Studies on Total Synthesis of Bioactive Indole Alkaloids Subincanadine A-G

Thesis Submitted to AcSIR

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DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

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Dedicated to

My Parents and Teachers

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **Studies on Total Synthesis of Bioactive Indole Alkaloids Subincanadine A-G** submitted by **Mr. Manojkumar Gulabrao Kalshetti** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **Studies on Total Synthesis of Bioactive Indole Alkaloids Subincanadine A-G** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph. D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. N. P. Argade**, Senior Principal Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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CONTENTS

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…Manojkumar

ABBREVATIONS

Ac_2O	Acetic anhydride
AcOH	Acetic Acid
AcCl	Acetyl chloride
$AlCl_3$	Aluminium chloride
AlH_3	Aluminium hydride/Alane
AllylMgCl	Allylmagnesium chloride
AllylBr	Allyl bromide
n-BuLi	*n*-Butyllithium
t-BuOH	*tert*-Butyl alcohol
Boc_2O	Di-*tert*-butyl dicarbonate
CH_2O	Formaldehyde
CH_3CHO	Acetaldehyde
CH_3CN	Acetonitrile
$CHCl_3$	Chloroform
CuI	Copper(I) iodide
CuBr	Copper(I) bromide
CuCN	Copper(I) cyanide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulphoxide
DMF	*N*,*N*-Dimethylformamide
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DIPEA	*N*,*N*-Diisopropylethylamine
DIBAL-H	Diisobutylaluminium hydride
DEPT	Distortionless enhancement by polarization transfer
2 D NMR	Two-dimensional nuclear magnetic resonance spectroscopy
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethyl acetate
Et_3N	Triethylamine
g	Grams
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HCl	Hydrochloric acid
IR	Infra-red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
LiHMDS	Lithium hexamethyldisilazide
LDA	Lithium diisopropylamide
LAH	Lithium aluminium hydride
LiOH	Lithium hydroxide
$LiBH_4$	Lithium borohydride

LiBr	Lithium bromide
m-CPBA	*meta*-Chloroperoxybenzoic acid
M+	Molecular ion
Me	Methyl
MeMgI	Methylmagnesium iodide
MeOH	Methanol
MOMCl	Methoxymethyl chloride
MEMCl	2-Methoxyethoxymethyl chloride
min	Minute
mg	Miligram
mL	Milliliter
Mp	Melting point
MS	Mass spectrum
MsCl	Methanesulfonyl chloride
Ms	Mesyl
NaH	Sodium hydride
NaOH	Sodium hydroxide
$NaIO_4$	Sodium periodate
$NaBH_3CN$	Sodium cyanoborohydride
NMR	Nuclear magnetic resonance
NaHMDS	Sodium hexamethyldisilazide
$NaBH_4$	Sodium borohydride
NMO	*N*-Methylmorpholine *N*-oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
OsO_4	Osmium tetroxide
ORTEP	Oak ridge thermal-ellipsoid plot
Pd/C	Palladium on activated charcoal
Ph	Phenyl
PPh_3	Triphenylphosphine
PCC	Pyridinium chlorochromate
PivCl	Pivaloyl chloride
PhSeCl	Benzeneselenenyl chloride
Py	Pyridine
Rf	Retention factor
SmI_2	Samarium(II) iodide
TBAF	Tetra-*n*-butylammonium fluoride
TBSCl	*tert*-Butyldimethylsilyl chloride
p-TsCl	*p*-Toluenesulfonyl chloride
Ts	Tosyl
p-TSA	*p*-Toluenesulfonic acid
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TMSCl	Trimethylsilyl chloride
TPAP	Tetrapropylammonium perruthenate
TOFMS	Time-of-flight mass spectrometer
Zn	Zinc

GENERAL REMARKS

1. All solvents were distilled and dried before use
2. Petroleum ether refers to the fraction collected in the boiling range 60–80°C
3. Organic layers after every extraction were dried over anhydrous sodium sulfate
4. Column Chromatographic purifications were performed over silica gel (60–120 & 230–400 mesh)
5. 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)
6. IR Spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}
7. ^{1}H and ^{13}CNMR and DEPT spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 400 MHz, 500 MHz and JEOL ECX 400 instruments using TMS or solvent residue as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet, dq = doublet of quartet and app = apparent
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25°C using sodium D light
9. Enantiomeric excess was determined on Agilent HPLC instrument equipped with a chiral column
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump
11. All melting points are uncorrected and the temperatures are in centigrade scale
12. The compounds, scheme and reference numbers given in each chapter/section refers to that particular chapter/section only

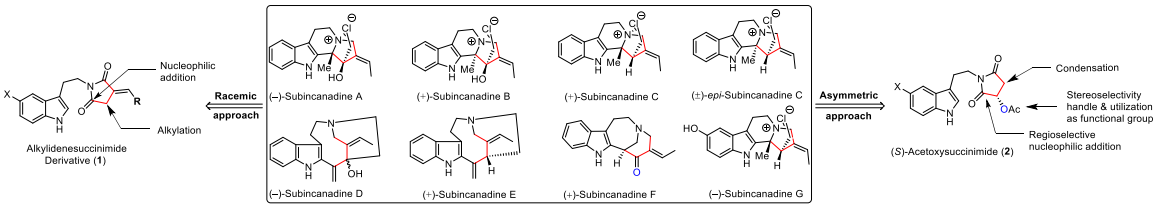
Synopsis of the Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

Name of the Candidate	Mr. Manojkumar Gulabrao Kalshetti
Degree Enrolment No. & Date	Ph. D. in Chemical Sciences (10CC13A26011); August 2013
Title of the Thesis	Studies on Total Synthesis of Bioactive Indole Alkaloids Subincanadine A–G
Research Supervisor	Dr. Narshinha P. Argade (AcSIR, CSIR-NCL, Pune)

Introduction

Indoles are an important class of compounds and the building block for large number of structurally diverse alkaloids with a wide range of biological activities. Morever some of them in clinical use and hence they are the target compounds of interest for large number of synthetic organic chemists.[1] The structurally interesting and biologically important cytotoxic alkaloids subincanadines A−G were isolated from bark of the Brazilian medicinal plant *Aspidosperma subincanum* by Ohsaki and coworkers in 2002.[2] The interesting biological activities and unique molecular architectures of these compounds have attracted immediate attention and they became important synthetic targets due to their limited availability from natural sources. Development of synthetic or biosynthetic routes for these subincanadine indole alkaloids is a challenging task for chemists. A few new synthetic routes to the target compounds from figure 1 have been reported in recent literature.[3] In the present dissertation work synthetic strategies have been described to access the core ring system of subincanadine family, which have subsequently led to the concise and efficient total synthesis of natural and unnatural subincanadine alkaloids. (Figure 1).[4–8]

Figure 1. Potent cytotoxic alkaloids subincanadines A–G and their retrosynthetic analysis.



Statement of Problem

The synthesis of bioactive natural products subincanadines A–G involving new concise routes from the commercially available starting materials is of current interest.

Methodology Used

1.The products were characterized by the advanced analytical and spectroscopic techniques such as high field ^{1}H & ^{13}C NMR, FT-IR, LC-MS and HRMS.

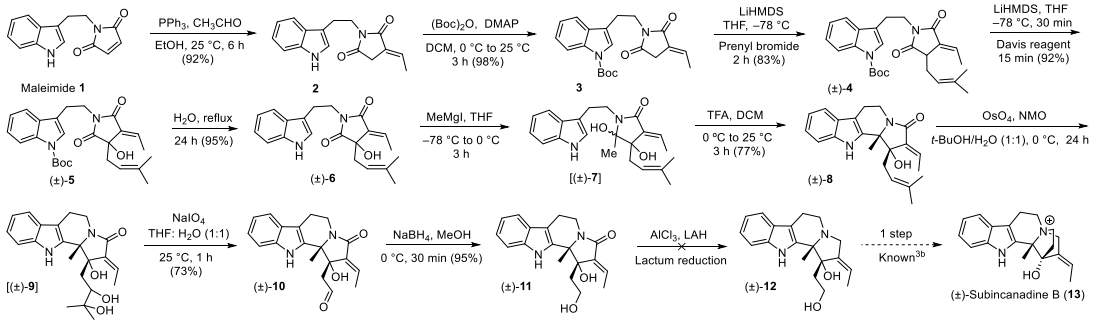
2. Single crystal X-ray crystallographic study has been carried out to determine the relative stereochemistry.

3. The optical purity of enantiomerically enriched target compounds has been determined by using chiral HPLC analysis and comparing their specific rotation with those reported in the literature.

Sample Results

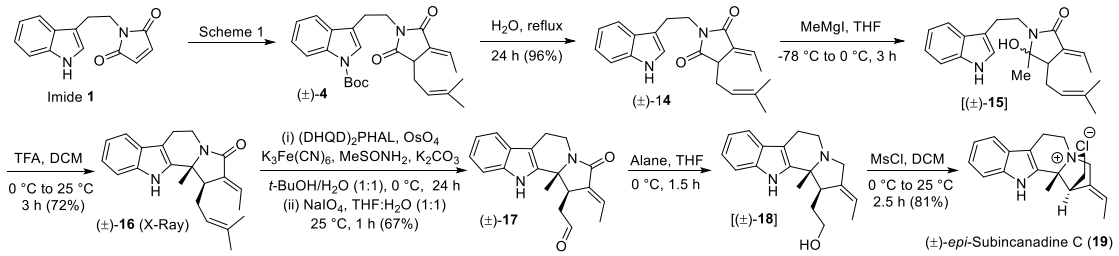
1. Starting from indolylmaleimide, concise and efficient synthesis of (±)-subincanadine B framework has been accomplished via Davis hydroxylation as a key step. The penultimate step reduction of lactum carbonyl is in progress and in the preliminary studies we have faced the difficulty of S_N2' reaction leading to undesired elimination of tertiary hydroxyl group. We feel that the suitable protection of the tertiary alohol moiety is essential prior to cyclization and the work is in active progress.

Scheme 1. In Progress Synthesis of (±)-Subincanadine B via Imperative Davis Hydroxylation and Intramolecular Pictet–Spengler Cyclization

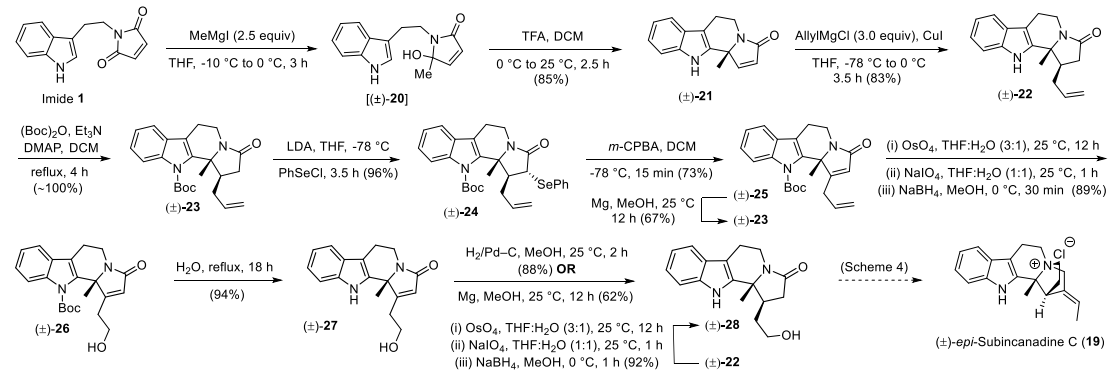


2. Starting from indolylmaleimide, concise and efficient total syntheses of (±)-*epi*-subincanadine C have been accomplished via stereoselective Wittig olefination, base induced selective mono-prenylation, regioselective Grignard reaction, Diastereoselective Pictet–Spengler cyclization, regioselective oxidative carbon–carbon double bond cleavage, one-pot reductions and intramolecular cyclization pathway. An attempted synthesis of (±)-subincanadine C via diastereoselective Grignard addition to the *α,β*-unsaturated *γ*-lactam or diastereoselective reduction of a carbon–carbon double bond also resulted in yet another route to (±)-*epi*-subincanadine C.

Scheme 2. Synthesis of (±)-*epi*-Subincanadine C via Diastereoselective Intramolecular Pictet–Spengler Cyclization



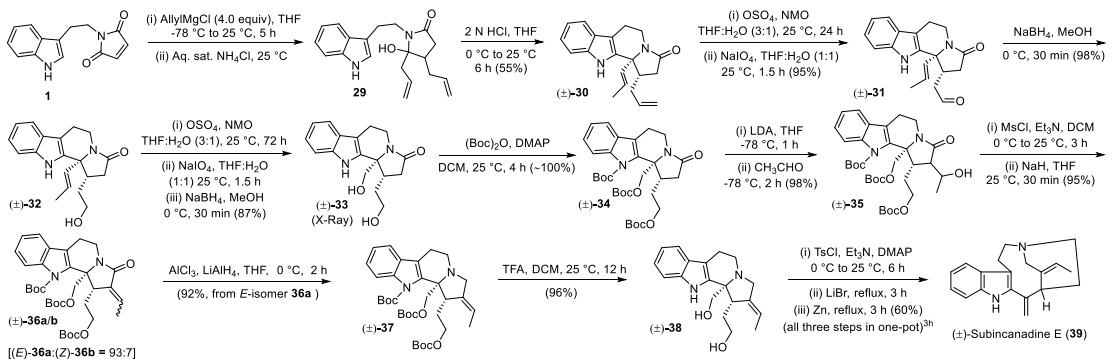
Scheme 3. Opposite Stereoselections in Michael Addition and Reductions of *α,β*-Unsaturated *γ*-Lactams Leading to Exclusive *syn*-Products: An Attempted Synthesis of (±)-Subincanadine C



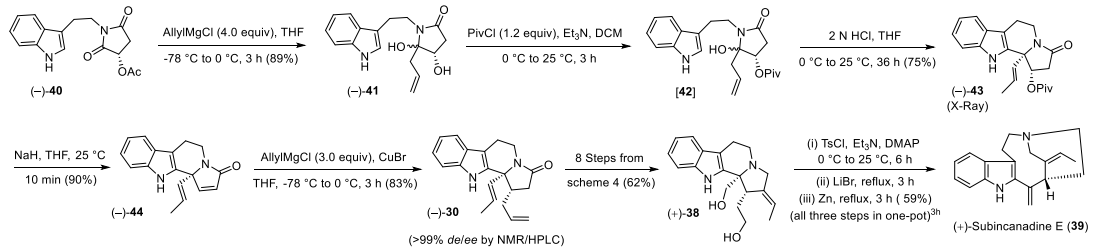
In summary, an early stage stereoselective introduction of the desired carbon–carbon double bond via Wittig reaction was useful to activate methylene protons for base induced smooth prenylation and also to govern the regioselectivity in Grignard addition. Diastereoselective practical approaches to (±)-*epi*-subincanadine C have been developed via regioselective oxidative carbon–carbon double bond cleavage and an exceptional *syn*-stereoselection in Michael addition of allyl-cuprate to the unsaturated γ-lactam.

3. A facile synthesis of (±)-subincanadine E has been described from tryptamine-based maleimide. 1,2-Addition of Grignard reagent to maleimide, internal activation of formed lactamol for in situ 1,4-addition of Grignard reagent, and associated position-specific allylic rearrangement in diastereoselective Pictet−Spengler cyclization were the key steps. Enantioselective first total synthesis of naturally occurring cytotoxic (+)-subincanadine E was also accomplished from (*S*)-acetoxysuccinimide via an unusual *syn*-addition of cuprate to the *α,β*-unsaturated lactam. *Sinister* absolute configuration has been assigned to (+)-subincanadine E on the basis of total synthesis. (*S*)-Acetoxy group in the succinimide precursor was initially employed to impart regioselectivety and stereoselectivity and then as a suitable leaving group to generate the desired conjugated lactam.

Scheme 4. Synthesis of (±)-Subincanadine E via Grignard Additions, Allylic Rearrangement, Pictet–Spengler Cyclization, Condensation and Ring Expansion Route



Scheme 5. Enantioselective Synthesis (+)-Subincanadine E from (*S*)-Acetoxysuccinimide via an Unanticipated *Syn*-addition of the Cuprate.

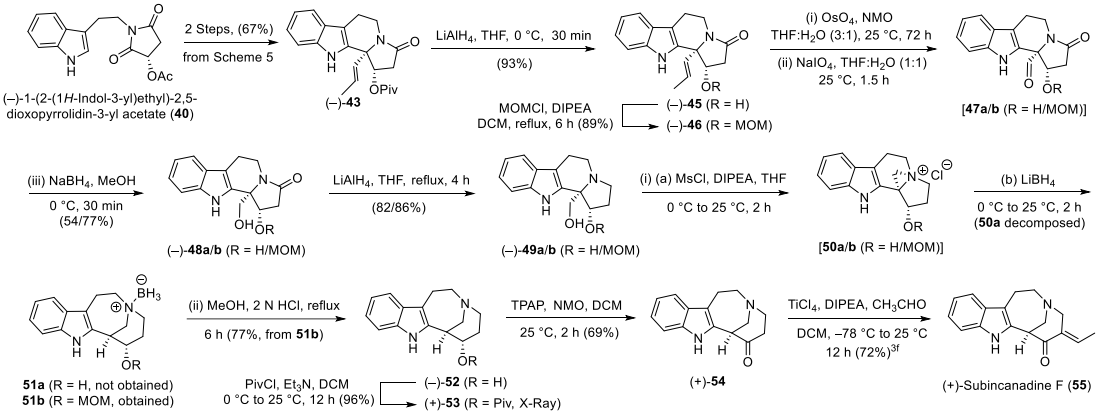


In summary, from the readily available maleimide/succinimide we have described new efficient approach to (±)/(+)-subincanadine E and established its absolute configuration. The 1,4-addition of Grignard reagent to the internally activated lactamol, witnessed position selective allylic rearrangements in succinimide derived lactamols and stereoselective *syn*-addition of cuprate to the unsaturated lactam are noteworthy.

4.Enantioselective synthesis of cytotoxic indole alkaloid (+)-subincanadine F was accomplished starting from the corresponding (*S*)-acetoxysuccinimide via aziridinium ring formation and its reductive ring expansions route. Regioselective and stereoselective

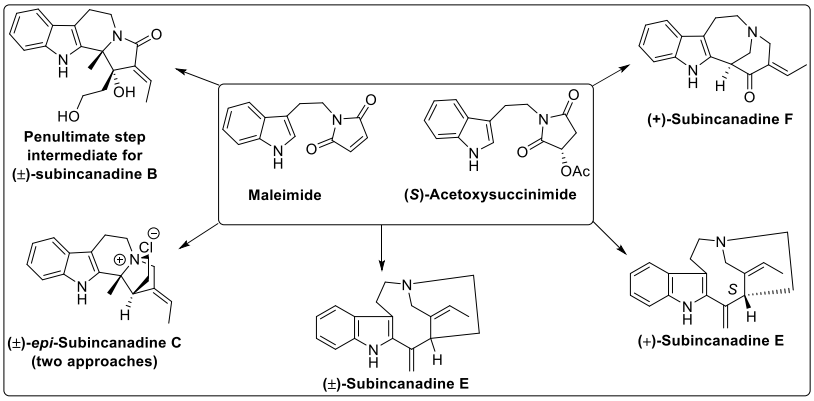
reductive aziridinium carbon–nitrogen bond cleavage comprising ring expansions was a key step. The (*S*)-OMOM protection of hydroxyl moiety adjacent to a benzylic carbon of in situ formed aziridinium system was necessary for lithium borohydride induced reductive ring expansions and it also served as a latent source of essential ketone carbonyl group for the generation of α,β-conjugated system.

Scheme 6. Remarkable Regioselective and Stereoselective Reductive Aziridinium Ring Cleavage Accomplishing Practical Synthesis (+)-Subincanadine F.



In summary, we have accomplished enantioselective practical synthesis of (+)-subincanadine F from the systematically structured aziridinium chloride with remarkable regioselective and stereoselective embarking of hydride nucleophile with the inversion of configuration. The obtained regioselectivity has been governed by benzylic carbon atom reactivity over its steric conjecture and the relative thermodynamic stability of formed product. The MOM protection of an adjacent free secondary hydroxyl group was essential from aziridinium substrate stability point of view. To the best of our knowledge, this is an exceptional example of aziridinium ring cleavage stereoselectively assembling the bridged system and conceptually it will be useful from involved basic chemistry and applications point of view.

Overall conclusion: Present dissertation describes multistep total synthesis of (±)-subincanadine B framework, (±)-*epi*-subincanadine C, (±)-subincanadine E, (+)-subincanadine E and (+)-subincanadine F from the readily available maleimides and (*S*)-acetoxysuccinimides as the starting materials. The key reactions involved in above specified syntheses are Davis hydroxylation, regioselective Grignard addition, internal activation of lactamol leading to in situ 1,4-addition of Grignard reagent, associated position-specific allylic rearrangement in diastereoselective Pictet−Spengler cyclization, stereoselective *syn*-addition of cuprate to the unsaturated lactam and regioselective and stereoselective reductive aziridinium backbone carbon–nitrogen bond cleavage with hydride nucleophile comprising ring expansions. We have accomplished enantioselective first total synthesis of (+)-subincanadine E and assigned the *Sinister* absolute configuration. Large number of natural and unnatural subincanadine class of compounds have been synthesized and will be useful from biological activities point of view.



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Chapter 1

A Concise Account on the Chemistry of Bioactive Indole Alkaloids Subincanadines A to G and Proposed Biogenetic Congeners

1.1 Introduction

Alkaloids represent an enormous and highly structurally diverse group of secondary metabolites. The presence of rightly placed nitrogen in their molecular entity confers exceptionally high biological activity to this class of compounds. Alkaloids display large variety in their chemical structures and they have been classified depending upon the presence of heterocyclic ring in their chemical structures. The indole alkaloids is a largest class and comprises of more than 4000 diversified members. The indole alkaloid **1** in nature originates from amino acid tryptophan; whose genesis is well-established from shikimic acid pathway. The first indole alkaloid strychnine (**2**) was isolated by Pierre Joseph Pelletier and Joseph Bienaimé Caventou in 1818 from the plants of genus *Strychnos* (Figure 1).[1] The correct structural assignment of strychnine was done in 1947 after a "decades-long chemical degradative assault"[2,3] however presence of a commanding indole core in the structure of strychnine was recognized earlier. Indole (**1**) itself was first obtained by Adolf von Baeyer in 1866 during the degradation studies of indigo (**3**). Since then there has been strong interest in this area from synthetic chemists and biologists due to the complex structural architectures and conferred biological activities such as leishmanicide,[4] anticholinesterasic,[5] anti-HIV-1,[6] antifungal,[7] antiaddiction,[8] anti-malarial,[9a] antiarrhythmic[9b,c] and adrenergic blocking,[9d] exhibited by several indole alkaloids and some of them have been used in earlier and modern medicines (Figure 2). Large number of indole alkaloids has been isolated from plants such as *Rauvolfia serpentine*, *Aspidosperma* and *Tabernanthe*/*Tabernaemontana* belonging to the *Apocynaceae* family[10,11] and also from animals, microorganisms and recently from marine sources.[12] The indole nucleus is one of the most significant ring systems from pharmaceutical point of view and it has been termed as "privileged structure".[13] There are three major factors that contribute to the complexity and bioactivity of indole alkaloids *viz.* (i) polycyclic nature of the frameworks, (ii) the contiguous stereocenters and (iii) presence of quaternary centers.

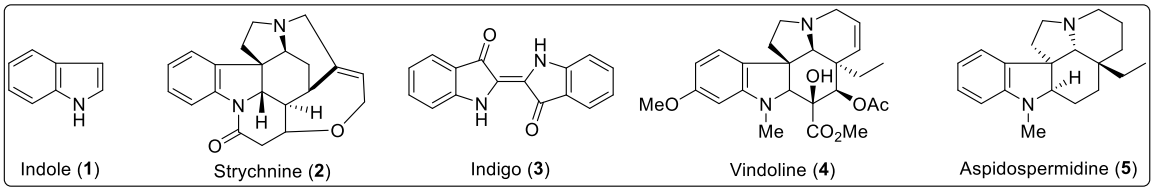


Figure 1. Representative indole alkaloids.

The challenge in construction of such complex structural indole alkaloids has driven research on the total syntheses of these towards a continuous activity in the large section

of synthetic organic chemist's community. Some classical molecules such as strychnine (**2**),[14] vindoline (**4**)[15] and aspidospermidine (**5**)[16] have been frequently synthesized by using elegant new synthetic strategies.

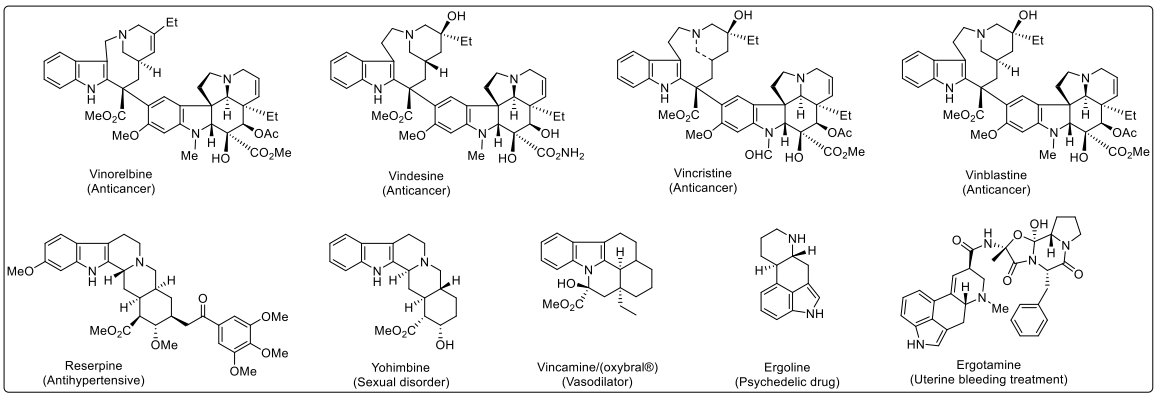


Figure 2. Indole moiety containing drugs.

1.2 Background

The chemistry of indole alkaloids is well documented in number of comprehensive reviews, articles and it is continuously updated in Natural Product Reports.[12,17,18] Those reviews authoritatively describe nice account on isolation, characterisation, bioactivity and total synthesis of naturally occurring indole alkaloids. The new polycyclic indole alkaloids subincanadines A–G were isolated in 2002 by Ohsaki and co-workers from the bark of Brazilian medicinal plant *Aspidosperma subincanum* in nearly 0.002% yields (Figure 3).[19a,b] The report also neatly describes structural elucidations with the help of MS, HRMS, ^{1}H NMR, ^{13}C NMR and 2D NMR analysis and biological activities of **6**–**12**. The systematic structural scrutiny reveals that subincanadines A–C (**6**–**8**) are novel quaternary indole alkaloids with an unprecedented 1-azoniatricyclo[4.3.3.0]undecane moiety, subincanadines D (**9**) and E (**10**) bear 1-azabicyclo[5.2.2]undecane skeleton and the subincanadine F (**11**) is built up of 1-azabicyclo[4.3.1]decane framework. The subincanadine E is also named as pericine and it was first isolated by Stockigt and co-workers in 1982 from *Picralima nitida* commonly known as *akuamma* tree.[19c] The dried seeds of *Picralima nitida* have been used in traditional medicine as an unapproved drug throughout West Africa, particularly in Ghana as well as in the Ivory Coast and Nigeria. Subincanadine E (**10**) effectively binds to opioid receptors having an IC_{50} = 0.6 μg/mL and it is around 6 times more potent than the codeine.[19d] Similarly the exotic azabicyclodecane framework bearing (+)-subincanadine F exhibits potent cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 2.40 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 4.80 μg/mL). The interesting biological activities and unique

fascinating molecular architectures of these alkaloids have attracted immediate attention from chemist's community and they have become the synthetic targets of interest as a

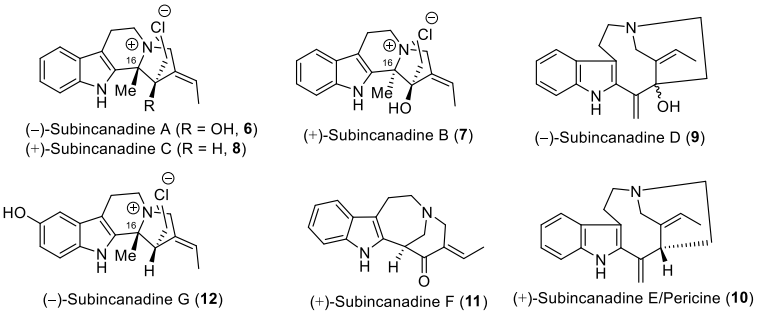


Figure 3. Bioactive indole alkaloids subincanadines A–G.

result of their much inadequate availability from natural sources. The presence of quaternary asymmetric carbon atom at C–16 position is a characteristic that distinguishes these alkaloids from hitherto known monoterpenoid indole alkaloids having a *β*-carboline skeleton.[20] Well-designed one total synthesis of each subincanadine A, B, C and E, and four total syntheses of subincanadine F have been reported in contemporary literature. In the total synthesis of these alkaloids stereoselective assembly of polycyclic scaffolds with conservation of asymmetry throughout the synthetic sequence are important points.

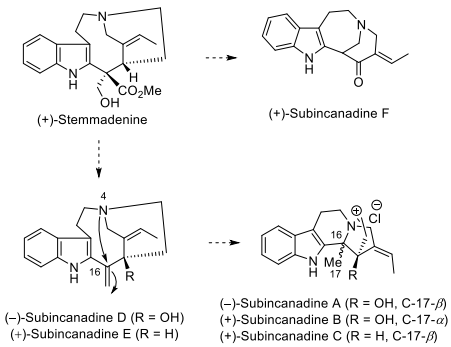


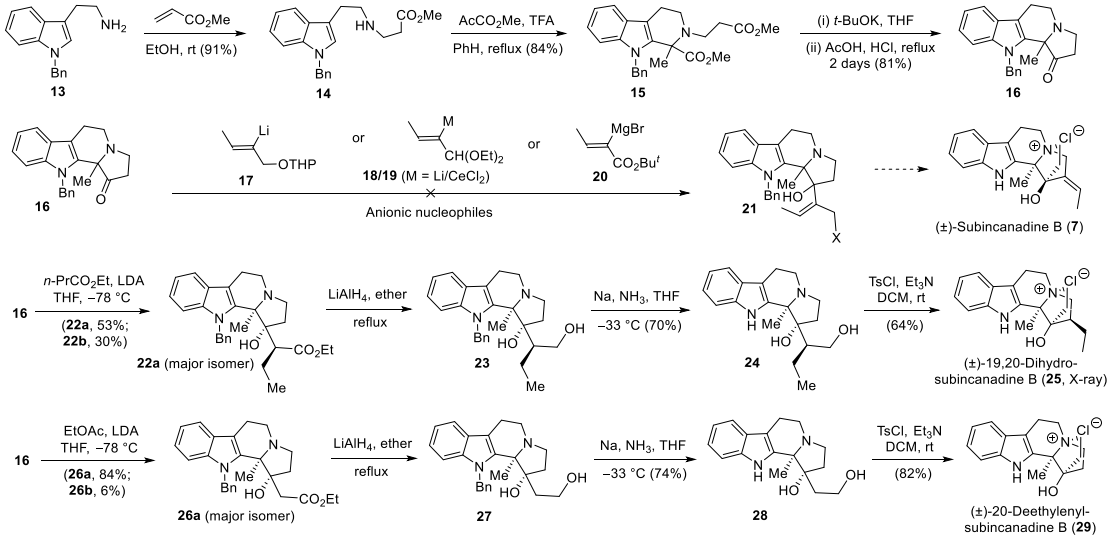
Figure 4. (+)-Stemmadenine the proposed biogenetic precursor of subincanadines A–F.

Kobayashi proposed that subincanadines D–F could be biosynthetically resulting from stemmadenine via two different pathways. Furthermore the subincanadines A–C could be forming from subincanadine D and E through the C–N bond formation between tertiary N–4 and exocyclic carbon–carbon double bond at C–16 position (Figure 4).[19a]

1.3 Concise Account on Synthesis of Subincanadines A–F

Well-planned diastereoselective/enantioselective synthesis of subincanadine A, B, C, E and F have been recently reported; however synthesis of subincanadine D and G are still awaited.

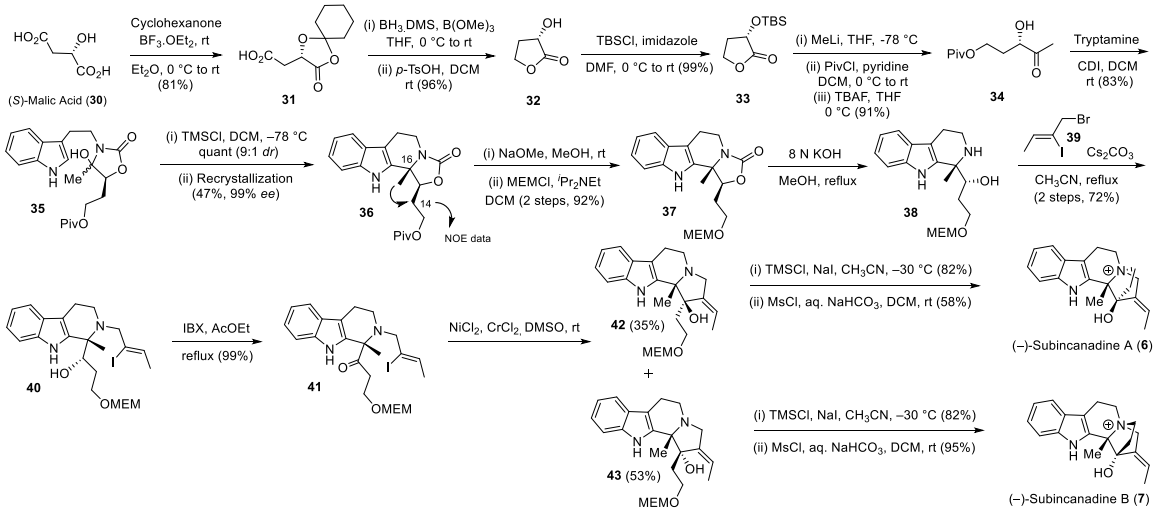
1.3.1 Subincanadine A and B: At first Zhai and co-workers in 2006 took an initiative to assemble the subincanadine architecture and effectively constructed racemic pentacyclic framework to accomplish synthesis of two unnatural analogues of subincanadine B; namely 19,20-dihydrosubincanadine B and 20-deethylenylsubincanadine B (Scheme 1).[21]



Scheme 1. First Synthetic Approach Towards the Total Synthesis of (±)-Subincanadine A and B

Treatment of benzyl protected tryptamine **13** with methyl acrylate in EtOH provided *aza*-Michael adduct **14** in 91% yield and then it was transformed into tricyclic diester **15** in 84% yield via Pictet–Spengler reaction with methyl pyruvate in presence of trifluoroacetic acid in refluxing benzene. Dieckmann condensation of **15** using *t*-BuOK followed by decarboxylative hydrolysis of the corresponding *β*-keto ester using HCl/AcOH reflux conditions provided tetracyclic ketone **16** in 93% yield over two steps. Large amount of efforts were devoted to incorporate suitable side chain onto ring D of *N*-protected tetracyclic ketone **16** in order to generate the desired precursor of subincanadine B. A variety of anionic nucleophiles **17** to **20** of different size and reactivity were employed to react with ketone carbonyl of **16** with a hope of completing the total synthesis of subincanadine B. Unfortunately all those attempts were unsuccessful due to the presence of quaternary carbon atom adjacent to a ketone moiety and overall reactivity of the incoming nucleophiles. Therefore they next pursued synthesis of analogue of subincanadine B by taking the advantage of successful formation of adduct **22a** from the reaction of ketone **16** with lithium enolate of ethyl butyrate. Reduction of ester group in **22a** with $LiAlH_4$ followed by deprotection of *N*-benzyl group employing sodium in liquid ammonia provided compound **24** in 70% yield. Finally tosylation of resultant primary hydroxyl group in **24** and subsequent intramolecular ammonium bridge formation

furnished the (±)-19,20-dihydrosubincanadine B (**25**) in 64% yield. Similarly the reaction of lithium enolate of ethyl acetate with ketone **16** provided adduct **26a** and further repetition of same sequence in the earlier transformation provided (±)-20-deethylenylsubincanadine B (**29**) in very good overall yield. In the present neat attempt authors quickly assembled the tetracyclic ketone **16**; however the fine tuning of vinylic carbanion reactivity appears essential to meet with success.



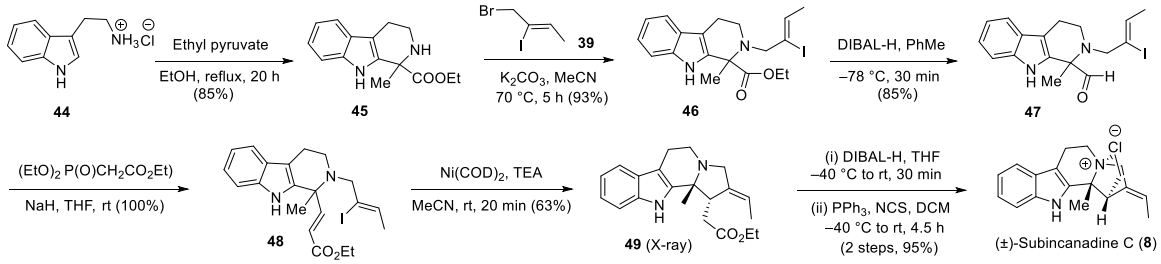
Scheme 2. First Asymmetric Total Synthesis of Subincanadine A and B

In the same year 2006, Takayama and co-workers successfully completed first asymmetric total synthesis of (–)-subincanadine A and antipode (–)-subincanadine B starting from commercially available (*S*)-malic acid via intramolecular diastereoselective Pictet-Spengler cyclization and Nozaki-Hiyama-Kishi reaction as the key steps (Scheme 2).[22] Their synthesis commenced from the intramolecular Pictet-Spengler reaction of carbamate **35**, which tethered tryptamine and enantiomerically pure ketone **34**. Hydroxy-ketone **34** was initially prepared from *γ*-lactone **32** via four-step sequence. Protection of secondary hydroxyl group in **32** with TBSCl followed by reaction with methyl lithium, further protection of resultant primary hydroxyl group with pivaloyl chloride and finally deprotection of secondary hydroxyl group resulted in enantiomerically pure precursor **34**. Carbamate **35** was obtained by the condensation of tryptamine and hydroxy-ketone **34** with 1,1`-carbonyldiimidazole (CDI) in 83% yield and in solution it exists as hemi-aminoketal. Initially several acids were screened to get high diastereoselectivity in Pictet-Spengler cyclization of **35**, however best yield and selectivity was obtained with TMSCl as a Lewis acid at −78 °C affording 9:1 mixture of diastereomers in quantitative yield. The obtained mixture was separated by recrystallization to provide single diastereomer **36**

with 99% *ee*. Stereochemistry of product **36** was confirmed by NOE experiment in which the angular methyl C–16 and sidechain of C–14 were having *syn*-relationship with each other. Protection of **36** was switched to MEM ether **37** by following conventional procedures. The decarbonylation of **37** was performed by basic hydrolysis and the resultant secondary amine **38** was chemoselectively and regioselectively alkylated with allylic bromide **39** to furnish vinyl iodide **40** in 72% overall yield starting from **37**. The secondary alcohol group in **40** was oxidized in presence of IBX to afford ketone **41**, which was a key substrate for the construction of D ring via Nozaki-Hiyama-Kishi reaction. Reaction of **41** with $NiCl_2$ and $CrCl_2$ in DMSO at room temperature provided mixture of two tetracyclic compounds **42** and **43** in 35% and 53% yield respectively and stereochemistry of both of them was fixed by NOE experiments. In the final stage protecting group of primary alcohol in **42** and **43** was removed by treatment with TMSCl/NaI in MeCN and the resultant free alcohols were mesylated under standard reaction conditions to deliver the in situ cyclized pentacyclic quaternary ammonium salts (–)-subincanadine A (**6**) and (–)-subincanadine B (*ent*-**7**) in 58 and 95% yields respectively. Overall authors have performed the Pictet-Spengler cyclization with very high stereoselectivty but the intramolecular Nozaki-Hiyama-Kishi reaction with ketone carbonyl turned out to be less diastereselective; however fortunately it helped in accomplishing the synthesis of both (–)-subincanadine A and an antipode (–)-subincanadine B.

1.3.2 Subincanadine C: First total synthesis of (±)-subincanadine C was published from Hongbin Zhai's research group in 2011 and remarkably it was accomplished without using any protection-deprotection chemistry (Scheme 3).[23] The pentacyclic indole alkaloid was synthesized in six steps from known intermediate **45** by performing $Ni(COD)_2$-mediated intramolecular Michael addition as a key step. The intramolecular Pictet-Spengler reaction of tryptamine hydrochloride (**44**) with ethyl pyruvate afforded known compound **45** in 85% yield, which was subsequently regioselectively alkylated with allyl bromide **39** in presence of potassium carbonate to obtain the corresponding desired vinylic iodide **46** in 93% yield. The controlled reduction of ester group in **46** to the corresponding aldehyde **47** followed by Horner-Wadsworth Emmons (HWE) olefination afforded unsaturated ester **48** in 85% overall yield. The key intramolecular Michael addition on well-structured compound **48** was carefully examined under various reaction conditions to obtain tetracyclic compound **49** and the optimized 63% yield was

obtained by using combination of 5 equiv of $Ni(COD)_2$ and 10 equiv of trimethylamine. The relative stereochemistry of formed product **49** was unambiguously confirmed by X-ray crystallographic analysis. Finally reduction of ester group in compound **49** with DIBAL-H in THF afforded required primary alcohol, which was transformed into the corresponding chloride by using NCS/PPh_3 to directly obtain the in situ cyclized product (±)-subincanadine C (**8**) in 93% overall yield. The authors have accomplished concise and efficient protection free total synthesis of (±)-subincanadine C via noteworthy nickel catalyzed intramolecular Michael addition and chiral version of this protocol will be feasible and rewarding.

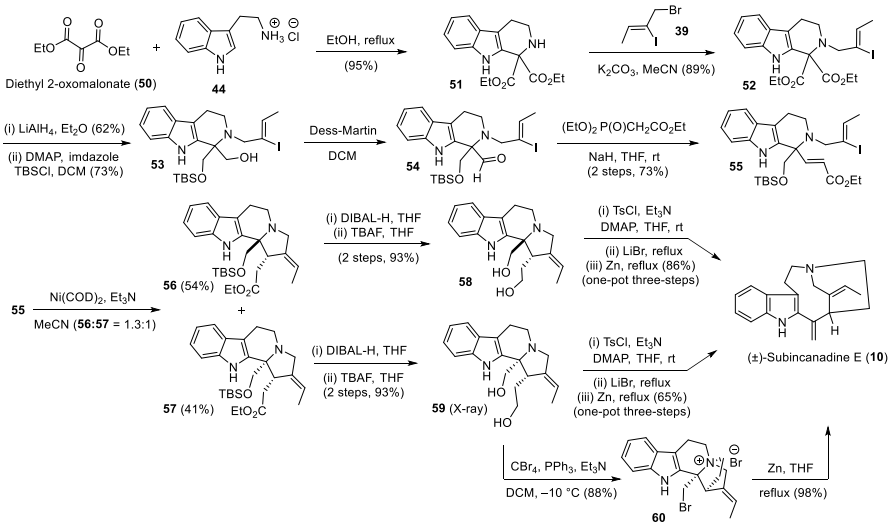


Scheme 3. First Total Synthesis of (±)-Subincanadine C

1.3.3 Subincanadine D: This new indole alkaloid bears 1-azabicyclo[5.2.2]undecane framework comprising of two exocyclic carbon–carbon double bonds and an asymmetric carbon with free tertiary hydroxyl moiety; the total synthesis of this exotic target is still awaited.

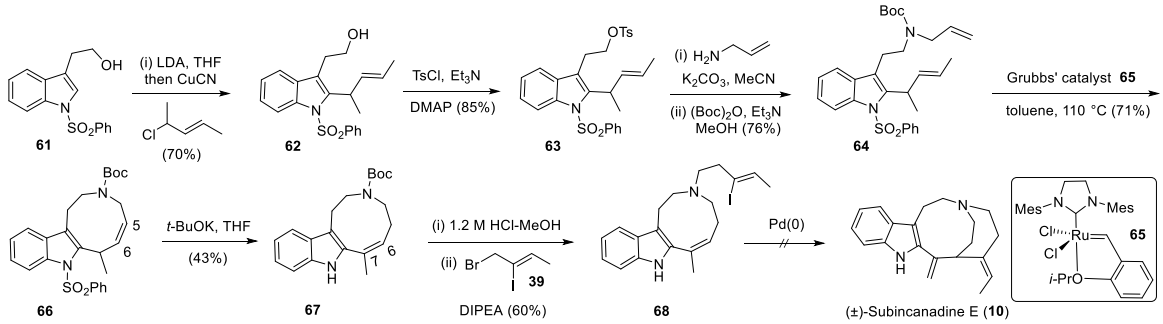
1.3.4 Subincanadine E: Zhai and co-workers in 2014 reported first total synthesis of (±)-subincanadine E in 10 steps starting from tryptamine hydrochloride. The key reactions in above mentioned synthesis were transformation of primary alcohols to the corresponding bromides with in situ cyclization to form 1-azoniatricyclo[4.3.3.0]undecane backbone **60** and novel zinc-mediated ring expansion for construction of unique 1-azabicyclo[5.2.2]undecane system with a generation of desired exocyclic double bond (Scheme 4).[24] At first Pictet−Spengler condensation of commercially available tryptamine hydrochloride **44** with diethyl 2-oxomalonate (**50**) was performed to obtain product **51** in 95% yield. The subsequent regioselective *N*-alkylation of formed **51** with allyl bromide **39** afforded tertiary amine **52** in 89% yield. Aldehyde **54** was obtained in three-step operation inclusive of (i) reduction of diester **52** to the corresponding *gem*-diol, (ii) controlled protection of one of the hydroxyls to obtain mono-TBS ether **53** and (iii) oxidation of the second hydroxyl group to the corresponding aldehyde. The authors directly subjected aldehyde **54** to next step without any purification for stability issues.

HWE olefination of **54** with triethyl phosphonoacetate in presence of NaH provided unsaturated ester **55** in 73% yield over two steps. The $Ni(COD)_2$ driven intramolecular Michael addition of **55** was realized in the presence of triethylamine at ambient temperature and separable tetracyclic diastereomeric products **56** and **57** (*dr* =1.3:1) were obtained in 54% and 41% yields respectively. Reduction of esters group in **56** and **57** with DIBAL-H followed by deprotection of silyl ether with TBAF respectively provided diols **58** and **59** in 93% yields. The structure of diol **59** was established by X-ray diffraction analysis. The sequential treatment of diol **58** with $TsCl/Et_3N$/DMAP and LiBr to form the corresponding dibromide, in situ intramolecular cyclization to generate pentacyclic quaternary ammonium salt and finally the zinc-mediated fragmentation leading to ring expansion with the creation of exocyclic double bond provided (±)-subincanadine E (**10**) in one-pot with 86% overall yield. Similarly the target molecule (±)-**10** was also obtained in one-pot from the other diastereomer **59** using above specified three-step protocol. In addition diastereomer **59** on treatment with $CBr_4/PPh_3/Et_3N$ afforded pentacyclic ammonium bromide **60** in 88% yield; which on reaction with zinc in refluxing THF also provided the (±)-subincanadine E (**10**) in almost quantitative yield. In contrast the diastereomer **58** on reaction with $CBr_4/PPh_3/Et_3N$ under exactly same conditions which were applied to **59**, failed to provide the expected pentacyclic ammonium salt alike **60** and it could be attributed to relative difference in reactivity of two diastereomers. Though authors obtained the poor diastereoselectivity in intramolecular Michael addition reaction of **55**, they could successfully transform both the diastereomers into target compound subincanadine E (**10**). In the present synthesis the art of ring expansion reaction involving simultaneous generation of exocyclic double bond is extraordinary.



Scheme 4. First Total Synthesis of (±)-Subincanadine E

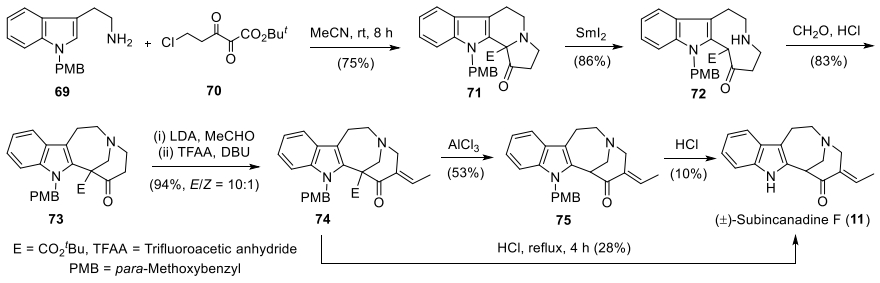
Bennasar *et al* in 2015 reported an attempted synthesis of subincanadine E (**10**). Their synthetic strategy to the bridged indole alkaloid subincanadine E was based on interesting combination of a ring-closing metathesis (RCM) and intramolecular Heck cyclization (Scheme 5).[25] After the successful construction of tricyclic nine-membered central ring **66** via RCM-based route, they did the deprotection of both protecting groups in a stepwise fashion. However the regioselectively *N*-allylated product **68** did not undergo intramolecular Heck coupling to deliver the desired 1-azabicyclo[5.2.2]undecane framework of subincanadine E (**10**). Sadlowski *et al* also attempted the similar combination of RCM-Heck approach to synthesize subincanadine E but unfortunately their plan also was not successful.[26] We feel that the intramolecular Heck coupling was not feasible due to the nine membered ring size and development of more precise conditions for ring closure is essential.



Scheme 5. Exploratory Studies Towards the Total Synthesis of Subincanadine E

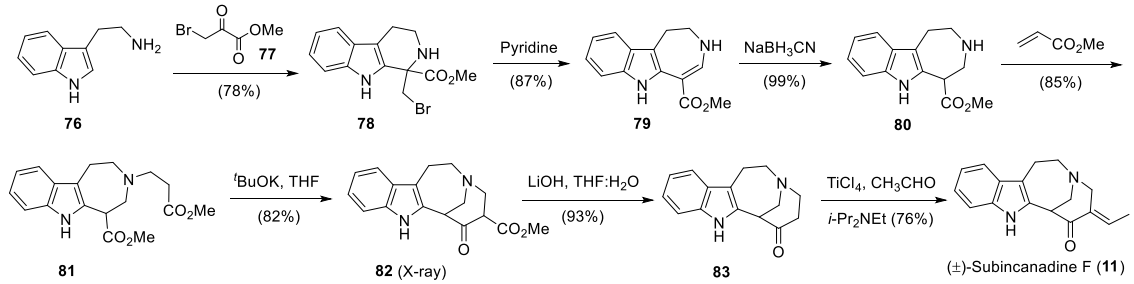
Recently Kam and co-workers have proposed that (+)-subincanadine E is a common biogenetic precursor of five different indole based structurally interesting natural products and to maintain subincanadine theme continuity their chemistry has been separately discussed in sections 1.4 and 1.5 of the present chapter (Figure 5).[27]

1.3.5 Subincanadine F: Structural architecture point of view among the rich and diverse families of monoterpenoid indole alkaloids,[28] subincanadine F stands out as only known member to feature a 1-azabicyclo[4.3.1]decane bridged system. Till date three racemic and one asymmetric synthesis of subincanadine F (**11**) are known in the literature.



Scheme 6. First Total Synthesis of (±)-Subincanadine F

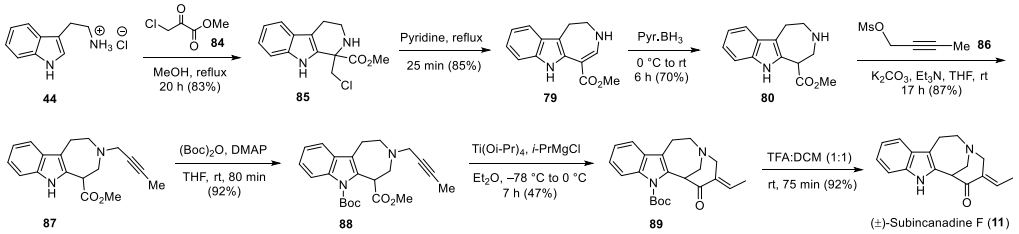
In 2006 Zai and co-workers reported first total synthesis of (±)-subincanadine F (**11**) via construction of challenging tetracyclic core by SmI_2-mediated ring opening and bridge-forming Mannich reactions as the key steps (Scheme 6).[29] The synthesis started from condensation of 1-(*para*-methoxybenzyl)tryptamine (**69**) with halodiketoester **70** in acetonitrile at room temperature to afford tetracyclic ketoester **71** in a 75% yield. The above mentioned one-pot procedure for assembly of **71** was stimulated by an in situ generated equivalent amount of HCl. The samarium diiodide mediated ring-opening of **71** provided the 6-5-9 tricyclic product **72** in 86% yield via the cleavage of an activated C–N bond. Exposure of **72** to formalin in the presence of hydrochloric acid delivered the tetracyclic 1-azabicyclo[4.3.1]decane framework **73** of subincanadine F in 83% yield. The (*E*)-ethenyl group adjacent to ketone carbonyl in **11** was introduced by treatment of **73** with LDA followed by MeCHO at –78 °C and the formed aldol condensation product on dehydration with TFAA/DBU/DMAP delivered mixture of geometric isomers **74** (*E*/*Z*, 10:1) in 94% yield over two steps. Finally, treatment of **74** with refluxing hydrochloric acid provided (±)-subincanadine F (**11**) in 28% yield via hydrolytic decarboxylation and deprotection of PMB protecting group. Overall authors have very nicely accomplished first total synthesis of (±)-subincanadine F and we feel that the further refinement in reactions conditions to improve the last step yield will be advantageous.



Scheme 7. Second Total Synthesis of (±)-Subincanadine F

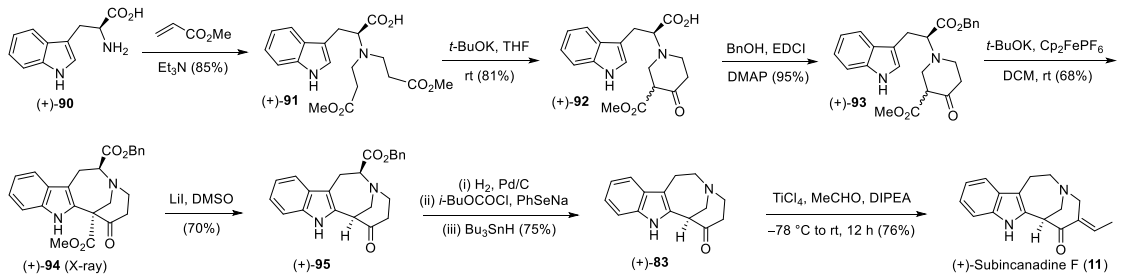
Li and co-workers reported the protecting group free 7-step total synthesis of (±)-subincanadine F (**11**) from tryptamine with 33% overall yield via chemoselective Dieckmann condensation as a key step (Scheme 7).[30] Pictet–Spengler condensation reaction of tryptamine (**76**) and bromopyruvate **77** adduct provided the cyclized compound **78** in 78% yield, which was then treated with pyridine at reflux temperature to obtain ring expanded product **79** in 87% yield. The reduction of conjugated carbon–carbon double bond in compound **79** with $NaBH_3CN$ furnished ester **80** in quantitative yield. The regioselective *aza*-Michael addition reaction of **80** with methyl acrylate in methanol at room temperature provided the desired diester **81**. The

chemoselective Dieckmann condensation of diester **81** in presence of *t*-BuOK in THF at room temperature took place smoothly to provide condensation product **82** in 82% yield; whose structure was unambiguously confirmed by its X-ray diffraction experiments. Treatment of compound **82** with lithium hydroxide in aqueous THF under reflux conditions gave the corresponding decarboxylated product **83** in 93% yield. Finally, the (*E*)-ethenyl group adjacent to ketone carbonyl in **83** was introduced by reaction with acetaldehyde in presence of $TiCl_4$ as a Lewis acid in DCM at –78 °C to afford (±)-subincanadine F (**11**) with 76% yield. The two noteworthy points in present synthesis are ring expansion of tetrahydropyridoindole to tetrahydroazepinoindole via in situ aziridine intermediate formation and the obtained desired selectivity in Dieckmann condensation.



Scheme 8. Third Total Synthesis of (±)-Subincanadine F

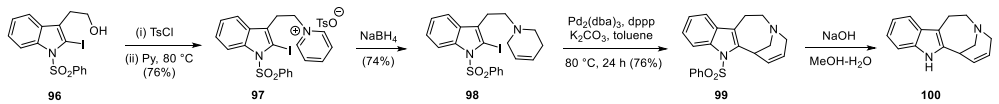
Waters and co-workers in 2010 accomplished total synthesis of (±)-subincanadine F in seven steps by employing titanium-induced intramolecular nucleophilic acyl substitution (INAS) reaction as a key step for construction of desired bridged ring system (Scheme 8).[31] Pictet–Spengler condensation of tryptamine hydrochloride (**44**) and halo-keto-ester **84** provided (chloromethyl)tetrahydro-*β*-carboline adduct **85**, which in refluxing pyridine provided the expected ring expanded indoloazepine ester **79**. Alternatively the reduction of conjugated carbon–carbon double bond in **79** with pyridine-borane complex gave its saturated congener **80**. Regioselective alkylation of azepine nitrogen in **80** was achieved by using butynyl mesylate **86** in presence of K_2CO_3/Et_3N to provide butynyl amine **87** in 87% yield. The Boc-protection of indole nitrogen provided key substrate **88** for titanium-mediated INAS reaction. The reaction of alkyne **88** with Ti(O*i*-Pr)$_4$ and *i*-PrMgCl solution in Et_2O at –78 °C followed by slow warming to 0 °C resulted in cyclization to stereoselectively form bridged tetracyclic enone **89** in 47% yield. Finally the removal of *N*-Boc group in **89** was done in presence of trifluoroacetic acid to furnish (±)-subincanadine F (**11**) in 92% yield. In the present synthesis formation of a bicyclic system via intramolecular nucleophilic cyclization between appropriately placed ester and alkyne moieties with the stereoselective generation of desired *α*,*β*-unsaturated ketone in one-pot is commendable.



Scheme 9. Asymmetric First Total Synthesis of (+)-Subincanadine F

Li and co-workers also reported the asymmetric first total synthesis of indole alkaloid (+)-subincanadine F (**11**) starting from commercially available D-tryptophan and determined its absolute configuration. Unusual 7-*endo*-trig stereoselective radical cyclization was used as a key step for the construction of desired bridged azabicyclic system (Scheme 9).[32] The reaction of D-tryptophan (**90**) with excess of methyl acrylate in aqueous methanol provided double *aza*-Michael addition product (+)-**91** in 85% yield. Dieckmann condensation of (+)-**91** using *t*-BuOK provided the cyclized product (+)-**92** in 81% yield, which was further converted to the corresponding benzyl ester (+)-**93** by reaction with BnOH/EDCI/DMAP in 95% yield. The oxidative radical cyclization reaction of (+)-**93** with Cp_2FePF_6 as oxidant in presence of *t*-BuOK was carefully investigated and expected cyclized product (+)-**94** was obtained as a single stereoisomer in 68% yield, whose stereochemistry was finally established by X-ray diffraction analysis. The removal of ester moiety in product (+)-**94** was done by treatment with LiI in DMSO at 180 °C to obtain (+)-**95** in 70% yield without any racemization. Removal of benzyl group in (+)-**95** by Pd/C-catalyzed hydrogenation provided the carboxylic acid in quantitative yield, which was converted to the corresponding phenylseleno ester by reaction with *i*-BuOCOCl/PhSeNa. Further treatment of the formed phenylseleno ester with Bu_3SnH/AIBN afforded the desired product (+)-**83** in 75% yield over two steps. Finally, the $TiCl_4$/ethyldiisopropylamine-mediated condensation of (+)-**83** with acetaldehyde at –78 °C to room temperature furnished the target molecule (+)-subincanadine F (**11**) in 76% yield. In the present approach highly enantioselective intramolecular radical cyclization driven by remotely placed asymmetric ester group was an important step in total synthesis.

In addition, Solé *et al* have demonstrated quick assembly of the tetracyclic core of (±)-subincanadine F by using a palladium catalyzed 7-*exo* Heck cyclization pathway (Scheme 10).[33]



Scheme 10. Synthesis of Tetracyclic Core of Subincanadine F via 7-*exo* Heck Cyclization

Treatment of *N*-protected iodotryptophol **96** with *p*-toluenesulfonyl chloride afforded the corresponding sulfonic acid ester, which upon reaction with pyridine formed the pyridinium salt **97**. Reduction of pyridinium salt **97** with sodium borohydride in methanol delivered the expected tetrahydropyridine **98** in 74% yield. After having compound **98** in hand they neatly studied intramolecular Heck cyclization reaction to construct the bridged system. After screening various ligands and bases with metal Pd as a catalyst, they obtained 76% yield of bridged tetracyclic system **99** by using $Pd_2(dba)_3$ as metal catalyst and dppp as ligand in presence of K_2CO_3 in toluene at 80 °C. In the present studies, Heck coupling reaction took place due to appropriate ring sizes and synthesis of target compound with few functional group transformations sounds achievable.

Overall these bridged subincanadine alkaloids bearing fixed positions of two nitrogen atoms and the exocyclic carbon–carbon double bonds have been meticulously synthesized employing several elegant intramolecular cyclization strategies. Recently the (+)-subincanadine E has gained unique identity as a proposed biogenetic precursor of five different structurally new alkaloids. In this context their chemistry has been briefly discussed in the following section.

1.4 Natural Congeners of Subincanadine E: Synthesis and Proposed Biosynthesis from Subincanadine

Kam and co-workers group in their dedicated efforts have isolated five indole alkaloids from Malaysian *Kopsia arborea* species, namely valparicine (**101**), known apparicine (**102**)[34] arboridinine (**103**), arborisidine (**104**) and arbornamine (**105**) along with subincanadine E (**10**) (Figure 5).[27] On the basis of rational structural evaluations of subincanadine E (**10**) and other five different alkaloids they initially proposed it as biogenetic precursor of all those natural product and later on in two cases they have also proved their hypothesis by accomplishing partial synthesis of them from subincanadine E (**10**) (Scheme 11).

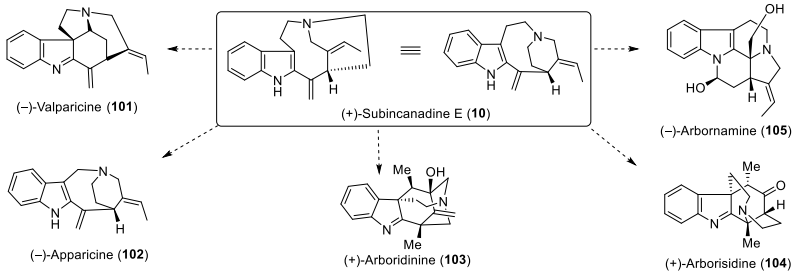
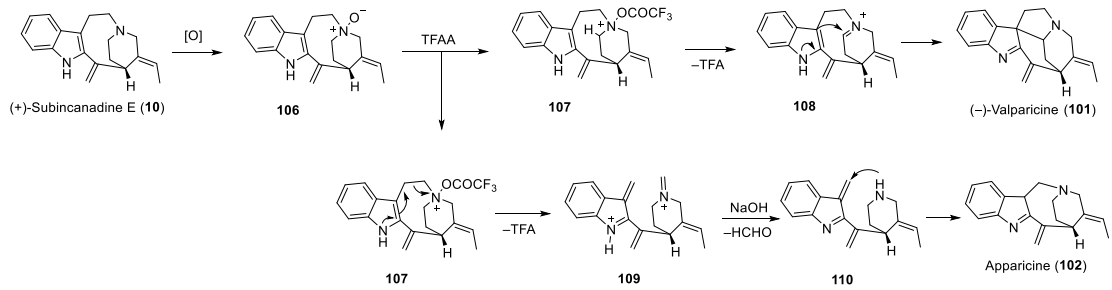


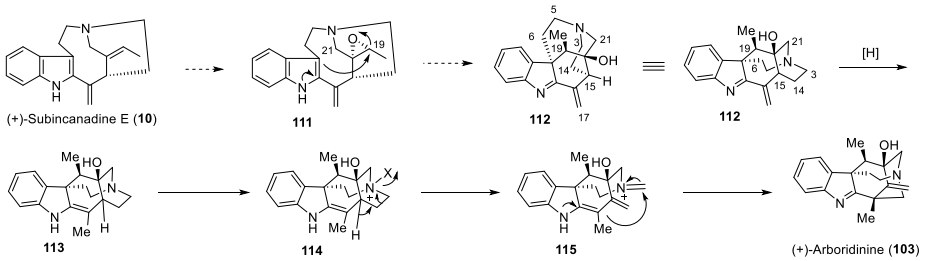
Figure 5. Subincanadine E as a common biogenetic precursor.

1.4.1 Valparicine and Apparicine: Synthesis of valparicine and apparicine was carried out from subincanadine E by using the Potier–Polonovski[35] reaction (Schemes 11). Subincanadine E (**10**) was converted into corresponding *N*-oxide **106** and its treatment with trifluoroacetic anhydride in DCM at –10 °C for 30 min followed by hydrolysis of iminium moiety in **109** with NaOH furnished valparicine (**101**) in 4% yield and apparicine (**102**) in 5% yield. They could further improve the yield of valparicine (**101**) to 10% and apparicine (**102**) to 26% by carrying out the same reaction with excess of TFAA under high dilution conditions (100 mL DCM). The proposed mechanism for present one-pot chemical transformation of subincanadine E to valparicine and apparicine via intramolecular cyclizations is quite acceptable and such type of enzyme and/or metal ion driven biogenetic pathways appear logical.



Scheme 11. Synthesis of Valparicine and Apparicine from Subincanadine E via Common Intermediate Involving Two Different Intramolecular Cyclizations

1.4.2 Arboridinine: The structure of arboridinine represents a new skeleton of the monoterpenoid indoles and it possesses an unprecedented pentacyclic cage moiety bound by two azepane, cyclohexyl and piperidine rings. The structure and absolute configuration of alkaloid was determined based on MS, NMR and X-ray diffraction analysis. A possible biogenetic pathway to arboridinine from subincanadine E (**10**) has also been presented in this report (Scheme 12).[27b] Selective oxidation of ethylidene double bond in **10** forms the corresponding epoxide **111** and subsequent nucleophilic attack from electron rich indole at C–19 epoxide carbon generates the six-membered ring with incorporation of 18–Me substituent in polycyclic imine **112**. Reduction via conjugate addition of hydride leads to the enamine **113** and having transformed to an intermediate with suitable leaving group on N–4 position followed by a Grob-like fragmentation results in the tetracyclic iminium intermediate **115**. Finally intramolecular attack by enamine furnishes the desired alkaloid arboridinine (**103**). Such type of thermodynamic stability driven heteroatom inspired multiple transformations in alkaloid chemistry are reasonable from involved mechanistic points of view.



Scheme 12. Proposed Biogenetic Pathway for Subincanadine E to Arboridinine Transformation

1.4.3 Arborisidine: Kam and co-workers proposed biogenetic pathway of two new monoterpene indole alkaloids arborisidine (**104**) incorporating indolizidine and cyclohexanone moieties fused to an indole unit and arbornamine (**105**) incorporating an unprecedented 6-5-6-5-6 "arbornane" skeleton; distinct from the well-known eburnan or tacaman 6-5-6-6-6 skeleton (Figure 6).[27c]

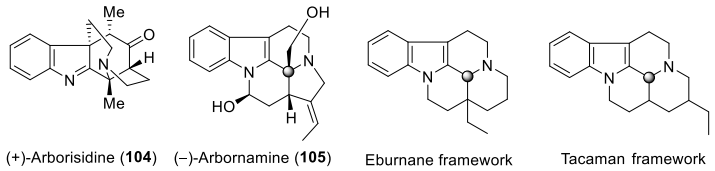
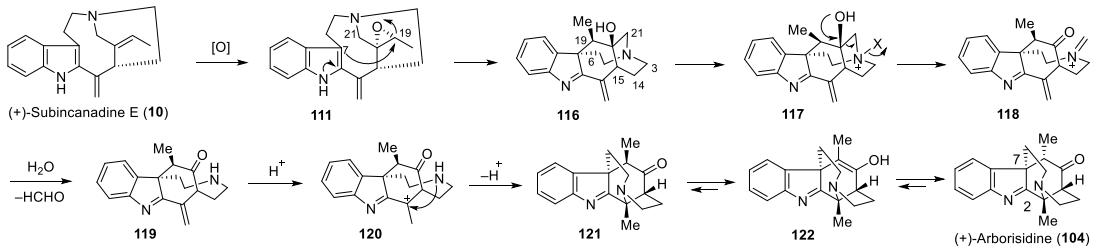


Figure 6. Monoterpene indole alkaloids.

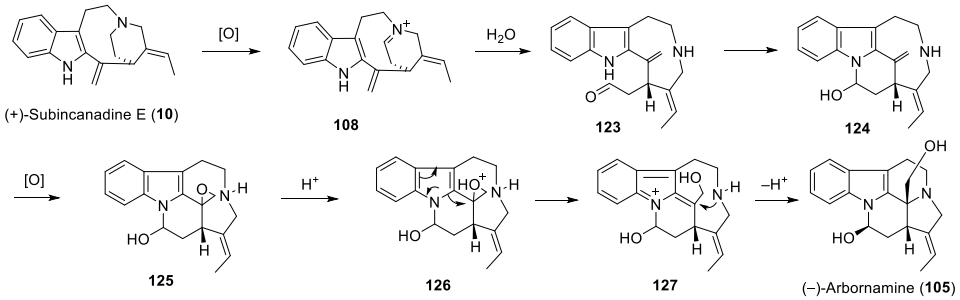


Scheme 13. A Possible Biogenetic Pathway for Subincanadine E to Arborisidine Transformation

Arborisidine (**104**) represents a new skeleton of monoterpenoid indole alkaloids characterized by an unusual and intriguing pentacyclic skeleton incorporating indolizidine and cyclohexanone moieties fused to an indole unit at C–2 and C–7 positions. A possible biogenetic pathway to this alkaloid from subincanadine E (**10**) has been depicted in scheme 13.[27c] Accordingly Kam and co-workers proposed selective oxidation of **10** to the epoxide **111** and its intramolecular epoxide ring opening by the attack from electron rich C–7 position of indole leading to the pentacyclic tertiary alcohol **116**. Installation of an appropriate leaving group on N–4 atom followed by a Grob-like fragmentation generates an iminium ion **118**. Hydrolysis of the iminium ion with loss of formaldehyde forms amino ketone **119**. Protonation of the exocyclic double bond in **119** to form **120** followed

by intramolecular nucleophilic attack of N–4 atom on resultant tertiary carbocation provides pentacyclic ketone **121** possessing the essential ring system of arborisidine. Subsequent keto-enol-mediated epimerization of **121** via **122** forms thermodynamically more stable epimer arborisidine (**104**). Overall it is a nice proposal of enzyme catalyzed epoxidation leading to oxidative transformation of (+)-subincanadine E to (+)-arborisidine.

1.4.4 Arbornamine: A possible biogenetic pathway to arbornamine (**105**) starting from subincanadine E (**10**) has been illustrated in scheme 14.[27c] Oxidation of **10** leads to the iminium ion **108** and which on hydrolytic cleavage transforms to aldehyde **123**. Intramolecular nucleophilic attack of indole nitrogen generates the tetracyclic *gem*-aminol **124**. Selective oxidation of the exocyclic double bond leading to epoxide **125** and subsequent lone-pair assisted epoxide ring cleavage forms **127**. Finally the conjugate addition of secondary amine results in hydroxymethyl-substituted pentacycle (−)-arbornamine (**105**). The proposed biogenetic pathway for brideged tetracylic subincanadine E to angular pentacyclic arbornamine translation is noteworthy from mechanistic point of view.



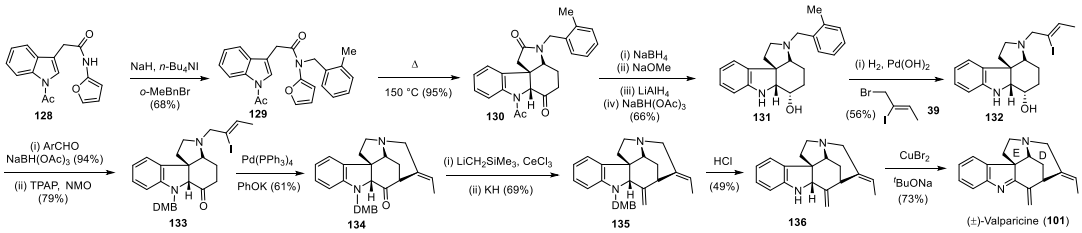
Scheme 14. A Possible Biogenetic Pathway for Subincanadine E to Arbornamine Conversion

Overall nice plausible biogenesis involving sound mechanistic proposals have been described by the authors and we feel that isolation and characterization of crucial intermediates is essential from confirmation point of view, although it is a difficult task.

1.5 Total Synthesis of Valparicine, Apparicine, Arboridinine, Arborisidine and Arbornamine

1.5.1 Valparicine:

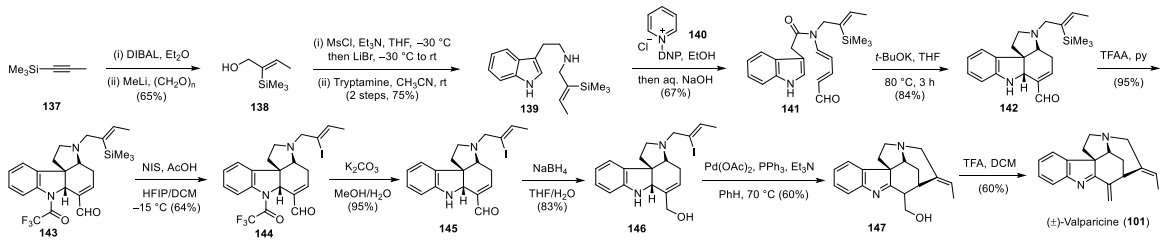
Valparicine has attracted immediate attention from synthetic community due to its unique architecture along with pronounced cytotoxic activity against KB and Jurkat cells and till date two racemic synthesis of this alkaloid have been known in the literature.



Scheme 15. First Total Synthesis of (±)-Valparicine

Padwa and co-workers in 2008 reported first total synthesis of valparicine (**101**) involving intramolecular [4+2]-cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran as a key reaction to provide *aza*-tetracyclic substructure containing ABCE-rings of the valparicine (Scheme 15).[36] The D-ring of natural product was assembled from *aza*-tetracyclic intermediate by an intramolecular palladium catalyzed enolate-driven cross-coupling between *N*–tethered vinyl iodide in **133** and keto functionality. Their synthesis began with protection of amide nitrogen in **128** with *o*-methylbenzyl bromide to form **129** (68% yield) for desired smooth intramolecular cycloaddition reaction. The presence of a large *o*-methylbenzyl group on amido nitrogen atom makes the corresponding reactive conformer highly populated thereby promoting desired intramolecular cycloaddition reaction. Heating of **129** at 150 °C in a microwave reactor in the presence of trace amount of MgI_2 for 30 min provided azatetracycle **130** in 95% yield (Scheme 15). The stereoselective reduction of keto group in **130** with $NaBH_4$ followed by *N*–deacetylation using NaOMe and reduction of lactam carbonyl group with $LiAlH_4$ resulted in enamine. It was further reduced by using $NaBH(OAc)_3$ to give alcohol **131** as a major diastereomer in 65% yield over four-step sequence. *o*-Methylbenzyl group in **131** was removed by catalytic hydrogenation and the subsequent *N*–alkylation with *Z*–1-bromo-2-iodobut-2-ene (**39**) provided alcohol **132** in 56% overall yield. Condensation of indoline nitrogen present in **132** with 2,4-dimethoxybenzaldehyde in the presence of $NaBH(OAc)_3$ afforded nitrogen-protected 2,4-dimethoxybenzylamine (DMB) derivative in 94% yield. Oxidation of secondary alcohol with tetrapropylammonium perruthenate (TPAP) provided the corresponding ketone **133** in 79% yield. The key intramolecular palladium-catalyzed cross-coupling was carried out on **133** by using $Pd(PPh_3)_4$ and PhOK for the installation of D ring. Delightfully, the above mentioned reaction proceeded smoothly and provided *aza*-pentacycle **134** in 61% yield. The next important assignment was installation of exocyclic carbon–carbon double bond. Reaction of trimethyl-silylmethyl lithium and cerium(III) chloride with keto carbonyl in **134** followed by heating of resultant alcohol with potassium hydride in THF delivered the C–16 methylene

unit bearing compound **135** in 69% yield. The DMB-protecting group was removed by warming **135** with HCl/MeOH to produce **136** in 49% yield. To complete the total synthesis, all that remained was an oxidation of the C–N single bond between the C–2 and N–1 position. Number of oxidizing reagents such as IBX, TPAP, MnO_2 were tried and also the Swern oxidation; however none of these reactions delivered the expected product. Finally stirring a sample of **136** with copper bromide and sodium *tert*-butoxide at 25 °C for 40 min resulted in the formation of (±)-valparicine (**101**) in 73% yield. Overall authors have accomplished an elegant total synthesis of valparicine via well designed [4+2] cycloaddition and palladium catalysed intramolecular cyclization as the key steps.

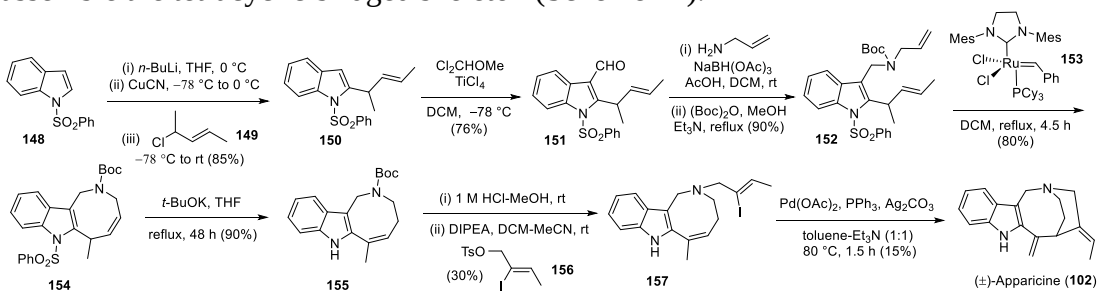


Scheme 16. Second Total Synthesis of (±)-Valparicine

Vanderwal and co-workers in 2011 reported the second total synthesis of (±)-valparicine (**101**) by using intramolecular Diels−Alder cycloaddition reaction of tryptamine-derived Zincke aldehydes as a key step to generate tetracycle ABCE (Scheme 16).[37] Hydroalumination of **137** with DIBAL-H followed by treatment of resultant vinylalane with methyllithium and reaction of the corresponding aluminate with paraformaldehyde afforded allylic alcohol **138**. Product **138** was converted to the corresponding allylic bromide via mesylate and then used for alkylation of tryptamine. Zincke aldehyde **141** was produced from secondary amine **139** under conventional conditions in 67% yield. Zincke aldehyde **141** on treatment with potassium *tert*-butoxide underwent anionic bicyclization and produced tetracycle **142** in 84% yield, as a single diastereomer. At this stage an iododesilylation reaction was required to provide Heck substrate **145**; however several attempts to directly get the desired vinyl iodide from **142** by variation of solvents, additives, source of I^+ and temperature were inefficient and they could obtain **145** only in 19% yield after the painstaking chromatographic separation. This reaction was primarily difficult because of preferential iodination of the electron-rich aromatic ring over iodosilylation. Above mentioned difficulty in chemoselectivity was circumvented and desired iodide **145** was obtained in a more reasonable 63% overall yield by three-step protocol involving, (i) temporary *N*-trifluoroacetylation of the indoline to reduce

reactivity of electron rich aromatic ring, (ii) iodination with NIS in 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) as a cosolvent to provide optimal reactivity and to avoid issues of stereochemical infidelity and (iii) deprotection of trifluoroacetate group. Aldehyde group of **145** was reduced with $NaBH_4$ to provide allylic alcohol **146**, which upon treatment with Pd-catalysed Heck reaction gave the imine **147** in very good overall yield via an enamine to imine isomerisation reaction after the β-hydride elimination. Finally trifluoroacetic acid induced dehydration of primary alcohol in **147** provided valparicine (**101**) in 60% yield. The present approach to valparicine is complementary to earlier synthesis by Padwa and co-workers.

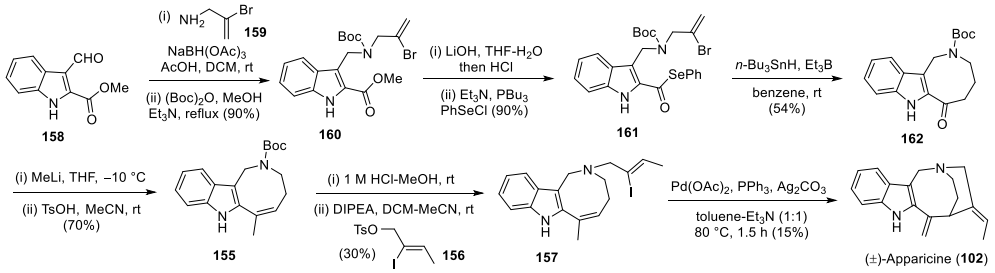
1.5.2 Apparicine: Bennasar and co-workers in 2009 reported first total synthesis of (±)-apparicine from 1-(phenylsulfonyl)indole (**148**) by using key reactions, (i) RCM reaction to create the central eight-membered ring containing tricyclic ABC substructure, (ii) base-promoted carbon–carbon double bond isomerization with an in situ indole nitrogen deprotection and (iii) finally challenging vinyl halide Heck cyclization reaction to assemble the tetracyclic bridged skeleton (Scheme 17).[38]



Scheme 17. First Total Synthesis of (±)-Apparicine

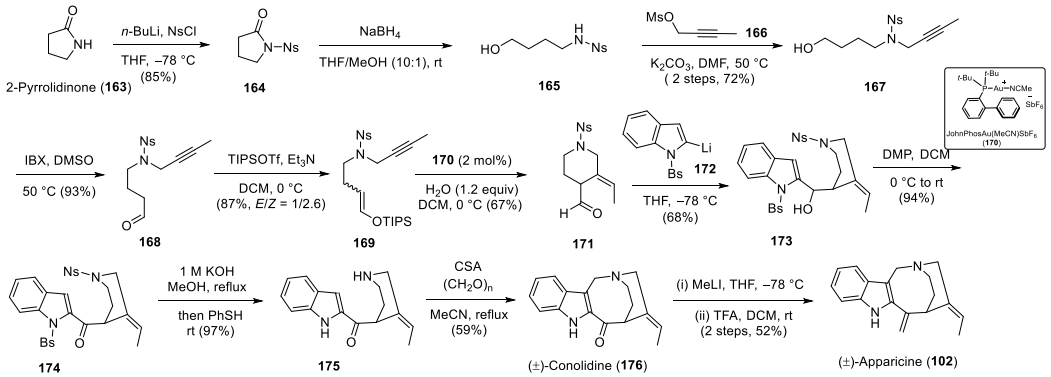
Their synthesis started with *n*-BuLi and CuCN mediated coupling reaction of 1-(phenylsulfonyl)indole (**148**) with (*E*)-4-chloro-2-pentene (**149**). The resultant indole **150** was then structured to RCM precursor **152** in four steps with 58% overall yield via Friedel–Crafts formylation, reductive amination of aldehyde **151** with allylamine and consequent protection of the formed allylic amine with Boc-anhydride. Ring closure metathesis reaction of diene **152** with second-generation Grubbs' catalyst **153** provided the 6-methylazocinoindole **154** in 80% yield. The base-induced desired carbon–carbon double bond isomerization and deprotection of indole *N*-phenylsulfonyl group by *t*-BuOK in refluxing THF delivered the desired compound **155** in 90% yield. The *N*-Boc deprotection of **155** proceeded effectively by treatment with HCl/MeOH at room temperature. The resultant unstable secondary amine was directly alkylated with (*Z*)-2-iodo-2-butenyl tosylate (**156**) to provide **157** in 30% yield over two steps. Final intramolecular coupling of the vinyl iodide and the alkene in **157** was realized in presence

of $Pd(OAc)_2/PPh_3$ and Ag_2CO_3 in toluene–Et_3N (1:1) at 80 °C with the formation of apparicine (**102**) in 15% yield. Overall authors have achieved first total synthesis of target compound via RCM-Heck based strategy by using two different protecting groups.



Scheme 18. Second Total Synthesis of (±)-Apparicine

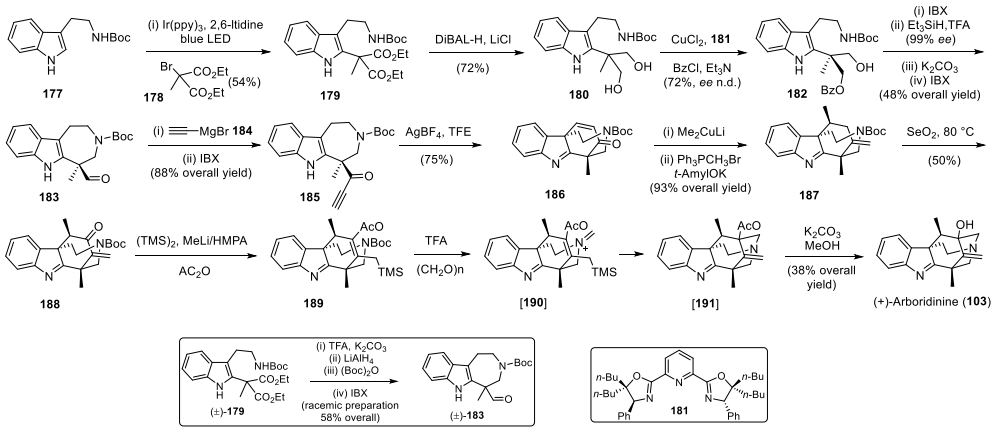
In the same year 2009 Bennasar and co-workers reported second synthesis of (±)-apparicine (**102**) by using 2-indolylacyl radical cyclization for construction of central eight membered tricyclic ring and intramolecular vinyl halide Heck reaction for ring closure of strained 1-azabicyclo[4.2.2]decane framework as the key reactions (Scheme 18).[39] Their synthesis began with reductive coupling of aldehyde **158** with 2-bromo-2-propenylamine (**159**) followed by usual protection of the resultant secondary amine with Boc-anhydride to provide ester **160**, which was converted into phenylselenyl ketone **161** through the corresponding carboxylic acid. Treatment of selenoester **161** with *n*-Bu_3SnH as a radical mediator and Et_3B as a radical initiator provided the desired ring closed ketone **162** in 54% yield. Finally, reaction of ketone **162** with methyllithium followed by dehydration of the resulting tertiary alcohol under acidic conditions (TsOH, CH_3CN, rt) smoothly furnished known alkene **155** in 70% yield. The formed intermediate **155** was transformed into target compound apparicine (**102**) by repeating known sequence of reactions from their earlier synthesis.[38] These syntheses suffer from low yield in last three steps and proper selection of catalyst along with refinements in reaction conditions will be favorable.



Scheme 19. Third Total Synthesis of (±)-Apparicine

Takayama and co-workers in 2016 have achieved total synthesis of (±)-apparicine (**102**) in 12 steps from commercially available 2-pyrolidinone. The synthesis was characterized by first gold(I)-catalyzed 6-*exo*-dig cyclization with silyl enol ethers having an internal alkynyl group (Scheme 19).[40] Synthesis commenced with treatment of 2-pyrrolidinone (**163**) with 2-nitrobenzenesulfonyl chloride in presence of *n*-butyllithium to obtain nitrobenzenesulfonamide **164** in 85% yield, which was further transformed into alcohol **165** by reduction with sodium borohydride in THF and methanol mixture. The reaction of alcohol **165** with alkylating reagent **166** afforded internal alkyne **167** in 72% yield. IBX-Oxidation of primary alcohol moiety in **167** provided aldehyde **168** in 93% yield. Treatment of aldehyde **168** with TIPSOTf in the presence of Et_3N gave alkynyl silyl enol ether **169** as mixture of geometrical isomers (*E*/*Z* = 1/2.6) in 87% yield. They investigated the novel gold(I)-catalyzed 6-*exo*-dig cyclization of silyl enol ether **169** under various reaction conditions and the use of 2 mol % JohnPhosAu(MeCN)SbF_6 **170** and 1.2 equivalents of water in CH_2Cl_2 at 0 °C yielded **171** in 67% yield. Coupling of aldehyde **171** with 2-lithio-benzenesulfonyl-indole **172** furnished mixture of diastereomeric alcohols **173** in 68% yield (*dr* = 18:1). Dess–Martin periodinane oxidation of the resultant secondary alcohol delivered ketone **174** in 94% yield. The brosylate protecting group in compound **174** was removed with potassium hydroxide in methanol at reflux temperature and it was followed by deprotection of the nosylate group with PhSH in same pot to afford Micalizio's intermediate **175** in 97% yield. To construct the central eight membered ring of target molecule, well designed indole derivative **175** was treated with CSA and paraformaldehyde in MeCN to provide (±)-conolidine (**176**) in 65% yield. Finally 1,2-addition of MeLi to ketone **176** provided the corresponding tertiary alcohol and its subsequent trifluoroacetic acid induced dehydration gave (±)-apparicine (**102**) in 52% yield over two steps. In the present synthesis insertion of one carbon unit using paraformaldehyde to generate eight membered ring in acceptable yield provides reasonably good solution to the earlier described low yielding intramolecular Heck protocol in such type of compounds.

1.5.3 Arboridinine: Snyder and coworkers in 2018 reported first total synthesis of unique pentacyclic cage skeleton containing indole alkaloid (±)/(+)-arboridinine (**103**). Key reactions involved in the synthesis were metal-mediated 6-*endo*-dig cyclization to design tetracyclic indolenine core and use of reversed polarity *aza*-Prins cyclization to provide tertiary allylic alcohol with final cage structure (Scheme 20).[41]

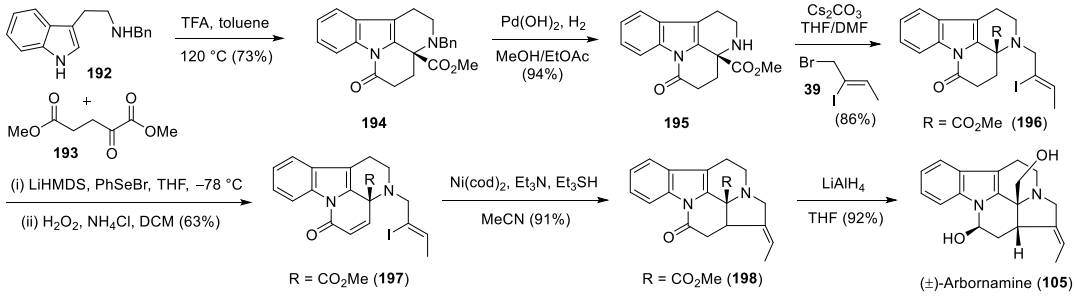


Scheme 20. First Total Synthesis of (±)/(+)-Arboridinine

Their synthesis began with construction of racemic as well as enantiospecific 7-membered ring in the target compound. At first photoirradiation driven generation of malonyl radical from **178** and its coupling with the electron-rich aromatic ring of Boc-protected tryptamine **177** smoothly afforded the C–2 functionalized indole **179** in 54% yield. Three step protocol involving deprotection-lactamization, reduction with $LiAlH_4$ and then a one-pot reprotection-oxidation using $(Boc)_2O$ and IBX provided the 7-membered ring containing aldehyde (±)-**183** with 58% overall yield. Employing the precedent established by Kang and co-workers, prochiral 1,3-diol **180** was resolved using ligand **181** in the presence of CuCl, BzCl and Et_3N to smoothly provide indole-containing compound **182** in 72% yield with high % *ee*. The oxidation and reductive amination of **182** furnished the Boc-protected azepinoindole core in 68% yield with 96% *ee* and further debenzoylation followed by oxidation completed the synthesis of enantioenriched aldehyde **183**. The Grignard reaction with **183** followed by IBX-oxidation of formed alcohol delivered the precursor **185** in 88% overall yield. Tetracyclic compound **186** was obtained from **185** in 75% yield by using novel metal mediated 6-*endo*-dig cyclization in presence of catalytic amounts of $AgBF_4$ in 2,2,2-trifluoroethanol (TFE) as solvent. The selective 1,4-addition using methyl cuprate and consequent Wittig reaction with ketone afforded alkene **187** in 93% overall yield. The allylic oxidation of **187** using excess of SeO_2 in 1,4-dioxane provided enone **188** in 50% yield. The newly formed *α,β*-unsaturated ketone motif was then converted into the compound **189** as a key precursor for *aza*-Prins cyclization through the nucleophilic 1,4-addition of an anion from trimethylsilyl and in situ trapping of the resulting enolate as its enol acetate. The Boc-deprotection in compound **189** with TFA followed by treatment with paraformaldehyde provided corresponding iminium intermediate **190**, which smoothly underwent in situ *aza*-Prins cyclization to form compound **191**. Finally K_2CO_3/MeOH mediated de-acylation of **191**

delivered the (±)/(+)-arboridinine (**103**) in 38% overall yield over three steps. In the present synthesis well designed *aza*-Prins reaction is important from strategic point of view.

1.5.4 Arbornamine: Yang and co-workers in 2018 reported first total synthesis of the distinctive monoterpene indole alkaloid (±)-arbornamine (**105**) in 6 steps with 31% overall yield from three easily available known compounds **39**, **192** and **193** (Scheme 21).[42]



Scheme 21. First Total Synthesis of (±)-Arbornamine

The synthesis features a cascade involving a Pictet−Spengler cyclization and intramolecular ammonolysis to create the tetracyclic core of arbornamine (**105**) in a single step. The subsequent elaboration of **197** into **105** was achieved by key reductive Heck reaction and global reduction of lactam and ester carbonyls. The tetracyclic *δ*-lactam **194** was obtained in 73% yield by heating the benzyl-protected tryptamine derivative **192** with dimethyl keto-ester **193** in presence of TFA in refluxing toluene. In order to remove the benzyl protecting group, *δ*-lactam **194** was first exposed to hydrogenolysis conditions using Pearlman's catalyst and later on alkylated with readily available (*Z*)-1-bromo-2-iodobut-2-ene (**39**) to provide the corresponding vinyl iodide **196** in 81% overall yield. The vinyl iodide **196** with typical selenation and selenoxide-elimination protocol provided conjugated tetracyclic *δ*-lactam **197** in 63% yield over two steps. Reductive Heck cyclization mediated by $Ni(cod)_2$ was investigated and the desired pentacyclic product **198** was obtained in 91% yield. Finally *δ*-lactam and methyl ester were reduced with lithium aluminum hydride to provide (±)-arbornamine (**105**) in 92% yield. The well-planned benzyl protection for the generation of desired tetracyclic core in one-pot and nickel-catalyzed intramolecular cyclization are the key features in this concise and efficient synthesis.

Overall six racemic and one asymmetric total synthesis of structurally complex subincanadine biogenetic congeners have been discussed briefly; however synthesis of

arborisidine is still awaited. An elegant new chemistry has been reported in those syntheses involving metal-catalyzed intramolecular cyclizations as key steps.

1.6 Summary

In summary, we have presented a concise account of the recently isolated structurally interesting and biologically important indole alkaloids subincanadines A–G as well as their natural congeners. More specifically the subincanadines E and F are potent anticancer agents and therefore Brazilian medicinal plant Aspidosperma subincanum are consumed for medical benefits as an unapproved drug. The subincanadine E alkaloid is structurally flexible and five different proposed biogenetic congeners of the same have been originated via splendid mechanistic circus. All these indole alkaloids are tryptamine based and encompass novel bridged skeleton (except arbornamine) along with exocylic carbon–carbon double bond (except arborisidine). Total synthesis of these target compounds have been neatly pursued since 2006 for both the synthetic challenge in tailoring bridged architectures and conversed biological activity point of view. Till date one enantioselective total synthesis of each subincanadine A, subincanadine B, subincanadine F and arboridinine have been reported in the contemporary literature. However several racemic total synthesis of these alkaloids subincanadine E (one), subincanadine F (three), valparicine (two), apparicine (three), arboridinine (one) and arbornamine (one) are also known in the literature. As expected all these indole alkaloids were synthesized starting from tryptamine derivatives except apparicine, employing variety of elegant synthetic strategies. It is noteworthy that metal chemistry has played a central role in realizing all those total synthesis. The key diastereoselective/enantioselective steps involved in those total syntheses were Pictet-Spengler cyclization, intramolecular Nozaki-Hiyama-Kishi reaction, intramolecular Michael addition, SmI_2-mediated ring opening and bridge-forming Mannich reaction, chemoselective Dieckmann condensation, titanium-induced intramolecular nucleophilic acyl substitution reaction, unusual 7-endo-trig stereoselective radical cyclization, intramolecular [4+2]-cycloaddition/rearrangement cascade reaction, intramolecular Heck cyclization leading to difficult bridged system, intramolecular Diels-Alder reaction, RCM reaction to create eight-membered ring system, gold(I)-catalyzed 6-exo-dig cyclization and aza-Prins cyclization. Overall total syntheses of all those alkaloids involving large amount of new chemistry are strategically important and have been

presented herein with the help of twenty one schemes and nearly hundred contemporary references from various reputed international journals.

We strongly believe that it is an important area of research in indole alkaloid chemistry with broad scope and it will be of continuing interest to both the synthetic and medicinal chemists. More specifically new concise and efficient enantioselective total synthesis of potent subincanadine E and F will be commendable from their practical applications point of view. Positively there will be interminable promising advancements in the knowledge and in this context, as part of present dissertation; we have accomplished conceptually new synthesis of some of the natural/unnatural target compounds. Our synthetic strategies towards the total synthesis of these subincanadine natural products and their synthetic analogues will be discussed with complete details in the second and third chapters of present dissertation.

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Chapter 2

Synthetic Studies on Indole Alkaloids

(±)-Subincanadine B and C

Section A

In Progress Synthesis of (±)-Subincanadine B via Imperative Davis Hydroxylation

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 first section presents results of ongoing synthesis of (±)-subincanadine B. The second section describes a diastereoselective synthesis of (±)-*epi*-subincanadine C along with our systematic studies on the synthesis of (±)-subincanadine C. 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.

2A.1 Background

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

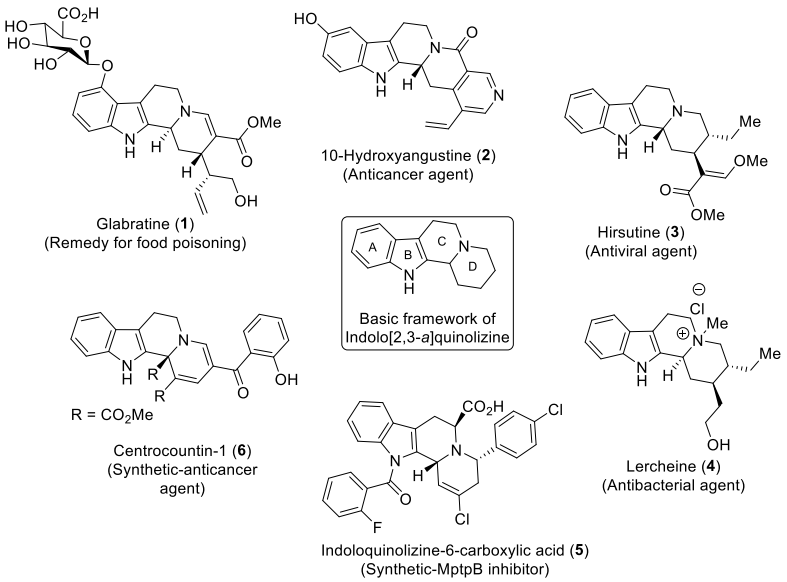


Figure 1. Bioactive natural and synthetic products with indolo[2,3-*a*] quinolizine framework.

Subincanadines A–C and G (**7**–**10**) structurally containing rare 6-5-6-5 architecture with characteristic chiral quaternary center at C–16 position, which distinct them from most abundant and diverse group of indole alkaloid eburnanes and tacamans with 6-5-6-6 framework (Figures 1–3). Subincanadines A–G were isolated from the bark of Brazilian medicinal plant *Aspidosperma subincanum* in 2002 by Oshaki and co-workers.[13] Even though the tetrahydro-*β*-carboline pyrrolidine scaffold present in subincanadines is rare, it also exists in recently isolated arbornamine (**11**) and tabertinggine (**12**) (Figure 2).[14,15]

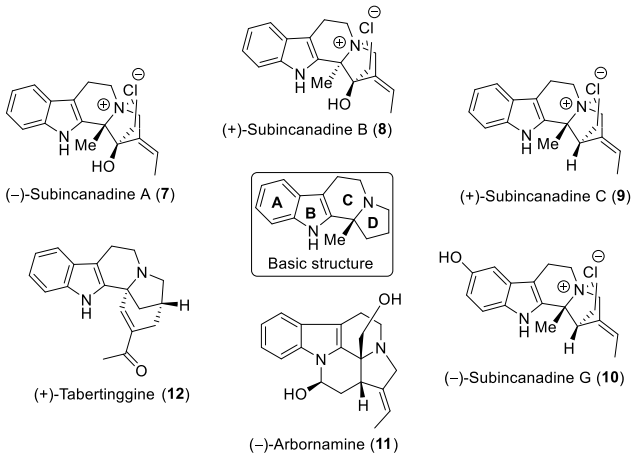


Figure 2. Indole alkaloids containing unusual 6-5-6-5 (A-B-C-D) framework.

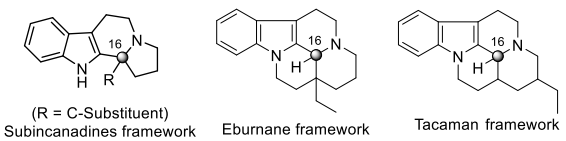


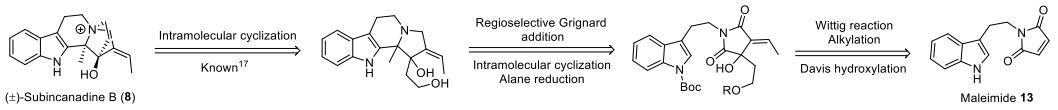
Figure 3. Difference between subincanadines, eburnane and tacaman framework.

Subincanadine B (**8**), a novel quaternary pentacyclic indole alkaloid, featuring an unprecedented 1-azoniatricyclo[4.3.3.$0^{1,5}$]undecane skeleton was isolated in only 0.002% yield. The complex architecture and scarcity of subincanadines B in nature have directed immediate attention from synthetic community and it became important synthetic target. Zhai and co-workers in 2006 have reported first synthetic approach towards the synthesis of (±)-subincanadine B and their efforts efficiently resulted in synthesis of two pentacyclic analogues of subincanadine B (19,20-dihydrosubincanadine B and 20-deethylenylated subincanadine B; please see chapter 1; scheme 1 and page no. 5).[16] In the same year 2006 Takayama and co-workers reported first asymmetric total synthesis of (–)-subincanadine A (**7**) and enantiomer of (+)-subincanadine B (**8**) starting from commercially available (*S*)-

malic acid involving an intramolecular diastereoselective Pictet-Spengler cyclization and an intramolecular Nozaki-Hiyama-Kishi reaction as the key steps (please see chapter 1; scheme 2 and page no. 6).[17] Elegant diastereoselective synthetic routes to other indole alkaloids subincanadine C (**9**), arbornamine (**11**) and tabertinggine (**12**) have also been reported in the contemporary literature.[18–20] However, enantioselective synthesis of subincanadines B, C, G (**8**–**10**), arbornamine (**11**) and tabertinggine (**12**) are still awaited.

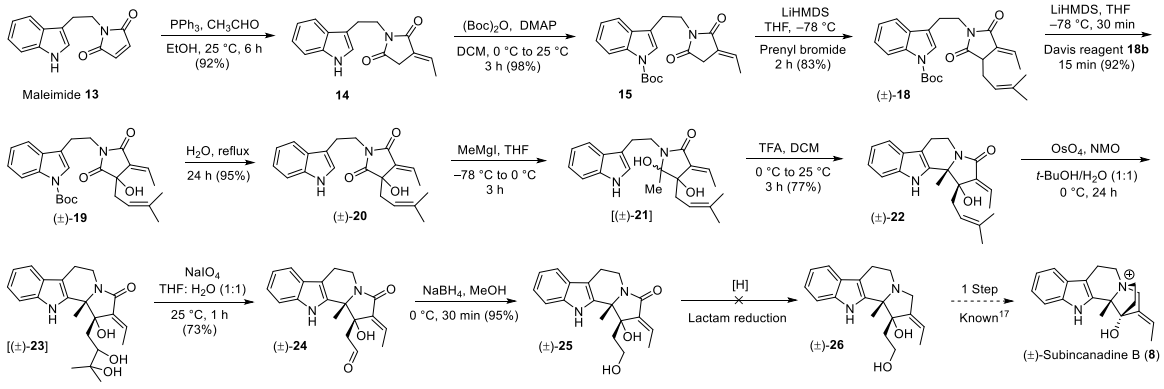
2A.2 Results and Discussion

A careful inspection of (±)-subincanadine B (**8**) structure revealed that retro-synthetically tryptamine based maleimide **13** would be the potential building block for its diastereoselective total synthesis (Scheme 1). In continuation of our studies on total synthesis of bioactive natural products by using cyclic anhydride and their derivatives;[21–25] we herein present the detailed systematic studies towards the synthesis of (±)-subincanadine B via imperative Davis hydroxylation and an intramolecular Pictet-Spengler cyclization as the key steps (Schemes 1 to 4).

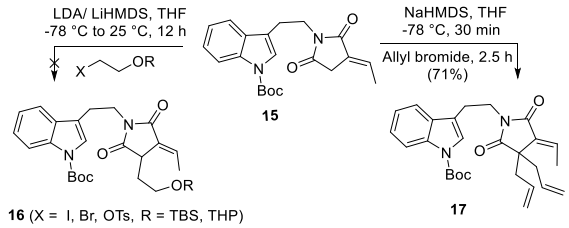


Scheme 1. Concise Retrosynthetic Analysis of (±)-Subincanadine B

At first Wittig reaction of imide **13** with acetaldehyde was planned for the stereoselective generation of desired exocyclic carbon–carbon double bond, activation of methylene group in the formed imide moiety for base induced alkylation/allylation and also to differentiate the reactivity of two imide carbonyls to impart complete regioselectivity. Indolylmaleimide **13** on triphenylphosphine induced Wittig reaction with acetaldehyde exclusively delivered the alkylidenesuccinimide **14** in 92% yield (Scheme 2).[26,27] The *E*-geometry of carbon–carbon double bond in product **14** was established on the basis of deshielding of a vinylic proton (δ 6.88) due to its *peri*-interaction with an imide carbonyl group. As described in scheme 3, all attempts on LDA/LiHMDS induced alkylation of compound **15** using various alkylating agents to directly introduce the protected β-hydroxyethyl chain to obtain product **16** were unsuccessful, plausibly due to the lower reactivity of corresponding alkyl halides/tosylate. Base-induced allylation of imide **15** using allyl bromide was feasible, but always resulted in the diallylated imide **17** as a



Scheme 2. Synthesis of Tetracyclic Framework of (±)-Subincanadine B via Novel Davis Hydroxylation and Intramolecular Pictet–Spengler Cyclization



Scheme 3. Attempted Base Induced Mono-Alkylations

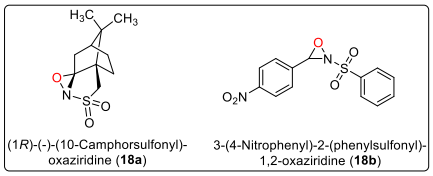
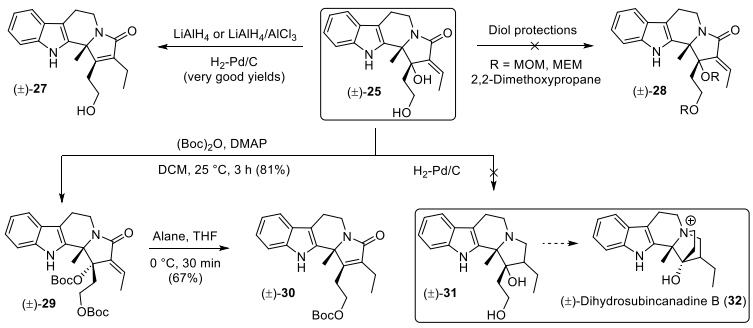


Figure 4. Davis reagents.

major product in very good yields. The above specified difficulty of diallylation was circumvented by using bulky prenyl bromide to exclusively obtain the mono-prenylated product **18** in 83% yield. All attempts to get enantio-enriched **19** by reaction with enantiomerically pure Davis reagent **18a** were unsuccessful and resulted in the formation of scalemic mixture of two enantiomers in 60:40 ratio, even at –78 °C (Figure 4). The LiHMDS induced hydroxylation of compound **18** using Davis reagent **18b**[28] successfully provided the desired compound (±)-**19** in 92% yield. Direct transformation of the imide **19** into hydroxy-indolizinoindolone **22** in one-pot via regioselective Grignard reaction with MeMgI, acid induced Boc-deprotection and diastereoselective Pictet–Spengler cyclization were inefficient and the desired product **22** was formed in very low yield. All those one-pot transformations always resulted in excessive decomposition due to an acid sensitive nature of the initially formed lactamol intermediate and unfortunately the prerequisite Boc-deprotection reaction was relatively slow. Imide **19** was also prone for hydrolytic cleavage under acidic conditions and therefore the Boc-deprotection was planned under neutral reaction conditions. Imide **19** in refluxing water[29] underwent smooth Boc-deprotection and provided the desired product **20** in 95% yield. Regioselective reaction of methylmagnesium iodide with the relatively more reactive

unconjugated imide carbonyl moiety in succinimide **20** followed by an immediate trifluoroacetic acid induced diastereoselective Pictet–Spengler cyclization[17,30] of the formed lactamol **21** exclusively furnished the expected *syn*-product **22** in 77% yield, via the corresponding flat iminium-ion intermediate. The structure of formed *syn*-indolizinoindolone **22** was confirmed on the basis of 2 D NMR analyses. Selective osmium tetraoxide induced dihydroxylation reaction of more electron rich carbon–carbon double bond in compound **22** at 0 °C provided required diol **23**; which was used for the next step without any purification for polarity issues. The obtained diol **23** on sodium periodate induced cleavage resulted in aldehyde **24** in 73% yield over two steps. One-pot alane ($LiAlH_4/AlCl_3$) reduction of aldehyde and lactam units in compound **24** to get the known compound **26** was planned but unfortunately always resulted in excessive decomposition. The reaction of aldehyde **24** with $NaBH_4$ in MeOH at 0 °C furnished more stable diol **25** in 95% yield. Next reduction of lactam carbonyl in **25** with various reducing agents such as alane, $LiAlH_4$, borane, DIBAL, $Et_3SiH/Ru_3(CO)_{12}$, $(EtO)_3SiH/Ru_3(CO)_{12}$[31] in different solvents at various temperature were examined to get compound **26** for the completion of formal synthesis of (±)-subincanadine B. Unfortunat-



Scheme 4. Lactam Reduction Leading to Formation Undesired S_N2' elimination product

ly under all above specified conditions we did not obtain the desired compound **26**; instead it always underwent S_N2' elimination leading to formation of undesired product **27** in very good yield (Scheme 4). Protection of hydroxyl units in compound **25** as *O*-MEM ether or ketal was also not fruitful under different set of reaction conditions. However double Boc-protection was feasible but the formed product was also very prone to undergo undesired S_N2' elimination and similarly delivered the product **30**. Finally we planned to synthesize (±)-dihydrosubincanadine B (**32**) via reduction of the carbon–carbon double bond in compound **25** to prevent S_N2' elimination reaction. The H_2-Pd/C hydrogenation of carbon–carbon double bond in **25** was also difficult and unfortunately once again it provided the undesired elimination product **27**. Diol **25** featured a rather rigid

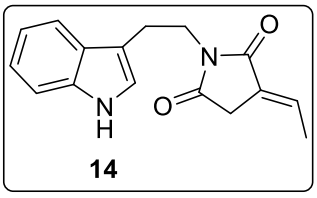
skeleton and the steric accessibility around hydroxyl groups needs to be taken into consideration while selecting suitable protecting groups. At this stage we concluded that protection of tertiary hydroxyl group prior to tetracycle formation will be useful to accomplish the synthesis of (±)-subincanadine B and further work is in active progress.

2A.3 Summary

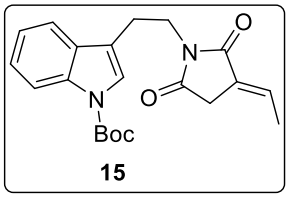
In summary, synthesis of tetracyclic framework of (±)-subincanadine B has been accomplished via an early stage stereoselective introduction of the desired carbon–carbon double bond by using Wittig reaction and it was useful to activate methylene protons for base induced smooth prenylation, hydroxylation and also to govern the regioselectivity in Grignard addition reaction. The penultimate step reduction of well-designed lactam carbonyl is under investigation and in preliminary studies we have faced the difficulty of S_N2' reaction leading to undesired elimination of tertiary hydroxyl group. We feel that the suitable protection of the tertiary alcohol moiety is essential prior to cyclization and the work is in active progress. Our present approach is quite flexible and will provide efficient synthetic paths to other similar hydroxyl bearing related alkaloids including subincanadine D.

2A.4 Experimental Section

(*E*)-1-[2-(1*H*-Indol-3-yl)ethyl]-3-ethylidenepyrrolidine-2,5-dione (14). To a stirred solution of compound **13** (5.00 g, 20.83 mmol) in ethanol (80 mL) was added triphenylphosphine (6.54 g, 24.99 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 30 min at the same temperature and then acetaldehyde (1.76 mL, 31.24 mmol) was added at 0 °C. The reaction mixture was further stirred for 5.5 h and allowed to reach 25 °C. The resultant mass was filtered through Buckner funnel and washed with ethanol. The obtained solid product was dried by using vacuum pump to afford compound **14** as a white solid (5.06 g, 92%). Mp 163–165 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 (d, J = 7.4 Hz, 3H), 3.09 (t, J = 7.7 Hz, 2H), 3.16 (s, 2H), 3.91 (t, J = 7.7 Hz, 2H), 6.84–6.91 (m, 1H), 7.06 (s, 1H), 7.14 (t, J = 7.9 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 8.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 23.5, 31.7, 39.2, 111.1, 112.2, 118.7, 119.4, 122.0, 122.1, 126.7, 127.4, 133.5, 136.1, 169.8, 174.1; HRMS (ESI) (m/z) $[M+Na]^+$ calcd for $C_{16}H_{16}N_2O_2Na$ 291.1104, found 291.1105; IR ($CHCl_3$) ν_{max} 3373, 1760, 1701 cm^{-1}.



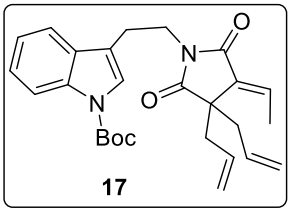
14



15

***tert*-Butyl (*E*)-3-[2-(3-Ethylidene-2,5-dioxopyrrolidin-1-yl)ethyl]-1*H*-indole-1-carboxylate (15).** To a stirred solution of compound **14** (4.50 g, 16.79 mmol) in CH_2Cl_2 (60 mL) was added $(Boc)_2O$ (4.24 mL, 18.47 mmol) at 25 °C and catalytic amount of DMAP (204 mg, 1.68 mmol) and the reaction mixture was stirred for 3 h. Reaction was quenched with water and aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) afforded compound **15** as a white solid (5.90 g, 98%). Mp 137–139 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.68 (s, 9H), 1.89 (d, J = 7.3 Hz, 3H), 3.01 (t, J = 7.3 Hz, 2H), 3.21 (s, 2H), 3.89 (t, J = 7.6 Hz, 2H), 6.82–6.94 (m, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.48 (br s, 1H), 7.67 (d, J = 7.3 Hz, 1H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.4, 23.4, 28.2, 31.8, 38.3, 83.4, 115.2, 116.8, 118.9, 122.5, 123.3, 124.4, 126.6, 130.2, 133.8, 135.5, 149.6, 169.6, 173.9; ESIMS (*m*/*z*) 369 $[M+H]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{24}N_2O_4Na$ 391.1628, found 391.1629; IR ($CHCl_3$) ν_{max} 1715, 1680, 1608 cm^{-1}.

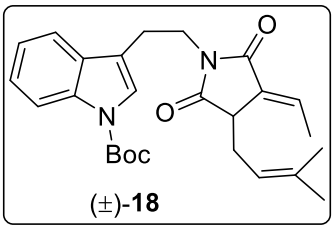
***tert*-Butyl (*E*)-3-[2-(3,3-Diallyl-4-ethylidene-2,5-dioxopyrrolidin-1-yl)ethyl]-1*H*-indole-1-carboxylate (17).** To a stirred solution of compound **15** (500 mg, 1.35 mmol) in dry THF (10 mL) was dropwise added a solution of LiHMDS in hexane (1 M, 1.35 mL, 1.35 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred for 30 min and allyl bromide (116 μL, 1.35 mmol) was added dropwise. The reaction mixture was further stirred for 2 h at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl. Solvent THF was removed in vacuo and the reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 20:80) afforded compound **17** as a white solid (225 mg, 37%; 71% brsm). Mp 144–146 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.67 (s, 9H), 2.00 (d, J = 7.6 Hz, 3H), 2.56 (dd, J = 13.6 and 7.4 Hz, 2H), 2.67 (dd, J = 13.6 and 7.9 Hz, 2H), 2.93 (t, J = 7.9 Hz, 2H), 3.85 (t, J = 8.0 Hz, 2H), 4.98 (d, J = 10.1 Hz, 2H), 5.06 (d, J = 17.1 Hz, 2H), 5.41–5.50 (m, 2H), 7.01 (q, J = 7.7 Hz, 1H), 7.27 (t, J = 8.2 Hz, 1H), 7.32 (t, J = 7.0 Hz, 1H), 7.45 (s, 1H), 7.68 (d, J



17

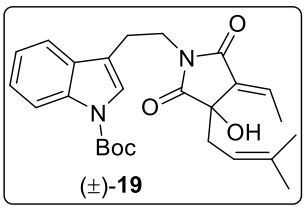
= 7.6 Hz, 1H), 8.13 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 23.6, 28.2, 38.2, 40.0, 51.7, 83.4, 115.2, 116.8, 119.1, 119.3, 122.6, 123.4, 124.4, 130.2, 130.9, 131.6, 134.9, 169.6, 178.8, 135.5, 149.6; ESIMS (*m*/*z*) 449 $[M+H]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{27}H_{32}N_2O_4Na$ 471.2254, found 471.2248; IR ($CHCl_3$) ν_{max} 1726, 1704, 1670 cm^{-1}.

***tert*-Butyl (*E*)-3-{2-[3-Ethylidene-4-(3-methylbut-2-en-1-yl)-2,5-dioxopyrrolidin-1-yl]ethyl}-1*H*-indole-1-carboxylate (18).** To a stirred solution of compound **15** (3.00 g, 8.15 mmol) in dry THF (30 mL) was dropwise added a solution of LiHMDS in hexane (1 M, 8.15 mL, 8.15 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred for 30 min and prenyl bromide (941 μL, 8.15 mmol) was added dropwise. The reaction mixture was further stirred for 2 h at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl. Solvent THF was removed in vacuo and the obtained residue was dissolved in EtOAc (60 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 25:75) afforded compound (±)-**18** as thick oil (2.94 g, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60 (d, *J* = 3.7 Hz, 6H), 1.67 (s, 9H), 1.94 (d, *J* = 7.4 Hz, 3H), 2.51–2.58 (m, 1H), 2.70–2.77 (m, 1H), 2.94 (t, *J* = 7.9 Hz, 2H), 3.40 (t, *J* = 5.2 Hz, 1H), 3.80–3.90 (m, 2H), 4.95 (t, *J* = 6.7 Hz, 1H), 6.92 (qd, *J* = 7.3 and 2.1 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 8.6 Hz, 1H), 7.47 (s, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 8.14 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 17.9, 23.5, 25.7, 28.2, 28.7, 38.1, 42.4, 83.4, 115.2, 116.8, 117.5, 119.0, 122.5, 123.2, 124.4, 130.2, 130.4, 134.0, 135.5, 136.1, 149.6, 169.7, 177.1; HRMS (ESI) $[M+Na]^+$ calcd for $C_{26}H_{32}N_2O_4Na$ 459.2254, found 459.2250; IR ($CHCl_3$) ν_{max} 1705, 1675, 1608 cm^{-1}.



(±)-**18**

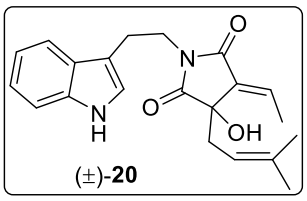
***tert*-Butyl (*E*)-3-{2-[4-Ethylidene-3-hydroxy-3-(3-methylbut-2-en-1-yl)-2,5 dioxopyrrolidin-1-yl]ethyl}-1*H*-indole-1-carboxylate (19).** To a stirred solution of compound **18** (2.80 g, 6.42 mmol) in dry THF (30 mL) was dropwise added a solution of LiHMDS in hexane (1 M, 6.42 mL, 6.42 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred for 30 min and Davis reagent **18b** (2.36 g, 7.70 mmol) in anhydrous THF (10 mL) was added in a dropwise fasion. The reaction mixture was further stirred for 15 min at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl. Solvent THF was removed in vacuo and the obtained



(±)-**19**

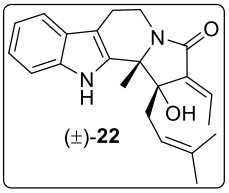
residue was dissolved in EtOAc (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 25:75) afforded compound (±)-**19** as thick oil (2.66 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 3H), 1.62 (s, 3H), 1.67 (s, 9H), 2.13 (d, J = 6.9 Hz, 3H), 2.57–2.65 (m, 1H), 2.74–2.82 (m, 1H), 2.88–3.02 (m, 3H), 3.85 (t, J = 7.8 Hz, 2H), 4.89 (t, J = 8.2 Hz, 1H), 7.05 (q, J = 7.3 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.3 Hz, 1H), 7.47 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 17.9, 23.4, 25.9, 28.2, 37.0, 38.0, 75.2, 83.5, 115.3, 115.6, 116.6, 118.9, 122.6, 123.3, 124.5, 130.2, 131.4, 135.5, 138.2, 138.3, 149.6, 168.0, 178.0; ESIMS (m/z) 475 $[M+Na]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{26}H_{32}N_2O_5Na$ 475.2203, found 475.2198; IR ($CHCl_3$) ν_{max} 3376, 1730 cm^{-1}.

(*E*)-1-[2-(1*H*-Indol-3-yl)ethyl]-4-ethylidene-3-hydroxy-3-(3-methylbut-2-en-1 yl)pyrrolidine-2,5-dione (20). The compound (±)-**19** (2.50 g, 5.53 mmol) and distilled water (60 mL) mixture was refluxed for 24 h. The reaction mixture was allowed to reach 25 °C and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 60:40) afforded (±)-**20** as a solid (1.85 g, 95%). Mp 131–133 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60 (s, 3H), 1.61 (s, 3H), 2.12 (d, J = 7.7 Hz, 3H), 2.40 (br s, 1H), 2.58 (dd, J = 13.7 and 6.9 Hz, 1H), 2.75 (dd, J = 13.5 and 9.2 Hz, 1H), 2.97–3.08 (m, 2H), 3.86 (t, J = 7.6 Hz, 2H), 4.87 (t, J = 8.1 Hz, 1H), 7.03 (q, J = 7.7 Hz, 1H), 7.08 (s, 1H), 7.14 (t, J = 7.7 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.3, 17.9, 23.5, 25.9, 36.7, 38.9, 75.1, 111.2, 112.1, 115.6, 118.8, 119.4, 122.1 (2C), 127.3, 131.5, 136.1, 137.9, 138.2, 168.1, 178.0; ESIMS (m/z) 375 $[M+Na]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{24}N_2O_3Na$ 375.1679, found 375.1677; IR ($CHCl_3$) ν_{max} 3477, 3383, 1769, 1706 cm^{-1}.



(±)-**20**

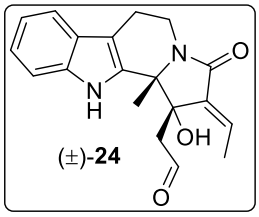
(*E*)-2-Ethylidene-1-hydroxy-11b-methyl-1-(3-methylbut-2-en-1-yl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (22). To a stirred solution of compound (±)-**20** (1.50 g, 4.26 mmol) in dry THF (20 mL) was added solution of methylmagnesium iodide in diethyl ether



(±)-**22**

(3 M, 4.97 mL, 14.9 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was allowed to reach 0 °C in next 3 h and quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (25 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded intermediate lactamol **21**; which was immediately used for the next step without any further purification. To a stirred solution of lactamol **21** in CH_2Cl_2 (20 mL) was added TFA (847 μL, 11.1 mmol) at 0 °C and the reaction mixture was stirred for 3 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with $NaHCO_3$, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 50:50) afforded compound (±)-**22** as a white solid (1.14 g, 77%). Mp 167–169 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.52 (s, 3H), 1.62 (s, 3H), 1.70 (s, 3H), 1.85 (d, J = 7.3 Hz, 3H), 2.60 (dd, J = 15.2 and 4.9 Hz, 1H), 2.64–2.84 (m, 3H), 3.14 (td, J = 11.9 and 5.5 Hz, 1H), 4.22 (dd, J = 12.8 and 6.1 Hz, 1H), 5.30 (t, J = 6.7 Hz, 1H), 5.39 (s, 1H), 6.47 (q, J = 7.3 Hz, 1H), 6.94 (t, J = 7.9 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 7.30–7.43 (m, 2H), 10.30 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 13.7, 18.0, 19.7, 22.1, 25.9, 35.8, 36.1, 65.5, 79.2, 107.0, 111.4, 117.6, 118.2, 120.5, 120.8, 126.2, 132.35, 132.39, 136.1 (2C), 137.0, 168.2; ESIMS (m/z) 351 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_2$ 351.2067, found 351.2069; IR ($CHCl_3$) ν_{max} 3330, 1710 cm^{-1}.

(*E*)-2-[2-Ethylidene-1-hydroxy-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl]acetaldehyde (24). To a stirred solution of compound **22**

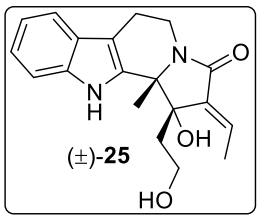


(±)-**24**

(1.00 g, 2.85 mmol) in THF:H_2O (3:1, 25 mL) was added NMO (50% in water, 3.34 mL, 14.29 mmol) and catalytic amount of OsO_4 (0.20 mL, 0.50 M solution in *t*-BuOH) at 0 °C and reaction mixture was stirred for 24 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ and further stirred for 30 min. Aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried triol **23** was directly used for next step. To a stirred solution of obtained triol in THF: H_2O (1:1, 35 mL) was added $NaIO_4$ (2.42 g, 11.40 mmol) at 25 °C in three equal

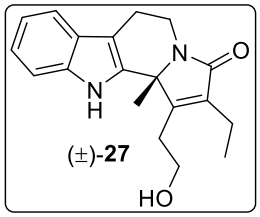
lots. The reaction mixture was diluted with EtOAc and after 1 h the separated organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, EtOAc–PE, 50:50) afforded compound **24** as a solid (675 mg, 73%). Mp 123–125 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60 (s, 3H), 2.03 (d, J = 7.7 Hz, 3H), 2.75 (dd, J = 15.7 and 5.0 Hz, 1H), 2.97–3.05 (m, 1H), 3.09 (s, 1H), 3.15 (d, J = 17.6 Hz, 1H), 3.21 (td, J = 11.8 and 5.0 Hz, 1H), 3.43 (d, J = 17.2 Hz, 1H), 4.55 (dd, J = 13.4 and 6.5 Hz, 1H), 6.83 (q, J = 7.6 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 9.12 (s, 1H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 20.3, 24.0, 36.3, 49.3, 65.9, 78.6, 110.1, 111.4, 118.4, 119.6, 122.5, 126.6, 133.9, 135.6, 135.9, 136.3, 166.8, 202.2; ESIMS (*m*/*z*) 347 $[M+Na]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{20}N_2O_3Na$ 347.1366, found 347.1369; IR ($CHCl_3$) ν_{max} 3331, 1718, 1698 cm^{-1}.

(*E*)-2-Ethylidene-1-hydroxy-1-(2-hydroxyethyl)-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (25). To a stirred solution of aldehyde **24**



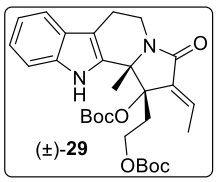
(±)-**25**

(640 mg, 1.97 mmol) in MeOH (15 mL) was added the $NaBH_4$ (110 mg 2.96 mmol) at 0 °C in two equal lots and reaction mixture was stirred for 30 min. The reaction was quenched with aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (20 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, DCM–MeOH, 2:98) afforded compound **25** as a solid (610 mg, 95%). Mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.65 (s, 3H), 1.93 (d, J = 14.9 Hz, 1H), 1.98 (d, J = 7.6 Hz, 3H), 2.35–2.45 (m, 1H), 2.68 (dd, J = 15.7 and 5.4 Hz, 1H), 3.01 (br s, 1H), 3.06–3.15 (m, 1H), 3.25 (td, J = 11.8 and 5.3 Hz, 1H), 4.04 (d, J = 8.0 Hz, 2H), 4.43 (dd, J = 6.7 and 6.9 Hz, 1H), 4.78 (s, 1H), 6.72 (q, J = 7.7 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.4, 19.5, 21.8, 36.2, 36.5, 60.0, 64.3, 82.4, 108.8, 111.2, 118.2, 119.2, 122.0, 126.8, 134.4, 135.5, 136.2, 137.0, 170.5; ESIMS (*m*/*z*) 349 $[M+Na]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{22}N_2O_3Na$ 349.1523, found 349.1519; IR ($CHCl_3$) ν_{max} 3677, 3618, 3449, 1659 cm^{-1}.



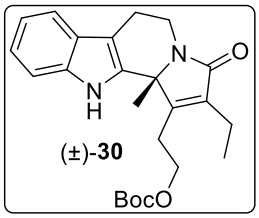
2-Ethyl-1-(2-hydroxyethyl)-11b-methyl-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-3-one (27). The solution of $AlCl_3$ (55 mg, 4.14 mmol) in THF (5 mL) was added dropwise to a stirred suspension of LAH (46 mg, 1.24 mmol) in THF (15 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min and to it solution of lactam **25** (90 mg, 0.28 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and the reaction was quenched with saturated aqueous Na_2SO_4. Reaction mixture was diluted with EtOAc (10 mL), filtered through Celite pad and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, PE–EtOAc, 25:75) afforded amine **27** as a yellow solid (54 mg, 63%). Mp 127–129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (t, J = 7.3 Hz, 3H), 1.73 (s, 3H), 2.30 (q, J = 7.7 Hz, 2H), 2.79 (dd, J = 15.3 and 4.6 Hz, 1H), 2.83–2.91 (m, 1H), 2.91–3.03 (m, 2H), 3.15–3.25 (m, 1H), 3.85–3.92 (m, 1H), 3.93–4.01 (m, 1H), 4.61 (dd, J = 13.1 and 5.8 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.3, 17.4, 22.1, 24.6, 29.9, 36.0, 61.2, 64.5, 108.1, 111.1, 118.6, 119.6, 122.1, 126.6, 134.4, 135.9, 136.4, 153.8, 171.3; ESIMS (m/z) 311 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{23}N_2O_2$ 311.1754, found 311.1750; IR ($CHCl_3$) ν_{max} 3328, 1662 cm^{-1}.

(*E*)-2-{1-[(tert-Butoxycarbonyl)oxy]-2-ethylidene-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl}ethyl *tert*-butyl carbonate (29). To a stirred solution of diol **25** (70 mg, 0.21 mmol) in CH_2Cl_2 was added $(Boc)_2O$ (108 μL, 0.47 mmol) and catalytic amount of DMAP (3 mg, 0.02 mmol) and the reaction mixture was stirred at 25 °C for 3 h. Reaction was quenched with water and aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 25:75) afforded compound **29** as a solid (91 mg, 81%). Mp 113–115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 1.55 (s, 9H), 1.73 (s, 3H), 2.01 (d, J = 7.9 Hz, 3H), 2.65–2.95 (m, 4H), 3.17 (td, J = 12.2 and 4.3 Hz, 1H), 4.37–4.45 (m, 1H), 4.54–4.66 (m, 2H), 6.93 (q, J = 7.3 Hz, 1H), 7.07 (t, J = 7.3 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 20.5, 25.7, 27.1, 27.8, 33.2, 36.8, 62.8, 66.2,

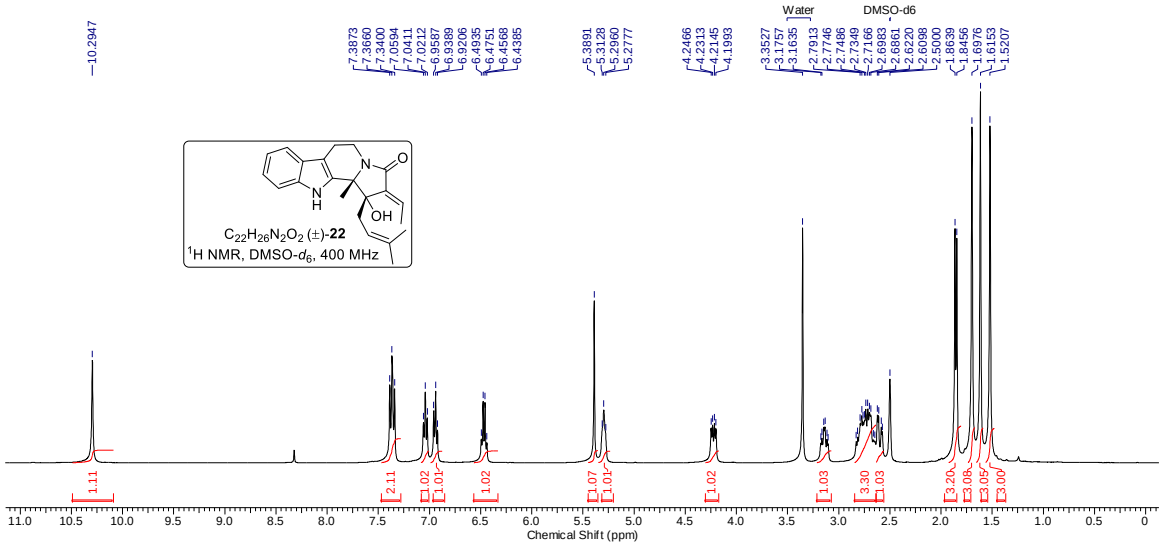


82.2, 83.1, 84.8, 110.2, 110.8, 118.4, 119.3, 122.0, 126.5, 132.7, 133.2, 135.8, 136.3, 151.1, 153.4, 165.9; ESIMS (*m*/*z*) 549 $[M+Na]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{29}H_{38}N_2O_7Na$ 549.2571, found 549.2570; IR ($CHCl_3$) ν_{max} 3431, 1734 cm^{-1}.

***tert*-Butyl {2-[2-Ethyl-11b-methyl-3-oxo-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-1-yl]ethyl} carbonate (30).** The solution of $AlCl_3$ (18 mg, 0.14 mmol) in THF (5 mL) was added dropwise to a stirred suspension of LAH (16 mg, 0.42 mmol) in THF (15 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min and solution of lactam **29** (50 mg, 0.09 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and the reaction was quenched with saturated aqueous Na_2SO_4. Reaction mixture was diluted with EtOAc (10 mL), filtered through Celite pad and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, EtOAc–PE, 30:70) afforded amine **30** as solid (26 mg, 67%). Mp 105–107 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, J = 7.3 Hz, 3H), 1.62 (s, 9H), 1.67 (s, 3H), 2.30 (q, J = 7.9 Hz, 2H), 2.75–2.93 (m, 2H), 2.93–3.13 (m, 2H), 3.13–3.27 (m, 1H), 3.88–4.00 (m, 1H), 4.16 (td, J = 11.3 and 4.9 Hz, 1H), 4.62 (dd, J = 13.4 and 6.1 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 17.6, 22.0, 25.0, 25.5, 27.8, 35.8, 63.8, 64.4, 83.6, 108.2, 111.2, 118.6, 119.6, 122.2, 126.4, 133.6, 136.5, 137.2, 149.5, 154.7, 170.4; ESIMS (*m*/*z*) 411 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{31}N_2O_4$ 411.2278, found 411.2276; IR ($CHCl_3$) ν_{max} 3360, 1730, 1677 cm^{-1}.



2A.5 Selected Spectra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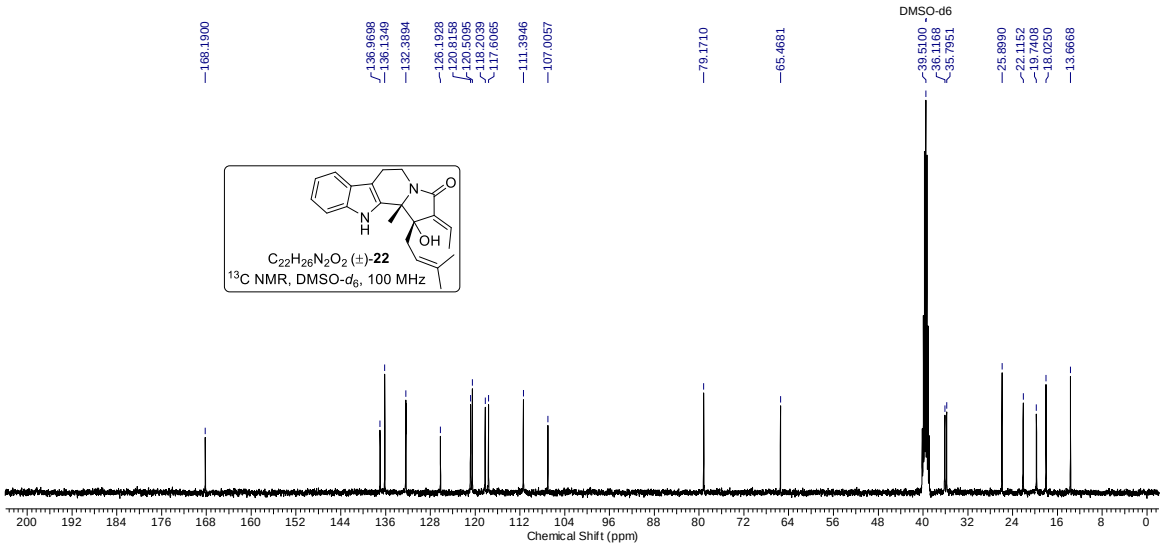
7.3660
7.3400
7.0594
7.0411
7.0212
6.9587
6.9389
6.9206
6.4935
6.4751
6.4568
6.4385
5.3891
5.3128
5.2960
5.2777
4.2466
4.2313
4.2145
4.1993
3.3527
3.1757
3.1635
2.7913
2.7746
2.7486
2.7349
2.7166
2.6983
2.6861
2.6220
2.6098
2.5000
1.8639
1.8456
1.6976
1.6153
1.5207
N
O
N
H
OH
C22H26N2O2 (±)-22
1H NMR, DMSO-d6, 400 MHz
1.11
2.11
1.02
1.01
1.02
1.07
1.01
1.02
1.03
3.30
1.03
3.20
3.06
3.05
3.00
Chemical Shift (ppm)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132.3894
126.1928
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120.5095
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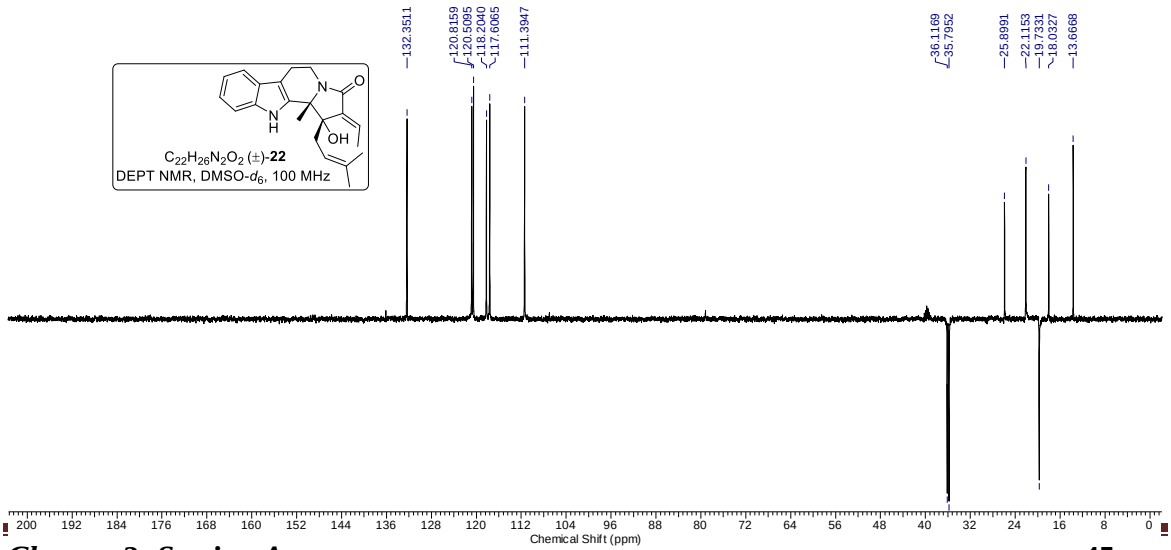
111.3946
107.0057
79.1710
65.4681
39.5100
36.1168
35.7951
25.8990
22.1152
19.7408
18.0250
13.6668
N
O
N
H
OH
C22H26N2O2 (±)-22
13C NMR, DMSO-d6, 100 MHz
Chemical Shift (ppm)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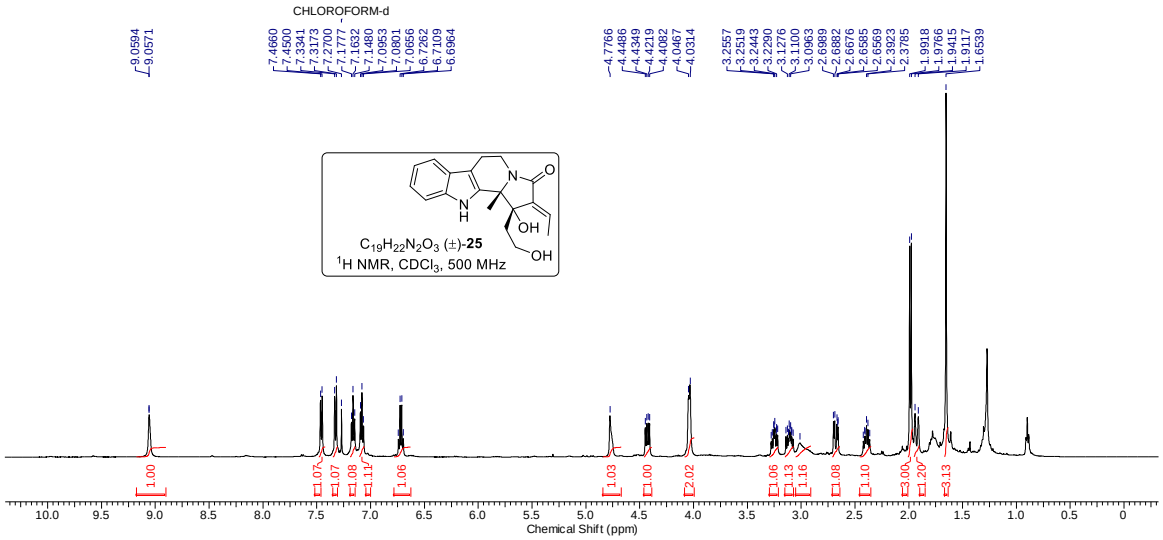
120.8159
120.5095
118.2040
117.6065
111.3947
36.1169
35.7952
25.8991
22.1153
19.7331
18.0327
13.6668
N
O
N
H
OH
C22H26N2O2 (±)-22
DEPT NMR, DMSO-d6, 100 MHz
Chemical Shift (ppm)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7.1480
7.0953
7.0801
7.0656
6.7282
6.7109
6.6964
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4.4082
4.0467
4.0314
3.2557
3.2519
3.2443
3.2290
3.1276
3.1100
3.0963
2.6989
2.6882
2.6676
2.6585
2.6569
2.3923
2.3785
1.9918
1.9766
1.9415
1.9117
1.6539
C19H22N2O3 (±)-25
1H NMR, CDCl3, 500 MHz
1.00
1.07
1.07
1.08
1.14
1.06
1.03
1.00
2.02
1.06
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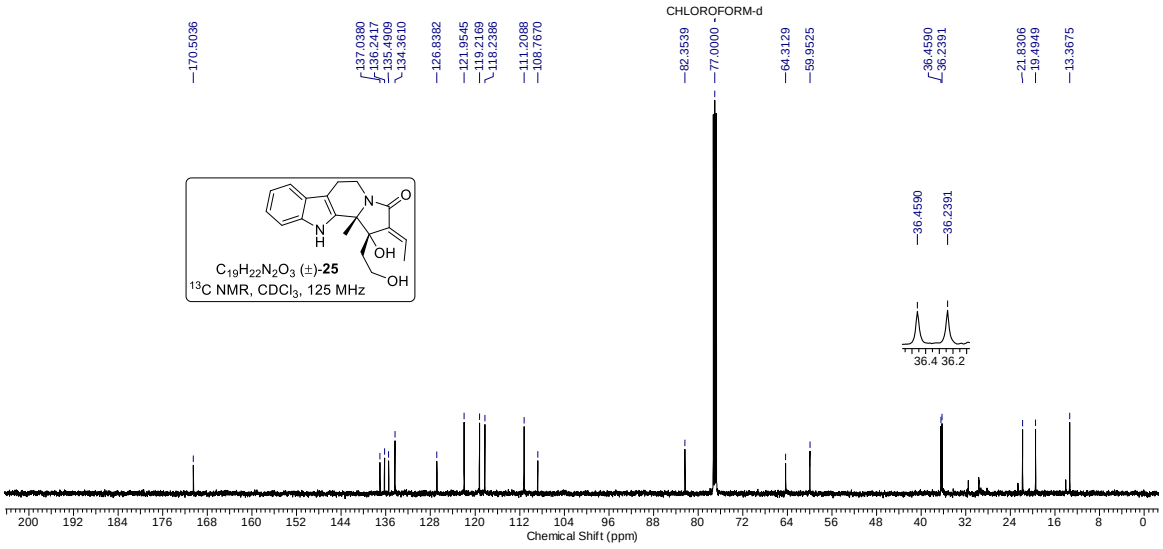
1.08
1.10
3.00
1.20
3.13
Chemical Shift (ppm)


CHLOROFORM-d
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119.2169
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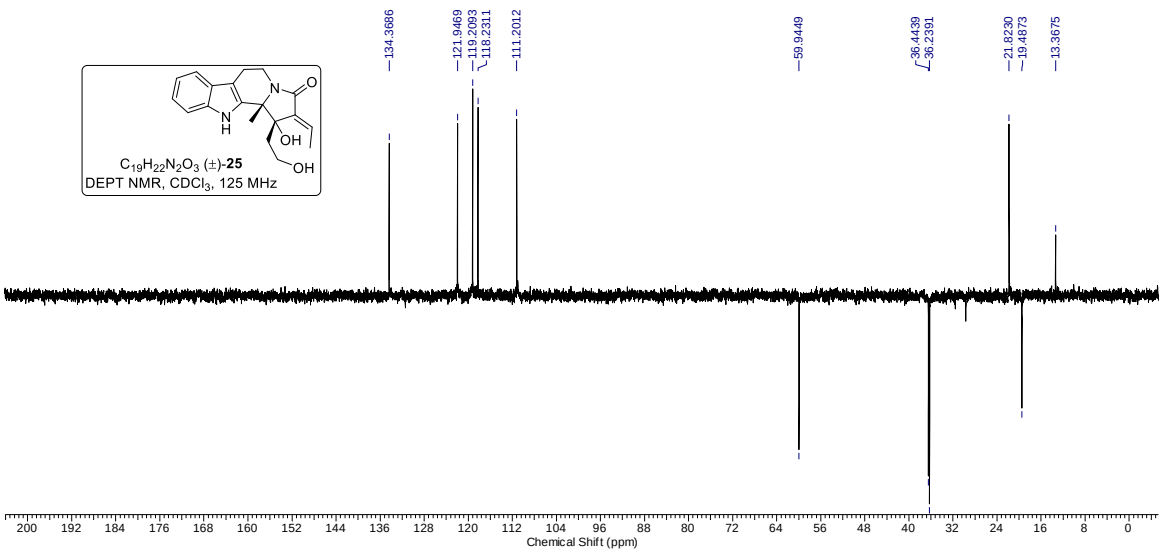
111.2088
108.7670
82.3539
77.0000
64.3129
59.9525
36.4590
36.2391
21.8306
19.4949
13.3675
C19H22N2O3 (±)-25
13C NMR, CDCl3, 125 MHz
36.4 36.2
Chemical Shift (ppm)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118.2311
111.2012
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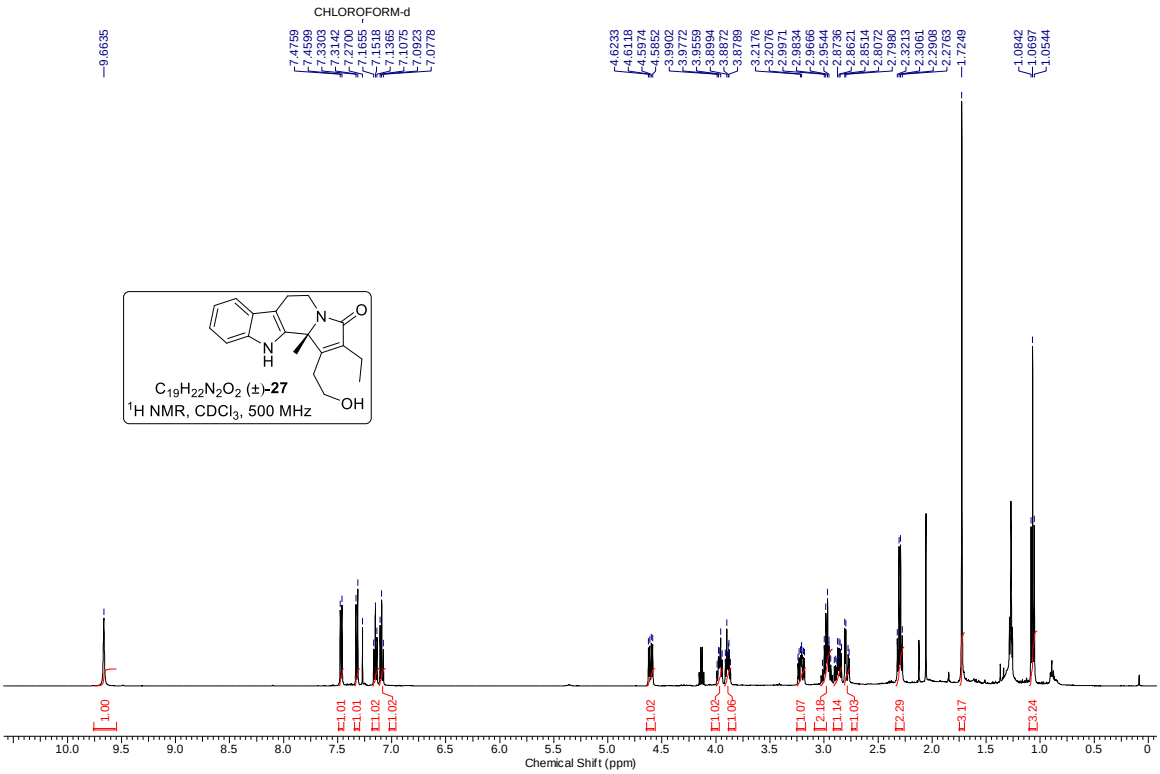
13.3675
C19H22N2O3 (±)-25
DEPT NMR, CDCl3, 125 MHz
Chemical Shift (ppm)


CHLOROFORM-d
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7.3303
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7.1075
7.0923
7.0778
4.6233
4.6118
4.5974
4.5852
3.9902
3.9772
3.9559
3.8994
3.8872
3.8789
3.2176
3.2076
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2.9834
2.9666
2.9544
2.8736
2.8621
2.8514
2.8072
2.7980
2.3213
2.3061
2.2908
2.2763
1.7249
1.0842
1.0697
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1.00
1.01
1.01
1.02
1.02
1.02
1.02
1.06
1.07
2.18
1.14
1.03
2.29
3.17
3.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)
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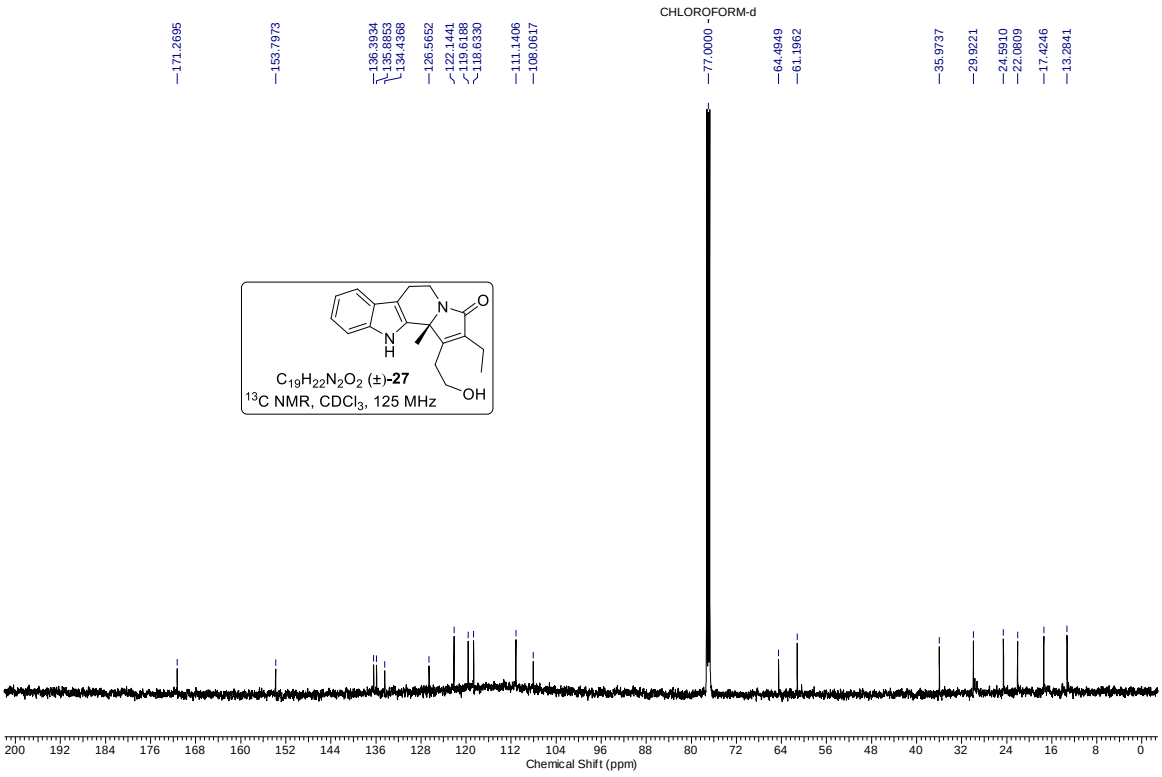
O
H
OH
C19H22N2O2 (±)-27
1H NMR, CDCl3, 500 MHz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134.4368
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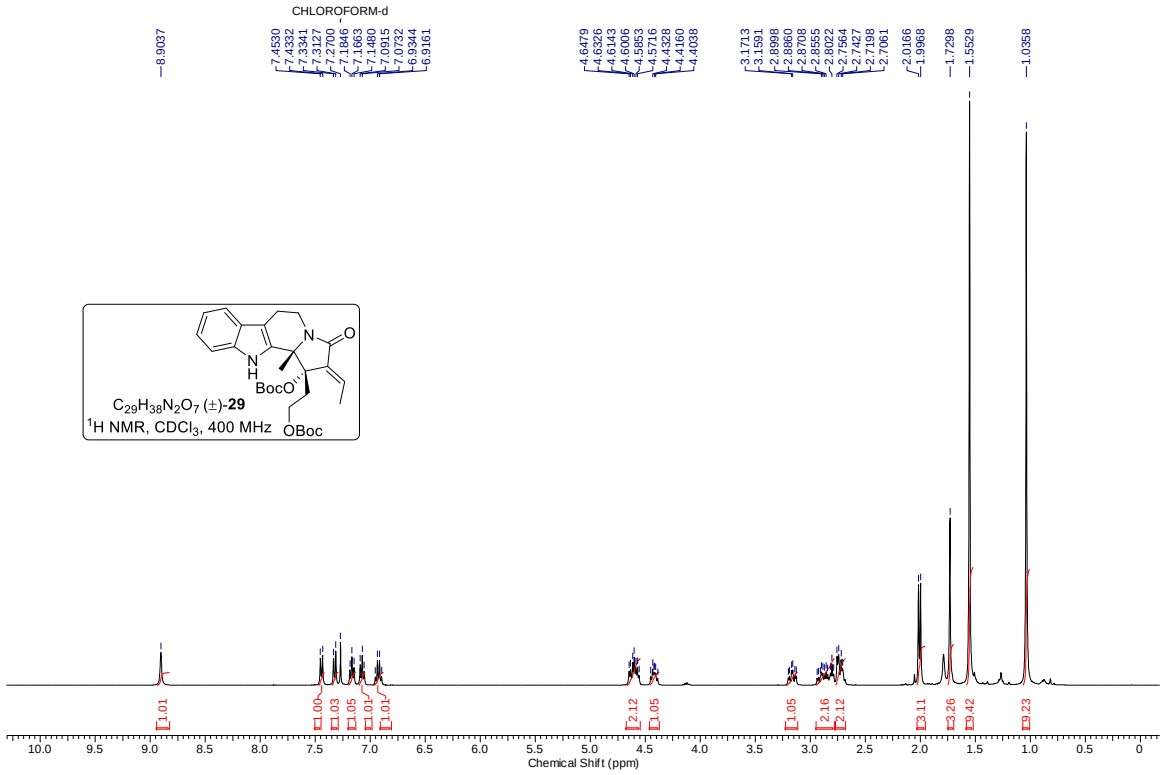
119.6188
118.6330
111.1406
108.0617
77.0000
64.4949
61.1962
35.9737
29.9221
24.5910
22.0809
17.4246
13.2841
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)
N
O
H
OH
C19H22N2O2 (±)-27
13C NMR, CDCl3, 125 MHz


CHLOROFORM-d
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7.1846
7.1663
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7.0915
7.0732
6.9344
6.9161
4.6479
4.6326
4.6143
4.6006
4.5853
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1.7798
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1.01
1.00
1.03
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1.05
1.05
2.16
2.12
3.11
3.26
3.42
3.23
Chemical Shift (ppm)
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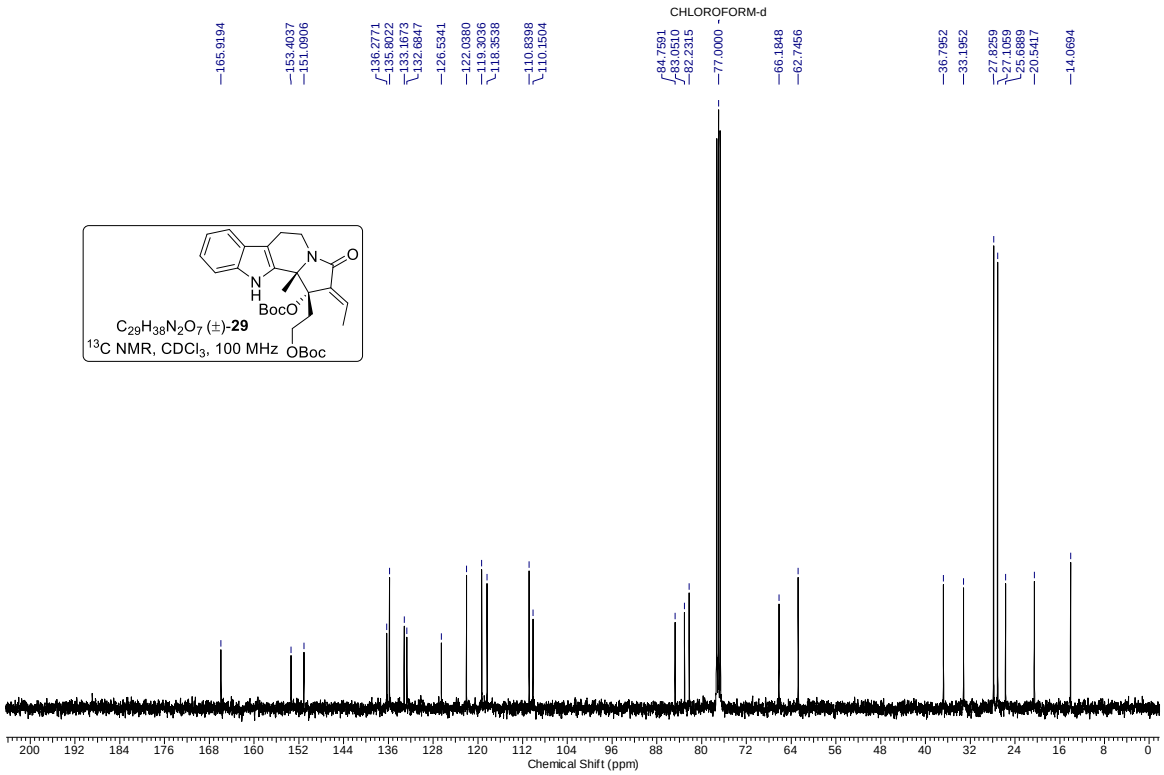
1H NMR, CDCl3, 400 MHz
BocO
OBoc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132.6847
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118.3538
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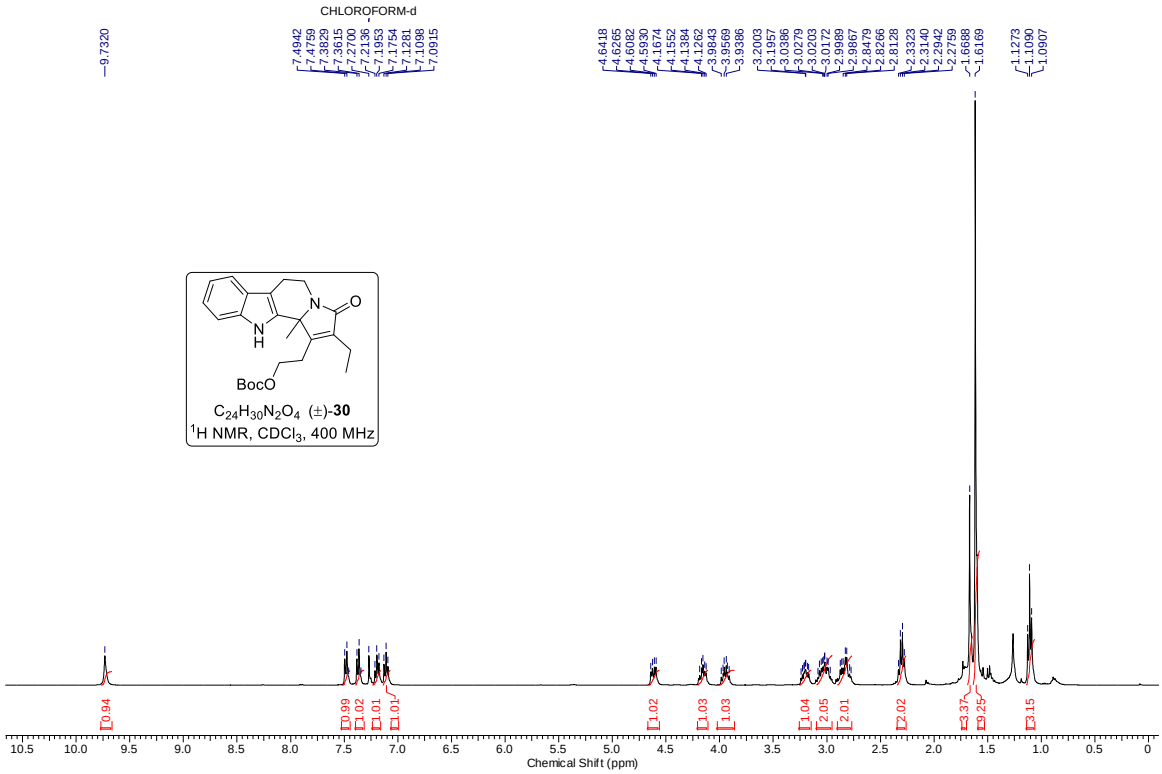
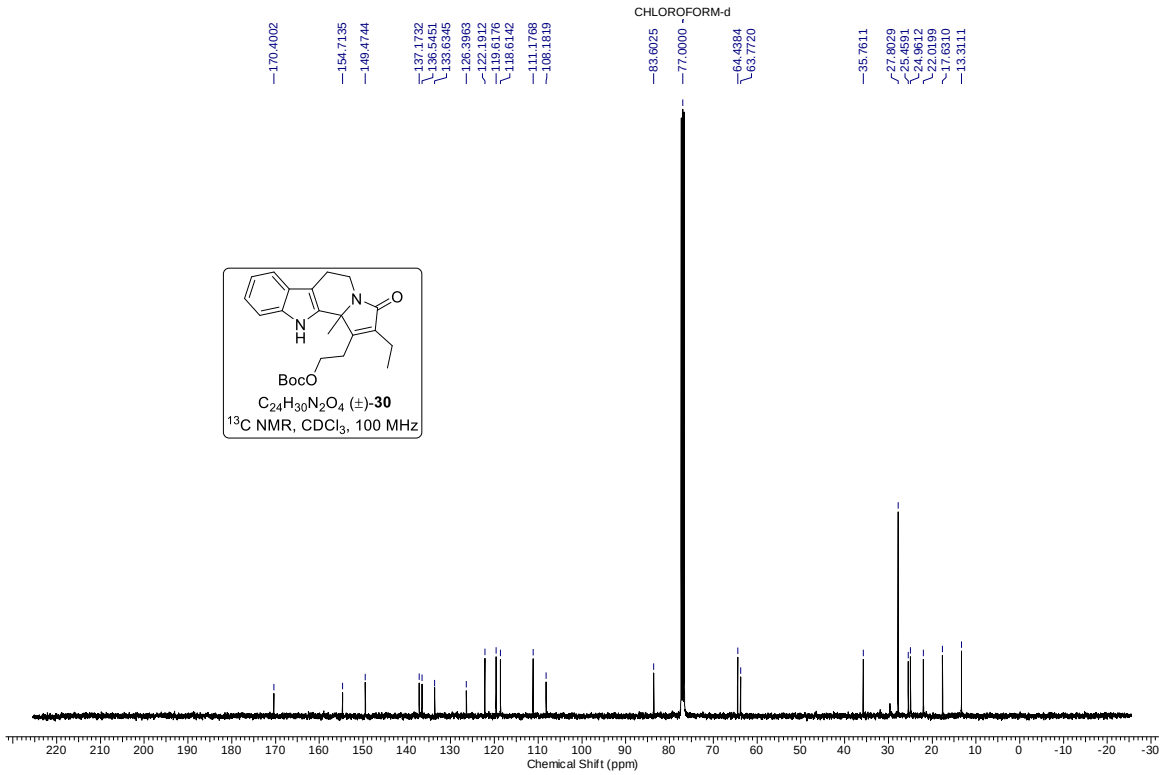
110.1504
84.7591
83.0510
82.2315
77.0000
66.1848
62.7456
36.7952
33.1952
27.8259
27.1059
25.6889
20.5417
14.0694
Chemical Shift (ppm)
C29H38N2O7 (±)-29
13C NMR, CDCl3, 100 MHz
BocO
OBoc


CHLOROFORM-d
BocO
$C_{24}H_{30}N_2O_4$ (±)-30
^{1}H NMR, $CDCl_3$, 400 MHz
Chemical Shift (ppm)


CHLOROFORM-d
BocO
$C_{24}H_{30}N_2O_4$ (±)-30
^{13}C NMR, $CDCl_3$, 100 MHz
Chemical Shift (ppm)

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Chapter 2

Section B

Diastereoselective Synthesis of (±)-*epi*-Subincanadine C

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

2B.1 Background

The structurally novel and medicinally important cytotoxic alkaloids subincanadines A–G (**1a**–**g**) were isolated in 2002 by Ohsaki and co-workers from the Brazilian medicinal plant *Aspidosperma subincanum* (Figure 1).[1,2] Subincanadine C (**1c**), a novel quaternary indole alkaloid, featuring an unprecedented 1-azoniatricyclo[4.3.3.$0^{1,5}$]undecane skeleton was isolated in only 0.002% yield. Zhai and co-workers have reported the first protection free synthesis of (±)-subincanadine C via novel $Ni(COD)_2$-mediated intramolecular Michael addition pathway (Please see chapter 1; scheme 3 and page no. 8).[3] Elegant enantioselective/diastereoselective synthetic routes to other subincanadines A, B, E and F have been reported in the contemporary literature.[4–13] However, synthesis of subincanadines D (**1d**) and G (**1g**) are still awaited.

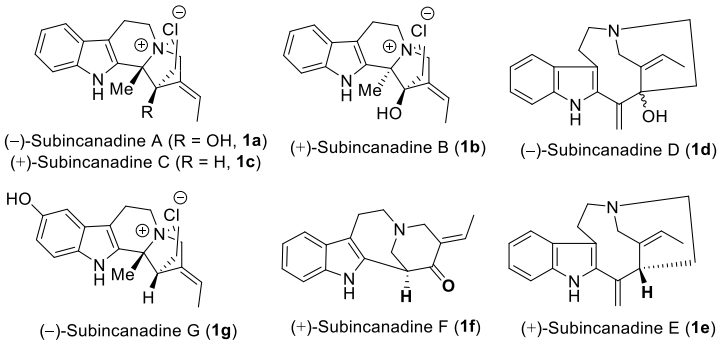
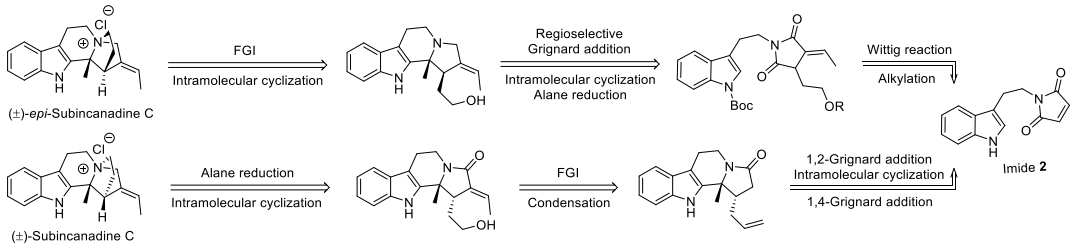


Figure 1. Potent cytotoxic alkaloids subincanadines A–G.

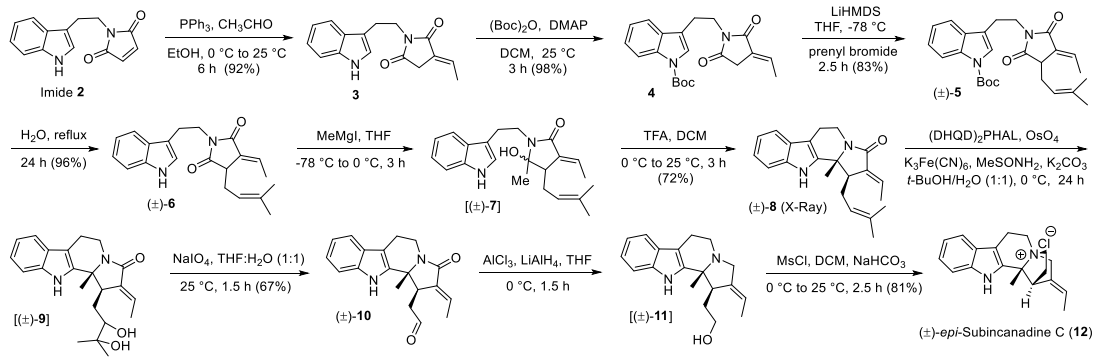
2B.2 Results and Discussion

We initially prepared a plan for the synthesis of (±)-*epi*-subincanadine C and (±)-subincanadine C and their concise retrosynthetic analysis have been depicted in scheme 1. The 1-[2-(1*H*-indol-3-yl)ethyl]-1*H*-pyrrole-2,5-dione (**2**) contains well positioned 14-carbons and requisite functional groups for initial design of 14-carbon containing tetracyclic indolizinoindolone framework and then its transformation into the bridged alkaloid (±)-subincanadine C (**1c**). Therefore we reasoned that the maleimide derivative **2** would be a potential precursor to synthesize both (±)-*epi*-subincanadine C and (±)-subincanadine C via diastereoselective Pictet–Spengler cyclization and diastereoselective cuprate addition or reduction of carbon–carbon double bond as the key reactions. In continuation of our studies on total synthesis of bioactive natural products from the cyclic anhydride and derivatives;[14–18] we herein describe the diastereoselective synthesis of (±)-*epi*-subincanadine C and an attempted synthesis of (±)-subincanadine C (Schemes 1 to 3).



Scheme 1. Concise Retrosynthetic Analysis of (±)-*epi*-Subincanadine C and (±)-Subincanadine C

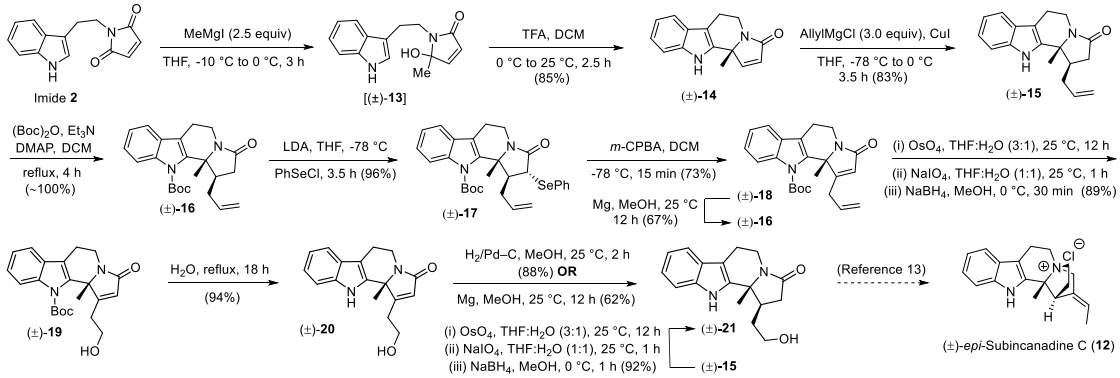
Our synthesis commenced from the earlier synthesized known compound **5** from imide **2** (please see chapter 2; scheme 2 and page no. 35). reaction of indolylmaleimide **2** on triphenylphosphine induced Wittig reaction with acetaldehyde[19,20] followed by *N*-Boc protection and smooth alkylation by using bulky prenyl bromide exclusively provided the mono-prenylated product **5** in 75% overall yield in three steps (Scheme 2). The All attempts to directly transform the imide **5** into indolizinoindolone **8** in one-pot via regioselective Grignard reaction, acid induced Boc-deprotection and diastereoselective Pictet–Spengler cyclization were inefficient and the desired product was formed only in 10 to 15% yield. All those one-pot transformations always resulted in excessive decomposition due to an acid sensitive nature of the initially formed lactamol intermediate and unfortunately the prerequisite Boc-deprotection reaction was relatively slow. Imide **5** was also prone for hydrolytic cleavage under acidic conditions and therefore the Boc-deprotection was planned under neutral reaction conditions. Imide **5** in refluxing water[21] underwent smooth Boc-deprotection and provided the desired product **6** in 96% yield. Regioselective reaction of methylmagnesium iodide with the relatively more reactive unconjugated imide carbonyl moiety in succinimide derivative **6** followed by an immediate trifluoroacetic acid induced diastereoselective Pictet–Spengler cyclization[22] of the formed lactamol **7** exclusively furnished the expected *syn*-product **8** in 72% yield, via the corresponding flat iminium-ion intermediate. The structure of formed *syn*-indolizinoindolone **8** was confirmed on the basis of X-ray crystallographic data. Osmium tetraoxide induced dihydroxylation reaction of compound **8** was not selective and two different types of carbon–carbon double bonds underwent smooth dihydroxylations to directly yield the corresponding tetrol product in high yield. The reaction of compound **8** under Sharpless dihydroxylation conditions[23] was regioselective at 0 °C and the more electron rich carbon–carbon double bond selectively reacted to deliver the required diol **9**;



Scheme 2. Synthesis of (±)-*epi*-Subincanadine C via Diastereoselective Intramolecular Pictet–Spengler Cyclization

this was used for the next step without any purification for polarity issues. The obtained diol **9** on sodium periodate induced cleavage resulted in aldehyde **10** in 67% yield. One-pot alane reduction of aldehyde and lactam units in compound **10** delivered the desired product **11**. The formed amine **11** was very unstable plausibly due to the high air-oxidation propensity and it was immediately used for the next step without any purification and characterization.[3] The obtained product **11** on treatment with mesyl chloride underwent clean mesylation and in situ intramolecular cyclization to provide the final product (±)-*epi*-subincanadine C (**12**) in 81% yield. The obtained analytical and spectral data for (±)-*epi*-subincanadine C (**12**) were in complete agreement with the assigned structure and it was obtained in 10 steps with 28% overall yield.

An *anti*-addition of cuprate to the *α,β*-unsaturated *γ*-methyllactam was essential to accomplish synthesis of (±)-subincanadine C. However, the recent literature precedents including one from our research group state that exclusive *syn*-addition of cuprate takes place on such type of substrates and the scientific reason for such unusual stereoselections



Scheme 3. Opposite Stereoselections in Michael Addition and Reductions of *α,β*-Unsaturated *γ*-Lactams Leading to Exclusive *syn*-Products: An Attempted Synthesis of (±)-Subincanadine C

is still unknown.[13,24,25] As depicted in scheme 3, we planned to study the feasibility of *anti*-addition of cuprate to indolizinoindolone **14** to accomplish synthesis of (±)-subincanadine C. Imide **2** on selective 1,2-addition of methylmagnesium iodide followed by acid-induced Pictet–Spengler cyclization furnished the desired indolizinoindolone **14** in 85% yield over two steps. The planned 1,4-addition of allyl cuprate to compound **14** also exclusively yielded an unusual *syn*-addition product **15** in 83% yield. The *syn*-orientation of methyl and allyl groups in product **15** was initially established by 2 D NMR studies. Finally we decided to study the stereoselectivity in reduction of carbon–carbon double bond of *α*,*β*-unsaturated *γ*-lactam with a hope to obtain *anti*-relationship between two substituents, which was essential for the accomplishment of synthesis of (±)-subincanadine C. Therefore product **15** was *N*-Boc-protected and treated with LDA/phenylselenyl chloride, which formed the relatively more stable isomer **17** in 96% yield over two steps. The compound **17** on oxidative elimination of phenylselenium resulted in the expected *α*,*β*-unsaturated *γ*-lactam **18** in 73% yield. Lactam **18** on reaction with Mg/MeOH underwent selective reduction of the *α*,*β*-unsaturated double bond and again exclusively formed the *syn*-product **16** in 67% yield. The compound **18** on OsO_4-dihydroxylation, oxidative cleavage and $NaBH_4$ reduction yielded alcohol **19** in 89% yield, which on Boc-deprotection furnished the desired *α*,*β*-unsaturated lactam **20** in 94% yield. The catalytic hydrogenation of compound **20** with H_2/Pd–C and also the reduction by radical pathway using Mg/MeOH took place in a usual fashion and unfortunately both provided only the *syn*-product **21** in very good yields. The compound **15** on dihydroxylation and oxidative cleavage followed by reduction also directly delivered the same product **21** in 92% yield. The *syn*-relation of methyl and *β*-hydroxyethyl groups in thus formed product **21** was also confirmed by X-ray crystallographic analysis of its *O*-pivaloyl derivative (compound **22** from experimental section). The product **21** can be transformed into (±)-*epi*-subincanadine C (**12**) via double Boc-protection, dehydrative condensation with acetaldehyde and reductive intramolecular cyclization pathway.[13] Thus an attempt to synthesize (±)-subincanadine C (**1c**) has also resulted in yet another efficient approach to (±)-*epi*-subincanadine C (**12**).

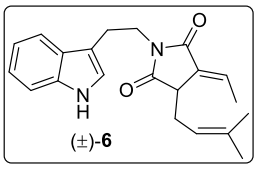
2B.3 Summary

In summary, diastereoselective practical approaches to (±)-epi-subincanadine C have been developed via regioselective oxidative carbon–carbon double bond cleavage and an exceptional syn-stereoselection in Michael addition of cuprate to the unsaturated γ-

lactam. The proper scientific reasoning for such type of unusual stereoselectivities is essential and still remains as an unanswered challenging question. Our present approach is quite flexible and will provide efficient synthetic paths to subincanadines A–G and focused mini-library of their congeners and derivatives for SAR studies.

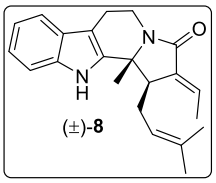
2B.4 Experimental Section

(*E*)-1-[2-(1*H*-Indol-3-yl)ethyl]-3-ethylidene-4-(3-methylbut-2-en-1-yl)pyrrolidine-2,5-dione (6). The compound (±)-**5** (1.70 g, 3.89 mmol) and distilled water (60 mL) mixture was refluxed for 24 h. The reaction mixture was allowed to reach 25 °C and extracted with EtOAc (3 × 40 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 50:50) afforded (±)-**6** as a yellow solid (1.25 g, 96%). Mp 117–119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 6H), 1.93 (d, J = 7.4 Hz, 3H), 2.48–2.58 (m, 1H), 2.65–2.76 (m, 1H), 2.98–3.06 (m, 2H), 3.35–3.40 (m, 1H), 3.80–3.92 (m, 2H), 4.94 (t, J = 8.2 Hz, 1H), 6.86–6.94 (m, 1H), 7.08 (br s, 1H), 7.11–7.23 (m, 2H), 7.35 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 8.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.9, 17.9, 23.7, 25.7, 28.6, 38.9, 42.4, 111.0, 112.3, 117.6, 118.9, 119.4, 121.9, 122.1, 127.4, 130.5, 133.7, 136.1, 136.2, 169.9, 177.3; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{25}N_2O_2$ 337.1911, found 337.1909; IR ($CHCl_3$) ν_{max} 3479, 1703, 1674, 1603 cm^{-1}.



(±)-**6**

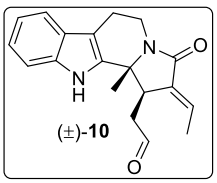
(*E*)-2-Ethylidene-11b-methyl-1-(3-methylbut-2-en-1-yl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (8). To a stirred solution of compound (±)-**6** (1.00 g, 2.99 mmol) in dry THF (20 mL) was added solution of methylmagnesium iodide in diethyl ether (3 M, 2.20 mL, 6.55 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was allowed to reach 0 °C in next 3 h and quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (30 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded intermediate lactamol **7**; which was immediately used for the next step without any further purification. To a stirred solution of lactamol **7** in CH_2Cl_2 (20 mL) was added TFA (605 μL, 7.81 mmol) at 0 °C and the reaction mixture was stirred for 3 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was



(±)-**8**

extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with $NaHCO_3$, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 50:50) afforded compound (±)-**8** as a white solid (715 mg, 72%). Mp 236–238 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60 (s, 3H), 1.75 (s, 3H), 1.84 (d, J = 7.4 Hz, 3H), 1.90 (s, 3H), 2.53–2.65 (m, 1H), 2.73 (dd, J = 15.1 and 4.9 Hz, 2H), 2.92–3.02 (m, 1H), 3.23–3.33 (m, 2H), 4.56 (dd, J = 13.3 and 6.1 Hz, 1H), 5.41 (t, J = 7.3 Hz, 1H), 6.68 (qd, J = 7.3 and 2.4 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 8.49 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.5, 18.2, 20.6, 22.9, 25.8, 28.2, 35.9, 45.7, 60.8, 107.4, 110.9, 118.4, 119.6, 122.0, 123.2, 126.7, 130.2, 134.3, 134.7, 135.7, 138.1, 168.7; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{27}N_2O$ 335.2118, found 335.2109; IR ($CHCl_3$) ν_{max} 3468, 1698, 1661 cm^{-1}.

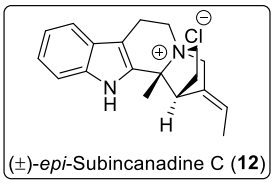
(*E*)-2-[2-Ethylidene-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl]acetaldehyde (10). To a stirred slurry of $K_3Fe(CN)_6$ (1.20 g, 3.59 mmol), K_2CO_3 (495 mg, 3.59 mmol), $MeSO_2NH_2$ (113 mg, 1.19 mmol), $(DHQD)_2$-PHAL (l,4-bis-9-*o*-dihydroquinidinephthalazine) (46 mg, 5 mole %) and OsO_4 in *tert*-butyl alcohol (0.50 M, 0.20) in *tert*-butyl alcohol:water (1:1) mixture (50 mL) was added compound (±)-**8** (400 mg, 1.19 mmol) at 0 °C and the heterogeneous reaction mixture was vigorously stirred at same temperature for 24 h. The reaction was quenched by adding saturated solution of $Na_2S_2O_3$ and it was further stirred for 30 min. The reaction mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with 2 N KOH (20 mL) and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried diol **9** was directly used for next step. To a stirred solution of diol **9** in THF:H_2O (1:1, 20 mL) was added $NaIO_4$ (1.20 g, 5.82 mmol) in two equal lots at 25 °C and the reaction was monitored by TLC. The reaction mixture was stirred for 1.5 h and diluted with EtOAc (25 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, PE–EtOAc, 40:60) afforded compound (±)-**10** as a solid (247 mg, 67%). Mp 97–99 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.49 (s, 3H), 1.77 (d, J = 7.4 Hz, 3H), 2.73 (dd, J = 15.7 and 4.6 Hz, 1H), 2.88–3.00 (m, 1H), 3.04–3.22 (m, 2H), 3.30 (td, J = 12.0 and 3.7 Hz, 1H), 3.87 (d, J = 11.3 Hz, 1H), 4.57 (dd, J =



(±)-**10**

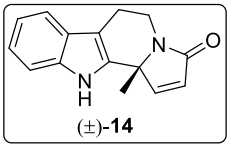
13.3 and 6.8 Hz, 1H), 6.64 (q, *J* = 4.9 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 1H), 7.46 (d, *J* = 6.5 Hz, 1H), 9.37 (s, 1H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 20.5, 23.3, 36.2, 37.3, 45.4, 59.5, 106.7, 111.3, 118.3, 119.5, 122.1, 126.5, 130.4, 134.1, 135.7, 138.3, 167.3, 203.2; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{21}N_2O_2$ 309.1598, found 309.1594; IR ($CHCl_3$) ν_{max} 3398, 1720, 1665 cm^{-1}.

(*E*)-2-Ethylidene-11b-methyl-2,3,5,6,11,11b-hexahydro-1*H*-1,4-ethanoindolizino(8,7-*b*)indol-4-ium (*epi*-Subincanadine C, 12). The solution of $AlCl_3$ (64 mg, 0.48 mmol) in THF (5 mL) was added dropwise to a stirred suspension of LAH (54 mg, 1.46 mmol) in THF (15 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min and solution of lactam-aldehyde (±)-**10** (75 mg, 0.24 mmol) in THF (5 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the reaction was quenched with saturated aqueous Na_2SO_4. Reaction mixture was diluted with EtOAc (20 mL), filtered through Celite pad and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded amine-alcohol **11** which was directly used for the next step without any purification. To a stirred solution of amine-alcohol **11** in CH_2Cl_2 (6 mL) were added saturated aqueous $NaHCO_3$ solution (0.21 mL) and methanesulfonyl chloride (28 mg, 0.36 mmol) at 0 ^oC under argon atmosphere. The reaction mixture was allowed to reach 25 ^oC in 2.5 h and concentrated in vacuo. The purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 10:90) afforded compound (±)-**12** as a white amorphous solid (54 mg, 81%). ^{1}H NMR (CD_3OD, 400 MHz) δ 1.72 (d, *J* = 6.8 Hz, 3H), 1.79 (s, 3H), 2.00–2.22 (m, 1H), 2.69–2.79 (m, 1H), 3.26 (q, *J* = 6.4 Hz, 2H), 3.67–3.87 (m, 3H), 3.91–4.02 (m, 3H), 4.27 (d, *J* = 14.2 Hz, 1H), 5.18 (q, *J* = 6.8 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.2, 19.0, 20.3, 28.1, 44.7, 47.8, 59.9, 64.3, 78.5, 105.0, 112.5, 118.4, 119.4, 120.8, 123.8, 127.2, 132.6, 133.2, 138.1; ESIMS (*m*/*z*) HRMS (ESI) $[M]^+$; calcd for $C_{19}H_{23}N_2^+$ 279.1856, found 279.1858; IR ($CHCl_3$) ν_{max} 3376, 1621 cm^{-1}.



(±)-*epi*-Subincanadine C (**12**)

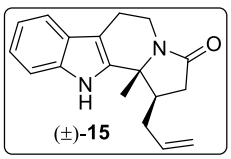
11b-Methyl-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-3-one (14). To a stirred solution of compound **2** (4.00 g, 16.66 mmol) in dry THF (50 mL) was added a solution of methylmagnesium iodide in diethyl ether (3 M, 12.2 mL, 36.66 mmol) in a dropwise mode at −10 °C under



(±)-**14**

argon atmosphere. The reaction mixture was allowed to reach 0 °C in next 3 h and quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (100 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded lactamol **13** which was directly used for the next step. To a stirred solution of lactamol **13** in CH_2Cl_2 (30 mL) was added TFA (3.80 mL, 49.99 mmol) at 0 °C and the reaction mixture was stirred for 2.5 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with $NaHCO_3$, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, PE–EtOAc, 30:70) afforded compound (±)-**14** as a white solid (3.37 g, 85%). Mp 242–244 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 3H), 2.79–2.96 (m, 2H), 3.26–3.35 (m, 1H), 4.63 (dd, J = 13.3 and 6.0 Hz, 1H), 6.17 (d, J = 6.0 Hz, 1H), 7.12 (td, J = 7.3 and 0.9 Hz, 1H), 7.19 (td, J = 7.6 and 0.9 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 5.9 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 8.99 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 24.4, 35.6, 64.5, 107.4, 111.0, 118.8, 119.8, 122.4, 125.8, 126.6, 133.8, 136.2, 151.7, 171.2; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{15}N_2O$ 239.1179, found 239.1177; IR ($CHCl_3$) ν_{max} 3347, 1663 cm^{-1}.

1-Allyl-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (15).

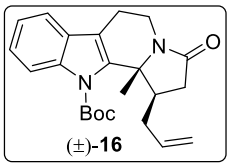


(±)-**15**

To a stirred solution of compound (±)-**14** (2.00 g, 8.40 mmol) and CuI (319 mg, 1.68 mmol) in dry THF (25 mL) was added a solution of allylmagnesium chloride in THF (2 M, 14.7 mL, 29.4 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was allowed to reach 0 °C in 3.5 h and the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 40:60) afforded compound (±)-**15** as a white solid (1.95 g, 83%). Mp 164–166 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 3H), 2.28–2.38 (m, 1H), 2.40–2.65 (m, 4H), 2.78–2.85 (m, 2H), 2.96–3.07 (m, 1H), 4.50 (dt, J = 12.8 and 3.7 Hz, 1H), 5.25–5.38 (m, 2H), 5.87–6.00 (m, 1H), 7.13 (t, J = 7.9 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.50

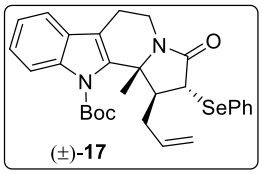
(d, J = 8.0 Hz, 1H), 8.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 21.5, 34.9, 35.0, 37.3, 44.0, 61.7, 107.4, 111.0, 117.8, 118.5, 119.8, 122.2, 126.5, 135.8, 137.2, 137.4, 171.3; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$ 281.1648, found 281.1646; IR ($CHCl_3$) ν_{max} 3424, 1671 cm^{-1}.

***tert*-Butyl 1-Allyl-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (16).** To a stirred solution of compound (±)-**15** (1.80 g, 6.42 mmol) in CH_2Cl_2 (25 mL) were added $(Boc)_2O$ (1.47 mL, 6.42 mmol) and catalytic amount of DMAP (78 mg, 0.642 mmol) at 25 °C and the reaction mixture was refluxed for 4 h. Reaction was quenched with water at 25 °C and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 40:60) afforded compound (±)-**16** as thick oil (2.40 g, ~100%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.72 (s, 9H), 1.86 (s, 3H), 1.99–2.07 (m, 1H), 2.29 (dd, J = 17.9 and 2.7 Hz, 1H), 2.40 (dd, J = 17.9 and 9.9 Hz, 1H), 2.61 (dd, J = 16.2 and 5.0 Hz, 1H), 2.76–2.84 (m, 1H), 2.86–2.93 (m, 1H), 2.96–3.05 (m, 1H), 3.25 (td, J = 12.6 and 5.0 Hz, 1H), 4.41 (dd, J = 13.4 and 6.9 Hz, 1H), 5.10–5.30 (m, 2H), 5.70–5.79 (m, 1H), 7.24 (t, J = 7.3 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 7.3 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5, 22.4, 28.2, 34.7, 35.6, 36.4, 38.0, 65.1, 84.2, 115.5, 115.7, 116.8, 118.2, 122.8, 124.5, 128.7, 135.4, 136.7, 140.0, 150.1, 175.6; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{29}N_2O_3$ 381.2173, found 381.2168; IR ($CHCl_3$) ν_{max} 1735, 1674 cm^{-1}.



(±)-**16**

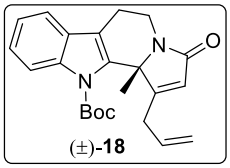
***tert*-Butyl 1-Allyl-11b-methyl-3-oxo-2-(phenylselanyl)-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (17).** Freshly prepared solution of LDA in THF (1 M, 6.63 mL, 6.63 mmol) was added to a stirred solution of compound (±)-**16** (2.10 g, 5.52 mmol) in THF (25 mL) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred at −78 °C for 1 h and solution of phenylselenyl chloride (1.05 g, 5.52 mmol) in THF (10 mL) was slowly added to the reaction mixture. The reaction was stirred for 2.5 h and quenched by aqueous NH_4Cl at −78 °C. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column



(±)-**17**

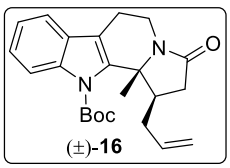
chromatography (silica gel, 60–120 mesh, EtOAc–PE, 40:60) afforded compound (±)-**17** as a yellow solid (2.80 g, 96%). Mp 137–139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 9H), 1.77 (s, 3H), 2.03 (q, J = 8.5 Hz, 1H), 2.55 (dd, J = 16.5 and 5.5 Hz, 1H), 2.73–2.84 (m, 1H), 2.85–2.92 (m, 1H), 2.93–3.03 (m, 1H), 3.22 (td, J = 12.5 and 5.5 Hz, 1H), 3.80 (d, J = 1.8 Hz, 1H), 4.40 (dd, J = 13.4 and 6.7 Hz, 1H), 5.00–5.15 (m, 2H), 5.55–5.70 (m, 1H), 6.82–6.92 (m, 3H), 7.20–7.37 (m, 5H), 7.94 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 22.9, 28.2, 35.2, 36.9, 45.5, 46.2, 63.7, 84.1, 115.1, 115.8, 117.3, 118.3, 122.7, 124.4, 127.0, 128.2, 128.3, 129.0, 135.2, 136.2, 136.3, 139.3, 150.0, 173.3; HRMS (ESI) calcd for $C_{29}H_{33}N_2O_3Se$ 537.1651, found 537.1650; IR ($CHCl_3$) ν_{max} 1734, 1593 cm^{-1}.

***tert*-Butyl 1-Allyl-11b-methyl-3-oxo-3,5,6,11b-tetrahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (18).** To a solution of compound (±)-**17** (2.50 g, 4.67 mmol) in



(±)-**18**

CH_2Cl_2 (25 mL) was added *m*-CPBA (~77%, 1.25 g, 5.60 mmol) at –78 °C under argon atmosphere and the reaction mixture was stirred for 15 min. The reaction was quenched with Et_3N (3.50 mL) at –78 °C. The reaction mixture extracted with CH_2Cl_2 (50 mL) and organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 50:50) afforded compound (±)-**18** as a white solid (1.29 g, 73%). Mp 158–160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (s, 9H), 2.11 (s, 3H), 2.76 (d, J = 16 Hz, 1H), 2.82–2.95 (m, 1H), 3.09 (dd, J = 18.9 and 8.0 Hz, 1H), 3.31 (t, J = 11.5 Hz, 1H), 3.44 (d, J = 18.3 Hz, 1H), 4.57 (dd, J = 14.1 and 5.7 Hz, 1H), 5.10–5.22 (m, 2H), 5.83 (s, 1H), 5.85–5.95 (m, 1H), 7.24 (t, J = 8.8 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9, 24.9, 28.3, 33.9, 34.0, 68.0, 84.6, 114.9, 118.1, 118.85, 118.91, 122.4, 122.8, 125.3, 128.2, 133.5, 135.1, 136.6, 151.0, 166.1, 169.1; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{27}N_2O_3$ 379.2016, found 379.2018; IR ($CHCl_3$) ν_{max} 1739, 1676 cm^{-1}.

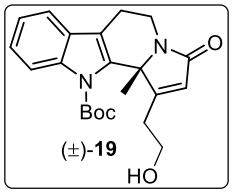


(±)-**16**

***tert*-Butyl 1-Allyl-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (16).** To a solution of compound (±)-**18** (100 mg, 0.26 mmol) in MeOH (10 mL) was added activated Mg turnings (32 mg, 1.32 mmol) at 25 °C under argon atmosphere and the reaction mixture was stirred for 12 h. The reaction was quenched with aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved

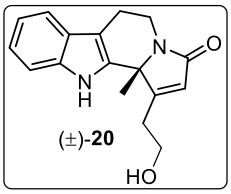
in EtOAc (20 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) once again afforded compound (±)-**16** as a solid (67 mg, 67%).

***tert*-Butyl 1-(2-Hydroxyethyl)-11b-methyl-3-oxo-3,5,6,11b-tetrahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (19).** To a stirred solution of compound (±)-**18**

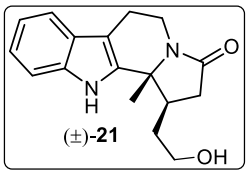


(950 mg, 2.51 mmol) in THF:H_2O (3:1, 30 mL) was added NMO (50% in water, 1.80 mL, 7.53 mmol) and catalytic amount of OsO_4 solution in *t*-BuOH (0.50 M, 0.20 mL) at 25 °C and reaction mixture was stirred for 12 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ and further stirred for 30 min. The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried diastereomeric mixture of diol was directly used for next step. To a stirred solution of obtained diol in THF:H_2O (1:1, 20 mL) was added $NaIO_4$ (1.20 g, 5.76 mmol) at 25 °C in two equal lots. The reaction mixture was stirred for 1 h and diluted with EtOAc (30 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained aldehyde was immediately used for the next reaction without any purification. To a stirred solution of aldehyde in MeOH (10 mL) was added the $NaBH_4$ (184 mg, 4.97 mmol) at 0 °C. The reaction was stirred for 30 min and quenched with aqueous NH_4Cl. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (25 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 5:95) afforded compound (±)-**19** as a solid (854 mg, 89%). Mp 123–125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74 (s, 9+1H), 2.09 (s, 3H), 2.62–2.72 (m, 1H), 2.75 (dd, J = 16.1 and 4.9 Hz, 1H), 2.86–3.02 (m, 2H), 3.30 (td, J = 11.9 and 4.9 Hz, 1H), 3.92 (t, J = 6.7 Hz, 2H), 4.56 (dd, J = 13.4 and 6.1 Hz, 1H), 5.92 (s, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 24.8, 28.3, 32.1, 34.0, 60.3, 68.5, 84.7, 114.9, 118.9, 119.0, 121.9, 122.8, 125.2, 128.2, 135.0, 136.7, 151.1, 164.3, 169.2; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_4$ 383.1965, found 383.1963; IR ($CHCl_3$) ν_{max} 3444, 1729, 1675 cm^{-1}.

1-(2-Hydroxyethyl)-11b-methyl-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-3-one (20). The compound (±)-**19** (800 mg, 2.09 mmol) and distilled water (50 mL) mixture was refluxed for 18 h. The reaction mixture was allowed to reach 25 °C and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 5:95) afforded (±)-**20** as a solid (555 mg, 94%). Mp 137–139 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.69 (s, 3H), 2.69–2.82 (m, 2H), 2.84–2.98 (m, 2H), 3.20–3.28 (m, 1H), 3.89 (td, J = 4.9 and 2.3 Hz, 2H), 4.47 (dd, J = 13.4 and 4.6 Hz, 1H), 5.96 (s, 1H), 7.00 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 23.1, 24.4, 31.7, 37.5, 60.3, 68.2, 108.3, 112.2, 119.3, 120.3, 120.9, 123.0, 127.7, 134.5, 138.4, 168.1, 173.9; ESIMS (*m*/*z*) 283 $[M+H]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{18}N_2O_2Na$ 305.1260, found 305.1258; IR ($CHCl_3$) ν_{max} 3348, 1669 cm^{-1}.



1-(2-Hydroxyethyl)-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (21). *Method A*: To a stirred solution of compound (±)-**20** (100 mg, 0.35 mmol) in MeOH (7 mL) was added activated Pd/C (10 mg, 10 wt%) at 25 °C and the reaction mixture was stirred under balloon pressure hydrogen atmosphere for 2 h. The reaction mixture was filtered to remove Pd/C and concentration of the filtrate in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 5:95) afforded compound (±)-**21** as a solid (88 mg, 88%).

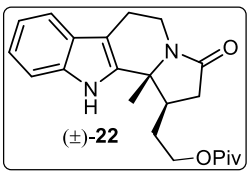


Method B. To a solution of compound (±)-**20** (100 mg, 0.35 mmol) in a dry MeOH (10 mL) was added activated Mg turnings (59 mg, 2.48 mmol) at 25 °C under argon atmosphere and the reaction mixture was stirred for 12 h. The reaction was quenched with aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (10 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 5:95) yielded pure (±)-**21** as a solid (62 mg, 62%).

Method C. To a stirred solution of compound (±)-**15** (100 mg, 0.35 mmol) in THF:H_2O (3:1, 12 mL) was added NMO (50% in water, 417 μL, 1.78 mmol) and catalytic amount

of OsO_4 solution in *t*-BuOH (0.50 M, 0.05 mL) at 25 °C and the reaction mixture was stirred for 12 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ and further stirred for 30 min. The aqueous layer was extracted in EtOAc (2 × 20 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained diol was directly used for next step. To a stirred solution of obtained diol in THF:H_2O (1:1, 10 mL) was added $NaIO_4$ (169 mg, 0.79 mmol) at 25 °C in two lots and the reaction was monitored by TLC. The reaction mixture was stirred for 1 h and diluted with EtOAc (40 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo yielded the aldehyde which was immediately used for next reaction for stability issue. To a stirred solution of above mentioned aldehyde in MeOH (8 mL) was added $NaBH_4$ (26 mg, 0.70 mmol) at 0 °C and reaction mixture was stirred for 1 h. The reaction was quenched with aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (15 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 5:95) afforded compound (±)-**21** as a solid (93 mg, 92%). Mp 117–119 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.48 (s, 3H), 1.70–1.81 (m, 1H), 2.27–2.46 (m, 3H), 2.53–2.59 (m, 1H), 2.65–2.74 (m, 1H), 2.79 (dd, *J* = 15.6 and 4.8 Hz, 1H), 3.05 (td, *J* = 12.2 and 4.8 Hz, 1H), 3.55–3.63 (m, 1H), 3.68–3.75 (m, 1H), 4.36 (dd, *J* = 13.1 and 6.1 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 19.7, 22.5, 33.5, 36.2, 37.7, 43.7, 61.5, 63.9, 107.0, 112.2, 119.0, 120.1, 122.6, 127.8, 138.1, 139.0, 174.3; ESIMS (*m*/*z*) HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{20}N_2O_2Na$ 307.1417, found 307.1413; IR ($CHCl_3$) ν_{max} 3390, 1670 cm^{-1}.

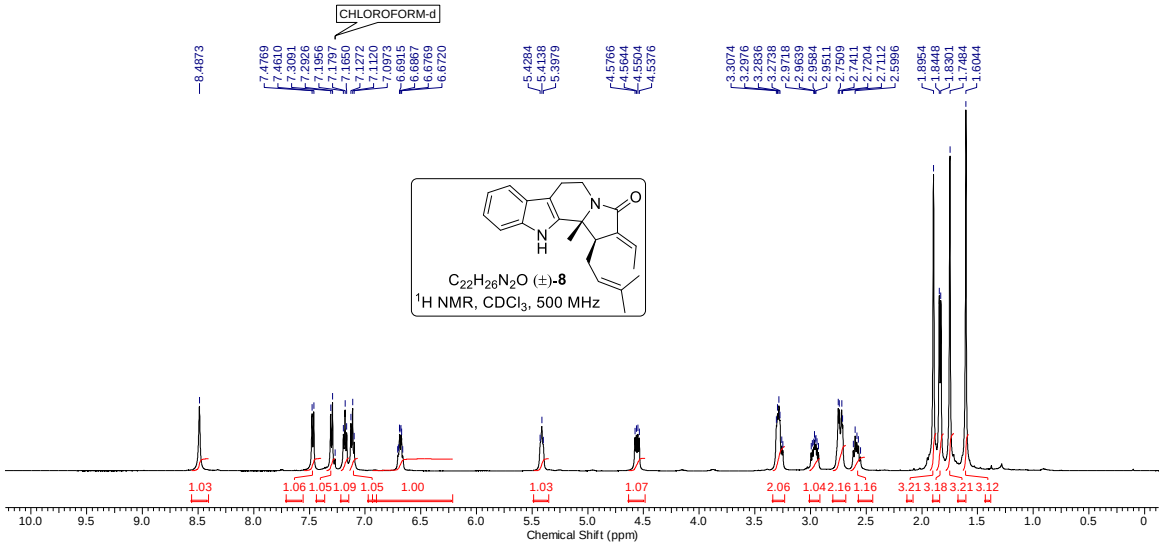
2-[11b-Methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl]ethyl Pivalate (22). To a stirred solution of compound (±)-**21** (100 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) were slowly added Et_3N (147 μL, 1.05 mmol) and pivCl (65 μL, 0.52 mmol) at 0 °C. The reaction mixture was stirred for 5 h allowing reach 25 °C and the reaction was quenched with water. The saperated aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layer was washed with aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by



(±)-**22**

column chromatography (silica gel, 230–400 mesh, EtOAc–PE, 30:70) afforded compound (±)-**22** as a solid (111 mg, 86%). Mp 214–216 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9H), 1.49 (s, 3H), 1.88–2.00 (m, 1H), 2.25–2.48 (m, 3H), 2.64 (dd, *J* = 14.6 and 6.0 Hz, 1H), 2.80–2.85 (m, 2H), 2.98–3.10 (m, 1H), 4.10–4.26 (m, 2H), 4.50 (d, *J* = 12.8 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 8.32 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 21.4, 27.1, 29.7, 34.9, 37.0, 38.7, 41.6, 61.5, 62.9, 107.4, 111.1, 118.5, 119.9, 122.3, 126.5, 136.1, 137.3, 171.2, 178.7; ESIMS (*m*/*z*) 369 $[M+H]^+$; HRMS (ESI) $[M+Na]^+$ calcd for $C_{22}H_{28}N_2O_3Na$ 391.1992, found 391.1989; IR ($CHCl_3$) ν_{max} 3469, 1719, 1676 cm^{-1}.

2B.5 Selected Spectra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7.3091
7.2926
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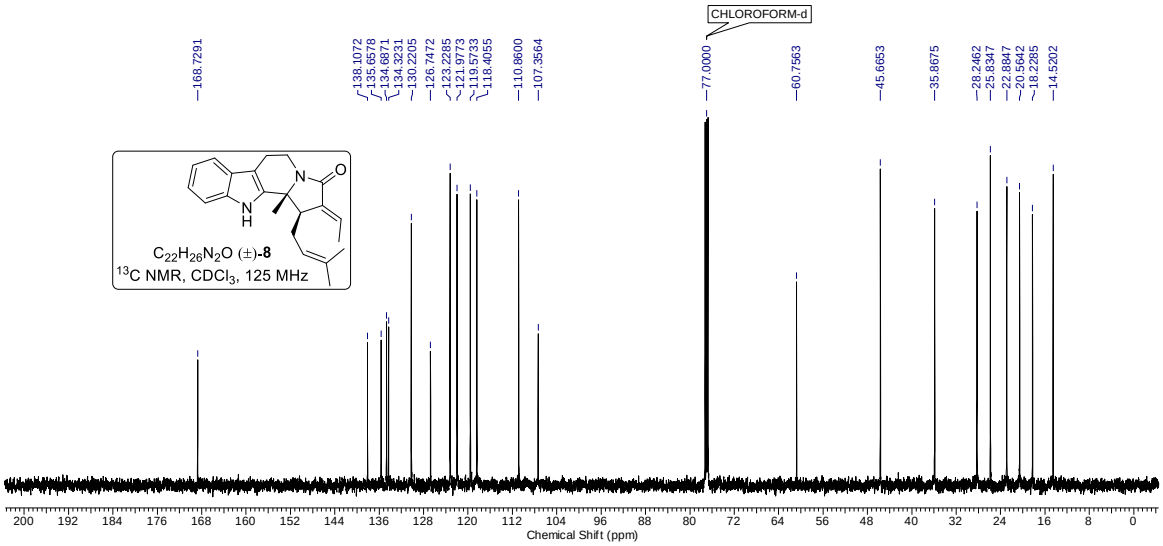
7.1120
7.0973
6.6915
6.6867
6.6769
6.6720
5.4284
5.4138
5.3979
4.5766
4.5644
4.5504
4.5376
3.3074
3.2976
3.2836
3.2738
3.2718
2.9639
2.9584
2.9511
2.7509
2.7411
2.7204
2.7112
2.5996
1.8954
1.8448
1.8301
1.7484
1.6044
N
O
N
H
C22H26N2O (±)-8
1H NMR, CDCl3, 500 MHz
1.03
1.06
1.05
1.09
1.05
1.00
1.03
1.07
2.06
1.04
2.16
1.16
3.21
3.18
3.21
3.12
Chemical Shift (ppm)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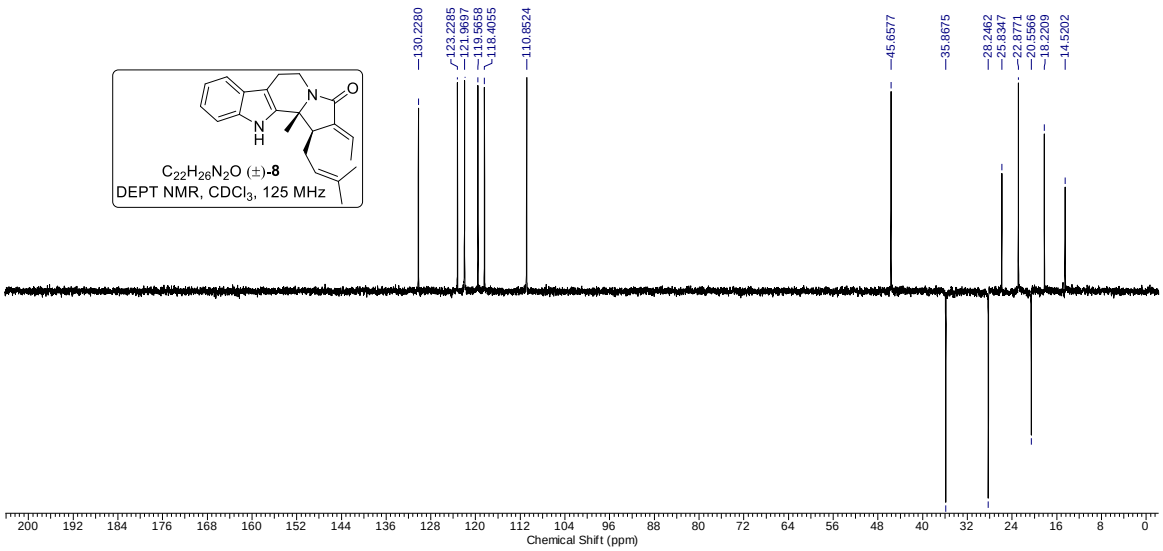
118.4055
110.8600
107.3564
77.0000
60.7563
45.6653
35.8675
28.2462
25.8347
22.8847
20.5642
18.2285
14.5202
N
O
N
H
C22H26N2O (±)-8
13C NMR, CDCl3, 125 MHz
Chemical Shift (ppm)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22.8771
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14.5202
N
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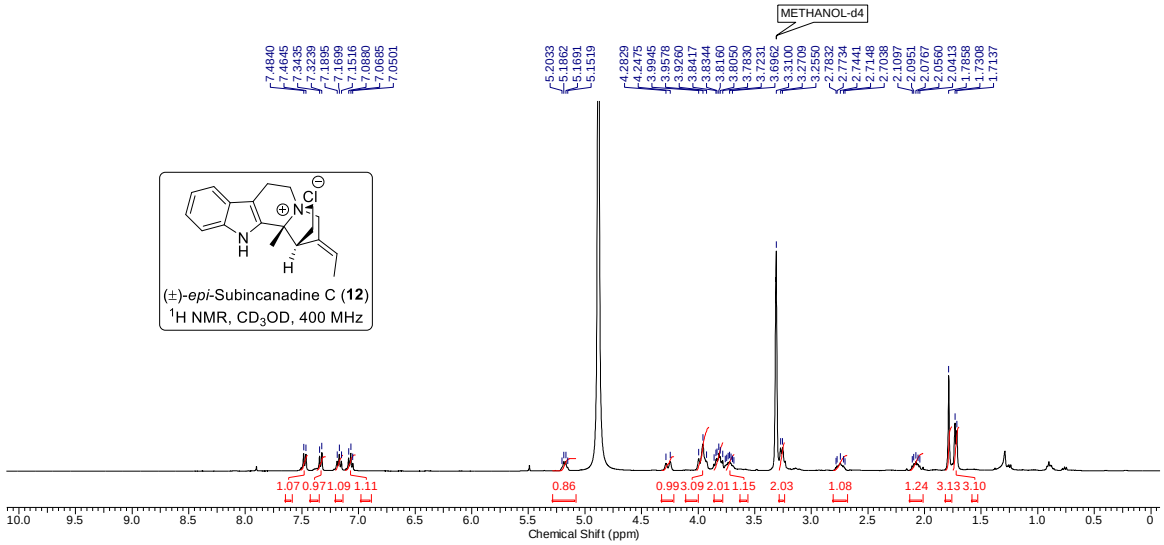
N
H
C22H26N2O (±)-8
DEPT NMR, CDCl3, 125 MHz
Chemical Shift (ppm)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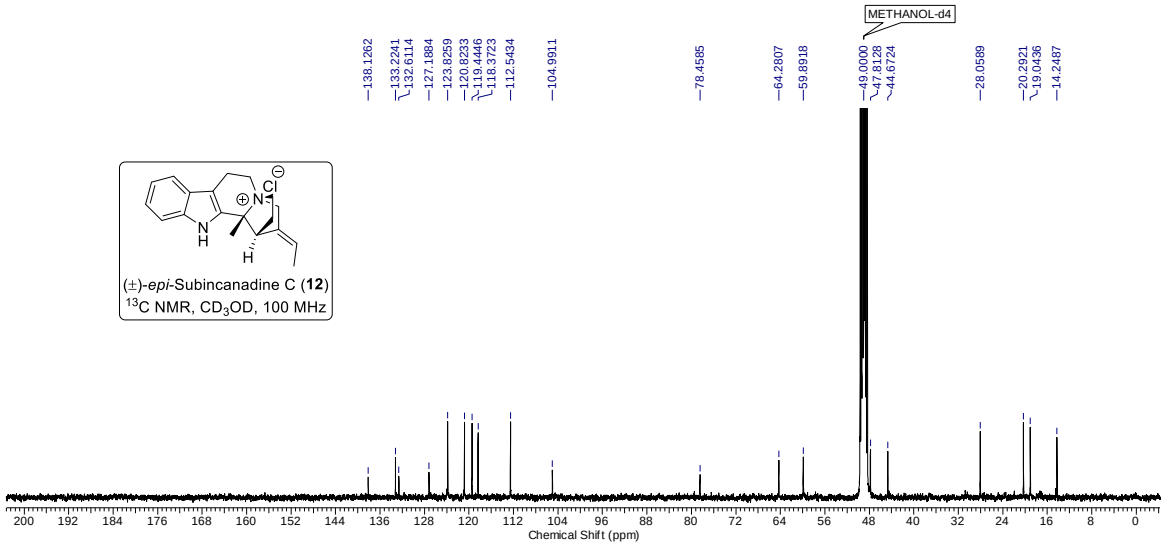
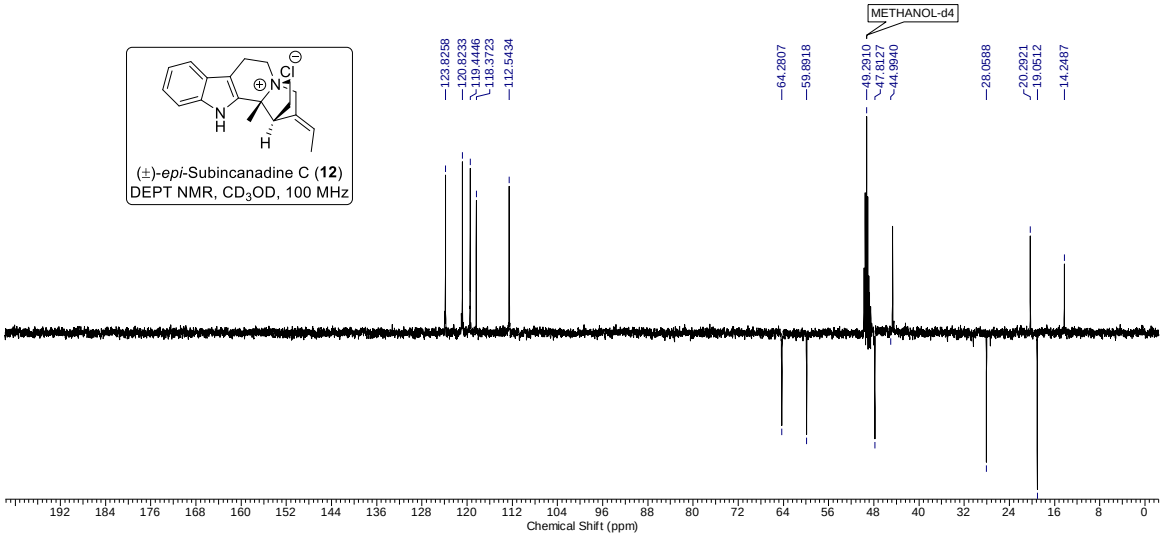
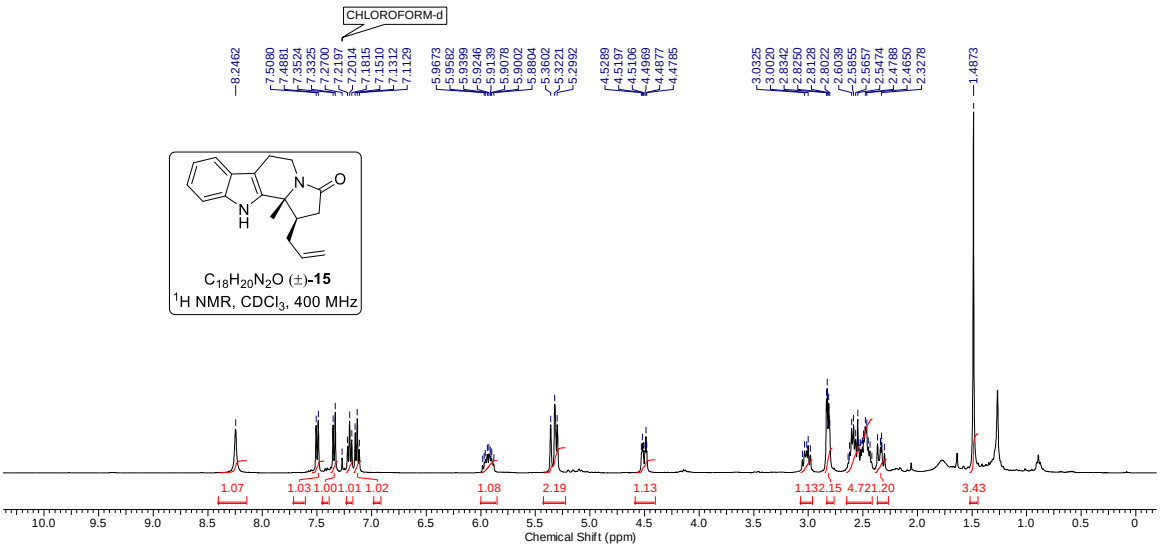
1H NMR, CD3OD, 400 MHz
Chemical Shift (ppm)


METHANOL-d4
(±)-epi-Subincanadine C (12)
13C NMR, CD3OD, 100 MHz
Chemical Shift (ppm)


METHANOL-d4
(±)-epi-Subincanadine C (12)
DEPT NMR, CD3OD, 100 MHz
Chemical Shift (ppm)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7.2014
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7.1510
7.1312
7.1129
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5.9246
5.9139
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5.9002
5.8904
5.8862
5.3221
5.2992
4.5289
4.5197
4.5106
4.4969
4.4877
4.4785
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3.0020
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2.8022
2.6039
2.5855
2.5657
2.5474
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1.4873
C18H20N2O (±)-15
1H NMR, CDCl3, 400 MHz
1.07
1.03
1.00
1.01
1.02
1.08
2.19
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1.13
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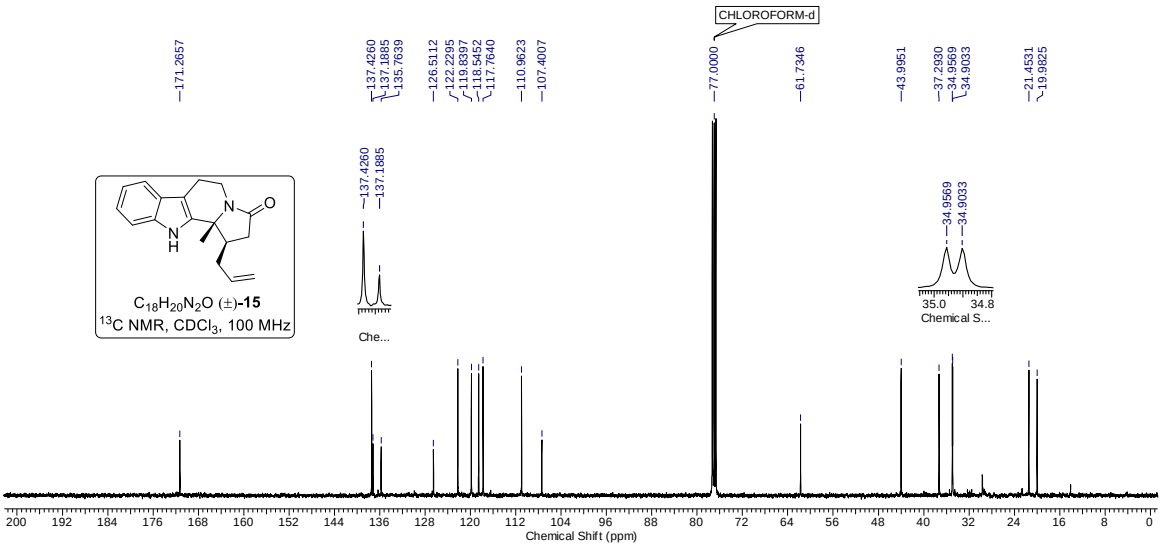
4.72
1.20
3.43
Chemical Shift (ppm)


CHLOROFORM-d
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135.7639
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118.5432
117.7640
110.9623
107.4007
77.0000
61.7346
43.9951
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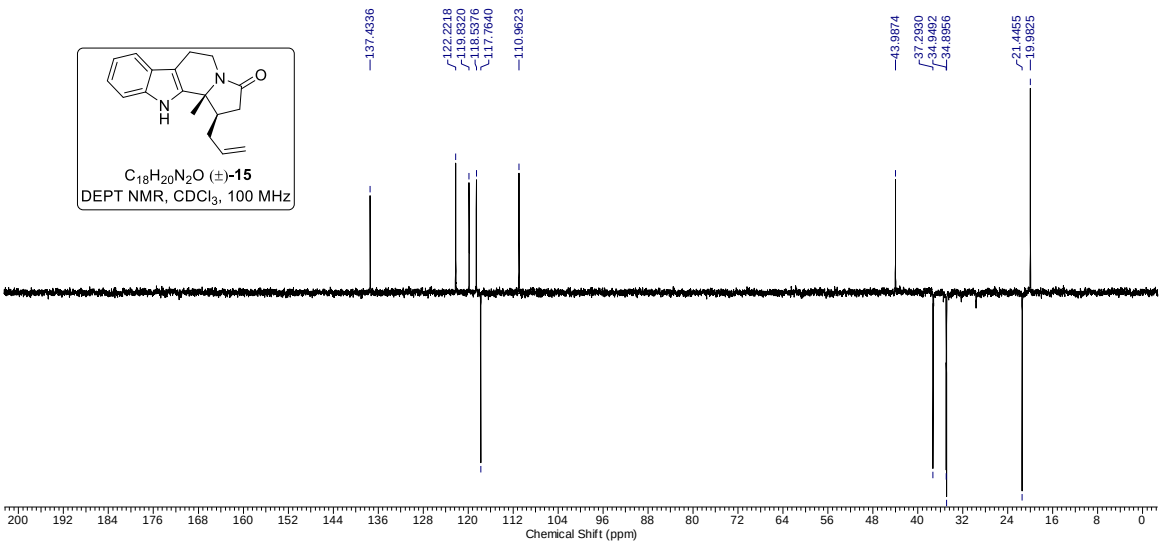
34.9033
21.4531
19.9825
C18H20N2O (±)-15
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)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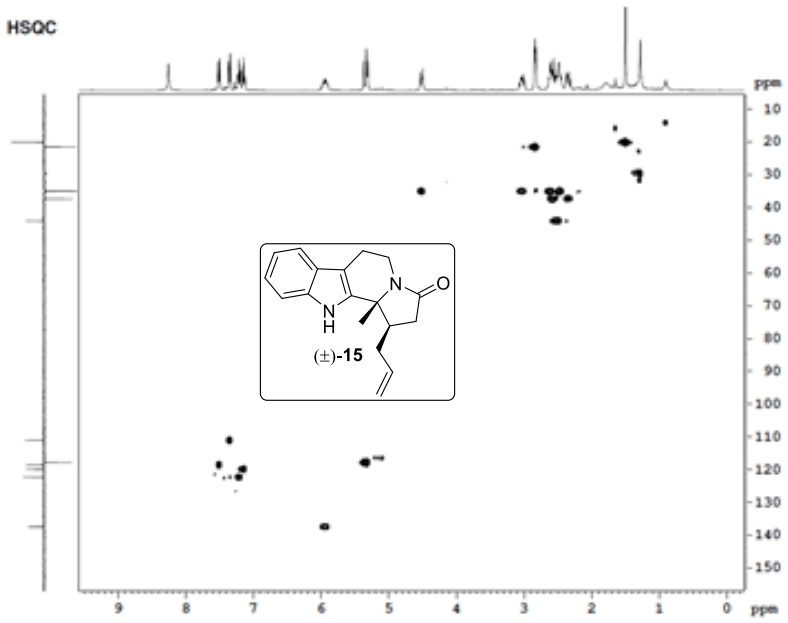
21.4455
19.9825
C18H20N2O (±)-15
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)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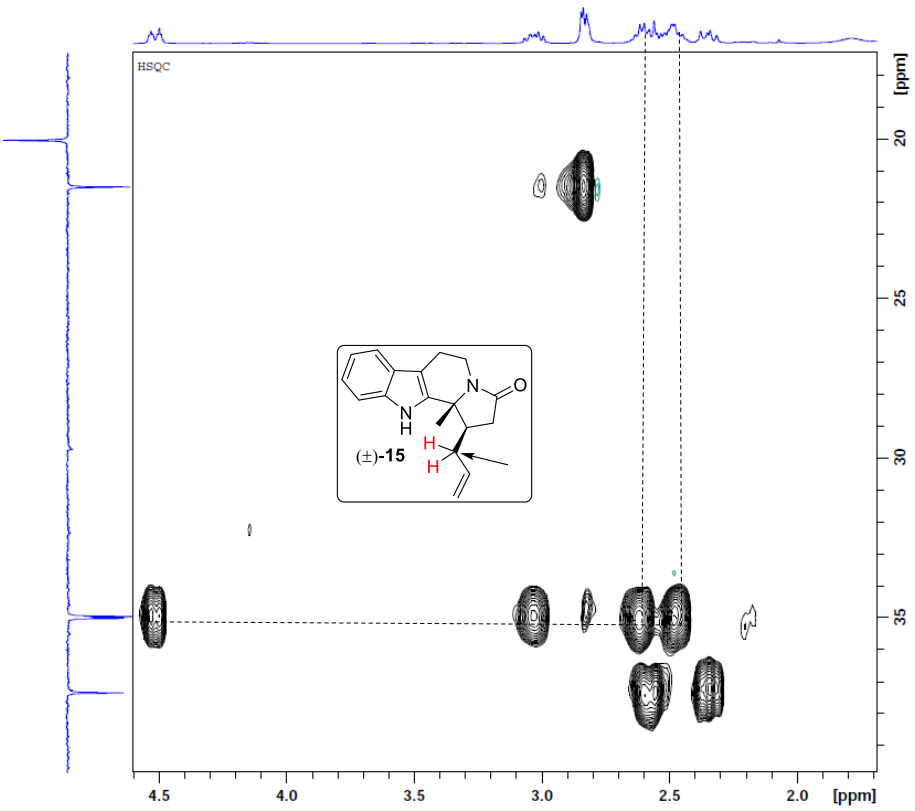
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9
8
7
6
5
4
3
2
1
0
ppm
N
H
O
(±)-15

HSQC 1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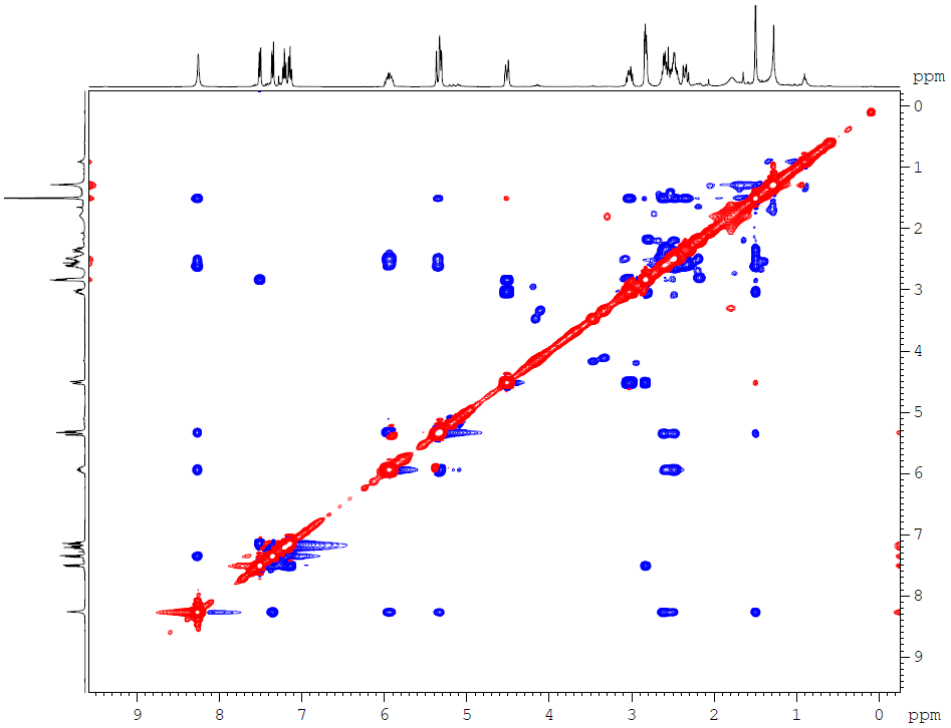
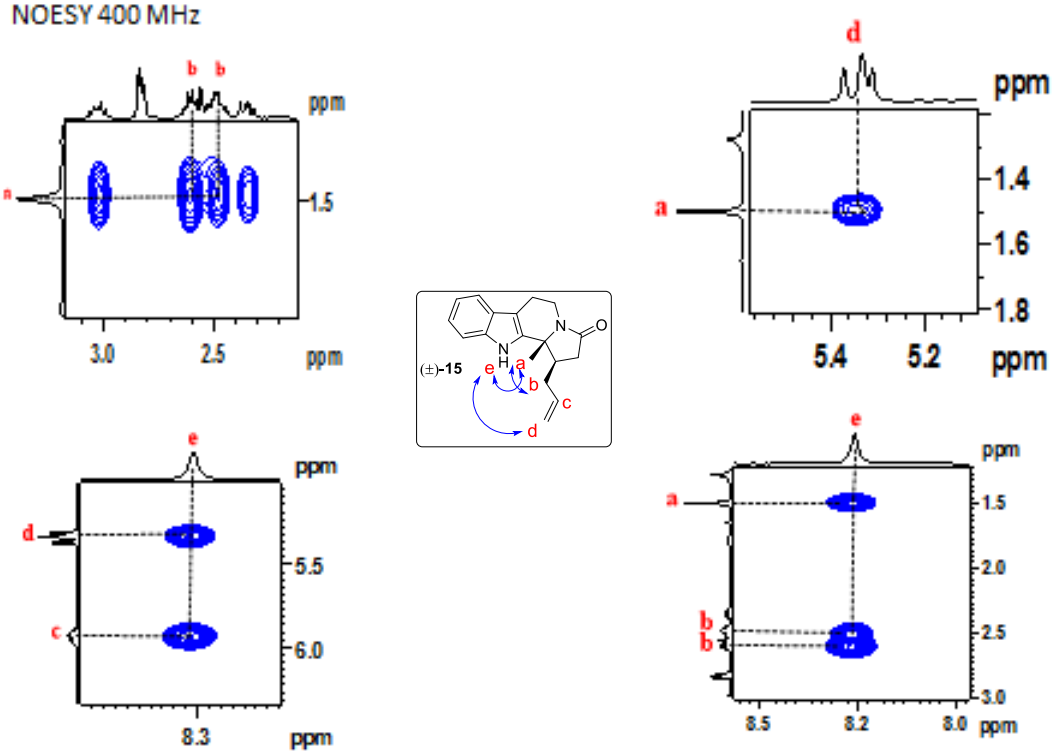
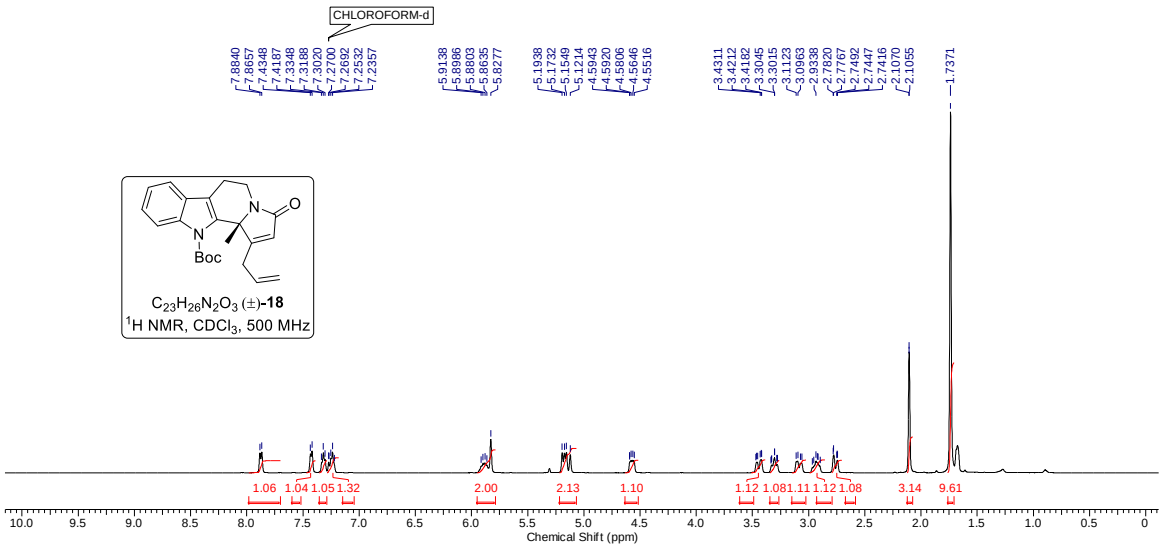
2.5
2.0
[ppm]
N
H
O
H
H
(±)-15

NOESY



NOESY 400 MHz

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7.2532
7.2357
5.9138
5.8986
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5.8655
5.8277
5.1938
5.1732
5.1549
5.1214
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4.5516
3.4311
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3.4182
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3.3015
3.1123
3.0963
2.9338
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2.7492
2.7447
2.7416
2.1070
2.1055
1.7371
Boc
C23H26N2O3 (±)-18
1H NMR, CDCl3, 500 MHz
1.06
1.04
1.05
1.32
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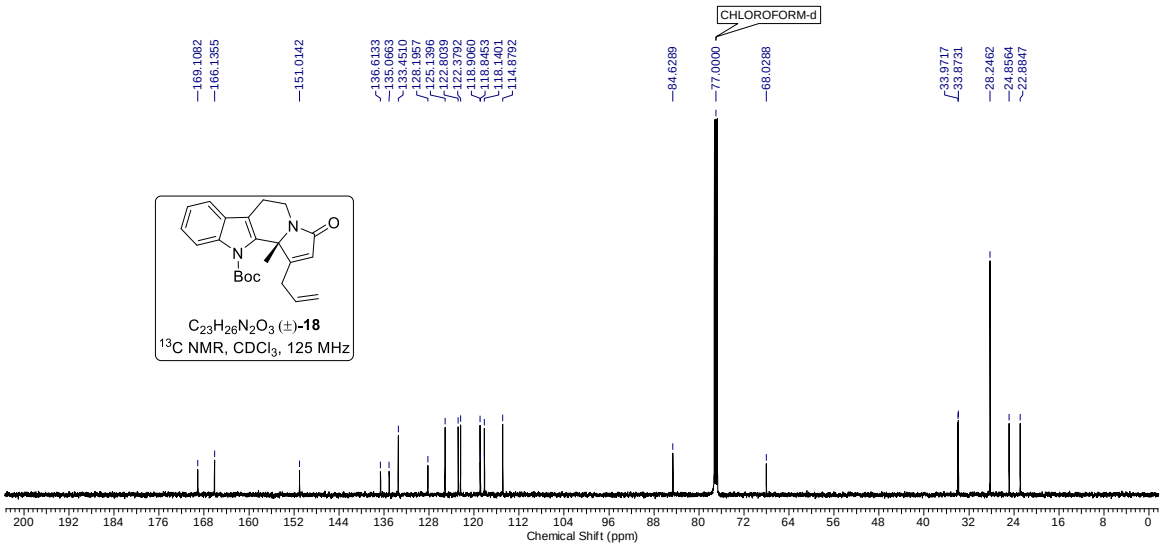
1.10
1.12
1.08
1.11
1.12
1.08
3.14
9.61
Chemical Shift (ppm)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118.9060
118.8453
118.1401
114.8792
84.6289
77.0000
68.0288
33.9717
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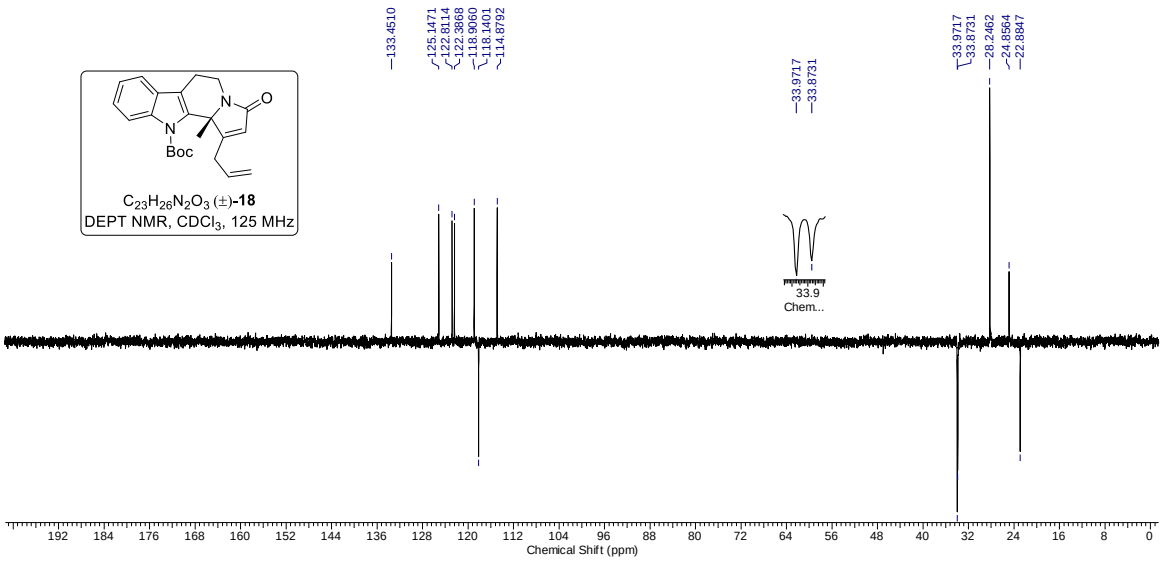
22.8847
Boc
C23H26N2O3 (±)-18
13C NMR, CDCl3, 125 MHz
Chemical Shift (ppm)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118.1401
114.8792
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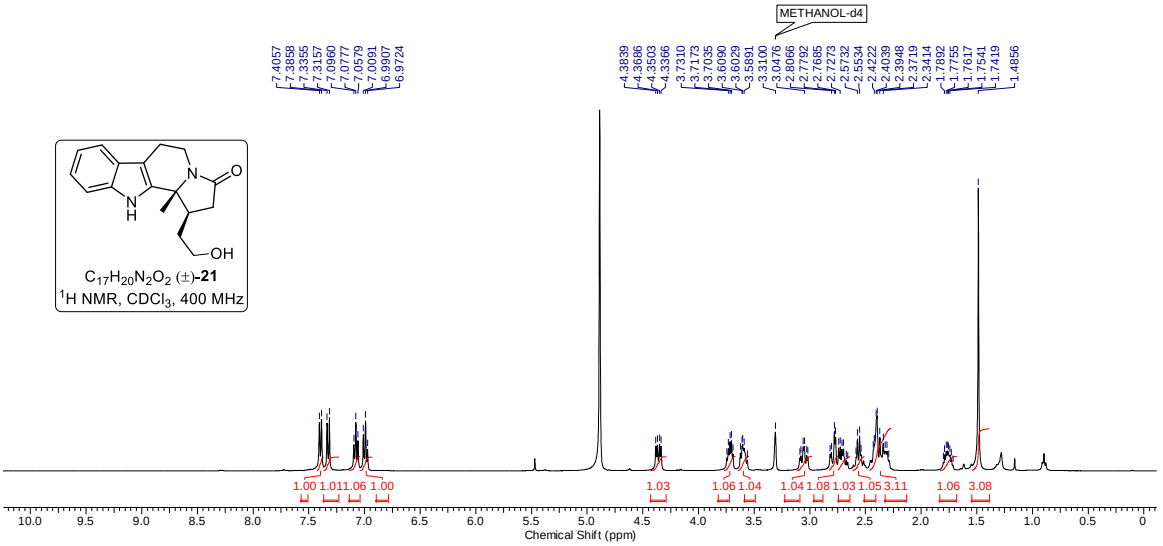
33.8731
33.9
Chem...
Boc
C23H26N2O3 (±)-18
DEPT NMR, CDCl3, 125 MHz
Chemical Shift (ppm)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1.7419
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1.00 1.01 1.06 1.00
1.03
1.06 1.04
1.04 1.08 1.03 1.05 3.11
1.06 3.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)
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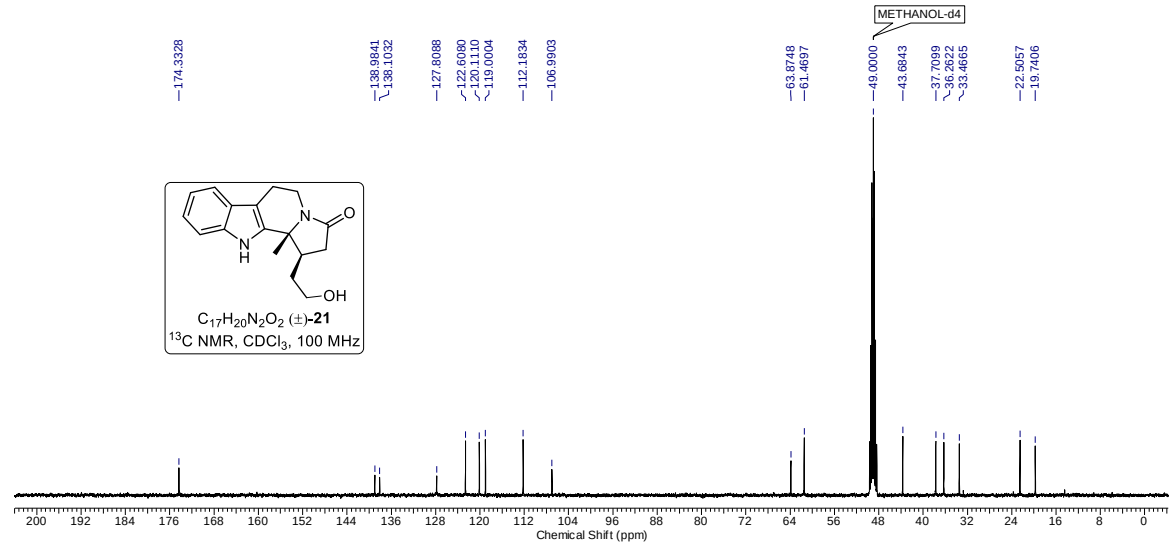
O
N
H
OH
C17H20N2O2 (±)-21
1H NMR, CDCl3, 400 MHz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127.8088
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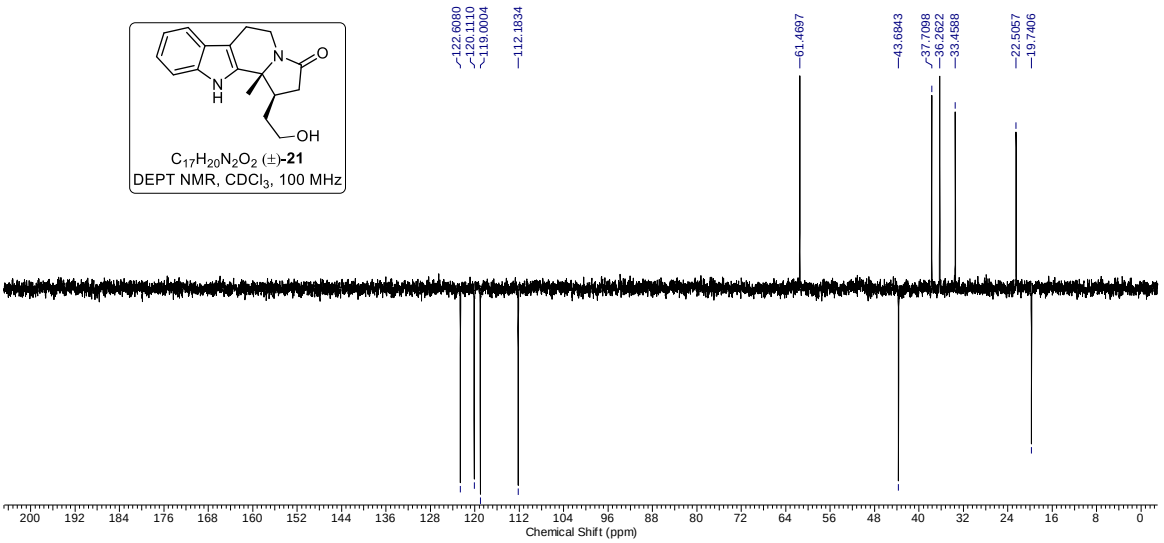
119.0004
112.1834
106.9903
63.8748
61.4697
49.0000
43.6843
37.7099
36.2622
33.4665
22.5057
19.7406
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)
N
O
N
H
OH
C17H20N2O2 (±)-21
13C NMR, CDCl3, 100 MHz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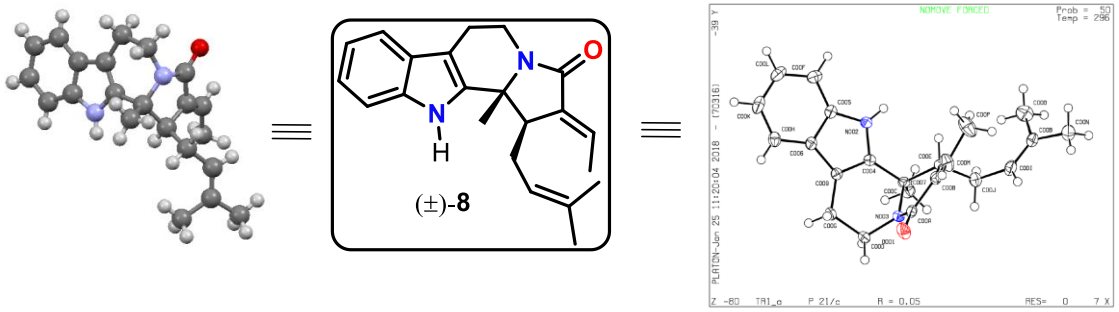
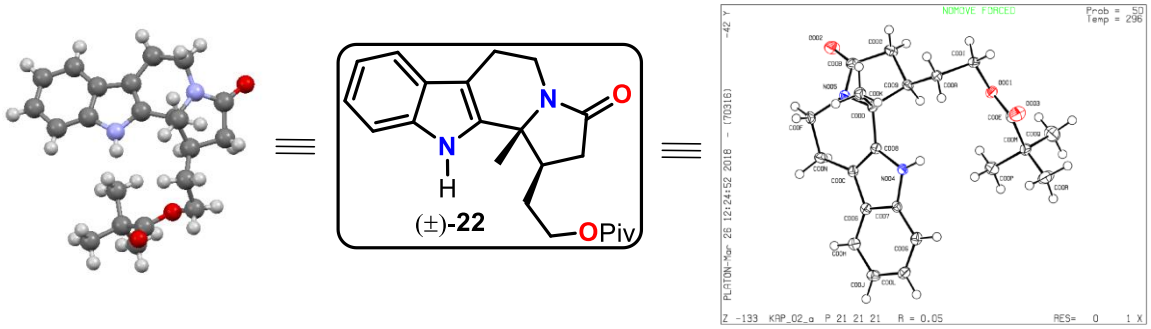
61.4697
43.6843
37.7098
36.2622
33.4588
22.5057
19.7406
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)
N
O
N
H
OH
C17H20N2O2 (±)-21
DEPT NMR, CDCl3, 100 MHz

2B.6 X-ray Crystal structures of compound (±)-8 and (±)-22





2B.7 References

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Chapter 3

Synthesis of Indole Alkaloids (±)/(+)-Subincanadine E and (+)-Subincanadine F

Section A

Position Specific Allylic Rearrangement in Stereoselective Pictet–Spengler Cyclization: Total Synthesis of (±)/(+)-Subincanadine E and Determination of Absolute Configuration

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 first section presents total synthesis of (±)/(+)-subincanadine E and determination of its absolute configuration as a result of enantioselective first synthesis. The second section describes regioselective and stereoselective reductive aziridinium ring cleavage leading to azabicyclodecane architecture and its application in enantioselective synthesis of (+)-subincanadine F. The detailed experimental procedures, complete tabulated analytical and spectral data, some selected NMR spectra and references have been appropriately included at the end of each section.

3A.1 Background

Subincanadines A–G (**1**–**7**) were isolated in 0.002% yield from the bark of Brazilian medicinal plant *Aspidosperma subincanum* mart and among these (+)-subincanadine E (**5**) and F (**6**) bear unique 1-azabicyclo[5.2.2]undecane and 1-azabicyclo[4.3.1]decane moiety

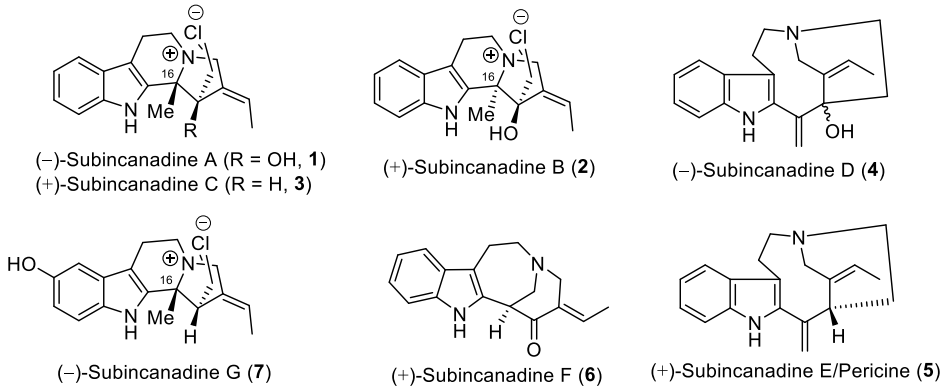


Figure 1. Bioactive indole alkaloids subincanadines A–G.

respectively. Biological activity point of view (+)-subincanadine E (**5**) exhibits most potent cytotoxicity against murine lymphoma L1210 cells ($IC_{50,}$ 0.3 μg/mL) & human epidermoid carcinoma KB cells ($IC_{50,}$ 4.4 μg/mL) and (+)-subincanadine F (**6**) also in vitro has potent cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 2.40 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 4.80 μg/mL).[1] The interesting biological activities and fascinating molecular architectures of these compounds have attracted immediate attention and became the synthetic targets as a result of their limited availability from natural sources.

3A.2 Concise Account of Subincanadine E Synthesis

Zai and co-workers in 2014 reported the first total synthesis of (±)-subincanadine E by using novel Zinc mediated fragmentation as a key reaction for construction of challenging nine membered ring (please see chapter 1; scheme 4 and page no. 9).[2a] In addition to

successful synthesis of Zai and co-workers, Bennasar *et al* in 2015 reported synthetic approach to the bridged indole alkaloid subincanadine E framework, based on the combination of ring-closing metathesis (RCM) and Heck cyclization. After construction of tricyclic nine-membered central ring via RCM-based route, the ring closure on the strained 1-azabicyclo[5.2.2]undecane framework of the subincanadine E by using the corresponding vinyl halide Heck coupling was systematically pursued but unfortunately it was not successful (please see chapter 1; scheme 5 and page no. 10).[2b]

3A.3 Results and Discussion

Total Synthesis of (±)/(+)-Subincanadine E and Determination of Absolute Configuration

The structurally interesting and biologically important cytotoxic alkaloids subincanadines A–G were isolated in 2 to 14 mg quantities from 100 grams bark of the Brazilian medicinal plant *Aspidosperma subincanum* by Ohsaki and co-workers in 2002 (Figure 1).[1] (+)-Subincanadine E is also named as pericine and it was first isolated from *Picralima nitida* by Stöckigt and co-workers in 1982.[3] Recently, Kam and co-workers have proposed that the (*S*)-subincanadine E is a common biogenetic precursor of five structurally unprecedented monoterpenoid indole alkaloids valparicine (**8**), apparicine (**9**),[4] arboridinine (**10**),[5a] (+)-arborisidine (**11**) and (–)-arbornamine (**12**) (Figure 2).[5b]

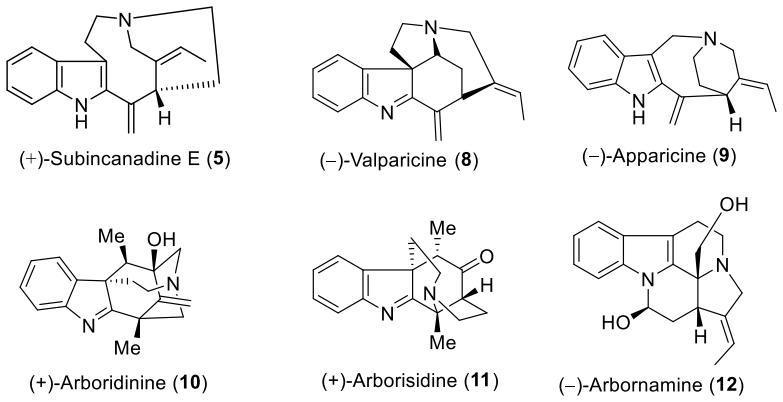
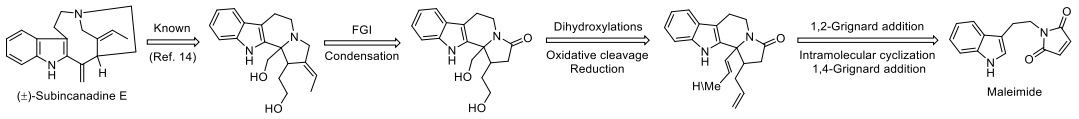


Figure 2. Biogenetic precursor (+)-subincanadine E derived novel natural products.

(+)-Subincanadine E endures unique structural architecture and in vitro exhibits potent cytotoxicity against murine lymphoma L1210 cells ($IC_{50,}$ 0.3 μg/mL) & human epidermoid carcinoma KB cells ($IC_{50,}$ 4.4 μg/mL).[1] A few new synthetic routes to the target compounds from figure 1 have been reported in recent literature.[2a,6–13] Zhai and co-workers in 2014 reported the first total synthesis of (±)-subincanadine E.[2a] Development of new

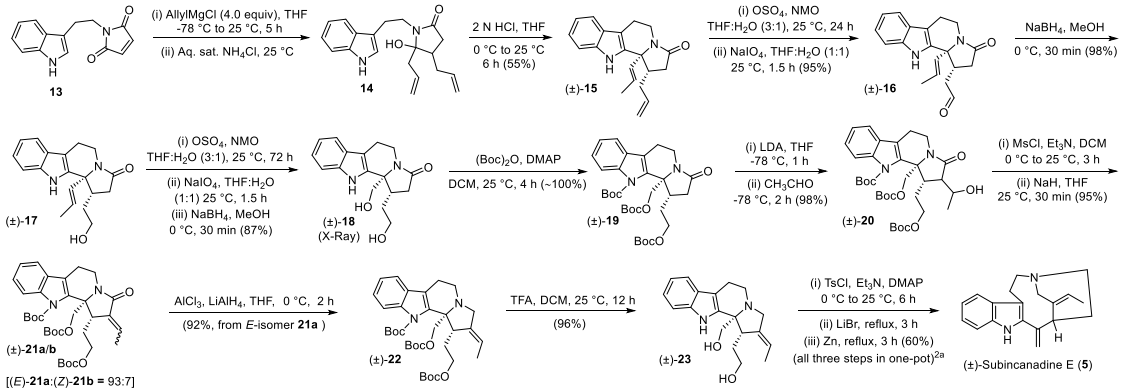
synthetic approaches for (+)/(–)-subincanadine E is essential from its exceptional structural features, promising biological activity and establishment of stereochemistry point of view. Retrosynthetically, corresponding tryptamine derived maleimide would be the potential precursor for total synthesis of (±)-subincanadine E (Scheme 1). Moreover (*R*)- and (*S*)-acetoxysuccinimides may also serve as appropriate starting materials for enantioselective synthesis of (+)- and (–)-subincanadines E. In continuation of our studies on the use of cyclic anhydrides to synthesize bioactive natural products;[14–18] we herein present synthesis of (±)-subincanadine E and natural isomer (+)-subincanadine E from the readily available corresponding imides as starting materials (Schemes 1–5).



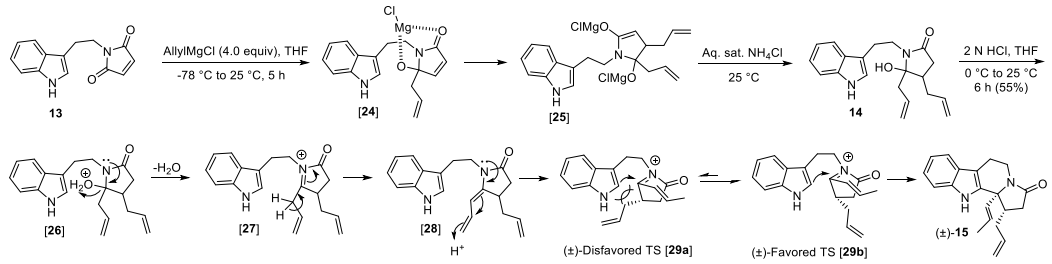
Scheme 1. Concise Retrosynthetic Analysis of (±)-Subincanadine E

Reaction of maleimide **13** with four equivalents of vinylmagnesium bromide at –78 °C resulted in decomposition of reaction mixture. One-pot reaction of maleimide **13** with four equivalents of allylmagnesium chloride at –78 °C followed by acidification with hydrochloric acid at 25 °C directly delivered the two allyl groups introduced and one of the double bond rearranged cyclized product (±)-**15** in ~20% yield (Scheme 2). Remarkably, two different types of coupling reactions of Grignard reagent with maleimide **13** and acid catalyzed diastereoselective intramolecular cyclization involving position specific allylic rearrangement took place in one-pot. Quenching of the above described Grignard reaction with saturated aqueous ammonium chloride to obtain the intermediate product (±)-1**4** and its immediate reaction with 2 N HCl provided the desired product (±)-**15** in 55% yield. The plausible mechanisms for reactions of Grignard reagent with maleimide and acid catalyzed intramolecular Pictet−Spengler cyclization involving position specific allylic rearrangement have been depicted in scheme 3. On the basis of control experiments described in scheme 4; the 1,2-addition of Grignard reagent to maleimide **13** takes place first and forms the magnesium complex **24**, which internally activates lactam moiety for in situ 1,4-addition of Grignard reagent and delivers the lactamol **14**.[19] Lactamol **14** on treatment with 2 N HCl underwent amide nitrogen driven dehydration to form the diene intermediate **28**, which on selective rearrangement of the double bond followed by diastereoselective intramolecular cyclization directly resulted in

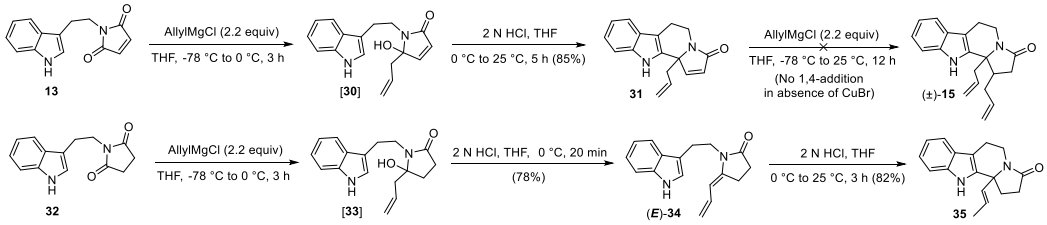
the essential product (±)-**15**. The in situ allylic rearrangement was eventually useful to appropriately tailor the carbon chain at an angular position. Mechanistically above mentioned intramolecular Pictet−Spengler cyclization takes place via flat iminium ion intermediate and the incoming nucleophile approaches from less hindered side in the



Scheme 2. Synthesis of (±)-Subincanadine E via Grignard Additions, Allylic Rearrangement, Pictet–Spengler Cyclization, Condensation and Ring Expansion Route



Scheme 3. Plausible Mechanisms for Couplings of Grignard Reagent with Maleimide and Intramolecular Cyclization Involving Position Specific Allylic Rearrangement



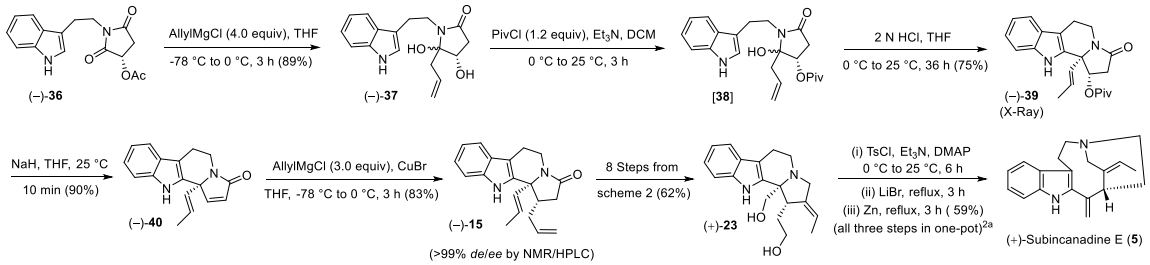
Scheme 4. Model Studies on Grignard Addition to Imides, Allylic Rearrangement, Isolation of the Proposed Diene Intermediate and Intramolecular Cyclizations

favored intermediate **29b** resulting in *syn*-product (±)-**15**.[7,20] Reaction of maleimide **13** with 2.20 equivalents of allylmagnesium chloride at –78 °C exclusively formed the lactomol intermediate **30** (Scheme 4). The sensitive lactamol **30** on immediately performed acid induced intramolecular cyclization furnished the corresponding *α,β*-unsaturated indolizinoindolone **31** in 85% yield, without an allylic rearrangement. The

indolizinoindolone **31** did not undergo 1,4-addition of Grignard reagent in absence of CuBr due to the lack of substrate/reagent activation. The witnessed in situ allylic rearrangement was specific to the succinimide derived lactamols and it was feasible to isolate an exclusively formed diene intermediate **34**[21] in the model transformation of succinimide **32** to indolizinoindolone **35**. The exclusive formation of relatively more stable diene (*E*)-**34** could be attributed to the effective conjugation of lone pair on nitrogen atom.

Direct transformation of two different types of carbon–carbon double bonds in compound (±)-**15** via dihydroxylation, oxidative cleavage and reduction to the corresponding product (±)-diol **18** was low yielding. The stepwise transformations of terminal and internal olefins in compound (±)-**15** initially provided primary alcohol (±)-**17** in 93% yield and then the desired (±)-diol **18** in 87% yield (Scheme 2). The structure of advanced intermediate (±)-diol **18** was unambiguously established by X-ray crystallographic data and it also confirmed the formation of *syn*-product (±)-**15** in the above mentioned Pictet−Spengler cyclization (Figure 3). Boc-protection of indole nitrogen atom and two primary alcohol units in compound (±)-**18** provided the required product (±)-**19** in quantitative yield. Condensation of (±)-lactam **19** with acetaldehyde followed by mesylation of the formed alcohol and stereoselective elimination of mesylate delivered the column chromatographically separable mixture of *α*,*β*-unsaturated lactam (±)-**21a** as a major product in 88% yield and (±)-**21b** as a minor product in 7% yield, over three steps. As expected the vinylic proton of a major *E*-isomer (±)-**21a** was more deshielded (6.56 ppm) compared to the corresponding minor *Z*-isomer (±)-**21b** (5.82 ppm) due to the five membered *peri*-intraction with a *γ*-lactam carbonyl. Alane-reduction of a lactam carbonyl in compound (±)-**21a** to (±)-amine **22** in 92% yield followed by trifluoroacetic acid induced deprotection of three Boc-groups furnished the known (±)-diol **23** in 96% yield. A one-pot three-step transformation of (±)-diol **23** under Zhai and co-workers conditions[2a] delivered the desired (±)-subincanadine E (**5**) in 60% yield. The analytical and spectral data obtained for (±)-diol **23** and (±)-subincanadine E (**5**) were in complete agreement with the reported data.[1,2a]

Finally we planned the enantioselective synthesis of (+)/(–)-subincanadine E (**5**) from (*S*)-acetoxysuccinimide **36**[22] (Scheme 5). As expected, Grignard reagent regioselectively attacked on the more reactive imide carbonyl of (*S*)-acetoxysuccinimide **36** and directly delivered the corresponding deacylated single diastereomer (–)-**37** in 89% yield. Acid



Scheme 5. Enantioselective Synthesis (+)-Subincanadine E from (*S*)-Acetoxysuccinimide via an Unanticipated *Syn*-addition of the Cuprate

catalyzed Pictet–Spengler cyclization of (–)-hydroxy-lactamol **37** was not diastereoselective and provided nearly 1:1 mixture of the corresponding diastereomers in 73% yield. (–)-Hydroxy-lactamol **37** on treatment with pivaloyl chloride and triethylamine selectively formed the corresponding sterically hindered lactamol intermediate **38** in quantitative yield; which was used for the next step without purification and characterization for stability issues. Acid-catalyzed Pictet–Spengler cyclization of lactamol **38** was stereoselective and exclusively provided the expected double bond rearranged cyclized *syn*-product (–)-**39** in 75% yield. The structure of product (–)-**39** was also established by X-ray crystallographic data and it confirmed the *syn*-relationship between the angular alkenyl chain and *O*-pivaloyl group (Figure 4). Base-induced elimination of pivaloyl group in compound (–)-**39** resulted in the *α,β*-unsaturated lactam **40** in 90% yield. The addition of allyl-cuprate to (–)-lactam **40** was highly diastereoselctive, but unexpectedly resulted in the *syn*-product (–)-**15** in 83% yield with >99% *de*/*ee* (by ^{1}H NMR/HPLC). The analytical and spectral data obtained for *syn*-product (–)-**15** were in complete agreement with the earlier obtained data for *syn*-product (±)-**15** from scheme 2. Such type of *syn*-addition precedence is known in the literature, however genesis of stereoselection still remains an unanswered question.[23,24] The *syn*-product (–)-**15** was transformed to (+)-diol **23** in 62% overall yield by repeating 8-steps from scheme 2. One-pot three-step transformation of (+)-diol **23** under Zhai and co-workers conditions[14] delivered the desired (+)-subincanadine E (**5**) in 59% yield. The analytical and spectral data obtained for (+)-subincanadine E (**5**) were in complete agreement with the reported data[1,2a] including specific rotations {natural[1] $[\alpha]^{25}_{D}$ +39.0 (*c* 1.0 MeOH), synthetic **5** $[\alpha]^{25}_{D}$ +42.3 (*c* 0.12 MeOH)}. Enantioselective first total synthesis of (+)-subincanadine E (**5**) was accomplished from (*S*)-acetoxysuccinimide **36** with 18% overall yield and *Sinister* configuration has been assigned to the natural product.

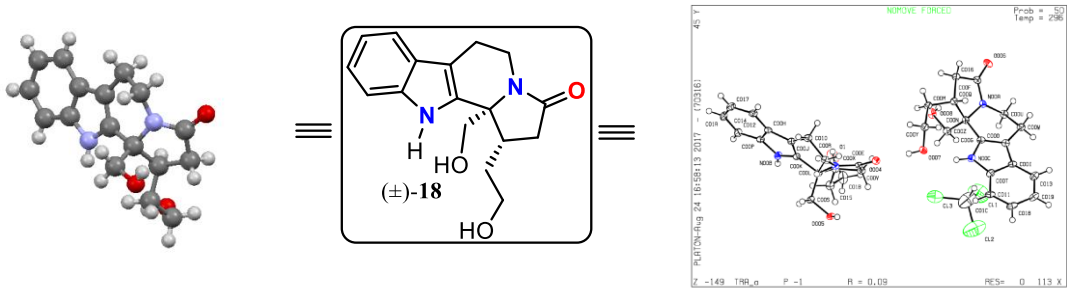


Figure 3. X-ray crystal structures of compound (±)-**18**.

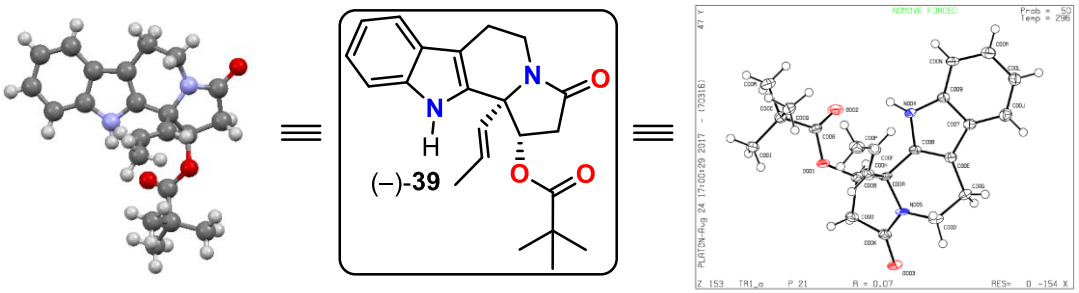
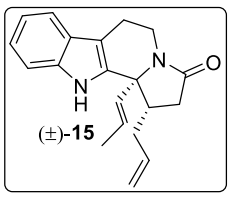


Figure 4. X-ray crystal structures of compound (–)-**39**.

3A.4 Summary

In summary, from the readily available maleimide/succinimide we have described new efficient approach to (±)/(+)-subincanadine E and established its absolute configuration. The 1,4-addition of Grignard reagent to the internally activated lactamol, witnessed position selective allylic rearrangements in succinimide derived lactamols and stereoselective syn-addition of cuprate to the unsaturated lactam are noteworthy. Our present synthetic strategy is flexible and will pave efficient enantioselective routes to subincanadines A–G and focused mini-library of their unnatural congeners and derivatives for SAR studies.

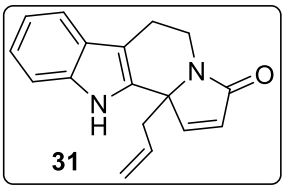
3A.5 Experimental Section

1-Allyl-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (15). 

To a stirred solution of compound **13**[25] (2.00 g, 8.33 mmol) in dry THF (40 mL) was added solution of allylmagnesium chloride in THF (2 M, 16.06 mL, 33.33 mmol) in a dropwise mode at –78 °C under argon atmosphere. The reaction mixture was stirred for 1 h at same temperature and then allowed to reach 25 °C. It was further stirred for 4 h and

the reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (80 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded lactamol **14** which was directly used for the next step. To a stirred solution of lactamol **14** in THF (25 mL) was added 2 N HCl (1.50 mL) at 0 °C and the reaction mixture was stirred for 6 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) afforded single diastereomer (±)-**15** as a yellow solid (1.40 g, 55%). Mp 83−85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (d, J = 6.1 Hz, 3H), 2.27–2.48 (m, 2H), 2.48–2.63 (m, 3H), 2.75–3.00 (m, 3H), 4.46 (dd, J = 12.2 and 4.9 Hz, 1H), 5.24–5.33 (m, 2H), 5.35–5.45 (m, 1H), 5.61 (d, J = 15.9 Hz, 1H), 5.87–6.00 (m, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 21.4, 34.8, 35.3, 37.1, 44.4, 65.9, 108.6, 111.0, 117.7, 118.5, 119.8, 122.2, 126.4, 127.5, 129.0, 134.6, 135.8, 137.1, 171.6; ESIMS (m/z) 307 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_2O$ 307.1805, found 307.1802; IR ($CHCl_3$) ν_{max} 3284, 1681 cm^{-1}.

11b-Allyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (31). To a stirred

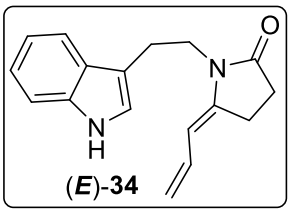


31

solution of compound **13** (300 mg, 1.25 mmol) in dry THF (10 mL) was added a solution of allylmagnesium chloride in THF (2 M, 1.37 mL, 2.75 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred for 1.5 h at same temperature and then it was allowed to reach 0 °C in next 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo afforded lactamol **30**; which was directly used for the next step. To a stirred solution of lactamol **30** in THF (10 mL) was added 2 N HCl (0.30 mL) at 0 °C and the reaction mixture was stirred for 5 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine and dried

over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 50:50) afforded compound (±)-**31** as a yellow solid (280 mg, 85%). Mp 191−193 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70–2.96 (m, 4H), 3.32 (dt, J = 12.5 and 5.5 Hz, 1H), 4.62 (dd, J = 13.4 and 6.1 Hz, 1H), 5.15 (d, J = 13.4 Hz, 1H), 5.19 (d, J = 6.1 Hz, 1H), 5.68 (sext, J = 6.7 Hz, 1H), 6.21 (d, J = 6.1 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.35 (t, J = 5.5 Hz, 1H), 7.36 (d, J = 6.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 35.9, 41.9, 67.0, 107.9, 111.1, 118.8, 119.8, 119.9, 122.4, 126.5, 126.8, 131.0, 132.9, 136.3, 150.1, 171.6; ESIMS (m/z) 265 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ 265.1335, found 265.1337; IR ($CHCl_3$) ν_{max} 3459, 1678 cm^{-1}.

(*E*)-1-[2-(1*H*-Indol-3-yl)ethyl]-5-allylidenepyrrolidin-2-one (34). To a stirred solution

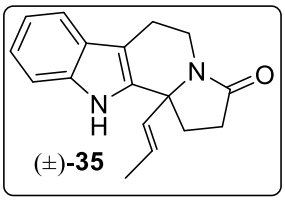


(***E***)-**34**

of compound **32** (500 mg, 2.10 mmol) in dry THF (15 mL) was added a solution of allylmagnesium chloride in THF (2 M, 2.10 mL, 4.20 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred for 1.5 h at same temperature and then allowed to reach 0 °C in next 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded lactamol **33**; which was directly used for the next step. To a stirred solution of lactamol **33** in THF (12 mL) was added 2 N HCl (0.50 mL) at 0 °C and the reaction mixture was stirred for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 50:50) afforded compound **34** as a white solid (428 mg, 78%). Mp 105−107 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40–2.60 (m, 2H), 2.70–2.90 (m, 2H), 3.04 (t, J = 8.2 Hz, 2H), 3.83 (t, J = 7.7 Hz, 2H), 4.98 (d, J = 10.2 Hz, 1H), 5.08 (d, J = 16.8 Hz, 1H), 5.60 (d, J = 11.0 Hz, 1H), 6.30–6.55 (m, 1H), 7.08 (d, J = 2.2 Hz, 1H), 7.05–7.30 (m, 2H), 7.36 (d, J = 7.1 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7, 22.5, 28.6, 40.7, 102.6, 111.2, 112.5, 112.8, 118.5, 119.4, 121.96, 122.00, 127.4, 131.6, 136.2, 142.5, 175.7; ESIMS (m/z) 289 $[M+Na]^+$; HRMS

(ESI) calcd for $C_{17}H_{18}N_2ONa$ 289.1311, found 289.1314; IR ($CHCl_3$) ν_{max} 3423, 1681, 1601 cm^{-1}.

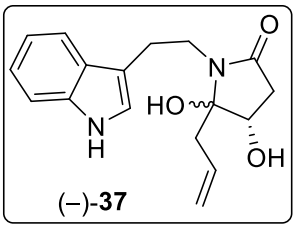
(*E*)-11b-(Prop-1-en-1-yl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (35). To a stirred solution of compound **34** (400 mg, 1.50 mmol) in THF (10 mL) was



(±)-**35**

added 2 N HCl (0.50 mL) at 0 °C and the reaction mixture was stirred for 3 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 40:60) afforded compound **35** as a white solid (328 mg, 82%). Mp 177−179 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.70 (d, J = 6.8 Hz, 3H), 2.25 (q, J = 10.9 Hz, 1H), 2.39–2.51 (m, 2H), 2.69 (td, J =17.4 and 9.5 Hz, 1H), 5.80 (dd, J = 15.4 and 5.2 Hz, 1H), 2.85–2.94 (m, 1H), 3.09 (dt, J = 16.9 and 5.5 Hz, 1H), 4.44 (dd, J = 13.1 and 6.1 Hz, 1H), 5.42 (qd, J = 15.4 and 6.4 Hz, 1H), 5.70 (d, J = 15.3 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.4, 21.1, 30.4, 32.1, 34.9, 63.3, 108.0, 111.0, 118.4, 119.6, 122.0, 126.5, 127.3, 131.2, 134.9, 136.2, 173.2; ESIMS (m/z) 267 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1494; IR ($CHCl_3$) ν_{max} 3419, 1677 cm^{-1}.

(–)-(4*S*)-1-[2-(1*H*-Indol-3-yl)ethyl]-5-allyl-4,5-dihydroxypyrrolidin-2-one (37). To a

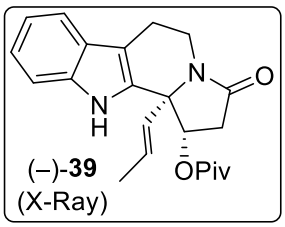


(–)-**37**

stirred solution of compound (–)-**36** (2.00 g, 6.66 mmol) in dry THF (30 mL) was added a solution of allylmagnesium chloride in THF (2 M, 13.33 mL, 26.66 mmol) in a dropwise mode at –78 °C under argon atmosphere. The reaction mixture was allowed to reach 0 °C in next 3 h and then quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (80 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 2:98) afforded compound (–)-**37** as foam (1.70 g, 89%). $[\alpha]^{25}_D$ –18.7 (*c* 0.2 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33–2.44 (m, 2H), 2.55 (dd, J = 14.6 and 7.3 Hz, 1H), 2.69 (dd, J = 17.7 and 6.7 Hz, 1H), 3.00 (d, J = 4.9 Hz, 1H), 3.03–3.12 (m, 1H), 3.13–3.22 (m,

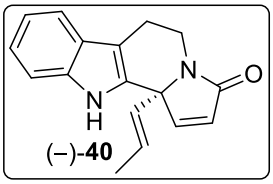
1H), 3.33–3.44 (m, 1H), 3.61 (s, 1H), 3.66–3.77 (m, 1H), 4.16 (br s, 1H), 5.14 (d, *J* = 7.9 Hz, 1H), 5.17 (s, 1H), 5.68 (sext, *J* = 7.3 Hz, 1H), 7.04 (s, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 39.0, 40.3, 41.3, 68.8, 91.0, 111.3, 113.1, 118.9, 119.4, 120.1, 122.0, 122.2, 127.3, 131.3, 136.2, 172.4; ESIMS (*m*/*z*) 323 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366, found 323.1363; IR ($CHCl_3$) ν_{max} 3619, 3478, 3352, 1678 cm^{-1}.

(–)-(1*S*,11b*R*)-3-Oxo-11b-[(*E*)-prop-1-en-1-yl]-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl Pivalate (39). To a stirred solution of lactamol (–)-**37** (1.70 g, 5.66 mmol) in CH_2Cl_2 (25 mL) were slowly added Et_3N (1.93 mL, 14.16 mmol) and pivCl (1.10 mL, 8.49 mmol) at 0 °C. The reaction mixture was stirred for 3 h allowing reach 25 °C and the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layer was washed with aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried *O*-pivaloyl lactamol **38** was directly used for the next step. To a stirred solution of lactamol **38** in THF (20 mL) was added 2 N HCl (2.00 mL) at 0 °C and the reaction mixture was stirred for 36 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 20:80) afforded single diastereomer (–)-**39** as a solid (1.50 g, 75%). Mp 171−173 °C; $[\alpha]^{25}_D$ –59.3 (*c* 0.25 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 1.67 (d, *J* = 7.3 Hz, 3H), 2.73 (dd, *J* = 15.2 and 4.9 Hz, 1H), 2.82–2.99 (m, 3H), 3.06 (dt, *J* = 12.2 and 4.9 Hz, 1H), 4.45 (dd, *J* = 12.8 and 6.1 Hz, 1H), 5.30–5.45 (m, 2H), 5.52 (d, *J* = 15.9 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 9.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 20.7, 27.2, 35.2, 36.5, 39.0, 68.3, 73.2, 109.3, 111.5, 118.3, 119.5, 122.3, 126.3, 127.8, 131.4, 132.8, 135.7, 169.3, 179.6; ESIMS (*m*/*z*) 367 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{27}N_2O_3$ 367.2016, found 367.2011; IR ($CHCl_3$) ν_{max} 3390, 1684, 1612 cm^{-1}.



(–)-**39**
(X-Ray)

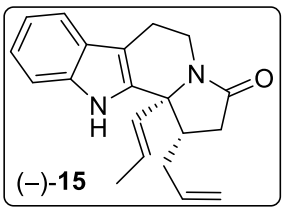
(–)-(*S*,*E*)-11b-(Prop-1-en-1-yl)-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-3-one (40). To a stirred suspension of NaH (410 mg, 10.24 mmol) in dry THF (25 mL) was



(–)-**40**

slowly added the solution of compound (–)-**39** (1.50 g, 4.098 mmol) in THF (10 mL) in dropwise mode at 25 °C. The reaction was monitored by TLC and quenched with aqueous NH_4Cl after 10 min. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 50:50) afforded compound (–)-**40** as a white solid (972 mg, 90%). Mp 211−213 °C; $[\alpha]^{25}_{D}$ –298.4 (*c* 0.2 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69 (d, *J* = 6.1 Hz, 3H), 2.80 (dd, *J* = 15.5 and 5.5 Hz, 1H), 2.86–2.99 (m, 1H), 3.24 (dt, *J* = 12.2 and 4.3 Hz, 1H), 4.54 (dd, *J* = 13.1 and 6.7 Hz, 1H), 5.46 (d, *J* = 15.2 Hz, 1H), 5.51–5.62 (m, 1H), 6.18 (d, *J* = 6.1 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 6.1 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 21.9, 35.1, 68.2, 109.2, 111.0, 118.8, 119.8, 122.5, 126.4, 126.5, 128.6, 130.6, 131.1, 136.3, 149.7, 170.8 ; ESIMS (*m*/*z*) 265 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ 265.1335, found 265.1337; IR ($CHCl_3$) ν_{max} 3462, 1677 cm^{-1} .

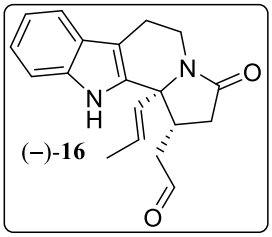
(–)-(1*S*,11b*R*)-1-Allyl-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H* indolizino(8,7-*b*)indol-3-one (15). To a stirred solution of compound (–)-**40** (900 mg, 3.40 mmol) in dry THF (25 mL) containing CuBr (48 mg, 0.34 mmol) was added a solution of allylmagnesium chloride (2 M in THF, 5.10 mL, 10.22 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was allowed to reach 0 °C in 3 h and the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (40 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) afforded compound (–)-**15** as a white solid (865 mg, 83%). Mp 83−85 °C; $[\alpha]^{25}_{D}$ –87.0 (*c* 0.22 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (d, *J* = 6.1 Hz, 3H), 2.27–2.48 (m, 2H), 2.48–2.63 (m, 3H), 2.75–3.00 (m, 3H), 4.46 (dd, *J* = 12.2 and 4.9 Hz, 1H), 5.24–5.33 (m, 2H), 5.35–5.45 (m, 1H), 5.61 (d, *J* = 15.9 Hz, 1H), 5.87–6.00 (m, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 21.4, 34.8, 35.3, 37.1, 44.4, 65.9, 108.6, 111.0,



(–)-**15**

117.7, 118.5, 119.8, 122.2, 126.4, 127.5, 129.0, 134.6, 135.8, 137.1, 171.6; ESIMS (*m*/*z*) 307 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_2O$ 307.1805, found 307.1802; IR ($CHCl_3$) ν_{max} 3284, 1681 cm^{-1}.

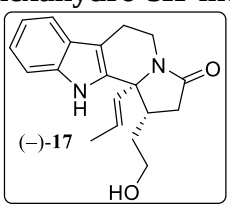
(–)-2-{(1*R*,11b*S*)-3-Oxo-11b-[(*E*)-prop-1-en-1-yl]-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl}acetaldehyde (16). To a stirred solution of compound (–)-**15**



(–)-**16**

(800 mg, 2.61 mmol) in THF:H_2O (3:1, 25 mL) was added NMO (50% in water, 3.05 mL, 13.07 mmol) and catalytic amount of OsO_4 (0.20 mL, 0.5 M solution in *t*-BuOH) at 25 °C and the reaction mixture stirred for 24 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ and further stirred for 30 min. Aqueous layer was extracted in EtOAc (3 × 30 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained diol was directly used for next step. To a stirred solution of obtained diol in THF:H_2O (1:1, 30 mL) was added $NaIO_4$ (1.25 gm, 5.88 mmol) at 25 °C in three equal lots and the reaction was monitored on TLC. The reaction mixture diluted with EtOAc (50 mL) after 1.5 h and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 40:60) afforded compound (–)-**16** as a solid (764 mg, 95%). Mp 97−99 °C; $[\alpha]^{25}_D$ –94.2 (*c* 0.1 $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70 (d, *J* = 6.1 Hz, 3H), 2.25 (dd, *J* = 16.8 and 9.5 Hz, 1H), 2.67–2.98 (m, 4H), 2.98–3.20 (m, 3H), 4.44 (dd, *J* = 12.8 and 5.7 Hz, 1H), 5.38–5.50 (m, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 9.67 (s, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.6, 21.0, 35.5, 36.2, 37.2, 47.2, 66.1, 108.3, 111.4, 118.4, 119.6, 122.2, 126.4, 128.4, 130.0, 135.1, 136.0, 171.0, 202.0; ESIMS (*m*/*z*) 309 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_2$ 309.1598, found 309.1590; IR ($CHCl_3$) ν_{max} 3376, 3020, 1725, 1677, 1601 cm^{-1}.

(–)-(1*S*,11b*R*)-1-(2-Hydroxyethyl)-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (17). To a stirred solution of aldehyde (–)-

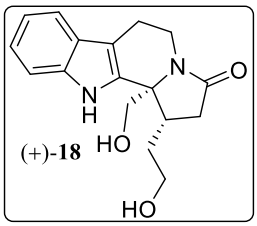


(–)-**17**

16 (740 mg, 2.40 mmol) in MeOH (15 mL) was added the $NaBH_4$ (133 mg 3.60 mmol) at 0 °C in two equal lots and reaction mixture was stirred for 30 min. The reaction was quenched with aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (40 mL) and the organic layer was washed with

brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, DCM–MeOH, 2:98) afforded compound (–)-**17** as a solid (739 mg, 98%). Mp 110−112 °C; $[\alpha]^{25}_D$ –212.1 (*c* 0.13 $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.65–1.80 (m, 1H), 1.73 (d, *J* = 5.4 Hz, 3H), 2.25–2.35 (m, 1H), 2.39 (dd, *J* = 15.1 and 11.9 Hz, 1H), 2.45–2.55 (m, 1H), 2.59 (dd, *J* = 15.3 and 7.7 Hz, 1H), 2.70–2.83 (m, 2H), 2.96 (dt, *J* = 11.6 and 5.8 Hz, 1H), 3.55–3.65 (m, 1H), 3.65–3.75 (m, 1H), 4.30–4.37 (m, 1H), 5.36 (qd, *J* = 15.5 and 6.5 Hz, 1H), 5.72 (d, *J* = 16.0 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 17.9, 22.6, 34.3, 36.4, 37.9, 44.0, 61.7, 68.1, 108.4, 112.4, 119.2, 120.3, 122.9, 127.9, 129.2, 129.8, 136.3, 138.4, 174.8; ESIMS (*m*/*z*) 311 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_2$ 311.1754, found 311.1749; IR ($CHCl_3$) ν_{max} 3333, 1666 cm^{-1}.

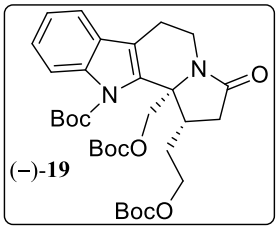
(+)-(1*S*,11b*S*)-1-(2-Hydroxyethyl)-11b-(hydroxymethyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (18). To a stirred solution of compound (–)-**17** (700 mg, 2.25 mmol) in THF:H_2O (3:1, 25 mL) was added NMO (50% in water, 2.60 mL, 11.29 mmol) and catalytic amount of OsO_4 (0.15 mL, 0.50 M solution in *t*-BuOH) at 25 °C and reaction mixture was stirred for 72 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ and further stirred for 30 min. The aqueous layer was extracted with EtOAc (3 × 40 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried triol was directly used for next step. To a stirred solution of obtained triol in THF:H_2O (1:1, 35 mL) was added $NaIO_4$ (2.10 gm, 10.17 mmol) at 25 °C in three equal lots. The reaction mixture was diluted with EtOAc (60 mL) after 1.5 h and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained aldehyde was immediately used for the next reaction without any purification. To a stirred solution of aldehyde in MeOH (15 mL) was added the $NaBH_4$ (171 mg, 4.63 mmol) at 0 °C. The reaction was quenched with aqueous NH_4Cl after 30 min and reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 7:93) afforded compound (+)-**18** as a solid (589 mg, 87%). Mp 117−119 °C; $[\alpha]^{25}_D$ +382.6 (*c* 0.21 MeOH); ^{1}H NMR



(+)-**18**

(DMSO-d_6, 400 MHz) δ 1.80–1.95 (m, 1H), 2.22–2.47 (m, 4H), 2.52–2.65 (m, 1H), 2.74 (dd, *J* = 15.3 and 4.9 Hz, 1H), 3.05 (dt, *J* = 12.5 and 4.9 Hz, 1H), 3.37–3.47 (m, 1H), 3.50–3.60 (m, 1H), 3.69 (dd, *J* = 11.6 and 4.9 Hz, 1H), 3.85 (dd, *J* = 11.6 and 6.1 Hz, 1H), 4.28 (dd, *J* = 12.8 and 6.1 Hz, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 5.16 (t, *J* = 5.5 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 10.82 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3, 31.8, 34.6, 37.6, 40.9, 59.7, 62.4, 65.1, 106.4, 111.4, 117.9, 118.7, 121.1, 126.2, 135.5, 136.2, 171.9; ESIMS (*m*/*z*) 301 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_3$ 301.1547, found 301.1542; IR ($CHCl_3$) ν_{max} 3500, 3284, 1670, 1628 cm^{-1} .

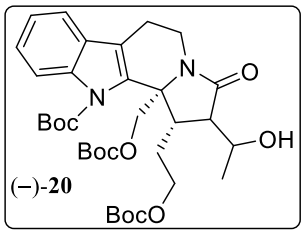
(–)-*tert*-Butyl (1*S*,11b*S*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl)oxy]methyl}-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (19). To a stirred solution of diol (+)-**18** (210 mg, 0.70 mmol) in



(–)-**19**

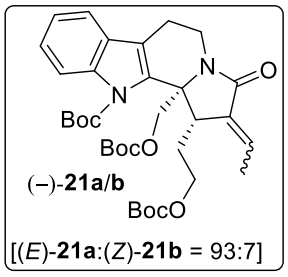
CH_2Cl_2 was added $(Boc)_2O$ (0.535 mL, 2.45 mmol) and catalytic amount of DMAP (17 mg, 0.14 mmol) and the reaction mixture was stirred at 25 °C for 4 h. Reaction was quenched with water and aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 15:85) afforded compound (−)-**19** as a solid (418 mg, 99%). Mp 72−74 °C; $[\alpha]^{25}_D$ −116.3 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 1.47 (s, 9H), 1.72 (s, 9H), 1.95 (sept, *J* = 6.7 Hz, 1H), 2.38 (dd, *J* = 17.1 and 6.7 Hz, 1H), 2.55–2.80 (m, 4H), 2.93 (sept, *J* = 6.7 Hz, 1H), 3.37 (dd, *J* = 12.8 and 5.5 Hz, 1H), 4.01–4.10 (m, 1H), 4.11–4.20 (m, 1H), 4.44 (dd, *J* = 13.7 and 7.3 Hz, 1H), 4.90 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 27.6, 27.7, 28.2, 31.2, 34.5, 37.5, 37.6, 66.0, 66.1, 67.7, 81.9, 82.3, 84.8, 115.6, 118.6, 119.0, 122.9, 125.3, 128.4, 135.0, 136.0, 150.4, 153.2, 153.6, 173.8; ESIMS (*m*/*z*) 601 $[M+H]^+$; HRMS (ESI) calcd for $C_{32}H_{45}N_2O_9$ 601.3120, found 601.3113; IR ($CHCl_3$) ν_{max} 1738, 1678, 1600 cm^{-1}

(–)-*tert*-Butyl (1*S*,11b*S*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl) oxy]methyl}-2-(1-hydroxyethyl)-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (20). Freshly prepared solution of LDA in THF (1 M, 0.50 mL, 0.50 mmol) was added to a stirred solution of compound (−)-**19** (200



mg, 0.33 mmol) in THF (10 mL) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred for 1 h at −78 °C and solution of acetaldehyde (75 μL, 1.33 mmol) in THF (3 mL) was slowly added to the reaction mixture. The reaction was quenched after 2 h by using aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) afforded compound (−)-**20** as a solid (210 mg, 98%). Mp 63−65 °C; $[\alpha]^{25}_{D}$ –111.4 (*c* 0.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, *J* = 6.1 Hz, 3H), 1.37 (s, 9H), 1.47 (s, 9H), 1.73 (s, 9H), 1.92 (sept, *J* = 6.9 Hz, 1H), 2.37 (dd, *J* = 8.2 and 3.4 Hz, 1H), 2.55–2.72 (m, 3H), 2.90–3.00 (m, 1H), 3.44 (sext, *J* = 5.7 Hz, 2H), 3.71 (s, 1H), 4.05–4.15 (m, 1H), 4.18–4.25 (m, 1H), 4.44 (dd, *J* = 13.3 and 6.9 Hz, 1H), 4.93 (d, *J* = 5.0 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1, 20.5, 27.6, 27.8, 28.3, 30.4, 35.3, 39.6, 53.9, 65.4, 66.5, 66.9, 68.7, 81.9, 82.3, 85.0, 116.0, 118.2, 118.5, 123.0, 125.2, 128.5, 134.8, 135.6, 150.2, 153.0, 153.5, 176.6; ESIMS (*m*/*z*) 645 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{49}N_2O_{10}$ 645.3382, found 645.3365; IR ($CHCl_3$) ν_{max} 3556, 1736, 1667 cm^{-1}.

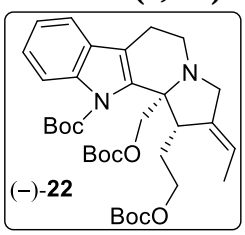
(–)-*tert*-Butyl (1*S*,11b*S*,*E*/*Z*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl)oxy]methyl}-2-ethylidene-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (21a/b). To a stirred solution of alcohol (–)-**20**



(150 mg, 0.232 mmol) in CH_2Cl_2 (8 mL) was slowly added Et_3N (95 μL, 0.697 mmol) and MsCl (26 μL, 0.348 mmol) at 0 °C. The reaction mixture was stirred for 3 h and allowed to reach 25 °C. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained mesylate was directly used for next step without any purification. To a stirred suspension of NaH (20 mg, 0.498 mmol) in dry THF (10 mL) was slowly added the solution of *O*-mesylate in THF (5 mL) in dropwise mode at 25 °C. The reaction was quenched with aqueous NH_4Cl after 30 min and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over

Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, EtOAc–PE, 20:80) afforded compound (−)-**21b** as a solid (10 mg, 7%) and (−)-**21a** as a solid (128 mg, 88%). **21a:** Mp 77−79 °C; $[\alpha]^{25}_{D}$ –124.3 (*c* 0.2 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 1.48 (s, 9H), 1.70 (d, *J* = 6.7 Hz, 3H), 1.75 (s, 9H), 1.88–1.98 (m, 1H), 2.37–2.50 (m, 1H), 2.61 (dd, *J* = 16.5 and 5.5 Hz, 1H), 2.99 (ddd, *J* = 11.3, 10.7 and 6.7 Hz, 1H), 3.59 (dt, *J* = 12.2 and 5.5 Hz, 1H), 3.78 (dd, *J* = 10.1 and 4.9 Hz, 1H), 3.97 (q, *J* = 8.0 Hz, 1H), 4.15–4.24 (m, 1H), 4.45 (dd, *J* = 13.4 and 7.3 Hz, 1H), 4.80 (d, *J* = 11.6 Hz, 1H), 5.22 (d, *J* = 11.6 Hz, 1H), 6.56 (q, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 19.8, 27.4, 27.7, 28.2, 29.1, 36.0, 39.3, 64.7, 65.5, 67.6, 81.6, 82.0, 84.6, 115.9, 118.3, 118.8, 122.7, 124.8, 128.7, 131.1, 134.0, 134.3, 135.5, 150.2, 152.9, 153.5, 170.9; ESIMS (*m*/*z*) 627 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{47}N_2O_9$ 627.3276, found 627.3268; IR ($CHCl_3$) ν_{max} 1734, 1682 cm^{-1}. **21b:** Mp 73−74 °C; $[\alpha]^{25}_{D}$ –111.3 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 1.49 (s, 9H), 1.73 (s, 9H), 1.78–1.90 (m, 1H), 2.15 (d, *J* = 7.3 Hz, 3H), 2.40–2.51 (m, 1H), 2.63 (dd, *J* = 16.5 and 4.9 Hz, 1H), 3.00 (ddd, *J* = 16.2, 10.7 and 7.3 Hz, 1H), 3.40 (d, *J* = 11.6 Hz, 1H), 3.50 (dt, *J* = 11.6 and 5.5 Hz, 1H), 4.02–4.12 (m, 1H), 4.22–4.32 (m, 1H), 4.46 (dd, *J* = 13.4 and 7.3 Hz, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 5.08 (d, *J* = 11.6 Hz, 1H), 5.82 (q, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 6.7 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 20.1, 27.5, 27.8, 28.3, 28.9, 35.3, 42.7, 64.4, 65.0, 67.2, 81.7, 82.0, 85.6, 116.0, 118.4, 118.8, 122.8, 124.9, 128.8, 131.8, 134.8, 135.1, 135.6, 150.2, 153.1, 153.6, 170.1; ESIMS (*m*/*z*) 627 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{47}N_2O_9$ 627.3276, found 627.3266; IR ($CHCl_3$) ν_{max} 1736, 1681 cm^{-1}.

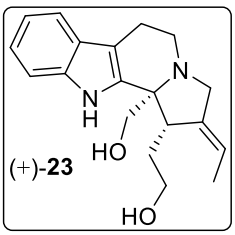
(–)-*tert*-Butyl (1*S*,11b*S*,*E*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl)oxy]methyl}-2-ethylidene-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (22). The solution of $AlCl_3$ (42 mg, 0.319 mmol) in THF (5 mL) was added dropwise to a stirred suspension of LAH (35 mg, 0.958 mmol) in THF (15 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min and solution of lactam (−)-**21a** (100 mg, 0.159 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and the reaction was quenched with saturated aqueous Na_2SO_4 at 0 °C. Reaction mixture was



(–)-**22**

diluted with EtOAc (20 mL), filtered through Celite pad and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, PE–EtOAc, 25:75) afforded amine (−)-**22** as a solid (90 mg, 92%). Mp 67−69 °C; $[\alpha]^{25}_D$ −37.4 (*c* 0.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 9H), 1.73 (s, 9H), 1.85–2.00 (m, 1H), 2.16 (sext, *J* = 12.8 Hz, 1H), 2.49 (dd, *J* = 17.1 and 5.5 Hz, 1H), 3.00–3.25 (m, 3H), 3.50–3.60 (m, 1H), 3.69 (d, *J* = 12.2 Hz, 2H), 4.02 (q, *J* = 7.9 Hz, 1H), 4.17–4.25 (m, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 5.09 (q, *J* = 7.3 Hz, 1H), 5.24 (d, *J* = 11.0 Hz, 1H), 7.15–7.30 (m, 2H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 15.8, 27.5, 27.8, 27.9, 28.3, 41.0, 43.3, 52.9, 65.4, 67.4, 70.9, 81.37, 81.40, 84.0, 115.8, 117.2, 118.0, 118.3, 122.2, 124.1, 129.3, 135.0, 136.2, 139.1, 150.5, 153.3, 153.7; ESIMS (*m*/*z*) 613 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{49}N_2O_8$ 613.3483, found 613.3481; IR ($CHCl_3$) ν_{max} 1734 cm^{-1}.

(+)-2-[(1*S*,11b*S*,*E*)-2-Ethylidene-11b-(hydroxymethyl)-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl]ethan-1-ol (23). To a stirred solution of compound (−)-**22**

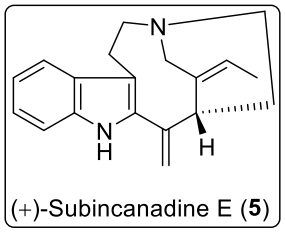


(+)-**23**

(75 mg, 0.122 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.188 mL, 2.44 mmol) at 0 °C. The ice bath was removed after 30 min and the reaction mixture was further stirred for 12 h at 25 °C. On complete consumption of starting material (by TLC) the reaction was quenched by adding saturated aqueous $NaHCO_3$ at 0 °C. Aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained TFA salt of amine was dissolved in DCM (5 mL). The salt was neutralized with 4 N NaOH and aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo and followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 10:90) afforded compound (+)-**23** as a solid (36 mg, 96%). Mp 186−187 °C; $[\alpha]^{25}_D$ +29.6 (*c* 0.32 MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.49 (d, *J* = 6.7 Hz, 3H), 1.85 (sext, *J* = 6.7 Hz, 1H), 2.10 (sext, *J* = 6.7 Hz, 1H), 2.53 (dd, *J* = 15.9 and 5.5 Hz, 1H), 3.00–3.10 (m, 1H), 3.17 (dd, *J* = 14.0 and 6.1 Hz, 1H), 3.24–3.50 (m, 3H), 3.57–3.77 (m, 3H), 3.87 (d, *J* = 10.4 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 5.17 (q, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.9, 16.5, 32.7, 43.9,

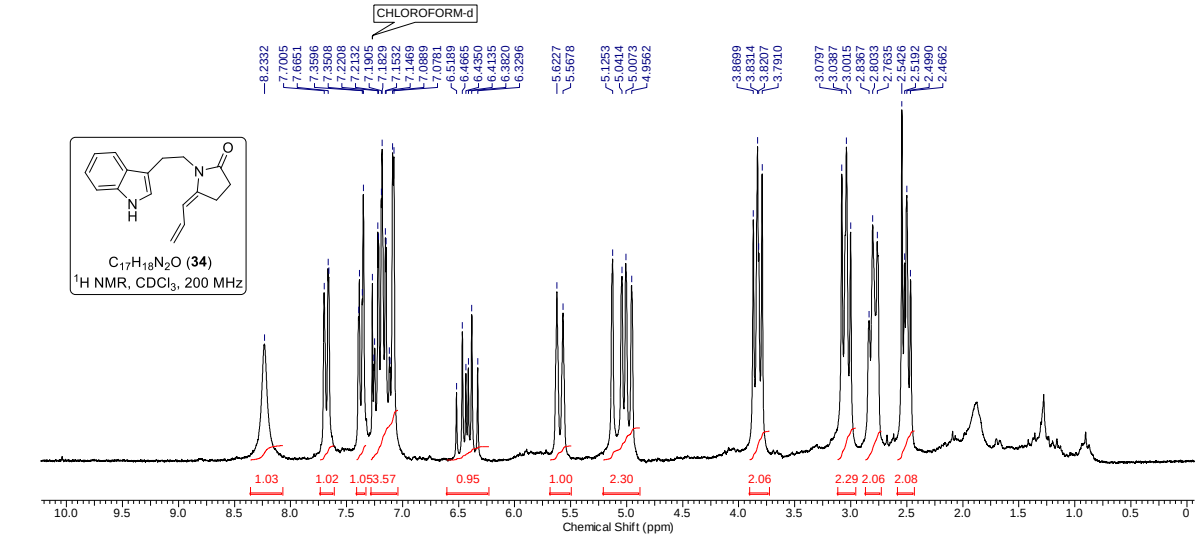
44.6, 54.3, 61.4, 66.3, 68.4, 108.1, 112.1, 118.3, 118.8, 119.6, 122.2, 128.3, 137.3, 137.9, 140.7; ESIMS (*m*/*z*) 313 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{25}N_2O_2$ 313.1919, found 313.1908; IR (Nujol) ν_{max} 3422, 3267 cm^{-1}.

(+)-(6*S*,*E*)-5-Ethylidene-7-methylene-1,4,5,6,7,8-hexahydro-2*H*-3,ethanoazonino(5,4-*b*)indole (Subincanadine E, 5). To a stirred solution of compound (+)-**23** (16 mg, 0.051 mmol) in THF (7 mL) was added Et_3N (83 μL, 0.614 mmol), DMAP (6.20 mg, 0.051 mmol) and *p*-TsCl (58 mg, 0.307 mmol) at 0 °C. The reaction mixture was stirred for 6 h and allowed to reach 25 °C. On the complete consumption of starting material, LiBr (52 mg, 0.614 mmol) was added and the mixture was refluxed for 3 h. The reaction mixture was allowed to reach 25 °C and zinc dust (80 mg, 1.228 mmol) was added to the reaction mixture. The reaction mixture was again refluxed for 3 h under argon atmosphere. The reaction mixture was concentrated in vacuo and to the obtained residue was added saturated solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layer was dried over Na_2SO_4. Concentration of organic layer in vacuo followed by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 10:90) of the obtained residue provided (+)-subincanadine E (**5**) as a white solid (8 mg, 59%). Mp 143−144 °C; $[\alpha]^{25}_D$ +42.3 (*c* 0.12 MeOH), {lit.[1] $[\alpha]^{25}_D$ +39.0 (*c* 1.0 MeOH)}; ^1H NMR (CD_3OD, 400 MHz) δ 1.75–1.92 (m, 1H), 1.83 (d, *J* = 6.7 Hz, 3H), 2.41 (sept, *J* = 7.4 Hz, 1H), 3.11 (dt, *J* = 12.1 and 6.1 Hz, 1H), 3.21 (d, *J* = 17.7 Hz, 1H), 3.30–3.45 (m, 2H), 3.69 (d, *J* = 13.4 Hz, 1H), 3.89 (t, *J* = 15.2 Hz, 1H), 3.97 (d, *J* = 15.2 Hz, 1H), 4.15–4.30 (m, 2H), 5.58 (d, *J* = 9.8 Hz, 2H), 6.09 (q, *J* = 7.3 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.1, 21.0, 26.4, 42.4, 46.9, 53.5, 59.1, 109.3, 112.1, 118.9, 120.6, 120.7, 123.6, 129.1, 129.2, 132.1, 137.0, 137.5, 143.3; ESIMS (*m*/*z*) 313 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{23}N_2$ 279.1856, found 279.1857; IR (Nujol) 3403 cm^{-1}.



(+)-Subincanadine E (**5**)

3A.6 Selected Spectra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7.0781
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2.4990
2.4662
C17H18N2O (34)
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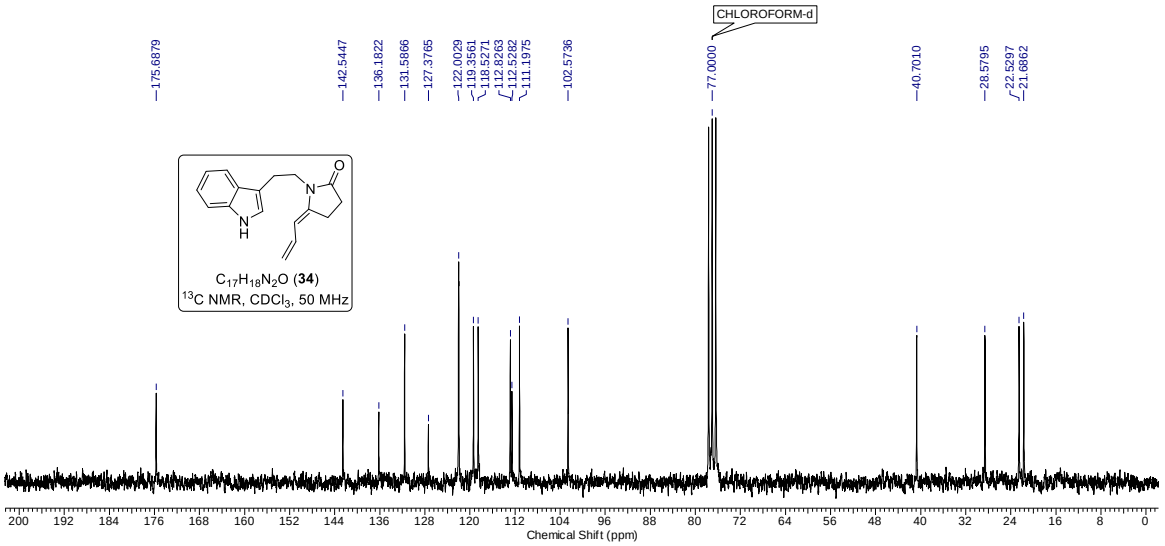
1.00
2.30
2.06
2.29
2.06
2.08
Chemical Shift (ppm)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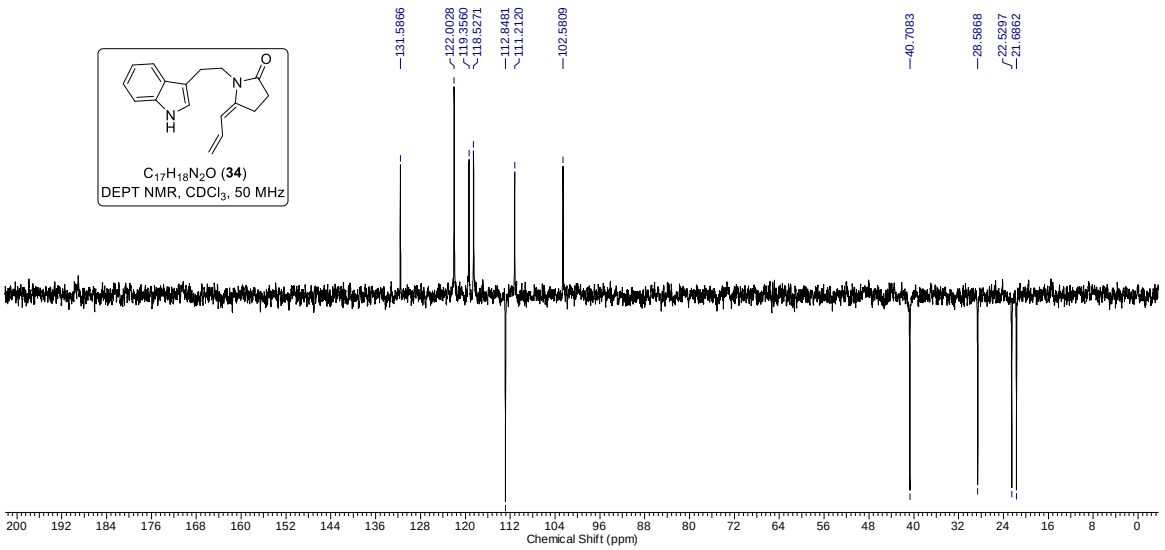
22.5297
21.6862
C17H18N2O (34)
13C NMR, CDCl3, 50 MHz
Chemical Shift (ppm)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C17H18N2O (34)
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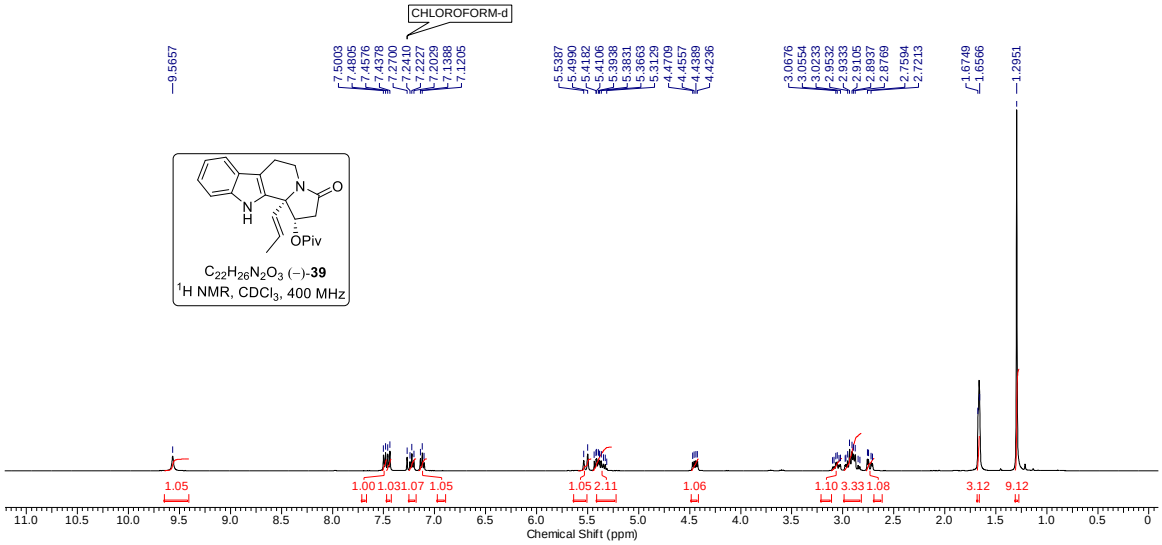
Chemical Shift (ppm)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7.1205
5.5387
5.4990
5.4192
5.4106
5.3938
5.3831
5.3663
5.3129
4.4709
4.4557
4.4389
4.4236
3.0676
3.0554
3.0233
2.9532
2.9333
2.9105
2.8937
2.8769
2.7594
2.7213
1.6749
1.6566
1.2951
OPiv
C22H26N2O3 (−)-39
1H NMR, CDCl3, 400 MHz
1.05
1.00
1.03
1.07
1.05
1.05
2.11
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1.10
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1.08
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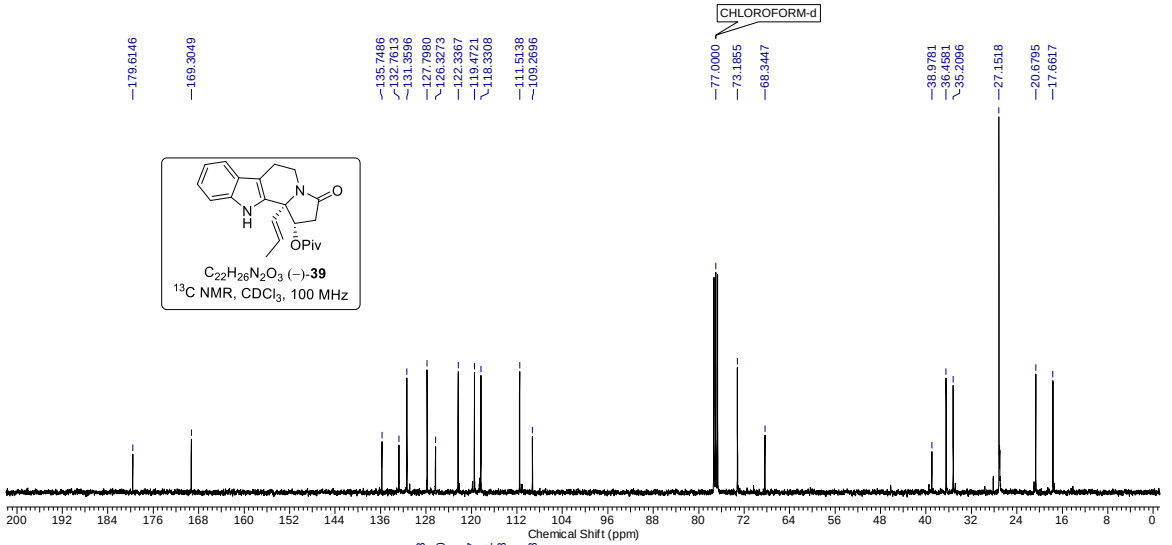
9.12
Chemical Shift (ppm)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OPiv
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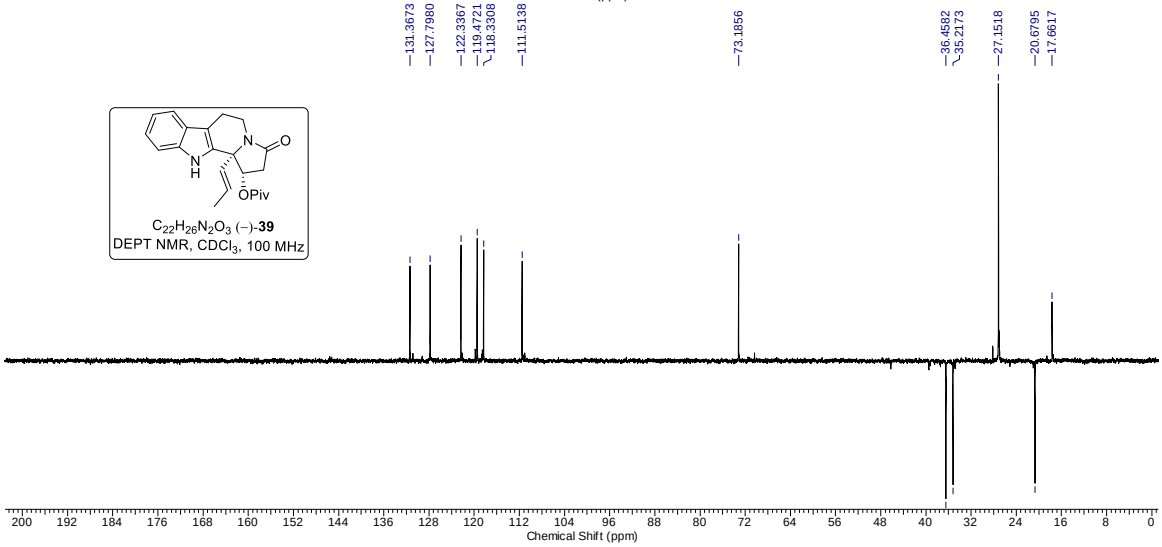
Chemical Shift (ppm)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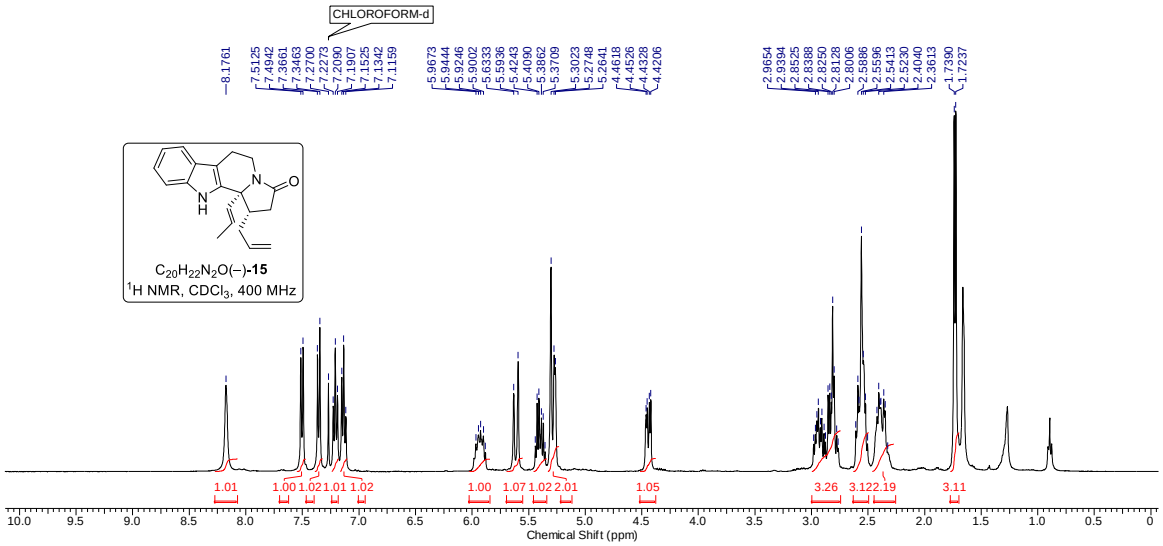
Chemical Shift (ppm)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5.6333
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4.4328
4.4206
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2.8250
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2.8006
2.5886
2.5596
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C20H22N2O(–)-15
1H NMR, CDCl3, 400 MHz
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1.00
1.02
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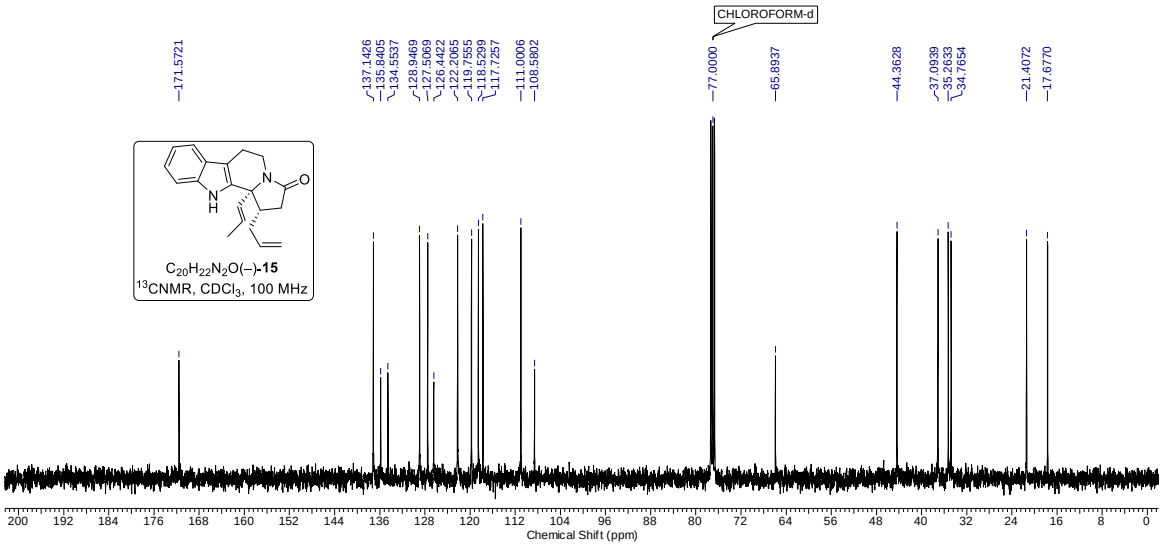
2.19
3.11
Chemical Shift (ppm)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111.0006
108.5802
77.0000
65.8937
44.3628
37.0939
35.2633
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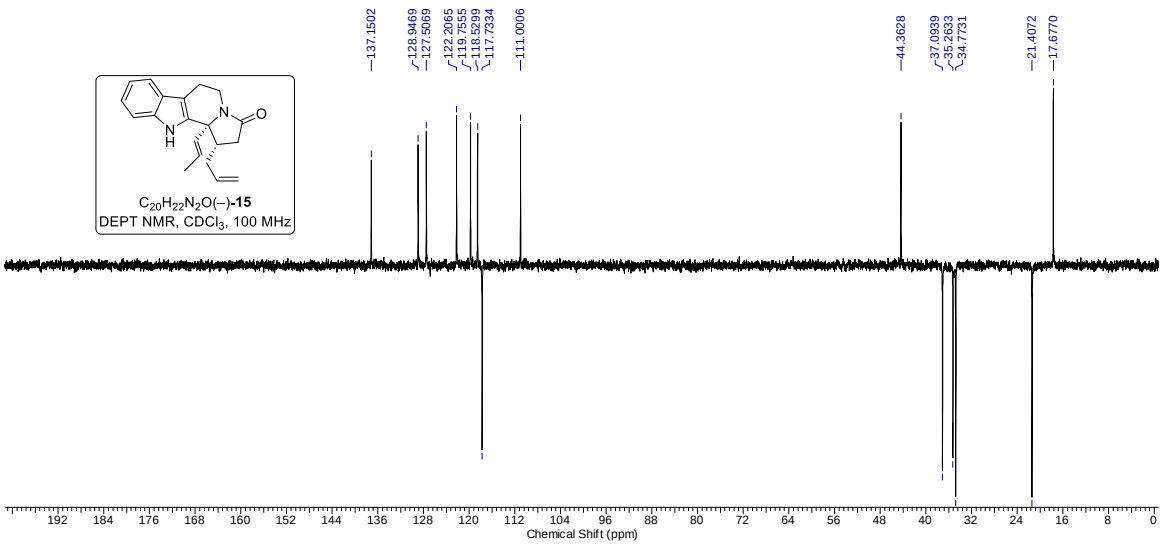
21.4072
17.6770
C20H22N2O(–)-15
13CNMR, CDCl3, 100 MHz
Chemical Shift (ppm)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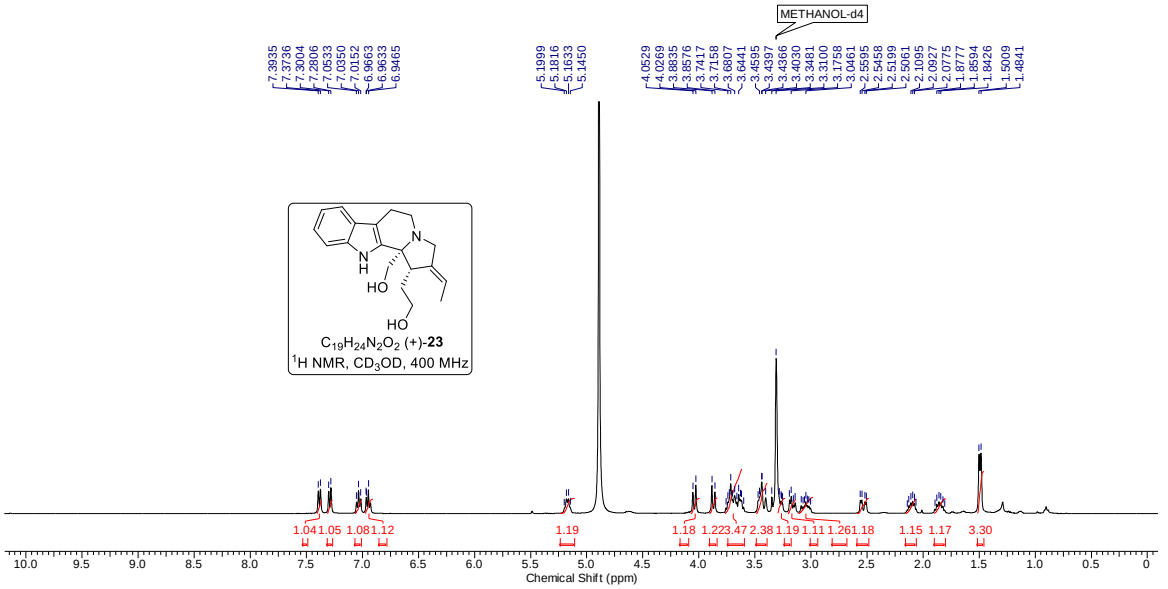
C20H22N2O(–)-15
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)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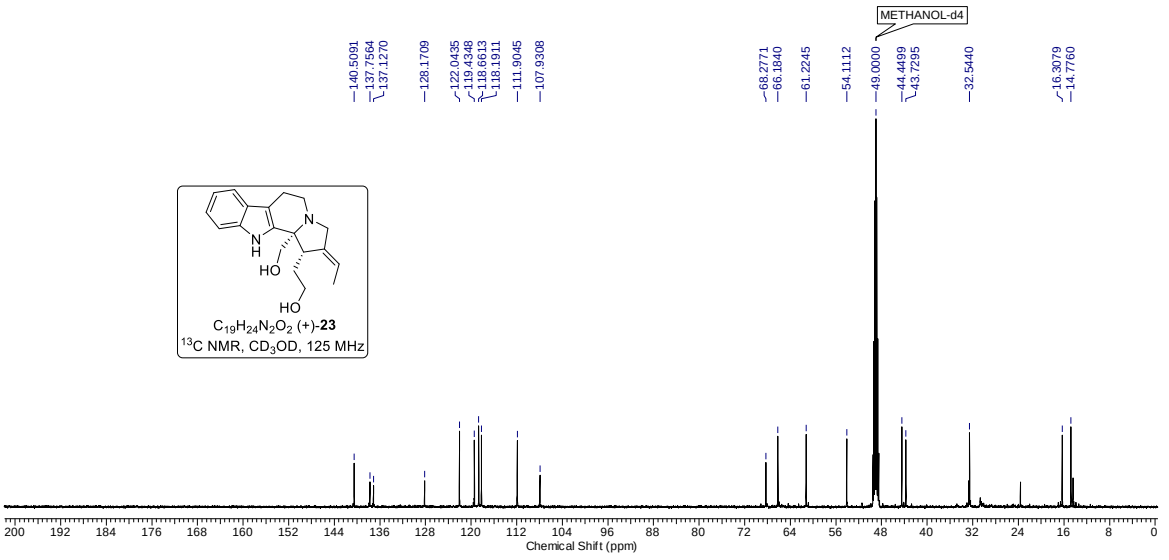
4.0529 4.0269 3.8835 3.8576 3.7417 3.7158 3.6807 3.6441 3.4595 3.4397 3.4366 3.4030 3.3481 3.3100 3.1758 3.0461 2.5595 2.5458 2.5199 2.5061 2.1095 2.0927 2.0775 1.8777 1.8594 1.8426 1.5009 1.4841
HO
HO
C19H24N2O2 (+)-23
1H NMR, CD3OD, 400 MHz
1.04 1.05 1.08 1.12
1.19
1.18 1.22 3.47 2.38 1.19 1.11 1.26 1.18
1.15 1.17 3.30
Chemical Shift (ppm)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HO
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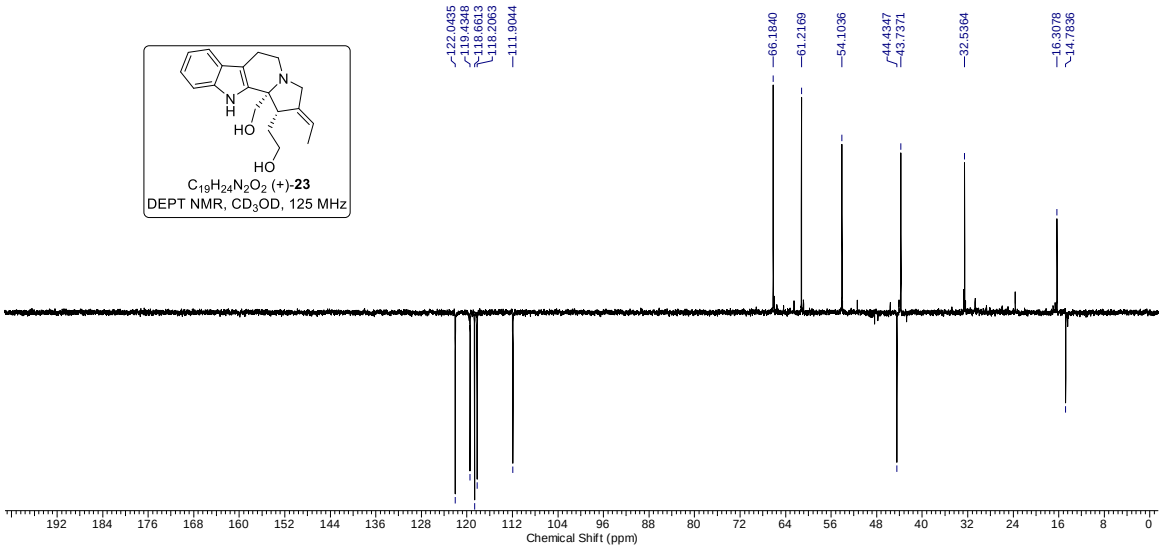
13C NMR, CD3OD, 125 MHz
Chemical Shift (ppm)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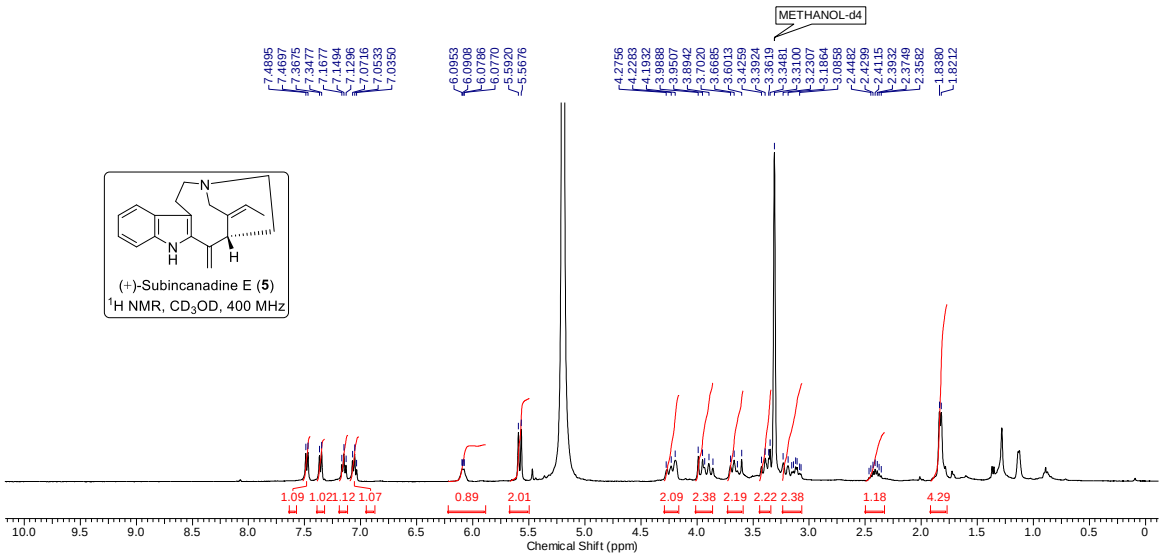
HO
C19H24N2O2 (+)-23
DEPT NMR, CD3OD, 125 MHz
Chemical Shift (ppm)


METHANOL-d4
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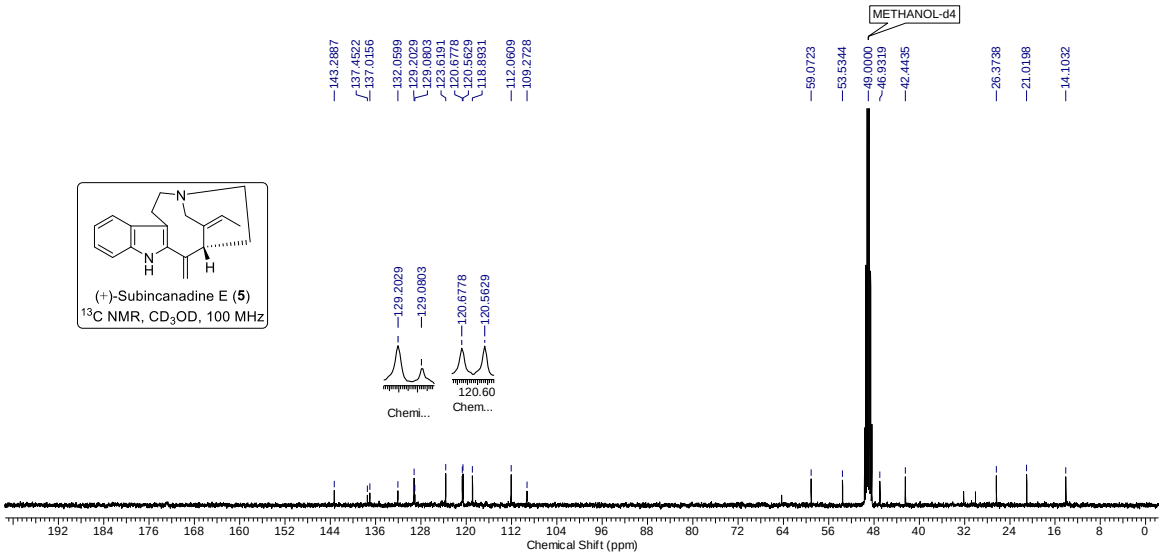
Chemical Shift (ppm)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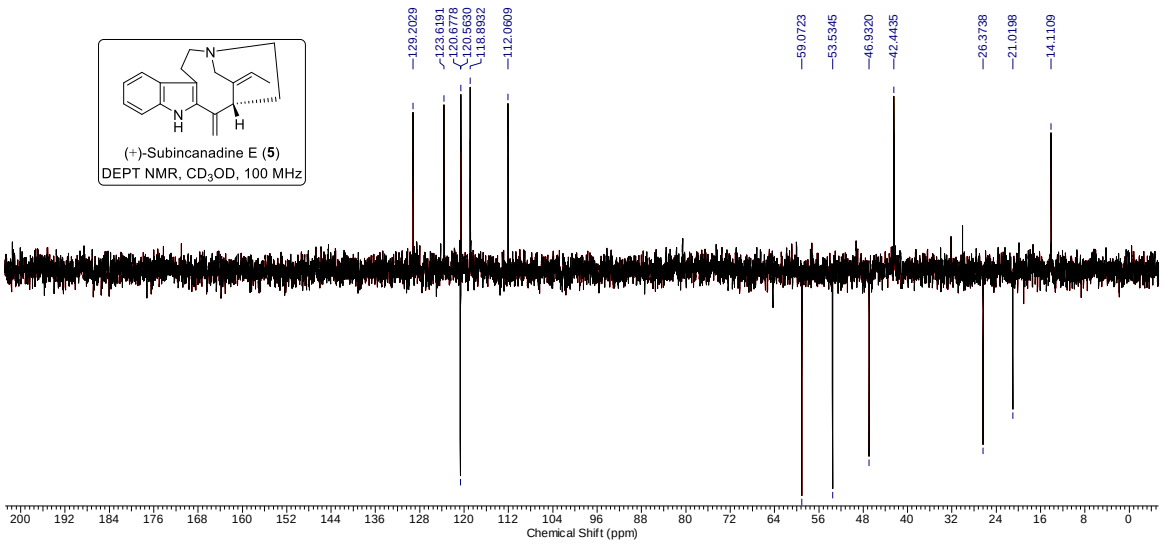
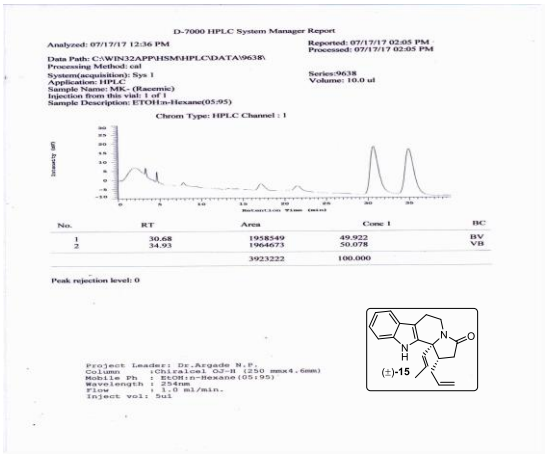
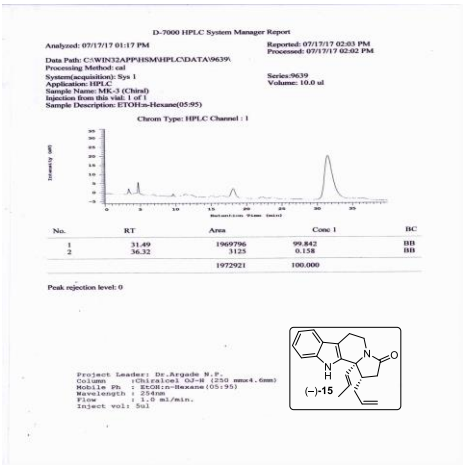
13C NMR, CD3OD, 100 MHz
Chemical Shift (ppm)


(+)-Subincanadine E (5)
DEPT NMR, CD3OD, 100 MHz
Chemical Shift (ppm)

3A.7 HPLC Plots of Compound (±)/(–)-15





3A.8 References

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Chapter 3

Section B

Regioselective and Stereoselective Reductive Aziridinium Ring Cleavage Leading to Azabicyclodecane Architecture: Enantioselective Synthesis of (+)-Subincanadine F

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

3B.1 Background

The indole alkaloid class of compounds is famous for their variety of exciting structural features coupled with very broad range of biological activities and some of them are in clinical use.[1a–d] The medicinally important cytotoxic indole alkaloids subincanadines A–G (**1**–**7**) possessing novel structural architectures were isolated by Ohsaki and co-workers in 2002 from the Brazilian medicinal plant *Aspidosperma subincanum* (Figure 1).[2a,b] The

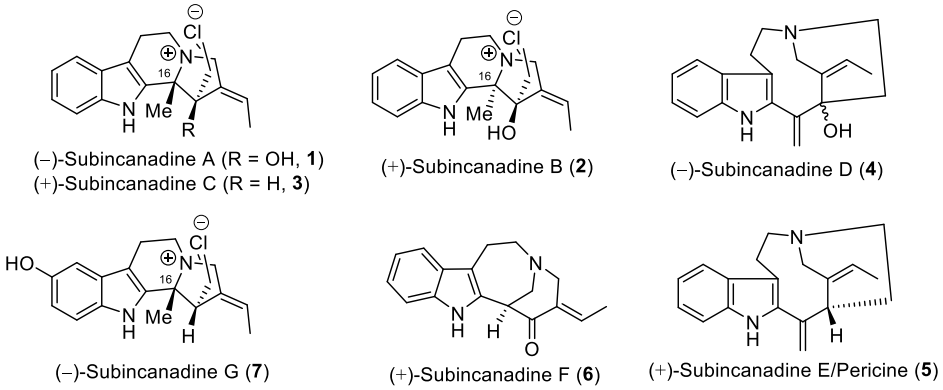
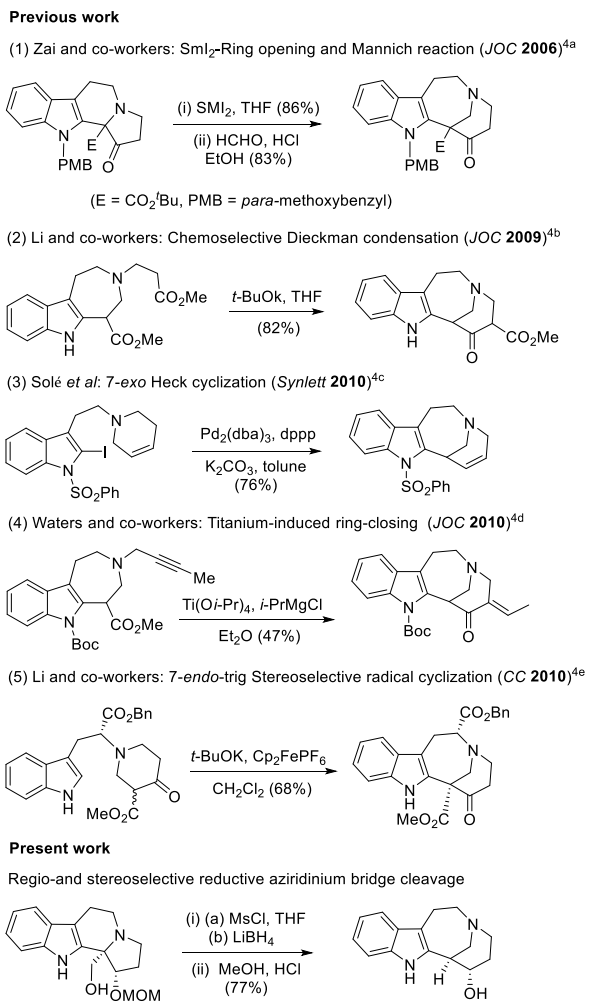


Figure 1. Potent cytotoxic subincanadines A–G alkaloids.

exotic azabicyclodecane framework bearing (+)-subincanadine F (**6**) was isolated only in 0.002% yield and it in vitro exhibits potent cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 2.40 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 4.80 μg/mL). Well-planned diastereoselective/enantioselective synthesis of subincanadines A (**1**), B (**2**), C (**3**), E (**5**) and F (**6**) have been recently reported;[3a,b,4a–e,5a–e] however synthesis of subincanadines D and G are still not described. Till date three racemic and one asymmetric synthesis of present target compound subincanadine F (**6**) have been reported in the contemporary literature.[4a,b,d,e] Rapid construction of the 1-azabicyclo[4.3.1]decane skeleton employing different types of intramolecular cyclization protocols is a challenging task in total synthesis of subincanadine F (**6**, Scheme 1). Zhai and co-workers reported the first total synthesis of (±)-subincanadine F (**6**) in 2006 and the unique bridge-containing tetracyclic basic skeleton was efficiently assembled by using SmI_2-promoted ring expansion followed by an acid-induced Mannich reaction pathway (please see chapter 1; scheme 6 and page no. 10).[4a] Waters and co-workers have accomplished total synthesis of (±)-subincanadine F (**6**) by taking the advantage of a titanium induced intramolecular nucleophilc acyl substitution reaction for the construction of bridge-fused ring system (please see chapter 1; scheme 8 and page no. 12).[4d] Li and co-workers initially completed total synthesis of (±)-subincanadine F (**6**) via chemoselective Dieckmann condensation as a key step[4b] and later on accomplished the asymmetric first

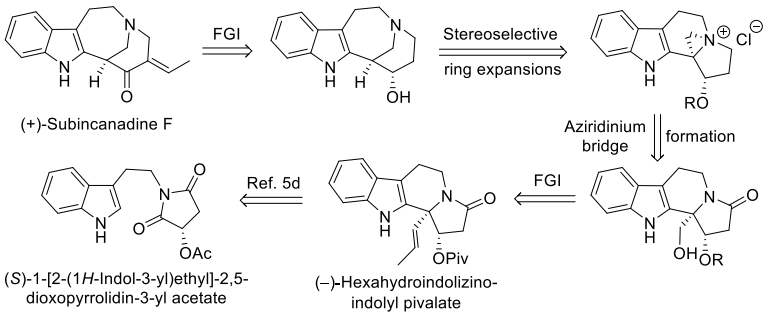


Scheme 1. Crucial Intramolecular Cyclization Reactions Involved in Earlier Total Synthesis of Subincanadine F and the Key Reaction in Present Work

synthesis of natural enantiomer (+)-subincanadine F (**6**) via an uncommon 7-*endo*-trig stereoselective radical cyclization route (please see chapter 1, scheme 7 and 9, page no. 11 and 13 respectively).[4e] In addition Solé *et al* have demonstrated quick assembly of the tetracyclic core of (±)- subincanadine F (**6**) by using a 7-*exo* Heck cyclization route.[4c] The chemoselective, regioselective and enantioselective nucleophilic cleavage of aziridinium ring systems is a fascinating assignment of current interest from its large number of plausible imperious synthetic applications point of view.[6–9] In this context we herein describe the enantioselective synthesis of (+)-subincanadine F (**6**) starting from readily available (*S*)-acetoxysuccinic anhydride via regioselective and stereoselective aziridinium ring expansions as a significant step (Schemes 2–4).

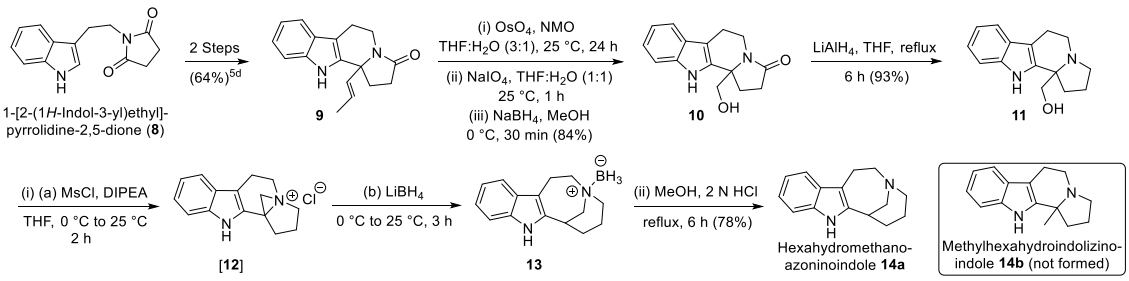
3B.2 Results and Discussion

In continuation of our studies on total synthesis of bioactive natural products from the cyclic anhydride and derivatives;[10a–e] very recently we accomplished the enantioselective first total synthesis of (+)-subincanadine E (**5**) starting from easily accessible (–)-hexahydroindolizinoindolyl pivalate.[5d] We reasoned that the above specified pivalate derivative would also serve as a common precursor for well-organized synthesis of present target compound (+)-subincanadine F (**6**). A concise retrosynthetic analysis of (+)-subincanadine F has been depicted in scheme 2. The carbon chain on an angular



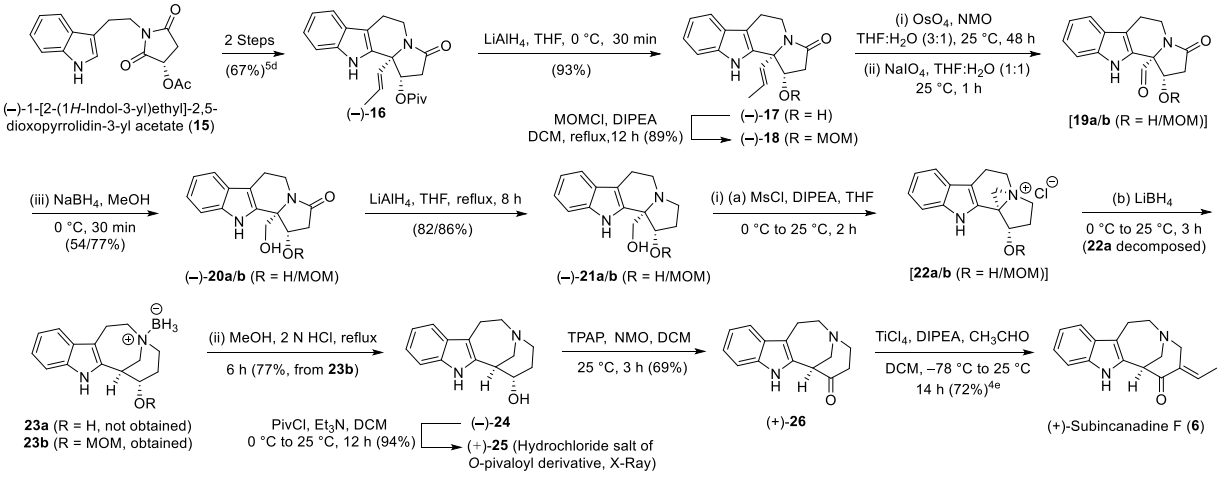
Scheme 2. Concise Retrosynthetic Analysis of (+)-Subincanadine F via Aziridinium Ring Expansions Pathway

carbon atom of pivalate derivative can be efficiently tailored into the desired aziridine ring by using few straight forward functional group transformations. The reactive benzylic position in aziridinium ring can direct the regioselectivity in reductive ring opening reaction. Moreover an oxygen function adjacent to the aziridinium ring system would also serve as a genesis of requisite ketone carbonyl group for the generation of *α,β*-unsaturated system. To confirm the feasibility of above mentioned basic synthetic proposal, a logical plan to initially design the model compound azabicyclodecane via regioselective ring opening of aziridinium moiety was prepared as illustrated in scheme 3.



Scheme 3. Model Studies on Regioselective Reductive Aziridinium Ring Cleavage Strategy

At first the required starting material hexahydroindolizinoindolone **9** was synthesized from the corresponding succinimide derivative **8** using our recently reported two-step protocol (Scheme 3).[5d] Osmium tetraoxide induced dihydroxylation of carbon–carbon double bond in compound **9** followed by sodium periodate cleavage of formed diol resulted in the corresponding aldehyde. The formed aldehyde was immediately subjected to sodium borohydride reduction without any purification and characterization for stability issues and the required alcohol **10** was obtained in 84% yield. Lithium aluminum hydride reduction of a lactam carbonyl in compound **10** under reflux conditions delivered the corresponding amine **11** in 93% yield. The obtained amino-alcohol **11** on treatment with mesyl chloride underwent clean mesylation followed by in situ intramolecular cyclization and quantitatively provided the planned aziridinium salt **12** (confirmed by mass spectrometry). An aziridinium ring in compound **12** can undergo two different types of regioselective reductive ring cleavages.[7b] The nucleophilic attack of hydride ion on relatively more reactive benzylic quaternary carbon atom in aziridinium ring **12** would lead to a desired product hexahydromethanoazoninindole **14a**. However the nucleophilic attack of hydride ion on relatively less reactive but unhindered methylene carbon atom in aziridinium ring **12** would lead to a undesired product methylhexahydroindolizinoindole **14b**. At this stage the above specified aziridinium ring cleavage reaction on compound **12** was thoroughly studied by using several reducing agents. The aziridinium compound **12** on treatment with sodium borohydride in THF remained unreacted. The lithium aluminum hydride, DIBALH and alane mediated reductive ring cleavage of aziridinium salt **12** under different set of reaction conditions met with failure overall resulting in excessive decompositions. The present noteworthy observation could be attributed to the higher reactivity of both substrate and reducing agents. Fortunately, the lithium borohydride promoted regioselective reductive aziridinium ring cleavage of compound **12** in THF was feasible plausibly due to its relatively much higher solubility and it exclusively delivered the intended product **14a** in 78% yield via the corresponding boron complex **13**. In the above specified nucleophilic reaction incoming hydride ion regioselectively attacked on more reactive benzylic quaternary carbon atom with a spontaneous cleavage of the backbone carbon–nitrogen aziridinium bond resulting in a bridged system with ring expansions. Finally the aimed basic skeleton hexahydromethanoazoninindole **14a** was exclusively obtained by successfully addressing regioselectivity issue in the proposed plan for synthesis of subincanadine F (**6**).



Scheme 4. Remarkable Regioselective and Stereoselective Reductive Aziridinium Ring Cleavage Accomplishing Practical Synthesis (+)-Subincanadine F

In the next part of studies systematic enantioselective synthesis of subincanadine F was planned employing our earlier designed potential precursor hexahydroindolizinoindolyl pivalate (–)-**16**.[5d] The deprotection of *O*-pivaloyl group in compound (–)-**16**, standard transformation of carbon–carbon double bond to hydroxyl-aldehyde **12a**, its reduction to diol (–)-**20a** and further reduction of a lactam carbonyl to amine furnished the corresponding diol precursor (–)-**21a** in very good overall yield (Scheme 4). Diol (–)-**21a** on treatment with mesyl chloride neatly formed the in situ cyclized aziridinium chloride **22a** (confirmed by mass spectrometry) via selective mono-mesylation of primary alcohol unit. Unfortunately, all attempts on lithium bororhydride influenced transformation of aziridinium chloride **22a** to rings expanded product **23a** met with failure under variety of reaction conditions. All above mentioned reductive cleavage experiments on **22a** ultimately resulted in decomposition and were indicative of fact that the suitable protection of free secondary hydroxyl group is essential.

On the basis of reaction conditions employed for conversion of alcohol (–)-**17** to aziridinium chloride **22a**, the MOM protection of hydroxyl unit was planned and accordingly product (–)-**18** was obtained in 89% yield. The compound (–)-**18** was transformed to the mono-MOM protected diol (–)-**21b** in very good overall yield by repeating same reactions sequence. Diol (–)-**21b** on treatment with mesyl chloride furnished the expected aziridinium chloride **22b** (confirmed by mass spectrometry) via mesylation and in situ intramolecular cyclization. The planned stereoselective lithium borohydride reduction of aziridinium chloride **22b** exclusively provided an anticipated boron complex **23b**. The obtained product **23b** was purified by silica gel chromatography

and then it was subjected to refluxing dilute hydrochloric acid treatment to break boron complex and also to de-protect the MOM group in one-pot to provide product (–)-**24** in 77% yield. The structural and stereochemical assignments of formed alcohol (–)-**24** were finally established on the basis of X-ray crystallographic data of its *O*-pivaloyl derivatives hydrochloride salt (+)-**25** (Figure 2). Mechanistically in the proposed intermediate **22c**, the incoming smaller size hydride nucleophile approaches from the α-face (opposite side of the breaking C–N bond) to stereoselectively cleave an azridinium bridge (Figure 3). O-

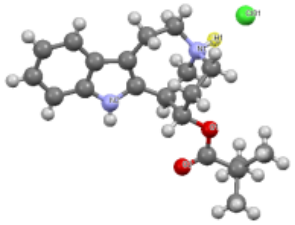


Figure 2. X-ray crystal structure of *O*-pivaloyl derivatives hydrochloride salt [compound (+)-**25**].

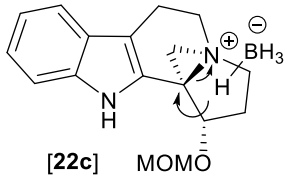


Figure 3. Proposed intermediate for regioselective and stereoselective hydride transfer from α-face resulting in the inversion of configuration.

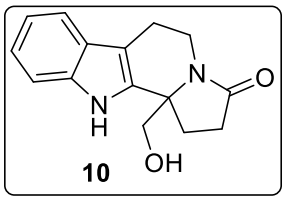
verall S_N2 reaction with inversion of configuration takes place to deliver the preferred product with desired stereochemistry; however the sign of configuration remains same due to change in priority sequence. The initially studied Dess–Martin periodinane (DMP) oxidation of alcohol (–)-**24** was found to be low yielding with some amount of decomposition. However oxidation of alcohol (–)-**24** with catalytic amount of tetrapropylammonium perruthenate (TPAP) in presence of NMO as an oxidant smoothly delivered the known (+)-ketone **26** in 69% yield and also once again confirmed the structure and stereochemistry assignments. The repetition of known[4e] $TiCl_4$-induced stereoselective coupling of ketone (+)-**26** with acetaldehyde furnished the natural product (+)-subincanadine F (**6**) in 72% yield. The obtained analytical and spectral data including specific rotations for both ketone (+)-**26** and (+)-subincanadine F (**6**) were in complete agreement with the reported data.[2a,4e]

3B.3 Summary

In summary, we have accomplished enantioselective practical synthesis of (+)-subincanadine F from the systematically structured aziridinium chloride with remarkable regioselective and stereoselective embarking of hydride nucleophile with the inversion of configuration. The obtained regioselectivity has been governed by benzylic carbon atom reactivity over its steric conjecture and the relative thermodynamic stability of formed product. The MOM protection of an adjacent free secondary hydroxyl group was essential from aziridinium substrate stability point of view. To the best of our knowledge, this is an exceptional example of aziridinium ring cleavage stereoselectively assembling the bridged system and conceptually it will be useful from involved basic chemistry and applications point of view.

3B.4 Experimental Section

(±)-11b-(Hydroxymethyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (10). To a stirred solution of compound **9** (1.00 g, 3.75 mmol) in THF:H_2O (3:1, 20 mL)

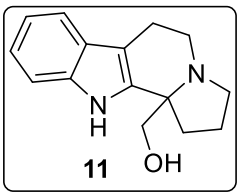


10

was added NMO (50% in water, 2.20 mL, 9.39 mmol) and catalytic amount of OsO_4 (0.20 mL, 0.50 M solution in *t*-BuOH) at 25 °C and the reaction mixture was stirred for 24 h. The reaction was quenched with saturated solution of Na_2SO_3 and the reaction mixture was further stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried diol was directly used for next step. To a stirred solution of diol in THF:H_2O (1:1, 20 mL) was added $NaIO_4$ (2.12 g, 9.99 mmol) at 25 °C in three equal lots. The reaction mixture was further stirred for 1 h and then diluted with EtOAc (20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained aldehyde was immediately used for the next step without any purification. To a stirred solution of aldehyde in MeOH (15 mL) was added $NaBH_4$ (291 mg, 7.57 mmol) at 0 °C. The reaction mixture was further stirred for 30 min and reaction was quenched with aqueous NH_4Cl. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 2:98) afforded compound **10** as a solid (808 mg, 84%). Mp 166–

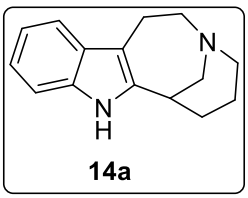
168 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 2.08–2.15 (m, 1H), 2.37 (ddd, J = 16.8, 10.5 and 1.9 Hz, 1H), 2.61 (ddd, J = 12.6, 9.9 and 2.3 Hz, 1H), 2.72–2.81 (m, 3H), 3.22–3.30 (m, 1H), 3.81 (d, J = 11.9 Hz, 1H), 3.88 (d, J = 12.2 Hz, 1H), 4.39 (ddd, J = 13.4, 5.4 and 1.5 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 22.0, 29.5, 32.5, 36.6, 66.2, 66.9, 108.0, 112.1, 119.0, 120.0, 122.6, 127.8, 135.7, 138.1, 176.7; ESIMS (*m*/*z*) HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{16}N_2O_2Na$ 279.1104, found 279.1103; IR ($CHCl_3$) ν_{max} 3618, 3329, 1655 cm^{-1}.

(±)-[2,3,6,11-Tetrahydro-1*H*-indolizino(8,7-*b*)indol-11b(5*H*)-yl]methanol (11). To a stirred suspension of LAH (505 mg, 13.67 mmol) in THF (25 mL) was slowly added compound **10** (700 mg, 2.79 mmol) in THF (10 mL) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach room temperature and then refluxed for 6 h. The reaction was quenched with slow addition of saturated Na_2SO_4 at 0 °C. Reaction mixture was diluted with EtOAc (20 mL), filtered through Celite pad and the organic layer was dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 5:95) afforded compound **11** as a solid (615 mg, 93%). Mp 135–137 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.67–1.80 (m, 1H), 1.80–1.94 (m, 1H), 194–2.05 (m, 1H), 2.32–2.42 (m, 1H), 2.57 (d, J = 15.3 Hz, 1H), 2.90–3.10 (m, 3H), 3.10–3.35 (m, 3H), 3.66 (s, 2H), 7.07–7.23 (m, 2H), 7.30–7.38 (m, 1H), 7.45–7.55 (m, 1H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 23.2, 33.8, 42.6, 50.0, 63.4, 65.8, 107.8, 110.9, 118.3, 119.5, 121.7, 126.9, 136.0, 136.2; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{19}N_2O$ 243.1492, found 243.1495; IR ($CHCl_3$) ν_{max} 3463, 3304 cm^{-1}.



11

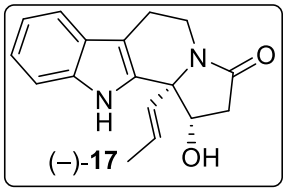
(±)-1,4,5,6,7,8-Hexahydro-2*H*-3,7-methanoazonino(5,4-*b*)indole (14a). To a stirred solution of compound **11** (230 mg, 0.95 mmol) in THF (10 mL) were added *N*,*N*-diisopropylethylamine (DIPEA) (364 μL, 2.09 mmol) and methanesulfonyl chloride (110 μL, 1.42 mmol) at 0 °C under argon atmosphere. The stirred reaction mixture was allowed to reach 25 °C in 2 h. To the above reaction mixture $LiBH_4$ (100 mg, 4.75 mmol) was added at 0 °C and it was further stirred for 3 h allowing to reach 25 °C. The reaction was quenched with slow addition of saturated aqueous NH_4Cl at 0 °C. The reaction mixture was diluted with EtOAc (20 mL) and the organic layer was washed with brine, dried over



14a

Na_2SO_4 and concentrated in vacuo. The purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, EtOAc– PE, 30:70) afforded the boron complex **13** as a white amorphous solid. The obtained solid was dissolved in MeOH (6 mL) plus 2 N HCl (230 μL) at 25 °C and the reaction mixture was refluxed for 6 h. MeOH was removed in vacuo and the obtained residue was dissolved in CH_2Cl_2 (20 mL) and the formed hydrochloride salt was neutralized with 4 N NaOH at 0 °C. The organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo to directly afford the compound **14a** as a solid (166 mg, 78%). Mp 122–124 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.26–1.30 (m, 1H), 1.35–1.42 (m, 1H), 1.72–1.85 (m, 1H), 1.90–2.03 (m, 2H), 2.95–3.40 (m, 8H), 6.97 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 21.0, 25.9, 31.3, 35.5, 50.8, 55.1, 56.4, 111.4, 111.6, 118.4, 119.6, 121.9, 130.2, 137.0, 140.0; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{19}N_2$ 227.1543, found 227.1544; IR ($CHCl_3$) ν_{max} 3284 cm^{-1}.

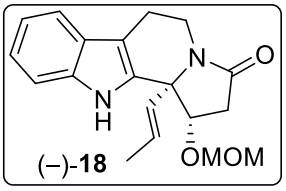
(–)-(1*S*,11b*R*)-1-Hydroxy-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (17). To a stirred suspension of LAH (404 mg, 10.92 mmol) in THF (20 mL) was slowly added compound (–)-**16** (2.00 g, 5.46 mmol) in THF (15 mL) at 0 °C under argon atmosphere and the reaction mixture was stirred for 30 min at same temperature. The reaction was quenched with slow addition of saturated aqueous Na_2SO_4 at 0 °C. Reaction mixture was diluted with EtOAc (30 mL), filtered through Celite pad and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 1:99) afforded compound (–)-**17** as a yellow solid (1.43 g, 93%). Mp 87–89 °C; $[\alpha]^{25}_D$ –37.3 (*c* 0.72 $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (d, J = 6.1 Hz, 3H), 2.70–3.00 (m, 4H), 3.00–3.15 (m, 1H), 4.35–4.65 (m, 3H), 5.45–5.60 (m, 1H), 5.84 (d, J = 15.3 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.3 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 21.2, 34.9, 38.8, 67.2, 73.7, 108.0, 111.0, 118.5, 119.7, 122.3, 126.3, 126.4, 130.6, 133.8, 136.3, 170.7; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_2$ 283.1441, found 283.1433; IR ($CHCl_3$) ν_{max} 3618, 3337, 1659 cm^{-1}.



(–)-**17**

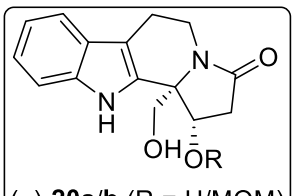
(–)-(1*S*,11b*R*)-1-(Methoxymethoxy)-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (18). To a stirred solution of compound (–)-

17 (700 mg, 2.48 mmol) in CH_2Cl_2 (15 mL) were slowly added DIPEA (1.73 mL, 9.92 mmol), MOMCl (595 μL, 7.44 mmol) and catalytic amount of DMAP (76 mg, 0.62 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and then refluxed for 12 h. The reaction was quenched with water at 25 °C. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layer was washed with aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc– PE, 50:50) afforded compound (–)-**18** as a solid (720 mg, 89%). Mp 126–128 °C; $[\alpha]^{25}_{D}$ –54.8 (*c* 1.5 $CHCl_3$) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.76 (d, *J* = 6.5 Hz, 3H), 2.72–2.90 (m, 4H), 2.92–3.00 (m, 1H), 3.57 (s, 3H), 4.31 (t, *J* = 9.2 Hz, 1H), 4.45 (dd, *J* = 12.8 and 4.2 Hz, 1H), 4.87 (d, *J* = 7.6 Hz, 1H), 4.93 (d, *J* = 7.6 Hz, 1H), 5.35–5.45 (m, 1H), 5.80 (d, *J* = 15.7 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.7, 21.1, 34.2, 37.6, 56.8, 66.3, 83.3, 98.8, 108.9, 111.3, 118.4, 119.5, 122.1, 126.3, 127.6, 129.5, 133.9, 136.1, 168.7; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{23}N_2O_3$ 327.1703, found 327.1703; IR ($CHCl_3$) ν_{max} 3320, 1683 cm^{-1}.



(–)-**18**

(–)-(1*S*,11b*S*)-1-Hydroxy-11b-(hydroxymethyl)-1,2,5,6,11,11b-hexahydro-3*H* indolizino(8,7-*b*)indol-3-one (20a)/(–)-(1*S*,11b*S*)-11b-(Hydroxymethyl)-1-(methoxymethoxy)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (20b).



(–)-**20a**/**b** (R = H/MOM)

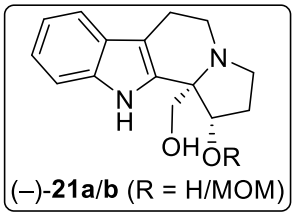
To a stirred solution of compound (–)-**17/18** (610 mg, 2.16/1.87 mmol) in THF:H_2O (3:1, 20 mL) was added NMO (50% in water, 1.51/1.31 mL, 6.48/5.61 mmol) and catalytic amount of OsO_4 (0.20 mL, 0.50 M solution in *t*-BuOH) at 25 °C and reaction mixture was stirred for 48 h. The reaction was quenched with saturated solution of Na_2SO_3 and further stirred for 30 min. The organic layer was separated and aqueous layer was extracted with EtOAc (30 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried diol was directly used for next step. To a stirred solution of diol in THF:H_2O (1:1, 15 mL) was added $NaIO_4$ (1.15/1.00 g, 5.40/4.67 mmol) at 25 °C in three equal lots. The reaction mixture was stirred for 1 h and then diluted with EtOAc (25 mL). The organic layer was washed with brine, dried over Na_2SO_4 and

concentrated in vacuo. The obtained aldehyde was immediately used for the next step without any purification. To a stirred solution of aldehyde in MeOH (10 mL) was added the $NaBH_4$ (200/173 mg, 5.40/4.67 mmol) at 0 °C and further stirred for 30 min. The reaction was quenched with aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 5:95) afforded compound (–)-**20a/b** as a solid [317 mg of (–)-**20a** (54% yield) and 455 mg of (–)-**20b (**77% yield)].

20a: Mp 106–108 °C; $[\alpha]^{25}_{D}$ –64.5 (*c* 0.33 $CHCl_3$) ^{1}H NMR (CD_3OD, 400 MHz) δ 2.62 (dd, *J* = 15.9 and 8.6 Hz, 1H), 2.68–2.90 (m, 3H), 3.21 (td, *J* = 12.5 and 4.9 Hz, 1H), 3.89 (d, *J* = 12.2 Hz, 1H), 4.25 (d, *J* = 12.2 Hz, 1H), 4.38–4.50 (m, 2H), 6.70 (t, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 22.1, 36.4, 41.4, 63.5, 68.0, 74.3, 108.3, 112.2, 119.0, 120.1, 122.7, 127.8, 134.6, 138.2, 173.8; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_3$ 273.1234, found 273.1227; IR ($CHCl_3$) ν_{max} 3619, 3330, 1670 cm^{-1}.

20b: Mp 113–115 °C; $[\alpha]^{25}_{D}$ –77.6 (*c* 0.35 $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75–3.00 (m, 5H), 3.10–3.22 (m, 1H), 3.65 (s, 3H), 4.02 (d, *J* = 12.2 Hz, 1H), 4.17 (d, *J* = 12.2 Hz, 1H), 4.41 (t, *J* = 9.1 Hz, 1H), 4.55–4.65 (m, 1H), 4.93 (s, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 35.0, 38.9, 56.8, 64.2, 65.6, 82.7, 99.2, 108.7, 111.3, 118.5, 119.7, 122.4, 126.3, 132.8, 136.2, 170.1; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{20}N_2O_4Na$ 339.1315, found 339.1314; IR ($CHCl_3$) ν_{max} 3333, 1680 cm^{-1}.

(–)-(1*S*,11b*S*)-11b-(Hydroxymethyl)-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-ol (21a)/(–)-[(1*S*,11b*S*)-1-(Methoxymethoxy)-2,3,6,11-tetrahydro-1*H*-indolizino(8,7-*b*)indol-11b(5*H*)-yl]methanol (21b).



(–)-**21a/b** (R = H/MOM)

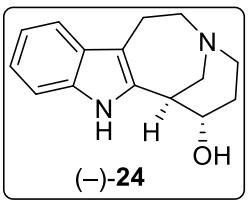
To a stirred suspension of LAH (162/138 mg, 4.40/3.75 mmol) in THF (10 mL) was slowly added compound (–)-**20a/b** (240 mg, 0.88/0.75 mmol) in THF (10 mL) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach room temperature and then refluxed for 8 h. The reaction was quenched with slow addition of saturated aqueous Na_2SO_4 at 0 °C. Reaction mixture was diluted with EtOAc (20 mL),

filtered through Celite pad and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 7:93) afforded compound (–)-**21a/b** as solid [186 mg of (–)-**21a** (82% yield) and 229 mg of (–)-**21b (**86% yield)].

21a: Mp 142–144 °C; $[\alpha]^{25}_{D}$ –38.7 (*c* 0.1 $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78–1.95 (m, 1H), 2.00–2.20 (m, 1H), 2.61 (d, *J* = 17.1 Hz, 1H), 2.90 (sextet, *J* = 8.6 Hz, 2H), 3.15–3.45 (m, 3H), 3.97 (d, *J* = 11.6 Hz, 1H), 4.19 (d, *J* = 11.6 Hz, 1H), 4.54 (t, *J* = 6.1 Hz, 1H), 5.09 (s, 2H), 7.05–7.20 (m, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 33.5, 44.1, 47.1, 63.1, 67.7, 77.9, 107.2, 111.4, 118.1, 119.4, 122.1, 126.2, 132.6, 136.4; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{19}N_2O_2$ 259.1441, found 259.1443; IR ($CHCl_3$) ν_{max} 3619, 3287 cm^{-1}.

21b: Mp 115–117 °C; $[\alpha]^{25}_{D}$ –237.3 (*c* 0.52 MeOH) ^{1}H NMR (CD_3OD, 400 MHz) δ 1.80–1.95 (m, 2H), 2.56 (dd, *J* = 15.8 and 4.3 Hz, 1H), 2.88–3.03 (m, 2H), 3.07–3.35 (m, 3H), 3.44 (s, 3H), 3.86 (d, *J* = 11.0 Hz, 1H), 4.05 (d, *J* = 10.4 Hz, 1H), 4.37 (t, *J* = 5.5 Hz, 1H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.84 (d, *J* = 6.7 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 16.9, 31.6, 45.4, 48.5, 56.1, 65.2, 68.5, 84.4, 97.9, 109.1, 112.1, 118.8, 119.7, 122.4, 128.0, 135.1, 138.1; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{23}N_2O_3$ 303.1703, found 303.1704; IR ($CHCl_3$) ν_{max} 3620, 3362 cm^{-1}.

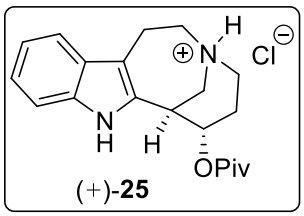
(–)-(6*S*,7*R*)-1,4,5,6,7,8-Hexahydro-2*H*-3,7-methanoazonino(5,4-*b*)indol-6-ol (24). To a stirred solution of compound (–)-**21b** (92 mg, 0.30 mmol) in dry THF (8 mL) were added DIPEA (115 μL, 0.66 mmol) and methanesulfonyl chloride (35 μL, 0.45 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C in 2 h. To the above reaction mixture $LiBH_4$ (32 mg, 1.50 mmol) was added slowly at 0 °C and the reaction mixture was further stirred for 3 h allowing to reach 25 °C. The reaction was quenched with slow addition of saturated aqueous NH_4Cl at 0 °C. The reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, EtOAc–PE, 30:70) afforded boron complex **23b** as a white amorphous solid. The obtained solid was dissolved in MeOH (5 mL) plus 2 N HCl (100 μL) and the reaction mixture was refluxed for 6 h. MeOH was removed in



(–)-**24**

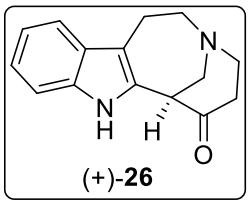
vacuo and the obtained residue was dissolved in CH_2Cl_2 (10 mL). The formed hydrochloride salt was neutralized with 4 N NaOH at 0 °C. The separated aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated in vacuo to directly afford compound (–)-**24** as a white solid (57 mg, 77%). Mp 157–159 °C; $[\alpha]^{25}_D$ –48.4 (*c* 0.2 MeOH) ^{1}H NMR (CD_3OD, 400 MHz) δ 1.39 (d, *J* = 14.0 Hz, 1H), 1.95 (td, *J* = 14.3 and 2.4 Hz, 1H), 2.83–3.25 (m, 6H), 3.28–3.38 (m, 1H), 3.45 (td, *J* = 13.7 and 3.6 Hz, 1H), 3.72 (dd, *J* = 14.0 and 3.1 Hz, 1H), 4.10 (s, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 26.9, 28.7, 42.9, 44.5, 49.2, 56.6, 69.3, 111.4, 112.2, 118.5, 119.6, 121.9, 130.4, 137.0, 138.5; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{19}N_2O$ 243.1492, found 243.1495; IR ($CHCl_3$) ν_{max} 3621, 3197 cm^{-1}.

(+)-(6*S*,7*R*)-6-(Pivaloyloxy)-1,2,3,4,5,6,7,8-octahydro-3,7-methanoazonino(5,4-*b*)indol-3-ium Chloride (25). To a stirred solution of alcohol (–)-**24** (10 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) were slowly added Et_3N (17 μL, 0.12 mmol), pivCl (15 μL, 0.12 mmol) at 0 °C. The reaction mixture was stirred for 12 h allowing to reach 25 °C and the reaction was quenched with water. The separated aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layer was washed with aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 2:98) afforded compound (+)-**25** as white solid (14 mg 94%). Mp 213–215 °C; $[\alpha]^{25}_D$ +48.6 (*c* 0.25 MeOH) ^{1}H NMR (CD_3OD, 400 MHz) δ 1.31 (s, 9H), 1.85 (d, *J* = 15.9 Hz, 1H), 2.15–3.26 (m, 1H), 3.30–3.77 (m, 8H), 3.80 (dd, *J* = 13.4 and 3.7 Hz, 1H), 5.16 (br s, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 22.7, 23.6, 27.5, 37.0, 40.1, 46.3, 56.9, 69.0, 71.5, 111.96, 112.00, 118.8, 120.3, 123.2, 129.4, 134.1, 137.3, 178.6; ESIMS (*m*/*z*) HRMS (ESI) $[M]^+$ calcd for $C_{20}H_{27}N_2O_2$ 327.2067, found 327.2068; IR ($CHCl_3$) ν_{max} 3398, 1682, 1600 cm^{-1}.



(+)-**25**

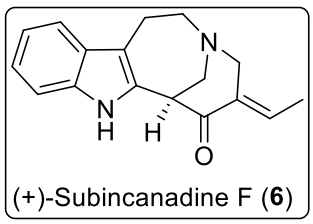
(+)-(7*R*)-1,2,4,5,7,8-Hexahydro-6*H*-3,7-methanoazonino(5,4-*b*)indol-6-one (26). To a stirred solution of alcohol (–)-**24** (19 mg, 0.07 mmol) in CH_2Cl_2 (5 mL) was added catalytic amount of tetrapropylammonium perruthenate (TPAP) (5 mg, 0.01 mmol) and unhydrous solid NMO



(+)-**26**

(24 mg, 0.21 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 3 h at the same temperature and then diluted with CH_2Cl_2 (10 mL). The reaction mixture was filtered through Celite pad and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 2:98) afforded compound (+)-**26** as solid (13 mg 69%). Mp 118–120 °C; $[\alpha]^{25}_D$ +164.3 (c 1.0 $CHCl_3$), {lit.[4e] $[\alpha]^{25}_D$ +158.7 (c 1.0 $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.23 (dd, J = 14.9 and 3.4 Hz, 1H), 2.72–2.82 (m, 1H), 3.07–3.15 (m, 1H), 3.15–3.27 (m, 1H), 3.38–3.60 (m, 5H), 3.63 (s, 1H), 3.76 (d, J = 14.1 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 38.9, 50.8, 54.5, 55.2, 55.3, 110.7, 113.1, 118.1, 119.6, 122.3, 128.9, 132.0, 135.3, 207.3; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$ 241.1335, found 241.1336; IR ($CHCl_3$) ν_{max} 3223, 1699 cm^{-1}.

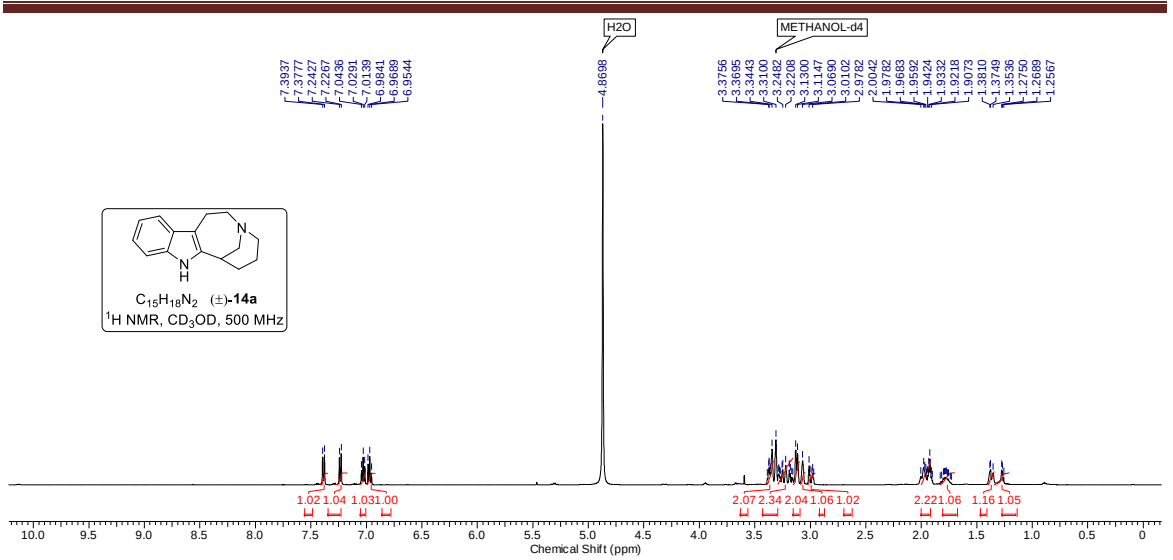
(+)-(7*R*,*E*)-5-Ethylidene-1,2,4,5,7,8-hexahydro-6*H*-3,7-methanoazonino[5,4-*b*]indol-6-one (Subincanadine F, 6). To a stirred solution of ketone (+)-**26** (8 mg, 0.033 mmol) in CH_2Cl_2 (3 mL) was added $TiCl_4$ (1.00 M solution in CH_2Cl_2, 50 μL, 0.049 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred at same temperature for 5 min and then DIPEA (10 μL, 0.052 mmol) was added slowly. The reaction mixture was further stirred for 30 min at same temprature and anhydrous acetaldehyde (2.20 M solution in CH_2Cl_2, 0.05 mL, 0.115 mmol) was added in dropwise fashion. The resulting reaction mixture was stirred at –78 °C for 2 h and then at 25 °C for 12 h. The reaction was quinched with saturated aqueous $NaHCO_3$ and the separated aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 2:98) afforded compound (+)-**6** as yellow amorphous solid (6 mg 72%). $[\alpha]^{25}_D$ +187.3 (*c* 0.25 $CHCl_3$), {lit.[4e] $[\alpha]^{23}_D$ +198.4 (*c* 0.25 $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.82 (d, J = 8.4 Hz, 3H), 2.88 (ddd, J = 16.4, 5.0 and 3.1 Hz, 1H), 3.03 (ddd, J = 16.4, 10.7 and 3.1 Hz, 1H), 3.30–3.36 (m, 1H), 3.38–3.50 (m, 1H), 3.60–3.68 (m, 2H), 3.76 (d, J = 14.1 Hz, 1H), 3.89 (d, J = 16.8 Hz, 1H), 4.08 (d, J = 16.4 Hz, 1H), 6.71 (q, J = 7.3 Hz, 1H), 7.09 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 8.14 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ



(+)-Subincanadine F (**6**)

13.7, 23.3, 49.6, 50.7, 51.9, 55.8, 110.8, 114.3, 117.9, 119.5, 122.0, 128.5, 132.7, 135.0, 135.4, 136.1, 194.6; ESIMS (*m*/*z*) HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1493; IR ($CHCl_3$) ν_{max} 3391, 1679, 1620 cm^{-1}.

3B.5 Selected Spectra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7.0291
7.0139
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6.9689
6.9544
4.8698
3.3756
3.3695
3.3443
3.3100
3.2482
3.2208
3.1300
3.1147
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3.0102
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2.0042
1.9782
1.9683
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1.3810
1.3749
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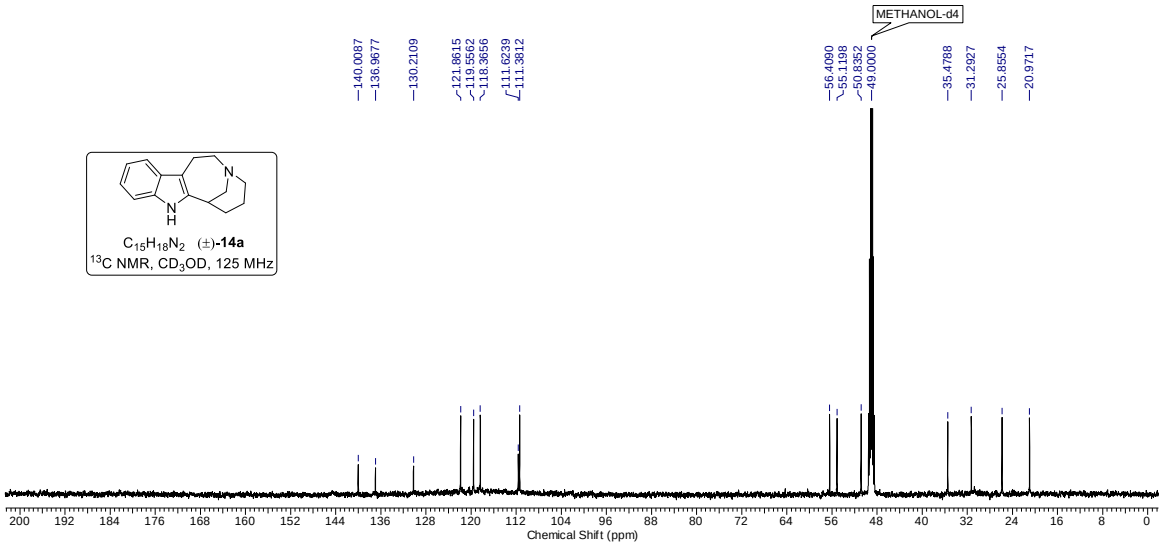
1.2750
1.2689
1.2567
1.02 1.04 1.03 1.00
2.07 2.34 2.04 1.06 1.02
2.22 1.06
1.16 1.05
Chemical Shift (ppm)
C15H18N2 (±)-14a
1H NMR, CD3OD, 500 MHz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130.2109
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111.6239
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55.1198
50.8352
49.0000
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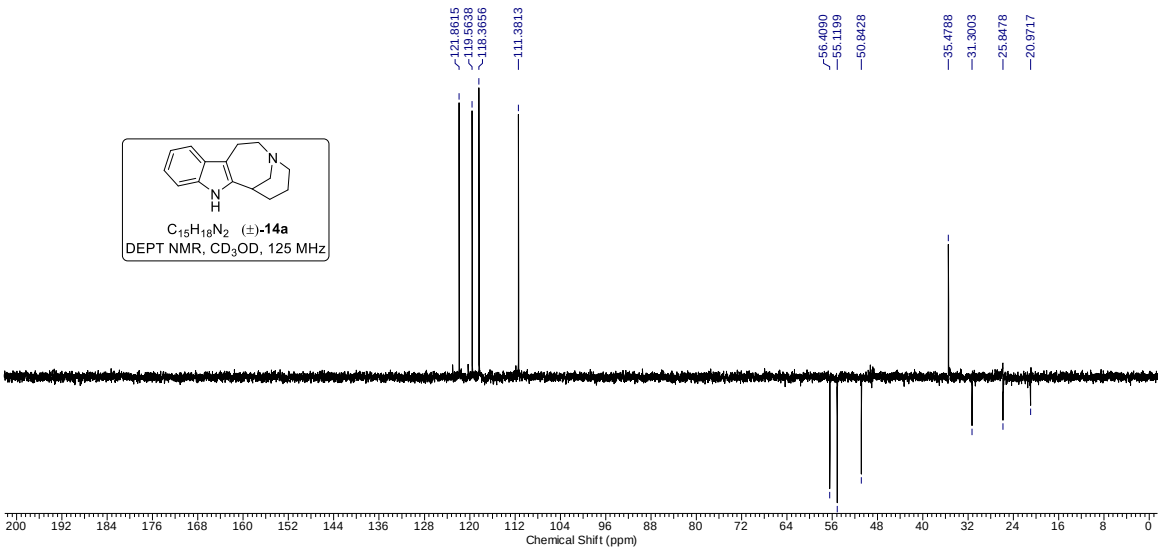
Chemical Shift (ppm)
C15H18N2 (±)-14a
13C NMR, CD3OD, 125 MHz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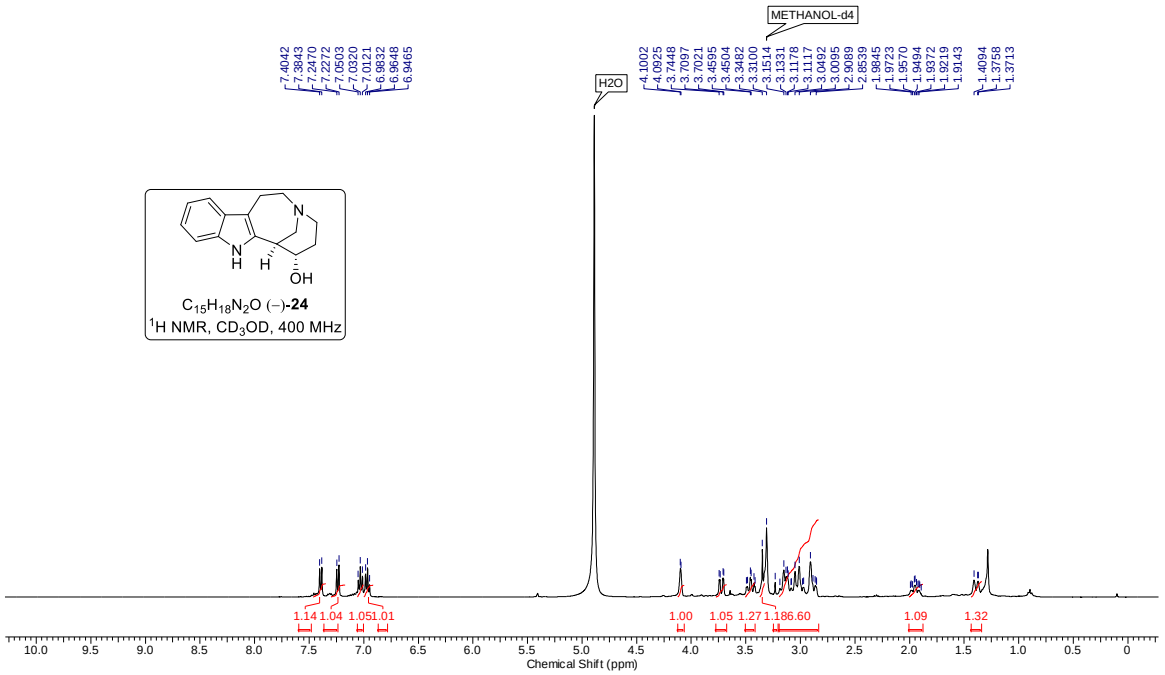
119.5638
118.3656
111.3813
56.4090
55.1199
50.8428
35.4788
31.3003
25.8478
20.9717
Chemical Shift (ppm)
C15H18N2 (±)-14a
DEPT NMR, CD3OD, 125 MHz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7.2470
7.2272
7.0503
7.0320
7.0121
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6.9465
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4.0925
3.7448
3.7097
3.7021
3.4595
3.4504
3.3482
3.3100
3.1514
3.1331
3.1178
3.1117
3.0492
3.0095
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2.8539
1.9845
1.9723
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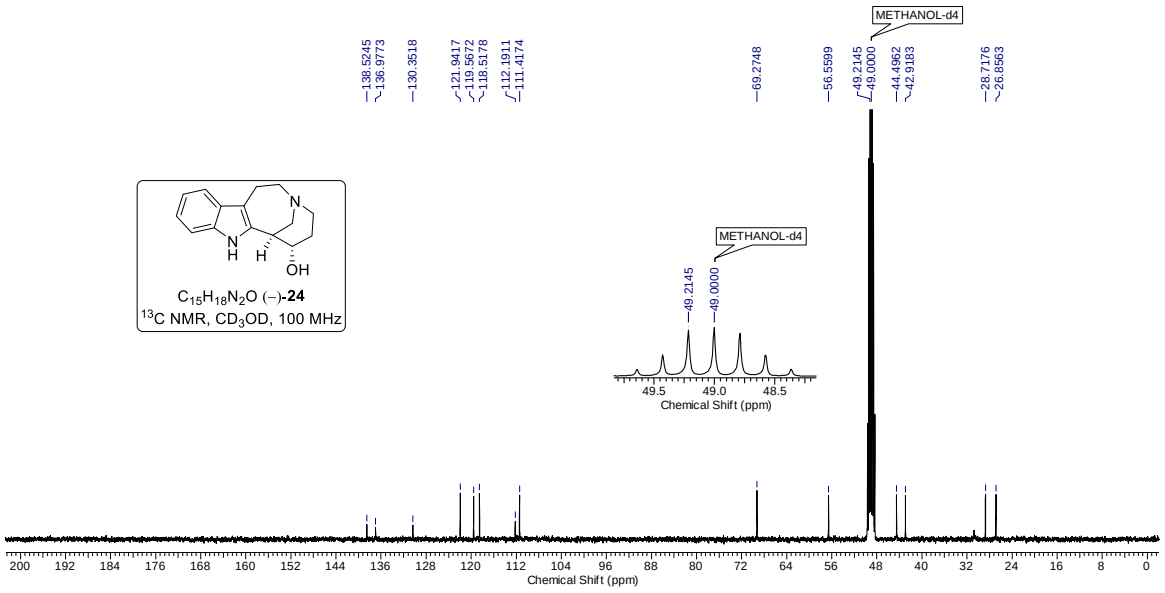
1.9372
1.9219
1.9143
1.4094
1.3758
1.3713
N
H
H
OH
C15H18N2O (−)-24
1H NMR, CD3OD, 400 MHz
1.14 1.04 1.05 1.01
1.00 1.05 1.27 1.18 6.60
1.09
1.32
Chemical Shift (ppm)


METHANOL-d4
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119.5672
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49.2145
49.0000
44.4962
42.9183
28.7176
26.8563
N
H
H
OH
C15H18N2O (−)-24
13C NMR, CD3OD, 100 MHz
METHANOL-d4
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49.0000
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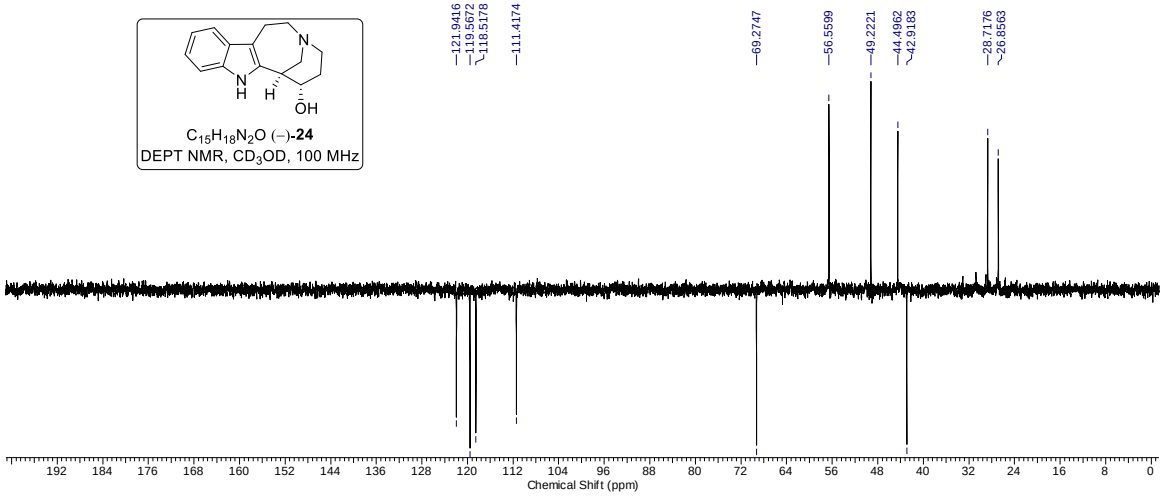
49.0
48.5
Chemical Shift (ppm)
Chemical Shift (ppm)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69.2747
56.5599
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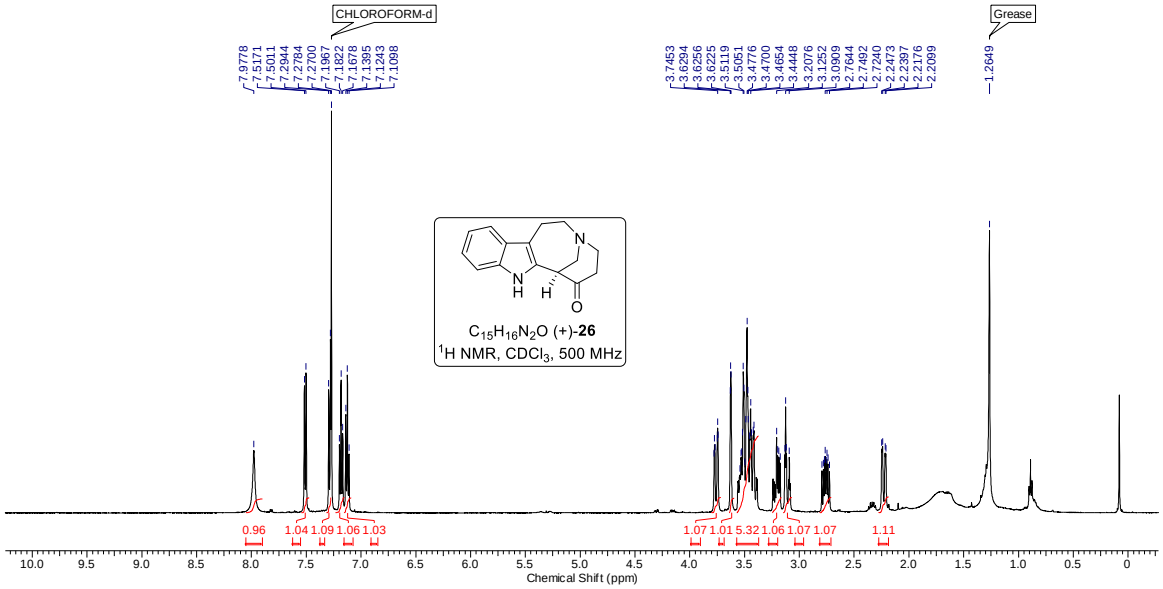
N
H
H
OH
C15H18N2O (−)-24
DEPT NMR, CD3OD, 100 MHz
Chemical Shift (ppm)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7.5011
7.2944
7.2784
7.2700
7.1967
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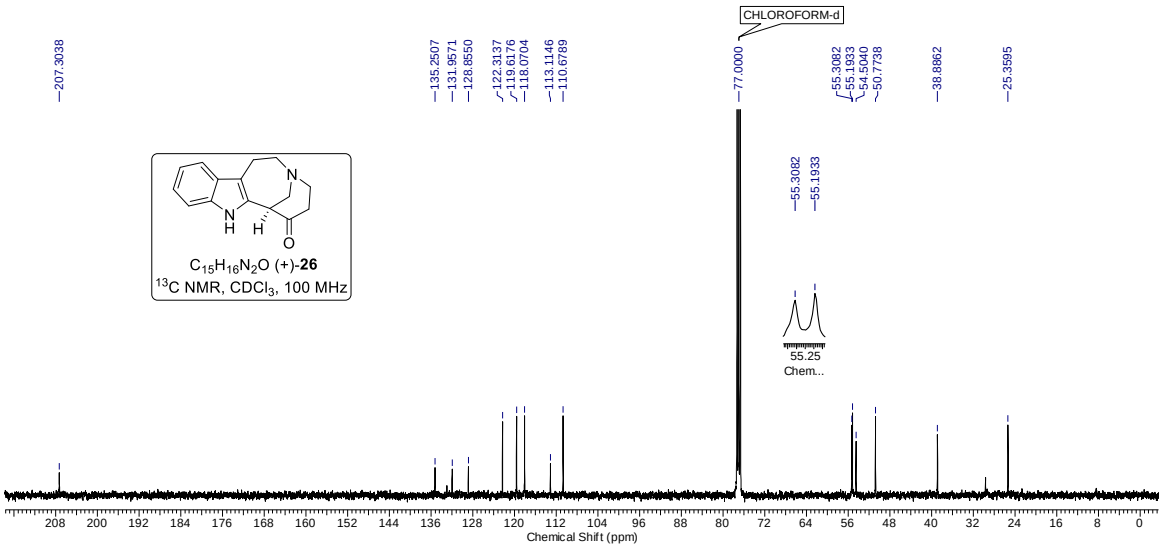
7.1395
7.1243
7.1098
3.7453
3.6294
3.6256
3.6225
3.5119
3.5051
3.4776
3.4700
3.4654
3.4448
3.2076
3.1252
3.0909
2.7644
2.7492
2.7240
2.2473
2.2397
2.2176
2.2099
1.2649
0.96
1.04
1.09
1.06
1.03
1.07
1.01
5.32
1.06
1.07
1.07
1.11
C15H16N2O (+)-26
1H NMR, CDCl3, 500 MHz
Chemical Shift (ppm)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118.0704
113.1146
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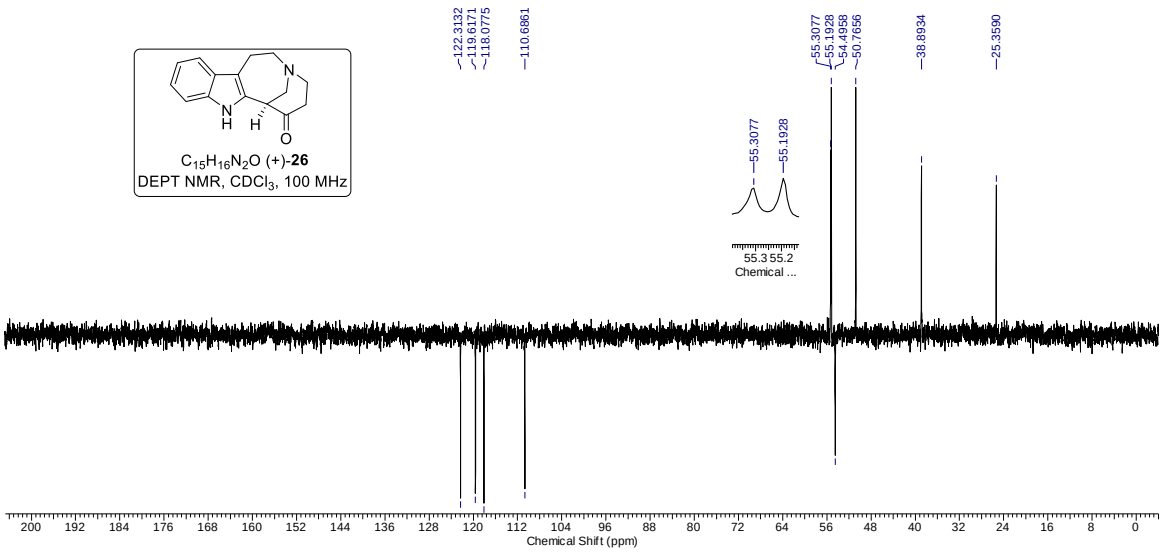
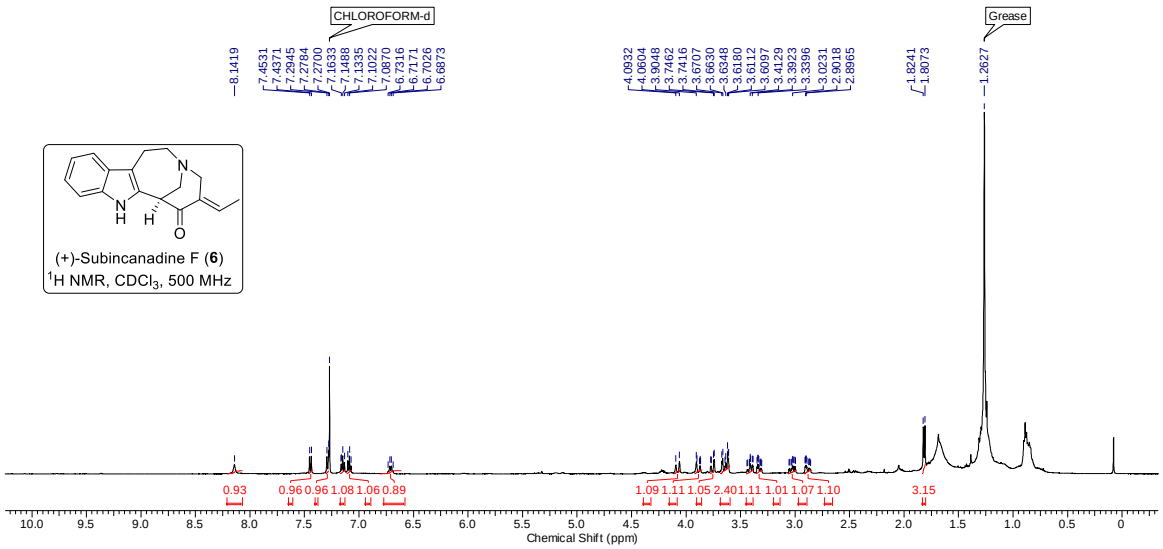
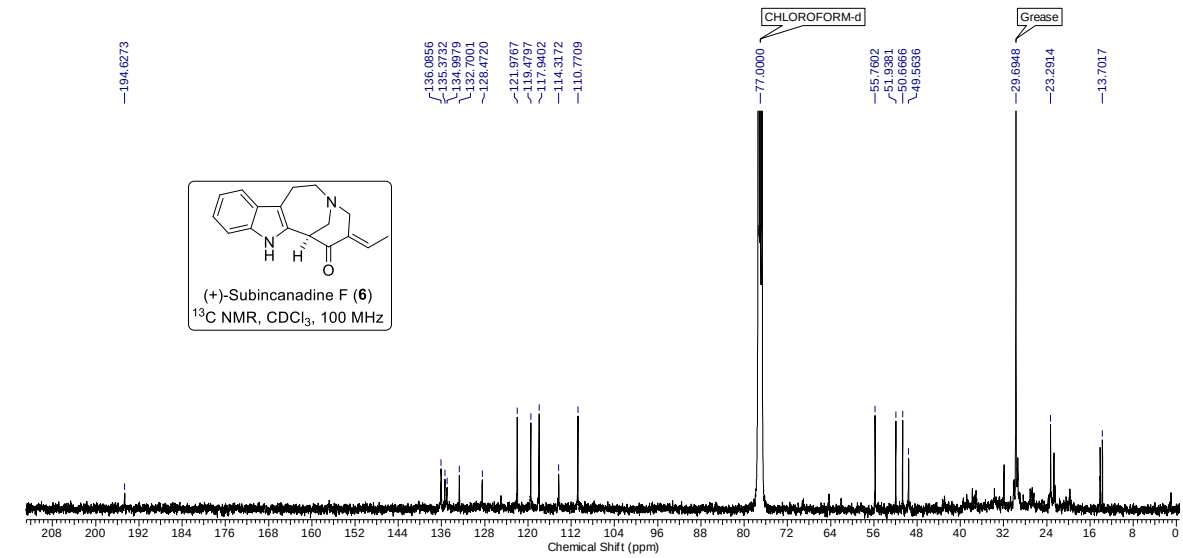
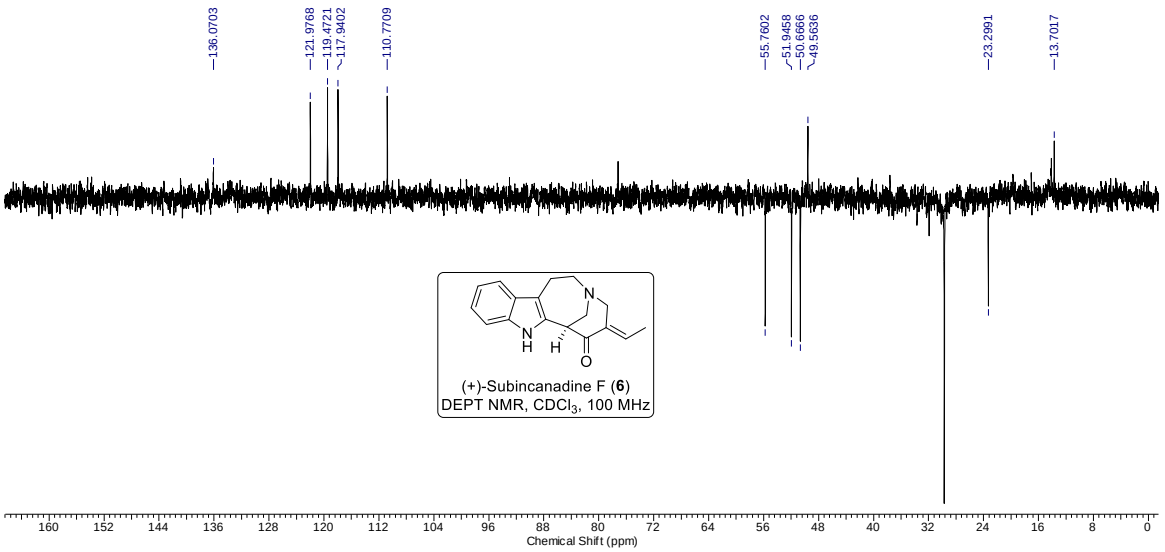
55.3082
55.1933
54.5040
50.7738
38.8862
25.3595
55.25
Chem...
C15H16N2O (+)-26
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


122.3132
119.6171
118.0775
110.6861
55.3077
55.1928
54.4958
50.7656
38.8934
25.3590
55.3 55.2
Chemical ...
C15H16N2O (+)-26
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


CHLOROFORM-d
Grease
(+)-Subincanadine F (6)
1H NMR, CDCl3, 500 MHz
Chemical Shift (ppm)


CHLOROFORM-d
Grease
(+)-Subincanadine F (6)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


(+)-Subincanadine F (6)
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)

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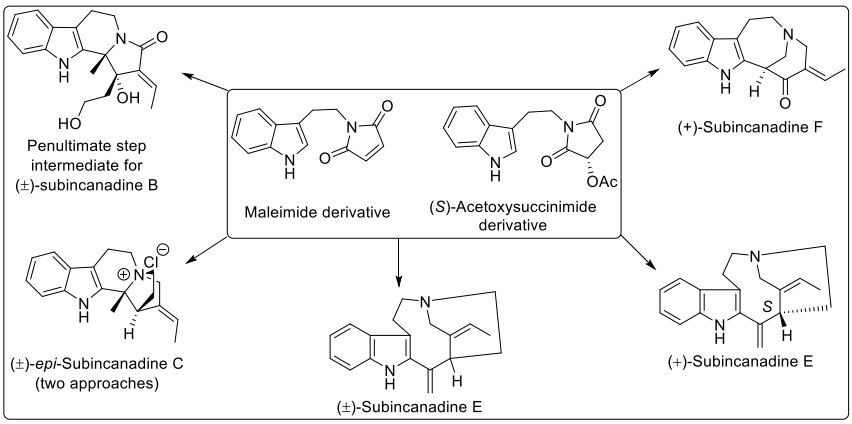
The indole alkaloids are an important class of compounds from their fascinating structural topographies and remarkable bioactivities points of view. On the basis of these points large amount of efforts towards the isolation, total synthesis and bioactivity studies of indole alkaloids have been devoted by chemist's community worldwide. An elegant reviews authoritatively summarizing the indole alkaloids chemistry have been published by many groups, very recently by Klas and co-workers in 2018. The chapter one of present dissertation describes a concise account on the recently isolated structurally interesting and biologically important indole alkaloids subincanadines A–G as well as their natural biogenetic congeners. The subincanadine E alkaloid is structurally flexible and five different proposed biogenetic congeners of the same have been originated via splendid mechanistic proposals. All those indole alkaloids are tryptamine based and encompass novel bridged skeleton (except arbornamine) along with exocylic carbon–carbon double bond (except arborisidine). We have neatly pursued the brief literature account on the isolation, bioactivity and diastereoselective/enantioselective total synthesis of all these natural products since its beginning from 2006 including unsuccessful attempts. It is noteworthy that metal chemistry has played a central role in realizing all those total synthesis. Overall total syntheses of all those alkaloids involving large amount of new chemistry are strategically important and have been presented herein with the help of twenty one schemes and nearly hundred contemporary references from various reputed international chemistry journals. The chapter two and three of present dissertation provide our contribution on total synthesis of subincanadines B, C, E and F alkaloids implementing conceptually new synthetic approaches mainly starting from anhydride and their derivatives.

We have accomplished synthesis of tetracyclic framework of (±)-subincanadine B via an early stage stereoselective introduction of the desired carbon–carbon double bond, by using Wittig reaction and it was useful to activate methylene protons for base induced smooth prenylation, hydroxylation and also to govern the regioselectivity in Grignard addition reaction. The penultimate step reduction of well-designed lactam carbonyl is under investigation and in preliminary studies we have faced the difficulty of S_N2' reaction leading to undesired elimination of tertiary hydroxyl group. We feel that the suitable protection of the tertiary alcohol moiety is essential prior to cyclization and this work is ongoing in our laboratory. Diastereoselective practical approaches to (±)-epi-subincanadine C have been developed via intramolecular diastereoselective Pictet-

Spengler cyclization, regioselective oxidative carbon–carbon double bond cleavage. We have also systematically studied the total synthesis (±)-subincanadine C via diastereoselective 1,4-addition of allyl Grignard reagent as well as diastereoselective reduction of carbon–carbon double bond and developed another efficient route to (±)-epi-subincanadine C. Exceptional syn-stereoselection in Michael addition of cuprate to the unsaturated γ-lactam was unusual and proper scientific reasoning for such type of uncommon stereoselectivities is essential and it still remains as an unanswered challenging question.

Starting from the readily available tryptamine based maleimide/(S)-acetoxysuccinimide we have described new efficient approach to (±)/(+)-subincanadine E and established its absolute configuration on the basis of enantioselective first total synthesis. The 1,4-addition of Grignard reagent to the internally activated lactamol, witnessed position selective desired allylic rearrangements in succinimide derived racemic as well as enantiomerically pure lactamols are noteworthy in this synthesis. We have also accomplished enantioselective practical synthesis of (+)-subincanadine F from the systematically structured aziridinium chloride with remarkable regioselective and stereoselective embarking of hydride nucleophile with the inversion of configuration. The obtained regioselectivity has been governed by benzylic carbon atom reactivity over its steric conjecture and the relative thermodynamic stability of formed product. The MOM protection of an adjacent free secondary hydroxyl group was essential from aziridinium substrate stability point of view. To the best of our knowledge, this is an exceptional example of aziridinium ring cleavage stereoselectively assembling the bridged system and conceptually it will be useful from involved basic chemistry and applications point of view.



Overall the present dissertation describes multistep synthesis of (±)-subincanadine B framework, two approaches for (±)-epi-subincanadine C, (±)-subincanadine E from readily available tryptamine based maleimides and more specifically synthesis of natural enantiomers (+)-subincanadine E and (+)-subincanadine F from the readily available (S)-acetoxysuccinimide as the starting materials. The total synthesis of above depicted all indole alkaloids were successfully accomplished by using Davis hydroxylation, regioselective Grignard addition, internal activation of lactamol leading to in situ 1,4-addition of Grignard reagent, associated position-specific allylic rearrangement in diastereoselective Pictet−Spengler cyclization, stereoselective syn-addition of cuprate to the unsaturated lactam and regioselective and stereoselective reductive aziridinium backbone carbon–nitrogen bond cleavage with hydride nucleophile comprising ring expansions as the key reactions.

All these studies provided 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 would be useful in designing several important complex natural products and natural product hybrids for structure activity relationship studies. A look at the recent literature also revealed that the histogram of the indole chemistry is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed indole would maintain the high positive slope in the present day world of medicinal and synthetic chemistry. In our opinion, a combination of natural and hybrid indole alkaloids would serve as a launching pad to fight against new generation diseases. In a broader prospective one can state with a positive feel that lot of indole based new drugs and agrochemicals will capture highly demanding place in providing services to plant kingdom, animal kingdom and also for the welfare of human beings. Finally, on the basis of exposure to the literature of indole alkaloids 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. Total Synthesis of (±)/(+)-Subincanadine E and Determination of Absolute Configuration
   Kalshetti, M. G.; Argade, N. P. *J. Org. Chem.* **2017**, *82*, 11126.

2. Diastereoselective Synthesis of (±)-*epi*-Subincanadine C
   Kalshetti, M. G.; Argade, N. P. *ACS Omega* ***2018***, *3*, 5308.

3. Regioselective and Stereoselective Reductive Aziridinium Ring Cleavage Leading to Azabicyclodecane Architecture: Enantioselective Synthesis of (+)-Subincanadine F
   Kalshetti, M. G.; Argade, N. P. *J. Org. Chem.* **2018**, *83*, 12164.

4. Stereoselective Synthesis of Subincanadine Alkaloids Framework
   Kalshetti, M. G.; Argade, N. P. *Indian J. Chem.* **2018**, *57B*, Communicated.

5. Progress in total synthesis of subincanadine alkaloids and their congeners
   Kalshetti, M. G.; Argade, N. P. *Org. Biomol. Chem.* **2019**, *17*, 745 (Review).