Total Synthesis of (±)-Periconianone A and (+)-Dibenzyl-Banistenoside B

by

Suhag Sanjay Patil
10CC17A26008

A thesis submitted to the
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in

SCIENCE

Under the supervision of
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and under the co-supervision of
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April-2022

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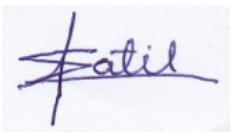

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Date: 16/04/2022	Date: 16/04/2022	Date: 16/04/2022

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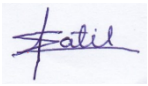

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Dedicated to

My Parents and Teachers

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CONTENTS

Acknowledgement

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shaping my life and making me who I am today. Special thanks to my wife, Shubhra for her sacrifise and support during my tough times.

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Suhag Sanjay Patil

AcOH	acetic acid
AcCl	acetyl chloride
Ac_2O	acetic anhydride
Å	angstrom
Ar	aryl
MeCN	acetonitrile
Bn	benzyl
Boc	*tertiary*-butyloxycarbonyl
Br	bromo
brs	broad singlet
Bu	butyl
t-Bu	*tertiary*-butyl
calcd.	Calculated
cm^{-1}	1/centimeter
C–C	carbon-carbon
C–H	carbon-hydrogen
C–N	carbon-nitrogen
C–O	carbon-oxygen
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
CH_3CN	acetonitrile
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

DMSO	dimethylsulphoxide
DMSO-d_6	deutriated dimethylsulphoxide
dd	doublet of doublet
d	doublet (in NMR) or day(s) (in Scheme)
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
J	coupling constant (in NMR)
mass (ESI+)	electron spray ionization mass spectroscopy
min	minute(s)
m	multiplet
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
m/z	mass to charge ratio
Me	methyl
MHz	megahertz
N	normality
nM	nanomolar(s)
NMR	nuclear magnetic resonance

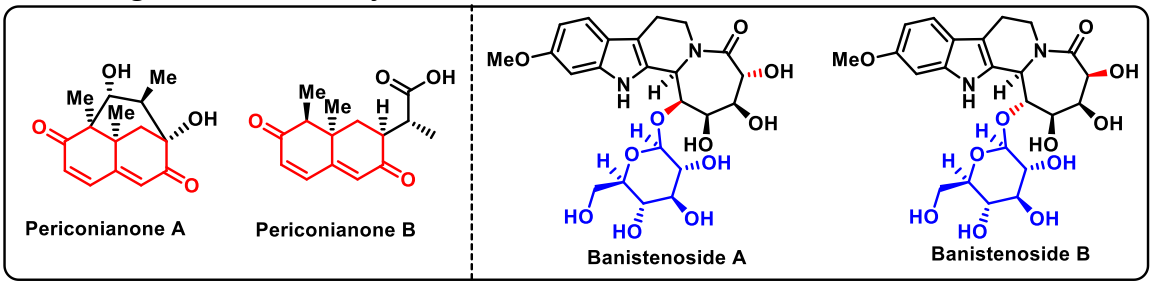
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
S_N	nucleophilic substitution
sec	secondary
t	triplet
tert	tertiary
THF	tetrahydrofuran
TFA	trifluroacetic acid
TLC	thin layer chromatography
UV	ultraviolet
v/v	volume by volume
wt/v	weight by volume
°C	degree celsius
μM	micromolar
mg	milligram
μmol	micromolar

- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Solvents were dried using standard protocols or through MBRAUN (MB SPS-800) solvent purification system (SPS).
- All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring.
- Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.
- Progress of reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, 2,4-DNP, $KMnO_4$, ninhydrin solution followed by heating with a heat gun for ~15 sec.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Melting points of solids were measured using scientific melting point apparatus (Buchi 565).
- Deuterated solvents for NMR spectroscopic analyses were used as received.
- All ^{1}H NMR, ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, 500 MHz spectrometer. Coupling constants were measured in Hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.
- HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, QExactive).
- Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film.
- Optical rotation values were recorded on P-2000 polarimeter at 589 nm.
- Chemical nomenclature (IUPAC) and structures were generated using Chem Bio Draw Ultra.

AcSIR	**Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemical Sciences**
Name of the Candidate	Mr. Suhag Sanjay Patil
Degree Enrollment No. &Date	Ph. D. in Chemical Sciences (10CC17A26008); August 2017
Title of the Thesis	Total Synthesis of (±)-Periconianone A and (+)-Dibenzyl-Banistenoside B
Research Supervisor	Dr. Narshinha P. Argade

1. Introduction

Natural products and their related moieties have historically been incredible as a source of therapeutic agents. It has been estimated that approximately over half of the pharmaceuticals in clinical use today are derived from natural products. Natural products chemistry actually began with the work of Serturner, who first isolated Morphine from the opium poppy in 1803.[1] Neuroinflammation (also known as inflammation of the central nervous system) is a response arising in connection to infections, toxic substances, or traumatic brain injury. These inflammations are associated with a variety of serious neurodegenerative diseases, *viz.* Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS).[2] Some time ago, we have initiated a program for the synthesis and SAR studies of such 2,6-dione scaffolds in search of lead compounds. Previously we have synthesized botryosphaeridione, pleodendione and hoaensieremodione along with several analogs around these scaffolds and tested their anti-inflammatory potential. In continuation to our efforts in this direction, we focused our attention on more potent sesquiterpenoids from this class, periconianone A and periconianone B isolated from the endophytic fungus *Periconia sp* earlier synthesised by Gademann's group.[2,3] Structurally, periconianone A is a complex molecule, considering five contiguous chiral centres inclusive of three quaternary chiral centers which pose challenges to synthetic chemists. Indole alkaloids also show a prominent effect on neurological disorders. *Banisteriopsis caapi*, a plant for treating neurodegenerative disorders relevant to Parkinson's disease, has been found mainly in Brazil, Bolivia, Colombia, Ecuador, and Peru.[4] During the chemical and biological standardization of *Banisteriopsis caapi*, Samoylenko et al. found potent in vitro MAO-A inhibitory and antioxidant activities. Inspired by the novel structural features, a biological activity, we planned to synthesize the banistenoside A and banistenoside B natural products and their close analogs.[4] The yohimbine natural products are a family of pentacyclic indole alkaloids derived from the amino acid tryptophan and the secoiridoid monoterpene secologanin.[5] In the present work, a new synthetic route to access the core ring system of indole alkaloids having yohimbine skeleton, along with new analogs that have been synthesized for the SAR studies.



2. Statement of Problem

The total synthesis of sesquiterpenoid and indol alkaloidal natural products periconianone A and banistenoside B along with the yohimbine analogs involving new concise and efficient routes from the simple commercially available starting materials are of current interest.

3. Objectives

Total synthesis of complex bioactive natural products from the commercially available starting materials.

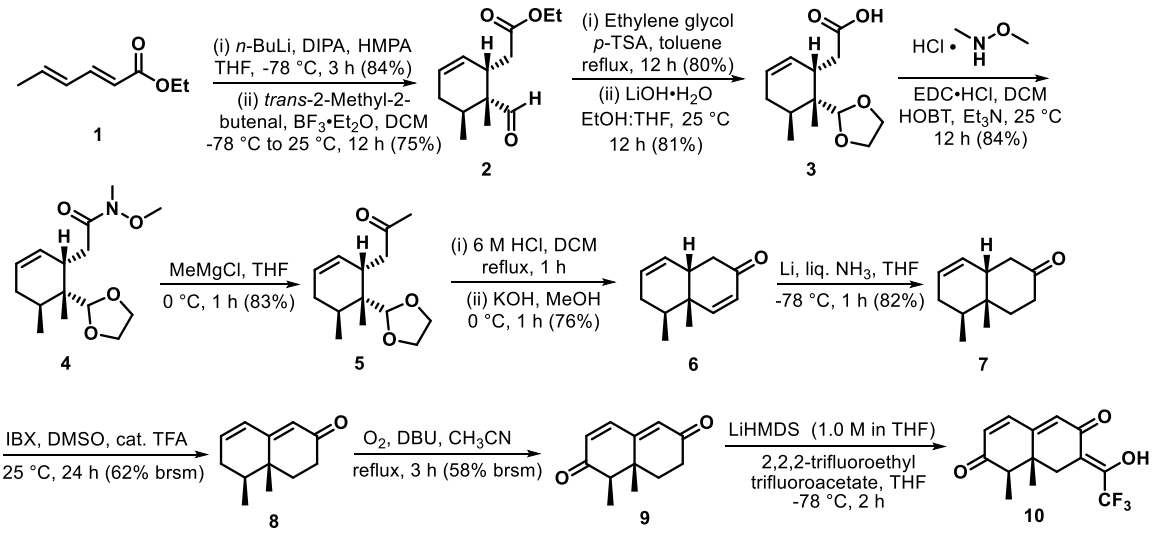
4. Methodology

(i) The products were characterized by advanced analytical and spectroscopic techniques such as high field ^{1}H & ^{13}C NMR, FT-IR, LC-MS, and HRMS.
(ii) A single-crystal X-ray crystallographic study has been done to determine the relative stereochemistry.

5. Results

(i) Diastereoselective total synthesis of (±)-periconianone A, an eremophilane-type sesquiterpenoid with impressive neural anti-inflammatory potential has been accomplished. Diels-Alder/aldol strategy to construct tetrahydro-naphthalene-2,6-dione scaffold, allylic oxidation of dienone using DBU/O_2 and postulated biomimetic aldol reaction to construct 6·6·6 tricyclic system are the highlights of the present synthesis. Besides, the synthesized (±)-periconianone A; two close analogs were tested for their neural anti-inflammatory activity using various assays and found that the structurally simplified analog is superior to (±)-periconianone A.

Scheme 1. Gram Scale Synthesis of Decalin Core from our Research Group and its Application for Diastereoselective Total Synthesis of (±)-Periconianone A



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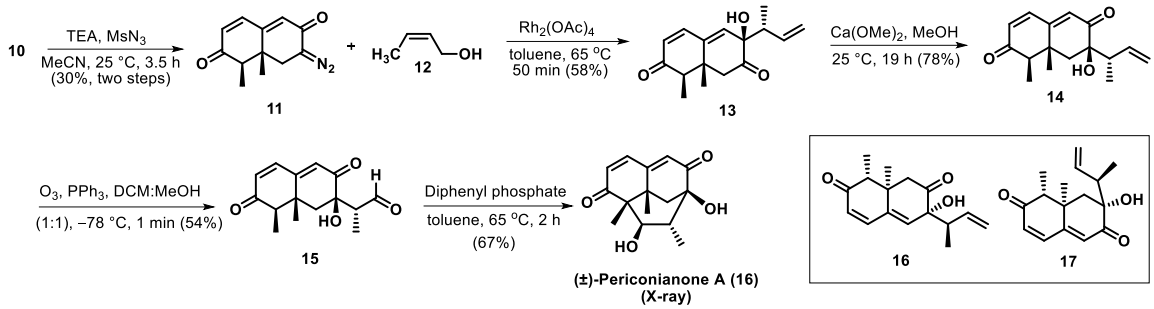


In summary, we have achieved the total synthesis of (±)-periconianone A using Diels-Alder/aldol chemistry developed for the construction of decalin skeleton in our lab and the chemistry developed by Gademann's group. The synthesized (±)-periconianone A and its two analogs were tested for their neuroanti-inflammatory activity using various assays and markers. Based on the results, a close and simplified bicyclic analog **17** of periconianone A seems to be superior with respect to its parent compound and warrants further investigation. During this project execution, we also discovered a mild method for allylic oxidation of dienones using DBU/O_2. Further scope of this method and SAR studies around periconianone A scaffold are the future directions of this project.

(ii) The well-known Diels Alder reaction along with the reductive amination and intramolecular Pictet-Spingler reaction with indole (11 examples) promoted formation of pentacyclic core has been described (Scheme2). With the help of this strategy, we feel that the total synthesis of natural products alloyohimbane and yohimbane appear plausible. There are different members of the rauwolfia alkaloid family. These alkaloids posses a wide range of interesting biological activities, including antihypertensive and antipsychotic.

Scheme 2. General Procedure for the Synthesis of Pentacyclic Core

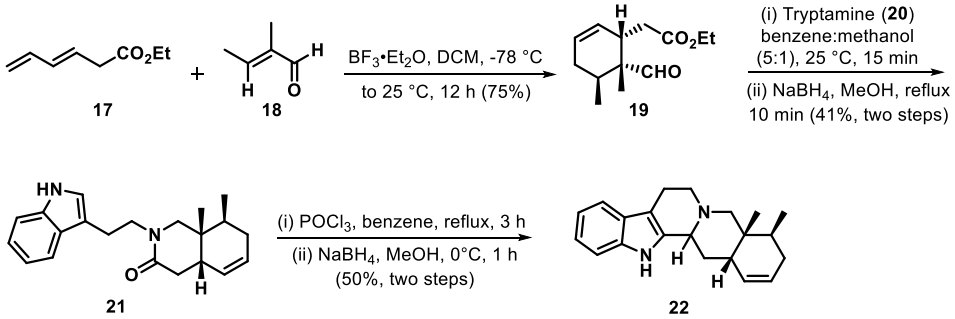
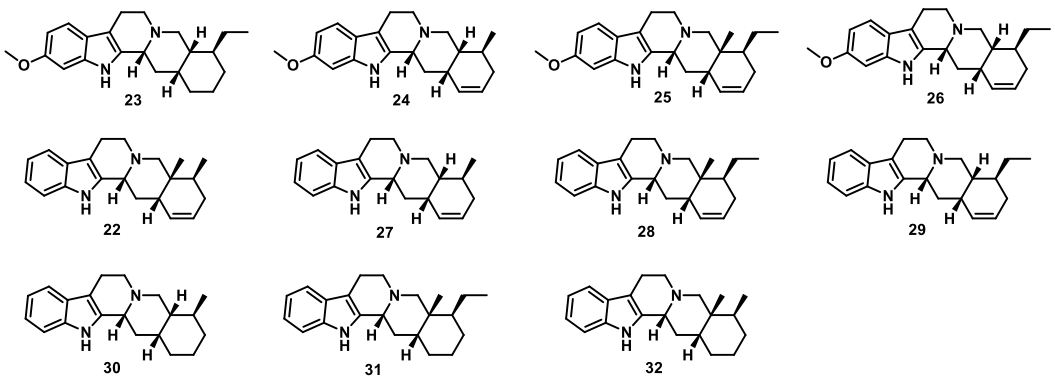


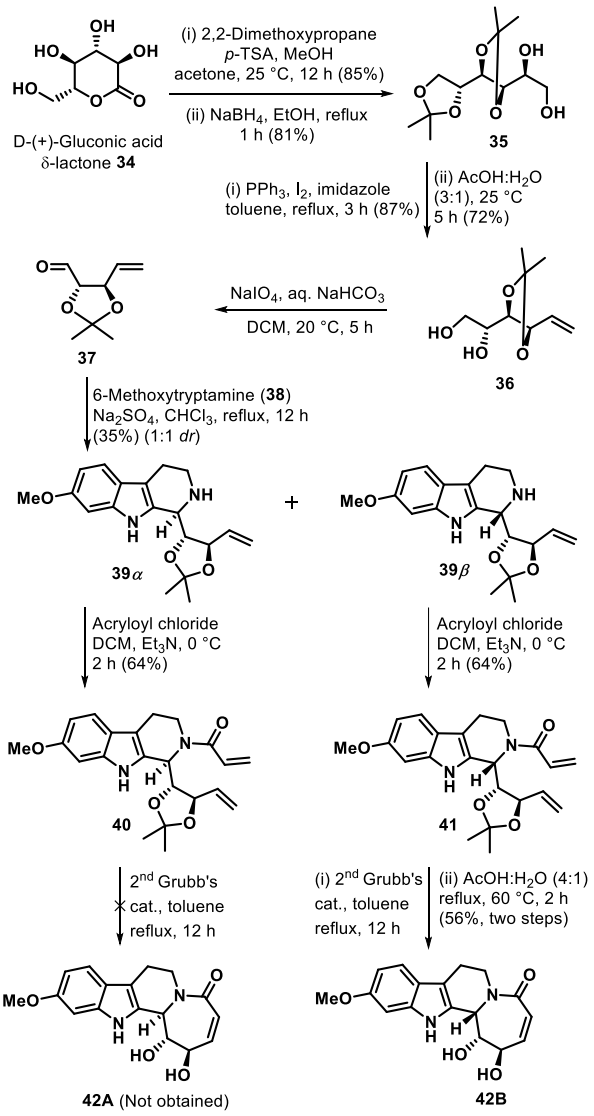
Figure 1. Reserpine Analogs Synthesized.



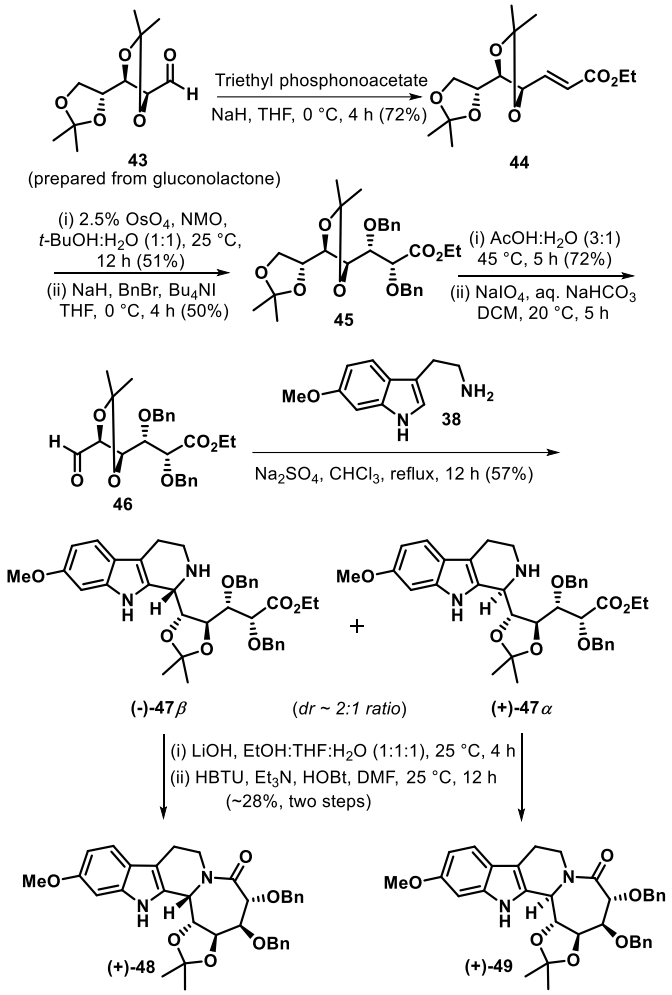
In summary, a new efficient and straightforward method for the synthesis of pentacyclic core of reserpine has been demonstrated. It will be useful for the synthesis of a broad range of desired bioactive natural and unnatural indole alkaloids. We have synthesized 11 reserpine analogs for SAR studies and stereochemistry of most of the compounds have been confirmed by the X-ray crystallography. We also believe that the current protocol has a scale-up potential and will be useful for large-scale production of several rauwolfia alkaloid family natural products of commercial interest.

(iii) Banistenoside A and banistenoside B possessing a unique "azepino(1,2-*a*)tetrahydro-*β*-carboline" carbon framework were isolated from the stem of *Banisteriopsis caapi*.[4] Herein, we report the first total synthesis of dibenzyl derivative of the untouched natural product in the last two decades, banistenoside B. The key steps involve construction of 6·5·6·7 tetracyclic core using Pictet-Spengler reaction and intramolecular amide coupling. The stereoselective glycation was achieved using a gold catalyst, and silver triflate in the late stage of synthesis. The stereochemistry of most of the essential compounds were confirmed by X-ray crystallography (Scheme 3 to 6).

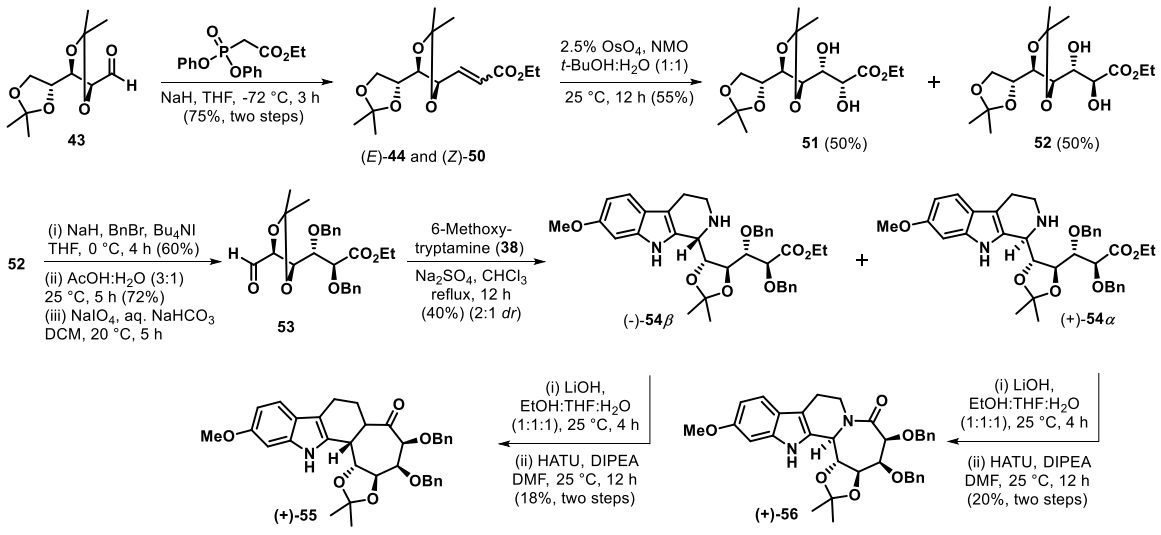
Scheme 3. Synthesis of Tetracyclic Core of Banistenoside B



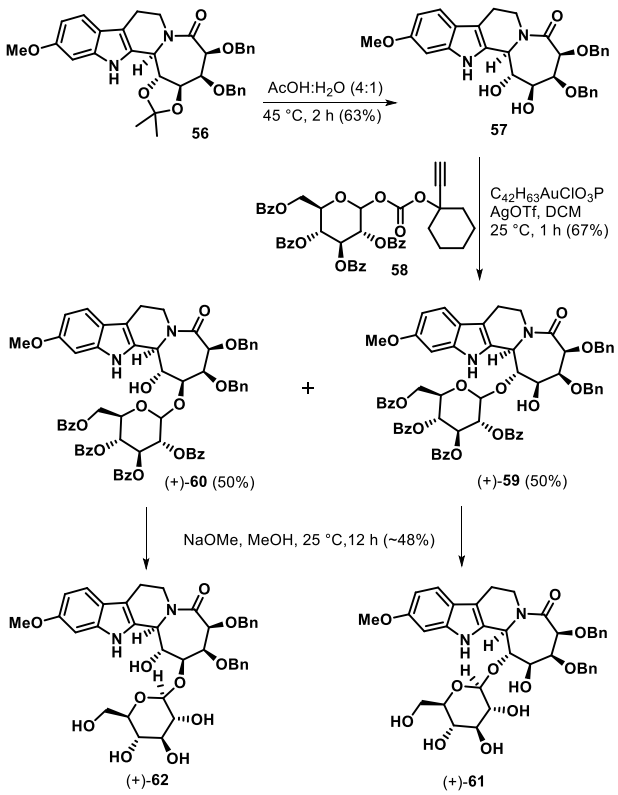
Scheme 4. Synthesis of Tetracyclic Core of Banistenoside



Scheme 5. Synthesis of Tetracyclic Core of Banistenoside B



Scheme 6. Total Synthesis of 12,13-Dibenzyl-Banistenoside B



In summary, we have successfully achieved the first total synthesis of dibenzyl derivative of natural product banistenoside B, containing 10 stereocentres with the longest linear sequence of 14 steps. Along with natural product, few close analogs **42**, **48**, **49**, **55**, **56**, **62**, and a few demethoxy analogs were synthesized for further SAR studies. The key transformation includes well-known Pictet-Spengler reaction, lactamization and stereoselective glycation reaction were the key steps to building natural products' the tetracyclic core characteristics.

6. Conclusion: Starting from ethyl sorbate and tiglic aldehyde, diastereoselective total synthesis of periconianone A has been demonstrated via Diels-Alder/aldol chemistry developed for the construction of decalin skeleton in our lab and α-ketol rearrangement as a key step. During this project execution, we also discovered a mild method for allylic oxidation of dienones using DBU/O_2. The present new strategy to construct pentacyclic indole alkaloidal analogs of yohimbine will be useful from biological activities point of views. Stereoselective total synthesis of banistenoside B has been accomplished via remarkable Pictet-Spengler reaction and regioselective glycation reaction using gold catalyst.

7. Future direction

Stereoselective total synthesis of complex bioactive indole alkaloids and their medicinal properties study.

8. Publications

(1) Neural Anti-inflammatory Natural Product Periconianone A: Total Synthesis and Biological Evaluation, H. P. Kalmode, **S. S. Patil**, K. L. Handore, P. R. Athawale, A. Basu,* and D. S. Reddy* *Eur. J. Org. Chem.* **2019**, 2376-2381.
(2) Total Synthesis of 12,13-Dibenzyl-Banistenoside B and Analogs, **S. S. Patil**, G. R. Jachak, G. R. Krishna, N. P. Argade,* and D. S. Reddy* *Eur. J. Org. Chem.* **2022**,
(3) Regioselective Concise Synthetic Route to Pentacyclic Core for Rauwolfia Alkaloids **Patil, S. S.;** Reddy, D. S. (Manuscript under preparation)

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Chapter 1

Total Synthesis and Biological Evaluation of Sesquiterpene Natural Product: (±)-Periconianone A

Section A

Brief Introduction of Terpenes and Related Natural Products/Drugs

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

This chapter is divided into two sections. In the first section, we have briefly introduced terpenes and their classification based on the number of isoprene units. We have also provided information about the applications of different naturally occurring terpenes for plants and humans. The second section describes reported enantioselective total synthesis of periconianone A along with our synthetic studies on the total synthesis of (±)-periconianone A and its bioactive analogs. In this section, we have also summarized the biological activity study of natural product (±)-periconianone A, an eremophilane-type sesquiterpenoid, and its two analogs. The detailed experimental procedures, complete tabulated analytical and spectral data, and selected NMR spectra have been appropriately included at the end of the section.

1A.1 Introduction

In nature, terpenes are compounds that contain hydrocarbon skeleton with the formula $(C_5H_8)n$. Over 30,000 terpenes are known in the present literature, produced mainly through plants, particularly flowering plants, which shows a remarkably high number of terpenes.[1] The carbon skeleton of terpenes is build-up by the isoprene units $(C_5)n$; it's an isoprene rule given by Ruzicka and Wallach.[2,3] Most of the part is built up from isoprene units, mostly from plant origin; all-natural compounds are denoted as terpenes. As being a large and diverse group, terpenes are also known as terpenoids.[3] Basically, the word terpenes originate from the turpentine so-called "resin of pine trees." The term terpene was first introduced by German scientist August Kekule in 1866. Most of the time, people use the terms terpenes and terpenoids interchangeably. Terpenoids are nothing but modified terpenes that contain additional functional groups, generally oxygen.[4] The work on polymethylenes and higher terpenes, and also the first synthesis of male sex hormones, Leopold Ružička was awarded 1939 Nobel Prize in chemistry. On the basis of the number of carbon atoms, terpenes are divided into different classes like monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}) (Figure 1).[5] Terpenoids are isoprene-based natural products with important roles in the metabolism of all organisms. The terpenes play different roles as they can also help plants to recover from damage and being part of plants' immune systems to keep away infection.[6] Terpenes having strong but pleasant odors can be helpful for the protection of their hosts and also to attract the pollinators. Terpenes have diverse use for human beings

and many terpenes are bioactive. Terpene's specific fragrances and flavours make them useful for perfumes, cosmetics, food, and drinks product preprations.[7]

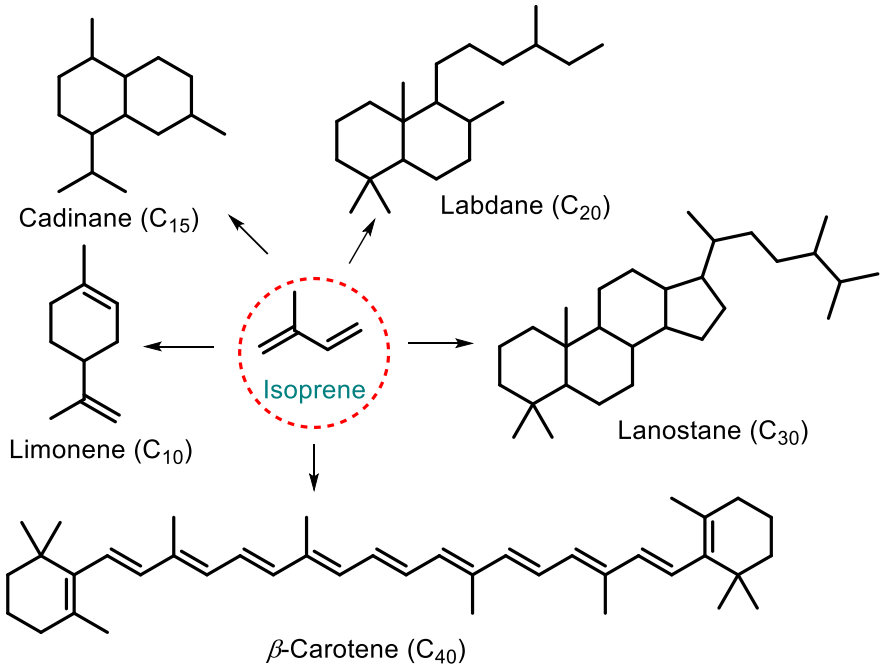
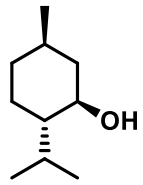
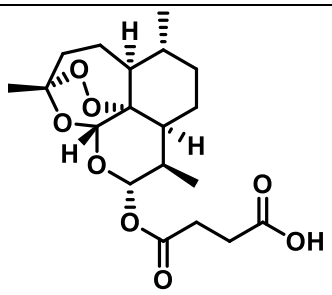
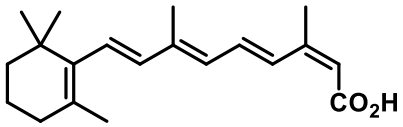
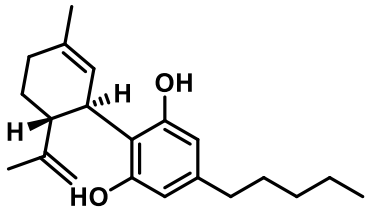
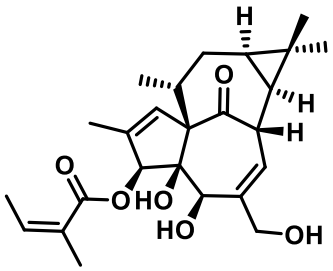


Figure 1. General Examples of Different Terpenes.

Terpenes having different roles includes hormones, membrane fluidity determinants, oxidants, etc. Terpenes are present in many essential oils, and due to their pleasant smell, it is a necessary part of many therapies like aromatherapy. Many terpenoids are used as anti-cancer drugs like taxol and its derivatives. It has a diverse role in foods, drugs, cosmetics, vitamins, hormones, and so on. Terpenes are the most diverse group of naturally occurring compounds with various medical properties.[6,7] Terpenes have different uses; they can be used as natural rubber while they could be precursors for synthetic polymers. A mixture of terpenes obtained from pine tree resin distillation is used commercially as a solvent. Traditionally terpenes are also used for medicinal purposes like curcumin which has many biological activities, including anti-inflammatory, anti-cancer, antiseptic, antioxidant, astringent, antiplasmodial, etc. Nowadays modern medication uses large scales of terpene for various treatment drugs and some of the selected examples are presented in table 1. Terpenes have been effectively involved in preparing medication useful to enhance skin penetration and also to prevent inflammatory diseases.[8] Along with these properties, terpenes also consent for flexibility in way of administration and suppression of side effects.

Table 1. Representative Terpene Based Drugs

Sr. No.	Drugs Containing Terpene Skeleton	Biological Activity
1	 Menthol	It is used for the treatment of minor aches and pains of the muscles/joints (such as arthritis, backache, sprains), also causing the skin to feel cool and then warm.
2	 Artesunate	It is a medication used for the treatment of malaria, it is also used as part of combination therapy, such as artesunate plus mefloquine.
3	 Isotretinoin	It is used for the treatment of severe acne, prevent certain skin cancers (squamous-cell carcinoma), usually lethal skin disease, and lamellar ichthyosis.
4	 Cannabidiol	It is used for seizure disorder (epilepsy), also used for anxiety, pain, a muscle disorder called dystonia, Parkinson disease, Crohn disease.
5	 Ingenol mebutate	It is used to treat actinic keratosis (flat, scaly growths on the skin caused by too much sun exposure), it is cytotoxic agent works by killing fast-growing cells such as the abnormal cells associated with actinic keratoses.

1A.2 Classification of Terpenes

As the terpenes are build-up by the isoprene subunits, on the basis of a number of isoprene units, terpenes are subclassified in the following part.

1A.2.1 Monoterpenes

Monoterpenes are the light molecules built up with the two-isoprene units having (C_{10}) carbons. Monoterpenes can evaporate quickly and refer as "top notes" in the perfume industry. Monoterpenes are found in different parts of plants. Essential oils are rich in monoterpenes. Monoterpenes can be present in the linear or ring (monocyclic or bicyclic) form. Modified monoterpenes containing oxygen and nitrogen atoms are known as monoterpenoids.[9] There are approximately 1500 monoterpenes documented. Mainly these compounds occur in free form, but in the iridoid series occur as glycosides. Monoterpenes are universal natural products, primarily found in plants, often observed in various spices, herbs, conifers, citrus, and fruits. Several monoterpenes like linalool, hinokitiol, ocimene exhibit fungicidal and antibacterial activities. The unique structure of monoterpenes has high chemical lability and optical activity.[10] Monoterpenes can play a crucial role in producing building blocks for a wide range of valuable fine chemicals. Due to their volatile nature, they act as volatile signaling compounds to attract insects to their host plant or to repel them. Eristic flavor and aroma of the plant possessing monoterpene confers different properties to the plants.

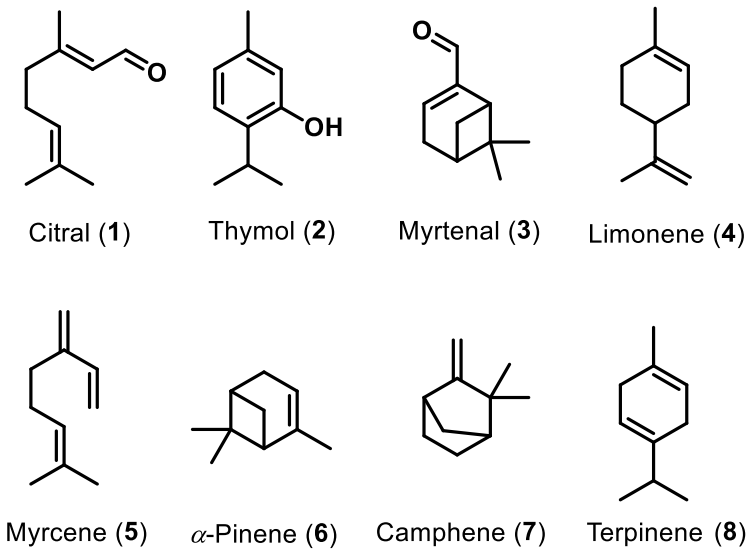
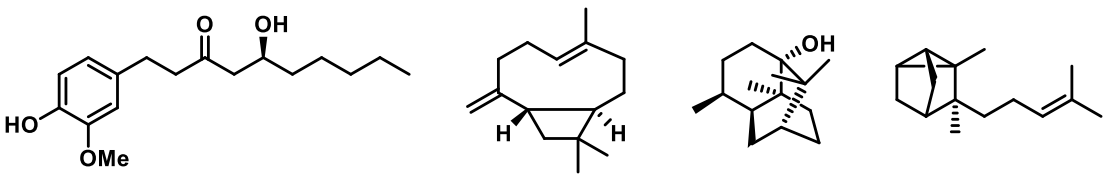


Figure 2. Examples of Monoterpenes.

More specifically, lemon citral (**1**) is an essential constituent of smell, thymol (**2**) is helpful for flavor in mandarin oranges, limonene (**4**), and geranyl are elements of flower scents and attract plant pollinators. One of the prime derivatives of a monoterpene, *α*-pinene (**6**) was very effective against axenic and intracellular amastigotes (Figure 2). The numerous monoterpenes have anti-inflammatory, antimicrobial, antipruritic, antioxidant, analgesic, and hypotensive pharmacological properties.[11] It has been observed that essential oils from many species have antimicrobial properties; detailed analysis revealed that these properties are due to monoterpenes. As many monoterpenes possess anti-cancer properties found in animal studies makes them interesting subject for detailed investigations for their mode of action as anti-cancer compounds.[12]

1A.2.2 Sesquiterpenes

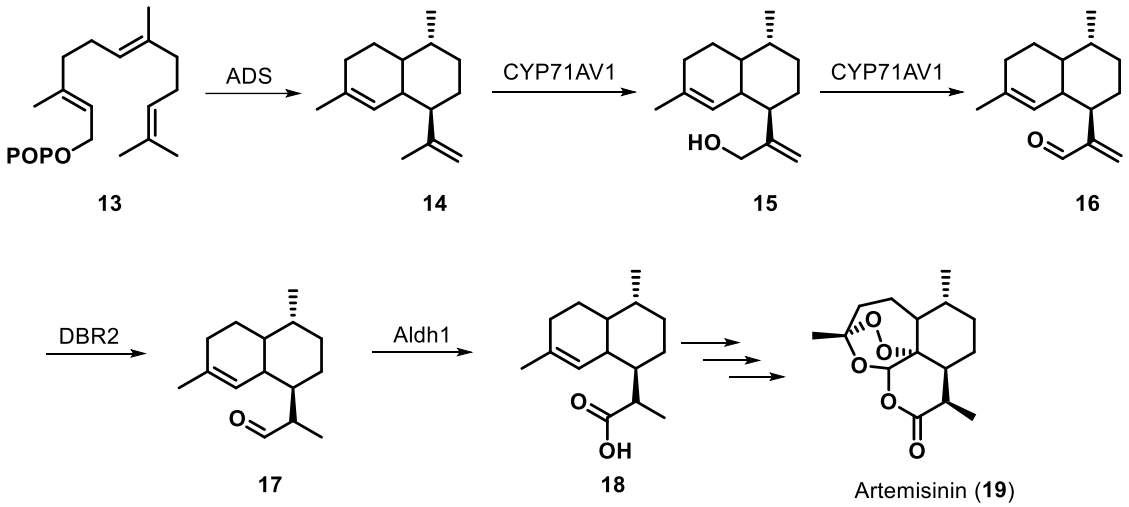
The chemistry and biological origin point of view, sesquiterpenes are the most widely occurring, most broadly studied, and best-understood families of natural products. It is a class of secondary metabolites containing three isoprene unites and has linear, cyclic, bicyclic, tricyclic, and lactone rings. These compounds are not as volatile as monoterpenes.[13] These compounds have strong odors and great potential for stereochemical diversity. For example, due to its volatile nature, geosmin gives an earthy test and characteristic odor on a rainy day. In sesquiterpenes, cyclic forms are more common than monoterpenes because of their increased length of the carbon chain. Along with higher plants, sesquiterpenes are also found in other living systems such as fungi and marine organisms.[13,14] Naturally, sesquiterpenes are present in hydrocarbons or oxygenated forms like lactones, acids, alcohols, ketones. They are responsible for acquainted scents and tastes, for instance, ginger (gingerol **9**), rosemary, clove (*β*-caryophyllene **10**), cannabis, patchouli (patchoulol **11**), and sandalwood (*α*-santalene **12**) (Figure 3).[15]



Gingerol (**9**) *β*-Caryophyllene (**10**) Patchoulol (**11**) *α*-Santalene (**12**)

Figure 3. Examples of Sesquiterpenes.

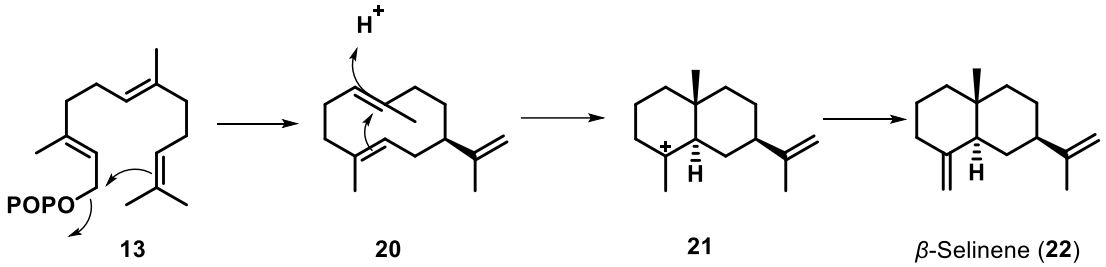
Plant families like Geraniaceae, Lamiaceae, Rutaceae, Gingeraceae, Cannabaceae, and Myrtaceae are principal producers of sesquiterpene volatiles. These essential oils are well documented for their use in traditional herbal medicine such as aromatherapy and Ayurvedic medicine. There is currently less scientific evidence that their use deliberates actual medical benefits, yet their use remains extensive due to the aesthetic, cultural significance, and history.[16] Several highly functionalized, non-volatile sesquiterpenes of plant origin have demonstrated particular biological activity. The endoperoxide sesquiterpene lactone artemisinin (**19)** and its derivatives are the promising new group of drugs against malaria today. Artemisinin (**19**) was isolated from the *Artemisia annua*, has been developed from Chinese traditional herbal remedy. It is useful against *Plasmodium spp*. infections which are the causative agent of malaria. Artemisinin and its derivatives show excellent antimalarial activity and kill the parasite in human blood at its asexual stages of development. Due to the complex structure of artemisinin, chemical synthesis is lengthy and low yielding, and thus for the worldwide supply relies predominantly on the extraction of the plant *Artemisia annua*.[17]



Scheme 1. Proposed Biosynthesis of Artemisinin

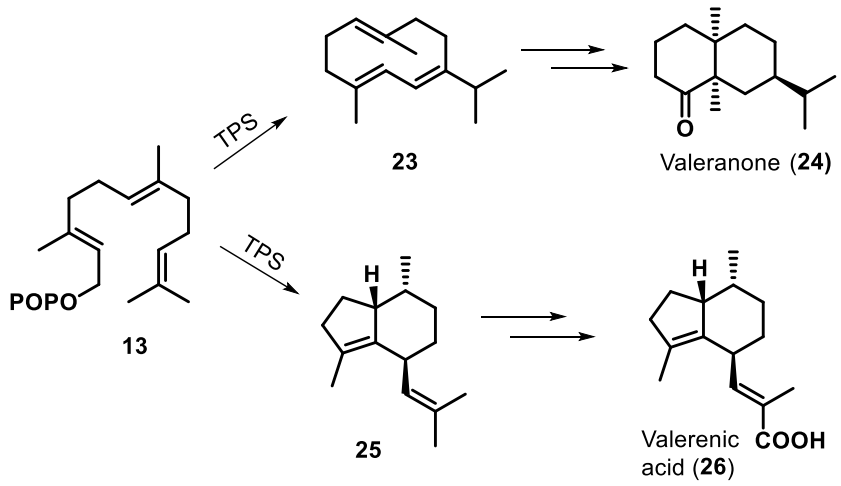
The biosynthesis of artemisinin starts with the farnesyl diphosphate (FDP) **13** to amorpha-4,11-diene **14** by amorpha-4,11-diene synthase (ADS), the cloning and expression of CYP71AV1 convert amorpha-4,11-diene into artemisinic alcohol **15** and artemisinic aldehyde **16**. Artemisinic aldehyde **16** on reaction with double bond reductase 2 (DBR2) reduces to dihydroartemisinic aldehyde **17**, which can be

converted into dihydroartemisinic acid **18** by aldehyde dehydrogenase 1 (Aldh1). Conversion of dihydroartemisinic acid **18** to artemisinin (**19**) involves the photooxidative formation of the endoperoxide ring; however, the details of this process are currently under extensive studies (Scheme 1).[17]



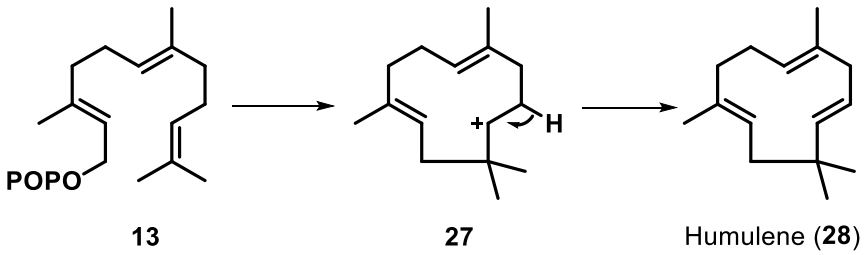
Scheme 2. Proposed Biosynthetic Pathway of *β*-Selinene

The *β*-selinene (**22**) is a major sesquiterpene hydrocarbon of calamondin orange fruits. This can be isolated from the *C. macrophylla* which is growing widely in Uttarakhand, Himalaya. *β*-Selinene has been used to treat many ailments like rheumatism and stomach problems, to cure cuts and injuries, used for digestive and abdominal troubles. The biosynthesis of *β*-selinene starts with the formation bicyclic skeleton by the cyclization of farnesyl diphosphate (FDP) **13** to the eudesmane cation **21** via germacrene A (**20**). The protein, which is associated with the endoplasmic reticulum catalyzes the Mg^{2+} dependent cyclization of farnesyl diphosphate (FDP) **13** to *β*-selinene (**22**) (Scheme 2).[18,19]



Scheme 3. Biosynthetic Pathway of Valeranone and Valerenic Acid

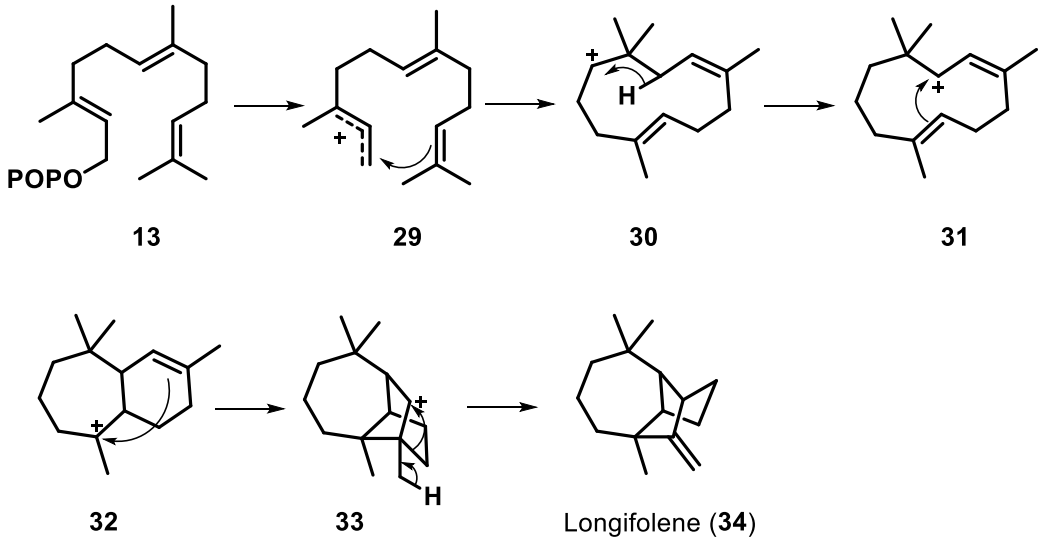
Valerian is an herbal product isolated from the roots of *Valeriana officinalis*. Valerian is beneficial for treating insomnia. The biological activities of valerian have been attributed to valerenic acid and its putative biosynthetic precursor valerenadiene. The above sesquiterpenes found in *V. officinalis* roots. *V. officinalis* grows as a wild herb in very diverse habitats around the globe. Valerian was used in relieving the stress of air raids in England during WWII.[20] The most significant biological efficacy of valerian has been correlated with freshly harvested, carefully dried root preparations along with the iridoid alkaloid and sesquiterpene content of these preparations. Biosynthetic pathway shows the cyclization of farnesyl diphosphate (FDP) **13** by a sesquiterpene synthase (TPS) to germacrene C (**23**) which can be converted into the valeranone (**24**) by the internal ring formation and hydroxylation/reduction sequence. Biosynthetically farnesyl diphosphate (FDP) **13** can also be cyclized into the valerena1,10-diene **25** by the sesquiterpene synthase (TPS)**,** which on hydroxylation/oxidation on one of the terminal methyl of the isobutenyl side chain gets converted into the valerenic acid (**26**) (Scheme 3). Humulene (**28**) is the component of the essential oil that is isolated from the flowering cone of the hops plant, *Humulus lupulus*. Humulene, also known as α-humulene and it has been found in many aromatic plants such as *Salvia officinalis*. It shows anti-inflammatory activity. Humulene is also effective against the yellow fever mosquito, inhibitory effects on tumor necrosis factor-α (TNF-α) and interleukin-1 β (IL1B), it also shows insect repellent properties. Biosynthetically humulene is derived from farnesyl diphosphate (FDP) **13**. Under the action of sesquiterpene synthesis enzymes, the loss of diphosphate from FDP and the formed allylic cation is highly susceptible to intramolecular attacks (Scheme 4).[21]



Scheme 4. Biosynthetic Pathway of Humulene

Another commonly found high-boiling liquid hydrocarbon longifolene is the common chemical of pine resins isolated from the *Pinus longifolia*. It is a tricyclic

sesquiterpene commonly found in pines and higher plants. Longifolene acts as a natural antibacterial and kills a variety of airborne viruses and fungal spores when introduced to the air. Longifolene can decrease anxiety symptoms when inhaled; it shows a noticeably relaxing and sedative nature. Interestingly it can also improve your breathing while in the air. It has an effective anti-inflammatory effect that provides both broncho-dilating and anti-spasmodic properties, making it easier to breathe. The proposed biosynthetic route of longifolene starts with farnesyl diphosphate (FDP) **13** through a cationic polycyclization cascade. After the loss of the pyrophosphate group, cyclization of the distal alkene gives intermediate **30**, which on 1,3-hydride shift forms intermediate **31**. After two additional cyclization's, intermediate **33** produces longifolene (**34**) via a 1,2-alkyl migration (Scheme 5).[22]



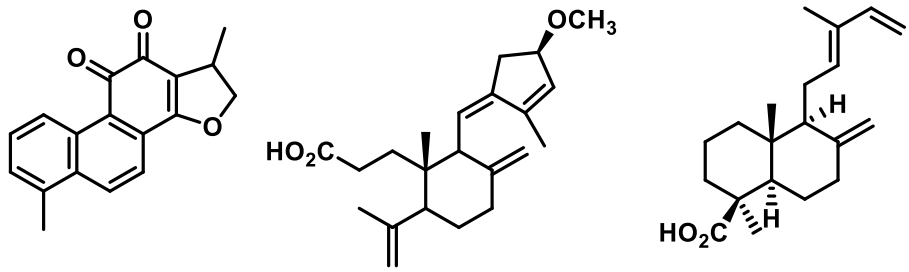
Scheme 5. Proposed Biosynthetic Pathway of Longifolene

Overall, we have described the sesquiterpene class of relevant selected natural products with concise account of their proposed biogenetic pathways and potential bioactivities.

1A.2.3 Diterpenes

They belong to a versatile class of chemical compounds composed of four isoprene units, having the molecular formula $C_{20}H_{32}$, it is found in different natural sources; plants, animals, and fungi. The compounds of this class showed significant biological activities such as antimicrobial, anti-inflammatory, antifungal, and anti-cancer. Some diterpenes also showed cardiovascular activity, such as forskolin, grayanotoxin, marrubenol, eleganolone, and 14-deoxyandrographolide. Diterpenes have mostly been applied to treat cancers, cardiovascular diseases, inflammation, and

cerebrovascular diseases, for example the well-known paclitaxel, ginkgolides, and andrographolide.[23] *Salvia miltiorrhiza* belongs to the Lamiaceae family; its dry root has been effective in promoting blood circulation, regulating heat, calming the nerves, and relieving pain. Tanshinone (**35**), isolated from *S. miltiorrhiza* is used in traditional Chinese medicine for the treatment of inflammatory diseases and cardiovascular treatment. It also exhibits several pharmacological properties such as anti-cancer, antibacterial, and antiviral effects.[24] Nudiflopene F (**36**) shows strong interactions with the iNOS protein by targeting residues of the active cavities of iNOS n BV-2 cells. Nudiflopene F was isolated from the Leaves of *Callicarpa nudiflora*.[25] Communic acid (**37**) is from a group of diterpenes with labdane skeletons found in many plant species belonging to genus *Juniperus*; it is mainly found in leaves, fruits, and bark (Figure 4). They show different biological activities antimycobacterial, antibacterial, antitumoral, hypolipidemic, relaxing smooth muscle, etc. Communic acid has a strong cytotoxic activity in a brine shrimp bioassay with LD_{50} 0.16 μg/mL. It is a suitable building block for efficiently preparing interesting bioactive natural products such as nagilactone F, ambrox, 19-hydroxyferruginol, bruceantin, and others.[26]



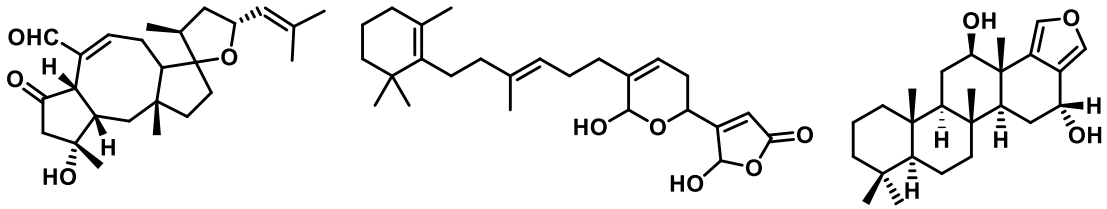
Tanshinone I (**35**) Nudiflopene F (**36**) Communic acid (**37**)

Figure 4. Representative Diterpenes.

1A.2.4 Sesterterpenes

Along with the C_{25} carbon skeleton, sesterterpenes are slightly more than 1000 and have been isolated from various natural sources. However, they are found extensively in bacteria, fungi, insects, and plants. Ophiobolin A (**38**) was the first sesterterpene isolated and labeled in *Ophiobolus miyabeanus*, a plant pathogenic fungus. The biosynthetic pathways of sesterterpene have recently been investigated in plants and fungi; terpene synthase (TPS) and prenyltransferase (PT) are required for the production of sesterterpene scaffolds.[27] The sesterterpene from marine sponge

metabolites manoalide (**39**) shows antibiotic activity against staphylococcus aureus and streptomyces pyogenes. The activity of most of the sesterterpenes are unknown because there are a smaller number of purified sesterterpenes from natural sources. Up to the present time, only nearly 140 sesterterpenes and two types of such relevant enzymes have been identified. Sesterstatins 4 (**40**) is pentacyclic furanosesterterpenes and it inhibited in vitro the growth of various cancer cell lines, including murine P338 leukemia and human BXPC-3 pancreas, U251 central nervous system, RPMI-7951 melanoma (Figure 5).[28]

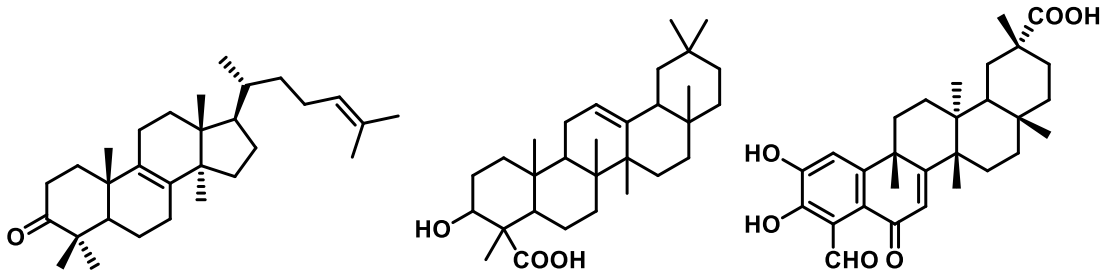


Ophiobolin A (**38**) Manoalide (**39**) Sesterstatin 4 (**40**)

Figure 5. Representative Sesterterpenes.

1A.2.5 Triterpenes

It is a class of chemical compounds composed of six isoprene units with the molecular formula $C_{30}H_{48}$. Triterpenes are mostly found in nature in the cyclic form with 1–5 ring systems. The triterpenes are complex molecules that are one of the most abundant and diverse groups of plant natural products. Simple triterpenes are components of specialized membranes and surface waxes and may possibly act as signaling molecules, whereas complex glycosylated triterpenes provide protection against pests and pathogens. Triterpenes have an extensive range of applications in the industrial biotechnology sectors of food and health.[29] Triterpenes have several antidiabetic mechanisms, and they can inhibit enzymes involved in glucose metabolism to normalize plasma glucose and insulin levels by preventing the development of insulin resistance. Triterpenes show different biological activities, including anti-inflammatory, antitumoral agents, antimicrobial, and antiviral, as well as being immunomodulator compounds.[30] Penasterone (**41**) isolated from the marine sponge *Penares incrustans* exhibit anti-immunoglobulin (Ig) E activity in a dose-dependent manner (Figure 6). The pentacyclic triterpene compound boswellic acid (**42**) was isolated from the genus *Boswellia*; it is a major component of the resin. It exhibits anti-inflammatory behavior by inhibiting leukotriene synthesis, and it also decreases the symptoms of asthma.[31]

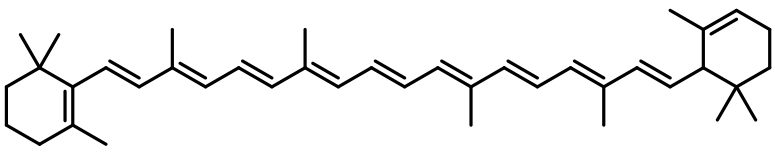


Penasterone (**41**) Boswellic acid (**42**) Demethylzeylasteral (**43**)

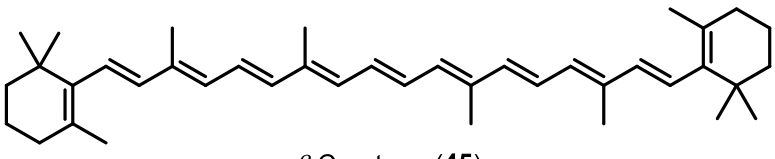
Figure 6. Examples of Triterpenes.

1A.2.6 Tetraterpenes

Tetraterpene is a class of terpenes consisting of eight isoprene units having a C_{40} carbon skeleton. The orange, yellow, or animal pigments and red fat-soluble plants known as carotenoids are classed as tetraterpenes. They are synthesized by oxygenic phototrophs, land plants, algae, cyanobacteria, anoxygenic phototrophs, purple bacteria, green sulfur bacteria, green filamentous bacteria, and heliobacteria. They are found in algae, plants, photosynthetic bacteria. Several carotenoids such as β-cryptoxanthin and β-carotene are well known as provitamin A carotenoids.[32] The dietary carotenoids, containing non-provitamin A carotenoids are considered to play a role in anticipation of common chronic diseases such as CVD, cancers, age-related macular degeneration. Carotenoids occur in the leaves, roots, and shoots of all higher plants and serve as color filters for photosynthesis giving rise to the red and yellow color of the leaves during fall. Carotenes are yellow, orange, and red pigments found mainly in vegetables, fruit, and dark green leafy vegetables. There are two types of carotenes found in the carrot's the alpha and beta carotenes (Figure 7).[32,33]



α-Carotene (**44**)



β-Carotene (**45**)

Figure 7. α-Carotene and β-Carotene

Those terpenes having more than eight isoprene unites are referred to as polyterpenes. The most widely used natural polymer is the natural rubber synthesized by enzymatic polymerization of isopentenyl pyrophosphate, and the repeat unit structure is isoprene. Polyterpene resin also known as terpene polymer is produced using only the renewable material mixed terpene. Polyterpene resin is highly compatible with numerous polymer materials such as SIS, polyolefins, styrene elastomer or natural rubber. The wide applications of polyterpene resins are well known in adhesives and in the preparation of adhesive tapes.[34]

1A.3 Summary

In summary, we have presented different terpenes, their biological importance and their broad classifications. More emphasis has been given to the detailed classification of the terpenes along with their probable biosynthetic pathways. It is a largest class of compounds which are not only useful for humans but also for the plants, animals, etc. The evolution of highly functionalized plant terpenes resulting in chemical diversification across the plant kingdom by the introduction of oxygen into olefin of terpene hydrocarbons and condensations with derivatives from other natural products families, such as short and branched chain fatty acids, amino acids, and phenolic compound is noteworthy. Essential oils and their monoterpenes have an interesting effect on human physiology, and they have been used in different culture for seasoning meals due to their antimicrobial and antioxidant effects. The monoterpenes have an anti-cancer property in animals and which makes them an interesting subject for detailed studies on their mode of action as chemo-preventive and anti-cancer compounds. Essential oils from the sesquiterpenes are useful for the pollination in the plants, they can also show different biological properties such as anti-malarial, prevention of neurodegeneration, antimigraine activity, analgesic and sedative activities and treatment of ailments. Members of the triterpenoids are biologically active, among which are the adaptogens, anti-melanoma, chemo preventive, anti-inflammatory, and anti-arthritic. In various countries triterpene's carotenoids are used as traditional medicine for antidiabetic remedies. Our research group has been actively intricate in the synthesis of bioactive natural product from sesquiterpene class such as botryosphaeridione, pleodendione, hoaensieremodione, nootkatone. We strongly believe that compounds from sesquiterpenes class will be of continuing interest to both the synthetic and medicinal chemists. Our synthetic

strategies towards total synthesis of eremophilane type sesquiterpenes natural product (±)-periconianone A and their bioactive analogs will be discussed in details in the second section of this chapter.

1A.4 References

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Chapter 1

Section B

Total Synthesis and Biological Evaluation of (±)-Periconianone A and its Analogs

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

1B.1 Background

Neuroinflammation (also known as inflammation of the central nervous system) is a response arising in connection to the infections, toxic substances, or traumatic brain injury. These inflammations are associated with a variety of serious neurodegenerative diseases, *viz.* Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS).[1] In literature, compounds with dihydro-, tetrahydro-naphthalene-2,6-dione scaffolds are promising for treating such diseases arising out of CNS inflammations (Figure 1).[2,3] A few years ago, we initiated a program for the synthesis and SAR studies of such 2,6-dione scaffolds in search of lead compounds. Previously, we have synthesized pleodendione (**1**), hoaensieremodione (**2**), and botryosphaeridione (**3**) along with several analogs around these scaffolds. We tested their anti-inflammatory potential, which resulted in the identification of two potential leads.[4] Continuing our efforts in this direction, we focused our attention on more potent sesquiterpenoids from this class, periconianone A (**4**) and periconianone B (**5**) isolated from the endophytic fungus *Periconia sp.*[2] Their structures were established on the basis of NMR, 2D NMR, HRMS, and single-crystal X-ray diffraction studies. Structurally, periconianone A is a complex molecule, considering three quaternary chiral centers which pose challenges to synthetic chemists. Compounds periconianone A (**4**) and periconianone B (**5**) exhibited significant inhibition of LPS-induced NO production with IC_{50} values of 0.15 and 0.38 μM, which are comparatively more potent than the curcumin (**6**) (IC_{50} = 3.9 μM).[1,2]

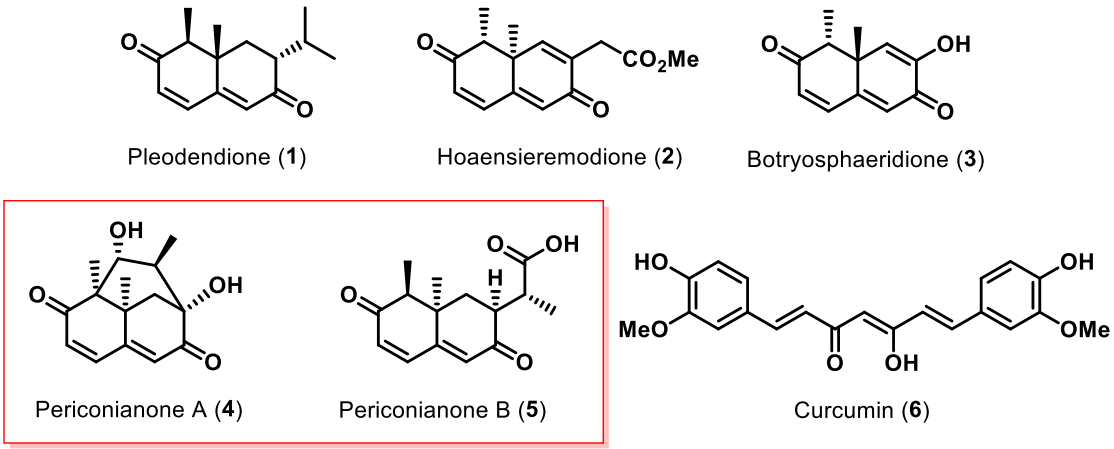


Figure 1. Structure of Natural Products Based on Dihydro-, Tetrahydronapththalene-2,6-dione Scaffolds and Curcumin.

These results suggest that compounds based on 2,6-dione scaffolds are the promising lead structure for treating CNS disorders induced by microglia endogenous immune cells that play critical roles in neurodegenerative disorders.

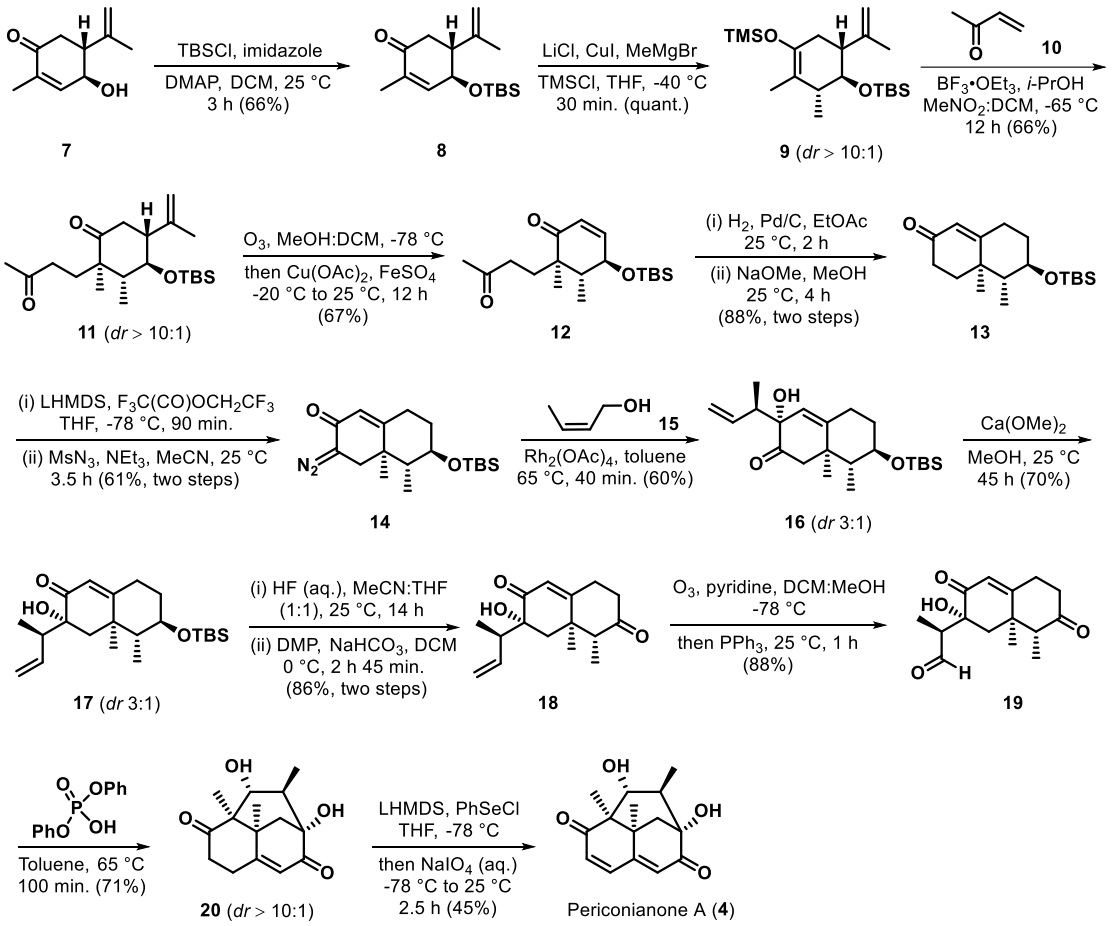
1B.1.1 Introduction to Neuroinflammation

Neuroinflammation is a response that is related to the nervous tissue of the brain and spinal cord, which can be caused by various kinds of infection, autoimmunity, toxic metabolites, traumatic brain injury, and viruses, etc. This inflammation is mediated by the production of chemokines, cytokines, secondary messengers, and reactive oxygen species.[5] The microglia, the resident innate immune cells from the central nervous system (CNS) are activated in response to these signals. The activated microglia produces numerous cytokine and inflammatory mediators, including tumour necrosis factor alpha (TNF-α), chemokine (C-C motif) ligand 2 (CCL-2), and interleukin 6 (IL-6). There are numerous diseases related to neurological disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), Multiple Sclerosis (MS) associated with neuroinflammation, which damage the brain cells (neurons) and get worse over time.[6] In the late stage of both these diseases, the neurodegeneration leads to the unadorned weakening in memory. Therefore, any efforts towards synthesizing of effective and safe treatments is worth. In this connection we became interested in the synthesis decalin based natural products scaffold.

1B.1.2 Reported Synthesis of Periconianone A

Gademann and co-workers in 2017 reported the first enantioselective total synthesis of periconianone A (**4**), in 17 steps by employing Rh-mediated O−H insertion followed by a spontaneous Claisen reaction and an α-ketol rearrangement (Scheme 1). The total synthesis starts with known γ-hydroxycarvone **7** [which is prepared from the (*R*)-carvone in two steps], which on TBS protection using TBSCl in DCM gave silyl ether **8**.[7] Conjugate addition reaction was carried on silyl ether **8** under CuI, LiCl condition using MeMgBr along with the trapping of the resulting enolate at −40 °C temperature to obtain TMS enol ether **9**. The product **9** was obtained with good diastereoselectivity (*dr* > 10:1) in quantitative yield.[8] TMS enol ether **9** on Lewis's acid-catalyzed Michael addition to methyl vinyl ketone (**10)** under BF_3•OEt_2, *i*-PrOH condition afforded diketone compound **11** with 66% yield.[9] The isopropenyl group from compound **11** was removed via ozonolysis of terminal double bond followed by

treatment with $Cu(OAc)_2$, $FeSO_4$ to form enone **12** in 67% yield.[10] Compound **12** on double bond reduction with H_2, Pd/C in ethyl acetate followed by intramolecular aldol condensation reaction with NaOMe in MeOH furnished decalin compound **13**. Octalone **13** on reaction with the trifluoroethyl trifluoroacetate in LHMDS afforded trifluoro acylated intermediate, which on diazotization reaction by using mesyl azide and Et_3N provided the diazoketone **14** (61%, two steps).[11] The obtained diazoketone **14** on the reaction with the alcohol **15** in the presence of $Rh_2(OAc)_4$ yielded *α*-allylated *α*-hydroxyketone **16** with 60% yield, which on conjugation driven *α*-ketol rearrangement with $Ca(OMe)_2$ gave the desired compound **17**.[12] The removal of TBS group from compound **17** followed by the oxidation of secondary hydroxy group using Dess-Martin periodinane (DMP) afforded compound **18**. Ozonolysis of terminal olefin in compound **18** gave the well structured key intermediate aldehyde **19** for the aldol rection.



Scheme 1. Total Synthesis of Periconianone A

Aldehyde **19** on treatment with diphenyl phosphate in toluene at 65 °C afforded the tricyclic core **20** of the natural product in 71% yield. Which on α-selenylation using phenylselenyl chloride, LHMDS in THF and the $NaIO_4$ oxidation gave periconianone A (**4**) with 45% yield.[13,14] The key element of the synthetic route is the removal of isopropenyl group which is also a directing group for stereoselective synthesis.

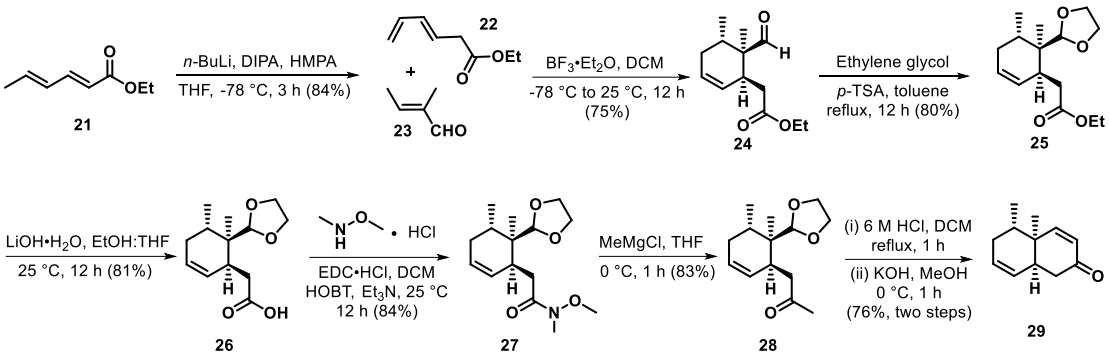
1B.2 Result and Discussion (Present Research Work)

Based on the interesting structural features and biological activity of the periconianone A and neural anti-inflammatory activity; we become interested in the synthesis of several related compounds and testing of their biological activity with keeping following objectives in mind.

- Total synthesis of the natural product and related analogs in sufficient quantity for the further biological activity studies.
- Biological evaluation of the synthesized compounds to identify the superior bioactive compound.

1B.2.1 Gram Scale Synthesis of Enone

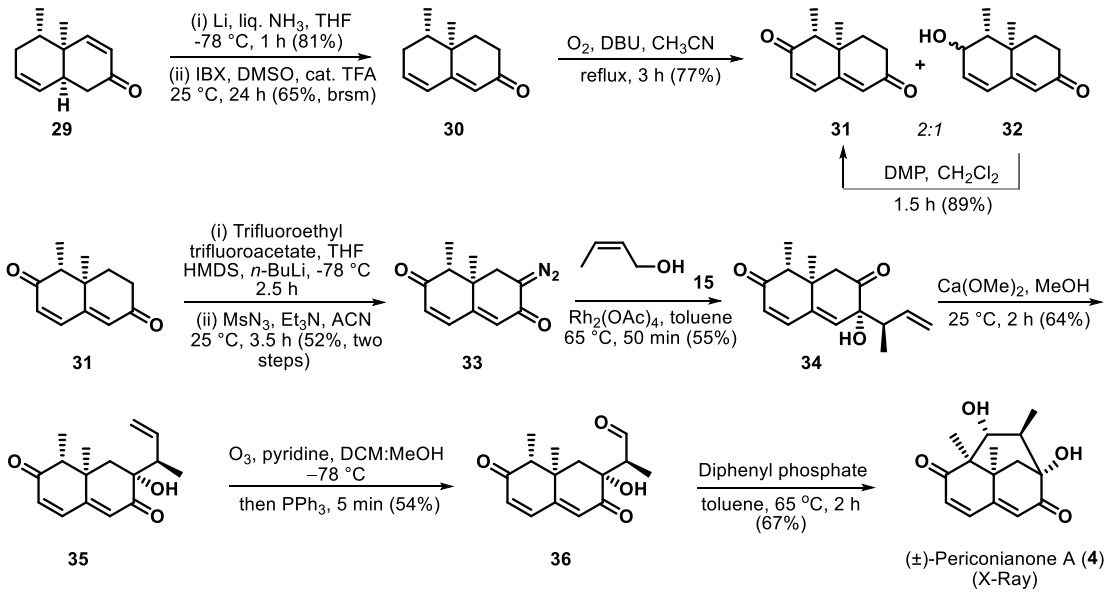
The synthesis of periconianone A starts with gram scale synthesis of decalin intermediate using well optimised strategy in our laboratory (Scheme 2).[15] Synthesis started with the deconjugation of double bound in the commercially available ethyl sorbate (**21**) by in situ generation of LDA using DIPA, *n*-BuLi, HMPA in THF at -78 °C to generate compound **22**. The classical Diels-Alder reaction was carried out in between deconjugated ethyl sorbate (**22**) and tiglic aldehyde (**23**) in the presence of BF_3•Et_2O in DCM at -78 °C to 25 °C to furnish compound **24** with 75% yield.[16] The acetal protection of the aldehyde **24** was carried out by using ethylene glycol, *p*-TSA in toluene to afford compound **25**, which on ester hydrolysis under basic condition, LiOH, EtOH:THF at 25 °C resulted in acid **26** with 81% yield.[15] Compound **26** on treatment with the methoxymethyl amine in EDC•HCl, HOBT, Et_3N resulted in the formation of Weinreb amide **27**.[17] Amide **27** was converted into the ketone **28** using methyl magnesium chloride. Acetal deprotection in acidic condition using 6M HCl generated aldehyde intermediate, which on intramolecular aldol condensation resulted in the required decalin compound **29** (76%, two steps). Thus starting from ethyl sorbate (**21**), the desired decalin product **29** was obtained in eight steps with 22% overall yield.[18]



Scheme 2. Synthesis of Key Intermediate Enone

1B.2.2 Synthesis of (±)-Periconianone A

Synthesis of the targeted compound began with the reduction of conjugated enone double bond in compound **29** using Birch reduction condition Li, liq. NH_3, in THF at -78 °C, which on regeneration of double bond using IBX oxidation gave the compound **30** bearing the extension of conjugation (Scheme 3). Towards the introduction of additional oxygen functionality on decalin moiety **30**, various conditions such as [NMM, ACN, 80 °C, 12 h; DIPEA, ACN, 80 °C, 12 h; DABCO, ACN, 80 °C, 12 h; PDC/TBHP, benzene, 25 °C, 16 h; $Pd(OH)_2$/TBHP(5 eq.), DCM, 25 °C, 12 h] were screened to get the dienone **31**, but with poor yields. Better yields were obtained by using a simple DBU/O_2 condition with a clean reaction profile.[19] We also isolated allylic alcohol **32** as a minor product from this reaction, which was then converted to the desired enone **31** using DMP.



Scheme 3. Total Synthesis of (±)-Periconianone A

This seems to be an interesting method for allylic oxidation of dienone system. Although there was one related reaction (along with double bond migration) documented in the literature, it need to be studied systematically. Currently, we are exploring the scope of the allylic oxidation of dienone moieties. Compound **31** was then transformed to the corresponding diazoketone **33** using standard procedure in 52% yield over two steps.[20] Here, we followed the protocol developed by Gademann's group to introduce side chain in highly stereoselective manner. The diazoketone **33** upon reaction with *cis*-crotyl alcohol **15** and dirhodium tetraacetate in toluene gave compound **34**, which on α-ketol rearrangement using calcium methoxide in methanol resulted in compound **35** as a major diastereomer. This observation is very similar to that of Gademann's observation.[21] Considering the presence of two additional double bonds in the molecule, ozonolysis was carried out in presence of pyridine in CH_2Cl_2:MeOH mixture for very short time (~ 5 min) followed by quenching with PPh_3 furnished desired aldehyde **36**, setting the stage for the key intramolecular aldol reaction. Our precursor of aldol reaction has flat structure than the one used in Gademann's synthetic sequence, and the same reaction went with ease in presence of diphenyl phosphate to afford the target tricyclic (±)-periconianone A (**4**) in 67% yield (Scheme 3).[21] All the obtained analytical and spectral data for product **4** were in complete agreement with the reported data. The obtained product structure was also further confirmed by single crystal x-ray structure (Figure 2). Overall, starting from decalin **29**, (±)-periconianone A (**4**) was obtained in nine steps with 2.7% overall yield.

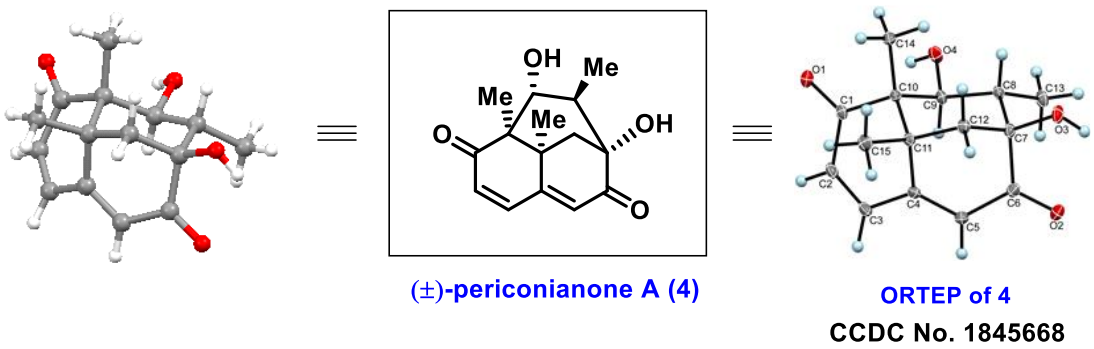


Figure 2. X-Ray Crystal Structure of (±)-Periconianone A.

1B.2.3 Biological Evaluation

The natural product (±)-periconianone A (**4**) (NDS-101501) along with the two analogs compound **34** (NDS-101503) and **35** (NDS-101502) were screened for their

neural anti-inflammatory potential in the presence of LPS-induced inflammation on N9 cells of the microglia in the mouse. In the neural inflammation large amount of pro-inflammatory cytokine and inflammatory mediators such as TNF-α, CCL-2, and IL-6 were released.[22] During the inflammatory process, large quantities of the inflammatory mediators were produced by the inducible isoforms of iNOS and COX-2, along with this body which can also release large quantity of NO which amplify inflammatory response to multiple fold.[23] Accordingly, all the compounds were evaluated for there neural anti-inflammatory activity against TNF-α, CCL-2, IL-6 in Dr. Anirban Basu's laboratory at National Brain Research Centre Gurugram (NBRC), Haryana, India. They have also checked the cytotoxicity of these compounds on N9 cells by taking the concentration range from 0-100 μM.

Structure-Activity Relationships (SAR):

First, MTT assay was performed on all three compounds and the cytotoxicity was measured. None of the compound showed any cytotoxicity on N9 cell till 40 μM of concentration (Figure 3A). Then, the anti-inflammatory potency of compounds **4** (NDS-101501), **34** (NDS-101503) and **35** (NDS-101502) was determined by measuring the level of intracellular reactive oxygen species (ROS) in LPS treated N9 cells. The ROS generation is a key marker for inflammation and is reported in several cases as a triggering factor for apoptosis.[24] As depicted in figure 3B, increase of ROS in LPS treatment was reduced dramatically in presence of **35** (NDS-101502) as analyzed by mean fluorescence intensity (MFI).

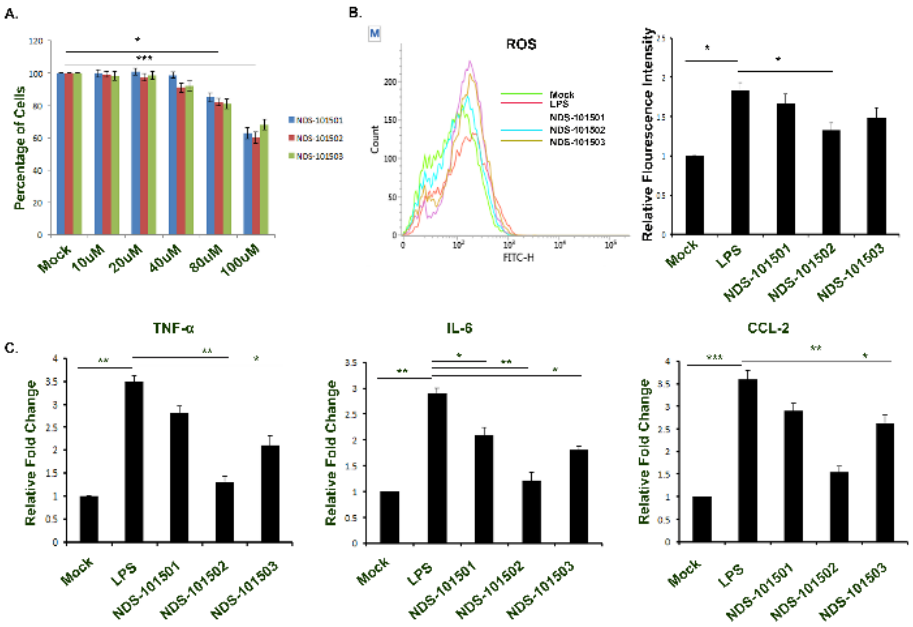


Figure 3. Anti-inflammatory activity of **4** (NDS-101501), **34** (NDS-101503) and **35** (NDS-101502): [A] MTS assay to determine the cytotoxic concentration of compounds in N9 cells, [B] FACS analysis for ROS production in LPS stimulated N9 cells, [C] Measurement of selected cytokine (TNF-α, IL-6 and CCL-2) levels. *p < 0.05, **p < 0.01, ***p<0.001].

Under the pathogenic attack in CNS, the activated microglia release numerous pro-inflammatory cytokine and inflammatory mediators. Hence, the microglia cell line provides an excellent model for compounds screening and the evaluation of potential inhibitors of the inflammatory response. LPS treatment can induce inflammation, resulting in the extreme production of numerous pro-inflammatory mediators including TNF-α, CCL-2 and IL-6.[22] Our data shows although all three compounds were effective in decreasing cytokine level in LPS stimulated N9 cells, compound **17** (NDS-101502) was the most effective one (Figure 3C).

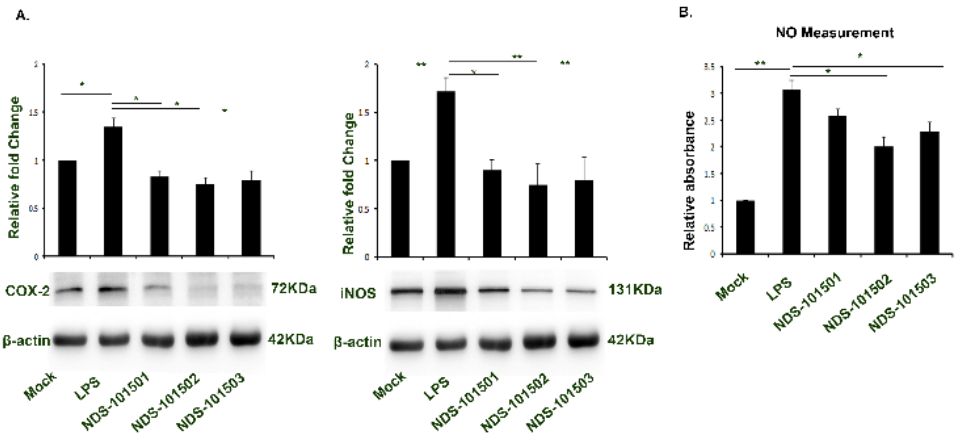


Figure 4. Anti-inflammatory activity of **4** (NDS-101501), **34** (NDS-101503) and **35** (NDS-101502) through NO production: [A] iNOS and COX-2 level were measured after 24 hours of LPS stimulation in N9 cells. β-actin was used as loading control. [B] NO production was measured using Griess reagent. Data was validated with three independent experiments. *p < 0.05, **p < 0.01].

Inflammation is the body's first response of the immune system to infection or irritation. During the inflammatory process, large quantities of the inflammatory mediators are produced by the inducible isoforms of iNOS and COX-2. Thus, we checked the levels of iNOS and COX-2 by immunoblotting in response to drugs treatment in LPS administered cells.[23] We found that all three selected compounds are

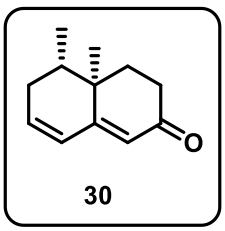
efficient in reducing iNOS and COX-2 levels compared to LPS (Figure 4A) at 25μM. Then, all the compounds were evaluated for their inhibition of NO production in LPS stimulated N9 cells and nitrite levels, a strong metabolite of NO, were measured in culture media using nitric oxide colorimetric assay kit. During inflammation, a large quantity of NO is produced and in turn amplifies inflammatory response to multiple folds. The primary results indicated that compound **35** (NDS-101502) was more effective in decreasing NO level in LPS treated cell (Figure 4B) which is a simplified analog of tricyclic periconianone A.

1B.3 Summary

In summary, we have accomplished the total synthesis of (±)-periconianone A using the Diels-Alder/aldol chemistry developed for the construction of decalin skeleton in our lab and the chemistry developed by Gademann's group. The synthesized (±)-periconianone A and its two analogs were tested for their neuroanti-inflammatory activity using various assays and markers. Based on the results, a close and simplified bicyclic analog of periconianone A seems to be superior with respect to its parent compound and warrants further investigation. During this project execution, we also discovered a mild method for allylic oxidation of dienones using DBU/O_2. Further scope of this method and SAR studies around periconianone A scaffold are the future directions of this project.

1B.4 Experimental Section

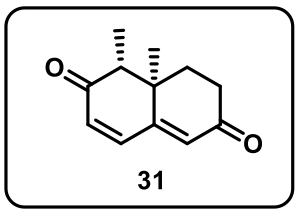
(4a*R*,5*S*)-4a,5-Dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (30). A solution of α,β-unsaturated ketone **29** (4.4 g, 25 mmol) in THF (60 mL) was added to liquid ammonia (120 mL) at –78 °C. Lithium (2.1 g, 300 mmol) was added in small pieces and reaction mixture was stirred at –78 °C for 1 h. After consumption of starting material (by TLC), solid NH_4Cl (3.0 g) was added and ammonia was allowed to evaporate at room temperature. Water (30 mL) was added and reaction mixture was extracted with EtOAc (2 × 60 mL). Combined organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford intermediate ketone (3.6 g, 81%) which was treated with IBX (17 g, 60 mmol) in DMSO (80 mL) at room temperature and stirred for 24 h. After the completion (by TLC), the reaction mixture was quenched with saturated



30

aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with EtOAc (3 × 60 mL) and combined organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purified by column chromatography (silica gel 100-200, 1.0:9.0; ethyl acetate:petroleum ether as eluent) afforded **30** (2.3 g, 65%) as colorless oil. **^{1}H NMR ($CDCl_3$, 400 MHz) δ** 6.26–6.16 (m, 1 H), 6.15–6.06 (m, 1 H), 5.66 (s, 1 H), 2.59–2.49 (m, 1 H), 2.45–2.38 (m, 1 H), 2.24 –2.16 (m, 1 H), 2.11–1.99 (m, 2 H), 1.75–1.65 (m, 2 H), 1.01 (s, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ** 199.7, 163.6, 138.2, 128.1, 123.5, 38.0, 36.1, 34.0, 33.8, 32.4, 14.9, 14.3; **HRMS (ESI) *m*/*z*** $[M+H]^+$ calcd for $C_{12}H_{17}O$ 177.1274, found 177.1273; **IR ($CHCl_3$) ν_{max}** 2978, 1671 cm^{-1}.

(1*R*,8a*R*)-1,8a-Dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (31). To a stirred solution of **30** (0.530 g, 3.007 mmol) in dry acetonitrile (12 mL) oxygen gas was bubbled for a period of 30 min at rt. DBU (1.13 mL, 7.52 mmol) was added dropwise and the reaction mixture was refluxed for a period of 3.5 h under O_2 atmosphere. The reaction mass was diluted with ice cold water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated to give crude product. Which was purified by column chromatography (17:83; ethyl acetate-petroleum ether) to obtain **31** (0.297 g, 52%) as an off white solid. Alcohol (**32**) was obtained at eluent system (28:72; ethyl acetate:petroleum ether) as yellowish oily liquid (0.148 g, 25%). The obtained ratio of **31**:**32** was 2:1.



31

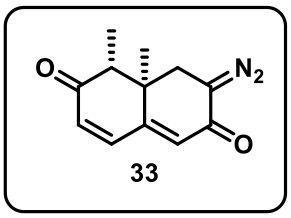
Data for **31**: Off white solid. **Mp** 108–110 °C; **^{1}H NMR ($CDCl_3$, 400 MHz) δ** 7.00 (d, *J* = 9.2 Hz, 1 H), 6.23 (d, *J* = 9.2 Hz, 1 H), 6.05 (br. s., 1 H), 2.62–2.50 (m, 3 H), 2.19–2.10 (m, 1 H), 2.06–1.97 (m, 1 H), 1.16 (br. s., 6 H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ** 199.8, 198.6, 159.2, 142.2, 132.1, 129.0, 52.0, 39.8, 34.2, 33.3, 18.1, 6.9; **HRMS (ESI) *m*/*z*** $[M+H]^+$ calcd for $C_{12}H_{15}O_2$ 191.1067, found 191.1064; **IR ($CHCl_3$) ν_{max}** 1655, 1607, 1574, 755 cm^{-1}.

(4a*R*,5*R*)-6-Hydroxy-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (32). Yellowish oily liquid; **^{1}H NMR ($CDCl_3$, 400 MHz) δ** 6.19–6.13 (m, 2H), 5.76 (s, 1H), 4.07 (d, *J* = 9.6 Hz, 1H), 2.55–2.49 (m, 1H), 2.44 (dd, *J* = 5.4, 2.1 Hz, 1H), 2.05 (ddd, *J* = 13.2, 5.3, 2.2 Hz, 1H), 1.80 – 1.72 (m, 2H), 1.56–1.52 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ** 199.6, 162.1, 140.2,

128.4, 124.8, 71.3, 47.6, 37.4, 33.8, 33.2, 16.3, 10.4; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{12}H_{17}O_2$ 193.1223, found 193.1220; **IR ($CHCl_3$)** ν_{max} 3048, 1655, 1607, 1574, 890 cm^{-1}.

Experimental procedure for oxidation of 32 to 31: $NaHCO_3$ (1.9 g, 22.6 mmol) and Dess-Martin periodinane (2.4 g, 5.65 mmol) were added sequentially to a solution of **32** (0.543 g, 2.82 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the mixture was stirred for 1.5 h at this temperature. The mixture was diluted with CH_2Cl_2 and sat. aq. $Na_2S_2O_3$ solution was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (17:83; ethyl acetate:petroleum ether) to obtained **31** (0.478 g, 89%) as an off white solid.

(1*R*,8a*R*)-7-Diazo-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (33).



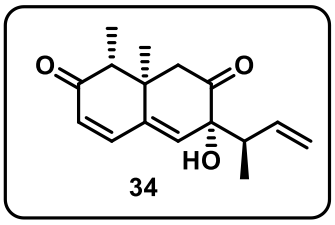
33

To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (0.922 mL, 8.04 mmol) in 36 mL of THF and then cooled at 0 °C in an ice-water bath while *n*-butyllithium solution (1.6 M in *n*-hexane, 5.1 mL, 8.04 mmol) was added rapidly over 1 min. After 10 min, the resulting solution was cooled at –78 °C in a dry ice-acetone bath while a solution of **31** (1.39 g, 7.31 mmol) in 24 mL of THF was added dropwise over 15 min *via* syringe. The resulting yellow solution was stirred for 30 min at –78 °C and then 2,2,2-trifluoroethyl trifluoroacetate (1.3 mL, 9.50 mmol) was added rapidly by syringe in one portion. The mixture was stirred for 90 min at –78 °C and then quenched by addition of sat. aq. NH_4Cl solution and diluted with EtOAc. The layers were separated and the aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated to give crude trifluoro methylated compound (2.6 g, quant.) as a yellowish oil.

Crude trifluoro methylated compound (2.6 g, 12.02 mmol) was dissolved in MeCN (40 mL). NEt_3 (5.1 mL, 36.1 mmol) was added, followed by dropwise addition of a solution of MsN_3 (4.1 mL, 48.1 mmol) over a period of 15 min. The yellow mixture was stirred for 3.5 h at rt, before it was diluted with EtOAc and washed with 1.0 M aq. NaOH solution. After separation, the aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layer was washed with water, dried over Na_2SO_4,

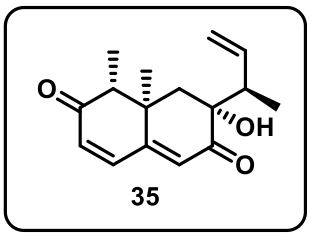
filtered and concentrated. The residue was purified by flash column chromatography (17:83; EtOAc:petroleum ether) to give **33** (1.02 g, 52% over two steps) as a pale-yellow solid. **Mp** 118–120 °C; **^{1}H NMR ($CDCl_3$, 400 MHz) δ** 7.01 (d, *J* = 9.8 Hz, 1 H), 6.27–6.14 (m, 2 H), 3.02 (d, *J* = 13.4 Hz, 1 H), 2.75 (d, *J* = 13.4 Hz, 1 H), 2.60 (q, *J* = 6.3 Hz, 1 H), 1.18 (d, *J* = 6.7 Hz, 3 H), 1.13 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ** 198.8, 182.5, 153.8, 141.9, 131.1, 130.0, 60.9, 50.8, 39.1, 33.5, 19.3, 7.1; **HRMS (ESI) *m/z*** $[M+Na]^+$ calcd for $C_{12}H_{12}O_2N_2Na$ 239.0791, found 239.0787; **IR ($CHCl_3$) ν_{max}** 2089, 1668, 1616, 834 cm^{-1}.

(3*R*,8*R*,8a*R*)-3-((*R*)-But-3-en-2-yl)-3-hydroxy-8,8a-dimethyl-8,8a-dihydro naphthalene-2,7(1*H*,3*H*)-dione (34). To a solution of rhodium acetate (0.036 g, 0.081 mmol) and *cis*-2-buten-1-ol **15** (3.34 g, 46.24 mmol) in toluene (10 mL) at 65 °C was added dropwise a solution of **33** (0.500 g, 2.31 mmol) in toluene (5 mL) over a period of 10 min and the mixture was stirred for an additional 40 min at this temperature. The solvent was evaporated and the residue purified by flash column chromatography (08:92; EtOAc:petroleum ether) to give **34** (0.331 g, 55%) as a yellowish oily liquid. **^{1}H NMR ($CDCl_3$, 500 MHz) δ** 6.93 (d, *J* = 9.9 Hz, 1 H), 6.04 (d, *J* = 9.9 Hz, 1 H), 5.94 (s, 1 H), 5.87–5.77 (m, 1 H), 5.21–5.08 (m, 2 H), 3.62 (s, 1 H), 2.91 (d, *J* = 12.2 Hz, 1 H), 2.77 (q, *J* = 6.5 Hz, 1 H), 2.61 (d, *J* = 12.2 Hz, 1 H), 2.53 (td, *J* = 7.1, 14.9 Hz, 1 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 1.02–0.95 (m, 6 H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ** 210.0, 198.6, 143.3, 141.0, 137.7, 134.3, 127.8, 117.5, 78.2, 51.5, 48.8, 48.5, 46.1, 20.4, 14.9, 7.1; **HRMS (ESI) *m/z*** $[M+Na]^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1305, found 283.1298; **IR ($CHCl_3$) ν_{max}** 3478, 1718, 1675, 1632, 1590, 665 cm^{-1}.



34

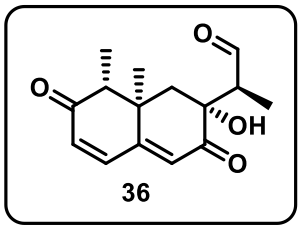
(1*R*,7*R*,8a*R*)-7-((*R*)-But-3-en-2-yl)-7-hydroxy-1,8a-dimethyl-1,7,8,8a-tetrahydro naphthalene-2,6-dione (35). A solution of **34** (0.140 g, 0.540 mmol) and $Ca(OMe)_2$ (0.165 g, 1.61 mmol) in MeOH (15 mL) was stirred for 2 h at 25 °C sat. aq. NH_4Cl solution was added slowly and the mixture was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (09:91; EtOAc:petroleum ether) to give **35** (0.084 g, 64%) as off-



35

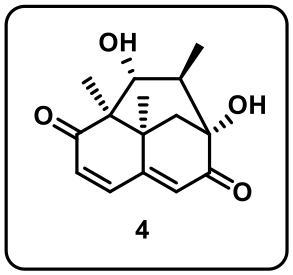
white solid. **Mp** 128-130 °C; **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.04 (d, *J* = 9.9 Hz, 1 H), 6.26 (d, *J* = 9.9 Hz, 1 H), 6.18 (s, 1 H), 5.93 (ddd, *J* = 7.6, 10.3, 17.2 Hz, 1 H), 5.26–5.11 (m, 2 H), 3.49 (q, *J* = 7.1 Hz, 1 H), 2.76 (quin, *J* = 6.9 Hz, 1 H), 2.61 (q, *J* = 6.4 Hz, 1 H), 2.33 (s, 1 H), 2.01 (s, 1 H), 1.26 (s, 3 H), 1.18 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.1 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 200.1, 199.7, 160.5, 141.7, 137.6, 132.4, 127.9, 117.5, 75.5, 52.2, 45.9, 40.3, 39.5, 22.8, 14.6, 7.3 **HRMS (ESI)** ***m/z*** $[M+Na]^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1305, found 283.1303; **IR ($CHCl_3$)** ν_{max} 3412, 1720, 1666, 721cm^{-1}.

(*S*)-2-((2*R*,8*R*,8a*R*)-2-Hydroxy-8,8a-dimethyl-3,7-dioxo-1,2,3,7,8,8a-hexahydro naphthalen-2-yl)propanal (36). A solution of **35** (0.073 g, 0.280 mmol), pyridine (0.0904 mL, 1.12 mmol) in CH_2Cl_2/MeOH (7 mL, 1:1) was cooled to –78 °C and ozone was bubbled through the solution until the yellow color disappeared (4-5 min). The reaction mixture was sequentially purged with oxygen and nitrogen. PPh_3 (0.147 g, 0.561 mmol) was added and the mixture was allowed to warm to rt. After stirring for 1 h, the solvent was removed by evaporation to afford crude product. Which was purified by column chromatography (17:83; ethyl acetate:petroleum ether) to obtain aldehyde **36** (0.040 g, 54%), as a light-yellow oil. Due to its unstable nature, it was used in the next step without further characterization.



36

(1*R*,7*R*,8a*S*,9*R*,10*R*)-7,10-Dihydroxy-1,8a,9-trimethyl-1,7,8,8a-tetrahydro-1,7-ethanonaphthalene-2,6-dione (4). To a stirred solution of aldehyde **36** (0.041 g, 0.16 mmol) in toluene (7 mL) was added diphenyl phosphate (0.020 g, 0.0781 mmol) and the mixture was heated at 65 °C for 2 h. After complete consumption of starting material checked by TLC, the yellow solution was partitioned between sat. aq. $NaHCO_3$ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography over silica gel (22:78; EtOAc:petroleum ether) afforded periconianone A, **4** (0.027 g, 67%) as a brown solid. **Mp** 174–176 °C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 7.30 (d, *J* = 9.5 Hz, 1 H), 6.15 (br. s., 1 H), 6.08 (d, *J* = 9.5 Hz, 1 H), 4.03 (br. s., 1 H), 3.54 (d, *J* = 9.9 Hz, 1 H), 2.22 (d, *J* = 13.7 Hz, 1 H), 1.94–1.85



4

(m, 2 H), 1.79 (br. s., 1 H), 1.30 (br. s., 3 H), 1.26 (br. s., 3 H), 0.93 (d, *J* = 5.3 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 200.6, 198.8, 162.5, 142.2, 129.9, 122.5, 75.8, 73.8, 55.7, 44.7, 44.6, 39.8, 24.4, 11.9, 7.9; **HRMS (ESI)** ***m/z*** $[M+Na]^+$ calcd for $C_{15}H_{18}O_4Na$ 285.1097, found 285.1093; **IR ($CHCl_3$)** ν_{max} 3413, 1665, 1610, 1570, 754 cm^{-1}.

Crystal data of (±)-periconianone A (4): X-ray intensity data measurements of **4** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus sealed tube diffraction source (Mo-Kα = 0.710 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from two sets of 20 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 40 seconds keeping the sample–to-detector distance fixed at 4.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. Molecular diagrams were generated using ORTEP-33 and Mercury programs. Geometrical calculations were performed using SHELXTL and PLATON. All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An ORTEP III view of both compounds were drawn with 50% probability displacement ellipsoids and H–atoms are shown as small spheres of arbitrary radii. Crystallographic data for intermediate ($C_{15}H_{18}O_4$): M = 262.29, Crystal dimensions 0.21 x 0.13 x 0.08 mm^3, monoclinic, space group *P*21/c, a = 13.0416(7), b = 9.0841(5), c = 12.0489(7) Å, β = 117.269(2)°, V = 1268.81(12) $Å^3$, Z = 4, ρcalcd = 1.373 gcm^{-3}, μ (Mo-Kα) = 0.09 mm^{-1}, F(000) = 560, $2\theta_{max}$ = 30.6°, T = 100(2) K, 79055 reflections collected, 3887 unique reflections (Rint=0.0327), 3673 observed (I > 2σ (I)) reflections, multi-scan absorption correction, *T*min = 0.980, *T*max = 0.992, 177 refined parameters, No. of restraints 0, S = 0.98, R_1 = 0.0353, wR_2 = 0.0922 (all data R = 0.0370, wR_2= 0.0937), maximum and minimum residual electron densities; Δρmax = 0.47, Δρmin= -0.35 ($eÅ^{-3}$).

Crystallographic data for compound intermediate deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1845668.

```
Bond precision:  C-C = 0.0013 A          Wavelength=0.71073

Cell:           a=13.0416(7)    b=9.0841(5)         c=12.0489(7)
                alpha=90        beta=117.269(2)     gamma=90
Temperature:    100 K

                Calculated                Reported
Volume          1268.81(12)               1268.81(12)
Space group     P 21/c                    P 21/c
Hall group      -P 2ybc                   -P 2ybc
Moiety formula  C15 H18 O4                C15 H18 O4
Sum formula     C15 H18 O4                C15 H18 O4
Mr              262.29                    262.29
Dx,g cm-3       1.373                     1.373
Z               4                         4
Mu (mm-1)       0.099                     0.099
F000            560.0                     560.0
F000'           560.31
h,k,lmax        18,13,17                  18,12,17
Nref            3903                      3887
Tmin,Tmax       0.985,0.992               0.980,0.992
Tmin'           0.979

Correction method= # Reported T Limits: Tmin=0.980 Tmax=0.992
AbsCorr = MULTI-SCAN

Data completeness= 0.996          Theta(max)= 30.614

R(reflections)= 0.0353( 3673)     wR2(reflections)= 0.0937( 3887)

S = 0.975                 Npar= 177
```

Protocol for neural anti-inflammatory assay:

Cell culture and LPS treatment

Mouse microglial cell line N9 was a kind gift from Prof. Maria Pedroso de Lima, Center for Neuroscience and Cell Biology, University of Coimbra, Portugal. The cell lines were grown at 37 °C in Roswell Park Memorial Institute medium (RPMI-1640) supplemented with 10 % fetal bovine serum, 100 units/mL penicillin, and 100 µg/mL streptomycin. Cells were seeded in six well plate and after attaining subconfluency serum free RPMI was added followed by lipopolysaccharides (LPS, Sigma, USA) from *Salmonella enterica* treatment at 1 µg/mL concentration.

Cytotoxicity assay

Viability of cultured cells were determined by (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma) as described earlier.[25] N9 cells were seeded in triplicate at a density of 2×10^4 cells per well on a 96-well plate. After 12 h, cells were treated with varying concentrations (0-100 µM) of all the compounds in a serum free condition for another 24 h. MTT solution (0.5 mg/mL) was then added to each well and incubate for 4 h at 37°C. At the end of the incubation period, the medium was removed and the resulting purple formazan was solubilized with acidic isopropanol (0.1 N HCl in absolute isopropanol), and the absorbance was measured at 570 nm (Tecan infinite M200Pro, Switzerland).

Nitric oxide (NO) measurement

Nitrite, a stable oxidized product of NO, was measured in culture supernatant using Nitric Oxide Colorimetric Assay Kit (Biovision, a kind gift from Dr. Shiv Sharma). After overnight seeding in 96-well plate (2×10^4 cells/well), N9 cells were treated with LPS (Sigma, USA) at a concentration of 1µg/ml along with 25 µM of each compound (as determined from cytotoxicity assay) in serum-free culture for 24 h. Following treatment, media was collected and centrifuged at 2,000 rpm for 5 min to remove cellular debris. After collecting the supernatant sample was processed with the manufacturer's protocol. Briefly, nitrate reductase mixture and enzyme cofactor were mixed with sample and incubated for 1 h. Further, enhancer was added to each sample followed by addition of Griess reagent 1 and 2 and then incubated for 10 min in dark. After incubation, absorbance was measured at 560 nm (Tecan infinite M200Pro, Switzerland).

Reactive oxygen species (ROS) measurement

Intracellular ROS generation in control and treated cells was assessed using the cell permeable, non-polar H_2O_2 sensitive dye 5-(and-6)-chlromethyl-2′,7′-dichlorodihydrofluorescein diacetate (CM-H2DCFDA) (Sigma Aldrich, USA) as described previously.[22] The extent to which H_2O_2 is generated is defined as the extent of ROS generation. Briefly N9 cells were incubated with LPS at concentration of 1 µg/mL along with 25 µM of each compound in serum-free culture for 24 h. Upon treatment, the cells were further treated with H2DCFDA (5 µM) for 1 h at 37°C. Cells were washed twice with 1× PBS and fluorescent intensity of the cells was measured using BD FACS Verse and data was analyzed in FAC Suit software.

Immunoblotting

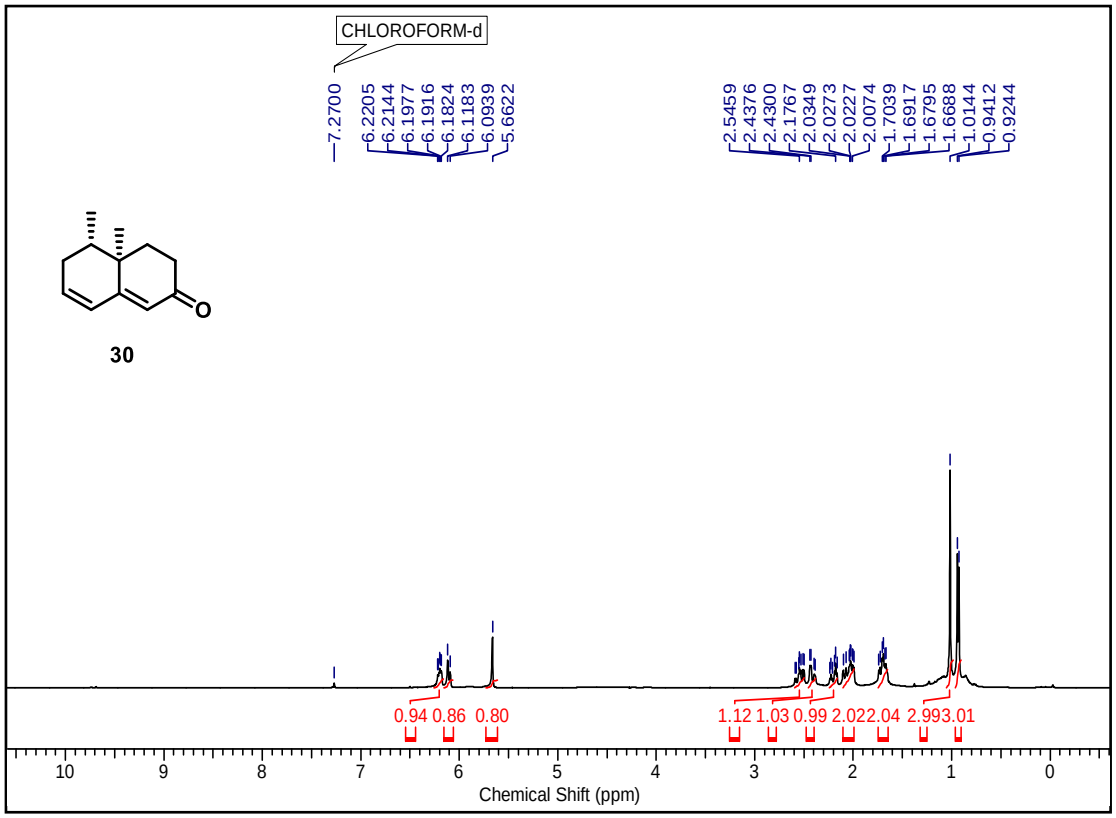
N9 cells were seeded in six well plate and then after 12 h it was changed to serum free media followed by LPS and drug treatment. After 24 h of treatment plates were washed with 1X PBS and then processed for protein isolation. Protein concentration was estimated by BCA method. For immunoblot, 20 µg protein of each sample was separated on (7-10%) polyacrylamide gels, electrophoresed, and transferred onto nitro cellulose membrane. After being blocked with 5% skimmed milk, the membranes were incubated with primary antibodies against COX-2 (1:1000; Santa Cruz, USA), iNOS (1:1000; Millipore, USA). After extensive washes with 0.1% PBS-Tween, blots were incubated with the Anti-Rabbit and Anti- mouse peroxidase-conjugated secondary antibodies (Vector Laboratories, USA). The blots were processed for development using chemiluminescence reagent (Millipore, USA). The images were captured and analysed using the Uvitech Cambridge using NineAlliance software (Uvitech, United Kingdom). β-actin antibody (1:10,000; Sigma, USA) was used as loading control.

Cytokine bead array

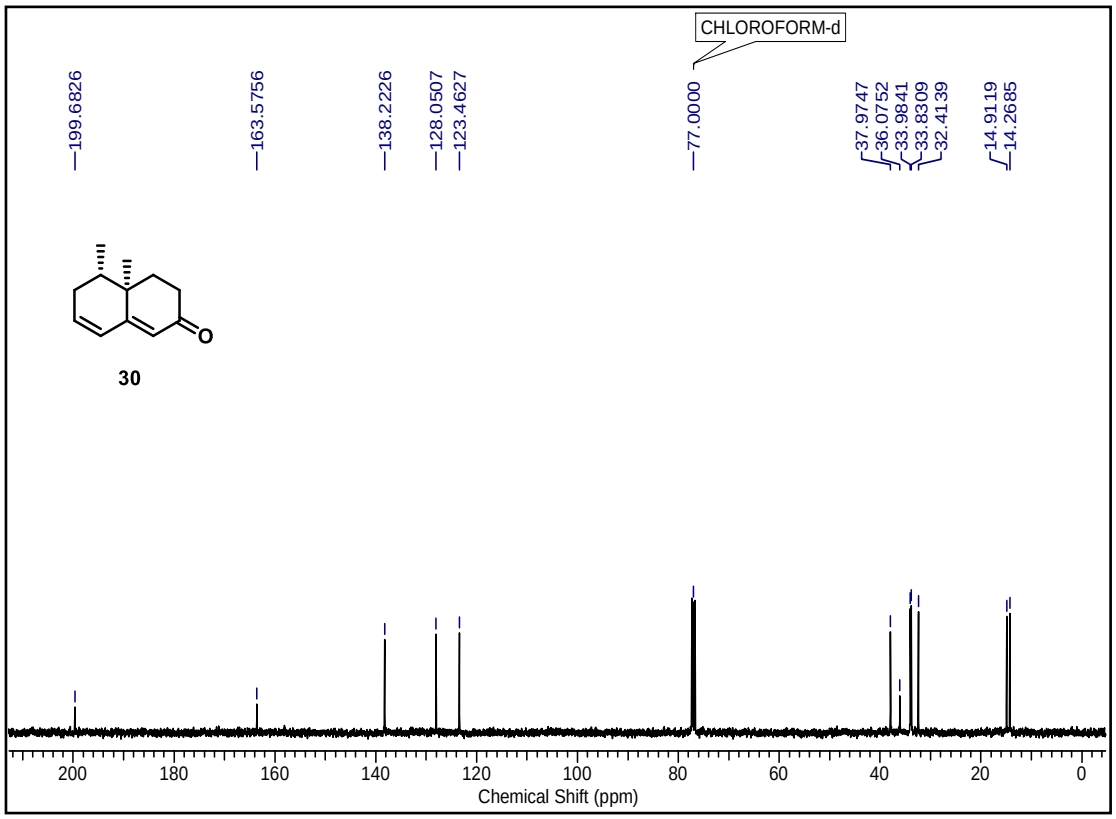
Cytokines level in LPS stimulated N9 cells were measured by the cytokine bead array (CBA) kit (BD Biosciences, NJ, USA). After overnight seeding of cells in 6-well plate, they were treated with LPS along with compounds for 24 h and then supernatant was collected. 30 µL of bead mix, containing a population of beads that have been coated with capture antibodies for cytokines, along with equal volume of PE-conjugated detection antibodies were incubated with 30 µL samples for 2 h at room temperature in dark and then the beads were acquired using FACSuit Software in FACS Verse as indicated earlier.[26]

1B.5 Selected Spectra

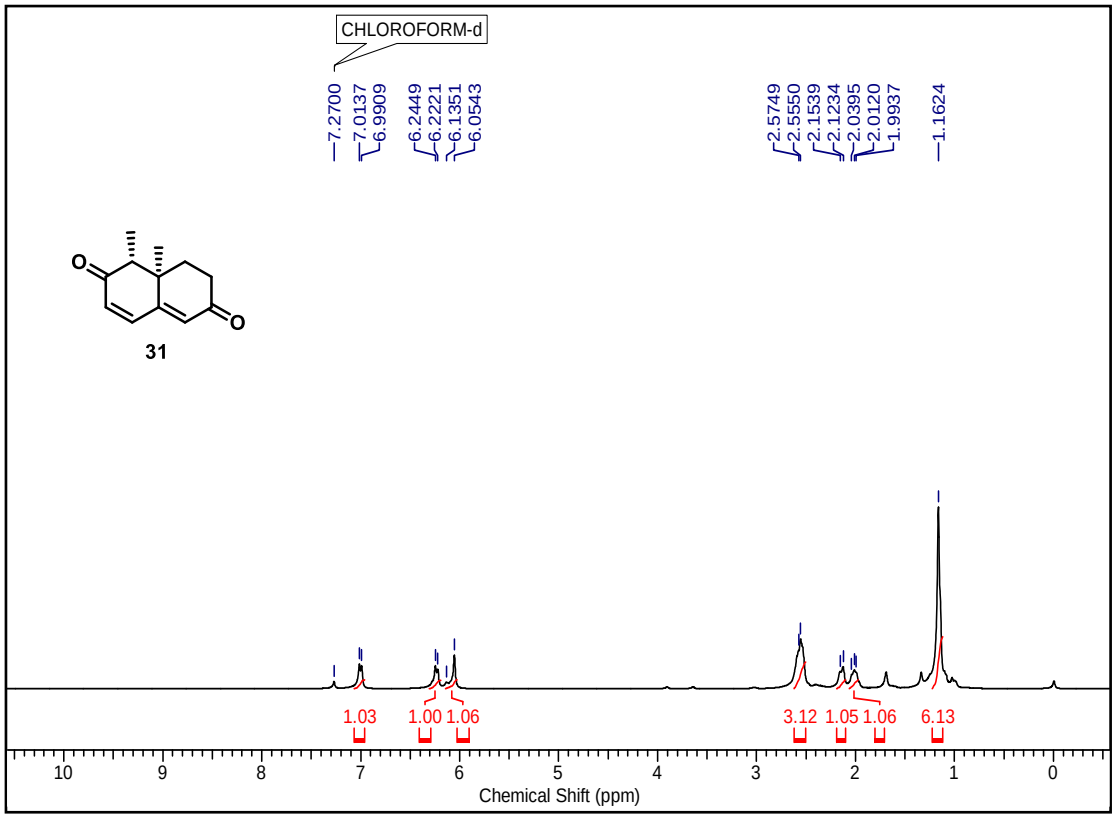
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 30



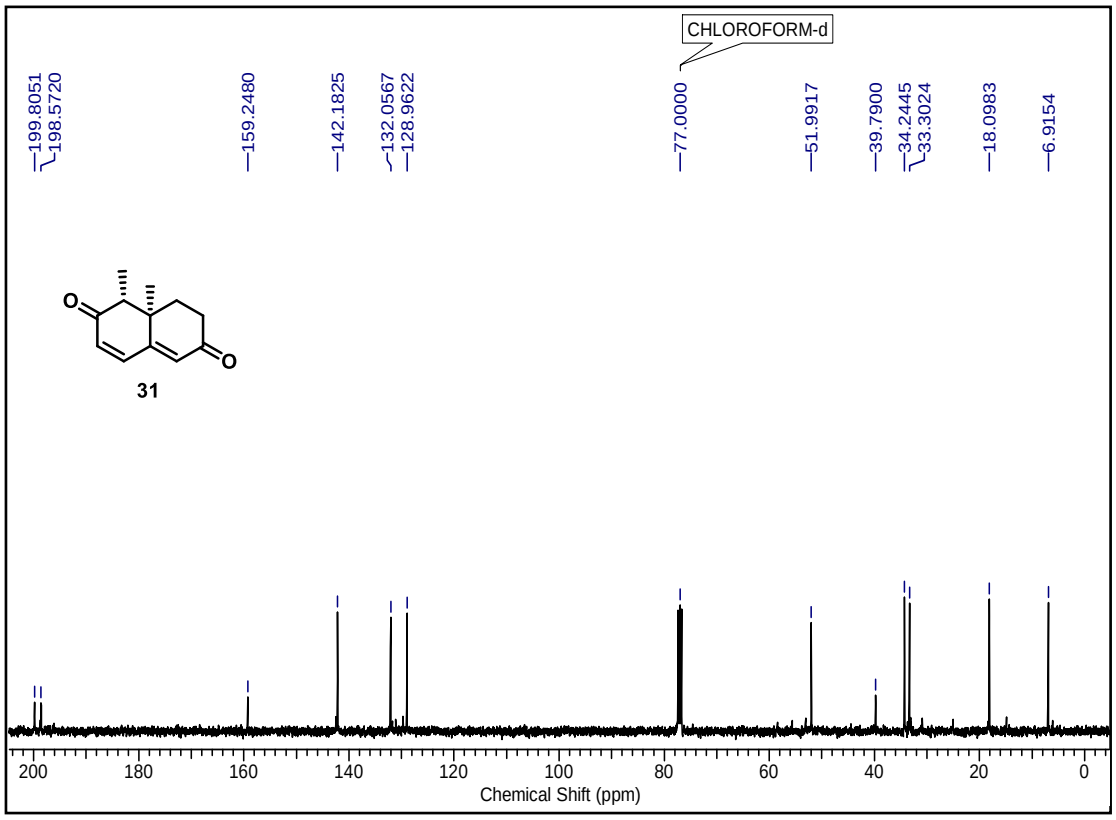
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 30



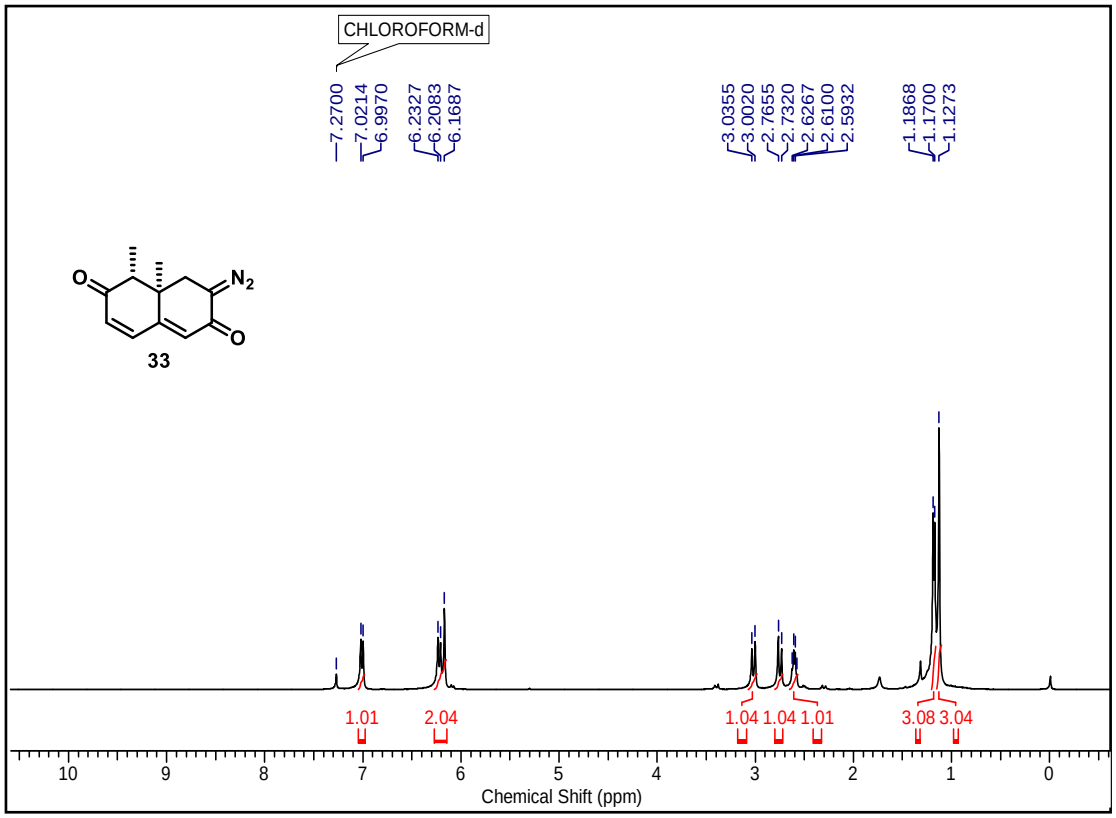
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 31



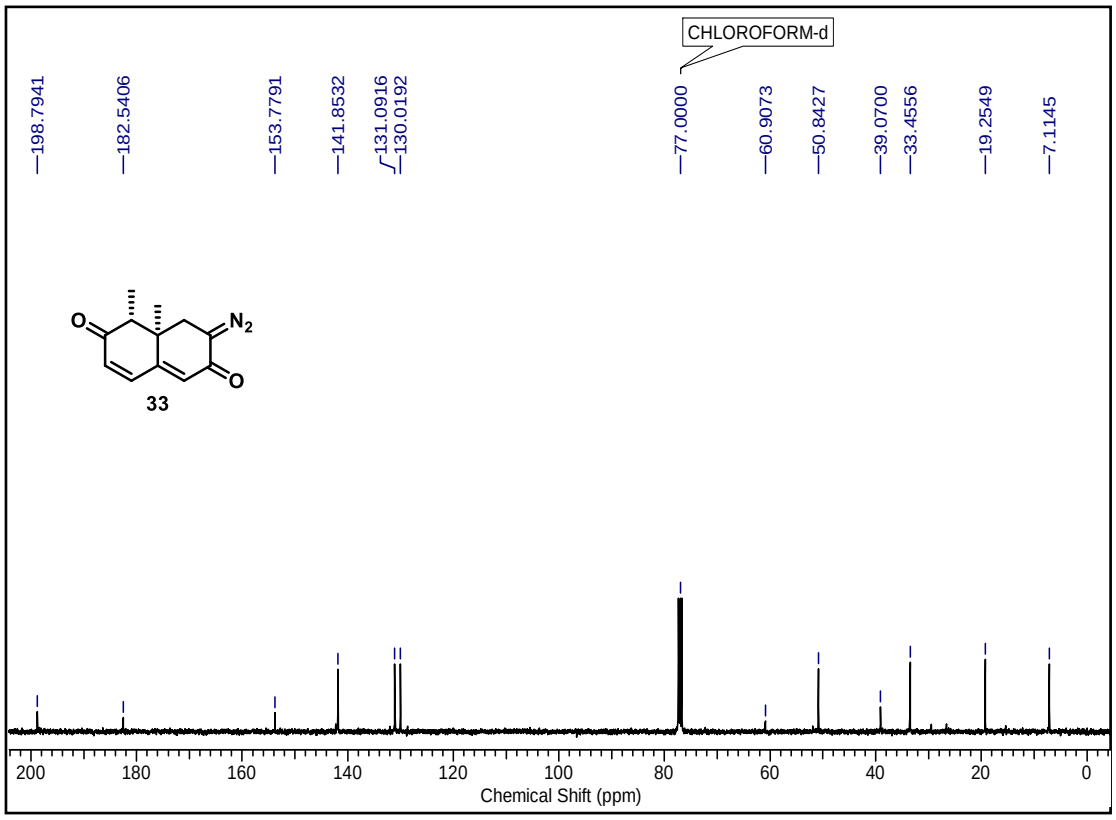
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 31



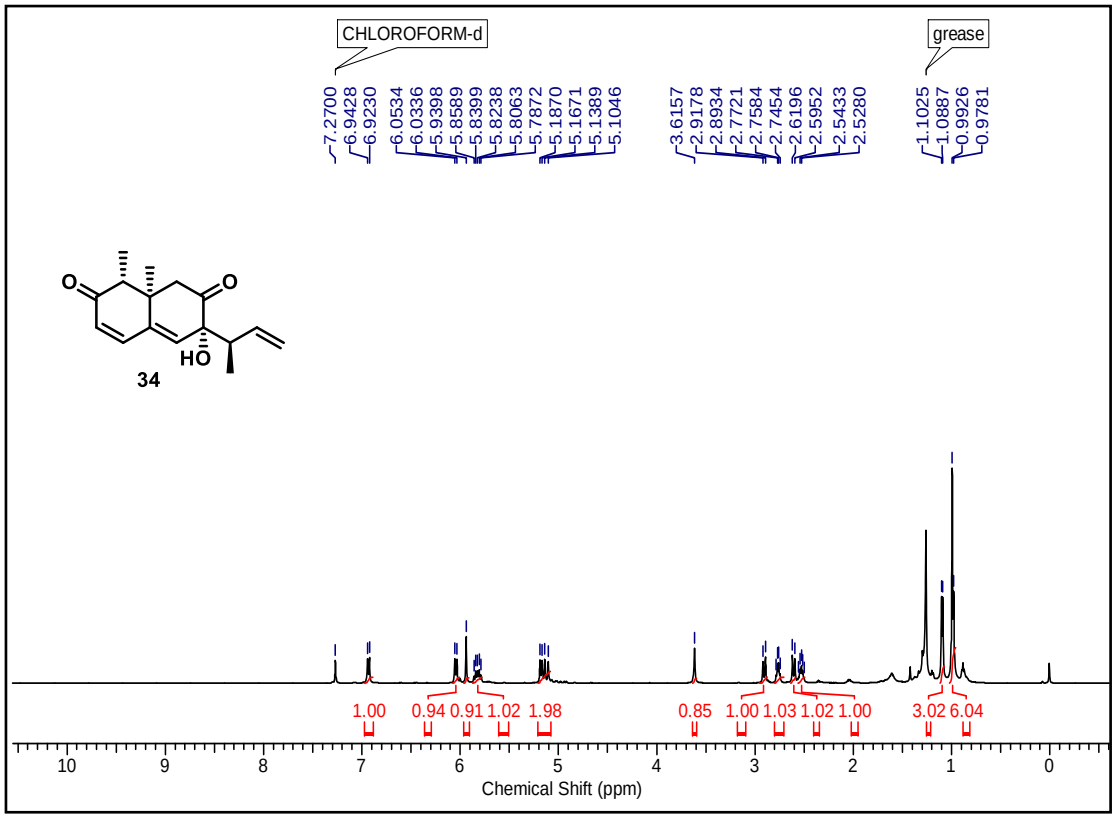
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 33



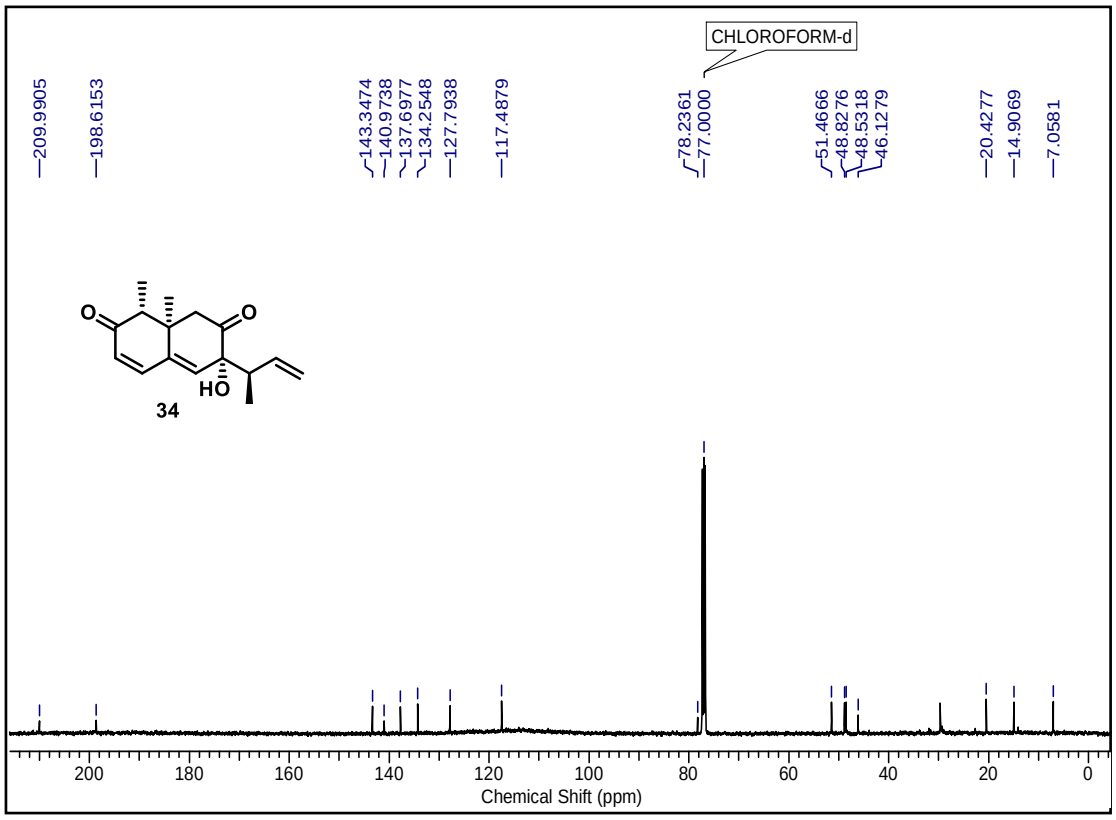
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 33



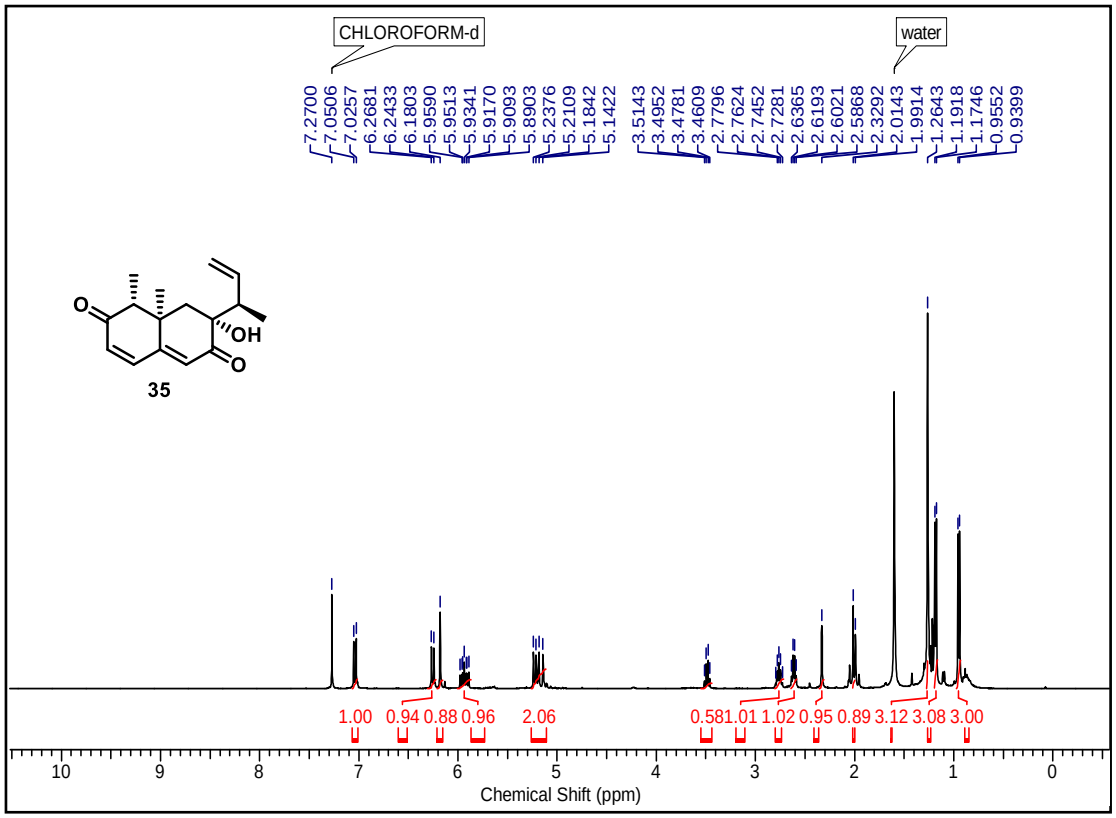
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 34



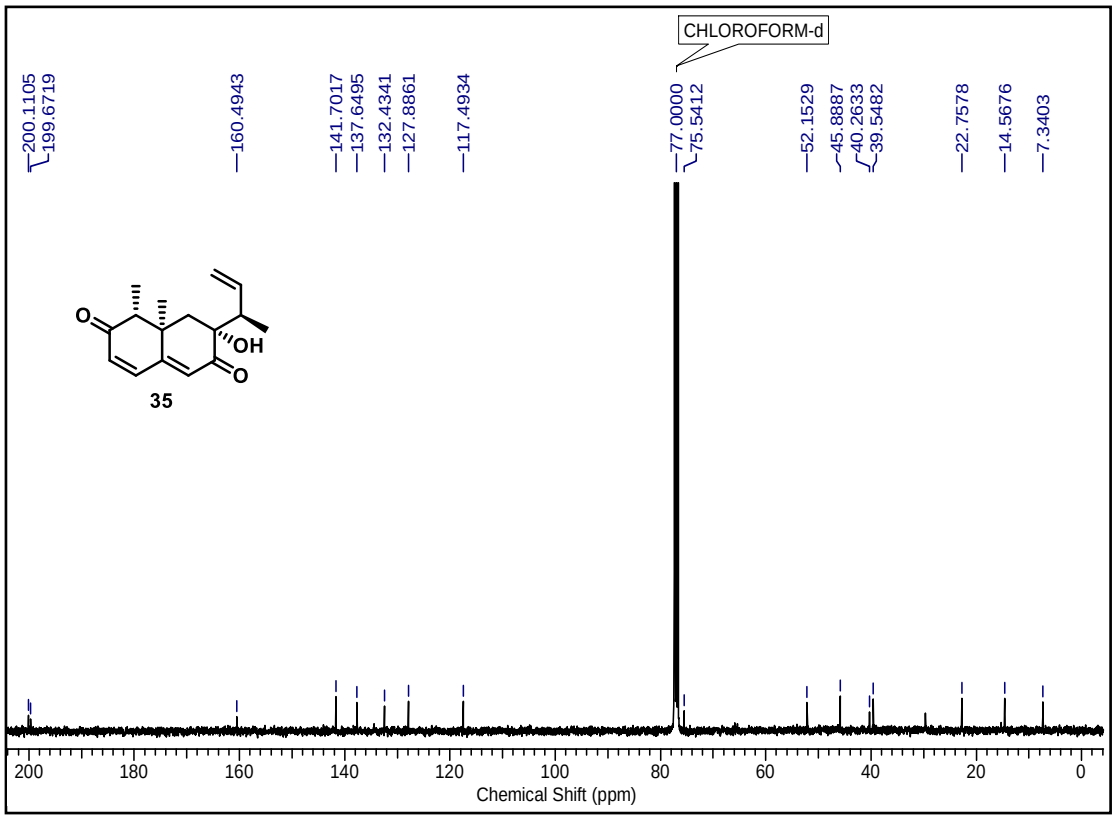
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 34



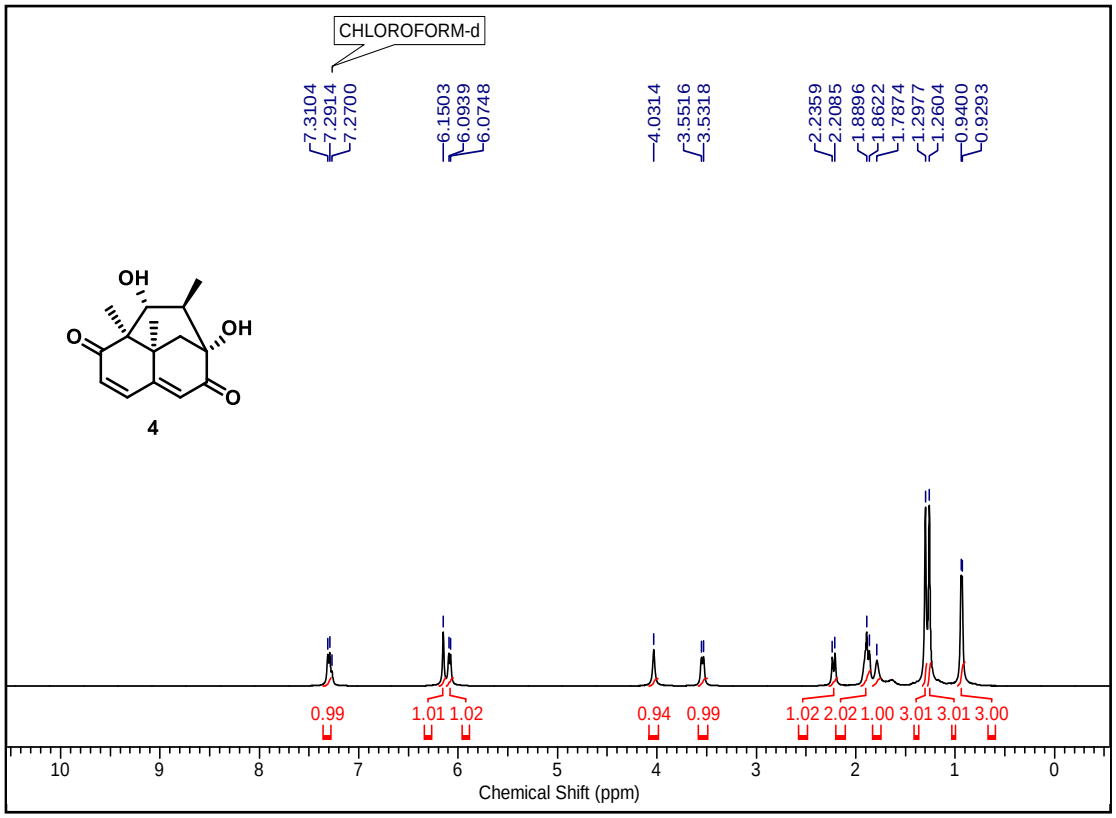
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 35



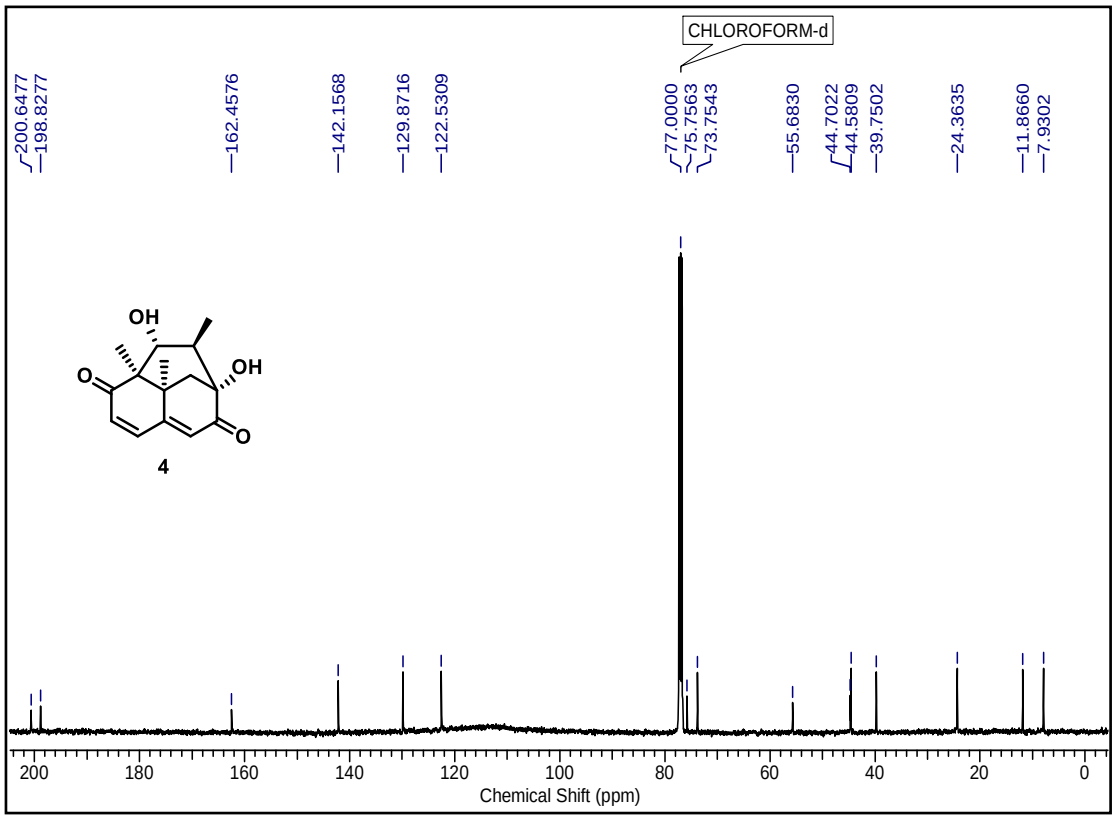
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 35



^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 4



^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 4



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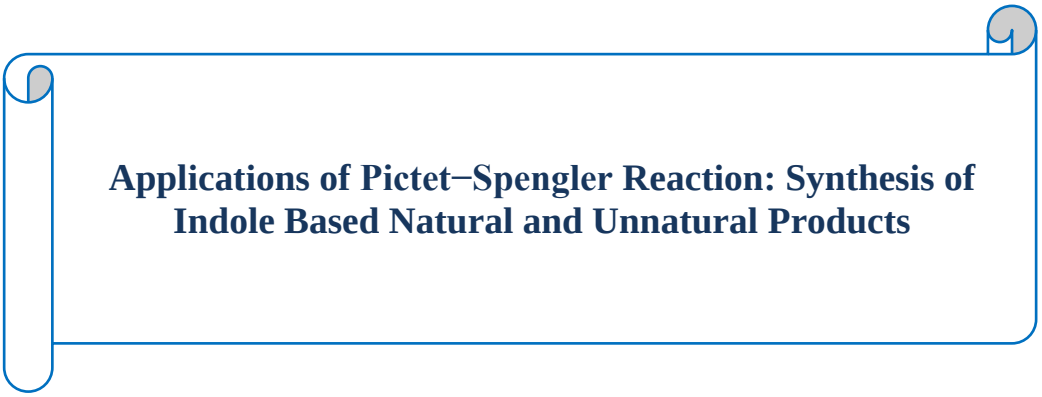
Chapter 2

Synthetic Studies on Biologically Active Indole Alkaloidal Natural Product and Related Analogs

Section A



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

This chapter is divided into three sections. In the first section, we have summarized the uses of Pictet−Spengler reaction in the synthesis of different natural products and related heterocyclic systems. In the second section, we have presented the total synthesis of azepino(1,2-*a*)tetrahydro-*β*-carboline carbon framework and the dibenzyl derivative of the natural product banistenoside B and their close analogs. In the third section, we have shown the concise size synthetic route for the the construction of pentacyclic core of reserpine. By using this strategy, we have synthesized 11 analogs of reserpine, which are included in third section. The detailed experimental procedures, complete tabulated analytical and spectral data, and selected NMR spectra have been appropriately included at the end of the section.

2A.1 Introduction

The importance of biologically active alkaloids is well known and they have been widely used in the folk medicine. Their importance in drug discovery programs is proven and hence their total synthesis is of significant interest.[1] Pictet−Spengler reaction is one of the most important, practical, and versatile method for the synthesis of novel indole-based heterocycles, natural products and drug molecules. Pictet−Spengler reaction is essential for two reasons: the first being nature uses the enzyme "Pictet Spenglerases" to develop important intermediates useful for biological pathways to natural products, such as strictosidine (**1**), reserpine (**2**), and several others.

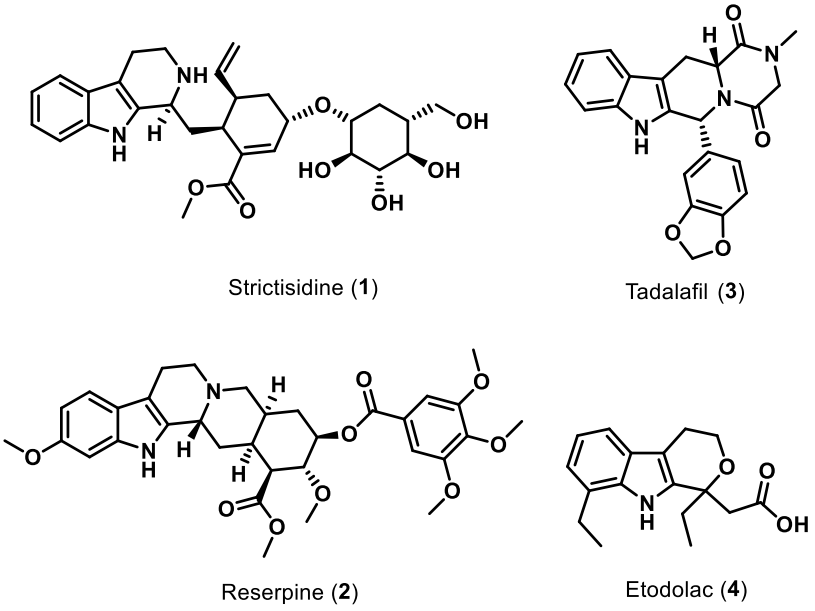
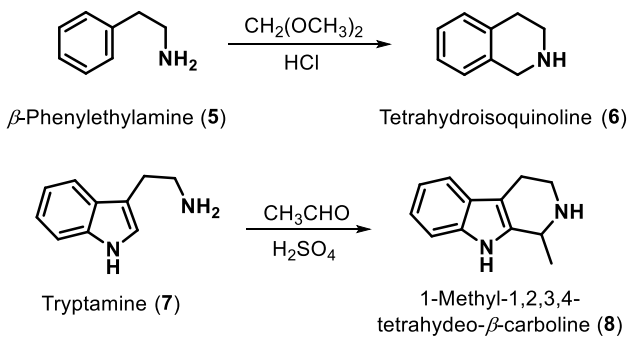


Figure 1. Bioactive Tetrahydro-*β*-carboline Derivatives.

The second reason is its use in the creation of bioactive structures for the development of new medicines, such as tadalafil (**3**) and etodolac (**4**) having a stereocenter adjacent to an aromatic ring (Figure 1).[2]

2A.2 Applications of Pictet–Spengler Reaction

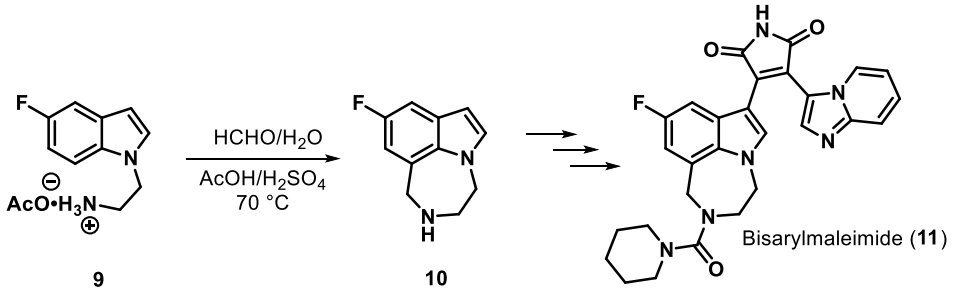
Amé Pictet and Theodor Spengler first invented the Pictet–Spengler reaction at the University of Geneva in 1911, while condensing the *β*-phenylethylamine (**5**) with the formaldehyde dimethylacetal in the presence of HCl, and obtained the tetrahydroisoquinoline (**6**) as illustrated in scheme 1.[3]



Scheme 1. Examples of Pictet–Spengler Reaction

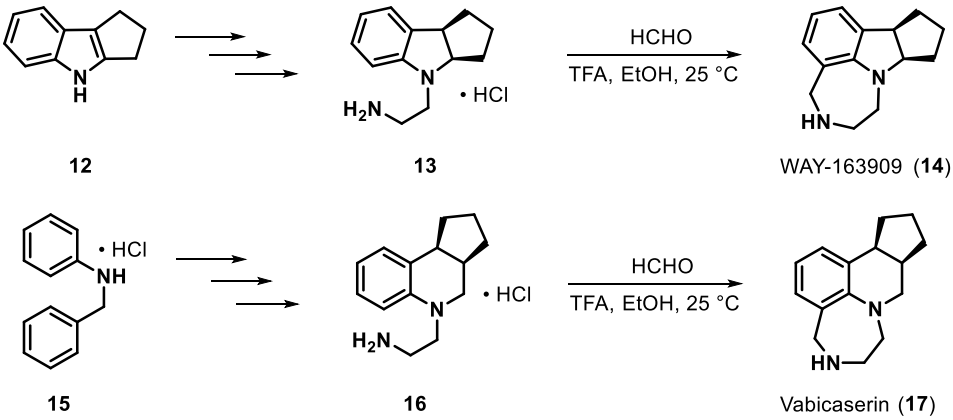
The Pictet–Spengler cyclization becomes one of the most important synthetic strategies particularly for the construction of the natural products bearing isoquinoline and indole alkaloid frameworks. The reaction has undergone continuous refinements and found broader applications in converting *N*-acylated, *N*-alkylated, and *N*-sulfonylated derivatives of phenylethylamine to the target compounds. After nearly two decades from the discovery of Pictet–Spengler reaction, Tatsui used tryptamine for the construction of 1-methyl-1,2,3,4-tetrahydeo-*β*-carboline (**8**).[4] These compounds **6** and **8** became the structural key element for the different complex isoquinoline and indole alkaloids, which are of enormous physiological and therapeutic significance.[4] Traditionally Pictet–Spengler reaction is carried out in the presence of acid catalyst in protic solvent; however, the reaction also works well with good yields in aprotic medium without any acid catalyst. The generated imine intermediate in the reaction is not much electrophilic and demands acid catalyst, however the nucleophilic aromatic rings such as indole, pyrrole give high yields even under mild conditions.[5] The Pictet–Spengler reaction is widely used in both basic and applied research. It became an important reaction in the field of organic synthesis to

design diverse range of *β*-carbolines. Tetrahydro-*β*-carbolines were isolated from many plants of South American origin. They also play an important role in the intoxicating snuffs used by Indian tribes. Some of the tetrahydro-*β*-carbolines show significant activity to inhibit monoamine oxidase A.[6] Pictet−Spengler reaction is now used for the synthesis of a large variety of different heterocyclic compounds. Magnus and co-workers used the Pictet−Spengler reaction for the activation of the C-7 carbon position to make the benzodiazepine tricyclic fragment **10** for the synthesis of the bisarylmaleimide **11** with 33% overall yield (Scheme 2). Bisarylmaleimide **11** shows the glycogen synthase kinase-3 (GSK3) inhibitory activity.[7]



Scheme 2. Pictet−Spengler Based Synthesis of Bisarylmaleimide

Pictet−Spengler reaction can also be used in the synthesis of drug molecules. Hooker and co-workers have synthesized the two potent drugs WAY-163909 (**14**) and vabicaserin (**17**) having potent pharmacokinetic activity against the serotonin subtype 2C ($5HT_{2C}$) receptor (Scheme 3). These are the most effective drugs for the treatment of several CNS disorders.[8]

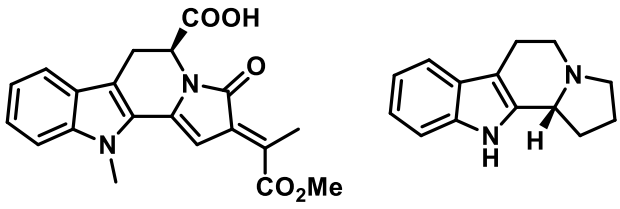


Scheme 3. Synthesis of WAY-163909 and Vabicaserin

Application of Pictet−Spengler reaction for the synthesis of different natural products has become the most important strategy to design polycyclic indole alkaloids skeleton. Pentacyclic molecule such as yohimbine, which becomes a starting point for making different natural products having activity against cancer-relevant GPCR targets. Herein we have depicted a few natural products which are having polyheterocyclic structures and which have been synthesized by using Pictet−Spengler reaction.

Tetracyclic Indole Alkaloids with the 7,12-Diaza 6•5•6•5 Ring Skeleton

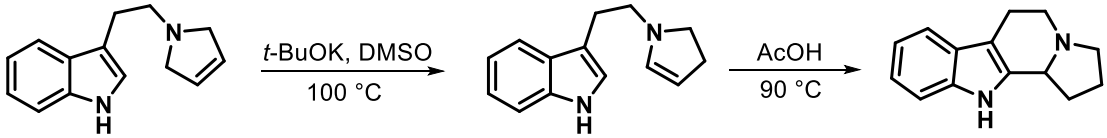
The indole alkaloids with teracycle having 6•5•6•5 ring skeleton are tetrahydro-*β*-carboline pyrrolidine scaffolds which are rare in nature (Figure 2).



Chaetogline A (**18**) Harmicine (**19**)

Figure 2. Chaetogline A and Harmicine Alkaloids.

The harmicine (**19**) is a useful starting material for the synthesis of several other more complex natural products. It can also be used as a model substrate in alkaloid synthesis and has created the impression as a product in substrate scope tables for methodology development. This alkaloid exhibits an extensive range of pharmacological activities, including antipyretic, antispasmodic, and anticancer properties. Large number of synthetic sequences are known for harmicine (**19**) and most of them include Pictet−Spengler reaction as a key step (Scheme 4).[9]



20 **21** Harmicine (**19**)

Scheme 4. Synthesis of Harmicine

Tetracyclic Indole Alkaloids with the 7,12-Diaza 6•5•6•6 Ring Skeleton

Plenty of tetrahydro-*β*-carbolines having this 6•5•6•6 indole alkaloidal skeleton are present in nature; some of them have been shown in figure 3. Indole alkaloids with

plant-based origin show various pharmacological activities, including antibacterial, antiviral, antifungal, antimalarial, anti-inflammatory, analgesic antidepressant, anticancer, hypotensive, anticholinesterase, antileishmanial, antiplatelet, antidiarrheal, spasmolytic, lipid-lowering, antidiabetic, and antimycobacterial activities.[10]

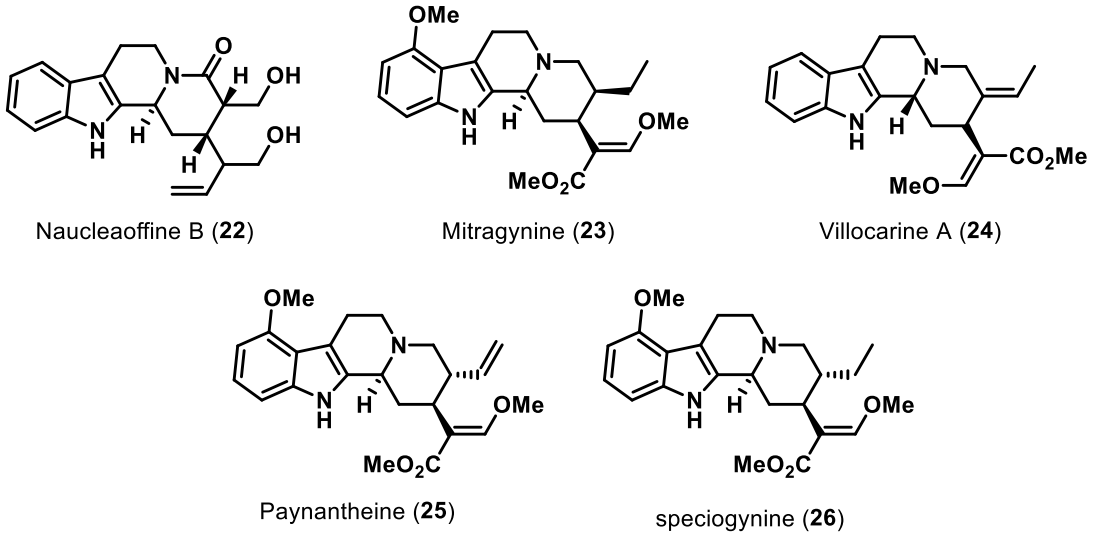
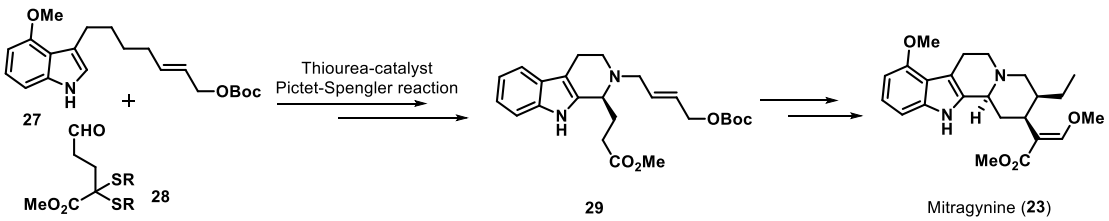


Figure 3. Representative Indole Alkaloids.

Several indole alkaloids have been isolated from the *Mitragyna speciosa* leaves including mitragynine (**23**) and it exhibits effective fever and pain reliever activities. It is also the key component for anti-inflammatory properties and suppresses PEG-2 production in the COX-2 pathway. The key intermediate **29** was constructed via thiourea-catalyzed Pictet−Spengler cyclization of tryptamine derivative **27** and the aldehyde **28** (Scheme 5).[11]



Scheme 5. Route Towards Mitragynine Synthesis Via Pictet−Spengler Reaction

Tetracyclic Indole Alkaloids with the 7,12-Diaza 6•5•6•7 Ring Skeleton

The literature search revealed that tetrahydro-*β*-carboline natural products with the 6•5•6•7 skeleton is unique and only two indole alkaloidal natural products

banistenoside A (**30**) and banistenoside B (**31**) are known till date (Figure 4).[12] Their total synthesis using Pictet−Spengler reaction becomes the most important part of synthetic sequences. In our literature search, we did not find any tetrahydro-*β*-carbolines natural products with the 6•5•6•8 and 6•5•6•9 skeletons.

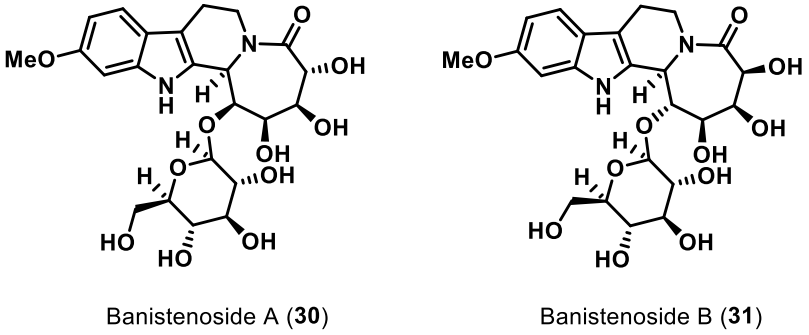


Figure 4. Banistenoside A and Banistenoside B.

2A.3 Summary

In summary, we have given a brief introduction about the role of Pictet−Spengler reaction and its importance in the synthesis of β-carboline natural products. We also have explained in brief the mechanistic aspects of the reaction. The role of acidic medium or presence of nucleophilic aromatic ring such as indole, pyrrole give high yields under mild conditions. The structurally interesting compounds, the banistenoside A and B also show specific biological activity against MAO-A and MAO-B enzymes and our synthetic strategies towards stereoselective total synthesis of banistenoside B and closely related analogs will be discussed in details in the second section of this chapter.

2A.4 References

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Chapter 2

Section B

Total Synthesis of Indole Alkaloidal Natural Product: (+)-Dibenzyl-Banistenoside B

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

2B.1 Background

Natural products play an vital role in drug discovery since most of the synthesized drugs have a natural product origin.[1] *Banisteriopsis caapi*, a plant for treating neurodegenerative disorders relevant to Parkinson's disease (PD) has been found in Brazil, Bolivia, Colombia, Ecuador, and Peru.[2] *B. caapi* is used in combination with the *Psychotria viridis* to make a popular sacred and psychoactive drink Ayahuasca, which stimulates creative thinking and visual creativity. According to the literature, no such traditional drinks have been prepared only from *B. caapi* to serve the purpose. In PD, there is damage in neurons from the substantia nigra of the brain that affects dopamine production, which is responsible for the brain's ability to control movement. Antioxidants can control this as an adjuvant with dopamine agonist or monoamine oxidase (MAO) inhibitors.[3] The identities of different *Banisteriopsis* species are mostly unknown due to the scarcity of fertile collections and lack of detailed taxonomic study. The harmine and the stem extract of *Banisteriopsis caapi* showed a concentration-dependent inhibition of MAO-A, which increases the dopamine release from rat striatal slices.[4] During the chemical/biological standardization of *Banisteriopsis caapi* for neurological disorders relevant to PD, Samoylenko *et al*. used an extract of *Banisteriopsis caapi* cultivar Da Vine, collected in Oahu, Hawaii, and demonstrated potent in vitro MAO-A inhibitory and antioxidant activities.

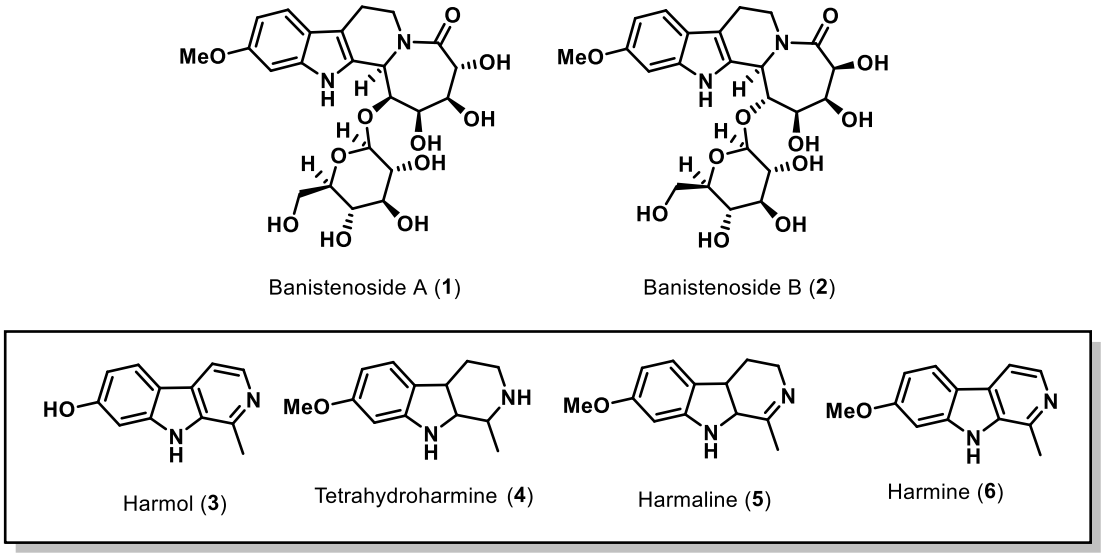


Figure 1. Compounds Isolated from *Banisteriopsis Caapi*.

Further studies resulted in the isolation of two new *β*-carboline alkaloidal glycosides, banistenoside A (**1**) and banistenoside B (**2**), along with the four known *β*-carboline alkaloids harmol (**3**), tetrahydroharmine (**4**), harmaline (**5**) and harmine (**6**) from the

same extract (Figure 1).[5] Samoylenko *et al*. have mentioned in their isolation paper that the *β*-carboline alkaloidal glycosides banistenoside A (**1**) and banistenoside B (**2**) are insoluble in most of the NMR solvents. Therefore they have converted both the compounds to the heptaacetyl derivatives and confirmed their structures and stereochemistry on the basis of NMR, 2D NMR, HRMS, IR studies (Figure 2).[5] In continuing our group's interest in synthesizing a structurally challenging molecules with virtuous biological values, we were interested in taking this as a target product.[6] Inspired by the novel structural features, biological activity, we planned to synthesize these natural products and their close analogs.

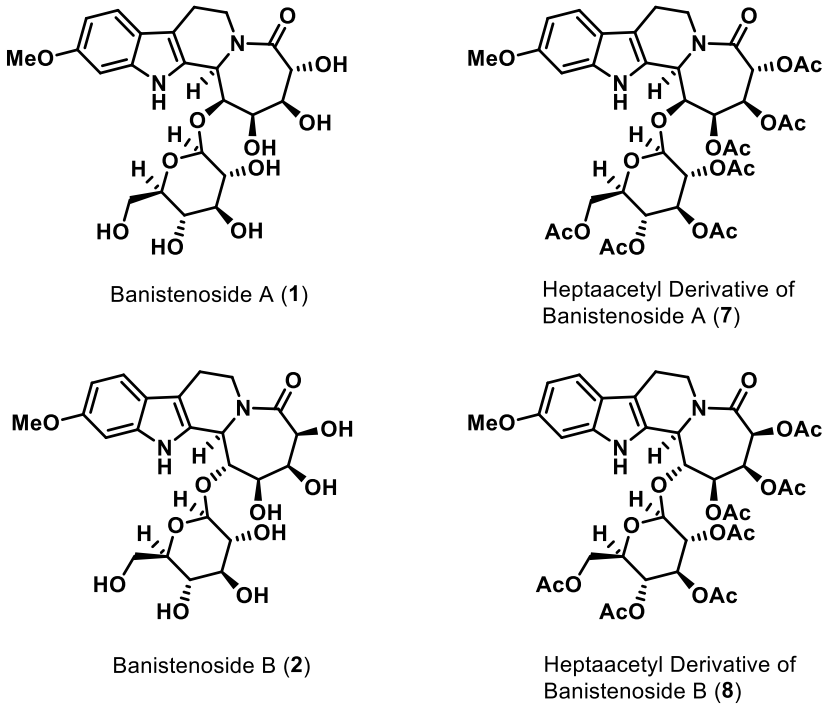


Figure 2. Banistenoside A and B and their Heptaacetyl Derivatives.

2B.1.1 Parkinson's Disease (PD)

The disease was first discovered by the English doctor James Parkinson in 1817 as he published an article on the Shaking Palsy, the condition named after him.[7] It is a neurological disorder that mainly affects the ability to control movement. This disease is primarily caused when nerve cells (neurons) from the substantia nigra become impaired and/or die. These cells typically produce an essential brain chemical known as dopamine, which helps the brain cells communicate. When these cells are damaged or die, dopamine production decreases. Results into the causes of the movement problems of Parkinson's.[8] People with Parkinson's disease also suffer from the loss of

norepinephrine. Another neurotransmitter which helps with autonomic functions such as heart rate, digestion, breathing, and blood pressure. The most common symptoms in PD include shaking of head and hand, rigidity in the limbs, fessing problems in walking, disbalancing leads to fall, etc.[9] There is no permanent treatment for the PD, but initial treatment is the medications with levodopa (L-DOPA), dopamine agonists, and MAO-B inhibitors (Figure 3).[10] As time increases, the effect of medication decreases, so the medications may be given in combination or with higher doses. There were about 6.2 million people affected with PD globally by 2015. The rate of formation PD is 1.5 times more in men than the women.[11]

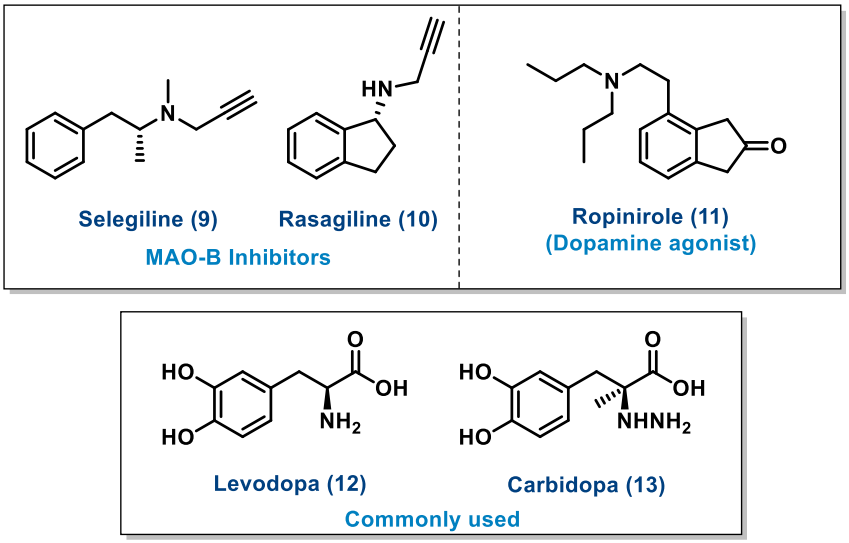
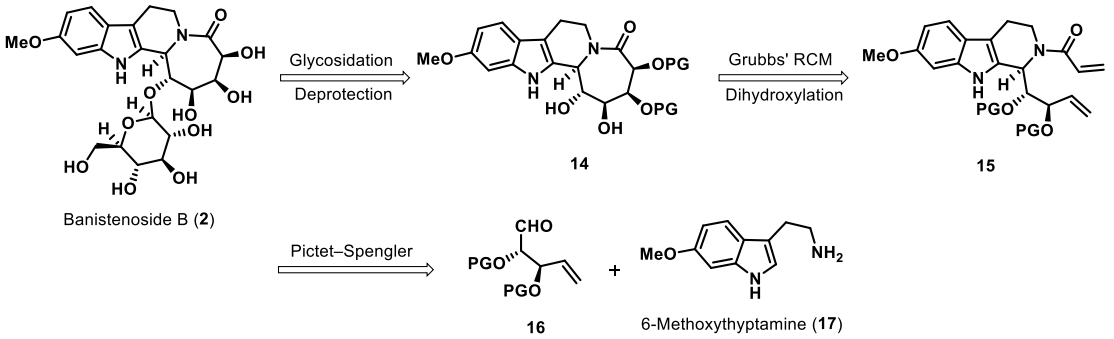


Figure 3. Commonly Used Drugs in Parkinson's Disease.

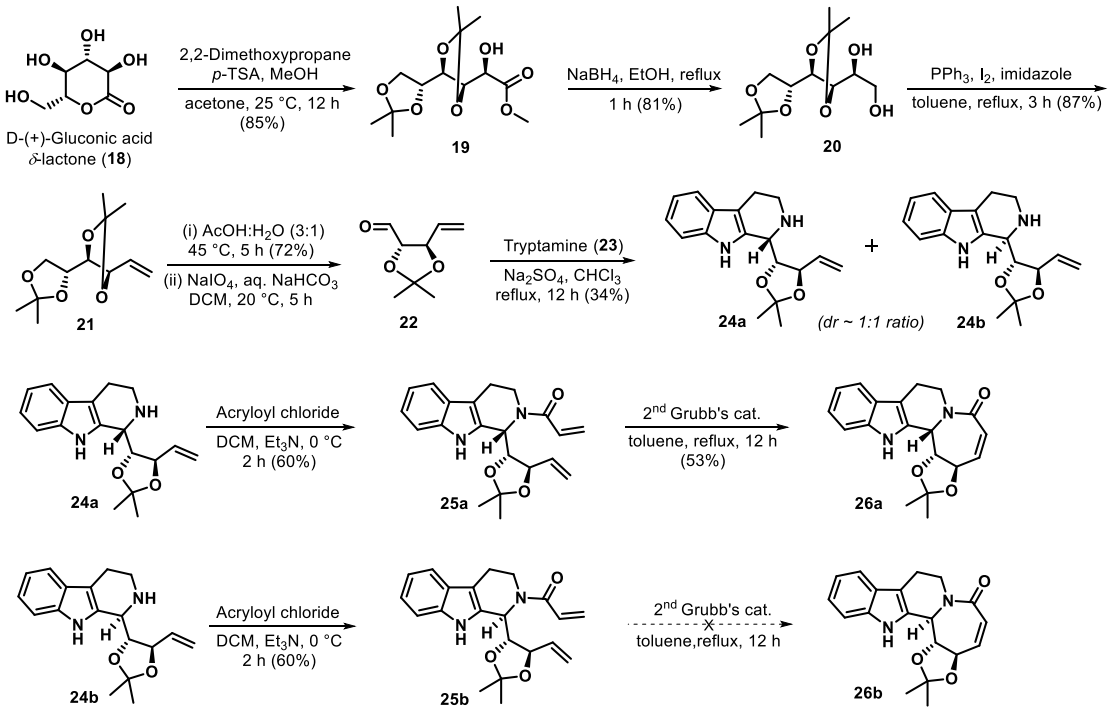
2B.2 Result and Discussion (Present Research Work)

The total synthesis of banistenoside B, a natural product with a unique "azepino(1,2-*a*)tetrahydro-*β*-carboline" carbon framework has remained unattempted for two decades. We planned the synthesis of banistenoside B using 6-methoxytryptamine (**17**), and the retrosynthesis has been depicted in scheme 1. The target compound banistenoside B (**2**) was envisioned from tetracyclic compound **14** through stereoselective glycosidation and deprotection sequence. Compound **14** could be synthesized from compound **15** through the Grubbs' ring-closing metathesis and dihydroxylation. Compound **15** was planned from the Pictet-Spengler reaction between aldehyde intermediate **16** and 6-methoxytryptamine (**17**).



Scheme 1. Retrosynthetic Route of Banistenoside B

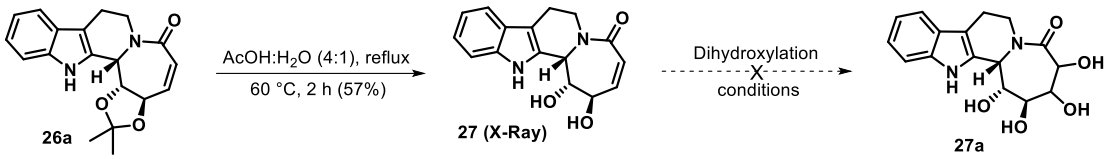
Our total synthesis endeavors began with commercially available D-(+)-gluconic acid δ-lactone (**18**) (Scheme 2). The acetonide protection of the δ-gluconolactone (**18**) with *p*-TSA and 2,2-dimethoxypropane gave the α-hydroxy ester compound **19**, followed by reduction of ester functional group using $NaBH_4$ in EtOH yielded compound **20**.[12] The vicinal diol **20** was converted into olefin using triphenylphosphine, imidazole, and iodine to obtain compound **21**.[13] Compound **21** on regioselective acetonide deprotection of terminal acetonide group using AcOH:H_2O (3:1) followed by the oxidative cleavage with $NaIO_4$ delivered aldehyde **22**.[14,15]



Scheme 2. Synthesis of Tetracyclic Core of Banistenoside via RCM

With aldehyde **22** in hands, we set for the first key reaction of the sequence Pictet−Spengler with tryptamine **23**. Here, we have used tryptamine instead of 6-methoxytryptamine for the reaction's optimization purpose, due to the high cost of 6-

methoxytryptamine. A diastereomeric mixture of **24a** and **24b** in the ratio of 1:1 with 34% yield was obtained and which was separated by column chromatography.[16] The following steps were run in parallel with the pure diastereomers **24a** and **24b**. Firstly the acylation was carried out by using acryloyl chloride and triethylamine in DCM to give di-olefinic compounds **25a** and **25b**.[17,18] Synthesis continued with ring-closing metathesis of compounds **25a** and **25b** using Grubbs' 2nd generation catalyst in toluene.[19] We got the tetracyclic compound **26a** but were unable to synthesize compound **26b**. We also have tried the ring-closing metathesis reaction of **25b** using Grubbs' 1st generation catalyst, but we did not get the desired compound **26b**. Then we tried several reaction conditions for the dihydroxylation of double bond adjacent to carbonyl in compound **26a**, [OsO_4, NMO, acetone:H_2O (2:1); OsO_4, NMO, TEMDA, *t*-BuOH:H_2O (2:1); OsO_4, NMO, *t*-BuOH:H_2O (2:1); OsO_4, py; $NaIO_4$, $RuCl_3$, $CeCl_3.7H_2O$, EtOAc:CH_3CN:H_2O; OsO_4, NMO, citric acid] but we were unable to obtain the dihydroxylation product.



Scheme 3. Acetonide Deprotection and an Attempted Dihydroxylation

The compound **26a** on further acetonide deprotection under the acidic condition using AcOH:H_2O (4:1) provided compound **27**, which also failed to undergo dihydroxylation of double bond adjacent to carbonyl to deliver **27a** (Scheme 3). The stereochemistry of all the stereocentres in compound **27** was confirmed by a single-crystal X-ray study (Figure 4).

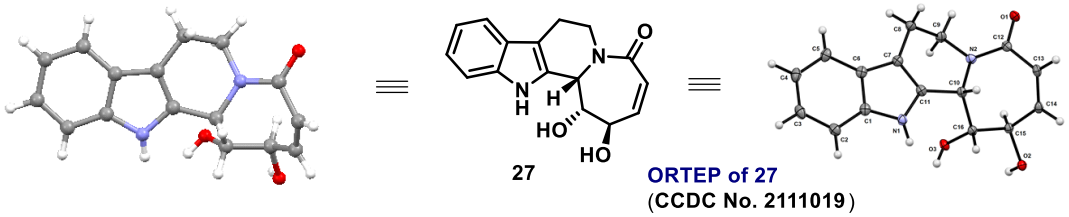


Figure 4. X-Ray Crystal Structure of Dihydroxy Compound **27**.

Several reaction conditions as depicted in table 1 were tried for dihydroxylation of compound **27**. As we can see in the table, reactions were carried out under OsO_4,

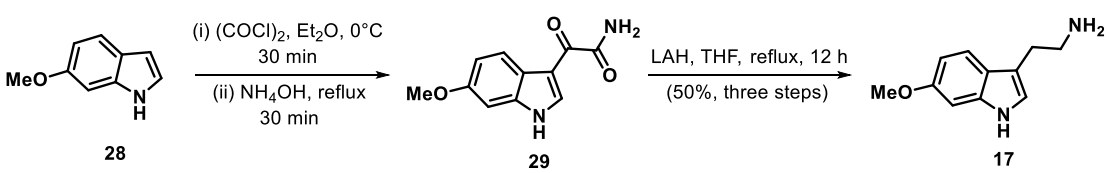
NMO condition most of the time and we ended up with the starting material only; in some cases there was a decomposition of starting material.

Table 1. Dihydroxylation Reaction Conditions Tried for Dihydroxy Compound **27**

Sr. No.	Reaction conditions	Result
1	OsO_4, NMO, acetone:H_2O (2:1), 25 °C, 5 h	SM recovered
2	OsO_4, NMO, acetone:H_2O (2:1), reflux, 60 °C, 12 h	SM recovered
3	OsO_4, NMO, TEMDA, *t*-BuOH:H_2O (2:1), 25 °C, 12 h	SM recovered
4	OsO_4, NMO, *t*-BuOH:H_2O (2:1), reflux, 60 °C, 12 h	SM got decomposed
5	OsO_4, py, 25 °C, 12 h	Desired product was not obtained
6	$NaIO_4$, $RuCl_3$, $CeCl_3.7H_2O$, EtOAc:CH_3CN:H_2O	SM recovered
7	OsO_4, NMO, citric acid	Desired product was not obtained

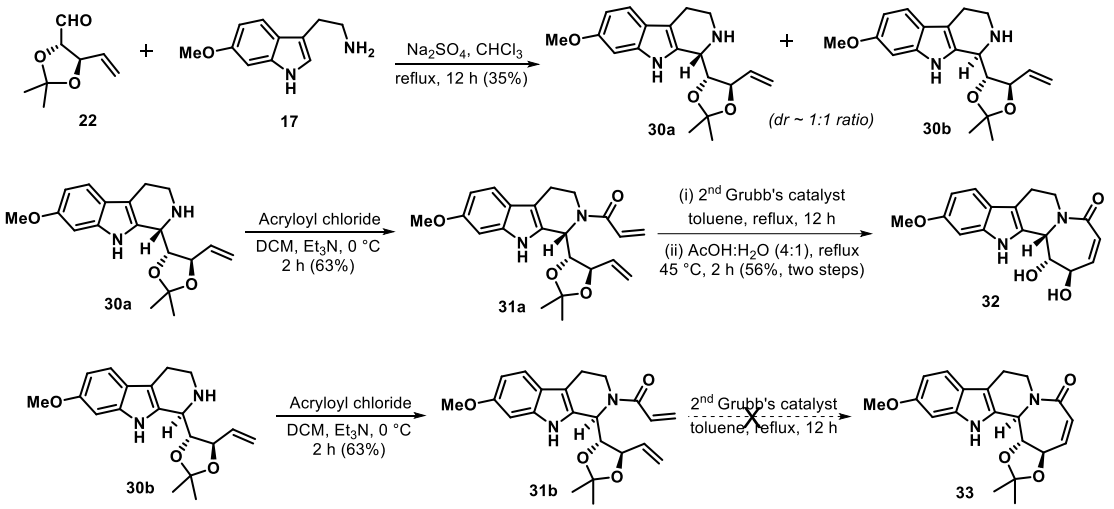
SM = Starting Material

Meanwhile, we were working on the synthesis of 6-methoxytryptamine (**17**) by using 6-methoxyindole (**28**) as a starting material (Scheme 4). By using Woodward's protocol, we have synthesized 6-methoxytryptamine (**17**) by reacting the 6-methoxyindole with oxalyl chloride in diethyl ether followed by treatment with NH_4OH to get the *β*-6-methoxyindolyl-glyoxylic acid amide (**29**). This compound **29** on refluxing with LAH in diethyl ether yielded the desired 6-methoxytryptamine (**17**).[20]



Scheme 4. Synthesis of 6-Methoxytryptamine

Aldehyde **22** from scheme 2 was used for the Pictet−Spengler reaction with 6-methoxytryptamine (**17**) to obtain the diastereomeric mixture **30a** and **30b** in 35% yield with 1:1 diastereomeric ratio. These compounds **30a** and **30b** were separated by column chromatography as pure compounds and forwarded separately for further reactions (Scheme 5).[21,22]



Scheme 5. Synthesis of Tetracyclic Core of Banistenoside B via RCM

Firstly, the acylation was carried out by using acryloyl chloride and triethylamine in DCM to get the desired di-olefinic compounds **31a** and **31b**.[17,18] Synthesis continued with ring-closing metathesis using Grubbs' 2nd generation catalyst in toluene followed by acetonide deprotection under the acidic condition to get the compound **32**.[19] Here, we have got the tetracyclic compound **32**, but we were unable to synthesize compound **33**. Similarly, we also have tried a few conditions for the dihydroxylation of compound **32** as shown in table 2. Unfortunately, we did not get any practical success on this dihydroxylation also.

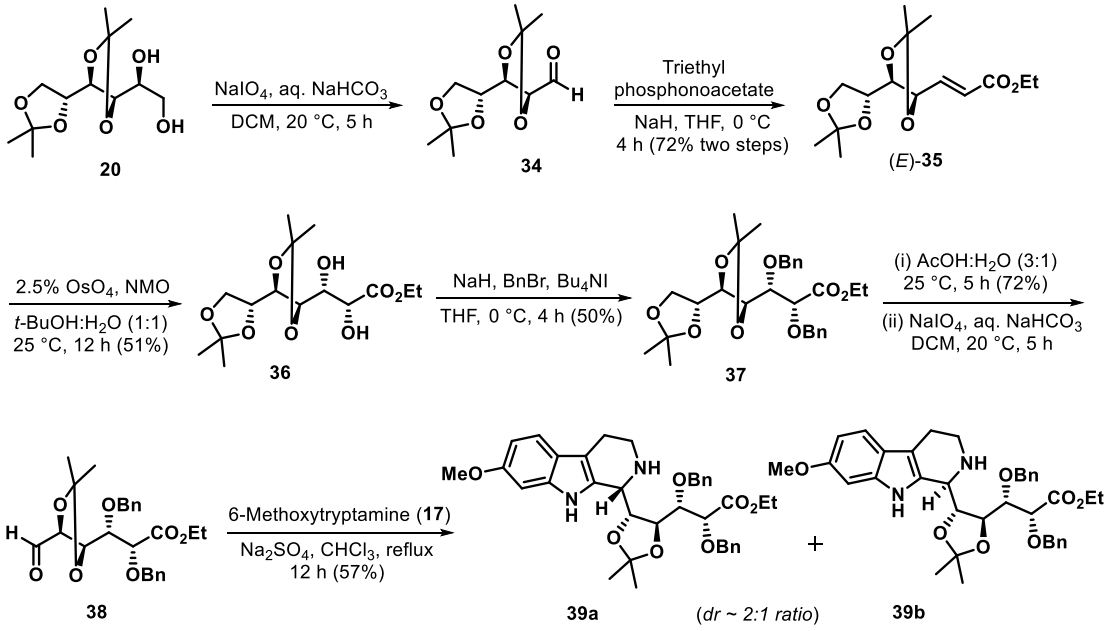
Table 2. Dihydroxylation Reaction Conditions Studied for Dihydroxy Compound **32**

Sr. No.	Reaction conditions	Result
1	OsO_4, NMO, acetone:H_2O (2:1), 25 °C, 5 h	SM recovered
2	OsO_4, NMO, TEMDA, *t*-BuOH:H_2O (2:1), 25 °C, 12 h	SM recovered

3	$NaIO_4$, $RuCl_3$, $CeCl_3.7H_2O$, EtOAc:CH_3CN:H_2O	SM recovered
4	OsO_4, py, 25 °C, 12 h	Desired product was not obtained
5	OsO_4, NMO, citric acid, 25 °C, 12 h	Desired product was not obtained

SM = Starting Material

After several unproductive attempts to synthesize the intermediate product **14** from scheme 1, we revised our retrosynthetic approach to synthesize banistenoside B (**2**). In the new synthesis path, we focused on maintaining the stereocentres of all the hydroxy groups in the synthetic route. Thus, we started our synthesis using aldehyde intermediate **34,** which can be synthesized by oxidative cleavage of diol **20** (previously shown in scheme 2) using $NaIO_4$ in DCM (Scheme 6). The aldehyde intermediate **34** on Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate in the presence of NaH in THF furnished known compound (*E*)-**35** in 72% yield.[23,24] Compound **35** was further subjected to the dihydroxylation using OsO_4, NMO in *t*-BuOH:H_2O (1:1) to afford dihydroxy compound **36**, which on benzyl protection with BnBr, NaH in THF gave the compound **37**.[25] Compound **37** on terminal acetonide deprotection under acidic conditions followed by oxidative cleavage using $NaIO_4$ gave the aldehyde intermediate **38**.[14,15]



Scheme 6. New Approach Towards Banistenoside B via Wittig Reaction

The Pictet-Spengler reaction between aldehyde intermediate **38** and 6-methoxytryptamine (**17**) in chloroform afforded a diastereomeric mixture of **39a** and **39b** with the diastereomeric ratio of 2:1 in 57% yield.[21,22] After separating the mixture of diastereomers **39a** and **39b** using column chromatography, following reactions were carried in parallel on pure diastereomers **39a** and **39b**. Our next move was to do the intramolecular lactamization to make the seven membered ring for which we tried several conditions as shown in the table 3. We have tried the cyclization in microwave under different solvent or using bases but we did not get our desired product. We have also tried cyclization using different bases, strong bases like LiHMDS, LDA but did not get any practical success on cyclization.

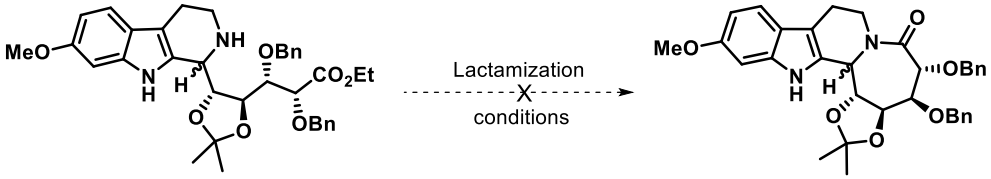


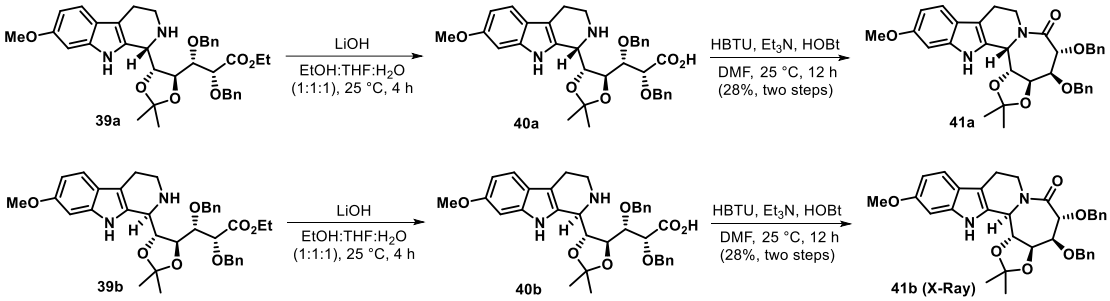
Table 3. Different Reaction Conditions Tried for Lactamization.

Sr. No.	Reaction Conditions	Result
1	EtOH, 60 °C, MW, 1 h	SM recovered
2	MW, Et_3N, EtOH, 1 h	SM recovered
3	ODCB, 100 °C, MW, 1 h	SM got decomposed
4	K_2CO_3, ODCB, 100 °C, MW, 1 h	SM recovered
5	K_2CO_3, DMF, reflux, 12 h	Desired product was not obtained
6	Et_3N, EtOH, reflux, 12 h	Desired product was not obtained
7	LiHMDS, THF, O °C-25 °C, 12 h	Desired product was not obtained

8	DIPA, *n*-BuLi, THF, -78 °C- 25 °C, 12 h	Desired product was not obtained

ODCB: *o*-Dichlorobenzene; DIPA: Diisopropylamine. SM = Starting Material

Then we decided to do cyclization via the ester hydrolysis under basic condition using LiOH in EtOH:THF:H_2O (1:1:1) to give the corresponding amino acid **40a** and **40b**. These amino acid **40a** and **40b** on intramolecular cyclization using coupling reagent HBTU, HOBt, Et_3N in DMF afforded two tetracyclic compounds **41a** and **41b** (28%, two steps) (Scheme 7).[26] A single-crystal X-ray study confirmed the structure of compound **41b** and its stereochemistry; on that basis, we also confirmed the stereochemistry of the other diastereomer **41a** (Figure 5).



Scheme 7. Synthesis of Tetracyclic Core of Banistenoside B via Lactamization

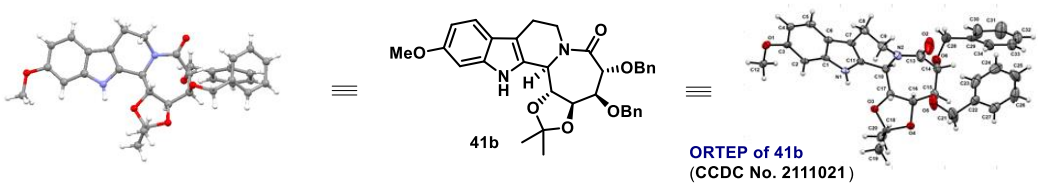
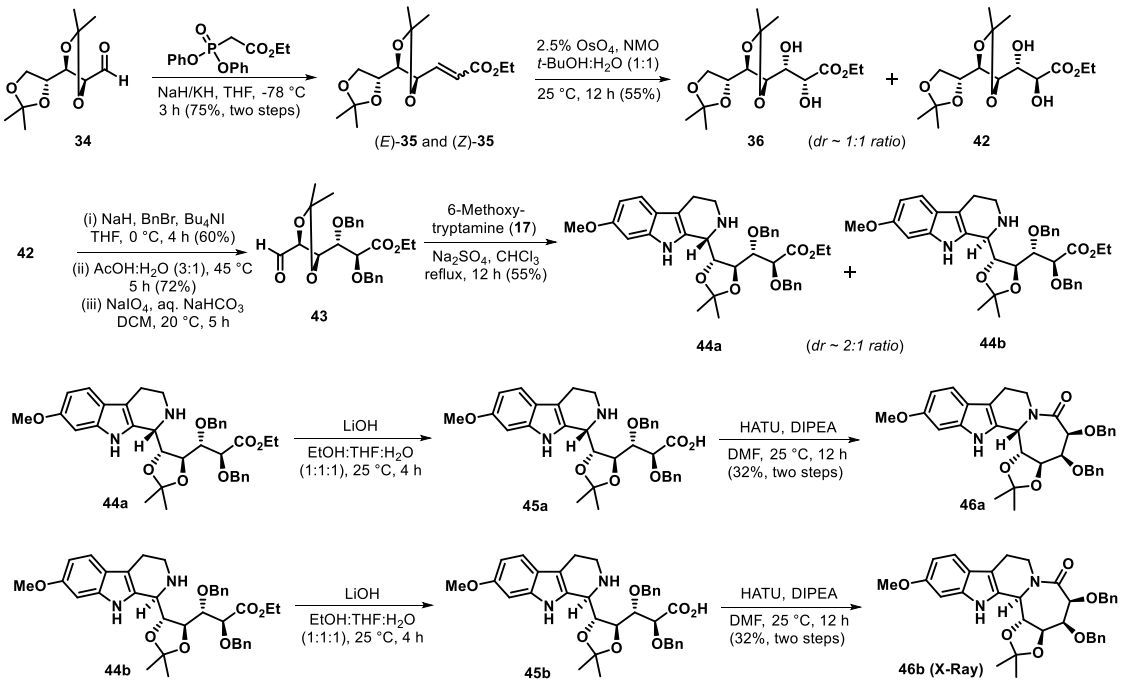


Figure 5. X-Ray Crystal Structure of Compound **41b**.

On the basis of synthesis of tetracyclic core **41b** having undesired stereochemistry at C-13 carbon, our modified plan to obtain the desired (*Z*)-olefin **35** started with Ando olefination (Scheme 8). Ando modification of Horner-Wadsworth-Emmons's reaction of aldehyde **34** with freshly prepared ethyl 2-(diphenoxyphosphoryl) acetate, NaH/KH in THF provided the mixture of (*E*)-**35** and (*Z*)-**35**, which upon further dihydroxylation by using OsO_4, NMO constricted two dihydroxy compounds **36** and **42** with 1:1 ratio in 55% yield.[27] After separation by column chromatography, compound **42** was utilized for further reactions. Benzyl protection of compound **42** followed by regioselective acetonide deprotection in acidic medium furnished diol,

which was oxidized with $NaIO_4$ to give the required aldehyde intermediate **43**. Aldehyde intermediate **43** on Pictet-Spengler reaction with 6-methoxytryptamine (**17**) provided two expected diastereoisomers **44a** and **44b** with the 2:1 ratio (55% yield).[21,22] After purification with the column chromatography on silica gel, compounds **44a** and **44b** were forwarded separately for the synthesis of tetracyclic compounds **46a** and **46b** using ester hydrolysis under alkaline conditions followed by intramolecular cyclization as shown in scheme 8.[26] The single-crystal X-ray study was performed for compound **46b** to assign the illustrated stereochemistry (Figure 6). At the final stage, with all the stereocentres set on the tetracyclic scaffold **46b**, the last challenging step was to connect the glucose ring to the scaffold **46b** having appropriate regio- and stereochemistry.



Scheme 8. Synthesis of Tetracyclic Core of Banistenoside B via Ando Olefination

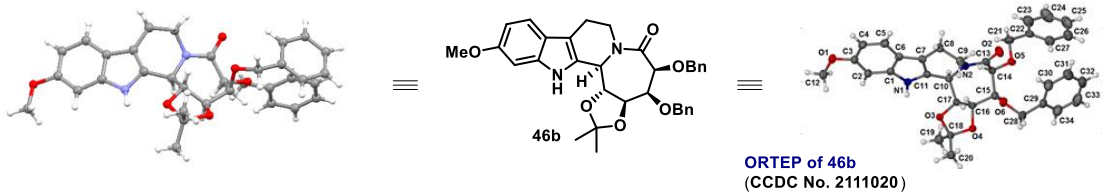
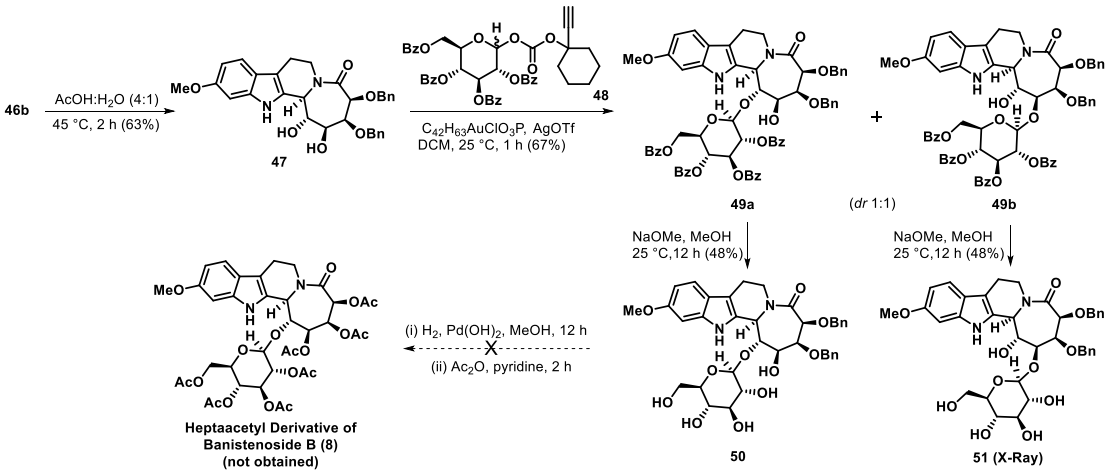


Figure 6. X-Ray Crystal Structure of Compound **41b**.

Compound **46b** on acetonide deprotection using AcOH:H_2O (4:1) yielded compound **47** (63% yield) (Scheme 9). The glycation reaction using Hotha's protocol was carried out on compound **47** using substrate **48** (obtained from D-glucose) in the presence of chloro[tris(2,4-di-*tert*-butylphenyl)phosphite]gold and silver triflate to afford two regioisomeric compounds **49a** and **49b** (67% yield) (Scheme 10).[28] The compounds **49a** and **49b** were separated and forwarded for benzoyl deprotection with sodium methoxide in methanol to afford compounds **50** and **51** (~48% yield). Although all starting material was consumed, the obtained yield was on the lower side plausibly due to decomposition.[29] The X-ray crystallographic analysis unambiguously confirmed the structure of compound **51**; which also indirectly confirmed the structure of other regioisomeric compounds **50** (Figure 7). Due to the, solubility issues of natural products banistenoside A (**1**) and banistenoside B (**2**) mentioned by Samoylenko *et al*. in their isolation paper, we tried to synthesize the reported heptaacetyl derivative of banistenoside B; via debenzylation, acylation pathway.[5] Unfortunately, both H_2, Pd/C and H_2, $Pd(OH)_2$ induced debenzylation in MeOH resulted in complete decomposition and hence we were unable to synthesize the actual target compound.



Scheme 9. Synthesis of Dibenzyl Banistenoside B

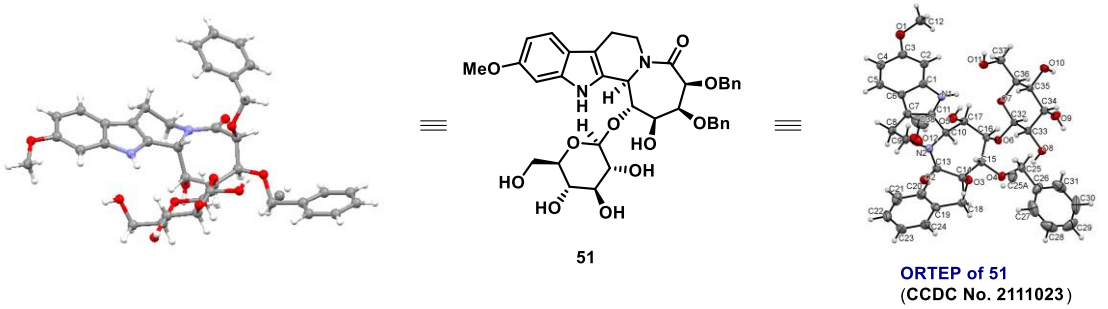
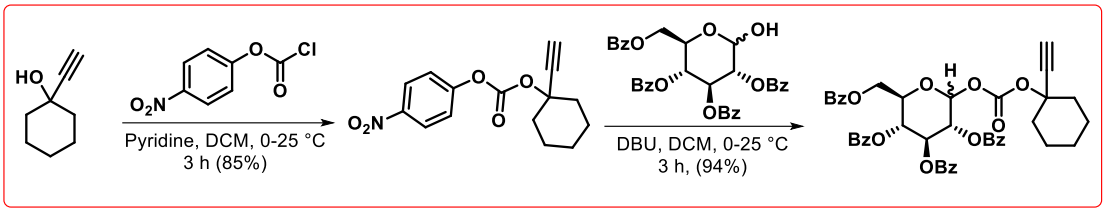


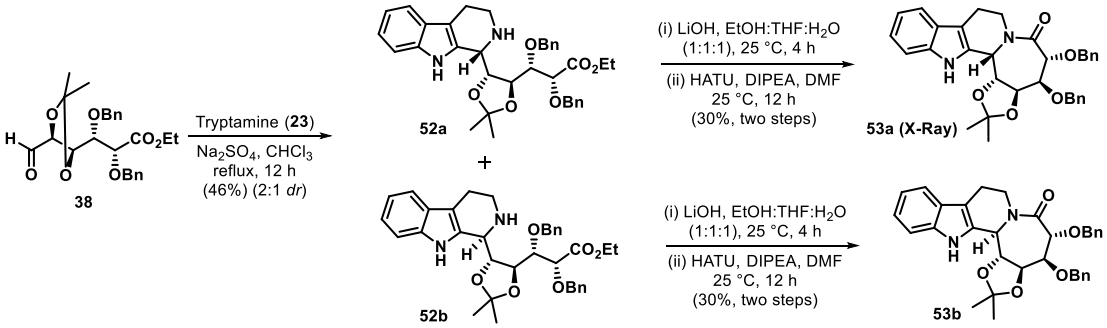
Figure 7. X-Ray Crystal Structure of Pentahydroxy Compound **51**.

We also have synthesized few demethoxy analogs which will be useful for SAR studies. Aldehyde **38** from scheme 6 on the Pictet−Spengler reaction with tryptamine (**23**) provided the diastereomeric mixture **52a** and **52b** in 55% yield with 2:1 diastereomeric ratio.



Scheme 10. Synthesis of Substrate **48** Using Hotha's Protocol

After purification with the column chromatography on silica gel, compounds **52a** and **52b** were forwarded separately for the synthesis of tetracyclic compounds **53a** and **53b** using ester hydrolysis under alkaline conditions followed by intramolecular cyclization (Scheme 11). The single-crystal X-ray study was performed for compound **53a** to assign the illustrated stereochemistry (Figure 8).



Scheme 11. Synthesis of Demethoxy Analogs

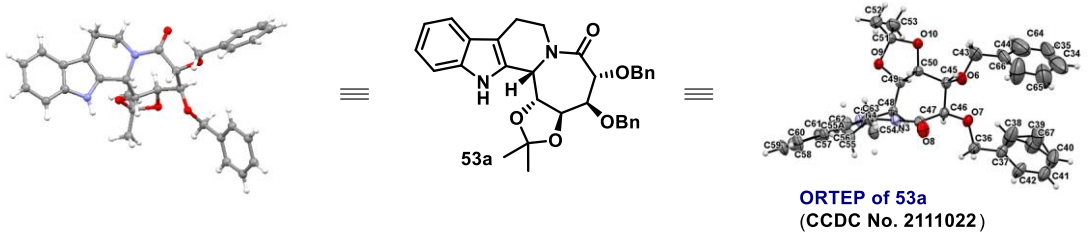


Figure 8. X-Ray Crystal Structure of Tetracyclic Compound **53a**.

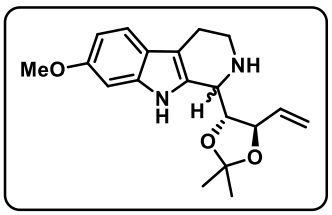
2B.3 Summary

*In summary, we have successfully achieved the total Synthesis of dibenzyl derivative of natural product banistenoside B (**2**) having 10 stereocentres using linear sequence*

*of 14 steps. Along with dibenzylated natural product, few close analogs **27**, **32**, **41a**, **41b**, **46a**, **51**, and a few demethoxy analogs were synthesized for further SAR studies. Overall, the Pictet-Spengler reaction followed by lactamization and stereoselective glycation reactions are the key steps in the synthesis of dibenzyl derivative of natural product. However, the obtained lower yields and weak diastereoselectivities in Pictet-Spengler reactions could be a result of plausible retro Pictet-Spengler reactions and associated decompositions of respective aldehydes.*

2B.4 Experimental Section

1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (30a & 30b). To a solution of aldehyde **22** (2 g, 12.820 mmol) in chloroform (40 mL) at room temperature was added 6-methoxytryptamine (**17**) (3.65 g, 19.230 mmol) and Na_2SO_4 (0.9 g, 6.406 mmol). The reaction mixture was refluxed for 12 hours at 70 °C. After 12 h, the solvent was evaporated under reduced pressure, and the crude compound was purified by column chromatography on silica gel (60:40; petroleum ether:EtOAc) to afford pure product as a red sticky liquid **30a** and **30b** as diastereomeric mixture (1.5 g, 35%) with the diastereomeric ratio 1:1.

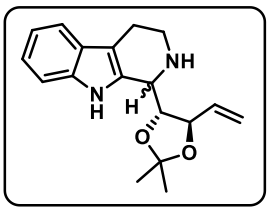


(*S*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (30a). Red sticky liquid (0.750 g) **$[\alpha]_D^{27}$** = + 129.37 (*c* = 2.0, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.22 (br. s., 1 H), 7.39 (d, *J* = 8.5 Hz, 1 H), 6.84 (s, 1 H), 6.79 (dd, *J* = 1.8, 8.5 Hz, 1 H), 5.95 (ddd, *J* = 7.0, 10.1, 17.1 Hz, 1 H), 5.37 (d, *J* = 17.1 Hz, 1 H), 5.29 (d, *J* = 11.0 Hz, 1 H), 4.48 (br. s., 1 H), 4.23 (t, *J* = 7.6 Hz, 1 H), 4.13 (dd, *J* = 3.4, 8.2 Hz, 1 H), 3.86 (s, 3 H), 3.37 (td, *J* = 3.7, 12.7 Hz, 1 H), 3.00–2.91 (m, 1 H), 2.71 (br. s., 2 H), 1.96 (br. s., 1 H), 1.57 (s, 3 H), 1.47 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 156.3, 136.5, 136.3, 131.1, 121.6, 119.1, 118.6, 110.6, 108.9, 108.8, 94.8, 82.0, 78.5, 55.7, 52.5, 43.3, 27.1, 26.6, 22.8; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{19}H_{25}N_2O_3$ 329.1860, Found 329.1859; **IR ($CHCl_3$)** ν_{max} 2953, 1618, 1163, 1028 cm^{-1}.

(*R*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (30b). Red sticky liquid (0.750 g) **$[\alpha]_D^{27}$** = – 60.42 (*c* = 1.5, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.18 (br. s., 1 H), 7.38 (d, *J* =

8.6 Hz, 1 H), 6.84 (d, *J* = 2.1 Hz, 1 H), 6.78 (dd, *J* = 2.3, 8.5 Hz, 1 H), 5.94 (ddd, *J* = 7.1, 10.2, 17.2 Hz, 1 H), 5.40–5.26 (m, 2 H), 4.52–4.47 (m, 1 H), 4.24–4.19 (m, 1 H), 4.12 (dd, *J* = 3.5, 8.4 Hz, 1 H), 3.86 (s, 3 H), 3.37 (td, *J* = 4.0, 12.8 Hz, 1 H), 3.00–2.91 (m, 1 H), 2.71 (td, *J* = 2.3, 4.3 Hz, 2 H), 1.73 (br. s., 1 H), 1.56 (s, 3 H), 1.46 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 156.3, 136.3, 132.0, 128.6, 128.5, 121.5, 119.4, 118.6, 110.5, 108.9, 94.8, 81.8, 78.5, 55.7, 52.5, 43.2, 27.1, 26.6, 22.6; **HRMS (ESI)** ***m/z*** $[M+H]^+$ Calcd for $C_{19}H_{25}N_2O_3$ 329.1860, found 329.1858; **IR ($CHCl_3$)** ν_{max} 2935, 1624, 1213, 1030 cm^{-1}.

1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole (24a & 24b). Compound **24a** and **24b** can be synthesized from aldehyde



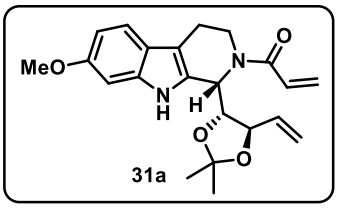
22 (1.7 g, 10.891 mmol) and tryptamine **23** (2.61 g, 16.337 mmol) with the same procedure followed for the synthesis of compound (**30a** and **30**). The crude compound was purified by column chromatography on silica gel (60:40; petroleum ether:EtOAc) to afford pure product as a red sticky liquid **24a** and **24b** as diastereomeric mixture (1.1 g, 34%) with the diastereomeric ratio 1:1.

(*S*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (24a). Red sticky liquid (0.55 g) **$[\alpha]_D^{26}$** = + 2.28 (*c* = 1.6, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.53 (br. s., 1 H), 7.51 (d, *J* = 8.2 Hz, 1 H), 7.40–7.36 (m, 1 H), 7.18 (dt, *J* = 1.4, 7.6 Hz, 1 H), 7.10 (dt, *J* = 0.9, 7.3 Hz, 1 H), 6.06–5.94 (m, 1 H), 5.51 (td, *J* = 1.2, 17.3 Hz, 1 H), 5.29 (td, *J* = 1.2, 10.4 Hz, 1 H), 4.59–4.53 (m, 1 H), 4.21–4.16 (m, 1 H), 3.86 (dd, *J* = 7.6, 8.9 Hz, 1 H), 3.35–3.29 (m, 1 H), 3.04 (ddd, *J* = 5.0, 8.8, 12.7 Hz, 1 H), 2.83–2.70 (m, 2 H), 2.22 (br. s., 1 H), 1.59 (s, 3 H), 1.50 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 136.3, 135.5, 134.0, 127.0, 121.7, 119.1, 118.3, 118.1, 110.9, 109.6, 109.0, 83.0, 81.7, 56.2, 42.8, 27.2, 27.1, 22.3; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{18}H_{23}N_2O_2$ 299.1754, found 299.1753; **IR ($CHCl_3$)** ν_{max} 2923, 1648, 1158, 1037 cm^{-1}.

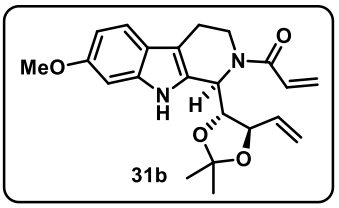
(*R*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (24b). Red sticky liquid (0.55 g) **$[\alpha]_D^{26}$** = + 13.55 (*c* = 0.8, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.53 (br. s., 1 H), 7.51 (d, *J* = 8.2 Hz, 1 H), 7.40–7.36 (m, 1 H), 7.18 (dt, *J* = 1.4, 7.6 Hz, 1 H), 7.10 (dt, *J* = 0.9, 7.3 Hz, 1 H), 6.06–5.94 (m, 1 H), 5.51 (td, *J* = 1.2, 17.3 Hz, 1 H), 5.29 (td, *J* = 1.2, 10.4 Hz, 1 H), 4.59–4.53 (m, 1 H), 4.21–4.16 (m, 1 H), 3.86 (dd, *J* = 7.6, 8.9 Hz, 1 H), 3.35–3.29 (m,

1 H), 3.04 (ddd, *J* = 5.0, 8.8, 12.7 Hz, 1 H), 2.83–2.70 (m, 2 H), 1.59 (s, 3 H), 1.50 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 136.3, 135.5, 134.0, 127.0, 121.7, 119.1, 118.3, 118.1, 110.9, 109.6, 109.0, 83.0, 81.7, 56.2, 42.8, 27.2, 27.1, 22.3; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{18}H_{23}N_2O_2$ 299.1754, found 299.1754; **IR ($CHCl_3$)** ν_{max} 2923, 1648, 1158, 1037 cm^{-1}.

1-((*S*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)prop-2-en-1-one (31a). To a stirred solution of compound **30a** (0.5 g, 1.523 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added acryloyl chloride (0.2 mL, 2.285 mmol) followed by triethylamine (0.7 mL, 4.570 mmol) and stirred at 0 °C for 2 hours. After 2 h, saturated $NaHCO_3$ solution (20 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure and crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford compound **31a** (0.350 g, 63%) as a pale yellow solid. **Mp** 151–153 °C; **$[\alpha]_D^{26}$** = + 130.04 (*c* = 2.5, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.26 (br. s., 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 2.3 Hz, 1 H), 6.77 (dd, *J* = 2.3, 8.4 Hz, 1 H), 6.62 (dd, *J* = 10.7, 16.8 Hz, 1 H), 6.31 (dd, *J* = 1.9, 17.2 Hz, 1 H), 5.91 (d, *J* = 9.9 Hz, 1 H), 5.79–5.71 (m, 2 H), 5.37 (d, *J* = 16.8 Hz, 1 H), 5.23–5.18 (m, 1 H), 4.77 (t, *J* = 8.0 Hz, 1 H), 4.17–4.11 (m, 1 H), 3.97–3.92 (m, 1 H), 3.85 (s, 3 H), 3.41–3.32 (m, 1 H), 2.84–2.72 (m, 2 H), 1.61 (s, 3 H), 1.45 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 166.7, 156.4, 136.8, 134.9, 131.1, 128.5, 127.7, 120.7, 119.1, 118.6, 109.5, 109.2, 108.0, 94.8, 81.2, 80.4, 55.6, 51.3, 42.3, 27.1, 27.1, 22.4; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_4$ 383.1965, found 383.1961; **IR ($CHCl_3$)** ν_{max} 3360, 2987, 1633, 1047 cm^{-1}.

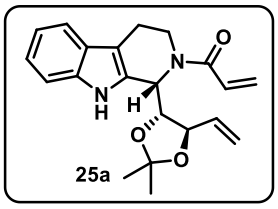


1-((*R*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)prop-2-en-1-one (31b). Compound **31b** can be synthesized from compound **30b** (0.5 g, 1.523 mmol) with the same procedure followed for the synthesis of compound **31a.** The crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford compound **31b** (0.350 g, 63%) as a pale yellow solid. **Mp**



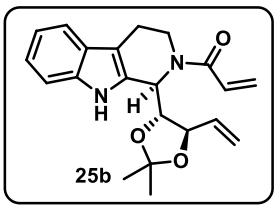
155–157 °C; **[α]$_D^{26}$** = – 51.60 (*c* = 2.0, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.23 (s, 1 H), 7.34 (d, *J* = 8.6 Hz, 1 H), 6.91 (d, *J* = 2.1 Hz, 1 H), 6.77 (dd, *J* = 2.3, 8.5 Hz, 1 H), 6.61 (dd, *J* = 10.6, 16.8 Hz, 1 H), 6.30 (dd, *J* = 1.8, 16.8 Hz, 1 H), 5.91 (d, *J* = 9.6 Hz, 1 H), 5.78–5.69 (m, 2 H), 5.41–5.34 (m, 1 H), 5.20 (dd, *J* = 1.1, 10.3 Hz, 1 H), 4.77 (t, *J* = 7.8 Hz, 1 H), 4.14 (dd, *J* = 3.7, 14.2 Hz, 1 H), 3.94 (dd, *J* = 8.1, 9.6 Hz, 1 H), 3.86 (s, 3 H), 3.37 (ddd, *J* = 4.4, 11.4, 14.2 Hz, 1 H), 2.87–2.71 (m, 2 H), 1.62 (s, 3 H), 1.44 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 166.8, 156.5, 136.9, 134.9, 131.2, 128.5, 127.8, 120.8, 119.1, 118.6, 109.5, 109.3, 108.0, 94.9, 81.2, 80.4, 55.7, 51.3, 42.4, 27.1, 27.0, 22.4; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_4$ 383.1965, found 383.1966; **IR ($CHCl_3$)** ν_{max} 3364, 2992, 1627, 1046 cm^{-1}.

1-((*S*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)prop-2-en-1-one (25a). Compound **25a** can be synthesized



from compound **24a** (1 g, 3.353 mmol) with the same procedure followed for the synthesis of compound **31a.** The crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford compound **25a** (0.69 g, 60%) as a pale yellow solid. **Mp** 154–156 °C; **[α]$_D^{26}$** = + 104.44 (*c* = 2.0, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.40 (br. s., 1 H), 7.49 (d, *J* = 7.3 Hz, 1 H), 7.40 (d, *J* = 7.9 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.15–7.09 (m, 1 H), 6.64 (dd, *J* = 10.7, 16.8 Hz, 1 H), 6.34 (d, *J* = 17.1 Hz, 1 H), 5.97 (d, *J* = 9.2 Hz, 1 H), 5.81–5.71 (m, 2 H), 5.40 (d, *J* = 17.1 Hz, 1 H), 5.22 (d, *J* = 9.8 Hz, 1 H), 4.80 (t, *J* = 7.9 Hz, 1 H), 4.20–4.14 (m, 1 H), 3.96 (t, *J* = 8.9 Hz, 1 H), 3.43–3.34 (m, 1 H), 2.88–2.78 (m, 2 H), 1.64 (s, 3 H), 1.46 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 166.8, 136.1, 134.9, 132.5, 128.6, 127.7, 126.4, 122.1, 119.5, 119.1, 118.1, 111.1, 109.6, 108.1, 81.1, 80.4, 51.3, 42.4, 27.1, 27.1, 22.4; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{21}H_{25}N_2O_3$ 353.1860, found 353.1855; **IR ($CHCl_3$)** ν_{max} 3455, 2993, 1218, 1049 cm^{-1}.

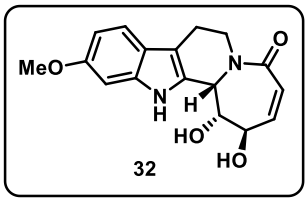
1-((*R*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)prop-2-en-1-one (25b). Compound **25b** can be synthesized



from compound **24b** (1 g, 3.353 mmol) with the same procedure followed for the synthesis of compound **31a.** The crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford compound **25b** (0.69 g, 60%) as a pale yellow solid. **Mp** 159–161 °C; **[α]$_D^{26}$** = – 78.04 (*c* = 0.8,

$CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.30 (s, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.22–7.17 (m, 1 H), 7.15–7.10 (m, 1 H), 6.71 (dd, *J* = 10.5, 16.9 Hz, 1 H), 6.33 (dd, *J* = 1.8, 16.9 Hz, 1 H), 6.00 (s, 1 H), 5.90 (ddd, *J* = 6.9, 10.4, 17.1 Hz, 1 H), 5.78 (dd, *J* = 1.8, 10.5 Hz, 1 H), 5.49 (d, *J* = 16.9 Hz, 1 H), 5.32 (d, *J* = 11.0 Hz, 1 H), 4.34–4.28 (m, 1 H), 4.26 (d, *J* = 6.9 Hz, 1 H), 4.22–4.18 (m, 1 H), 3.80–3.70 (m, 1 H), 2.86–2.79 (m, 2 H), 1.47 (s, 3 H), 1.42 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 167.1, 136.0, 134.7, 130.0, 128.4, 127.9, 126.4, 122.1, 119.9, 119.6, 118.1, 111.0, 109.7, 108.9, 81.9, 78.1, 48.7, 43.2, 26.8, 26.8, 22.0; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{21}H_{25}N_2O_3$ 353.1860, found 353.1855; **IR ($CHCl_3$)** ν_{max} 3457, 2995, 1217, 1050 cm^{-1}.

(1*R*,2*R*,13b*S*)-1,2-Dihydroxy-11-methoxy-1,2,7,8,13,13b-hexahydro-5*H*-azepino [1',2':1,2]pyrido[3,4-*b*]indol-5-one (32). By taking the di-olefinic compound **31a**

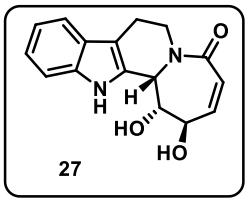


32

(0.250 g, 0.654 mmol) in toluene (150 mL), purged the solution with argon for 10-15 min. Then add G-II (0.011 g, 0.013 mmol) catalyst and reflux the reaction mixture at 110 °C for 12 h. After 12 h, the reaction mixture was cooled to room temperature and the solvent was evaporated through reduced pressure to obtain acetonide protected tetracyclic intermediate (190 mg crude), which was used for further reaction. The above crude compound was taken in AcOH: H_2O (4:1) (15 mL) solution and the reaction mixture were stirred at 45 °C for 3 hours. After the completion of the reaction, the solvent was evaporated under reduced pressure. The solid residue was dissolved in ethyl acetate (30 mL), and quenched the reaction mixture with a saturated solution of $NaHCO_3$ (10 mL), and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous sodium sulphate, concentrated and the crude compound was purified by column chromatography on silica gel (90:10; dichloromethane:methanol) to afford dihydroxy compound **32** (0.115 g, 56% over two steps) as a colorless solid. ; **Mp** 189–191 °C; **$[\alpha]_D^{26}$** = + 74.05 (*c* = 1.5, $CHCl_3$); **^{1}H NMR (CD_3OD, 500 MHz)** δ 7.29 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 1.9 Hz, 1 H), 6.67 (dd, *J* = 2.1, 8.6 Hz, 1 H), 6.40 (dd, *J* = 3.6, 11.6 Hz, 1 H), 5.99 (dd, *J* = 2.3, 11.8 Hz, 1 H), 5.03 (br. s., 1 H), 4.81 (d, *J* = 5.7 Hz, 1 H), 4.43–4.40 (m, 1 H), 4.35 (td, *J* = 3.2, 6.5 Hz, 1 H), 3.80 (s, 3 H), 3.40 (dt, *J* = 4.2, 12.2 Hz, 1 H), 2.84 (dd, *J* = 2.3, 15.3 Hz, 1 H), 2.71–2.64 (m, 1 H); **^{13}C NMR (CD_3OD, 125 MHz)** δ 170.7, 157.8, 144.3, 139.4, 129.1, 125.6, 122.6, 119.4, 111.2,

109.7, 96.1, 83.5, 76.4, 58.0, 56.2, 41.0, 21.9; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_4$ 315.1339, found 315.1331; **IR ($CHCl_3$)** ν_{max} 3367, 2929, 1445, 1026 cm^{-1}.

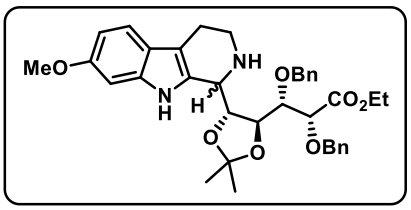
(1*R*,2*R*,13b*S*)-1,2-Dihydroxy-1,2,7,8,13,13b-hexahydro-5*H*-azepino[1',2':1,2] pyrido[3,4-*b*]indol-5-one (27). Compound **27** can be synthesized from compound



27

25a (0.250 g, 0.710 mmol) by the same procedure followed for the synthesis of compound **32**. The crude compound was purified by column chromatography on silica gel (90:10; dichloromethane:methanol) to afford dihydroxy compound **27** (0.11 g, 53% over two steps) as a colorless solid. **Mp** 209–211 °C; $[\alpha]_D^{26}$ = + 70.20 (*c* = 1.5, $CHCl_3$); **^{1}H NMR (CD_3OD, 500 MHz)** δ 7.46 (d, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.11 (t, *J* = 7.4 Hz, 1 H), 7.05–7.00 (m, 1 H), 6.44 (dd, *J* = 3.8, 11.4 Hz, 1 H), 6.02 (d, *J* = 11.8 Hz, 1 H), 5.10 (br. s., 1 H), 4.88 (d, *J* = 5.3 Hz, 1 H), 4.49–4.46 (m, 1 H), 4.41–4.37 (m, 1 H), 3.44 (dt, *J* = 3.8, 12.2 Hz, 1 H), 2.94–2.89 (m, 1 H), 2.78–2.71 (m, 1 H); **^{13}C NMR (CD_3OD, 125 MHz)** δ 170.7, 144.4, 138.6, 130.5, 128.1, 125.6, 122.6, 120.0, 118.8, 112.2, 111.2, 83.6, 76.4, 58.0, 41.0, 21.9; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1234, found 285.1235; **IR ($CHCl_3$)** ν_{max} 3440, 3301, 1590, 1084 cm^{-1}.

Ethyl (2*R*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-5-(7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (39a & 39b).



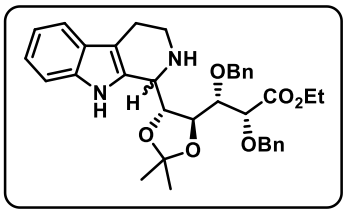
To a solution of aldehyde **38** (2.5 g, 5.653 mmol) in chloroform (40 mL) was added 6-methoxy tryptamine (**17**) (1.6 g, 8.480 mmol) and Na_2SO_4 (0.8 g, 5.653 mmol) at room temperature. The reaction mixture was refluxed for 12 hours at 70 °C. After 12 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude compound was purified by column chromatography on silica gel (60:40; petroleum ether:EtOAc) to afford pure product as a red sticky liquid **39a** and **39b** (2 g, 57%) with the diastereomeric ratio 2:1.

Ethyl (2*R*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-5-((*S*)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (39a). Red sticky liquid (1.33 g) $[\alpha]_D^{27}$ = – 14.73 (*c* = 0.4, $CHCl_3$); **^{1}H NMR ^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.38 (s, 1 H), 7.49–7.45 (m, 2 H), 7.43–7.28 (m, 8 H), 6.77–6.73 (m, 2

H), 6.28 (d, *J* = 9.2 Hz, 1 H), 5.19 (d, *J* = 11.6 Hz, 1 H), 4.94–4.87 (m, 2 H), 4.35–4.21 (m, 3 H), 4.18–4.05 (m, 2 H), 4.00–3.95 (m, 1 H), 3.88–3.84 (m, 1 H), 3.83 (s, 3 H), 3.32–3.24 (m, 1 H), 2.97 (br. s., 1 H), 2.80–2.65 (m, 3 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.35 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 162.8, 156.3, 147.0, 136.5, 128.6 (3C), 128.5, 128.5 (2C), 128.5, 128.4, 128.4, 128.3 (3C), 128.2, 123.8, 121.3, 120.9, 118.7, 110.1, 109.1, 108.9, 94.8, 82.8, 74.6, 74.5, 61.5, 55.7, 55.5, 42.6, 27.1, 27.0, 21.5, 14.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3060; **IR ($CHCl_3$)** ν_{max} 2926, 1732, 1148, 1081 cm^{-1}.

Ethyl (2*R*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-5-((*R*)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (39b). Red sticky liquid (0.66 g) $[\alpha]_D^{27}$ = + 25.50 (*c* = 0.4, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.36 (s, 1 H), 7.38–7.32 (m, 3 H), 7.27–7.13 (m, 7 H), 6.80–6.77 (m, 2 H), 6.23 (d, *J* = 9.1 Hz, 1 H), 5.07 (d, *J* = 10.8 Hz, 1 H), 4.71 (d, *J* = 10.8 Hz, 1 H), 4.64 (dd, *J* = 7.9, 9.2 Hz, 1 H), 4.39–4.37 (m, 1 H), 4.27 (dq, *J* = 1.8, 7.1 Hz, 3 H), 4.18 (dd, *J* = 5.1, 7.9 Hz, 2 H), 3.86 (s, 3 H), 3.85–3.84 (m, 1 H), 3.84–3.81 (m, 1 H), 3.31–3.25 (m, 1 H), 2.91 (ddd, *J* = 4.8, 8.7, 13.0 Hz, 1 H), 2.63–2.57 (m, 1 H), 2.54–2.47 (m, 1 H), 2.12 (br. s., 1 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.35–1.31 (m, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 162.6, 156.3, 146.2, 136.4, 135.8, 130.2, 128.6 (3C), 128.6, 128.6, 128.5, 128.5, 128.5, 128.5, 125.4 (3C), 121.4 (2C), 118.7, 110.7, 109.4, 108.9, 94.7, 81.9, 74.8, 72.3, 61.5, 55.8, 53.7, 42.7, 27.0, 26.4, 22.2, 14.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3062; **IR ($CHCl_3$)** ν_{max} 2921, 1731, 1213, 1077 cm^{-1}.

Ethyl (2*R*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-2,2-dimethyl-5-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1,3-dioxolan-4-yl)propanoate (52a & 52b).



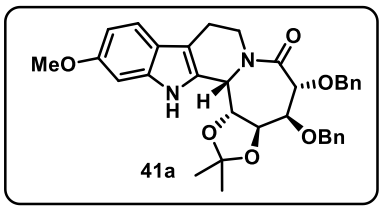
Compound **52a** and **52b** can be synthesized from aldehyde **38** (1 g, 2.261 mmol) and Tryptamine **23** (0.543 g, 3.392 mmol) with the same procedure followed for the synthesis of compound (**39a** and **39b**). The crude compound was purified by column chromatography on silica gel (60:40; petroleum ether:EtOAc) to afford pure product as a red sticky liquid **52a** and **52b** as diastereomeric mixture (0.6 g, 46%) with the diastereomeric ratio 2:1.

Ethyl (2*R*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-2,2-dimethyl-5-((*S*)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1,3-dioxolan-4-yl)propanoate (52a). Red

sticky liquid (0.4 g) **$[\alpha]_D^{26}$** = + 6.020 (*c* = 0.6, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.99 (s, 1 H), 7.49–7.46 (m, 1 H), 7.34–7.31 (m, 3 H), 7.31–7.27 (m, 4 H), 7.25–7.19 (m, 3 H), 7.14–7.07 (m, 3 H), 4.80 (dd, *J* = 3.1, 11.2 Hz, 2 H), 4.53 (dd, *J* = 11.2, 17.7 Hz, 2 H), 4.32–4.28 (m, 2 H), 4.27 (d, *J* = 3.3 Hz, 1 H), 4.26–4.20 (m, 2 H), 4.15 (dd, *J* = 5.7, 8.7 Hz, 1 H), 4.09 (dd, *J* = 3.3, 8.6 Hz, 1 H), 3.20–3.14 (m, 1 H), 2.85 (ddd, *J* = 5.6, 9.1, 13.0 Hz, 1 H), 2.66–2.60 (m, 2 H), 2.41 (br. s., 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 171.4, 136.8, 136.6, 135.8, 129.0 (2C), 128.6(2C), 128.5, 128.4, 128.3 (2C), 128.1 (2C), 127.8, 126.7, 121.9, 119.4, 118.1, 111.0, 110.0, 109.5, 80.9, 80.2, 77.7, 75.9, 73.7, 73.2, 61.4, 52.7, 42.3, 27.3, 26.4, 21.3, 14.1; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{35}H_{41}N_2O_6$ 585.2959, found 585.2947; **IR ($CHCl_3$)** ν_{max} 2986, 1724, 1103, 1017cm^{-1}.

Ethyl (2*R*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-2,2-dimethyl-5-((*R*)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1,3-dioxolan-4-yl)propanoate (52b). Red sticky liquid (0.2 g) **$[\alpha]_D^{26}$** = + 27.41 (*c* = 2.3, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.94 (s, 1 H), 7.40 (d, *J* = 7.3 Hz, 1 H), 7.27–7.23 (m, 3 H), 7.23–7.20 (m, 3 H), 7.19 (d, *J* = 1.6 Hz, 1 H), 7.17–7.11 (m, 3 H), 7.07–6.99 (m, 3 H), 4.72 (dd, *J* = 3.7, 11.2 Hz, 2 H), 4.45 (dd, *J* = 11.3, 19.9 Hz, 2 H), 4.27–4.23 (m, 2 H), 4.19 (d, *J* = 3.0 Hz, 1 H), 4.18–4.11 (m, 2 H), 4.06–3.99 (m, 2 H), 3.11–3.04 (m, 1 H), 2.81–2.73 (m, 1 H), 2.58–2.51 (m, 2 H), 2.39 (br. s., 1 H), 1.40 (s, 3 H), 1.29 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 171.5, 137.1, 137.0, 135.7, 132.5, 128.7 (2C), 128.5 (2C), 128.3 (2C), 128.2 (2C), 128.2, 127.9, 127.2, 121.5, 119.1, 118.0, 110.9, 110.6, 109.3, 81.4, 81.1, 78.4, 76.1, 74.0, 73.3, 61.3, 53.6, 42.8, 27.4, 26.6, 22.4, 14.1; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{35}H_{41}N_2O_6$ 585.2959, found 585.2949; **IR ($CHCl_3$)** ν_{max} 2984, 1725, 1104, 1019 cm^{-1}.

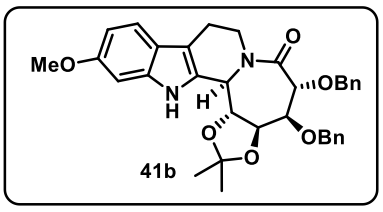
(3a*S*,4*S*,5*R*,14b*S*,14c*R*)-4,5-Bis(benzyloxy)-12-methoxy-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4'',5'':3',4']azepino[1',2':1,2]pyrido[3,4-*b*]indol-6-one (41a).



To a solution of compound **39a** (0.5 g, 0.813 mmol) in EtOH:THF:H_2O (1:1:1) (30 mL) was added LiOH (0.061 g, 2.567 mmol) at 0 °C. The reaction mixture was left at room temperature for 2 hours. After 2 h, The reaction mixture was quenched with 1N HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulphate. The solvent was removed

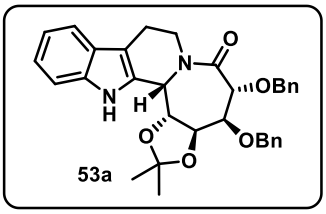
under reduced pressure to obtain an intermediate acid (370 mg crude) which was used for further reaction. The above crude compound (0.370 g, 0.631 mmol) was taken in DMF (5 mL) under argon atmosphere at room temperature and added HBTU (0.311 g, 0.820 mmol) followed by Et_3N (0.17 mL, 1.262 mmol) and HOBt (0.017 g, 0.126 mmol) at room temperature. Leave the reaction mixture for the next 12 h of stirring at room temperature. After 12 h, dilute the reaction mixture with ethyl acetate (30 mL) and remove the DMF with ice-cold water. Wash the organic layer with saturated $NaHCO_3$ (10 mL), 1N HCl (10 mL) and brine solution. The solvent was evaporated through reduced pressure and the crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford tetracyclic compound **41a** (0.130 g, 28% over two steps) as a colorless solid. **Mp** 117–119 °C; **$[\alpha]_D^{26}$** = + 24.24 (*c* = 1.5, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.32 (s, 1 H), 7.42 (d, *J* = 8.6 Hz, 1 H), 7.40–7.35 (m, 3 H), 7.35–7.31 (m, 2 H), 7.29 (dd, *J* = 1.8, 4.9 Hz, 3 H), 7.24 (dd, *J* = 2.8, 6.7 Hz, 2 H), 6.90 (d, *J* = 2.0 Hz, 1 H), 6.80 (dd, *J* = 2.3, 8.6 Hz, 1 H), 5.47 (d, *J* = 8.5 Hz, 1 H), 4.98–4.92 (m, 1 H), 4.80 (s, 2 H), 4.69 (d, *J* = 6.4 Hz, 1 H), 4.63 (d, *J* = 11.5 Hz, 1 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.34 (dd, *J* = 2.3, 8.9 Hz, 1 H), 4.27 (dd, *J* = 2.4, 6.4 Hz, 1 H), 4.03 (t, *J* = 8.8 Hz, 1 H), 3.87 (s, 3 H), 3.14–3.07 (m, 1 H), 2.90–2.84 (m, 1 H), 2.79–2.70 (m, 1 H), 1.62 (s, 3 H), 1.45 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 170.4, 156.6, 138.0, 137.6, 136.4, 128.5 (2C), 128.2 (2C), 128.2, 128.1, 128.0 (2C), 127.5, 127.4 (2C), 120.6, 118.9, 110.8, 109.3, 109.2, 95.0, 83.3, 81.6, 75.5, 73.0, 73.0, 72.0, 55.7, 50.5, 39.8, 27.1, 26.7, 20.7; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2646; **IR ($CHCl_3$)** ν_{max} 3361, 2920, 1635, 1083 cm^{-1}.

(3a*S*,4*S*,5*R*,14b*R*,14c*R*)-4,5-Bis(benzyloxy)-12-methoxy-2,2-dimethyl3a,4,5,8,9, 14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4'',5'':3',4']azepino[1',2':1,2]pyrido[3,4-*b*] indol-6-one (41b). Compound **41b** can be synthesized from **39b** (0.5 g, 0.813 mmol) with the same procedure followed for the synthesis of compound **41a**. The crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford tetracyclic compound **41b** (0.130 g, 28% over two steps) as a colorless solid. **Mp** 122–124 °C; **$[\alpha]_D^{26}$** = + 52.68 (*c* = 2.4, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 7.84 (s, 1 H), 7.42–7.37 (m, 5 H), 7.37–7.31 (m, 4 H), 7.30–7.28 (m, 2 H), 6.88 (d, *J* = 2.3 Hz, 1 H), 6.80



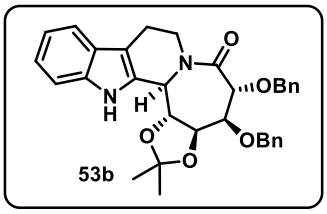
(dd, *J* = 2.1, 8.6 Hz, 1 H), 5.22 (d, *J* = 6.5 Hz, 1 H), 4.94 (d, *J* = 11.1 Hz, 1 H), 4.86 (d, *J* = 12.2 Hz, 1 H), 4.78 (d, *J* = 11.1 Hz, 1 H), 4.76–4.71 (m, 1 H), 4.57 (dd, *J* = 6.5, 8.8 Hz, 1 H), 4.43–4.35 (m, 2 H), 4.23 (dd, *J* = 3.4, 6.1 Hz, 1 H), 3.86 (s, 3 H), 3.75 (dd, *J* = 3.4, 9.2 Hz, 1 H), 3.28–3.21 (m, 1 H), 2.95–2.89 (m, 1 H), 2.81–2.73 (m, 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 166.9, 157.0, 141.2, 138.1, 137.6, 137.3, 128.2 (2C), 128.2 (2C), 128.1 (2C), 128.0 (2C), 127.6, 127.6, 125.5, 120.8, 119.0, 117.0, 109.9, 109.1, 105.9, 94.7, 87.0, 82.6, 76.4, 75.5, 72.9, 55.7, 41.8, 27.3, 26.1, 21.7; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2646; **IR ($CHCl_3$)** ν_{max} 3338, 2926, 1635, 1087 cm^{-1}.

(3a*S*,4*S*,5*R*,14b*S*,14c*R*)-4,5-Bis(benzyloxy)-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4'',5'':3',4']azepino[1',2':1,2] pyrido[3,4-*b*]indol-6-one



(53a). Compound **53a** can be synthesized from **52a** (0.2 g, 0.342 mmol) with the same procedure followed for the synthesis of compound **41a**. The crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford tetracyclic compound **53a** (0.10 g, 30% over two steps) as a colorless solid. **Mp** 154–156 °C; **$[\alpha]_D^{26}$** = + 2.19 (*c* = 0.5, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.37 (br. s., 1 H), 7.53 (d, *J* = 7.3 Hz, 1 H), 7.44–7.29 (m, 6 H), 7.23 (d, *J* = 7.3 Hz, 1 H), 7.18–7.09 (m, 2 H), 6.97 (t, *J* = 7.0 Hz, 2 H), 6.90 (d, *J* = 6.7 Hz, 2 H), 4.87–4.74 (m, 3 H), 4.52–4.47 (m, 2 H), 4.41 (d, *J* = 4.9 Hz, 1 H), 4.31 (d, *J* = 11.0 Hz, 1 H), 4.18 (t, *J* = 8.2 Hz, 1 H), 3.93–3.85 (m, 1 H), 3.81 (br. s., 1 H), 3.50 (s, 1 H), 3.01–2.90 (m, 1 H), 2.82 (d, *J* = 15.3 Hz, 1 H), 1.57 (br. s., 3 H), 1.51 (br. s., 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 168.9, 137.8, 136.6, 136.2, 130.8, 128.3 (2C), 128.2 (2C), 128.2 (2C), 127.9 (2C), 127.8, 127.6, 126.4, 122.3, 119.7, 118.5, 111.2 (2C), 110.0, 82.8, 81.9, 78.8, 74.8, 72.9, 72.3, 57.7, 43.2, 27.3, 27.0, 21.4; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{33}H_{35}N_2O_5$ 539.2540, found 539.2542; **IR ($CHCl_3$)** ν_{max} cm^{-1} 3319, 2907, 1650, 1078 cm^{-1}.

(3a*S*,4*S*,5*R*,14b*R*,14c*R*)-4,5-Bis(benzyloxy)-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4'',5'':3',4']azepino[1',2':1,2] pyrido[3,4-*b*]indol-6-one



(53b). Compound **53b** can be synthesized from **52b** (0.2 g, 0.342 mmol) with the same procedure followed for the synthesis of compound **41a**. The crude compound was purified by column chromatography on silica gel (70:30;

petroleum ether:EtOAc) to afford tetracyclic compound **53b** (0.10 g, 30% over two steps) as a colorless solid. **Mp** 160–163 °C; **$[\alpha]_D^{26}$** = + 1.26 (*c* = 0.8, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 8.08 (br. s., 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 6.9 Hz, 2 H), 7.37 (dd, *J* = 6.1, 8.0 Hz, 5 H), 7.34–7.32 (m, 1 H), 7.32–7.27 (m, 3 H), 7.23–7.19 (m, 1 H), 7.16–7.12 (m, 1 H), 5.25 (d, *J* = 6.1 Hz, 1 H), 4.94 (d, *J* = 11.4 Hz, 1 H), 4.87 (d, *J* = 11.8 Hz, 1 H), 4.78 (d, *J* = 11.4 Hz, 1 H), 4.77–4.72 (m, 1 H), 4.61 (dd, *J* = 6.5, 8.8 Hz, 1 H), 4.43–4.37 (m, 2 H), 4.24 (dd, *J* = 3.2, 6.3 Hz, 1 H), 3.75 (dd, *J* = 3.4, 8.8 Hz, 1 H), 3.29–3.22 (m, 1 H), 2.96 (td, *J* = 3.5, 15.5 Hz, 1 H), 2.80 (ddt, *J* = 3.4, 5.1, 10.4 Hz, 1 H), 1.48 (s, 3 H), 1.35 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 169.9, 138.3, 137.3, 136.9, 128.4 (2C), 128.3 (2C), 128.2, 128.0 (2C), 127.9 (2C), 127.8, 127.8, 127.7, 126.3, 122.4, 119.7, 118.3, 111.6, 111.2, 111.1, 81.2, 78.0, 74.9, 73.8, 72.4, 51.2, 41.3, 26.8, 26.6, 20.7; **HRMS (ESI) *m/z*** $[M+H]^+$ calcd for $C_{33}H_{35}N_2O_5$ 539.2540, found 539.2539; **IR ($CHCl_3$)** ν_{max} 3302, 2911, 1650, 1077 cm^{-1}.

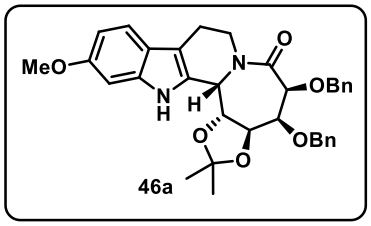
Ethyl (2*S*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-5-(7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl) propanoate (44a & 44b). To a solution of aldehyde **43** (1 g, 2.261 mmol) in chloroform (40 mL) was added 6-methoxytryptamine (**17**) (0.644 g, 3.392 mmol) and Na_2SO_4 (0.32 g, 2.261 mmol) at room temperature. The reaction mixture was refluxed for 12 hours at 70 °C. After 12 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude compound was purified by column chromatography on silica gel using (60:40; petroleum ether:EtOAc) to afford pure product as a red sticky liquid **44a** and **44b** as diastereomeric mixture (0.77 g, 55%) with the diastereomeric ratio 2:1.

Ethyl (2*S*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-5-((*S*)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (44a). Red sticky liquid (0.512 g) **$[\alpha]_D^{27}$** = – 10.63 (*c* = 2.2, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.38 (s, 1 H), 7.41–7.34 (m, 3 H), 7.34–7.28 (m, 8 H), 6.82 (d, *J* = 2.1 Hz, 1 H), 6.76 (dd, *J* = 2.3, 8.5 Hz, 1 H), 4.78 (dd, *J* = 11.4, 15.8 Hz, 2 H), 4.57–4.47 (m, 4 H), 4.25–4.15 (m, 3 H), 4.04 (d, *J* = 8.8 Hz, 1 H), 3.96 (dd, *J* = 3.5, 7.0 Hz, 1 H), 3.85 (s, 3 H), 3.09 (td, *J* = 4.5, 12.5 Hz, 1 H), 2.77 (ddd, *J* = 5.3, 8.0, 12.8 Hz, 1 H), 2.65–

2.51 (m, 2 H), 1.98 (br. s., 1 H), 1.53 (s, 3 H), 1.40 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 170.3, 156.2, 137.4, 137.2, 136.4, 132.9, 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.9, 127.8, 121.6, 118.6, 109.8, 109.5, 108.7, 94.9, 81.8, 81.5, 78.6, 78.2, 73.5, 72.7, 61.0, 55.8, 55.7, 42.4, 27.7, 27.4, 22.5, 14.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3051 **IR ($CHCl_3$)** ν_{max} 2927, 1733, 1453, 1094 cm^{-1}.

Ethyl (2*S*,3*S*)-2,3-Bis(benzyloxy)-3-((4*S*,5*R*)-5-((*R*)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (44b). Red sticky liquid (0.256 g) $[\alpha]_D^{27}$ = + 27.42 (*c* = 2.2, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.02 (s, 1 H), 7.39–7.33 (m, 3 H), 7.33–7.30 (m, 6 H), 7.28 (d, *J* = 2.9 Hz, 2 H), 6.72 (dd, *J* = 2.3, 8.6 Hz, 1 H), 6.58 (d, *J* = 2.1 Hz, 1 H), 4.86 (d, *J* = 11.1 Hz, 2 H), 4.52 (d, *J* = 10.6 Hz, 1 H), 4.48–4.44 (m, 2 H), 4.36–4.30 (m, 2 H), 4.25–4.19 (m, 1 H), 4.13–4.07 (m, 2 H), 3.94 (dd, *J* = 1.6, 8.9 Hz, 1 H), 3.81 (s, 3 H), 3.06–2.99 (m, 1 H), 2.78 (ddd, *J* = 4.3, 10.6, 12.9 Hz, 1 H), 2.59–2.53 (m, 1 H), 2.44 (dtd, *J* = 2.4, 5.1, 7.8 Hz, 1 H), 1.55 (s, 3 H), 1.32 (s, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 169.8, 156.1, 137.4, 136.8, 136.4, 131.4, 128.8 (2C), 128.4 (2C), 128.4 (2C), 128.1, 127.9 (2C), 127.8, 121.7, 118.4, 110.5, 109.2, 108.7, 94.8, 82.4, 81.9, 78.5, 76.1, 73.5, 72.7, 61.0, 55.7, 54.0, 42.9, 27.7, 26.4, 22.6, 13.9; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3065; **IR ($CHCl_3$)** ν_{max} 2919, 1735, 1457, 1091cm^{-1}.

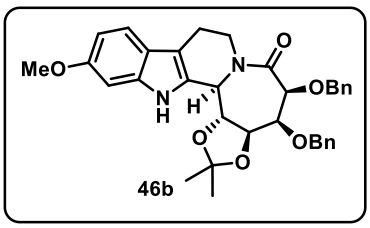
(3a*S*,4*S*,5*S*,14b*S*,14c*R*)-4,5-Bis(benzyloxy)-12-methoxy-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4'',5'':3',4']azepino[1',2':1,2]pyrido[3,4-*b*]indol-6-one (46a). To a solution of compound, **44a** (0.5 g, 0.813 mmol) in EtOH:THF:H_2O (1:1:1) (30 mL) was added LiOH (0.061 g, 2.567 mmol) at 0 °C. The reaction mixture was left at room temperature for 2 hours. After 2 h, The reaction mixture was quenched with 1N HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water (10 mL) and brine (10 ml), dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain an intermediate acid (360 mg crude), which was used as such for further reaction. The above crude compound (0.360 g, 0.614 mmol) was taken in DMF (5 mL) under argon atmosphere at room temperature and added HATU (0.30 g, 0.792



46a

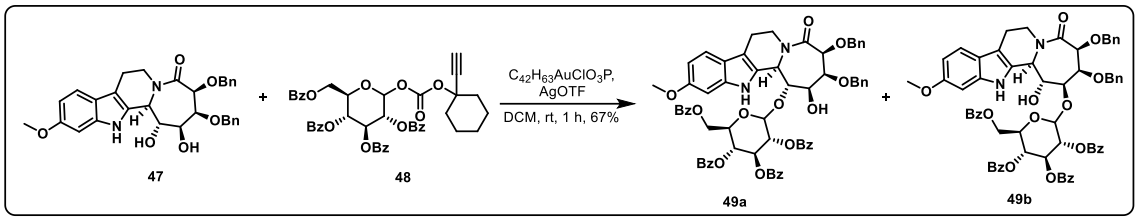
mmol) followed by DIPEA (0.14 mL, 0.729 mmol) at room temperature. Leave the reaction mixture for the next 12 hours of stirring at room temperature. After 12 h, dilute the reaction mixture with ethyl acetate (30 mL) and remove the DMF with ice-cold water. Wash the organic layer with saturated $NaHCO_3$ (10 mL), 1N HCl (10 mL) and brine. The solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography on silica gel (70:30 petroleum ether/ethyl acetate) to afford tetracyclic compound **46a** (0.150 g, 32% over two steps) as a colorless solid. **Mp** 180–182 °C; **$[\alpha]_D^{26}$** = + 94.44 (*c* = 2.4, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.22 (s, 1 H), 7.42–7.38 (m, 5 H), 7.37 (s, 1 H), 7.36–7.28 (m, 4 H), 7.28–7.23 (m, 1 H), 6.90 (d, *J* = 2.1 Hz, 1 H), 6.81 (dd, *J* = 2.1, 8.6 Hz, 1 H), 5.22–5.15 (m, 1 H), 5.07 (d, *J* = 12.4 Hz, 1 H), 4.96 (d, *J* = 12.0 Hz, 1 H), 4.83 (d, *J* = 12.4 Hz, 1 H), 4.73 (d, *J* = 8.8 Hz, 1 H), 4.43–4.37 (m, 3 H), 4.00 (t, *J* = 8.8 Hz, 1 H), 3.87 (s, 3 H), 3.81 (dd, *J* = 2.1, 8.9 Hz, 1 H), 3.03 (dt, *J* = 3.9, 12.1 Hz, 1 H), 2.90–2.77 (m, 2 H), 1.60 (s, 3 H), 1.43 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 168.9, 156.8, 138.6, 137.8, 137.6, 128.4 (2C), 128.0 (2C), 127.7 (3C), 127.4 (2C), 127.2, 127.2, 120.5, 119.0, 111.6, 110.2, 109.4, 95.0, 83.6, 79.3, 76.6, 74.8, 73.1, 72.1, 55.7, 51.5, 39.4, 27.0, 26.4, 20.8; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2646; **IR ($CHCl_3$)** ν_{max} 3313, 2926, 1156, 1087 cm^{-1}.

(3a*S*,4*S*,5*S*,14b*R*,14c*R*)-4,5-Bis(benzyloxy)-12-methoxy-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4'',5'':3',4']azepino[1',2':1,2]pyrido[3,4-*b*]indol-6-one (46b).



Compound **46b** can be synthesized from **44b** (0.5 g, 0.813 mmol) with the same procedure followed for the synthesis of compound **41a**. The crude compound was purified by column chromatography on silica gel (70:30; petroleum ether:EtOAc) to afford tetracyclic compound **46b** (0.150 g, 32% over two steps) as a colorless solid. **Mp** 185–187 °C; **$[\alpha]_D^{26}$** = + 109.91 (*c* = 2.4, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.37 (s, 1 H), 7.38 (d, *J* = 8.6 Hz, 1 H), 7.3–7.32 (m, 4 H), 7.32–7.30 (m, 4 H), 7.29 (dd, *J* = 1.7, 2.7 Hz, 2 H), 6.85 (d, *J* = 2.1 Hz, 1 H), 6.79 (dd, *J* = 2.3, 8.6 Hz, 1 H), 5.64 (d, *J* = 5.9 Hz, 1 H), 5.25 (dd, *J* = 6.0, 9.4 Hz, 1 H), 4.82–4.76 (m, 1 H), 4.74–4.68 (m, 2 H), 4.55 (d, *J* = 11.9 Hz, 1 H), 4.34 (d, *J* = 5.4 Hz, 1 H), 4.22–4.14 (m, 2 H), 3.86 (s, 3 H), 3.85–3.81 (m, 1 H), 3.60 (ddd, *J* = 4.3, 8.5, 12.7 Hz, 1 H), 2.96 (dddd, *J* = 1.9, 4.6, 8.6, 15.5 Hz, 1 H), 2.73–2.63 (m, 1 H), 1.53 (s, 3 H), 1.46 (s, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 156.6, 138.1, 137.1, 136.8, 128.5, 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.2, 128.0, 127.8, 127.5 (2C), 120.9, 118.8, 111.7, 110.7, 109.3, 94.9, 81.8, 73.9, 73.2, 73.1, 71.7, 55.7, 54.0, 45.2, 26.9, 26.4, 21.0; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2640; **IR ($CHCl_3$)** ν_{max} 3327, 2924, 1155, 1085 cm^{-1}.



(2*R*,3*R*,4*S*,5*R*,6*R*)-2-((Benzoyloxy)methyl)-6-(((1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-bis(benzyloxy)-2-hydroxy-11-methoxy-5-oxo-2,3,4,5,7,8,13,13b-octahydro-1*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-1-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (49a). To a compound **46b** (100 mg, 0.175 mmol) was added AcOH: H_2O (4:1) (15 mL) solution and the reaction mixture was stirred at 45 °C for 3 hours. After completion of the reaction, the reaction mixture was dried under the vacuum to give the solid residue. The solid residue was dissolved in ethyl acetate (20 mL), quenched the reaction mixture with a saturated solution of $NaHCO_3$ (10 mL), and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous sodium sulphate, concentrated and the crude compound was purified by column chromatography (silica gel) to afford di-hydroxy tetracyclic compound **47** (70 mg, 78%) as a colorless solid. To a solution of di-hydroxy tetracyclic compound **47** (70 mg, 0.132 mmol) in CH_2Cl_2 at room temperature was added compound **48** (118 mg, 0.159 mmol) followed by a small quantity of molecular sieves (5 Å). After stirring the reaction mixture for 5 min, [Tris(2,4-di-tert-butylphenyl)phosphite]gold chloride (17 mg, 0.019 mmol) and silver trifluoromethanesulfonate (3 mg, 0.019 mmol) were added and the reaction mixture was stirred for 2 hours at room temperature. After 2 h the reaction mixture was filtered through a short pad of celite and washed with CH_2Cl_2 (10 mL). The combined organic solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography on silica gel

(60:40; petroleum ether:EtOAc) to afford a pure product as a yellow liquid **49a** and **49b** as regioisomeric mixture (70 mg, 67%), with the ratio 1:1.

Yellow liquid (35 mg) $[\alpha]_D^{26}$ = + 7.34 (*c* = 1.0, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.03 (dd, *J* = 1.3, 8.4 Hz, 2 H), 7.91 (dd, *J* = 1.3, 8.3 Hz, 2 H), 7.68–7.62 (m, 3 H), 7.51–7.46 (m, 4 H), 7.35–7.28 (m, 7 H), 7.26–7.22 (m, 9 H), 7.09 (dd, *J* = 1.2, 7.3 Hz, 2 H), 6.87 (t, *J* = 7.8 Hz, 2 H), 6.63–6.58 (m, 2 H), 5.98 (s, 1 H), 5.33 (dd, *J* = 1.3, 3.0 Hz, 1 H), 5.29─5.23 (m, 2 H), 4.90–4.83 (m, 1 H), 4.70–4.58 (m, 4 H), 4.44–4.39 (m, 2 H), 4.24 (dd, *J* = 5.3, 12.1 Hz, 1 H), 4.13 (d, *J* = 7.1 Hz, 1 H), 4.08–4.03 (m, 2 H), 3.99–3.96 (m, 1 H), 3.84 (s, 3 H), 3.80 (td, *J* = 2.8, 5.6 Hz, 1 H), 3.68–3.66 (m, 1 H), 3.37 (dt, *J* = 4.1, 12.4 Hz, 1 H), 2.83 (dd, *J* = 2.8, 15.6 Hz, 1 H), 2.67–2.59 (m, 1 H), 1.64 (br. s., 1 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 168.8, 165.8, 164.8, 164.0, 156.5, 137.1, 137.0, 135.9, 134.3, 133.6, 133.3, 133.0, 130.0 (2C), 129.7 (2C), 129.6 (2C), 129.5, 128.9, 128.8, 128.5 (3C), 128.4 (3C), 128.4 (2C), 128.3, 128.2, 128.2 (2C), 128.2 (3C), 128.1 (3C), 128.1 (2C), 128.1, 127.7, 127.6, 125.6, 121.7, 120.7, 118.5, 110.8, 109.2, 97.3, 94.9, 86.4, 74.0, 73.6, 72.1, 71.8, 70.4, 68.3, 67.7, 63.9, 55.7, 47.6, 40.6, 20.1; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{65}H_{59}N_2O_{15}$ 1107.3910, found 1107.3922; **IR ($CHCl_3$)** ν_{max} 3422, 2954, 1725, 1262, 1093 cm^{-1}.

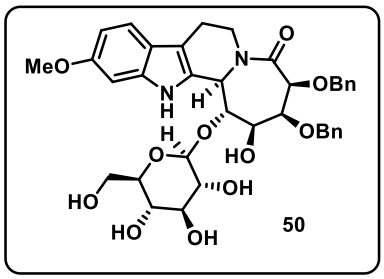
(2*R*,3*R*,4*S*,5*R*)-2-((Benzoyloxy)methyl)-6-(((1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-bis(benzyloxy)-1-hydroxy-11-methoxy-5-oxo-2,3,4,5,7,8,13,13b-octahydro-1*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-2-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyltribenzoate (49b).

Yellow liquid (35 mg); $[\alpha]_D^{26}$ = + 4.50 (*c* = 1.5, $CHCl_3$); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.65 (br. s., 1 H), 7.98 (d, *J* = 7.3 Hz, 4 H), 7.87 (d, *J* = 7.5 Hz, 2 H), 7.84–7.81 (m, 2 H), 7.58–7.54 (m, 1 H), 7.51–7.46 (m, 1 H), 7.43–7.36 (m, 5 H), 7.34–7.28 (m, 4 H), 7.26–7.20 (m, 5 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 7.17–7.11 (m, 3 H), 7.11–7.05 (m, 2 H), 7.00 (br. s., 1 H), 6.81 (dd, *J* = 2.2, 8.6 Hz, 1 H), 6.14 (br. s., 1 H), 5.97–5.92 (m, 1 H), 5.91–5.79 (m, 1 H), 5.63–5.58 (m, 1 H), 4.70 (dd, *J* = 2.6, 12.3 Hz, 1 H), 4.64–4.58 (m, 1 H), 4.49–4.36 (m, 4 H), 4.35–4.22 (m, 3 H), 4.22–3.98 (m, 3 H), 3.85 (s, 3 H), 3.83–3.77 (m, 1 H), 3.24–3.15 (m, 1 H), 2.78–2.70 (m, 1 H), 2.64–2.54 (m, 1 H), 1.70 (br. s., 1 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 170.2, 166.2, 165.7, 165.4, 156.4, 137.7, 137.6, 137.0, 133.6, 133.2, 133.2, 129.8 (3C), 129.7 (3C), 129.7 (4C), 129.6 (3C), 129.3, 129.1, 128.7, 128.4 (3C), 128.4 (4C), 128.3 (3C), 128.2 (3C), 128.1(3C), 128.0 (4C), 127.7, 127.6, 127.5, 121.1, 118.5, 110.2, 109.2, 95.1, 75.9, 72.8, 72.4, 72.1, 69.5, 62.6, 55.6 (2C), 40.5, 20.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for

$C_{65}H_{59}N_2O_{15}$ 1107.3910, found 1107.3915; **IR ($CHCl_3$)** ν_{max} 3423, 2956, 1726, 1261, 1091 cm^{-1}.

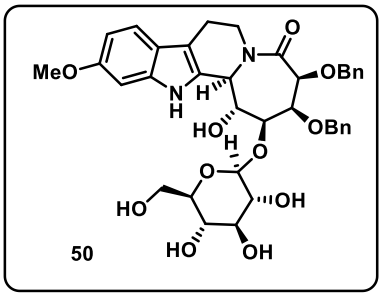
(1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-Bis(benzyloxy)-1,2-dihydroxy-11-methoxy-1,2,3,4,7,8,13, 13b-octahydro-5*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-5-one (47). Colorless solid; **Mp** 207–210 °C; **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 8.47 (br. s., 1 H), 7.45–7.41 (m, 2 H), 7.40–7.37 (m, 2 H), 7.36–7.33 (m, 5 H), 7.33–7.29 (m, 2 H), 6.86–6.82 (m, 1 H), 6.78 (dd, *J* = 2.3, 8.6 Hz, 1 H), 5.16–5.08 (m, 2 H), 4.99 (d, *J* = 11.8 Hz, 1 H), 4.61 (d, *J* = 11.3 Hz, 1 H), 4.59–4.51 (m, 2 H), 4.39 (d, *J* = 11.9 Hz, 1 H), 4.13 (d, *J* = 3.3 Hz, 1 H), 3.82 (s, 3 H), 3.66 (t, *J* = 9.0 Hz, 1 H), 3.54–3.46 (m, 1 H), 3.00–2.92 (m, 1 H), 2.84–2.75 (m, 2 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 167.9, 156.7, 137.7, 137.7, 137.5, 128.7 (2C), 128.5 (2C), 128.4 (2C), 128.0, 127.8, 127.7 (2C), 127.5, 120.5, 119.0, 111.6, 109.1, 94.9, 80.2, 78.1, 77.2, 74.0, 72.4, 71.8, 55.6, 52.3, 38.4, 20.9; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{31}H_{33}N_2O_6$ 529.2333, found 529.2327; **IR ($CHCl_3$)** ν_{max} 3325, 2924, 1627, 1082 cm^{-1}.

(1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-Bis(benzyloxy)-2-hydroxy-11-methoxy-1-(((2*R*,3*R*,4*S*,5*S*, 6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-1,2,3,4,7, 8,13,13b-octahydro-5*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-5-one (50). To a solution of compound **49a** (0.1 g, 0.090 mmol) in methanol (5 mL) at room temperature was added sodium methoxide (0.055 g, 1.084 mmol). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was evaporated in vacuum and the crude compound was purified by column chromatography on silica gel (90:10; dichloromethane/methanol) to afford pentahydroxy compound **50** (30 mg, 48%) as a colorless solid. **$[\alpha]_D^{26}$** = + 24.82 (*c* = 1.0, $CHCl_3$); **^{1}H NMR (Acetone-d_6, 400 MHz)** δ 9.86 (s, 1 H), 7.41–7.39 (m, 3 H), 7.38–7.35 (m, 1 H), 7.33 (d, *J* = 1.4 Hz, 1 H), 7.31 (dd, *J* = 0.9, 3.4 Hz, 1 H), 7.24–7.22 (m, 2 H), 7.16–7.12 (m, 1 H), 7.02 (t, *J* = 7.6 Hz, 2 H), 6.87 (d, *J* = 2.1 Hz, 1 H), 6.73 (dd, *J* = 2.3, 8.6 Hz, 1 H), 6.16 (s, 1 H), 5.64–5.59 (m, 1 H), 4.84–4.78 (m, 1 H), 4.72–4.68 (m, 1 H), 4.65 (s, 1 H), 4.63–4.59 (m, 2 H), 4.30 (d, *J* = 4.5 Hz, 1 H), 4.22–4.16 (m, 1 H), 4.05 (dd, *J* = 3.7, 5.3 Hz, 1 H), 4.02–3.98 (m, 1 H), 3.87 (d, *J* = 4.6 Hz, 1 H), 3.82 (s, 3 H), 3.77 (dd, *J* = 1.6, 3.3 Hz, 1 H), 3.62–3.54 (m, 2 H), 3.53–3.47 (m, 2 H), 3.42–3.36 (m, 1 H), 3.32–3.23 (m, 2



H), 2.87–2.83 (m, 3 H), 2.82–2.80 (m, 1 H), 2.65–2.55 (m, 1 H); **^{13}C NMR (Acetone-d_6, 125 MHz)** δ 169.4, 157.3, 139.1, 138.8, 138.2, 138.2, 130.4, 129.8, 129.3, 129.2, 128.9, 128.8, 128.6, 128.6, 126.7, 122.0, 121.3, 119.2, 110.6, 109.5, 99.0, 95.9, 87.8, 79.0, 77.3, 74.7, 74.5, 74.0, 73.9, 73.7, 71.4, 70.4, 62.9, 55.8, 48.9, 41.1, 21.0; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{37}H_{43}N_2O_{11}$ 691.2861, found 691.2855. **IR ($CHCl_3$)** ν_{max} 3368, 2910, 1627, 1075 cm^{-1}.

(1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-Bis(benzyloxy)-1-hydroxy-11-methoxy-2-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-1,2,3,4,7,8,13,13b-octahydro-5*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-5-one (51).



50

Compound **51** can be synthesized from the compound **49b** (0.1 g, 0.090 mmol) by the same procedure followed for compound **50**. Purified by column chromatography on silica gel (90:10; dichloromethane:methanol) to obtain compound **51** (30 mg, 48%) as a colorless solid; **$[\alpha]_D^{26}$** = + 18.99 (*c* = 1.0, $CHCl_3$); **^{1}H NMR (Acetone-d_6, 500 MHz)** δ 9.59 (br. s., 1 H), 7.45 (d, *J* = 6.9 Hz, 2 H), 7.39 (d, *J* = 7.2 Hz, 2 H), 7.38–7.34 (m, 2 H), 7.32–7.27 (m, 2 H), 7.26–7.22 (m, 2 H), 7.20 (d, *J* = 6.9 Hz, 1 H), 7.07 (s, 1 H), 6.67 (dd, *J* = 2.3, 8.4 Hz, 1 H), 6.33 (br. s., 1 H), 4.86 (d, *J* = 12.2 Hz, 1 H), 4.83–4.80 (m, 1 H), 4.79–4.73 (m, 1 H), 4.72–4.68 (m, 4 H), 4.64 (s, 1 H), 4.43 (br. s., 1 H), 4.33 (dd, *J* = 4.2, 10.3 Hz, 1 H), 4.20–4.14 (m, 1 H), 4.02 (br. s., 1 H), 3.93–3.88 (m, 1 H), 3.76 (s, 3 H), 3.58–3.55 (m, 1 H), 3.53–3.48 (m, 1 H), 3.42–3.34 (m, 2 H), 3.19 (dt, *J* = 3.8, 12.4 Hz, 1 H), 2.87 (s, 3 H), 2.83 (s, 1 H), 2.77–2.71 (m, 1 H), 2.61–2.54 (m, 1 H); **^{13}C NMR (Acetone-d_6, 125 MHz)** δ 170.2, 157.1, 139.5, 139.4, 138.9, 131.5, 129.3 (2C), 129.0 (2C), 128.6 (2C), 128.5 (2C), 128.5, 128.2, 122.1, 118.8, 110.1, 109.3, 107.1, 96.5, 86.2, 85.8, 78.0, 77.5, 76.3, 75.8, 74.6, 73.5, 72.1, 71.6, 62.9, 55.8, 49.9, 41.1, 21.1; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{37}H_{43}N_2O_{11}$ 691.2861, found 691.2858; **IR ($CHCl_3$)** ν_{max} 3383, 2960, 1627, 1077 cm^{-1}.

SC-XRD: The single crystal X-ray diffraction measurements were performed to determine the crystal structure of compounds **27**, **41b**, **46b**, **51** and **53a** at 100 K using APEX3 (Bruker, 2016; Bruker D8 VENTURE Kappa Duo PHOTON II CPAD) diffractometer having graphite-monochromatized (CuKα = 1.54178 Å). While the **53a**

sample collected in the MoKα source and the crystal structure was refined using the Olex2 software. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of unit cell parameters and an orientation matrix were calculated from 40 frames (36 frames for the compound **53a**), and the cell refinement was performed by SAINT-Plus (Bruker, 2016). An optimized strategy used for data collection consisted of different sets of φ and ω scans with 0.5º steps φ/ω. The data were collected with a time frame of 10 sec for all five components by setting the sample to detector distance fixed at 40 cm. All the data points were corrected for Lorentzian, polarization, and absorption effects using SAINT-Plus and SADABS programs (Bruker, 2016). SHELXL 2018/3 (Sheldrick, 2015) was used for structure solution, and full-matrix least-squares refinement on F2.8 The molecular graphics of ORTEP diagrams were performed by Mercury software. The crystal symmetry of all the five components were cross-checked by running the cif files through PLATON (Spek, 2020) software and notified that no additional symmetry was observed. The Encifer software was used to correct the cif files.

Table 4. Crystallographic information details of compounds **27**, **41b**, **46b**, **51**, and **53a**

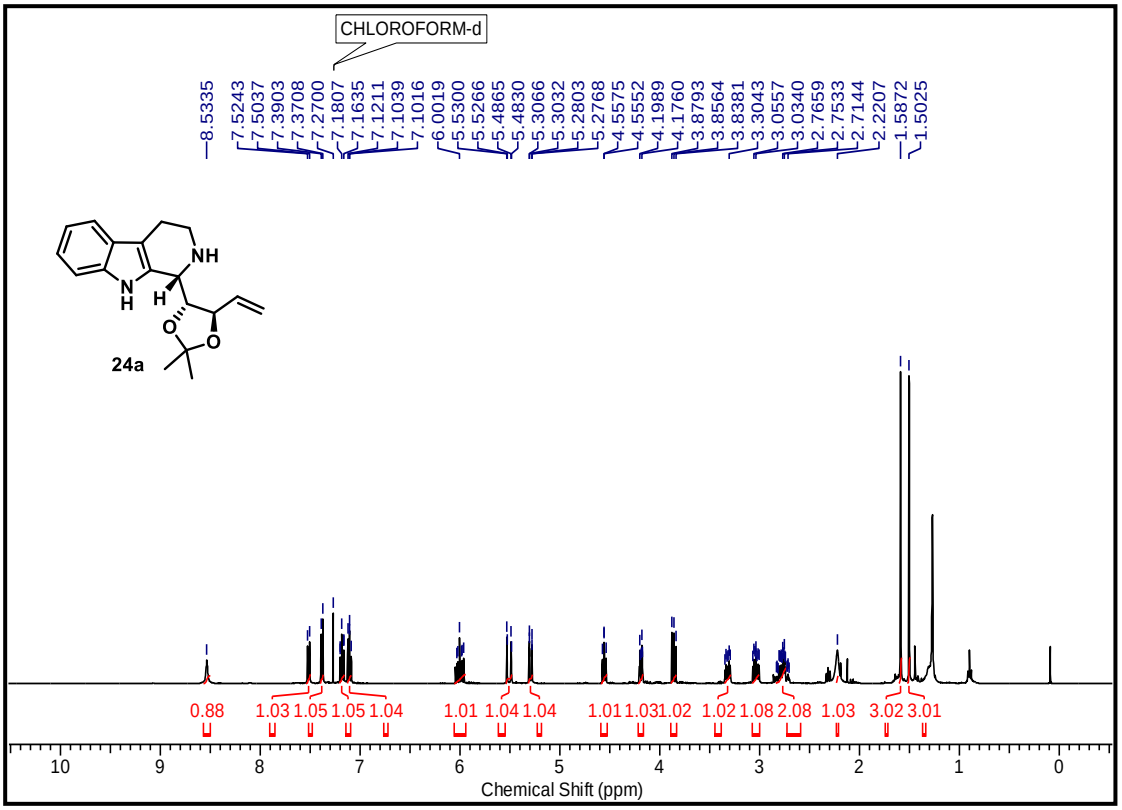
Crystal data	**41b**	**46b**	**51**	**27**	**53a**
Chemical formula	$C_{34}H_{36}N_2O_6$	$C_{34}H_{36}N_2O_6$	$C_{37}H_{42}N_2O_{11}\cdot CH_3O$	$C_{16}H_{16}N_2O_3$	$2(C_{33}H_{33.50}N_2O_5)$, $2(C_{33}H_{34}N_2O_5)$
Formula weight (M_r)	568.65	568.65	721.76	284.31	2153.48
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
Temperature T (K)	100(2)	100(2)	100(2)	100(2)	100(2)
a (Å)	6.5346(15)	6.1245(5)	8.6603(3)	6.7124(3)	12.070(4)
b (Å)	7.964(3)	8.2164(6)	11.1093(3)	6.9667(3)	12.062(4)
c (Å)	27.494(6)	28.510(2)	35.9413(10)	13.9060(5)	19.437(6)
α (°)	90	90	90	90	90
β (°)	94.722(14)	92.796(3)	90	96.3070(10)	91.344(13)

γ (°)	90	90	90	90	90
Z	2	2	4	2	1
Volume ($Å^3$)	1426.0(7)	1432.93(19)	3457.91(18)	646.35(5)	2828.9(15)
Source of radiation	CuKα	CuKα	CuKα	CuKα	MoKα
D_{calc} (g cm^{-3})	1.324	1.318	1.386	1.461	1.264
Crystal size (mm)	0.33x 0.2x 0.16	0.43x 0.28x 0.22	0.36x 0.26x 0.18	0.3x 0.24x 0.18	0.3x0.23 x0.16
μ (mm^{-1})	0.736	0.733	0.861	0.838	0.085
Absolute structure parameter	0.12 (11)	-0.07(8)	−0.05 (7)	0.05(9)	0.1(4)
Data collection					
Diffractometer	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD	Bruker D8 VENTURE Kappa Duo PHOTON II CPAD
Absorption correction	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)	Multi-scan (SADABS; Bruker, 2016)
T_{min}, T_{max}	0.6371, 0.7536	0.6102, 0.7536	0.6724, 0.7533	0.6148, 0.7536	0.5126, 0.7458
No. of measured, independent and observed [I > 2σ(I)] reflections	20465, 4908, 4479	16438, 5270, 4763	102547, 6574, 5422	7210, 2466, 2406	62291, 12289, 10522
Theta range (°)	4.84-72.43	4.66-72.25	2.46-68.94	6.40-72.36	2.61-27.31
R_{int}	0.0758	0.0477	0.080	0.0305	0.0707
Refinement					
R[F^2 > 2σ(F^2)], wR(F^2)	0.070	0.0358	0.050	0.0295, 0.0783	0.0582, 0.1451
GOF on F^2	1.28	1.073	1.13	1.041	1.061

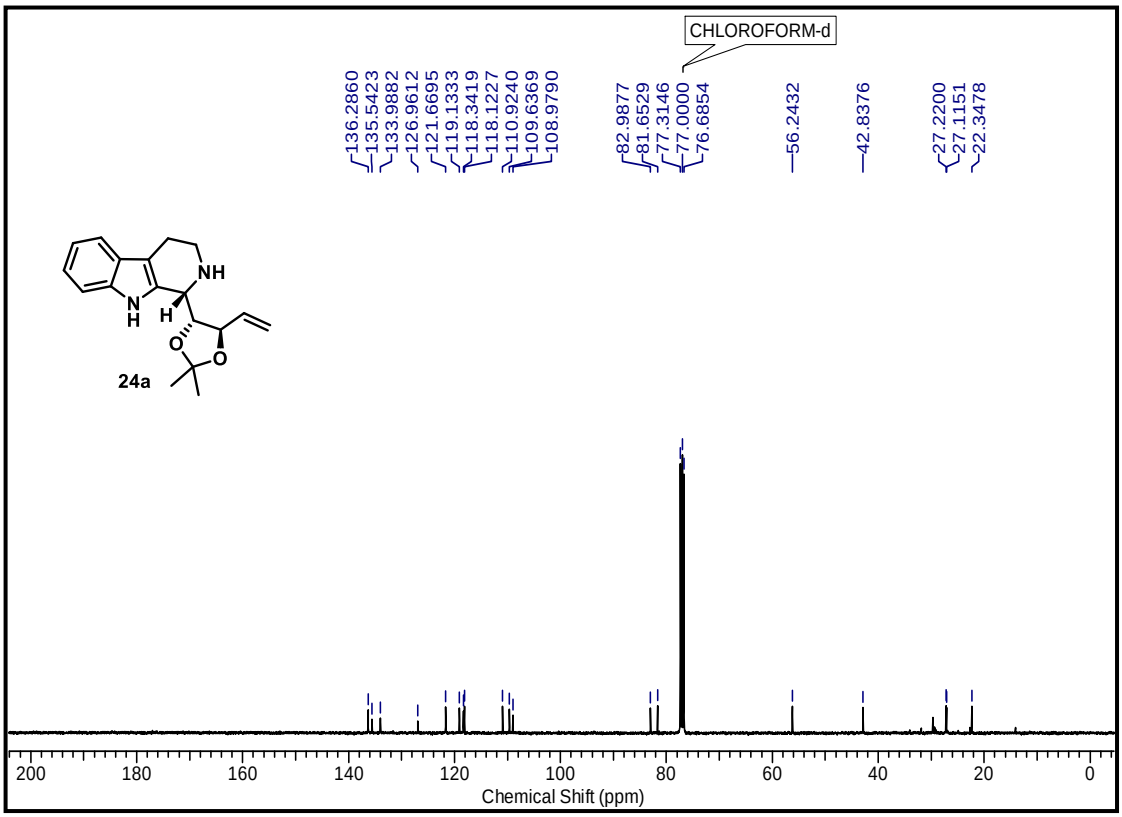
No. of independent reflections	4908	5270	6574	2466	12289
No. of parameters	383	387	492	196	754
F_000	604	604	1532	300	1143
No. of restraints	1	1	0	1	6
H-atom treatment	constr	constr	constr	constr	constr
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $A^{\circ-3}$)	0.34, -0.36	0.300, -0.249	0.33, -0.34	0.251, -0.179	0.596, -0.396
CCDC number	2111021	2111020	2111023	2111019	2111022

1B.5 Selected Spectra

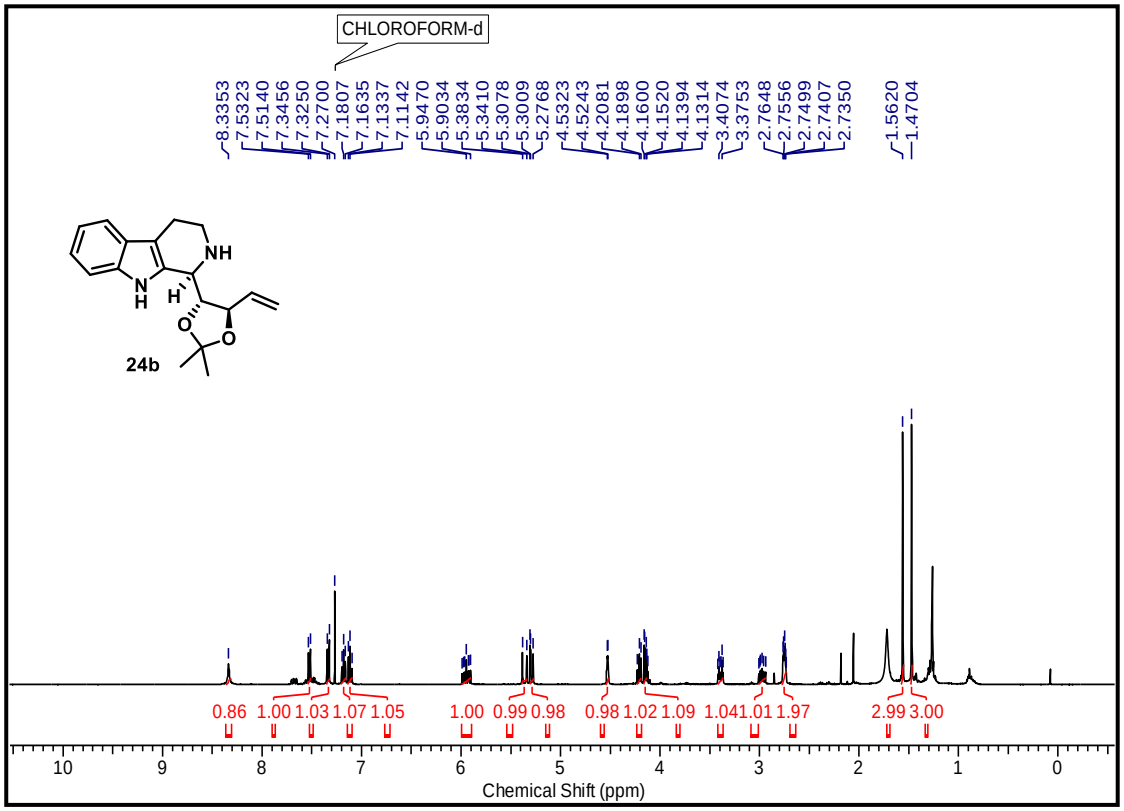
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 24a



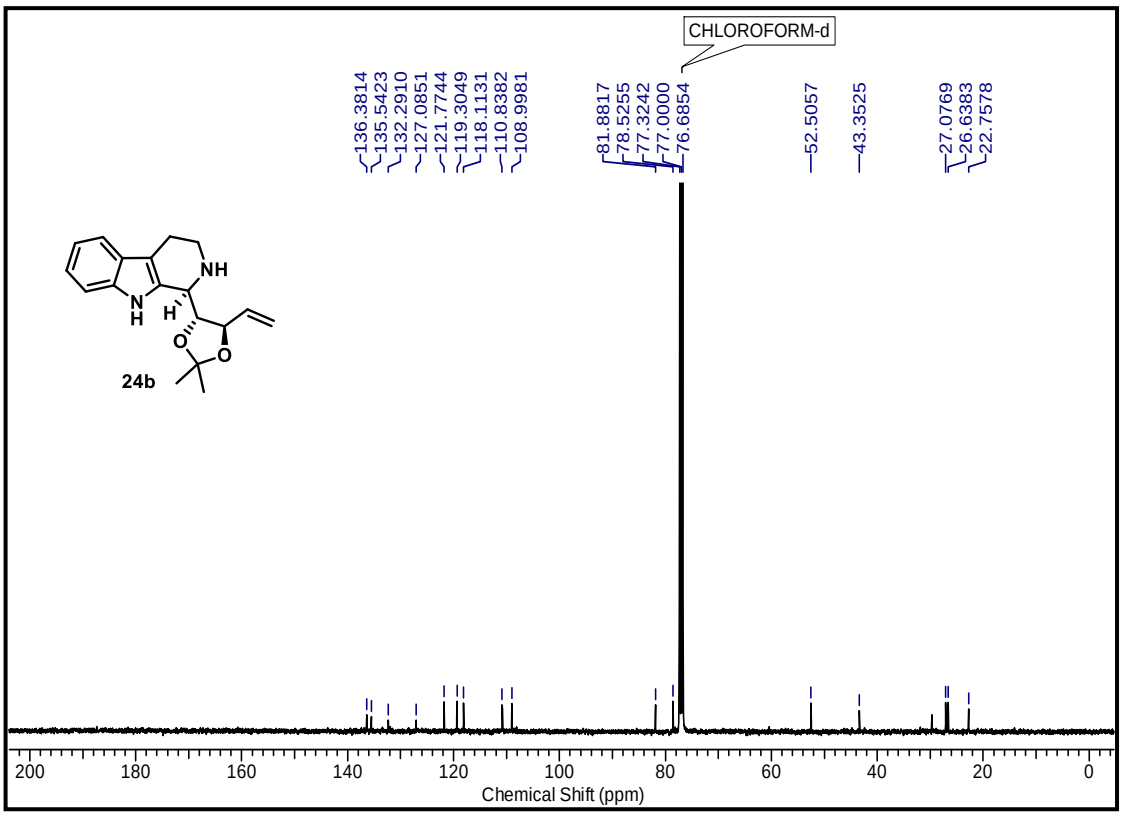
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 24a



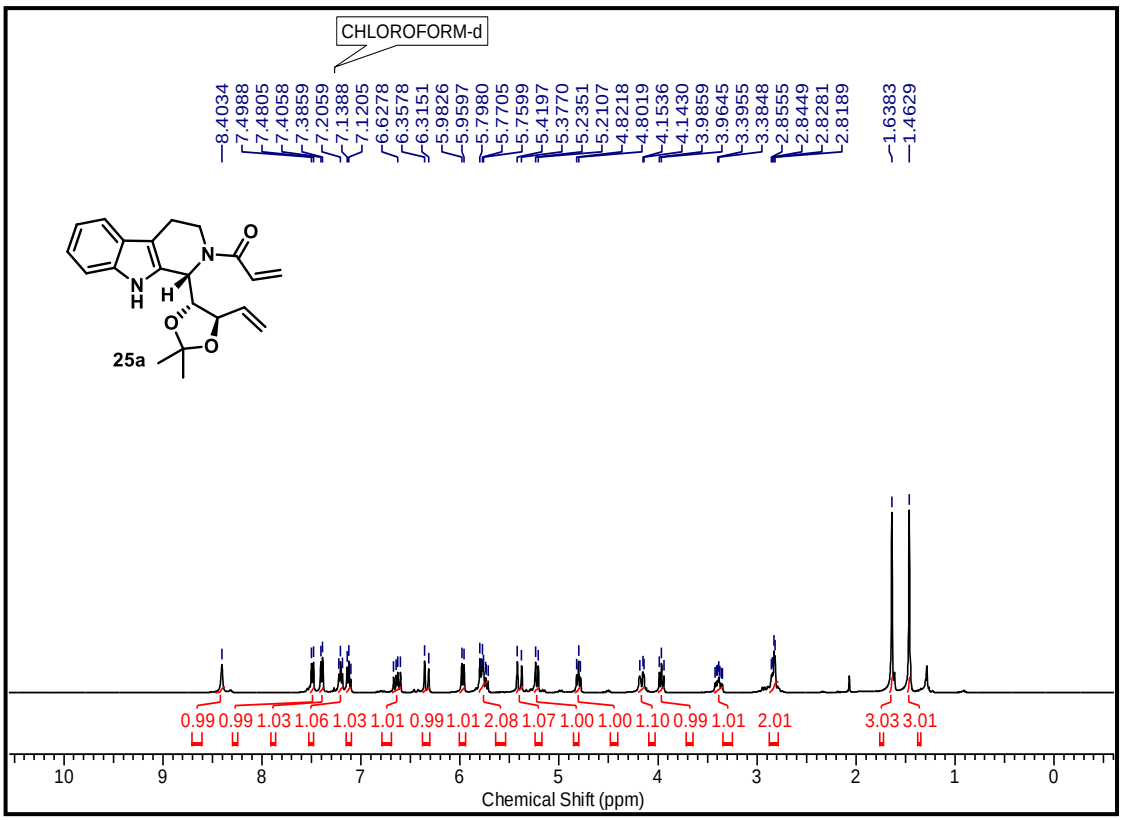
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 24b



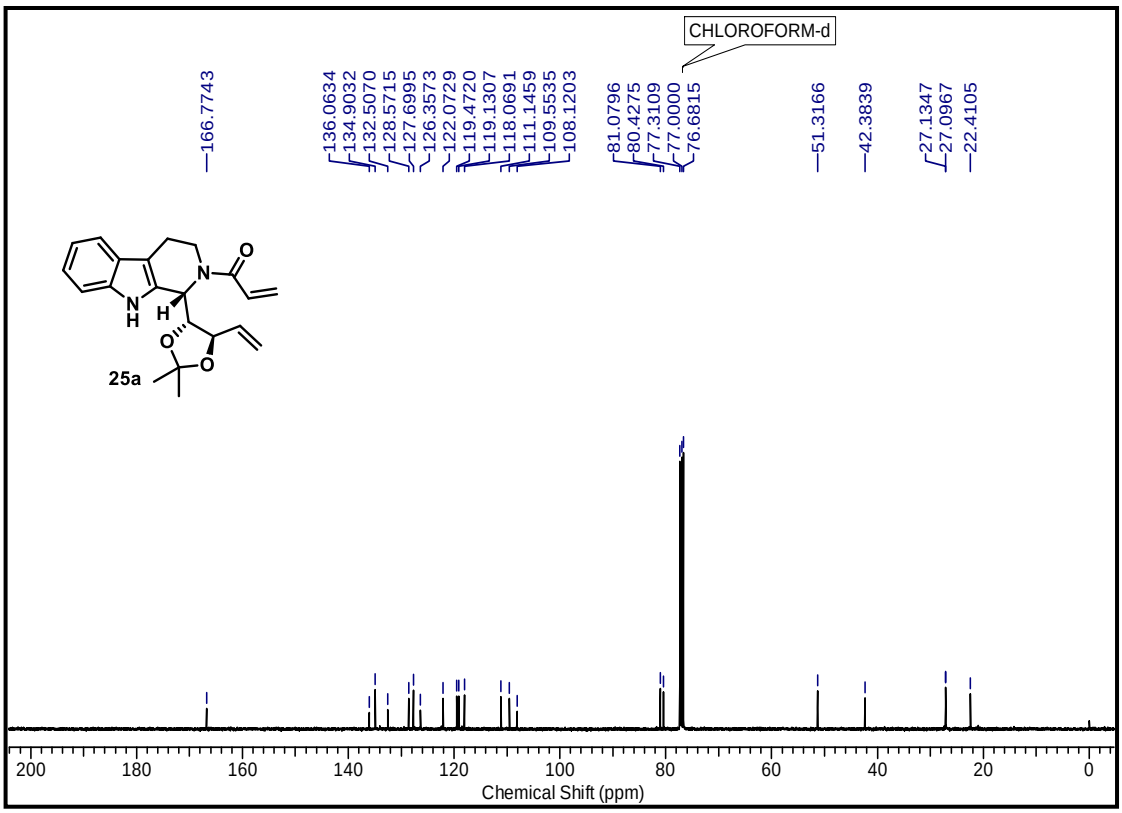
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 24b



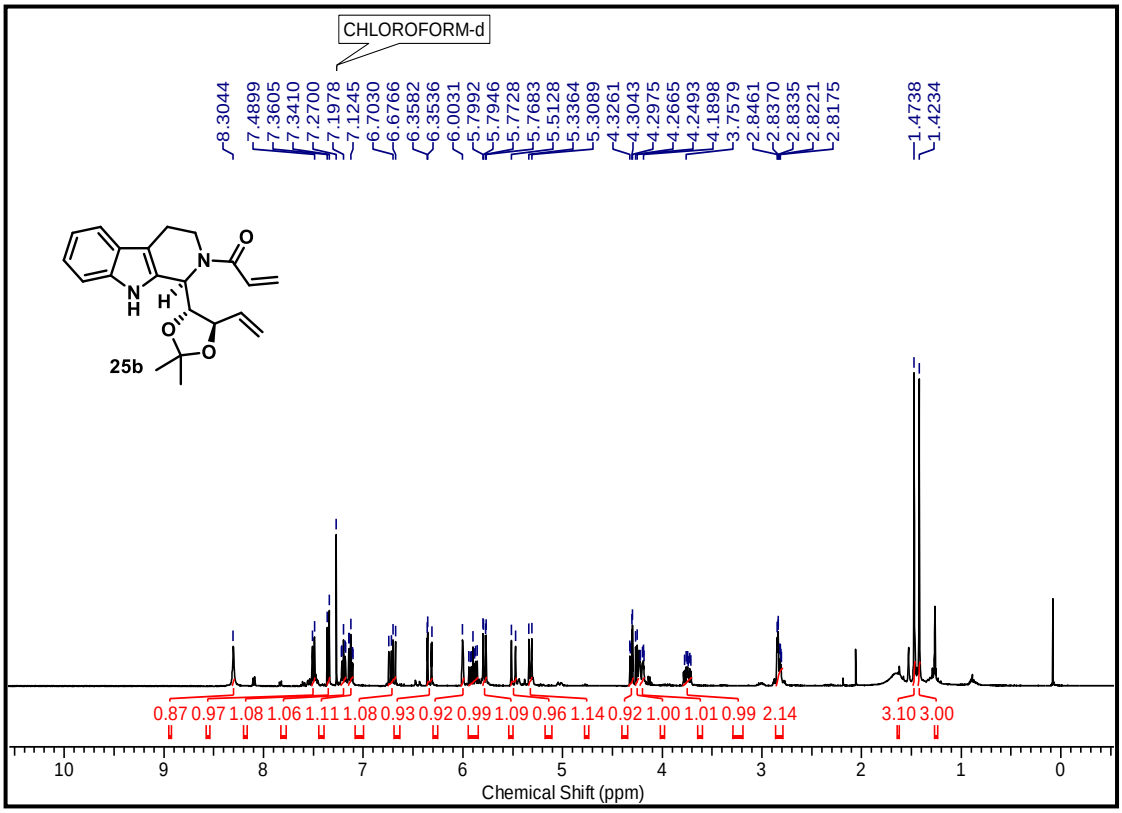
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 25a



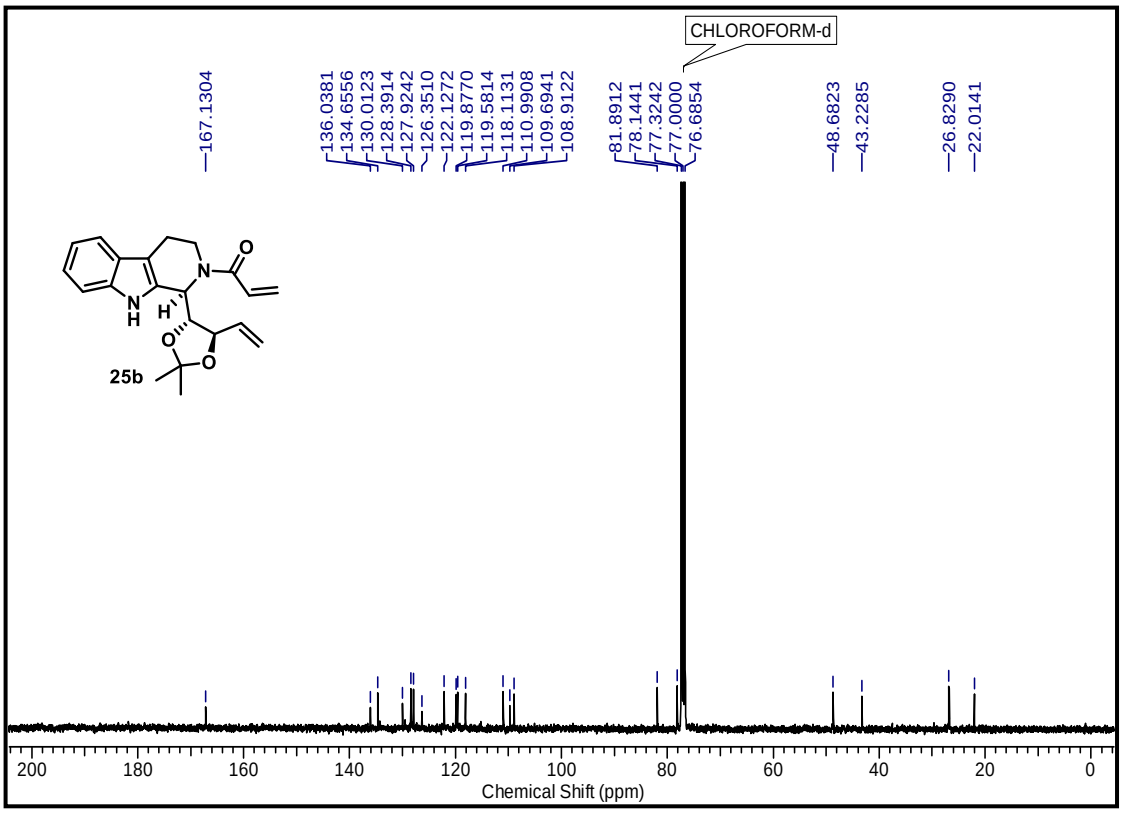
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 25a



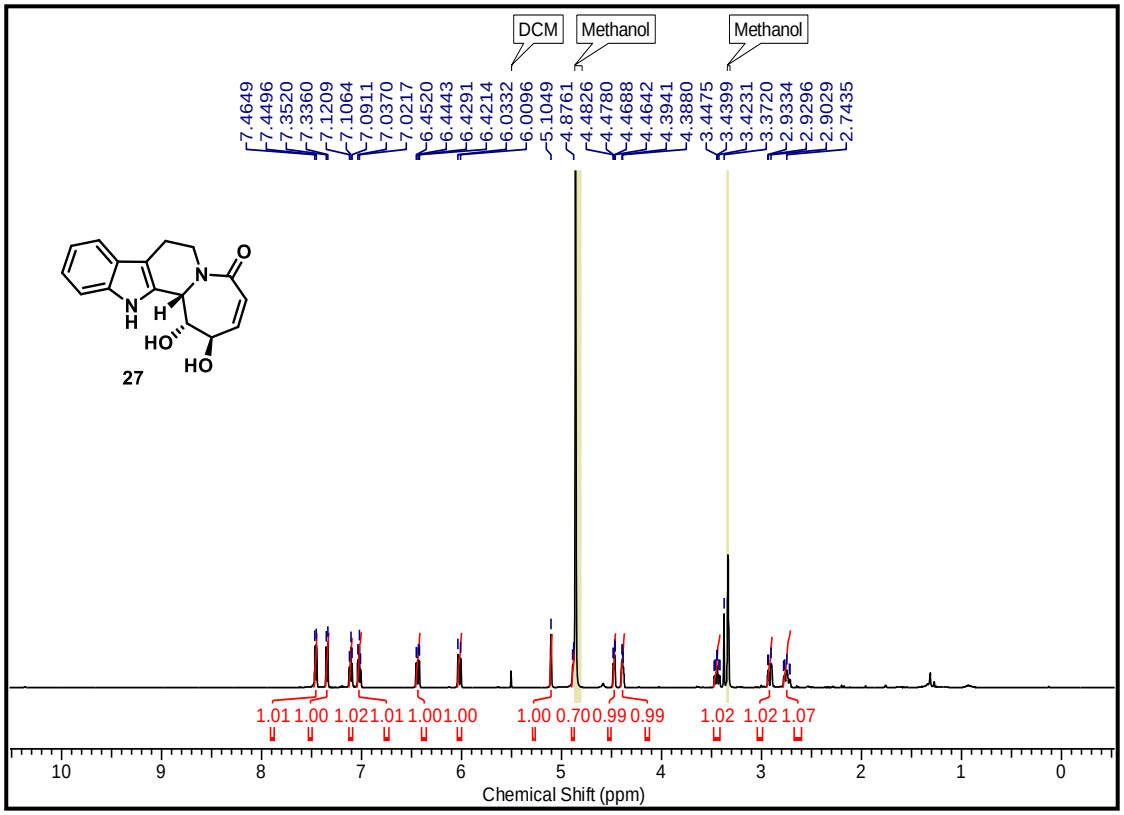
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 25b



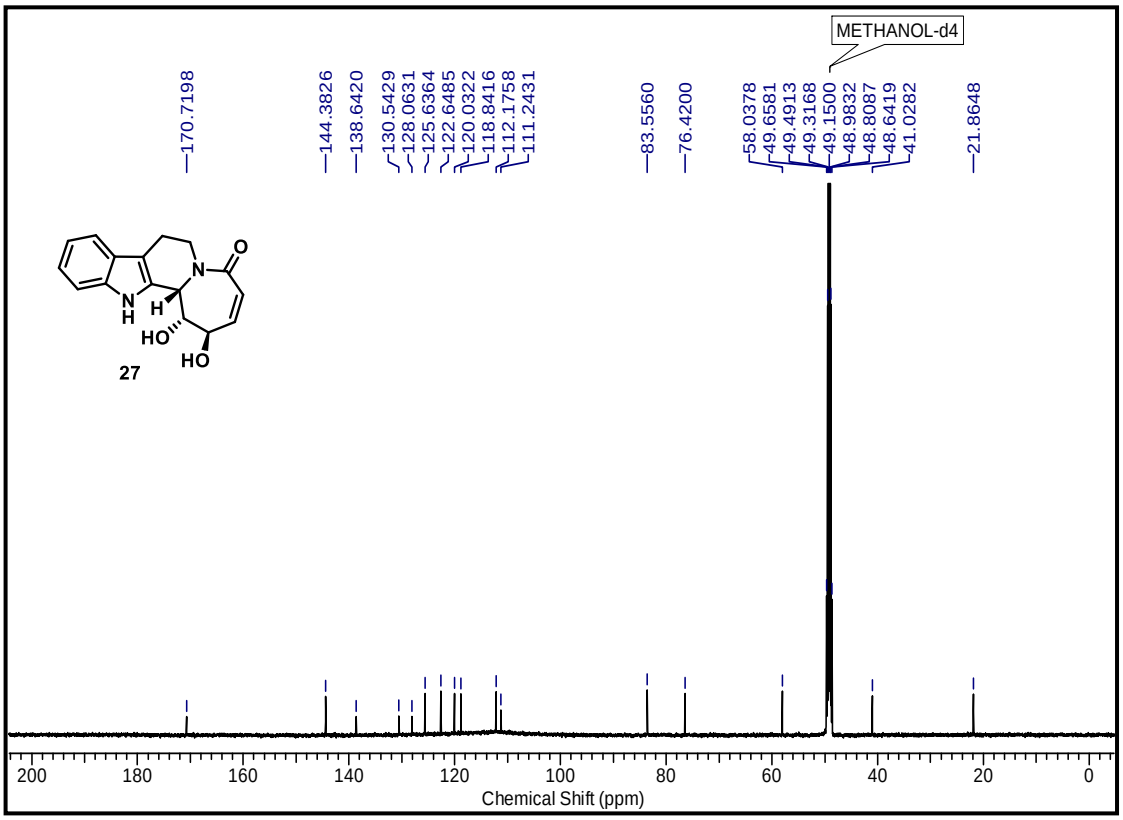
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 25b



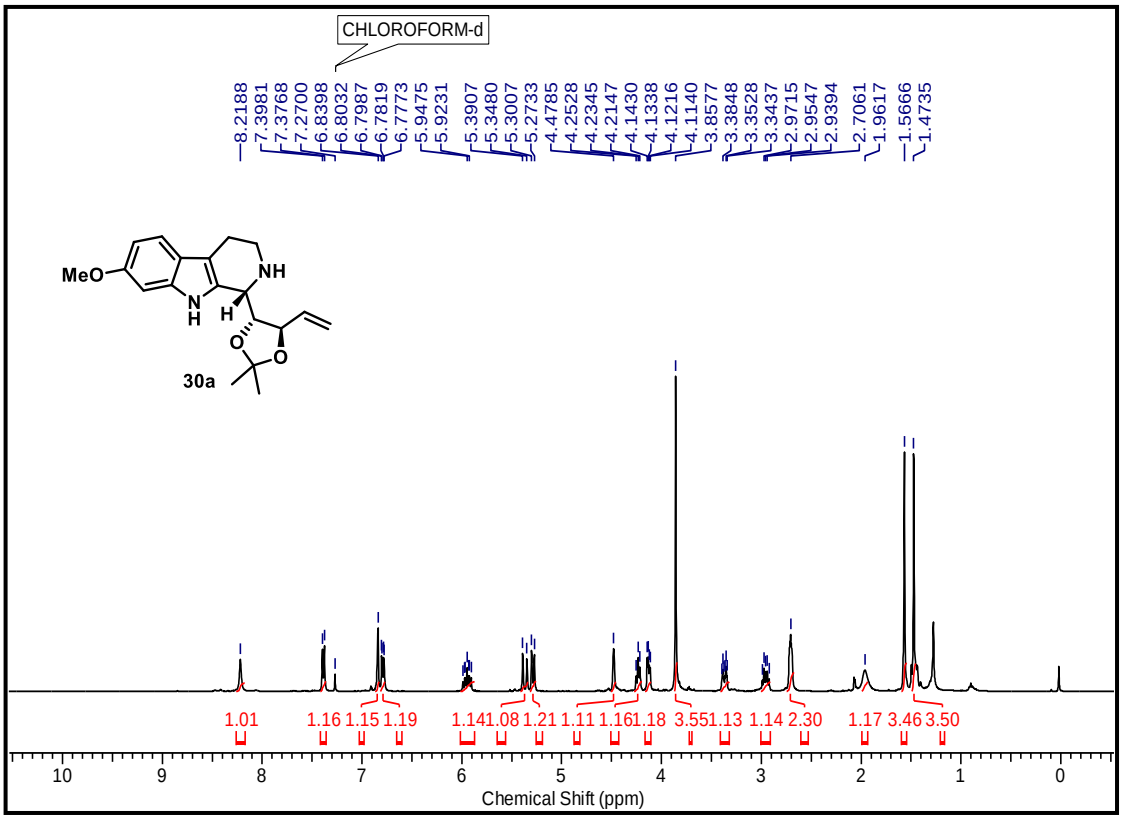
^{1}H NMR (CD_3OD, 500 MHz) of Compound 27



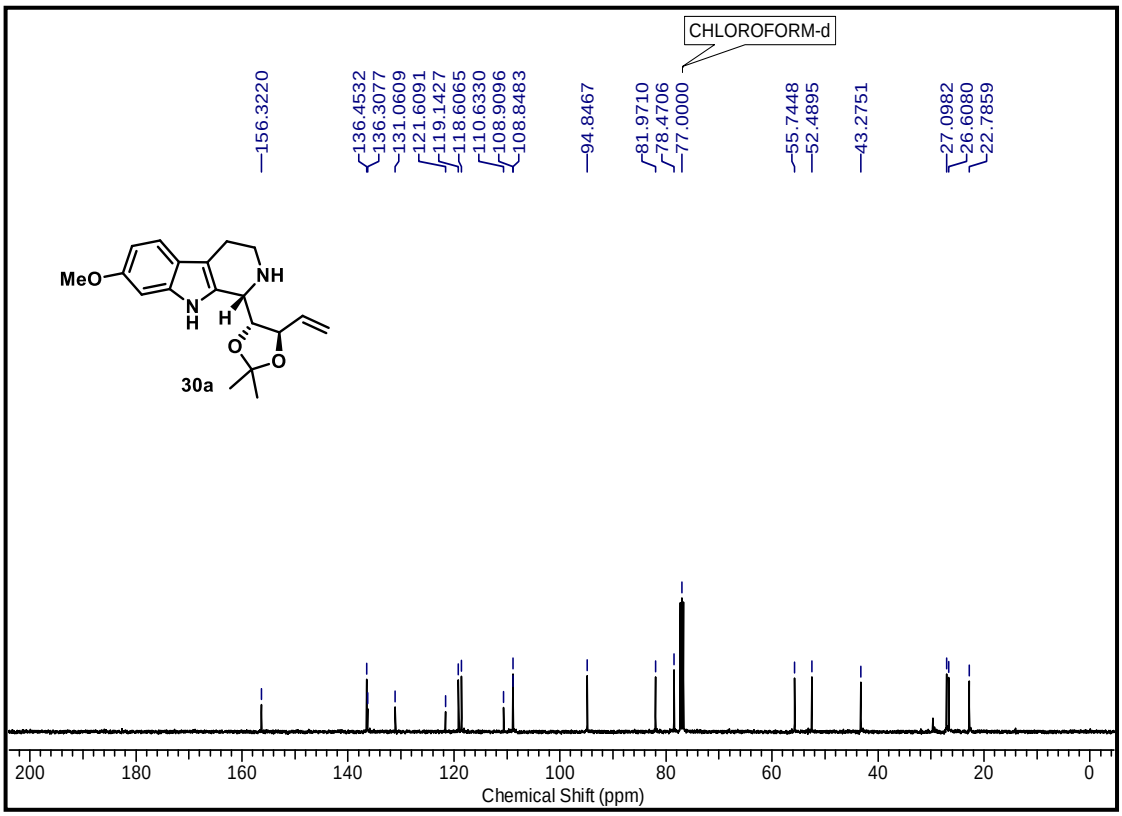
^{13}C NMR (CD_3OD, 125 MHz) of Compound 27



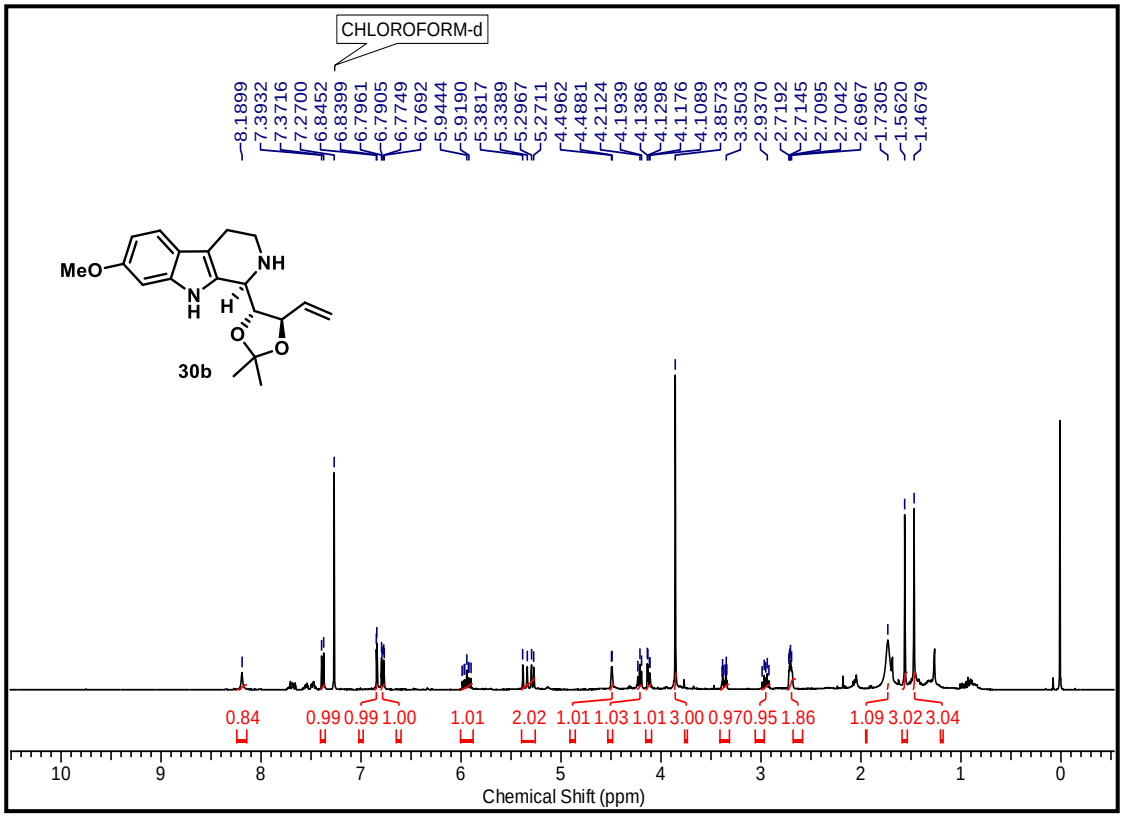
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 30a



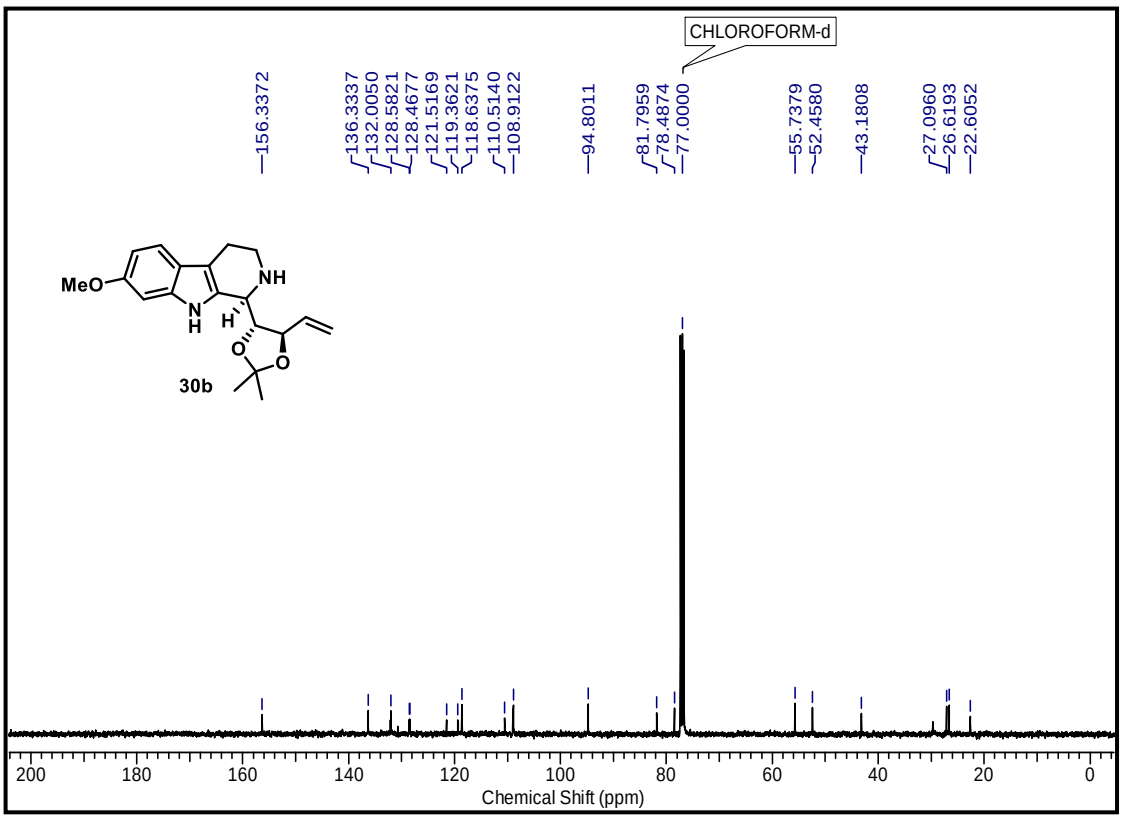
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 30a



^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 30b



^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 30b



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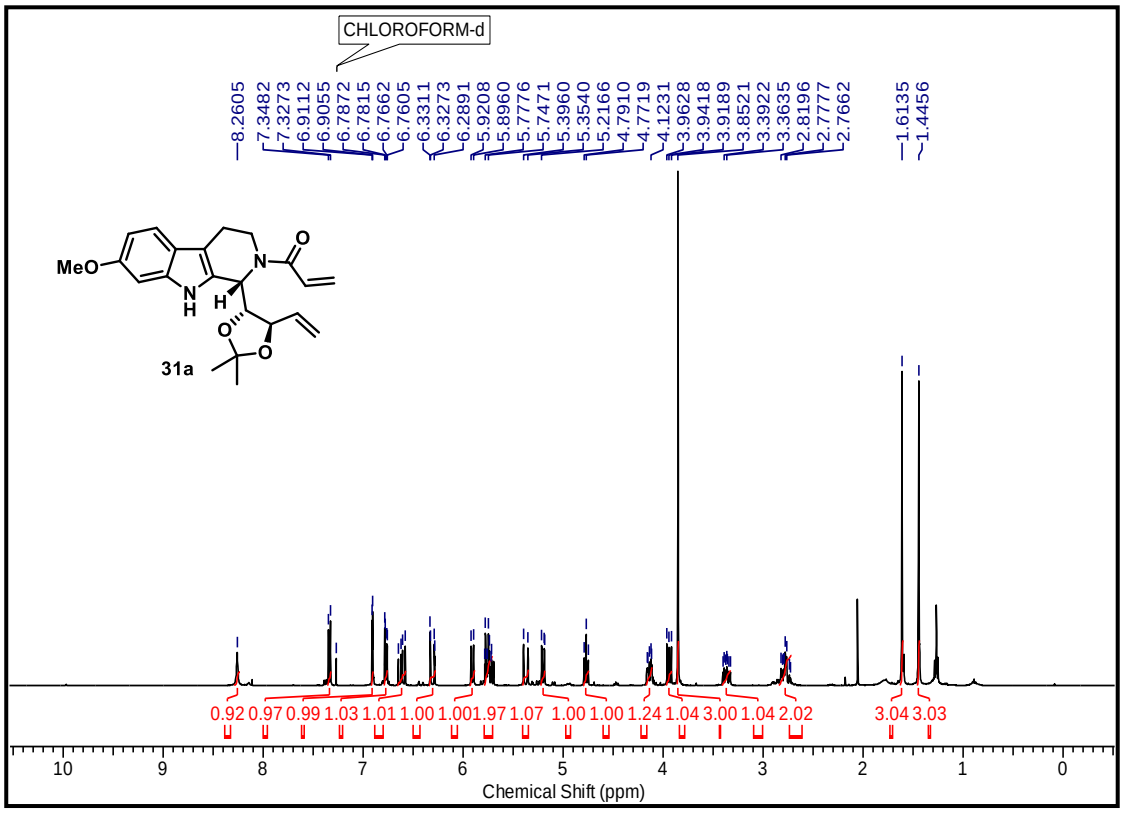
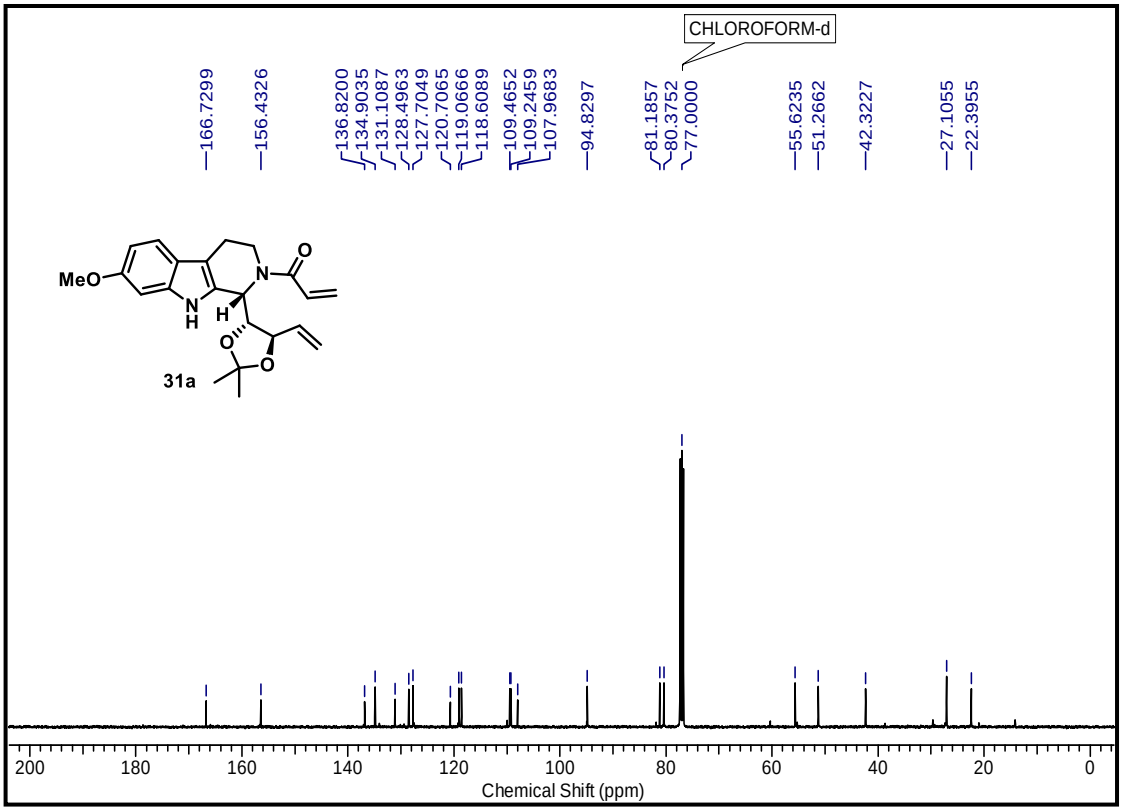


^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 31a



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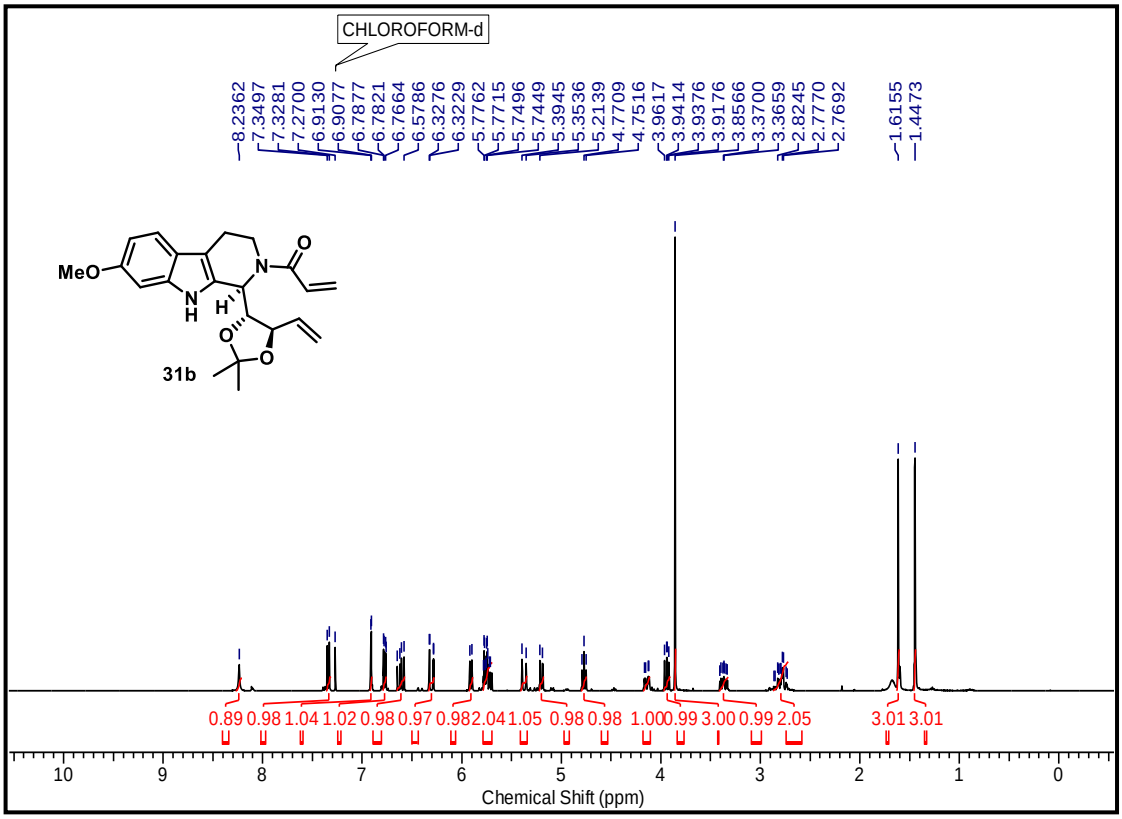
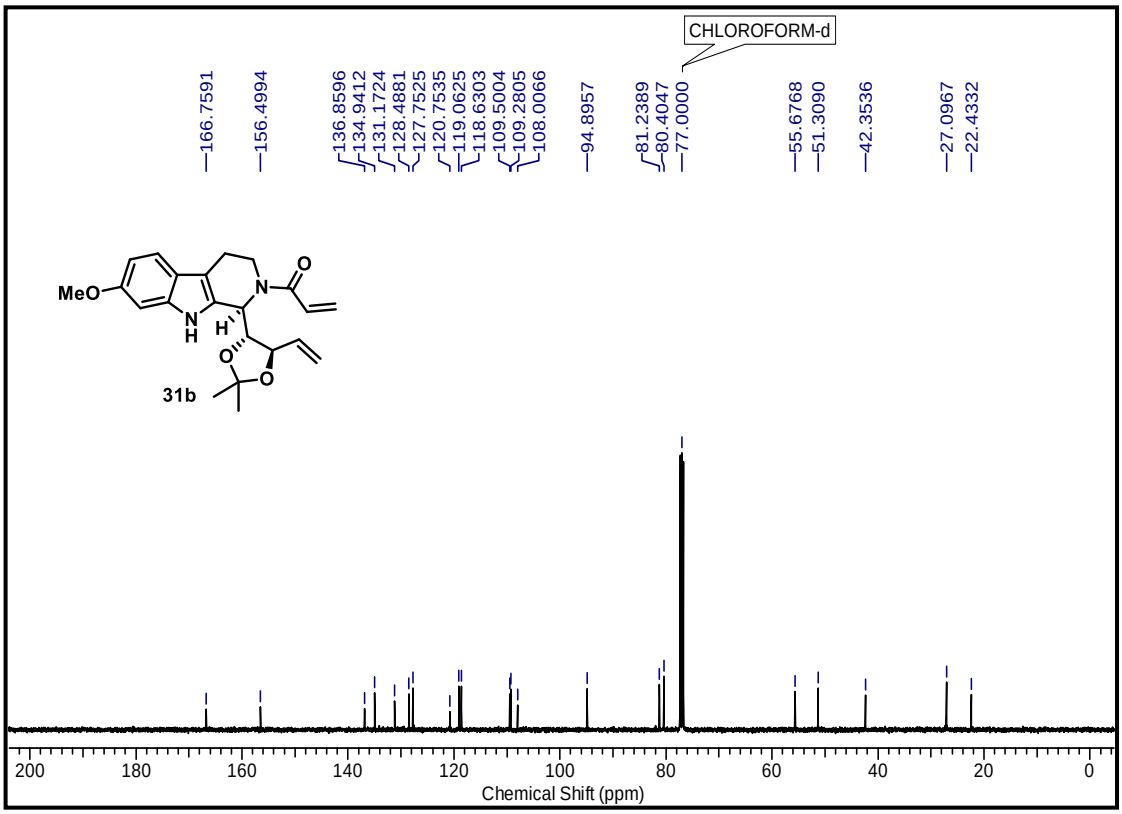
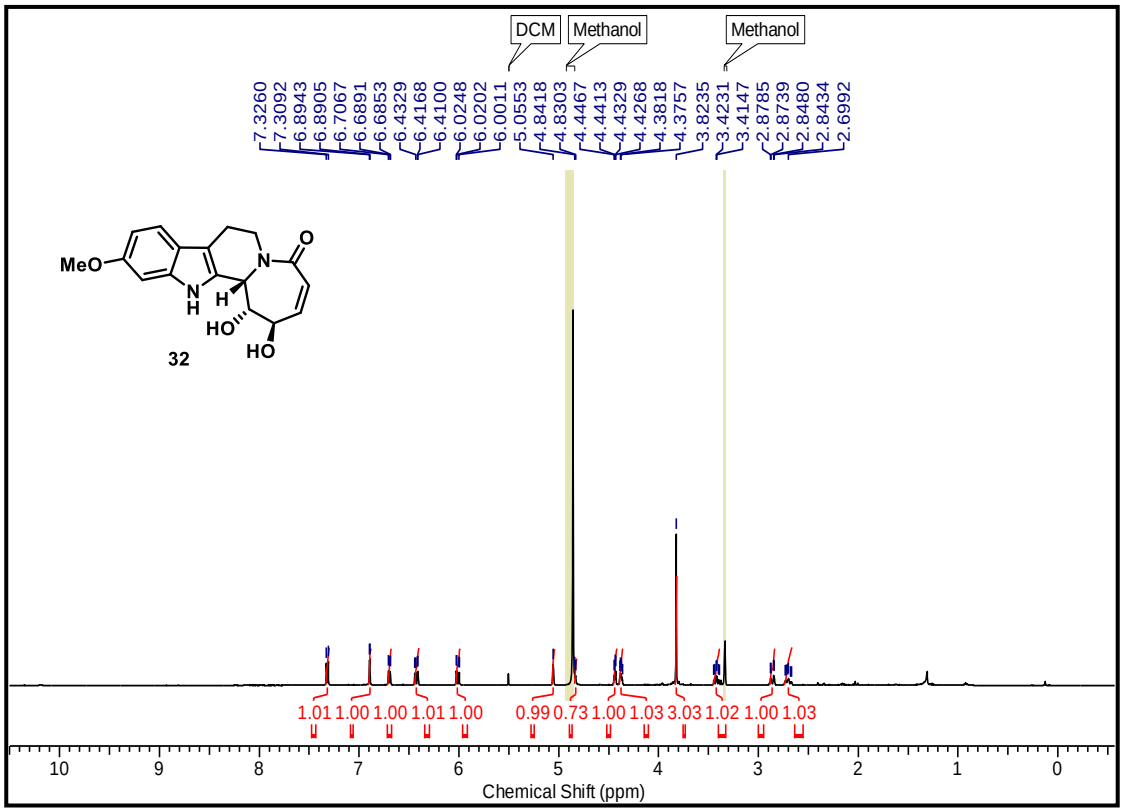


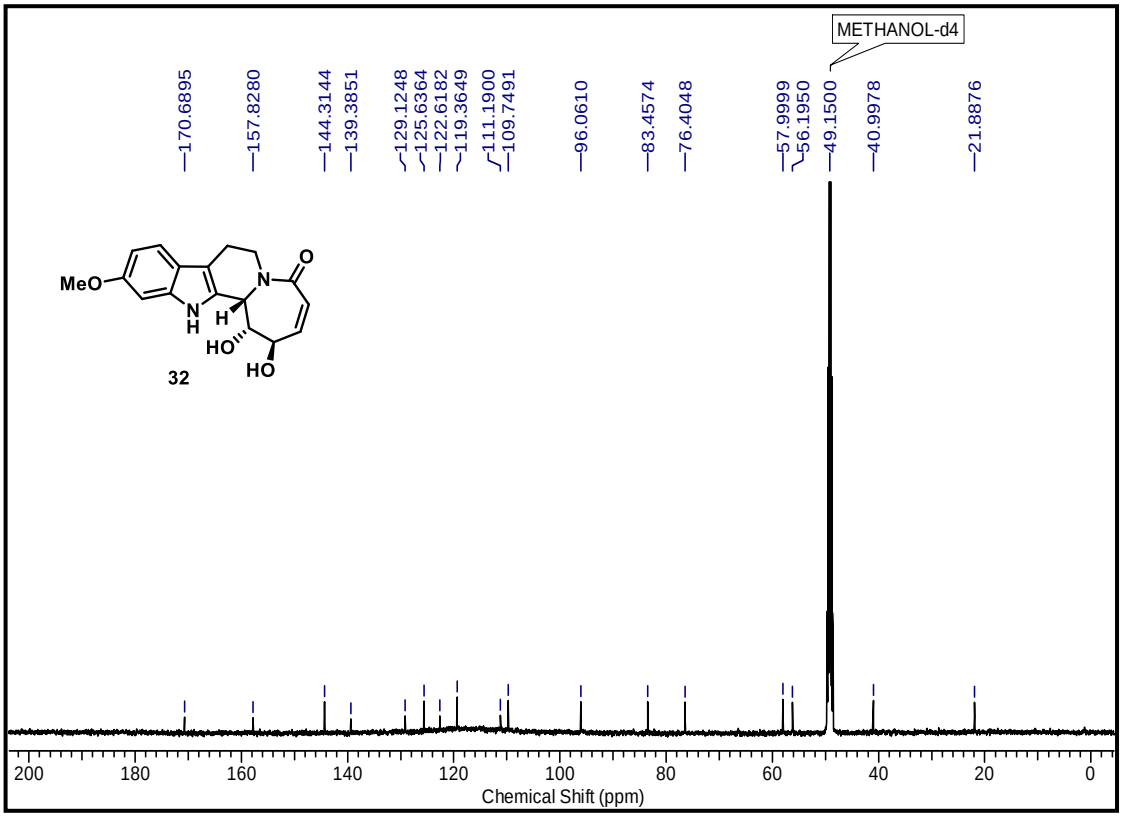
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 31b



^{1}H NMR (CD_3OD, 500 MHz) of Compound 32



^{13}C NMR (CD_3OD, 125 MHz) of Compound 32



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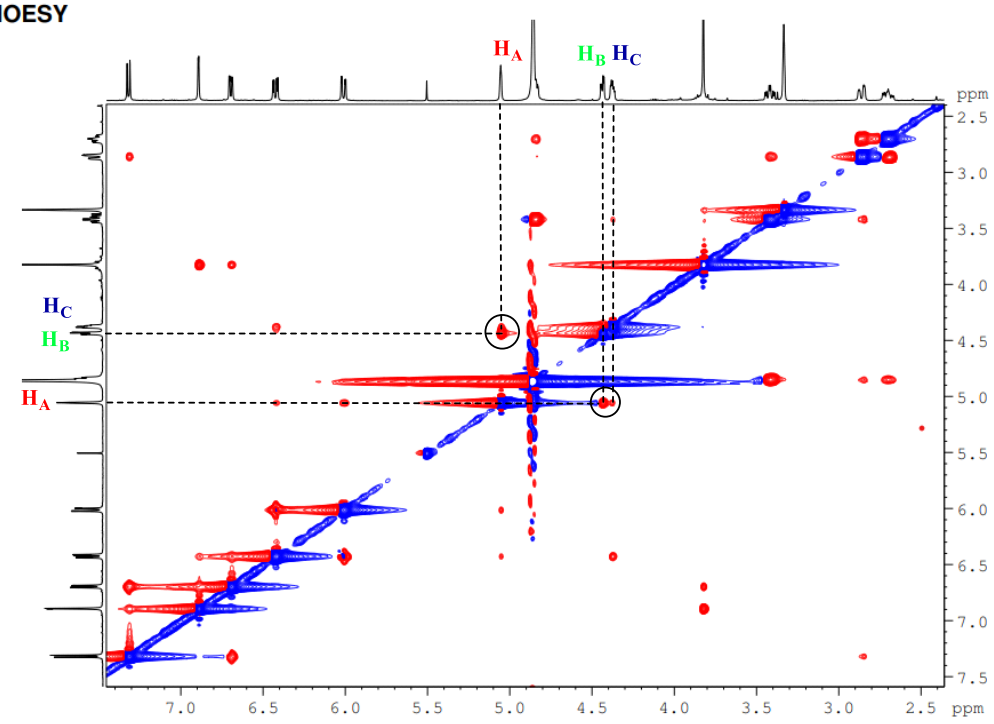

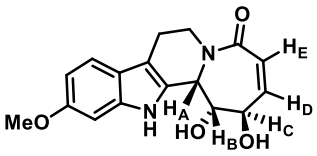

32

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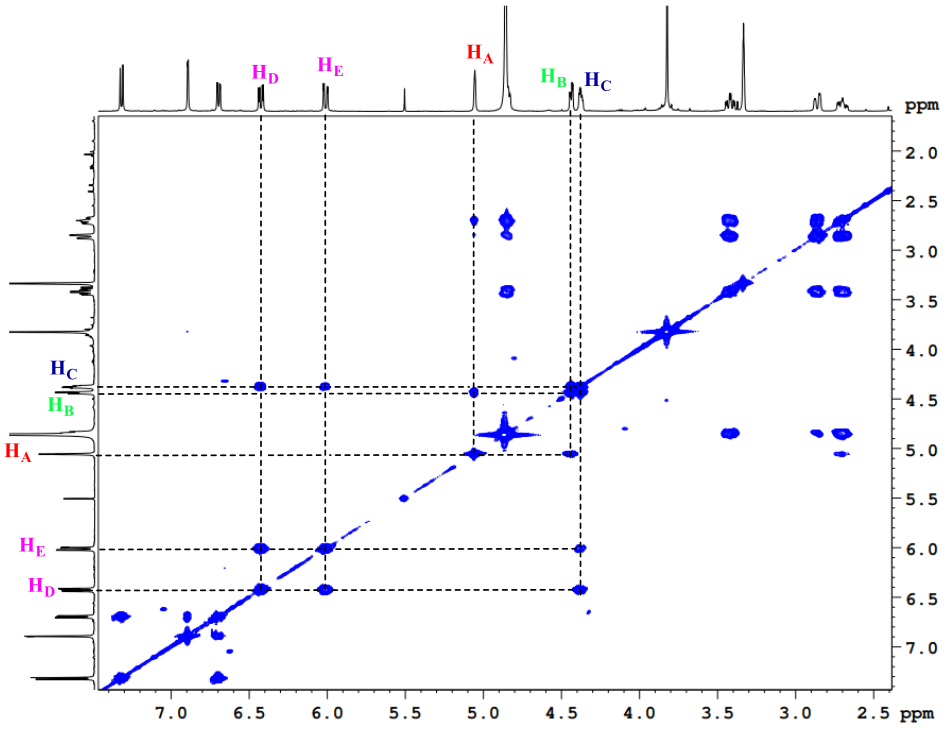

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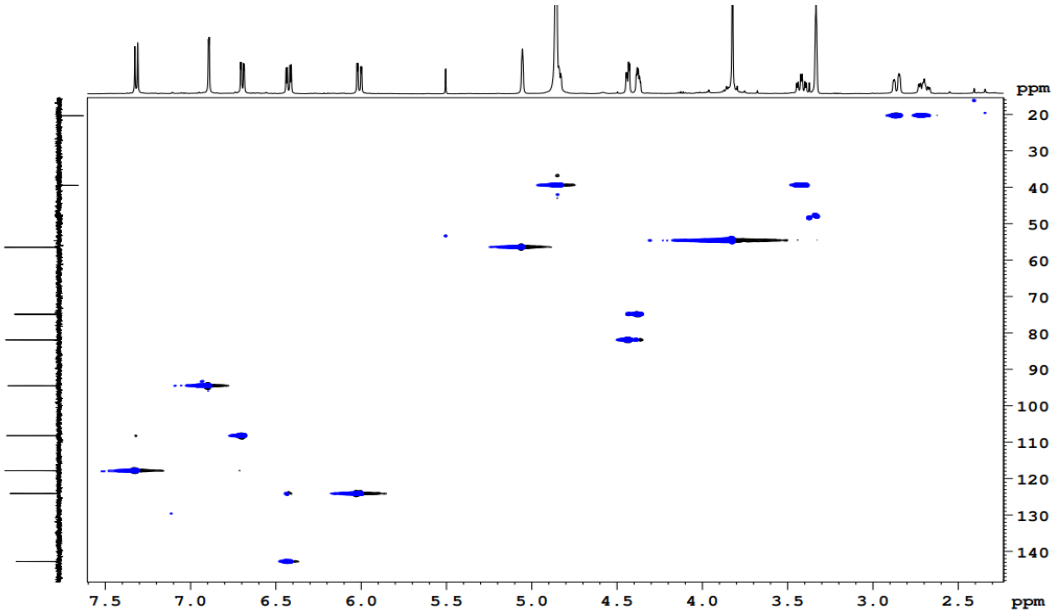
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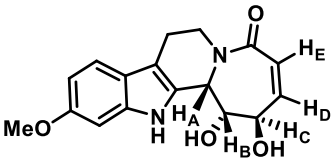
2.5
ppm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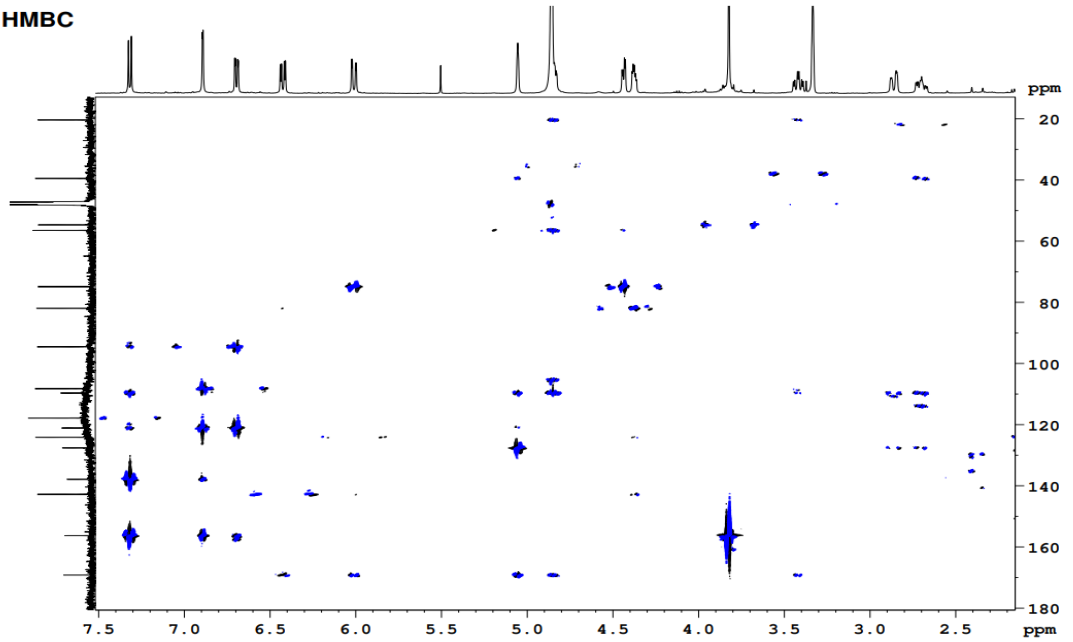
H_B
OH
H_C

32

HMBC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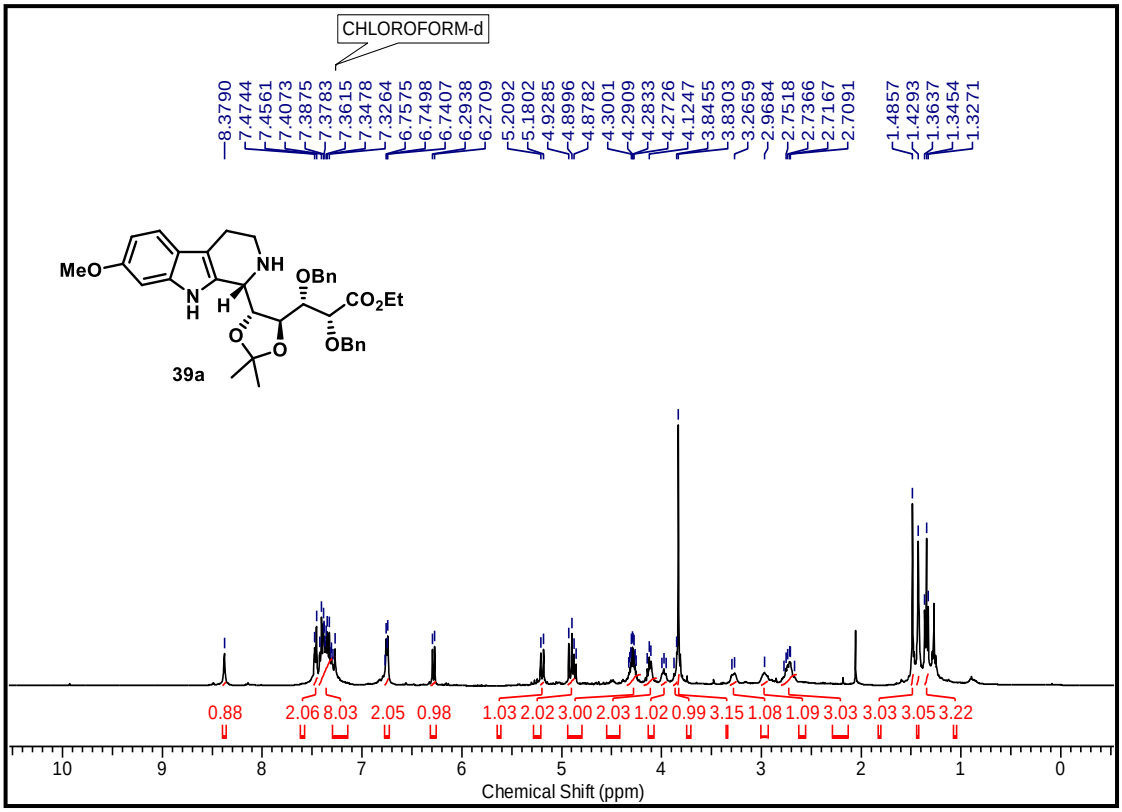
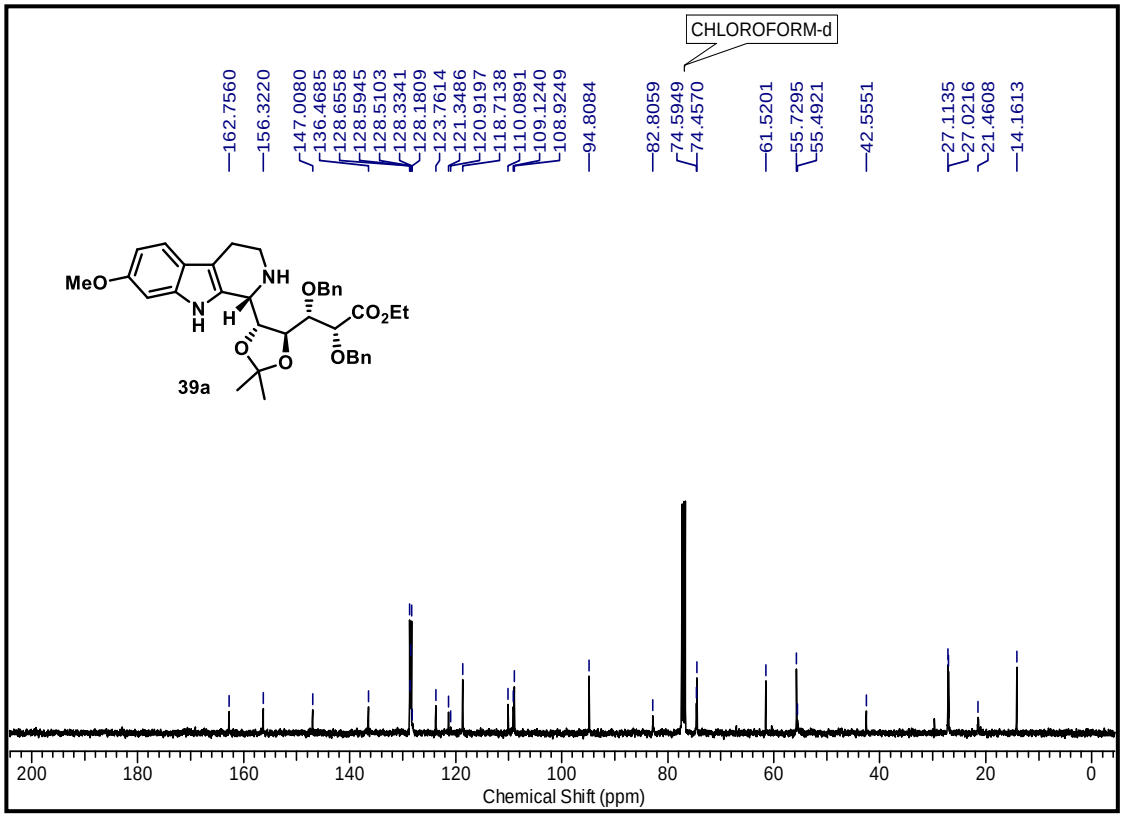
2.5
ppm

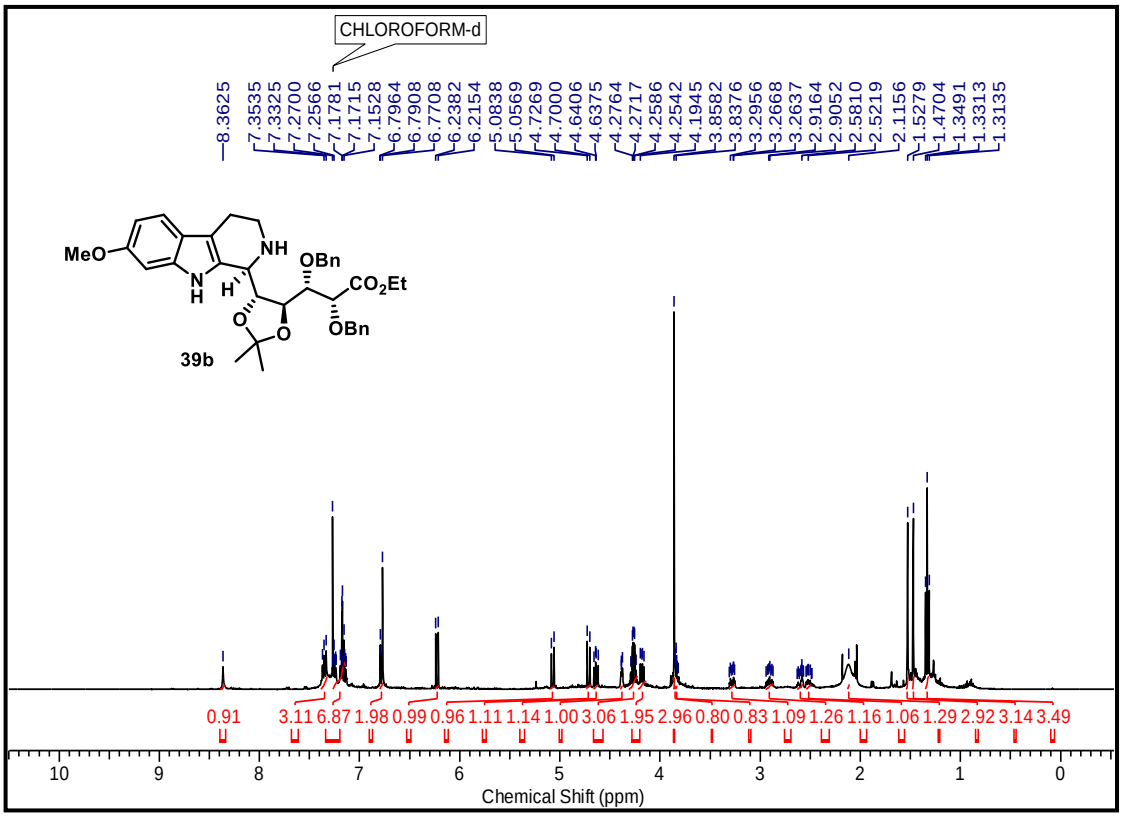
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 39a



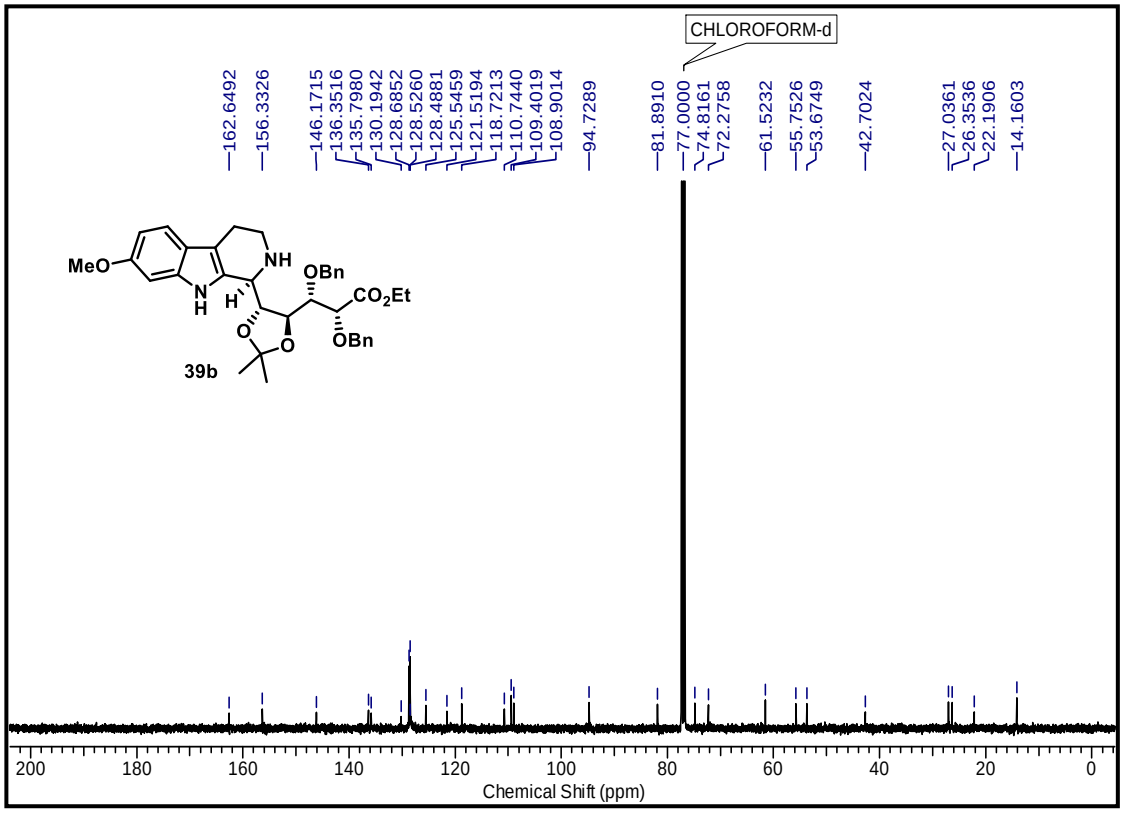
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 39a



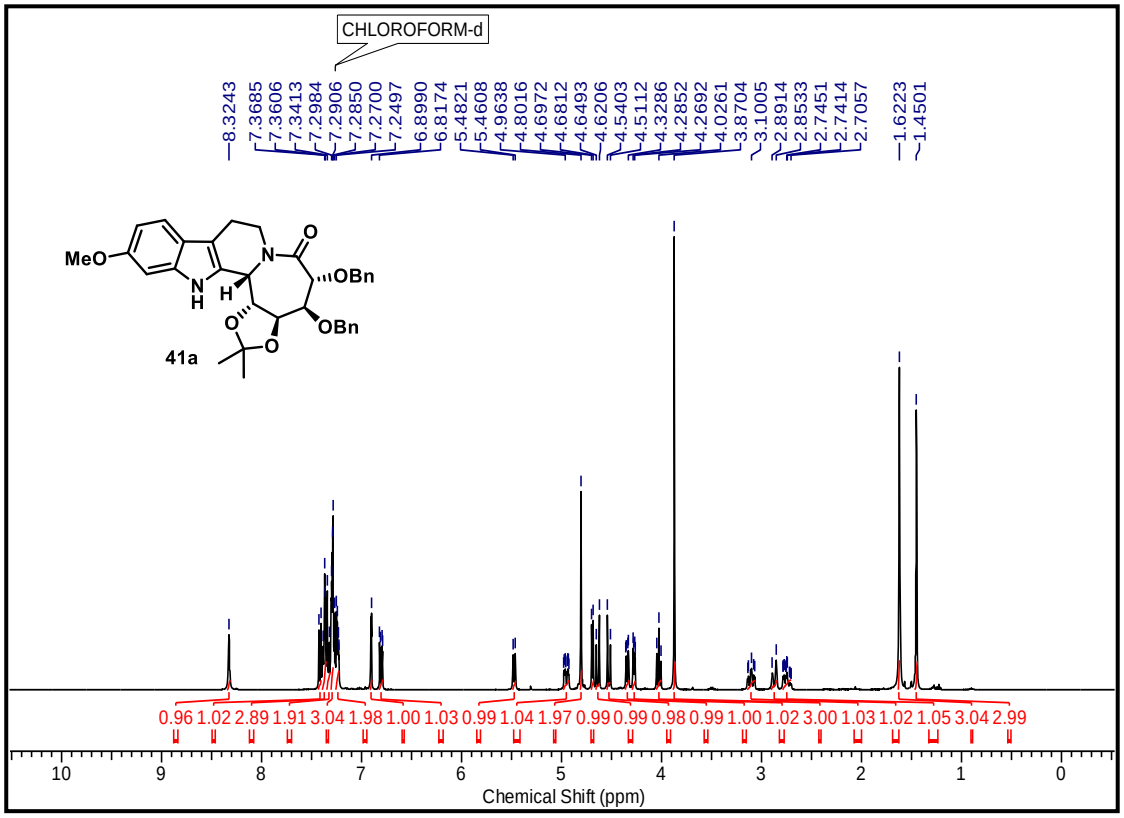
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 39b



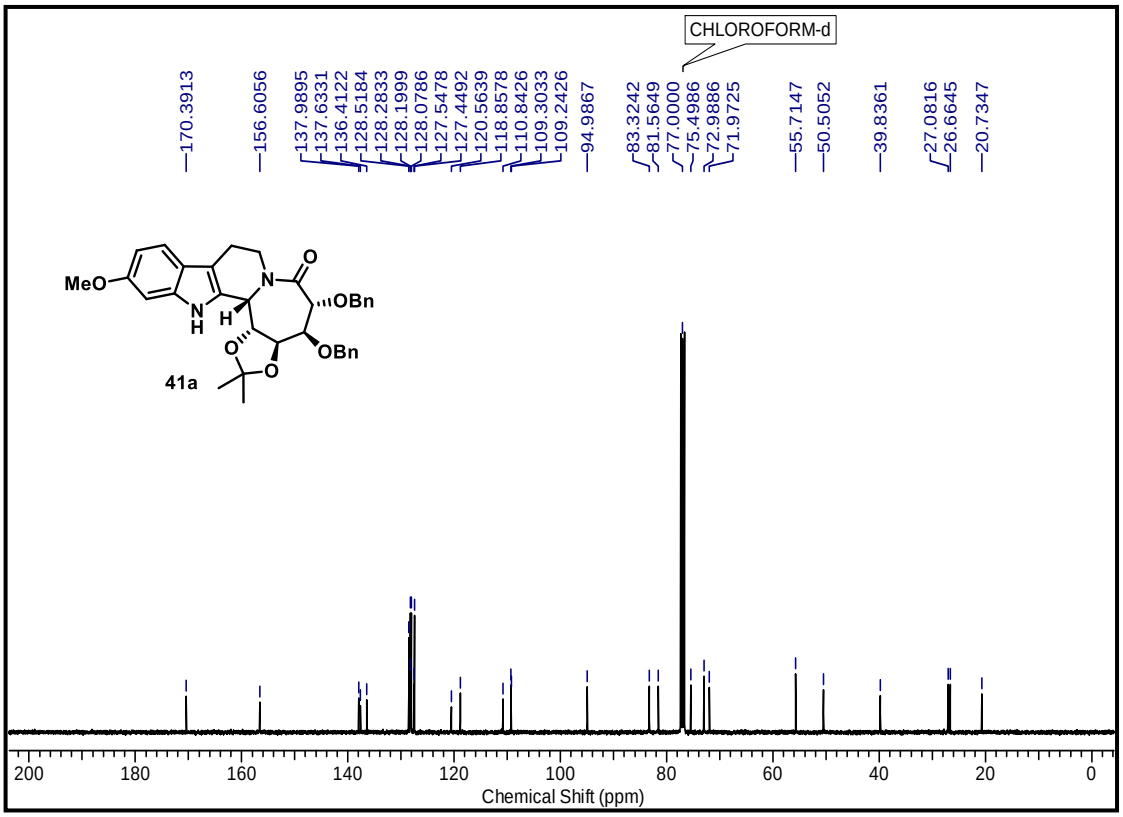
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 39b



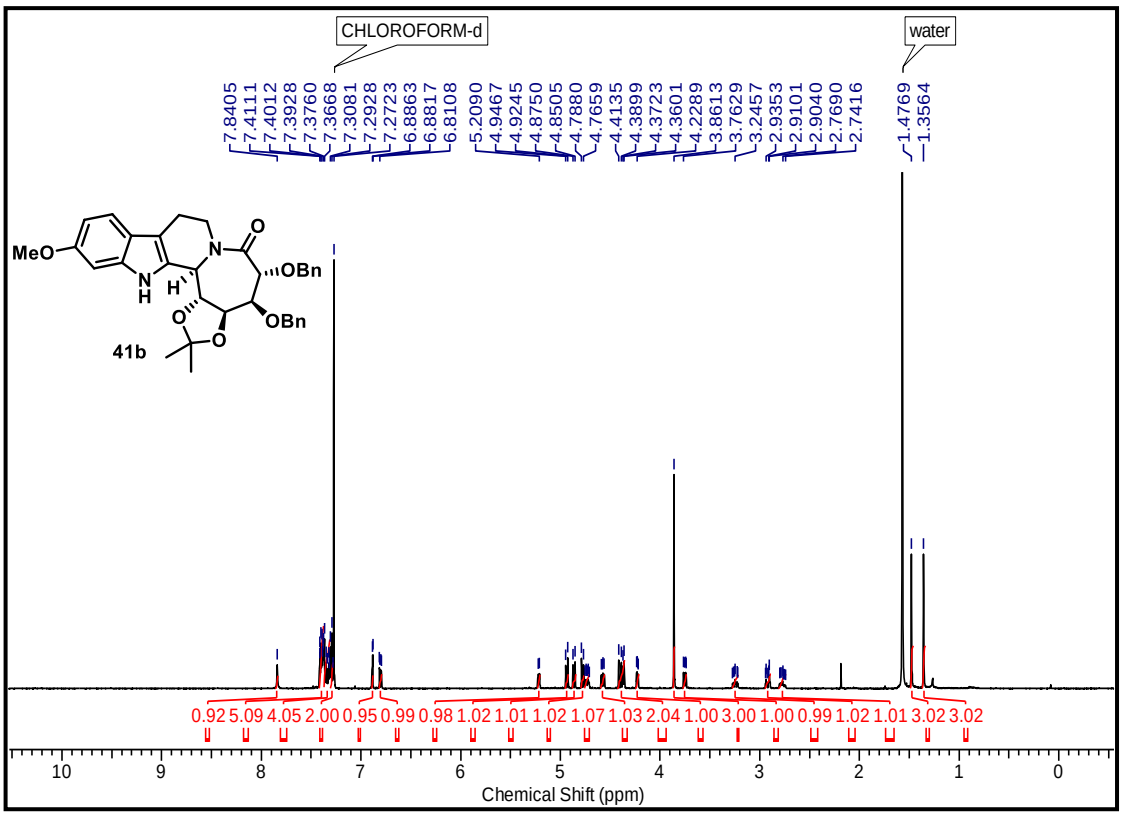
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 41a



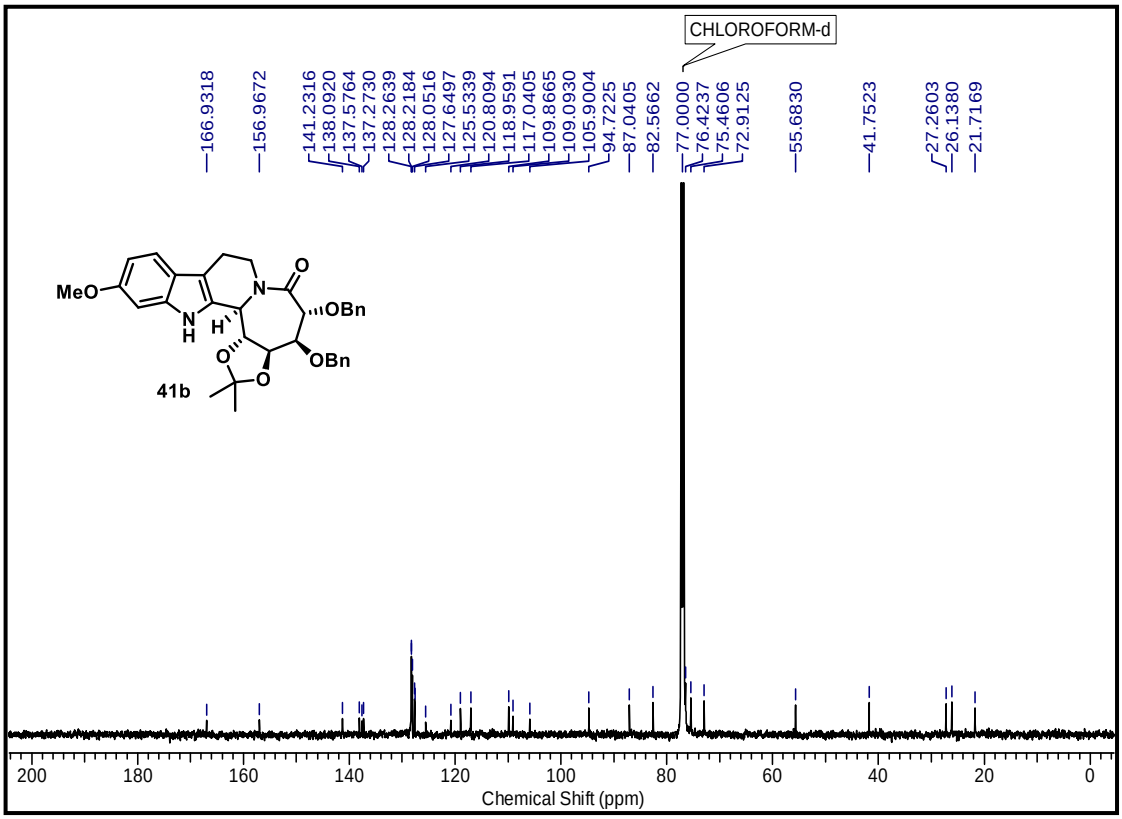
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 41a



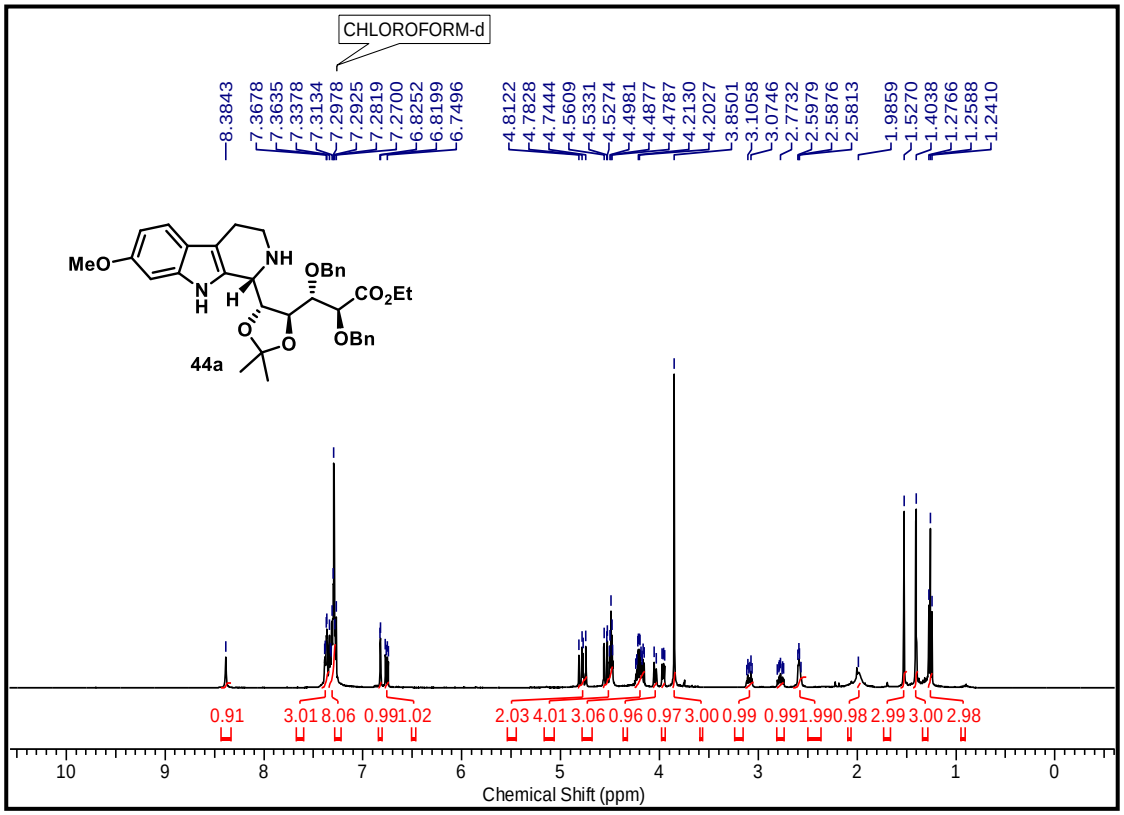
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 41b



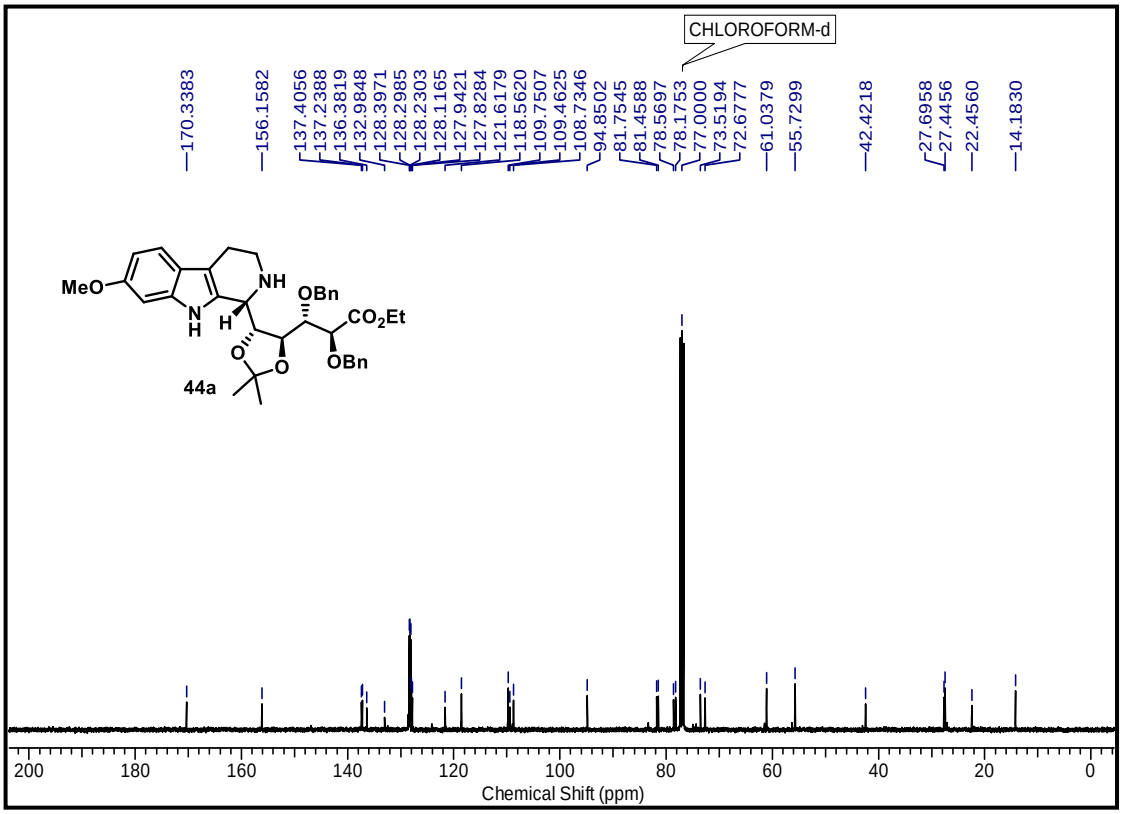
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 41b



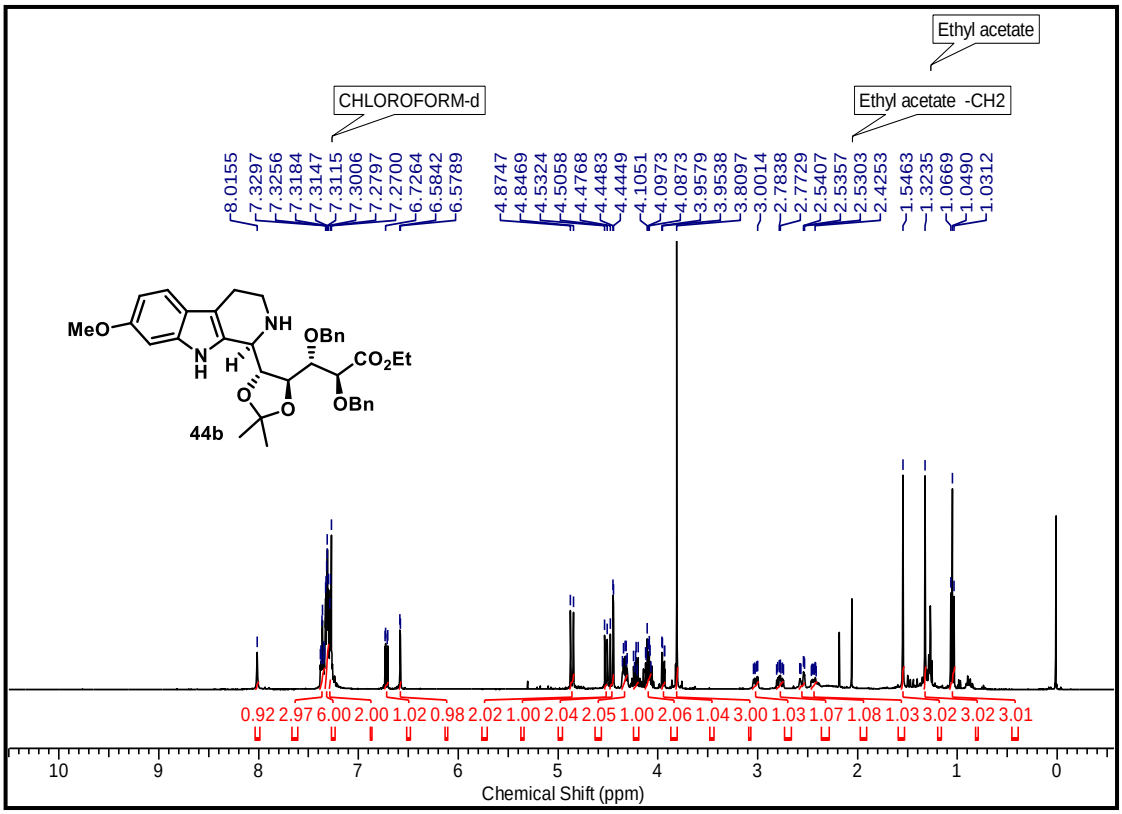
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 44a



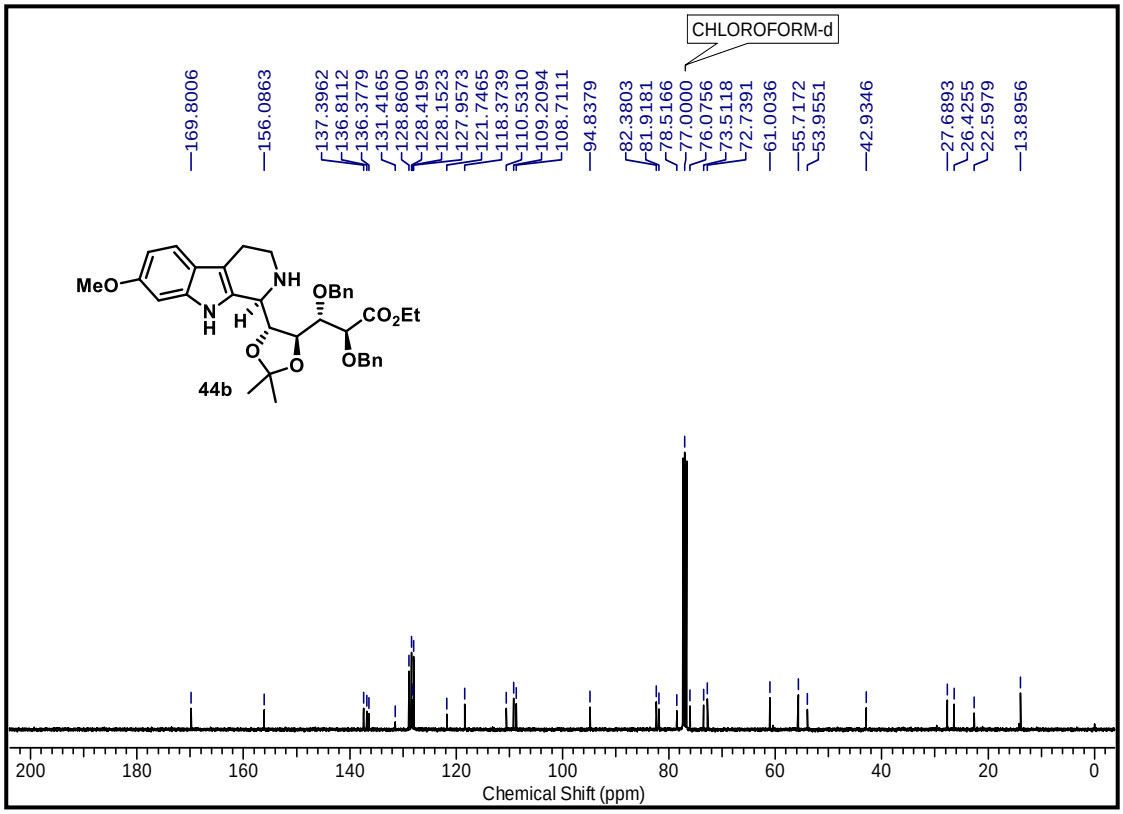
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 44a



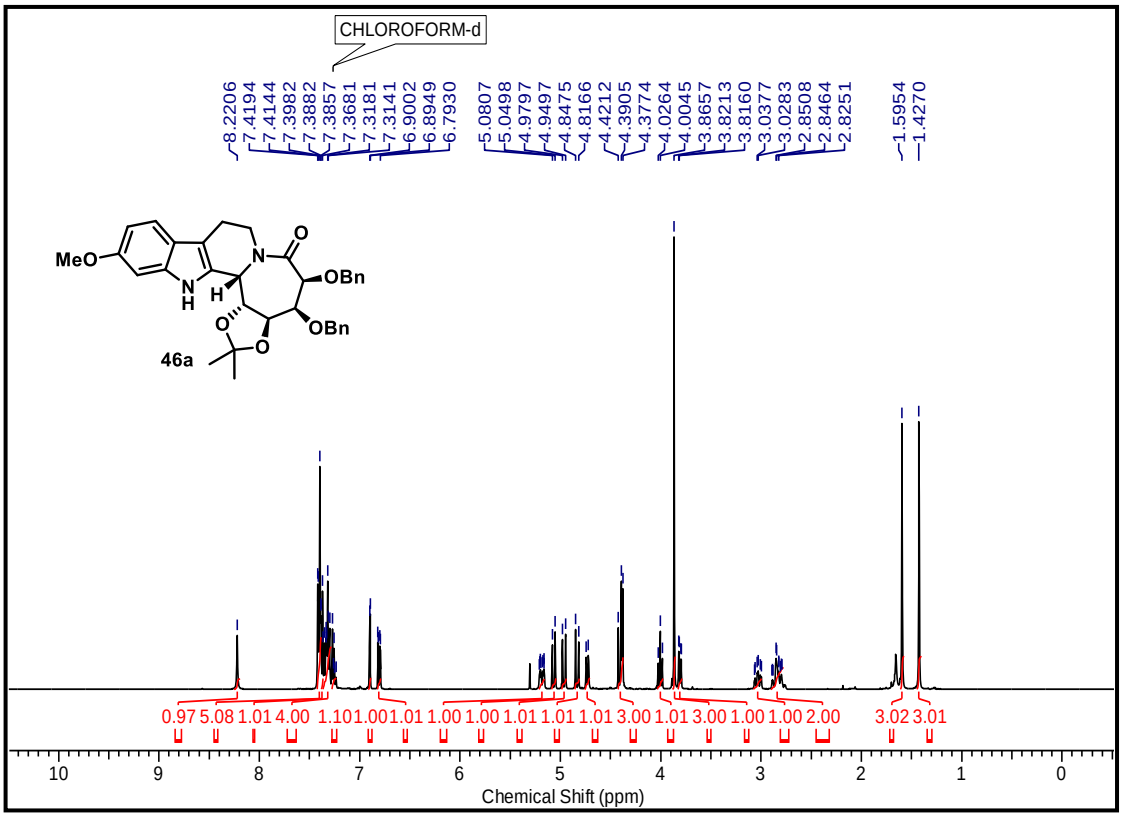
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 44b



^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 44b



^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 46a



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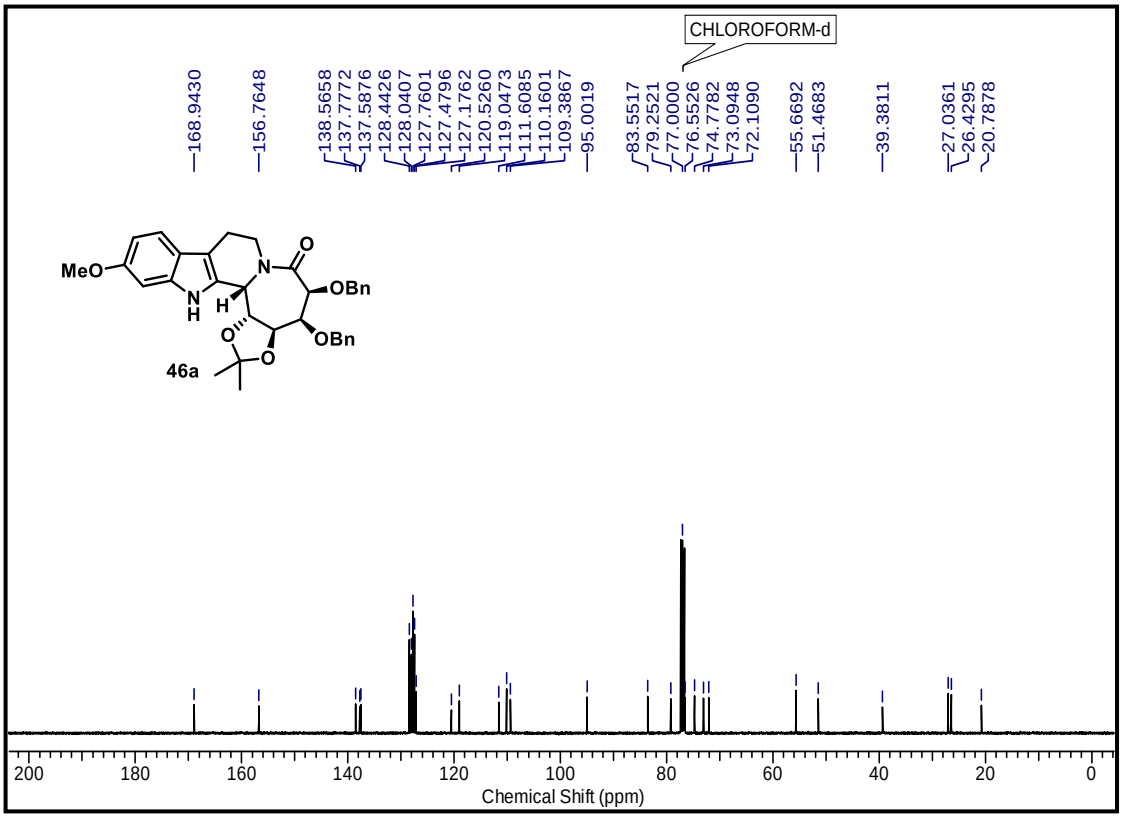

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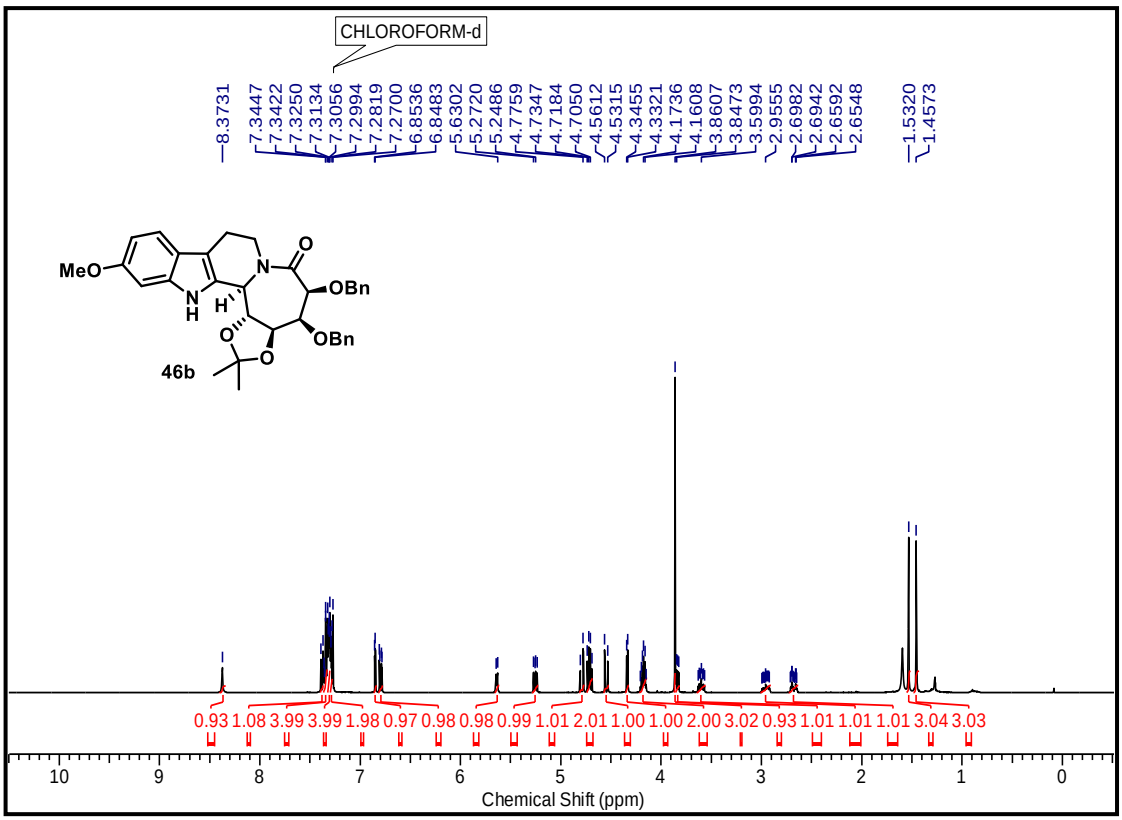

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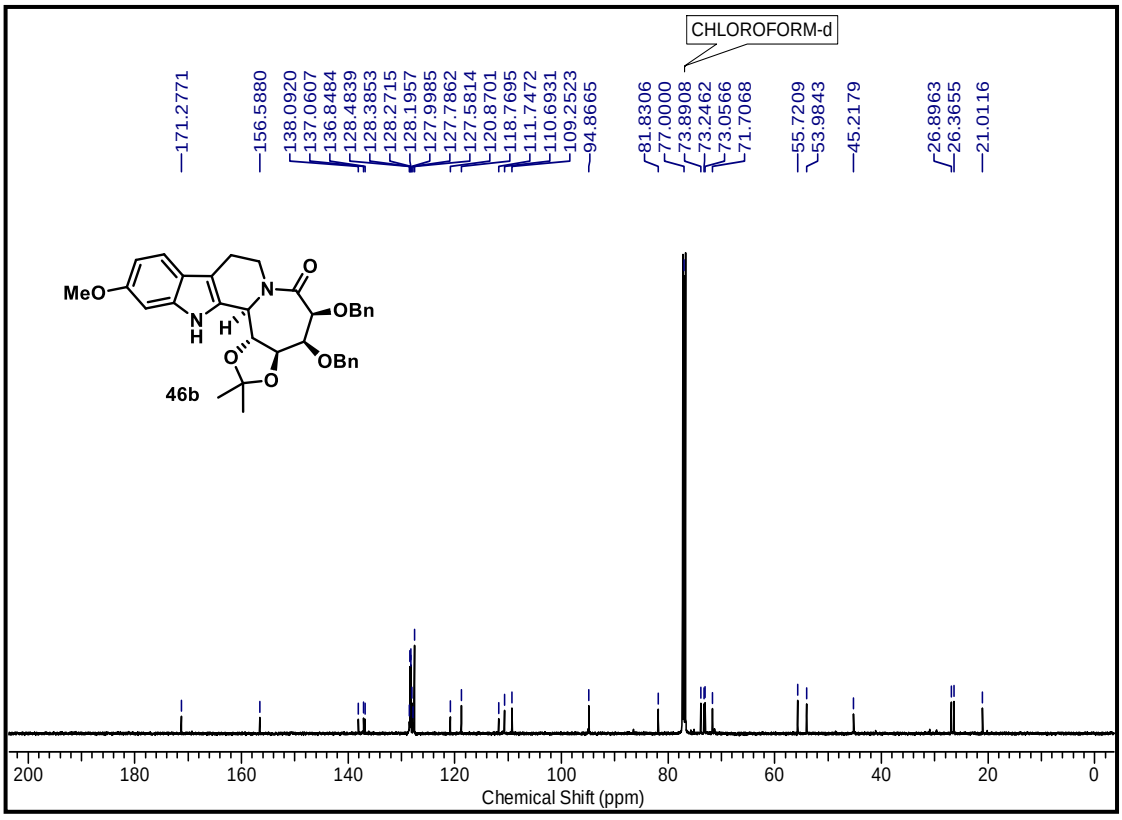

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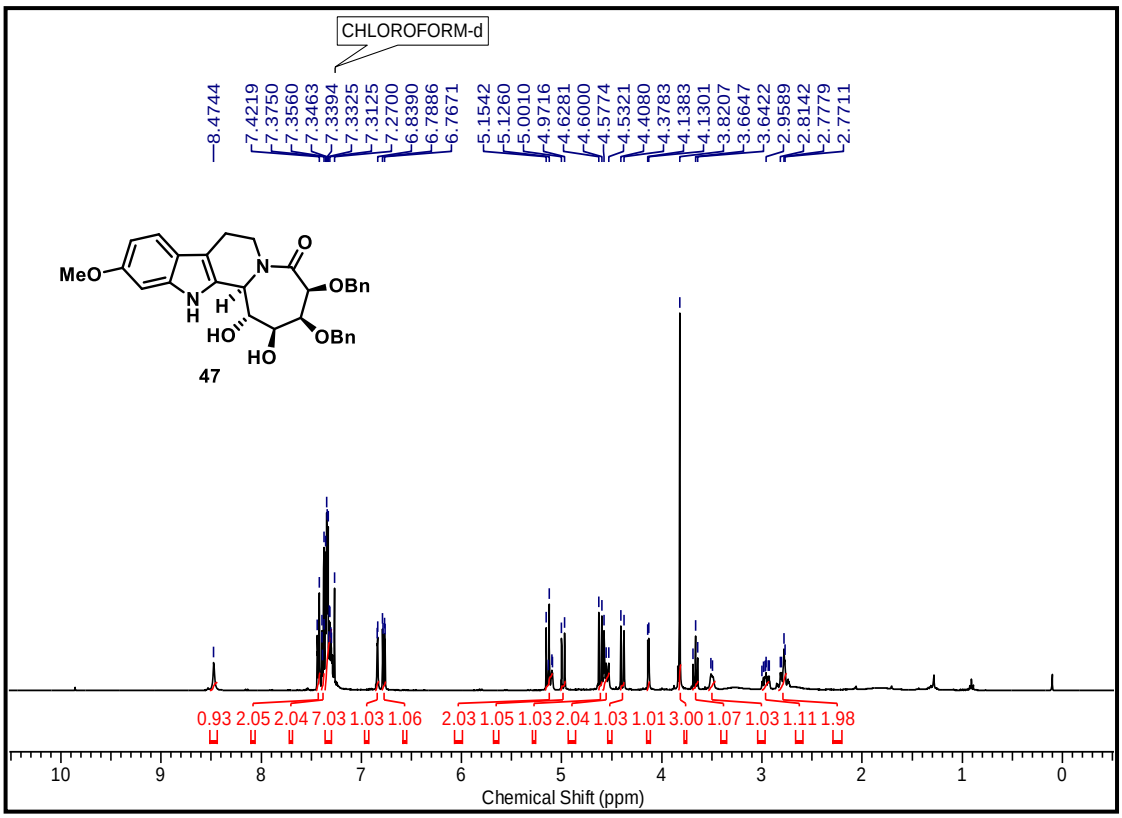

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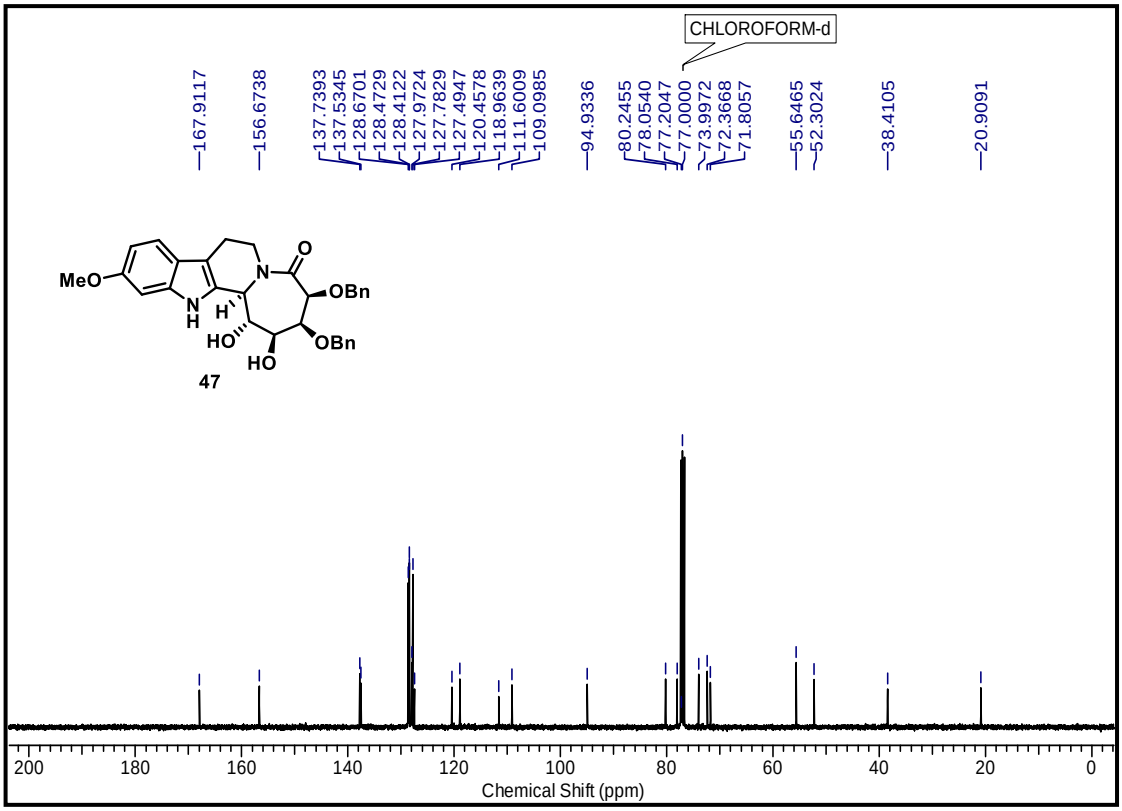

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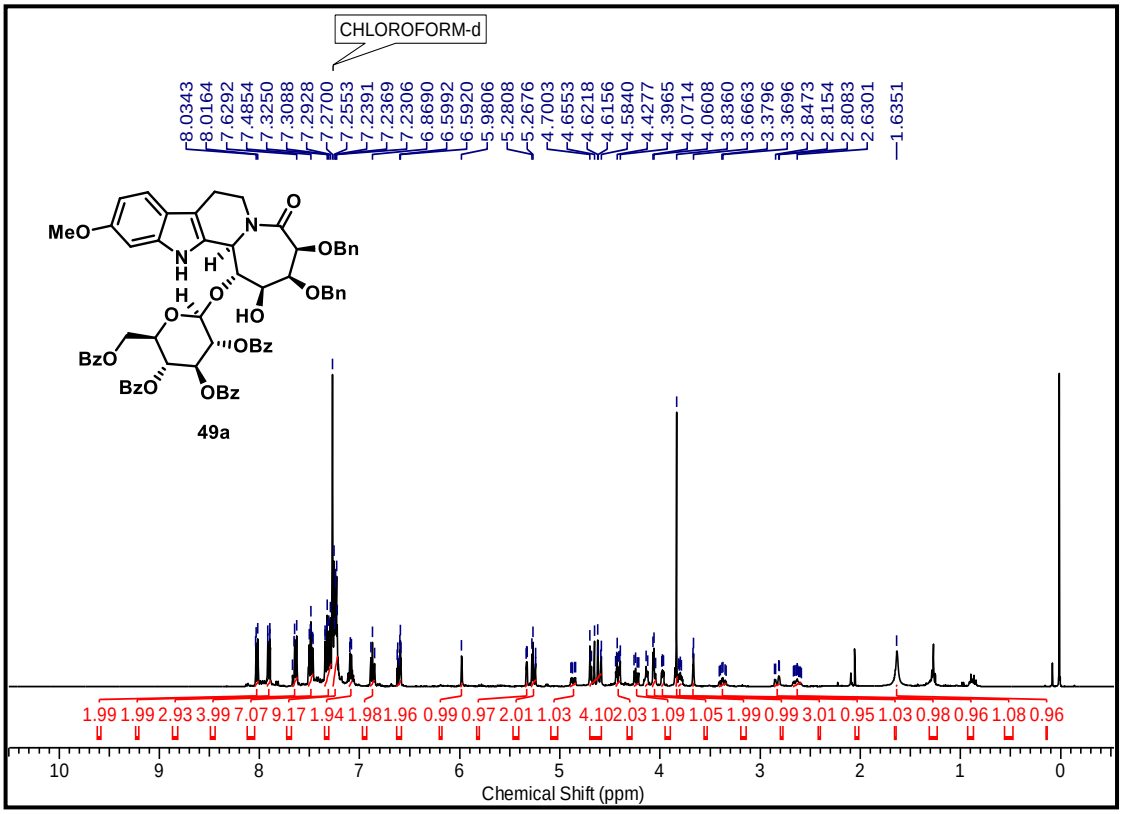

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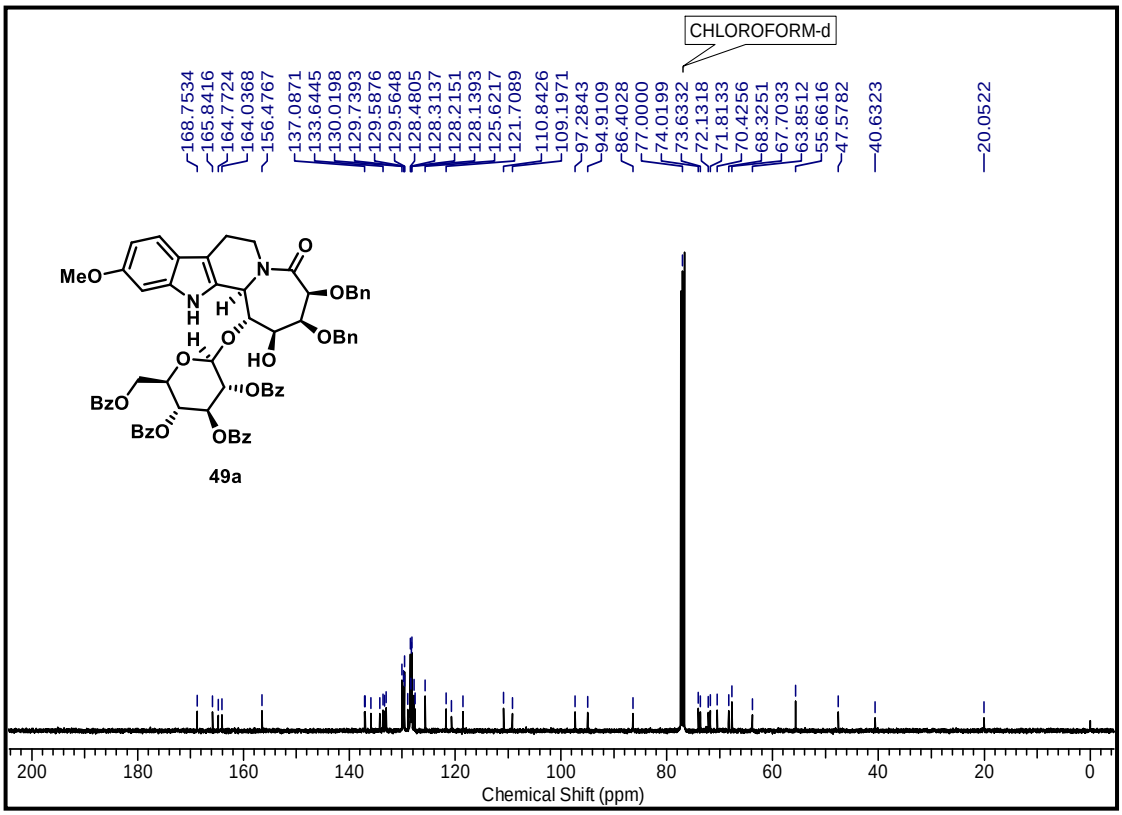

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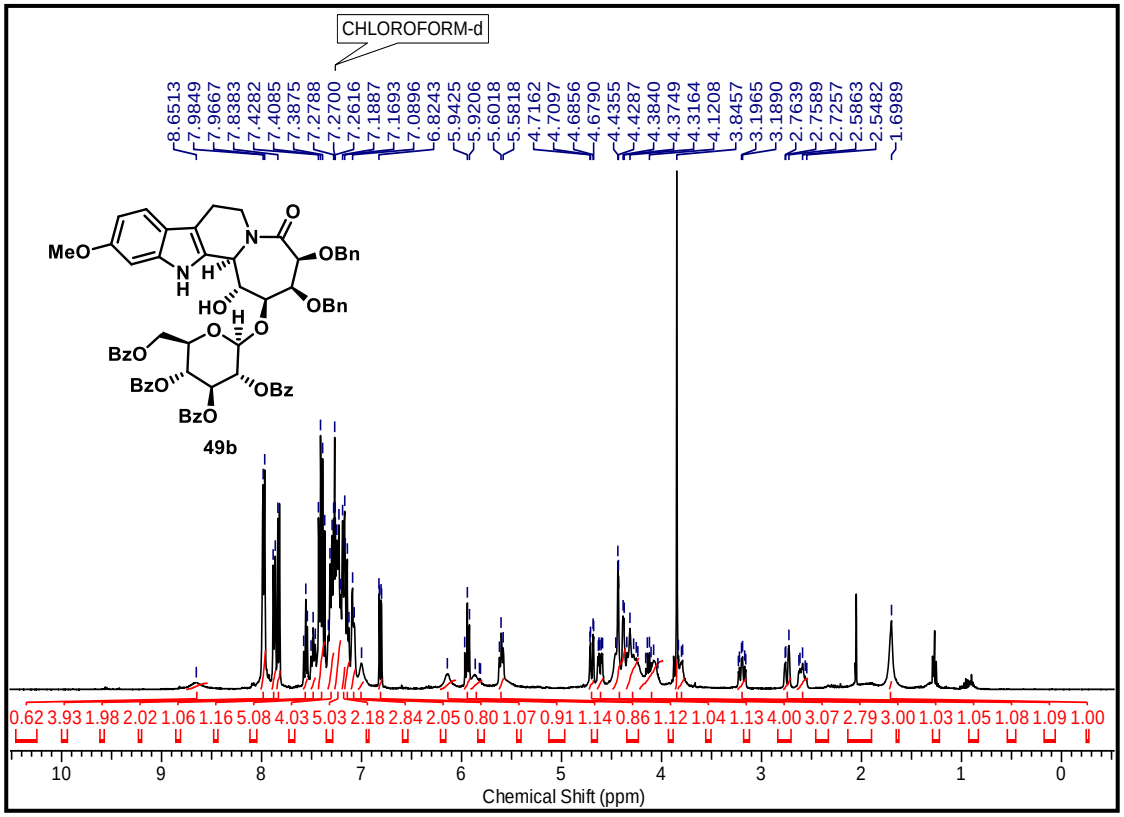

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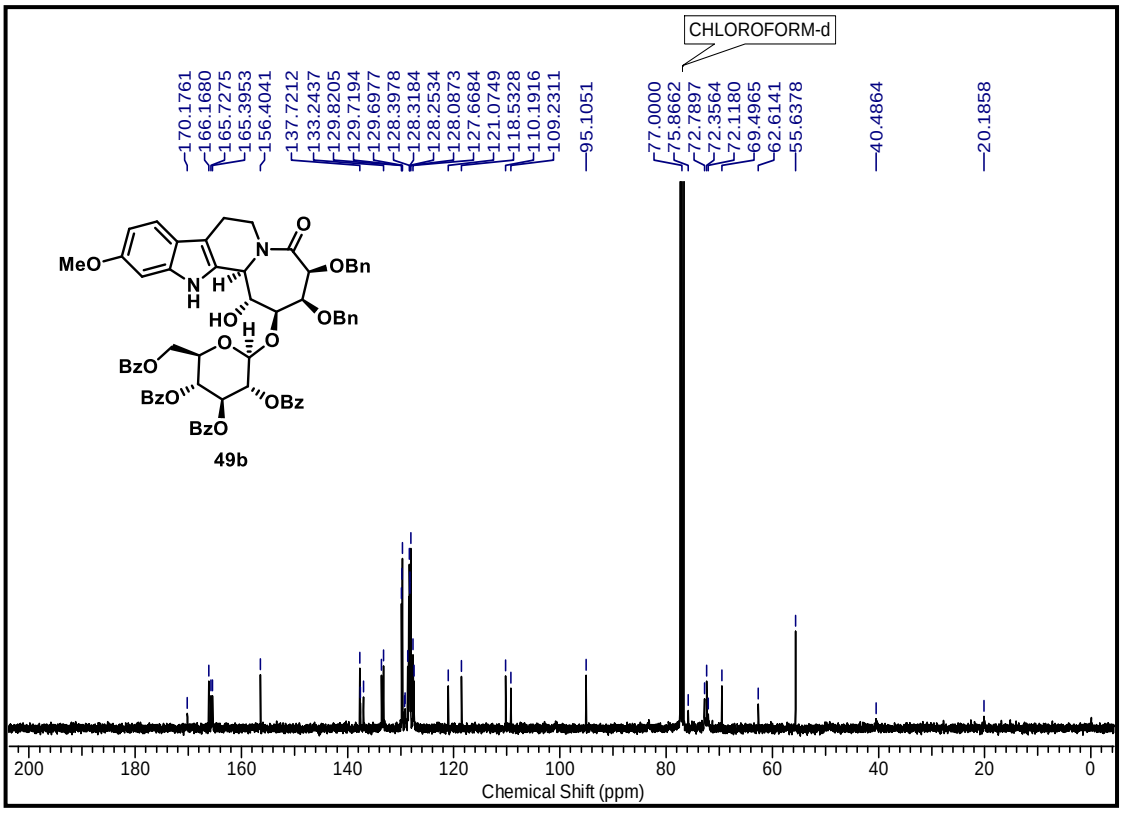
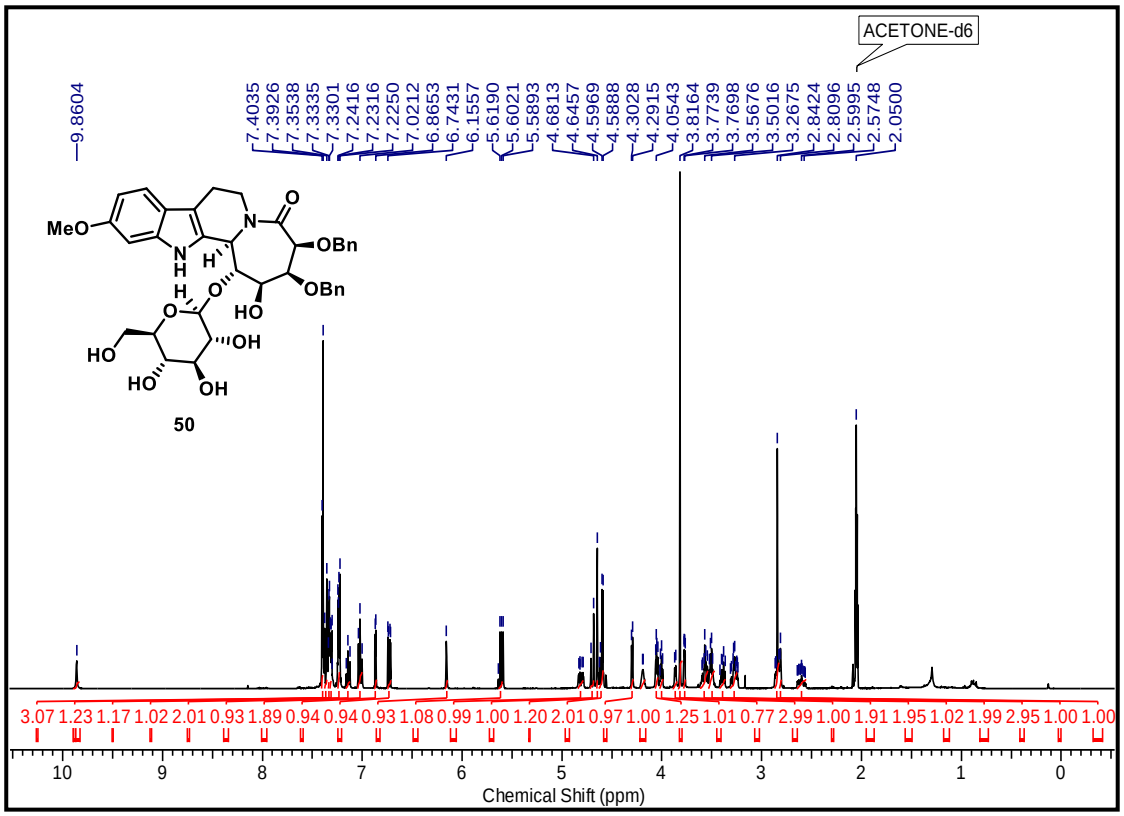
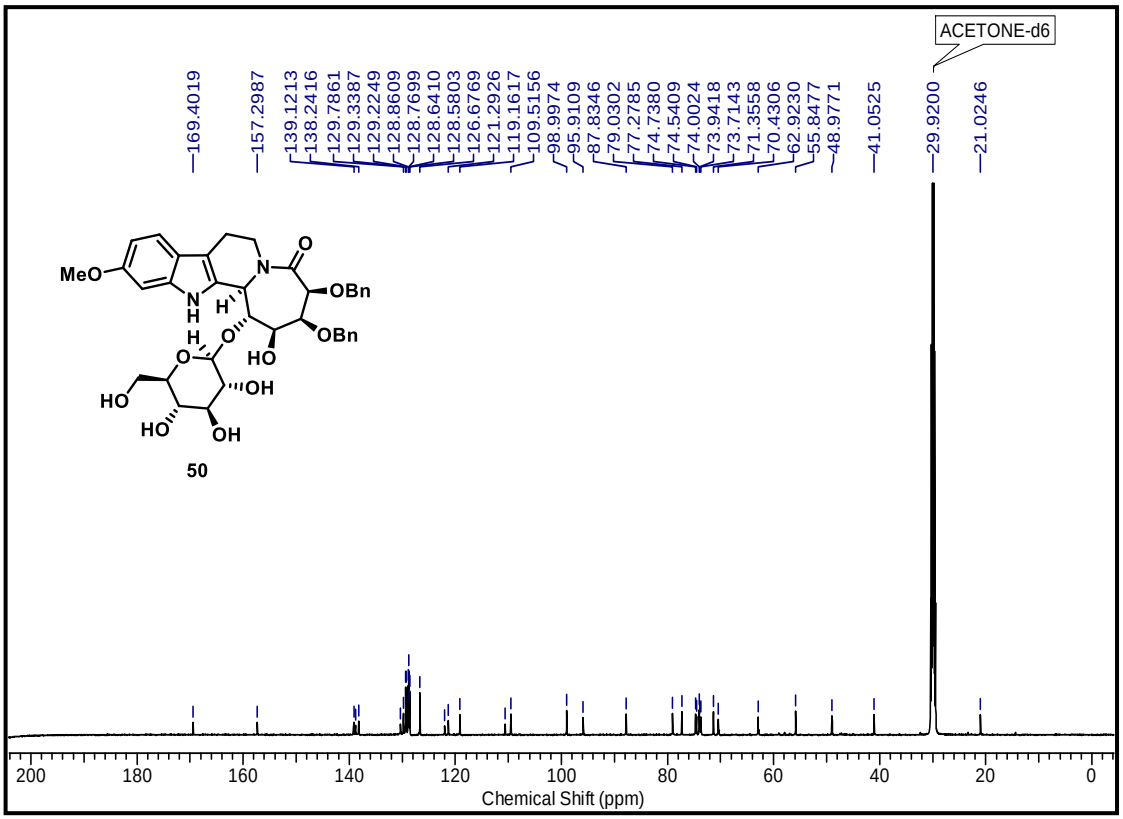


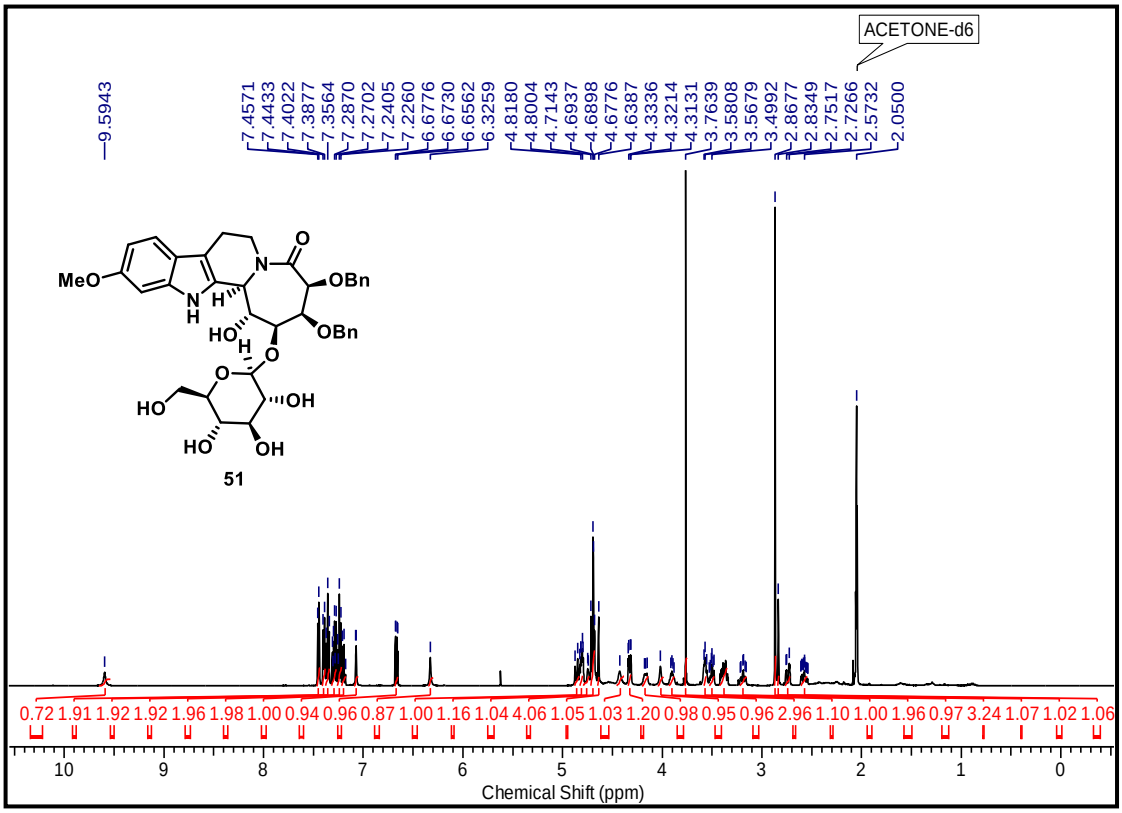
^{1}H NMR (Acetone-d_6, 400 MHz) of Compound 50



^{13}C NMR (Acetone-d_6, 125 MHz) of Compound 50



^{1}H NMR (Acetone-d_6, 500 MHz) of Compound 51



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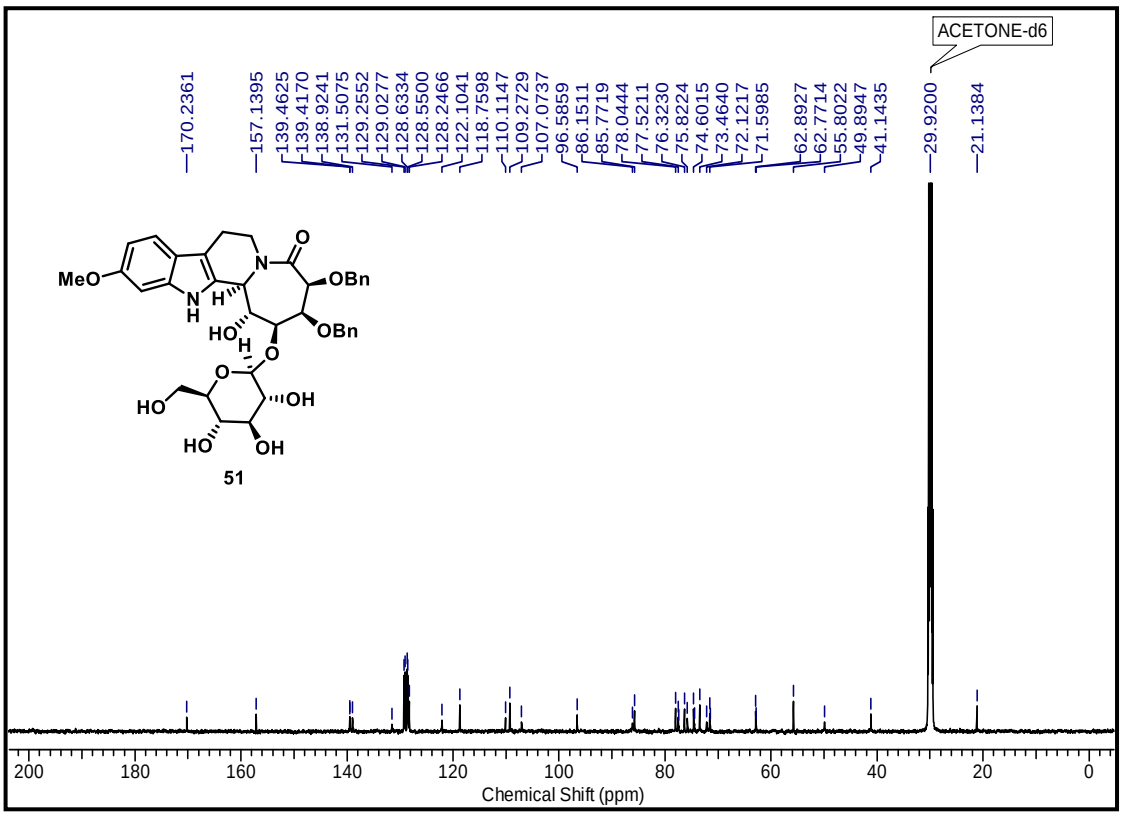

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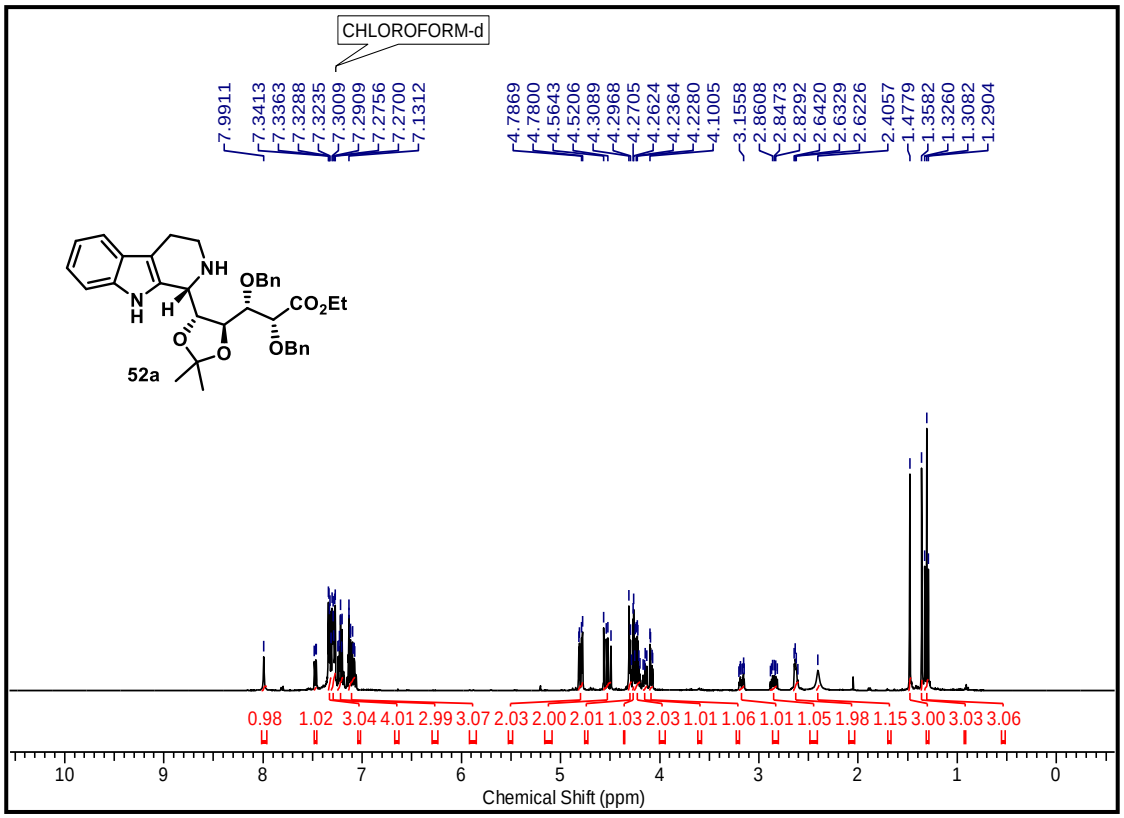
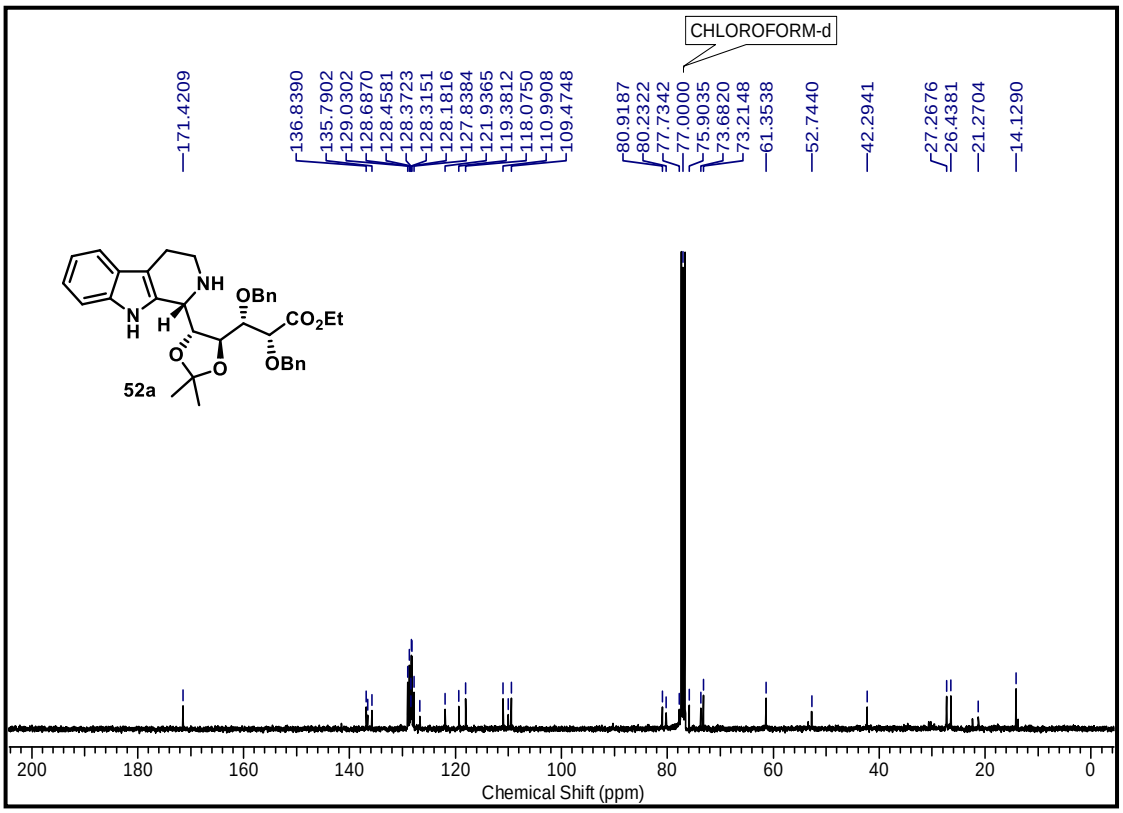


^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 52a



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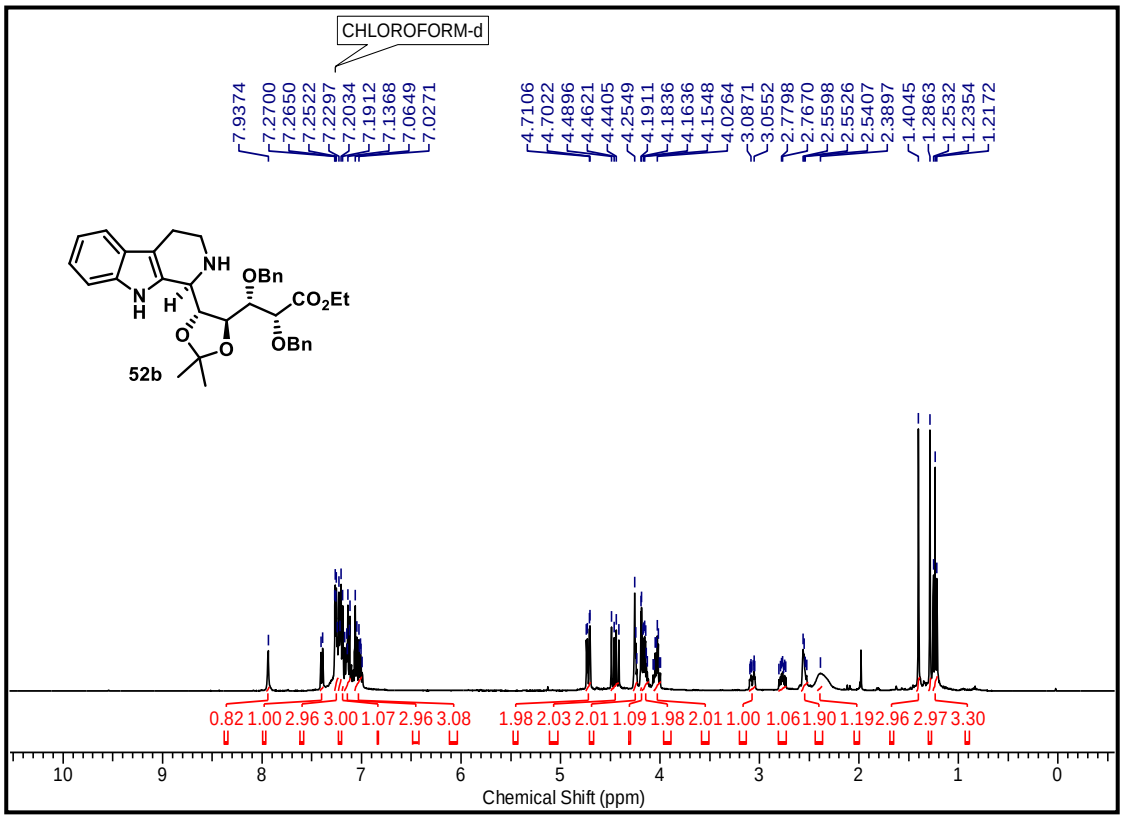

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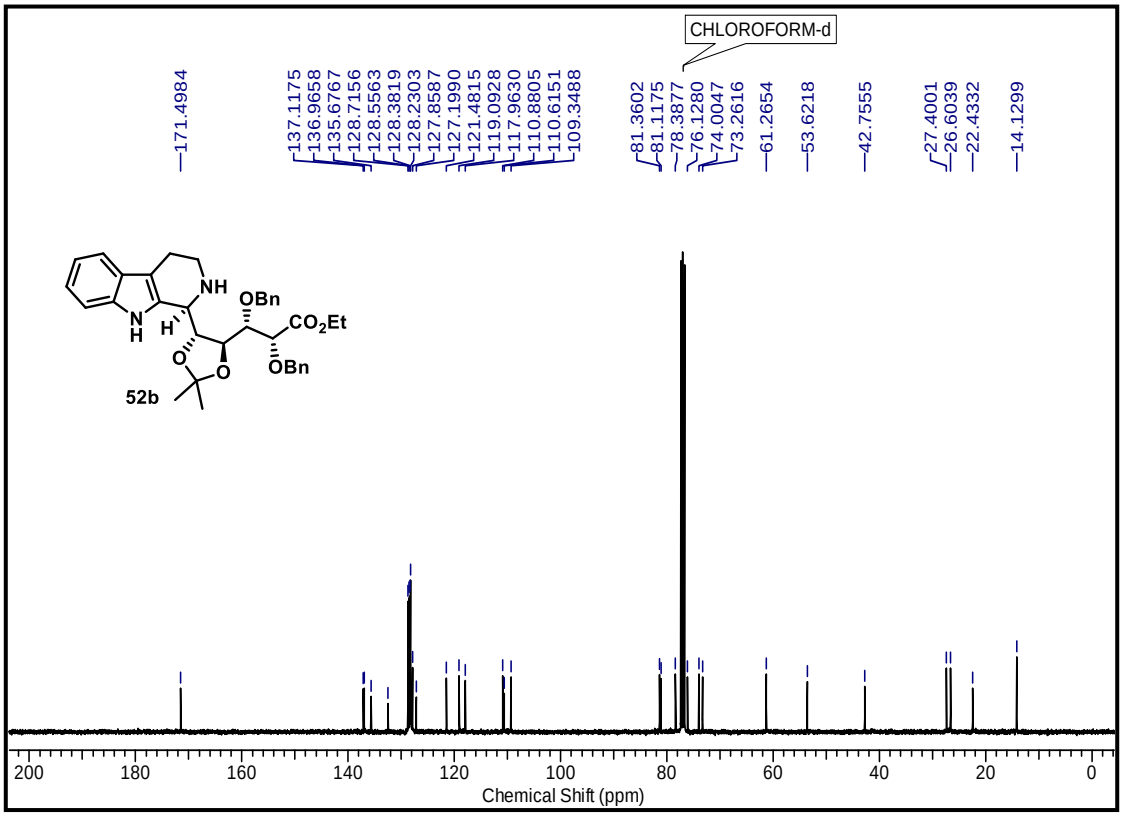

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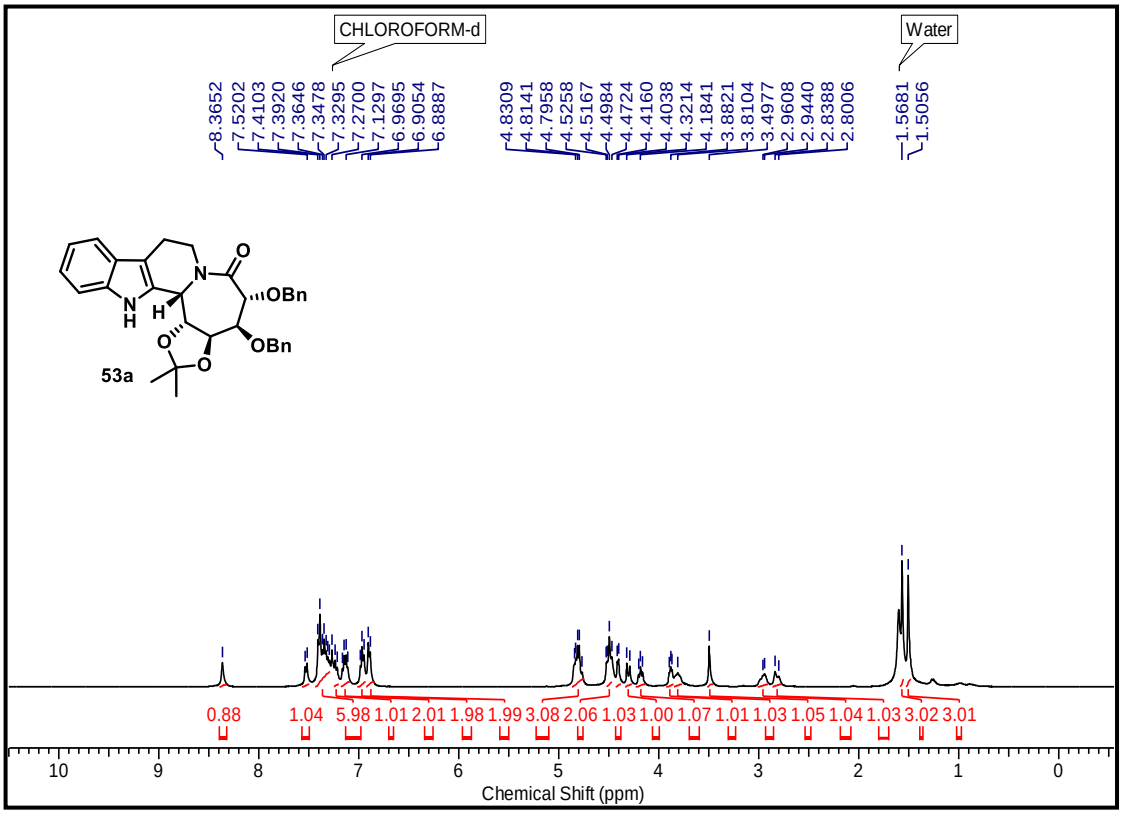

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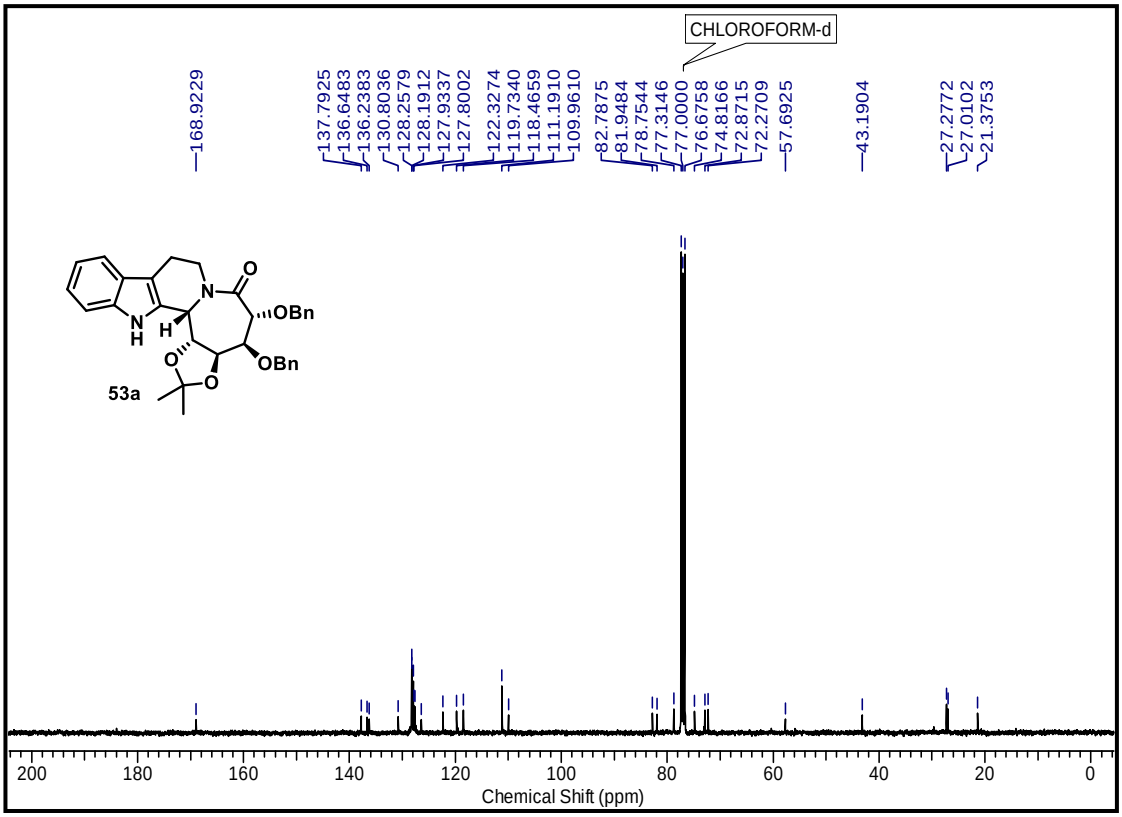

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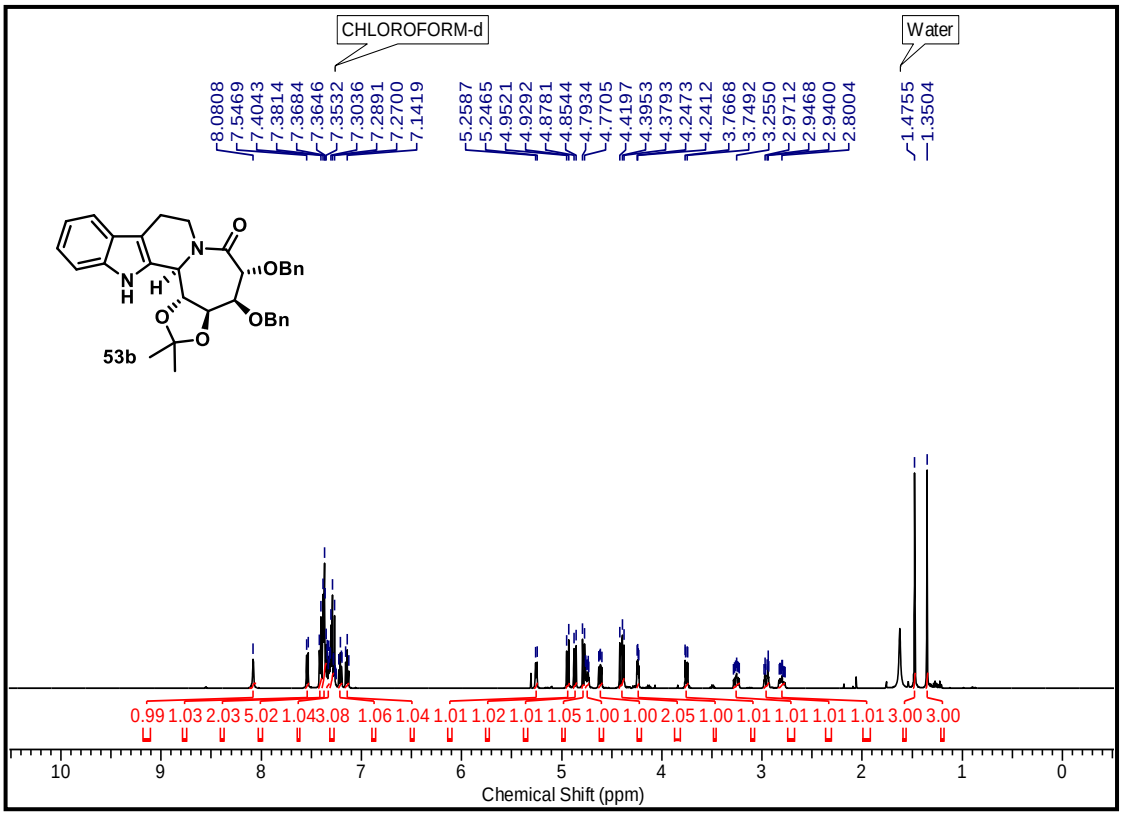

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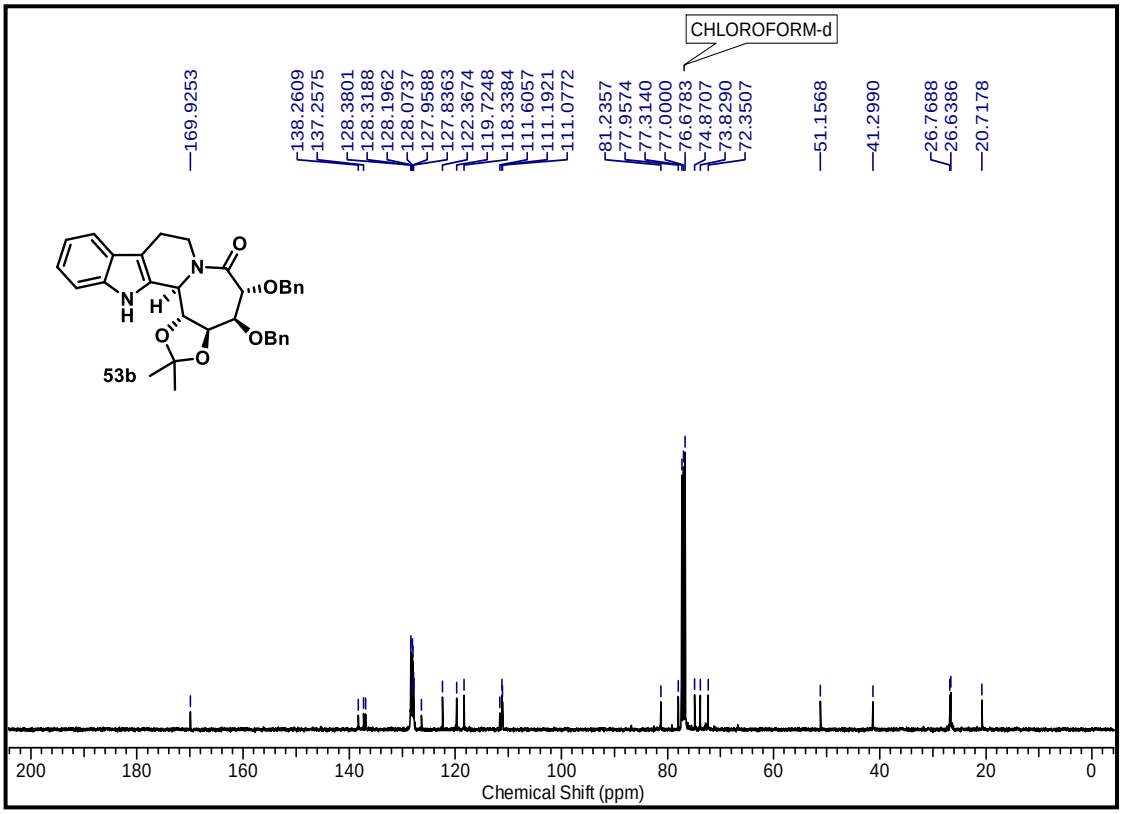

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Chapter 2

Section C

Concise Route Towards the Synthesis of Pentacyclic Core of Reserpine

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

2C.1 Introduction

The *Rauwolfia,* which belongs to Apocynaceae family is a genus of evergreen trees and shrubs, so-called devil peppers. It includes more than 100 species that are commonly found in Asia, Africa, Latin America, and various oceanic islands.[1] From an ancient time in India *R serpentina* was used in Folk medicine which shows biological activity against a wide variety of diseases, including febrile conditions, insect and snake bites, malaria, dysentery, febrifuge, abdominal pain, uterine stimulant, and cure for insanity. In the Indian manuscripts, this plant is mentioned as sarpagandha and chandrika.[2] There are more than 50 indole alkaloids that have been isolated from the *Rauwolfia,* which contains a common 5 and 6 carbon heterocyclic ring structure with one ring junction nitrogen atom. The different indole alkaloids isolated from *Rauwolfia* are reserpine, canescine, isoserine, isoserpiline, lankanescine, neoajmaline, yohimbine, raucaffricine, ajmalicine, raubasine, rauwolfinine, recanescine, isoajmaline, sarpagine, serpentine, serpentinine, thebaine, papaverine, yohimbinine, etc (Figure 1).[3] Reserpine is one of the major indole alkaloid of the plant, found majorly in the root and lower amounts in the stems and leaves. The reserpine was first isolated in 1931 by Sen and Bose. The medicinal role of the compound and its chemistry was reported in 1952 by CIBA lab, Switzerland and also reported as drug in the same year for the treatment of hypertension, thyrotoxicosis, and tachycardia.[4]

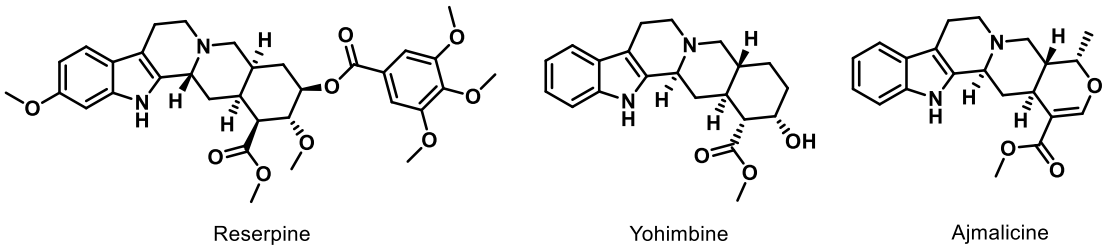


Figure 1. *Rauwolfia* Indole Alkaloids.

The high blood pressure can cause various problems to the patient including damage to the heart, brain, blood vessels, kidneys and other parts of the body. The reserpine lowers the activity of nervous system lowering the heartbeats and relaxation in blood vessels. It can also help in the treatment of various psychotic symptoms.[5] Because of the development of better drugs for this purpose and the side effects of the reserpine, now a days it is very rarely used. Most common side effect is nasal congestion.

Reserpine also causes nasal congestion, stomach cramps, weight gain, vomiting, gastric intolerance, gastric ulceration, nausea, and diarrhea. Because of these side effects there is study carried out on synthesis of different potent analogs related to the reserpine scaffold.

2C.2 Different Synthetic Approaches Towards Reserpine

In the figure 2 we have shown the different synthetic approaches for reserpine. The first total synthesis of was accomplished by Woodward *et al*. in 1957, which also gave the information about relative configuration of reserpine.[6] The Sparks *et al*. (2003) have reported two different synthetic ways for construction of D and E ring of reserpine using stereochemically controlled intramolecular Diels–Alder reaction.[7] In 1989 the Gilbert Stork synthesized the reserpine with the stereospecific approach. In continuation of their work on this topic Stork *et al*. have developed three approaches for the regio- and stereoselective synthesis of reserpine in 2005.[8] After reviewing the synthetic approaches for the reserpine, Huang and Chen (2007) have proposed the synthetic route by using the economical (−)-shikimic acid as chiral pool for the construction of E-ring segment.[9] In 2012 Yar *et al*. have followed different protocol for the synthesis, they used the photocyclization approach for the synthesis of reserpine. Their synthesis is mainly focused on the en-amide photocyclization for the constriction of D-ring in reserpine.[10]

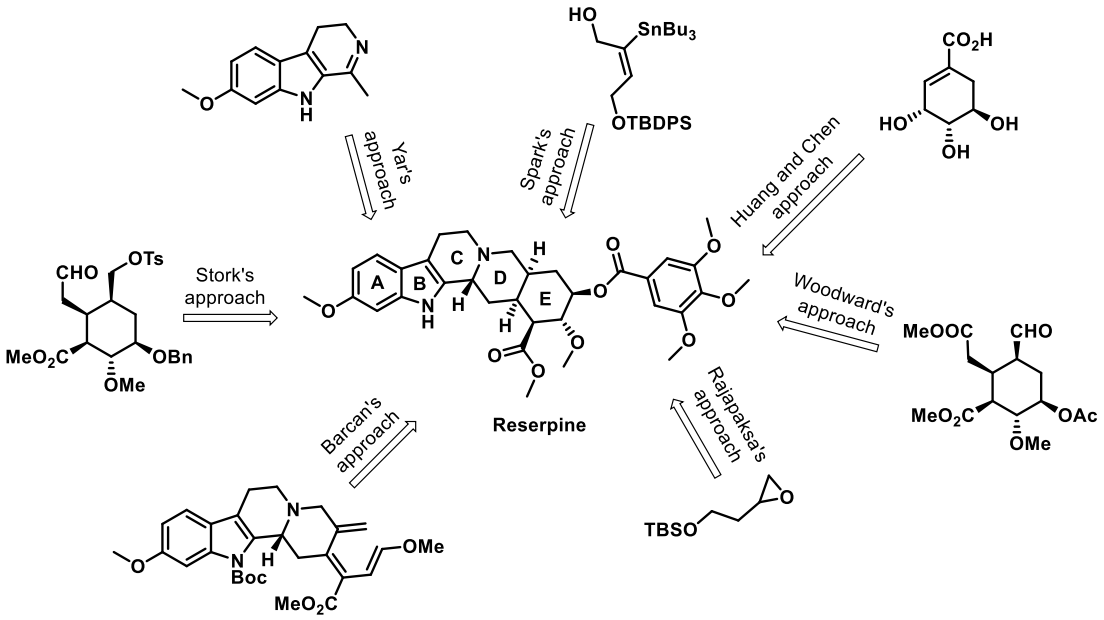
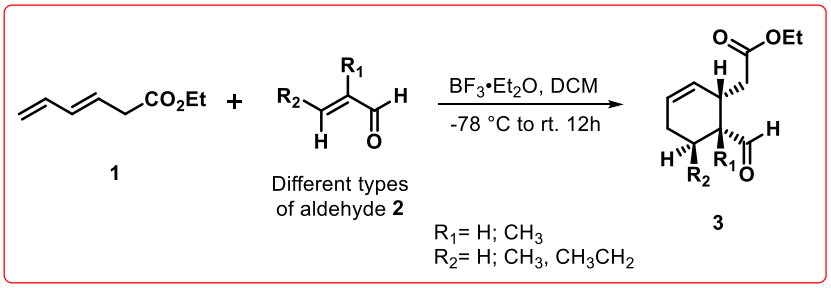


Figure 2. Different Synthetic Approaches for Reserpine.

The synthetic sequence of Barcan *et al*. include an effective tandem cross-coupling/torquoselective 6π electrocyclization, which maintain the chirality at C3 and C18 positions in reserpine alkaloids.[11] The key feature of Rajapaksa *et al*. synthesis is use of chiral catalyst-controlled formal aza-Diels–Alder reaction in the synthesis of complex alkaloids. The aza-Diels–Alder reaction and highly diastereoselective approach were used for the construction of tetracyclic core of natural product.[12]

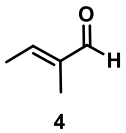
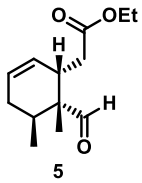
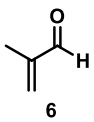
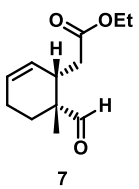
2C.3 Result and Discussion (Present Research Work)

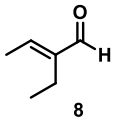
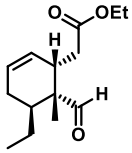
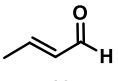
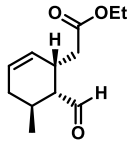
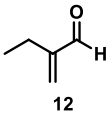
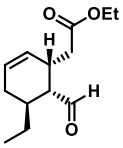
There are many ways of making pentacyclic core of indole alkaloids such as reserpine, yohimbine, ajmalicine etc. We worked on the synthesis of different analogs of reserpine by using well established Diels–Alder reaction condition in our lab to construct the cyclic aldehyde-ester, as elutriated in the periconianone A synthesis. We have reacted different α,β-unsaturated aldehydes substrates with the deconjugated ethyl sorbate to obtain the cyclic aldehyde ester using BF_3•Et_2O in DCM (Scheme 1, Table 1).[13]



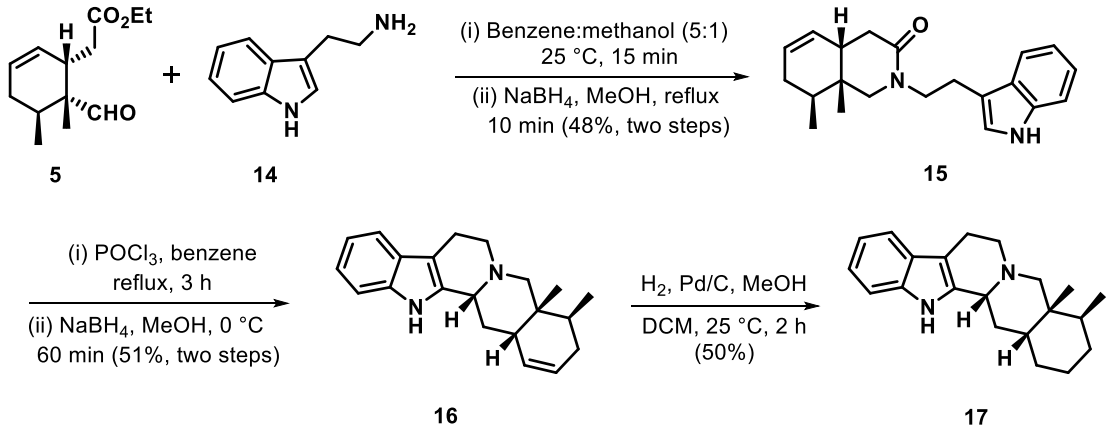
Scheme 1. Optimized Condition for Diels–Alder Reaction.

Table 1. Reactions of Deconjugated Ethyl Sorbate with Unsaturated Aldehydes.

Aldehyde Substrate	Product	Yield
 4	 5	75%
 6	 7	60%

 8	 9	**67%**
 10	 11	**72%**
 12	 13	**70%**

After making different cyclic aldehyde ester substrates our next step was to react these substrates with tryptamine. The cyclic aldehyde ester **5** were dissolved in benzene:methanol (5:1) solution and reacted with tryptamine (**14**) to get the imine intermediate which was reduced with $NaBH_4$ in methanol to obtain the cyclic amide intermediate **15**.[14] This amide intermediate **15** on treatment with $POCl_3$ in benzene followed by $NaBH_4$ reduction generated the pentacyclic compound **16**.[15] The double bond in the compound **16** was reduced with H_2, Pd/C in methnol:DCM to obtain the compound **17** (Scheme 2). The stereochemistry was confirmed by taking the X-ray of few synthesized analogs (Figures 3 and 4).



5 14 15 16 17

Scheme 2. Synthesis of Pentacyclic Compound

This is the concise synthetic route by using which we can access different types of indole alkaloidal natural products. We have synthesized focused mini library of a few

analogs using this protocol (Figure 5). The biological evaluation of these analogs has been planned in near future.

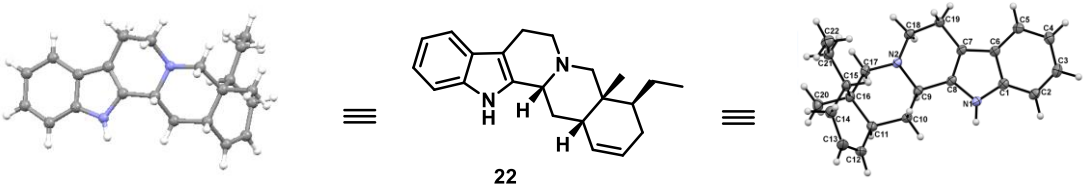


Figure 3. X-Ray Crystal Structure of Compound **22**.

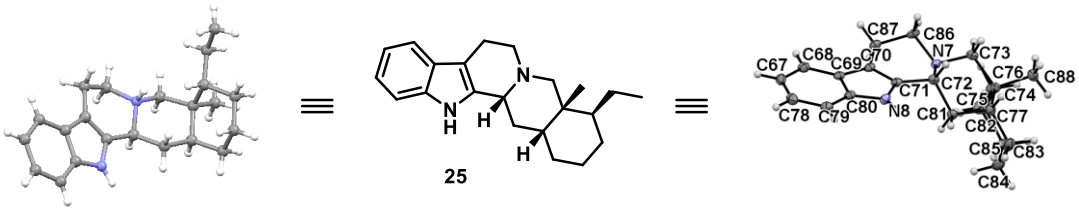


Figure 4. X-Ray Crystal Structure of Compound **25**.

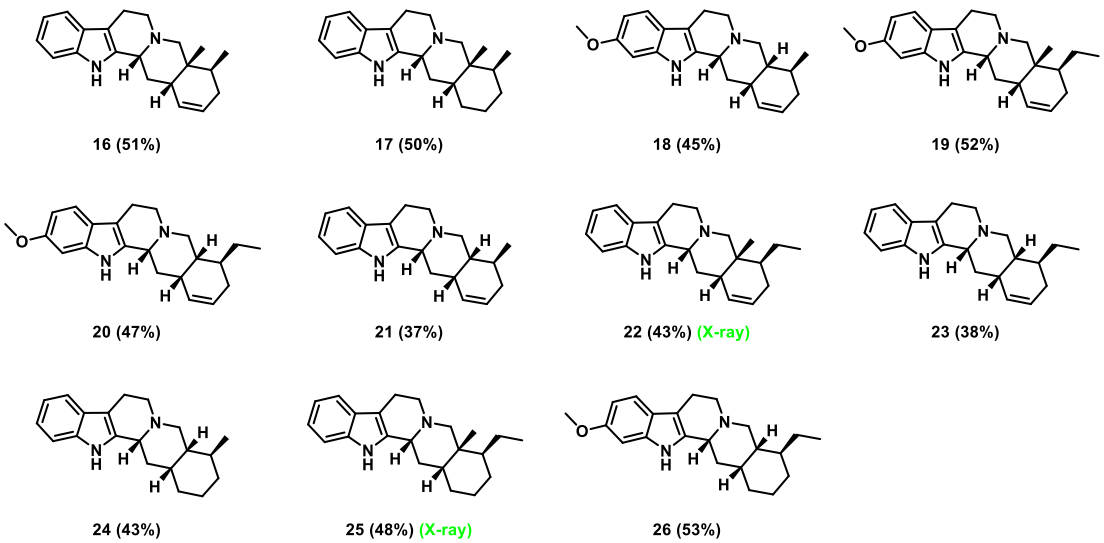


Figure 5. Synthesized Reserpine Analogs.

2C.4 Summary

In summary, a new efficient and straightforward method for the synthesis of pentacyclic core of reserpine has been demonstrated. It will be useful for the synthesis of a broad range of desired bioactive natural and unnatural indole alkaloids. We have

synthesized 11 reserpine analogs for SAR studies and stereochemistry of most of the compounds have been confirmed by the X-ray crystallography. We also believe that the current protocol has a scale-up potential and will be useful for large-scale production of several rauwolfia alkaloid family natural products of commercial interest.

2C.5 Experimental Section

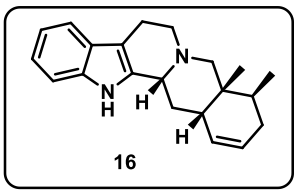
General Procedure for the Synthesis of Cyclic Amide Intermediate (15). Compound **5** (0.2 g, 1.09 mmol) was firstly dissolved in benzene:methanol (5:1) (12 mL) to which was added tryptamine **14** (0.175 g, 1.09 mmol) and the reaction mixture was stirred at room temperature for 15 min. Then solvent was evaporated under reduced pressure and then methanol (15 mL) was added under argon along with the $NaBH_4$ (0.206 g, 5.45 mmol). The reaction mixture was refluxed with stirring for 1 h. After an hour solvent was evaporated using reduced pressure, then reaction mixture was quenched with 2N HCl (10 mL) after dissolving the residue in DCM. The solvent was evaporated through reduced pressure and the crude compound was purified by column chromatography on silica gel (60:40; petroleum ether:EtOAc) to afford cyclic amide intermediate **15** (0.14 g, 48%) as a yellow sticky liquid.

General Procedure for Pentacyclic Compounds (16). To a solution of amide **15** (0.05 g, 0.155 mmol) in benzene (10 mL) at room temperature was added $POCl_3$ (0.04 mL, 0.31 mmol). The reaction mixture was refluxed for 2.5 h at 80 °C. Then the benzene was evaporated under the reduced pressure and crude compound was dissolved in methanol (10 mL). In the reaction mixture $NaBH_4$ (0.014 g, 0.0388 mmol) was added at room temperature and kept under stirring for 1 h. After 1 h, the reaction mixture was quenched with 3-4 drops of AcOH, and dissolved in ethyl acetate (20 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. The reaction mixture was concentrated under reduced pressure and crude compound was purified by column chromatography on silica gel (85:15; petroleum ether:EtOAc) to afford compound **16** (0.024 g, 50%) as a white solid.

General Procedure for H_2, Pd/C Reduction of Double Bond (17). The compound **16** (0.05 g, 0.163 mmol) in dichloromethane:methanol (1:1) (10 mL)was purged the solution with argon for 10-15 min. Then Pd/C (0.012 g, 0.114 mmol) catalyst was added and the reaction mixture was stirred at room temperature under H_2 atmosphere for 2 h. After 2 h, reaction mixture was filtered through celite and solution was

concentrated under reduced pressure. The crude compound was purified by column chromatography on silica gel (85:15; petroleum ether:EtOAc) to afford compound **17** (0.025 g, 50%) as a white solid.

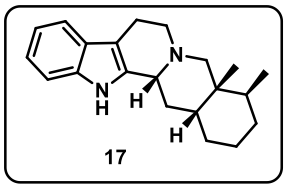
(4*S*,4a*R*,13b*R*,14a*S*)-4,4a-Dimethyl-3,4,4a,5,7,8,13,13b,14,14a-decahydroindolo



16

[2',3':3,4]pyrido[1,2-*b*]isoquinoline (16). Mp 119–122 °C; **^{1}H NMR (CDCl$_3$, 400 MHz)** δ 7.70 (br. s., 1 H), 7.49 (d, *J* = 7.3 Hz, 1 H), 7.31 (d, *J* = 7.8 Hz, 1 H), 7.21–7.10 (m, 2 H), 5.69–5.58 (m, 2 H), 3.18 (dd, *J* = 2.1, 11.7 Hz, 1 H), 3.06–2.96 (m, 3 H), 2.76–2.69 (m, 1 H), 2.58–2.50 (m, 1 H), 2.41–2.31 (m, 2 H), 2.08 –2.03 (m, 2 H), 1.93–1.86 (m, 1 H), 1.83–1.76 (m, 1 H), 1.65–1.58 (m, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.82 (s, 3 H); **^{13}C NMR (CDCl$_3$, 125 MHz)** δ 136.0, 135.2, 129.5, 127.5, 126.6, 121.2, 119.3, 118.1, 110.7, 108.3, 64.6, 60.6, 53.5, 43.5, 35.1, 35.0, 32.2, 27.4, 21.9, 18.4, 14.7; **HRMS (ESI) *m/z*** $[M+H]^+$ calcd for $C_{21}H_{27}N_2$ 307.2165, found 307.2164; **IR (CHCl$_3$)** ν_{max} 3196, 2920, 1450, 1324 cm^{-1}.

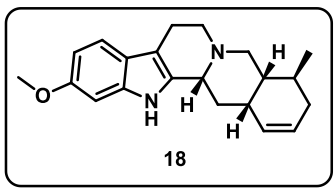
(4*S*,4a*R*,13b*R*,14a*R*)-4,4a-Dimethyl-1,2,3,4,4a,5,7,8,13,13b,14,14a-dodecahydro



17

indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (17). Mp 115–118 °C; **^{1}H NMR (CDCl$_3$, 400 MHz)** δ 7.72 (br. s., 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.16–7.07 (m, 2 H), 3.23–3.17 (m, 1 H), 3.00–2.98 (m, 1 H), 2.98–2.95 (m, 1 H), 2.75–2.68 (m, 1 H), 2.58–2.47 (m, 1 H), 2.26 (ddd, *J* = 4.0, 6.7, 12.6 Hz, 1 H), 2.12–2.05 (m, 1 H), 1.96 (d, *J* = 11.8 Hz, 1 H), 1.93 - 1.84 (m, 1 H), 1.71–1.55 (m, 3 H), 1.50–1.43 (m, 2 H), 1.41 (br. s., 1 H), 1.38v 1.26 (m, 2 H), 0.86 (s, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); **^{13}C NMR (CDCl$_3$, 125 MHz)** δ 135.9, 135.5, 127.5, 121.1, 119.3, 118.1, 110.6, 108.1, 65.4, 60.9, 53.4, 42.2, 36.3, 31.5, 30.8, 29.8, 27.3, 21.8, 21.3, 19.2, 15.8; **HRMS (ESI) *m/z*** $[M+H]^+$ calcd for $C_{21}H_{29}N_2$ 309.2362, found 309.2369; **IR (CHCl$_3$)** ν_{max} 3074, 2955, 1452, 1128 cm^{-1}.

(4*S*,4a*R*,13b*R*,14a*S*)-11-Methoxy-4-methyl-3,4,4a,5,7,8,13,13b,14,14a-decahydro indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (18). Mp 139–142 °C; **^{1}H NMR (CDCl$_3$,**

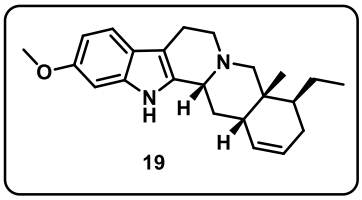


18

400 MHz) δ 7.72 (br. s., 1 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 6.84 (s, 1 H), 6.80–6.74 (m, 1 H), 5.66–5.57 (m, 1 H), 5.55–5.48 (m, 1 H), 3.83 (s, 3 H), 3.29 (d, *J* = 11.0 Hz, 1 H), 3.15–3.06 (m, 1 H), 3.05–2.96 (m, 1 H), 2.86–2.80

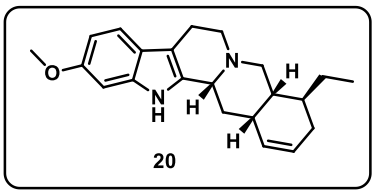
(m, 1 H), 2.73–2.60 (m, 2 H), 2.42–2.38 (m, 1 H), 2.16 (d, *J* = 12.2 Hz, 1 H), 2.09 (br. s., 1 H), 1.93 (br. s., 1 H), 1.80 (d, *J* = 11.0 Hz, 2 H), 1.46–1.39 (m, 1 H), 1.29–1.21 (m, 1 H), 0.92 (d, *J* = 6.7 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 156.0, 136.7, 133.7, 129.2, 125.8, 122.0, 118.6, 108.7, 107.9, 95.0, 60.5, 59.6, 55.7, 53.3, 42.1, 35.9, 34.6, 33.9, 28.9, 21.8, 14.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{21}H_{27}N_2O$ 323.2023, found 323.2015; **IR ($CHCl_3$)** ν_{max} 3013, 2905, 1629, 1154 cm^{-1}.

(4*S*,4a*R*,13b*R*,14a*S*)-4-Ethyl-11-methoxy-4a-methyl-3,4,4a,5,7,8,13,13b,14,14a-decahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (19). Mp 128–131 °C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 7.64 (br. s., 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 6.82 (d, *J* = 2.3 Hz, 1 H), 6.76 (dd, *J* = 2.1, 8.6 Hz, 1 H), 5.66–5.60 (m, 2 H), 3.84 (s, 3 H), 3.16 (d, *J* = 11.4 Hz, 1 H), 3.06 (d, *J* = 12.2 Hz, 1 H), 2.98–2.88 (m, 2 H), 2.68–2.62 (m, 1 H), 2.55–2.47 (m, 1 H), 2.20 (dd, *J* = 4.2, 16.4 Hz, 1 H), 2.11–2.05 (m, 1 H), 2.04–1.99 (m, 2 H), 1.85 (dd, *J* = 4.0, 12.0 Hz, 1 H), 1.66–1.61 (m, 2 H), 1.57 (d, *J* = 12.6 Hz, 1 H), 1.51–1.46 (m, 1 H), 0.91–0.89 (t, *J* = 7.3 Hz, 3 H), 0.79 (s, 3 H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 155.9, 136.7, 134.1, 129.2, 126.5, 122.0, 118.5, 108.6, 108.1, 95.1, 64.4, 60.6, 55.8, 53.4, 44.0, 35.4, 35.0, 33.8, 28.7, 21.9, 21.7, 19.3, 12.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{23}H_{31}N_2O$ 351.2438, found 351.2435; **IR ($CHCl_3$)** ν_{max} 2953, 2923, 1462, 1153 cm^{-1}.



19

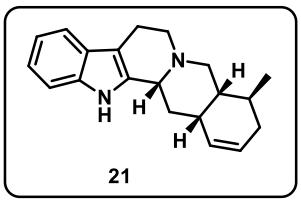
(4*S*,4a*R*,13b*R*,14a*S*)-4-Ethyl-11-methoxy-3,4,4a,5,7,8,13,13b,14,14a-decahydro indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (20). Mp 148–151 °C; **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.82 (br. s., 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 6.80 (d, *J* = 1.9 Hz, 1 H), 6.79–6.75 (m, 1 H), 5.60 (td, *J* = 2.4, 9.8 Hz, 1 H), 5.51 (d, *J* = 10.0 Hz, 1 H), 3.82 (s, 3 H), 3.25 (d, *J* = 11.0 Hz, 1 H), 3.09 (dd, *J* = 5.7, 10.4 Hz, 1 H), 3.03–2.94 (m, 1 H), 2.86 (dd, *J* = 3.2, 10.8 Hz, 1 H), 2.72–2.61 (m, 2 H), 2.47 (t, *J* = 11.1 Hz, 1 H), 2.24–2.17 (m, 1 H), 2.12–2.00 (m, 3 H), 1.88–1.80 (m, 1 H), 1.64–1.58 (m, 1 H), 1.47–1.40 (m, 1 H), 1.37 (d, *J* = 11.6 Hz, 1 H), 1.24 (ddd, *J* = 7.1, 10.9, 13.4 Hz, 1 H), 0.96 (t, *J* = 7.3 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 155.9, 136.7, 133.7, 129.7, 126.0, 122.0, 118.6, 108.6, 107.9, 95.1, 60.5, 59.5, 55.7, 53.2, 42.8, 37.0, 36.0, 35.3, 29.5, 21.8, 20.2, 12.8; **HRMS (ESI)** ***m/z***



20

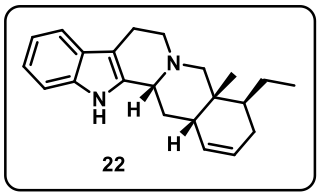
$[M+H]^+$ calcd for $C_{22}H_{29}N_2O$ 337.2258, found 337.2254; **IR ($CHCl_3$)** ν_{max} 3012, 2924, 1499, 1198 cm^{-1}.

(4*S*,4a*R*,13b*R*,14a*S*)-4-Methyl-3,4,4a,5,7,8,13,13b,1414a-decahydroindolo[2',3':

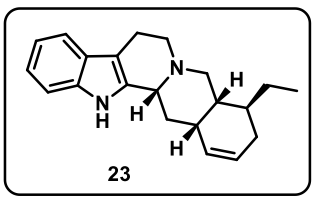


3,4]pyrido[1,2-*b*]isoquinoline (21). Mp 133–136 °C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 7.79 (br. s., 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.17–7.08 (m, 2 H), 5.63 (ddd, *J* = 2.3, 4.8, 7.4 Hz, 1 H), 5.53 (d, *J* = 9.9 Hz, 1 H), 3.34 (d, *J* = 10.3 Hz, 1 H), 3.12 (dd, *J* = 5.9, 11.3 Hz, 1 H), 3.06–2.99 (m, 1 H), 2.86 (dd, *J* = 3.2, 10.9 Hz, 1 H), 2.74 (dd, *J* = 4.0, 15.1 Hz, 1 H), 2.67 (dt, *J* = 4.2, 11.3 Hz, 1 H), 2.45–2.37 (m, 2 H), 2.19 (td, *J* = 2.9, 12.1 Hz, 1 H), 2.11 (t, *J* = 11.3 Hz, 1 H), 1.98–1.93 (m, 1 H), 1.83–1.78 (m, 2 H), 1.45 (d, *J* = 11.8 Hz, 1 H), 0.94 (d, *J* = 6.9 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 135.9, 134.9, 129.2, 127.5, 125.9, 121.3, 119.4, 118.1, 110.7, 108.2, 60.5, 59.7, 53.3, 42.2, 35.9, 34.7, 34.0, 28.9, 21.8, 14.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{20}H_{25}N_2$ 293.1952, found 293.1962; **IR ($CHCl_3$)** ν_{max} 3013, 2908, 1554, 1377 cm^{-1}.

(4*S*,4a*R*,13b*R*,14a*S*)-4-Ethyl-4a-methyl-3,4,4a,5,7,8,13,13b,14,14a-decahydro



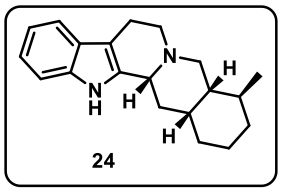
indolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (22). Mp 135–138 °C; **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.71 (br. s., 1 H), 7.48 (d, *J* = 7.3 Hz, 1 H), 7.30 (d, *J* = 7.3 Hz, 1 H), 7.16–7.07 (m, 2 H), 5.64 (br. s., 2 H), 3.20 (d, *J* = 11.6 Hz, 1 H), 3.08 (d, *J* = 11.6 Hz, 1 H), 3.02–2.93 (m, 2 H), 2.69 (d, *J* = 14.6 Hz, 1 H), 2.57–2.49 (m, 1 H), 2.21 (dd, *J* = 4.3, 16.5 Hz, 1 H), 2.10–2.02 (m, 3 H), 1.90–1.84 (m, 1 H), 1.69–1.57 (m, 4 H), 0.92–0.87 (t, *J* = 7.3 Hz, 3 H), 0.80 (s, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 136.0, 135.3, 129.2, 127.4, 126.5, 121.2, 119.3, 118.0, 110.7, 108.4, 64.4, 60.5, 53.4, 44.0, 35.4, 35.0, 33.8, 28.7, 21.9, 21.7, 19.3, 12.2; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{29}N_2$ 321.2347, found 321.2334; **IR ($CHCl_3$)** ν_{max} 3015, 2954, 1465, 1318 cm^{-1}.



(4*S*,4a*R*,13b*R*,14a*S*)-4-Ethyl-3,4,4a,5,7,8,13,13b,14,14a-decahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (23). Mp 140–143 °C; **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.78 (br. s., 1 H), 7.48 (d, *J* = 7.5 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 1

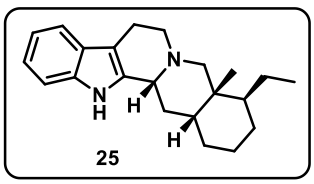
H), 7.19–7.06 (m, 2 H), 5.61 (td, *J* = 2.2, 9.9 Hz, 1 H), 5.53 (d, *J* = 10.3 Hz, 1 H), 3.35 (d, *J* = 11.1 Hz, 1 H), 3.14 (dd, *J* = 5.8, 10.9 Hz, 1 H), 3.07–2.97 (m, 1 H), 2.89 (dd, *J* = 3.3, 10.9 Hz, 1 H), 2.78–2.71 (m, 1 H), 2.70–2.63 (m, 1 H), 2.50 (t, *J* = 11.1 Hz, 1 H), 2.22–2.14 (m, 2 H), 2.08 (d, *J* = 3.4 Hz, 1 H), 2.06–2.02 (m, 1 H), 1.90 – 1.84 (m, 1 H), 1.62 (dd, *J* = 3.0, 8.4 Hz, 1 H), 1.43 (d, *J* = 11.6 Hz, 1 H), 1.27 (br. s., 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 135.9, 134.8, 129.6, 127.4, 126.1, 121.3, 119.4, 118.1, 110.7, 108.2, 60.4, 59.4, 53.2, 42.7, 37.0, 36.0, 35.3, 29.5, 21.7, 20.1, 12.8; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{21}H_{27}N_2$ 307.2156, found 307.2169; **IR ($CHCl_3$)** ν_{max} 3014, 2935, 1564, 1456 cm^{-1}.

(4*S*,4a*R*,13b*R*,14a*R*)-4-Methyl-1,2,3,4,4a,5,7,8,13,13b,14,14a-dodecahydroindolo [2',3':3,4]pyrido[1,2-b]isoquinoline (24). Mp 118–121 °C;



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (br. s., 1 H), 7.50–7.46 (m, 1 H), 7.30 (dd, *J* = 0.9, 7.2 Hz, 1 H), 7.16–7.06 (m, 2 H), 3.24 (dd, *J* = 1.9, 11.5 Hz, 1 H), 3.13–3.08 (m, 1 H), 3.07–2.98 (m, 1 H), 2.80 (dd, *J* = 3.6, 11.1 Hz, 1 H), 2.76–2.70 (m, 1 H), 2.62 (dt, *J* = 4.4, 11.0 Hz, 1 H), 2.32 (t, *J* = 11.1 Hz, 1 H), 2.05–2.00 (m, 1 H), 1.91 (td, *J* = 3.6, 7.1 Hz, 1 H), 1.87 (br. s., 1 H), 1.74–1.69 (m, 1 H), 1.65 (td, *J* = 3.8, 11.2 Hz, 1 H), 1.58–1.56 (m, 2 H), 1.54–1.49 (m, 2 H), 1.39–1.32 (m, 1 H), 1.28–1.25 (m, 1 H), 0.94 (d, *J* = 7.3 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 135.9, 135.0, 127.5, 121.2, 119.3, 118.1, 110.7, 108.1, 60.2, 60.0, 53.3, 44.3, 37.4, 34.1, 33.7, 33.5, 30.6, 21.7, 20.4, 13.4; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{20}H_{27}N_2$ 295.2136, found 295.2145; **IR ($CHCl_3$)** ν_{max} 3015, 2954, 1552, 1374 cm^{-1}.

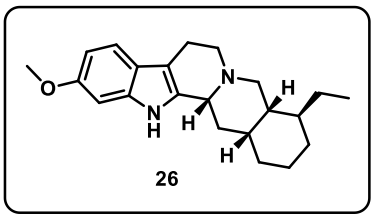
(4*S*,4a*R*,13b*R*,14a*R*)-4-Ethyl-4a-methyl-1,2,3,4,4a,5,7,8,13,13b,14,14a-dodeca hydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (25). Mp 131–134 °C;



^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (br. s., 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.16–7.08 (m, 2 H), 3.21 (d, *J* = 11.4 Hz, 1 H), 3.02 (d, *J* = 11.8 Hz, 1 H), 3.00–2.94 (m, 2 H), 2.74–2.67 (m, 1 H), 2.57–2.49 (m, 1 H), 2.09 (q, *J* = 12.3 Hz, 1 H), 2.04–1.96 (m, 1 H), 1.94 (d, *J* = 11.8 Hz, 1 H), 1.92–1.85 (m, 1 H), 1.71 (d, *J* = 12.2 Hz, 1 H), 1.66–1.53 (m, 4 H), 1.53–1.49 (m, 1 H), 1.49–1.42 (m, 1 H), 1.38 (d, *J* = 13.4 Hz, 1 H), 1.09 (dq, *J* = 4.8, 13.0 Hz, 1 H), 0.91–0.87 (t, *J* = 7.4 Hz, 3 H), 0.85 (s, 3 H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 136.0, 135.7, 127.5, 121.2,

119.3, 118.1, 110.7, 108.3, 65.3, 60.8, 53.3, 42.6, 36.9, 36.7, 31.7, 27.2, 26.8, 22.5, 21.9, 21.2, 19.9, 12.8; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{31}N_2$ 323.2432, found 323.2437; **IR ($CHCl_3$)** ν_{max} 2923, 2797, 1451, 1375 cm^{-1}.

(4*S*,4a*R*,13b*R*,14a*R*)-4-Ethyl-11-methoxy-1,2,3,4,4a,5,7,8,13,13b,14,14a-dodeca hydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (26). Mp 149–152 °C; **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.63 (br. s., 1 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 2.0 Hz, 1 H), 6.76 (dd, *J* = 2.3, 8.6 Hz, 1 H), 3.83 (s, 3 H), 3.18 (d, *J* = 11.5 Hz, 1 H), 3.12–3.04 (m, 1 H), 3.03–2.94 (m, 1 H), 2.78 (dd, *J* = 3.5, 11.0 Hz, 1 H), 2.68 (d, *J* = 15.3 Hz, 1 H), 2.63–2.55 (m, 1 H), 2.38 (t, *J* = 11.1 Hz, 1 H), 1.99 (td, *J* = 3.2, 12.4 Hz, 1 H), 1.82 (d, *J* = 14.0 Hz, 1 H), 1.74–1.68 (m, 3 H), 1.60–1.56 (m, 1 H), 1.48 (dd, *J* = 4.0, 7.4 Hz, 2 H), 1.40 (d, *J* = 7.4 Hz, 1 H), 1.38–1.33 (m, 2 H), 1.31–1.26 (m, 2 H), 0.90 (t, *J* = 7.4 Hz, 3 H); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 155.9, 136.7, 133.8, 122.0, 118.6, 108.6, 107.9, 95.0, 60.2, 59.8, 55.7, 53.4, 45.2, 38.2, 37.7, 34.8, 33.6, 28.7, 21.8, 20.2, 18.9, 12.7; **HRMS (ESI)** ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{31}N_2O$ 339.2478, found 339.2471; **IR ($CHCl_3$)** ν_{max} 2921, 1712, 1628, 1156 cm^{-1}.



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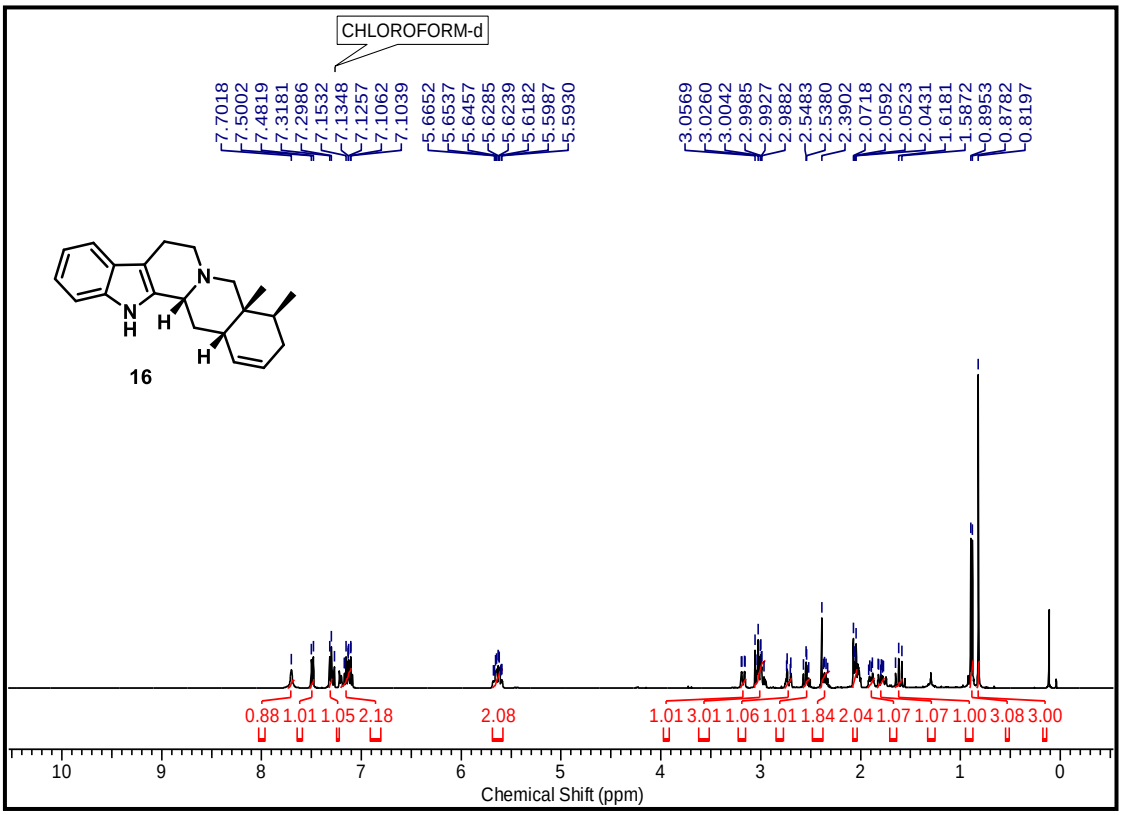
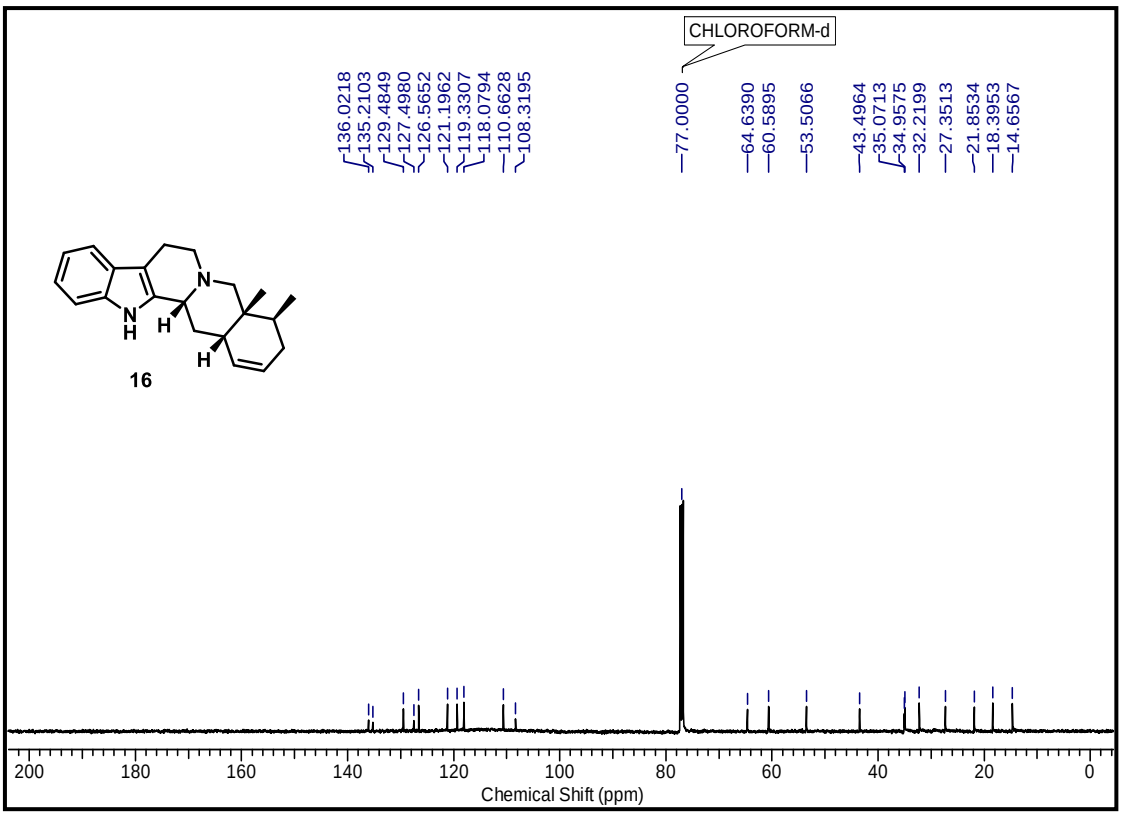
2C.6 Selected Spectra

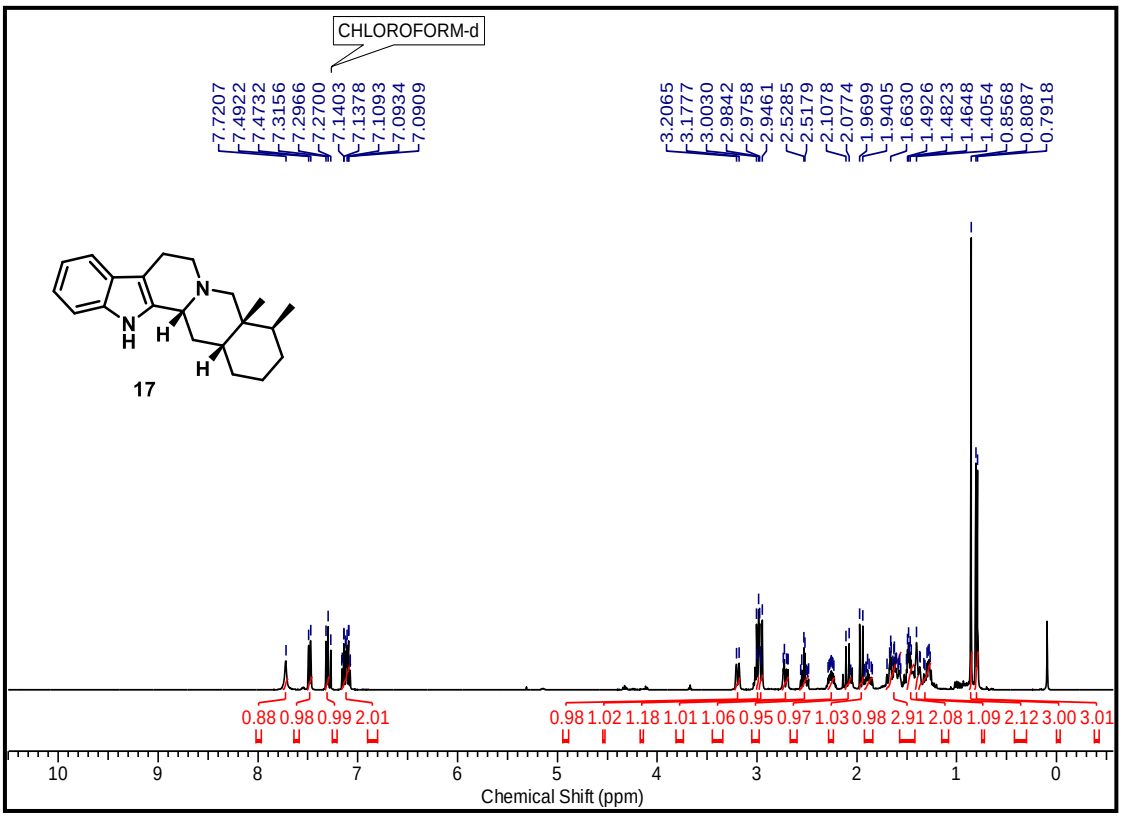
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 16



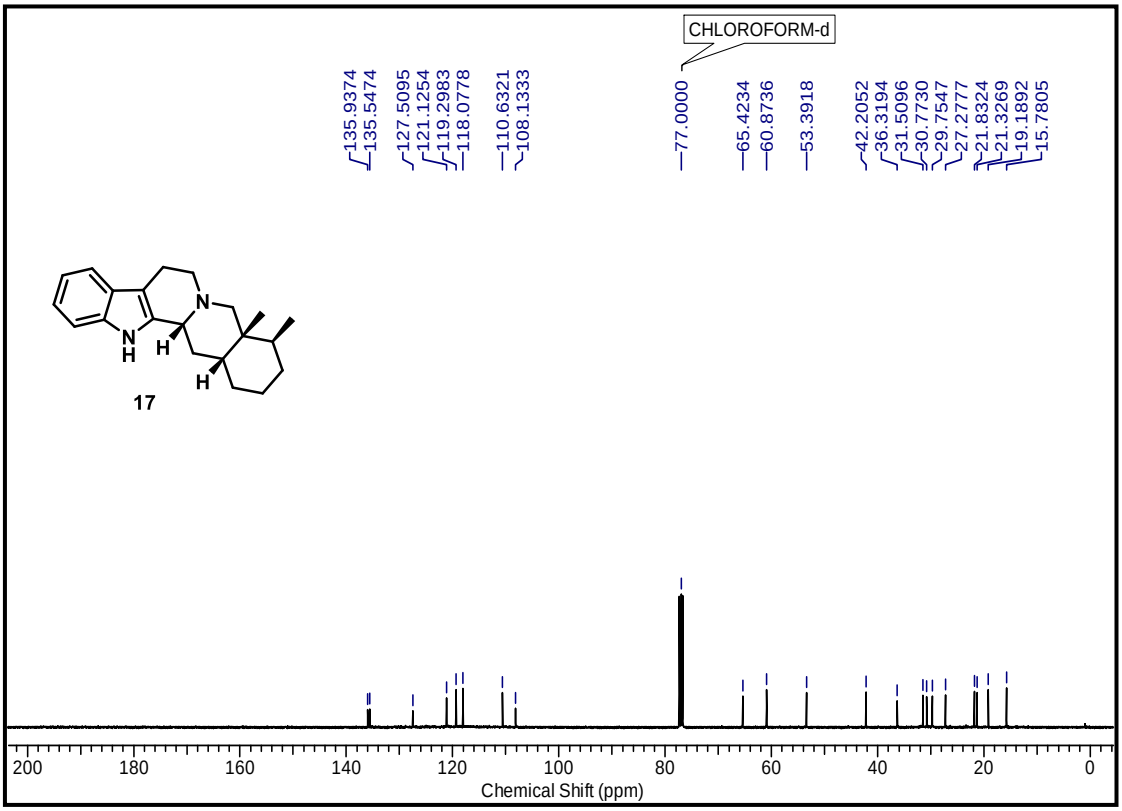
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 16



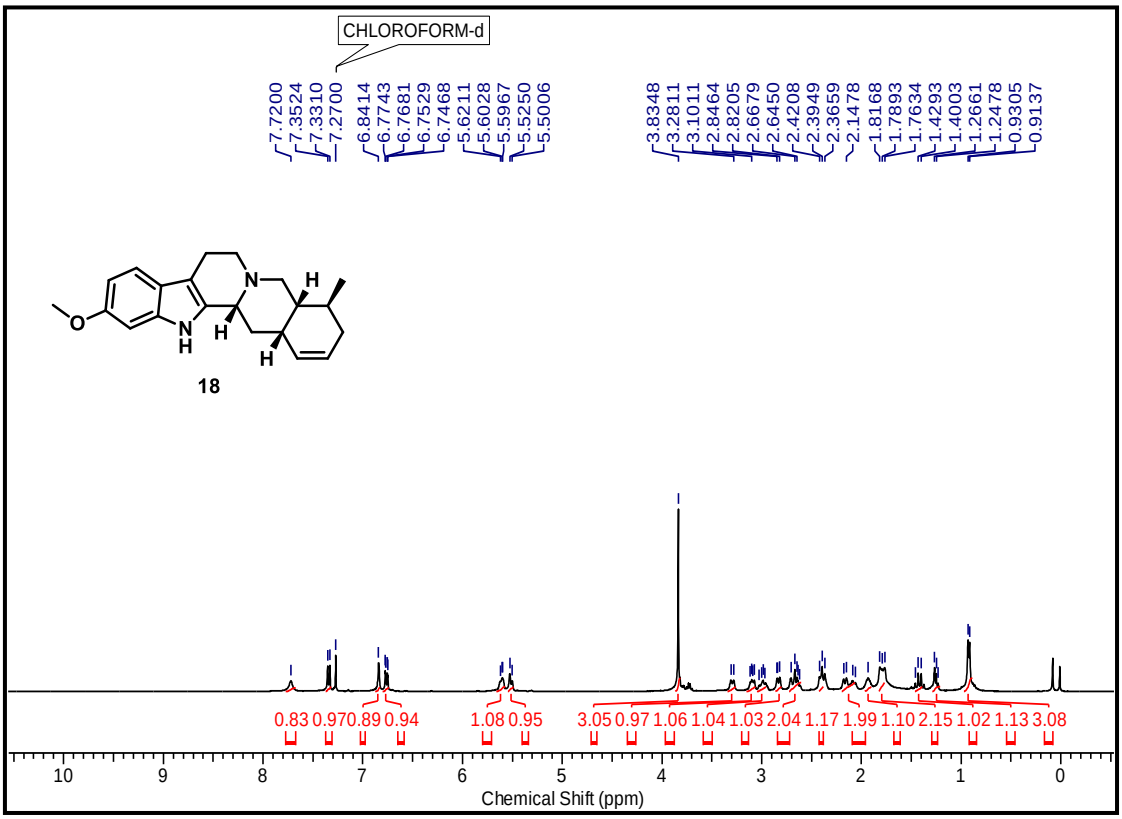
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 17



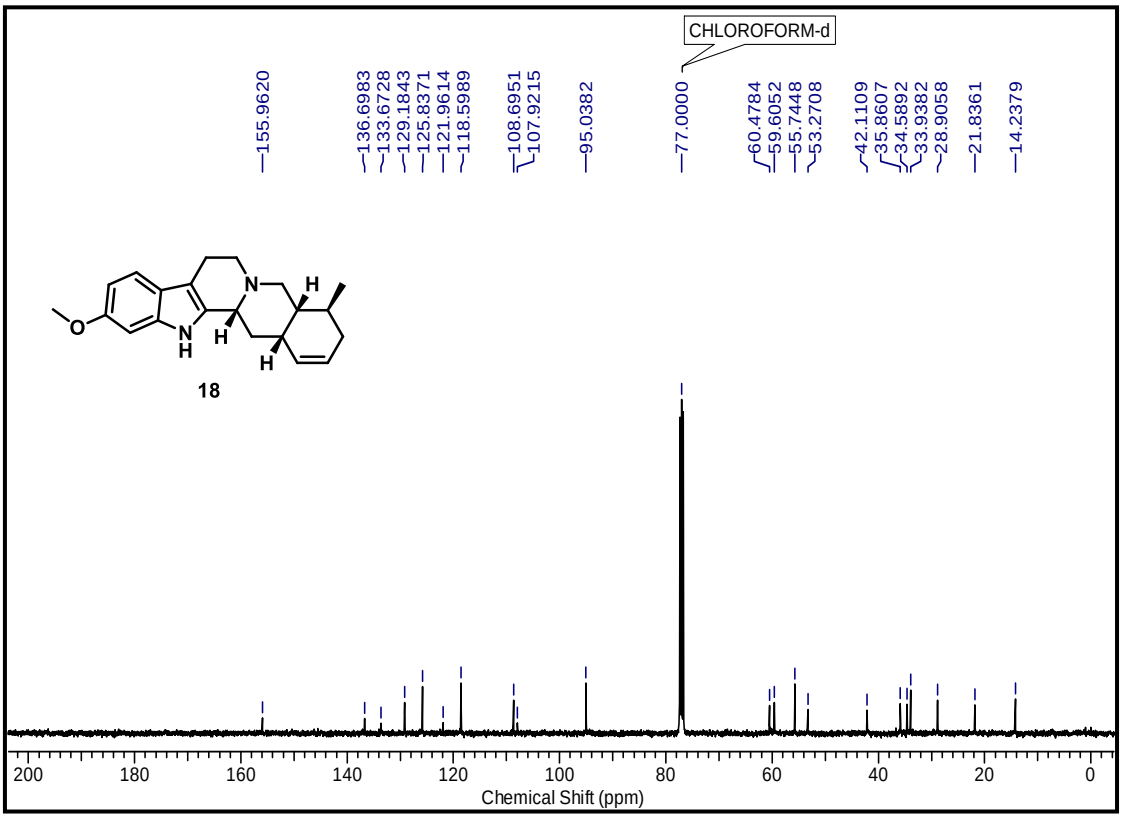
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 17



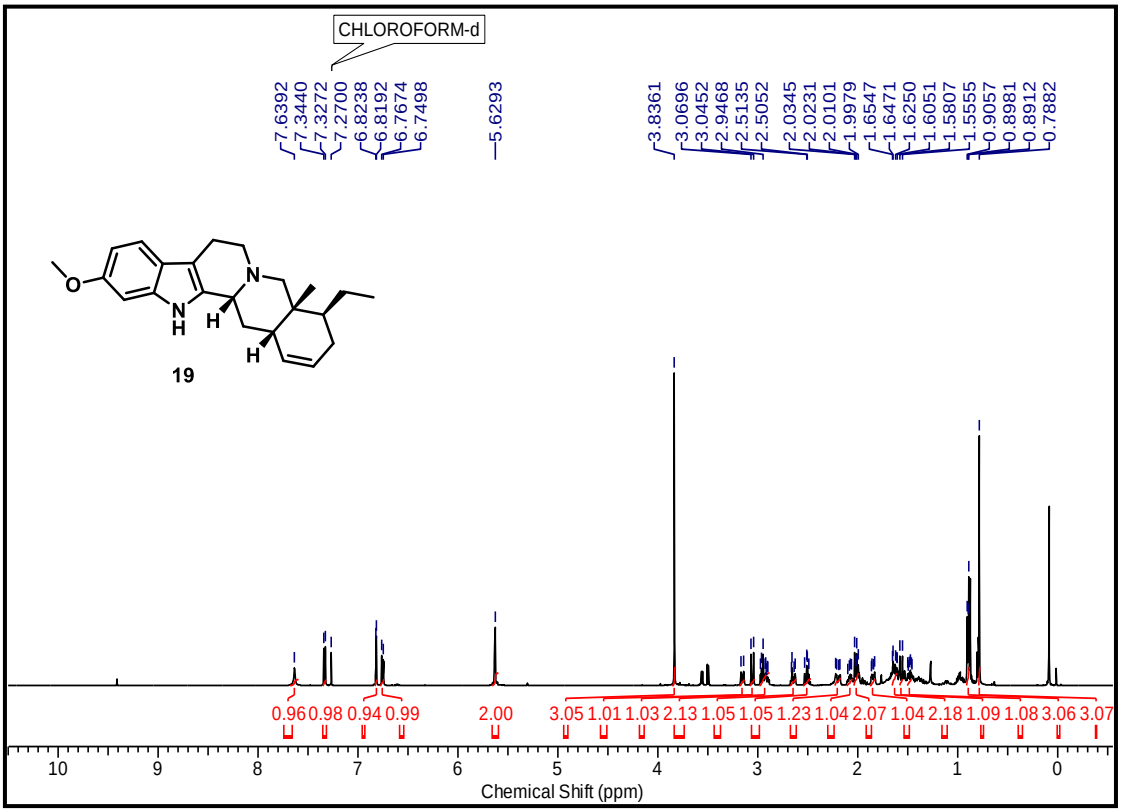
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 18



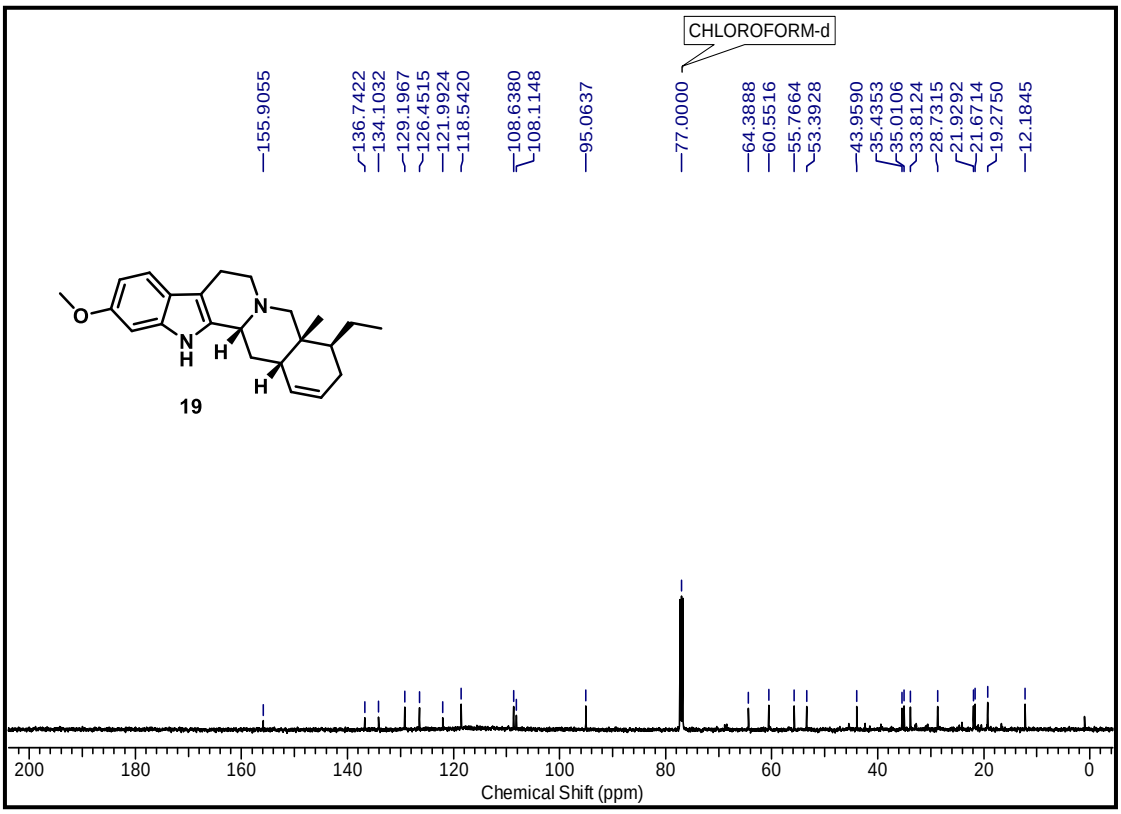
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 18



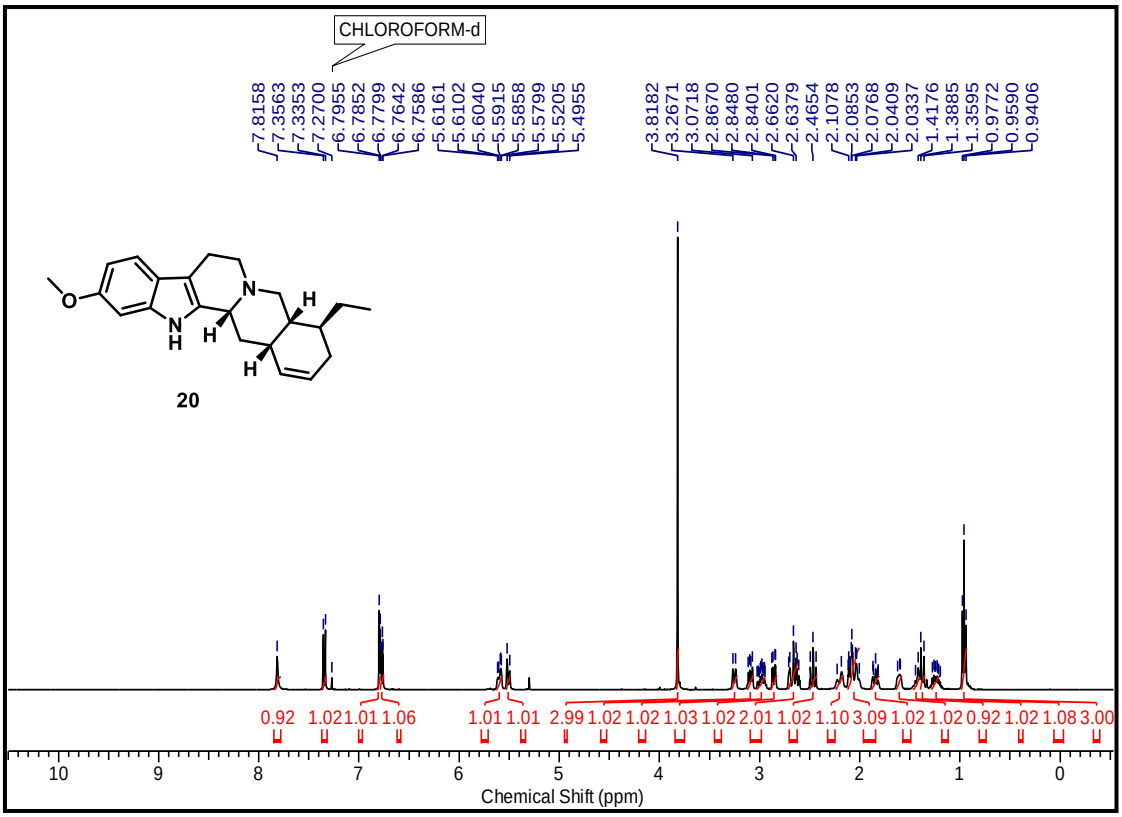
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 19



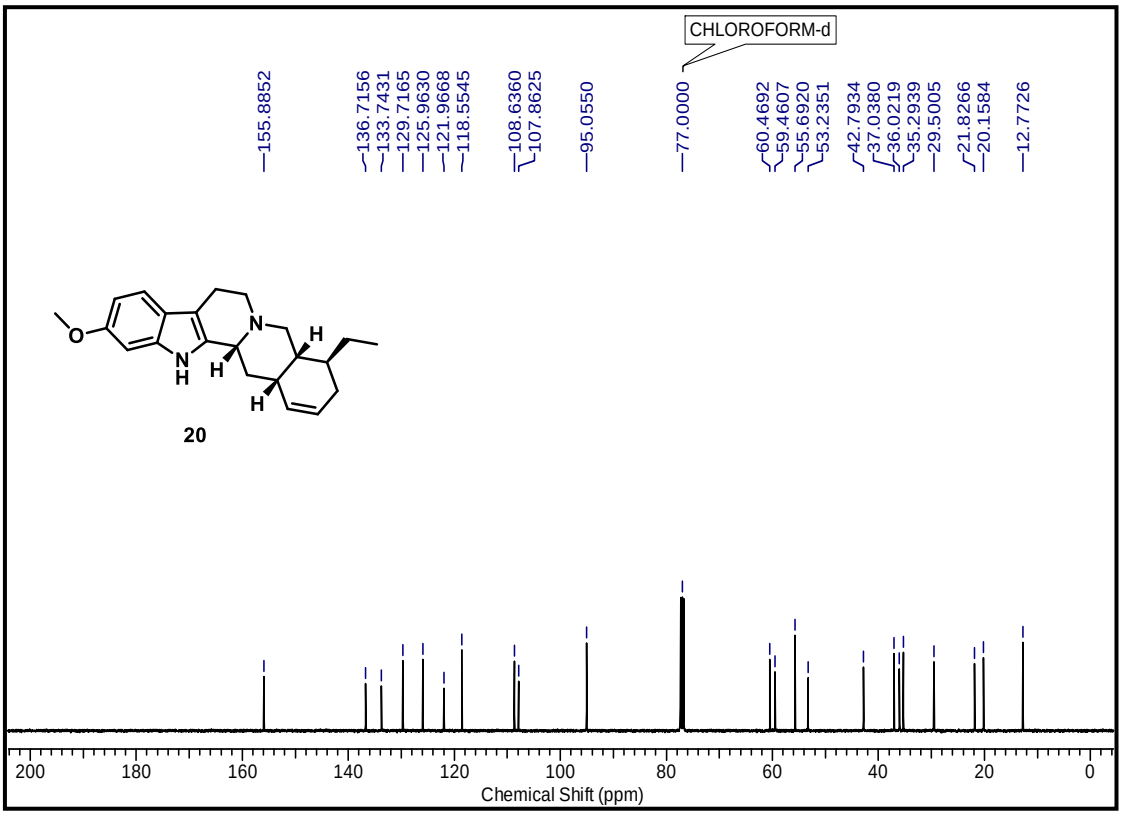
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 19



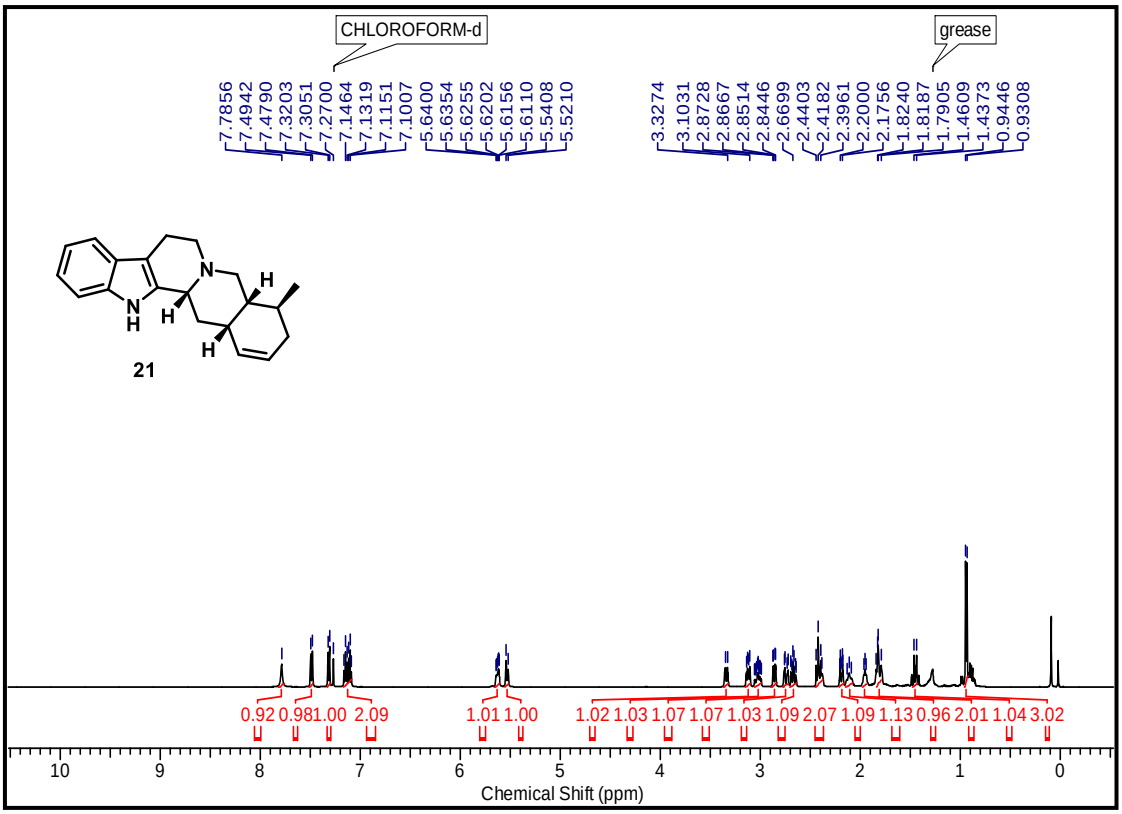
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 20



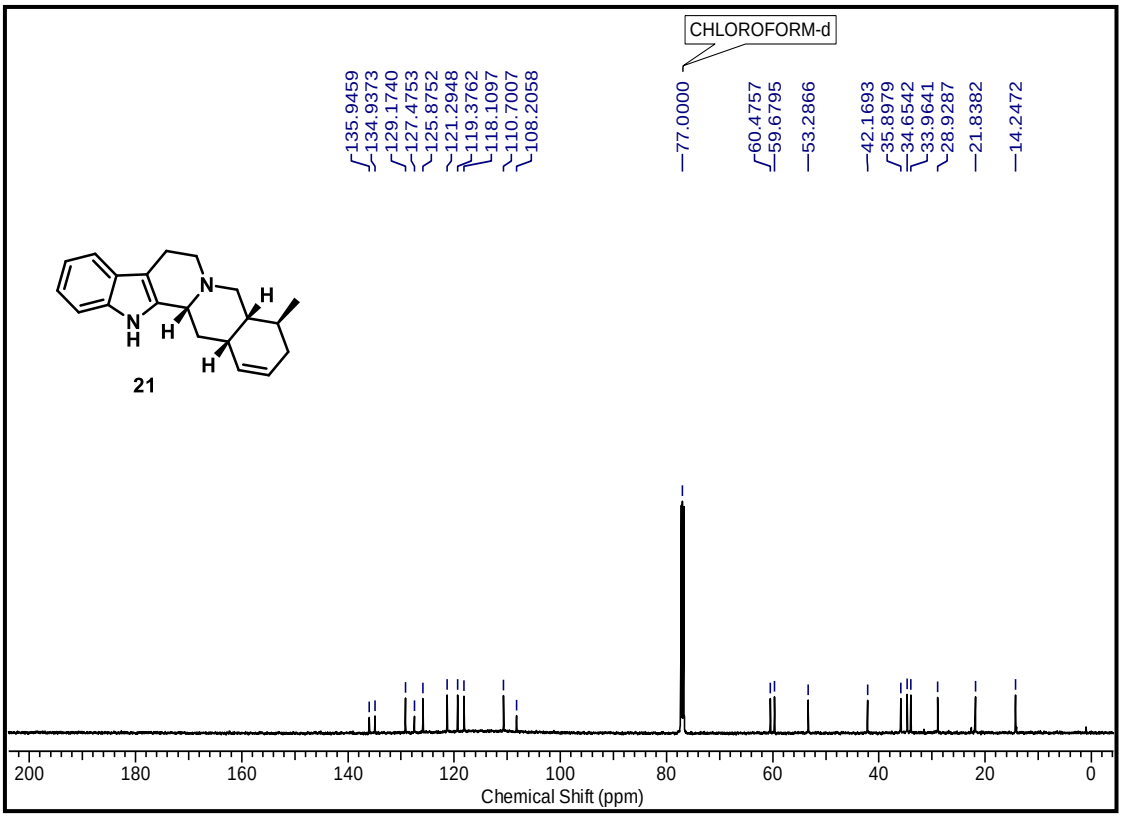
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 20



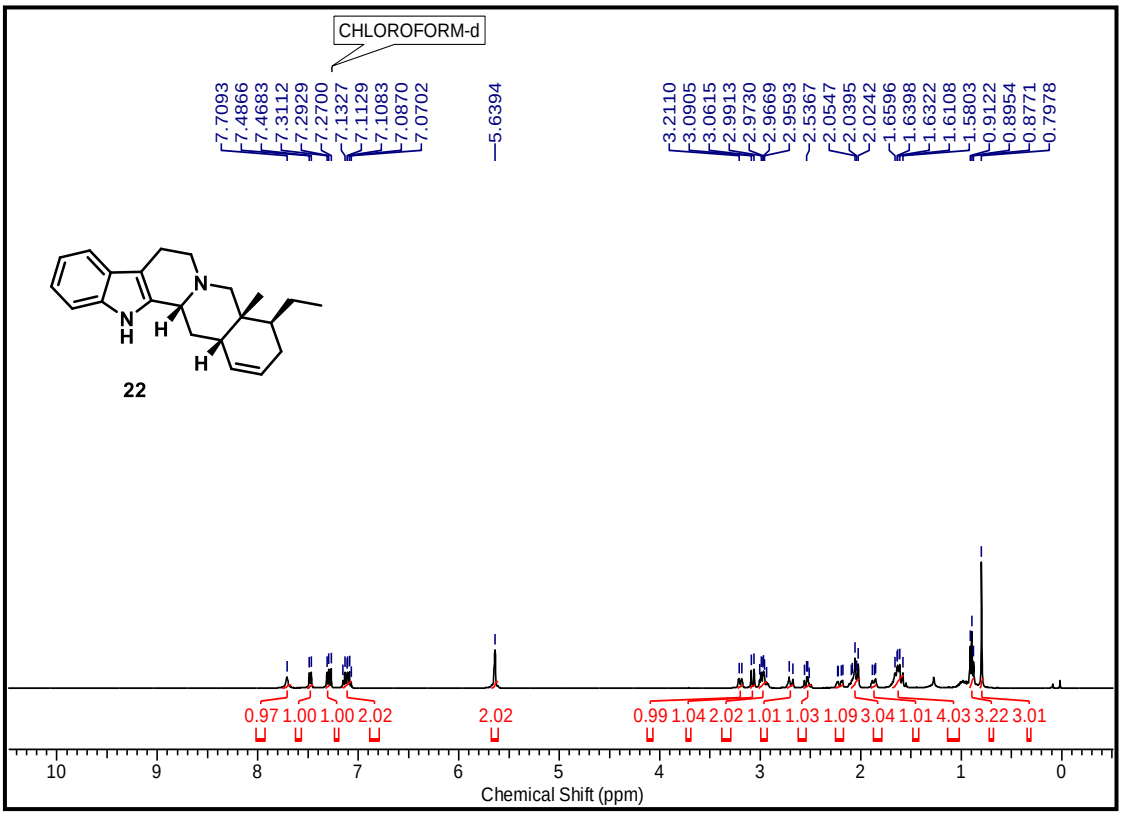
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 21



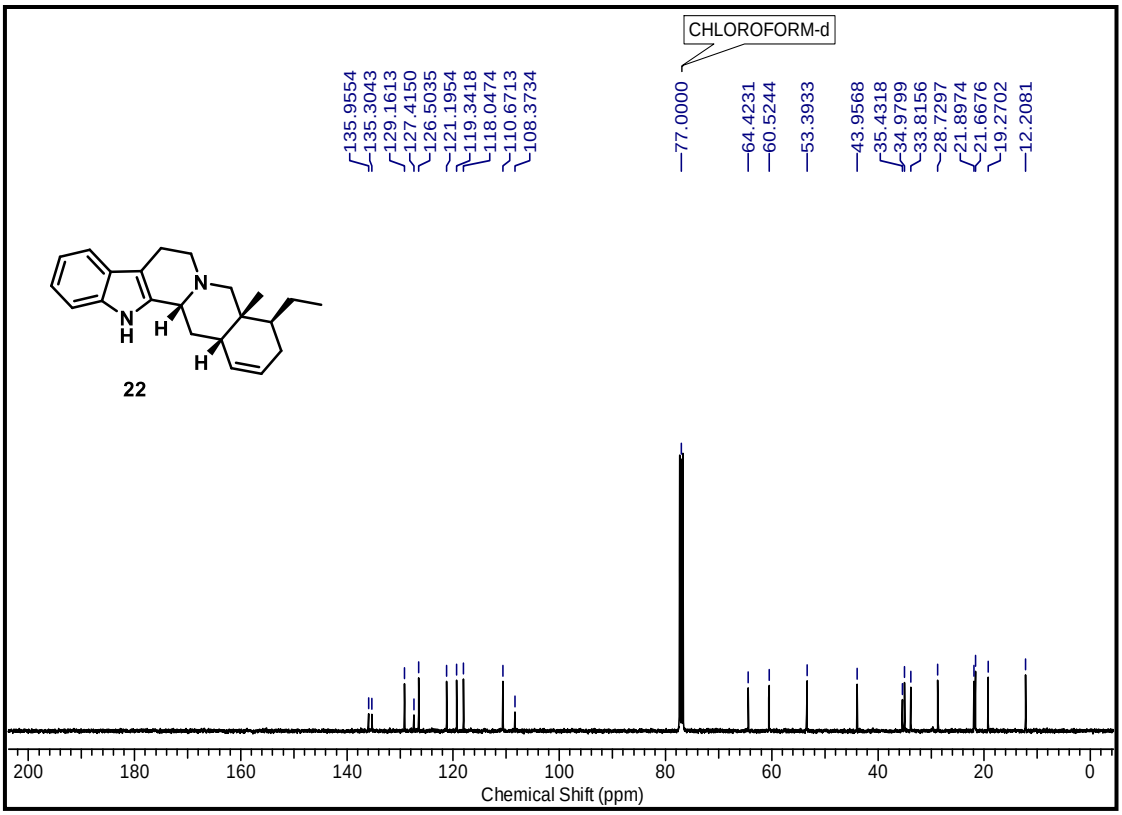
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 21



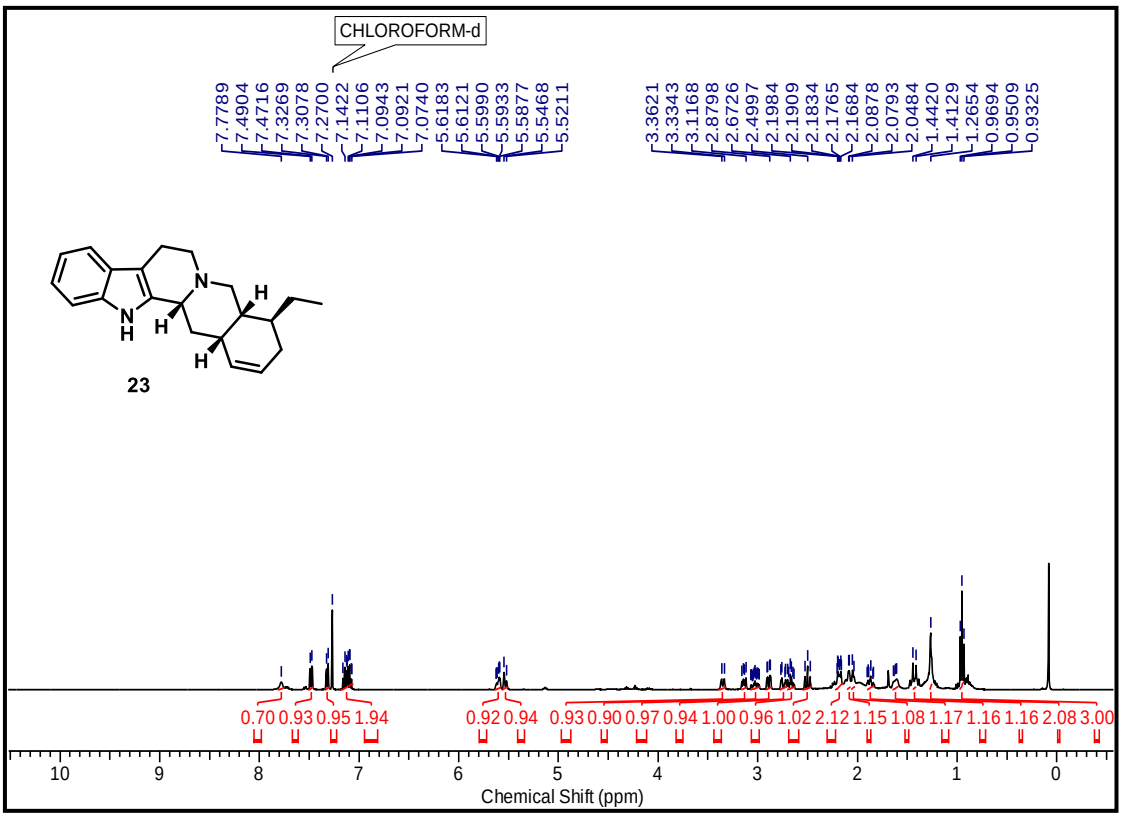
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 22



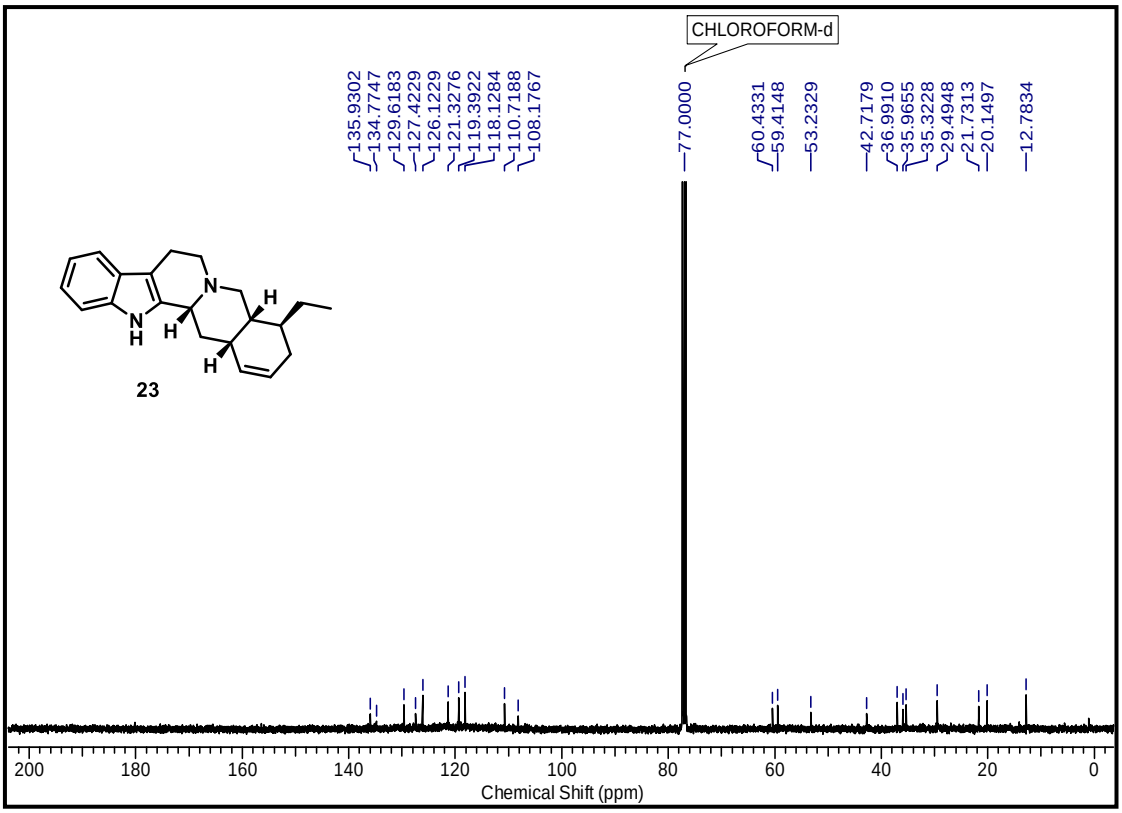
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 22



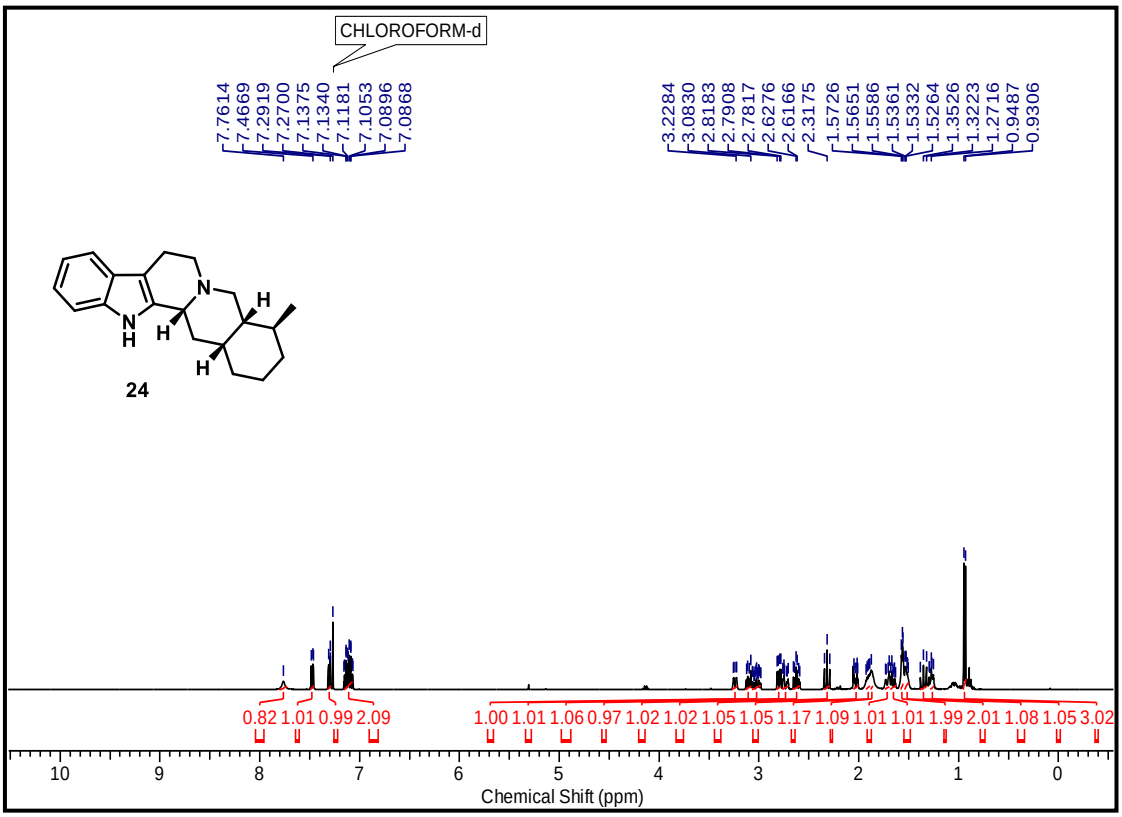
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 23



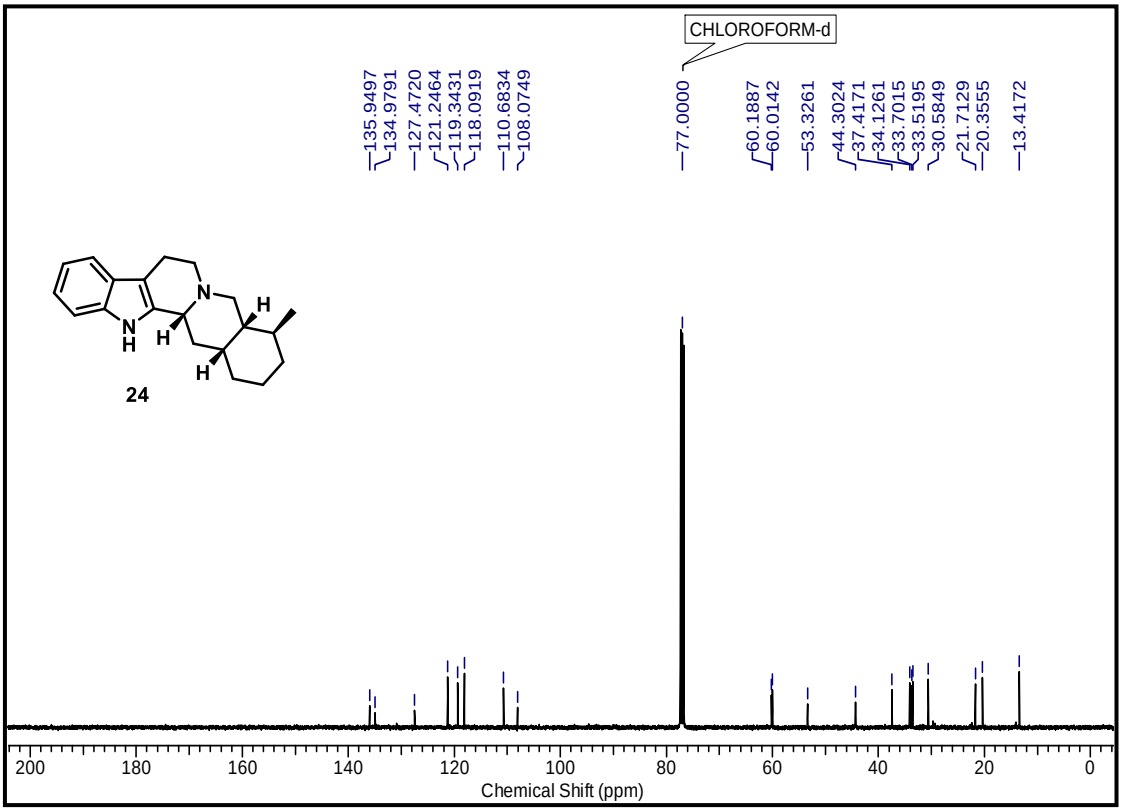
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 23



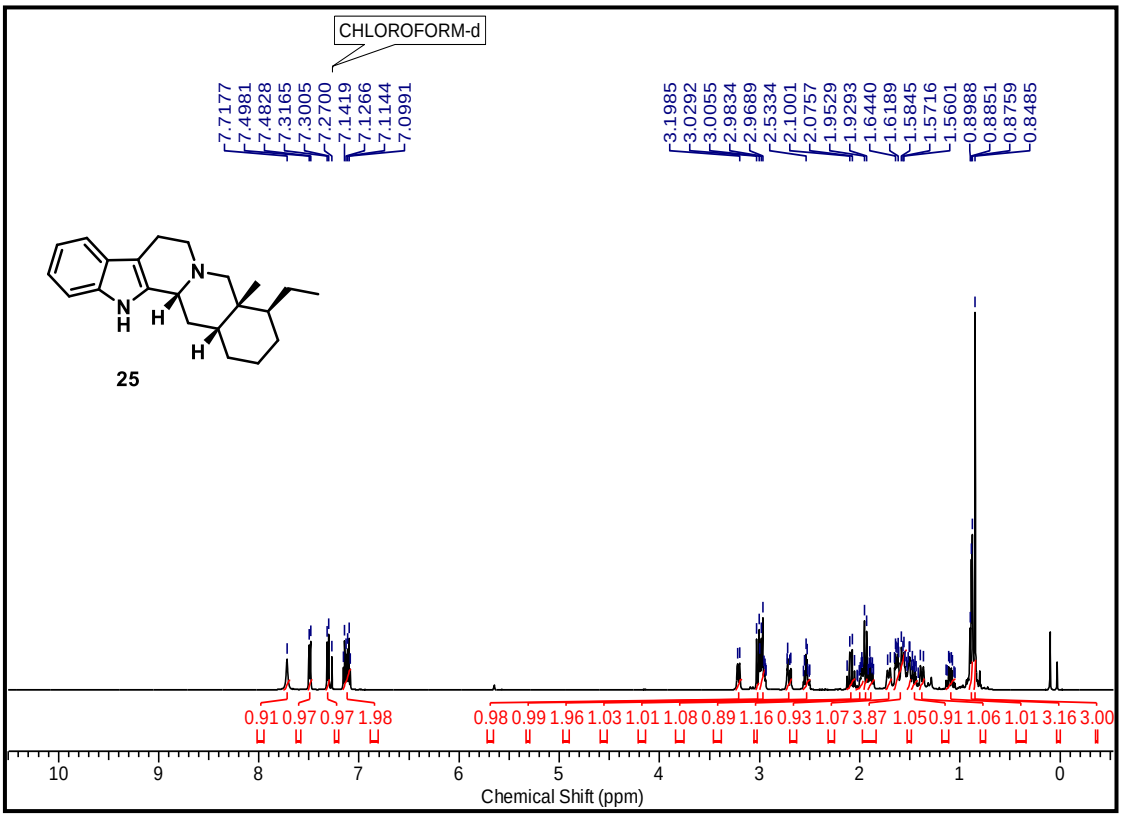
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 24



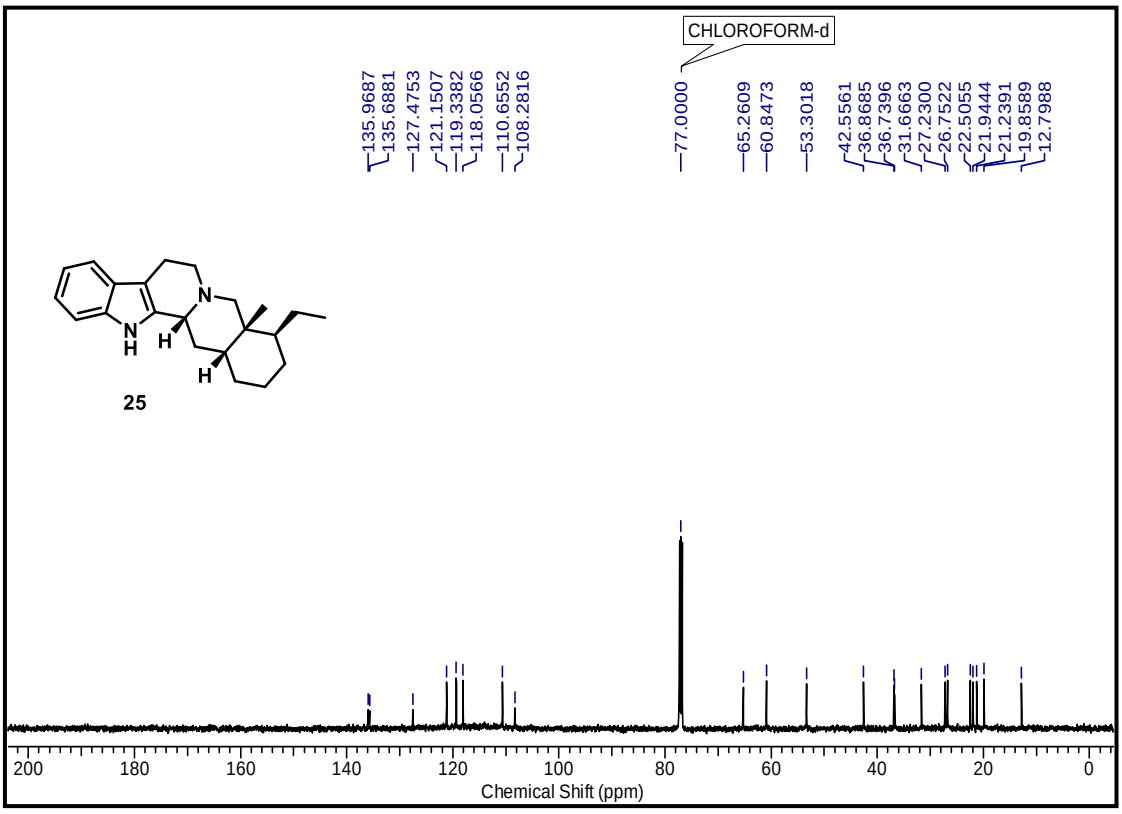
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 24



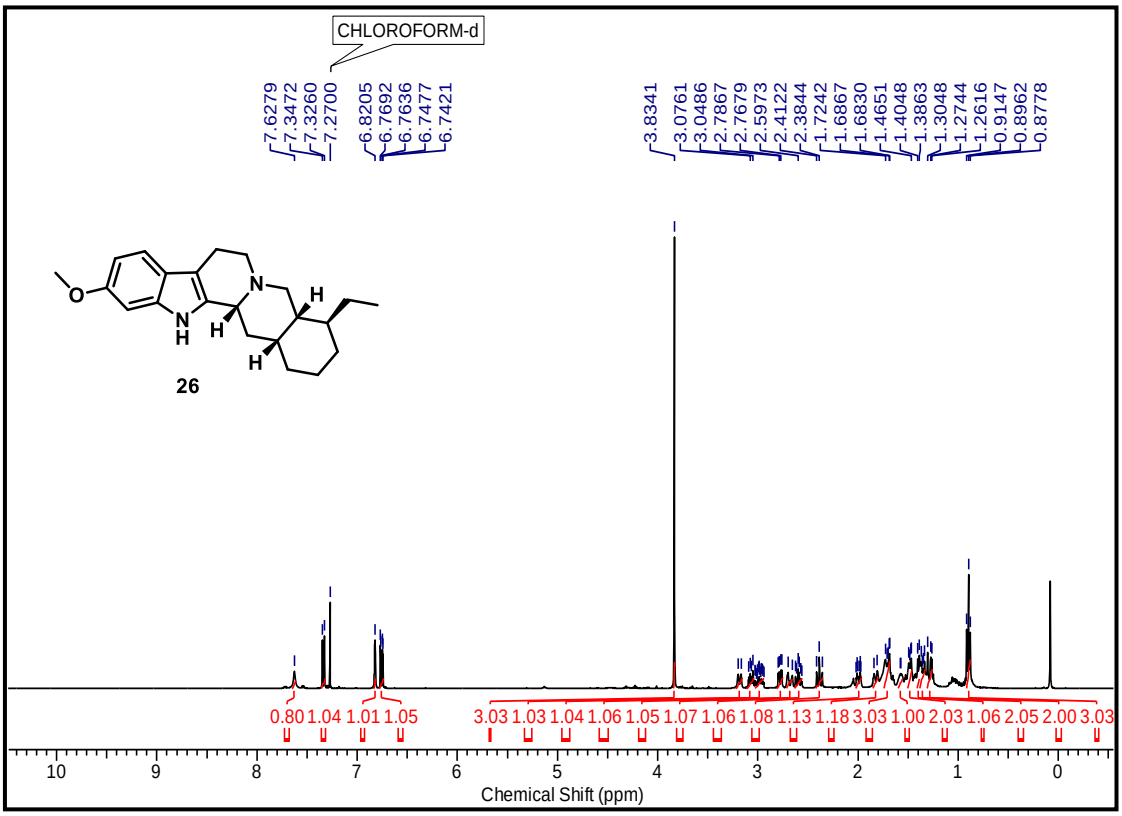
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 25



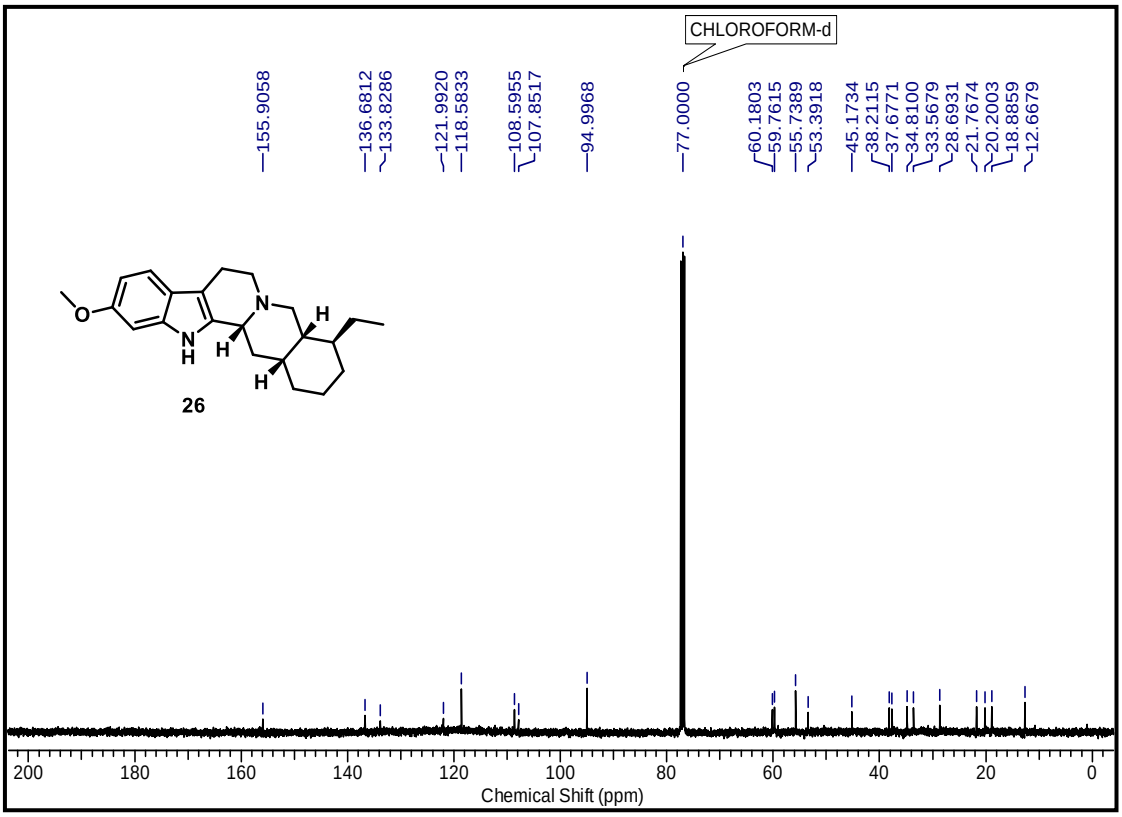
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 25



^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 26



^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 26



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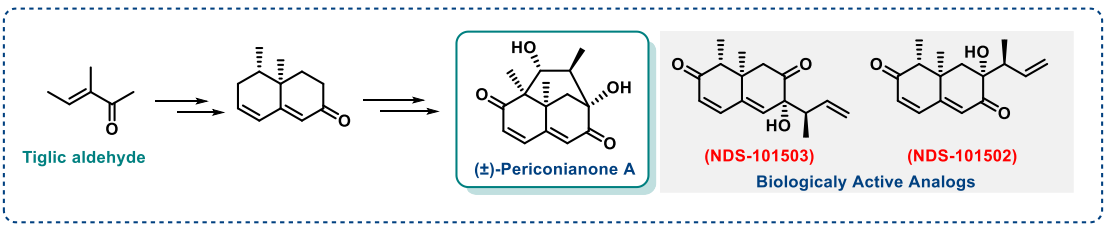
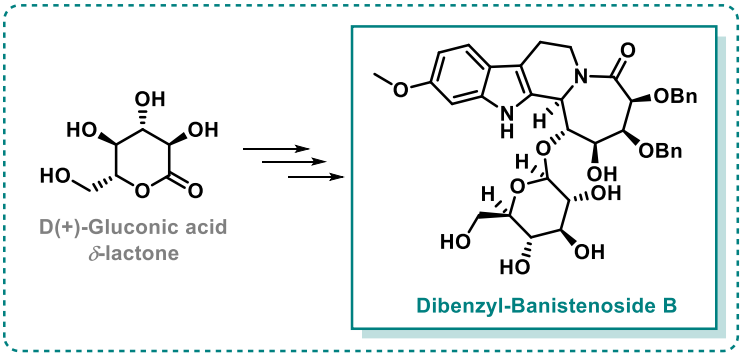
The terpenes are important class of natural products, which show their importance in the essential oils, drugs, perfumes, cosmetics, in food and drink products. Terpenes are important for plants in the pollinations and also protect the plant by repelling the predators due to the strong chemical reactions. It is a largest class of compounds which are not only useful for humans but also for the plants, animals, etc. Because of the presence of large number compounds terpenes are classified into different classes which we have been included in our first chapter in section A. We gave the brief introduction of different classes of terpenes based on the number of isoprene units in the natural products. Terpenes are useful for many drugs synthesis and few of them have been included in this chapter. Due to presence of antimicrobial and antioxidant effects the monoterpenes have been used in different culture for seasoning meals. As our compound periconianone A belongs to the sesquiterpene class, we have given the brief information about the same and also shown the biological path ways of different natural products of this class. Essential oils from the sesquiterpenes are useful for the pollination in the plants, they can also show different biological properties such as anti-malarial, prevention of neurodegeneration, antimigraine activity, analgesic and sedative activities and treatment of ailments.

We have accomplished synthesis of (±)-periconianone A by using the Diels-Alder/aldol chemistry developed for the construction of decalin skeleton in our lab. The stereochemistry of the natural product was confirmed by using X-ray crystallography. Along with the natural product we have synthesized two new biologically active compounds. The anti-inflammatory activity of these compounds is more compared to the (±)-periconianone A. In the synthetic process of this natural product, we developed a new mild strategy for the allylic oxidation of dienones using DBU/O_2.



In the second chapter we have explained the role of Pictet-Spengler reaction in the synthesis of different indole alkaloids. We also have explained the mechanistic aspects of the reaction along with the effect of acidic medium or presence of aromatic ring system on the yield or stereochemistry of the product. We also introduced the different

class of tetracyclic indole alkaloids with the different ring skeleton. While investigating the biologically active indole alkaloids we have notice that the banistenoside A and B are having the challenging structure and with virtuous biological values. We have achieved first total synthesis of (+)*-dibenzyl-banistenoside B using Pictet-Spengler reaction, lactamization, and glycation reaction. We have successfully maintained the all 10 stereocentres in the molecule and stereochemistry of most of the essential compound were confirmed by using X-ray crystallography. Along with dibenzylated natural product we have synthesized few close analogs for further SAR studies.*



We also have developed the new concise synthetic route for the construction of pentacyclic core of reserpine, which has been included in this chapter. By using this strategy, we have synthesized 11 analogs of reserpine and their relative stereochemistry was confirmed by using X-ray crystallographic data of few synthesized analogs. We also believe that the current protocol has a scale-up potential and will be useful for large-scale production of several rauwolfia alkaloid family natural products of commercial interest.

Overall, both terpenes and indole alkaloids studies will be of continuing interest to organic and medicinal chemists from their novel structural architectures and promising bioactivities point of view.

ABSTRACT

Name of the Student: Mr. Suhag Sanjay Patil
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Faculty of Study: Chemical Science
Year of Submission: 2022
AcSIR academic center/CSIR Lab:
CSIR-National Chemical Laboratory, Pune
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Name of the Co-Supervisor: Dr. D. S. Reddy

Title of the thesis: Total Synthesis of (±)-Periconianone A and (+)-Dibenzyl-Banistenoside B

The work included in this thesis is mainly based on the total synthesis of the natural products and development of useful synthetic methods. The terpenes are largest class of compounds which are not only useful for humans but also for the plants, animals, etc. Here in the first chapter, we have included the total synthesis of (±)-Periconianone A by using the Diels-Alder/aldol chemistry developed for the construction of decalin skeleton in our lab. We have also included biological activity of (±)-periconianone A and its two analogs were tested for their neuroanti-inflammatory activity using various assays and markers. During this project execution, we also discovered a mild method for allylic oxidation of dienones using DBU/O_2.

The second chapter includes the total synthesis of indole alkaloidal natural product Banistenoside B and the development of concise synthetic route for the synthesis of pentacyclic core of reserpine. We also have explained the mechanistic aspects of the reaction along with the effect of acidic medium or presence of aromatic ring system on the yield or stereochemistry of the product. We have achieved first total synthesis of (+)-dibenzyl-banistenoside B using Pictet-Spengler reaction, lactamization, and glycation reaction. We also have developed the new concise synthetic route for the construction of pentacyclic core of reserpine, using this strategy, we have synthesized 11 analogs of reserpine.

List of Publications

1. Neural Anti-inflammatory Natural Product Periconianone A: Total Synthesis and Biological Evaluation
   Kalmode, H. P.; **Patil, S. S.;** Handore, K. L.; Athawale, P. R.; Dandela, R.; Verma, A. K.; Basu, A.; Reddy, D. S. *Eur. J. Org. Chem.* **2019**, 2376.

2. Total Synthesis of 12,13-Dibenzyl-Banistenoside B and Analogs
   Patil, S. S.; Jachak, G. R.; Krishna, G. R.; Argade, N. P.; Reddy, D. S. *Eur. J. Org. Chem.* **2022**,
   https://doi.org/10.1002/ejoc.202200222

3. Regioselective Concise Synthetic Route to Pentacyclic Core for Rauwolfia Alkaloids **Patil, S. S.;** Reddy, D. S. (Manuscript under preparation)

Patents

1. Decalin derivatives, a process for the preparation and pharmaceutical composition thereof (**PCT/IN2019/050779**).

List of Posters Presentation with Details

1. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2019**)

Title: Neural Anti-inflammatory Natural Product Periconianone A: Total Synthesis and Biological Evaluation.

Abstract: Total synthesis and biological evaluations of (±)-periconianone A has been carried out. Diels-Alder/aldol strategy to construct tetrahydro-naphthalene-2,6-dione scaffold, allylic oxidation of dienone using DBU/O_2 and postulated biomimetic aldol reaction to construct 6/6/6 tricyclic system are the key highlights. Neural anti-inflammatory assays showed that structurally simplified analog found to be superior to (±)-periconianone A.

List of Conference Attended with Details

1. NCL-RF Annual Students' Conference, CSIR-National Chemical Laboratory, 2018.
2. NCL-RF Annual Students' Conference, CSIR-National Chemical Laboratory, 2019.

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Title: Neural Anti-inflammatory Natural Product Periconianone A: Total Synthesis and Biological Evaluation

Authors: Hanuman P Kalmode, Suhag S Patil, Kishor L Handore, Paresh R Athawale, Rambabu Dandela, Abhishek K Verma, Anirban Basu, and D Srinivasa Reddy

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Neural Anti-inflammatory Natural Product Periconianone A: Total Synthesis and Biological Evaluation

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Abstract: Total synthesis of periconianone A, an eremophilane-type sesquiterpenoid with impressive neural anti-inflammatory potential, has been accomplished. Diels-Alder/aldol strategy to construct tetrahydro-naphthalene-2,6-dione scaffold, allylic oxidation of dienone using DBU/O_2 and postulated biomimetic aldol reaction to construct 6/6/6 tricyclic system are the highlights of the present synthesis. Besides, the synthesized (±)-periconianone A and two close analogs were tested for their neural anti-inflammatory activity using various assays. In the course of our study we found a structurally simplified analog is superior to (±)-periconianone A.

Introduction

Neuroinflammation (also known as inflammation of central nervous system) is a response arising in connection to the infections, toxic substances or traumatic brain injury. These inflammations are associated with a variety of serious neurodegenerative diseases *viz.* Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS)[1]. In literature, compounds with dihydro-, tetrahydro-naphthalene-2,6-dione scaffolds are promising for treating such diseases arising out of CNS inflammations (Figure 1).[2,3] Some time ago, we have initiated a program for the synthesis and related SAR studies of such 2,6-dione scaffolds in search of lead compounds.

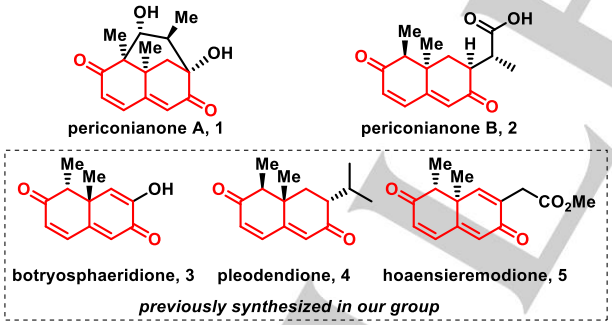

Figure 1. Natural products with tetrahydro-naphthalene-2,6-dione scaffold.

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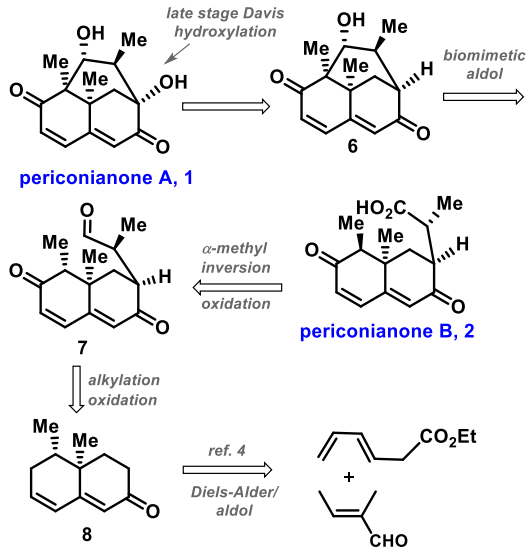
Previously we have synthesized botryosphaeridione (**3**), pleodendione (**4**) and hoaensieremodione (**5**) along with several analogs around these scaffolds and tested their anti-inflammatory potential which resulted in the identification of two potential leads.[4] In continuation to our efforts in this direction, we focused our attention on periconianone A (**1**) and periconianone B (**2**), more potent sesquiterpenoids from this class, isolated from endophytic fungus *Periconia sp.* F-31.[2] Structurally, periconianone A is a complex molecule, considering three quaternary chiral centers which pose challenges to synthetic chemists. Here, we report details of our efforts in total synthesis and biological evaluation of synthesized compounds.

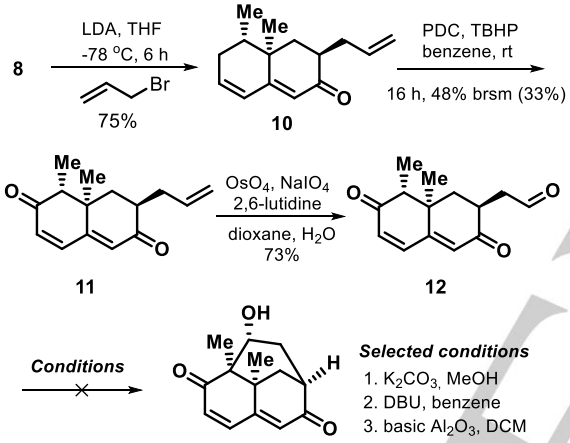
Results and Discussion

Retrosynthetic analysis of the target periconianones is compiled below. We thought of taking help from the postulated biosynthesis proposed by Zhang et al.[2] and planned our strategy as described in Scheme 1, in particular, intramolecular aldol reaction as a key step to construct the tricyclic compound **6** from aldehyde **7** followed by late-stage hydroxylation such as Davis method (Scheme 1).[5] Moreover, the proposed biosynthesis also suggested the formation of periconianone B from same aldehyde intermediate **7** via oxidation. Thus, the inversion of both α-methyls in aldehyde **7** followed by oxidation would provide periconianone B. Key aldehyde **7** was traced from known intermediate **8**[6] prepared in 10 steps in our group using Diels-Alder/aldol strategy, through side chain installation followed by functional group interconversions.



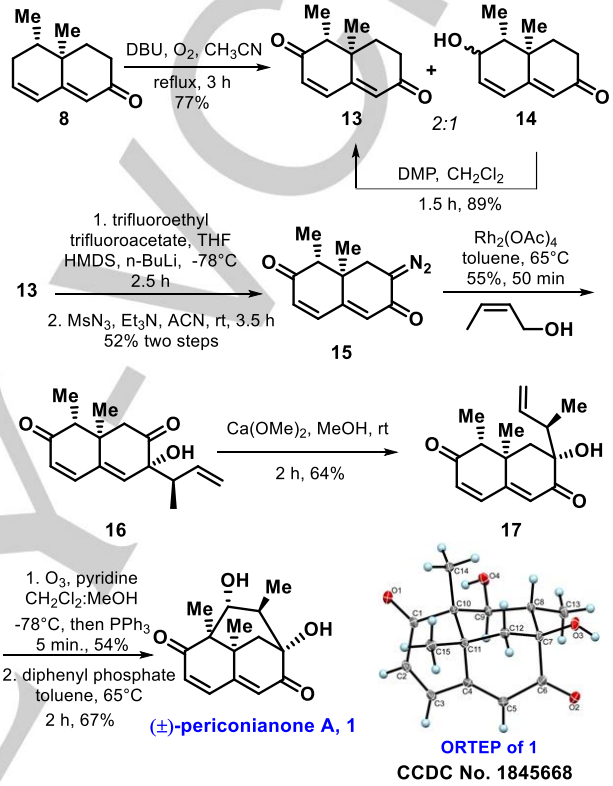
Scheme 1. Retrosynthesis based on proposed biosynthesis.

As an onset, we have designed a model study, in particular to check the feasibility of intramolecular aldol reaction to form tricyclic skeleton of the target molecule. Accordingly, allylation on **8** resulted in the formation of **10** as a single diastereomer (judged by NMR) in 75% yield. It was then subjected for allylic oxidation using excess PDC/TBHP with low yield of desired dienone **11**. As it was a model substrate, we did not try further optimization but generated sufficient material to go forward. The conversion of terminal olefin to aldehyde was achieved using Lemieux–Johnson oxidation condition. We have made a few attempts on aldehyde **12** for the desired intramolecular aldol reaction[7] but unfortunately they were unsuccessful (Scheme 2). While we were working on this project an elegant total synthesis of periconianone A appeared in the literature by Gademann's group, in which the pre-final step of the synthesis mimics the biogenesis. They also reported various unsuccessful attempts with different conditions and surprisingly diphenyl phosphate was a success to them.[8]



Scheme 2. Unsuccessful model study towards **1**.

Inspired from this report, we redesigned our strategy and began our synthesis from **8**. Towards the introduction of additional oxygen functionality on decalin moiety, various conditions were screened to get the dienone **13**, but with poor yields. Better yields were obtained by using a simple condition of DBU/O_2 which gave a clean reaction profile. We also isolated allylic alcohol **14** as a minor product from this reaction, which was then converted to the desired enone **13** using Dess-Martin periodinane (DMP). This seems to be an interesting method of allylic oxidation of dienone system. Although there was one related reaction (along with double bond migration) documented in the literature, it was not studied systematically.[9] Currently, we are in the process of testing the scope of the reaction. Compound **13** was then transformed to the corresponding diazoketone **15** using standard procedure in 52% yield over two steps.[10] Here, we followed the protocol developed by Gademann's group to introduce side chain in highly stereoselective manner. The diazoketone **15** upon reaction with *cis*-crotyl alcohol and dirhodium tetraacetate in toluene gave compound **16**, which on α-ketol rearrangement using calcium methoxide in methanol resulted in compound **17** as a major diastereomer.[8] This observation is very similar to that of Gademann's observation. Considering the presence of two additional double bonds in the molecule, ozonolysis was carried out in presence of pyridine in CH_2Cl_2:MeOH mixture for very short time (~ 5 min) followed by quenching with PPh_3 furnished desired aldehyde, setting the stage for the key intramolecular aldol reaction. Although our precursor of aldol reaction had flatter structure than the one used in Gademann's synthetic sequence, the reaction went with ease in presence of diphenyl phosphate to afford the target tricyclic (±)-periconianone A in 67% yield. All the spectral data was in complete agreement with the reported data. The required structure was also further confirmed by single crystal x-ray structure (Scheme 3).[11] Gademann's[8] and our synthesis of (±)-periconianone A involves equal steps (17 steps) having overall yield (8.5% vs 5.6%).



Scheme 3. Total synthesis of (±)-periconianone A

The biological activity of synthesized (±)-periconianone A and their analogues (**16** and **17**) were evaluated for their anti-inflammatory property. First, Cytotoxicity of all the compounds was tested through MTT assay. Various concentration of drug ranging from 10-100 μM were used and it was observed that 40 μM concentration for compounds doesn't show any cytotoxic effect on N9 (mouse microglia) cells (Figure 2A). The ROS generation is a key marker for inflammation and is reported in several cases as a triggering factor for apoptosis[12] So, our next aim was to check the anti-inflammatory property of compounds by measuring intracellular Reactive oxygen level (ROS) which was induced by LPS treatment to the N9 cells. Our flow cytometric analysis data suggest a dramatic decrease in intracellular ROS level after **17** (NDS-101502) treatment as compared to only LPS treated samples (Figure 2B). During Brain insult or any pathogenic infection, microglial cells respond and get activated resulted in secretion of various cytokines and other inflammatory mediators[13]. Here we choose the microglial cell line that provides an excellent model to understand and screen anti-inflammatory property of compounds. LPS treatment is known to activate microglia and induces the release of numerous pro-inflammatory mediators including TNF-α, CCL-2 and IL-6. CBA analysis of cytokine level reveals although all three compounds were capable of inhibiting cytokine after LPS induction of N9

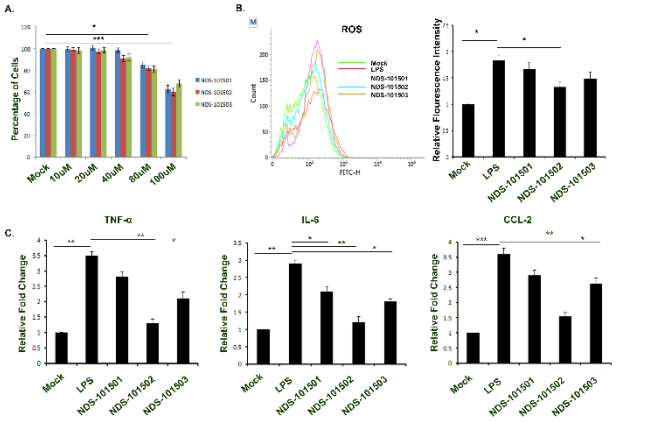


Figure 2. Anti-inflammatory activity of **1** (NDS-101501), **17** (NDS-101502) and **16** (NDS-101503): [A] MTS assay to determine the cytotoxic concentration of compounds in N9 cells, [B] FACS analysis for ROS production in LPS stimulated N9 cells, [C] Measurement of selected cytokine (TNF-α, IL-6 and CCL-2) levels. *p < 0.05, **p < 0.01, ***p<0.001]

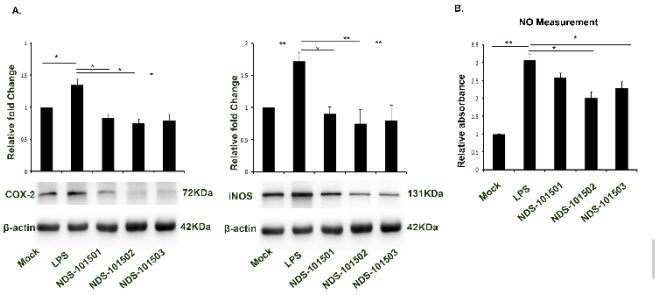


Figure 3. Anti-inflammatory activity of **1** (NDS-101501), **17** (NDS-101502) and **16** (NDS-101503) through NO production [A] iNOS and COX-2 level were measured after 24 hours of LPS stimulation in N9 cells. β-actin was used as loading control. B) NO production was measured using Griess reagent. Data was validated with three independent experiments.*p < 0.05, **p < 0.01.]

cells, compound **17** (NDS-101502) was most effective as compared to others (Figure 2C). Inflammation is a fundamental response of host defence response to injury, infectious agents, autoimmune responses or tissue ischaemia. The previous report suggests the production of iNOS and COX-2 during microglial activation and inflammation intrigued us to check for its expression level in response to the drug after LPS treated cells[14]. Our immunoblot data suggests a significant decrease in expression of iNOS and COX-2 after drug treatment and all the three drugs were found to be efficient in inhibition at 25 μM. Importance of Nitric Oxide (NO) in host defence during infection like bacterial, fungal or viral infections, has been previously explained. However, uncontrolled production of NO induces tissue damage associated with acute and chronic inflammations. Here, using calorimetric assay we have measured the level of NO in LPS induced N9 cells and their inhibition in presence of the drug. Our data indicated that compound **17** (NDS-101502), a simplified analogue of tricyclic periconianone A was most effective in decreasing NO level in LPS treated cell (Figure 3B).

Conclusions

In conclusion, we have achieved the total synthesis of (±)-periconianone A using the Diels-Alder/aldol chemistry developed for the construction of decalin skeleton in our lab and the chemistry developed by Gademann's group. The synthesized (±)-periconianone A and its two analogs were tested for their neuro anti-inflammatory activity using various assays and markers. Based on the results, a close and simplified bicyclic analog of periconianone A seems to be superior with respect to its parent compound and warrants further investigation. During this project execution, we also discovered a mild method for allylic oxidation of dienones using DBU/O_2. Further scope of this method and SAR studies around periconianone A scaffold are the future directions of this project.

Experimental Section

General Information

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-DNP, $KMnO_4$ solution or Iodine adsorbed on silica gel followed by heating with a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Melting points (mp) were determined using a Bruker capillary melting point apparatus and are uncorrected. *S*/R** nomenclature has used to show the relative stereochemistry of product. Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200, 400 or 500 MHz spectrometer. Coupling constants were measured in Hertz. Chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet. HRMS (ESI) were recorded on ORBITRAP mass analyser (Thermo Scientific, QExactive). Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

(4a*R,5*S**)-3-allyl-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (10):** To a solution of diisopropylamine (0.96 mL, 6.83 mmol) in dry THF (15 mL) was added a solution of *n*-butyllithium (1.6 M in *n*-hexane, 4.27 mL, 6.83 mmol) at –78 °C. The reaction was stirred for 30 min at –78 °C and **8** (0.4 g, 2.3 mmol) in THF (5 mL) was added dropwise via syringe. After stirring for 30 min, HMPA (1.2 mL, 6.83 mmol) was added. After stirring for a further 20 min, allyl bromide (1.96 mL, 2.3 mmol) was added slowly. After stirring for 2 h at –78 ºC the mixture was warmed to room temperature and then stirred for a further 16 h. The reaction was quenched with 1N aqueous HCl (25 mL) extracted with EtOAc (3 × 40 mL) and combined organic layer was washed with water (40 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. Purification by column chromatography over silica gel (0.5:9.5; ethyl acetate-petroleum ether as eluent) afforded **10** (0.369 g, 75%) as colorless oil.

Data for **10**: colorless oil; $IR_{u_{max}}$ (film): 1657, 1621, 1589, 991 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21–6.16 (m, 1H), 6.11 (dd, *J* = 9.8, 2.4 Hz, 1H), 5.83–5.73 (m, 1H), 5.67 (s, 1H), 5.09–5.02 (m, 2H), 2.77–2.70 (m, 1H), 2.56–2.49 (m, 1H), 2.23–2.13 (m, 2H), 2.11–2.02 (m, 2H), 1.73–1.64 (m, 1H), 1.41 (t, *J* = 13.5 Hz, 1H), 1.03 (s, 3H), 0.94 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 162.9, 138.1, 136.5, 127.9, 123.6, 116.7, 42.0, 39.7, 38.2, 36.7, 34.3, 32.5, 15.6, 14.5; HRMS (ESI) calc. for $C_{15}H_{21}O$ $[M+H]^+$ 217.1587, found 217.1586.

(1*R,8a*R**)-7-allyl-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (11):** To a stirred solution of **10** (0.190 g, 0.878 mmol) in benzene (20 mL) was added TBHP (5 M in decane, 0.9 mL, 4.39 mmol) and 4 Å MS (0.2 g) at room temperature. After 5 min, PDC (1.65 g, 4.39 mmol) was added and reaction mixture was stirred for 16 h. The reaction mixture was diluted with EtOAc (15 mL), filtered through a celite bed, and washed with EtOAc (3 × 15 mL). The filtrate was concentrated in *vacuo*. Purification by column chromatography over silica gel (12:88; ethyl acetate-petroleum ether as eluent) afforded **11** (0.066 g, 48% brsm, 33%) as light yellow solid.

Data for **11**: Light yellow solid; mp 110–112 °C; IRu_{max}(film): 1665, 1612, 1580, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 9.8 Hz, 1H), 6.21 (d, *J* = 9.8 Hz, 1H), 6.04 (s, 1H), 5.77 (ddd, *J* = 10.0, 7.3 Hz, 1H), 5.11–5.06 (m, 2H), 2.80–2.71 (m, 1H), 2.62–2.46 (m, 2H), 2.16 (ddd, *J* = 18.0, 14.1, 6.2 Hz, 2H), 1.69 (t, *J* = 13.6 Hz, 1H), 1.16 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 199.7, 158.8, 142.2, 135.7, 132.2, 128.9, 117.5, 52.3, 41.5, 40.5, 40.0, 33.6, 18.7, 7.1; HRMS (ESI) calcd for $C_{15}H_{19}O_2$ $[M+H]^+$ 231.1380, found 231.1379.

2-((2*S,8*R**,8a*R**)-8,8a-dimethyl-3,7-dioxo-1,2,3,7,8,8a-hexahydronaphthalen-2-yl)acetaldehyde (12):** To a solution of compound **11** (0.060 g, 0.258 mmol) in dioxane-water (3:1, 8 mL) were added 2,6-lutidine (0.06 mL, 0.517 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 0.058 mL, 0.0051 mmol), and $NaIO_4$ (0.120 g, 1.034 mmol). The reaction was stirred at 25 °C and monitored by TLC. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) was added. The organic layer was separated, and the water layer was extracted by CH_2Cl_2 (2 × 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed, and the product was purified with silica gel column chromatography (20:80; ethyl acetate-petroleum ether as eluent) afforded aldehyde **12** (0.044 g, 73%) as a colorless oil.

Data for **12**: Colorless oil; IRu_{max}(film): 2853, 2766, 1722, 1690, 1642, 1603, 969 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.01 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.8 Hz, 1H), 6.07 (s, 1H), 3.17–3.02 (m, 2H), 2.61–2.46 (m, 2H), 2.11 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.84 (t, *J* = 13.2 Hz, 1H), 1.24 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H). HRMS (ESI) calcd for $C_{14}H_{17}O_3$ $[M+H]^+$ 233.1178, found 233.1174.

(1*R,8a*R**)-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (13) and (4a*R**,5*R**)-6-hydroxy-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (14):** To a stirred solution of **8** (0.530 g, 3.007 mmol) in dry acetonitrile (12 mL) oxygen gas was bubbled for a period of 30 min at rt. DBU (1.13 mL, 7.52 mmol) was added dropwise and the reaction mixture was refluxed for a period of 3.5 h under O_2 atmosphere. The reaction mass was diluted with ice cold water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated to give crude product. Which was purified by column chromatography (17:83; ethyl acetate-petroleum ether) to obtain **13** (0.297 g, 52%) as an off white solid. Alcohol (**14**) was obtained at eluent system (28:72; ethyl acetate-petroleum ether) as yellowish oily liquid (0.148 g, 25%). The obtained ratio of **13**:**14** was 2:1.

Data for **13**: Off white solid; mp 108-110 °C; IRu_{max} (film): 1655, 1607, 1574, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 9.2 Hz, 1H), 6.22 (d, *J* = 9.3 Hz, 1H), 6.04 (s, 1H), 2.55 (d, *J* = 8.3 Hz, 3H), 2.13 (d, *J* = 11.7 Hz, 1H), 2.03–1.98 (m, 1H), 1.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 198.7, 159.4, 142.3, 132.2, 129.1, 52.1, 39.9, 34.4, 33.4, 18.2, 7.0; HRMS (ESI) calc. for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067, found 191.1064.

Data for **14**: Yellowish oily liquid; IRu_{max} (film): 3048, 1655, 1607, 1574, 890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19–6.13 (m, 2H), 5.76 (s, 1H), 4.07 (d, *J* = 9.6 Hz, 1H), 2.55–2.49 (m, 1H), 2.44 (dd, *J* = 5.4, 2.1 Hz, 1H), 2.05 (ddd, *J* = 13.2, 5.3, 2.2 Hz, 1H), 1.80–1.72 (m, 2H), 1.56–1.52 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 162.1, 140.2, 128.4, 124.8, 71.3, 47.6, 37.4, 33.8, 33.2, 16.3, 10.4; HRMS (ESI) calc. for $C_{12}H_{17}O_2$ $[M+H]^+$ 193.1223, found 193.1220.

Experimental procedure for oxidation of 14 to 13: $NaHCO_3$ (1.9 g, 22.6 mmol) and DMP (2.4 g, 5.65 mmol) were added sequentially to a solution of **14** (0.543 g, 2.82 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the mixture was stirred for 1.5 h at this temperature. The mixture was diluted with CH_2Cl_2 and sat. aq. $Na_2S_2O_3$ solution was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (17:83; ethyl acetate-petroleum ether) to obtained **13** (0.478 g, 89%) as an off white solid.

(1*R,8a*R**)-7-diazo-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (15):** To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 0.922 mL, 8.04 mmol) in 36 mL of THF and then cooled at 0 °C in an ice-water bath while *n*-butyllithium solution (1.6 M in *n*-hexane, 5.1 mL, 8.04 mmol) was added rapidly over 1 min. After 10 min, the resulting solution was cooled at –78 °C in a dry ice-acetone bath while a solution of **13** (1.39 g, 7.31 mmol) in 24 mL of THF was added dropwise over 15 min via syringe. The resulting yellow solution was stirred for 30 min at –78 °C and then 2,2,2-trifluoroethyl trifluoroacetate (1.3 mL, 9.50 mmol) was added rapidly by syringe in one portion. The mixture was stirred for 90 min at –78 °C and then quenched by addition of sat. aq. NH_4Cl solution and diluted with EtOAc. The layers were separated and the aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated to give crude trifluoromethylated compd. (2.6 g, quant.) as a yellowish oil.

Crude trifluoromethylated compound (2.6 g, 12.02 mmol) was dissolved in MeCN (40 mL). NEt_3 (5.1 mL, 36.1 mmol) was added, followed by dropwise addition of a solution of MsN_3 (4.1 mL, 48.1 mmol) over a period of 15 min. The yellow mixture was stirred for 3.5 h at rt, before it was diluted with EtOAc and washed with 1.0 M aq. NaOH solution. After separation, the aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (17:83; EtOAc–petroleum ether) to give **15** (1.02 g, 52% over two steps) as a pale yellow solid.

Data for **15**: Pale yellow solid; mp 118-120 °C; IRu_{max} (film): 2089, 1668, 1616, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 9.7 Hz, 1H), 6.22 (d, *J* = 9.9 Hz, 1H), 6.16 (s, 1H), 3.01 (d, *J* = 13.9 Hz, 1H), 2.74 (d, *J* = 13.9 Hz, 1H), 2.59 (dd, *J* = 12.9, 6.3 Hz, 1H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 182.7, 153.9, 142.0, 131.2, 130.1, 61.0, 51.0, 39.2, 33.6, 19.4, 7.2; HRMS (ESI) calc. for $C_{12}H_{12}O_2N_2Na$ $[M+Na]^+$ 239.0791, found 239.0787.

(3*R,8*R**,8a*R**)-3-((*R**)-but-3-en-2-yl)-3-hydroxy-8,8a-dimethyl-8,8a-dihydronaphthalene-2,7(1*H*,3*H*)-dione (16):** To a solution of rhodium acetate (0.036 g, 0.081 mmol) and *cis*-2-buten-1-ol (3.34 g, 46.24 mmol) in toluene (10 mL) at 65 °C was added dropwise a solution of **15** (0.500 g, 2.31 mmol) in toluene (5 mL) over a period of 10 min and the mixture was stirred for an additional 40 min at this temperature. The solvent was evaporated and the residue purified by flash column chromatography (08:92; EtOAc–petroleum ether) to give **16** (0.331 g, 55%) as a yellowish oily liquid.

Data for **16**: Yellowish oily liquid; IRu_{max} (film): 3478, 1718, 1675, 1632, 1590, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, *J* = 9.8 Hz, 1H),

6.03 (d, *J* = 9.8 Hz, 1H), 5.93 (s, 1H), 5.85–5.78 (m, 1H), 5.17 (d, *J* = 10.1 Hz, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 3.60 (s, 1H), 2.90 (d, *J* = 12.3 Hz, 1H), 2.76 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.60 (d, *J* = 12.2 Hz, 1H), 2.56–2.49 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 198.7, 143.5, 141.1, 137.8, 134.4, 127.9, 117.6, 78.3, 51.6, 48.9, 48.6, 46.2, 20.5, 15.0, 7.2; HRMS (ESI) calc. for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1305, found 283.1298.

(1*R,7*R**,8a*R**)-7-((*R**)-but-3-en-2-yl)-7-hydroxy-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (17):** A solution of **16** (0.140 g, 0.540 mmol) and $Ca(OMe)_2$ (0.165 g, 1.61 mmol) in MeOH (15 mL) was stirred for 2 h at rt. sat. aq. NH_4Cl solution was added slowly and the mixture was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (09:91; EtOAc–petroleum ether) to give **17** (0.084 g, 64%) as off white solid.
Data for **17**: Off white solid; mp 128-130 °C; IRu_{max} (film): 3412, 1720, 1666, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 9.9 Hz, 1H), 6.24 (dd, *J* = 9.8, 4.9 Hz, 1H), 6.17 (s, 1H), 5.97–5.88 (m, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 2.77–2.74 (m, 1H), 2.60 (q, *J* = 6.7 Hz, 1H), 2.32 (s, 1H), 2.05–1.94 (m, 1H), 1.25 (s, 3H), 1.18–1.16 (m, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 199.8, 160.6, 141.8, 137.8, 132.5, 128.0, 117.6, 75.7, 52.3, 46.0, 40.4, 39.7, 22.9, 14.7, 7.4 HRMS (ESI) calc. for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1305, found 283.1303.

(*S)-2-((2*R**,8*R**,8a*R**)-2-hydroxy-8,8a-dimethyl-3,7-dioxo-1,2,3,7,8,8a-hexahydronaphthalen-2-yl)propanal (aldehyde):** A solution of **17** (0.073 g, 0.280 mmol), pyridine (0.0904 mL, 1.12 mmol) in CH_2Cl_2/MeOH (7 mL, 1:1) was cooled to –78 °C and ozone was bubbled through the solution until the yellow color disappeared (4-5 min). The reaction mixture was sequentially purged with oxygen and nitrogen. PPh_3 (0.147 g, 0.561 mmol) was added and the mixture was allowed to warm to rt. After stirring for 1 h, the solvent was removed by evaporation to afford crude product. Which was purified by column chromatography (17:83; ethyl acetate-petroleum ether) to obtain aldehyde (0.040 g, 54%), as a light yellow oil. Due to its unstable nature it was used in the next step without further characterization.

(1*R,7*R**,8a*S**,9*R**,10*R**)-7,10-dihydroxy-1,8a,9-trimethyl-1,7,8,8a-tetrahydro-1,7-ethano-naphthalene-2,6-dione (1)**
To a stirred solution of aldehyde (0.041 g, 0.16 mmol) in toluene (7 mL) was added diphenyl phosphate (0.020 g, 0.0781 mmol) and the mixture was heated at 65 °C for 2 h. After complete consumption of starting material checked by TLC, the yellow solution was partitioned between sat. aq. $NaHCO_3$ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography over silica gel (22:78; EtOAc–petroleum ether) afforded periconianone A, **1** (0.027 g, 67%) as a brown solid.
Data for **1**: Brown solid; mp 174-176 °C; IRu_{max} (film): 3413, 1665, 1610, 1570, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.6 Hz, 1H), 6.14 (s, 1H), 6.07 (d, *J* = 9.7 Hz, 1H), 4.02 (s, 1H), 3.53 (d, *J* = 9.7 Hz, 1H), 2.21 (d, *J* = 13.8 Hz, 1H), 1.87 (d, *J* = 13.8 Hz, 2H), 1.77 (s, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 0.92 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 198.9, 162.6, 142.3, 130.0, 122.6, 75.9, 73.9, 55.8, 44.8, 44.7, 39.9, 24.5, 12.0, 8.0; HRMS (ESI) calc. for $C_{15}H_{18}O_4Na$ $[M+Na]^+$ 285.1097, found 285.1093.

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Keywords: Periconianone A • Diels-Alder/aldol • Allylic oxidation • Neuroinflammation • Cytotoxicity

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Layout 2:

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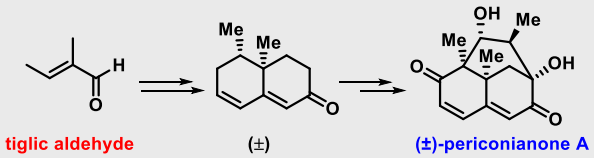

Total synthesis and neuro anti-inflammatory activity of the complex 6/6/6 carbocyclic sesquiterpenoid (±)-periconianone A and its analogues are described.

Total Synthesis and Biological Evaluation*

Hanuman P. Kalmode,[a] Suhag S. Patil,[a,b] Kishor L. Handore,[a,b] Paresh R. Athawale,[a,b] Rambabu Dandela,[a] Abhishek Kumar Verma,[c] Anirban Basu[c] and D. Srinivasa Reddy[a,b]**

Page No. – Page No.
Neural Anti-inflammatory Natural Product Periconianone A: Total Synthesis and Biological Evaluation

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Accepted Article

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Total Synthesis of 12,13-Dibenzyl-Banistenoside B and Analogs

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Dedication ((optional))

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Abstract: Banistenosides A and B possessing a unique "azepino(1,2-*a*)tetrahydro-*β*-carboline" carbon framework were isolated from the stem of *Banisteriopsis caapi* showed MAO-A inhibition. Herein, we report the total synthesis of dibenzyl derivative of the untouched natural product in the last two decades, Banistenoside B. The key steps involve construction of 6.5.6.7 tetracyclic core using Pictet-Spengler reaction and intramolecular amide coupling. The stereoselective glycation was achieved through Hotha's protocol using gold catalyst, and silver triflate in the late stage of synthesis. The stereochemistry of most of the essential compounds were confirmed by X-ray crystallography.

Introduction

Natural products play a vital role in drug discovery since most synthesized drugs have a natural product origin.[1] *Banisteriopsis caapi*, a plant for treating neurodegenerative disorders relevant to Parkinson's disease (PD) has been found in countries such as Brazil, Bolivia, Colombia, Ecuador, and Peru.[2] In PD, there is damage in neurons from the substantia nigra of the brain that affects dopamine production which is responsible for the brain's ability to control movement. Antioxidants can control this as an adjuvant with dopamine agonist or Monoamine oxidase (MAO) inhibitors.[3]

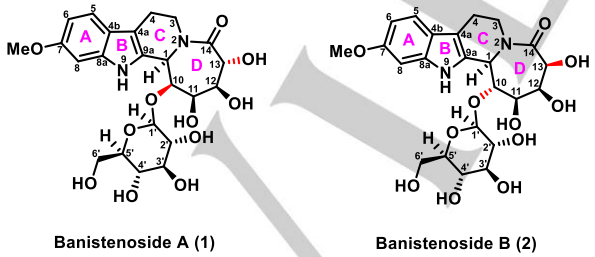
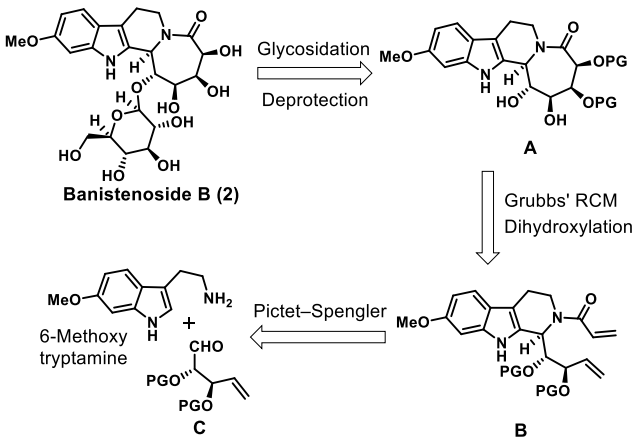


Figure 1. Structures of Banistenoside A and B.

The identities of different *Banisteriopsis* species are mostly unknown due to the scarcity of fertile collections and lack of detailed taxonomic study. The harmine and the stem extract of *Banisteriopsis caapi* showed a concentration-dependent inhibition of MAO-A, which increases dopamine release from rat striatal slices.[4] During the chemical/biological standardization of *Banisteriopsis caapi* for neurological disorders relevant to PD, Samoylenko et al. found an extract of *Banisteriopsis caapi* cultivar Da Vine, collected in Oahu, Hawaii, demonstrated potent in vitro MAO-A inhibitory and antioxidant activities. Further studies resulted in the isolation of two new *β*-carboline alkaloidal glycosides, Banistenoside A (**1**) and Banistenoside B (**2**) (Figure 1), along with the four known *β*-carboline alkaloids from the same extract.[5] In continuing our group's interest in synthesizing a structurally challenging molecules with virtuous biological values, we were interested in taking this as a target.[6] Inspired with the novel structural features, biological activity, we planned to synthesize these natural products and their close analogs.

Results and Discussion

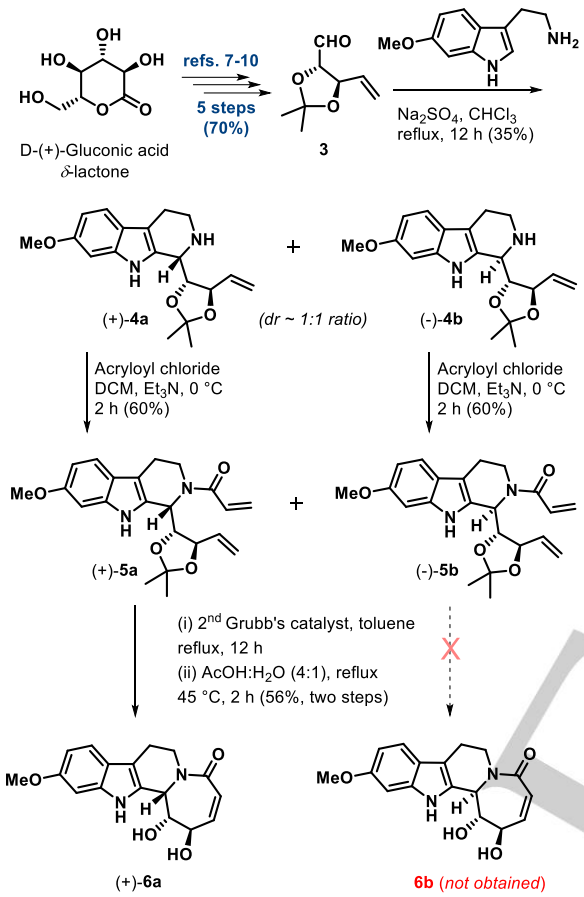
The retrosynthetic analysis for the Banistenoside B (**2**) is depicted in scheme 1. The target compound Banistenoside B was envisioned from tetracyclic compound **A** through stereoselective glycosidation and deprotection sequence. Compound **A** could be synthesized from compound **B** through the Grubbs' ring-closing metathesis and dihydroxylation. Compound **B** was planned from the Pictet-Spengler reaction between aldehyde intermediate **C** and 6-methoxytryptamine.



Scheme 1. Retrosynthetic Route for the Synthesis of Banistenoside B.

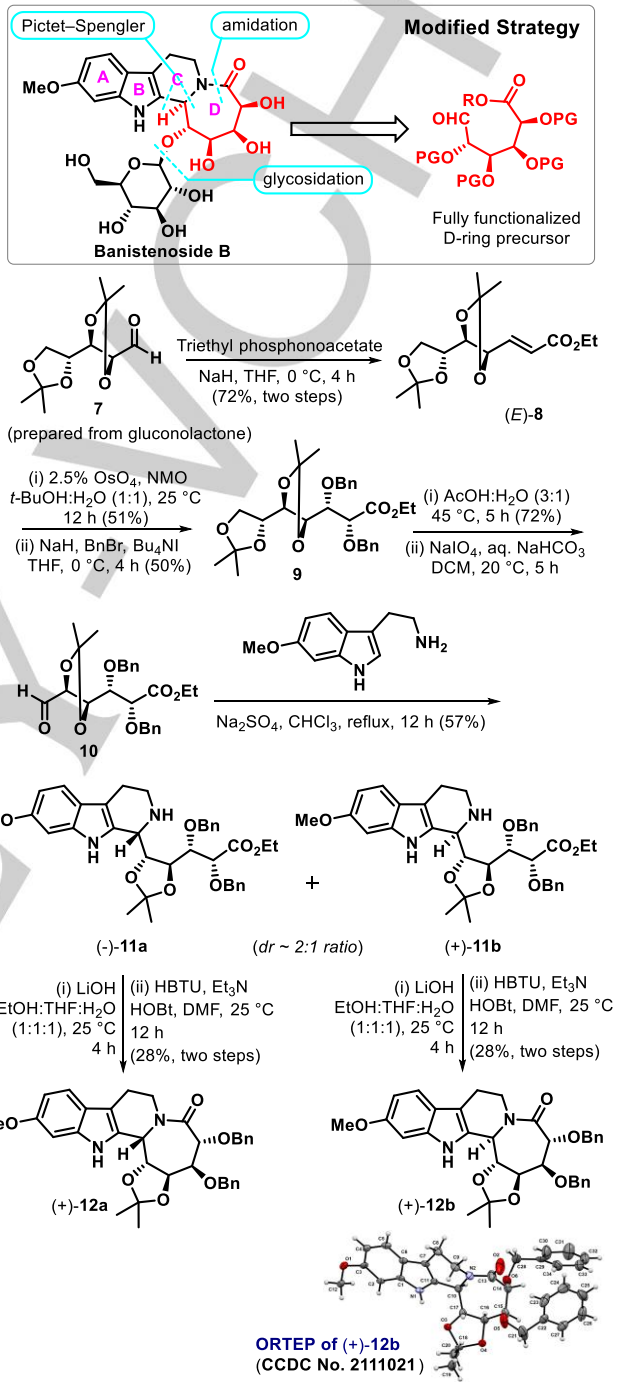
Our synthesis began with commercially available D-(+)-gluconic acid *δ*-lactone. The aldehyde intermediate **3** can be

synthesized in gram scale from D-(+)-gluconic acid δ-lactone according to the known protocol in 5 steps with 70% overall yield.[7-10] With aldehyde intermediate **3** in hands, we set for the first key reaction of the sequence Pictet-Spengler cyclization under neutral conditions in consideration of the stability of the acetal with the freshly prepared 6-methoxytryptamine from 6-methoxyindole (Scheme 2).[11-13]



Scheme 2. Synthesis of Tetracyclic Core of Banistenoside B via RCM.

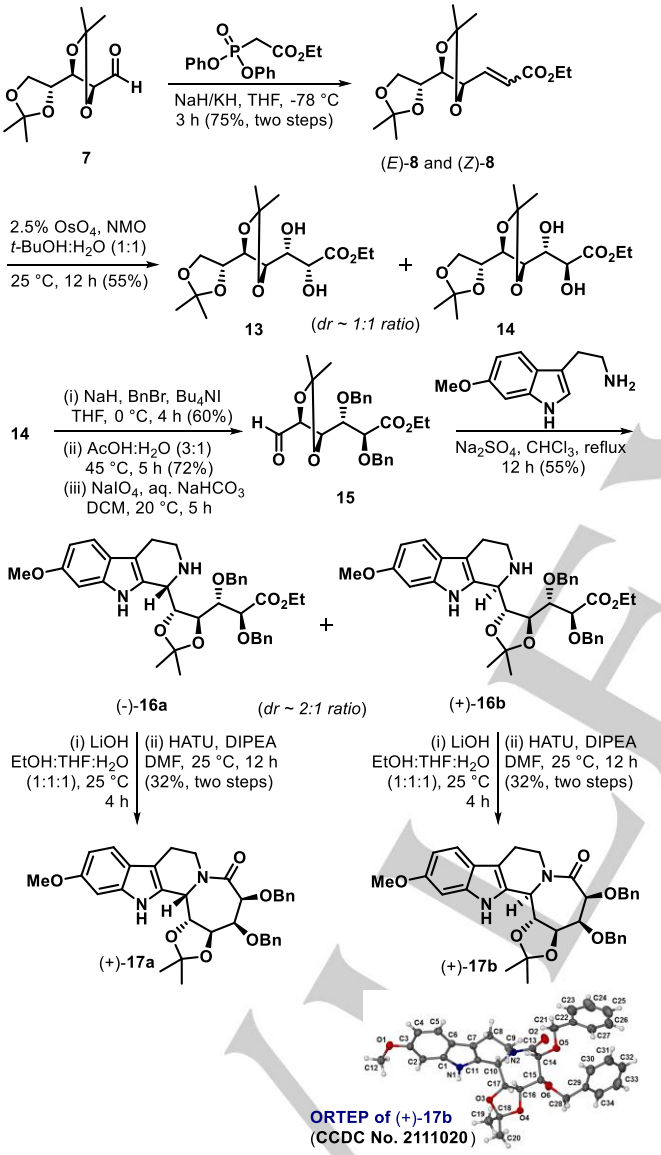
A diastereomeric mixture of **4a** and **4b** in the ratio of 1:1 and yield of 35% was obtained, which were separated by column chromatography. The following steps were run in parallel with the pure diastereomers **4a** and **4b**. Firstly the acylation was carried out by using acryloyl chloride and triethylamine in DCM to give di-olefinic compounds **5a** and **5b**.[14] Synthesis continued with ring-closing metathesis of compounds **5a** and **5b** using Grubbs' 2nd generation catalyst in toluene followed by acetonide deprotection using AcOH:H_2O (4:1).[15] Here, the RCM reaction of the other diastereomer compound **5a** resulted in the formation of compound **6a**, but the RCM reaction of compound **5b** failed to give the corresponding cyclized product **6b**. Unfortunately, after exploring several reaction conditions [OsO_4, NMO, acetone:H_2O (2:1); OsO_4, NMO, TEMDA, *t*-BuOH:H_2O (2:1); OsO_4, NMO, *t*-BuOH:H_2O (2:1); OsO_4, py; $NaIO_4$, $RuCl_3$, $CeCl_3.7H_2O$, EtOAc:CH_3CN:H_2O; OsO_4, NMO, citric acid] we had no practical success on dihydroxylation of compound **6a**. However, an attempted Boc-protection of free indole nitrogen was also unsuccessful in our hands.



Scheme 3. Synthesis of Tetracyclic Core of Banistenoside B via Lactamization.

After several unproductive attempts to synthesize the intermediate **A**, we revised our retrosynthetic approach to synthesize Banistenoside B (**2**) (Scheme 3). In the new synthesis path, we focused on maintaining the stereocentres of all the hydroxy groups in the synthetic route, thus we started our synthesis using aldehyde intermediate **7** which can be

synthesized from D-(+)-gluconic acid δ-lactone with 80% overall yield in three steps.[7] The aldehyde intermediate **7** on Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate in the presence of NaH in THF furnished known compound (*E*)-**8** in 72% yield.[16] Compound **8** was further subjected to the dihydroxylation using OsO_4, NMO in *t*-BuOH:H_2O (1:1), followed by benzyl protection of the resulting diol to afford known compound **9**.[17] Compound **9** on terminal acetonide deprotection under acidic conditions followed by oxidative cleavage using $NaIO_4$ gave the aldehyde intermediate **10**.

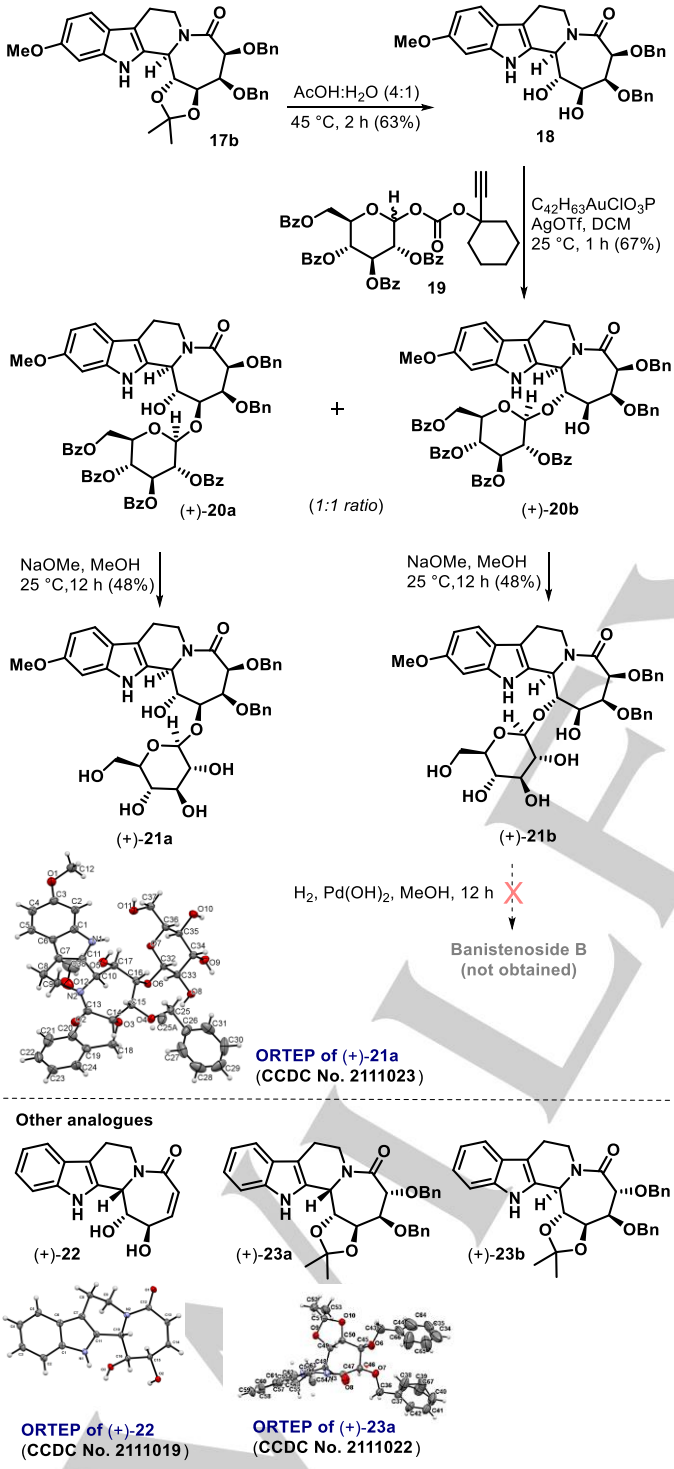


Scheme 4. Synthesis of Desired Tetracyclic Core of Banistenoside B via Ando Olefination.

The Pictet-Spengler reaction between aldehyde intermediate **10** and 6-methoxytryptamine in chloroform afforded a diastereomeric mixture of **11a** and **11b** with the diastereomeric ratio of 2:1 and yield of 57% was obtained.[11-13] After separating this mixture of diastereomers **11a** and **11b** using column chromatography, following reactions were carried in parallel on pure diastereomers **11a** and **11b**. The ester hydrolysis under basic condition using LiOH in EtOH:THF:H_2O (1:1:1) to give the corresponding amino acid which on intramolecular cyclization using coupling reagent HBTU, HOBt, Et_3N in DMF afforded two tetracyclic compounds **12a** and **12b** (28%, two steps).[18] A single-crystal X-ray study confirmed the structure of compound **12b** and its stereochemistry; on that basis, we have confirmed the stereochemistry of the other diastereomer **12a**.

On the basis of synthesis of tetracyclic core (+)-**12b** having undesired stereochemistry at C-13 carbon, our plan to obtain the desired (*Z*)-olefin **8** started with Ando olefination.[16a] Ando modification of Horner-Wadsworth-Emmons reaction of aldehyde **7** with freshly prepared ethyl 2-(diphenoxyphosphoryl) acetate, NaH/KH in THF provided the mixture of (*E*)-**8** and (*Z*)-**8**, which upon further dihydroxylation by using OsO_4, NMO constricted two dihydroxy compounds **13** and **14** with the ratio of (1:1) (55% yield) (Scheme 4).[16,19] After separation by column chromatography, compound **14** was utilized for further reactions. Benzyl protection of compound **14** followed by regioselective acetonide deprotection in acidic medium furnished diol, which was oxidized with $NaIO_4$ to give the required aldehyde intermediate **15**. Aldehyde intermediate **15** on Pictet-Spengler reaction with 6-methoxytryptamine provided two expected diastereoisomers **16a** and **16b** with the 2:1 ratio (55%).[13] After purification by column chromatography on silica gel, compounds **16a** and **16b** were forwarded separately for the synthesis of tetracyclic compounds **17a** and **17b** using ester hydrolysis under alkaline conditions followed by intramolecular cyclization as shown in scheme 4.[18] The single-crystal X-ray study was performed for compound **17b** to assign the illustrated relative stereochemistry. At the final stage, with all the stereocentres set on the tetracyclic scaffold **17b**, the last challenging step was to connect the glucose ring to the scaffold **17b** with exact regio- and stereochemistry. Compound **17b** on acetonide deprotection using AcOH:H_2O (4:1) yielded compound **18** (63%). The glycation reaction using Hotha's protocol was carried out in between compound **18** and substrate **19**, which was prepared using D-glucose, in the presence of chloro[tris(2,4-di-*tert*-butylphenyl)phosphite]gold and silver triflate afforded two regioisomeric compounds **20a** and **20b** (67% yield) (Scheme 5).[20] The compounds **20a** and **20b** were clearly separated and forwarded for benzoyl deprotection with sodium methoxide in methanol to afford compounds **21a** and **21b** (~48%). Although all starting material was consumed the obtained yield was on the lower side plausibly due to decomposition.[21] The X-ray crystallographic analysis unambiguously confirmed the structure of compound **21a**; which also unambiguously confirmed the structure of other regioisomeric compounds **21b**. The solubility issues of natural products Banistenoside A (**1**) and Banistenoside B (**2**) have been discussed by Samoylenko *et al*. during the process of isolation of natural products.[5] Hence, we planned to overcome the solubility problem by making the

reported heptaacetyl derivative of Banistenoside B; via debenzylation, acylation pathway. Unfortunately, both H_2, Pd/C and H_2, $Pd(OH)_2$ induced debenzylation in MeOH resulted in complete decomposition and hence we were unable to synthesize the actual target compound.



Scheme 5. Synthesis of Dibenzyl Derivative of Banistenoside B and Analogs.

In addition, a few analogues were also synthesized using tryptamine in the same fashion useful for SAR studies.

Conclusions

In summary, we have successfully achieved the total synthesis of dibenzyl derivative of natural product Banistenoside B (**2**), which contains 10 stereocentres with the longest linear sequence of 14 steps. Along with dibenzylated natural product, few close analogs **6a**, **12a**, **12b**, **17a**, **17b**, **21a**, and a few demethoxy analogs were synthesized for further SAR studies. Overall, the Pictet-Spengler reaction followed by lactamization and stereoselective glycation reactions are the key steps in the synthesis of dibenzyl derivative of natural product. However, the obtained lower yields and weak diastereoselectivities in Pictet-Spengler reactions could be a result of plausible retro Pictet-Spengler reactions and associated decompositions of respective aldehydes.

Experimental Section

General Information

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, $KMnO_4$, ninhydrin solution followed by heating with a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^1H NMR, ^{13}C NMR spectra were obtained using 200 MHz, 400 MHz, 500 MHz spectrometers. Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, QExactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on an FT-IR Bruker Alpha II spectrometer as a solution of chloroform. Chemical nomenclature was generated using Chembiodraw ultra14.0. Melting points of solids were measured in the melting point apparatus (Buchi 565), which were uncorrected. Optical rotation values were recorded on a P-2000 polarimeter at 589 nm.

1-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole [(+)-4a & (-)-4b]: To a solution of aldehyde **3** (2 g, 12.820 mmol) in chloroform (40 mL) at room temperature was added 6-methoxy tryptamine (3.65 g, 19.230 mmol) and Na_2SO_4 (0.9 g, 6.406 mmol). The reaction mixture was refluxed for 12 hours at 70 °C. After 12 h, the solvent was evaporated under reduced pressure, and the crude compound was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (60:40)

to afford pure product as a red sticky liquid (+)-**4a** and (-)-**4b** as diastereomeric mixture (1.5 g, 35%) with the diastereomeric ratio of 1:1.

Data for (+)-**4a**: red sticky liquid; Yield= 0.750 g; **$[\alpha]_D^{27}$** = + 129.37 (*c* = 2.0, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 2953, 1618, 1163, 1028; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.22 (br. s., 1 H), 7.39 (d, *J* = 8.5 Hz, 1 H), 6.84 (s, 1 H), 6.79 (dd, *J* = 1.8, 8.5 Hz, 1 H), 5.95 (ddd, *J* = 7.0, 10.1, 17.1 Hz, 1 H), 5.37 (d, *J* = 17.1 Hz, 1 H), 5.29 (d, *J* = 11.0 Hz, 1 H), 4.48 (br. s., 1 H), 4.23 (t, *J* = 7.6 Hz, 1 H), 4.13 (dd, *J* = 3.4, 8.2 Hz, 1 H), 3.86 (s, 3 H), 3.37 (td, *J* = 3.7, 12.7 Hz, 1 H), 3.00–2.91 (m, 1 H), 2.71 (br. s., 2 H), 1.96 (br. s., 1 H), 1.57 (s, 3 H), 1.47 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.3, 136.5, 136.3, 131.1, 121.6, 119.1, 118.6, 110.6, 108.9, 108.8, 94.8, 82.0, 78.5, 55.7, 52.5, 43.3, 27.1, 26.6, 22.8; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{19}H_{25}N_2O_3$ 329.1860, Found 329.1859.

Data for (-)-**4b**: red sticky liquid; Yield= 0.750 g; **$[\alpha]_D^{27}$** = – 60.42 (*c* = 1.5, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 2935, 1624, 1213, 1030; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 (br. s., 1 H), 7.38 (d, *J* = 8.6 Hz, 1 H), 6.84 (d, *J* = 2.1 Hz, 1 H), 6.78 (dd, *J* = 2.3, 8.5 Hz, 1 H), 5.94 (ddd, *J* = 7.1, 10.2, 17.2 Hz, 1 H), 5.40–5.26 (m, 2 H), 4.52–4.47 (m, 1 H), 4.24–4.19 (m, 1 H), 4.12 (dd, *J* = 3.5, 8.4 Hz, 1 H), 3.86 (s, 3 H), 3.37 (td, *J* = 4.0, 12.8 Hz, 1 H), 3.00–2.91 (m, 1 H), 2.71 (td, *J* = 2.3, 4.3 Hz, 2 H), 1.73 (br. s., 1 H), 1.56 (s, 3 H), 1.46 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.3, 136.3, 132.0, 128.6, 128.5, 121.5, 119.4, 118.6, 110.5, 108.9, 94.8, 81.8, 78.5, 55.7, 52.5, 43.2, 27.1, 26.6, 22.6; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{19}H_{25}N_2O_3$ 329.1860, found 329.1858.

1-((*S*)-1-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)prop-2-en-1-one [(+)-5a]: To a stirred solution of compound (+)-**4a** (0.5 g, 1.523 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added acryloyl chloride (0.2 mL, 2.285 mmol) followed by triethylamine (0.7 mL, 4.570 mmol) and stirred at 0 °C for 2 hours. After 2 h, saturated $NaHCO_3$ solution (20 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was concentrated under reduced pressure and crude compound was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (70:30) to afford compound (+)-**5a** (0.350 g, 60%) as a pale yellow solid.

Data for (+)-**5a**: pale yellow solid; **mp** 151–153 °C; **$[\alpha]_D^{27}$** = + 130.04 (*c* = 2.5, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3360, 2987, 1633, 1047; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.26 (br. s., 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 6.91 (d, *J* = 2.3 Hz, 1 H), 6.77 (dd, *J* = 2.3, 8.4 Hz, 1 H), 6.62 (dd, *J* = 10.7, 16.8 Hz, 1 H), 6.31 (dd, *J* = 1.9, 17.2 Hz, 1 H), 5.91 (d, *J* = 9.9 Hz, 1 H), 5.79–5.71 (m, 2 H), 5.37 (d, *J* = 16.8 Hz, 1 H), 5.23–5.18 (m, 1 H), 4.77 (t, *J* = 8.0 Hz, 1 H), 4.17–4.11 (m, 1 H), 3.97–3.92 (m, 1 H), 3.85 (s, 3 H), 3.41–3.32 (m, 1 H), 2.84–2.72 (m, 2 H), 1.61 (s, 3 H), 1.45 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.7, 156.4, 136.8, 134.9, 131.1, 128.5, 127.7, 120.7, 119.1, 118.6, 109.5, 109.2, 108.0, 94.8, 81.2, 80.4, 55.6, 51.3, 42.3, 27.1, 27.1, 22.4; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{22}H_{27}N_2O_4$ 383.1965, found 383.1961.

1-((*R*)-1-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methoxy-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)prop-2-en-1-one [(-)-5b]: Compound (-)-**5b** can be synthesized from (-)-**4b** (0.5 g, 1.523 mmol) by the same procedure followed for compound (+)-**5a**. Purified by column chromatography on silica gel (70:30 petroleum ether/ethyl acetate): (0.350 g, 60%) as a pale yellow solid.

Data for (-)-**5b**: pale yellow solid; **mp** 155–157 °C; **$[\alpha]_D^{27}$** = – 51.60 (*c* = 2, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3364, 2992, 1627, 1046; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 (s, 1 H), 7.34 (d, *J* = 8.6 Hz, 1 H), 6.91 (d, *J* = 2.1 Hz, 1 H), 6.77 (dd, *J* = 2.3, 8.5 Hz, 1 H), 6.61 (dd, *J* = 10.6, 16.8 Hz, 1 H), 6.30 (dd, *J* = 1.8, 16.8 Hz, 1 H), 5.91 (d, *J* = 9.6 Hz, 1 H), 5.78–5.69 (m, 2 H), 5.41–5.34 (m, 1 H), 5.20 (dd, *J* = 1.1, 10.3 Hz, 1 H), 4.77 (t, *J* = 7.8 Hz, 1 H), 4.14 (dd, *J* = 3.7, 14.2 Hz, 1 H), 3.94 (dd, *J* = 8.1, 9.6 Hz, 1 H), 3.86 (s, 3 H), 3.37 (ddd, *J* = 4.4, 11.4, 14.2 Hz, 1 H), 2.87–2.71 (m, 2 H), 1.62 (s, 3 H), 1.44 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.8, 156.5, 136.9, 134.9, 131.2, 128.5, 127.8, 120.8, 119.1, 118.6, 109.5, 109.3, 108.0, 94.9, 81.2, 80.4, 55.7, 51.3, 42.4, 27.1, 27.0, 22.4; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{22}H_{27}N_2O_4$ 383.1965, found 383.1966.

(1*R*,2*R*,13b*S*)-1,2-dihydroxy-11-methoxy-1,2,7,8,13,13b-hexahydro-5*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-5-one [(+)-6a]: By taking the di-olefinic compound (+)-**5a** (0.250 g, 0.654 mmol) in toluene (150 mL), purged the solution with argon for 10-15 min. Then add G-II (0.011 g, 0.013 mmol) catalyst and reflux the reaction mixture at 110 °C for 12 h. After 12 h, the reaction mixture was cooled to room temperature and the solvent was evaporated through reduced pressure to obtain acetonide protected tetracyclic intermediate compound **5a-1** (190 mg crude), which was used for further reaction.[3] The above crude compound was taken in AcOH: H_2O (4:1) (15 mL) solution and the reaction mixture was stirred at 45 °C for 3 hours. After the completion of the reaction, the solvent was evaporated under reduced pressure. The solid residue was dissolved in ethyl acetate (30 mL), and quenched the reaction mixture with a saturated solution of $NaHCO_3$ (10 mL), and extracted with ethyl acetate (2 X 10 mL). The combined organic layer was dried over anhydrous sodium sulphate, concentrated and the crude compound was purified by column chromatography on silica gel using Dichloromethane/Methanol (90:10) to afford dihydroxy compound (+)-**6a** (0.115 g, 56% over two steps) as a colorless solid.

Data for (+)-**6a**: colorless solid; **mp** 189–191 °C; $[\alpha]_D^{26}$ = + 74.05 (*c* = 1.5, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3367, 2929, 1445, 1026; **^{1}H NMR (500 MHz, CD_3OD)** δ 7.29 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 1.9 Hz, 1 H), 6.67 (dd, *J* = 2.1, 8.6 Hz, 1 H), 6.40 (dd, *J* = 3.6, 11.6 Hz, 1 H), 5.99 (dd, *J* = 2.3, 11.8 Hz, 1 H), 5.03 (br. s., 1 H), 4.81 (d, *J* = 5.7 Hz, 1 H), 4.43–4.40 (m, 1 H), 4.35 (td, *J* = 3.2, 6.5 Hz, 1 H), 3.80 (s, 3 H), 3.40 (dt, *J* = 4.2, 12.2 Hz, 1 H), 2.84 (dd, *J* = 2.3, 15.3 Hz, 1 H), 2.71–2.64 (m, 1 H); **^{13}C NMR (125 MHz, CD_3OD)** δ 170.7, 157.8, 144.3, 139.4, 129.1, 125.6, 122.6, 119.4, 111.2, 109.7, 96.1, 83.5, 76.4, 58.0, 56.2, 41.0, 21.9; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_4$ 315.1339, found 315.1331.

(1*R*,2*R*,13b*S*)-1,2-dihydroxy-1,2,7,8,13,13b-hexahydro-5*H*-azepino [1',2':1,2]pyrido[3,4-*b*]indol-5-one [(+)-22]: Compound (+)-**22** prepared by the same procedure followed for compound (+)-**6a**.

Data for (+)-**22**: colorless solid; **mp** 209–211 °C; **$[\alpha]_D^{26}$** = + 70.20 (*c* = 1.5, $CHCl_3$).; **IR ν_{max}(film)**: cm^{-1} 3440, 3301, 1590, 1084; **^{1}H NMR (500 MHz, CD_3OD)** δ 7.46 (d, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.11 (t, *J* = 7.4 Hz, 1 H), 7.05–7.00 (m, 1 H), 6.44 (dd, *J* = 3.8, 11.4 Hz, 1 H), 6.02 (d, *J* = 11.8 Hz, 1 H), 5.10 (br. s., 1 H), 4.88 (d, *J* = 5.3 Hz, 1 H), 4.49–4.46 (m, 1 H), 4.41–4.37 (m, 1 H), 3.44 (dt, *J* = 3.8, 12.2 Hz, 1 H), 2.94–2.89 (m, 1 H), 2.78–2.71 (m, 1 H); **^{13}C NMR (125 MHz, CD_3OD)** δ 170.7, 144.4, 138.6, 130.5, 128.1, 125.6, 122.6, 120.0, 118.8, 112.2, 111.2, 83.6, 76.4, 58.0, 41.0, 21.9; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O_3$ 285.1234, found 285.1235.

Ethyl (2*R*,3*S*)-2,3-bis(benzyloxy)-3-((4*S*,5*R*)-5-(7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate [(-)-11a & (+)-11b]: To a solution of aldehyde **10** (2.5 g, 5.653 mmol) in chloroform (40 mL) was added 6-methoxy tryptamine (1.6 g, 8.480 mmol) and Na_2SO_4 (0.8 g, 5.653 mmol) at room temperature. The reaction mixture was refluxed for 12 hours at 70 °C. After 12 h, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude compound was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (60:40) to afford pure product as a red sticky liquid (-)-**11a** and (+)-**11b** (2 g, 57%) with the diastereomeric ratio of 2:1.

Data for (-)-**11a**: red sticky liquid; Yield= 1.33 g; **$[\alpha]_D^{27}$** = – 14.73 (*c* = 0.4, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 2926, 1732, 1148, 1081; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (s, 1 H), 7.49–7.45 (m, 2 H), 7.43–7.28 (m, 8 H), 6.77–6.73 (m, 2 H), 6.28 (d, *J* = 9.2 Hz, 1 H), 5.19 (d, *J* = 11.6 Hz, 1 H),

4.94–4.87 (m, 2 H), 4.35–4.21 (m, 3 H), 4.18–4.05 (m, 2 H), 4.00–3.95 (m, 1 H), 3.88–3.84 (m, 1 H), 3.83 (s, 3 H), 3.32–3.24 (m, 1 H), 2.97 (br. s., 1 H), 2.80–2.65 (m, 3 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.35 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.8, 156.3, 147.0, 136.5, 128.6 (3C), 128.5, 128.5 (2C), 128.5, 128.4, 128.4, 128.3 (3C), 128.2, 123.8, 121.3, 120.9, 118.7, 110.1, 109.1, 108.9, 94.8, 82.8, 74.6, 74.5, 61.5, 55.7, 55.5, 42.6, 27.1, 27.0, 21.5, 14.2; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3060.

Data for (+)-**11b**: red sticky liquid; Yield= 0.66 g; **$[\alpha]_D^{27}$** = + 25.50 (*c* = 0.4, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 2921, 1731, 1213, 1077; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.36 (s, 1 H), 7.38–7.32 (m, 3 H), 7.27–7.13 (m, 7 H), 6.80–6.77 (m, 2 H), 6.23 (d, *J* = 9.1 Hz, 1 H), 5.07 (d, *J* = 10.8 Hz, 1 H), 4.71 (d, *J* = 10.8 Hz, 1 H), 4.64 (dd, *J* = 7.9, 9.2 Hz, 1 H), 4.39–4.37 (m, 1 H), 4.27 (dq, *J* = 1.8, 7.1 Hz, 3 H), 4.18 (dd, *J* = 5.1, 7.9 Hz, 2 H), 3.86 (s, 3 H), 3.85–3.84 (m, 1 H), 3.84–3.81 (m, 1 H), 3.31–3.25 (m, 1 H), 2.91 (ddd, *J* = 4.8, 8.7, 13.0 Hz, 1 H), 2.63–2.57 (m, 1 H), 2.54–2.47 (m, 1 H), 2.12 (br. s., 1 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.35 - 1.31 (m, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.6, 156.3, 146.2, 136.4, 135.8, 130.2, 128.6 (3C), 128.6, 128.6, 128.5, 128.5, 128.5, 128.5, 125.4 (3C), 121.4 (2C), 118.7, 110.7, 109.4, 108.9, 94.7, 81.9, 74.8, 72.3, 61.5, 55.8, 53.7, 42.7, 27.0, 26.4, 22.2, 14.2; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3062.

(3a*S*,4*S*,5*R*,14b*S*,14c*R*)-4,5-bis(benzyloxy)-12-methoxy-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4",5":3',4']azepino [1',2':1,2]pyrido[3,4-*b*]indol-6-one [(+)-12a]: To a solution of compound (-)-**11a** (0.5 g, 0.813 mmol) in EtOH:THF:H_2O (1:1:1) (30 mL) was added LiOH (0.061 g, 2.567 mmol) at 0 °C. The reaction mixture was left at room temperature for 2 hours. After 2 h, The reaction mixture was quenched with 1N HCl (10 mL) and extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with water (10 mL) and brine (10 ml), dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain an intermediate acid **11a-1** (370 mg crude) which was used for further reaction. The above crude compound (0.370 g, 0.631 mmol) was taken in DMF (5 mL) under argon atmosphere at room temperature and added HBTU (0.311 g, 0.820 mmol) followed by Et_3N (0.17 mL, 1.262 mmol) and HOBt (0.017 g, 0.126 mmol) at room temperature. Leave the reaction mixture for the next 12 h of stirring at room temperature. After 12 h, dilute the reaction mixture with ethyl acetate (30 mL) and remove the DMF with ice-cold water. Wash the organic layer with saturated $NaHCO_3$ (10 mL), 1N HCl (10 mL) and brine solution. The solvent was evaporated through reduced pressure and the crude compound was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (70:30) to afford tetracyclic compound (+)-**12a** (0.130 g, 28% over two steps) as a colorless solid.

Data for (+)-**12a**: colorless solid; **mp** 117–119 °C; **$[\alpha]_D^{26}$** = + 24.24 (*c* = 1.5, $CHCl_3$); **IR ν_{max}(film):** cm^{-1} 3361, 2920, 1635, 1083; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.32 (s, 1 H), 7.42 (d, *J* = 8.6 Hz, 1 H), 7.40–7.35 (m, 3 H), 7.35–7.31 (m, 2 H), 7.29 (dd, *J* = 1.8, 4.9 Hz, 3 H), 7.24 (dd, *J* = 2.8, 6.7 Hz, 2 H), 6.90 (d, *J* = 2.0 Hz, 1 H), 6.80 (dd, *J* = 2.3, 8.6 Hz, 1 H), 5.47 (d, *J* = 8.5 Hz, 1 H), 4.98–4.92 (m, 1 H), 4.80 (s, 2 H), 4.69 (d, *J* = 6.4 Hz, 1 H), 4.63 (d, *J* = 11.5 Hz, 1 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.34 (dd, *J* = 2.3, 8.9 Hz, 1 H), 4.27 (dd, *J* = 2.4, 6.4 Hz, 1 H), 4.03 (t, *J* = 8.8 Hz, 1 H), 3.87 (s, 3 H), 3.14–3.07 (m, 1 H), 2.90–2.84 (m, 1 H), 2.79–2.70 (m, 1 H), 1.62 (s, 3 H), 1.45 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** 170.4, 156.6, 138.0, 137.6, 136.4, 128.5 (2C), 128.2 (2C), 128.2, 128.1, 128.0 (2C), 127.5, 127.4 (2C), 120.6, 118.9, 110.8, 109.3, 109.2, 95.0, 83.3, 81.6, 75.5, 73.0, 73.0, 72.0, 55.7, 50.5, 39.8, 27.1, 26.7, 20.7; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2646.

(3a*S*,4S,5*R*,14b*S*,14c*R*)-4,5-bis(benzyloxy)-12-methoxy-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo[4",5":3',4']azepino [1',2':1,2]pyrido[3,4-*b*]indol-6-one [(+)-12b]: Compound (+)-**12b** can be synthesized from (+)-**11b** (0.5 g, 0.813 mmol) by the same procedure followed for compound (+)-**12a**. Purified by column chromatography on silica gel (70:30 petroleum ether/ethyl acetate): (0.130 g, 28% over two steps) as a colorless solid**.**

Data for (+)-**12b**: colorless solid **mp** 122–124 °C; **$[\alpha]_D^{26}$** = + 52.68 (*c* = 2.4, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3338, 2926, 1635, 1087; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84 (s, 1 H), 7.42–7.37 (m, 5 H), 7.37–7.31 (m, 4 H), 7.30– 7.28 (m, 2 H), 6.88 (d, *J* = 2.3 Hz, 1 H), 6.80 (dd, *J* = 2.1, 8.6 Hz, 1 H), 5.22 (d, *J* = 6.5 Hz, 1 H), 4.94 (d, *J* = 11.1 Hz, 1 H), 4.86 (d, *J* = 12.2 Hz, 1 H), 4.78 (d, *J* = 11.1 Hz, 1 H), 4.76–4.71 (m, 1 H), 4.57 (dd, *J* = 6.5, 8.8 Hz, 1 H), 4.43–4.35 (m, 2 H), 4.23 (dd, *J* = 3.4, 6.1 Hz, 1 H), 3.86 (s, 3 H), 3.75 (dd, *J* = 3.4, 9.2 Hz, 1 H), 3.28–3.21 (m, 1 H), 2.95–2.89 (m, 1 H), 2.81–2.73 (m, 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.9, 157.0, 141.2, 138.1, 137.6, 137.3, 128.2 (2C), 128.2 (2C), 128.1 (2C), 128.0 (2C), 127.6, 127.6, 125.5, 120.8, 119.0, 117.0, 109.9, 109.1, 105.9, 94.7, 87.0, 82.6, 76.4, 75.5, 72.9, 55.7, 41.8, 27.3, 26.1, 21.7; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2646.

(3a*S*,4*S*,5*R*,14b*S*,14c*R*)-4,5-bis(benzyloxy)-2,2-dimethyl-3a,4,5,8,9,14, 14b,14c-octahydro-6*H*-[1,3]dioxolo[4",5":3',4']azepino[1',2':1,2] pyrido[3,4-*b*]indol-6-one [(+)-23a]: Compound (+)-**23a** was prepared by the same procedure followed for compound (+)-**12a**.

Data for (+)-**23a**: colorless solid; **mp** 154–156 °C; **$[\alpha]_D^{26}$** = + 2.19 (*c* = 0.5, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3319, 2907, 1650, 1078; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.37 (br. s., 1 H), 7.53 (d, *J* = 7.3 Hz, 1 H), 7.44–7.29 (m, 6 H), 7.23 (d, *J* = 7.3 Hz, 1 H), 7.18–7.09 (m, 2 H), 6.97 (t, *J* = 7.0 Hz, 2 H), 6.90 (d, *J* = 6.7 Hz, 2 H), 4.87–4.74 (m, 3 H), 4.52– 4.47 (m, 2 H), 4.41 (d, *J* = 4.9 Hz, 1 H), 4.31 (d, *J* = 11.0 Hz, 1 H), 4.18 (t, *J* = 8.2 Hz, 1 H), 3.93–3.85 (m, 1 H), 3.81 (br. s., 1 H), 3.50 (s, 1 H), 3.01–2.90 (m, 1 H), 2.82 (d, *J* = 15.3 Hz, 1 H), 1.57 (br. s., 3 H), 1.51 (br. s., 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.9, 137.8, 136.6, 136.2, 130.8, 128.3 (2C), 128.2 (2C), 128.2 (2C), 127.9 (2C), 127.8, 127.6, 126.4, 122.3, 119.7, 118.5, 111.2 (2C), 110.0, 82.8, 81.9, 78.8, 74.8, 72.9, 72.3, 57.7, 43.2, 27.3, 27.0, 21.4; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{33}H_{35}N_2O_5$ 539.2540, found 539.2542.

(3a*S*,4*S*,5*R*,14b*R*,14c*R*)-4,5-bis(benzyloxy)-2,2-dimethyl-3a,4,5,8,9,14, 14b,14c-octahydro-6*H*-[1,3]dioxolo[4",5":3',4']azepino[1',2':1,2] pyrido[3,4-*b*]indol-6-one [(+)-23b]: Compound (+)-**23b** was prepared by the same procedure followed for compound (+)-**12a**.

Data for (+)-**23b**: colorless solid **mp** 160–163 °C; **$[\alpha]_D^{26}$** = + 1.26 (*c* = 0.8, $CHCl_3$).; **IR ν_{max}(film)**: cm^{-1} 3302, 2911, 1650, 1077; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.08 (br. s., 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 6.9 Hz, 2 H), 7.37 (dd, *J* = 6.1, 8.0 Hz, 5 H), 7.34–7.32 (m, 1 H), 7.32–7.27 (m, 3 H), 7.23–7.19 (m, 1 H), 7.16–7.12 (m, 1 H), 5.25 (d, *J* = 6.1 Hz, 1 H), 4.94 (d, *J* = 11.4 Hz, 1 H), 4.87 (d, *J* = 11.8 Hz, 1 H), 4.78 (d, *J* = 11.4 Hz, 1 H), 4.77–4.72 (m, 1 H), 4.61 (dd, *J* = 6.5, 8.8 Hz, 1 H), 4.43–4.37 (m, 2 H), 4.24 (dd, *J* = 3.2, 6.3 Hz, 1 H), 3.75 (dd, *J* = 3.4, 8.8 Hz, 1 H), 3.29–3.22 (m, 1 H), 2.96 (td, *J* = 3.5, 15.5 Hz, 1 H), 2.80 (ddt, *J* = 3.4, 5.1, 10.4 Hz, 1 H), 1.48 (s, 3 H), 1.35 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.9, 138.3, 137.3, 136.9, 128.4 (2C), 128.3 (2C), 128.2, 128.0 (2C), 127.9 (2C), 127.8, 127.8, 127.7, 126.3, 122.4, 119.7, 118.3, 111.6, 111.2, 111.1, 81.2, 78.0, 74.9, 73.8, 72.4, 51.2, 41.3, 26.8, 26.6, 20.7; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{33}H_{35}N_2O_5$ 539.2540, found 539.2539.

Ethyl (2*S*,3*S*)-2,3-bis(benzyloxy)-3-((4*S*,5*R*)-5-(7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate [(-)-16a & (+)-16b]: To a solution of aldehyde **15** (1 g, 2.261 mmol) in chloroform (40 mL) was added 6-methoxy tryptamine (0.644 g, 3.392 mmol) and Na_2SO_4 (0.32 g, 2.261 mmol) at room temperature. The reaction mixture was refluxed for 12 hours at 70 °C. After 12 h, the reaction mixture was

cooled to room temperature and the solvent was evaporated under reduced pressure. The crude compound was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (60:40) to afford pure product as a red sticky liquid (-)-**16a** and (+)-**16b** as diastereomeric mixture (0.77 g, 55%) with the diastereomeric ratio of 2:1.

Data for (-)-**16a**: red sticky liquid; Yield= 0.512 g; $[\alpha]_D^{27}$ = – 10.63 (*c* = 2.2, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 2927, 1733, 1453, 1094; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (s, 1 H), 7.41–7.34 (m, 3 H), 7.34–7.28 (m, 8 H), 6.82 (d, *J* = 2.1 Hz, 1 H), 6.76 (dd, *J* = 2.3, 8.5 Hz, 1 H), 4.78 (dd, *J* = 11.4, 15.8 Hz, 2 H), 4.57– 4.47 (m, 4 H), 4.25–4.15 (m, 3 H), 4.04 (d, *J* = 8.8 Hz, 1 H), 3.96 (dd, *J* = 3.5, 7.0 Hz, 1 H), 3.85 (s, 3 H), 3.09 (td, *J* = 4.5, 12.5 Hz, 1 H), 2.77 (ddd, *J* = 5.3, 8.0, 12.8 Hz, 1 H), 2.65–2.51 (m, 2 H), 1.98 (br. s., 1 H), 1.53 (s, 3 H), 1.40 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.3, 156.2, 137.4, 137.2, 136.4, 132.9, 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.9, 127.8, 121.6, 118.6, 109.8, 109.5, 108.7, 94.9, 81.8, 81.5, 78.6, 78.2, 73.5, 72.7, 61.0, 55.8, 55.7, 42.4, 27.7, 27.4, 22.5, 14.2; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3051.

Data for (+)-**16b**: red sticky liquid; Yield= 0.256 g; $[\alpha]_D^{27}$ = + 27.42 (*c* = 2.2, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 2919, 1735, 1457, 1091; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (s, 1 H), 7.39–7.33 (m, 3 H), 7.33–7.30 (m, 6 H), 7.28 (d, *J* = 2.9 Hz, 2 H), 6.72 (dd, *J* = 2.3, 8.6 Hz, 1 H), 6.58 (d, *J* = 2.1 Hz, 1 H), 4.86 (d, *J* = 11.1 Hz, 2 H), 4.52 (d, *J* = 10.6 Hz, 1 H), 4.48–4.44 (m, 2 H), 4.36–4.30 (m, 2 H), 4.25–4.19 (m, 1 H), 4.13–4.07 (m, 2 H), 3.94 (dd, *J* = 1.6, 8.9 Hz, 1 H), 3.81 (s, 3 H), 3.06–2.99 (m, 1 H), 2.78 (ddd, *J* = 4.3, 10.6, 12.9 Hz, 1 H), 2.59–2.53 (m, 1 H), 2.44 (dtd, *J* = 2.4, 5.1, 7.8 Hz, 1 H), 1.55 (s, 3 H), 1.32 (s, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.8, 156.1, 137.4, 136.8, 136.4, 131.4, 128.8 (2C), 128.4 (2C), 128.4 (2C), 128.1, 127.9 (2C), 127.8, 121.7, 118.4, 110.5, 109.2, 108.7, 94.8, 82.4, 81.9, 78.5, 76.1, 73.5, 72.7, 61.0, 55.7, 54.0, 42.9, 27.7, 26.4, 22.6, 13.9; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{36}H_{43}N_2O_7$ 615.3065, found 615.3065.

(3a*S*,4*S*,5*S*,14b*S*,14c*R*)-4,5-bis(benzyloxy)-12-methoxy-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo [4'',5'':3',4']azepino[1',2':1,2]pyrido[3,4-*b*]indol-6-one [(+)-17a]: To a solution of compound, (-)-**16a** (0.5 g, 0.813 mmol) in EtOH:THF:H_2O (1:1:1) (30 mL) was added LiOH (0.061 g, 2.567 mmol) at 0 °C. The reaction mixture was left at room temperature for 2 hours. After 2 h, The reaction mixture was quenched with 1N HCl (10 mL) and extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with water (10 mL) and brine (10 ml), dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain an intermediate acid **16a-1** (360 mg crude), which was used as such for further reaction. The above crude compound (0.360 g, 0.614 mmol) was taken in DMF (5 mL) under argon atmosphere at room temperature and added HATU (0.30 g, 0.792 mmol) followed by DIPEA (0.14 mL, 0.729 mmol) at room temperature. Leave the reaction mixture for the next 12 hours of stirring at room temperature. After 12 h, dilute the reaction mixture with ethyl acetate (30 mL) and remove the DMF with ice-cold water. Wash the organic layer with saturated $NaHCO_3$ (10 mL), 1N HCl (10 mL) and brine. The solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography on silica gel (70:30 petroleum ether/ethyl acetate) to afford tetracyclic compound (+)-**17a** (0.150 g, 32% over two steps) as a colorless solid.

Data for (+)-**17a**: colorless solid; **mp** 180–182 °C; $[\alpha]_D^{26}$ = + 94.44 (*c* = 2.4, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3313, 2926, 1156, 1087; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.22 (s, 1 H), 7.42–7.38 (m, 5 H), 7.37 (s, 1 H), 7.36–7.28 (m, 4 H), 7.28–7.23 (m, 1 H), 6.90 (d, *J* = 2.1 Hz, 1 H), 6.81 (dd, *J* = 2.1, 8.6 Hz, 1 H), 5.22–5.15 (m, 1 H), 5.07 (d, *J* = 12.4 Hz, 1 H), 4.96 (d, *J* = 12.0 Hz, 1 H), 4.83 (d, *J* = 12.4 Hz, 1 H), 4.73 (d, *J* = 8.8 Hz, 1 H), 4.43–4.37 (m, 3 H), 4.00 (t, *J* = 8.8 Hz, 1 H), 3.87 (s, 3 H), 3.81 (dd, *J* = 2.1, 8.9 Hz, 1 H), 3.03 (dt, *J* = 3.9, 12.1 Hz, 1 H), 2.90–2.77 (m, 2 H), 1.60 (s, 3 H), 1.43 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 168.9, 156.8, 138.6, 137.8, 137.6, 128.4 (2C), 128.0 (2C), 127.7 (3C), 127.4 (2C), 127.2, 127.2, 120.5, 119.0, 111.6, 110.2, 109.4, 95.0, 83.6, 79.3, 76.6, 74.8, 73.1, 72.1, 55.7, 51.5, 39.4, 27.0, 26.4, 20.8; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2646.

(3a*S*,4*S*,5*S*,14b*R*,14c*R*)-4,5-bis(benzyloxy)-12-methoxy-2,2-dimethyl-3a,4,5,8,9,14,14b,14c-octahydro-6*H*-[1,3]dioxolo [4'',5'':3',4']azepino[1',2':1,2]pyrido[3,4-*b*]indol-6-one[(+)-17b]: Compound (+)-**17b** can be synthesized from (+)-**16b** (0.5 g, 0.813 mmol) by the same procedure followed for compound (+)-**17a**. Purified by column chromatography on silica gel (70:30 petroleum ether/ethyl acetate): (0.150 g, 32% over two steps) as a colorless solid.

Data for (+)-**17b**: colorless solid; **mp** 185–187 °C; $[\alpha]_D^{26}$ = + 109.91 (*c* = 2.4, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3327, 2924, 1155, 1085; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.37 (s, 1 H), 7.38 (d, *J* = 8.6 Hz, 1 H), 7.3 – 7.32 (m, 4 H), 7.32–7.30 (m, 4 H), 7.29 (dd, *J* = 1.7, 2.7 Hz, 2 H), 6.85 (d, *J* = 2.1 Hz, 1 H), 6.79 (dd, *J* = 2.3, 8.6 Hz, 1 H), 5.64 (d, *J* = 5.9 Hz, 1 H), 5.25 (dd, *J* = 6.0, 9.4 Hz, 1 H), 4.82–4.76 (m, 1 H), 4.74–4.68 (m, 2 H), 4.55 (d, *J* = 11.9 Hz, 1 H), 4.34 (d, *J* = 5.4 Hz, 1 H), 4.22–4.14 (m, 2 H), 3.86 (s, 3 H), 3.85–3.81 (m, 1 H), 3.60 (ddd, *J* = 4.3, 8.5, 12.7 Hz, 1 H), 2.96 (dddd, *J* = 1.9, 4.6, 8.6, 15.5 Hz, 1 H), 2.73–2.63 (m, 1 H), 1.53 (s, 3 H), 1.46 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 171.3, 156.6, 138.1, 137.1, 136.8, 128.5, 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.2, 128.0, 127.8, 127.5 (2C), 120.9, 118.8, 111.7, 110.7, 109.3, 94.9, 81.8, 73.9, 73.2, 73.1, 71.7, 55.7, 54.0, 45.2, 26.9, 26.4, 21.0; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{34}H_{37}N_2O_6$ 569.2646, found 569.2640.

(1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-bis(benzyloxy)-1,2-dihydroxy-11-methoxy-1,2,3,4,7,8,13,13b-octahydro-5*H*-azepino[1',2':1,2] pyrido[3,4-*b*]indol-5-one (18): To a compound **17b** (100 mg, 0.175 mmol) was added AcOH: H_2O (4:1) (15 mL) solution and the reaction mixture was stirred at 45 °C for 3 hours. After completion of the reaction, the reaction mixture was dried under the vacuum to give the solid residue. The solid residue was dissolved in ethyl acetate (20 mL), quenched the reaction mixture with a saturated solution of $NaHCO_3$ (10 mL), and extracted with ethyl acetate (2 X

10 mL). The combined organic layer was dried over anhydrous sodium sulphate, concentrated and the crude compound was purified by column chromatography (silica gel) (50:50 petroleum ether/ethyl acetate) to afford di-hydroxy tetracyclic compound **18** (70 mg, 78%) as a colorless solid.

Data for **18**: a colorless solid; yield= 70 mg; **mp** 207–210 °C; **IR ν_{max}(film):** 3325, 2924, 1627, 1082; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.47 (br. s., 1 H), 7.45–7.41 (m, 2 H), 7.40–7.37 (m, 2 H), 7.36–7.30 (m, 7 H), 6.86–6.82 (m, 1 H), 6.78 (dd, *J* = 2.3, 8.6 Hz, 1 H), 5.16–5.09 (m, 2 H), 4.99 (d, *J* = 11.8 Hz, 1 H), 4.61 (d, *J* = 11.3 Hz, 1 H), 4.59–4.52 (m, 2 H), 4.39 (d, *J* = 11.9 Hz, 1 H), 4.13 (d, *J* = 3.3 Hz, 1 H), 3.82 (s, 3 H), 3.66 (t, *J* = 9.0 Hz, 1 H), 3.54–3.46 (m, 1 H), 3.00–2.92 (m, 1 H), 2.84–2.75 (m, 2 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.9, 156.7, 137.7, 137.7, 137.5, 128.7 (2C), 128.5 (2C), 128.4 (2C), 128.0, 127.8, 127.7 (2C), 127.5, 120.5, 119.0, 111.6, 109.1, 94.9, 80.2, 78.1, 77.1, 74.0, 72.4, 71.8, 55.6, 52.3, 38.4, 20.9; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{31}H_{33}N_2O_6$ 529.2333, found 529.2327.

(2*R*,3*R*,4*S*,5*R*)-2-((benzoyloxy)methyl)-6-(((1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-bis(benzyloxy)-2-hydroxy-11-methoxy-5-oxo-2,3,4,5,7,8, 13,13b-octahydro-1*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-1-yl)oxy) tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate [(+)-20b]: To a solution of di-hydroxy tetracyclic compound **18** (70 mg, 0.132 mmol) in CH_2Cl_2 at room temperature was added compound **19** (118 mg, 0.159 mmol) followed by a small quantity of molecular sieves (5 Aº). After stirring the reaction mixture for 5 min, [Tris(2,4-di-tert-butylphenyl)phosphite]gold chloride (17 mg, 0.019 mmol) and silver trifluoromethanesulfonate (3 mg, 0.019 mmol) were added and the reaction mixture was stirred for 2 hours at room temperature. After 2 h the reaction mixture was filtered through a short pad of celite and washed with CH_2Cl_2 (10 mL). The combined organic solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (60:40) to afford a pure product as a yellow liquid (+)-**20a** and (+)-**20b** as regioisomeric mixture (70 mg, 67%), with the ratio (1:1).

Data for (+)-**20b**: yellow liquid; yield= 35 mg; **$[\alpha]_D^{26}$** = + 7.34 (*c* = 1.0, $CHCl_3$); **IR ν_{max}(film):** cm^{-1} 3422, 2954, 1725, 1262, 1093; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.03 (dd, *J* = 1.3, 8.4 Hz, 2 H), 7.91 (dd, *J* = 1.3, 8.3 Hz, 2 H), 7.66–7.61 (m, 3 H), 7.51–7.46 (m, 4 H), 7.35–7.32 (m, 3 H), 7.32–7.27 (m, 5 H), 7.26–7.24 (m, 6 H), 7.23–7.22 (m, 2 H), 7.11–7.06 (m, 2 H), 6.87 (t, *J* = 7.8 Hz, 2 H), 6.63–6.58 (m, 2 H), 5.98 (s, 1 H), 5.33 (dd, *J* = 1.3, 3.0 Hz, 1 H), 5.29–5.23 (m, 2 H), 4.87 (dd, *J* = 4.3, 13.1 Hz, 1 H), 4.70 (s, 1 H), 4.69–4.65 (m, 1 H), 4.63–4.58 (m, 2 H), 4.45–4.39 (m, 2 H), 4.24 (dd, *J* = 5.3, 12.1 Hz, 1 H), 4.16–4.12 (m, 1 H), 4.09–4.03 (m, 2 H), 3.99–3.96 (m, 1 H), 3.84 (s, 3 H), 3.80 (dt, *J* = 2.4, 5.5 Hz, 1 H), 3.68–3.66 (m, 1 H), 3.37 (dt, *J* = 4.1, 12.4 Hz, 1 H), 2.83 (dd, *J* = 2.8, 15.6 Hz, 1 H), 2.68–2.58 (m, 1 H), 1.64 (br. s., 1 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.8, 165.8, 164.8, 164.0, 156.5, 137.1, 137.0, 135.9, 134.3, 133.6, 133.3, 133.0, 130.0 (2C), 129.7 (2C), 129.6 (2C), 129.5, 128.9, 128.8, 128.5 (3C), 128.4 (3C), 128.4 (2C), 128.3, 128.2, 128.2 (2C), 128.2 (3C), 128.1 (3C), 128.1 (2C), 128.1, 127.7, 127.6, 125.6, 121.7, 120.7, 118.5, 110.8, 109.2, 97.3, 94.9, 86.4, 74.0, 73.6, 72.1, 71.8, 70.4, 68.3, 67.7, 63.9, 55.7, 47.6, 40.6, 20.1; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{65}H_{59}N_2O_{15}$ 1107.3910, found 1107.3922.

(2*R*,3*R*,4*S*,5*R*)-2-((benzoyloxy)methyl)-6-(((1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-bis(benzyloxy)-1-hydroxy-11-methoxy-5-oxo-2,3,4,5,7,8, 13,13b-octahydro-1*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-2-yl)oxy) tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate [(+)-20a]: Data for (+)-**20a**: yellow liquid; yield= 35 mg; **$[\alpha]_D^{26}$** = + 4.50 (*c* = 1.5, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3423, 2956, 1726, 1261, 1091; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.66 (br. s., 1 H), 7.98 (d, *J* = 7.3 Hz, 4 H), 7.87 (d, *J* = 7.5 Hz, 2 H), 7.83 (dd, *J* = 1.1, 8.3 Hz, 2 H), 7.58–7.54 (m, 1 H), 7.50–7.46 (m, 1 H), 7.43–7.36 (m, 5 H), 7.34–7.27 (m, 4 H), 7.27–7.21 (m, 5 H), 7.18 (d, *J* = 7.8 Hz, 3 H), 7.16–7.12 (m, 2 H), 7.10–7.05 (m, 2 H), 7.00 (br. s., 1 H), 6.81 (dd, *J* = 2.2, 8.6 Hz, 1 H), 6.14 (br. s., 1 H), 5.97–5.92 (m, 1 H), 5.91–5.79 (m, 1 H), 5.62–5.58 (m, 1 H), 4.70 (dd, *J* = 2.6, 12.3 Hz, 1 H), 4.64–4.58 (m, 1 H), 4.50–4.36 (m, 4 H), 4.36–4.16 (m, 4 H), 4.16–4.02 (m, 2 H), 3.85 (s, 3 H), 3.79 (d, *J* = 5.3 Hz, 1 H), 3.24–3.15 (m, 1 H), 2.78–2.71 (m, 1 H), 2.64–2.54 (m, 1 H), 1.70 (br. s., 1 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.2, 166.2, 165.7, 165.4, 156.4, 137.7, 137.6, 137.0, 133.6, 133.2, 133.2, 129.8 (3C), 129.7 (3C), 129.7 (4C), 129.6 (3C), 129.3, 129.1, 128.7, 128.4 (3C), 128.4 (4C), 128.3 (3C), 128.2 (3C), 128.1(3C), 128.0 (4C), 127.7, 127.6, 127.5, 121.1, 118.5, 110.2, 109.2, 95.1, 75.9, 72.8, 72.4, 72.1, 69.5, 62.6, 55.6 (2C), 40.5, 20.2; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{65}H_{59}N_2O_{15}$ 1107.3910, found 1107.3915.

(1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-bis(benzyloxy)-2-hydroxy-11-methoxy-1-(((3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2*H*-pyran-2-yl)oxy)-1,2,3,4,7,8,13,13b-octahydro-5*H*-azepino [1',2':1,2]pyrido[3,4-*b*]indol-5-one [(+)-21b]: To a solution of compound (+)-**20b** (0.1 g, 0.090 mmol) in methanol (5 mL) at room temperature was added sodium methoxide (0.055 g, 1.084 mmol). The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was evaporated in vacuum and the crude compound was purified by column chromatography on silica gel (90:10 Dichloromethane/Methanol) to afford pentahydroxy compound (+)-**21b** (30 mg, 48%) as a colorless solid.

Data for **(+)-21b**: colorless solid; **$[\alpha]_D^{26}$** = + 24.82 (*c* = 1.0, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3368, 2910, 1627, 1075; **^{1}H NMR (400 MHz, acetone d_6)** δ 9.86 (s, 1 H), 7.41–7.39 (m, 3 H), 7.38–7.35 (m, 1 H), 7.33 (d, *J* = 1.4 Hz, 1 H), 7.31 (dd, *J* = 0.9, 3.4 Hz, 1 H), 7.24–7.22 (m, 2 H), 7.16–7.12 (m, 1 H), 7.02 (t, *J* = 7.6 Hz, 2 H), 6.87 (d, *J* = 2.1 Hz, 1 H), 6.73 (dd, *J* = 2.3, 8.6 Hz, 1 H), 6.16 (s, 1 H), 5.64 - 5.59 (m, 1 H), 4.84–4.78 (m, 1 H), 4.72–4.68 (m, 1 H), 4.65 (s, 1 H), 4.63–4.59 (m, 2 H), 4.30 (d, *J* = 4.5 Hz, 1 H), 4.22–4.16 (m, 1 H), 4.05 (dd, *J* = 3.7, 5.3 Hz, 1 H), 4.02–3.98 (m, 1 H), 3.87 (d, *J* = 4.6 Hz, 1 H), 3.82 (s, 3 H), 3.77 (dd, *J* = 1.6, 3.3 Hz, 1 H), 3.62–3.54 (m, 2 H), 3.53–3.47 (m, 2 H), 3.42–3.36 (m, 1 H), 3.32–3.23 (m, 2 H), 2.87–2.83 (m, 3 H), 2.82–2.80 (m, 1 H), 2.65–2.55 (m, 1 H); **^{13}C NMR (125 MHz, acetone d_6)** δ 169.4,

157.3, 139.1, 138.8, 138.2, 138.2, 130.4, 129.8, 129.3, 129.2, 128.9, 128.8, 128.6, 128.6, 126.7, 122.0, 121.3, 119.2, 110.6, 109.5, 99.0, 95.9, 87.8, 79.0, 77.3, 74.7, 74.5, 74.0, 73.9, 73.7, 71.4, 70.4, 62.9, 55.8, 48.9, 41.1, 21.0; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{37}H_{43}N_2O_{11}$ 691.2861, found 691.2855.

(1*R*,2*S*,3*S*,4*S*,13b*R*)-3,4-bis(benzyloxy)-1-hydroxy-11-methoxy-2-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2*H*-pyran-2-yl)oxy)-1,2,3,4,7,8,13,13b-octahydro-5*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-5-one [(+)-21a]: Compound (+)-**21a** can be synthesized from (+)-**20a** (0.1 g, 0.090 mmol) by the same procedure followed for compound (+)-**21b**. Purified by column chromatography on silica gel (90:10 Dichloromethane/Methanol): (30 mg, 48%) as a colorless solid;

Data for (+)-**21a**: colorless solid; $[\alpha]_D^{26}$ = + 18.99 (*c* = 1.0, $CHCl_3$); **IR ν_{max}(film)**: cm^{-1} 3383, 2960, 1627, 1077; **^{1}H NMR (500 MHz, acetone d_6)** δ 9.59 (br. s., 1 H), 7.45 (d, *J* = 6.9 Hz, 2 H), 7.39 (d, *J* = 7.2 Hz, 2 H), 7.38─7.34 (m, 2 H), 7.32─7.27 (m, 2 H), 7.26─7.22 (m, 2 H), 7.20 (d, *J* = 6.9 Hz, 1 H), 7.07 (s, 1 H), 6.67 (dd, *J* = 2.3, 8.4 Hz, 1 H), 6.33 (br. s., 1 H), 4.86 (d, *J* = 12.2 Hz, 1 H), 4.83─4.80 (m, 1 H), 4.79─4.73 (m, 1 H), 4.72─4.68 (m, 4 H), 4.64 (s, 1 H), 4.43 (br. s., 1 H), 4.33 (dd, *J* = 4.2, 10.3 Hz, 1 H), 4.20─4.14 (m, 1 H), 4.02 (br. s., 1 H), 3.93─3.88 (m, 1 H), 3.76 (s, 3 H), 3.58─3.55 (m, 1 H), 3.53─3.48 (m, 1 H), 3.42─3.34 (m, 2 H), 3.19 (dt, *J* = 3.8, 12.4 Hz, 1 H), 2.87 (s, 3 H), 2.83 (s, 1 H), 2.77─2.71 (m, 1 H), 2.61─2.54 (m, 1 H); **^{13}C NMR (125 MHz, acetone d_6)** δ 170.2, 157.1, 139.5, 139.4, 138.9, 131.5, 129.3 (2C), 129.0 (2C), 128.6 (2C), 128.5 (2C), 128.5, 128.2, 122.1, 118.8, 110.1, 109.3, 107.1, 96.5, 86.2, 85.8, 78.0, 77.5, 76.3, 75.8, 74.6, 73.5, 72.1, 71.6, 62.9, 55.8, 49.9, 41.1, 21.1; **HRMS (ESI) *m/z***: $[M+H]^+$ Calcd for $C_{37}H_{43}N_2O_{11}$ 691.2861, found 691.2858.

CCDC/CSD: 2111021 (for (+)-**12b**), 2111020 (for (+)-**17b**), 2111023 (for (+)-**21a**), 2111019 (for (+)-**22**), 2111022 (for (+)-**23a**)

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Keywords: Au-catalyst • Multiple steps total synthesis • Natural products • Pictet-Spengler reaction • Wittig reaction

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Layout 2:

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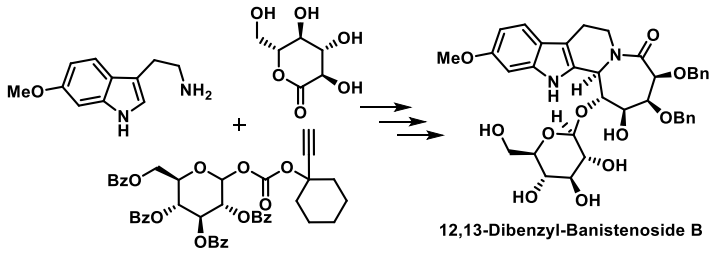

Key building blocks

Key Topic*

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Total Synthesis of 12,13-Dibenzyl-Banistenoside B and Analogs

Herein, we report the total synthesis of dibenzyl derivative of Banistenoside B. The key steps involve construction of 6.5.6.7 tetracyclic core using Pictet-Spengler reaction and intramolecular amide coupling. The stereochemistry of important compounds was confirmed by X-ray crystallography.

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