Cyclic Anhydrides and Imides to Indole Based Novel Natural and Unnatural Products

by

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Under the supervision of

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Certificate

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Date: 01/06/2021

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Name: Dr. Narshinha P. Argade

Date: 01/06/2021

Place: Pune

Dedicated to

My Parents and Teachers

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CONTENTS

Research is a never-ending process involving a team of persons striving to attain newer horizons in the sciences. This thesis would not have been completed without the encouragement and co-operation of my parents, teachers, relatives, friends and all well-wishers. I take this opportunity to express my deep gratitude to one and all.

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…Santosh

ABBREVATIONS

Ac_2O	Acetic anhydride
AcOH	Acetic acid
AcCl	Acetyl chloride
AIBN	Azobisisobutyronitrile
$AlCl_3$	Aluminium chloride
$AlMe_3$	Trimethylaluminium
AlH_3	Aluminium hydride/Alane
AllylMgCl	Allylmagnesium chloride
AllylBr	Allyl bromide
BBr_3	Boron tribromide
BnBr	Benzyl bromide
n-BuLi	*n*-Butyllithium
n-Bu_3SnH	Tributyltin hydride
t-BuOH	*tert*-Butyl alcohol
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
$CeCl_3 \cdot 7H_2O$	Cerium(III) chloride heptahydrate
Cs_2CO_3	Cesium carbonate
CH_2O	Formaldehyde
HCO_2H	Formic acid
CH_3CHO	Acetaldehyde
CH_3CN	Acetonitrile
$CHCl_3$	Chloroform
$COCl_2$	Phosgene
CuI	Copper(I) iodide
CuBr	Copper(I) bromide
CuCN	Copper(I) cyanide
$Cu(OAc)_2$	Cupric acetate
$ClCO_2Et$	Ethyl chloroformate
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DABCO	1,4-Diazabicyclo(2.2.2)octane
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMA	Dimethylacetamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulphoxide
DMF	*N*,*N*-Dimethylformamide
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DIPEA	*N*,*N*-Diisopropylethylamine
DIBAL-H	Diisobutylaluminium hydride
DEPT	Distortionless enhancement by polarization transfer
2 D NMR	Two-dimensional nuclear magnetic resonance spectroscopy
dr	*Diastereomeric ratio*
CH_2N_2	Diazomethane
Et_2O	Diethyl ether

DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzo-quinone
ee	*Enantiomeric excess*
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDTA	Ethylenediaminetetraacetic acid
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethyl acetate
Et_3N	Triethylamine
$FeCl_3$	Iron(III) chloride
g	Grams
h	Hours
HOBt	Hydroxybenzotriazole
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HCl	Hydrochloric acid
IR	Infra-red
MeI	Iodomethane
IBX	2-Iodoxybenzoic acid
K_3PO_4	Tripotassium posphate
K_2CO_3	Potassium carbonate
$KMnO_4$	Potassium permanganate
LiHMDS	Lithium hexamethyldisilazide
$LiBH(Et)_3$	Lithium triethylborohydride
LDA	Lithium diisopropylamide
$LiAlH_4$	Lithium aluminium hydride
LiOH	Lithium hydroxide
$LiBH_4$	Lithium borohydride
LiBr	Lithium bromide
m-CPBA	*meta*-Chloroperoxybenzoic acid
M+	Molecular ion
Me	Methyl
MeMgI	Methylmagnesium iodide
MeMgCl	Methylmagnesium chloride
MeOH	Methanol
MOMCl	Methoxymethyl chloride
MEMCl	2-Methoxyethoxymethyl chloride
Min	Minute
Mg	Magnesium
mg	Miligram
mL	Milliliter
Mp	Melting point
MS	Molecular sieves
MsCl	Methanesulfonyl chloride
AgOTf	Silver trifluoromethanesulfonate
NaH	Sodium hydride
NaI	Sodium iodide

NaCl	Sodium chloride
NaOH	Sodium hydroxide
$NaIO_4$	Sodium periodate
$NaBH_3CN$	Sodium cyanoborohydride
$NaNO_2$	Sodium nitrite
NH_4Cl	Ammonium chloride
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
NaHMDS	Sodium hexamethyldisilazide
N-Selectride	Sodium *tri-sec*-butylborohydride
$NaBH_4$	Sodium borohydride
$NaBH_3CN$	Sodium cyanoborohydride
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
NaOMe	Sodium methoxide
NMO	*N*-Methylmorpholine *N*-oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
OsO_4	Osmium tetroxide
$(COCl)_2$	Oxalyl chloride
ORTEP	Oak ridge thermal-ellipsoid plot
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromate
KCN	Potassium cyanide
KOH	Potassium hydroxide
KBH_4	Potassiumborohydride
K-Selectride	Potassium *tri-sec*-butylborohydride
t-BuOK	Potassium *tert*-butoxide
Ph	Phenyl
PPh_3	Triphenylphosphine
n-Bu_3P	Tributylphosphine
$P(OEt)_3$	Triethyl phosphite
PCC	Pyridinium chlorochromate
$PdCl_2$	Palladium(II) chloride
$Pd(OAc)_2$	Palladium(II) acetate
PivCl	Pivaloyl chloride
PhSeCl	Benzeneselenenyl chloride
$POCl_3$	Phosphoryl chloride
CH_3COCO_2H	Pyruvic acid
CH_3COCO_2Me	Methyl pyruvate
CH_3COCO_2Et	Ethyl pyruvate
Py	Pyridine
P_2O_5	Phosphorus pentoxide
Rf	Retention factor
SmI_2	Samarium(II) iodide
$SOCl_2$	Thionyl chloride
H_2SO_4	Sulfuric acid
SeO_2	Selenium dioxide
$AgSbF_6$	Silver hexafluoroantimonate(V)

Ag_2O	Silver oxide
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulfate
TBAF	*Tetra-n*-butylammonium fluoride
Et_3SiH	Triethylsilane
TBSCl	*tert*-Butyldimethylsilyl chloride
TMEDA	Tetramethylethylenediamine
TBAS	Tetrabutylammonium hydrogensulfate
TBHP	*tert*-Butyl hydroperoxide
TsCl	4-Toluenesulfonyl chloride
Ts	Tosyl
p-TSA	*p*-Toluenesulfonic acid
$TsNHNH_2$	*p*-Toluenesulfonhydrazide
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TMSCl	Trimethylsilyl chloride
TPAP	Tetrapropylammonium perruthenate
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TOFMS	Time-of-flight mass spectrometer
Zn	Zinc
$ZnCl_2$	Zinc chloride

GENERAL REMARKS

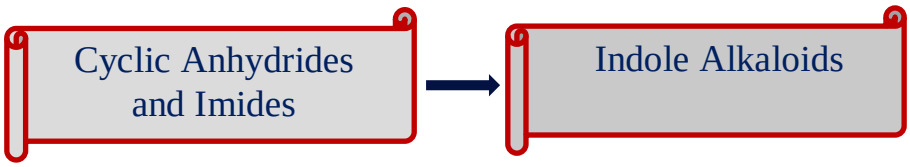
1. All solvents were distilled and dried before use
2. Petroleum ether refers to the fraction collected in the boiling range 60–80 °C
3. Organic layers after every extraction were dried over anhydrous sodium sulfate
4. Column Chromatographic purifications were performed over silica gel (60–120 & 230–400 mesh)
5. TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol), phosphomolybdic acid (in ethanol) and ninhydrin (in ethanol)
6. IR Spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}
7. ^{1}H and ^{13}CNMR and DEPT spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 400 MHz, 500 MHz and JEOL ECX 400 instruments using TMS or solvent residue as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet and dq = doublet of quartet
8. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump
9. Single crystal X-ray data were collected on D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer and Super Nova source X-ray Diffractometer
10. All melting points are uncorrected and the temperatures are in centigrade scale
11. The compound, scheme, figure, table and reference numbers given in each chapter/section refers to that particular chapter/section only

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. Santosh Vasantrao Shelar
Degree Enrollment No. &Date	Ph. D. in Chemical Sciences (10CC14A26004); August 2014
Title of the Thesis	Cyclic Anhydrides and Imides to Indole Based Novel Natural and Unnatural Products
Research Supervisor	Dr. Narshinha P. Argade

1. Introduction

Indole alkaloids are an important class of compounds, and these structurally diverse alkaloids possess a wide range of biological activities. They are predominantly found in plants and are common in individual families of flowering plants.[1] A few of them are in clinical use and therefore are the target compounds of interest for the synthetic organic chemist's community.[2] Development of synthetic or biosynthetic routes for these indole alkaloids is a challenging task for chemists. New elegant synthetic ways to our selected target indole alkaloids have been reported in recent literature.[3] In the present work, we have described the total synthesis of novel indole based natural and unnatural products using indole/indole-based amines and cyclic anhydrides/imides as potential precursors (Figure 1).

Figure 1. Synthesis of novel indole-based products from cyclic anhydrides and imides



2. Statement of Problem

The total synthesis of natural and unnatural indole alkaloids cordatanine, donaxaridine, donaxarine, methyl ester of chaetogline A and (±)-6-hydroxy-1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one involving new concise and efficient routes from the simple commercially available starting materials are of current interest.

3. Objectives

Reactions of indole and indole based amines with cyclic anhydrides and imides for the synthesis of structurally interesting and biologically important natural and unnatural products.

4. Methodology

i. The products were characterized by advanced analytical and spectroscopic techniques

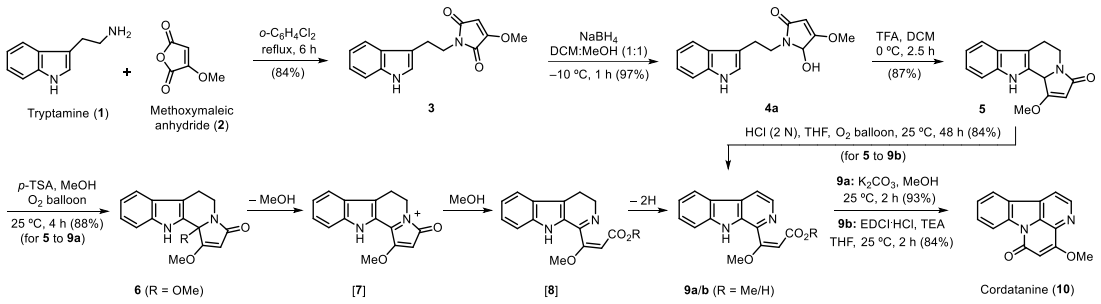
such as high field ^{1}H & ^{13}C NMR, FT-IR, LC-MS, and HRMS.

ii. A single-crystal X-ray crystallographic study has been done to determine the relative stereochemistry.

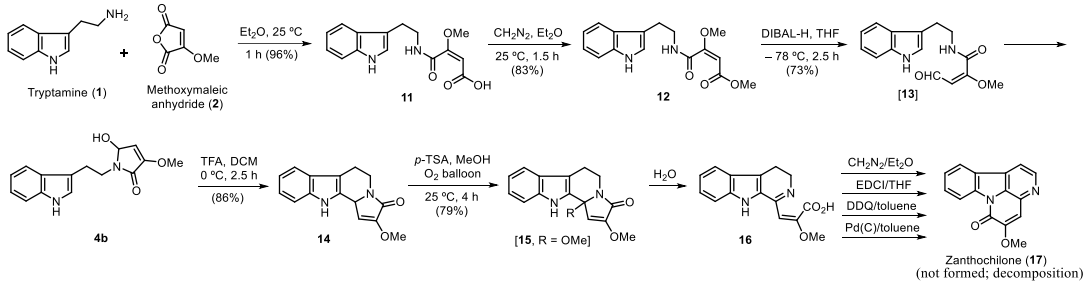
5. Results

i. Starting from tryptamine and methoxymaleic anhydride, concise and efficient total synthesis of cordatanine has been accomplished via regioselective reduction of methoxymaleimide, acid- catalyzed intramolecular cyclization of the formed lactamol, in situ stepwise oxidations leading to aromatization and intramolecular cyclization with the exchange of *N*-regioselectivty. An attempted synthesis of regioisomeric natural product zanthochilone has been described in brief with reversal of reduction selectivity.

Scheme 1. Concise and Efficient Regioselective Total Synthesis of Cordatanine Involving Stepwise Oxidative Aromatization



Scheme 2. Attempted Regioselective Synthesis of Zanthochilone Involving Reversal in Reduction Selectivity

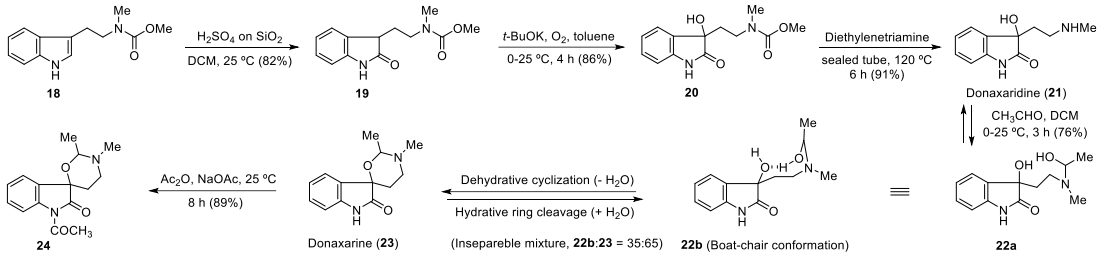


In summary, practical total synthesis of cordatanine has been completed by taking the advantage of facile oxygen promoted stepwise oxidative aromatization. Synthesis of two regioisomeric methoxyl-substituted pyrrolotetrahydrocarbazoles from methoxymaleimide and methyl ester of methoxymaleamic acid is noteworthy. Unfortunately, we were unable to complete the first total synthesis of isomeric zanthochilone alkaloid due to the decomposition of penultimate step product under the sets of our reaction conditions.

ii. Facile regioselective oxidation of indoles to 2-oxindoles (14 examples) promoted by sulfuric acid adsorbed on silica gel has been described. The present oxidation strategy is also employed to accomplish total synthesis of natural products donaxaridine and donaxarine. Based on analytical and spectral data it is evidenced that the donaxarine stays

in equilibrium with its hydrated ring-opened form. The structural features essential for such type of oxidation and plausible mechanism are discussed.

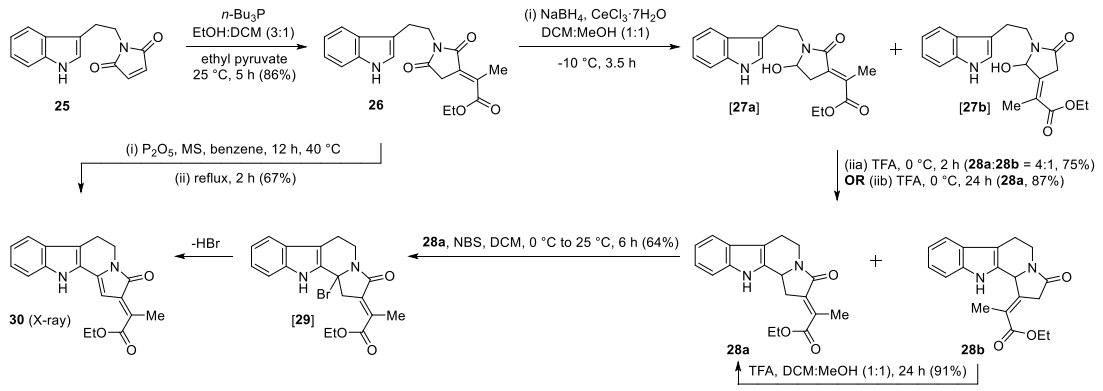
Scheme 3. Stepwise Oxidations of Indole Moiety Leading to Facile Synthesis of Donaxaridine and Donaxarine



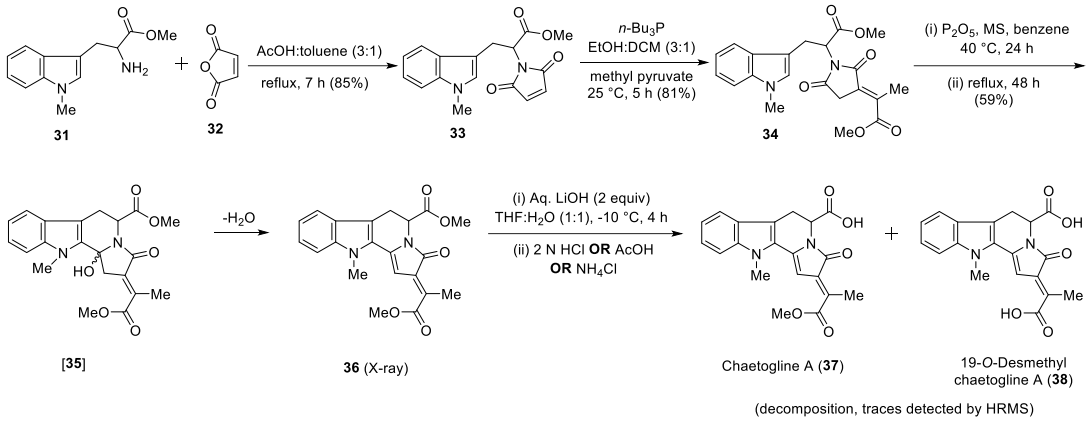
In summary, a new efficient and straightforward method for regioselective oxidation of indoles to 2-oxindoles using sulfuric acid adsorbed on silica gel as a reagent has been demonstrated. It will be useful for the synthesis of a broad range of desired bioactive natural and unnatural oxindoles. A plausible mechanism has been proposed, and the presence of free proton on the indole nitrogen atom is essential for the formation of a complex with sulfuric acid. The present practical oxidation reaction induced by heterogeneous reagent nicely addresses the product stability concerns and functional group tolerance issues. We also believe that the current protocol has a scale-up potential and will be useful for large-scale production of several oxindole derivatives of commercial interest.

iii. A facile synthesis of methyl ester of chaetogline A is reported starting from the corresponding methyl 1-methyltryptophanatederived maleimide. A stereoselective Wittig olefination with a carbonyl function in methyl pyruvate followed by phosphorous pentoxideinduced regioselective dehydrative cyclization are the essential reactions. An acid-induced thermodynamically driven stereoselective β- to α-position migration of the exocyclic C=C bond unit in ethyl tetrahydroindolizinoindolylidenepropanoate is described.

Scheme 4. Approaches to Chaetogline A Framework from Tryptamine Derived Maleimide



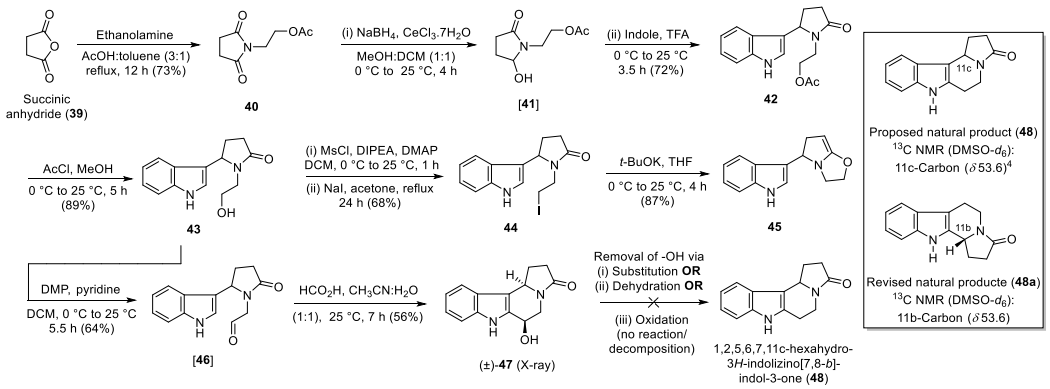
Scheme 5. Total Synthesis of Methyl Ester of Chaetogline A



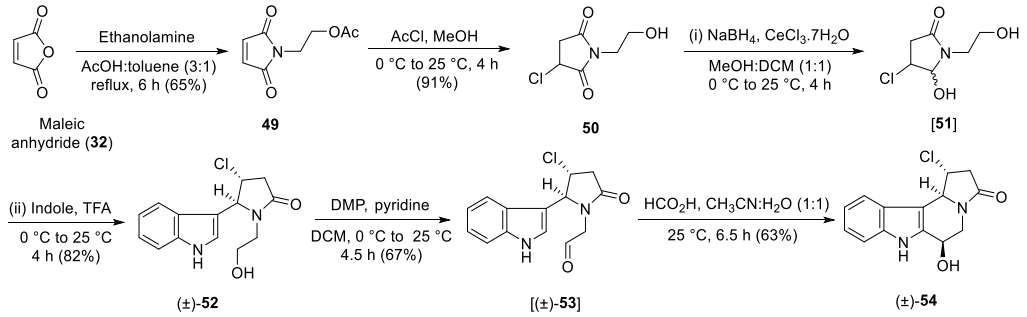
In summary, we have demonstrated the synthesis of the methyl ester of chaetoglinate A via the introduction of the desired exocyclic double bond using a Wittig olefination with methyl pyruvate and a thermodynamically favorable extension of conjugation driven dehydrative cyclization pathway. The present Wittig reaction with alkyl pyruvates is general in nature. It can be useful to neatly design a variety of desired precursors essential for the total synthesis of several natural and unnatural products.

iv. Chemo-, regio- and diastereoselective coupling reactions of indole with imide derivatives leading to unique heterocyclic systems are demonstrated. Acid-induced 3-position coupling reactions of indole with cyclic imide derived lactamols followed by acid promoted 2-position cyclizations with the corresponding aldehydes are described to obtain the indolizinoindolones and benzoindolizinoindolone. Base induced 2-position coupling reactions of *N*-tosylindole with *N*-(2-iodoethyl)imides and the subsequent cyclization's provide indolylepoxypyrrolooxazole, indolylpyrrolooxazolone and indolyloxazoloisoindolone. Reductive cleavage of indolyloxazoloisoindolone to the corresponding alcohol followed by mesylation and base promoted *N*-cyclization affords the in-situ air-oxidized pentacyclic product hydroxyisoindolopyrazinoindolone. Regioisomeric structural revision of the natural product from 1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one to 1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one is also reported in the present studies focussed on the methodologies for heterocyclic synthesis.

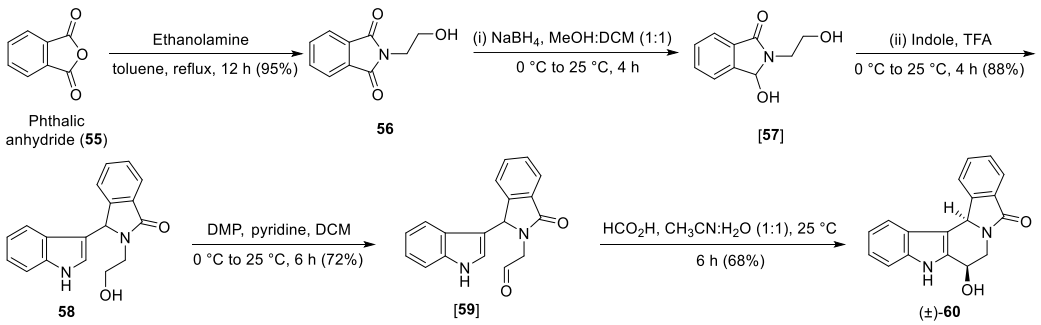
Scheme 6. Synthesis of hydroxyindolizinoindolone via acid promoted reaction of indole with succinimide based lactamol



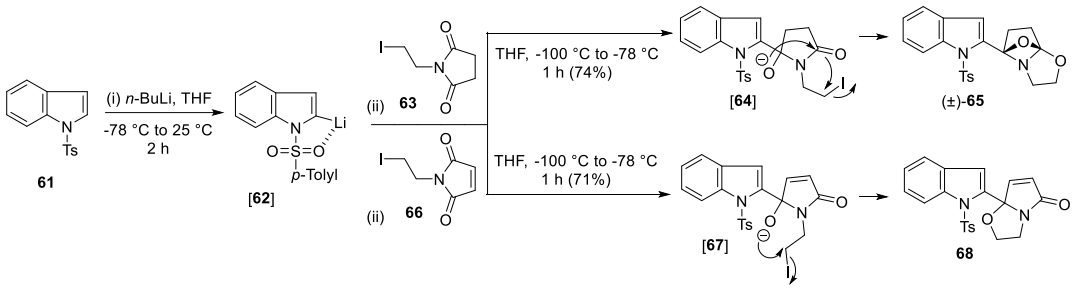
Scheme 7. Regioselective and Diasteroselective Coupling Reactions of Indole with Chlorosuccinimide Based Lactamol



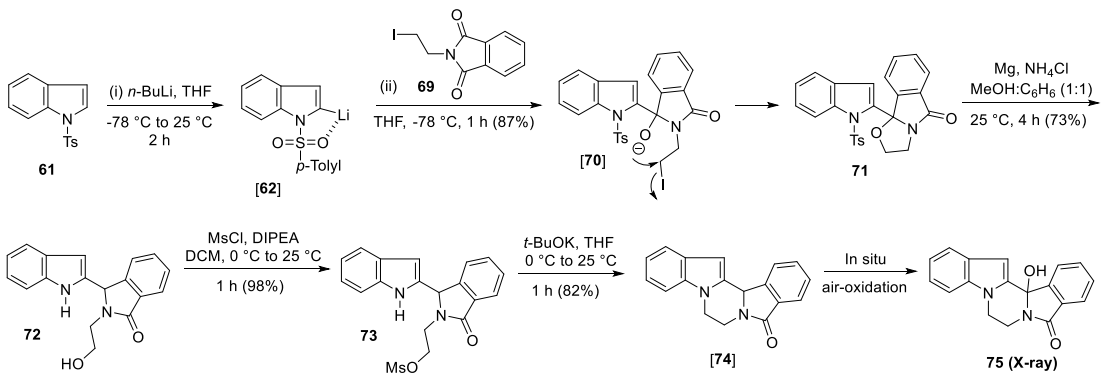
Scheme 8. Regioselective Coupling Reactions of Indole with Phthalimide Based Lactamol



Scheme 9. Base Induced Regioselective Coupling Reactions of *N*-Tosylindole with *N*-2-Iodoethylsuccinimide and *N*-2-Iodoethylmaleimide

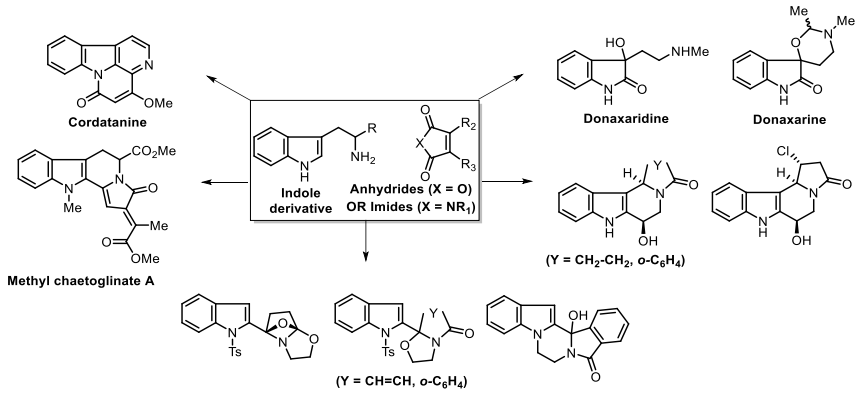


Scheme 10. Base Induced Regioselective Coupling Reactions of *N*-Tosylindole with *N*-2-Iodoethylphthalimide Assembling Hydroxyisoindolopyrazinoindolone



In summary, we have demonstrated selective coupling reactions of indole with cyclic imide derivatives leading to structurally interesting important heterocyclic systems. The selective formation of exotic labile bridged compound indolylepoxypyrrolooxazole at minus hundred degrees and witnessed facile air-oxidation to form hydroxyisoindolopyrazinoindolone are noteworthy. We believe that the present new selective 1/2/3-position carbon–carbon and carbon–nitrogen bond-forming reactions of indole with the cyclic imide precursors are important from the basic chemistry point of view and will provide an avenue for indole-based heterocycles.

6. Conclusion: Present dissertation describes multistep total synthesis of cordatanine, donaxaridine, donaxarine, ethyl ester of chaetogline A framework, methyl ester of chaetogline A, hydroxyindolizinoindolone, 1-chloro-6-hydroxy-indolizinoindolone, benzoindolizinoindolone, bridged (±)-indolylepoxypyrrolooxazole, indolylpyrrolooxazolone, indolyloxazoloisoindolone and hydroxyisoindolopyrazinoindolone from the readily available cyclic anhydrides and indole derivative as the starting materials. The key reactions involved in above specified synthesis are oxidation, regioselective reduction, Pictet−Spengler cyclization, Wittig olefination with alkyl pyruvate, acid induced regioselective 3-position coupling on indole with lactamol, oxidative 2-position cyclizations, base induced regioselective 2-position coupling reactions of *N*-tosylindole with *N*-(2-iodoethyl)imides and regioselective cyclization at 1-position on indole. We reasoned and did the isomeric revision in the structural assignment of proposed natural product [1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one]. Many indole-based natural and unnatural products have been synthesized and will be useful from biological activities point of view.



Basically, starting from cyclic anhydrides and imides we have demonstrated the total synthesis of structurally interesting and biologically important indole-based natural and unnatural products involving novel oxidation reactions.

7. Future direction

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

8. Publications

(i) Shelar, S. V.; Argade, N. P. *ACS Omega* **2017**, *2*, 3945–3950.
(ii) Shelar, S. V.; Argade, N. P. *Org. Biomol. Chem.* **2019**, *17*, 6671–6677.

(iii) Shelar, S. V.; Argade, N. P. *Synthesis* **2021**, *53*, 2897–2902.
(iv) Shelar, S. V.; Argade, N. P. *Org. Biomol. Chem.* **2021**, *19*, 6160–6169.

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(1) (a) Yan, W.; Zhao, S. S.; Ye, Y. H.; Zhang, Y. Y.; Zhang, Y.; Xu, J. Y.; Yin, S. M.; Tan, R. X. *J. Nat. Prod.* **2019**, *82*, 2132−2137. (b) Li, Q.; Deng, A.-J.; Li, L.; Wu, L.-Q.; Ji, M.; Zhang, H.-J.; Li, Z.-H.; Ma, L.; Zhang, Z.-H.; Chen, X.-G.; Qin, H.-L. *J. Nat. Prod.* **2017**, *80*, 2189–2198. (c) Yan, W.; Ge, H. M.; Wang, G.; Jiang, N.; Mei, Y. N.; Jiang, R.; Li, S. J.; Chen, C. J.; Jiao, R. H.; Xu, Q.; Ng, S. W.; Tan, R. X. *Proc. Natl. Acad. Sci. U.S.A.* **2014**, *111*, 18138−18143. (d) Wetzel, I.; Allmendinger, L.; Bracher. F. *J. Nat. Prod.* **2009**, *72*, 1908–1910. (e) Agatón, F. S.; Lagoutte, D.; Poupon, E.; Roblot, F.; Fournet, A.; Gantier, J.-C.; Hocquemiller, R. *J. Nat. Prod.* **2005**, *68*, 1581–1587. (f) Ubaidullaev K. A.; Shakirov. R.; Yunusov S. Y. *Khim. Prir. Soedin.*, **1976**, *12*, 553–554.
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(3) (a) Bisht, G. S.; Chaudhari, M. B.; Gupte, V. S.; Gnanaprakasam, B. *ACS Omega* **2017**, *2*, 8234–8252. (b) Tadano, S.; Sugimachi, Y.; Sumimoto, M.; Tsukamoto, S.; Ishikawa, H. *Chem. Eur. J.* **2016**, *22*, 1277–1291. (c) Fang, H. W.; Liao, Y.-R.; Hwang, T.-L.; Shieh, P.-C.; Lee, K.-H.; Hung, H.-Y.; Wu, T.-H. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3822–3824. (d) Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2010**, *66*, 1441–1446. (e) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, *60*, 1152–1154.

Chapter 1

Concise Account of Cyclic Anhydrides and Imides to Indole Alkaloids

1.1 Introduction

Alkaloids are naturally occurring basic organic compounds that contain at least one nitrogen atom. In addition to carbon, hydrogen, and nitrogen, alkaloids may also contain oxygen, sulfur, and other chlorine, bromine, and phosphorus atoms. They are one of the largest classes of secondary metabolites produced by living organisms. The presence of basic nitrogen atoms makes them particularly pharmacologically active. Since most of the alkaloids are amines, they form soluble salts after reacting with acids. Thus the term alkaloid is derived from 'alkali-like,' which was first introduced by the pharmacist W. Meissner in 1819.[1] This term was further modified. The 'true alkaloid' compound fulfills the following four requirements: (a) the nitrogen atom is a part of a heterocyclic system, (b) the compound should have a complex molecular structure, (c) the compound should possess modest pharmacological activity, and (d) the compound is restricted to the plant kingdom.

However, the above definition of alkaloids is not particularly valid today,[2,3] and they are regarded as a naturally occurring nitrogenous compound. Pelletier[2] has given a more specified meaning, as described below.

"*An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state of limited distribution in living organisms*"

1.2 Biological Activities of Alkaloids

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

Alkaloids often have many pharmacological activities which contain various physiological activities in humans and animals. Alkaloids containing plants have been used for dye, spices, and drugs since the beginning of civilization.[6] Opium isolated from *Papaver somniferam* L. was used as a medicine as early as 4000 B. C in ancient Sumer, the world's first civilization's birthplace. Morphine (*Papaver somniferam*) is the first

alkaloid to be isolated in pure form in 1805 by W. Sertürner (Figure 1). It acts as an indispensable analgesic used for the treatment of severe pain. Some other physiologically effective alkaloids are nicotine, cocaine, caffeine, quinine, and codeine.

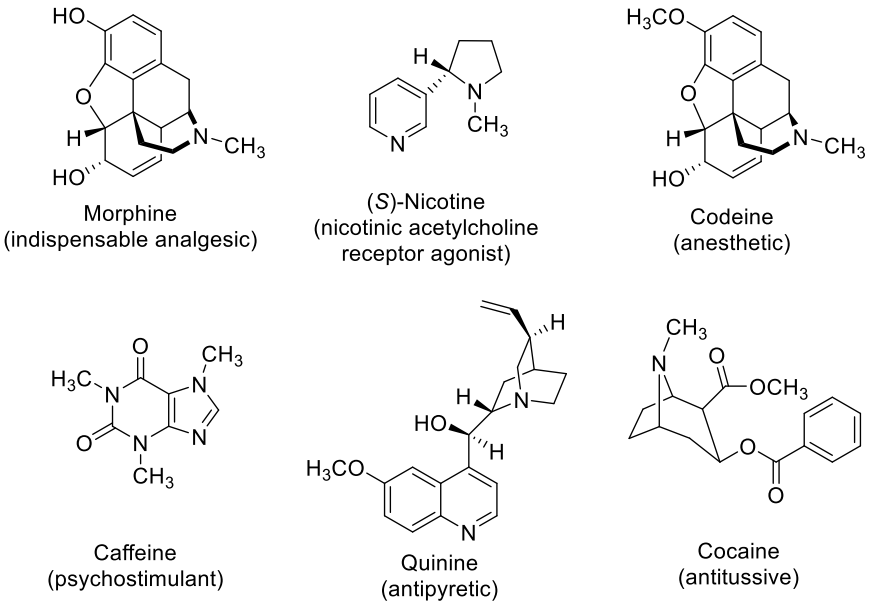


Figure 1. Pharmacologically active alkaloids

1.3 Classification of Alkaloids

Alkaloids display much diversity in their chemical structures, botanical and biochemical origins and pharmacological activities. Therefore several systems of classifications are promising and are mostly classified as follows.[7,8]

(i) Taxonomical classification: It is based on the spreading of alkaloids in various plant families, such as solanaceous or papilionaceous alkaloids. They are also grouped as per the name of the genus, e.g., ephedra, cinchona, etc.

(ii) Biosynthetic classification: This depends on the precursor from which the alkaloids have been biosynthesized in the plant. Therefore the variety of alkaloids with dissimilar taxonomic distribution and physiological activities can be brought under one group, in case they are derived from the identical precursor, e.g., indole alkaloids derived from tryptophan are grouped together. Amino acid derived alkaloids are grouped in the same class, such as lysine, ornithine, tyrosine, tryptophan, phenylalanine, etc.

(iii) Pharmacological classification: It is based on the physiological action or biological activities of alkaloids on animals; like CNS stimulants, depressants, analgesics,

purgatives, sympathomimetics, etc. It is independent of chemical nature of alkaloids. The alkaloids may have more than one physiological action, e.g., morphine is narcotic-analgesic and however quinidine is a cardiac sedative.

(iv) Chemical classification: It is the most established way to identify the alkaloids and are categorized into three divisions.

(a) True alkaloids: They are nitrogen-containing heterocycles and are originated from amino acids.

(b) Proto alkaloids: Non-heterocyclic but are derived from amino acids.

(c) Pseudo alkaloids: These are nitrogen heterocyclic ring containing products obtained from terpenoids or purines but not from amino acids.

1.4 Indole Alkaloids

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

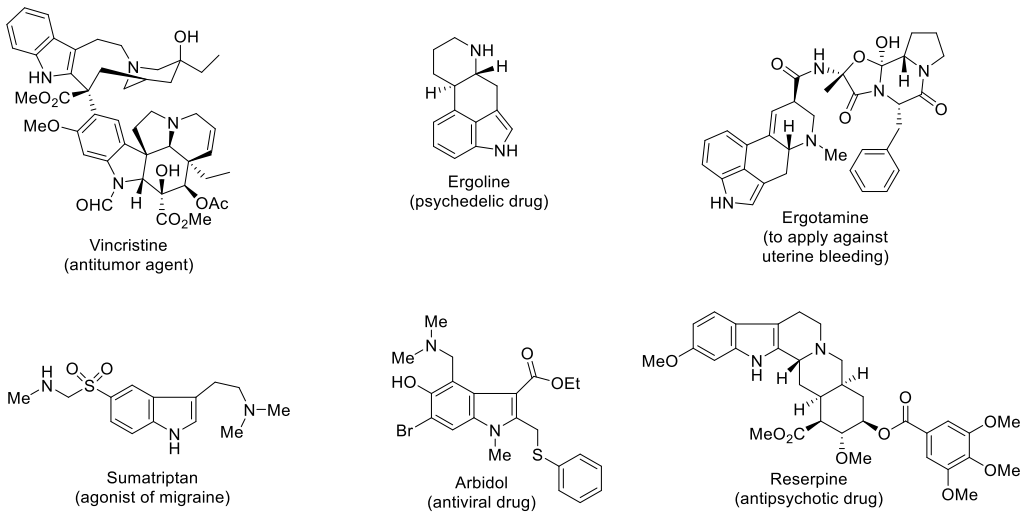


Figure 2. Drugs containing indole moiety

1.4.1 Classification of Indole Alkaloids

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

(A) Non-isoprenoid Indole Alkaloids: Figure 3

(i) Simple indole derivatives: For example; serotonine, gramine, and glycozoline (carbazole alkaloid)

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

(iii) Pyrroloindole alkaloids: For example; physostigmine

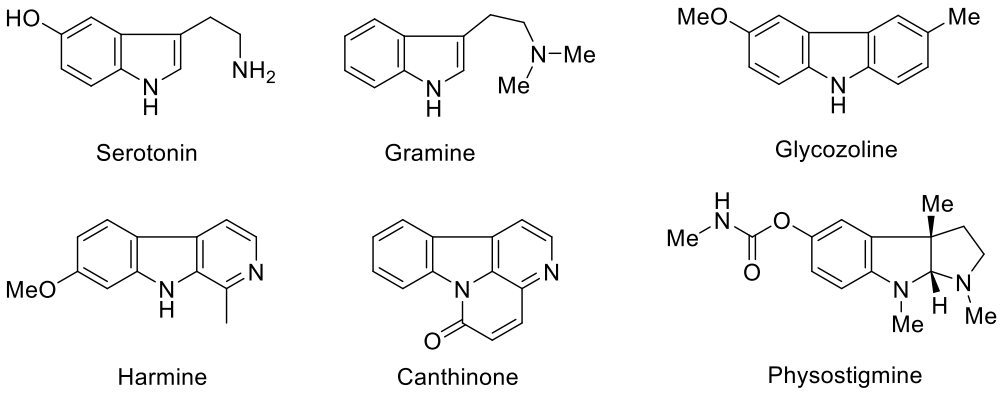


Figure 3. Representative non-isoprenoid indole alkaloids

(B) Isoprenoid Indole Alkaloids

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

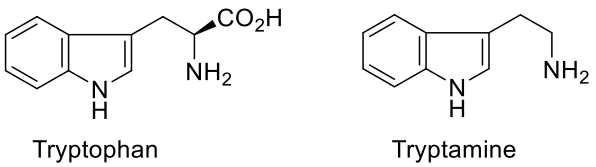


Figure 4. Tryptophan and tryptamine

(i) Ergot alkaloids:

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

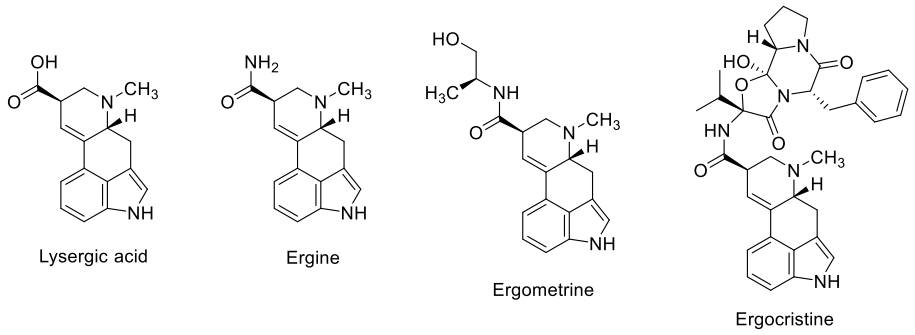


Figure 5. Representative ergot alkaloids

(ii) Monoterpene indole alkaloids:

This alkaloid class containing C_9 or C_{10} unit originated from secologanin (see Scheme 1). Depending on the structure of residues, this class is divided into three subclasses named by a typical genus or species of the plant, which contain such alkaloids (Figure 6); (a) corynanthe, (b) iboga, and (c) aspidosperma.

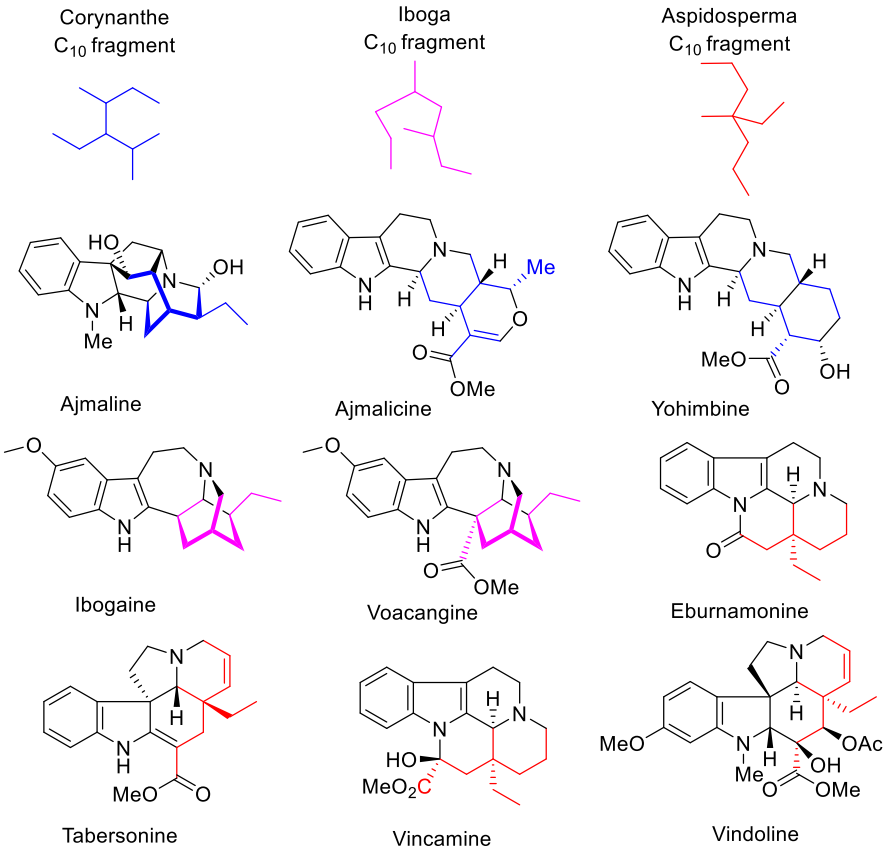


Figure 6. Representative monoterpene indole alkaloids

(iii) Bisindole alkaloids: For example; voacamine and vinblastine (Figure 7)

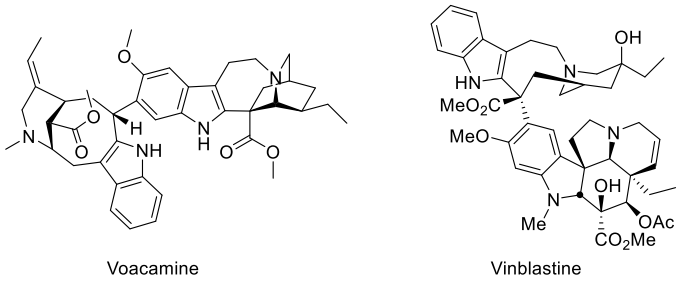
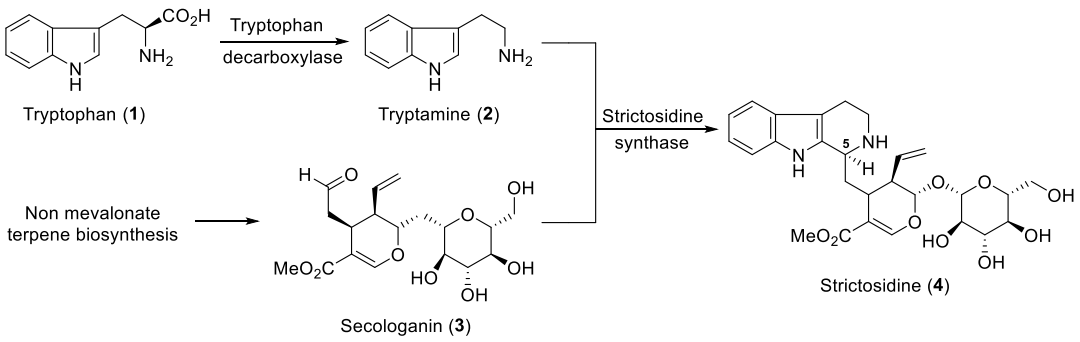


Figure 7. Representative bisindole alkaloids

1.4.2 Biosynthesis of Monoterpene Indole Alkaloids

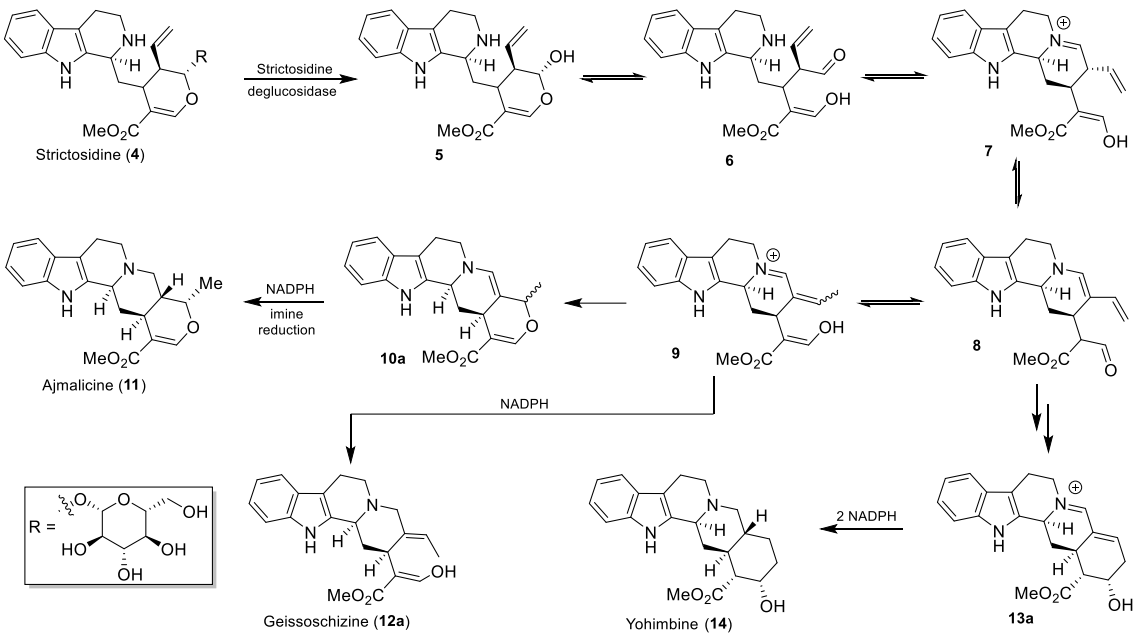
All monoterpene indole alkaloids have been originated from tryptophan and iridoid terpene secologanin (**3**) (Scheme 1).[10] Tryptophan decarboxylate converts tryptophan (**1**) to tryptamine (**2**).[11] The monoterpene secologanin is biosynthetically produced from isopentenyl pyrophosphate (IPP) via non-mevalonate pathway.[12] In the first committed step of terpene indole alkaloid biosynthesis, the enzyme strictosidine synthase catalyzes stereoselective Pictet-Spengler cyclization[13] between tryptamine and secologanin to provide strictosidine (**4**).[14–17]



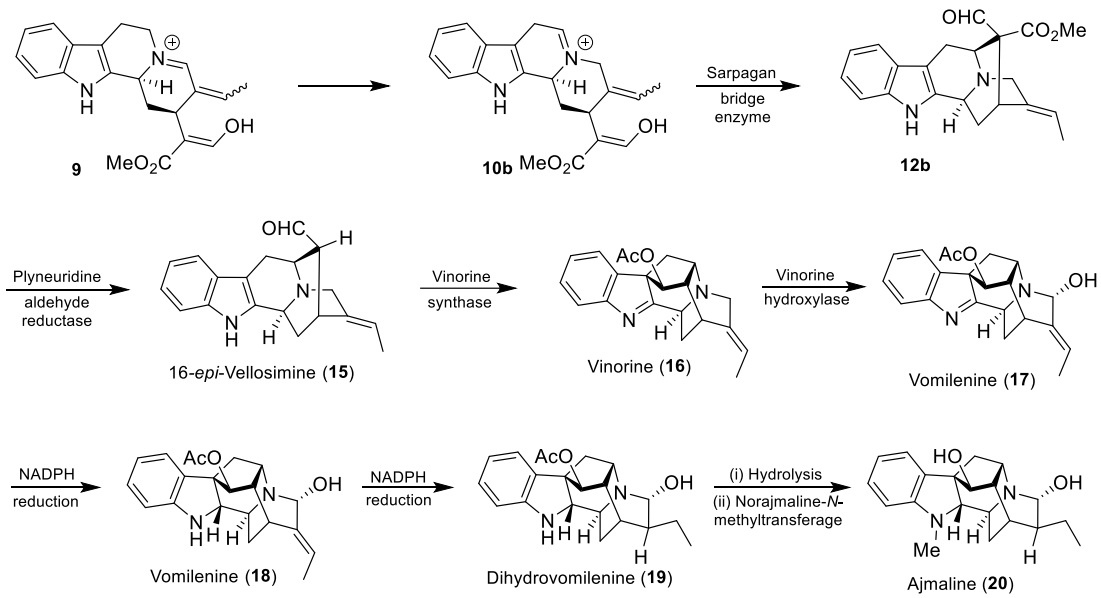
Scheme 1. Biosynthesis of Monoterpene Indole Alkaloid Strictosidine

The mechanism and the control of the processes by which most of the families of monoterpene indole alkaloids are produced from strictosidine is one of the most challenging tasks in the study of secondary metabolism. Important information about crucial intermediates of the biosynthetic pathways has been obtained via trapping experiments, isotope-labeling studies, and feeding studies.[18–22] In many cases, the biosynthetic step's active enzymes have been isolated and characterized.[22–24] Biosynthetic

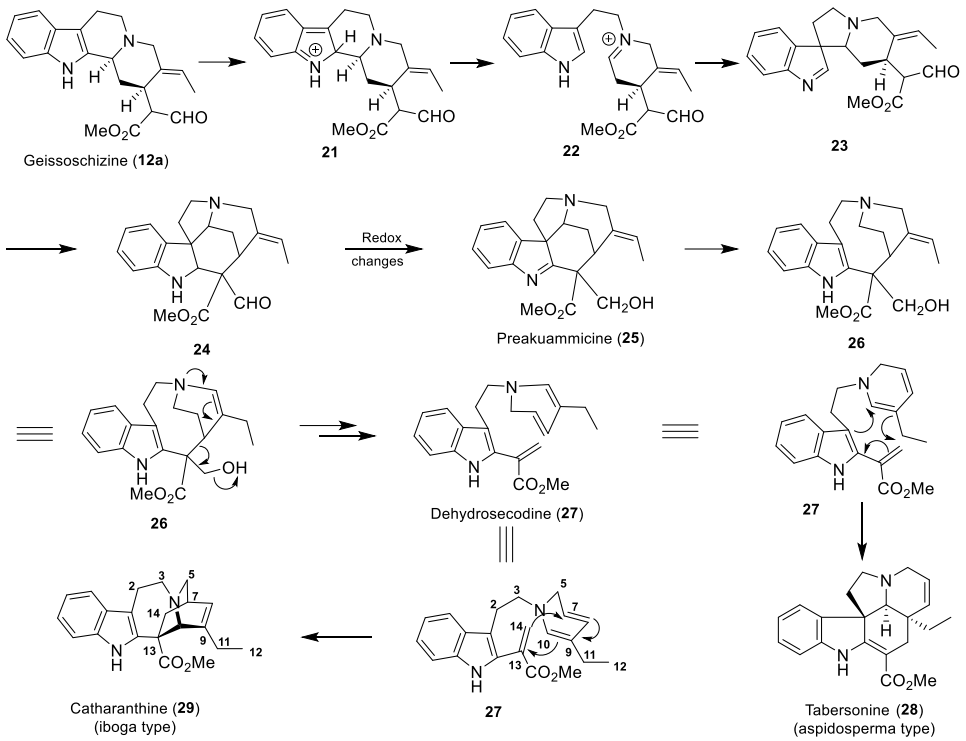
pathways of major monoterpene indole alkaloids have been presented schematically in schemes 2 to 5.



Scheme 2. Proposed Biosynthesis of Corynanthe Alkaloids Ajmalicine, Geissoschizine and Yohimbine

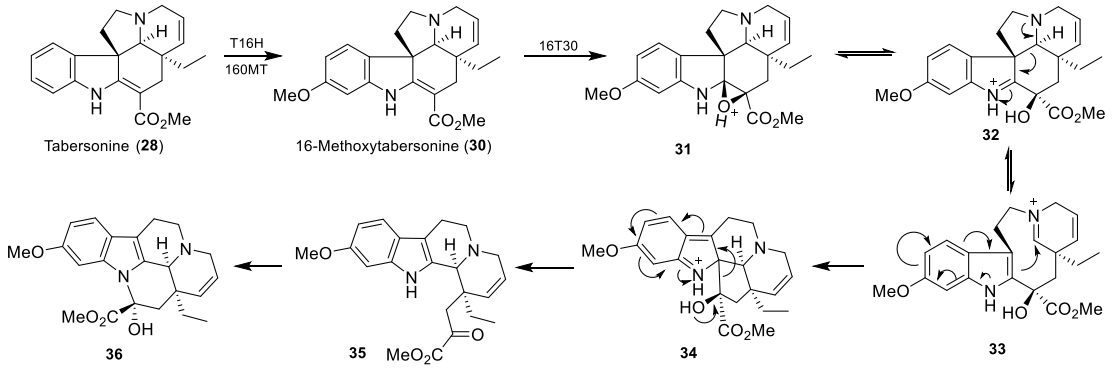


Scheme 3. Ajmaline Biosynthesis from Deglycosylated Strictosidine



Scheme 4. Proposed Biosynthetic Pathway of Aspidosperma and Iboga Alkaloids

There is a long standing hypothesis that aspidosperma and eburnamine type alkaloids are biogenetically related.[25] Recently, O′Connor and co-workers have provided evidence for this hypothesis where the enzyme 16-methoxytabersonine 3-oxygenase (16T30) catalyzes the formation of epoxide of 16-methoxytabersonine (**30**), which undergoes rearrangement to vinca-eburna type compound **36** (Scheme 5).[26] Hence, it was suggested that 16T30 homologue is involved in the biosynthesis of vincamine and related compounds from figure 6.



Scheme 5. Biosynthesis of Vinca-Eburna type Compound from Tabersonine

1.5 Synthesis of Indole Alkaloids Using Cyclic Anhydrides and Cyclic Imides

Cyclic anhydrides and imides have been used as versatile building blocks to synthesize various bioactive natural products (Figure 8).[27-34] More specifically, maleic anhydride and its derivatives are more important from biological and synthetic application points of view.[35-40] It is a versatile synthon where all the sites are amenable for various reactions and exert exceptional selectivity towards several nucleophiles. In past decades, many naturally occurring maleic anhydrides and their derivatives have been isolated, and many of them display important pharmacological activities. Methylmaleic anhydride (citraconic anhydride) is the most widely used monoalkyl substituted maleic anhydride. Many synthetic derivatives of natural anhydrides have been prepared and biologically examined in the last two decades. Other important cyclic anhydrides used as a synthon are succinic anhydride, methoxymaleic anhydride, dimethylmaleic anhydride, (*S*)/(*R*)-acetoxysuccinic anhydride, glutaric anhydride, *N*-CBz protected glutamic anhydride, phthalic anhydride, homophthalic anhydride and its derivatives, etc. Based on the past two decades extensive work on cyclic anhydrides and their derivatives to bioactive natural and unnatural products many interesting results in the synthesis of these compounds using novel carbon–carbon and carbon-heteroatom bond-forming reactions have been published from our research group, including indole alkaloids (Scheme 6 to 10).[41-49] Also, recently, three comprehensive reviews have been published dedicated to the cyclic anhydride class of natural products.[27,50,51]

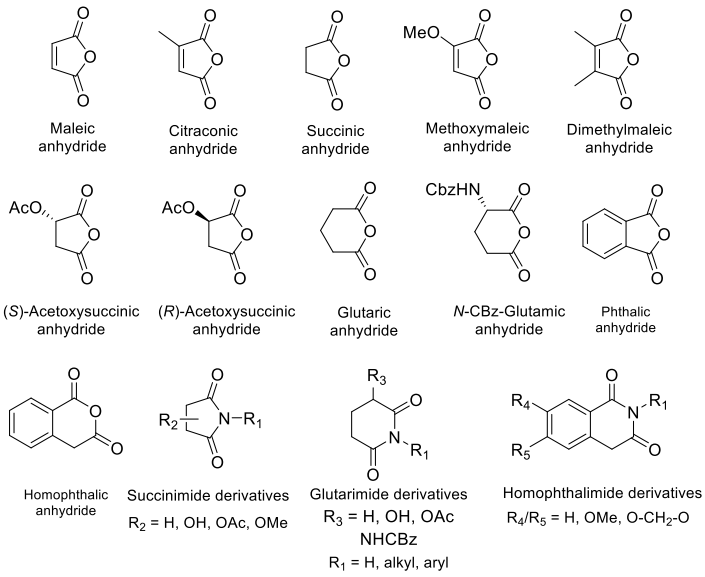
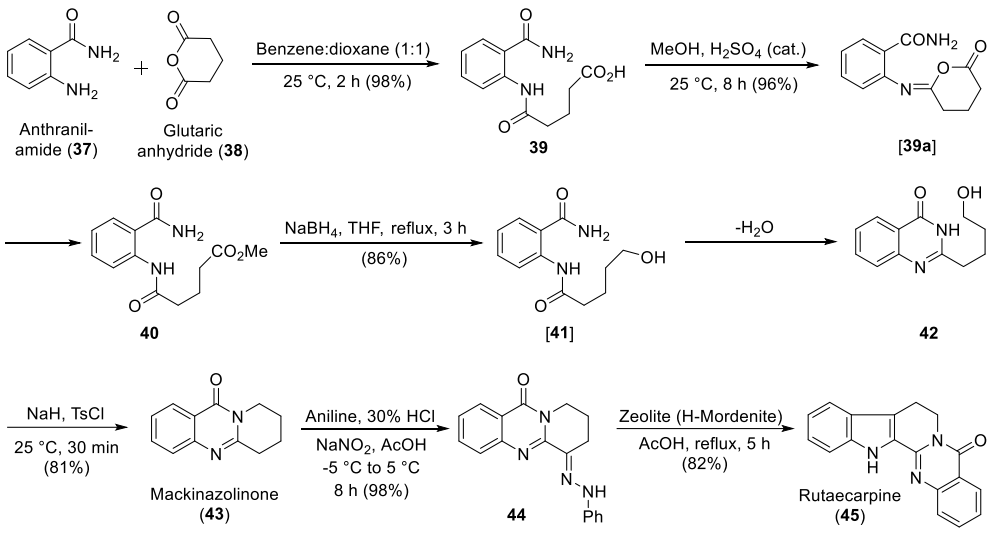


Figure 8. Important cyclic anhydrides and cyclic imides as potential precursors for synthesis of bioactive natural products

1.5.1 Cyclic Anhydrides and Cyclic Imides to Indole Alkaloids from our Research Group

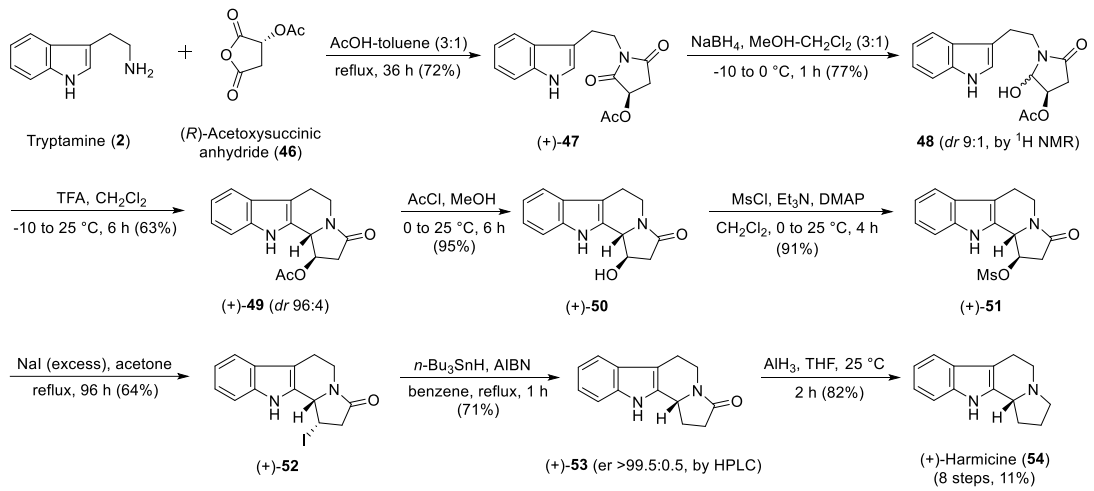
Argade and co-workers have reported an elegant synthesis of bioactive natural product rutaecarpine (**45**) using zeolite-induced Fischer-indole synthesis as a key step (Scheme 6).[52] The reaction of anthranilamide (**37**) with glutaric anhydride (**38**) furnished the corresponding *o*-amidoglutaranilic acid (**39**) in 98% yield. The compound **39** on treatment with methanol in the presence of the catalytic amount of H_2SO_4 provided the methyl ester **40** plausibly via the corresponding isoimide **39a**. The reduction of ester **40** with $NaBH_4$ provided intermediate alcohol **41**, which, after post-reaction work, underwent intramolecular dehydrative cyclization to afford quinazolinone **42** in 86% yield. Treatment of **42** with TsCl and NaH provided natural product mackinazolinone (**43**) via intramolecular cyclization. The compound **43** on reaction with in situ generated diazonium salt of aniline formed the hydrazone **44** in 98% yield. The hydrazone on zeolite (*H*-Mordenite) induced Fischer-indole synthesis afforded the natural product rutaecarpine (**45**) in 82% yield.



Scheme 6. Synthesis of Rutaecarpine from Glutaric Anhydride

Argade and co-workers have reported the stereoselective total synthesis of (+)-harmicine (**54**) from (*R*)-acetoxysuccinic anhydride (**46**) using intramolecular diastereoselective *N*-acyliminium cyclization as a key step (Scheme 7).[53] Condensation of tryptamine (**2**) with (*R*)-acetoxysuccinic anhydride (**46**) under refluxing conditions provided (*R*)-

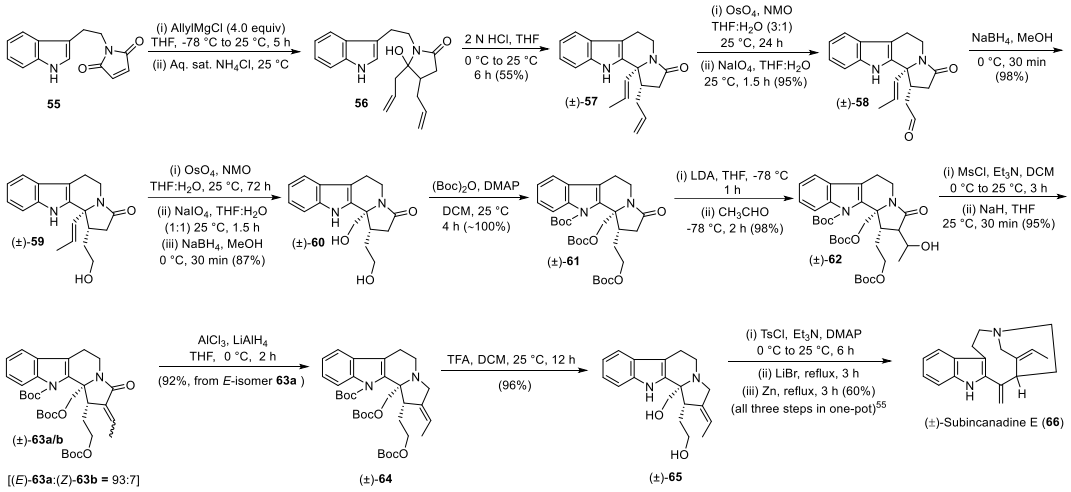
acetoxysuccinimide derivative (+)-**47** in 72% yield. Regioselective reduction of the more reactive imide carbonyl by $NaBH_4$ provided the lactamol **48** as a (9:1) mixture of diastereomers. TFA mediated highly diastereoselective intramolecular *N*-acyliminium cyclization of the hemiaminal **48** provided the tetracyclic lactam (+)-**49** in 63% yield with *d.r* 96:4. The major diastereomer (+)-**49** was smoothly deacylated using acetyl chloride with MeOH to provide the hydroxy compound (+)-**50**. Conversion of the secondary hydroxy compound (+)-**50** to the corresponding mesylate (+)-**51** followed by its nucleophilic displacement with iodide provided the iodo compound (+)-**52**. Tributyltin hydride mediated de-iododination of (+)-**52** formed the desired chiral lactam (+)-**53** in 71% yield (>99.5:0.5 *ee*:*dr*, by HPLC). Finally, in situ generated alane mediated reduction of the γ-lactam group of (+)-**53** to the corresponding cyclic amine furnished (+)-harmicine (**54**) in 82% yield and with a 11% overall yield.



Scheme 7. Synthesis of (+)-Harmicine from (*R*)-Acetoxysuccinimide

Argade and co-workers have reported total synthesis of (±)- and (+)-subincanadine E (**66**) starting from tryptamine derived maleimide **55** and (*S*)-acetoxysuccinimides **47** (Schemes 8 and 9).[54] The reaction of maleimide **55** with excess of allylmagnesium chloride at –78 °C and then acidification directly formed the selectively one of the double bond rearranged cyclized product (±)-**57** in 55% yield (Scheme 8). Two different coupling reactions of Grignard reagent with maleimide **55** and diastereoselective cyclization with position specific allylic rearrangement took place in one-pot. The allylic rearrangement was beneficial to construct the carbon chain at an angular position. The planned transformations of terminal and internal olefins in product (±)-**57** initially yielded primary alcohol (±)-**59** in

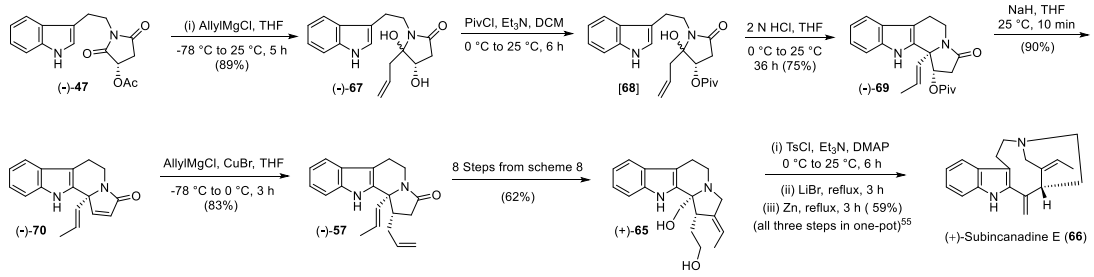
93% yield and then the (±)-diol **60** in 87% yield. Boc-protections of nitrogen and two alcohols in compound (±)-**60** furnished the product (±)-**61** in quantitative yield. Reaction of (±)-lactam **61** with acetaldehyde and subsequent stereoselective elimination of mesylate formed the lactam (±)-**63a** as a major product in 88% yield and minor (±)-**63b** in 7% yield, over three steps. Alane-reduction of a lactam (±)-**63a** to (±)-amine **64** in 92% yield and trifluoroacetic acid driven deprotection of three Boc-groups provided the known (±)-diol **65** in 96% yield. The conversion of (±)-diol **65** under Zhai and co-workers conditions[55] furnished the desired (±)-subincanadine E (**66**) in 60% yield.



Scheme 8. Total Synthesis of (±)-Subincanadine E from Maleimide

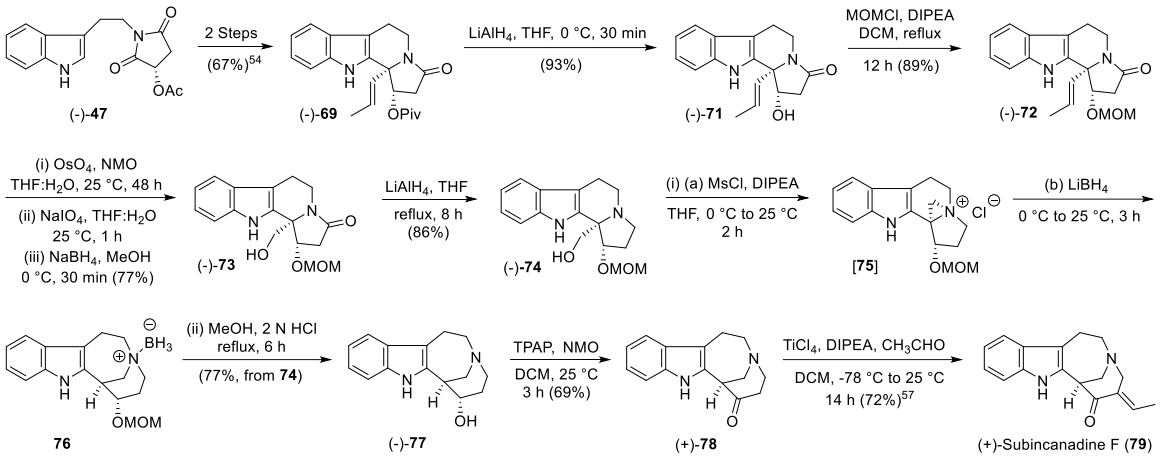
The enantioselective synthesis of (+)-subincanadine E (**66**) has been reported from (*S*)-acetoxysuccinimide **47** (Scheme 9). Grignard reagent on regioselective reaction with the more reactive imide carbonyl of (*S*)-acetoxysuccinimide **47** selectively delivered the corresponding deacylated diastereomer (–)-**67** in 89% yield. (–)-Hydroxy-lactamol **67** on treatment with pivaloyl chloride and triethylamine selectively formed the corresponding sterically hindered lactamol intermediate **68** in quantitative yield. Acid-catalyzed stereoselective Pictet–Spengler cyclization of lactamol **68** provided the double bond rearranged cyclized *syn*-product (–)-**69** in 75% yield. The elimination of pivaloyl group in product (–)-**69** delivered the *α,β*-unsaturated lactam **70** in 90% yield. Allyl-cuprate addition to (–)-lactam **70** was diastereoselctive and unexpectedly formed in the *syn*-product (–)-**57** in 83% yield with >99% *de*/*ee*. The *syn*-product (–)-**57** was similarly converted to (+)-diol **65** in 62% overall yield using 8-steps from scheme 8. One-pot transformation of (+)-diol **65** under Zhai and co-workers conditions[55] formed the natural

isomer (+)-subincanadine E (**66**) in 59% yield. Enantioselective first total synthesis of (+)-subincanadine E (**66**) was completed with 18% overall yield and *Sinister* configuration was assigned to the natural product.



Scheme 9. Total Synthesis (+)-Subincanadine E from (*S*)-Acetoxysuccinimide

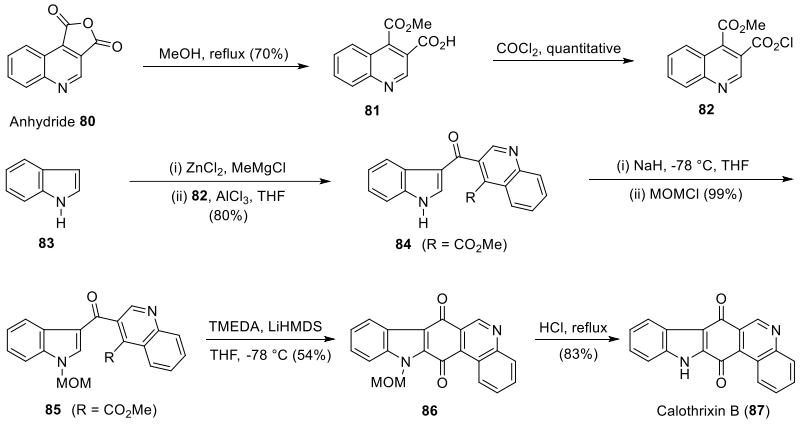
Argade and co-workers have reported an enantioselective synthesis of (+)-subincanadine F (**79**) from (*S*)-acetoxysuccinic anhydride (**46**) via regio- and stereoselective aziridinium ring expansions as a key step (Scheme 10).[56] An author's earlier designed potential precursor hexahydroindolizinoindolyl pivalate (–)-**69**[54] on deprotection of *O*-pivaloyl group in compound (–)-**69**, an essential –MOM protection of hydroxyl unit in alcohol **71** to form **72**, transformation of carbon–carbon double bond to hydroxyl-aldehyde and reduction to alcohol (–)-**73**, and reduction to amine provided the desired precursor (–)-**74** in very good overall yield. Alcohol (–)-**74** on reaction with mesyl chloride delivered the in situ cyclized aziridinium chloride **75** via mesylation of primary alcohol unit. The stereoselective lithium borohydride reduction of aziridinium chloride **75** provided the corresponding boron complex **76**. The purified product **76** was treated with refluxing dilute hydrochloric acid to break boron complex and deprotection of the –MOM group to provide product (–)-**77** in 77% yield. Mechanistically, the incoming hydride approaches from the α-face (opposite to C–N bond) and stereoselectively cleaves an azridinium bridge and the obtained regioselectivity was governed by benzylic carbon atom reactivity. Overall, the inversion of configuration delivers preferred product with desired stereochemistry. The oxidation of alcohol (–)-**77** with tetrapropylammonium perruthenate (TPAP) in presence of NMO smoothly provided the known (+)-ketone **78** in 69% yield. The known[57] $TiCl_4$-induced coupling of ketone (+)-**78** with acetaldehyde delivered the natural product (+)-subincanadine F (**79**) in 72% yield.



Scheme 10. Selective Aziridinium Ring Cleavage Leading to (+)-Subincanadine F

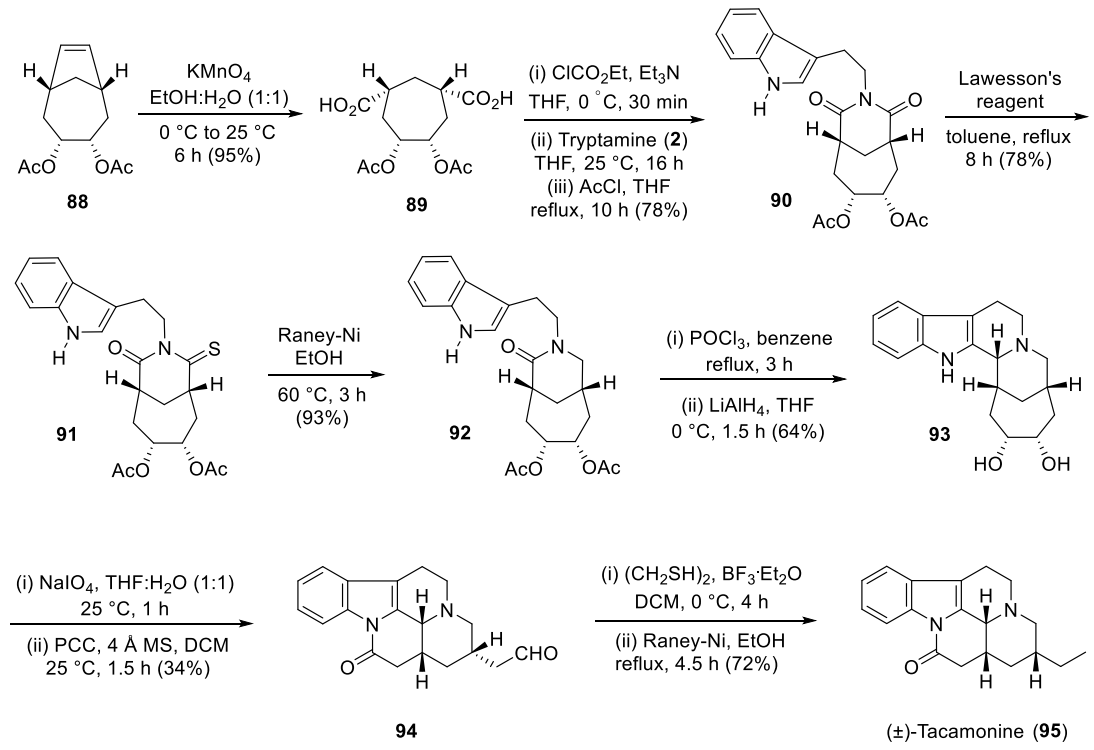
1.5.2 Cyclic Anhydrides and Cyclic Imides to Indole Alkaloids from other Research Groups:

Chai and co-workers have reported a concise route to calothrixin B (**87**) from quinoline anhydride **80** (Scheme 11).[58] Regioselective methanolysis of the anhydride **80** by using anhydrous methanol under reflux conditions exclusively provided the 4-mono methyl ester **81** in 70% yield. Fridel-Crafts reaction of indole (**83**) with the corresponding acid chloride of **82** furnished the desired coupled product **84** in 80% yield. The precursor **84** was protected as *N*-MOM derivative **85** using standard conditions. Lithiation of compound **85** by using LiHMDS in presence TMEDA followed by cyclization afforded the product **86** in 54% yield. Finally, *N*-MOM deprotection in DMSO under acidic condition provided the calothrixin B (**87**) in 83% yield.



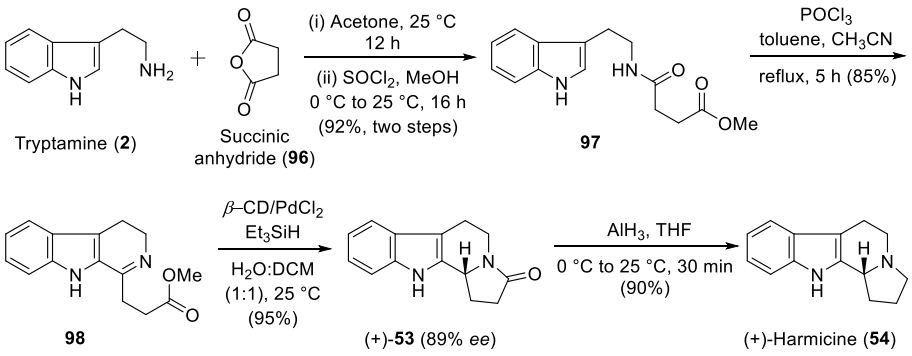
Scheme 11. Synthesis of Calothrixin B from Quinoline Based Anhydride

Ho and Lin have reported stereocontrolled approach to the pentacyclic alkaloid (±)-tacamonine (**95**) via bridged glutarimide (±)-**90** (Scheme 12).[59] The bridged diacetate (±)-**88** was subjected to oxidative cleavage using $KMnO_4$ to provide the diacid (±)-**89** in 95% yield. The relative configuration of the stereogenic centers were confirmed by the X-ray diffraction data of the diacid (±)-**89**. The diacid was transformed to the bridged glutarimide (±)-**90** in three steps. The glutarimide was converted to the lactam (±)-**92** via corresponding thiolactam formation followed by desulfurization with Raney-Ni. Subjecting the lactam (±)-**92** to Bischler–Napieralski reaction followed by diastereoselective hydride reduction from the *β*-face of the bridged-locked iminium salt afforded the amino-diol (±)-**93** in 64% yield. Cleavage of the diol by $NaIO_4$ followed by PCC oxidation formed the pentacyclic dialdehyde, which spontaneously cyclized with the proximal aldehyde to yield the corresponding unstable aminol (mixture of epimers). Aminol was directly oxidized to provide lactam-aldehyde (±)-**94** in 34% yield over two steps. The aldehyde was transformed to (±)-tacamonine (**95**) via the corresponding ethylenedithioacetal and subsequent desulfurization with Raney-Ni in 72% yield over two steps.



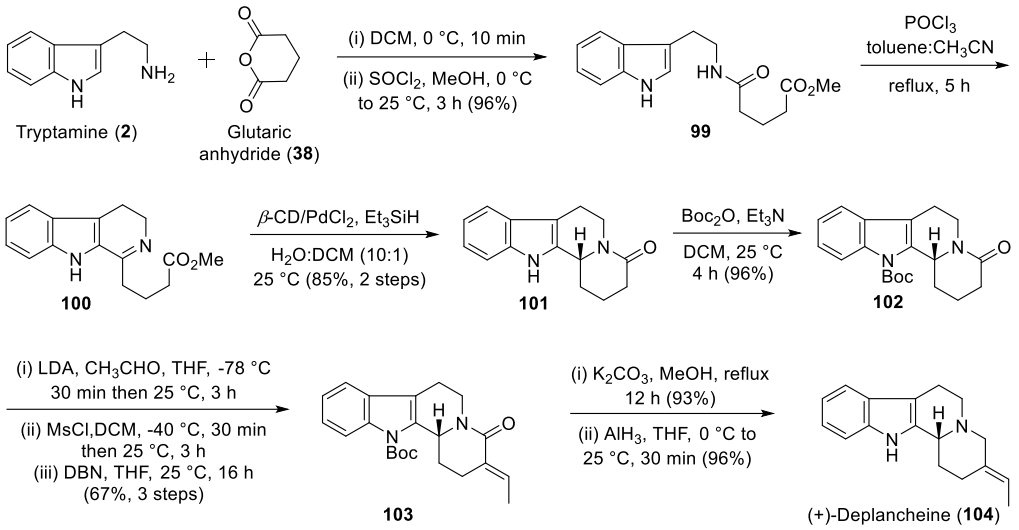
Scheme 12. Stereoselective Synthesis (±)-Tacamonine via Bridged Glutarimide

Pilli and co-workers have reported asymmetric reduction of dihydro-*β*-carboline to the corresponding tetrahydro-*β*-carboline by using supramolecular lyophilized complex formed from *β*-cyclodextrin/imines as an enzyme mimetic and palladium hydride as the reducing agent.[60] The methodology has been applied for the syntheses of (*R*)-harmicine (**54**) and (*R*)-deplancheine (**104**) (Schemes 13 and 14). Treatment of tryptamine (**2**) with succinic anhydride (**96**) followed by esterification of the corresponding acid formed the ester **97** in 92% yield over two steps (Schemes 13). Bischler–Napieralski reaction of **97** using $POCl_3$ provided imine **98** in 85% yield. The imine **98** was subjected to the asymmetric supramolecular reduction condition by using *β*-CD/$PdCl_2$-Et_3SiH system to provide lactam (+)-**53** in 95% yield (89% *ee*), via spontaneous lactamization. AlH_3 reduction of the lactam **53** afforded (+)-harmicine (**54**) in 90% yield.



Scheme 13. Supramolecular Approach for the Synthesis of (+)-Harmicine from Succinic Anhydride

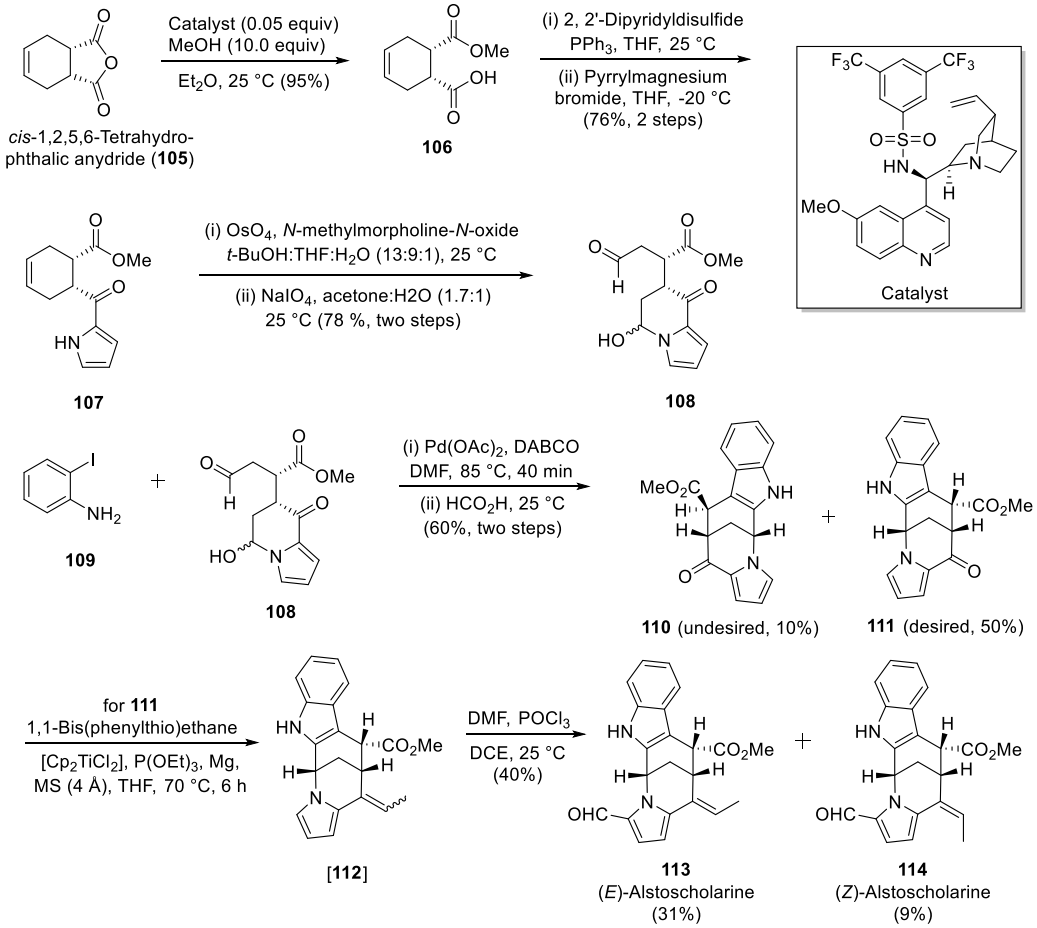
The same methodology also provided indolo[2,3-*a*]quinolizidine core and which was successfully used for the total synthesis of indole alkaloid (+)-deplancheine (**104**) (Scheme 14). Thus the reaction of tryptamine (**2**) with glutaric anhydride (**38**) followed by esterification with $SOCl_2$/MeOH yielded the product **99** in 96% yield over two steps. Compound **99** after Bischler–Napieralski reaction and asymmetric supramolecular reduction provided the lactam **101** in 85% yield over two steps with 90% *ee*. Boc-protection of indole nitrogen in **101** furnished compound **102** in 96% yield. The reaction of enolate of *N*-Boc protected lactam **102** and acetaldehyde to the corresponding alcohol followed by its mesylation and elimination using DBN yielded product **103** in 67% overall yield in three steps. K_2CO_3/MeOH induced *N*-Boc deprotection followed by lactam carbonyl reduction using AlH_3 provided (+)-deplancheine (**104**) in 89% yield (two steps).



Scheme 14. Supramolecular Approach for the Synthesis of (+)-Deplancheine from Glutaric Anhydride

Zhu and co-workers have completed the first enantioselective total synthesis of (*E*)- and (*Z*)-alstoscholarines in eight steps (Scheme 15).[61] The reaction of *cis*-1,2,5,6-tetrahydrophthalic anhydride (**105**) with MeOH in the presence of catalyst afforded hemiester **106** in 95% yield with 93% *ee*. Conversion of the carboxylic acid into the 2-ketopyrrole using two steps protocol, *viz* (i) addition of 2,2'-dipyridyldisulfide and PPh_3 in THF at 25 °C to form the intermediate 2-pyridylthioester and (ii) direct addition of pyrryl magnesium bromide in THF at −20 °C provided 2-ketopyrrole **107** as the only regioisomer in 76% yield over two steps. Dihydroxylation of **107** afforded the corresponding diol. The diol was submitted to oxidative cleavage using $NaIO_4$ at 25 °C to provide intermediate bis(aldehyde). The formed intermediate spontaneously cyclized and formed the six-membered hemiaminal **108** as a mixture of two diastereoisomers in 78% yield over two steps. The key palladium-catalyzed heteroannulation reaction between *ortho*-iodoaniline (**109**) and aldehyde **108** took place under optimized conditions [$Pd(OAc)_2$, DABCO (2.0 equiv), DMF, 85 °C, 40 min]. The desired pentacyclic product **111** was obtained in 50% yield over two steps along with the undesired pentacyclic compound **110** in 10% yield. Conversion of the ketone moiety in compound **111** into an ethylidene turned out to be quite challenging. Ethylidenation of **111** using Takeda's reagent took place smoothly to provide the desired compound **112**. Due to the low stability of **112**, it was immediately submitted to Vilsmeier–Haack formylation conditions to afford (*E*)-alstoscholarine (**113**) and (*Z*)-alstoscholarine (**114**) (3:1 ratio) in 40% yield over two steps. The two isomers were separated by preparative thin-layer chromatography

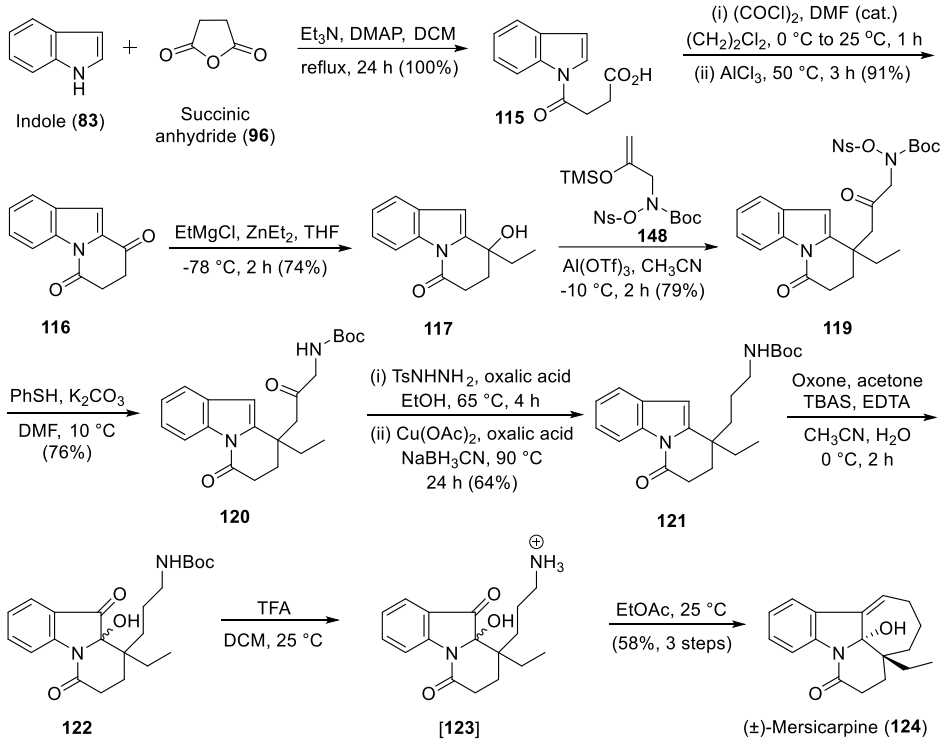
on silica gel. The analytical and spectral data of these two synthetic alstoscholarines were identical with the reported data for the natural products. The proposed 3*S*, 15*R*, 16*R* absolute configuration of (*E*)-and (*Z*)-alstoscholarine was confirmed by the present synthesis.



Scheme 15. Total Synthesis of (*E*)- and (*Z*)-Alstoscholarine from *cis*-1,2,5,6-Tetrahydrophthalic Anhydride

Han and co-workers have reported a concise synthesis of (±)-mersicarpine (**124**) by using $Al(OTf)_3$ catalyzed construction of quarternary centre (Scheme 16).[62,63] Amidation of indole (**83**) with succinic anhydride (**96**) provided the desired indole carboxylic acid **115** in quantitative yield. Compound **115** was transformed to tricyclic *δ*-lactam **116** as a single regioisomer in 91% yield, by using Friedel-Crafts acylation. Regioselective addition of EtMgCl to the keto-lactam **116** in the presences of $ZnCl_2$ provided tertiary alcohol **117** in 74% yield. $Al(OTf)_3$ catalyzed regioselective addition of silyl vinyl ether **118** to allylic alcohol **117** afforded the ketone **119** with the generation of carbon–carbon bond.

Deprotection of nosyl group in compound **119** by $PhSH/K_2CO_3$, reduction of the carbonyl group by modified one pot Wolff-Kishner protocol using tosyl hydrazide in the presence of oxalic acid, and in situ reduction of the tosylhydrazone intermediate with a combination of $NaBH_3CN$ and $Cu(OAc)_2$ in the presences of oxalic acid furnished the desired product **121** in 64% yield. Oxidation of compound **121** under Kerr's condition[64] proceeded cleanly to furnish the indolone precursor **122**, which upon *N*-Boc deproctection using TFA in DCM followed by overnight stirring in ethyl acetate afforded the natural product (±)-mersicarpine (**124**) via the intermediate **123** in 58% yield over three steps.

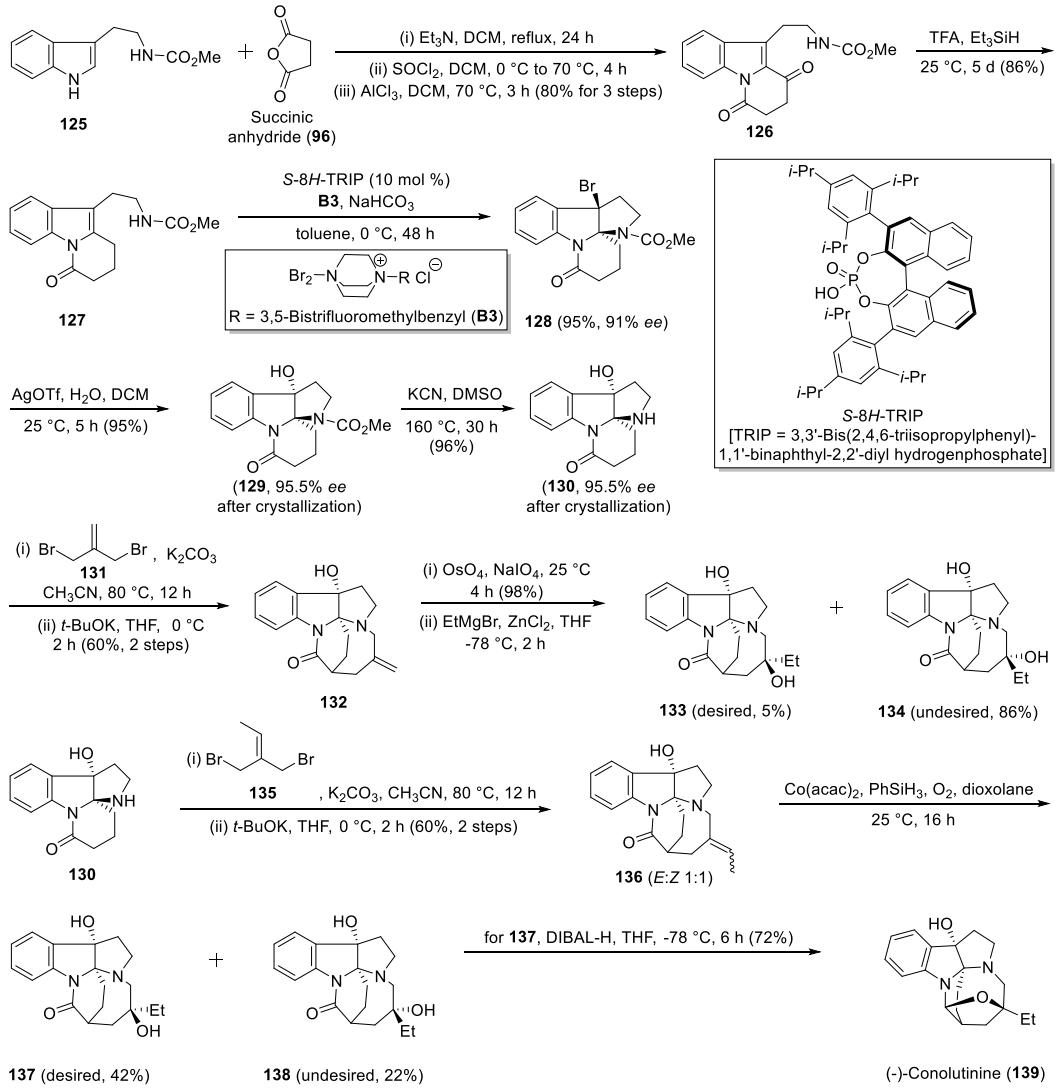


Scheme 16. Synthesis of (±)-Mersicarpine from Succinic Anhydride

Conolutinine (**139**), a new member of terpenoid indole alkaloid was isolated from Malaysian *Tabernaemontana* by Kam and co-workers in 2009.[65] It exhibits interesting activity to reverse multidrug resistance in vincristine-resistant KB cells.[66] Its gross structure was determined by extensive 2D NMR studies and the absolute configuration was empirically proposed via its hypothetical biosynthetic origin from velbanamine.

Xie and co-workers have reported first enantioselective synthesis of cyclotryptamine alkaloid (–)-conolutinine (**139**) by using asymmetric bromocyclization of tryptamine as a key step (Scheme 17).[66] Reaction of tryptamine derivative **125** with succinic anhydride

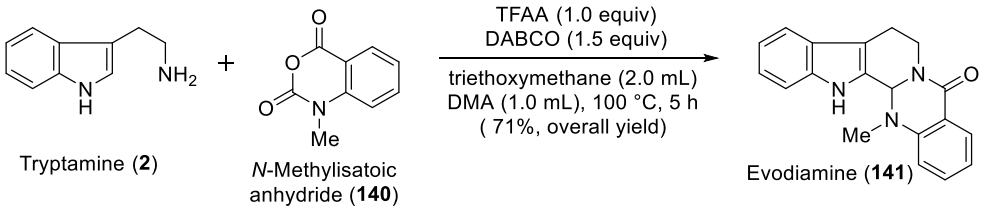
(**96**) followed by intramolecular Fridel-Crafts reaction provided the ketone **126** in 80% yield over three steps. The ketone moiety of **126** was reduced by using TFA/Et_3SiH to furnish product **127** in 86% yield. Enantioselective intramolecular bromocyclizaton[67] of **127** by using DABCO-derived brominating agent **B3** and binapthol-derived chiral phosphoric acid catalyst 8*H*-*S*-TRIP afforded 3-bromohexahydropyrrolo[2,3,-*b*]indole **128** in 95% yield with 91% *ee*. Reaction of bromide in **128** of AgOTf provided hydroxyl-pyrroloindoline **129** in 95% yield. The carbomethoxy group was cleaved by heating **129** with KCN in DMSO at 160 ˚C to provide pyrroloindoline **130** in 96% yield. The K_2CO_3 mediated *N*-allylation of amine **130** with allylic dibromide **131** followed by



Scheme 17. Xie's Enantioselective Synthesis of (–)-Conolutinine from Succinic Anhydride

intramolecular cyclization using *t*-BuOK smoothly furnished the pentacycle **132** in 60% yield over two steps. Oxidative cleavage of the exocyclic double bond in **132** followed by stereoselective ethylation of the formed ketone provided tertiary alcohol. Unfortunately, the undesired isomer **134** was the major product, indicating that the *β*-face of the pentacycle intermediate is sterically less crowded. To get the desired diastereomer **133** as a major product; direct hydration of olefin was employed by taking advantage of the inherent spatial bias of the pentacycle framework. For this purpose, pentacycle **136** was prepared from **130** and allylic dibromide **135** via alkylation and intramolecular cyclization. Metal mediated radical oxidation of hydrochloride salt of **136** by using Mukaiyama's procedure[68] furnished the desired tertiary alcohol **137** in 42% yield. Partial reduction of the amide **137** by DIBAL-H to the geminal aminohydrin intermediate followed by concomitant intramolecular cyclization afforded the natural product (–)-conolutinine (**139**) in 72% yield.

Wu and co-workers have reported the one-pot total synthesis of evodiamine (**141**) using a three-component reaction (Scheme 18).[69] One-pot synthesis of evodiamine was accomplished in 71% yield from tryptamine (**2**), *N*-methylisatoic anhydride (**140**) and triethoxymethane by using 1.0 equiv of TFAA and 1.5 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO). Various acids and bases were screened to obtain better yield.



Scheme 18. One-Pot Total Synthesis of Evodiamine from *N*-Methylisatoic Anhydride

1.6 Summary

In summary, we have presented a concise account on alkaloids, their biological importance, and their broad classifications. More emphasis has been given to the detailed classification of indole alkaloids along with the recent studies in their probable biosynthetic pathways. From the present discussion, it reveals that cyclic anhydrides and cyclic imides are versatile synthons in organic synthesis. These molecules with multiple

functionalities have been effective in building the backbones of many structurally complex and medicinally important compounds in a convergent manner. Their efficacy as a potential starting material has been exemplified by the syntheses of various indole alkaloids in our research group e.g., rutaecarpine, harmicine, subincanadine E, subincanadine F, and various indole alkaloids other from group e.g., calothrixin B, tacamonine, harmicine, deplancheine, (E) and (Z)-alstoscholarine, mersicarpine, conolutinine and evodiamine. We have tried our best to summarize year 2000 on words cyclic anhydrides and cyclic imides to indole alkaloids chemistry, however no pretension of completion has been claimed. In the past two decades, our research group has been actively involved in the synthesis of bioactive natural and unnatural products using cyclic anhydrides and imides as a potential starting materials. In this context, our synthetic studies towards indole alkaloids have been presented using appropriate cyclic anhydrides and imides as a versatile synthon. We have successfully synthesized indole alkaloid cordatanine by using regioselective reduction of methoxymaleimide, acid-catalyzed intramolecular cyclization of the formed lactamol, in situ stepwise oxidations leading to aromatization, and intramolecular cyclization with the exchange of N-regioselectivity. We have completed the synthesis of indole alkaloids donaxaridine and donaxarine by using regioselective oxidation of indoles to 2-oxindoles promoted by sulfuric acid adsorbed on silica gel. We have synthesized methyl-protected chaetoglinate A via the introduction of the desired exocyclic double bond using first Wittig olefination with methyl pyruvate. We have demonstrated chemo-, regio- and diastereoselective acid/base induced coupling reactions of indoles with cyclic imide derivatives leading to structurally interesting and biologically important novel heterocyclic systems containing indole nucleus. The above-specified synthesis of natural and unnatural products will be discussed in chapter 2 of the present dissertation.

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Chapter 2

❑ Reactions of Indole and Indole Based Amines with Cyclic Anhydrides and Imides Leading to Structurally Interesting and Biologically Important Natural and Unnatural Products

Section A

Total Synthesis of Bioactive Canthine Alkaloid Cordatanine Comprising in Situ Double Oxidative Aromatization of Tetrahydrocarbazole

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

This chapter is divided into four sections. The first section presents total synthesis of bioactive canthine alkaloid cordatanine comprising in situ double oxidative aromatization of tetrahydrocarbazole. An attempted synthesis of regioisomeric natural product zanthochilone has been described in brief with reversal of reduction selectivity. The second section describes regioselective oxidation of indoles to 2-oxindoles. The developed oxidation strategy has been used to accomplish total synthesis of natural products donaxaridine and donaxarine. The third section presents Wittig reactions of maleimide-derived stabilized ylides with alkyl pyruvates to complete a concise synthesis of methyl ester of (±)-chaetogline A. The fourth section describes chemo-, regio- and diastereoselective coupling reactions of indole with imide derivatives leading to novel heterocyclic systems. Regioisomeric structural revision of the natural product from 1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*]indol-3-one to 1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one is also reported in the present studies focussed on the methodologies for heterocyclic synthesis. The detailed experimental procedures, complete tabulated analytical and spectral data, some selected NMR spectra and X-ray data have been appropriately included at the end of each section.

2A.1 Background

The canthines are a subclass of *β*-carboline alkaloids with a supplementary D-ring (Figure 1). The parent compound, canthin-6-one was first isolated from *Pentaceras australis* in

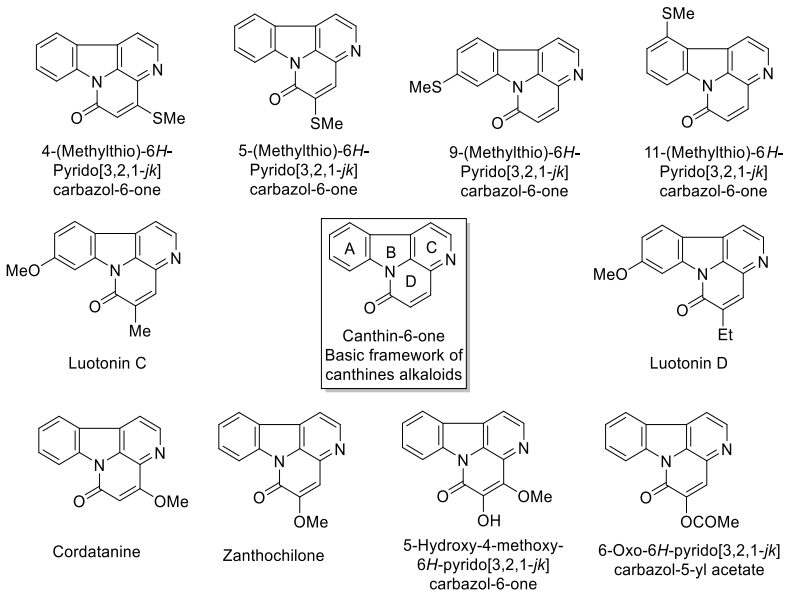


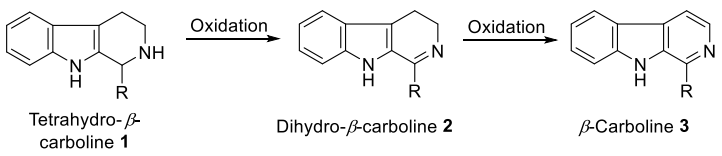
Figure 1. Bioactive natural products with canthines alkaloids framework

1952.[1] The literature search revealed that 200 natural products have the canthin-6-one core within their framework, including >40 pentacyclic products. 4,5-Dihydrotetracyclic congeners also coexist with canthin-6-ones in natural sources. Selected canthin-6-ones have been reported to have potential therapeutic applications such as antifungal,[2–4] anticancer,[5,6] antiparasitic,[7–9] antibacterial,[10–12] and antiviral (HIV).[13,14] One of the reports claims for canthin-6-ones as agents to treat erectile dysfunction,[15] cancer chemoprevention[16] and to reduce elevated levels of proinflammatory cytokines and nitric oxide production by lipopolysaccharide-stimulated macrophages.[17] The first total synthesis of canthin-6-one was reported in 1966 via a Bischer−Napieralski approach starting from tryptophan.[18]

2A.1.1 Aerobic Oxidation for the Oxidative Transformation of Tetrahydro-*β*-carbolines or Dihydro-*β*-carbolines to Aromatic *β*-carbolines

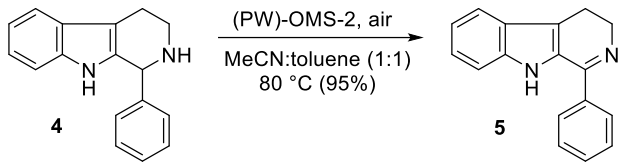
Oxidative conversion of tetrahetro-*β*-carboline **1** to the corresponding *β*-carboline **3** is a challenging assignment to the organic chemists (Scheme 1). The literature on this category of oxidations revealed that generally tetrahydro-*β*-carbolines **1** are transformed to *β*-carbolines **3** using metal-catalyzed (Pd, Ir) dehydrogenation[19] or oxidation by stoichiometric quantity of oxidants like DDQ,[20] $KMnO_4$,[21] MnO_2,[22] S,[23] 2-iodoxybenzoic acid,[24] pyridinium dichromate[25] and selenium dioxide.[26] The dehydrogenations carried out by using transition metal catalysts often suffered due to the use of unfavorable strong oxidants which are not environment friendly. Hence, the development of mild, effective, and environment friendly methods for the conversion of tetrahydro-*β*-carbolines **1** to *β*-carbolines **3** are very much required.

The air-oxygen is a clean and green oxidant and it has several advantages like cheapness, free availability, safety and non-toxicity. Therefore, several oxidation reactions involving air oxygen as an oxidant are known.[27] The oxidative conversion of tetrahydro-*β*-carbolines **1** to *β*-carbolines **3** needs special attention because of its low solubility in many nonpolar and aprotic organic solvents.

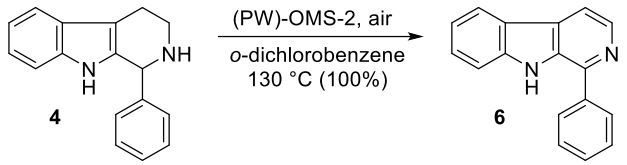


Scheme 1. Stepwise Oxidation of Representative Tetrahydro-*β*-Carboline to *β*-Carboline

Zhao and co-workers in 2021 reported air-oxidation of tetrahydro-*β*-carboline to aromatic *β*-carboline by using OMS-2 composite catalyst (Schemes 2 and 3).[28] The OMS-2 is a mixed catalyst (PW)-OMS-2, which is prepared by using different Mn(II) salts such as $MnCl_2$, $Mn(NO_3)_2$, $Mn(Ac)_2$, $MnCO_3$, $MnSO_4 \cdot H_2O$ and anhydrous $MnSO_4$ with sodium phosphotungstate as the dopant. They proved that the [PW]-OMS-2 is very good catalyst for oxidation of tetrahydro-*β*-carboline to *β*-carboline under the oxygen atmosphere. As a result of optimization, the two best reaction conditions developed are as follows: (a) the use of [PW]-OMS-2 as a catalyst to transform **4** to partial dehydrogenation product 3,4-dihydro-*β*-carboline **5** at 80 °C in a mixed solvent acetonitrile:toluene (1:1) (Scheme 2) and (b) the use of [PW]-OMS-2 as a catalyst on **4** in *o*-dichlorobenzene at 130 °C to obtain the completely dehydrogenated product *β*-carboline **6** (Scheme 3).



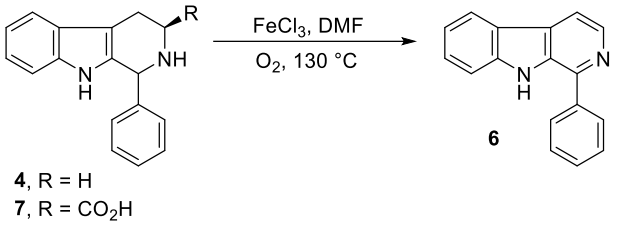
Scheme 2. Aerobic Oxidation of Tetrahydro-*β*-Carboline to 3,4-Dihydro-*β*-Carboline



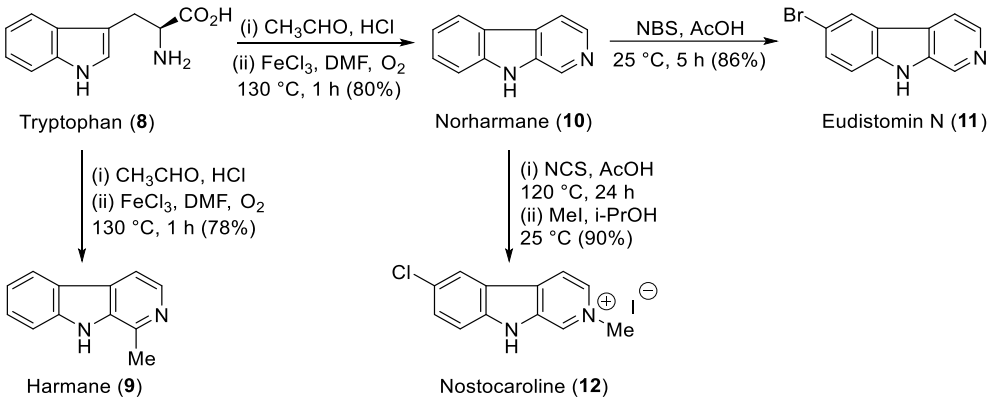
Scheme 3. Aerobic Oxidation of Tetrahydro-*β*-Carboline to *β*-Carboline

Mordi and co-workers in 2021 reported a convenient synthesis of *β*-carbolines by iron-catalyzed aerobic decarboxylative/dehydrogenative aromatization of tetrahydro-*β*-carbolines under the air atmosphere (Scheme 4).[29] Treatment of **4** in the presence of 10 mol% of $FeCl_3$ in DMF at 100 °C resulted in a moderate yield of product **6**. Screening of iron (III) compounds showed slightly higher catalytic reaction over iron (II). Satisfactory yields were obtained in polar solvents such as DMF and DMSO, while small amounts were obtained in non-polar solvents such as 1,4-dioxane and toluene. The reaction in a protic solvent such as water gave no product. The best yield 82% was obtained by performing the reaction at 130 °C. As an application of this method, Mordi and co-

workers have reported the total synthesis of harmane (**9**), norharmane (**10**), eudistomin N (**11**) and nostocarboline (**12**) using $FeCl_3$-catalysis (Scheme 5).

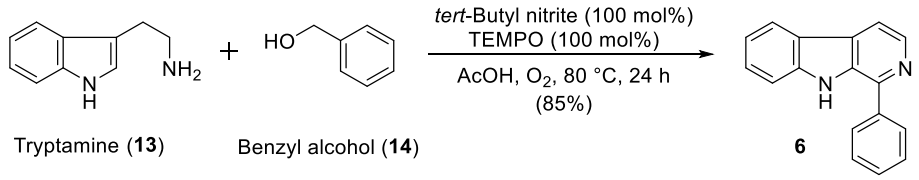


Scheme 4. Iron-Catalyzed Aerobic Oxidation of Tetrahydro-*β*-Carboline to *β*-Carboline



Scheme 5. Collective Synthesis of *β*-Carboline Natural Products

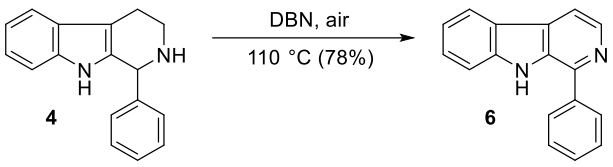
Xu and co-workers in 2020 reported the first transition metal-free alcohol-based aerobic oxidative Pictet–Spengler reaction, which can provide direct selective construction of tetrahydro-*β*-carboline, dihydro-*β*-carboline and *β*-carboline skeletons under the mild reaction conditions (Scheme 6).[30] The screening of catalysts indicated that the transition metal free mixture of *tert*-butyl nitrite (TBN) and 2,2,6,6-tetramethylpiperidyl-1-oxy



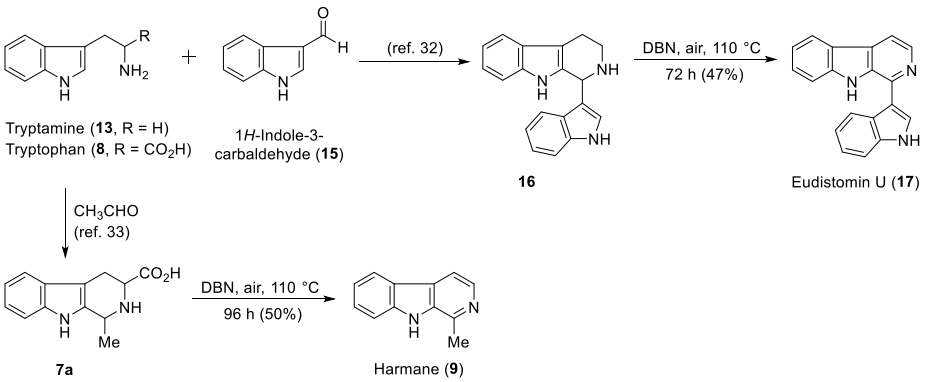
Scheme 6. Mild and Direct Aerobic Oxidative Pictet–Spengler Reaction of Tryptamines with Alcohols

(TEMPO) was more efficient and provides higher transformation of tryptamine (**13**) and benzyl alcohol (**14**) to compound **6** under the oxygen atmosphere. This method is also useful for the synthesis of dihydro-*β*-carboline.

Chen and co-workers in 2019 reported the organic base-promoted efficient oxidative aromatization of tetrahydro-*β*-carbolines into *β*-carbolines under air atmosphere (Scheme 7).[31] They selected tetrahydro-*β*-carboline **4** as the model substrate. DBN and DBU were more effective organic bases due to the stabilization of their conjugate acids by the resonance of two nitrogen atoms. They applied this methodology and synthesized the natural *β*-carboline alkaloids eudistomin U (**17**) and harmane (**9**) via DBN catalyzed aerobic oxidation of tetrahydro-*β*-carboline to *β*-carboline (Scheme 8).



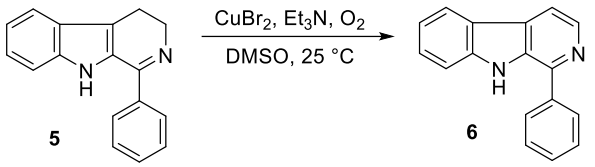
Scheme 7. Organic Base Catalyzed Aerobic Oxidation of Tetrahydro- *β*-Carboline to *β*-Carboline



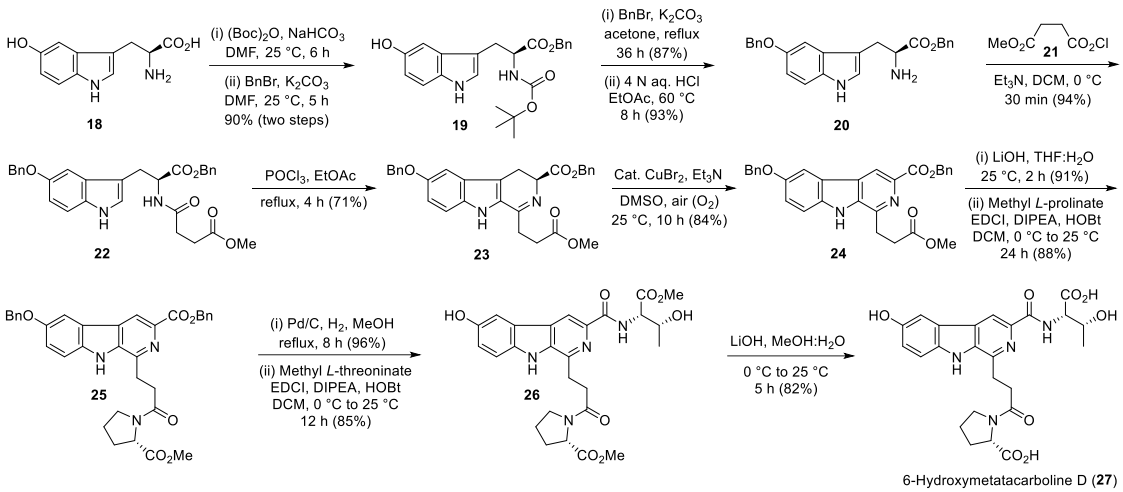
Scheme 8. Total Synthesis of Eudistomin U and Harmane via DBN Catalyzed Aerobic Oxidation

Shi and co-workers in 2018 reported the $CuBr_2$ catalyzed mild oxidation of 3,4-dihydro-*β*-carbolines and its application in total synthesis of 6-hydroxymetatacarboline D (Schemes 9 and 10).[34] Initially, oxidative translation of 3,4-dihydro-1-phenyl-*β*-carboline (**5**) to 1-phenyl-*β*-carboline (**6**) was examined (Scheme 9). The $CuBr_2$ induced aerobic oxidation of **5** and yielded the desired compound **6** in very good yield. Base DBU was

essential to obtain the product *β*-carboline **6** in high yield. Similarly, Shi and co-workers have also completed the first total synthesis of 6-hydroxymetatacarboline D (**27**) in 12 steps with 22% overall yield (Scheme 10).



Scheme 9. $CuBr_2$ Catalyzed Aerobic Oxidation of 3,4-Dihydro-*β*-Carbolines to *β*-Carbolines

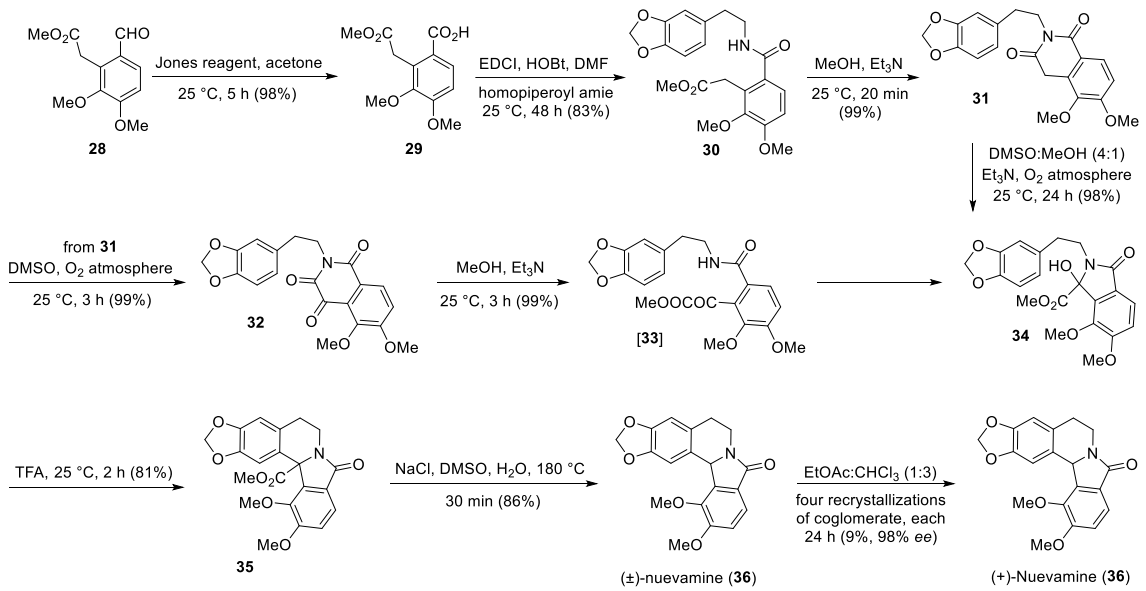


Scheme 10. Total Synthesis of 6-Hydroxymetatacarboline D Using $CuBr_2$ Catalyzed Air-Oxidation of 3,4-Dihydro-*β*-Carbolines to *β*-Carbolines

2A.1.2 Aerobic Oxidations Reported on Our Research Group

Argade and co-workers in 2008 reported the total synthesis of nuevamine by taking the advantage of facile air-oxidation propensity of the active methylene group in homophthalimide to the corresponding carbonyl group (Scheme 11).[35,36] The aldehyde **28** on Jones oxidation gave the desired 3,4-dimethoxyhomophthalic acid mono-ester **29** in 98% yield. The EDCI induced coupling reaction of **29** with homopiperonyl amine gave the homophthalamic acid methyl ester **30** in 83% yield. The ester **30** in methanol, on treatment with triethylamine at 25 °C gave the homophthalimide **31** in quantitative yield. The solution of imide **31** in DMSO:MeOH mixture (4:1), on treatment with triethylamine under the oxygen atmosphere furnished **34** in 98% yield via the facile air-oxidation

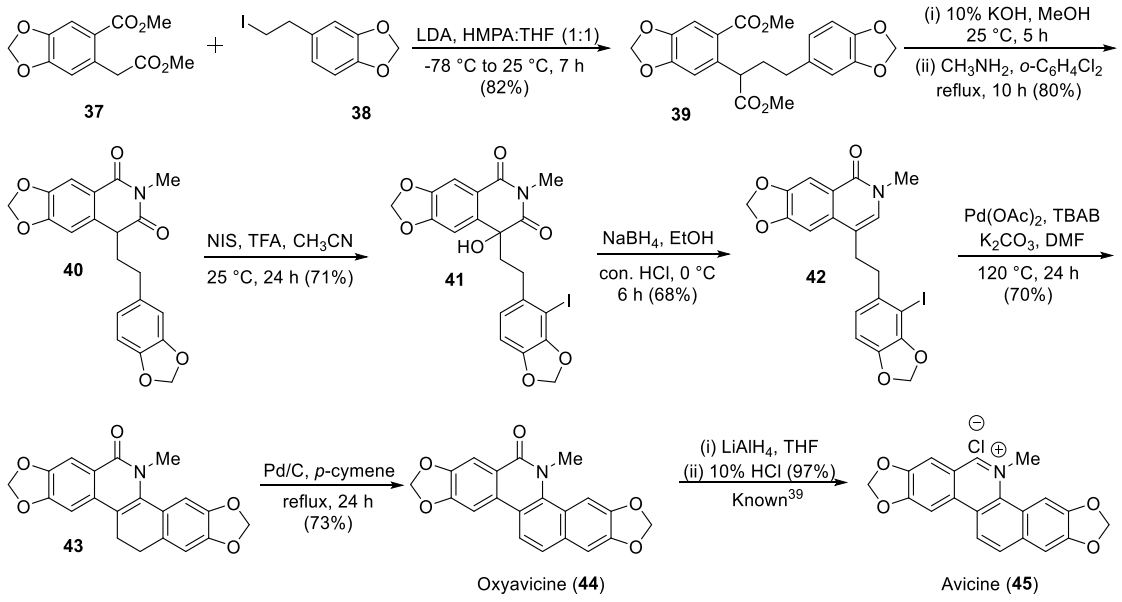
pathway. In a control experiment, imide **31** in DMSO under the oxygen environment for 48 h at the room temperature underwent the facile air-oxidation of methylene group in **31** to form the trione **32** in 99% yield. Treatment on compound **32** with triethylamine and methanol provided the product **34** via the unisolable intermediate **33**. The lactamol **34** on TFA catalyzed cyclization gave the compound **35** in 81% yield. The decarboxylation of **35** in the absence of oxygen, gave the desired natural product (±)-nuevamine (**36**) in 86% yield. Starting from aldehyde **28**, the nuevamine was obtained in six steps with 55% overall yield. The single crystal X-ray data indicated that the crystalline nuevamine racemate is a rare conglomerate. As expected, the four successive recrystallizations of (±)-**36** from ethyl acetate:chloroform mixture (3:1) led to the spontaneous resolution to furnish the enantiomerically pure (+)-nuevamine (**36**) in 9% recrystallization yield with 98% *ee*.



Scheme 11. Synthesis of Nuevamine via Air-Oxidation

Argade and co-workers in 2012 reported the convergent synthesis of oxyavicine (**44**) with an intramolecular Heck-coupling reaction as the key step (Scheme 12).[37,38] Synthesis started from diester **37**, which on base catalyzed alkylation with iodo compound **38** gave coupling product **39** in 82% yield. The hydrolysis of diester **39** using potassium hydroxide provided the corresponding dicarboxylic acid. The obtained dicarboxylic acid was treated with aqueous solution of methyl amine to form the corresponding salt. The

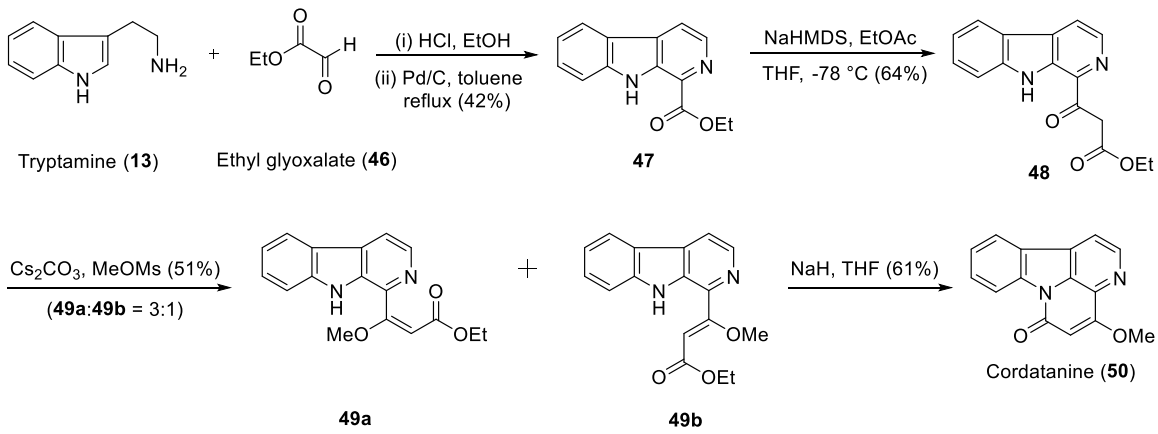
cyclization of the salt in refluxing *o*-dichlorobenzene provided the *N*-methylhomophthalimide **40** in 80% yield. At this step they planned to introduce the iodine at an appropriate position in an aryl part of an alkyl unit in imide **40** for the Heck coupling reaction. The selective iodination of the activated aryl moiety in compound **40** using *N*-iodosuccinimide in the presence of a TFA formed the iodo-compound. In the above specified iodination reaction of compound **40**, air-oxidation of the activated methine carbon also took place simultaneously to form the hydroxylated iodo-compound **41** in 71% yield. The regioselective $NaBH_4$ reduction of the more reactive unconjugated carbonyl group of the homophthlimide **41** followed by the acid-catalyzed dehydration took place in one-pot to provide the desired pivotal building block **42** in 68% yield. Palladium-catalyzed Heck coupling reaction of thus formed unsaturated lactam **42** under the standard set of reaction conditions delivered the desired oxyavicine architecture **43** in 70% yield. Finally, the palladium on charcoal induced dehydrogenation of compound **43** in refluxing *p*-cymene furnished the natural product oxyavicine (**44**) in 73% yield. The oxyavicine was obtained in six steps with 16% overall yield. The conversion of oxyavicine (**44**) to the avicine (**45**) alkaloid with 97% efficiency is known in the literature.[39]



Scheme 12. Synthesis of Oxyavicine and Formal Synthesis of Avicine via Air-Oxidation

2A.1.3 Reported Concise Synthesis of Cordatanine

Wu and co-workers in 2015 reported the first total synthesis of the target compound cordatanine in four steps via Pictet-Spengler reaction (Scheme 13).[40] Pictet-Spengler reaction of tryptamine (**13**) and ethyl glyoxalate (**46**) followed by direct oxidative aromatization with palladium on charcoal formed the aromatic β-carboline **47**. Reaction of ethyl acetate enolate with β-carboline **47** gave β-keto ester **48** in 64% yield. The *O*-methylation of product **48** using cesium carbonate (Cs_2CO_3) gave *E*- and *Z*-mixture of products **49a** and **49b** in 3:1 ratio, respectively. They performed the intramolecular cyclization on the mixture of **49a** and **49b** using sodium hydride as a base and obtained the desired β-carboline alkaloid cordatanine (**50**) in 61% yield.



Scheme 13. First Total Synthesis of Cordatanine

2A.2 Results and Discussion (Present Research Work)

Total Synthesis of Bioactive Canthine Alkaloid Cordatanine Comprising in Situ Double Oxidative Aromatization of Tetrahydrocarbazole

Canthines are an important section of β-carboline alkaloids and nearly 200 canthinone alkaloids exhibiting broad range of potential bioactivities have been known in the literature.[41,42] Pentralis [6*H*-indolo(3,2,1-*de*)(1,5)naphthyridin-6-one] from figure 2 was first isolated in 1952 and several strategically elegant syntheses of this class of compounds are known in the contemporary literature.[41–47] The anti-HIV alkaloid cordatanine (4-methoxycanthin-6-one) was isolated from *Drymaria cordata* in 1986 and then from *Drymaria diandra* in 2004 (EC_{50} 0.699 μg/mL).[48–50] The antifungal alkaloid

zanthochilone (5-methoxycanthin-6-one) has been isolated from the plant species *Zanthoxylum chiloperone* var. *angustifolium*.[2,3] Total synthesis of cordatanine and zanthochilone is a challenging task of current interest from their structural features, potential bioactivities and the seasonal changes affecting on their concentration in natural sources points of view.[2,3,48–50] Recently, Wu et al accomplished synthesis of cordatanine in four steps with 8% overall yield and unambiguously confirmed its revised structural assignment (Scheme 13);[40,49,50] while synthesis of zanthochilone is awaited. In continuation of our studies on the use of cyclic anhydrides to synthesize bioactive natural products;[51–55] we herein report facile regioselective approach to cordatanine and attempted synthesis of zanthochilone from the readily available common precursors tryptamine and methoxymaleic anhydride[56] (Schemes 14 to 17).

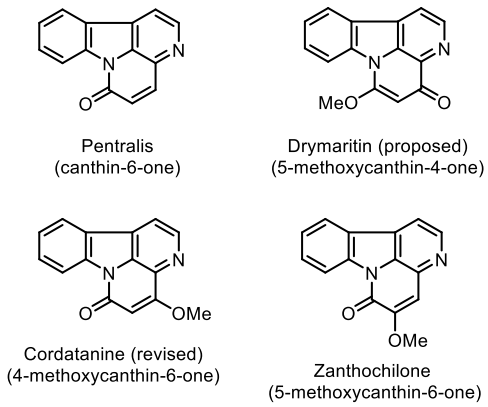
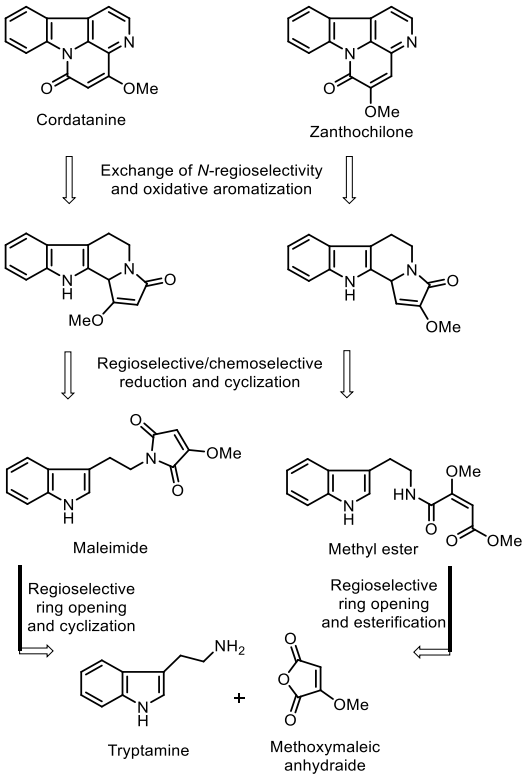


Figure 2. Representative bioactive canthin alkaloids

A concise retrosynthetic analysis of regioisomeric natural products cordatanine (**50**) and zanthochilone (**65**) has been depicted in scheme 14 aiming synthesis of two regioisomeric pyrrolotetrahydrocarbazole intermediates, intramolecular exchange of nitrogen regioselectivity and aromatization of ring C. Reaction of tryptamine (**13**) with the freshly prepared methoxymaleic anhydride (**51**)[56] in refluxing *o*-dichlorobenzene delivered the required methoxymaleimide **52** in 84% yield via regioselective ring opening of **51** followed by intramolecular dehydrative cyclization route (Scheme 15). Regioselective $NaBH_4$ reduction of more reactive mesomerically non-conjugated imide carbonyl in **52** exclusively formed the lactamol **53a** in 97% yield. In the above specified reaction mesomeric conjugation of lone pair of oxygen from methoxyl group deactivates one of

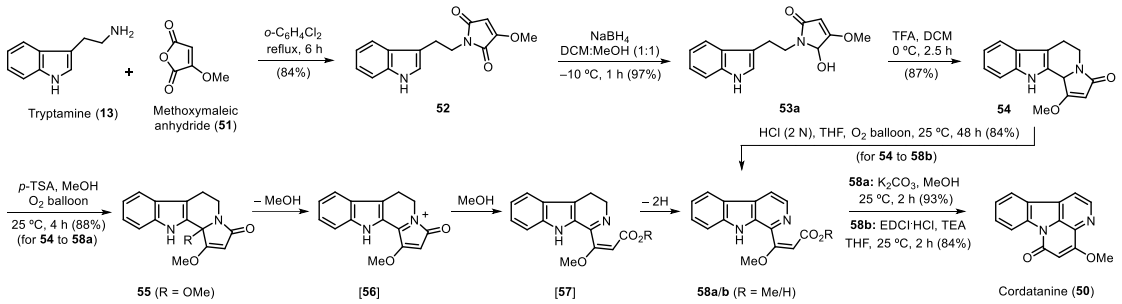
the carbonyl group and the sterically hindered carbonyl undergoes selective reduction. Lactamol **53a** was fairly stable to the silica gel column chromatographic purification and



Scheme 14. Concise Retrosynthetic Analysis of Regioisomeric Cordatanine and Zanthochilone Alkaloids

did not display any noticeable signs of associated decomposition. Acid-catalyzed intramolecular dehydrative cyclization of lactamol **53a** furnished the pyrrolotetrahydrocarbazole **54** in 87% yield. At this stage it was planned to perform the methanolysis of pyrrolotetrahydrocarbazole **54** and then the oxidative aromatization. Accordingly performed reaction of pyrrolotetrahydrocarbazole **54** with *p*-TSA/MeOH at room temperature under atmospheric conditions directly provided the completely aromatized ester **58a** in acceptable yields (~50%) in 24 hours. In the above-mentioned reaction, both methanolysis of lactam to ester and double air-oxidative aromatization of the ring C took place in one-pot. As expected, repetition of the same reaction under balloon pressure oxygen atmosphere delivered product **58a** with 88% yield in just 4 hours. Careful TLC monitoring of the above reaction also revealed that it would be feasible to isolate one of the reaction intermediate in the transformation of **54** to **58a**. Thus, the reaction of **54** with *p*-TSA/MeOH at room temperature under oxygen

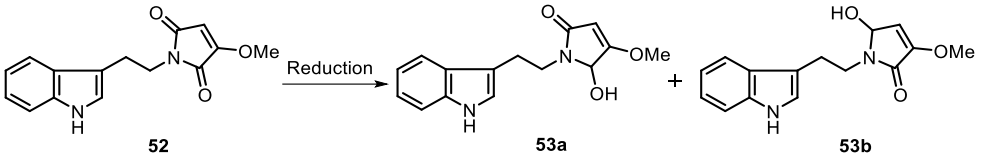
atmosphere was arrested after one hour and we could successfully isolate the formed intermediate product pyrrolotetrahydrocarbazole **55** bearing labile angular methoxyl group, in 47% yield. The anti-cancer drug mitomycin C contains such type of angular oxygen function responsible for its several fold higher activity than the corresponding mitosanes.[57] The intermediate product **55** on similar treatment with *p*-TSA/MeOH at room temperature under oxygen atmosphere also delivered the expected product **58a** in very good yield. Thus, we propose that mechanistically first the methoxyl group gets introduced at the highly reactive benzylic angular position of compound **54** via radical mechanism to form the product **55**, which on protonation followed by elimination of methanol forms the reactive iminium ion intermediate **56**, which quickly undergoes methanolysis to deliver the corresponding dihydroester **57** and finally the formed ester **57** in situ oxidizes to yield the stable aromatic penultimate product **58a**. Alternatively performed reaction of pyrrolotetrahydrocarbazole **54** with HCl/THF at room temperature under oxygen atmosphere plausibly followed similar type of mechanistic pathway and also furnished the expected acid **58b** in 84% yield. Finally, both K_2CO_3/MeOH catalyzed intramolecular cyclization of ester **58a** and EDCI-induced intramolecular dehydrative cyclization of acid **58b** resulted into the desired natural product cordatanine (**50**) in 93% and 84% yields respectively. The obtained analytical and spectral data for cordatanine (**50**) was in complete agreement with reported data.[40,49,50]



Scheme 15. Concise and Efficient Regioselective Total Synthesis of Cordatanine Involving Stepwise Oxidative Aromatization

In the next part of studies, synthesis of regioisomeric second target compound zanthochilone (**65**) was logically planned via reversal in regioselective reduction of methoxymaleimide **52** and selected results on reduction of imide **52** have been summarized in table 1. DIBAL-H reduction of imide **52** at –78 °C provided silica gel column chromatographically separable mixture of lactamols **53a** (undesired) and **53b**

(desired) in 72% yield but only with 68:32 ratio (Scheme 16; Table 1, entry 5). We feel that in the reduction of imide **52** small amount of desired isomer **53b** is formed at lower temperature due to the steric hindrance of methoxyl group and also could be due to the



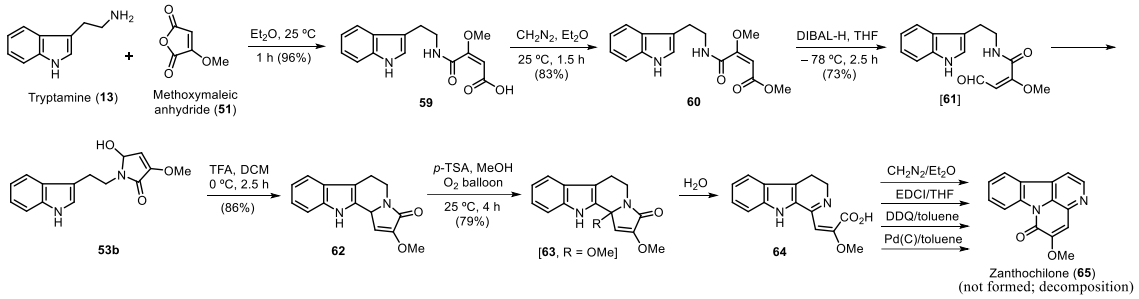
Scheme 16. Regioselective Reduction of Methoxymaleimide

Table 1. Study on Reversal of Regioselectivity in the Reduction of Methoxymaleimide

Sr. No.	Reduction Conditions	Yield (53a:53b)
1	$NaBH_4$ (5.00 equiv), DCM:MeOH (1:1), –10 °C, 1 h	97% (100:0)
2	KBH_4 (5.00 equiv), DCM:MeOH (1:1), –10 °C, 1 h	94% (100:0)
3	*K*-Selectride (3.30 equiv), THF, –78 °C, 2 h	88% (95:5)
4	*N*-Selectride (3.30 equiv), THF, –78 °C, 2 h	83% (94:6)
5	DIBAL-H (3.30 equiv), THF, –78 °C, 2.5 h	72% (68:32)
6	DIBAL-H (3.30 equiv), THF, –100 °C, 3 h	SM-PPT

partial decline in the mesomeric deactivation. Regioselective ring opening of methoxymaleic anhydride (**51**) with tryptamine (**13**) in diethyl ether formed maleamic acid **59** in 96% yield; which upon diazomethane esterification resulted in the corresponding ester **60** in 83% yield (Scheme 17). The alternatively performed controlled chemoselective DIBAL-H reduction of ester **60** at –78 °C exclusively furnished the desired lactamol **53b** in 73% yield via the corresponding unisolable intermediate aldehyde **61**. Acid-catalyzed intramolecular dehydrative cyclization of lactamol **53b** yielded the planned regioisomeric pyrrolotetrahydrocarbazole **62** in 86% yield. Accordingly performed reaction of pyrrolotetrahydrocarbazole **62** with *p*-TSA/MeOH at room temperature under balloon pressure oxygen atmosphere delivered the acid **64** in 79% yield, but without the aromatization of ring C. We presume that in the pyrrolotetrahydrocarbazole **62**, hydrolysis of γ-lactam to form acid **64** was preferred over the methanolysis for steric reasons. In the acid **64** conjugation of methoxyl group with labile imine moiety could be the cause for deactivation of system which plausibly

prohibited in situ oxidative aromatization of ring C. Remarkably, the propensity of oxidation of ring C is dependent on reactivity of imine moiety and the position of methoxyl group. All attempts to transform the acid **64** to zanthochilone (**65**) via diazomethane esterification, EDCI mediated intramolecular dehydrative cyclization and DDQ/Pd(C)-oxidation of ring C met with failure and ended up in excessive decompositions of reaction mixtures.



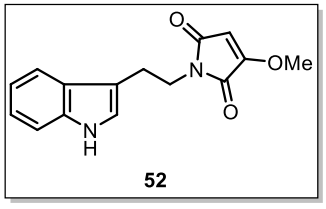
Scheme 17. Attempted Regioselective Synthesis of Zanthochilone Involving Reversal in Reduction Selectivity

2A.3 Summary

In conclusion, practical total synthesis of cordatanine has been accomplished by taking the advantage of facile oxygen promoted stepwise oxidative aromatization. Synthesis of two regioisomeric methoxyl-substituted pyrrolotetrahydrocarbazoles from methoxymaleimide and methyl ester of methoxymaleamic acid is noteworthy. Unfortunately, we were unable to complete the first total synthesis of isomeric zanthochilone alkaloid due to the decomposition of penultimate step product under the sets of our reaction conditions.

2A.4 Experimental Section

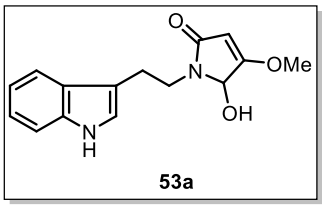
1-[2-(1*H*-Indol-3-yl)ethyl]-3-methoxy-1*H*-pyrrole-2,5-dione (52). Stirred solution of



tryptamine (**13**; 2.00 g, 12.48 mmol) and methoxymaleic anhydride (**51**; 1.60 g, 12.48 mmol) in *o*-dichlorobenzene (20 mL) was heated at reflux for 6 h. After cooling the reaction mixture, it was loaded on silica gel (60–120 mesh) column and initially the column was eluted with petroleum ether for the removal of *o*-dichlorobenzene and then it was eluted with ethyl acetate–petroleum ether mixture (3:7) to obtain pure

methoxymaleimide **52** as a yellow crystalline solid (2.83 g, 84%). Mp 126–128 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.07 (t, J = 8.0 Hz, 2H), 3.83 (t, J = 8.0 Hz, 2H), 3.90 (s, 3H), 5.37 (s, 1H), 7.06 (d, J = 2.2 Hz, 1H), 7.14 (t, J = 7.1 Hz, 1H), 7.20 (t, J = 7.1 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 8.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.4, 38.1, 58.8, 96.1, 111.1, 112.2, 118.8, 119.4, 122.0, 122.1, 127.4, 136.2, 160.9, 165.6, 170.1; ESIMS (m/z) 293 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{14}O_3N_2Na$ 293.0897, found 293.0894; IR ($CHCl_3$) ν_{max} 3385, 1714, 1643 cm^{-1}.

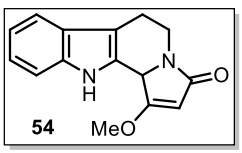
1-[2-(1*H*-Indol-3-yl)ethyl]-5-hydroxy-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (53a).



53a

To a stirred solution of compound **52** (2.00 g, 7.40 mmol) in MeOH:CH_2Cl_2 (1:1, 20 mL) was added $NaBH_4$ (840 mg, 22.22 mmol) at –10 °C. The reaction mixture was stirred for 1 h at the same temperature and the reaction was quenched with saturated aq. NH_4Cl (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded lactamol **53a** as a colorless solid (1.95 g, 97%). Mp 58–60 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.02 (t, J = 7.3 Hz, 2H), 3.45–3.65 (m, 1H), 3.69 (s, 3H), 3.75–3.95 (m, 1H), 3.95–4.10 (br s, 1H), 4.91 (s, 1H), 5.06 (d, J = 5.9 Hz, 1H), 6.96 (s, 1H), 7.08 (t, J = 8.5 Hz, 1H), 7.17 (t, J = 9.5 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 8.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.4, 39.4, 58.3, 81.0, 93.2, 111.2, 112.9, 118.7, 119.3, 121.9, 122.0, 127.3, 136.2, 170.7, 173.8; ESIMS (m/z) 295 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{16}O_3N_2Na$ 295.1053, found 295.1052; IR ($CHCl_3$) ν_{max} 3620, 3477, 1676, 1641 cm^{-1}.

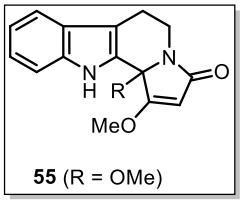
1-Methoxy-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-b)indol-3-one (54). To a stirred solution of lacamol **53a** (1.50 g, 5.51 mmol) in CH_2Cl_2 (20 mL) was dropwise added trifluoroacetic acid (0.84 mL, 11.02 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2.5 h. The reaction was quenched with saturated aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded product **54** as a faint yellow solid (1.21 g, 87%). Mp 140–142



54

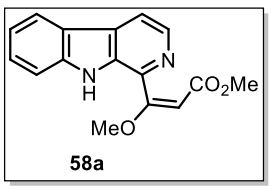
°C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.70–3.00 (m, 2H), 3.03–3.23 (m, 1H), 3.89 (s, 3H), 4.64 (dd, *J* = 13.2 and 5.1 Hz, 1H), 5.12 (s, 1H), 5.25 (s, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 8.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 37.3, 56.8, 58.7, 94.4, 109.2, 111.0, 118.7, 119.8, 122.5, 126.6, 128.0, 136.3, 172.3, 174.2; ESIMS (*m*/*z*) 255 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_2N_2$ 255.1128, found 255.1125; IR ($CHCl_3$) ν_{max} 3408, 1651, 1603 cm^{-1}.

1,11b-Dimethoxy-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-3-one (55). To a stirred solution of compound **54** (300 mg, 1.18 mmol) in MeOH (20 mL) was added *p*-TSA (1.01 g, 5.90 mmol) at 25 °C under oxygen atmosphere. Reaction mixture was stirred for 1 h and the reaction was quenched with saturated aq. $NaHCO_3$ (5 mL). MeOH was removed in vacuo and the residue was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent afforded product **55** as a colorless solid (157 mg, 47%). Mp 80–82 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.78 (dd, *J* = 15.6 and 4.4 Hz, 1H), 2.83–2.95 (m, 1H), 3.15–3.28 (m, 1H), 3.28 (s, 3H), 3.93 (s, 3H), 4.50 (dd, *J* = 13.2 and 5.4 Hz, 1H), 5.16 (s, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2, 35.5, 50.7, 58.8, 86.6, 95.0, 111.4, 111.7, 119.4, 119.9, 123.3, 125.9, 128.6, 136.4, 171.2, 172.7; ESIMS (*m*/*z*) 285 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{17}O_3N_2$ 285.1234, found 285.1231; IR ($CHCl_3$) ν_{max} 3408, 1731, 1602 cm^{-1}.



55 (R = OMe)

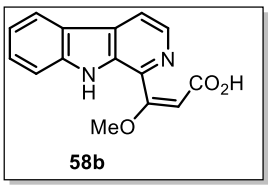
Methyl (*E*)-3-Methoxy-3-[9*H*-pyrido(3,4-*b*)indol-1-yl]acrylate (58a). To a stirred solution of compound **54** (300 mg, 1.18 mmol) in MeOH (20 mL) was added *p*-TSA (1.01 g, 5.90 mmol) at 25 °C under oxygen atmosphere. Reaction mixture was stirred for 4 h and the reaction was quenched with saturated aq. $NaHCO_3$ (5 mL). MeOH was removed in vacuo and the residue was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent provided product **58a** as thick yellow oil (293 mg, 88%). ^{1}H NMR



58a

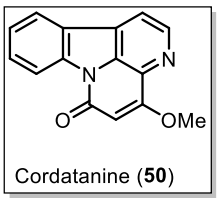
($CDCl_3$, 400 MHz) δ 3.54 (s, 3H), 3.93 (s, 3H), 5.58 (s, 1H), 7.29 (t, J = 6.5 Hz, 1H), 7.45–7.60 (m, 2H), 7.99 (s, 1H), 8.10 (d, J = 7.3 Hz, 1H), 8.47 (s, 1H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.4, 56.8, 95.4, 111.8, 115.8, 120.3, 121.3, 121.7, 128.9, 130.4, 133.9, 136.3, 137.8, 140.7, 165.6, 167.1; ESIMS (*m*/*z*) 283 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}O_3N_2$ 283.1077, found 283.1070; IR ($CHCl_3$) ν_{max} 3432, 1722, 1602 cm^{-1}.

(*E*)-3-Methoxy-3-[9*H*-pyrido(3,4-*b*)indol-1-yl]acrylic Acid (58b). To a stirred solution of compound **54** (300 mg, 1.18 mmol) in THF (5 mL) was added dilute HCl (2 N, 5 mL) at 25 °C under oxygen atmosphere. Reaction mixture was stirred for 48 h and precipitated solid was filtered, washed with ethyl acetate (10 mL) and vacuum dried to obtain acid **58b** as a yellow solid (265 mg, 84%). Mp 128–132 °C, ^{1}H NMR (CD_3OD, 500 MHz) δ 4.11 (s, 3H), 6.05 (s, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.50 (d, J = 6.1 Hz, 1H), 8.75 (d, J = 6.1 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 58.9, 101.3, 114.0, 119.0, 121.2, 123.5, 124.5, 130.0, 132.4, 133.9, 134.9, 137.3, 146.1, 160.5, 168.5; ESIMS (*m*/*z*) 269 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{13}O_3N_2$ 269.0921, found 269.0915; IR ($CHCl_3$) ν_{max} 3425, 1738, 1599 cm^{-1}.



58b

4-Methoxy-6*H*-indolo(3,2,1-*de*)(1,5)naphthyridin-6-one (50). *Method A.* To a stirred solution of ester **58a** (200 mg, 0.71 mmol) in MeOH (10 mL) was added K_2CO_3 (196 mg, 1.41 mmol) at 25 °C and the reaction mixture was stirred for 2 h. Methanol was removed in vacuo and the residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent afforded cordatanine (**50**) as a yellow solid (165 mg, 93%).

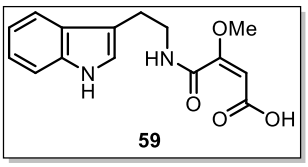


Cordatanine (**50**)

Method B. To a stirred solution of carboxylic acid **58b** (200 mg, 0.746 mmol) in THF (10 mL) was added EDCI·HCl (314 mg, 1.64 mmol), DMAP (9 mg, 0.074 mmol) and Et_3N (0.350 mL, 2.46 mmol) at 25 °C and the reaction mixture was stirred for 2 h. The reaction was quenched with water (2 mL) and reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–

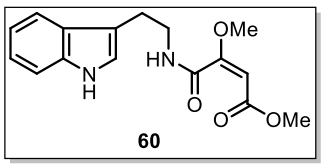
petroleum ether (1:1) as an eluent afforded cordatanine (**50**) as a yellow solid (156 mg, 84%). Mp 182–183 °C (lit.[9] mp 181–183 °C), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (s, 3H), 6.13 (s, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.93 (d, J = 4.9 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 8.57 (d, J = 8.3 Hz, 1H), 8.78 (d, J = 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.9, 101.8, 116.9 (2C), 122.6, 124.3, 125.0, 130.5, 131.0, 131.96, 132.03, 139.3, 145.1, 160.9, 164.1; ESIMS (*m*/*z*) 251 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{11}O_2N_2$ 251.0815, found 251.0811; IR ($CHCl_3$) ν_{max} 1662, 1649, 1620 cm^{-1}.

(*E*)-4-{[2-(1*H*-Indol-3-yl)ethyl]amino}-3-methoxy-4-oxobut-2-enoic Acid (59). To a stirred solution of methoxymaleic anhydride (**51**; 2.40 g, 18.72 mmol) in Et_2O (30 mL) was added tryptamine (**13**; 3.00 g, 18.72 mmol) at 25 °C and the reaction mixture was stirred for 1 h. The precipitated product was filtered, washed with Et_2O (25 mL) and dried under vacuum to obtain carboxylic acid **59** as a colorless solid (5.184 g, 96%). Mp 170–172 °C, ^{1}H NMR (CD_3OD, 400 MHz) δ 3.01 (t, J = 7.3 Hz, 2H), 3.58 (t, J = 7.3 Hz, 2H), 3.72 (s, 3H), 5.39 (s, 1H), 7.00 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 7.09 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 25.9, 41.9, 57.1, 100.4, 112.4, 112.7, 113.1, 119.4, 119.7, 122.5, 123.7, 128.9, 138.3, 161.3, 166.0; ESIMS (*m*/*z*) 289 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}O_4N_2$ 289.1183, found 289.1178; IR ($CHCl_3$) ν_{max} 3369, 3281, 1701, 1623, 1600 cm^{-1}.



59

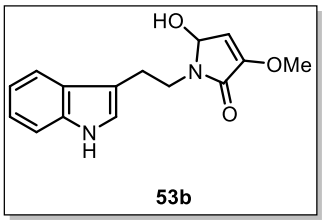
Methyl (*E*)-4-{[2-(1*H*-Indol-3-yl)ethyl]amino}-3-methoxy-4-oxobut-2-enoate (60). To a stirred solution of acid **59** (1.00 g, 3.47 mmol) in Et_2O and methanol (1:1, 20 mL) was added solution of diazomethane in Et_2O at 25 °C until persistence of a yellow colour. Reaction mixture was stirred for 1.5 h and concentrated in vacuo. The obtained residue was extracted with ethyl acetate (3 × 20 mL) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent afforded ester **60** as gum (870 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (t, J = 7.3 Hz, 2H), 3.66 (s, 3H), 3.71 (t, J = 7.9 Hz, 2H), 3.74 (s, 3H), 5.21 (s, 1H), 6.66 (br s, 1H), 7.07 (s, 1H), 7.12 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.21 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.9, 29.8, 51.8, 56.3, 94.9, 111.2, 112.7, 118.7, 119.4,



60

122.1, 122.2, 127.3, 136.4, 161.5, 162.3, 166.8; ESIMS (*m*/*z*) 303 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{19}O_4N_2$ 303.1339, found 303.1335; IR ($CHCl_3$) ν_{max} 3422, 1714, 1618 cm^{-1}.

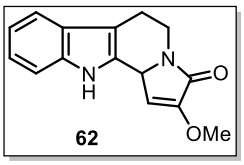
1-[2-(1*H*-Indol-3-yl)ethyl]-5-hydroxy-3-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (53b).



53b

To a stirred solution of ester **60** (500 mg, 1.66 mmol) in THF (10 mL) was dropwise added DIBAL-H (1 M in cyclohexane, 5.50 mL) at –78 °C under argon atmosphere and the reaction mixture was stirred for 2.5 h. The reaction was quenched with saturated potassium sodium tartrate (5 mL), stirred for 1 h and concentrated in vacuo. The obtained residue was extracted with ethyl acetate (3 ×20 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded alcohol **53b** as a colorless solid (329 mg, 73%). Mp 70–72 °C, ^{1}H NMR (acetone-d_6, 400 MHz) δ 2.95–3.15 (m, 2H), 3.50–3.60 (m, 1H), 3.71 (s, 3H), 3.75–3.85 (m, 1H), 4.97 (d, J = 9.8 Hz, 1H), 5.35 (d, J = 9.5 Hz, 1H), 5.69 (s, 1H), 7.02 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 7.18 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 10.02 (br s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 25.2, 40.8, 57.6, 80.2, 108.5, 112.3, 113.2, 119.4, 119.5, 122.2, 123.3, 128.6, 137.8, 154.1, 164.5; ESIMS (*m*/*z*) 273 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}O_3N_2$ 273.1234, found 273.1229; IR ($CHCl_3$) ν_{max} 3621, 3374, 1704, 1599 cm^{-1}.

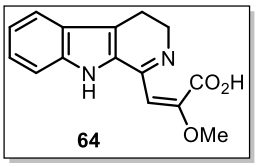
2-Methoxy-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-3-one (62). To a stirred solution of alcohol **53b** (300 mg, 1.10 mmol) in CH_2Cl_2 (10 mL) was dropwise added trifluoroacetic acid (0.17 mL, 2.20 mmol) at 0 °C and the reaction mixture was stirred for 2.5 h. The reaction was quenched with saturated aq. $NaHCO_3$ (3 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent afforded product **62** as a faint brown solid (240 mg, 86%). Mp 136–138 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55–2.75 (m, 2H), 3.00–3.13 (m, 1H), 3.57 (s, 3H), 4.45 (dd, J = 13.1 and 5.5 Hz, 1H), 5.11 (s, 1H), 6.03 (s, 1H), 6.86 (t, J = 7.3 Hz, 1H), 6.95 (t, J = 7.9 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 10.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 38.0, 53.8, 56.7, 106.3, 107.0,



62

110.6, 117.9, 118.7, 121.3, 126.1, 130.9, 136.0, 151.6, 165.0; ESIMS (*m*/*z*) 255 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_2N_2$ 255.1128, found 255.1124; IR ($CHCl_3$) ν_{max} 3421, 1735, 1597 cm^{-1}.

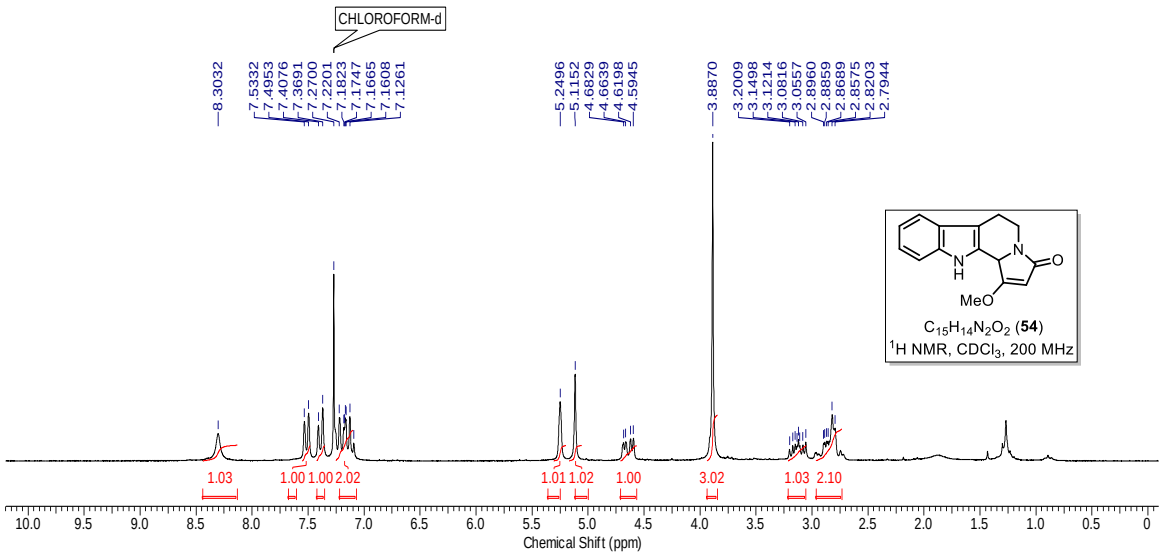
(*E*)-3-[4,9-Dihydro-3*H*-pyrido(3,4-*b*)indol-1-yl]-2-methoxyacrylic Acid (64). To a

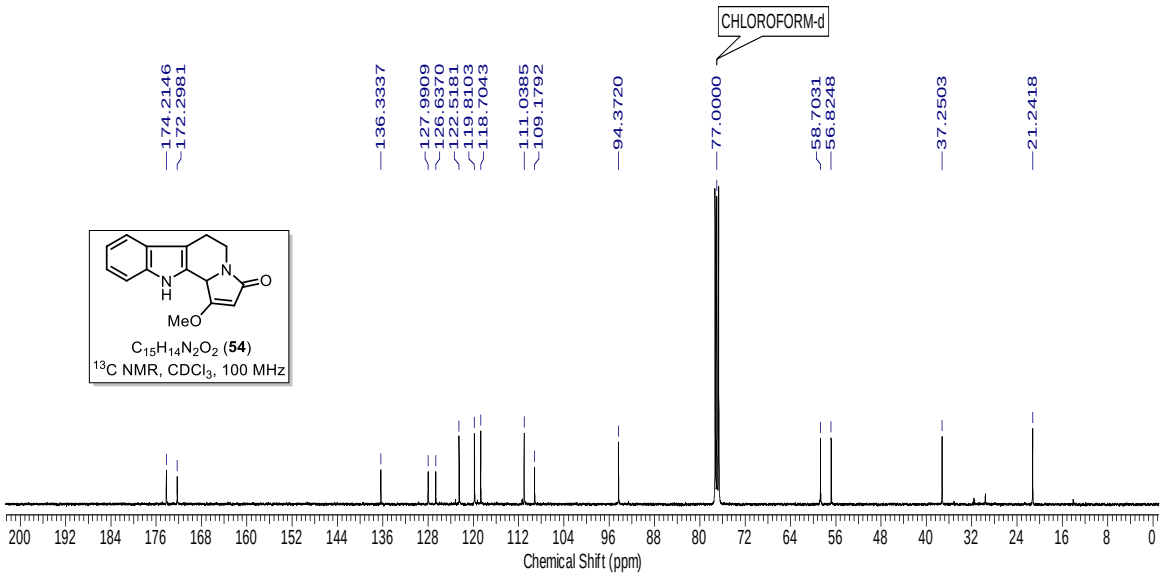


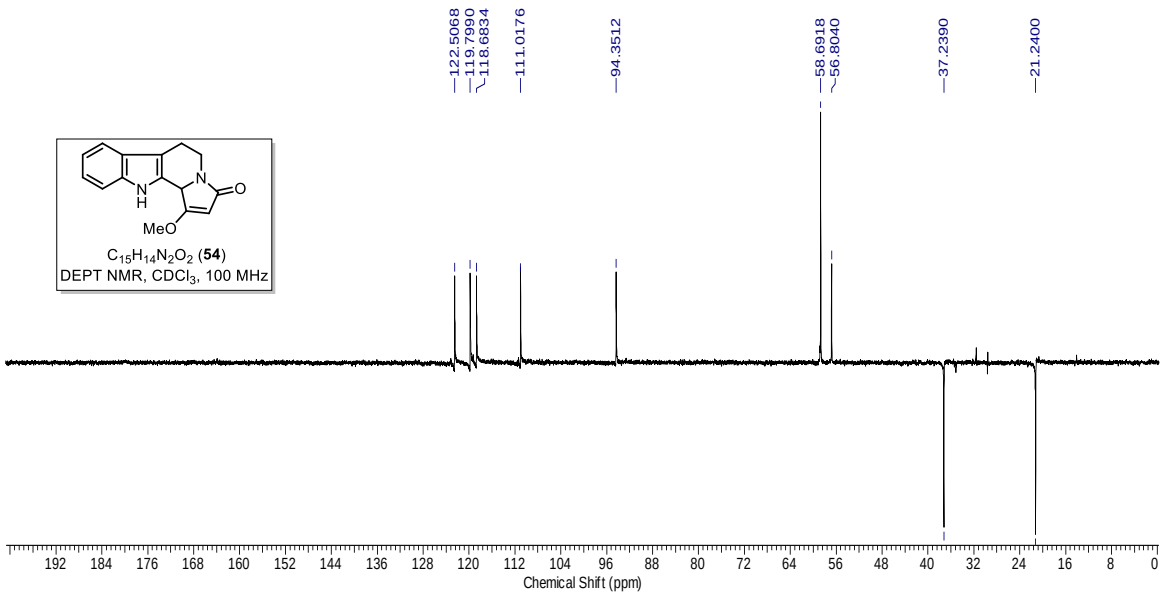
64

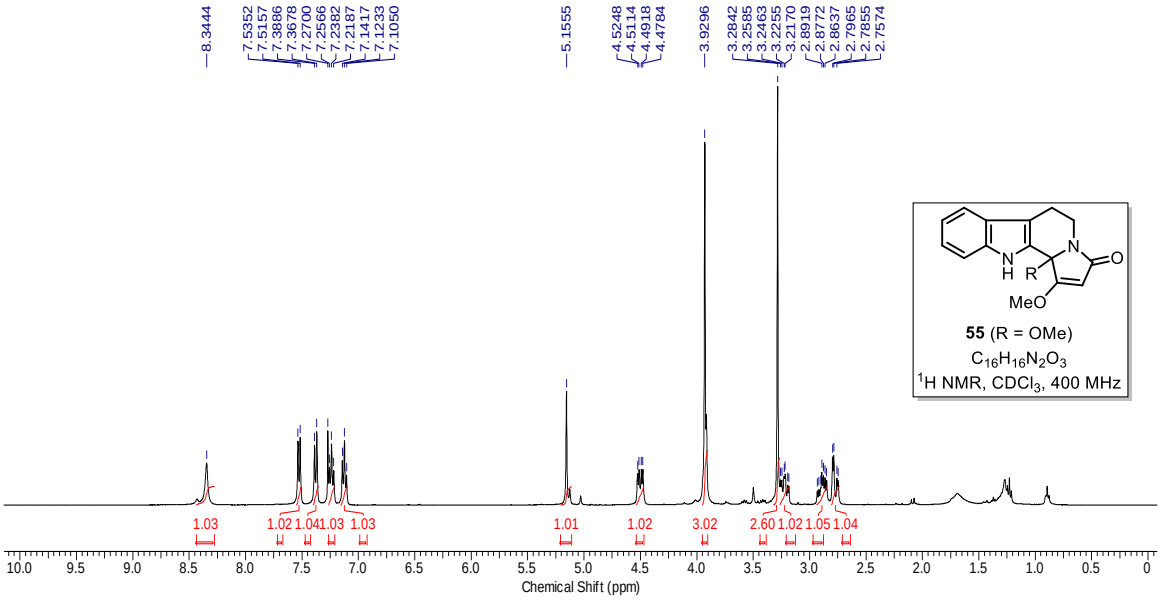
stirred solution of compound **62** (200 mg, 0.78 mmol) in MeOH (20 mL) was added *p*-TSA (677 mg, 3.93 mmol) at 25 °C under oxygen atmosphere. Reaction mixture was stirred for 4 h and the reaction was quenched with saturated aq. $NaHCO_3$ (3 mL). MeOH was removed in vacuo and the residue was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent provided acid **64** as a yellow solid (168 mg, 79%). Mp 140–142 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ 3.11 (t, *J* = 7.9 Hz, 2H), 3.70–3.80 (m, 2H), 3.89 (s, 3H), 6.65 (s, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 8.54 (br s, 1H), 10.73 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 40.4, 52.7, 87.0, 112.1, 118.3, 120.1, 120.9, 125.7, 125.9, 126.5, 138.0, 154.8, 164.8, 176.3; ESIMS (*m*/*z*) 271 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_3N_2$ 271.1077, found 271.1081; IR ($CHCl_3$) ν_{max} 3422, 1738, 1597 cm^{-1}.

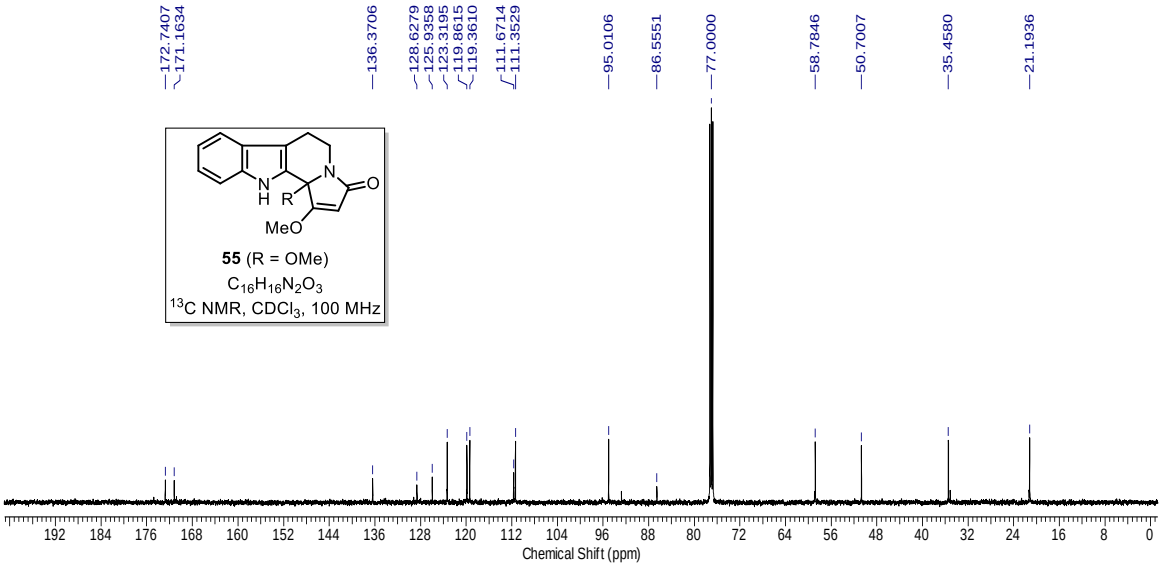
2A.5 Selected Spectra

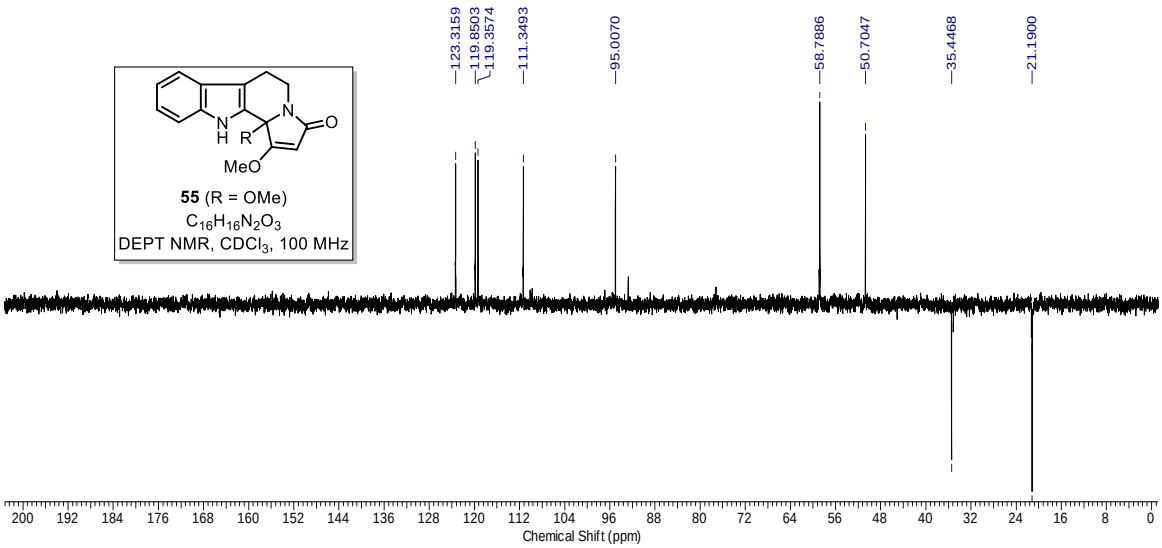

CHLOROFORM-d
8.3032
7.5332
7.4953
7.4076
7.3691
7.2700
7.2201
7.1823
7.1747
7.1665
7.1608
7.1261
5.2496
5.1152
4.6829
4.6639
4.6198
4.5945
3.8870
3.2009
3.1498
3.1214
3.0816
3.0557
2.8960
2.8859
2.8689
2.8575
2.8203
2.7944
1.03
1.00
1.00
2.02
1.01
1.02
1.00
3.02
1.03
2.10
MeO
C15H14N2O2 (54)
1H NMR, CDCl3, 200 MHz
Chemical Shift (ppm)

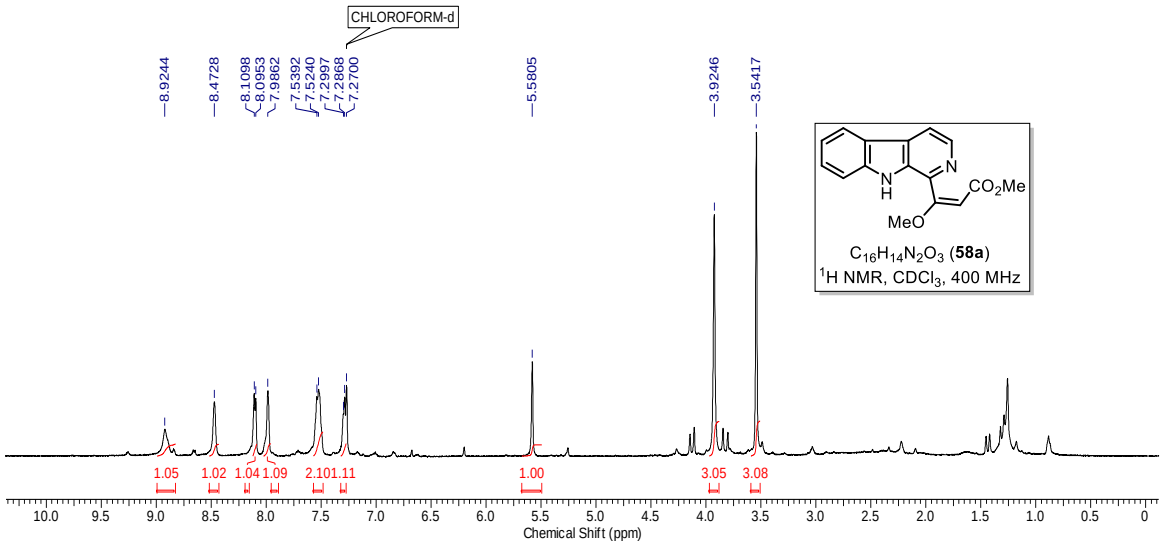

CHLOROFORM-d
174.2146
172.2981
136.3337
127.9909
126.6370
122.5181
119.8103
118.7043
111.0385
109.1792
94.3720
77.0000
58.7031
56.8248
37.2503
21.2418
MeO
C15H14N2O2 (54)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)

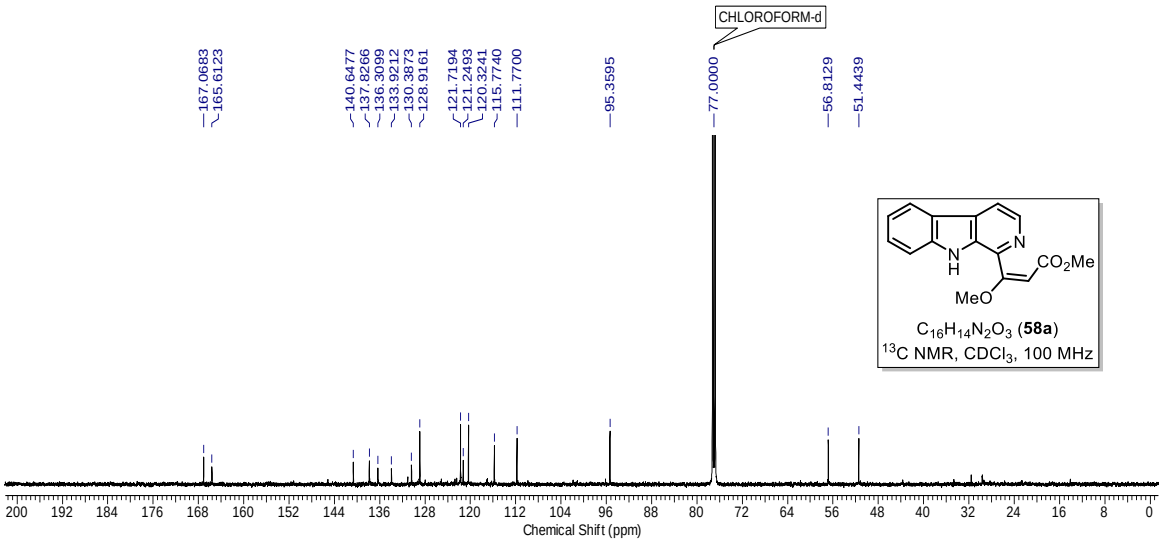

122.5068
119.7990
118.6834
111.0176
94.3512
58.6918
56.8040
37.2390
21.2400
MeO
C15H14N2O2 (54)
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)

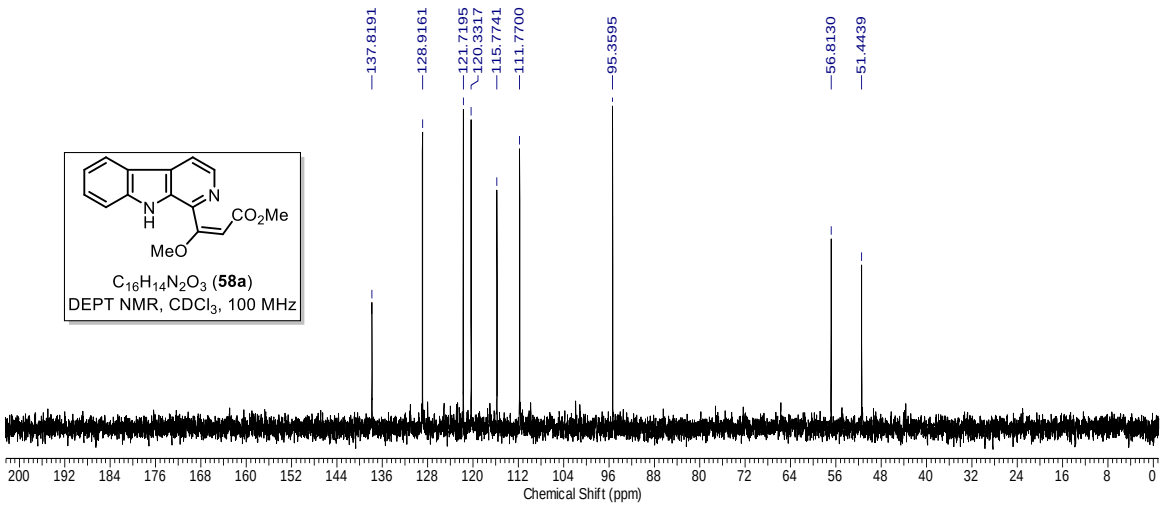

8.3444
7.5352
7.5157
7.3886
7.3678
7.2700
7.2566
7.2382
7.2187
7.1417
7.1233
7.1050
5.1555
4.5248
4.5114
4.4918
4.4784
3.9296
3.2842
3.2585
3.2463
3.2255
3.2170
2.8919
2.8772
2.8637
2.7965
2.7855
2.7574
1.03
1.02
1.04
1.03
1.03
1.01
1.02
3.02
2.60
1.02
1.05
1.04
Chemical Shift (ppm)
55 (R = OMe)
C16H16N2O3
1H NMR, CDCl3, 400 MHz

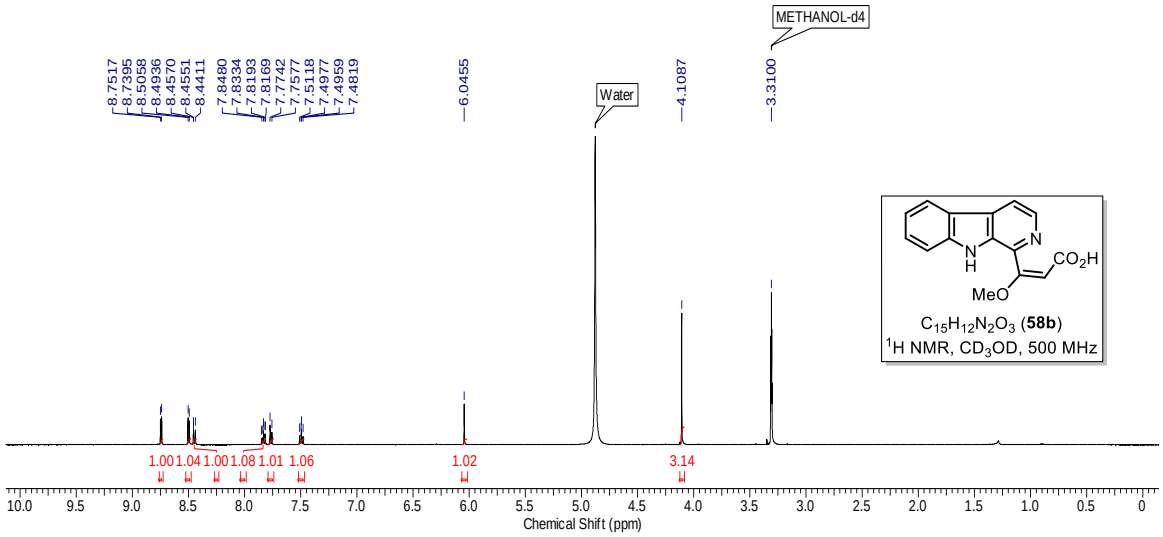

172.7407
171.1634
136.3706
128.6279
125.9358
123.3195
119.8615
119.3610
111.6714
111.3529
95.0106
86.5551
77.0000
58.7846
50.7007
35.4580
21.1936
Chemical Shift (ppm)
55 (R = OMe)
C16H16N2O3
13C NMR, CDCl3, 100 MHz

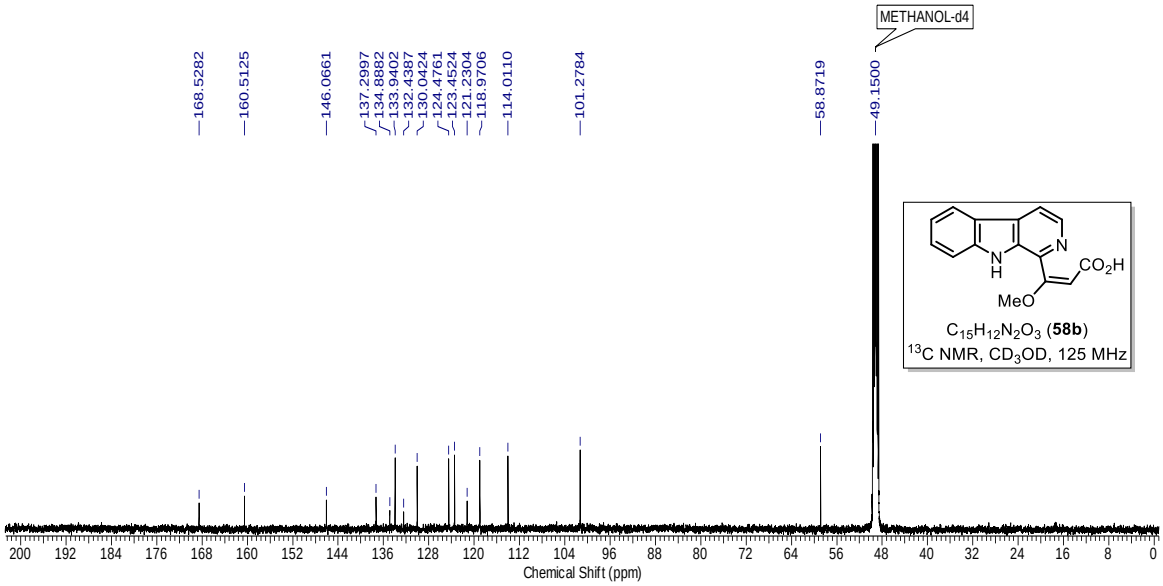

123.3159
119.8503
119.3574
111.3493
95.0070
58.7886
50.7047
35.4468
21.1900
Chemical Shift (ppm)
55 (R = OMe)
C16H16N2O3
DEPT NMR, CDCl3, 100 MHz

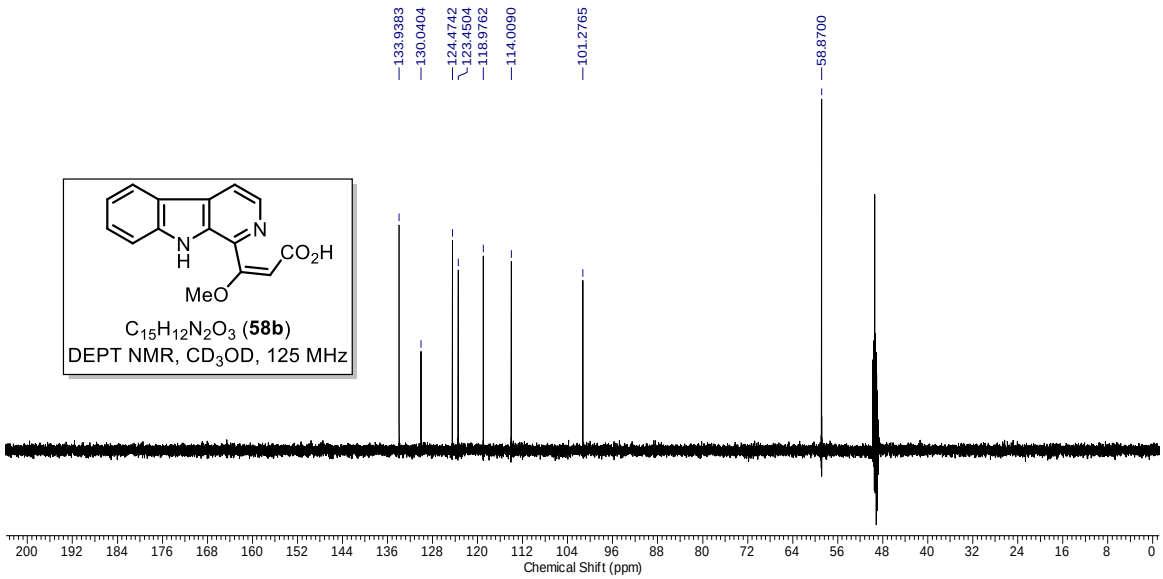

CHLOROFORM-d
8.9244
8.4728
8.1098
8.0953
7.9862
7.5392
7.5240
7.2997
7.2868
7.2700
5.5805
3.9246
3.5417
1.05
1.02
1.04
1.09
2.10
1.11
1.00
3.05
3.08
Chemical Shift (ppm)
$C_{16}H_{14}N_2O_3$ (**58a**)
^{1}H NMR, $CDCl_3$, 400 MHz

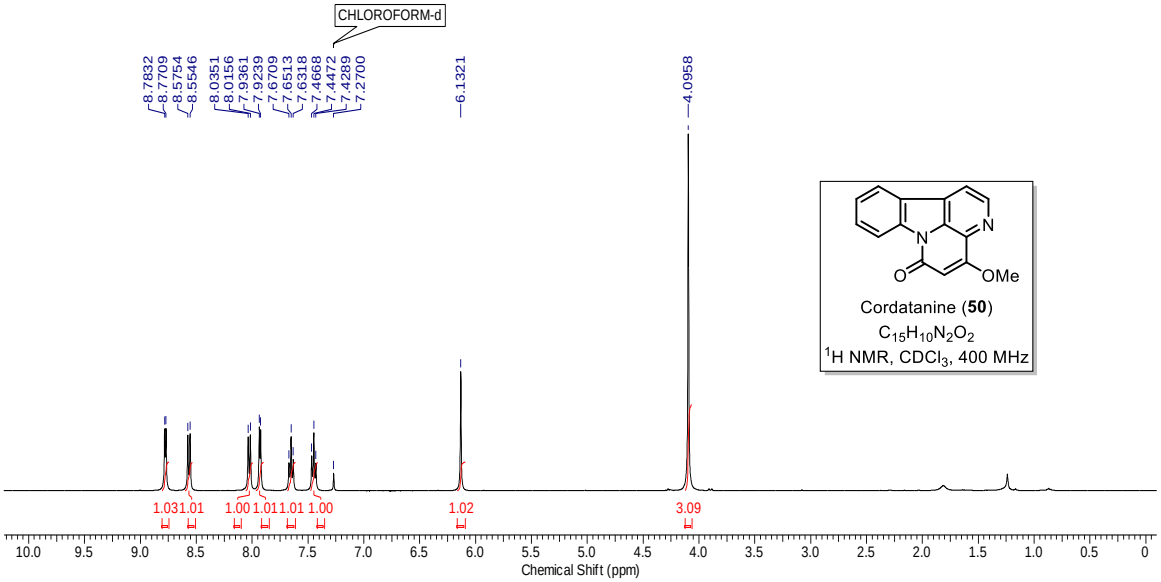

CHLOROFORM-d
167.0683
165.6123
140.6477
137.8266
136.3099
133.9212
130.3873
128.9161
121.7194
121.2493
120.3241
115.7740
111.7700
95.3595
77.0000
56.8129
51.4439
Chemical Shift (ppm)
$C_{16}H_{14}N_2O_3$ (**58a**)
^{13}C NMR, $CDCl_3$, 100 MHz

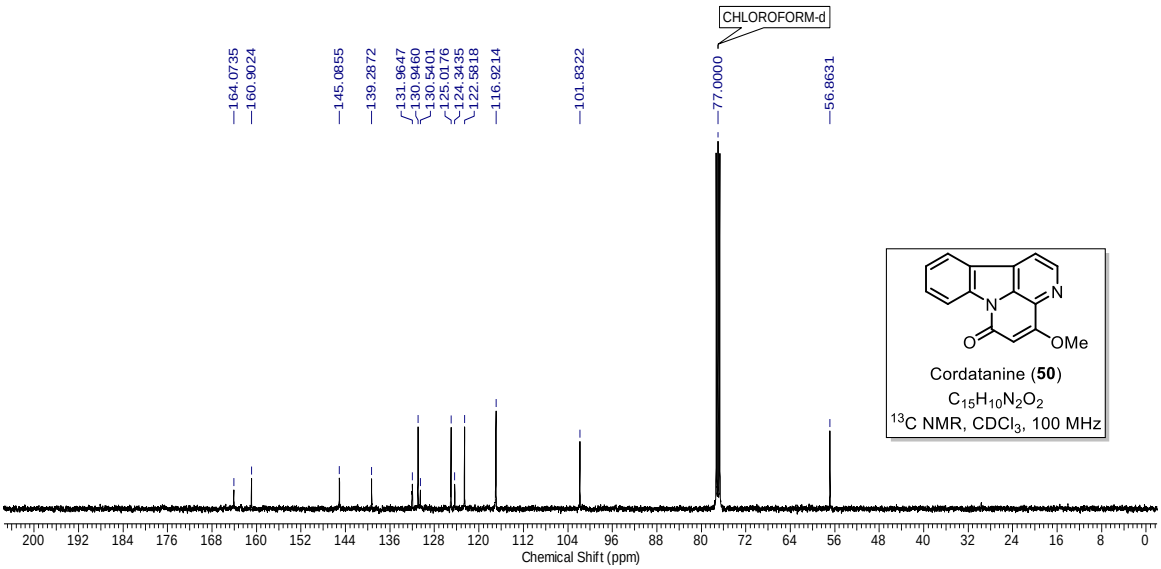

137.8191
128.9161
121.7195
120.3317
115.7741
111.7700
95.3595
56.8130
51.4439
Chemical Shift (ppm)
$C_{16}H_{14}N_2O_3$ (**58a**)
DEPT NMR, $CDCl_3$, 100 MHz

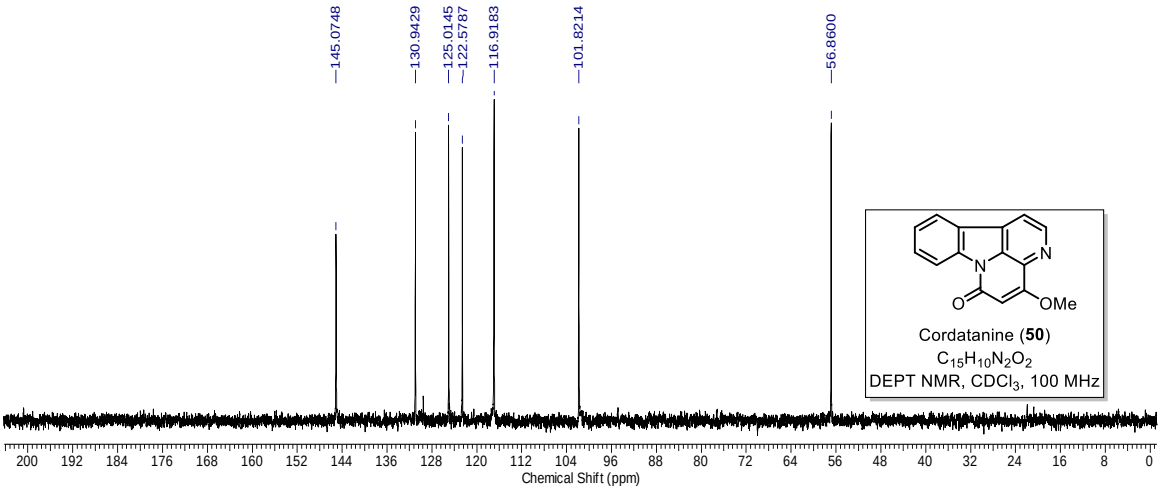

METHANOL-d4
Water
8.7517
8.7395
8.5058
8.4936
8.4570
8.4551
8.4411
7.8480
7.8334
7.8193
7.8169
7.7742
7.7577
7.5118
7.4977
7.4959
7.4819
6.0455
4.1087
3.3100
1.00 1.04 1.00 1.08 1.01 1.06
1.02
3.14
Chemical Shift (ppm)
$C_{15}H_{12}N_2O_3$ (**58b**)
^{1}H NMR, CD_3OD, 500 MHz

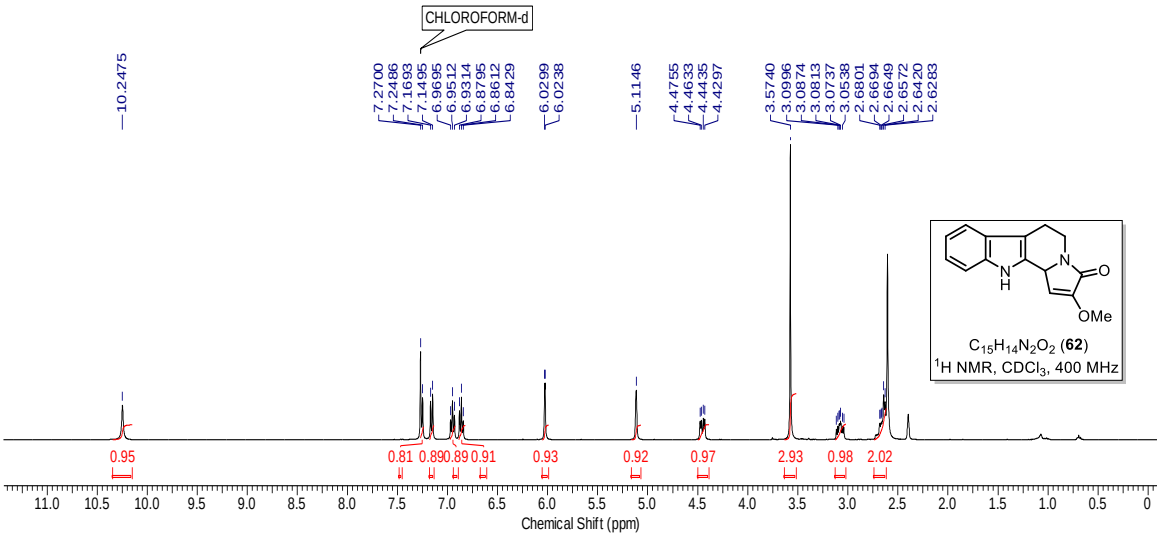

METHANOL-d4
168.5282
160.5125
146.0661
137.2997
134.8882
133.9402
132.4387
130.0424
124.4761
123.4524
121.2304
118.9706
114.0110
101.2784
58.8719
49.1500
Chemical Shift (ppm)
$C_{15}H_{12}N_2O_3$ (**58b**)
^{13}C NMR, CD_3OD, 125 MHz

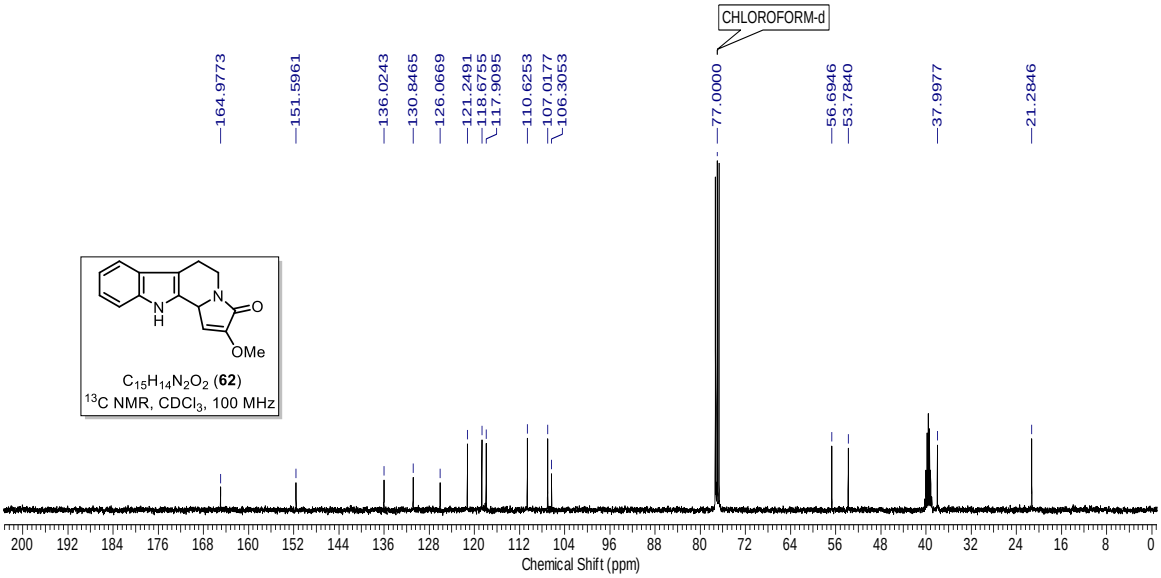

133.9383
130.0404
124.4742
123.4504
118.9762
114.0090
101.2765
58.8700
Chemical Shift (ppm)
$C_{15}H_{12}N_2O_3$ (**58b**)
DEPT NMR, CD_3OD, 125 MHz

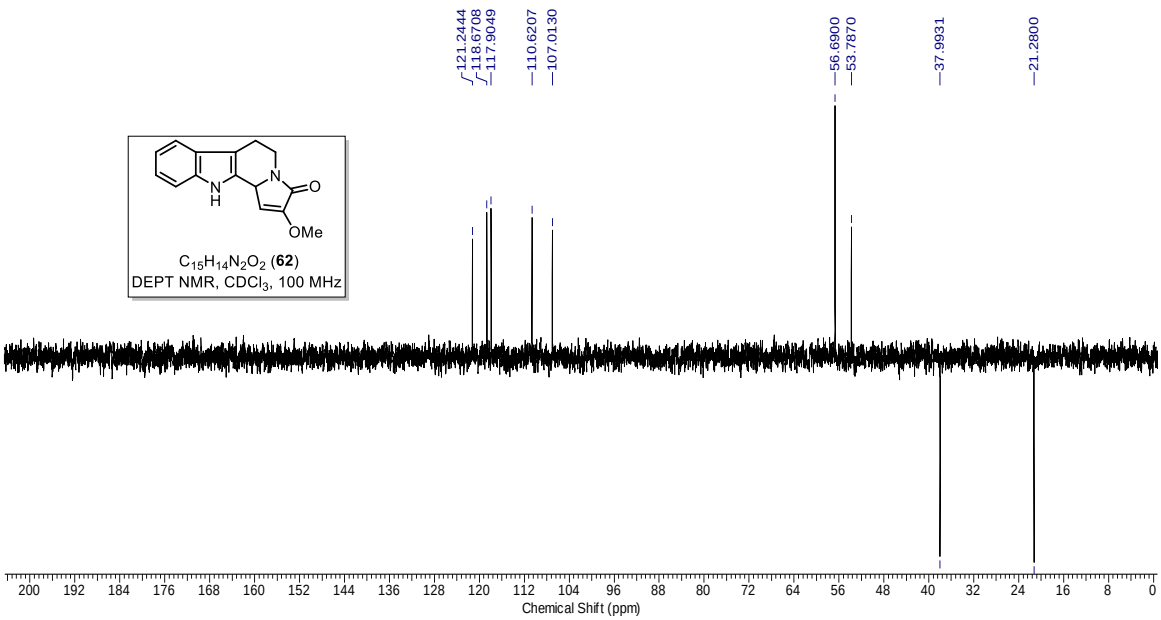

CHLOROFORM-d
8.7832
8.7709
8.5754
8.5546
8.0351
8.0156
7.9361
7.9239
7.6709
7.6513
7.6318
7.4668
7.4472
7.4289
7.2700
6.1321
4.0958
1.03 1.01 1.00 1.01 1.01 1.00 1.02 3.09
Chemical Shift (ppm)
Cordatanine (50)
$C_{15}H_{10}N_2O_2$
^{1}H NMR, $CDCl_3$, 400 MHz

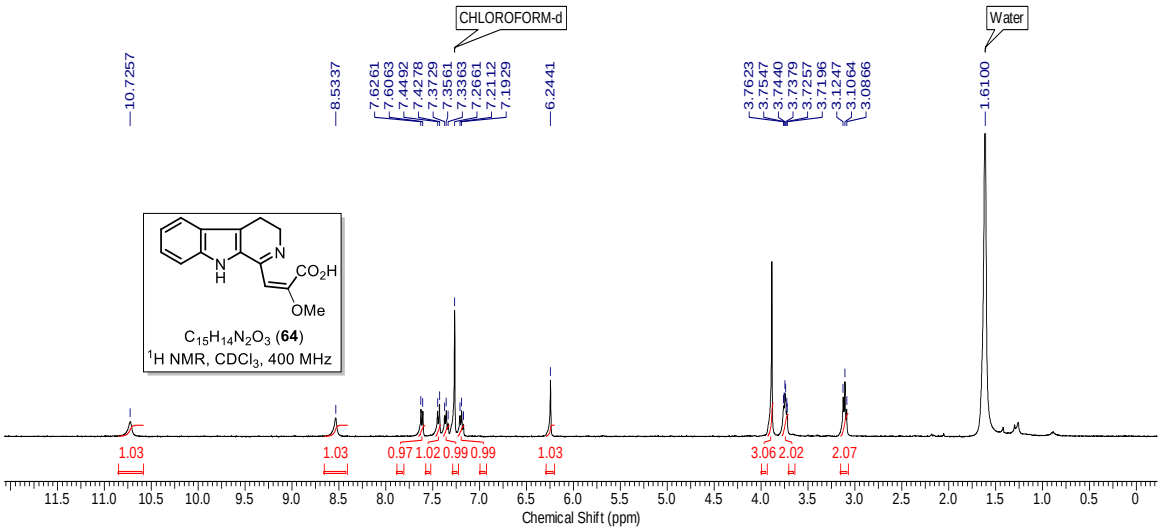

CHLOROFORM-d
164.0735
160.9024
145.0855
139.2872
131.9647
130.9460
130.5401
125.0176
124.3435
122.5818
116.9214
101.8322
77.0000
56.8631
Chemical Shift (ppm)
Cordatanine (50)
$C_{15}H_{10}N_2O_2$
^{13}C NMR, $CDCl_3$, 100 MHz

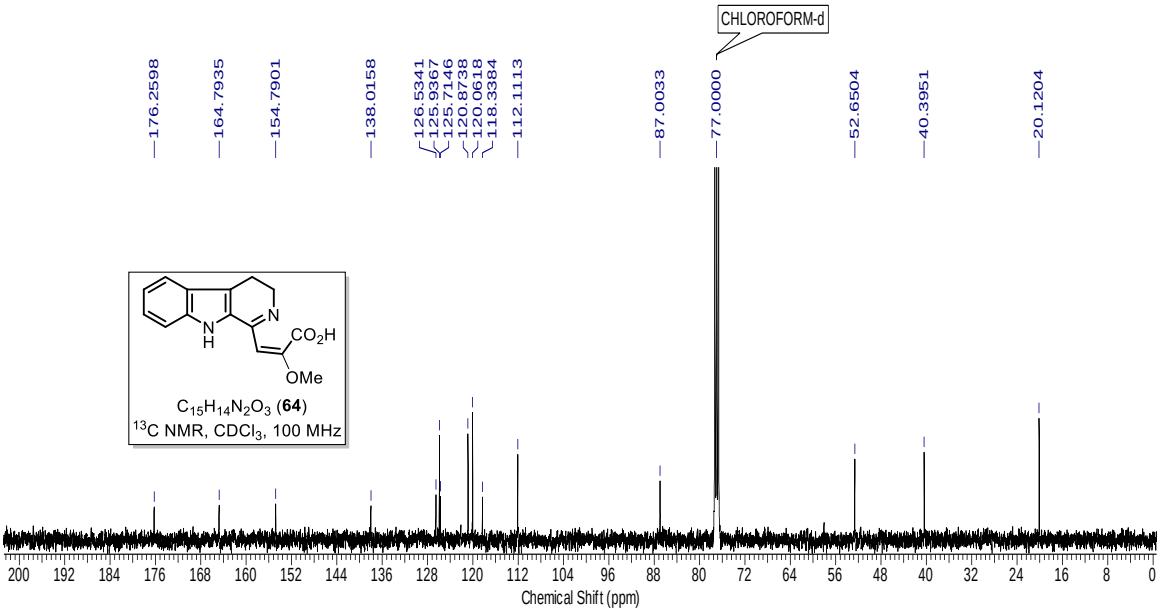

145.0748
130.9429
125.0145
122.5787
116.9183
101.8214
56.8600
Chemical Shift (ppm)
Cordatanine (50)
$C_{15}H_{10}N_2O_2$
DEPT NMR, $CDCl_3$, 100 MHz

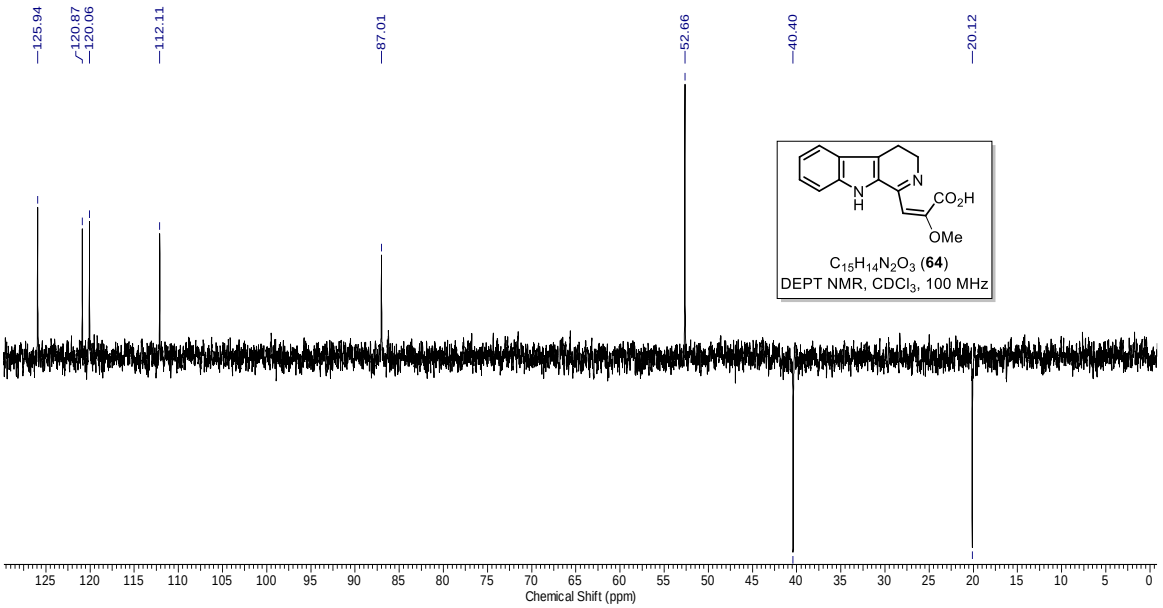

CHLOROFORM-d
10.2475
7.2700
7.2486
7.1693
7.1495
6.9695
6.9512
6.9314
6.8795
6.8612
6.8429
6.0299
6.0238
5.1146
4.4755
4.4633
4.4435
4.4297
3.5740
3.0996
3.0874
3.0813
3.0737
3.0538
2.6801
2.6694
2.6649
2.6572
2.6420
2.6283
0.95
0.81
0.89
0.89
0.91
0.93
0.92
0.97
2.93
0.98
2.02
OMe
C15H14N2O2 (62)
1H NMR, CDCl3, 400 MHz
Chemical Shift (ppm)


CHLOROFORM-d
164.9773
151.5961
136.0243
130.8465
126.0669
121.2491
118.6755
117.9095
110.6253
107.0177
106.3053
77.0000
56.6946
53.7840
37.9977
21.2846
OMe
C15H14N2O2 (62)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


121.2444
118.6708
117.9049
110.6207
107.0130
56.6900
53.7870
37.9931
21.2800
OMe
C15H14N2O2 (62)
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


CHLOROFORM-d
Water
10.7257
8.5337
7.6261
7.6063
7.4492
7.4278
7.3729
7.3561
7.3363
7.2661
7.2112
7.1929
6.2441
3.7623
3.7547
3.7440
3.7379
3.7257
3.7196
3.1247
3.1064
3.0866
1.6100
CO2H
OMe
N
H
C15H14N2O3 (64)
1H NMR, CDCl3, 400 MHz
1.03
1.03
0.97
1.02
0.99
0.99
1.03
3.06
2.02
2.07
Chemical Shift (ppm)


CHLOROFORM-d
176.2598
164.7935
154.7901
138.0158
126.5341
125.9367
125.7146
120.8738
120.0618
118.3384
112.1113
87.0033
77.0000
52.6504
40.3951
20.1204
CO2H
OMe
N
H
C15H14N2O3 (64)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


125.94
120.87
120.06
112.11
87.01
52.66
40.40
20.12
CO2H
OMe
N
H
C15H14N2O3 (64)
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)

2A.6 References

1. Haynes, H. F.; Nelson, E. R.; Price, J. R. *Aust. J. Sci. Res., Ser. A* **1952**, *5*, 387.
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Chapter 2

Section B

Regioselective Oxidation of Indoles to 2-Oxindoles: Total Synthesis of Donaxaridine and Donaxarine

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

2B.1 Background

Oxidation of indoles is a fundamental organic transformation to deliver diverse range of versatile nitrogen-containing compounds, particularly 2-oxindoles, which have been widely used in organic synthesis and drug discovery (Figure 1).[1–5] The electron-rich property of indoles allows the oxidation to occur under many oxidation conditions. However, a mixture of oxidative products is observed for indole oxidation due to the competition between nitrogen, C2 and C3 positions in the indole, potential rearrangements and over-oxidation.[6–8] Therefore, it is not surprising that only a small number of oxidants have been used for the three major types of the indole oxidation (i) oxidative rearrangement of tetrahydro-β-carbolines to spirooxindoles,[9–15] (ii) oxidation of C3-substituted indoles to 2-oxindoles[16] and (iii) oxidative cleavage of C2, C3-disubstituted indole to 2-keto acetanilide (Witkop oxidation).[17,18] Although these oxidants under the optimized conditions could solve the chemoselectivity and regioselectivity issues with high yields. In a literature search, it was noted that many methods exist for the oxindoles from non-indole precursors. However, the direct transfer of indoles into the corresponding 2-oxindoles is still a big challenge.

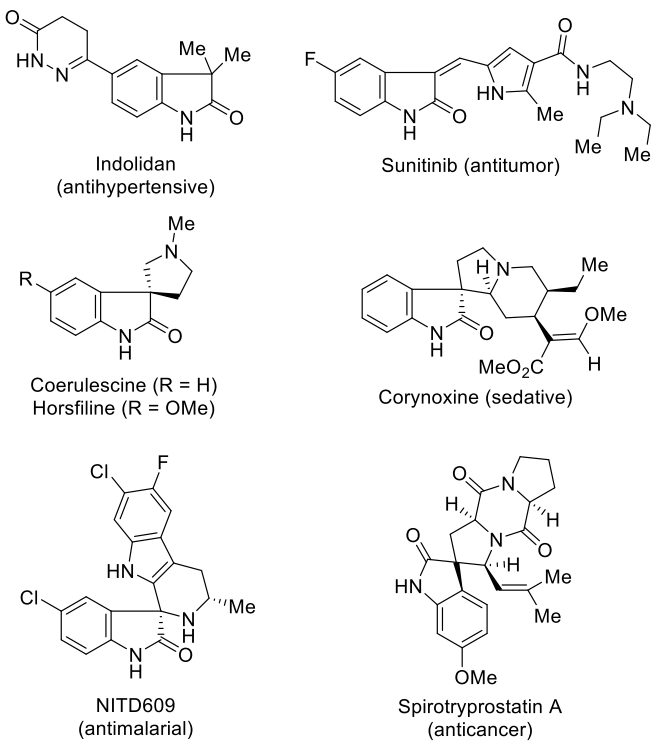
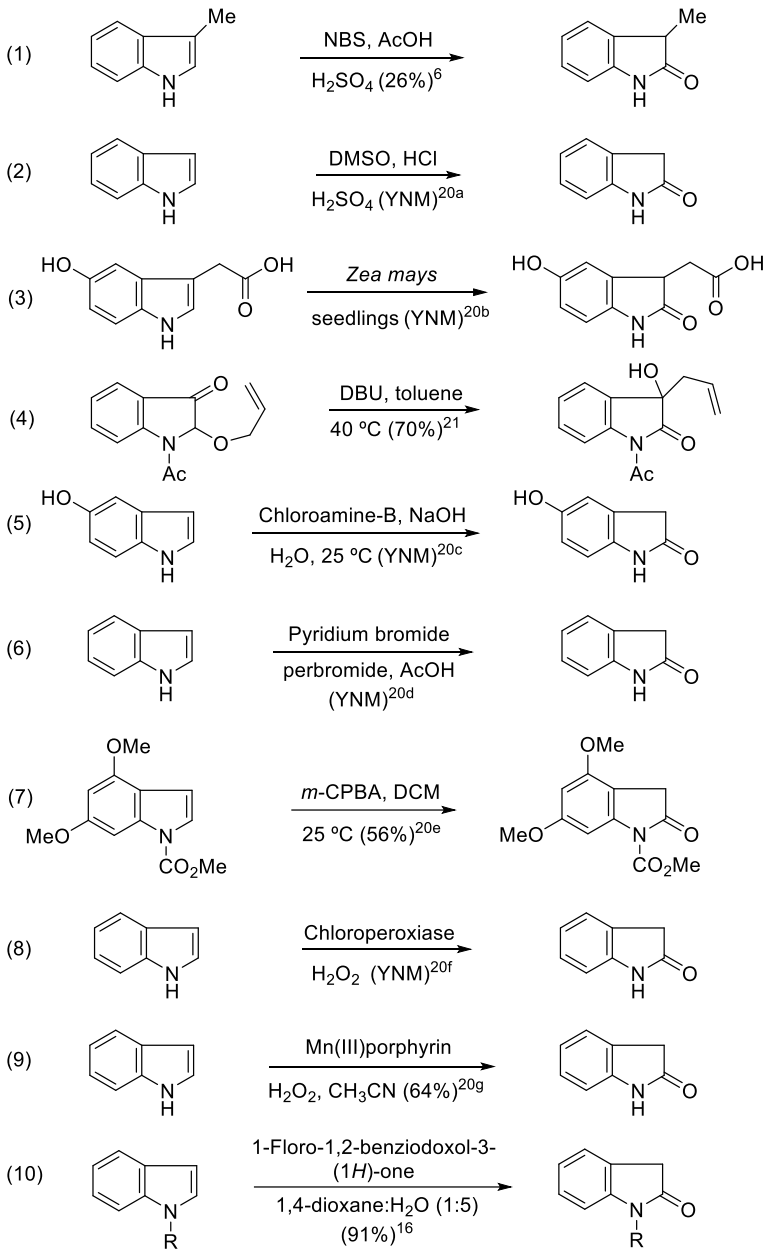


Figure 1. Representative drugs and natural products comprising of 2-oxindole moiety

2B.1.1 Oxidation of Indole to 2-Oxindole

Regioselective oxidations of indoles to 2-oxindoles and 3-oxindoles have been very important reactions from the synthetic organic chemistry perspective.[19] Several elegant inorganic, organic and bioorganic reagents for the oxidation reactions of indoles to 2-oxindoles have been reported in earlier and contemporary literature, and a few selected methods have been depicted in scheme 1.[6,16,20,21]

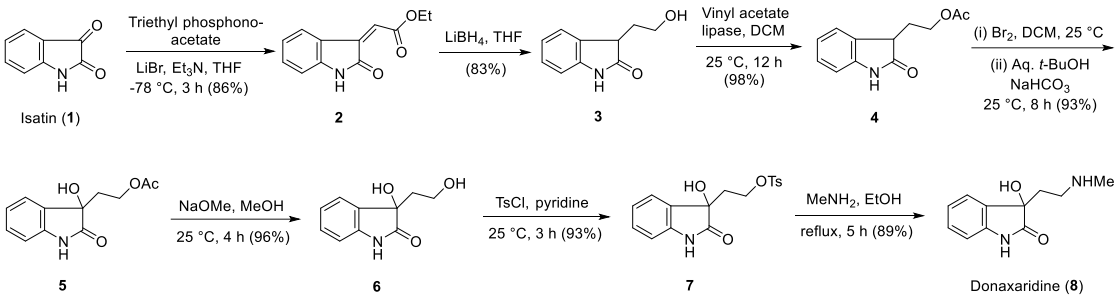


(YNM: Yield not mentioned)

Scheme 1. Selected Chemical and Biomimetic Oxidation Reactions of Indoles to 2-Oxindoles

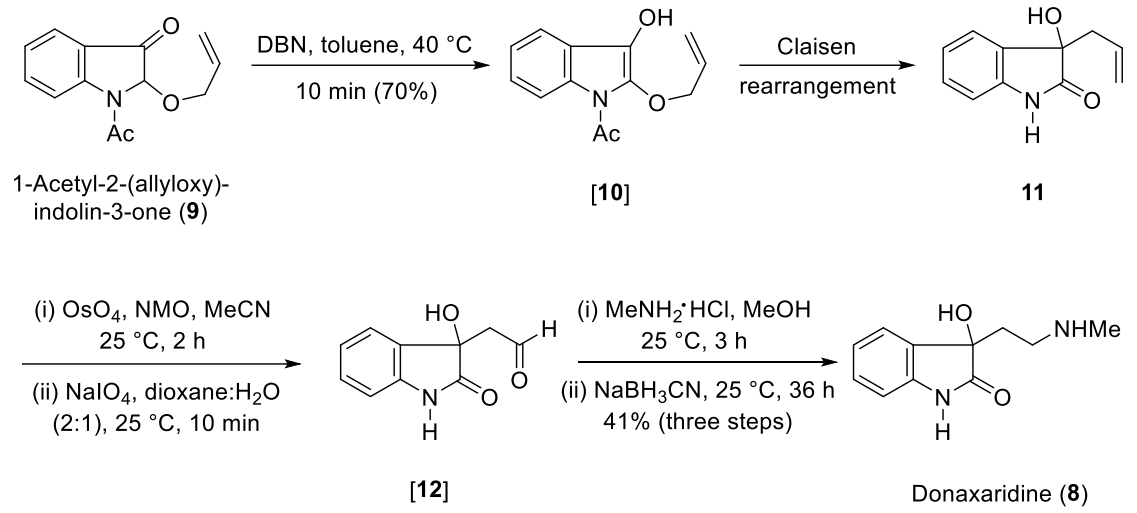
2B.1.2 Reported Synthesis of Donaxaridine

MacLeod and co-workers in 1997 reported the first total synthesis of donaxaridine (Scheme 2).[22] The Horner-Wadsworth-Emmons reaction on isatin (**1**) with triethyl phosphonoacetate in THF at –78 °C provided the conjugated ethyl ester product **2** in 86% yield. Reduction of a conjugated ester using lithium borohydride in THF afforded alcohol **3**. Acetyl protection of alcohol **3** was achieved by enzymatic transesterification using vinyl acetate and lipase from *Candida antarctica* (NOVA SP-435). The mildness of the reaction conditions and simple workup prohibited any side reactions involving the 3-position. Bromination of compound **4** followed by displacement of the bromine using $NaHCO_3$ in 50% aqueous *t*-BuOH provided hydroxy compound **5** in 93% yield. Deprotection of acetate group present in compound **5** with sodium methoxide in methanol gave the diol **6** in 96% yield. The diol **6** on selective *O*-tosylation by using TsCl in pyridine afforded the compound **7**. Treatment of the tosylate **7** with excess methylamine in methanol provided the natural product donaxaridine (**8**) in 89% yield.



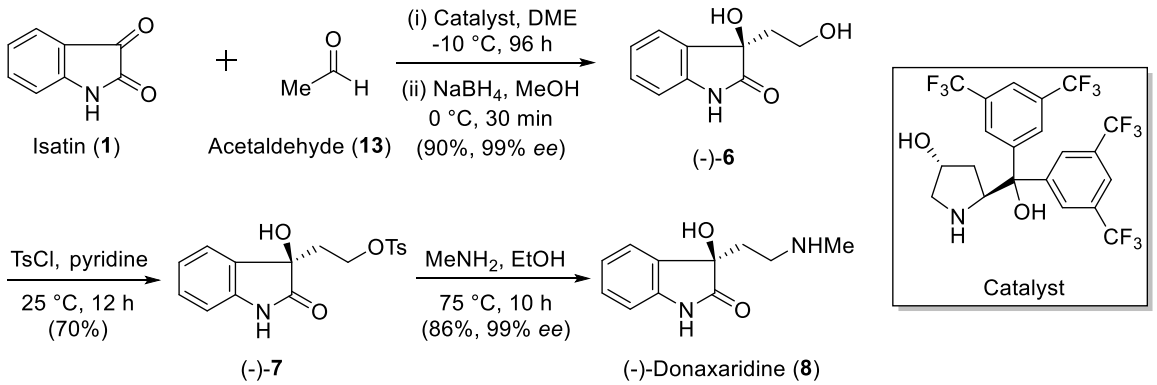
Scheme 2. Total Synthesis of Donaxaridine from Isatin

Kawasaki and co-workers in 2004 reported the total synthesis of donaxaridine via Claisen rearrangement as a key step (Scheme 3).[21] The synthesis started from 1-acetyl-2-(allyloxy)-indolin-3-one (**9**), which was prepared by using a known procedure.[23] Compound **9** was treated with DBN in toluene at 40 °C to provide compound **11** via the enolized intermediate **10** and the classical Claisen rearrangement. Osmium tetraoxide induced dihydroxylation reaction of compound **11** at 25 °C provided the diol. The diol on sodium periodate-induced cleavage resulted in an intermediate aldehyde **12**. Reductive amination of the aldehyde **12** with $NaBH_3CN$ in the presence of methylammonium chloride furnished donaxaridine (**8**) in 41% yield over four steps.



Scheme 3. Total Synthesis of Donaxaridine via Claisen Rearrangement

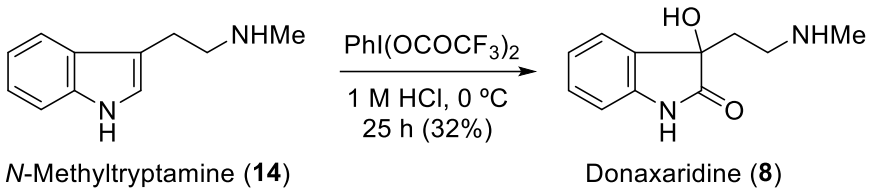
Yuan and co-workers in 2010 reported the first enantioselective total synthesis of donaxaridine via aldol reaction (Scheme 4).[24] Enantioselective aldol reaction of isatin (**1**) with acetaldehyde (**13**) in the presence of optically active catalyst in DME at –10 °C provided the aldol adduct. Reduction of the aldol adduct by using $NaBH_4$ in MeOH at 0 °C gave diol (–)-**6** in 90% yield with 99% *ee*. The conversion of diol (–)-**6** under Rasmussen and MacLeod conditions[22] furnished the desired (-)-donaxaridine (**8**) in 60% yield with 99% *ee*. Enantioselective first total synthesis of (-)-donaxaridine (**8**) was accomplished in four steps with 54% overall yield.



Scheme 4. Total Synthesis of Donaxaridine via Enantioselective Aldol Reaction

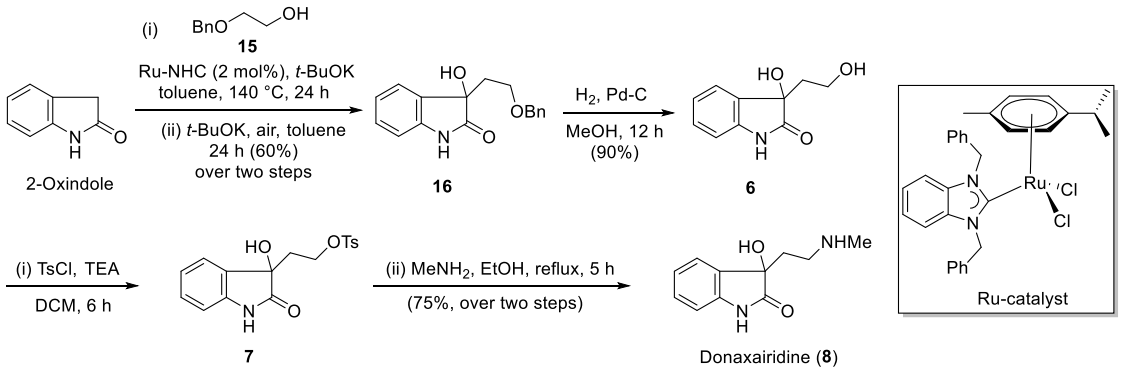
Ishikawa and co-workers in 2016 reported the one step synthesis of donaxaridine from *N*-methyltryptamine (Scheme 5).[25] Reaction of *N*-methyltryptamine (**14**) with

$PhI(OCOCF_3)_2$ in presence of 1 M HCl at 0 °C for 25 h to an afforded the Donaxaridine (**8**) in 32% yield.



Scheme 5. Synthesis of Donaxaridine from *N*-Methyltryptamine

Gnanaprakasam and co-workers in 2017 reported the total synthesis of donaxaridine via Ru-catalyzed domino C−H alkylation and hydroxylation (Scheme 6).[26] Reaction of 2-oxindole with 2-benzyloxy-1-ethanol (**15**) in the presence of potassium *tert*-butoxide and Ru-NHC catalyst was heated at 140 °C for 24 h to obtain the coupling product. Which on base mediated aerobic C−H hydroxylation using oxygen atmosphere gave the quaternary hydroxyl product **16** in 60% yield. Deprotection of the *O*-benzyl group present in compound **16** under catalytic hydrogenation (5% Pd-C) afforded the dihydroxy-functionalized product **6** in 90% yield. The conversion of diol **6** under Rasmussen and MacLeod conditions,[22] selective *O*-tosylation of the primary alcohol followed by the reaction with methylamine in ethanol afforded the donaxaridine (**8**) in 75% yield.



Scheme 6. Total Synthesis of Donaxaridine via Ru-Catalyzed Domino C−H Alkylation and Hydroxylation

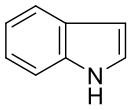
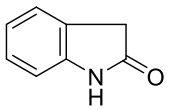
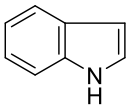
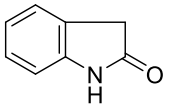
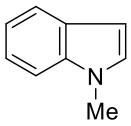
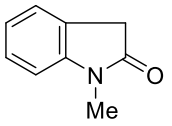
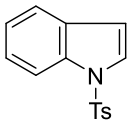
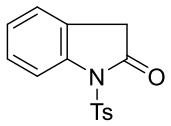
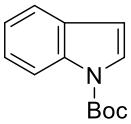
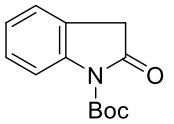
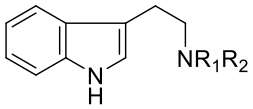
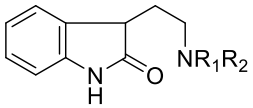
2B.2 Results and Discussion (Present Research Work)

Regioselective Oxidation of Indoles to 2-Oxindoles

Application of an appropriate oxidizing reagent and the development of suitable reaction conditions for smooth transformation of a variety of indoles to the corresponding 2-oxindole derivatives are challenging tasks from the point of view of the reactivity and overall stability of the formed products.[1,19,20] As a continuation of our studies on the total synthesis of recently isolated bioactive natural products,[27] we attempted the intramolecular cyclization of one of the indole bearing compounds facilitated by the adsorption of concentrated sulfuric acid on silica gel and observed the unexpected effective formation of the corresponding 2-oxindole derivative. In this context we herein report the simple and efficient sulfuric acid promoted regioselective oxidation of indoles to 2-oxindoles and its application in the synthesis of natural products (Tables 1 and 2; Schemes 7 and 8).

The reaction of indole (**17a**, 1.00 g) with concentrated sulfuric acid adsorbed on silica gel (60–120 mesh, 1.00 g) in dichloromethane at 25 °C was monitored by TLC. The above-specified reaction at the end of ten hours selectively furnished the corresponding pure 2-oxindole (**18a**) in 78% yield (Table 1; entry 1). However, the same reaction in 1,2-dichoroethane as a solvent was slow and furnished 2-oxindole (**18a**) only in 62% yield (Table 1, entry 2). The change of silica gel mesh size to 100–200 and 230–400 mesh for the adsorption of sulfuric acid and repetition of the same reaction in dichloromethane did not show any noticeable changes in the reaction time and yield. The recycling and reuse of the recovered sulfuric acid adsorbed on the silica gel reagent slowed down the rate of the oxidation reaction due to nearly 35% loss of sulfuric acid (by weight and NaOH titration) during first use. In a control experiment, the direct reaction of indole (**17a**) with concentrated sulfuric acid in dichloromethane resulted in complete decomposition. The substrates *N*-methylindole (**17b**) and *N*-tosylindole (**17c**) on treatment with H_2SO_4 adsorbed on SiO_2 remained unreacted and the expected 2-oxindole products **18b** and **18c** were not formed, indicating that the presence of the hydrogen atom on the indole nitrogen is necessary for the progression of oxidation (Table 1, entries 3 and 4). The reaction of *N*-Boc protected indole **17d** with H_2SO_4 adsorbed on SiO_2 resulted in the complete decomposition of the reaction mixture mostly via the acid catalyzed Boc-deprotection route (Table 1, entry 5). The indole-based amines **17e–h** on reaction with H_2SO_4 adsorbed on SiO_2 also remained completely unreacted possibly due to the formation of the corresponding salts by protonation of free amine groups (Table 1, entry 6).

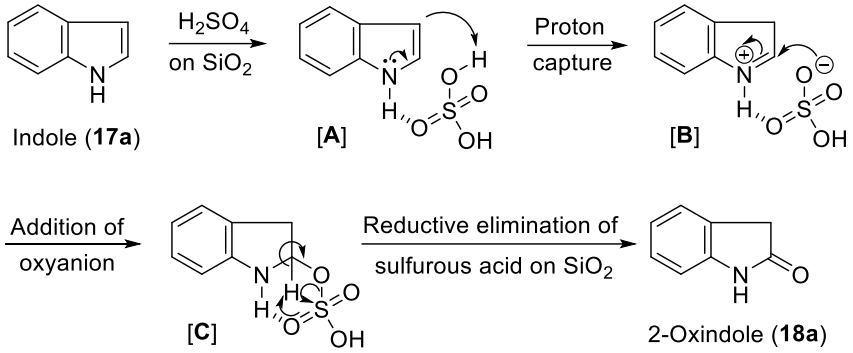
Table 1. Study of H_2SO_4 Adsorbed on SiO_2 Facilitated Regioselective Oxidation of Indole Derivatives

Entry	Starting Materials **17a-h**	Reaction Conditions[a,b]	Products **18a-h** (% yield)
1	 **17a**	H_2SO_4 on SiO_2 DCM, 25 °C, 10 h	 **18a** (78%)
2	 **17a**	H_2SO_4 on SiO_2 $ClCH_2CH_2Cl$ 25 °C, 18 h	 **18a** (62%)
3	 **17b**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **18b** (not formed)[c]
4	 **17c**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **18c** (not formed)[c]
5	 **17d**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **18d** (not obtained)[d]
6	 **17e** (R_1 = R_2 = H) **17f** (R_1 = H, R_2 = Me) **17g** (R_1 = R_2 = Me) **17h** (R_1 = H, R_2 = CH_2Ph)	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **18e-h** (not formed)[c]

[a] One mL of conc. H_2SO_4 was adsorbed on ten gram of SiO_2 (60–120 mesh) and used in weight:weight ratio for all starting materials; [b] monitored by TLC; [c] starting material recovered; [d] decomposition

On the basis of the results summarized in Table 1, a plausible reaction mechanism of the oxidation of indole (**17a**) to 2-oxindole (**18a**) driven by the adsorption of H_2SO_4 on SiO_2 is illustrated in scheme 7. Mechanistically, the indole (**17a**) dissolved in dichloromethane penetrates into the SiO_2 cavities and complexes with adsorbed H_2SO_4 through hydrogen bonding to form intermediate **A**. Intermediate **A** captures the proton via the delocalization

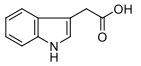
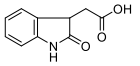
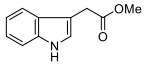
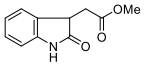
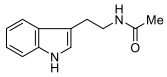
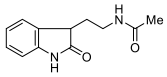
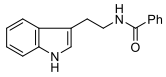
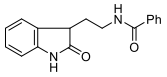
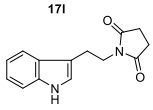
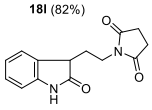
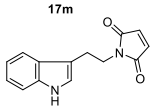
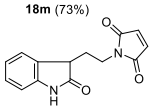
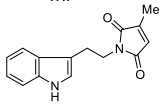
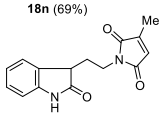
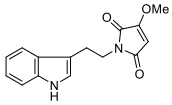
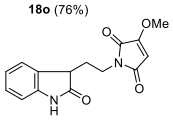
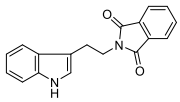
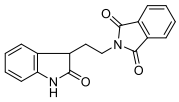
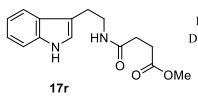
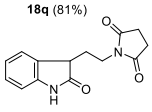
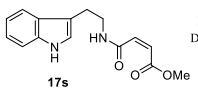
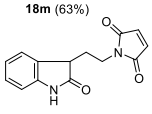
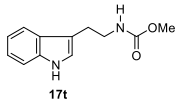
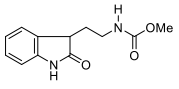
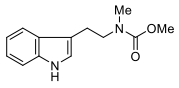
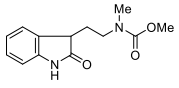
of the nitrogen lone pair to form the iminium salt **B**. Addition of oxyanions to the formed reactive iminium double bond in a concerted/stepwise fashion results in another intermediate **C** with an overall addition of sulfuric acid across the carbon–carbon double bond in an indole moiety. Finally, oxidation of indole to 2-oxindole takes place via the reductive elimination of sulfurous acid (HO-SO-OH) involving the hexavalent to tetravalent state transformation of sulfur. Overall, the oxidant is sulfuric acid and it gets converted into unstable sulfurous acid, which in the presence of dissolved oxygen transforms back to sulfuric acid and also partly degrades into sulfur dioxide.



Scheme 7. Plausible Mechanism of the Regioselective Oxidation of Indole to 2-Oxindole Induced by the Adsorption of H_2SO_4 on SiO_2

At this stage we decided to systematically study the substrate scope, functional group tolerance and application of the present indole to 2-oxindole transformation protocol for the synthesis of unnatural and natural products (Table 2, Scheme 8). The indole-3-acetic acid (**17i**) on treatment with H_2SO_4 adsorbed on SiO_2 underwent facile oxidation and afforded the desired natural product 2-oxindole-3-acetic acid (**18i**) (isolated from *Zea mays* seedlings)[28] in quantitative yield (Table 2, entry 2), which was not very stable to column chromatographic purifications due to associated stability and polarity issues. Therefore, the formed product was quickly filtered through a silica gel column using DCM–MeOH as an eluent to obtain the very expensive pure acid **18i** in 82% yield. The analytical and spectral data obtained for 2-oxindole-3-acetic acid (**18i**) were in complete agreement with the reported data.[28,29] 2-Oxindole-3-acetic acid (**18i**) on treatment with diazomethane afforded the corresponding ester **18j** in 94% yield. However, the methyl indole-3-acetate (**17j**) on reaction with H_2SO_4 adsorbed on SiO_2 resulted in the formation of a complex mixture and did not provide the expected methyl 2-oxindole-3- acetate (**18j**)

Table 2. Regioselective Oxidation of Indoles to 2-Oxindoles Induced by the Adsorption of H_2SO_4 on SiO_2

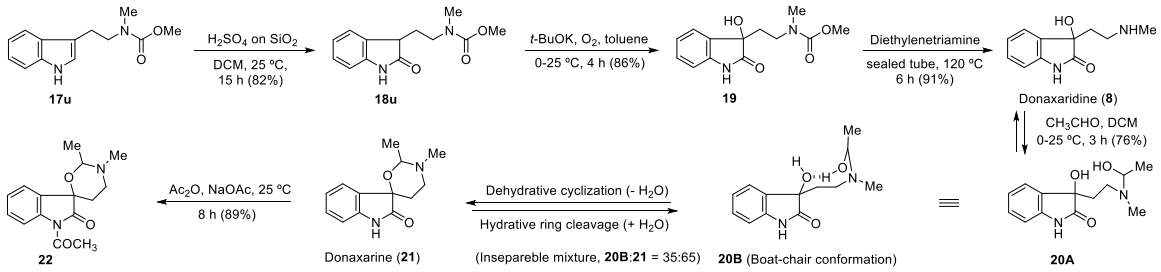
Entry	Starting Materials **17a,i-u**	Reaction Conditions[a]	Products **18a,i-q,t,u** (% yield)
1	 **17a**	H_2SO_4 on SiO_2 DCM, 25 ºC, 10 h	 **18a** (natural product, 78%)
2	 **17i**	H_2SO_4 on SiO_2 DCM, 25 ºC, 16 h	 **18i** (natural product, 82%)
3	 **17j**	H_2SO_4 on SiO_2 DCM, 25 ºC, 8 h	 **18j** (not obtained)[b]
4	 **17k**	H_2SO_4 on SiO_2 DCM, 25 ºC, 18 h	 **18k** (71%)
5	 **17l**	H_2SO_4 on SiO_2 DCM, 25 ºC, 12 h	 **18l** (82%)
6	 **17m**	H_2SO_4 on SiO_2 DCM, 25 ºC, 16 h	 **18m** (73%)
7	 **17n**	H_2SO_4 on SiO_2 DCM, 25 ºC, 14 h	 **18n** (69%)
8	 **17o**	H_2SO_4 on SiO_2 DCM, 25 ºC, 16 h	 **18o** (76%)
9	 **17p**	H_2SO_4 on SiO_2 DCM, 25 ºC, 20 h	 **18p** (74%)
10	 **17q**	H_2SO_4 on SiO_2 DCM, 25 ºC, 18 h	 **18q** (81%)
11	 **17r**	H_2SO_4 on SiO_2 DCM, 25 ºC, 24 h	 **18m** (63%)
12	 **17s**	H_2SO_4 on SiO_2 DCM, 25 ºC, 24 h	 **18n** (68%)
13	 **17t**	H_2SO_4 on SiO_2 DCM, 25 ºC, 12 h	 **18t** (78%)
14	 **17u**	H_2SO_4 on SiO_2 DCM, 25 ºC, 15 h	 **18u** (82%)

[a] Monitored by TLC; [b] decomposition

(Table 2, entry 3). Amide bearing indoles **17k** and **17l** on reaction with H_2SO_4 adsorbed on SiO_2 provided the corresponding 2-oxindoles **18k** and **18l** in 71% and 82% yields, respectively (Table 2, entries 4 and 5). The cyclic imide bearing indoles **17m–q** on reaction with H_2SO_4 adsorbed on SiO_2 also delivered the desired 2-oxindoles **18m–q** in 69–81% yields (Table 2, entries 6–10). Amic ester bearing indoles **17r** and **17s** on reaction with H_2SO_4 adsorbed on SiO_2 directly furnished the corresponding cyclic imides bearing 2-oxindoles **18m** and **18n** in 63% and 68% yields, respectively, via in situ intramolecular cyclization followed by the oxidation pathway (Table 2, entries 11 and 12). Carbamate bearing indoles **17t** and **17u** on reaction with H_2SO_4 adsorbed on SiO_2 delivered the corresponding 2-oxindoles **18t** and **18u** in 78% and 82% yields, respectively (Table 2, entries 13 and 14). The results summarized in table 2 clearly revealed that the present oxidation reactions are compatible with carboxylic acid, amide, cyclic imide and carbamate functional groups. On the basis of the obtained results, we believe that the sulfuric acid adsorbed on silica gel reagent will be quite compatible with several other non-amine substituents and functional groups bearing substrates.

The natural products donaxaridine (**8**) and donaxarine (**21**) were isolated from *Arundo donax* in 1976.[30] To date five different total syntheses of donaxaridine (**8**) have been accomplished by employing several elegant strategies (Scheme 2 to 6).[21,22,24–26] The total synthesis of natural products **8** and **21** was planned starting from the obtained carbamate bearing 2-oxindole **18u** as a potential precursor (Table 2, entry 14; Scheme 8). Compound **18u** on reaction with molecular oxygen in the presence of *t*-BuOK underwent smooth benzylic hydroxylation and delivered the desired product **19** in 86% yield.[31] The cleavage of carbamate in compound **19** with TBAF in THF or 2 N HCl in methanol under reflux conditions was not successful and the starting material remained unreacted. However, diethylenetriamine assisted carbamate cleavage[32] of compound **19** in a sealed tube at 120 °C furnished the desired donaxaridine (**8**) in 91% yield. The analytical and spectral data obtained for donaxaridine (**8**) were in complete agreement with the reported data.[30,21,22,24–26] Donaxaridine (**8**) on treatment with acetaldehyde in $CH_2Cl_2/CHCl_3$ at 25 °C/reflux conditions always resulted in a mixture of geminal-aminohydrin intermediate **20B** and the natural product donaxarine (**21**) in 76% yield. As expected, TLC of the reaction mixture revealed that donaxarine (**21**) has a higher R_f-value and geminal-aminohydrin intermediate **20B** has a lower R_f-value than the starting material donaxaridine (**8**). All our attempts to separate the above specified mixture of products by

using silica gel column chromatography and also by using HPLC were unsuccessful and always resulted in an inseparable mixture of products **20B** and **21** in 35:65 ratio (by ^{1}H NMR). Therefore, on the basis of analytical and spectral data it is demonstrated that donaxarine (**21**) always stays in equilibrium with its hydrated ring opened form **20B**. Plausibly the formed geminal-aminohydrin intermediate **20B** is stabilized by the depicted intramolecular hydrogen bonding in an 8-membered boat–chair conformation[33] and the mixture of compounds **20B** and **21** is an example of a delicately balanced stability-driven hydration–dehydration equilibrium. Finally, the mixture of compounds **20B** and **21** on reaction with Ac_2O/NaOAc exclusively afforded the *N*-acyl derivative **22** of donaxarine (**21**) in 89% yield.



Scheme 8. Stepwise Oxidations of the Indole Moiety Leading to the Facile Synthesis of Donaxaridine and Donaxarine

2B.3 Summary

In conclusion, we have demonstrated a new simple and efficient method for regioselective oxidation of indoles to 2-oxindoles using sulfuric acid adsorbed on silica gel as a reagent. This will be useful for the synthesis of a broad range of the desired bioactive natural and unnatural oxindoles. A plausible mechanism has been proposed and the presence of free protons on the indole nitrogen atom is essential for the formation of a complex with sulfuric acid. The present practical oxidation reaction induced by the heterogeneous reagent suitably addresses the product stability concerns and functional group tolerance issues. We also believe that the present protocol has scale-up potential and will be useful for large-scale production of several oxindole derivatives of commercial interest.

2B.4 Experimental Section

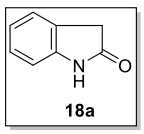
Preparation of the Sulfuric Acid Adsorbed on Silica Gel

A solution of concentrated sulfuric acid (1.00 mL) in acetone (10 mL) was added to a suspension of silica gel (10.00 g, 60–120 mesh) in acetone (15 mL) under vigorous stirring at room temperature. After 1 h acetone was removed on a rotatory evaporator in vacuo and the obtained residue was dried by using vacuum pump. A free-flowing powder of sulfuric acid adsorbed on silica gel was obtained in quantitative yield (12.87 g). The quantitative loading of sulfuric acid on silica gel was checked by weight and also by sodium hydroxide titration.

General Procedure for Oxidation of Indoles to 2-Oxindoles

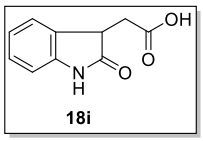
To a stirred solution of indole (1.00 g) in CH_2Cl_2 (20 mL) was added sulfuric acid adsorbed on silica gel (1.00 g) at 25 °C and the reaction was monitored by TLC. The reaction mixture was filtrated and the filtrate was washed with saturated aq. $NaHCO_3$ (10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using ethyl acetate–petroleum ether as an eluent provided the desired 2-oxindole.

Indolin-2-one (18a): According to the general procedure and by using ethyl acetate–petroleum ether (0.5:9.5) as an eluent, **18a** was obtained as a brown solid (886 mg, 78%). Mp 128–130 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 2H), 6.90 (dd, J = 8.2 and 1.0 Hz, 1H), 7.02 (td, J = 7.7 and 1.0 Hz, 1H), 7.17–7.30 (m, 2H), 8.73 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.3, 109.8, 122.3, 124.6, 125.3, 127.9, 142.5, 178.0; ESIMS (m/z) 156 $[M+Na]^+$; HRMS (ESI) calcd for C_8H_7ONNa 156.0420, found 156.0417; IR ($CHCl_3$) ν_{max} 3174, 1732, 1687, 1617 cm^{-1}.



18a

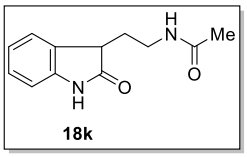
2-(2-Oxoindolin-3-yl)acetic Acid (18i): According to the general procedure and by using methanol–dichloromethane (0.5:9.5) as an eluent, **18i** was obtained as a white crystalline solid (179 mg, 82%). Mp 140–142 °C, ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.69 (dd, J = 17.0 and 7.0 Hz, 1H), 2.90 (dd, J = 17.3 and 4.2 Hz, 1H), 3.50–3.70 (m, 1H), 6.81 (d, J = 7.3 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 7.05–7.30 (m, 2H), 10.38 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 34.0, 41.8, 109.2, 121.2, 123.7, 127.8, 129.4, 142.9, 172.3, 178.3; ESIMS (m/z) 214 $[M+Na]^+$;



18i

HRMS (ESI) calcd for $C_{10}H_9O_3NNa$ 214.0475, found 214.0474; IR (Nujol) ν_{max} 3362, 2800–2700, 1710 cm^{-1}.

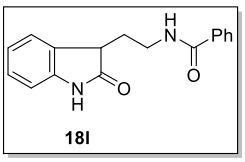
***N*-[2-(2-Oxoindolin-3-yl)ethyl]acetamide (18k):** According to the general procedure and



18k

by using ethyl acetate–petroleum ether (4:6) as an eluent, **18k** was obtained as a yellow solid (77 mg, 71%). Mp 130–132 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95 (s, 3H), 2.02–2.11 (m, 1H), 2.20–2.29 (m, 1H), 3.42–3.55 (m, 3H), 6.42 (br s, 1H), 6.90 (d, J = 7.7 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 8.65 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.2, 30.0, 37.2, 44.4, 109.8, 122.7, 124.2, 128.2, 129.2, 141.1, 170.5, 180.3; ESIMS (m/z) 241 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{14}O_2N_2Na$ 241.0947, found 241.0943; IR ($CHCl_3$) ν_{max} 3301, 3012, 1710, 1650 cm^{-1}.

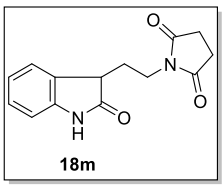
***N*-[2-(2-Oxoindolin-3-yl)ethyl]benzamide (18l):** According to the general procedure and



18l

by using ethyl acetate–petroleum ether (1:1) as an eluent, **18l** was obtained as a brown solid (174 mg, 82%). Mp 178–180 °C, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.97 (br s, 1H), 2.13 (br s, 1H), 3.40–3.60 (m, 3H), 6.84 (d, J = 6.0 Hz, 1H), 6.97 (br s, 1H), 7.18 (br s, 1H), 7.35 (d, J = 5.4 Hz, 1H), 7.45 (br s, 2H), 7.50 (d, J = 5.3 Hz, 1H), 7.83 (d, J = 5.3 Hz, 2H), 8.56 (br s, 1H), 10.42 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 30.1, 36.6, 43.3, 109.3, 121.3, 124.2, 127.2, 127.7, 128.2, 129.5, 131.1, 134.5, 142.6, 166.2, 178.9; ESIMS (m/z) 281 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}O_2N_2$ 281.1285, found 281.1280; IR ($CHCl_3$) ν_{max} 3346, 2944, 1711, 1638 cm^{-1}.

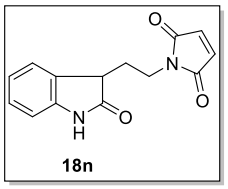
1-[2-(2-Oxoindolin-3-yl)ethyl]pyrrolidine-2,5-dione (18m): According to the general



18m

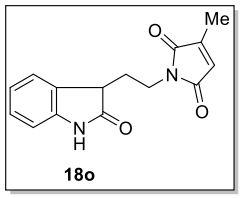
procedure and by using ethyl acetate–petroleum ether (4:6) as an eluent, **18m** was obtained as a yellow solid (117 mg, 73%). Mp 152–154 °C, 1H NMR (DMSO-d_6, 200 MHz) δ 1.56–2.03 (m, 1H), 2.03–2.25 (m, 1H), 2.50 (s, 4H), 3.03–3.65 (m, 3H), 6.82 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 10.40 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 27.2, 27.9, 35.2, 43.1, 109.3, 121.3, 123.9, 127.8, 129.0, 142.7, 177.5, 178.3; ESIMS (m/z) 259 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{15}O_3N_2$ 259.1077, found 259.1074; IR (Nujol) ν_{max} 3272, 1714, 1612 cm^{-1}.

1-[2-(2-Oxoindolin-3-yl)ethyl]-1*H*-pyrrole-2,5-dione (18n): According to the general procedure and by using ethyl acetate–petroleum ether (4:6) as an eluent, **18n** was obtained as a yellow solid (184 mg, 69%). Mp 124–126 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20–2.35 (m, 1H), 2.35–2.50 (m, 1H), 3.52 (br s, 1H), 3.57–3.71 (m, 1H), 3.71–3.85 (m, 1H), 6.56 (s, 2H), 6.89 (d, J = 7.3 Hz, 1H), 7.02 (t, J = 6.7 Hz, 1H), 7.19 (t, J = 6.7 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.1, 34.8, 43.8, 110.0, 122.5, 124.0, 128.1, 128.5, 133.9, 141.5, 170.5, 179.3; ESIMS (m/z) 279 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{12}O_3N_2Na$ 279.0740, found 279.0736; IR (Nujol) ν_{max} 3382, 1712 cm^{-1}.



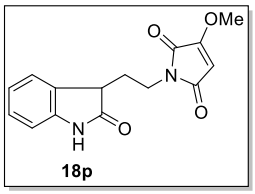
18n

3-Methyl-1-[2-(2-oxoindolin-3-yl)ethyl]-1*H*-pyrrole-2,5-dione (18o): According to the general procedure and by using ethyl acetate–petroleum ether (1:1) as an eluent, **18o** was obtained as a yellow solid (161 mg, 76%). Mp 132–134 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.98 (d, J = 1.8 Hz, 3H), 2.15–2.55 (m, 2H), 3.51 (t, J = 5.3 Hz, 1H), 3.55–3.85 (m, 2H), 6.18 (q, J = 1.9 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 7.01 (td, J = 7.5 and 1.0 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 8.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.8, 28.3, 34.9, 43.8, 109.9, 122.4, 124.0, 127.1, 128.0, 128.6, 141.4, 145.4, 170.6, 171.5, 179.1; ESIMS (m/z) 271 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_3N_2$ 271.1077, found 271.1074; IR ($CHCl_3$) ν_{max} 3282, 1708, 1625 cm^{-1}.



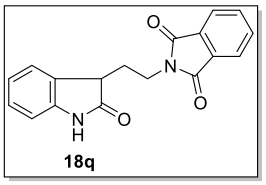
18o

3-Methoxy-1-[2-(2-oxoindolin-3-yl)ethyl]-1*H*-pyrrole-2,5-dione (18p): According to the general procedure and by using ethyl acetate–petroleum ether (4:6) as an eluent, **18p** was obtained as a white solid (78 mg, 74%). Mp 166–168 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.90–2.02 (m, 1H), 2.07–2.18 (m, 1H), 3.35–3.55 (m, 3H), 3.84 (s, 3H), 5.75 (s, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 10.39 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.2, 34.2, 43.0, 59.1, 96.9, 109.4, 121.3, 123.8, 127.7, 128.9, 142.6, 160.8, 165.1, 170.1, 178.2; ESIMS (m/z) 287 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_4N_2$ 287.1026, found 287.1024; IR ($CHCl_3$) ν_{max} 3422, 1721, 1676 cm^{-1}.

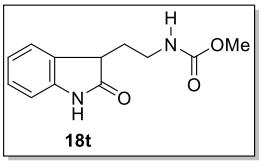


18p

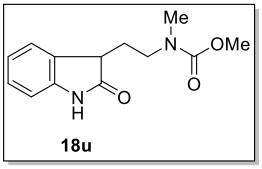
2-[2-(2-Oxoindolin-3-yl)ethyl]isoindoline-1,3-dione (18q): According to the general procedure and by using ethyl acetate–petroleum ether (3:7) as an eluent, **18q** was obtained as a brown solid (256 mg, 81%). Mp 190–192 °C, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.02–2.15 (m, 1H), 2.20–2.32 (m, 1H), 3.52 (t, J = 6.9 Hz, 1H), 3.55–3.67 (m, 1H), 3.67–3.80 (m, 1H), 6.79 (d, J = 9.9 Hz, 1H), 6.86 (t, J = 9.2 Hz, 1H), 7.10 (t, J = 9.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.79 (br s, 4H), 10.40 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 28.0, 34.7, 43.2, 109.3, 121.2, 122.9, 123.8, 127.6, 128.9, 131.7, 134.2, 142.7, 167.7, 178.3; ESIMS (m/z) 307 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{15}O_3N_2$ 307.1077, found 307.1073; IR (Nujol) ν_{max} 3380, 1712 cm^{-1}.



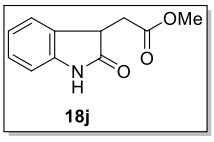
Methyl [2-(2-Oxoindolin-3-yl)ethyl]carbamate (18t): According to the general procedure and by using ethyl acetate–petroleum ether (3:7) as an eluent, **18t** was obtained as a gummy solid (418 mg, 78%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.73–1.90 (m, 1H), 1.90–2.05 (m, 1H), 3.03–3.23 (m, 2H), 3.37 (s, 3H), 3.30–3.45 (m, 1H), 6.82 (d, J = 9.2 Hz, 1H), 6.95 (t, J = 9.3 Hz, 1H), 7.17 (t, J = 9.2 Hz, 1H), 7.23 (br s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 10.39 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 30.6, 37.6, 42.9, 51.3, 109.3, 121.3, 124.1, 127.7, 129.5, 142.6, 156.7, 178.8; ESIMS (m/z) 257 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{14}O_3N_2Na$ 257.0897, found 257.0892; IR (Nujol) ν_{max} 3375, 3141, 1699, 1616 cm^{-1}.



Methyl Methyl[2-(2-oxoindolin-3-yl)ethyl]carbamate (18u): According to the general procedure and by using ethyl acetate–petroleum ether (4:6) as an eluent, **18u** was obtained as a gummy solid (418 mg, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) (rotameric mixture) δ 2.07–2.30 (m, 2H), 2.89 (s, 3H), 3.27–3.39 (m, 1.50H), 3.47 (t, J = 6.1 Hz, 1H), 3.55–3.72 (m, 3.50H), 6.85–6.95 (m, 1H), 7.00–7.08 (m, 1H), 7.15–7.42 (m, 2H), 8.70–9.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.3, 34.0, 34.6, 43.6, 45.5, 46.2, 52.6, 109.7, 122.37, 122.44, 123.9, 124.1, 124.3, 128.0, 128.1, 129.2, 141.66, 141.71, 156.9, 157.0, 179.8, 180.1; ESIMS (m/z) 271 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_3N_2Na$ 271.1053, found 271.1047; IR ($CHCl_3$) ν_{max} 3255, 3012, 2927, 1699, 1618 cm^{-1}.

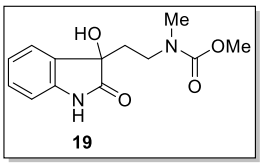


Methyl 2-(2-Oxoindolin-3-yl)acetate (18j). A solution of diazomethane in Et_2O was added to a stirred solution of acid **18i** (150 mg, 0.785 mmol) in methanol (5 mL) until persistence of yellow colour. Reaction mixture



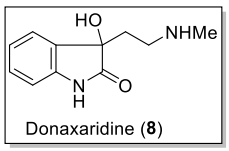
was stirred at 25 °C for 1 h and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (10 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using methanol–dichloromethane (0.2:9.8) as an eluent afforded ester **18j** as a white crystalline solid (151 mg, 94%). Mp 170–172 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.84 (dd, J = 16.8 and 8.0 Hz, 1H), 3.10 (dd, J = 17.0 and 4.2 Hz, 1H), 3.71 (s, 3H), 3.83 (dd, J = 8.0 and 4.6 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.20–7.25 (m, 2H), 8.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.6, 42.3, 52.0, 109.9, 122.5, 124.1, 128.3, 128.7, 141.5, 171.5, 179.1; ESIMS (m/z) 228 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{11}O_3NNa$ 228.0631, found 228.0627; IR ($CHCl_3$) ν_{max} 3427, 1706, 1615 cm^{-1}.

Methyl [2-(3-Hydroxy-2-oxoindolin-3-yl)ethyl](methyl)carbamate (19). To a stirred solution of compound **18u** (500 mg, 2.01 mmol) in dry toluene (10 mL) was added *t*-BuOK (453 mg, 4.03 mmol) at 0 °C under oxygen atmosphere. The reaction mixture was stirred at 0 °C to 25 °C for 4 h and the reaction was quenched by saturated aqueous NH_4Cl solution (2 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using methanol–dichloromethane (0.3:9.7) as an eluent afforded product **19** as a gummy solid (457 mg, 86%). ^{1}H NMR (DMSO-d_6, 400 MHz) (rotameric mixture) δ 1.95 (s, 2H), 2.70 (s, 3H), 3.17 (s, 2H), 3.40–3.60 (m, 3H), 5.98 (s, 1H), 6.81 (d, J = 7.3 Hz, 1H), 6.97 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 6.7 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.5, 33.9, 35.0, 35.4, 43.1, 43.5, 52.2, 74.1, 109.7, 121.7, 123.9, 129.1, 131.7, 141.6, 155.7, 178.8; ESIMS (m/z) 287 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_4N_2Na$ 287.1002, found 287.0996; IR ($CHCl_3$) ν_{max} 3259, 1716, 1676, 1621 cm^{-1}.



19

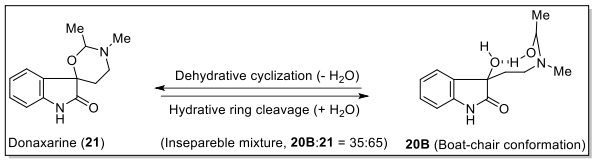
3-Hydroxy-3-[2-(methylamino)ethyl]indolin-2-one (8). To a 10 mL sealed tube equipped with a magnetic stirring bar were added compound **19** (200 mg, 0.76 mmol) and diethylenetriamine (0.33 mL, 3.04 mmol) and the tube was sealed with a Teflon-lined screw cap. The tube was heated at 120 °C for 6 h. The crude reaction mixture was directly purified by silica gel (230–400 mesh) column chromatography by using ethyl acetate–petroleum ether (6:4) as



Donaxaridine (**8**)

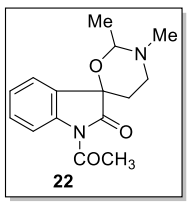
an eluent to afford product **8** as a white solid (160 mg, 91%). Mp 174–176 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (td, J = 13.0 and 9.2 Hz, 1H), 2.76 (ddd, J = 12.8, 6.3 and 1.6 Hz, 1H), 2.97 (s, 3H), 3.23–3.30 (m, 1H), 3.35 (td, J = 9.4 and 1.1 Hz, 1H), 4.40–4.90 (br s, 2H), 6.70 (t, J = 7.2 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.88 (dd, J = 8.0 and 1.2 Hz, 1H), 7.12 (td, J = 8.2 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.2, 32.9, 45.7, 79.4, 118.1, 118.4, 125.2, 125.7, 129.2, 145.8, 175.2; ESIMS (m/z) 207 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{15}O_2N_2$ 207.1128, found 207.1125; IR (Nujol) ν_{max} 3350, 1708 cm^{-1}.

2',3'-Dimethylspiro[indoline-3,6'-(1,3)oxazinan]-2-one (21). To a solution of



compound **8** (150 mg, 0.728 mmol) in dichloromethane (10 mL) was added acetaldehyde (50 μL, 0.788 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C to 25 °C for 3 h and the reaction mixture was concentrated in vacuo. The direct silica gel (60–120 mesh) column chromatographic purification of the resulting residue by using ethyl acetate–petroleum ether (1:1) as an eluent furnished an equilibrium mixture of natural product donaxarine (**21**) and its *gem*-aminohydrin precursor **20B** as a white solid (128 mg, 76%). Mp 176–182 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) [equilibrium mixture of natural product donaxarine (**21**) and its precursor **20B** in 65:35 ratio] δ 1.39 (d, J = 5.4 Hz, 1.95H), 1.51 (d, J = 5.4 Hz, 1.05 H), 2.38–2.57 (m, 2H), 2.97 (s, 1.95 H), 3.02 (s, 1.05 H), 3.42–3.49 (m, 1H), 3.55–3.65 (m, 1H), 4.08 (br s, 1H), 4.76 (quintet, J = 6.1 Hz, 0.35 H), 5.53 (q, J = 6.1 Hz, 0.65 H), 6.71 (d, J = 6.9 Hz, 0.65 H), 6.82 (d, J = 8.4 Hz, 0.35 H), 6.80–6.95 (m, 2H), 7.08–7.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 21.0, 30.3, 30.5, 35.5, 36.1, 45.8, 46.1, 76.5, 79.8, 81.5, 117.3, 118.7, 120.0, 120.9, 123.8, 125.2, 125.3, 128.0, 128.1, 141.4, 143.0, 172.8, 174.0; ESIMS (m/z) 255 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_2N_2Na$ 255.1104, found 255.1098; IR ($CHCl_3$) ν_{max} 3293, 2933, 1684, 1606 cm^{-1}.

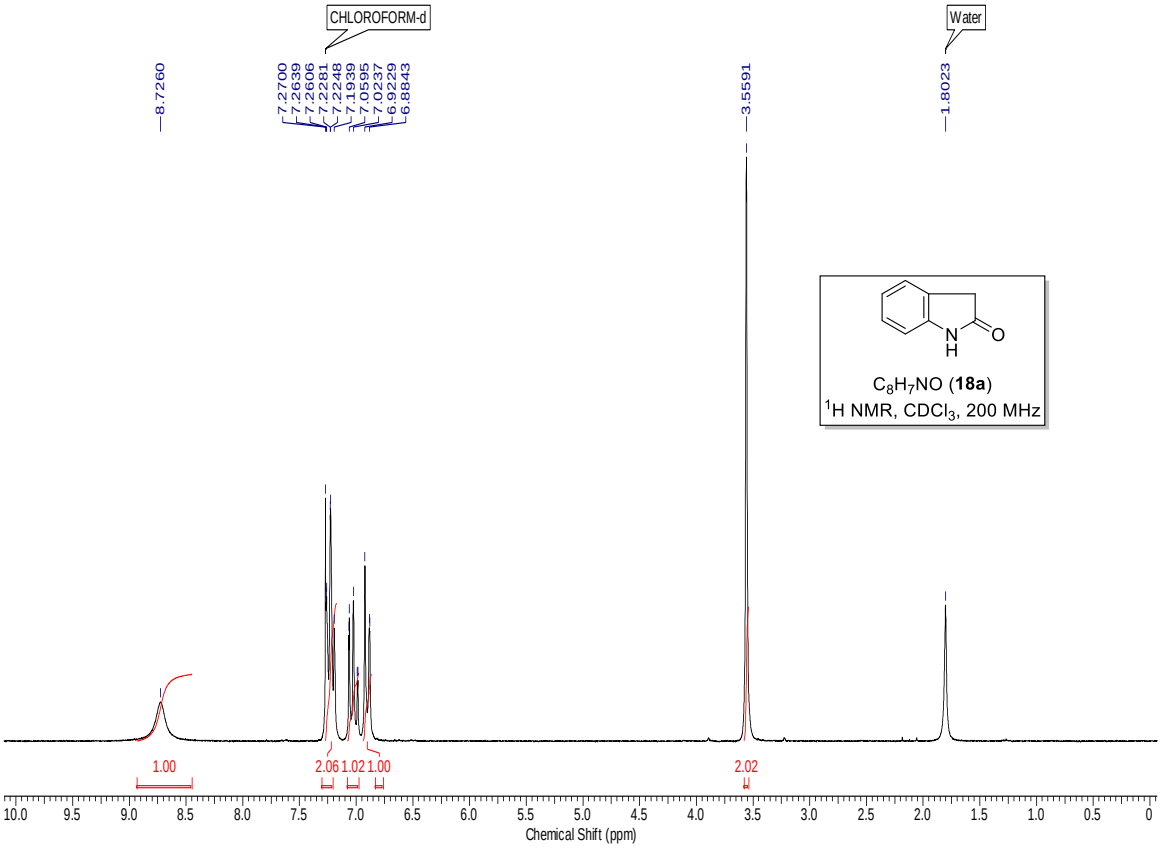
1-Acetyl-2',3'-dimethylspiro[indoline-3,6'-[1,3]oxazinan]-2-one (22). To a solution of



above mixture of natural product donaxarine (**21**) and its precursor **20B** (50 mg, 0.216 mmol) in acetic anhydride (4 mL) was added sodium acetate (53 mg, 0.862 mmol) and the reaction mixture was stirred at 25 °C for 8 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (10 mL) and washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel

(230–400 mesh) column chromatographic purification of the residue by using ethyl acetate–petroleum ether (3:7) as an eluent afforded product **22** as a white solid (52 mg, 89%). Mp 204–206 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (d, J = 6.5 Hz, 3H), 2.25 (s, 3H), 2.40 (quintet, J = 7.3 Hz, 1H), 2.74 (quintet, J = 6.9 Hz, 1H), 2.88 (s, 3H), 3.43–3.50 (m, 1H), 3.57–3.64 (m, 1H), 6.32 (q, J = 6.5 Hz, 1H), 7.17–7.30 (m, 3H), 7.37 (t, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 23.1, 30.4, 32.9, 46.0, 77.7, 78.5, 123.6, 125.7, 126.3, 128.5, 132.3, 136.2, 170.4, 171.4; ESIMS (m/z) 275 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{19}O_3N_2$ 275.1390, found 275.1389; IR ($CHCl_3$) ν_{max} 1693, 1662 cm^{-1}.

2A.5 Selected Spectra


CHLOROFORM-d
Water
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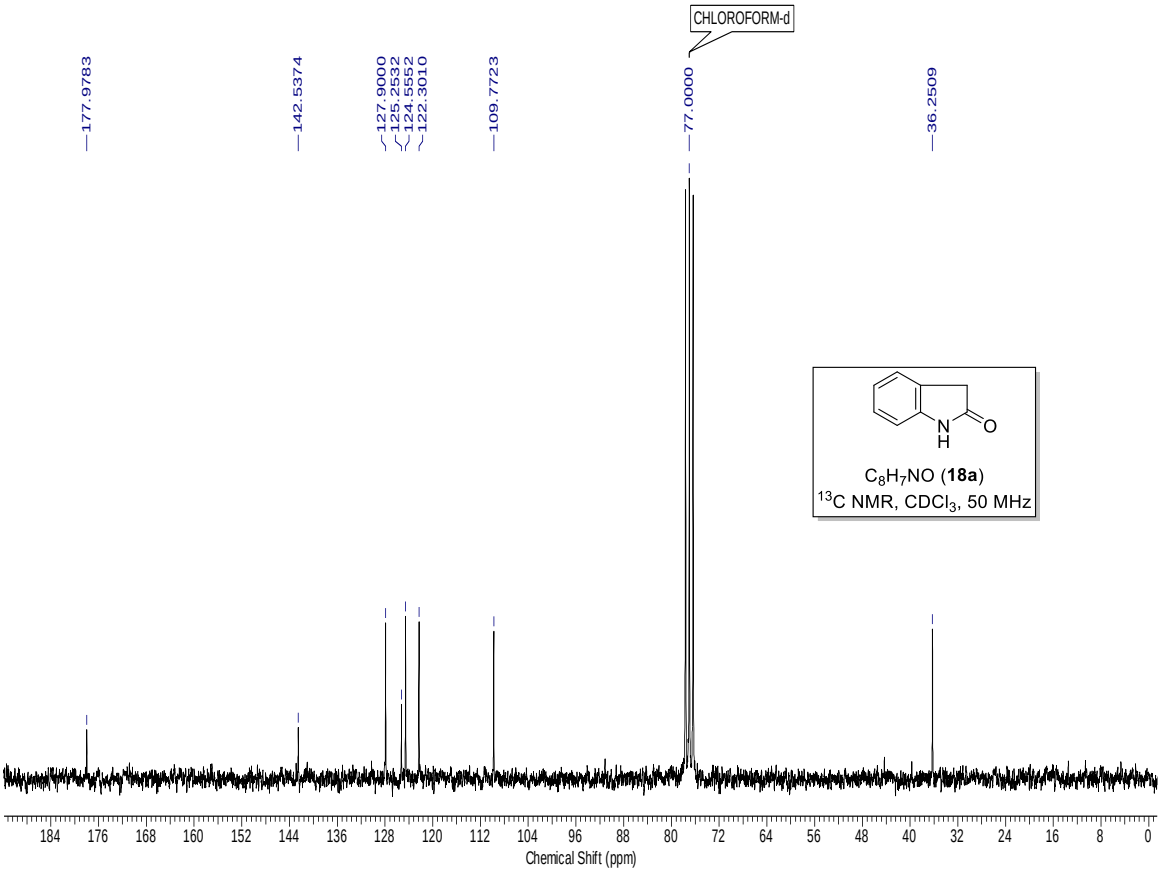
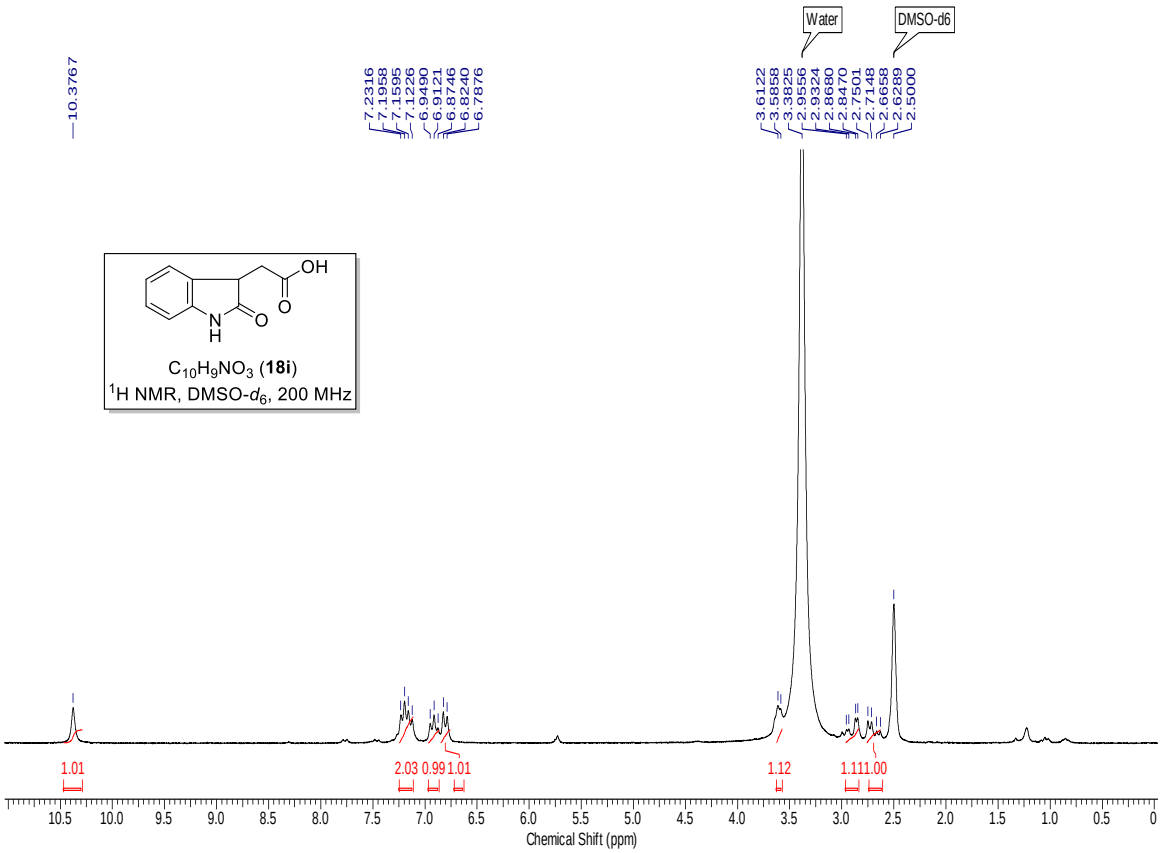
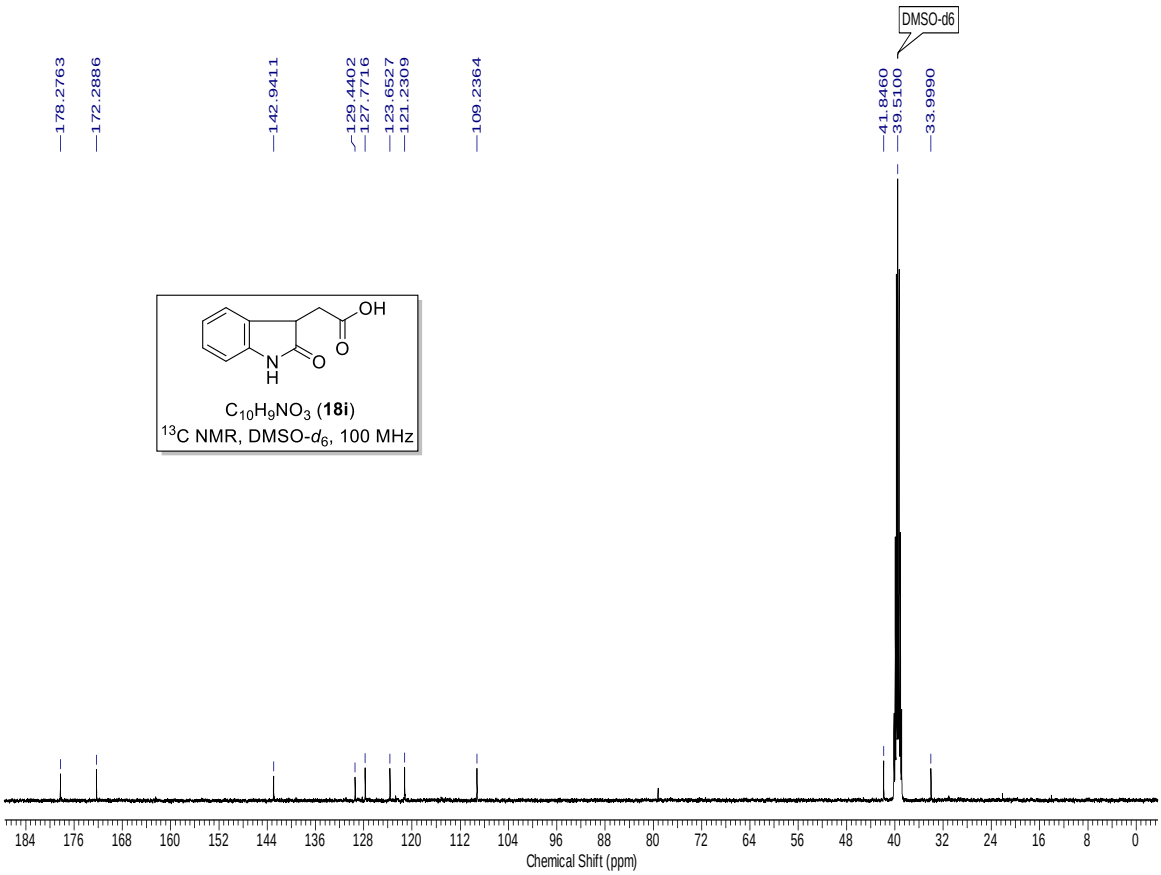
7.2700
7.2639
7.2606
7.2281
7.2248
7.1939
7.0595
7.0237
6.9229
6.8843
3.5591
1.8023
1.00
2.06
1.02
1.00
2.02
Chemical Shift (ppm)
C8H7NO (18a)
1H NMR, CDCl3, 200 MHz


CHLOROFORM-d
177.9783
142.5374
127.9000
125.2532
124.5552
122.3010
109.7723
77.0000
36.2509
Chemical Shift (ppm)
C8H7NO (18a)
13C NMR, CDCl3, 50 MHz


Water
DMSO-d6
10.3767
7.2316
7.1958
7.1595
7.1226
6.9490
6.9121
6.8746
6.8240
6.7876
3.6122
3.5858
3.3825
2.9556
2.9324
2.8680
2.8470
2.7501
2.7148
2.6658
2.6289
2.5000
OH
O
N
H
O
C10H9NO3 (18i)
1H NMR, DMSO-d6, 200 MHz
1.01
2.03
0.99
1.01
1.12
1.11
1.00
Chemical Shift (ppm)


DMSO-d6
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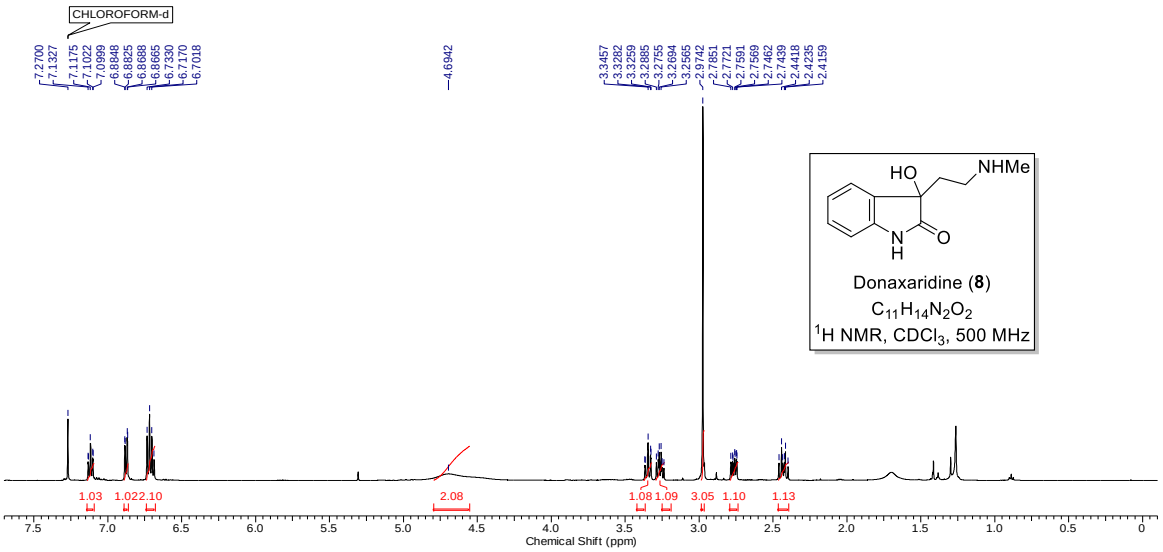
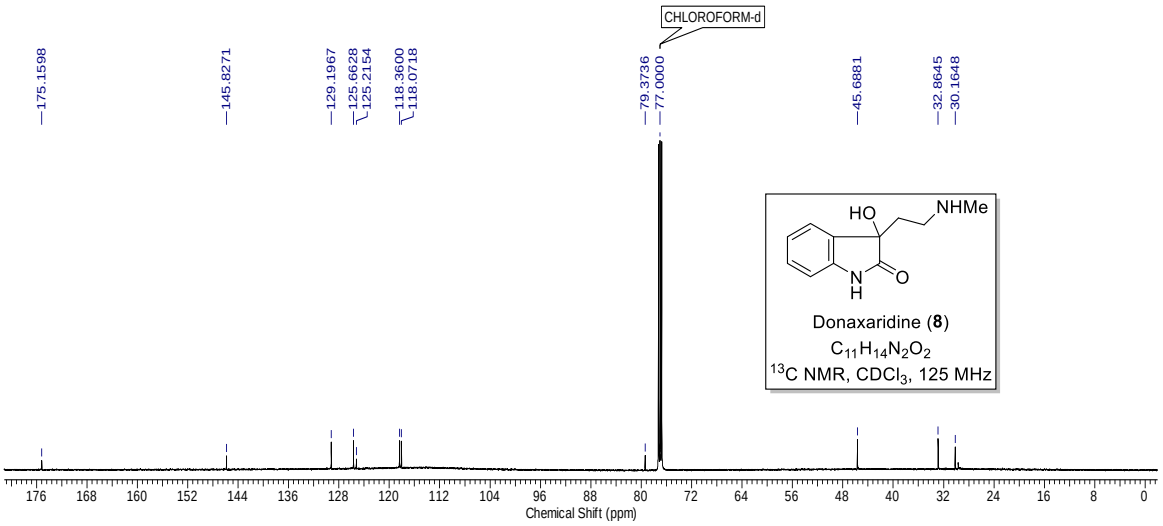
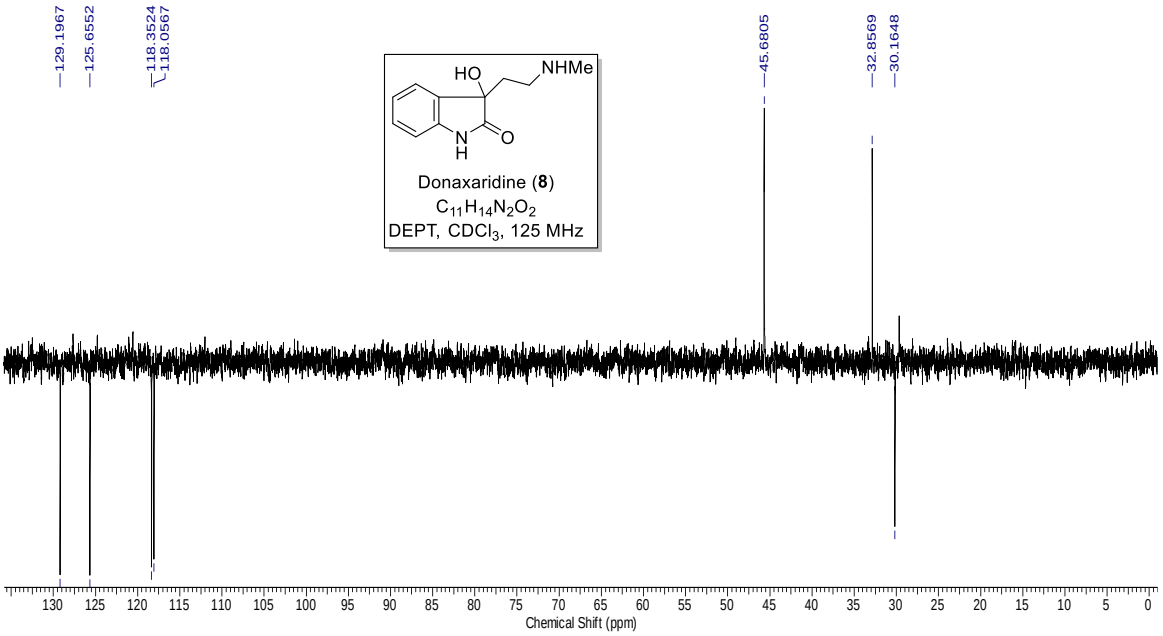
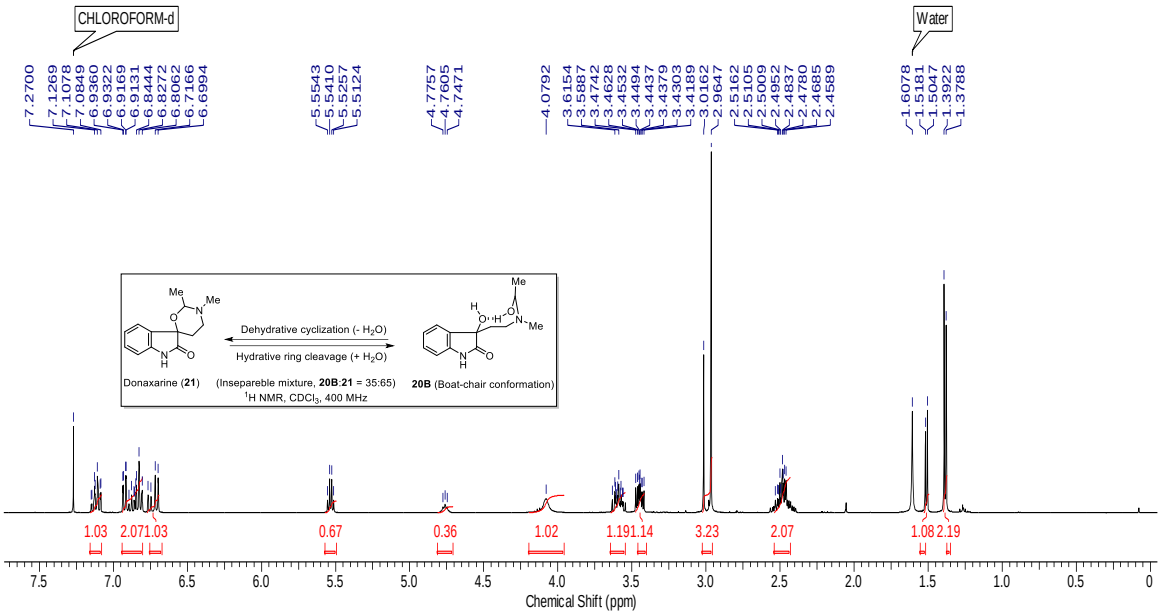
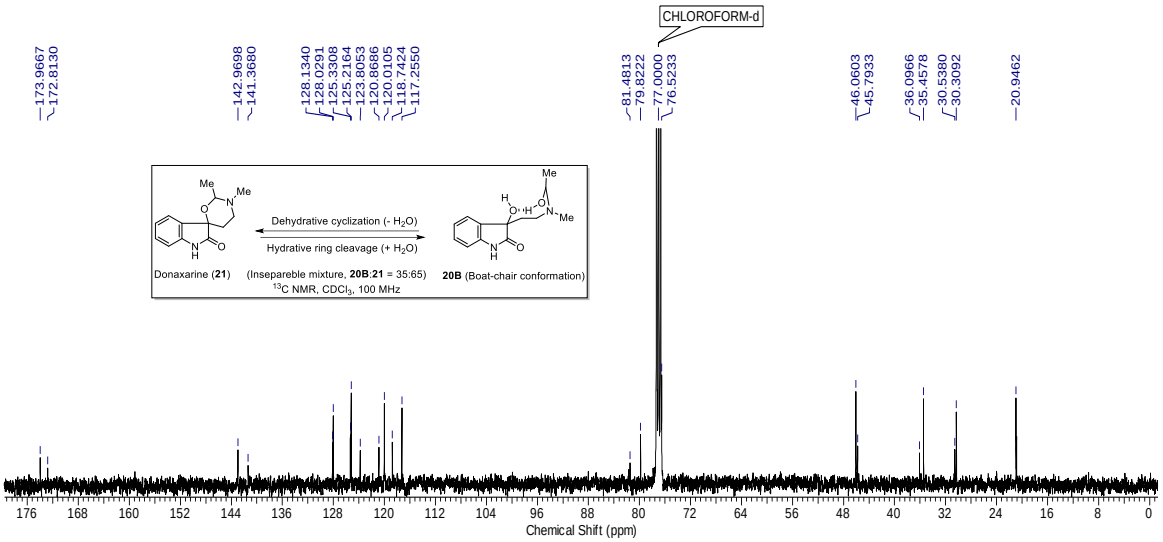
172.2886
142.9411
129.4402
127.7716
123.6527
121.2309
109.2364
41.8460
39.5100
33.9990
OH
O
N
H
O
C10H9NO3 (18i)
13C NMR, DMSO-d6, 100 MHz
Chemical Shift (ppm)

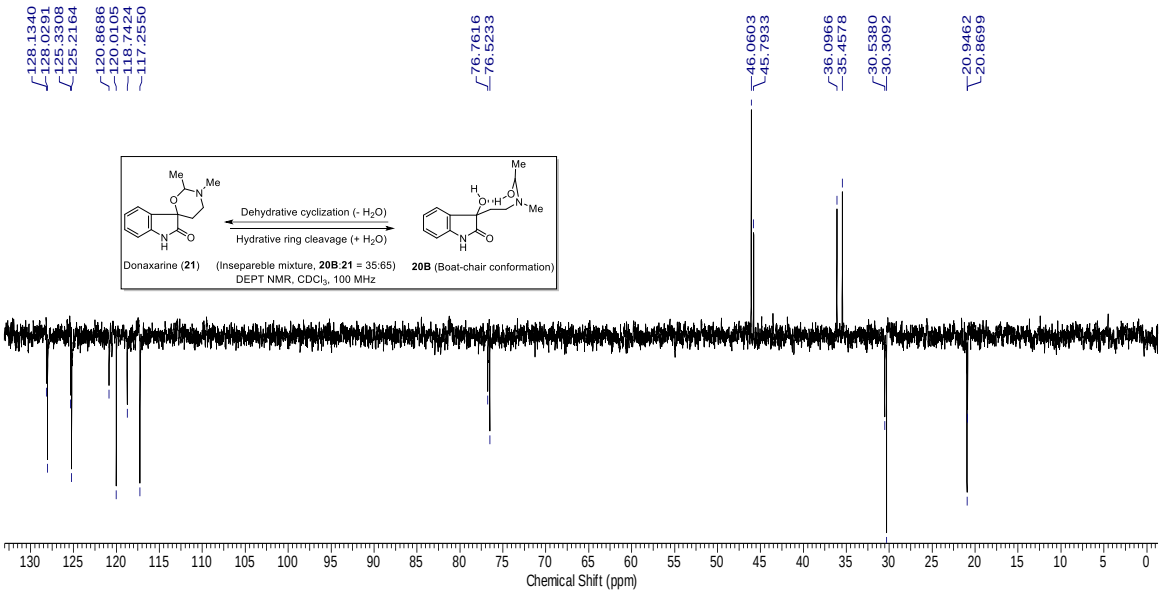

CHLOROFORM-d
7.2700
7.1327
7.1175
7.1022
7.0999
6.8848
6.8825
6.8688
6.8665
6.7330
6.7170
6.7018
4.6942
3.3457
3.3282
3.3259
3.2885
3.2755
3.2694
3.2565
2.7742
2.7651
2.7721
2.7591
2.7569
2.7462
2.7439
2.4418
2.4235
2.4159
HO
NHMe
N
H
O
Donaxaridine (8)
C11H14N2O2
1H NMR, CDCl3, 500 MHz
1.03
1.02
2.10
2.08
1.08
1.09
3.05
1.10
1.13
Chemical Shift (ppm)

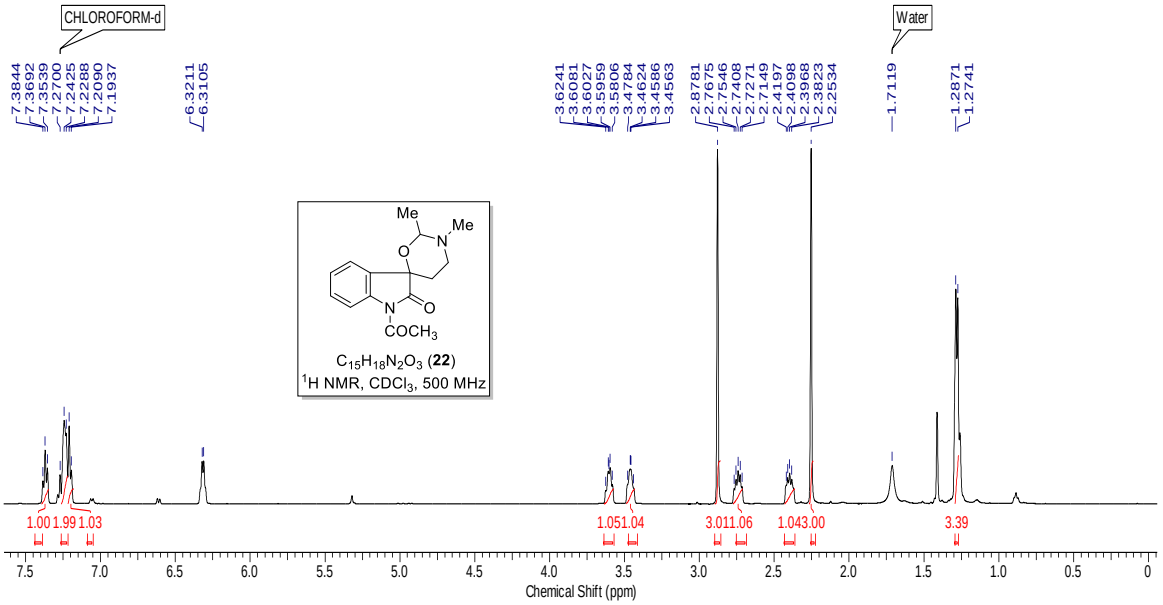

175.1598
145.8271
129.1967
125.6628
125.2154
118.3600
118.0718
CHLOROFORM-d
79.3736
77.0000
45.6881
32.8645
30.1648
HO
NHMe
N
H
O
Donaxaridine (8)
C11H14N2O2
13C NMR, CDCl3, 125 MHz
Chemical Shift (ppm)

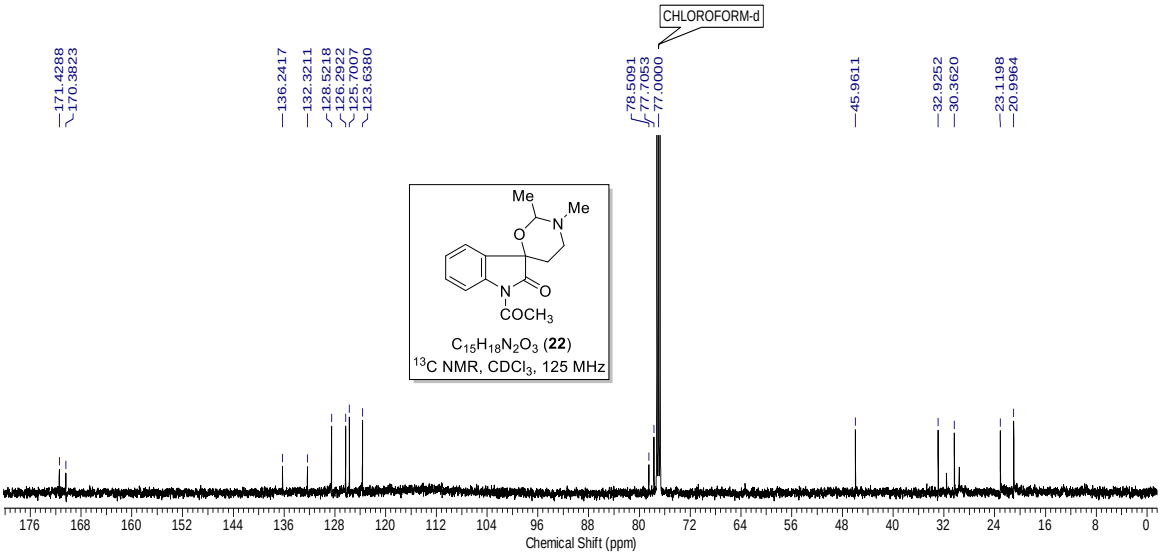

129.1967
125.6552
118.3524
118.0567
45.6805
32.8569
30.1648
HO
NHMe
N
H
O
Donaxaridine (8)
C11H14N2O2
DEPT, CDCl3, 125 MHz
Chemical Shift (ppm)

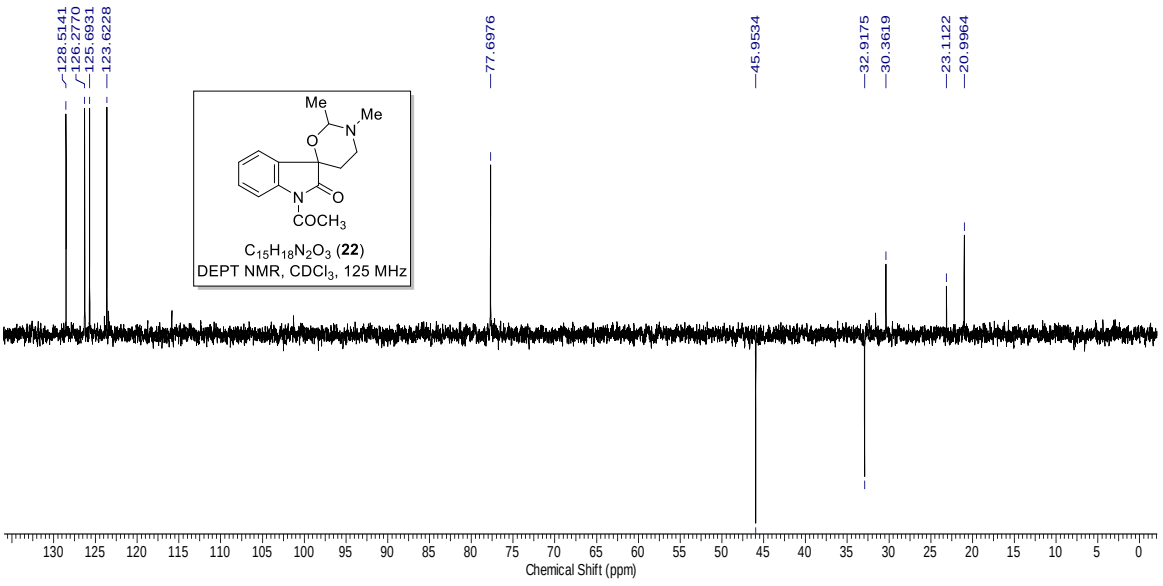

CHLOROFORM-d
Water
Dehydrative cyclization (- H2O)
Hydrative ring cleavage (+ H2O)
Donaxarine (21)
(Inseparable mixture, 20B:21 = 35:65)
20B (Boat-chair conformation)
1H NMR, CDCl3, 400 MHz
1.03 2.07 1.03 0.67 0.36 1.02 1.19 1.14 3.23 2.07 1.08 2.19
Chemical Shift (ppm)


CHLOROFORM-d
Dehydrative cyclization (- H2O)
Hydrative ring cleavage (+ H2O)
Donaxarine (21)
(Inseparable mixture, 20B:21 = 35:65)
20B (Boat-chair conformation)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


Dehydrative cyclization (- H2O)
Hydrative ring cleavage (+ H2O)
Donaxarine (21)
(Inseparable mixture, 20B:21 = 35:65)
20B (Boat-chair conformation)
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


CHLOROFORM-d
Water
7.3844
7.3692
7.3559
7.2700
7.2425
7.2288
7.2090
7.1937
6.3211
6.3105
3.6241
3.6081
3.6027
3.5959
3.5806
3.4784
3.4624
3.4586
3.4563
2.8781
2.7675
2.7546
2.7408
2.7271
2.7149
2.4197
2.4098
2.3968
2.3823
2.2534
1.7119
1.2871
1.2741
Me
Me
O
N
N
O
COCH3
C15H18N2O3 (22)
1H NMR, CDCl3, 500 MHz
1.00 1.99 1.03
1.051.04
3.011.06
1.043.00
3.39
Chemical Shift (ppm)


CHLOROFORM-d
171.4288
170.3823
136.2417
132.3211
128.5218
126.2922
125.7007
123.6380
78.5091
77.7053
77.0000
45.9611
32.9252
30.3620
23.1198
20.9964
Me
Me
O
N
N
O
COCH3
C15H18N2O3 (22)
13C NMR, CDCl3, 125 MHz
Chemical Shift (ppm)


128.5141
126.2770
125.6931
123.6228
77.6976
45.9534
32.9175
30.3619
23.1122
20.9964
Me
Me
O
N
N
O
COCH3
C15H18N2O3 (22)
DEPT NMR, CDCl3, 125 MHz
Chemical Shift (ppm)

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Chapter 2

Section C

Wittig Reactions of Maleimide Derived Stabilized Ylides with Alkyl Pyruvates: Concise Approach to Methyl Ester of (±)-Chaetogline A

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

2C.1 Background

Indole alkaloids are famous due to their natural occurrence and numerous bioactivities and they are good candidates in the drug discovery program.[1] The biogenesis of most of the indole alkaloids originates from *β*-tryptamine, a decarboxylation outcome of tryptophan. The biogenesis involves initial formation of a Schiff base from *β*-tryptamine and aldehyde or ketone and subsequent cyclization to yield tetrahydro-*β*-carboline.[2] Pictet−Spengler reaction has been widely used in several organic reactions.[3] Although it is highly studied in the plant biogenesis, much less evidence regarding the Pictet−Spengler reactions in fungi is known. The chaetoglines A−H have been isolated as the first fungal indole alkaloids in 2014 (Figure 1).[4] The same group in 2019 isolated the two known natural products chaetogline A and chaetogline F along with the two unknown natural products 19-*O*-desmethylchaetogline A and 20-*O*-desmethylchaetogline F from marine fish-derived fungus *Chaetomium globosum* 1C51 (Figure 1).[5]

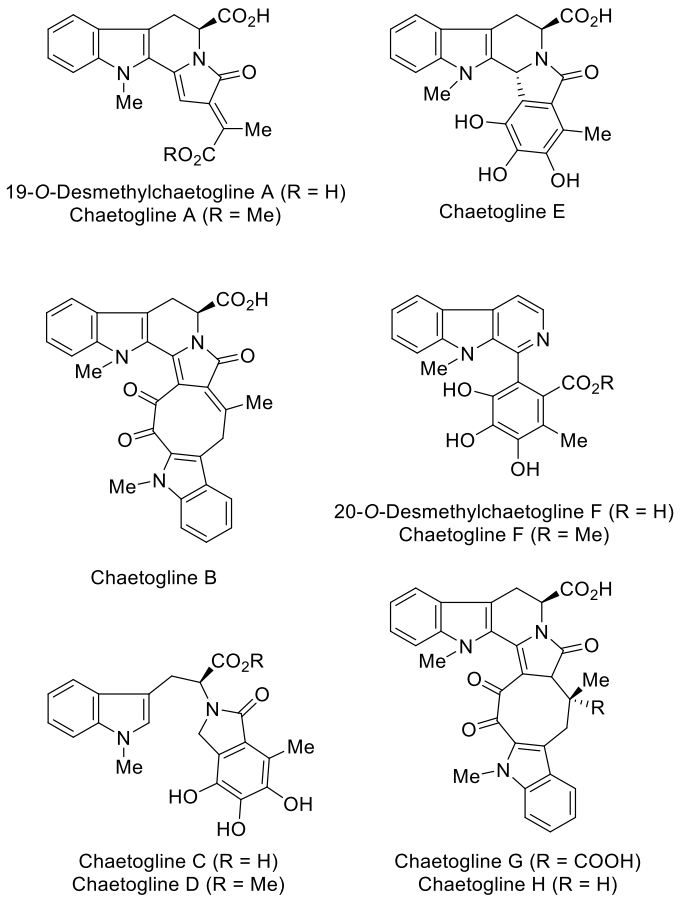
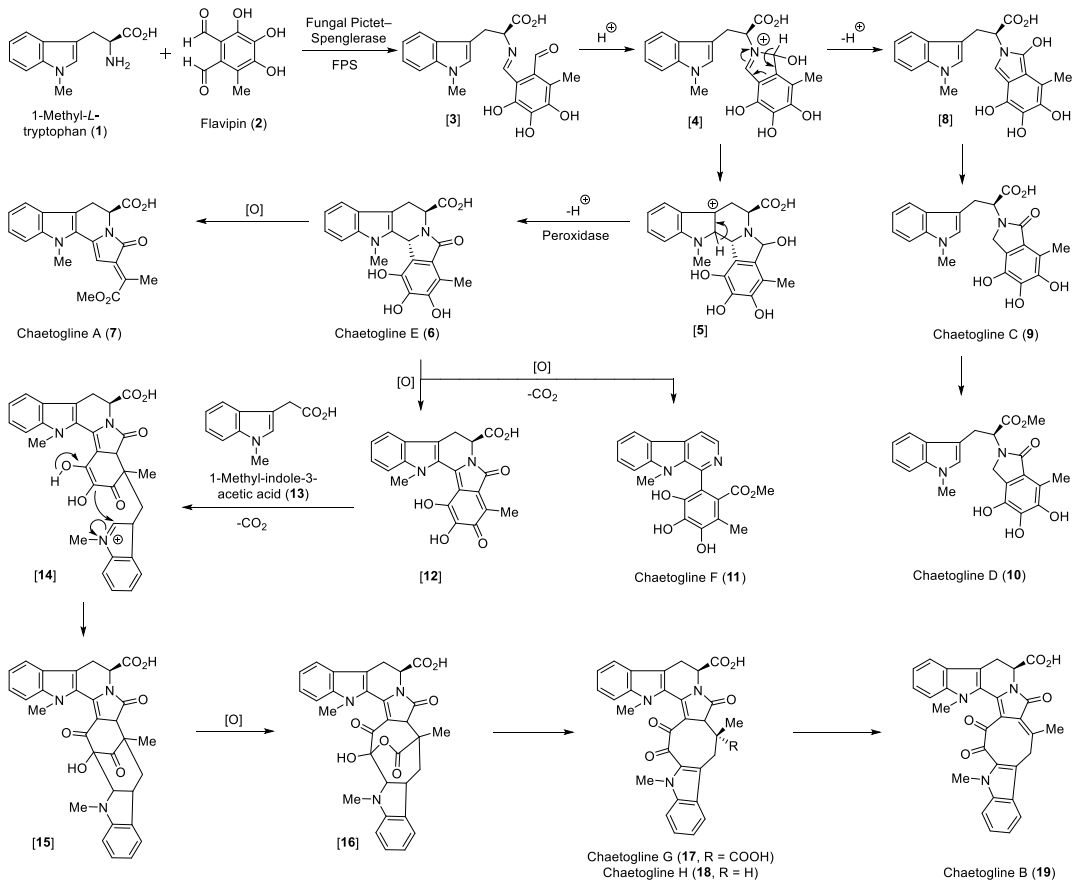


Figure 1. Chaetogline alkaloids derived from methyl tryptophan and flavipin by the fungus *Chaetomium globosum* 1C51

2C.1.1 Fungus Motivated Biotransformation's Utilizing 1-Methyl-*L*-Tryptophan and Flavipin

The first fungal indole alkaloids chaetoglines A−H were reported by Tan and co-workers (Scheme 1).[4] The enzymatic reaction of 1-methyl-*L*-tryptophan (**1**) with flavipin (**2**) in the presences of fungal Pictet–Spenglerase delivers the intermediate **3**. Intermediate **3** tautomerizes via **4** and **8** with a lower reaction barrier around 5.17 kcal/mol to give an energetically much more stable product of chaetogline C (**9**, −31.97 kcal/mol). Methyl esterification of chaetogline C (**9**) provides the chaetogline D (**10**). The intermediate **4** undergoes an intramolecular cyclization to form intermediate **5**, which gives chaetogline E (**6**) via removal of proton followed by oxidation by using peroxidase. Chaetogline E (**6**) upon oxidative cleavage of aromatic ring from the phthalide part yields chaetogline A (**7**). The oxidative and decarboxylative aromatization followed by methanolysis of chaetogline E (**6**) results in chaetogline F (**11**). Chaetogline E (**6**) oxidizes to intermediate **12**, which gives **14** via the decarboxylative reaction with 1-methyl-indole-3-acetic acid (**13**), which is derived from 1-methyl-*L*-tryptophan by the fungi. Intermediate **14**

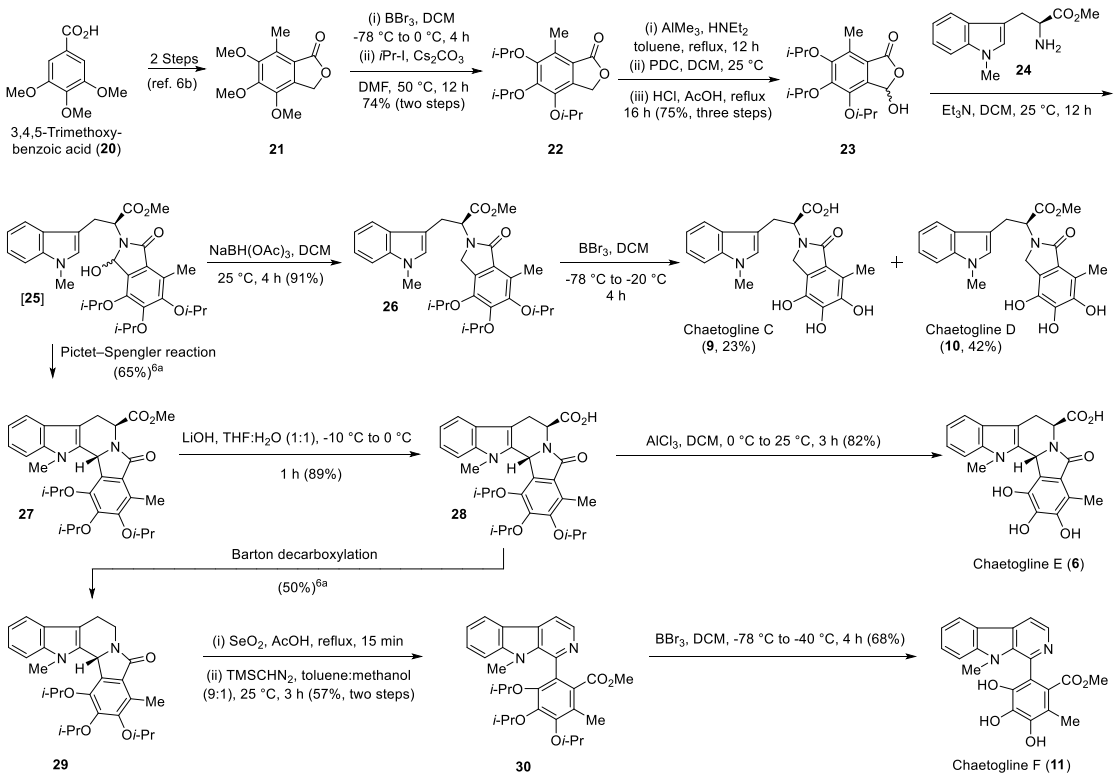


Scheme 1. Fungus Motivated Biotransformations Leading to Novel Chaetoglines

undergoes intramolecular cyclization, monooxygenation and isomerization to form chaetogline G (**17**), which upon decarboxylation gives chaetogline H (**18**). Oxidation of chaetogline H (**18**) forms chaetogline B (**19**). Overall, as a result of complex microbial interactions these potentially bioactive chaetoglines have been formed.

2C.1.2 Reported Synthesis of Chaetoglines C to F

The first total syntheses of chaetoglines C to F have been reported by Lei and co-workers in 2019 (Scheme 2).[6a] The synthesis began with the known lactone **21**,[6b] deprotection of *O*-methyl moieties in lactone **21** by using boron tribromide followed by isopropyl protections were preferred for better yields. Lactone **22** on aminolysis yields the benzyl alcohol derivative, which was subsequently oxidized to the corresponding aldehyde by employing PDC. The next hydrolysis and cyclization provided the hemiacetal **23** in 75% yield. Condensation between hemiacetal **23** and *N*-methyl tryptophan methyl ester (**24**) provided the hemiaminal **25**. Reduction of the hemiaminal **25** provided lactam **26** in 91% yield. Deprotection of isopropyl groups by using boron tribromide provided chaetoglines C (**9**) and D (**10**) in 23% and 42% yield,

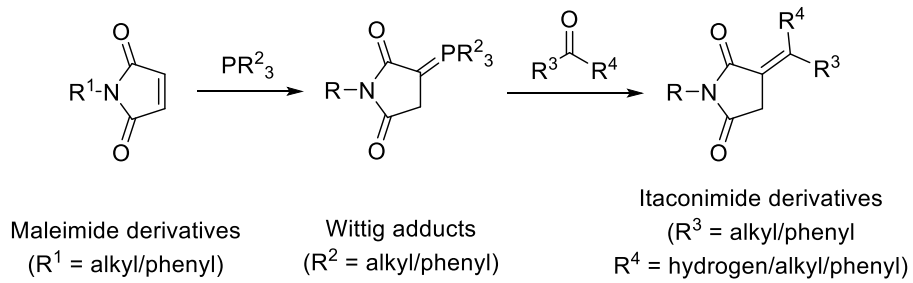


Scheme 2. Collective Total Synthesis of Chaetoglines C to F

respectively. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated the stereoselective Pictet–Spengler reaction with hemiacetal **25** provided cyclized compound **27** in 65% yield. Hydrolysis of methyl ester in compound **27** using lithium hydroxide gave carboxylic acid **28**. Deprotection of isopropyl groups in compound **28** by using aluminum trichloride provided chaetogline E (**6**) in nine steps with 21% overall yield. The synthesis of chaetogline F (**11**) was accomplished by removal of carboxylic acid group in compound **28** by using Barton decarboxylation protocol. The obtained compound **29** was aromatized by using selenium dioxide oxidation, which was followed by the methylation with trimethylsilyl diazomethane to obtain the product **30**. Boron tribromide mediated deprotection of isopropyl groups in compound **30** gave chaetogline F (**11**) in 68% yield.

2C.1.3 Reported Wittig Reactions of Maleimide Derived Stabilized Ylides with Ketone

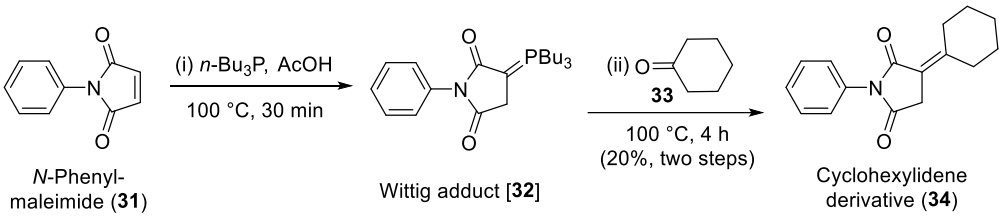
The Wittig reaction was reported in 1954 by Georg Wittig and his co-worker Ulrich Schöllkopf. Professor Wittig won the Nobel Prize in Chemistry in 1979 for this highly useful contribution.[7,8] Wittig reaction provides the respective olefin from the reaction of aldehyde or ketone with phosphonium ylide.[9,10] Geometry of Wittig product (*E*- or *Z*-olefin) depends on ylides. Stabilized ylides give the *trans*-olefins and non-stabilized ylides provided the *cis*-olefins. A phosphonium ylides can also be prepared from maleic anhydride/maleimide derivatives via in situ proton shift.[11] Maleimide-derived stabilized ylides reactions with aldehydes[12] are well known in the literature, but their reactions with ketones are not much studied (Scheme 3).



Scheme 3. Representative Wittig Reactions of Maleimides with Aldehydes and Ketones

Hedaya and Theodoropulos in 1968 reported the first interaction of maleimide-derived ylides with a ketone (Scheme 4).[11,13] The reaction of *N*-phenylmaleimide (**31**) with

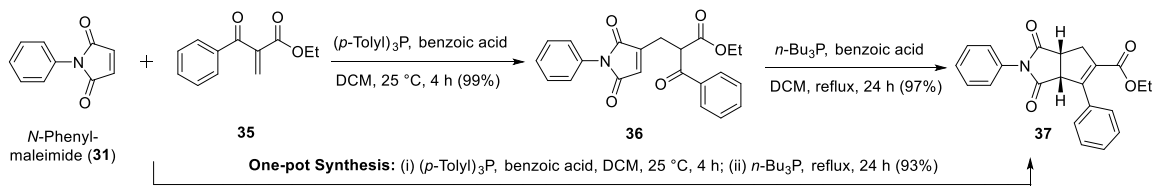
tributyl phosphine in acetic acid produced Wittig adduct **32**. Addition of excess cyclohexanone to the Wittig adduct **32** at the heating conditions for 4 h provided the desired cyclohexylidene derivative **34** in 20% yield.



Scheme 4. Wittig Reaction of Maleimide-Derived Ylide with Cyclohexanone

He and co-workers in 2013 reported the Rauhut−Currier reaction between maleimides and enones followed by Wittig reaction with a ketone (Scheme 5).[14] The reaction of *N*-phenylmaleimide (**31**) and 2-benzoyl acrylate **35** in the presence of (*p*-tolyl)$_3$P with protic additive benzoic acid in DCM at 25 °C for 4 h yieled the coupling product **36** in 99% yield. The compound **36** on reaction with a stoichiometric amount of tributylphosphine and benzoic acid smoothly got converted into a bicyclic product **37** with double-bond migration as a single diastereomer in 97% yield.

The control experiment results analysis revealed that (*p*-tolyl)$_3$P is effective to form the product **36** and PBu$_3$ is effective to induce the next cyclization. After analyzing the results, they developed a one-pot dual phosphine relay strategy, did the cross-coupling reaction of maleimide **31** and enone **35** using (*p*-tolyl)$_3$P reagent. Subsequently, the second phosphine PBu$_3$ (1.20 equiv) was added into the reaction mixture to fulfill the cyclization step. The bicyclic compound **37** was formed in 93 % yield via a one-pot dual phosphine relay strategy.

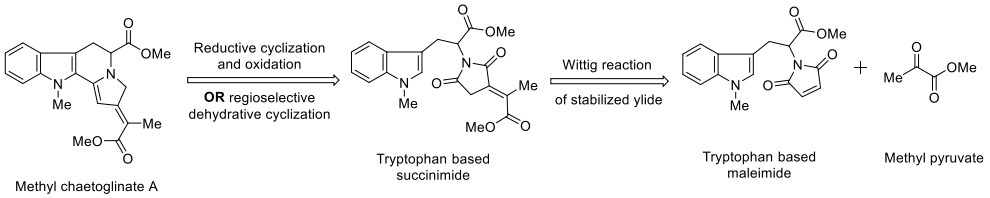


Scheme 5. Rauhut−Currier Reaction between Maleimide and Enone Followed by Wittig Reaction

2C.2 Results and Discussion (Present Research Work)

Wittig Reactions of Maleimide Derived Stabilized Ylides with Alkyl Pyruvates: Concise Approach to Methyl Ester of (±)-Chaetogline A

The structurally fascinating and biologically imperative indole alkaloids have been frequent synthetic targets due to their well-provided multipurpose practical applications.[15–18] The structurally unprecedented indole alkaloids chaetoglines A–H, desmethylchaetogline A and desmethylchaetogline F were obtained from *Chaetomium globosum* 1C51 fungus motivated biotransformation's between 1-methyl-*L*-tryptophan and flavipin (3,4,5-trihydroxy-6-methylphthalaldehyde) (Figure 1).[4,5] It is proposed that the Schiff base formed from above specified amine and aldehyde undergoes Pictet–Spengler cyclization to initially generate chaetogline E, which upon oxidative cleavage of aromatic ring from the phthalide part yields chaetogline A (Scheme 1).[5] Chaetogline alkaloids are of significance from a biomedicine and agrochemical point of view. More specifically, (–)-chaetogline A and (–)-19-*O*-desmethylchaetogline A inhibit the crop pathogenic microbes *Sclerotinia sclerotiorum* and *Xanthomonas oryzae*.[6,19–21] Starting from the methyl ester of 1-methyl-*L*-tryptophan and a suitably substituted hydroxyphthalide, an elegant biogenetic type collective total synthesis of chaetoglines C–F have been recently reported by Lei and co-workers (Scheme 2).[6a] However, the syntheses of all other chaetogline alkaloids are still not reported. In continuation of our studies on the transformation of cyclic anhydrides/imides to bioactive natural products,[22–24] we planned for the total synthesis of chaetogline A and 19-*O*-desmethylchaetogline A. A concise retrosynthetic analysis of methyl chaetoglinate A is described in scheme 6. The maleimide obtained from methyl ester of 1-methyltryptophan on stereoselective trialkylphosphine induced Wittig reaction with methyl pyruvate followed by regioselective reductive-cyclization, or dehydrative-cyclization would constitute an easy access to the chaetogline A framework.



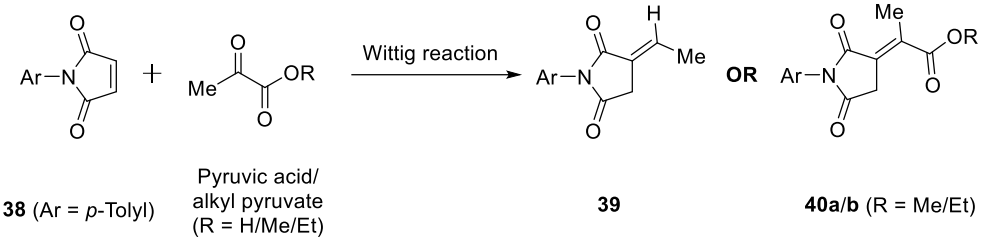
Scheme 6. Retrosynthetic Analysis of Chaetogline A with the Corresponding Maleimide as a Potential Precursor

Accordingly, we describe the synthesis of the methyl ester of chaetogline A (Schemes 6 to 8). Maleimide- and citraconimide-derived, in situ generated stabilized phosphorous ylides react with aliphatic and aromatic aldehydes and furnish the corresponding thermodynamically more stable Wittig products (*E*)-alkylidinesuccinimides in high yields.[11,12,25] A few Wittig olefination reactions of related ylides with ketones are also known.[11,13,14] To the best of our knowledge, Wittig reaction of above-mentioned ylides with an activated carbonyl moiety in alkyl pyruvate is not reported to date. Therefore, systematic studies on the above-specified reaction were essential from a practical application point of view. In this context, we planned to introduce a suitably substituted exocyclic carbon−carbon double bond in a target compound by using the reaction of maleimide-derived stabilized ylide with methyl pyruvate. Initially studied reactions of maleimide **38** based ylides with pyruvic acid stereoselectively formed the corresponding in situ decarboxylated thermodynamically more stable (*E*)- alkylidinesuccinimide **39** in 48% and 57% yields (Table 1, entries 1 and 2). The (*E*)-configuration in product **39** was established on the basis ^{1}H NMR data. The vinylic proton in product **39** appeared downfield due to the *peri*-interaction with an imide carbonyl group. Finally, it was confirmed by comparison with an authentic sample, which was directly synthesized from the reaction of maleimide-derived Wittig reagent with acetaldehyde.[12,25] It is important to note that in these reactions, the conjugated acid intermediates undergo decarboxylation at room temperature, specifically under neutral reaction conditions. The Wittig reactions of above-mentioned ylides with methyl pyruvate and ethyl pyruvate were cleanly achievable. They stereoselectively provided the corresponding (*E*)-alkylidinesuccinimides products **40a** and **40b** in 81% to 91% yields (Table 1, entries 3 to 6).

At first, the synthesis of a model system was planned from tryptamine-derived maleimide **41**. A ylide derived from maleimide **41** and tributylphosphine on reaction with ethyl pyruvate exclusively delivered the corresponding (*E*)-alkylidenesuccinimide **42** in 86% yield (Scheme 7). The Wittig reaction was performed in EtOH:DCM (3:1) instead of acetone for solubility issues. Reduction of imide **42** with $NaBH_4/CeCl_3$ was not regioselective and resulted in a mixture of unisolable lactamols **43a** and **43b** (by TLC). The above-specified reaction mixture on treatment with trifluoroacetic acid for 2 h provided column chromatographically separable Pictet–Spengler cyclization products **44a** and **44b** in a 4:1 ratio with 75% yield. The proton NMR signal for an angular methane proton in compound **44a** appeared as a doublet of doublet [4.92 (dd, J = 7.3 and 5.6 Hz,

1H)], while in compound **44b** it appeared as a relatively more deshielded singlet [5.74 (s, 1H)]. Analysis of complete spectral data neatly supported their isomeric structural assignments. Surprisingly, a continuation of reaction as mentioned above for 24 h

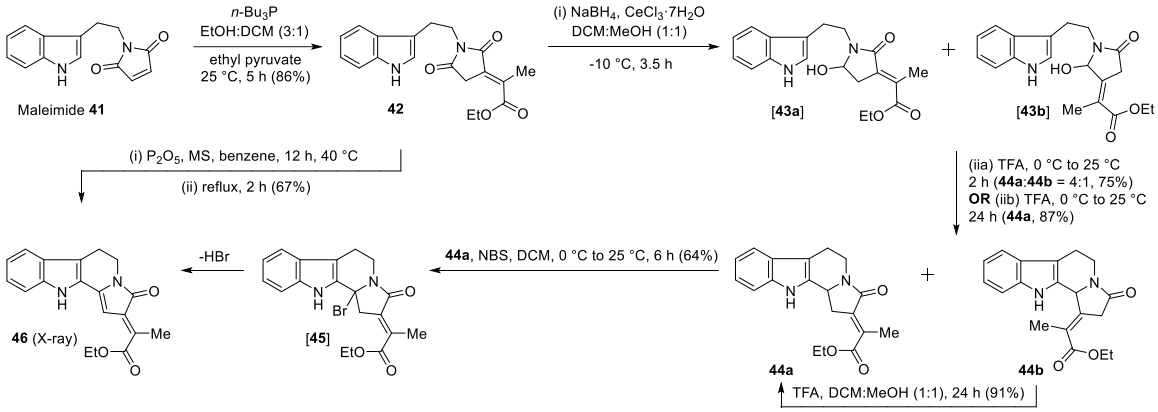
Table 1. Wittig Reactions of Maleimide Derived Stabilized Ylides with Pyruvic Acid and Alkyl Pyruvates



Entry	Reaction conditions	Product (yield)
1	PPh_3, CH_3COCO_2H, acetone, 25 °C, 8 h	**39** (48%)
2	*n*-Bu_3P, CH_3COCO_2H, acetone, 25 °C, 8 h	**39** (57%)
3	PPh_3, CH_3COCO_2Me, acetone, 25 °C, 4 h	**40a** (81%)
4	*n*-Bu_3P, CH_3COCO_2Me, acetone, 25 °C, 4 h	**40a** (86%)
5	PPh_3, CH_3COCO_2Et, acetone, 25 °C, 4 h	**40b** (86%)
6	*n*-Bu_3P, CH_3COCO_2Et, acetone, 25 °C, 4 h	**40b** (91%)

exclusively formed the desired product **44a** in 87% yield. In a control experiment, regioisomer **44b** under a similar set of reaction conditions was completely transformed into **44a** in 24 h with 91% yield. Overall, under acidic conditions the undesired isomer **44b** got transformed into the conjugated thermodynamically more stable isomer **44a**. In a thermodynamically controlled transformation of **44b** to **44a**, the migration of exocyclic carbon−carbon double bond moiety at the β-position to the α-position plausibly takes place via reversible Pictet–Spengler reaction pathway.[26] Regioselective NBS-bromination of **44a** at the more reactive angular benzylic position formed unisolable intermediate **45**, which upon subsequent dehydrobromination furnished the requisite model compound **46** in 64% yield. The reaction of imide **42** with phosphorous pentoxide under reflux conditions was low yielding due to starting material decomposition. However, a

phosphorous pentoxide driven extension of conjugation favored regioselective dehydrative cyclization of imide **42** under the controlled heating at 40 °C followed reflux resulted in the same dark red colored model compound **46** in acceptable yield (67%). The structure of product **46** was unambiguously established on the basis of ^{1}H NMR, ^{13}C NMR, HRMS and X-ray crystallographic data. X-ray data for product **46** confirmed the *E*-configuration of the exocyclic carbon−carbon double bond in the corresponding starting compound **42** and supported the assigned *E*-configuration for all other reported Wittig products (Figure 2).



Scheme 7. Approaches to Chaetogline A Framework from Tryptamine Derived Maleimide

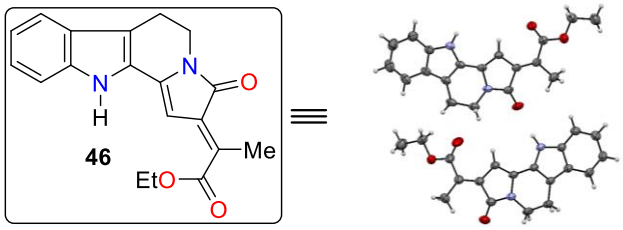
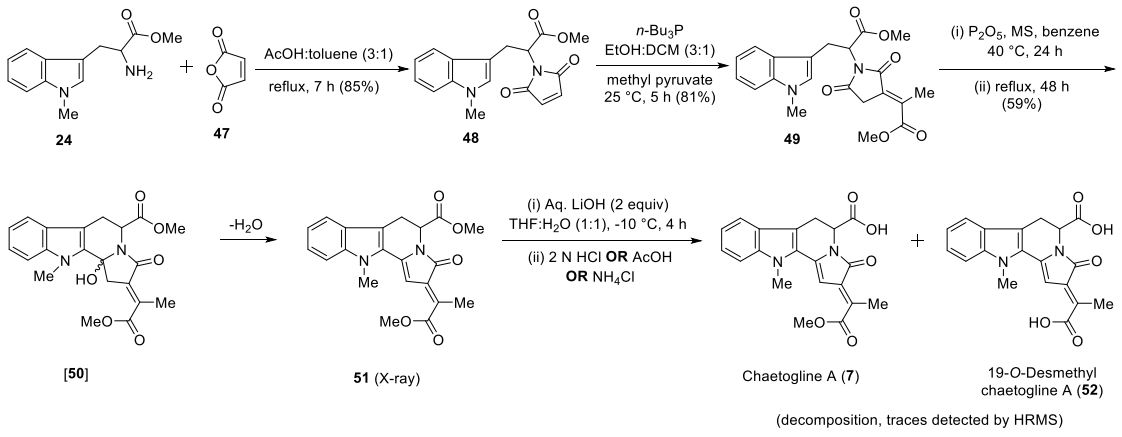


Figure 2. X-ray crystal structure of ethyl (*E*)-2-[3-oxo-6,11-dihydro-3*H*-indolizino(8,7-b)indol-2(5*H*)-ylidene]propanoate

The reaction of methyl 1-methyltryptophanate (**24**) with maleic anhydride (**47**) in refluxing acetic acid-toluene mixture provided the desired maleimide **48** in 85% yield via anhydride ring opening followed by a dehydrative cyclization (Scheme 8). Similarly, the reaction of maleimide **48** with methyl pyruvate in the presence of tributylphosphine stereoselectively delivered the corresponding (*E*)-imide **49** in 81% yield. Phosphorous pentoxide induced regioselective dehydrative cyclization of imide **49** in refluxing benzene

provided the methyl chaetoglinate A skeleton **51** in 59% yield (74% based on the recovery of starting material). The above-specified reaction was less efficient in refluxing toluene, plausibly due to stability issues. Finally, the methyl ester structure of chaetogline A (**51**) was confirmed by using X-ray crystallographic data (Figure 3). Unfortunately, all our attempts involving acid/base induced hydrolysis of ester moieties in compound **51** met with failure and always resulted in immediate decomposition. Base induced hydrolysis of compound **51** under conditions described by Lei and co-workers (LiOH, THF/H_2O, –10 to 0 °C, 1 h)[6a] followed by acidification with dilute hydrochloric acid/acetic acid/ammonium chloride also caused nearly complete decomposition. However, an immediately taken HRMS of the decomposed material revealed the existence of traces of both chaetogline A (**7**) and 19-*O*-desmethylchaetogline A (**52**). In the above-mentioned stepwise hydrolysis of diester **51**, at first more reactive unconjugated ester gets hydrolyzed to form chaetogline A (**7**) and then the hydrolysis of conjugated ester forms 19-*O*-desmethylchaetogline A (**52**). Attempts to transform diester **51** to products **7** and **52** using KF/TBAF (decomposition), K_2CO_3/THF:H_2O (no reaction) and 2 N HCl (decomposition) also failed. Based on several experiments performed for hydrolysis of diester **51**, we feel that the resultant mono-acid **7** and di-acid **52** are unstable under acidic/basic conditions and consequently decompose due to hydrolytic/decarboxylative/oxidative cleavages.[27] Unfortunately, the repetition of scheme 8 by using enantiomerically pure methyl 1-methyl-*L*-tryptophanate (**24**) resulted in excessive racemization during the transformation of maleimide **48** to alkylidinesuccinimide **49**.



Scheme 8. Synthesis of Methyl Ester of Chaetogline A

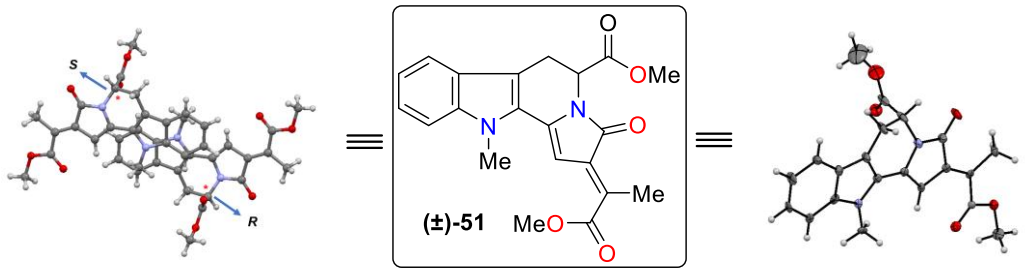


Figure 3. X-ray crystal structures of (±)-methyl (*E*)-2-(1-methoxy-1-oxopropan-2-ylidene)-11-methyl-3-oxo-2,5,6,11-tetrahydro-3*H*-indolizino(8,7-b)indole-5-carboxylate

2C.3 Summary

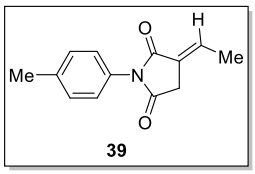
In conclusion, we have demonstrated the synthesis of the methyl ester of chaetoglinate A via the introduction of the desired exocyclic double bond using a Wittig olefination with methyl pyruvate and a thermodynamically favorable extension of conjugation driven dehydrative cyclization pathway. The present Wittig reaction with alkyl pyruvates is general in nature. It can be useful to neatly design a variety of desired precursors essential for the total synthesis of several natural and unnatural products.

2C.4 Experimental Section

General Procedure for Wittig Reaction of Maleimide with Pyruvic Acid/Alkyl Pyruvates

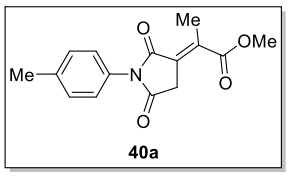
To a stirred solution of maleimide **38** (200 mg, 1.07 mmol) in acetone (5 mL) was added *n*-Bu_3P (0.29 mL, 1.18 mmol)/PPh_3 (309 mg, 1.18 mmol) in dropwise/portion wise fashion at 25 °C under argon atmosphere. The reaction mixture was stirred for 30 min at the same temperature and then pyruvic acid (0.15 mL, 2.14 mmol)/methyl pyruvate (90%, 0.24 mL, 2.14 mmol)/ethyl pyruvate (0.24 mL, 2.14 mmol) was added slowly. The reaction was monitored by TLC and upon completion the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (25 mL), and the resultant solution was washed with water (15 mL), brine (15 mL), and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) chromatographic purification of the resulting residue using ethyl acetate–petroleum ether as eluent afforded the corresponding Wittig product **39**/**40a**/**40b** (Table 1).

(*E*)-3-Ethylidene-1-(*p*-tolyl)pyrrolidine-2,5-dione (39): White solid; Mp 142–144 °C,



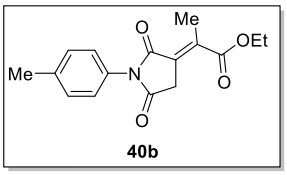
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (dt, J = 7.6 and 1.5 Hz, 3H), 2.39 (s, 3H), 3.38–3.42 (m, 2H), 6.97–7.05 (m, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5, 21.2, 32.0, 126.2, 126.4, 129.3, 129.8, 134.9, 138.6, 168.9, 173.3; ESIMS (*m*/z) 216 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{14}O_2N$ 216.1019, found 216.1019; IR ($CHCl_3$) ν_{max} 1683, 1628 cm^{-1}.

Methyl (*E*)-2-[2,5-Dioxo-1-(*p*-tolyl)pyrrolidin-3 ylidene]propanoate (40a): White



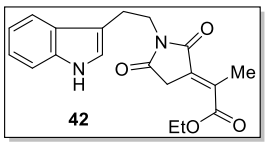
solid; Mp 150–152 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 2.55 (t, J = 2.3 Hz, 3H), 3.83 (q, J = 2.3 Hz, 2H), 3.87 (s, 3H), 7.20 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1, 21.2, 36.4, 52.6, 126.3, 128.9, 129.8, 130.8, 137.7, 138.9, 167.3, 169.0, 172.8; ESIMS (*m*/z) 274 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{16}O_4N$ 274.1074, found 274.1070; IR ($CHCl_3$) ν_{max} 1771, 1710, 1640 cm^{-1}.

Ethyl (*E*)-2-[2,5-Dioxo-1-(*p*-tolyl)pyrrolidin-3-ylidene]propanoate (40b): White solid;



Mp 214–216 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (t, J = 6.9 Hz, 3H), 2.40 (s, 3H), 2.55 (t, J = 2.3 Hz, 3H), 3.82 (q, J = 2.3 Hz, 2H), 4.32 (q, J = 6.9 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 15.1, 21.2, 36.3, 61.8, 126.3, 128.9, 129.8, 130.3, 138.2, 138.9, 166.9, 169.1, 172.9; ESIMS (*m*/z) 288 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{18}O_4N$ 288.1230, found 288.1226; IR ($CHCl_3$) ν_{max} 1769, 1707, 1630 cm^{-1}.

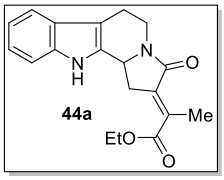
Ethyl (*E*)-2-{1-[2-(1*H*-Indol-3-yl)ethyl]-2,5-dioxopyrrolidin-3-



ylidene}propanoate(42). To a stirred solution of maleimide **41** (2.00 g, 8.33 mmol) in EtOH:DCM (3:1, 25 mL) was added *n*-Bu_3P (2.26 mL, 9.17 mmol) in dropwise fashion at 25 °C under argon atmosphere. The reaction mixture was stirred for 30 min at the same temperature and then ethyl pyruvate (1.85 mL, 16.7 mmol) was added slowly. The reaction mixture was further stirred for 5 h and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (50 mL) and the resultant solution was washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM as an eluent afforded **42** as a white solid (2.44 g, 86%). Mp 162–164 °C, ^{1}H

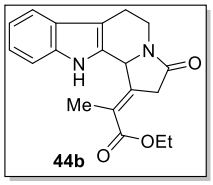
NMR ($CDCl_3$, 500 MHz) δ 1.36 (t, *J* = 7.3 Hz, 3H), 2.52 (t, *J* = 1.9 Hz, 3H), 3.08 (t, *J* = 8.0 Hz, 2H), 3.59 (q, *J* = 1.9 Hz, 2H), 3.91 (t, *J* = 8.0 Hz, 2H), 4.29 (q, *J* = 7.3 Hz, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 8.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 14.9, 23.5, 36.2, 39.3, 61.7, 111.1, 112.2, 118.7, 119.5, 122.05, 122.14, 127.4, 130.7, 136.2, 137.1, 167.0, 169.9, 173.6; ESIMS (*m*/z) 341 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_4N_2$ 341.1496, found 341.1501; IR ($CHCl_3$) ν_{max} 3474, 1766, 1670, 1645 cm^{-1}.

Ethyl (*E*)-2-[3-Oxo-5,6,11,11b-tetrahydro-1*H*-indolizino(8,7-b)indol-2(3*H*)-ylidene]propanoate (44a). To a stirred solution of imide **42** (500 mg, 1.47 mmol) in MeOH:DCM (1:1, 20 mL) was added $CeCl_3 \cdot 7H_2O$ (1.92 g, 5.15 mmol) at –10 °C and then $NaBH_4$ (835 mg, 22.05 mmol) was added in portion wise manner. The reaction mixture was stirred for 3.5 h at the same temperature and acidified with TFA (1.12 mL, 14.7 mmol) at 0 °C until completely acidic. The reaction mixture was further stirred at 25 °C for 24 h and quenched with saturated aq. $NaHCO_3$ (5 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The resultant solution was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded **44a** as pale-yellow solid (415 mg, 87%). Mp 180–182 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, *J* = 7.1 Hz, 3H), 2.48 (t, *J* = 2.2 Hz, 3H), 2.81–2.88 (m, 1H), 2.89–2.99 (m, 1H), 3.00–3.10 (m, 1H), 3.17 (td, *J* = 11.3 and 5.4 Hz, 1H), 3.76 (ddd, *J* = 18.4, 7.8 and 1.9 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.67 (dd, *J* = 12.9 and 5.4 Hz, 1H), 4.92 (dd, *J* = 7.3 and 5.6 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 8.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 14.2, 20.9, 33.8, 38.1, 51.3, 61.0, 108.5, 111.0, 118.4, 119.9, 122.3, 126.7, 132.9, 133.0, 136.3, 138.1, 167.0, 168.2; ESIMS (*m*/z) 325 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_3N_2$ 325.1547, found 325.1554; IR ($CHCl_3$) ν_{max} 3444, 1642 cm^{-1}.



44a

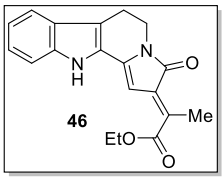
The repetition of the reaction at 25 °C for 2 h time resulted in regioisomeric mixture of **44a** and **44b**. Silica gel (230–400 mesh) column chromatographic purification of the mixture using ethyl acetate–petroleum ether (7:3) as an eluent afforded major isomer **44a** as pale-yellow solid (286 mg,



44b

60%) and minor isomer **44b** as pale-yellow solid (71 mg, 15%). Minor isomer **44b**: Mp 146–148 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, J = 6.9 Hz, 3H), 2.35 (s, 3H), 2.76 (ddd, J = 15.7, 5.3 and 1.5 Hz, 1H), 3.02–3.15 (m, 1H), 3.25 (td, J = 13.0 and 5.3 Hz, 1H), 3.42 (dt, J = 23.7 and 2.3 Hz, 1H), 3.73 (d, J = 23.7 Hz, 1H), 4.22–4.32 (m, 2H), 4.60 (dd, J = 13.0 and 6.1 Hz, 1H), 5.74 (s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.74 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 16.8, 20.1, 38.0, 38.6, 59.8, 61.1, 110.5, 111.1, 118.5, 120.2, 122.9, 123.5, 126.9, 130.3, 136.0, 143.3, 166.7, 173.0; ESIMS (m/z) 325 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_3N_2$ 325.1547, found 325.1550; IR ($CHCl_3$) ν_{max} 3444, 1641 cm^{-1}.

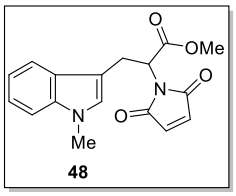
Ethyl (*E*)-2-[3-Oxo-6,11-dihydro-3*H*-indolizino(8,7-b)indol-2(5*H*)-ylidene]propanoate (46). Method A. To a stirred solution of **44a** (100 mg, 0.31 mmol) in DCM (6 mL) was dropwise added a solution of freshly crystalized NBS (89 mg, 0.50 mmol) in DCM (2 mL) at 0 °C and the reaction mixture was stirred at 25 °C for 6 h. The reaction was quenched with saturated aq. $NaHCO_3$ (1 mL). DCM was removed in vacuo and the obtained residue was dissolved in ethyl acetate (20 mL). The resultant solution was washed successively with water (10 mL), aq. $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (9:1) as an eluent afforded **46** as dark red color crystalline solid (64 mg, 64%). Mp 212–214 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 3.12 (t, J = 6.4 Hz, 2H), 3.90 (t, J = 6.4 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 6.73 (s, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.53 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 14.5, 20.5, 37.2, 61.2, 95.4, 111.6, 116.3, 119.6, 120.6, 124.9, 125.0, 126.2, 131.7, 135.8, 136.7, 138.4, 168.4, 168.8; ESIMS (m/z) 323 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_3N_2$ 323.1390, found 323.1392; IR ($CHCl_3$) ν_{max} 3462, 1685, 1635 cm^{-1}.



Method B. To a stirred solution of imide **42** (100 mg, 0.29 mmol) in dry benzene (10 mL) were added 4 Å molecular sieves (50 mg) and P_2O_5 (1.23 g, 4.35 mmol) under an argon atmosphere at 25 °C. The above reaction mixture was first heated at 40 °C for 12 h and then refluxed for 2 h. The reaction mixture was concentrated in vacuo and to the obtained residue was added ethyl acetate (10 mL) at 0 °C. The above reaction mixture was slowly added ice-cold water (10 mL), and it was carefully made basic (pH 8) by

adding solid K_2CO_3. The reaction mixture was extracted with ethyl acetate (3 × 15 mL), and the combined organic layer was washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (9:1) as an eluent afforded **46** as a dark red color crystalline solid (64 mg, 67%; 83% based on the recovery of starting material) and unreacted imide **42** (19 mg material).

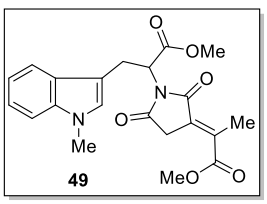
Methyl 2-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-3-(1-methyl-1*H*-indol-3 yl)propanoate (48). To a stirred solution of amine **24** (1.00 g, 4.31 mmol) in



48

AcOH:toluene (3:1, 30 mL) was added maleic anhydride (**47**, 760 mg, 7.76 mmol) at 25 °C under argon atmosphere and the reaction mixture was refluxed for 7 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (40 mL). The resultant solution was washed with aq. $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM as an eluent afforded maleimide **48** as yellow oil (1.14 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.61–3.68 (m, 2H), 3.70 (s, 3H), 3.80 (s, 3H), 5.06 (dd, J = 9.9 and 6.1 Hz, 1H), 6.57 (s, 2H), 6.85 (s, 1H), 7.09 (t, J = 8.4 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 32.6, 52.8 (2C), 109.2, 118.5, 119.0, 121.6, 127.3, 127.6, 134.0 (2C), 136.8, 169.5, 169.9; ESIMS (*m*/z) 313 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}O_4N_2$ 313.1183, found 313.1185; IR ($CHCl_3$) ν_{max} 1748, 1714, 1641 cm^{-1}.

Methyl (*E*)-2-[3-(1-Methoxy-1-oxopropan-2-ylidene)-2,5-dioxopyrrolidin-1-yl]-3-(1-methyl-1*H*-indol-3-yl)propanoate (49). To a stirred solution of maleimide **48** (900 mg,

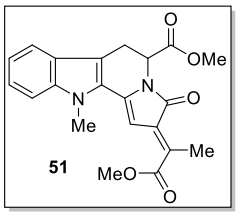


49

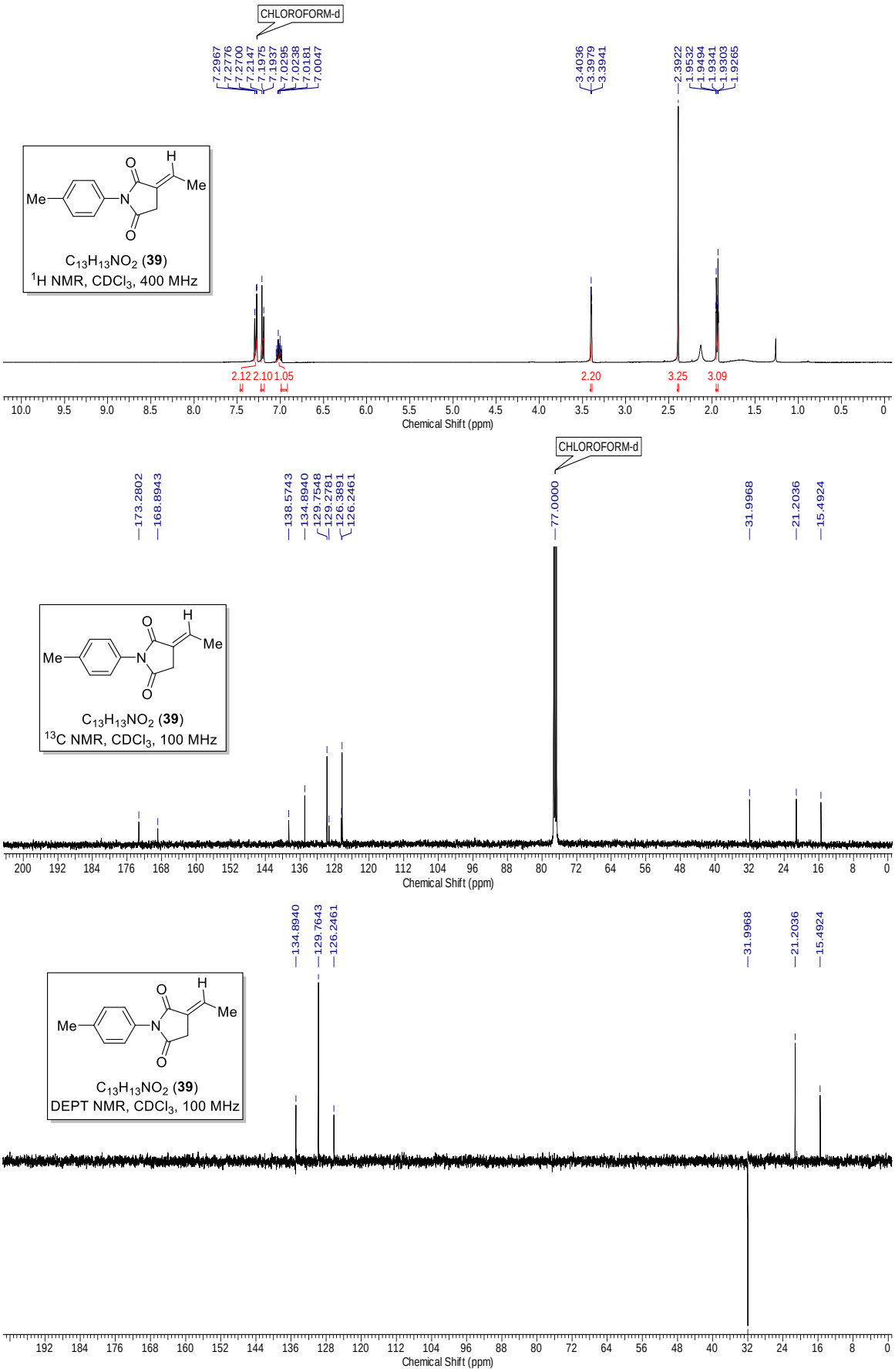
2.88 mmol) in EtOH:DCM (3:1, 25 mL) was added *n*-Bu_3P (0.78 mL, 3.17 mmol) in dropwise fashion at 25 °C under argon atmosphere. The reaction mixture was stirred for 30 min at same temperature and then methyl pyruvate (90%, 0.65 mL, 5.76 mmol) was added slowly. The reaction mixture was further stirred for 5 h and then concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (30 mL) and the resultant solution was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400

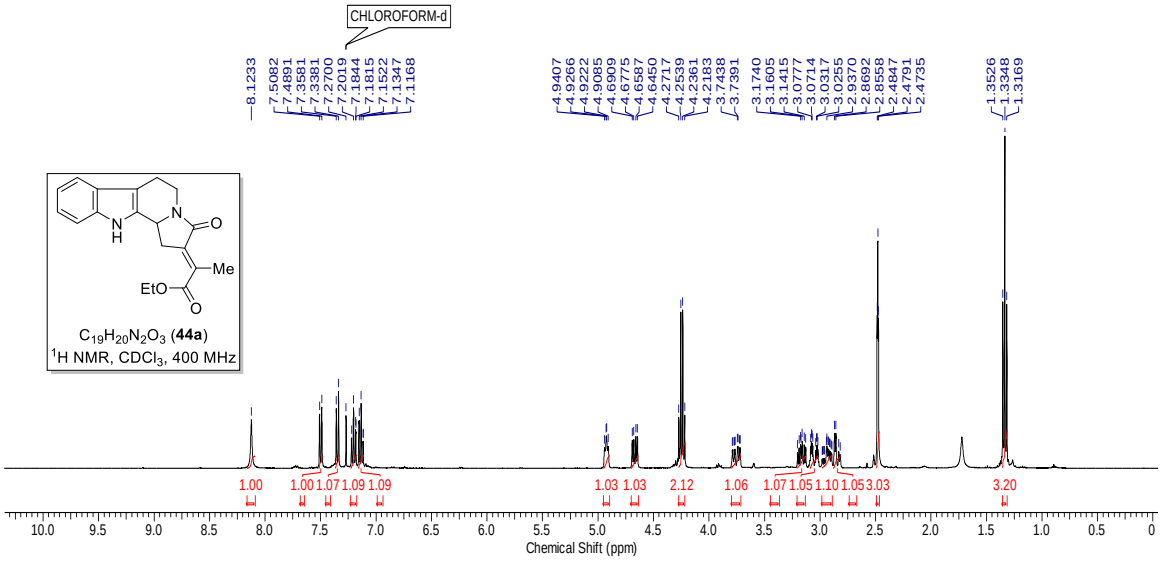
mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded imide **49** as a white color solid (930 mg, 81%). Mp 152–154 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (t, J = 2.0 Hz, 3H), 3.41 (dq, J = 22.8 and 2.0 Hz, 1H), 3.51 (dq, J = 22.8 and 2.0 Hz, 1H), 3.64 (d, J = 7.7 Hz, 2H), 3.72 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 5.16 (dd, J = 8.6 and 7.1 Hz, 1H), 6.90 (s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 23.9, 32.7, 36.0, 52.5, 52.8, 53.3, 109.2, 118.2, 119.2, 121.7, 127.4, 127.7, 130.6, 136.8, 136.9, 137.1, 167.2, 168.99, 169.01, 172.8; ESIMS (m/z) 399 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}O_6N_2$ 399.1551, found 399.1562; IR ($CHCl_3$) ν_{max} 1708, 1645 cm^{-1}.

Methyl (*E*)-2-(1-Methoxy-1-oxopropan-2-ylidene)-11-methyl-3-oxo-2,5,6,11-tetrahydro-3*H*-indolizino(8,7-b)indole-5-carboxylate (51). To a stirred solution of imide **49** (100 mg, 0.25 mmol) in dry benzene (15 mL) were added 4 Å molecular sieves (40 mg) and P_2O_5 (1.06 g, 3.75 mmol) in one portion under argon atmosphere. The above reaction mixture was heated at 40 °C for 24 h and then refluxed for 48 h. The reaction mixture was concentrated in vacuo and to the obtained residue was added ethyl acetate (15 mL) at 0 °C. To the above reaction mixture was slowly added ice cold water (20 mL) and it was carefully made basic (pH 8) by adding solid K_2CO_3. The reaction mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (8:2) as an eluent afforded **51** as dark red color crystalline solid (56 mg, 59%; 74% based on recovery of starting material) and unreacted imide **49** (20 mg) Mp 182–184 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (s, 3H), 3.33 (dd, J = 16.4 and 7.1 Hz, 1H), 3.63 (s, 3H), 3.74 (dd, J = 16.5 and 1.0 Hz, 1H), 3.89 (s, 3H), 3.95 (s, 3H), 5.24 (d, J = 6.4 Hz, 1H), 7.03 (s, 1H), 7.13–7.20 (m, 1H), 7.30–7.38 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 23.7, 31.5, 49.7, 52.2, 52.9, 98.1, 109.5, 112.8, 119.8, 120.3, 124.8, 125.3, 125.9, 132.1, 134.9, 136.5, 140.1, 168.6, 168.8, 170.6; ESIMS (m/z) 381 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{21}O_5N_2$ 381.1445, found 381.1447; IR ($CHCl_3$) ν_{max} 1641 cm^{-1}.



2C.5 Selected Spectra


CHLOROFORM-d
7.2967
7.2776
7.2700
7.2147
7.1975
7.1937
7.0295
7.0238
7.0181
7.0047
3.4036
3.3979
3.3941
2.3922
1.9532
1.9494
1.9341
1.9303
1.9265
Me
Me
O
H
N
O
C13H13NO2 (39)
1H NMR, CDCl3, 400 MHz
2.12
2.10
1.05
2.20
3.25
3.09
Chemical Shift (ppm)
CHLOROFORM-d
173.2802
168.8943
138.5743
134.8940
129.7548
129.2781
126.3891
126.2461
77.0000
31.9968
21.2036
15.4924
C13H13NO2 (39)
13C NMR, CDCl3, 100 MHz
Chemical Shift (ppm)
134.8940
129.7643
126.2461
31.9968
21.2036
15.4924
C13H13NO2 (39)
DEPT NMR, CDCl3, 100 MHz
Chemical Shift (ppm)


CHLOROFORM-d
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7.4891
7.3581
7.3381
7.2700
7.2019
7.1844
7.1815
7.1522
7.1347
7.1168
4.9407
4.9266
4.9222
4.9085
4.6909
4.6775
4.6587
4.6450
4.2717
4.2539
4.2361
4.2183
3.7438
3.7391
3.1740
3.1605
3.1415
3.0777
3.0714
3.0317
3.0255
2.9370
2.8692
2.8558
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2.4735
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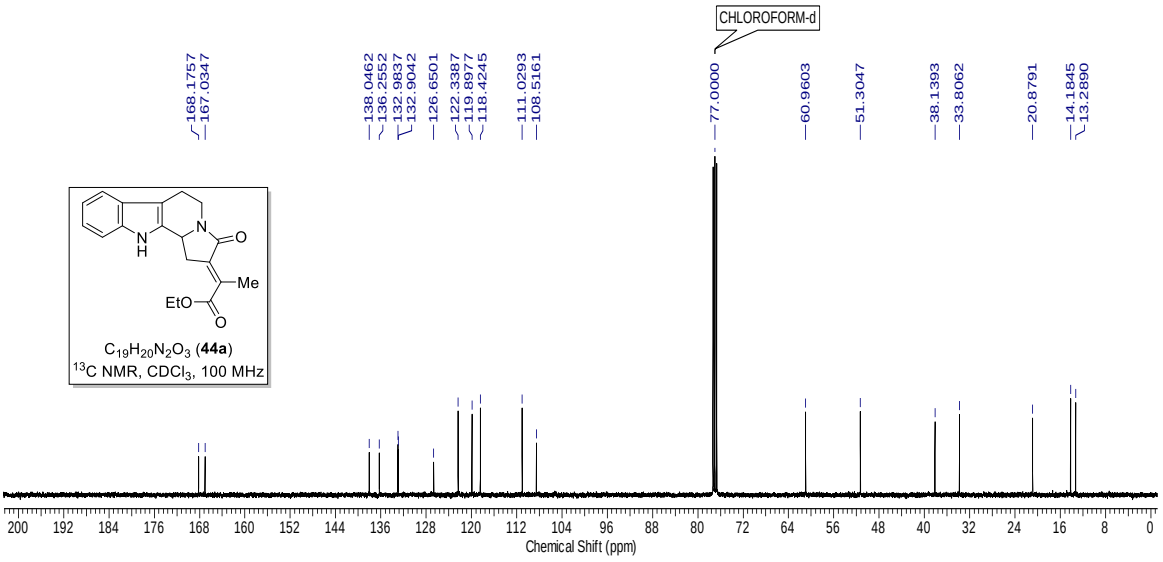
1.00
1.07
1.09
1.09
1.03
1.03
2.12
1.06
1.07
1.05
1.10
1.05
3.03
3.20
Me
EtO
O
$C_{19}H_{20}N_2O_3$ (**44a**)
^{1}H NMR, $CDCl_3$, 400 MHz
Chemical Shift (ppm)


CHLOROFORM-d
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167.0347
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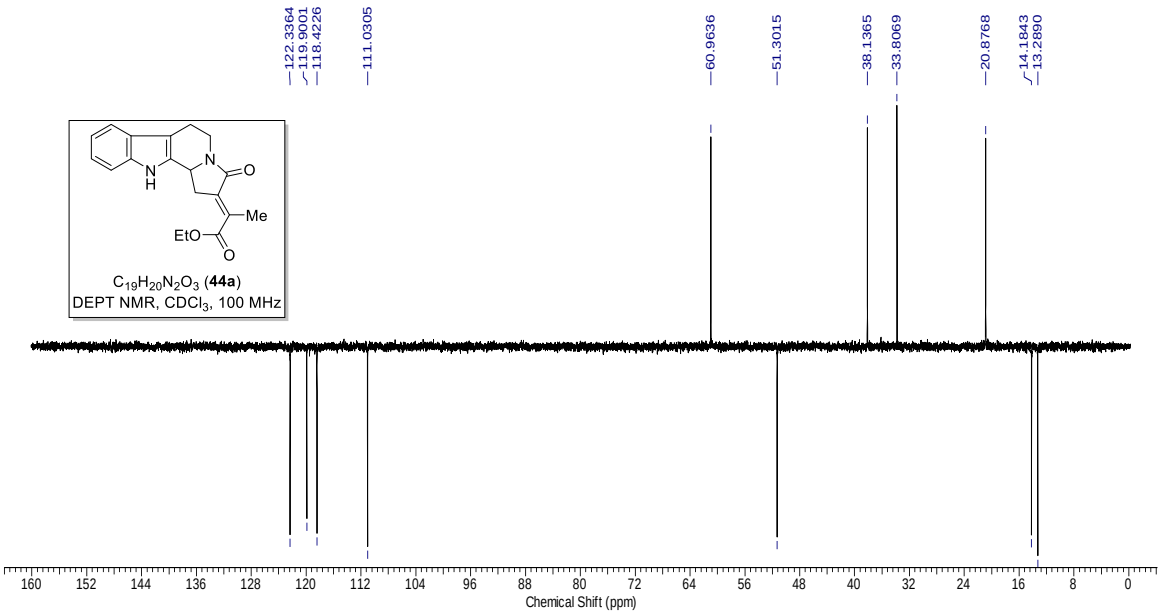
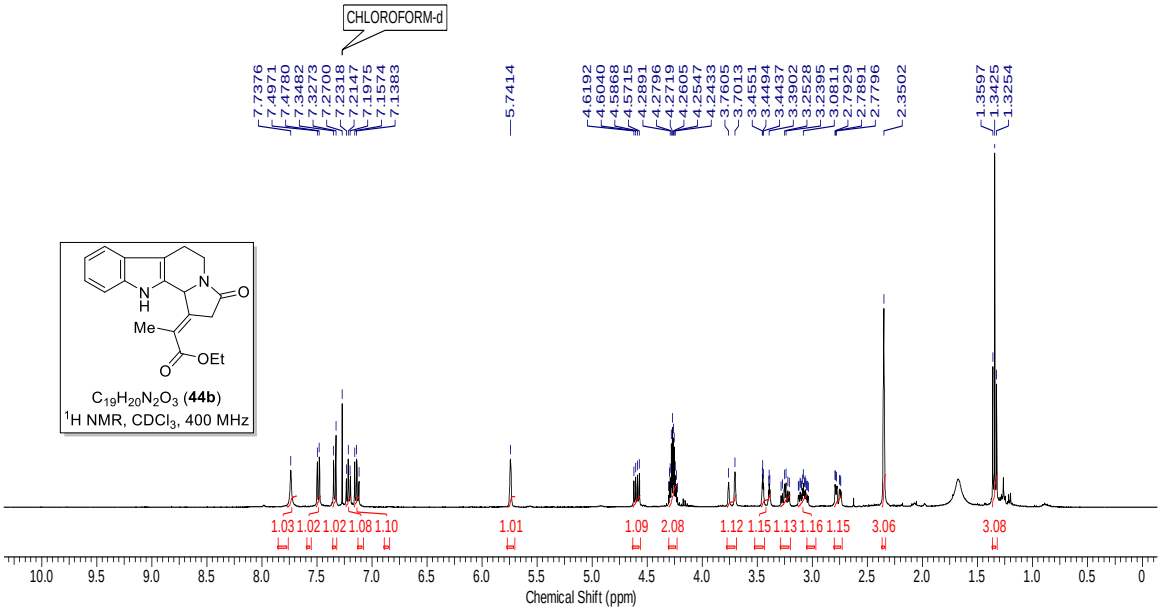
136.2552
132.9837
132.9042
126.6501
122.3387
119.8977
118.4245
111.0293
108.5161
77.0000
60.9603
51.3047
38.1393
33.8062
20.8791
14.1845
13.2890
Me
EtO
O
$C_{19}H_{20}N_2O_3$ (**44a**)
^{13}C NMR, $CDCl_3$, 100 MHz
Chemical Shift (ppm)


122.3364
119.9001
118.4226
111.0305
60.9636
51.3015
38.1365
33.8069
20.8768
14.1843
13.2890
Me
EtO
O
$C_{19}H_{20}N_2O_3$ (**44a**)
DEPT NMR, $CDCl_3$, 100 MHz
Chemical Shift (ppm)


CHLOROFORM-d
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7.4780
7.3482
7.3272
7.2700
7.2318
7.2147
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7.1383
5.7414
4.6192
4.6040
4.5868
4.5715
4.2891
4.2796
4.2719
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4.2433
3.7605
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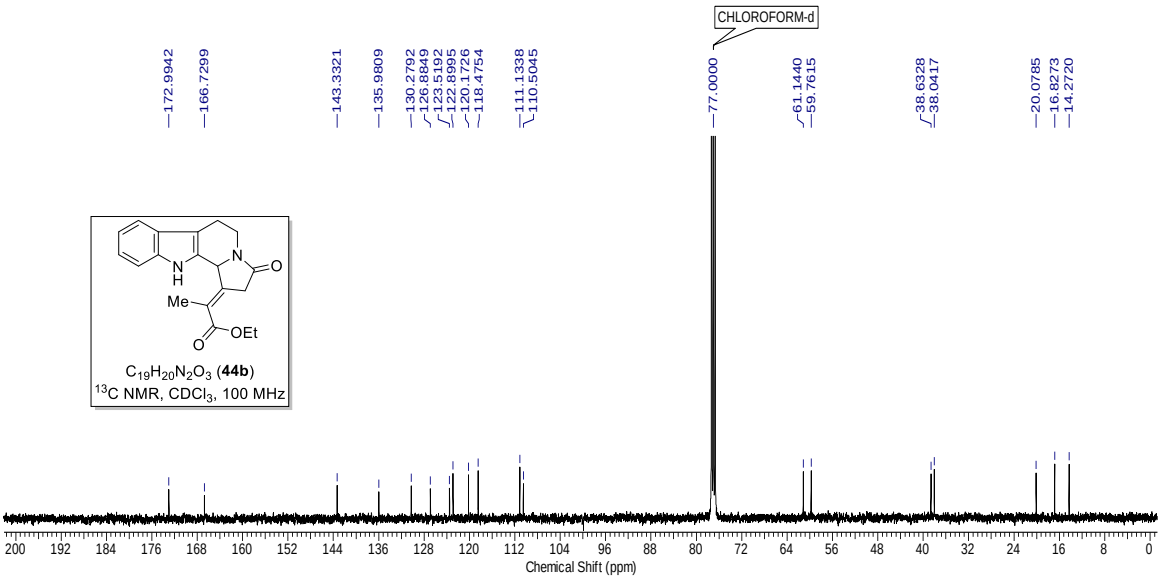
3.4551
3.4494
3.4437
3.3902
3.2528
3.2395
3.0811
2.7929
2.7891
2.7796
2.3502
1.3597
1.3425
1.3254
1.03 1.02 1.02 1.08 1.10
1.01
1.09 2.08
1.12 1.15 1.13 1.16 1.15
3.06
3.08
Chemical Shift (ppm)
C19H20N2O3 (44b)
1H NMR, CDCl3, 400 MHz


CHLOROFORM-d
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143.3321
135.9809
130.2792
126.8849
123.5192
122.8995
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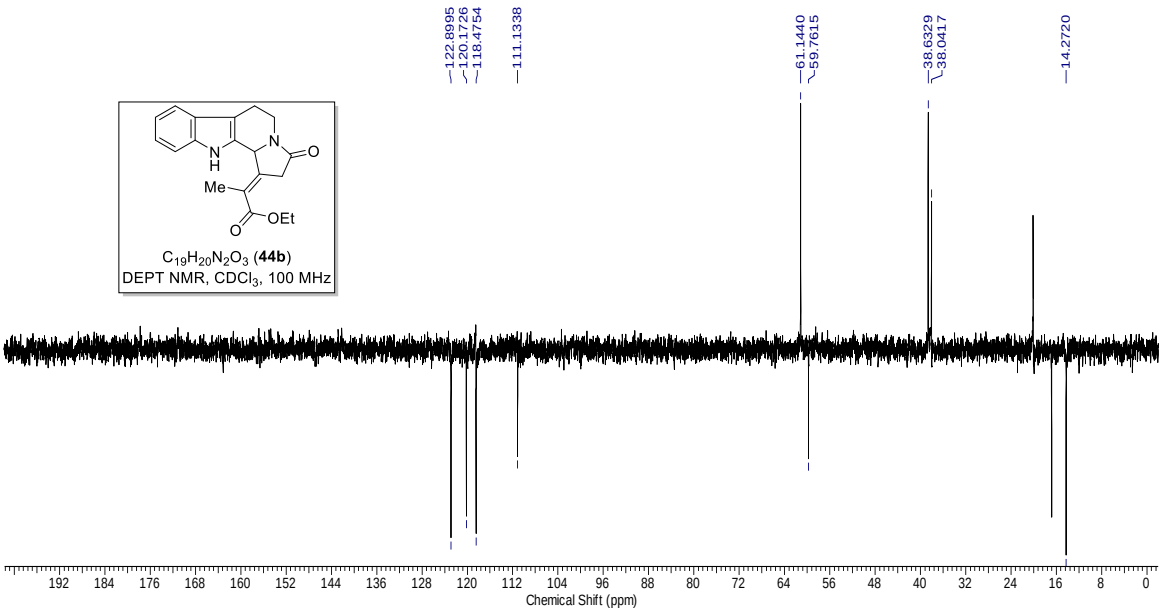
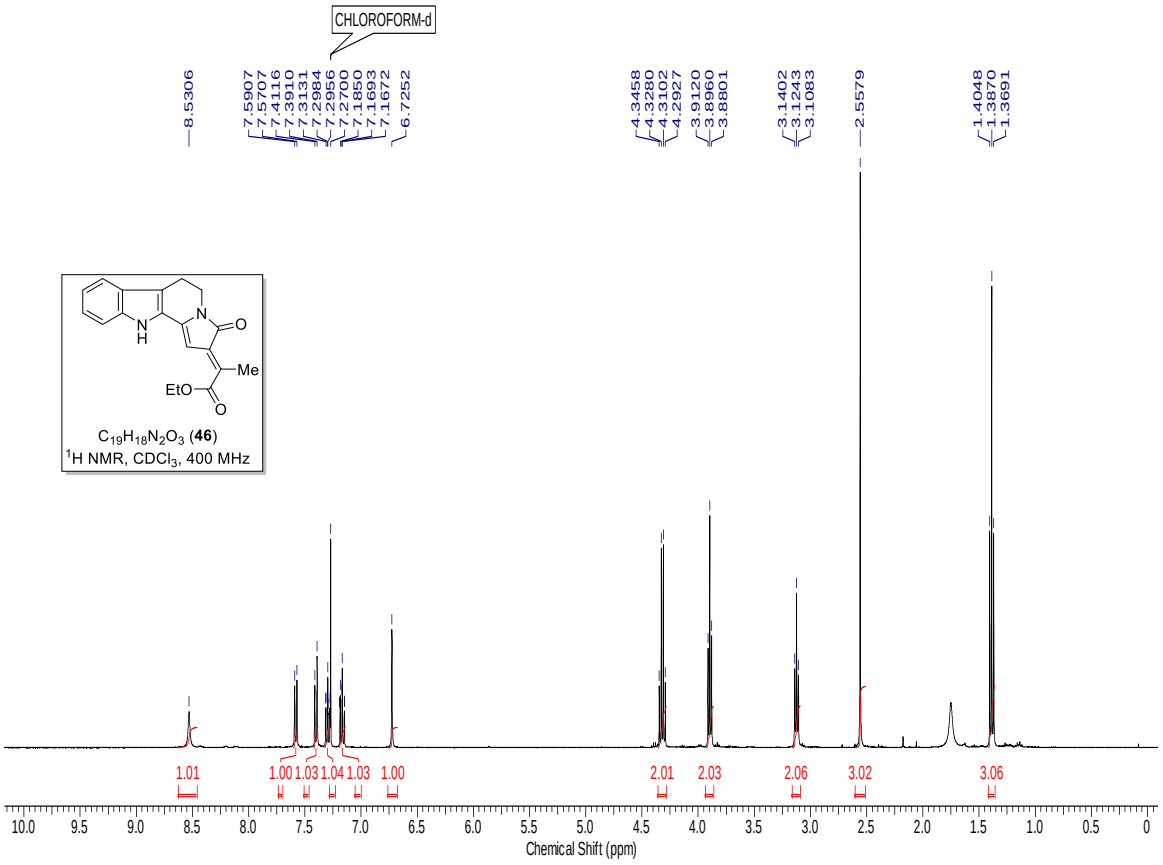
118.4754
111.1338
110.5045
77.0000
61.1440
59.7615
38.6328
38.0417
20.0785
16.8273
14.2720
Chemical Shift (ppm)
C19H20N2O3 (44b)
13C NMR, CDCl3, 100 MHz


122.8995
120.1726
118.4754
111.1338
61.1440
59.7615
38.6329
38.0417
14.2720
Chemical Shift (ppm)
C19H20N2O3 (44b)
DEPT NMR, CDCl3, 100 MHz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7.1693
7.1672
6.7252
4.3458
4.3280
4.3102
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3.9120
3.8960
3.8801
3.1402
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3.1083
2.5579
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Me
EtO
O
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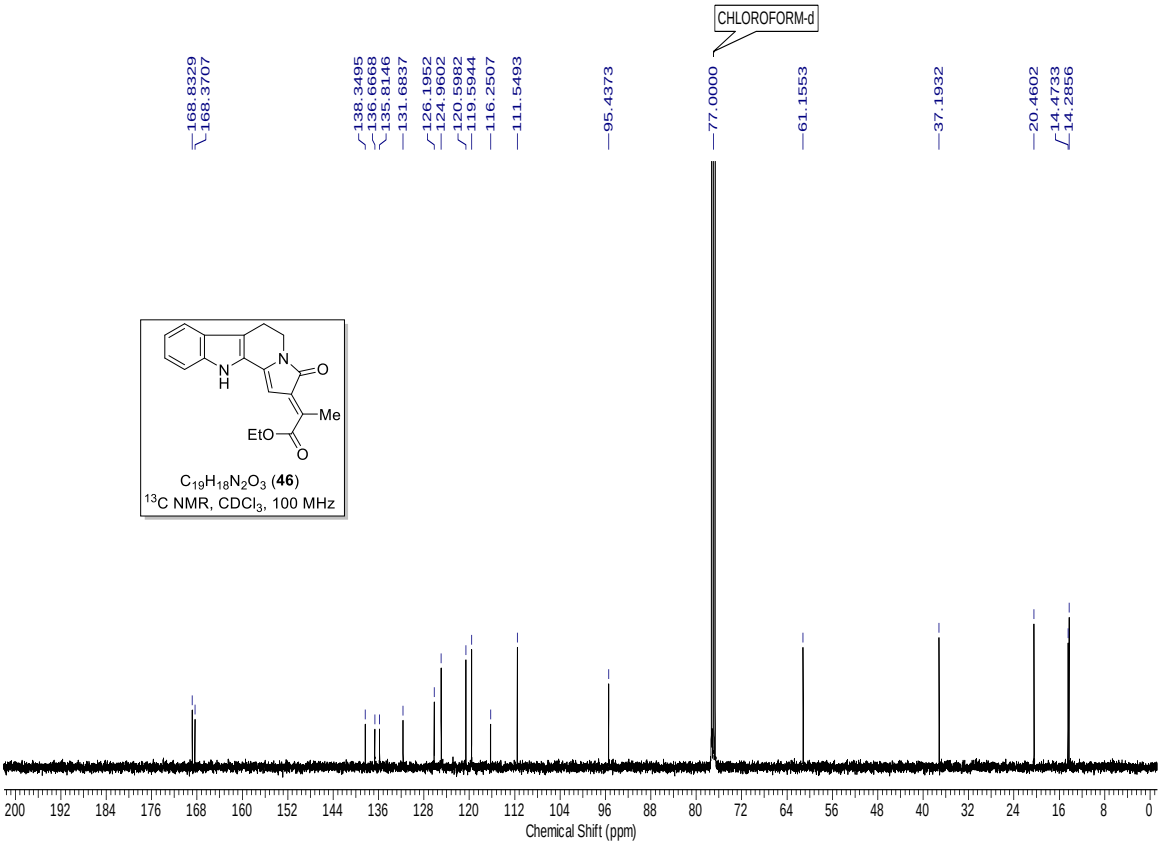
Chemical Shift (ppm)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95.4373
77.0000
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37.1932
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O
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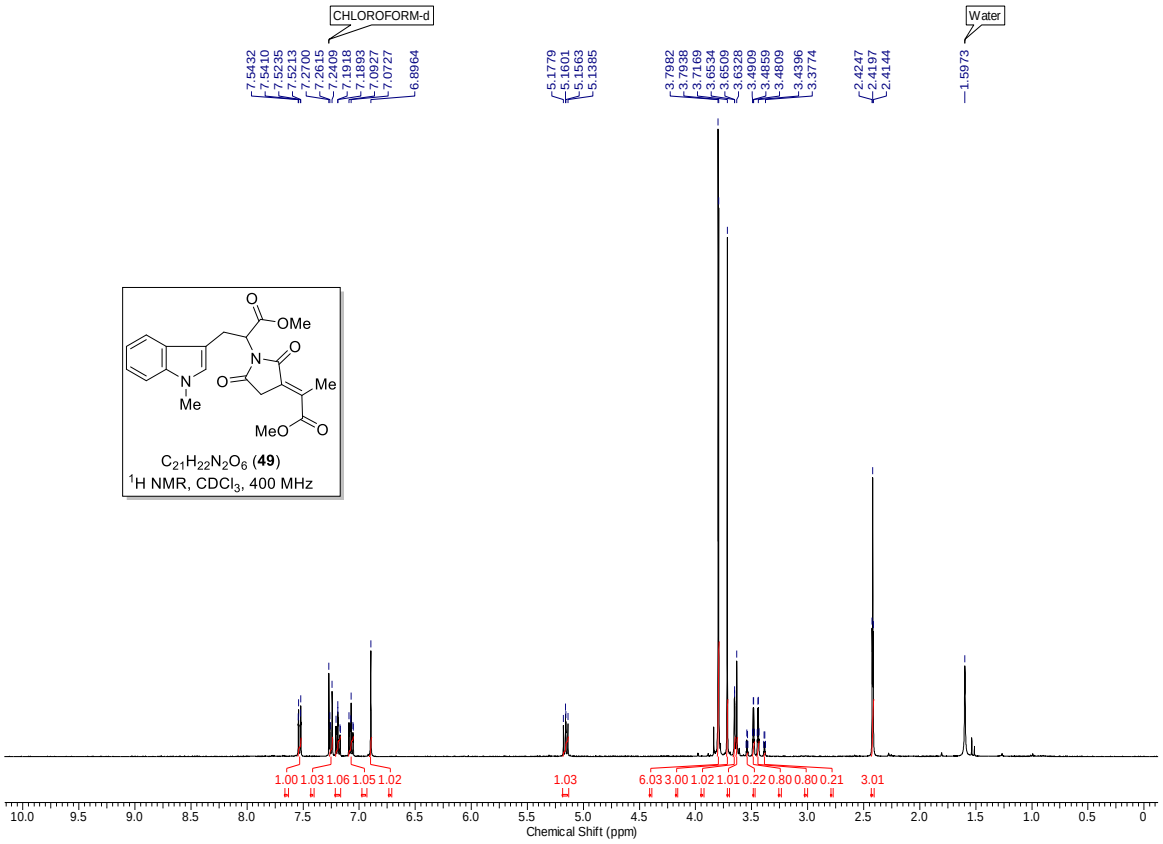
Chemical Shift (ppm)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5.1563
5.1385
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3.4809
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3.3774
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2.4197
2.4144
1.5973
OMe
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O
Me
N
Me
MeO
O
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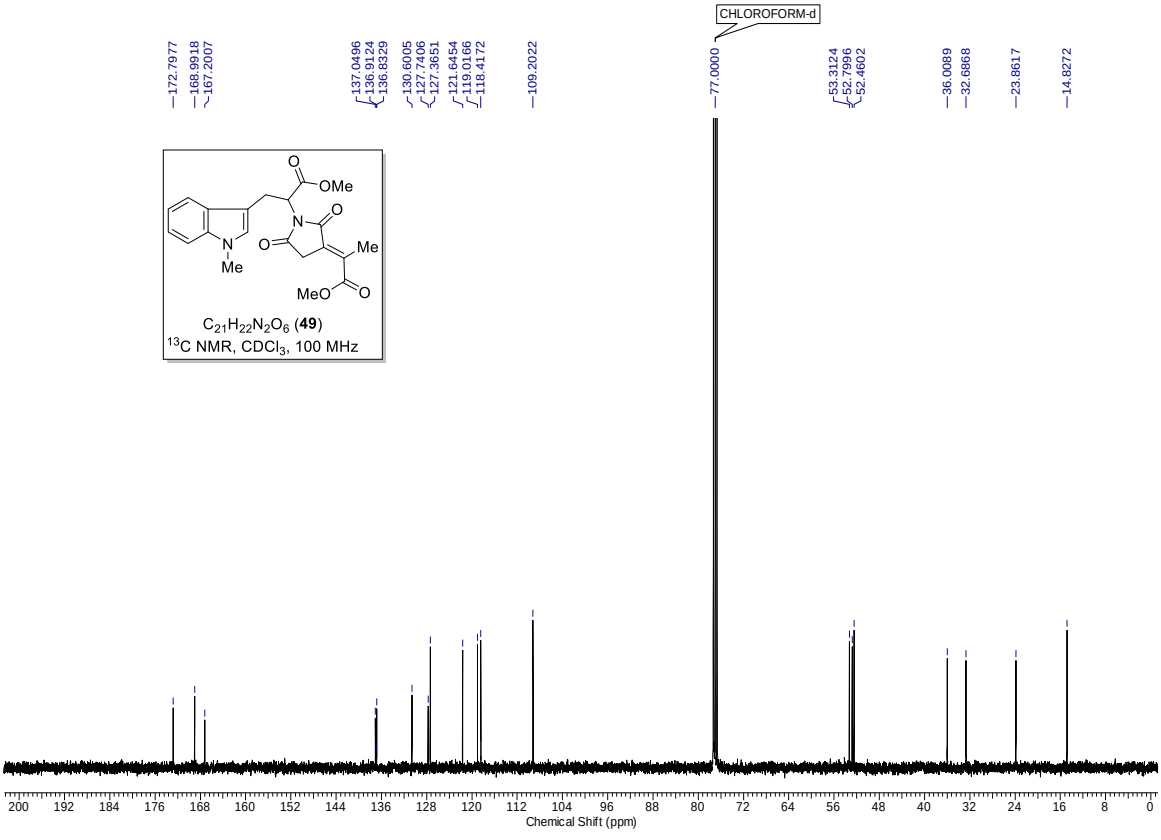
1.03
6.03 3.00 1.02 1.01 0.22 0.80 0.80 0.21
3.01
Chemical Shift (ppm)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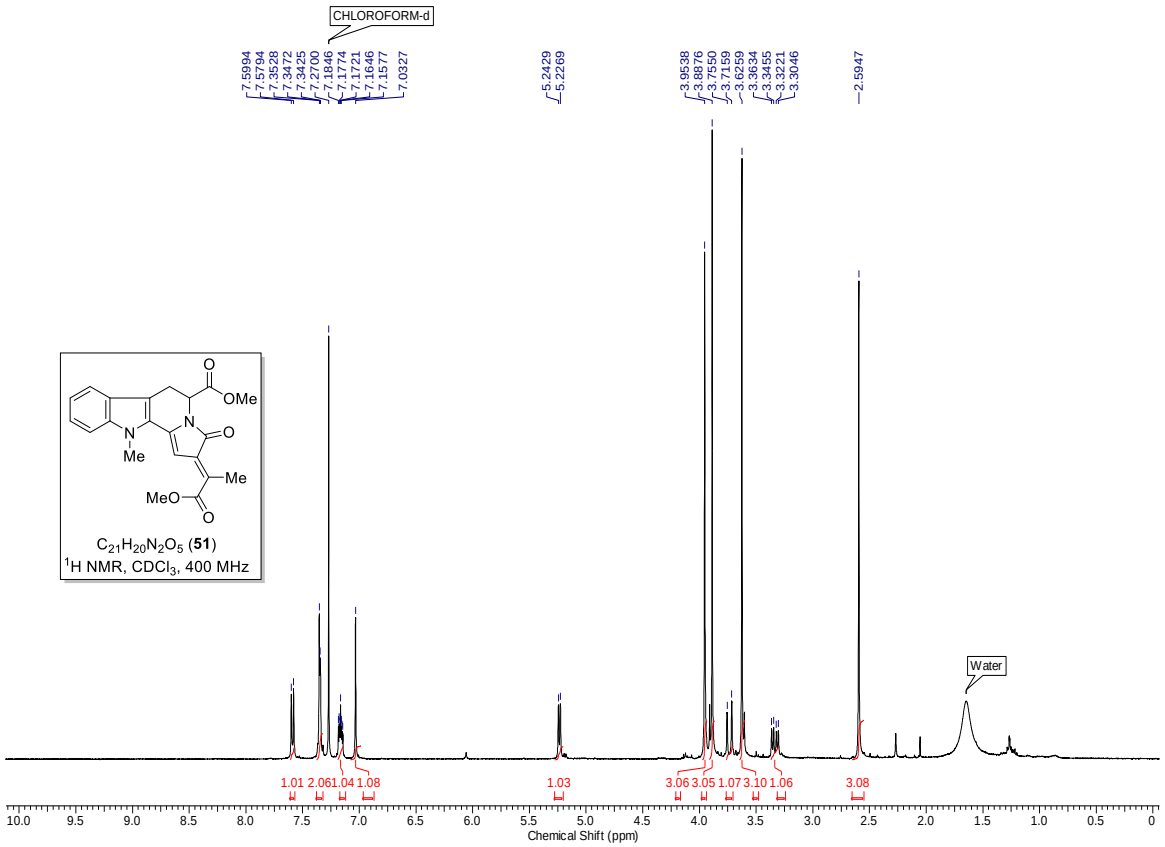
Chemical Shift (ppm)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3.3221
3.3046
2.5947
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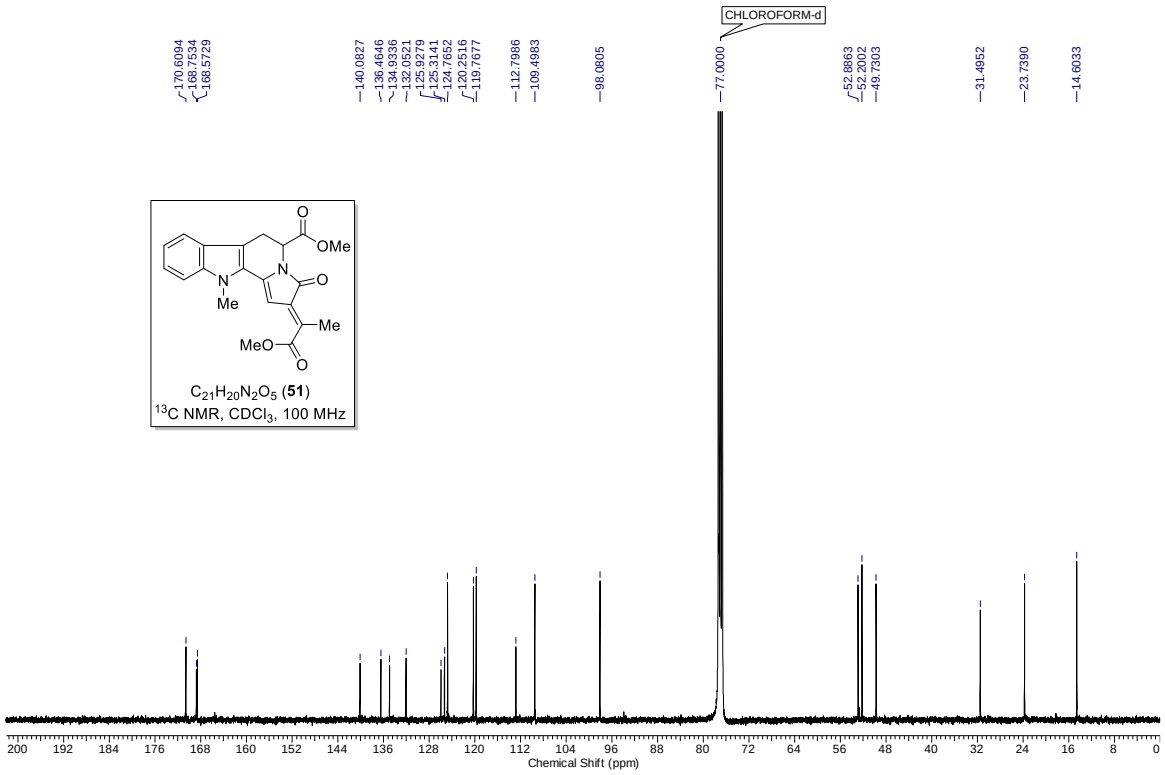
1H NMR, CDCl3, 400 MHz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119.7677
112.7986
109.4983
98.0805
77.0000
52.8863
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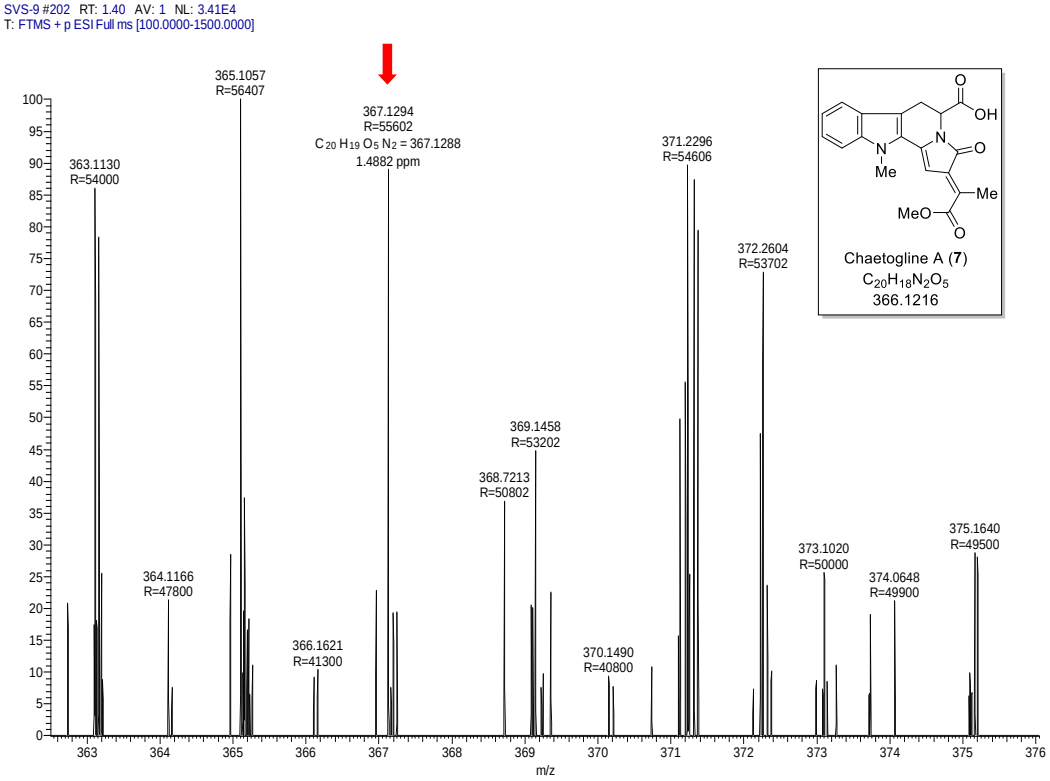
Chemical Shift (ppm)
C21H20N2O5 (51)
13C NMR, CDCl3, 100 MHz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373.1020
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R=49900
364.1166
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Chaetogline A (7)
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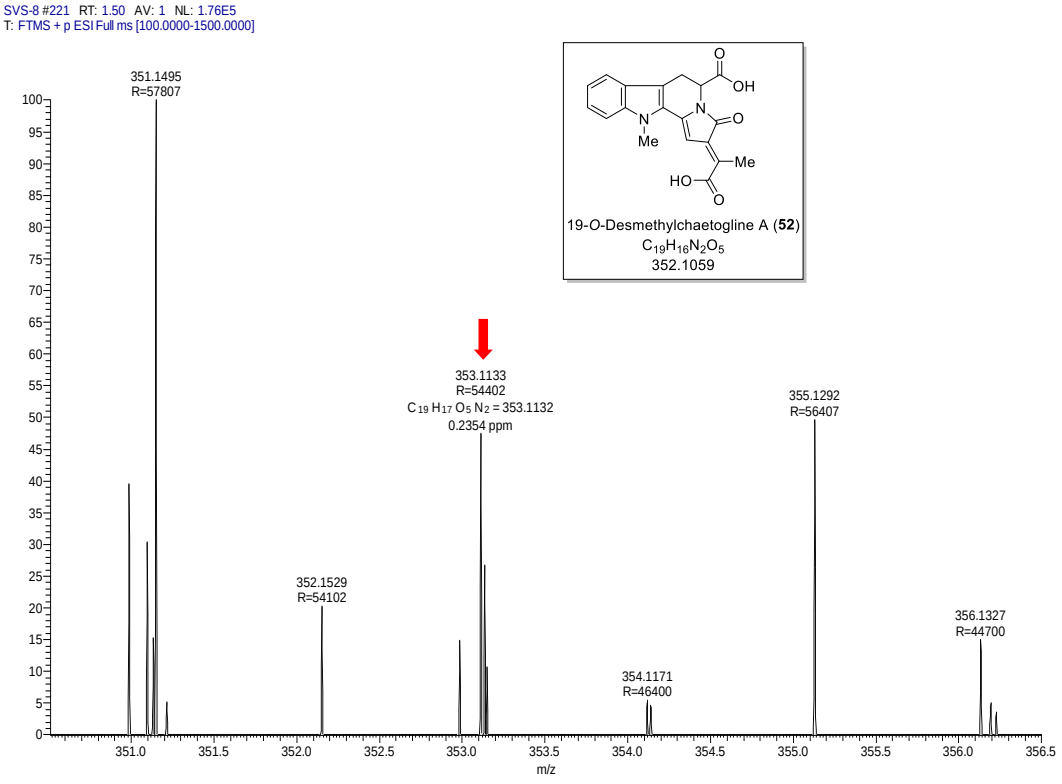
m/z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R=44700
354.1171
R=46400
19-O-Desmethylchaetogline A (52)
C19H16N2O5
352.1059
m/z

2C.6 References

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Chapter 2

Section D

Facile Synthesis of Novel Heterocycles from Indole and Imide Derivatives

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

2D.1 Background

Indole is an aromatic heterocyclic organic compound with the formula C_8H_7N. It has a bicyclic structure, containing a six-membered benzene ring attached to a five-membered pyrrole ring. Indole is extensively distributed in nature and can be produced by a variety of bacteria. As an intercellular signal molecule, indole regulates various features of bacterial physiology, including spore formation, plasmid stability, resistance to drugs, biofilm formation and virulence.[1] The indole system has been one of the most studied heterocycles in terms of skeletal modification.[2] This is simply due to the high biological relevance of indoles in nature and it being part of several important natural products or pharmaceuticals including alkaloids. Indole alkaloids are the largest class of natural products with various structural topographies and possess very large number of bioactivities. Few representative indoles-based bioactive natural and unnatural products have been depicted in figure 1.[3–7] Synthetic chemists are very much keen to develop novel synthetic strategies for their total synthesis.

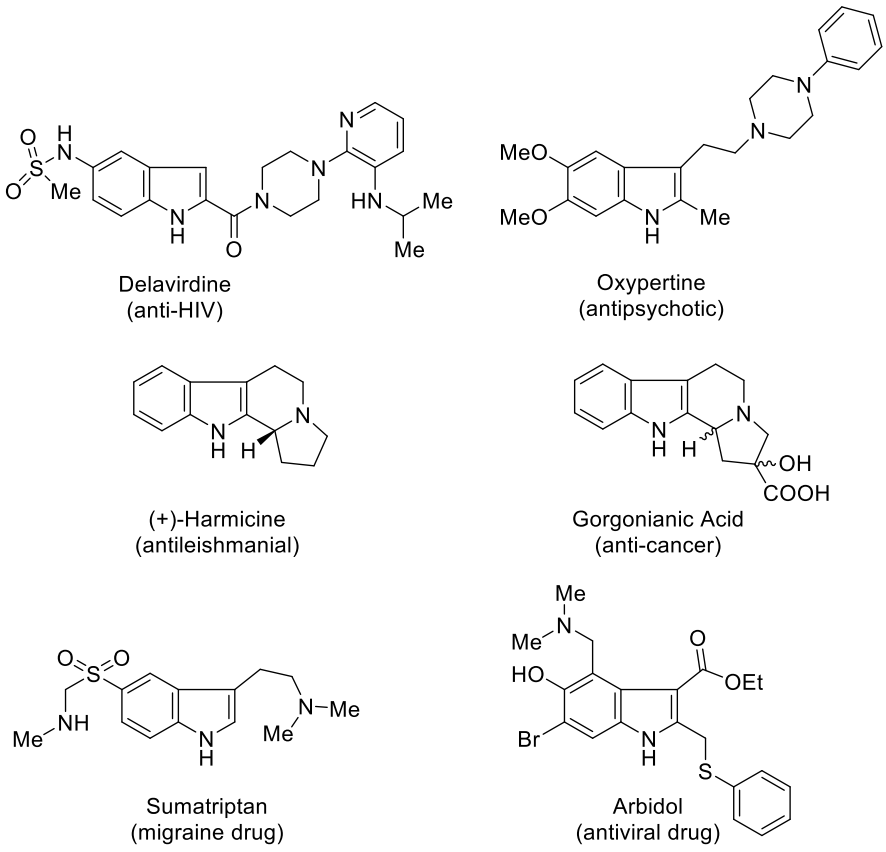
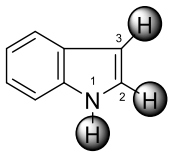


Figure 1. Representative indole-based products

2D.1.1 Reported Chemo-, Regio- and Stereoselective Coupling Reactions at Two and Three-Positions of Indoles

Indole is not basic, it acts like pyrrole, the lone pair of electrons on the nitrogen atom is part of aromaticity, therefore is not available for protonation. Indole is primarily protonated at the C-3 position, rather than nitrogen, due to the enamine-like reactivity. Primary indole has three open sides for coupling as depicted in figure 2. Coupling reactions of indole nitrogen with various substrates are well studied[8] and herein we have summarized a few selected C-2 and C-3 coupling reactions of indoles.

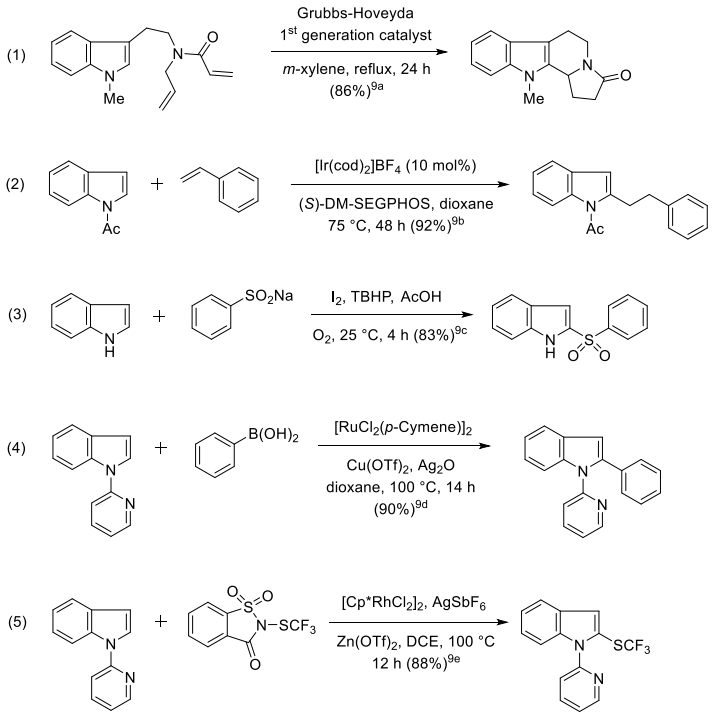


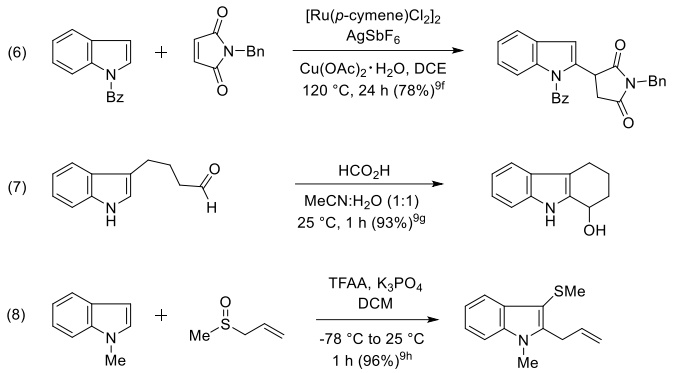
Indole

Figure 2. Selective 1/2/3-coupling of the indole core

2D.1.2 Reported C-2 Couplings of Indoles

The C-2 position of indole for C−H functionalizations are challenging with compared to the C-3 position and indole nitrogen. The selected transformations on C-2 functionalizations are depicted in scheme 1.[9]

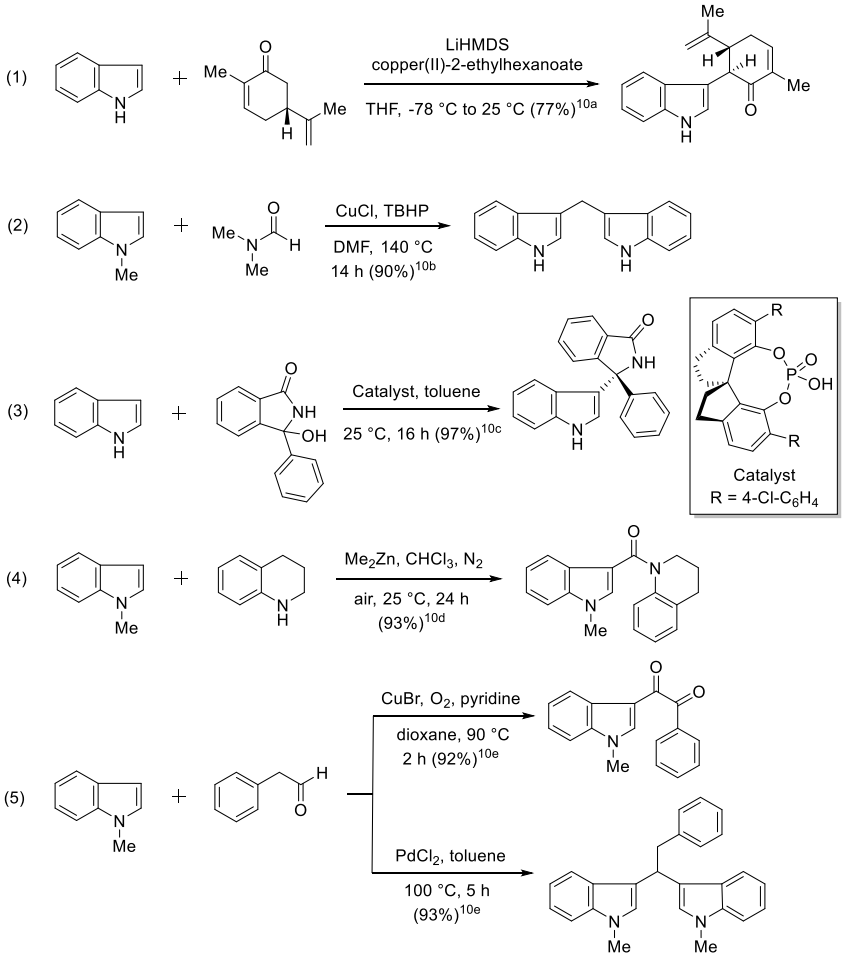


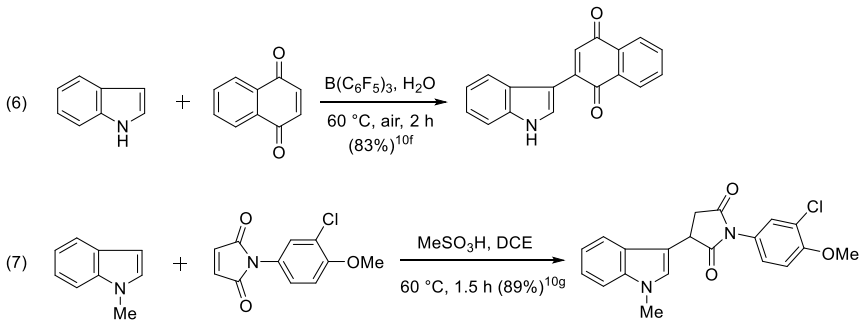


Scheme 1. Selected C-2 Coupling Reactions of Indoles

2D.1.3 Reported C-3 Couplings of Indoles

The C-3 alkylation of indole can be achieved by catalytic methods, such as Friedel–Crafts alkylation, allylic alkylation and conjugated addition. The selected examples on C-3 functionalizations are presented in scheme 2.[10]

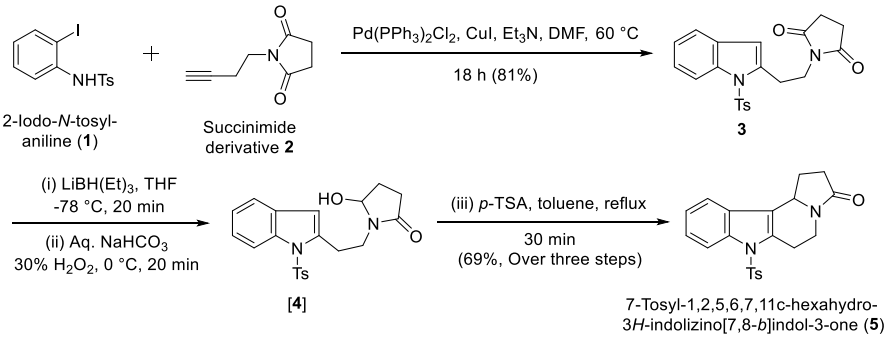




Scheme 2. Selected C-3 Coupling Reactions of Indole

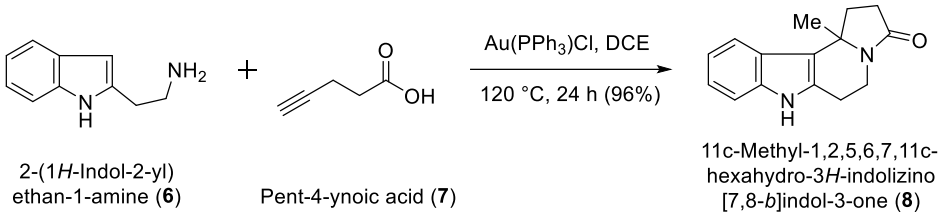
2D.1.4 Reported Synthesis of [1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol -3-one] Framework (Recently Reported Natural Products Skeleton)

Grigg and co-workers in 2008 reported the synthesis of *N*-tosyl protected [1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one] via Sonogashira reaction (Scheme 3).[11] The Sonogashira reaction of 2-iodo-*N*-tosyl-aniline (**1**) with *N*-alkynylimide **2** in the presence of bistriphenylphosphine palladium (II) chloride [$Pd(PPh_3)_2Cl_2$], copper iodide and triethylamine in DMF furnished the succinimide **3** in 81% yield. Reduction of succinimide **3** in the presence of lithium triethylborohydride at -78 °C for 20 min followed by addition of aq. $NaHCO_3$ and 30% H_2O_2 to the same reaction mixture gave lactamol intermediate **4**. The lactamol **4** on refluxing with *p*-TSA in toluene provided the desired compound **5** in 69% yield over three steps.



Scheme 3. Sonogashira/*N*-Acyliminium Ion Aromatic π-Cyclization Leading to 7-Tosyl-1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one

Zhao and co-workers in 2019 reported the gold-catalyzed highly selective cascade reaction to furnish a novel indole-fused skeleton (Scheme 4).[12] The reaction of amine **6** with carboxylic acid **7** in the presence of gold-catalyst [$Au(PPh_3)Cl$] in 1,2-dichloroethane directly provided the desired product **8** in 96% yield.



2-(1*H*-Indol-2-yl) ethan-1-amine (**6**)

Pent-4-ynoic acid (**7**)

11c-Methyl-1,2,5,6,7,11c-hexahydro-3*H*-indolizino [7,8-*b*]indol-3-one (**8**)

Scheme 4. Gold-Catalyzed Construction of Indolizinoindolone

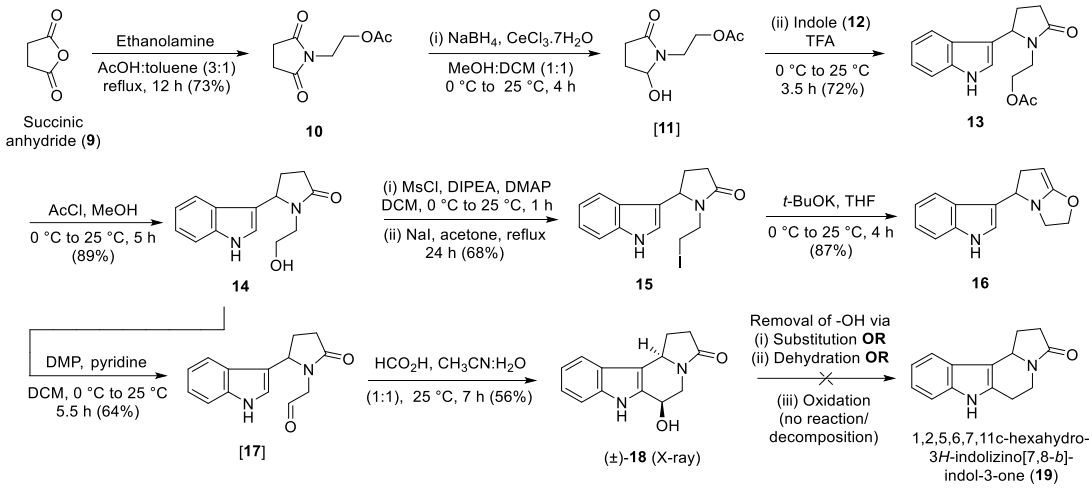
2D.2 Results and Discussion (Present Research Work)

Facile Synthesis of Novel Heterocycles from Indole and Imide Derivatives

Total synthesis of indole alkaloids, and indole-based new heterocyclic systems have been a challenging task for the past several decades.[8,13–21] In this context, a large number of systematically studied chemo-, regio- and stereoselective coupling reactions at 1/2/3-position of indoles have been reported.[9–11,22–36] In continuation of our studies on the applications of cyclic anhydrides/imides in the synthesis of bioactive alkaloid natural products;[37–40] we planned to explore carbon–carbon bond-forming regioselective coupling reactions of indole with the well-structured imide derivatives. In this context, we herein describe selective 2-position and 3-position coupling reactions of indole with imide derivatives and the subsequent cyclization's to constitute four different types of structurally attractive heterocyclic systems (Schemes 5 to 9).

The reaction of succinic anhydride (**9**) with ethanolamine in refluxing mixture of AcOH:toluene (3:1) provided succinimide **10** in 73% yield (Scheme 5). $NaBH_4$ reduction of succinimide **10** in the presence of $CeCl_3$ furnished a lactamol intermediate **11** and it was further used without any purification due to the stability issues. TFA-induced reaction of lactamol **11** with indole (**12**) was highly regioselective and yielded the 3-position coupled indolylpyrrole **13** in 72% yield, over 2-steps. De-acylation of compound **13**, mesylation of the formed alcohol **14** and its treatment with sodium iodide delivered the corresponding iodide **15** in 61% yield, over 3-steps. Iodide **15** in the presence of *t*-BuOK underwent enolization and formed the undesired cyclized product indolylpyrrole **16** in 87% yield. However, DMP-oxidation of alcohol **14** to the corresponding aldehyde intermediate **17** in 64% yield followed by formic acid mediated diastereoselective 2-position cyclization delivered the desired indolizinoindolone **18** in 56% yield. The stereochemical structural assignment of the product (±)-**18** was based on X-ray crystallographic data (Figure 3) and we feel that the orientation of a lone pair on lactam nitrogen atom governs the stereochemistry. Unfortunately, several attempts for the

removal of hydroxyl group in compound (±)-**18** to obtain the recently isolated natural product 1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one (**19**)[41] always resulted in no reaction or decomposition [conversion into a good leaving group (-OTs/-OMs) followed by hydride displacement, acid-induced dehydration followed by double bond reduction and oxidation to a ketone (PCC/PDC/DMP/TPAP) followed by reduction].



Scheme 5. Synthesis of Hydroxyindolizinoindolone via Acid Promoted Reaction of Indole with Succinimide Based Lactamol

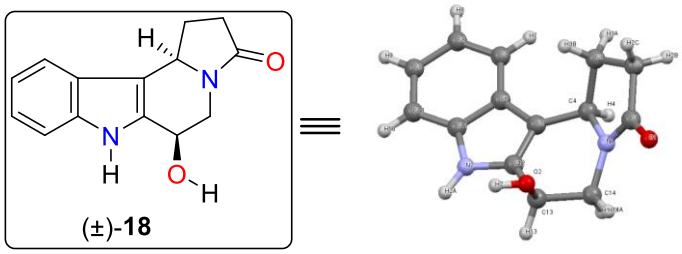


Figure 3. X-ray crystal structure of (±)-6-hydroxy-1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one

The literature search revealed that 2-(2-aminoethyl)indole (**6**) is not a natural product and the isolation of product **19** along with tryptamine based tetrahydropyrroloazepinoindole-3-carbaldehyde (**20**) indicated a plausibility of logical regioisomeric structural reassignment of the natural product **19** (Figure 4).[41] The structural assignment of **19** has been done based on IR, NMR, 2D NMR, and HRMS data.[41] At this stage, we carefully checked the ^{1}H and ^{13}C NMR data of product **18** and the structurally similar known compounds **8**[12] and **19**.[41] More specifically, the positions of 11c-methine carbon atoms in their ^{13}C NMR spectra. The delta value for 11c-methine carbon atom in product **19** was

relatively lower, but matched with **19a**. Recently, we reported the total synthesis of (+)-harmicine from (*R*)-acetoxysuccinic anhydride and tryptamine via advanced intermediate (+)-**19a**.[42] The postulation was correct and ^{1}H and ^{13}C NMR spectra of products **19** and **19a** in DMSO-d_6 were superimposable (Table 1). Thus, based on present studies on heterocyclic synthesis, the structure of proposed natural product 1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one (**19**) has been revised as the regioisomeric compound 1,2,5,6,11,11bhexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (**19a**).

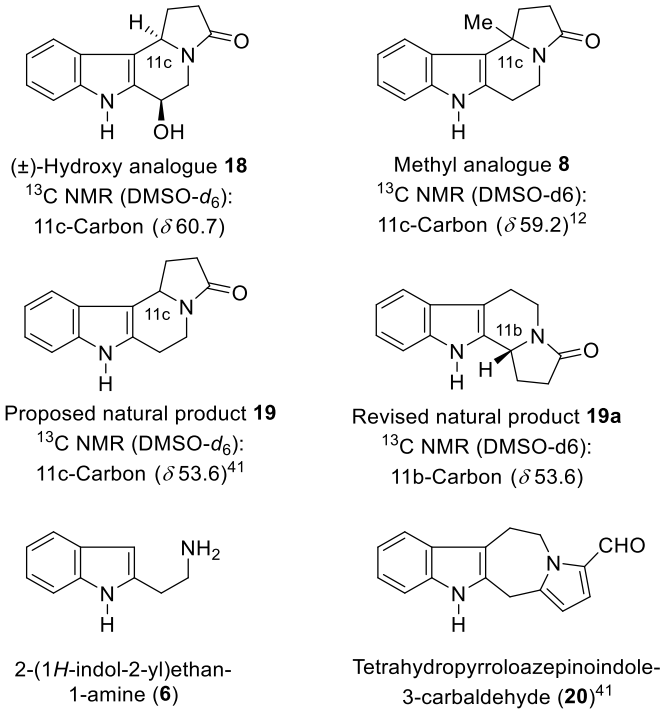


Figure 4. Proposed and revised natural product along with the synthetic analogues

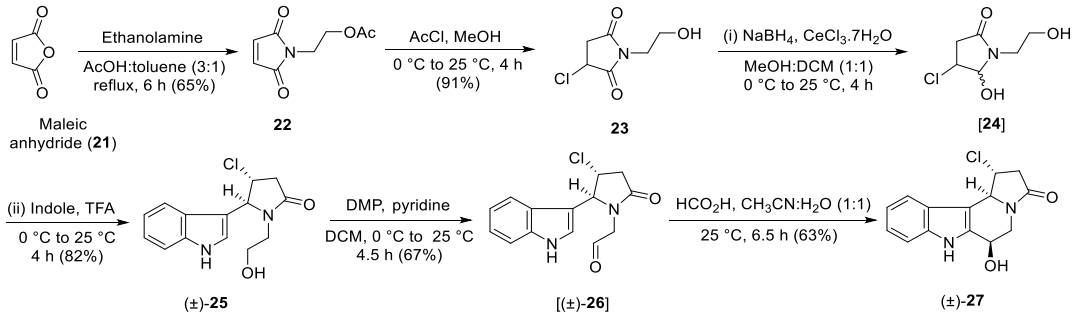
In continuation of our studies on heterocyclic synthesis, the reaction of maleic anhydride (**21**) with ethanolamine provided acetoxymaleimide **22** in 65% yield (Scheme 6). Maleimide **22** on treatment with AcCl/MeOH directly yielded chlorosuccinimide **23** in 91% yield via the desired de-acylation and an unplanned addition of HCl across the carbon–carbon double bond. Regioselective $NaBH_4$-reduction of the more reactive imide carbonyl group in chlorosuccinimide **23** formed the corresponding lactamol intermediate **24**. Acid induced diastereoselective coupling reaction of lactamol **24** at the 3-position of indole furnished pyrrole derivative (±)-**25** in 82% yield over 2-steps. Mechanistically, indole selectively attacked from the less hindered side of the formed iminium ion intermediate. DMP-oxidation of hydroxyl group in compound (±)-**25** to the corresponding

Table 1. Comparison of ^{1}H and ^{13}C NMR Spectral Data of Proposed Natural Product 19 and Revised Natural Product (+)-19a

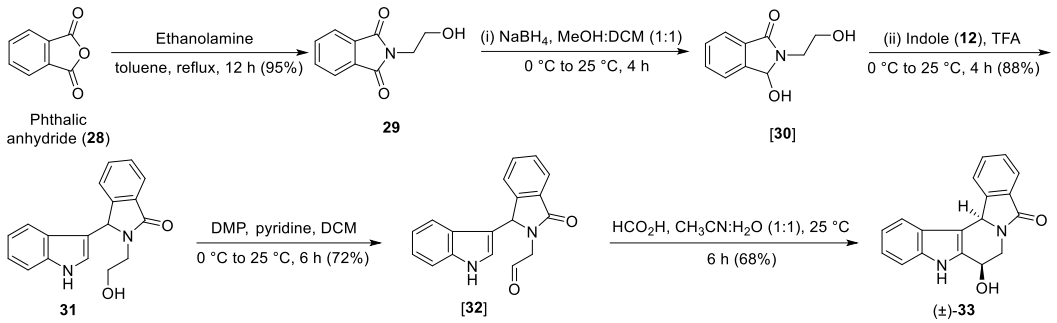
Proposed Natural Product 19 (Reference 41)			Revised Natural Product (+)-19a (Present Work)	
^{1}H NMR (DMSO-d_6, 400 MHz) δ	^{13}C NMR (DMSO-d_6, 100 MHz) δ (δ40.0 Ref. Lock)†	^{13}C NMR (DMSO-d_6, 100 MHz) δ (δ39.5 Ref. Lock)	^{1}H NMR (DMSO-d_6, 200 MHz) δ	^{13}C NMR (DMSO-d_6, 50 MHz) δ (δ39.5 Ref. Lock)
1.77 (m, 1H)	21.2	20.7	1.70–1.91 (m, 1H)	20.7
2.25 (m, 1H)	25.9	25.4	2.20–2.37 (m, 1H)	25.4
2.49 (m, 1H)	31.5	31.0		31.0
2.54 (m, 1H)	37.3	36.8	2.38–2.84 (m, 4H)	36.9
2.63 (m, 1H)	54.1	53.6		53.6
2.73 (dd, *J* = 15.2 and 4.0 Hz, 1H)	106.4	105.9		105.9
2.95 (ddd, *J* = 12.4, 12.4, 4.0 Hz, 1H)	111.6	111.1	2.98 (dt, *J* = 12.1 and 4.9 Hz, 1H)	111.1
4.26 (dd, *J* = 12.4, 6.0 Hz, 1H)	118.3	117.8	4.27 (dd, *J* = 12.9 and 4.7 Hz, 1H)	117.8
4.89 (m, 1H)	119.1	118.6	4.91 (t, *J* = 7.3 Hz, 1H)	118.6
6.95 (br dd, *J* = 7.6, 7.2 Hz, 1H)	121.5	121.0	6.97 (dt, *J* = 7.1 and 0.9 Hz, 1H)	121.0
7.04 (br dd, *J* = 8.0, 7.2 Hz, 1H)	126.9	126.4	7.07 (dt, *J* = 6.9 and 1.3 Hz, 1H)	126.4
7.30 (br d, *J* = 8.0 Hz, 1H)	135.1	134.6	7.33 (d, *J* = 7.4 Hz, 1H)	134.6
7.38 (br d, *J* = 7.6 Hz, 1H)	136.6	136.1	7.40 (d, *J* = 7.3 Hz, 1H)	136.1
11.00 (br s, 1H)	172.8	172.3	11.04 (br s, 1H)	172.3

† ***In the isolation paper authors have locked the DMSO-d_6 signal at δ40.00 (ref. 41)***

aldehyde (±)-**26** followed by formic acid mediated diastereoselective cyclization provided the indolizinoindolone (±)-**27** in 63% yield. Similarly, the preparation of hydroxyphthalimide **29**, its $NaBH_4$-reduction to lactamol **30** followed by the coupling reaction with indole to form the product **31**, DMP-oxidation of alcohol **31** to aldehyde **32** and the subsequent diastereoselective cyclization furnished the benzoindolizinoindolone **33** in very good overall yield (Scheme 7).



Scheme 6. Regioselective and Diastereoselective Coupling Reactions of Indole with Chlorosuccinimide Based Lactamol

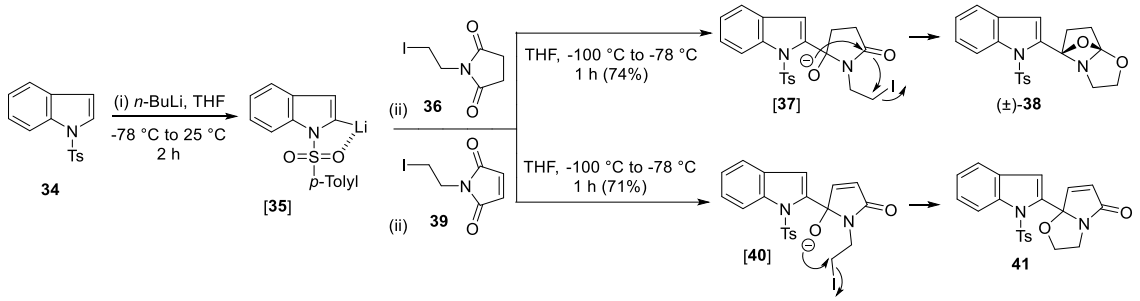


Scheme 7. Regioselective Coupling Reactions of Indole with Phthalimide Based Lactamol

N-Tosylindole (**34**) on treatment with *n*-BuLi at -78 °C to 25 °C smoothly formed the corresponding 2-lithio *N*-tosylindole (**35**) (Scheme 8).[9d] The initially studied coupling reaction of 2-lithio *N*-tosylindole (**35**) with *N*-2-iodoethylsuccinimide (**36**) at -78 °C resulted in the instantaneous decomposition. However, the same reaction at -100 °C to -78 °C formed an unanticipated bridged indolylepoxypyrrolooxazole (±)-**38** in 74% yield, comprising of an unusual 1,3-oxazetidine moiety. An absence of the lactam carbonyl signal in ^{13}C NMR spectrum of (±)-**38** was the best hint for structural assignment.

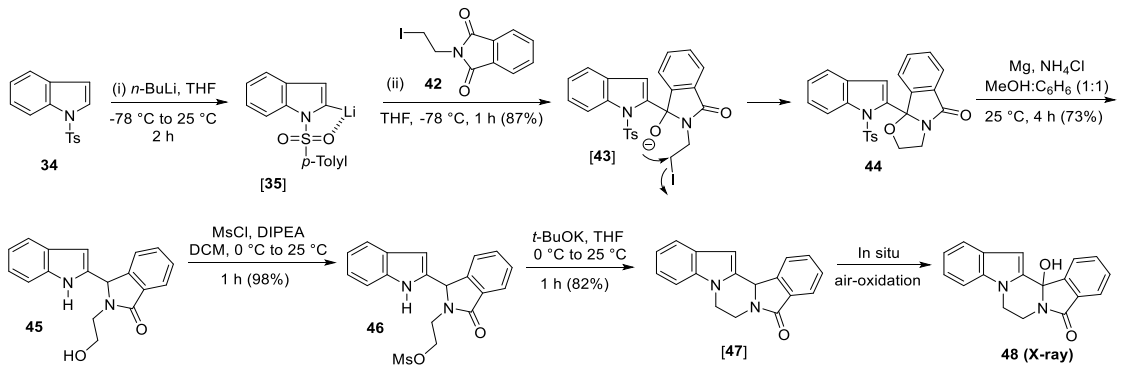
Mechanistically, 2-lithio *N*-tosylindole (**35**) reacts with a carbonyl group of imide **36** to form the corresponding oxyanion **37**, which internally attacks on the proximal second carbonyl group and thus formed oxyanion displaces iodide resulting in the remarkable product (±)-**38**. There were no difficulties in the isolation, silica gel column chromatographic purification and spectral characterization of the product (±)-**38**. However, the formed labile indolylepoxypyrrolooxazole (±)-**38** underwent hydrolytic and/or oxidative decomposition in nearly 48 hours. The reaction of 2-lithio *N*-tosylindole (**35**) with *N*-2-iodoethylmaleimide (**39**) at -100 °C to -78 °C followed a straightforward pathway and yielded the corresponding indolylpyrrolooxazolone **41** in 71% yield.

Unfortunately, all our attempts to deprotect tosylate group in products **38** and **41** using Mg/MeOH[43,44] resulted in complete decompositions of the reaction mixtures.



Scheme 8. Base Induced Regioselective Coupling Reactions of *N*-Tosylindole with *N*-2-Iodoethylsuccinimide and *N*-2-Iodoethylmaleimide

The reaction of 2-lithio *N*-tosylindole (**35**) with *N*-2-iodoethylphthalimide (**42**) at -78 °C neatly resulted in the expected indolyloxazoloisoindolone **44** in 87% yield (Scheme 9). Indolyloxazoloisoindolone **44** on treatment with Mg/MeOH[43,44] underwent tosylate deprotection and reductive oxazole ring cleavage to directly furnish the corresponding alcohol **45** in 73% yield. Conversion of alcohol **45** to mesylate and *t*-BuOK induced regioselective *N*-cyclization delivered in situ air-oxidized hydroxyisoindolopyrazinoindolone **48** (82% yield), via the corresponding unisolable intermediate **47**. The X-ray crystallographic data confirmed ring-closed structure of a *gem*-aminohydrin moiety containing product **48** (Figure 5). Such type of base induced in situ air-oxidations of electron-deficient carbon atoms in similar compounds are known.[45–48]



Scheme 9. Base Induced Regioselective Coupling Reaction of *N*-Tosylindole with *N*-2-Iodoethylphthalimide Leading to Hydroxyisoindolopyrazinoindolone

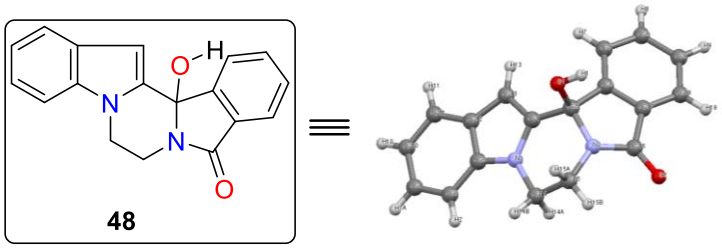


Figure 5. X-ray crystal structure of 13b-Hydroxy-6,7-dihydroisoindolo[1',2':3,4]pyrazino[1,2-a]indol-9(13b*H*)-one

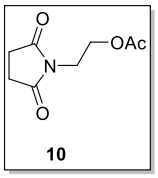
2D.3 Summary

In conclusion, we have demonstrated selective coupling reactions of indole with cyclic imide derivatives leading to structurally interesting important heterocyclic systems. The selective formation of exotic labile bridged compound indolylepoxypyrrolooxazole at minus hundred degrees and witnessed facile air-oxidation to form hydroxyisoindolopyrazinoindolone are noteworthy. We believe that the present new selective 1/2/3-position carbon–carbon and carbon–nitrogen bond-forming reactions of indole with the cyclic imide precursors are important from the basic chemistry point of view and will provide an avenue for indole-based heterocycles.

2D.4 Experimental Section

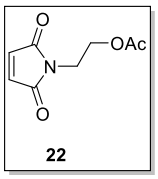
General Procedure for Preparation of Imide

2-(2,5-Dioxopyrrolidin-1-yl)ethyl Acetate (10). To a stirred solution of ethanolamine



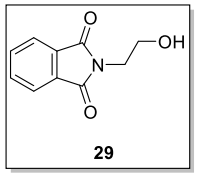
(2.50 g, 40.93 mmol) in AcOH:toluene (3:1, 50 mL) was added succinic anhydride (**9**, 6.14 g, 61.39 mmol) at 25 °C and the reaction mixture was refluxed for 12 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with aq. $NaHCO_3$, water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:1) as an eluent afforded succinimide **10** as pale-yellow oil (5.53 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.01 (s, 3H), 2.72 (s, 4H), 3.77 (t, J = 5.4 Hz, 2H), 4.22 (t, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 28.1, 37.9, 60.8, 170.9, 177.1; ESIMS (m/z) 186 $[M+H]^+$; HRMS (ESI) calcd for $C_8H_{11}O_4NNa$ 208.0580, found 208.0578; IR ($CHCl_3$) ν_{max} 1739, 1703 cm^{-1}.

2-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl Acetate (22): It was prepared according to the general procedure, silica gel column purified using ethyl acetate–petroleum ether (7:3) as an eluent and obtained as a white solid (4.90 g, 65%). Mp 78–80 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s, 3H), 3.80 (t, J = 5.5 Hz, 1H), 4.23 (t, J = 5.2 Hz, 2H), 6.73 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 36.9, 61.4, 134.2, 170.4, 170.8; ESIMS (*m*/*z*) 184 $[M+H]^+$; HRMS (ESI) calcd for $C_8H_{10}O_4N$ 184.0610, found 184.0608; IR ($CHCl_3$) ν_{max} 1714 cm^{-1}.



22

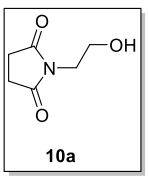
2-(2-Hydroxyethyl)isoindoline-1,3-dione (29). To a stirred solution of ethanolamine (3.00 g, 49.11 mmol) in toluene (70 mL) was added phthalic anhydride (**28**, 9.46 g, 63.85 mmol) at 25 °C and the reaction mixture was refluxed for 12 h. Toluene was removed in vacuo and the obtained residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with aq. $NaHCO_3$, water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using DCM–MeOH (49:1) as an eluent afforded phthalimide **29** as a white solid (8.90 g, 95%). Mp 128–130 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10–2.50 (br s, 1H), 3.85–3.95 (m, 4H), 7.70–7.77 (m, 2H), 7.84–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.9, 61.1, 123.4, 132.0, 134.1, 168.8; ESIMS (*m*/*z*) 192 $[M+H]^+$; HRMS (ESI) calcd for $C_{10}H_9O_3NNa$ 214.0475, found 214.0474; IR ($CHCl_3$) ν_{max} 3470, 1768, 1695 cm^{-1}.



29

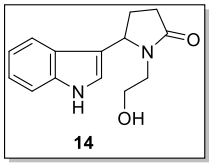
General Procedure for Deprotection of Acetyl Group

1-(2-Hydroxyethyl)pyrrolidine-2,5-dione (10a). AcCl (4.20 mL, 59.40 mmol) was added dropwise to a stirred solution of imide **10** (2.00 g, 10.80 mmol) in MeOH (25 mL) at 0 °C. The reaction mixture was stirred for 6 h allowing the temperature to reach 25 °C and concentrated in vacuo. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–methanol (97:3) as an eluent afforded imide **10a** as colourless oil (1.49 g, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (br s, 1H), 2.76 (s, 4H), 3.73–3.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.2, 41.6, 60.5, 177.9; ESIMS (*m*/*z*) 144 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3444, 1770, 1698 cm^{-1}.



10a

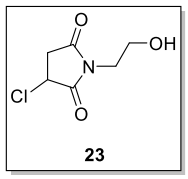
1-(2-Hydroxyethyl)-5-(1*H*-indol-3-yl)pyrrolidin-2-one (14): It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (97:3) as an eluent and obtained as a white solid (2.28 g, 89%). Mp 78–80 °C, ^{1}H NMR ($CDCl_3$, 400



14

MHz) δ 2.20 (br s, 1H), 2.25–2.38 (m, 1H), 2.45–2.75 (m, 3H), 3.07–3.15 (m, 1H), 3.52–3.65 (m, 3H), 5.05 (t, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 8.36 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 30.7, 45.0, 57.5, 61.6, 111.7, 115.1, 118.9, 120.2, 122.8, 122.9, 125.1, 136.9, 177.3; ESIMS (*m*/*z*) 245 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{17}O_2N_2$ 245.1285, found 245.1281; IR ($CHCl_3$) ν_{max} 3270, 1653 cm^{-1}.

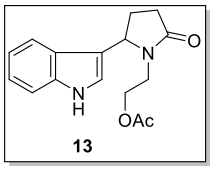
3-Chloro-1-(2-hydroxyethyl)pyrrolidine-2,5-dione (23): It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (99:1) as an eluent and obtained as colourless oil (2.12 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97 (dd, *J* = 18.7 and 3.8 Hz, 1H), 3.38 (dd, *J* = 19.1 and 8.4 Hz, 1H), 3.75–3.90 (m, 4H), 4.69 (dd, *J* = 8.4 and 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2, 42.1, 48.6, 59.9, 173.45, 173.52; ESIMS (*m*/*z*) 178 $[M+H]^+$; HRMS (ESI) calcd for $C_6H_9O_3NCl$ 178.0271, found 178.0266; IR ($CHCl_3$) ν_{max} 3478, 1785, 1709 cm^{-1}.



23

General Procedure for 3-Position Coupling Reaction of Indole with Lactamol

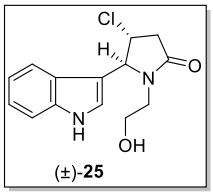
2-[2-(1*H*-Indol-3-yl)-5-oxopyrrolidin-1-yl]ethyl Acetate (13). To a stirred solution of imide **10** (3.00 g, 16.20 mmol) in MeOH:DCM (1:1, 50 mL) was added cerium(*III*) chloride heptahydrate ($CeCl_3.7H_2O$) (15.09 g, 40.50 mmol) at 0 °C and then $NaBH_4$ (1.53 g, 40.50 mmol) was added in portion wise manner. The reaction mixture was stirred at the same temperature for 1 h and then it was further stirred for 3 h allowing the temperature to reach 25 °C. The same reaction mixture was again cooled at 0 °C and indole (**12**, 2.09 g, 17.82 mmol) was added to the reaction mixture. The reaction mixture was slowly acidified with TFA (4.34 mL, 56.70 mmol) until completely acidic (pH 2) and it was further stirred for 3.5 h allowing the temperature to reach 25 °C. It was quenched with saturated aq. $NaHCO_3$ (7 mL), concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (70 mL). The resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (13:7) as an eluent afforded **13** as foam (3.34 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (s, 3H), 2.18–2.32 (m, 1H), 2.43–2.70 (m, 3H), 2.95 (dt, *J* = 13.9 and 4.8 Hz, 1H), 3.90–4.03 (m, 2H), 4.18–4.25 (m, 1H), 5.08 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* =



13

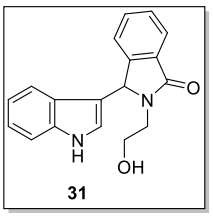
7.5 Hz, 1H), 7.16 (s, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 8.31 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 27.2, 30.6, 39.6, 56.1, 61.3, 111.7, 115.0, 118.9, 120.2, 122.69, 122.74, 125.2, 136.9, 170.9, 175.6; ESIMS (*m*/*z*) 287 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{19}O_3N_2$ 287.1390, found 287.1386; IR ($CHCl_3$) ν_{max} 3282, 1736, 1671 cm^{-1}.

(±)-4-Chloro-1-(2-hydroxyethyl)-5-(1H-indol-3-yl)pyrrolidin-2-one (25): It was prepared according to the general procedure, silica gel column purified using ethyl acetate–pet ether (4:1) as an eluent and obtained as a cream colour solid (2.57 g, 82%). Mp 118–120 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (dd, *J* = 17.6 and 4.7 Hz, 1H), 3.10–3.22 (m, 2H), 3.70–3.80 (m, 3H), 4.48–4.55 (m, 1H), 5.17 (d, *J* = 3.9 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 8.40 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.6, 45.0, 56.5, 61.2, 67.1, 111.5, 111.9, 118.5, 120.6, 123.07, 123.12, 124.9, 136.9, 173.1; ESIMS (*m*/*z*) 279 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}O_2N_2Cl$ 279.0900, found 279.0910; IR ($CHCl_3$) ν_{max} 3298, 1667 cm^{-1}.



(±)-**25**

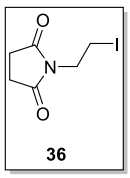
2-(2-Hydroxyethyl)-3-(1*H*-indol-3-yl)isoindolin-1-one (31): It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (24:1) as an eluent and obtained as a cream colour solid (2.02 g, 88%). Mp 172–174 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80–2.83 (br s, 1H), 3.35 (td, *J* = 15.2 and 4.6 Hz, 1H), 3.72 (t, *J* = 5.4 Hz, 2H), 3.81 (td, *J* = 14.5 and 4.6 Hz, 1H), 5.88 (s, 1H), 6.84 (br s, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.34 (br s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.44–7.52 (m, 2H), 7.95 (d, *J* = 6.1 Hz, 1H), 8.84 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2, 59.9, 61.9, 110.2, 111.6, 118.8, 120.1, 122.6, 123.2, 123.3, 125.1, 128.3, 131.5, 132.0, 136.9, 146.3, 169.9; ESIMS (*m*/*z*) 293 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}O_2N_2$ 293.1290, found 293.1296; IR ($CHCl_3$) ν_{max} 3327, 1663 cm^{-1}.



31

General Procedure for Conversion of Alcohol to the Corresponding Iodide

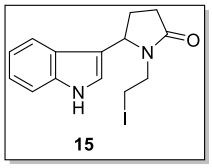
1-(2-Iodoethyl)pyrrolidine-2,5-dione (36). To a stirred solution of imide **10a** (1.40 g, 9.78 mmol) in dry DCM (20 mL) were added DIPEA (4.26 mL, 24.45 mmol) and MsCl (0.90 mL, 11.74 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h allowing the temperature to reach 25 °C and concentrated in vacuo. The obtained residue on direct silica gel (230–



36

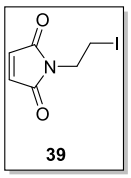
400 mesh) column chromatographic purification using ethyl acetate–pet ether (7:3) as an eluent afforded mesylate **10b** (2.00 g, 92%). To a stirred solution of mesylate **10b** (1.80 g, 8.14 mmol) in anhydrous acetone (40 mL) was added NaI (12.20 g, 81.36 mmol) at 25 °C and the reaction mixture was refluxed for 24 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–pet ether (3:7) as an eluent afforded iodoimide **36** as a yellow solid (1.63 g, 79%). Mp 54–56 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.76 (s, 4H), 3.33 (t, J = 7.2 Hz, 2H), 3.91 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ –1.1, 28.1, 40.6, 176.5; ESIMS (m/z) 253 $[M+H]^+$; HRMS (ESI) calcd for $C_6H_9O_2NI$ 253.9678, found 253.9692; IR ($CHCl_3$) ν_{max} 1772, 1707 cm^{-1}.

5-(1*H*-Indol-3-yl)-1-(2-iodoethyl)pyrrolidin-2-one (15): It was prepared according to the general procedure, silica gel column purified using ethyl acetate–petroleum ether (4:1) as an eluent and obtained as a yellow solid (986 mg, 68%). Mp 128–130 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22–2.32 (m, 1H), 2.47–2.72 (m, 3H), 3.00–3.08 (m, 1H), 3.12–3.29 (m, 2H), 3.93–4.01 (m, 1H), 5.12 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 4.5 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 8.27 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.3, 27.1, 30.7, 43.2, 56.0, 111.7, 114.9, 118.9, 120.3, 122.8 (2C), 125.1, 136.9, 175.3; ESIMS (m/z) 355 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}ON_2I$ 355.0302, found 355.0296; IR ($CHCl_3$) ν_{max} 3279, 1667 cm^{-1}.



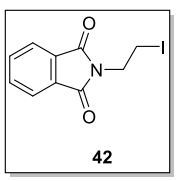
15

1-(2-Iodoethyl)-1*H*-pyrrole-2,5-dione (39): It was prepared according to the general procedure, silica gel column purified using ethyl acetate–pet ether (1:3) as an eluent and obtained as a yellow solid (947 mg, 67%). Mp 42–44 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.33 (t, J = 7.2 Hz, 2H), 3.92 (t, J = 6.9 Hz, 2H), 6.75 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.01, 39.9, 134.2, 170.0; ESIMS (m/z) 251 $[M+H]^+$; HRMS (ESI) calcd for $C_6H_7O_2NI$ 251.9521, found 251.9516; IR ($CHCl_3$) ν_{max} 1713 cm^{-1}.



39

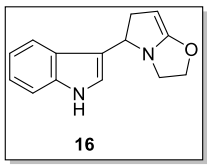
2-(2-Iodoethyl)isoindoline-1,3-dione (42): It was prepared according to the general procedure, silica gel column purified using ethyl acetate–pet ether (3:7) as an eluent and obtained as a white solid (1.94 g, 82%). Mp 98–100 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (t, J = 7.6 Hz, 2H), 4.09 (t, J = 6.9 Hz, 2H), 7.73–7.79 (m, 2H), 7.85–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100



42

MHz) δ –0.09, 40.0, 123.5, 131.8, 134.2, 167.7; ESIMS (*m*/*z*) 301 $[M+H]^+$; HRMS (ESI) calcd for $C_{10}H_9O_2NI$ 301.9678, found 301.9697; IR ($CHCl_3$) ν_{max} 1770, 1705 cm^{-1}.

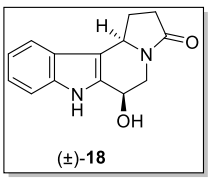
5-(1*H*-Indol-3-yl)-2,3,5,6-tetrahydropyrrolo[2,1-*b*]oxazole (16). To a stirred solution of compound **15** (300 mg, 0.85 mmol) in dry THF (6 mL) was added *t*-BuOK (210 mg, 1.86 mmol) at 0 °C and the reaction mixture was stirred for 4 h allowing the temperature to reach 25 °C. The reaction was quenched with saturated aq. NH_4Cl (3 mL) and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (15 mL) and the resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7:3) as an eluent afforded **16** as a white solid (167 mg, 87%). Mp 118–120 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ 2.15–2.23 (m, 1H), 2.47–2.60 (m, 2H), 2.62–2.72 (m, 1H), 4.38 (s, 1H), 4.40 (d, *J* = 5.5 Hz, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 7.11 (dd, *J* = 13.0 and 7.6 Hz, 1H), 7.17 (t, *J* = 6.1 Hz, 1H), 7.25 (t, *J* = 6.1 Hz, 1H), 7.41 (d, *J* = 6.7 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 8.27 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3, 30.1, 54.2, 96.5, 111.6, 115.0, 118.4, 119.9, 121.2, 122.5, 125.1, 128.1, 136.8, 173.9; ESIMS (*m*/*z*) 227 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{15}ON_2$ 227.1179, found 227.1176; IR ($CHCl_3$) ν_{max} 3293, 1682, 1636 cm^{-1}.



16

General Procedure for Cyclization Reaction of Indole and Aldehyde Moiety

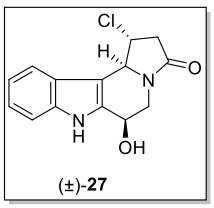
(±)-6-Hydroxy-1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*]indol-3-one (18). To a stirred solution of alcohol **14** (1.50 g, 6.14 mmol) in anhydrous DCM (20 mL) were added Dess-Martin periodinane (3.91 g, 9.21 mmol) and pyridine (0.740 mL, 9.21 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 5.5 h allowing the temperature to reach 25 °C. The reaction mixture was diluted with DCM (20 mL) and quenched with mixture of aq. Sodium thiosulfate (40%, 5 mL) plus saturated aq. $NaHCO_3$ (5 mL). It was extracted with DCM (30 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by immediate silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:1) as an eluent afforded aldehyde **17** as a brown solid (952 mg, 64%). To a stirred solution of aldehyde **17** (900 mg, 3.71 mmol) in MeCN:H_2O (1:1, 15 mL) was added formic acid (1.40 mL, 37.15 mmol) at 25 °C. The



(±)-18

reaction mixture was stirred for 7 h and the reaction was quenched with saturated aq. $NaHCO_3$ (3 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (20 mL). The resultant solution was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM–MeOH (24:1) as an eluent afforded **(±)-18** as a white solid (504 mg, 56%). Mp 224–226 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.67–1.75 (m, 1H), 2.28 (dd, J = 16.8 and 8.4 Hz, 1H), 2.45–2.55 (m, 1H), 2.73–2.83 (m, 1H), 3.09 (dd, J = 13.4 and 2.3 Hz, 1H), 4.18 (d, J = 13.7 Hz, 1H), 4.74 (dd, J = 6.5 and 2.3 Hz, 1H), 4.86 (dd, J = 9.5 and 6.1 Hz, 1H), 5.32 (d, J = 6.1 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 11.11 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.8, 31.5, 45.4, 53.9, 60.7, 111.7, 112.1, 118.7, 118.8, 121.7, 123.7, 133.1, 136.2, 172.9; ESIMS (m/z) 243 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{14}O_2N_2Na$ 265.0952, found 265.0952; IR ($CHCl_3$) ν_{max} 3254, 1650 cm^{-1}.

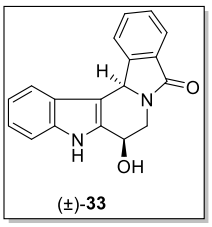
(±)-1-Chloro-6-hydroxy-1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*]indol-3-one



(±)-**27**

(27): It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (24:1) as an eluent and obtained as a white solid (126 mg, 63%). Mp 202–204 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.82 (dd, J = 16.4 and 9.9 Hz, 1H), 3.00 (dd, J = 16.0 and 8.4 Hz, 1H), 3.10 (d, J = 12.2 Hz, 1H), 4.22 (d, J = 13.7 Hz, 1H), 4.42 (q, J = 7.6 Hz, 1H), 4.70 (d, J = 6.9 Hz, 1H), 5.07 (d, J = 7.6 Hz, 1H), 5.39 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 11.34 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 41.7, 45.3, 56.8, 60.5, 63.0, 108.6, 111.8, 119.2, 120.1, 122.0, 123.7, 134.5, 136.2, 169.9; ESIMS (m/z) 277 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{13}O_2N_2ClNa$ 299.0563, found 299.0558; IR ($CHCl_3$) ν_{max} 3415, 1659 cm^{-1}.

(±)-6-Hydroxy-5,6,7,13b-tetrahydro-9*H*-benzo[1,2]indolizino[7,8*b*]indol-9-one (33):

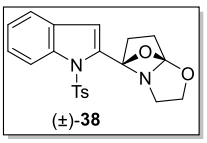


(±)-**33**

It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (97:3) as an eluent and obtained as a white solid (95 mg, 68%). Mp 188–190 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.55 (d, J = 14.0 Hz, 1H), 4.83 (br s, 1H), 5.42 (d, J = 4.3 Hz, 1H), 6.06 (s, 1H), 7.13 (t, J = 6.1 Hz, 2H), 7.37 (d, J = 7.3 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.66 (t, J = 7.3 Hz, 2H), 7.75 (d, J = 7.3 Hz, 1H), 8.07 (d, J = 7.3

Hz, 1H), 8.19 (d, J = 7.3 Hz, 1H), 11.29 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 45.9, 57.7, 61.8, 108.3, 111.9, 119.3, 119.9, 121.9, 123.2, 124.1, 124.4, 128.2, 131.8, 132.2, 134.1, 136.3, 145.3, 168.1; ESIMS (m/z) 291 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{14}O_2N_2Na$ 313.0952, found 313.0969; IR ($CHCl_3$) ν_{max} 3272, 1734, 1667 cm^{-1}.

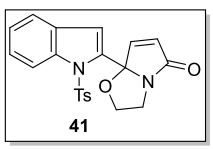
(±)-5-(1-Tosyl-1*H*-indol-2-yl)tetrahydro-5*H*-5,7aepoxypyrrolo[2,1-*b*]oxazole (38). To a stirred solution of 1-tosyl-1*H*-indole (**34**, 300 mg, 1.11 mmol) in dry THF (8 mL) was dropwise added *n*-butyllithium (2.00 M in cyclohexane; 1.27 mL, 2.54 mmol) at –78 °C under argon atmosphere. The reaction mixture was further stirred for 2 h allowing the temperature to reach 25 °C. The reaction mixture was again cooled to –100 °C and solution of iodo compound **36** (310 mg, 1.22 mmol) in dry THF (8 mL) was added in a dropwise fashion. The reaction mixture was further stirred for 1 h allowing the temperature to reach –78 °C and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (20 mL). The resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3:7) as an eluent afforded (±)-**38** as thick colourless oil (325 mg, 74%).



(±)-**38**

^{1}H NMR (acetone-d_6, 500 MHz) δ 2.37 (s, 3H), 2.48 (ddd, J = 16.6, 9.9 and 3.1 Hz, 1H), 2.62–2.72 (m, 1H), 2.79 (dd, J = 17.2 and 8.8 Hz, 1H), 2.91 (ddd, J = 13.7, 9.9 and 2.7 Hz, 1H), 2.98 (br s, 1H), 3.40 (br s, 1H), 3.76–3.84 (m, 1H), 3.95–4.04 (m, 1H), 6.86 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 8.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.7 Hz, 2H), 8.31 (d, J = 8.4 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 21.5, 33.0, 34.4, 42.7, 66.7, 100.1, 112.3, 116.0, 122.5, 124.6, 126.3, 128.1, 129.1, 130.5 (2C), 137.5, 139.5, 140.5, 146.1; ESIMS (m/z) 397 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{21}O_4N_2S$ 397.1222, found 397.1217; IR ($CHCl_3$) ν_{max} 1686, 1635 cm^{-1}.

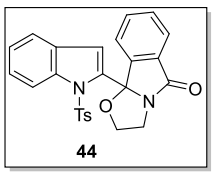
7a-(1-Tosyl-1*H*-indol-2-yl)-2,3-dihydropyrrolo[2,1-*b*]oxazol-5(7a*H*)-one (41). To a stirred solution of 1-tosyl-1*H*-indole (**34**, 500 mg, 1.84 mmol) in dry THF (10 mL) was dropwise added *n*-butyllithium (2.00 M in cyclohexane; 2.12 mL, 4.24 mmol) at –78 °C under argon atmosphere. The reaction mixture was further stirred for 2 h allowing the temperature to reach 25 °C. The reaction mixture was again cooled to –100 °C and solution of iodo compound **39** (510 mg, 2.03 mmol) in dry THF (10 mL) was added in a dropwise fashion. The reaction



41

mixture was further stirred for 1 h allowing the temperature to reach –78 °C and the reaction was quenched with saturated aqueous NH_4Cl (4 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:3) as an eluent afforded **41** as a brown solid (520 mg, 71%). Mp 144–146 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.27 (ddd, J = 10.7, 6.6 and 5.0 Hz, 1H), 3.56 (q, J = 7.6 Hz, 1H), 3.84–3.92 (m, 1H), 4.18 (td, J = 8.3 and 5.1 Hz, 1H), 6.08 (d, J = 5.8 Hz, 1H), 6.94 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 5.9 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 41.8, 70.0, 99.8, 112.1, 115.0, 122.5, 123.9, 125.8, 127.2, 127.4, 127.8, 129.4, 135.4, 136.4, 138.8, 144.8, 150.3, 176.4; ESIMS (*m*/*z*) 395 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{19}O_4N_2S$ 395.1065, found 395.1068; IR ($CHCl_3$) ν_{max} 1710, 1598 cm^{-1}.

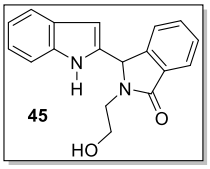
9b-(1-Tosyl-1*H*-indol-2-yl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one (44). To a stirred solution of 1-tosyl-1*H*-indole (**34**, 1.50 g, 5.53 mmol) in dry THF (20 mL) was dropwise added *n*-butyllithium (2.00 M in cyclohexane; 6.36 mL, 12.71 mmol) at –78 °C under argon atmosphere. The reaction mixture was further stirred for 2 h allowing the temperature to reach 25 °C. The reaction mixture was again cooled to –78 °C and solution of iodo compound **42** (1.83 g, 6.08 mmol) in dry THF (8 mL) was added in a dropwise fashion. The reaction mixture was further stirred for 1 h at –78 °C and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (40 mL). The resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1:4) as an eluent afforded **44** as a white solid (1.90 g, 87%). Mp 202–204 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 2.63 (br s, 1H), 3.85 (br s, 1H), 3.95–4.05 (m, 1H), 4.18 (q, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.24 (br s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.54–7.63 (m, 6H), 7.83–7.87 (m, 1H), 8.40 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 41.4, 70.0, 97.8, 111.5, 115.7, 121.3,



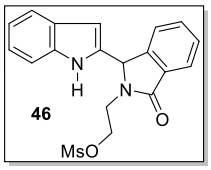
44

123.9, 124.1, 125.8, 126.5, 128.0, 129.5, 130.5, 131.8, 133.2, 133.3, 135.8, 136.7, 139.7, 144.6, 145.3, 174.2; ESIMS (*m*/*z*) 445 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{21}O_4N_2S$ 445.2117, found 445.2213; IR ($CHCl_3$) ν_{max} 1720, 1599 cm^{-1}.

2-(2-Hydroxyethyl)-3-(1*H*-indol-2-yl)isoindolin-1-one (45). To a stirred solution of *N*-tosyl protected compound **44** (1.50 g, 4.50 mmol) in MeOH:benzene (1:1; 20 mL) were sequentially added activated magnesium turning (1.23 g, 50.62 mmol) and ammonium chloride (2.71 g, 50.62 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 4 h and quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (30 mL). The resultant solution was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM–MeOH (24:1) as an eluent afforded **45** as a white solid (720 mg, 73%). Mp 102–104 °C, ^{1}H NMR (acetone-d_6, 400 MHz) δ 3.13–3.22 (m, 1H), 3.65–3.78 (m, 2H), 3.92 (dt, *J* = 14.5 and 5.4 Hz, 1H), 4.08 (t, *J* = 6.1 Hz, 1H), 6.09 (s, 1H), 6.75 (d, *J* = 1.5 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.48–7.60 (m, 3H), 7.76 (d, *J* = 6.9 Hz, 1H), 10.18 (br s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 44.2, 60.6, 61.2, 104.1, 111.2, 120.3, 121.2, 122.8, 123.9, 124.3, 129.2, 129.4, 132.6, 133.1, 135.2, 138.4, 146.1, 168.8; ESIMS (*m*/*z*) 293 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{16}O_4N_2Na$ 315.1104, found 315.1101; IR ($CHCl_3$) ν_{max} 3284, 1663 cm^{-1}.

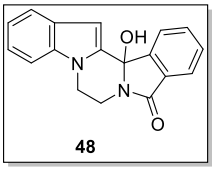


2-[1-(1*H*-Indol-2-yl)-3-oxoisoindolin-2-yl]ethyl Methanesulfonate (46). To a stirred solution of alcohol **45** (500 mg, 1.71 mmol) in anhydrous DCM (10 mL) were added DIPEA (0.75 mL, 4.28 mmol) and MsCl (0.16 mL, 2.05 mmol) at 0 °C under an argon atmosphere. The reaction mixture was further stirred for 1 h allowing the temperature to reach 25 °C and concentrated in vacuo. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–pet ether (4:1) as an eluent afforded mesylate compound **46** as a white solid (621 mg, 98%). Mp 174–176 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94 (s, 3H), 3.46 (ddd, *J* = 15.2, 7.1 and 4.4 Hz, 1H), 4.08 (dt, *J* = 15.1 and 4.6 Hz, 1H), 4.34–4.45 (m, 2H), 5.95 (s, 1H), 6.81 (d, *J* = 1.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 9.10 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100



MHz) δ 37.6, 40.2, 60.0, 67.5, 104.7, 111.4, 120.1, 120.7, 122.8, 123.45, 123.51, 127.8, 129.0, 130.8, 132.1, 132.4, 137.2, 144.3, 168.9; ESIMS (*m*/*z*) 371 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_4N_2S$ 371.1060, found 371.1054; IR ($CHCl_3$) ν_{max} 3416, 1683 cm^{-1}.

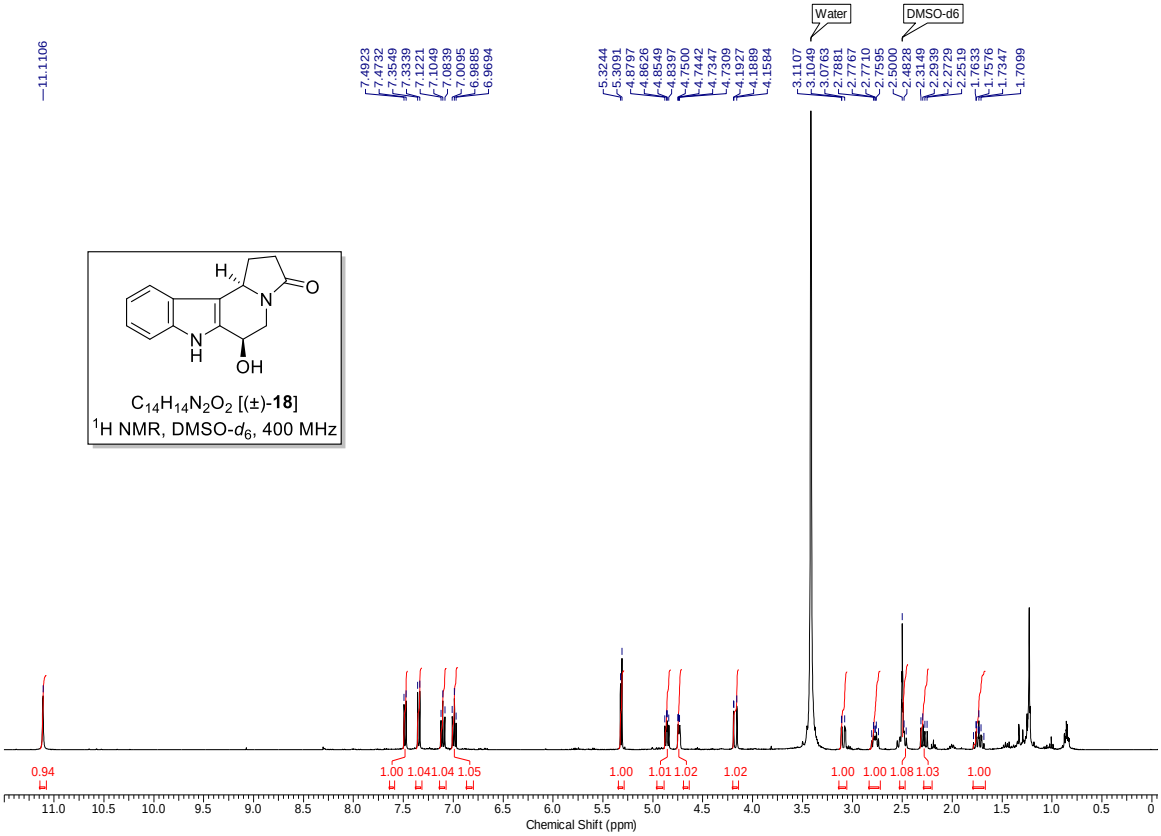
13b-Hydroxy-6,7-dihydroisoindolo[1',2':3,4]pyrazino[1,2-*a*]indol-9(13b*H*)-one (48).

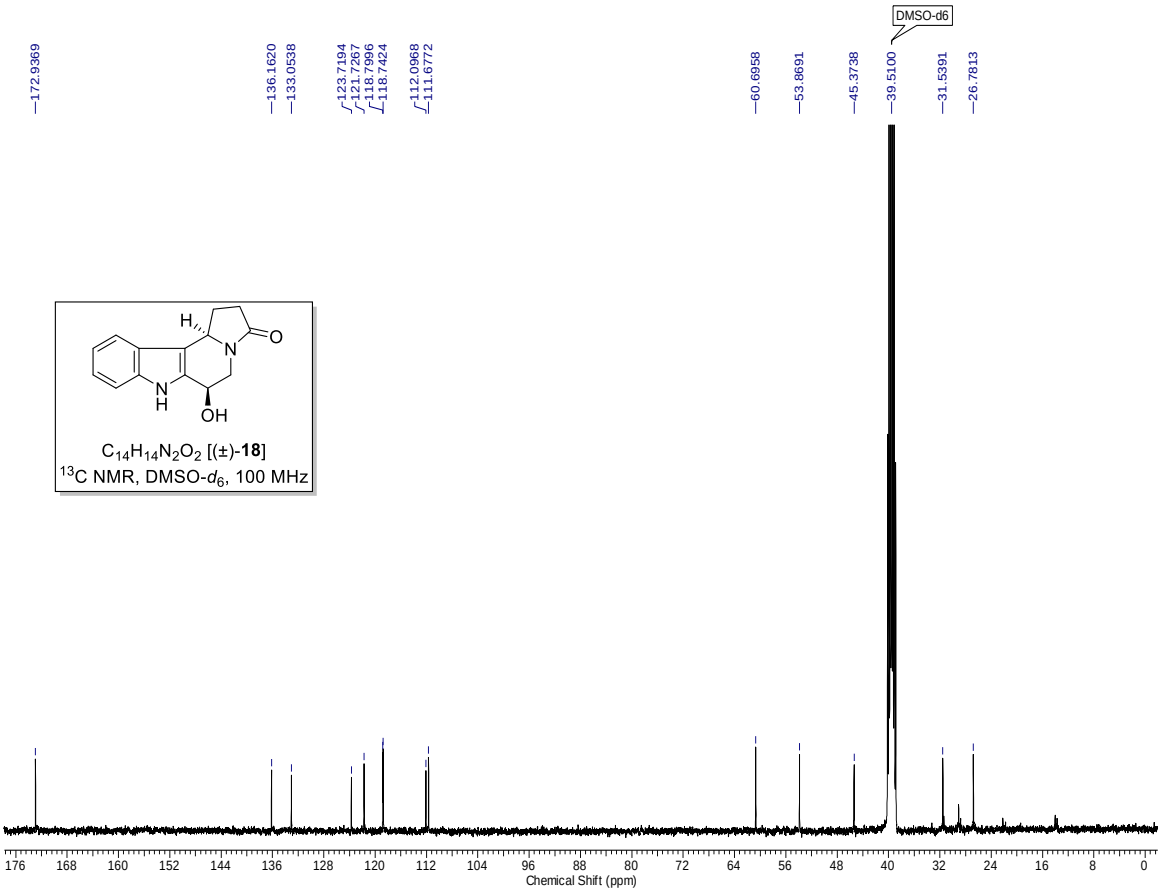


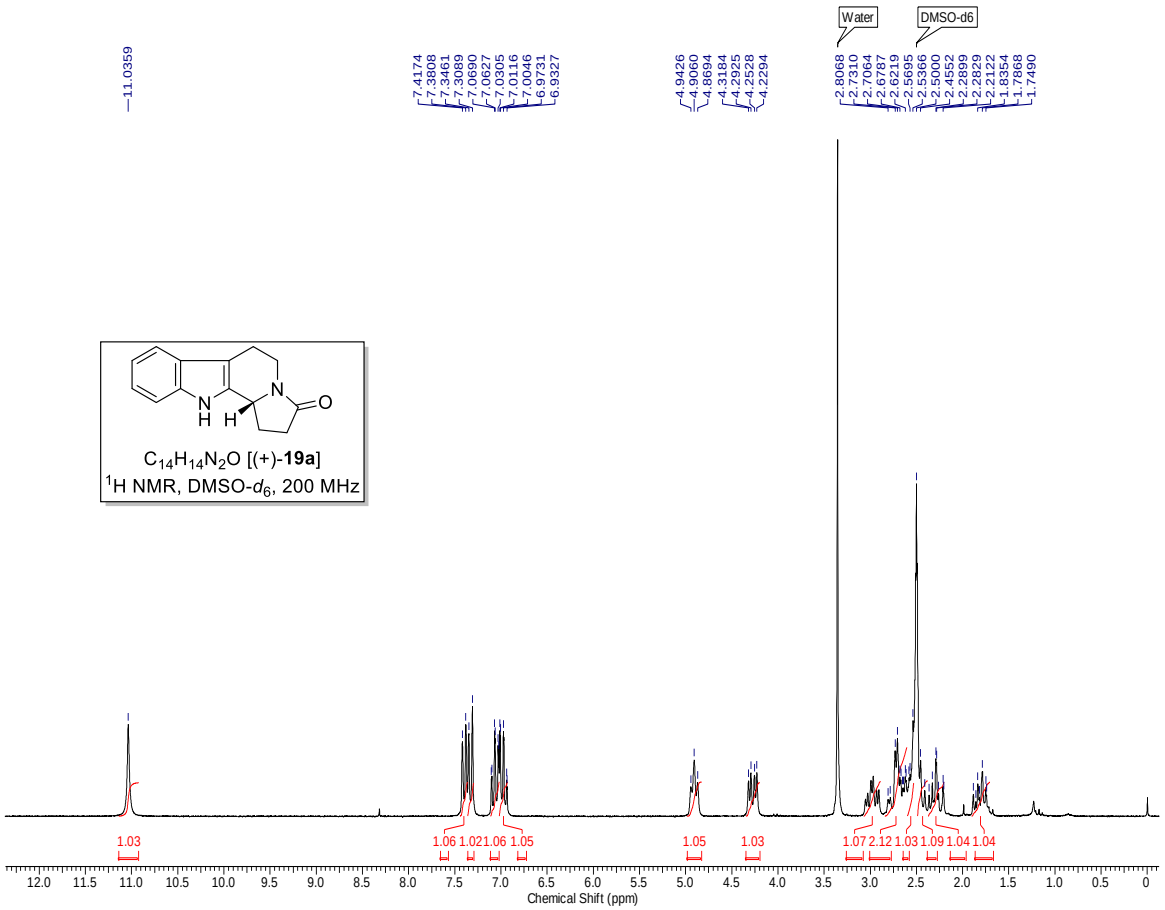
48

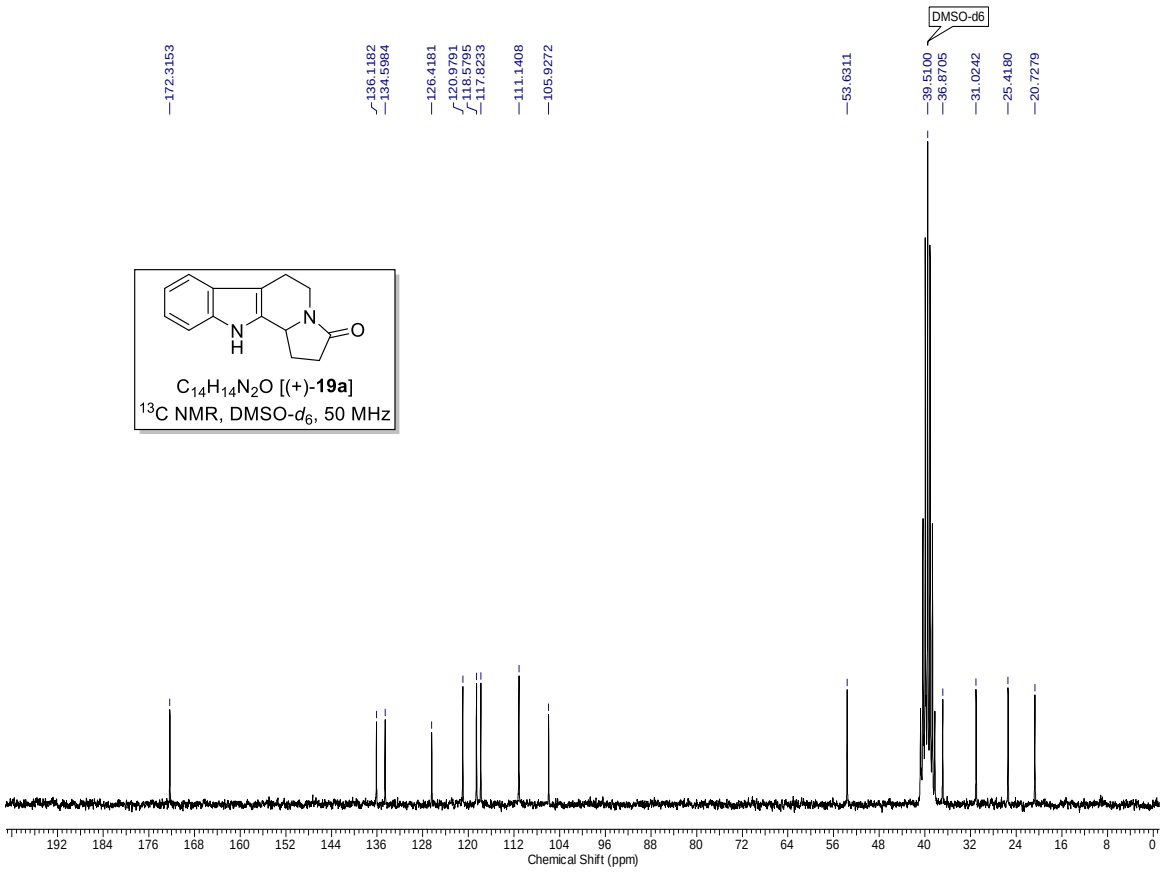
To a stirred solution of *t*-BuOK (46 mg, 0.40 mmol) in dry THF (4 mL) was dropwise added solution of mesylate **46** (100 mg, 0.27 mmol) in THF (5 mL) at 0 °C under argon atmosphere. The reaction mixture was further stirred for 1 h allowing the temperature to reach 25 °C and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (20 mL). The resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (4:1) as an eluent afforded **48** as a white solid (64 mg, 82%). Mp 162–164 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.78–3.98 (m, 2H), 4.40 (dd, *J* = 10.2 and 3.4 Hz, 1H), 4.49 (dd, *J* = 11.4 and 3.4 Hz, 1H), 6.90 (s, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.33 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.75 (t, *J* = 7.4 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.7, 40.8, 83.4, 99.9, 110.1, 120.1, 120.5, 121.8, 122.7, 123.4, 127.0, 129.5, 130.0, 132.9, 135.2, 135.9, 147.8, 165.5; ESIMS (*m*/*z*) 291 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{15}O_2N_2$ 291.1133, found 291.1136; IR ($CHCl_3$) ν_{max} 3416, 1706, 1593 cm^{-1}.

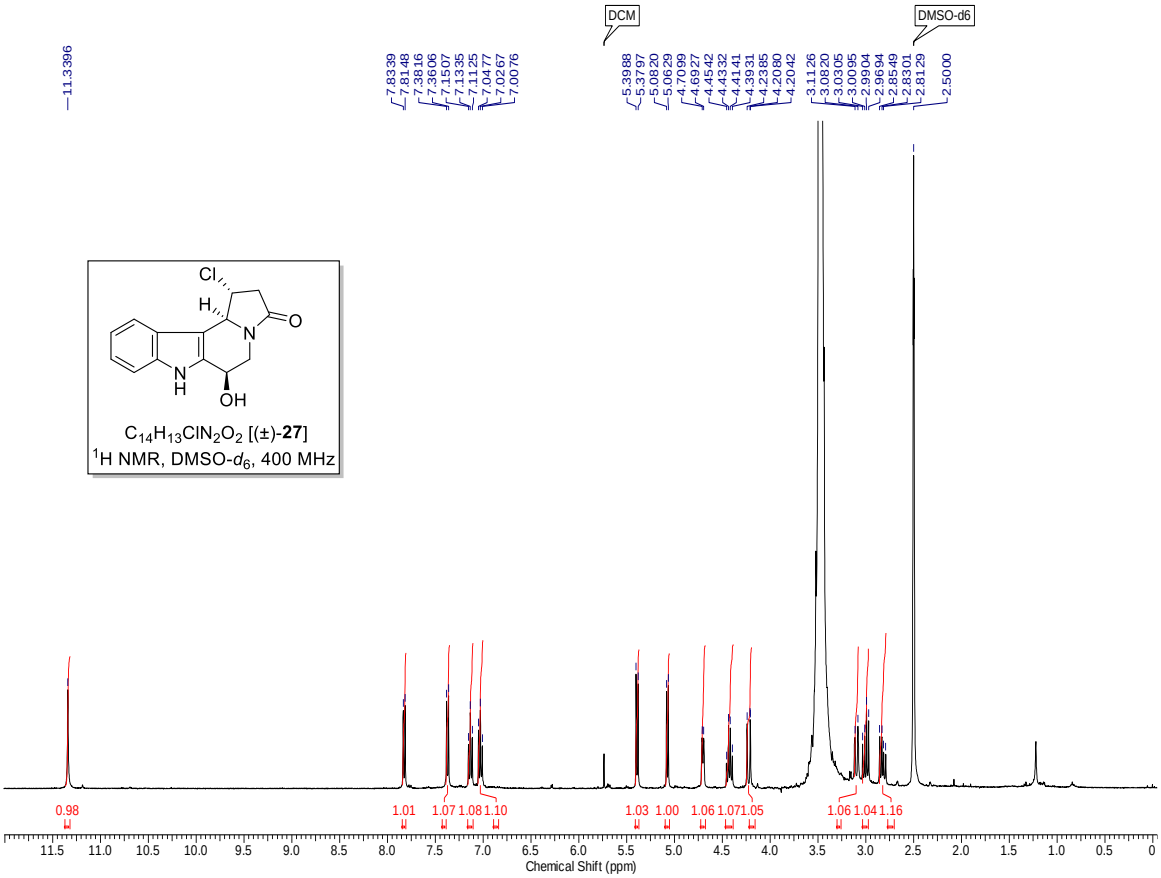
2D.5 Selected Spectra

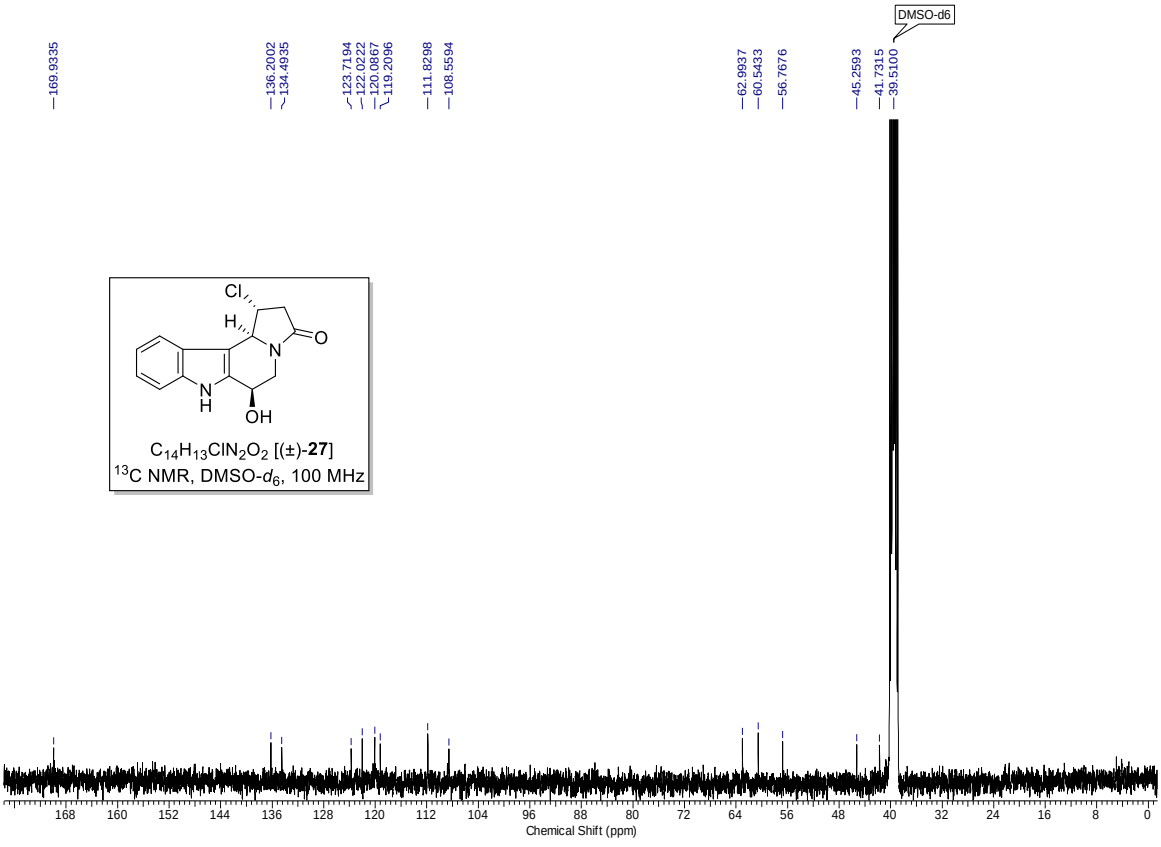

Water
DMSO-d6
11.1106
7.4923
7.4732
7.3549
7.3339
7.1221
7.1049
7.0839
7.0095
6.9885
6.9694
5.3244
5.3091
4.8797
4.8626
4.8549
4.8397
4.7500
4.7442
4.7347
4.7309
4.1927
4.1889
4.1584
3.1107
3.1049
3.0763
2.7881
2.7767
2.7710
2.7595
2.5000
2.4828
2.3149
2.2939
2.2729
2.2519
1.7633
1.7576
1.7347
1.7099
H
N
O
N
H
OH
C14H14N2O2 [(±)-18]
1H NMR, DMSO-d6, 400 MHz
0.94
1.00
1.04
1.05
1.00
1.01
1.02
1.02
1.00
1.00
1.08
1.03
1.00
Chemical Shift (ppm)

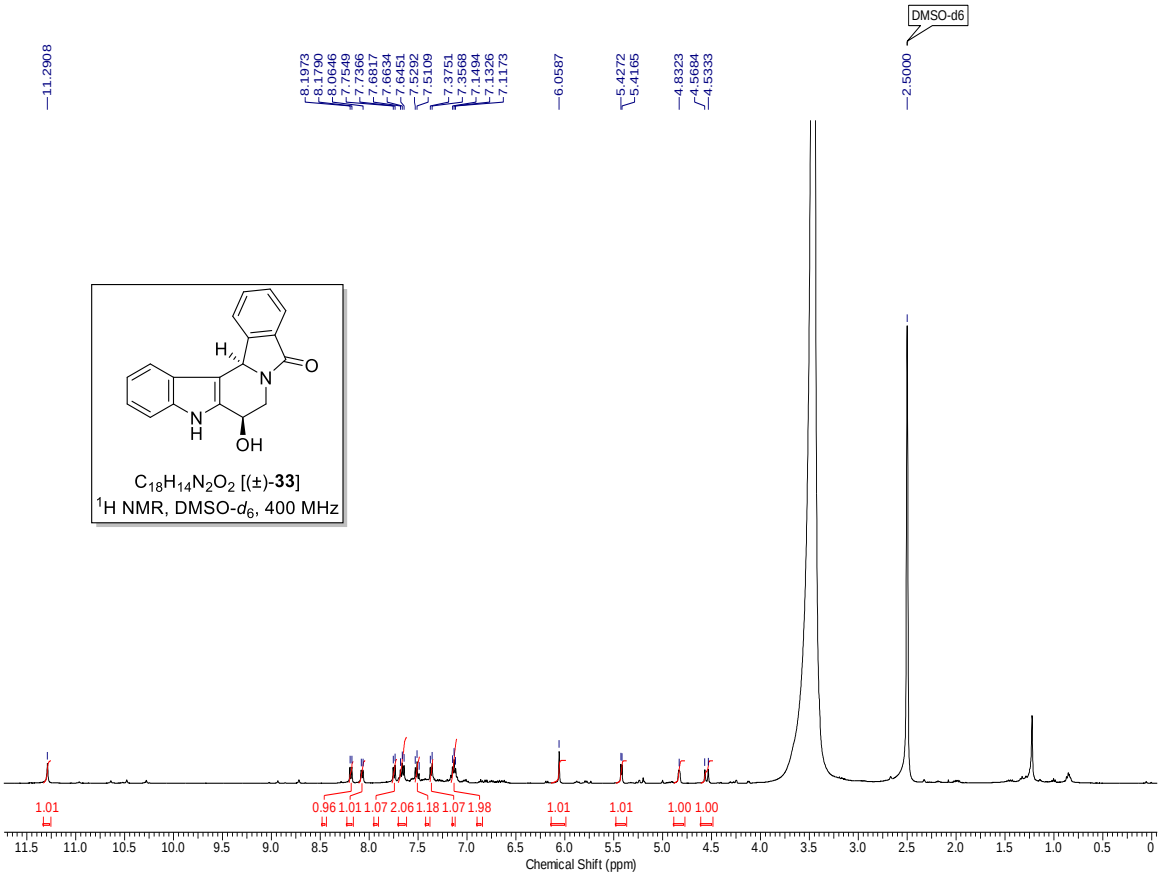

DMSO-d6
172.9369
136.1620
133.0538
123.7194
121.7267
118.7996
118.7424
112.0968
111.6772
60.6958
53.8691
45.3738
39.5100
31.5391
26.7813
H
N
O
N
H
OH
C14H14N2O2 [(±)-18]
13C NMR, DMSO-d6, 100 MHz
Chemical Shift (ppm)


Water
DMSO-d6
11.0359
7.4174
7.3808
7.3461
7.3089
7.0690
7.0627
7.0305
7.0116
7.0046
6.9731
6.9327
4.9426
4.9060
4.8694
4.3184
4.2925
4.2528
4.2294
2.8068
2.7310
2.7064
2.6787
2.6219
2.5695
2.5366
2.5000
2.4552
2.2899
2.2829
2.2122
1.8354
1.7868
1.7490
N
H
H
N
O
C14H14N2O [(+)-19a]
1H NMR, DMSO-d6, 200 MHz
1.03
1.06
1.02
1.06
1.05
1.05
1.03
1.07
2.12
1.03
1.09
1.04
1.04
Chemical Shift (ppm)

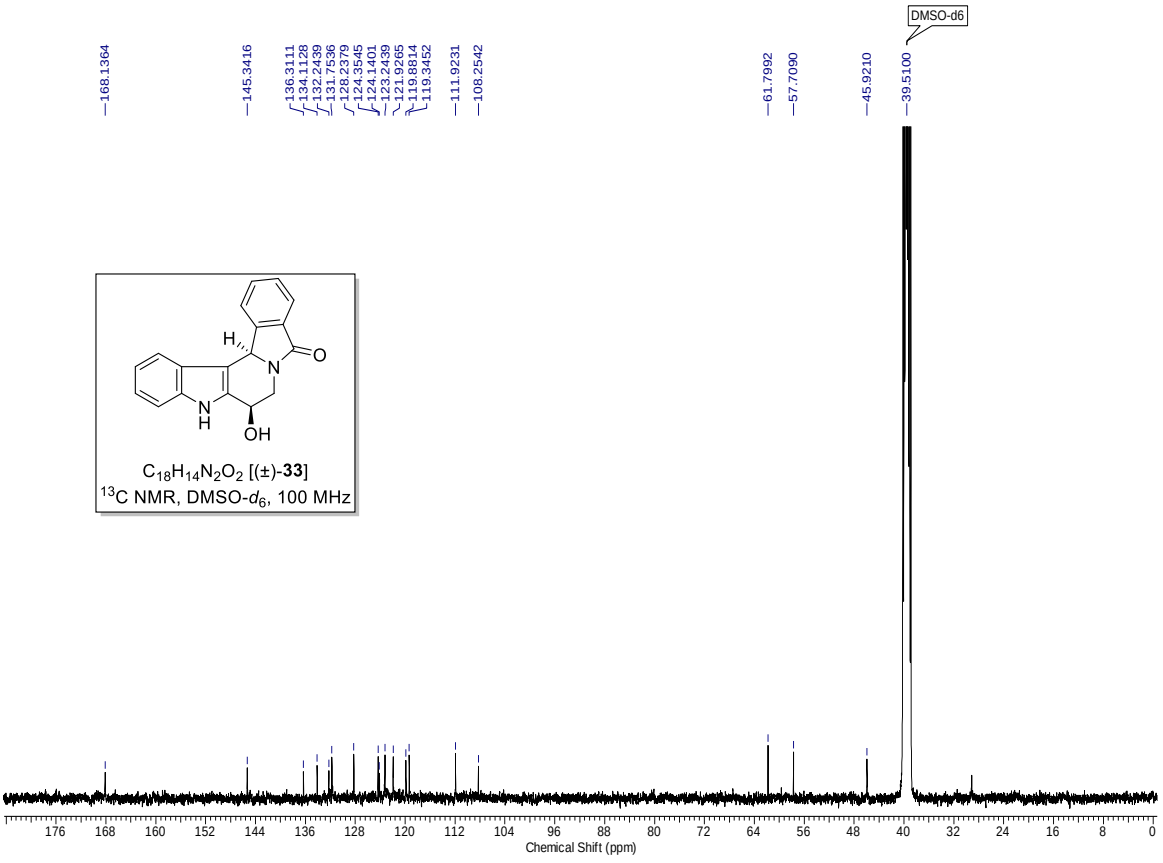

DMSO-d6
172.3153
136.1182
134.5984
126.4181
120.9791
118.5795
117.8233
111.1408
105.9272
53.6311
39.5100
36.8705
31.0242
25.4180
20.7279
N
H
N
O
C14H14N2O [(+)-19a]
13C NMR, DMSO-d6, 50 MHz
Chemical Shift (ppm)


DCM
DMSO-d6
11.3396
7.8339
7.8148
7.3816
7.3606
7.1507
7.1335
7.1125
7.0477
7.0267
7.0076
5.3988
5.3797
5.0820
5.0629
4.7099
4.6927
4.4542
4.4332
4.4141
4.3931
4.2385
4.2080
4.2042
3.1126
3.0820
3.0305
3.0095
2.9904
2.9694
2.8549
2.8301
2.8129
2.5000
Cl
H
N
O
N
H
OH
C14H13ClN2O2 [(±)-27]
1H NMR, DMSO-d6, 400 MHz
0.98
1.01
1.07
1.08
1.10
1.03
1.00
1.06
1.07
1.05
1.06
1.04
1.16
Chemical Shift (ppm)

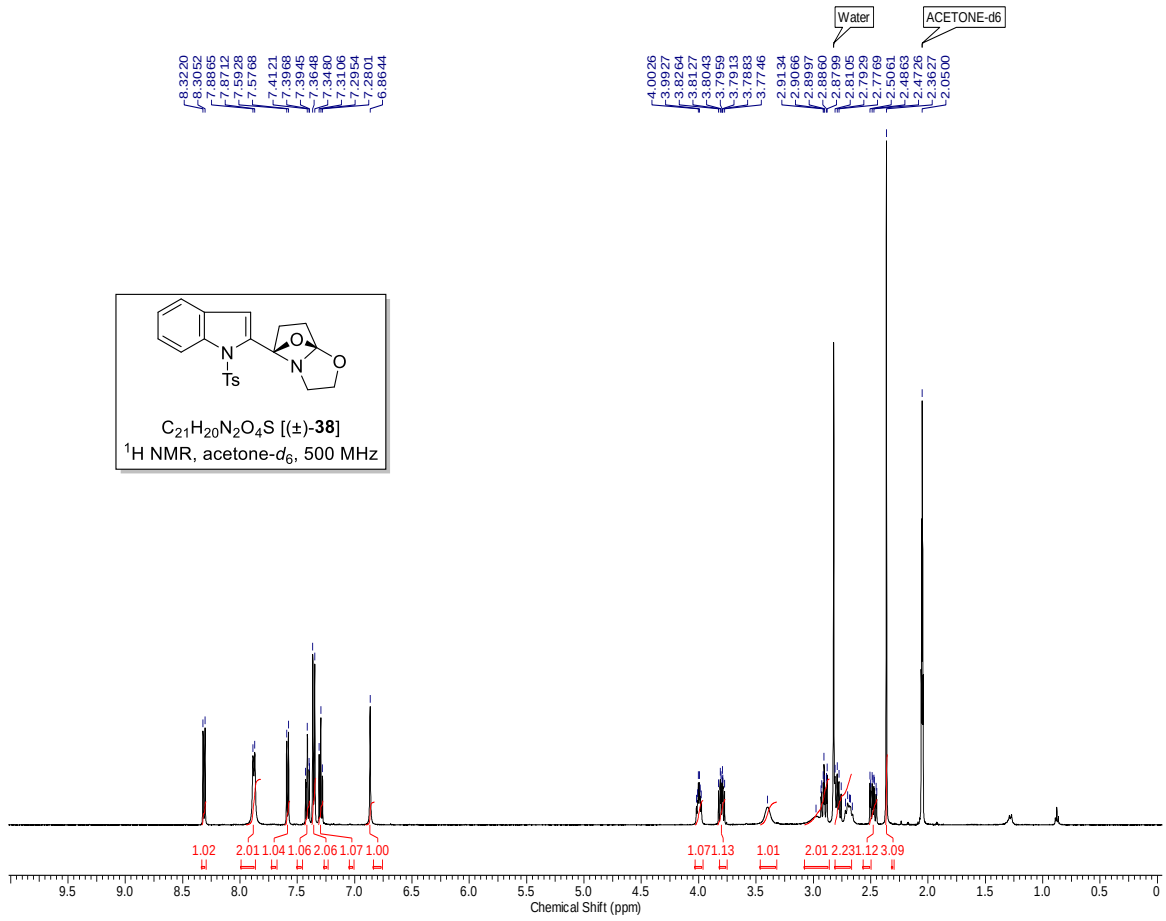

DMSO-d6
169.9335
136.2002
134.4935
123.7194
122.0222
120.0867
119.2096
111.8298
108.5594
62.9937
60.5433
56.7676
45.2593
41.7315
39.5100
Cl
H
N
O
N
H
OH
C14H13ClN2O2 [(±)-27]
13C NMR, DMSO-d6, 100 MHz
Chemical Shift (ppm)

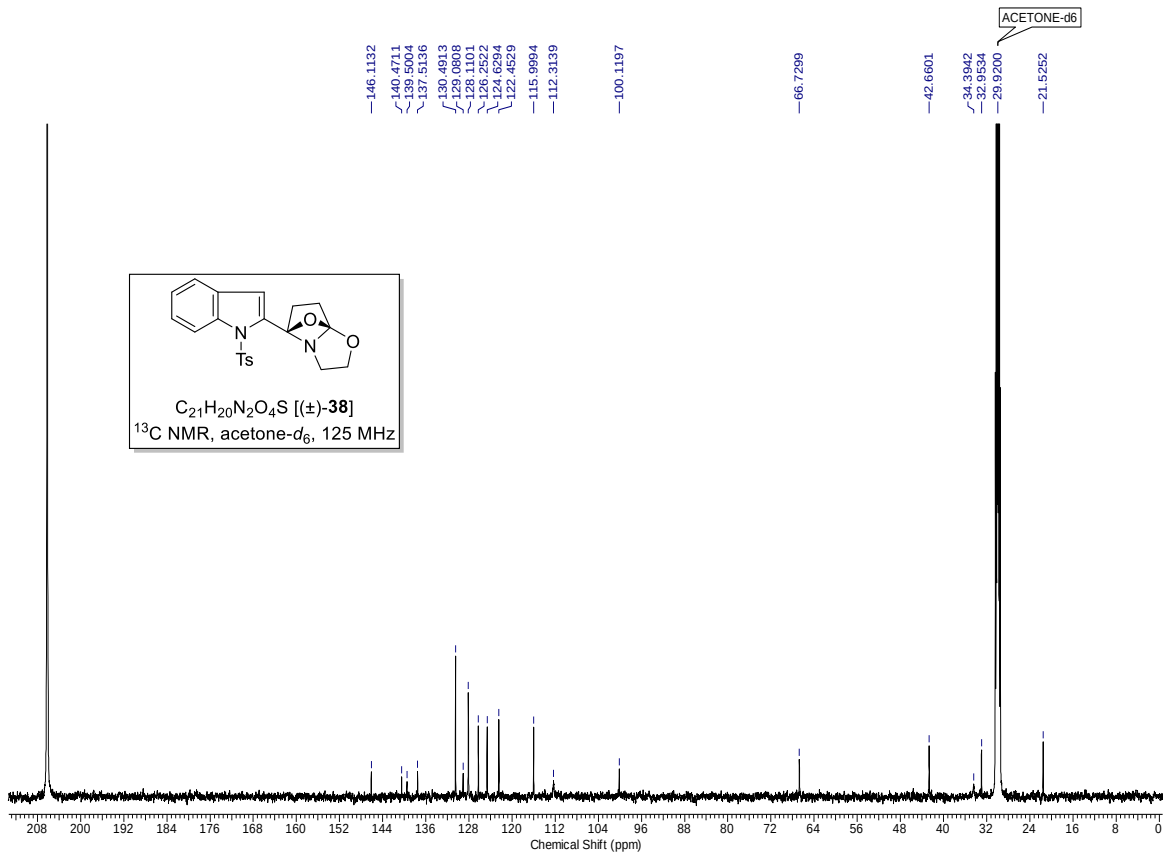


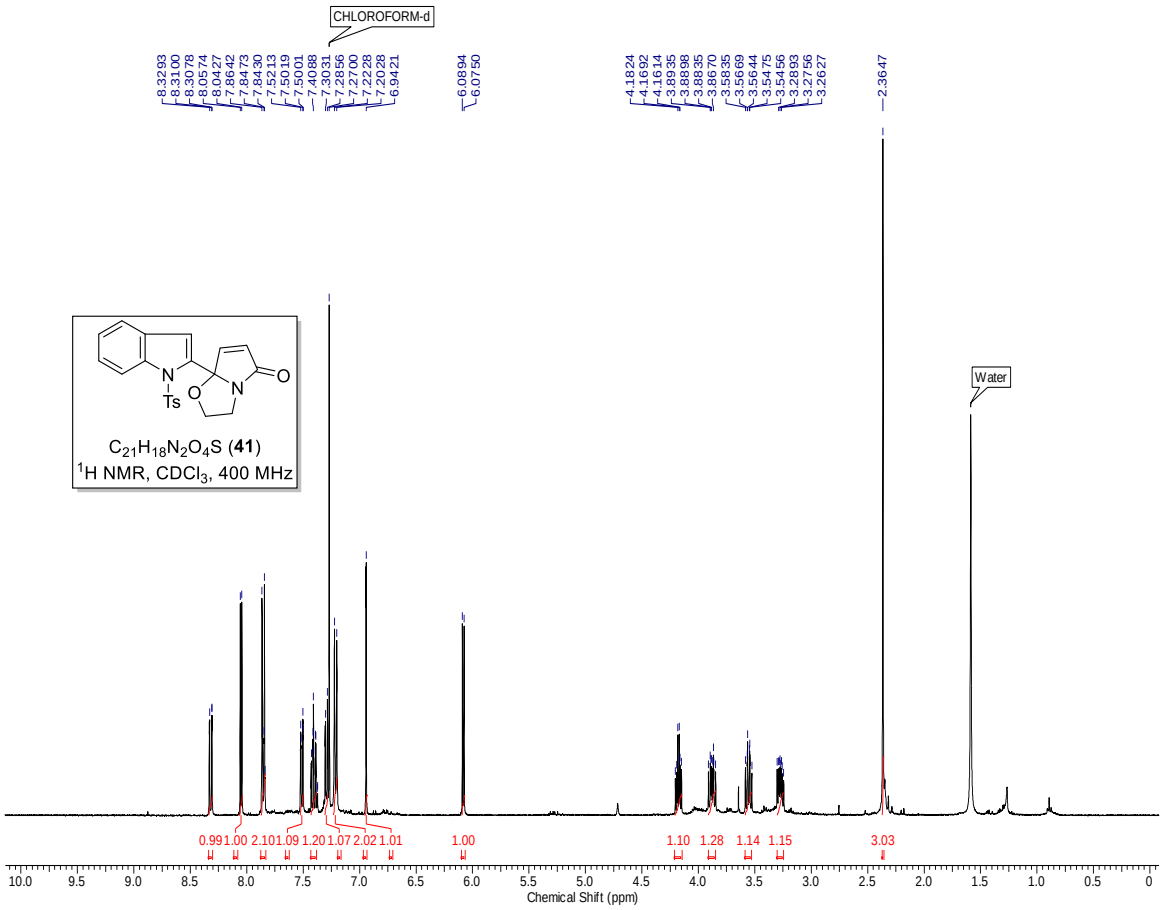
$C_{18}H_{14}N_2O_2$ [(±)-**33**]
^{1}H NMR, DMSO-d_6, 400 MHz

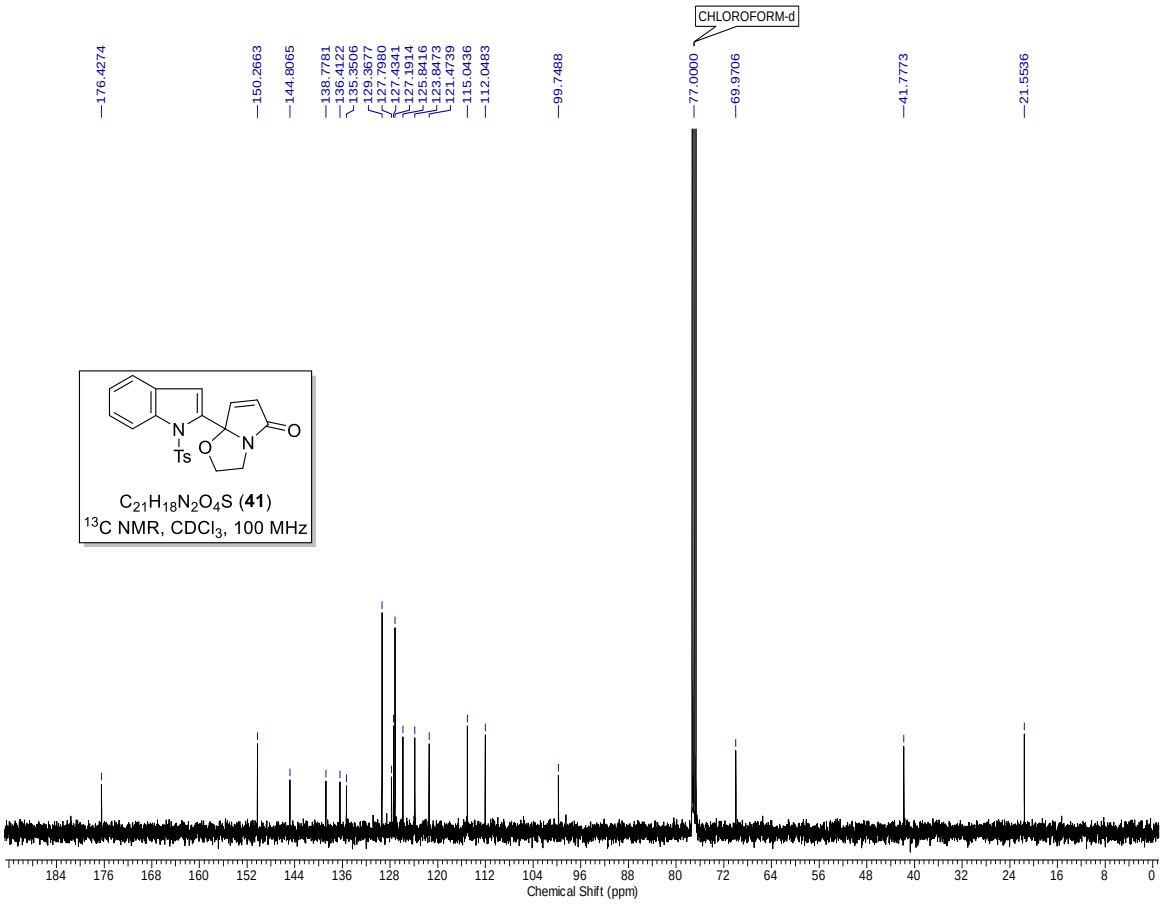


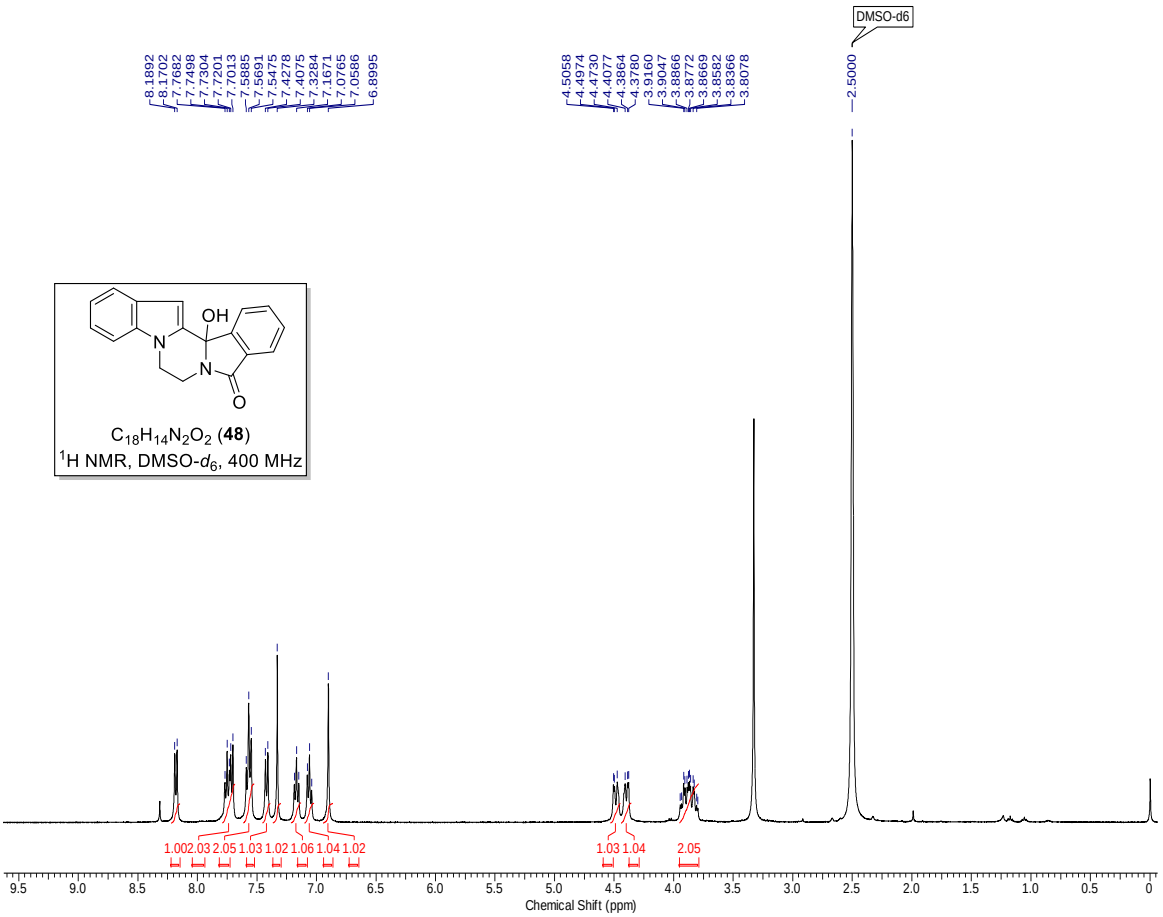
$C_{18}H_{14}N_2O_2$ [(±)-**33**]
^{13}C NMR, DMSO-d_6, 100 MHz

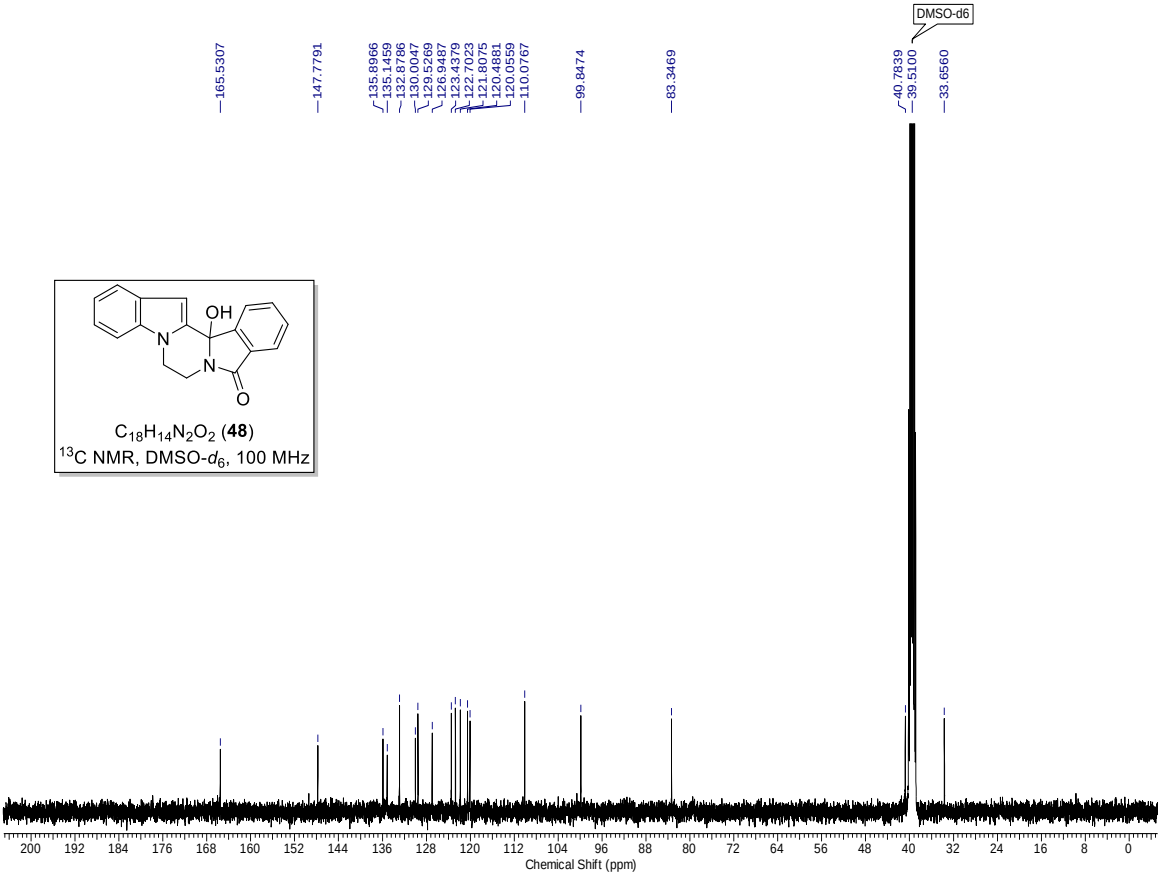

Water
ACETONE-d6
8.3220
8.3052
7.8865
7.8712
7.5928
7.5768
7.4121
7.3968
7.3945
7.3648
7.3480
7.3106
7.2954
7.2801
6.8644
4.0026
3.9927
3.8264
3.8127
3.8043
3.7959
3.7913
3.7883
3.7746
2.9134
2.9066
2.8997
2.8860
2.8799
2.8105
2.7929
2.7769
2.5061
2.4863
2.4726
2.3627
2.0500
Ts
C21H20N2O4S [(±)-38]
1H NMR, acetone-d6, 500 MHz
1.02
2.01
1.04
1.06
2.06
1.07
1.00
1.07
1.13
1.01
2.01
2.23
1.12
3.09
Chemical Shift (ppm)


ACETONE-d6
146.1132
140.4711
139.5004
137.5136
130.4913
129.0808
128.1101
126.2522
124.6294
122.4529
115.9994
112.3139
100.1197
66.7299
42.6601
34.3942
32.9534
29.9200
21.5252
Ts
C21H20N2O4S [(±)-38]
13C NMR, acetone-d6, 125 MHz
Chemical Shift (ppm)


CHLOROFORM-d
Water
Ts
$C_{21}H_{18}N_2O_4S$ (41)
^{1}H NMR, $CDCl_3$, 400 MHz
Chemical Shift (ppm)


CHLOROFORM-d
Ts
$C_{21}H_{18}N_2O_4S$ (41)
^{13}C NMR, $CDCl_3$, 100 MHz
Chemical Shift (ppm)


DMSO-d6
8.1892
8.1702
7.7682
7.7498
7.7304
7.7201
7.7013
7.5885
7.5691
7.5475
7.4278
7.4075
7.3784
7.1671
7.0765
7.0586
6.8995
4.5058
4.4974
4.4770
4.4077
4.3864
4.3780
3.9160
3.9047
3.8866
3.8772
3.8669
3.8582
3.8366
3.8078
2.5000
OH
N
N
O
C18H14N2O2 (48)
1H NMR, DMSO-d6, 400 MHz
1.00 2.03 2.05 1.03 1.02 1.06 1.04 1.02
1.03 1.04
2.05
Chemical Shift (ppm)


DMSO-d6
165.5307
147.7791
135.8966
135.1459
132.8786
130.0047
129.5269
126.9487
123.4379
122.7023
121.8075
120.4881
120.0559
110.0767
99.8474
83.3469
40.7839
39.5100
33.6560
OH
N
N
O
C18H14N2O2 (48)
13C NMR, DMSO-d6, 100 MHz
Chemical Shift (ppm)

2D.6 References

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The indole alkaloids are an important class of compounds from their fascinating structural topographies and remarkable bioactivities. Based on these points large amount of efforts towards the isolation, total synthesis and bioactivity studies of indole alkaloids have been devoted by the chemist's community worldwide. Many of them, such as reserpine, vincristine, vinblastine, arbidol and ergotamine, are used in medicine. Elegant reviews authoritatively summarizing the indole alkaloids chemistry have been published by many groups, Concise literature account on the synthesis of various indole alkaloids reported by different research groups using cyclic anhydrides and cyclic imides as potential synthons has been presented in chapter one. We have summarised the brief literature account on the isolation, bioactivity and diastereoselective/enantioselective total synthesis of all these natural products from the year 2000 to 2021. Overall total syntheses of all those alkaloids involving a large amount of new chemistry are strategically important and have been described herein with the help of eighteen schemes and nearly a seventy contemporary references from various reputed international chemistry journals. The chapter two of the present dissertation provides our contribution on the total synthesis of cordatanine, donaxaridine, donaxarine, methyl chaetoglinate A and acid/base induced 1/2/3-position coupling reactions of indole leading to structurally interesting indole-based products implementing conceptually new synthetic approaches mainly starting from cyclic anhydrides and cyclic imides.

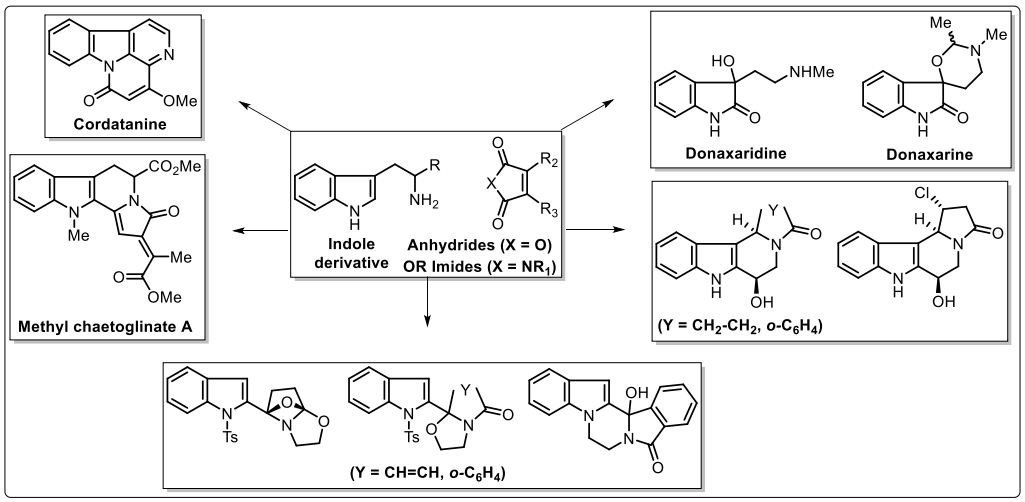
We have accomplished total synthesis of cordatanine starting from tryptamine and methoxymaleic anhydride via regioselective reduction of methoxymaleimide, acid-catalyzed intramolecular cyclization of the formed lactamol, in situ stepwise oxidations leading to aromatization and intramolecular cyclization with the exchange of N-regioselectivity. An attempted synthesis of regioisomeric natural product zanthochilone has been described in brief with reversal of reduction selectivity.

Facile regioselective oxidation of indoles to 2-oxindoles promoted by sulfuric acid adsorbed on silica gel is reported. The demonstrated practical site-selective heterogeneous oxidation reactions conveniently take place with a broad substrate scope and functional group tolerances. The present oxidation strategy is also employed to accomplish the total synthesis of natural products donaxaridine and donaxarine. On the basis of analytical and spectral data, it is evidenced that donaxarine stays in equilibrium with its hydrated ring-opened form. The structural features essential for this type of oxidation and plausible mechanism are discussed in brief.

Facile synthesis of methyl ester of chaetogline A is reported starting from the corresponding methyl 1-methyltryptophanate derived maleimide. A stereoselective Wittig olefination with a carbonyl function in methyl pyruvate followed by phosphorous pentoxide induced regioselective dehydrative cyclization are the essential reactions. The reactions of maleimide-based ylides with pyruvic acid stereoselectively formed the corresponding in situ decarboxylated thermodynamically more stable E-alkylidinesuccinimide. An acid-induced thermodynamically driven stereoselective β- to α-position migration of the exocyclic C=C bond unit in ethyl tetrahydroindolizinoindolylidenepropanoate is described.

Chemo-, regio- and diastereoselective coupling reactions of indole with imide derivatives leading to unique heterocyclic systems are demonstrated. Acid-induced 3-position coupling reactions of indole with cyclic imide derived lactamols followed by acid promoted 2-position cyclizations with the corresponding aldehydes are described to obtain the indolizinoindolones and benzoindolizinoindolone. Base induced 2-position coupling reactions of N-tosylindole with N-(2-iodoethyl)imides and the subsequent cyclization's provide indolylepoxypyrrolooxazole, indolylpyrrolooxazolone and indolyloxazoloisoindolone. Reductive cleavage of indolyloxazoloisoindolone to the corresponding alcohol followed by mesylation and base promoted N-cyclization affords the in situ air-oxidized pentacyclic product hydroxyisoindolopyrazinoindolone. Regioisomeric structural revision of the natural product from 1,2,5,6,7,11c-hexahydro-3H-indolizino(7,8-b)indol-3-one to 1,2,5,6,11,11b-hexahydro-3H-indolizino(8,7-b)indol-3-one is also reported in the present studies focussed on the methodologies for heterocyclic synthesis.

Overall, the present dissertation describes the multistep synthesis of cordatanine, donaxaridine, donaxarine, methyl ester of chaetogline A and structurally interesting important heterocyclic systems. The total synthesis of the above depicted all indole alkaloids was successfully accomplished using regioselective reduction, Pictet−Spengler cyclization, air-oxidation, regioselective oxidation, Wittig olefination, acid/base induced 1/2/3-position coupling reactions of indole, reductive cleavage of carbon-nitrogen bond and carbon-oxygen bond as the key reactions.



All these studies provided us an excellent opportunity for learning a lot of new fundamental and applied chemistry not just from our work but also from the vast literature in this field. We also feel that the approaches we have developed are quite general and useful in designing several important complex natural products and natural product hybrids for structure-activity relationship studies. A look at the recent literature also revealed that the histogram of the indole chemistry is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed indoles would maintain the high positive slope in the present-day world of medicinal and synthetic chemistry. In our opinion, a combination of natural and hybrid indole alkaloids would serve as a launching pad to fight against new generation diseases. In a broader prospective, one can state with a positive feel that lot of indole-based new drugs and agrochemicals will capture a highly demanding place in providing services to plant kingdom, animal kingdom, and human beings welfare. Finally, based on exposure to the literature of indole alkaloids chemistry and our contribution to the same, it can be said with assurance that this interesting discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry in the future.

ABSTRACT

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Title of the thesis: Cyclic Anhydrides and Imides to Indole Based Novel Natural and Unnatural Products

The indole alkaloids are an essential class of compounds from their fascinating structural topographies and remarkable bioactivities. Based on these points, many efforts towards the isolation, total synthesis and bioactivity studies of indole alkaloids have been devoted by the chemist's community worldwide. Chapter One includes the concise literature account on the synthesis of various indole alkaloids reported by different research groups using cyclic anhydrides and cyclic imides as potential synthons. We have summarised the brief literature on the isolation, bioactivity and diastereoselective/enantioselective total synthesis of all these natural products from the year 2000 to 2021.

Chapter two includes four sections (section A to D). Section A includes total synthesis of cordatanine via stepwise oxidations leading to aromatization and intramolecular cyclization with the exchange of *N*-regioselectivity. An attempted synthesis of regioisomeric natural product zanthochilone has been described in brief with reversal of reduction selectivity. In section B includes facile regioselective oxidation of indoles to 2-oxindoles promoted by sulfuric acid adsorbed on silica gel is described. The current oxidation strategy is also employed to accomplish the total synthesis of natural products donaxaridine and donaxarine. In section C includes the facile synthesis of methyl ester of chaetogline A via stereoselective Wittig olefination with a carbonyl function in methyl pyruvate followed by phosphorous pentoxide induced regioselective dehydrative cyclization are the essential reactions. An acid-induced thermodynamically driven stereoselective β- to α-position migration of the exocyclic C=C bond unit in ethyl tetrahydroindolizinoindolylidenepropanoate is described. Section D includes chemo-, regio- and diastereoselective coupling reactions of indole with imide derivatives leading to unique heterocyclic systems are demonstrated. Acid-induced 3-position coupling reactions of indole with cyclic imide-derived lactamols followed by acid-promoted 2-position cyclizations with the corresponding aldehydes are described to obtain the indolizinoindolones and benzoindolizinoindolone. The base induced 2-position coupling reactions of *N*-tosylindole with *N*-(2-iodoethyl)imides and the subsequent cyclization provide indolylepoxypyrrolooxazole indolylpyrrolooxazolone and indolyloxazoloisoindolone. Regioisomeric structural revision of the natural product from 1,2,5,6,7,11c-hexahydro-3*H*-indolizino(7,8-*b*)indol-3-one to 1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one is also reported.

Overall conclusion, starting from cyclic anhydrides and imides we have demonstrated the total synthesis of structurally interesting and biologically important indole based natural and unnatural products involving novel oxidation reactions.

List of Publications Emanating from the Thesis Work

1. Total Synthesis of Bioactive Canthine Alkaloid Cordatanine Comprising in Situ Double Oxidative Aromatization of Tetrahydrocarbazole
   Shelar, S. V.; Argade, N. P. ***ACS Omega* 2017, *2*, 3945−3950.**
   DOI: 10.1021/acsomega.7b00609

2. Regioselective Oxidation of Indoles to 2-Oxindoles
   Shelar, S. V.; Argade, N. P. ***Org. Biomol. Chem*. 2019, *17*, 6671–6677.**
   DOI: 10.1039/c9ob00764d

3. Wittig Reactions of Maleimide Derived Stabilized Ylides with Alkyl Pyruvates: Concise Approach to Methyl Ester of (±)-Chaetogline A
   Shelar, S. V.; Argade, N. P. ***Synthesis* 2021, *53*, 2897–2902.**
   DOI: 10.1055/a-1477-6043

4. Facile Synthesis of Indolizinoindolone, Indolylepoxypyrrolooxazole, Indolylpyrrolooxazolone and Isoindolopyrazinoindolone Heterocycles from Indole and Imide Derivatives
   Shelar, S. V.; Argade, N. P. ***Org. Biomol. Chem*. 2021, *19*, 6160–6169.**
   DOI: 10.1039/d1ob00754h

List of Posters Presentation with Details

1. Poster Presentation in 'National Science Day Celebrations 2018' held in CSIR-NCL Pune, India (February 25-27, **2018**)

   Tital: Total Synthesis of Bioactive Canthine Alkaloid Cordatanine Comprising in Situ Double Oxidative Aromatization of Tetrahydrocarbazole

   Abstract: Starting from tryptamine and methoxymaleic anhydride, concise and efficient total synthesis of cordatanine has been accomplished via regioselective reduction of methoxymaleimide, acid-catalyzed intramolecular cyclization of the formed lactamol, in situ stepwise oxidations leading to aromatization, and intramolecular cyclization with the exchange of *N*-regioselectivity. An attempted synthesis of regioisomeric natural product zanthochilone has been described in brief with reversal of reduction selectivity.

List of Conference Attended with Details

1. 17^{th} CRSI National Symposium in Chemistry 2015 held in CSIR-NCL Pune, India (February 2015)

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Total Synthesis of Bioactive Canthine Alkaloid Cordatanine Comprising in Situ Double Oxidative Aromatization of Tetrahydrocarbazole

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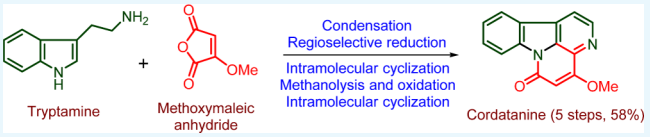
Supporting Information

ABSTRACT: Starting from tryptamine and methoxymaleic anhydride, concise and efficient total synthesis of cordatanine has been accomplished via regioselective reduction of methoxymaleimide, acid-catalyzed intramolecular cyclization of the formed lactamol, in situ stepwise oxidations leading to aromatization, and intramolecular cyclization with the exchange of N-regioselectivity. An attempted synthesis of regioisomeric natural product zanthochilone has been described in brief with reversal of reduction selectivity.



INTRODUCTION

Canthines are an important section of β-carboline alkaloids, and nearly 200 canthinone alkaloids exhibiting a broad range of potential bioactivities have been reported in the literature.[1,2] Pentralis (6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one) from Figure 1 was first isolated in 1952, and several strategically

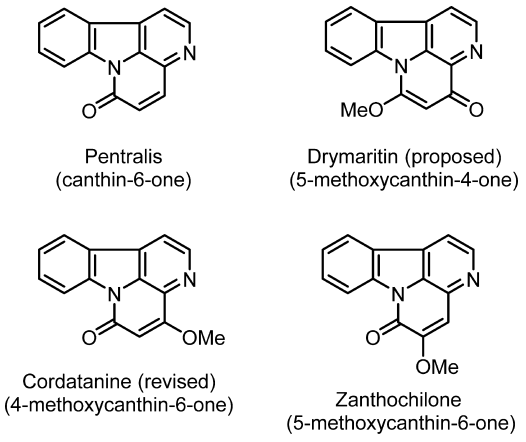


Figure 1. Representative bioactive canthin alkaloids.

elegant syntheses of this class of compounds are known in the contemporary literature.[1−7] The anti-human immunodeficiency virus alkaloid, cordatanine (4-methoxycanthin-6-one), was isolated from *Drymaria cordata* in 1986 and then from *Drymaria diandra* in 2004 (EC_{50} 0.699 μg/mL).[8−10] The antifungal alkaloid, zanthochilone (5-methoxycanthin-6-one), has been isolated from the plant species *Zanthoxylum chiloperone* var. *angustifolium*.[11,12] The total synthesis of cordatanine and zanthochilone is a challenging task and is of current interest due to their structural features, potential bioactivities, and the seasonal changes that affect their concentration in natural sources.[8−13] Recently, Wu et al. accomplished the synthesis of cordatanine in four steps with an 8% overall yield and unambiguously confirmed its revised structural assignment;[9,10,14] the synthesis of zanthochilone, however, is awaited. In continuation of our studies on the use of cyclic anhydrides to synthesize bioactive natural products,[15−19] we herein report a facile regioselective approach to cordatanine and attempted synthesis of zanthochilone from the readily available common precursors, tryptamine and methoxymaleic anhydride[20] (Schemes 1−4).

RESULTS AND DISCUSSION

A concise retrosynthetic analysis of regioisomeric natural products cordatanine and zanthochilone has been depicted in scheme 1, aiming at the synthesis of two regioisomeric pyrrolotetrahydrocarbazole intermediates, intramolecular exchange of nitrogen regioselectivity, and aromatization of ring C. The reaction of tryptamine (**1**) with the freshly prepared methoxymaleic anhydride (**2**)[20] in refluxing *o*-dichlorobenzene delivered the required methoxymaleimide **3** in 84% yield via regioselective ring opening of **2**, followed by the intramolecular dehydrative cyclization route (Scheme 2). Regioselective $NaBH_4$ reduction of more reactive mesomerically nonconjugated imide carbonyl in **3** exclusively formed the lactamol, **4a**, in 97% yield. In the above specified reaction, mesomeric conjugation of a lone pair of oxygen from the methoxyl group deactivates one of the carbonyl groups, and the sterically hindered carbonyl undergoes selective reduction. Lactamol **4a** was fairly stable to the silica gel column chromatographic purification and did not display any noticeable signs of associated decomposition. Acid-catalyzed intramolecular dehy-

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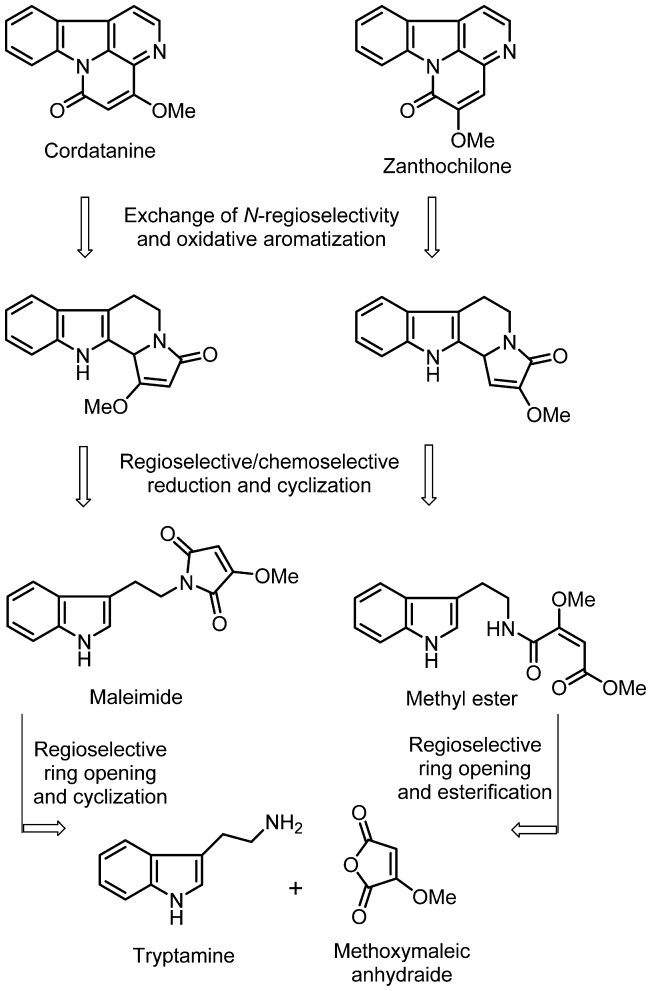
Scheme 1. Concise Retrosynthetic Analysis of Regioisomeric Cordatanine and Zanthochilone Alkaloids



drative cyclization of lactamol **4a** furnished the pyrrolotetrahydrocarbazole, **5**, in 87% yield. At this stage, it was planned to perform the methanolysis of pyrrolotetrahydrocarbazole **5**, followed by oxidative aromatization. Accordingly performed reaction of pyrrolotetrahydrocarbazole **5** with *p*-toluenesulfonic acid (*p*-TSA)/MeOH at room temperature under atmospheric conditions directly provided the completely aromatized ester, **9a**, in acceptable yields (~50%) in 24 h. In the above-mentioned reaction, both methanolysis of lactam to ester and double air-oxidative aromatization of the ring C took place in one pot. As expected, repetition of the same reaction under a balloon pressure oxygen atmosphere delivered product **9a** in 88% yield in just 4 h. Careful thin-layer chromatography monitoring of the above reaction also revealed that it would be feasible to isolate one of the reaction intermediates in the transformation of **5**−**9a**. Thus, the reaction of **5** with *p*-TSA/MeOH at room temperature under an oxygen atmosphere was arrested after 1 h, and we could successfully isolate the formed intermediate product, pyrrolotetrahydrocarbazole **6**, bearing a labile angular methoxyl group, in 47% yield. The anticancer drug, mitomycin C, contains such a type of angular oxygen function, which is responsible for its several-fold higher activity than the corresponding mitosanes.[21] Intermediate product **6** on similar treatment with *p*-TSA/MeOH at room temperature under an oxygen atmosphere also delivered the expected product, **9a**, in very good yield. Thus, we propose that mechanistically first the methoxyl group gets introduced at the highly reactive benzylic angular position of compound **5** via the radical mechanism to form product **6**, which on protonation followed by elimination of methanol forms the reactive iminium ion intermediate, **7**, which quickly undergoes methanolysis to deliver the corresponding dihydroester, **8**, and finally the formed ester, **8**, oxidizes in situ to yield the stable aromatic penultimate product, **9a**. An alternatively performed reaction of pyrrolotetrahydrocarbazole **5** with HCl/tetrahydrofuran (THF) at room temperature under an oxygen atmosphere plausibly followed a similar type of mechanistic pathway and also furnished the expected acid, **9b**, in 84% yield. Finally, both K_2CO_3/MeOH-catalyzed intramolecular cyclization of ester **9a** and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI)-induced intramolecular dehydrative cyclization of acid **9b** resulted in the desired natural product, cordatanine (**10**), in 93 and 84% yields, respectively. The obtained analytical and spectral data for cordatanine (**10**) were in complete agreement with the reported data.[9,10,14]

In the next part of the study, the synthesis of the second regioisomeric target compound, zanthochilone, was logically planned via reversal in regioselective reduction of methoxymaleimide **3**, and selected results on the reduction of imide **3** have been summarized in Table 1. Diisobutylaluminum hydride (DIBAL-H) reduction of imide **3** at −78 °C provided a silica gel column chromatographically separable mixture of lactamols **4a** (undesired) and **4b** (desired) in 72% yield but with only a 68:32 ratio (Scheme 3; Table 1, entry 5). We feel that in the reduction of imide **3**, a small amount of desired isomer **4b** is formed at a lower temperature due to the steric hindrance of

Scheme 2. Concise and Efficient Regioselective Total Synthesis of Cordatanine Involving Stepwise Oxidative Aromatization

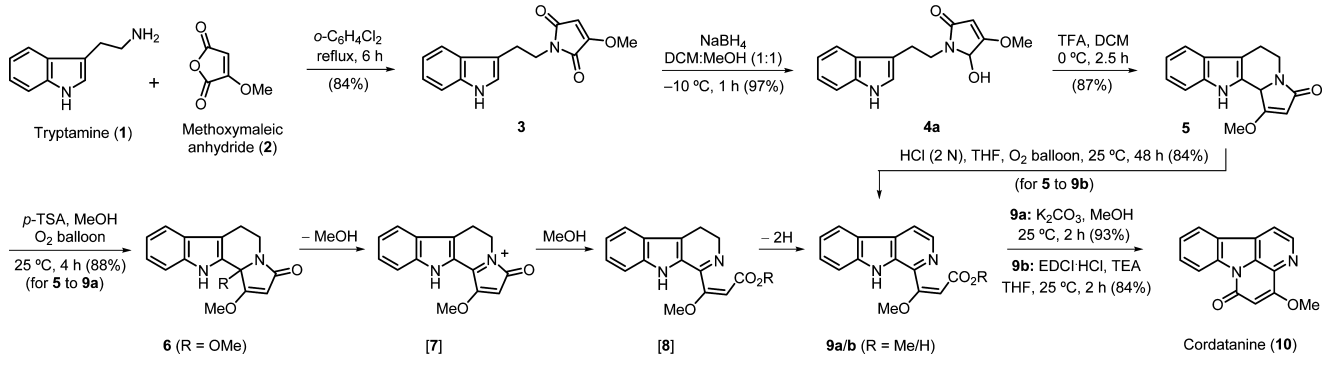


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Table 1. Study on Reversal of Regioselectivity in the Reduction of Methoxymaleimide

sr. no.	reduction conditions	yield (**4a**/**4b**)
1	$NaBH_4$ (5.00 equiv), DCM/MeOH (1:1), −10 °C, 1 h	97% (100:0)
2	KBH_4 (5.00 equiv), DCM/MeOH (1:1), −10 °C, 1 h	94% (100:0)
3	K-selectride (3.30 equiv), THF, −78 °C, 2 h	88% (95:5)
4	N-selectride (3.30 equiv), THF, −78 °C, 2 h	83% (94:6)
5	DIBAL-H (3.30 equiv), THF, −78 °C, 2.5 h	72% (68:32)
6	DIBAL-H (3.30 equiv), THF, −100 °C, 3 h	SM-PPT

the methoxyl group and could also be due to the partial decline in the mesomeric deactivation. Regioselective ring opening of methoxymaleic anhydride (**2**) with tryptamine (**1**) in diethyl ether formed maleamic acid **11** in 96% yield, which upon diazomethane esterification resulted in corresponding ester **12** in 83% yield (Scheme 4). The alternatively performed controlled chemoselective DIBAL-H reduction of ester **12** at −78 °C exclusively furnished the desired lactamol, **4b**, in 73% yield via the corresponding unisolable intermediate aldehyde, **13**. Acid-catalyzed intramolecular dehydrative cyclization of lactamol **4b** yielded the planned regioisomeric pyrrolotetrahydrocarbazole, **14**, in 86% yield. Accordingly performed reaction of pyrrolotetrahydrocarbazole **14** with *p*-TSA/MeOH at room temperature under a balloon pressure oxygen atmosphere delivered acid **16** in 79% yield but without the aromatization of ring C. We presume that in pyrrolotetrahydrocarbazole **14**, hydrolysis of γ-lactam to form acid **16** was preferred over the methanolysis for steric reasons. In acid **16**, conjugation of the methoxyl group with a labile imine moiety could be the cause for the deactivation of the system, which plausibly prohibited in situ oxidative aromatization of ring C. Remarkably, the propensity of oxidation of ring C is dependent on the reactivity of the imine moiety and the position of the methoxyl group. All attempts to transform acid **16** to zanthochilone (**17**) via diazomethane esterification, EDCI-mediated intramolecular dehydrative cyclization, and 1,2-dichloro 4,5-dicyanoquinone/Pd(C)-oxidation of ring C met with failure and ended up in excessive decompositions of the reaction mixtures.

CONCLUSIONS

In summary, practical total synthesis of cordatanine has been accomplished by taking advantage of facile oxygen-promoted stepwise oxidative aromatization. The synthesis of two regioisomeric methoxyl-substituted pyrrolotetrahydrocarbazoles from methoxymaleimide and methyl ester of methoxymaleamic acid is noteworthy. Unfortunately, we were unable to complete the first total synthesis of isomeric zanthochilone alkaloid due to the decomposition of the product of the penultimate step under the sets of our reaction conditions.

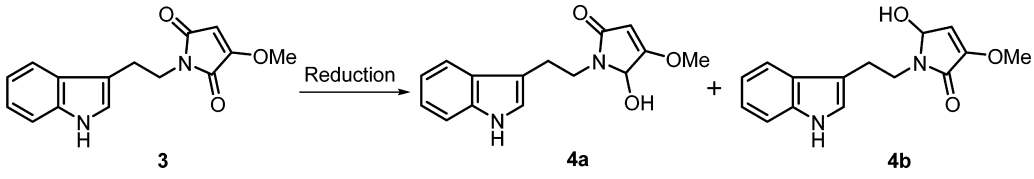
EXPERIMENTAL SECTION

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR, and 500 MHz NMR spectrometers using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on 400 NMR (100 MHz) and 500 NMR (125 MHz) spectrometers. Mass spectra were taken on a mass spectrometry time-of-flight (MS-TOF) mass spectrometer. High-resolution MS (HRMS) (electrospray ionization (ESI)) were taken on the Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on a Fourier transform infrared spectrometer. Column chromatographic separations were carried out on silica gel (60−120 and 230−400 mesh). Commercially available starting materials and reagents were used.

*1-[2-(1H-Indol-3-yl)ethyl]-3-methoxy-1H-pyrrole-2,5-dione (**3**).* A stirred solution of tryptamine (**1**; 2.00 g, 12.48 mmol) and methoxymaleic anhydride (**2**; 1.60 g, 12.48 mmol) in *o*-dichlorobenzene (20 mL) was heated at reflux for 6 h. After cooling the reaction mixture, it was loaded on a silica gel (60−120 mesh) column, and initially the column was eluted with petroleum ether for the removal of *o*-dichlorobenzene and then it was eluted with ethyl acetate−petroleum ether mixture (3:7) to obtain pure methoxymaleimide **3** as a yellow crystalline solid (2.83 g, 84%). Mp 126−128 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.07 (t, *J* = 8.0 Hz, 2H), 3.83 (t, *J* = 8.0 Hz, 2H), 3.90 (s, 3H), 5.37 (s, 1H), 7.06 (d, *J* = 2.2 Hz, 1H), 7.14 (t, *J* = 7.1 Hz, 1H), 7.20 (t, *J* = 7.1 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 8.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.4, 38.1, 58.8, 96.1, 111.1, 112.2, 118.8, 119.4, 122.0, 122.1, 127.4, 136.2, 160.9, 165.6, 170.1; ESIMS (*m*/*z*) 293 [M + Na]$^+$; HRMS (ESI) calcd for $C_{15}H_{14}O_3N_2Na$, 293.0897; found, 293.0894; IR ($CHCl_3$) ν_{max} 3385, 1714, 1643 cm^{-1}.

*1-[2-(1H-Indol-3-yl)ethyl]-5-hydroxy-4-methoxy-1,5-dihydro-2H-pyrrol-2-one (**4a**).* To a stirred solution of compound **3** (2.00 g, 7.40 mmol) in MeOH/CH_2Cl_2 (1:1, 20 mL) was added $NaBH_4$ (840 mg, 22.22 mmol) at −10 °C. The reaction mixture was stirred for 1 h at the same temperature, and the reaction was quenched with saturated aq NH_4Cl (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (8:2) as an eluent afforded lactamol **4a** as a colorless solid (1.95 g, 97%). Mp 58−60 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.02 (t, *J* = 7.3 Hz, 2H), 3.45−3.65 (m, 1H), 3.69 (s, 3H), 3.75−3.95 (m, 1H), 3.95−4.10 (br s, 1H), 4.91 (s, 1H), 5.06 (d, *J* = 5.9 Hz, 1H), 6.96 (s, 1H), 7.08 (t, *J* = 8.5 Hz, 1H), 7.17 (t, *J* = 9.5 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 8.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.4, 39.4, 58.3, 81.0, 93.2, 111.2, 112.9, 118.7, 119.3, 121.9, 122.0, 127.3, 136.2, 170.7, 173.8; ESIMS (*m*/*z*) 295 [M +

Scheme 3. Regioselective Reduction of Methoxymaleimide



3 4a 4b

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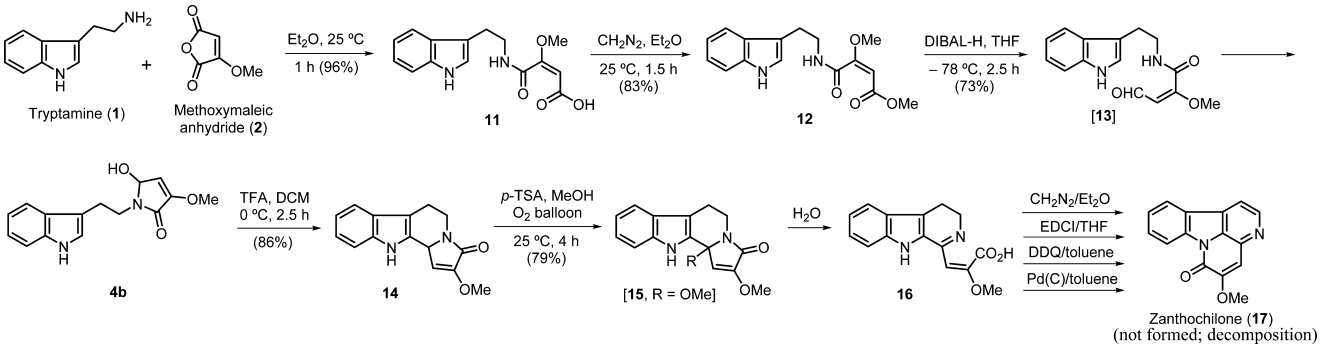
Scheme 4. Attempted Regioselective Synthesis of Zanthochilone Involving Reversal in Reduction Selectivity



Na]$^+$; HRMS (ESI) calcd for $C_{15}H_{16}O_3N_2Na$, 295.1053; found, 295.1052; IR ($CHCl_3$) ν_{max} 3620, 3477, 1676, 1641 cm^{-1}.

*1-Methoxy-5,6,11,11b-tetrahydro-3H-indolizino(8,7-b)-indol-3-one (**5**).* To a stirred solution of lactamol **4a** (1.50 g, 5.51 mmol) in CH_2Cl_2 (20 mL), trifluoroacetic acid was added dropwise (0.84 mL, 11.02 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2.5 h. The reaction was quenched with saturated aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (7:3) as an eluent afforded product **5** as a faint yellow solid (1.21 g, 87%). Mp 140−142 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.70−3.00 (m, 2H), 3.03−3.23 (m, 1H), 3.89 (s, 3H), 4.64 (dd, J = 13.2 and 5.1 Hz, 1H), 5.12 (s, 1H), 5.25 (s, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 8.3 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 8.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 37.3, 56.8, 58.7, 94.4, 109.2, 111.0, 118.7, 119.8, 122.5, 126.6, 128.0, 136.3, 172.3, 174.2; ESIMS (m/z) 255 [M + H]$^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_2N_2$, 255.1128; found, 255.1125; IR ($CHCl_3$) ν_{max} 3408, 1651, 1603 cm^{-1}.

*1,11b-Dimethoxy-5,6,11,11b-tetrahydro-3H-indolizino-(8,7-b)indol-3-one (**6**).* To a stirred solution of compound **5** (300 mg, 1.18 mmol) in MeOH (20 mL) was added *p*-TSA (1.01 g, 5.90 mmol) at 25 °C under an oxygen atmosphere. The reaction mixture was stirred for 1 h, and the reaction was quenched with saturated aq $NaHCO_3$ (5 mL). MeOH was removed in vacuo, and the residue was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (6:4) as an eluent afforded product **6** as a colorless solid (157 mg, 47%). Mp 80−82 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.78 (dd, J = 15.6 and 4.4 Hz, 1H), 2.83−2.95 (m, 1H), 3.15−3.28 (m, 1H), 3.28 (s, 3H), 3.93 (s, 3H), 4.50 (dd, J = 13.2 and 5.4 Hz, 1H), 5.16 (s, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2, 35.5, 50.7, 58.8, 86.6, 95.0, 111.4, 111.7, 119.4, 119.9, 123.3, 125.9, 128.6, 136.4, 171.2, 172.7; ESIMS (m/z) 285 [M + H]$^+$; HRMS (ESI) calcd for $C_{16}H_{17}O_3N_2$, 285.1234; found, 285.1231; IR ($CHCl_3$) ν_{max} 3408, 1731, 1602 cm^{-1}.

*Methyl (E)-3-Methoxy-3-[9H-pyrido(3,4-b)indol-1-yl]-acrylate (**9a**).* To a stirred solution of compound **5** (300 mg, 1.18 mmol) in MeOH (20 mL) was added *p*-TSA (1.01 g, 5.90 mmol) at 25 °C under an oxygen atmosphere. The reaction mixture was stirred for 4 h, and the reaction was quenched with saturated aq $NaHCO_3$ (5 mL). MeOH was removed in vacuo, and the residue was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (7:3) as an eluent provided product **9a** as a thick yellow oil (293 mg, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.54 (s, 3H), 3.93 (s, 3H), 5.58 (s, 1H), 7.29 (t, J = 6.5 Hz, 1H), 7.45−7.60 (m, 2H), 7.99 (s, 1H), 8.10 (d, J = 7.3 Hz, 1H), 8.47 (s, 1H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.4, 56.8, 95.4, 111.8, 115.8, 120.3, 121.3, 121.7, 128.9, 130.4, 133.9, 136.3, 137.8, 140.7, 165.6, 167.1; ESIMS (m/z) 283 [M + H]$^+$; HRMS (ESI) calcd for $C_{16}H_{15}O_3N_2$, 283.1077; found, 283.1070; IR ($CHCl_3$) ν_{max} 3432, 1722, 1602 cm^{-1}.

*(E)-3-Methoxy-3-[9H-pyrido(3,4-b)indol-1-yl]acrylic Acid (**9b**).* To a stirred solution of compound **5** (300 mg, 1.18 mmol) in THF (5 mL) was added dilute HCl (2 N, 5 mL) at 25 °C under an oxygen atmosphere. The reaction mixture was stirred for 48 h, and the precipitated solid was filtered, washed with ethyl acetate (10 mL), and vacuum dried to obtain acid **9b** as a yellow solid (265 mg, 84%). Mp 128−132 °C, ^{1}H NMR (CD_3OD, 500 MHz) δ 4.11 (s, 3H), 6.05 (s, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.50 (d, J = 6.1 Hz, 1H), 8.75 (d, J = 6.1 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 58.9, 101.3, 114.0, 119.0, 121.2, 123.5, 124.5, 130.0, 132.4, 133.9, 134.9, 137.3, 146.1, 160.5, 168.5; ESIMS (m/z) 269 [M + H]$^+$; HRMS (ESI) calcd for $C_{15}H_{13}O_3N_2$, 269.0921; found, 269.0915; IR ($CHCl_3$) ν_{max} 3425, 1738, 1599 cm^{-1}.

*4-Methoxy-6H-indolo(3,2,1-de)(1,5)naphthyridin-6-one (**10**). Method A.* To a stirred solution of ester **9a** (200 mg, 0.71 mmol) in MeOH (10 mL) was added K_2CO_3 (196 mg, 1.41 mmol) at 25 °C, and the reaction mixture was stirred for 2 h. Methanol was removed in vacuo, and the residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:1) as an eluent afforded cordatanine (**10**) as a yellow solid (165 mg, 93%).

Method B. To a stirred solution of carboxylic acid **9b** (200 mg, 0.746 mmol) in THF (10 mL) was added EDCI·HCl (314

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mg, 1.64 mmol), 4-(dimethylamino) pyridine (9 mg, 0.074 mmol), and Et_3N (0.350 mL, 2.46 mmol) at 25 °C, and the reaction mixture was stirred for 2 h. The reaction was quenched with water (2 mL), and reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (1:1) as an eluent afforded cordatanine (**10**) as a yellow solid (156 mg, 84%). Mp 182−183 °C (lit.[9] mp 181−183 °C), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (s, 3H), 6.13 (s, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.93 (d, J = 4.9 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 8.57 (d, J = 8.3 Hz, 1H), 8.78 (d, J = 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.9, 101.8, 116.9 (2C), 122.6, 124.3, 125.0, 130.5, 131.0, 131.96, 132.03, 139.3, 145.1, 160.9, 164.1; ESIMS (m/z) 251 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{11}O_2N_2$, 251.0815; found, 251.0811; IR ($CHCl_3$) ν_{max} 1662, 1649, 1620 cm^{-1}.

*(E)-4-{[2-(1H-Indol-3-yl)ethyl]amino}-3-methoxy-4-oxobut-2-enoic Acid (**11**).* To a stirred solution of methoxymaleic anhydride (**2**; 2.40 g, 18.72 mmol) in Et_2O (30 mL) was added tryptamine (**1**; 3.00 g, 18.72 mmol) at 25 °C, and the reaction mixture was stirred for 1 h. The precipitated product was filtered, washed with Et_2O (25 mL), and dried under vacuum to obtain carboxylic acid **11** as a colorless solid (5.184 g, 96%). Mp 170−172 °C, ^{1}H NMR (CD_3OD, 400 MHz) δ 3.01 (t, J = 7.3 Hz, 2H), 3.58 (t, J = 7.3 Hz, 2H), 3.72 (s, 3H), 5.39 (s, 1H), 7.00 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 7.09 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 25.9, 41.9, 57.1, 100.4, 112.4, 112.7, 113.1, 119.4, 119.7, 122.5, 123.7, 128.9, 138.3, 161.3, 166.0; ESIMS (m/z) 289 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}O_4N_2$, 289.1183; found, 289.1178; IR ($CHCl_3$) ν_{max} 3369, 3281, 1701, 1623, 1600 cm^{-1}.

*Methyl (E)-4-{[2-(1H-Indol-3-yl)ethyl]amino}-3-methoxy-4-oxobut-2-enoate (**12**).* To a stirred solution of acid **11** (1.00 g, 3.47 mmol) in Et_2O and methanol (1:1, 20 mL) was added a solution of diazomethane in Et_2O at 25 °C until persistence of a yellow color. The reaction mixture was stirred for 1.5 h and concentrated in vacuo. The obtained residue was extracted with ethyl acetate (3 × 20 mL), and the combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (6:4) as an eluent afforded ester **12** as a gum (870 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (t, J = 7.3 Hz, 2H), 3.66 (s, 3H), 3.71 (t, J = 7.9 Hz, 2H), 3.74 (s, 3H), 5.21 (s, 1H), 6.66 (br s, 1H), 7.07 (s, 1H), 7.12 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.21 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.9, 29.8, 51.8, 56.3, 94.9, 111.2, 112.7, 118.7, 119.4, 122.1, 122.2, 127.3, 136.4, 161.5, 162.3, 166.8; ESIMS (m/z) 303 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{19}O_4N_2$, 303.1339; found, 303.1335; IR ($CHCl_3$) ν_{max} 3422, 1714, 1618 cm^{-1}.

*1-[2-(1H-Indol-3-yl)ethyl]-5-hydroxy-3-methoxy-1,5-dihydro-2H-pyrrol-2-one (**4b**).* To a stirred solution of ester **12** (500 mg, 1.66 mmol) in THF (10 mL), DIBAL-H was added dropwise (1 M in cyclohexane, 5.50 mL) at −78 °C under an argon atmosphere, and the reaction mixture was stirred for 2.5 h. The reaction was quenched with saturated potassium sodium tartrate (5 mL), stirred for 1 h, and concentrated in vacuo. The obtained residue was extracted with ethyl acetate (3 × 20 mL), and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230−400 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (7:3) as an eluent afforded alcohol **4b** as a colorless solid (329 mg, 73%). Mp 70−72 °C, ^{1}H NMR (acetone-d_6, 400 MHz) δ 2.95−3.15 (m, 2H), 3.50−3.60 (m, 1H), 3.71 (s, 3H), 3.75−3.85 (m, 1H), 4.97 (d, J = 9.8 Hz, 1H), 5.35 (d, J = 9.5 Hz, 1H), 5.69 (s, 1H), 7.02 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 7.18 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 10.02 (br s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 25.2, 40.8, 57.6, 80.2, 108.5, 112.3, 113.2, 119.4, 119.5, 122.2, 123.3, 128.6, 137.8, 154.1, 164.5; ESIMS (m/z) 273 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}O_3N_2$, 273.1234; found, 273.1229; IR ($CHCl_3$) ν_{max} 3621, 3374, 1704, 1599 cm^{-1}.

*2-Methoxy-5,6,11,11b-tetrahydro-3H-indolizino(8,7-b)-indol-3-one (**14**).* To a stirred solution of alcohol **4b** (300 mg, 1.10 mmol) in CH_2Cl_2 (10 mL), trifluoroacetic acid was added dropwise (0.17 mL, 2.20 mmol) at 0 °C, and the reaction mixture was stirred for 2.5 h. The reaction was quenched with saturated aq $NaHCO_3$ (3 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (6:4) as an eluent afforded product **14** as a faint brown solid (240 mg, 86%). Mp 136−138 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55−2.75 (m, 2H), 3.00−3.13 (m, 1H), 3.57 (s, 3H), 4.45 (dd, J = 13.1 and 5.5 Hz, 1H), 5.11 (s, 1H), 6.03 (s, 1H), 6.86 (t, J = 7.3 Hz, 1H), 6.95 (t, J = 7.9 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 10.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 38.0, 53.8, 56.7, 106.3, 107.0, 110.6, 117.9, 118.7, 121.3, 126.1, 130.9, 136.0, 151.6, 165.0; ESIMS (m/z) 255 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_2N_2$, 255.1128; found, 255.1124; IR ($CHCl_3$) ν_{max} 3421, 1735, 1597 cm^{-1}.

*(E)-3-[4,9-Dihydro-3H-pyrido(3,4-b)indol-1-yl]-2-methoxyacrylic Acid (**16**).* To a stirred solution of compound **14** (200 mg, 0.78 mmol) in MeOH (20 mL) was added *p*-TSA (677 mg, 3.93 mmol) at 25 °C under an oxygen atmosphere. The reaction mixture was stirred for 4 h, and the reaction was quenched with saturated aq $NaHCO_3$ (3 mL). MeOH was removed in vacuo, and the residue was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (7:3) as an eluent provided acid **16** as a yellow solid (168 mg, 79%). Mp 140−142 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.11 (t, J = 7.9 Hz, 2H), 3.70−3.80 (m, 2H), 3.89 (s, 3H), 6.65 (s, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 8.54 (br s, 1H), 10.73 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 40.4, 52.7, 87.0, 112.1, 118.3, 120.1, 120.9, 125.7, 125.9, 126.5, 138.0, 154.8, 164.8, 176.3; ESIMS (m/z) 271 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_3N_2$, 271.1077; found, 271.1081; IR ($CHCl_3$) ν_{max} 3422, 1738, 1597 cm^{-1}.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00609.

^{1}H NMR, ^{13}C NMR, and distortionless enhancement by polarization transfer spectra of all compounds (PDF)

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†S.V.S. did the complete experimental work.

Author Contributions

The manuscript was written through contribution of both authors.

Notes

The authors declare no competing financial interest.

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Regioselective oxidation of indoles to 2-oxindoles†

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Facile regioselective oxidation of indoles to 2-oxindoles promoted by sulfuric acid adsorbed on silica gel is reported. The demonstrated practical site-selective heterogeneous oxidation reactions conveniently take place with a broad substrate scope and functional group tolerances. The present oxidation strategy is also employed to accomplish the total synthesis of natural products donaxaridine and donaxarine. On the basis of analytical and spectral data it is evidenced that donaxarine stays in equilibrium with its hydrated ring opened form. The structural features essential for this type of oxidation and plausible mechanism are discussed in brief.

Introduction

The 2-oxindole moiety is present in a large number of bioactive natural and unnatural products, clinically used drugs and drug intermediates (Fig. 1).[1] Regioselective oxidations of indoles to 2-oxindoles and 3-oxindoles have been very important reactions from the synthetic organic chemistry point of view.[2] Several elegant inorganic, organic and bioorganic reagents for the oxidation reactions of indoles to 2-oxindoles have been reported in earlier and contemporary literature and a few selected methods have been depicted in Scheme 1.[3] Application of an appropriate oxidizing reagent and the development of suitable reaction conditions for smooth transformation of a variety of indoles to the corresponding 2-oxindole derivatives are challenging tasks from the point of view of the reactivity and overall stability of the formed products.[1–3] As a continuation of our studies on the total synthesis of recently isolated bioactive natural products,[4] we attempted the intramolecular cyclization of one of the indole bearing compounds facilitated by the adsorption of concentrated sulfuric acid on silica gel and observed the unexpected effective formation of the corresponding 2-oxindole derivative. In this context we herein report the simple and efficient sulfuric acid promoted regioselective oxidation of indoles to 2-oxindoles and its application in the synthesis of natural products (Tables 1 and 2; Schemes 2 and 3).

Results and discussion

The reaction of indole (**1a**, 1.00 g) with concentrated sulfuric acid adsorbed on silica gel (60–120 mesh, 1.00 g) in dichloromethane at 25 °C was monitored by TLC. The above specified reaction at the end of ten hours selectively furnished the corresponding pure 2-oxindole (**2a**) in 78% yield (Table 1; entry 1). However, the same reaction in 1,2-dichoroethane as a solvent was slow and furnished 2-oxindole (**2a**) only in 62% yield (Table 1, entry 2). The change of silica gel mesh size to

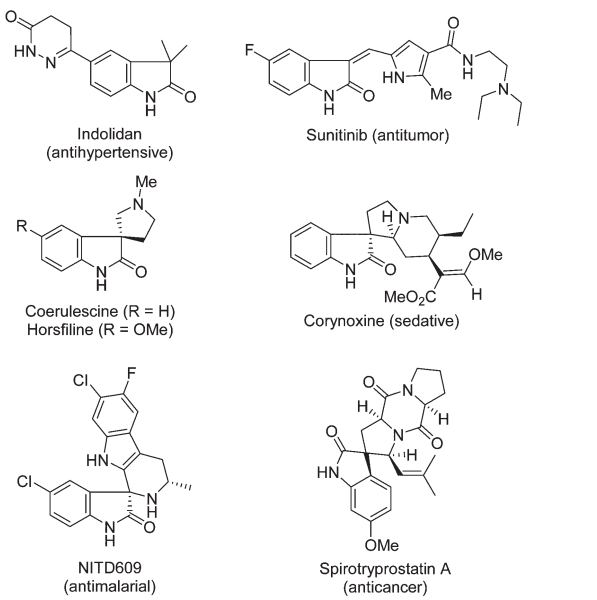

Fig. 1 Representative drugs and natural products containing a 2-oxindole moiety.[1]

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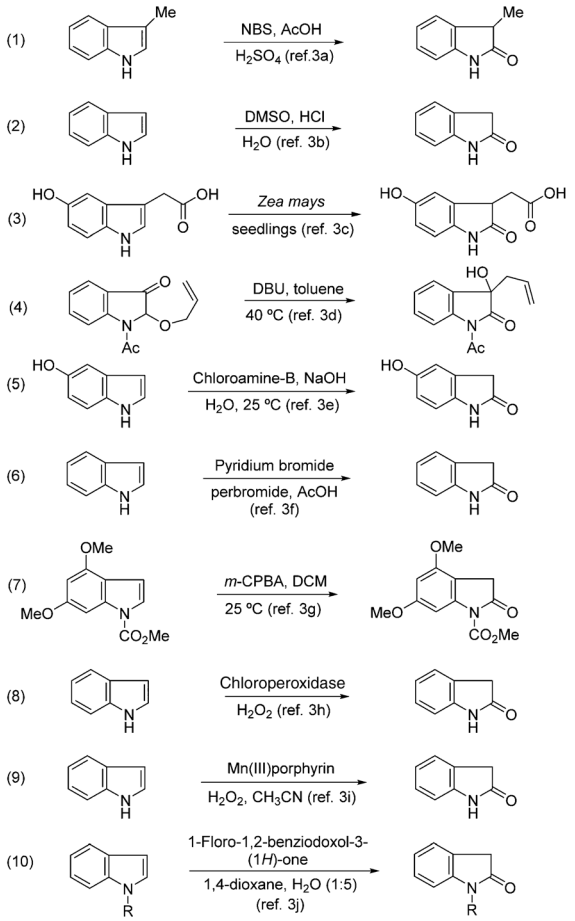
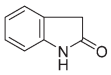
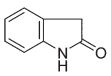
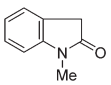
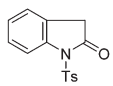
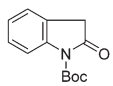
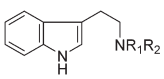
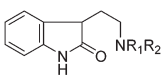


Scheme 1 Selected chemical and biomimetic oxidation reactions of indoles to 2-oxindoles.

Table 1 Study of the regioselective oxidation of indole derivatives facilitated by the adsorption of H_2SO_4 on SiO_2

Entry	Starting materials **1a–h**	Reaction conditions[a,b]	Products **2a–h** (% yield)
1	 **1a**	H_2SO_4 on SiO_2 DCM, 25 °C, 10 h	 **2a** (78%)
2	 **1a**	H_2SO_4 on SiO_2 $ClCH_2CH_2Cl$, 25 °C, 18 h	 **2a** (62%)
3	 **1b**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **2b** (not formed)[c]
4	 **1c**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **2c** (not formed)[c]
5	 **1d**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **2d** (not obtained)[d]
6	 **1e** (R_1 = R_2 = H) **1f** (R_1 = H, R_2 = Me) **1g** (R_1 = R_2 = Me) **1h** (R_1 = H, R_2 = CH_2Ph)	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **2e-h** (not formed)[c]

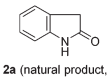
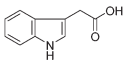
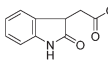
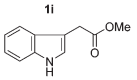
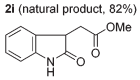
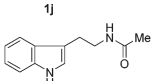
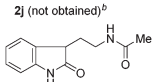
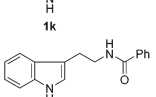
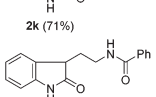
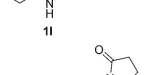
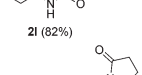
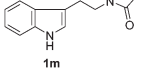
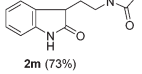
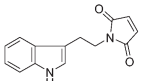
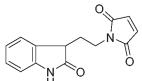
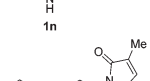
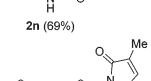
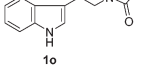
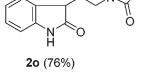
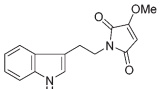
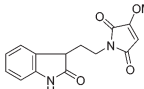
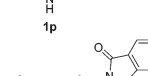
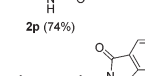
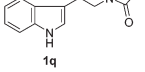
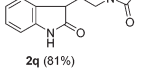
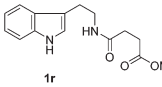
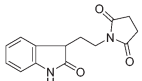
[a] One mL of conc. H_2SO_4 was adsorbed on ten grams of SiO_2 (60–120 mesh) and used in weight : weight ratio for all starting materials. [b] Monitored by TLC. [c] Starting material recovered. [d] Decomposition.

100–200 and 230–400 mesh for the adsorption of sulfuric acid and repetition of the same reaction in dichloromethane did not show any noticeable changes in the reaction time and yield. The recycling and reuse of the recovered sulfuric acid adsorbed on the silica gel reagent slowed down the rate of the oxidation reaction due to nearly 35% loss of sulfuric acid (by weight and NaOH titration) during first use. In a control experiment, the direct reaction of indole (**1a**) with concentrated sulfuric acid in dichloromethane resulted in complete decomposition. The substrates *N*-methylindole (**1b**) and *N*-tosylindole (**1c**) on treatment with H_2SO_4 adsorbed on SiO_2 remained unreacted and the expected 2-oxindole products **2b** and **2c** were not formed, indicating that the presence of the hydrogen atom on the indole nitrogen is necessary for the progression of oxidation (Table 1, entries 3 and 4). The reaction of *N*-Boc protected indole **1d** with H_2SO_4 adsorbed on SiO_2 resulted in the complete decomposition of the reaction mixture mostly *via* the acid catalyzed Boc-deprotection route (Table 1, entry 5). The indole-based amines **1e–h** on reaction with H_2SO_4 adsorbed on SiO_2 also remained completely unreacted possibly due to the formation of the corresponding salts by protonation of free amine groups (Table 1, entry 6).

On the basis of the results summarized in Table 1, a plausible reaction mechanism of the oxidation of indole (**1a**) to oxindole (**2a**) driven by the adsorption of H_2SO_4 on SiO_2 is illustrated in Scheme 2. Mechanistically, the indole (**1a**) dissolved in dichloromethane penetrates into the SiO_2 cavities and complexes with adsorbed H_2SO_4 through hydrogen bonding to form intermediate **A**. Intermediate **A** captures the proton *via* the delocalization of the nitrogen lone pair to form the iminium salt **B**. Addition of oxyanions to the formed reactive iminium double bond in a concerted/stepwise fashion results in another intermediate **C** with an overall addition of sulfuric acid across the carbon–carbon double bond in an indole moiety. Finally, oxidation of indole to 2-oxindole takes place *via* the reductive elimination of sulfurous acid (HO-SO-OH) involving the hexavalent to tetravalent state transformation of sulfur. Overall the oxidant is sulfuric acid and it gets converted into unstable sulfurous acid, which in the presence of dissolved oxygen transforms back to sulfuric acid and also partly degrades into sulfur dioxide.

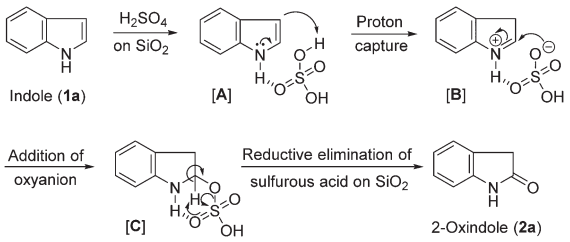
At this stage we decided to systematically study the substrate scope, functional group tolerance and application of the present indole to 2-oxindole transformation protocol for the

Table 2 Regioselective oxidation of indoles to 2-oxindoles induced by the adsorption of H_2SO_4 on SiO_2

Entry	Starting materials **1a,i–u**	Reaction conditions[a]	Products **2a,i–q,t,u** (% yield)
1	 **1a**	H_2SO_4 on SiO_2 DCM, 25 °C, 10 h	 **2a** (natural product, 78%)
2	 **1i**	H_2SO_4 on SiO_2 DCM, 25 °C, 16 h	 **2i** (natural product, 82%)
3	 **1j**	H_2SO_4 on SiO_2 DCM, 25 °C, 8 h	 **2j** (not obtained)[b]
4	 **1k**	H_2SO_4 on SiO_2 DCM, 25 °C, 18 h	 **2k** (71%)
5	 **1l**	H_2SO_4 on SiO_2 DCM, 25 °C, 12 h	 **2l** (82%)
6	 **1m**	H_2SO_4 on SiO_2 DCM, 25 °C, 16 h	 **2m** (73%)
7	 **1n**	H_2SO_4 on SiO_2 DCM, 25 °C, 14 h	 **2n** (69%)
8	 **1o**	H_2SO_4 on SiO_2 DCM, 25 °C, 16 h	 **2o** (76%)
9	 **1p**	H_2SO_4 on SiO_2 DCM, 25 °C, 20 h	 **2p** (74%)
10	 **1q**	H_2SO_4 on SiO_2 DCM, 25 °C, 18 h	 **2q** (81%)
11	 **1r**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **2m** (63%)
12	 **1s**	H_2SO_4 on SiO_2 DCM, 25 °C, 24 h	 **2n** (68%)
13	 **1t**	H_2SO_4 on SiO_2 DCM, 25 °C, 12 h	 **2t** (78%)
14	 **1u**	H_2SO_4 on SiO_2 DCM, 25 °C, 15 h	 **2u** (82%)

[a] Monitored by TLC. [b] Decomposition.

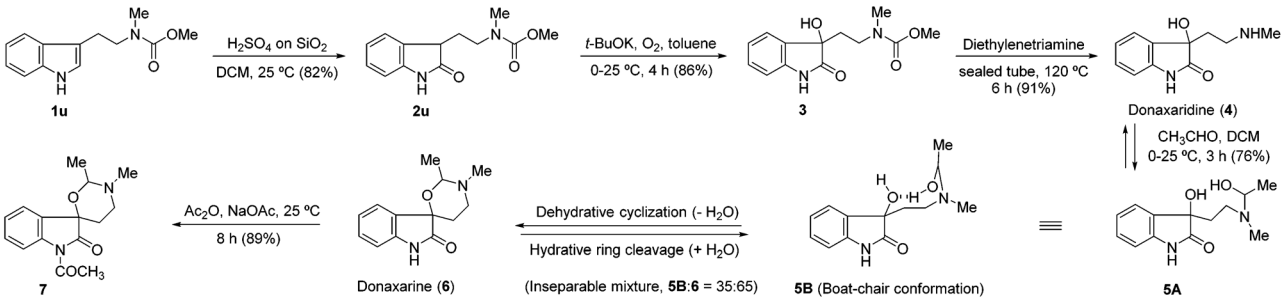
synthesis of unnatural and natural products (Table 2, Scheme 3). The indole-3-acetic acid (**1i**) on treatment with H_2SO_4 adsorbed on SiO_2 underwent facile oxidation and afforded the desired natural product 2-oxindole-3-acetic acid



Scheme 2 Plausible mechanism of the regioselective oxidation of indole to 2-oxindole induced by the adsorption of H_2SO_4 on SiO_2.

(**2i**) (isolated from *Zea mays* seedlings)[5] in quantitative yield (Table 2, entry 2), which was not very stable to column chromatographic purifications due to associated stability and polarity issues. Therefore the formed product was quickly filtered through a silica gel column using DCM–MeOH as an eluent to obtain the very expensive pure acid **2i** in 82% yield. The analytical and spectral data obtained for 2-oxindole-3-acetic acid (**2i**) were in complete agreement with the reported data.[5,6] 2-Oxindole-3-acetic acid (**2i**) on treatment with diazomethane afforded the corresponding ester **2j** in 94% yield. However, the methyl indole-3-acetate (**1j**) on reaction with H_2SO_4 adsorbed on SiO_2 resulted in the formation of a complex mixture and did not provide the expected methyl 2-oxindole-3-acetate (**2j**) (Table 2, entry 3). Amide bearing indoles **1k** and **1l** on reaction with H_2SO_4 adsorbed on SiO_2 provided the corresponding 2-oxindoles **2k** and **2l** in 71% and 82% yields, respectively (Table 2, entries 4 and 5). The cyclic imide bearing indoles **1m–q** on reaction with H_2SO_4 adsorbed on SiO_2 also delivered the desired 2-oxindoles **2m–q** in 69–81% yields (Table 2, entries 6–10). Amic ester bearing indoles **1r** and **1s** on reaction with H_2SO_4 adsorbed on SiO_2 directly furnished the corresponding cyclic imides bearing 2-oxindoles **2m** and **2n** in 63% and 68% yields, respectively, *via in situ* intramolecular cyclization followed by the oxidation pathway (Table 2, entries 11 and 12). Carbamate bearing indoles **1t** and **1u** on reaction with H_2SO_4 adsorbed on SiO_2 delivered the corresponding 2-oxindoles **2t** and **2u** in 78% and 82% yields, respectively (Table 2, entries 13 and 14). The results summarized in Table 2 clearly revealed that the present oxidation reactions are compatible with carboxylic acid, amide, cyclic imide and carbamate functional groups. On the basis of the obtained results we believe that the sulfuric acid adsorbed on silica gel reagent will be quite compatible with several other non-amine substituents and functional groups bearing substrates.

The natural products donaxaridine (**4**) and donaxarine (**6**) were isolated from *Arundo donax* in 1976.[7] To date five different total syntheses of donaxaridine (**4**) have been accomplished by employing several elegant strategies.[8] The total synthesis of natural products **4** and **6** was planned starting from the obtained carbamate bearing 2-oxindole **2u** as a potential precursor (Table 2, entry 14; Scheme 3). Compound **2u** on reaction with molecular oxygen in the presence of *t*-BuOK underwent smooth benzylic hydroxylation and delivered the desired product **3** in 86% yield.[9] The cleavage of carbamate in com-



Scheme 3 Stepwise oxidations of the indole moiety leading to the facile synthesis of donaxaridine and donaxarine.

pound **3** with TBAF in THF or 2 N HCl in methanol under reflux conditions was not successful and the starting material remained unreacted. However, diethylenetriamine assisted carbamate cleavage[10] of compound **3** in a sealed tube at 120 °C furnished the desired donaxaridine (**4**) in 91% yield. The analytical and spectral data obtained for donaxaridine (**4**) were in complete agreement with the reported data.[7,8] Donaxaridine (**4**) on treatment with acetaldehyde in $CH_2Cl_2/CHCl_3$ at 25 °C/reflux conditions always resulted in a mixture of geminal-aminohydrin intermediate **5B** and the natural product donaxarine (**6**) in 76% yield. As expected TLC of the reaction mixture revealed that donaxarine (**6**) has a higher R_f-value and geminal-aminohydrin intermediate **5B** has a lower R_f-value than the starting material donaxaridine (**4**). All our attempts to separate the above specified mixture of products by using silica gel column chromatography and also by using HPLC were unsuccessful and always resulted in an inseparable mixture of products **5B** and **6** in 35 : 65 ratio (by ^{1}H NMR). Therefore on the basis of analytical and spectral data it is demonstrated that donaxarine (**6**) always stays in equilibrium with its hydrated ring opened form **5B**. Plausibly the formed geminal-aminohydrin intermediate **5B** is stabilized by the depicted intramolecular hydrogen bonding in an 8-membered boat–chair conformation[11] and the mixture of compounds **5B** and **6** is an example of a delicately balanced stability-driven hydration–dehydration equilibrium. Finally, the mixture of compounds **5B** and **6** on reaction with Ac_2O/NaOAc exclusively afforded the *N*-acyl derivative **7** of donaxarine (**6**) in 89% yield.

Conclusions

In summary, we have demonstrated a new simple and efficient method for regioselective oxidation of indoles to 2-oxindoles using sulfuric acid adsorbed on silica gel as a reagent. This will be useful for the synthesis of a broad range of the desired bioactive natural and unnatural oxindoles. A plausible mechanism has been proposed and the presence of free protons on the indole nitrogen atom is essential for the formation of a complex with sulfuric acid. The present practical oxidation reaction induced by the heterogeneous reagent suitably addresses the product stability concerns and functional group tolerance issues. We also believe that the present protocol has scale-up potential and will be useful for large-scale production of several oxindole derivatives of commercial interest.

Experimental section

General description

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz) and 500 NMR (125 MHz) spectrometers. Mass spectra were recorded on a MS-TOF mass spectrometer. HRMS (ESI) was performed using an Orbitrap (quadrupole plus ion trap) and a TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 mesh) and (230–400 mesh). Commercially available indole, tryptamine, indole-3-acetic acid, *t*-BuOK, sulfuric acid, diethylenetriamine, acetaldehyde, acetic anhydride and sodium acetate were used.

Preparation of sulfuric acid adsorbed on silica gel

A solution of concentrated sulfuric acid (1.00 mL) in acetone (10 mL) was added to a suspension of silica gel (10.00 g, 60–120 mesh) in acetone (15 mL) under vigorous stirring at room temperature. After 1 h acetone was removed using a rotary evaporator *in vacuo* and the obtained residue was dried by using a vacuum pump. A free-flowing powder of sulfuric acid adsorbed on silica gel was obtained in a quantitative yield (12.87 g). The quantitative loading of sulfuric acid on silica gel was checked by weight and also by sodium hydroxide titration.

General procedure for the oxidation of indoles to 2-oxindoles

To a stirred solution of indole (1.00 g) in CH_2Cl_2 (20 mL) was added sulfuric acid adsorbed on silica gel (1.00 g) at 25 °C and the reaction was monitored by TLC. The reaction mixture was filtered and the filtrate was washed with saturated aq. $NaHCO_3$ (10 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using ethyl acetate–petroleum ether as an eluent provided the desired 2-oxindole.

Indolin-2-one (2a). According to the general procedure and by using ethyl acetate–petroleum ether (0.5 : 9.5) as an eluent, **2a** was obtained as a brown solid (886 mg, 78%). Mp 128–130 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 2H), 6.90 (dd, J = 8.2 and 1.0 Hz, 1H), 7.02 (td, J = 7.7 and 1.0 Hz, 1H), 7.17–7.30 (m, 2H), 8.73 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.3, 109.8, 122.3, 124.6, 125.3, 127.9, 142.5, 178.0; ESIMS (m/z) 156 $[M + Na]^+$; HRMS (ESI) calcd for C_8H_7ONNa 156.0420, found 156.0417; IR ($CHCl_3$)ν_{max} 3174, 1732, 1687, 1617 cm^{-1}.

2-(2-Oxoindolin-3-yl)acetic acid (2i). According to the general procedure and by using methanol–dichloromethane (0.5 : 9.5) as an eluent, **2i** was obtained as a white crystalline solid (179 mg, 82%). Mp 140–142 °C, ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.69 (dd, J = 17.0 and 7.0 Hz, 1H), 2.90 (dd, J = 17.3 and 4.2 Hz, 1H), 3.50–3.70 (m, 1H), 6.81 (d, J = 7.3 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 7.05–7.30 (m, 2H), 10.38 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 34.0, 41.8, 109.2, 121.2, 123.7, 127.8, 129.4, 142.9, 172.3, 178.3; ESIMS (m/z) 214 $[M + Na]^+$; HRMS (ESI) calcd for $C_{10}H_9O_3NNa$ 214.0475, found 214.0474; IR (Nujol)ν_{max} 3362, 2800–2700, 1710 cm^{-1}.

***N*-[2-(2-Oxoindolin-3-yl)ethyl]acetamide (2k).** According to the general procedure and by using ethyl acetate–petroleum ether (4 : 6) as an eluent, **2k** was obtained as a yellow solid (77 mg, 71%). Mp 130–132 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95 (s, 3H), 2.02–2.11 (m, 1H), 2.20–2.29 (m, 1H), 3.42–3.55 (m, 3H), 6.42 (br s, 1H), 6.90 (d, J = 7.7 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 8.65 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.2, 30.0, 37.2, 44.4, 109.8, 122.7, 124.2, 128.2, 129.2, 141.1, 170.5, 180.3; ESIMS (m/z) 241 $[M + Na]^+$; HRMS (ESI) calcd for $C_{12}H_{14}O_2N_2Na$ 241.0947, found 241.0943; IR ($CHCl_3$)ν_{max} 3301, 3012, 1710, 1650 cm^{-1}.

***N*-[2-(2-Oxoindolin-3-yl)ethyl]benzamide (2l).** According to the general procedure and by using ethyl acetate–petroleum ether (1 : 1) as an eluent, **2l** was obtained as a brown solid (174 mg, 82%). Mp 178–180 °C, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.97 (br s, 1H), 2.13 (br s, 1H), 3.40–3.60 (m, 3H), 6.84 (d, J = 6.0 Hz, 1H), 6.97 (br s, 1H), 7.18 (br s, 1H), 7.35 (d, J = 5.4 Hz, 1H), 7.45 (br s, 2H), 7.50 (d, J = 5.3 Hz, 1H), 7.83 (d, J = 5.3 Hz, 2H), 8.56 (br s, 1H), 10.42 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 30.1, 36.6, 43.3, 109.3, 121.3, 124.2, 127.2, 127.7, 128.2, 129.5, 131.1, 134.5, 142.6, 166.2, 178.9; ESIMS (m/z) 281 $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}O_2N_2$ 281.1285, found 281.1280; IR ($CHCl_3$)ν_{max} 3346, 2944, 1711, 1638 cm^{-1}.

1-[2-(2-Oxoindolin-3-yl)ethyl]pyrrolidine-2,5-dione (2m). According to the general procedure and by using ethyl acetate–petroleum ether (4 : 6) as an eluent, **2m** was obtained as a yellow solid (117 mg, 73%). Mp 152–154 °C, ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.56–2.03 (m, 1H), 2.03–2.25 (m, 1H), 2.50 (s, 4H), 3.03–3.65 (m, 3H), 6.82 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 10.40 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 27.2, 27.9, 35.2, 43.1, 109.3, 121.3, 123.9, 127.8, 129.0, 142.7, 177.5, 178.3; ESIMS (m/z) 259 $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_{15}O_3N_2$ 259.1077, found 259.1074; IR (Nujol)ν_{max} 3272, 1714, 1612 cm^{-1}.

1-[2-(2-Oxoindolin-3-yl)ethyl]-1*H*-pyrrole-2,5-dione (2n). According to the general procedure and by using ethyl acetate–petroleum ether (4 : 6) as an eluent, **2n** was obtained as a yellow solid (184 mg, 69%). Mp 124–126 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20–2.35 (m, 1H), 2.35–2.50 (m, 1H), 3.52 (br s, 1H), 3.57–3.71 (m, 1H), 3.71–3.85 (m, 1H), 6.56 (s, 2H), 6.89 (d, J = 7.3 Hz, 1H), 7.02 (t, J = 6.7 Hz, 1H), 7.19 (t, J = 6.7 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.1, 34.8, 43.8, 110.0, 122.5, 124.0, 128.1, 128.5, 133.9, 141.5, 170.5, 179.3; ESIMS (m/z) 279 $[M + Na]^+$; HRMS (ESI) calcd for $C_{14}H_{12}O_3N_2Na$ 279.0740, found 279.0736; IR (Nujol)ν_{max} 3382, 1712 cm^{-1}.

3-Methyl-1-[2-(2-oxoindolin-3-yl)ethyl]-1*H*-pyrrole-2,5-dione (2o). According to the general procedure and by using ethyl acetate–petroleum ether (1 : 1) as an eluent, **2o** was obtained as a yellow solid (161 mg, 76%). Mp 132–134 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.98 (d, J = 1.8 Hz, 3H), 2.15–2.55 (m, 2H), 3.51 (t, J = 5.3 Hz, 1H), 3.55–3.85 (m, 2H), 6.18 (q, J = 1.9 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 7.01 (td, J = 7.5 and 1.0 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 8.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.8, 28.3, 34.9, 43.8, 109.9, 122.4, 124.0, 127.1, 128.0, 128.6, 141.4, 145.4, 170.6, 171.5, 179.1; ESIMS (m/z) 271 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_3N_2$ 271.1077, found 271.1074; IR ($CHCl_3$)ν_{max} 3282, 1708, 1625 cm^{-1}.

3-Methoxy-1-[2-(2-oxoindolin-3-yl)ethyl]-1*H*-pyrrole-2,5-dione (2p). According to the general procedure and by using ethyl acetate–petroleum ether (4 : 6) as an eluent, **2p** was obtained as a white solid (78 mg, 74%). Mp 166–168 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.90–2.02 (m, 1H), 2.07–2.18 (m, 1H), 3.35–3.55 (m, 3H), 3.84 (s, 3H), 5.75 (s, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 10.39 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.2, 34.2, 43.0, 59.1, 96.9, 109.4, 121.3, 123.8, 127.7, 128.9, 142.6, 160.8, 165.1, 170.1, 178.2; ESIMS (m/z) 287 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{15}O_4N_2$ 287.1026, found 287.1024; IR ($CHCl_3$)ν_{max} 3422, 1721, 1676 cm^{-1}.

2-[2-(2-Oxoindolin-3-yl)ethyl]isoindoline-1,3-dione (2q). According to the general procedure and by using ethyl acetate–petroleum ether (3 : 7) as an eluent, **2q** was obtained as a brown solid (256 mg, 81%). Mp 190–192 °C, ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.02–2.15 (m, 1H), 2.20–2.32 (m, 1H), 3.52 (t, J = 6.9 Hz, 1H), 3.55–3.67 (m, 1H), 3.67–3.80 (m, 1H), 6.79 (d, J = 9.9 Hz, 1H), 6.86 (t, J = 9.2 Hz, 1H), 7.10 (t, J = 9.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.79 (br s, 4H), 10.40 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 28.0, 34.7, 43.2, 109.3, 121.2, 122.9, 123.8, 127.6, 128.9, 131.7, 134.2, 142.7, 167.7, 178.3; ESIMS (m/z) 307 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{15}O_3N_2$ 307.1077, found 307.1073; IR (Nujol)ν_{max} 3380, 1712 cm^{-1}.

Methyl [2-(2-oxoindolin-3-yl)ethyl]carbamate (2t). According to the general procedure and by using ethyl acetate–petroleum ether (3 : 7) as an eluent, **2t** was obtained as a gummy solid (418 mg, 78%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.73–1.90 (m, 1H), 1.90–2.05 (m, 1H), 3.03–3.23 (m, 2H), 3.37 (s, 3H), 3.30–3.45 (m, 1H), 6.82 (d, J = 9.2 Hz, 1H), 6.95 (t, J = 9.3 Hz, 1H), 7.17 (t, J = 9.2 Hz, 1H), 7.23 (br s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 10.39 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 30.6,

37.6, 42.9, 51.3, 109.3, 121.3, 124.1, 127.7, 129.5, 142.6, 156.7, 178.8; ESIMS (*m*/*z*) 257 [M + Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{14}O_3N_2Na$ 257.0897, found 257.0892; IR (Nujol)ν_{max} 3375, 3141, 1699, 1616 cm^{-1}.

Methyl methyl[2-(2-oxoindolin-3-yl)ethyl]carbamate (2u). According to the general procedure and by using ethyl acetate–petroleum ether (4 : 6) as an eluent, **2u** was obtained as a gummy solid (418 mg, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) (rotameric mixture) δ 2.07–2.30 (m, 2H), 2.89 (s, 3H), 3.27–3.39 (m, 1.50H), 3.47 (t, J = 6.1 Hz, 1H), 3.55–3.72 (m, 3.50H), 6.85–6.95 (m, 1H), 7.00–7.08 (m, 1H), 7.15–7.42 (m, 2H), 8.70–9.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.3, 34.0, 34.6, 43.6, 45.5, 46.2, 52.6, 109.7, 122.37, 122.44, 123.9, 124.1, 124.3, 128.0, 128.1, 129.2, 141.66, 141.71, 156.9, 157.0, 179.8, 180.1; ESIMS (*m*/*z*) 271 [M + Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_3N_2Na$ 271.1053, found 271.1047; IR ($CHCl_3$)ν_{max} 3255, 3012, 2927, 1699, 1618 cm^{-1}.

Methyl 2-(2-oxoindolin-3-yl)acetate (2j). A solution of diazomethane in Et_2O was added to a stirred solution of acid **2i** (150 mg, 0.785 mmol) in methanol (5 mL) until the persistence of a yellow colour. The reaction mixture was stirred at 25 °C for 1 h and concentrated *in vacuo*. The obtained residue was dissolved in ethyl acetate (10 mL) and the organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using methanol–dichloromethane (0.2 : 9.8) as an eluent afforded ester **2j** as a white crystalline solid (151 mg, 94%). Mp 170–172 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.84 (dd, J = 16.8 and 8.0 Hz, 1H), 3.10 (dd, J = 17.0 and 4.2 Hz, 1H), 3.71 (s, 3H), 3.83 (dd, J = 8.0 and 4.6 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.20–7.25 (m, 2H), 8.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.6, 42.3, 52.0, 109.9, 122.5, 124.1, 128.3, 128.7, 141.5, 171.5, 179.1; ESIMS (*m*/*z*) 228 [M + Na]$^+$; HRMS (ESI) calcd for $C_{11}H_{11}O_3NNa$ 228.0631, found 228.0627; IR ($CHCl_3$)ν_{max} 3427, 1706, 1615 cm^{-1}.

Methyl [2-(3-hydroxy-2-oxoindolin-3-yl)ethyl](methyl)carbamate (3). To a stirred solution of compound **2u** (500 mg, 2.01 mmol) in dry toluene (10 mL) was added *t*-BuOK (453 mg, 4.03 mmol) at 0 °C under an oxygen atmosphere. The reaction mixture was stirred from 0 °C to 25 °C for 4 h and the reaction was quenched with saturated aqueous NH_4Cl solution (2 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using methanol–dichloromethane (0.3 : 9.7) as an eluent afforded product **3** as a gummy solid (457 mg, 86%). ^{1}H NMR (DMSO-d_6, 400 MHz) (rotameric mixture) δ 1.95 (s, 2H), 2.70 (s, 3H), 3.17 (s, 2H), 3.40–3.60 (m, 3H), 5.98 (s, 1H), 6.81 (d, J = 7.3 Hz, 1H), 6.97 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 6.7 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.5, 33.9, 35.0, 35.4, 43.1, 43.5, 52.2, 74.1, 109.7, 121.7, 123.9, 129.1, 131.7, 141.6, 155.7, 178.8; ESIMS (*m*/*z*) 287 [M + Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_4N_2Na$ 287.1002, found 287.0996; IR ($CHCl_3$)ν_{max} 3259, 1716, 1676, 1621 cm^{-1}.

3-Hydroxy-3-[2-(methylamino)ethyl]indolin-2-one (Donaxaridine, 4). To a 10 mL sealed tube equipped with a magnetic stirring bar were added compound **3** (200 mg, 0.76 mmol) and diethylenetriamine (0.33 mL, 3.04 mmol) and the tube was sealed with a Teflon-lined screw cap. The tube was heated at 120 °C for 6 h. The crude reaction mixture was directly purified by silica gel (230–400 mesh) column chromatography by using ethyl acetate–petroleum ether (6 : 4) as an eluent to afford product **4** as a white solid (160 mg, 91%). Mp 174–176 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (td, J = 13.0 and 9.2 Hz, 1H), 2.76 (ddd, J = 12.8, 6.3 and 1.6 Hz, 1H), 2.97 (s, 3H), 3.23–3.30 (m, 1H), 3.35 (td, J = 9.4 and 1.1 Hz, 1H), 4.40–4.90 (br s, 2H), 6.70 (t, J = 7.2 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.88 (dd, J = 8.0 and 1.2 Hz, 1H), 7.12 (td, J = 8.2 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.2, 32.9, 45.7, 79.4, 118.1, 118.4, 125.2, 125.7, 129.2, 145.8, 175.2; ESIMS (*m*/*z*) 207 [M + H]$^+$; HRMS (ESI) calcd for $C_{11}H_{15}O_2N_2$ 207.1128, found 207.1125; IR (Nujol)ν_{max} 3350, 1708 cm^{-1}.

2′,3′-Dimethylspiro[indoline-3,6′-(1,3)oxazinan]-2-one (Donaxarine, 6). To a solution of compound **4** (150 mg, 0.728 mmol) in dichloromethane (10 mL) was added acetaldehyde (50 μL, 0.788 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred from 0 °C to 25 °C for 3 h and the reaction mixture was concentrated *in vacuo*. The direct silica gel (60–120 mesh) column chromatographic purification of the resulting residue by using ethyl acetate–petroleum ether (1 : 1) as an eluent furnished an equilibrium mixture of natural product donaxarine (**6**) and its *gem*-aminohydrin precursor **5B** as a white solid (128 mg, 76%). Mp 176–182 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) [equilibrium mixture of the natural product donaxarine (**6**) and its precursor **5B** in a 65 : 35 ratio] δ 1.39 (d, J = 5.4 Hz, 1.95H), 1.51 (d, J = 5.4 Hz, 1.05 H), 2.38–2.57 (m, 2H), 2.97 (s, 1.95 H), 3.02 (s, 1.05 H), 3.42–3.49 (m, 1H), 3.55–3.65 (m, 1H), 4.08 (br s, 1H), 4.76 (quintet, J = 6.1 Hz, 0.35 H), 5.53 (q, J = 6.1 Hz, 0.65 H), 6.71 (d, J = 6.9 Hz, 0.65 H), 6.82 (d, J = 8.4 Hz, 0.35 H), 6.80–6.95 (m, 2H), 7.08–7.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 21.0, 30.3, 30.5, 35.5, 36.1, 45.8, 46.1, 76.5, 79.8, 81.5, 117.3, 118.7, 120.0, 120.9, 123.8, 125.2, 125.3, 128.0, 128.1, 141.4, 143.0, 172.8, 174.0; ESIMS (*m*/*z*) 255 [M + Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_2N_2Na$ 255.1104, found 255.1098; IR ($CHCl_3$)ν_{max} 3293, 2933, 1684, 1606 cm^{-1}.

1-Acetyl-2′,3′-dimethylspiro[indoline-3,6′-[1,3]oxazinan]-2-one (7). To a solution of the above mixture of the natural product donaxarine (**6**) and its precursor **5B** (50 mg, 0.216 mmol) in acetic anhydride (4 mL) was added sodium acetate (53 mg, 0.862 mmol) and the reaction mixture was stirred at 25 °C for 8 h. The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (10 mL) and washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the residue by using ethyl acetate–petroleum ether (3 : 7) as an eluent afforded product **7** as a white solid (52 mg, 89%). Mp

204–206 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (d, J = 6.5 Hz, 3H), 2.25 (s, 3H), 2.40 (quintet, J = 7.3 Hz, 1H), 2.74 (quintet, J = 6.9 Hz, 1H), 2.88 (s, 3H), 3.43–3.50 (m, 1H), 3.57–3.64 (m, 1H), 6.32 (q, J = 6.5 Hz, 1H), 7.17–7.30 (m, 3H), 7.37 (t, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 23.1, 30.4, 32.9, 46.0, 77.7, 78.5, 123.6, 125.7, 126.3, 128.5, 132.3, 136.2, 170.4, 171.4; ESIMS (m/z) 275 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{19}O_3N_2$ 275.1390, found 275.1389; IR ($CHCl_3$)ν_{max} 1693, 1662 cm^{-1}.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Synthesis S. V. Shelar, N. P. Argade Paper

Wittig Reactions of Maleimide-Derived Stabilized Ylides with Alkyl Pyruvates: Concise Approach to Methyl Ester of (±)-Chaetogline A

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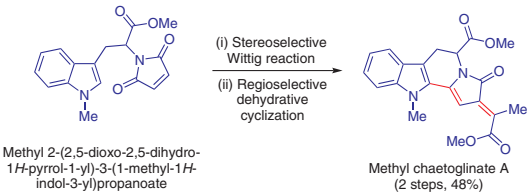

Methyl 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-3-(1-methyl-1*H*-indol-3-yl)propanoate

Methyl chaetoglinate A (2 steps, 48%)

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Abstract A facile synthesis of methyl ester of chaetogline A is reported starting from the corresponding methyl 1-methyltryptophanate-derived maleimide. A stereoselective Wittig olefination with a carbonyl function in methyl pyruvate followed by phosphorous pentoxide-induced regioselective dehydrative cyclization are the essential reactions. An acid-induced thermodynamically driven stereoselective β- to α-position migration of the exocyclic C=C bond unit in ethyl tetrahydroindolizinoindolylidenepropanoate is described.

Key words natural product, chaetogline A, amino acid, maleimide, methyl pyruvate, Wittig reaction, dehydrative cyclization

The structurally fascinating and biologically imperative indole alkaloids have been frequent synthetic targets due to their well-provided multipurpose practical applications.[1–4] The structurally unprecedented indole alkaloids chaetoglines A–H, desmethylchaetogline A, and desmethylchaetogline F were obtained from *Chaetomium globosum* 1C51 fungus motivated biotransformations between 1-methyl-L-tryptophan and flavipin (3,4,5-trihydroxy-6-methylphthaldehyde) (Figure 1).[5,6] It is proposed that the Schiff base formed from above specified amine and aldehyde undergoes Pictet–Spengler cyclization to initially generate chaetogline E, which upon oxidative cleavage of aromatic ring from the phthalide part yields chaetogline A.[6] Chaetogline alkaloids are of significance from a biomedicine and agrochemical point of view. More specifically, (–)-chaetogline A and (–)-19-*O*-desmethylchaetogline A inhibit the crop pathogenic microbes *Sclerotinia sclerotiorum* and *Xanthomonas oryzae*.[6–9] Starting from the methyl ester of 1-methyl-L-tryptophan and a suitably substituted hydroxyphthalide, an elegant biogenetic type collective total synthesis of chaetoglines C–F have been recently reported by Lei and co-workers.[10] However, the syntheses of all other chaetogline alkaloids are still not reported. In continuation of our studies on the transformation of cyclic anhydrides/imides to bioactive natural products,[11–13] we planned for the total synthesis of chaetogline A and 19-*O*-desmethylchaetogline A. A concise retrosynthetic analysis of methyl chaetoglinate A is described in Scheme 1. The maleimide obtained from methyl ester of 1-methyltryptophan on stereoselective trialkylphosphine-induced Wittig reaction with methyl pyruvate followed by regioselective reductive-cyclization, or dehydrative-cyclization would constitute an easy access to the chaetogline A framework.

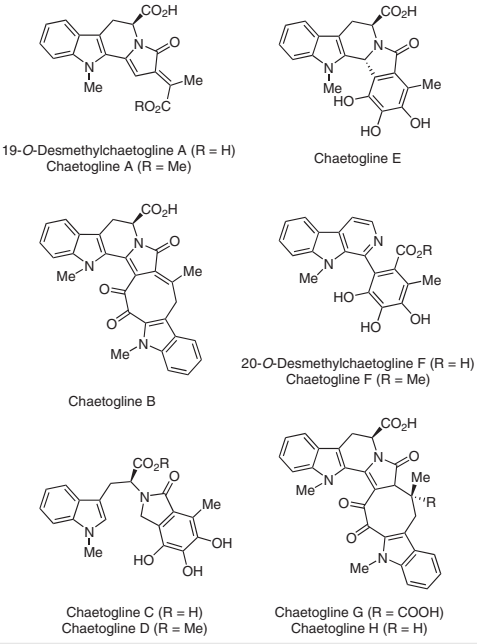
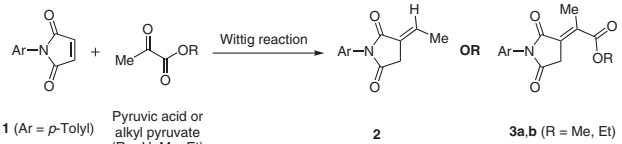


Figure 1 Chaetogline alkaloids derived from methyl tryptophan and flavipin by using fungus *Chaetomium globosum* 1C51

Accordingly, we herein report the synthesis of the methyl ester of chaetogline A (Schemes 1 to 3). Maleimide- and citraconimide-derived, in situ generated stabilized phosphorous ylides react with aliphatic and aromatic aldehydes and furnish the corresponding thermodynamically more stable Wittig products (*E*)-alkylidinesuccinimides in high yields.[14–16] A few Wittig olefination reactions of related ylides with ketones are also known.[16–18] To the best of our knowledge, Wittig reaction of above-mentioned ylides with an activated carbonyl moiety in alkyl pyruvate is not reported to date. Therefore, systematic studies on the above-specified reaction are essential from a practical application point of view. In this context, we planned to introduce a suitably substituted exocyclic C=C bond in a target compound by using the reaction of maleimide-derived stabilized ylide with methyl pyruvate. Initially studied reactions of maleimide **1** based ylides with pyruvic acid stereoselectively formed the corresponding in situ decarboxylated thermodynamically more stable *E*-alkylidinesuccinimide **2** in 48% and 57% yield, respectively (Table 1, entries 1 and 2). The *E*-configuration in product **2** was established on the basis ^{1}H NMR data. The vinylic proton in product **2** appeared downfield due to the *peri*-interaction with an imide carbonyl group. Finally, it was confirmed by comparison with an authentic sample, which was directly synthesized from the reaction of maleimide-derived Wittig reagent with acetaldehyde.[14,15] It is important to note that in these reactions, the conjugated acid intermediates undergo decarboxylation at room temperature, specifically under neutral reaction conditions. The Wittig reactions of above-mentioned ylides with methyl pyruvate and ethyl pyruvate were cleanly achievable. They stereoselectively provided the corresponding *E*-alkylidinesuccinimides products **3a** and **3b** in 81% to 91% yield, respectively (entries 3 to 6).

At first, the synthesis of a model system was planned from tryptamine-derived maleimide **4**. A ylide derived from maleimide **4** and tributylphosphine on reaction with ethyl pyruvate exclusively delivered the corresponding *E*-alkylidenesuccinimide **5** in 86% yield (Scheme 2). The Wittig reaction was performed in EtOH:DCM (3:1) instead of acetone for solubility issues. Reduction of imide **5** with $NaBH_4$:$CeCl_3$ was not regioselective and resulted in a mixture of unisolable lactamols **6a** and **6b** (by TLC). The above-specified reaction mixture on treatment with trifluoroacetic acid for 2 hours provided column chromatographically separable Pictet–Spengler cyclization products **7a** and **7b** in

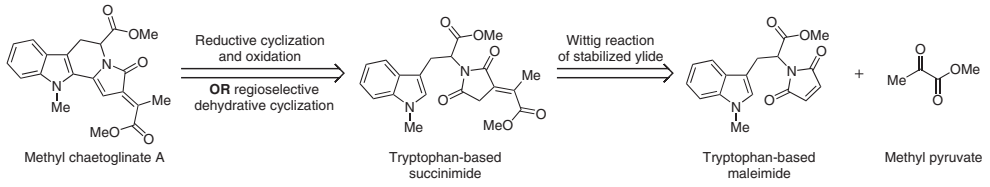
Table 1 Wittig Reactions of Maleimide-Derived Stabilized Ylides with Pyruvic Acid and Alkyl Pyruvates



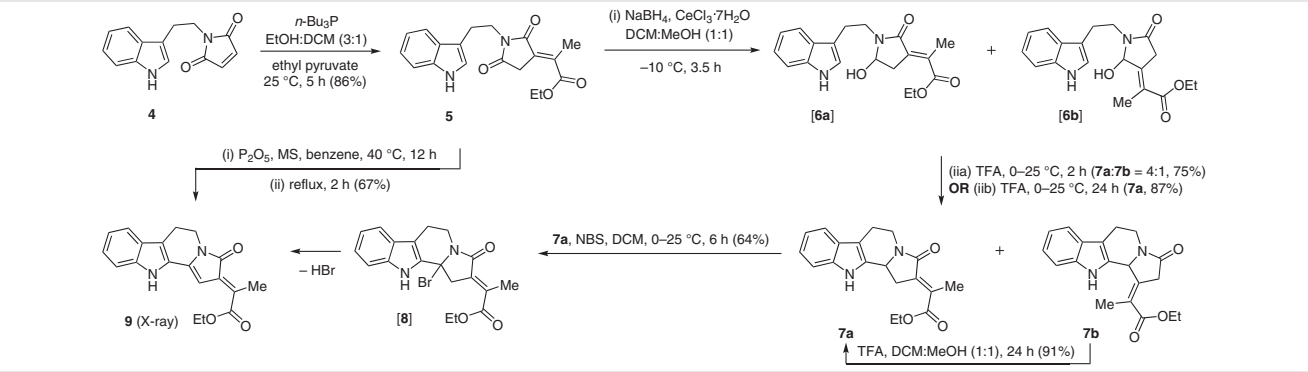
1 (Ar = *p*-Tolyl) Pyruvic acid or alkyl pyruvate (R = H, Me, Et) **2** **3a**,**b** (R = Me, Et)

Entry	Reaction conditions	Product (yield)
1	PPh_3, $MeCOCO_2H$, acetone, 25 °C, 8 h	**2** (48%)
2	*n*-Bu_3P, $MeCOCO_2H$, acetone, 25 °C, 8 h	**2** (57%)
3	PPh_3, $MeCOCO_2Me$, acetone, 25 °C, 4 h	**3a** (81%)
4	*n*-Bu_3P, $MeCOCO_2Me$, acetone, 25 °C, 4 h	**3a** (86%)
5	PPh_3, $MeCOCO_2Et$, acetone, 25 °C, 4 h	**3b** (86%)
6	*n*-Bu_3P, $MeCOCO_2Et$, acetone, 25 °C, 4 h	**3b** (91%)

a 4:1 ratio in 75% yield. The ^{1}H NMR signal for an angular methine proton in compound **7a** appeared as a doublet of doublet [4.92 (dd, *J* = 7.3, 5.6 Hz, 1 H)], while in compound **7b** it appeared as a relatively more deshielded singlet [5.74 (s, 1 H)]. Analysis of complete spectral data neatly supported their isomeric structural assignments. Surprisingly, a continuation of reaction as mentioned above for 24 hours exclusively formed the desired product **7a** in 87% yield. In a control experiment, regioisomer **7b** under a similar set of reaction conditions was completely transformed into **7a** in 24 hours in 91% yield. Overall, under acidic conditions the undesired isomer **7b** got transformed into the conjugated thermodynamically more stable isomer **7a**. In a thermodynamically controlled transformation of **7b** to **7a**, the migration of exocyclic C=C bond moiety at the β-position to the α-position plausibly takes place via reversible Pictet–Spengler reaction pathway.[19] Regioselective NBS-bromination of **7a** at the more reactive angular benzylic position formed unisolable intermediate **8**, which upon subsequent dehydrobromination furnished the requisite model compound **9** in 64% yield. The reaction of imide **5** with phosphorous pentoxide under reflux conditions was low yielding due to starting material decomposition. However, a phosphorous pentoxide driven extension of conjugation favored regioselective dehydrative cyclization of imide **5** under the controlled heating at 40 °C followed by reflux resulting in the same dark red colored model compound **9** in acceptable



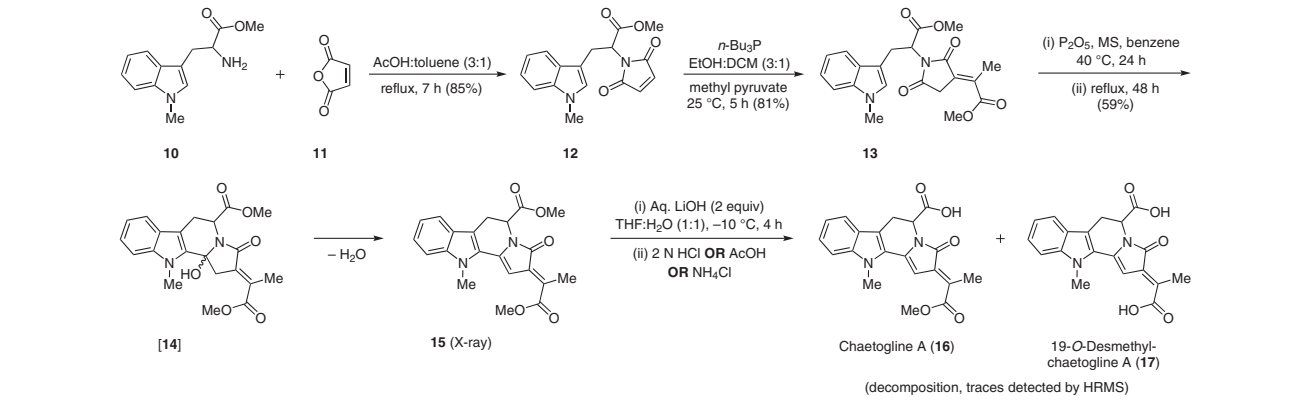
Scheme 1 Retrosynthetic analysis of methyl chaetoglinate A leading to the corresponding maleimide as a potential precursor



Scheme 2 Approaches to chaetogline A framework from tryptamine derived maleimide

yield (67%). The structure of product **9** was unambiguously established on the basis of ^{1}H NMR, ^{13}C NMR, HRMS, and X-ray crystallographic data. X-ray data for product **9**[20] confirmed the *E*-configuration of the exocyclic C=C bond in the corresponding starting compound **5** and supported the assigned *E*-configuration for all other reported Wittig products.

The reaction of methyl 1-methyltryptophanate (**10**) with maleic anhydride (**11**) in refluxing acetic acid:toluene mixture provided the desired maleimide **12** in 85% yield via anhydride ring opening followed by a dehydrative cyclization (Scheme 3). Similarly, the reaction of maleimide **12** with methyl pyruvate in the presence of tributylphosphine stereoselectively delivered the corresponding *E*-imide **13** in 81% yield. Phosphorus pentoxide induced regioselective dehydrative cyclization of imide **13** in refluxing benzene provided the methyl chaetoglinate A skeleton **15** in 59% yield (74% based on the recovery of starting material). The above-specified reaction was less efficient in refluxing toluene, plausibly due to stability issues. Finally, the methyl ester structure of chaetogline A **15** was confirmed by using X-ray crystallographic data.[20] Unfortunately, all our attempts involving acid/base-induced hydrolysis of ester moieties in compound **15** met with failure and always resulted in immediate decomposition. Base-induced hydrolysis of compound **15** under conditions described by Lei and co-workers (LiOH, THF:H_2O, –10 to 0 °C, 1 h)[10] followed by acidification with dilute hydrochloric acid or acetic acid or ammonium chloride also caused nearly complete decomposition. However, an immediately taken HRMS of the decomposed material revealed the existence of traces of both chaetogline A (**16**) and 19-*O*-desmethylchaetogline A (**17**). In the above-mentioned stepwise hydrolysis of diester **15**, at first more reactive unconjugated ester gets hydrolyzed to form chaetogline A (**16**) and then the hydrolysis of conjugated ester forms 19-*O*-desmethylchaetogline A (**17**). Attempts to transform diester **15** to products **16** and **17** using KF/TBAF (decomposition), K_2CO_3/THF:H_2O (no reaction), and 2 N HCl (decomposition) also failed. Based on several experiments performed for hydrolysis of diester **15**, we feel that the resultant mono-acid **16** and di-acid **17** are unstable under acidic/basic conditions and consequently decompose due to hydrolytic/decarboxylative/oxidative cleavages.[21] Unfortunately, the repetition of Scheme 3 by using enantiomerically pure methyl 1-methyl-L-tryptophanate (**10**) resulted in excessive racemization during the transformation of maleimide **12** to alkylidinesuccinimide **13**.



Scheme 3 Total synthesis of methyl ester of chaetogline A (**15**)

In summary, we have demonstrated the synthesis of the methyl ester of chaetoglinate A via the introduction of the desired exocyclic double bond using a Wittig olefination with methyl pyruvate and a thermodynamically favorable extension of conjugation driven dehydrative cyclization pathway. The present Wittig reaction with alkyl pyruvates is general in nature. It can be useful to neatly design a variety of desired precursors essential for the total synthesis of several natural and unnatural products.

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 400 MHz NMR and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 400 NMR (100 MHz) and 500 NMR (125 MHz) spectrometers. Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrophotometer. Column chromatographic separations were carried out on silica gel (60–120 and 230–400 mesh). Commercially available *p*-toluidine, maleic anhydride, pyruvic acid, methyl pyruvate, ethyl pyruvate, PPh_3, *n*-Bu_3P, tryptamine, $NaBH_4$, $CeCl_3{\cdot}7H_2O$, trifluoroacetic acid, NBS, and P_2O_5 were used. Methyl 1-methyltryptophanate was freshly prepared before use.

Wittig Reaction of Maleimide with Pyruvic Acid/Alkyl Pyruvates; General Procedure

To a stirred solution of maleimide **1** (200 mg, 1.07 mmol) in acetone (5 mL) was added *n*-Bu_3P (0.29 mL, 1.18 mmol)/PPh_3 (309 mg, 1.18 mmol) in dropwise/portion wise fashion at 25 °C under argon atmosphere. The reaction mixture was stirred for 30 min at the same temperature and then pyruvic acid (0.15 mL, 2.14 mmol)/methyl pyruvate (90%, 0.24 mL, 2.14 mmol)/ethyl pyruvate (0.24 mL, 2.14 mmol) was added slowly. The reaction was monitored by TLC and upon completion, the mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (25 mL), and the resultant solution was washed with H_2O (15 mL) and brine (15 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) chromatographic purification of the resulting residue using EtOAc:PE as eluent afforded the corresponding Wittig product **2**/**3a**/**3b** (For yield, see Table 1).

(*E*)-3-Ethylidene-1-(*p*-tolyl)pyrrolidine-2,5-dione (2)

White solid; mp 142–144 °C.

IR ($CHCl_3$): 1683, 1628 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94 (dt, *J* = 7.6, 1.5 Hz, 3 H), 2.39 (s, 3 H), 3.38–3.42 (m, 2 H), 6.97–7.05 (m, 1 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.5, 21.2, 32.0, 126.2, 126.4, 129.3, 129.8, 134.9, 138.6, 168.9, 173.3.

MS (ESI): *m*/*z* = 216 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_2$: 216.1019; found: 216.1019.

Methyl (*E*)-2-[2,5-Dioxo-1-(*p*-tolyl)pyrrolidin-3-ylidene]propanoate (3a)

White solid; mp 150–152 °C.

IR ($CHCl_3$): 1771, 1710, 1640 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.40 (s, 3 H), 2.55 (t, *J* = 2.3 Hz, 3 H), 3.83 (q, *J* = 2.3 Hz, 2 H), 3.87 (s, 3 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.1, 21.2, 36.4, 52.6, 126.3, 128.9, 129.8, 130.8, 137.7, 138.9, 167.3, 169.0, 172.8.

MS (ESI): *m*/*z* = 274 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}NO_4$: 274.1074; found: 274.1070.

Ethyl (*E*)-2-[2,5-Dioxo-1-(*p*-tolyl)pyrrolidin-3-ylidene]propanoate (3b)

White solid; mp 214–216 °C.

IR ($CHCl_3$): 1769, 1707, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (t, *J* = 6.9 Hz, 3 H), 2.40 (s, 3 H), 2.55 (t, *J* = 2.3 Hz, 3 H), 3.82 (q, *J* = 2.3 Hz, 2 H), 4.32 (q, *J* = 6.9 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 15.1, 21.2, 36.3, 61.8, 126.3, 128.9, 129.8, 130.3, 138.2, 138.9, 166.9, 169.1, 172.9.

MS (ESI): *m*/*z* = 288 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO_4$: 288.1230; found: 288.1226.

Ethyl (*E*)-2-{1-[2-(1*H*-Indol-3-yl)ethyl]-2,5-dioxopyrrolidin-3-ylidene}propanoate (5)

To a stirred solution of maleimide **4** (2.00 g, 8.33 mmol) in EtOH:DCM (3:1, 25 mL) was added *n*-Bu_3P (2.26 mL, 9.17 mmol) in dropwise fashion at 25 °C under argon atmosphere. The reaction mixture was stirred for 30 min at the same temperature and then ethyl pyruvate (1.85 mL, 16.7 mmol) was added slowly. The mixture was further stirred for 5 h and concentrated in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the resultant solution was washed with H_2O (25 mL) and brine (25 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM as an eluent afforded **5** as a white solid; yield: 2.44 g (86%); mp 162–164 °C.

IR ($CHCl_3$): 3474, 1766, 1670, 1645 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.36 (t, *J* = 7.3 Hz, 3 H), 2.52 (t, *J* = 1.9 Hz, 3 H), 3.08 (t, *J* = 8.0 Hz, 2 H), 3.59 (q, *J* = 1.9 Hz, 2 H), 3.91 (t, *J* = 8.0 Hz, 2 H), 4.29 (q, *J* = 7.3 Hz, 2 H), 7.09 (d, *J* = 2.3 Hz, 1 H), 7.14 (t, *J* = 7.5 Hz, 1 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.72 (d, *J* = 7.7 Hz, 1 H), 8.07 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.1, 14.9, 23.5, 36.2, 39.3, 61.7, 111.1, 112.2, 118.7, 119.5, 122.05, 122.14, 127.4, 130.7, 136.2, 137.1, 167.0, 169.9, 173.6.

MS (ESI): *m*/*z* = 341 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_4$: 341.1496; found: 341.1501.

Ethyl (*E*)-2-[3-Oxo-5,6,11,11b-tetrahydro-1*H*-indolizino[8,7-*b*]indol-2(3*H*)-ylidene]propanoate (7a)

To a stirred solution of imide **5** (500 mg, 1.47 mmol) in MeOH:DCM (1:1, 20 mL) was added $CeCl_3{\cdot}7H_2O$ (1.92 g, 5.15 mmol) at –10 °C and then $NaBH_4$ (835 mg, 22.05 mmol) was added in portion wise manner. The reaction mixture was stirred for 3.5 h at the same temperature and acidified with TFA (1.12 mL, 14.7 mmol) at 0 °C until completely acidic. The mixture was further stirred at 25 °C for 24 h and quenched with sat. aq $NaHCO_3$ (5 mL). The mixture was concentrated

in vacuo and the obtained residue was dissolved in EtOAc (30 mL). The resultant solution was washed with H_2O (30 mL) and brine (30 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using EtOAc:PE (7:3) as an eluent afforded **7a** as a pale yellow solid; yield: 415 mg (87%); mp 180–182 °C.

IR ($CHCl_3$): 3444, 1642 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, *J* = 7.1 Hz, 3 H), 2.48 (t, *J* = 2.2 Hz, 3 H), 2.81–2.88 (m, 1 H), 2.89–2.99 (m, 1 H), 3.00–3.10 (m, 1 H), 3.17 (td, *J* = 11.3, 5.4 Hz, 1 H), 3.76 (ddd, *J* = 18.4, 7.8, 1.9 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.67 (dd, *J* = 12.9, 5.4 Hz, 1 H), 4.92 (dd, *J* = 7.3, 5.6 Hz, 1 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 8.12 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.3, 14.2, 20.9, 33.8, 38.1, 51.3, 61.0, 108.5, 111.0, 118.4, 119.9, 122.3, 126.7, 132.9, 133.0, 136.3, 138.1, 167.0, 168.2.

MS (ESI): *m*/*z* = 325 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_3$: 325.1547; found: 325.1554.

The repetition of the reaction at 25 °C for 2 h time resulted in a regioisomeric mixture of **7a** and **7b**. Silica gel (230–400 mesh) column chromatographic purification of the mixture using EtOAc:PE (7:3) as an eluent afforded the major isomer **7a** as a pale yellow solid (286 mg, 60%) and the minor isomer **7b** as a pale yellow solid (71 mg, 15%).

Minor Isomer 7b

Mp 146–148 °C.

IR ($CHCl_3$): 3444, 1641 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, *J* = 6.9 Hz, 3 H), 2.35 (s, 3 H), 2.76 (ddd, *J* = 15.7, 5.3, 1.5 Hz, 1 H), 3.02–3.15 (m, 1 H), 3.25 (td, *J* = 13.0, 5.3 Hz, 1 H), 3.42 (dt, *J* = 23.7, 2.3 Hz, 1 H), 3.73 (d, *J* = 23.7 Hz, 1 H), 4.22–4.32 (m, 2 H), 4.60 (dd, *J* = 13.0, 6.1 Hz, 1 H), 5.74 (s, 1 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.74 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 16.8, 20.1, 38.0, 38.6, 59.8, 61.1, 110.5, 111.1, 118.5, 120.2, 122.9, 123.5, 126.9, 130.3, 136.0, 143.3, 166.7, 173.0.

MS (ESI): *m*/*z* = 325 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_3$: 325.1547; found: 325.1550.

Ethyl (*E*)-2-[3-Oxo-6,11-dihydro-3*H*-indolizino[8,7-*b*]indol-2(5*H*)-ylidene]propanoate (9)

Method A: To a stirred solution of **7a** (100 mg, 0.31 mmol) in DCM (6 mL) was dropwise added a solution of freshly crystallized NBS (89 mg, 0.50 mmol) in DCM (2 mL) at 0 °C and the reaction mixture was stirred at 25 °C for 6 h. The reaction was quenched with sat. aq $NaHCO_3$ (1 mL). DCM was removed in vacuo and the obtained residue was dissolved in EtOAc (20 mL). The resultant solution was washed successively with H_2O (10 mL), aq $NaHCO_3$ (10 mL), and brine (10 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using EtOAc:PE (9:1) as an eluent afforded **9** as a dark red crystalline solid; yield: 64 mg (64%); mp 212–214 °C.

IR ($CHCl_3$): 3462, 1685, 1635 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (t, *J* = 7.1 Hz, 3 H), 2.56 (s, 3 H), 3.12 (t, *J* = 6.4 Hz, 2 H), 3.90 (t, *J* = 6.4 Hz, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 6.73 (s, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 8.53 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 14.5, 20.5, 37.2, 61.2, 95.4, 111.6, 116.3, 119.6, 120.6, 124.9, 125.0, 126.2, 131.7, 135.8, 136.7, 138.4, 168.4, 168.8.

MS (ESI): *m*/*z* = 323 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_3$: 323.1390; found: 323.1392.

Method B: To a stirred solution of imide **5** (100 mg, 0.29 mmol) in anhyd benzene (10 mL) were added 4 Å molecular sieves (50 mg) and P_2O_5 (1.23 g, 4.35 mmol) under an argon atmosphere at 25 °C. The above reaction mixture was first heated at 40 °C for 12 h and then refluxed for 2 h. The mixture was concentrated in vacuo and to the obtained residue was added EtOAc (10 mL) at 0 °C. The above mixture was slowly added to ice-cold H_2O (10 mL), and carefully made basic (pH 8) by adding solid K_2CO_3. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with H_2O (25 mL) and brine (25 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using EtOAc:PE (9:1) as an eluent afforded **9** as a dark red crystalline solid (64 mg, 67%; 83% based on the recovery of starting material) and the unreacted imide **5** (19 mg material).

Methyl 2-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-3-(1-methyl-1*H*-indol-3-yl)propanoate (12)

To a stirred solution of amine **10** (1.00 g, 4.31 mmol) in AcOH:toluene (3:1, 30 mL) was added maleic anhydride (**11**; 760 mg, 7.76 mmol) at 25 °C under argon atmosphere and the reaction mixture was refluxed for 7 h. The mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (40 mL). The resultant solution was washed with aq $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM as an eluent afforded maleimide **12** as a yellow oil; yield: 1.14 g (85%).

IR ($CHCl_3$): 1748, 1714, 1641 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.61–3.68 (m, 2 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 5.06 (dd, *J* = 9.9, 6.1 Hz, 1 H), 6.57 (s, 2 H), 6.85 (s, 1 H), 7.09 (t, *J* = 8.4 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.26 (d, *J* = 9.2 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.5, 32.6, 52.8 (2 C), 109.2, 118.5, 119.0, 121.6, 127.3, 127.6, 134.0 (2 C), 136.8, 169.5, 169.9.

MS (ESI): *m*/*z* = 313 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_4$: 313.1183; found: 313.1185.

Methyl (*E*)-2-[3-(1-Methoxy-1-oxopropan-2-ylidene)-2,5-dioxopyrrolidin-1-yl]-3-(1-methyl-1*H*-indol-3-yl)propanoate (13)

To a stirred solution of maleimide **12** (900 mg, 2.88 mmol) in EtOH:DCM (3:1, 25 mL) was added *n*-Bu_3P (0.78 mL, 3.17 mmol) in dropwise fashion at 25 °C under argon atmosphere. The reaction mixture was stirred for 30 min at the same temperature and then methyl pyruvate (90%, 0.65 mL, 5.76 mmol) was added slowly. The reaction mixture was further stirred for 5 h and then concentrated in vacuo. The obtained residue was dissolved in EtOAc (30 mL) and the resultant solution was washed with H_2O (30 mL) and brine (30 mL), and

dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using EtOAc:PE (7:3) as an eluent afforded imide **13** as a white solid; yield: 930 mg (81%); mp 152–154 °C.

IR ($CHCl_3$): 1708, 1645 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.42 (t, *J* = 2.0 Hz, 3 H), 3.41 (dq, *J* = 22.8, 2.0 Hz, 1 H), 3.51 (dq, *J* = 22.8, 2.0 Hz, 1 H), 3.64 (d, *J* = 7.7 Hz, 2 H), 3.72 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 5.16 (dd, *J* = 8.6, 7.1 Hz, 1 H), 6.90 (s, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 7.19 (t, *J* = 7.4 Hz, 1 H), 7.25 (d, *J* = 8.2 Hz, 1 H), 7.53 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.8, 23.9, 32.7, 36.0, 52.5, 52.8, 53.3, 109.2, 118.2, 119.2, 121.7, 127.4, 127.7, 130.6, 136.8, 136.9, 137.1, 167.2, 168.99, 169.01, 172.8.

MS (ESI): *m*/*z* = 399 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_6$: 399.1551; found: 399.1562.

Methyl (*E*)-2-(1-Methoxy-1-oxopropan-2-ylidene)-11-methyl-3-oxo-2,5,6,11-tetrahydro-3*H*-indolizino[8,7-*b*]indole-5-carboxylate (15) (Methyl Chaetoglinate A)

To a stirred solution of imide **13** (100 mg, 0.25 mmol) in anhyd benzene (15 mL) were added 4 Å molecular sieves (40 mg) and P_2O_5 (1.06 g, 3.75 mmol) in one portion under argon atmosphere. The above reaction mixture was heated at 40 °C for 24 h and then refluxed for 48 h. The mixture was concentrated in vacuo and to the obtained residue was added EtOAc (15 mL) at 0 °C. To the above mixture was slowly added ice-cold H_2O (20 mL) and was carefully made basic (pH 8) by adding solid K_2CO_3. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using EtOAc:PE (8:2) as an eluent afforded **15** as a dark red crystalline solid; yield: 56 mg (59%; 74% based on recovery of starting material) and the unreacted imide **13** (20 mg); mp 182–184 °C.

IR ($CHCl_3$): 1641 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.60 (s, 3 H), 3.33 (dd, *J* = 16.4, 7.1 Hz, 1 H), 3.63 (s, 3 H), 3.74 (dd, *J* = 16.5, 1.0 Hz, 1 H), 3.89 (s, 3 H), 3.95 (s, 3 H), 5.24 (d, *J* = 6.4 Hz, 1 H), 7.03 (s, 1 H), 7.13–7.20 (m, 1 H), 7.30–7.38 (m, 2 H), 7.59 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.6, 23.7, 31.5, 49.7, 52.2, 52.9, 98.1, 109.5, 112.8, 119.8, 120.3, 124.8, 125.3, 125.9, 132.1, 134.9, 136.5, 140.1, 168.6, 168.8, 170.6.

MS (ESI): *m*/*z* = 381 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_5$: 381.1445; found: 381.1447.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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Facile synthesis of indolizinoindolone, indolylepoxypyrrolooxazole, indolylpyrrolo-oxazolone and isoindolopyrazinoindolone heterocycles from indole and imide derivatives†

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Chemo-, regio- and diastereoselective coupling reactions of indole with imide derivatives leading to unique heterocyclic systems are demonstrated. Acid-induced 3-position coupling reactions of indole with cyclic imide derived lactamols followed by acid promoted 2-position cyclizations with the corresponding aldehydes are described to obtain the indolizinoindolones and benzoindolizinoindolones. Base induced 2-position coupling reactions of *N*-tosylindole with *N*-(2-iodoethyl)imides and the subsequent cyclizations provide indolylepoxypyrrolooxazole, indolylpyrrolooxazolone and indolyloxazoloisoindolone. Reductive cleavage of indolyloxazoloisoindolone to the corresponding alcohol followed by mesylation and base promoted *N*-cyclization affords the *in situ* air-oxidized pentacyclic product hydroxyisoindolo-pyrazinoindolone. A regioisomeric structural revision of the natural product from 1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*]indol-3-one to 1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one is also reported in the present studies focussed on the methodologies for heterocyclic synthesis.

Introduction

A large number of structurally interesting and medicinally important indole alkaloids are known in the literature. The total synthesis of indole alkaloids and indole-based new heterocyclic systems has been a challenging task for several decades.[1–10] In this context, a large number of systematically studied chemo-, regio- and stereoselective coupling reactions at 1/2/3-positions of indoles have been reported.[11–35] Recently, Zhao and co-workers have reported gold-catalyzed selective coupling reactions of costly 1,3-unsubstituted 2-(1*H*-indol-2-yl) ethanamines with alkynoic acids to obtain the target compound indolizinoindolone.[17] More specifically, Grigg *et al.* performed the Sonogashira reaction of *N*-alkynylimides with 2-iodophenol/2-iodo-*N*-tosylaniline and obtained the indolizinoindolones.[35] In continuation of our studies on the applications of cyclic anhydrides/imides in the synthesis of bioactive alkaloid natural products,[36–39] we planned to explore the metal-free carbon–carbon bond-forming regioselective coupling reactions of indole with the well-structured imide derivatives (Fig. 1). In this context, we herein report selective 2-position and 3-position coupling reactions of indole with imide derivatives and the subsequent cyclizations to constitute four different types of structurally attractive heterocyclic systems (Schemes 1–5).

Results and discussion

The reaction of succinic anhydride (**1**) with ethanolamine in a refluxing mixture of AcOH : toluene (3 : 1) provided succinimide **2** in 73% yield (Scheme 1). $NaBH_4$ reduction of succinimide **2** in the presence of $CeCl_3$ furnished a lactamol intermediate **3** and it was further used without any purification due to stability issues. TFA-induced indole reaction with lactamol **3** was highly regioselective and yielded the 3-position coupled indolylpyrrole **4** in 72% yield, over 2 steps. De-acylation of compound **4**, mesylation of the formed alcohol **5**, and its treatment with sodium iodide delivered the corresponding iodide **6** in 61% yield, over 3 steps. Iodide **6** in the presence of *t*-BuOK underwent enolization and formed the undesired cyclized product indolylpyrrole **7** in 87% yield. However, DMP-oxidation of alcohol **5** to the corresponding aldehyde intermediate **8** in 64% yield followed by formic acid-mediated diastereoselective 2-position cyclization delivered the desired indolizinoindolone **9** in 56% yield. The stereochemical structural assignment of the product (±)-**9** was based on X-ray crystallo-

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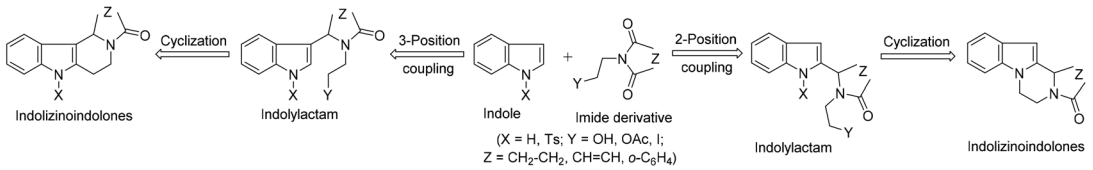
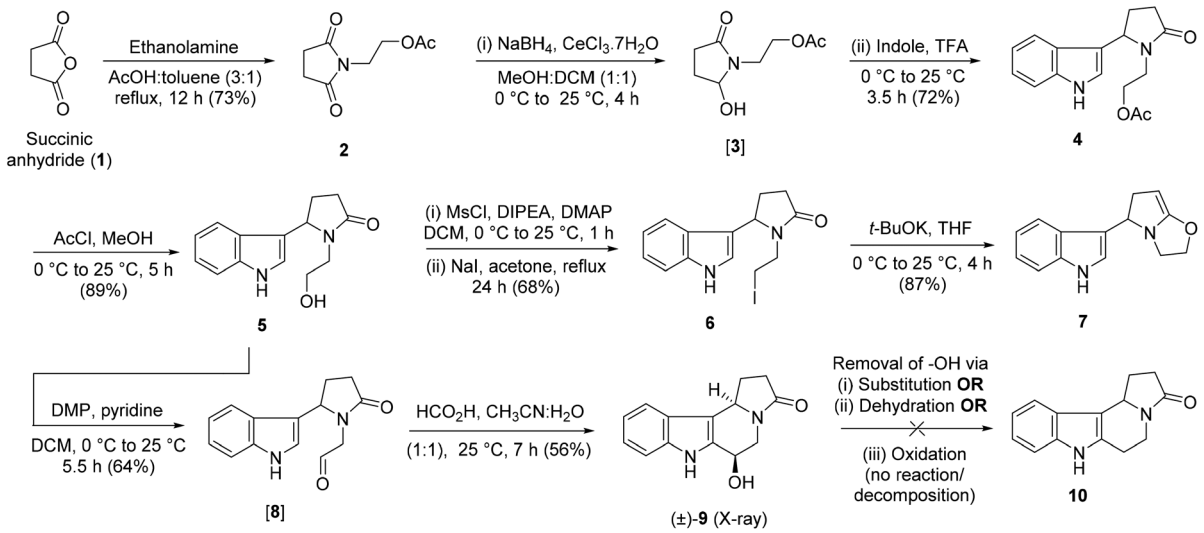
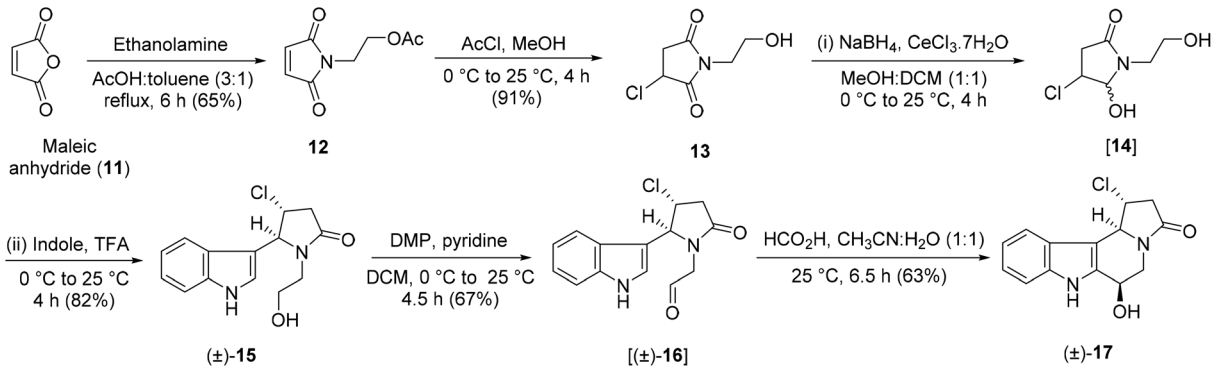


Fig. 1 Stepwise 3,2- and 2,1-position coupling reactions of indole with imide derivatives.



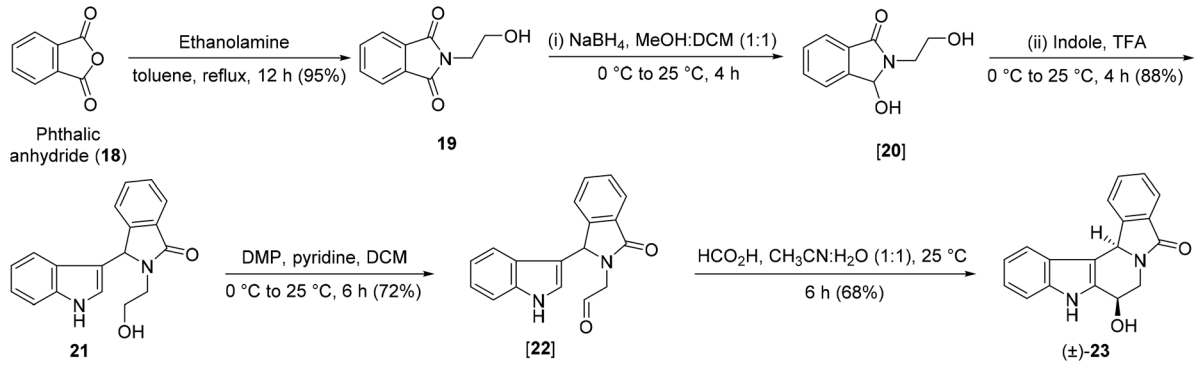
Scheme 1 Synthesis of hydroxyindolizinoindolone *via* acid promoted reaction of indole with succinimide based lactamol.



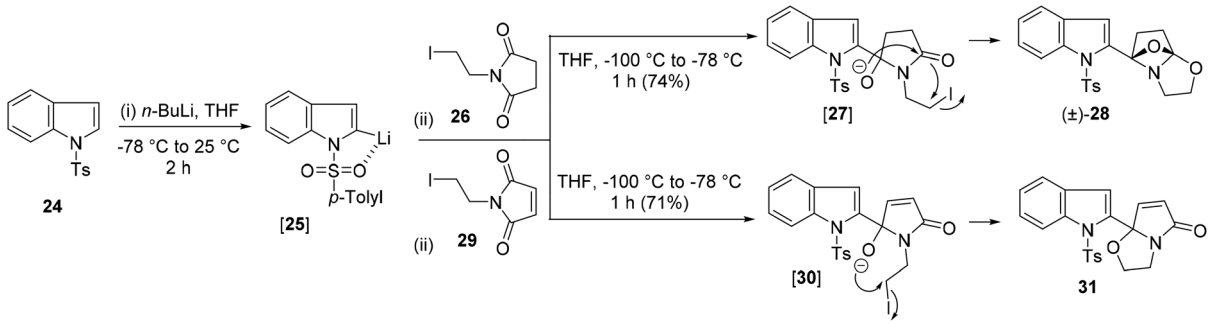
Scheme 2 Regioselective and diastereoselective coupling reactions of indole with chlorosuccinimide based lactamol.

graphic data, and we feel that the orientation of a lone pair on a lactam nitrogen atom governs the stereochemistry. Unfortunately, several attempts for the removal of a hydroxyl group in compound (±)-**9** to obtain the recently isolated natural product 1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*] indol-3-one (**10**)[40] always resulted in no reaction or decomposition [conversion into a good leaving group (-OTs/-OMs/xanthate) followed by hydride/radical displacement, acid-induced dehydration followed by double bond reduction and oxidation to a ketone (PCC/PDC/DMP/TPAP) followed by reduction].

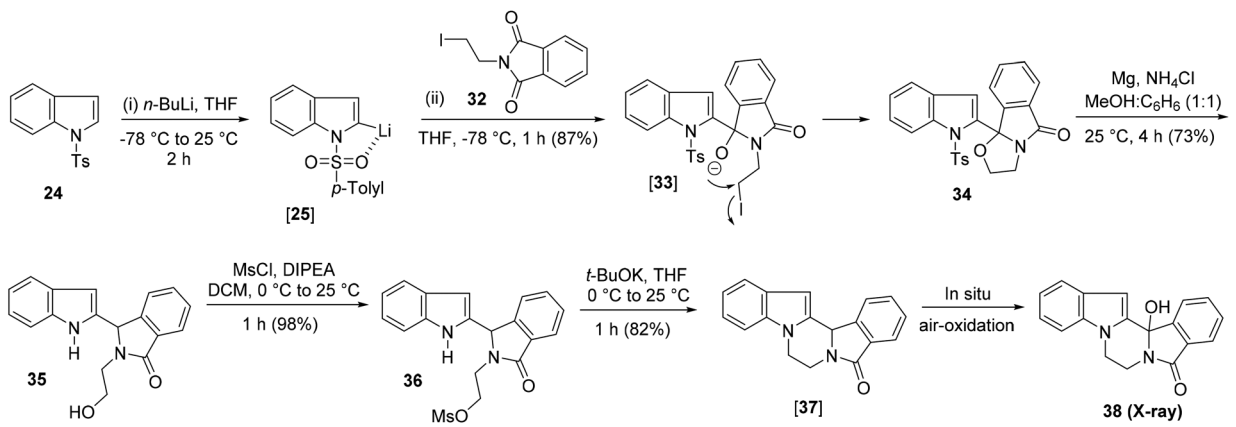
In continuation of our studies on heterocyclic synthesis, the performed reaction of maleic anhydride (**11**) with ethanolamine provided the acetoxymaleimide **12** in 65% yield (Scheme 2). Maleimide **12** on treatment with AcCl/MeOH directly yielded chlorosuccinimide **13** in 91% yield *via* the desired de-acylation and an unplanned addition of HCl across the carbon–carbon double bond. Regioselective $NaBH_4$-reduction of the more reactive imide carbonyl group in chlorosuccinimide **13** formed the corresponding lactamol intermediate **14.** Acid-induced diastereoselective coupling reaction of lactamol **14** at the 3-position of indole furnished the pyrrole



Scheme 3 Regioselective coupling reactions of indole with phthalimide based lactamole.



Scheme 4 Base induced regioselective coupling reactions of *N*-tosylindole with *N*-2-iodoethylsuccinimide and *N*-2-iodoethylmaleimide.



Scheme 5 Base induced regioselective coupling reaction of *N*-tosylindole with *N*-2-iodoethylphthalimide leading to hydroxyisoindolopyrazinoindolone.

derivative (±)-**15** in 82% yield over 2 steps. Mechanistically, indole selectively attacks from the less hindered side of the formed iminium ion intermediate. Comparing the ^{1}H and ^{13}C NMR data of compounds **5** and **15** confirmed the assigned regioselectivity in product **15** (position of the chlorine atom). DMP-oxidation of a hydroxyl group in compound (±)-**15** to the corresponding aldehyde (±)-**16** followed by formic acid-mediated diastereoselective cyclization provided the indolizinoindolone (±)-**17** in 63% yield. Similarly, the preparation of hydroxyphthalimide **19**, its $NaBH_4$-reduction to lactamol **20** followed by the coupling reaction with indole to form the product **21**, DMP-oxidation of alcohol **21** to aldehyde **22** and the subsequent diastereoselective cyclization furnished the benzoindolizinoindolone **23** in very good overall yield (Scheme 3).

Consequently, we herein also report the regioisomeric structural assignment of the proposed natural product **10**. The literature search revealed that 2-(2-aminoethyl)indole (**10b**) is not

a natural product and the isolation of product **10** along with tryptamine based tetrahydropyrroloazepinoindole-3-carbaldehyde (**10c**) indicated a plausibility of logical regioisomeric structural reassignment of the natural product **10** (Fig. 2).[40] The structural assignment of **10** has been done based on IR, NMR, 2D NMR, and HRMS data.[40] At this stage, we carefully checked the ^{1}H and ^{13}C NMR data of product **9** and the structurally similar known compounds **9a**[17] and **10**,[40] more specifically, the positions of 11c-methine carbon atoms in their ^{13}C NMR spectra. The delta value for the 11c-methine carbon atom in product **10** was relatively lower but matched with that of **10a**. Recently, we reported the total synthesis of (+)-harmicine from (*R*)-acetoxysuccinic anhydride and tryptamine *via* the advanced intermediate (+)-**10a**.[41] The postulation was correct and the ^{1}H and ^{13}C NMR spectra of products **10** and **10a** in DMSO-d_6 were superimposable (comparison table has been provided in the ESI†). Thus, based on the present studies on heterocyclic synthesis, the structure of the proposed natural product 1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*]indol-3-one (**10**) has been revised as the regioisomeric compound 1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (**10a**).

In the second part of the studies we planned to perform the 2-position coupling reactions of indole with imide derivatives. *N*-Tosylindole (**24**) on treatment with *n*-BuLi at −78 °C to 25 °C smoothly formed the corresponding 2-lithio-*N*-tosylindole (**25**) (Scheme 4).[26] The initially studied coupling reaction of 2-lithio-*N*-tosylindole (**25**) with *N*-2-iodoethylsuccinimide (**26**) at −78 °C resulted in instantaneous decomposition. However, the same reaction at −100 °C to −78 °C formed an unanticipated bridged indolylepoxypyrrolooxazole (±)-**28** in 74% yield, comprising an unusual 1,3-oxazetidine moiety. The absence of the lactam carbonyl signal in the ^{13}C NMR spectrum of (±)-**28** was the best hint for structural assignment. Mechanistically, 2-lithio-*N*-tosylindole (**25**) reacts with a carbonyl group of imide **26** to form the corresponding oxyanion **27**, which internally attacks the proximal second carbonyl group and the thus-formed oxyanion displaces iodide resulting in the remarkable product (±)-**28**. There were no difficulties in the isolation, silica gel column chromatographic purification, and spectral characterization of the product (±)-**28**. However, the formed labile indolylepoxypyrrolooxazole (±)-**28** underwent hydrolytic and/or oxidative decomposition in nearly 48 hours. The 2-lithio-*N*-tosylindole (**25**) reaction with *N*-2-iodoethylmaleimide (**29**) at −100 °C to −78 °C followed a straightforward pathway and yielded the corresponding indolylpyrrolooxazolone **31** in 71% yield. Mechanistically, 2-lithio-*N*-tosylindole (**25**) reacts with a carbonyl group of imide **29** to form the corresponding oxyanion **30** and due to the less reactivity of the conjugated lactam carbonyl group a direct displacement of iodide takes place resulting in the product **31**. Unfortunately, all our attempts to deprotect the tosylate group in products **28** and **31** using Mg/MeOH[42,43] resulted in complete decompositions of the reaction mixtures.

The reaction of 2-lithio-*N*-tosylindole (**25**) with *N*-2-iodoethylphthalimide (**32**) at −78 °C neatly resulted in the expected indolyloxazoloisoindolone **34** in 87% yield (Scheme 5). Indolyloxazoloisoindolone **34** on treatment with Mg/MeOH[42,43] underwent tosylate deprotection and reductive oxazole ring cleavage to directly furnish the corresponding alcohol **35** in 73% yield. Conversion of alcohol **35** to mesylate and *t*-BuOK induced regioselective *N*-cyclization delivered *in situ* air-oxidized hydroxyisoindolopyrazinoindolone **38** (82% yield), *via* the corresponding unisolable intermediate **37**. The X-ray crystallographic data confirmed the ring-closed structure of a *gem*-aminohydrin moiety containing product **38**. Such a type of base induced *in situ* air-oxidation of electron-deficient carbon atoms in similar compounds is known.[44–48]

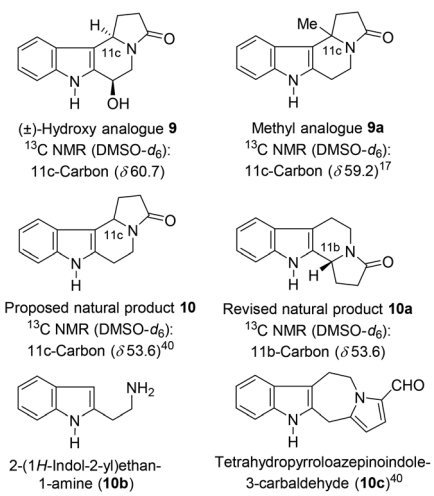


Fig. 2 Proposed and revised natural products along with their synthetic analogues.

Conclusions

We have demonstrated selective acid and base catalyzed coupling reactions of indole with cyclic imide derivatives leading to structurally interesting important heterocyclic systems. The selective formation of the exotic labile bridged compound indolylepoxypyrrolooxazole at minus hundred degrees and the witnessed facile air-oxidation to form hydroxyisoindolopyrazinoindolone are noteworthy. We believe that the present metal-free new selective 1/2/3-position carbon–carbon and carbon–nitrogen bond-forming reactions of indole with the cyclic imide precursors are important from the basic chemistry perspective and will provide an avenue for indole based heterocycles.

Experimental section

General description

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz NMR and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR

(100 MHz) and 500 NMR (125 MHz) spectrometers. Mass spectra were recorded on an MS-TOF mass spectrometer. HRMS (ESI) spectra were recorded using Orbitrap (quadrupole plus ion trap) and TOF mass analyzers. IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 and 230–400 mesh). Commercially available succinic anhydride, maleic anhydride, phthalic anhydride, ethanolamine, sodium borohydride, cerium(III) chloride heptahydrate, indole, trifluoroacetic acid, acetyl chloride, methanesulfonyl chloride, *N*,*N*-diisopropylethylamine, sodium iodide, potassium *tert*-butoxide, Dess–Martin periodinane, formic acid, pyridine and *n*-butyllithium (2.00 M in cyclohexane) were used. Freshly activated magnesium turnings and freshly prepared 1-tosyl-1*H*-indole were used.

General procedure for preparation of imide

2-(2,5-Dioxopyrrolidin-1-yl)ethyl acetate (2). To a stirred solution of ethanolamine (2.50 g, 40.93 mmol) in AcOH : toluene (3 : 1, 50 mL) was added succinic anhydride (**1**, 6.14 g, 61.39 mmol) at 25 °C and the reaction mixture was refluxed for 12 h. The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with aq. $NaHCO_3$, water, and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3 : 1) as an eluent afforded succinimide **2** as a pale-yellow oil (5.53 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.01 (s, 3H), 2.72 (s, 4H), 3.77 (t, J = 5.4 Hz, 2H), 4.22 (t, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 28.1, 37.9, 60.8, 170.9, 177.1; ESIMS (m/z) 186 $[M + H]^+$; HRMS (ESI) calcd for $C_8H_{11}O_4NNa$ 208.0580, found 208.0578; IR ($CHCl_3$) ν_{max} 1739, 1703 cm^{-1}.

2-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl acetate (12). It was prepared according to the general procedure, silica gel column purified using ethyl acetate–petroleum ether (7 : 3) as an eluent and obtained as a white solid (4.90 g, 65%). Mp 78–80 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s, 3H), 3.80 (t, J = 5.5 Hz, 1H), 4.23 (t, J = 5.2 Hz, 2H), 6.73 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 36.9, 61.4, 134.2, 170.4, 170.8; ESIMS (m/z) 184 $[M + H]^+$; HRMS (ESI) calcd for $C_8H_{10}O_4N$ 184.0610, found 184.0608; IR ($CHCl_3$) ν_{max} 1714 cm^{-1}.

2-(2-Hydroxyethyl)isoindoline-1,3-dione (19). To a stirred solution of ethanolamine (3.00 g, 49.11 mmol) in toluene (70 mL) was added phthalic anhydride (**18**, 9.46 g, 63.85 mmol) at 25 °C and the reaction mixture was refluxed for 12 h. Toluene was removed *in vacuo* and the obtained residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with aq. $NaHCO_3$, water, and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using DCM–MeOH (49 : 1) as an eluent afforded phthalimide **19** as a white solid (8.90 g, 95%). Mp 128–130 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10–2.50 (br s, 1H), 3.85–3.95 (m, 4H), 7.70–7.77 (m, 2H), 7.84–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.9, 61.1, 123.4, 132.0, 134.1, 168.8; ESIMS (m/z) 192 $[M + H]^+$; HRMS (ESI) calcd for $C_{10}H_9O_3NNa$ 214.0475, found 214.0474; IR ($CHCl_3$) ν_{max} 3470, 1768, 1695 cm^{-1}.

General procedure for deprotection of the acetyl group

1-(2-Hydroxyethyl)pyrrolidine-2,5-dione (2a). AcCl (4.20 mL, 59.40 mmol) was added dropwise to a stirred solution of imide **2** (2.00 g, 10.80 mmol) in MeOH (25 mL) at 0 °C. The reaction mixture was stirred for 6 h allowing the temperature to reach 25 °C and concentrated *in vacuo*. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–methanol (97 : 3) as an eluent afforded imide **2a** as a colourless oil (1.49 g, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (br s, 1H), 2.76 (s, 4H), 3.73–3.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.2, 41.6, 60.5, 177.9; ESIMS (m/z) 144 $[M + H]^+$; IR ($CHCl_3$) ν_{max} 3444, 1770, 1698 cm^{-1}.

1-(2-Hydroxyethyl)-5-(1*H*-indol-3-yl)pyrrolidin-2-one (5). It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (97 : 3) as an eluent and obtained as a white solid (2.28 g, 89%). Mp 78–80 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (br s, 1H), 2.25–2.38 (m, 1H), 2.45–2.75 (m, 3H), 3.07–3.15 (m, 1H), 3.52–3.65 (m, 3H), 5.05 (t, J = 7.4 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 8.36 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 30.7, 45.0, 57.5, 61.6, 111.7, 115.1, 118.9, 120.2, 122.8, 122.9, 125.1, 136.9, 177.3; ESIMS (m/z) 245 $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_{17}O_2N_2$ 245.1285, found 245.1281; IR ($CHCl_3$) ν_{max} 3270, 1653 cm^{-1}.

3-Chloro-1-(2-hydroxyethyl)pyrrolidine-2,5-dione (13). It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (99 : 1) as an eluent and obtained as a colourless oil (2.12 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97 (dd, J = 18.7 and 3.8 Hz, 1H), 3.38 (dd, J = 19.1 and 8.4 Hz, 1H), 3.75–3.90 (m, 4H), 4.69 (dd, J = 8.4 and 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2, 42.1, 48.6, 59.9, 173.45, 173.52; ESIMS (m/z) 178 $[M + H]^+$; HRMS (ESI) calcd for $C_6H_9O_3NCl$ 178.0271, found 178.0266; IR ($CHCl_3$) ν_{max} 3478, 1785, 1709 cm^{-1}.

General procedure for 3-position coupling reaction of indole with lactamol

2-[2-(1*H*-Indol-3-yl)-5-oxopyrrolidin-1-yl]ethyl acetate (4). To a stirred solution of imide **2** (3.00 g, 16.20 mmol) in MeOH : DCM (1 : 1, 50 mL) was added cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) (15.09 g, 40.50 mmol) at 0 °C and then $NaBH_4$ (1.53 g, 40.50 mmol) was added portionwise. The reaction mixture was stirred at the same temperature for 1 h and then it was further stirred for 3 h allowing the temperature to reach 25 °C. The same reaction mixture was again cooled at 0 °C and indole (2.09 g, 17.82 mmol) was added to the reaction mixture. The reaction mixture was slowly acidified with TFA (4.34 mL, 56.70 mmol) until completely acidic (pH 2) and it was further stirred for 3.5 h allowing the temperature to reach

25 °C. It was quenched with saturated aq. $NaHCO_3$ (7 mL), concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (70 mL). The resultant solution was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (13 : 7) as an eluent afforded **4** as foam (3.34 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (s, 3H), 2.18–2.32 (m, 1H), 2.43–2.70 (m, 3H), 2.95 (dt, J = 13.9 and 4.8 Hz, 1H), 3.90–4.03 (m, 2H), 4.18–4.25 (m, 1H), 5.08 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.16 (s, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 8.31 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 27.2, 30.6, 39.6, 56.1, 61.3, 111.7, 115.0, 118.9, 120.2, 122.69, 122.74, 125.2, 136.9, 170.9, 175.6; ESIMS (m/z) 287 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{19}O_3N_2$ 287.1390, found 287.1386; IR ($CHCl_3$) ν_{max} 3282, 1736, 1671 cm^{-1}.

(±)-4-Chloro-1-(2-hydroxyethyl)-5-(1*H*-indol-3-yl)pyrrolidin-2-one (15). It was prepared according to the general procedure, silica gel column purified using ethyl acetate–petroleum ether (4 : 1) as an eluent and obtained as a cream colour solid (2.57 g, 82%). Mp 118–120 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (dd, J = 17.6 and 4.7 Hz, 1H), 3.10–3.22 (m, 2H), 3.70–3.80 (m, 3H), 4.48–4.55 (m, 1H), 5.17 (d, J = 3.9 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 8.40 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.6, 45.0, 56.5, 61.2, 67.1, 111.5, 111.9, 118.5, 120.6, 123.07, 123.12, 124.9, 136.9, 173.1; ESIMS (m/z) 279 $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}O_2N_2Cl$ 279.0900, found 279.0910; IR ($CHCl_3$) ν_{max} 3298, 1667 cm^{-1}.

2-(2-Hydroxyethyl)-3-(1*H*-indol-3-yl)isoindolin-1-one (21). It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (24 : 1) as an eluent and obtained as a cream colour solid (2.02 g, 88%). Mp 172–174 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80–2.83 (br s, 1H), 3.35 (td, J = 15.2 and 4.6 Hz, 1H), 3.72 (t, J = 5.4 Hz, 2H), 3.81 (td, J = 14.5 and 4.6 Hz, 1H), 5.88 (s, 1H), 6.84 (br s, 1H), 6.90 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.34 (br s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.44–7.52 (m, 2H), 7.95 (d, J = 6.1 Hz, 1H), 8.84 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2, 59.9, 61.9, 110.2, 111.6, 118.8, 120.1, 122.6, 123.2, 123.3, 125.1, 128.3, 131.5, 132.0, 136.9, 146.3, 169.9; ESIMS (m/z) 293 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{17}O_2N_2$ 293.1290, found 293.1296; IR ($CHCl_3$) ν_{max} 3327, 1663 cm^{-1}.

General procedure for conversion of alcohol to the corresponding iodide

1-(2-Iodoethyl)pyrrolidine-2,5-dione (26). To a stirred solution of imide **2a** (1.40 g, 9.78 mmol) in dry DCM (20 mL) were added DIPEA (4.26 mL, 24.45 mmol) and MsCl (0.90 mL, 11.74 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h allowing the temperature to reach 25 °C and concentrated *in vacuo*. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–petroleum ether (7 : 3) as an eluent afforded mesylate **2b** (2.00 g, 92%). To a stirred solution of mesylate **2b** (1.80 g, 8.14 mmol) in anhydrous acetone (40 mL) was added NaI (12.20 g, 81.36 mmol) at 25 °C and the reaction mixture was refluxed for 24 h. The reaction mixture was allowed to reach room temperature and concentrated *in vacuo*. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–pet ether (3 : 7) as an eluent afforded iodoimide **26** as a yellow solid (1.63 g, 79%). Mp 54–56 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.76 (s, 4H), 3.33 (t, J = 7.2 Hz, 2H), 3.91 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.1, 28.1, 40.6, 176.5; ESIMS (m/z) 253 $[M + H]^+$; HRMS (ESI) calcd for $C_6H_9O_2NI$ 253.9678, found 253.9692; IR ($CHCl_3$) ν_{max} 1772, 1707 cm^{-1}.

5-(1*H*-Indol-3-yl)-1-(2-iodoethyl)pyrrolidin-2-one (6). It was prepared according to the general procedure, silica gel column purified using ethyl acetate–petroleum ether (4 : 1) as an eluent and obtained as a yellow solid (986 mg, 68%). Mp 128–130 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22–2.32 (m, 1H), 2.47–2.72 (m, 3H), 3.00–3.08 (m, 1H), 3.12–3.29 (m, 2H), 3.93–4.01 (m, 1H), 5.12 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 4.5 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 8.27 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.3, 27.1, 30.7, 43.2, 56.0, 111.7, 114.9, 118.9, 120.3, 122.8 (2C), 125.1, 136.9, 175.3; ESIMS (m/z) 355 $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}ON_2I$ 355.0302, found 355.0296; IR ($CHCl_3$) ν_{max} 3279, 1667 cm^{-1}.

1-(2-Iodoethyl)-1*H*-pyrrole-2,5-dione (29). It was prepared according to the general procedure, silica gel column purified using ethyl acetate–petroleum ether (1 : 3) as an eluent and obtained as a yellow solid (947 mg, 67%). Mp 42–44 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.33 (t, J = 7.2 Hz, 2H), 3.92 (t, J = 6.9 Hz, 2H), 6.75 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.01, 39.9, 134.2, 170.0; ESIMS (m/z) 251 $[M + H]^+$; HRMS (ESI) calcd for $C_6H_7O_2NI$ 251.9521, found 251.9516; IR ($CHCl_3$) ν_{max} 1713 cm^{-1}.

2-(2-Iodoethyl)isoindoline-1,3-dione (32). It was prepared according to the general procedure, silica gel column purified using ethyl acetate–petroleum ether (3 : 7) as an eluent and obtained as a white solid (1.94 g, 82%). Mp 98–100 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (t, J = 7.6 Hz, 2H), 4.09 (t, J = 6.9 Hz, 2H), 7.73–7.79 (m, 2H), 7.85–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −0.09, 40.0, 123.5, 131.8, 134.2, 167.7; ESIMS (m/z) 301 $[M + H]^+$; HRMS (ESI) calcd for $C_{10}H_9O_2NI$ 301.9678, found 301.9697; IR ($CHCl_3$) ν_{max} 1770, 1705 cm^{-1}.

5-(1*H*-Indol-3-yl)-2,3,5,6-tetrahydropyrrolo[2,1-*b*]oxazole (7). To a stirred solution of compound **6** (300 mg, 0.85 mmol) in dry THF (6 mL) was added *t*-BuOK (210 mg, 1.86 mmol) at 0 °C and the reaction mixture was stirred for 4 h allowing the temperature to reach 25 °C. The reaction was quenched with saturated aq. NH_4Cl (3 mL) and the reaction mixture was concentrated *in vacuo*. The obtained residue was dissolved in ethyl acetate (15 mL) and the resultant solution was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (7 : 3) as an eluent afforded **7** as a white solid (167 mg, 87%). Mp 118–120 °C, ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 2.15–2.23 (m, 1H), 2.47–2.60 (m, 2H), 2.62–2.72 (m, 1H), 4.38 (s, 1H), 4.40 (d, J = 5.5 Hz, 1H), 5.34 (d, J = 6.4 Hz, 1H), 6.96 (d, J = 1.5 Hz, 1H), 7.11 (dd, J = 13.0 and 7.6 Hz, 1H), 7.17 (t, J = 6.1 Hz, 1H), 7.25 (t, J = 6.1 Hz, 1H), 7.41 (d, J = 6.7 Hz, 1H), 7.57 (d, J = 6.4 Hz, 1H), 8.27 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3, 30.1, 54.2, 96.5, 111.6, 115.0, 118.4, 119.9, 121.2, 122.5, 125.1, 128.1, 136.8, 173.9; ESIMS (m/z) 227 $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_{15}ON_2$ 227.1179, found 227.1176; IR ($CHCl_3$) ν_{max} 3293, 1682, 1636 cm^{-1}.

General procedure for cyclization reaction of indole and an aldehyde moiety

(±)-6-Hydroxy-1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*]indol-3-one (9). To a stirred solution of alcohol **5** (1.50 g, 6.14 mmol) in anhydrous DCM (20 mL) were added Dess–Martin periodinane (3.91 g, 9.21 mmol) and pyridine (0.740 mL, 9.21 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 5.5 h allowing the temperature to reach 25 °C. The reaction mixture was diluted with DCM (20 mL) and quenched with a mixture of aq. sodium thiosulfate (40%, 5 mL) plus saturated aq. $NaHCO_3$ (5 mL). It was extracted with DCM (30 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by immediate silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1 : 1) as an eluent afforded aldehyde **8** as a brown solid (952 mg, 64%). To a stirred solution of aldehyde **8** (900 mg, 3.71 mmol) in MeCN : H_2O (1 : 1, 15 mL) was added formic acid (1.40 mL, 37.15 mmol) at 25 °C. The reaction mixture was stirred for 7 h and the reaction was quenched with saturated aq. $NaHCO_3$ (3 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (20 mL). The resultant solution was washed with brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM–MeOH (24 : 1) as an eluent afforded (±)-**9** as a white solid (504 mg, 56%). Mp 224–226 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.67–1.75 (m, 1H), 2.28 (dd, J = 16.8 and 8.4 Hz, 1H), 2.45–2.55 (m, 1H), 2.73–2.83 (m, 1H), 3.09 (dd, J = 13.4 and 2.3 Hz, 1H), 4.18 (d, J = 13.7 Hz, 1H), 4.74 (dd, J = 6.5 and 2.3 Hz, 1H), 4.86 (dd, J = 9.5 and 6.1 Hz, 1H), 5.32 (d, J = 6.1 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 11.11 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.8, 31.5, 45.4, 53.9, 60.7, 111.7, 112.1, 118.7, 118.8, 121.7, 123.7, 133.1, 136.2, 172.9; ESIMS (m/z) 243 $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_{14}O_2N_2Na$ 265.0952, found 265.0952; IR ($CHCl_3$) ν_{max} 3254, 1650 cm^{-1}.

(±)-1-Chloro-6-hydroxy-1,2,5,6,7,11c-hexahydro-3*H*-indolizino[7,8-*b*]indol-3-one (17). It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (24 : 1) as an eluent and obtained as a white solid (126 mg, 63%). Mp 202–204 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.82 (dd, J = 16.4 and 9.9 Hz, 1H), 3.00 (dd, J = 16.0 and 8.4 Hz, 1H), 3.10 (d, J = 12.2 Hz, 1H), 4.22 (d, J = 13.7 Hz, 1H), 4.42 (q, J = 7.6 Hz, 1H), 4.70 (d, J = 6.9 Hz, 1H), 5.07 (d, J = 7.6 Hz, 1H), 5.39 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 11.34 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 41.7, 45.3, 56.8, 60.5, 63.0, 108.6, 111.8, 119.2, 120.1, 122.0, 123.7, 134.5, 136.2, 169.9; ESIMS (m/z) 277 $[M + H]^+$; HRMS (ESI) calcd for $C_{14}H_{13}O_2N_2ClNa$ 299.0563, found 299.0558; IR ($CHCl_3$) ν_{max} 3415, 1659 cm^{-1}.

(±)-6-Hydroxy-5,6,7,13b-tetrahydro-9*H*-benzo[1,2]indolizino[7,8-*b*]indol-9-one (23). It was prepared according to the general procedure, silica gel column purified using DCM–MeOH (97 : 3) as an eluent and obtained as a white solid (95 mg, 68%). Mp 188–190 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.55 (d, J = 14.0 Hz, 1H), 4.83 (br s, 1H), 5.42 (d, J = 4.3 Hz, 1H), 6.06 (s, 1H), 7.13 (t, J = 6.1 Hz, 2H), 7.37 (d, J = 7.3 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.66 (t, J = 7.3 Hz, 2H), 7.75 (d, J = 7.3 Hz, 1H), 8.07 (d, J = 7.3 Hz, 1H), 8.19 (d, J = 7.3 Hz, 1H), 11.29 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 45.9, 57.7, 61.8, 108.3, 111.9, 119.3, 119.9, 121.9, 123.2, 124.1, 124.4, 128.2, 131.8, 132.2, 134.1, 136.3, 145.3, 168.1; ESIMS (m/z) 291 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{14}O_2N_2Na$ 313.0952, found 313.0969; IR ($CHCl_3$) ν_{max} 3272, 1734, 1667 cm^{-1}.

(±)-5-(1-Tosyl-1*H*-indol-2-yl)tetrahydro-5*H*-5,7a-epoxypyrrolo[2,1-*b*]oxazole (28). To a stirred solution of 1-tosyl-1*H*-indole (**24**, 300 mg, 1.11 mmol) in dry THF (8 mL) was added dropwise *n*-butyllithium (2.00 M in cyclohexane; 1.27 mL, 2.54 mmol) at −78 °C under an argon atmosphere. The reaction mixture was further stirred for 2 h allowing the temperature to reach 25 °C. The reaction mixture was again cooled to −100 °C and a solution of iodo compound **26** (310 mg, 1.22 mmol) in dry THF (8 mL) was added in a dropwise fashion. The reaction mixture was further stirred for 1 h allowing the temperature to reach −78 °C and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (20 mL). The resultant solution was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (3 : 7) as an eluent afforded (±)-**28** as a thick colourless oil (325 mg, 74%). ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.37 (s, 3H), 2.48 (ddd, J = 16.6, 9.9 and 3.1 Hz, 1H), 2.62–2.72 (m, 1H), 2.79 (dd, J = 17.2 and 8.8 Hz, 1H), 2.91 (ddd, J = 13.7, 9.9 and 2.7 Hz, 1H), 2.98 (br s, 1H), 3.40 (br s, 1H), 3.76–3.84 (m, 1H), 3.95–4.04 (m, 1H), 6.86 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 8.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.7 Hz, 2H), 8.31 (d, J = 8.4 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 21.5, 33.0, 34.4, 42.7, 66.7, 100.1, 112.3, 116.0, 122.5, 124.6, 126.3, 128.1, 129.1, 130.5 (2C), 137.5, 139.5, 140.5, 146.1; ESIMS (m/z) 397 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{21}O_4N_2S$ 397.1222, found 397.1217; IR ($CHCl_3$) ν_{max} 1686, 1635 cm^{-1}.

7a-(1-Tosyl-1*H*-indol-2-yl)-2,3-dihydropyrrolo[2,1-*b*]oxazol-5(7a*H*)-one (31). To a stirred solution of 1-tosyl-1*H*-indole (**24**, 500 mg, 1.84 mmol) in dry THF (10 mL) was added dropwise

n-butyllithium (2.00 M in cyclohexane; 2.12 mL, 4.24 mmol) at −78 °C under an argon atmosphere. The reaction mixture was further stirred for 2 h allowing the temperature to reach 25 °C. The reaction mixture was again cooled to −100 °C and a solution of iodo compound **29** (510 mg, 2.03 mmol) in dry THF (10 mL) was added in a dropwise fashion. The reaction mixture was further stirred for 1 h allowing the temperature to reach −78 °C and the reaction was quenched with saturated aqueous NH_4Cl (4 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (30 mL). The resultant solution was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1 : 3) as an eluent afforded **31** as a brown solid (520 mg, 71%). Mp 144–146 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.27 (ddd, J = 10.7, 6.6 and 5.0 Hz, 1H), 3.56 (q, J = 7.6 Hz, 1H), 3.84–3.92 (m, 1H), 4.18 (td, J = 8.3 and 5.1 Hz, 1H), 6.08 (d, J = 5.8 Hz, 1H), 6.94 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 5.9 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 41.8, 70.0, 99.8, 112.1, 115.0, 122.5, 123.9, 125.8, 127.2, 127.4, 127.8, 129.4, 135.4, 136.4, 138.8, 144.8, 150.3, 176.4; ESIMS (*m*/*z*) 395 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{19}O_4N_2S$ 395.1065, found 395.1068; IR ($CHCl_3$) ν_{max} 1710, 1598 cm^{-1}.

9b-(1-Tosyl-1*H*-indol-2-yl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one (34). To a stirred solution of 1-tosyl-1*H*-indole (**24**, 1.50 g, 5.53 mmol) in dry THF (20 mL) was added dropwise *n*-butyllithium (2.00 M in cyclohexane; 6.36 mL, 12.71 mmol) at −78 °C under an argon atmosphere. The reaction mixture was further stirred for 2 h allowing the temperature to reach 25 °C. The reaction mixture was again cooled to −78 °C and a solution of iodo compound **32** (1.83 g, 6.08 mmol) in dry THF (8 mL) was added in a dropwise fashion. The reaction mixture was further stirred for 1 h at −78 °C and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (40 mL). The resultant solution was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (1 : 4) as an eluent afforded **34** as a white solid (1.90 g, 87%). Mp 202–204 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 2.63 (br s, 1H), 3.85 (br s, 1H), 3.95–4.05 (m, 1H), 4.18 (q, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.24 (br s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.54–7.63 (m, 6H), 7.83–7.87 (m, 1H), 8.40 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 41.4, 70.0, 97.8, 111.5, 115.7, 121.3, 123.9, 124.1, 125.8, 126.5, 128.0, 129.5, 130.5, 131.8, 133.2, 133.3, 135.8, 136.7, 139.7, 144.6, 145.3, 174.2; ESIMS (*m*/*z*) 445 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{21}O_4N_2S$ 445.2117, found 445.2213; IR ($CHCl_3$) ν_{max} 1720, 1599 cm^{-1}.

2-(2-Hydroxyethyl)-3-(1*H*-indol-2-yl)isoindolin-1-one (35). To a stirred solution of *N*-tosyl protected compound **34** (1.50 g, 4.50 mmol) in MeOH : benzene (1 : 1; 20 mL) were sequentially added activated magnesium turnings (1.23 g, 50.62 mmol) and ammonium chloride (2.71 g, 50.62 mmol) at 25 °C under an argon atmosphere. The reaction mixture was stirred for 4 h and quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (30 mL). The resultant solution was washed with brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using DCM–MeOH (24 : 1) as an eluent afforded **35** as a white solid (720 mg, 73%). Mp 102–104 °C, ^{1}H NMR (acetone-d_6, 400 MHz) δ 3.13–3.22 (m, 1H), 3.65–3.78 (m, 2H), 3.92 (dt, J = 14.5 and 5.4 Hz, 1H), 4.08 (t, J = 6.1 Hz, 1H), 6.09 (s, 1H), 6.75 (d, J = 1.5 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.48–7.60 (m, 3H), 7.76 (d, J = 6.9 Hz, 1H), 10.18 (br s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 44.2, 60.6, 61.2, 104.1, 111.2, 120.3, 121.2, 122.8, 123.9, 124.3, 129.2, 129.4, 132.6, 133.1, 135.2, 138.4, 146.1, 168.8; ESIMS (*m*/*z*) 293 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{16}O_4N_2Na$ 315.1104, found 315.1101; IR ($CHCl_3$) ν_{max} 3284, 1663 cm^{-1}.

2-[1-(1*H*-Indol-2-yl)-3-oxoisoindolin-2-yl]ethyl Methanesulfonate (36). To a stirred solution of alcohol **35** (500 mg, 1.71 mmol) in anhydrous DCM (10 mL) were added DIPEA (0.75 mL, 4.28 mmol) and MsCl (0.16 mL, 2.05 mmol) at 0 °C under an argon atmosphere. The reaction mixture was further stirred for 1 h allowing the temperature to reach 25 °C and concentrated *in vacuo*. The obtained residue on direct silica gel (230–400 mesh) column chromatographic purification using ethyl acetate–petroleum ether (4 : 1) as an eluent afforded mesylate compound **36** as a white solid (621 mg, 98%). Mp 174–176 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94 (s, 3H), 3.46 (ddd, J = 15.2, 7.1 and 4.4 Hz, 1H), 4.08 (dt, J = 15.1 and 4.6 Hz, 1H), 4.34–4.45 (m, 2H), 5.95 (s, 1H), 6.81 (d, J = 1.5 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 9.10 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.6, 40.2, 60.0, 67.5, 104.7, 111.4, 120.1, 120.7, 122.8, 123.45, 123.51, 127.8, 129.0, 130.8, 132.1, 132.4, 137.2, 144.3, 168.9; ESIMS (*m*/*z*) 371 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_4N_2S$ 371.1060, found 371.1054; IR ($CHCl_3$) ν_{max} 3416, 1683 cm^{-1}.

13b-Hydroxy-6,7-dihydroisoindolo[1′,2′:3,4]pyrazino[1,2-*a*]indol-9(13b*H*)-one (38). To a stirred solution of *t*-BuOK (46 mg, 0.40 mmol) in dry THF (4 mL) was added dropwise a solution of mesylate **36** (100 mg, 0.27 mmol) in THF (5 mL) at 0 °C under an argon atmosphere. The reaction mixture was further stirred for 1 h allowing the temperature to reach 25 °C and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (20 mL). The resultant solution was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using ethyl acetate–pet-

roleum ether (4 : 1) as an eluent afforded **38** as a white solid (64 mg, 82%). Mp 162–164 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.78–3.98 (m, 2H), 4.40 (dd, J = 10.2 and 3.4 Hz, 1H), 4.49 (dd, J = 11.4 and 3.4 Hz, 1H), 6.90 (s, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.17 (t, J = 7.1 Hz, 1H), 7.33 (s, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.4 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.7, 40.8, 83.4, 99.9, 110.1, 120.1, 120.5, 121.8, 122.7, 123.4, 127.0, 129.5, 130.0, 132.9, 135.2, 135.9, 147.8, 165.5; ESIMS (m/z) 291 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{15}O_2N_2$ 291.1133, found 291.1136; IR ($CHCl_3$) ν_{max} 3416, 1706, 1593 cm^{-1}.

Conflicts of interest

There are no conflicts to declare.

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