STUDIES ON SYNTHESIS OF BIOACTIVE ALKALOIDS FROM CYCLIC ANHYDRIDES AND DERIVATIVES

THESIS

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DOCTOR OF PHILOSOPHY

IN CHEMISTRY

By

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(Research Guide)

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DECEMBER 2015

Dedicated to My Supreme Beloved

Sri Sri Thakur Anukulchandra

and

My Parents

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Studies on Synthesis of Bioactive Alkaloids from Cyclic Anhydrides and Derivatives***" which is being submitted to the ***Savitribai Phule Pune University*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Pravat Mondal*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

December 2015
Pune

Dr. N. P. Argade
(Research Guide)

Candidate's Declaration

I hereby declare that the research work incorporated in the thesis entitled "***Studies on Synthesis of Bioactive Alkaloids from Cyclic Anhydrides and Derivatives***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***Savitribai Phule Pune University***, has been carried out by me at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India, from July 2009 to December 2015 under the supervision of Dr. Narshinha P. Argade. This work has not been submitted in part or full by me for a degree or diploma to this or any other University or Institution.

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I would like to extend my thanks to Debasisda, Sujitda, Patida, Analda, Sumantrada, Garaida, Parthada, Chandanda, Tamasda, Shyamda, Krishanuda, Saikatda, Kakada, Animeshda, Binoyda, Sajalda, Gobindada, Bashavda, Arupda, Jhumurdi, Achintya, Arya, Arpan, Anjan, Arijit, Avik, Late Agnimitra, Dos, Kanak, Subha, Prithiviraj, Tanay, Sanjeev, Prathit, Susanta, Himadri Pathak, Tanaya, Munmun Ghosh, Sankha, Chini, Prasenjit, Ramkrishna, Jagadish, Akash, Pradip, Bikas, Soumen Das, Soumen Dey, Saibal Bhowmik, Anup, Hridesh, Monalisa, Sayantan Acharya, Anirudha, Arunava, Atanu, Suman, Santanu, Sudip, Manik, Bittu, Santigopal, Pranab, Tapas, Tamal, Suvrasis, Soumik, Rahul, Turbasu, Debu, Sayan, Gourav, Suvendu, Koushik, Manzoor Wasim, Shomsuvra, Indradeep, Bilu, Arjun, Saibal Bera, Sayantan Pal, Sutanu, Tamal kanti, Anirban, Basu, Sandipan, Himadri Sasmal, Anagh, Koushik Dey, Pranoy, Sanjukta, Pankaj and my all other friends for making my stay at NCL very comfortable and memorable one.

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Finally, my acknowledgement would not be completed without thanking the God, for giving me the strength and the determination to overcome the hardship faced in my life.

Pravat

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General Remarks

- All the solvents used were purified using the known literature procedures.
- Petroleum ether used in the experiments was of 60–80 °C boiling range.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether–ethyl acetate mixture, unless otherwise mentioned (silica gel, 60–120 mesh/100–200 mesh/230–400 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol), phosphomolybdic acid (in ethanol) and ninhydrin (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull, neat or in chloroform solution (concentration 0.05 to 10%) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker and Jeol ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), ACF 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethyl silane.
- Mass spectra were taken on MS-TOF mass spectrometer.
- HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer.
- All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
- All the compounds previously known in the literature were characterized by comparison of IR and NMR spectra as well as melting point with authentic samples.
- All the new experiments were repeated two or more times.
- Starting materials were obtained from commercial sources or prepared using known procedures.

Abbreviations

Å	Angstrom
Ac	Acetyl
Aq.	Aqueous
AIBN	2,2'-Azobisisobutyronitrile
B.C	Before Chirst
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bz	Benzoyl
cat.	Catalytic
CBz	Carboxy benzyl
β-CD	*β*-Cyclodextrin
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropyl ethyl amine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulphoxide
dr	Diastereomeric ratio
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride
Ed.	Edited
ETDA	Ethylenediamine tetraacetic acid
ee	Enantiomeric excess
ESI	Electro spray ionization
equiv	Equivalent
h	Hour(s)
HRMS	High resolution mass spectra
HPLC	High performance liquid chromatography
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IC	Inhibitory concentration
Im	Imidazole
IR	Infra Red
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LED	Light emitting diode
LiHMDS	Lithium bis(trimethylsilyl)amide
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)

mmol	Millimole(s)
MOMCl	Methoxy methyl chloride
Mp	Melting point
MS	Mass Spectrum
Ms	Methanesulfonyl (mesyl)
MsCl	Methanesulfonyl chloride (mesyl chloride)
MS-TOF	Time-of-flight mass spectrometry
MW	Microwave
NaHMDS	Sodium bis(trimethylsilyl)amide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate
PE	Petroleum ether
TBAS	Tetrabutylammonium hydrogen sulfate
p-TSA	*p*-Toluenesulfonic acid
TsCl	*p*-Toluenesulfonyl chloride
Py	Pyridine
SAR	Structure activity relationship
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyl dimethylsilyl
TBME	*tert*-butyl methyl ether
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPAP	Tetrapropylammonium perruthenate
TsDPEN	Tosyl diphenylethylene diamine
TS	Transition state

Abstract

Bioactive alkaloids occupy an important position in basic and applied chemistry and play an indispensable role in medicinal chemistry. Among them indole alkaloids represent an important class; because several molecules of these class of alkaloids have broad range of clinical and pharmacological utility (Figure 1). Thus a straight forward synthetic approach towards these classes of alkaloids would provide the necessary basis for intensified structural investigation of their highly attractive spectrum of therapeutic effects. Hence keeping this in mind, we have devised a strategy to synthesize novel indole alkaloids by using cyclic anhydrides and their derivatives as the potential precursors.

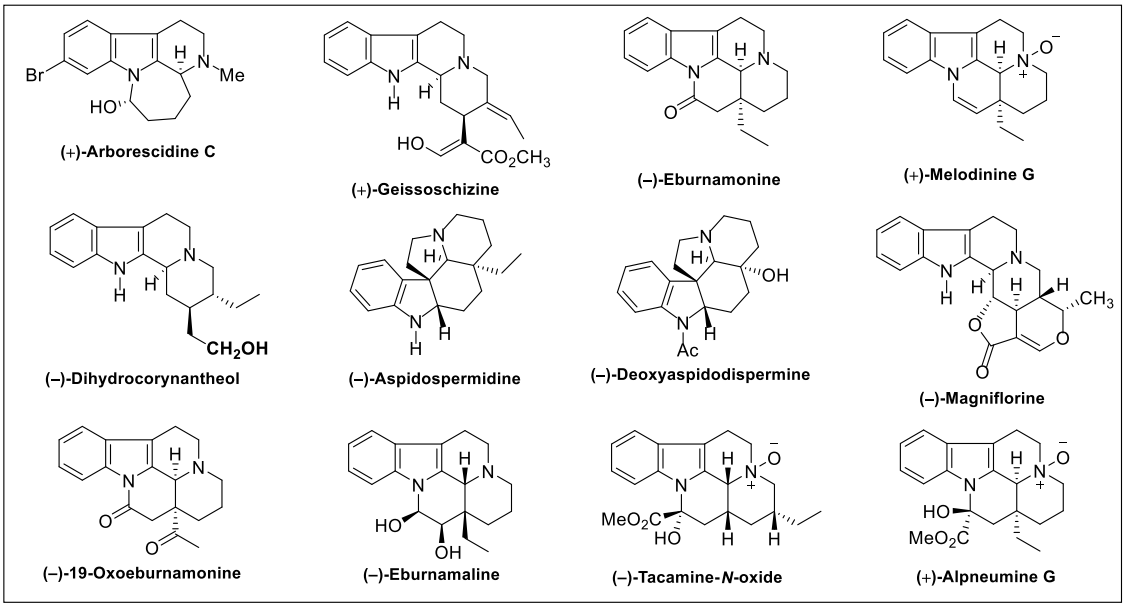


Figure 1. Bioactive indole alkaloids

The present dissertation is divided into three chapters. The first chapter portrays a contemporary literature account on the applications of the cyclic anhydrides and their derivatives in the synthesis of indole alkaloids. The second chapter describes synthesis of tetrahydro-*β*-carboline alkaloids (+)-harmicine, (*S*)-desbromoarborescidine A–C and (*S*)-deplancheine. The third chapter describes synthesis of vinca-eburna & tacaman type alkaloids (+)-3-epitacamonine, (–)-vindeburnol, (±)-eburnamonine, (±)-melohenine B, (±)-eburnaminol and (±)-larutensine utilizing cyclic imide as a potential precursor (Figure 2).

Note: Independent figure, scheme & structure numbers have been used for each section.

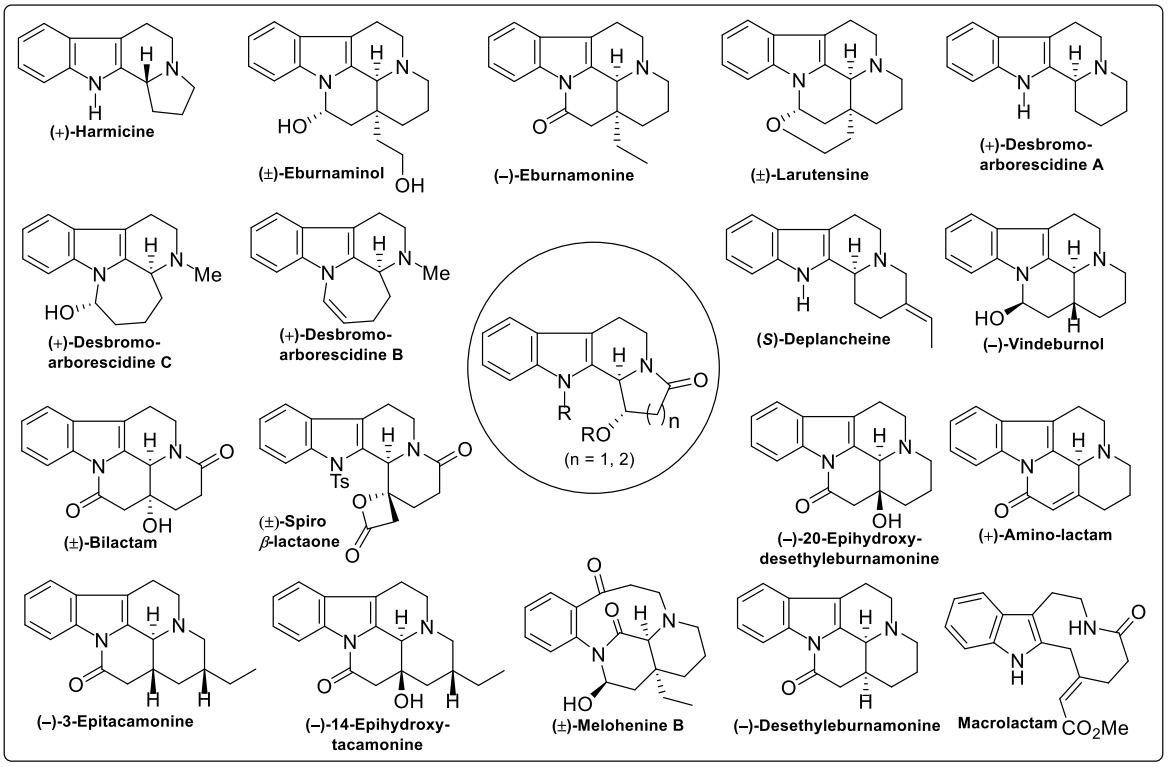


Figure 2. Bioactive indole alkaloids & their analogues synthesized.

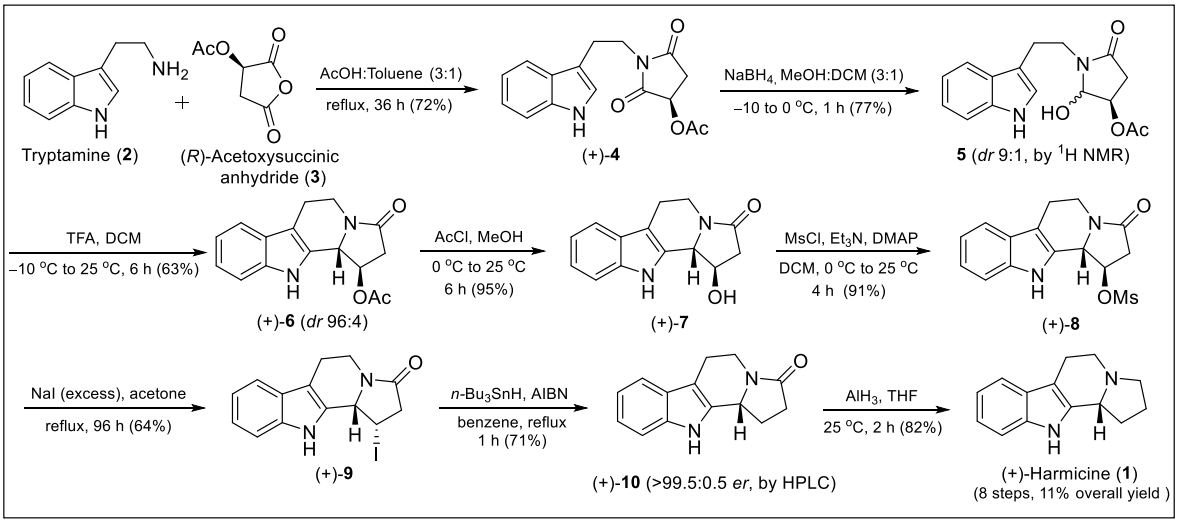
<u>Chapter One</u>: A Concise Account on the Application of Cyclic Anhydrides and Cyclic Imides in the Syntheses of Indole Alkaloids

Classification of alkaloids, more specifically indole alkaloids along with their biosynthesis have been briefly presented in this chapter. Cyclic anhydrides and cyclic imides are important synthons for the synthesis of bioactive natural and unnatural products. Syntheses of various indole alkaloids utilizing cyclic anhydrides and cyclic imides as a potential starting material have been also briefly described in this chapter.

<u>Chapter Two</u>: Studies on the Synthesis of Tetrahydro-*β*-Carboline Alkaloids

Section A: Synthesis of (+)-Harmicine

A brief account on previous syntheses of (±)/(+)/(–)-harmicine have been presented schematically. A facile convergent access to an important indole alkaloid (+)-harmicine has been described starting from tryptamine and (*R*)-acetoxysuccinic anhydride via the corresponding acetoxysuccinimide with very good overall yield. Regioselective reduction of an unsymmetrical imide carbonyl group and acid catalyzed stereoselective intramolecular cyclization were the involved key features. The handle to induce asymmetry was finally detached via the corresponding iodide by using tributytin hydride chemistry (Scheme 1).

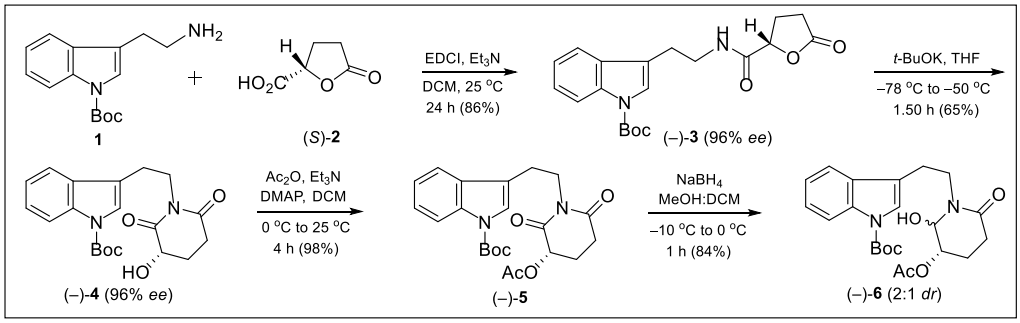


Scheme 1. Synthesis of (+)-harmicine

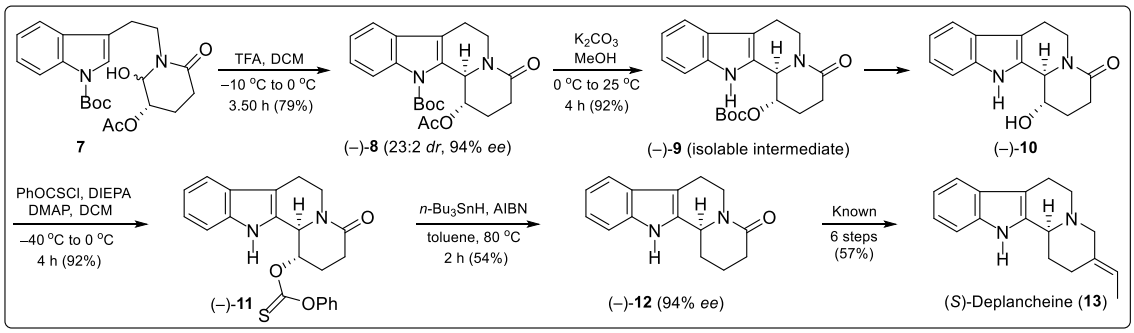
Overall, tryptamine and (*R*)-acetoxysuccinic anhydride were synthetically tailored to (+)-harmicine in a sequential fashion via dehydrative coupling, regioselective reduction, stereoselective intramolecular cyclization, overall deoxygenation and reduction pathway in very good overall yield with high enantiomeric purity. Specifically, the synthesis of enantiomerically pure (+)-harmicine has been accomplished from readily available staring materials using simple reaction conditions and in absence of transition metal catalysis. The present route is general in nature and will be useful to design the focused mini-library of its analogs and congeners for SAR studies.

Section B: Enantioselective Total Synthesis of Desbromoarborescidines A–C and the Formal Synthesis of (*S*)-Deplancheine

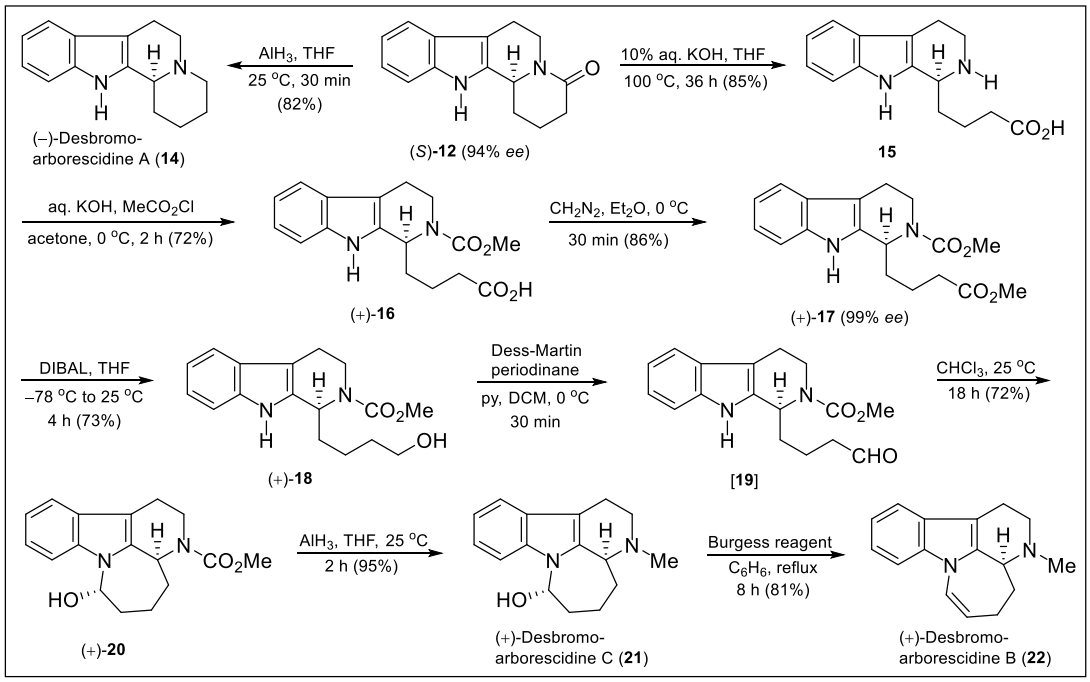
A brief account on previous syntheses of arborescidines/desbromoarborescidines A–C and deplancheine has been presented. Starting from Boc-protected tryptamine and (*S*)-tetrahydro-5-oxo-2-furancarboxylic acid, facile enantioselective total synthesis of desbromoarborescidines A−C and the formal synthesis of (*S*)-deplancheine have been accomplished via a common intermediate (*S*)-indolo[2,3-*a*]quinolizine (Schemes 2–4).



Scheme 1. Synthesis of (*S*)-acetoxyglutarimide



Scheme 2. Stereoselective synthesis of pivotal intermediate (*S*)-indolo[2,3-*a*]quinolizine: formal synthesis of (*S*)-deplancheine



Scheme 3. Synthesis of enantiomerically pure desbromoarborescidines A–C from (*S*)-indolo[2,3-*a*]quinolizine

Synthesis of enantiomerically pure (*S*)-acetoxyglutarimide, stereoselective reductive intramolecular cyclization, hydroxyl group-assisted in situ *N*-Boc-deprotection, selective deoxygenation of the xanthate ester, and lactam hydrolysis followed by an appropriate exchange of nitrogen regioselectivity in intramolecular cyclization were the decisive steps. Overall, we have demonstrated enantioselective convergent approach to deplancheine and desbromoarborescidines A–C from the corresponding (*S*)-acetoxyglutarimide. All the three different oxygen functions present in (*S*)-acetoxyglutarimide were rationally utilized in a remarkable chemo-, regio- and stereoselective fashion to design these four desired tantamount targets in very good overall yields and high enantiomeric purities, using appropriate protecting groups. The present practical approach to these products is general in nature and would be useful to synthesize their potential analogues and congeners for

SAR studies. The witnessed in situ intramolecular Boc-group migration-deprotection is notable from mechanistic point of view. The chiral intermediate (1*S*,12*R*)-1-hydroxy-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (**12**) is noteworthy and it will serve as an important synthon to design several other bioactive indole alkaloids.

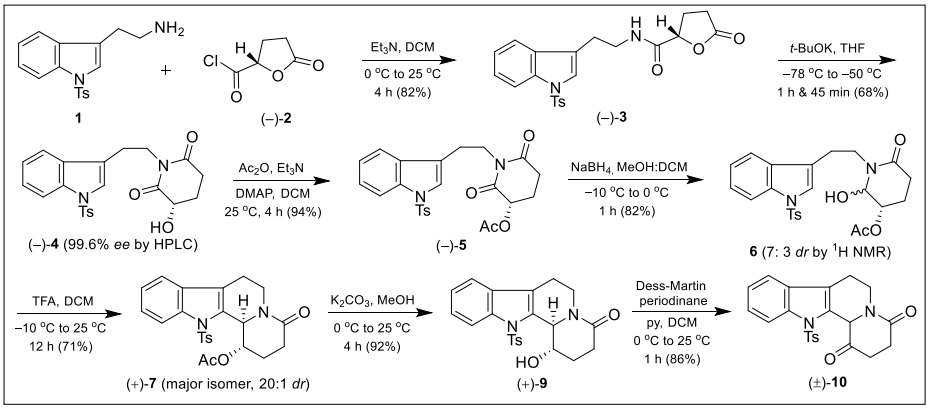
<u>Chapter Three</u>: Lactam Carbonyl as a Switch to Tailor the Stereoselectivity in Ester-Aldol Reaction: Diastereoselective/Enantioselective Synthesis of Vinca-Eburna and Tacaman Alkaloids and Analogues Thereof

Section A: Concise Literature Account of Indole Alkaloids Eburnamonine, Eburnaminol, Larutensine, Melohenine B, Tacamonine and Vindeburnol

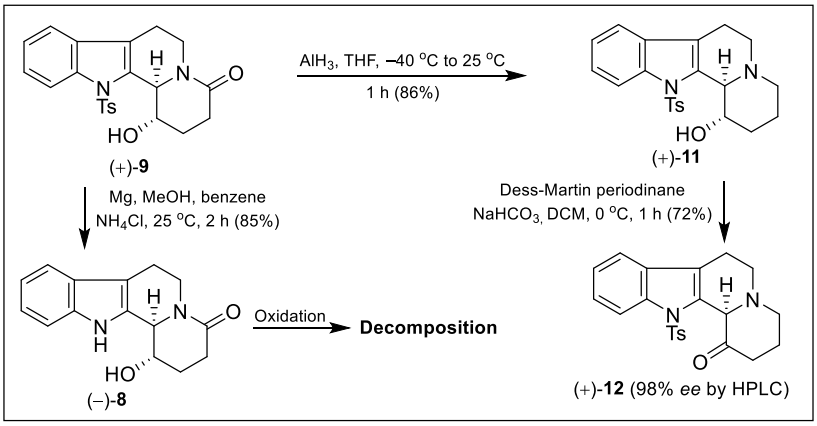
A concise literature account of indole alkaloids eburnamonine, eburnaminol, larutensine, melohenine B, tacamonine and vindeburnol has been presented.

Section B: Diastereoselective/Enantioselective Synthesis of Indole Alkaloids 3-Epitacamonine, Eburnamonine, Eburnaminol, Larutensine, Melohenine B, and Vindeburnol

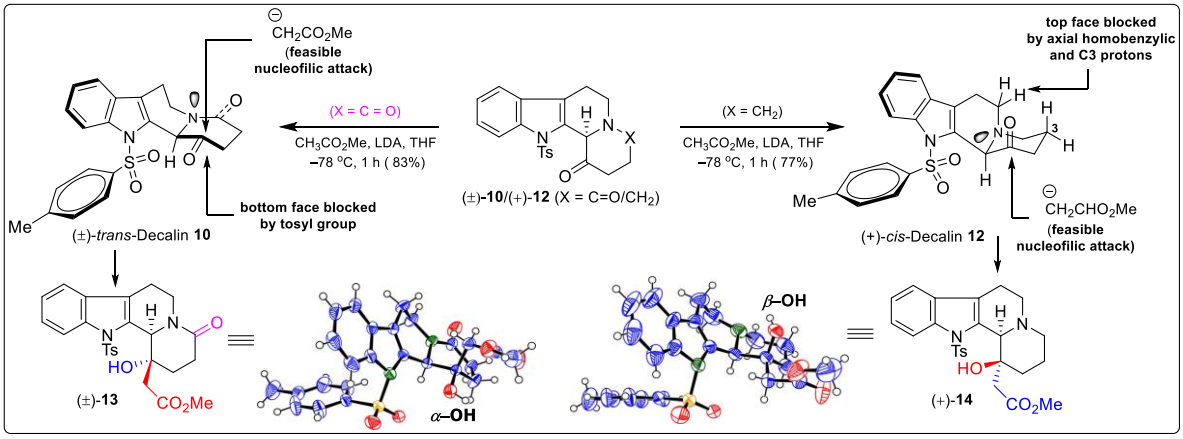
Starting from (–)-/(±)-acetoxyglutarimide enantioselective/diastereoselective multistep synthesis of indole alkaloids (–)-3-epitacamonine, (±)-eburnamonine, (±)-melohenine B, (±)-eburnaminol, (±)-larutensine and (–)-vindeburnol have been demonstrated via a common intermediate (+)-/(±)-1-hydroxy-12-tosyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1H)-one with very good overall yields. The acetoxy function from (–)-/(±)-acetoxyglutarimide was initially used as a handle to induce the enantioselectivety/diastereoselectivity and then as a latent source of ketone carbonyl group. Most importantly, the lactam carbonyl group functioned as a switch to alter the stereoselectivity in ester aldol reactions of hexahydroindolo[2,3-*a*]quinolizinones. In addition, syntheses of several pharmacologically important enantiomerically pure synthetic analogues of these natural products have also been described.



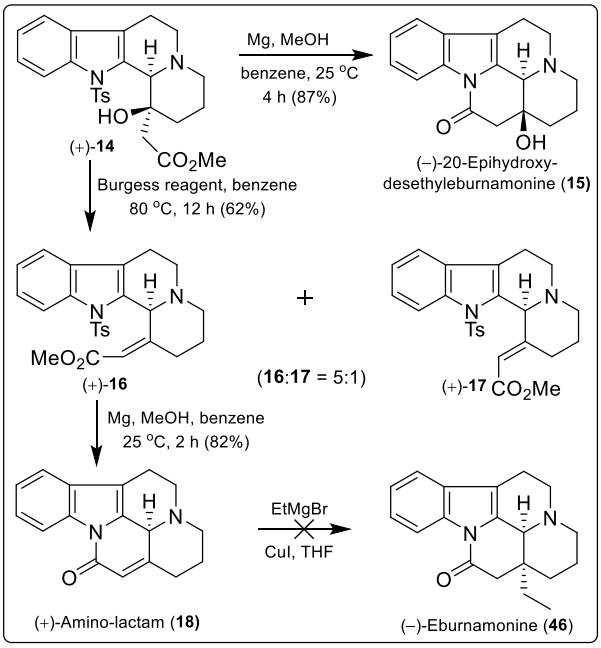
Scheme 1: Stereoselective synthesis of (±)-keto-lactam



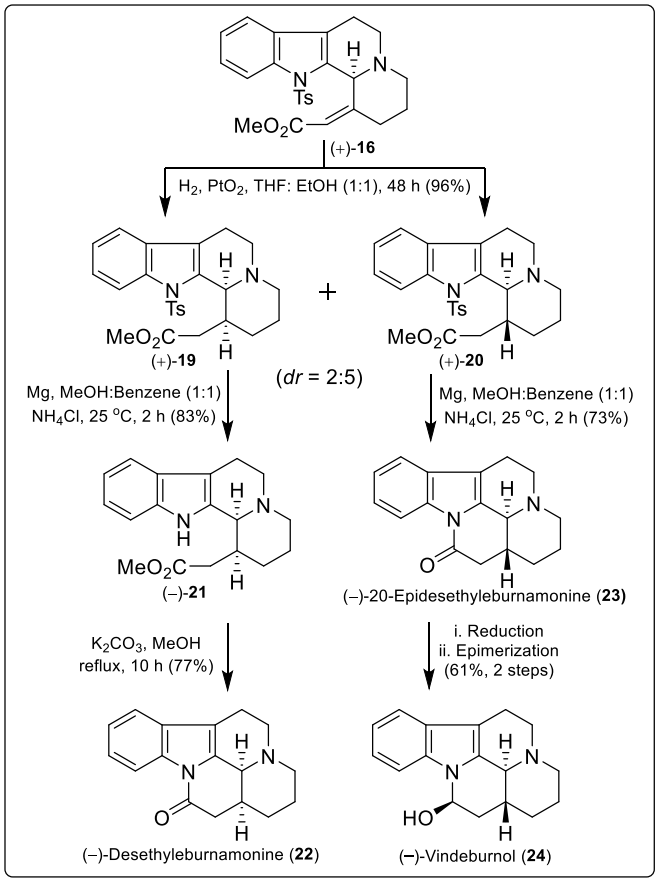
Scheme 2: Stereoselective synthesis of (±)-keto-amine



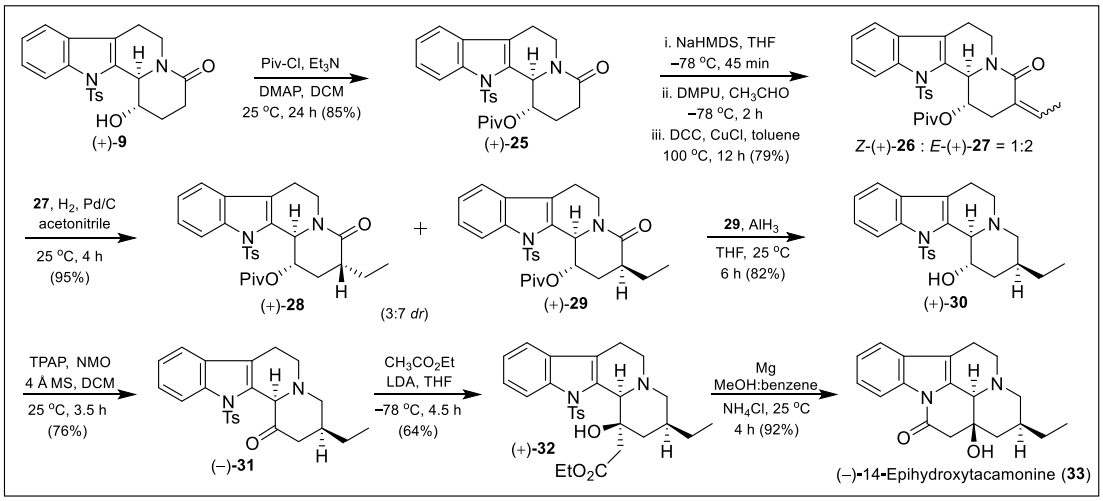
Scheme 3. Lactam carbonyl as a switch to alter the stereoselectivity in ester aldol reactions of hexahydroindolo[2,3-a]quinolizinones



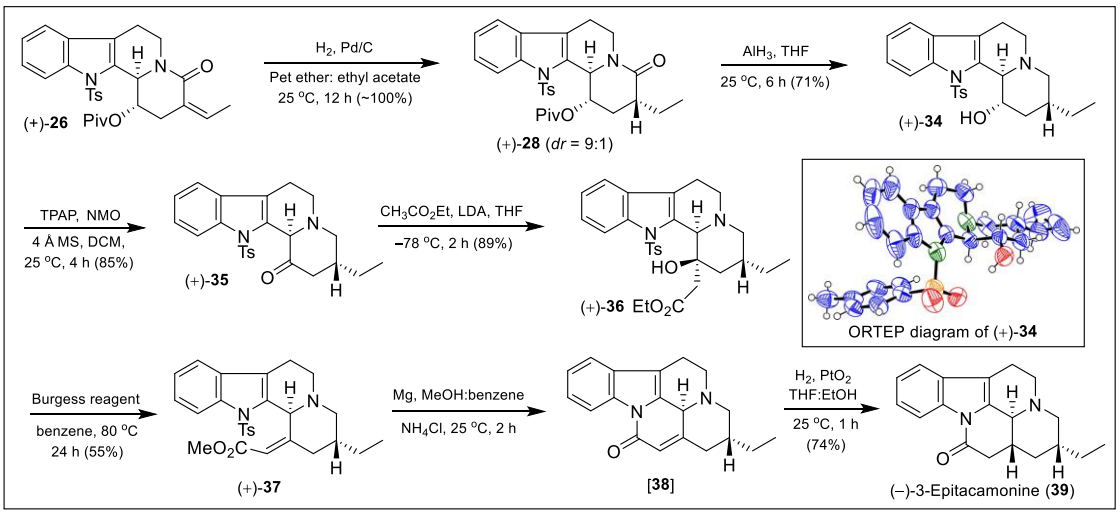
Scheme 4. Enantioselective synthesis of (–)-20-epihydroxydesethyleburnamonine and (+)-amino-lactam



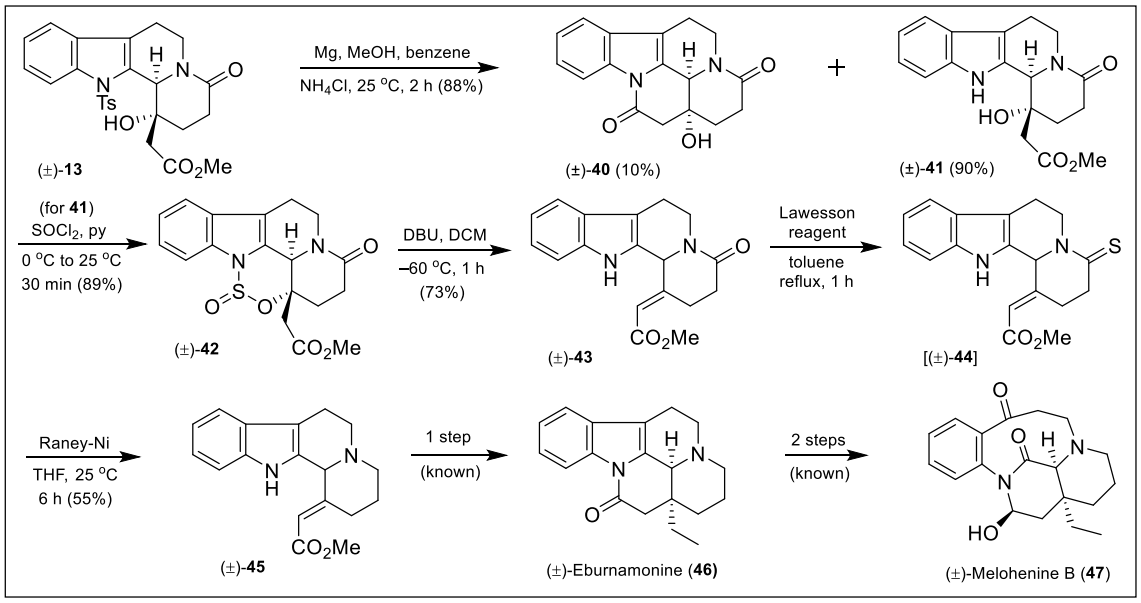
Scheme 5. Enantioselective synthesis of (–)-desethyleburnamonine, (–)-20-epidesethyleburnamonine and (–)-vindeburnol



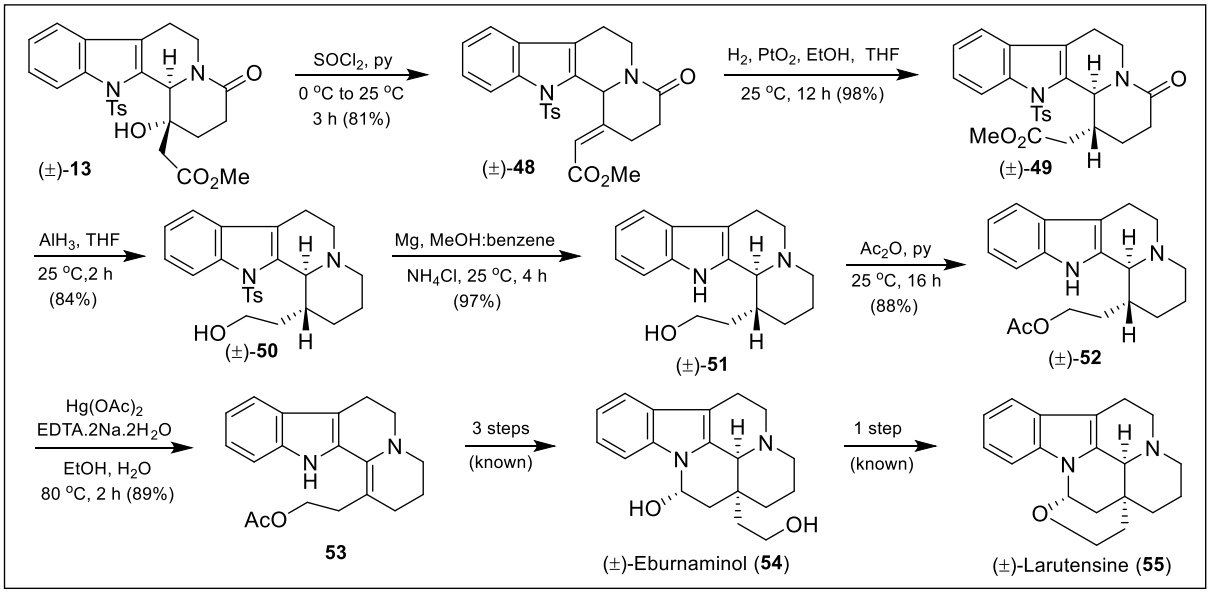
Scheme 6. Enantioselective total synthesis of (–)-14-epihydroxytacamonine



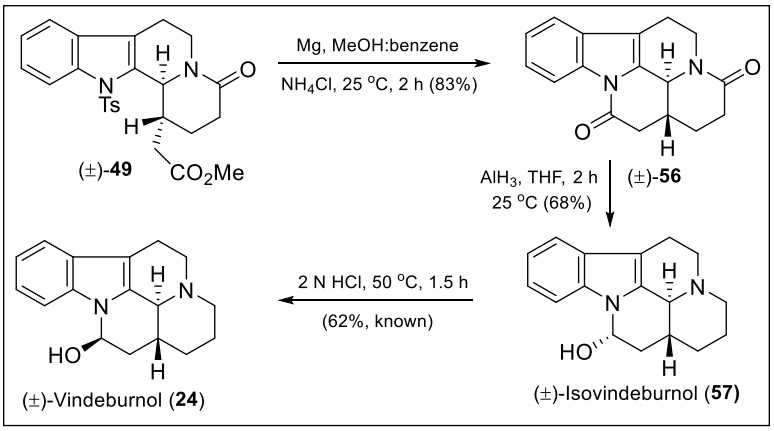
Scheme 7. Enantioselective total synthesis of (–)-3-epitacamonine



Scheme 8. Formal synthesis of (±)-eburnamonine and (±)-melohenine B



Scheme 9. Formal synthesis of (±)-eburnaminol and (±)-larutensine



Scheme 10. Diastereoselective formal synthesis of (±)-vindeburnol

We have completed facile enantioselective/diastereoselective synthesis of indole alkaloids (–)-3-epitacamonine, (±)-eburnamonine, (±)-melohenine B, (±)-eburnaminol, (±)-larutensine and (–)-vindeburnol. The first precise stepwise use of all the three oxygen functions in (–)-/(±)-acetoxyglutarimide in a chemo-, regio- and stereoselective manner to craft the desired target compounds is noteworthy. The amine-lactam switch system was developed and successfully used for the stereoselective embarking of an incoming nucleophile in ester aldol reactions. The obtained two different stereochemical outcomes were rationally used for a stereoselective design of indole alkaloids, their analogues and congeners. We feel that our present protocol is general in nature and will be useful to synthesize several natural and unnatural indole based structurally interesting and biologically important architectures for SAR studies.

In summary, starting from cyclic anhydrides and imides we have completed total synthesis of several enantiomerically pure indole alkaloids.

Chapter 1

A Concise Account on the Application of Cyclic Anhydrides and Cyclic Imides in the Syntheses of Indole Alkaloids

This chapter features the following topics:

1.1 Alkaloids

A natural product is a chemical substance which is being produced by a plant or an animal. The substances which contain basic nitrogen atom isolated from nature are called alkaloids. They are one of the largest classes of secondary metabolite produced by living organisms. The presence of basic nitrogen atom makes them particularly pharmacologically active. Since most of the alkaloids are amines, they form soluble salts after reacting with acids. Thus the term alkaloid is derived from 'alkali-like', which was first introduced by the pharmacist W. Meissner in 1819.[1] This term was further modified and the 'true alkaloid' was defined as compounds satisfying four requirements:

The nitrogen atom is a part of heterocyclic system.

The compound should have complex molecular structure.

The compound should possess modest pharmacological activity.

The compound is restricted to plant kingdom.

However, for some reasons the above definition is not particularly valid today.[2,3] Thus, today the concept of alkaloid has been elaborated and it is regarded as a naturally occurring nitrogenous compound. A more specified definition has been given by Pelleter:[2]

An alkaloid is a cyclic organic compound containing nitrogen in negative oxidation state which is of limited distribution among living organisms.

1.2 Biological Activities of Alkaloids

Alkaloids are having many important biological activities. They are significant for the protection and survival of plants because they act in the defence mechanism against micro-organisms (antibacterial and anti-fungal activities), insects and herbivores (feeding deterrents) and also against other plants by means of allelopathically active chemicals. They also function as signal compounds, attract pollinating or seed-dispersing insects and represent adaptive characters that have been subjected to natural selection during evolution.[4] Curare alkaloids were used as the active ingredients of arrow poisons.[5] In those curare alkaloids, more specifically tubocuranine has muscle relaxant properties like it has been employed as relaxants of skeletal muscle during surgery to control convulsions.

Alkaloids often have many pharmacological activities which includes various physiological activities in humans and animals. Alkaloids containing plants have been used for dye, spices and drugs long back in the beginning of civilization.[6] Opium isolated from *Papaver somniferam* L. was used as a medicine as early as 4000 B. C in anicient Sumer, the birth place of world's first civilization. Morphine (**1**) (*Papaver somniferam*) is the first alkaloid to be isolated in pure form in 1805 by W. Sertürner (Figure 1). It acts as an indispensable analgesic, used for the treatment of severe pain. Quinine (**2**) is most known for its antimalarial activity and remains on the market as an antipyretic (fever suppressant). Some other physiologically effective alkaloids are caffeine (**3**, psychostimulant), cocaine (**4**, local anesthetic), nicotine (**5**, nicotinic acetylcholine receptor agonist) and codeine (**6**, antitussive).

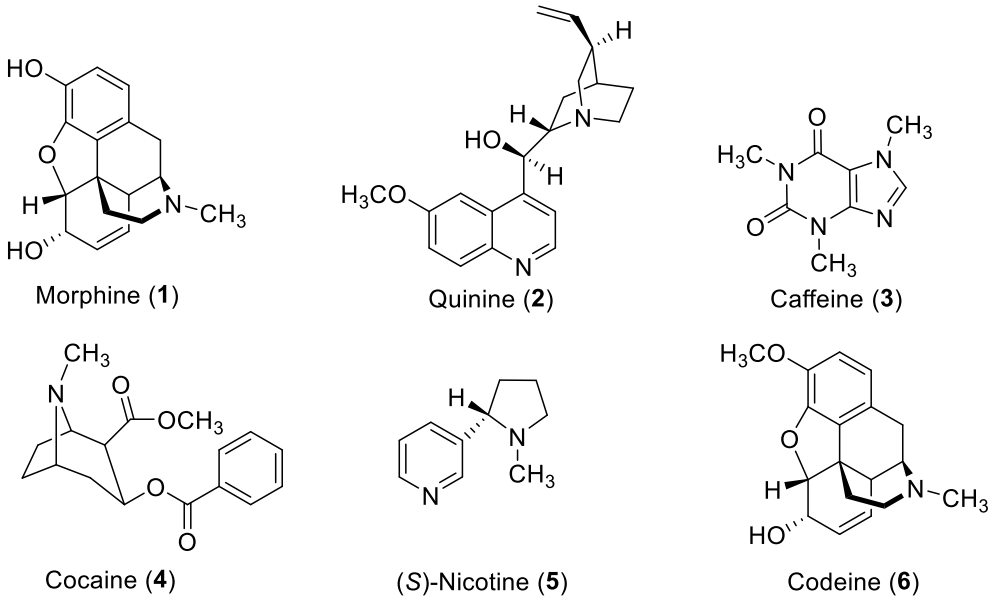


Figure 1. Pharmacologically active alkaloids

1.3 Classification of Alkaloids

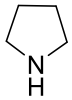
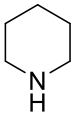
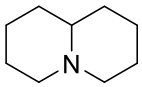
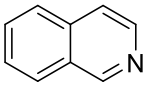
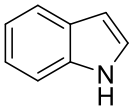
Alkaloids display a great variety in their botanical and biochemical origin, in chemical structure and in pharmacological activity. Hence, many different systems of classifications are possible. Broadly they have been classified into three groups as follows.[7,8]

I. According to their source

II. According to their chemical structure (hetereocyclic/non-hetereocyclic)

The above groups have been briefly described in tabular format.

I. Classification of alkaloids according to their source

Alkaloid Class	**Basic Structure**	**Biosynthetic Precursor**	**Example**
Pyrrolidine		Omithine	Hygrin
Tropane		Omithine	Atropine, Cocaine
Piperidine		Lysine	Coniine
Quinolizidine		Lysine	Lupinine
Isoquinoline		Tyrosine	Codeine, Morphine
Indole		Tryptophan	Psilocybin, Reserpine, Strychnine

II. Classification of alkaloids according to their chemical structure

A. Heterocyclic Alkaloids

Alkaloid Class	**Example**
i. Indole	Strychnine, Lysergic acid, Ergotamine
ii. Isoquinoline	Papaverine
iii. Morphinan	Morphine, Codeine, Thebaine
iv. Tropane	Atropine, Hyoscyamine, Cocaine, Scopolamine
v. Pyridine	Nicotine
vi. Piperidine	Piperine, Coniine
vii. Quinoline	Quinine
viii. Purine	Caffeine, Theobromine, Theophylline

ix. Indolizidine	Castanospermine, Swainsonine
x. Imidazole	Pilocarpine
xi. Steroidal	Solanidine, Conessine, Funtumine
xii. Terpenoid	Aconitine, Atisine, Lyctonine

B. Non-heterocyclic Alkaloids

i. Phenylalkylamine derivatives (for example; ephedrine, mescaline and capsaicin)

ii. Taxol (a modified diterpene pseudo alkaloid)

iii. Pachysandrine A (steroid with *N*-containing C-17 side-chain)

iv. Jurubin (steroid with 3-amino group)

v. Erythromycin (an antibiotic)

1.4 Indole Alkaloids

Indole alkaloids contain a basic indole ring skeleton in their structure. It is one of the largest classes of alkaloids comprising more than 4000 members. Many of them possess important biological activities whereas some of them are used in medicine (Figure 2). In nature indole alkaloids come from tryptophan which originates from the shikimic acid pathway. Many of them are of mixed-origin, where terpene based geraniol acts as a precursor.[9]

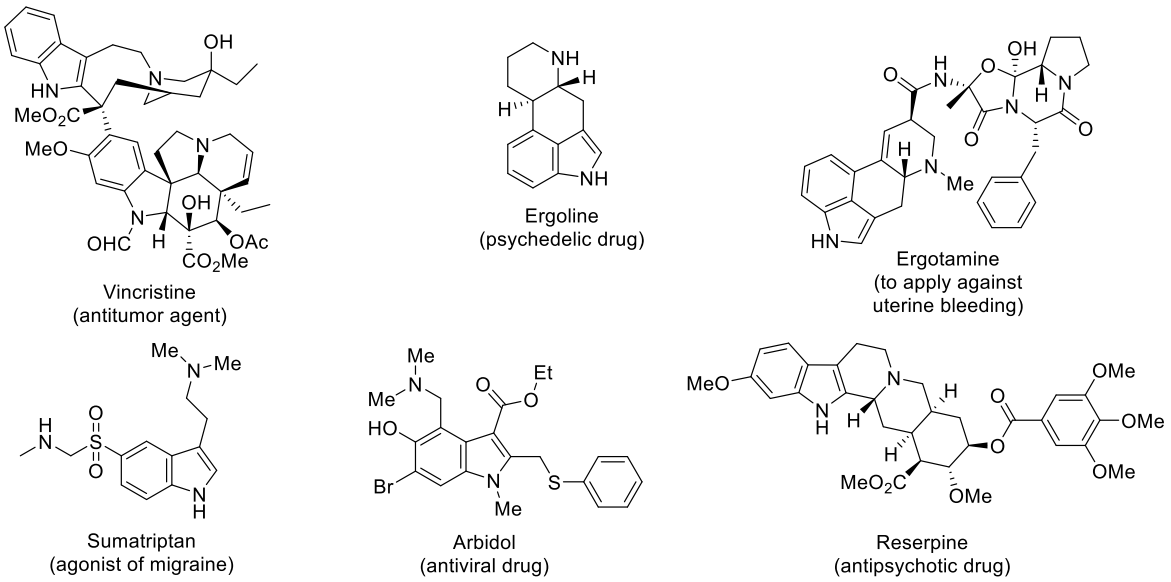


Figure 2. Drugs containing indole moiety

1.4.1 Classification of Indole Alkaloids

Depending on their biosynthetic origin, indole alkaloids are classified into two groups.

A. Non-isoprenoid Indole Alkaloids (Figure 3)

i. Simple indole derivatives: For example; serotonine (**7**), gramine (**8**) and glycozoline (**9**, carbazole alkaloid)

ii. Simple derivatives of *β*-carbolines: For example; harmine (**10**) and canthinone (**11**)

iii. Pyrolo-indole alkaloids: For example; physostigmine (**12**)

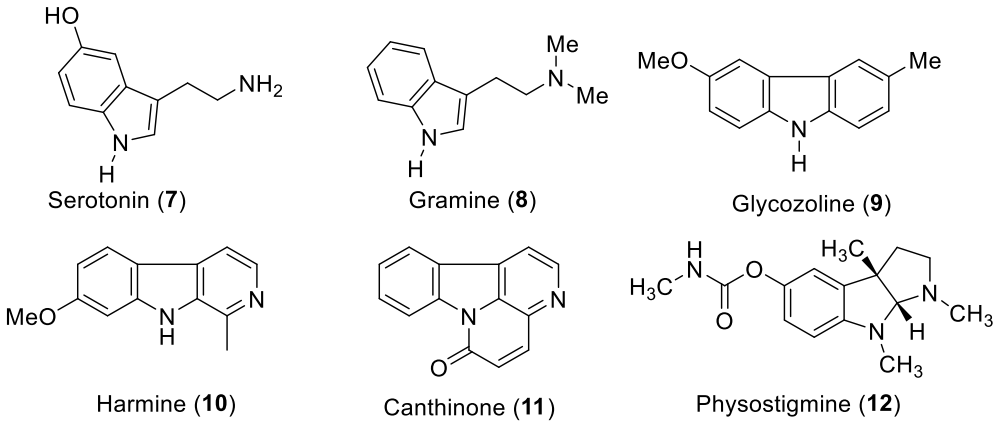


Figure 3. Representative non-isoprenoid indole alkaloids

B. Isoprenoid Indole Alkaloids

Isoprenoid indole alkaloids contain residues of tryptophan (**13**) or tryptamine (**14**) (Figure 4) along with isoprenoid building blocks derived from dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate. It is divided into three categories.

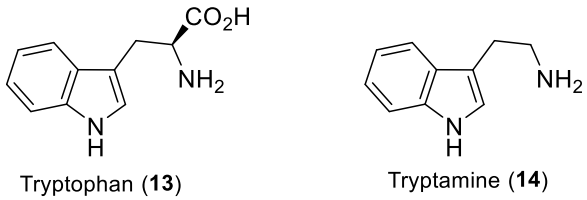


Figure 4. Tryptophan and tryptamine

i. Ergot alkaloids:

These are a class of hemiterpenoid indole alkaloids related to lysergic acid (**15**). They are formed via multistage reactions between tryptophan and DMAPP (Figure 5), for example; ergine (**16**), ergometrine (**17**) and ergocristine (**18**).

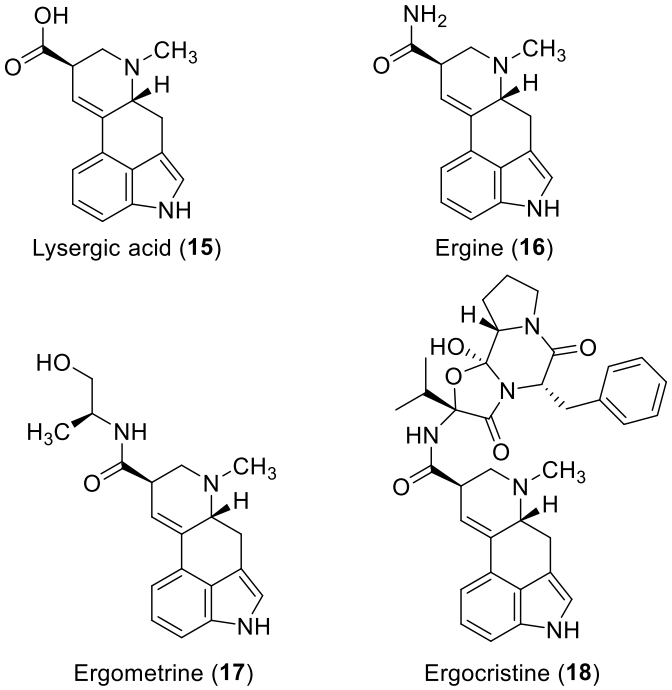


Figure 5. Representative ergot alkaloids

ii. Monoterpene indole alkaloids:

This class of alkaloids contain C_9 or C_{10} unit originated from secologanin (**19**) (see Scheme 1 for structure of **19**). Depending on the structure of residues, this class is divided into three subclasses named by a typical genus or species of the plant which contain such alkaloids; (a) corynanthe, (b) iboga and (c) aspidosperma.

Representative examples of monoterpene indole alkaloids have been given in figure 6.

Type	Number of carbon unit present in the monoterpenoid fragment	
	C_9	C_{10}
Corynanthe	Ajmaline (**20**)	Ajmalicine (**21**), Yohimbine (**22**)
Iboga	Ibogaine (**23**)	Voacangine (**24**)
Aspidosperma	Eburnamonine (**25**)	Tabersonine (**26**), Vincamine (**27**), Vindoline (**28**)

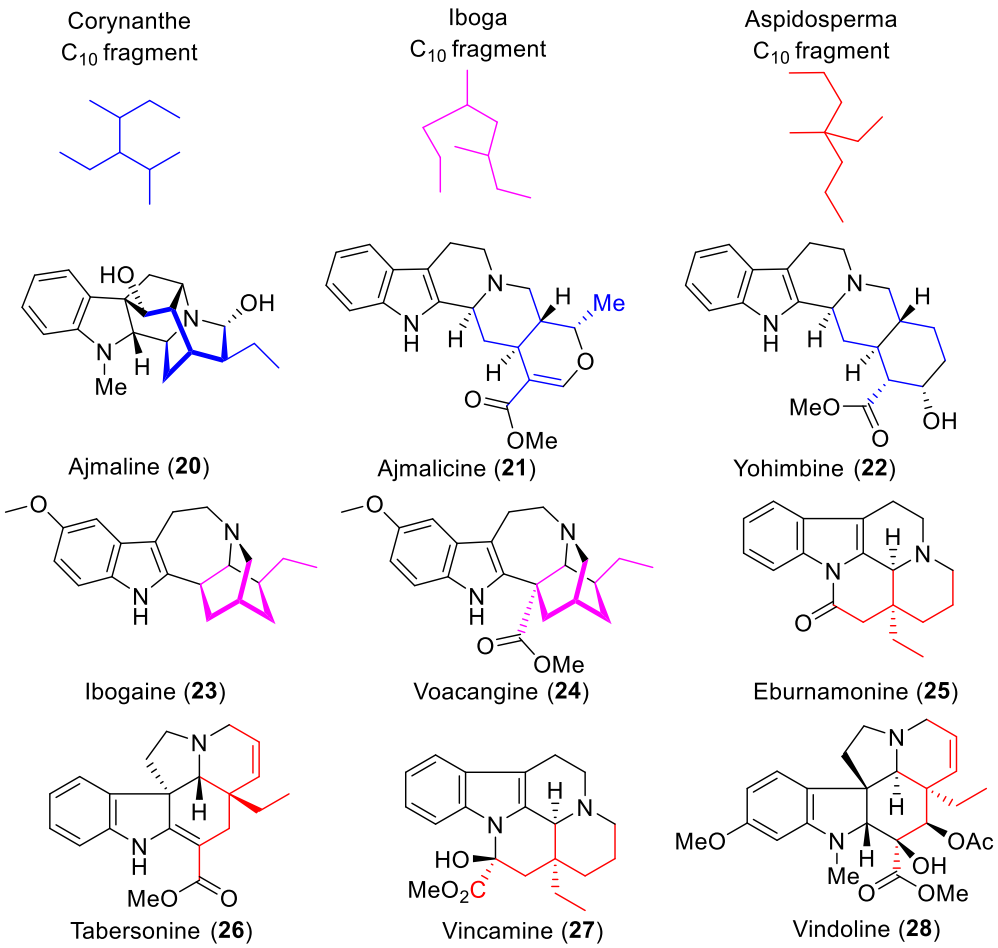


Figure 6. Representative monoterpene indole alkaloids

iii. Bisindole alkaloids: For example; voacamine (**29**) and vinblastine (**30**) (Figure 7)

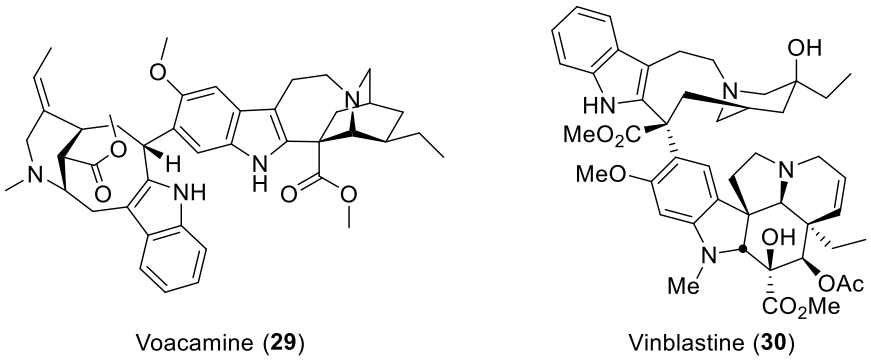
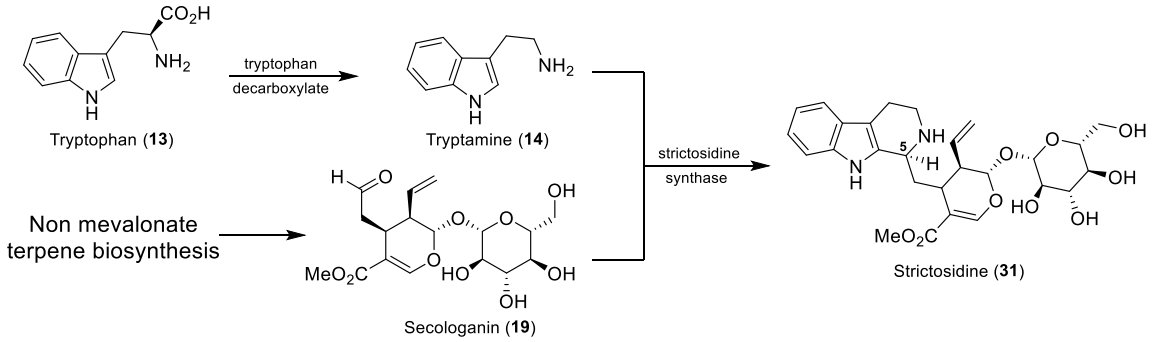


Figure 7. Representative bisindole alkaloids

1.4.2 Biosynthesis of Monoterpene Indole Alkaloids

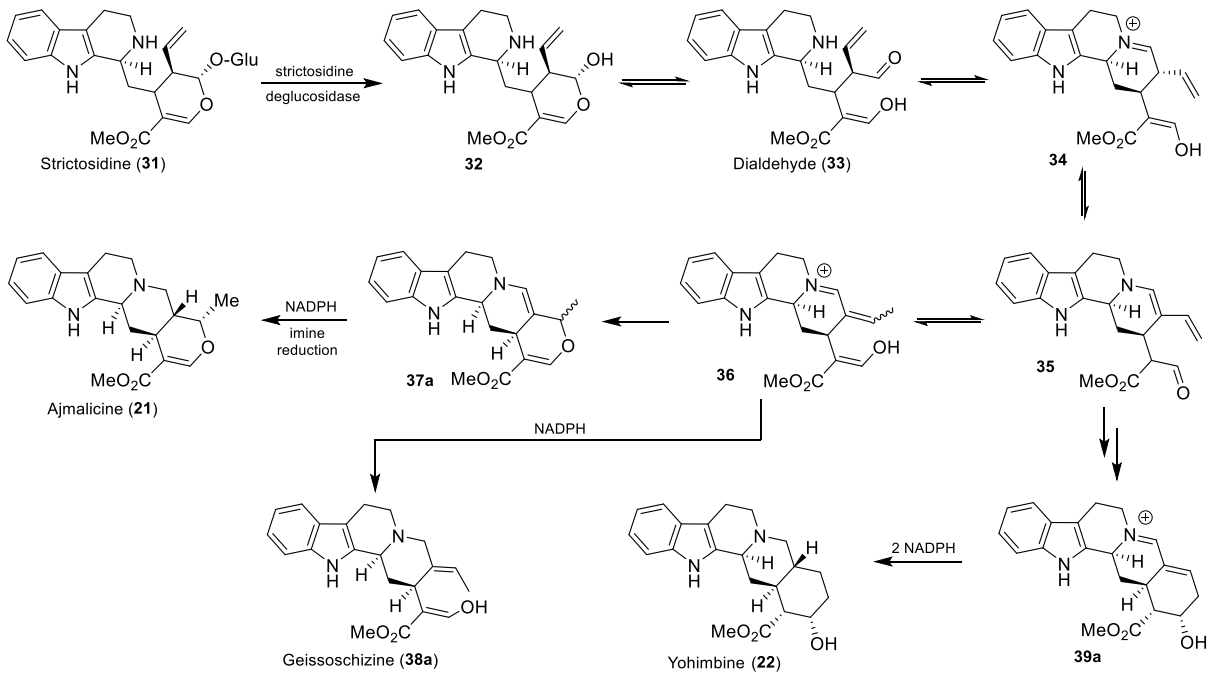
All monoterpene indole alkaloids have been originated from tryptophan and iridoid terpene secologagin (**31**).[10] Tryptophan decarboxylate converts tryptophan (**13**) to tryptamine (**14**).[11] The monoterpene secologanin is biosynthetically produced from isopentenyl pyrophosphate (IPP) via non-mevalonate pathway.[12] In the first committed step of terpene indole alkaloid biosynthesis, the enzyme strictosidine synthase catalyzes stereoselective

Pictet-Spengler cyclization[13] between tryptamine and secologanin to provide strictosidine (**31**) (Scheme 1).[14-17]

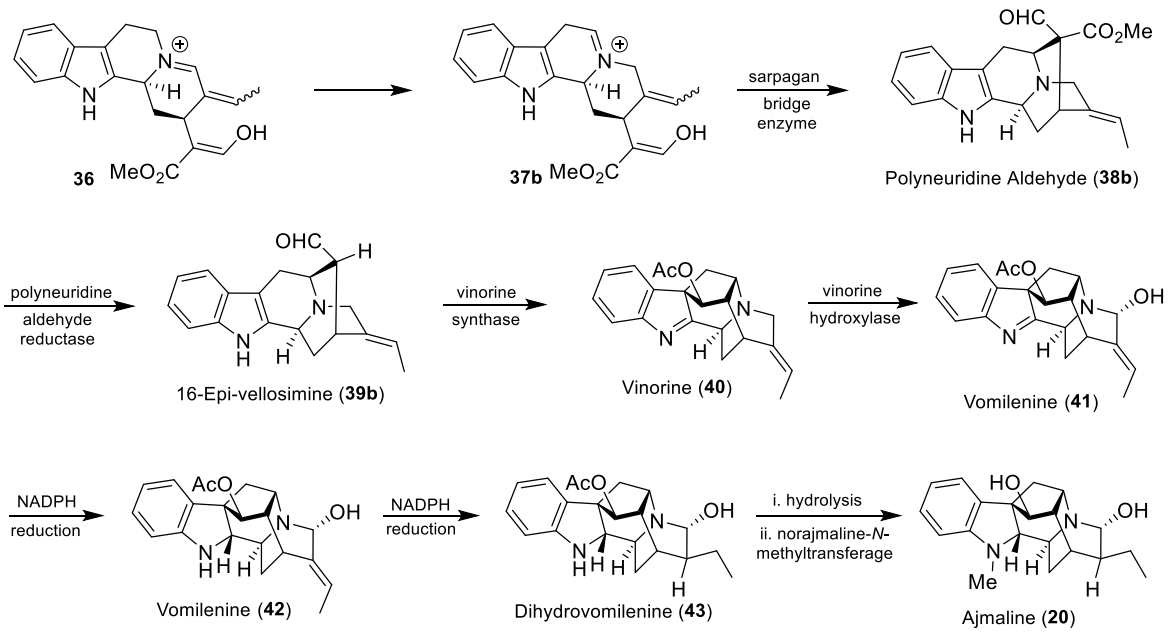


Scheme 1. Synthesis of strictosidine in monoterpene indole alkaloid biosynthesis

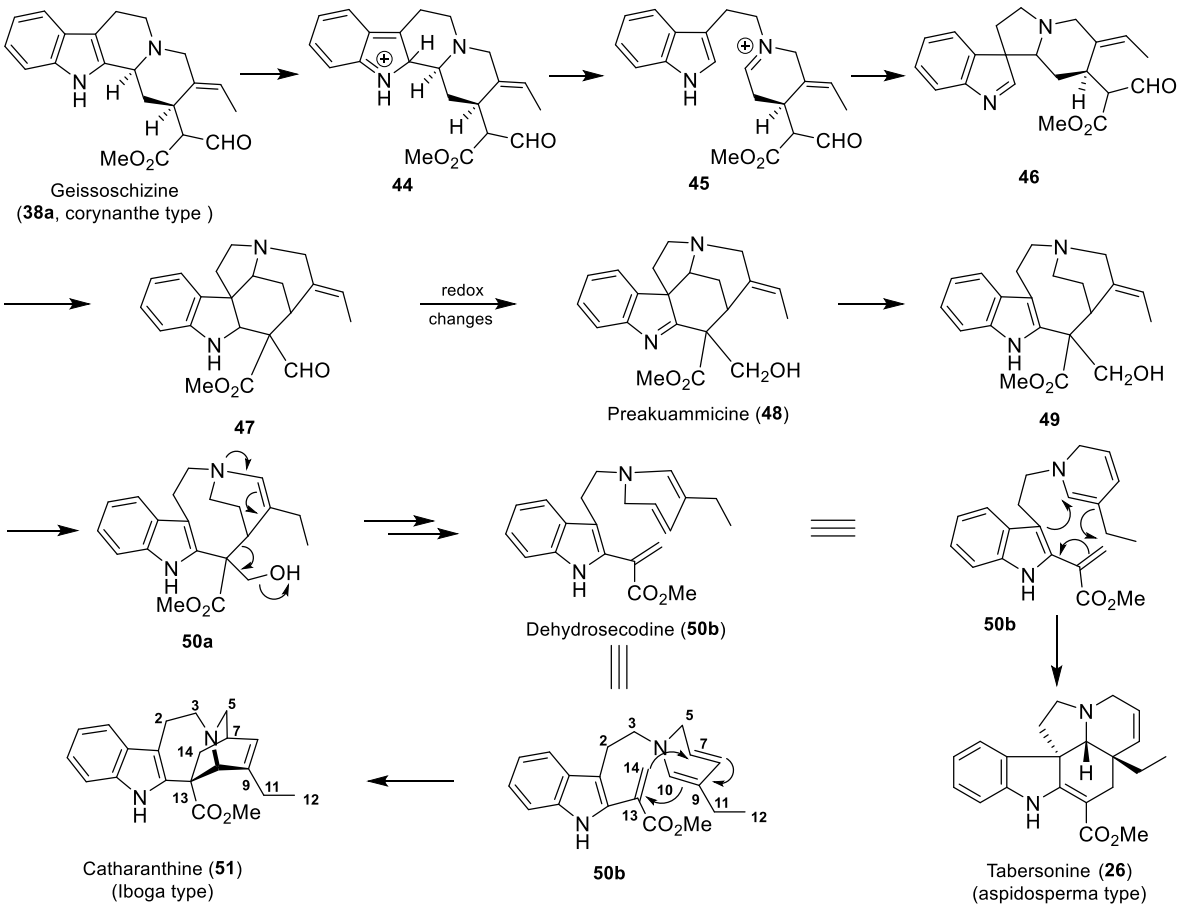
The mechanism and the control of the processes by which most of the families of monoterpene indole alkaloids are produced from strictosidine is one of the most challenging tasks in the study of secondary metabolism. Important information about crucial intermediates of the biosynthetic pathways has been obtained via trapping experiment, isotope labelling studies and feeding studies.[18-22] In many cases the involved enzymes for the biosynthetic step have been isolated and characterized.[22-24] Biosynthetic pathways of major monterepene indole alkaloids have been presented schematically in schemes 2-5.



Scheme 2. Proposed biosynthesis of corynanthe alkaloids ajmalicine, geissoschizine and yohimbine

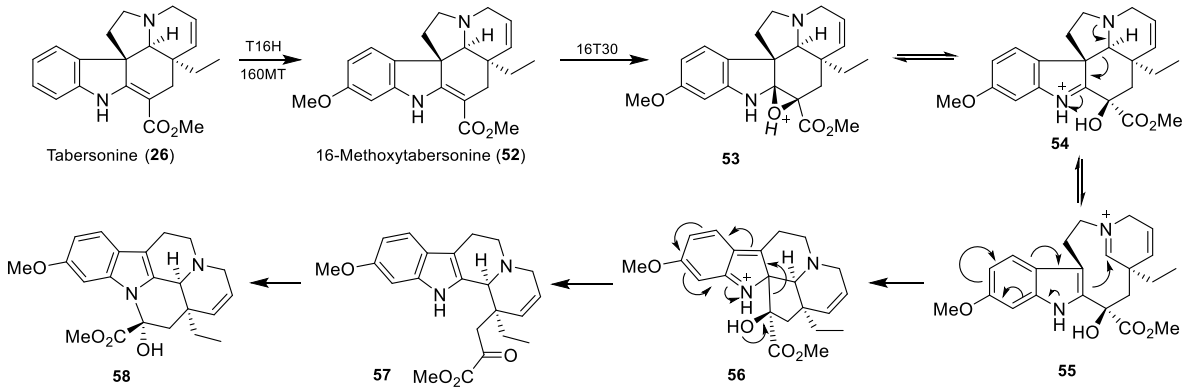


Scheme 3. Ajmaline biosynthesis from deglycosylated strictosidine



Scheme 4. Proposed biosynthetic pathway of aspidosperma and iboga alkaloids

There is a long standing hypothesis that aspidosperma and eburnamine type alkaloids are biogenetically related.[25] Recently O′Connor and co-workers have provided evidence for this hypothesis where the enzyme 16-methoxy tabersonine 3-oxygenase (16T30) catalyzes the formation of epoxide of 16-methoxytabersonine (**52**) which undergoes rearrangement to vinca-eburna type compound **58** (Scheme 5).[26] Hence it was suggested that 16T30 homologue is involved in the biosynthesis of vincamine (**27**) and related compounds.



Scheme 5. Biosynthesis of vinca-eburna type compound from tabersonine

1.5 Synthesis of Indole Alkaloids Using Cyclic Anhydrides and Cyclic Imides

Cyclic anhydrides and imides have been used as versatile building blocks in the synthesis of various bioactive natural products (Figure 8, Table 1).[27-34] More specifically maleic anhydride (**59**) and its derivatives are more important from both biological and synthetic application point of view.[35-40] It is a versatile synthon where all the sites are amenable for variety of reactions and exerts exceptional selectivity towards several nucleophiles. In past decades large number of naturally occurring maleic anhydrides and their derivatives has been isolated and many of them display important pharmacological activities. Methylmaleic anhydride (**60**, citraconic anhydride) is the most widely useful among the monoalkyl substituted maleic anhydrides. Many synthetic derivatives of natural anhydrides have been prepared and biologically examined extensively in the last two decades. Other important cyclic anhydrides used as a synthon are, succinic anhydride (**61**), methoxy maleic anhydride (**62**), dimethylmaleic anhydride (**63**), (*S*)/(*R*)-acetoxysuccinic anhydride (**64**/**65**), glutaric anhydride (**66**), *N*-CBz protected glutamic anhydride (**67**), homopthalic anhydride (**68**) and its derivatives etc. On the basis of past two decades extensive work on cyclic anhydrides and their derivatives to bioactive natural and unnatural products many interesting results in the synthesis of these compounds using novel carbon–carbon and

carbon–heteroatom bond forming reactions have been published from our group.[41-49] Also recently two comprehensive reviews have been published dedicated to the cyclic anhydride class of natural products.[27,50]

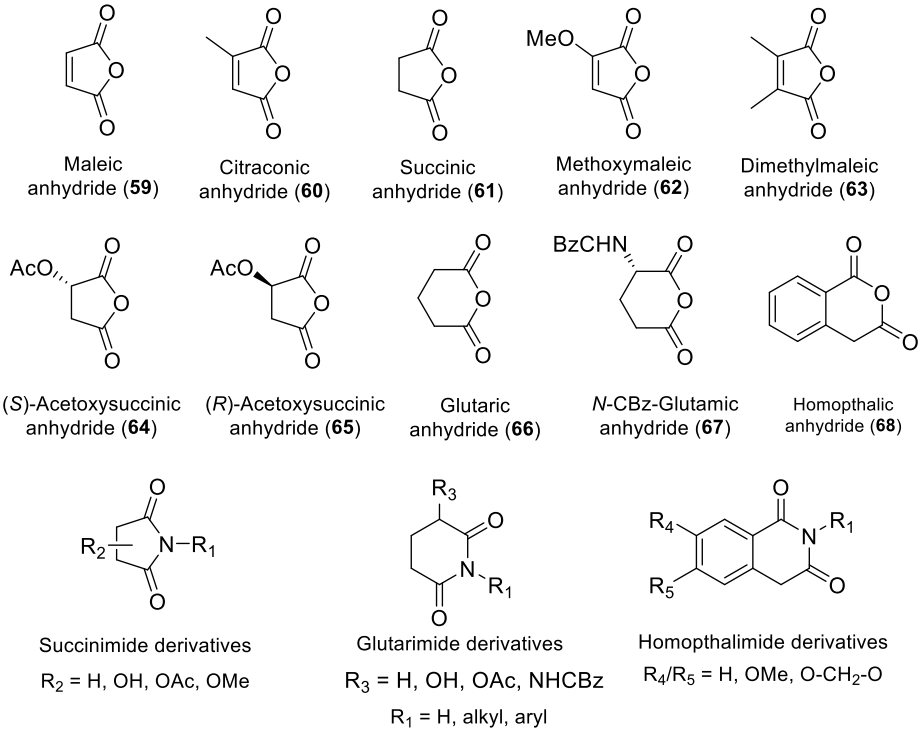
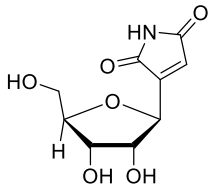
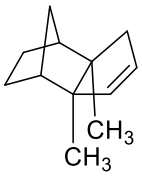
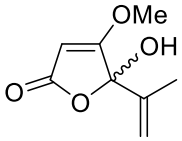
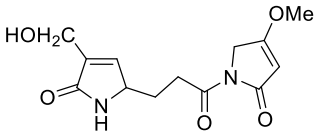
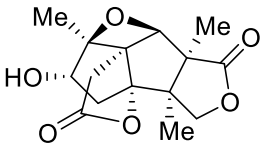
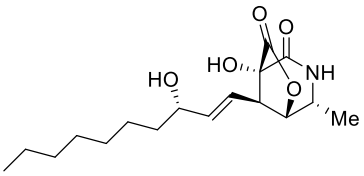
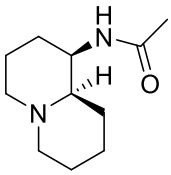
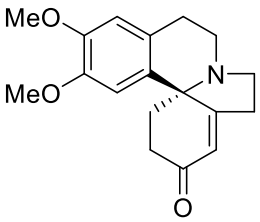
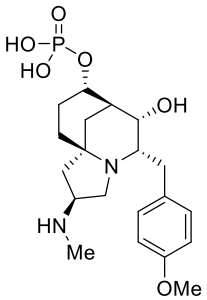


Figure 8. Important cyclic anhydrides and cyclic imides as potential precursors for synthesis of bioactive natural products

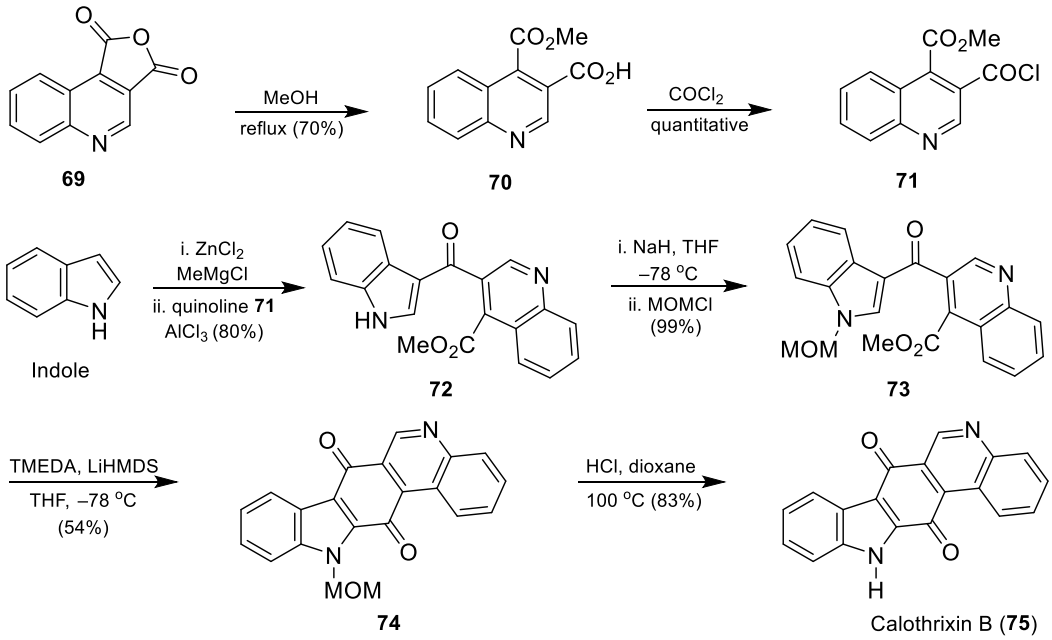
Table 1. Important applications of cyclic anhydrides/imides in natural products synthesis

No.	Compound	Source	Activity	Ref.
1	 Showdomycin	*Streptomyces showdoensis*	Antibiotic	51,52
2	 (±)-Albene	*Petasites albus*	Not known	53

3	 Penicillic acid	*Lyngbya majuscule* (marine blue-green algae)	Antimicrobial and antitumor	54
4	 Pukelimide	*Lyngbya majuscule* (marine blue-green algae)	Not known	55
5	 (±)-Merrilactone A	*Illicium merrillianum*	Neurotropic agent	56
6	 (+)-Awajanomycin	*Acremonium* sp. AWA16-1	Cytotoxic against A549 cells	57
7	 Epiquinamide	*Epipedobates tricolor*	Nicotinic agonist	58
8	 (+)-Demethoxy-erythratidinone	*Erythrina lithosperma*	Curare-like and hypnotic activity	32
9	 FR901483	*Cladobotryum* sp. No. 11231	Potent immuno-suppressant	59

Cyclic Anhydrides and Cyclic Imides to Indole Alkaloids:

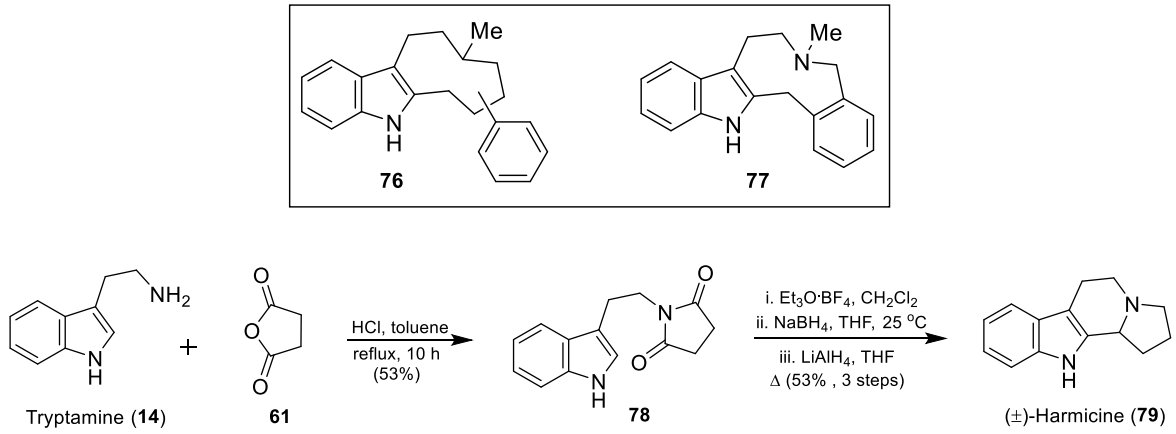
Chai and co-workers have reported a concise route to calothrixin B from quinoline anhydride **69** (Scheme 6).[60] Regioselective methanolysis of the anhydride **69** by using anhydrous methanol under reflux conditions exclusively provided the 4-mono methyl ester **70** in 70% yield. Fridel-Crafts reaction of indole with the corresponding acid chloride of



Scheme 6. Synthesis of calothrixin B from quinoline anhydride

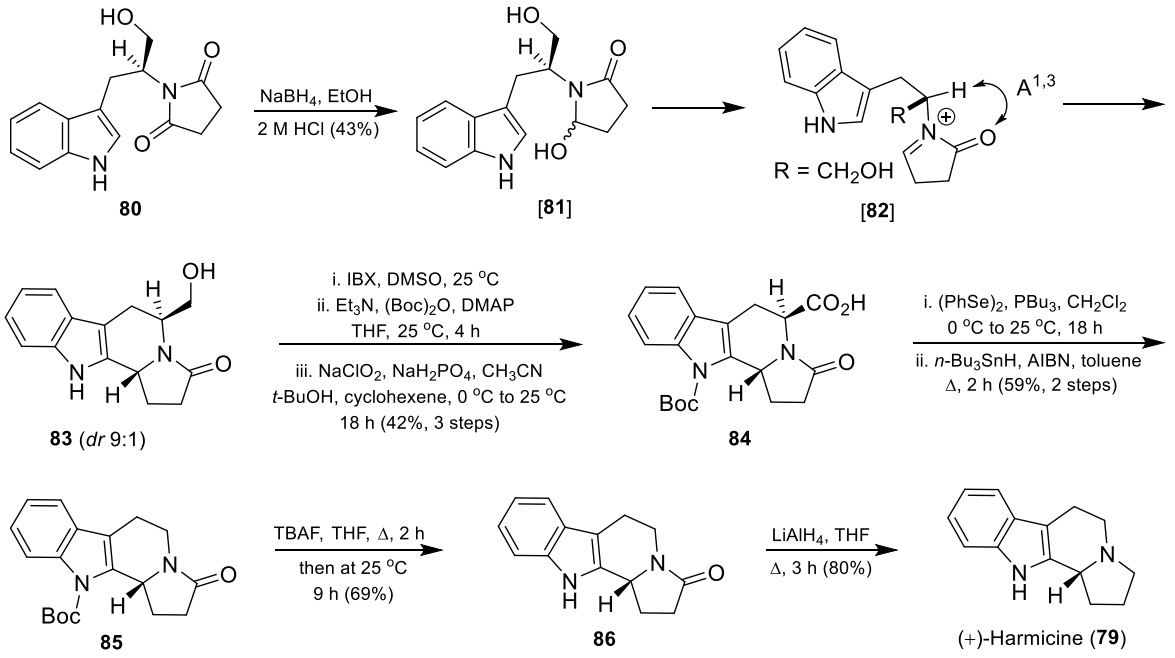
70 furnished the desired coupled product **72** in 80% yield. The precursor **72** was protected as *N*-MOM derivative **73** using standard conditions. Lithiation of compound **73** by using LiHMDS in presence TMEDA followed by cyclization afforded the product **74** in 54% yield. Finally *N*-MOM deprotection in DMSO under acidic condition provided calothrixin B (**75**) in 83% yield.

Lehmann and co-workers while pursuing synthesis of compounds with general structures **76** and **77** to be used as dopamine/serotonin receptor ligands, have described synthesis of (±)-harmicine using succinic anhydride (**61**) as a starting material (Scheme 7).[61] Tryptamine (**14**) was condensed with succinic anhydride to provide the corresponding succinimide **78** in 53% yield. Treatment of compound **78** with Meerwin's reagent followed by $NaBH_4$ reduction of the resultant iminium salt and finally reduction of lactam carbonyl group by $LiAlH_4$ afforded (±)-harmicine (**79**) in 53% yield (3 steps).



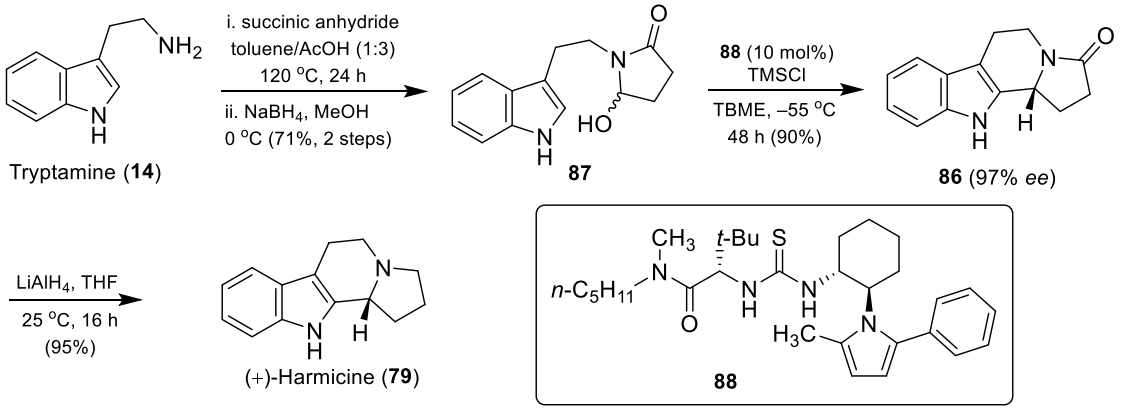
Scheme 7. Lehmann's synthesis of (±)-harmicine

Allin et al. reported an asymmetric synthesis of indole alkaloid (+)-harmicine by using highly diastereoselective *N*-acyliminium ion cyclization as a key synthetic step (Scheme 8).[62] The synthesis commenced from chiral succinimide derivative **80** which was prepared from the corresponding *β*-amino alcohol of tryptophan and succinic anhydride.[63] Subjecting imide **80** to $NaBH_4$ reduction in ethanol with the addition of 2 M HCl directly resulted in a highly diastereoselective cyclization to provide indolizidino[8,7-*b*]indole derivative **83** as a 9:1 diastereomeric mixture in 43% yield. The relative configuration of **83** was confirmed from X-ray crystallographic data. The high degree of stereocontrol can be explained from a preferred conformation having minimal $A^{1,3}$ strain between H-atom at the stereogenic center of the tryptophanol moiety and the lactam carbonyl group in the transition state **82**.[64] Oxidation of primary alcohol group in **83** to the corresponding aldehyde by IBX followed by Boc-protection of indole NH and Pinnick oxidation of the resultant aldehyde furnished the carboxylic acid **84** in 42% yield in 3 steps. Compound **84** was transformed to the corresponding acyl selenide derivative and subsequent tin-mediated deacylation yielded the core indolizidino[8,7-*b*]indole ring system **85** in 59% yield (2 steps). *N*-Boc deprotection by TBAF provided compound **86**, which was followed by reduction of lactam carbonyl using $LiAlH_4$ to afford the natural product (+)-harmicine (**79**) in 80% yield.

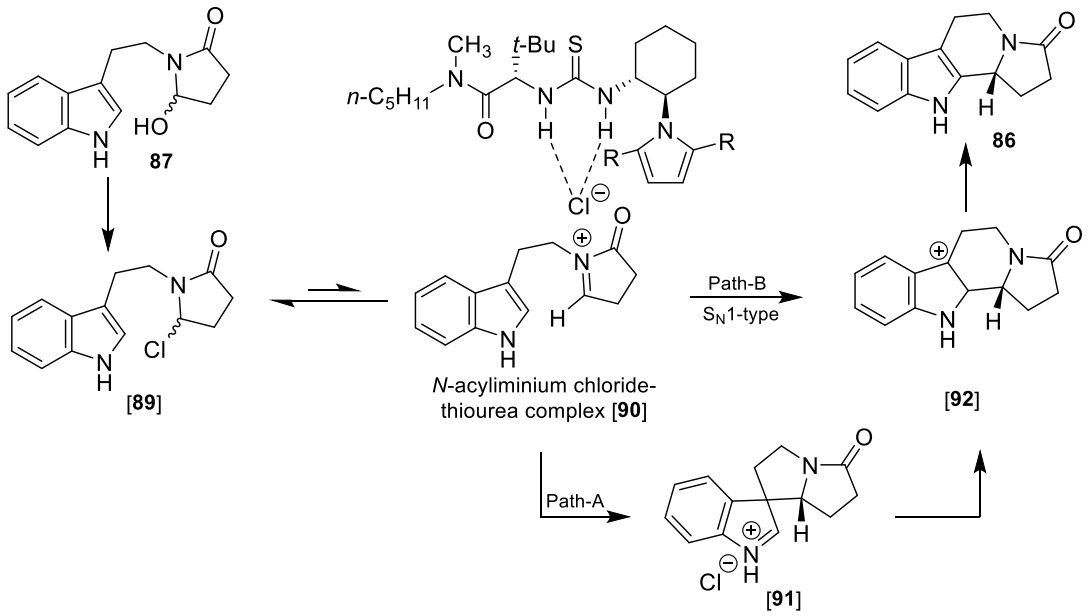


Scheme 8. Allin's synthesis of (+)-harmicine from chiral succinimide derivative

In 2007, Jacobsen and co-workers have reported application of enantioselective thiourea organocatalysis for Pictet-Spengler type cyclizations of *β*-indolyl ethyl hydroxylactams.[65] They have also described asymmetric synthesis of (+)-harmicine (Scheme 9a). Condensation of tryptamine (**14**) with succinic anhydride followed by reduction of lactam carbonyl of the resultant succinimide by $NaBH_4$ provided the precursor hydroxylactam **87** in 71% yield (2 steps). Asymmetric Pictet-Spengler cyclization of **87** in presence of chiral thiourea catalyst **88** provided the tetracyclic lactam **86** in 90% yield with 97% *ee*. The lactam **86** was transformed into the natural product (+)-harmicine under LAH-reduction condition. In this reaction thiourea catalyst promotes enantioselective cyclization by inducing dissociation of the chloride counter ion and by forming a chiral *N*-acyliminium chloride-thiourea complex (Scheme 9b).



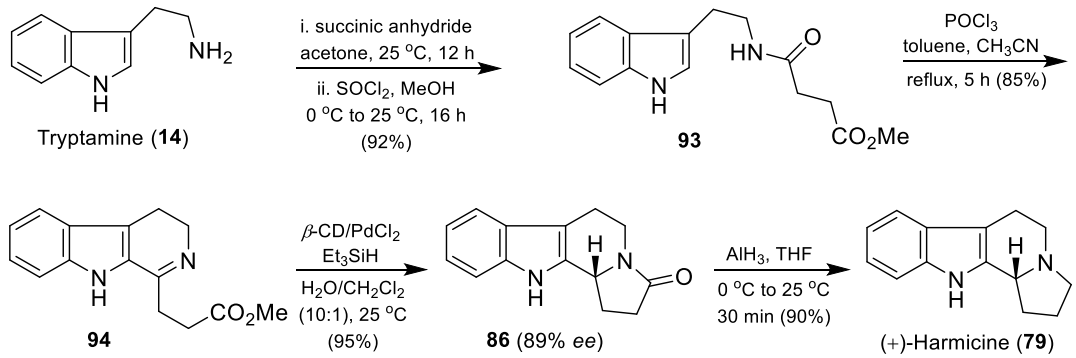
Scheme 9a. Synthesis of (+)-harmicine using thiourea organocatalysis



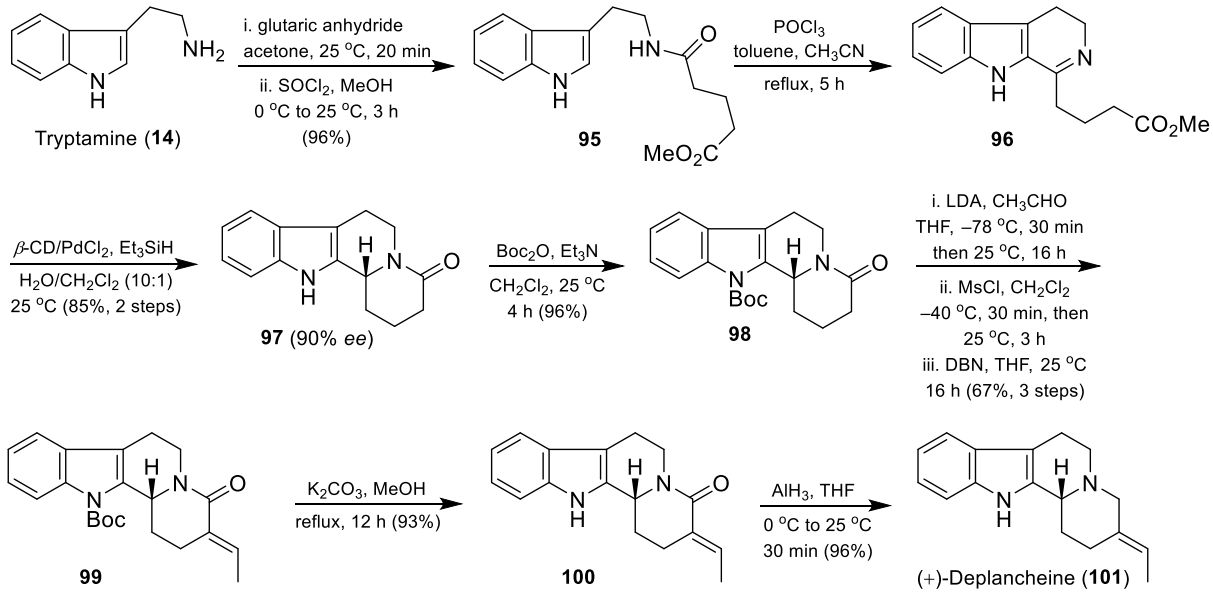
Scheme 9b. Proposed reaction mechanism of thiourea organocatalysis

Pilli and co-workers have reported asymmetric reduction of dihydro-*β*-carboline to the corresponding tetrahydro-*β*-carboline by using supramolecular lyophilized complex formed from *β*-cyclodextrin/imines as an enzyme mimetic and palladium hydride as the reducing agent.[66] The methodology has been applied for the syntheses of (*R*)-harmicine and (*R*)-deplancheine (Schemes 10 and 11). Treatment of tryptamine (**14**) with succinic anhydride followed by esterification of the corresponding acid formed the ester **93** in 92% yield. Bischler–Napieralski reaction of **93** using $POCl_3$ provided imine **94** in 85% yield. The imine **94** was subjected to the asymmetric supramolecular reduction condition by using *β*-CD/$PdCl_2$-Et_3SiH system to provide lactam **86** in 95% yield (89% *ee*) via spontaneous lactamization. AlH_3 reduction of the lactam **86** afforded (+)-harmicine (**79**) in 90% yield. With the same methodology they also have prepared indolo[2,3-*a*]quinolizidine core and successfully achieved the total synthesis of indole alkaloid (+)-deplancheine. Thus the reaction of tryptamine (**14**) with glutaric anhydride (**66**) followed by esterification with $SOCl_2$/MeOH yielded the amide **95** in 96% yield. Compound **95** after Bischler–Napieralski reaction and asymmetric supramolecular reduction provided the lactam **97** in 85% yield (2 steps) with 90% *ee*. Boc-protection of indole NH in **97** furnished compound **98** in 96% yield. The aldol reaction of lithium enolate of *N*-Boc protected lactam **98** with acetaldehyde followed by mesylation of the *β*-hydroxy alcohol and subsequent elimination of the mesylate with DBN provided *E*-ethylidene derivative **99** in 67% yield. *N*-Boc deprotection with K_2CO_3/MeOH followed by reduction of lactam

carbonyl using in situ generated AlH_3 afforded (+)-deplancheine (**101**) in 89% yield (2 steps).



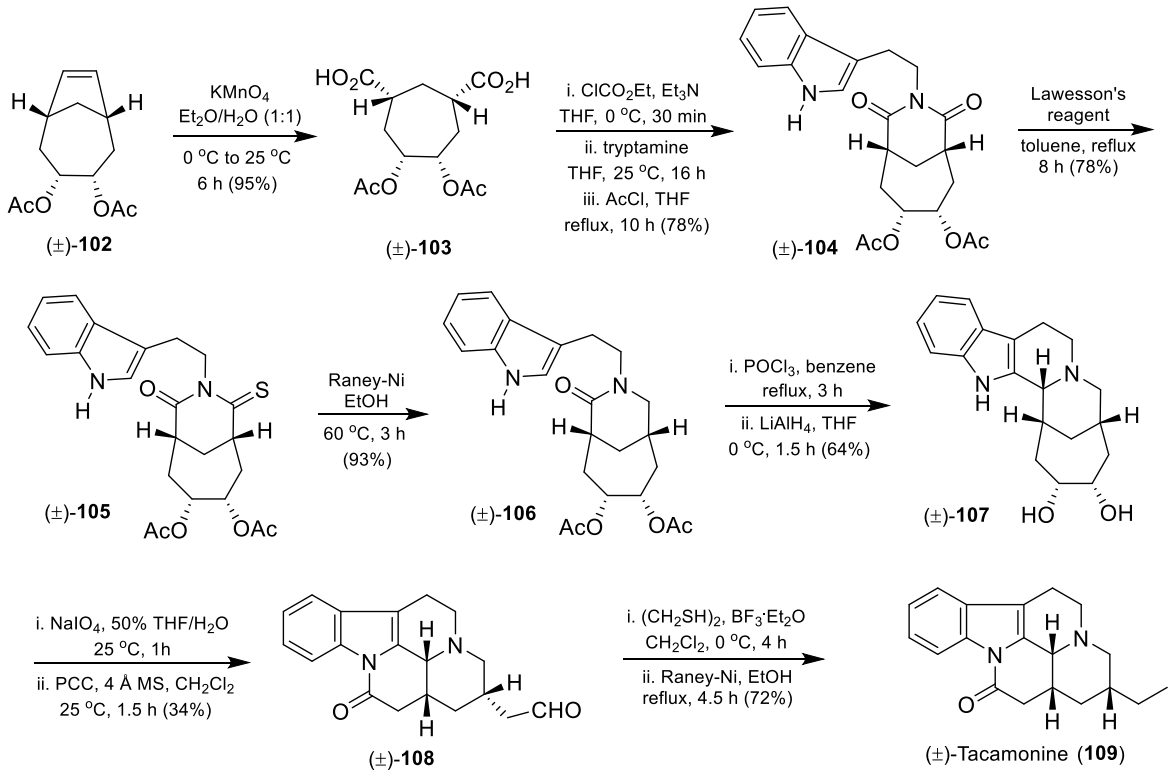
Scheme 10. Supramolecular approach for the synthesis of (+)-harmicine



Scheme 11. Supramolecular approach for the synthesis of (+)-deplancheine

Ho and Lin have reported stereocontrolled approach to the pentacyclic alkaloid (±)-tacamonine (**109**) via bridged glutarimide (±)-**104** (Scheme 12).[67] The bridged diacetate (±)-**102** was subjected to oxidative cleavage using $KMnO_4$ to provide the diacid (±)-**103** in 95% yield. The relative configuration of the stereogenic centres were confirmed by the X-ray diffraction data of the diacid (±)-**103**. The diacid was transformed to the bridged glutarimide (±)-**104** in two steps (first amide formation with tryptamine by using $ClCO_2Et/Et_3N$ system and finally ring closure by using AcCl). The glutarimide was converted to the lactam (±)-**106** via corresponding thiolactam formation followed by desulfurization with Raney-Ni. Subjecting the lactam (±)-**106** to Bischler–Napieralski reaction followed by stereoselective hydride reduction from the β-face of the bridged-

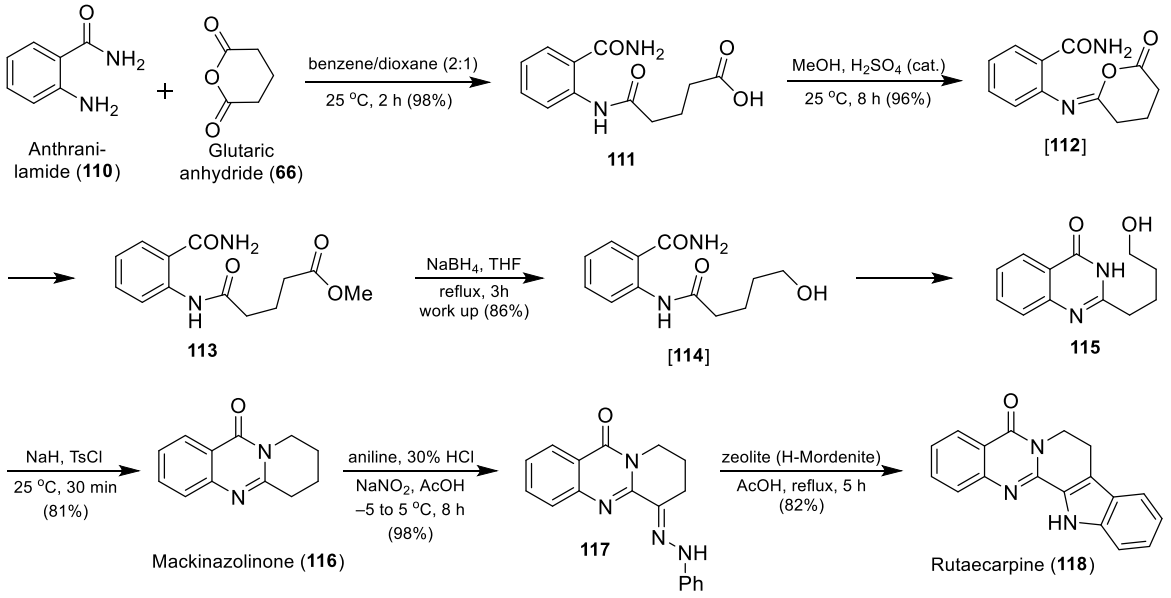
locked iminium salt afforded the amino-diol (±)-**107** in 64% yield. Cleavage of the diol by $NaIO_4$ formed the pentacyclic dialdehyde which spontaneously cyclized with the proximal aldehyde to yield the corresponding unstable aminol (mixture of epimers) which was oxidized directly to provide lactam-aldehyde (±)-**108** in 34% yield (2 steps). The aldehyde was transformed to (±)-tacamonine (**109**) via the corresponding ethylenedithioacetal and subsequent desulfurization by Raney-Ni in 72% yield (2 steps).



Scheme 12. Stereoselective synthesis (±)-tacamonine via bridged glutarimide

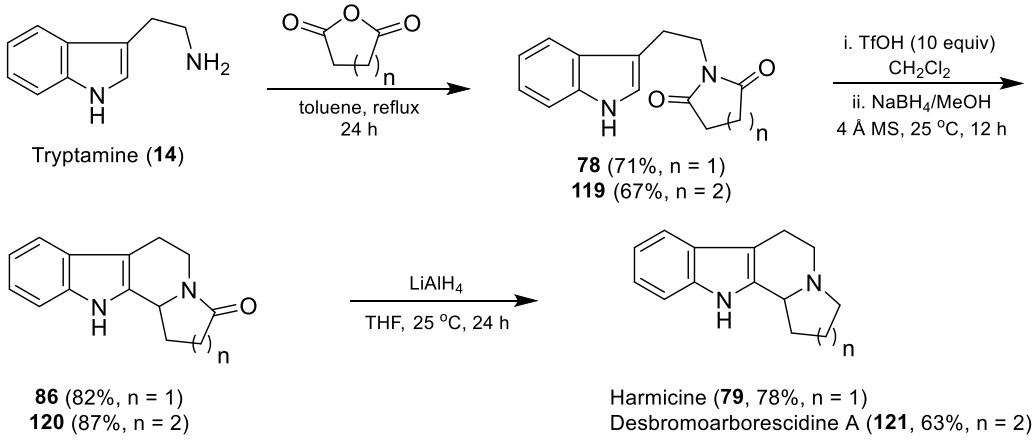
Mhaske and Argade have demonstrated an elegant synthesis of bioactive natural product rutaecarpine (**118**) using zeolite induced Fischer-indole synthesis as a key step (Scheme 13).[68] The reaction of anthranilamide (**110**) with glutaric anhydride (**66**) furnished the corresponding *o*-amidoglutaranilic acid (**111**) in 98% yield. The compound **111** on treatment with methanol in presence of catalytic amount of H_2SO_4 provided the methyl ester **113** plausibly via the corresponding isoimide **112**. Reduction of ester **113** with $NaBH_4$ provided the intermediate alcohol **114** which after post reaction work up underwent intramolecular dehydrative cyclization to afford quinazolinone **115** in 86% yield. Treatment of **115** with TsCl and NaH provided natural product mackinazolinone (**116**) via intramolecular cyclization. The compound **116** on reaction with in situ generated diazonium salt of aniline formed the hydrazone **117** in 98% yield. The hydrazone on

zeolite (H-Mordenite) induced Fischer-indole synthesis afforded the natural product rutaecarpine (**118**) in 82% yield.



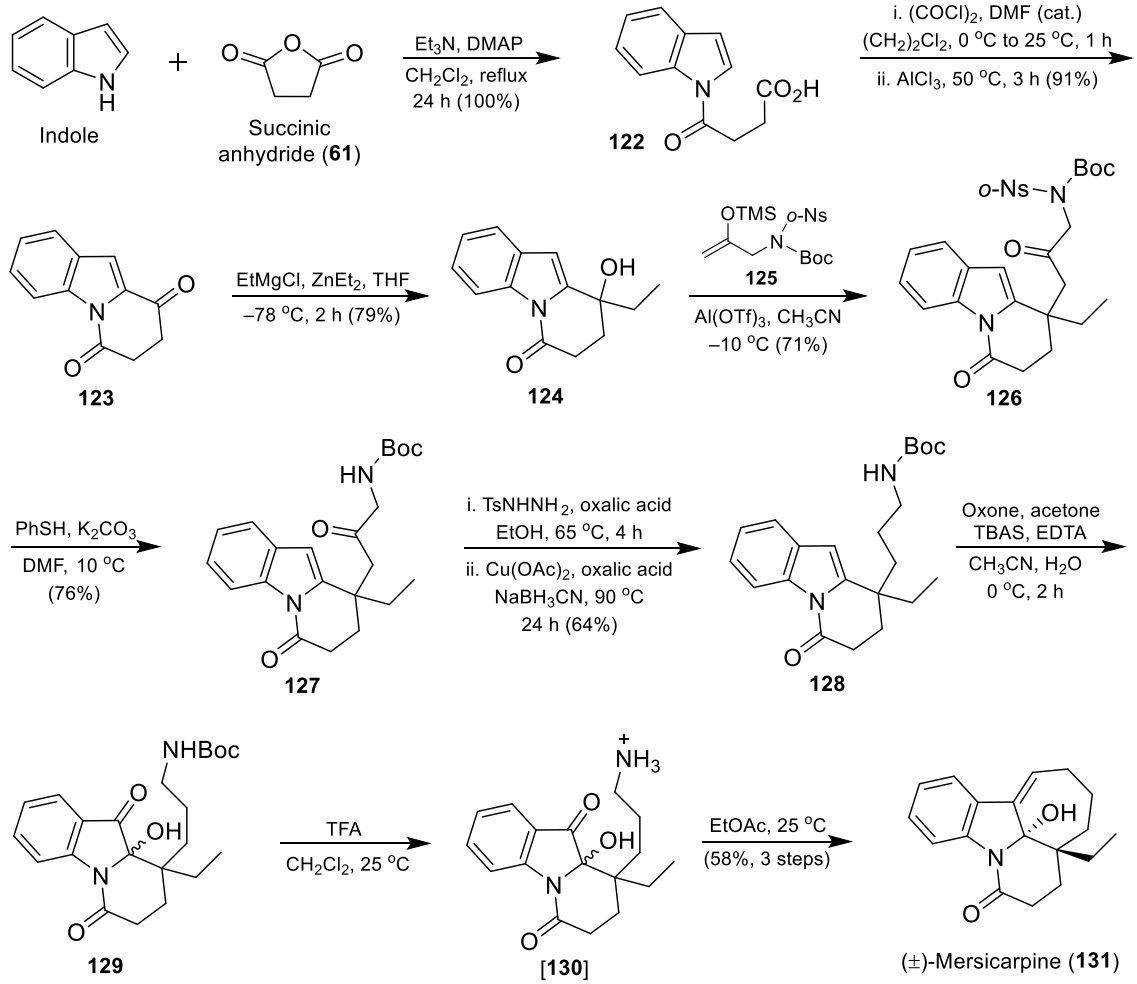
Scheme 13. Synthesis of rutaecarpine via Fischer-indole synthesis

Mangalaraj and Ramanathan have reported efficient synthesis of tetrahydro-*β*-carboline via BrØnsted acid activation of imide carbonyl group and applied to the synthesis of indole alkaloids (±)-harmicine (**79**) and (±)-desbromoarborescidine (**121**) (Scheme 14).[69] Condensation of tryptamine (**14**) with succinic anhydride and glutaric anhydride provided the corresponding succinimide **78** and glutarimide **119** in 71% and 67% yields respectively. Triflic acid mediated activation of imide carbonyls of **78** & **119** followed by intramolecular cyclization and reduction using $NaBH_4$/MeOH afforded the lactams **86** & **120** in 82% and 87% yields respectively. Reduction of lactam carbonyls in **86** & **120** by $LiAlH_4$ furnished the natural products (±)-harmicine (**79**) and (±)-desbromoarborescidine A (**121**) in 78% and 63% yields respectively.



Scheme 14. Synthesis of (±)-harmicine & (±)-desbromoarborescidine A via imide activation

Han and co-workers have reported a concise synthesis of (±)-mersicarpine (**131**) by using $Al(OTf)_3$ catalyzed facile construction of quarternary stereocentre via the allylic substitution of tertiary alcohol (Scheme 15).[70,71] Amidation of indole with succinic



Scheme 15. Synthesis of (±)-Mesicarpine

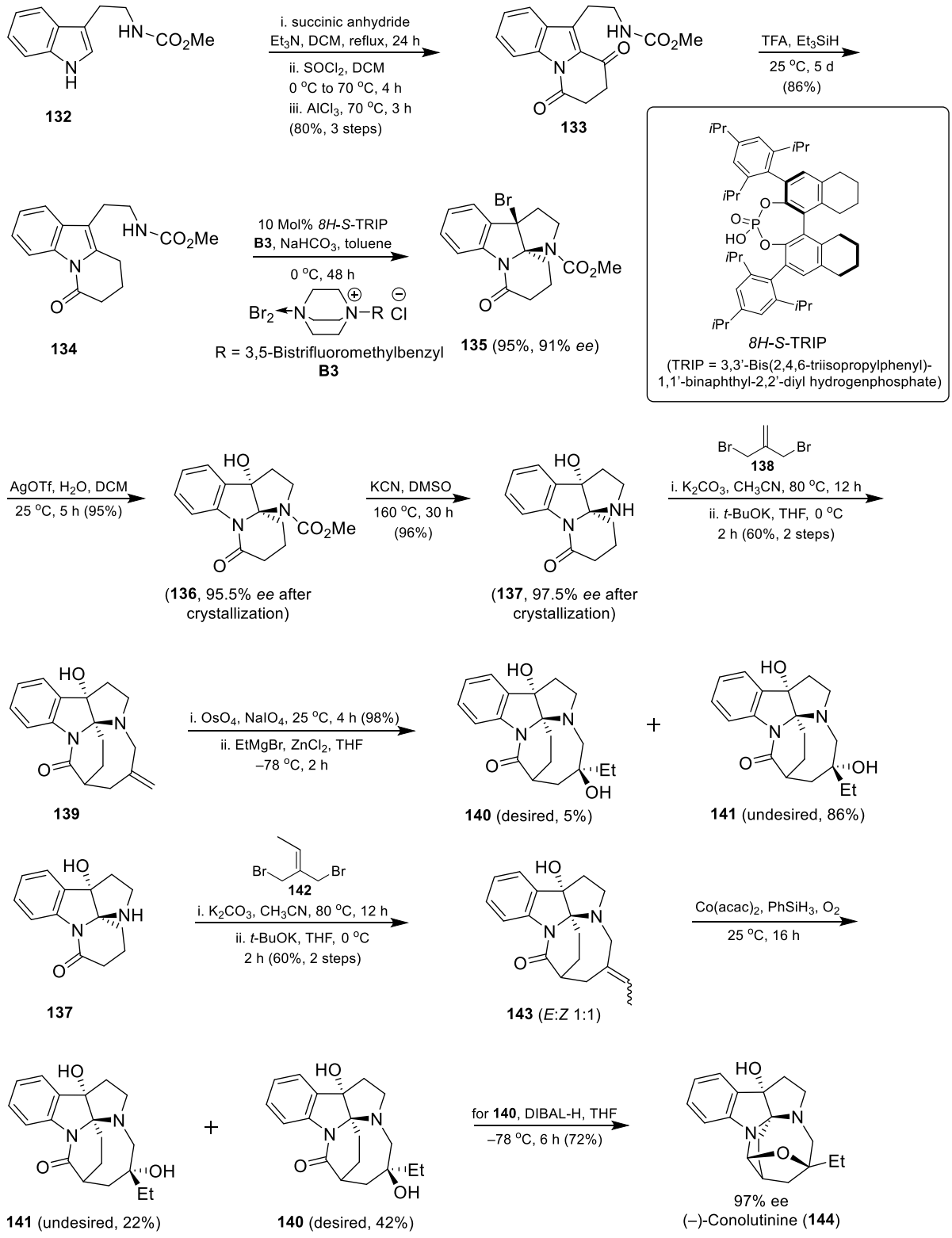
anhydride (**61**) provided the desired indole carboxylic acid **122** in quantitative yield. Compound **122** was transformed to tricyclic *δ*-lactam ketone **123** as a single regioisomer by using Friedel-Crafts acylation in 91% yield. Regioselective addition of EtMgCl to the keto-lactam **123** provided tertiary alcohol **124** in 74% yield using $ZnEt_2$ as an additive. $Al(OTf)_3$ catalyzed regioselective addition of silyl vinyl ether **125** to allylic alcohol **124** afforded the ketone **126** with the generation of quaternary carbon–carbon bond. Deprotection of nosyl group by $PhSH/K_2CO_3$ followed by reduction of the carbonyl group by modified one pot Wolff-Kishner protocol using tosyl hydrazide in the presence of oxalic acid, followed by an in situ reduction of the tosylhydrazone intermediate with a combination of $NaBH_3CN$, $Cu(OAc)_2$ and oxalic acid furnished the desired product **128** in 64% yield. Oxidation of compound **128** under Kerr's condition[72] proceeded cleanly to

furnish the indolone precursor **129** which after *N*-Boc deproctection using TFA in CH_2Cl_2 followed by replacing CH_2Cl_2 with ethyl acetate and overnight stirring the intermediate compound **130** afforded the natural product (±)-mersicarpine (**131**) in 58% yield (3 steps).

Conolutinine (**144**), a new member of terpenoid indole alkaloid was isolated from Malaysian *Tabernaemontana* by Kam and co-workers in 2009.[73] It shows interesting activity to reverse multidrug resistance in vincristine-resistant KB cells.[74] Its gross structure was determined by extensive 2 D NMR studies and the absolute configuration was empirically proposed via its hypothetical biosynthetic origin from velbanamine.

Xie and co-workers have reported first enantioselective synthesis of cyclotryptamine alkaloid (–)-conolutinine (**144**) by using asymmetric bromocyclization of tryptamine as a key step (Scheme 16).[74] Reaction of tryptamine derivative **132** with succinic anhydride followed by intramolecular Fridel-Crafts reaction provided the ketone **133** in 80% yield (3 steps). The ketone moiety of **133** was removed by using TFA/Et_3SiH to furnish indole **134** in 86% yield. Enantioselective intramolecular bromocyclizaton[75] of indole **134** by using DABCO-derived brominating agent **B3** and binapthol-derived chiral phosphoric acid catalyst *8H-S*-TRIP afforded 3-bromohexahydropyrrolo[2,3,-*b*]indole **135** in 95% yield and 91% *ee*. Hydrolysis of the bromide in **135** with the assistance of AgOTf provided hydroxyl-pyrroloindoline **136** in 95% yield, whose relative structure was established by X-ray crystallography data. The carbomethoxy group was cleaved by heating **136** with KCN in DMSO at 160 ^oC to provide pyrroloindoline **137** in 96% yield. The K_2CO_3 mediated *N*-allylation of amine **137** with allylic dibromide **138** followed by intramolecular cyclization using *t*-BuOK smoothly furnished the pentacycle **139** in 60% yield (2 steps). Oxidative cleavage of the exocyclic double bond in **139** followed by diastereoselective ethylation reaction of EtMgBr/$ZnCl_2$ with the formed ketone provided tertiary alcohol but unfortunately in favor of undesired isomer **141** (*dr* 1:15), indicating that the *β*-face of the pentacycle intermediate was sterically less crowded. For getting the desired diastereomer **140** as a major product; direct hydration of olefin was employed by taking advantage of the inherent spatial bias of the pentacycle framework. For this purpose pentacycle **143** was prepared from **137** and allylic dibromide **142** via alkylation and intramolecular cyclization. Metal mediated radical oxidation of hydrochloride salt of **143** using Mukaiyama's procedure[76] furnished the desired tertiary alcohol **140** in 42% yield. Partial reduction of the amide **140** by DIBAL-H to the geminal aminohydrin intermediate

followed by concomitant intramolecular acetal formation afforded the natural product (–)-conolutinine (**144**) in 72% yield.



Scheme 16. Xie's enantioselective synthesis of (–)-conolutinine

1.6 Summary

In summary, we have presented a concise account on alkaloids, their biological importance and their broad classifications. More emphasis has been given on the detailed classification of indole alkaloids along with the recent studies in their probable biosynthetic pathways. From the present discussion, it reveals that cyclic anhydrides and cyclic imides are versatile synthons in organic synthesis. These molecules with multiple functionalities have been effective in building the backbones of many structurally complex and medicinally important compounds in a convergent manner. Their efficacy as a potential starting material has been exemplified by the syntheses of various indole alkaloids e.g calothrixin B, harmicine, desbromoarborescidine A, tacamonine, rutaecarpine and more recently mersicarpine and conolutinine. We have tried our best to summarize cyclic anhydrides and cyclic imides to indole alkaloids chemistry; however no pretension of completion has been claimed. Since two decades, our group has been actively involved in the synthesis of bioactive natural and unnatural products using cyclic anhydrides and their derivatives as a potential starting material. In this context, our synthetic studies towards tetrahydro-β-carbolines, vinca-eburna and tacaman alkaloids have been presented using appropriate cyclic imides as a versatile synthons. We have successfully synthesised (+)-harmicine, (S)-desbromoarborescidine A–C, (S)-deplancheine by using stereoselective reductive cyclization of appropriate (R)/(S)-acetoxy succinimide/glutarimide derivatives and exchange of nitrogen regioselectivity. We have been also successful in the synthesis of indole alkaloids (+)-3-epitacamonine, (–)-vindeburnol, (±)-eburnamonine, (±)-melohenine B, (±)-eburnaminol and (±)-larutensine by using stereoselective ester-aldol reactions of hexahydroindolo[2,3-a]quinolizinones. The above specified synthesis will be discussed in chapter 2 and 3 of the present dissertation.

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Chapter 2

Studies on the Synthesis of Tetrahydro-*β*-Carboline Alkaloids

This chapter features the following topics:

Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

This chapter is divided into two sections.

The **Section A** presents the synthesis of (+)-harmicine by using stereoselective *N*-acyliminium ion cyclization as a key step (figure).

The **Section B** describes enantioselective total synthesis of desbromoarborescidines A–C and the formal Synthesis of (*S*)-deplancheine. This section presents an efficient use of (*S*)-acetoxyglutarimide derivative as a chiral building block for the stereoselective synthesis of tetrahydro-*β*-carboline alkaloids.

The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end of each section.

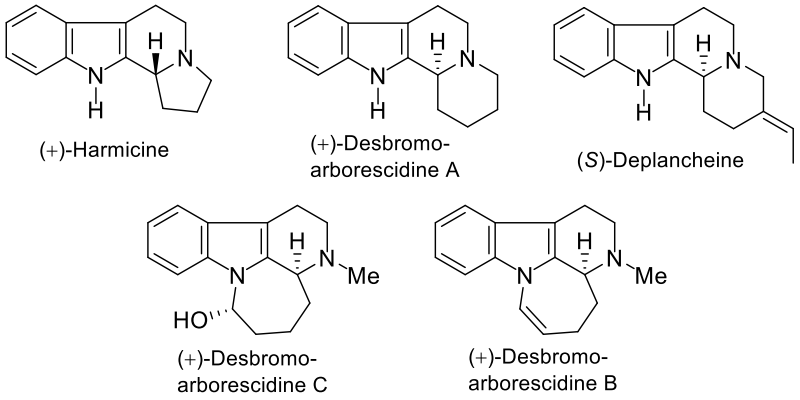


Figure. Natural and unnatural bioactive tetrahydro-*β*-carboline alkaloids synthesized

Chapter 2: Section A

Synthesis of (+)-Harmicine

This section A of chapter 2 features the following topics:

2A.1 Background

Tetrahydro-*β*-carbolines (TH*β*Cs) are biologically active alkaloids which are found in mammalian tissues, fluids, brain and also in plant sources (Figure 1). They show a variety of potent pharmacological and biological activities. Fruit containing TH*β*Cs act as an antioxidants and free radical scavengers.[1]

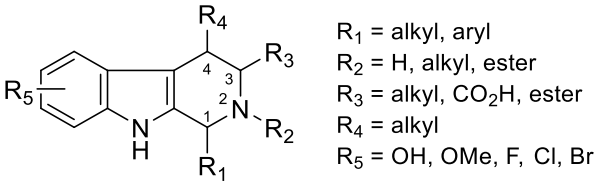


Figure 1. General representation of tetrahydro-*β*-carbolines

Harmicine (**1**) is a chiral tetrahydro-*β*-carboline with the presence of a rare tetracyclic pyrrolidine skeleton. It was isolated from the leaves of Malaysian plant *Kopsia griffithii* in 1997 by Kam and co-workers.[2] Structurally, it consists of an indole unit and an indolizidine unit. A few examples of this class are reserpine (**2**, antipsychotic and antihypertensive drug),[3] vellosimine (**3**, curare-like activity)[4] and vincamine (**4**, peripheral vasodilator).[5] Tadalafil (**5**),[6] a TH*β*C scaffold containing compound is currently one of the highest selling synthetic drug in the market (Figure 2).

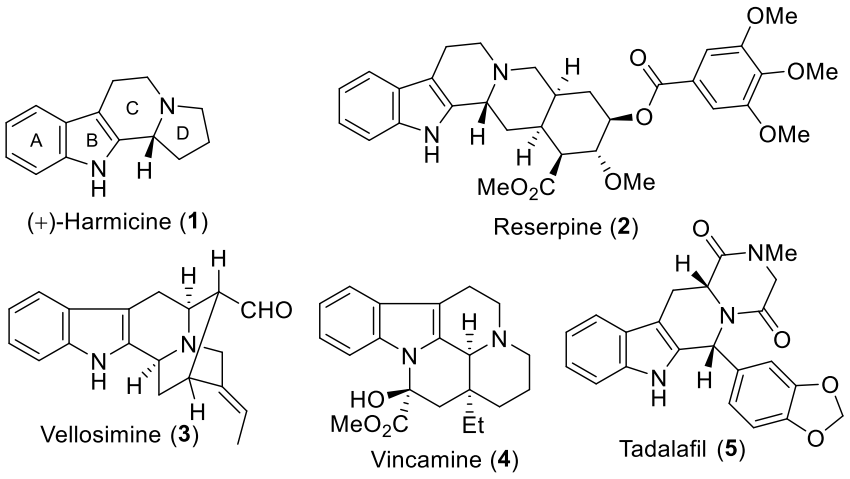


Figure 2. Tetrahydro-*β*-carboline unit containing natural and unnatural bioactive compounds

Harmicine exhibits potential antileishmanial and antinociceptive activities.[7,8] Harmicine together with its analogues have been found to possess α_2-adrenoceptor affinity.[9] Even though the TH*β*C pyrrolidine scaffold present in harmicine is rare, still it exists in few

structurally similar indole alkaloids like compound **6**,[10] recently isolated four L-tryptophan derived pyrrolidines (**7a-d**),[11,12] the more complex bridged tabertinggine (**8**),[13] the bridged quaternary salts subincanadine A-G (**9a-d**),[14,15] excelsinidine (**10**)[16] and in 17-norexcelsinidine (**11**)[17] (Figure 3).

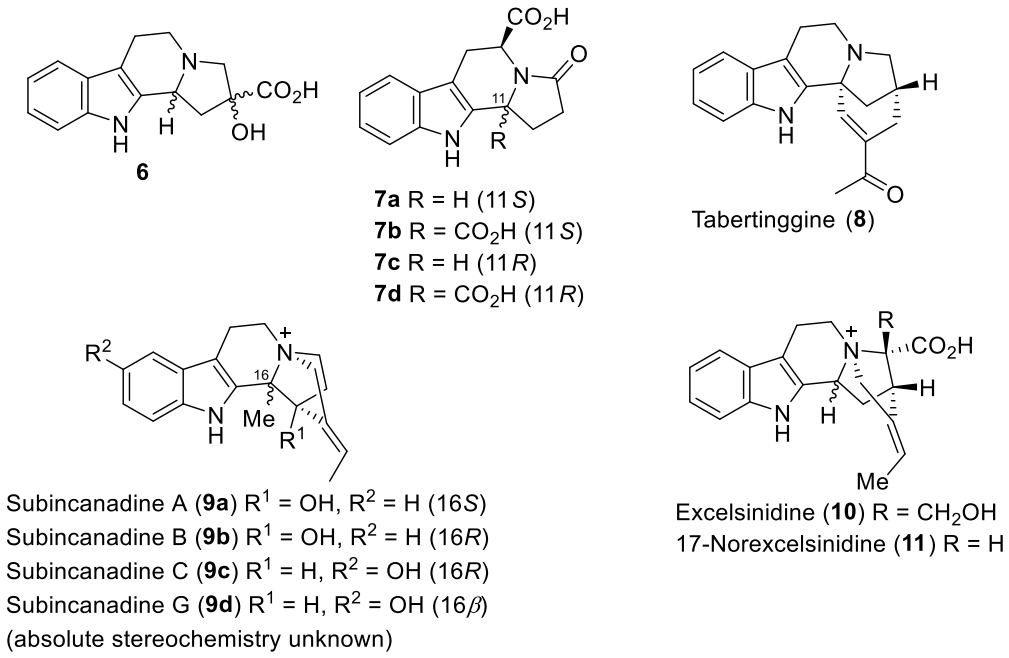


Figure 3. Alkaloids containing the harmicine framework

2A.2 Brief Account of Harmicine Syntheses

A well number of approaches for the synthesis of harmicine are known. Prior to its isolation, it was synthesized by five different groups in racemic form. Harmicine was first prepared by Ashcroft et al. in 1981.[18] In those cases it was a relatively simple but important hetereocyclic template for making complex molecules and also an appropriate substrate for exploring methodological studies. After its isolation from natural resources, harmicine became a important target compound. The first asymmetric synthesis for the unnatural (–)-harmicine was reported by Oshawa in 2002.[19] Czarnocki and co-workers reported the first asymmetric synthesis of the natural isomer (+)-harmicine by using asymmetric transfer hydrogenation (ATH) of an iminium salt employing ruthenium catalyst in 2007.[20] Recently, shortest synthesis of (±)-harmicine has been reported by Sanaboina et al. utilising a Pictet-Spengler cascade reaction between tryptamine and 4-chlorobutyraldehyde.[21] Jacobsen and co-workers have reported an elegant asymmetric synthesis of (+)-harmicine by using enantioselective Pictet-Spengler type reactions utilizing chiral thiourea organocatalyst.[22] Harmicine has been extensively reviewed on

three recent occasions.[23-25] However to avoid the repetition of the contents present in those nicely drafted reviews, a brief schematic presentation of the syntheses of harmicine is given below in figures 4 to 6.

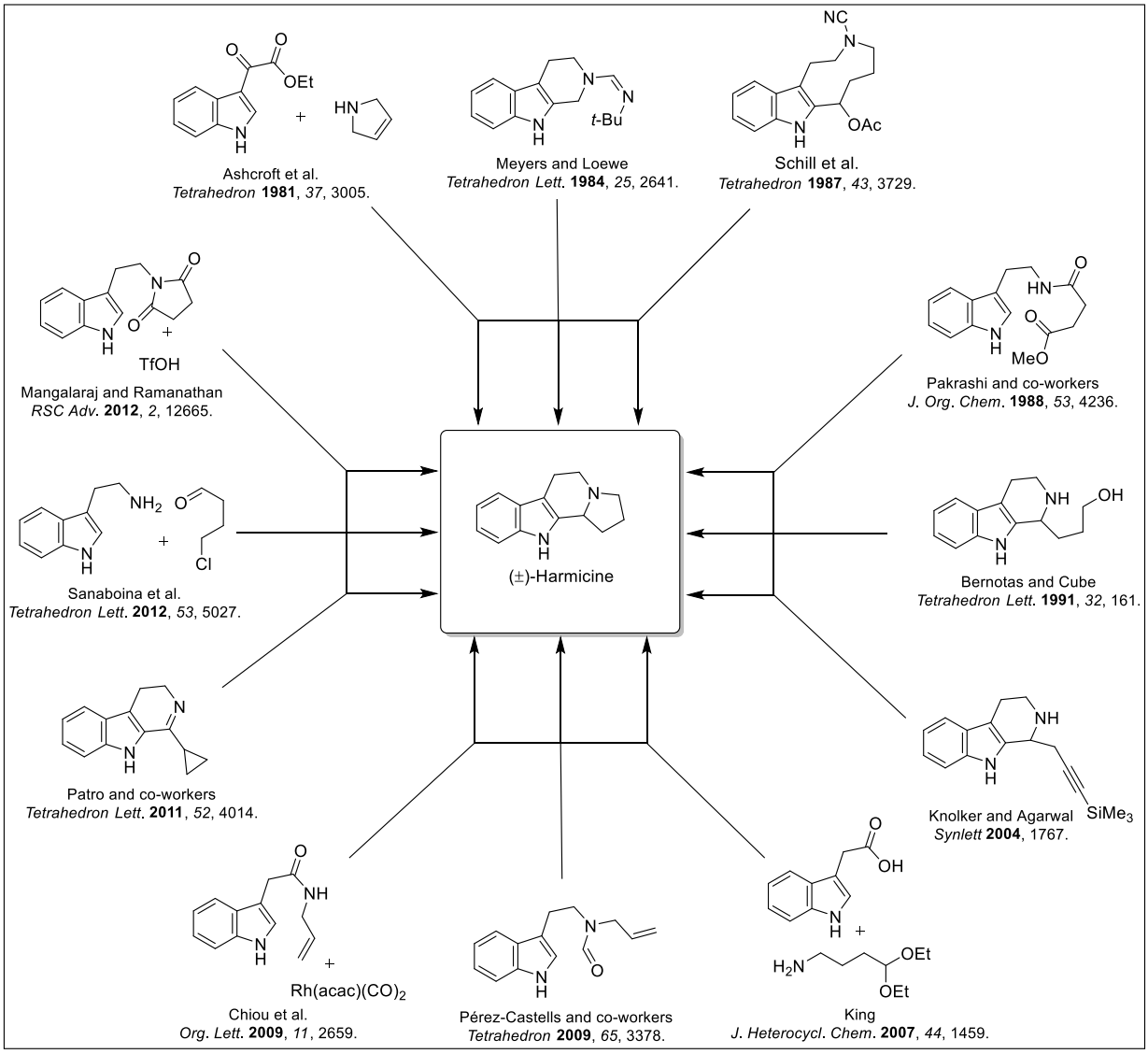


Figure 4. Schematic representation of (±)-harmicine syntheses

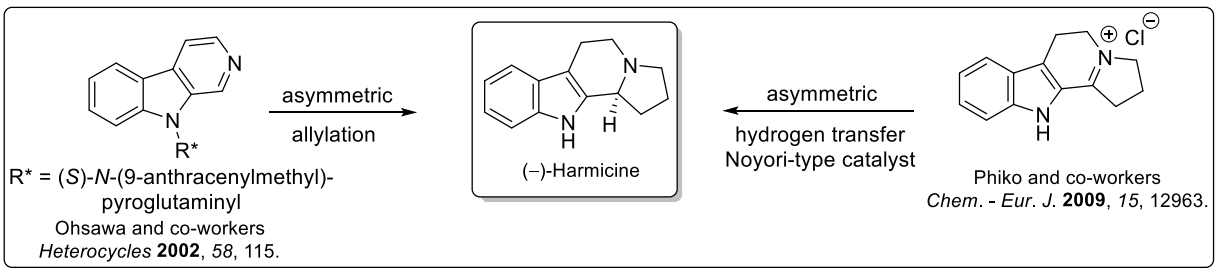


Figure 5. Schematic representation of (–)-harmicine syntheses

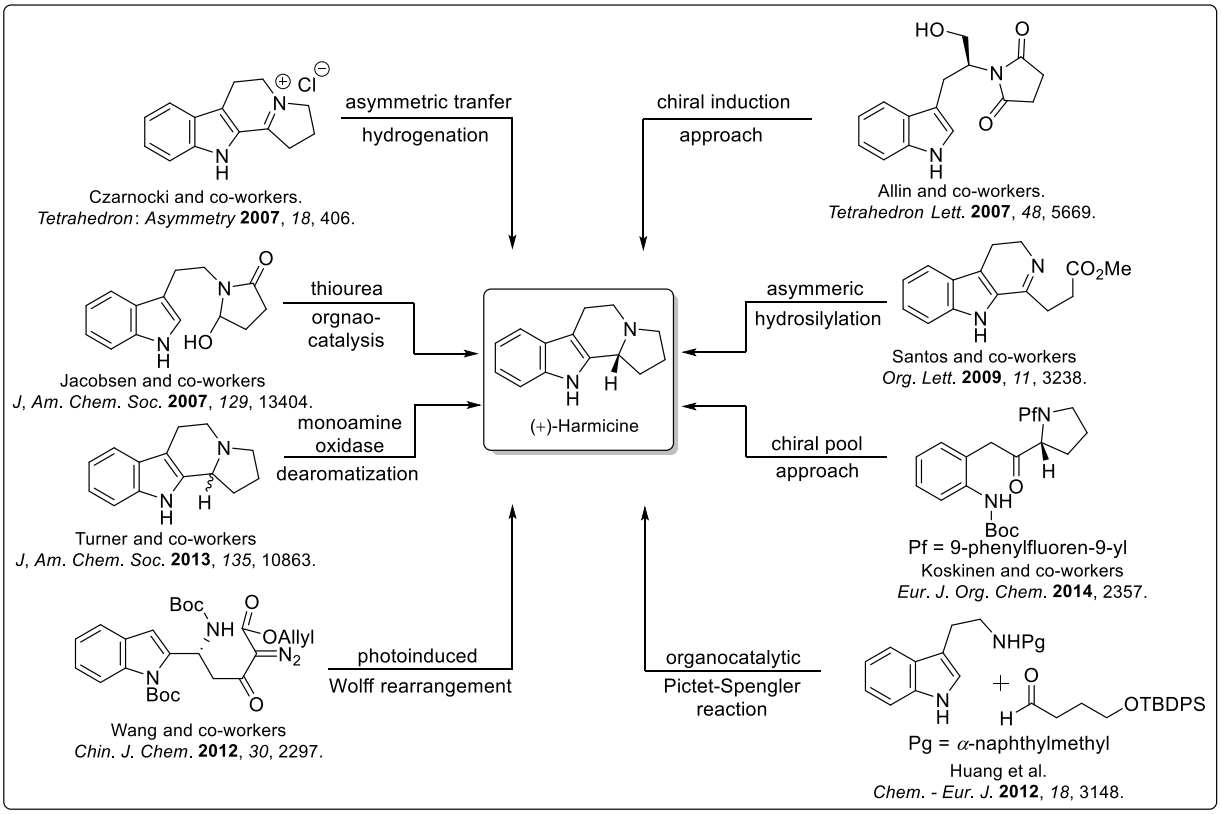
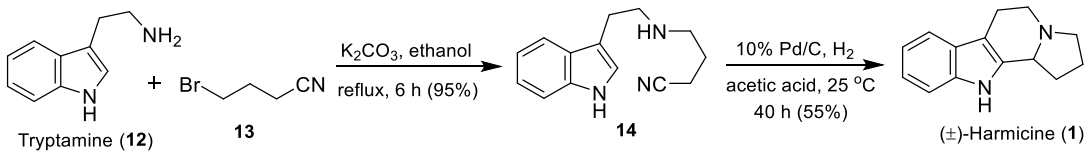


Figure 6. Schematic representation of (+)-harmicine syntheses

There has been continuous study for the synthesis of harmicine and its analogues due to their potent biological activity.[7] Very recently, Kusurkar and Pakhare have reported synthesis of (±)-harmicine[26] after the publication of recent review article. The reductive Pictet-Spengler cyclization, where the cyano group was used instead of corresponding aldehyde with the amine for the synthesis of tetrahydro-*β*-carbonyls and *β*-carbonyls. Thus the reaction of tryptamine (**12**) and 4-bromobutyronitrile (**13**) provided compound **14** with the selective monosubstitution. Treatment of **14** with 10% Pd/C in acetic acid under hydrogen atmosphere at 25 ^{o}C provided (±)-harmicine as a major product (Scheme 1).

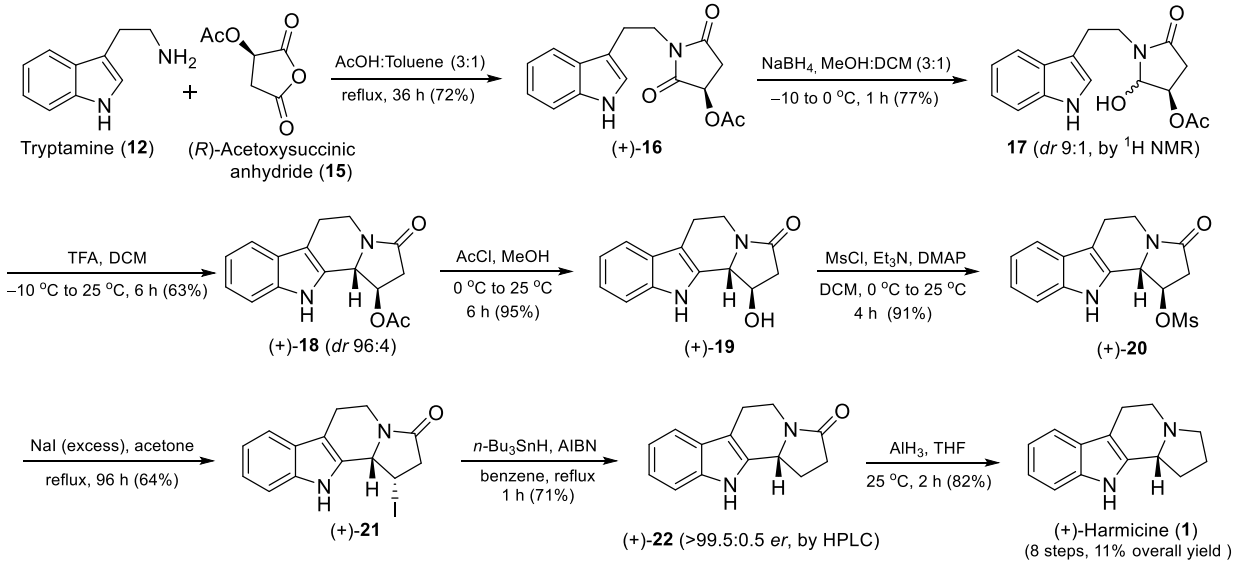


Scheme 1. Kusurkar's synthesis of (±)-harmicine

2A.3 Results and Discussion: Present Work

A careful scrutiny of harmicine structure revealed that retro-synthetically tryptamine and (*R*)-acetoxysuccinic anhydride would be the potential building blocks to stereoselectively constitute a total synthesis of the target compound.

The reaction of tryptamine (**12**) with (*R*)-acetoxysuccinic anhydride (**15**) in refluxing acetic acid and toluene mixture furnished (*R*)-acetoxysuccinimide **16** in 72% yield. Mechanistically, the regioselective nucleophilic ring opening of an unsymmetrical anhydride **15** at more reactive carbonyl group adjacent to a acetate function to form the corresponding succinanilic acid intermediate followed by intramolecular dehydrative cyclization delivered the desired imide product (+)-**16**. The regioselective sodium borohydride reduction of more reactive imide carbonyl group in compound **16** provided lactamol **17** in 77% yield with ~9:1 diastereomeric ratio (by ^{1}H NMR). Such type of lactamol units is known to display the ring–chain tautomerism[27] and hence to keep the complete control on diastereoselectivity is a difficult task. The intramolecular cyclization of relatively less stable lactamol **17** to product **18** by using sulfuric acid adsorbed on silica gel or the BF_3;Et_2O were not efficient and we could get the required product only in 35–40% yield. However under a controlled reaction conditions, the chemoselective trifluoroacetic acid induced intramolecular *N*-acyliminium cyclization of a masked aldehyde in **17** at –10 °C to rt furnished the desired cyclized product (+)-**18** in very good yield with high stereoselectivity (63%, 24:1 *dr*). In the above specified reaction use of organic acid as a reagent at lower reaction temperature was essential for a stability



Scheme 2. Stereoselective total synthesis of (+)-harmicine

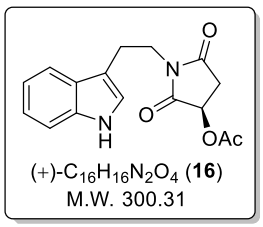
issue of starting material. In this *N*-acyliminium cyclization the high degree of diastereoselectivity is attributed to the formation of flat iminium ion intermediate followed by the stereoselective intramolecular nucleophilic attack from the less hindered α-side. The formation of product **18** as a major isomer could also be ascribed to the relatively more thermodynamic stability of the formed isomer. The mixture of diastereoisomers **18** was quantitatively separated by using silica gel column chromatography. The major isomer (+)-**18** on treatment with AcCl/MeOH underwent a smooth deacylation reaction to exclusively provide the product (+)-**19** in 95% yield. In the above specified reaction, release of a controlled amount of hydrochloric acid was responsible for deacylation. At this stage the detachment of stereoselectivity handle, the (*R*)-hydroxyl group in compound **19** was desired to obtain the product (*R*)-**22**. As expected first the secondary alcohol (+)-**19** was converted to the corresponding mesylate derivative (+)-**20** in 91% yield. The compound (+)-**20** on treatment with excess NaI in refluxing acetone for 96 h provided the iodo compound (+)-**21** in 64% yield with an inversion of configuration due to S_N2 type displacement by the iodide as a nucleophile. The compound (+)-**21** on de-iodination by using tributyltin hydride in presence of AIBN gave the desired chiral product (+)-**22** in 71% yield (>99.5:0.5 *er*, by HPLC). Finally alane-mediated reduction of γ-lactam to cyclic amine furnished the enantiomerically pure alkaloid (+)-**1** in 82% yield. The analytical and spectral data obtained for the (+)-harmicine (**1**) was in complete agreement with the reported data[22] and it was obtained in linear 8-steps with 11% overall yield.[28]

2A.4 Summary

In summary, tryptamine and (R)-acetoxysuccinic anhydride were synthetically tailored to (+)-harmicine in a sequential fashion via dehydrative coupling, regioselective reduction, stereoselective intramolecular cyclization, overall deoxygenation and reduction pathway in very good overall yield with high enantiomeric purity. Specifically, the synthesis of enantiomerically pure (+)-harmicine has been accomplished from readily available staring materials using simple reaction conditions and in absence of transition metal catalysis. The present route is general in nature and will be useful to design the focused mini-library of its analogs and congeners for SAR studies.

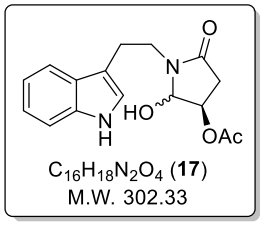
2A.5 Experimental Section

(+)-(*R*)-1-(2-(1*H*-Indol-3-yl)ethyl)-2,5-dioxopyrrolidin-3-yl Acetate (16). To a stirred suspension of tryptamine (**12**, 2.00 g, 12.50 mmol) in toluene (10 mL) was added (*R*)-acetoxysuccinic anhydride (**15**, 1.97 g, 12.50 mmol) and the reaction mixture was stirred for 10 min. AcOH (20 mL) was added to the above reaction mixture and it was refluxed for 36 h. Reaction mixture was allowed to cool to 25 ^{o}C and concentrated in vacuo. To the obtained residue was added ethyl acetate (50 mL) and the organic layer was washed with saturated $NaHCO_3$ solution (20 mL × 2), brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the obtained residue by using petroleum ether–ethyl acetate (1:1) as an eluent yielded (*R*)-acetoxysuccinimide (+)-**16** as a white solid (2.70 g, 72% yield). Mp 126–128 °C; $[\alpha]^{25}_{D}$ +19.6 (*c* 0.10 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.58 (dd, *J* = 20 and 6 Hz, 1H), 3.07 (dd, *J* = 18 and 8 Hz, 1H), 3.09 (t, *J* = 8 Hz, 2H), 3.87 (t, *J* = 8 Hz, 2H), 5.30 (dd, *J* = 9 and 6 Hz, 1H), 7.00–7.28 (m, 3H), 7.36 (d, *J* = 6 Hz, 1H), 7.66 (d, *J* = 6 Hz, 1H), 8.06 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5, 23.1, 35.6, 39.8, 67.3, 111.2, 111.7, 118.5, 119.5, 122.1, 122.2, 127.3, 136.1, 169.8, 173.2, 173.4; ESIMS (*m*/*z*) 323 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{16}N_2O_4Na$ 323.1002, found 323.1001; IR (neat) 3429, 1735, 1696 cm^{-1}.



(+)-$C_{16}H_{16}N_2O_4$ (**16**)
M.W. 300.31

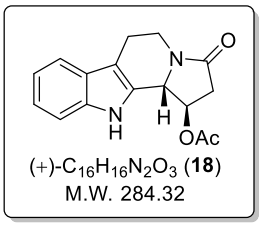
(3*R*)-1-(2-(1*H*-Indol-3-yl)ethyl)-2-hydroxy-5-oxopyrrolidin-3-yl Acetate (17). To a stirred solution of (*R*)-acetoxysuccinimide **16** (2.00 g, 6.66 mmol) in MeOH:CH_2Cl_2 (2:1, 30 mL) was periodically added $NaBH_4$ (304 mg, 8.00 mmol) at –10 ^{o}C over 5 min. The reaction mixture was stirred at 0 ^{o}C for 1 h and quenched with a mixture of saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL). The reaction mixture was extracted with CH_2Cl_2 (50 mL × 3) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the obtained residue by using ethyl acetate–petroleum ether (80:20) as an eluent afforded lactamol **17** (9:1 *dr*, by ^{1}H NMR) as white foam (1.55 g, 77% yield). **Major isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.59 (ddd, *J* = 20, 18 and 10 Hz, 2H), 2.95–3.11 (m, 2H), 3.53 (quintet, *J* = 5 Hz, 1H), 3.50–3.65 (br s, 1H), 3.80 (quintet, *J* = 5 Hz, 1H), 5.01 (q, *J* = 5 Hz, 1H), 5.08 (br s, 1H), 6.97 (s, 1H), 7.11 (t, *J* = 10 Hz, 1H), 7.19 (t, *J* = 10 Hz, 1H), 7.34 (d, *J* = 10 Hz, 1H),



$C_{16}H_{18}N_2O_4$ (**17**)
M.W. 302.33

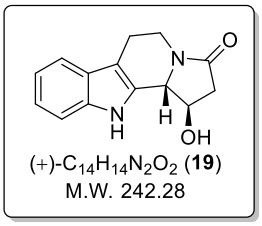
7.61 (d, J = 10 Hz, 1H), 8.26 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 23.5, 34.9, 41.0, 67.8, 82.1, 111.3, 112.6, 118.5, 119.4, 122.0, 122.1, 127.2, 136.2, 170.4, 171.2; ESIMS (m/z) 325 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{18}N_2O_4Na$ 325.1159, found 325.1152; IR ($CHCl_3$) 3331, 1740, 1667 cm^{-1}.

(+)-(1*R*,11b*S*)-3-Oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl Acetate (18). To a stirred solution of lactamol **17** (1.50 g, 4.96 mmol) in CH_2Cl_2 (30 mL) at −10 °C was added TFA (1.00 mL, 12.4 mmol) and the reaction mixture was stirred at −10 °C to 25 °C for 6 h. The reaction was quenched with saturated aq. $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by the silica gel (230–400 mesh) column chromatographic purification of the obtained residue by using ethyl acetate–petroleum ether (70:30) as an eluent afforded a minor diastereomer (35 mg, 2.5%) and the required major diastereomer (+)-**18** as a yellowish solid (853 mg, 60.5% yield). **Major isomer 18**: Mp 140–142 °C; $[\alpha]^{25}_D$ +75.6 (c 0.16 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.65–3.20 (m, 5H), 4.57 (dd, J = 9 and 6 Hz, 1H), 4.85 (br d, J = 4 Hz, 1H), 5.28 (ddd, J = 10, 5 and 2 Hz, 1H), 7.05–7.55 (m, 4H), 9.23 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5, 21.1, 36.7, 38.0, 63.1, 71.5, 109.0, 111.3, 118.3, 119.6, 122.5, 126.5, 129.9, 136.0, 170.4, 172.3; ESIMS (m/z) 307 $[M+Na]^+$; HRMS (ESI) calcd for $C_{16}H_{16}N_2O_3Na$ 307.1053, found 307.1052; IR (neat) 1772, 1736, 1677 cm^{-1}.



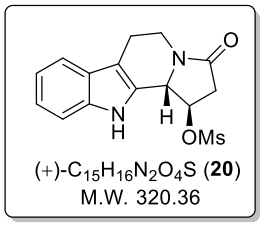
(+)-$C_{16}H_{16}N_2O_3$ (**18**)
M.W. 284.32

(+)-(1*R*,11b*S*)-1-Hydroxy-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (19). To a stirred solution of acetate **18** (850 mg, 3.00 mmol) in MeOH (20 mL) at 0 °C was dropwise added AcCl (3 mL, 42 mmol). The ice bath was removed and reaction mixture was stirred at 25 °C for 6 h and concentrated in vacuo. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification by using ethyl acetate–methanol (98:2) as an eluent afforded pure product (+)-**19** as a white solid (688 mg, 95% yield). Mp 182–184 °C; $[\alpha]^{25}_D$ +139.3 (c 0.62 MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 2.45–2.90 (m, 4H), 2.95–3.15 (m, 1H), 4.22–4.50 (m, 2H), 4.63 (br s, 1H), 4.75 (d, J = 4 Hz, 1H), 6.93–7.15 (m, 2H), 7.25–7.50 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 21.8, 38.5, 41.7, 63.7, 72.1, 108.4, 112.2, 118.9, 120.1, 122.7, 128.0, 132.6, 138.4, 173.7;

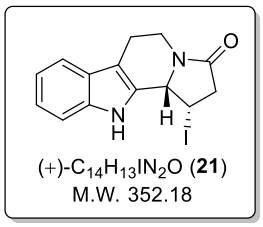


(+)-$C_{14}H_{14}N_2O_2$ (**19**)
M.W. 242.28

ESIMS (*m*/*z*) 243 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{14}N_2O_2Na$ 265.0947, found 265.0947; IR (neat) 3196, 1651 cm^{-1}.

(+)-(1*R*,11b*S*)-3-Oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl Methanesulfonate (20). 

Anhydrous Et_3N (0.62 mL, 4.46 mmol) was added to a stirred solution of alcohol **19** (600 mg, 2.48 mmol) and DMAP (61 mg, 0.50 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon atmosphere. To the above reaction mixture was added methanesulfonyl chloride (0.29 mL, 3.72 mmol) and it was allowed to reach 25 °C and further stirred for 4 h. The concentration of reaction mixture in vacuo followed by direct silica gel (60–120 mesh) column chromatographic purification of the obtained residue by using petroleum ether–ethyl acetate (60:40) as an eluent afforded mesylate (+)-**20** as a yellow solid (722 mg, 91% yield). Mp 86–88 °C; $[\alpha]^{25}_D$ +73.2 (*c* 0.10 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.70–3.15 (m, 5H), 3.22 (s, 3H), 4.50–4.65 (m, 1H), 5.10–5.20 (m, 1H), 5.25–5.42 (m, 1H), 7.05–7.25 (m, 2H), 7.38 (d, *J* = 8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 1H), 8.89 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.6, 37.6, 37.8, 38.6, 61.3, 75.8, 109.8, 111.5, 118.4, 119.9, 122.8, 126.3, 128.9, 136.4, 168.7; ESIMS (*m*/*z*) 343 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_4S$ 321.0904, found 321.0901; IR (neat) 1681 cm^{-1}.

(+)-(1*S*,11b*S*)-1-Iodo-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (21). 

To a stirred solution of mesylate **20** (200 mg, 0.63 mmol) in anhydrous acetone (15 mL) was added excess of NaI (1.88 g, 12.6 mmol) and the reaction mixture was refluxed for 96 h. The reaction mixture was concentrated in vacuo and the obtained residue on direct silica gel (230–400 mesh) column chromatographic purification by using ethyl acetate–petroleum ether (80:20) as an eluent afforded the product (+)-**21** as foam (140 mg, 64% yield). $[\alpha]^{25}_D$ +326 (*c* 0.05 $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50–3.05 (m, 4H), 3.40 (m, 1H), 4.31 (d, *J* = 12 Hz, 1H), 4.57 (br s, 1H), 5.08 (br s, 1H), 6.99 (t, *J* = 8 Hz, 1H), 7.08 (t, *J* = 8 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H), 10.99 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.9, 31.5, 37.2, 45.9, 59.1, 108.3, 111.6, 118.5, 119.0, 121.7, 126.3, 134.0, 136.4, 170.6; ESIMS (*m*/*z*) 375 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{13}N_2OINa$ 374.9965, found 374.9957; IR (neat) 3021, 1679 cm^{-1}.

(+)-(*R*)-1,2,5,6,11,11b-Hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (22). To a stirred solution of iodide **21** (100 mg, 0.28 mmol) and AIBN (5 mg, 0.03 mmol) in dry benzene (8 mL) was added *n*-Bu_3SnH (0.15 mL, 0.56 mmol) at 25 °C and the reaction mixture was stirred for 15 min under argon atmosphere. Then the reaction mixture was refluxed for 1 h and benzene was distilled off in vacuo. The obtained residue was dissolved in acetonitrile (20 mL) and washed with hexane (15 mL × 3). Concentration of acetonitrile layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using ethyl acetate–methanol (95:5) as an eluent afforded product (+)-**22** as a white solid (46 mg, 71% yield; >99.5:0.5 *er*, by HPLC). Mp 242–244 °C; lit.[29] 250 °C; $[\alpha]^{25}_D$ +238 (*c* 0.05 $CHCl_3$); lit.[29] $[\alpha]^{25}_D$ +234 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90–2.00 (m, 1H), 2.47–2.68 (m, 3H), 2.80–2.91 (m, 2H), 3.00–3.08 (m, 1H), 4.55 (ddd, *J* = 8, 5 and 5 Hz, 1H), 4.95 (dt, *J* = 8 and 5 Hz, 1H), 7.13 (t, *J* = 10 Hz, 1H), 7.20 (t, *J* = 10 Hz, 1H), 7.35 (d, *J* = 10 Hz, 1H), 7.50 (d, *J* = 10 Hz, 1H), 8.05 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 25.7, 31.6, 37.6, 54.2, 108.4, 111.0, 118.5, 119.9, 122.3, 126.8, 133.1, 136.3, 173.2; ESIMS (*m*/*z*) 249 $[M+Na]^+$; IR (neat) 3244, 1772, 1661 cm^{-1}.

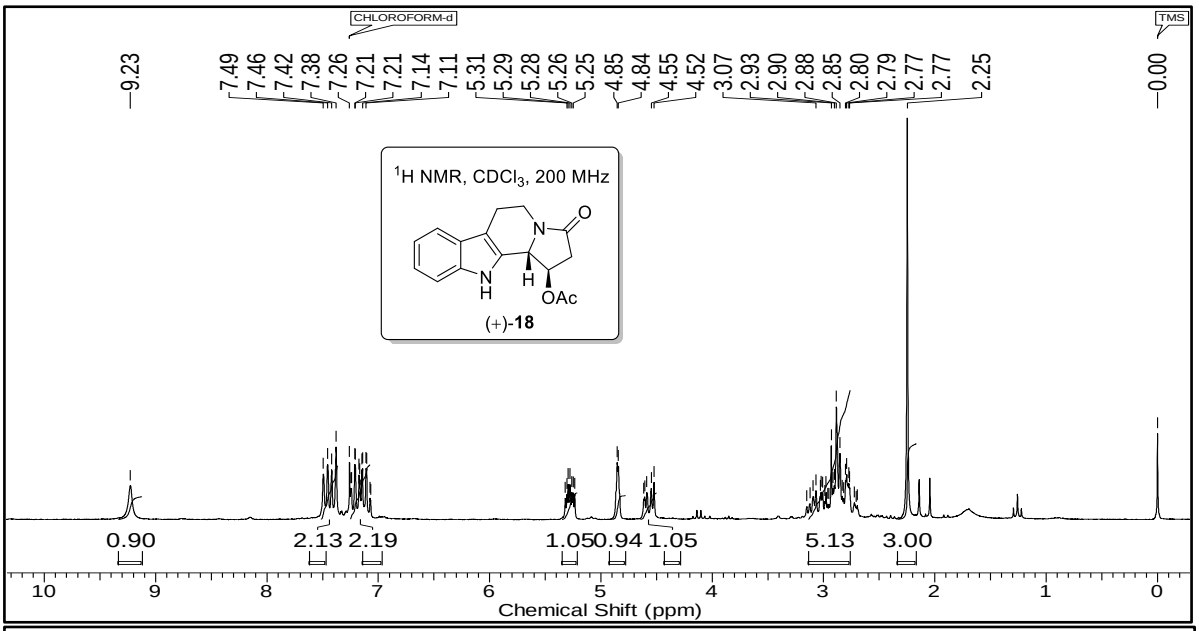
(+)-$C_{14}H_{14}N_2O$ (**22**)
M.W. 226.28

(+)-(*R*)-2,3,5,6,11,11b-Hexahydro-1*H*-indolizino[8,7-*b*]indole (Harmicine, 1). To a stirred slurry of $AlCl_3$ (20 mg, 0.15 mmol) in THF (4 mL) was added suspension of $LiAlH_4$ (19 mg, 0.50 mmol) in THF (2 mL) at 0 °C under argon atmosphere. After stirring for 10 min, solution of lactam **22** (40 mg, 0.18 mmol) in THF (2 mL) was added to the above reaction mixture in a dropwise manner and it was stirred for 2 h at 25 °C. The reaction was quenched with saturated aq. NH_4Cl (2 mL) and it was filtered through Celite pad. The residue was washed with ethyl acetate (10 mL × 3) and the filtrate was dried over Na_2SO_4 and concentrated in vacuo. Silica gel (230–400 mesh) column chromatographic purification of the obtained residue by using chloroform–methanol (80:20) as an eluent afforded (+)–harmicine (**1**) as a yellowish solid (31 mg, 82% yield). Mp 158–160 °C; lit.[29] 160–161 °C; $[\alpha]^{25}_D$ +98 (*c* 0.1 $CHCl_3$); lit.[29] $[\alpha]^{25}_D$ +105 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75–2.00 (m, 3H), 2.24–2.38 (m, 1H), 2.65–2.80 (m, 1H), 2.85–3.05 (m, 3H), 3.05–3.20 (m, 1H), 3.30–3.40 (m, 1H), 4.32 (br s, 1H), 7.11 (t, *J* = 8 Hz, 1H), 7.16 (t, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 8.43 (br s, 1H); ^{13}C NMR

(+)-Harmicine (**1**)
$C_{14}H_{16}N_2$
M.W. 212.30

(100 MHz, $CDCl_3$) δ 17.7, 23.2, 29.5, 46.0, 49.5, 57.2, 107.3, 110.9, 118.0, 119.3, 121.5, 127.0, 134.4, 136.1; ESIMS (*m*/*z*) 213 $[M+H]^+$; IR (neat) 2922, 1449 cm^{-1}.

2A.6 Selected Spectra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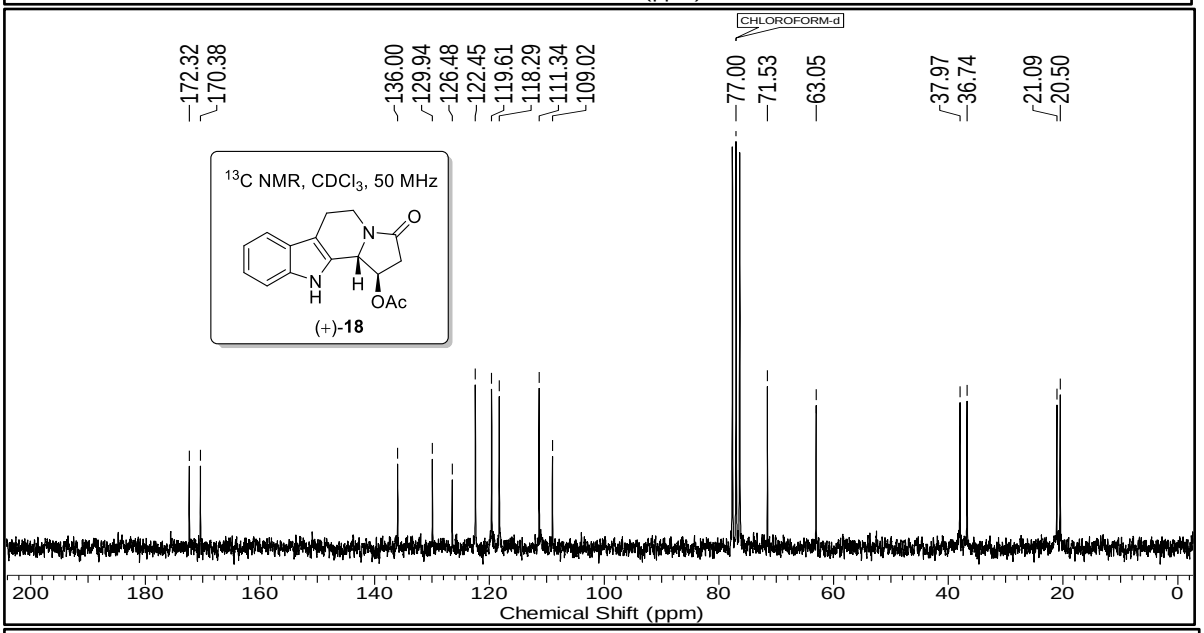
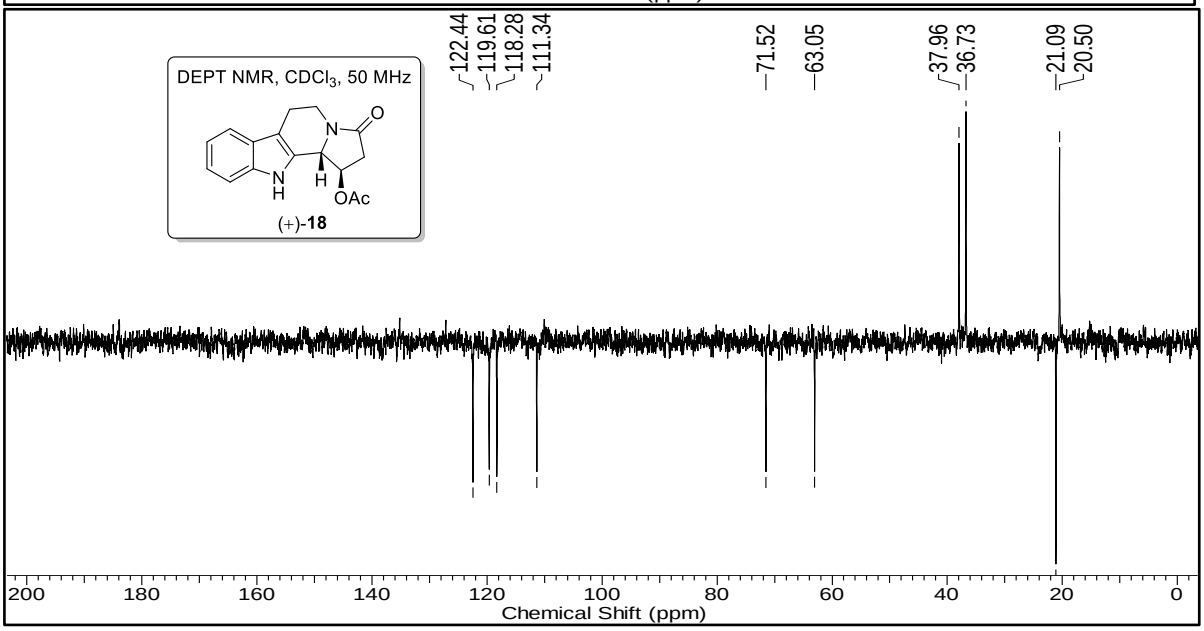
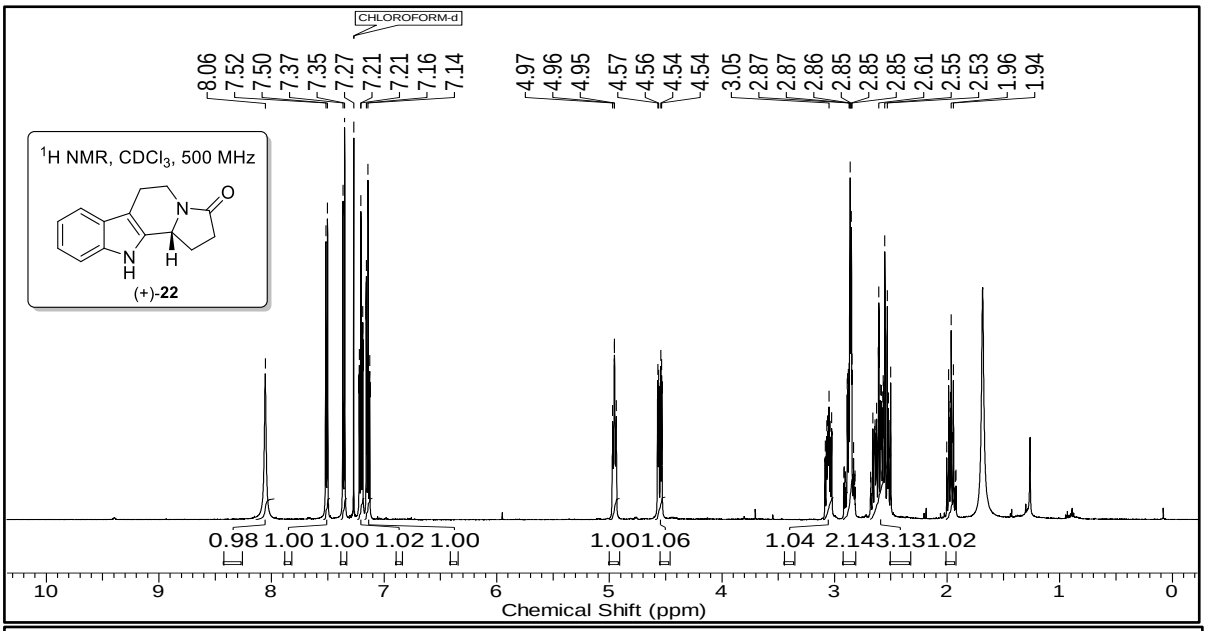
5.31 5.29 5.28 5.26 5.25
4.85 4.84 4.55 4.52
3.07 2.93 2.90 2.88 2.85 2.80 2.79 2.77 2.77 2.25
0.00
^{1}H NMR, $CDCl_3$, 200 MHz
(+)-18
0.90 2.13 2.19 1.05 0.94 1.05 5.13 3.00
Chemical Shift (ppm)


CHLOROFORM-d
172.32 170.38
136.00 129.94 126.48 122.45 119.61 118.29 111.34 109.02
77.00 71.53 63.05
37.97 36.74
21.09 20.50
^{13}C NMR, $CDCl_3$, 50 MHz
(+)-18
Chemical Shift (ppm)


122.44 119.61 118.28 111.34
71.52 63.05
37.96 36.73
21.09 20.50
DEPT NMR, $CDCl_3$, 50 MHz
(+)-18
Chemical Shift (ppm)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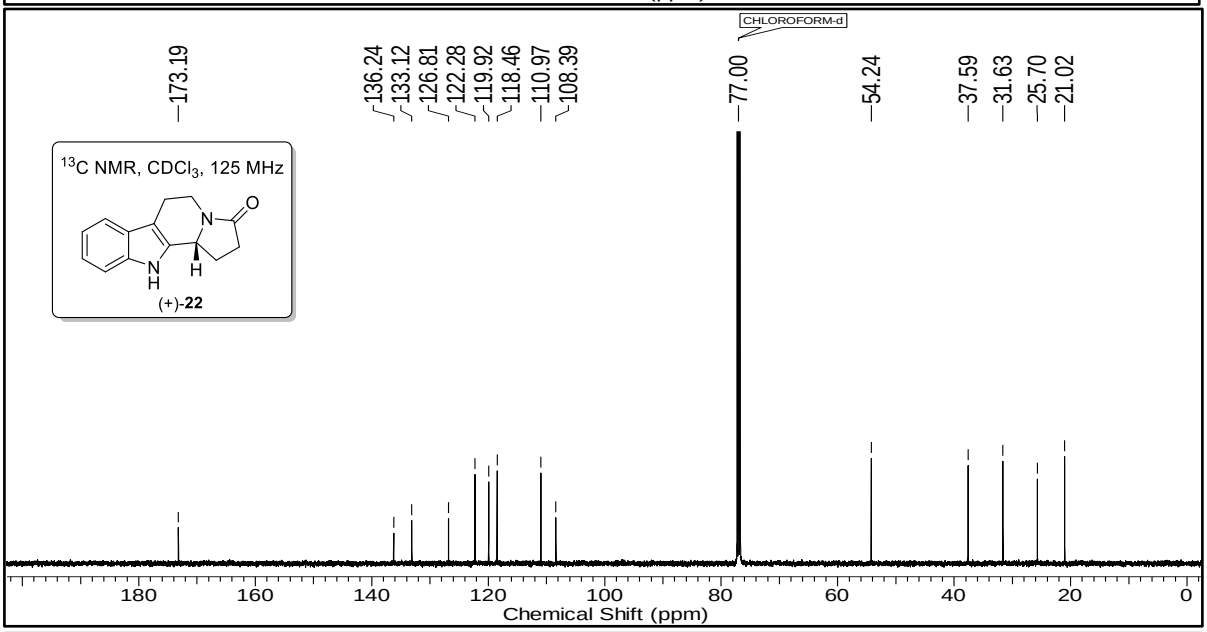
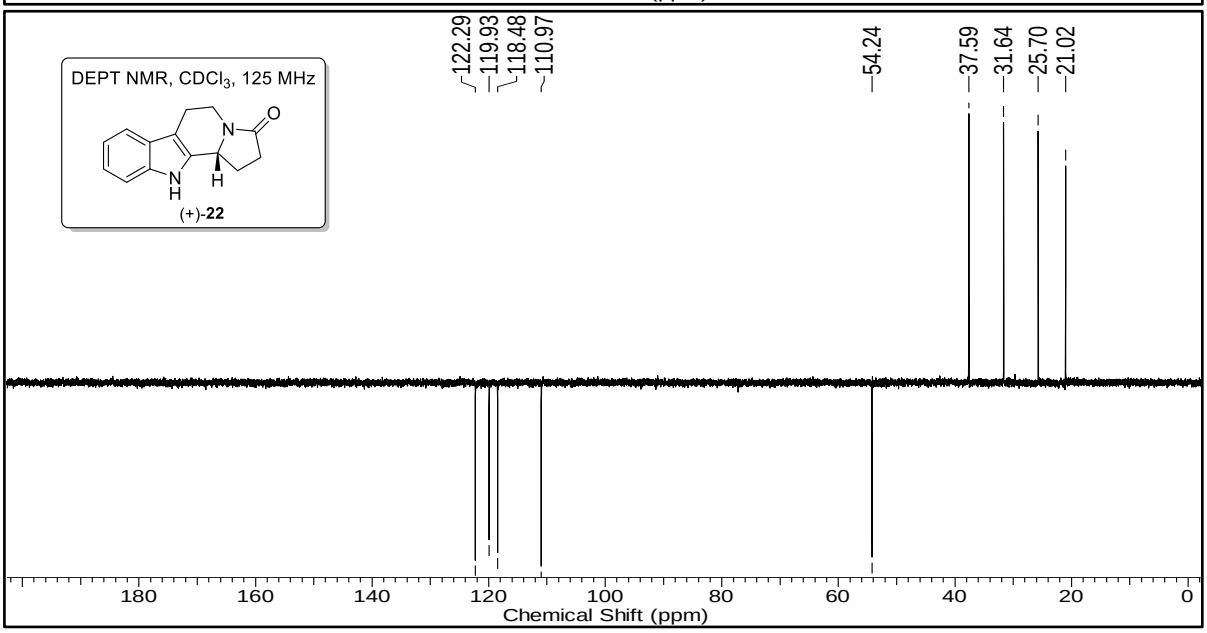
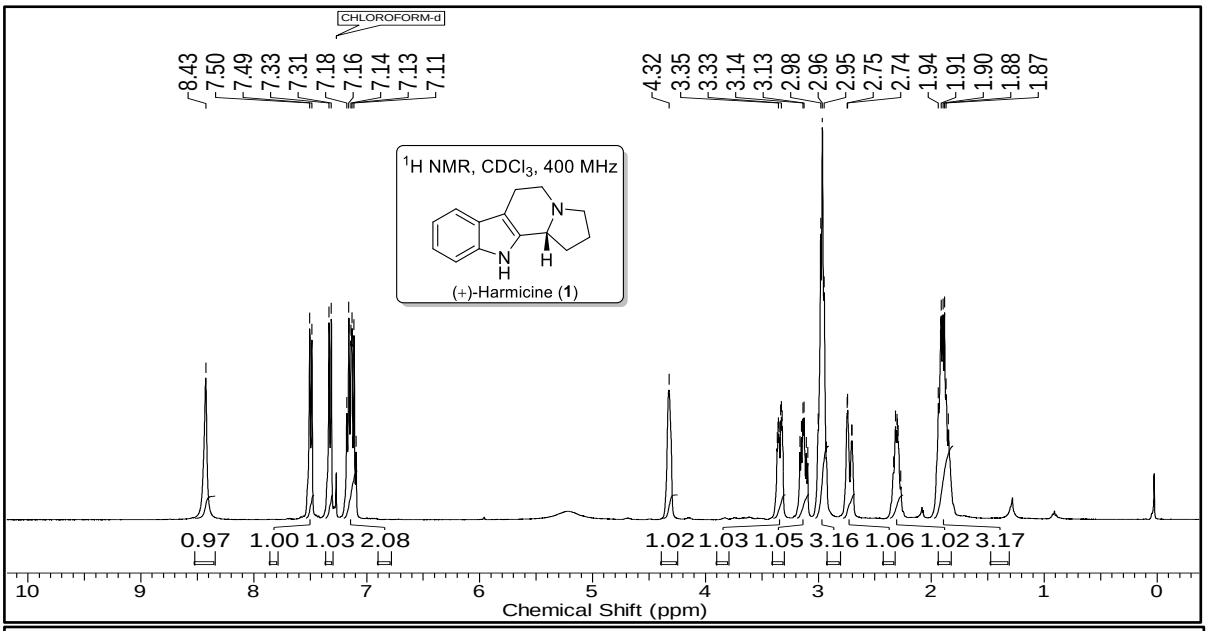
4.97 4.96 4.95 4.57 4.56 4.54 4.54
3.05 2.87 2.87 2.86 2.85 2.85 2.85 2.61 2.55 2.53 1.96 1.94
^{1}H NMR, $CDCl_3$, 500 MHz
(+)-22
0.98 1.00 1.00 1.02 1.00 1.00 1.06 1.04 2.14 3.13 1.02
Chemical Shift (ppm)


CHLOROFORM-d
173.19
136.24 133.12 126.81 122.28 119.92 118.46 110.97 108.39
77.00
54.24
37.59 31.63 25.70 21.02
^{13}C NMR, $CDCl_3$, 125 MHz
(+)-22
Chemical Shift (ppm)


122.29 119.93 118.48 110.97
54.24
37.59 31.64 25.70 21.02
DEPT NMR, $CDCl_3$, 125 MHz
(+)-22
Chemical Shift (ppm)


CHLOROFORM-d
8.43 7.50 7.49 7.33 7.31 7.18 7.16 7.14 7.13 7.11
4.32 3.35 3.33 3.14 3.13 2.98 2.96 2.95 2.75 2.74 1.94 1.91 1.90 1.88 1.87
^{1}H NMR, $CDCl_3$, 400 MHz
(+)-Harmicine (1)
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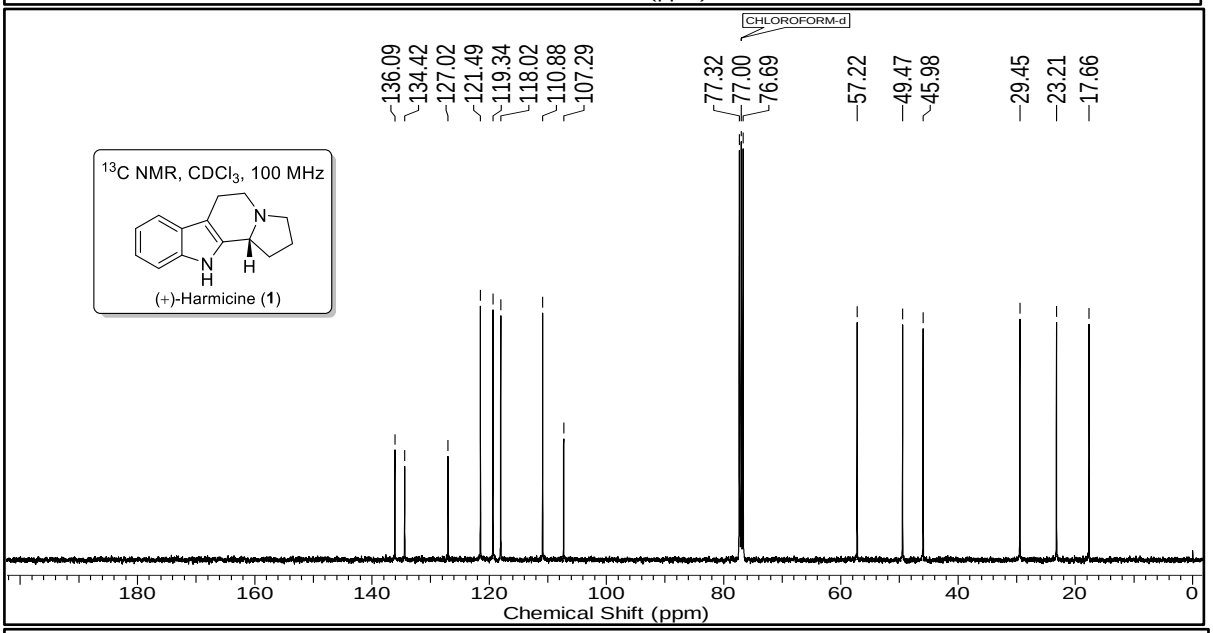
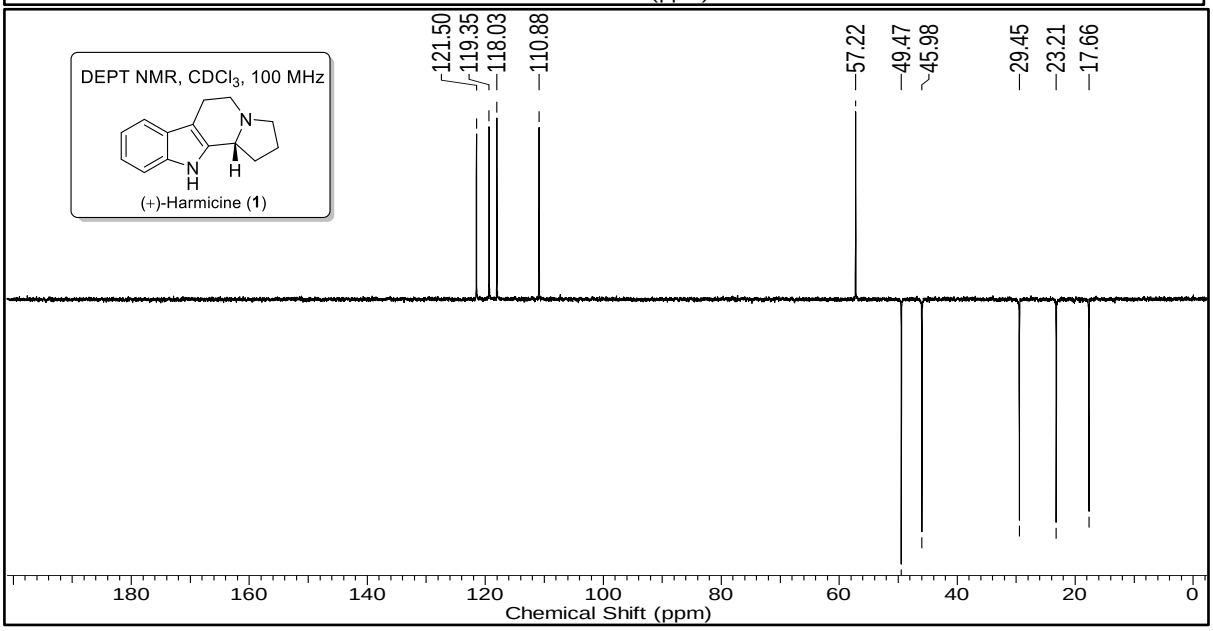
1.02 1.03 1.05 3.16 1.06 1.02 3.17
Chemical Shift (ppm)


CHLOROFORM-d
136.09 134.42 127.02 121.49 119.34 118.02 110.88 107.29
77.32 77.00 76.69
57.22 49.47 45.98
29.45 23.21 17.66
^{13}C NMR, $CDCl_3$, 100 MHz
(+)-Harmicine (1)
Chemical Shift (ppm)


121.50 119.35 118.03 110.88
57.22 49.47 45.98
29.45 23.21 17.66
DEPT NMR, $CDCl_3$, 100 MHz
(+)-Harmicine (1)
Chemical Shift (ppm)

HPLC Data of (±)-22:

Shimadzu CLASS-VP V6.12 SP5
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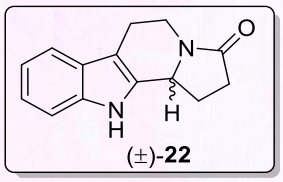
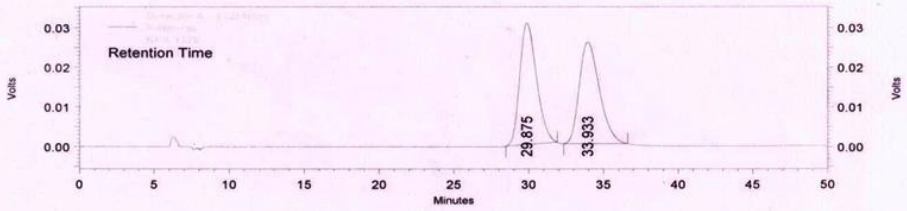
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1329
User: System
Acquired: 7/15/11 3:08:36 PM
Printed: 7/15/11 4:37:37 PM
Sample Name P-Har-rac



(±)-**22**



Detector A - 1 (254nm)

Retention Time	C Area	Area %
29.875	2403389	49.975
33.933	2405768	50.025
Totals	4809157	100.000

Project Leader :Dr. N. P. Argade
Column :Chiralcel OD-H (4.6x250 mm)
Mobile Phase :IPA : Pet Ether (15:85)
Flow Rate : 0.5ml/min (Pressure 400psi)
Wavelength : 254nm
Con. : 1.2mg/1.5ml
Inject vol. :5uL

Kunte

HPLC Data of (+)-22:

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1328
User: System
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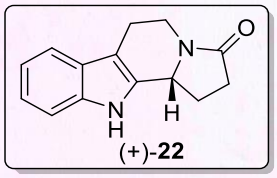
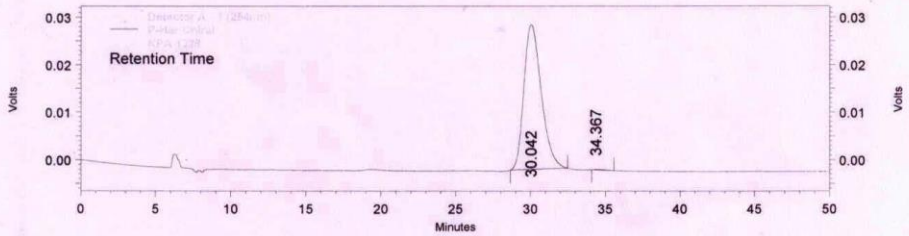
Printed: 7/15/11 3:15:09 PM
Sample Name P-Har-Chiral



(+)-**22**



Detector A - 1 (254nm)

Retention Time	C Area	Area %
30.042	2465604	99.793
34.367	5104	0.207
Totals	2470708	100.000

Project Leader :Dr. N. P. Argade
Column :Chiralcel OD-H (4.6x250 mm)
Mobile Phase :IPA : Pet Ether (15:85)
Flow Rate : 0.5ml/min (Pressure 400psi)
Wavelength : 254nm
Con. : 1.5mg/1.5ml
Inject vol. :5uL

Kunte

2A.7 References

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Chapter 2: Section B

Enantioselective Total Synthesis of Desbromoarborescidines A–C and the Formal Synthesis of (*S*)-Deplancheine

This section B of chapter 2 features the following topics:

2B.1 Background

The indole alkaloids have been imperative targets due to their novel structural architectures, wide range of promising biological activities and the current clinical applications.[1-6] More specifically, the indolo[2,3-*a*]quinolizine template is of great significance because many natural products embodying this framework have wide range of biological activities; for example, the antibacterial lercheine (**1**),[7] the antiviral natural product hirsutine (**2**),[8] the cytotoxic compound 10-hydroxyangustine (**3**)[9] as well as the antiplasmodial agent glabratine (**4**).[7] Some important synthetic compounds like anticancer centrocountin-1 (**5**) and related phosphatase inhibitor **6** also have indolo[2,3-*a*]quinolizine framework (Figure 1).[10-12]

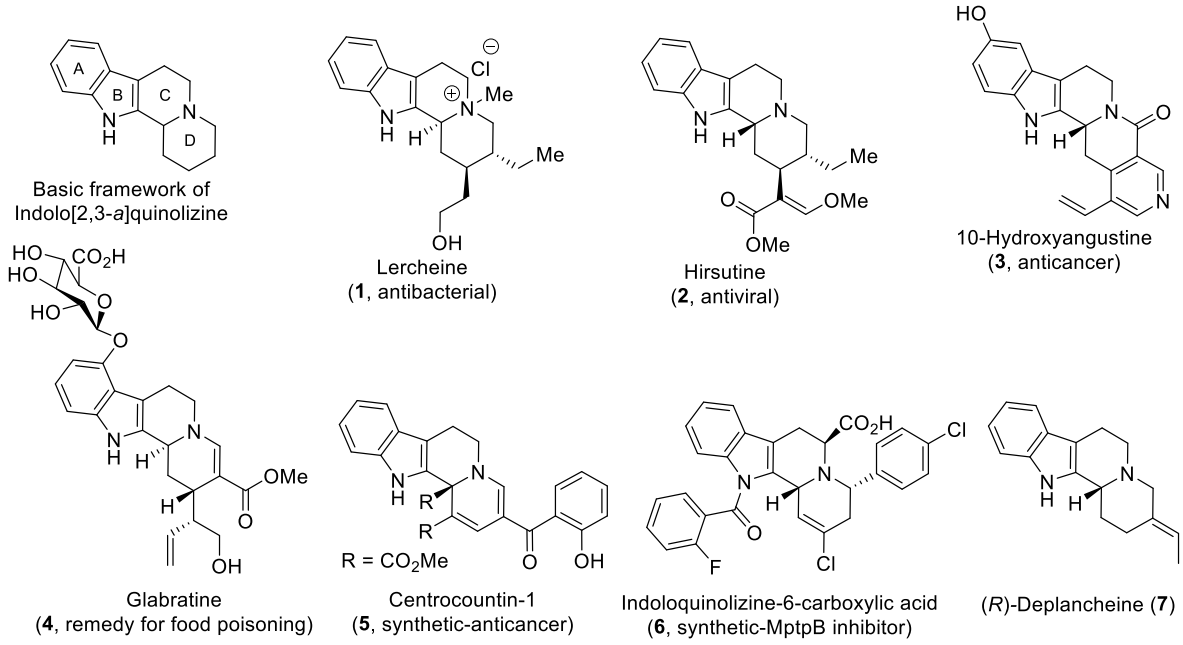


Figure 1. Bioactive natural and synthetic compounds containing the indolo[2,3-*a*]quinolizine framework

The simplest alkaloid containing the indolo[2,3-*a*]quinolizine core is desbromoarborescidine A. It was isolated from the leaves of *Dracontomelum mangiferum* by Johns and Lamberton in 1966.[13-15] The other simplest indoloquinolizidine, *R*-(+)-deplancheine was isolated from the stem and berk of New Caledonian plant *Alstonia deplanchei*[16] as well as from *Alstonia undulata*[17] and from the South American *Aspidosperma maregravianum*.[18] Desbromoarborescidine A and deplancheine became the target compounds to show the efficacy of the methodologies developed for the synthesis of indolo[2,3-*a*]quinolizine scaffold. In 1993, Païs and co-workers isolated another four new

brominated alkaloids of the tetrahydro-*β*-carboline family, the arborescidines A–D (**9**–**12**) from a marine tunicate *Pseudodistoma arborescens* (Figure 2).[19,20] Arborescidines, desbromoarborescidines and their derivatives have been recently tested against four human tumor cell lines: gastric adenocarcinoma (AGS), lung cancer (SK-MES-1), bladder carcinoma (J82) and leukemia (HL-60) cells, and they exhibited antiproliferative activity (IC_{50}, 9 to >100 μM).[21]

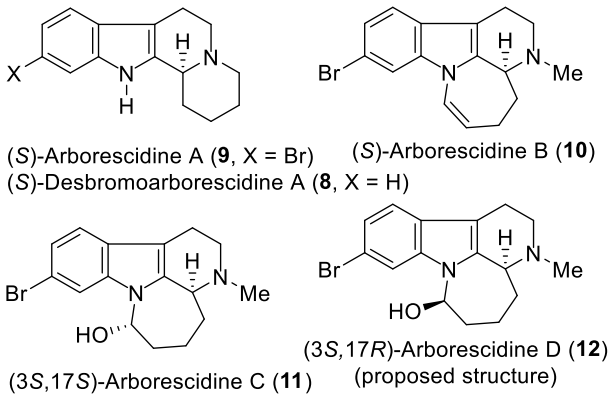


Figure 2. Bioactive arborescidine alkaloids

2B.2 Brief Account on Syntheses of Arborescidines/Desbromoarborescidines A–C and Deplancheine

The indole alkaloid desbromoarborescidine A (**8**) was synthesized before its isolation in racemic form.[22-26] Its first synthesis was accomplished by Keufer in 1950.[22] The first asymmetric synthesis of desbromoarborescidine A as well as its absolute configuration was established by Yamada and Kunieda in 1967 by applying Fischer indole protocol on optically active hexahydro-2*H*-quinolizinone.[15] The first racemic synthesis of arborescidines A–C were reported by Koomen and co-workers in 1998 and based on the synthesis of proposed structure of arborescidine D, a structural revision has been recommended.[27] Rawal and co-workers reported the enantioselective total synthesis of antipodes of arborescidines A−C and confirmed the assigned absolute stereochemistry of these natural products.[28] The absolute configuration of deplancheine was established by Mayers and co-workers in 1986 through the synthesis of antipode (*S*)-deplancheine.[29] Allin et al. have reported stereospecific synthesis of both the enantiomers of deplancheine (**7**) by using stereoselective cyclization reaction to form the indolo[2,3-*a*]quinolizine framework from a nonracemic chiral template.[30] Syntheses of desbromoarborescidine/arborescidine A (**8**/**9**) and deplancheine (**7**) have been presented schematically in figures 3–8 whereas the

syntheses of desbromoarborescidine (**8**)/arborescidine B and C (**10**/**11**) have been described briefly in schemes 1–3.

2B.2.1 Schematic Presentation of Arborescidines/Desbromoarborescidines A Syntheses

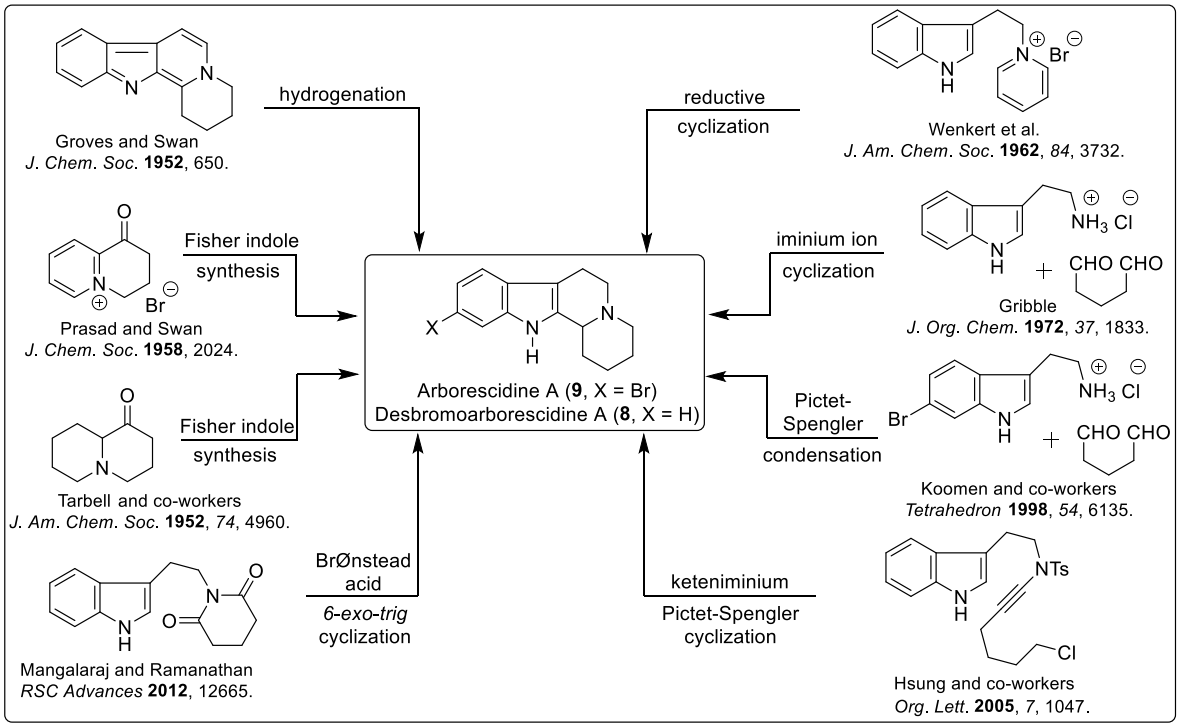


Figure 3. Schematic representation of (±)-desbromoarborescidine/arborescidine A syntheses

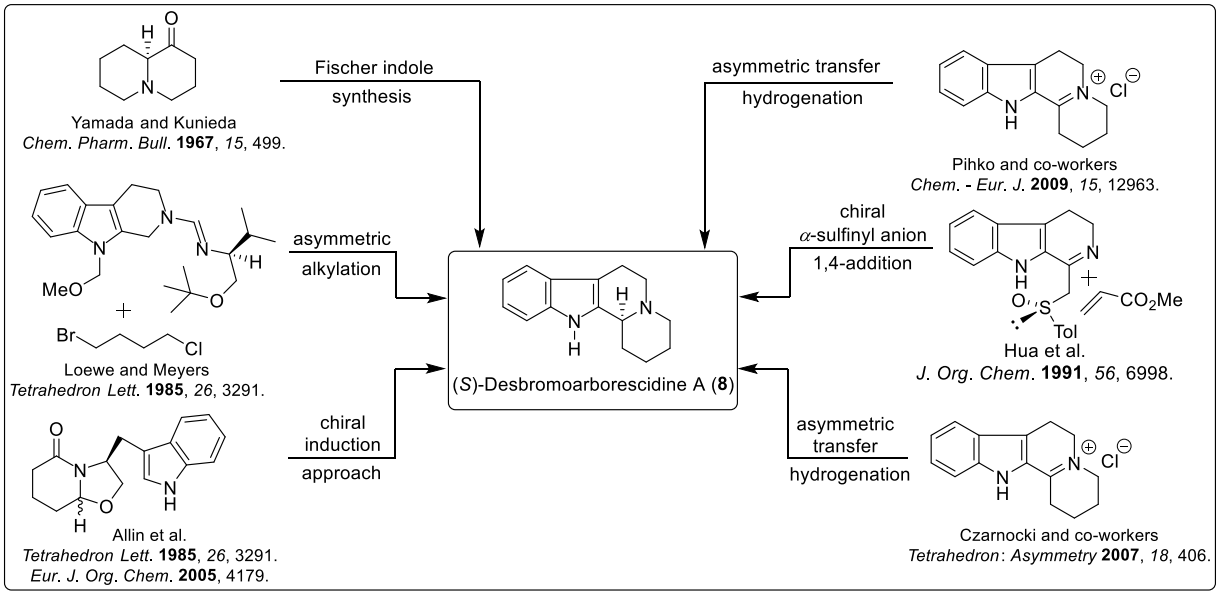


Figure 4. Schematic representation of (*S*)-desbromoarborescidine A syntheses

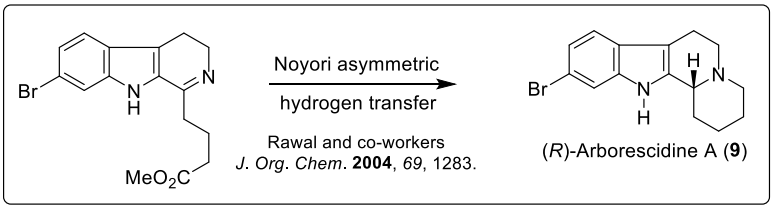
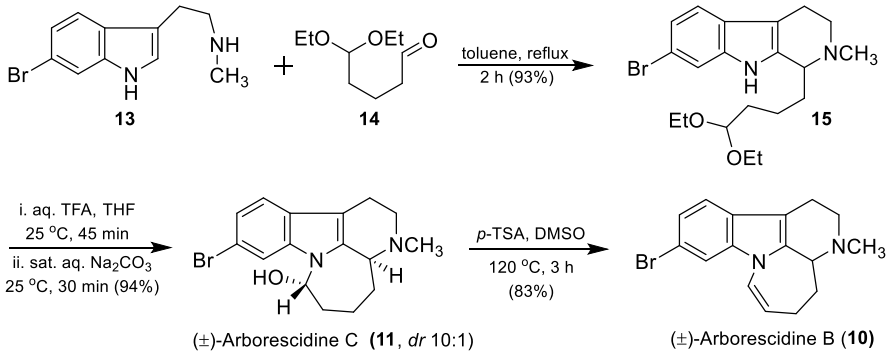


Figure 5. Schematic representation of (*R*)-arborescidine A synthesis

2B.2.2 Syntheses of Arborescidines/Desbromoarborescidines B and C

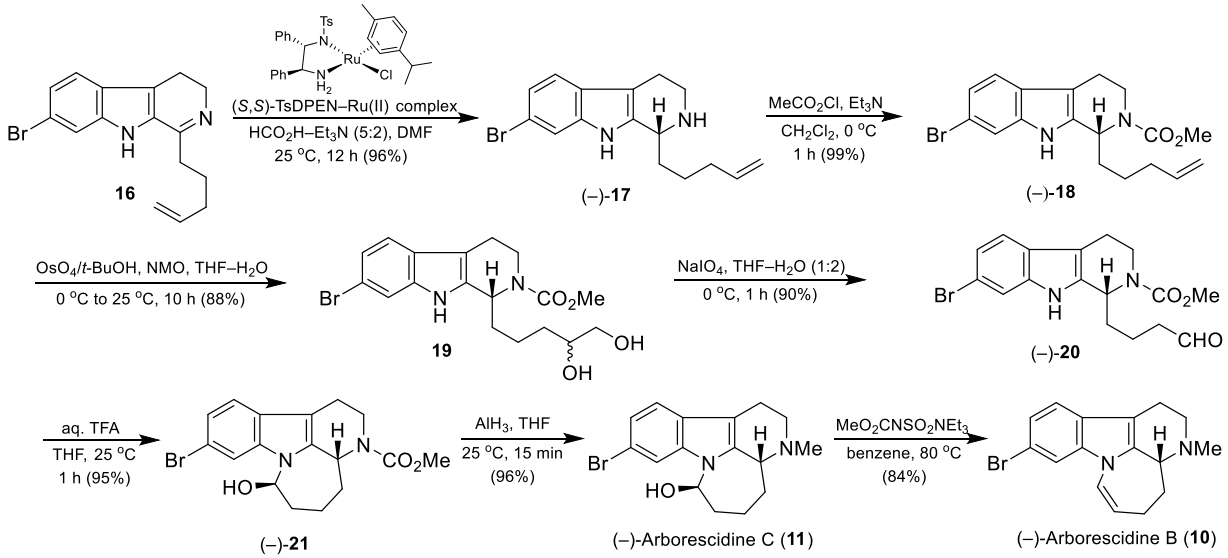
Koomen and co-workers have reported first total synthesis of (±)-arborescidines B and C from 6-bromo-*N*-methyltryptamine **13** (Scheme 1).[27] Compound **13** was condensed with 5,5-diethoxypentanal (**14**) using nonacidic aprotic Pictet-Spengler reaction condition in refluxing toluene to provide acetal **15** in 93% yield. Deprotection of acetal **15** using aqueous TFA under thermodynamic condition resulted in a diastereoselective cyclization with the formation of azapine ring structure to provide (±)-arborescidine C (**11**, *dr* 10:1) in 73% yield (after crystallization). The stereochemistry of **11** was established by using NOESY NMR studies. Compound **11** on treatment with *p*-TSA in DMSO at 120 ^{o}C provided the enamine bearing (±)-arborescidine B (**10**) in 83% yield.



Scheme 1. First total synthesis of (±)-arborescidine B and C

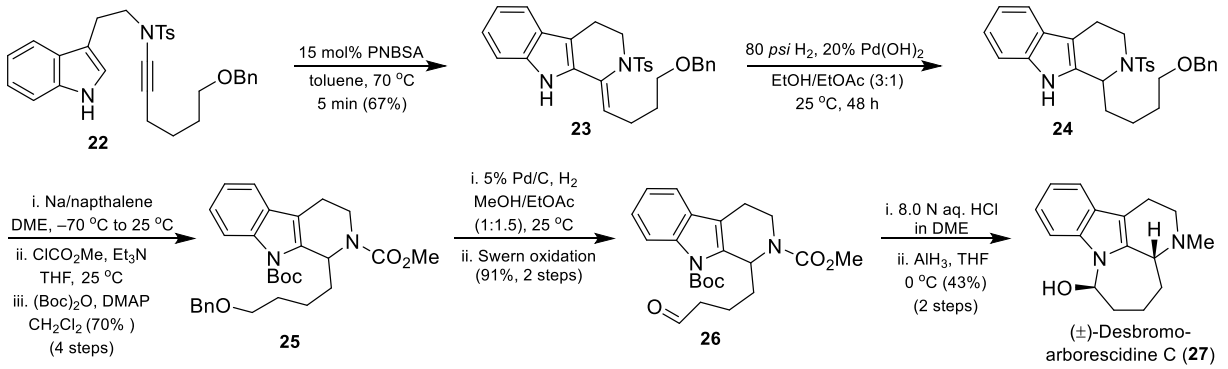
Rawal and co-workers have reported first enantioselective total synthesis of antipodes of arborescidines B and C by using Noyori asymmetric hydrogen-transfer reaction of appropriately functionalized *β*-carboline derivatives (Scheme 2).[28] Imine **16** was subjected to Noyori asymmetric hydrogen-transfer reaction by using (*S*,*S*)-TsDPEN–Ru(II) complex in DMF to provide amine (–)-**17** in 96% yield. Protection of the secondary amine as carbamate delivered the compound (–)-**18** in 99% yield with 93% *ee*. Dihydroxylation of the terminal olefin in (–)-**18** by OsO_4/*t*-BuOH, NMO in THF–H_2O furnished the diol **19** as a diastereomeric mixture in 88% yield. Oxidative cleavage of diol **19** by $NaIO_4$ gave the unstable aldehyde (–)-**20** in 90% yield. As such treatment of the

obtained aldehyde **20** with aq. TFA provided >20:1 mixture of *trans*:*cis*-**21** in 95% yield. Reduction of carbomethoxy group in **21** by AlH_3 afforded (–)-arborescidine C (**11**) in 96% yield. Treatment of (–)-arborescidine C (**11**) with Burgess reagent in refluxing benzene provided (–)-arborescidine B (**10**) in 84% yield.



Scheme 2. First enantioselective total synthesis of (–)-arborescidine B and C

Hsung and co-workers have demonstrated BrØnsted acid catalyzed stereoselective arene-ynamide cyclizations and this methodology has been applied for the synthesis of (±)-arborescidine C (Scheme 3).[31] Indole-tethered ynamide **22** on treatment with PNBSA (*p*-nitrobenzenesulfonic acid) underwent stereoselective keteniminium Pictet-Spengler cyclization to provide enamine **23** in 67% yield. Enamine **23** was reduced under hydrogenation condition to give compound **24**. Surprisingly, benzyl ether was not cleaved under that condition. Sodium napthalide induced *N*-Ts deproctection followed by



Scheme 3. Synthesis of (±)-arborescidine C via keteniminium Pictet-Spengler cyclization

protection of secondary amine as methoxycarbamate and Boc-protection of indole-NH furnished compound **25** in overall 70% yield (4 steps). At this stage the benzyl ether was deprotected by H_2/Pd-C and the formed primary alcohol was oxidized under Swern

condition to deliver the aldehyde **26** in 91% yield (2 steps). The aldehyde **26** on treatment with 8 N HCl underwent diastereoselective cyclization to provide the *trans*-aminol which after alane reduction furnished (±)-desbromoarborescidine C (**27**) in 43% yield (2 steps).

2B.2.3 Schematic Presentation of Deplancheine Syntheses

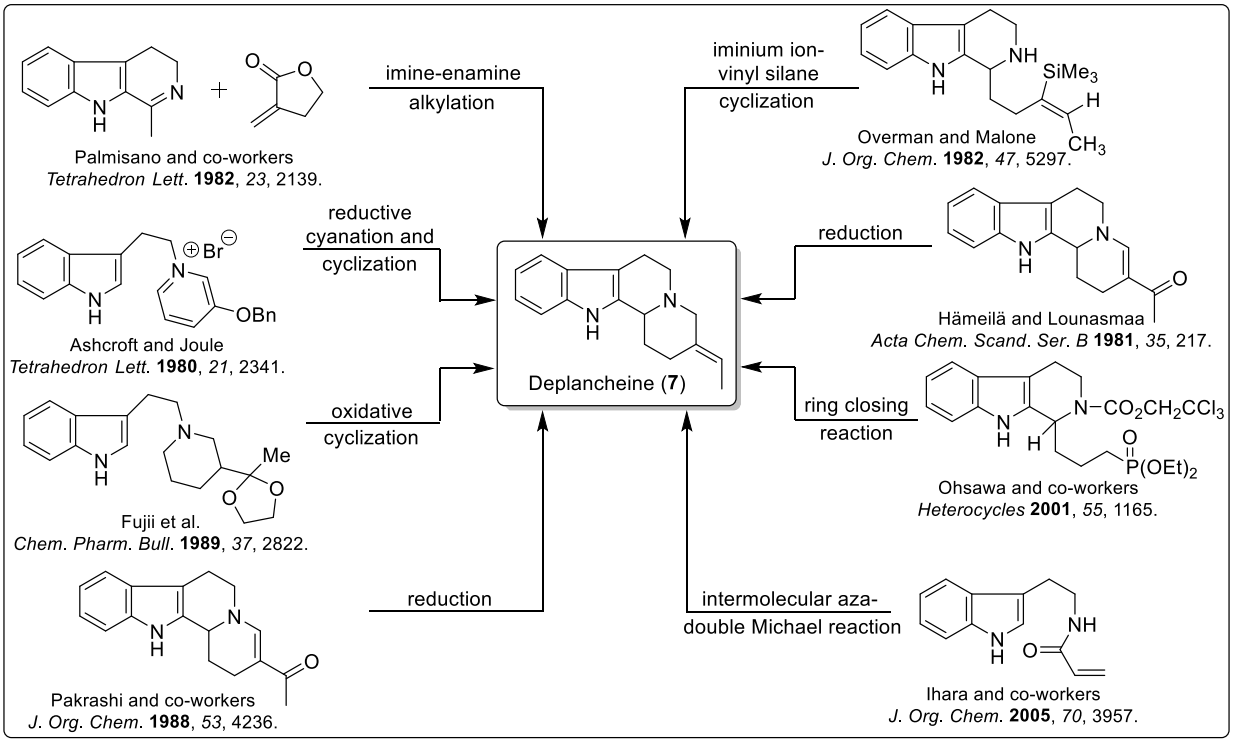


Figure 6. Schematic representation of (±)-deplancheine syntheses

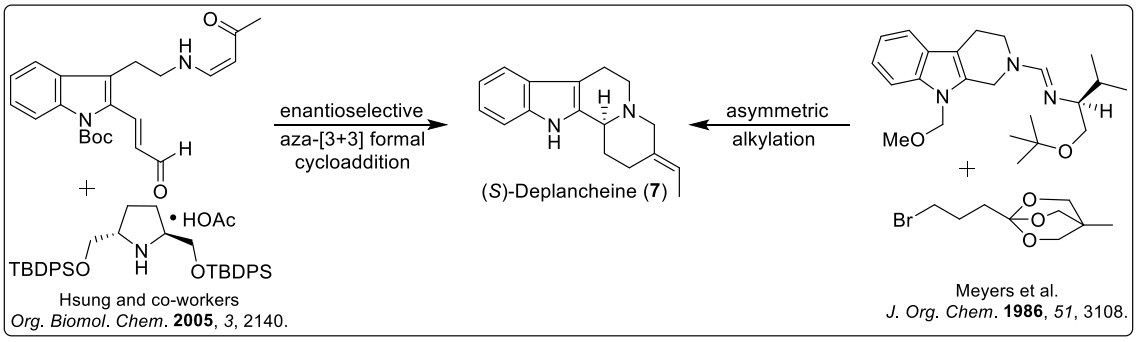


Figure 7. Schematic representation of (*S*)-deplancheine syntheses

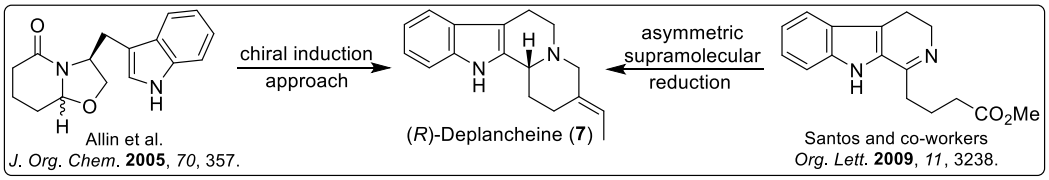
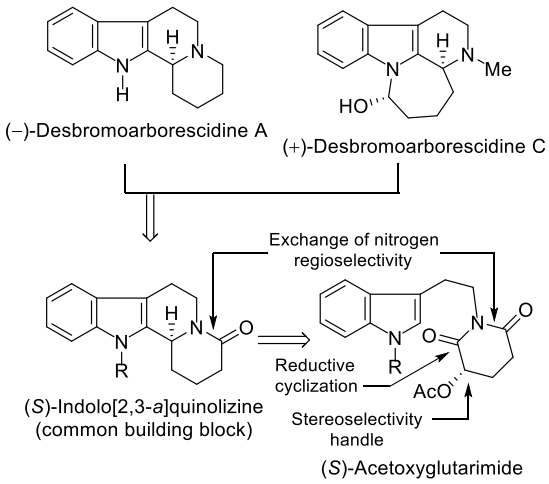


Figure 8. Schematic representation of (*R*)-deplancheine syntheses

2B.3 Results and Discussion: Present Work

A careful scrutiny of desbromoarborescidines A–C structures and their retrosynthetic analysis revealed that they are the analogous indole alkaloids containing skeletonal 15-carbon and 2-nitrogen atoms (Scheme 4). We reasoned that (*S*)-acetoxyglutarimide has similar 15-carbon skeleton along with appropriately placed 2-nitrogens and it would be a suitable precursor for the synthesis of target compounds viz., (i) the (*S*)-acetoxy function would serve as best detachable handle to embark the stereoselectivity, (ii) regioselective reduction of an imide carbonyl to the lactamol followed by an intramolecular stereoselective cyclization would provide an access to desbromoarborescidine A and (iii) hydrolytic cleavage of *δ*-lactam unit in the advanced intermediate (*S*)-indolo[2,3-*a*]quinolizine followed by an alternate intramolecular cyclization utilizing the indole nitrogen atom would constitute a path to desbromoarborescidines B & C.

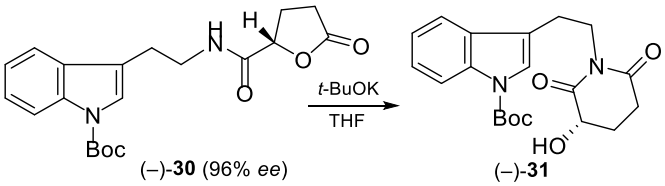


Scheme 4. Retrosynthetic analysis of desbromoarborescidines A and C

The enantiomerically pure starting material (*S*)-tetrahydro-5-oxo-2-furancarboxylic acid (*S*)-**28** was prepared from (*S*)-glutamic acid by using known procedure.[32] EDCI induced dehydrative coupling reaction of Boc-protected tryptamine **29** with enantiomerically pure acid (*S*)-**28** furnished the desired product (–)-**30** in 86% yield with 96% *ee* (by HPLC) (Scheme 5). Control experiments on base catalyzed rearrangement of amidolactone (–)-**30** to the desired (*S*)-hydroxyglutarimide (–)-**31** revealed that the starting material is very much prone to recemize. Hence the yield and enantiomeric purity of formed ring expansion product are highly dependent on molar amount of base used, reaction temperature and time.[33,34] The results obtained on the basis of systematic studies

on conversion of compound (–)-**30** to (–)-**31** have been summarized in table 1. The use of 0.45 equivalents of *t*-BuOK at –78 to –50 °C in 1.50 h time furnished the product (–)-**31** in

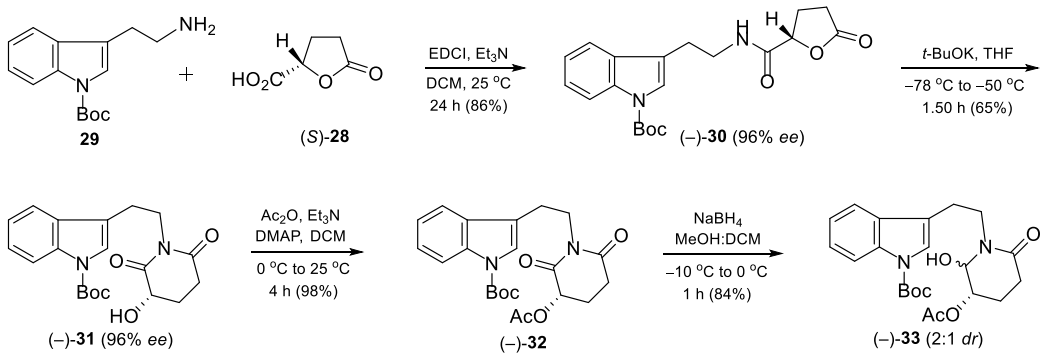
Table 1. Base catalyzed rearrangement of (*S*)-amidolactone to (*S*)-hydroxyglutarimide



entry	*t*-BuOK (equiv)	temp. °C	time (h)	% yield[a]	% ee[b]
1	0.60	–78 to –40	3.00	82	68
2	0.50	–78 to –40	3.00	72	80
3	0.50	–78 to –40	2.00	68	89
4	0.45	–78 to –50	2.00	66	91
5	**0.45**	**–78 to –50**	**1.50**	**65**	**96**
6	0.40	–78 to –50	2.00	56	92

[a] Isolated yields, [b]determined by chiral HPLC

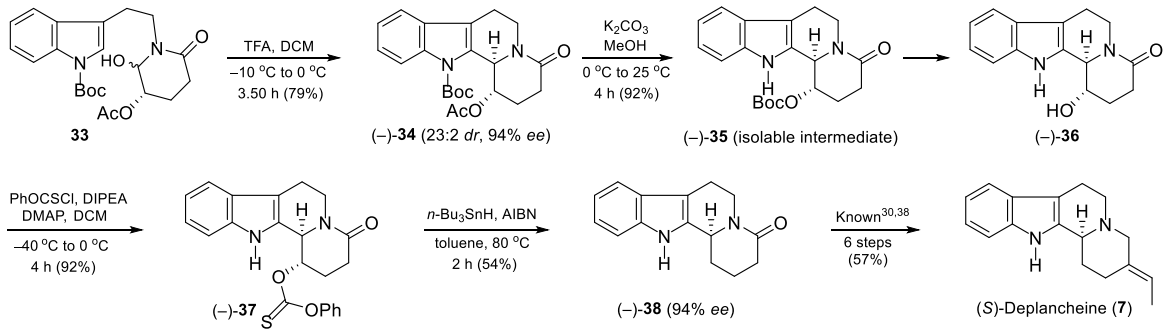
65% yield with 96% enantiomeric purity (Table 1, entry 5). The (*S*)-hydroxyl group in compound (–)-**31** was transformed to the corresponding acetate (–)-**32** in 98% yield by using acetic anhydride and triethylamine. The regioselective sodium borohydride reduction of more reactive imide carbonyl group in compound (–)-**32** provided product **33** in 84% yield with ~2:1 diastereomeric ratio (by ^{1}H NMR). Such type of lactamol units is known to display the ring–chain tautomerism[35] and hence to keep the complete control on diastereoselectivity is a difficult task. However under a controlled reaction conditions, the



Scheme 5. Synthesis of (*S*)-acetoxyglutarimide

chemoselective trifluoroacetic acid induced intramolecular cyclization of lactamol **33** at –10 to 0 °C furnished the desired tetracyclic intermediate (–)-**34** in very good yield with high stereoselectivity (79%, 23:2 *dr*), via the *N*-acyliminium ion intermediate (Scheme 6).

The present reaction was chemoselective as the Boc-protection remained intact with the use of two equivalents of TFA at lower temperature. In this *N*-acyliminium ion cyclization, the high degree of diastereoselectivity is attributed to the formation of flat iminium ion intermediate followed by the stereoselective intramolecular nucleophilic attack from the less hindered *β*-side. However the repetition of above experiment at –78 to 0 °C did not show any further refinement in diastereoselectivity and/or yield. The mixture of diastereoisomers **34** was quantitatively separated by using flash column chromatography and the required major isomer retained 94% enantiopurity (by HPLC).



Scheme 6. Stereoselective synthesis of pivotal intermediate (*S*)-indolo[2,3-*a*]quinolizine: formal synthesis of (*S*)-deplancheine

The major isomer (–)-**34** on treatment with K_2CO_3/MeOH underwent both one-pot deacylation and *N*-Boc-deprotection[36] in four hours to exclusively provide the product (–)-**36** in 92% yield. In the conversion of (–)-**34** to (–)-**36**, tlc-monitoring of the reaction progress indicated that one of the intermediate formed has a sufficient life span and its isolation would be feasible. Hence the above mentioned reaction was arrested after one hour time and immediate silica gel column chromatography of the reaction mass was performed. We could successfully isolate the intermediate (–)-**35** in almost 26% yield along with some amounts of both starting material and final product. Thus mechanistically the deacylation followed by an in situ intramolecular *N*-Boc-group migration to the proximal hydroxyl oxygen function takes place to form the intermediate (–)-**35**, which on methanolysis provides product (–)-**36**. The observed intramolecular 1,5-Boc migration is attributed to the geometrical features and the unusual carbamate to carbonate transformation is significant from basic chemistry point of view. Finally the absolute and relative stereochemistry of product (–)-**36** was confirmed by using single crystal X-ray crystallographic data (Figure 9). We feel that our present protocol will mirror to provide (+)-**36** from the corresponding (*R*)-glutamic acid. At this stage the detachment of stereo-

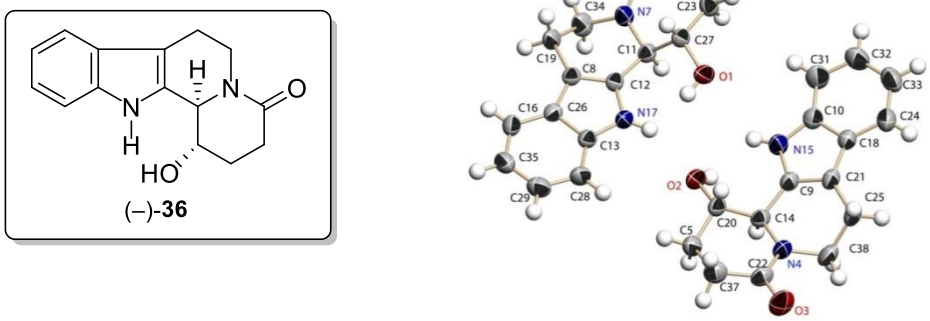
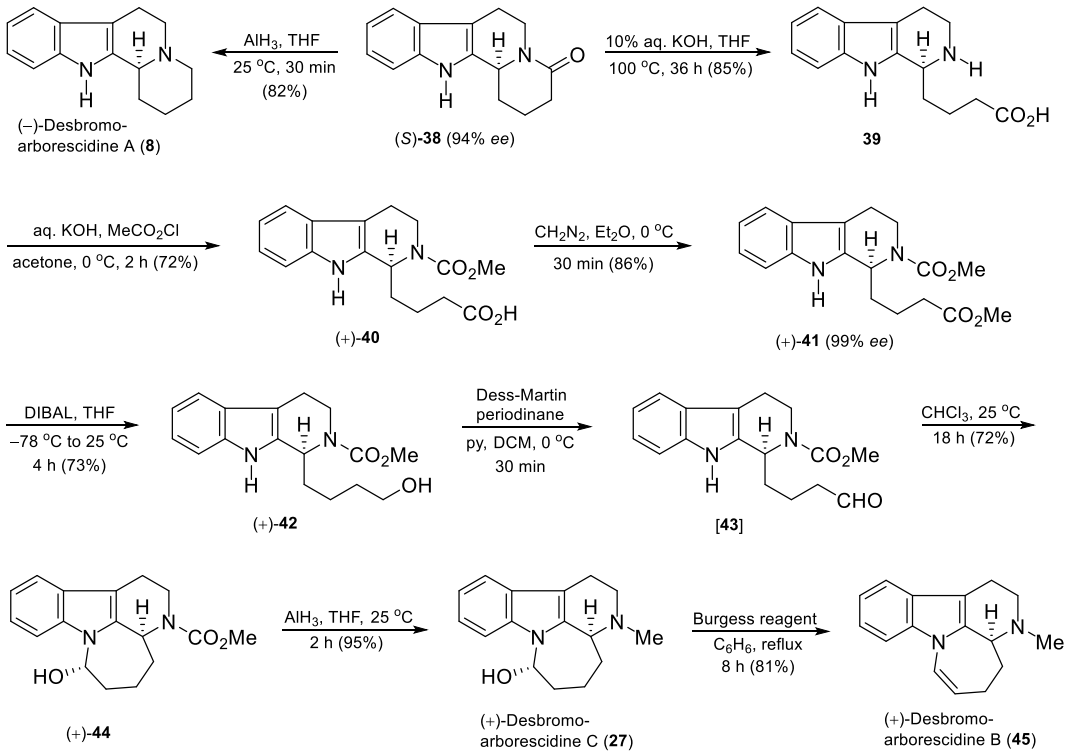


Figure 9. Ortep drawing of compound (–)-**36**. Thermal ellipsoids set to 50% probability level.

Note: *Complete details of crystallographic data have been reported in the SI part of publication: Mondal, P.; Argade, N. P. J. Org. Chem.* ***2013****, 78, 6802.*

selectivity handle, the (*S*)-hydroxyl group in compound (–)-**36** was decided to obtain the product (*S*)-**38**. In our hands the preparation of mesylate derivative of compound (–)-**36** followed by its displacement by iodide resulted mostly in elimination product owing to the higher acidity of an adjacent methine proton. Alternatively, the chemoselective reaction of compound (–)-**36** with excess of phenyl chlorothionoformate in presence of diisopropylethylamine exclusively provided the xanthate ester (–)-**37** in 92% yield. The xanthate ester (–)-**37** was not very stable and hence it was quickly filtered through the silica gel column and immediately used for the next step. The xanthate ester (–)-**37** on Barton–McCombie deoxygenation[37] using tributyltin hydride in presence of AIBN gave the desired common chiral building block (*S*)-**38** in 54% yield (94% *ee*, by HPLC). The analytical and spectral data obtained for compound (*S*)-**38** was in complete agreement with the reported data.[38] Thus the desired common intermediate (*S*)-**38** was obtained in 8-steps with 15% overall yield. A six-step synthetic protocol to transform the compound (*S*)-**38** to (*S*)-deplancheine (**7**, antipode) in very good overall yield is known.[30,38,39]

In the next part of studies, syntheses of desbromoarborescidines A–C were planned from an advanced intermediate (*S*)-**38** (Scheme 7). Aluminum hydride reduction of δ-lactam carbonyl in compound (*S*)-**38** provided the natural product (*S*)-desbromoarborescidine A (**8**) in 82% yield. The exchange of nitrogen regioselectivity in intermediate (*S*)-**38** was then envisioned for synthesis of desbromoarborescidines B and C. The hydrolytic cleavage of δ-lactam unit in compound (*S*)-**38** was specifically intended under basic conditions to avoid recemization issues.[40]



Scheme 7. Synthesis of enantiomerically pure desbromoarborescidines A–C from (*S*)-indolo[2,3-*a*]quinolizine

The compound (*S*)-**38** on hydrolysis with aqueous KOH followed by an acidification provided product **39** in 85% yield. At this stage a selective carbomethoxy protection of piperidine nitrogen in compound **39** was undertaken, as initially it would serve as a protecting group and later on the source of essential methyl group. The regioselective reaction of more reactive piperidine nitrogen with methyl chloroformate in presence of KOH gave the corresponding carbamate derivative (+)-**40** in 72% yield. The compound (+)-**40** on treatment with diazomethane formed the required ester (+)-**41** in 86% yield (99% *ee*, by HPLC). The enhancement in % *ee* could be plausibly due to the sizeable deletion of minor isomer during the process of post reaction neutralization followed by precipitation of compound **39**. DIBAL reduction of ester (+)-**41** furnished the corresponding alcohol (+)-**42** in 73% yield. The Dess–Martin periodinane oxidation of alcohol (+)-**42** formed aldehyde **43**. However, all our attempts to isolate the aldehyde **43** in pure form met with failure and it was always contaminated with the further cyclized product (+)-**44** (by ^{1}H NMR). The above mixture of products on stirring in chloroform at room temperature for 18 hours underwent the smooth stereoselective intramolecular cyclization to exclusively yield the desired *trans*-aminol (+)-**44** in 72% yield. The catalytic amount of hydrochloric acid present in the chloroform was responsible for the above mentioned intramolecular cyclization. On the basis of NMR data, all four products and

intermediate **40**–**44** were designated as the rotameric mixtures and it is in accordance with literature precedent.[31] The conversion of (+)-aminol **44** to (+)-desbromoarborescidines C and B has been known in the literature.[21] Similarly, alane reduction of carbomethoxy group in compound (+)-**44** to the methyl group furnished the desired (3*S*,17*S*)-desbromoarborescidine C (**27**) in 95% yield. (3*S*,17*S*)-Desbromoarborescidine C (**27**) on treatment with Burgess reagent provided the corresponding dehydration product (*S*)-desbromoarborescidine B (**45**) in 81% yield. The analytical and spectral data obtained for desbromoarborescidines A–C were in complete agreement with reported data.[19,20,27,31] Starting from Boc-protected tryptamine **29**,[41] the desbromoarborescidines A/C/B (**8**/**27**/**45**) were respectively obtained in 9/15/16 steps with 13/4/3% overall yields.[42]

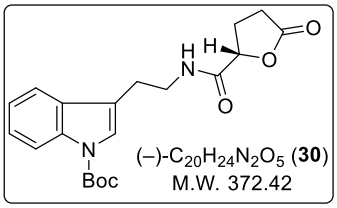
2B.4 Summary

*In summary, we have demonstrated enantioselective convergent approach to deplancheine and desbromoarborescidines A–C from the corresponding (S)-acetoxyglutarimide. All the three different oxygen functions present in (S)-acetoxyglutarimide were rationally utilized in a remarkable chemo-, regio- and stereoselective fashion to design these four desired tantamount targets in very good overall yields and high enantiomeric purities, using an appropriate protecting groups. The present practical approach to these products is general in nature and would be useful to synthesize their potential analogues and congeners for SAR studies. The witnessed in situ intramolecular Boc-group migration-deprotection is notable from mechanistic point of view. The chiral intermediate (1S,12R)-1-hydroxy-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (**38**) is noteworthy and it will serve as an important synthon to design several other bioactive indole alkaloids.*

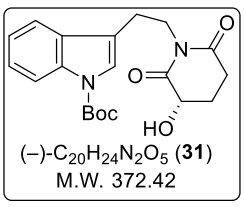
2B.5 Experimental Section

Commercially available (L)-glutamic acid, EDCI, *t*-BuOK, $NaBH_4$, TFA, *o*-phenyl chlorothionoformate, *n*-Bu_3SnH, AIBN, methyl chloroformate, DIBAL, Dess–Martin periodinane and Burgess reagent were used.

(–)-*tert*-Butyl (*S*)-3-(2-(5-Oxotetrahydrofuran-2-carboxamido)ethyl)-1*H*-indole-1-carboxylate (30). A solution of Boc-protected tryptamine (**29**, 5.50 g, 21.13 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a stirred suspension of acid (*S*)-**28** (2.75 g, 21.13 mmol) and EDCI (8.10 g, 42.26 mmol) in CH_2Cl_2 (80 mL) at 0 °C under argon atmosphere. To the above reaction mixture was added Et_3N (8.80 mL, 63.4 mmol) in a dropwise fashion and it was stirred at room temperature for 24 h. The reaction was quenched with water (25 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:2) as an eluent gave pure amide (–)-**30** as a white solid (6.76 g, 86% yield; 96% *ee*). Mp 100–102 °C; $[\alpha]^{25}_{D}$ –13.6 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.67 (s, 9H), 2.17–2.40 (m, 1H), 2.43–2.68 (m, 3H), 2.94 (t, *J* = 8 Hz, 2H), 3.63 (q, *J* = 8 Hz, 2H), 4.81 (t, *J* = 8 Hz, 1H), 6.59 (br t, *J* = 4 Hz, 1H), 7.24 (dt, *J* = 8 and 2 Hz, 1H), 7.33 (dt, *J* = 8 and 2 Hz, 1H), 7.41 (s, 1H), 7.53 (dd, *J* = 6 and 2 Hz, 1H), 8.13 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.9, 25.6, 27.4, 28.1, 38.9, 77.3, 83.6, 115.3, 117.1, 118.7, 122.5, 123.1, 124.5, 130.2, 135.5, 149.5, 169.4, 175.6; ESIMS (*m*/*z*) 395 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{24}N_2O_5Na$ 395.1577, found 395.1571; IR ($CHCl_3$) ν_{max} 3431, 3020, 1789, 1727, 1677 cm^{-1}.

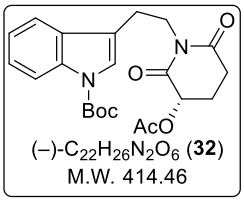


(–)-*tert*-Butyl (*S*)-3-(2-(3-Hydroxy-2,6-dioxopiperidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (31). A suspension of *t*-BuOK in THF (0.45 M, 5.35 mL) was added dropwise over a period of 10 min to a stirred solution of amido-lactone (–)-**30** (2.00 g, 5.36 mmol) in THF (30 mL) at –78 °C under argon atmosphere. The reaction mixture was stirred and allowed to reach –50 °C in 1 h. It was further stirred at the same temperature for 30 min. The reaction was quenched with saturated aq. NH_4Cl (5 mL) and THF was removed in



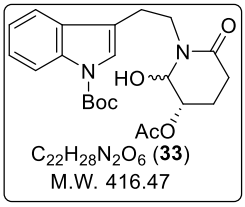
vacuo. To the reaction mixture was added ethyl acetate (150 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:1) as an eluent yielded (*S*)-hydroxyglutarimide (–)-**31** as a white solid (1.30 g, 65% yield; 96% *ee*). Mp 136–138 °C; $[\alpha]^{25}_{D}$ –47.9 (*c* 0.108 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.67 (s, 9H), 1.89 (dq, *J* = 12 and 6 Hz, 1H), 2.28–2.43 (m, 1H), 2.55–2.75 (m, 1H), 2.83–3.00 (m, 1H), 2.93 (t, *J* = 6 Hz, 2H), 3.58 (br s, 1H), 3.93–4.28 (m, 3H), 7.28 (dt, *J* = 8 and 2 Hz, 1H), 7.34 (dt, *J* = 8 and 2 Hz, 1H), 7.45 (s, 1H), 7.70 (dd, *J* = 8 and 2 Hz, 1H), 8.13 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.4, 25.2, 28.1, 30.7, 40.2, 68.2, 83.5, 115.2, 116.9, 119.0, 122.5, 123.3, 124.4, 130.3, 135.4, 149.6, 171.1, 175.1; ESIMS (*m*/*z*) 395 $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{24}N_2O_5Na$ 395.1577, found 395.1571; IR ($CHCl_3$) ν_{max} 3517, 1730, 1679 cm^{-1}.

(–)-*tert*-Butyl (*S*)-3-(2-(3-Acetoxy-2,6-dioxopiperidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (32). To a stirred solution of hydroxyimide (–)-**31** (4.20 g, 11.28 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (1.88 mL, 13.54 mmol), Ac_2O (1.60 mL, 16.92 mmol) and catalytic amount of DMAP (20 mg). The reaction mixture was allowed to reach room temperature and further stirred for 4 h. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with saturated aq. $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (6:4) as an eluent afforded pure acetoxyimide (–)-**32** as a white solid (4.60 g, 98% yield). Mp 104–106 °C; $[\alpha]^{25}_{D}$ –30.5 (*c* 0.106 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64 (s, 9H), 1.97–2.25 (m, 2H), 2.20 (s, 3H), 2.58–2.78 (m, 1H), 2.78–2.98 (m, 3H), 3.89–4.13 (m, 2H), 5.45 (dd, *J* = 10 and 6 Hz, 1H), 7.18 (dt, *J* = 8 and 2 Hz, 1H), 7.24 (dt, *J* = 8 and 2 Hz, 1H), 7.36 (s, 1H), 7.63 (dd, *J* = 6 and 2 Hz, 1H), 8.04 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.7, 23.1, 23.4, 28.1, 30.4, 40.3, 68.6, 83.4, 115.1, 117.0, 119.1, 122.5, 123.4, 124.4, 130.3, 135.4, 149.6, 169.1, 169.8, 170.6; ESIMS (*m*/*z*) 437 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_6Na$ 437.1683, found 437.1675; IR ($CHCl_3$) ν_{max} 1734, 1686 cm^{-1}.

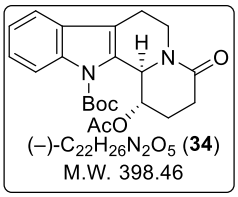


(–)-$C_{22}H_{26}N_2O_6$ (**32**)
M.W. 414.46

***tert*-Butyl 3-(2-((3*S*)-3-Acetoxy-2-hydroxy-6-oxopiperidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (33).** To a stirred solution of (*S*)-acetoxyglutarimide (–)-**32** (2.00 g, 4.83 mmol) in MeOH:CH_2Cl_2 (2:1, 30 mL) mixture was added $NaBH_4$ (550 mg, 14.5 mmol) in small portions at –10 °C over 5 min. The stirred reaction mixture was allowed to reach 0 °C in 1 h and the reaction was quenched with saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL). The reaction mixture was further stirred vigorously at 0 °C for 5 min and it was extracted with CH_2Cl_2 (75 mL × 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded the required lactamol **33** (2:1 *dr*) as a thick oil (1.69 g, 84%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.66 (s, 9H), 2.01 (s, 1H), 2.08 (s, 2H), 2.10–2.35 (m, 2H), 2.40–2.64 (m, 2H), 2.93–3.08 (m, 2H), 3.50–3.63 (m, 1H), 3.75–3.94 (m, 1H), 4.83–5.00 (m, 2H), 7.20–7.27 (m, 1H), 7.27–7.35 (m, 1H), 7.41 (s, 1H), 7.58–7.65 (m, 1H), 8.10 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.4, 20.5, 20.9, 21.0, 23.7, 23.8, 27.4, 28.2, 29.3, 29.7, 45.9, 46.4, 69.5, 70.0, 79.8, 81.4, 83.5, 115.3, 117.8, 119.0, 119.1, 122.49, 122.53, 123.07, 123.11, 124.4, 130.3, 135.4, 149.7, 169.4, 169.9, 170.4; ESIMS (*m*/*z*) 439 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{28}N_2O_6Na$ 439.1840, found 439.1836; IR ($CHCl_3$) ν_{max} 3384, 1734, 1635 cm^{-1}.

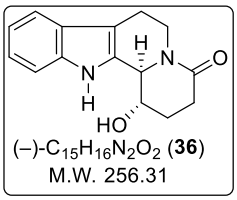


(–)-*tert*-Butyl (1*S*,12b*R*)-1-Acetoxy-4-oxo-1,3,4,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (34). To a stirred solution of lactamol **33** (3.50 g, 8.40 mmol) in CH_2Cl_2 (50 mL) at –10 °C was added TFA (1.36 mL, 16.8 mmol) in dropwise fashion. The reaction mixture was stirred in between –10 °C and 0 °C for 3.50 h and quenched with saturated aq. $NaHCO_3$ (5 mL). Then the reaction mixture was extracted with CH_2Cl_2 (75 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent first afforded the minor diastereomer (200 mg, 6%) and then the required major diastereomer (–)-**34** as a white foam (2.44 g, 73% yield; 94% *ee*). **Major isomer 34:** Mp 63–65 °C; $[\alpha]^{25}_D$ –136.1 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$,



200 MHz) δ 1.68 (s, 9H), 1.70–1.85 (m, 1H), 1.95–2.10 (m, 1H), 2.15 (s, 3H), 2.33–2.50 (m, 1H), 2.50–3.00 (m, 4H), 4.98–5.17 (m, 1H), 5.30–5.38 (m, 1H), 5.41–5.50 (m, 1H), 7.21–7.40 (m, 2H), 7.46 (dd, J = 8 and 2 Hz, 1H), 8.00 (dd, J = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 21.4, 23.4, 27.3, 27.9, 40.6, 59.9, 70.6, 84.6, 115.2, 118.2, 120.7, 122.9, 124.8, 128.5, 131.8, 136.7, 150.2, 169.5, 169.6; ESIMS (m/z) 421 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_5Na$ 421.1739, found 421.1724; IR (Nujol) ν_{max} 1733, 1652 cm^{-1}.

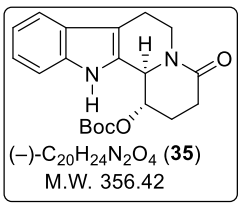
(–)-(1*S*,12b*R*)-1-Hydroxy-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one



(–)-$C_{15}H_{16}N_2O_2$ (**36**)
M.W. 256.31

(36). Anhydrous K_2CO_3 (666 mg, 4.82 mmol) was added to a stirred solution of acetate (–)-**34** (2.40 g, 6.02 mmol) in MeOH (30 mL) at 0 ^oC. Then the reaction mixture was further stirred for 4 h at 25 ^oC and it was concentrated in vacuo. The obtained residue was directly purified by silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–methanol (98:2) as an eluent to afford the Boc-deprotected alcohol (–)-**36** as a white solid (1.42 g, 92% yield). Mp 247–249 °C; $[\alpha]^{25}_D$ –169.4 (c 0.1 MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.80–1.87 (m, 2H), 2.25–2.34 (m, 1H), 2.43 (td, J = 20 and 5 Hz, 1H), 2.57–2.70 (m, 2H), 2.79 (dt, J = 15 and 5 Hz, 1H), 3.90 (quintet, J = 5 Hz, 1H), 4.57 (d, J = 10 Hz, 1H), 4.80 (dd, J = 15 and 5 Hz, 1H), 5.90 (d, J = 5 Hz, 1H), 6.96 (t, J = 10 Hz, 1H), 7.04 (t, J = 10 Hz, 1H), 7.38 (d, J = 10 Hz, 1H), 7.42 (d, J = 10 Hz, 1H), 10.38 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.0, 28.2, 29.7, 40.6, 60.0, 68.6, 108.0, 112.2, 118.1, 119.1, 121.5, 126.4, 133.8, 136.4, 168.7; ESIMS (m/z) 279 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_2$ 257.1285, found 257.1281; IR (Nujol) ν_{max} 3292, 1715, 1612 cm^{-1}.

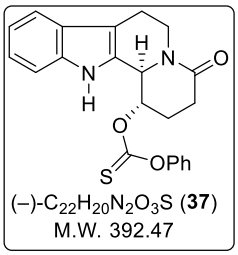
(–)-*tert*-Butyl ((1*S*,12b*R*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl) Carbonate (35). The above described reaction was performed on 100 mg scale and arrested after 1 h. Similar work up procedure followed by the silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent afforded the desired carbonate intermediate (–)-**35** as a white foam (23 mg, 26% yield). Mp 74–76 °C; $[\alpha]^{25}_D$ –42.8 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 9H), 2.00–2.10 (m, 1H), 2.15–2.24 (m, 1H), 2.50–2.58 (m, 1H), 2.67–2.94 (m, 4H), 4.87 (d, J = 5 Hz, 1H), 4.98–5.04 (m, 1H), 5.09–5.18 (m, 1H), 7.14 (t, J = 10 Hz, 1H), 7.22 (t, J = 10 Hz, 1H), 7.37 (d, J = 10 Hz, 1H), 7.52 (d, J = 10 Hz, 1H), 8.58 (s,



(–)-$C_{20}H_{24}N_2O_4$ (**35**)
M.W. 356.42

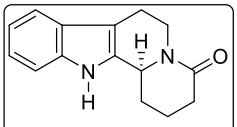
1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9, 24.8, 27.8, 28.8, 40.8, 58.1, 74.6, 83.9, 110.9, 111.1, 118.4, 119.8, 122.5, 126.5, 130.5, 136.1, 152.8, 168.8; ESIMS (*m*/*z*) 357 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_4$ 357.1809, found 357.1806; IR ($CHCl_3$) ν_{max} 3473, 1746, 1635 cm^{-1}.

(–)-(1*S*,12b*R*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl Phenyl Carbonate (37). Anhydrous DIPEA (1.02 mL, 5.85 mmol) was added dropwise to a stirred solution of alcohol (–)-**36** (500 mg, 1.95 mmol) and DMAP (71.5 mg, 0.59 mmol) in CH_2Cl_2 (30 mL) at –40 °C under argon atmosphere and the reaction mixture was stirred for 10 min. To the above reaction mixture was added *o*-phenyl chlorothionoformate (0.81 mL, 5.85 mmol) in a dropwise fashion and it was stirred at –15 °C to 0 °C for 4 h. The direct concentration of reaction mixture in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (6:4) as an eluent afforded the xanthate ester (–)-**37** as a yellow foam (704 mg, 92% yield). Mp 82–84 °C; $[\alpha]^{25}_D$ –48.1 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20–2.40 (m, 2H), 2.58–2.68 (m, 1H), 2.73–2.88 (m, 2H), 2.88–3.05 (m, 2H), 5.10–5.30 (m, 2H), 5.78 (s, 1H), 7.13–7.60 (m, 9H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 23.7, 28.3, 41.3, 58.0, 80.2, 111.2, 111.6, 118.5, 120.0, 121.7, 122.7, 126.6, 127.0, 129.7, 129.8, 136.2, 153.0, 168.4, 193.9; ESIMS (*m*/*z*) 415 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{20}N_2O_3SNa$ 415.1087, found 415.1082; IR ($CHCl_3$) ν_{max} 3361, 1714, 1652 cm^{-1}.



(–)-$C_{22}H_{20}N_2O_3S$ (**37**)
M.W. 392.47

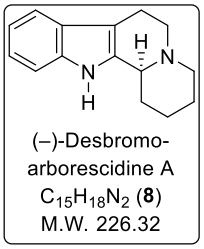
(–)-(*S*)-2,3,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (38). Pre-dried 50 mL round bottom flask was charged with xanthate ester (–)-**37** (500 mg, 1.27 mmol), AIBN (21 mg, 0.13 mmol) and dry toluene (20 mL). The stirred reaction mixture was purged with argon for 15 min and then *n*-Bu_3SnH (0.55 mL, 2.05 mmol) was added dropwise at 25 °C. The reaction mixture was heated at 80 °C for 2 h. Toluene was distilled off in vacuo and acetonitrile (40 mL) was added to the crude residue. The acetonitrile layer was washed with hexane (15 mL × 3) and concentrated in vacuo. The silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate as an eluent afforded the desired deoxygenated product (*S*)-**38** as a yellowish solid (165 mg, 54% yield; 94% *ee*). Mp 194–196 °C; $[\alpha]^{25}_D$ –220.2 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500



(–)-$C_{15}H_{16}N_2O$ (**38**)
M.W. 240.31

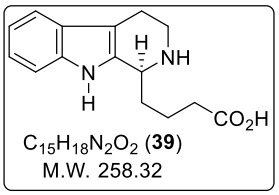
MHz) δ 1.70–2.00 (m, 3H), 2.35–2.55 (m, 2H), 2.55–2.65 (m, 1H), 2.72–2.95 (m, 3H), 4.80 (dd, *J* = 10 and 5 Hz, 1H), 5.13–5.24 (m, 1H), 7.13 (t, *J* = 10 Hz, 1H), 7.19 (t, *J* = 10 Hz, 1H), 7.35 (d, *J* = 10 Hz, 1H), 7.52 (d, *J* = 10 Hz, 1H), 8.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 21.0, 29.0, 32.4, 40.2, 54.4, 109.5, 110.9, 118.4, 119.8, 122.1, 126.8, 133.3, 136.2, 169.3; ESIMS (*m*/*z*) 241 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}N_2O$ 241.1335, found 241.1332; IR ($CHCl_3$) ν_{max} 3283, 1733, 1623 cm^{-1}.

(–)-(*S*)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (Desbromoarborescidine A, 8). A flame dried round-bottomed flask was charged with $AlCl_3$ (22 mg, 0.16 mmol) and THF (4 mL) under argon atmosphere. The stirred reaction mixture was cooled to 0 °C and a suspension of $LiAlH_4$ (21 mg, 0.55 mmol) in THF (2 mL) was added dropwise. After stirring for 10 min at 0 °C, a solution of lactam (*S*)-**38** (44 mg, 0.18 mmol) in THF (2 mL) was added dropwise to the above reaction mixture. Then it was stirred for 30 min at 25 °C and quenched by the addition of saturated aq. NH_4Cl (2 mL). The reaction mixture was filtered through Celite and the solid residue was washed with ethyl acetate (10 mL × 3). The filtrate was dried over Na_2SO_4 and concentrated in vacuo. The silica gel (230–400 mesh) column chromatographic purification of the resulting residue using chloroform–methanol (9:1) as an eluent afforded desbromoarborescidine A (**8**) as a white solid (34 mg, 82% yield). Mp 148–150 °C; $[\alpha]^{25}_D$ –80.5 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42–1.57 (m, 1H), 1.60 (dq, *J* = 12 and 4 Hz, 1H), 1.70–1.85 (m, 2H), 1.91 (d, *J* = 12 Hz, 1H), 2.06 (dd, *J* = 12 and 4 Hz, 1H), 2.41 (dt, *J* = 12 and 4 Hz, 1H), 2.60–2.78 (m, 2H), 2.98–3.09 (m, 2H), 3.10 (t, *J* = 4 Hz, 1H), 3.24 (d, *J* = 8 Hz, 1H), 7.11 (t, *J* = 8 Hz, 1H), 7.15 (t, *J* = 8 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 24.3, 25.7, 29.9, 53.5, 55.7, 60.2, 108.0, 110.7, 118.1, 119.3, 121.2, 127.4, 135.1, 135.9; ESIMS (*m*/*z*) 227 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3476, 1599 cm^{-1}.



(–)-Desbromo-arborescidine A
$C_{15}H_{18}N_2$ (**8**)
M.W. 226.32

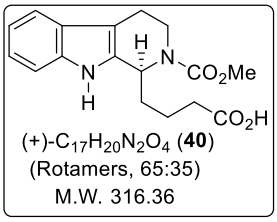
(*S*)-4-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)butanoic Acid (39). Aqueous KOH (10%, 20 mL) was added dropwise to a stirred solution of lactam (*S*)-**38** (300 mg, 1.25 mmol) in THF (4 mL) at 25 °C. The reaction mixture was heated at 100 °C for 36 h and allowed to reach 25 °C. The reaction mixture was then cooled to 0 °C and slowly neutralized by the dropwise addition of 2 N HCl. The hydrolyzed compound started precipitating in between pH 8 to 7. The formed precipitate was filtered and dried to obtain the required acid **39** as a white



$C_{15}H_{18}N_2O_2$ (**39**)
M.W. 258.32

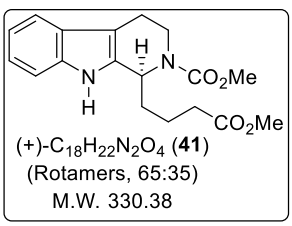
solid (274 mg, 85% yield). Mp 198–200 °C; ^{1}H NMR (D_2O, 200 MHz) δ 1.69 (t, J = 6 Hz, 1H), 1.76 (t, J = 8 Hz, 1H), 1.91 (q, J = 8 Hz, 1H), 2.00–2.25 (m, 1H), 2.44 (t, J = 8 Hz, 2H), 2.90–3.04 (m, 2H), 3.20–3.38 (m, 1H), 3.65 (td, J = 12 and 6 Hz, 1H), 4.45–4.57 (m, 1H), 7.13 (dt, J = 8 and 2 Hz, 1H), 7.24 (dt, J = 8 and 2 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 7.54 (d, J = 8 Hz, 1H); ^{13}C NMR (D_2O, 50 MHz) δ 20.3, 22.3, 33.2, 35.7, 44.0, 55.5, 108.6, 114.1, 120.9, 122.3, 125.2, 128.1, 131.4, 138.8, 180.5; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2$ 259.1441, found 259.1439; IR (Nujol) ν_{max} 3350, 1791, 1623 cm^{-1}. The NMR data of product **39** was collected as its mono-hydrochloride for solubility reasons.

(+)-(*S*)-4-(2-(Methoxycarbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)butanoic Acid (40). A solution of KOH (117 mg, 2.09 mmol) in water (2 mL) was added at 0 °C to a stirred suspension of amine **39** (270 mg, 1.05 mmol) in acetone:water mixture (1:1, 8 mL). The reaction mixture was stirred for 10 min and methyl chloroformate (0.09 mL, 1.15 mmol) was added dropwise at the same temperature. It was further stirred for 2 h at 0 ^{o}C and slowly neutralized with 2 N HCl. Acetone was removed in vacuo and the crude residue was extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:9) as an eluent provided the carbamate (+)-**40** as a white foam (238 mg, 72% yield). Mp 56–58 °C; $[\alpha]^{25}_D$ +77.0 (*c* 4.8 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (br s, 3H), 1.90 (br s, 1H), 2.41 (br s , 2H), 2.64 (s, 0.35H), 2.68 (s, 0.65H), 2.79 (br s, 1H), 3.16 (br d, J = 12 Hz, 1H), 3.71 (s, 1.05H), 3.75 (s, 1.95H), 4.30 (d, J = 12 Hz, 0.65H), 4.48 (d, J = 8 Hz, 0.35H), 5.16 (s, 0.35H), 5.34 (s, 0.65H), 6.95–7.15 (m, 2H), 7.25 (d, J = 8 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 8.32 (s, 0.35H), 8.57 (s, 0.65H), 8.50–9.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 21.1, 21.4, 33.4, 33.7, 34.0, 38.3, 38.5, 51.1, 52.9, 53.0, 107.8, 108.5, 111.0, 117.9, 118.1, 119.3, 121.7, 126.6, 133.6, 134.0, 136.0, 156.4, 156.9, 178.4; ESIMS (*m*/*z*) 339 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_4$ 317.1496, found 317.1494; IR ($CHCl_3$) ν_{max} 3333, 2700–2500, 1700, 1685 cm^{-1}.



(+)-$C_{17}H_{20}N_2O_4$ (**40**)
(Rotamers, 65:35)
M.W. 316.36

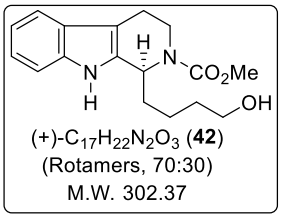
(+)-Methyl (*S*)-1-(4-Methoxy-4-oxobutyl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indole-2-carboxylate (41). Ether solution of diazomethane was added dropwise at 0 °C to a stirred solution of acid (+)-**40** (230 mg, 0.73



(+)-$C_{18}H_{22}N_2O_4$ (**41**)
(Rotamers, 65:35)
M.W. 330.38

mmol) in diethyl ether and THF mixture (1:1, 6 mL) until the persistence of light yellow color. The reaction mixture was stirred at 0 °C for 30 min and the solvent was removed under reduced pressure. The silica gel (60–120 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (6:4) as an eluent afforded the pure ester (+)-**41** as a colorless gummy solid (206 mg, 86% yield). $[\alpha]^{25}_{D}$ +91.0 (*c* 0.14 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85 (quintet, *J* = 6 Hz, 4H), 2.43 (t, *J* = 8 Hz, 2H), 2.60–3.00 (m, 2H), 3.05–3.30 (m, 1H), 3.69 (s, 3H), 3.75 (s, 3H), 4.25–4.60 (br m, 1H), 5.19 (br s, 0.35H), 5.33 (br s, 0.65H), 7.09 (t, *J* = 8 Hz, 1H), 7.16 (t, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 8.08 (br s, 0.35H), 8.18 (br s, 0.65H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 21.3, 33.5, 33.9, 34.2, 38.3, 38.5, 51.0, 51.6, 52.8, 107.9, 108.6, 110.9, 117.9, 119.3, 121.6, 126.7, 133.7, 134.1, 136.0, 156.3, 156.6, 174.1; ESIMS (*m*/*z*) 353 $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{23}N_2O_4$ 331.1652, found 331.1648; IR ($CHCl_3$) ν_{max} 3331, 1735, 1685, 1623 cm^{-1}.

(+)-Methyl (*S*)-1-(4-Hydroxybutyl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indole-2-carboxylate (42). DIBAL solution (1 M in cyclohexane, 0.60 mL) was added dropwise at –78 °C to a stirred solution of ester (+)-**41** (200 mg, 0.60 mmol) in THF (8 mL) under argon atmosphere. The stirred reaction mixture was allowed to reach 25 °C in 4 h. The reaction was quenched at 0 °C with saturated aq. potassium sodium tartrate (4 mL). It was then stirred at 25 °C for 1 h and concentrated in vacuo to remove the THF. The obtained residue was extracted with CH_2Cl_2 (25 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded the alcohol (+)-**42** as a yellowish foam (134 mg, 73% yield). Mp 56–58 °C; $[\alpha]^{25}_{D}$ +89.9 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40–1.75 (m, 4H), 1.75–2.07 (m, 2H), 2.60–3.00 (m, 2H), 3.05–3.35 (m, 1.30H), 3.35–3.55 (m, 0.70H), 3.55–3.75 (m, 2H), 3.83 (s, 3H), 4.38 (dd, *J* = 10 and 2 Hz, 0.70H), 4.54 (d, *J* = 10 Hz, 0.30H), 5.21 (br s, 0.30H), 5.40 (br s, 0.70H), 7.05–7.24 (m, 2H), 7.32 (dd, *J* = 8 and 2 Hz, 1H), 7.51 (dd, *J* = 8 and 2 Hz, 1H), 8.81 (br s, 0.30H), 9.26 (br s, 0.70H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 21.4, 22.3, 22.5, 32.1, 34.1, 34.4, 38.3, 38.4, 51.4, 51.7, 52.6, 52.9, 62.2, 107.3, 108.0, 110.9, 117.8, 118.0, 119.0, 119.1, 121.3, 121.5, 126.5, 134.0, 134.5, 136.0, 156.4, 156.8; ESIMS (*m*/*z*) 325 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3405, 3468, 1684, 1623 cm^{-1}.



(+)-$C_{17}H_{22}N_2O_3$ (**42**)
(Rotamers, 70:30)
M.W. 302.37

(+)-Methyl (3a*S*,7*S*)-7-Hydroxy-1,3a,4,5,6,7-hexahydro-3,7a-diazacyclohepta[*jk*]fluorene-3(2*H*)-carboxylate (44). To a stirred solution of alcohol (+)-**42** (130 mg, 0.43 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added Dess–Martin periodinane (274 mg, 0.65 mmol) followed by pyridine (0.05 mL, 0.65 mmol) under argon atmosphere. After stirring for 30 min at the same temperature, the reaction mixture was diluted with CH_2Cl_2 (6 mL) and quenched with mixture of aq. sodium thiosulphate (40%, 2 mL) plus saturated aq. $NaHCO_3$ (2 mL). It was then extracted with CH_2Cl_2 (20 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by immediate silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent resulted the mixture of aldehyde **43** and further cyclized product (+)-**44** as a yellow liquid (by ^{1}H NMR). The above mixture of products was then further stirred in chloroform (8 mL) at 25 °C for 18 h. The concentration of above chloroform solution in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (6:4) as an eluent afforded the desired cyclized compound (+)-**44** as a yellow gummy solid (93 mg, 72% yield). $[\alpha]^{25}_D$ +110.4 (*c* 0.25 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62 (t, *J* = 12 Hz, 1H), 1.80 (d, *J* = 8 Hz, 2H), 2.00–2.14 (m, 1H), 2.25–2.50 (m, 2H), 2.60–2.82 (m, 2H), 3.04 (t, *J* = 12 Hz, 1.50H), 3.28 (br s, 0.50H), 3.72 (s, 1.50H), 3.74 (s, 1.50H), 4.31 (d, *J* = 12 Hz, 0.50H), 4.49 (d, *J* = 12 Hz, 0.50H), 5.31 (d, *J* = 12 Hz, 0.50H), 5.41 (d, *J* = 12 Hz, 0.50 Hz), 6.23 (d, *J* = 4 Hz, 1H), 7.11 (t, *J* = 8 Hz, 1H), 7.19 (t, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 21.3, 21.6, 33.3, 33.9, 38.8, 39.1, 52.4, 52.7, 52.8, 76.1, 108.4, 108.9, 109.6, 118.2, 118.3, 119.47, 119.53, 121.55, 121.64, 126.3, 135.7, 136.5, 155.7, 156.0; ESIMS (*m*/*z*) 323 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3384, 1683, 1615 cm^{-1}.

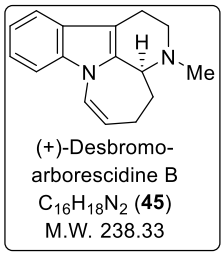
(+)-$C_{17}H_{20}N_2O_3$ (**44**)
Rotamers, (50:50)
M.W. 300.36

(+)-(3a*S*,7*S*)-3-Methyl-1,2,3,3a,4,5,6,7-octahydro-3,7a-diazacyclohepta[*jk*]fluoren-7-ol (Desbromoarborescidine C, 27). To a stirred solution of carbamate (+)-**44** (90 mg, 0.30 mol) in dry THF (3 mL) at 25 °C was added a solution of AlH_3 (1.55 M, 0.40 mL, 0.60 mmol) and the reaction mixture was stirred for 2 h under argon atmosphere. The reaction was quenched with aq. saturated Na_2SO_4 (2 mL) and filtered. The residue was washed with CH_2Cl_2 (30 mL) and the filtrate was dried over Na_2SO_4. Concentration of

(+)-Desbromo-arborescidine C (**27**)
$C_{16}H_{20}N_2O$
M.W. 256.35

the filtrate in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using chloroform–methanol (9:1) as an eluent afforded desbromoarborescidine C (**27**) as a white solid (73 mg, 95% yield). Mp 140–142 °C; $[\alpha]^{25}_{D}$ +3.2 (*c* 0.25 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (dq, *J* = 12 and 4 Hz, 1H), 1.66 (qt, *J* = 12 and 4 Hz, 1H), 1.80–1.90 (m, 1H), 2.20 (tq, *J* = 12 and 4 Hz, 1H), 2.30–2.41 (m, 2H), 2.56 (s, 3H), 2.73–2.88 (m, 1H), 2.81 (d, *J* = 4 Hz, 2H), 3.11 (quintet, *J* = 8 Hz, 1H), 3.80 (d, *J* = 8 Hz, 1H), 6.24 (dd, *J* = 8 and 4 Hz, 1H), 7.11 (dt, *J* = 8 and 4 Hz, 1H), 7.19 (dt, *J* = 8 and 4 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 20.1, 32.0, 34.2, 42.2, 50.4, 61.4, 76.4, 108.4, 108.6, 118.3, 119.4, 121.4, 126.5, 136.1, 136.7; ESIMS (*m*/*z*) 257 $[M+H]^+$; IR (Nujol) ν_{max} 3365, 1612 cm^{-1}.

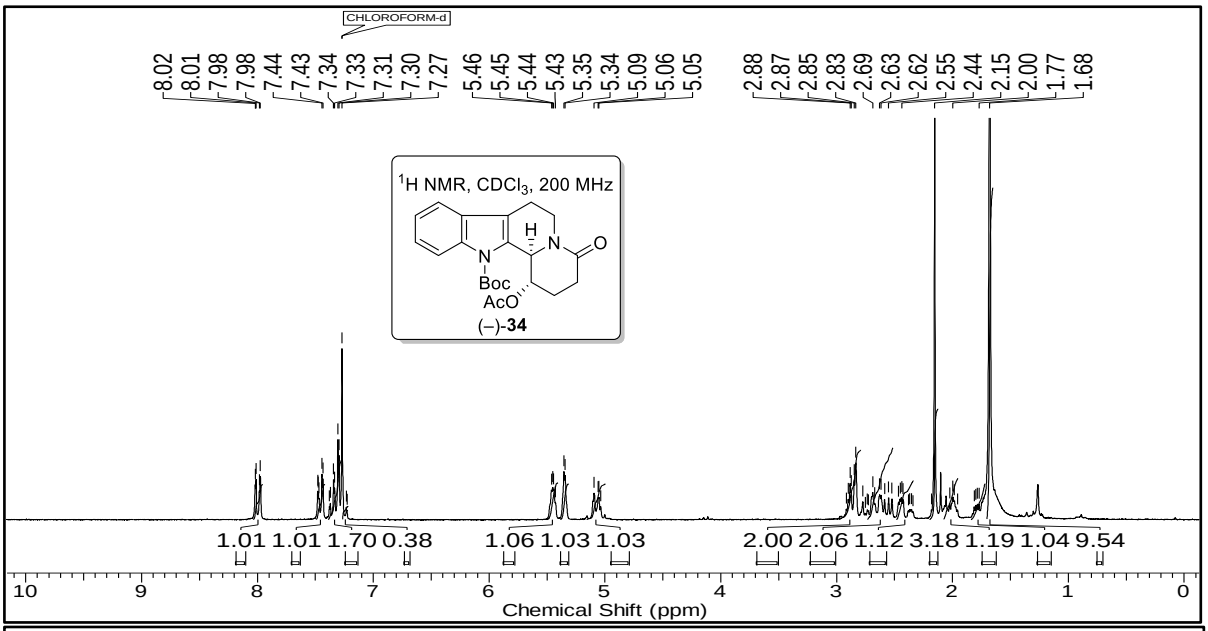
(+)-(*S*)-3-Methyl-1,2,3,3a,4,5-hexahydro-3,7a-diazacyclohepta[*jk*]fluorene



(+)-Desbromo-arborescidine B
$C_{16}H_{18}N_2$ (**45**)
M.W. 238.33

(Desbromoarborescidine B, 45). Burgess reagent (95 mg, 0.40 mmol) was added at 25 °C to a stirred solution of aminol **27** (50 mg, 0.20 mmol) in dry benzene (10 mL) under argon atmosphere. The reaction mixture was refluxed for 8 h and then allowed to reach 25 °C. The reaction mixture was diluted with ethyl acetate (25 mL) and washed three times with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (95:5) as an eluent afforded desbromoarborescidine B (**45**) as a brown solid (38 mg, 81% yield). Mp 98–100 °C; $[\alpha]^{25}_{D}$ +62.1 (*c* 0.36 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91 (dq, *J* = 12 and 4 Hz, 1H), 2.34–2.50 (m, 2H), 2.50–2.63 (m, 1H), 2.57 (s, 3H), 2.70–2.80 (m, 2H), 2.90–3.02 (m, 1H), 3.18 (dd, *J* = 12 and 4 Hz, 1H), 3.45 (d, *J* = 12 Hz, 1H), 5.07 (td, *J* = 8 and 4 Hz, 1H), 6.95 (d, *J* = 12 Hz, 1H), 7.15 (t, *J* = 8 Hz, 1H), 7.22 (t, *J* = 8 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 28.0, 29.9, 42.4, 52.8, 62.5, 109.1, 109.2, 110.0, 118.2, 120.2, 121.8, 122.0, 126.9, 136.1, 137.1; ESIMS (*m*/*z*) 239 $[M+H]^+$; IR (Nujol) ν_{max} 1674 cm^{-1}.

2B.6 Selected Spectra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8.02 8.01 7.98 7.98 7.44 7.43 7.34 7.33 7.31 7.30 7.27
5.46 5.45 5.44 5.43 5.35 5.34 5.09 5.06 5.05
2.88 2.87 2.85 2.83 2.69 2.63 2.62 2.55 2.44 2.15 2.00 1.77 1.68
^{1}H NMR, CDCl$_3$, 200 MHz
(–)-34
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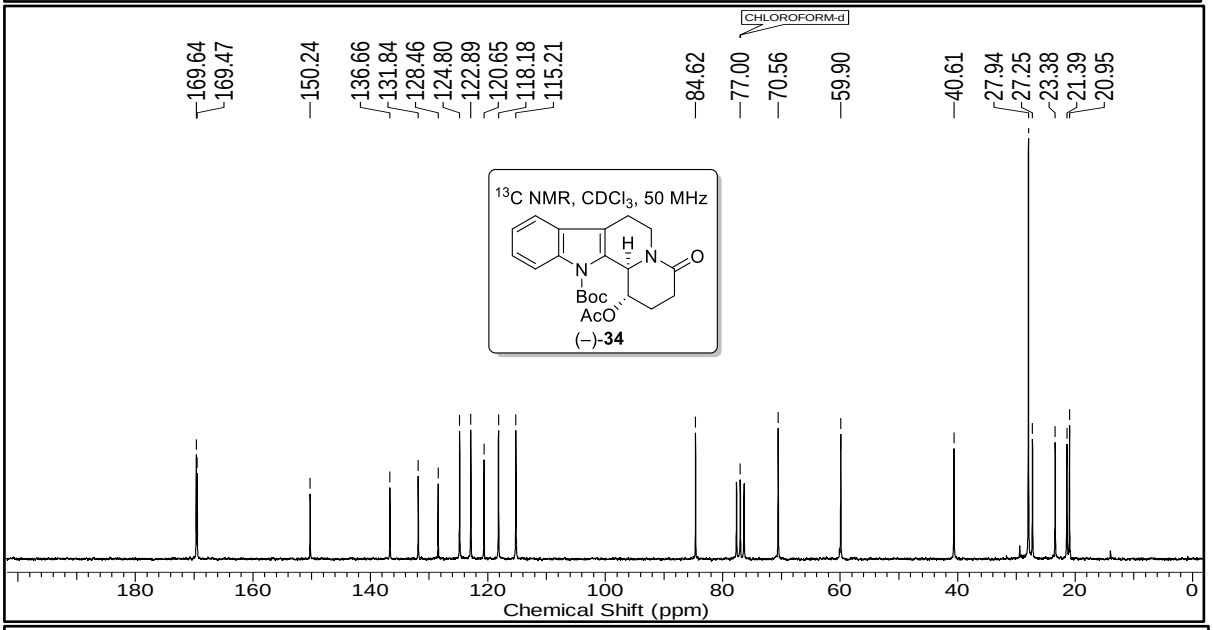
1.06 1.03 1.03
2.00 2.06 1.12 3.18 1.19 1.04 9.54
Chemical Shift (ppm)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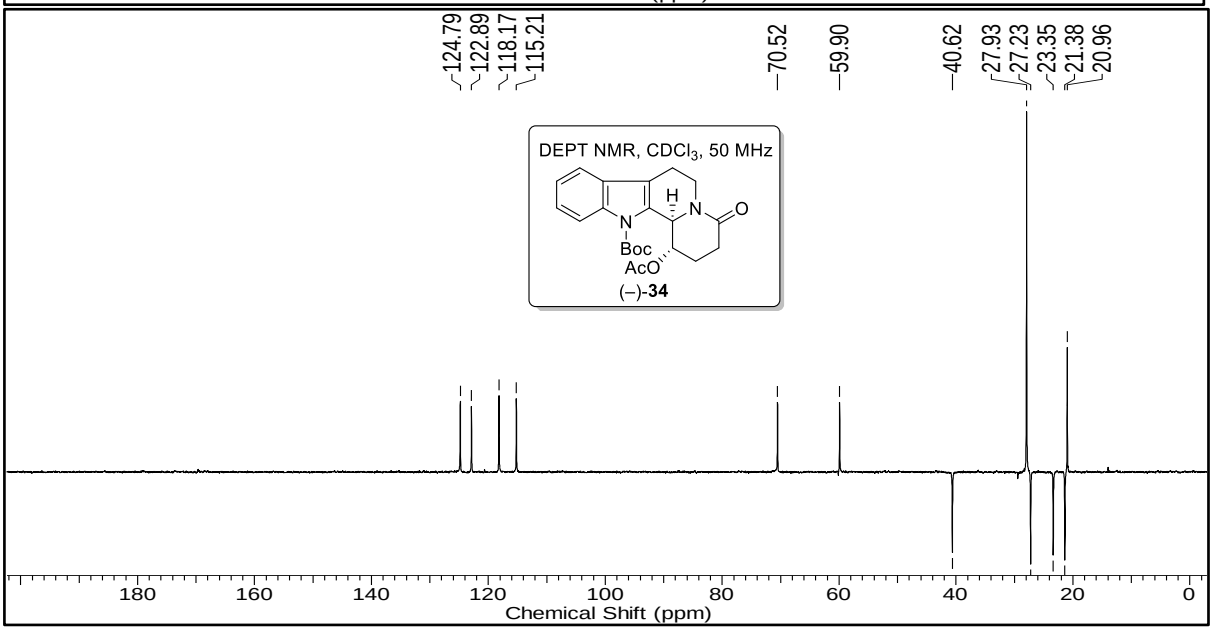
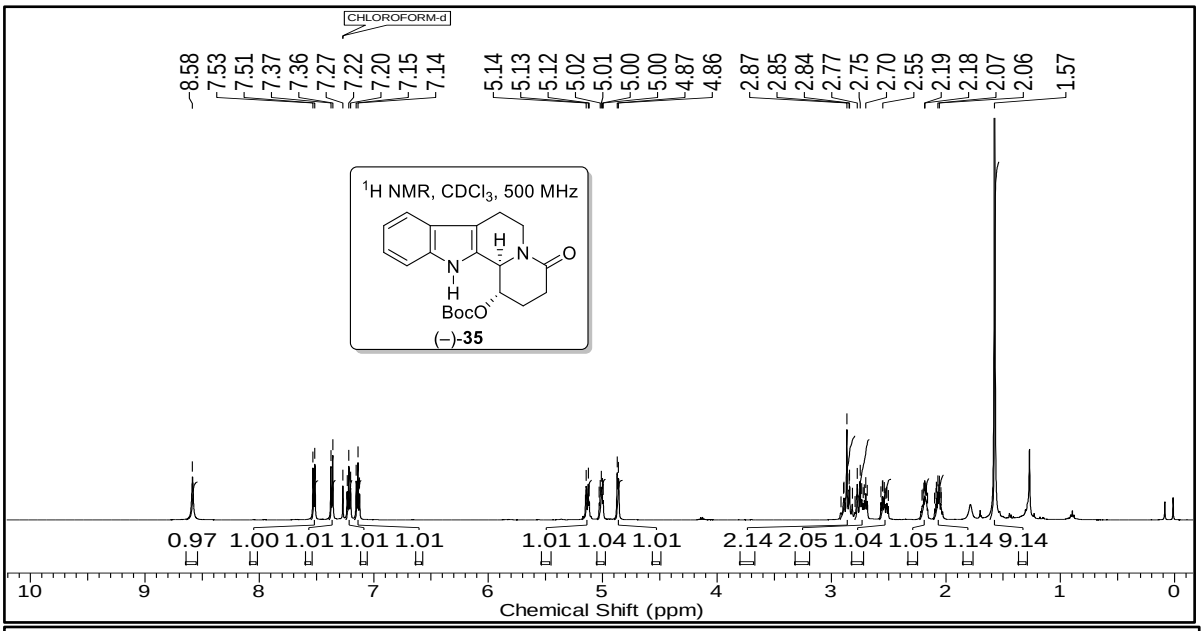
169.64 169.47 150.24 136.66 131.84 128.46 124.80 122.89 120.65 118.18 115.21
84.62 77.00 70.56 59.90 40.61 27.94 27.25 23.38 21.39 20.95
^{13}C NMR, CDCl$_3$, 50 MHz
(–)-34
Chemical Shift (ppm)


124.79 122.89 118.17 115.21
70.52 59.90 40.62 27.93 27.23 23.35 21.38 20.96
DEPT NMR, CDCl$_3$, 50 MHz
(–)-34
Chemical Shift (ppm)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5.14 5.13 5.12 5.02 5.01 5.00 5.00 4.87 4.86
2.87 2.85 2.84 2.77 2.75 2.70 2.55 2.19 2.18 2.07 2.06 1.57
^{1}H NMR, $CDCl_3$, 500 MHz
(–)-35
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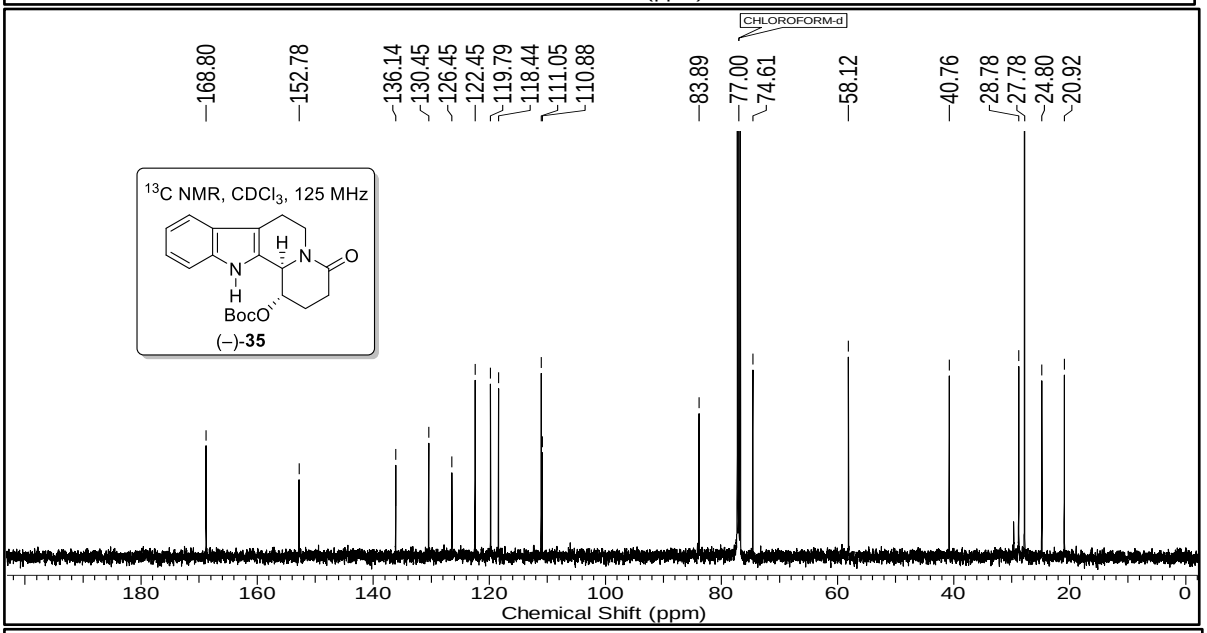
Chemical Shift (ppm)


CHLOROFORM-d
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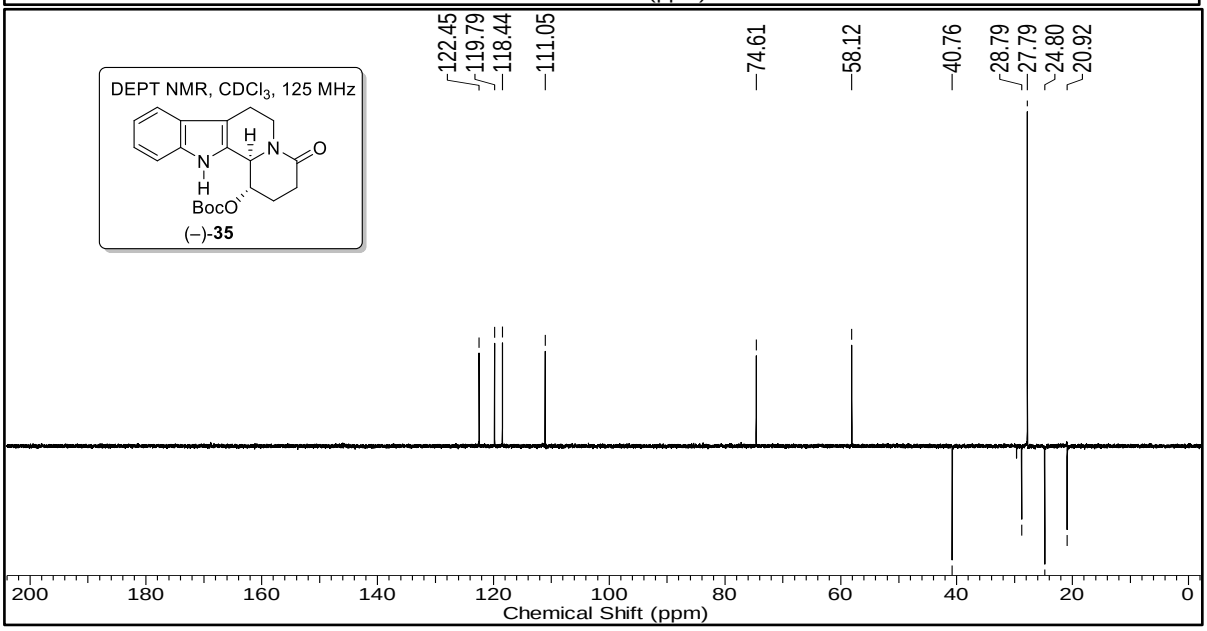
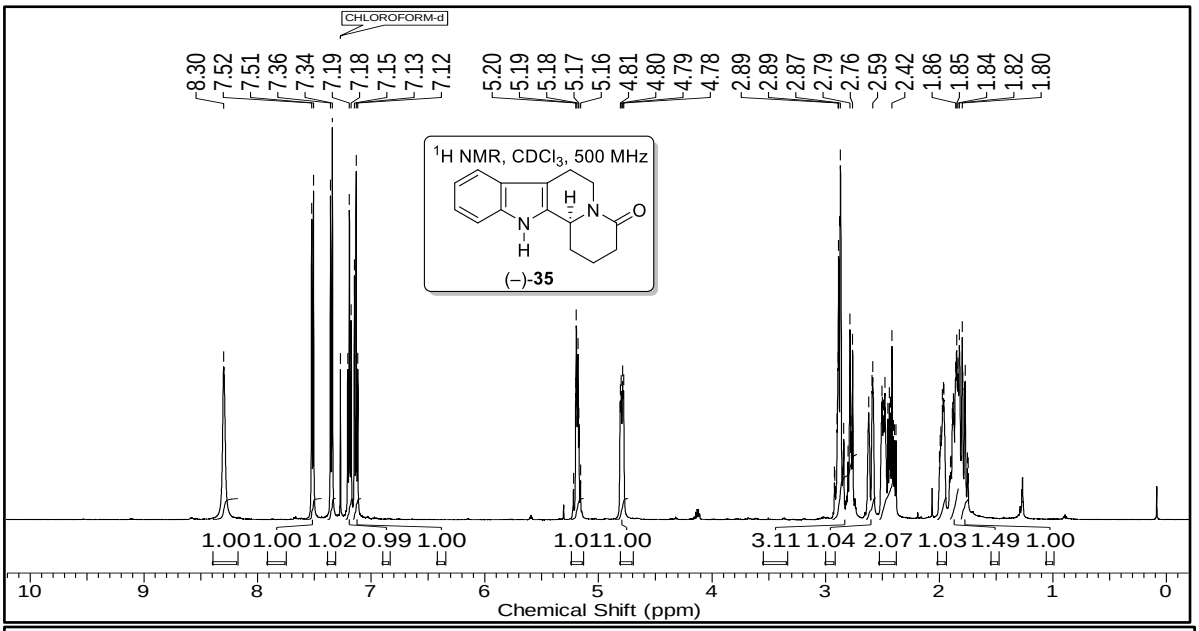
83.89 77.00 74.61 58.12 40.76 28.78 27.78 24.80 20.92
^{13}C NMR, $CDCl_3$, 125 MHz
(–)-35
Chemical Shift (ppm)


122.45 119.79 118.44 111.05 74.61 58.12 40.76 28.79 27.79 24.80 20.92
DEPT NMR, $CDCl_3$, 125 MHz
(–)-35
Chemical Shift (ppm)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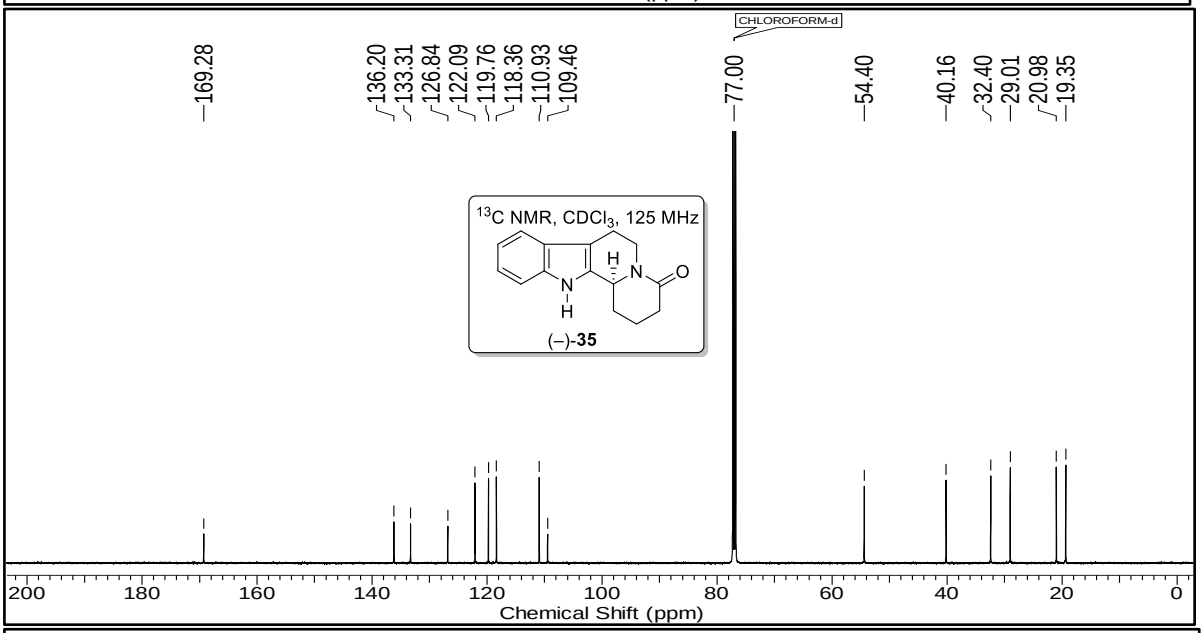
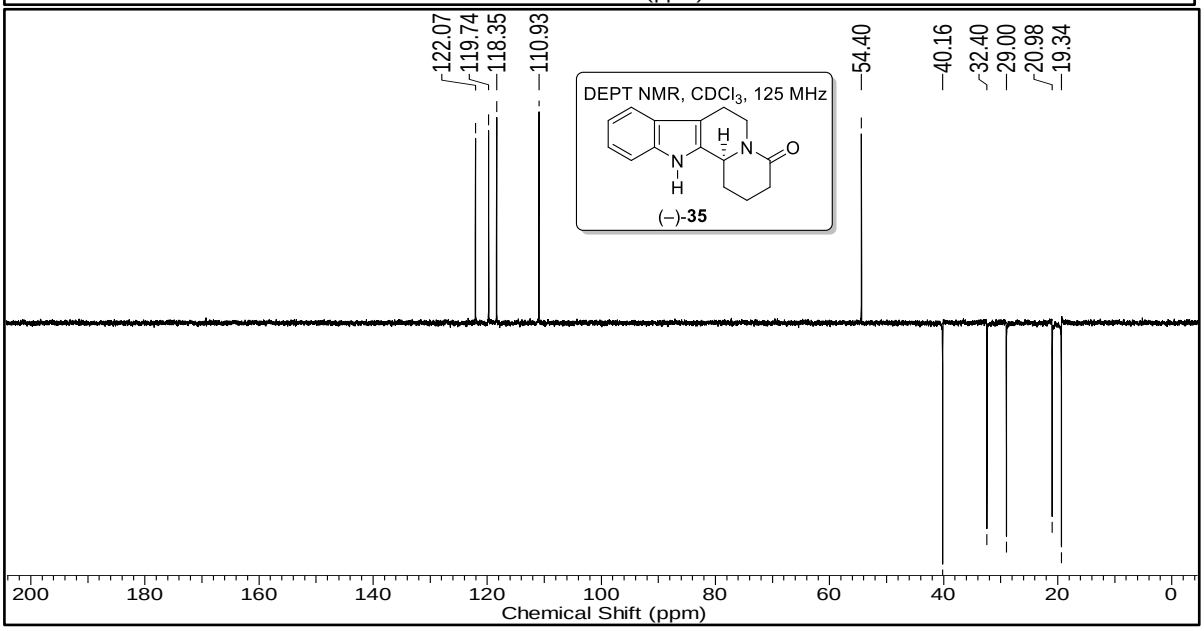
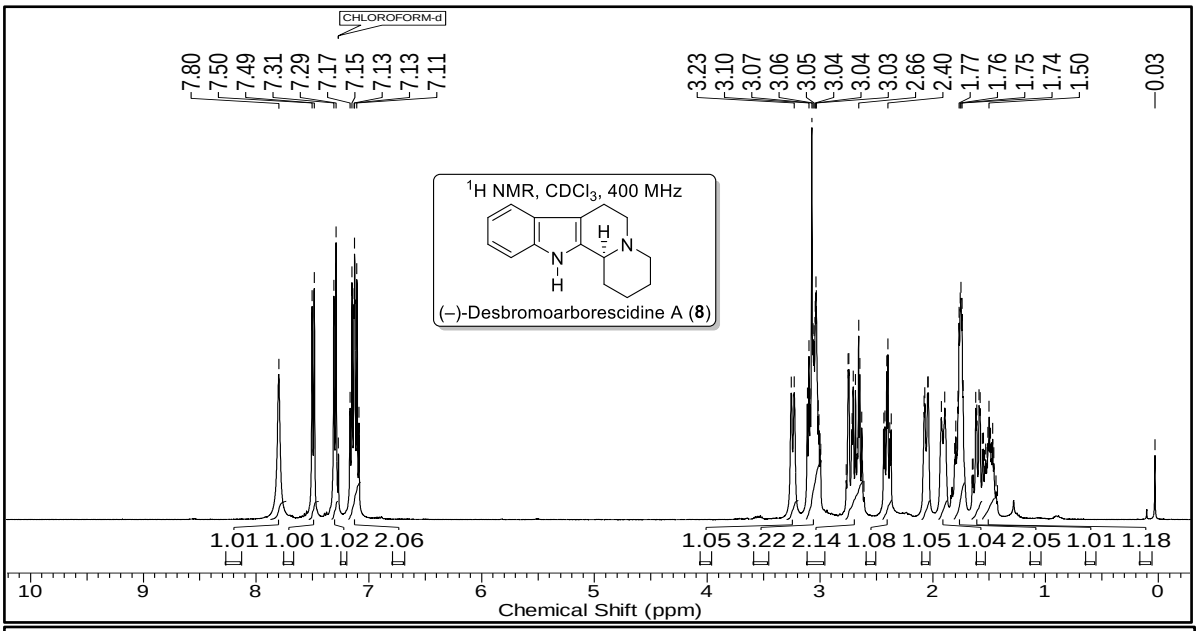
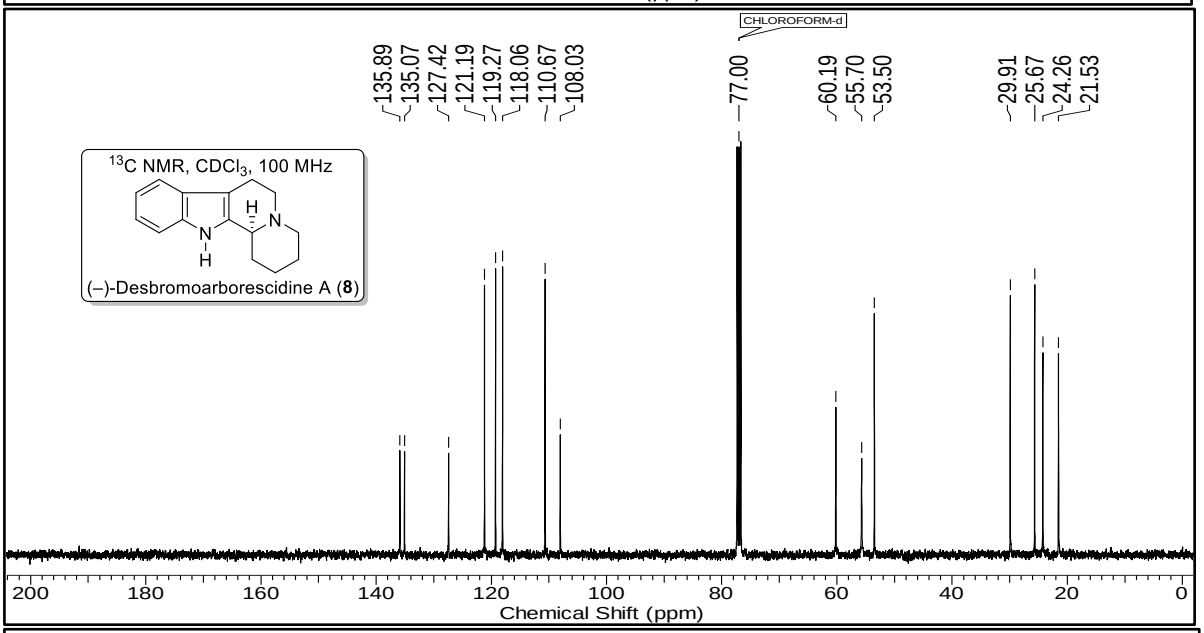
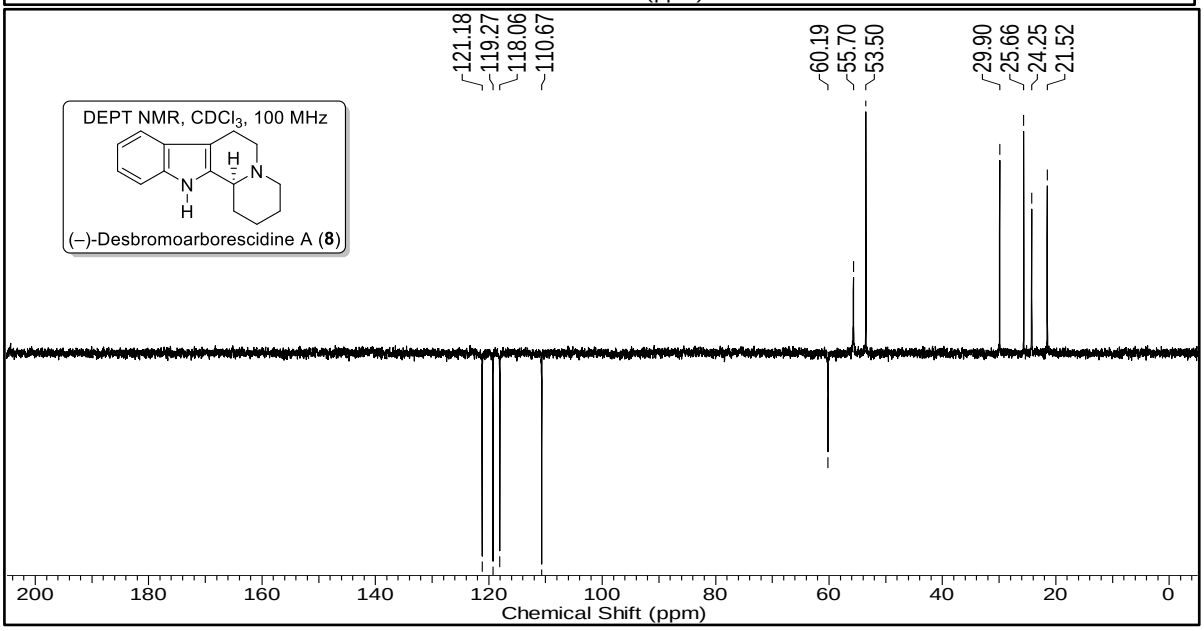
5.20 5.19 5.18 5.17 5.16 4.81 4.80 4.79 4.78
2.89 2.89 2.87 2.79 2.76 2.59 2.42
1.86 1.85 1.84 1.82 1.80
^{1}H NMR, $CDCl_3$, 500 MHz
(–)-35
1.00 1.00 1.02 0.99 1.00 1.01 1.00 3.11 1.04 2.07 1.03 1.49 1.00
Chemical Shift (ppm)

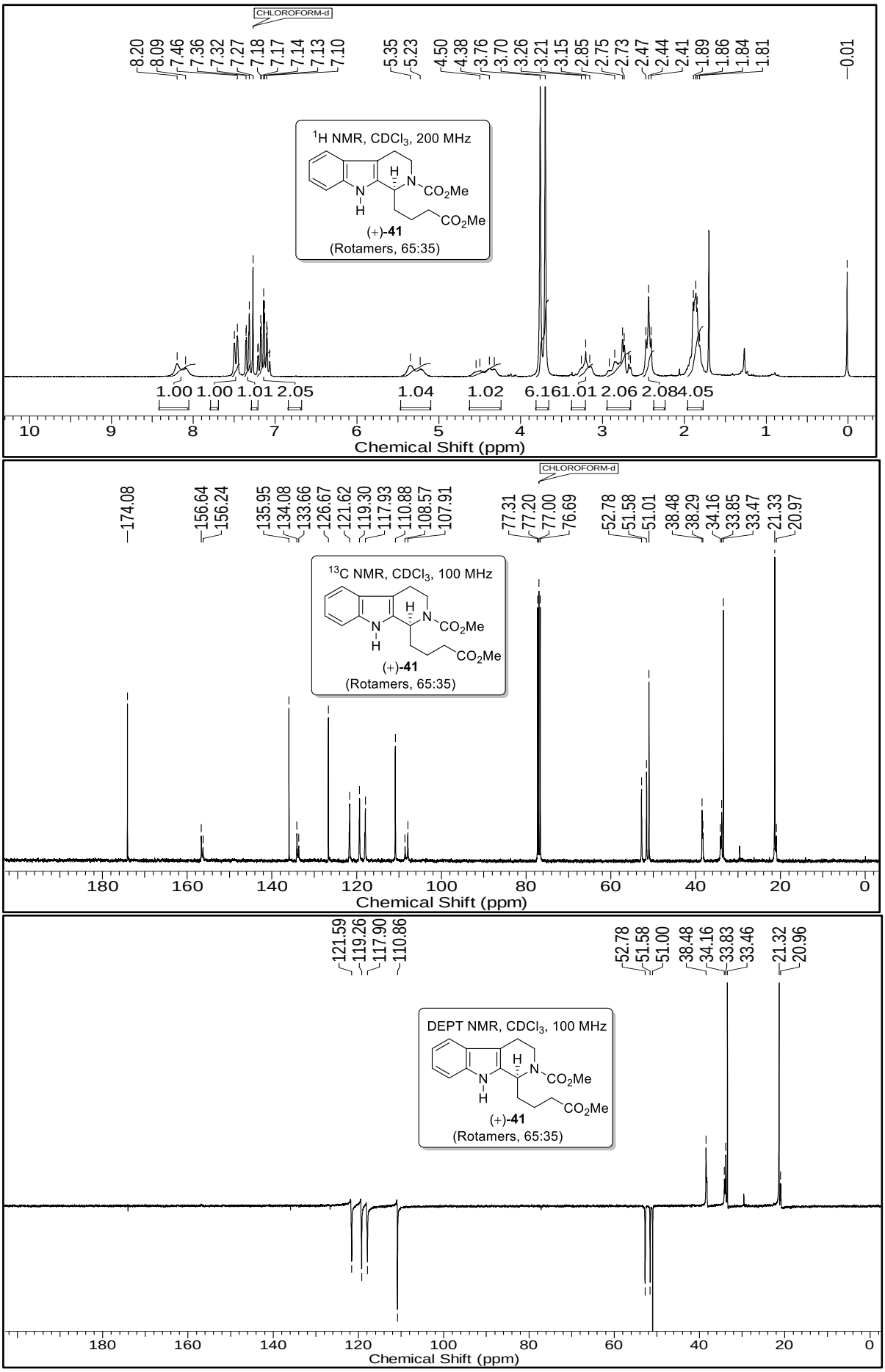

CHLOROFORM-d
169.28
136.20 133.31 126.84 122.09 119.76 118.36 110.93 109.46
77.00
54.40
40.16 32.40 29.01 20.98 19.35
^{13}C NMR, $CDCl_3$, 125 MHz
(–)-35
Chemical Shift (ppm)

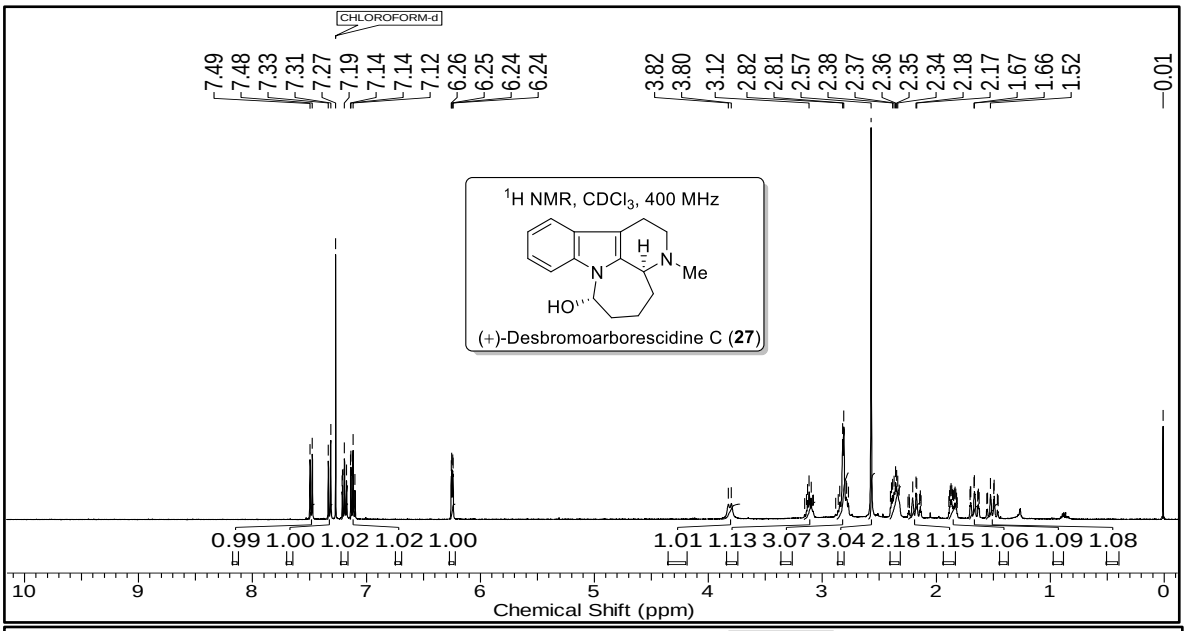

122.07 119.74 118.35 110.93
54.40
40.16 32.40 29.00 20.98 19.34
DEPT NMR, $CDCl_3$, 125 MHz
(–)-35
Chemical Shift (ppm)

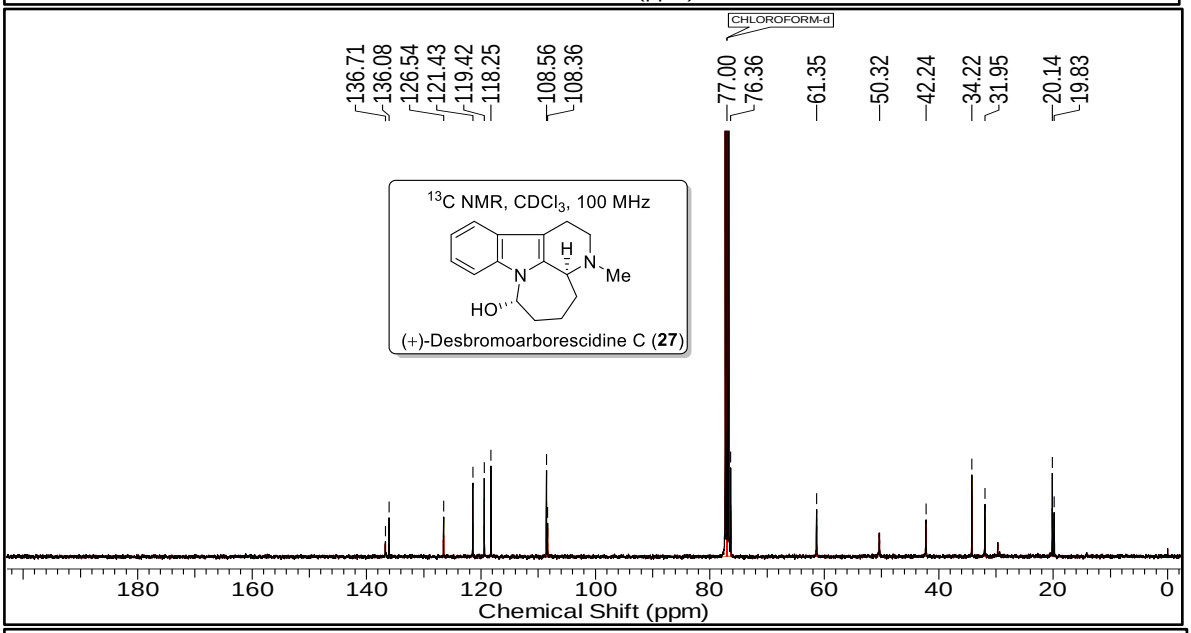

CHLOROFORM-d
7.80 7.50 7.49 7.31 7.29 7.17 7.15 7.13 7.13 7.11
3.23 3.10 3.07 3.06 3.05 3.04 3.04 3.03 2.66 2.40 1.77 1.76 1.75 1.74 1.50
0.03
^{1}H NMR, $CDCl_3$, 400 MHz
(–)-Desbromoarborescidine A (8)
1.01 1.00 1.02 2.06
1.05 3.22 2.14 1.08 1.05 1.04 2.05 1.01 1.18
Chemical Shift (ppm)

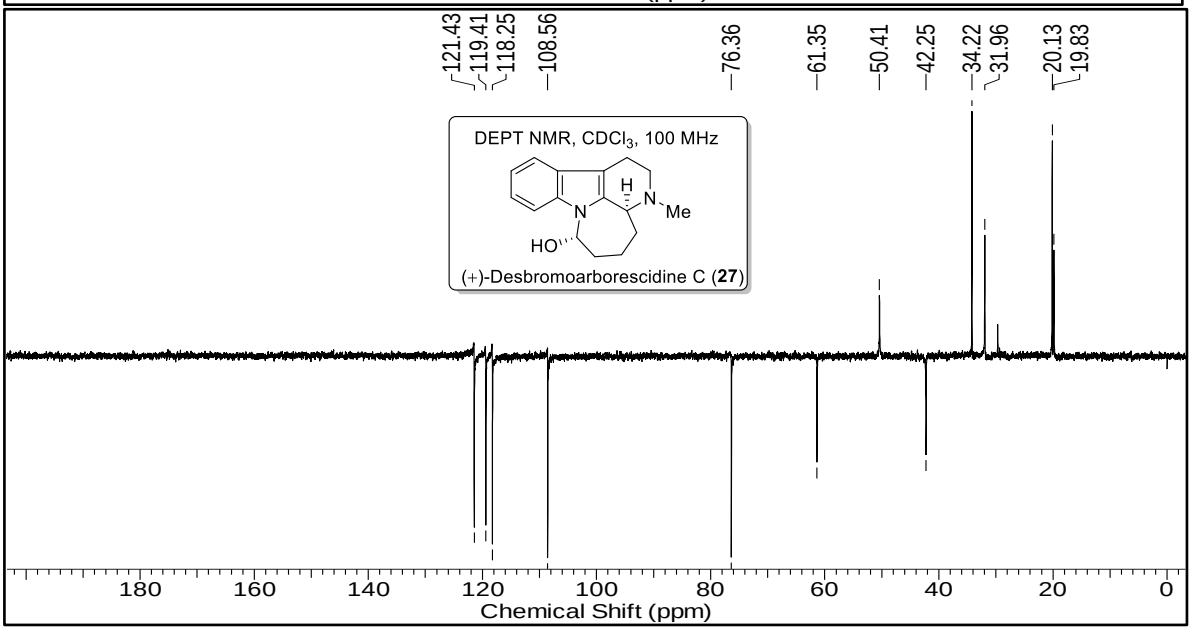

CHLOROFORM-d
135.89 135.07 127.42 121.19 119.27 118.06 110.67 108.03
77.00
60.19 55.70 53.50
29.91 25.67 24.26 21.53
^{13}C NMR, $CDCl_3$, 100 MHz
(–)-Desbromoarborescidine A (8)
Chemical Shift (ppm)

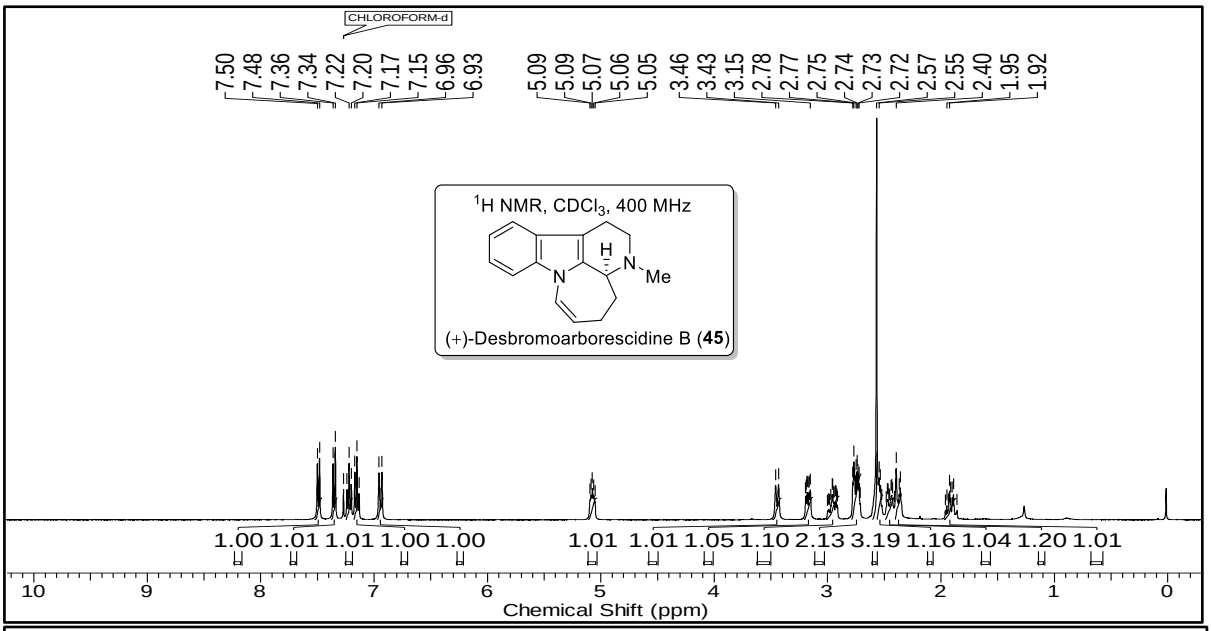

121.18 119.27 118.06 110.67
60.19 55.70 53.50
29.90 25.66 24.25 21.52
DEPT NMR, $CDCl_3$, 100 MHz
(–)-Desbromoarborescidine A (8)
Chemical Shift (ppm)

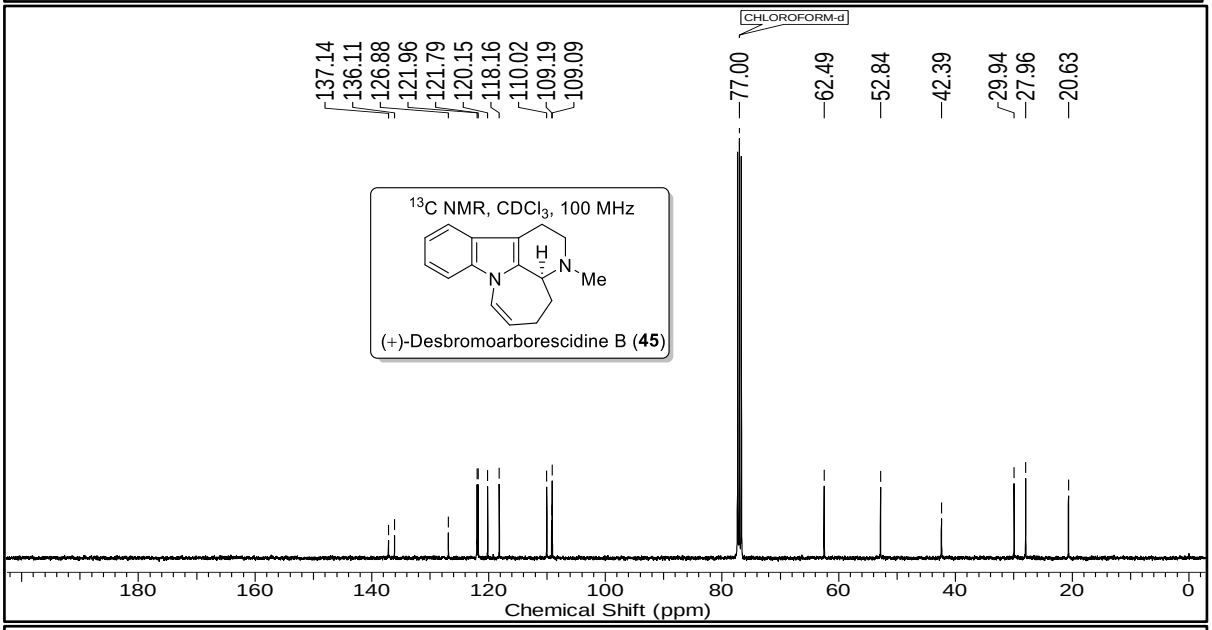

CHLOROFORM-d
8.20 8.09 7.46 7.36 7.32 7.27 7.18 7.17 7.14 7.13 7.10
5.35 5.23
4.50 4.38 3.76 3.70 3.26 3.21 3.15 2.85 2.75 2.73 2.47 2.44 2.41
1.89 1.86 1.84 1.81
0.01
1H NMR, CDCl3, 200 MHz
(+)-41
(Rotamers, 65:35)
1.00 1.00 1.01 2.05 1.04 1.02 6.16 1.01 2.06 2.08 4.05
Chemical Shift (ppm)
CHLOROFORM-d
174.08
156.64 156.24
135.95 134.08 133.66 126.67 121.62 119.30 117.93 110.88 108.57 107.91
77.31 77.20 77.00 76.69
52.78 51.58 51.01
38.48 38.29 34.16 33.85 33.47
21.33 20.97
13C NMR, CDCl3, 100 MHz
(+)-41
(Rotamers, 65:35)
Chemical Shift (ppm)
121.59 119.26 117.90 110.86
52.78 51.58 51.00 38.48 34.16 33.83 33.46 21.32 20.96
DEPT NMR, CDCl3, 100 MHz
(+)-41
(Rotamers, 65:35)
Chemical Shift (ppm)

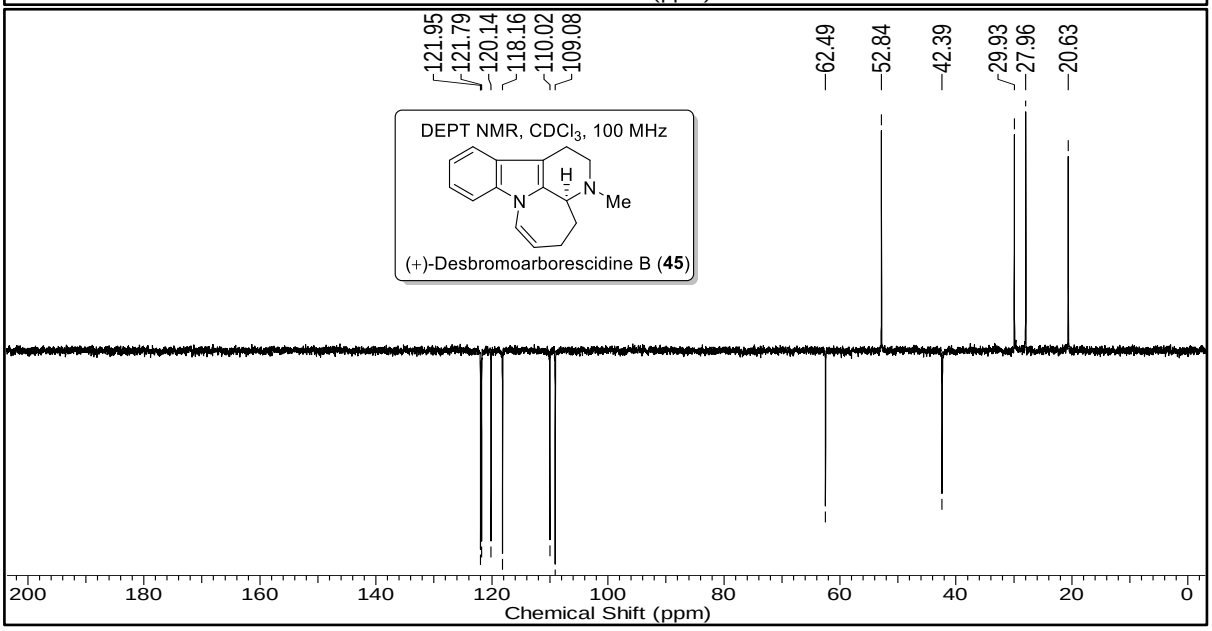

CHLOROFORM-d
7.49 7.48 7.33 7.31 7.27 7.19 7.14 7.14 7.12 6.26 6.25 6.24 6.24
3.82 3.80 3.12 2.82 2.81 2.57 2.38 2.37 2.36 2.35 2.34 2.18 2.17 1.67 1.66 1.52
0.01
^{1}H NMR, CDCl$_3$, 400 MHz
(+)-Desbromoarborescidine C (27)
0.99 1.00 1.02 1.02 1.00
1.01 1.13 3.07 3.04 2.18 1.15 1.06 1.09 1.08
Chemical Shift (ppm)


CHLOROFORM-d
136.71 136.08 126.54 121.43 119.42 118.25 108.56 108.36
77.00 76.36 61.35 50.32 42.24 34.22 31.95 20.14 19.83
^{13}C NMR, CDCl$_3$, 100 MHz
(+)-Desbromoarborescidine C (27)
Chemical Shift (ppm)


121.43 119.41 118.25 108.56 76.36 61.35 50.41 42.25 34.22 31.96 20.13 19.83
DEPT NMR, CDCl$_3$, 100 MHz
(+)-Desbromoarborescidine C (27)
Chemical Shift (ppm)

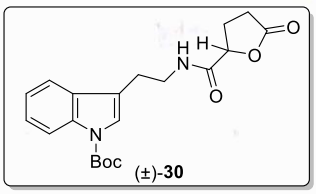

CHLOROFORM-d
7.50 7.48 7.36 7.34 7.22 7.20 7.17 7.15 6.96 6.93
5.09 5.09 5.07 5.06 5.05
3.46 3.43 3.15 2.78 2.77 2.75 2.74 2.73 2.72 2.57 2.55 2.40 1.95 1.92
^{1}H NMR, $CDCl_3$, 400 MHz
(+)-Desbromoarborescidine B (45)
1.00 1.01 1.01 1.00 1.00
1.01 1.01 1.05 1.10 2.13 3.19 1.16 1.04 1.20 1.01
Chemical Shift (ppm)


CHLOROFORM-d
137.14 136.11 126.88 121.96 121.79 120.15 118.16 110.02 109.19 109.09
77.00 62.49 52.84 42.39 29.94 27.96 20.63
^{13}C NMR, $CDCl_3$, 100 MHz
(+)-Desbromoarborescidine B (45)
Chemical Shift (ppm)

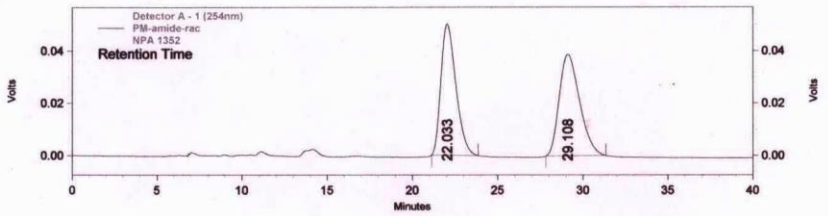

121.95 121.79 120.14 118.16 110.02 109.08
62.49 52.84 42.39 29.93 27.96 20.63
DEPT NMR, $CDCl_3$, 100 MHz
(+)-Desbromoarborescidine B (45)
Chemical Shift (ppm)

HPLC data of (±)-30

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1352
User: System
Acquired: 4/13/12 11:49:05 AM
Printed: 6/18/12 5:14:06 PM
Sample Name PM-amide-rac



(±)-**30**

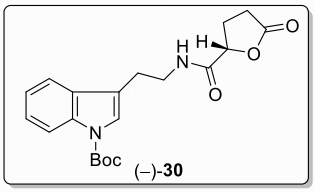


Detector A - 1 (254nm)

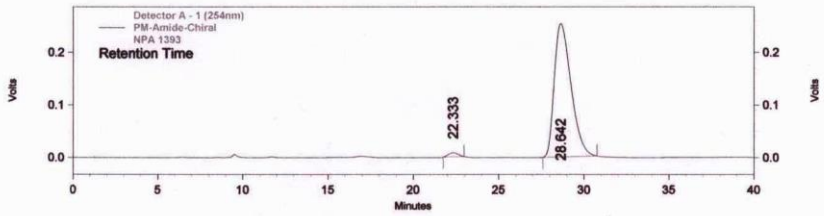
Retention Time	C Area	Area %
22.033	3071955	48.796
29.108	3223590	51.204
Totals	6295545	100.000

HPLC data of (–)-30

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1393
User: System
Acquired: 7/6/12 3:16:05 PM
Printed: 7/6/12 3:58:48 PM
Sample Name PM-Amide-Chiral



(–)-**30**



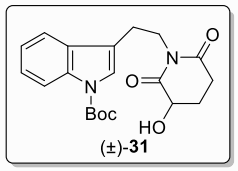
Detector A - 1 (254nm)

Retention Time	C Area	Area %
22.333	308511	1.752
28.642	17301778	98.248
Totals	17610289	100.000

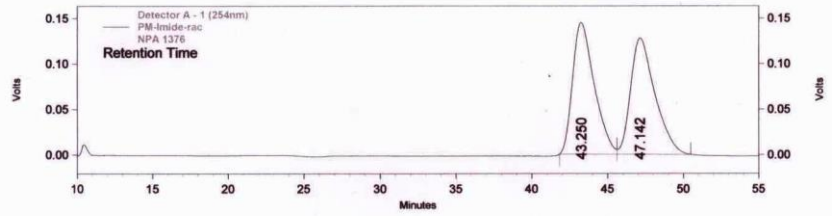
Project Leader: Dr. N. P. Argade
Column : Chiralcel OD-H (250 x 4.6 mm)
Mobile Phase : IPA: Pet Ether (30:70)
Wavelength : 254 nm
Flow Rate : 0.5 ml/min (31 kgf)
Conc. : 1.5 mg/ 1.0 ml
Inj. Vol. : 05 µl

HPLC data of (±)-31

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1376
User: System
Acquired: 5/7/12 12:44:55 PM
Printed: 5/7/12 1:52:05 PM
Sample Name PM-Imide-rac



(±)-**31**

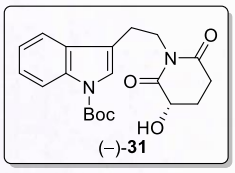


Detector A - 1 (254nm)

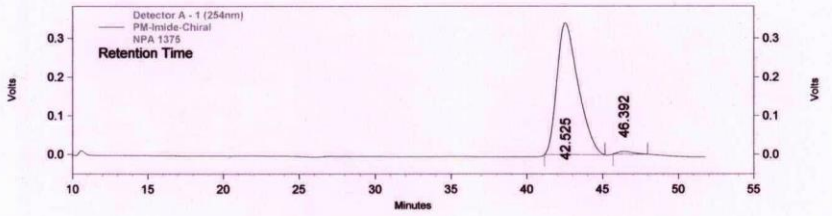
Retention Time	C Area	Area %
43.250	14395166	50.104
47.142	14335260	49.896
Totals	28730426	100.000

HPLC data of (–)-31

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1375
User: System
Acquired: 5/7/12 11:26:07 AM
Printed: 5/7/12 1:53:15 PM
Sample Name PM-Imide-Chiral



(–)-**31**



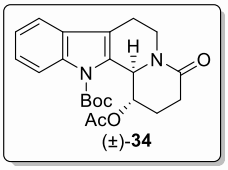
Detector A - 1 (254nm)

Retention Time	C Area	Area %
42.525	33253469	98.598
46.392	472995	1.402
Totals	33726464	100.000

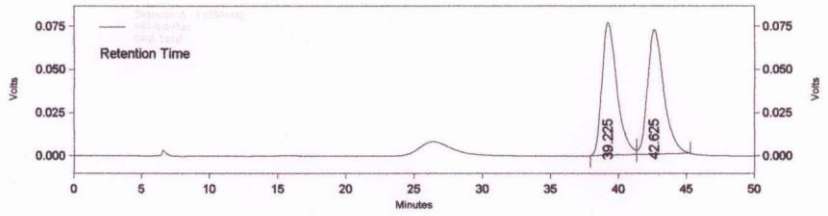
Project Leader: Dr. N. P. Argade
Column : Chiralcel OD-H (250 x 4.6 mm)
Mobile Phase : EtOH: Pet Ether (05:95)
Wavelength : 254 nm
Flow Rate : 0.5 ml/min (30 kgf)
Conc. : 1.5 mg/ 1.0 ml
Inj. Vol. : 05 µl

HPLC data of (±)-34

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1418
User: System
Acquired: 12/5/12 2:24:49 PM
Printed: 4/25/13 1:22:07 PM
Sample Name PM-A-5-Rac



(±)-34

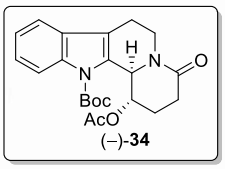


Detector A - 1 (254nm)

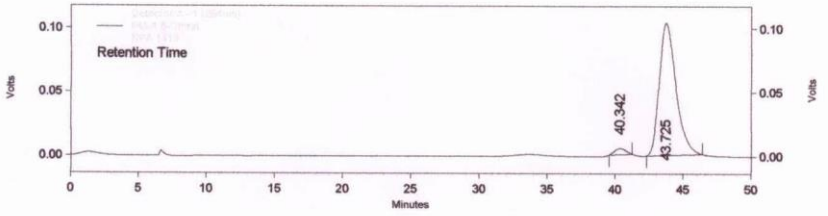
Retention Time	C Area	Area %
39.225	5891284	49.503
42.625	6009609	50.497
Totals	11900893	100.000

HPLC data of (–)-34

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1419
User: System
Acquired: 12/5/12 3:16:49 PM
Printed: 4/25/13 1:25:35 PM
Sample Name PM-A-5-Chiral



(–)-34



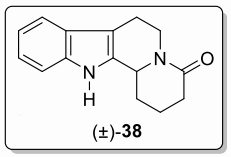
Detector A - 1 (254nm)

Retention Time	C Area	Area %
40.342	273462	3.003
43.725	8834069	96.997
Totals	9107531	100.000

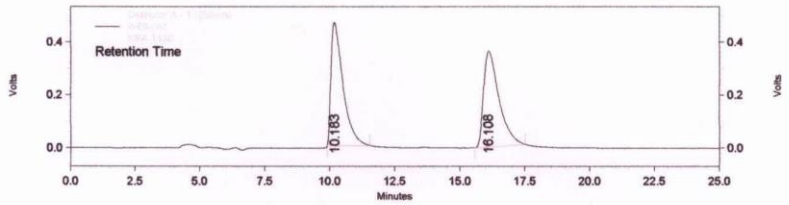
Project Leader: Dr. N. P. Argade
Column : Kromasil 5-AmyCoat (250 x 4.6 mm)
Mobile Phase : IPA: n-Hexane (03:97)
Wavelength : 254 nm
Flow Rate : 0.5 ml/min (305 psi)
Conc. : 1.0 mg/ 2.5 ml
Inj. Vol. : 05 µl

HPLC data of (±)-38

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Instrument 2 Default Method.met
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1430
User: System
Acquired: 1/4/13 1:31:44 PM
Printed: 1/4/13 3:59:15 PM
Sample Name A-08-rac



(±)-38



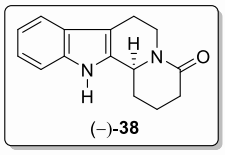
Detector A - 1 (230nm)

Retention Time	C Area	Area %
10.183	14917619	49.887
16.108	14985072	50.113
Totals	29902691	100.000

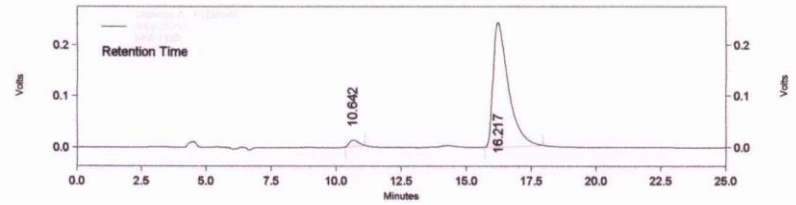
HPLC data of (–)-38

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Instrument 2 Default Method.met
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1432
User: System
Acquired: 1/4/13 2:26:15 PM
Printed: 1/4/13 3:55:20 PM
Sample Name A-08-chiral

Data



(–)-38



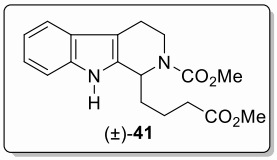
Detector A - 1 (230nm)

Retention Time	C Area	Area %
10.642	281724	2.762
16.217	9919554	97.238
Totals	10201278	100.000

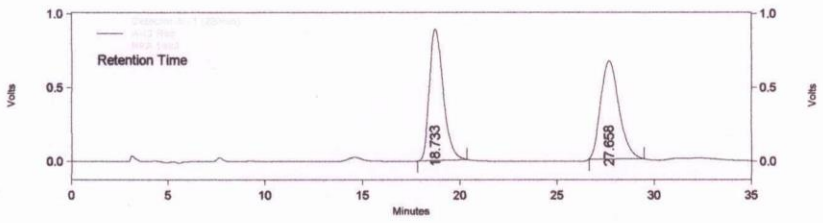
Project Leader: Dr. N. P. Argade
Column : Kromasil 5-AmyCoat (250 x 4.6 mm)
Mobile Phase : IPA: Pet Ether (15:85)
Wavelength : 230 nm
Flow Rate : 0.7 ml/min (520 psi)
Conc. : 1.0 mg/ 1.0 ml
Inj. Vol. : 05 µl

HPLC data of (±)-41

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1433
User: System
Acquired: 2/19/13 3:39:47 PM
Printed: 4/25/13 1:02:45 PM
Sample Name A-12 Rac



(±)-**41**

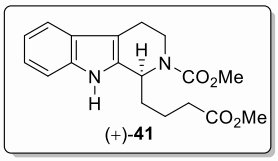


Detector A - 1 (230nm)

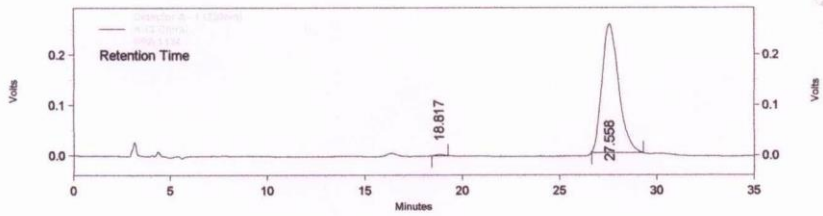
Retention Time	C Area	Area %
18.733	43984250	50.237
27.658	43570032	49.763
Totals	87554282	100.000

HPLC data of (+)-41

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1434
User: System
Acquired: 2/19/13 4:16:17 PM
Printed: 4/25/13 1:10:02 PM
Sample Name A-12 Chiral



(+)-**41**



Detector A - 1 (230nm)

Retention Time	C Area	Area %
18.817	63458	0.415
27.558	15240529	99.585
Totals	15303987	100.000

Project Leader: Dr. N. P. Argade
Column : Kromasil 5-AmyCoat (250 x 4.6 mm)
Mobile Phase : IPA: Pet Ether (10:90)
Wavelength : 230 nm
Flow Rate : 1.0 ml/min (705 psi)
Conc. : 1.0 mg/ 1.0 ml
Inj. Vol. : 10 µl

2B.7 References

(1) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761.

(2) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57.

(3) Fu, L. *Top. Heterocycl. Chem.* **2010**, *26*, 433.

(4) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

(5) Amat, M.; Perez, M.; Bosch, J. *Synlett* **2011**, 143.

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Chapter 3

Lactam Carbonyl as a Switch to Tailor the Stereoselectivity in Ester-Aldol Reaction: Diastereoselective/Enantioselective Synthesis of Vinca-Eburna and Tacaman Alkaloids and Analogues Thereof

This chapter features the following topics:

Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

This chapter is divided into two sections.

The **Section A** presents concise literature accounts of the indole alkaloids eburnamonine, eburnaminol, larutensine, melohenine B, tacamonine and vindeburnol. The combine literature account of these alkaloids is very vast. To make this section little concise, few schematic presentations have been given along with brief description with keeping due respect to the full literature accounts.

The **Section B** describes enantioselective/diastereoselective synthesis of vinca-eburna, tacaman alkaloids and their important analogues. Lactam-amine switch system has been developed to tailor the stereoselectivity in ester-aldol reactions of hexahydroindolo[2,3-a]quinilizinones. This section also describes the successful use of chiral acetoxy group in (*S*)-acetoxyglutarimide in a dual role i.e. first as a stereochemical handle and later most importantly as a functional group.

The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end of section B.

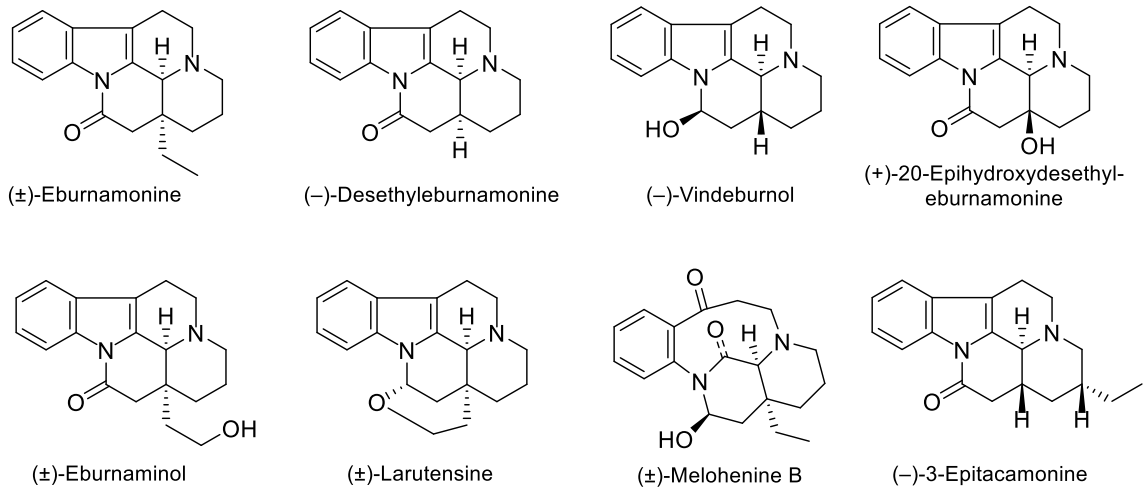


Figure. Natural and unnatural bioactive indole alkaloids synthesized

Chapter 3: Section A

Concise Literature Account of Indole Alkaloids Eburnamonine, Eburnaminol, Larutensine, Melohenine B, Tacamonine and Vindeburnol

This section A of chapter 3 features the following topics:

3A.1 Background

Cancer (malignant tumour or malignant neoplasm) is a group of diseases involving an abnormal growth and proliferation of cells.[1] There are more than 100 different known cancers that affect humans and are rapidly spreading worldwide. It was estimated that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons living with cancer around the world in a year.[2] Cancer is the second leading cause of death, where one in four deaths is due to cancer.

Medicinal plants are the most important source of life saving drugs for the majority of the world's population. The use of plant products in the treatment of cancer has been of contemporary interest.[3] The potential use of medicinal plants for the treatment of cancer was first recognised by U.S National Cancer Institute (NCI) in 1950's and since then there has been a continuing interest in the discovery of new anticancer agents. Some of the plants which display anticancer activity are *Podophyllum hexandrum, Mistletoe, Catharanthus roseus, Taxus brevifolia, Allium sativum, Astragalus gummifera, Curcuma longa, Aloe barbadensis, Crocus sativus, Vitex agnus, Withania somnifera, Pleiospermium alatum, Broccoli, Camptotheca, Camellia sinensis, Azadirachta indica* and several others.[3]

The vinca-eburna alkaloids from Madagascar periwinkle plant *Catharanthus roseus* (Apocynaceae family) have been the most successful of higher plant materials used in cancer chemotherapy. Vinca alkaloids are the second-most-used class of cancer drugs and will stay among the original cancer therapies.[4] A number of bisindole alkaloids having potential antileukaemic activity have been isolated and two of them, vinblastine (**1**) and vincristine (**2**) are now commercially extracted from *Catharanthus roseus*. They are used either alone or in combination with other forms of therapy for cancer treatment. Vinblastine (**1**) is mainly useful in the treatment of Hodgkin's disease, a cancer affecting the lymph glands, spleen and liver. Vincristine (**2**) is also clinically more important and it is especially used in the treatment of childhood leukaemia. Vinflunine (**3**), new synthetic vinca alkaloid is recently being approved in Europe for medicinal treatment (Figure 1).[4]

Vinca-eburna alkaloids also display varied pharmacological activities on the cell multiplication, cardiovascular system and brain functions. Many of their synthetic derivatives are also pharmacologically active and safer to be administered than the natural plant alkaloids themselves. Vincamine (**4**), L-eburnamonine (**5**), vindeburnol (**6**, RU 24722) and vinpocetine (**7**, semisynthetic) all share modulatory effects on brain circulation

and neuronal homeostasis and bear antihypoxic and neuroprotective potencies to various degrees. The most active compound of this class is vinpocetine.[5]

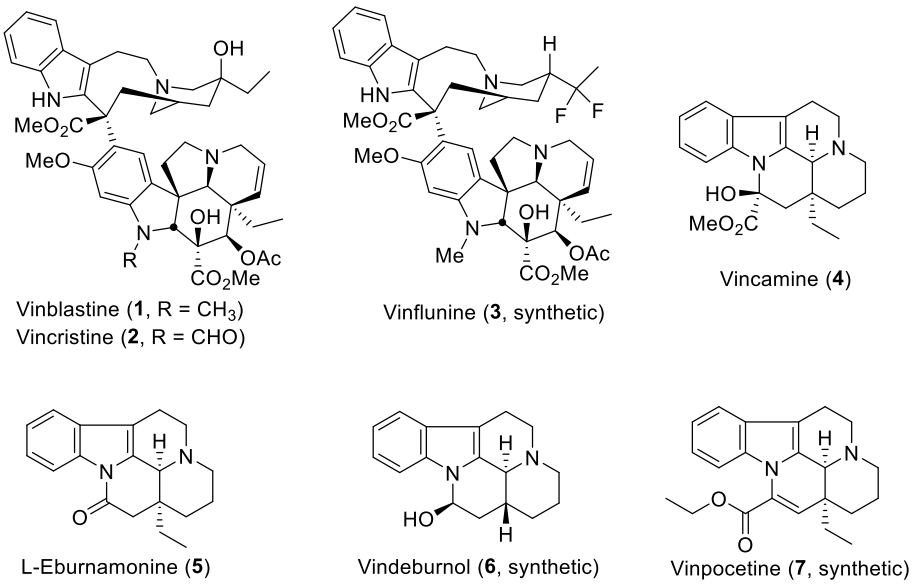


Figure 1. Bioactive vinca-eburna alkaloids and their synthetic analogues

The eburna alkaloid D-(+)-eburnamonine was first isolated from *Hunteria eburnean* by Bartlett and Taylor in 1959.[6] Interestingly both the (+) and (–) enantiomers as well as the racemic eburnamonine exist in nature. The (–)-eburnamonine (isolated from *Vinca minor*),[7] known as vincamone or vinburnine is a drug that possesses a stimulating activity for muscle and it is used as cerebrotonic, and also acts as prolyl oligopeptidase inhibitor (IC_{50} = 8 μM),[8,9] whereas both enantiomers have hypotensive effects. The other vinca-eburna alkaloids (–)-eburnaminol (**8**) and (+)-larutensine (**9**) were isolated from bark and stems of *Kopsia larutensis* by Hadi and co-workers in 1991 (Figure 2).[10] Eburnamonine and eburnaminol have an angular pentacyclic ring system with *cis*-geometry between D and E ring, comprising of a quaternary carbon (C-20) whereas larutensine contains hexacyclic ring system with an additional ether linkage between C-16 and C-18 (F ring). The novel alkaloid melohenine B (**10**, cytotoxic) was recently isolated from the Chinese plant *Melodinus henryi*.[11] It possess a striking 6/9/6/6 core skeleton and since its isolation a number of related alkaloids (**11**-**13**) have been identified from other plants of the Apocynaceae family.[12-14] Several derivatives of eburnamonine including the ethyl group lacking compounds, desethyleburnamonine (**14**) and 20-epidesethyleburnamonine (**15**) possess interesting pharmacological properties.[15,16] (–)-Vindeburnol (**6**) is also one of the promising synthetic analogue and it is a potent central vasodilator which also provides benefit for severe depression.[5,17-20] Recent results indicate

that the treatment with vindeburnol which targets locus coeruleus survival would be beneficial to multiple sclerosis patients.[20]

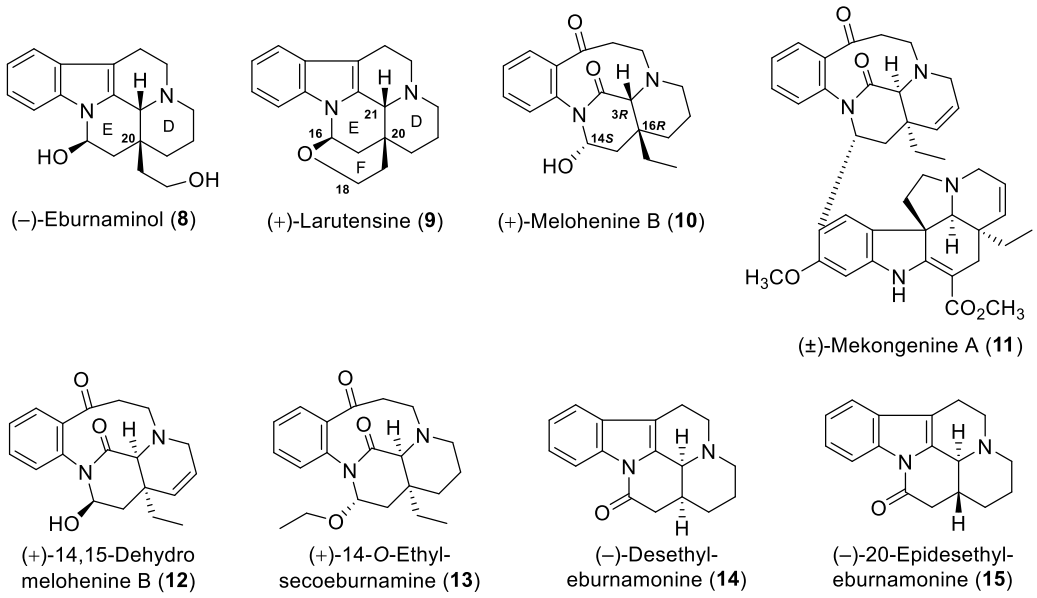


Figure 2. Representative natural products and eburna derivatives

The (+)-tacamonine (**16**), isolated from *Tabernaemontana eglandulosa* Stapf. (anti snake poisioning) belongs to tacaman class of indole alkaloid where the main difference from vinca-eburna class is the presence of ethyl group away from the D and E ring junction keeping an additional stereocenter bearing protons which are *cis* to each other (C-3, C-14 & C-20) (Figure 3).[21] During the last decade tacamonine has received more attention because of its

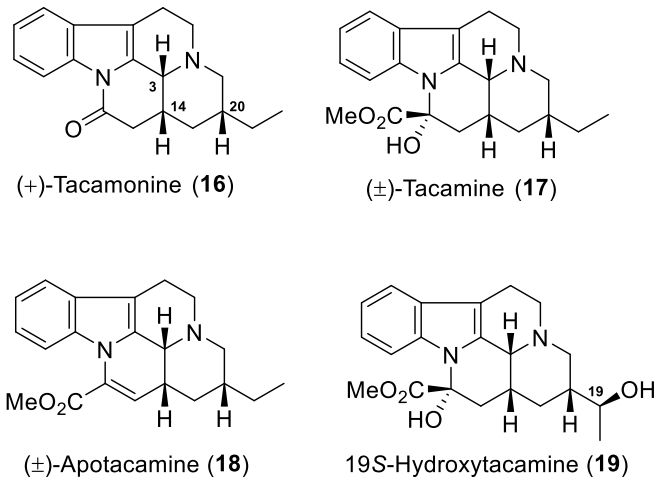


Figure 3. Representative tacaman alkaloids

close structural similarity with the known cerebral vasodilator (–)-eburnamonine (**5**). Some of the other members of tacaman family are tacamine (**17**), apotacamine (**18**) and 19*S*-hydroxy tacamine (**19**) which are potential hypotensive and cerebral vasodilator candidates.[22,23] Since most of the above mentioned target compounds were isolated few decades ago, many well designed racemic and asymmetric syntheses of them are known in the literature. Hence in most of the cases, the earlier syntheses of those target compounds will be presented schematically with respect to the available high amount of literature present. Therefore syntheses of eburnamonine, vindeburnol and racemic synthesis of tacamonine have been presented schematically in figures 4–6 whereas syntheses of eburnaminol, larutensine, melohenine B, vindeburnol, asymmetric synthesis of tacamonine and synthesis of 3-epitacamonine have been described briefly in schemes 1–9.

3A.2 Brief Literature Account of Eburnamonine and Melohenine B Syntheses

Several strategies for the synthesis of eburnamonine and its structural analogues are reported. The most common approach is to first prepare appropriately the requisite [ABCD]-type indolo[2,3-*a*]quinolizidine ring system followed by ring closure to form the final E-ring. The usual methods for their synthesis are Pictet-Spengler cyclization,[24,25] a Michael-type alkylation of the "Wenkert enamine"[26,27] or an annulation reaction of a dihydro-*β*-carboline derivative.[28,29] Bartlett and Taylor reported the first synthesis of (±)-eburnamonine by the condensation between *β*-ethyl-*β*-formyl adipic acid and tryptamine in 1960.[30] The *cis*-D/E ring junction of (±)-eburnamonine was established by Wenkert and Wickberg in 1965 by using oxidative enamine alkylation.[31] Szántay and co-workers have reported the first synthesis of (–)-eburnamonine by resolution of *α*-hydroxyiminoester with D-dibenzoyl tartaric acid in 1983.[32] Kaufman and Grieco have described synthesis of (±)-eburnamonine using intermolecular imino Diels-Alder reaction.[33] An elegant synthesis of (–)-eburnamonine has been reported by Schultz and Pettus by using diastereoselective Birch reduction-alkylation of chiral benzamide derivative.[34] A short synthesis of (±)-eburnamonine has been demonstrated by Ghosh and Kawahama utilizing stereoselective 1,4-addition of ethyl Grignard to conjugated indoloquinolizidine ester.[35] Recently Prasad and Nidhiry have described enantiospecific synthesis (+)-eburnamonine by utilizing Johnson–Claisen ortho ester rearrangement to construct the quarternary chiral center as a key step.[36]

3A.2.1 Schematic Presentation of Eburnamonine Syntheses

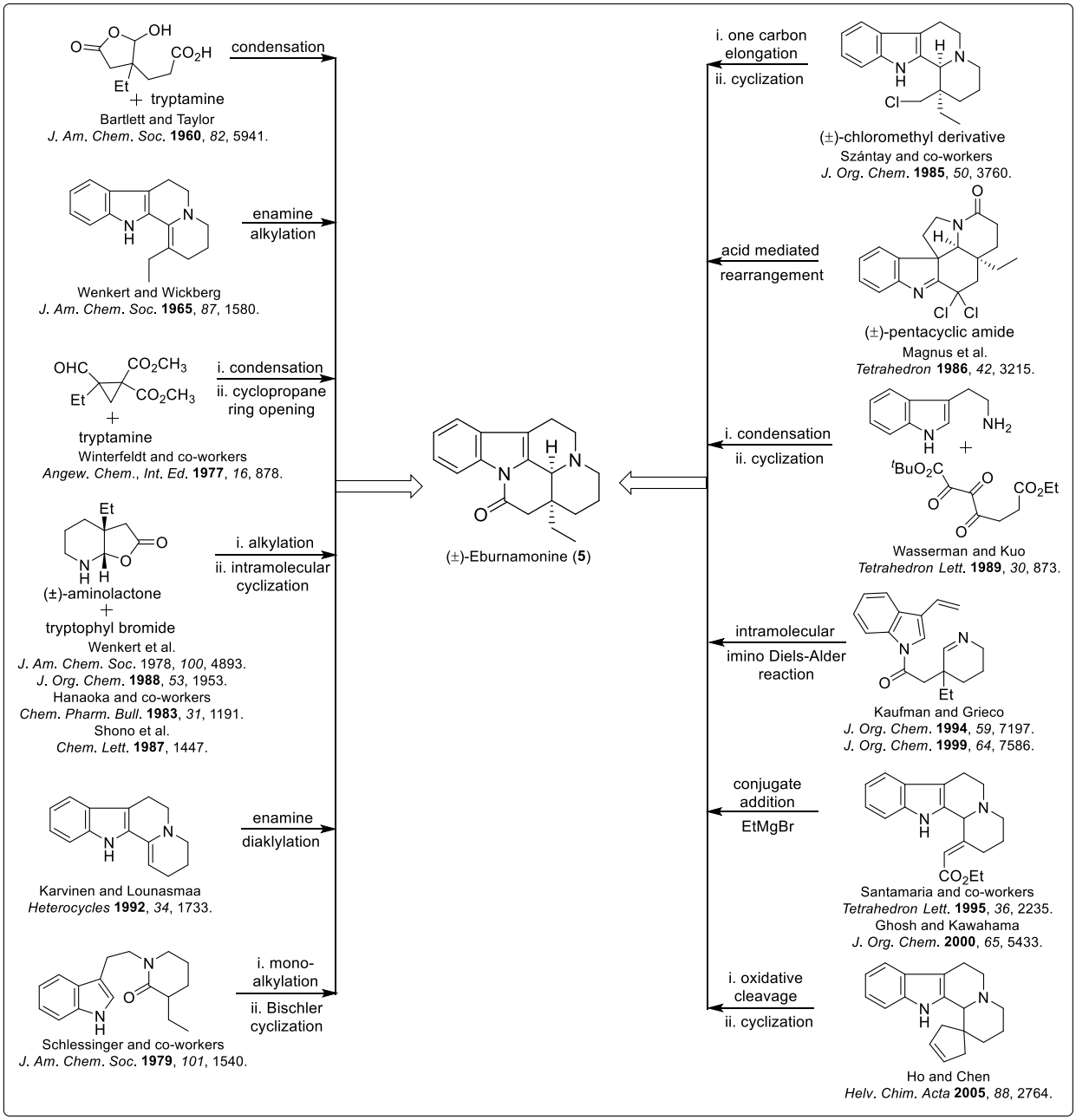


Figure 4. Schematic representation of (±)-eburnamonine syntheses

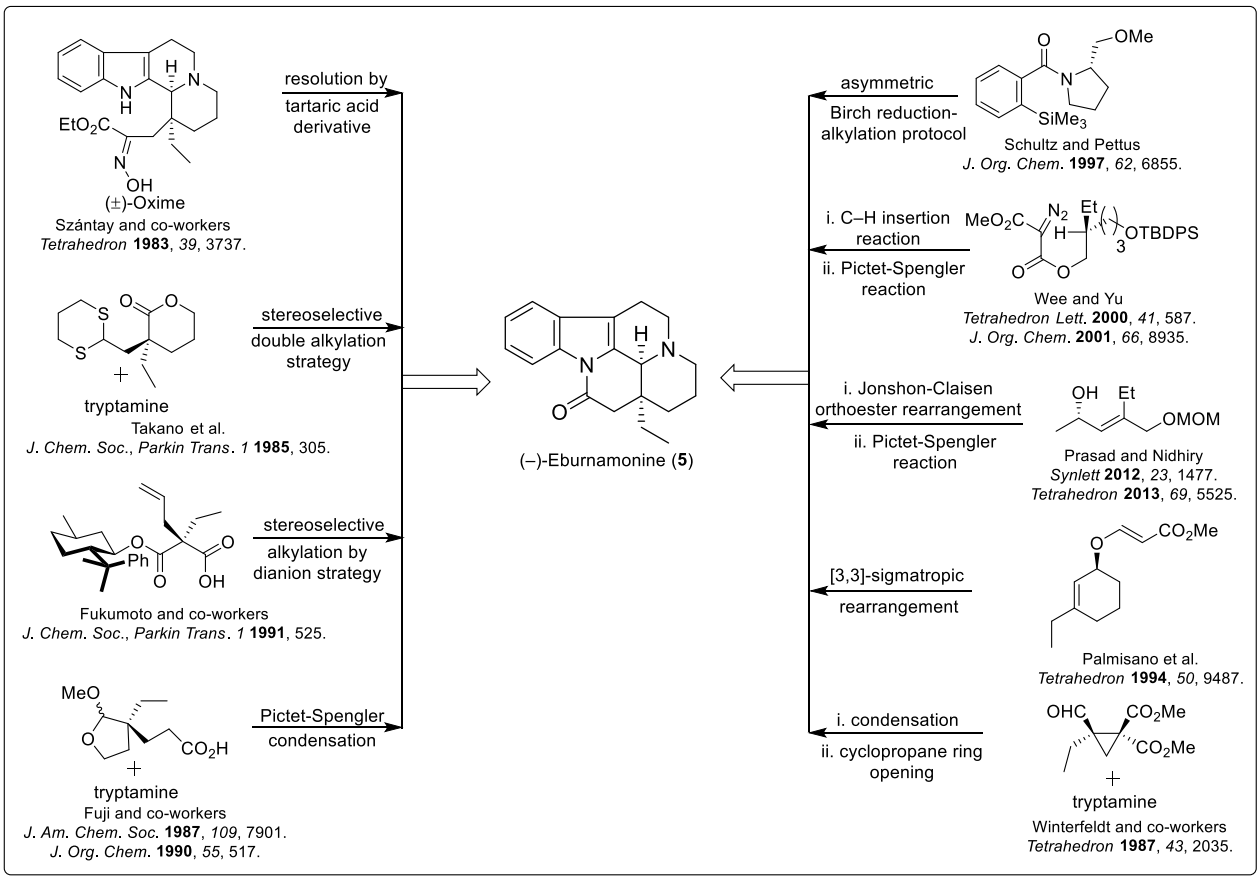
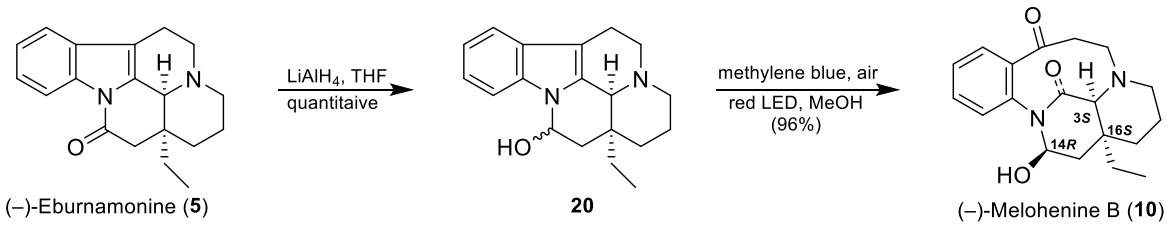


Figure 5. Schematic representation of (–)-eburnamonine syntheses

3A.2.2 Synthesis of Melohenine B

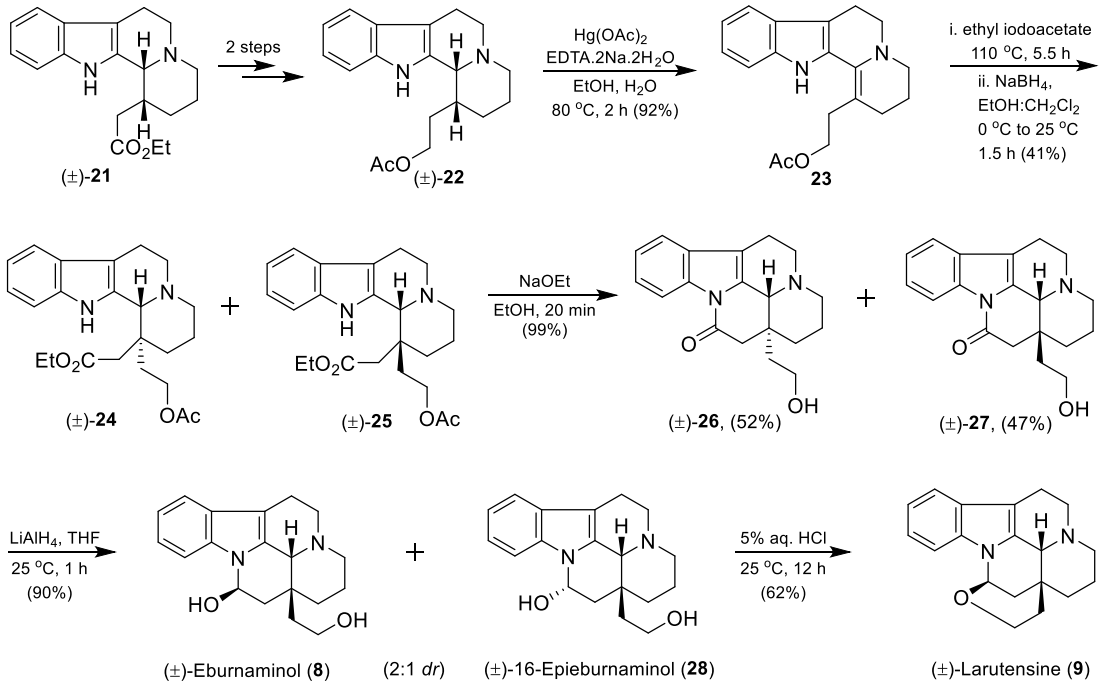
Westwood and co-workers have reported the first asymmetric synthesis of (–)-melohenine B (antipode) from (–)-eburnamonine (**5**) and assigned the absolute configuration of natural (+)-melohenine B as 3*R*, 14*S* and 16*R* (Scheme 1).[37] $LiAlH_4$ reduction of (–)-eburnamonine (**5**) provided diastereomeric mixture of aminol **20**. Treatment of mixture of **20** with singlet oxygen furnished (–)-melohenine B (**10**) as a single diastereomer via photo induced oxidative cleavage of indole ring in 96% yield.



Scheme 1. Synthesis of (–)-melohenine B by oxidative cleavage of indole ring

3A.3 Brief Literature Account of Eburnaminol and Larutensine Syntheses

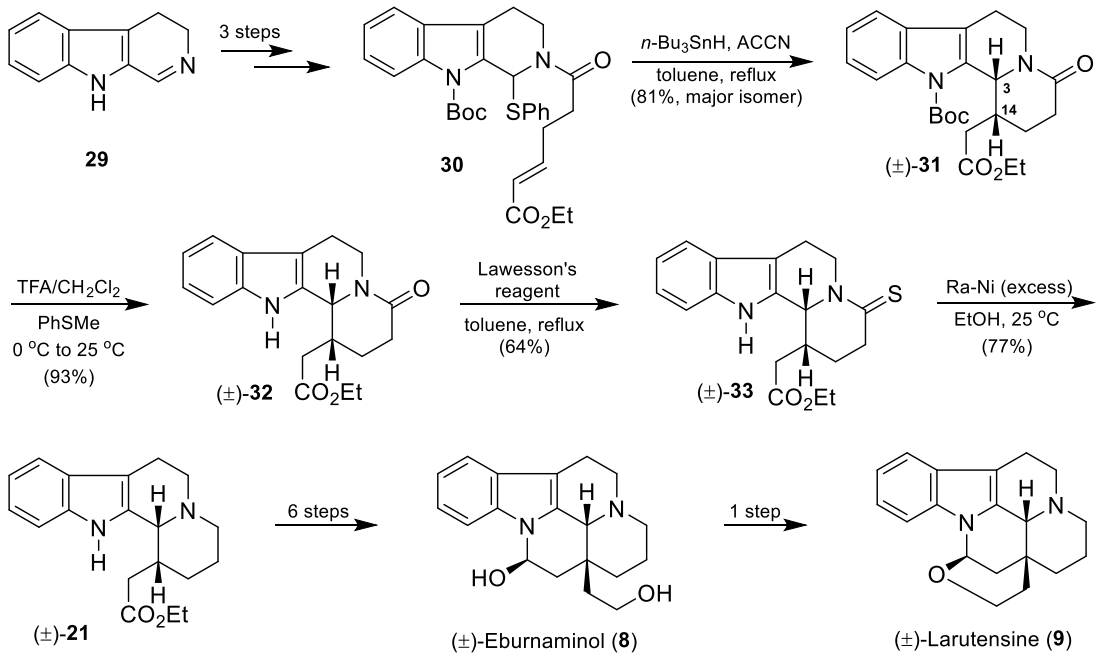
Lounasmaa and Karvinen have reported the first racemic synthesis of eburnaminol and larutensine.[38] The ester (±)-**21** was transformed to compound (±)-**22** via ester reduction and acetyl protection of the primary alcohol (Scheme 2). The acetate (±)-**22** was oxidized by using Fuji's condition to provide the enamine **23** in 92% yield. The enamine **23** was alkylated by using ethyl iodoacetate; reduction of the resultant iminium salt with $NaBH_4$ furnished column chromatographically inseparable diastereomeric mixture of esters (±)-**24** and (±)-**25** in overall 41% yield. The mixture of esters (±)-**24** and (±)-**25** was treated with sodium ethoxide in ethanol to provide the separable mixture of 21-*epi*-18-hydroxyeburnamonine (±)-**26** and 18-hydroxyeburnamonine (±)-**27** in 52% and 47% yields respectively. Reduction of 18-hydroxyeburnamonine (±)-**27** with $LiA1H_4$ furnished a separable 2:1 mixture of (±)-eburnaminol (**8**) and 16-epieburnaminol (**28**) in nearly 60% and 30% yields respectively. Treatment of mixture of (±)-**8** and (±)-**28** with 5% aq. HCl at 25 ^{o}C resulted in a diastereoselective intramolecular cyclization to provide (±)-larutensine (**9**) in 62% yield.



Scheme 2. Synthesis of (±)-eburnaminol and (±)-larutensine

Hunter and co-workers have reported a new method to prepare inolo[2,3-*a*]quinolizidines based on 6-*exo*-*trig* radical cyclization (Scheme 3).[39] The radical precursor conjugated ester **30** was prepared from dihydro-*β*-carboline **29** in three steps. The compound **30** upon subjecting to standard radical conditions by using *n*-Bu_3SnH and

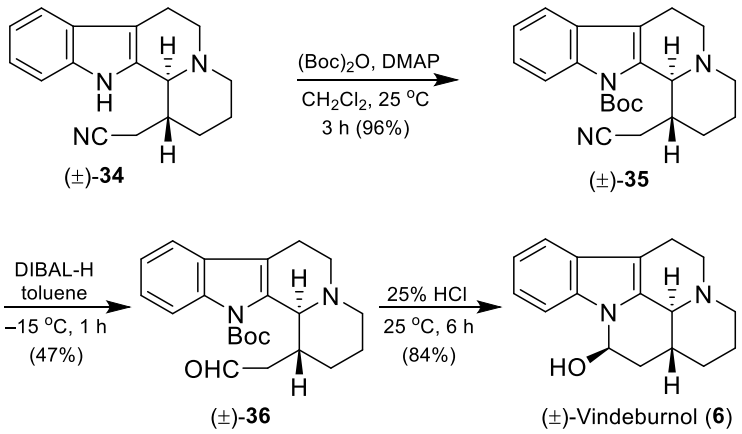
ACCN [1,1′-azobis(dicyclohexylcarbonitrile)] diastereoselectively provided the tetracyclic compound *cis*-(±)-**31** in 81% yield (81:12 *dr*). The *cis* relationship between the H-3 and H-14 proton was confirmed from the single crystal X-ray structure of the corresponding carboxylic acid of *cis*-(±)-**31**. *N*-Boc group deproctection using TFA and thioanisole followed by conversion of lactam to thiolactam by Lawesson's reagent provided the compound (±)-**33** in 59% yield (2 steps). Desulfurization of (±)-**33** using excess of Raney-nickel delivered the known compound (±)-**21** in 77% yield. Synthesis of (±)-eburnaminol (**8**) and (±)-larutensine (**9**) are known from compound (±)-**21** in moderate yields (6/7 steps).[38]



Scheme 3. Formal synthesis of (±)-eburnaminol and (±)-larutensine

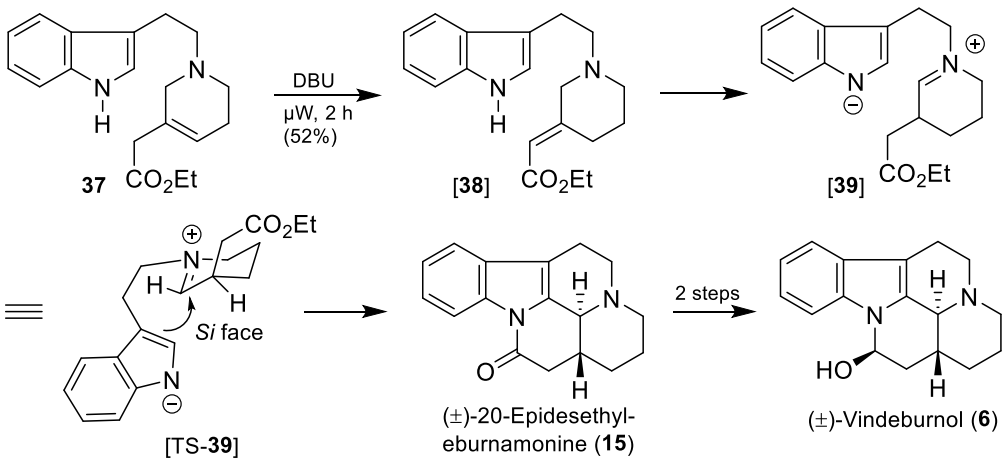
3A.4 Brief Literature Account of Vindeburnol Syntheses

Lounasmaa et al. have reported synthesis of vindeburnol (**6**, RU 24722) starting from the corresponding nitrile (Scheme 4).[18] Boc-protection of the known *trans*-compound (±)-**34**[16] provided product (±)-**35** in 96% yield. Reduction of the nitrile (±)-**35** by DIBAL-H afforded the aldehyde (±)-**36** in 47% yield. Aldehyde (±)-**36** on treatment with 25% HCl at 25 ^{o}C underwent a diastereoselective cyclization to provide (±)-vindeburnol (**6**) in 84% yield.



Scheme 4. Synthesis of (±)-vindeburnol

Mann and co-workers have reported one pot DBU mediated allylamine-enamine isomerization followed by Pictet-Spengler condensation of an indolo-tetrahydropyridine ethyl ester **37** to afford (±)-20-epidesethyleburnamonine (**15**) under microwave irradiation in 52% yield (Scheme 5).[19] The diastereoselective formation of *trans* D/E ring junction can be explained by the preferential attack of the π-nucleophile of indole moiety from the less hindered *Si*-face of the iminium moiety where the bulky acetate group adopts a pseuoaxial position (TS-**39**). Two step synthesis of (±)-vindeburnol (**6**) from compound (±)-**15** via hydride reduction and epimerization is known in literature.[40]



Scheme 5. Formal synthesis of (±)-vindeburnol

3A.5 Brief Literature Account of Tacamonine Syntheses

The main challenge in the synthesis of tacaman alkaloids is to control the relative stereochemistry of the all three stereocentres at C-3, C-14 and C-20 (all *cis*-hydrogens). The main strategies involved in their syntheses are Bischler-Napieralski cyclization,[41] a double aza-Michael reaction,[42] radical cyclization chemistry,[43] ring closing metathesis to

form a piperidinone ring followed by 1,4-addition to introduce the requisite side chain[44] as well as the other more classical methods.[45-47] Lévy and co-workers reported racemic synthesis of all four possible isomers of tacamonine well before its isolation as a natural product.[41] The first asymmetric synthesis of (+)-tacamonine (**16**) was reported by Fukumoto and co-workers by using radical cyclization.[48] Lavilla et al. have reported synthesis of (±)-tacamonine through tandem non-biomimetic oxidation of dihydropyridines and Zn-mediated radical addition reactions.[43] England and Padwa have utilized an intramolecular [3+2]-cycloaddition reaction of a *α*-diazo-indoloamide as a key step for the synthesis of (±)-tacamonine.[49]

3A.5.1 Schematic Presentation of (±)-Tacamonine Syntheses

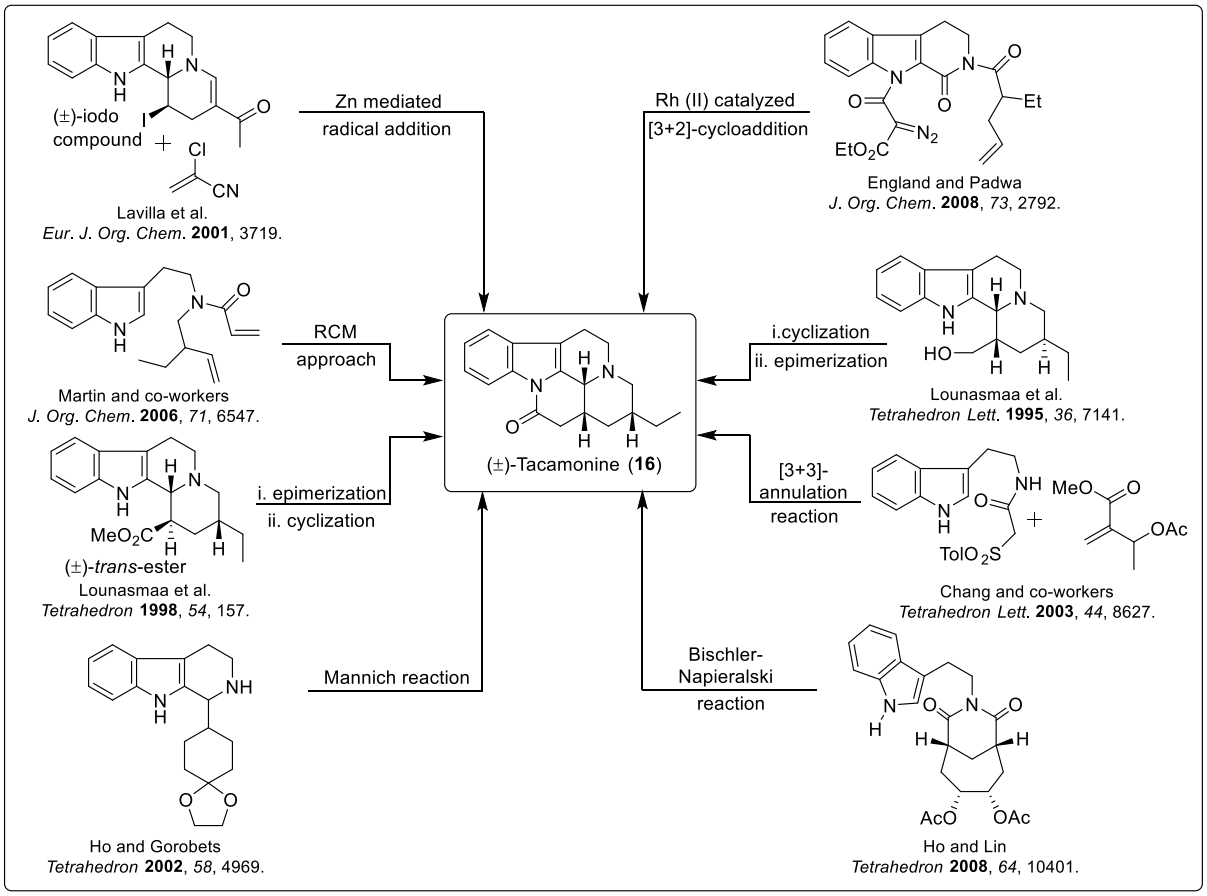
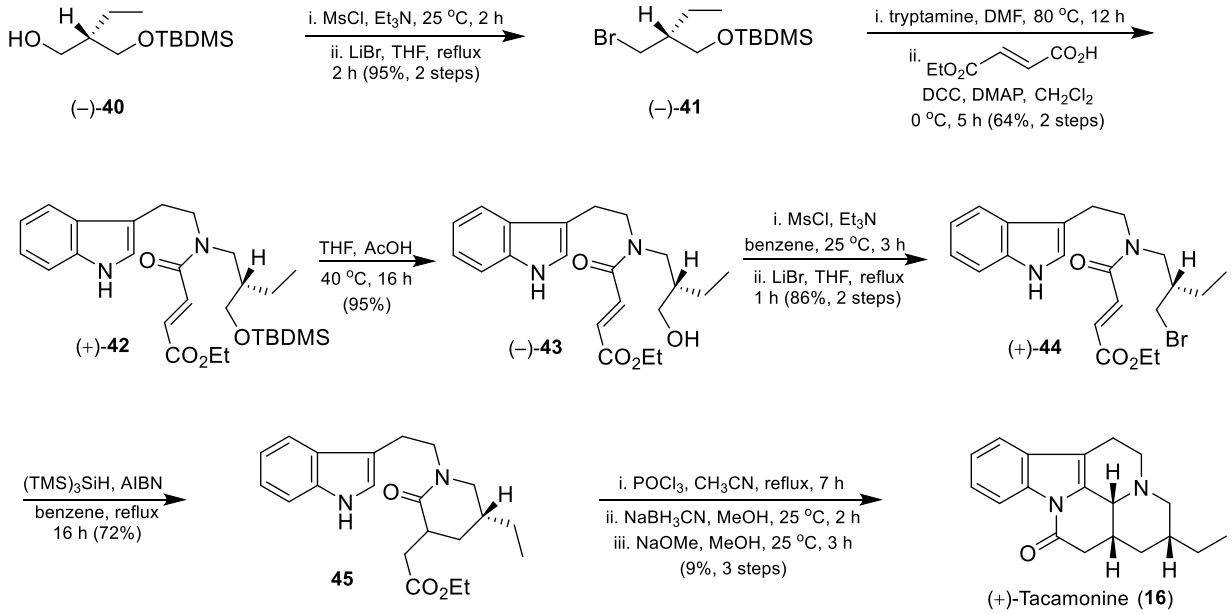


Figure 6. Schematic representation of (±)-tacamonine syntheses

3A.5.2 Asymmetric Synthesis of (+)-Tacamonine

Fukumoto and co-workers have reported the synthesis of (+)-tacamonine by using 6-*exo*-*trig* radical cyclization as a key step (Scheme 6).[48] The optically pure alcohol (–)-**40** was transformed to the bromo derivative (–)-**41** in 95% yield via the corresponding mesylate followed by its nucleophilic displacement by bromide. Treatment of tryptamine with

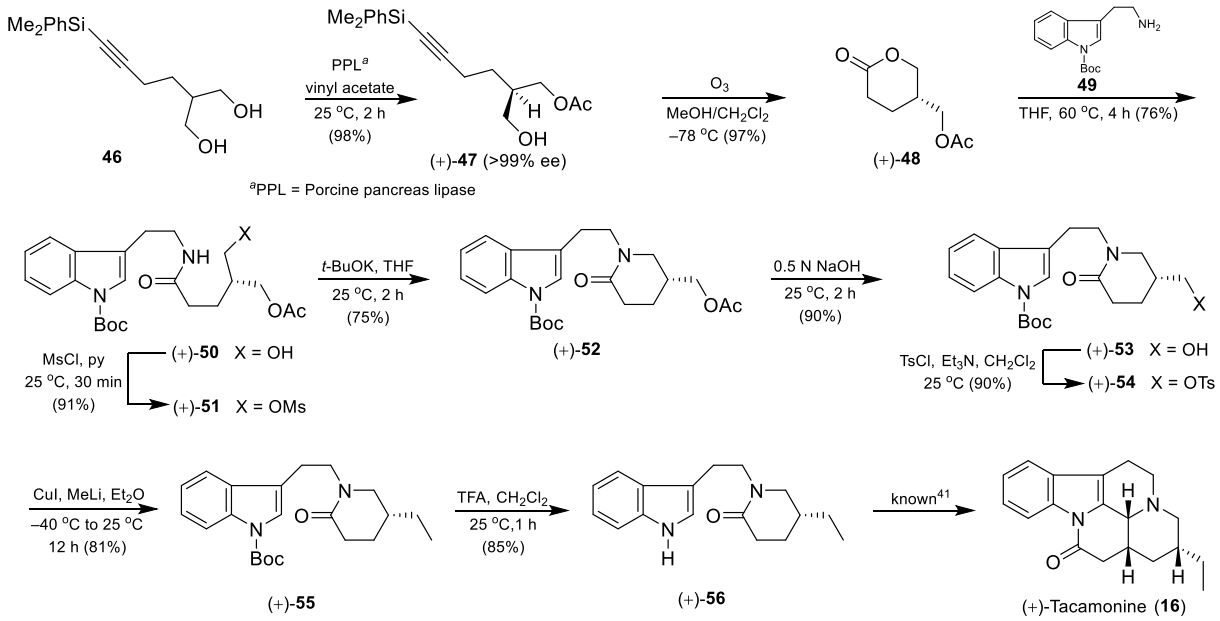
bromide (–)-**41** followed by coupling of the resultant secondary amine with fumaric acid monoethyl ester provided the amide (+)-**42** in 64% yield (2 steps). The TBDMS ether group in (+)-**42** was deprotected by AcOH to give the alcohol (–)-**43** in 95% yield. The mesylation of (–)-**43** followed by substitution reaction with LiBr furnished the radical precursor (+)-**44** in 86% yield. The most anticipated radical cyclization of bromo compound (+)-**44** with $(TMS)_3SiH$ and AIBN in refluxing benzene afforded the cyclized compound **45** as a diastereomeric mixture. The amide **45** upon treatment with $POCl_3$ followed by reduction of the iminium salt with $NaBH_3CN$ and finally ring closure of the product with sodium methoxide in methanol formed (+)-tacamonine (**16**) in 9% yield over 3 steps.



Scheme 6. Asymmetric synthesis of (+)-tacamonine by radical cyclization

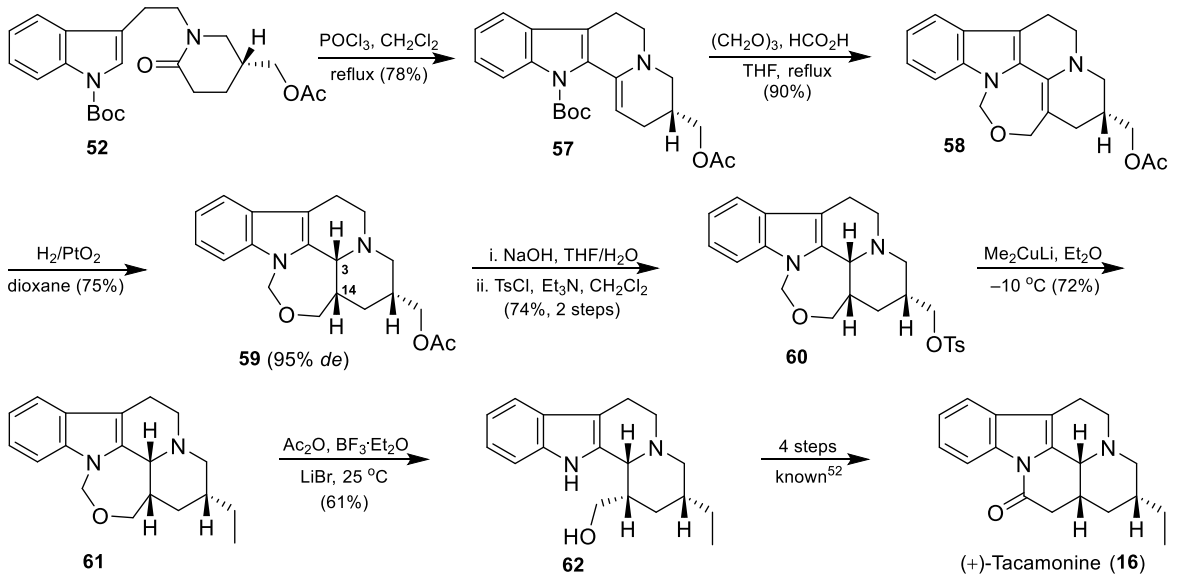
Lesma and co-workers have reported enantioselective formal synthesis of (+)-tacamonine by using desymmetrized 2-substituted propane-1,3-diols (Scheme 7).[50] Enantioselective esterification of symmetrical diol **46** with PPL (Porcine pancreas lipase) provided monoacetate (+)-**47** in 98% yield with 99% *ee*. Ozonization of (+)-**47** afforded the lactone (+)-**48** in 97% yield. Ring opening of the lactone (+)-**48** with Boc-protected tryptamine **49** furnished the amide (+)-**50** in 76% yield. The primary alcohol group in (+)-**50** was transformed to the corresponding mesylate (+)-**51** and subjected to intramolecular cyclization using *t*-BuOK to provide lactam (+)-**52** in 75% yield. Finally in order to homologate the acetoxymethy group, the acetate was hydrolyzed to give the alcohol (+)-**53** which on reaction with tosyl chloride provided the tosylate (+)-**54**. Organometallic displacement of –OTs group by Me_2CuLi followed by *N*-Boc deprotection by TFA

provided the lactam (+)-**56** in 69% yield (2 steps). Synthesis of (±)-tacamonine (**16**) is known from (±)-**56** by using Bischler-Napieralski cyclization.[41]



Scheme 7. Formal synthesis of (+)-tacamonine by enzymatic desymmetrization

In 2001, Lesma and co-workers also reported the synthesis of (+)-tacamonine by using stereocontrolled reduction of an oxazepinohexahydroindolo[2,3-*a*]quinolizine derivative (Scheme 8).[51] The previously reported lactam **52** was treated with $POCl_3$ to provide the enamine **57** in 78% yield. The *N*-Boc protected enamine **57** was reacted with excess aq. formaldehyde in presence of catalytic amount of formic acid to form the pentacyclic compound **58** in 90% yield. Stereoselective hydrogenation of enamine double

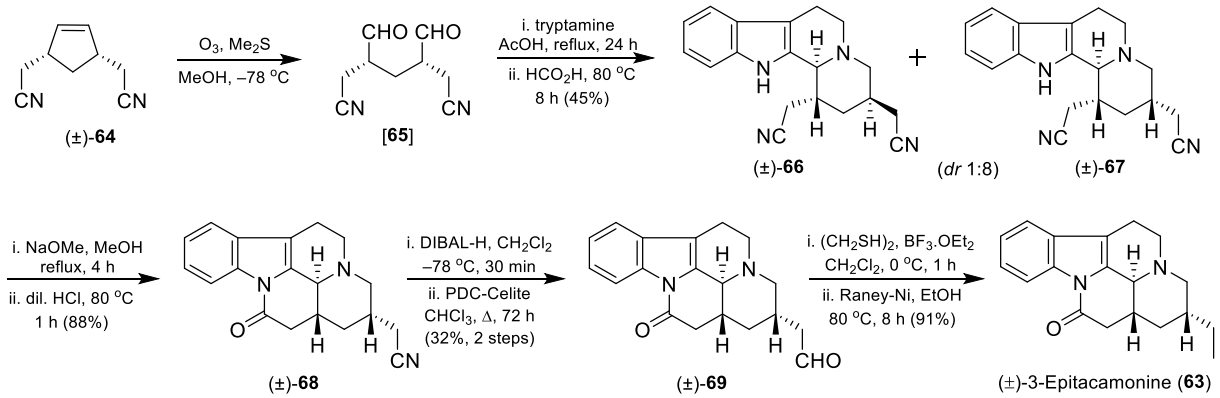


Scheme 8. Enantioselective formal synthesis of (+)-tacamonine

bond in **58** by H_2/PtO_2 furnished the compound **59** having 3β H and 14β H configuration in 75% yield with 95% *de*. After establishing all three absolute configurations required for the tacamonine framework the next task was to homologate the acetoxy methyl side chain at C-20. This was performed in three steps involving acetate hydrolysis, tosylation and displacement of tosylate by Me_2CuLi to provide compound **61** in 53% yield (3 steps). Removal of methylene bridge in **61** with $BF_3{\cdot}Et_2O$ provided the known compound **62** in 61% yield. Synthesis of (+)-tacamonine was accomplished from **62** using known procedure in 4 steps with 48% yield.[52]

3A.5.3 Synthesis of (±)-3-Epitacamonine

Ho and Su have reported synthesis of (±)-3-epitacamonine (**63**) starting from meso-dinitrile **64** (Scheme 9).[53] Ozonolysis of (±)-**64** furnished the unstable dinitrile aldehyde **65**. Reaction of **65** with tryptamine in refluxing AcOH and subsequent treatment with formic acid provided the tetracyclic β-carboline derivatives minor *trans-trans* (±)-**66** and major *trans-cis* (±)-**67** in 45% yield (*dr* 1:8). The major isomer **67** on treatment with NaOMe in methanol under controlled condition followed by acidification provided the pentacyclic nitrile (±)-**68** in 88% yield. Reduction of **68** by DIBAL followed by oxidation by PDC afforded the aldehyde (±)-**69** in 32% yield (2 steps). Deoxygenation of aldehyde **69** via ethylene dithioacetal by reaction with Raney-Ni in refluxing ethanol afforded (±)-3-epitacamonine (**63**) in 91% yield.



Scheme 9. Synthesis of (±)-3-epitacamonine

3A.6 Summary

In summary, we have presented a concise literature account of indole alkaloids eburnamonine, eburnaminol, larutensine, melohenine B, tacamonine and vindeburnol. The main features in those syntheses are construction of quaternary stereocenter, Pictet-Spengler cyclization, Bischler-Napieralski cyclization, imino Diels-Alder reaction, 6-exo-trig radical cyclization, diastereoselective Birch reduction-alkylation, Zn-mediated radical addition reaction and intramolecular [3+2]-cycloaddition reaction. Overall, well designed novel methodologies for the construction of the core structure of those indole alkaloids along with remarkable approaches for the synthesis of the target compounds have been known in the literature. Our studies towards the synthesis of those vinca-eburna and tacaman alkaloids and their analogues will be discussed in details in the section B of the present chapter.

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Chapter 3: Section B

Diastereoselective/Enantioselective Synthesis of Indole Alkaloids 3-Epitacamonine, Eburnamonine, Eburnaminol, Larutensine, Melohenine B and Vindeburnol

This section B of chapter 3 features the following topics:

3B.1 Rationale of the Present Work

Indole alkaloids encompass very fascinating structural architects coupled with a broad range of biological activities (Figure 1). Moreover, some of them are in clinical use and hence for past several decades they are the target compounds of interest for large number of synthetic organic chemists.[1,2] The bioactive (+)/(–)-eburnamonine from *Hunteria eburnean* (eumetabolic vasoregulator drug and prolyl oligopeptidase inhibitor; IC_{50} = 8 μM), eburnaminol and larutensine from *Kopsia larutensis* belong to a vinca-eburnan class of indole alkaloids and have an angular pentacyclic ring system with *cis*-geometry comprising of a quaternary carbon. The (+)-tacamonine from *Tabernaemontana eglandulosa* Stapf. (anti snake poisioning) is a regioisomer of eburnamonine and belongs to tacaman class of indole alkaloid where the main difference is the presence of ethyl group away from the D and E ring junction keeping an additional stereocenter which are *cis* to each other (C-3, C-14 & C-20). The novel alkaloid melohenine B was recently isolated from the chinese plant *Melodinus henryi*.[3–6] Several elegant diastereoselective and enantioselective total synthesis of above specified indole alkaloids have been reported in the earlier and contemporary literature.[7–10] (–)-Vindeburnol (RU 24722) is their one of the promising synthetic analogue and it is potent central vasodilator which also provides benefit for severe depression.[11a–d] Recent results indicate that the treatment with vindeburnol which targets locus coeruleus survival would be beneficial to multiple sclerosis patients.[11d]

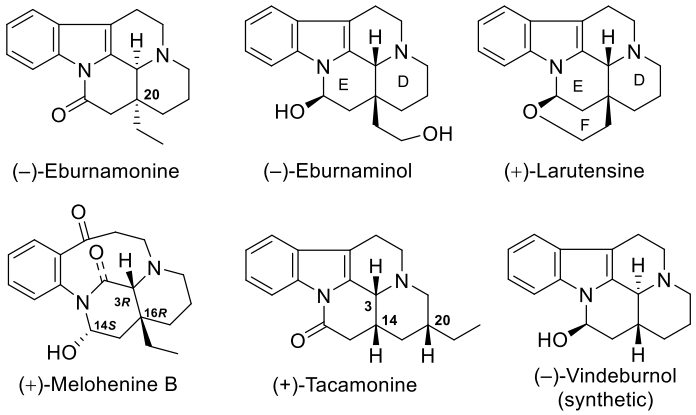


Figure 1. Representative indole alkaloids and derived melohenine B

Development of a chemical switch to keep an appropriate control on reaction is very important in synthetic organic chemistry from the basic chemistry and an application point of view and it is of current interest.[12] In continuation with our studies on cyclic anhydrides and their conversions to bioactive natural products,[13] we herein report the lactam carbonyl

in hexahydroindolo[2,3-*a*]quinolizinones as a switch to tailor the stereoselectivity in carbanionic nucleophilic reactions with ketone moieties and their application to accomplish the concise stereoselective collective synthesis[14] of structurally interesting indole based essential target compounds (Schemes 1–10).

3B.2 Results and Discussion: Present Work

The retrosynthetic analysis of major vinca/eburnan/tacaman alkaloids revealed that the (*R*)/(*S*)-acetoxyglutarimide would be a potential precursor for the collective total synthesis of these target compounds from stereoselectivity, appropriate functional groups and inherent reactive sites point of view (Figure 2).

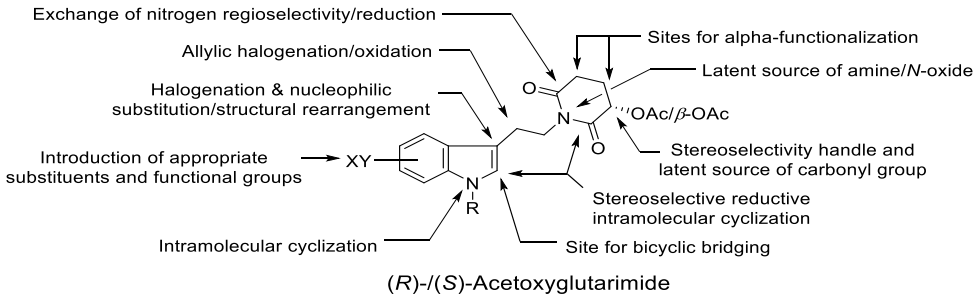
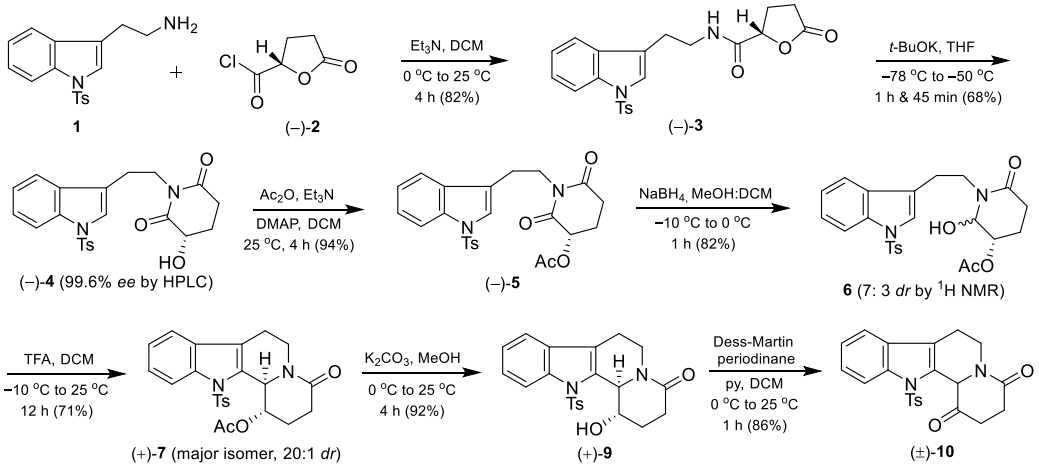
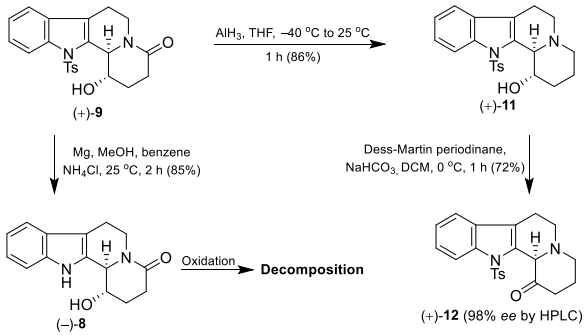


Figure 2. Multiple reactive sites present in pivotal retrosynthetic precursors for vinca, eburnan and tacaman alkaloids

Base-catalyzed coupling reaction of a tosyl-protected tryptamine **1**[15a] with the acid chloride (–)-**2**[15b] delivered the amide (–)-**3** in 82% yield, which upon treatment with *t*-BuOK resulted in the desired rearranged product (–)-acetoxyglutarimide **4** in 68% yield (99.6% *ee*, by HPLC)[13c] (Scheme 1). The acylation of hydroxyimide (–)-**4** followed by regio- and stereoselective sodium borohydride reduction of the corresponding formed acetoxyimide (–)-**5** furnished the corresponding lactamol **6** in 77% yield over two steps with 7:3 as the

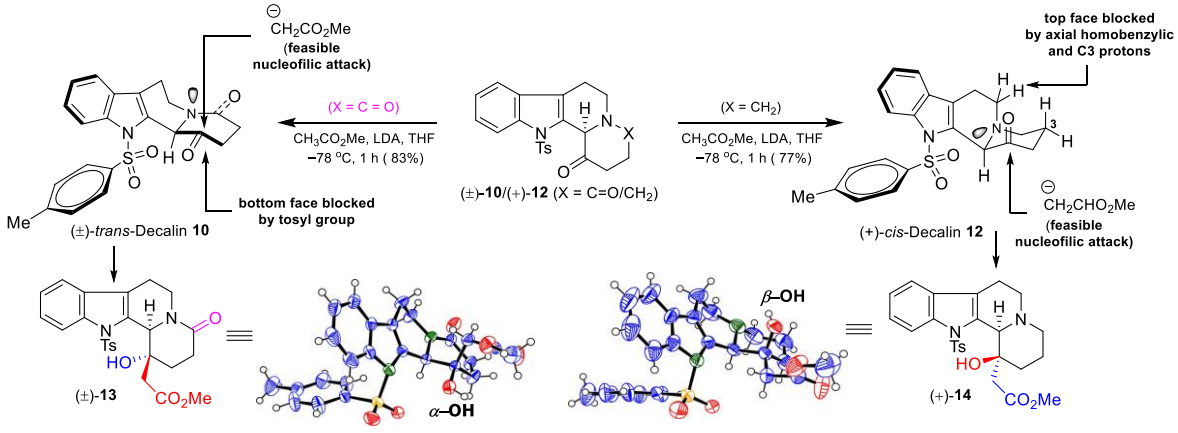


Scheme 1. Stereoselective synthesis of (±)-keto-lactam



Scheme 2. Stereoselective synthesis of (±)-keto-amine

diastereomeric ratio (by ^{1}H NMR). The acid catalyzed stereoselective intramolecular cyclization of the diastereomeric mixture of lactamol **6** provided desired product (+)-**7** in 71% yield via the corresponding flat iminium ion intermediate (20:1 *dr*). The purified product (+)-**7** on magnesium methoxide induced deacylation followed by detosylation ensued into the known compound (–)-hydroxylactam **8** in 85% yield (Scheme 2).[13c] Oxidation of (–)-hydroxylactam **8** with several oxidizing agents such as PCC, IBX, DMP and DMSO/Ac_2O was not successful and always ended up with complete decomposition, indicating that the *N*-protection is requisite for the essential oxidation of proximal secondary hydroxyl group. The K_2CO_3/MeOH mediated selective deacylation of (+)-**7** formed the required common building block (+)-**9** in 92% yield. The (+)-hydroxy-lactam **9** on DMP-oxidation provided the desired keto-lactam **10** in 86% yield but unfortunately with complete racemization. Plausibly, the formed enantiomerically pure product was highly prone for racemization due to the presence of highly acidic methine proton. We could successfully circumvent the above specified problem of instantaneous racemization by performing the reduction of lactam carbonyl to form the corresponding aminol (+)-**11** followed by DMP-oxidation of the hydroxyl group to obtain the enantiomerically pure ketone (+)-**12** in 62% yield over two steps (98% *ee*, by HPLC).

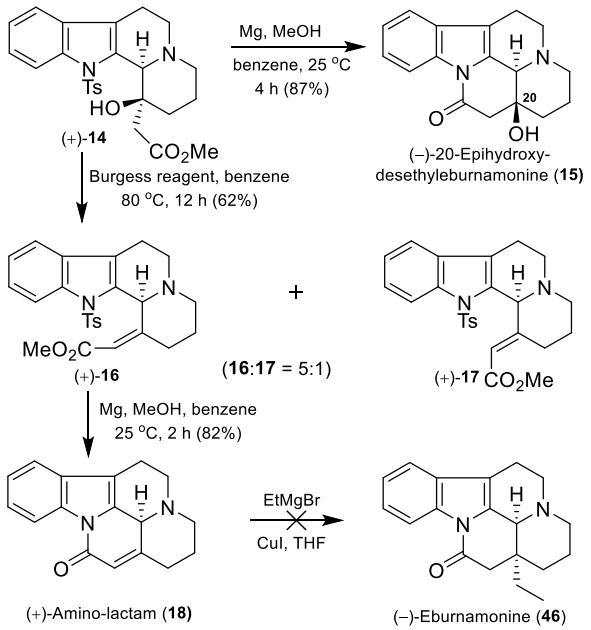


Scheme 3. Lactam carbonyl as a switch to alter the stereoselectivity in ester aldol reaction

The ester-aldol reactions of (±)-keto-lactam **10** (obtained from racemic **5**) and (+)-keto-amine **12** with the lithium enolate of methyl acetate at –78 °C were highly stereoselective and exclusively provided the corresponding products (±)-**13** and (+)-**14** in 83% and 77% yields respectively (Scheme 3). A careful scrutiny of analytical and spectral data obtained for both the compounds (±)-**13** and (+)-**14** and their X-ray crystallographic analyses revealed that the adjacent methine proton and tertiary hydroxyl group are *syn* to each other in product (±)-**13** and *anti* to each other in product (+)-**14**. In case of compound (±)-**10** the incoming nucleophile approaches in a normal fashion from the expected less hindered *β*-side to attack on a ketone carbonyl to deliver the corresponding *α*-hydroxy product (±)-**13**. While in case of compound (+)-**12** the incoming nucleophile approaches from the relatively less hindered *α*-side and attacks on a ketone carbonyl to furnish the desired *β*-hydroxy product (+)-**14** with an opposite stereochemistry. On the basis of X-ray crystallographic data of compound (+)-**34** from scheme 7, we propose that the compound (+)-**12** exists in a relatively more stable *cis*-decalin form to avoid the eclipsing interaction between the ketone carbonyl and sulfone groups. Thus in a *cis*-decalin form of compound (+)-**12** the homobenzylic methylene group will be in a axial orientation and one of the proton from the methylene group and the C3-position axial proton will sterically block the *β*-side and compel the incoming nucleophile to approach from the *α*-side accounting for the reversal of stereoselectivity. Finally the formed product shuffles from *cis*-decalin to the *trans*-decalin form to deliver the stable product (+)-**14** via an umbrella motion in amines. Overall in the (±)-1,4-keto-lactam **10** and (+)-1,4-keto-amine **12**, the same incoming carbanionic nucleophile exclusively attacks on the ketone carbonyl in a face selective manner and in principle the lactam carbonyl in compound (±)-**12** functions as a stereochemical switch. However, the above explanation about the selectivity is our proposal and we feel that molecular modeling studies will be highly useful to explain the observed fact in details with more appropriate scientific explanations. Indeed, the molecular modeling studies and related calculations will provide a clear picture about the three dimensional orientations of each component in compound (±)-**10** in both *cis*-decalin and *trans*-decalin form with respect to stability.

The collective synthesis of target compounds was planned from above specified two different sterochemical outcomes. The precursor (+)-**14** on treatment with magnesium in methanol and benzene mixture (1:1) underwent a smooth *N*-detosylation and supplied

an in situ cyclized product (–)-20-epihydroxydesethyleburmamonine (**15**) in 87 % yield (Scheme 4). In above reaction the use of benzene as a co-solvent was essential for the



Scheme 4. Enantioselective synthesis of (–)-20-epihydroxydesethyleburnamonine and (+)-amino-lactam

starting material solubility issue. The lactamization process to form (–)-**15** with *trans*-ring fusion was very fast due to the 1,2-equatorial-equatorial orientations of the cyclizing groups. The (+)-*β*-hydroxyester **14** on treatment with Burgess reagent underwent stereoselective dehydration to form a separable mixture of corresponding (+)-*Z*-**16** and (+)-*E*-**17** products in 62% yield with 5:1 isomeric ratio. Mechanistically, in the *syn*-elimination involving cyclic transition state, an active *β*-oriented methylene proton is picked up preferentially to form the (+)-*Z*-**16** as a major isomer (Figure 3). The precursor (+)-*Z*-**16**

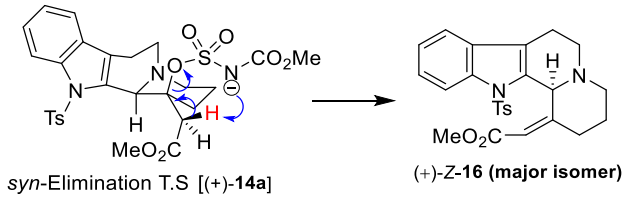
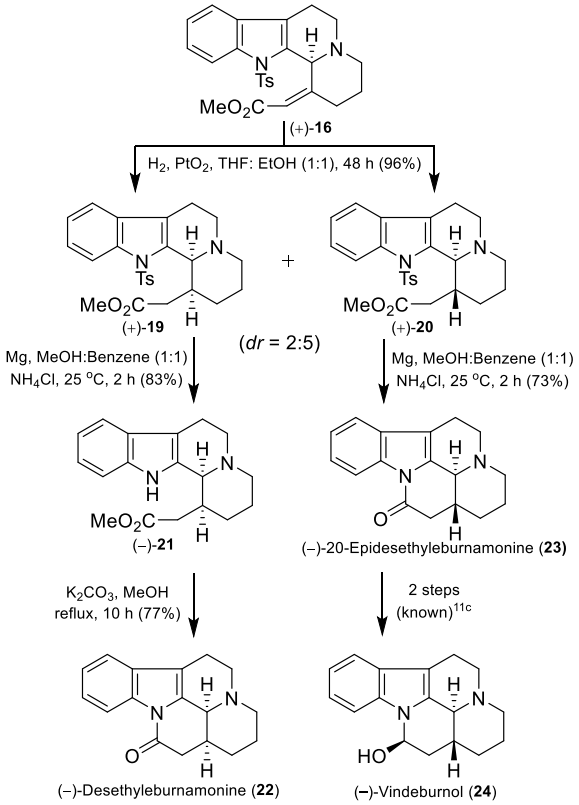


Figure 3. Proposed mechanism for *syn*-elimination

on reaction with magnesium in methanol and benzene mixture (1:1) exclusively supplied the cyclized product (+)-amino-lactam **18** in 82% yield with preservation of carbon–carbon double bond. Unfortunately, all the three starting materials **16**/**17**/**18** on treatment with EtMgBr/CuI remained unreacted and failed to provide the desired product (–)-

eburnamonine precursor/(–)-eburnamonine (Figure 1). Herein the *β*-positive carbon in *α,β*-unsaturated systems was not accessible to an in situ generated EtCuMgBr from either face for both steric and electronic reasons.

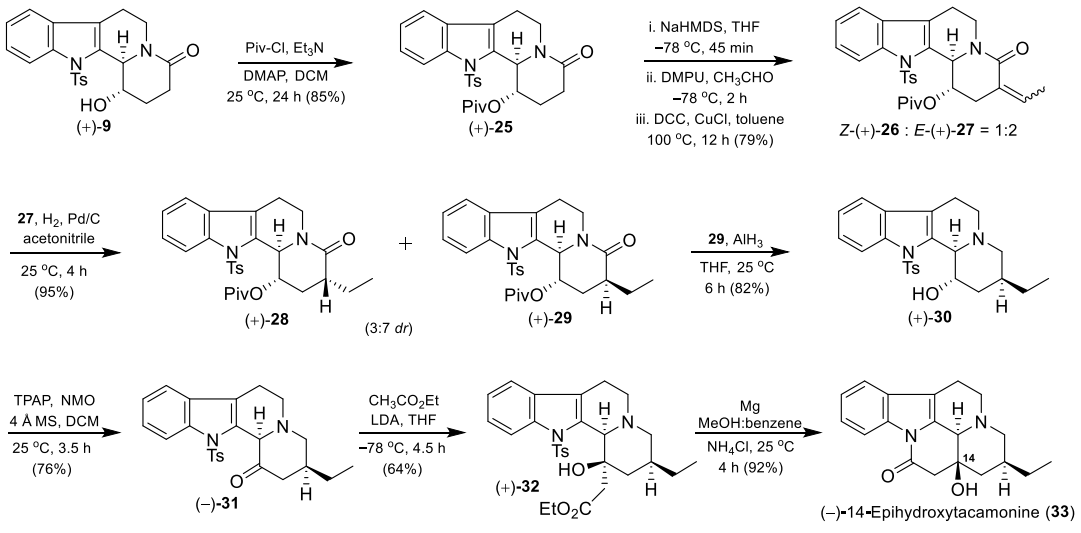


Scheme 5. Enantioselective synthesis of (–)-desethyleburnamonine, (–)-20-epidesethyleburnamonine and (–)-vindeburnol

The major isomer (+)-*Z*-**16** on catalytic hydrogenation over platinum formed the diastereomeric mixture of products (+)-*cis*-**19** [allylic methine proton: 3.83 (s, 1H)] and (+)-*trans*-**20** [allylic methine proton: 4.54 (d, J = 8 Hz, 1H)] in 96% yield with 2:5 ratio (Scheme 5). The separated major isomer (+)-**20** on detosylation directly furnished the cyclized product (–)-20-epidesethyleburnamonine **(23)** in 73% yield. The transformation of (–)-**23** to (–)-vindeburnol (**24**) via hydride reduction followed by an acid-catalyzed epimerization at the aminohydrin carbon through dehydration-rehydration pathway is known with very good overall yield.[11c] The minor isomer (+)-**19** on detosylation initially delivered the uncyclized product (–)-**21** in 83% yield; herein concomitant lactamization with *cis*-ring fusion was not feasible due to the 1,2-equatorial-axial orientations of the cyclizing groups. However the compound (–)-**21** on treatment with K_2CO_3 in refluxing methanol resulted into the desired cyclized product (–)-desethyleburmamonine (**22**) in 77% yield. Particularly the allylic methine proton in compound (–)-**22** with *cis*-ring

junction was relatively highly deshielded due to the peri-interaction with *syn*-oriented lactam carbonyl group and appeared at 4.43 ppm.

In the next part of our studies, synthetic approaches for the tacamonine derivatives were planned. The compound (+)-**9** would be an appropriate imtermediate for the α-functionalization of lactam and hence at first the hindered secondary alcohol (+)-**9** was protected as pivaloyl ester (+)-**25** by using excess pivaloyl chloride (Scheme 6). The sodium enolate generated from (+)-**25** on reaction with acetaldehyde in the presence of DMPU at –78 ^{o}C provided a mixture of diastereomeric β-hydroxy lactams. The alcohols on DCC-CuCl induced *syn*-elimination resulted in a separable mixture of conjugated lactams (+)-*Z*-**26** and (+)-*E*-**27** in 1:2 ratio (79% yield). As expected the vinylic proton of a major isomer (+)-*E*-**27** was more deshielded (7.02 ppm) due to the five membered peri-interaction with a lactam carbonyl. The isomer (+)-*E*-**27** on catalytic hydrogenation in acetonitrile delivered a separable mixture of diastereoisomers (+)-*trans*-**28** and (+)-*cis*-**29** in 3:7 ratio (95% yield). The stereochemical assignments of (+)-*trans*-**28** and (+)-*cis*-**29** were initially confirmed by NOSEY NMR studies (Figure 4 and selected spectra). The above catalytic hydrogenation was less selective in methanol or petroleum ether-ethyl acetate mixture leading to ~ 1:1 mixture of compounds **28** and **29**. The major isomer (+)-*cis*-**29** on alane mediated deprotection of pivaloyl group and reduction of a lactam carbonyl followed by the TPAP/NMO oxidation of the formed alcohol (+)-**30** delivered a ketone (–)-**31** in 76% yield over two steps. The stereoselective ester-aldol reaction of



Scheme 6. Enantioselective total synthesis of (–)-14-epihydroxytacamonine

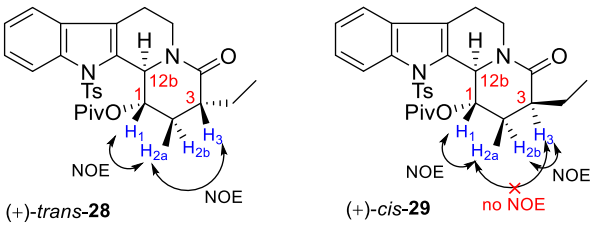
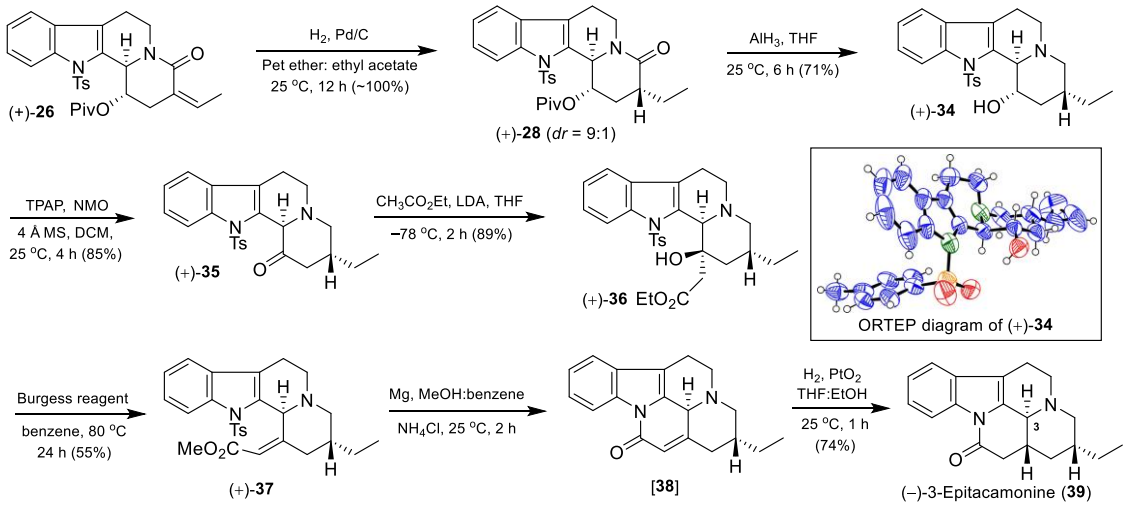


Figure 4. Stereochemical assignments of (+)-*trans*-**28** and (+)-*cis*-**29**

ketone (–)-**31** with the lithium enolate of ethyl acetate exclusively afforded the expected *β*-hydroxy ester (+)-**32** in 64% yield. All our attempts to eliminate the *β*-hydroxy group in compound (+)-**32** to obtain the corresponding *α,β*-unsaturated ester met with failure; plausibly due to the 1,3-diaxial steric interactions between the hydroxyl and ethyl group. However detosylation of compound (+)-**32** directly resulted into the desired product (–)-14-epihydroxytacamonine (**33**) in 92% yield.

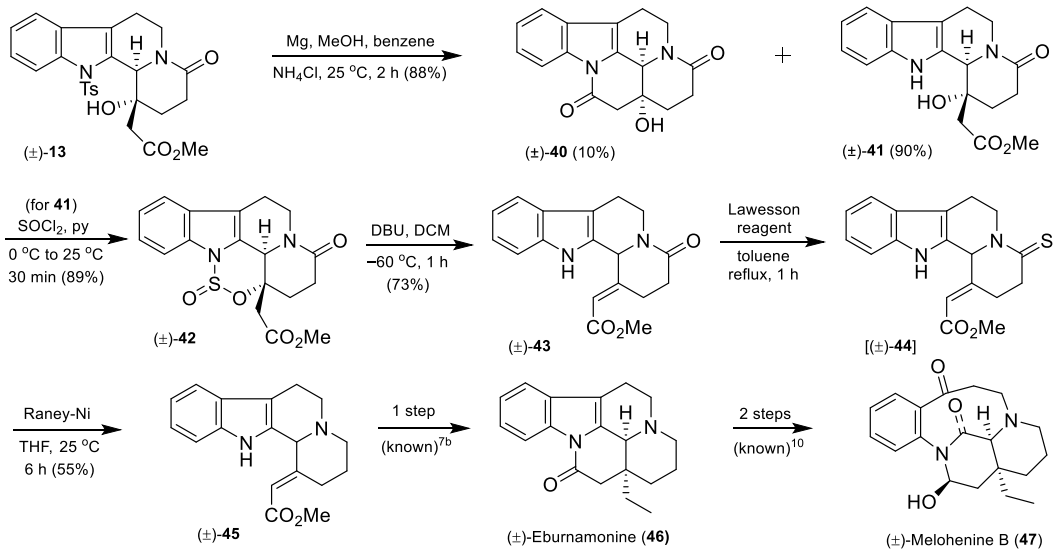


Scheme 7. Enantioselective total synthesis of (–)-3-epitacamonine

Interestingly, the minor isomer (+)-*Z*-**26** on catalytic hydrogenation in petroleum ether-ethyl acetate mixture delivered the product (+)-*trans*-**28** with high diastereoselectivity (9:1 *dr*) in 90% yield (Scheme 7). The product (+)-*trans*-**28** on alane mediated deprotection and reduction followed by the TPAP/NMO oxidation of formed alcohol (+)-**34** delivered a ketone (+)-**35** in 60% yield over two steps. The absolute stereochemistry of crystalline amino alcohol (+)-**34** was established on the basis of X-ray crystallographic data. As anticipated the ester-aldol reaction of ketone (+)-**35** with the lithium enolate of ethyl acetate again exclusively provided the desired *β*-hydroxy compound (+)-**36** in 89% yield. As expected the alcohol (+)-**36** on treatment with Burgess reagent delivered the *syn*-elimination product (+)-*Z*-**37** in 55% yield. The product (+)-*Z*-**37** on detosylation in situ formed the lactam **38**, which on an immediate stereoselective reduction of the *α,β*-

unsaturated carbon–carbon double bond by using H_2/PtO_2 delivered the (–)-3-epitacamonine (**39**)[16] in 74% yield. Plausibly due to the presence of α-oriented ethyl group, the adsorption of olefin on platinum surface takes place from the β-face with the stereoselective formation of the final product (–)-**39**.

The synthesis of vinca-eburna class of (±)-eburnamonine alkaloid was intended from our racemic common precursor (±)-**13**. The common precursor (±)-**13** on treatment with magnesium in methanol plus benzene mixture (1:1) underwent a smooth *N*-detosylation and supplied a separable mixture of an in situ cyclized and the uncyclized products (±)-**40** and (±)-**41** respectively with 88% combine yield in 2 h (**40**:**41** = 1:9) (Scheme 8). As expected the lactamization process of (±)-**41** to (±)-**40** with a *cis*-ring fusion was slow due to the 1,2-equatorial-axial orientations of cyclizing groups. Hence it was feasible to obtain the desired (±)-**41** as a major product even after arresting the reaction on complete consumption of a starting material. However, the same reaction on



Scheme 8. Formal synthesis of (±)-eburnamonine and (±)-melohenine B

overnight stirring resulted in an exclusive formation of product (±)-**40** in high yield. The major product (±)-**41** on treatment with thionyl chloride and pyridine directly provided the corresponding isolable cyclic sulfuramidite (±)-**42** in 89% yield. We presume that the formation of sulfuramidite (±)-**42** takes place in a stepwise fashion via the corresponding unisolable sulfuramidous chloride intermediate. An increase in reaction time with a hope to directly obtain the desired elimination product (±)-**43** resulted in excessive decomposition of the formed sulfuramidite (±)-**42**. The eliminative cleavage of sulfuramidite (±)-**42** to the corresponding α,β-unsaturated ester (±)-**43** was both

base/temperature sensitive and it was also prone to transform back into the starting material (±)-**41** at and above 0 °C. Nonetheless, the compound (±)-**42** on treatment with DBU in DCM at –60 °C stereoselectively formed the thermodynamically more stable desired (*E*)-isomer (±)-**43** in 73% yield with the release of sulfur dioxide as a leaving

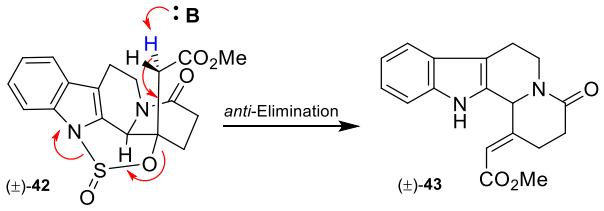


Figure 5. Proposed mechanism for anti-elimination

group (Figure 5). The 2 D NMR studies (see selected spectra) indicated that the vinylic proton has strong NOE interactions with proximal proton on indole nitrogen. The lactam (±)-**43** on reaction with Lawesson reagent[17] transformed into the expected intermediate thiolactam (±)-**44** (by TLC), which on an immediate Raney-Nickel mediated desulfurization reaction delivered the *α*,*β*-unsaturated ester (±)-**45** in 55% yield over two steps. Starting from the corresponding ethyl ester one-step synthesis of (±)-eburnamonine (**46**) via the stereoselective Michael addition of a cuprate from the less hindered *α*-side with very good yield is known. [7b] The two-step transformation of (±)-**46** to (±)-melohenine B (**47**) through an oxidative ring expansion is also known.[10]

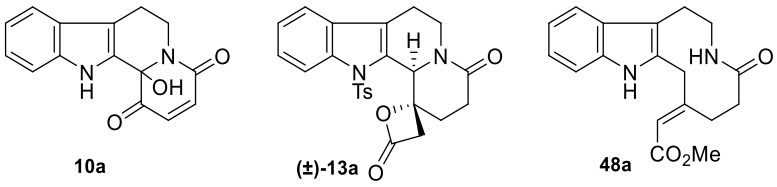
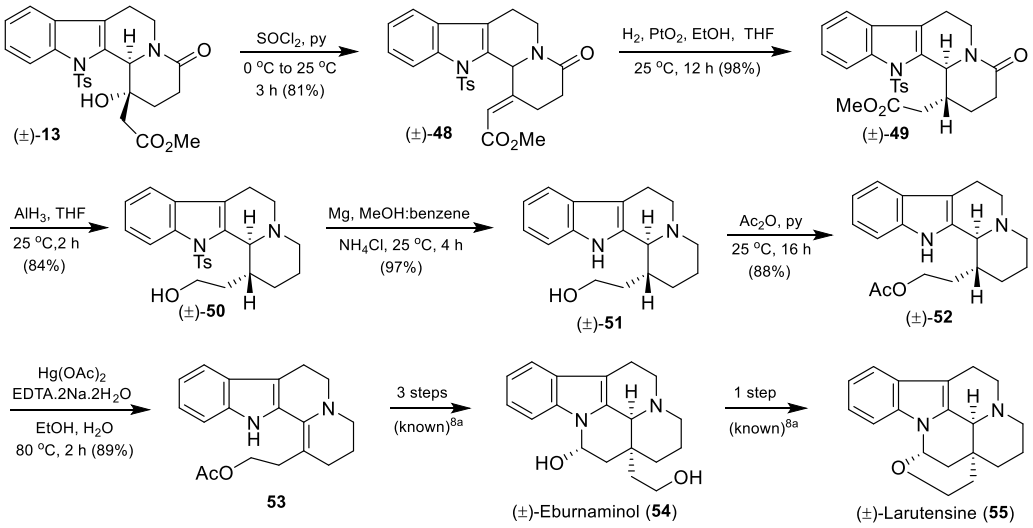


Figure 6. Some of the exclusively formed unexpected products

The formal synthesis of yet another two interesting natural products (±)-ebumaminol (**54**) and (±)-larutensine (**55**) was planned from the precursor (±)-**13**, but this time using an intermediate **53** which does not contain a tetrahedral stereogenic center (Scheme 9). The initially studied Horner–Wadsworth–Emmons (HWE) reaction on ketone (±)-**10** to directly form the corresponding *α*,*β*-unsaturated ester was not successful for steric reasons. The above reaction instead delivered the corresponding relatively more stable air-oxidized product (±)-**10a** in 62% yield proving its propensity towards the facile air-oxidation process (Figure 6). The involved *N*-detosylation, introduction of an angular hydroxyl group and oxidative dehydrogenation reaction to form the doubly conjugated

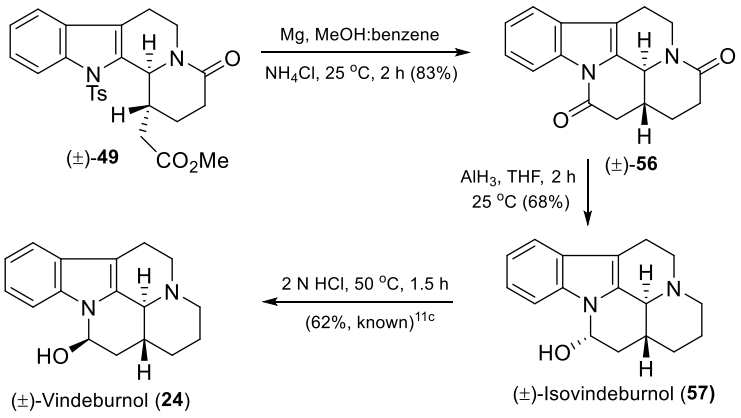
carbon–carbon double bond to form (±)-**10a** took place in one-pot. The alternatively performed *p*-TSA mediated dehydration of *β*-hydroxyester (±)-**13** also resulted in the corresponding unexpected spiro *β*-lactone (±)-**13a** in 85% yield. However the thionyl chloride persuaded dehydration of tertiary alcohol (±)-**13** exclusively provided the thermodynamically more stable *α*,*β*-unsaturated ester (±)-*E*-**48** in 81% yield. An attempted naphthalene radical induced *N*-detosylation of product (±)-*E*-**48** caused the deprotection but with a ring expansion via the cleavage of more reactive internal carbon–nitrogen single bond to form a 10-membered macrolactam (±)-**48a** in 56% yield.[18] The treatment of compound (±)-**48** with magnesium in methanol plus benzene or sodium amalgam in



Scheme 9. Formal synthesis of (±)-eburnaminol and (±)-larutensine

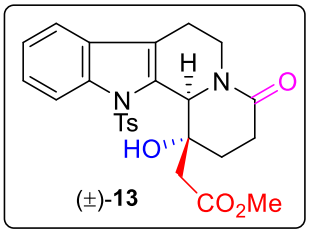
methanol ensued in planned *N*-detosylation, but it was accompanied with a non-stereospecific reduction of *α*,*β*-unsaturated carbon–carbon double bond resulting in ~1:1 mixture of the corresponding diastereomers (by ^{1}H NMR). Finally the catalytic hydrogenation of carbon–carbon double bond in *α*,*β*-unsaturated ester (±)-*E*-**48** using H_2/PtO_2 was stereoselective and exclusively formed the product (±)-**49** in 98% yield. Plausibly the bulk of *N*-tosyl group dictates the site for adsorption of *π*-lobes on the platinum catalyst resulting in a relative *trans*-geometry of the adjacent methine protons. The precursor (±)-**49** on reaction with red-Al directly furnished the desired (±)-aminoalcohol **51**, but only in 25 to 30% yield. Alane reduction of (±)-**49** resulted into the desired product (±)-aminoalcohol **50** in 84% yield. Both the ester to alcohol and lactam to amine reductions took place in one-pot with an intact preservation of *N*-tosyl protection. The coupling constant (J = 8 Hz) for angular methine proton in ^{1}H NMR also confirmed the assigned *trans* stereochemistry of an adjacent methine protons in compound (±)-**50**.

The *N*-detosylation of (±)-**50** followed by selective *O*-acylation of the formed alcohol (±)-**51** resulted in product (±)-**52** with 85% yield over two steps. The product (±)-**52** on Fujii-oxidation[19] [$Hg(OAc)_2$/EDTA.2Na.2H_2O; oxidative dehydrogenation] delivered the known product **53** in 89% yield via formation of the corresponding iminium intermediate followed by an instantaneous intramolecular prototrophic shift. Starting from compound **53** a three-step stereoselective synthesis of (±)-eburnaminol (**54**) through enamine alkylation followed by a reductive intramolecular cyclization and the one-step transformation of (±)-**54** to (±)-larutensine (**55**) via an intramolecular dehydrative cyclization are known.[8a]



Scheme 10. Diastereoselective formal synthesis of (±)-vindeburnol

Finally the advanced precursor (±)-**49** on reaction with magnesium in methanol plus benzene underwent a smooth *N*-detosylation followed by a concomitant intramolecular cyclization resulting in lactam (±)-**56** in 83% yield (Scheme 10). The lactamization process of (±)-**49** to (±)-**56** with *trans* ring fusion was very fast due to the 1,2-equatorial-equatorial orientations of the cyclizing groups and hence it was not feasible to stop the reaction at an intermediate stage as described earlier for the corresponding *cis*-ring fusion system in scheme 5. The lactam (±)-**56** on alane reduction supplied the kinetically controlled product (±)-isovindeburnol **57** in 68% yield. Acid catalyzed epimerzation at the *gem*-aminohydrin center of (±)-isovindeburnol **57** to deliver the thermodynamically more stable (±)-vindeburnol (**24**) via the dehydration-rehydration pathway is well known in the literature.[11c]



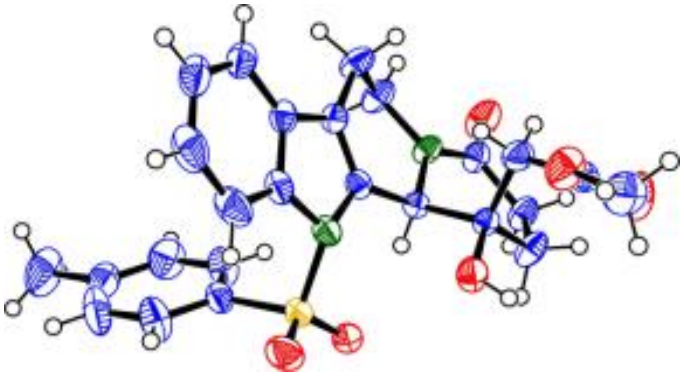


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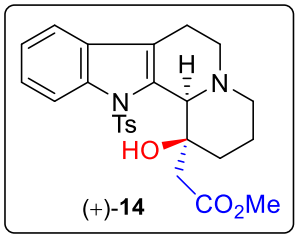
Figure 7. Ortep drawing of compound (±)-**13**. Thermal ellipsoids set to 50% probability level.



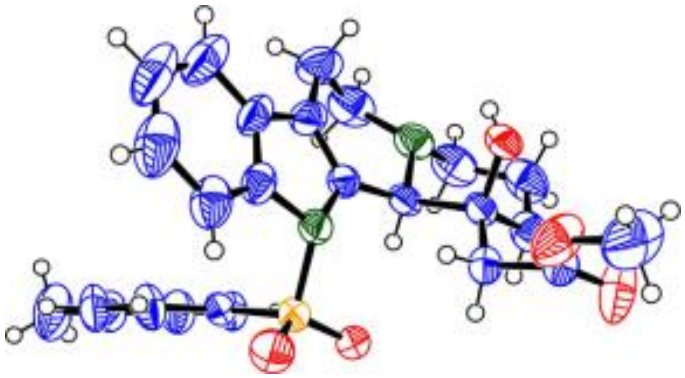


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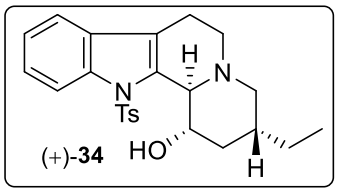
Figure 8. Ortep drawing of compound (+)-**14**. Thermal ellipsoids set to 50% probability level.



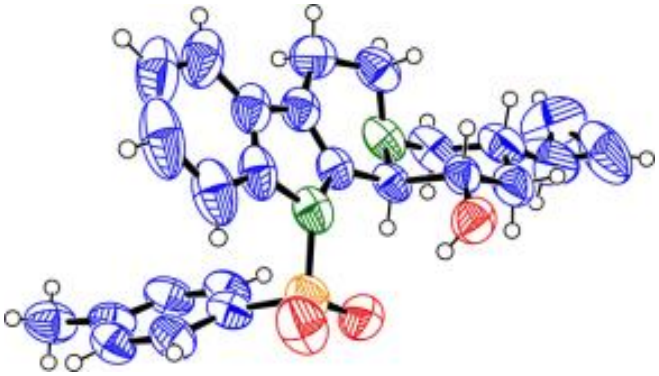


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Figure 9. Ortep drawing of compound (+)-**34**. Thermal ellipsoids set to 50% probability level.

Note: *Complete details of crystallographic data will be reported in the SI part of publication.*

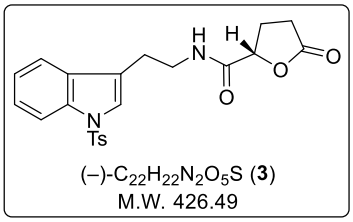
3B.3 Summary

In summary, we have completed facile enantioselective/diastereoselective synthesis of indole alkaloids (–)-3-epitacamonine, (±)-eburnamonine, (±)-melohenine B, (±)-eburnaminol, (±)-larutensine and (–)-vindeburnol. The first precise stepwise use of all the three oxygen functions in (–)-/(±)-acetoxyglutarimide in a chemo-, regio- and stereoselective manner to craft the desired target compounds is noteworthy. We could resolve the witnessed issue of racemization by transforming the lactam functionality to the corresponding amine, thus reducing the acidity of methine proton. The amine-lactam switch system was developed and successfully used for the stereoselective embarking of an incoming nucleophile in ester aldol reactions. The obtained two different stereochemical outcomes were rationally used for a stereoselective design of indole alkaloids, their analogues and congeners. We feel that our present protocol is general in nature and will be useful to synthesize several natural and unnatural indole based structurally interesting and biologically important architectures for SAR studies.

3B.4 Experimental Section

Commercially available *t*-BuOK, Dess-Martin periodinane, tetrapropylammonium perruthenate (TPAP), NMO, *n*-butyllithium, diisopropylamine, DMPU, Burgess reagent, tetrabutylammonium fluoride, platinum dioxide, magnesium foils, DBU, Lawesson's reagent, aluminium chloride, lithium aluminium hydride, acetic anhydride and mercuric acetate were used.

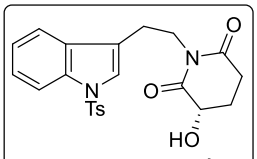
(–)-(*S*)-5-Oxo-*N*-(2-(1-tosyl-1*H*-indol-3-yl)ethyl)tetrahydrofuran-2-carboxamide (3).



(–)-$C_{22}H_{22}N_2O_5S$ (**3**)
M.W. 426.49

A mixture of (*S*)-5-oxotetrahydrofuran-2-carboxylic acid (4.16 g, 32.00 mmol) (prepared from L-glutamic acid by using known procedure[13c]) and thionyl chloride (8.00 mL, 110 mmol) was refluxed for 6 h under argon atmosphere. The excess of thionyl chloride was removed in vacuo and the obtained residue was dissolved in dry CH_2Cl_2 (40 mL). A solution of tosyl-protected tryptamine[15a] (**1**, 10.00 g, 31.80 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a stirred solution of acid chloride (–)-**2**[15b] at 0 °C under argon atmosphere. To the above reaction mixture was added Et_3N (8.85 mL, 63.60 mmol) in a dropwise fashion and it was stirred at 25 °C for 4 h. The reaction was quenched with water (25 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (230–400) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:2) as an eluent gave pure amido-lactone (–)-**3** as gummy solid (11.12 g, 82% yield). $[\alpha]^{25}_{D}$ –9.92 (*c* 0.40 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.03–2.20 (m, 1H), 2.21 (s, 3H), 2.32–2.58 (m, 3H), 2.79 (t, *J* = 8 Hz, 2H), 3.34–3.60 (m, 2H), 4.69 (t, *J* = 8 Hz, 1H), 6.50 (t, *J* = 6 Hz, 1H), 7.05–7.25 (m, 4H), 7.27 (s, 1H), 7.37 (dd, *J* = 6 and 2 Hz, 1H), 7.64 (d, *J* = 10 Hz, 2H), 7.84 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 24.9, 25.7, 27.4, 38.6, 77.3, 113.6, 119.17, 119.23, 123.1, 123.3, 124.8, 126.7, 129.9, 130.5, 135.0, 135.1, 144.9, 169.4, 175.8; ESIMS (*m*/*z*) 449 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{22}N_2O_5SNa$ 449.1142, found 449.1141; IR (neat) ν_{max} 3321, 1784, 1733, 1677 cm^{-1}.

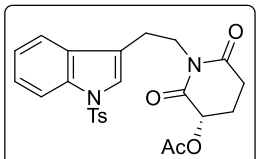
(–)-(*S*)-3-Hydroxy-1-(2-(1-tosyl-1*H*-indol-3-yl)ethyl)piperidine-2,6-dione (4). To a



(–)-$C_{22}H_{22}N_2O_5S$ (**4**)
M.W. 426.49

stirred solution of amido-lactone (–)-**3** (4.30 g, 10.08 mmol) in THF (30 mL) was added suspension of *t*-BuOK in THF (0.45 M, 10.00 mL) in a dropwise fashion over a period of 10 min at –78 °C under argon atmosphere. The reaction mixture was allowed to reach –50 °C in 1 h and then it was further stirred at the same temperature for 45 min. The reaction was quenched with saturated aq. NH_4Cl (10 mL) and THF was removed in vacuo. To the reaction mixture was added ethyl acetate (100 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:1) as an eluent yielded (*S*)-hydroxyglutarimide (–)-**4** as a white solid (2.92 g, 68% yield; 99.6% *ee*). Mp 168–170 °C; $[\alpha]^{25}_{D}$ –49.37 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 (dq, *J* = 10 and 5 Hz, 1H), 2.27–2.35 (m, 1H), 2.36 (s, 3H), 2.62 (ddd, *J* = 20, 15 and 5 Hz, 1H), 2.82–2.91 (m, 1H), 2.93 (t, *J* = 10 Hz, 2H), 3.55 (s, 1H), 3.96–4.05 (m, 1H), 4.06–4.12 (m, 1H), 4.16 (dd, *J* = 10 and 5 Hz, 1H), 7.25 (d, *J* = 5 Hz, 1H), 7.29 (t, *J* = 10 Hz, 1H), 7.34 (t, *J* = 10 Hz, 1H), 7.43 (s, 1H), 7.66 (d, *J* = 5 Hz, 1H), 7.79 (d, *J* = 5 Hz, 2H), 8.00 (d, *J* = 5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 23.3, 25.2, 30.7, 39.9, 68.2, 113.6, 118.9, 119.5, 123.2, 123.6, 124.8, 126.8, 129.8, 130.7, 135.0, 135.3, 144.9, 171.1, 175.1; ESIMS (*m*/*z*) 449 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{22}N_2O_5SNa$ 449.1142, found 449.1132; IR (neat) ν_{max} 3448, 1729, 1661 cm^{-1}.

(–)-(*S*)-2,6-Dioxo-1-(2-(1-tosyl-1*H*-indol-3-yl)ethyl)piperidin-3-yl Acetate (5). To a

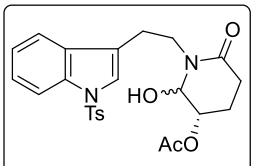


(–)-$C_{24}H_{24}N_2O_6S$ (**5**)
M.W. 468.52

stirred solution of hydroxyimide (–)-**4** (6.00 g, 14.07 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (2.35 mL, 16.88 mmol), Ac_2O (1.99 mL, 21.10 mmol) and DMAP (50 mg). The reaction mixture was allowed to reach 25 °C and further stirred for 4 h. The reaction was quenched with water (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with saturated aq. $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (6:4) as an eluent afforded pure acetoxyimide (–)-**5** as a white solid (6.20 g, 94% yield). Mp 135–138 °C; $[\alpha]^{25}_{D}$ –44.57 (*c* 2.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.09–2.21 (m, 2H), 2.22 (s, 3H), 2.34 (s, 3H), 2.52–2.78 (m, 1H),

2.80–3.05 (m, 1H), 2.89 (t, *J* = 8 Hz, 2H), 3.85–4.20 (m, 2H), 5.45 (dd, *J* = 12 and 8 Hz, 1H), 7.22 (d, *J* = 8 Hz, 2H), 7.20–7.38 (m, 2H), 7.40 (s, 1H), 7.67 (dd, *J* = 6 and 2 Hz, 1H), 7.76 (d, *J* = 8 Hz, 2H), 7.97 (dd, *J* = 6 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.7, 21.5, 23.1, 23.3, 30.3, 39.9, 68.5, 113.6, 119.0, 119.7, 123.2, 123.5, 124.7, 126.7, 129.8, 130.6, 135.0, 135.2, 144.8, 169.1, 169.8, 170.5; ESIMS (*m*/*z*) 491 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{24}N_2O_6SNa$ 491.1247, found 491.1238; IR ($CHCl_3$) ν_{max} 1743, 1685 cm^{-1}.

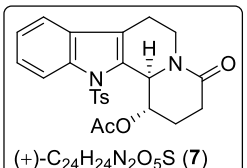
(3*S*)-2-Hydroxy-6-oxo-1-(2-(1-tosyl-1*H*-indol-3-yl)ethyl)piperidin-3-yl Acetate (6). To



$C_{24}H_{26}N_2O_6S$ (**6**)
M.W. 470.54

a stirred solution of (*S*)-acetoxyglutarimide (–)-**5** (2.00 g, 4.27 mmol) in MeOH:CH_2Cl_2 (2:1, 30 mL) mixture was added $NaBH_4$ (324 mg, 8.54 mmol) in small portions at –10 ^{o}C over 5 min. The stirred reaction mixture was allowed to reach 0 ^{o}C in 1 h and the reaction was quenched with mixture of saturated aq. NH_4Cl (5 mL) and brine (5 mL). The reaction mixture was further stirred vigorously at 0 ^{o}C for 10 min and it was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded the required lactamol **6** (7:3 *dr*) as white foam (1.65 g, 82% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.78–1.93 (m, 1H), 1.96 (s, 1H), 2.08 (s, 2H), 2.15–2.35 (m, 1H), 2.29 (s, 1H), 2.30 (s, 2H), 2.35–2.60 (m, 2H), 2.90–3.05 (m, 2H), 3.48–3.90 (m, 2.70H), 4.50–4.55 (br s, 0.30H), 4.78–4.90 (m, 1H), 4.93 (s, 1H), 7.13–7.35 (m, 4H), 7.37 (s, 1H), 7.55–7.60 (m, 1H), 7.65–7.80 (m, 2H), 7.90–8.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.2, 20.5, 20.8, 21.0, 21.5, 23.7, 27.3, 29.2, 45.4, 45.9, 69.4, 69.9, 79.6, 81.3, 113.6, 119.6, 119.9, 123.1, 123.2, 124.8, 126.7, 129.8, 130.7, 134.9, 135.0, 144.9, 169.5, 169.96, 170.0, 170.5; ESIMS (*m*/*z*) 493 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{26}N_2O_6SNa$ 493.1404, found 493.1397; IR (neat) ν_{max} 3312, 1739, 1620 cm^{-1}.

(+)-(1*S*,12b*R*)-4-Oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl

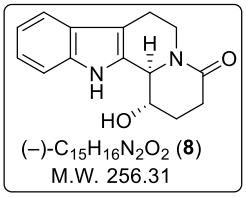


(+)-$C_{24}H_{24}N_2O_5S$ (**7**)
M.W. 452.53

Acetate (7). To a stirred solution of lactamol **6** (3.80 g, 8.08 mmol) in CH_2Cl_2 (50 mL) at –10 ^{o}C was added TFA (1.23 mL, 16.16 mmol) in a dropwise fashion. The reaction mixture was stirred at 25 ^{o}C for 12 h and the reaction was quenched with saturated aq. $NaHCO_3$ (5 mL).

The reaction mixture was extracted with CH_2Cl_2 (50 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent first afforded the minor diastereomer (124 mg, 3.4% yield) and then the required major diastereomer (+)-**7** as white foam (2.47 g, 67.6% yield). Major isomer (+)-**7**: $[\alpha]^{25}_{D}$ +64.65 (*c* 1.6 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70–1.85 (m, 1H), 2.00–2.20 (m, 1H), 2.21 (s, 3H), 2.28 (s, 3H), 2.30–2.90 (m, 5H), 5.05 (dd, *J* = 12 and 4 Hz, 1H), 5.26 (q, *J* = 4 Hz, 1H), 5.83–5.92 (m, 1H), 7.05 (d, *J* = 8 Hz, 2H), 7.20–7.38 (m, 3H), 7.38 (d, *J* = 8 Hz, 2H), 8.08 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 21.5, 21.9, 23.4, 27.6, 40.7, 60.4, 71.3, 117.0, 118.7, 124.9, 125.7, 126.7, 127.3, 129.2, 130.8, 132.3, 133.0, 138.8, 145.0, 169.7, 170.1; ESIMS (*m*/*z*) 475 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{25}N_2O_5S$ 453.1479, found 453.1469; IR (neat) ν_{max} 1736, 1642 cm^{-1}.

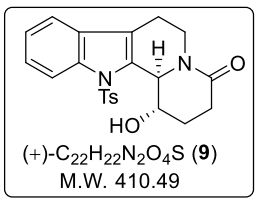
(–)-(1*S*,12b*R*)-1-Hydroxy-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one



(–)-$C_{15}H_{16}N_2O_2$ (**8**)
M.W. 256.31

(8). To stirred solution of *N*-tosyl protected acetate (+)-**7** (50 mg, 0.11 mmol) in MeOH:benzene mixture (4 mL,1:1) were sequentially added activated magnesium turnings (26 mg, 1.10 mmol) and NH_4Cl (59 mg, 1.10 mmol) at 25 ^{o}C under argon atmosphere. The reaction mixture was stirred for 2 h and the reaction was quenched with saturated aq. NH_4Cl (2 mL) and 1 N HCl (1 mL). Solvent was removed in vacuo and the residue was dissolved in ethyl acetate (15 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–methanol (98:2) as an eluent afforded the known hydroxy compound (–)-**8** (24 mg, 85% yield) as a white solid.[13c] Mp 248–249 °C; $[\alpha]^{25}_{D}$ –171.2 (*c* 0.20 MeOH).

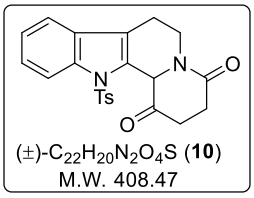
(+)-(1*S*,12b*R*)-1-Hydroxy-12-tosyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (9). To a stirred solution of acetate (+)-**7** (2.00 g, 4.42 mmol) in MeOH (30 mL) was added anhydrous K_2CO_3 (610 mg, 4.42 mmol) at 0 ^{o}C. The reaction mixture was stirred for 4 h at 25 ^{o}C and concentrated in vacuo. The obtained residue was directly purified by silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–petroleum ether (8:2) as an eluent to afford the secondary alcohol (+)-**9** as a white



(+)-$C_{22}H_{22}N_2O_4S$ (**9**)
M.W. 410.49

solid (1.67 g, 92% yield). Mp 204–206 °C; $[\alpha]^{25}_{D}$ +80.34 (*c* 2.14 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60–1.80 (m, 1H), 1.90–2.10 (m, 1H), 2.29 (s, 3H), 2.30–2.95 (m, 5H), 3.43 (br s, 1H), 4.78 (br s, 1H), 5.00–5.20 (m, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.20–7.40 (m, 3H), 7.42 (d, *J* = 8 Hz, 2H), 8.11 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 22.0, 26.1, 27.4, 40.1, 64.2, 69.4, 116.8, 118.7, 125.0, 125.6, 126.3, 126.6, 129.4, 130.7, 132.2, 133.7, 138.3, 145.3, 171.1; ESIMS (*m*/*z*) 433 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{22}N_2O_4SNa$ 433.1192, found 433.1193; IR (neat) ν_{max} 3443, 1626 cm^{-1}.

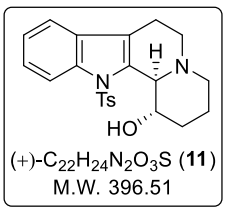
(±)-12-Tosyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-1,4-dione (10). To a



(±)-$C_{22}H_{20}N_2O_4S$ (**10**)
M.W. 408.47

stirred solution of alcohol (+)-**9** (200 mg, 0.49 mmol) in CH_2Cl_2 (6 mL) was added fresh Dess–Martin periodinane (624 mg, 1.47 mmol) and pyridine (0.12 mL, 1.47 mmol) at 0 °C under argon atmosphere. After stirring for 1 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (6 mL) and quenched with mixture of aq. sodium thiosulphate (40%, 2 mL) plus saturated aq. $NaHCO_3$ (2 mL). It was then extracted with CH_2Cl_2 (20 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent resulted the ketone (±)-**10** as white foam (171 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.35 (s, 3H), 2.55–3.25 (m, 7H), 4.76 (dd, *J* = 12 and 4 Hz, 1H), 6.01 (s, 1H), 7.15–7.40 (m, 4H), 7.45 (dd, *J* = 8 and 2 Hz, 1H), 7.74 (d, *J* = 8 Hz, 2H), 7.83 (dd, *J* = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.2, 21.6, 30.6, 33.2, 38.6, 60.0, 114.2, 118.8, 119.9, 123.5, 125.1, 126.9, 127.1, 128.3, 129.8, 135.4, 136.4, 145.1, 171.6, 200.5; ESIMS (*m*/*z*) 431 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{20}N_2O_4SNa$ 431.1036, found 431.1028; IR (neat) ν_{max} 1739, 1684 cm^{-1}. [The same reaction was also carried out on higher scale with (±)- **9** (1.00 g, 2.44 mmol)].

(+)-(1*S*,12b*R*)-12-Tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-ol (11).

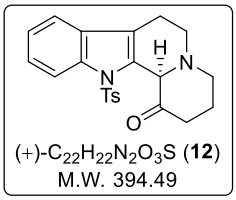


(+)-$C_{22}H_{24}N_2O_3S$ (**11**)
M.W. 396.51

A flame dried round-bottomed flask was charged with $AlCl_3$ (146 mg, 1.10 mmol) and THF (6 mL) under argon atmosphere. The stirred reaction mixture was cooled to 0 °C and a suspension of $LiAlH_4$ (125 mg, 3.30 mmol) in THF (3 mL) was added dropwise. After stirring for 15 min at 0 °C, the ice bath was removed. A solution of lactam **11** (500 mg, 1.10 mmol) in THF (6 mL) was added dropwise to the above reaction mixture at –40 °C. Then it was

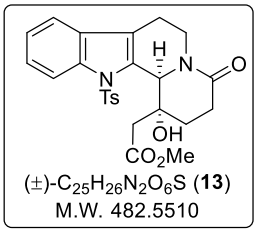
stirred for 1 h allowing to reach at 25 °C and quenched by the addition of saturated aq. Na_2SO_4 (4 mL). The reaction mixture was filtered through Celite and the residue was washed with ethyl aceatate (30 mL). The filtrate was dried over Na_2SO_4 and concentrated in vacuo. The silica gel (230–400 mesh) column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (94:6) as an eluent afforded the amino alcohol (+)-**11** as white foam (377 mg, 86% yield). $[\alpha]^{25}_D$ +203.1 (*c* 0.53 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50–1.75 (m, 2H), 1.75–2.10 (m, 1H), 2.10–2.35 (m, 1H), 2.27 (s, 3H), 2.65–2.90 (m, 3H), 3.05–3.20 (m, 2H), 3.25–3.42 (m, 1H), 3.76 (dt, *J* = 10 and 4 Hz, 1H), 4.34 (d, *J* = 8 Hz, 1H), 7.10 (d, *J* = 8 Hz, 2H), 7.15–7.35 (m, 3H), 7.49 (d, *J* = 8 Hz, 2H), 8.07 (dd, *J* = 6 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.46, 21.49, 21.6, 36.2, 44.2, 54.4, 61.7, 69.3, 116.0, 118.4, 119.9, 124.0, 124.6, 126.4, 129.6, 130.8, 133.8, 135.9, 137.4, 144.7; ESIMS (*m*/*z*) 419 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_3S$ 397.1580, found 397.1576; IR (neat) ν_{max} 3401, 1641 cm^{-1}.

(+)-(*R*)-12-Tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-one (12). To a stirred solution of alcohol (+)-**11** (300 mg, 0.76 mmol) in CH_2Cl_2 (15 mL) was added Dess–Martin periodinane (967 mg, 2.28 mmol) and $NaHCO_3$ (638 mg, 7.6 mmol) at 0 °C under argon atmosphere. After stirring for 1 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and quenched with mixture of aq. sodium thiosulphate (40%, 6 mL) and saturated aq. $NaHCO_3$ (6 mL). It was then extracted with CH_2Cl_2 (20 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent resulted the ketone (+)-**12** as yellow foam (215 mg, 72% yield; 98% *ee*). $[\alpha]^{25}_D$ +67.41 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.95–3.30 (m, 9H), 2.32 (s, 3H), 3.46 (dt, *J* = 12 and 4 Hz, 1H), 5.17 (s, 1H), 7.10–7.30 (m, 4H), 7.30–7.45 (m, 1H), 7.70–7.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 21.9, 27.9, 41.0, 46.4, 54.2, 66.4, 114.0, 117.9, 118.6, 123.1, 124.3, 127.0, 129.3, 129.7, 130.8, 135.8, 136.1, 144.6, 206.8; ESIMS (*m*/*z*) 417 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_3S$ 395.1424, found 395.1417; IR (neat) ν_{max} 1720 cm^{-1}.



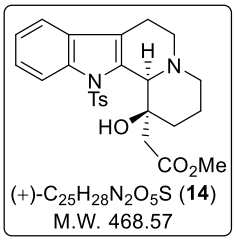
(+)-$C_{22}H_{22}N_2O_3S$ (**12**)
M.W. 394.49

(±)-Methyl 1-Hydroxy-4-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (13). To a solution of LDA in THF [prepared by the addition of BuLi (1.60 M in hexane, 4.60 mL, 7.35 mmol) to a solution of $Pr^{i}_{2}NH$ (1.24 mL, 8.82 mmol) in dry THF (6 mL) at 0 °C for 20 min] was added methyl acetate (0.64 mL, 8.08 mmol) at –78 °C under argon atmosphere. After stirring the reaction mixture for 1 h, a solution of (±)-**10** (1.00 g, 2.45 mmol) in dry THF (8 mL) was added to the reaction mixture at –78 °C. The reaction mixture was stirred for 1 h at –78 °C and quenched with saturated aq. NH_4Cl solution. THF was removed in vacuo and the residue was dissolved in ethyl acetate (50 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent yielded (±)-**13** as a white solid (0.91 g, 83% yield). Mp 181–183 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.00–2.45 (m, 4H), 2.45–2.95 (m, 5H), 2.28 (s, 3H), 3.39 (s, 3H), 4.31 (s, 1H), 4.80–5.00 (m, 1H), 5.48 (s, 1H), 7.06 (d, J = 8 Hz, 2H), 7.15–7.45 (m, 5H), 8.16 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 21.5, 29.7, 33.9, 37.7, 38.7, 51.6, 61.0, 74.2, 117.3, 118.6, 124.8, 125.8, 126.5, 127.5, 129.3, 129.8, 131.0, 132.6, 138.8, 145.0, 171.07, 171.13; ESIMS (m/z) 505 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{26}N_2O_6SNa$ 505.1404, found 505.1404; IR (neat) ν_{max} 3385, 1727, 1641 cm^{-1}.



(±)-$C_{25}H_{26}N_2O_6S$ (**13**)
M.W. 482.5510

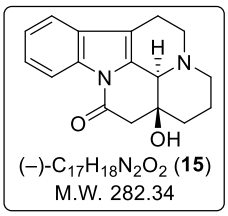
(+)-Methyl 2-((1*S*,12b*R*)-1-Hydroxy-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (14). To a stirred solution of LDA in THF [prepared by the addition of *n*-BuLi (1.60 M in hexane, 0.96 mL, 1.53 mmol) to a solution of $Pr^{i}_{2}NH$ (0.24 mL, 1.68 mmol) in dry THF (2 mL) at 0 °C for 20 min] was added a solution of methyl acetate (0.13 mL, 1.68 mmol) in dry THF (0.50 mL) at –78 °C under argon atmosphere. The reaction mixture was stirred for 1 h and to it was added a solution of (+)-**12** (200 mg, 0.51 mmol) in dry THF (4 mL) at –78 °C. The reaction mixture was further stirred for 1 h at –78 °C, quenched with saturated aqueous NH_4Cl solution (5 mL) and THF was removed in vacuo. To the obtained residue was added ethyl acetate (30 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–



(+)-$C_{25}H_{28}N_2O_5S$ (**14**)
M.W. 468.57

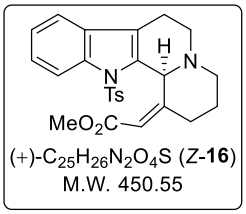
petroleum ether (8:2) as an eluent yielded (+)-**14** as a white solid (183 mg, 77% yield). Mp 178–180 °C; $[\alpha]^{25}_{D}$ +96.41 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (dd, *J* = 12 and 4 Hz, 1H), 1.77 (dt, *J* = 12 and 4 Hz, 1H), 2.05–2.20 (m, 2H), 2.23 (s, 3H), 2.50–2.60 (m, 1H), 2.65–2.80 (m, 2H), 2.97 (d, *J* = 16 Hz, 1H), 3.04 (dt, *J* = 12 and 4 Hz, 1H), 3.15 (dd, *J* = 8 and 4 Hz, 1H), 3.20 (d, *J* = 16 Hz, 1H), 3.58–3.70 (m, 1H), 3.67 (s, 3H), 4.27 (br s, 1H), 4.37 (s, 1H), 7.01 (d, *J* = 8 Hz, 2H), 7.15–7.30 (m, 3H), 7.32 (d, *J* = 8 Hz, 2H), 8.06 (d, *J* = 8 Hz, 1H); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 19.5, 21.6, 22.7, 38.1, 44.8, 47.4, 51.8, 56.2, 65.1, 73.7, 118.2, 119.6, 125.86, 125.90, 127.5, 128.0, 130.3, 133.3, 133.6, 135.4, 139.7, 146.1, 173.5; ESIMS (*m*/*z*) 491 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_5S$ 469.1792, found 469.1785; IR (neat) ν_{max} 3405, 1724 cm^{-1}.

(–)-(41*R*,13a*S*)-13a-Hydroxy-2,3,5,6,13,13a-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(41*H*)-one (15). To stirred solution of *N*-tosyl protected *β*-hydroxy ester (+)-**14** (20 mg, 0.04 mmol) in MeOH:benzene (1:1; 2 mL) were sequentially added activated magnesium turnings (10 mg, 0.40 mmol) and NH_4Cl (21 mg, 0.40 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 4 h and quenched with saturated aq. NH_4Cl (2 mL). Solvent was removed in vacuo and the residue was extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded the cyclized compound (–)-**15** (10 mg, 87% yield) as a white solid. Mp 164–166 °C; $[\alpha]^{25}_{D}$ –115.6 (*c* 0.42 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (dt, *J* = 8 and 4 Hz, 1H), 1.71 (d, *J* = 12 Hz, 1H), 1.85 (d, *J* = 12 Hz, 1H), 2.00 (q, *J* = 12 Hz, 1H), 2.36 (t, *J* = 8 Hz, 1H), 2.55–2.75 (m, 3H), 2.75–3.20 (m, 6H), 7.20–7.35 (m, 2H), 7.41 (d, *J* = 8 Hz, 1H), 8.36 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.09, 21.14, 34.4, 44.7, 51.6, 54.2, 63.0, 69.4, 114.2, 116.4, 118.1, 123.8, 124.4, 129.7, 131.8, 135.5, 166.5; ESIMS (*m*/*z*) 305 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ 283.1441, found 283.1435; IR (neat) ν_{max} 3331, 1705, 1646 cm^{-1}.



(–)-$C_{17}H_{18}N_2O_2$ (**15**)
M.W. 282.34

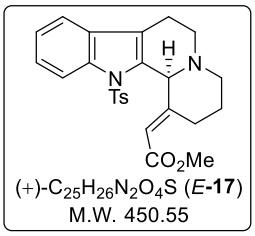
(+)-Methyl (*S*,*Z*)-2-(12-Tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (16). To a stirred solution of tertiary alcohol (+)-**14** (130 mg, 0.28 mmol) in dry benzene (6 mL) was added Burgess reagent (200 mg, 0.84 mmol) at 25 °C under argon atmosphere. The



(+)-$C_{25}H_{26}N_2O_4S$ (*Z*-**16**)
M.W. 450.55

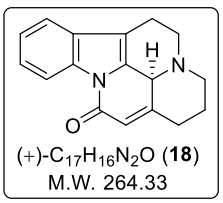
reaction mixture was refluxed for 12 h and then allowed to reach 25 ^{o}C. The reaction mixture was diluted with ethyl acetate (30 mL) and the organic layer was washed three times with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded minor isomer (+)-*E*-**17** as yellowish gum (13 mg, 10% yield) and by further elution with ethyl acetate–methanol (98:2) as an eluent afforded major isomer (+)-*Z*-**16** as a yellowish solid (104 mg, 52% yield). Major isomer (+)-*Z*-**16**: Mp 135–137 °C; $[\alpha]^{25}_{D}$ +60.8 (*c* 0.45 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (d, *J* = 16 Hz, 1H), 2.28 (s, 3H), 2.45–2.58 (m, 1H), 2.68 (dd, *J* = 16 and 8 Hz, 1H), 2.75–2.95 (m, 2H), 3.09 (s, 3H), 3.17 (d, *J* = 16 Hz, 1H), 3.25–3.45 (m, 2H), 3.52 (dt, *J* = 12 and 8 Hz, 1H), 3.59 (d, *J* = 16 Hz, 1H), 5.45 (s, 1H), 5.75 (s, 1H), 7.12 (d, *J* = 8 Hz, 2H), 7.18–7.35 (m, 3H), 7.52 (d, *J* = 8 Hz, 2H), 8.14 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 21.4, 21.5, 40.7, 40.9, 50.7, 51.1, 56.6, 115.7, 118.5, 120.7, 124.0, 124.6, 125.1, 126.4, 129.7, 130.4, 130.6, 134.0, 134.3, 137.1, 144.6, 172.1; ESIMS (*m*/*z*) 451 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_4S$ 451.1686, found 451.1682; IR (neat) ν_{max} 1735, 1597 cm^{-1}.

(+)-Methyl (*S*,*E*)-2-(12-Tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (17). Minor isomer (+)-*E*-**17**: $[\alpha]^{25}_{D}$ +27.65 (*c* 0.80 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.80 (d, *J* = 10 Hz, 1H), 1.95–2.10 (m, 1H), 2.27 (dt, *J* = 15 and 5 Hz, 1H), 2.31 (s, 3H), 2.69 (dd, *J* = 15 and 5 Hz, 1H), 2.75–2.87 (m, 2H), 3.47 (dt, *J* = 15 and 5 Hz, 1H), 3.61 (s, 3H), 3.05–3.20 (m, 2H), 4.09 (d, *J* = 15 Hz, 1H), 5.11 (s, 1H), 5.21 (s, 1H), 7.16 (d, *J* = 10 Hz, 2H), 7.25 (t, *J* = 10 Hz, 1H), 7.31 (t, *J* = 10 Hz, 1H), 7.39 (d, *J* = 10 Hz, 1H), 7.63 (d, *J* = 10 Hz, 2H), 8.09 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 21.9, 26.1, 29.7, 43.5, 50.9, 55.2, 62.3, 114.8, 116.6, 118.7, 119.0, 123.5, 124.7, 126.5, 129.6, 129.8, 132.4, 135.5, 136.5, 144.7, 158.9, 166.5; ESIMS (*m*/*z*) 473 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_4S$ 451.1686, found 451.1681; IR (neat) ν_{max} 1714, 1650, 1599 cm^{-1}.



(+)-$C_{25}H_{26}N_2O_4S$ (*E*-**17**)
M.W. 450.55

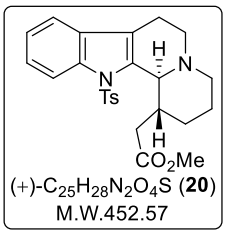
(+)-(*S*)-2,3,5,6-Tetrahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(41*H*)-one (18). To a stirred solution of conjugated ester (+)-*Z*-**16** (20 mg, 0.04 mmol) in MeOH:benzene (1:1; 2 mL) were sequentially added activated magnesium turnings (11 mg, 0.44 mmol) and NH_4Cl

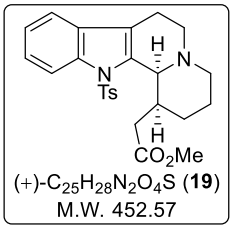


(+)-$C_{17}H_{16}N_2O$ (**18**)
M.W. 264.33

(24 mg, 0.44 mmol) at 25 ^{o}C under argon atmosphere. The reaction mixture was stirred for 2 h and quenched with saturated aq. NH_4Cl (5 mL). Solvent was removed in vacuo and the residue was extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate:petroleum ether (8:2) as an eluent afforded the cyclized compound (+)-**18** (10 mg, 82% yield) as brownish gummy solid. $[\alpha]^{25}_{D}$ +45.4 (*c* 0.6 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05–2.50 (m, 2H), 2.50–2.77 (m, 2H), 2.77–3.10 (m, 3H), 3.10–3.60 (m, 3H), 4.03 (br s, 1H), 5.62 (q, *J* = 2 Hz, 1H), 7.15–7.45 (m, 3H), 8.20–8.35 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 21.1 (2 C), 26.9, 49.0, 52.5, 57.0, 113.5, 117.1, 119.6, 122.8, 125.4, 125.6, 129.7, 131.6, 134.2, 136.5, 168.5; ESIMS (*m*/*z*) 265 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ 265.1335, found 265.1335; IR (neat) ν_{max} 1704, 1643, 1602 cm^{-1}.

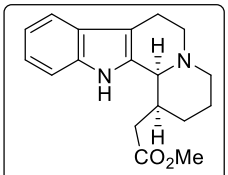
(+)-Methyl 2-((1*R*,12b*S*)-12-Tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (20). To a stirred solution of conjugated ester (+)-*Z*-**16** (50 mg, 0.11 mmol) in THF and ethanol (4 mL, 1:1) mixture at 25 ^{o}C was added a catalytic amount of PtO_2 (5 mg, 0.02 mmol). The resulting mixture was hydrogenated at ballon pressure for 48 h, filtered through a pad of Celite by washing with ethyl acetate (20 mL). Concentration of filtrate in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (4:6) as an eluent afforded minor *cis*-isomer (+)-**19** as colourless gum (14 mg, 27% yield) and by further elution with DCM–methanol (98:2) as an eluent afforded major *trans*-isomer (+)-**20** as colourless gum (36 mg, 69% yield). Major *trans*-isomer (+)-**20**: $[\alpha]^{25}_{D}$ +60.2 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38–1.55 (m, 2H), 1.95 (d, *J* = 12 Hz, 2H), 2.25 (s, 3H), 2.42 (dq, *J* = 12 and 4 Hz, 1H), 2.58 (dd, *J* = 16 and 8 Hz, 1H), 2.65–2.80 (m, 2H), 2.83–2.90 (m, 1H), 2.92 (dd, *J* = 16 and 4 Hz, 1H), 3.15–3.35 (m, 2H), 3.50–3.60 (m, 1H), 3.59 (s, 3H), 4.54 (d, *J* = 8 Hz, 1H), 7.06 (d, *J* = 8 Hz, 2H), 7.17–7.30 (m, 3H), 7.43 (d, *J* = 8 Hz, 2H), 8.07 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 21.3, 21.5, 32.0, 34.0, 38.5, 42.3, 51.4, 55.0, 59.6, 116.4, 118.5, 120.7, 124.3, 124.5, 126.6, 129.4, 131.4, 133.5, 137.5, 144.4, 173.9; ESIMS (*m*/*z*) 475 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_4S$ 453.1843, found 453.1834; IR (neat) ν_{max} 1729 cm^{-1}.



(+)-Methyl 2-((1*S*,12b*S*)-12-Tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (19). 

(+)-$C_{25}H_{28}N_2O_4S$ (**19**)
M.W. 452.57

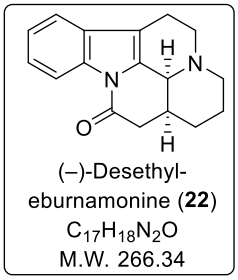
Minor *cis*-isomer (+)-**19**: $[\alpha]^{25}_D$ +31.6 (*c* 0.90 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55 (d, *J* = 8 Hz, 1H), 1.75–2.00 (m, 4H), 2.26 (s, 3H), 2.40 (d, *J* = 16 Hz, 1H), 2.46–2.65 (m, 3H), 2.76 (dt, *J* = 12 and 2 Hz, 1H), 2.90 (dd, *J* = 12 and 2 Hz, 1H), 3.01 (d, *J* = 12 Hz, 1H), 3.32 (br s, 1H), 3.52 (s, 3H), 3.83 (s, 1H), 7.04 (d, *J* = 8 Hz, 2H), 7.15–7.30 (m, 3H), 7.45 (d, *J* = 8 Hz, 2H), 8.06 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 21.5, 22.9, 28.6, 32.5, 35.6, 51.2, 51.4, 56.7, 64.9, 116.9, 118.3, 124.4, 124.6, 125.3, 126.8, 129.0, 131.2, 133.2, 136.4, 138.8, 144.3, 174.0; ESIMS (*m*/*z*) 475 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_4S$ 453.1843, found 453.1837; IR (neat) ν_{max} 1720 cm^{-1}.

(–)-Methyl 2-((1*S*,12b*S*)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (21). 

(–)-$C_{18}H_{22}N_2O_2$ (**21**)
M.W. 298.39

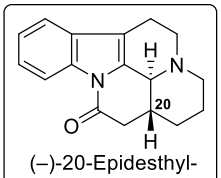
To stirred solution of *N*-tosyl protected *cis*-ester (+)-**19** (12 mg, 0.02 mmol) in MeOH:benzene (1:1; 2 mL) were sequentially added activated magnesium turnings (7 mg, 0.30 mmol) and NH_4Cl (21 mg, 0.40 mmol) at 25 ^oC under argon atmosphere. The reaction mixture was stirred for 2 h and quenched with saturated aq. NH_4Cl (5 mL). Solvent was removed in vacuo and the residue was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded the pure compound (–)-**21** (6.50 mg, 83% yield) as colourless gummy solid. $[\alpha]^{25}_D$ –13.8 (*c* 0.50 $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.61 (d, *J* = 15 Hz, 1H), 1.67–1.78 (m, 1H), 1.78–1.92 (m, 2H), 2.23 (dd, *J* = 15 and 15 Hz, 1H), 2.37 (t, *J* = 10 Hz, 1H), 2.47–2.60 (m, 2H), 2.65–2.77 (m, 2H), 2.87–3.05 (m, 3H), 3.45 (s, 1H), 3.56 (s, 3H), 7.09 (t, *J* = 10 Hz, 1H), 7.15 (t, *J* = 10 Hz, 1H), 7.34 (d, *J* = 10 Hz, 1H), 7.48 (d, *J* = 10 Hz, 1H), 8.04 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 21.5, 28.6, 32.6, 33.2, 51.6, 53.6, 56.4, 63.7, 110.3, 111.0, 118.0, 119.3, 121.4, 127.3, 133.3, 136.3, 175.1; ESIMS (*m*/*z*) 299 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{23}N_2O_2$ 299.1754, found 299.1760; IR (neat) ν_{max} 1718 cm^{-1}.

(–)-(41*S*,13a*S*)-2,3,5,6,13,13a-Hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(41*H*)-one (Desethyleburnamonine, 22). To a stirred solution of compound (–)-**21** (6 mg, 0.02 mmol) in methanol (2 mL) was added anhydrous K_2CO_3. The reaction mixture was refluxed for 10 h under argon atmosphere and quenched with saturated aq. NH_4Cl (2 mL). MeOH was removed in vacuo and the residue was extracted with CH_2Cl_2 (5 mL × 2). Concentration of CH_2Cl_2 in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (98:2) as an eluent afforded (–)-desethyleburnamonine (**22**) as a white solid (4 mg, 77% yield). Mp 150–152 °C (lit.[11b] mp 153–154 °C); $[\alpha]^{25}_D$ –75.2 (*c* 0.20 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60–1.70 (m, 4H), 2.42–2.52 (m, 2H), 2.53–2.58 (m, 1H), 2.68 (d, *J* = 5 Hz, 1H), 2.71 (d, *J* = 5 Hz, 1H), 2.89–2.98 (m, 1H), 3.00 (dd, *J* = 15 and 5 Hz, 1H), 3.35–3.38 (m, 1H), 3.39 (d, *J* = 5 Hz, 1H), 4.40–4.45 (m, 1H), 7.30 (dt, *J* = 10 and 5 Hz, 1H), 7.34 (dt, *J* = 10 and 5 Hz, 1H), 7.46 (dd, *J* = 10 and 5 Hz, 1H), 8.39 (dd, *J* = 10 and 5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.4, 24.6, 25.3, 34.3, 39.7, 44.5, 50.4, 53.4, 112.8, 116.3, 118.1, 123.9, 124.5, 129.8, 131.2, 134.5, 167.3; ESIMS (*m*/*z*) 267 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1492; IR (neat) ν_{max} 1725 cm^{-1}.



(–)-Desethyl-eburnamonine (**22**)
$C_{17}H_{18}N_2O$
M.W. 266.34

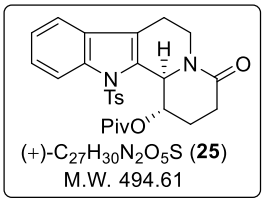
(–)-(41*S*,13a*R*)-2,3,5,6,13,13a-Hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(41*H*)-one (20-Epidesethyleburnamonine, 23). To stirred solution of *N*-tosyl protected *trans*-ester (+)-**20** (20 mg, 0.04 mmol) in MeOH:benzene (1:1; 2 mL) were sequentially added activated magnesium turnings (9.60 mg, 0.40 mmol) and NH_4Cl (21.40 mg, 0.40 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 2 h and quenched with saturated aq. NH_4Cl (4 mL). Solvent was removed in vacuo and the residue was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded the (–)-20-epidesethyleburnamonine (–)-**23** (8.60 mg, 73% yield) as a white solid. Mp 138–140 °C (lit.[11a] mp 136–139 °C); $[\alpha]^{25}_D$ –92.9 (*c* 0.28 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.35 (m, 1H), 1.81–1.97 (m, 3H), 1.97–2.10 (m, 1H), 2.33–2.43 (m, 1H), 2.52 (dd, *J* = 16 and 12 Hz, 1H), 2.65 (dt, *J* = 12 and 4 Hz, 1H), 2.69–2.81 (m, 2H),



(–)-20-Epidesethyl-eburnamonine (**23**)
$C_{17}H_{18}N_2O$
M.W. 266.34

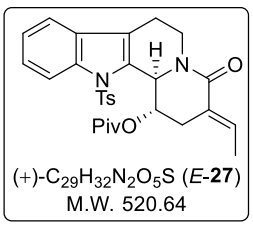
2.86 (d, *J* = 12 Hz, 1H), 2.90–3.02 (m, 1H), 3.08 (td, *J* = 8 and 4 Hz, 1H), 3.17 (dd, *J* = 12 and 4 Hz, 1H), 7.20–7.35 (m, 2H), 7.42 (d, *J* = 8 Hz, 1H), 8.34 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 25.4, 30.0, 37.9, 39.6, 52.2, 54.6, 62.0, 111.8, 116.2, 118.2, 123.9, 124.2, 129.9, 134.1, 135.2, 167.7; ESIMS (*m*/*z*) 267 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1486; IR (neat) ν_{max} 1727 cm^{-1}.

(+)-(1*S*,12b*R*)-4-Oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl Pivalate (25). To a stirred solution of hydroxyl compound **(+)-9** (1.42 g, 3.46 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (4.81 mL, 34.60 mmol), pivaloyl chloride (4.26 mL, 34.60 mmol) and DMAP (428 mg, 3.46 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and further stirred for 24 h. The reaction was quenched with saturated aq. $NaHCO_3$ solution (15 mL) at 0 °C and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (6:4) as an eluent afforded pure pivaloyl ester (+)-**25** as white foam (1.45 g, 85% yield). $[\alpha]^{25}_D$ +75.70 (*c* 1.07 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.31 (s, 9H), 1.69 (ddt, *J* = 12, 5 and 5 Hz, 1H), 2.08–2.15 (m, 1H), 2.27 (s, 3H), 2.35–2.42 (m, 1H), 2.48 (d, *J* = 15 Hz, 1H), 2.59 (ddd, *J* = 18, 15 and 5 Hz, 1H), 2.67 (dt, *J* = 10 and 5 Hz, 1H), 2.73–2.82 (m, 1H), 5.06 (dd, *J* = 15 and 5 Hz, 1H), 5.21 (br s, 1H), 5.91 (br s, 1H), 7.05 (d, *J* = 10 Hz, 2H), 7.20–7.27 (m, 2H), 7.33 (dd, *J* = 10 and 5 Hz, 1H), 7.36 (d, *J* = 10 Hz, 2H), 8.10 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 22.0, 23.2, 27.2, 27.3, 38.8, 41.0, 60.9, 71.1, 117.1, 118.7, 124.9, 125.7, 126.6, 127.4, 129.2, 130.9, 132.5, 133.1, 138.8, 144.9, 170.2, 177.0; ESIMS (*m*/*z*) 495 $[M+H]^+$; HRMS (ESI) calcd for $C_{27}H_{31}N_2O_5S$ 495.1948, found 495.1942; IR ($CHCl_3$) ν_{max} 1728, 1642 cm^{-1}.



(+)-$C_{27}H_{30}N_2O_5S$ (**25**)
M.W. 494.61

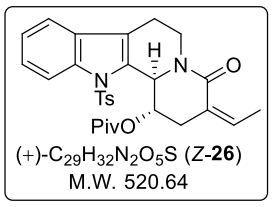
(+)-(1*S*,12b*R*,*E*)-3-Ethylidene-4-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl Pivalate (27). To a stirred solution of compound (+)-**25** (1.40 g, 2.69 mmol) in dry THF (15 mL) was added NaHMDS (1 M in THF, 5.38 mL, 5.38 mmol) dropwise at –78 °C under argon atmosphere. After stirring for 45 min at same temperature, DMPU (0.65 mL, 5.38 mmol) and solution of acetaldehyde (1.51 mL, 26.90 mmol) in dry THF (3 mL) were added to the reaction mixture. The reaction mixture was stirred at –78 °C for 2 h



(+)-$C_{29}H_{32}N_2O_5S$ (*E*-**27**)
M.W. 520.64

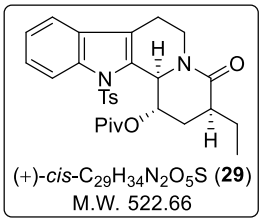
and quenched with saturated aq. NH_4Cl (5 mL). THF was removed in vacuo and the obtained residue was extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent provided the crude secondary alcohol (1.30 g, 2.42 mmol) as a diastereomeric mixture. To a stirred solution of the crude alcohol in dry toluene (20 mL) were sequentially added CuCl (1.91 g, 19.36 mmol) and DCC (2.00 g, 9.68 mmol) at 25 ^oC under argon atmosphere. The stirred reaction mixture was heated at 100 ^oC for 12 h and allowed to reach 25 ^oC. It was filtered through a pad of Celite, washed with ethyl acetate (20 mL) and concentrated in vacuo. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using petroleum ether–ethyl acetate (7:3) as an eluent to afford first the minor isomer *Z*-(+)-**26** as yellowish foam (388 mg, 26% yield) and then the major isomer *E*-(+)-**27** as yellowish foam (766 mg, 53% yield). Major isomer *E*-(+)-**27**: $[\alpha]^{25}_D$ +8.60 (*c* 0.58 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (s, 9H), 1.77 (d, *J* = 8 Hz, 3H), 2.27 (s, 3H), 2.52 (d, *J* = 16 Hz, 1H), 2.60 (d, *J* = 12 Hz, 1H), 2.65–2.80 (m, 2H), 2.89 (dd, *J* = 16 and 8 Hz, 1H), 4.95–5.10 (m, 1H), 5.25–5.40 (m, 1H), 5.40–5.50 (m, 1H), 6.95–7.10 (m, 3H), 7.20–7.45 (m, 5H), 8.14 (d, *J* = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 21.5, 22.0, 27.1, 28.1, 38.8, 40.4, 58.1, 71.9, 116.9, 118.8, 124.8, 125.6, 126.5, 126.8, 126.9, 129.3, 130.6, 132.4, 132.8, 136.5, 138.7, 144.9, 165.9, 177.6; ESIMS (*m*/*z*) 521 $[M+H]^+$; HRMS (ESI) calcd for $C_{29}H_{33}N_2O_5S$ 521.2105, found 521.2104; IR ($CHCl_3$) ν_{max} 1725, 1660, 1615 cm^{-1}.

(+)-(1*S*,12b*R*,*Z*)-3-Ethylidene-4-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl Pivalate (26). Minor isomer *Z*-(+)-**26**: $[\alpha]^{25}_D$ +4.40 (*c* 0.52 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (s, 9H), 2.11 (dd, *J* = 8 and 4 Hz, 3H), 2.27 (s, 3H), 2.38 (d, *J* = 16 Hz, 1H), 2.51 (d, *J* = 16 Hz, 1H), 2.65 (dd, *J* = 16 and 4 Hz, 1H), 2.68–2.82 (m, 2H), 5.05–5.15 (m, 1H), 5.17 (br s, 1H), 5.78–5.88 (m, 2H), 7.05 (d, *J* = 8 Hz, 2H), 7.20–7.35 (m, 3H), 7.37 (d, *J* = 8 Hz, 2H), 8.10 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 21.5, 22.1, 27.1, 33.8, 38.7, 40.4, 60.6, 71.7, 117.0, 118.7, 124.9, 125.5, 125.7, 126.6, 127.3, 129.2, 130.8, 132.6, 132.9, 137.8, 138.8, 144.9, 165.5, 177.1; ESIMS (*m*/*z*) 521 $[M+H]^+$; HRMS (ESI) calcd for $C_{29}H_{33}N_2O_5S$ 521.2105, found 521.2098; IR ($CHCl_3$) ν_{max} 1725, 1665, 1626 cm^{-1}.



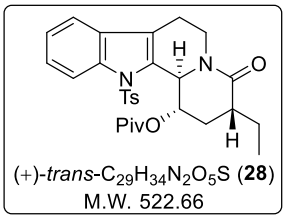
(+)-$C_{29}H_{32}N_2O_5S$ (*Z*-**26**)
M.W. 520.64

(+)-(1*S*,3*S*,12b*R*)-3-Ethyl-4-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl Pivalate (29). To a stirred solution of conjugated lactam *E*-(+)-**27** (500 mg, 1.15 mmol) in acetonitrile (40 mL) was added a palladium on activated charcoal (112 mg, 10 wt%) at 25 °C. The resulting mixture was hydrogenated at ballon pressure hydrogen atmosphere for 4 h, filtered through a pad of Celite by washing with ethyl acetate (40 mL). Concentration of filtrate in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:1) as an eluent afforded major *cis*-isomer (+)-**29** as white foam (334 mg, 66.5% yield) and by further elution using petroleum ether–ethyl acetate (6.5:3.5) as an eluent afforded minor *trans*-isomer (+)-**28** as white foam (143 mg, 28.5% yield). Major *cis*-isomer (+)-**29**: $[\alpha]^{25}_{D}$ +57.60 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 10 Hz, 3H), 1.30 (s, 9H), 1.41–1.51 (m, 1H), 1.56 (dt, *J* = 15 and 5 Hz, 1H), 1.92–2.20 (m, 1H), 2.13 (td, *J* = 15 and 5 Hz, 1H), 2.27 (s, 3H), 2.47–2.55 (m, 2H), 2.62–2.75 (m, 2H), 5.02 (dd, *J* = 15 and 5 Hz, 1H), 5.29 (s, 1H), 5.69 (q, *J* = 5 Hz, 1H), 7.05 (d, *J* = 10 Hz, 2H), 7.21–7.29 (m, 2H), 7.33 (dt, *J* = 15 and 5 Hz, 1H), 7.36 (d, *J* = 10 Hz, 2H), 8.11 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.3, 21.5, 22.0, 22.8, 27.1, 29.0, 37.2, 38.8, 40.7, 59.5, 71.8, 117.0, 118.7, 124.8, 125.6, 126.6, 127.0, 129.2, 130.7, 132.7, 133.3, 138.7, 144.9, 172.8, 177.2; ESIMS (*m*/*z*) 523 $[M+H]^+$; HRMS (ESI) calcd for $C_{29}H_{35}N_2O_5S$ 523.2261, found 523.2250; IR ($CHCl_3$) ν_{max} 1727, 1641 cm^{-1}.



(+)-*cis*-$C_{29}H_{34}N_2O_5S$ (**29**)
M.W. 522.66

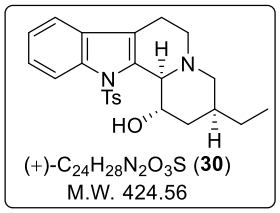
(+)-(1*S*,3*R*,12b*R*)-3-Ethyl-4-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl Pivalate (28). To a stirred solution of conjugated lactam *Z*-(+)-**26** (300 mg, 0.58 mmol) in petroleum ether:ethyl acetate (1:1) (30 mL) was added a palladium on activated charcoal (62 mg, 10 wt%) at 25 °C. The resulting mixture was hydrogenated at ballon pressure hydrogen atmosphere for 12 h, filtered through a pad of Celite by washing with ethyl acetate (25 mL). Concentration of filtrate in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (3:1) as an eluent afforded minor *cis*-isomer (+)-**29** as white foam (30 mg, 10% yield) and by further elution using petroleum ether–ethyl acetate (6.5:3.5) as an eluent afforded major *trans*-isomer (+)-**28** as white foam (271 mg, 90% yield). Major *trans*-isomer (+)-**28**: $[\alpha]^{25}_{D}$ +27.50 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, *J* = 8 Hz, 3H), 1.30 (s, 9H), 1.70–1.85 (m, 1H), 1.94–2.08



(+)-*trans*-$C_{29}H_{34}N_2O_5S$ (**28**)
M.W. 522.66

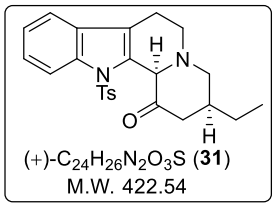
(m, 2H), 2.08–2.17 (m, 1H), 2.27 (s, 3H), 2.49–2.62 (m, 3H), 2.65–2.75 (m, 1H), 5.00–5.08 (m, 1H), 5.13–5.20 (m, 1H), 5.42 (d, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 2H), 7.20–7.36 (m, 5H), 8.12 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.6, 21.5, 21.9, 26.5, 27.1, 29.5, 38.8, 40.3, 41.6, 58.4, 72.8, 117.1, 118.7, 124.9, 125.6, 126.5, 127.2, 129.1, 130.7, 132.6, 133.0, 138.9, 144.8, 172.4, 177.8; ESIMS (m/z) 523 $[M+H]^+$; HRMS (ESI) calcd for $C_{29}H_{35}N_2O_5S$ 523.2261, found 523.2259; IR ($CHCl_3$) ν_{max} 1724, 1635 cm^{-1}.

(+)-(1*S*,3*S*,12b*R*)-3-Ethyl-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-ol (30). A flame dried round-bottomed flask was charged with $AlCl_3$ (152 mg, 1.14 mmol) and THF (3 mL) under argon atmosphere. The stirred reaction mixture was cooled to 0 ^oC and a suspension of $LiAlH_4$ (130 mg, 3.42 mmol) in THF (3 mL) was added dropwise. After stirring for 15 min at 0 ^oC, solution of lactam (+)-**29** (300 mg, 0.57 mmol) in THF (4 mL) was added dropwise to the above reaction mixture. Then it was stirred for 6 h at 25 ^oC and quenched by the addition of saturated aq. Na_2SO_4 (2 mL). The reaction mixture was filtered through Celite and the solid residue was washed with ethyl acetate (30 mL). The filtrate was dried over Na_2SO_4 and concentrated in vacuo. The silica gel (230–400 mesh) column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (96:4) as an eluent afforded the amino alcohol (+)-**30** as yellowish semi-solid (200 mg, 82% yield). $[\alpha]^{25}_D$ +116.4 (c 3.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 10 Hz, 3H), 1.18–1.33 (m, 2H), 1.83 (td, J = 15 and 5 Hz, 1H), 1.95 (br s, 1H), 2.24 (s, 3H), 2.32–2.42 (m, 2H), 2.81 (dd, J = 10 and 5 Hz, 1H), 2.83–2.92 (m, 1H), 3.01 (dt, J = 10 and 5 Hz, 1H), 3.26 (dd, J = 10 and 5 Hz, 1H), 3.60–3.85 (br s, 2H), 4.45 (s, 1H), 4.76 (s, 1H), 7.01 (d, J = 10 Hz, 2H), 7.15–7.30 (m, 3H), 7.36 (d, J = 10 Hz, 2H), 8.07 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.6, 19.2, 21.5, 27.0, 32.5, 35.3, 49.5, 53.6, 63.3, 68.5, 117.4, 118.4, 124.0, 124.7, 124.9, 126.8, 128.9, 131.8, 131.9, 135.0, 138.9, 144.6; ESIMS (m/z) 425 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_3S$ 425.1893, found 425.1886; IR ($CHCl_3$) ν_{max} 3416, 1601 cm^{-1}.



(+)-$C_{24}H_{28}N_2O_3S$ (**30**)
M.W. 424.56

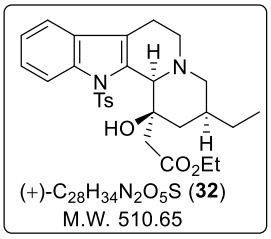
(–)-(3*S*,12b*R*)-3-Ethyl-12-tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-one (31). To a stirred solution of alcohol (+)-**30** (150 mg, 0.35 mmol) in CH_2Cl_2 (8 mL) was added tetrapropylammonium perruthenate (39 mg, 0.11 mmol) followed by NMO (82 mg, 0.70 mmol) and 4 Å molecular sieves (50 mg) at 25 ^oC under argon



(+)-$C_{24}H_{26}N_2O_3S$ (**31**)
M.W. 422.54

atmosphere. After stirring for 3.5 h at the same temperature, the reaction mixture was filtered through a pad of Celite by washing with CH_2Cl_2 (20 mL). Concentration of filtrate in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (7:3) as an eluent afforded the keto-amine (–)-**31** as yellowish gum (113 mg, 76% yield). $[\alpha]^{25}_{D}$ –32.6 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, *J* = 8 Hz, 3H), 1.45–1.65 (m, 2H), 2.25–2.45 (m, 2H), 2.34 (s, 3H), 2.63–2.73 (m, 1H), 2.78–3.10 (m, 5H), 3.29 (dd, *J* = 12 and 4 Hz, 1H), 4.86 (s, 1H), 7.15–7.30 (m, 4H), 7.38 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.77 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.2, 21.6, 22.1, 26.1, 40.3, 45.1, 50.4, 58.6, 67.3, 114.2, 118.6, 119.0, 123.1, 124.3, 127.0, 129.4, 129.6, 130.6, 135.8, 136.5, 144.5, 203.8; ESIMS (*m*/*z*) 423 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_3S$ 423.1737, found 423.1731; IR ($CHCl_3$) ν_{max} 1724 cm^{-1}.

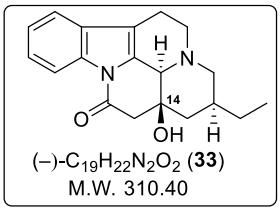
(+)-Ethyl 2-((1*S*,3*S*,12b*R*)-3-Ethyl-1-hydroxy-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (32). To a stirred solution of LDA in THF [prepared by the addition of *n*-BuLi (1.60 M in hexane, 0.65 mL, 1.04 mmol) to a solution of Pr^i_2NH (0.18 mL, 1.25 mmol) in dry THF (2 mL) at 0 ^{o}C for 20 min] was added a solution of ethyl acetate (0.11 mL, 1.14 mmol) in dry THF (0.50 mL) at –78 ^{o}C under argon atmosphere. After the reaction mixture was stirred for 1 h, a solution of keto-amine (–)-**31** (110 mg, 0.26 mmol) in dry THF (4 mL) was added at –78 ^{o}C. The reaction mixture was further stirred for 4.5 h at –78 ^{o}C, quenched with saturated aqueous NH_4Cl solution (5 mL) and THF was removed in vacuo. To the reaction mixture was added ethyl acetate (50 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent yielded *β*-hydroxy ester (+)-**32** as yellowish gum (85 mg, 64% yield). $[\alpha]^{25}_{D}$ +21.42 (*c* 0.90 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, *J* = 10 Hz, 3H), 1.28 (t, *J* = 10 Hz, 3H), 1.66 (q, *J* = 10 Hz, 2H), 1.97 (dd, *J* = 15 and 5 Hz, 1H), 2.16 (d, *J* = 20 Hz, 1H), 2.25 (s, 3H), 2.47 (d, *J* = 15 Hz, 2H), 2.70–2.82 (m, 2H), 2.98 (d, *J* = 10 Hz, 1H), 3.04 (d, *J* = 15 Hz, 1H), 3.12 (d, *J* = 15 Hz, 1H), 3.13–3.20 (m, 1H), 3.27 (br s, 1H), 4.07–4.20 (m, 2H), 4.32 (s, 1H), 7.01 (d, *J* = 10 Hz, 2H), 7.17–7.22 (m, 2H), 7.25–7.30 (m, 1H), 7.33 (d, *J* = 10 Hz, 2H), 8.08 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0, 14.2, 21.5, 22.6, 28.2, 35.0, 40.1, 43.8, 50.0,



(+)-$C_{28}H_{34}N_2O_5S$ (**32**)
M.W. 510.65

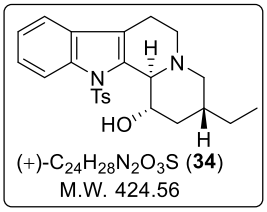
59.1, 60.4, 66.5, 73.6, 117.6, 118.4, 124.8, 124.9, 127.0, 128.1, 128.8, 131.9, 133.46, 133.47, 139.0, 144.5, 172.3; ESIMS (*m*/*z*) 511 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{35}N_2O_5S$ 511.2261, found 511.2264; IR ($CHCl_3$) ν_{max} 3425, 1735 cm^{-1}.

(–)-(2*S*,41*R*,13a*S*)-2-Ethyl-13a-hydroxy-2,3,5,6,13,13a-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(41*H*)-one (14-Epihydroxytacamonine, 33). To stirred solution of *N*-tosyl protected *β*-hydroxy ester (+)-**32** (20 mg, 0.04 mmol) in MeOH:benzene (1:1; 2 mL) were sequentially added activated magnesium turnings (10 mg, 0.40 mmol) and NH_4Cl (21 mg, 0.40 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 4 h and quenched with saturated aq. NH_4Cl (5 mL). Solvent was removed in vacuo and the residue was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (98:2) as an eluent afforded the (–)-14-epihydroxytacamonine (**33**) as semi-solid (11 mg, 92% yield). $[\alpha]^{25}_D$ –102.06 (*c* 0.40 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 0.98 (t, *J* = 10 Hz, 3H), 1.63–1.81 (m, 4H), 1.96 (d, *J* = 15 Hz, 1H), 2.55–2.61 (m, 2H), 2.65 (dd, *J* = 15 and 5 Hz, 1H), 2.71–2.78 (m, 2H), 2.87–3.00 (m, 3H), 3.12–3.17 (m, 2H), 7.25–7.35 (m, 2H), 7.42 (d, *J* = 10 Hz, 1H), 8.35 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 13.5, 21.1, 27.8, 35.6, 37.8, 45.3, 52.0, 58.2, 64.0, 70.6, 114.3, 116.4, 118.1, 123.8, 124.5, 129.7, 131.9, 135.6, 166.6; ESIMS (*m*/*z*) 311 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_2$ 311.1754, found 311.1754; IR ($CHCl_3$) ν_{max} 3416, 1707 cm^{-1}.



(–)-$C_{19}H_{22}N_2O_2$ (**33**)
M.W. 310.40

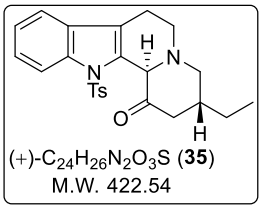
(+)-(1*S*,3*R*,12b*R*)-3-Ethyl-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-ol (34). A flame dried round-bottomed flask was charged with $AlCl_3$ (133 mg, 1.00 mmol) and THF (3 mL) under argon atmosphere. The stirred reaction mixture was cooled to 0 °C and a suspension of $LiAlH_4$ (114 mg, 3.00 mmol) in THF (3 mL) was added dropwise. After stirring for 15 min at 0 °C, a solution of lactam (+)-**28** (260 mg, 0.50 mmol) in THF (3 mL) was added dropwise to the above reaction mixture. Then it was stirred for 6 h at 25 °C and quenched by the addition of saturated aq. Na_2SO_4 (2 mL). The reaction mixture was filtered through Celite and the solid residue was washed with ethyl acetate (20 mL). The filtrate was dried over Na_2SO_4 and concentrated in vacuo. The silica



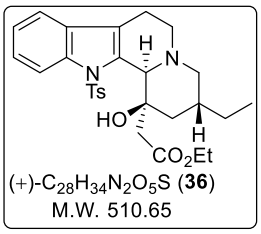
(+)-$C_{24}H_{28}N_2O_3S$ (**34**)
M.W. 424.56

gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent afforded the amino alcohol (+)-**34** as a white crystalline solid (150 mg, 71% yield). Mp 138–140 °C; $[\alpha]^{25}_{D}$ +213.49 (*c* 0.62 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, *J* = 8 Hz, 3H), 1.15–1.40 (m, 3H), 1.83–1.97 (m, 1H), 2.25 (s, 3H), 2.36 (d, *J* = 12 Hz, 1H), 2.70–2.82 (m, 3H), 2.91 (d, *J* = 8 Hz, 1H), 3.16 (d, *J* = 12 Hz, 1H), 3.20–3.38 (m, 2H), 3.70–3.80 (m, 1H), 4.35 (d, *J* = 8 Hz, 1H), 7.11 (d, *J* = 8 Hz, 2H), 7.15–7.29 (m, 2H), 7.32 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 2H), 8.06 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.3, 21.4, 21.5, 26.5, 33.3, 42.5, 44.2, 60.0, 60.9, 69.4, 115.9, 118.5, 119.4, 124.0, 124.6, 126.6, 129.6, 130.5, 133.7, 135.3, 137.3, 144.7; ESIMS (*m*/*z*) 425 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_3S$ 425.1893, found 425.1891; IR ($CHCl_3$) ν_{max} 3417, 1631 cm^{-1}.

(+)-(3*R*,12b*R*)-3-Ethyl-12-tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-one (35). To a stirred solution of alcohol (+)-**34** (140 mg, 0.33 mmol) in CH_2Cl_2 (6 mL) was added tetrapropylammonium perruthenate (47 mg, 0.13 mmol) followed by NMO (116 mg, 0.99 mmol) and 4 Å molecular sieves (50 mg) at 25 °C under argon atmosphere. After stirring for 4 h at the same temperature, the reaction mixture was filtered through a pad of Celite by washing with CH_2Cl_2 (20 mL). Concentration of solvents in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (7:3) as an eluent afforded the keto-amine (+)-**35** as yellowish gum (118 mg, 85% yield). $[\alpha]^{25}_{D}$ +56.35 (*c* 0.52 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, *J* = 10 Hz, 3H), 1.41 (sextet, *J* = 5 Hz, 1H), 1.48 (sextet, *J* = 5 Hz, 1H), 2.34 (s, 3H), 2.36–2.47 (m, 2H), 2.65 (td, *J* = 10 and 5 Hz, 1H), 2.72–2.82 (m, 2H), 2.87–2.93 (m, 1H), 3.00–3.06 (m, 1H), 3.12 (dd, *J* = 15 and 10 Hz, 1H), 3.24 (dd, *J* = 15 and 5 Hz, 1H), 5.12 (s, 1H), 7.15–7.25 (m, 4H), 7.39 (d, *J* = 10 Hz, 1H), 7.76 (d, *J* = 10 Hz, 2H), 7.79 (dd, *J* = 10 and 5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.1, 21.5, 22.1, 27.0, 41.7, 46.7, 46.9, 60.2, 65.9, 114.0, 117.9, 118.6, 123.1, 124.3, 127.0, 129.3, 129.7, 130.8, 135.9, 136.1, 144.6, 206.5; ESIMS (*m*/*z*) 423 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_3S$ 423.1737, found 423.1736; IR ($CHCl_3$) ν_{max} 1725 cm^{-1}.

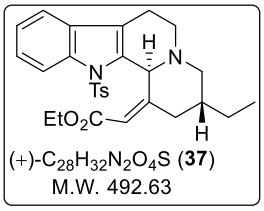


(+)-Ethyl 2-((1*S*,3*R*,12b*R*)-3-Ethyl-1-hydroxy-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (36). To a stirred solution of LDA in THF [prepared by the addition of *n*-BuLi (1.60 M in hexane, 0.60 mL, 0.96 mmol) to a solution of $Pr^{i}_{2}NH$ (0.16 mL, 1.15 mmol) in dry THF (2 mL) at 0 °C for 20 min] was added a solution of ethyl acetate (0.10 mL, 1.06 mmol) in dry THF (0.50 mL) at –78 °C under argon atmosphere. After the reaction mixture was stirred for 1 h, a solution of keto-amine (–)-**31** (100 mg, 0.24 mmol) in dry THF (4 mL) was added at –78 °C. The reaction mixture was further stirred for 2 h at –78 °C, quenched with saturated aqueous NH_4Cl solution (5 mL) and THF was removed in vacuo. To the reaction mixture was added ethyl acetate (25 mL) and the separated organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent yielded (+)-**36** as yellowish gum (108 mg, 89% yield). $[\alpha]^{25}_{D}$ +45.67 (*c* 0.70 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, *J* = 10 Hz, 3H), 1.29 (t, *J* = 10 Hz, 3H), 1.24–1.34 (m, 2H), 1.38 (t, *J* = 10 Hz, 1H), 2.06–2.16 (m, 1H), 2.18–2.23 (m, 1H), 2.24 (s, 3H), 2.56–2.64 (m, 1H), 2.69 (t, *J* = 10 Hz, 1H), 2.73–2.82 (m, 2H), 2.94 (d, *J* = 15 Hz, 1H), 3.19 (d, *J* = 15 Hz, 1H), 3.16–3.22 (m, 1H), 3.70–3.77 (m, 1H), 4.07–4.21 (m, 2H), 4.22–4.35 (br s, 1H), 4.36 (s, 1H), 7.02 (d, *J* = 10 Hz, 2H), 7.15–7.30 (m, 3H), 7.34 (d, *J* = 10 Hz, 2H), 8.07 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.3, 14.1, 21.5, 21.9, 26.7, 30.0, 43.4, 43.6, 47.1, 60.6, 60.9, 63.8, 73.1, 117.2, 118.5, 124.6, 124.8, 126.3, 126.8, 129.0, 131.9, 132.3, 133.4, 138.6, 144.4, 172.9; ESIMS (*m*/*z*) 511 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{35}N_2O_5S$ 511.2261, found 511.2261; IR ($CHCl_3$) ν_{max} 3427, 1733 cm^{-1}.



(+)-$C_{28}H_{34}N_2O_5S$ (**36**)
M.W. 510.65

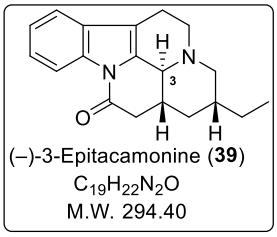
(+)-Ethyl (*Z*)-2-((3*R*,12b*S*)-3-Ethyl-12-tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (37). To a stirred solution of tertiary alcohol (+)-**36** (60 mg, 0.12 mmol) in dry benzene (10 mL) was added Burgess reagent (114 mg, 0.48 mmol) at 25 °C under argon atmosphere. The reaction mixture was refluxed for 24 h and then allowed to reach 25 °C. The reaction mixture was diluted with ethyl acetate (25 mL) and washed three times with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent



(+)-$C_{28}H_{32}N_2O_4S$ (**37**)
M.W. 492.63

afforded conjugated ester (*Z*)-(+)-**37** as colourless gum (32 mg, 55% yield). $[\alpha]^{25}_{D}$ +7.34 (*c* 0.80 $CHCl_3$); ^{1}H NMR (CD_3COCD_3, 400 MHz) δ 0.80 (t, *J* = 8 Hz, 3H), 1.00 (t, *J* = 8 Hz, 3H), 1.35–1.50 (m, 2H), 2.28 (s, 3H), 2.42 (br s, 1H), 2.55–2.75 (m, 2H), 2.85–2.95 (m, 1H), 3.04 (d, *J* = 16 Hz, 1H), 3.11 (d, *J* = 16 Hz, 1H), 3.25–3.40 (m, 3H), 3.45–3.55 (m, 1H), 3.58 (d, *J* = 16 Hz, 1H), 5.36 (s, 1H), 5.69 (s, 1H), 7.21 (d, *J* = 8 Hz, 2H), 7.22 (t, *J* = 8 Hz, 1H), 7.30 (t, *J* = 8 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 8.12 (d, *J* = 8 Hz, 1H); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 11.5, 14.2, 21.4, 22.3, 27.4, 32.6, 41.3, 43.3, 57.9, 58.3, 60.5, 116.7, 119.5, 122.1, 125.2, 125.4, 127.5, 130.4, 130.7, 131.49, 131.52, 131.9, 135.2, 138.2, 146.1, 171.5; ESIMS (*m*/*z*) 493 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{33}N_2O_4S$ 493.2156, found 493.2154; IR ($CHCl_3$) ν_{max} 1734, 1598 cm^{-1}.

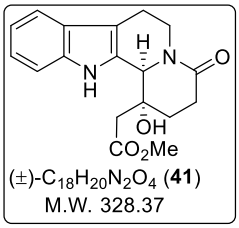
(–)-(2*R*,41*S*,13a*R*)-2-Ethyl-2,3,5,6,13,13a-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12(41*H*)-one (3-Epitacamonine, 39). To a stirred solution of conjugated ester (*Z*)-(+)-**37** (20 mg, 0.04 mmol) in MeOH:benzene (1:1; 2 mL) were sequentially added activated magnesium turnings (14 mg, 0.60 mmol) and NH_4Cl (32 mg, 0.60 mmol) at 25 ^oC under argon atmosphere. The reaction mixture was stirred for 2 h and quenched with saturated aq. NH_4Cl (4 mL). Solvent was removed in vacuo and the residue was extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo to provide crude amino-lactam **38** (12 mg). To a stirred solution of **38** in THF and ethanol (1:1, 2 mL) mixture was added PtO_2 (5.00 mg, 0.02 mmol) at 25 ^oC. The resulting mixture was hydrogenated at ballon pressure for 1 h, filtered through a pad of Celite by washing with ethyl acetate (20 mL). Concentration of filtrate in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using petroleum ether: ethyl acetate (4:6) as an eluent afforded (–)-3-epitacamonine (**39)** (9 mg, 74% yield) as a white solid. Mp 170–172 °C (lit.[16] mp 174 ^oC); $[\alpha]^{25}_{D}$ –79.40 (*c* 0.15 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (dt, *J* = 10 and 5 Hz, 2H), 0.96 (t, *J* = 10 Hz, 3H), 1.26–1.40 (m, 2H), 1.81 (br s, 1H), 2.00 (td, *J* = 10 and 5 Hz, 1H), 2.05 (t, *J* = 10 Hz, 2H), 2.53 (dd, *J* = 20 and 10 Hz, 1H), 2.65 (dt, *J* = 10 and 5 Hz, 1H), 2.69–2.76 (m, 1H), 2.79 (dd, *J* = 20 and 5 Hz, 1H), 2.92–3.02 (m, 1H), 3.12 (dd, *J* = 10 and 2 Hz, 1H), 3.20 (dd, *J* = 10 and 5 Hz, 1H), 7.27–7.33 (m, 2H), 7.43 (dd, *J* = 10 and 2 Hz, 1H), 8.36 (dd, *J* = 10 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.4, 21.4, 27.1, 36.4, 37.7, 38.0, 39.6,



(–)-3-Epitacamonine (**39**)
$C_{19}H_{22}N_2O$
M.W. 294.40

52.2, 60.4, 61.9, 111.8, 116.1, 118.3, 123.9, 124.2, 129.9, 133.8, 135.2, 167.8; ESIMS (*m*/*z*) 295 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 1705 cm^{-1}.

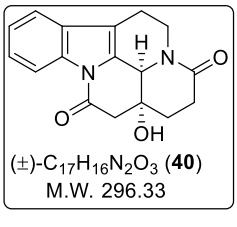
(±)-Methyl 1-Hydroxy-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (41). To stirred solution of *N*-tosyl protected *β*-hydroxy ester (±)-**13** (400 mg, 0.83 mmol) in MeOH:benzene mixture (14 mL,1:1) were sequentially added activated magnesium turnings (199 mg, 8.30 mmol) and NH_4Cl (444 mg, 8.30 mmol) at 25 ^oC under argon atmosphere. The reaction mixture was stirred for 2 h and the reaction was quenched with saturated aq. NH_4Cl (4 mL) and 1 N HCl (4 mL). Solvent was removed in vacuo and the residue was dissolved in ethyl acetate (40 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded the major uncyclized compound (±)-**41** (215 mg, 79.2% yield) as a white solid and then the minor cyclized compound (±)-**40** (22 mg, 8.8% yield) as colourless gummy solid.



(±)-$C_{18}H_{20}N_2O_4$ (**41**)
M.W. 328.37

Major product (±)-**41**: Mp 202–204 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.10–2.20 (m, 3H), 2.40–2.55 (m, 1H), 2.54 (d, *J* = 20 Hz, 1H), 2.64–2.89 (m, 4H), 3.66 (s, 3H), 4.71 (s, 1H), 4.82 (br s, 1H), 5.07–5.13 (m, 1H), 7.12 (dt, *J* = 8 and 2 Hz, 1H), 7.20 (dt, *J* = 8 and 2 Hz, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 8.90 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 29.9, 31.9, 35.2, 40.1, 52.2, 61.2, 72.4, 111.2, 111.3, 118.3, 119.5, 122.3, 126.1, 129.5, 136.1, 168.3, 173.5; ESIMS (*m*/*z*) 351 $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{20}N_2O_4Na$ 351.1315, found 351.1310; IR (neat) ν_{max} 3376, 1732, 1603 cm^{-1}.

(±)-13a-Hydroxy-1,2,5,6,13,13a-hexahydro-3*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-3,12(4^1*H*)-dione (Minor Product 40): Colourless gummy solid; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.50 (dt, *J* = 16 and 4 Hz, 1H), 1.72 (dd, *J* = 12 and 4 Hz, 1H), 2.07 (dd, *J* = 16 and 4 Hz, 1H), 2.55–2.83 (m, 4H), 2.76 (d, *J* = 16 Hz, 1H), 3.04 (dt, *J* = 12 and 8 Hz, 1H), 4.71 (dd, *J* = 12 and 8 Hz, 1H), 4.78 (br s, 1H), 5.88 (s, 1H), 7.31 (quintet, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 1H), 8.20 (d, *J* = 8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.8, 28.2, 29.4, 41.2, 46.5, 59.9, 68.2, 114.2, 115.4, 118.7, 124.1, 124.7, 129.7, 133.2, 133.5, 165.9, 168.6; ESIMS (*m*/*z*) 297 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_3$ 297.1234, found 297.1231; IR ($CHCl_3$) ν_{max} 3446, 1719, 1634 cm^{-1}.



(±)-$C_{17}H_{16}N_2O_3$ (**40**)
M.W. 296.33

(±)-Methyl 5-Oxido-1-oxo-2,3,10,11-tetrahydro-1*H*-4-oxa-5-thia-5a,11a-diazabenzo[cd]fluoranthen-3a(3a1*H*)-yl)acetate (42). To a stirred solution of (±)-**41** (150 mg, 0.46 mmol) in pyridine (6 mL) was added thionyl chloride (0.20 mL, 2.76 mmol) at 0 °C. Ice bath was removed and the reaction mixture was stirred at 25 °C for 30 min. The reaction mixture was then poured into a mixture of ethyl acetate (10 mL) and crushed ice. The residue was extracted with ethyl acetate (15 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent afforded the cyclic sulfuramidite (±)-**42** (152 mg, 89% yield) as a yellowish white solid. Mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06 (d, J = 16 Hz, 1H), 2.35 (q, J = 8 Hz, 1H), 2.60–2.95 (m, 6H), 3.03 (dt, J = 12 and 4 Hz, 1H), 3.69 (s, 3H), 4.89 (dd, J = 12 and 4 Hz, 1H), 5.14 (s, 1H), 7.30–7.45 (m, 2H), 7.57 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 29.8, 30.6, 34.3, 37.8, 52.4, 56.3, 84.4, 112.6, 115.0, 119.5, 123.7, 124.7, 128.6, 129.0, 137.8, 168.1, 168.4; ESIMS (m/z) 397 $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_5SNa$ 397.0829, found 397.0826; IR (neat) ν_{max} 1731, 1649 cm^{-1}.

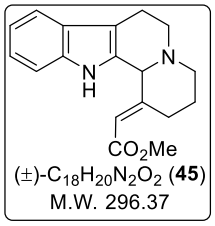
(±)-$C_{18}H_{18}N_2O_5S$ (**42**)
M.W. 374.41

(±)-Methyl (*E*)-2-(4-Oxo-3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (43). To a stirred solution of compound (±)-**42** (50 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) was added DBU (0.03 mL, 0.20 mmol) at –60 °C under argon atmosphere. The reaction mixture was stirred at same temperature for 1 h. The reaction was quenched with saturated aq. NH_4Cl (2 mL) and the reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (1:1) as an eluent yielded conjugated ester (±)-**43** as a brownish yellow solid (30 mg, 73% yield). Mp 171–173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (dt, J = 12 and 4 Hz, 1H), 2.46 (dt, J = 16 and 4 Hz, 1H), 2.60–2.70 (m, 1H), 2.75 (d, J = 12 Hz, 1H), 2.90–3.06 (m, 2H), 3.80 (s, 3H), 3.80–3.85 (m, 1H), 5.03 (q, J = 8 Hz, 1H), 5.31 (s, 1H), 6.14 (s, 1H), 7.13 (t, J = 8 Hz, 1H), 7.19 (t, J = 8 Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 23.0, 32.4, 41.4, 51.7, 61.1, 110.9, 111.2, 117.1, 118.5, 120.0, 122.6, 127.4, 129.4, 135.8, 153.1, 165.8, 168.9; ESIMS (m/z)

(±)-$C_{18}H_{18}N_2O_3$ (**43**)
M.W. 310.35

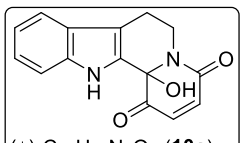
311 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3$ 311.1390, found 311.1386; IR (neat) ν_{max} 3272, 1709, 1625 cm^{-1}.

(±)-Methyl (*E*)-2-(3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (45). To a stirred solution of compound (±)-**43** (10 mg, 0.03 mmol) in dry toluene was added Lawesson's reagent (12 mg, 0.03 mmol) at 25 °C under argon atmosphere. The reaction mixture was refluxed for 1 h, cooled to 25 °C. Toluene was removed in vacuo and the obtained residue was quickly purified by silica gel (230–400 mesh) column chromatography by using petroleum:ethyl acetate (6:4) to provide the thiolactam (±)-**44** (8 mg, 0.02 mmol) which was immediately used for the next step. A solution of (±)-**44** in dry THF (1 mL) was added dropwise to a stirred solution of freshly prepared Raney nickel (100 mg) suspension in dry THF (2 mL) at 25 °C. The reaction mixture was vigorously stirred for stirred for 6 h at 25 °C under 1 atmosphere hydrogen pressure, filtered through a pad of Celite by washing with ethyl acetate (15 mL). Concentration of filtrate under vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent yielded conjugated ester (±)-**45** (5 mg, 55% yield) as a brownish yellow gum. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.75–1.95 (m, 2H), 2.70–2.82 (m, 2H), 2.90 (br s, 1H), 2.95–3.12 (m, 4H), 3.25–3.35 (m, 1H), 3.73 (s, 3H), 4.62 (s, 1H), 5.89 (s, 1H), 7.13 (t, J = 10 Hz, 1H), 7.19 (t, J = 10 Hz, 1H), 7.34 (d, J = 10 Hz, 1H), 7.52 (d, J = 10 Hz, 1H), 7.81 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.7, 25.4, 26.6, 49.9, 50.4, 51.3, 63.0, 108.8, 111.1, 116.9, 118.4, 119.7, 122.1, 127.1, 135.9, 166.6; ESIMS (*m*/*z*) 297 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ 297.1598, found 297.1589; IR ($CHCl_3$) ν_{max} 3275, 1706, 1645 cm^{-1}.



(±)-$C_{18}H_{20}N_2O_2$ (**45**)
M.W. 296.37

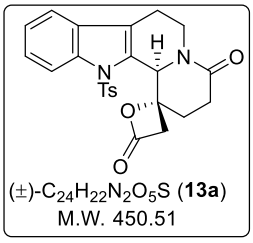
(±)-12b-Hydroxy-6,7,12,12b-tetrahydroindolo[2,3-*a*]quinolizine-1,4-dione (10a). To a stirred solution of ketone (±)-**10** (50 mg, 0.12 mmol) in THF (2 mL) at 25 °C was added dropwise tetrabutylammonium fluoride (1.0 M in THF, 0.18 mL, 0.18 mmol) and the reaction mixture was stirred for 3 h. The reaction was quenched with saturated aq. NH_4Cl (2 mL) and solvent was removed in vacuo. The residue was dissolved in ethyl acetate (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using petroleum ether–ethyl acetate (6:4) as an eluent afforded the oxidized compound (±)-**10a** (19 mg, 58% yield) as a yellow solid. Mp 175–177 °C; ^1H NMR



(±)-$C_{15}H_{12}N_2O_3$ (**10a**)
M.W. 268.27

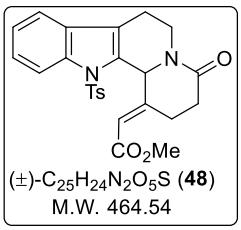
(DMSO-d_6, 400 MHz) δ 2.05–2.18 (m, 1H), 2.40–2.55 (m, 1H), 2.58–2.72 (m, 1H), 3.03–3.20 (m, 1H), 6.70 (d, J = 12 Hz, 1H), 6.82 (d, J = 12 Hz, 1H), 6.88 (s, 1H, D_2O exchangeable), 7.16 (t, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 11.96 (s, 1H, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.7, 28.1, 90.0, 104.5, 112.5, 119.4, 119.9, 120.3, 120.8, 125.2, 126.6, 130.2, 137.6, 174.6, 180.8; ESIMS (*m*/*z*) 269 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_3$ 269.0921, found 269.0915; IR (neat) ν_{max} 3284, 1724, 1676 cm^{-1}.

(±)-12-Tosyl-2,3,6,7,12,12b-hexahydro-4*H*-spiro[indolo[2,3-*a*]quinolizine-1,2'-oxetane]-4,4'-dione (13a). To a stirred solution of (±)-**13** (20 mg, 0.04 mmol) in dry toluene (3 mL) was added anhydrous *p*-TSA (8 mg, 0.05 mmol) at 25 ^{o}C and the reaction mixture was refluxed for 4.5 h. Toluene was removed in vacuo and the residue was dissolved in ethyl acetate (15 mL). The organic layer was washed with saturated aq. $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent afforded the spirolactone (±)-**13a** (16 mg, 85% yield) as gummy solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.27 (s, 3H), 2.30–2.80 (m, 6H), 2.84 (d, J = 16 Hz, 1H), 2.95–3.20 (m, 1H), 3.35–3.55 (m, 1H), 4.45–4.65 (m, 1H), 5.59 (s, 1H), 7.05 (d, J = 8 Hz, 2H), 7.15–7.45 (m, 5H), 8.08 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 22.5, 28.1, 28.8, 37.2, 45.7, 63.7, 89.1, 117.3, 119.1, 125.4, 126.1, 126.8, 128.6, 129.2, 129.3, 130.9, 131.3, 138.7, 145.3, 170.1, 175.2; ESIMS (*m*/*z*) 473 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{22}N_2O_5SNa$ 473.1142, found 473.1145; IR (neat) ν_{max} 1783, 1698 cm^{-1}.



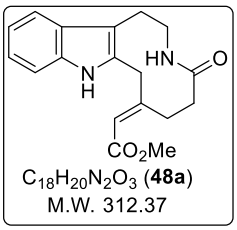
(±)-$C_{24}H_{22}N_2O_5S$ (**13a**)
M.W. 450.51

(±)-Methyl (*E*)-2-(4-Oxo-12-tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (48). To a stirred solution of (±)-**13** (600 mg, 1.24 mmol) in pyridine (8 mL) was added thionyl chloride (0.45 mL, 6.22 mmol) at 0 ^{o}C. Ice bath was removed and the reaction mixture was stirred at 25 ^{o}C for 3 h. The reaction mixture was then poured into mixture of ethyl acetate (15 mL) and crushed ice. The aqueous layer was extracted with ethyl acetate (25 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent afforded the conjugated ester (±)-4**8** (468 mg,



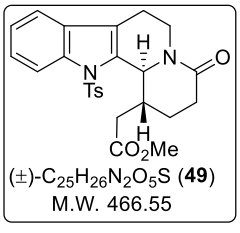
(±)-$C_{25}H_{24}N_2O_5S$ (**48**)
M.W. 464.54

81% yield) as a yellowish white solid. Mp 150–152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (s, 3H), 2.55–3.00 (m, 5H), 3.14 (dd, J = 20 and 8 Hz, 1H), 3.30–3.45 (m, 1H), 3.61 (s, 3H), 4.60–4.70 (m, 1H), 5.22 (s, 1H), 5.94 (s, 1H), 7.18 (d, J = 8 Hz, 2H), 7.32 (t, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 2H), 8.19 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 21.6, 25.7, 31.3, 38.5, 51.1, 56.0, 114.6, 115.3, 118.9, 122.9, 124.2, 125.7, 126.3, 128.7, 129.1, 129.9, 134.6, 136.9, 145.3, 156.8, 166.5, 172.3; ESIMS (m/z) 487 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_5SNa$ 487.1298, found 487.1299; IR (neat) ν_{max} 1791, 1713, 1652 cm^{-1}.



$C_{18}H_{20}N_2O_3$ (**48a**)
M.W. 312.37

(±)-Methyl (*E*)-2-(4-Oxo-1,2,3,4,5,6,8,9-octahydro-7*H*-azecino[5,4-*b*]indol-7-ylidene)acetate (48a). To a stirred solution of naphthalene (108 mg, 0.85 mmol) in THF (4 mL) at 25 °C was carefully added a piece of metal sodium (12 mg, 0.52 mmol) under argon atmosphere. The reaction mixture was stirred for 30 min to form a greenish blue solution. THF solution (2 mL) of conjugated ester (±)-**48** (60 mg, 0.13 mmol) was dropwise added to the reaction mixrture at –78 °C. After 20 min, the reaction was quenched with saturated aq. NH_4Cl (2 mL). The reaction mixture was extracted with ethyl acetate (15 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded the macrolactam (±)-**48a** (23 mg, 56% yield) as gummy solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10–2.35 (m, 3H), 2.46 (br s, 1H), 2.83 (br s, 2H), 3.22 (br s, 2H), 3.42 (br s, 1H), 3.69 (d, J = 16 Hz, 1H), 3.77 (s, 3H), 5.53 (br s, 1H), 6.42 (s, 1H), 7.11 (t, J = 8 Hz, 1H), 7.18 (t, J = 8 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 8.04 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 30.4, 34.6, 38.9, 40.5, 52.2, 110.8, 110.9, 118.2, 119.4, 121.9, 123.5, 127.3, 132.1, 135.7, 141.9, 172.5, 172.9; ESIMS (m/z) 313 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3$ 313.1547, found 313.1547; IR (neat) ν_{max} 3301, 3262, 1722, 1649 cm^{-1}.

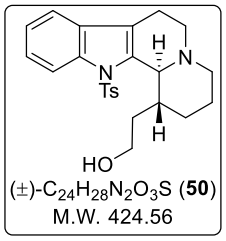


(±)-$C_{25}H_{26}N_2O_5S$ (**49**)
M.W. 466.55

(±)-Methyl 4-Oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (49). To a stirred solution of conjugated ester (±)-**48** (200 mg, 0.43 mmol) in ethanol and THF mixture (8 mL, 1:1) was added a catalytic amount of PtO_2 (10 mg, 0.04 mmol) at 25 °C. The resulting mixture was stirred under ballon pressure hydrogen atmosphere for 12

h and filtered through a pad of Celite by washing with ethyl acetate (40 mL). The reaction mixture was concentrated in vacuo to afford the hydrogenated compound (±)-**49** (197 mg, 98% yield) as gummy solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.73 (t, J = 4 Hz, 1H), 1.78 (t, J = 4 Hz, 1H), 2.27 (s, 3H), 2.30–2.80 (m, 6H), 2.96 (dd, J = 16 and 6 Hz, 1H), 3.11 (sextet, J = 6 Hz, 1H), 3.68 (s, 3H), 4.96 (dd, J = 12 and 4 Hz, 1H), 5.01–5.08 (m, 1H), 7.04 (d, J = 8 Hz, 2H), 7.20–7.35 (m, 3H), 7.34 (d, J = 8 Hz, 2H), 8.11 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 21.8, 22.9, 28.8, 36.3, 36.8, 41.4, 51.7, 59.8, 117.2, 118.6, 125.0, 125.5, 126.6, 127.4, 129.2, 131.1, 132.1, 135.4, 138.7, 145.0, 170.9, 172.4; ESIMS (m/z) 489 $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{26}N_2O_5SNa$ 489.1445, found 489.1444; IR ($CHCl_3$) ν_{max} 1734, 1642 cm^{-1}.

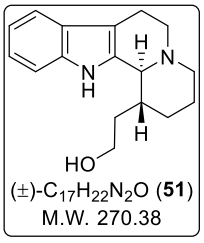
(±)-12-Tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)ethan-1-ol (50).



(±)-$C_{24}H_{28}N_2O_3S$ (**50**)
M.W. 424.56

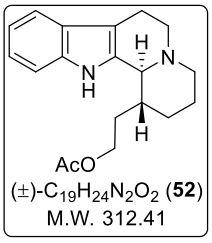
A flame dried round-bottomed flask was charged with $AlCl_3$ (28 mg, 0.21 mmol) and THF (2 mL) under argon atmosphere. The stirred reaction mixture was cooled to 0 ^{o}C and a suspension of $LiAlH_4$ (24 mg, 0.63 mmol) in THF (2 mL) was added dropwise. After stirring for 10 min at 0 ^{o}C, a solution of lactam-ester (±)-**49** (100 mg, 0.21 mmol) in THF (4 mL) was added dropwise to the above reaction mixture. It was stirred for 2 h at 25 ^{o}C and quenched by the addition of saturated aq. Na_2SO_4 (2 mL). The reaction mixture was filtered through Celite and the solid residue was washed with ethyl acetate (20 mL). The filtrate was dried over Na_2SO_4 and concentrated in vacuo. The silica gel column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (96:04) as an eluent afforded the alcohol (±)-**50** as gummy solid (76 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30–1.57 (m, 2H), 1.73–1.90 (m, 2H), 1.80–2.00 (m, 1H), 2.00–2.15 (m, 1H), 2.24 (s, 3H), 2.15–2.60 (m, 2H), 2.65–2.80 (m, 2H), 2.85–2.95 (br s, 1H), 3.00–3.22 (m, 2H), 3.45–3.55 (m, 1H), 3.55–3.68 (m, 1H), 3.73 (quintet, J = 8 Hz, 1H), 4.56 (d, J = 8 Hz, 1H), 7.06 (d, J = 8 Hz, 2H), 7.18 (t, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 2H), 8.04 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 20.5, 21.5, 29.8, 33.3, 35.8, 43.4, 53.4, 60.0, 60.4, 116.5, 118.4, 120.7, 124.2, 124.5, 126.7, 129.3, 131.3, 133.4, 137.6, 137.7, 144.4; ESIMS (m/z) 447 $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_3S$ 425.1893, found 425.1893; IR ($CHCl_3$) ν_{max} 3377, 1658, 1600 cm^{-1}.

(±)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-1-yl)ethan-1-ol (51). To stirred solution of *N*-tosyl protected amino alcohol (±)-**50** (75 mg, 0.18 mmol) in MeOH:benzene (4 mL, 1:1) were sequentially added activated magnesium turnings (200 mg, 8.30 mmol) and NH_4Cl (200 mg, 3.74 mmol) at 25 ^oC. The reaction mixture was stirred for 4 h and the reaction was quenched with saturated aq. NH_4Cl (5 mL) and 1 N HCl (2 mL). Solvent was removed in vacuo and the residue was extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (92:8) as an eluent afforded the *N*-tosyl deprotected amino alcohol (±)-**51** as a brownish white solid (46 mg, 97% yield). Mp 178–180 °C; ^1H NMR (CD_3OD, 400 MHz) δ 1.35–1.47 (m, 1H), 1.55–1.85 (m, 4H), 1.98–2.10 (m, 1H), 2.25 (br s, 1H), 2.75–3.10 (m, 5H), 3.40–3.50 (m, 1H), 3.63–3.78 (m, 2H), 3.88 (d, *J* = 8 Hz, 1H), 6.98 (t, *J* = 8 Hz, 1H), 7.06 (t, *J* = 8 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H), 7.40 (d, *J* = 8 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 20.76, 20.81, 21.7, 34.2, 36.2, 49.61, 49.64, 60.5, 61.9, 108.1, 112.0, 118.6, 119.8, 122.2, 128.3, 134.8, 137.8; ESIMS (*m*/*z*) 271 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{23}N_2O$ 271.1805, found 271.1797; IR (nujol) ν_{max} 3375, 3126 cm^{-1}.



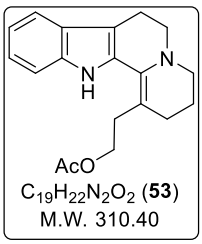
(±)-$C_{17}H_{22}N_2O$ (**51**)
M.W. 270.38

(±)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-1-yl)ethyl Acetate (52). To a stirred solution of (±)-**51** (40 mg, 0.15 mmol) in pyridine (2 mL) was added Ac_2O (0.30 mL, 3.18 mmol) at 25 ^oC. After stirring for 16 h, the reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with saturated aq. $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (94:6) as an eluent afforded the ester (±)-**52** as gummy solid (41.0 mg, 88% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.65–1.82 (m, 3H), 1.85–2.05 (m, 3H), 2.10 (s, 3H), 2.05–2.18 (m, 1H), 2.80–3.15 (m, 5H), 3.35–3.45 (m, 1H), 3.94–4.05 (m, 1H), 4.10–4.20 (m, 1H), 4.25–4.37 (m, 1H), 7.08 (t, *J* = 8 Hz, 1H), 7.17 (t, *J* = 8 Hz, 1H), 7.37–7.45 (m, 2H), 9.28 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 20.9, 21.0, 28.2, 31.1, 34.4, 49.2, 51.6, 60.0, 62.3, 107.8, 111.3, 118.0, 119.4, 121.9, 126.6, 131.5, 136.4, 171.8; ESIMS (*m*/*z*) 313$[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{25}N_2O_2$313.1911, found 313.1908; IR ($CHCl_3$) ν_{max} 3429, 1737 cm^{-1}.



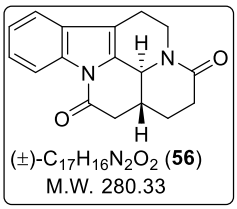
(±)-$C_{19}H_{24}N_2O_2$ (**52**)
M.W. 312.41

(±)-2-(2,3,4,6,7,12-Hexahydroindolo[2,3-*a*]quinolizin-1-yl)ethyl Acetate (53). To a stirred solution of acetate (±)-**52** (25 mg, 0.08 mmol) in ethanol (2 mL) were added a solution containing EDTA disodium salt dihydrate (70 mg, 0.24 mmol) and mercuric acetate (76 mg, 0.24 mmol) in water (3 mL) and the resulting solution was gently heated at 80 °C for 2 h. After cooling, CH_2Cl_2 was added to the reaction mixture and the two-phase mixture was basified to pH 11 with 5% aq. ammonia. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with saturated aq. $NaHCO_3$, brine and dried over Na_2SO_4. The filtration and concentration of organic layer in vacuo afforded the enamine (±)-**53** as brown gummy solid (22 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95–2.02 (m, 4H), 2.02–2.20 (m, 1H), 2.18 (s, 3H), 2.22–2.30 (m, 1H), 2.77 (dd, *J* = 8 and 8 Hz, 1H), 2.97 (t, *J* = 8 Hz, 2H), 3.03–3.15 (m, 3H), 4.24 (dd, *J* = 8 and 8 Hz, 2H), 7.10 (t, *J* = 8 Hz, 1H), 7.21 (t, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H), 10.13 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 21.8, 22.4, 30.0, 33.2, 52.0, 52.2, 63.5, 103.8, 111.5, 111.8, 118.1, 119.1, 122.3, 125.9, 129.3, 135.2, 137.4, 172.9; ESIMS (*m*/*z*) 311 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_2$ 311.1754, found 311.1750; IR ($CHCl_3$) ν_{max} 3361, 1728, 1634 cm^{-1}.



$C_{19}H_{22}N_2O_2$ (**53**)
M.W. 310.40

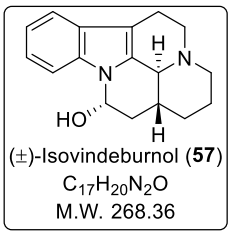
(±)-1,2,5,6,13,13a-Hexahydro-3*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-3,12(41*H*)-dione (56). Activated magnesium turnings (62.40 mg, 2.60 mmol) and NH_4Cl (65 mg, 1.22 mmol) were sequentially added to stirred solution of *N*-tosyl protected lactam (±)-**49** (60 mg, 0.13 mmol) in MeOH : benzene (1:1; 4 mL) at 25 °C. The reaction mixture was stirred for 2 h and quenched with saturated aq. NH_4Cl (1 mL) and 1 (N) HCl (1 mL). MeOH and benzene were removed in vacuo and the residue was extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl aceatate–petroleum ether (7:3) as an eluent afforded the pentacyclic compound (±)-**56** as a white solid (30 mg, 83%). Mp 172–174 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.77 (ddd, *J* = 25, 13 and 5 Hz, 1H), 2.03 (dd, *J* = 10 and 5 Hz, 1H), 2.21 (tq, *J* = 10 and 5 Hz, 1H), 2.55 (ddd, *J* = 20, 13 and 5 Hz, 1H), 2.65 (d, *J* = 20 Hz, 1H), 2.69 (dt, *J* = 15 and 5 Hz, 1H), 2.77–2.84 (m, 2H), 2.93 (dd, *J* = 20 and 5 Hz, 1H), 2.96–3.05 (m, 1H), 4.27 (d, *J* = 10 Hz, 1H), 5.09 (td, *J* = 10 and 5 Hz, 1H), 7.32 (dt, *J* = 10 and 5 Hz, 1H), 7.36 (dt, *J* = 10 and 5



(±)-$C_{17}H_{16}N_2O_2$ (**56**)
M.W. 280.33

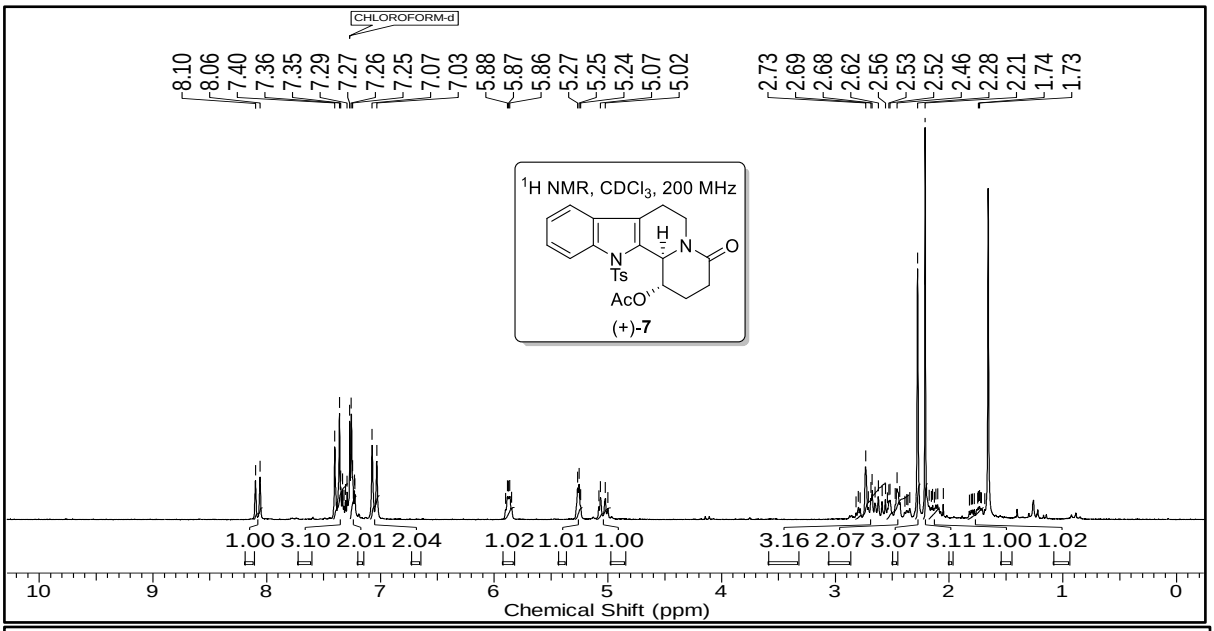
Hz, 1H), 7.46 (d, J = 10 Hz, 1H), 8.36 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.4, 25.9, 32.1, 37.2, 38.2, 38.9, 55.1, 112.6, 116.2, 118.6, 124.3, 125.0, 129.1, 132.1, 135.2, 166.7, 168.3; ESIMS (*m*/*z*) 281 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ 281.1285, found 281.1281; IR ($CHCl_3$) ν_{max} 1709, 1644 cm^{-1}.

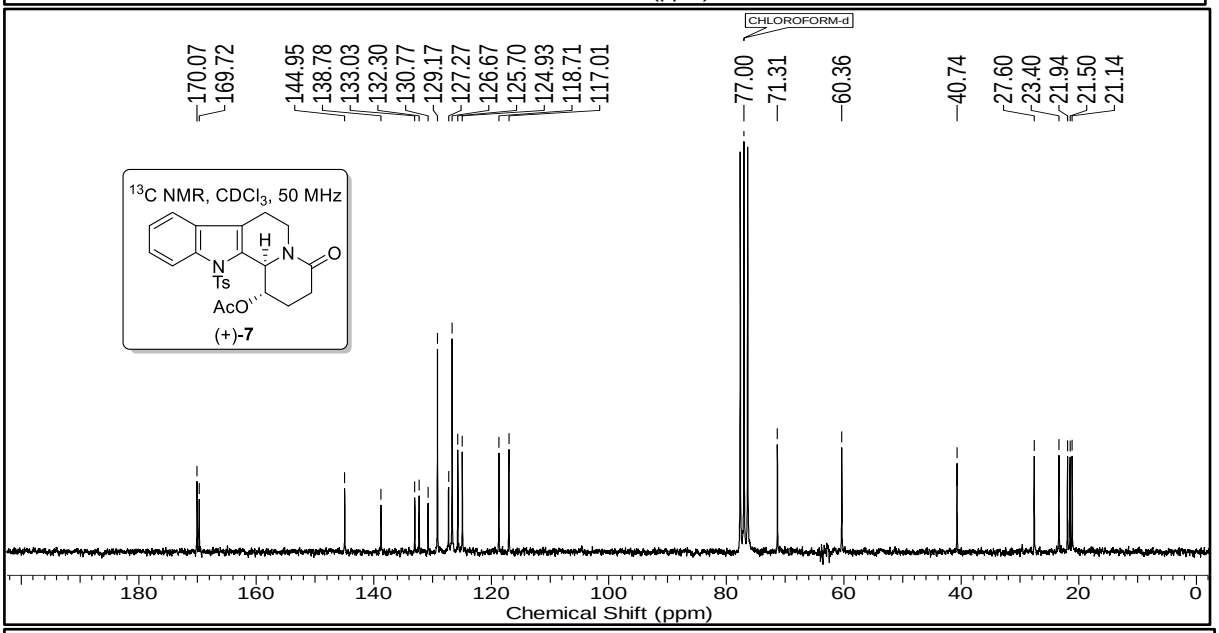
(±)-2,3,41,5,6,12,13,13a-Octahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12-ol (Isovindeburnol, 57). A flame dried round-bottomed flask was charged with $AlCl_3$ (12 mg, 0.09 mmol) and THF (1 mL) under argon atmosphere. The stirred reaction mixture was cooled to 0 °C and a suspension of $LiAlH_4$ (10 mg, 0.27 mmol) in THF (1 mL) was added dropwise. After stirring for 10 min at 0 °C, a solution of lactam (±)-**56** (25 mg, 0.09 mmol) in THF (2 mL) was added dropwise to the above reaction mixture. Then it was stirred for 2 h at 25 °C and quenched by the addition of saturated aq. Na_2SO_4 (2 mL). The reaction mixture was filtered through Celite and the solid residue was washed with ethyl aceatate (10 mL × 3). The filtrate was dried over Na_2SO_4 and concentrated in vacuo. The silica gel (230–400 mesh) column chromatographic purification of the resulting residue using CH_2Cl_2–methanol (96:04) as an eluent afforded the isovindeburnol (±)-**57** as a brownish solid (16 mg, 68%). Mp 246–248 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77–0.94 (m, 1H), 1.10–1.23 (m, 1H), 1.23–1.34 (m, 1H), 1.38–1.54 (m, 1H), 1.57–1.67 (m, 1H), 1.67–1.80 (m, 1H), 2.01–2.15 (m, 2H), 2.15–2.27 (m, 1H), 2.40–2.60 (m, 1H), 2.60–2.75 (m, 1H), 2.86–3.00 (m, 2H), 3.00–3.10 (m, 1H), 5.36 (t, J = 8 Hz, 1H), 7.00–7.25 (m, 2H), 7.43 (d, J = 8 Hz, 1H), 7.67 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 24.9, 29.5, 35.6, 39.5, 52.4, 54.5, 62.9, 79.0, 105.2, 112.3, 118.2, 120.1, 121.3, 128.6, 134.5, 138.0; ESIMS (*m*/*z*) 269 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{21}N_2O$269.1648, found 269.1645; IR ($CHCl_3$) ν_{max} 3345, 1720, 1645 cm^{-1}.

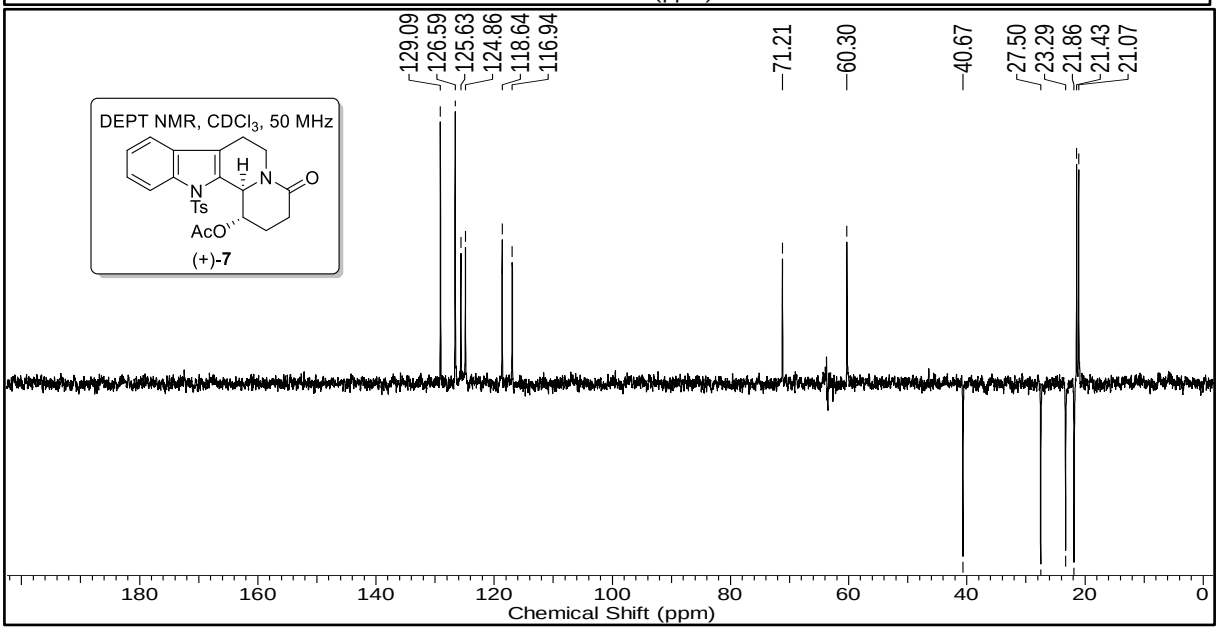


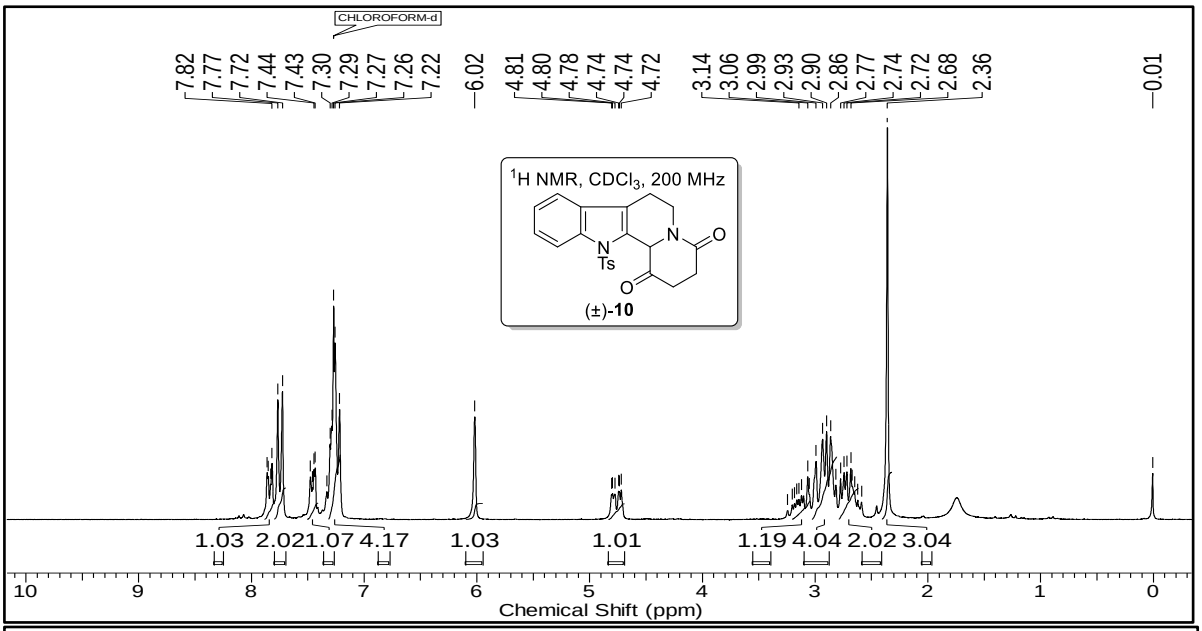
(±)-Isovindeburnol (**57**)
$C_{17}H_{20}N_2O$
M.W. 268.36

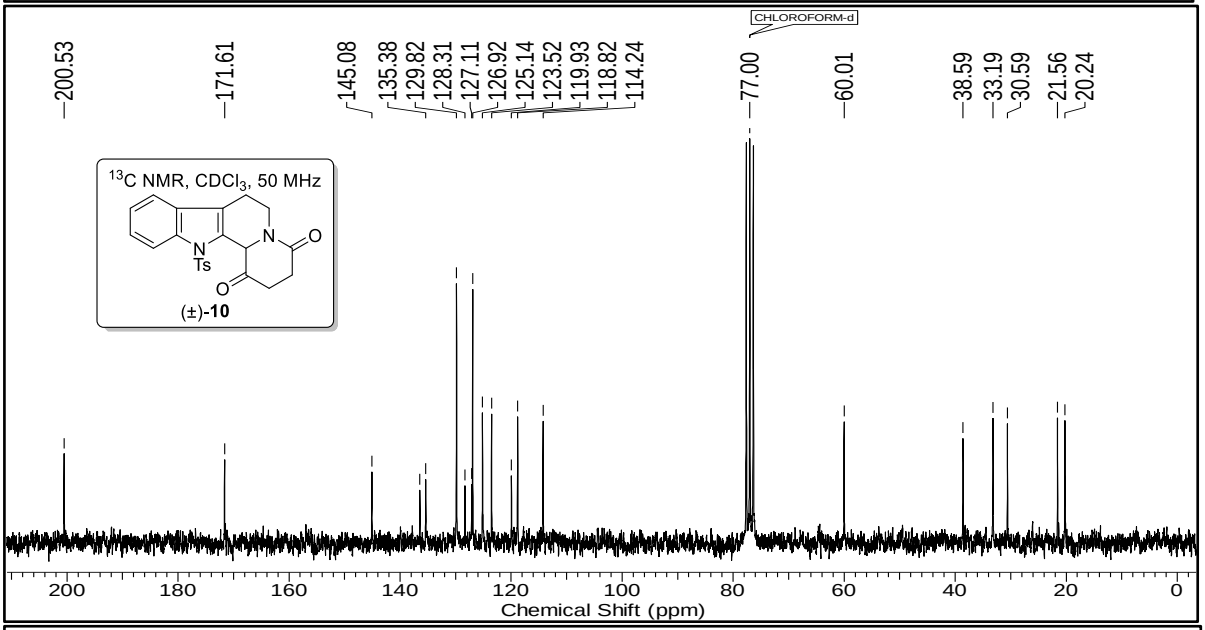
3B.5 Selected Spectra

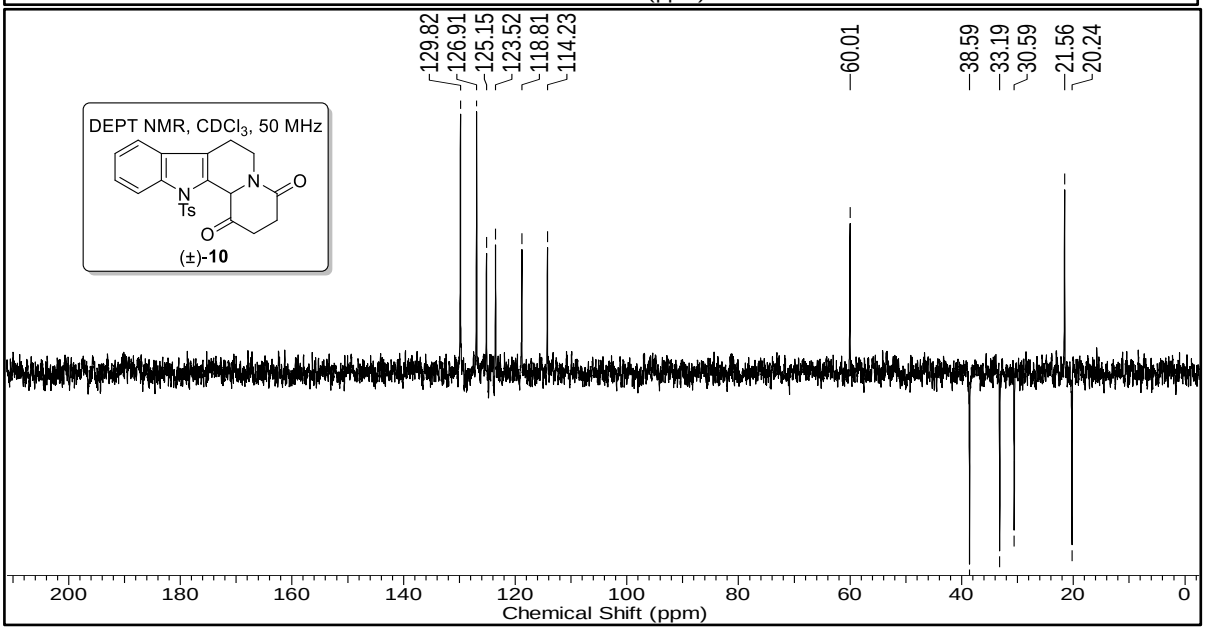

CHLOROFORM-d
8.10 8.06 7.40 7.36 7.35 7.29 7.27 7.26 7.25 7.07 7.03 5.88 5.87 5.86 5.27 5.25 5.24 5.07 5.02
2.73 2.69 2.68 2.62 2.56 2.53 2.52 2.46 2.28 2.21 1.74 1.73
^{1}H NMR, $CDCl_3$, 200 MHz
(+)-7
1.00 3.10 2.01 2.04 1.02 1.01 1.00 3.16 2.07 3.07 3.11 1.00 1.02
Chemical Shift (ppm)

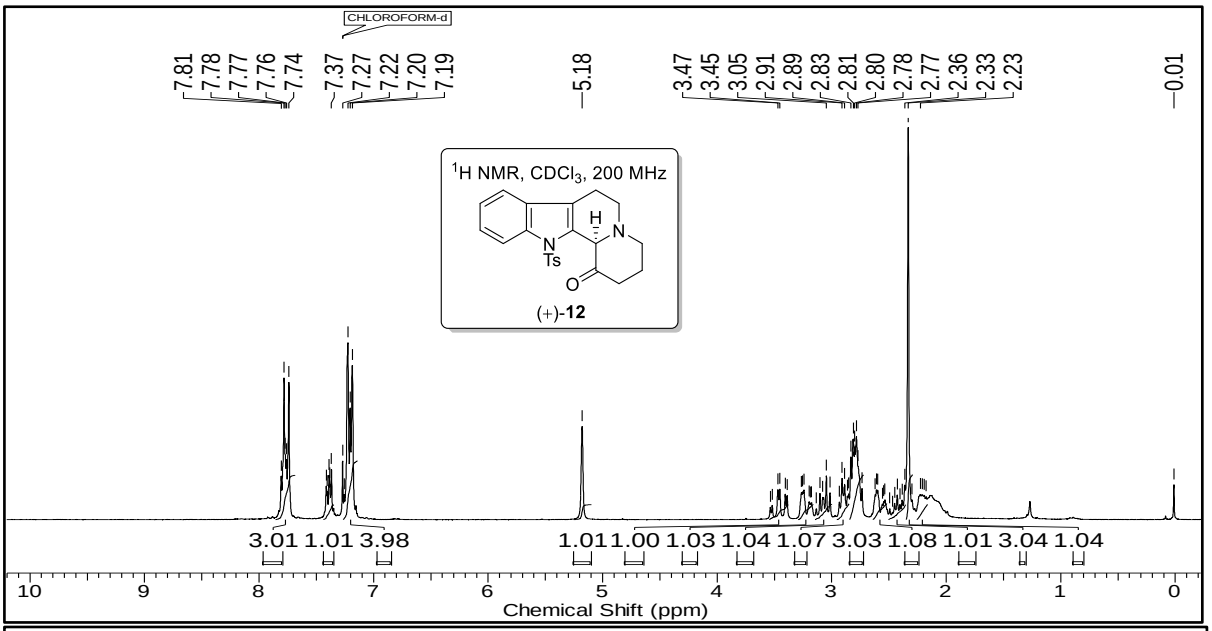

CHLOROFORM-d
170.07 169.72 144.95 138.78 133.03 132.30 130.77 129.17 127.27 126.67 125.70 124.93 118.71 117.01
77.00 71.31 60.36 40.74 27.60 23.40 21.94 21.50 21.14
^{13}C NMR, $CDCl_3$, 50 MHz
(+)-7
Chemical Shift (ppm)

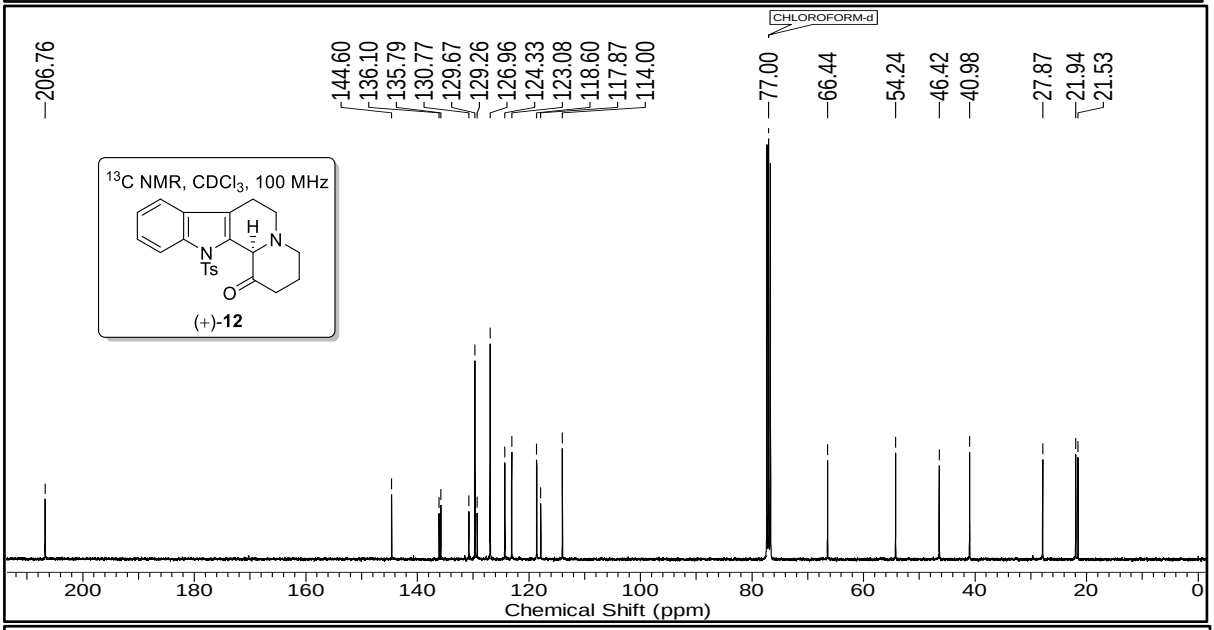

129.09 126.59 125.63 124.86 118.64 116.94
71.21 60.30 40.67 27.50 23.29 21.86 21.43 21.07
DEPT NMR, $CDCl_3$, 50 MHz
(+)-7
Chemical Shift (ppm)

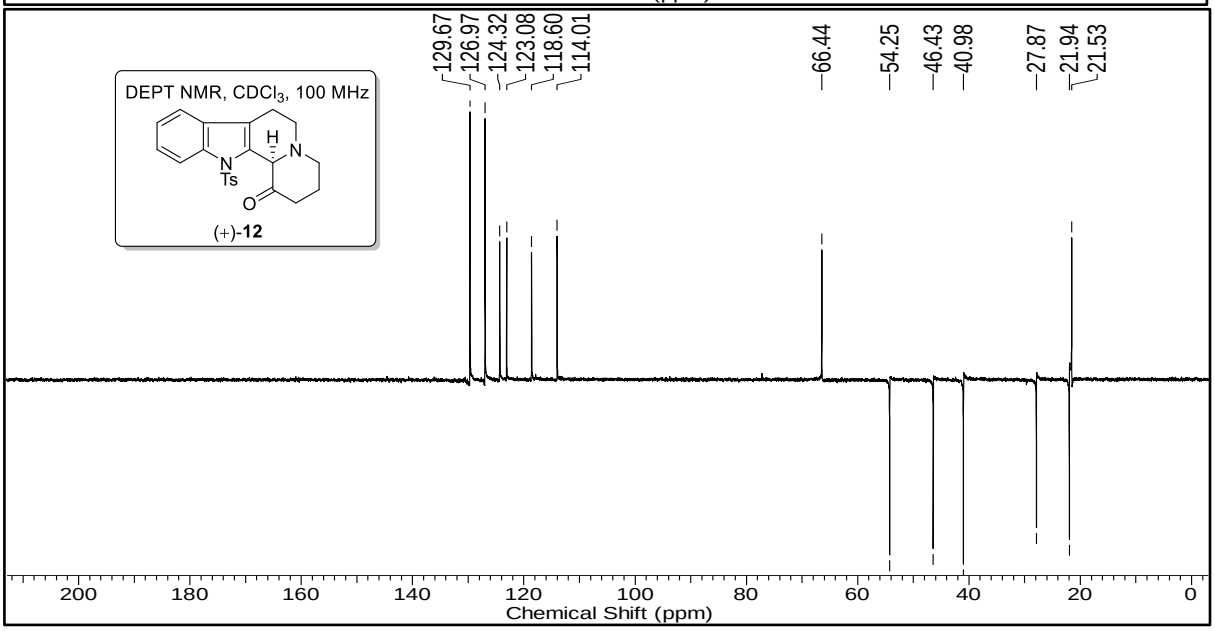

CHLOROFORM-d
7.82 7.77 7.72 7.44 7.43 7.30 7.29 7.27 7.26 7.22 6.02 4.81 4.80 4.78 4.74 4.74 4.72 3.14 3.06 2.99 2.93 2.90 2.86 2.77 2.74 2.72 2.68 2.36 0.01
^{1}H NMR, $CDCl_3$, 200 MHz
(±)-10
1.03 2.02 1.07 4.17 1.03 1.01 1.19 4.04 2.02 3.04
Chemical Shift (ppm)

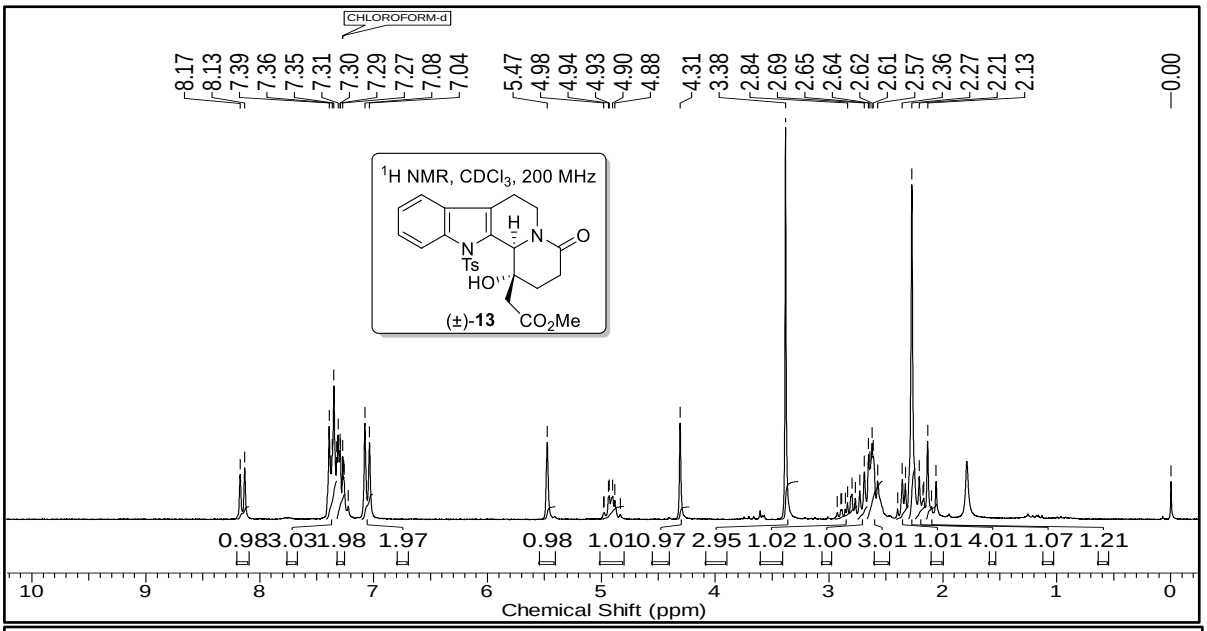

CHLOROFORM-d
200.53 171.61 145.08 135.38 129.82 128.31 127.11 126.92 125.14 123.52 119.93 118.82 114.24 77.00 60.01 38.59 33.19 30.59 21.56 20.24
^{13}C NMR, $CDCl_3$, 50 MHz
(±)-10
Chemical Shift (ppm)

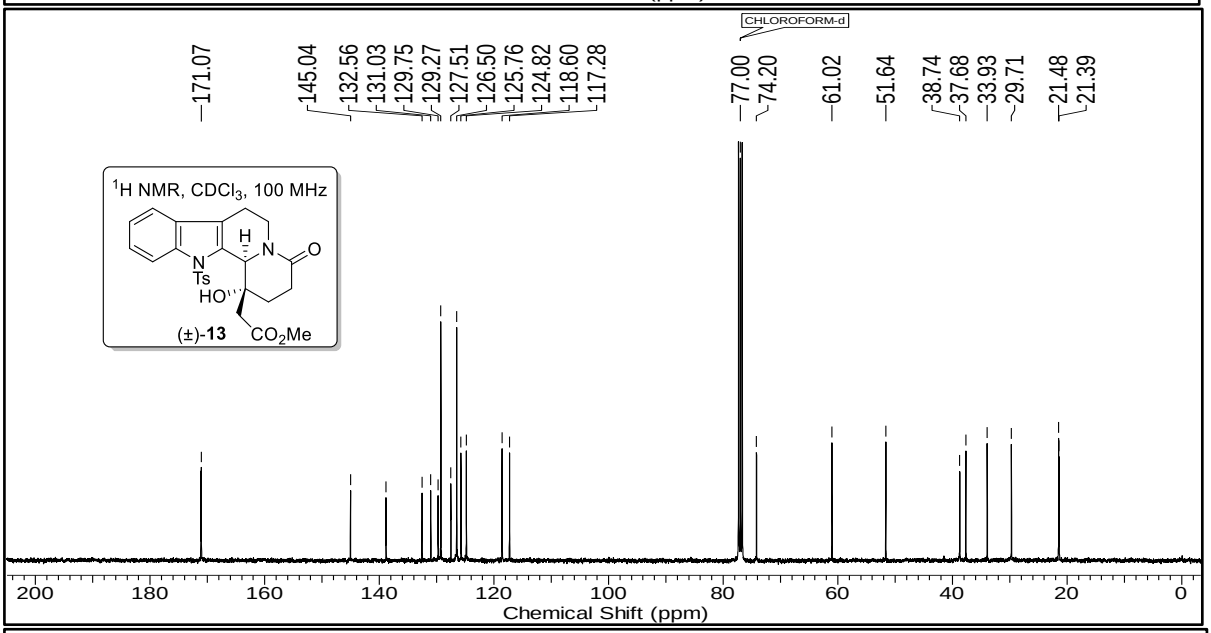

129.82 126.91 125.15 123.52 118.81 114.23 60.01 38.59 33.19 30.59 21.56 20.24
DEPT NMR, $CDCl_3$, 50 MHz
(±)-10
Chemical Shift (ppm)

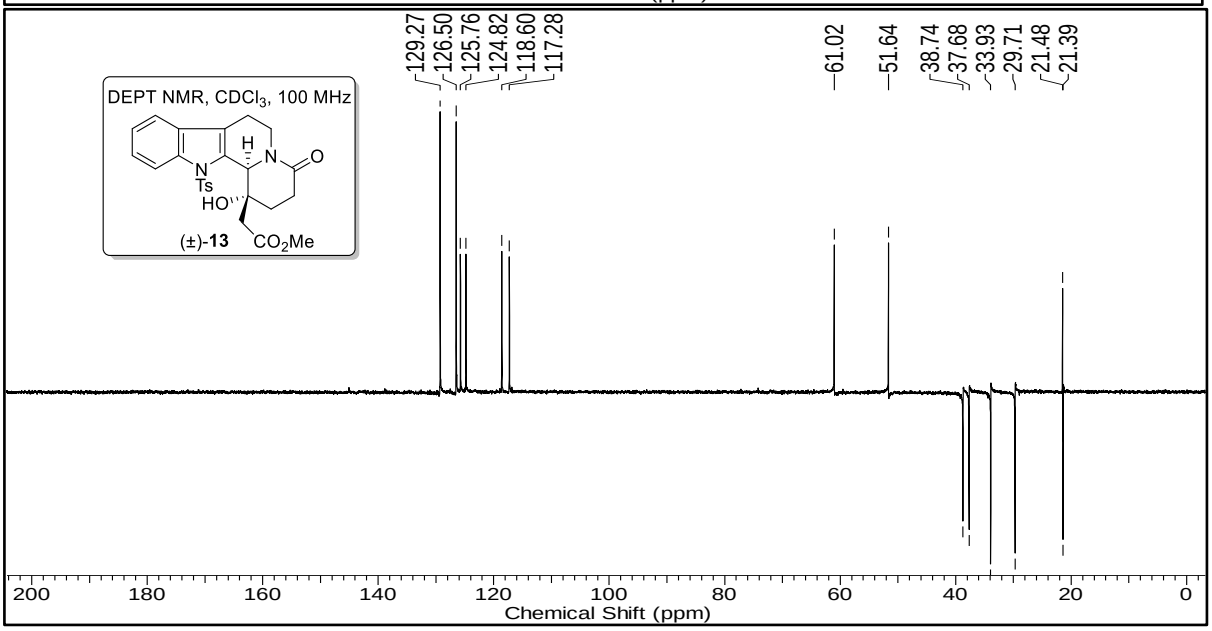

CHLOROFORM-d
7.81 7.78 7.77 7.76 7.74 7.37 7.27 7.22 7.20 7.19 5.18 3.47 3.45 3.05 2.91 2.89 2.83 2.81 2.80 2.78 2.77 2.36 2.33 2.23 0.01
^{1}H NMR, CDCl$_3$, 200 MHz
(+)-12
3.01 1.01 3.98 1.01 1.00 1.03 1.04 1.07 3.03 1.08 1.01 3.04 1.04
Chemical Shift (ppm)

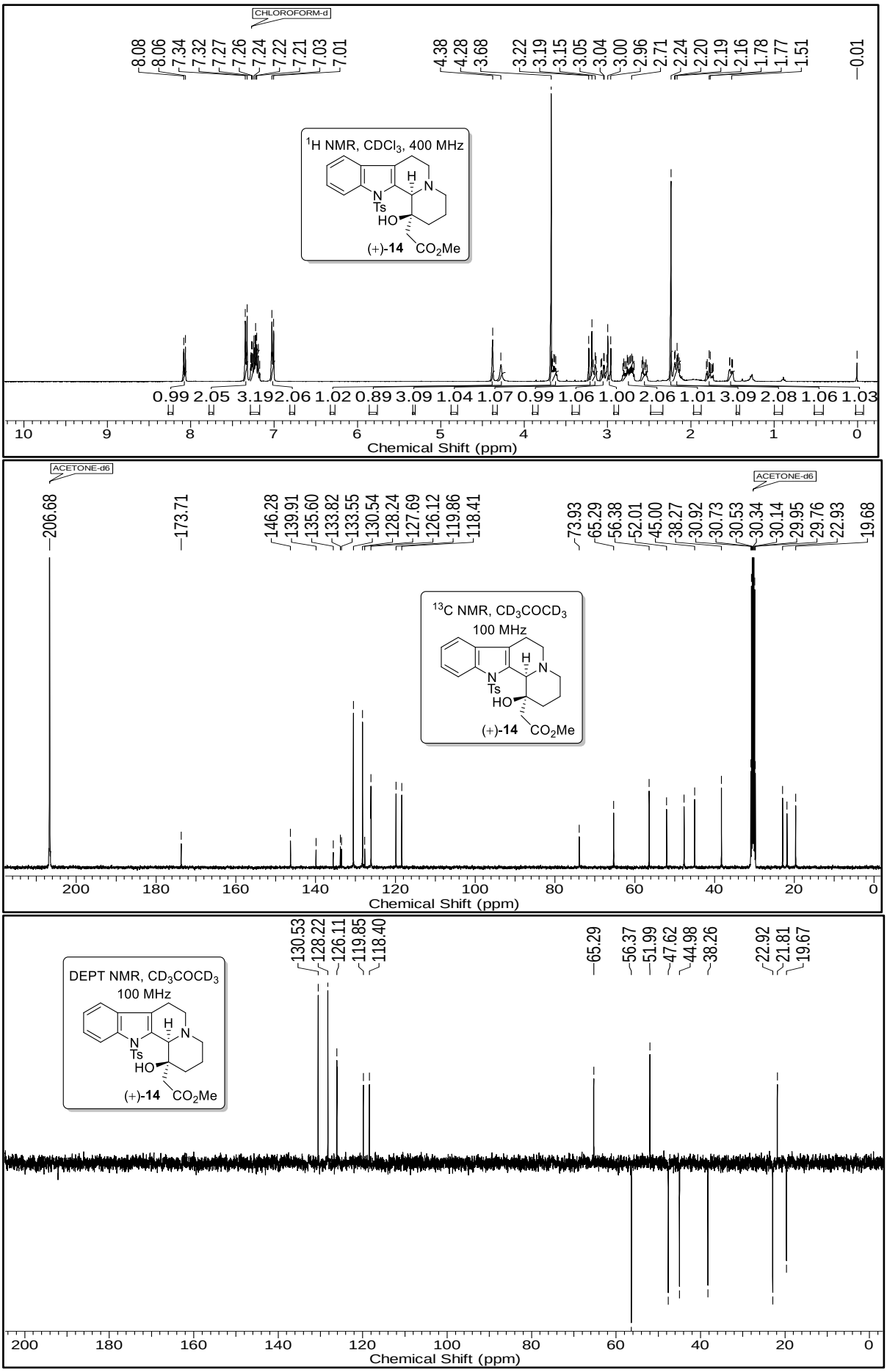

CHLOROFORM-d
206.76 144.60 136.10 135.79 130.77 129.67 129.26 126.96 124.33 123.08 118.60 117.87 114.00 77.00 66.44 54.24 46.42 40.98 27.87 21.94 21.53
^{13}C NMR, CDCl$_3$, 100 MHz
(+)-12
Chemical Shift (ppm)

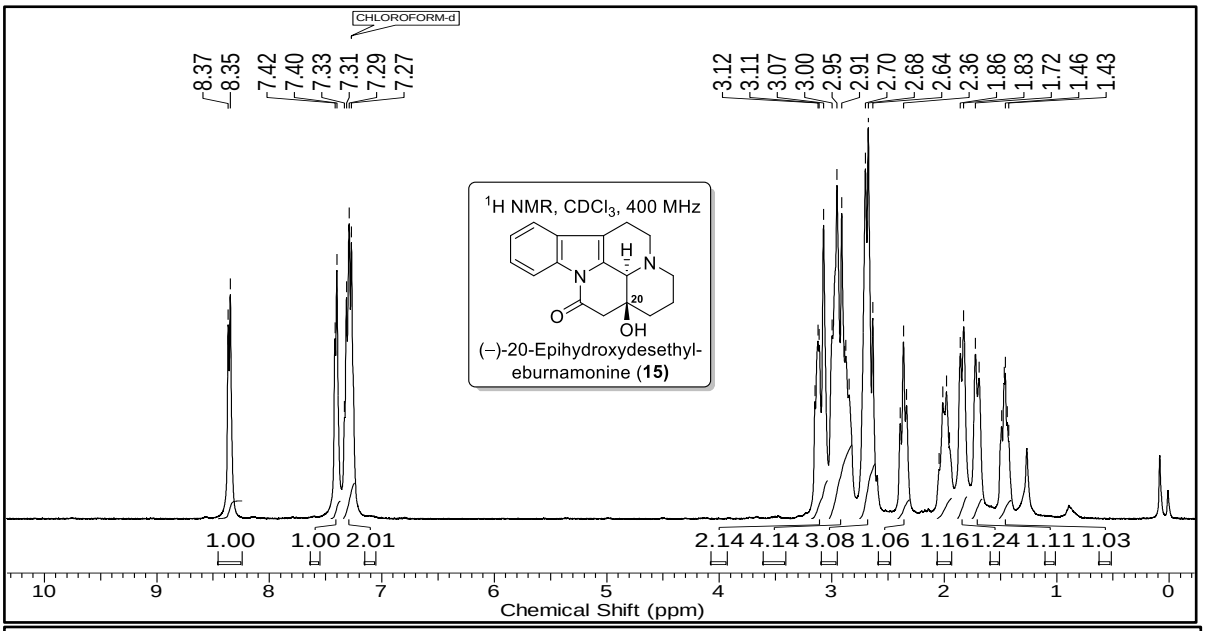

129.67 126.97 124.32 123.08 118.60 114.01 66.44 54.25 46.43 40.98 27.87 21.94 21.53
DEPT NMR, CDCl$_3$, 100 MHz
(+)-12
Chemical Shift (ppm)

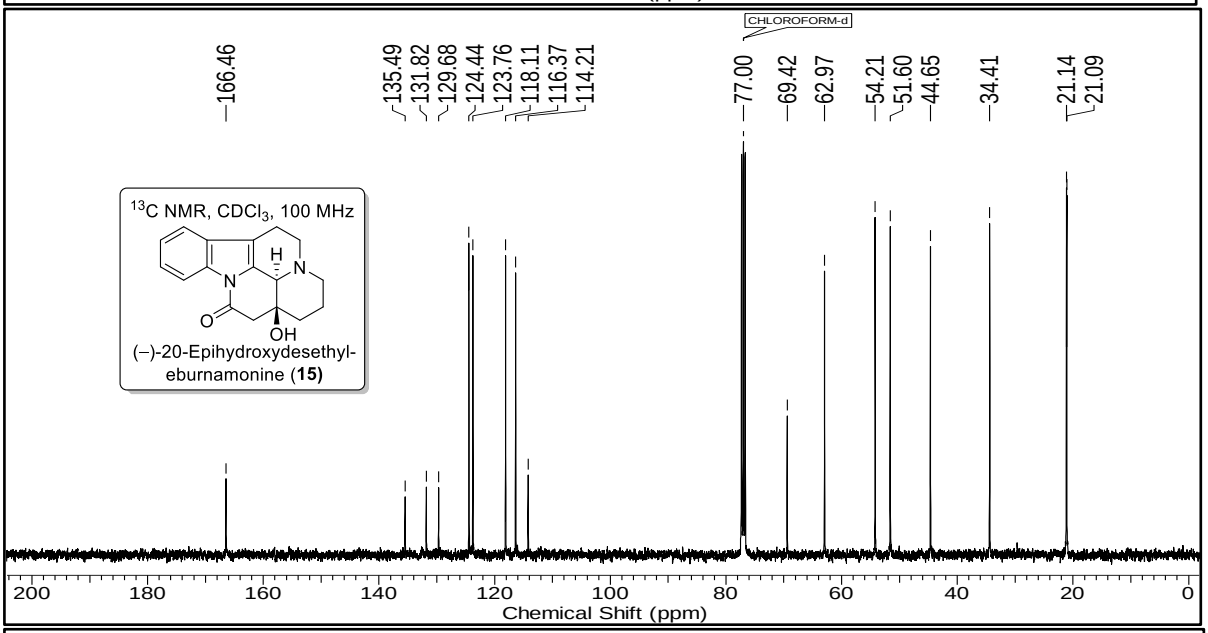

CHLOROFORM-d
8.17 8.13 7.39 7.36 7.35 7.31 7.30 7.29 7.27 7.08 7.04
5.47 4.98 4.94 4.93 4.90 4.88 4.31 3.38 2.84 2.69 2.65 2.64 2.62 2.61 2.57 2.36 2.27 2.21 2.13
0.00
^{1}H NMR, $CDCl_3$, 200 MHz
(±)-13
0.98 3.03 1.98 1.97 0.98 1.01 0.97 2.95 1.02 1.00 3.01 1.01 4.01 1.07 1.21
Chemical Shift (ppm)

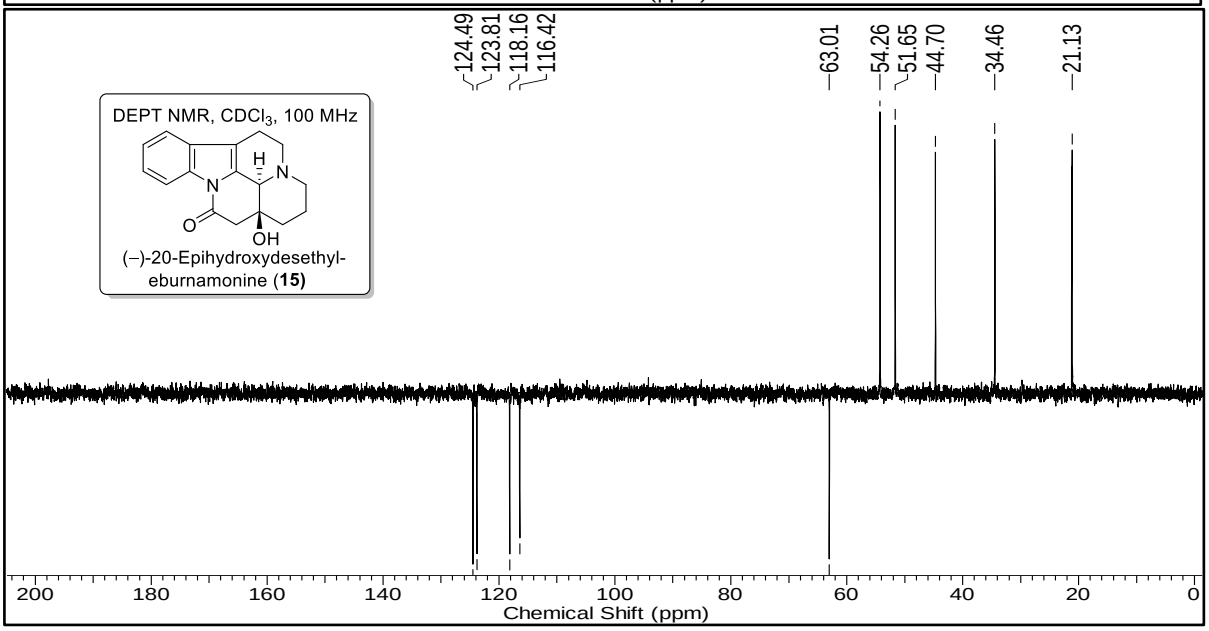

CHLOROFORM-d
171.07
145.04 132.56 131.03 129.75 129.27 127.51 126.50 125.76 124.82 118.60 117.28
77.00 74.20
61.02
51.64
38.74 37.68 33.93 29.71
21.48 21.39
^{1}H NMR, $CDCl_3$, 100 MHz
(±)-13
Chemical Shift (ppm)

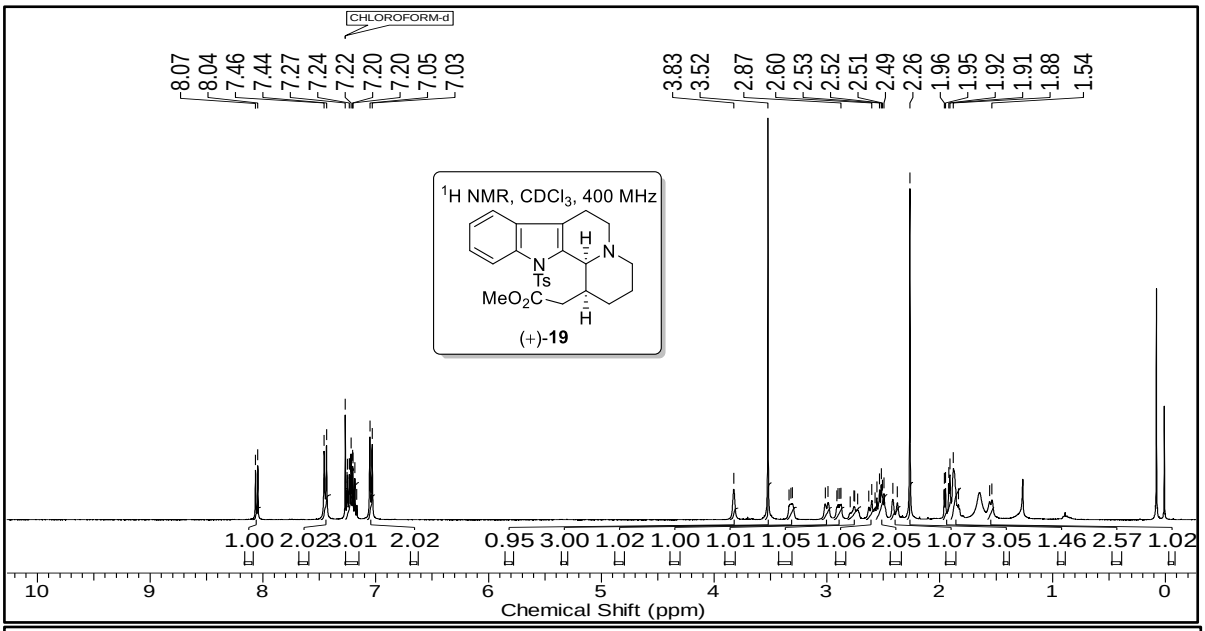

129.27 126.50 125.76 124.82 118.60 117.28
61.02
51.64
38.74 37.68 33.93 29.71 21.48 21.39
DEPT NMR, $CDCl_3$, 100 MHz
(±)-13
Chemical Shift (ppm)

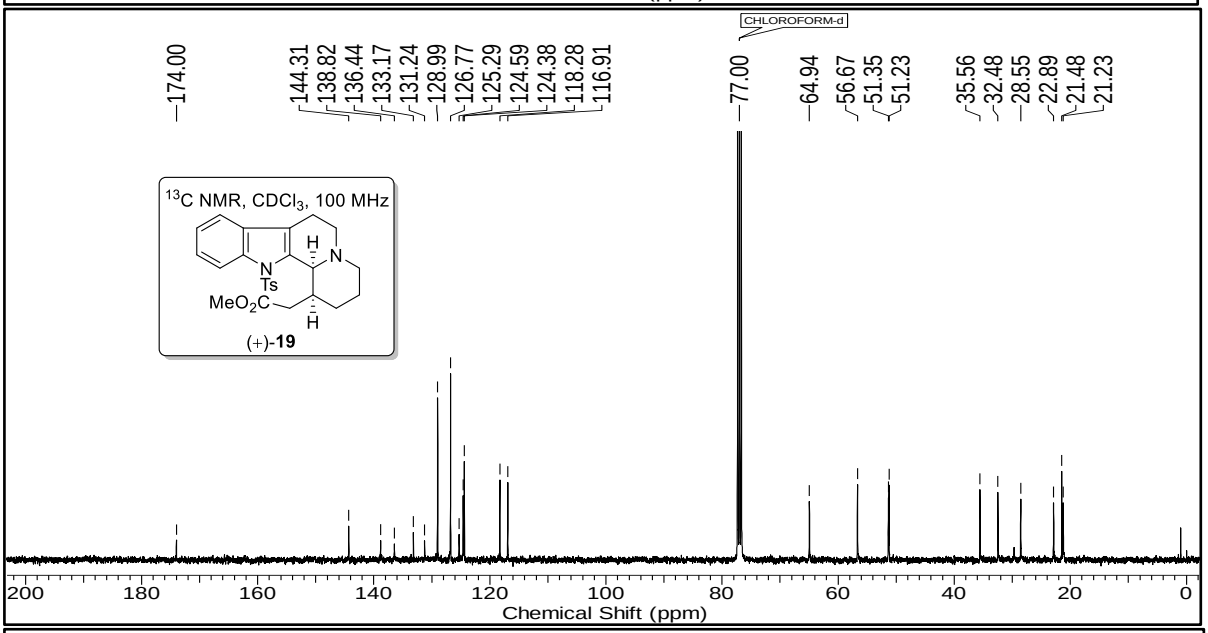

CHLOROFORM-d
8.08 8.06 7.34 7.32 7.27 7.26 7.24 7.22 7.21 7.03 7.01
4.38 4.28 3.68 3.22 3.19 3.15 3.05 3.04 3.00 2.96 2.71 2.24 2.20 2.19 2.16 1.78 1.77 1.51
0.01
^{1}H NMR, $CDCl_3$, 400 MHz
(+)-14
0.99 2.05 3.19 2.06 1.02 0.89 3.09 1.04 1.07 0.99 1.06 1.00 2.06 1.01 3.09 2.08 1.06 1.03
Chemical Shift (ppm)
ACETONE-d6
206.68
173.71
146.28 139.91 135.60 133.82 133.55 130.54 128.24 127.69 126.12 119.86 118.41
73.93 65.29 56.38 52.01 45.00 38.27 30.92 30.73 30.53 30.34 30.14 29.95 29.76 22.93 19.68
^{13}C NMR, CD_3COCD_3
100 MHz
(+)-14
Chemical Shift (ppm)
DEPT NMR, CD_3COCD_3
100 MHz
(+)-14
130.53 128.22 126.11 119.85 118.40
65.29 56.37 51.99 47.62 44.98 38.26 22.92 21.81 19.67
Chemical Shift (ppm)

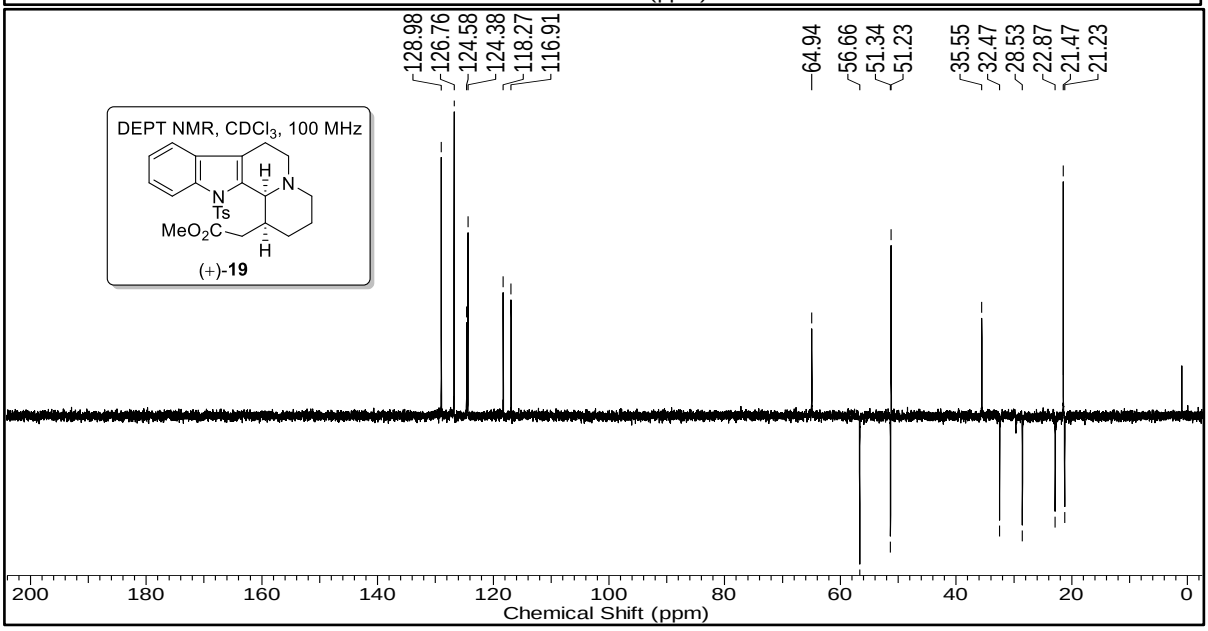

CHLOROFORM-d
8.37
8.35
7.42
7.40
7.33
7.31
7.29
7.27
3.12
3.11
3.07
3.00
2.95
2.91
2.70
2.68
2.64
2.36
1.86
1.83
1.72
1.46
1.43
^{1}H NMR, CDCl$_3$, 400 MHz
(–)-20-Epihydroxydesethyl-eburnamonine (**15**)
1.00
1.00
2.01
2.14
4.14
3.08
1.06
1.16
1.24
1.11
1.03
Chemical Shift (ppm)

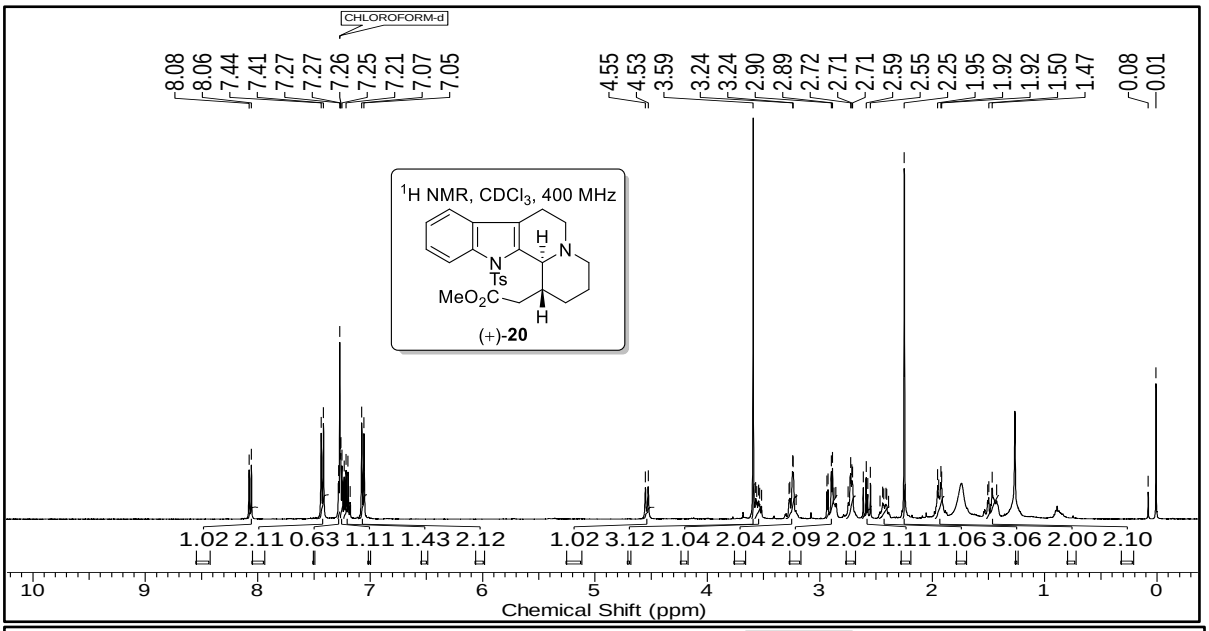

CHLOROFORM-d
166.46
135.49
131.82
129.68
124.44
123.76
118.11
116.37
114.21
77.00
69.42
62.97
54.21
51.60
44.65
34.41
21.14
21.09
^{13}C NMR, CDCl$_3$, 100 MHz
(–)-20-Epihydroxydesethyl-eburnamonine (**15**)
Chemical Shift (ppm)

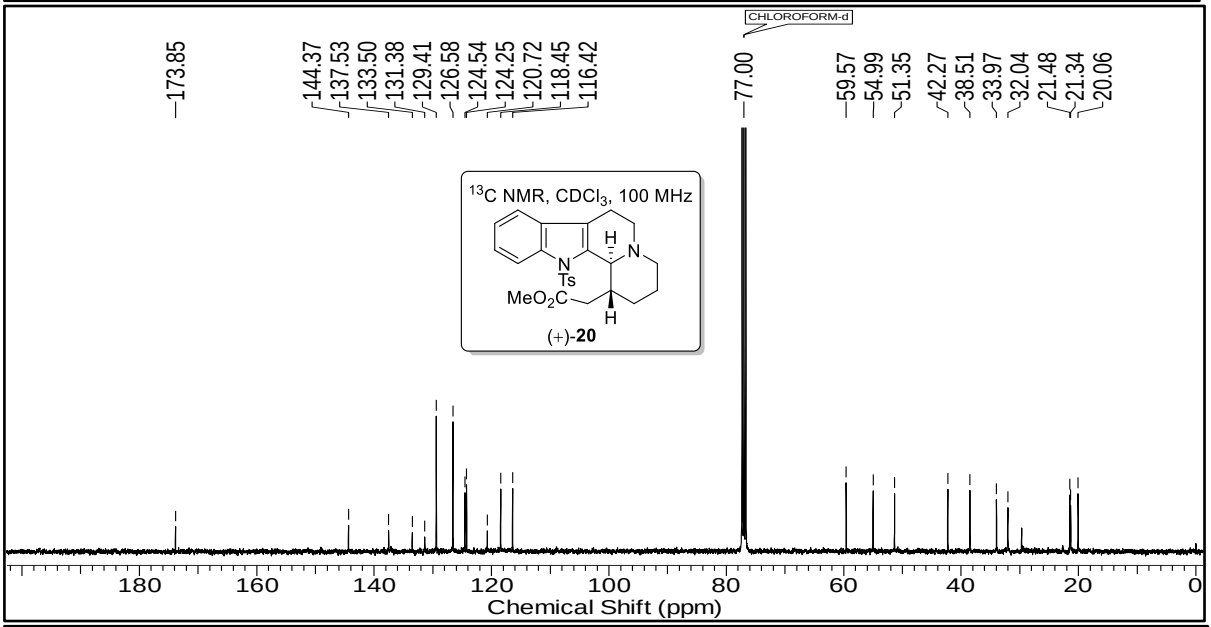

124.49
123.81
118.16
116.42
63.01
54.26
51.65
44.70
34.46
21.13
DEPT NMR, CDCl$_3$, 100 MHz
(–)-20-Epihydroxydesethyl-eburnamonine (**15**)
Chemical Shift (ppm)

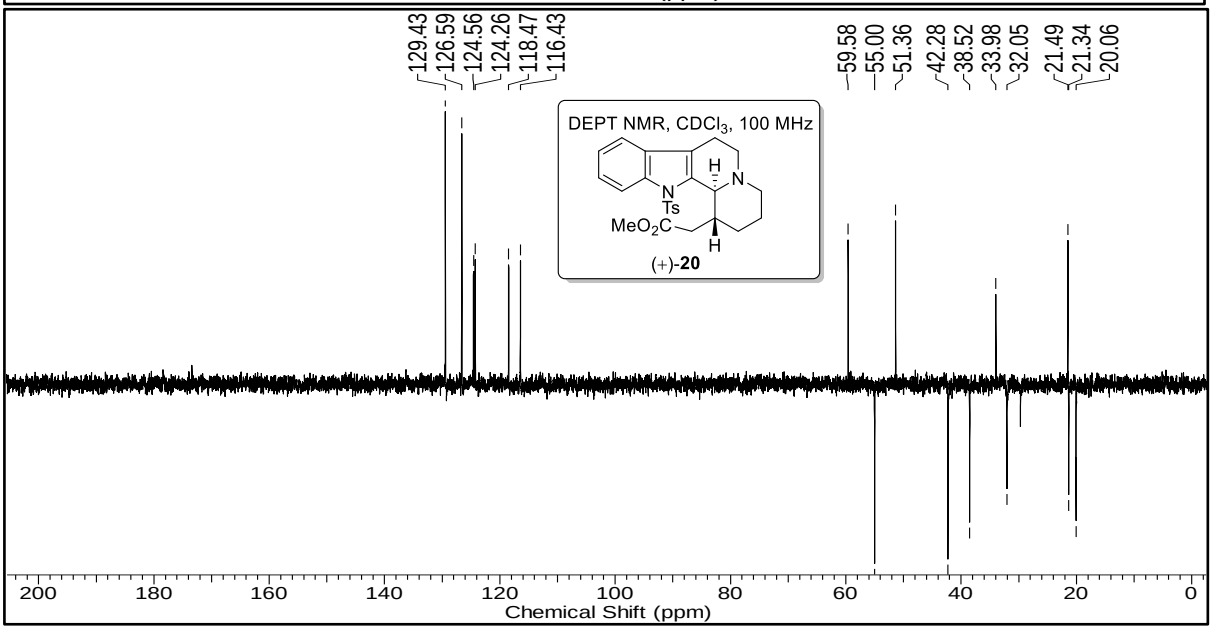

CHLOROFORM-d
8.07 8.04 7.46 7.44 7.27 7.24 7.22 7.20 7.20 7.05 7.03
3.83 3.52 2.87 2.60 2.53 2.52 2.51 2.49 2.26 1.96 1.95 1.92 1.91 1.88 1.54
^{1}H NMR, $CDCl_3$, 400 MHz
(+)-19
1.00 2.02 3.01 2.02 0.95 3.00 1.02 1.00 1.01 1.05 1.06 2.05 1.07 3.05 1.46 2.57 1.02
Chemical Shift (ppm)

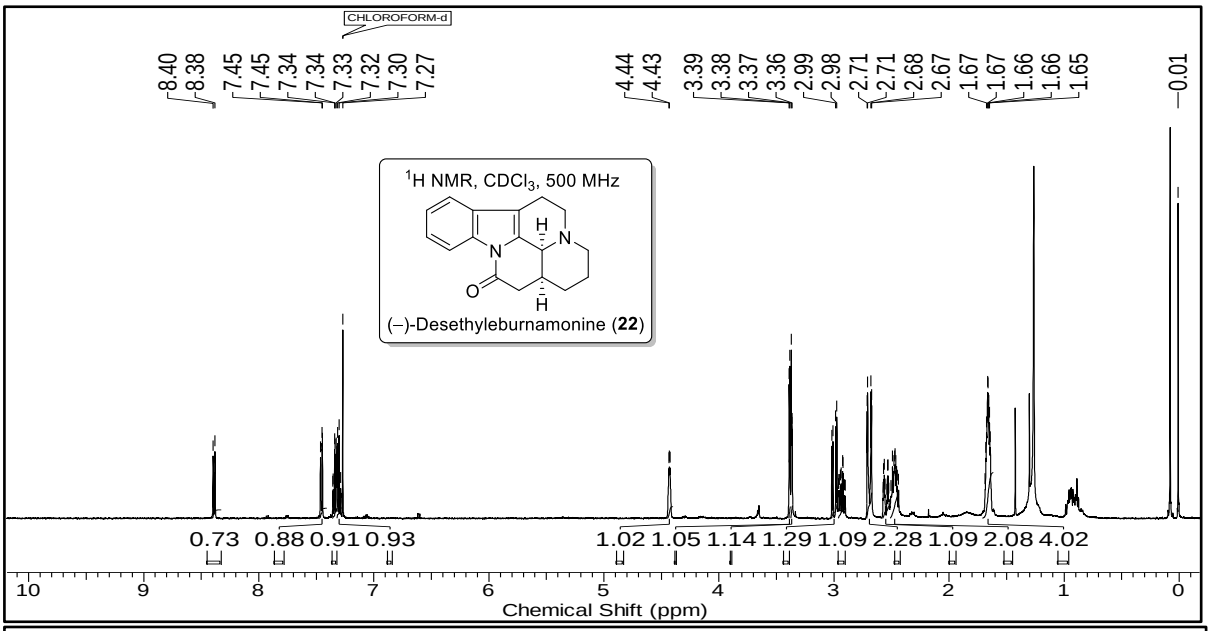

CHLOROFORM-d
174.00 144.31 138.82 136.44 133.17 131.24 128.99 126.77 125.29 124.59 124.38 118.28 116.91
77.00 64.94 56.67 51.35 51.23 35.56 32.48 28.55 22.89 21.48 21.23
^{13}C NMR, $CDCl_3$, 100 MHz
(+)-19
Chemical Shift (ppm)

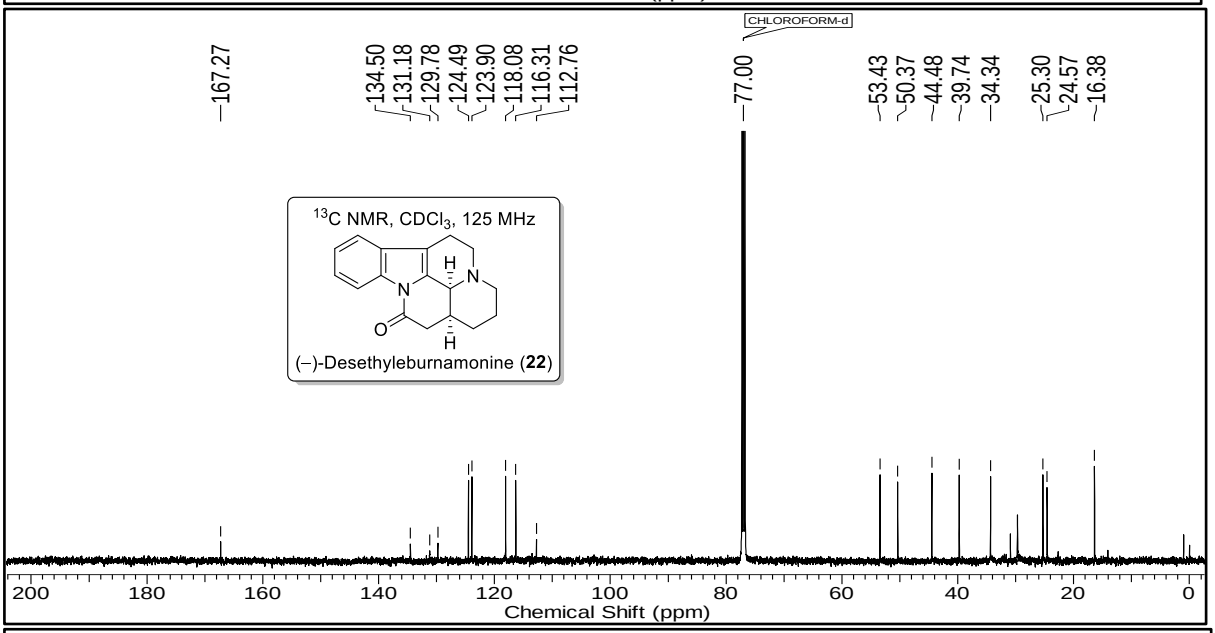

128.98 126.76 124.58 124.38 118.27 116.91
64.94 56.66 51.34 51.23 35.55 32.47 28.53 22.87 21.47 21.23
DEPT NMR, $CDCl_3$, 100 MHz
(+)-19
Chemical Shift (ppm)

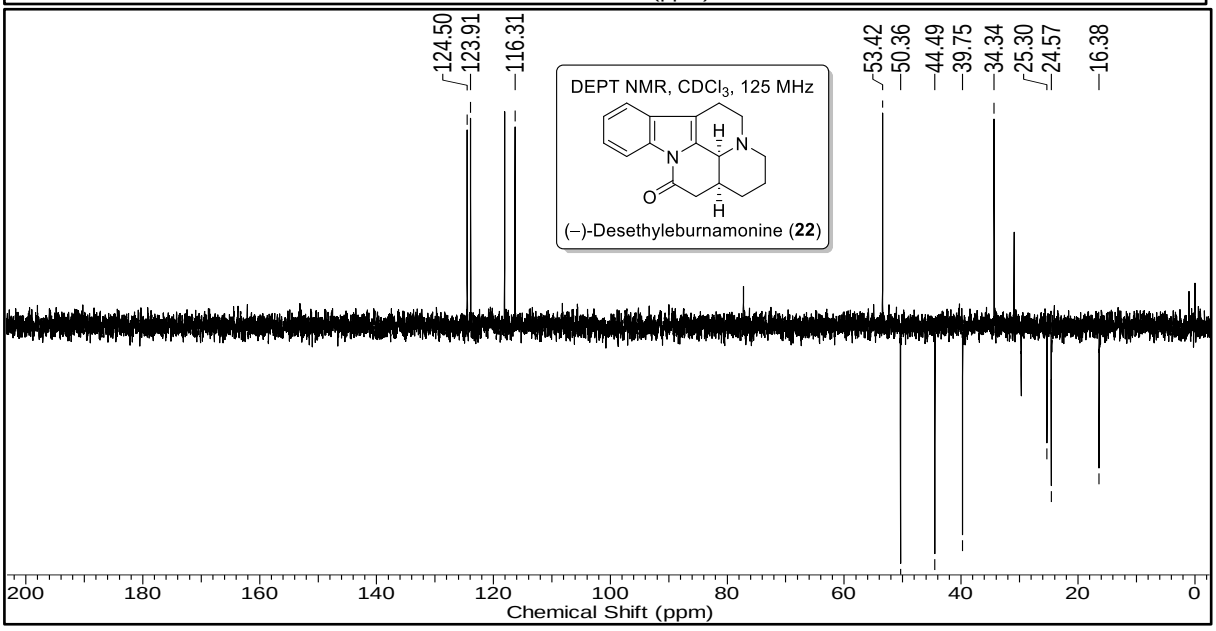

CHLOROFORM-d
8.08 8.06 7.44 7.41 7.27 7.27 7.26 7.25 7.21 7.07 7.05
4.55 4.53 3.59 3.24 3.24 2.90 2.89 2.72 2.71 2.71 2.59 2.55 2.25 1.95 1.92 1.92 1.50 1.47
0.08 0.01
^{1}H NMR, $CDCl_3$, 400 MHz
(+)-20
1.02 2.11 0.63 1.11 1.43 2.12
1.02 3.12 1.04 2.04 2.09 2.02 1.11 1.06 3.06 2.00 2.10
Chemical Shift (ppm)

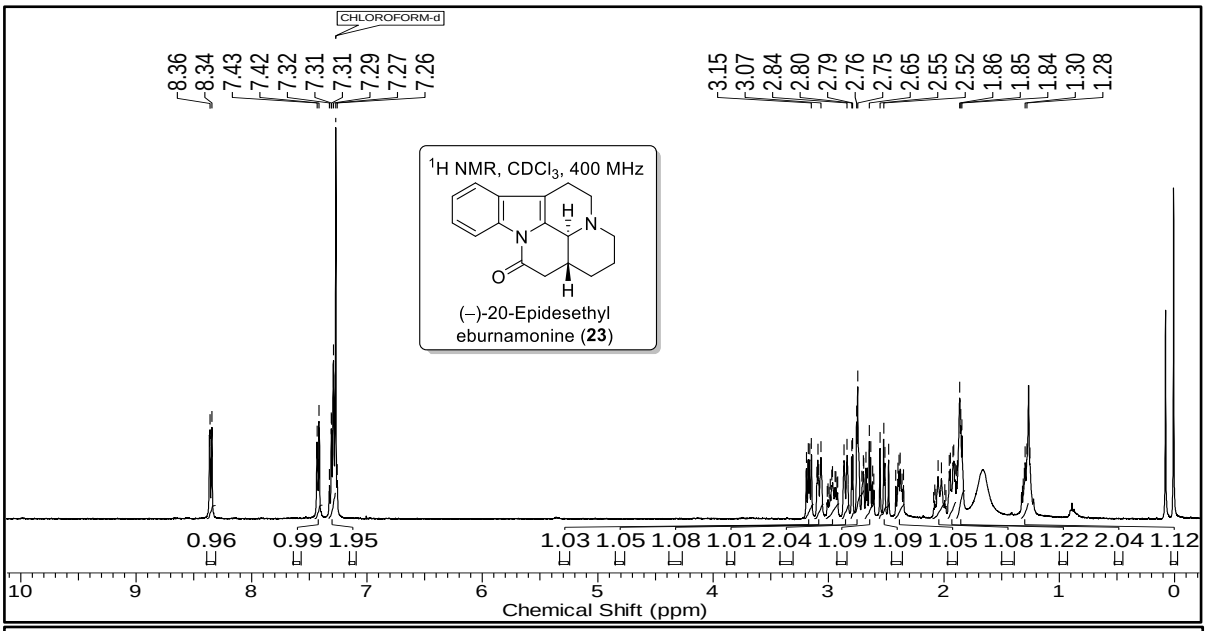

CHLOROFORM-d
173.85
144.37 137.53 133.50 131.38 129.41 126.58 124.54 124.25 120.72 118.45 116.42
77.00
59.57 54.99 51.35 42.27 38.51 33.97 32.04 21.48 21.34 20.06
^{13}C NMR, $CDCl_3$, 100 MHz
(+)-20
Chemical Shift (ppm)

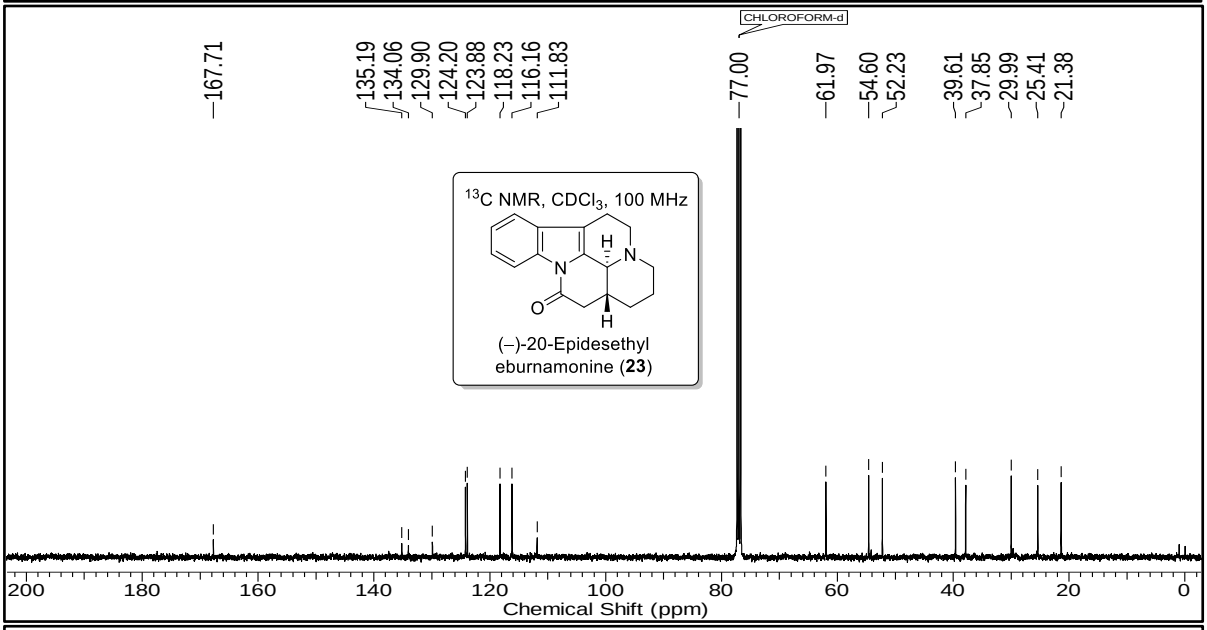

129.43 126.59 124.56 124.26 118.47 116.43
59.58 55.00 51.36 42.28 38.52 33.98 32.05 21.49 21.34 20.06
DEPT NMR, $CDCl_3$, 100 MHz
(+)-20
Chemical Shift (ppm)

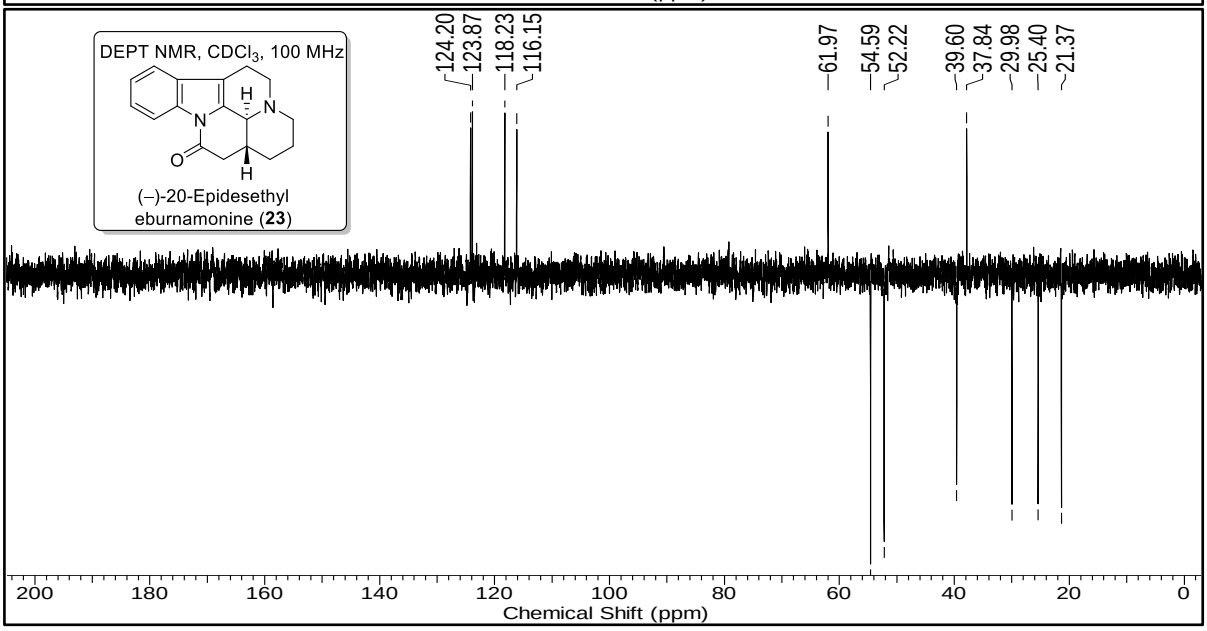

CHLOROFORM-d
8.40 8.38 7.45 7.45 7.34 7.34 7.33 7.32 7.30 7.27
4.44 4.43 3.39 3.38 3.37 3.36 2.99 2.98 2.71 2.71 2.68 2.67 1.67 1.67 1.66 1.66 1.65
0.01
^{1}H NMR, $CDCl_3$, 500 MHz
(–)-Desethyleburnamonine (**22**)
0.73 0.88 0.91 0.93
1.02 1.05 1.14 1.29 1.09 2.28 1.09 2.08 4.02
Chemical Shift (ppm)

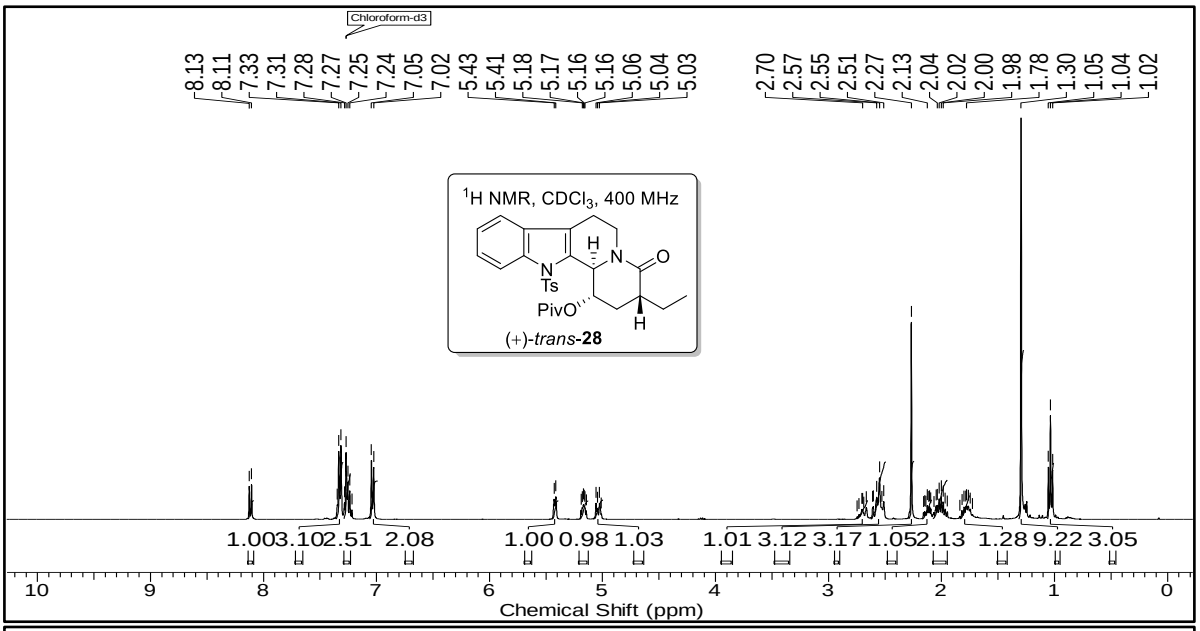

CHLOROFORM-d
167.27
134.50 131.18 129.78 124.49 123.90 118.08 116.31 112.76
77.00
53.43 50.37 44.48 39.74 34.34 25.30 24.57 16.38
^{13}C NMR, $CDCl_3$, 125 MHz
(–)-Desethyleburnamonine (**22**)
Chemical Shift (ppm)

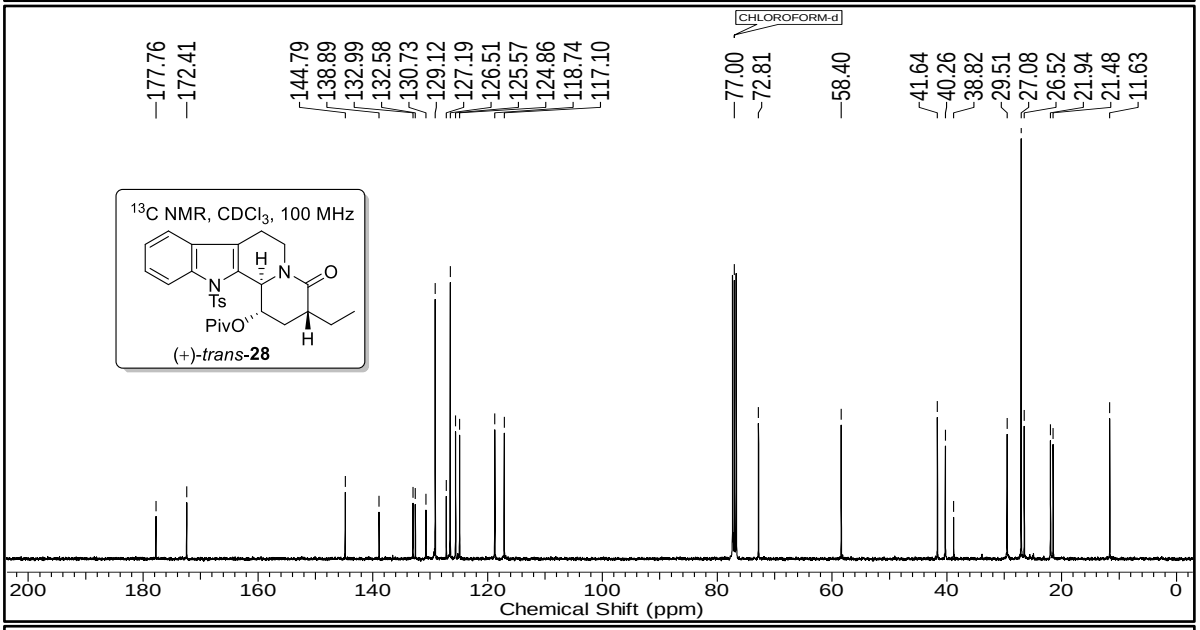

124.50 123.91 116.31
53.42 50.36 44.49 39.75 34.34 25.30 24.57 16.38
DEPT NMR, $CDCl_3$, 125 MHz
(–)-Desethyleburnamonine (**22**)
Chemical Shift (ppm)

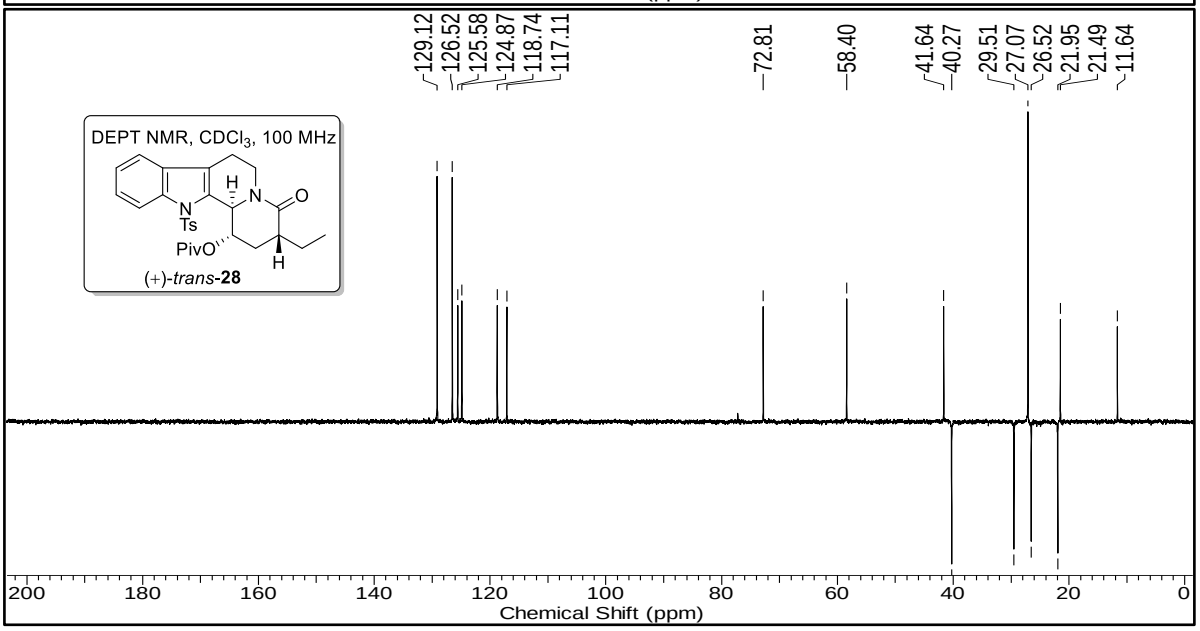

CHLOROFORM-d
8.36
8.34
7.43
7.42
7.32
7.31
7.31
7.29
7.27
7.26
3.15
3.07
2.84
2.80
2.79
2.76
2.75
2.65
2.55
2.52
1.86
1.85
1.84
1.30
1.28
^{1}H NMR, CDCl$_3$, 400 MHz
(–)-20-Epidesethyl eburnamonine (**23**)
0.96
0.99
1.95
1.03
1.05
1.08
1.01
2.04
1.09
1.09
1.05
1.08
1.22
2.04
1.12
Chemical Shift (ppm)


CHLOROFORM-d
167.71
135.19
134.06
129.90
124.20
123.88
118.23
116.16
111.83
77.00
61.97
54.60
52.23
39.61
37.85
29.99
25.41
21.38
^{13}C NMR, CDCl$_3$, 100 MHz
(–)-20-Epidesethyl eburnamonine (**23**)
Chemical Shift (ppm)

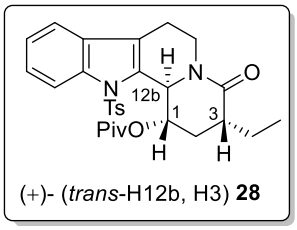

DEPT NMR, CDCl$_3$, 100 MHz
(–)-20-Epidesethyl eburnamonine (**23**)
124.20
123.87
118.23
116.15
61.97
54.59
52.22
39.60
37.84
29.98
25.40
21.37
Chemical Shift (ppm)


Chloroform-d3
8.13 8.11 7.33 7.31 7.28 7.27 7.25 7.24 7.05 7.02
5.43 5.41 5.18 5.17 5.16 5.16 5.06 5.04 5.03
2.70 2.57 2.55 2.51 2.27 2.13 2.04 2.02 2.00 1.98 1.78 1.30 1.05 1.04 1.02
^{1}H NMR, CDCl$_3$, 400 MHz
(+)-*trans*-**28**
1.00 3.10 2.51 2.08 1.00 0.98 1.03 1.01 3.12 3.17 1.05 2.13 1.28 9.22 3.05
Chemical Shift (ppm)

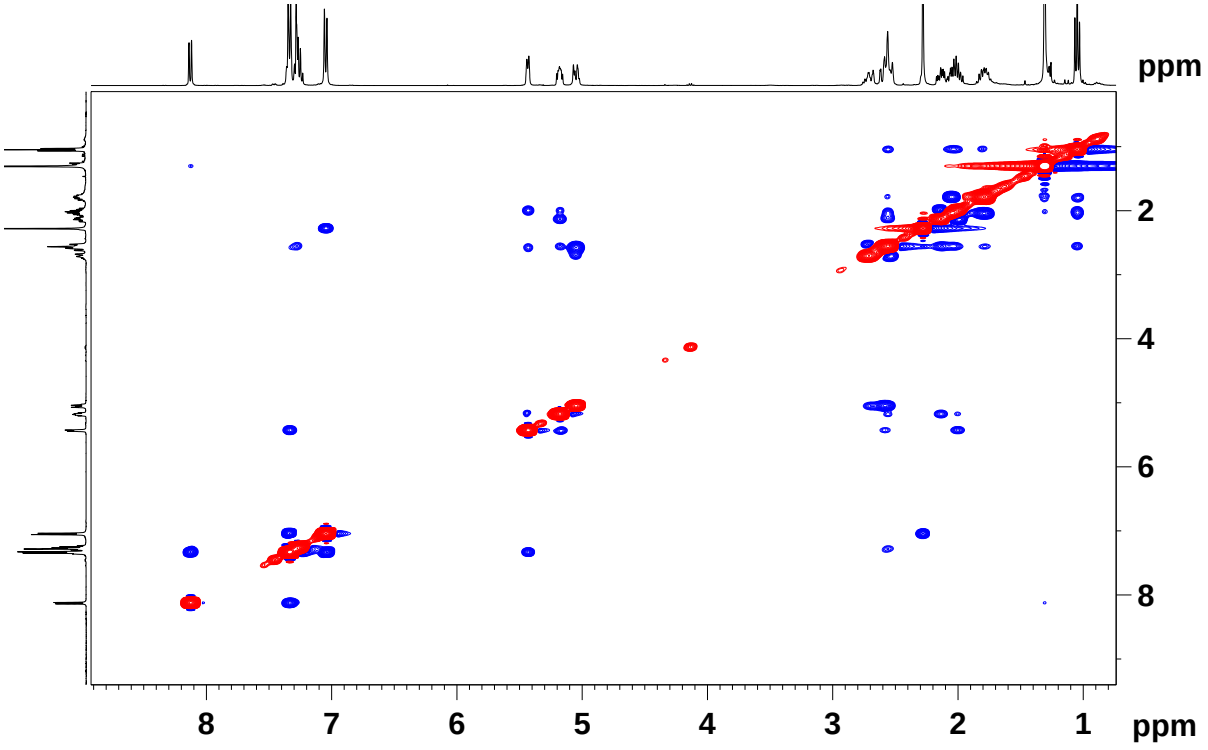

CHLOROFORM-d
177.76 172.41 144.79 138.89 132.99 132.58 130.73 129.12 127.19 126.51 125.57 124.86 118.74 117.10
77.00 72.81 58.40 41.64 40.26 38.82 29.51 27.08 26.52 21.94 21.48 11.63
^{13}C NMR, CDCl$_3$, 100 MHz
(+)-*trans*-**28**
Chemical Shift (ppm)


129.12 126.52 125.58 124.87 118.74 117.11
72.81 58.40 41.64 40.27 29.51 27.07 26.52 21.95 21.49 11.64
DEPT NMR, CDCl$_3$, 100 MHz
(+)-*trans*-**28**
Chemical Shift (ppm)

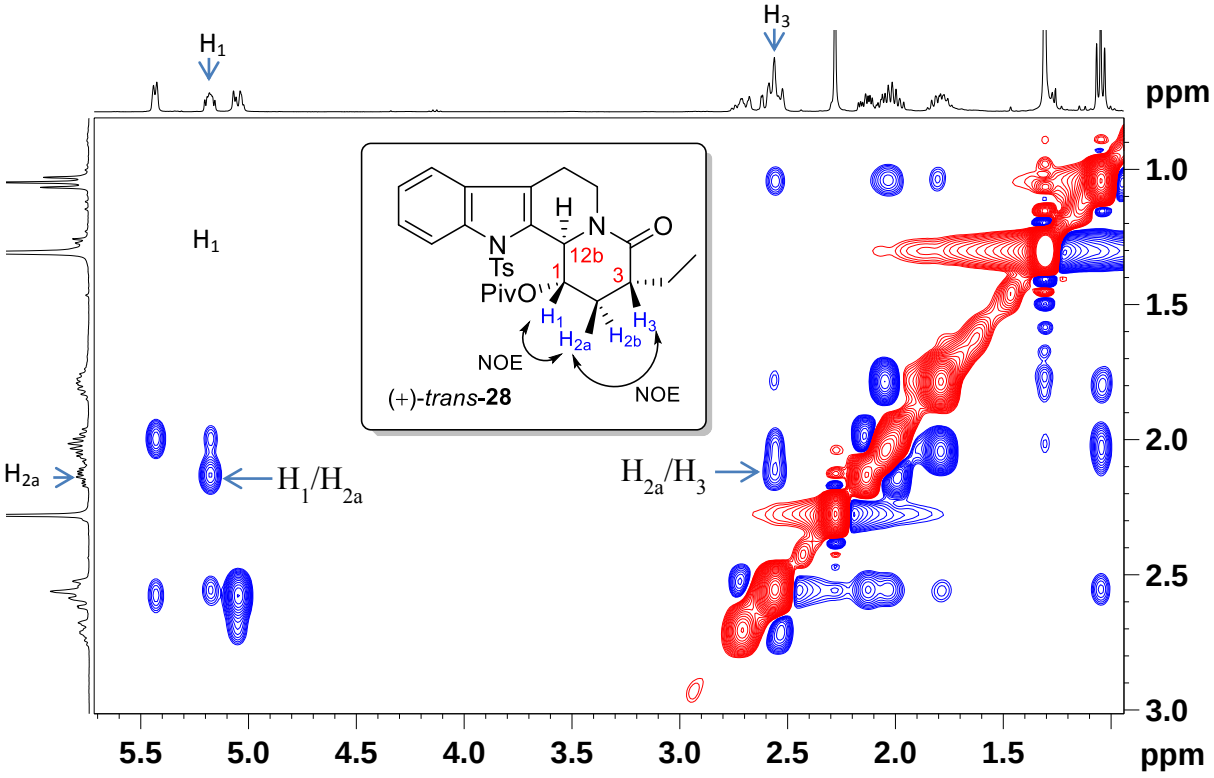
NOESY spectra of (+)-*trans*-**28**



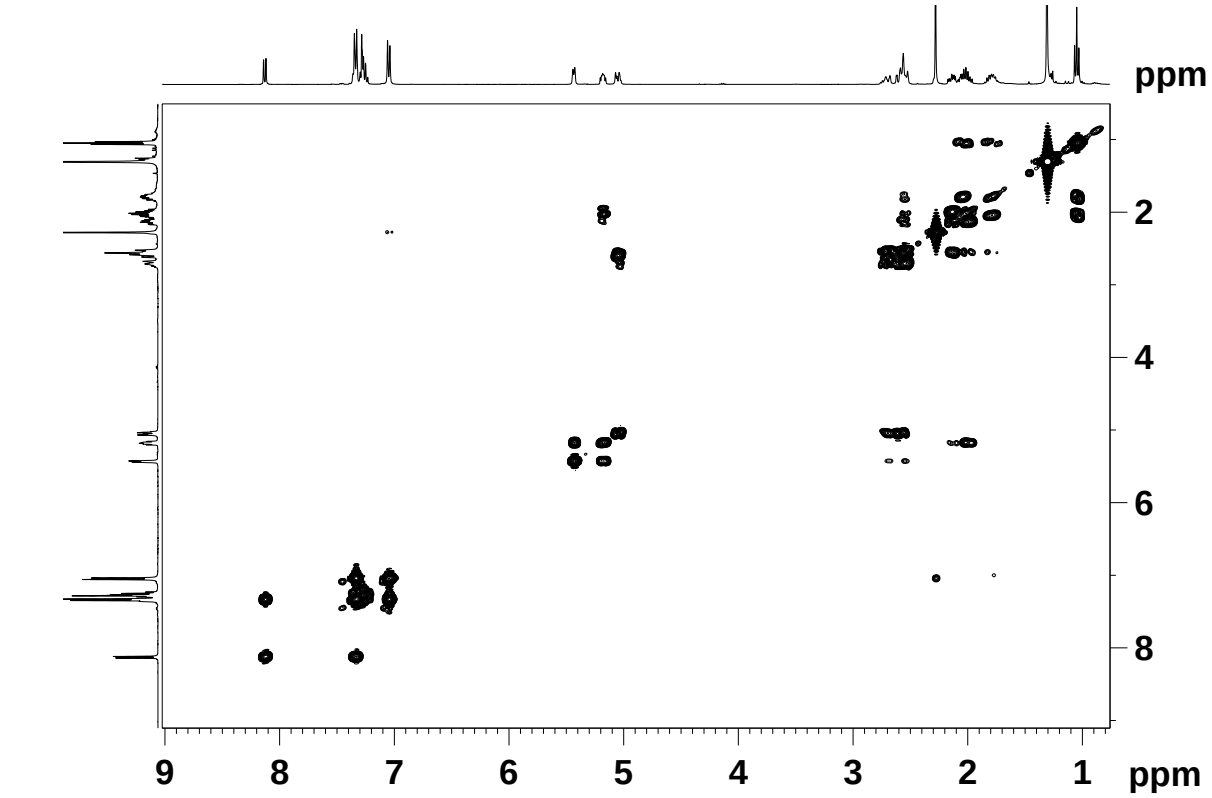
(+)- (*trans*-H12b, H3) **28**



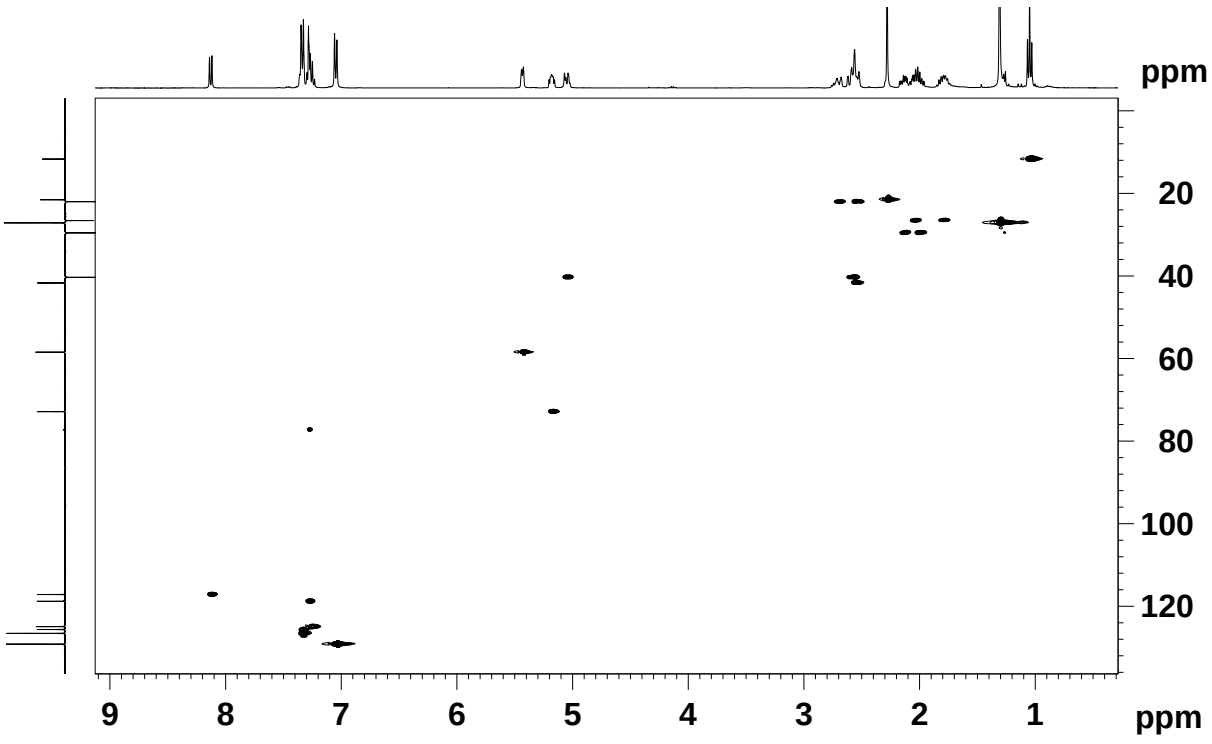
NOESY spectra of (+)-*trans*-**28**



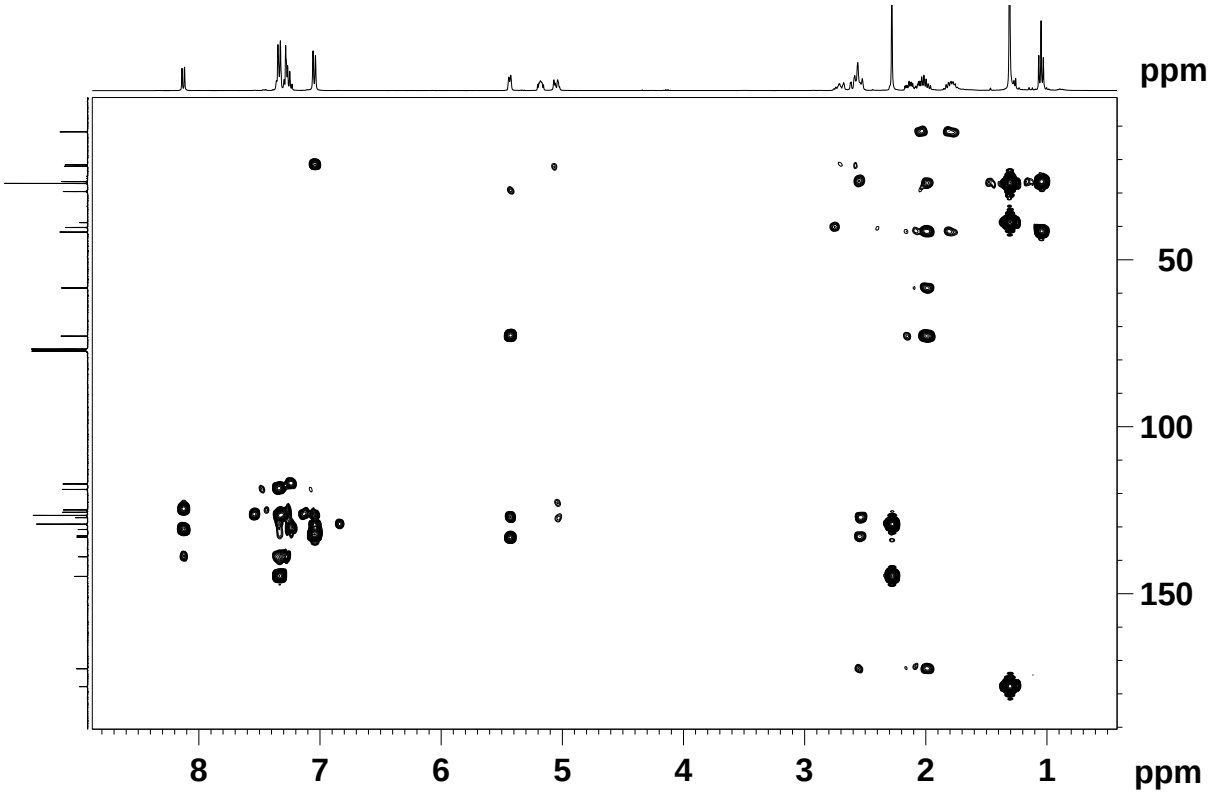
COSY spectra of (+)-*trans*-**28**

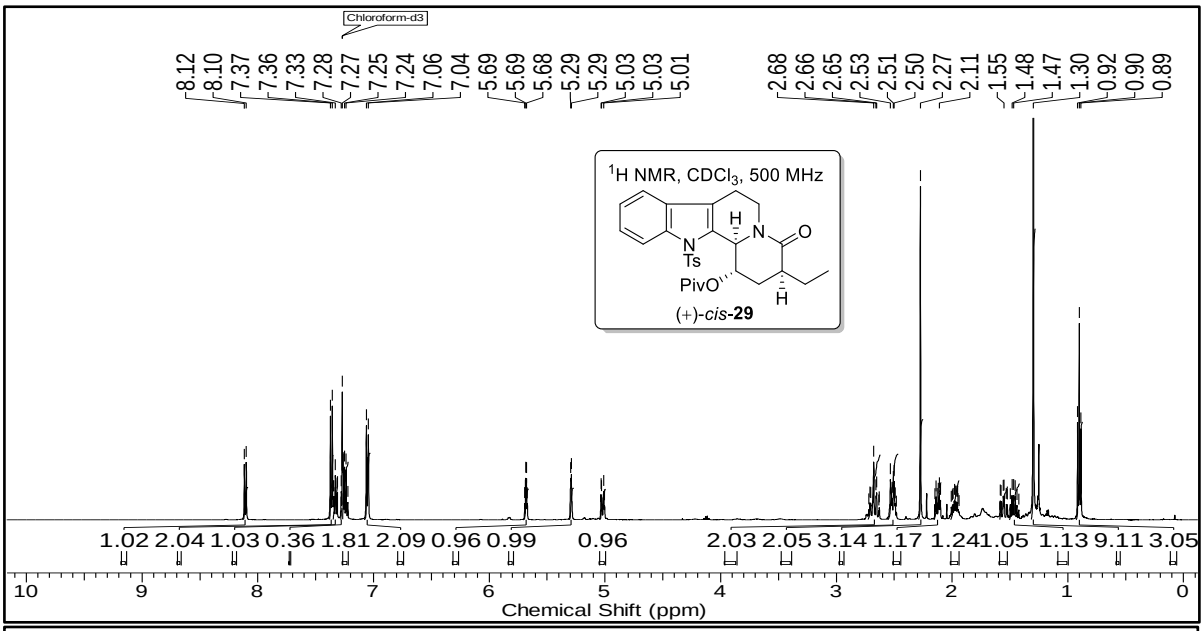


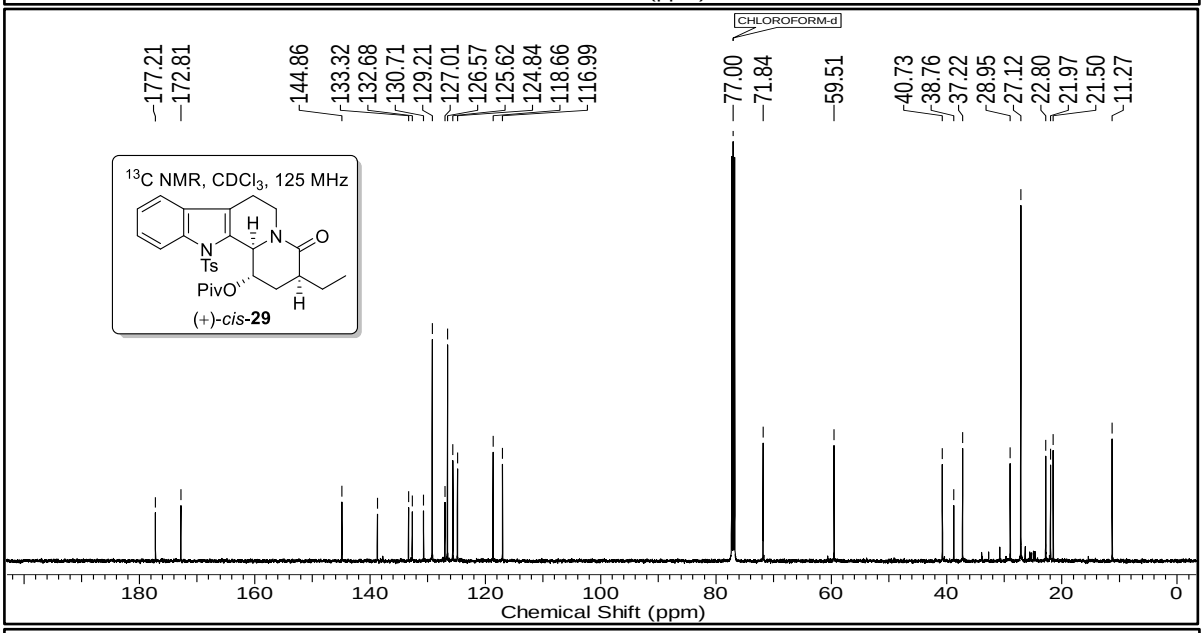
HSQC spectra of (+)-*trans*-**28**

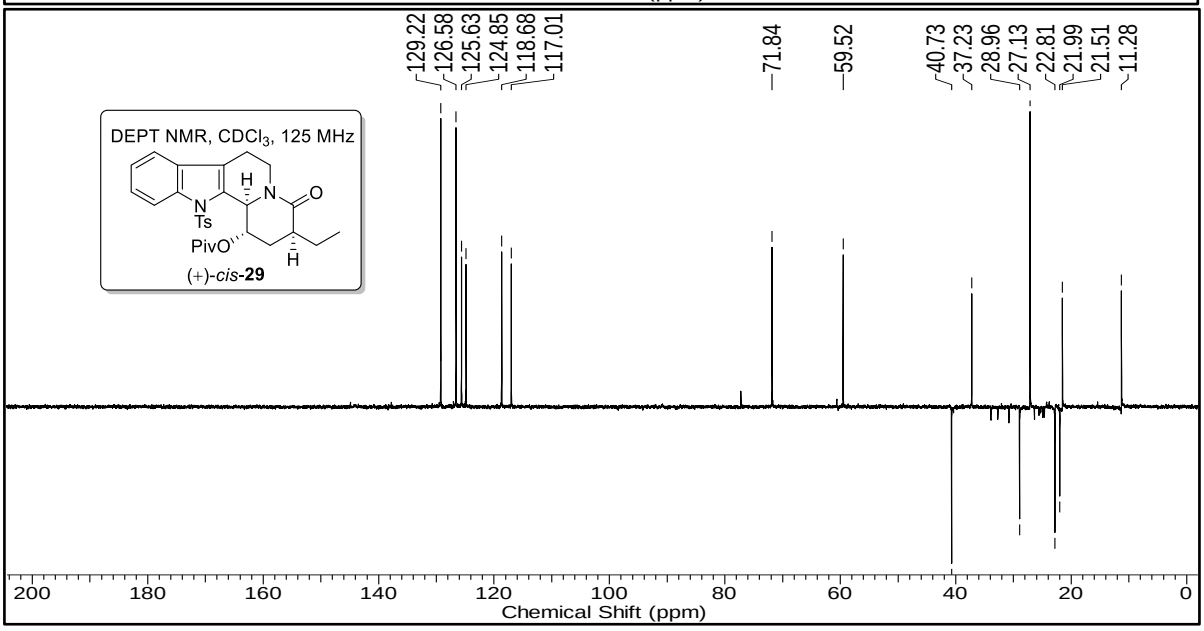


HMBC spectra of (+)-*trans*-**28**

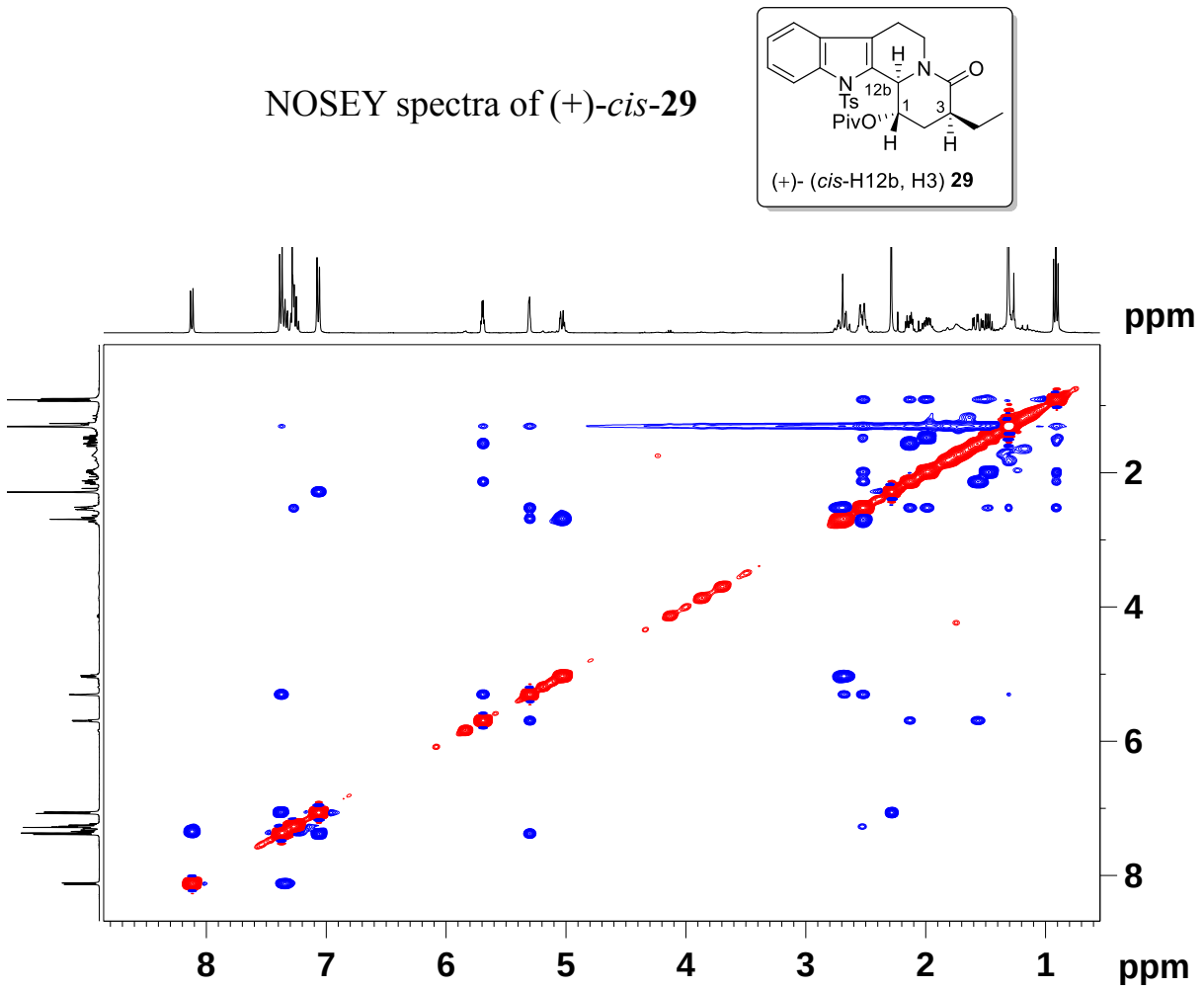



Chloroform-d3
8.12 8.10 7.37 7.36 7.33 7.28 7.27 7.25 7.24 7.06 7.04 5.69 5.69 5.68 5.29 5.29 5.03 5.03 5.01
2.68 2.66 2.65 2.53 2.51 2.50 2.27 2.11 1.55 1.48 1.47 1.30 0.92 0.90 0.89
^{1}H NMR, CDCl$_3$, 500 MHz
(+)-*cis*-**29**
1.02 2.04 1.03 0.36 1.81 2.09 0.96 0.99 0.96 2.03 2.05 3.14 1.17 1.24 1.05 1.13 9.11 3.05
Chemical Shift (ppm)

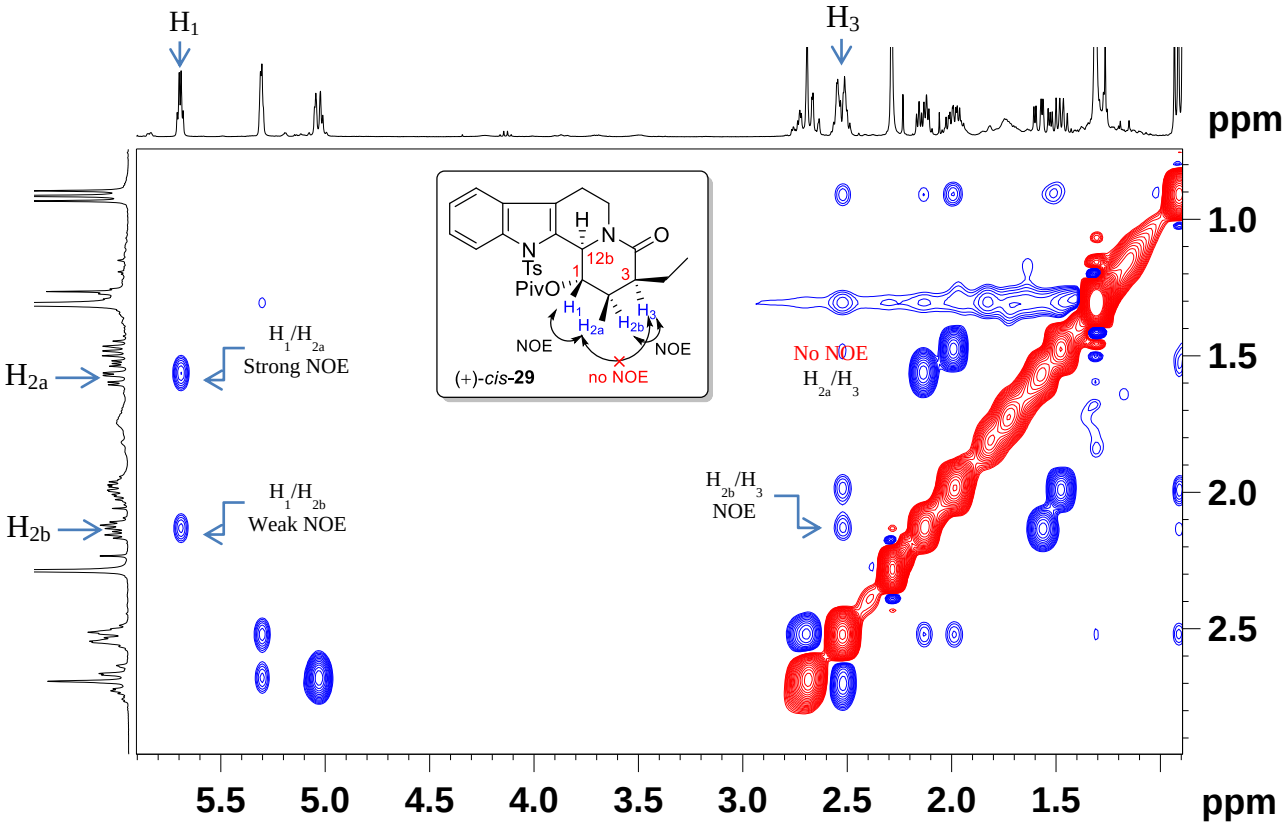

CHLOROFORM-d
177.21 172.81 144.86 133.32 132.68 130.71 129.21 127.01 126.57 125.62 124.84 118.66 116.99
77.00 71.84 59.51 40.73 38.76 37.22 28.95 27.12 22.80 21.97 21.50 11.27
^{13}C NMR, CDCl$_3$, 125 MHz
(+)-*cis*-**29**
Chemical Shift (ppm)


129.22 126.58 125.63 124.85 118.68 117.01
71.84 59.52 40.73 37.23 28.96 27.13 22.81 21.99 21.51 11.28
DEPT NMR, CDCl$_3$, 125 MHz
(+)-*cis*-**29**
Chemical Shift (ppm)

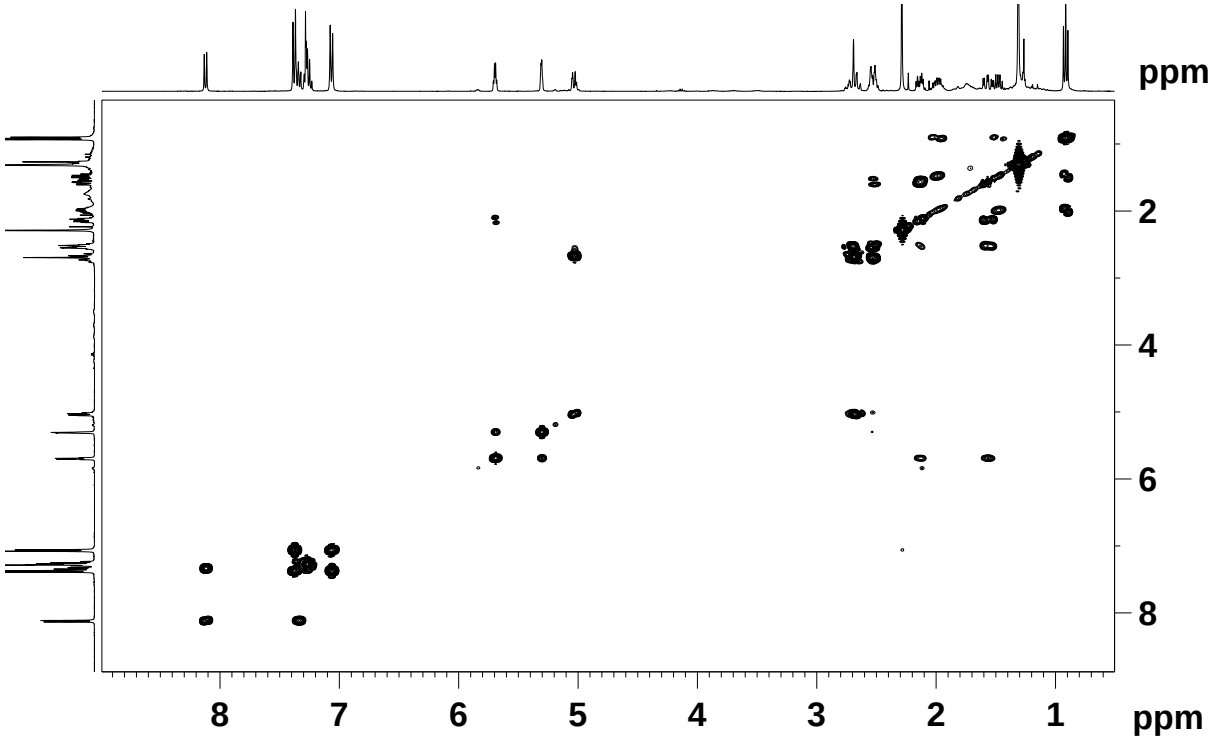
NOSEY spectra of (+)-*cis*-**29**



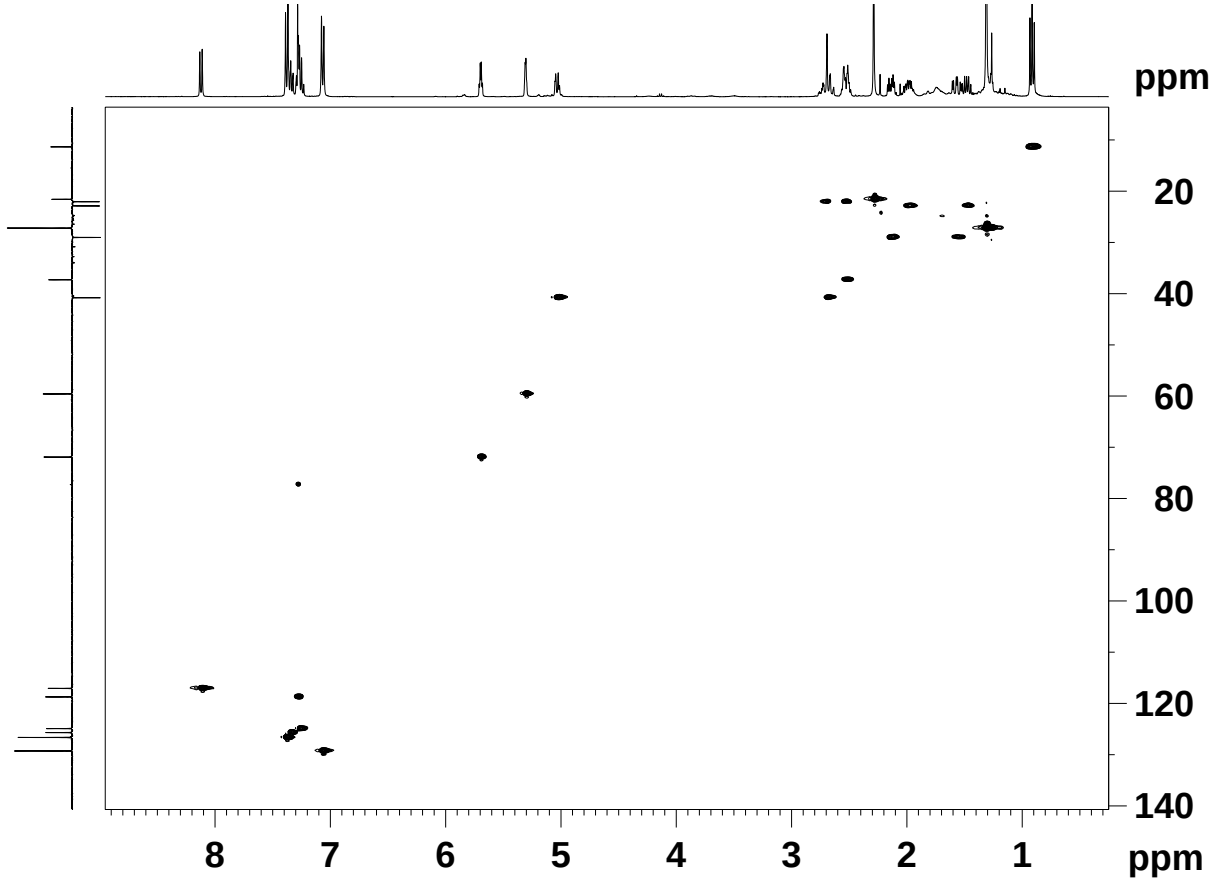
NOSEY spectra of (+)-*cis*-**29**



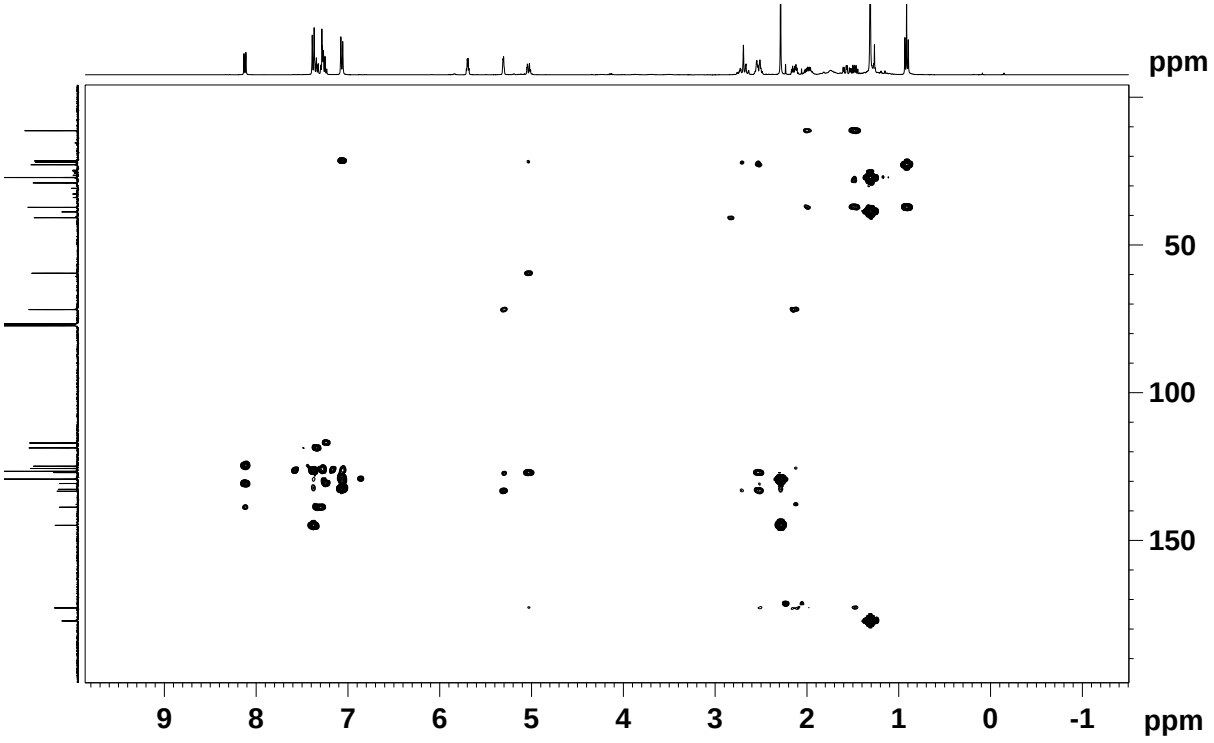
COSY spectra of (+)-*cis*-**29**

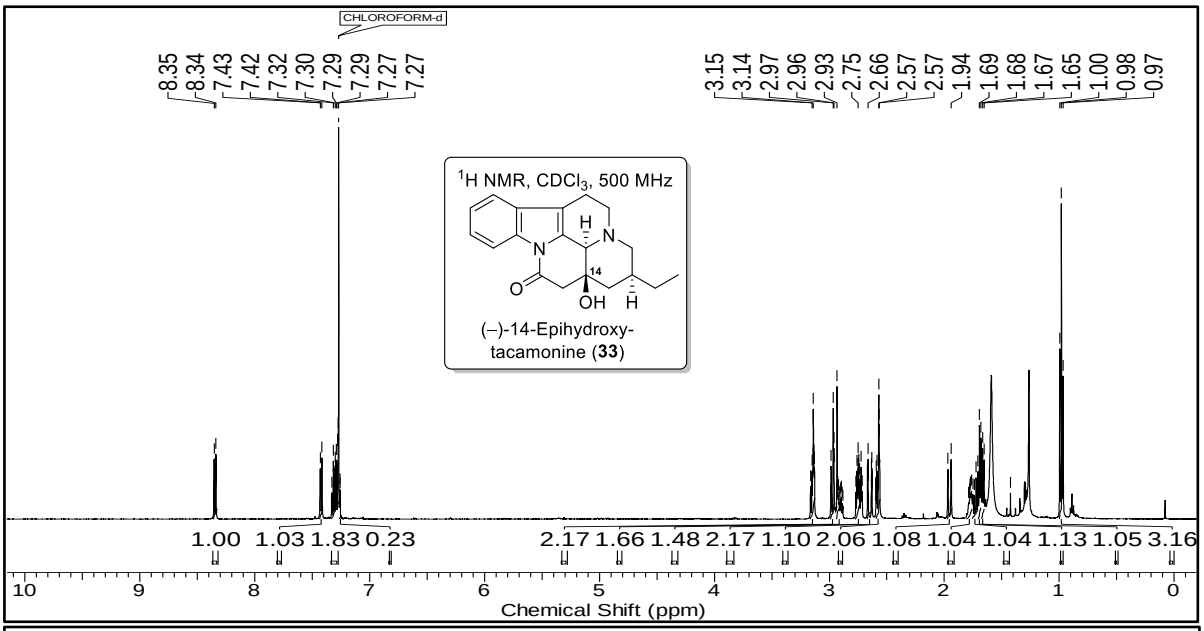


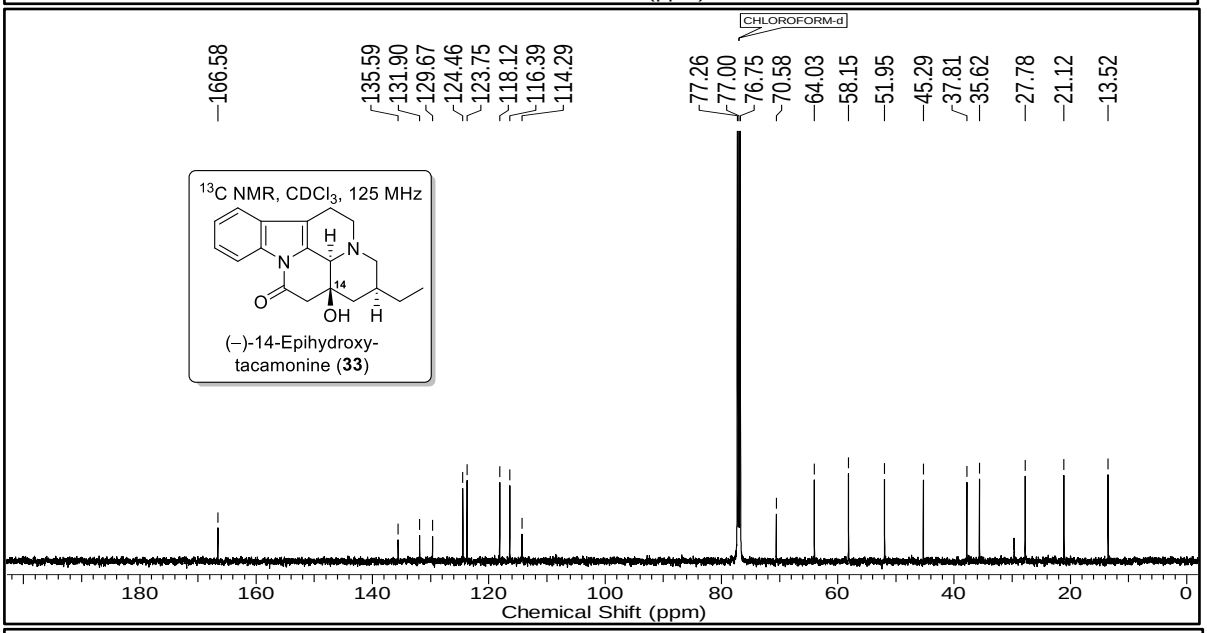
HSQC spectra of (+)-*cis*-**29**

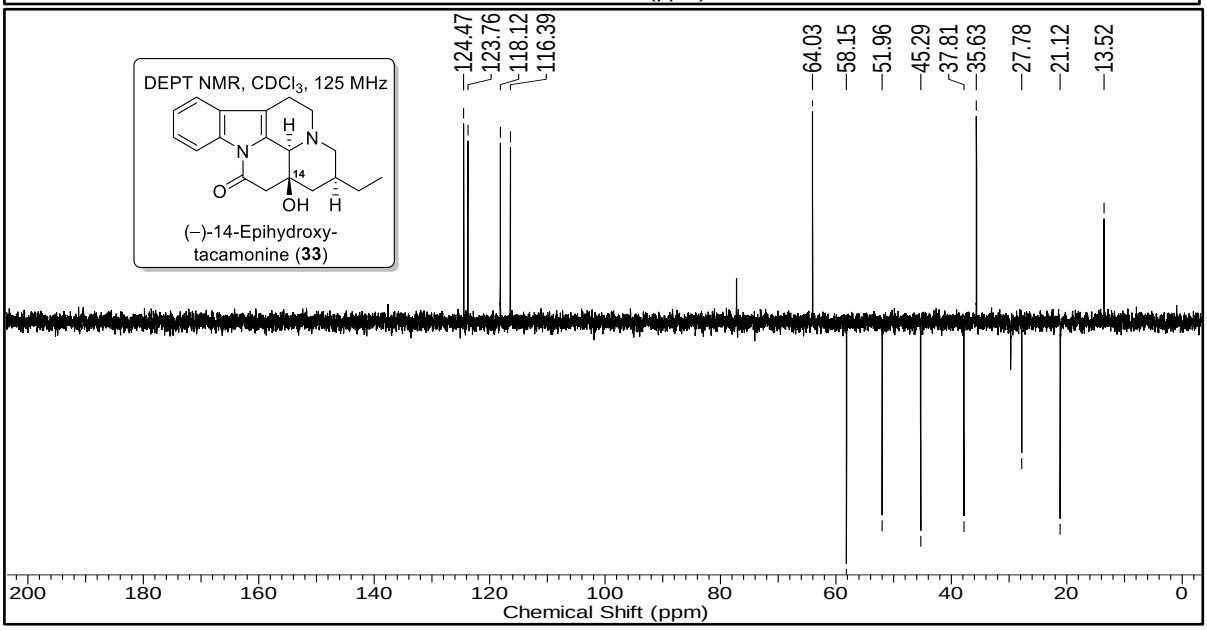


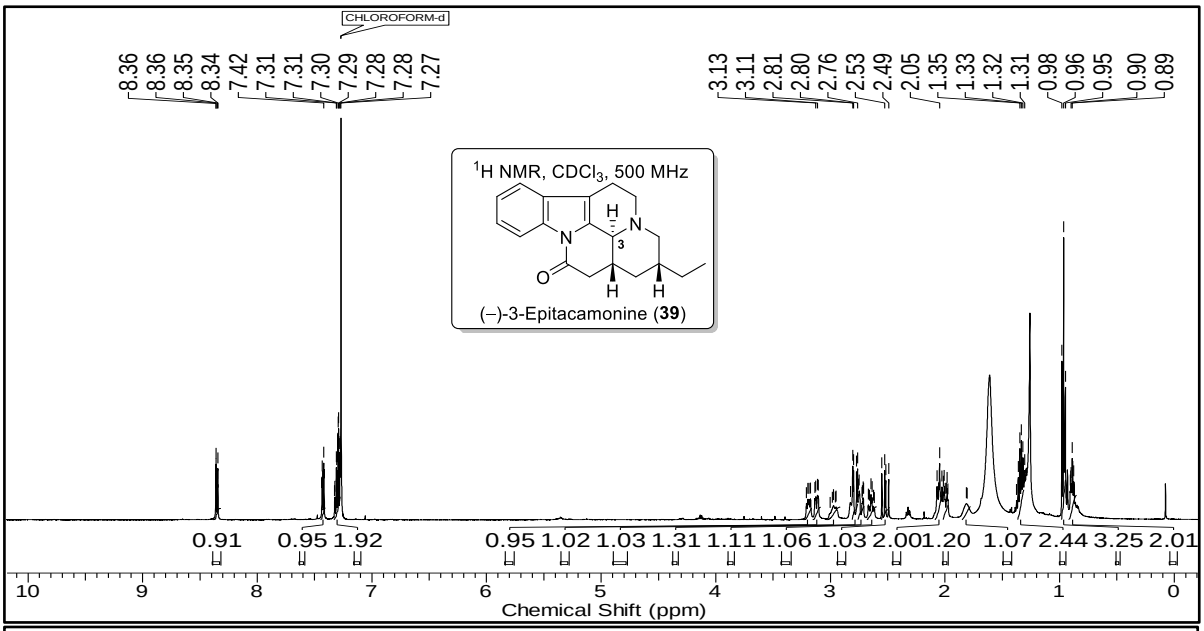
HMBC spectra of (+)-*cis*-**29**

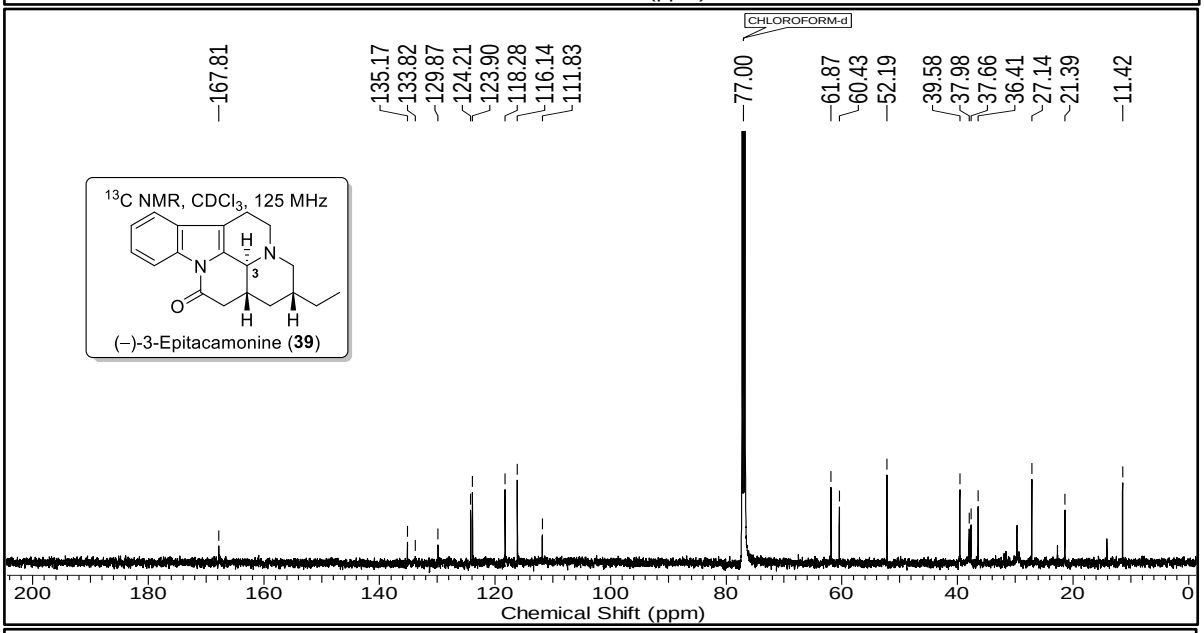


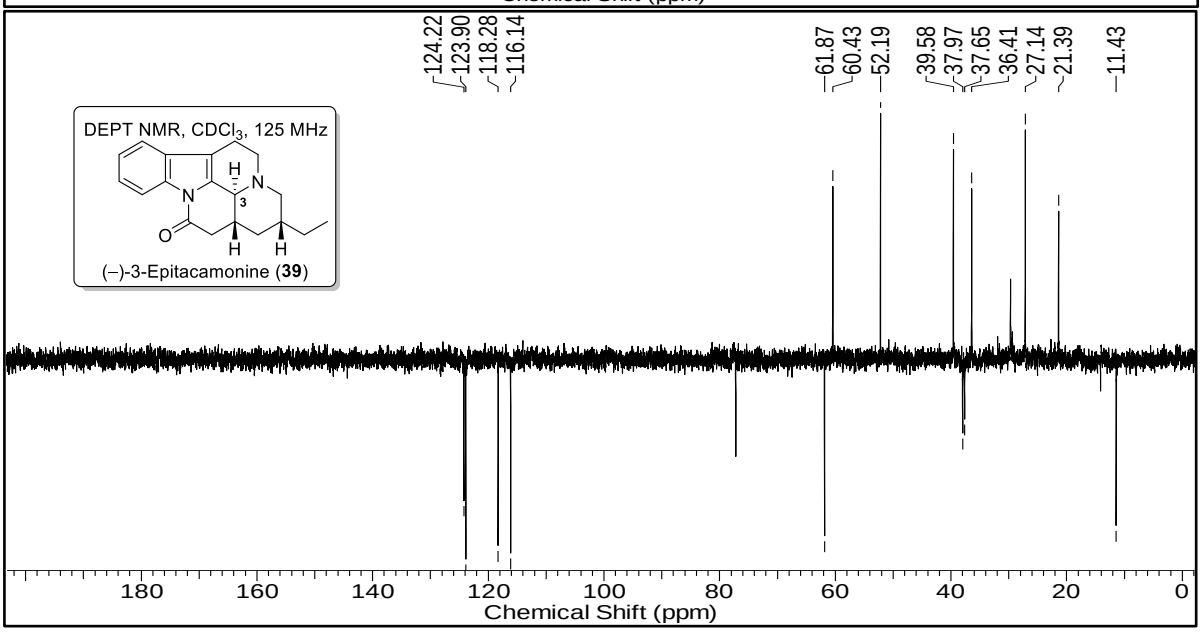

CHLOROFORM-d
8.35 8.34 7.43 7.42 7.32 7.30 7.29 7.29 7.27 7.27
3.15 3.14 2.97 2.96 2.93 2.75 2.66 2.57 2.57 1.94 1.69 1.68 1.67 1.65 1.00 0.98 0.97
^{1}H NMR, CDCl$_3$, 500 MHz
(–)-14-Epihydroxy-tacamonine (33)
1.00 1.03 1.83 0.23 2.17 1.66 1.48 2.17 1.10 2.06 1.08 1.04 1.04 1.13 1.05 3.16
Chemical Shift (ppm)

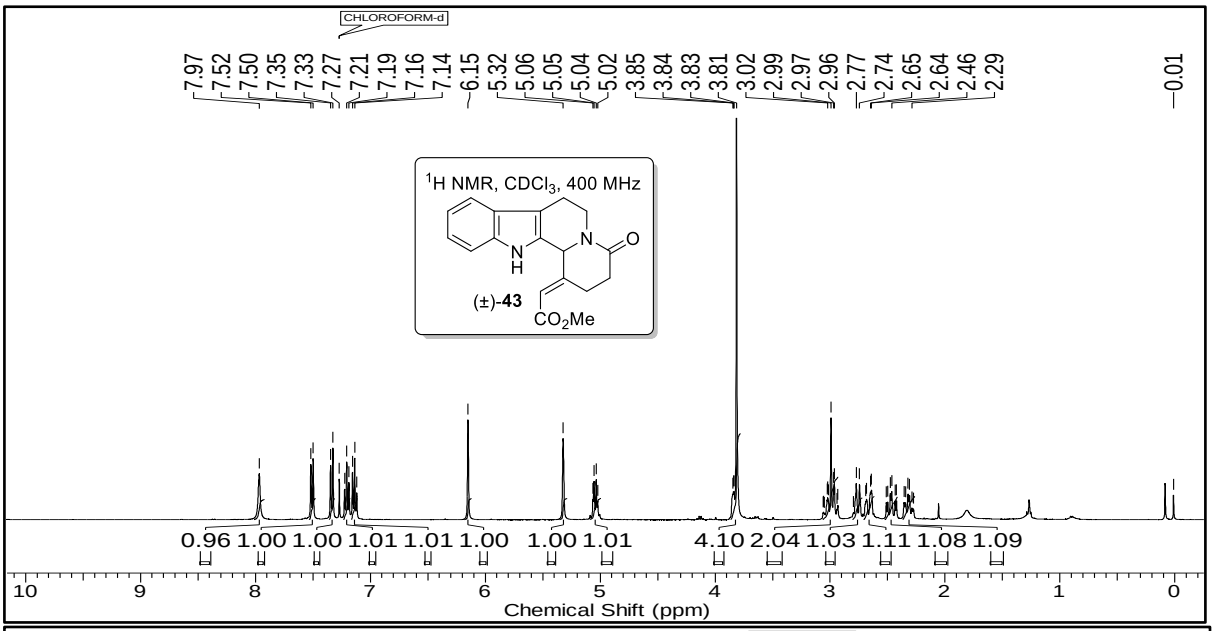

CHLOROFORM-d
166.58 135.59 131.90 129.67 124.46 123.75 118.12 116.39 114.29
77.26 77.00 76.75 70.58 64.03 58.15 51.95 45.29 37.81 35.62 27.78 21.12 13.52
^{13}C NMR, CDCl$_3$, 125 MHz
(–)-14-Epihydroxy-tacamonine (33)
Chemical Shift (ppm)

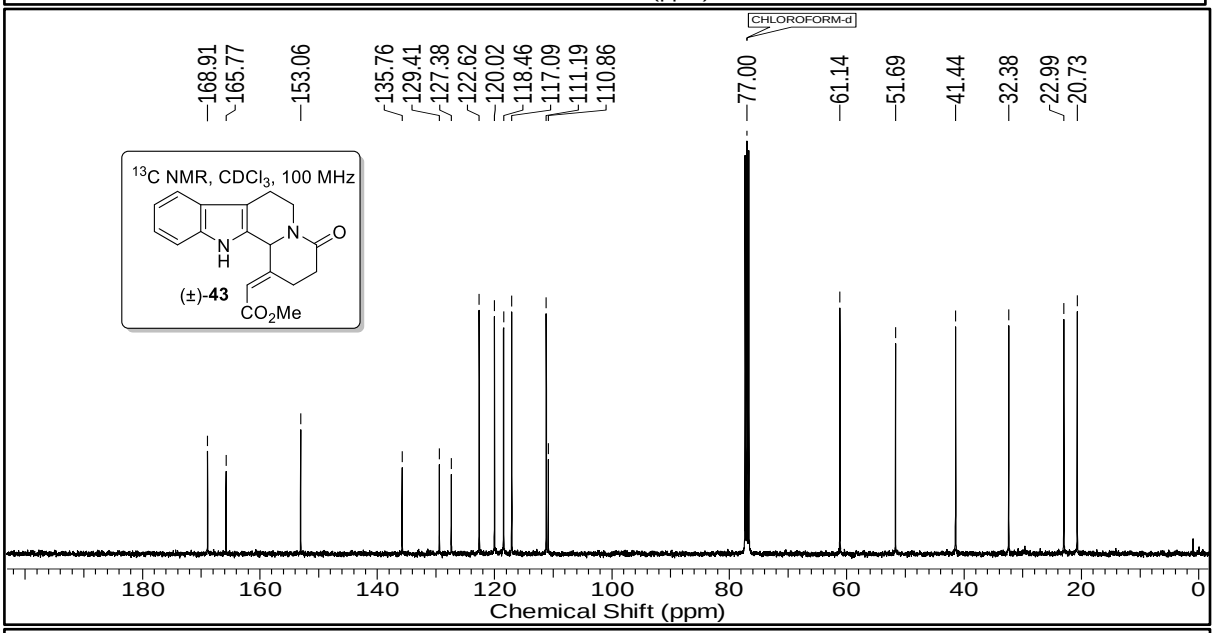

124.47 123.76 118.12 116.39
64.03 58.15 51.96 45.29 37.81 35.63 27.78 21.12 13.52
DEPT NMR, CDCl$_3$, 125 MHz
(–)-14-Epihydroxy-tacamonine (33)
Chemical Shift (ppm)

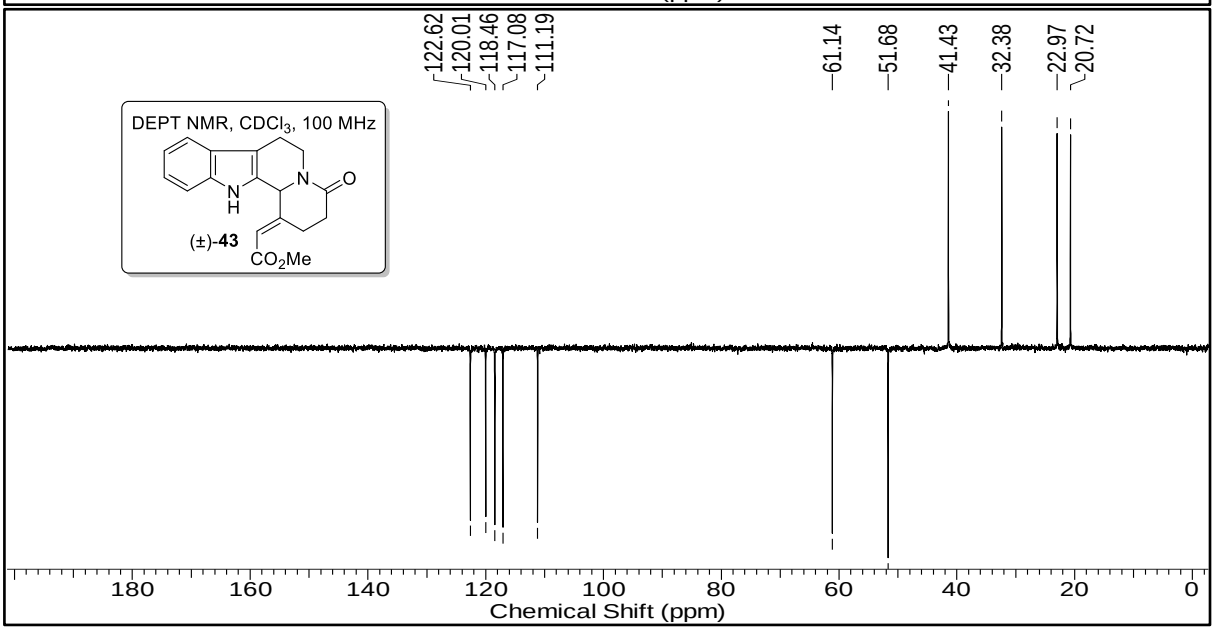

CHLOROFORM-d
8.36 8.36 8.35 8.34 7.42 7.31 7.31 7.30 7.29 7.28 7.28 7.27
3.13 3.11 2.81 2.80 2.76 2.53 2.49 2.05 1.35 1.33 1.32 1.31 0.98 0.96 0.95 0.90 0.89
^{1}H NMR, $CDCl_3$, 500 MHz
(–)-3-Epitacamonine (39)
0.91 0.95 1.92 0.95 1.02 1.03 1.31 1.11 1.06 1.03 2.00 1.20 1.07 2.44 3.25 2.01
Chemical Shift (ppm)


CHLOROFORM-d
167.81 135.17 133.82 129.87 124.21 123.90 118.28 116.14 111.83 77.00 61.87 60.43 52.19 39.58 37.98 37.66 36.41 27.14 21.39 11.42
^{13}C NMR, $CDCl_3$, 125 MHz
(–)-3-Epitacamonine (39)
Chemical Shift (ppm)

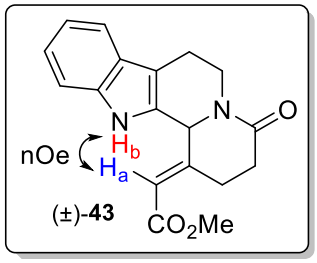

124.22 123.90 118.28 116.14 61.87 60.43 52.19 39.58 37.97 37.65 36.41 27.14 21.39 11.43
DEPT NMR, $CDCl_3$, 125 MHz
(–)-3-Epitacamonine (39)
Chemical Shift (ppm)

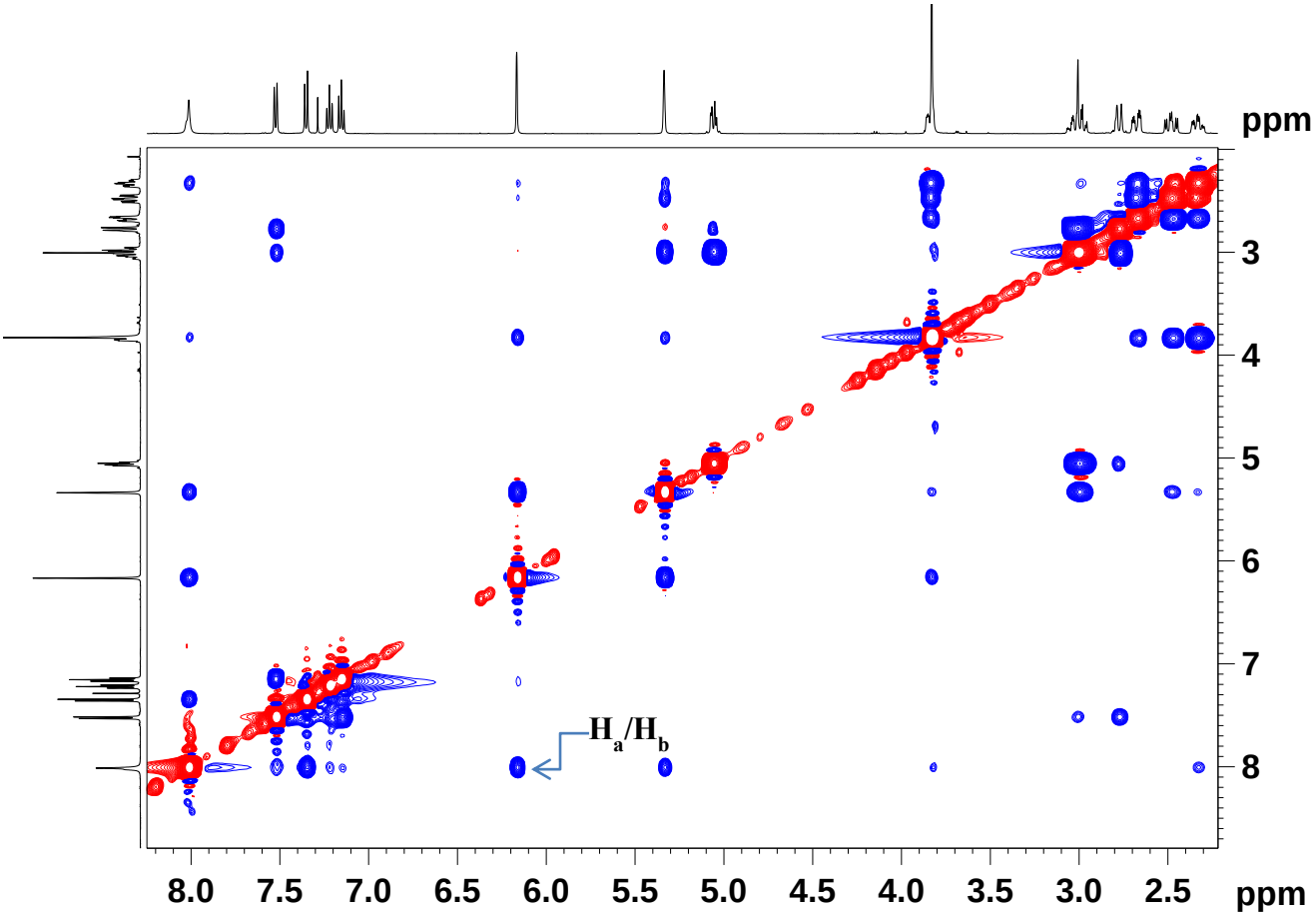

CHLOROFORM-d
7.97 7.52 7.50 7.35 7.33 7.27 7.21 7.19 7.16 7.14 6.15 5.32 5.06 5.05 5.04 5.02 3.85 3.84 3.83 3.81 3.02 2.99 2.97 2.96 2.77 2.74 2.65 2.64 2.46 2.29 0.01
^{1}H NMR, CDCl$_3$, 400 MHz
(±)-43
CO$_2$Me
0.96 1.00 1.00 1.01 1.01 1.00 1.00 1.01 4.10 2.04 1.03 1.11 1.08 1.09
Chemical Shift (ppm)

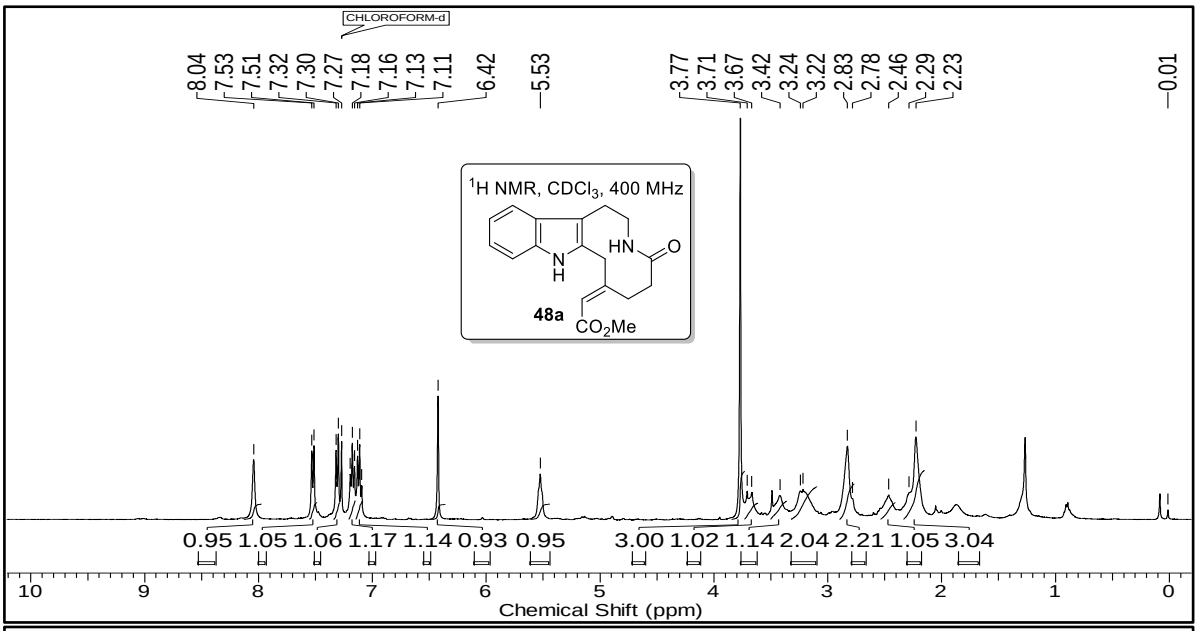

CHLOROFORM-d
168.91 165.77 153.06 135.76 129.41 127.38 122.62 120.02 118.46 117.09 111.19 110.86 77.00 61.14 51.69 41.44 32.38 22.99 20.73
^{13}C NMR, CDCl$_3$, 100 MHz
(±)-43
CO$_2$Me
Chemical Shift (ppm)

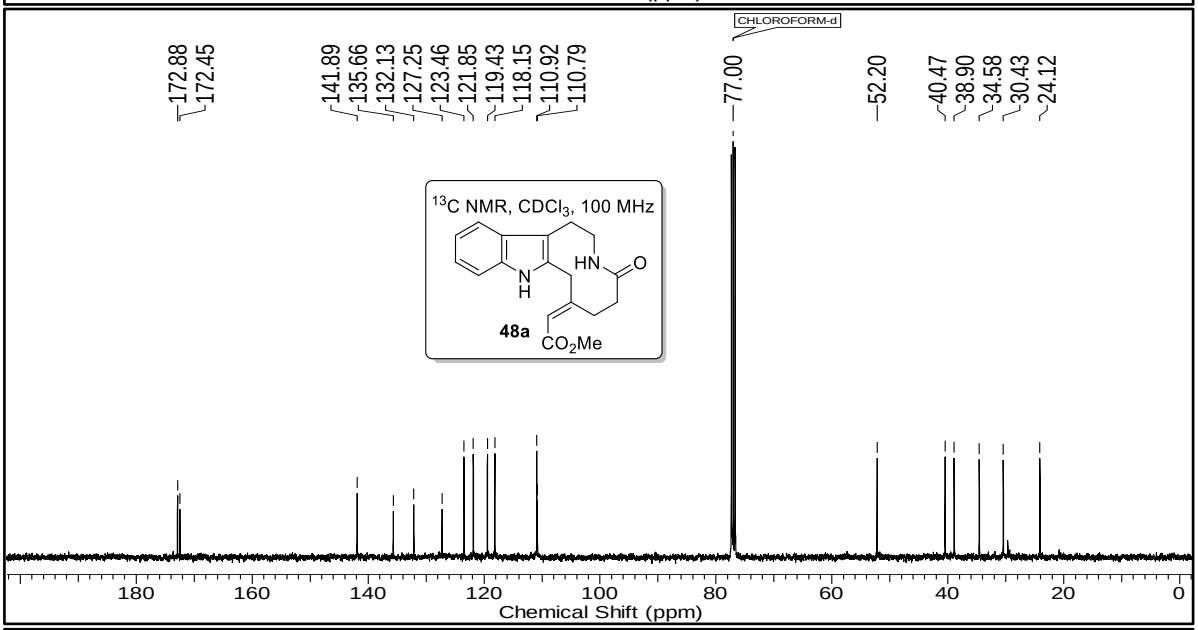

122.62 120.01 118.46 117.08 111.19 61.14 51.68 41.43 32.38 22.97 20.72
DEPT NMR, CDCl$_3$, 100 MHz
(±)-43
CO$_2$Me
Chemical Shift (ppm)

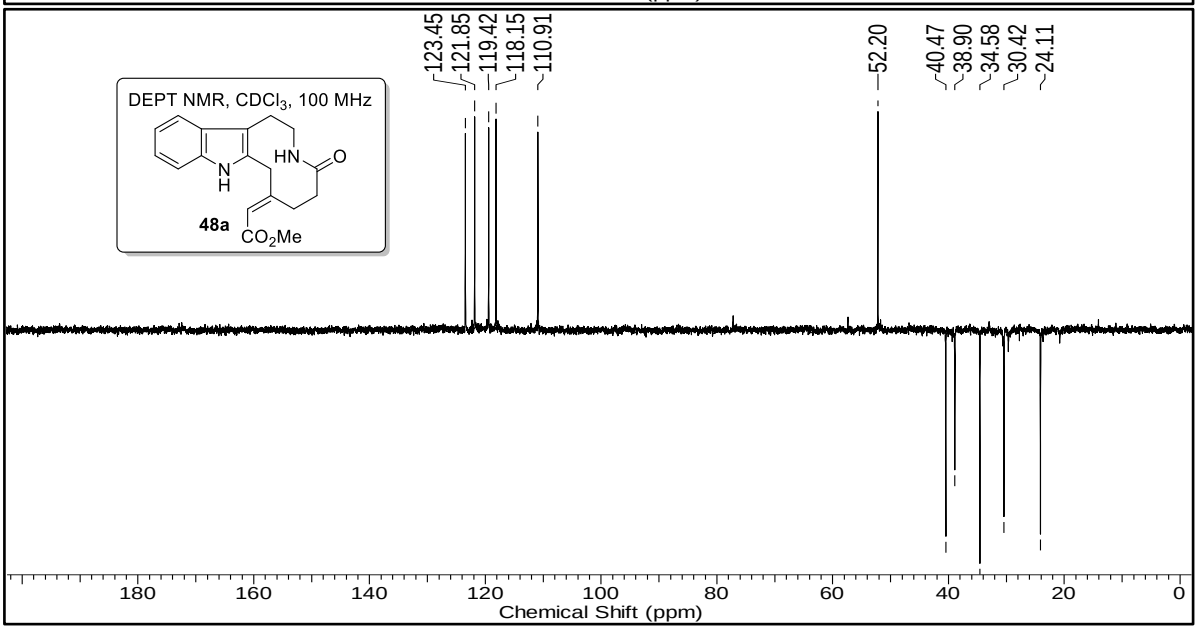
NOSEY spectra of (±)-**43**

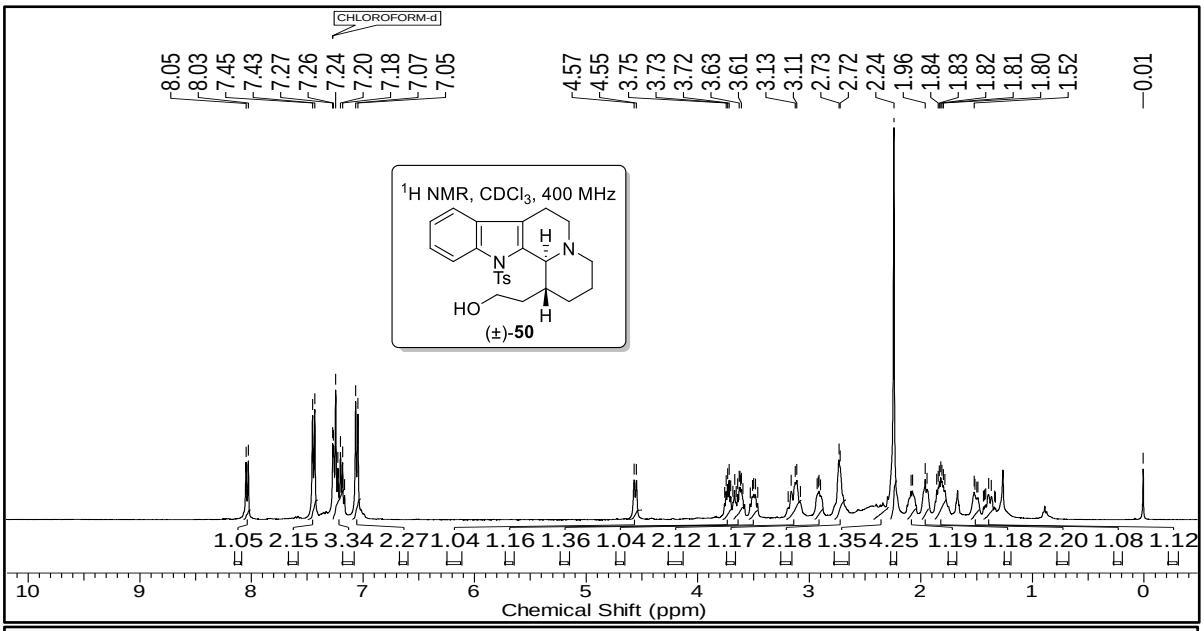


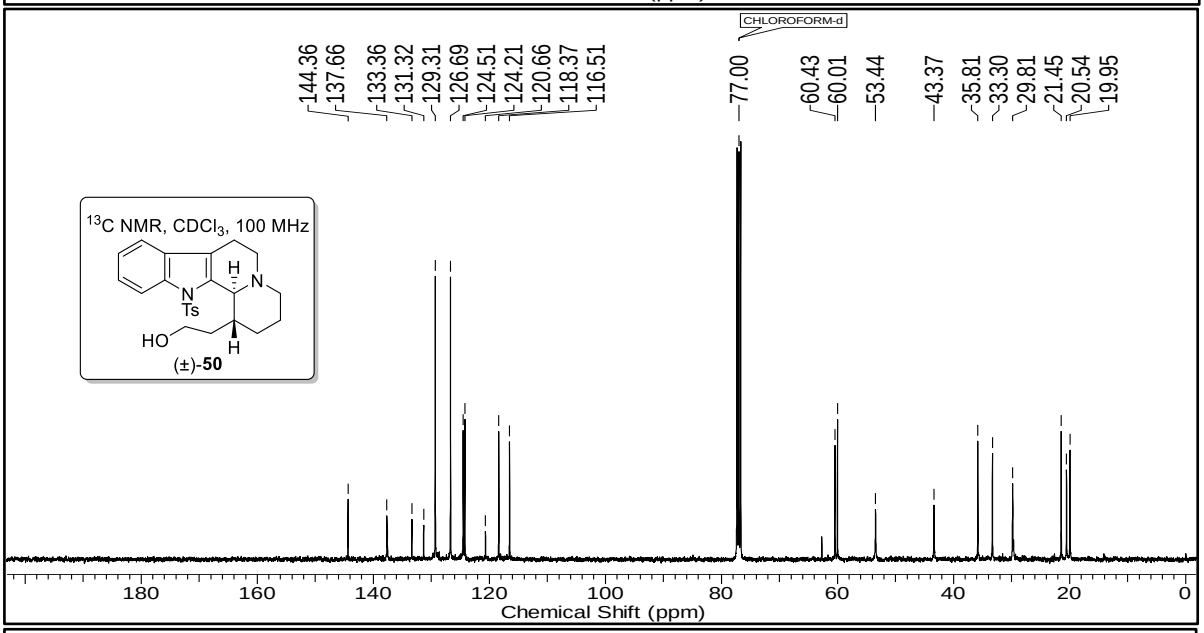


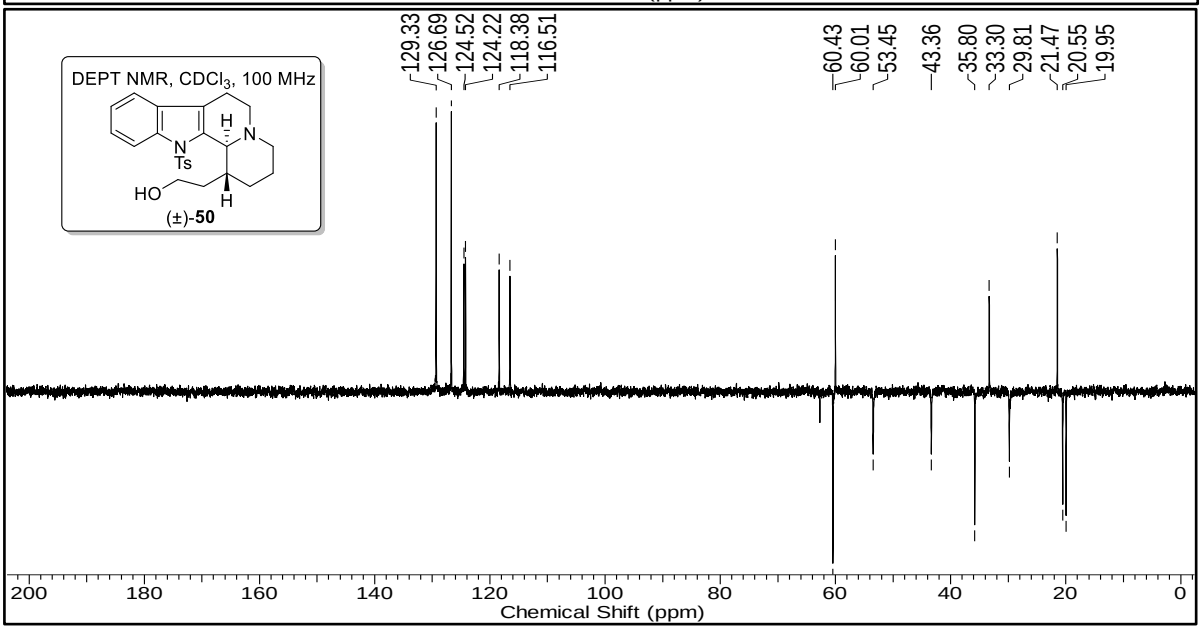

CHLOROFORM-d
8.04 7.53 7.51 7.32 7.30 7.27 7.18 7.16 7.13 7.11 6.42 5.53 3.77 3.71 3.67 3.42 3.24 3.22 2.83 2.78 2.46 2.29 2.23 0.01
^{1}H NMR, CDCl$_3$, 400 MHz
48a
0.95 1.05 1.06 1.17 1.14 0.93 0.95 3.00 1.02 1.14 2.04 2.21 1.05 3.04
Chemical Shift (ppm)

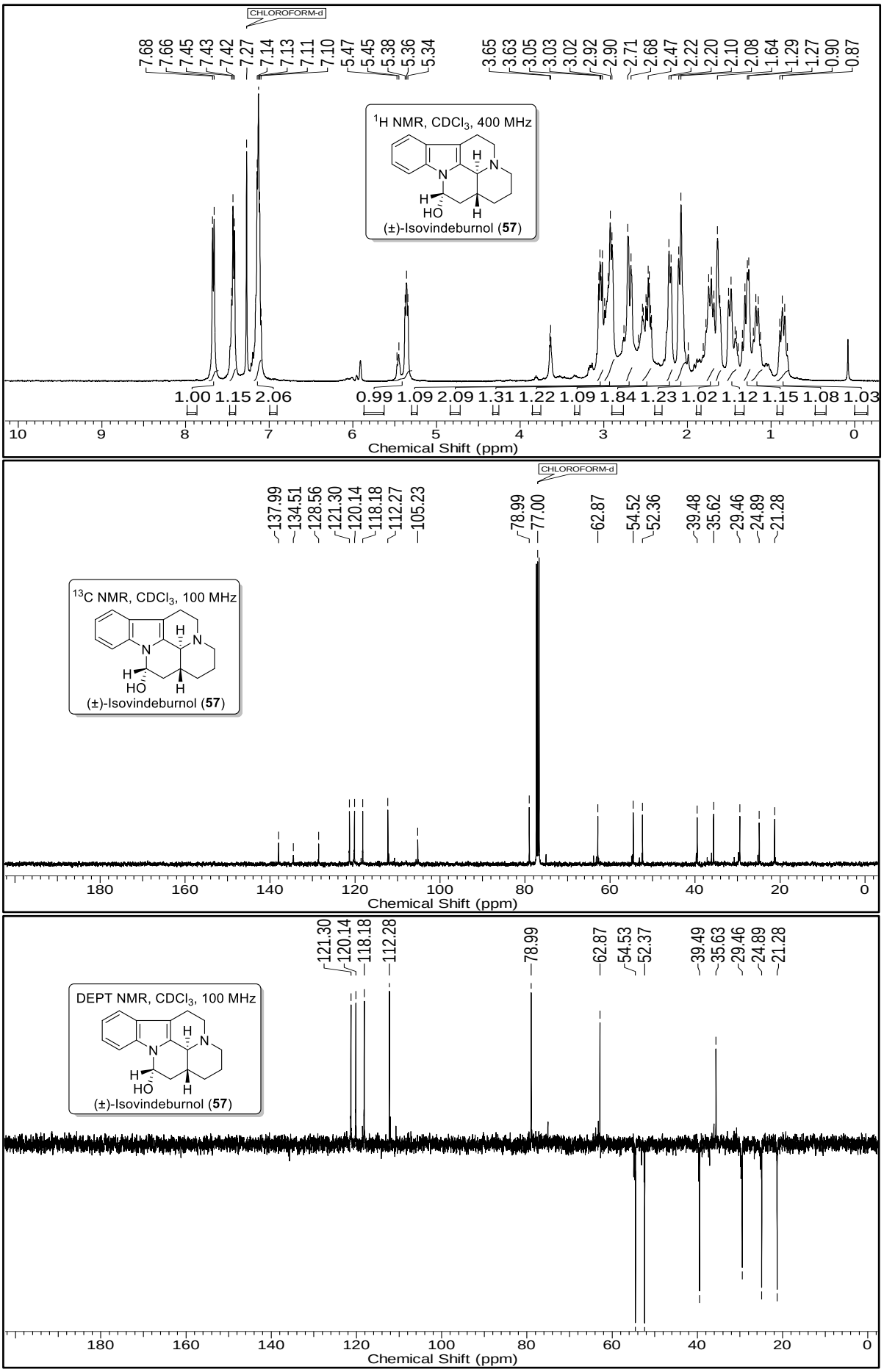

CHLOROFORM-d
172.88 172.45 141.89 135.66 132.13 127.25 123.46 121.85 119.43 118.15 110.92 110.79 77.00 52.20 40.47 38.90 34.58 30.43 24.12
^{13}C NMR, CDCl$_3$, 100 MHz
48a
Chemical Shift (ppm)


123.45 121.85 119.42 118.15 110.91 52.20 40.47 38.90 34.58 30.42 24.11
DEPT NMR, CDCl$_3$, 100 MHz
48a
Chemical Shift (ppm)


CHLOROFORM-d
8.05 8.03 7.45 7.43 7.27 7.26 7.24 7.20 7.18 7.07 7.05
4.57 4.55 3.75 3.73 3.72 3.63 3.61 3.13 3.11 2.73 2.72 2.24 1.96 1.84 1.83 1.82 1.81 1.80 1.52
0.01
^{1}H NMR, $CDCl_3$, 400 MHz
(±)-50
1.05 2.15 3.34 2.27 1.04 1.16 1.36 1.04 2.12 1.17 2.18 1.35 4.25 1.19 1.18 2.20 1.08 1.12
Chemical Shift (ppm)

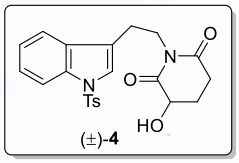

CHLOROFORM-d
144.36 137.66 133.36 131.32 129.31 126.69 124.51 124.21 120.66 118.37 116.51
77.00
60.43 60.01 53.44 43.37 35.81 33.30 29.81 21.45 20.54 19.95
^{13}C NMR, $CDCl_3$, 100 MHz
(±)-50
Chemical Shift (ppm)


129.33 126.69 124.52 124.22 118.38 116.51
60.43 60.01 53.45 43.36 35.80 33.30 29.81 21.47 20.55 19.95
DEPT NMR, $CDCl_3$, 100 MHz
(±)-50
Chemical Shift (ppm)

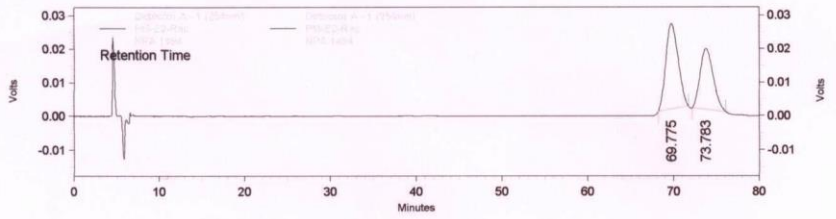

CHLOROFORM-d
7.68 7.66 7.45 7.43 7.42 7.27 7.14 7.13 7.11 7.10 5.47 5.45 5.38 5.36 5.34
3.65 3.63 3.05 3.03 3.02 2.92 2.90 2.71 2.68 2.47 2.22 2.20 2.10 2.08 1.64 1.29 1.27 0.90 0.87
^{1}H NMR, CDCl$_3$, 400 MHz
(±)-Isovindeburnol (57)
1.00 1.15 2.06 0.99 1.09 2.09 1.31 1.22 1.09 1.84 1.23 1.02 1.12 1.15 1.08 1.03
Chemical Shift (ppm)
CHLOROFORM-d
137.99 134.51 128.56 121.30 120.14 118.18 112.27 105.23
78.99 77.00 62.87 54.52 52.36 39.48 35.62 29.46 24.89 21.28
^{13}C NMR, CDCl$_3$, 100 MHz
(±)-Isovindeburnol (57)
Chemical Shift (ppm)
121.30 120.14 118.18 112.28 78.99 62.87 54.53 52.37 39.49 35.63 29.46 24.89 21.28
DEPT NMR, CDCl$_3$, 100 MHz
(±)-Isovindeburnol (57)
Chemical Shift (ppm)

HPLC profile of (±)-4

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1494
User: System
Acquired: 3/19/14 6:14:11 PM
Printed: 3/19/14 7:36:07 PM
Sample Name PM-E2-Rac



(±)-**4**

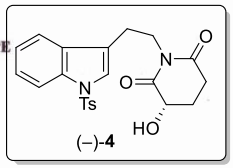


Detector A - 1 (254nm)

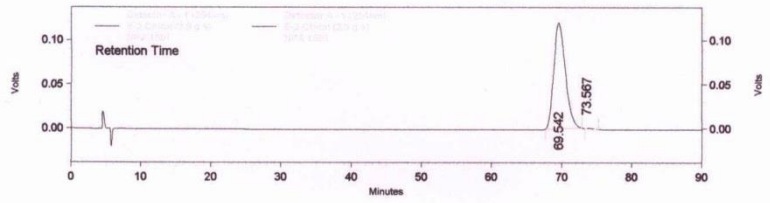
Retention Time	C Area	Area %
69.775	2558321	56.764
73.783	1948621	43.236
Totals	4506942	100.000

HPLC profile of (–)-4

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1501
User: System
Acquired: 3/26/14 5:18:54 PM
Printed: 3/26/14 7:10:20 PM
Sample Name E-2-Chiral (3.9 g s)



(–)-**4**

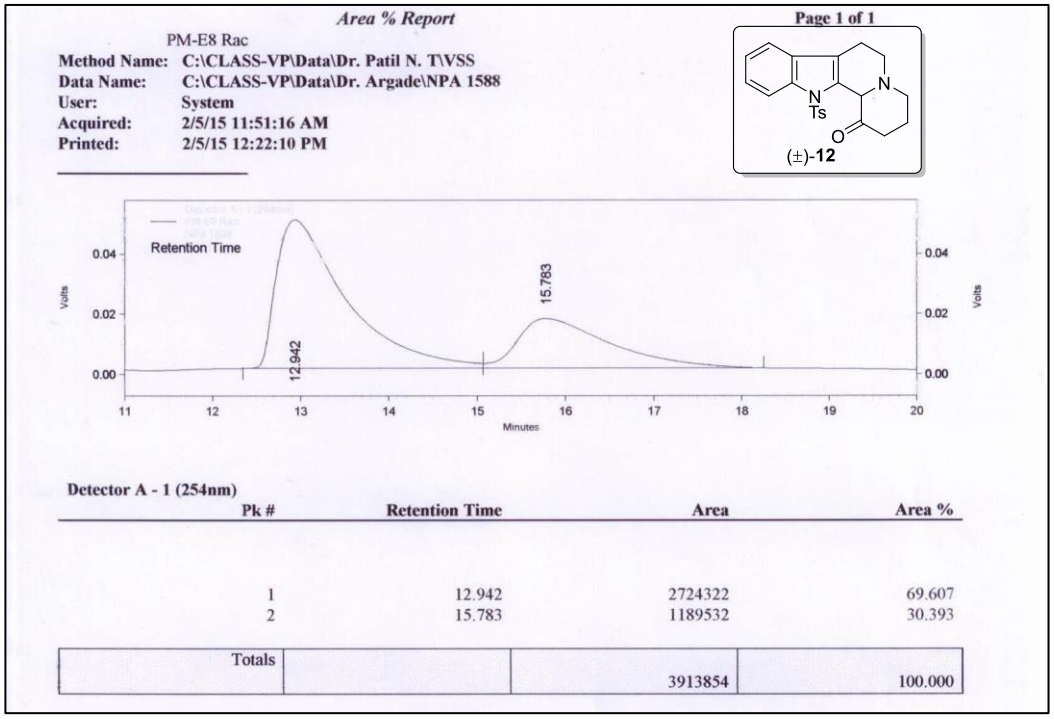


Detector A - 1 (254nm)

Retention Time	C Area	Area %
69.542	13780058	99.836
73.567	22598	0.164
Totals	13802656	100.000

Project Leader: Dr. N. P. Argade
Column : Kromasil 5-CelluCoat (250 x 4.6 mm)
Mobile Phase : EtOH: n-Hexane: TFA (08:92:0.1)
Wavelength : 254 nm
Flow Rate : 0.7 ml/min
Conc. : 1.0 mg/ 1.0 ml
Inj. Vol. : 5 µl

HPLC profile of (±)-12



Area % Report

PM-E8 Rac

Method Name: C:\CLASS-VP\Data\Dr. Patil N. T\VSS
Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1588
User: System
Acquired: 2/5/15 11:51:16 AM
Printed: 2/5/15 12:22:10 PM

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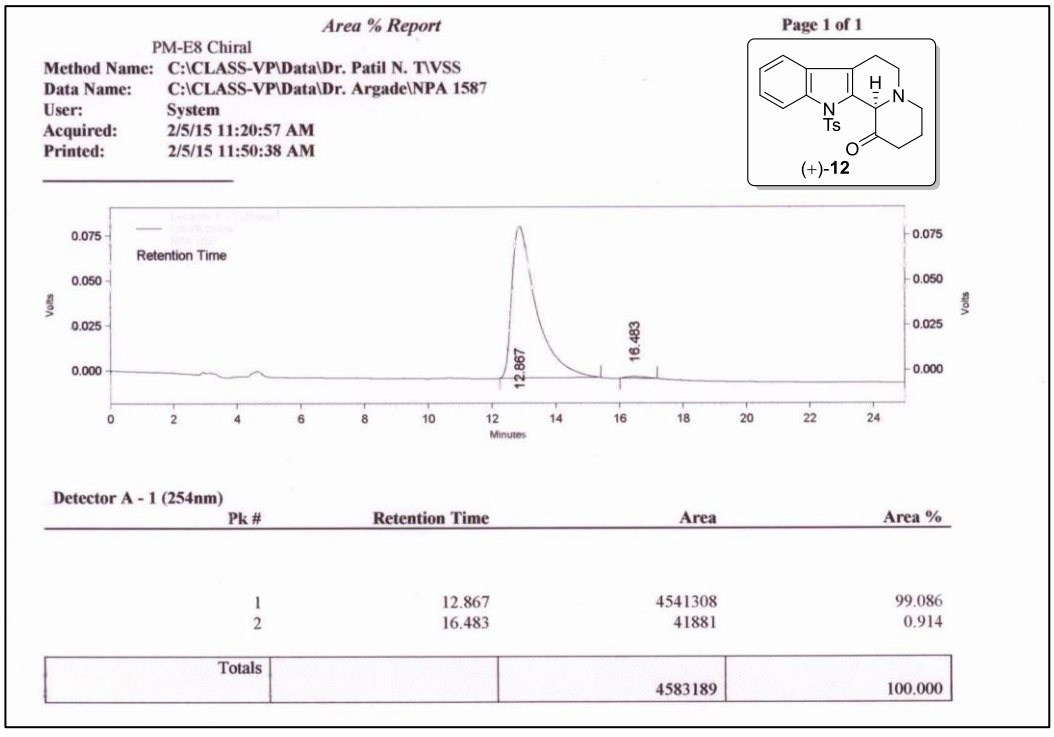
(±)-12

Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	12.942	2724322	69.607
2	15.783	1189532	30.393
Totals		3913854	100.000

HPLC profile of (+)-12



Area % Report

PM-E8 Chiral

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Data Name: C:\CLASS-VP\Data\Dr. Argade\NPA 1587
User: System
Acquired: 2/5/15 11:20:57 AM
Printed: 2/5/15 11:50:38 AM

Page 1 of 1

(+)-12

Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	12.867	4541308	99.086
2	16.483	41881	0.914
Totals		4583189	100.000

Project Leader: Dr. N. P. Argade
Column : ChiralCel OD-H (250 x 4.6 mm)
Mobile Phase : EtOH: Pet Ether: TFA (20:80:0.1)
Wavelength : 254 nm
Flow Rate : 1.0 ml/min
Conc. : 1.0 mg/ 1.0 ml
Inj. Vol. : 2 µl

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Overall Conclusion and Perspective

Present dissertation describes our efficient approach towards the synthesis of bioactive indole alkaloids and their important analogues using cyclic anhydrides and cyclic imides as potential starting materials. Indole alkaloids encompass very fascinating structural architects and their remarkable bioactivity has incited a lot of activity in the synthetic community towards their total synthesis. Many of them, such as reserpine, vincristine, vinblastine, arbidol and ergotamine are used in medicine. Concise literature account on synthesis of various indole alkaloids reported by different research groups using cyclic anhydrides and cyclic imides as potential synthon has been presented.

We have presented a brief literature account on the isolation, bioactivity and synthesis of tetrahydro-β-carboline harmicine, arborescidines A–C and deplancheine. We have described an efficient use of (R)/(S)-acetoxysuccinimide/glutarimide derivative as a chiral building block for the stereoselective synthesis of tetrahydro-β-carboline alkaloids.We have reported synthesis of (+)-harmicine using highly stereoselective N-acyliminium ion cyclization as a key step. We have also accomplished an efficient enantioselective synthesis of (S)-desbromoarborescidines A–C and formal synthesis of (S)-deplancheine using highly diastereoselective reductive intramolecular cyclization of (S)-acetoxyglutarimide derivative and exchange of nitrogen regioselectivity. We feel that in the present approach, the witnessed intramolecular N → O 1,5-migration of Boc-group is significant from a basic chemistry point of view. In this approach, we have used chiral acetoxy group as a stereoselectivity handle & later it was disconnected.

We have also presented a concise literature account on the isolation, bioactivity and synthesis of indole alkaloids eburnamonine, eburnaminol, larutensine, melohenine B, tacamonine and vindeburnol. We have demonstrated diastereoselective formal synthesis of vinca-eburna alkaloids (±)-eburnamonine, (±)-eburnaminol, (±)-larutensine. We have also accomplished enantioselective synthesis of (–)-desethyleburnamonine, (–)-3-epitacamonine and (–)-vindeburnol. We have reported for the first time where the lactam carbonyl acts as a stereochemical switch to alter the diastereoselectivity in ester-aldol reactions of hexahydroindolo[2,3-a]quinilizinones. In the present approach, we have used the chiral acetoxy group for two different roles. At first it acted as a stereoselectivity handle, later it was used as a functional group. We feel that our present protocol will be

useful to synthesize several natural and unnatural indole based structurally interesting and biologically important architectures for SAR studies.

In short, we have accomplished a concise and efficient synthesis of (+)-harmicine, (S)-desbromoarborescidines A–C, (S)-deplancheine, (±)-eburnamonine, (±)-eburnaminol, (±)-larutensine, (–)-desethyleburnamonine, (–)-3-epitacamonine and (–)-vindeburnol using cyclic anhydrides and cyclic imides.

All these studies bestowed us a nice opportunity for learning a lot of new basic and applied chemistry not just from our work but also from the vast literature in this field. We also feel that the approaches which we have developed are quite general and biogenetic in nature and would be useful in designing several important complex natural products and natural product hybrids for structure activity relationship studies. A close look at the recent literature also revealed that the histogram of the indole alkaloid chemistry is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed indole based compounds would maintain the high positive slope in the present day world of medicinal and synthetic chemistry. In our opinion, a combination of natural and synthetic indole containing compounds would serve as a launching pad to fight against new generation diseases. Finally, on the basis of exposure to the literature of indole alkaloid chemistry and our contribution to the same, it can be said with assurance that this interesting discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry in future.

List of Publications

1. Enantioselective Total Synthesis of Desbromoarborescidines A–C and the Formal Synthesis of (*S*)-Deplancheine
   Mondal, P.; Argade, N. P. *J. Org. Chem.* **2013**, *78*, 6802.

2. Synthesis of (+)-Harmicine
   Mondal, P.; Argade, N. P. *Synthesis* **2014**, *46*, 2591.

3. Lactam Carbonyl as a Switch to Alter the Stereoselectivity in Ester Aldol Reactions of Hexahydroindoloquinolizinones: Diversity Oriented Stereoselective Collective Synthesis of Bioactive Vinca, Eburnan and Tacaman Alkaloids and Analogues Thereof
   Mondal, P.; Argade, N. P. *Manuscript under review*.

Erratum

Erratum