Cyclic Anhydrides and Derivatives: Studies on Synthesis of Bioactive Alkaloids

by

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Under the supervision of

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Certificate

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Date: 18/05/2022

Place: Pune

Dedicated to

My Parents and Teachers

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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.

Finally, I would not complete my acknowledgment without thanking God for giving me the strength and the determination to overcome the hardships faced in my life.

~KAILAS

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
HCHO	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
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
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
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

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

AcSIR	**Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemical Sciences**
Name of the Candidate	Mr. Pandhade Kailas Rudrappa
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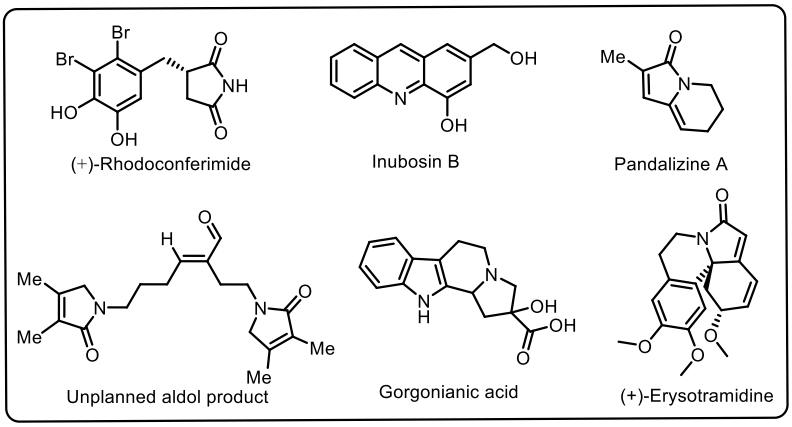
Title of the Thesis	Cyclic Anhydrides and Derivatives: Studies on Synthesis of Bioactive Alkaloids
Research Supervisor	Dr. Narshinha P. Argade

1. Introduction

In nature, there are many classes of naturally occurring organic compounds such as carbohydrates, lipids, proteins, amino acids, anthocyanins, flavonoids, steroids, and the one that seems to be quite remarkable is alkaloids.[1] Alkaloids are nitrogen-containing compounds that occur naturally in plants and microorganisms, marine organisms, and animals. Alkaloids showed substantial biological effects on animals and humans in minimal doses. Bioactive alkaloids have significant importance in chemistry and play a vital role basically in medicinal chemistry. Examples of alkaloids include morphine, codeine, coniine, quinine, scopolamine, hyoscyamine, atropine, caffeine, sanguinarine, and berberine.[1] Alkaloids are present in daily human life in food and drinks and as a stimulant. They show anti-inflammatory, anticancer, analgesics, local anesthetic, pain relief, neuropharmacological, antimicrobial, antifungal, and many other activities.[1] Alkaloids are useful as diet ingredients, supplements, and pharmaceuticals in medicine and other human life applications.[1] Alkaloids are also essential compounds in organic synthesis for screening new semisynthetic and synthetic compounds with possibly better biological activity than parent compounds. It is known that approximately over half of the pharmaceuticals in clinical use today are derived from bioactive natural products.

In life processes, imbalance of free radicals causes damage to cells resulting in aging and diseases such as atherosclerosis, cancer, cardiovascular disorder, diabetes, inflammation, Alzheimer and Parkinson's. Antioxidants play a vital role in protecting human beings from free radicals-induced damages.[2] Wang and co-workers in 2012 isolated a new potent antioxidant, natural product (+)-rhodoconferimide from the air-dried sample of *Rhodomela confervoides*.[2] Inubosin B is the most active member of the acridine alkaloids isolated from *Streptomyces sp.* IFM 11440 culture.[3] The inubosins initiate neuroregeneration via a neurogenine 2 pathway.[3] Tropical *Pandanus amaryllifolius* shrub from Southeast Asia is used in folk medicine for the treatment of gout, hyperglycemia, hypertension, and rheumatism.[4] Recently, the azabicyclic alkaloids pandalizines A−E have been isolated from aerial parts of *Pandanus* amaryllifolius species.[4] Indole alkaloids are an important class of compounds because they have a wide range of biological activities.[5] Gorgonianic acid, an indole-based alkaloid was isolated from the extract of the South China Sea *Gorgonian isis minobrachyblasta*.[5] The *Erythrina* family of alkaloids is a well-known natural product class that has received considerable attention over the past few decades.[6] Many members of this family possess curare-like activity, and the alkaloidal extracts have been used in indigenous medicine.[6] Many different approaches have been employed to synthesize this class of natural products. Hence, understanding the importance of bioactive alkaloids, we prepared a systematic plan to synthesize them using cyclic anhydride and their derivatives as potential precursors.



2. Statement of Problem

The first total synthesis of natural product (±)-rhodoconferimide and facile total synthesis of pandalizine A have been completed. The total synthesis of alkaloid gorgonianic acid is one step behind for its completion. The total synthesis of acridine alkaloid inubosin B and erythrina alkaloid erysotramidine are in active progress.

3. Objectives

Total synthesis of bioactive natural products from the cyclic anhydride and their derivatives.

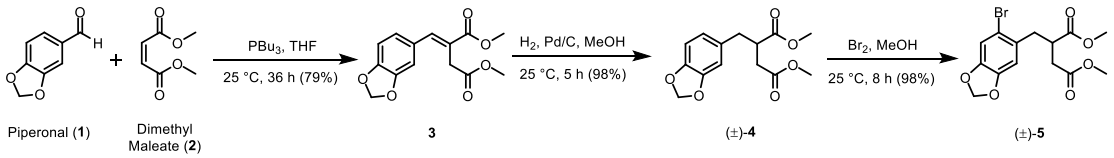
4. Methodology

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.

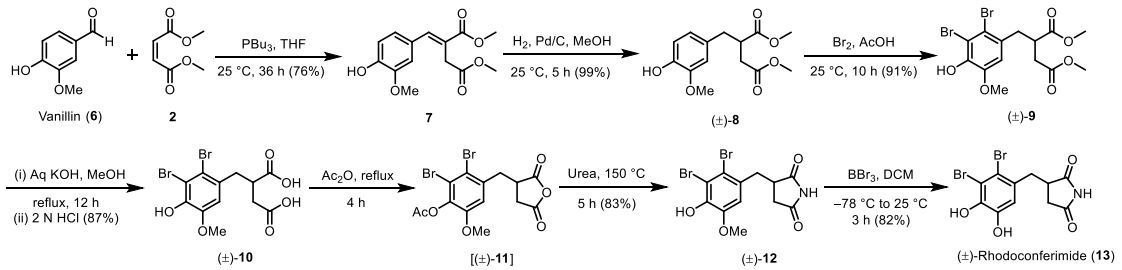
5. Results

(i) In our first approach for the total synthesis of potent antioxidant marine natural product (±)-rhodoconferimide, compound **4** was not sufficiently activated for regioselective dibromination (Scheme 1). Therefore, in the second approach, instead of piperonal we started with vanillin and successfully accomplished the synthesis of target compound. Appropriate sequencing of the reactions, regioselective electrophilic introduction of two bromine atoms on the properly activated aromatic ring and overall stability of catechol moiety were the synthetic concerns of the synthesis (Scheme 2).

Scheme 1. Synthesis of Mono-brominated Model Compound



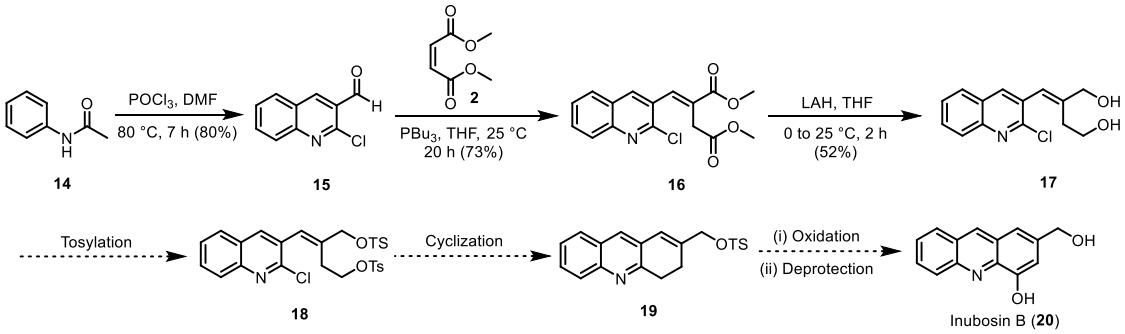
Scheme 2. First Total Synthesis of (±)-Rhodoconferimide via One-pot Regioselective Bromination



In summary, we have demonstrated the synthesis of (±)-rhodoconferimide via Wittig reaction, catalytic hydrogenation, selective brominations and imide formation. An appropriate regioselective double bromination of aromatic ring was a key step in the synthesis. Total synthesis of (±)-rhodoconferimide has been completedd without involving any separate protection step. It is noteworthy that structurally simple (+)-rhodoconferimide is more potent antioxidant than the multifunctional urceolatin.

(ii) Synthesis of inubosin B started with the Wittig reaction between dimethyl maleate and prepared quinaldehyde to form the corresponding alkene product. Reduction of the diester moiety directly gave corresponding diol product (Scheme 3).

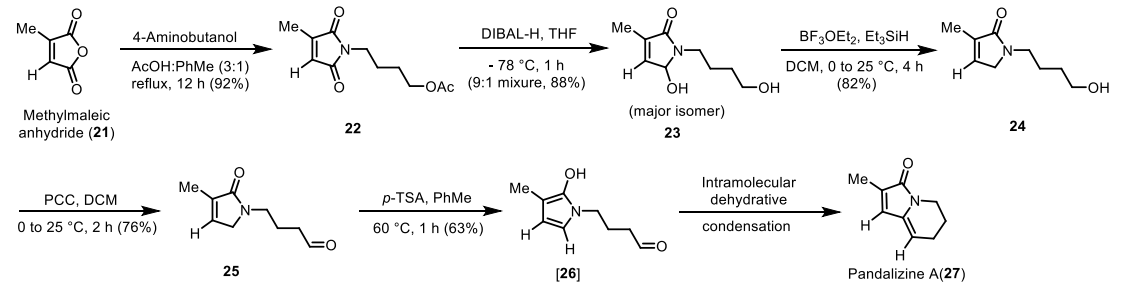
Scheme 3. In Progress Total Synthesis of Inubosin B



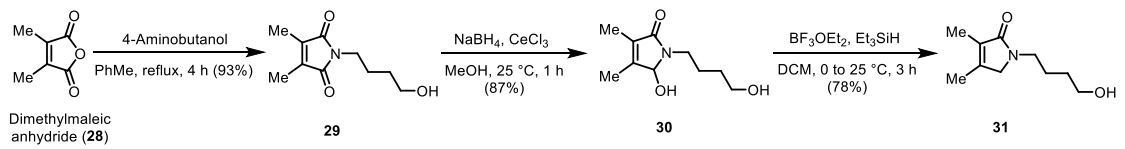
In summary, we are planning to synthesize inubosin B via reactions sequence as tosylation of the obtained diol, selective intramolecular cyclization, benzylic oxidation followed by aromatization, and finally deprotection of the hydroxy group.

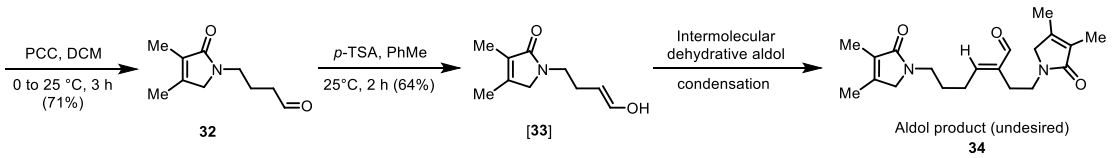
(iii) Starting from methylmaleic anhydride, a facile total synthesis of pandalizine A alkaloid is described via the regioselective reduction of methylmaleimide and acid-catalyzed enolization of butanal followed by chemoselective intramolecular dehydrative cyclization as the key steps (Scheme 4). It is noteworthy that the analogous model system with an additional *β*-methyl group followed an alternative chemoselective intermolecular aldol condensation pathway (Scheme 5).

Scheme 4. A Facile Total Synthesis of Pandalizine A Alkaloid



Scheme 5. Attempted Synthesis of Pandalizine A Derivative Leading to Facile Dimerization

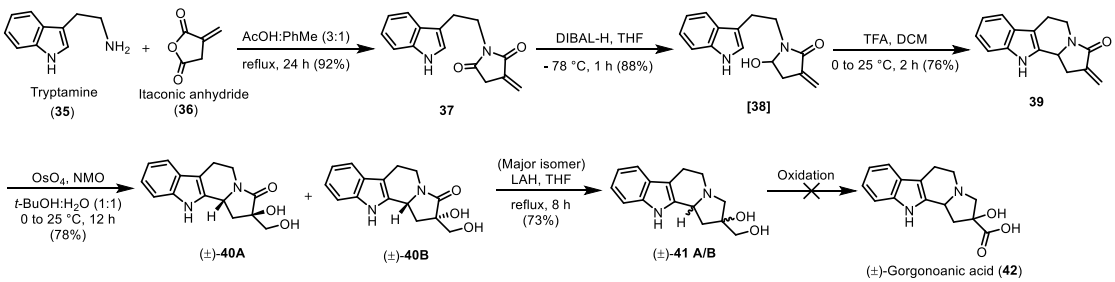




In summary, from readily available starting materials, we have completed the protection-free practical total synthesis of pandalizine A. The favored formation of an appropriately reactive cyclic enol intermediate for intramolecular cyclization is the basis of chemoselective ring closure. Overall, the *β*-methyl group governs the course of competitive carbon−carbon bond-forming reactions and functions as a chemoselectivity switch.

(iv) We commenced the total synthesis of indole alkaloid gorgonianic acid from readily available starting materials tryptamine and itaconic anhydride. The regioselective reduction of citraconimide followed by Pictet-Spengler cyclization and dihydroxylation of the conjugated double bond of the amide moity were the key steps (Scheme 6).

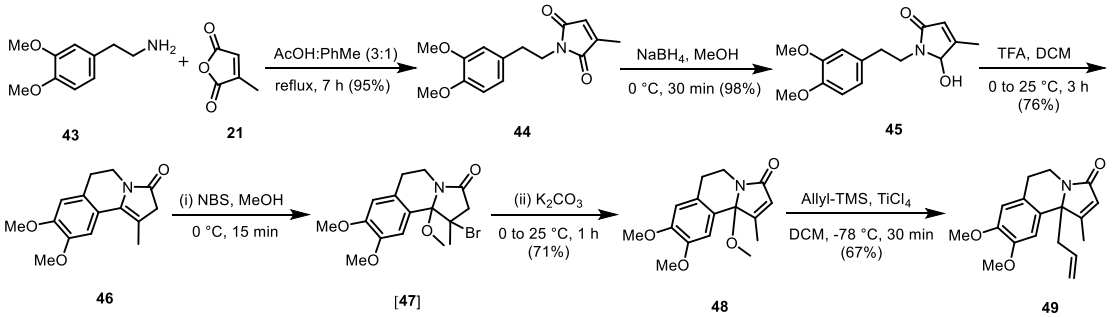
Scheme 6. Towards the Total Synthesis of Gorgonianic Acid

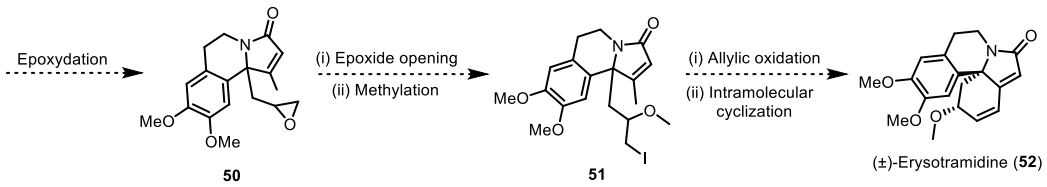


In summary, We have successfully completed the planned reaction sequence, and now we are one step behind for the completion of the total synthesis. Studies on oxidation of the last intermediate compound to the final product are in progress.

(v) A new strategy for the total synthesis of erysotramidine was planned with the imide formation reaction between dimethoxyphenethylamine and citraconic anhydride. Acid-catalyzed intramolecular cyclization of the synthesized lactamol furnished the enamine product via migration of the conjugated double bond to the more substituted side of compound. Bromination of enamine followed by its elimination in one step directly provided a conjugated imide. Allylation was the step that we have reached in the progression of synthesis (Scheme 7).

Scheme 7. In Progress Total Synthesis of Erysotramidine





In summary, Lewis acid-catalyzed allylation has been achieved in the progression of the total synthesis. Epoxidation of the terminal alkene followed by the regioselective opening of epoxide and subsequent methylation of the generated hydroxy group will furnish iodo compound **51** in the reaction sequence. Finally, oxidation of allylic position to the corresponding aldehyde and intramolecular cyclization between aldehyde with iodide using appropriate metal exchange/coupling reaction will accomplish the total synthesis of the final product.

6. Conclusion

We have developed a new approach for synthesizing bioactive alkaloids from cyclic anhydride and its derivatives. We have reported the first total synthesis of (±)-rhodoconferimide via regioselective double bromination of aromatic ring as a crucial step in the synthesis. We have completed the protection-free synthesis of pandalizine A using a chemoselective intramolecular cyclization pathway. At the same time, we observed the difference in chemoselectivity while the analogous model system with an additional *β*-methyl group furnishes the undesired aldol product. We are one step behind in completing the synthesis of gorgonianic acid, and the synthesis of inubosin B and erysotramidine are in progress.

7. Future direction

To complete the in progress synthesis of inubosin B, gorgonianic acid and erysotramidine.

8. Publications

(i) First Total Synthesis of (±)-Rhodoconferimide, **K. R. Pandhade**, N. P. Argade, *Synthesis* **2018**, *50*, 658–662.

(ii) Chemoselective Ring Closure of 4-(3-Methyl-2-oxo-2,5- dihydro-1H-pyrrol-1-yl) butanal Leading to Pandalizine A, M. B. Yadav, **K. R. Pandhade**, N. P. Argade, *ACS Omega* **2020**, *5*, 859−863.

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Chapter 1

A Concise Account on Cyclic Anhydrides and Derivatives to Bioactive Alkaloids

1.1 Introduction

Natural products are available from a wide variety of sources in the nature. Alkaloids appear to be unique among the various types of natural substances found in nature, including carbohydrates, anthocyanins, amino acids, flavonoids, lipids, proteins, and steroids. They are produced from amino acids and can be obtained as secondary metabolites from plants and animals.[1] Alkaloids are predominantly found in plants and are prevalent in some flowering plant groups, such as the opium poppy (*Papaver somniferum*) and the ergot fungus (*Claviceps*). Animals like the New World beaver (*Castor canadensis*) and Poison dart frogs (*Phyllobates*) also have a few alkaloids.[2] As nature's masterpieces, the alkaloid molecules had existed on this planet for billions of years before the Swiss botanist Carl F. W. Meissner coined the term 'alkaloid' in a modern scientific context during 1819. Alkaloids are a diversified group of naturally occurring organic compounds with a heterocyclic ring structure having at least one nitrogen atom as their structural determinant. The presence of adequately positioned nitrogen in their molecular structure affords exceptionally high biological activity to this class of compounds. Pelletier suggested a more precise definition of alkaloid in 1983: an alkaloid is a cyclic molecule in a negative oxidation state that contains nitrogen and has a limited distribution across living species.[3] Over 20,000 alkaloids have been reported in the literature to date.[4] Most alkaloids are colorless, bitter test, crystalline solids that are very marginally soluble in neutral and alkaline water solutions but readily soluble in acid and organic solvents like ether, chloroform, ethanol. Alkaloids are mostly crystalline compounds that react with acids to form salts. In addition to carbon, hydrogen, and nitrogen, alkaloids can contain oxygen, sulfur, as well as additional chlorine, bromine, and phosphorus atoms. At room temperature, some alkaloids (nicotine and coniine) are colorless liquids, whereas some others are colored solids, for example berberine is yellow and sanguinarine is red copper color (Figure 1).[1-5]

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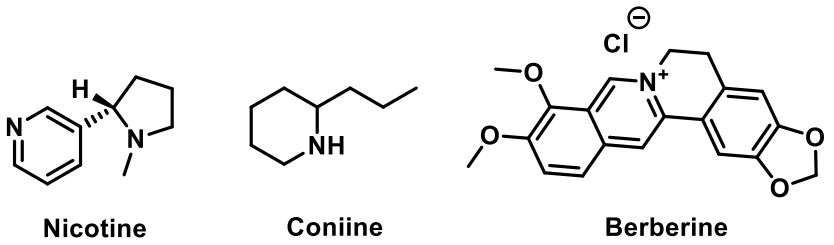
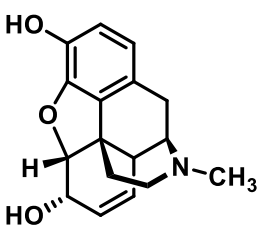


Figure 1. Examples of alkaloids

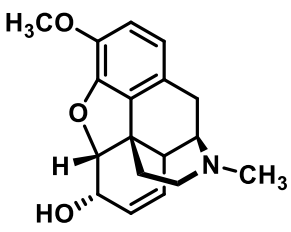
Alkaloids are still a fascinating subject, and they are now a topic of considerable scientific and economic interest, particularly in medicine and the pharmaceutical business.

1.2 Biological Activities of Alkaloids

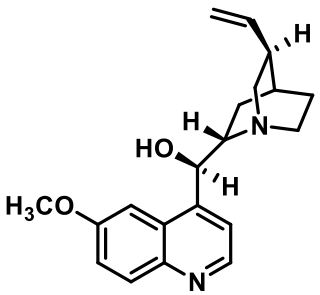
In living organisms alkaloids play a crucial role. They are essential for plant preservation and survival because they operate as a defence against microorganisms (antibacterial and antifungal activity).[6] Alkaloids are a natural substances that deters herbivorous species due to their bitter taste. They are employed as natural insecticides in some plants. It has been proposed that alkaloids in plants shield them from the damaging activity of some insect species. Alkaloids are important in medicine and various aspects of human life as diet elements, supplements, and medications.[7] Alkaloids exhibit promising biological impacts on animals and humans in very insignificant concentrations. Arrow poisons contain curare alkaloids as active components.[8] Tubocuranine, one of the curare alkaloids, has muscle relaxant effects that have been used to reduce convulsions during surgery as skeletal muscle relaxants. Certain alkaloids have been demonstrated to have anti-inflammatory, anticancer, analgesic, local anesthetic and pain relief, neuropharmacological, antibacterial, antifungal, and a wide range of other properties.[1,7] Alkaloids have a wide range of therapeutic characteristics. Many of them have local anesthetic abilities, but their clinical utility is limited. A German pharmacist, Friedrich Sertürner was the first to isolate morphine, one of the most critical alkaloids from the medical perspective (Figure 2).[7] This occurred in 1805 and became a key advancement in chemistry and pharmacology. This alkaloid is a potent narcotic that can be used to relieve pain, but its utility is restricted due to its addictive nature. Codeine is a morphine ether derivative that occurs naturally in the *Opium poppy* next to morphine, has good analgesic properties and has been shown to be non-addictive. Cocaine is a highly effective local anesthetic. Quinine is a potent antimalarial medication used in the treatment of malaria, but it has now been overtaken mainly by less toxic and more effective synthetic pharmaceuticals.



Morphine (analgesic)



Codeine (anesthetic)



Quinine (antipyretic)

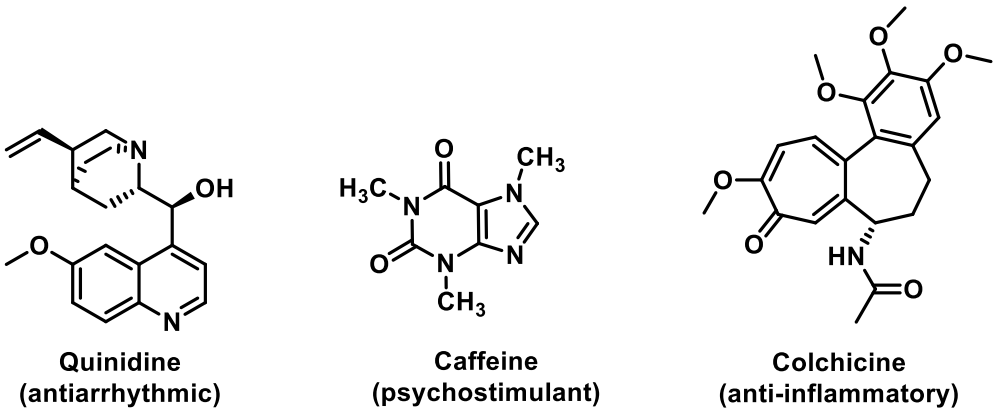


Figure 2. Pharmacologically active alkaloids

Quinidine, another alkaloid found in *Cinchona* species, is used in medicine to treat irregular heartbeats, sometimes known as arrhythmias. Caffeine is the most prevalent alkaloid and it is used as a flavor enhancer in soft drinks such as Coca-Cola and sports drinks. Colchicine is another alkaloid found in *Liliaceae* plants that has long been used to treat acute gout attacks. Lobeline, ephedrine, ergonovine, vincristine, vinblastine, and atropine are some of the other physiologically valuable alkaloids.[9] Alkaloids are also significant substances in organic synthesis for the development of novel semi-synthetic and synthetic drugs with possibly higher biological activity than their respective parent compounds.

1.3 Classification of Alkaloids

The botanical and biological origins, chemical structure, and pharmacological activity of alkaloids are all diverse. As a result, many different classification systems are feasible. The following major classes of alkaloids are commonly used in general.[10-12]

(i) Taxonomical Classification: The distribution of alkaloids in various plant families, such as solanaceous or papilionaceous alkaloids is used to classify them taxonomically. They are also categorized by the genus name, such as ephedra, cinchona, and so on.

(ii) Biosynthetic Classification: This is determined by the precursor from which the alkaloids in the plant were biosynthesized. As a result, a range of alkaloids with different taxonomic distributions and physiological activities can be grouped together if they are formed from the same precursor, such as indole alkaloids derived from tryptophan. Alkaloids generated from amino acids, such as lysine, ornithine, tyrosine, tryptophan, and phenylalanine are all classed together.

(iii) Pharmacological Classification: This method relies on the physiological effect or biological activities of alkaloids on animals, such as CNS stimulants, depressants,

purgatives, analgesics, sympathomimetics, and so on. It does not depend on the chemical characteristics of alkaloids. The alkaloids may have many physiological effects, such as morphine is a narcotic-analgesic, while quinidine is a cardiac sedative.

(iv) Chemical Classification: This is the most common method of identifying alkaloids, which are divided into three groups.[13,14]

(a) True Alkaloid: Structurally, these have nitrogen as a part of a cyclic ring system. These are more commonly found in nature and originated from amino acids. These true alkaloids are highly reactive substances with biological activity even in low doses. They form water-soluble salts, and most of them are well-defined crystalline substances that unite with acids to form salts. True alkaloids may occur in plants as in the free state, salts, or *N*-oxides. Examples of heterocyclic alkaloids include biologically active alkaloids, such as indicine *N*-oxide, serotonin, quinine, dopamine, castanospermine, and morphine **(**Figure 3).

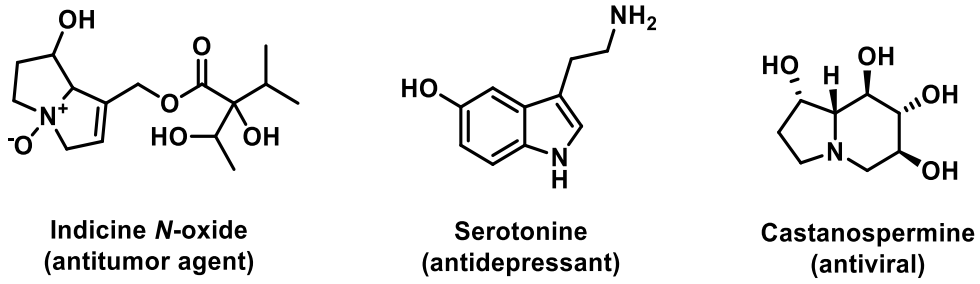


Figure 3. Examples of true alkaloids

(b) Proto Alkaloids: These are non-heterocyclic alkaloids obtained from amino acids. These are also called biological amines. These are less commonly found in nature. The nitrogen atom in these compounds is not part of any ring present in the structure. Ephedrine, adrenaline, and hordenine are a few examples of this class **(**Figure 4).

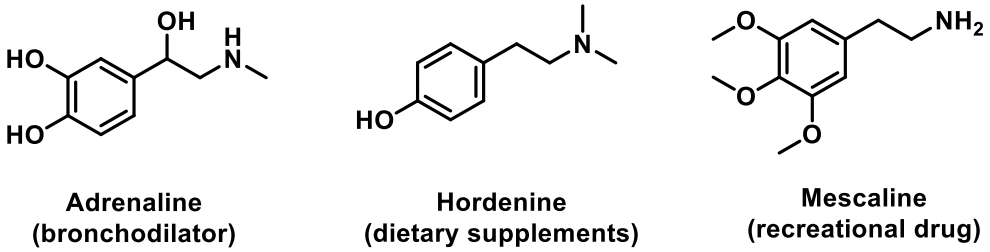


Figure 4. Examples of proto alkaloids

(c) Pseudo Alkaloids: These are nitrogen heterocyclic ring-containing compounds derived from terpenoids or purines but not from amino acids. In fact, amino acid pathways are correlated to pseudoalkaloids. They are produced from amino acid

precursors and postcursors. They can also be made due to amination and transamination processes in various amino acid precursors and postcursors. Caffeine, theobromine, and theophylline are well known as pseudo alkaloids **(**Figure 5).

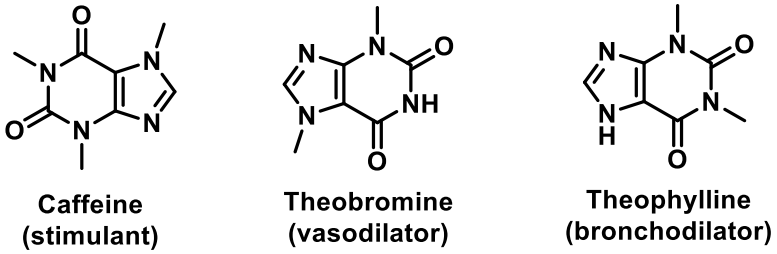


Figure 5. Examples of pseudo alkaloids

1.4 Heterocyclic Alkaloids

Heterocyclic alkaloids are among the most complex natural product classes to define, not only because of their structurally diverse skeletons derived from different amino acids but also due to their possible bioactivities. Heterocyclic alkaloids can be subdivided into the following groups based on the ring structure containing the nitrogen.[13,15]

(i) Indole Alkaloids: The structure of indole alkaloids includes a fundamental indole ring skeleton. It is one of the most diverse classes of alkaloids, with about 4000 members. Many of them have vital biological functions and some are useful as medicine (Figure 6). In nature, indole alkaloids produced from tryptophan originate from the shikimic acid pathway.[16]

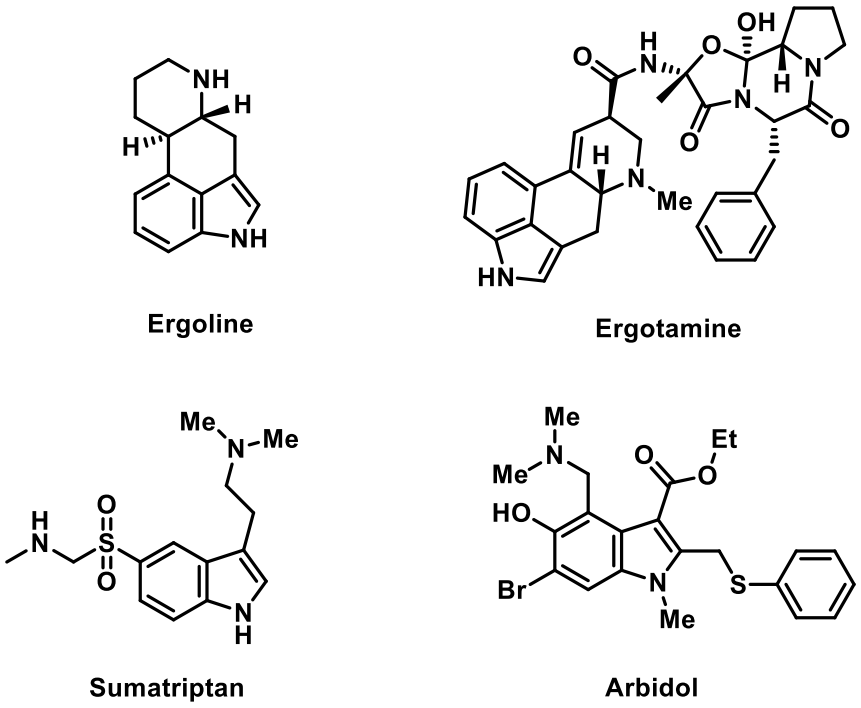


Figure 6. Representative indole alkaloids

(ii) Indolizidine Alkaloids: Indolizidine alkaloids are recognized as active biotoxins. Swainsonine is the most hazardous indolizidine alkaloid in terms of its harmful effect on animals. Castanospermine, a compound found in the seeds of Australian chestnut tree, is another example of indolizidine alkaloid (Figure 7).

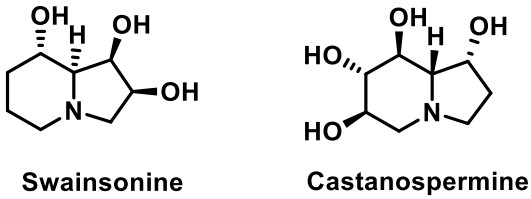


Figure 7. Representative indolizidine alkaloids

(iii) Isoquinoline Alkaloids: The most well-known isoquinoline alkaloids are morphine and codeine. They are derived from tyrosine or phenylalanine. Emetine, narcotine, papaverine, tubocurarine are the other examples of these alkaloids (Figure 8).

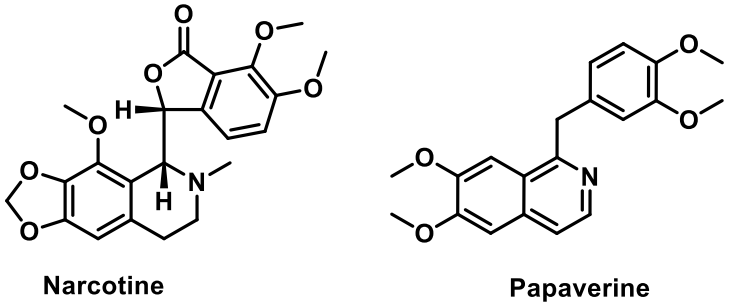


Figure 8. Representative isoquinoline alkaloids

(iv) Tropane Alkaloids: Tropane alkaloids are secondary metabolites that contain a tropane ring in their chemical structure and are classified as bicyclic [3.2.1] alkaloids (Figure 9). Many members of the *Solanaceae* plant family naturally have tropane alkaloids.[17]

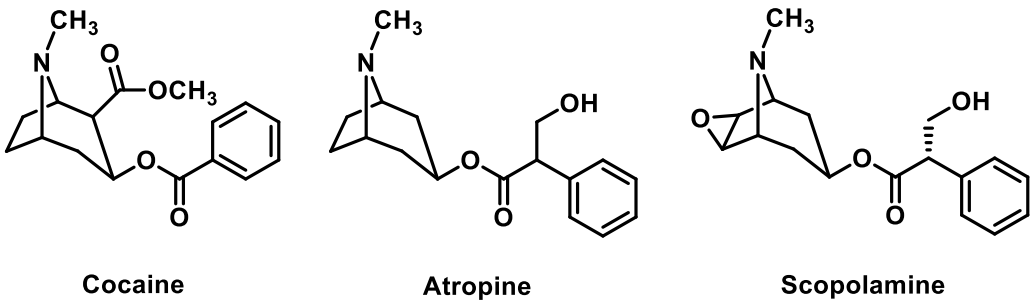


Figure 9. Representative tropane alkaloids

(v) Pyridine and Piperidine Alkaloids: The compounds of pyridine and piperidine alkaloids are plant bases and also isolated from insects, amphibians, and marine animals. They perform several different functions, such as train pheromones and defense mechanisms in insects. The examples are lobeline, trigonelline, and piperine (Figure 10).

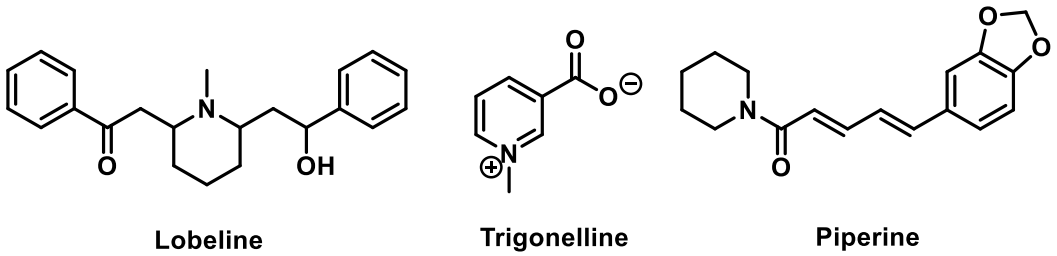


Figure 10. Representative pyridine and piperidine alkaloids

(vi) Imidazole Alkaloids: Essential biological building blocks like histidine and histamine-related hormones contain an imidazole ring structure. Alkaloids such as pilosine and (+)-pilocarpine are also examples of these classes (Figure 11).

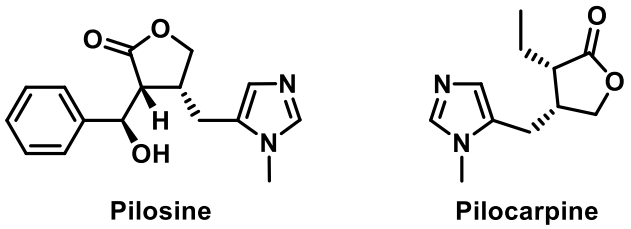


Figure 11. Representative imidazole alkaloids

(vii) Quinoline Alkaloids: Quinoline nucleus occurs in several natural compounds and synthetic derivatives displaying a broad range of biological activity. Quinoline alkaloids such as quinine, quinidine, cinchonine, and cinchonidine were the first drugs developed to treat malaria using *Cinchona* species (Figure 12).

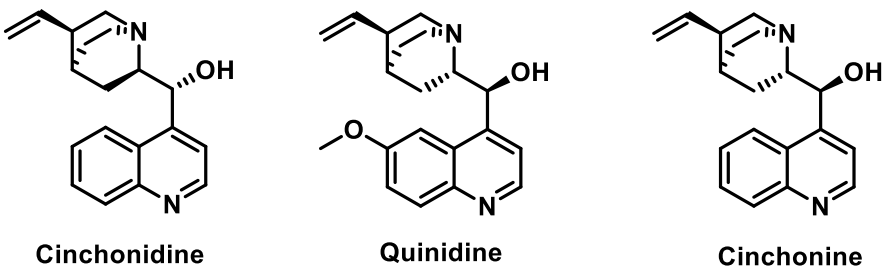


Figure 12. Representative quinoline alkaloids

(viii) Pyrrolizidine Alkaloids: Pyrrolizidine alkaloids, often known as necine bases are naturally occurring alkaloids based on the pyrrolizidine structure (Figure 13). Plants synthesize pyrrolizidine alkaloids as a defensive strategy against insect herbivores. Senecionine and seneciphylline are the most known pyrrolizidine alkaloids.

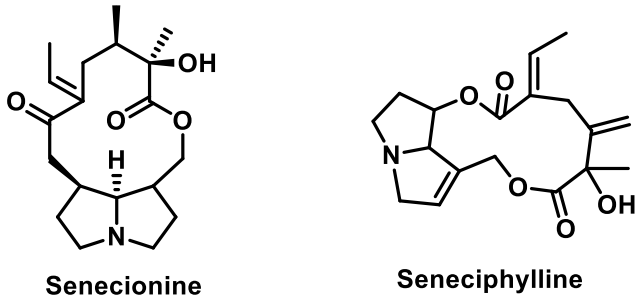


Figure 13. Representative pyrrolizidine alkaloids

(ix) Steroidal Alkaloids: They consist of organic ring backbones with nitrogen-based functional groups with steroidal skeleton. More specifically, their tetracyclic cyclopentanophenanthrene backbone is distinguished, marking their close relationship with sterols. Steroidal alkaloids have been studied for various bioactivities, including antibacterial, anti-inflammatory, antiestrogenic, and chemotherapeutic effects. Conessine is a type of steroidal alkaloid with antimalarial activity. Veratramine has distinct antitumor and antihypertension effects (Figure 14).

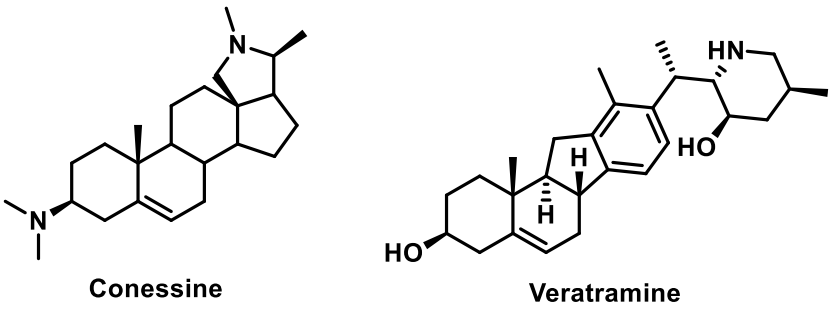


Figure 14. Representative steroidal alkaloids

(x) Terpenoid Alkaloids: Terpenoid alkaloids are pseudoalkaloids in which a nitrogen atom is introduced into the skeleton at a late stage of biosynthesis. Structure variety, fascinating chemistry, and promising pharmacological effects is a characteristic of this family of molecules. Atisine, salvinorin A, aconitine are examples of terpenoid alkaloids (Figure 15).

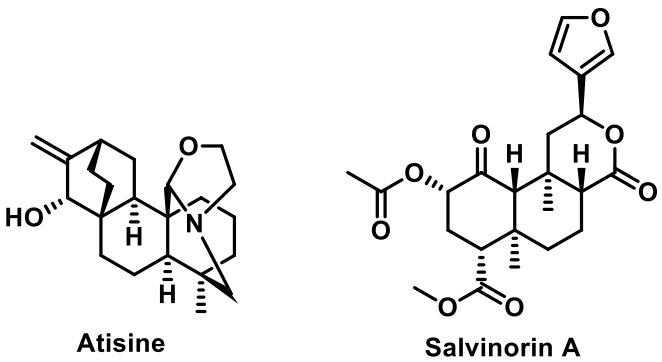


Figure 15. Representative terpenoid alkaloids

(xi) Purine Alkaloids: The most well-known nucleotide secondary metabolites are purine alkaloids. They are known as pseudoalkaloids because they are not generated from amino acids. Theobromine, theophylline, theacrine, and caffeine are the most common examples of purine alkaloids (Figure 16).

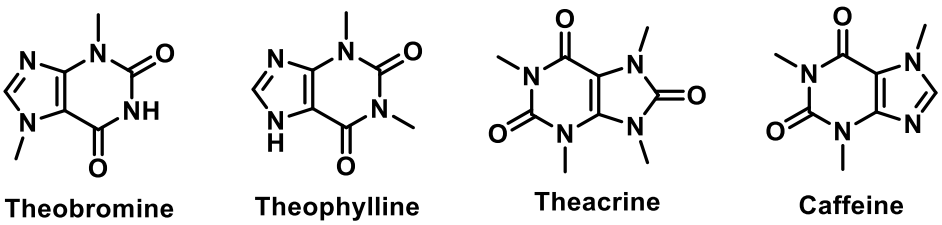


Figure 16. Representative purine alkaloids

(xii) Aporphine Alkaloids: Aporphine is a chemical compound having the formula $C_{17}H_{17}N$. The aporphine alkaloids, a subclass of quinoline alkaloids, have this chemical substructure as their core. Boldine is an aporphine class alkaloid found in the boldo tree. Apomorphine is mainly used to treat the symptoms of Parkinson's disease (Figure 17).

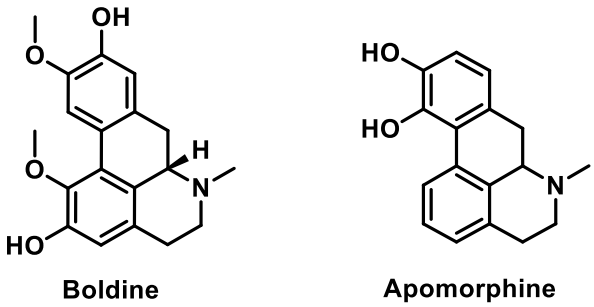


Figure 17. Representative aporphine alkaloids

(xiii) Quinolizidine Alkaloids: Quinolizidine alkaloids are natural products that contain a quinolizidine ring system. Frequently they are called lupin alkaloids because they are

present in all species of the large genus *Lupinus*. Lupanine, lupinine, epilupinine, sparteine, and lusitanine are examples of quinolizidine alkaloids (Figure 18).

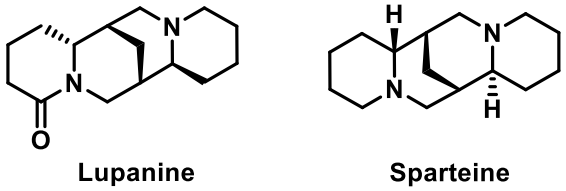


Figure 18. Representative quinolizidine alkaloids

(xiv) Pyrrole and Pyrrolidine Alkaloids: Hygrine, cuscohygrine, and stachydrine are three prominent examples of pyrrolidine alkaloids (Figure 19).

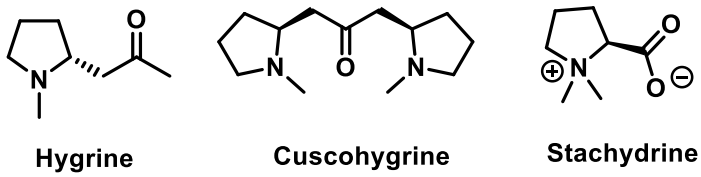


Figure 19. Representative pyrrole and pyrrolidine alkaloids

1.5 Application of Cyclic Anhydrides and Their Derivatives in Natural Products Synthesis

Cyclic anhydrides and their derivatives have been used as versatile building blocks to synthesize various bioactive natural products (Figure 20).[18-25] More specifically, maleic anhydride and its derivatives are more important from biological and synthetic applications points of view.[26-31] It is a versatile synthon with all of its sites suitable for a variety of reactions and high selectivity for a variety of nucleophiles. Many naturally occurring maleic anhydrides and their derivatives have been identified in the past few decades, and many of them have important medicinal properties. 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 extensively 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, homopthalic anhydride and its derivatives etc. Based on the last two decades significant research on cyclic anhydrides and their derivatives to bioactive natural products, many exciting results in synthesizing these natural compounds using novel carbon–carbon and carbon–heteroatom bond-forming reactions have been published from

our group.[32-41] In recent times, two extensive reviews on the cyclic anhydride class of natural compounds have been published.[18,42]

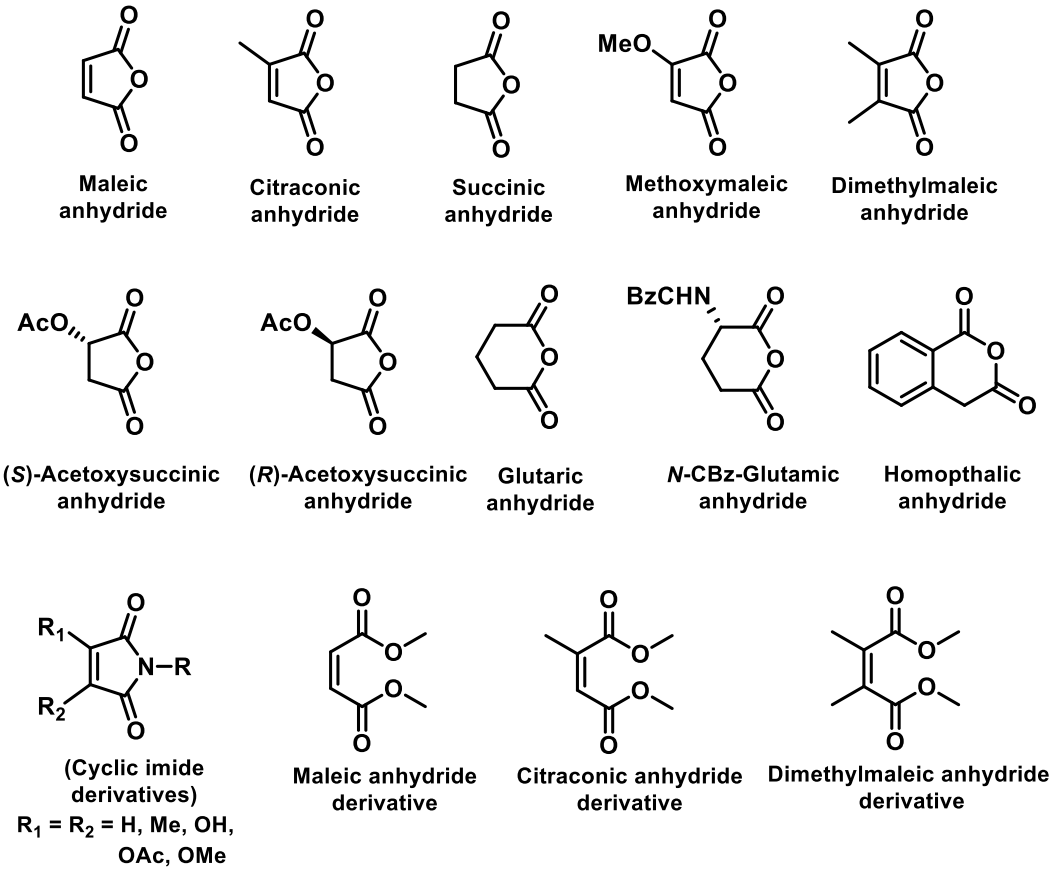
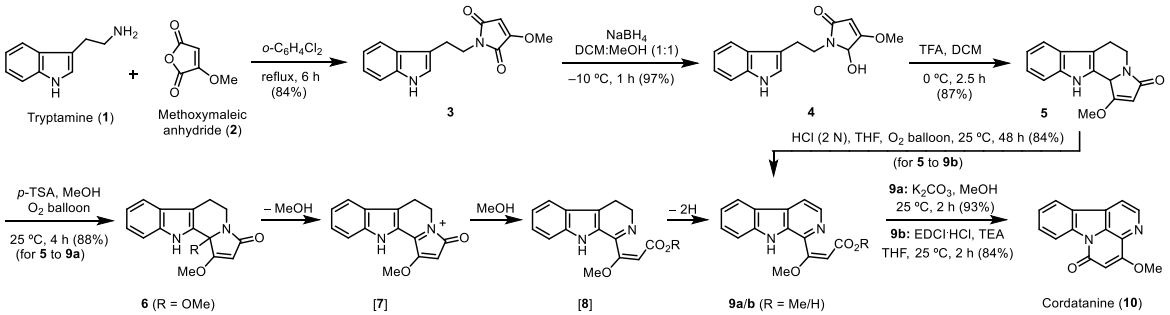


Figure 20. Important cyclic anhydrides and their derivatives as potential precursors for the synthesis of bioactive alkaloids

1.6 Representative Examples of Cyclic Anhydrides and Their Derivatives to Bioactive Alkaloids from our Research Laboratory

Synthesis of Cordatanine: Argade and co-workers have reported the facile regioselective approach to cordatanine from the readily available common precursor tryptamine (**1**) and methoxymaleic anhydride (**2**) using in situ stepwise oxidations leading to aromatization and intramolecular cyclization reactions (Scheme 1).[43] Reaction of methoxymaleic anhydride with tryptamine in refluxing *o*-dichlorobenzene directly furnished the required methoxy maleimide **3** in 84% yield via intramolecular dehydrative condensation reaction. Regioselective reduction of methoxymaleimide with $NaBH_4$ in DCM:MeOH at –10 °C provided the lactamol **4** in 97% yield by reducing more reactive non-conjugated imide carbonyl in **3.** Further, TFA catalyzed intramolecular cyclization reaction of lactamol **4** yielded pure pyrrolotetrahydrocarbazole **5** in 87% yield via plausible formation of corresponding iminium ion intermediate. The reaction of compound **5** with *p*-TSA in MeOH under oxygen condition at room temperature

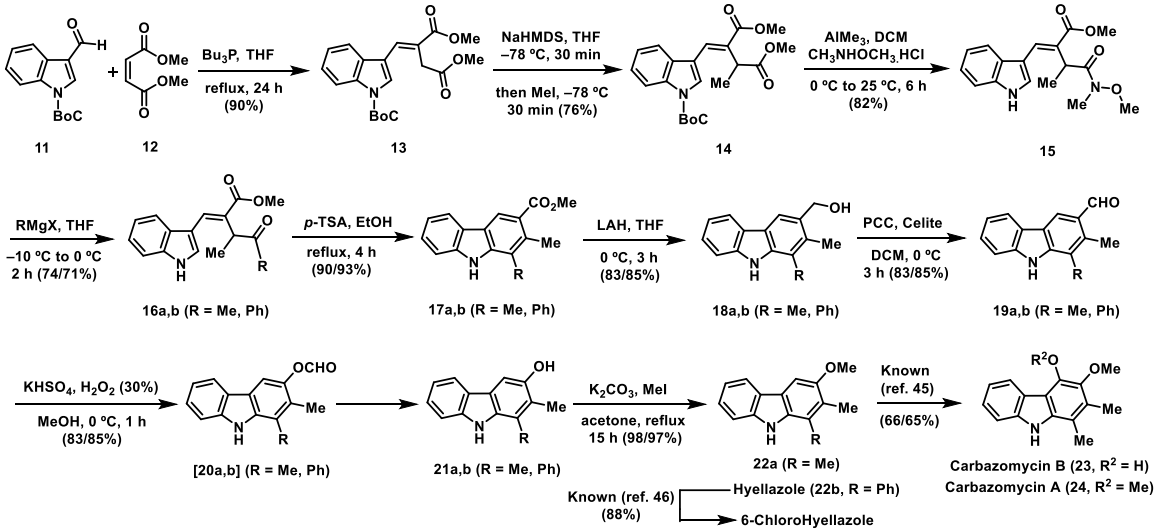
generated the completely aromatized ester **9a** with 88% yield in 4 hours. The formation of compound **9a** took place in one pot, first converting lactam to ester followed by in situ aromatization of the formed intermediate. The formation of acid derivative of **9a** followed the same reaction path in which the reaction of **5** with 2 N HCl in THF under an oxygen atmosphere at room temperature formed the acid **9b**. Base catalyzed intramolecular cyclization reaction of ester **9a** furnished final product cordatanine (**10**) in 93% yield. Similarly, EDCI induced intramolecular dehydrative cyclization of the acid derivative **9b** provided the desired natural product cordatanine (**10**) in 84% yield.



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

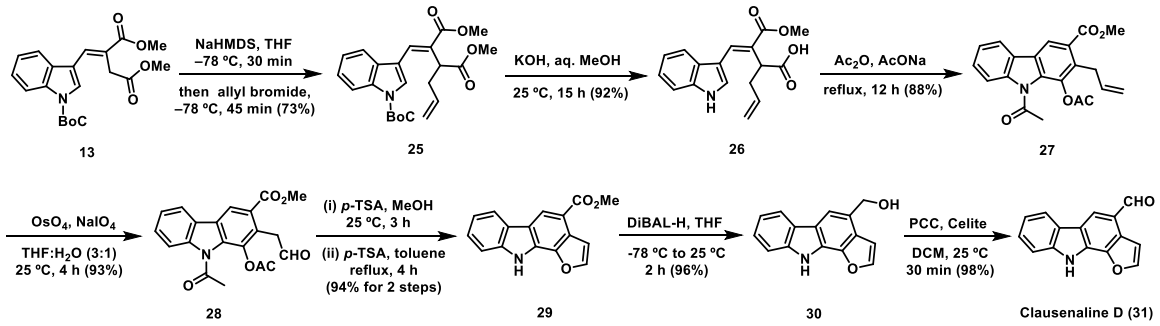
Synthesis of Carbazole Alkaloids: Argade and co-workers synthesized the important carbazole alkaloids carbazomycin A, carbazomycin B, hyellazole, chlorohyellazole, and clausenaline D from the readily available starting material Boc-protected 3-formylindole and dimethyl maleate.[44] The reaction of Boc-protected 3-formylindole (**11**) with the in situ generated ylide from TBP and dimethyl maleate (**12**) in refluxing THF stereoselectively furnished the desired (*E*)-alkene **13** in 90% yield after 24 h stirring (Scheme 2). The required product **14** was obtained from the NaHMDS mediated monomethylation of compound **13** using methyl iodide in dry THF at –78 °C temperature. Trimethylaluminum induced regioselective coupling reaction of *N*,*O*-dimethylhydroxylamine hydrochloride with unconjugated ester group of diester **14** provided the essential compound **15** in 82% yield. Reactions of methylmagnesium bromide and phenylmagnesium bromide with Weinreb amide **15** in dry THF at –10 °C delivered the required ketones **16a**,**b** in 74% and 71% yields respectively. Acid-catalyzed intramolecular cyclization of ketones **16a**,**b** delivered the cyclized products **17a**,**b** in 90% and 93% yields respectively. In the next two reactions, the ester group was reduced to alcohol using LAH and PCC mediated oxidation of generated alcohol provided the corresponding aromatic aldehydes **19a**,**b** in excellent yields. The Baeyer-Villiger

oxidation of aromatic aldehydes **19a**,**b** yielded unisolable formate esters, which hydrolyzed in situ to generate known phenolic compounds **21a**,**b** in good yields. The corresponding known methyl ether intermediate **22a** was obtained by the base-catalyzed chemoselective *O*-methylation of compound **21a**, from which the three-step synthesis of carbazomycin B (**23**) is known in the literature.[45] Carbazomycin B (**23**) produces carbazomycin A (**24**) in high yield after simple *O*-methylation.[45] Compound **21b** was methylated to form the natural product hyellazole (**22b**), from which a two-step synthesis of yet another natural product, 6-chlorohyellazole, is known in the literature.[46]



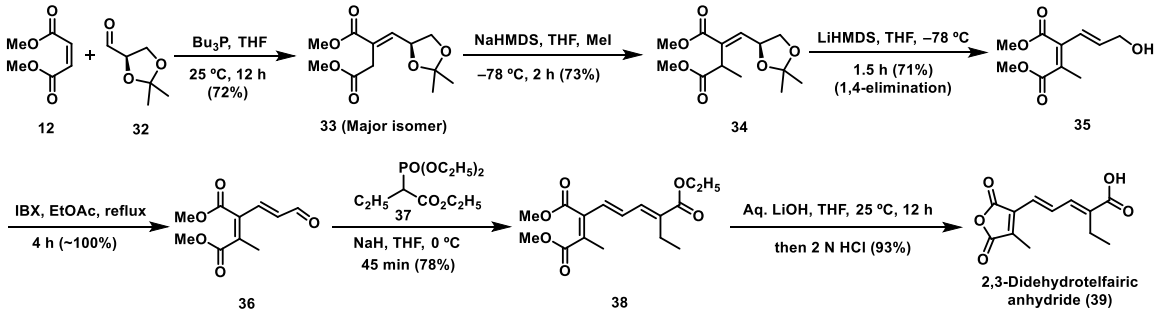
Scheme 2. Synthesis of Carbazole Alkaloids from Boc-Protected 3-Formylindole and Dimethyl Maleate

First Total Synthesis of Clausenaline D: The total synthesis of fused carbazole clausenaline D was initiated with the NaHMDS induced regioselective introduction of an allyl group on **13** using allyl bromide to yield the expected product **25** in 73% yield (Scheme 3).[44] KOH in aqueous MeOH, regioselectively converted the unconjugated ester to the acid, and subsequently removed the Boc-group to directly provide the Boc-deprotected monoacid **26** in 92% yield. The Ac_2O−AcONa promoted dehydrative intramolecular cyclization of product **26** provided the respective *N*- and *O*-acylated carbazole derivative **27** in 88% yield. OsO_4 and $NaIO_4$ mediated conversion of the double bond to the corresponding diol, followed by in situ oxidative cleavage yielded the required aliphatic aldehyde **28** in 93% yield. The furocarbazole **29** was obtained via a one-pot *p*-TSA in MeOH mediated double deacylation of **28**, followed by dehydrative intramolecular cyclization in refluxing *p*-TSA/toluene in 94% yield over two steps. Finally, reduction and then oxidation of aromatic ester **29** to the corresponding aldehyde resulted in synthesis of natural product clausenaline D (**31**) in excellent overall yield.



Scheme 3. First Total Synthesis of Clausenaline D

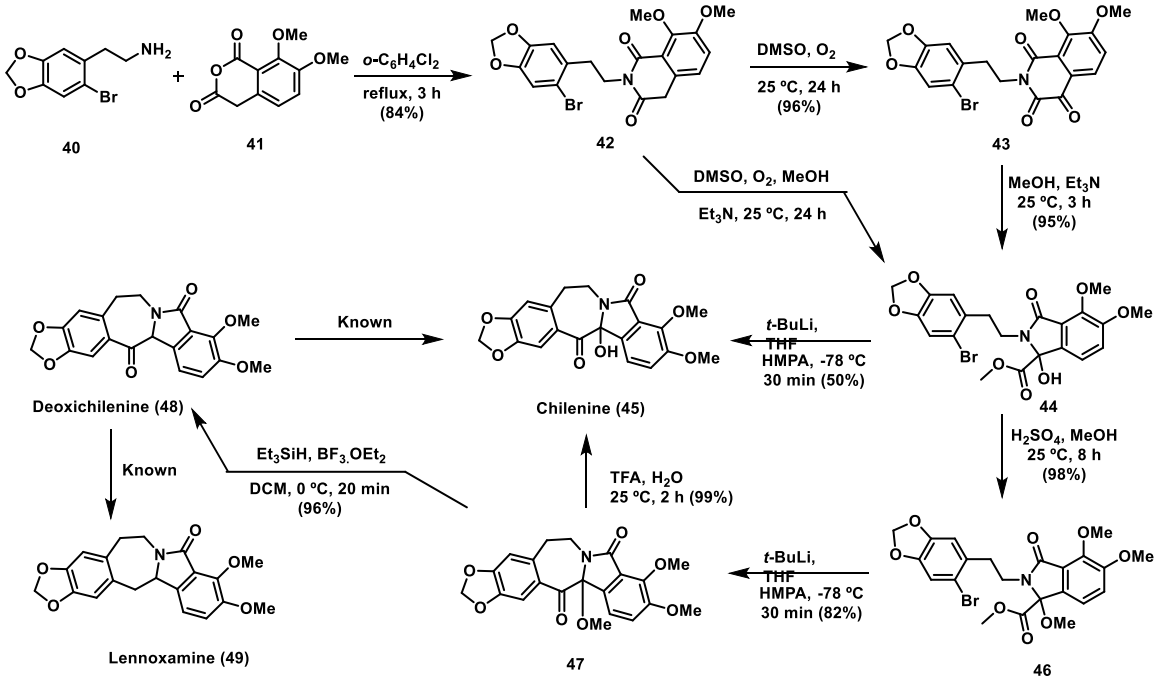
First Total Synthesis of 2,3-Didehydrotelfairic Anhydride: Argade and co-workers in 2013 reported the first total synthesis of the natural product 2,3-didehydrotelfairic anhydride via novel 1,4-elimination reaction in alkylidenesuccinate derivative (Scheme 4).[47] The Wittig reaction between dimethyl maleate (**12**) and carboxaldehyde **32** in THF provided the chromatographically inseparable *E*/*Z* mixture of alkene product **33** in 72% yield (*E*/*Z* = 19:1). The NaHMDS mediated methylation of alkene with methyl iodide in THF at –78 °C furnished the monomethylated pure product **34** in 73% yield. LiHMDS in THF at –78 °C induced 1,4-elimination in compound **34** and delivered the corresponding allylic alcohol **35** in 71% yield. IBX oxidation of **35** in refluxing ethyl acetate oxidized the allylic alcohol to the corresponding aldehyde **36** in quantitative yield. The Horner−Wadsworth−Emmons (HWE) reaction between aldehyde **36** and stabilized ylide generated from ethyl 2-(diethoxyphosphoryl)butanoate **37** under the basic conditions provided the desired major isomer **38** in 78% yield. Triester **38** on treatment with aqueous LiOH in THF delivered the desired natural product 2,3-didehydrotelfairic anhydride (**39**) in 93% yield. The natural product was synthesized in six steps with a 27% overall yield.



Scheme 4. First Total Synthesis of 2,3-Didehydrotelfairic Anhydride

Synthesis of Chilenine and Deoxychilenine: Argade and co-workers in 2011 reported the concise and efficient syntheses of (±)-chilenine and (±)-deoxychilenine via air oxidation of an activated benzylic position as a crucial step (Scheme 5).[48] Synthesis of

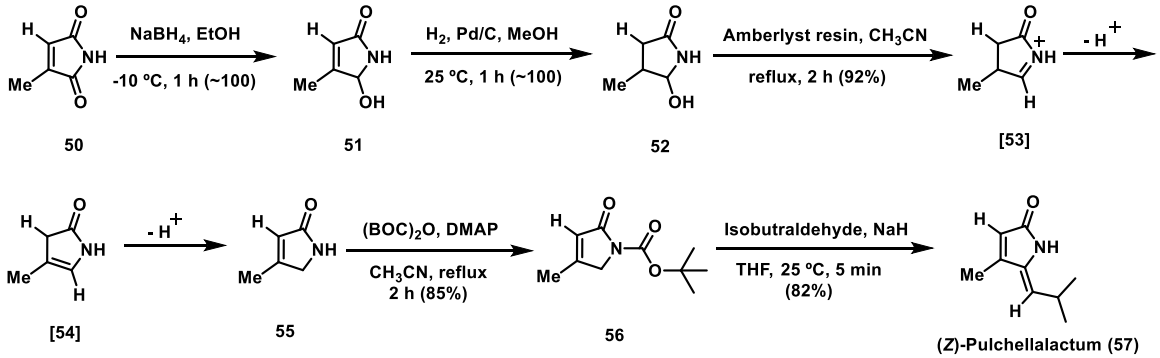
chilenine and deoxychilenine was commenced with the condensation reaction between 3,4-dimethoxyhomophthalic anhydride (**41**) and 6-bromo-homopiperonylamine (**40**) in refluxing dichlorobenzene to form the required homophthalimide **42** in 84% yield. The homophthalimide **42** under an oxygen atmosphere in DMSO underwent facile air oxidation at an activated benzylic position to provide trione **43** in 96% yield. Base-catalyzed regioselective methanolysis of trione generated the desired free ester-containing lactamol product **44** in 95% yield via the ring contraction mechanism. Treatment of lactamol **44** with *t*-BuLi in THF/HMPA at –78 °C on intramolecular acylation furnished target compound chilenine (**45**) in 50% yield. The free hydroxyl group in compound **44** was converted into methoxy compound **46** using concentrated sulfuric acid in excess methanol to improve the efficiency of the intramolecular acylation reaction. The yield of intramolecular acylation reaction was significantly enhanced up to 82% after using the previously used reaction protocol to furnish the compound **47**. Finally, compound **47** with aqueous TFA provided the chilenine (**45**) in quantitative yield. The treatment of compound **47** with $Et_3SiH/BF_3.OEt_2$ in DCM furnished another natural product deoxychilenine (**48**) in 96% yield. The transformation of deoxychilenine (**48**) into chilenine (**45**) and lennoxamine (**49**) are known in the literature.[49]



Scheme 5. Synthesis of Chilenine and Deoxychilenine

A Facile Synthesis of (*Z*)-Pulchellalactam: Argade and co-workers completed the five-step synthesis of naturally occurring CD45 protein tyrosine phosphatase inhibitor (*Z*)-

pulchellalactam using cyclic anhydride derivative, citraconimide as starting precursor (Scheme 6).[50] Highly regioselective $NaBH_4$ induced reduction of citraconimide **(50)** gave the corresponding lactamol **51** exclusively in quantitative yield. The catalytic hydrogenation of unsaturated hydroxylactum in MeOH provided the saturated hydroxylactum **52** in excellent yield. Acidic resin, Amberlyst catalyzed dehydration of hydroxylactum in refluxing CH_3CN converted the lactamol compound to the desired 4-methyl-3-pyrrolin-2-one (**55**) in 92% yield via iminium intermediate and in situ proton shift to form the more stabilized conjugated lactam. The lactam **55** on treatment with Boc-anhydride in CH_3CN at room temperature provided the Boc-protected lactam **56** in 85% yield. Base promoted stereoselective condensation of lactam **56** with isobutyraldehyde exclusively furnished the bioactive natural product (*Z*)-pulchellalactam (**57**) in 82% yield. The total synthesis of pulchellalactam was completed in five steps with a 64% overall yield.



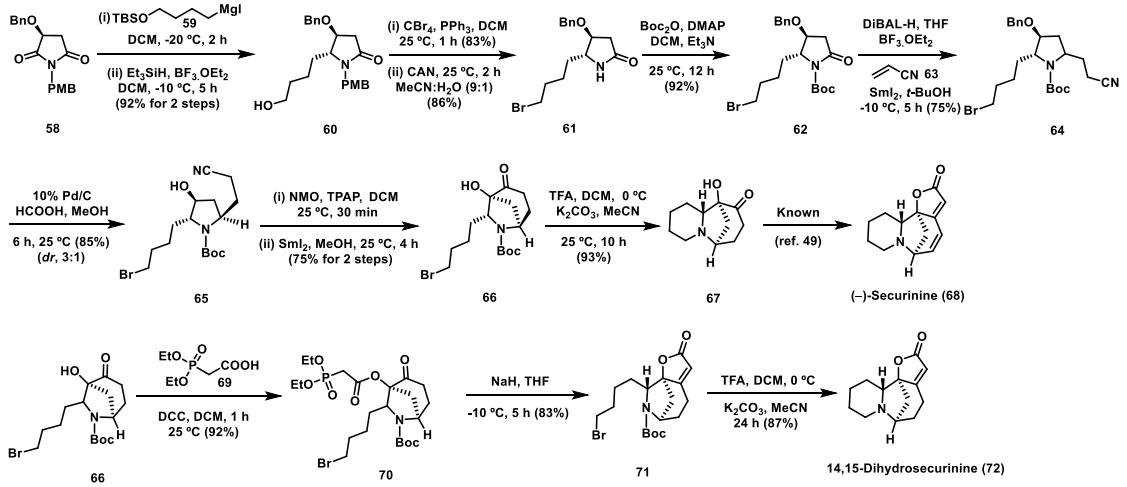
Scheme 6. A Facile Synthesis of (*Z*)-Pulchellalactam

1.7 Representative Example of Cyclic Anhydrides and Their Derivatives to Bioactive Alkaloids from the Literature

Asymmetric Total Synthesis of (−)-14,15-Dihydrosecurinine and The Formal Synthesis of (−)-Securinine: Pei-Qiang Huang and co-workers in 2015 reported the asymmetric total synthesis of (−)-14,15-dihydrosecurinine and the formal synthesis of (−)-securinine using succinimide derivative as starting material (Scheme 7).[51] The synthesis was commenced with the reductive alkylation reaction of PMB-protected maleimide **58** with Grignard reagent **59**, followed by the treatment of generated lactamol intermediate with Et_3SiH in the presence of excess Lewis acid, which provided the lactam **60** in 92% yield over two steps. The silyl protecting group was also removed using an excess amount of Lewis acid. Using carbon tetrabromide and triphenylphosphine in DCM, free hydroxyl group was transformed to the corresponding bromo compound in 83% yield, then CAN mediated deprotection of the PMB group yielded compound **61** in

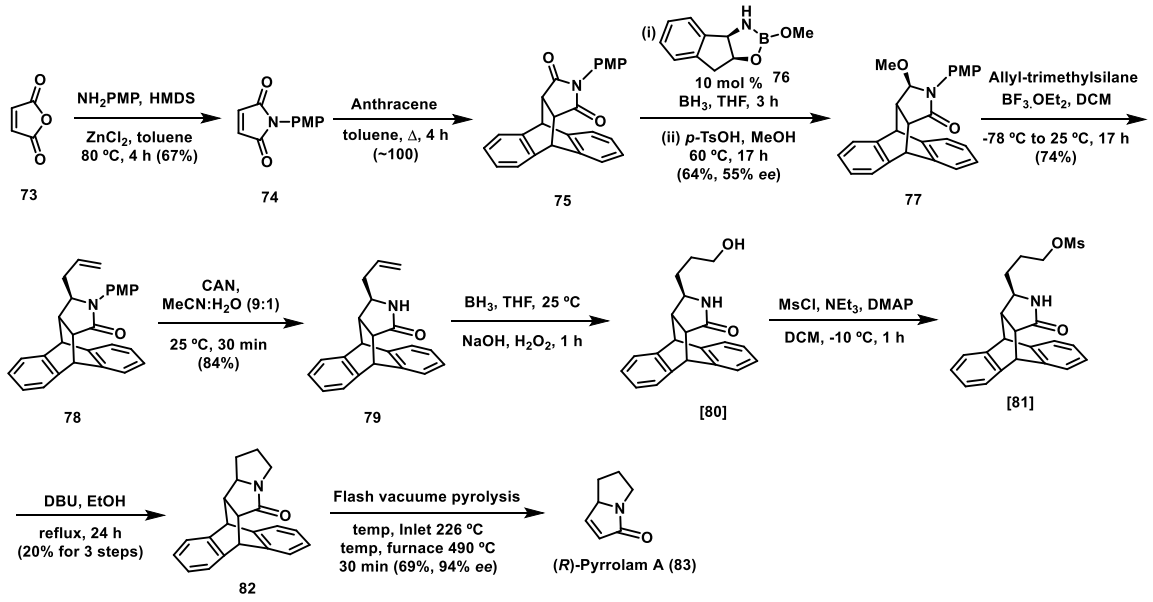
86% yield. Boc-protected lactam **62** was obtained in good yield using Boc-anhydride/DMAP/Et_3N in DCM at room temperature. One-pot partial reduction of lactam **62** using DIBAL-H in THF at –10 °C, followed by SmI_2 promoted reductive radical coupling with acrylonitrile (**63**) at the same reaction temperature yielded product **64** as an inseparable diastereomeric mixture in 75% yield. Debezylation of **64** provided the desired stereoisomer pyrrolidine **65** as the predominant product in a good diastereomeric ratio (*dr* 3:1). In the successive reactions, first the alcohol in pyrrolidine **65** was oxidized to the corresponding ketone using TPAP/NMO, then ketone was treated with excess SmI_2 in the presence of MeOH to generate the cyclized product **66** in 75% yield over two steps. Deprotection of the Boc group in **66** using TFA followed by K_2CO_3 mediated cyclization furnished the known tricyclic amine **67** in 93% yield, from which the total synthesis of (−)-securinine (**68**) is reported in the literature.[52]

Further, to synthesize (−)-14,15-dihydrosecurinine (**72**), the compound **66** was coupled with diethylphosphonoacetic acid **69** using DCC in DCM to form the desired phosphonate ester **70** in 92% of yield. NaH promoted intramolecular Horner−Wadsworth−Emmons olefination reaction of **70** in THF at –10 °C, provided the butanolide **71** in 83% yield. Finally, deprotection of the Boc-group followed by base mediated cyclization generated the required product 14,15-dihydrosecurinine (**72**) in 87% yield. From a common intermediate **66**, the formal total synthesis of (−)-securinine (**68**) was performed in 10-steps with an overall yield of 20% and the total synthesis of (−)-14,15-dihydrosecurinine (**72**) was accomplished in 12-steps with an overall yield of 14%.



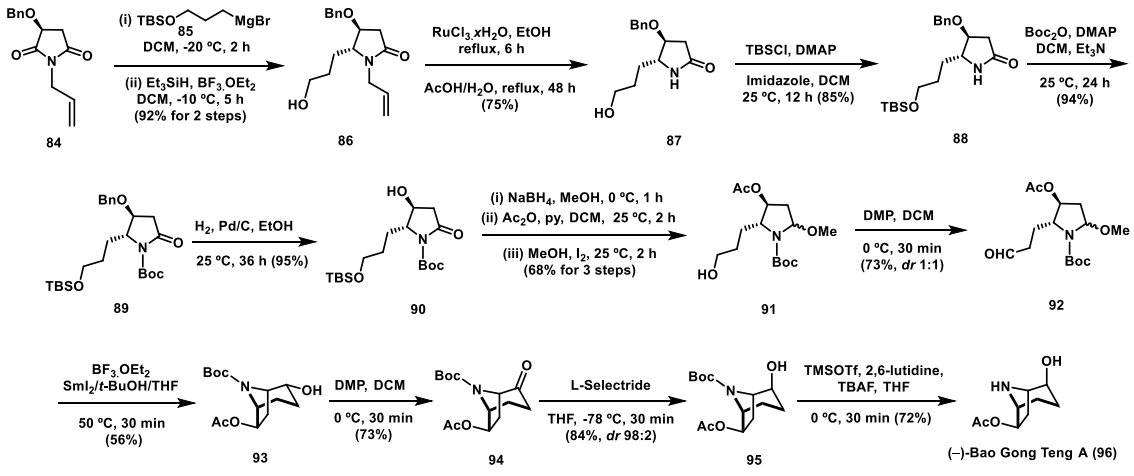
Scheme 7. Asymmetric Total Synthesis of (−)-14,15-Dihydrosecurinine and The Formal Synthesis of (−)-Securinine

Synthesis of Pyrrolam A: In 2014, Simon Jones and co-workers devised a technique for highly enantioselective desymmetrization of maleimide demonstrating the synthesis of pyrrolam A (Scheme 8).[53] The PMP-maleimide **74** was synthesized from the reaction between the maleic anhydride (**73**) and the *p*-methoxyphenyl amine in the presence of HMDS/$ZnCl_2$ in toluene at 80 °C. Diels-Alder reaction between PMP-maleimide **74** and anthracene in refluxing toluene delivered the cycloaddition product **75** in quantitative yield. Asymmetric reduction of cycloadduct **75** using BH_3 in the presence of an oxazaborolidine catalyst **76** in THF, followed by enantioselective conversion of the generated hydroxylactam to the corresponding methoxylactam, yielded compound **77** in 55% enantioselectivity. Lewis acid mediated displacement of the methoxy group of lactam **77** with allyl-trimethylsilane in DCM at -78 °C yielded allyl lactam **78** as a single diastereoisomer in 74% yield. Deprotection of the PMP group using CAN resulted in lactam **79** in 84% yield. The alcohol **80** was obtained via hydroboration of **79** with BH_3/THF, followed by treatment with NaOH/H_2O_2. Furthermore, by treatment of crude product **80** with methanesulfonyl chloride and triethylamine in DCM formed mesylate **81**. The mesylate on treatment with DBU in refluxing methanol provided the cyclized product **82** in 20% yield over three steps. Using the flash vacuum pyrolysis approach at 490 °C, the retro-Diels-Alder reaction of **82** produced the desired product (*R*)-pyrrolam A (**83**) in 69% yield and good enantioselectivity (94% *ee*).



Scheme 8. Synthesis of Pyrrolam A Using Enantioselective Desymmetrization of Maleimide

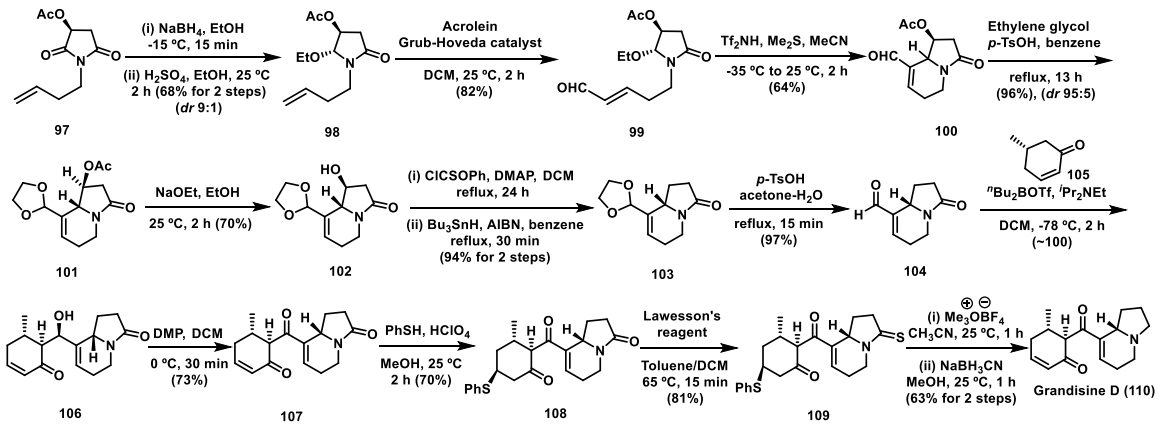
Asymmetric Total Synthesis of (-)-Bao Gong Teng A: Pei-Qiang Huang and co-workers in 2011 reported the enantioselective total synthesis of (–)-bao gong teng A via intramolecular reductive coupling of *N*,*O*-acetal with aldehyde is the key step (Scheme 9).[54] The synthesis was commenced with the reaction of allyl-protected maleimide **84** with Grignard reagent **85**, which generated the alkylated lactmol. Then treatment of lactamol intermediate with Et_3SiH in the presence of excess Lewis acid provided the lactam **86** in 82% yield over two steps (*dr* 98:2). Lactam **87** was obtained by deallylation of lactam **86** with $RhCl_3.xH_2O$ catalyzed double bond migration followed by acid catalyzed hydrolysis in 75% yield. TBS-protection of primary alcohol with TBSCl/DMAP in DCM afforded the lactam **88**, which was then treated with Boc-anhydride/DMAP/Et_3N in DCM to obtain the Boc-protected lactam **89** in 94% yield. Debenzylation of **89** with H_2, Pd/C in EtOH at room temperature furnished the compound **90** in good yield. Partial reduction of the lactam **90** with $NaBH_4$ in MeOH generated the hemiaminal as a diastereomeric mixture, which was further treated with Ac_2O/py in DCM to yield the bis-acetate. Treatment of crude labile bis-acetate with iodine in MeOH produced the desilylated and transacetylated required product *N*,*O*-acetal **91** in 68% yield over three steps. DMP mediated oxidation of the diastereomeric mixture **91** yielded the crucial precursor **92** in 73% yield (*dr* 1:1). Reaction of *N*,*O*-acetal **92** with $BF_3.OEt_2$ and a solution of SmI_2/*t*-BuOH in THF delivered the intended intramolecular coupling product **93** in 56% yield along with other plausible diastereomer.[55] On oxidation with Dess–Martin periodinane the major diastereomer **93** yielded the corresponding ketone **94**, which on reduction with L-selectride furnished the compound **95** in 84% yield (*dr* 98:2).



Scheme 9. Asymmetric Total Synthesis of (–)-Bao Gong Teng A

Finally, chemoselective removal of the Boc-group in compound **95** using TMSOTf/2,6-lutidine accomplished the total synthesis of (–)-bao gong teng A (**96**) in 72% yield. The total synthesis was completed in 14 steps with a 8% overall yield from the allyl maleimide precursor **84**.

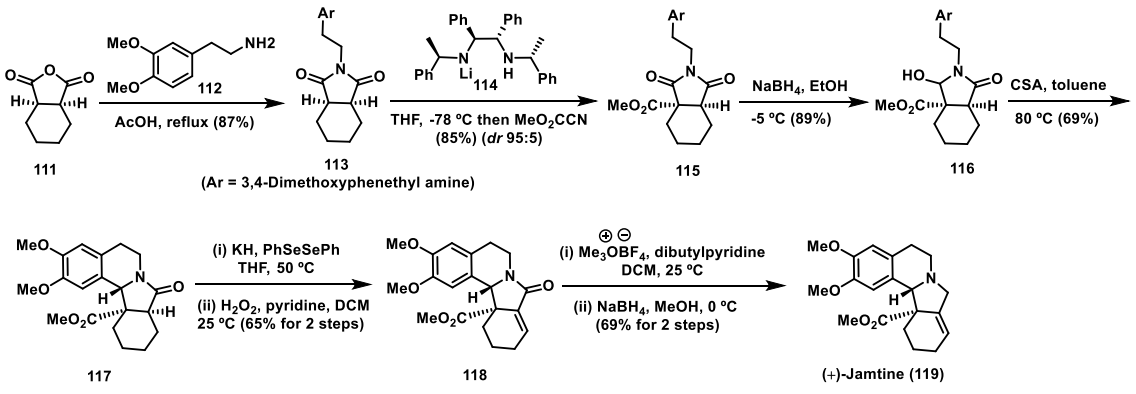
Total Synthesis of Grandisine D: Osamu Tamura and co-workers completed the total synthesis of grandisine D using Bronsted acid mediated Morita-Baylis-Hillman (MBH) ring-closure reaction (Scheme 10).[56] The regioselective reduction of imide **97** with $NaBH_4$ at -15 °C generated the hydroxy lactam, which on treatment with acidic EtOH furnished the ethoxy lactam **98** in 94% yield over two steps and good diastereoselectivity (*dr* 9:1). The key intermediate **99** was obtained via cross-metathesis of **98** with acrolein using the Grubbs-Hoveyda catalyst in 84% yield. Tf_2NH mediated Morita-Baylis-Hillman ring closure reaction of intermediate **99** in CH_3CN at -35 °C furnished the desired cyclized product **100** in 64% yield.[57] The stereochemistry of Morita-Baylis-Hillman product **100** was validated by converting aldehyde into acetal protection **101** and observing the significant differences in NOE interactions between *trans*-**101** and *cis*-**101** (*dr* 95:5). The acetoxy group of **101** was removed using the Barton-McCombie deoxygenation protocol in 70% yield. Lactam **102** was then converted to thionocarbonate and then subsequently treated with tributyltin hydride and a catalytic AIBN to produce deoxygenated lactam **103** in a 94% yield over two steps. Acid hydrolysis of the acetal **103** yielded corresponding aldehyde **104** with 97% yield. The essential aldol reaction between enone **105** with aldehyde **104** using boronenolate in DCM at -78 °C gave the hydroxy compound **106** in a quantitative yield as single isomer.



Scheme 10. Total Synthesis of Grandisine D

DMP-mediated oxidation of the hydroxy compound provided the corresponding unsaturated ketone **107** in 73% yield. The thiophenol adduct **108** was formed for the protection of the unsaturated ketone using PhSH in MeOH. Thiophenol adduct was treated with Lawesson's reagent to generate thioamide **109** in 81% yield. Finally, elimination of the thiol group followed the reduction of thioamide with Meerwein's salt and $NaBH_3CN$ accomplished the synthesis of grandisine D (**110**) in a 63% yield over two steps.

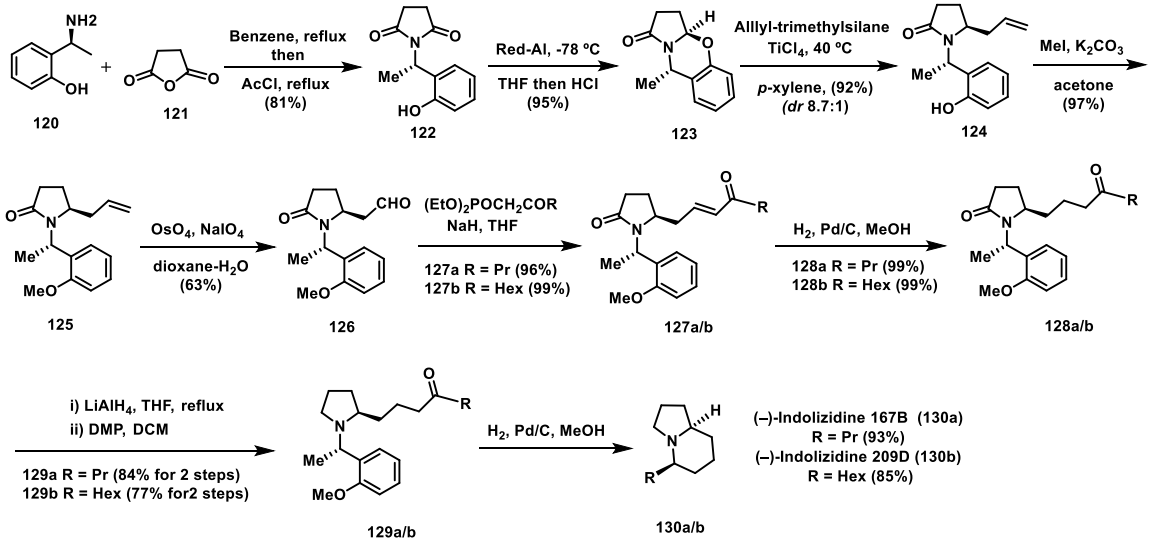
Asymmetric Total Synthesis of (+)-Jamtine: Nigel Simpkins and co-workers in 2003 reported the asymmetric total synthesis of (+)-jamtine (**119**) by using the chiral base approach (Scheme 11).[58] The synthesis was started with the reaction between commercially available anhydride **111** and 3,4-dimethoxyphenethyl amine (**112**) in refluxing acetic acid, which provided the required imide **113** in 87% yield via an intramolecular dehydrative condensation reaction. Chiral monolithiated diamine base **114** mediated carboxymethylation of imide **113** in THF at -78 °C furnished the compound **115** in 85% yield and high enantioselectivity.[59] Regioselective reduction of imide **115** using $NaBH_4$ in EtOH at -5 °C provided the hydroxy lactam **116** in a good yield. Acid-promoted intramolecular cyclization reaction of hydroxy lactam **116** produced the lactam **117** in 69% yield via iminium ion intermediate. After dehydrogenation with a selenoxide *syn*-elimination, unsaturated lactam **118** was produced in 65% yield over two steps. Treatment of unsaturated lactam with Meerwein's salt and then with $NaBH_4$ in MeOH accomplished the synthesis of (+)-jamtine (**119**) in 69% yield over two steps.



Scheme 11. Concise Asymmetric Total Synthesis of (+)-Jamtine

Asymmetric Synthesis of (−)-Indolizidine 167B and 209D: Chihiro Kibayashi and co-workers reported the asymmetric synthesis of (−)-indolizidine 167B and (−)-indolizidine 209D based on stereocontrolled allylation of a chiral tricyclic *N*-acyl-*N*,*O*-acetal (Scheme

12).[60] The imide **122** was obtained by refluxing succinic anhydride (**121**) with (*S*)-2-(1-aminoethyl)-phenol (**120**) in benzene and then refluxing it with AcCl in 81% yield. Partial reduction of obtained imide with Red-Al and subsequent treatment of the resultant hydroxylactam with acid resulted in the formation of essential *N*,*O*-acetal **123** as a single isomer in 95% yield. Allylation of the chiral tricyclic *N*,*O* acetal **123** in *p*-xylene at 40 °C using allyl-trimethyl silane and titanium tetrachloride furnished the desired allyl-lactam **124** in 92% yield (*dr* 8.7:1). Base mediated *O*-methylation of **124** with MeI in acetone afford the compound **125** in good yield. OsO_4 and $NaIO_4$ mediated conversion of the double bond in **125** to the corresponding diol followed by its oxidative cleavage generated the desired aliphatic aldehyde **126** in 63% yield. The Horner-Wadsworth-Emmons olefination reaction with phosphonate [$(EtO)_2POCH_2C(O)R$] gave (*E*)-enone **127a**,**b** as a single isomer in good yields. Hydrogenation of unsaturated ketone with H_2, Pd/C in MeOH provided the saturated ketone **128a**,**b** in quantitative yields. Reduction of compound **128a**,**b** with $LiAlH_4$ in refluxing THF, followed by Dess-Martin mediated oxidation of the generated amino alcohol afforded the ketone **129a/b** in 84/77% yields over two steps. One-pot hydrogenolysis of the *N*-benzyl moiety, followed by intramolecular reductive amination of **129a,b** in H_2, Pd/C in MeOH, furnished the (−)-indolizidine 167B/(−)-indolizidine 209D (**130a/b**) in 93/85% yields as single isomers.



Scheme 12. Asymmetric Synthesis of (−)-Indolizidine 167B and 209D

1.8 Summary

In this section, we have covered a quick overview of alkaloids, their diverse pharmacological actions, and the classification of alkaloids using all plausible

approaches. Heterocyclic alkaloids are classified more broadly because of their structural complexity. It is evident from this discussion that cyclic anhydrides and their derivatives are valuable synthons in organic synthesis. The versatile nature of cyclic anhydrides and their derivatives have proven them as efficient building blocks for constructing the backbones of several structurally complicated and medicinally essential molecules. Alkaloid natural products such as cordatanine, carbazomycin A, carbazomycin B, hyellazole, chlorohyellazole, 2,3-didehydrotelfairic anhydride, (±)*-chilenine,* (±)*-deoxychilenine,* (*Z*)*-pulchellalactam from our research group, and* (−)*-securinine,* (−)*-14,15-dihydrosecurinine, pyrrolam A,* (−)*-bao gong teng A, grandisine D,* (+)*-jamtine,* (−)*-indolizidine 167B,* (−)*-indolizidine 209D synthesized from different research group are nice examples of their utility as a potential starting materials in chemical synthesis. In this study, we tried our best to summarise the chemistry of cyclic anhydrides and their derivatives using selected examples in the context of bioactive alkaloids synthesis. For more than two decades, our group has been actively involved in the synthesis of bioactive natural and unnatural compounds employing cyclic anhydrides and their derivatives as promising starting materials. In this dissertation, we have documented our efforts to synthesize structurally different heterocyclic alkaloids using appropriate cyclic anhydrides and their derivatives as a starting point. In the next chapter, we have described the first total synthesis of* (±)*-rhodoconferimide via regioselective double bromination of the aromatic ring as a crucial step in the synthesis. We have also completed the protection-free synthesis of pandalizine A via a chemoselective intramolecular cyclization pathway. Simultaneously, we observed that the analogous model system of pandalizine A with an additional β-methyl group follows the opposite reaction pathway and forms the undesirable aldol product via an intermolecular condensation reaction. We have also discussed about our strategies and obtained results towards the synthesis of inubosin B, gorgonianic acid, and eysotramidine.*

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Chapter 2

Reactions of Cyclic Anhydrides and Derivatives: Synthesis of Biologically Important Alkaloids

Section 2A

First Total Synthesis of Marine Natural Product (±)-Rhodoconferimide

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

This chapter is divided into two sections. The first section presents first total synthesis of marine natural product (±)-rhodoconferimide via regioselective double bromination of the aromatic ring. The second section describes attempted strategies toward the synthesis of quinoline alkaloids inubosin B. At the end of each section, the detailed experimental procedures, tabulated analytical and spectral data, and NMR spectra have been included.

2A.1 Background

In life processes free radicals are continuously formed in the human body as a result of oxidative metabolism which is caused by the many chemical interactions and metabolic processes that occur in the body. They can have an adverse effect on important molecules like as DNA, lipids and proteins restricting their ability to function or leading them to behave abnormally. Free radical imbalance damages cells, resulting in aging and diseases like atherosclerosis, cancer, cardiovascular disease, diabetes, inflammation, ischemia-reperfusion damage, Alzheimer's disease and Parkinson's disease.[1-8] Antioxidants play a vital role in protecting human beings from free radicals-induced damages by scavenging or neutralizing them.[9-11] The most often used synthetic antioxidants are butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate (PG), and *tert*-butyl hydroquinone (TBHQ) (Figure 1).

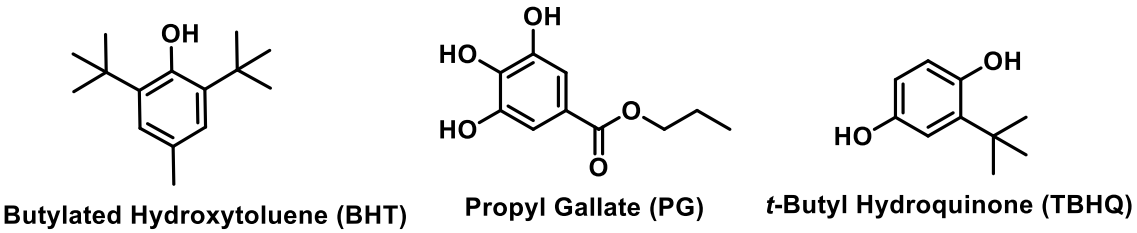


Figure 1. Known synthetic antioxidants

The use of synthetic antioxidants has been limited due to their lipid profile alteration and carcinogenic effects.[12,13] In this context the search for natural antioxidants has received significant attention.[14-20] Marine red algae *Rhodomela confervoides* occurs along the northern coastline of China and there it has been used as a food ingredient.[21-25] Wang and co-workers in 2012 isolated new nitrogen containing bromophenol derivatives from air-dried sample of *R. confervoides* (Figure 2). These bromophenols displayed strong scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals with IC_{50} values ranging from 5.22 to 23.60 μM as well as they also showed moderate activity

against 2,2-azino-bis(3-ethylbenzothiazoline-6-sulphonate) (ABTS) radicals with trolox equivalent antioxidant capacity (TEAC) values ranging from 2.11 to 3.58 μM (Table 1).[26,27]

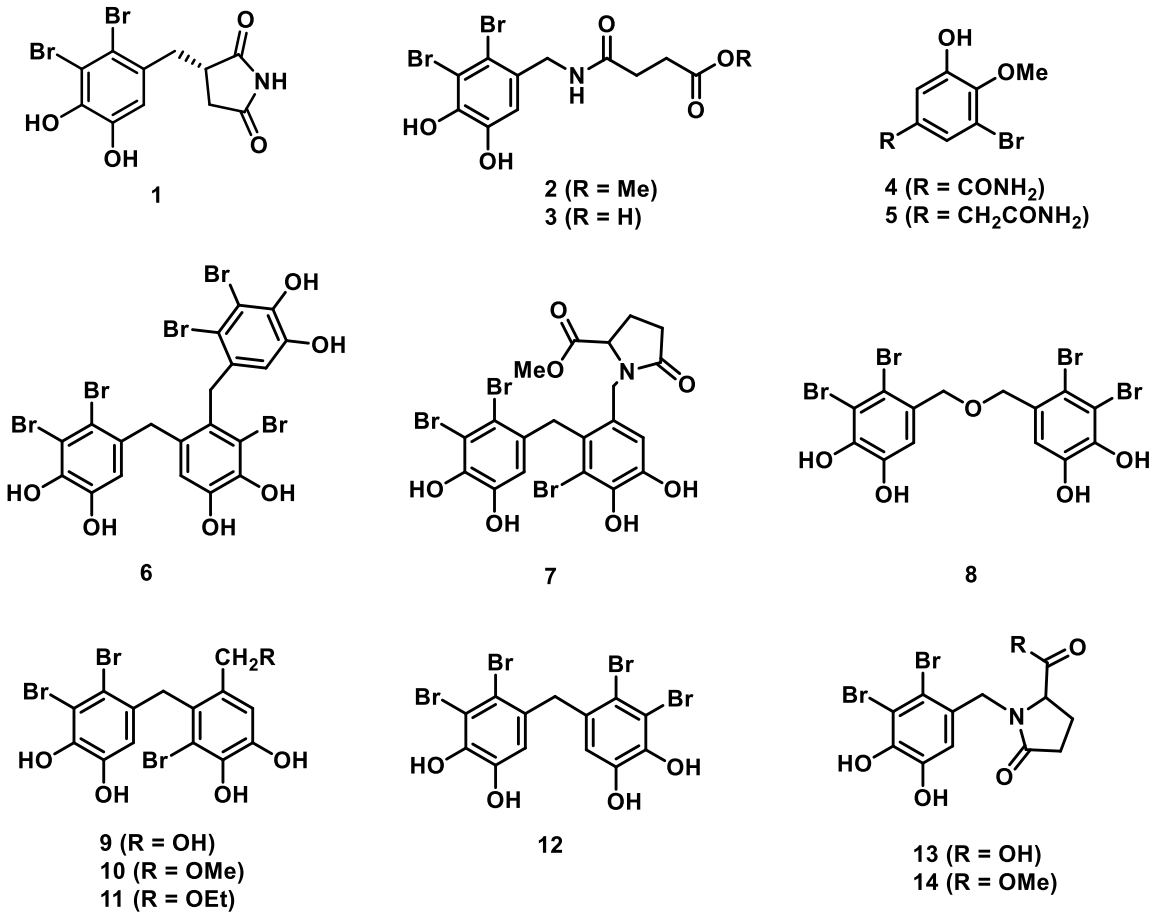


Figure 2. Nitrogen-containing bromophenol compounds from *Rhodomela confervoides*

Compound	DPPH radical scavenging activity IC_{50} (μM)	ABTS radical scavenging activity TEAC (μM)
1	5.22 ± 0.04	2.87 ± 0.10
2	5.70 ± 0.03	2.14 ± 0.08
3	5.43 ± 0.02	2.31 ± 0.11
4	23.60 ± 0.10	2.11 ± 0.04
5	20.81 ± 0.08	2.36 ± 0.08
6	8.90 ± 0.04	3.58 ± 0.13
7	13.60 ± 0.03	3.21 ± 0.13
8	17.61 ± 0.08	3.05 ± 0.13

9	19.60 ± 0.11	3.16 ± 0.14
10	14.32 ± 0.12	3.00 ± 0.13
11	13.81 ± 0.08	2.78 ± 0.12
12	16.91 ± 0.10	3.18 ± 0.13
13	15.90 ± 0.09	2.68 ± 0.11
14	18.50 ± 0.18	2.21 ± 0.12

Table 1. Radical-scavenging activity of compounds **1-14**

In continuation of our studies on total synthesis of recently isolated structurally interesting and biologically important natural products[28-30] from cyclic anhydrides and their derivatives, we decided to synthesize compound **1** (rhodoconferimide) because of its structural characteristics and higher biological activity as compared to all other bromophenols (Table 1). (+)-Rhodoconferimide exhibits 15-fold more potent free radical scavenging activity than the well-known synthetic antioxidant butylated hydroxytoluene (BHT). It is interesting to note that structurally simple (+)-rhodoconferimide is also more potent antioxidant than the multifunctional urceolatin and till date synthesis of rhodoconferimide is not known (Figure 3).[22]

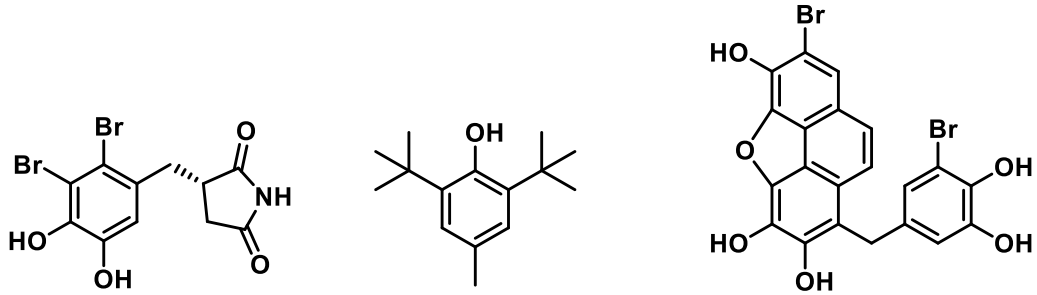
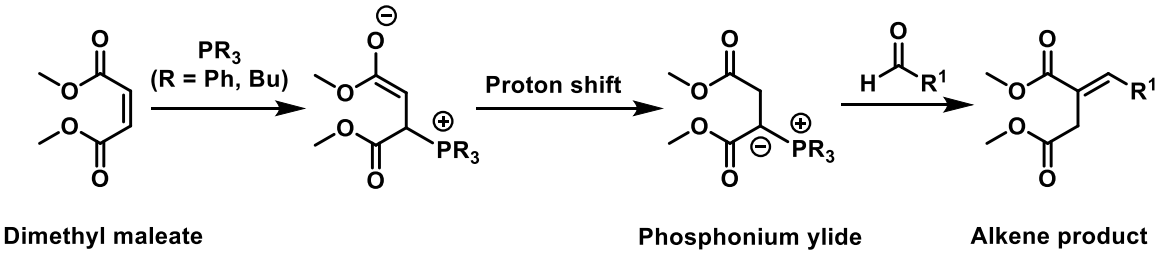


Figure 3. Natural and synthetic antioxidants

After carefully examining the rhodoconferimide structure, we planned to commence our synthesis with the laboratory used base-free modified Wittig reaction between an appropriate aromatic aldehyde and in situ generated stabilized phosphorous ylide from dimethyl maleate and tributyl phosphine.[31,32] The Wittig reaction also known as Wittig olefination was devised and described by Georg Wittig, a German scientist during 1954 and was awarded the Nobel Prize in Chemistry in 1979 for his outstanding

achievements.[33] Wittig reaction or Wittig olefination is a chemical reaction between an aldehyde or ketone with a phosphonium ylide providing the corresponding alkene.[34] Michel addition of phosphine ligand to dimethyl maleate followed by 1,2-proton shift generates stabilized ylide, which on reaction with aldehyde provides the corresponding (*E*)-alkene (Scheme 1).[32] Stabilized ylide provide the (*E*)-alkene while unstabilized ylide provide the (*Z*)-alkene.



Scheme 1. **Proposed Reaction Mechanism for Wittig Reaction**

Wittig reaction is one of the most significant and practical reaction used in the organic synthesis for chemoselective and regioselective olefination reaction with carbonyl compounds. Argade and co-workers reported the total synthesis of several natural products by using the Wittig reaction in the synthesis.[35-38] The Wittig reactions of cyclic anhydride and their derivatives derived stabilized ylides with aldehydes are well reported in the literature.[39,40] Some examples of cyclic anhydrides and its derivatives which are used as starting materials in the preparation of Wittig reagent are depicted in figure 4.

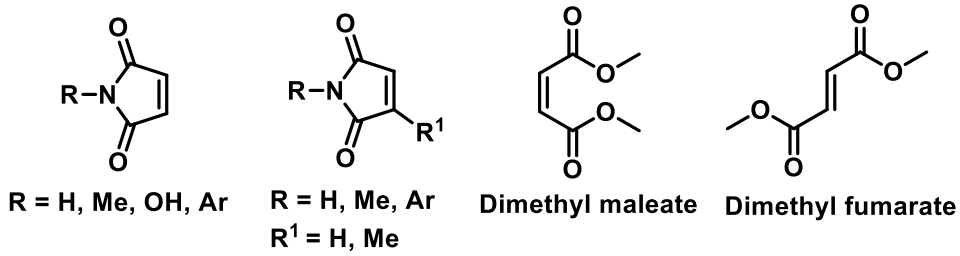
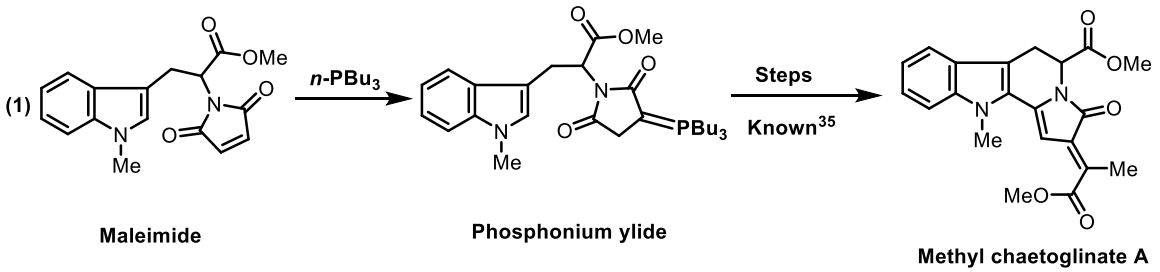
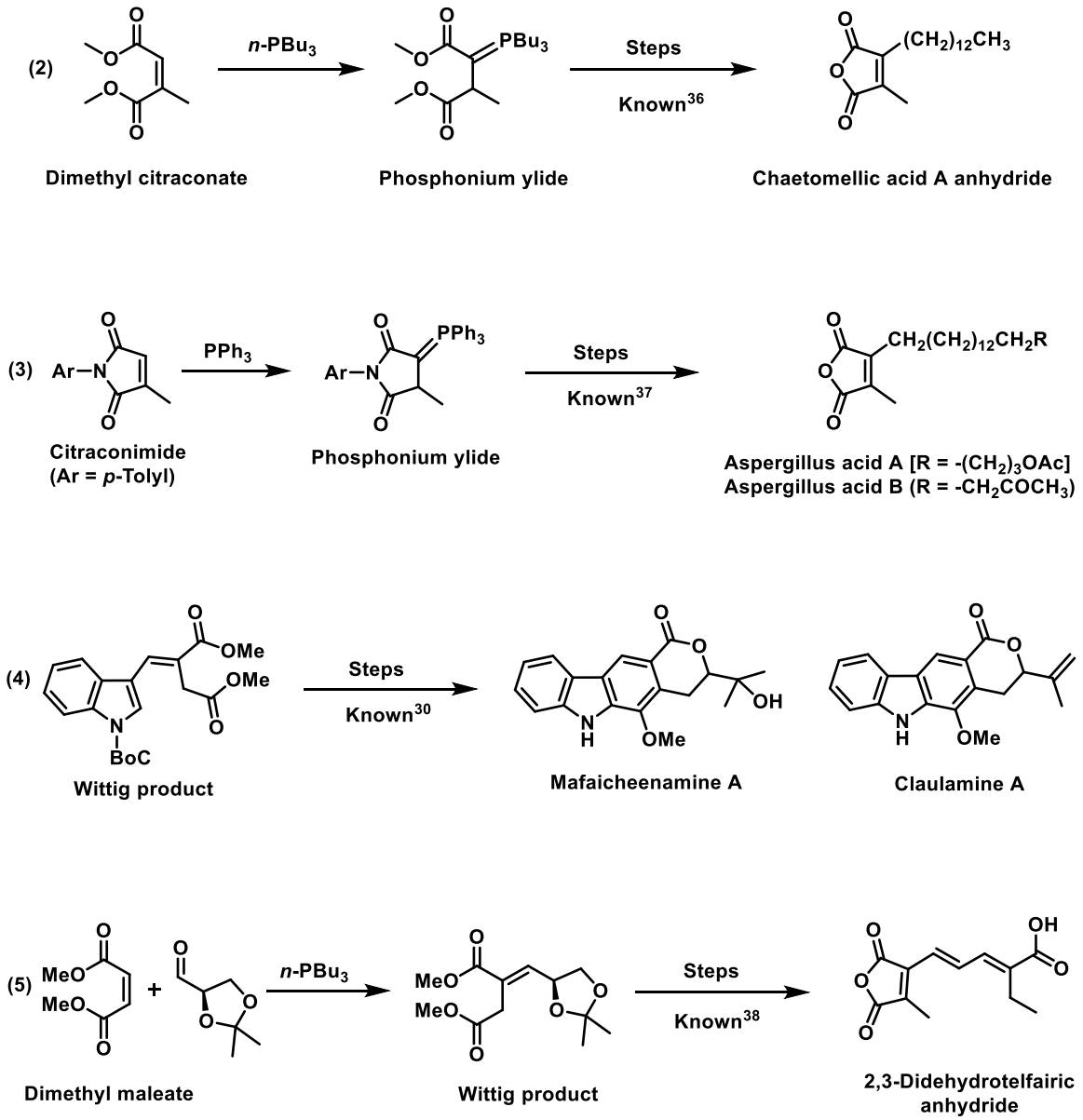


Figure 4. Starting materials for the preparation of stabilized Wittig reagents

Following are the examples of total synthesis of natural products that Argade and co-workers synthesized by using the above specified Wittig reaction strategy (Scheme 2).[35-38]





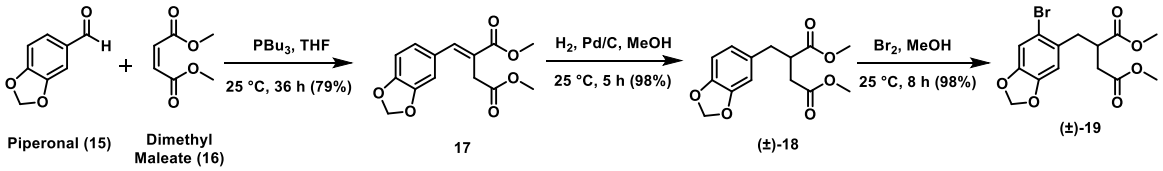
Scheme 2. Applications of Stabilized Wittig Reagents in Natural Products Synthesis

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

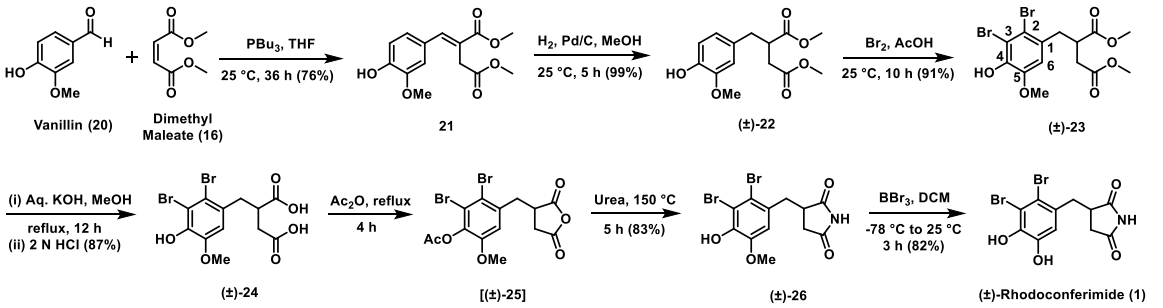
In continuation of our studies on total synthesis of recently isolated structurally interesting and biologically important natural products we herein describe the first total synthesis of (±)-rhodoconferimide from the readily available precursors vanillin and dimethyl maleate.[31] Synthesis of an appropriately penta-substituted aromatic ring bearing compounds is a challenging task from both electronic and steric reasons point of view. A careful scrutiny of rhodoconferimide structure revealed that 3,4-methylenedioxybenzaldehyde (piperonal), dimethyl maleate, elemental bromine and urea would be suitable chemical constituents to accomplish the practical total synthesis of

target compound. Appropriate sequencing of reactions, regioselective electrophilic introduction of two bromine atoms on the properly activated aromatic ring and overall stability of catechol moiety were the synthetic concerns.

Wittig reaction of in situ generated ylide from dimethyl maleate (**16**) and tributylphosphine with piperonal (**15**) exclusively supplied the (*E*)-olefin **17** in 79% yield (Scheme 3). The catalytic hydrogenation of (*E*)-olefin **17** to saturated diester **18** followed by its bromination in methanol solely formed the mono-brominated product **19** in 96% yield over two steps. The position of bromine atom in compound **19** was confirmed on the basis of two sharp singlets of aromatic protons in ^{1}H NMR spectrum. The compound **19** on treatment with excess of bromine (4.00 equiv) in acetic acid at 25 °C for 24 hours resulted in the inseparable mixture of corresponding mono- and di-brominated products in very good yield with 1:3 ratio (by ^{1}H NMR). Unfortunately, the aromatic ring system in compound **19** was not sufficiently activated for facile electrophilic introduction of the desired second bromine atom. Therefore, at this stage it was decided to commence the synthesis from vanillin instead of piperonal.



Scheme 3. Synthesis of Mono-brominated Model Compound



Scheme 4. First Total Synthesis of (±)-Rhodoconferimide via One-pot Regioselective Brominations

Wittig reaction of above specified compound **16** derived ylide with vanillin (**20**) furnished the required product **21** in 76% yield, which on catalytic reduction of carbon–carbon double bond provided the diester **22** in 99% yield (Scheme 4). The compound **22** on

treatment with excess of bromine (4.00 equiv) in acetic acid underwent smooth stepwise regioselective electrophilic aromatic substitutions and directly provided the desired dibromo compound **23** in 91% yield. In compound **23** the position two is *para* to the directing methoxy group while the position three is *ortho* to the relatively more electron rich hydroxyl group and therefore the introductions of two bromine atoms selectively took place at those positions. The introduction of third bromine atom at position six in compound **23** does not take place probably for less activation and/or steric hindrance reasons (presence of methoxy group instead of hydroxy moiety at position five). The diester **23** on base promoted hydrolysis yielded the dicarboxylic acid **24** in 87% yield. One-pot acetic anhydride induced transformation of dicarboxylic acid **24** to the corresponding anhydride **25** followed by its neat fusion with urea directly provided the in situ deacylated benzylsuccinimide **26** in 83% yield over two steps. Anhydride **25** was used for the next step without any purification and characterization due to its propensity towards the hydrolytic cleavage. Boron tribromide (BBr_3) induced demethylation of **26** at −78 °C delivered the final product (±)-rhodoconferimide (**1**) in 82% yield. The obtained analytical and spectral data for rhodoconferimide (**1**) were in complete agreement with the reported data[26] and it was obtained in seven steps with 41% overall yield.

In the present synthesis of (±)-rhodoconferimide application of vanillin as a starting material was strategically planned for the desired regioselective introduction of two bromine atoms. Thus on the basis of results described in schemes 3 and 4; we propose that the use of corresponding veratraldehyde, isovanillin and protocatechuic aldehyde derived products would plausibly deliver the undesired monobrominated, dibrominated and tribrominated products respectively.

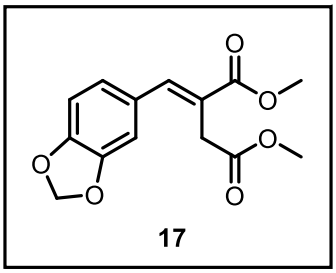
2A.3 Summary

Total synthesis of (±)*-rhodoconferimide has been demonstrated without involving any separate protection step. We believe that the bromophenol moiety in* (+)*-rhodoconferimide is responsible for antioxidant activity and the genesis of bromine atoms could be marine water.* (+)*-Rhodoconferimide is important from activity and utility point of view and this constituent from edible seaweed may find application as a food additive and/or drug candidate.*[41] *Present synthetic strategy is flexible and it will be useful to design focused mini library of rhodoconferimide derivatives and congeners for tailored antioxidant property studies. Moreover, conceptually the custom-made polymers derived*

from bromine containing compounds like rhodoconferimide will be useful to fabricate the marine water friendly durable fishing networks.

2A.4 Experimental Section

Dimethyl (*E*)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)succinate (17).



To a stirred solution of dimethyl maleate (**16**; 0.33 mL, 2.66 mmol) and piperonal (**15**; 0.40 mL, 2.66 mmol) in THF (10 mL) was dropwise added *n*-Bu_3P (0.85 mL, 3.46 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 36 h and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate 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 (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether mixture (2:8) as an eluent furnished product **17** as a white solid (586 mg, 79%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 2H), 3.74 (s, 3H), 3.82 (s, 3H), 6.00 (s, 2H), 6.80−6.92 (m, 3H), 7.81 (s, 1H).

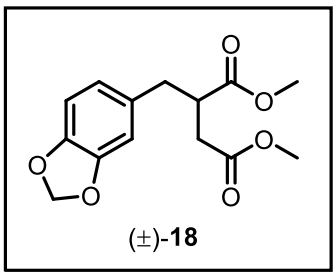
^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.5, 52.18, 52.22, 101.4, 108.6, 109.1, 124.0, 124.3, 128.8, 141.9, 147.9, 148.3, 167.9, 171.6.

HRMS (ESI) calcd for $C_{14}H_{14}O_6Na$ 301.0683, found 301.0678.

IR ($CHCl_3$) ν_{max} 1711, 1691 cm^{-1}.

Mp 78−80 °C.

Dimethyl 2-(Benzo[d][1,3]dioxol-5-ylmethyl)succinate (18).



To a stirred solution of compound **17** (500 mg, 1.79 mmol) in methanol (10 mL) was added activated Pd/C (50 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 °C for 5 h. The reaction mixture was filtered to remove Pd/C and the filtrate was concentrated in vacuo. The obtained compound was dissolved in ethyl acetate and the formed solution was washed with water, brine and dried over Na_2SO_4. The resultant solution was concentrated in vacuo and then dried by using vacuum pump to provide the pure product **18** as thick oil (493 mg, 98%).

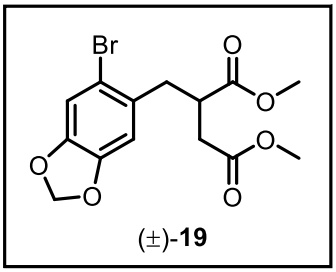
^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.41 (dd, J = 16.5 and 4.9 Hz, 1H), 2.66 (t, J = 9.8 Hz, 1H), 2.69 (t, J = 7.3 Hz, 1H), 2.96 (dd, J = 13.4 and 6.1 Hz, 1H), 3.02−3.13 (m, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 5.93 (s, 2H), 6.59 (d, J = 7.3 Hz, 1H), 6.65 (s, 1H), 6.73 (d, J = 7.3 Hz, 1H).

^{13}C NMR (CDCl$_3$, 50 MHz) δ 34.8, 37.4, 43.2, 51.8, 51.9, 100.9, 108.2, 109.2, 122.0, 131.8, 146.3, 147.7, 172.3, 174.6.

HRMS (ESI) calcd for $C_{14}H_{16}O_6Na$ 303.0839, found 303.0834.

IR (CHCl$_3$) ν_{max} 1733, 1601 cm^{-1}.

Dimethyl 2-{[6-Bromobenzo(d)(1,3)dioxol-5-yl]methyl}succinate (19).



(±)-**19**

To a stirred solution of compound **18** (200 mg, 0.71 mmol) in MeOH (10 mL) was added bromine (0.15 mL, 2.85 mmol) at 0 °C 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 EtOAc. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained bromo compound was purified by silica gel (60−120) column chromatography using ethyl acetate–petroleum ether mixture (2:8) as an eluent to furnish product **19** as thick oil (250 mg, 98%).

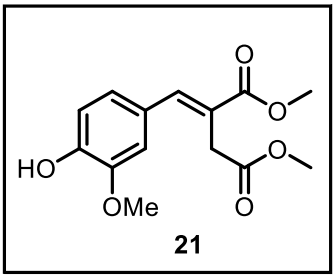
^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.46 (dd, J = 16.6 and 4.5 Hz, 1H), 2.60−2.90 (m, 2H), 2.95−3.60 (m, 2H), 3.65 (s, 3H), 3.68 (s, 3H), 5.95 (s, 2H), 6.66 (s, 1H), 6.98 (s, 1H).

^{13}C NMR (CDCl$_3$, 50 MHz) δ 35.0, 37.5, 41.6, 51.7, 52.0, 101.7, 110.5, 112.8, 114.9, 130.6, 147.29, 147.34, 172.0, 174.4.

HRMS (ESI) calcd for $C_{14}H_{15}O_6BrNa$ 380.9944, found 380.9941.

IR (CHCl$_3$) ν_{max} 1734, 1600 cm^{-1}.

Dimethyl (*E*)-2-(4-Hydroxy-3-methoxybenzylidene)succinate (21).



21

To a stirred solution of dimethyl maleate (**16**; 3.42 mL, 27.30 mmol) and vanillin (**20**; 4.15 g, 27.30 mmol) in THF (40 mL) was dropwise added *n*-Bu$_3$P (8.73 mL, 35.45 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 36 h and concentrated in vacuo. The obtained

residue was dissolved in ethyl acetate and the resultant solution was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether mixture (2:8) as an eluent furnished product **21** as a white solid (5.81 g, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.57 (s, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 6.27 (br s, 1H), 6.85−6.90 (m, 3H), 7.80 (s, 1H).

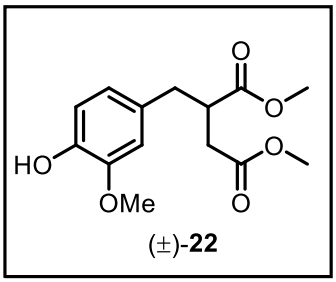
^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.5, 52.0, 52.1, 55.7, 111.7, 114.6, 123.2, 123.3, 126.9, 142.2, 146.5, 146.7, 168.0, 171.8.

HRMS (ESI) calcd for $C_{14}H_{16}O_6Na$ 303.0839, found 303.0833.

IR ($CHCl_3$) ν_{max} 3417, 1710, 1632 cm^{-1}.

Mp 89−91 °C.

Dimethyl 2-(4-Hydroxy-3-methoxybenzyl)succinate (22).



(±)-**22**

To a stirred solution of compound **21** (4.00 g, 14.28 mmol) in methanol (40 mL) was added activated Pd/C (400 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 °C for 5 h. The reaction mixture was filtered to remove Pd/C and the filtrate was concentrated in vacuo. The obtained compound was dissolved in ethyl acetate and the formed solution was washed with water, brine and dried over Na_2SO_4. The resultant solution was concentrated in vacuo and then dried by using vacuum pump to provide the pure product **22** as thick oil (3.98 g, 99%).

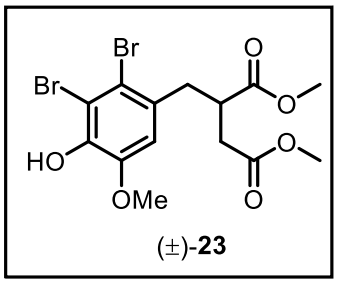
^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.41 (dd, J = 16.7 and 5.0 Hz, 1H), 2.60−2.68 (m, 1H), 2.72 (d, J = 8.2 Hz, 1H), 2.92−3.18 (m, 2H), 3.65 (s, 3H), 3.68 (s, 3H), 3.87 (s, 3H), 5.56 (s, 1H), 6.60−6.68 (m, 2H), 6.85 (d, J = 7.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.9, 37.5, 43.3, 51.7, 51.9, 55.9, 111.3, 114.3, 121.8, 129.9, 144.4, 146.5, 172.4, 174.7.

HRMS (ESI) calcd for $C_{14}H_{18}O_6Na$ 305.0996, found 305.0991.

IR ($CHCl_3$) ν_{max} 3539, 1733, 1611 cm^{-1}.

Dimethyl 2-(2,3-Dibromo-4-hydroxy-5-methoxybenzyl)succinate (23).



(±)-**23**

To a stirred solution of compound **22** (3.00 g, 10.63 mmol) in AcOH (30 mL) was added bromine (2.18 mL, 42.55 mmol) at 0 °C and the reaction mixture was stirred at 25 °C for 10 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, 5% aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained dibromo product was purified by silica gel (60−120) column chromatography using ethyl acetate–petroleum ether mixture (2:8) as an eluent to furnish the pure product **23** as a brown solid (4.20 g, 91%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.49 (dd, J = 16.6 and 4.5 Hz, 1H), 2.64−2.82 (m, 1H), 2.87−3.04 (m, 1H), 3.10−3.32 (m, 2H), 3.66 (s, 3H), 3.67 (s, 3H), 3.89 (s, 3H), 6.07 (br s, 1H), 6.71 (s, 1H).

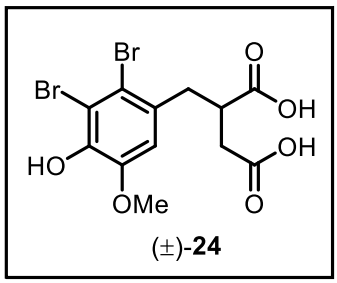
^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.2, 39.2, 41.5, 51.8, 52.0, 56.4, 112.1, 112.4, 118.1, 130.5, 143.3, 145.9, 172.0, 174.4.

HRMS (ESI) calcd for $C_{14}H_{16}O_6Br^{81}BrNa$ 462.9185, found 462.9172.

IR ($CHCl_3$) ν_{max} 3426, 1733, 1638 cm^{-1}.

Mp 106−108 °C.

2-(2,3-Dibromo-4-hydroxy-5-methoxybenzyl)succinic Acid (24).



(±)-**24**

To a stirred solution of ester **23** (1.00 g, 2.28 mmol) in methanol (15 mL) was added solution of KOH (1.30 g, 22.83 mmol) in water (5 mL) at 25 °C and the reaction mixture was refluxed for 12 h. The reaction mixture was allowed to reach 25 °C and then concentrated in vacuo. The obtained residue was diluted with EtOAc and acidified with 2 N HCl. The organic layer was separated and aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The obtained product was purified by silica gel (60−120 mesh) column chromatography using ethyl acetate–petroleum ether mixture as an eluent (3:7) to provide diacid **24** as a white solid (813 mg, 87%).

^{1}H NMR (CD_3OD, 500 MHz) δ 2.44 (dd, J = 16.8 and 4.2 Hz, 1H), 2.64 (dd, J = 17.0 and 8.8 Hz, 1H), 2.98 (td, J = 11.1 and 4.3 Hz, 1H), 3.12−3.21 (m, 2H), 3.87 (s, 3H), 6.88 (s, 1H).

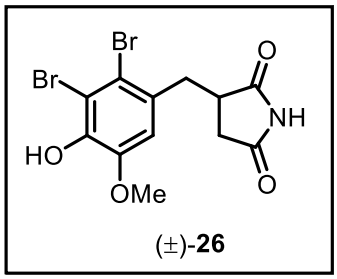
^{13}C NMR (CD_3OD, 125 MHz) δ 36.4, 40.4, 43.1, 57.0, 114.1 (2C), 118.8, 131.4, 145.9, 148.5, 175.5, 177.9.

HRMS (ESI) calcd for $C_{12}H_{12}O_6Br^{81}BrNa$ 434.8872, found 434.8861.

IR ($CHCl_3$) ν_{max} 3450, 1728, 1600 cm^{-1}.

Mp 159−161 °C.

3-(2,3-Dibromo-4-hydroxy-5-methoxybenzyl)pyrrolidine-2,5-dione (26).



(±)-**26**

A solution of diacid **24** (500 mg, 1.27 mmol) in Ac_2O (10 mL) was gently refluxed for 4 h under argon atmosphere. The reaction mixture was allowed to reach 25 °C and concentrated in vacuo. The obtained residue was dried by using vacuum pump and mixed with urea (229 mg, 3.80 mmol). The neat reaction mixture was heated at 150 °C for 5 h and then it was allowed to cool down to 25 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained product was purified by silica gel (230−400) column chromatography using methanol−dichloromethane mixture (1:9) as an eluent to provide in situ deacylated imide **26** as a white solid (415 mg, 83%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.42−2.60 (m, 2H), 2.81 (t, J = 13.4 Hz, 1H), 3.11−3.28 (m, 2H), 3.83 (s, 3H), 7.08 (s, 1H), 9.81 (s, 1H), 11.18 (br s, 1H).

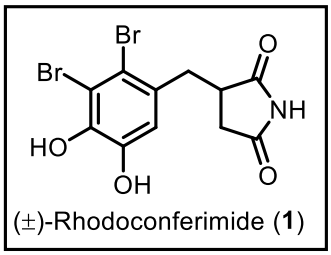
^{13}C NMR (DMSO-d_6, 50 MHz) δ 34.4, 37.5, 40.8, 56.4, 113.0, 113.4, 116.7, 129.9, 144.1, 147.3, 178.0, 180.6.

HRMS (ESI) calcd for $C_{12}H_{11}O_4NBr^{81}BrNa$ 415.8927, found 415.8919.

IR ($CHCl_3$) ν_{max} 3621, 3451, 1703 cm^{-1}.

Mp 204−206 °C.

3-(2,3-Dibromo-4,5-dihydroxybenzyl)pyrrolidine-2,5-dione (Rhodoconferimide, 1).



(±)-Rhodoconferimide (**1**)

To a stirred solution of compound **26** (170 mg, 0.43 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of BBr_3 in CH_2Cl_2 (0.61 mL, 0.65 mmol) at −78 °C over a period of 5 min under argon atmosphere. The reaction mixture was stirred for 3 h and allowed to reach 25 °C. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with water. The reaction mixture was extracted with EtOAc and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel (230−400) column chromatographic purification of the obtained compound using methanol−dichloromethane mixture (1:9) as an eluent furnished the pure product **1** as colorless thick oil (135 mg, 82%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.35 (dd, J = 17.7 and 4.3 Hz, 1H), 2.58 (dd, J = 18.0 and 9.2 Hz, 1H), 2.79 (dd, J = 12.2 and 10.4 Hz, 1H), 3.00−3.25 (m, 2H), 6.81 (s, 1H), 9.46 (s, 1H), 9.99 (s, 1H), 11.15 (s, 1H).

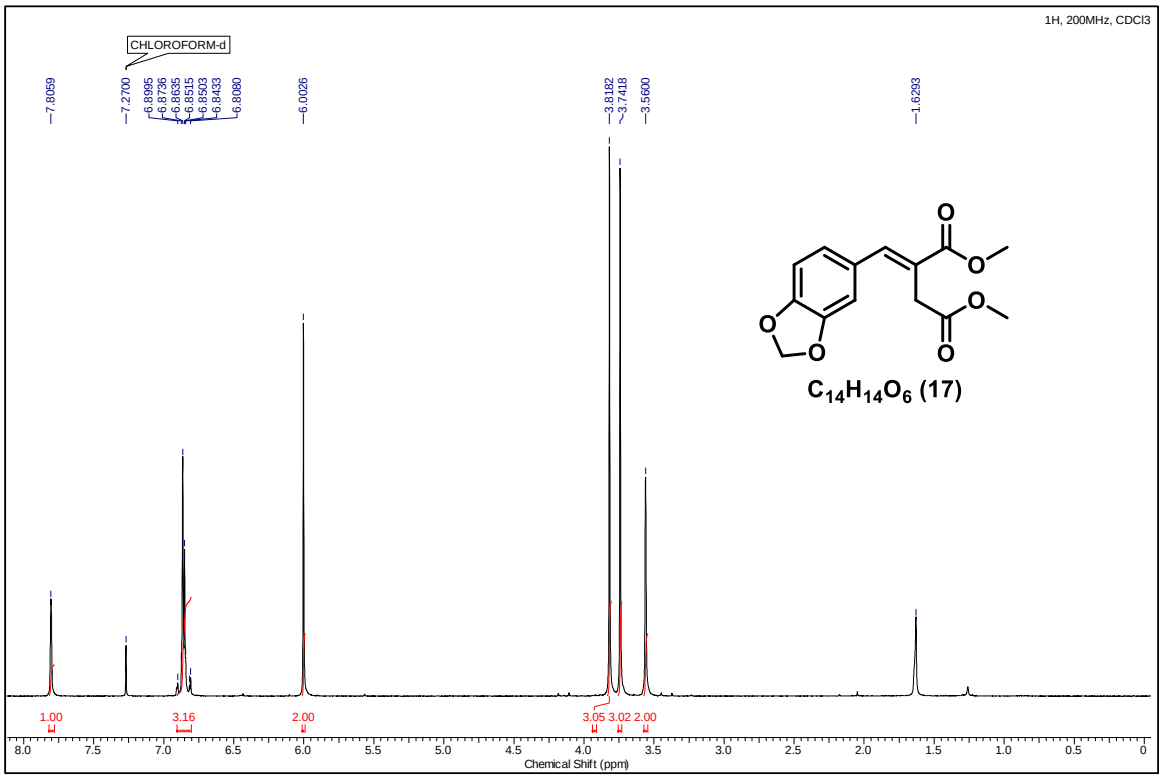
^{13}C NMR (DMSO-d_6, 50 MHz) δ 34.6, 37.1, 40.9, 113.5, 114.9, 116.5, 129.8, 143.5, 145.2, 178.0, 180.7.

HRMS (ESI) calcd for $C_{11}H_8O_4NBr^{81}Br$ 377.8794, found 377.8809 $[M-H]^-$.

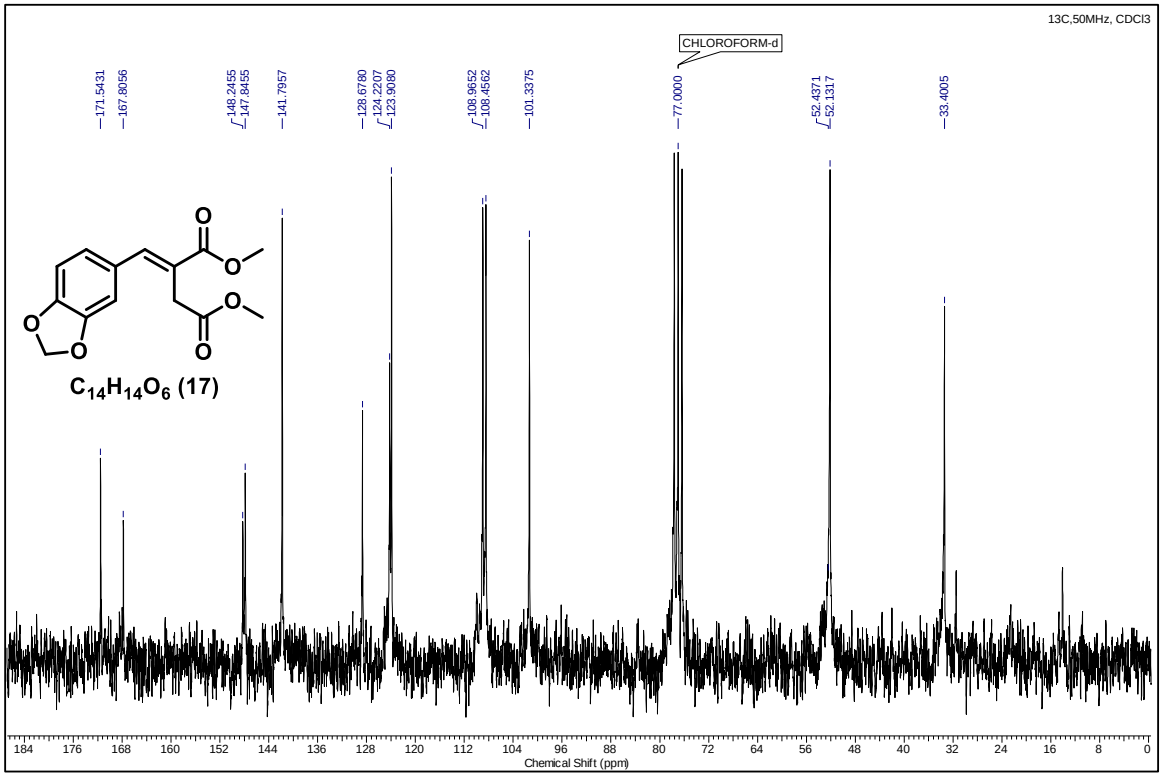
IR($CHCl_3$) ν_{max} 3600−3000, 1679, 1758 cm^{-1}.

2A.5 NMR Spectra of the Obtained Products

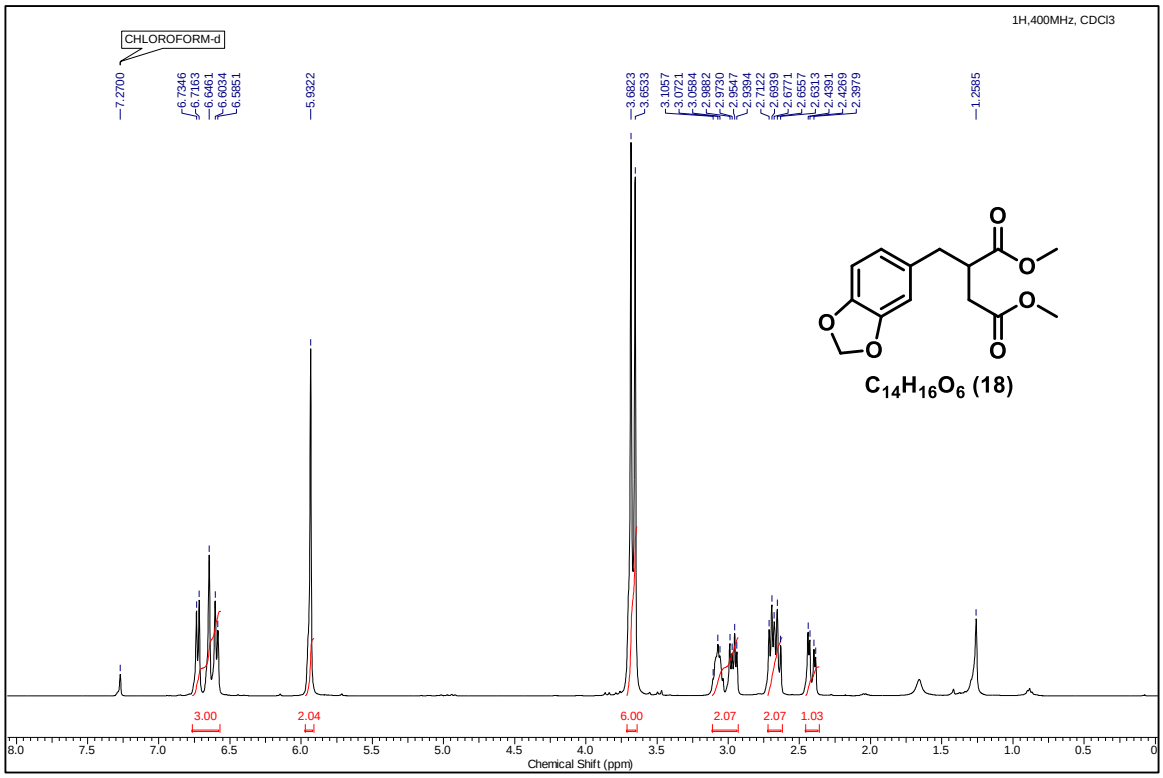
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 17



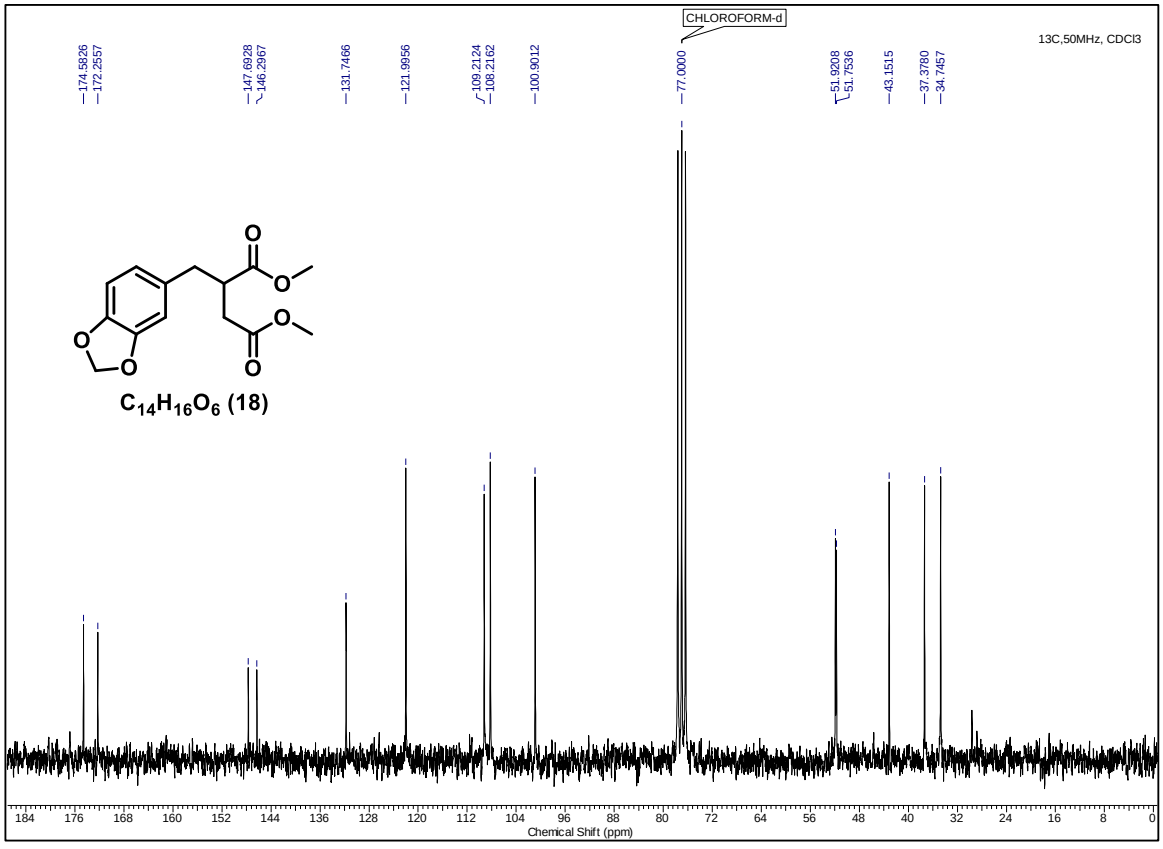
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 17



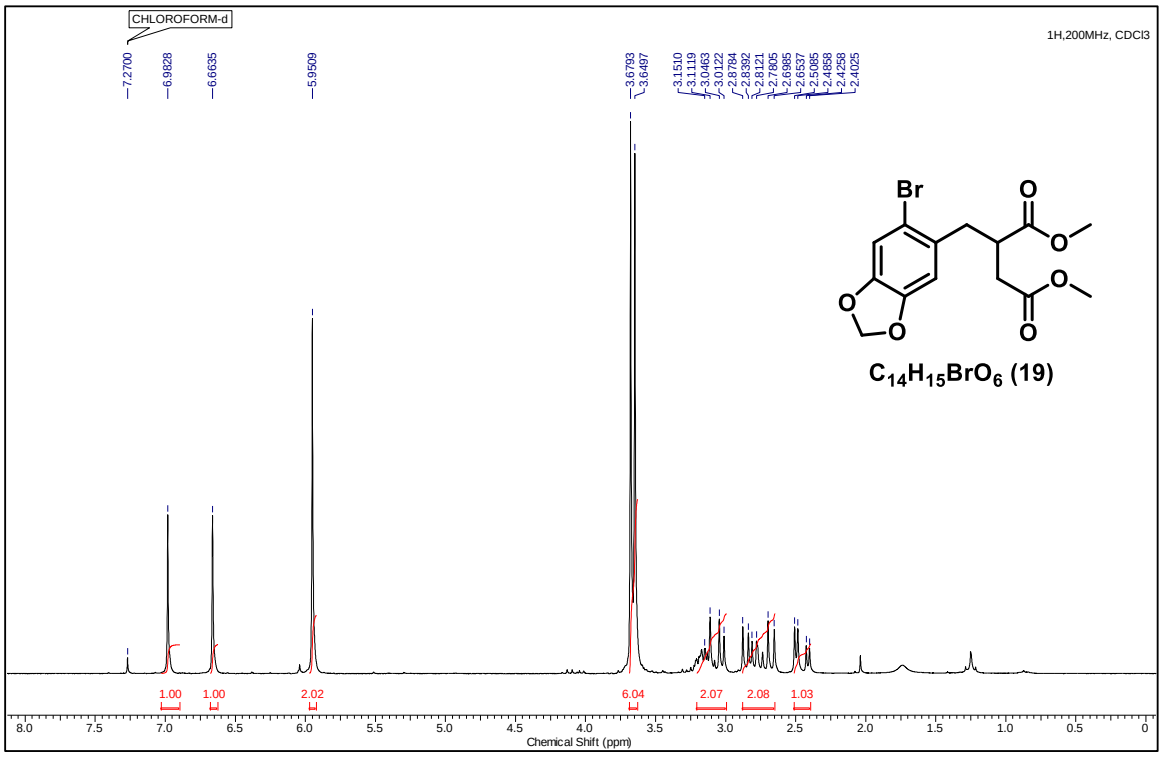
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 18



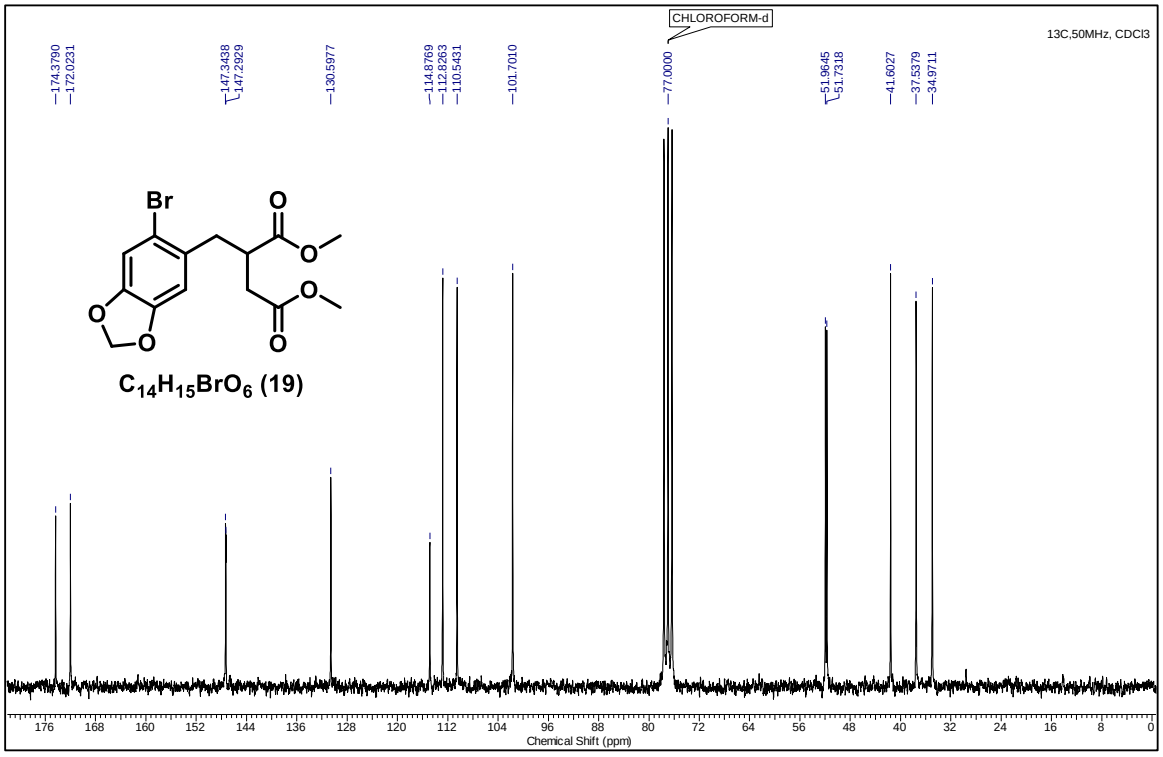
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 18



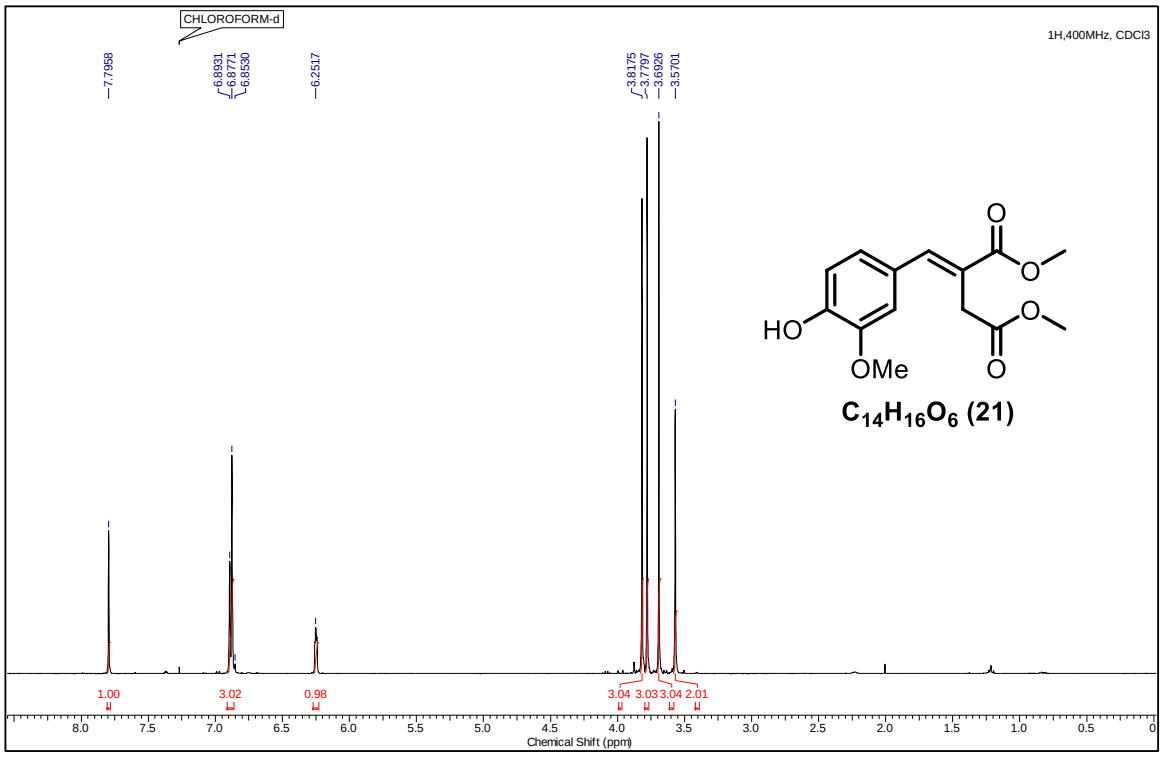
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 19



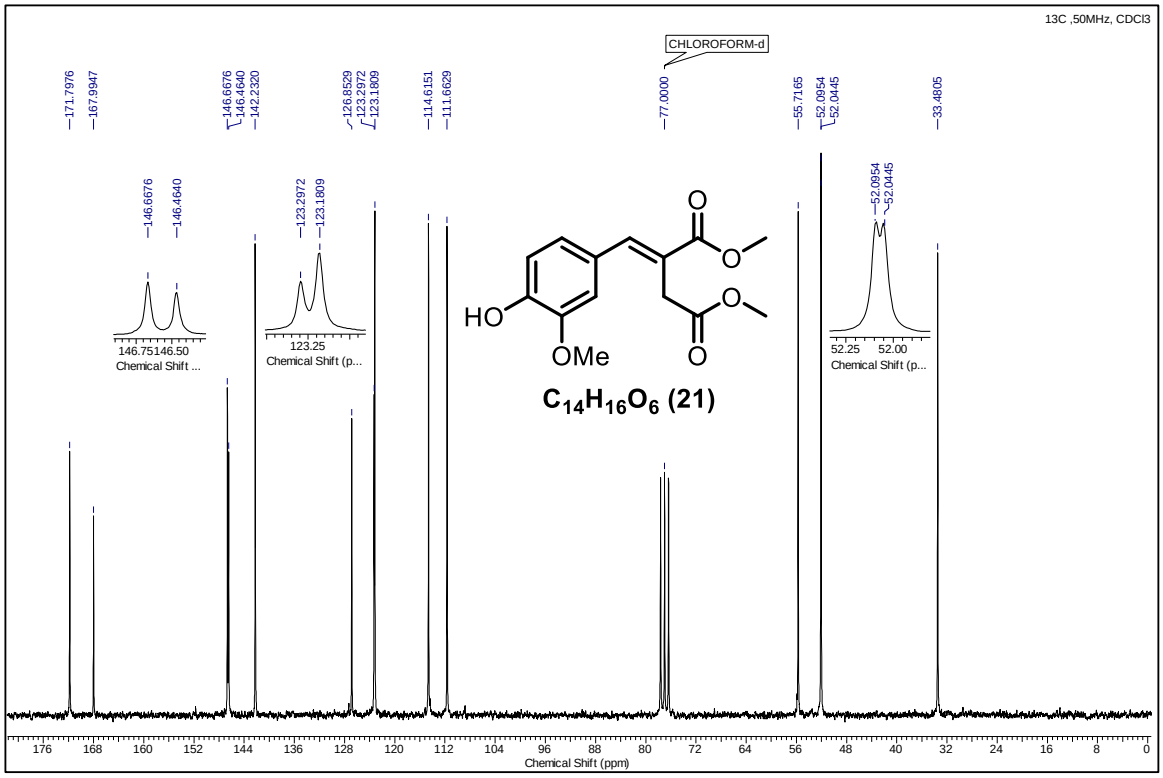
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 19



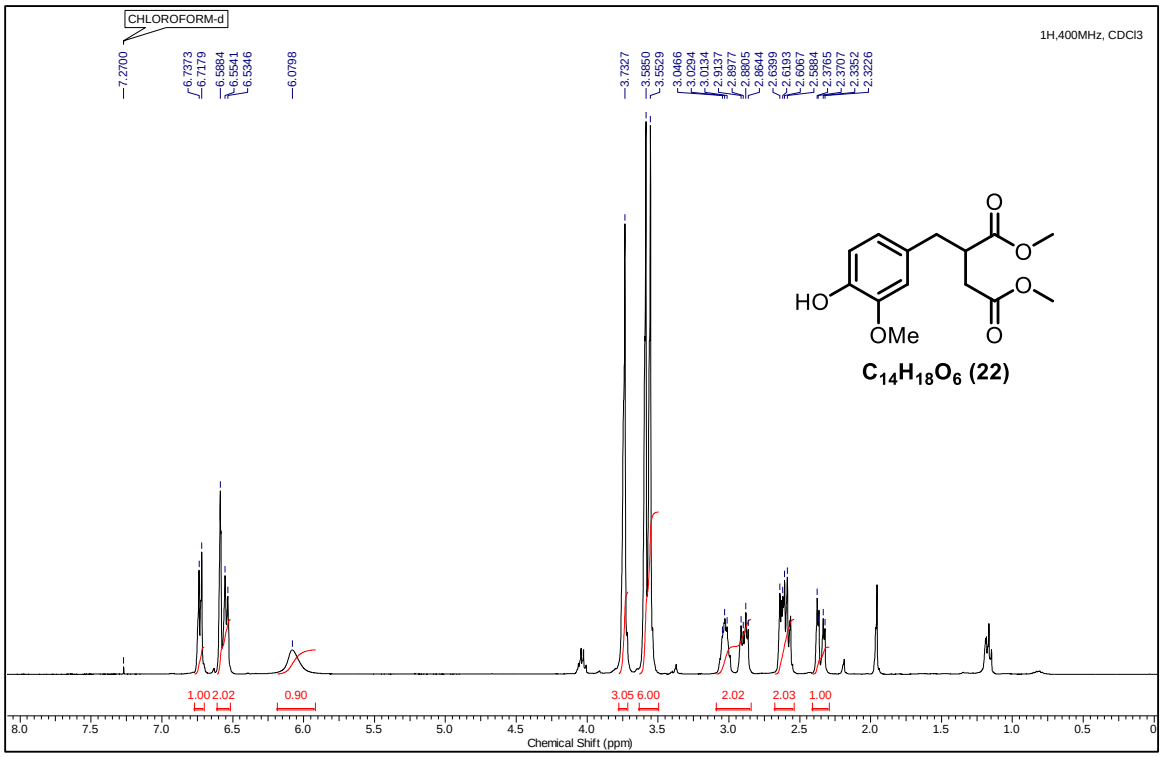
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 21



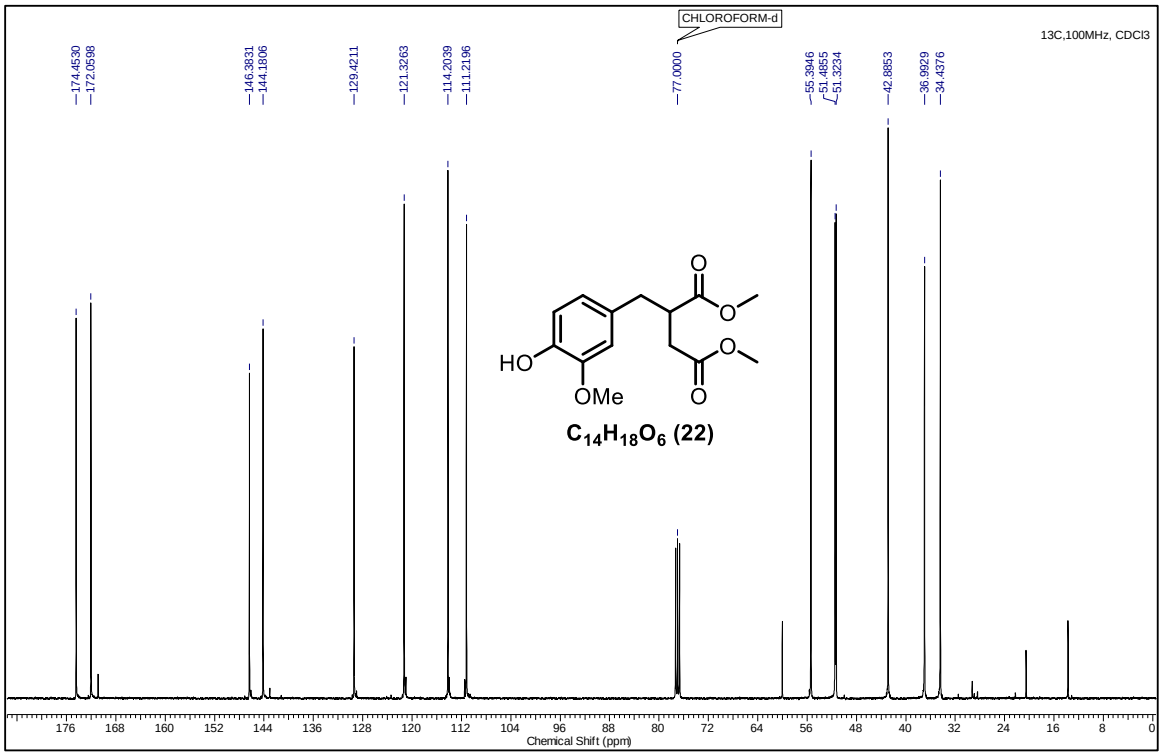
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 21



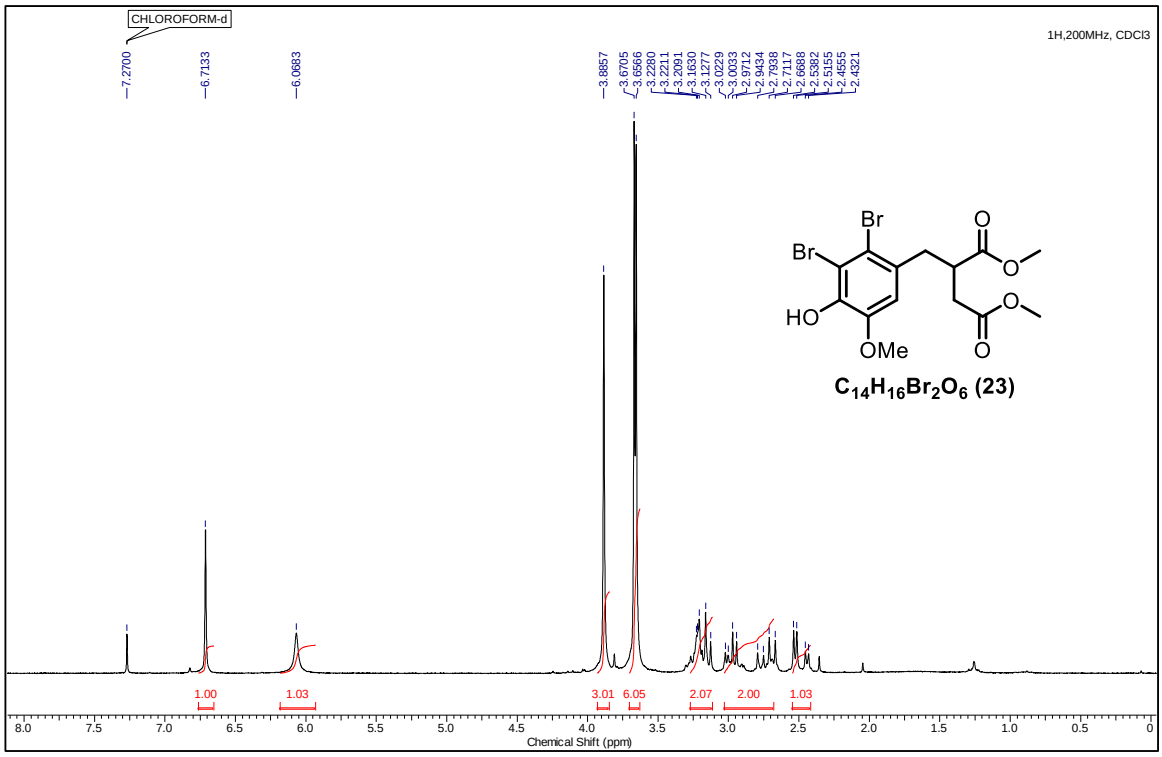
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 22



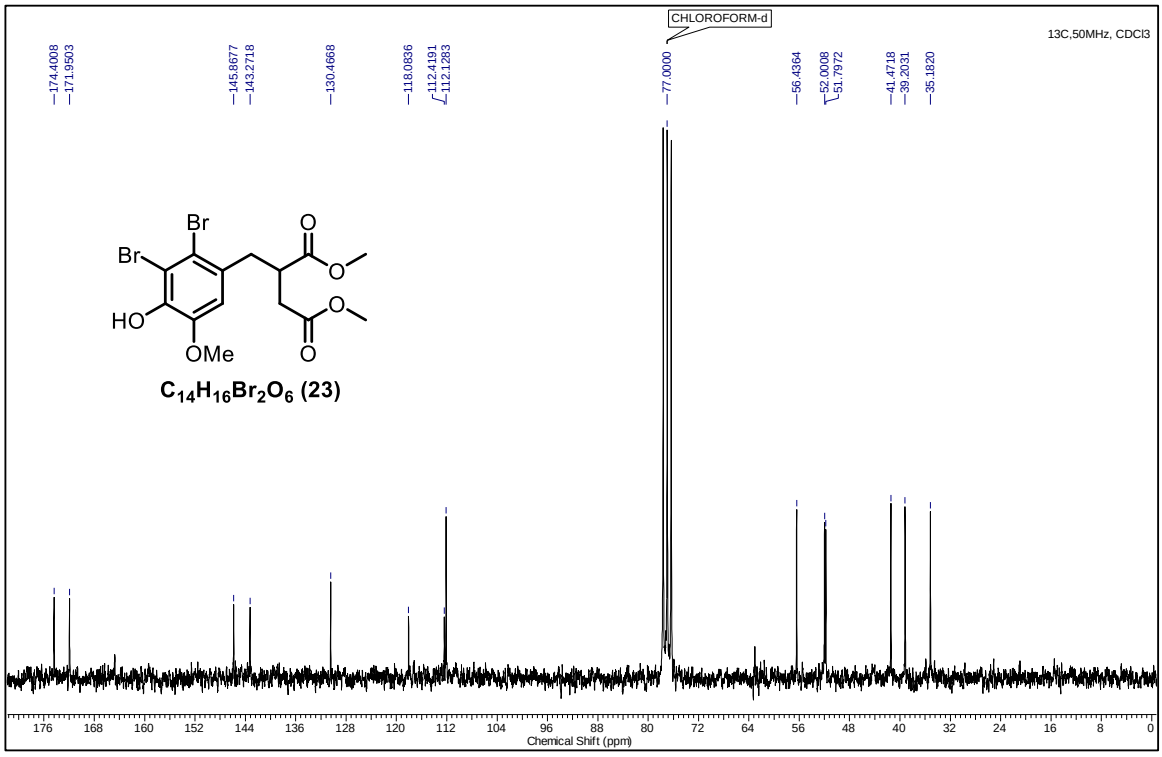
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 22



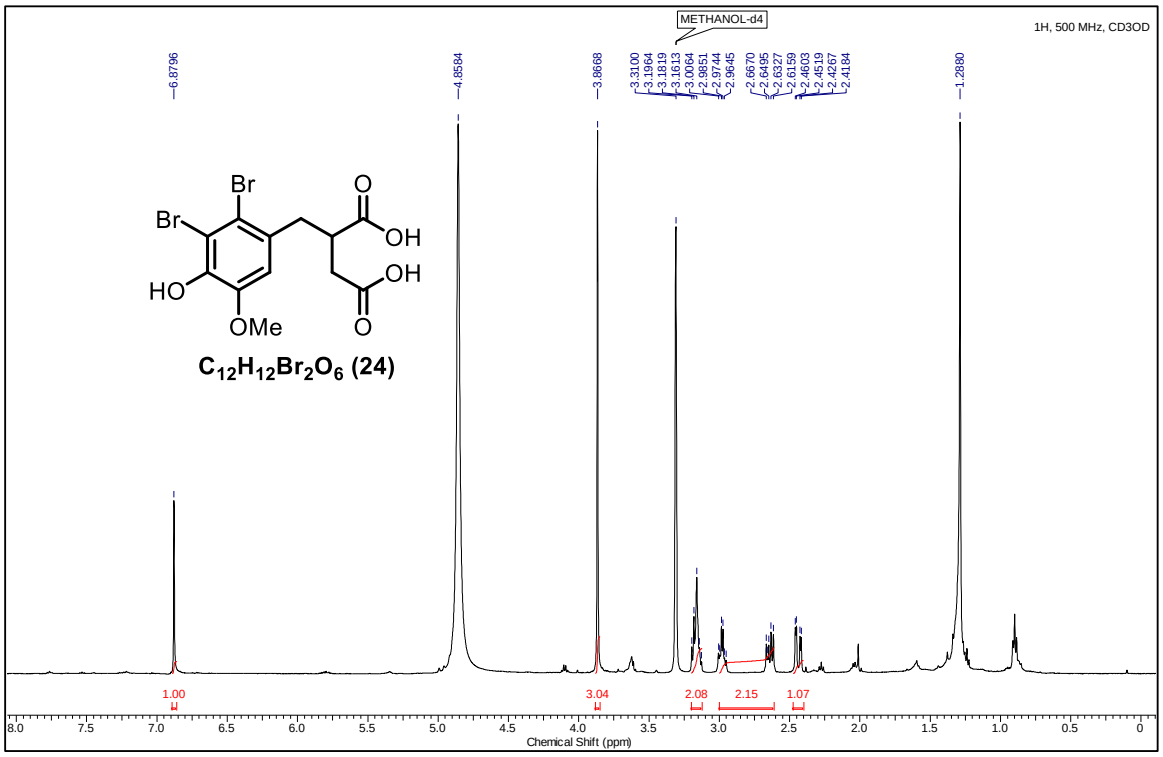
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 23



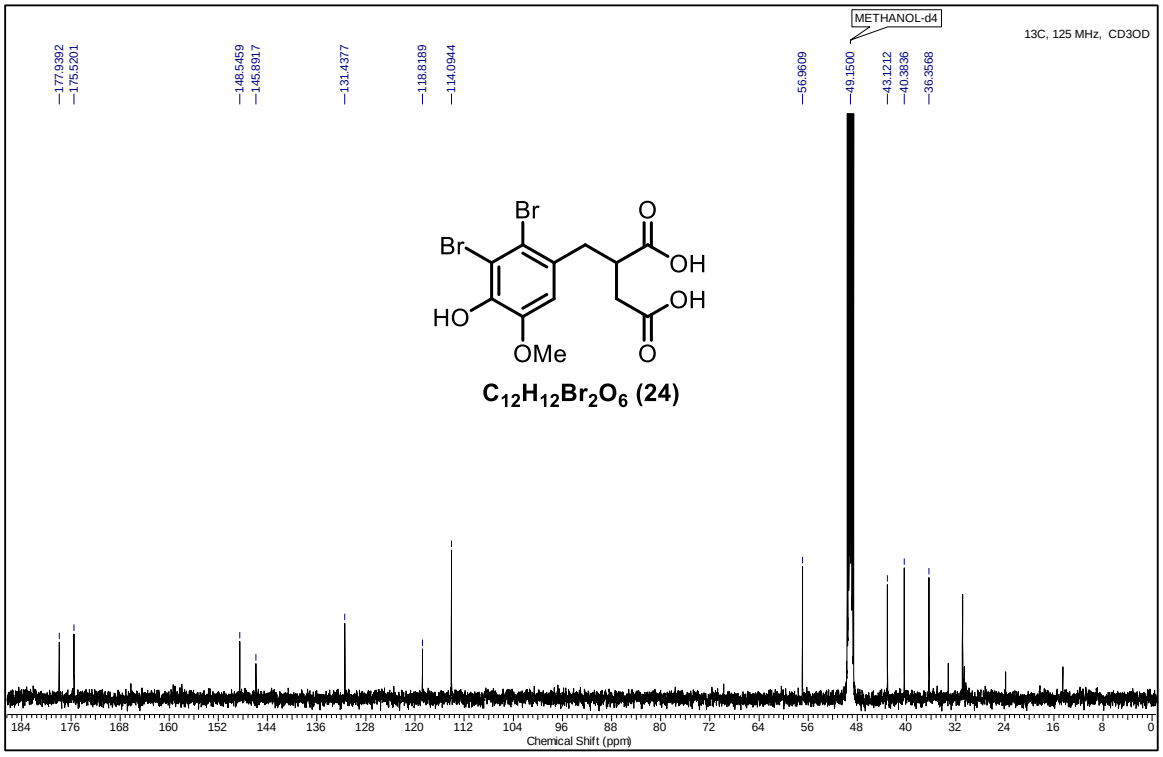
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 23



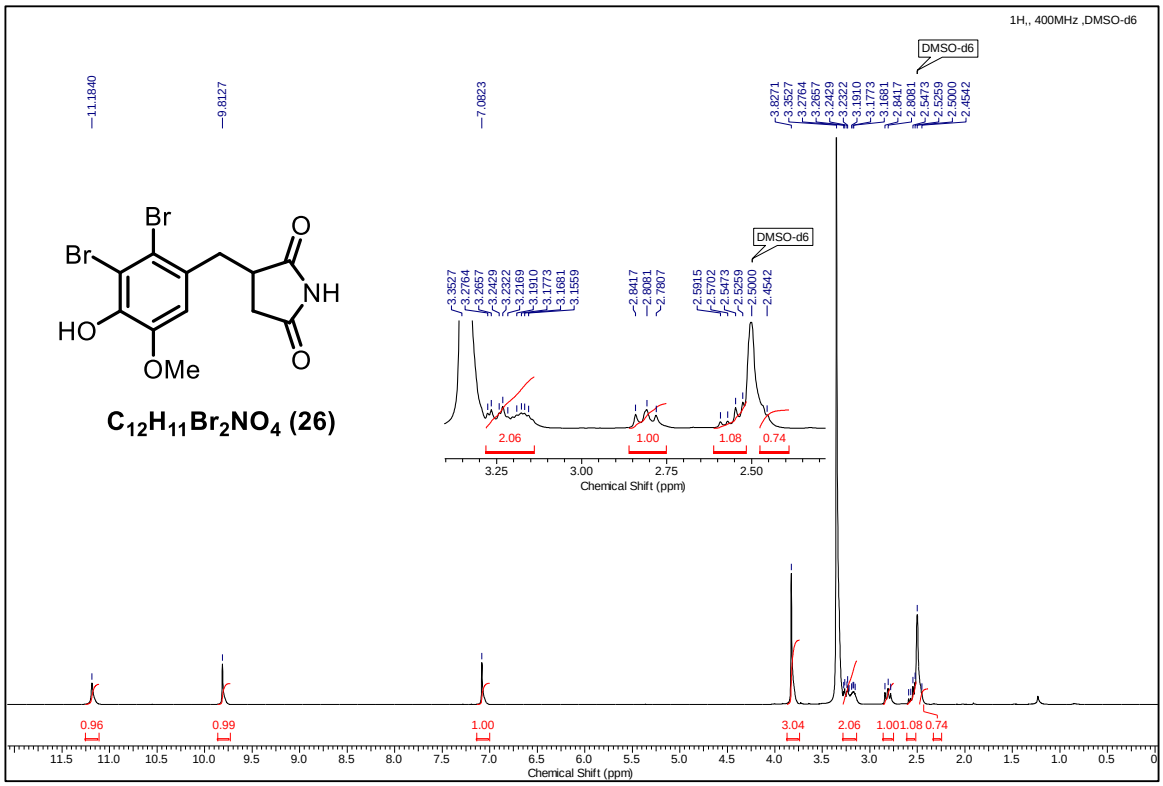
^{1}H NMR (CD_3OD, 500 MHz) of Compound 24



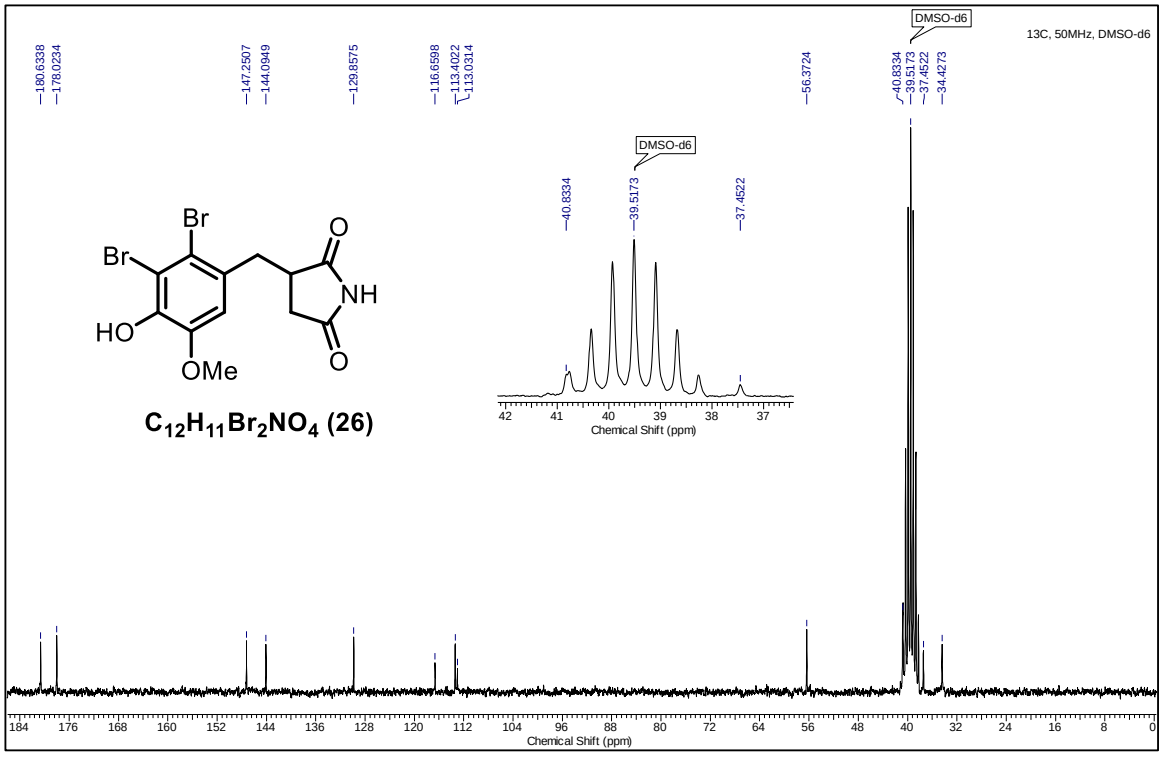
^{13}C NMR (CD_3OD, 125 MHz) of Compound 24



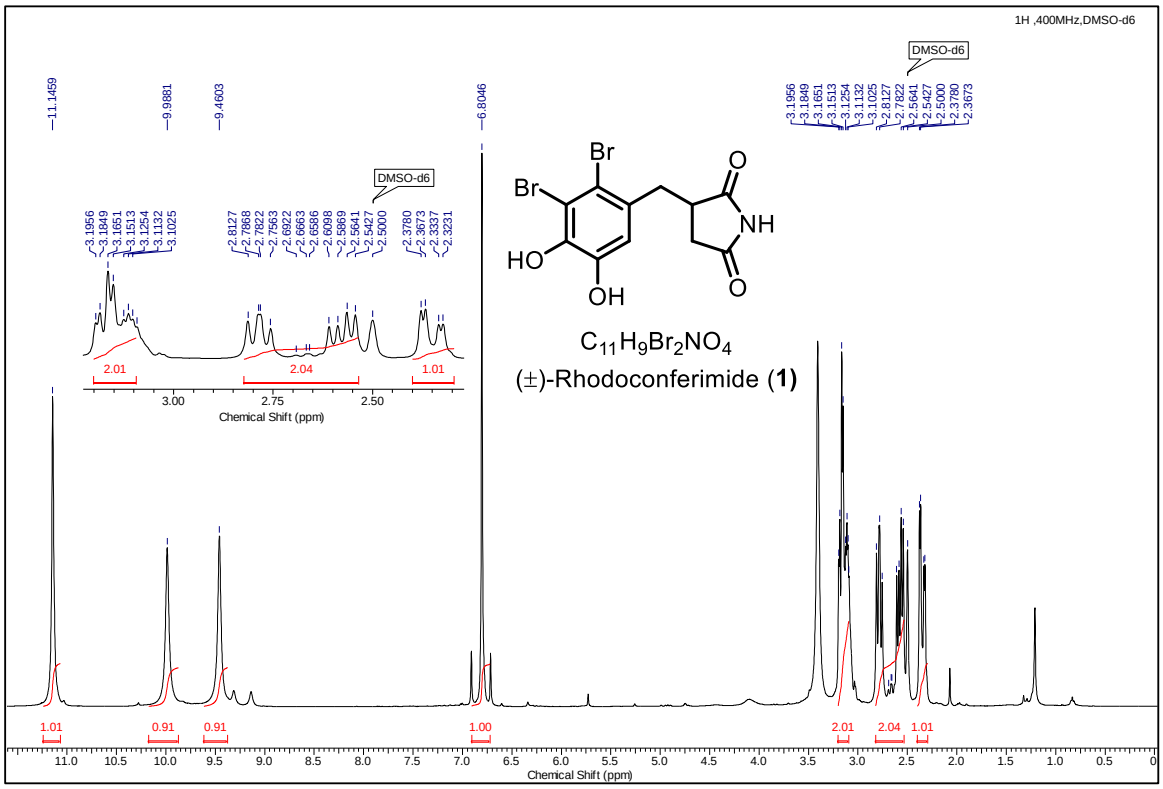
^{1}H NMR (DMSO-d_6, 400 MHz) of Compound 26



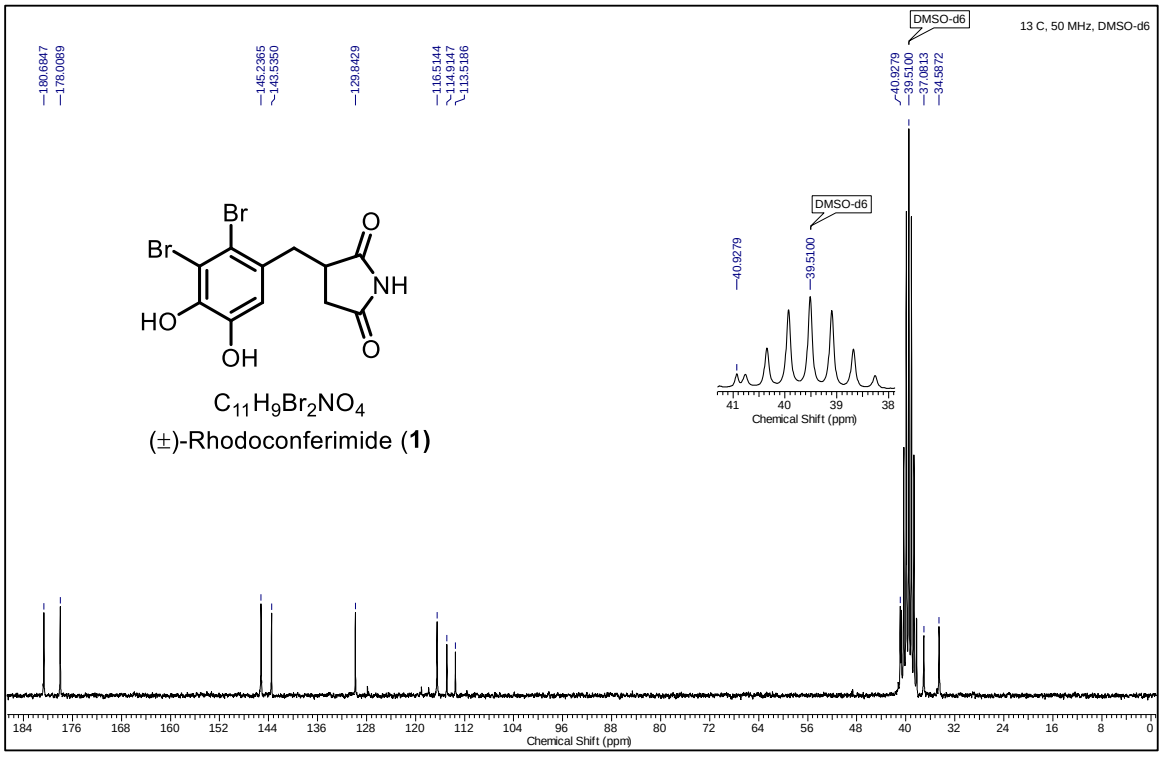
^{13}C NMR (DMSO-d_6, 50 MHz) of Compound 26



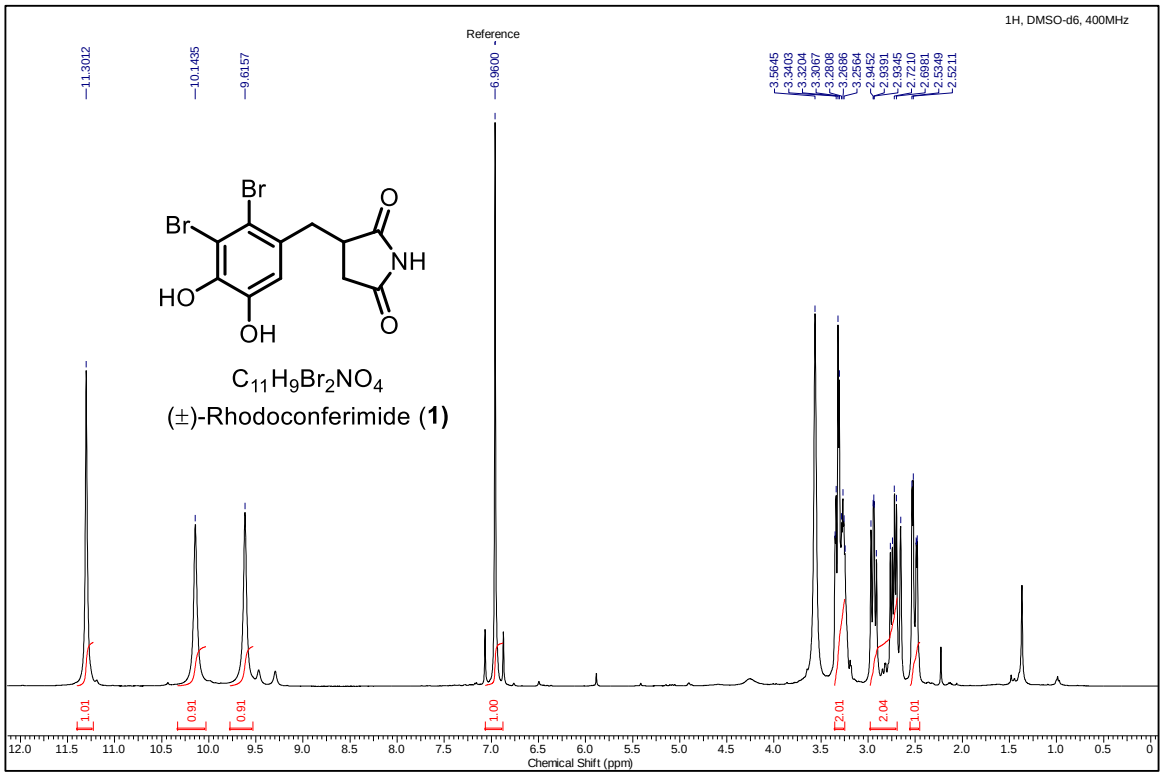
^{1}H NMR (DMSO-d_6, 400 MHz) of Compound 1



^{13}C NMR (DMSO-d_6, 50 MHz) of Compound 1



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



Note:

The noticed consistant minor difference in the delta values of all signals in ^{1}H NMR data of natural product is plausibly due to the error in picking up the correct signal for DMSO. As reported for natural product, if the signal for aromatic proton is locked at 6.96 ppm; all delta values match correctly (please see above ^{1}H NMR spectra).

2A.6 References

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Chapter 2

Reactions of Cyclic Anhydrides and Derivatives: Synthesis of Biologically Important Alkaloids

Section 2B

Attempts Towards the Synthesis of Inubosin B

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

2B.1 Background

Neurodegenerative diseases are conditions that cause particular regions of the brain to die.[1] They are some of the most difficult disorders to treat, having serious consequences. Neurodegenerative disorders are caused by the degeneration of nervous system cells (neurons) in the brain and spinal cord.[2] Changes in neuron cells force them to function inefficiently, finally resulting in death.[3-5] There is no practical solution for treating neurodegenerative disorders. Currently available drugs and therapy procedures focus on reducing the symptoms and preventing the progression of disease in patients. According to a few reports, new drugs that trigger neurogenesis in situ can treat people with neurological diseases by increasing the number of new neurons in their bodies.[6,7] Adult neurogenesis is the transformation of neural stem cells into neurons in order to compensate for the loss of neurons and so promoting neurogenesis could be a potential treatment for neurodegenerative diseases.[8-12]

Heterocyclic alkaloids are among the most important natural product classes to characterize because of their unique structural features and essential biological activities.[13-19] Inubosins A, B and C are the acridine alkaloids isolated from the extract of a culture of *Streptomyces sp.* IFM 11440 (Figure 1).[20]

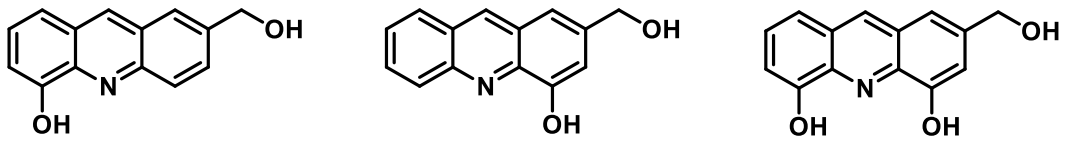
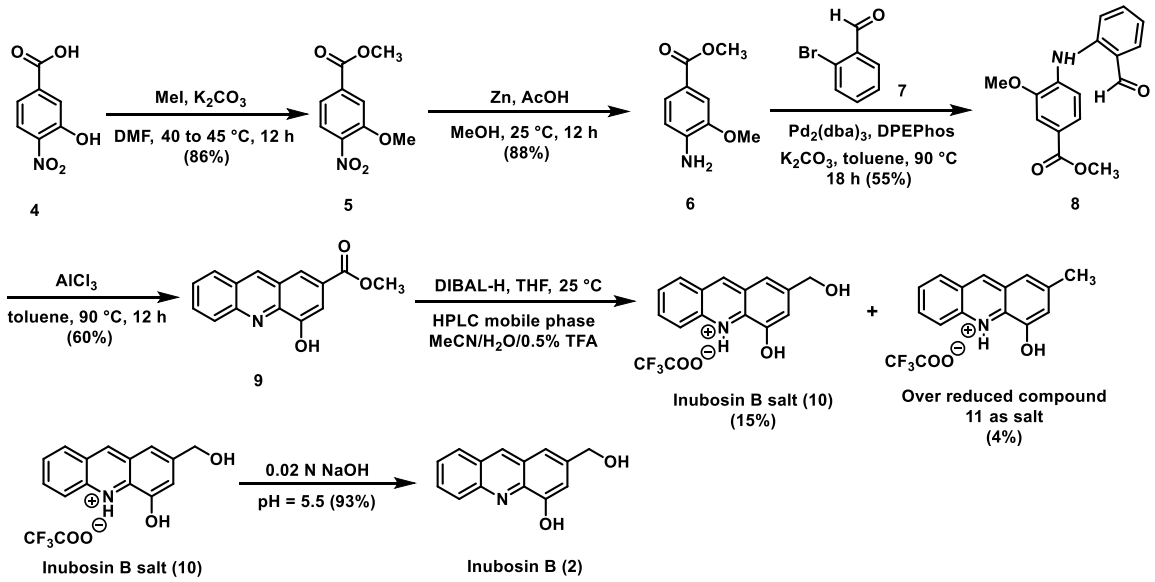


Figure 1. Structure of inubosins A-C

The studies on *Streptomyces sp.* IFM 11440 have revealed that they initiate neurogenesis by promoting the activity of neurogenin2 (Ngn2).[20] Neurogenin2 is a transcription factor that promotes the formation of neural stem cells. The Ngn2 promoter activity of inubosin B (**2**) was found to be the most effective of the three inubosins A, B and C. In addition, inubosin B increased the expression of genes involved in neural stem cell formation by stimulating their mRNA expression.[20] Inubosin B was shown to have a 2-fold higher activity than baicalin which is the only natural product that has been reported to promote Neurogenin2 mRNA expression in neural stem cells.[21]

2B.2 Reported Synthesis of Inubosin B

Recently, Hamissa and co-worker reported the total synthesis of inubosin B (**2**) via Buchwald-Hartwig amination and intramolecular cyclization followed by reduction reaction pathway (Scheme 1).[22] The total synthesis was commenced with the treatment of 3-hydroxy-4-nitrobenzoic acid (**4**) with methyl iodide, which resulted in methylation of the hydroxy group and subsequent conversion of acid to ester group to yield product **5** in 86% yield. Zn/AcOH induced reduction of nitro group furnished the corresponding amine **6** in 88% yield. Palladium-catalyzed Buchwald-Hartwig coupling reaction between amine **6** and 2-bromobenzaldehyde (**7**) provided the required aldehyde **8** in 55% yield. $AlCl_3$ promoted intramolecular cyclization of compound **8** delivered the desired cyclized product ester **9** in 60% yield. DIBAL-H mediated reduction of ester **9** over reduced the ester to the corresponding methyl compound **11**. To overcome this problem, HPLC was used to monitor the reaction and purification of the products. After monitoring the reaction with HPLC, the desired product inubosin B was obtained as TFA salt (**10**) which on treatment with aq. NaOH provided pure compound inubosin B (**2**) in 93% yield.

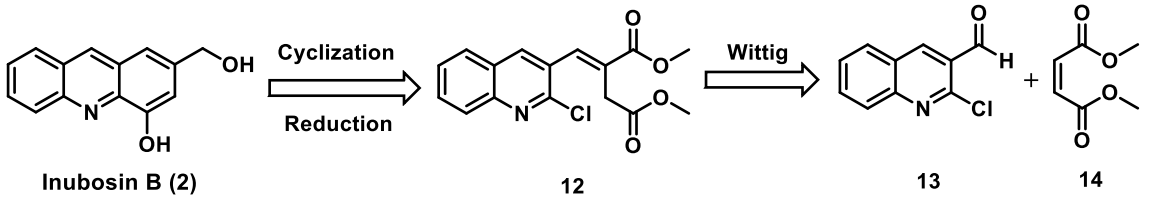


Scheme 1. Total Synthesis of Inubosin B

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

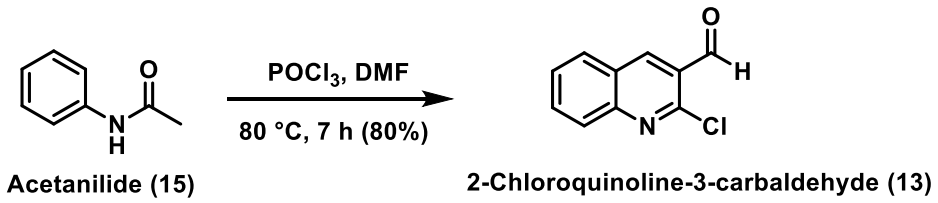
After careful examination of inubosin B (**2**) structure, it was found that retro-synthetically dimethyl maleate based Wittig reaction product would be the possible key intermediate to complete the total synthesis of inubosin B (Scheme 2). In continuation of our studies on the total synthesis of recently isolated structurally interesting and biologically important

natural products from cyclic anhydrides and their derivatives,[23-27] we herein present the attempted strategies towards the synthesis of inobosin B.



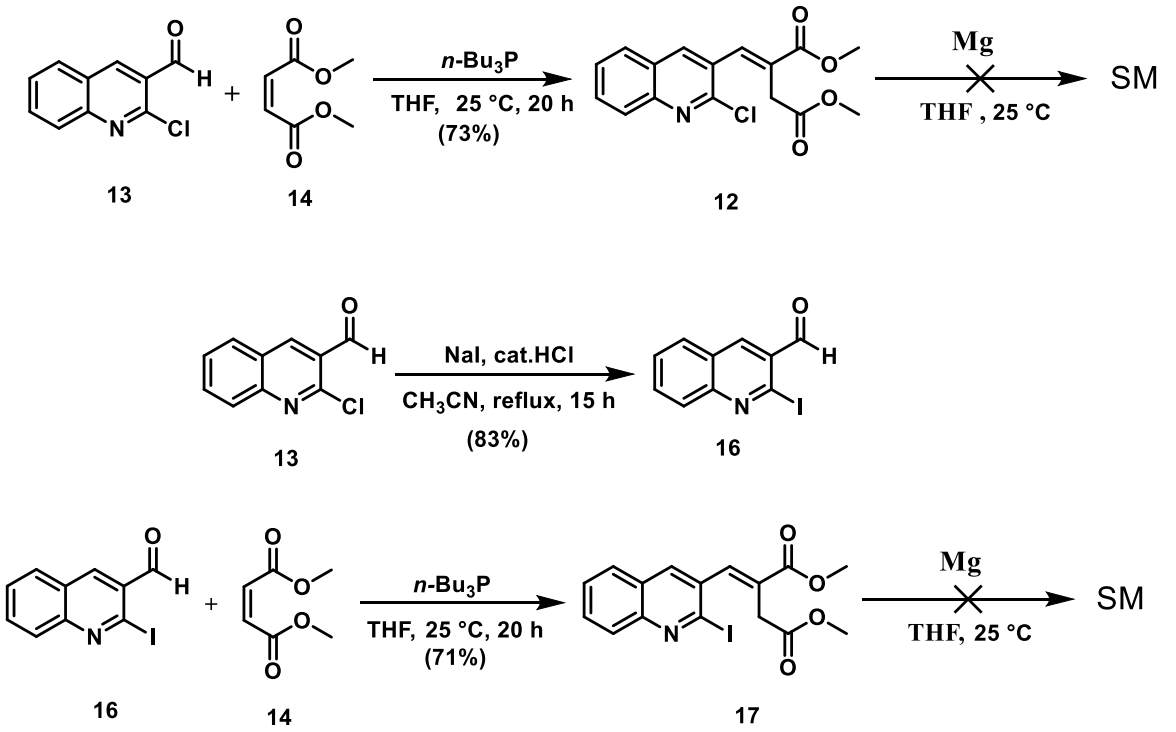
Scheme 2. Proposed Retrosynthetic Analysis for Inubosin B

The starting material for the proposed Wittig reaction, 2-chloroquinoline-3-carbaldehyde (**13**) was obtained by the reaction of acetanilide (**15**) with phosphorus oxychloride ($POCl_3$) in dimethylformamide (DMF) at 80 °C temperature (Scheme 3).[28]



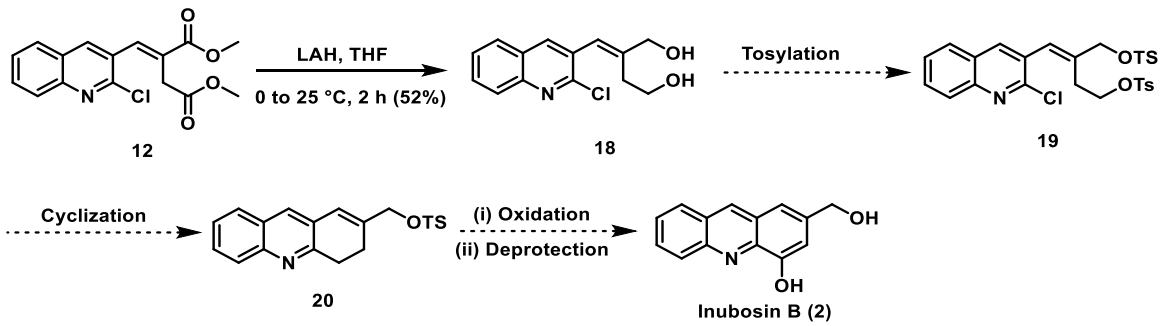
Scheme 3. Synthesis of 2-Chloroquinoline-3-carbaldehyde

Wittig reaction of 2-chloroquinoline-3-carbaldehyde (**13**) with in situ generated ylide from dimethyl maleate (**14**) and tributylphosphine exclusively provided the desired (*E*)-olefin **12** in 73% yield (Scheme 4). We assumed that the (*E*)-olefin **12** would be an appropriate substrate for the halogen-metal exchange reaction and subsequent intramolecular Grignard reaction to produce the required cyclized product. Hence we treated the (*E*)-olefin **12** with Mg metal and then stirred the reaction mixture at room temperature for 12 hours, but the reaction did not progress and the starting material was recovered. We tried the same reaction with THF in reflux condition, but it also did not work. We decided to replace the carbon-chloride bond in compound **12** with a carbon-iodide bond, as it would be better for the halogen-metal exchange reaction. The reaction of 2-chloroquinoline-3-carbaldehyde (**13**) with NaI in the presence of catalytic HCl provided the 2-iodoquinoline-3-carbaldehyde (**16**). Wittig reaction of 2-iodoquinoline-3-carbaldehyde (**16**) with in situ generated ylide from dimethyl maleate (**14**) and tributylphosphine provided the (*E*)-olefin **17** in 71% yield. Treatment of (*E*)-olefin **17** with Mg metal in THF at room temperature as well as reflux condition did not proceed and the starting material was recovered. Based on the results, we deduced that the presence of diester groups in compounds **12**/**17** was the reason for the reaction's failure.



Scheme 4. Attempts for the Intramolecular Cyclization Using Grignard Reactions

In the next attempt, the diester compound **12** was reduced to the dihydroxy compound **18** in 52% yield (Scheme 5). To accomplish the synthesis of inubosin B, we are planning to tosylate the diol **18**, then next execute selective intramolecular cyclization, benzylic oxidation and finally deprotection of the hydroxy group.



Scheme 5. New Proposed Route for the Synthesis of Inubosin B

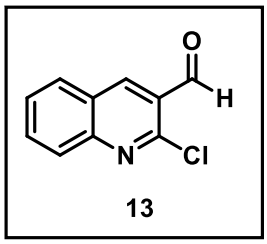
2B.4 Summary

We attempted intramolecular cyclization strategy using the Grignard reaction, but it was unsuccessful, possibly due to the presence of a chelating diester group. In our new approach, we propose to complete the synthesis of inubosin B by tosylation of the

obtained diol, selective intramolecular cyclization, benzylic oxidation, aromatization, and finally, deprotection of the hydroxy group.

2B.5 Experimental Section

2-Chloroquinoline-3-carbaldehyde (13).



13

To a cold solution of dimethylformamide (3.5 mL, 44.37 mmol), phosphorous oxychloride (12.5 mL, 133.11 mmol) was added drop wise. After 20 minutes, acetanilide (**15**; 2 g, 14.79 mmol) was added and the solution was stirred for 15-20 minutes at 0 °C, then the reaction mixture was maintained at 80 °C for 7 hours. The progress of the reaction was monitored by thin layer chromatography. After the completion of the reaction, the reaction mixture was poured over the crushed ice resulting in the formation of yellow solid compound 2-chloroquinoline-3-carbaldehyde. The solid was filtered using a Buchner funnel, washed with water and dried. The dry yellow product **13** (2.27 g, 80%) was used for the next reaction without further purification.

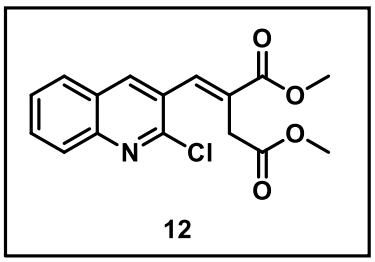
^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.84−7.70 (m, 1 H), 8.11−7.94 (m, 2 H), 8.30 (d, J = 8.2 Hz, 1 H), 9.01 (s, 1 H), 10.39 (s, 1 H).

^{13}C NMR (DMSO-d_6, 50 MHz) δ 126.3, 126.4, 127.8, 128.3, 130.2, 133.9, 141.4, 148.6, 149.0, 189.4.

IR ($CHCl_3$) ν_{max} 1695 cm^{-1}.

Mp 152−154 °C.

Dimethyl (*E*)-2-[(2-chloroquinolin-3-yl)methylene]succinate (12).



12

To a stirred solution of dimethyl maleate (**14**; 0.75 mL, 5.21 mmol) and 2-chloroquinoline-3-carbaldehyde (**13**; 1 g, 5.21 mmol) in THF was dropwise added *n*-Bu_3P (1.7 mL, 6.77 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 20 h and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate 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

(60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether mixture (1:9) as an eluent furnished product (*E*)-olefin **12** as a white solid (1.225 g, 73%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.46 (s, 2 H), 3.77 (s, 3 H), 3.89 (s, 3 H), 7.65−7.52 (m, 1 H), 7.88−7.72 (m, 2 H), 8.15−7.91 (m, 2 H), 8.20 (s, 1 H).

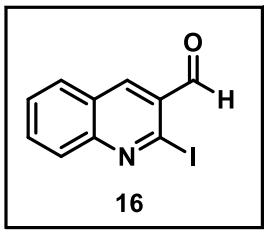
^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.6, 52.3, 52.6, 126.6, 127.6, 127.7, 127.9, 128.4, 129.0, 131.3, 137.5, 138.3, 147.4, 149.6, 166.8, 171.3.

HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{15}O_4NCl$ 320.0684, found 320.0684.

IR ($CHCl_3$) ν_{max} 1725, 1690 cm^{-1}.

Mp 164−166 °C.

2-Iodoquinoline-3-carbaldehyde (16).



16

2-Chloroquinoline-3-carbaldehyde (**13**; 1 g, 5.21 mmol), NaI (5.5 g, 36.47 mmol) and conc. HCl (0.2 mL) were mixed in CH_3CN. The reaction mixture was heated at 90 °C for 15 h. Then it was diluted with water and filtered using a Buchner funnel. The solid was washed first with sat. $NaHCO_3$ solution and then with water till the washings were neutral. The compound was then dried under vacuum to obtain the 2-iodoquinoline-3-carbaldehyde **16** (1.23 g, 83%), which was used without further purification in the next step.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71−7.62 (m, 1 H), 7.90 (ddd, J = 1.4, 7.0, 8.4 Hz, 1 H), 8.00 (d, J = 8.1 Hz, 1 H), 8.09 (d, J = 8.5 Hz, 1 H), 8.78 (s, 1 H), 10.58 (s, 1 H).

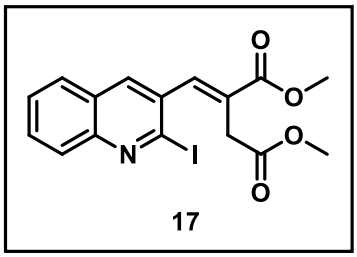
^{13}C NMR ($CDCl_3$, 100 MHz) δ 126.7, 126.9, 128.5, 129.0, 130.0, 133.9, 140.6, 149.9, 150.4, 189.5.

HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_7ONI$ 283.9567, found 283.9568.

IR ($CHCl_3$) ν_{max} 1705 cm^{-1}.

Mp 146−148 °C.

Dimethyl (*E*)-2-[(2-iodoquinolin-3-yl)methylene]succinate (17).



17

To a stirred solution of dimethyl maleate (**14**; 0.26 mL, 1.77 mmol) and 2-iodoquinoline-3-carbaldehyde (**16**; 500 mg, 1.77 mmol) in THF was dropwise added *n*-Bu_3P (0.58 mL, 2.30 mmol) at 25 °C under argon atmosphere. The reaction mixture was stirred for 20 h and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate 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 (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether mixture (1:9) as an eluent furnished product **17** as a white solid (513 mg, 71%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.41 (s, 2 H), 3.76 (s, 3 H), 3.91 (s, 3 H), 7.61 (s, 1 H), 7.82−7.70 (m, 2 H), 7.88 (s, 1 H), 8.01 (s, 1 H), 8.11−8.03 (m, 1 H).

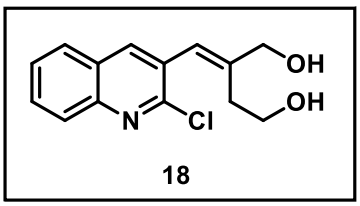
^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.6, 52.3, 52.6, 126.7, 127.8, 128.1, 128.3, 128.6, 131.0, 133.2, 135.7, 136.6, 142.5, 148.8, 166.9, 171.2.

HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{15}O_4NI$ 412.0040, found 412.0042.

IR ($CHCl_3$) ν_{max} 1720, 1685 cm^{-1}.

Mp 160−162 °C.

(*E*)-2-[(2-Chloroquinolin-3-yl)methylene]butane-1,4-diol (18).



18

To a solution of diester **12** (300 mg, 0.94 mmol) in dry THF was added LAH (178 mg, 4.70 mmol) at 0 °C under the nitrogen atmosphere. The reaction mixture was stirred for 2 h and allowed to reach room temperature. The reaction was quenched with the slow addition of a saturated aqueous solution of Na_2SO_4 at 0 °C temperature. Reaction mixture was diluted with EtOAc, filtered through a Celite pad 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 obtained residue using DCM–MeOH mixture (7:3) as an eluent furnished the diol product **18** as a yellow liquid (130 mg, 52%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.56 (t, J = 5.8 Hz, 2 H), 2.72 (br s, 2 H), 3.83 (t, J = 5.8 Hz, 2 H), 4.39 (s, 2 H), 6.76 (s, 1 H), 7.62−7.47 (m, 1 H), 7.84−7.66 (m, 2 H), 8.01 (d, J = 8.5 Hz, 1 H), 8.14 (s, 1 H).

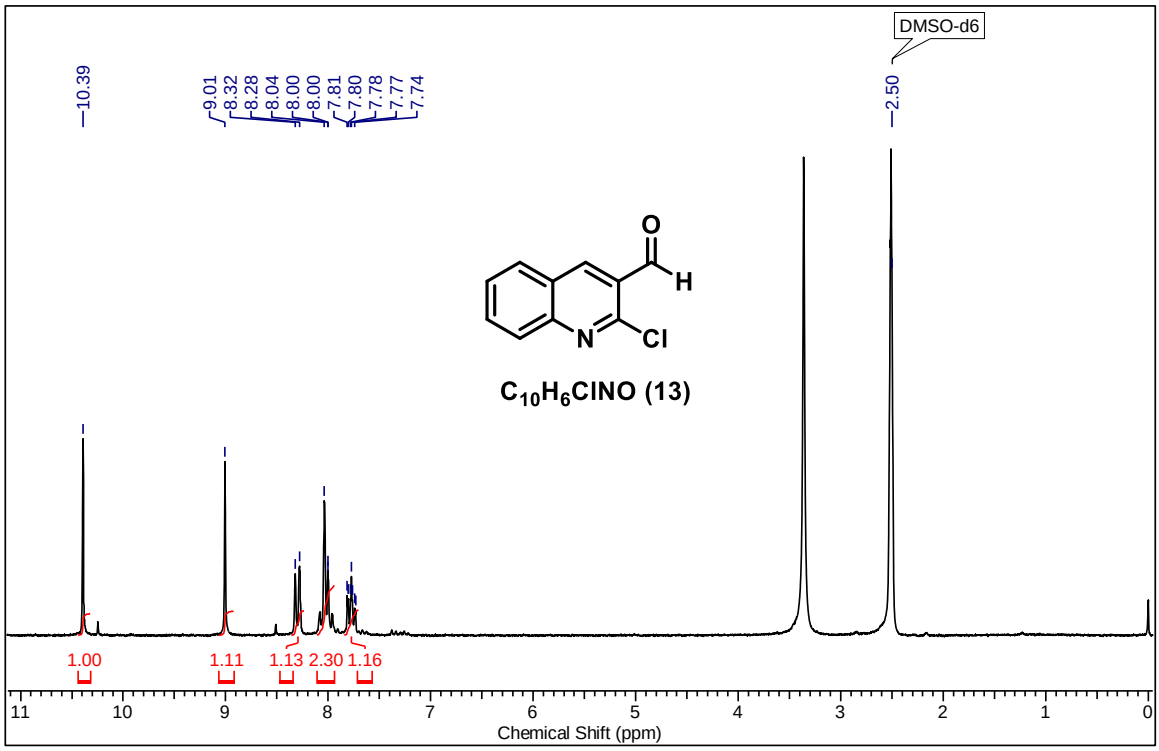
^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.5, 61.2, 67.2, 124.8, 127.0, 127.2, 127.6, 128.1, 129.5, 130.3, 138.3, 142.4, 146.5, 150.6.

HRMS (ESI) $[M + H]^+$ calcd for $C_{14}H_{15}O_2NCl$ 264.0786, found 264.0788.

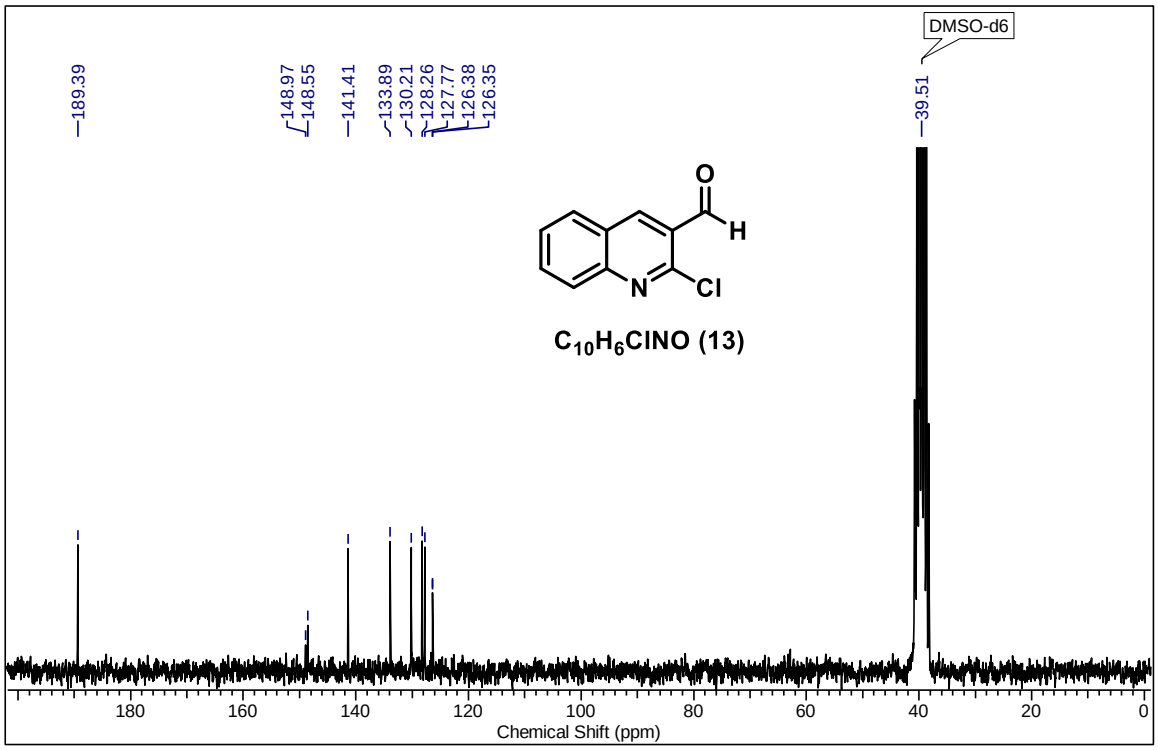
IR ($CHCl_3$) ν_{max} 3410, 3350 cm^{-1}.

2B.6 NMR Spectra of the Obtained Products

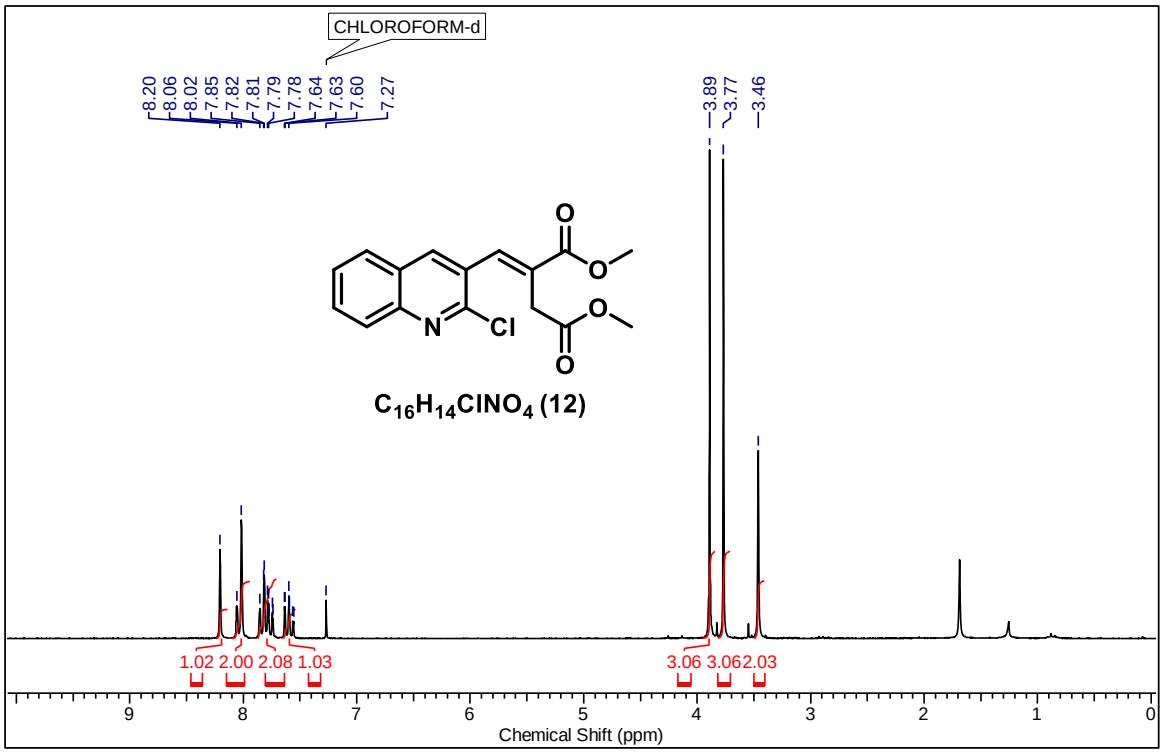
^{1}H NMR (DMSO-d_6, 200 MHz) of Compound 13



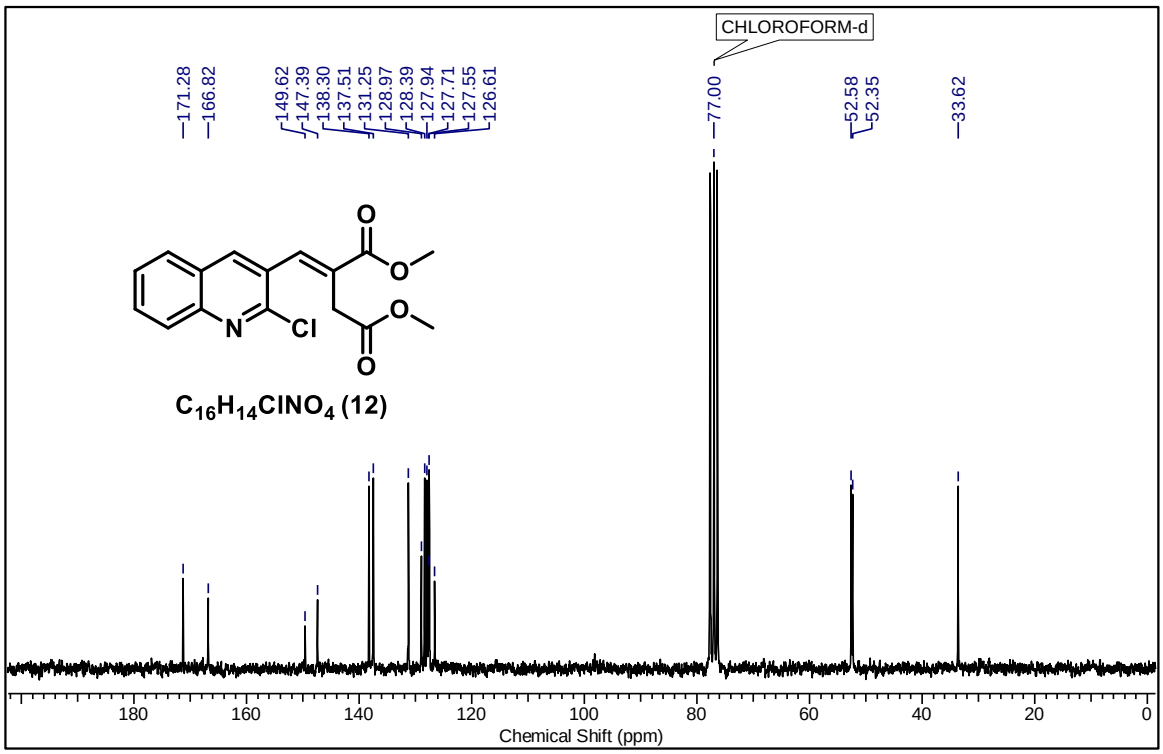
^{13}C NMR (DMSO-d_6, 50 MHz) of Compound 13



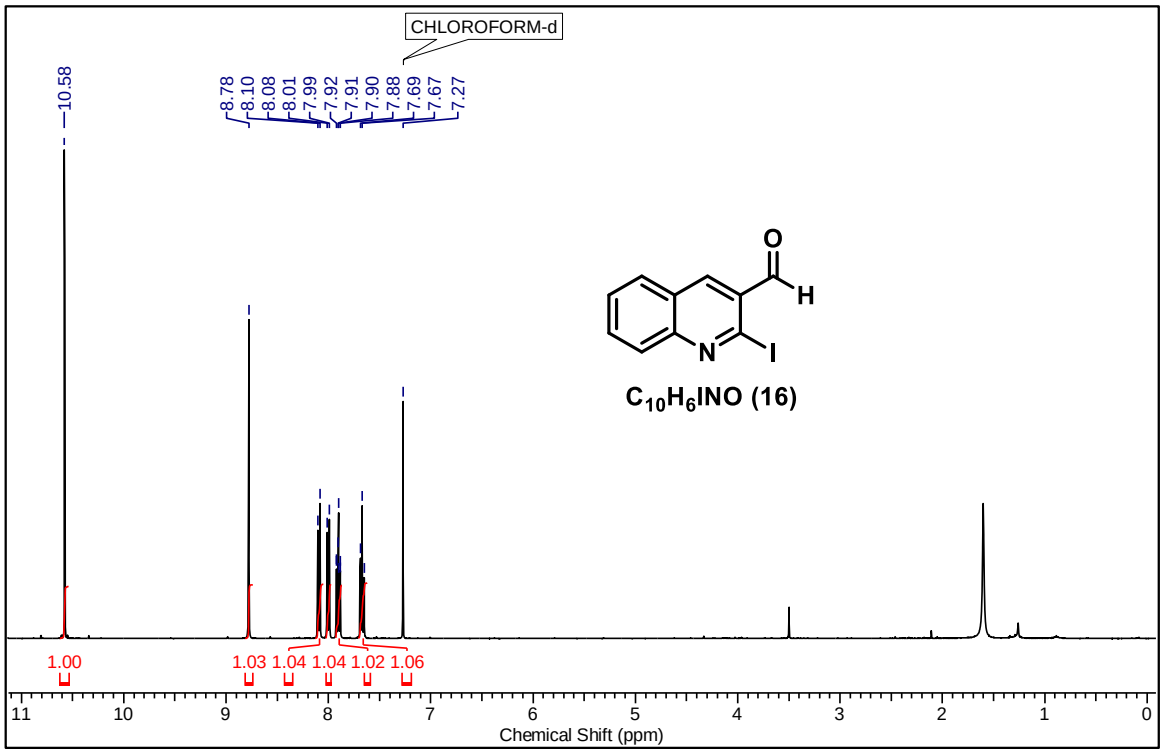
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 12



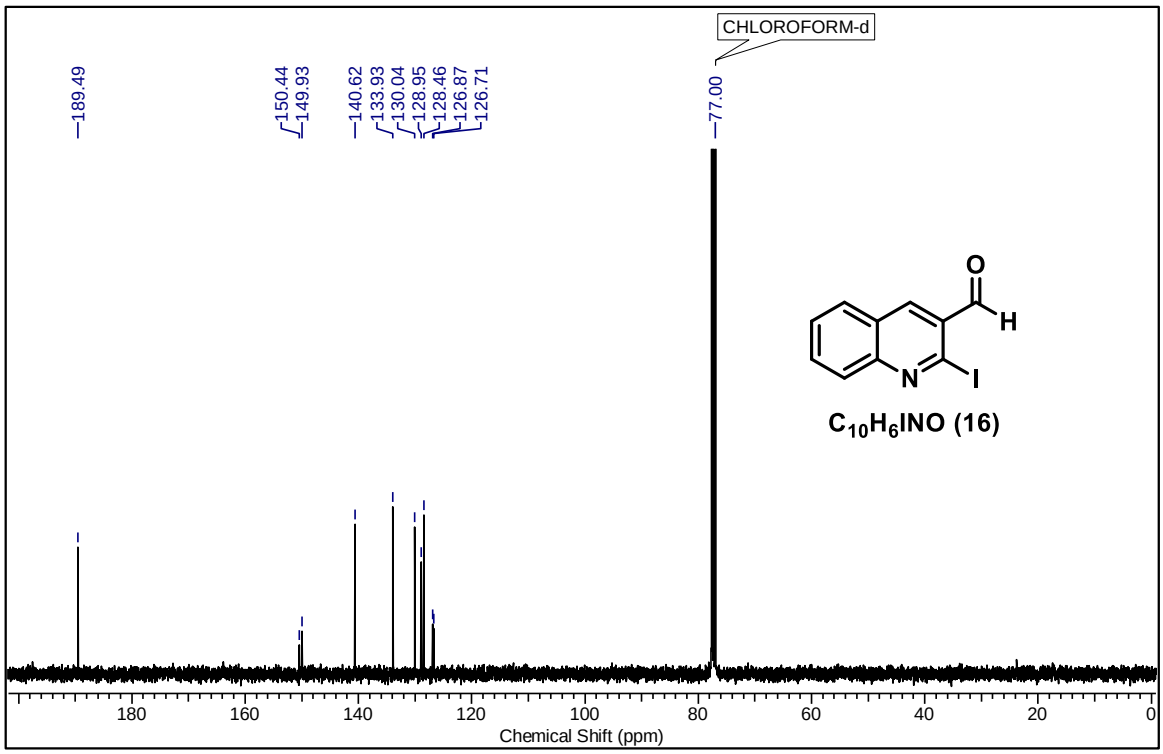
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 12



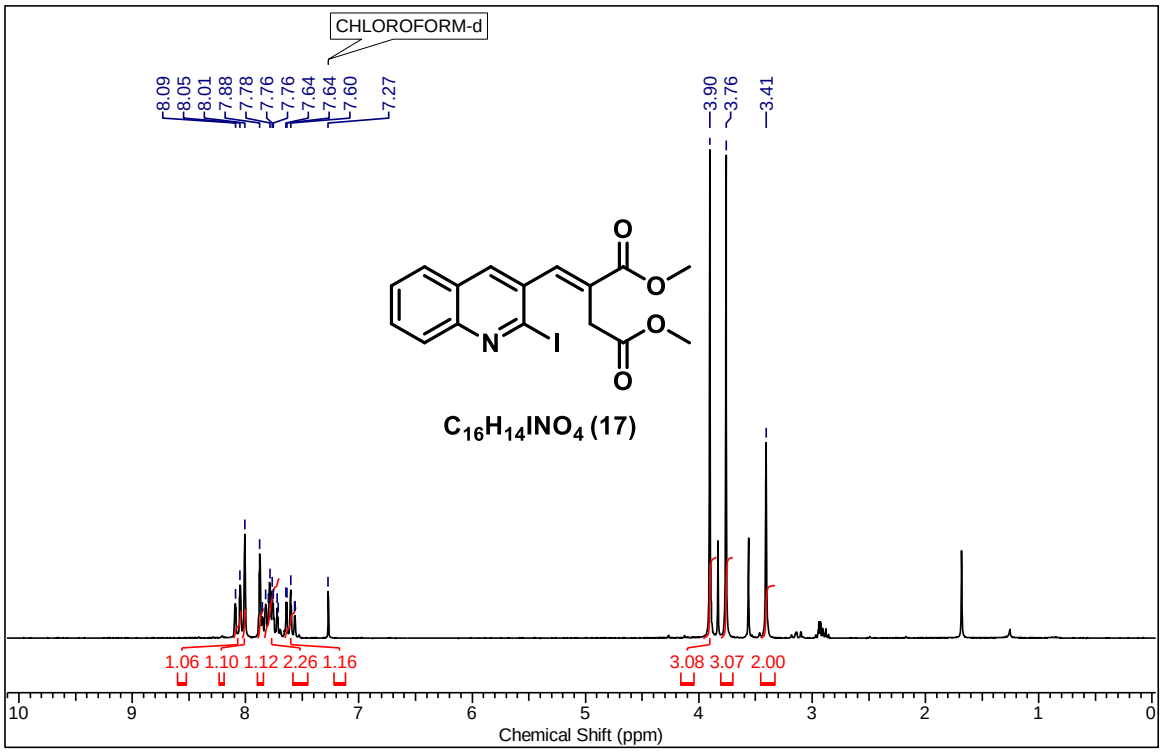
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 16



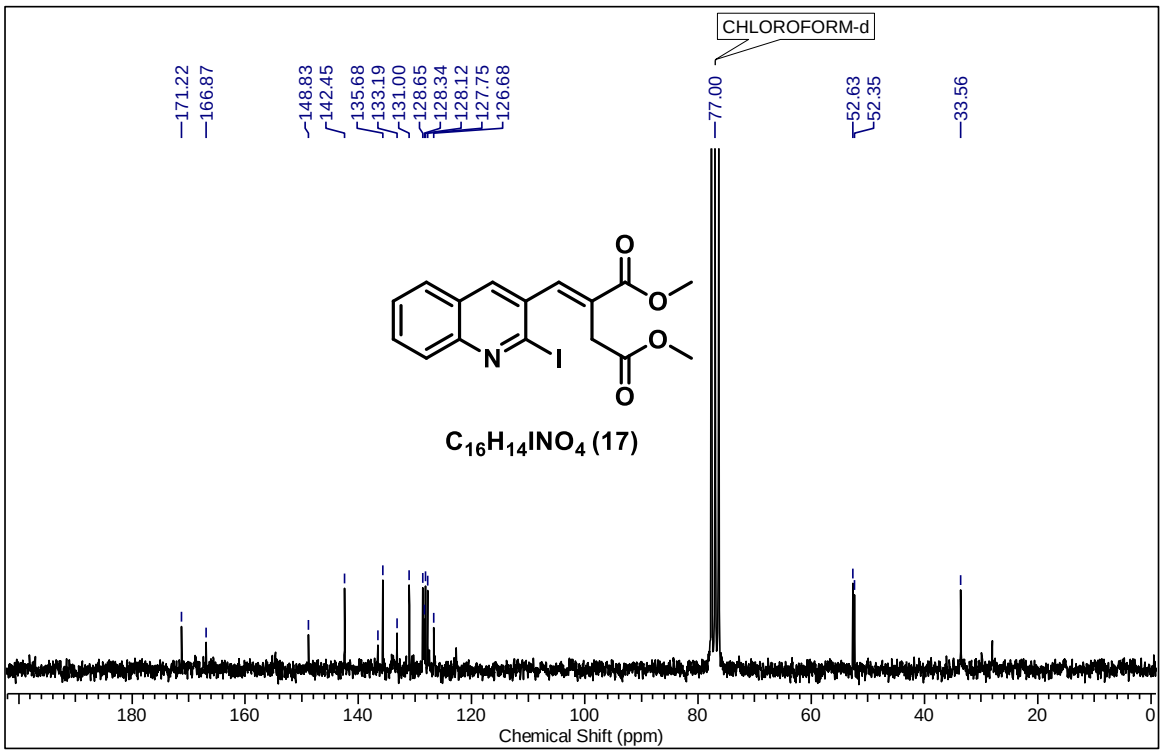
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 16



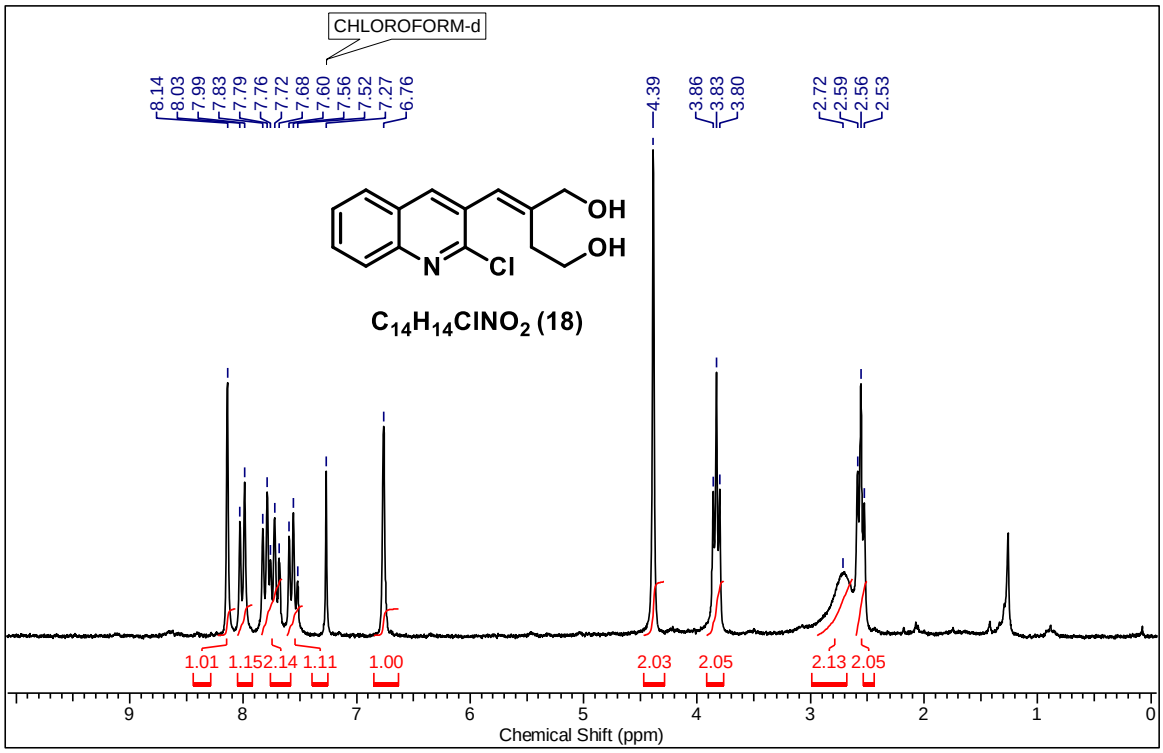
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 17



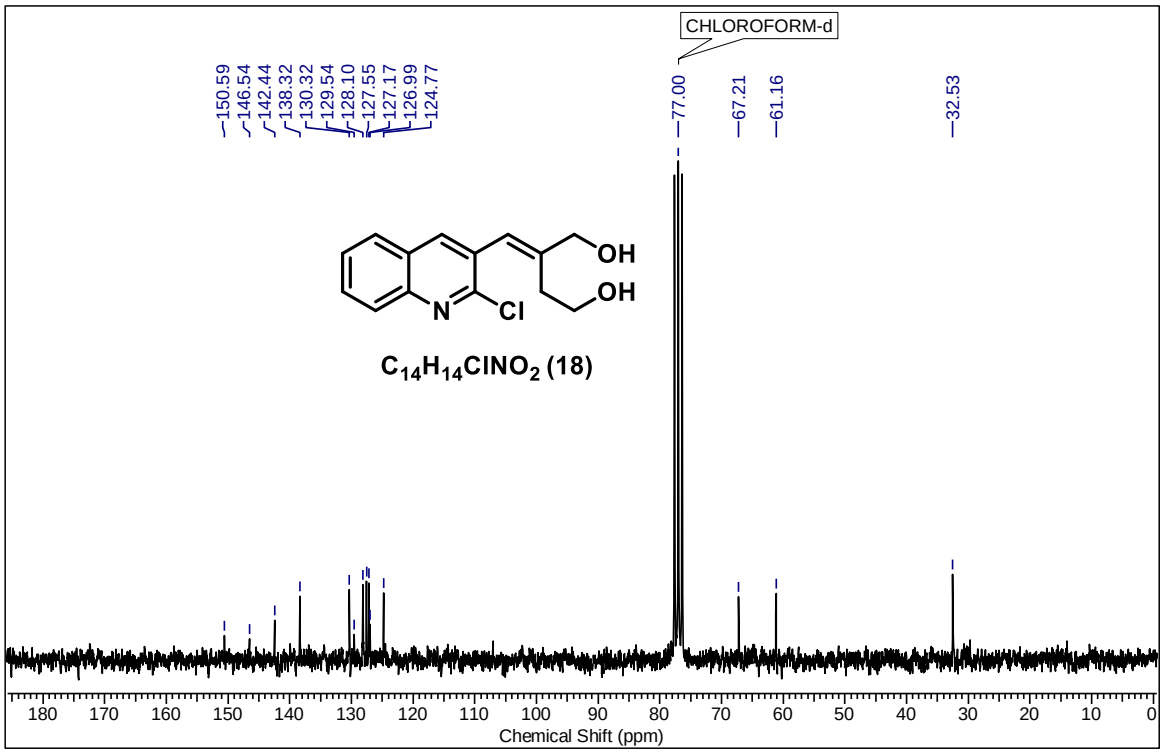
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 17



^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 18



^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 18



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Chapter 3

Regioselective Reduction Reactions of Cyclic Imides Leading to Synthesis of Bioactive Alkaloids

Section 3A

Chemoselective Ring Closure Leading to Synthesis of Pandalizine A and Formation of Unplanned Aldol Product from Analogous Model System

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

This chapter is divided into three sections. The first section presents five steps practical total synthesis of pandalizine A via chemoselective intramolecular dehydrative cyclization. We also noticed the chemoselectivity difference upon application of the same strategy on the analogous model system of pandalizine A. The second section describes synthetic study towards the indole alkaloid gorgonianic acid in which we are one step behind for completion of the total synthesis. In the third section, we have described a new strategy for the total synthesis of *Erythrinan* alkaloid erysotramidine in which we have completed the five steps in a progression of the synthesis. At the end of each section, the detailed experimental procedures, tabulated analytical and spectral data and NMR spectra have been included.

3A.1 Background

Alkaloids are important compounds that possess a broad range of effective biological activities and some of the novel azabicyclic alkaloids have an *α*,*β*-unsaturated lactam moiety in their structure (Figure 1).[1-5]

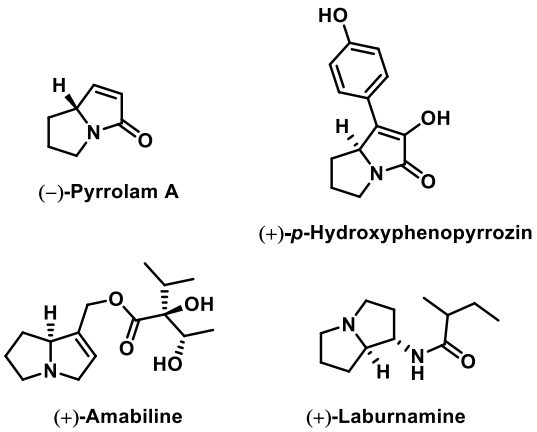


Figure 1. Representative bioactive azabicyclic natural products

Pandanus amaryllifolius trees or shrub-like plants are extensively found all across the tropics and extracts from this genus have been shown to exhibit a wide range of biological activities including antioxidant, antitubercular and cytotoxic activities. It has also been utilized as a flavoring agent from ancient times. *Pandanus amaryllifolius* is used in folk medicine to treat gout, hyperglycemia, hypertension and rheumatism.[6,7] A pharmacological investigation has also shown that *P. amaryllifolius* has antibacterial, antiviral, and tumor growth-inhibiting properties. Recently, the azabicyclic alkaloids pandalizines A (5.2 mg), B (4.5 mg), C (1.2 mg), D (1.3 mg) and E (1.2 mg) have been

isolated from 6.0 Kg of aerial parts of *Pandanus amaryllifolius* species and their structural and stereochemical assignments have been done on the basis of NMR, 2D NMR and circular dichroism studies (Figure 2).[6,7]

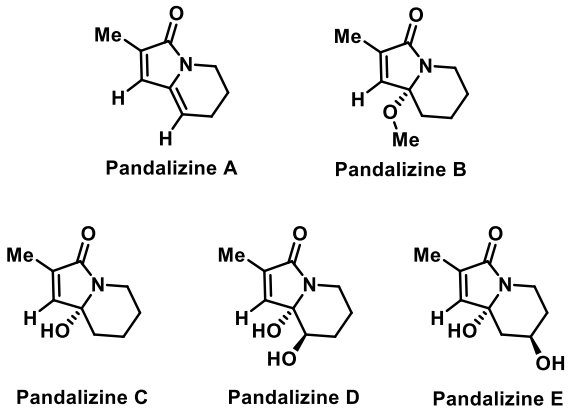
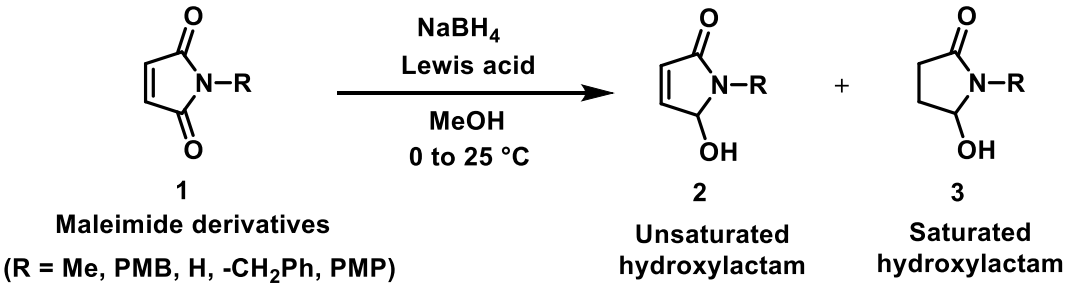


Figure 2. Azabicyclic pandalizines A-E alkaloids from *P. amaryllifolius*

It was also proposed that glutamic acid and leucine are biogenetic precursors of pandalizine alkaloids. Large numbers of well-established synthetic protocols to design azabicyclic frameworks are known in the contemporary literature.[8] In this context, very recently elegant total syntheses of pandalizine A, (±)-pandalizines B and (±)-pandalizines C have been accomplished via photooxidation of specifically synthesized furylalkylamine by Vassilikogiannakis and co-workers from Greece.[9,10] David Gueyrard and co-workers also reported the synthesis of indolizidine alkaloids pandalizins A via intramolecular modified Julia olefination reaction.[11] However, the synthesis of pandalizines D and E bearing an additional hydroxyl group at two different positions in ring-B are still awaited. To date, we have accomplished the total synthesis of a large number of bioactive natural products using cyclic anhydrides and their derivatives as potential precursors.[12-16] In continuation of our studies on the total synthesis of recently isolated structurally interesting and biologically important natural products, we planned to complete the total synthesis of pandalizine A via regioselective reduction of citraconimide followed by a substrate-specific chemoselective ring closure as the crucial reactions.[17]

Regioselective reduction of maleimide derivatives **1** to the corresponding appropriate hydroxylactams **2**/**3** is an important reaction for the synthesis of natural products (Scheme 1). The hydroxylactams **2**/**3** could be used as fundamental building blocks to achieve the synthesis of various heterocyclic compounds with important pharmacological properties.[18-21] Reduction of maleimide derivatives **1** using $NaBH_4$ is known to produce the unsaturated hydroxylactam **2** and saturated hydroxylactam **3** as the mixture of

products with a ratio of 41:59 (Table 1).[22] The pioneering work of Jean-Louis Luche and co-workers reported that the regioselectivity could be significantly increased by adding cerium chloride ($CeCl_3$) to the reaction mixture in MeOH.[23] Hence the regioselective 1,2-reduction of maleimide derivatives **1** using $NaBH_4$ and commercially available cerium chloride heptahydrate ($CeCl_3.7H_2O$) in MeOH exclusively provides the unsaturated hydroxylactam **2** in 91% yield. Similarly, Samarium chloride ($SmCl_3$) was also a competent Lewis acid and provides the unsaturated hydroxylactam **2** in 62% yield (Table1).[22]



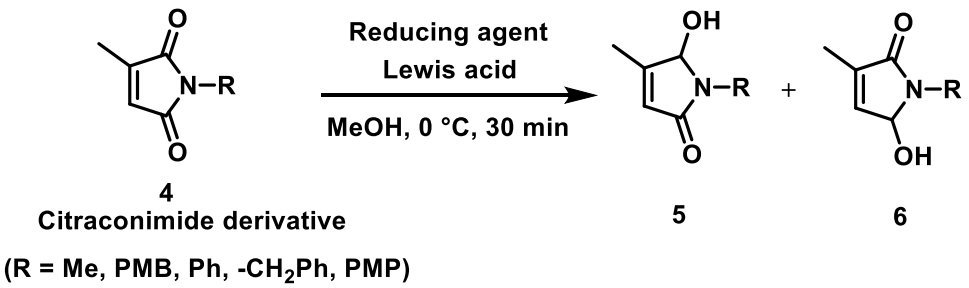
Scheme 1. Regioselective Reduction of Maleimide Derivatives

Entry	R	Lewis acid	Time	Product 2	Product 3
1	$-CH_2Ph$	-	1 h	41%	59%
2	$-CH_2Ph$	$CeCl_3.7H_2O$	1 h	91%	0%
3	$-CH_2Ph$	$SmCl_3$	2 h	62%	0%
4	Me	$CeCl_3.7H_2O$	1.5 h	90%	0%
5	H	$CeCl_3.7H_2O$	1 h	62%	0%

Table 1. Regioselective reduction studies of maleimide derivatives.

It was also reported that the regioselective reduction of citraconimide derivatives **4** could be plausible using the above mentioned method (Scheme 2).[22] $NaBH_4$ reduction of the citraconimide derivatives **4** gave a mixture of unsaturated hydroxylactam **5** and **6** in a ratio of 88:12 (Table 2). Boron atom binds to the unhindered carbonyl oxygen atom and hence the hydride anion approaches from less hindered side of the carbonyl group of citraconimide derivatives **4**, and attacks the more hindered side carbonyl carbon to give the hydroxylactam **5** in 88% yield as a major product.[22] A reversal in regioselectivity was observed by adding Lewis acid to the reaction mixture, such as citraconimide derivatives **4**; when treated with $NaBH_4$ and cerium chloride heptahydrate ($CeCl_3.7H_2O$) in MeOH

provides reverse regioselectivity with the unsaturated hydroxylactam **5** and **6** in a ratio of 29:71 (Table 2). Surprisingly, when DIBAL-H was used as a reducing agent, the reduction of citraconimide derivatives **4** showed greater regioselectivity with a ratio of 9:91. The coordination of cerium or aluminium atoms with the carbonyl group of citraconimide derivatives **4** induces a reversal in regioselectivity.[22] Cerium ion selectively forms the complexation with the less hindered side carbonyl group of the citraconimide derivatives **4** making the carbonyl group more reactive. As a result, the hydride anion reduces the less hindered side carbonyl group to provide hydroxylactam **6** as a major product. Similarly, the bulky reagent DIBAL-H binds to the less hindered side carbonyl group and regioselectively reduces that carbonyl group by intramolecular hydride transfer yielding hydroxylactam **6** as a major product.[24,25]

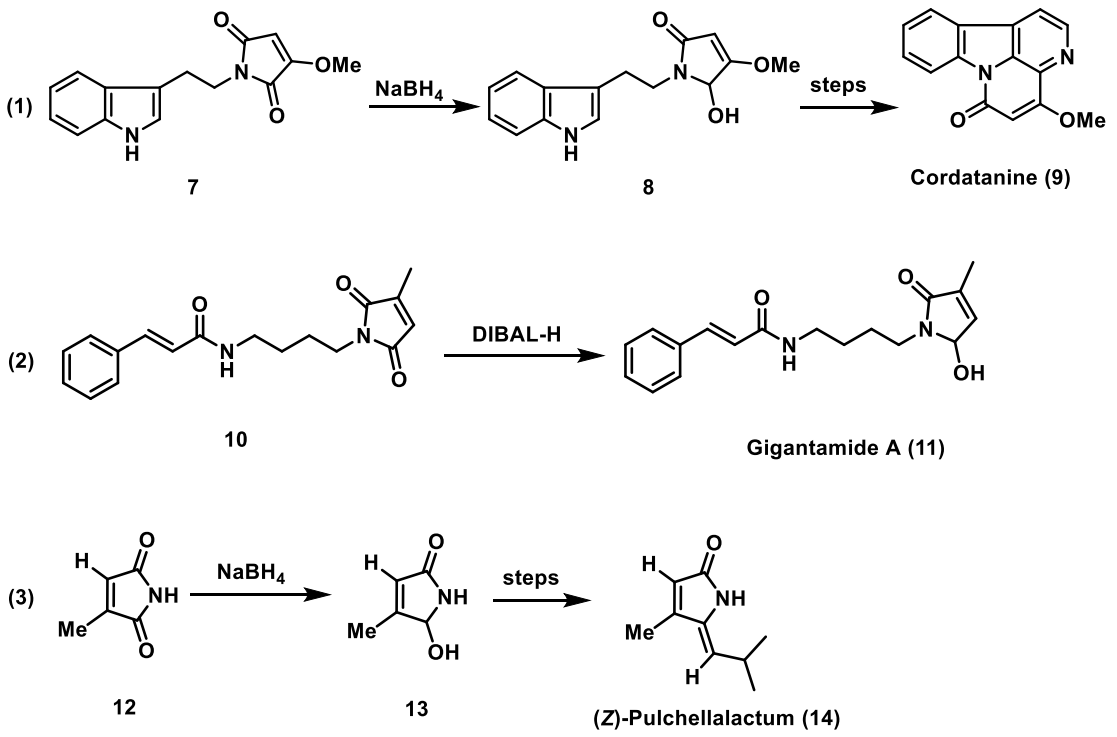


Scheme 2. Regioselective Reduction of Citraconimide Derivatives

Entry	R	Reducing agent	Lewis acid	5 + 6	Ratio 5:6
1	$-CH_2Ph$	$NaBH_4$	-	97%	88:12
2	$-CH_2Ph$	$NaBH_4$	$CeCl_3.7H_2O$	90%	29:71
3	$-CH_2Ph$	$NaBH_4$	$SmCl_3$	78%	35:65
4	$-CH_2Ph$	DIBAL-H	-	95%	9:91
5	Ph	$NaBH_4$	$CeCl_3.7H_2O$	87%	25:75

Table 2. Regioselective reduction studies of citraconimide derivatives.

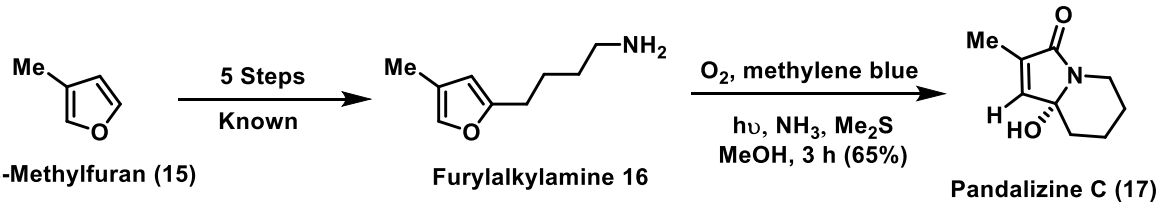
Argade and co-workers also applied regioselective reduction strategy to synthesize various natural products (Scheme 3).[26-28]

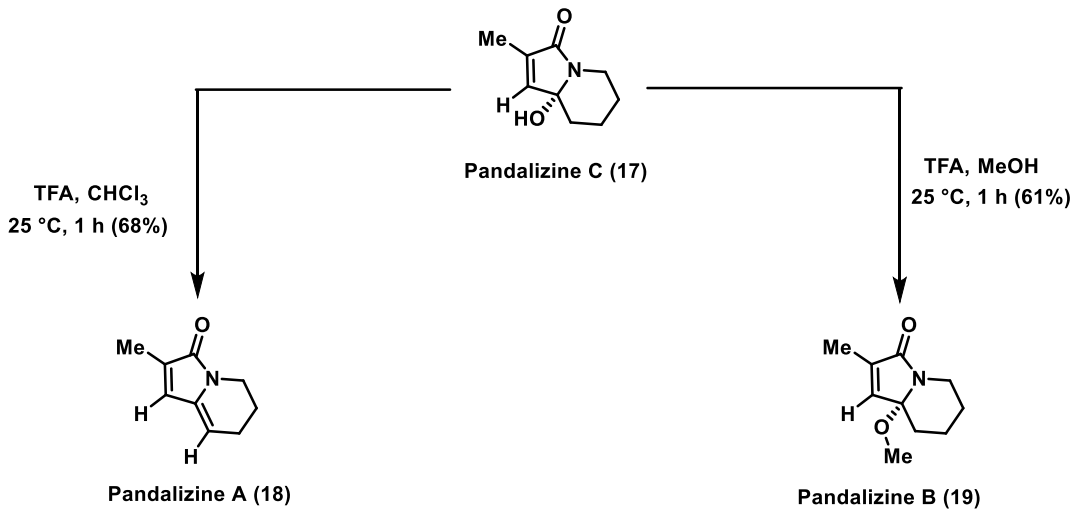


Scheme 3. Selected Examples of Regioselective Reductions Reported from our Research Group

3A.2 Reported Synthesis of Pandalizins A-C

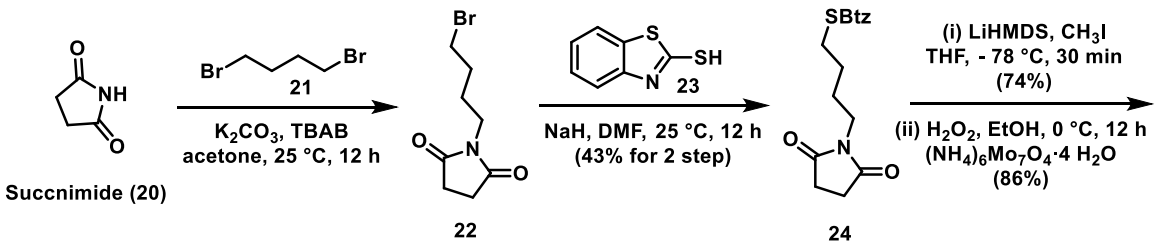
Georgios Vassilikogiannakis and co-workers reported the synthesis of indolizidine alkaloids pandalizins A-C from specifically synthesized furylalkylamine precursor via photooxidation reaction pathway (Scheme 4).[9,10] The furylalkylamine **16** was synthesized from the 3-methylfuran **(15)** using known protocol.[29] Furylalkylamine **16** was dissolved in methanol in which methylene blue (MB) was added as a photosensitizer at 0 °C temperature. Oxygen was gently bubbled through the reaction mixture while they were irradiated with light (300 W lamp). The photooxidation reaction of furylalkylamine **16** enables a cascade reaction sequence that generated the pandalizine C (**17**) in 65% yield. Treatment of pandalizine C (**17**) with TFA in chloroform provided the pandalizine A (**18**) with a 68% yield. Similarly, pandalizine C (**17**) on treatment with TFA in MeOH provided the pandalizine B (**19**) in a 61% yield.

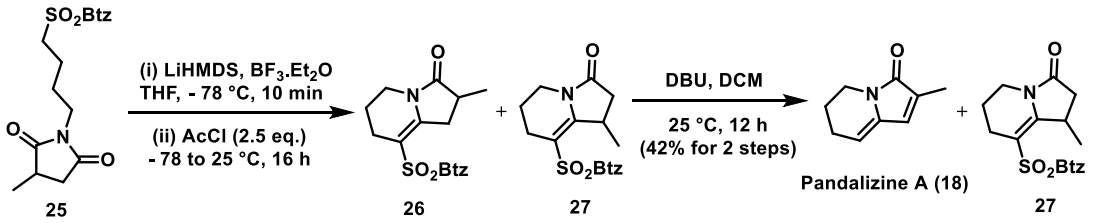




Scheme 4. Synthesis of Pandalizins A-C via Photooxidation Reaction

David Gueyrard and co-workers reported the synthesis of indolizidine alkaloid pandalizin A via intramolecular modified Julia olefination reaction (Scheme 5).[11] The synthesis was commenced with the *N*-alkylation reaction of succinimide (**20**) with 1,4- dibromobutane (**21**) under basic conditions, then treatment of the obtained compound **22** with 2-mercaptobenzothiazole (**23**) in DMF furnished the compound **24** in 43% yield over two steps.[30] Base-mediated monomethylation of compound **24** using MeI in THF at −78 °C in 74% yield followed by hydrogen peroxide and ammonium molybdate promoted oxidation of sulfur to sulphone provided the potential precursor benzothiazole sulfone **25** in 86% of yield. Benzothiazole sulfone **25** on treatment with LiHMDS/BF_3.OEt_2 in THF at −78 °C and then quenching with acetyl chloride furnished the vinyl sulphone **26** as major regioisomer and undesired minor regioisomer **27**. The obtained vinyl sulphones **26**/**27** were inseparable, therefore the inseparable mixture was directly treated with the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DCM at 25 °C to provide the natural product pandalizine A (**18**) in 42% yield over two steps, along with the unreacted vinyl sulphone **27**.

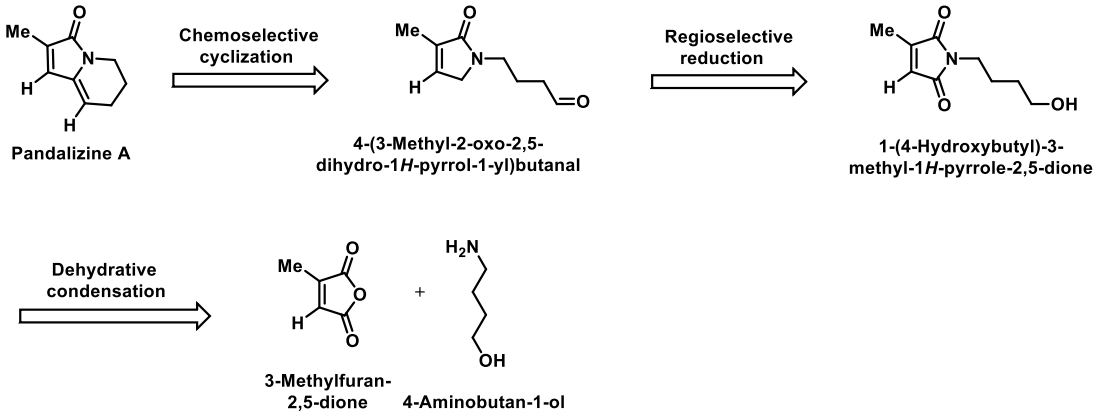




Scheme 5. Total Synthesis of Pandalizin A via Intramolecular Modified Julia Olefination Reaction

3A.3 Result and Discussion (Present Research Work)

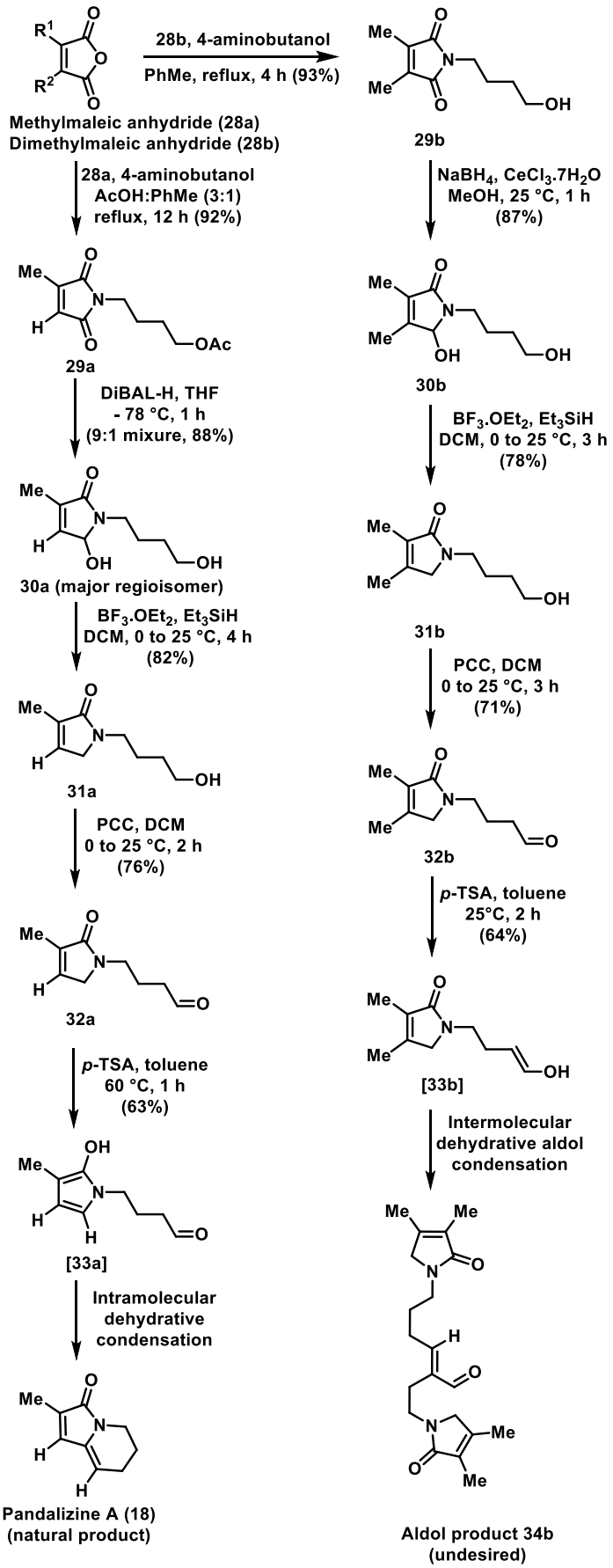
A systematic plan was prepared to synthesize pandalizine A from methylmaleic anhydride and the accordingly proposed concise retrosynthetic analysis is depicted in scheme 6. The regioselective reduction of citraconimide and chemoselective intramolecular cyclization of a well-structured substrate over possible intermolecular aldol condensation were the foreseen challenges in our synthetic strategy.[17]



Scheme 6. Concise Retrosynthetic Analysis of Pandalizine A

The reaction of methylmaleic anhydride (**28a**) with 4-aminobutanol in a refluxing mixture of acetic acid plus toluene directly furnished the corresponding imide **29a** in 92% yield via the dehydrative cyclization of the formed intermediate regioisomeric maleamic acids and the thermal acylation of free primary alcohol (Scheme 7). The reaction of imide **29a** with a bulky reducing agent such as DIBAL-H at −78 °C directly provided a column chromatographically inseparable regioisomeric mixture of desired deacylated major lactamol **30a** and the corresponding undesired minor isomer in a ~9:1 ratio (by ^{1}H NMR) with 88% yield. The structural assignment of lactamol **30a** was initially done on the basis of more deshielded ^{1}H NMR signal for β-vinylic proton at δ = 6.55, which was finally confirmed on completion of the total synthesis of pandalizine A. Further reduction of the above-mentioned mixture of lactamols using $BF_3.OEt_2$−Et_3SiH via a plausible formation of the corresponding iminium ion intermediates and purification of the crude product by

silica gel column chromatography yielded pure lactam **31a** in 82% yield. The PCC oxidation of the primary alcohol unit in lactam **31a** delivered the essential lactam aldehyde **32a** in 76% yield for further systematic intramolecular condensation studies. In our hands, the reactions of compound **32a** with bases such as DBU, NaH, LiHMDS, and NaHMDS resulted in a complex reaction mixture.[31] The lactam aldehyde **32a** on treatment with *p*-TSA in toluene at room temperature remained completely unreacted. However, the same reaction at 60 °C chemoselectively resulted in our target compound pandalizine A (**18**) in 63% yield via the formation of the corresponding enol intermediate **33a** and the intramolecular dehydrative condensation. In the present reaction, the formation of the significant enol intermediate **33a** initiated prior to the possible enolization of aldehyde moiety and feasible intermolecular aldol condensation. All our attempts to further improve the efficiency of the above-specified reaction by changing the reaction time and temperature were unsuccessful. The obtained NMR data for an analytically pure sample of pandalizine A (**18**) was completely matching with reported data.[6,9,10] The total synthesis of pandalizine A (**18**) was completed in five steps with 29% overall yield. The obtained natural product was highly prone to oxidative degradation under normal atmospheric conditions and got transformed into a complex mixture in 48 h. To demonstrate yet another example of such type of chemoselective cyclization, maleimide **29b** was synthesized in 93% yield by dehydrative condensation of dimethylmaleic anhydride (**28b**) with 4-aminobutanol in refluxing toluene (Scheme 7).[32] Symmetrical imide **29b** on $NaBH_4$ reduction formed lactamol **30b**, and its treatment with $BF_3.OEt_2$−Et_3SiH provided lactam **31b** in 68% overall yield over two steps. The PCC oxidation of alcohol **31b** yielded the desired substrate **32b** in 71% yield. Surprisingly, the reaction of lactam aldehyde **32b** with *p*-TSA in toluene at room temperature followed another pathway and underwent the chemoselective intermolecular dehydrative aldol condensation furnishing the undesired product **34b** in 64% yield via the preferential formation of an alternate enol intermediate **33b**. The repetition of the above specified reaction at 60 °C also exclusively resulted in the same product **34b**, but with 55% yield. Overall, the lactam aldehydes **32a** and **32b** follow two different reaction pathways under a similar set of reaction conditions due to the difference in the acidity of methylene proton in lactam moieties and relatively less steric hindrance noted by a conjugate base in the formation of the intermediate **33a**.



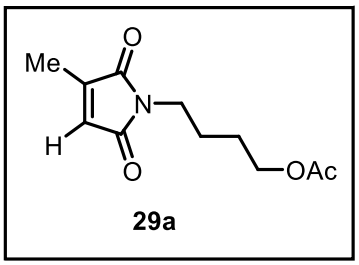
Scheme 7. Structure-Based Chemoselective Intramolecular Condensation versus Intermolecular Aldol Reaction: Simple and Efficient Synthesis of Pandalizines A

3A.4 Summary

In summary, from readily available starting materials, we have completed protection-free practical total synthesis of pandalizine A via a remarkable regioselective reduction and chemoselective intramolecular cyclization pathway. Present studies represent a unique example wherein actual natural product precursor indeed followed the expected chemoselective intramolecular cyclization route and furnished the target compound, while the analogous substrate with an additional β-methyl group delivered the undesired aldol product. We feel that the favored formation of an appropriately reactive cyclic enol intermediate for intramolecular cyclization is the genesis of delicately balanced chemoselectivity. Overall, the absence/presence of the β-methyl group governs the course of competitive carbon−carbon bond-forming reactions and functions as a chemoselectivity switch.

3A.5 Experimental Section

4-(3-Methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butyl Acetate (29a).



29a

To a solution of 4-aminobutanol (0.99 g, 11.13 mmol) in AcOH/PhMe (20 mL, 3:1) was added citraconic anhydride (**28a**; 1.25 g, 11.13 mmol), and the stirring reaction mixture was refluxed for 12 h. The reaction mixture was concentrated in vacuo, after attaining room temperature. The obtained residue was dissolved in EtOAc. The organic layer was washed with 10% aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained product was purified by using column chromatography (silica gel, 60−120 mesh, EtOAc−PE, 3:7) to furnish pure citraconimide **29a** as a colorless liquid (2.31 g, 92% yield).

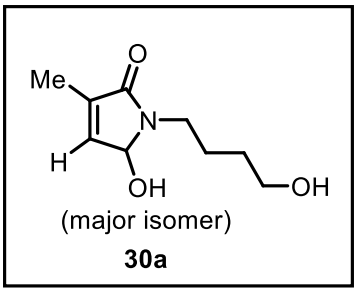
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.62 (quintet, J = 3.0 Hz, 4H), 2.02 (s, 3H), 2.06 (d, J = 1.8 Hz, 3H), 3.50 (t, J = 6.8 Hz, 2H), 4.05 (t, J = 6.1 Hz, 2H), 6.30 (q, J = 1.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.9, 20.9, 25.2, 25.9, 37.4, 63.7, 127.2, 145.5, 170.8, 171.0, 171.8.

HRMS (ESI) [M +Na]+ calcd for $C_{11}H_{15}NO_4Na$ 248.0893, found 248.0894.

IR ($CHCl_3$) ν_{max} 1721, 1709, 1644 cm^{-1}.

5-Hydroxy-1-(4-hydroxybutyl)-3-methyl-1,5-dihydro-2H-pyrrol-2-one [30a (Major Isomer)].



30a

To a solution of imide **29a** (1.0 g, 4.44 mmol) in dry THF (15 mL) was slowly added a solution of DIBAL-H in cyclohexane (1 M, 13.32 mL, 13.32 mmol) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at the same temperature. The reaction was quenched with a saturated aqueous solution of potassium sodium tartrate tetrahydrate and the reaction mixture was concentrated in vacuo. The formed product was dissolved in EtOAc, and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo. The column chromatographic purification of the obtained crude product (silica gel,

60−120 mesh, EtOAc−PE, 8:2) gave pure compound **30a** as a yellowish liquid (726 mg, 9:1 mixture, 88% yield).

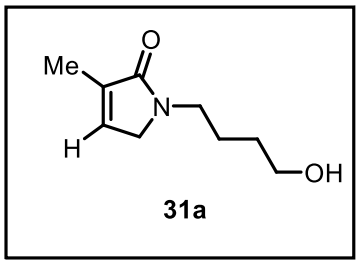
^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.45−1.80 (m, 4H), 1.87 (s, 2.70H), 2.05 (s,0.30H), 2.50−3.10 (br s, 1H), 3.27−3.55 (m, 2H), 3.55−3.75 (m, 2H), 4.00−4.60 (br s, 1H), 5.14 (s, 0.1H), 5.29 (s, 0.9H), 5.75 (br s, 0.1H), 6.55 (t, J = 1.5 Hz, 0.9H).

^{13}C NMR (CDCl$_3$, 50 MHz) δ 10.9, 25.2, 29.5, 39.6, 62.1, 82.0, 136.7, 138.5, 170.7.

HRMS (ESI) [M + Na]+ calcd for $C_9H_{15}NO_3Na$ 208.0944, found: 208.0945.

IR (CHCl$_3$) ν_{max} 3340, 1683 cm^{-1}.

1-(4-Hydroxybutyl)-3-methyl-1,5-dihydro-2H-pyrrol-2-one (31a).



31a

To a solution of compound **30a** plus minor isomer (600 mg, 3.24 mmol) in dry DCM (15 mL) were added $BF_3{\cdot}OEt_2$ (1.39 mL, 4.86 mmol) and Et_3SiH (0.57 mL, 4.86 mmol) dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 4 h and allowed to reach room temperature. The reaction mixture was concentrated in vacuo and the formed product was dissolved in EtOAc. The organic layer was washed with 10% aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo and column chromatographic purification of the obtained product (silica gel, 230−400 mesh, MeOH/DCM, 2:8) furnished pure lactam **31a** as a colorless liquid (458 mg, 82% yield).

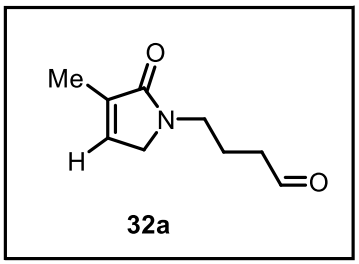
^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.45−1.80 (m, 4H), 1.89 (d, J = 1.8 Hz, 3H), 2.90−3.30 (br s, 1H), 3.51 (t, J = 6.7 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H), 3.84 (t, J = 1.9 Hz, 2H), 6.66 (q, J = 1.7 Hz, 1H).

^{13}C NMR (CDCl$_3$, 50 MHz) δ 11.3, 25.2, 29.4, 42.1, 50.6, 62.1, 135.0, 135.8, 172.2.

HRMS (ESI) [M + Na]+ calcd for $C_9H_{15}NO_2Na$ 192.0995, found 192.0997.

IR (CHCl$_3$) ν_{max} 3423, 1659 cm^{-1}.

4-(3-Methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanal (32a).



32a

To a solution of alcohol **31a** (400 mg, 2.36 mmol) in dry DCM (10 mL) was added PCC on Celite (0.66 g, 3.07 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 2 h allowing reaching room temperature. The reaction mixture was diluted with DCM and filtered through Celite using sintered funnel. The residue was washed with DCM and the filtrate was concentrated in vacuo. Purification of the obtained product by using column chromatography (silica gel, 230–400 mesh, MeOH:DCM, 1:9) furnished pure aldehyde **32a** as a colorless liquid (302 mg, 76% yield).

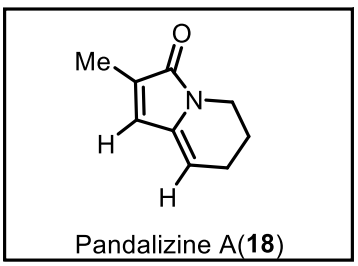
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.80–2.00 (m, 5H), 2.53 (t, J = 7.2 Hz, 2H), 3.50 (t, J = 6.9 Hz, 2H), 3.84 (t, J = 1.9 Hz, 2H), 6.68 (q, J = 1.6 Hz, 1H), 9.78 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.3, 21.1, 41.1, 41.7, 50.6, 135.1, 135.7, 172.3, 201.5.

HRMS (ESI) $[M + H]^+$ calcd for $C_9H_{14}NO_2$ 168.1019, found 168.1019.

IR ($CHCl_3$) ν_{max} 2856, 1714, 1665 cm^{-1}.

2-Methyl-6,7-dihydroindolizin-3(5*H*)-one (Pandalizine A, 18).



Pandalizine A(**18**)

To a stirred solution of aldehyde **32a** (200 mg, 1.20 mmol) in dry toluene (8 mL) was added *p*-TSA (617 mg, 3.59 mmol) under nitrogen atmosphere and the reaction mixture was heated at 60 °C for 1 h. The reaction mixture was concentrated in vacuo upon reaching room temperature. The obtained residue was dissolved in EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the product was purified by using column chromatography (silica gel, 230–400 mesh, MeOH:DCM, 1:9) to get pure product **18** as yellow liquid (112 mg, 63% yield).

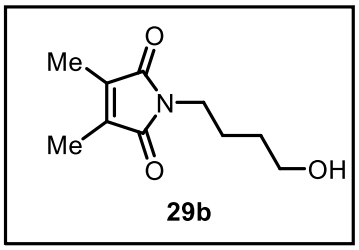
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.90 (quintet, J = 5.9 Hz, 2H), 1.96 (d, J = 0.9 Hz, 3H), 2.32 (q, J = 5.6 Hz, 2H), 3.63 (dd, J = 6.4 and 5.9 Hz, 2H), 5.43 (t, J = 4.7 Hz, 1H), 6.56 (q, J = 1.6 Hz, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 10.9, 21.6, 22.7, 37.9, 110.1, 127.8, 133.9, 137.9, 169.4.

HRMS (ESI) $[M + H]^+$ calcd for $C_9H_{12}NO$ 150.0913, found 150.0913.

IR (CHCl$_3$) ν_{max} 1656 cm^{-1}.

1-(4-Hydroxybutyl)-3,4-dimethyl-1*H*-pyrrole-2,5-dione (29b).



29b

To a solution of 4-aminobutanol (0.71 g, 7.93 mmol) in toluene (20 mL) was added dimethylmaleic anhydride (**28b**; 1.0 g, 7.93 mmol) and the stirring reaction mixture was refluxed for 4 h. After reaching the room temperature, the reaction mixture was concentrated in vacuo. The obtained product was dissolved in EtOAc. The organic layer was washed with 10% aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and column chromatographic purification of the formed residue (silica gel, 60–120 mesh, EtOAc–PE, 4:6) gave pure product **29b** as colorless liquid (1.45 g, 93% yield).

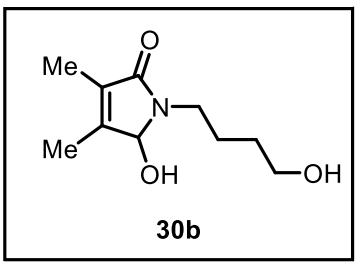
^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.46–1.54 (m, 2H), 1.57–1.65 (m, 2H), 1.91 (s, 6H), 2.34 (br s, 1H), 3.47 (t, J = 8.6 Hz, 2H), 3.60 (t, J = 7.6 Hz, 2H).

^{13}C NMR (CDCl$_3$, 125 MHz) δ 8.5, 25.0, 29.5, 37.5, 62.0, 137.0, 172.3.

HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_{16}NO_3$ 198.1125, found 198.1121.

IR (CHCl$_3$) ν_{max} 3451, 1768, 1703 cm^{-1}.

5-Hydroxy-1-(4-hydroxybutyl)-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (30b).



30b

To a solution of imide **29b** (1.0 g, 6.08 mmol) in MeOH (20 mL) was added $CeCl_3 \cdot 7H_2O$ (2.26 g, 6.08 mmol) at 0 °C and the reaction mixture was stirred for 5 min. To the above reaction mixture was added $NaBH_4$ (231 mg, 6.08 mmol) and it was further stirred for 1 h. The formed reaction mixture was concentrated in vacuo and the product was diluted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo provided crude

product and its column chromatographic purification (silica gel, 60–120 mesh, EtOAc–PE, 9:1) furnished pure compound **30b** as colorless liquid (876 mg, 87% yield).

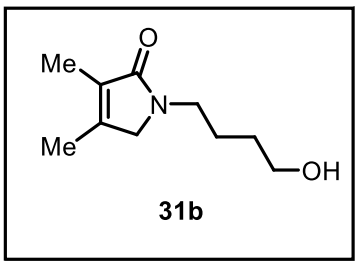
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.45–1.65 (m, 4H), 1.70 (s, 3H), 1.90 (s, 3H), 3.22–3.35 (m, 1H), 3.35–3.47 (m, 1H), 3.50–3.62 (m, 2H), 3.85–4.25 (br s, 1H), 5.03 (s, 1H), 5.25–5.70 (br s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.3, 11.1, 25.1, 29.5, 39.3, 61.7, 84.0, 128.5, 149.0, 171.5.

HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_{18}NO_3$ 200.1281, found 200.1277.

IR ($CHCl_3$) ν_{max} 3419, 1664 cm^{-1}.

1-(4-Hydroxybutyl)-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (31b).



31b

To a solution of compound **30b** (500 mg, 2.51 mmol) in dry DCM (15 mL) was added $BF_3{\cdot}OEt_2$ (1.44 mL, 5.02 mmol) and Et_3SiH (0.59 mL, 5.02 mmol) in a dropwise way at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 4 h and after reaching room temperature, it was concentrated in vacuo. The obtained residue was dissolved in EtOAc. The obtained organic layer was washed with 10% aqueous $NaHCO_3$, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo and column chromatographic purification of the residue (silica gel, 230–400 mesh, MeOH:DCM, 2:8) furnished pure product **31b** as colorless liquid (357 mg, 78% yield).

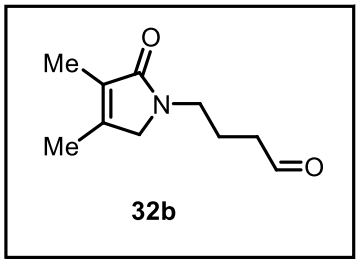
^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46–1.55 (m, 2H), 1.56–1.66 (m, 2H), 1.73 (s, 3H), 1.91 (s, 3H), 3.10–3.39 (br s, 1H), 3.39–3.45 (m, 2H), 3.58–3.63 (m, 2H), 3.70 (s, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.5, 12.8, 25.1, 29.4, 41.7, 54.1, 61.9, 128.6, 145.5, 172.9.

HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_{18}NO_2$ 184.1332, found 184.1329.

IR ($CHCl_3$) ν_{max} 3413, 1662 cm^{-1}.

4-(3,4-Dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanal (32b).



32b

To a solution of alcohol **31b** (200 mg, 1.09 mmol) in dry DCM (10 mL) was added PCC on Celite (706 mg, 3.28 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 2 h and allowed to reach room temperature. The reaction mixture after diluting with DCM was filtered through Celite using sintered funnel. The residue was washed with DCM and the filtrate was concentrated in vacuo. Column chromatographic purification of the obtained residue (silica gel, 230–400 mesh, MeOH:DCM, 1:9) furnished pure aldehyde **32b** as colorless liquid (141 mg, 71% yield).

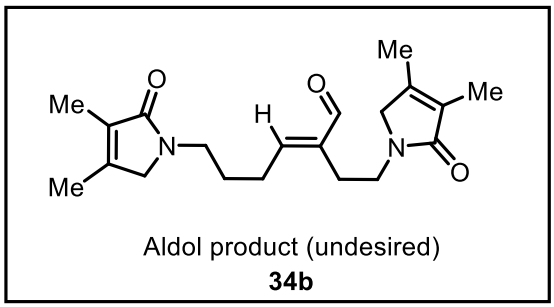
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (s, 3H), 1.89 (quintet, J = 7.6 Hz, 2H), 1.96 (s, 3H), 2.51 (t, J = 7.6 Hz, 2H), 3.46 (t, J = 6.9 Hz, 2H), 3.72 (s, 2H), 9.76 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 12.9, 21.1, 41.1, 41.3, 54.1, 128.7, 145.7, 173.0, 201.6.

HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_{16}NO_2$ 182.1176, found 182.1174.

IR ($CHCl_3$) ν_{max} 3433, 1707, 1665 cm^{-1}.

(*E*)-6-(3,4-Dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2-[2-(3,4-dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl]hex-2-enal (34b).



Aldol product (undesired)
34b

To a solution of aldehyde **32b** (100 mg, 0.55 mmol) in dry toluene (10 mL) was added *p*-TSA (283 mg, 1.65 mmol) under nitrogen atmosphere and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated in vacuo and the obtained product was dissolved in EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The dried organic layer was concentrated in vacuo and the obtained product was purified by column chromatography (silica gel, 230–400 mesh, MeOH:DCM, 1:9) to furnish pure aldol product **34b** as colorless liquid (61 mg, 64% yield).

^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.76 (s, 3H), 1.81 (s, 3H), 1.70– 1.85 (m, 2H), 1.95 (s, 3H), 1.97 (s, 3H), 2.44 (q, J = 9.6 Hz, 2H), 2.52 (t, J = 9.6 Hz, 2H), 3.42 (t, J = 8.6 Hz, 2H), 3.50 (t, J = 8.6 Hz, 2H), 3.77 (d, J = 4.8 Hz, 4H), 6.61 (t, J = 9.6 Hz, 1H), 9.36 (s, 1H).

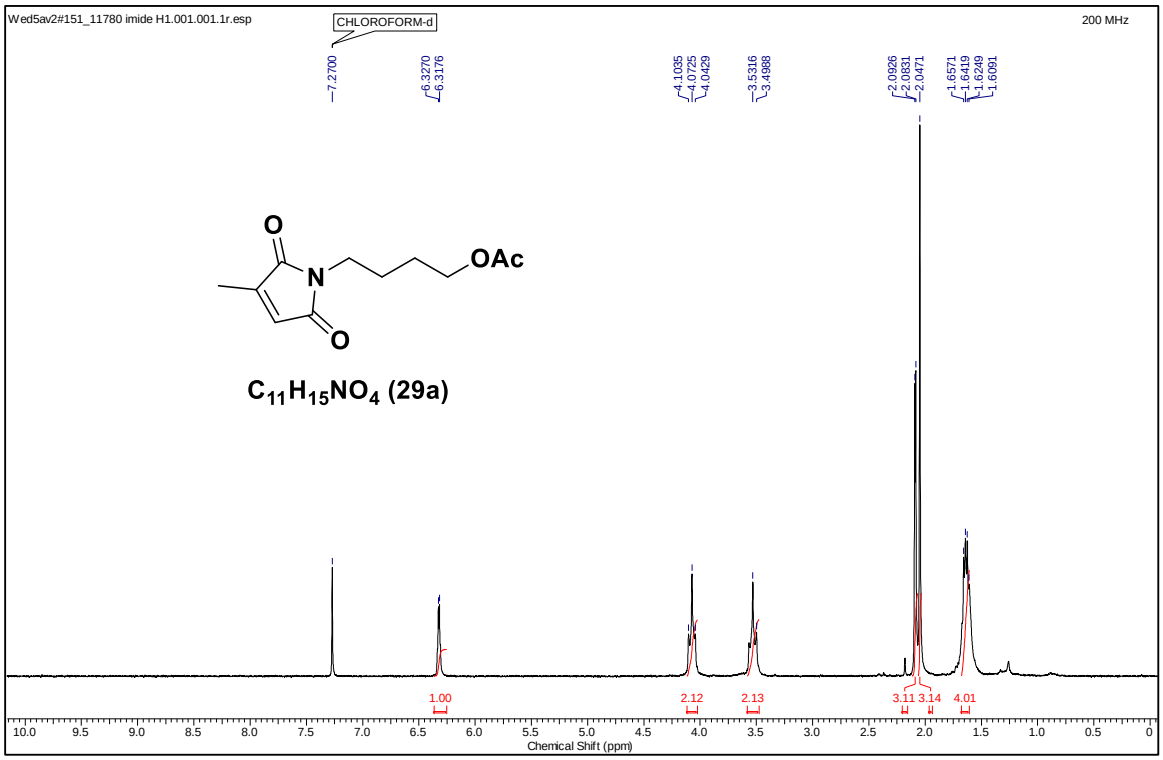
^{13}C NMR (CDCl$_3$, 125 MHz) δ 8.6, 8.7, 13.0 (2C), 23.3, 26.3, 27.7, 40.9, 41.5, 54.3, 54.6, 128.5, 128.8, 140.7, 145.7, 146.0, 156.1, 172.8, 172.9, 194.8.

HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{29}N_2O_3$ 345.2173, found 345.2167.

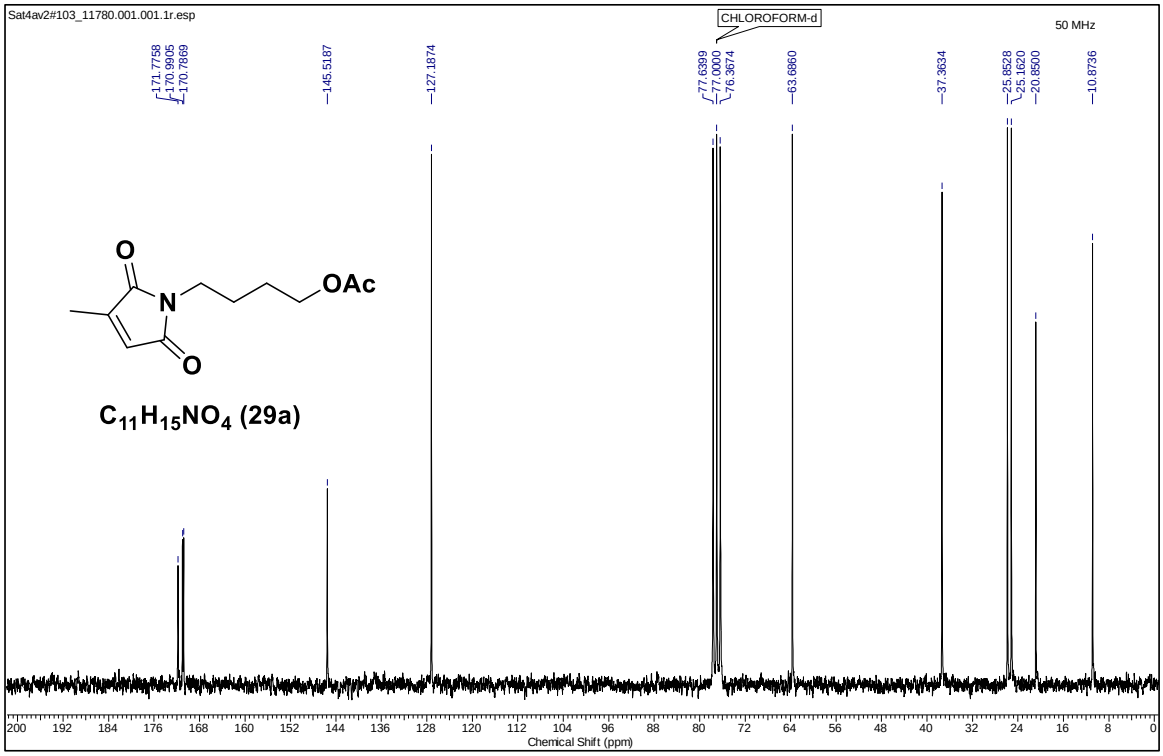
IR (CHCl$_3$) ν_{max} 1701, 1659 cm^{-1}.

3A.6 NMR Spectra of the Obtained Products

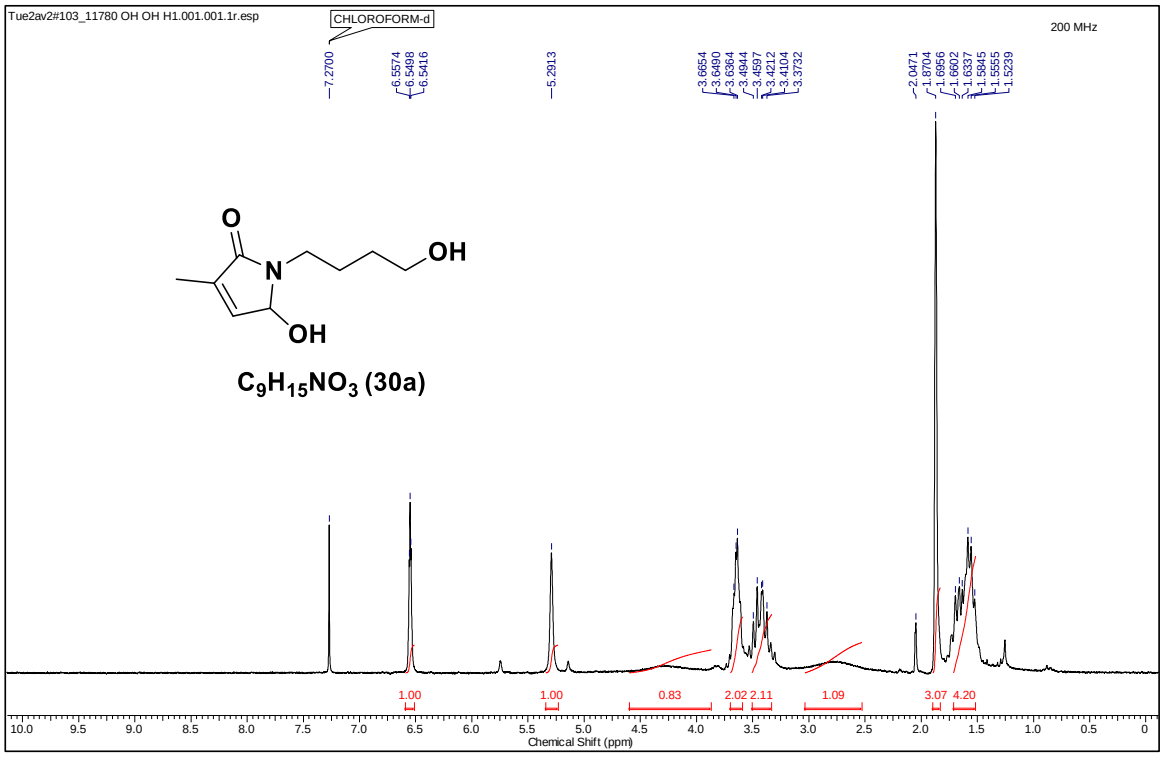
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 29a



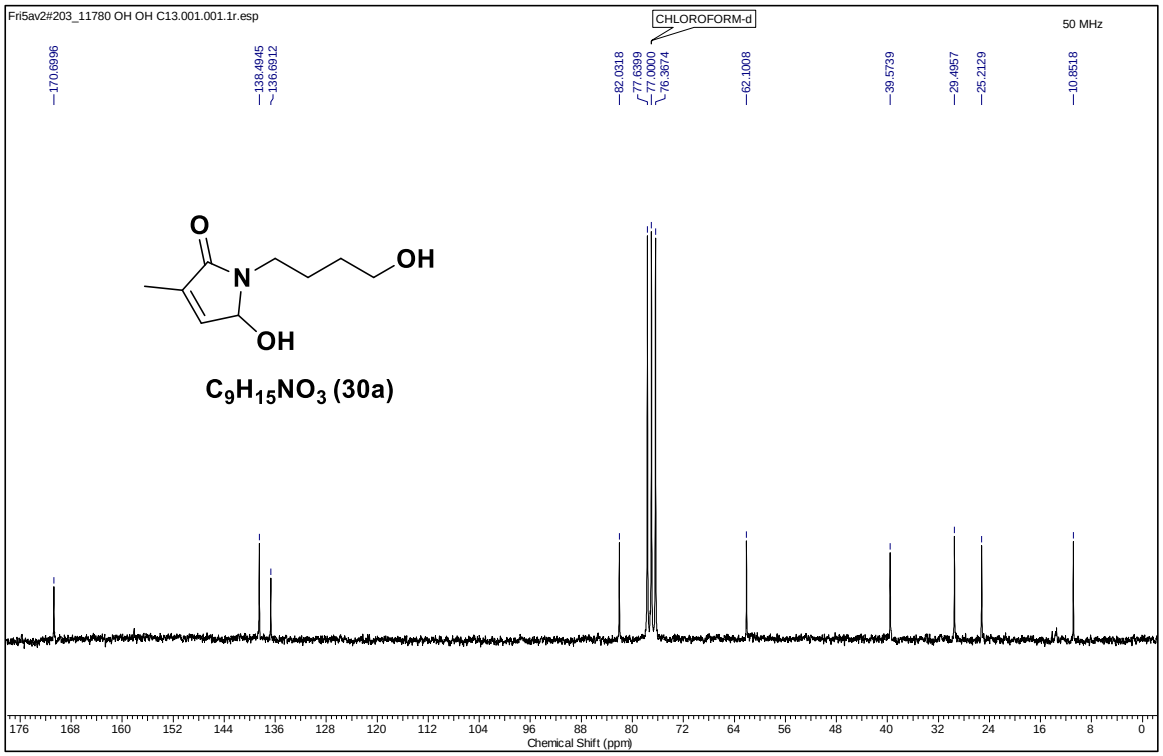
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 29a



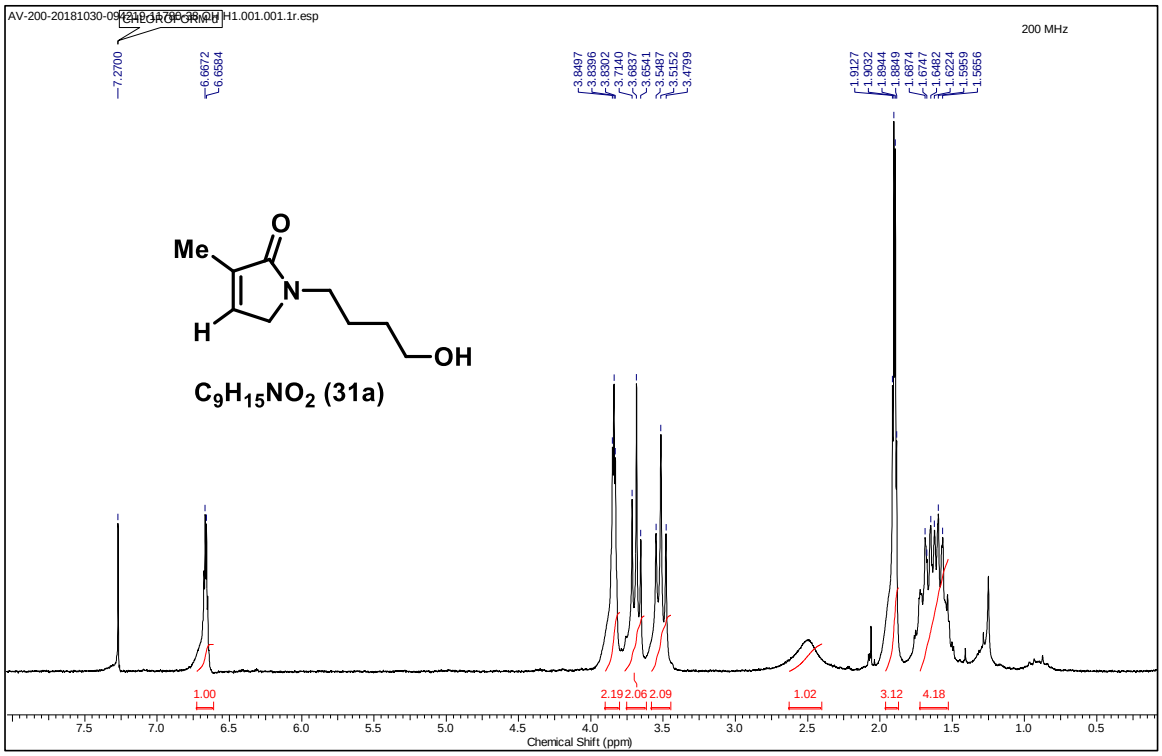
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 30a



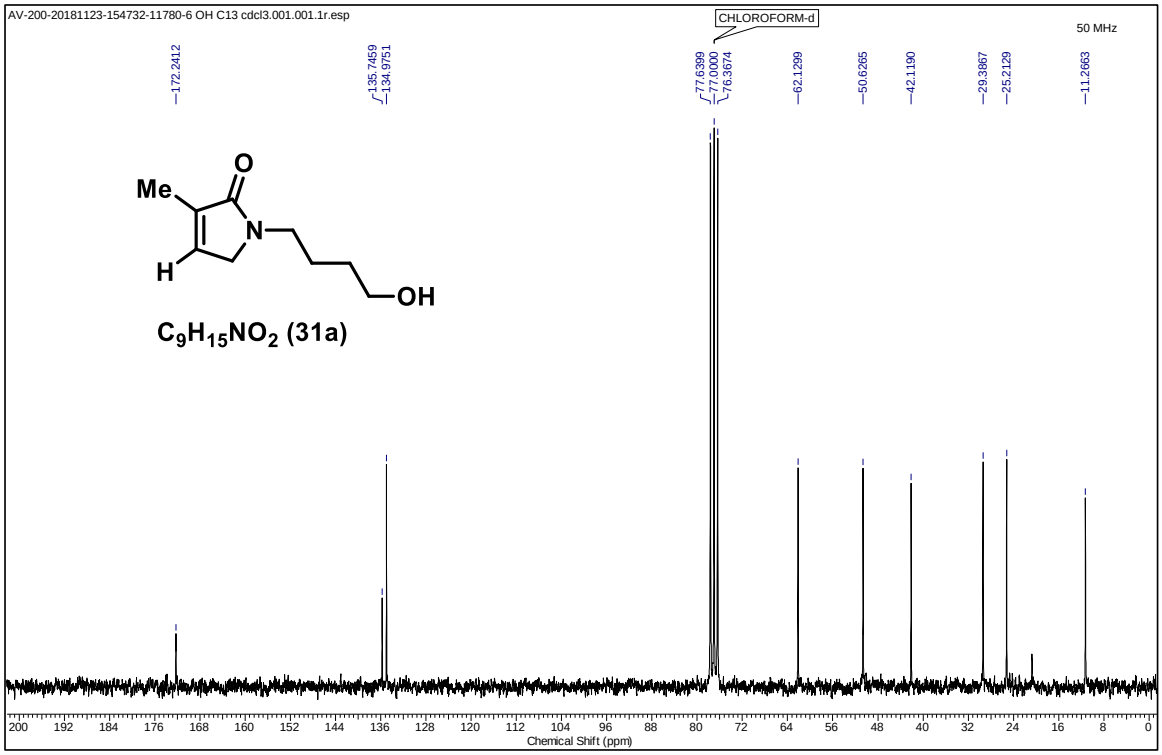
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 30a



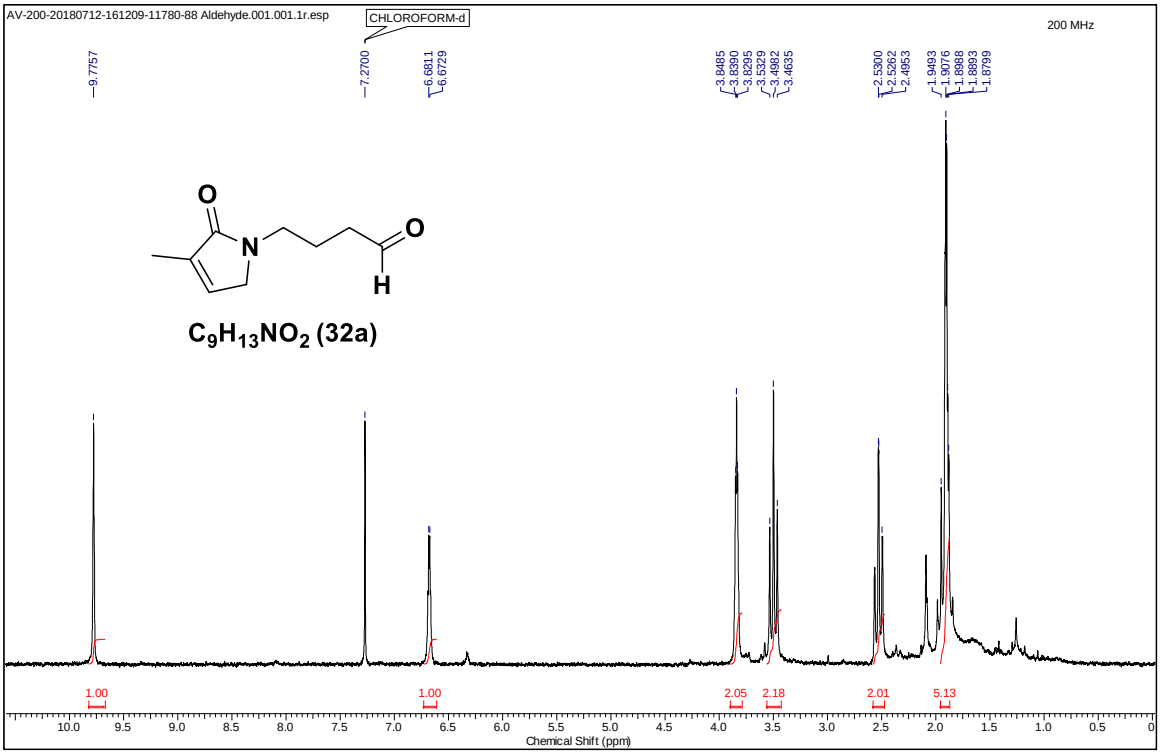
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 31a



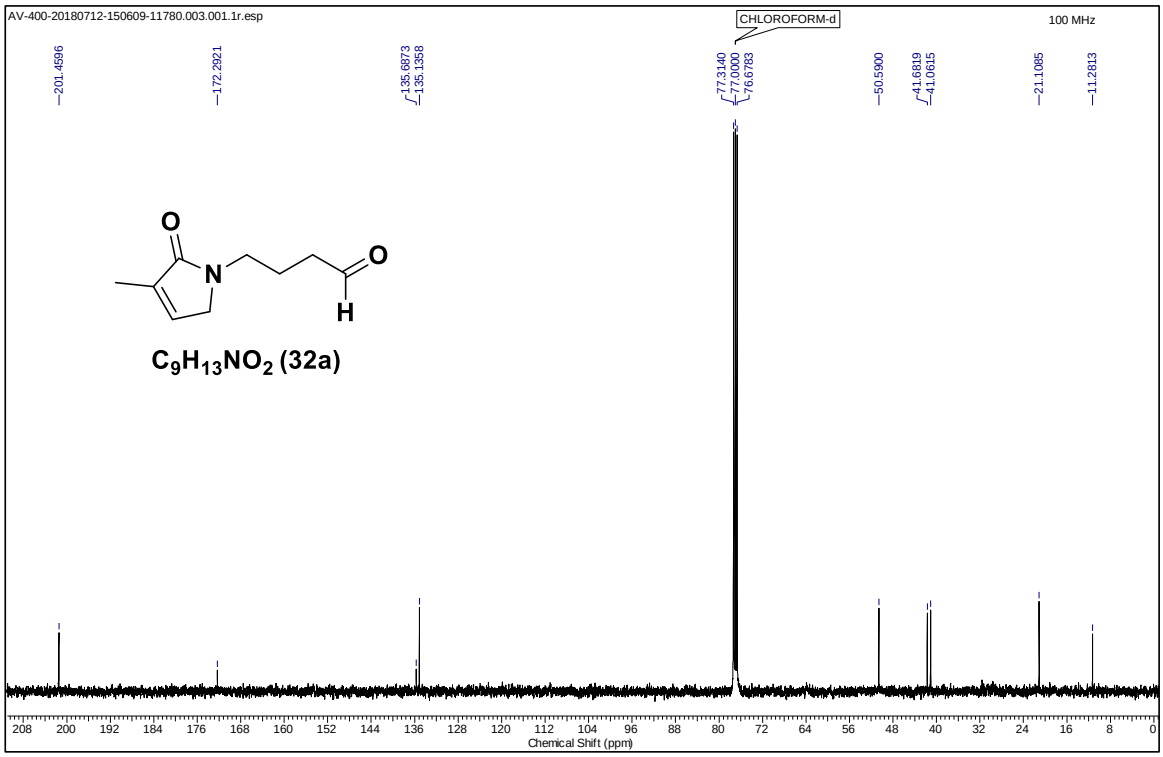
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 31a



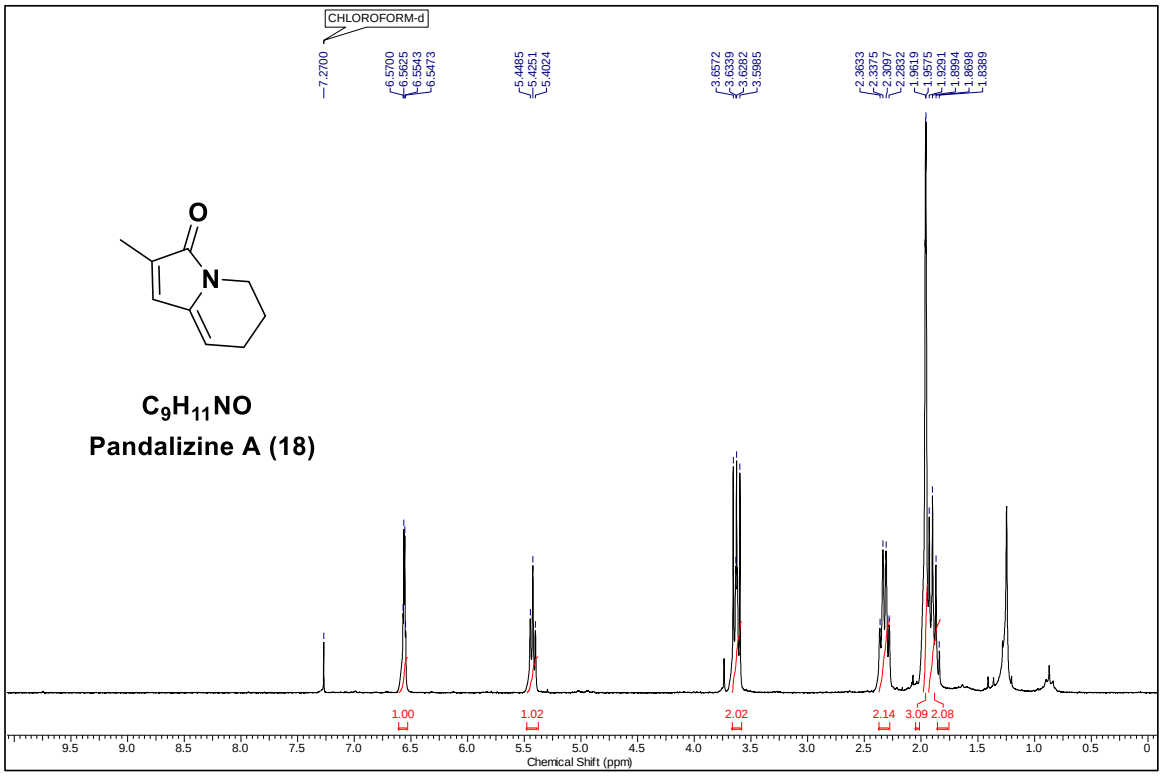
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 32a



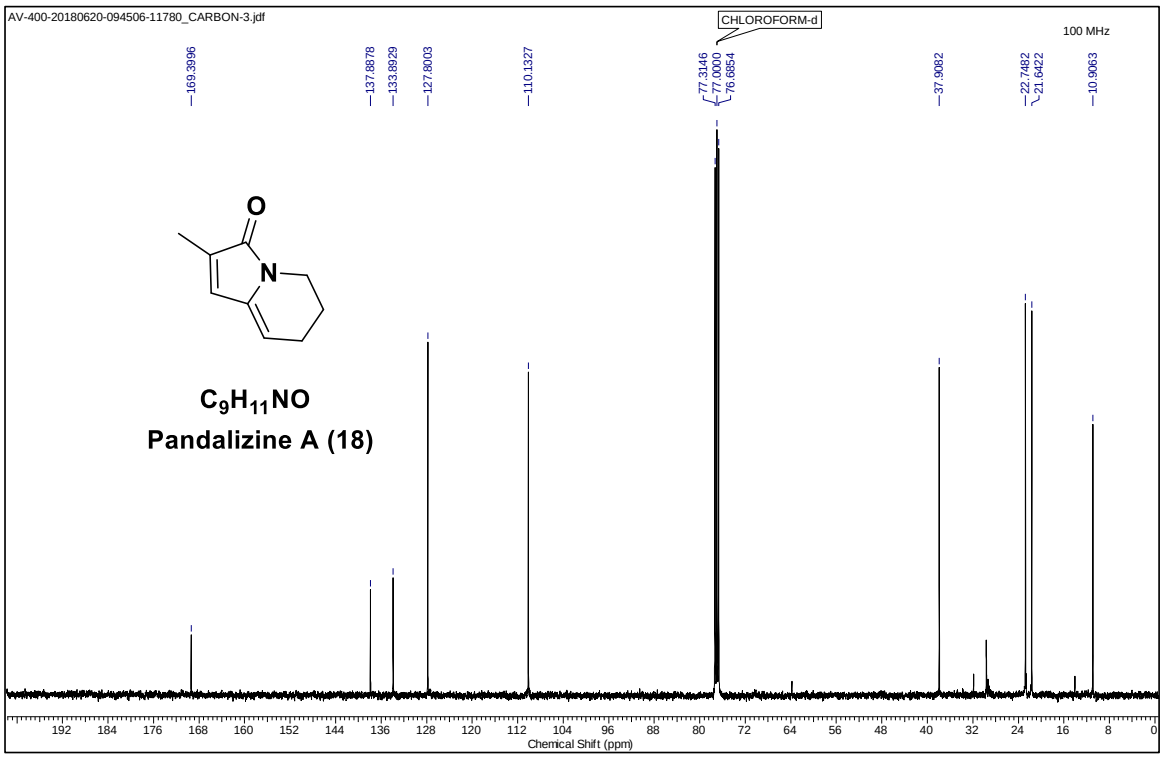
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 32a



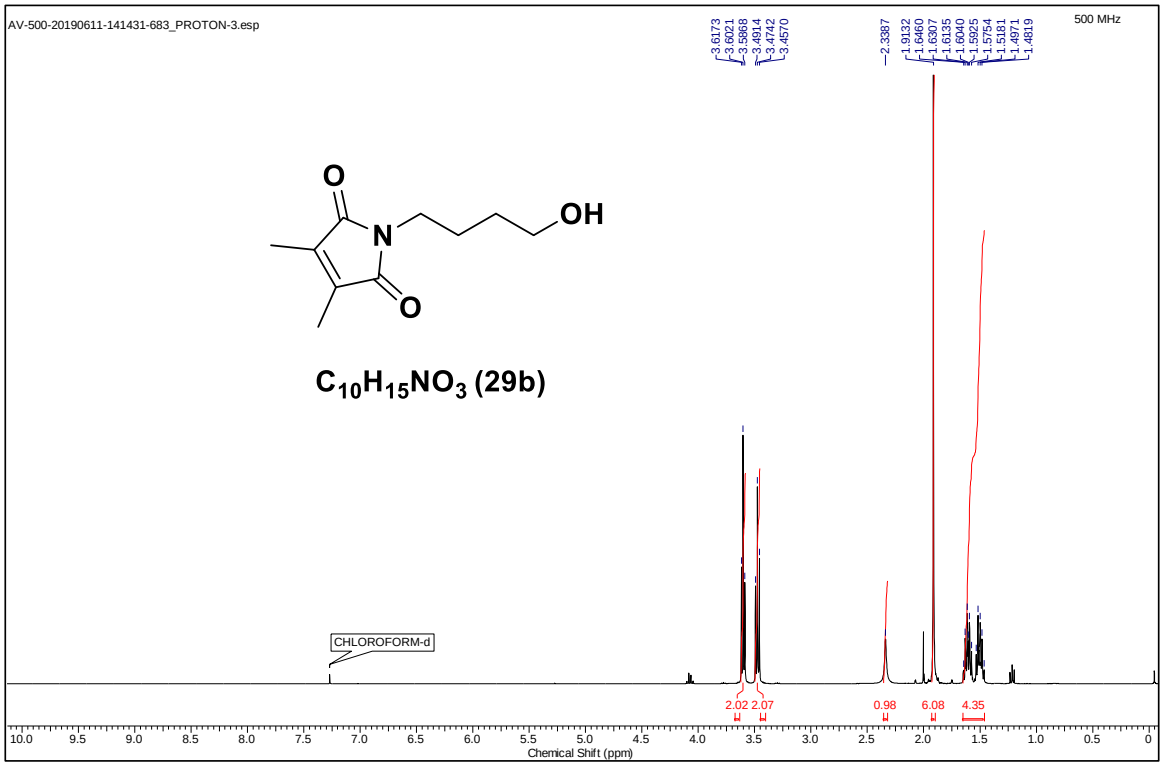
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 18



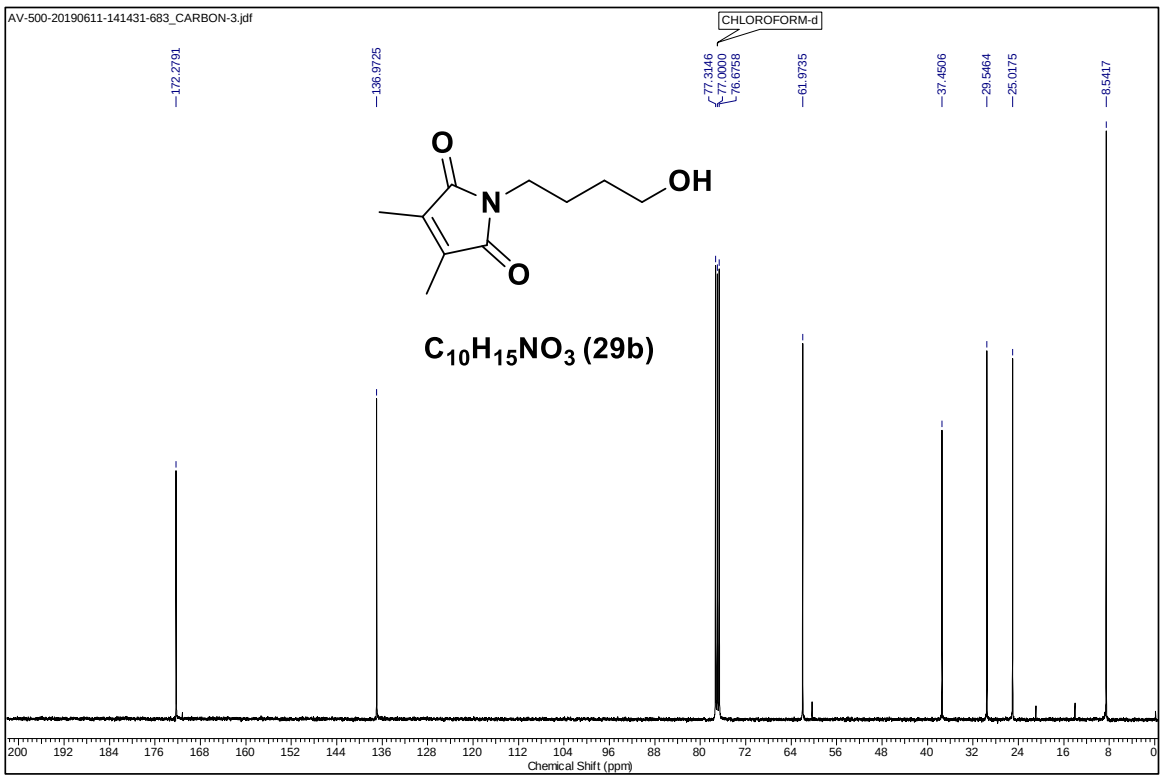
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 18



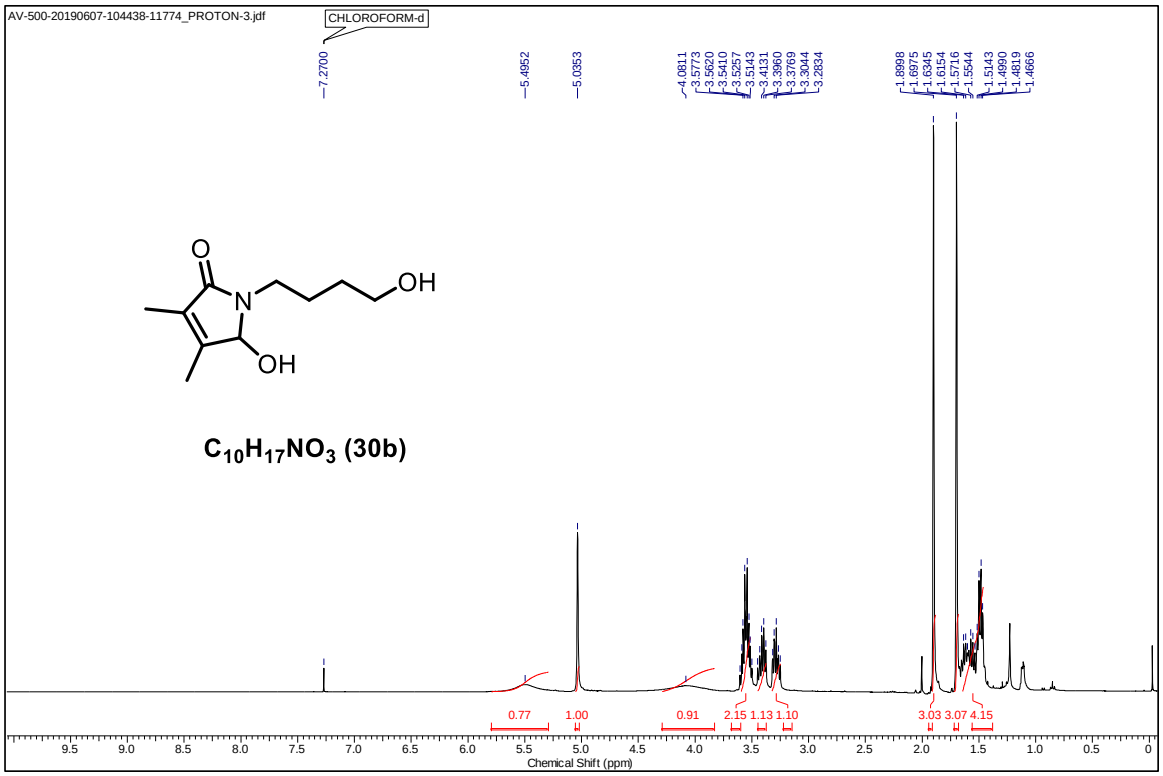
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 29b



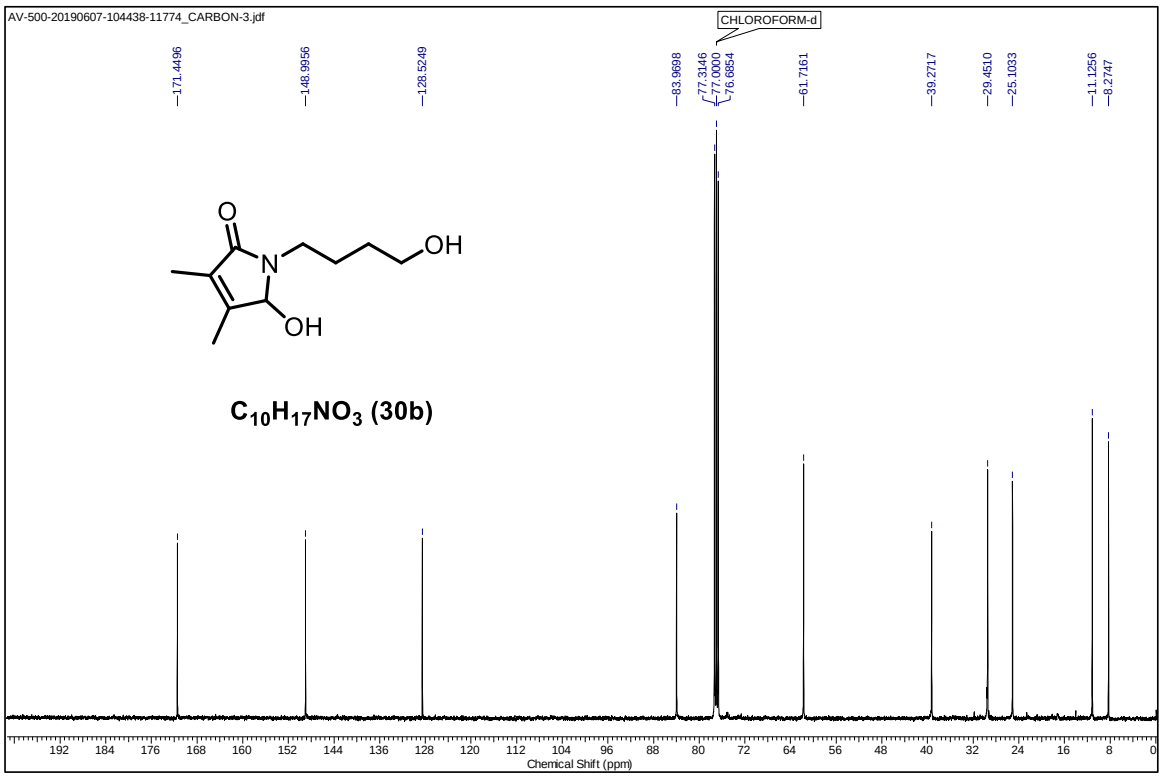
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 29b



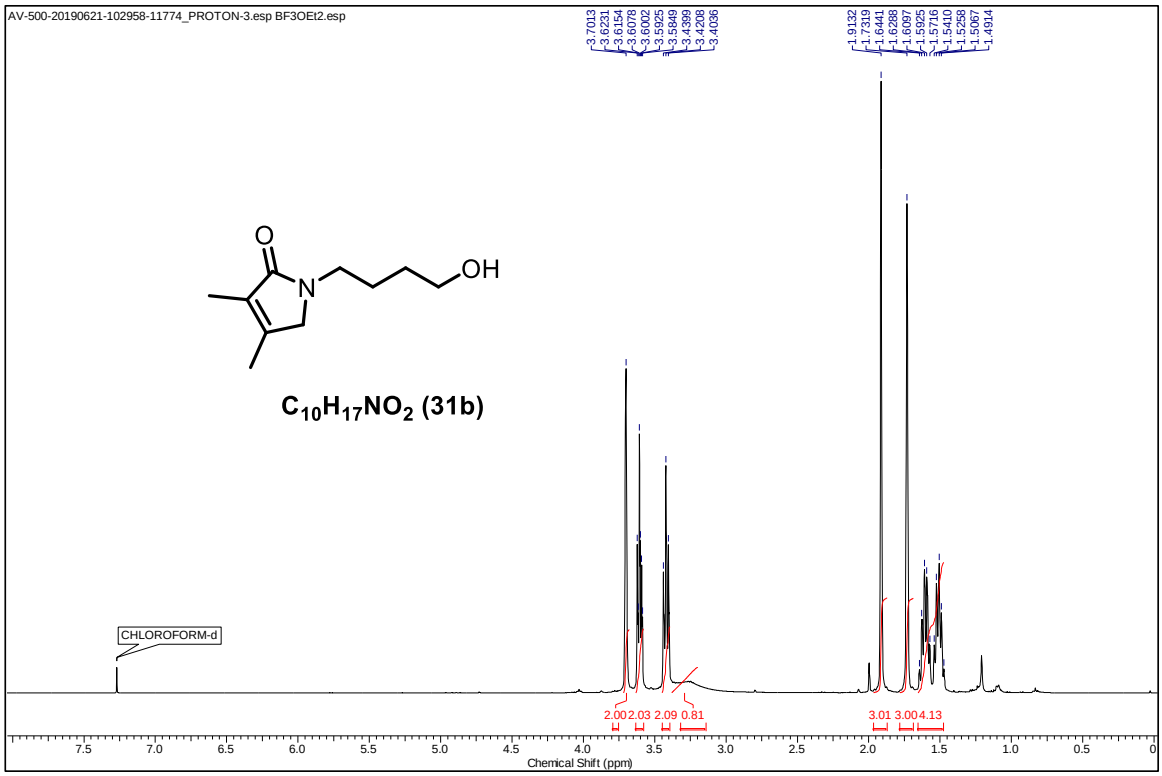
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 30b



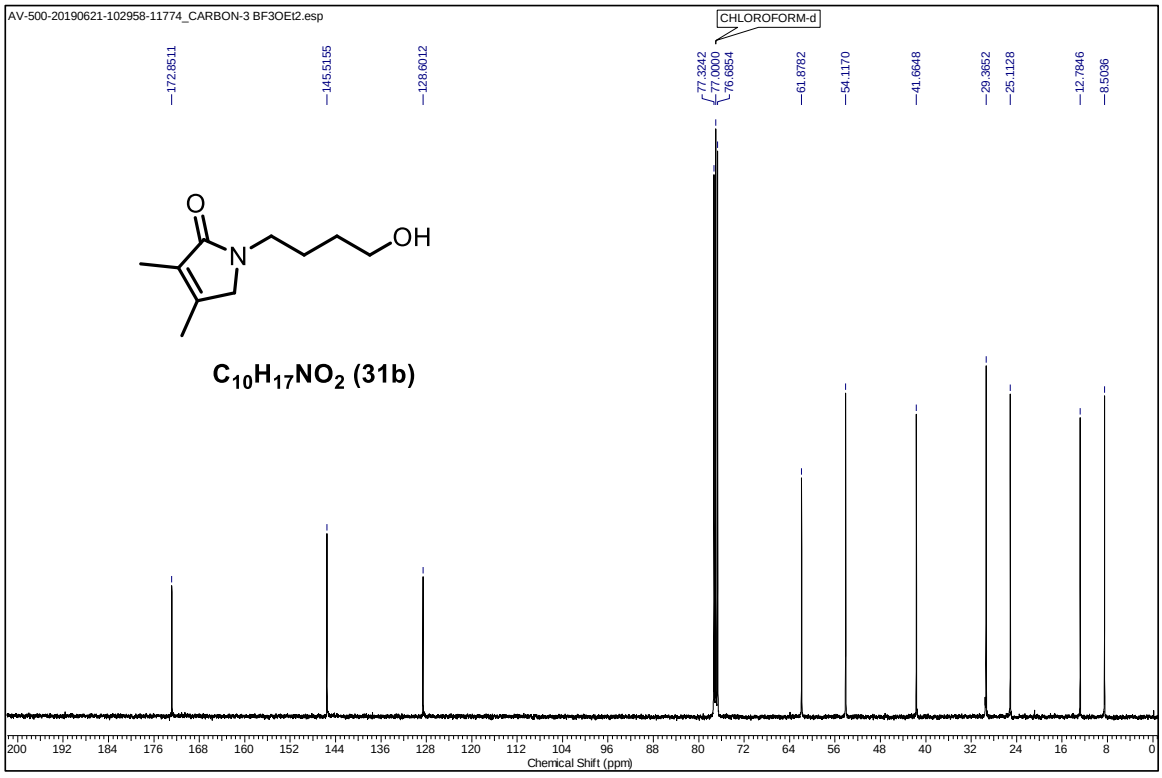
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 30b



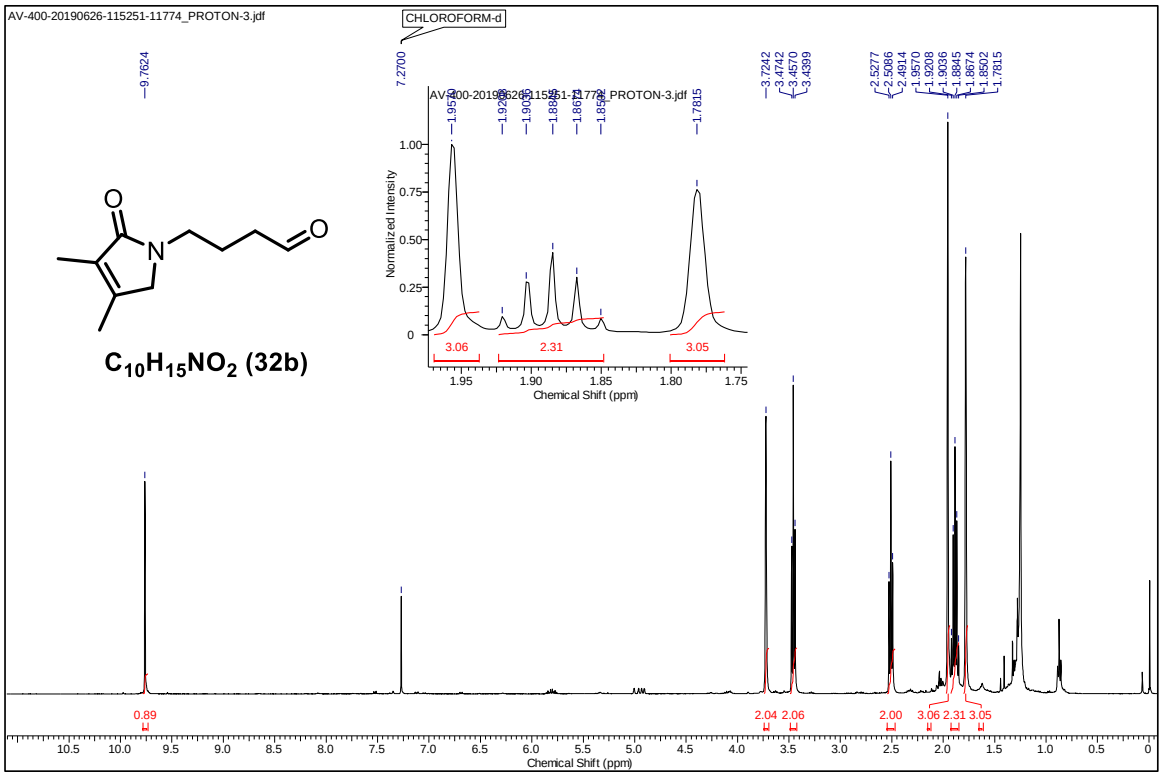
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 31b



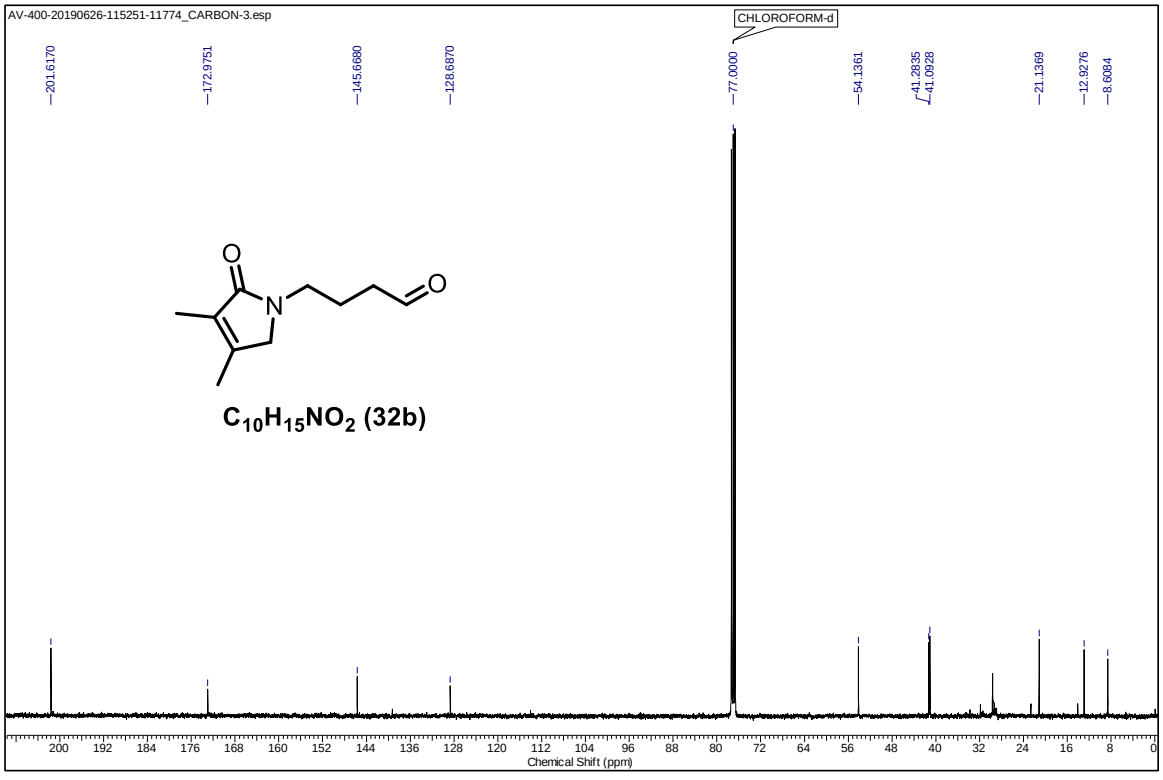
^{13}C NMR ($CDCl_3$, 125 MHz) of Compound 31b



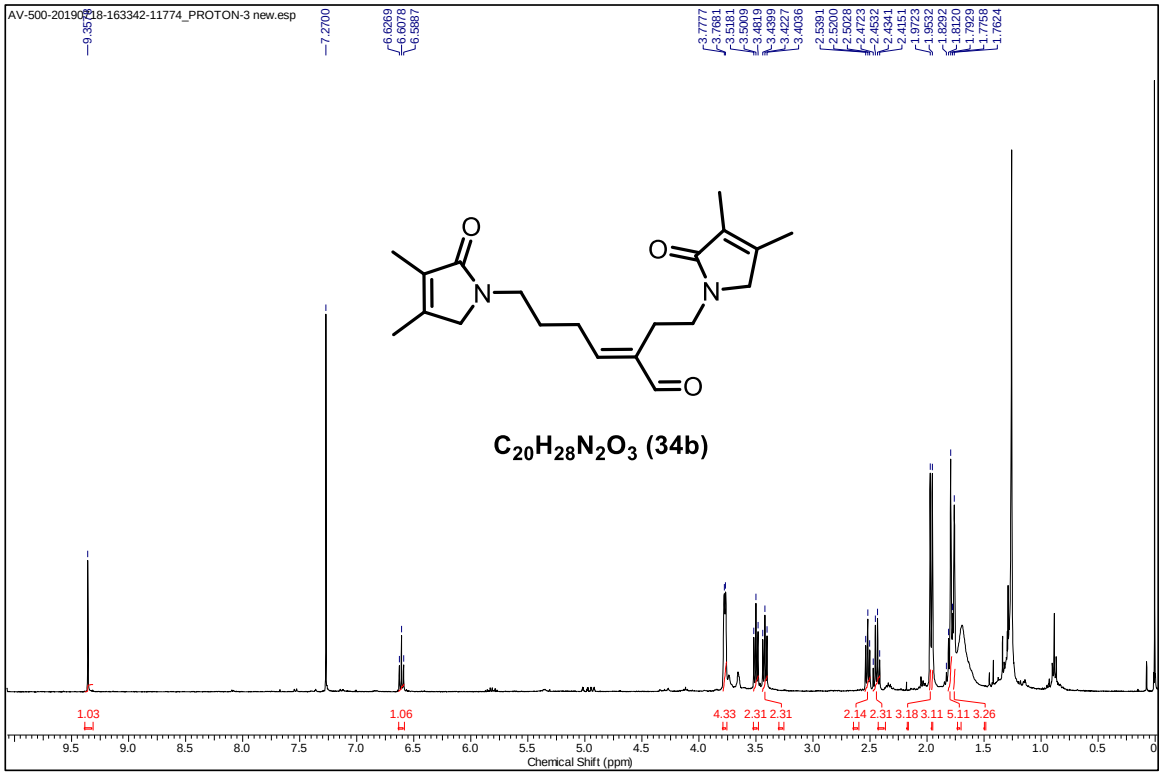
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 32b



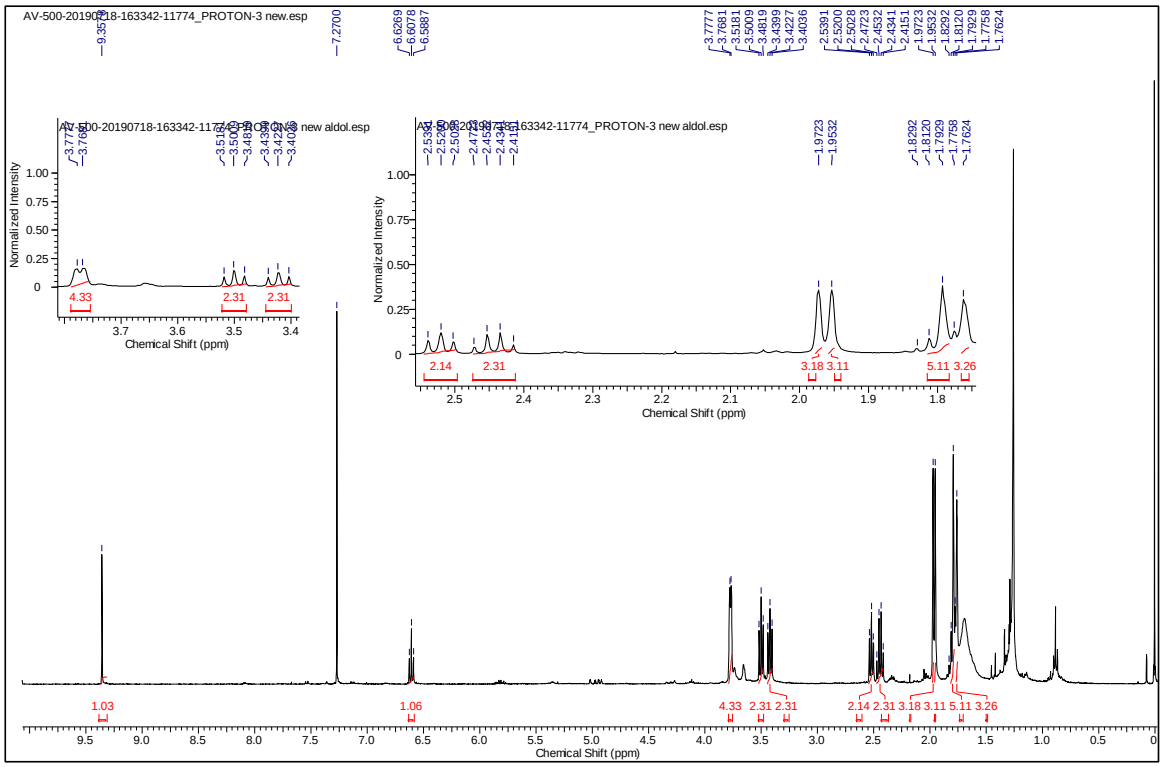
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 32b



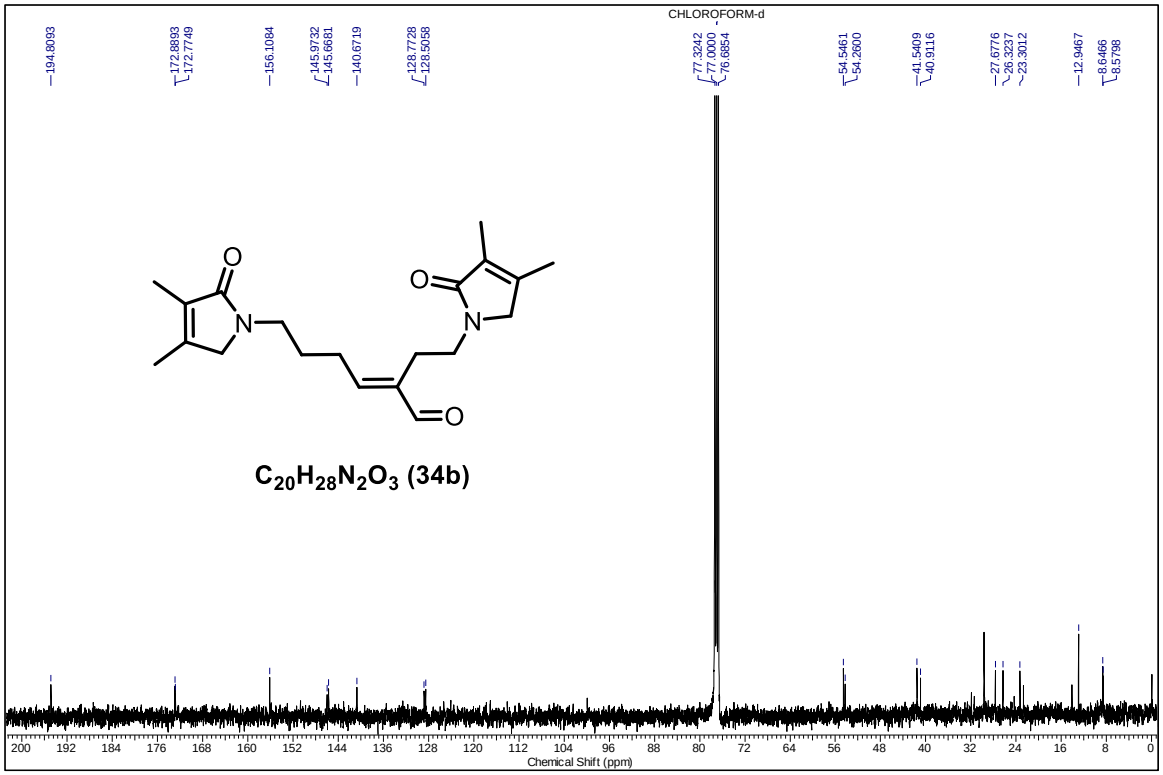
^{1}H NMR ($CDCl_3$, 500 MHz) of Compound 34b



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



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



3A.7 References

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Chapter 3

Regioselective Reduction Reactions of Cyclic Imides Leading to Synthesis of Bioactive Alkaloids

Section 3B

Study Towards the Synthesis of Indole Alkaloid Gorgonianic Acid

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

3B.1 Background

The structural diversity of alkaloids significantly expands our understanding of the chemical universe. As a result, they will be useful tools for exploring the undiscovered biological territory.[1] Heterocyclic alkaloids are among the most challenging natural products to define, not only because of their structurally distinctive skeletons derived from different amino acids but also because of their essential bioactivities. These nitrogen heterocycles are one of the most biologically active compounds and they are currently undergoing various clinical studies for the treatment of a wide range of disorders.[2-4] The indole heterocycles are well-known for their natural occurrence and wide range of bioactivities as a promising targets for new drug developments. The structural complexity found in distinct indole alkaloids have peaked much interest in the scientific community over the last few decades.[5-14]

The biogenesis of most indole alkaloids begins with the formation of a Schiff base from tryptamine and an aldehyde or ketone and then cyclization to form a tetrahydro-*β*-carboline system.[15,16] Tetrahydro-*β*-carboline exhibits various pharmacological and biological properties including antibacterial, anticancer, antiviral and anticonvulsant properties, which has sparked a growing interest in their synthesis.[17-19] Many synthetic and natural compounds have a tetrahydro-*β*-carboline moiety produced by the Pictet-Spengler reaction.[20,21] Many naturally occurring alkaloids have the tetrahydro-*β*-carboline moiety in their structure and some of them are depicted in figure 1.[22-25]

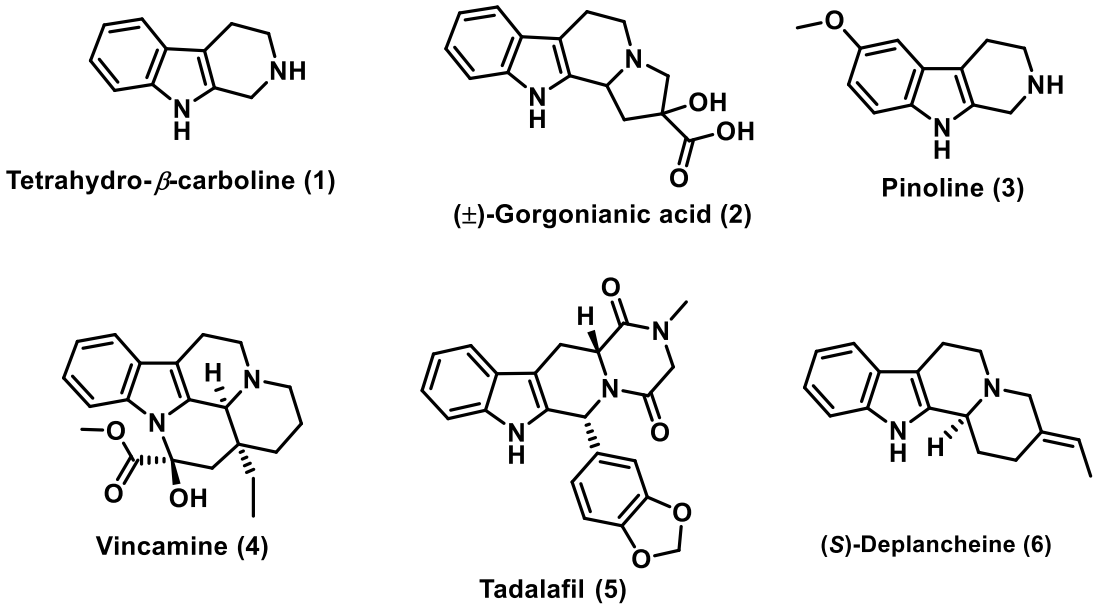


Figure 1. Tetrahydro-*β*-carboline unit containing natural and unnatural bioactive compounds

Gorgonianic acid (**2**) is an indole alkaloid with a tetrahydro-*β*-carboline structure containing a rare tetracyclic pyrrolidine skeleton. It was isolated from the ethanolic extracts of the South China Sea coral gorgonian *Isis minorbrachyblasta*.[22] Although there are no reports for the bioactivity of this natural product to date, the various tetrahydro-*β*-carboline pyrrolidine scaffold containing heterocyclic alkaloids exhibit important biological activities. Such compounds are as indole alkaloids like (+)-harmicine (**7**), the bridged tabertinggine (**8**), recently isolated L-tryptophan derived pyrrolidines (**9a-d**), excelsinidine (**10**) and norexcelsin (**11**) (Figure 2).[26-31]

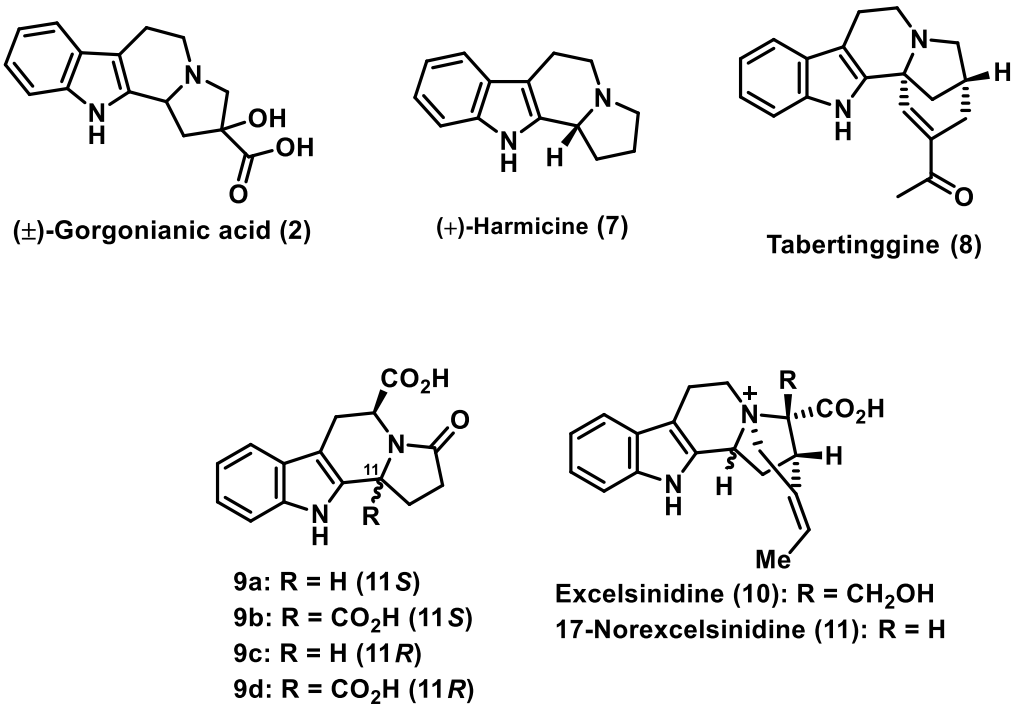
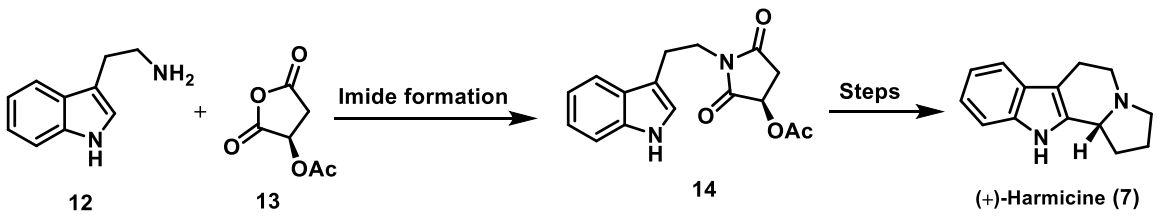


Figure 2. Alkaloids containing tetracyclic pyrrolidine skeleton

Recently, Argade and co-workers have reported the stereoselective total synthesis of (+)-harmicine (**7**) using regioselective reduction of acetoxysuccinimide (**14**) followed by intramolecular diastereoselective *N*-acyliminium cyclization reaction as a key step (Scheme 1).[26]

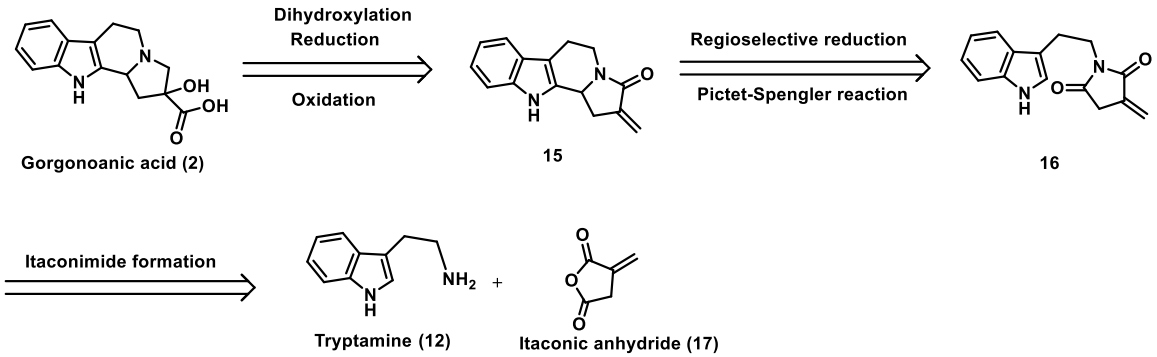


Scheme 1. Stereoselective Total Synthesis of (+)-Harmicine

We noticed that the structures of (±)-gorgonianic acid (**2**) and (+)-harmicine (**7**) are closely related to each other; the only apparent difference between them is the presence of an extra carboxylic acid group and quaternary hydroxyl group in gorgonianic acid (**2**) instead of a -CH_2- group in harmicine (**7**). In continuation of our studies on the total synthesis of recently isolated structurally interesting and biologically important natural products using cyclic anhydrides and their derivatives as potential precursors, we decided to synthesize gorgonianic acid (**2**) via regioselective reduction of itaconimide derivative followed by intramolecular cyclization as the crucial reactions.[32-36]

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

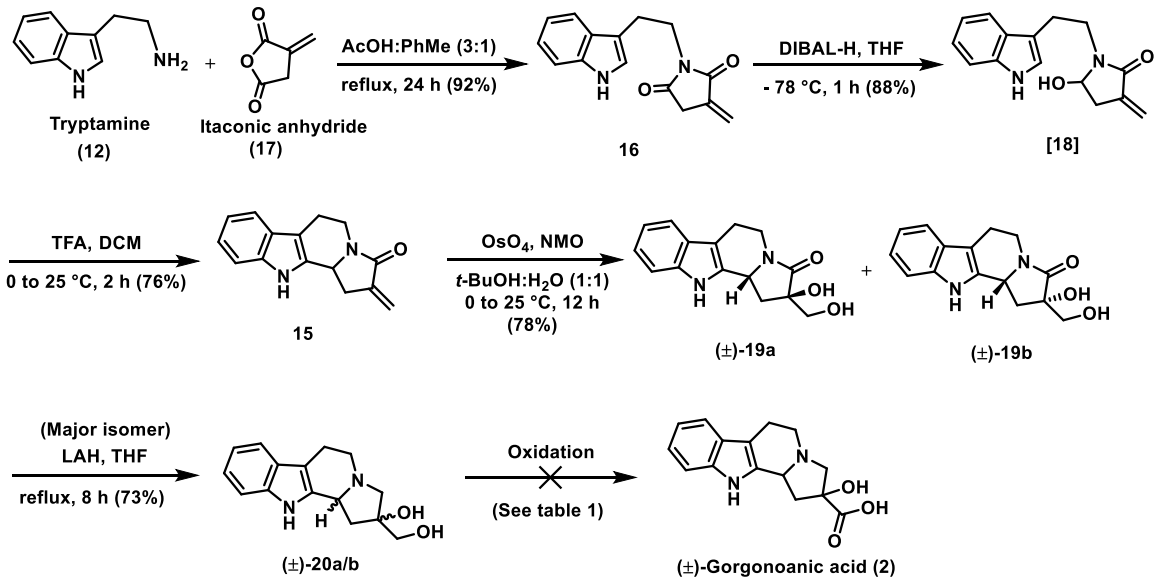
The structure of gorgonianic acid revealed that retro-synthetically tryptamine and itaconic anhydride would be used as potential building blocks to achieve total synthesis of the gorgonianic acid (Scheme 2). The regioselective reduction of itaconimide and acid-mediated Pictet-Spengler cyclization[37,38] were plausible key steps of our synthesis.



Scheme 2. Concise Retrosynthetic Analysis of Gorgonianic Acid

The reaction of tryptamine (**12**) with itaconic anhydride (**17**) in refluxing acetic acid and toluene mixture furnished the itaconimide **16** in 92% yield via intramolecular dehydrative cyclization reaction (Scheme 3). The regioselective reduction reaction of imide **16** with a bulky reducing agent such as DIBAL-H at −78 °C generated the crude lactamol product **18** in 88% yield, exclusively by reducing the more reactive unconjugated imide carbonyl group in compound **16**. Lactamol product **18** was used for the next step without any purification because of decomposition issues. Trifluoroacetic acid induced intramolecular Pictet–Spengler cyclization of the crude lactamol **18** furnished the tetrahydro-*β*-carboline structure containing desired cyclized product **15** in 76% yield via in situ generated corresponding iminium-ion intermediate. Osmium tetraoxide mediated dihydroxylation reaction of conjugated carbon-carbon double bond in compound **15** resulted in the column

chromatographically separated diol product as a diastereomeric mixture **19a/b** in 78% yield (*dr* 2:1). At this stage, the stereochemistry of both diastereomers **19a/b** is undetermined and the major diastereomer diol product was employed in the subsequent reaction to synthesize the target compound.



Scheme 3. Studies Towards the Synthesis of (±)-Gorgonianic Acid

LAH-induced reduction of the major diastereomer lactam **19a/b** in refluxing THF yielded the compound **20a/b** in 73% yield. Oxidation of the primary alcohol unit to the corresponding carboxylic acid is the crucial last step reaction to achieve the target compound gorgonianic acid. For this purpose, we studied several reaction conditions as indicated in table 1.

Sr. No.	Oxidation Conditions	Result
1	$KMnO_4$, acetone, water, 24 h	Decomposition
2	DMP, DCM, Ag_2O ($AgNO_3$, aq. NaOH), EtOH	Not Formed
3	MnO_2, DCM, Ag_2O ($AgNO_3$, aq. NaOH), EtOH	Not Formed
4	PDC, DMF	Decomposition
5	TEMPO, NaOCl	Decomposition

Table 1. Reaction conditions for the oxidation reaction.

Unfortunately, we have not yet found the suitable reaction condition to achieve the target even after attempting several oxidation reaction conditions and we are one step behind to

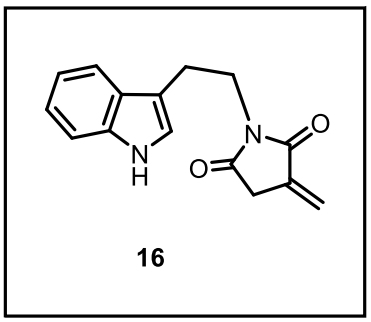
accomplish the first total synthesis of gorgonianic acid. We assume that completing the total synthesis of gorgonianic acid and determining the configuration will also disclose the configurations of compounds **19a/b** and **20a/b**.

3B.3 Summary

In summary, tryptamine and itaconic anhydride were promising starting materials for the formation of itaconimide, which was then regioselectively reduced and cyclized to yield the tetrahydro-β-carboline intermediate. Dihydroxylation of tetrahydro-β-carboline generates a mixture of diastereomers in which the major diastereomer has been reduced, leaving us one step behind in the total synthesis of gorgonianic acid. Studies on the oxidation of diol product to desired final compound are being investigated. A protection-deprotection approach will be used to complete the synthesis.

3B.4 Experimental Section

1-(2-(1H-Indol-3-yl)ethyl)-3-methylenepyrrolidine-2,5-dione (16).



16

To a stirred suspension of tryptamine (**12**; 2 g, 12.50 mmol) in toluene (10 mL) was added itaconic anhydride (**17**; 1.4 g, 12.50 mmol) and the reaction mixture was stirred for 10 min. AcOH (20 mL) was added to the above reaction mixture and then refluxed for 24 h. The reaction mixture was allowed to cool to the room temprature and concentrated in vacuo. The obtained residue was diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the obtained residue by using petroleum ether–ethyl acetate (1:1) as an eluent yielded itaconimide **16** as a white solid (2.92 g, 92% yield).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.98–3.12 (m, 2 H), 3.23 (t, J = 2.2 Hz, 2 H), 3.80–3.95 (m, 2 H), 5.57 (t, J = 2.0 Hz, 1 H), 6.31 (t, J = 2.4 Hz, 1 H), 7.02–7.07 (m, 1 H), 7.08–7.24 (m, 2 H), 7.29–7.36 (m, 1 H), 7.59–7.72 (m, 1 H), 8.05 (br s 1 H).

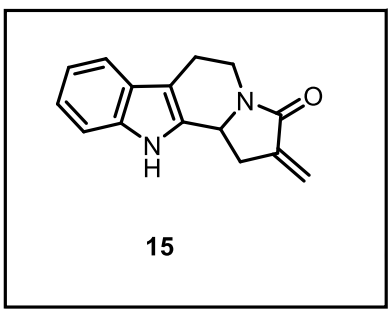
^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.5, 33.7, 39.4, 111.1, 112.2, 118.7, 119.5, 120.4, 122.0, 122.1, 127.4, 133.3, 136.1, 169.5, 173.8

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{15}O_2N_2$ 255.1128, found 255.1130.

IR ($CHCl_3$) ν_{max} 3377, 1740, 1596 cm^{-1}.

Mp 148−150 °C.

2-Methylene-1,2,5,6,11,11b-hexahydro-3H-indolizino[8,7-b]indol-3-one (15).



15

To a solution of imide **16** (1.0 g, 3.94 mmol) in dry THF (20 mL) was slowly added a solution of DIBAL-H in THF (1 M, 7.87 mL, 7.87 mmol) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at the same temperature. The reaction

was quenched with a saturated aqueous solution of potassium sodium tartrate tetrahydrate and the reaction mixture was concentrated in vacuo. The formed product was dissolved in EtOAc and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo to obtain crude lactamol **18** (880 mg, 88%). To a stirred solution of crude lactamol **18** (1 g, 3.92 mmol) in DCM (15 mL) at 0 °C was added TFA (1.34 mL, 11.76 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 2 h and allowed to reach room temperature. The reaction mixture was concentrated in vacuo and the formed product was dissolved in EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the obtained residue by using ethyl acetate–petroleum ether (60:40) as an eluent afforded pure lactam **15** as a yellowish solid (675 mg, 76% yield).

^{1}H NMR (Acetone-d_6, 500 MHz) δ 2.75–2.82 (m, 3 H), 3.13–3.21 (m, 1 H), 3.35 (m, J = 16.8, 8.0, 2.1 Hz, 1 H), 4.47–4.53 (m, 1 H), 5.03 (dd, J = 7.6, 5.7 Hz, 1 H), 5.33 (s, 1 H), 5.85 (s, 1 H), 7.02 (t, J = 7.3 Hz, 1 H), 7.09 (t, J = 7.3 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 10.19 (br s, 1 H).

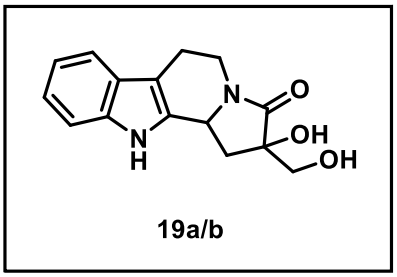
^{13}C NMR (Acetone-d_6, 125 MHz) δ 21.7, 32.2, 38.8, 52.4, 108.4, 112.1, 115.1, 119.0, 120.0, 122.4, 128.0, 135.1, 137.8, 141.5, 166.8.

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{15}ON_2$ 239.1179, found 239.1181.

IR ($CHCl_3$) ν_{max} 3263, 1676, 1654 cm^{-1}.

Mp 155−157 °C.

2-Hydroxy-2-(hydroxymethyl)-1,2,5,6,11,11b-hexahydro-3H-indolizino[8,7-b]indol-3-one (19a/b).



19a/b

To a stirred solution of lactam **15** (500 mg, 2.19 mmol) in *tert*-butyl alcohol:water (1:1) mixture (10 mL) at 0 °C was added OsO_4 in *tert*-butyl alcohol (1 M, 0.438 mL, 0.438 mmol) and 50% aqueous NMO solution (0.768 mL). The heterogeneous reaction mixture was vigorously stirred for 12 h. The reaction mixture was then quenched by adding saturated solution of $NaHSO_3$ and it was further

stirred for 30 min. The reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by the silica gel (100–200 mesh) column chromatographic purification of the obtained residue by using ethyl acetate–petroleum ether (95:05) as an eluent afforded diol product **19a/b** as a minor diastereomer (115 mg, 26%) and major diastereomer as colourless liquid (232 mg, 52% yield).

Major isomer:

^{1}H NMR (CD_3OD, 200 MHz) δ 2.27 (dd, J = 13.3, 8.0 Hz, 1 H), 2.52 (dd, J = 13.3, 6.8 Hz, 1 H), 2.74–2.86 (m, 2 H), 3.14 (ddd, J = 12.8, 10.2, 6.4 Hz, 1 H), 3.50 (d, J = 10.9 Hz, 1 H), 3.72 (d, J = 10.9 Hz, 1 H), 4.32–4.54 (m, 1 H), 5.08 (t, J = 7.5 Hz, 1 H), 6.87–7.16 (m, 2 H), 7.24–7.36 (m, 1 H), 7.40 (d, J = 7.3 Hz, 1 H).

^{13}C NMR (CD_3OD, 50 MHz) δ 22.2, 37.5, 39.3, 53.0, 65.2, 79.5, 107.8, 112.2, 119.0, 120.2, 122.7, 128.2, 134.6, 138.2, 174.6.

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{17}O_3N_2$ 273.1234, found 273.1235.

IR ($CHCl_3$) ν_{max} 3399, 3360, 2924, 1738 cm^{-1}.

Minor isomer:

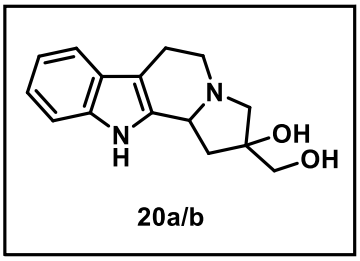
^{1}H NMR (CD_3OD, 200 MHz) δ 1.88–2.02 (m, 1 H), 2.78–2.89 (m, 2 H), 2.98–3.20 (m, 2 H), 3.58–3.65 (m, 1 H), 3.73–3.82 (m, 1 H), 4.36–4.53 (m, 1 H), 4.93–4.99 (m, 1 H), 6.96–7.12 (m, 2 H), 7.27–7.35 (m, 1 H), 7.37–7.45 (m, 1 H).

^{13}C NMR (CD_3OD, 50 MHz) δ 22.1, 39.3, 39.5, 52.7, 67.1, 79.67, 107.4, 112.2, 119.1, 120.2, 122.7, 128.2, 134.9, 138.4, 175.6.

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{17}O_3N_2$ 273.1234, found 273.1232.

IR ($CHCl_3$) ν_{max} 3384, 2924, 2855, 1738 cm^{-1}.

2-(Hydroxymethyl)-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indol-2-ol (20a/b).



20a/b

To a solution of lactam **19a/b** (300 mg, 1.10 mmol) in dry THF was added LAH (125 mg, 3.30 mmol) at 0 °C under the nitrogen atmosphere. The reaction mixture was stirred for 8 h under refluxing condition and allowed to

reach room temperature. The reaction was quenched with the slow addition of a saturated aqueous solution of Na_2SO_4 at 0 °C temperature. Reaction mixture was diluted with EtOAc, filtered through a Celite pad 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 obtained residue using DCM–MeOH mixture (7:3) as an eluent furnished the compound **20a/b** as a yellow liquid (208 mg, 73%).

^{1}H NMR (CD_3OD, 200 MHz) δ 2.18 (dd, J = 13.4, 7.7 Hz, 1 H), 2.34 (dd, J = 13.4, 7.1 Hz, 1 H), 2.72–2.99 (m, 2 H), 3.01–3.09 (m, 1 H), 3.12–3.28 (m, 2 H), 3.43 (d, J = 2.4 Hz, 2 H), 3.60 (s, 2 H), 4.65 (t, J = 6.9 Hz, 1 H), 6.96–7.12 (m, 2 H), 7.29 (d, J = 7.5 Hz, 1 H), 7.42 (d, J = 7.1 Hz, 1 H).

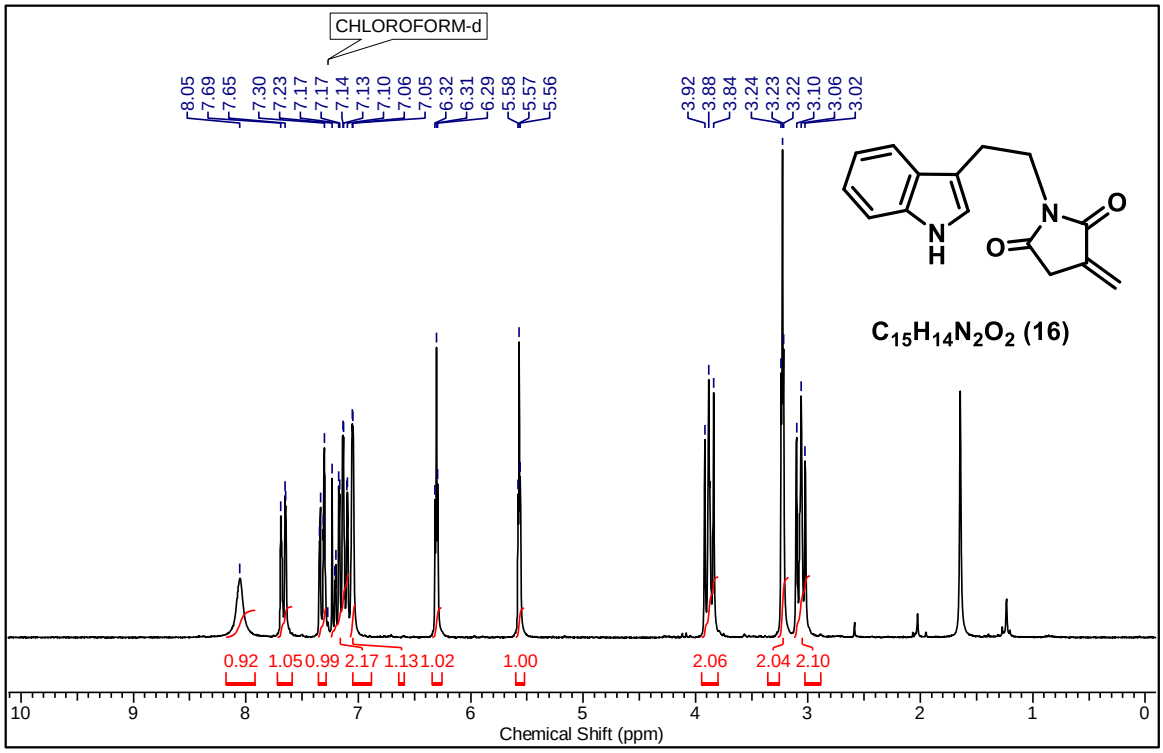
^{13}C NMR (CD_3OD, 50 MHz) δ 19.4, 42.0, 59.0, 62.0, 64.5, 68.2, 81.5, 107.2, 112.2, 119.0, 120.2, 122.6, 128.1, 133.7, 138.3.

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{18}O_2N_2$ 259.1441, found 259.1443.

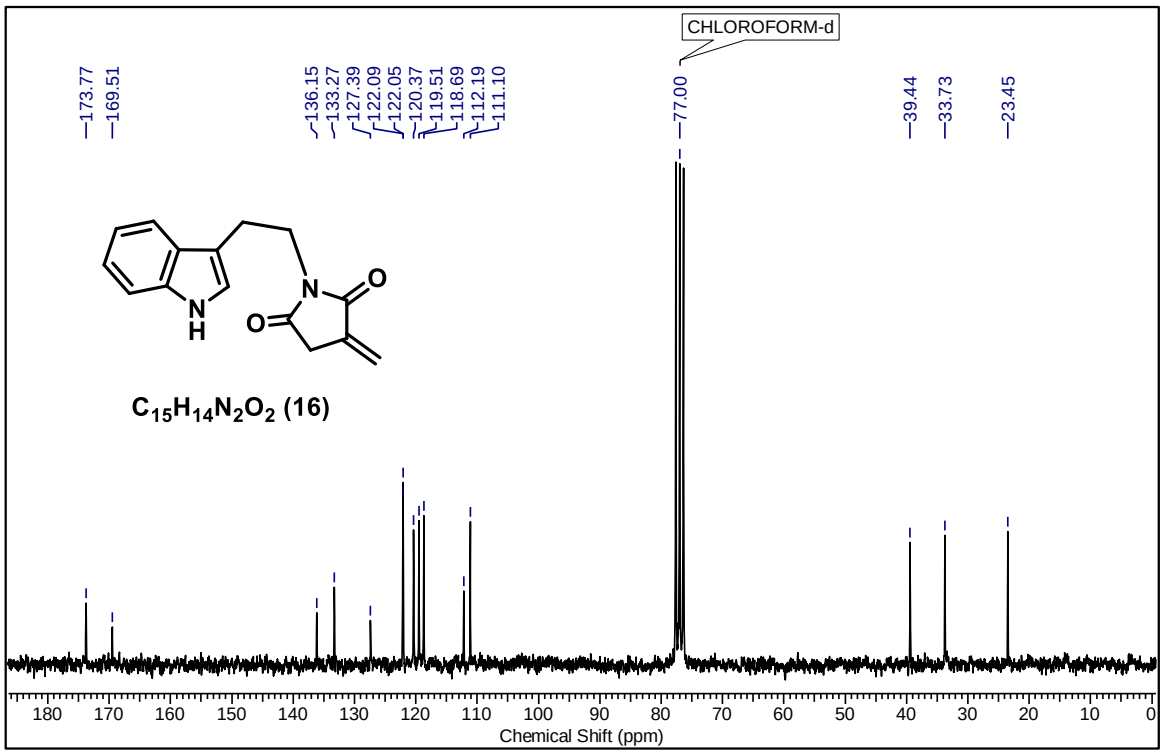
IR ($CHCl_3$) ν_{max} 3265, 3181, 2924, 2854 cm^{-1}.

3B.5 NMR Spectra of the Obtained Products

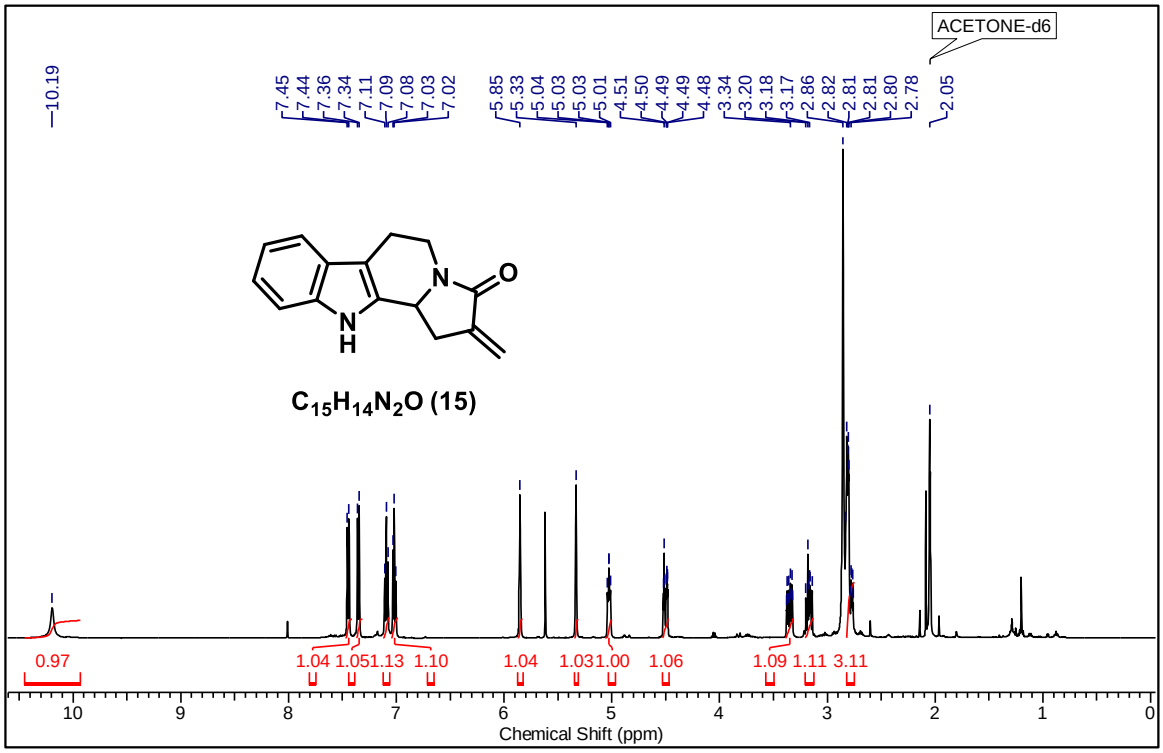
^{1}H NMR ($CDCl_3$, 200 MHz) of Compound 16



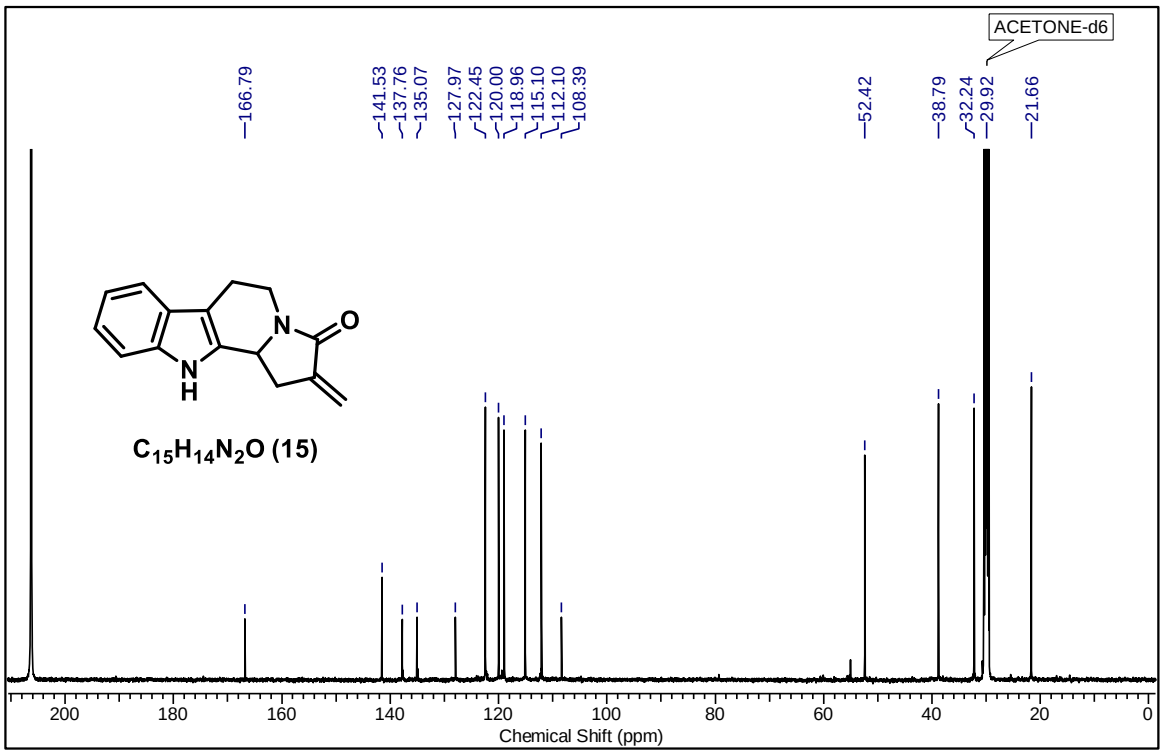
^{13}C NMR ($CDCl_3$, 50 MHz) of Compound 16



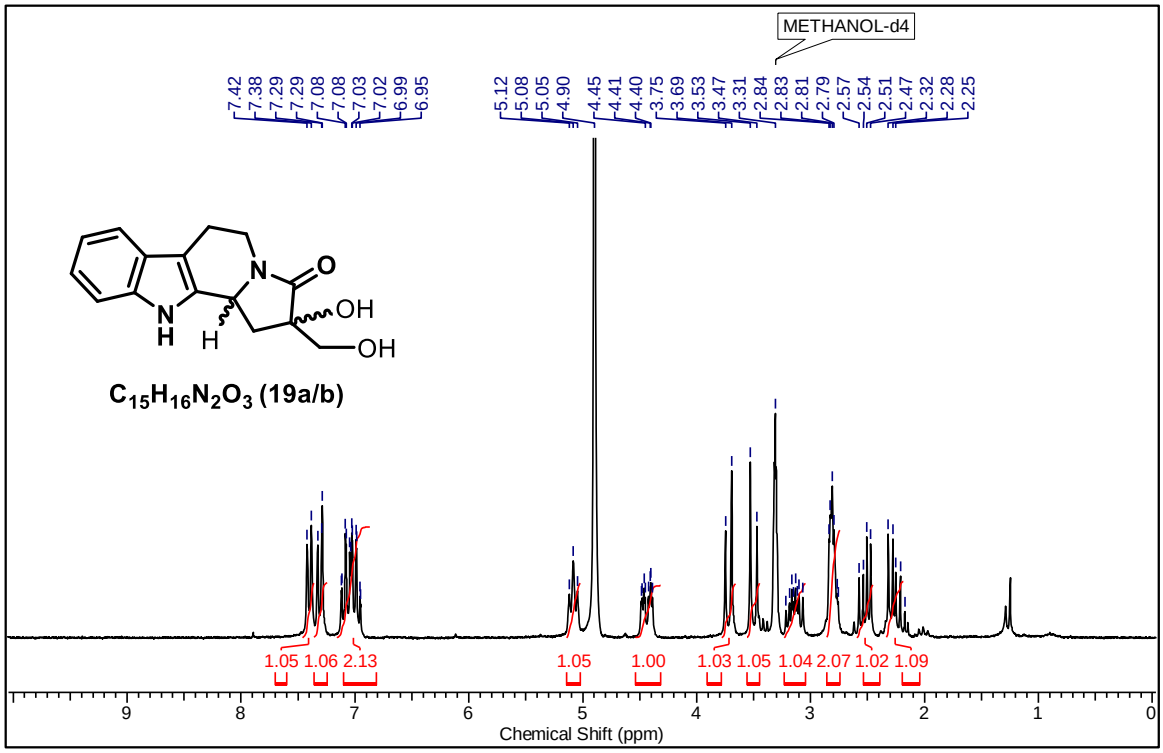
^{1}H NMR (Acetone-d_6, 500 MHz) of Compound 15



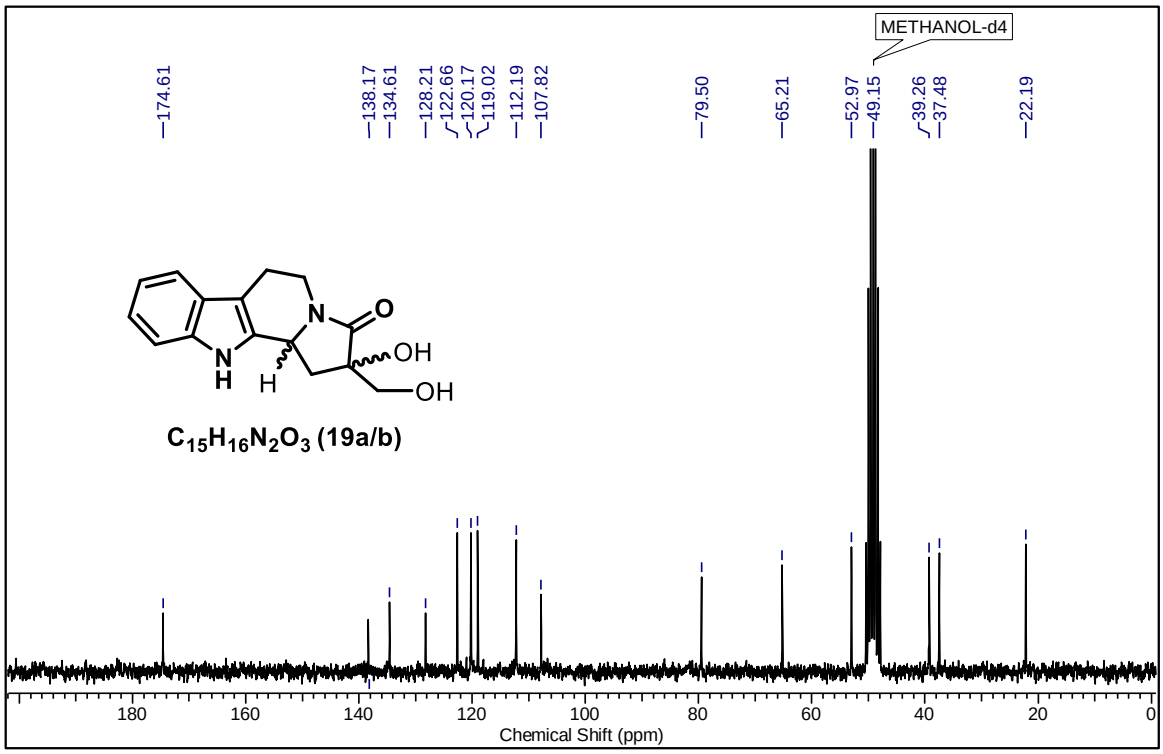
^{13}C NMR (Acetone-d_6, 125 MHz) of Compound 15



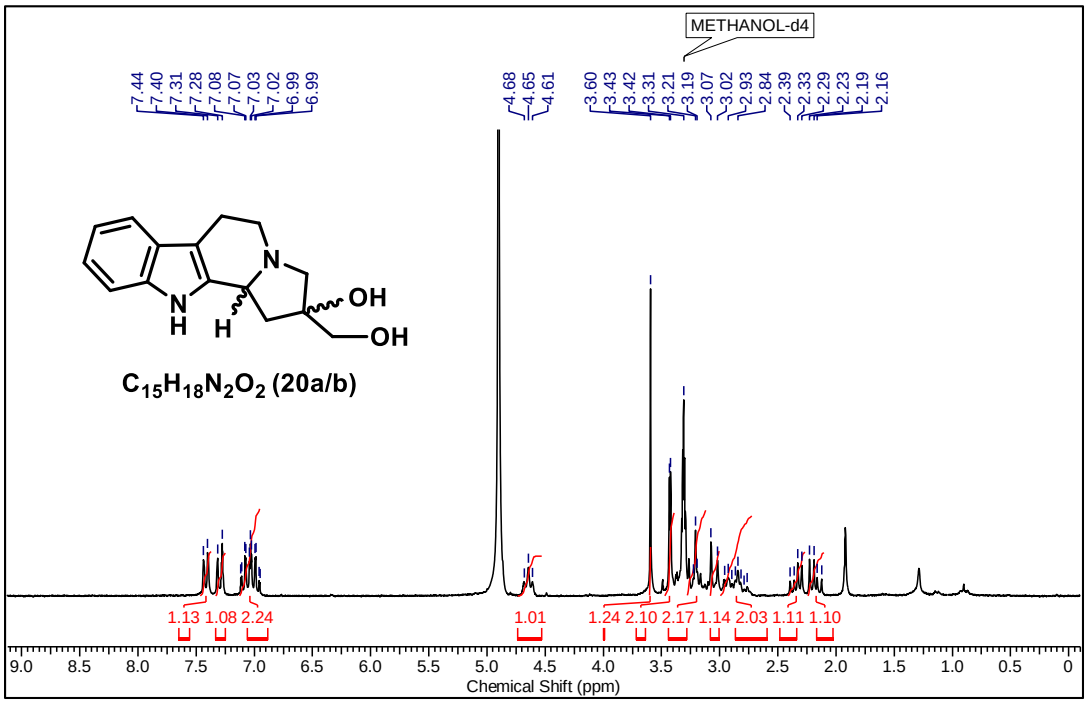
^{1}H NMR (CD_3OD, 200 MHz) of Compound 19a/b (Major isomer)



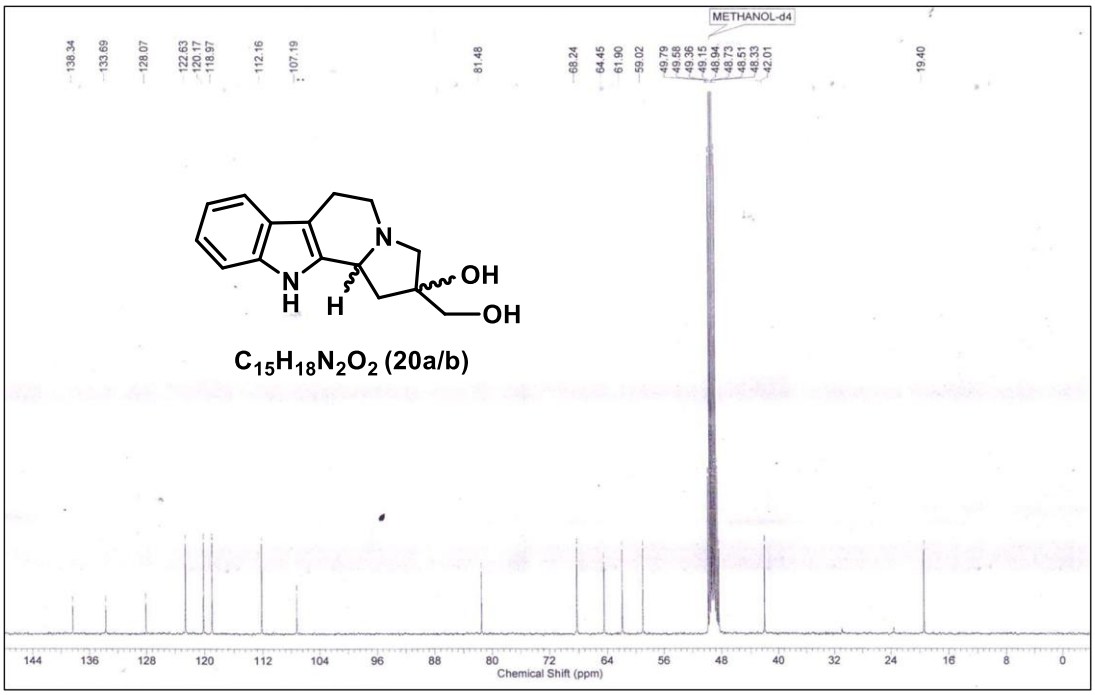
^{13}C NMR (CD_3OD, 50 MHz) of Compound 19a/b (Major isomer)



^{1}H NMR (CD_3OD, 200 MHz) of Compound 20a/b



^{13}C NMR (CD_3OD, 50 MHz) of Compound 20a/b



3B.6 References

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Chapter 3

Regioselective Reduction Reactions of Cyclic Imides Leading to Synthesis of Bioactive Alkaloids

Section 3C

In Progress Synthesis of *Erythrina* Alkaloid Erysotramidine

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

3C.1 Background

The *Erythrina* alkaloids are a structurally diversified group of natural tetracyclic products with a spiro-fused benzoisoquinoline structure in common (Figure 1). They are isolated from *Erythrina* plants prevalent in tropical and subtropical regions.[1] They have been utilized in traditional medicine and are known for their curare-like and hypnotic activities.[2] They also exhibit diverse pharmacological effects such as hypotensive, sedative, neuromuscular blocking actions, anticonvulsive properties and general CNS activity.[3-8] The *Erythrina* alkaloids are generally classified into two groups based on type of the D-rings as aromatic or non-aromatic (Figure 2).[1] Aromatic type example includes (+)-erysotramidine (**2**)/(+)-3-demethoxyerythratidinone (**3**) and non-aromatic example includes *β*-erythroidine (**4**)/(+)-cocculolidine (**5**). In recent decades, the *Erythrina* alkaloids have gained significant attention from the scientific community due to their unique biological properties and challenging tetracyclic skeleton with a quaternary carbon chiral center.[9-15]

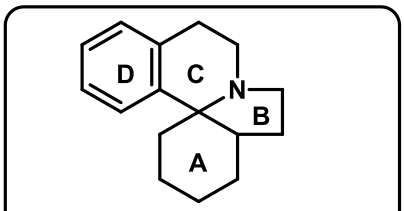


Figure 1. *Erythrina* tetracyclic core skeleton (**1**)

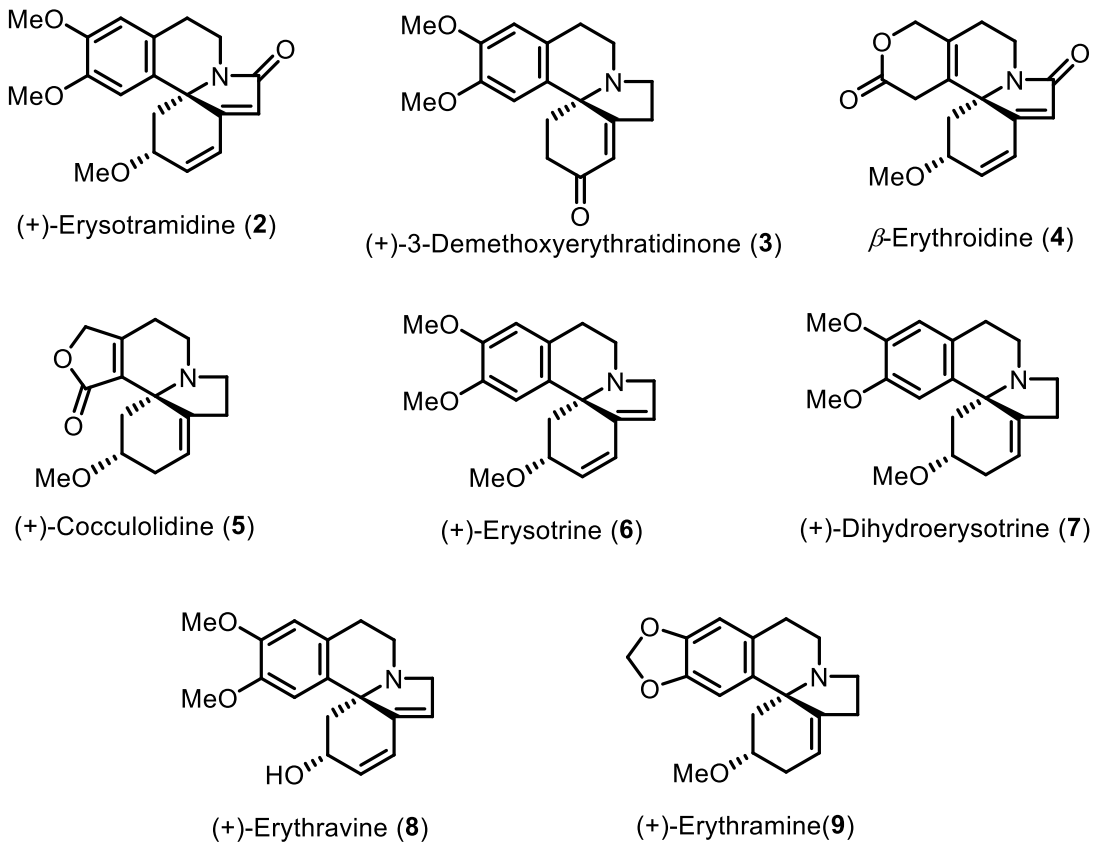


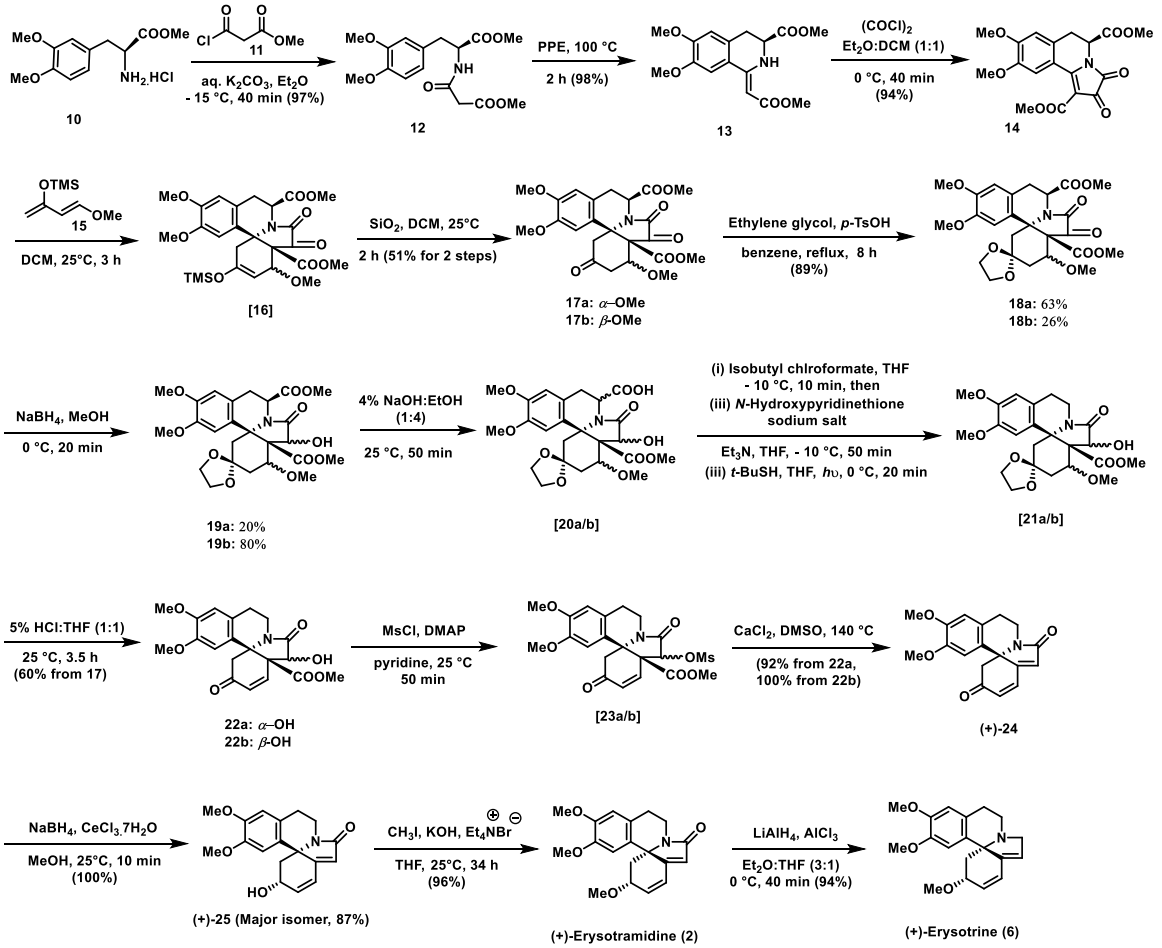
Figure 2. Some of the representative *Erythrina* alkaloids

In continuation of our studies on the total synthesis of recently isolated structurally interesting and biologically important natural products, we became interested in the total synthesis of erysotramidine (**2**) starting from citraconic anhydride. Regioselective reduction of citraconimide derivative followed by acid-catalyzed cyclization reaction would be the key steps.[16-20] Erysotramidine was islolated from the extract of *Erythrina arborescens* by Ito et al. in 1973.[21] In the literature, many different racemic, as well as enantioselective synthetic strategies have been developed to synthesize *Erythrina* alkaloids. We have summarized some of the selected recent approaches in the following part.[22-27]

3C.2 Synthetic Approaches Towards the Erysotramidine

(I) Tsuda and co-workers reported the first asymmetric synthesis of (+)-erysotramidine (**2**) and its deoxygenated product (+)-erysotrine (**6**) alkaloids from the chiral starting material (*S*)-3,4-dimethoxyphenylalaninemethyl ester by using asymmetric Diels-Alder reaction strategy under high pressure (Scheme 1).[28] The amide **12** was synthesized by reacting (*S*)-3,4-dimethoxyphenylalanine methyl ester hydrochloride (**10**) with methyl chloroformylacetate (**11**) in the presence of aqueous K_2CO_3 in diethyl ether with 97% yield. The amide **12** was first heated to 100 °C with polyphosphate ester (PPE) to produce compound **13** and then further treated with oxalyl chloride in dry Et_2O:CH_2Cl_2 (1:1) at room temperature to generate the dioxopyrroline **14** in 94% yield. The Diels-Alder reaction between 1-methoxy-3-trimethylsilloxybutadiene (**15**) and dioxopyrroline **14** at 25 °C, under a pressure of 10 kbar generated the intermediate **16**, which on treatment with silica gel (SiO_2) yielded the mixture of products **17a/b** in 51% yield. The mixture of **17a/b** was treated with the ethylene glycol in the presence of catalytic amount of *p*-TsOH in refluxing benzene to produce a mixture of ethylene acetals, which were separated by silica gel chromatography into the stereoisomers **18a/b** in 63/26% yield. $NaBH_4$ reduction of the stereoisomers **18a/b** in MeOH provided the compounds **19a/b** in 20/80% yield. Base-promoted selective hydrolysis of unhindered ester followed by its decarboxylation using Barton protocol[29] gave a mixture of **21a/b**. Acid hydrolysis of the **21a/b** generated the column chromatographically separated enones **22a/b** in 60% overall yield from **18a/b** and configuration of **22b** was confirmed by using the previously reported data.[30] Mesylation of both isomers **22a/b** followed by decarbomethoxylation using $CaCl_2$ in DMSO at 140 °C provided the same dienone compound (+)-**24** in excellent yields. Selective $NaBH_4$ reduction of dienone compound (+)-**24** resulted in the formation of

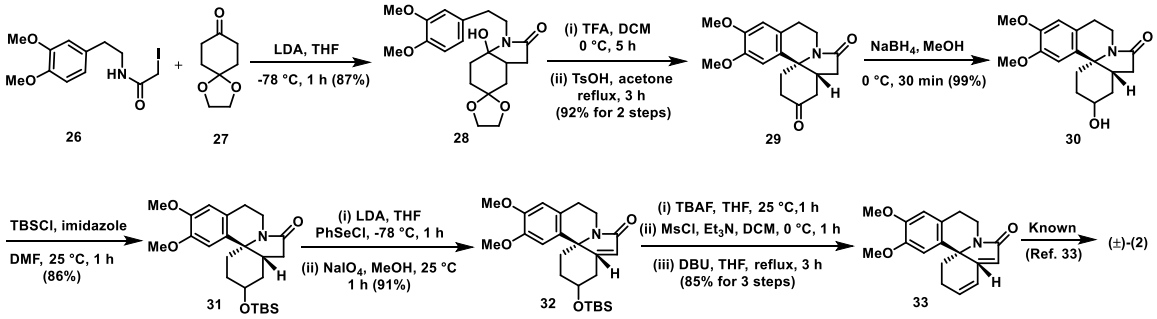
major isomer (+)-**25** in 87% yield. Base-induced methylation of (+)-**25** accomplished the total synthesis of (+)-erysotramidine (**2**) in 96% yield. Further complete reduction of the lactam moiety in (+)-erysotramidine using $LiAlH_4/AlCl_3$ provided them the deoxygenated product (+)-erysotrine (**6**) in 94% yield.



Scheme 1. Synthesis of (+)-Erysotramidine Using Diels-Alder Reaction

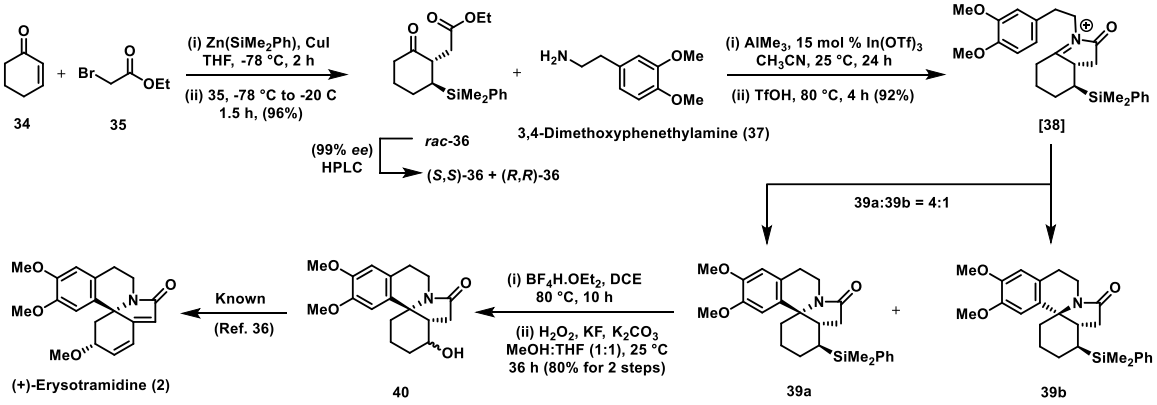
(II) Tu and co-workers developed a very efficient approach for the total synthesis of (±)-erysotramidine (**2**) via acid-mediated intramolecular cyclization reaction via iminium ion intermediate (Scheme 2).[31] The synthesis was initiated by the reaction of lithium enolate of ketone **27** with iodo amide **26** to generate the alkylated intermediate, which in situ attacks the carbonyl carbon of ketone to yield the lactamol product **28** in 87% yield. Acid-catalyzed intramolecular cyclization of lactamol **28** via iminium ion intermediate followed by TsOH-mediated acetal-deprotection in refluxing acetone furnished the tetracyclic ring compound **29** in 92% yield over two steps of the reaction.[32] Reduction of a ketone using $NaBH_4$ provided the alcohol **30** in quantitative yield, which was protected with the TBS group to obtain compound **31** in 86% yield. LDA-induced selenation of

lactam **31** and then, oxidative elimination of the generated selonoxide intermediate using $NaIO_4$ produced the unsaturated lactam **32** in 91% yield over two steps. TBAF-mediated deprotection of the TBS group in **32** formed the corresponding secondary alcohol, which was treated with MsCl to yield the mesylate intermediate. Finally, the elimination of mesyl group using DBU provided the known intermediate **33** in 85% yield over three steps. The total synthesis of (±)-erysotramidine (**2**) is known in the literature from intermediate **33**, via allylic oxidation followed by methylation of the generated alcohol.[33]



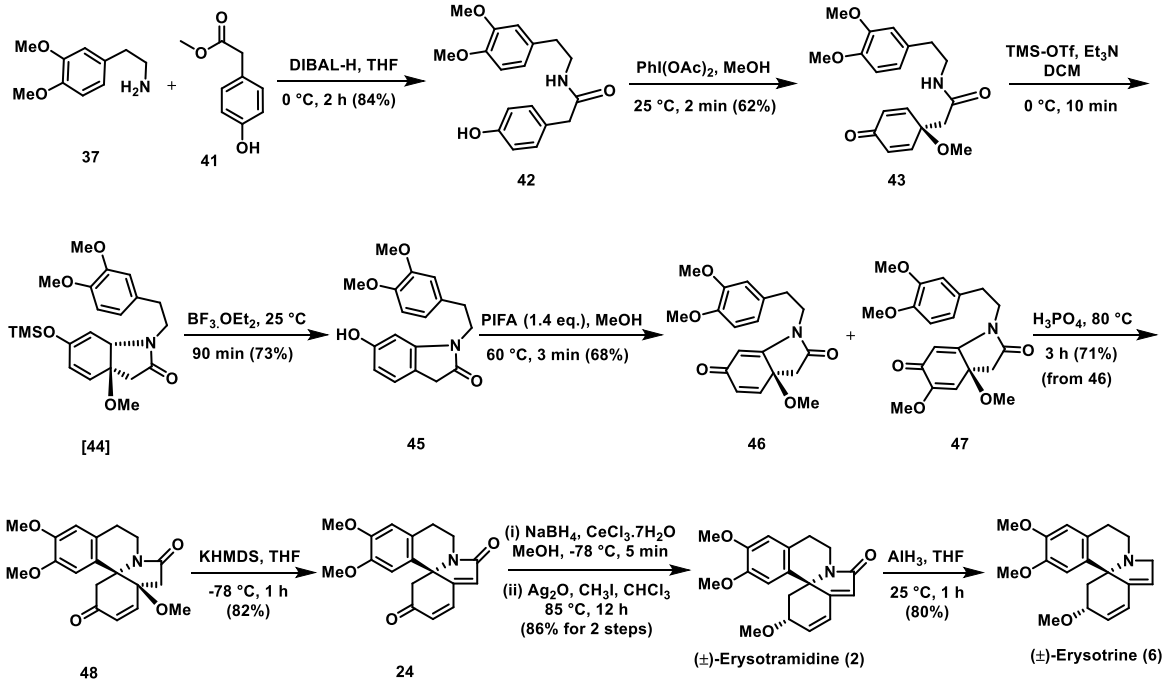
Scheme 2. Efficient Total Synthesis of (±)-Erysotramidine

(III) Tietze and co-workers reported the synthesis of (+)-erysotramidine by applying the one-pot domino reaction strategy (Scheme 3).[34] Oestreich protocol was followed to prepare cyclohexanone derivative **36** in which a conjugate addition of the silyl zincate to cyclohexenone (**34**) in the presence of catalytic amounts of CuI generated the enolate intermediate. Then in situ reaction of enolate intermediate with ethyl bromoacetate (**35**) delivered the required starting material ketoester **36** in 96% yield as a single diastereomer with *trans*-configuration.[35] Resolution of ketoester **36** on a chiral stationary phase provided the (*S*,*S*)-**36** and (*R*,*R*)-**36** with >99% *ee*. The ketoester (*S*,*S*)-**36** was treated with the phenylethylamine derivative **37** in the presence of two equivalents of $AlMe_3$ and 15 mol% of indium triflate in acetonitrile for 24 h. Then the addition of triflic acid generated iminium ion intermediate **38**, which underwent in situ cyclization to provide the desired spirocyclic compounds **39a/b** in 92% yield (*dr* 4:1). The two diastereomers **39a/b** were easily separated by column chromatography on silica gel. Finally, the Tamao-Fleming oxidation reaction was used to synthesize the alcohol **40**. The reaction of silane compound **39a** with tetrafluoroboric acid diethyl ether solution at 80 °C under microwave irradiation formed the fluoro silane intermediate, which was treated with H_2O_2 in the presence of KF to provide the alcohol **40** in 80% yield (*dr* 9:1). The transformation of intermediate **40** into (+)-erysotramidine (**2**) is known in the literature.[36]



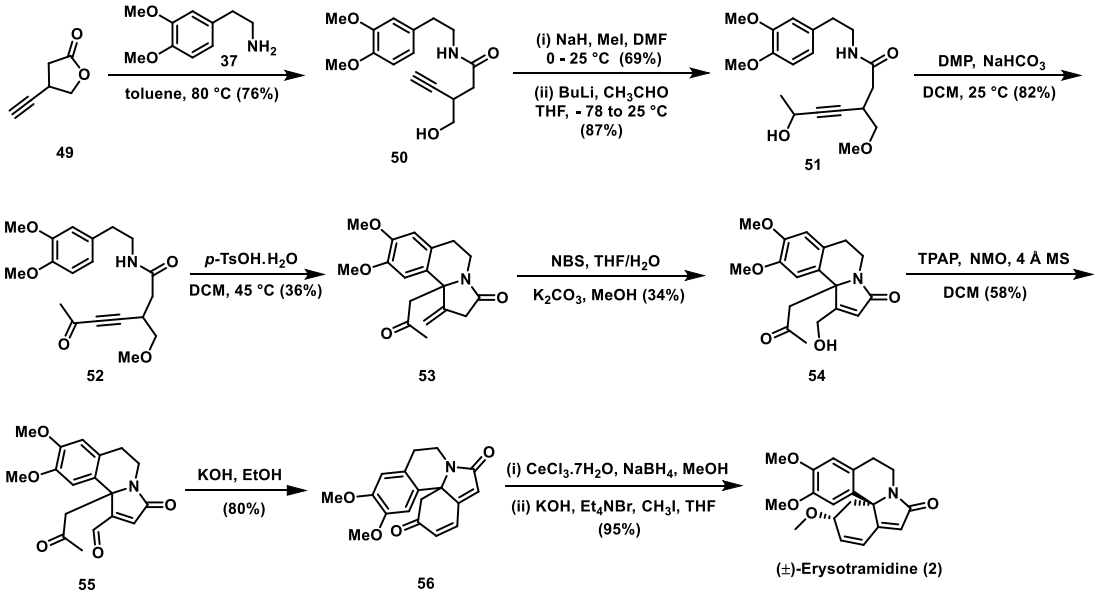
Scheme 3. Synthesis of (+)-Erysotramidine via Domino Process

(IV) Sylvain Canesi et al. published the diastereoselective synthesis of (±)-erysotramidine (**2**) and its deoxygenated product (±)-erysotrine (**6**) starting from the reaction between phenol and phenylethylamine derivative (Scheme 4).[37] The approach relies on the oxidative phenol dearomatizations controlled by a hypervalent iodine reagent. The synthesis started with the DIBAL-H promoted an amide linkage reaction between the laboratory-available chemicals phenylethylamine **37** and phenol ester **41** to yield a coupling product **42** in 84% yield.[38] The treatment of amide **42** with (diacetoxyiodo)benzene in methanol initiated the first oxidative dearomatization, which resulted in the functionalized dienone **43** in 62% yield. TMS-OTf was used to activate the enone functionality of dienone **43** resulting in the bicyclic intermediate **44**, which was then treated with Lewis acid to produce the aromatic compound **45** in 73% yield. Bis(trifluoroacetoxy)iodobenzene (PIFA) induced second oxidative dearomatization resulted in a separable mixture of the required dienone **46** and byproduct **47** having one extra methoxy group, in 68% yield with acceptable ratio of 3.5:1. Acid-catalyzed intramolecular cyclization of dienone **46** provided the tetracyclic product **48** in 71% yield via iminium ion intermediate. Tetracyclic compound **48** was reacted with KHMDS to provide the compound **24** in 82% via an E1cB mechanism. Luche reduction of the polyconjugated compound **24** provided the desired alcohol with high diastereoselectivity of 9:1. Methylation of the generated alcohol with methyl iodide in the presence of Ag_2O furnished the natural product (±)-erysotramidine (**2**) in 86% yield over two steps. (±)-Erysotramidine (**2**) was then treated with AlH_3 to give erysotrine (±)-(**6**) in 80% yield.



Scheme 4. Synthesis of (±)-Erysotramidine via Oxidative Phenol Dearomatization Reaction

(V) Xuegong She and co-worker developed an acid-promoted cascade cyclization reaction to synthesize (±)-erysotramidine (Scheme 5).[27]



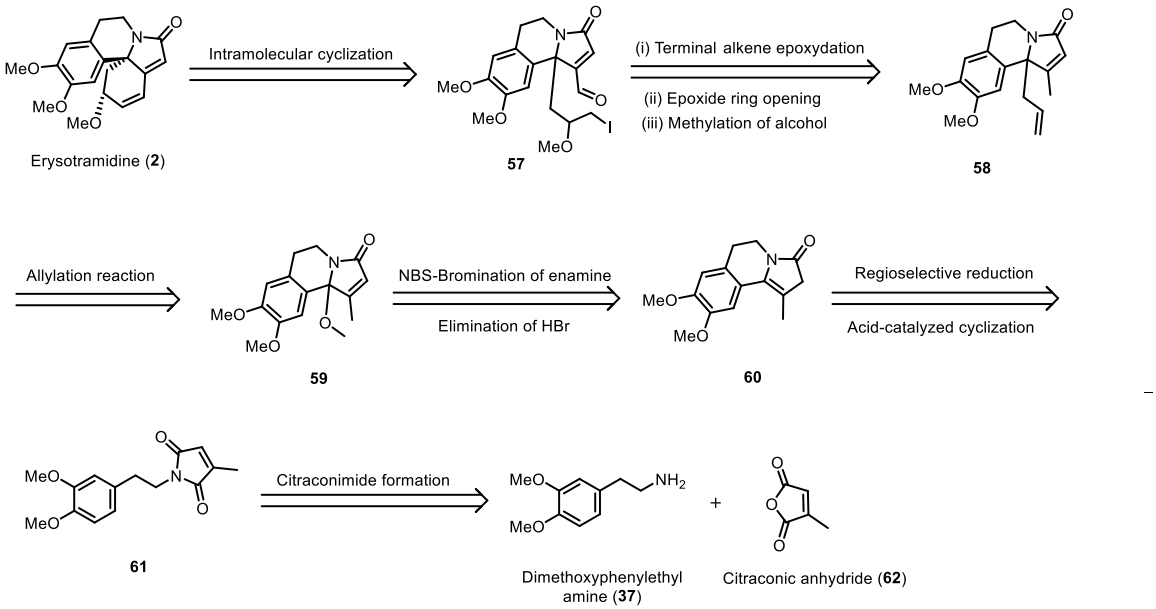
Scheme 5. Synthesis of (±)-Erysotramidine via Acid-Promoted Cascade Cyclization Reaction

Reaction of 3,4-dimethoxyphenethylamine (**37**) with laboratory synthesized lactone **49** in heating toluene at 80 °C provided the alkyne amide **50** in 97% yield. The free primary alcohol was methylated using methyl iodide, which was followed by acetylation reaction

of terminal alkyne yielding secondary alcohol **51** in 87% yield. DMP-induced oxidization of secondary alcohol **51** provided the key intermediate **52** for the cascade cyclization reaction, in 82% yield. *p*-TsOH acid-promoted cyclization-elimination product **53** was generated in 36% yield through the cascade cyclization reaction. NBS in THF/H_2O reaction was used to form the primary allylic alcohol, which was further oxidized to the aldehyde **55** in 58% yield. Intramolecular aldol cyclization reaction of compound **55** afforded the tetracyclic product **56** in 80% yield. Finally, Luche reduction of conjugated ketone compound **56** generated the alcohol and the subsequent methylation furnished (±)-erysotramidine (**2**) in 95% yield.

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

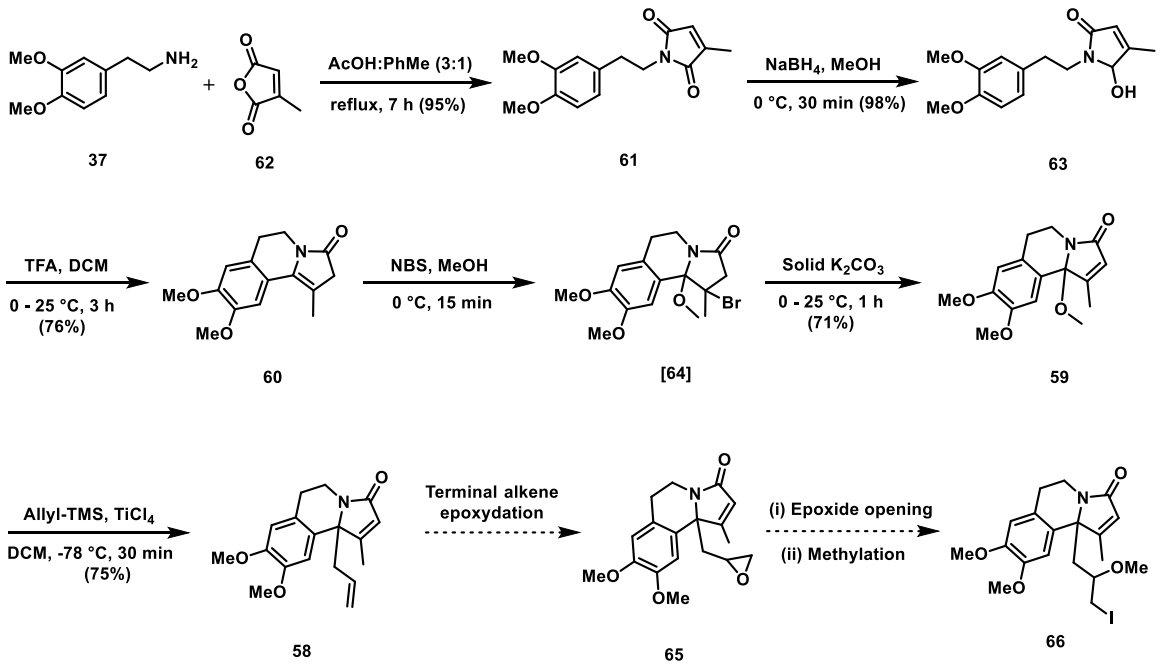
The synthesis of erysotramidine (**2**) from readily available starting precursors 3,4-dimethoxyphenylethyl amine (**37**) and citraconic anhydride (**62**) was planned using a systematic strategy. A concise retrosynthetic analysis has been shown in scheme 6. The regioselective reduction of citraconimide derivative, acid-catalyzed intramolecular cyclization reaction and formation of an active quaternary center were the synthetic challenges in our approach.

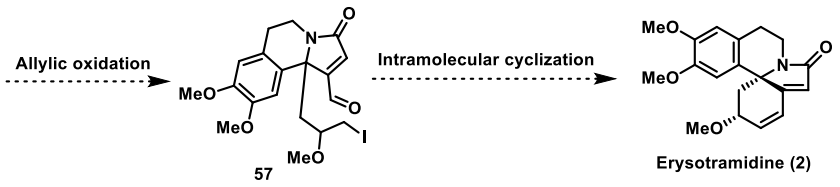


Scheme 6. Concise Retrosynthetic Analysis of Erysotramidine

The condensation reaction of 3,4-dimethoxyphenethylamine (**37**) with citraconic anhydride (**62**) in refluxing AcOH:PhMe (3:1) mixture furnished the citraconimide derivative **61** in 95% yield via intramolecular dehydrative cyclization reaction (Scheme

7). $NaBH_4$ induced regioselective reduction of citraconimide derivative **61** in MeOH at 0 °C exclusively generated the lactamol product **63** in 98% yield via complexing of boron with unhindered carbonyl followed by intramolecular hydride transfer to the hindered side of the carbonyl group of citraconimide derivatives **61**. TFA-promoted intramolecular cyclization reaction of lactamol product **63** provided the enamine compound **60** in 76% yield via formation of iminium ion intermediate and in situ migration of the less substituted conjugated double bond to the more substituted side of the compound. The enamine compound **60** was treated with NBS in MeOH at 0 °C to form the bromo intermediate **64**, which on further treatment with K_2CO_3 delivered the required active quaternary methoxy center containing conjugated imide product **59** in 71% yield. $TiCl_4$-catalyzed allylation of the compound **59** in DCM at -78 °C produced the compound **58** in 75% yield via formation of the iminium ion intermediate. We intend to continue our synthesis by performing an epoxidation reaction on the terminal alkene to produce compound **65**. Epoxide ring opening reaction of compound **65** to generate the secondary alcohol, which can then be converted to the methoxy compound **66**. We hope that allylic oxidation of compound **66** followed by intramolecular ring-closing reaction will provide the final product erysotramidine (**2**). All efforts in this direction are in progress in our laboratory.





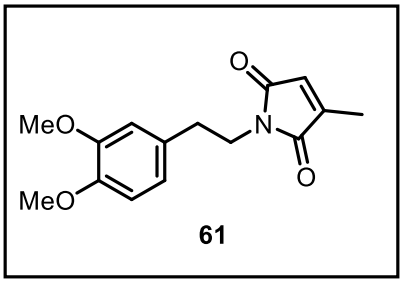
Scheme 7. Towards the Synthesis of (±)-Erysotramidine

3B.4 Summary

In conclusion, we feel that 3,4-dimethoxyphenethylamine and citraconic anhydride are the suitable starting materials for the synthesis of Erythrina alkaloid erysotramidine. Important steps in the synthesis include regioselective reduction of citraconimide derivative, acid-catalyzed intramolecular cyclization and in situ migration of the conjugated double bond to the more substituted side of the compound to yield enamine product. The NBS strategy was carefully planned to produce the requisite active quaternary methoxy center and conjugated imide in one pot. Using our proposed approach, we feel that we will be in a position to complete the total synthesis of the final product over the next few months' time.

3C.5 Experimental Section

1-(3,4-Dimethoxyphenethyl)-3-methyl-1H-pyrrole-2,5-dione (61).



61

To a solution of dimethoxyphenylethyl amine (**37;** 2 g, 11.04 mmol) in AcOH:PhMe (30 mL, 3:1) was added citraconic anhydride (**62;** 1.24 g, 11.04 mmol) and the stirring reaction mixture was refluxed for 7 h. The reaction mixture was concentrated in vacuo after attaining room temperature. The obtained residue was dissolved in EtOAc. The organic layer was washed with saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained product was purified by using column chromatography (silica gel, 60−120 mesh, EtOAc−PE, 3:7) to furnish pure citraconimide **61** as a white solid (2.85 g, 95% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (d, J = 1.7 Hz, 3 H), 2.80–2.86 (m, 2 H), 3.67–3.74 (m, 2 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 6.28 (q, J = 1.6 Hz, 1 H), 6.70–6.80 (m, 3 H).

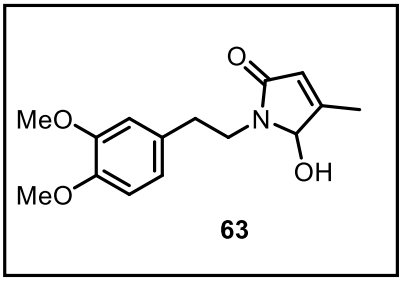
^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.9, 34.1, 39.1, 55.8 (2 C), 111.1, 111.8, 120.7, 127.2, 130.4, 145.5, 147.6, 148.8, 170.7, 171.6.

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{18}O_4N$ 276.1230, found 276.1233.

IR ($CHCl_3$) ν_{max} 1715, 1705, 1650 cm^{-1}.

Mp 156−158 °C.

1-(3,4-Dimethoxyphenethyl)-5-hydroxy-4-methyl-1,5-dihydro-2H-pyrrol-2-one (63).



63

To a solution of imide **61** (1.0 g, 3.63 mmol) in MeOH (15 mL) at 0 °C was added $NaBH_4$ (165 mg, 4.36 mmol) and it was stirred for 30 minutes. The formed reaction mixture was concentrated in vacuo and the product was diluted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo provided crude product and its

column chromatographic purification (silica gel, 60–120 mesh, EtOAc–PE, 1:1) furnished pure compound **63** as white solid (890 mg, 98% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (d, J = 1.4 Hz, 3 H), 2.84 (t, J = 7.3 Hz, 2 H), 3.12 (d, J = 11.4 Hz, 1 H), 3.42–3.51 (m, 1 H), 3.72 (dt, J = 14.0, 7.2 Hz, 1 H), 3.85 (s, 6 H), 4.86 (d, J = 11.3 Hz, 1 H), 5.71 (d, J = 1.5 Hz, 1 H), 6.72–6.76 (m, 2 H), 6.76–6.81 (m, 1 H).

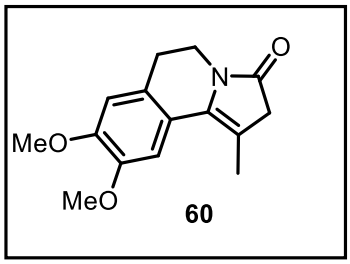
^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 34.2, 40.9, 55.9 (2 C), 85.4, 111.3, 111.9, 120.6, 122.5, 131.4, 147.6, 148.9, 157.8, 170.2.

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{20}O_4N$ 278.1387, found 278.1388.

IR ($CHCl_3$) ν_{max} 3350, 1720, 1680 cm^{-1}.

Mp 148−150 °C.

8,9-Dimethoxy-1-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-3(2H)-one (60).



60

To a stirred solution of lactamol **63** (1 g, 3.61 mmol) in DCM (15 mL) at 0 °C was added TFA (0.62 mL, 5.41 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 3 h and allowed to reach room temperature. The reaction mixture was concentrated in vacuo and the formed product was dissolved in EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by column chromatographic purification of the obtained residue (silica gel, 60–120 mesh, EtOAc–PE, 6:4) afforded pure lactam **60** as a grey solid (715 mg, 76% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3 H), 2.85 (t, J = 5.8 Hz, 2 H), 3.18 (s, 2 H), 3.68 (t, J = 5.8 Hz, 2 H), 3.91 (s, 6 H), 6.73 (s, 1 H), 7.13 (s, 1 H).

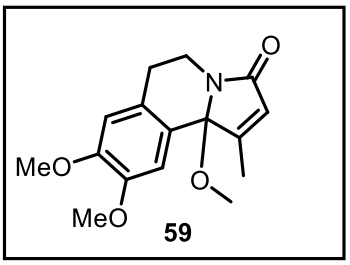
^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 29.5, 37.2, 43.5, 55.9, 56.0, 107.3, 109.4, 111.3, 120.6, 127.9, 131.9, 147.7, 148.7, 174.5.

HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{18}O_3N$ 260.1281, found 260.1286.

IR ($CHCl_3$) ν_{max} 3077, 1735, cm^{-1}.

Mp 164-166 °C.

8,9,10b-Trimethoxy-1-methyl-6,10b-dihydropyrrolo[2,1-a]isoquinolin-3(5H)-one (59).



59

To a stirred solution of compound **60** (500 mg, 1.93 mmol) in MeOH (15 mL) at 0 °C was added NBS (412 mg, 2.31 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 15 minutes then solid K_2CO_3 (400 mg, 2.89 mmol) was added to the reaction mixture. The reaction mixture was stirred for 1 h and allowed to reach room temperature. The reaction mixture was concentrated in vacuo and the formed product was dissolved in EtOAc. The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by column chromatographic purification of the obtained residue by using (silica gel, 60–120 mesh, EtOAc–PE, 8:2) gave pure methoxy lactam **59** as a brown solid (715 mg, 76% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22 (d, J = 1.5 Hz, 3 H), 2.55 (dd, J = 16.0, 2.5 Hz, 1 H), 2.83–2.93 (m, 1 H), 3.06–3.13 (m, 1 H), 3.15 (s, 3 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 4.31 (ddd, J = 13.0, 5.57, 1.3 Hz, 1 H), 5.93 (q, J = 1.4 Hz, 1 H), 6.62 (s, 1 H), 7.07 (s, 1 H).

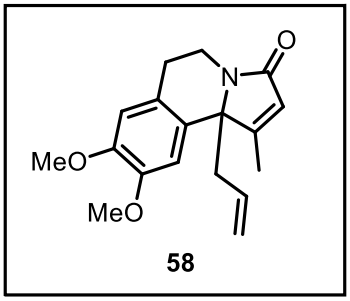
^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 29.4, 36.0, 49.9, 55.9, 56.0, 91.8, 110.3, 111.4, 124.5, 125.7, 128.3, 147.7, 149.2, 159.6, 171.3.

HRMS (ESI) $[M + H]^+$ calcd for for $C_{16}H_{20}O_4N$ 290.1387, found 290.1386.

IR ($CHCl_3$) ν_{max} 1730, 1685 cm^{-1}.

Mp 154−156 °C.

10b-Allyl-8,9-dimethoxy-1-methyl-6,10b-dihydropyrrolo[2,1-a]isoquinolin-3(5H)-one (58).



58

To a stirred solution of compound **59** (300 mg, 1.03 mmol) in DCM (15 mL) at -78 °C was added $TiCl_4$ (0.19 mL, 1.03 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 15 minutes, then allyl-TMS (0.14 mL, 1.24 mmol) was added to the reaction mixture. The reaction mixture was stirred for 30 minutes at same temperature. The reaction mixure was quenched with saturated $NaHCO_3$ solution

and concentrated in vacuo. The formed product was dissolved in EtOAc and organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by column chromatographic purification of the obtained residue (silica gel, 60–120 mesh, EtOAc–PE, 8:2) furnished allylic lactam **58** as a red solid (232 mg, 75% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (d, J = 1.5 Hz, 3 H), 2.59 (dd, J = 15.6, 3.1 Hz, 1 H), 2.66–2.80 (m, 2 H), 2.92 (ddd, J = 15.7, 12.1, 6.0 Hz, 1 H), 3.85 (s, 3 H), 3.91 (s, 3 H), 4.39–4.51 (m, 1 H), 5.01–5.15 (m, 2 H), 5.35–5.54 (m, 1 H), 5.88 (d, J = 1.4 Hz, 1 H), 6.63 (s, 1 H), 6.86 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0, 29.9, 35.8, 42.4, 55.8, 56.3, 69.5, 109.3, 112.2, 118.7, 123.8, 127.1, 128.3, 131.3, 147.4, 148.2, 161.8, 171.5.

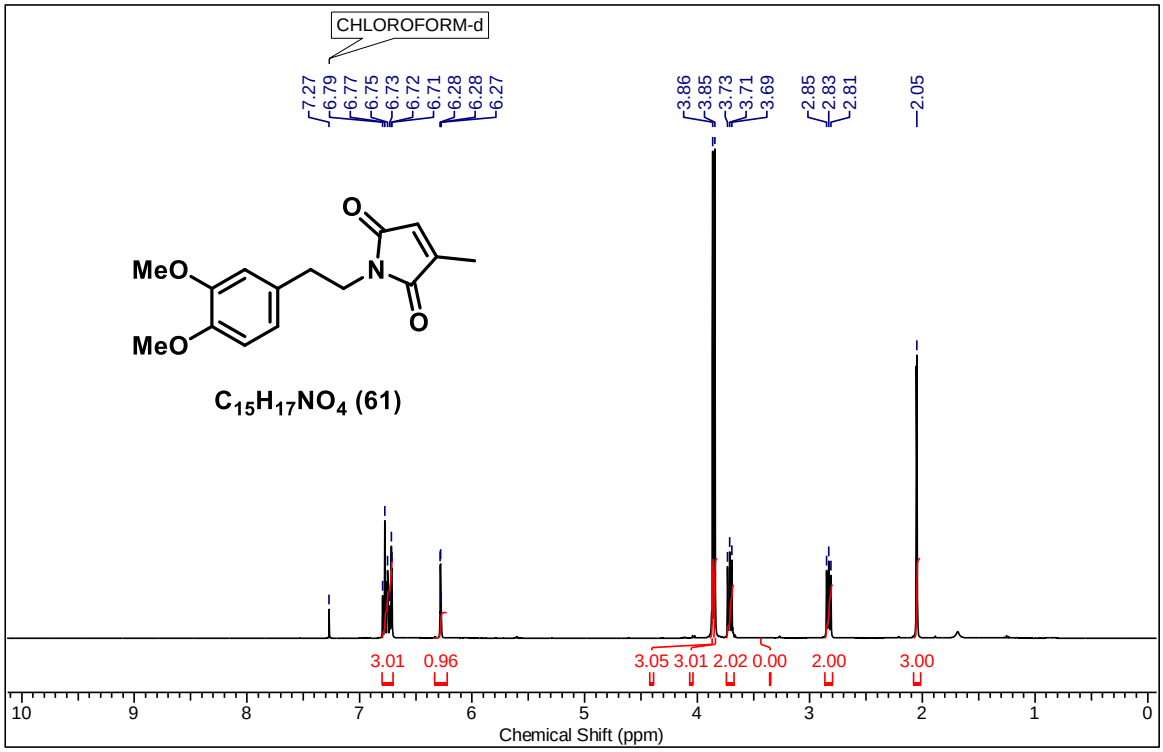
HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{22}O_3N$ 300.1594, found 300.1597.

IR ($CHCl_3$) ν_{max} 1740, 1680, 1596 cm^{-1}.

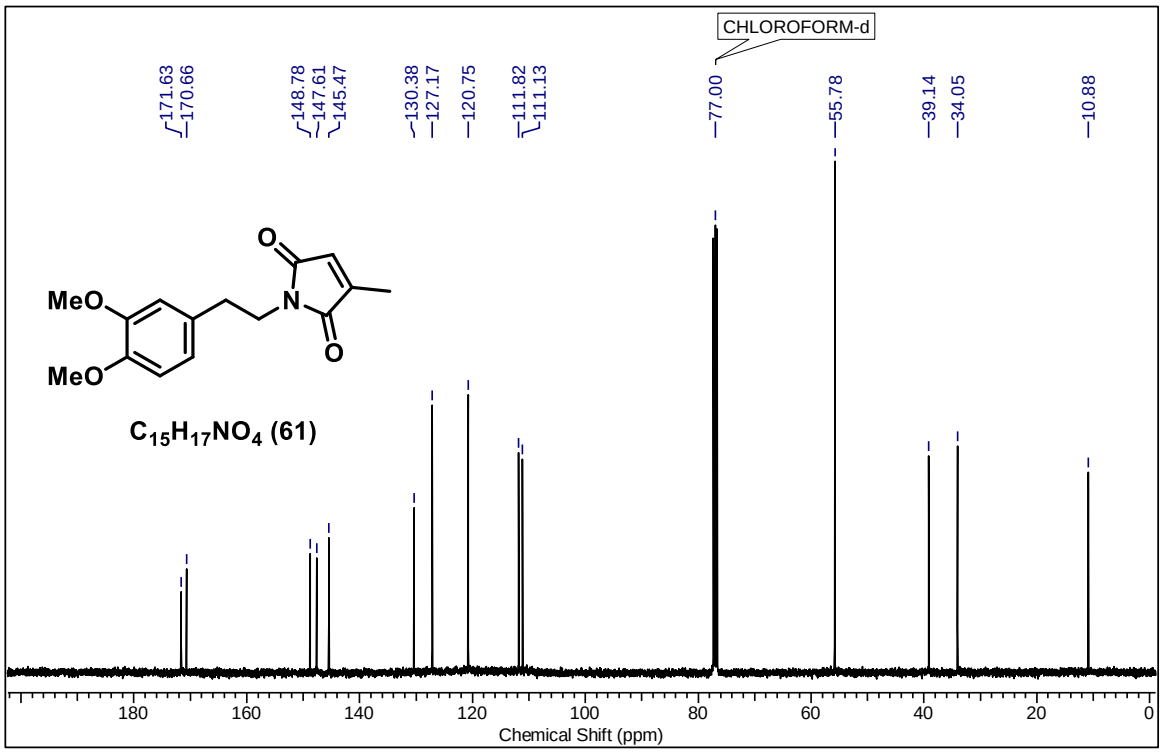
Mp 144−146 °C.

3C.6 NMR Spectra of the Obtained Products

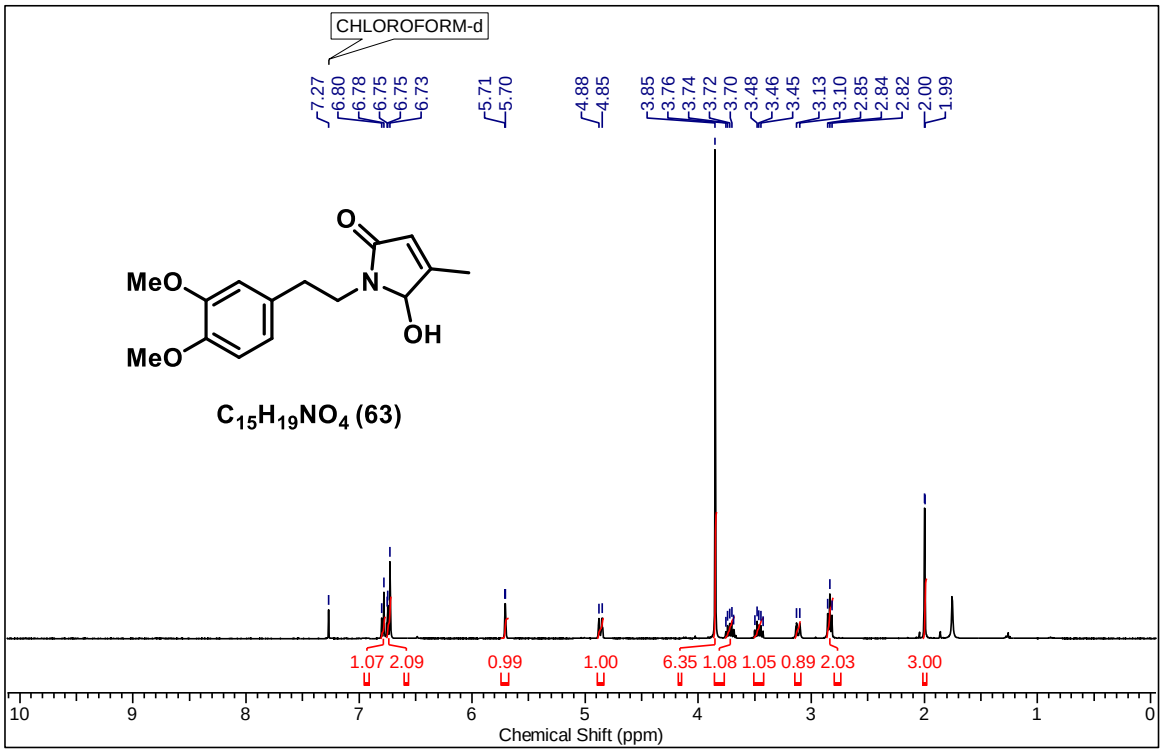
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 61



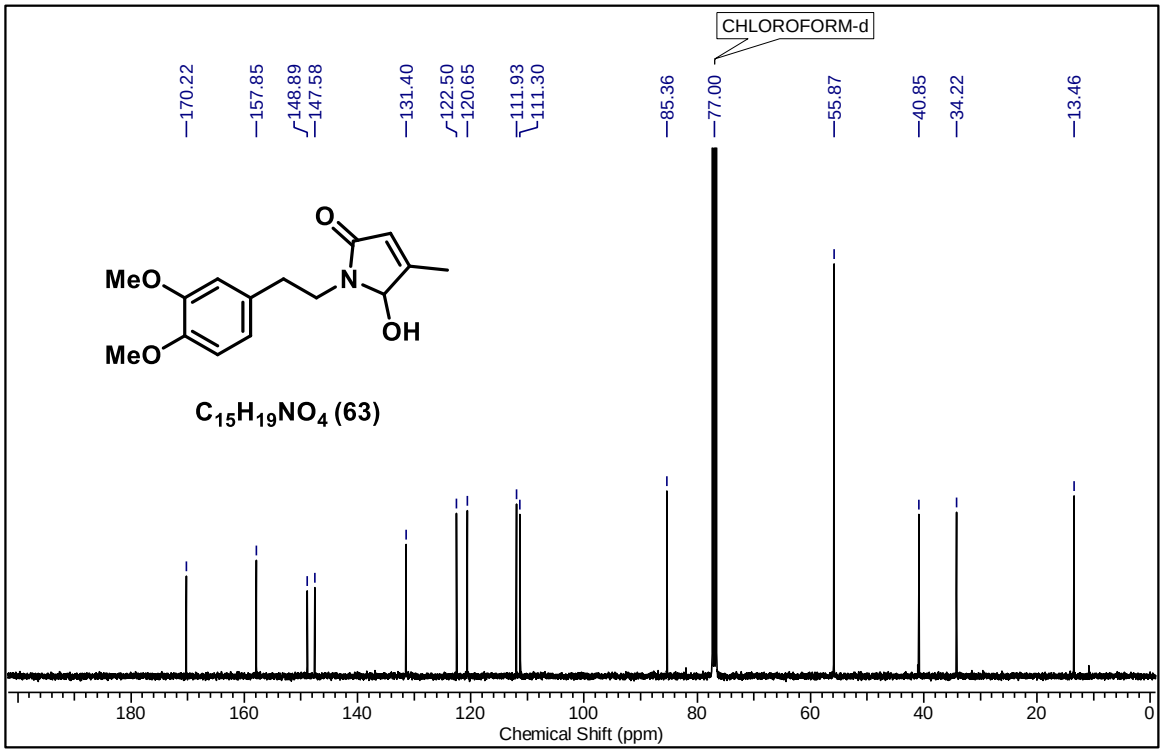
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 61



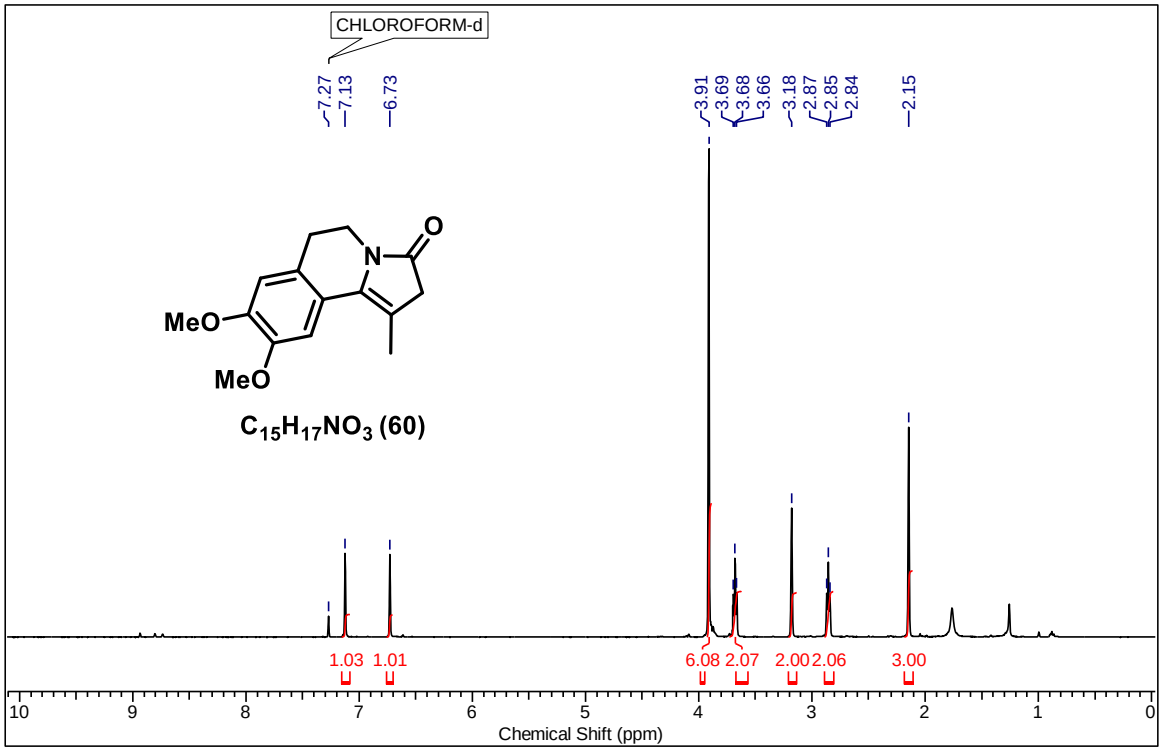
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 63



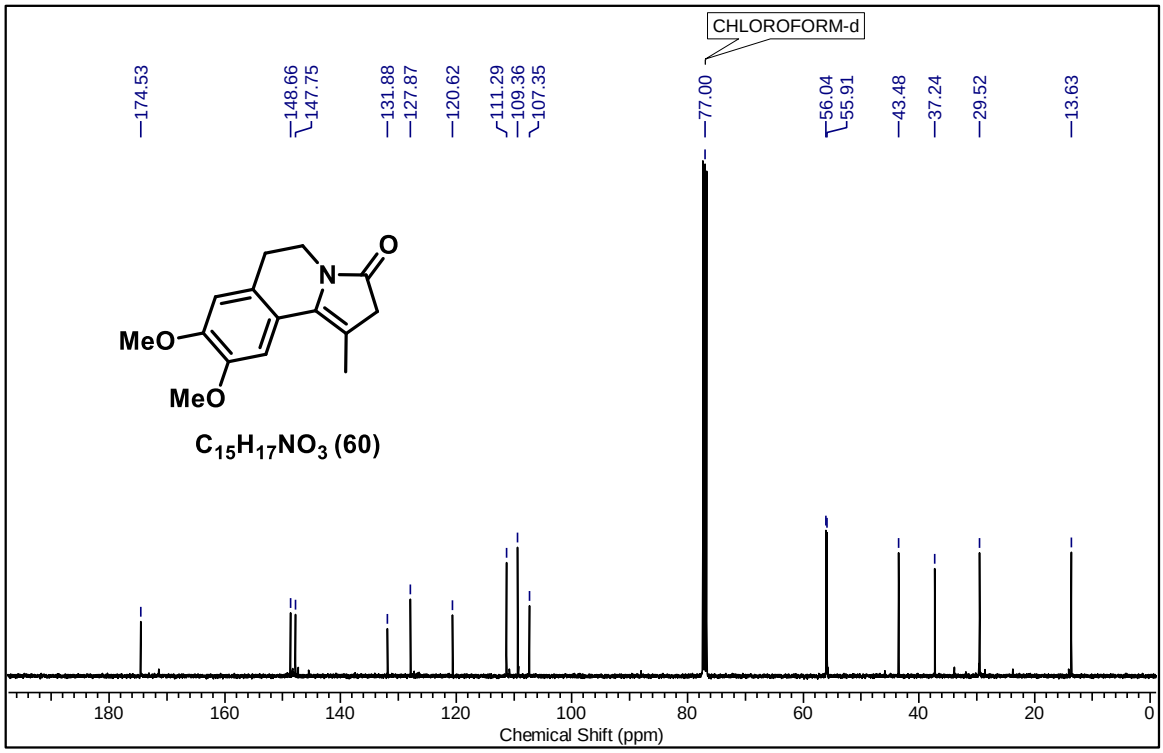
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 63



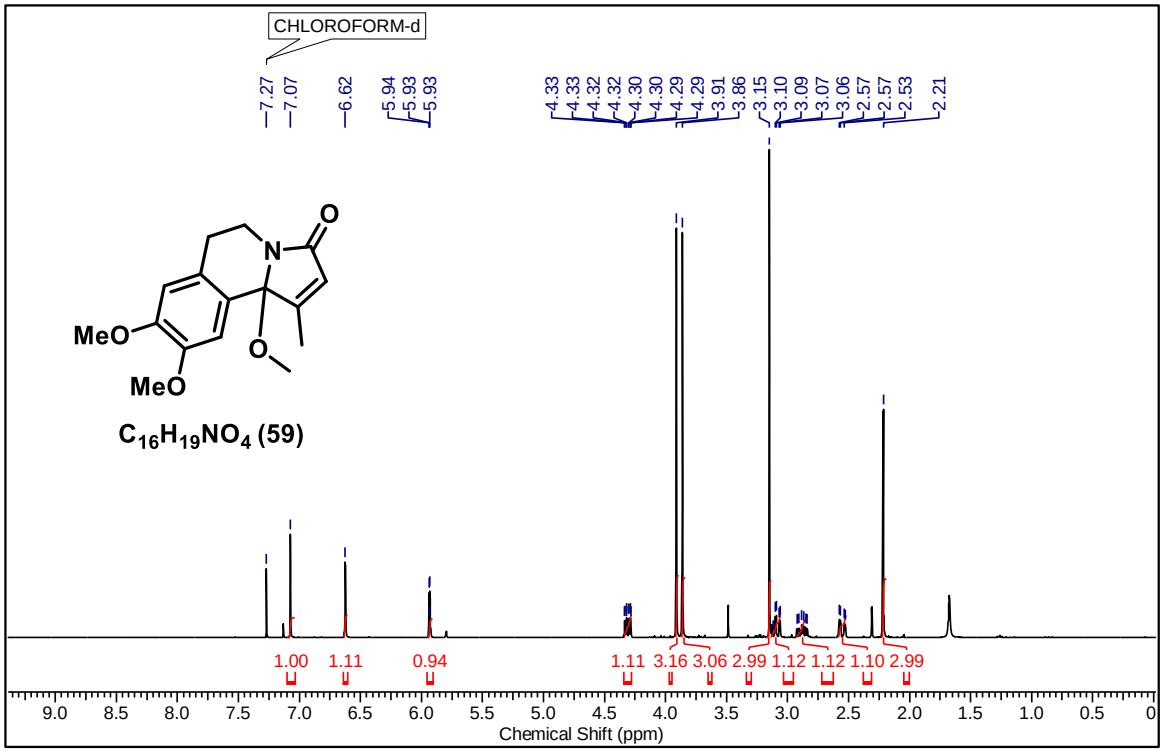
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 60



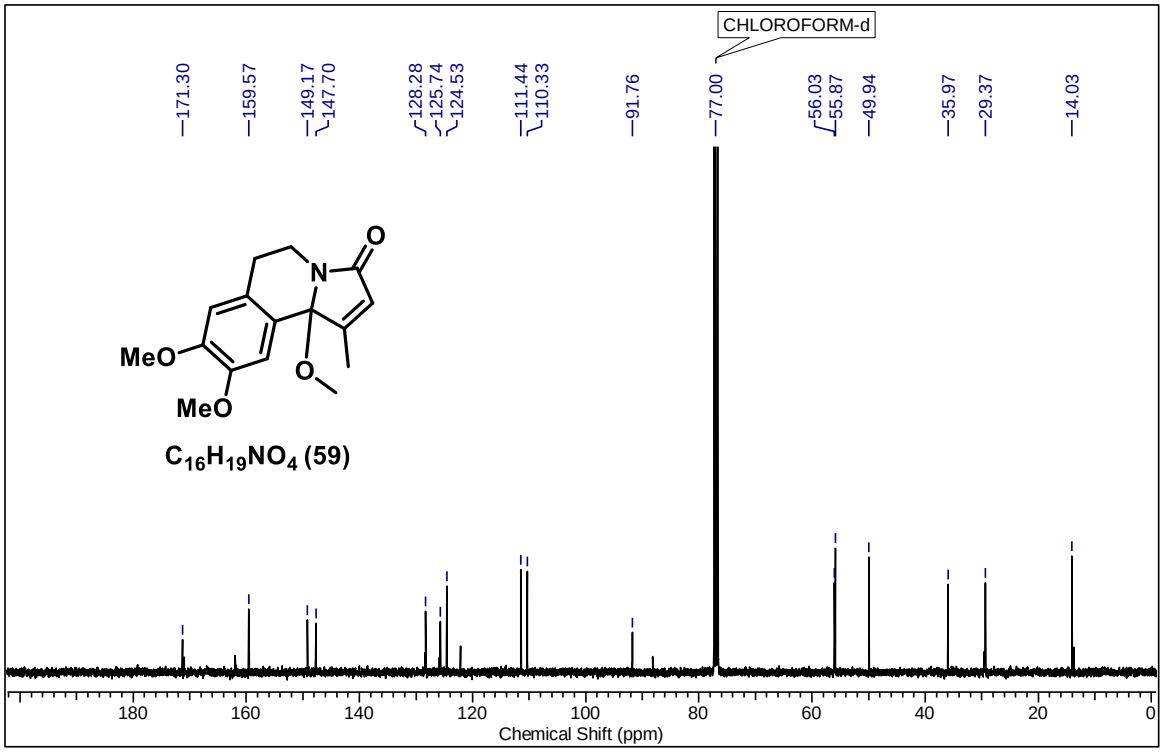
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 60



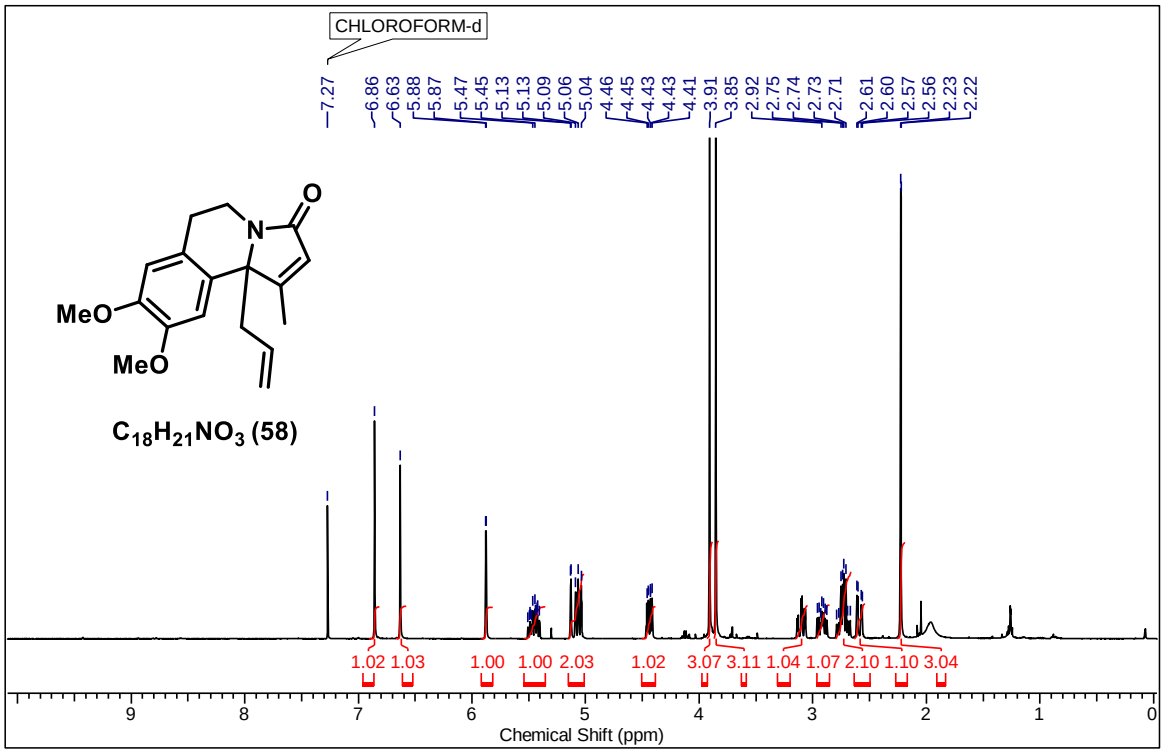
^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 59



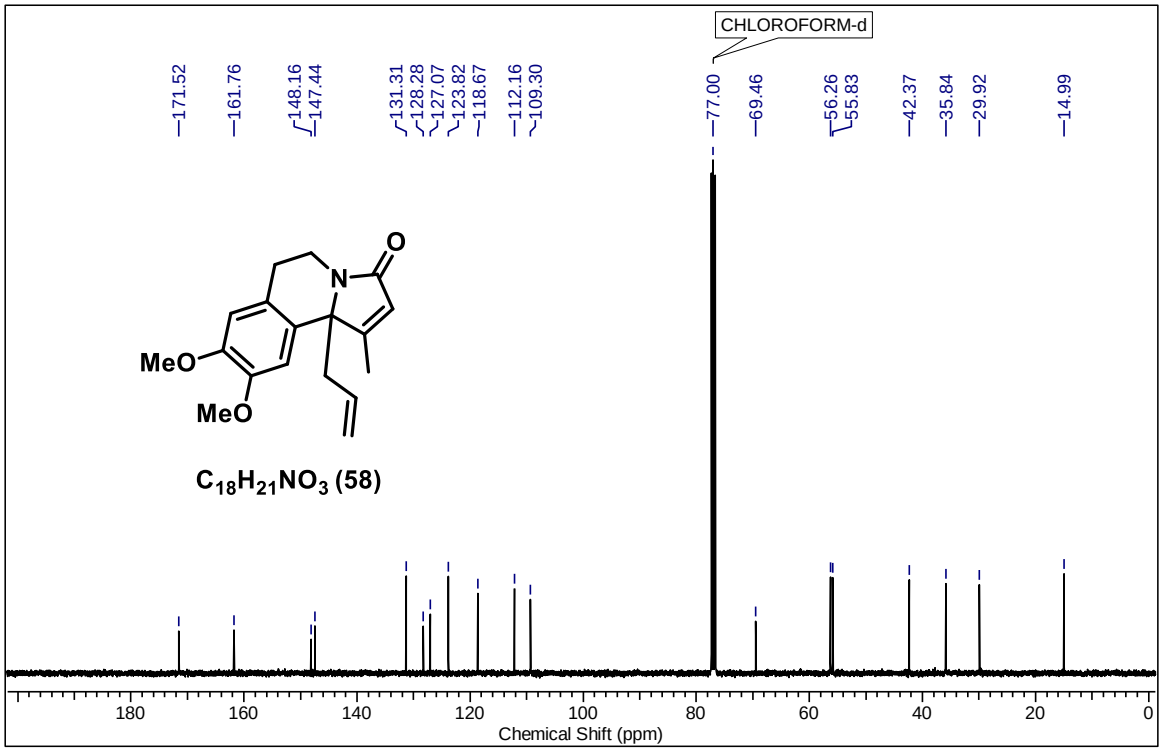
^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 59



^{1}H NMR ($CDCl_3$, 400 MHz) of Compound 58



^{13}C NMR ($CDCl_3$, 100 MHz) of Compound 58



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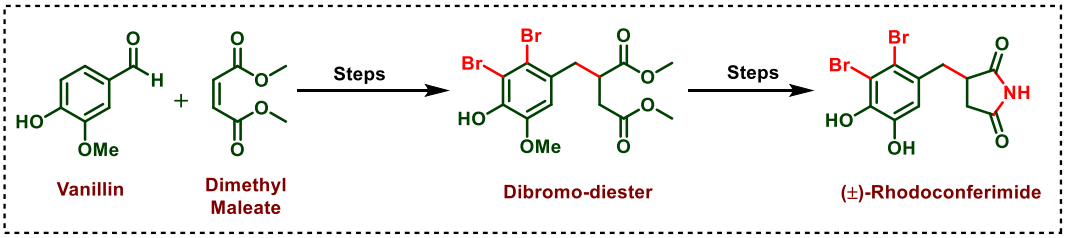
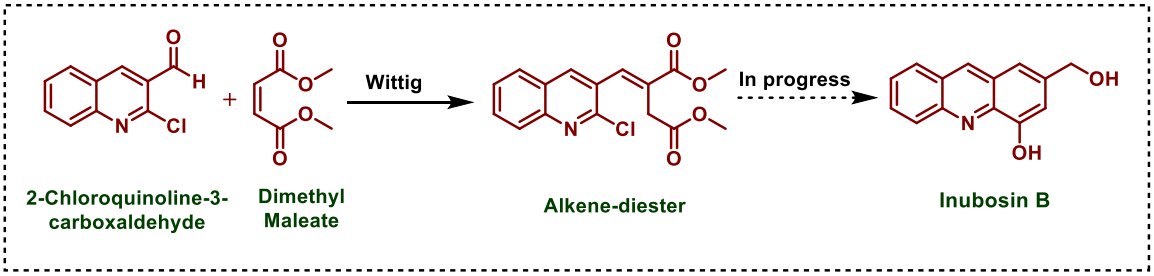
Bioactive alkaloids are an important class of natural products because of their unique structural features and remarkable bioactivities. Alkaloids play an essential role in medical and everyday life as dietary components, supplements, and drugs. Alkaloids are now a topic of considerable scientific and economic interest, particularly in medicine and the pharmaceutical business. Because of these concerns, the scientific community has become increasingly interested in bioactive alkaloid isolation, total synthesis, and pharmacological investigations. Important bioactive alkaloids include morphine, codeine, coniine, quinine, hyoscyamine, atropine, caffeine, ephedrine and ergonovine. Many groups have published comprehensive reviews describing the chemistry related to the bioactive alkaloids. Chapter one presents a concise literature review on the synthesis of different bioactive alkaloids published by various research groups employing cyclic anhydrides and their derivatives as potential precursors. We have outlined the literature account on the isolation, biological activities and synthetic approach of all these natural products from the year 2000 onwards. Overall in chapter one, we summarised the chemistry of cyclic anhydrides and their derivatives by describing several synthetic strategies in alkaloids synthesis through literature. The second and third chapters of this dissertation describe our contributions to the total synthesis of rhodoconferimide, pandalizine A and our efforts towards the synthesis of inubosin B, gorgonianic acid and eysotramidine utilizing new synthetic approaches primarily based on the chemistry of cyclic anhydrides and their derivatives.

We have accomplished the concise and efficient racemic total synthesis of potent antioxidant marine natural product rhodoconferimide starting from vanilline and dimethyl maleate via Wittig reaction, bromination and imide formation reaction. An appropriate regioselective double bromination of the aromatic ring was a crucial step in the synthesis. We propose that starting with an adequately substituted aldehyde was the key to synthesize the regioselective dibromination product and thus the natural product.

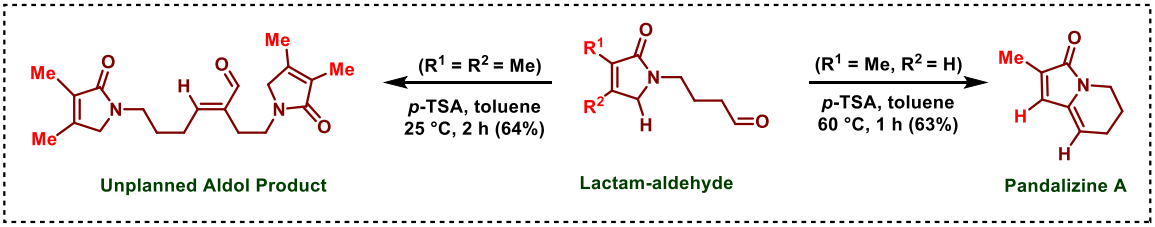


We have started synthesis of inubosin B using the Wittig reaction between laboratory prepared 2-chloroquinoline-3-carboxaldehyde and dimethyl maleate, which provided the

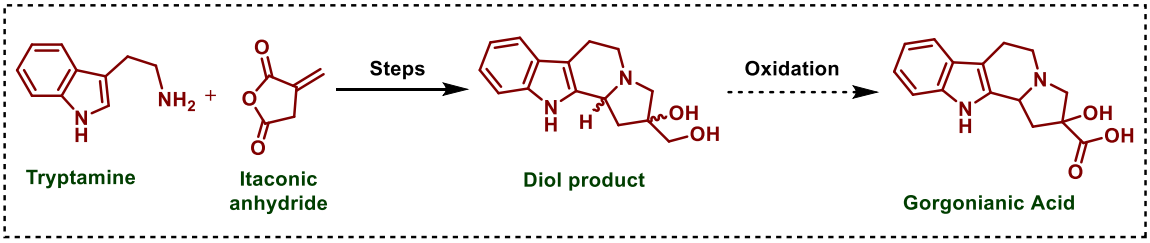
required alkene-diester compound. The Grignard reaction was used to attempt intramolecular cyclization, but it was ineffective, presumably due to the presence of a chelating diester group. We assume that our new approach will result in the total synthesis of inubosin B.



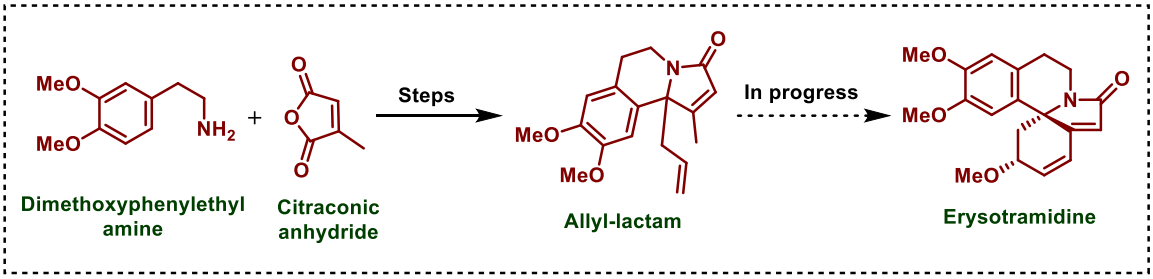
Starting from citraconic anhydride, facile total synthesis of pandalizine A alkaloid is described via the regioselective reduction of citraconimide and acid-catalyzed enolization of lactam-aldehyde followed by chemoselective intramolecular dehydrative cyclization as the key steps. It is noteworthy that the analogous model system with an additional β-methyl group followed an alternative chemoselective intermolecular aldol condensation pathway which generated the unplanned heterocyclic compound.



The synthesis of gorgonianic acid began with the reaction of tryptamine with itaconic anhydride to produce itaconimide, which on regioselective reduction, acid-promoted cyclization, and dihydroxylation yielded a mixture of diastereomers with the major diastereomer which was reduced to yield the diol product. The oxidation of the diol intermediate to the desired final product is being investigated.



The starting materials for the synthesis of Erythrina alkaloid erysotramidine were dimethoxyphenethylamine and citraconic anhydride. The regioselective reduction of citraconimide, acid-catalyzed intramolecular cyclization and in situ migration of the conjugated double bond to the more substituted side of the compound to generate the enamine product were all essential steps in the synthesis. The NBS approach was meticulously developed to yield both the active quaternary methoxy core and the conjugated imide in one pot. We are trying to complete the total synthesis of the final product in the upcoming days using our proposed efficient approach.



Overall the present dissertation describes the multistep synthesis of rhodoconferimide, pandalizine A and studies towards synthesis of structurally interesting important heterocyclic alkaloids inubosin B, gorgonianic acid and erysotramidine. Wittig olefination, regioselective dibromination, imide formation, regioselective reduction, acid-catalyzed intramolecular cyclization, Pictet–Spengler cyclization were used as key reactions in the synthesis of the above-mentioned synthetic approaches.

All of these studies offered us a nice opportunity to learn a new basic and applied research chemistry both from our work and from the vast literature in this field. We also believe that our strategies are can be used to design various natural products and natural product derivatives for structure-activity relationship studies. Finally, based on our exposure to heterocyclic bioactive alkaloids chemistry literature and our contributions to it, we can confidently state that this fascinating discipline will continue to expands its wings in the fields of organic and medicinal chemistry in the future.

ABSTRACT

Name of the Student: Mr. Kailas R. Pandhade
Registration No.: 10CC16A26029
Faculty of Study: Chemical Science
Year of Submission: 2022
AcSIR academic center/CSIR Lab:
CSIR-National Chemical Laboratory, Pune
Name of the Supervisor: Dr. N. P. Argade

Title of the thesis: Cyclic Anhydrides and Derivatives: Studies on Synthesis of Bioactive Alkaloids

Bioactive alkaloids are an important class of natural products because of their unique structural features and remarkable bioactivities. Alkaloids are now a considerable scientific and economic interest topic, particularly in medicine and the pharmaceutical business. Because of these concerns, the scientific community has become increasingly interested in bioactive alkaloid isolation, total synthesis, and pharmacological investigations. Chapter one presents a concise literature review on the synthesis of different bioactive alkaloids published by various research groups employing cyclic anhydrides and their derivatives as potential precursors. We have outlined the literature account on the isolation, biological activities and synthetic approaches to all these natural products from the year 2000 onwards.

Chapter two divided into two sections A and B. Section 2A presents the concise and efficient racemic total synthesis of potent antioxidant marine natural product rhodoconferimide starting from vanilline and dimethyl maleate via Wittig reaction, bromination and imide formation reaction. An appropriate regioselective double bromination of the aromatic ring was a crucial step in the synthesis. In section 2B, we have described our attempts toward the synthesis of inubosin B. We attempted intramolecular cyclization strategy using the Grignard reaction, but it was unsuccessful, possibly due to the presence of a chelating diester group. Chapter three divided into three sections A to C. Section 3A includes the facile total synthesis of pandalizine A alkaloid via regioselective reduction of citraconimide and acid-catalyzed enolization of lactam-aldehyde followed by chemoselective intramolecular dehydrative cyclization as the key steps. It is noteworthy that the analogous model system with an additional *β*-methyl group followed an alternative chemoselective intermolecular aldol condensation pathway. Section 2B includes synthetic strategies toward the indole alkaloid gorgonianic acid. The synthesis of gorgonianic acid began with the reaction of tryptamine with itaconic anhydride to produce itaconimide, which on regioselective reduction, acid-promoted cyclization, and dihydroxylation yielded a mixture of diastereomers with the major diastereomer, which was reduced to yield the diol product. The oxidation of the diol intermediate to the desired final product is being investigated. Section 3C includes the in progress synthesis of *Erythrina* alkaloid erysotramidine, starting with the reaction between dimethoxyphenethylamine and citraconic anhydride. The key steps were regioselective reduction, acid-catalyzed intramolecular cyclization with migration of the conjugated double bond and the formation of active quaternary methoxy core. We expect to complete the synthesis of final product using our proposed approach.

Overall conclusion, starting from cyclic anhydrides and their derivatives, we have developed a new synthetic approaches towards the synthesis of structurally interesting bioactive alkaloids.

List of Publications Emanating from the Thesis Work

1. First Total Synthesis of (±)-Rhodoconferimide
   Pandhade, **K. R.;** Argade, N. P. ***Synthesis* 2018, *50*, 658–662.**
   DOI: 10.1055/s-0036-1590944

2. Chemoselective Ring Closure of 4-(3-Methyl-2-oxo-2,5- dihydro-1H-pyrrol-1-yl) butanal Leading to Pandalizine A
   Yadav, M. B.; **Pandhade**, **K. R.** Argade, N. P. ***ACS Omega* 2020, *5*, 859−863.**
   DOI: 10.1021/acsomega.9b03760

List of Posters Presentation with Details

1. Poster Presentation in 'National Science Day Celebrations 2020' held in CSIR-NCL Pune, India (February 25-27, **2020**)
   Tital: Total Synthesis of (±)-Rhodoconferimide and Pandalizine A

   Abstract: Starting from vanillin and dimethyl maleate, a concise and efficient racemic total synthesis of the potent antioxidant marine natural product (±)-rhodoconferimide has been carried out via the Wittig reaction, catalytic hydrogenation, selective brominations, and imide formation. An appropriate regioselective double bromination of the aromatic ring was a key step in the synthesis. In second part, A facile total synthesis of pandalizine A alkaloid is described via the regioselective reduction of methylmaleimide and acid-catalyzed enolization of pyrrolbutanal followed by chemoselective intramolecular dehydrative cyclization as the key steps. It is noteworthy that the analogous model system with an additional *β*-methyl group followed an alternative chemoselective intermolecular aldol condensation pathway.

List of Conference Attended with Details

1. National Conference on Chirality (NCC-2017) held in Department of chemistry, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat (November 10-11, 2017)
2. Annual students' Conference 2019 held in CSIR-NCL Pune, India (November 28-29, 2019)

Synthesis K. R. Pandhade, N. P. Argade Paper

First Total Synthesis of (±)-Rhodoconferimide

Kailas R. Pandhade
Narshinha P. Argade*

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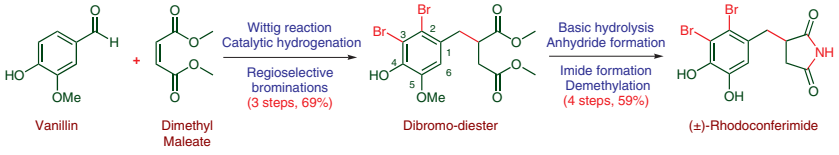

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DOI: 10.1055/s-0036-1590944; Art ID: ss-2017-z0547-op

Abstract Starting from vanillin and dimethyl maleate, a concise and efficient racemic total synthesis of the potent antioxidant marine natural product (±)-rhodoconferimide has been carried out via the Wittig reaction, catalytic hydrogenation, selective brominations, and imide formation. An appropriate regioselective double bromination of the aromatic ring was a key step in the synthesis.

Key words vanillin, bromination, (±)-rhodoconferimide, antioxidants, natural products, total synthesis

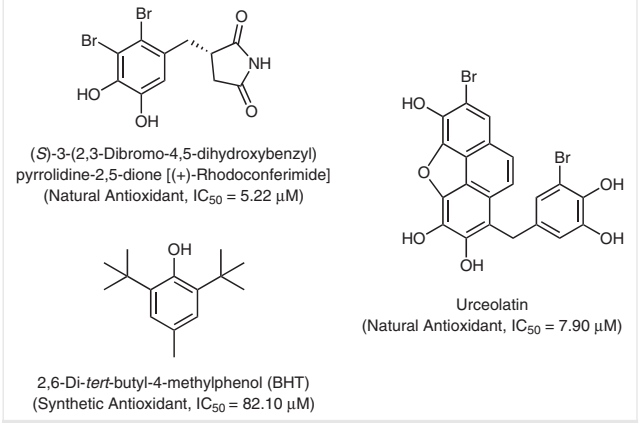
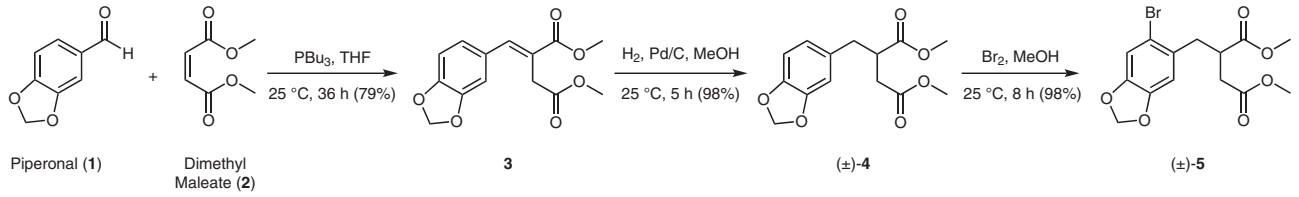


Figure 1 Natural and synthetic antioxidants (+)-rhodoconferimide, urceolatin, and BHT[22,26]

In life processes free radicals are continuously generated from oxygen metabolism. However, their imbalance causes damage to cells resulting in aging and diseases such as atherosclerosis, cancer, cardiovascular disorder, diabetes, inflammation, ischemia-reperfusion damage, Alzheimer's disease, and Parkinson's disease.[1–8] Antioxidants play a vital role in protecting human beings from free-radical-induced damage.[9–11] The use of synthetic antioxidants has been limited due to their lipid profile alteration and carcinogenic effects.[12,13] In this context the search for natural antioxidants has received significant attention.[14–20] The marine red alga *Rhodomela confervoides* occurs along the northern coastline of China and there it has been used as a food ingredient.[21–25] In 2012, Wang and co-workers isolated 10 mg of the new nitrogen-containing bromophenol (+)-rhodoconferimide from a 33 kg air-dried sample of *R. confervoides*.[26,27] (+)-Rhodoconferimide exhibits a 15-fold more potent free radical scavenging activity compared to the well-known synthetic antioxidant 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Figure 1).[26] In continuation of our studies on the total synthesis of recently isolated structurally interesting and biologically important natural products;[28–30] we herein report the first total synthesis of (±)-rhodoconferimide from the readily available precursors vanillin and dimethyl maleate.

Synthesis of an appropriately pentasubstituted aromatic ring bearing compounds is a challenging task for both electronic and steric reasons. A careful scrutiny of the rhodoconferimide structure revealed that 3,4-methylenedioxybenzaldehyde (piperonal), dimethyl maleate, elemental bromine, and urea would be suitable chemical constituents to accomplish the practical total synthesis of the target compound. Appropriate sequencing of the reactions, regioselective electrophilic introduction of two bromine atoms on the properly activated aromatic ring, and overall stability of the catechol moiety were the synthetic concerns. A Wittig reaction of the in situ generated ylide from dimethyl maleate (**2**) and tributylphosphine with piperonal (**1**) exclusively supplied the (*E*)-olefin **3** in 79% yield (Scheme 1). The catalytic hydrogenation of (*E*)-olefin **3** to saturated diester **4**, followed by the bromination of **4** in methanol solely



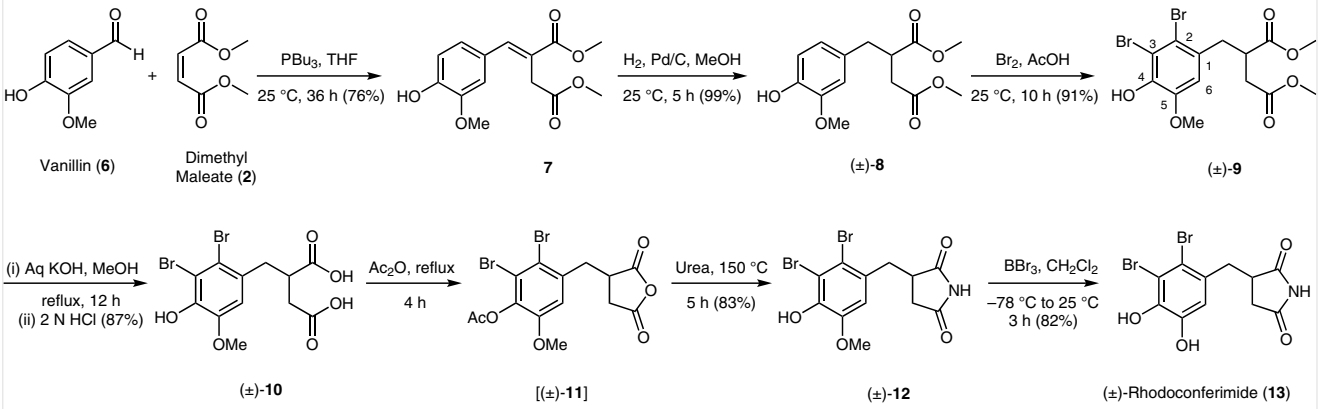
Scheme 1 Synthesis of monobrominated model compound

formed the monobrominated product **5** in 96% yield over two steps. The position of the bromine atom in compound **5** was confirmed on the basis of two sharp singlets of the aromatic protons in the ^{1}H NMR spectrum. Treatment of **4** with an excess of bromine (4.00 equiv) in acetic acid at 25 °C for 24 hours resulted in an inseparable mixture of the corresponding mono- and dibrominated products in very good yield in a 1:3 ratio (by ^{1}H NMR). Unfortunately, the aromatic ring system in compound **4** was not sufficiently activated for facile electrophilic introduction of the desired second bromine atom. Therefore, at this stage it was decided to commence the synthesis from vanillin instead of piperonal.

A Wittig reaction of vanillin (**6**) with the in situ generated ylide from dimethyl maleate (**2**) and tributylphosphine furnished the required product **7** in 76% yield; catalytic reduction of the carbon–carbon double bond provided diester **8** in 99% yield (Scheme 2). Treatment of **8** with an excess of bromine (4.00 equiv) in acetic acid resulted in smooth stepwise regioselective electrophilic aromatic substitutions and directly provided the desired dibromo compound **9** in 91% yield. In compound **9**, position 2 is *para* to the directing methoxy group, while position 3 is *ortho* to the relatively more electron-rich hydroxy group and therefore the introduction of the two bromine atoms selectively took place at those positions. The introduction of a third bromine atom at position 6 in compound **9** does not take place, probably due to less activation and/or steric hindrance reasons (presence of methoxy instead of hydroxy group at position 5). Base-promoted hydrolysis of diester **9** yielded dicarboxylic acid **10** in 87% yield. One-pot acetic anhydride induced transformation of dicarboxylic acid **10** to the corresponding anhydride **11**, followed by its neat fusion with urea directly provided the in situ deacylated benzylsuccinimide **12** in 83% yield over two steps. Anhydride **11** was used for the next step without any purification and characterization, due to its propensity towards hydrolytic cleavage. Boron tribromide (BBr_3) induced demethylation of **12** at –78 °C delivered the final product (±)-rhodoconferimide (**13**) in 82% yield. Rhodoconferimide (**13**) was obtained in seven steps in an overall yield of 41%, and its analytical and spectral data were in complete agreement with the reported data.[26,31]

In the present synthesis of (±)-rhodoconferimide, application of vanillin as a starting material was strategically planned for the desired regioselective introduction of two bromine atoms. Thus on the basis of the results described in Schemes 1 and 2, we propose that when the corresponding veratraldehyde, isovanillin, and protocatechuic aldehyde are used, the undesired monobrominated, dibrominated, and tribrominated products would result, respectively.

In summary, the total synthesis of (±)-rhodoconferimide was carried out without involving any separate protection step. We believe that the bromophenol moiety in (+)-rhodoconferimide is responsible for the antioxidant activity and the source of the bromine atoms could be marine water. It is noteworthy that the structurally simple (+)-rhodoconferimide is a more potent antioxidant than the multifunctional urceolatin from Figure 1. (+)-Rhodoconferimide



Scheme 2 First total synthesis of (±)-rhodoconferimide via one-pot regioselective brominations

is important from an activity and utility point of view and this constituent from edible seaweed may find application as a food additive and/or drug candidate.[32] The presented synthetic strategy is flexible and would be useful for designing a focused mini library of rhodoconferimide derivatives and congeners for tailored antioxidant property studies. Moreover, conceptually, custom-made polymers derived from bromine-containing compounds such as rhodoconferimide would be useful to fabricate marine-water-friendly durable fishing nets.

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR, and 500 MHz NMR spectrometers using residue solvent signals as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz) and 500 NMR (125 MHz) spectrometers. High-resolution MS (HRMS) [electrospray ionization (ESI)] were obtained on Orbitrap (quadrupole plus ion trap) and TOF mass analyzers. The IR spectra were recorded on an FTIR spectrophotometer. Column chromatographic separations were carried out on silica gel (60–120 and 230–400 mesh). Commercially available starting materials and reagents were used.

Dimethyl (*E*)-2-[Benzo(*d*)(1,3)dioxol-5-ylmethylene]succinate (3)

n-Bu_3P (0.85 mL, 3.46 mmol) was added dropwise to a stirred solution of dimethyl maleate (**2**; 0.33 mL, 2.66 mmol) and piperonal (**1**; 0.40 mL, 2.66 mmol) in THF (10 mL) at 25 °C under argon. The mixture was stirred for 36 h and then concentrated in vacuo. The obtained residue was dissolved in EtOAc (20 mL) and the resultant solution was washed with H_2O (20 mL) and brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by column chromatographic purification of the obtained residue (silica gel, 60–120 mesh, EtOAc–PE, 2:8) furnished product **3**.

Yield: 586 mg (79%); white solid; mp 78–80 °C.

IR ($CHCl_3$): 1711, 1691 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.56 (s, 2 H), 3.74 (s, 3 H), 3.82 (s, 3 H), 6.00 (s, 2 H), 6.80–6.92 (m, 3 H), 7.81 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.5, 52.18, 52.22, 101.4, 108.6, 109.1, 124.0, 124.3, 128.8, 141.9, 147.9, 148.3, 167.9, 171.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{14}O_6Na$: 301.0683; found: 301.0678.

Dimethyl 2-[Benzo(*d*)(1,3)dioxol-5-ylmethyl]succinate (4)

Activated Pd/C (50 mg, 10 wt%) was added to a stirred solution of **3** (500 mg, 1.79 mmol) in MeOH (10 mL) and the reaction mixture was stirred under a balloon pressure H_2 atmosphere at 25 °C for 5 h. The reaction mixture was filtered to remove the Pd/C, and the filtrate was concentrated in vacuo. The obtained compound was dissolved in EtOAc (20 mL) and the formed solution was washed with H_2O (20 mL) and brine (20 mL) and dried over Na_2SO_4. The resultant solution was concentrated in vacuo and then dried by using a vacuum pump to provide pure product **4**.

Yield: 493 mg (98%); thick oil.

IR ($CHCl_3$): 1733, 1601 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (dd, *J* = 16.5, 4.9 Hz, 1 H), 2.66 (t, *J* = 9.8 Hz, 1 H), 2.69 (t, *J* = 7.3 Hz, 1 H), 2.96 (dd, *J* = 13.4, 6.1 Hz, 1 H), 3.02–3.13 (m, 1 H), 3.65 (s, 3 H), 3.68 (s, 3 H), 5.93 (s, 2 H), 6.59 (d, *J* = 7.3 Hz, 1 H), 6.65 (s, 1 H), 6.73 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.8, 37.4, 43.2, 51.8, 51.9, 100.9, 108.2, 109.2, 122.0, 131.8, 146.3, 147.7, 172.3, 174.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}O_6Na$: 303.0839; found: 303.0834.

Dimethyl 2-{[6-Bromobenzo(*d*)(1,3)dioxol-5-yl]methyl}succinate (5)

Br_2 (0.15 mL, 2.85 mmol) was added to a stirred solution of **4** (200 mg, 0.71 mmol) in MeOH (10 mL) at 0 °C and the reaction mixture was stirred at 25 °C for 8 h. The mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (15 mL). The organic layer was washed with sat. aq $Na_2S_2O_3$ (10 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The obtained bromo compound was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 2:8) to furnish product **5**.

Yield: 250 mg (98%); thick oil.

IR ($CHCl_3$): 1734, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.46 (dd, *J* = 16.6, 4.5 Hz, 1 H), 2.60–2.90 (m, 2 H), 2.95–3.60 (m, 2 H), 3.65 (s, 3 H), 3.68 (s, 3 H), 5.95 (s, 2 H), 6.66 (s, 1 H), 6.98 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.0, 37.5, 41.6, 51.7, 52.0, 101.7, 110.5, 112.8, 114.9, 130.6, 147.29, 147.34, 172.0, 174.4.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}O_6BrNa$: 380.9944; found: 380.9941.

Dimethyl (*E*)-2-(4-Hydroxy-3-methoxybenzylidene)succinate (7)

n-Bu_3P (8.73 mL, 35.45 mmol) was dropwise added to a stirred solution of dimethyl maleate (**2**; 3.42 mL, 27.30 mmol) and vanillin (**6**; 4.15 g, 27.30 mmol) in THF (40 mL) at 25 °C under argon. The reaction mixture was stirred for 36 h and then concentrated in vacuo. The obtained residue was dissolved in EtOAc (100 mL) and the resultant solution was washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by column chromatographic purification of the obtained residue (silica gel, 60–120 mesh, EtOAc–PE, 2:8) furnished product **7**.

Yield: 5.81 g (76%); white solid; mp 89–91 °C.

IR ($CHCl_3$): 3417, 1710, 1632 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.57 (s, 2 H), 3.69 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 6.27 (br s, 1 H), 6.85–6.90 (m, 3 H), 7.80 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.5, 52.0, 52.1, 55.7, 111.7, 114.6, 123.2, 123.3, 126.9, 142.2, 146.5, 146.7, 168.0, 171.8.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}O_6Na$: 303.0839; found: 303.0833.

Dimethyl 2-(4-Hydroxy-3-methoxybenzyl)succinate (8)

Activated Pd/C (400 mg, 10 wt%) was added to a stirred solution of **7** (4.00 g, 14.28 mmol) in MeOH (40 mL) and the reaction mixture was stirred under a balloon pressure H_2 atmosphere at 25 °C for 5 h. The reaction mixture was filtered to remove the Pd/C and the filtrate was concentrated in vacuo. The obtained compound was dissolved in EtOAc (100 mL) and the formed solution was washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. The resultant solution was concentrated in vacuo and then dried by using a vacuum pump to provide pure product **8**.

Yield: 3.98 g (99%); thick oil.

IR ($CHCl_3$): 3539, 1733, 1611 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.41 (dd, *J* = 16.7, 5.0 Hz, 1 H), 2.60–2.68 (m, 1 H), 2.72 (d, *J* = 8.2 Hz, 1 H), 2.92–3.18 (m, 2 H), 3.65 (s, 3 H), 3.68 (s, 3 H), 3.87 (s, 3 H), 5.56 (s, 1 H), 6.60–6.68 (m, 2 H), 6.85 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.9, 37.5, 43.3, 51.7, 51.9, 55.9, 111.3, 114.3, 121.8, 129.9, 144.4, 146.5, 172.4, 174.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}O_6Na$: 305.0996; found: 305.0991.

Dimethyl 2-(2,3-Dibromo-4-hydroxy-5-methoxybenzyl)succinate (9)

Br_2 (2.18 mL, 42.55 mmol) was added to a stirred solution of **8** (3.00 g, 10.63 mmol) in AcOH (30 mL) at 0 °C and the reaction mixture was stirred at 25 °C for 10 h. The mixture was then concentrated in vacuo and the obtained residue was dissolved in EtOAc (40 mL). The organic layer was washed with sat. aq $Na_2S_2O_3$ (20 mL), 5% aq $NaHCO_3$ (20 mL), and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The obtained dibromo product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 2:8) to furnish pure product **9**.

Yield: 4.20 g (91%); brown solid; mp 106–108 °C.

IR ($CHCl_3$): 3426, 1733, 1638 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.49 (dd, *J* = 16.6, 4.5 Hz, 1 H), 2.64–2.82 (m, 1 H), 2.87–3.04 (m, 1 H), 3.10–3.32 (m, 2 H), 3.66 (s, 3 H), 3.67 (s, 3 H), 3.89 (s, 3 H), 6.07 (br s, 1 H), 6.71 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.2, 39.2, 41.5, 51.8, 52.0, 56.4, 112.1, 112.4, 118.1, 130.5, 143.3, 145.9, 172.0, 174.4.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}O_6Br^{81}BrNa$: 462.9185; found: 462.9172.

2-(2,3-Dibromo-4-hydroxy-5-methoxybenzyl)succinic Acid (10)

A solution of KOH (1.30 g, 22.83 mmol) in H_2O (5 mL) was added to a stirred solution of ester **9** (1.00 g, 2.28 mmol) in MeOH (15 mL) at 25 °C and the reaction mixture was refluxed for 12 h. The mixture was allowed to reach 25 °C and then concentrated in vacuo. The obtained residue was diluted with EtOAc (25 mL) and acidified with 2 N HCl (15 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The obtained product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 3:7) to provide diacid **10**.

Yield: 813 mg (87%); white solid; mp 159–161 °C.

IR ($CHCl_3$): 3450, 1728, 1600 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 2.44 (dd, *J* = 16.8, 4.2 Hz, 1 H), 2.64 (dd, *J* = 17.0, 8.8 Hz, 1 H), 2.98 (td, *J* = 11.1, 4.3 Hz, 1 H), 3.12–3.21 (m, 2 H), 3.87 (s, 3 H), 6.88 (s, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 36.4, 40.4, 43.1, 57.0, 114.1 (2 C), 118.8, 131.4, 145.9, 148.5, 175.5, 177.9.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{12}O_6Br^{81}BrNa$: 434.8872; found: 434.8861.

3-(2,3-Dibromo-4-hydroxy-5-methoxybenzyl)pyrrolidine-2,5-dione (12)

A solution of diacid **10** (500 mg, 1.27 mmol) in Ac_2O (10 mL) was gently refluxed for 4 h under an argon atmosphere. The reaction mixture was allowed to reach 25 °C and concentrated in vacuo. The obtained residue was dried by using a vacuum pump and mixed with urea (229 mg, 3.80 mmol). The neat reaction mixture was heated at 150 °C for 5 h and then it was allowed to cool down to 25 °C. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The obtained product was purified by column chromatography (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 1:9) to provide in situ deacylated imide **12**.

Yield: 415 mg (83%); white solid; mp 204–206 °C.

IR ($CHCl_3$): 3621, 3451, 1703 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.42–2.60 (m, 2 H), 2.81 (t, *J* = 13.4 Hz, 1 H), 3.11–3.28 (m, 2 H), 3.83 (s, 3 H), 7.08 (s, 1 H), 9.81 (s, 1 H), 11.18 (br s, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 34.4, 37.5, 40.8, 56.4, 113.0, 113.4, 116.7, 129.9, 144.1, 147.3, 178.0, 180.6.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{11}O_4NBr^{81}BrNa$: 415.8927; found: 415.8919.

3-(2,3-Dibromo-4,5-dihydroxybenzyl)pyrrolidine-2,5-dione (Rhodoconferimide, 13)

A solution of BBr_3 in CH_2Cl_2 (0.61 mL, 0.65 mmol) was added to a stirred solution of **12** (170 mg, 0.43 mmol) in anhyd CH_2Cl_2 (10 mL) at –78 °C over a period of 5 min under argon. The reaction mixture was stirred for 3 h and allowed to reach 25 °C. The reaction mixture was concentrated in vacuo and the obtained residue was diluted with H_2O. The reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layer was washed with brine (25 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by column chromatographic purification of the obtained compound (silica gel, 230–400 mesh, MeOH–CH_2Cl_2, 1:9) furnished pure product **13**.

Yield: 135 mg (82%); colorless thick oil.

IR ($CHCl_3$): 3600–3000, 1679, 1758 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (dd, *J* = 17.7, 4.3 Hz, 1 H), 2.58 (dd, *J* = 18.0, 9.2 Hz, 1 H), 2.79 (dd, *J* = 12.2, 10.4 Hz, 1 H), 3.00–3.25 (m, 2 H), 6.81 (s, 1 H), 9.46 (s, 1 H), 9.99 (s, 1 H), 11.15 (s, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 34.6, 37.1, 40.9, 113.5, 114.9, 116.5, 129.8, 143.5, 145.2, 178.0, 180.7.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_8O_4NBr^{81}Br$: 377.8794; found: 377.8809 [M – H]$^-$.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590944. NMR spectra of all the synthesized compounds are included.

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(31) The noticed consistent minor differences in the chemical shifts of all signals in the ^{1}H NMR data of the natural product are plausibly due to the error in picking up the correct signal for DMSO. As reported for the natural product, if the signal for the aromatic proton is locked at δ = 6.96 ppm, all chemical shift values match correctly (please see the ^{1}H NMR data SI-19 and SI-20 in the Supporting Information).
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Chemoselective Ring Closure of 4-(3-Methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanal Leading to Pandalizine A

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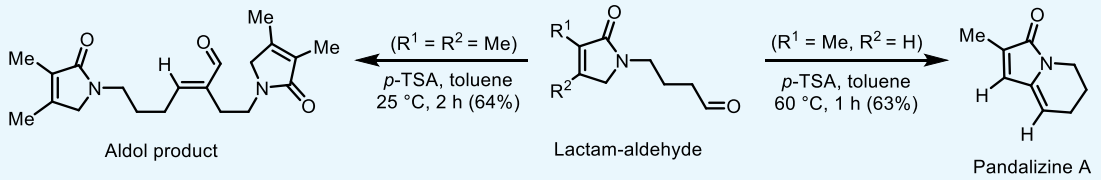
Supporting Information



ABSTRACT: Starting from methylmaleic anhydride, a facile total synthesis of pandalizine A alkaloid is described via the regioselective reduction of methylmaleimide and acid-catalyzed enolization of 4-(3-methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanal followed by chemoselective intramolecular dehydrative cyclization as the key steps. It is noteworthy that the analogous model system with an additional *β*-methyl group followed an alternative chemoselective intermolecular aldol condensation pathway.

INTRODUCTION

Alkaloids are important compounds that possess a broad range of effective biological activities, and some novel azabicyclic alkaloids are shown in Figure 1.[1−5] Tropical *Pandanus*

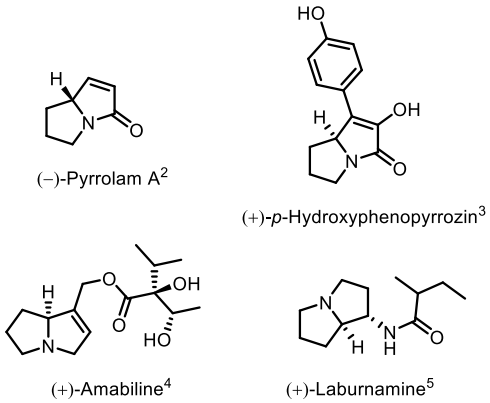


Figure 1. Representative bioactive azabicyclic natural products.[2−5]

amaryllifolius shrub from Southeast Asia is used in folk medicine for the treatment of gout, hyperglycemia, hypertension, and rheumatism.[6,7] Recently, the azabicyclic alkaloids pandalizines A (5.2 mg), B (4.5 mg), C (1.2 mg), D (1.3 mg), and E (1.2 mg) have been isolated from 6.0 kg of aerial parts of *P. amaryllifolius* species, and their structural and stereochemical assignments have been done on the basis of NMR, 2D NMR, and circular dichroism studies (Figure 2).[6,7] The authors have also proposed that glutamic acid and leucine are biogenetic precursors of all of these alkaloids. A large number of well-established synthetic protocols to design azabicyclic frame-

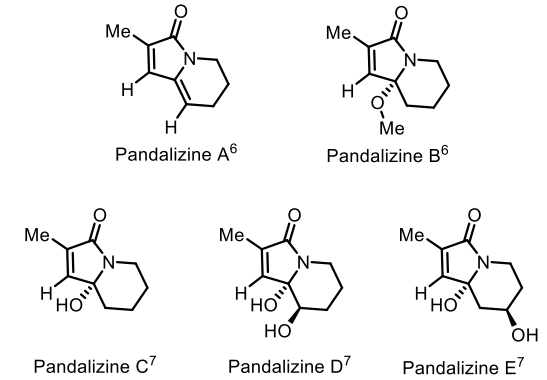


Figure 2. Azabicyclic pandalizines A−E alkaloids from *P. amaryllifolius*.[6,7]

works are known in the contemporary literature.[8] In this context, very recently, elegant total syntheses of pandalizine A, (±)-pandalizines B, and (±)-pandalizines C have been accomplished via photo-oxidation of specifically synthesized furylalkylamine by Vassilikogiannakis and co-workers from Greece (Scheme 1).[9,10] However, synthesis of pandalizines D and E bearing an additional hydroxyl group at two different positions in ring-B is still awaited. To date, we have accomplished the total synthesis of a large number of bioactive natural products using cyclic anhydrides and their derivatives as the potential precursors.[11−15] Now we report the total synthesis of pandalizine A via the regioselective reduction of

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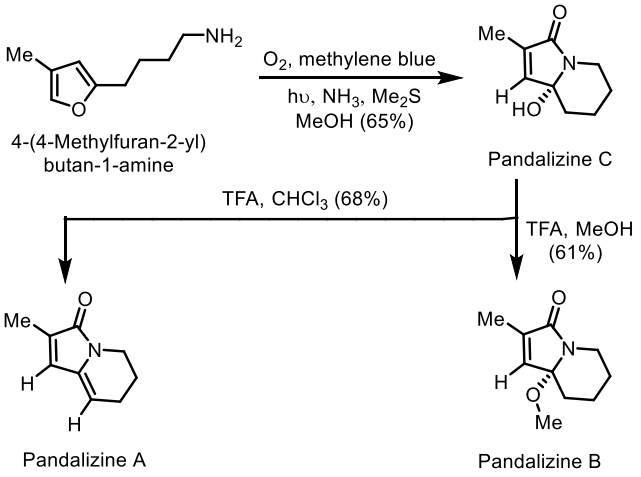
Scheme 1. Photooxygenation-Based Known Approach to Pandalizines A−C[9,10]



citraconimide followed by a substrate-specific chemoselective ring closure as crucial reactions (Schemes 2 and 3).

RESULTS AND DISCUSSION

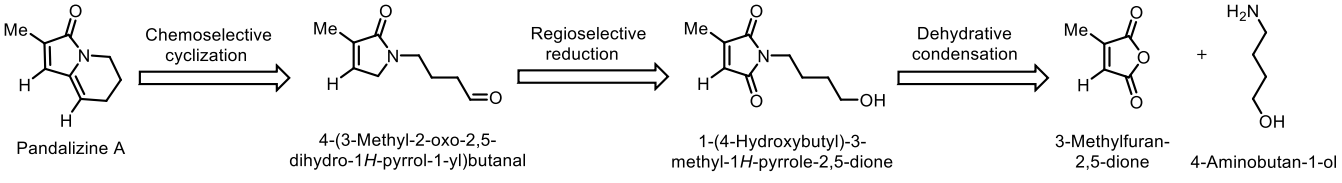
A systematic plan was prepared to synthesize pandalizine A from methylmaleic anhydride and the accordingly proposed concise retrosynthetic analysis is depicted in Scheme 2. The regioselective reduction of citraconimide and chemoselective intramolecular cyclization of a well-structured substrate over possible intermolecular aldol condensation were the foreseen challenges in our synthetic strategy. The reaction of methylmaleic anhydride (**1a**) with 4-aminobutanol in a refluxing mixture of acetic acid plus toluene directly furnished the corresponding imide **2a** in 92% yield via the dehydrative cyclization of the formed intermediate regioisomeric maleamic acids and the thermal acylation of free primary alcohol (Scheme 3). The reaction of imide **2a** with a bulky reducing agent such as DIBAL-H at −78 °C directly provided a column chromatographically inseparable regioisomeric mixture of desired deacylated major lactamol **3a** and the corresponding undesired minor isomer in a ∼9:1 ratio (by ^{1}H NMR) with 88% yield. The structural assignment of lactamol **3a** was initially done on the basis of more deshielded ^{1}H NMR signal for β-vinylic proton at δ = 6.55, which was finally confirmed on completion of the total synthesis of pandalizine A. Further reduction of the above-mentioned mixture of lactamols using BF_3OEt_2−Et_3SiH via a plausible formation of the corresponding iminium ion intermediates and purification of the crude product by silica gel column chromatography yielded pure lactam **4a** in 82% yield. The PCC oxidation of the primary alcohol unit in lactam **4a** delivered the essential lactam aldehyde **5a** in 76% yield for further systematic intramolecular condensation studies. In our hands, the reactions of compound **5a** with bases such as DBU, NaH, LiHMDS, and NaHMDS resulted in a complex reaction mixture.[16] The lactam aldehyde **5a** on treatment with *p*-TSA in toluene at room temperature remained completely unreacted. However, the same reaction at 60 °C chemoselectively resulted in our target compound pandalizine A (**7a**) in 63% yield via the formation of the corresponding enol intermediate **6a** and the intramolecular dehydrative condensation. In the present reaction, the formation of the significant enol intermediate **6a** initiated prior to the possible enolization of aldehyde moiety and feasible intermolecular aldol condensation. All our attempts to further improve the efficiency of the above-specified reaction by changing the reaction time and temperature were unsuccessful. The obtained NMR data for an analytically pure sample of pandalizine A (**7a**) was completely matching with reported data.[6,9,10] The total synthesis of pandalizine A (**7a**) was completed in five steps with 29% overall yield. The obtained natural product was highly prone to oxidative degradation under normal atmospheric conditions and got transformed into a complex mixture in 48 h.

To demonstrate yet another example of such type of chemoselective cyclization, maleimide **2b** was synthesized in 93% yield by dehydrative condensation of dimethylmaleic anhydride (**1b**) with 4-aminobutanol in refluxing toluene[17] (Scheme 3). Symmetrical imide **2b** on $NaBH_4$ reduction formed lactamol **3b**, and its treatment with BF_3OEt_2−Et_3SiH provided lactam **4b** in 68% overall yield over two steps. The PCC oxidation of alcohol **4b** yielded the desired substrate **5b** in 71% yield. Surprisingly, the reaction of lactam aldehyde **5b** with *p*-TSA in toluene at room temperature followed another pathway and underwent the chemoselective intermolecular dehydrative aldol condensation furnishing the undesired product **7b** in 64% yield via the preferential formation of an alternate enol intermediate **6b**. The repetition of the above-specified reaction at 60 °C also exclusively resulted in the same product **7b**, but with 55% yield. Overall, the lactam aldehydes **5a** and **5b** follow two different reaction pathways under a similar set of reaction conditions due to the difference in acidity of methylene proton in lactam moieties and relatively less steric hindrance noted by a conjugate base in the formation of the intermediate **6a**.

CONCLUSIONS

In summary, from readily available starting materials, we have completed protection-free practical total synthesis of pandalizine A via a remarkable regioselective reduction and chemoselective intramolecular cyclization pathway. Present studies represent a unique example wherein actual natural product precursor indeed followed expected chemoselective intramolecular cyclization route and furnished the target compound, while the analogous substrate with an additional β-methyl group delivered the undesired aldol product. We feel that the favored formation of an appropriately reactive cyclic enol intermediate for intramolecular cyclization is the genesis

Scheme 2. Concise Retrosynthetic Analysis of Pandalizine A



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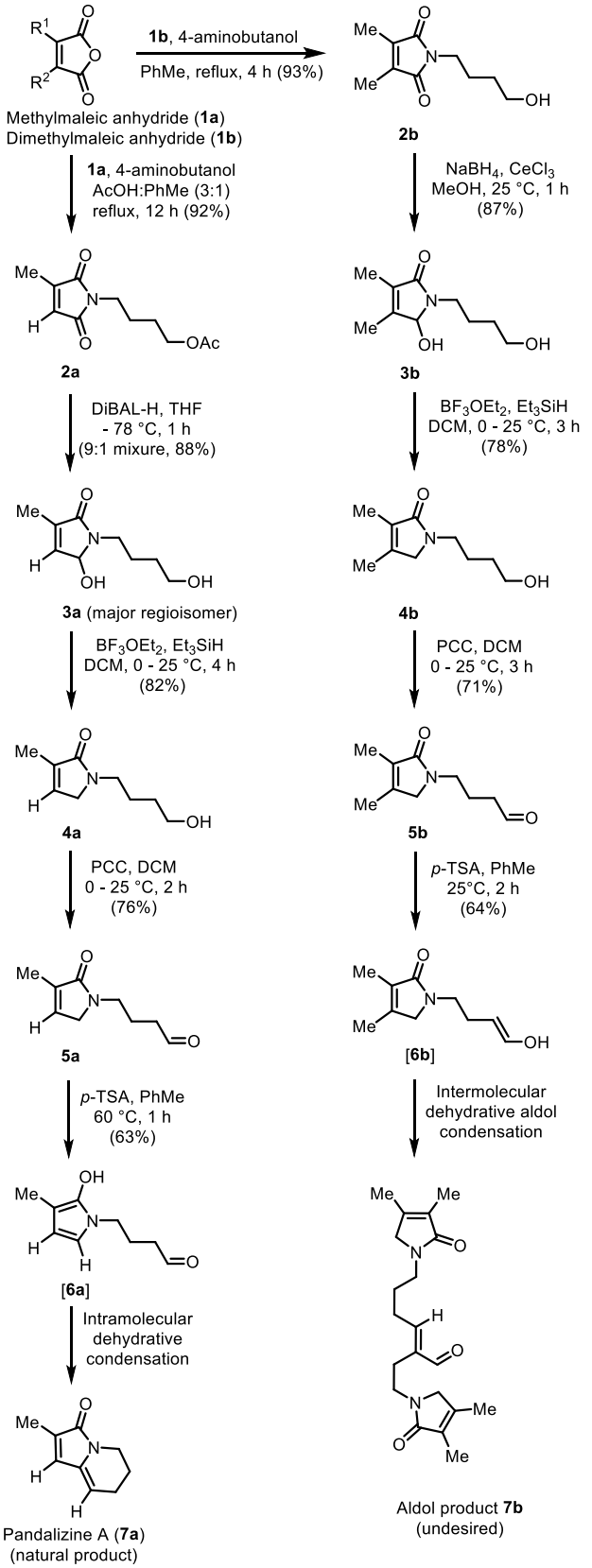
Scheme 3. Structure-Based Chemoselective Intramolecular Condensation versus Intermolecular Aldol Reaction: Simple and Efficient Synthesis of Pandalizines A



of delicately balanced chemoselectivity. Overall, the absence/presence of β-methyl group governs the course of competitive carbon−carbon bond-forming reactions and functions as a chemoselectivity switch.

EXPERIMENTAL SECTION

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200, 400, and 500 MHz NMR spectrometers using tetramethylsilane (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. High-resolution mass spectra [electrospray ionization (ESI)] were taken on 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.

4-(3-Methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-butyl Acetate (2a). To a solution of 4-aminobutanol (0.99 g, 11.13 mmol) in AcOH/PhMe (20 mL, 3:1) was added citraconic anhydride (**1a**, 1.25 g, 11.13 mmol), and the stirring reaction mixture was refluxed for 12 h. The reaction mixture was concentrated in vacuo, after attaining room temperature. The obtained residue was dissolved in EtOAc. The organic layer was washed with 10% aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and the obtained product was purified by using column chromatography (silica gel, 60−120 mesh, EtOAc−PE, 3:7) to furnish pure citraconimide **2a** as a colorless liquid (2.31 g, 92% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.30 (q, J = 1.9 Hz, 1H), 4.05 (t, J = 6.1 Hz, 2H), 3.50 (t, J = 6.8 Hz, 2H), 2.06 (d, J = 1.8 Hz, 3H), 2.02 (s, 3H), 1.62 (quintet, J = 3.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.8, 171.0, 170.8, 145.5, 127.2, 63.7, 37.4, 25.9, 25.2, 20.9, 10.9; HRMS (ESI) [M + Na]$^+$ calcd for $C_{11}H_{15}NO_4Na$ 248.0893, found 248.0894; IR ($CHCl_3$) ν_{max} 1721, 1709, 1644 cm^{-1}.

5-Hydroxy-1-(4-hydroxybutyl)-3-methyl-1,5-dihydro-2*H*-pyrrol-2-one [3a (Major Isomer) and the Corresponding Minor Regioisomer]. To a solution of imide (**2a**, 1.0 g, 4.44 mmol) in dry THF (15 mL) was slowly added a solution of DIBAL-H in cyclohexane (1 M, 13.32 mL, 13.32 mmol) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at the same temperature. The reaction was quenched with a saturated aqueous solution of potassium sodium tartrate tetrahydrate, and the reaction mixture was concentrated in vacuo. The formed product was dissolved in EtOAc, and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo. The column chromatographic purification of the obtained crude product (silica gel, 60−120 mesh, EtOAc−PE, 8:2) gave pure compound **3a** as a yellowish liquid (726 mg, 9:1 mixture, 88% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.55 (t, J = 1.5 Hz, 0.9H), 5.75 (br s, 0.1H), 5.29 (s, 0.9H), 5.14 (s, 0.1H), 4.60−4.00 (br s, 1H), 3.75−3.55 (m, 2H), 3.55−3.27 (m, 2H), 3.10−2.50 (br s, 1H), 2.05 (s, 0.30H), 1.87 (s, 2.70H), 1.80−1.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.7, 138.5, 136.7, 82.0, 62.1, 39.6, 29.5, 25.2, 10.9; HRMS (ESI) [M + Na]$^+$ calcd for $C_9H_{15}NO_3Na$ 208.0944, found: 208.0945; IR ($CHCl_3$) ν_{max} 3340, 1683 cm^{-1}.

1-(4-Hydroxybutyl)-3-methyl-1,5-dihydro-2*H*-pyrrol-2-one (4a). To a solution of compound (**3a** plus minor isomer, 600 mg, 3.24 mmol) in dry DCM (15 mL) were added $BF_3{\cdot}OEt_2$ (1.39 mL, 4.86 mmol) and Et_3SiH (0.57 mL, 4.86

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mmol) dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 4 h and allowed to reach room temperature. The reaction mixture was concentrated in vacuo, and the formed product was dissolved in EtOAc. The organic layer was washed with 10% aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo and column chromatographic purification of the obtained product (silica gel, 230−400 mesh, MeOH/DCM, 2:8) furnished pure lactam **4a** as a colorless liquid (458 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.66 (q, J = 1.7 Hz, 1H), 3.84 (t, J = 1.9 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H), 3.51 (t, J = 6.7 Hz, 2H), 3.30−2.90 (br s, 1H), 1.89 (d, J = 1.8 Hz, 3H), 1.80−1.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.2, 135.8, 135.0, 62.1, 50.6, 42.1, 29.4, 25.2, 11.3; HRMS (ESI) $[M + Na]^+$ calcd for $C_9H_{15}NO_2Na$ 192.0995, found 192.0997; IR ($CHCl_3$) ν_{max} 3423, 1659 cm^{-1}.

4-(3-Methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-butanal (5a). To a solution of alcohol (**4a**, 400 mg, 2.36 mmol) in dry DCM (10 mL) was added PCC on Celite (0.66 g, 3.07 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h allowing to reach room temperature. The reaction mixture was diluted with DCM and filtered through Celite using sintered funnel. The residue was washed with DCM, and the filtrate was concentrated in vacuo. The obtained product was purified by using column chromatography (silica gel, 230−400 mesh, MeOH/DCM, 1:9) to furnish pure aldehyde **5a** as a colorless liquid (302 mg, 76% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.78 (s, 1H), 6.68 (q, J = 1.6 Hz, 1H), 3.84 (t, J = 1.9 Hz, 2H), 3.50 (t, J = 6.9 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 2.00−1.80 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 201.5, 172.3, 135.7, 135.1, 50.6, 41.7, 41.1, 21.1, 11.3; HRMS (ESI) $[M + H]^+$ calcd for $C_9H_{14}NO_2$ 168.1019, found 168.1019; IR ($CHCl_3$) ν_{max} 2856, 1714, 1665 cm^{-1}.

2-Methyl-6,7-dihydroindolizin-3(5*H*)-one (Pandalizine A, 7a). To a stirred solution of aldehyde (**5a**, 200 mg, 1.20 mmol) in dry toluene (8 mL) was added *p*-TSA (617 mg, 3.59 mmol) under a nitrogen atmosphere, and the reaction mixture was heated at 60 °C for 1 h. The reaction mixture was concentrated in vacuo upon reaching room temperature. The obtained residue was dissolved in EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and the product was purified by column chromatography (silica gel, 230−400 mesh, MeOH/DCM, 1:9) to get pure product **7a** as a yellow liquid (112 mg, 63% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.56 (q, J = 1.6 Hz, 1H), 5.43 (t, J = 4.7 Hz, 1H), 3.63 (dd, J = 6.4 and 5.9 Hz, 2H), 2.32 (q, J = 5.6 Hz, 2H), 1.96 (d, J = 0.9 Hz, 3H), 1.90 (quintet, J = 5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 137.9, 133.9, 127.8, 110.1, 37.9, 22.7, 21.6, 10.9; HRMS (ESI) $[M + H]^+$ calcd for $C_9H_{12}NO$ 150.0913, found 150.0913. IR ($CHCl_3$) ν_{max} 1656 cm^{-1}.

1-(4-Hydroxybutyl)-3,4-dimethyl-1*H*-pyrrole-2,5-dione (2b). To a solution of 4-aminobutanol (0.71 g, 7.93 mmol) in toluene (20 mL) was added dimethylmaleic anhydride (**1b**, 1.0 g, 7.93 mmol), and the stirring reaction mixture was refluxed for 4 h. After reaching room temperature, the reaction mixture was concentrated in vacuo. The obtained product was dissolved in EtOAc. The organic layer was washed with 10% aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and column chromatographic purification of the formed residue (silica gel, 60−120 mesh, EtOAc−PE, 4:6) gave pure product **2b** as a colorless liquid (1.45 g, 93% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.60 (t, J = 7.6 Hz, 2H), 3.47 (t, J = 8.6 Hz, 2H), 2.34 (br s, 1H), 1.91 (s, 6H), 1.65−1.57 (m, 2H), 1.54−1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 137.0, 62.0, 37.5, 29.5, 25.0, 8.5; HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_{16}NO_3$ 198.1125, found 198.1121; IR ($CHCl_3$) ν_{max} 3451, 1768, 1703 cm^{-1}.

5-Hydroxy-1-(4-hydroxybutyl)-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (3b). To a solution of imide (**2b**, 1.0 g, 6.08 mmol) in MeOH (20 mL) was added $CeCl_3{\cdot}7H_2O$ (2.26 g, 6.08 mmol) at 0 °C, and the reaction mixture was stirred for 5 min. To the above reaction mixture was added $NaBH_4$ (231 mg, 6.08 mmol), and it was further stirred for 1 h. The formed reaction mixture was concentrated in vacuo, and the product was diluted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo provided the crude product, and its column chromatographic purification (silica gel, 60−120 mesh, EtOAc−PE, 9:1) furnished pure compound **3b** as a colorless liquid (876 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.70−5.25 (br s, 1H), 5.03 (s, 1H), 4.25−3.85 (br s, 1H), 3.62−3.50 (m, 2H), 3.47−3.35 (m, 1H), 3.35−3.22 (m, 1H), 1.90 (s, 3H), 1.70 (s, 3H), 1.65−1.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 149.0, 128.5, 84.0, 61.7, 39.3, 29.5, 25.1, 11.1, 8.3; HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_{18}NO_3$ 200.1281, found 200.1277; IR ($CHCl_3$) ν_{max} 3419, 1664 cm^{-1}.

1-(4-Hydroxybutyl)-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (4b). To a solution of compound **3b** (500 mg, 2.51 mmol) in dry DCM (15 mL) were added $BF_3{\cdot}OEt_2$ (1.44 mL, 5.02 mmol) and Et_3SiH (0.59 mL, 5.02 mmol) dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 4 h, and after reaching room temperature, it was concentrated in vacuo. The obtained residue was dissolved in EtOAc. The obtained organic layer was washed with 10% aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo and column chromatographic purification of the residue (silica gel, 230−400 mesh, MeOH/DCM, 2:8) furnished pure product **4b** as a colorless liquid (357 mg, 78% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.70 (s, 2H), 3.63−3.58 (m, 2H), 3.45−3.39 (m, 2H), 3.39−3.10 (br s, 1H), 1.91 (s, 3H), 1.73 (s, 3H), 1.66−1.56 (m, 2H), 1.55−1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 145.5, 128.6, 61.9, 54.1, 41.7, 29.4, 25.1, 12.8, 8.5; HRMS (ESI) $[M + H]^+$ calcd for $C_{10}H_{18}NO_2$ 184.1332, found 184.1329; IR ($CHCl_3$) ν_{max} 3413, 1662 cm^{-1}.

4-(3,4-Dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-butanal (5b). To a solution of alcohol **4b** (200 mg, 1.09 mmol) in dry DCM (10 mL) was added PCC on Celite (706 mg, 3.28 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h and allowed to reach room temperature. The reaction mixture after diluting with DCM was filtered through Celite using a sintered funnel. The residue was washed with DCM, and the filtrate was concentrated in vacuo. Column chromatographic purification of the obtained residue (silica gel, 230−400 mesh, MeOH/DCM, 1:9) furnished pure aldehyde **5b** as a colorless liquid (141 mg, 71% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (s, 1H), 3.72 (s, 2H), 3.46 (t, J = 6.9 Hz, 2H), 2.51 (t, J = 7.6 Hz, 2H), 1.96 (s, 3H), 1.89 (quintet, J = 7.6 Hz, 2H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6, 173.0, 145.7, 128.7, 54.1, 41.3, 41.1, 21.1, 12.9, 8.6; HRMS (ESI) $[M + H]^+$ calcd for

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$C_{10}H_{16}NO_2$ 182.1176, found 182.1174; IR ($CHCl_3$) ν_{max} 3433, 1707, 1665 cm^{-1}.

(*E*)-6-(3,4-Dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-2-[2-(3,4-dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl]hex-2-enal (7b). To a solution of aldehyde **5b** (100 mg, 0.55 mmol) in dry toluene (10 mL) was added *p*-TSA (283 mg, 1.65 mmol) under a nitrogen atmosphere, and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated in vacuo, and the obtained product was dissolved in EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The dried organic layer was concentrated in vacuo, and the obtained product was purified by column chromatography (silica gel, 230−400 mesh, MeOH/DCM, 1:9) to furnish pure aldol product **7b** as a colorless liquid (61 mg, 64% yield). ^1H NMR ($CDCl_3$, 500 MHz) δ 9.36 (s, 1H), 6.61 (t, J = 9.6 Hz, 1H), 3.77 (d, J = 4.8 Hz, 4H), 3.50 (t, J = 8.6 Hz, 2H), 3.42 (t, J = 8.6 Hz, 2H), 2.52 (t, J = 9.6 Hz, 2H), 2.44 (q, J = 9.6 Hz, 2H), 1.97 (s, 3H), 1.95 (s, 3H), 1.85−1.70 (m, 2H), 1.81 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.8, 172.9, 172.8, 156.1, 146.0, 145.7, 140.7, 128.8, 128.5, 54.6, 54.3, 41.5, 40.9, 27.7, 26.3, 23.3, 13.0 (2C), 8.7, 8.6; HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{29}N_2O_3$ 345.2173, found 345.2167; IR ($CHCl_3$) ν_{max} 1701, 1659 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03760.

^1H NMR and ^{13}C NMR spectra of all of the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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