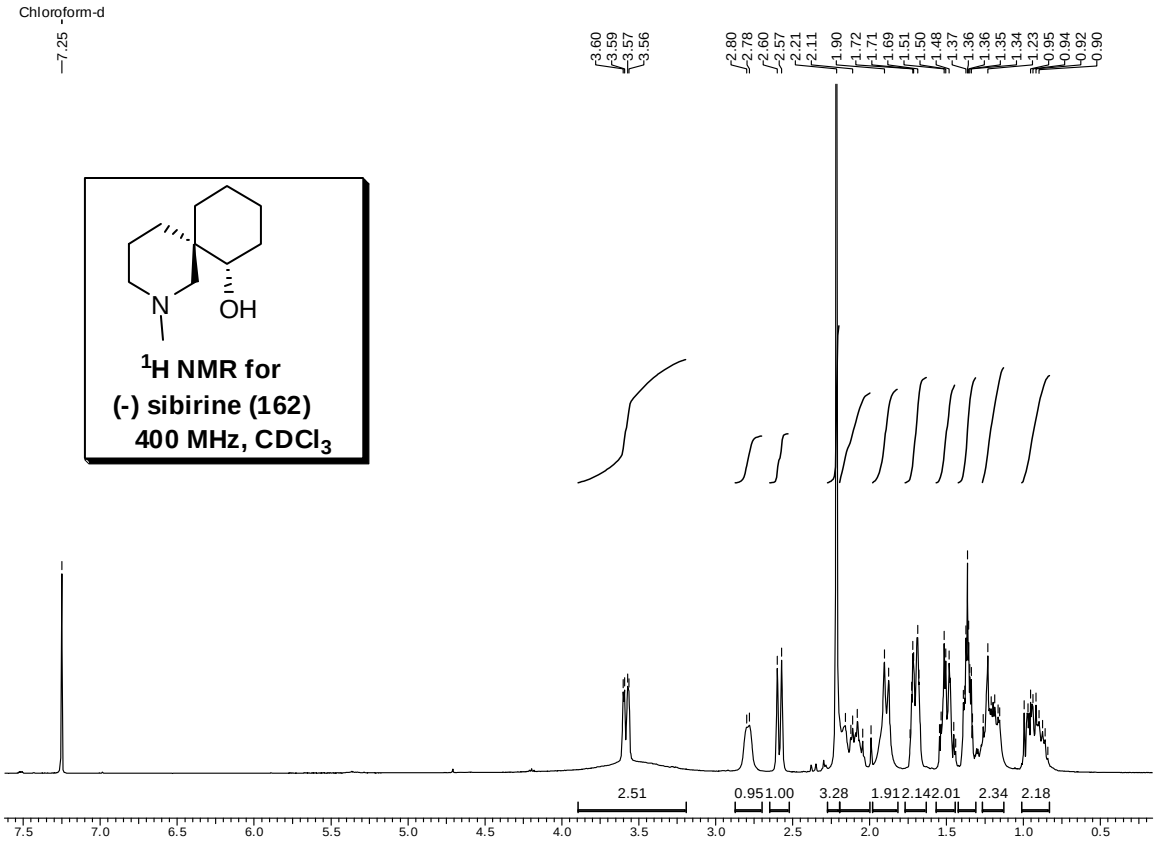

Chloroform-d
155.83
136.53
130.09
128.39
127.93
127.77
124.61
123.53
122.96
77.00
71.72
71.05
67.12
48.69
43.58
38.80
32.67
31.46
13C NMR for 216
125 MHz, CDCl3


130.03
128.34
127.89
127.73
124.56
123.54
122.84
71.67
71.08
67.07
48.59
43.53
32.73
31.40
DEPT for 216
125 MHz, CDCl3

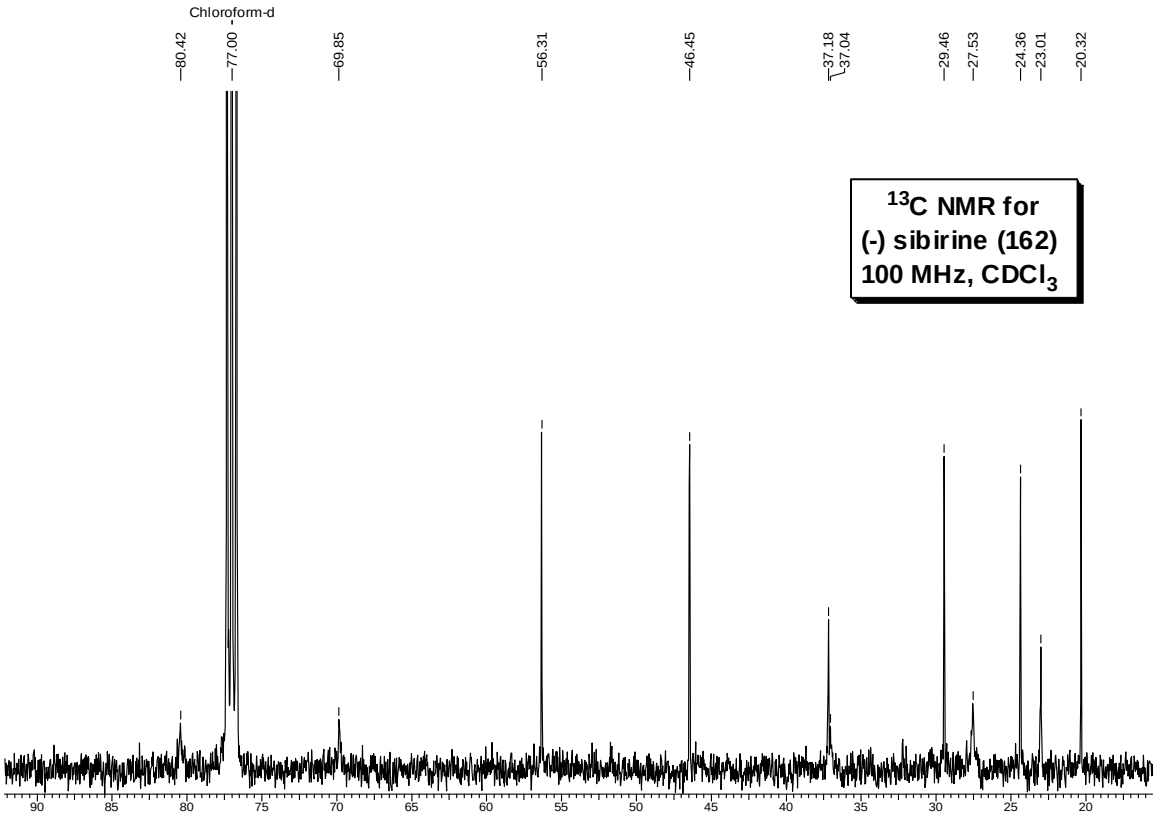

Chloroform-d
7.25
3.65
3.64
3.62
3.61
3.02
3.00
2.92
2.90
2.58
2.57
2.54
2.50
2.47
2.23
2.20
1.71
1.70
1.68
1.67
1.49
1.47
1.36
1.35
1.34
1.33
1.20
1.19
1.16
1.05
0.95
N
H
OH
1H NMR for
(-) Isonitramine (161)
400 MHz, CDCl3
3.07
1.03
0.99
1.03
2.15
2.46
1.15


Chloroform-d
80.43
77.00
60.67
47.15
36.66
36.11
29.68
28.68
24.25
23.04
20.21
13C NMR for
Isonitramine (161)
100 MHz, CDCl3

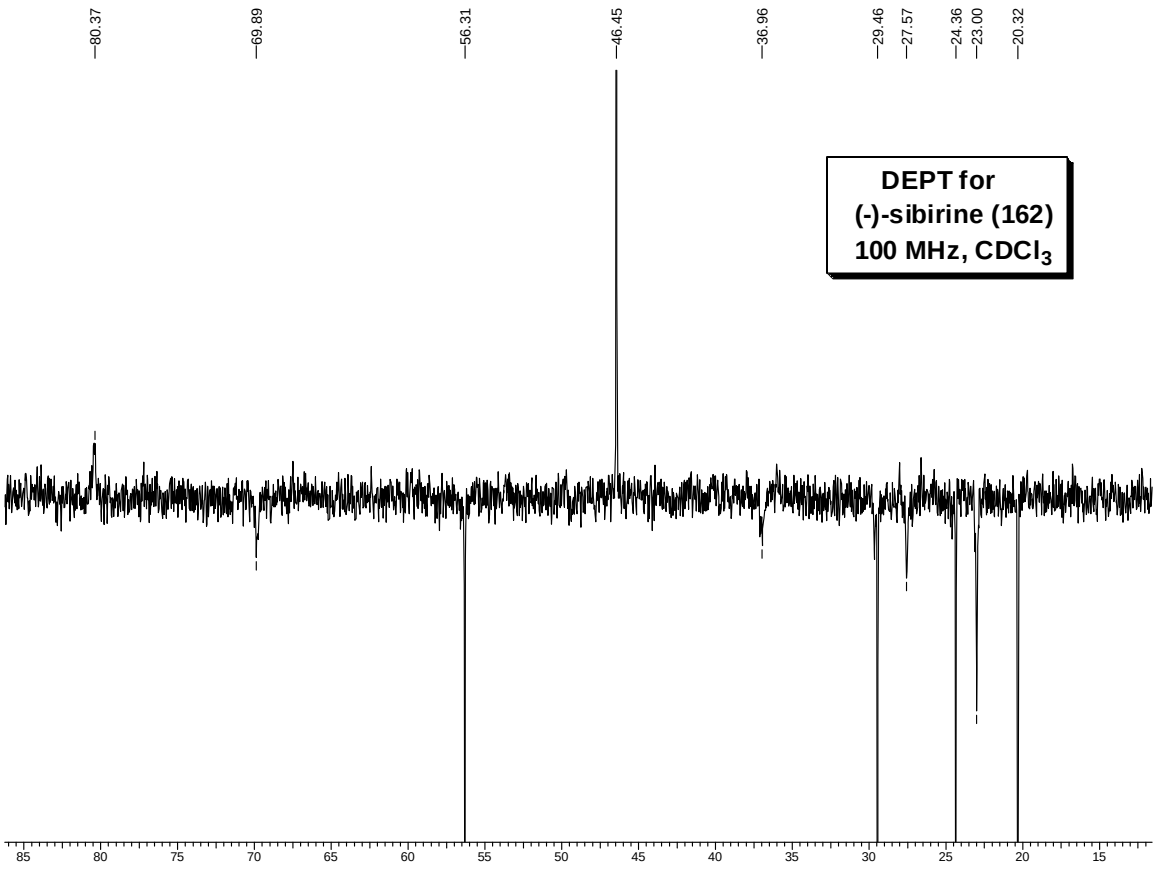

80.43
60.67
47.14
36.65
29.67
28.67
24.24
23.03
20.19
DEPT for
Isonitramine (161)
100 MHz, CDCl3



^{1}H NMR for (-) sibirine (162) 400 MHz, $CDCl_3$



^{13}C NMR for (-) sibirine (162) 100 MHz, $CDCl_3$


80.37
69.89
56.31
46.45
36.96
29.46
27.57
24.36
23.00
20.32
DEPT for
(-)-sibirine (162)
100 MHz, CDCl3
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15

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Publications:

1. Iminium ion cascade reaction in the total synthesis of (+)-vincadifformine
   Ganesh Pandey* Prasanna Kumara C and Vedavati. G Puranik
   -(communicated)
2. Enantioselective total syntheses of (-)-Isonitramine and (-)-Sibirine *via* ring closing metathesis reaction
   Ganesh Pandey* Prasanna kumara C
   - (manuscript under preparation)

Erratum